N-Hetereocyclic Carbene Catalysed (4+2) Annulations in the Synthesis of Natural Products

A thesis submitted for the degree of Doctor of Philosophy

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To my parents,

who have supported me greatly in all of my endeavours, academic, or otherwise. Thank you for providing me with every opportunity to succeed.

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the results of original work carried out by me, unless otherwise acknowledged, during the period 2015-2019, and has not been presented for examination for any degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publication from which they are derived.

Adam Ametovski

February 2019

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Shocking though it is, when I first stepped into David Lupton's office to enquire about honours projects, he had a great deal to say. If I'm honest with myself, in this brief meeting I understood at most 20% of the chemistry related topics. David, thank you for the opportunity to join your group, and in particular for your persistence in the early years of my PhD studies when I was, in my own words, a lousy student. The last 4 years have filled my head, and now, I can claim as much as anyone, to understand all(most) of what you have to say. To the rest of the Lupton family, thank you Mandy for the boxes of fruit and for making David apologise even when he wasn't being mean, and of course to Elsie for helping with the synthesis of my Δ^9-THC cake.

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Finally, to my oldest and dearest group of friends, who are too many to list (you know who you are), thank you for always having my back, even when I didn't believe that I deserved it. You have all, knowingly or unknowingly, helped me complete these studies and for that I love you!

Publications

(3) Enantioselective total synthesis of (-)-Δ^9-tetrahydrocannabinol via N-heterocyclic carbene catalysis

Adam Ametovski and David W. Lupton

Org. Lett. **2019**, *21*, 1212.

(2) Biomimetic and Biocatalytic Synthesis of Bruceol

Aaron J. Day, Joel H. Z. Lee, Quang D. Phan, Hui C. Lam, Adam Ametovski, Christopher J. Sumby, Stephen G. Bell and Jonathan H. George.

Angew. Chem. Int. Ed. **2018**, *58*, 1427.

(1) Enantioselective (4+2) annulation of donor-acceptor cyclobutanes by N-heterocyclic carbene catalysis

Alison Levens, Adam Ametovski and David W. Lupton

Angew. Chem. Int. Ed. **2016**, *55*, 16136.

Presentations

Poster Presentation: Enantioselective total synthesis of (–)-Δ^9-tetrahydrocannabinol via N-heterocyclic carbene catalysis

RACI 43rd Annual Synthesis Symposium, Melbourne, Victoria, Australia **2018**

Poster Presentation: Studies towards the synthesis (+)-bisabosqual A and (–)-Δ^9-tetrahydrocannabinol by N-heterocyclic carbene catalysis

BOSS XVI 16th Organic Synthesis Symposium, Brussels, Belgium **2018**

Oral Presentation: Enantioselective (4+2) annulation of donor-acceptor cyclobutanes by N-heterocyclic carbene catalysis

RACI 41st Annual Synthesis Symposium, Melbourne, Victoria, Australia **2016** (awarded the prize for best student oral presentation)

Poster Presentation: Enantioselective (4+2) annulation of donor-acceptor cyclobutanes by N-heterocyclic carbene catalysis

MonCat1 Inaugural Symposium, Clayton, Melbourne, Victoria **2016**

Abstract

Central to the improving the human condition, is the enhancing the efficiency of chemical syntheses that access biologically active natural products and pharmaceuticals. Such an endeavour is underpinned by the development of new catalytic, and robust methodologies that are capable of rapidly constructing complex chemical architectures. In this regard, N-hetereocyclic carbenes (NHCs) have been shown to provide stereochemically pure, and polycyclic scaffolds through a range of Umpolung and normal polarity intermediates. Despite this, at the time that doctoral studies commenced, only 4 instances of enantioselective reactions exploiting NHCs had been utilised in target-oriented synthesis and of these, only reactions proceeding through Umpolung intermediates were known.

The first chapter of this thesis provides an overview of the inception of enantioselective organocatalysis and highlights the impact of this catalytic mode with respect to enhancing the efficiency of chemical synthesis. Following this, a brief introduction to the wide variety of intermediates available to NHC catalysis, and the complex structures to which they give access, are presented. Finally, these reactive modes are discussed, where possible, with respect to their application in the synthesis of natural products and biologically relevant compounds.

The second chapter introduces the field of single electron transfer coupled NHC catalysis, with an emphasis on the enantioselective radical coupling reactions that are possible. Following this, efforts to exploit this mode of reactivity to access novel 4-carbon synthons *via* the radical cleavage of cyclopropanes is discussed. In these studies, both an inter- and intramolecular (4+2) annulation were explored using an appropriate 2-carbon donor, however, these reactions were not viable due unwanted side reactions facile polymerisation, decomposition or benzoin condensation pathways.

The third chapter details the discovery of the first enantioselective (4+2) annulation involving donor-acceptor (DA) cyclobutanes, that was achieved exploiting NHCs. The coupling of DA-cyclobutanes with α,β-unsaturated acyl fluorides generates densely functionalised cyclohexyl β-lactones with excellent stereochemical integrity. To assess the viability of such a reaction in the synthesis of natural products, the utility of the reaction was examined heavily with respect to substrate scope, scale-up, and product derivatisation.

In the fourth chapter, efforts to exploit the (4+2) annulation reaction developed in *Chapter 3* in the total synthesis of (+)-bisabosqual A are detailed. Three model studies were undertaken to asses the viability of this reaction in the prospective synthesis. Although introduction of the alkenyl sidechain, and stereospecific assembly of the tetracyclic core was possible, penta-substituted acyl fluorides mapping to the aromatic backbone of the natural product were poor substrates in the (4+2) annulation.

The fifth chapter describes an enantioselective synthesis of (–)-Δ^9-tetrahydrocannabinol (THC) and (–)-Δ^8-THC , enabled by the (4+2) annulation developed in *Chapter 3*. Several strategies to install the C^9 methyl group *via* (4+2) annulation reactions are discussed, however, a late stage installation strategy exploiting a new dual Krapcho decarboxylation procedure was developed.

Chapter six details experimental procedures and spectroscopic data of all compounds utilised in the studies of *Chapters 2–5.*

Abbreviations

Ac	Acetyl
Ar	Aryl
BBN	Borabicyclo(3.3.1)nonane
Bn	Benzyl
Bz	Benzoyl
cat.	Catalyst
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	(Dimethylamino)sulfur trifluoride
DBU	1,8-Diazabicy clo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DIBAL-H	Diisobutyl aluminium hydride
DIPEA	Diisopropylethyl amine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(Diphenylphosphino)ethane
d.r.	Diastereomeric ratio
EDTA	Ethylenediaminetetraacetic acid
E	Electrophile
EWG	Electron-withdrawing group
ee	Enantiomeric excess

e.r.	Enantiomeric ratio
eq.	Equation
equiv.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
h	Hours
HFIP	Hexafluoroisopropanol
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IMes	1,3-Bis(trimethylphenyl)imidazole-2-ylidene
^{i}Pr	*iso*-Propyl
IR	Infrared
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
KO^{t}Bu	Potassium *tert*-butoxide
L	Ligand
LA	Lewis acid
LB	Lewis base
LRMS	Low-resolution mass spectroscopy
Me	Methyl
Mes	Mesityl (2,4,6-trimethylphenyl)
min	Minutes
M.P.	Melting point
M. S.	Molecular sieves
N	Nucleophilicity parameter

NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
NR	No reaction
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PG	Protecting group
Ph	Phenyl
PivOH	Pivalic acid
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
*p*TsOH	*para*-Toluenesulfonic acid
R_f	Retention factor
rt	Room temperature
SM	Starting material
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
^{t}Bu	*tert*-Butyl
^{t}BuOH	*tert*-Butanol
temp.	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine

TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
TMSF	Trimethylsilyl fluoride
Tol	Tolyl
Ts	Tosyl
TTCE	Tetrachloroethylene

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Single electron transfer coupled NHC catalysis for annulations of cyclopropanes

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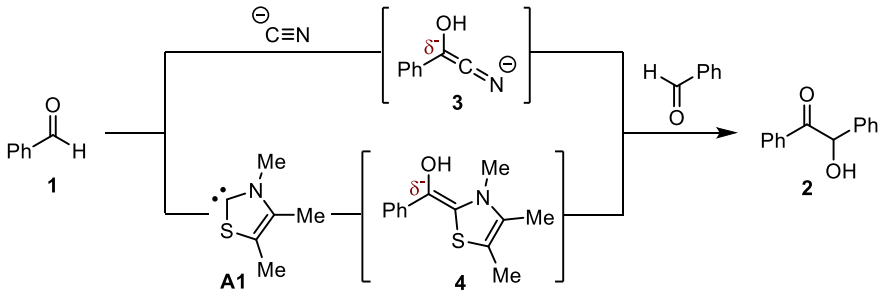
Chapter 1

N-Heterocyclic carbene organocatalysis and applications in total syntheses

1.1 Introduction

1.1.1 A brief history of organocatalysis

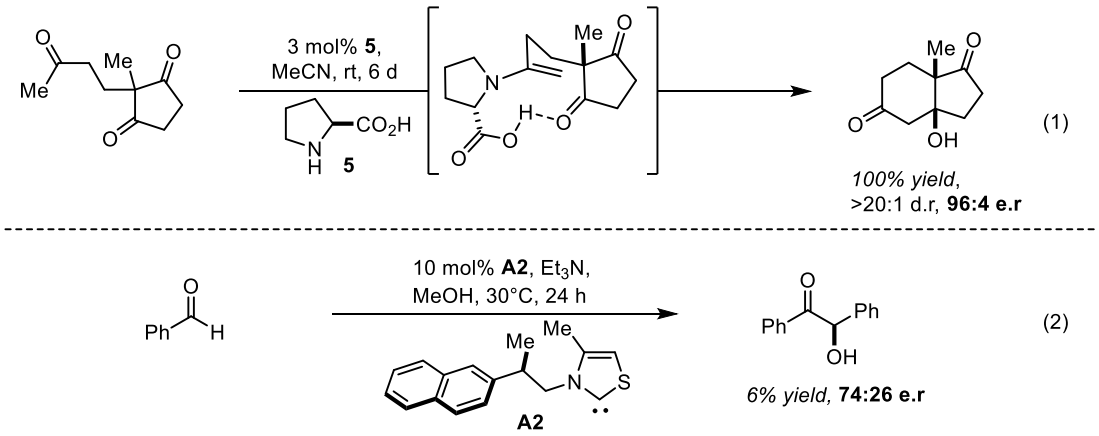
The potential for small organic molecules to catalyse organic transformations has been known since 1832 when Wöhler and Liebig first discovered the benzoin condensation. In this reaction, cyanide anions were shown to effect the dimerization of aldehydes **1** to give α-hydroxy ketones **2.**[1] Despite this early discovery, the action of cyanide was not understood for a further 70 years when Lapworth proposed umpoled intermediate **3** (Scheme 1.1).[2] Building upon this, Ukai and co-workers demonstrated that catalytic quantities of thiazolium salts enabled the same transformation in basic media,[3] while Breslow would later elucidate the mechanism of this reaction, implicating N-eterocyclic carbenes (NHCs) (i.e. thiazolylidene **A1**) as the active catalyst. Central to this proposal is the formation of Breslow intermediate **4**, or, the acyl anion equivalent, an Umpolong event that reverses the natural polarity of the carbonyl centre.[4]



Scheme 1.1. Cyanide and NHC mediated benzoin reaction.

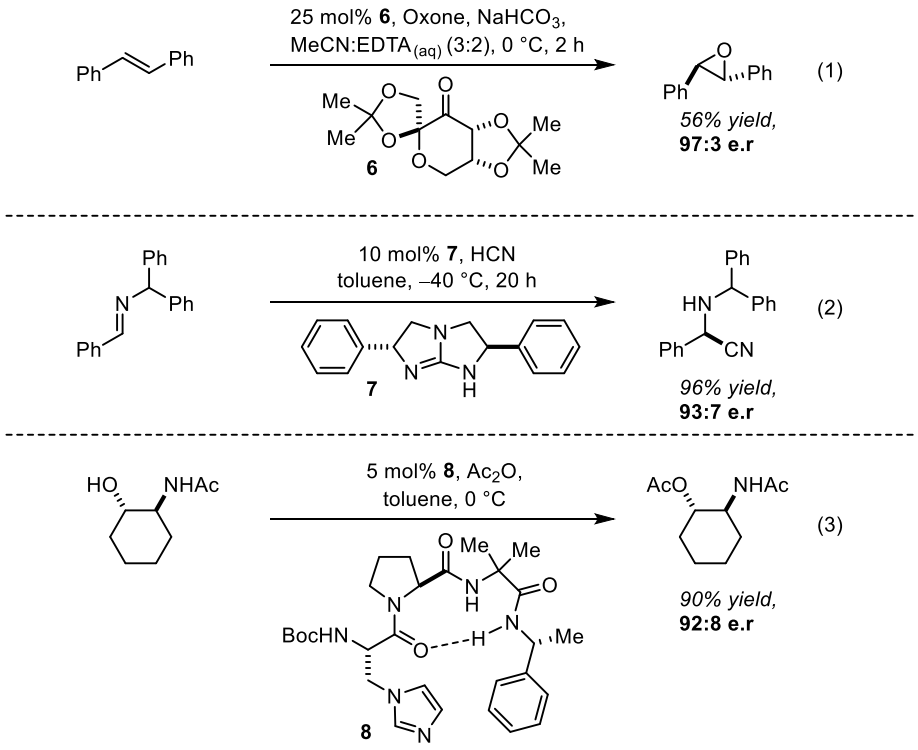
Following these seminal studies, an array of important organocatalytic transformations were discovered in the 20th century, including Morita-Bayliss-Hillman,[5] Stetter,[6] and acyl transfer[7] reactions to name a few. Despite these contributions, there were only sporadic advancements in the field of enantioselective organocatalysis. Most notable in this regard was the discovery of the Hajos–Parish–Eder–Sauer–Wiechert reaction in 1974, an enantioselective modification of the Robinson annulation catalysed by *(S)*-proline

(**5**) (Scheme 1.2, eq. 1).[8] Importantly, this represented the first example of an organocatalytic, enantioselective Aldol reaction, and has been employed widely in the industrial synthesis of optically pure steroids. In addition, the Benzoin reaction was rendered enantioselective in this time using homochiral NHC **A2**, however, both the chemical yield and enantioselectivity was poor (Scheme 1.2, eq. 2).[9]



Scheme 1.2. Enantioselective Hajos-Parrish and benzoin reactions.

In the late 1990s, these foundational studies were finally built upon, with a series of reports highlighting the potential for organocatalysis to enable highly enantioselective transformations. This commenced with the discovery of chiral ketone (i.e. **6**) catalysed enantioselective epoxidations by the groups of Shi (Scheme 1.3, eq. 1)[10], Denmark[11] and Yang[12]. Shortly thereafter, Corey (Scheme 1.3, eq. 2)[13] and Jacobsen[14] demonstrated for the first-time enantioselective hydrogen-bonding catalysis of the Strecker reaction using, for example, homochiral guanidine **7**. Also of note was Miller and co-workers' demonstration of a kinetic resolution of secondary alcohols effected by small peptides (i.e. **8**, Scheme 1.3, eq. 3)[15].



Scheme 1.3. Early enantioselective organocatalytic reactions.

Only in the year 2000 was organocatalysis truly conceptualised, and common modes of activation defined. Underpinning this was the studies of List[16] and MacMillan,[17] who demonstrated that the underlying mode of action permitting enamine and iminium catalysis may be adapted, offering wide-spread applicability to a variety of reaction manifolds. In the years following these publications, the field of enantioselective organocatalysis experienced rapid expansion, a phenomenon which continues nearly two decades later.[18]

A host of organocatalytic activation modes that enable highly enantioselective transformations are now established and have been exploited extensively in the syntheses of pharmaceuticals as well as complex polycyclic natural product targets.[19] The assembly of these structures has been aided using simple transformations such as desymmetrisation (i.e. (–)-rhazinilim (**9**)) and Prins cyclisation (i.e. (+)-estrone (**10**)), or significantly more complex multi-bond forming cascades, for example, in the synthesis of (–)-strychnine (**11**) and (+)-ibophyllidine (**12**) (Figure 1.1). Although transient bonding catalysis such as hydrogen-bonding (H-bond),[20] counterion,[21] and more recently, chiral Brønsted acid catalysis[22] have been well examined in this regard, catalysis *via* Lewis basic interactions has received the most attention. This may be in part due to the remarkable versatility of Lewis bases to enhance or even inverse both the nucleophilic (enamine/phosphine/NHC) and electrophilic (iminium/SOMO/phosphine/NHC) nature of substrates.[23] From this perspective, the now established field of NHC catalysis is of great interest.

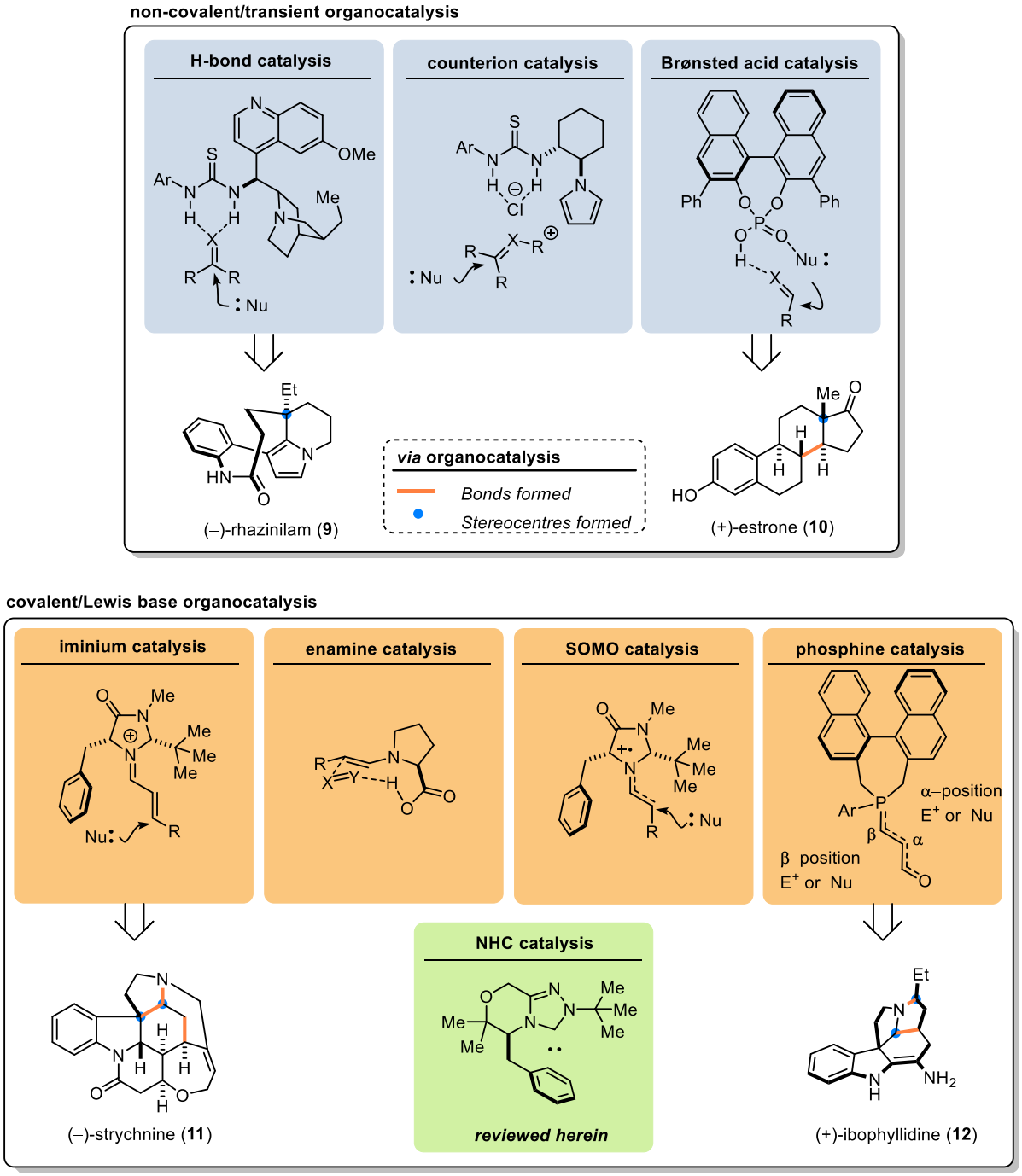


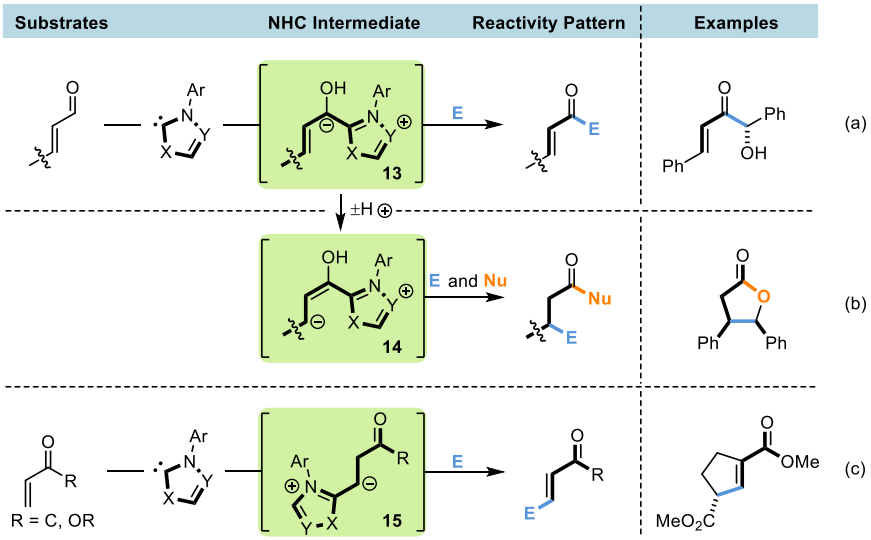
Figure 1.1. Activation modes of common organocatalysts.

1.2 NHC organocatalysis

Since the development of modern homochiral NHC scaffolds by the groups of Enders, Glorius, and Zeitler, NHC catalysis has emerged as a powerful method for constructing new C-X and C-C bonds with excellent diastereo- and enantioselectivity.[24] Notably, NHCs offer various modes of activation encompassing both Umpolung and normal polarity intermediates and enable cascade reactions capable of

rapidly constructing molecular complexity. Although not exhaustive, the common reactivity patterns of NHC derived intermediates and the chemical architectures that they access are introduced herein.

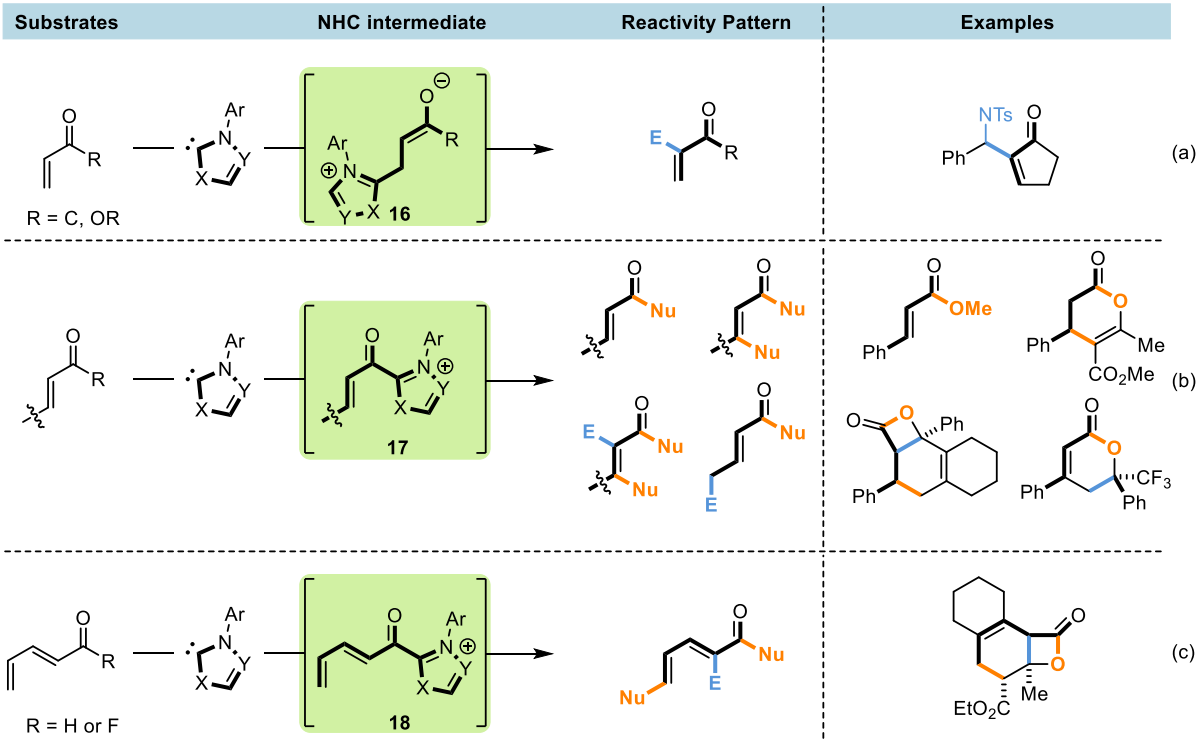
Modern NHC catalysis has been dominated by the polarity reversal of aldehydes by formation and reactions of the Breslow intermediate, or, acyl anion **13**. In this regard, the benzoin[1] and Stetter[6] reactions are most well-known, which couple **13** with aldehydes and Michael acceptors respectively (Scheme 1.4a). Bode[25] and Glorius[26] independently demonstrated that umpolung reactivity could be shuttled to the β-carbon *via* proton transfer to the NHC-homoenolate **14**, an intermediate typically trapped with aldehydes and ketones (Scheme 1.4b). Polarity reversal at the β-carbon is also possible through conjugate addition of NHCs to α,β-unsaturated compounds. Although the resultant β-azolium ylide **15** was first exploited in 2006 by Fu,[27] only in the last 3 years have enantioselective methods been realised (Scheme 1.4c).[28]



Scheme 1.4. Umpolung NHC intermediates and reaction patterns.

In the last decade, the utility of NHCs has seen substantial growth, with these versatile catalysts shown to engage transformations showcasing an array of normal polarity intermediates.[24g] Initially these reactions exploited intermediates analogous to those accessible through phosphine[29] and pyridine[30] Lewis base catalysis, however, novel reactive modes have now been developed. NHCs undergo conjugate addition to Michael acceptors to give the β-azolium enolate **16**, which engages in classic α-functionalisation reactions (i.e. aza-Morita-Bayliss-Hillman, Scheme 1.5, eq. 1).[31] Notably, acyl addition of NHCs with a wide range of unsaturated substrates accesses the α,β-unsaturated acyl azolium **17**, an intermediate possessing unique properties that has been implicated in vast array of transformations (Scheme 1.5, eq. 2). From **17**, functionalisation of the α, β, acyl, and even γ- carbons has been demonstrated, with several reactivity patterns giving rise to complex and enantioenriched cyclic scaffolds.[24i] Most recently Chi[32] and Lupton[33]

have exploited a higher unsaturated homolog, the dienyl acyl azolium **18**, in regio- and enantioselective bond formation at the γ-carbon, with subsequent α-functionalisation and acylation generating polycyclic frameworks (Scheme 1.5, eq. 3).

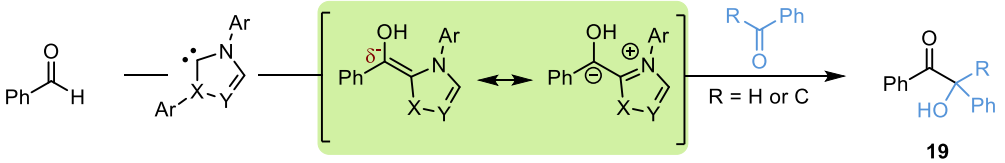


Scheme 1.5. Normal polarity NHC intermediates and reactivity patterns.

It is important to note that the vast series of intermediates are available from similar substrates, and that the high tunability of both the electronic character and the steric environment of NHC scaffolds mediates this divergent reactivity. Such diversity renders NHC catalysis an attractive tool for designing new bond-forming strategies that enhance the efficiency of complex target synthesis. It is not surprising that the number of total syntheses featuring NHC catalysis has increased significantly in recent years,[34] yet in this regard, only several of the abovementioned intermediates have been exploited. In the following sections, these modes of reactivity are discussed with reference to applications in the synthesis of natural products and biologically relevant compounds.

1.3 NHC catalysed benzoin condensations

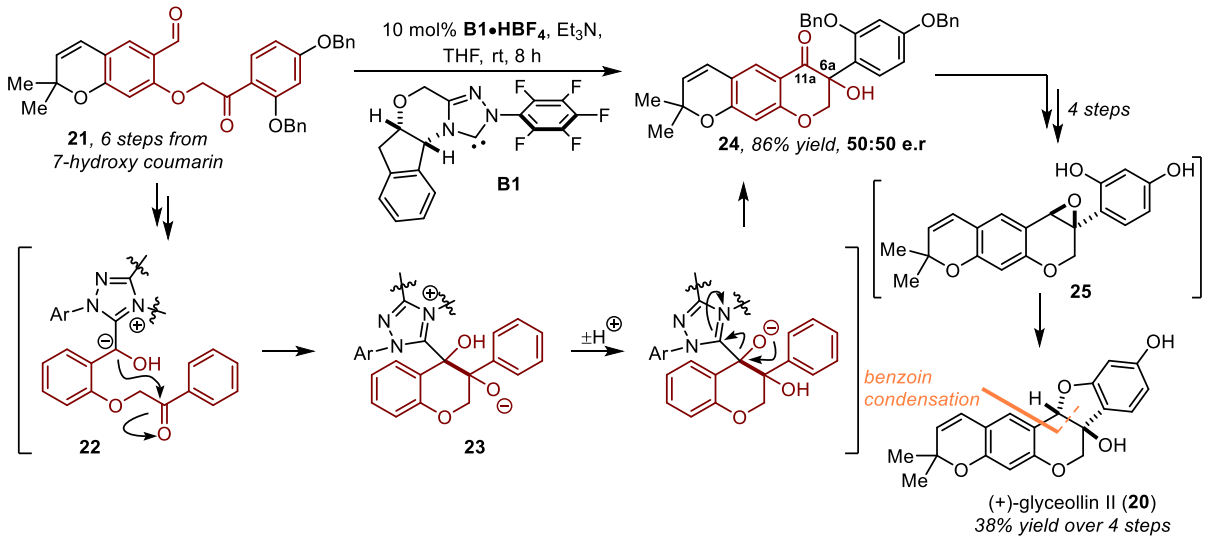
The benzoin condensation involves the self- and cross-coupling of aldehydes, or, coupling with ketones to produce α-hydroxy ketones (i.e. **19**, Scheme 1.6). Since its discovery, the reaction has received significant attention from the synthetic chemistry community, with NHC catalysis at the forefront of methodological development.[35] Using homochiral NHCs, the groups of Enders, Sheehan, and others, have demonstrated that excellent levels of enantioselectivity can be obtained in this process.[24b,36] Such synthetic utility has seen the benzoin reaction feature in a number of total syntheses, of which some representative examples are described.



Scheme 1.6. Representative benzoin condensation.

1.3.1 Synthesis of (+)-glyceollin II

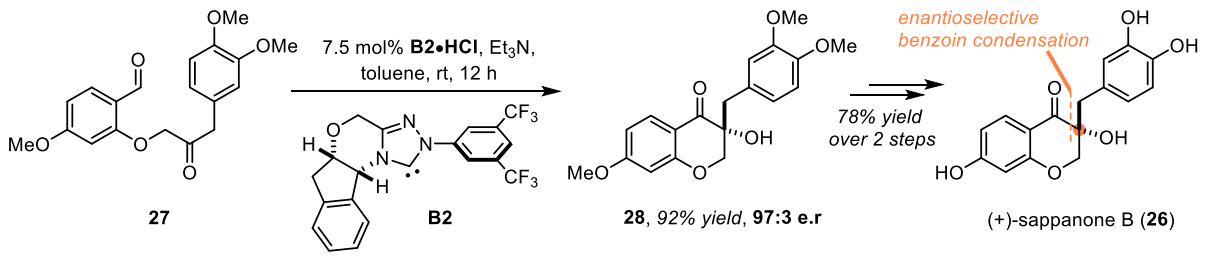
The glyceollins are phytoalexins isolated from parasite-infested soybeans which belong to the hydroxypterocarpan flavonoids.[37] Products of this family commonly exhibit antidiabetic properties[38] as well as potent cytotoxicity toward human breast and prostate cancer cells in vivo.[39] In an initial report by Erhardt and co-workers', the total synthesis of glyceollin II (**20**)[40] required highly toxic osmium tetroxide (OsO_4) to install oxygenation at C^{6a} and C^{11a}. Building upon this, an improved sequence has since been realised,[41] enabled by an NHC catalysed intramolecular benzoin condensation that eliminates the need for OsO_4 (Scheme 1.7). Typified by the cyclisation of keto-aldehyde **21**, the benzoin condensation proceeds *via* addition of NHC **B1** to the aldehyde and subsequent proton transfer to give acyl anion equivalent **22**. Intramolecular addition to the pendant ketone then provides alkoxide **23** before a proton transfer and catalyst elimination furnishes α-hydroxy ketone **24** in 86% yield. Interestingly, despite the use of a homochiral NHC, the authors note isolation of the product as a racemate, likely as a consequence of epimerisation. The total synthesis of (±)-glyceollin II (**20**) was completed from α-hydroxy ketone **24** in an additional four steps, including an elegant epoxidation and cyclisation sequence (i.e. **24**→**25**→**20**) to forge the *cis-cis* fused benzofuran.



Scheme 1.7. Benzoin condensation in the total synthesis of (±)-glyceollin II (**20**).

1.3.2 Synthesis of (+)-sappanone B

Isolated from the wood of *Caesalpinia sappan Leguminosae*, (+)-sappanone B (**26**) is a homoflavonoid[42] which is known to inhibit xanthine oxidase.[43] Such inhibitory activity is well suited to the treatment of hyperuricemia and related conditions such as gout.[44] Suzuki's 2007 report details the total synthesis of (+)-sappanone B (**26**) utilising a key intramolecular and enantioselective benzoin condensation step (Scheme 1.8).[45] The benzoin precursor, ketoaldehyde **27**, was derived from commercially available 3-methoxysalicylic acid in two steps. Exposure to NHC **B2** effected cyclisation to provide α-hydroxy ketone **28** in 92% yield and 97:3 e.r. It is important to note that through optimisation of the NHCs *N*-substituent from mesityl to 3,5-trifluoromethylphenyl, undesired aldol side-reactions could be suppressed, highlighting the tunability of these catalysts. The synthesis was completed by a two-step deprotection of α-hydroxy ketone **28**, furnishing (+)-sappanone B (**26**) in 8-steps and 23% overall yield.

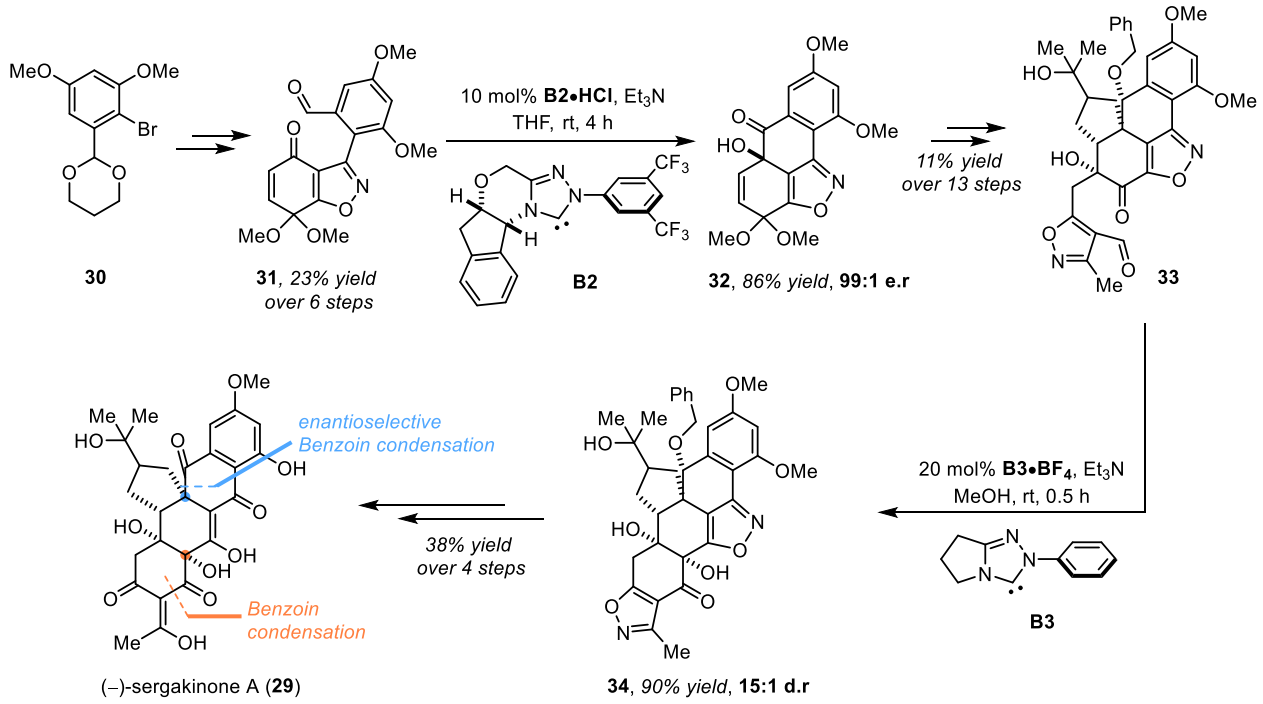


Scheme 1.8. Enantioselective benzoin condensation in the total synthesis of (+)-sappanone B.

1.3.3 Synthesis of (–)-seragakinone A

(-)-Seragakinone A (**29**) is an anthracycline derived fungal metabolite isolated from an unidentified fungus living symbiotically with marine sponge *Ceradictyon spongiosum*.[46] The heavily oxygenated nature and

stereochemistry rich pentacyclic core contains 4 contiguous stereocentres including one quaternary centre and two tertiary alcohols, and as such, poses a significant synthetic challenge. Suzuki and co-workers have cleverly navigated this complex structure, forging two rings using two separate benzoin condensation reactions (Scheme 1.9).[47] Starting from commercially available aryl bromide **30**, ketoaldehyde **31** was prepared in 23% yield over 6 steps. Upon exposure of ketoaldehyde **31** to homochiral NHC **B2**, utilised previously by Suzuki (*vide supra*), the intramolecular benzoin condensation proceeded smoothly generating tetracycle **32** in 86% yield and 99:1 e.r. A further 11-step sequence was required to generate a second benzoin precursor, aldehyde **33**, in 11% yield. Thus, after treatment with NHC **B3**, α-ketol **34** was obtained in 90% yield as a 15:1 mixture favouring the desired stereoisomer, as determined by X-ray crystallography. Finally, four additional steps were required to complete the synthesis with the natural product prepared in a total of 26 linear steps.

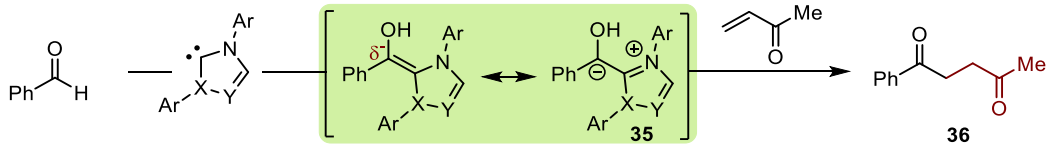


Scheme 1.9. Enantioselective benzoin condensation in the total synthesis of (–)-seragakinone A.

1.4 The Stetter reaction

The Michael addition of acyl anion equivalents (i.e. **35**) to α,β-unsaturated compounds, or commonly, the Stetter reaction,[6] represents the most efficient route to 1,4-dicarbonyl containing compounds (e.g. **36**, Figure 1.10). These are important synthons *en route* to biologically relevant pyrroles *via* the Paal-Knorr synthesis, and as such, the Stetter reaction has received significant attention in industrial settings. Although

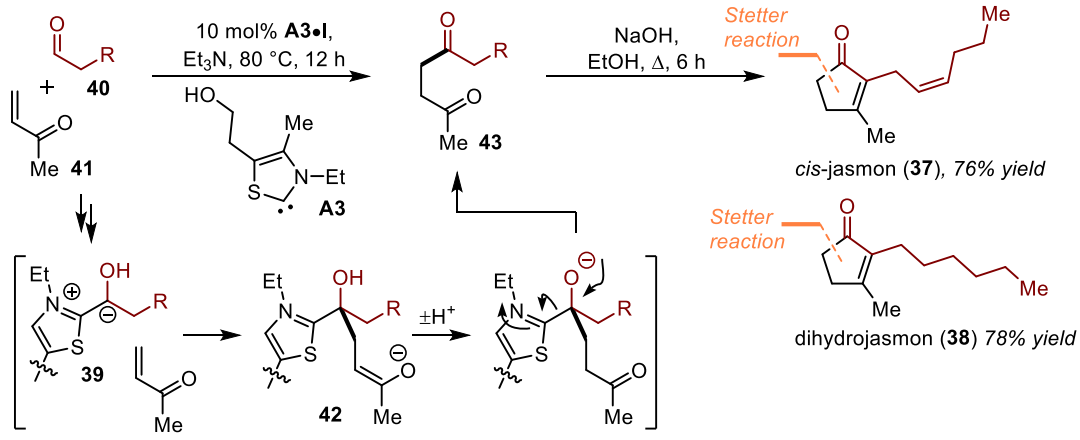
reports from Enders[48], Rovis,[49] and Hamada,[50] have established the viability of enantioselective intramolecular Stetter reactions, intermolecular variants have proved more challenging and are limited by restricted substrate scope.[24a, 24f] With respect to the α,β-unsaturated partner, highly activated substrates are often required to achieve enantioselectivity.[51] Furthermore, undesired self- and cross-benzoin pathways often plague intermolecular reactions, an issue which can be supressed using exotic Breslow precursors and thiazolium derived NHCs.[52] Although these strategies are successful, specific substrate requirements and the limited availability of homochiral thiazolium derived NHCs restricts their synthetic utility. Indeed, no enantioselective Stetter reactions feature in total syntheses, therefore, some notable examples of achiral variants are detailed in this section.



Scheme 1.10. An example of the Stetter reaction.

1.4.1 Synthesis of *cis*-jasmone and dihydrojasmone

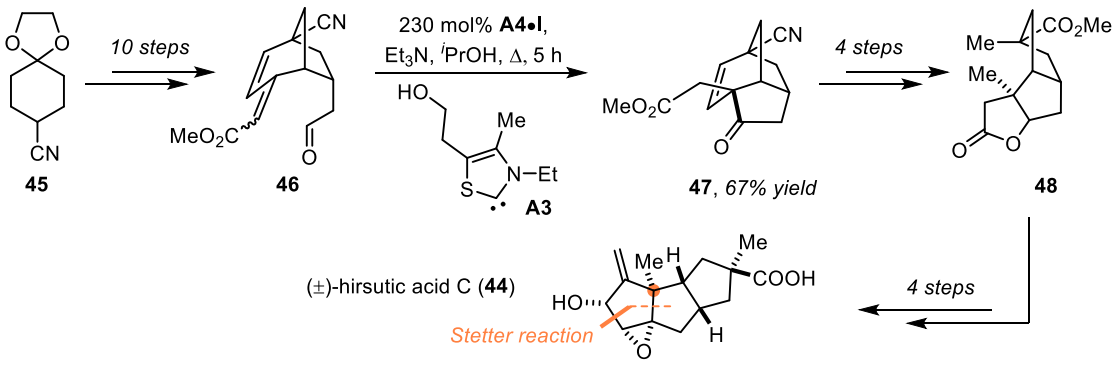
The jasmones are a series of cyclopentenones isolated from the jasmine plant and have considerable applications in the fragrance industry.[53] Stetter's noteworthy synthesis of *cis*-jasmone (**37**) and dihydrojasmone (**38**) in 1975 represents the first application of both NHC catalysis and a Stetter reaction in total synthesis (Scheme 1.11).[54] The Stetter reaction is typified by the formation of the acyl anion equivalent (i.e. the Breslow intermediate) **39** after addition of NHC **A3** to aldehyde **40** and proton transfer. Subsequent 1,4-addition of the Breslow intermediate to methylvinyl ketone (**41**) then generates enolate **42** before proton transfer and elimination of the catalyst provides the 1,4-diketone **43**. Finally, dehydrative aldol cyclisation furnishes *cis*-jasmone (**37**) and dihydrojasmone (**38**) in 76% and 78% yield respectively over two-steps.



Scheme 1.11. Intermolecular Stetter reaction in the total synthesis of *cis*-jasmone and dihydrojasmone.

1.4.2 Synthesis of (±)-hirsutic acid C

(±)-Hirsutic acid C (**44**) is a fungal metabolite isolated from *Stereum hirsutum* and exhibits both antibiotic and antitumor activity (Scheme 1.12).[55] The tricyclic sesquiterpenoid structure poses a significant challenge as it contains six contiguous stereocentres (7 in total), two of which are quaternary. Trost and co-workers' synthesis of (±)-hirsutic acid C (**44**) exemplifies the utility of the Stetter reaction, whereby the transformation forges a polycyclic framework and at the same time, a quaternary carbon.[56] The synthesis begins with the conversion of commercially available nitrile **45** to α,β-unsaturated ester **46** *via* a 10-step sequence. Upon exposure to thiazolylidene **A3**, α,β-unsaturated ester **46** underwent cyclisation *via* the Stetter reaction, delivering tricyclic ketone **47** in 67% yield. In this scenario, super-stoichiometric quantities (2.3 equivalents) of the catalyst were required, which presumably eliminates the opportunity for cross-benzoin pathways through rapid conversion of the aldehyde to the corresponding Breslow intermediate. Nevertheless, subsequent reduction, lactonisation, and ozonolysis accessed the known bicyclic lactone **48**,[57] that was converted to (±)-hirsutic acid C (**44**) in an additional 4-steps (19 total).



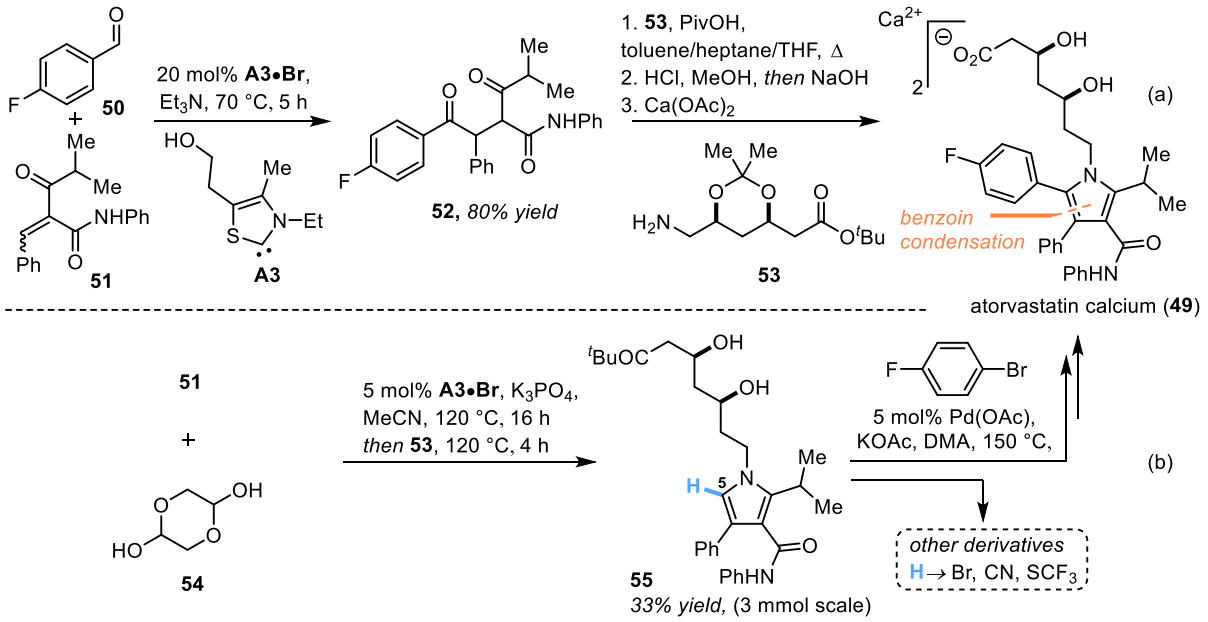
Scheme 1.12. Intramolecular Stetter reaction in the total synthesis of (±)-hirsutic acid C.

1.4.3 Synthesis of (±)-atorvastatin

Atorvastatin calcium (**49**), or Lipitor under its trade name (Pfizer), is a potent anti-hypercholesteremic agent, and is commonly considered the most successful drug in pharmaceutical history. Perhaps the most famous application of the Stetter reaction is within Pfizer's industrial synthesis of atorvastatin (Scheme 1.13, eq. 1).[58] Specifically, the reaction of 4-fluorobenzaldehyde (**50**) and carboxamide **51** catalysed by thiazolylidene **A3** was employed to great success to generate 1,4-diketone **52** in 80% yield. A Paal-Knorr pyrrole synthesis using amine **53**, with subsequent hydrolysis and calcium salt formation, furnished atorvastatin calcium (**49**).

In 2017, Glorius and Fleige reported a modified procedure whereby the Stetter and Paal-Knorr sequence were conducted as a one-pot, 3-component reaction (Scheme 1.13, eq. 2).[59] In this scenario,

glycoaldehyde **54** is utilised as a formaldehyde equivalent for the Stetter/hydroformylation reaction with carboxamide **51** under NHC catalysis. Subsequent addition of amine **53** to the reaction mixture enables a rare base mediated Paal-Knorr reaction to generate pyrrole **55** in 33% yield. Importantly, the one-pot procedure is amenable to modest scaling (3 mmol) and the unsubstituted pyrrole product **55** can be derivatised at C5 to deliver atorvastatin as well as various analogues.



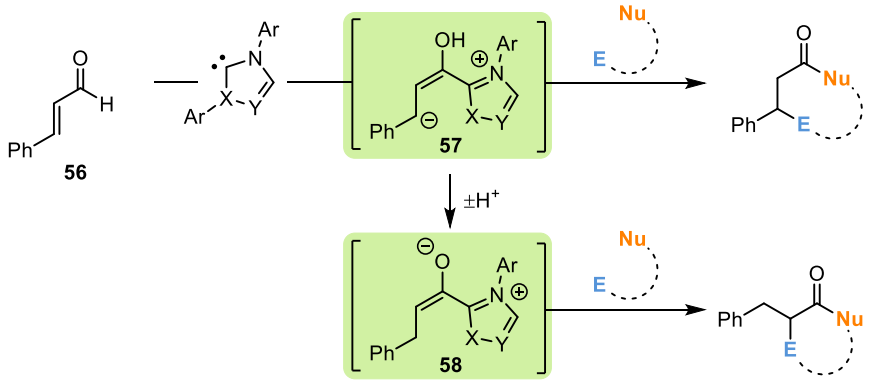
Scheme 1.13. Intermolecular Stetter reactions in synthesis of atorvastatin and analogues.

1.5 Lactone formation via the NHC-homoenolate

Addition of NHCs to α,β-unsaturated aldehydes (i.e. **56**) gives rise to NHC-homoenolate intermediates (i.e. **57**) after tautomerisation of the Breslow intermediate (Scheme 1.14). A typical transformation of **57** is underpinned by electrophilic trapping with aldehydes or ketones, with subsequent acylation providing γ-butyrolactones, however, linear products can also be synthesised using non-tethered reagents. An array of enantioselective annulations of the NHC-homoenolate have been developed, with several noteworthy examples in total syntheses.[24a,60]

An additional intermediate, the NHC acyl azolium enolate **58**, is also available *via* proton transfer from the homoenolate **57**. While this intermediate is of normal polarity, it possesses enhanced nucleophilicity and engages in highly enantioselective transformations to generate cyclic and linear scaffolds, although, in this scenario, with bond formation at the α- and acyl positions. Only a single example

of a reaction proceeding through the NHC-acylazolium enolate has found application in the enantioselective synthesis of complex natural products.

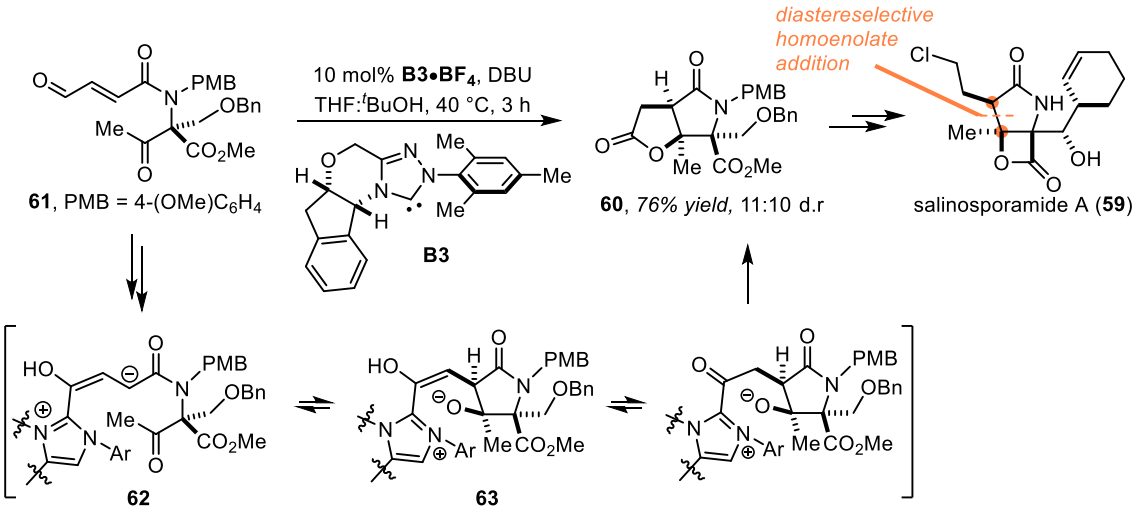


Scheme 1.14. Generalised reactivity of the NHC homoenolate and acyl azolium enolate.

1.5.1 Formal synthesis of (+)-salinosporamide A

(+)-Salinosporamide A (**59**) is a secondary metabolite isolated from marine actinomycete bacteria, and has garnered much interest as an anti-cancer agent. [61] The natural product exhibits considerable cytotoxicity towards Human HCT-116 colon carcinoma cells, amongst others, an unsurprising observation considering the *cis*-fused β-lactone/ɣ-lactam architecture. Both of these heterocyclic structures are found in a number of compounds that display significant biological activity.[62]

In 2009, Bode and co-workers realised a formal synthesis of salinosporamide A (**59**),[63] a route that exploits the annulation of an NHC-homoenolate and an internal ketone to access known ɣ-butyrolactone **60** (Scheme 1.15). This enantiospecific synthesis utilises the chiral pool strategy to access chiral α,β-unsaturated aldehyde **61**, the NHC reaction precursor. The key annulation of **61** is initiated by addition of NHC **B3** to the aldehyde and subsequent formation of homoenolate **62**. Addition of the homoenolate to the methyl ketone then provides alkoxide **63** before tautomerisation and acylation of the pendant alkoxide delivers the known ɣ-butyrolactone **60**. Although initially plagued with undesired side reactions resulting from intramolecular NHC-enolate and aldol pathways, an impressive optimisation led to synthetically practical yields (76%). Unfortunately, a similar improvement in the stereochemical outcome could not be realised, with homochiral NHC **B3** providing the greatest, albeit negligible, diastereoselectivity (11:10 d.r). Lam and co-workers previously demonstrated the elaboration of the intermediate ɣ-butyrolactone **60** to the natural product **59** over an additional eight steps.[64]

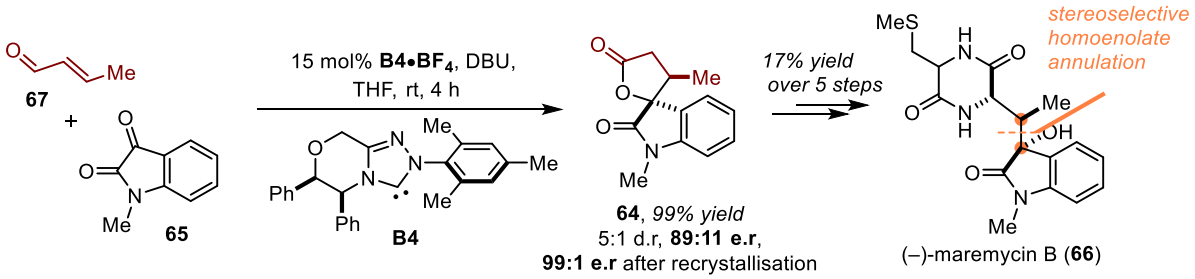


Scheme 1.15. Intramolecular NHC-homoenolate annulation in synthesis of (+)-salinosporamide.

1.5.2 Synthesis of (–)-maremycin B

Diketopiperazine containing alkaloids are a diverse family of natural products with biosynthetic origins in many plants, animals and fungi. These rigid and hetereoatom rich diketopiperazine structures allow binding to a wide variety of receptors and are therefore, attractive scaffolds for drug discovery.[65] Isolated from marine bacteria *Streptomyces,* maremycin B represents an example of these privileged structures and exhibits substantial anti-cancer properties.[66]

In 2012, Bode and co-workers developed a general method for the enantioselective synthesis of spirocyclic ɣ-butyrolactones (i.e. **64**) through annulation of NHC-homoenolate equivalents with isatins (i.e. **65**, Scheme 1.16).[67] In the same report, application of such a transformation in the synthesis of (–)-maremycin (**66**) was described. Thus, exposure of crotonaldehyde **67** and isatin **65** to homochiral NHC **B4** provided spirocyclic ɣ-butyrolactone **64** in excellent yield, albeit with modest selectivity (5:1 d.r, 89:11 e.r). Fortunately, further enantioenrichment was enabled by recrystallisation, before an additional 5-steps sequence was able to provide the natural product **66**.

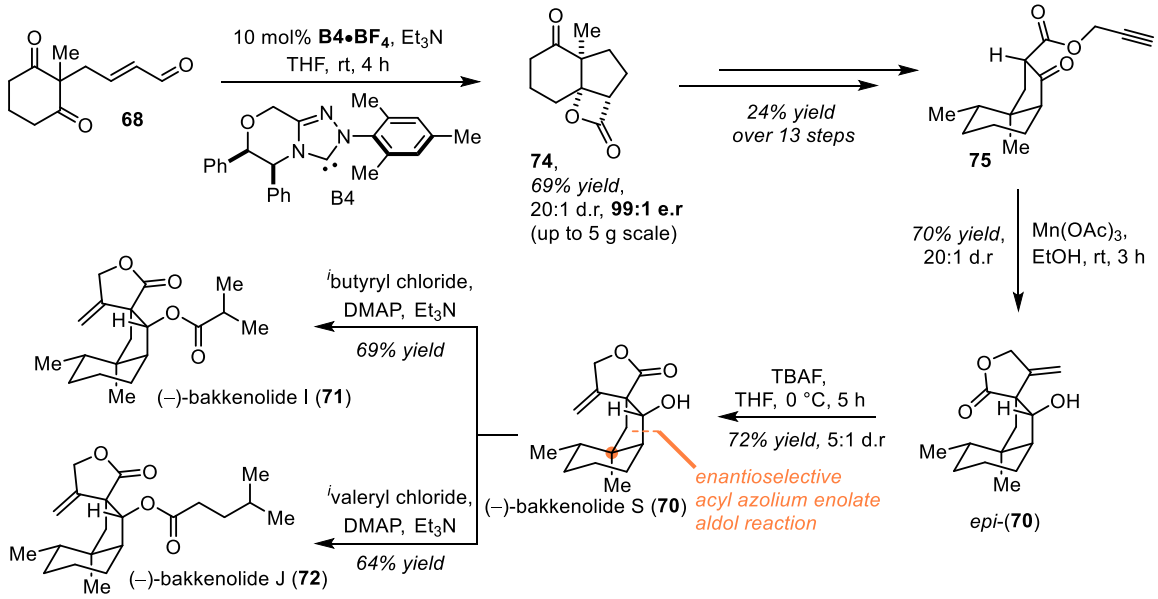


Scheme 1.16. Enantioselective NHC-homoenolate annulation in the synthesis of (–)-maremycin B.

1.5.3 Synthesis of (–)-bakkenolides I, J and S

The family of bakkane natural products are sesquiterpenes comprised of a *cis*-fused 5,6-hydrindane core, and a quaternary spirocyclic ɣ-butyrolactone bearing a rare β-methylene unit.[68] Commonly, these are isolated from the flower stalks of native Japanese *Petasites japonicas,* however, they are also constituents of plants indigenous to northern European areas. Biologically, the bakkenolides exhibit anti-feedant and anti-cancer activity, and have also been shown to inhibit platelet aggregation.[69]

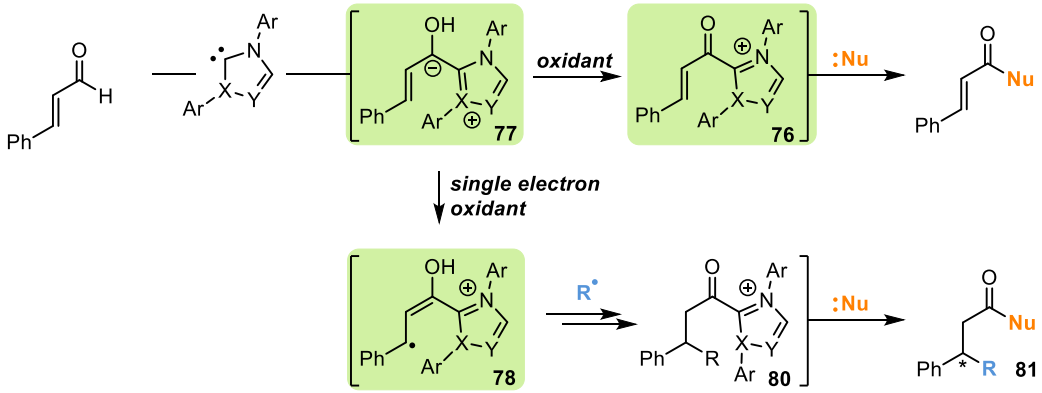
In 2010, Scheidt and co-workers developed a method for the desymmetrisation of aldehyde tethered 1,3-diketones (i.e. **68**) which generates hydroindanone fused β-lactones (i.e. **69**) with excellent stereochemical integrity (Scheme 1.17). In this case, trapping of the NHC-homoenolate does not occur, instead, the transformation proceeds *via* generation and addition of the NHC-azolium enolate (see Scheme 1.14) to a ketone followed by acylation. This procedure was subsequently applied to assemble the *cis*-fused 5,6-hydroindane core in the synthesis of (-)-bakkenolides S (**70**), I (**71**) and J (**72**).[70] Specifically, aldehyde **73**, itself prepared in two steps from methylcyclohexanedione, was treated with NHC **B4** to generate β-lactone **74** in 69% yield, >20:1 d.r and 99:1 e.r. Impressively, the reaction can be conducted with modest scaling (up to 5 g); a feature eluding many NHC catalysed reactions. Conversion of β-lactone **74** to propargylic ester **75** was achieved over 13-steps before manganese triacetate ($Mn(OAc)_3$) mediated cyclisation delivered, with complete diastereoselectivity, the undesired epimer *epi*-(**70**). Fortunately, a precedented[71] TBAF mediated inversion of the spirocyclic centre, which relies upon a thermodynamic retroaldol/aldol sequence allowed for synthesis (-)-bakkenolide S (**74**) and subsequently (**71**) and (**72**) by virtue of appropriate acylation.



Scheme 1.17. Desymmetrisation *via* the NHC-acylazolium enolate in the synthesis of (–)-bakkenolides.

1.6 Esterification via the NHC-acylazolium

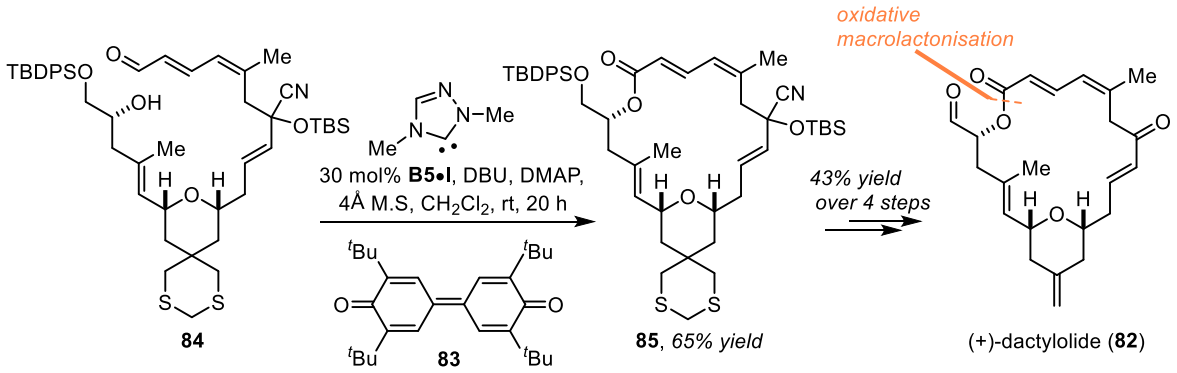
While more complex reactions of the NHC-homoenolate and -acyl azolium enolate conclude with terminal acylation *via* an NHC-acylazolium (i.e. **76**), its direct formation by oxidation of acyl anion equivalents (i.e. **77**) accommodates much simpler, albeit still challenging, acylation reactions (Scheme 1.18).[24a-d] It is important to note that single electron oxidation of NHC-acyl anion equivalents can also be achieved, whereby access to NHC-homoenolic radical **78** and subsequent enantioselective radical combination reactions have been realised. Typically, this mode of reaction also terminates with acylation *via* the acyl azolium (i.e. **79**→**80**→**81**),[72] however, as this field is in its infancy, there are no examples of it being exploited in total syntheses.



Scheme 1.18. Formation of the NHC-acylazolium via oxidation of the Breslow intermediate.

1.6.1 Synthesis of (+)-dactylolide

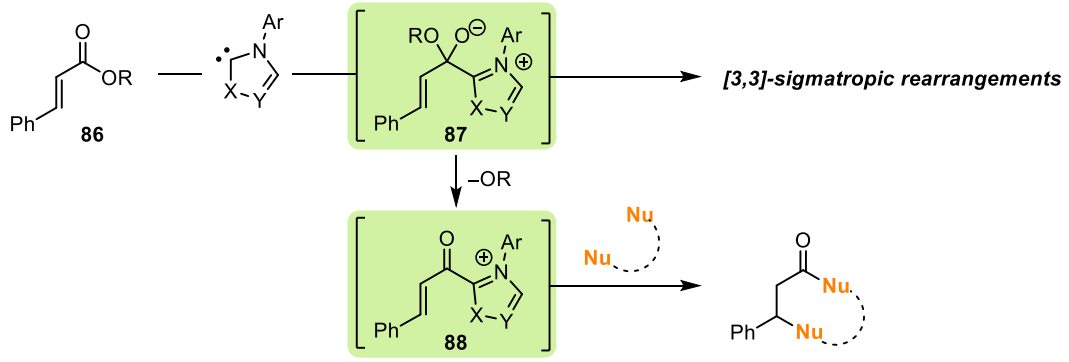
(+)-Dactylolide (**82**) is an 18-membered macrolide that was isolated from marine sponges *Dactylospongia sp.* native to Vanuatu[73] and like many macrolactone containing compounds,[74] is of biological interest owing to modest inhibitory activity toward human ovarian cancer and leukaemia cell lines. In 2012, Hong and co-workers reported the total synthesis (+)-dactylolide (**82**) featuring a key transformation that exemplifies the action of the NHC-acyl azolium (Scheme 1.19). Specifically, when exposed to NHC **B5** and quinone oxidant **83**, the late stage hydroxyaldehyde **84**, itself prepared in 11-steps from commercially available materials, engaged in a remarkable oxidative macrolactonisation to assemble the 18-membered lactone **85**. From **85**, the natural product was synthesised in 4 additional steps in 2% overall yield.



Scheme 1.19. Macrolactonisation via the NHC-acylazolium in the synthesis of (+)-dactylolide.

1.7 [3,3]-Sigmatropic rearrangements via the NHC-azolium alkoxide

In the course of studies to access the α,β-unsaturated acyl azolium *via* acyl substitution from ester oxidation state carbonyl compounds (i.e. **86**→**87**→**88**), the Lupton group discovered that NHC-azolium alkoxide **87** itself can partake in novel reaction pathways (Scheme 1.20). Lupton's seminal discovery showed that under NHC catalysis, enol ester substrates (i.e. **89**) underwent an unprecedented [3,3]-sigmatropic rearrangement *en route* to dihydropyranones (i.e. **90**) (*vide infra*).[75] This reactivity is exemplified in the following example whereby the method was exploited in the synthesis of (-)-7-deoxyloganin (**91**).

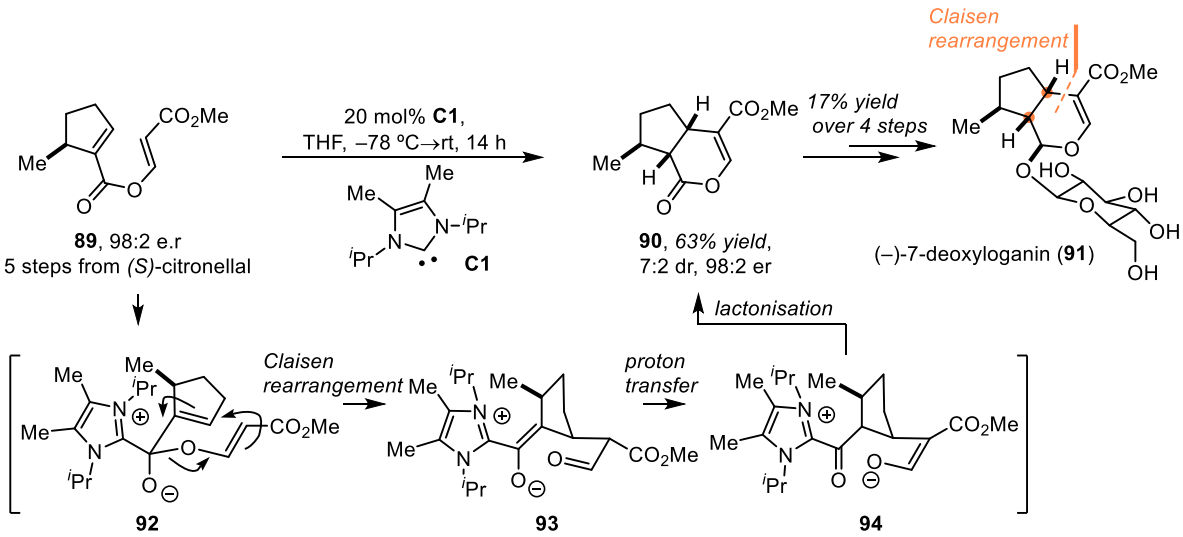


Scheme 1.20. Access to the NHC-azolium alkoxide **87** from ester substrates.

1.7.1 Synthesis of (–)-7-deoxyloganin

(-)-7-Deoxyloganin (**91**) is an iridoid containing natural product, and like many of these monoterpenoids, it contains a *cis*-fused cyclopentapyran core.[76] These iridoids typically possess significant bioactivity and have been implicated in biosynthesis of a variety of other alkaloid scaffolds.[77,78] In 2010, Lupton and co-workers exploited the NHC-azolium alkoxide in the synthesis of dihydropyranone **90**, an advanced intermediate that was subsequently elaborated to give the natural product **91**.[77a] An improved sequence to

the dihydropyranone precursor **89** was later realised, starting from *(S)*-citronellal (Scheme 1.21).[77b] It is proposed that the key NHC catalysed process begins with addition of NHC **C1** to enol ester **89** and formation of NHC-azolium alkoxide **92.** A typical result of this arrangement is a rate enhanced anionic oxy-Claisen rearrangement, which in this case generates NHC-azolium enolate **93.** Finally, a proton transfer yields a subsequent enolate species **94**, which upon acyl substitution furnished dihydropyranone **90** in 63% yield and 7:2 d.r. An additional four steps were required to complete the synthesis of (–)-7-deoxyloganin (**91**) which was obtained 3% overall yield over 10 linear steps.

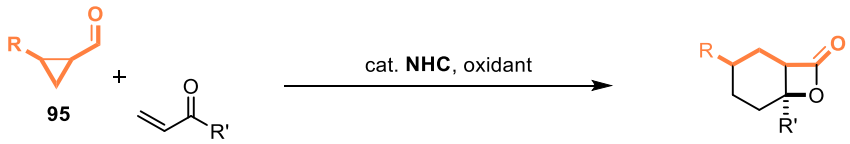


Scheme 1.21. NHC catalysed Claisen rearrangement of enol esters in the synthesis of (–)-7-deoxyloganin.

1.8 Objectives

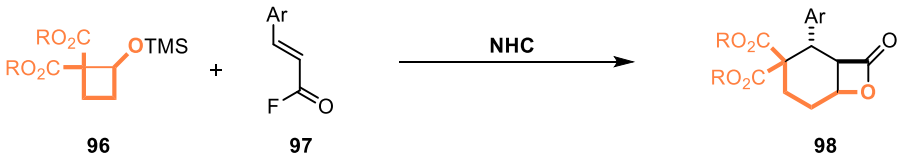
At the time that doctoral studies commenced, only four enantioselective NHC-catalysed reactions had been exploited in reports of total synthesis.[34] While enantioselective transformations of almost all NHC derived reactive intermediates are possible, and a number of these enable access to challenging quaternary centres, as well as macrocycles and complex polycyclic architectures, only three of these reactivity modes have found application. Moreover, these examples are dominated by the intramolecular reactions of acyl anion equivalents in single bond forming events; an observation that can be attributed to the often specific substrate requirements and limited scalability that plague many NHC catalysed methods. Ultimately, the studies described herein aimed to address deficiencies in exploitation of enantioselective NHC-catalysed reactions in efforts of total synthesis. It was proposed that this could be achieved by developing new, robust enantioselective NHC catalysed reactions that are scalable, exhibit broad substrate scope, and the products of which, are synthetically useful.

Despite significant advancements in the last 3 years, the field of single electron transfer-coupled NHC catalysis remains in its infancy. Inspired by the application of donor-acceptor cyclopropanes as three-carbon synthons in a wide variety of complex target syntheses,[79] *Chapter 2* describes efforts to exploit single electron transfer (SET)-coupled NHC catalysis to access four-carbon synthons from α-cyclopropyl aldehydes **95**, and subsequently develop new enantioselective (4+2) annulations (Scheme 1.22).



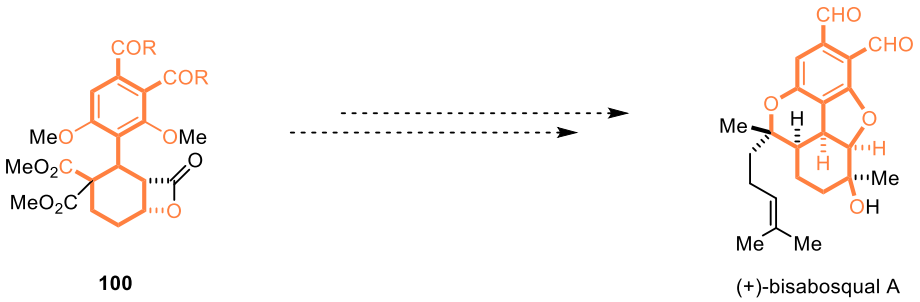
Scheme 1.22. SET-NHC catalysed (4+2) annulation of cyclopropanes.

While the use of donor-acceptor (DA) cyclopropanes as 3 carbon synthons in natural product synthesis has received significant attention,[78] little effort has been directed toward homologous DA-cyclobutanes. Guided by the previously reported NHC-catalysed (3+2) annulation of DA-cyclopropanes, *Chapter 3* details the development of an enantioselective (4+2) annulation of DA-cyclobutanes **96** with α,β-unsaturated acyl fluorides **97** in the preparation of densely functionalised cyclohexyl β-lactones **98** (Scheme 1.23)



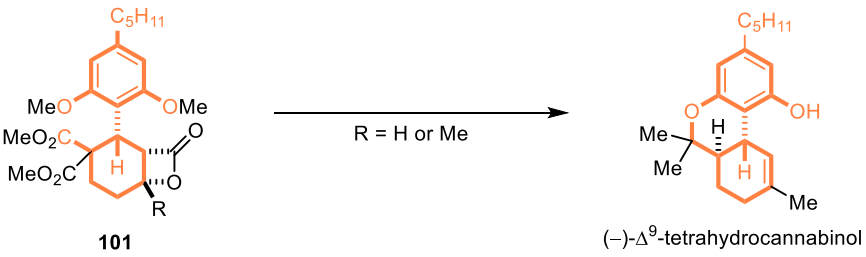
Scheme 1.23. NHC catalysed (4+2) annulation of DA-cyclobutanes.

(+)-Bisabosqual A is fungal metabolite which exhibits broad range anti-fungal properties, as well as having potential use in the treatment of hypercholesterolemia. In addition to this interesting bioactivity, the challenging tetracyclic architecture, as well as the complex stereochemical arrangement, render this natural product an attractive synthetic target. *Chapter 4* describes efforts to exploit the (4+2) annulation developed in *Chapter 3* to enable the first enantioselective synthesis of (+)-bisabosqual A *via* an appropriate β-lactone scaffold (i.e **100**) (Scheme 1.24).



Scheme 1.24. Synthesis of (+)-bisabosqual A exploiting ß-lactone **100**.

Although the medicinal properties of (–)-Δ^9-tetrahydrocannabinol have been known for hundreds of years, only recently has significant attention been directed towards exploiting this natural product as a pharmaceutical agent. *Chapter 5* showcases the synthetic utility of the (4+2) annulation developed in *Chapter 3* through access to lactones of type **101**, and ultimately, the enantioselective total synthesis of (–)-Δ^9-tetrahydrocannabinol (Scheme 1.25).



Scheme 1.25. Synthesis of (–)-Δ^9-tetrahydrocannabinol exploiting β-lactones.

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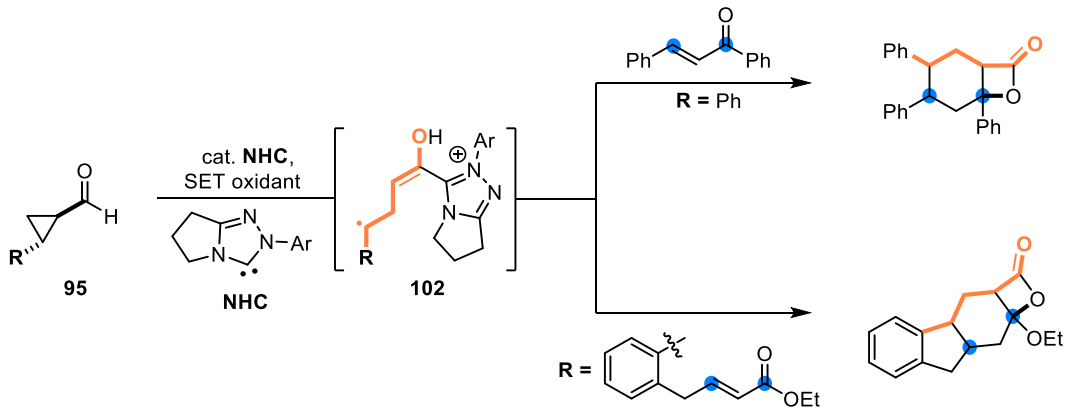
Chapter 1

Chapter 2

Single electron transfer coupled NHC catalysis for annulations of cyclopropanes

This chapter explores efforts to develop a new (4+2) annulation reaction via single electron transfer (SET) coupled N-heterocyclic carbene (NHC) catalysis. Studies focused on accessing radical cations ***103*** *derived from the Breslow intermediate of cyclopropanes* ***95****, and exploitation of these in a subsequent radical coupling with α,β-unsaturated electrophiles are discussed. Although facile polymerisation, (potentially suggestive of radical recombination via the desired NHC radical intermediate) was observed, no direct evidence for the formation of the radical cation* ***102*** *was observed.*



2.1 Introduction

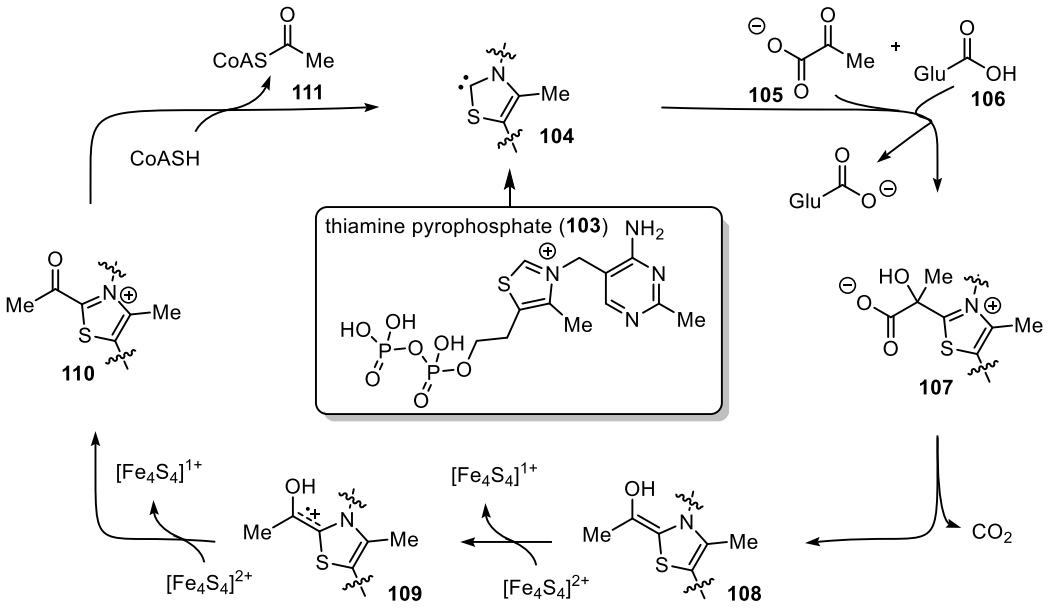
The release of ring strain by cyclopropane cleavage provides access to valuable three carbon synthons that have been exploited heavily in the synthesis of natural products.[1] In the course of endeavours to develop new N-hetereocyclic carbene (NHC) catalysed methods to assemble complex natural products, the exploitation of cyclopropanes in a novel mode of activation was examined. Specifically, it was recognised that single electron transfer (SET) coupled NHC catalysis, which gives access to

NHC-derived radical intermediates, could enable radical cleavage of a cyclopropane moiety and therefore provide new opportunities for reaction discovery. In this chapter, SET coupled NHC catalysis is introduced and efforts to exploit this mode of action in the development of a new (4+2) annulation reaction are described.

2.1.1 Inspiration for SET NHC catalysis

As described in *Chapter 1*, NHC catalysis provides access to an array of unique reactive intermediates, and through the interception of these, a multitude of enantioselective methods have been realised. Common to these and indeed all early NHC catalysed transformations is the operation of polar, or two-electron, mechanisms. More recently, the biochemistry of thiamine pyrophosphate (TPP) **103**, a thiazolium NHC precursor, has inspired a first generation of NHC mediated reactions that proceed *via* single electron mechanisms.[2]

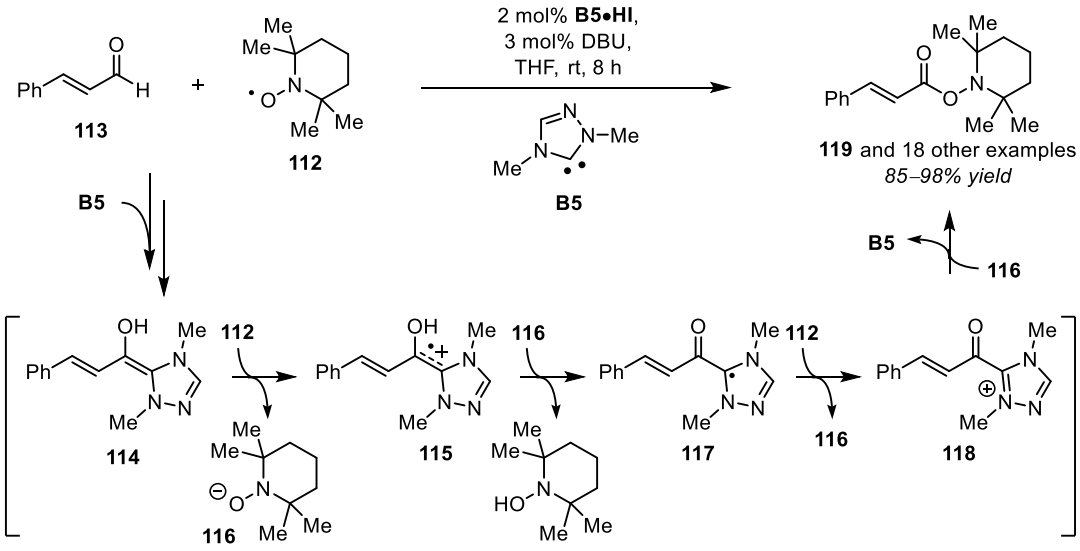
Pyruvate ferredoxin oxidoreductase (PFOR) catalyses the oxidative decarboxylation of pyruvate to form acetyl-CoA, in a reaction critical to glycolysis and the Kreb's cycle.[3] This CoA-dependant enzyme requires TPP (**103**) as an additional cofactor and operates *via* single electron transfer (SET) pathways (Scheme 2.1).[4] The proposed mechanism begins with addition of the TPP-carbene **104** to pyruvate **105**, before protonation assisted by a proximal glutamic acid residue **106**, and subsequent decarboxylation of **107** provides Breslow intermediate **108**. A single electron oxidation by an iron-sulfur cluster ($[Fe_4S_4]$) then generates the Breslow centred radical cation **109**, an



Scheme 2.1. PFOR catalysed decarboxylation of pyruvate.

intermediate that is key to all NHC catalysed reactions proceeding *via* SET mechanisms. Next, an additional [Fe_4S_4] mediated oxidation delivers the activated acetyl-TPP adduct **110**, which after thioesterification furnishes acetyl-CoA **111** and regenerates the catalyst species. Although extensive EPR and X-ray studies implicate radical cation **109**, the nature of this intermediate with respect to charge and radical distribution remains under debate.[5]

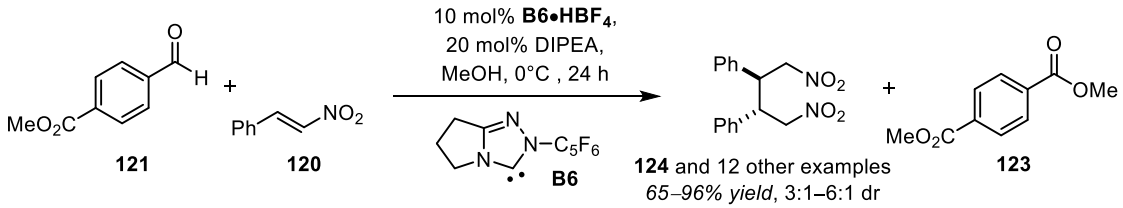
Guided by the action of PFOR, Studer and co-workers developed a biomimetic NHC catalysed oxidation of aldehydes using the organic single electron oxidant 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO) **112** (Scheme 2.2).[6] The reaction is initiated by addition of the NHC **B5** to aldehyde **113** and subsequent proton transfer to give the Breslow intermediate **114**. In this scenario, oxidation of **114** with TEMPO **112** generates Breslow centred radical cation **115** and concomitantly, TEMPO anion **116**. Deprotonation of **115** by the TEMPO anion **116** provides new radical species **117** which undergoes a second single electron oxidation to give NHC-acyl azolium **118**. Finally, esterification delivers the corresponding TEMPO ester products **119** in excellent yield and regenerates the catalyst. This seminal report was significant in establishing the viability of SET coupled NHC catalysis in non-biological systems and ultimately, opened avenues for exploration of this reactivity mode.



Scheme 2.2. NHC catalysed oxidation of aldehydes with TEMPO.

Despite the pioneering studies by Studer, the field of SET coupled NHC catalysis was inactive for 6 years before a subsequent report was published in 2015. In this study, Chi and co-workers describe the radical β,β-coupling of nitroalkenes **120** whereby the nitroalkene itself serves as a single electron oxidant, itself being reduced over the course of the reaction. In this scenario, benzaldehyde **121** is

oxidised sacrificially to the corresponding ester **123** through a mechanism analogous to that described above (Scheme 2.3).[7] A range of nitrostyrenes were well tolerated under the reaction conditions, allowing the dimerised products **123** to form in good to excellent yield and with moderate diastereoselectivity. When aliphatic nitroalkenes were employed, the corresponding products were isolated in significantly reduced yield, likely a consequence of no radical stabilisation which was offered by the adjacent phenyl group in the styrene derived substrates. Importantly, the suitability of NHC **B6** highlighted the possibility for enantioselective reactions of this class to be developed *via* known pyrrolidinone derived homochiral NHCs.[8]

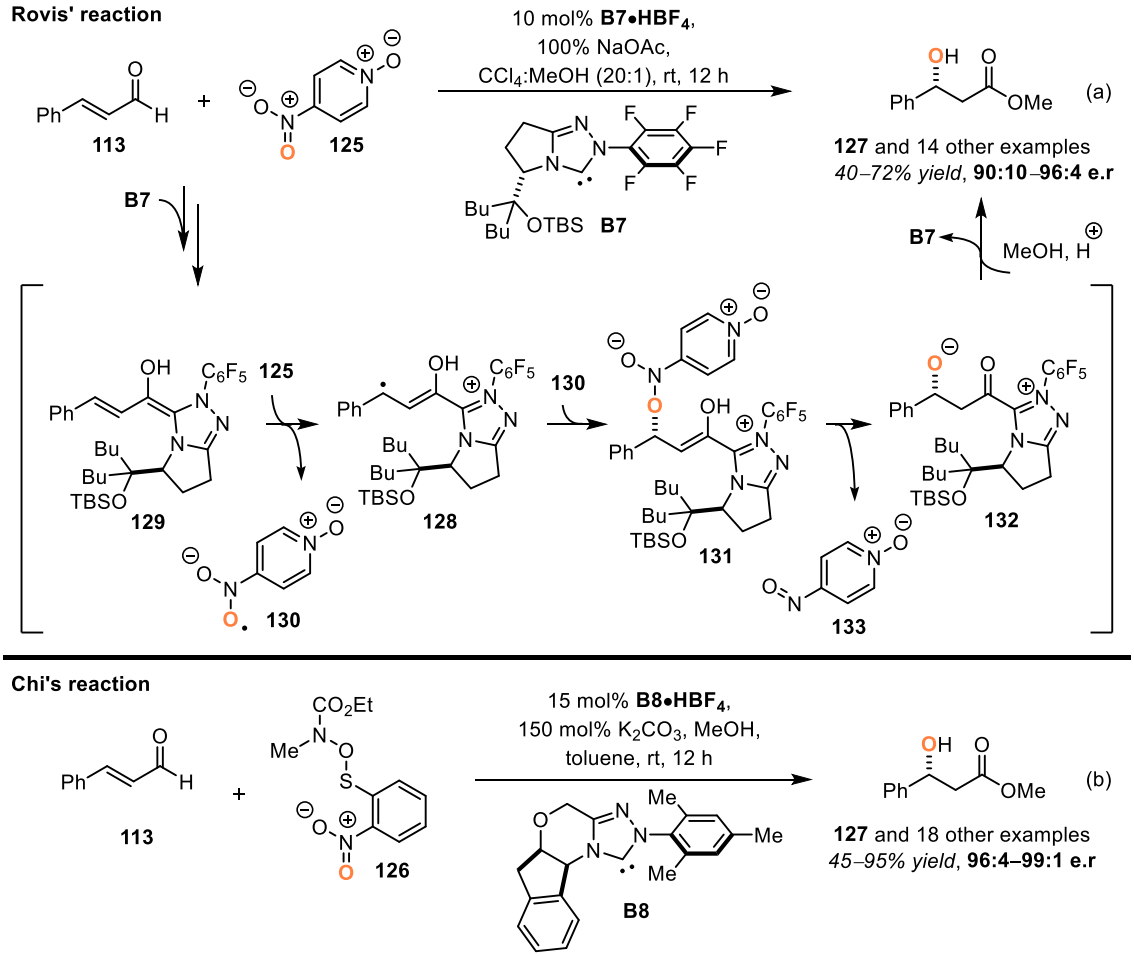


Scheme 2.3. NHC catalysed reductive ß,ß-coupling of nitroalkenes.

2.1.2 Enantioselective SET coupled NHC catalysis

A year later, the groups of Rovis (Scheme 2.4a) and Chi (Scheme 2.4b), almost simultaneously, reported the first in class enantioselective SET coupled NHC catalysed transformations.[9] Specifically, these reactions effect the β-hydroxylation of enals **113** using NHCs **B7** or **B8** and nitroarene oxidants **125** and **126** to furnish β-hydroxy esters **127** in good yield and with high enantioselectivity. These studies are widely considered a significant advancement as they render the reaction enantioselective and are the first to detail single electron oxidation of the Breslow intermediate to yield a new NHC derived homoenolic radical (i.e. **128**).

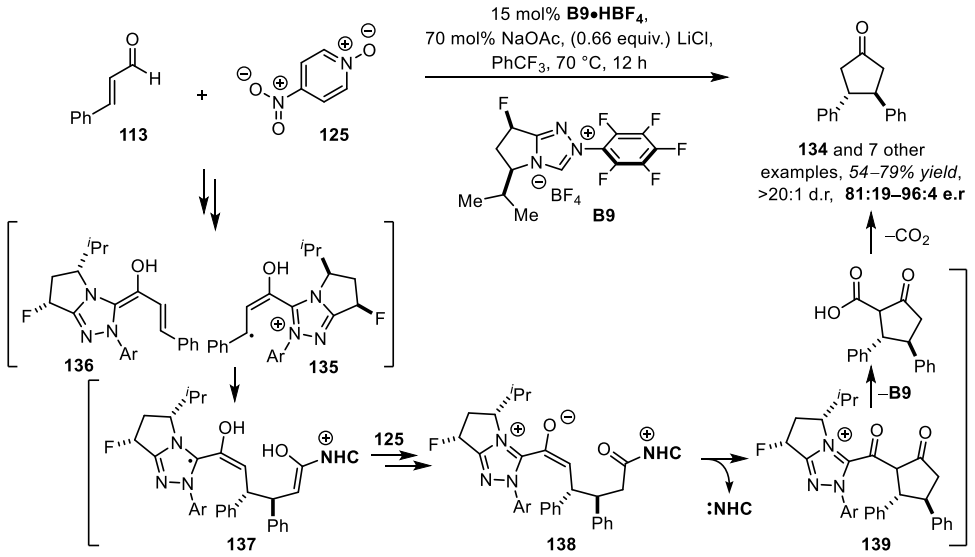
Detailed mechanistic investigations using electron paramagnetic resonance (EPR) trapping, radical clock reactions, and cyclic voltammetry were carried out, and a plausible mechanism for Rovis' version is described. According to this proposal, the reaction is initiated by NHC addition to enal **113** and formation of Breslow intermediate **129**. Single electron oxidation of **129** by nitropyridine *N*-oxide **125** generates homoenolic radical cation **128** with concomitant formation of nitro radical anion **130**. Radical-radical combination of these species then provides adduct **131** before *N-O* fragmentation and tautomerisation gives acyl azolium **132** and liberates nitroso pyridine **133**. Finally, protonation of the resultant alkoxide and esterification with methanol furnishes β-hydroxy ester **127** and regenerates the catalyst.



Scheme 2.4. NHC catalysed enantioselective ß-hydroxylation of enals.

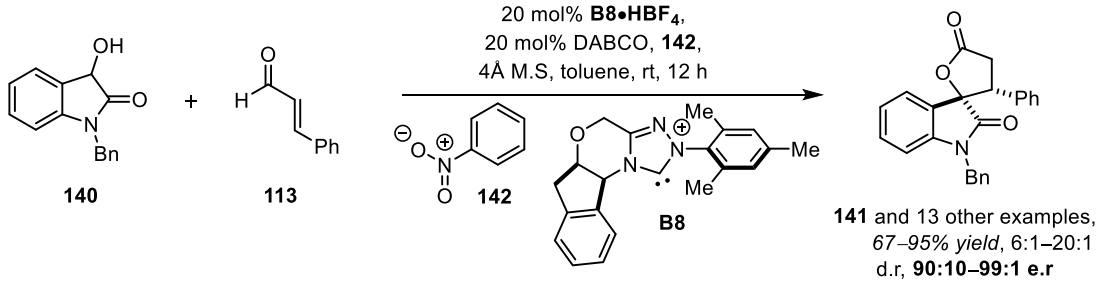
In the aforementioned studies, Rovis and co-workers isolated cyclopentanone products (i.e. **134**) when the reaction was carried out in non-nucleophillic solvent. They later developed this reaction in earnest to enable the homo- and cross-coupling of enals **113** to give cyclopentanones **134** as a single diastereomer, and with moderate to good enantioselectivity (Scheme 2.5).[10] Notably, in the absence of non-nucleophilic or protic solvent, β-hydroxylation is supressed and a rare C-C bond forming NHC turnover is observed.[11]

Mechanistically, the reaction is thought to proceed by similar initial steps to those described above, however, homoenolic radical **135** undergoes 1,4-addition with a second Breslow intermediate **136** to give *bis*-enol radical **137**. Next, single electron oxidation, deprotonation, and tautomerisation generate acyl azolium **138** which is intercepted by the pendant NHC-azolium enolate to assemble the cyclopentane **139**. Finally, acyl substitution with latent water followed by spontaneous decarboxylation provides the enantioenriched cyclopentanone **134**.



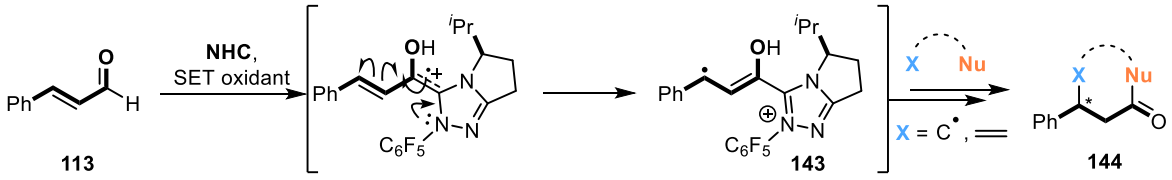
Scheme 2.5. NHC catalysed enantioselective synthesis of cyclopentanones from enals.

The most recent example of related enantioselective SET coupled NHC catalysis was reported in 2017 by Ye and co-workers.[12] They describe the (3+2) annulation of enals **113** and 3-hydroxy-2-oxindoles **140** to generate enantioenriched spirocyclic-ɣ-lactones **141** (Scheme 2.6). The reaction tolerates aryl and aliphatic substituents on both the aldehyde and as the *N*-substituent of the oxindole. Consistent with previous reports that exploit homoenolic radicals, was the requirement for a nitroarene derived oxidant (i.e. nitrobenzene **142**) .



Scheme 2.6. NHC catalysed enantioselective synthesis of spirocyclic-ɣ-lactones.

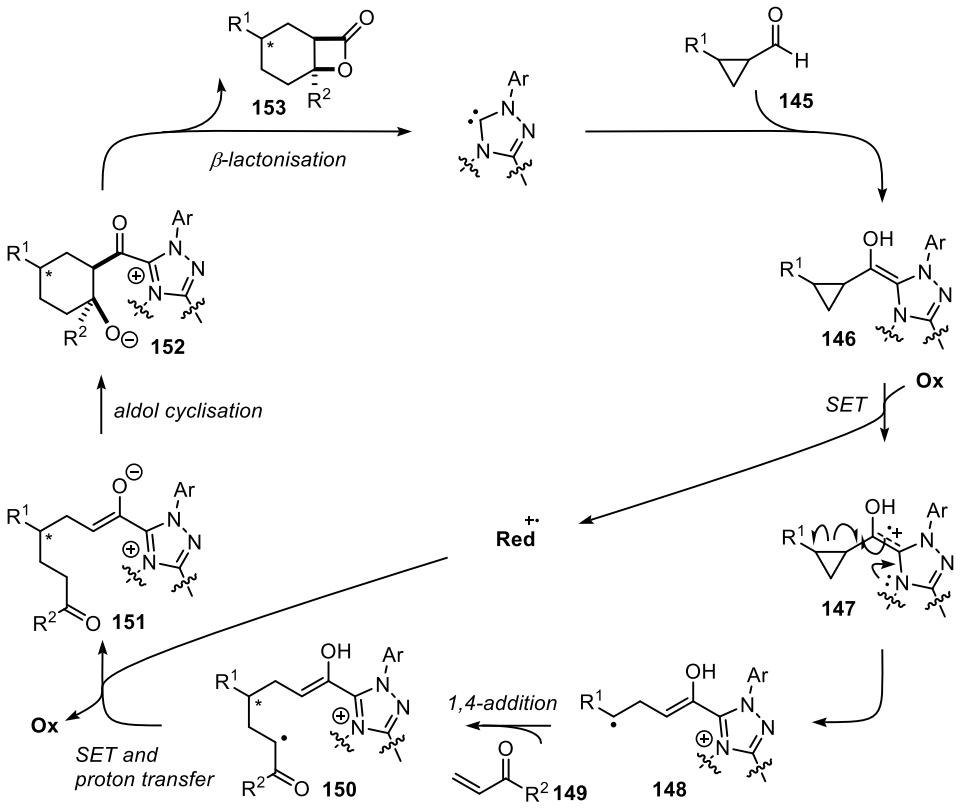
Although several additional reports of SET coupled NHC catalysis have been reported since,[13] the four reactions described here represent the only enantioselective examples. Of these, only two generate complex cyclic scaffolds. In the enantioselective examples of Rovis and Ye (see Schemes 2.5 and 2.6), enal **113** is utilised to access homoenolic radical cation **143** which, in both cases, serves as a 3-carbon donor and undergoes trapping with a carbon-centred radical or an alkene tethered nucleophile to deliver cyclic products (i.e. **144**, Scheme 2.7).



Scheme 2.7. Generic reactivity of the NHC-homoenolic radical cation.

2.1.3 Reaction design and objectives

Drawing upon inspiration from Rovis' enantioselective reactions, and the radical cleavage of cyclopropanes, it was proposed that a (4+2) annulation could be achieved by using α-cyclopropyl aldehydes **145** (Scheme 2.8). In the design, addition of an NHC to α-cyclopropyl aldehyde **145** provides Breslow intermediate **146**, that can undergo single electron oxidation to generate Breslow radical cation **147**. Next radical cleavage of the cyclopropane would provide enolic radical **148** which could be exploited as a 4-carbon donor and engage in a (4+2) annulation with an appropriate 2-carbon coupling partner (i.e. acrylate **149**). In this scenario, an enantioselective 1,4-addition of the radical **148** with **149** would generate α-radical **150** which undergoes a second SET to generate acylazolium enolate **151**. Finally, a proton transfer and intramolecular aldol/lactonisation sequence (i.e. **151**→**152**→**153**) would provide enantioenriched β-lactone products **153** and regenerate the catalyst.

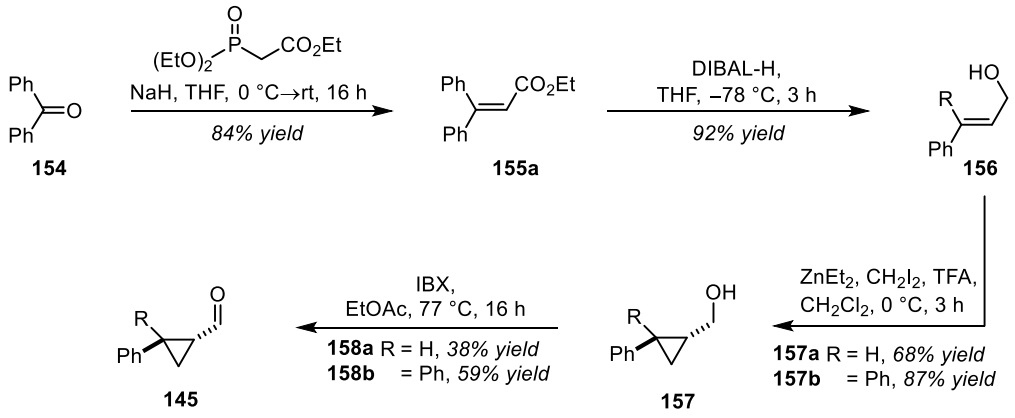


Scheme 2.8. Proposed (4+2) annulation using α-cyclopropyl aldehydes.

2.2 Research and Discussion

2.2.1 Intermolecular (4+2) annulation of α-cyclopropyl aldehydes

Studies commenced with the preparation of α-cyclopropyl aldehydes **145a** and **145b** bearing phenyl and diphenyl substituents respectively (Scheme 2.9). It was anticipated that benzylic stabilisation of the resultant radical intermediate would favour radical cleavage of the cyclopropane ring. To this end, benzophenone (**154**) was converted to the α,β-unsaturated ester **155a** following treatment with triethyphosphonoacetate[14] before reduction with diisobutylaluminium hydride (DIBAL-H) generated the corresponding allylic alcohol **156a**. Following the procedures of Lorenz,[15] **156a** (R = Ph) and commercially available cinnamoyl alcohol **156b** (R = H) underwent a modified Simmons-Smith cyclopropanation to provide the corresponding cyclopropyl alcohols **157a** and **157b**. Finally, oxidation with 2-iodoxybenzoic acid[16] (IBX) furnished the required α-cyclopropyl aldehydes **145a** and **145b**.



Scheme 2.9. Synthesis of α-cyclopropyl aldehydes **145**.

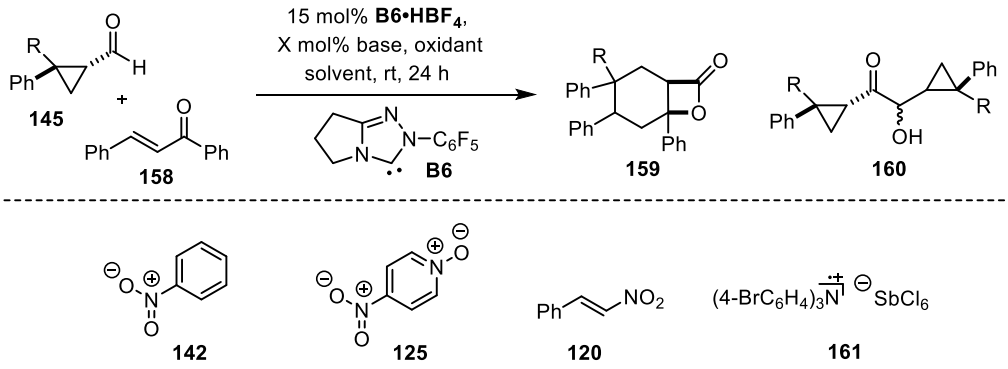
With cyclopropanes **145a** and **145b** in hand, the proposed (4+2) annulation was examined using chalcone **158** as the 2-carbon electrophilic coupling partner. NHC **B6** bearing *N*-pentafluorophenyl substitution was employed in the course of these experiments as this commonly provided optimal outcomes in previous studies with the coupling of homoenolic radicals. The suitability of this substituent likely relates its electron withdrawing capacity which leads to increased rate of formation of the Breslow intermediate compared to other NHCs,.[17]

Studies commenced with screening conditions analogous to those developed by Rovis, Chi, and Ye for the enantioselective coupling of homoenolic radicals. As intramolecular β-lactonisation would facilitate catalyst turnover in our design, methanol was omitted from initial experiments. Thus, α-cyclopropyl aldehyde **145a** and chalcone **158** were exposed to NHC **B6** and single electron oxidant

125 in carbon tetrachloride at room temperature (conditions of Rovis). Unfortunately, none of the desired β-lactone **159** was formed, instead, only trace amounts hydroxyketone **160** was isolated, a product of benzoin condensation. In addition, an uncharacterisable polymer accounted for the remainder of converted material (Table 2.1, entry 1). When potassium carbonate was employed as the base in toluene (conditions of Chi), benzoin condensation was promoted with **160** isolated in 15% yield, while polymerisation was supressed (Table 2.1, entry 2). Finally, when DABCO and nitrobenzene **142** were employed (conditions of Ye), the reaction failed (Table 2.1, entry 3).

Given that Chi's conditions (Table 2.1, entry 2) appeared likely to give the most significant degree of Breslow intermediate formation, we decided to examine alternate single electron oxidants with all other conditions remaining the same. Thus, nitrostyrene (**120**) was employed, which also served as the electrophile in this case (Scheme 2.1), hydroxyketone **160** was isolated in 5% yield alongside polymeric material (Table 2.1, entry 4). Employing Weitz ammonium salt **161** did not affect the outcome (Table 2.1, entry 5). To ensure alcoholic additives were not crucial for the progress SET pathways, the reaction was repeated with the addition of methanol, however, this caused the reaction to fail (Table 2.1, entry 6). Given preliminary studies through variation of solvents, bases and oxidants were unsuccessful, the reaction was explored with modification of the substrate. In this regard, diphenyl substituted aldehyde **145b** (R = Ph), which would generate a more stable radical (i.e. **148**, Scheme 2.8), was subjected to the same set of conditions used for the monophenyl substrate **145a**. In all cases the desired product was not observed with benzoin condensation completely supressed and polymerisation occurring to varying degrees (Table 2.1, entries 7-11). In these reactions, it is likely that increased steric bulk introduced by the additional phenyl substituent in **145b** supresses the benzoin condensation observed when monophenyl cyclopropane **145a** was employed.

Table 2.1. Selected optimisations for the SET (4+2) annulation of aldehydes **145**.

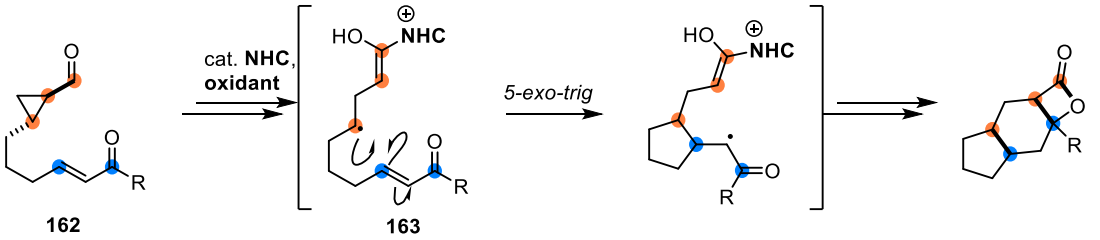


entry	R	oxidant	mol% base	solvent	conv[a]	result[b]
1	H	**125**	100% NaOAc	CCl_4	38%	**160** (<1%), polymer
2	"	"	150% K_2CO_3	toluene	43%	**160** (14%), polymer
3	"	**142**	20% DABCO	"	9%	-
4[c]	"	**120**	150% K_2CO_3	"	20%	**160** (5%), polymer
5	"	**161**	"	"	40%	**160** (5%), polymer
6[d]	"	**125**	"	"	5%	-
7	Ph	"	100% NaOAc	CCl_4	21%	polymer
8	"	"	150% K_2CO_3	toluene	15%	polymer
9	"	**142**	20% DABCO	"	7%	-
10[c]	"	**120**	150% K_2CO_3	"	20%	polymer
11[d]	"	**161**	"	"	32%	polymer

[a]Based on recovered starting material. [b]Chalcone reisolated. [c]No chalcone present, nitrostyrene serves as electrophile. [d]2 equiv. MeOH added.

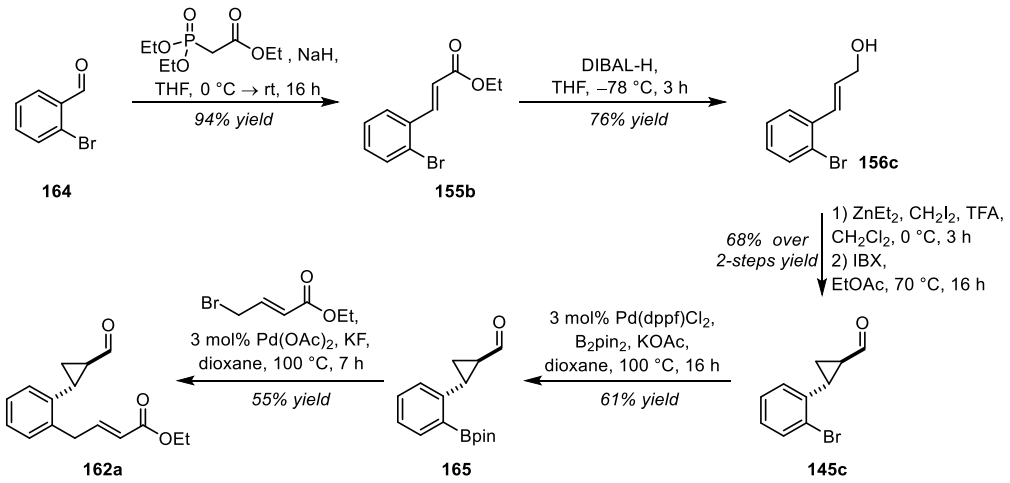
2.2.2 Intramolecular (4+2) annulation of a-cyclopropyl aldehyde 162a

Since the proposed intermolecular (4+2) annulation could not be achieved through variation of the base, solvent, oxidant and substrate, more significant modification of the reaction design was undertaken. Given that polymerisation remained the dominant pathway throughout these studies, it was proposed that a new substrate bearing a tethered electrophile (i.e. **162**) could enable the desired pathway through an intramolecular reaction (Scheme 2.10). Specifically, the corresponding enolic radical **163** generated from such a substrate would be poised to undergo a rapid 5-*exo*-trig cyclisation, and therefore, may outcompete polymerisation that may be occurring through potential radical intermediates.



Scheme 2.10. Proposed intramolecular reaction.

Accordingly, aldehyde **162a** was targeted, which contained the required α,β-unsaturated electrophile and a phenyl substituted cyclopropane motif (Scheme 2.11). The synthesis commenced with the conversion of commercially available 2-bromobenzaldehyde (**164**) to the corresponding α-cyclopropyl aldehyde **145c** using the sequence developed previously for the synthesis of cyclopropanes **145a** and **145b** (Scheme 2.9). To attach the desired electrophile, a modified procedure of Hsieh[18] was followed to effect a palladium catalysed borylation which gave boronate ester **165** (61% yield) before finally, Suzuki coupling with bromoethyl crotonate[19] furnished the desired tethered substrate **162a** (55% yield.)

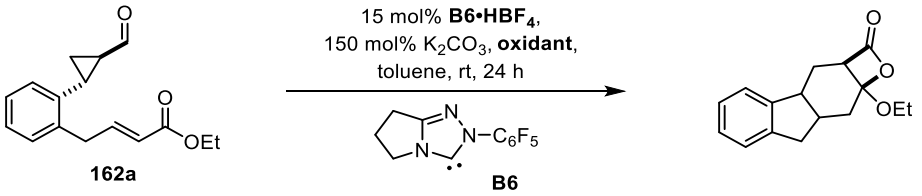


Scheme 2.11. Synthesis of cyclopropyl aldehyde **162a**.

Having synthesised the required α-cyclopropyl aldehyde **162a**, the intramolecular reaction was examined with a series of single electron oxidants. It was thought that the correct oxidant, in conjunction with conditions that were shown previously to promote formation of the Breslow intermediate (i.e. which formed benzoin product **160**, Table 2.1), would allow the transformation to be realised. To this end, **162a** was exposed to NHC **B6** and nitropyridine *N*-oxide **125**. Unfortunately, only decomposition of the converted material (15% conversion) was observed (Table 2.2, entry 1). Using nitrobenzene **142** as the oxidant allowed for greater conversion of the starting material **162a**

(21% conversion), however, no discernible products were isolated (Table 2.2, entry 2). Conversion of **162a** was further increased to 63% when the reaction was conducted with Weitz salt **161**, however, once again only decomposition of the starting material was observed (Table 2.2, entry 3). The reaction failed in the presence of nitrostyrene **120** (Table 2.2, entry 4), whilst ceric ammonium nitrate (CAN), a strong single electron oxidant, led to decomposition of the converted material (Table 2.2, entry 5).

Table 2.2. Selected optimisations for the intramolecular (4+2) annulation

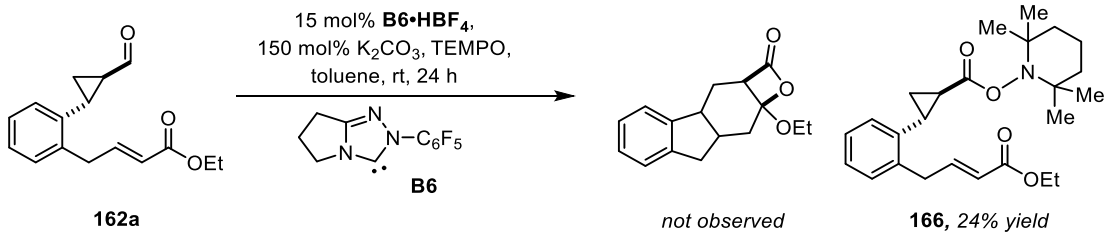


entry	oxidant	%conv[a]	result
1	**125**	15	decomp.
2	**142**	21	decomp.
3	**161**	63	decomp.
4	**120**	N/R	-
5	$(NH_4)_2Ce(NO_3)_6$	53	decomp.

[a]Based on recovered starting material.

2.2.3 Radical trapping experiments

In an effort to gain insight into the nature of the decomposition and polymerisation pathways, and therefore inform subsequent directions, a radical trapping experiment was performed. Given that TEMPO **112** effects single electron oxidation of the Breslow intermediate (see Scheme 2.2), it was proposed that employing TEMPO in this reaction design may reveal if decomposition occurs through radical cleavage of the cyclopropane or even the targeted enolic radical intermediate. To this end, a reaction of tethered aldehyde **162a** was conducted in the presence of TEMPO, however, none of the desired β-lactone or any radical trapped species were observed (Scheme 2.12). Instead, TEMPO ester **166** was isolated in 24% yield, which presumably forms *via* the mechanism described by Studer (see Scheme 2.2). This suggests that the Breslow radical cation of **162a** is indeed formed under these reaction conditions, however, instead of the desired cyclopropane cleavage, subsequent single electron oxidation *via* another equivalent of TEMPO occurs followed by esterification with the TEMPO anion.



162a *not observed* **166,** *24% yield*

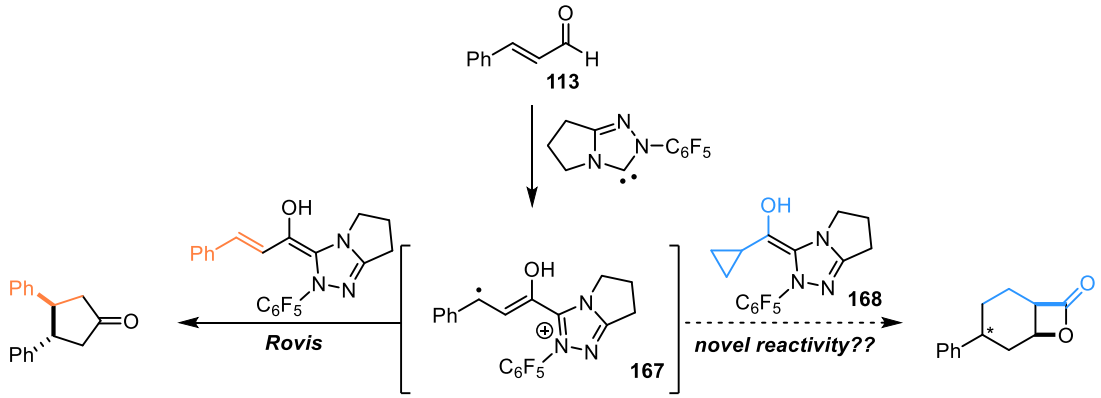
Scheme 2.12. Oxidation and radical trapping with TEMPO.

Concurrent to these studies, work from within our group demonstrated that donor-acceptor (DA) cyclobutanes, which are valuable 4-carbon synthons, engage in an enantioselective (4+2) annulation catalysed by NHCs. Keeping in mind our ultimate goals to develop methods for natural product synthesis, we were encouraged by this discovery, and given the challenges facing the exploitation of SET NHC catalysis to access 4-carbon synthons from cyclopropanes, efforts were redirected towards developing this (4+2) annulation.

2.3 Conclusions and outlook

Exploiting SET NHC catalysis to develop a new (4+2) annulation using α-cyclopropyl aldehydes was ultimately unsuccessful. The intermolecular reaction of α-cyclopropyl aldehydes **145a** and **145b** with chalcone or nitrostyrene resulted only in dimerisation of the aldehyde *via* benzoin condensation, or in polymerisation. While polymerisation may be suggestive of radical cleavage and recombination of the cyclopropane motif, a definitive conclusion could not be reached due to the absence of any characterisable products. Additionally, attempts to overcome polymerisation through an intramolecular reaction of a tethered substrate, α-cyclopropyl aldehyde **162a,** were also unsuccessful. Reactions with this substrate resulted only in decomposition. Finally, a radical trapping experiment using TEMPO revealed that single electron oxidation of the Breslow intermediate occurred under our conditions however, no direct evidence supporting formation of the desired enolic radical intermediate was observed.

Given these outcomes, future studies would focus on exploitation of a known homoenolic radical **167** which can be accessed from α,β-unsaturated aldehyde **113**. Akin to Rovis' coupling of **167** with a Breslow intermediate, a (4+2) annulation may be possible through coupling of this same intermediate with the Breslow intermediate derived from cyclopropyl aldehydes (i.e. **168**, Scheme 2.13



Scheme 2.13. Proposed coupling of a homoenolic radical and Breslow intermediate **168**.

2.4 References

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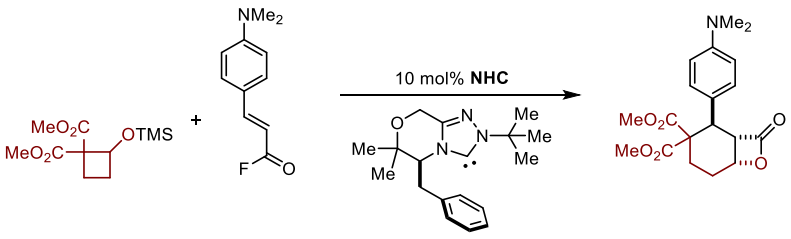
Chapter 3

Enantioselective N-hetereocyclic carbene catalysed (4+2) annulation of donor-acceptor cyclobutanes

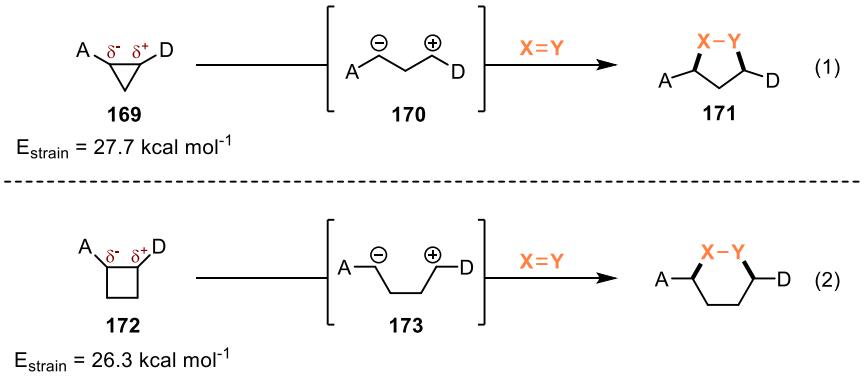
Using N-hetereocyclic carbene catalysis, the first enantioselective (4+2) annulation of donor-acceptor cyclobutanes has been realised. Their reaction with α,β-unsaturated acyl fluorides generates densely functionalised, cyclohexyl-fused β-lactones in excellent yield and with excellent stereochemical integrity. The reaction is amenable to modest scale up and the β-lactone products have been shown to have extensive synthetic utility. Specifically, decarboxylative and ring-opening derivatisations deliver heavily functionalised cyclohexanes, cyclohexenes, and quinolones. Additionally, antimicrobial screening revealed some products and their derivatives exhibit promising activity against several nosocomial pathogens.



3.1 Introduction

The development of new molecular synthons underpins the synthesis of complex chemical structures. To this end, donor-acceptor (DA) cyclopropanes[1] (i.e. **169**) have received significant attention within organic synthesis.[2] The polarised C-C bond between donor (D) and acceptor (A) substituents undergoes facile cleavage, driven by the release of ring strain, to yield 1,3-zwitterionic intermediates (i.e. **170**, Scheme 3.1, eq. 1). The formal 1,3-dipole synthon is commonly intercepted with dipolarophiles (X=Y) thereby providing cyclic scaffolds (i.e **171**). Despite possessing similar strain energy (*cf.* cyclopropanes), reactions

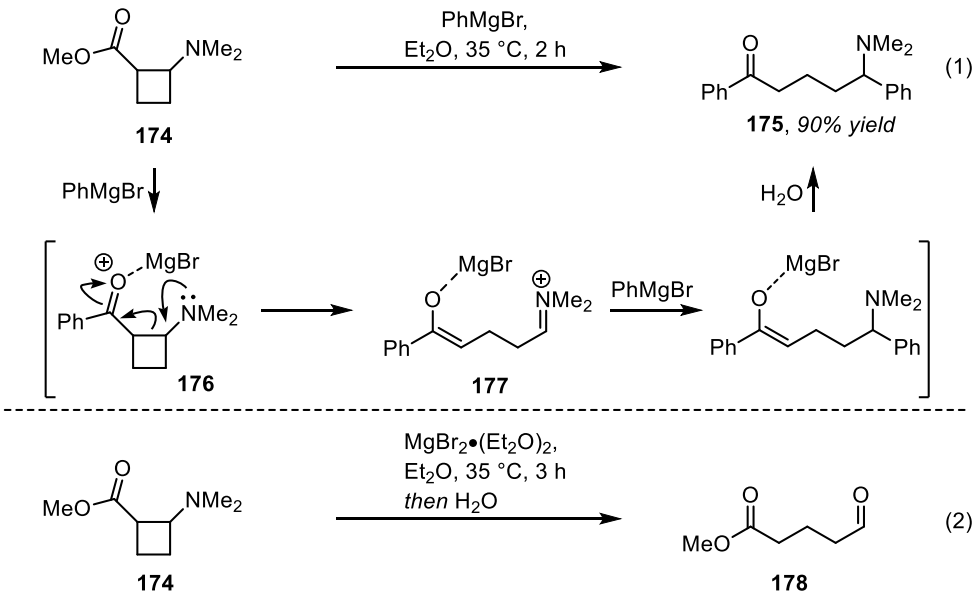
exploiting analogous DA-cyclobutanes **172** as 1,4-dipoles (i.e **17**, Scheme 3.1 eq. 2) are limited, particularly when considering enantioselective reactions.[3]



Scheme 3.1. Strain energy and generalised reactivity of DA-cyclopropanes and DA-cyclobutanes.

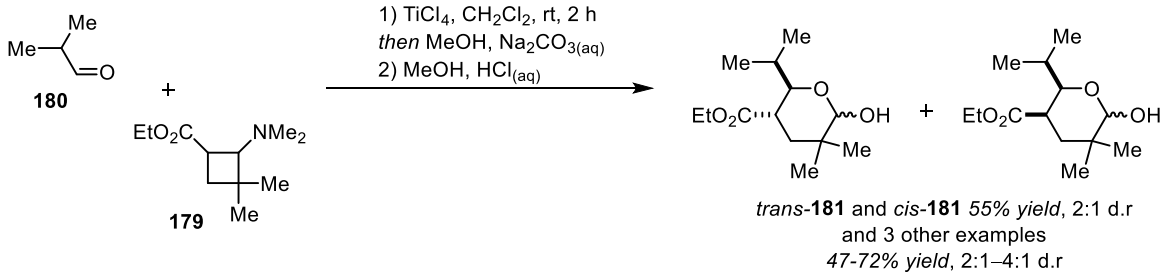
3.1.1 Annulation reactions of DA-cyclobutanes

In 1964 Hollis and co-workers reported the first ring-opening transformation of DA-cyclobutanes whereby the treatment of amino-substituted DA-cyclobutane **174** with phenylmagnesium bromide provided aminoketone **175** in 90% yield (Scheme 3.2, eq. 1).[4] Mechanistically, the reaction is thought to proceed by Grignard addition to the ester and loss of methoxide followed by formation of magnesiumbromide-carbonyl complex **176**. This results in weakening of the C-C bond and therefore ring-opening of the cyclobutane to deliver imine **177** before a second Grignard addition and disassociation of magnesium bromide delivers amino-ketone **175**. To examine the viability of magnesium bromide in the reaction, DA-cyclobutane **174** was exposed to magnesium bromide etherate ($MgBr_2 \bullet (Et_2O)_2$), which induced ring-opening to give the corresponding aldehyde **178** after hydrolytic workup (Scheme 3.2, eq. 2).



Scheme 3.2. Ring opening of amino-activated DA-cyclobutanes.

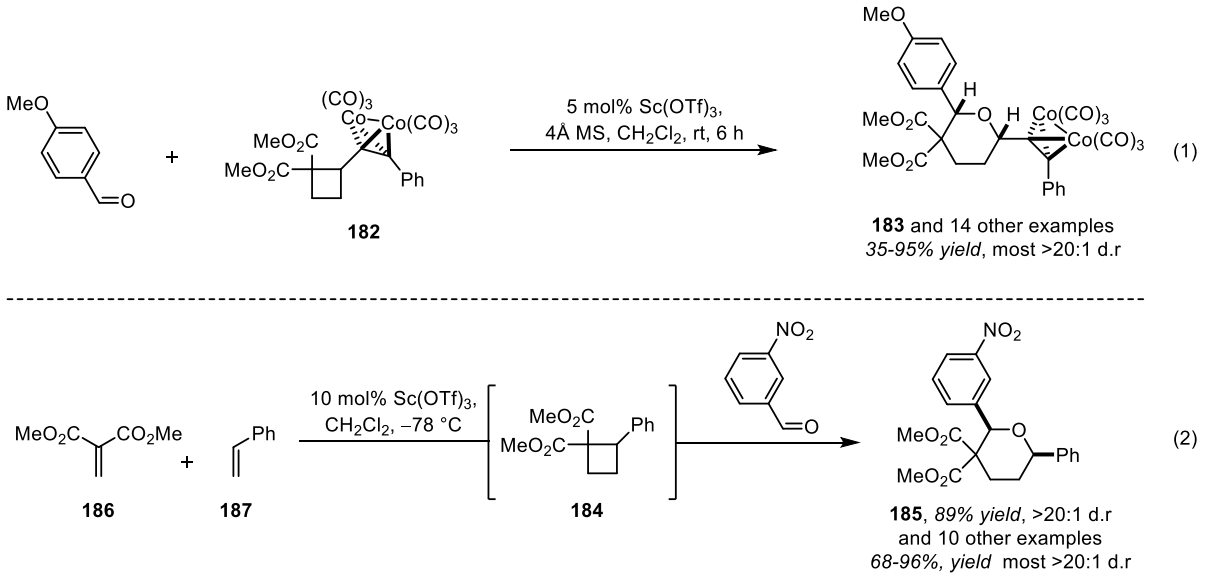
Despite this study and numerous reports of annulations of DA-cyclopropanes, exploitation of DA-cyclobutanes as a 1,4-dipole in analogous fashion was not realised until 1991. In this report, Saigo and co-workers detail the titanium (IV) chloride mediated (4+2) annulation of amino substituted DA-cyclobutanes **179** with aldehydes **180**,[5]which generates δ-lactols **181** in modest yields and diastereoselectivity (Scheme 3.3).



Scheme 3.3. TiCl mediated (4+2) annulation of DA-cyclobutanes with aldehydes.

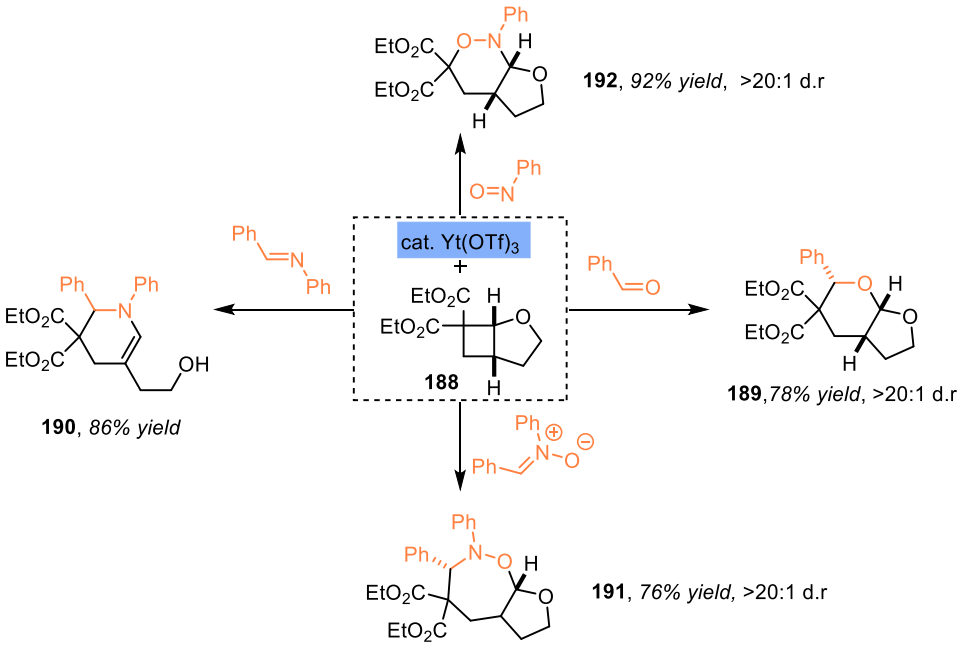
Surprisingly, 20 years separated this seminal report and subsequent studies of DA-cyclobutane annulations. In 2009, concurrent communications by Pritchard and Johnson described the scandium(III) triflate ($Sc(OTf)_3$) catalysed (4+2) annulation of DA-cyclobutanes bearing malonate acceptors and carbon based donors. Pritchard and co-workers demonstrated that cobalt alkyne complexes can be utilised as donor substituents as they offer stabilisation of the resultant 1,4 zwitterion intermediate as the Nicholas cation.[6] Thus, a $Sc(OTf)_3$ catalysed annulation of DA-cyclobutanes **182** with aldehydes was realised, with tetrahydropyrans **183** obtained in modest to good yield and with excellent diastereoselectivity (Scheme 3.4, eq.1). Although a range of aldehydes were tolerated, these were limited to electron rich or neutral aromatic species.

Johnson and co-workers were able to exploit DA-cyclobutanes **184** bearing aryl donor groups in the synthesis of tetrahydropyrans **185** (Scheme 3.4, eq. 2).[7] Notably, as $Sc(OTf)_3$ can catalyse the (2+2) cycloaddition of methylene malonates **186** and styrenes **187**, a one-pot synthesis of DA-cyclobutane **184** and its subsequent annulation could be achieved. With respect to generality, electron rich, electron poor and neutral aromatic substituents on both aldehyde and DA-cyclobutane partners were well tolerated.



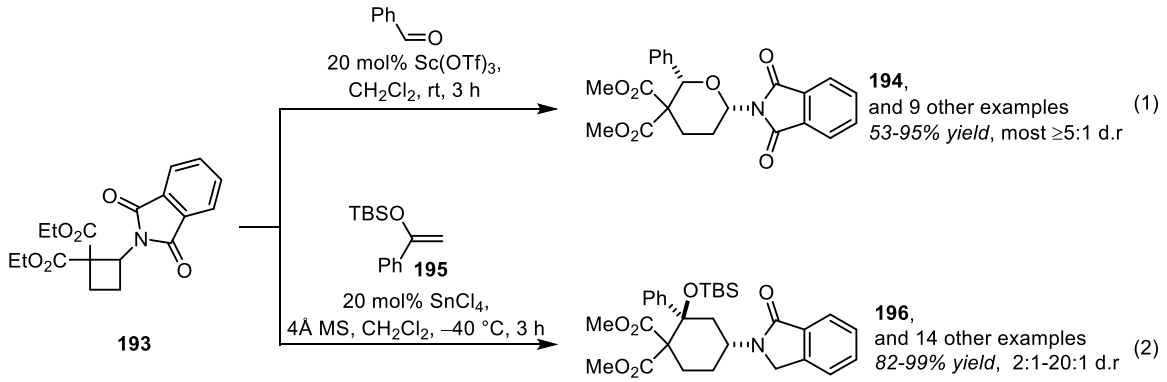
Scheme 3.4. (4+2) annulations of DA-cyclobutanes with alkyne-cobalt complex and aryl donors.

Pagenkopf and Waser have since thoroughly explored the use of hetereoatom donors on the cyclobutane and in these studies, the scope of dipolarophiles was also extended to allow the synthesis of more challenging hetereocycles and even cyclohexanes. Specifically, Pagenkopf and co-workers demonstrated the utility of alkoxy-substituted DA-cyclobutane **188** in ytterbium(III) triflate catalysed annulations with a range of dipolarophiles (Scheme 3.5).[8] Aldehydes,[8a] imines,[8b] nitrones[8c] and nitrosoarenes[8d] reacted smoothly with **188** to deliver tetrahydropyrans **189**, piperidines **190**, oxazepanes **191** and tetrahydrooxazines **192** in good yield and with complete diastereoselectivity.



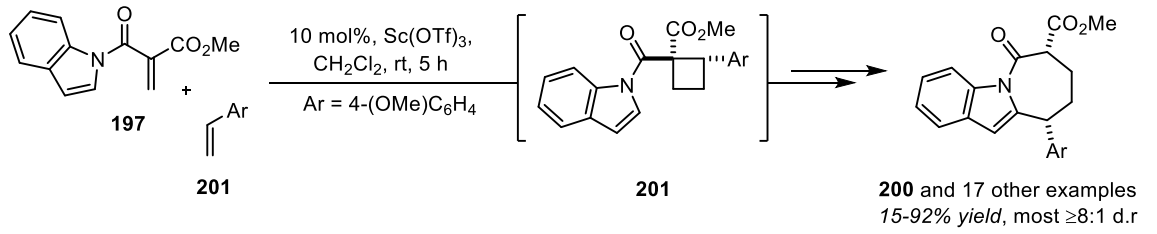
Scheme 3.5. Annulations of alkoxy-substituted DA-cyclobutanes with various dipolarophiles.

Waser was able to employ pthalimide protected amino DA-cyclobutanes **193** in the synthesis of amine substituted tetrahydropyrans **194**, catalysed by $Sc(OTf)_3$ (Scheme 3.6, eq. 1).[9] Unlike the early work of Saigo where the nitrogen functionality is lost upon hydrolytic work up, retention of the nitrogen was achieved by the use of pthalimide protection. The (4+2) annulation tolerates a variety of aromatic aldehydes, however, the diastereoselectivity was limited compared to analogous reactions using DA-cyclobutanes with alkoxy or aryl donors. Importantly, a more challenging all carbon variant was also possible using tin(IV) chloride as the catalyst and *tert*-butytdimethylsilyl enol ethers **195** as coupling partners. In this scenario, cyclohexylamines **196** were generated in excellent yield however, with varying diastereoselectivity (Scheme 3.6, eq. 2).



Scheme 3.6. (4+2) Annulations of pthalimide substituted DA-cyclobutanes.

The electrophilic centre generated upon ring opening of DA-cyclobutanes can also be trapped with an internal nucleophile. France and co-workers describe the (5+2) annulation of amido-acrylate **197** and stryrene **199** to deliver indolylazepines **200** in varying yields and with moderate diastereoselectivity (Scheme 3.7).[10] The reaction is thought to proceed *via* (2+2) cycloaddition to give DA-cyclobutane **201**, an isolable intermediate, which delivers the products following ring-cleavage and trapping with the tethered indole.

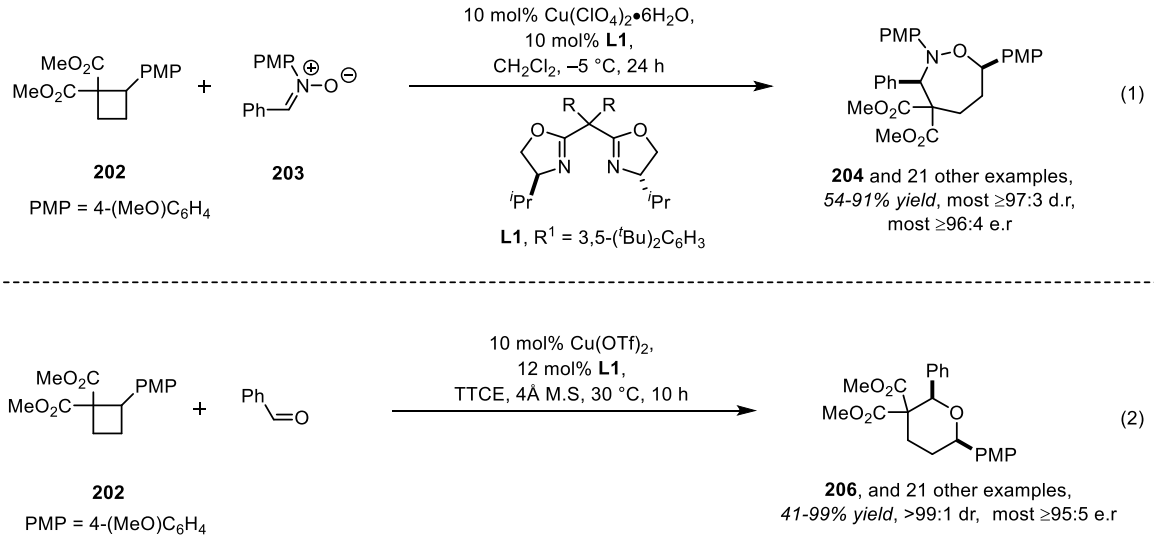


Scheme 3.7. (5+2) Annulation of DA-cyclobutanes with an internal nucleophile.

It is important to note that while most transformations of DA-cyclobutanes proceed with good to excellent diastereocontrol, achieving enantioselectivity in this class of reaction is significantly more challenging. At

the conception of these studies only a single example of enantioselective catalysis using DA-cyclobutanes was known. In 2015, Xie and Tang reported the enantioselective (4+3) annulation of DA-cyclobutanes **202** nitrones **203** catalysed by a homochiral copper complex (Scheme 3.8, eq. 1).[11] In this reaction, oxazepanes **204** were isolated in good to excellent yields and with excellent stereochemical integrity. In addition to aryl donors, the reaction tolerated both alkoxy and thioether based donor components.

More recently, Xie and Tang have now developed a protocol for the enantioselective synthesis of tetrahydropyrans **205** (Scheme 3.8, eq. 2).[12] Building upon Johnsons work with the non-enantioselective variant of this reaction, and using the same homochiral catalyst as used in their (4+3) annulation, the (4+2) annulation of DA-cyclobutanes **202** and aldehydes delivers various pyrans **206** in moderate to good yield and with excellent stereochemical integrity.



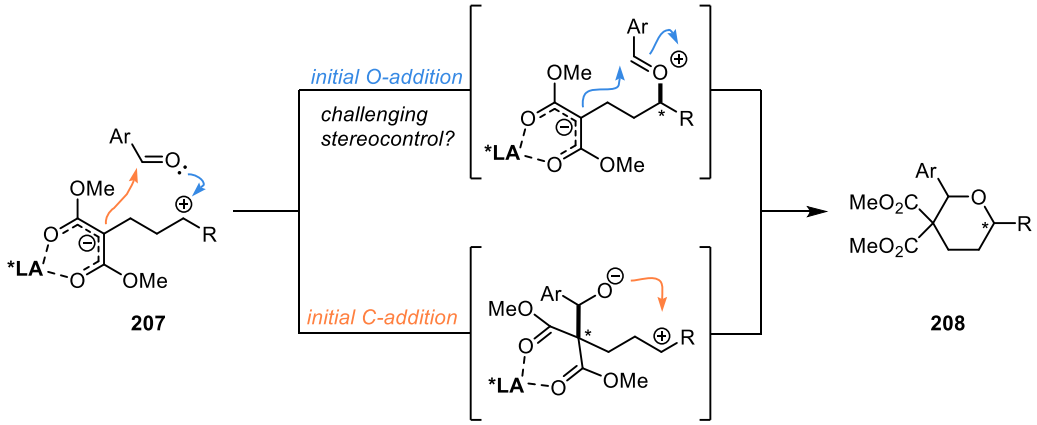
Scheme 3.8. Xie and Tang's enantioselective annulations of DA-cyclobutanes.

3.1.2 Reaction design and objectives

Examining the potential mechanisms through which 1,4-dipoles (i.e. **207**) and aldehydes react provides insight into the challenges in achieving enantiocontrol for this class of reaction (Scheme 3.9). Two mechanistic scenarios are possible for the synthesis of tetrahydropyran products **208**; initial *O*-addition of the aldehydic carbonyl or initial *C*-addition of the malonate nucleophile. In the former pathway, oxocarbenium formation sets a stereocentre remote from the Lewis acid catalyst, and is therefore a potential explanation for difficulties in achieving good stereochemical relay.

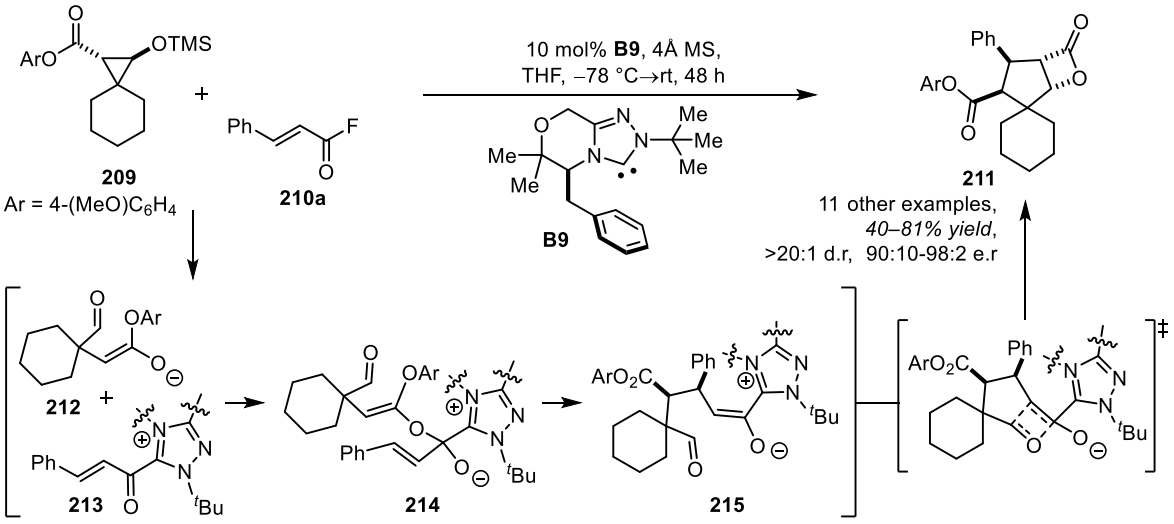
In the studies of Pritchard and co-workers,[6] electron rich aldehydes are required for the reaction to proceed, an observation that can be explained by a predominating *O*-addition mechanism whereby increased electron density provides a more nucleophilic oxygen, and stabilises the resulting oxocarbenium

ion. This is supported by Xie and Tang's[11] observations in their (4+3) annulation whereby the use of electron poor nitrones leads to decreased enantioinduction. An exception to this proposal is of course the recent enantioselective (4+2) annulation (Scheme 3.8, eq. 2) reported after the conclusion of these studies, in which both electron rich and electron poor aldehydes were well tolerated. Although this example overcomes issues with poor enantioselectivity, no mechanistic information is offered and it still remains likely that in the former examples, an *O*-addition mechanism predominates leading to difficulties in the transfer of chiral information.



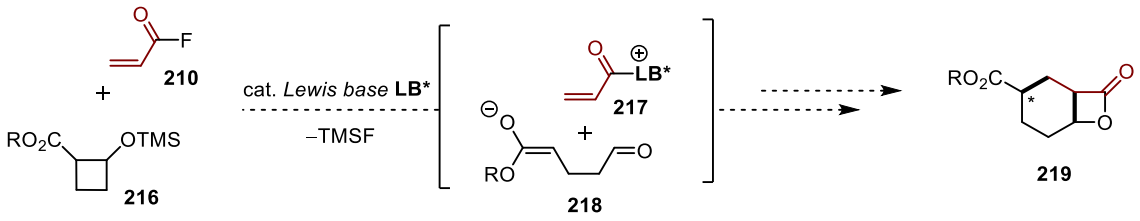
Scheme 3.9. Mechanistic scenarios for the (4+2) annulation of DA-cyclobutanes with aldehydes.

While our ultimate goal was the development of new NHC catalysed methodologies to enable the synthesis of natural products, we wished to concurrently address deficiencies in the enantioselective reactions of DA-cyclobutanes. Accordingly, attention turned to the (3+2) annulation of analogous DA-cyclopropanes discovered previously in the research group.[13] In this reaction, TMS ether-bearing DA-cyclopropanes **209** and α,β-unsaturated acyl fluorides **210** underwent coupling when treated with NHC **B9** to give cyclopentyl β-lactones **211** in excellent yield and stereochemical integrity.[13a] The reaction is initiated upon substitution of α,β-unsaturated acyl fluoride **210** by the NHC **B9** and concomitant desilylation of the cyclopropane **209**. Strain-induced retro-aldol cleavage of the cyclopropane then provides bifunctional enolate **212**, which undergoes *O*-addition to acyl azolium **213** to provide hemiacetal alkoxide **214**. Next, an enantioselective anionic oxy-Claisen (AOC) rearrangement results in formation of acylazolium enolate **215** before an asynchronous aldol/β-lactonisation process furnishes the heavily functionalised cyclopentanes **211**.



Scheme 3.10. NHC catalysed enantioselective (3+2) annulation of DA-cyclopropanes.

Guided by these previous studies, it was proposed that a related Lewis base approach exploiting DA-cyclobutanes **216**, would allow an enantioselective (4+2) annulation to be realised (Scheme 3.11). Specifically, Lewis base substitution of the acyl fluoride **210** and concurrent defluorination/desilylation would generate α,β-unsaturated acyl azolium **217** and 1,4-dipole **218** after retro-aldol cleavage of the cyclobutane . The close proximity of a covalently bound homochiral Lewis base catalyst provides good opportunity for chirality transfer in the postulated *C-O* bond formation and Claisen rearrangement sequence. In this scenario, enantioenriched cyclohexyl fused β-lactones **219** would be prepared.

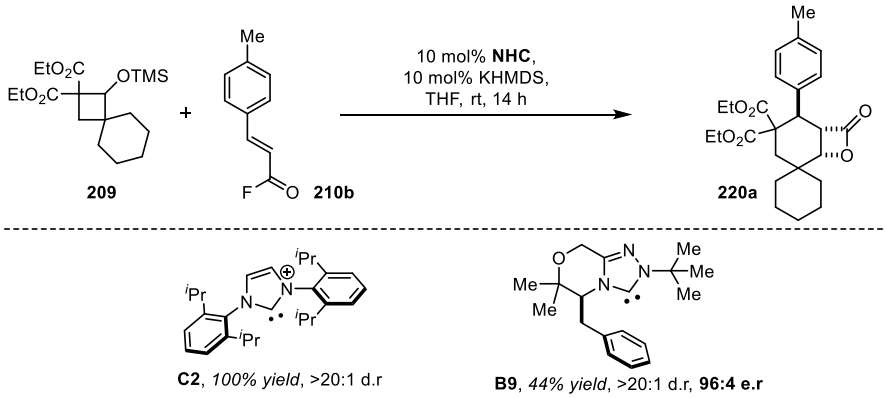


Scheme 3.11. Proposed enantioselective (4+2) annulation of DA-cyclobutanes and acyl fluorides.

3.2 Discovery and optimisation

The entirety of experiments relating to reaction discovery and optimisation of the proposed (4+2) annulation were carried out by a co-worker, Dr. Alison Levens.[14] A summary of key findings from these studies is detailed in this section, with particular emphasis on substrate modifications and reaction conditions which enabled a high yielding and enantioselective reaction. In this regard, the success of the reaction relied heavily upon the exploitation of diester-bearing DA-cyclobutanes (i.e **216a**), which provided superior outcomes compared to their mono-ester counterparts. Thus, when **216a** and

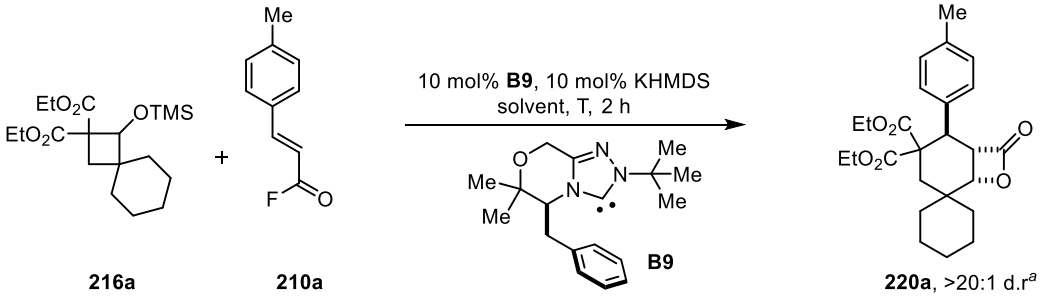
α,β-unsaturated acyl fluoride **210b** were exposed to NHC **C2**, the desired β-lactone **220a** was isolated in quantitative yield and with complete diastereoselectivity (Scheme 3.12). Screening of homochiral NHC catalysts revealed that the least nucleophilic and Lewis basic NHCs[15] were able to catalyse the reaction most effectively, with morpholinone-derived *N*-^{t}Bu-substituted NHC **B9** providing β-lactone **220a** with optimal yield (44%) and stereoselectivity (>20:1 d.r, 96:4 e.r).



Scheme 3.12. (4+2) annulation of malonate bearing DA-cyclobutanes and acyl fluroides.

Having established the optimal substrate and homochiral NHC catalyst, the reaction was optimised through variation of solvent and temperature. The parent result is provided for reference (Table 3.1, entry 1). Heating the reaction to 80 °C after addition of catalyst provided β-lactone **220a** with increased yield (59%) and enantiopurity[16] (97:3 e.r) (Table 3.1, entry 2). Conducting the reaction in dimethyl formamide (DMF) significantly improved the yield of **220a** (86%) however, with loss of enantioselectivity (93:7 e.r) (Table 3.1, entry 3). A compromise between yield and enantioselectivity was reached by employing a 9:1 mixture of THF:DMF, with β-lactone **220a** isolated in 73% yield and 97:3 e.r (Table 3.1, entry 4). Given the sensitivity to temperature, addition of the catalyst to a pre-heated solution (80 °C) of the substrates was trialled. Using this operation, the yield was increased (81%) while the enantiopurity of the product was unchanged (Table 3.1, entry 5). Finally, when potassium tetrafluoroborate (KBF_4), a Lewis acidic salt formed during NHC generation, was removed from the reaction media, **220a** was obtained with increased yield (93%) and identical enantioselectivity (Table 3.1, entry 6).

Table 3.1. Selected optimisation of reaction conditions.



216a **210a** **220a**, >20:1 d.r[a]

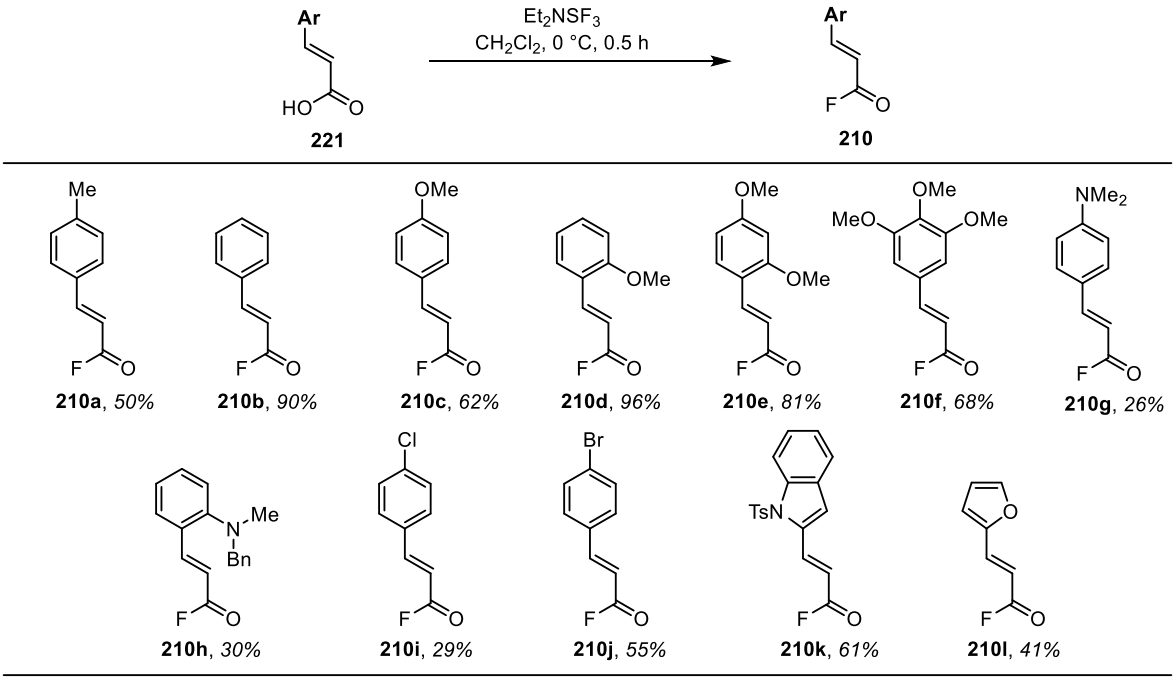
entry	T (˚C)	solvent	yield[b]	e.r[c]
1	rt	THF	44	94:6
2	rt→80	"	59	97:3
3	"	DMF	86	93:7
4	"	9:1 THF:DMF	73	97:3
5	80[d]	"	81	97:3
6[e]	"	"	93	97:3

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield after flash chromatography. [c] Enantiomeric ratio determined by chiral column HPLC analysis. [d] NHC added to mixture of substrates in 80 °C oil bath. [e] **B9** generated with equimolar KHMDS and separated from HMDS and KBF_4 by-products.

3.3 Reaction scope

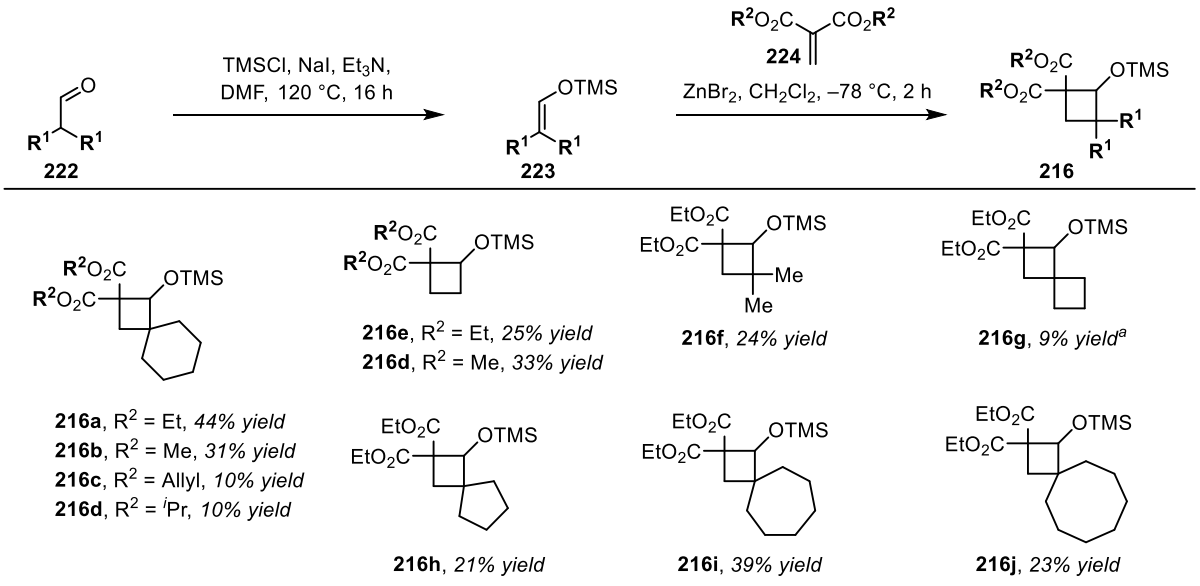
3.3.1 Synthesis of DA-cyclobutanes and α,β-unsaturated acyl fluorides

With optimal reaction conditions established, my role in this project was to aid in examining the generality of the (4+2) annulation and, in particular, to explore the synthetic utility of the reaction. In this endeavour, a number of new DA-cyclobutanes **216** and α,β-unsaturated acyl fluorides **210** were required. Preparation of the latter was relatively trivial with an array of electronically distinct α,β-unsaturated acyl fluorides **210a-l** prepared in good to moderate yield (26-96%) by treatment of the corresponding carboxylic acids **221** with diethylaminosulfur trifluoride[17] (DAST) (Scheme 3.13). Although these substrates were successfully purified *via* flash column chromatography on silica gel, varying degrees of hydrolysis during purification was observed, leading to variations in the isolated yield.



Scheme 3.13. Synthesis of α,ß-unsaturated acyl fluorides.

DA-cyclobutanes **216** were synthesized *via* a 2-step sequence, the first being treatment of commercially available acetaldehydes **222** with trimethylsilyl (TMS) chloride and triethylamine to provide TMS-enol ethers **223a-g** (Scheme 3.14).[18] Using a modified procedure of Roberts,[19] DA-cyclobutanes **216a-k** were then obtained in serviceable yields by zinc bromide-mediated (2+2) annulation of TMS-enol ethers **223a-g** and methylene malonates **224a-d.**



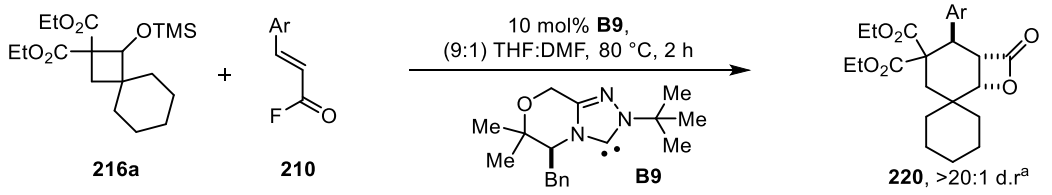
[a] Isolated yield over three-steps from cyclobutane methanol.

Scheme 3.14. Synthesis of malonate bearing DA-cyclobutanes.

3.3.2 Scope of the (4+2) annulation with respect to the acyl fluoride

With acyl fluorides **210a-l** in hand, their viability in the (4+2) annulation with DA-cyclobutane **216a** was examined. Electron poor, neutral and rich acyl fluorides reacted smoothly, providing the corresponding β-lactones in good to excellent yields (72-100%). While these were all well tolerated with respect to yield, the enantioselectivity was sensitive to the electronic properties of the β-aryl substituent. Thus, 4-methylphenyl and cinnamoyl acyl fluorides provided **220a** and **220b** with 95:5 and 97:3 e.r respectively (Table 3.2, entries 1 and 2). Increasing the electron density was beneficial for enantioselectivity with 4-methoxyphenyl, 4-dimethylaminophenyl and 2,4-dimethoxyphenyl acyl fluorides delivering β-lactones **220c-e** in 98:2–99:1 e.r (Table 3.2, entries 3–5). Despite the suitability of electron-rich acyl fluorides, introduction of methoxy groups to the *meta* position proved detrimental, with **220f** isolated in 96:4 e.r (Table 3.2, entry 6). Compared with electron-rich substrates, electron-poor 4-chlorophenyl and 4-bromophenyl substitution gave β-lactones **220g** and **220h** with reduced e.r (87:13 and 92:8 respectively) (Table 3.2, entries 7 and 8). Heteroaryl 3-indolyl and 2-furyl acyl fluorides were also well tolerated, with β-lactones **220i** and **220j** prepared with high enantiopurity (99:1 and 92:8 e.r) and yield (Table 3.2, entries 9 and 10).

Table 3.2. Scope of α,β-unsaturated acyl fluorides **210**.



entry	Ar	220	yield[b]	e.r[c]
1	4-MeC_6H_4	**220a**	93%	97:3
2	C_6H_5	**220b**	86%	95:5
3	4-$OMeC_6H_4$	**220c**	100%	98:2
4	2,4-$(OMe)_2C_6H_3$	**220d**	90%	99:1
5	4-$(Me)_2NC_6H_4$	**220e**	97%	99:1
6	3,4,5-$(OMe)_3C_6H_2$	**220f**	93%	96:4
7	4-BrC_6H_4	**220g**	80%	92:8
8	4-ClC_6H_4	**220h**	81%	87:13
9	3-Ts-indolyl	**220i**	83%	99:1
10	2-furyl	**220j**	72%	92:8

[a] Diastereomeric ratio determined by ^1H NMR analysis of the crude reation mixture. [b] Isolated yield after flash chromatography. [c] Enantiomeric ratio determined by chiral column HPLC analysis.

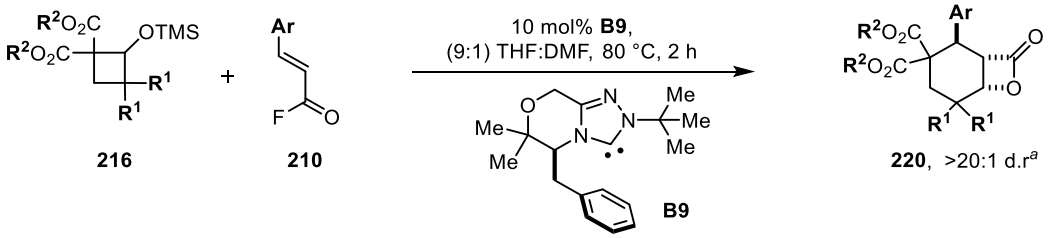
3.3.3 Scope of the (4+2) annulation with respect to the DA-cyclobutane

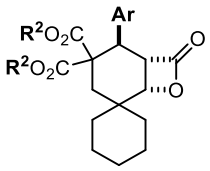
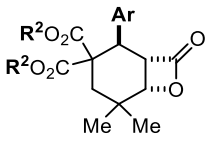
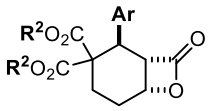
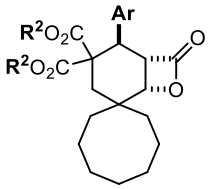
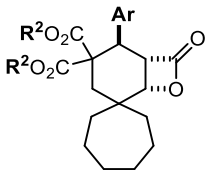
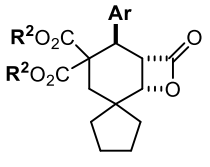
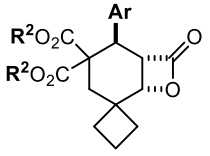
The scope of the (4+2) annulation with respect to the DA-cyclobutanes **216**a-jwas examined with a selection of acyl fluorides. Exchanging the ethyl ester component with methyl or allyl esters provided a similar outcome to the parent reaction, with β-lactones **220k** and **220l** obtained in excellent yield and with excellent stereochemical integrity (Table 3.3, entries 1 and 2). Increasing the steric bulk at this position using *iso*-propyl esters was detrimental to enantioselectivity, with the corresponding β-lactone **220m** isolated in good yield albeit with 94:6 e.r (Table 3.3, entry 3).

Next, the effect of substitution about the cyclobutane motif was explored. Removing the spirocyclic substitution was well tolerated, with dimethyl substituted DA-cyclobutane **216f** providing β-lactones **220n-p** in excellent yield (93–100%) and with excellent stereochemical integrity (97:3–99:1 e.r)(Table 3.3, entries 4-6). Removing all substitution *via* DA-cyclobutane **216e** decreased the enantioselectivity with **220q** isolated in 90:10 e.r (Table 3.3, entry 7) however, this could be improved by exploiting 4-dimethylaminophenyl, 2,4-dimethoxyphenyl and 2-methoxy phenyl acyl fluorides (Table 3.3, entries 8–10). The viability of unsubstituted DA-cyclobutanes **216e** and **216d** is particularly pleasing as substrates lacking substitution were not suitable in the analogous (3+2) annulation using DA-cyclopropanes (Scheme 3.10).[13a] Moreover, such generality renders reactions more valuable in the design and the synthesis of complex targets, a topic explored in depth in *Chapters 4 and 5.*

Increasing the size of the spirocycle was tolerated with cyclooctyl or -heptyl-fused cyclobutanes affording **220u-x** in good yields (75–94%) and with enantioselectivities (98:2–99:1 e.r) similar to the parent cyclohexyl analogues (Table 3.3, entries 11–14). Similarly, decreasing ring-size was also tolerated (except for **220y**), with cyclopentyl fused DA-cyclobutane **216** providing **220y-aa** in good yield and enantioselectivity (Table 3.3, entries 15–17). Finally, *bis*-cyclobutane **216g** was also viable, with the reaction providing β-lactones **220ab** and **220ac** in excellent yield, albeit with reduced enantioselectivity (93:7 e.r) (Table 3.3, entries 18 and 19).

Table 3.3. Scope of DA-cyclobutanes **216**.



entry	R[1]	Ar	R[2]	220	yield[b]	e.r[c]
1		4-OMeC$_6$H$_4$	Me	**220k**	84%	99:1
2		"	Ally	**220l**	88%	99:1
3		"	^{i}Pr	**220m**	86%	94:6
4		4-OMeC$_6$H$_4$	Et	**220n**	93%	97:3
5		2,4-(OMe)$_2$C$_6$H$_3$	"	**220o**	100%	99:1
6		2-Bn(Me)$_N$C$_6$H$_4$	"	**220p**	98%	99:1
7		4-OMeC$_6$H$_4$	"	**220q**	70%	90:10
8		4-(Me)$_2$NC$_6$H$_4$	"	**220r**	90%	96:4
9		2,4-(OMe)$_2$C$_6$H$_3$	"	**220s**	83%	97:3
10		2-OMeC$_6$H$_4$	Me	**220t**	87%	98:2
11		4-OMeC$_6$H$_4$	Et	**220u**	75%	98:2
12		2,4-(OMe)$_2$C$_6$H$_3$	"	**220v**	91%	99:1
13		4-OMeC$_6$H$_4$	"	**220w**	94%	98:2
14		2,4-(OMe)$_2$C$_6$H$_3$	"	**220x**	80%	98:2
15		4-OMeC$_6$H$_4$	"	**220y**	100%	89:11
16		4-(Me)$_2$NC$_6$H$_4$	"	**220z**	98%	98:2
17		2,4-(OMe)$_2$C$_6$H$_3$	"	**220aa**	99%	98:2
18		4-(Me)$_2$NC$_6$H$_4$	"	**220ab**	88%	93:7
19		2,4-(OMe)$_2$C$_6$H$_3$	"	**220ac**	81%	90:10

[a] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reation mixture. [b] Isolated yield after flash chromatography. [c] Enantiomeric ratio determined by chiral column HPLC analysis.

Pleasingly, crystals of diallyl malonate **220l** suitable for XRD analysis were grown by recrystallisation from *n*-hexane/isopropanol solution. Analysis using Cu Kα radiation source allowed the absolute stereochemical configuration of the β-lactone products **220** to be assigned as 1S, 2R, 6S (Figure 3.1). This assignment was important for selecting the correct enantiomer of NHC catalyst to obtain β-lactones that translate to the naturally occurring enantiomer of natural products in later studies *(see Chapters 4 and 5)*.

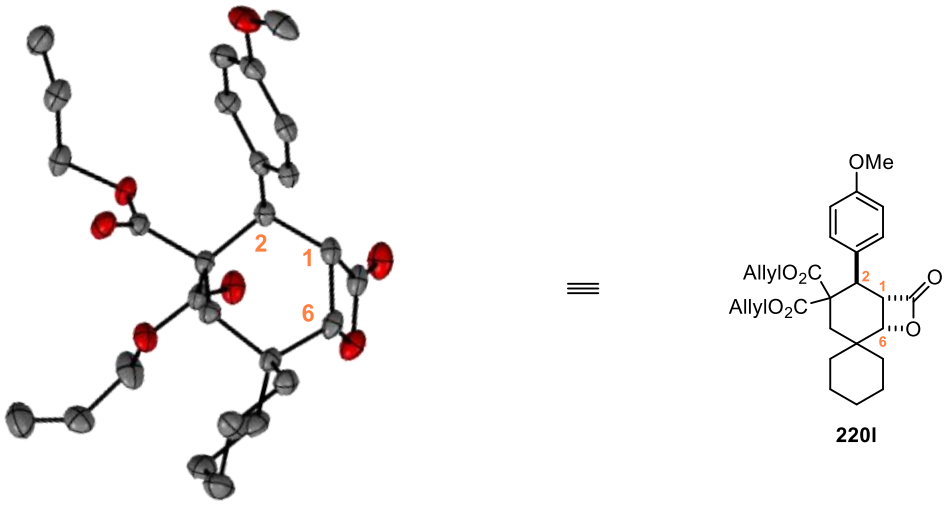
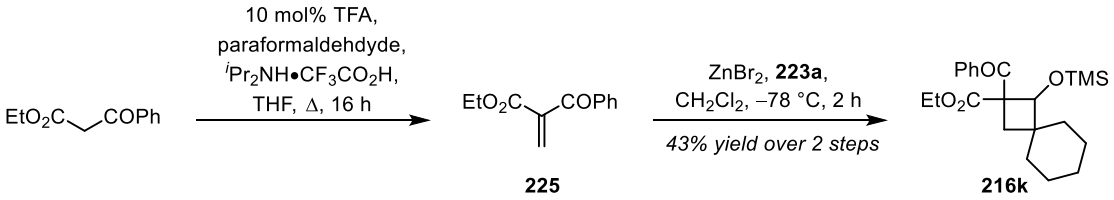


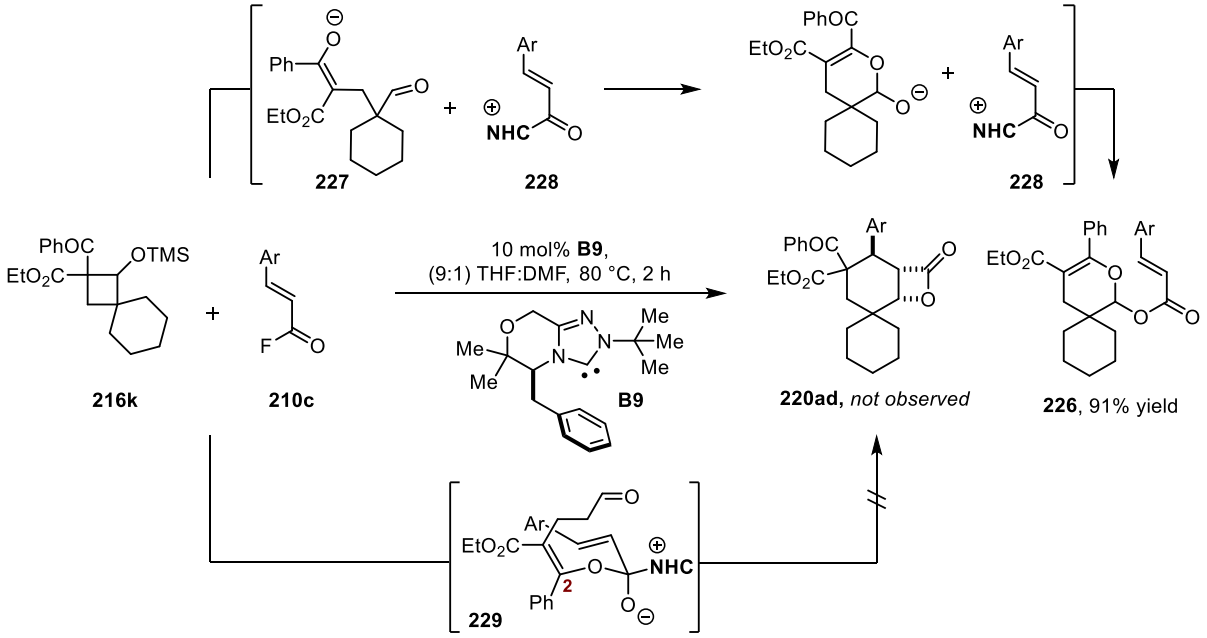
Figure 3.1. Crystal structure of ß-lactone **220l**.

In addition to geminal diesters, the β-ketoester containing DA-cyclobutane **216k** was assessed. This was synthesised as described previously by zinc bromide-mediated (2+2) annulation of acrylate **225** and TMS enol ether **224a** (Scheme 3.15).



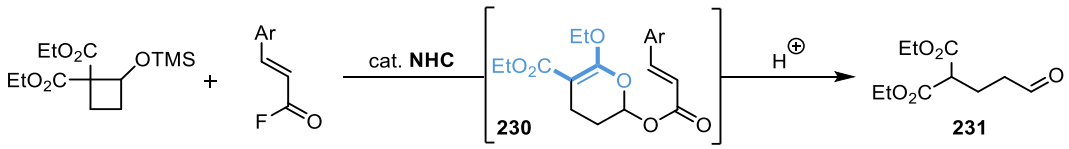
Scheme 3.15. Synthesis of a ß-ketoester containing DA-cyclobutane.

Unfortunately, when β-ketoester **216k** and acyl fluoride **210c** was subjected to the optimised reaction conditions, none of the expected β-lactone **220ad** was observed. Instead, lactol ester **226** was isolated in 91% yield and as the sole reaction product (Scheme 3.16). Presumably this is formed by cyclisation of enolate **227** followed by *O*-acylation with α,β-unsaturated acyl azolium **228**. The divergence in reaction outcome may pertain to the removal of C2 oxygenation in the hemiacetal alkoxide **229**, which in the former substrates, offers additional Ireland-type activation and therefore acceleration of the Claisen rearrangement.



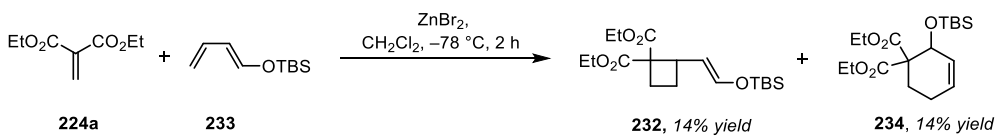
Scheme 3.16. Annulation of keto-ester derived DA-cyclobutane **216k**

Interestingly, across all optimisation experiments with malonate derived DA-cyclobutanes analogous lactol products (i.e. **230**) were not observed, despite the frequent isolation of quenched enolate products (i.e. **231**, Scheme 3.17) It is possible that under the reaction conditions these oxygenated products **231** are indeed formed, however, as these are α-ester ketene acetals, their detection is likely complicated due to rapid hydrolysis upon purification.



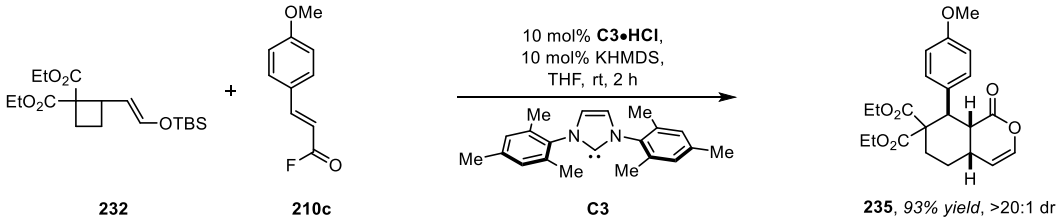
Scheme 3.17. Proposed formation and hydrolysis of ketene acetal **230**.

Next, the viability of the reaction with vinylogous DA-cyclobutane (i.e. **232**) systems was examined. While the synthesis of DA-cyclobutane **232** (OTBS = OTMS) was not possible due to difficulties isolating the precursor diene (i.e. **233**, OTBS = OTMS), utilising the more stable *tert*-butyldimethyl silyl protecting group enabled the isolation of cyclobutane **232**, albeit, as a partially separable mixture with the corresponding Diels-alder adduct **234** (Scheme 3.18).



Scheme 3.18. Synthesis of a vinylogous DA-cyclobutane.

When **232** was exposed to 10 mol% **C3**, the annulation with 4-methoxyphenyl acyl fluoride **210c** proceeded without event to give δ-lactone **235** in 91% yield as a single diastereoisomer (Scheme 3.19). Unfortunately, the reaction failed when NHC **B9** or indeed any homochiral catalysts were trialled. This result may be due to the more stable TBS protection (*cf.* TMS) requiring a more nucleophilic catalyst (i.e. **C3**) to initiate the reaction.



232 **210c** **C3** **235**, *93% yield*, >20:1 dr

Scheme 3.19. (4+2) Annulation of vinylogous DA-cyclobutane **232**.

The structure of δ-lactone **235** was confirmed by spectroscopic analysis. Comparison of the ^{1}H NMR spectrum of the product to the starting acyl fluoride showed loss of α,β-unsaturation, and the presence of a *para*-substituted aromatic ring (7.33 ppm, 2H and 6.75 ppm, 2H) (Figure 3.2). Comparison to the starting DA-cyclobutane revealed the disappearance of the cyclobutane methylene signals as well as the peak at 0.10 ppm corresponding to the TMS group, whilst indicating the presence of a diethyl malonate moiety. Most tellingly, the ^{1}H NMR spectrum of the product contained 2 downfield signals and 3 upfield signals each integrating for one proton, indicative of the alkene and methine protons respectively.

The most downfield of these signals at 6.52 ppm, is characteristic of an alkene proton with further deshielding by an adjacent oxygen atom and was assigned as H^{a}. It's splitting as a doublet of doublets is due to the doublet of doublet of doublets (overlapping) at 5.05 ppm, which is consistent an olefinic proton on the vicinal carbon, and as such, this signal was assigned to H^{b}. The overlapping methine signal at 3.90 ppm was assigned as H^{d} due to observed coupling (based on COSY NMR) to two methine signals at 3.41 ppm and 3.10 ppm, with the chemical shift suggestive of deshielding by carbonyl anisotropy. In turn, the methine doublet at 3.41 ppm was assigned as H^{e} based on its isolated coupling to H^{d} and the chemical shift which is typical of a cyclic and benzylic proton. The final methine signal at 3.10 ppm showed coupling (COSY NMR) to H^{a}, H^{b}, H^{d}, and the methylene signal at 2.21 ppm, which is consistent with assignment as H^{c}.

The downfield region of the ^{13}CNMR spectrum contained the required 3 peaks indicative of ester/lactone carbonyl groups, as well as 4 aromatic and two olefinic signals. In the upfield region, the required 11 aliphatic signals were all observed. IR analysis provided evidence for the the δ-lactone

functionality with the presence of a signal at 1771 cm^{-1}, separate from the resonance at 1724 cm^{-1} pertaining to the malonate esters.

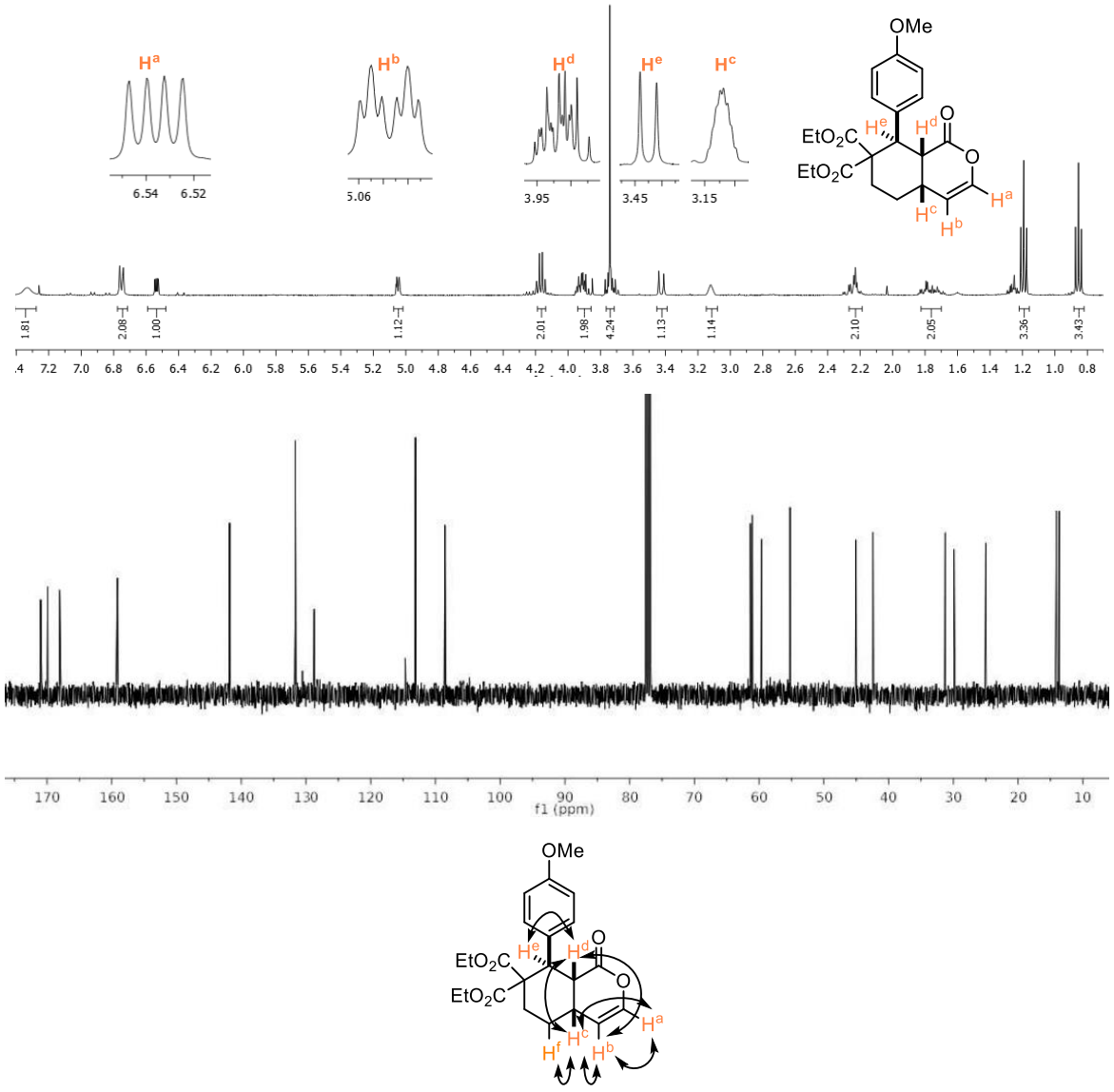


Figure 3.2 ^{1}H- and ^{13}C NMR and COSY interactions of δ-lactone **235** in $CDCl_3$ (400 and 100 MHz).

The relative stereochemistry was determined by NOESY NMR. A nuclear Overhauser effect was observed between H^d and H^c, supporting a *cis*-fused δ-lactone structure, whilst the absence of cross relaxation between H^d and H^e is suggestive of a *trans*-relationship between the lactone and aryl group (Figure 3.3). Furthermore, this stereochemical arrangement is consistent with the related β-lactones **220**.

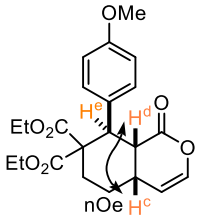


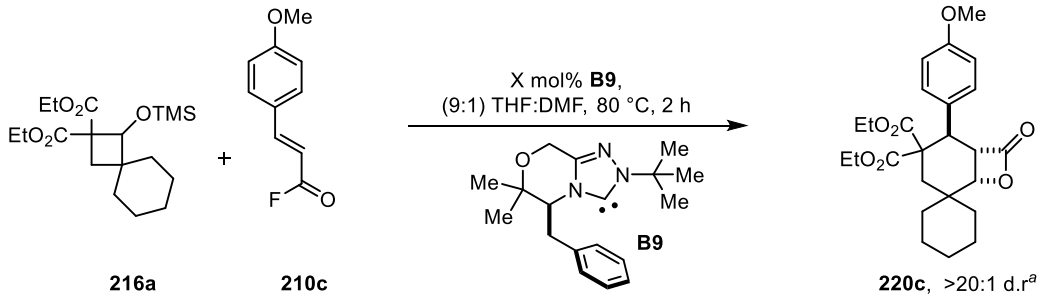
Figure 3.3. NOESY interactions of δ-lactone **235** in $CDCl_3$ (400 and 100 MHz).

3.4 Reaction utility

3.4.1 Reaction scale-up

Given the ultimate goal of applying this chemistry in natural product synthesis, the viability of larger scale (4+2) annulations was examined. Due to the long sequence (6-steps) required for catalyst synthesis, we wished to explore the viability of reducing catalyst loading. The parent reaction using 10 mol% **B9** is provided for reference (Table 3.4, entry 1). When conducted with 1 mol% **B9** the reaction proceeded sluggishly, with β-lactone **220c** isolated in significantly reduced yield (23%) and slightly decreased enantioselectivity (92:8) (Table 3.4, entry 2). Gratifyingly, using 3 mol% **B9**, β-lactone **220c** was obtained in good yield and with similar enantioselectivity to the reaction with 10 mol% **B9** (Table 3.4, entry 3).

Table 3.4. Optimisation of reduced catalyst loading.

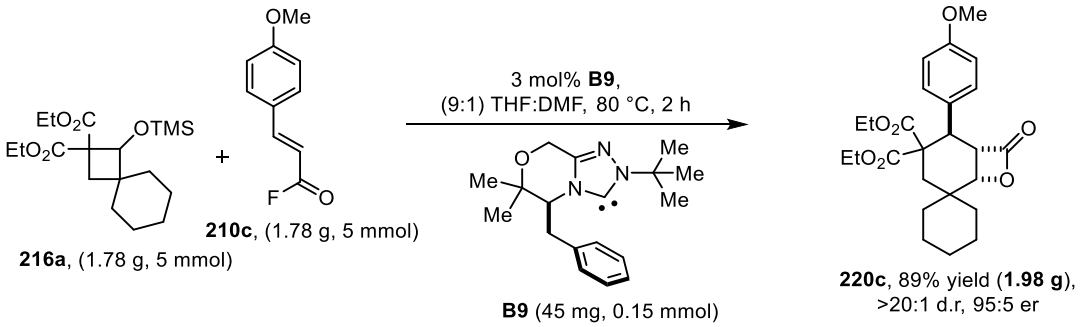


entry	X	yield[b]	e.r[c]
1	10	100%	97:3
2	1	23%	92:8
3	3	73%	96:4

[a] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield after flash chromatography. [c] Enantiomeric ratio determined by chiral column HPLC analysis.

Pleasingly, with the newly revised conditions, 1.78 g DA-cyclobutane **216a** (5 mmol) and 1.78 g of acyl fluoride **210c** (5 mmol) was coupled to produce 1.98 g of β-lactone **220c** in 89% yield and 95:5 e.r (*cf*

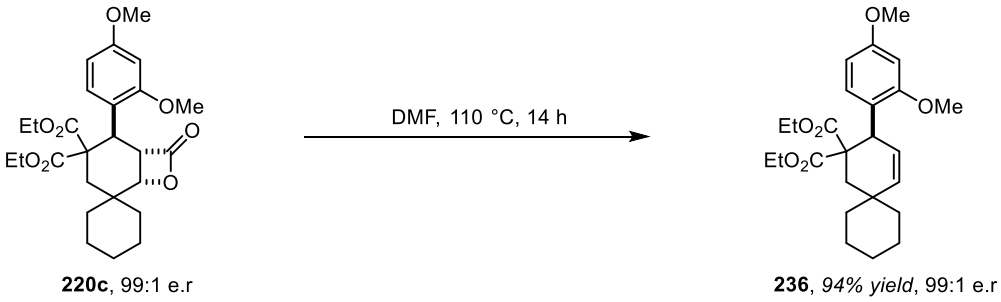
100% yield, 97:3 e.r), using only 45 mg of NHC **B9** (Scheme 3.20). This result was later surpassed, with related substrates coupled on up to 20 mol scale *(see Chapters 4 and 5).*



Scheme 3.20. (4+2) annulation on 5 mmol scale.

3.4.2 Product derivatisation

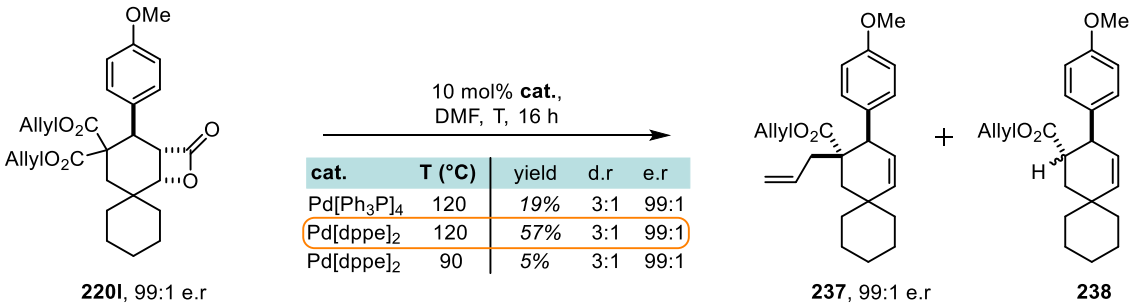
As part of studies to assess the utility of the (4+2) annulation, derivatisations of the β-lactone products were investigated. Initial studies focused on decarboxylative methods with respect to the β-lactone and malonate functionality. Upon heating cylcohexane **220c** in DMF, thermal decarboxylation of the β-lactone proceeded smoothly and cyclohexene **236** was obtained in excellent yield (94%) and with complete stereo-retention (Scheme 3.21).



Scheme 3.21. Thermal ß-lactone decarboxylation.

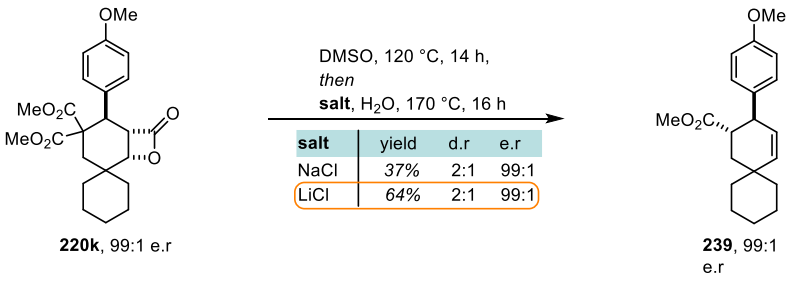
Thermal decarboxylation of the β-lactone[20] could also be coupled with decarboxylative allylation diallylmalonate ester moiety. Thus, treatment of diallylmalonate **220l** with 10 mol% tetrakis palladium triphenylphosphine ($Pd[Ph_3P]_4$) effected β-lactone decarboxylation, and decarboxylative allylation to give cyclohexene **237**, albeit in a modest 19% yield and 3:1 d.r (Scheme 3.22). In this case, the remainder of the converted material consisted of the corresponding protonation product **238**. Pleasingly, switching the catalyst to bis[1,2-bis(diphenylphosphino)ethane]palladium(0) ($Pd[dppe]_2$) suppressed undesired protonation and cyclohexene **237** was obtained in 57% yield, 3:1 d.r and with complete enantioretention. The reaction was also conducted at reduced temperature (90 °C) in an effort to engender greater

diastereocontrol. Unfortunately, minimal conversion was observed at these temperatures and **237** was isolated with identical diastereoselectivity (3:1 d.r). This is not unexpected as effecting the decarboxylative allylation of α,α-dialkyl malonates is sluggish due to thermodynamic challenges of ester enolate formation.[21]



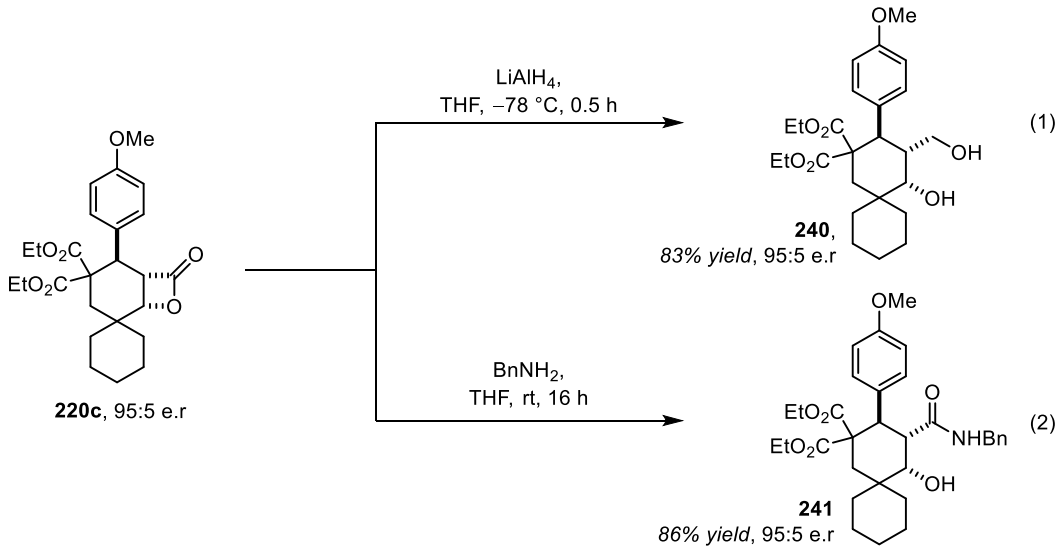
Scheme 3.22. Palladium catalysed decarboxylative allylation of diallyl malonate **220l**.

Simple Krapcho decarboxylation[22] could also be coupled with β-lactone decarboxylation. When dimethyl malonate **220k** with was treated with sodium chloride and heated to 170 °C, monoester **239** formed in 37% yield, as a 2:1 mixture of diastereomers and with complete enantioretention (Scheme 3.23). Using lithium chloride gave a significant increase in yield (64%), however the diastereoselectivity was unchanged. The limited diastereoselectivity is consistent with related reactions described in the literature, whereby diastereoselectivity is substrate dependant, and can only be controlled by an internal proton source.[23]



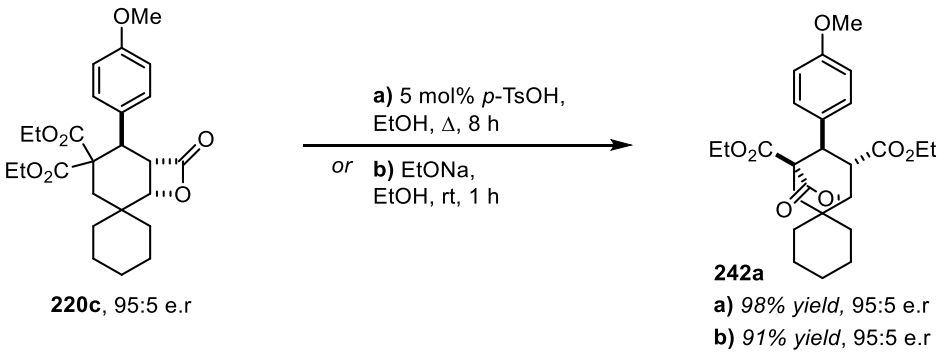
Scheme 3.23. Krapcho decarboxylation of dimethyl malonate **220k**.

Derivatisations which avoid β-lactone decarboxylation were also investigated. Careful moderation of reaction time and temperature allowed a highly chemoselective reduction of the β-lactone motif in the presence of two ester functionalities. Thus, treatment of β-lactone **220c** with lithium aluminium hydride ($LiAlH_4$) at –78 °C for 30 minutes provided diol **240** in 83% yield and with complete stereoretention (Scheme 3.24, eq. 1). Simple β-lactone cleavage using benzylamine was also possible with amide **241** isolated in 86% yield and with complete stereoretention (Scheme 3.24, eq. 2).



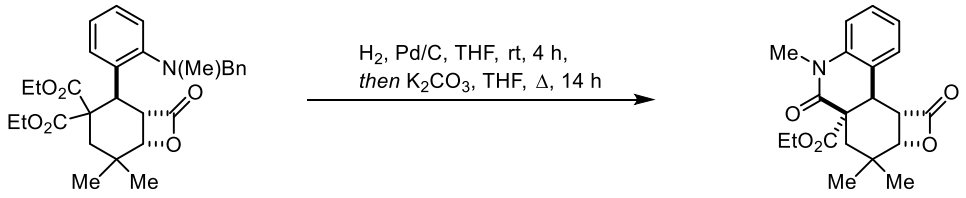
Scheme 3.24. Reduction and aminolysis of ß-lactone **220c**.

When ring-opening was attempted using alcoholic nucleophiles, an unexpected transannular lactonisation occurred and [2.2.2]-bicyclic lactone **242a** was isolated. This process occurred in 8 hours under acidic conditions using *p*-toluenesulfonic acid (Scheme 3.25a) however, was significantly more facile (1 h) when mediated by base (Scheme 3.25b). In both cases the lactone **242a** was isolated in excellent yield (91% and 98%) and with complete stereoretention.



Scheme 3.25. Acid and base mediated ethanolysis of ß-lactone **220c**.

Finally, deprotection of aniline **220p**[24] by treatment with palladium on activated charcoal under a hydrogen atmosphere allowed access to the corresponding quinolone **243** (Scheme 3.26). Lactamisation with the pendant ethyl esters occurred spontaneously upon exposure to silica, or in deuterated chloroform, or even when stored as a neat material. Unfortunately, under any of these conditions, the cyclisation occurred with no diastereoselectivity. Addition of potassium carbonate *in situ* following debenzylation improved diastereoselectivity, with dihydroqunolinone **243** isolated in 94% yield as a 5:1 mixture of diastereomers, and with complete enantioretention.



220p, 99:1 e.r

243, *94% yield*, 5:1 d.r, 99:1 e.r

Scheme 3.26. Synthesis of dihydroquinolinone **243**.

3.4.3 Antimicrobial screening of β-lactones and derivatives

Antibiotic resistance represents one the greatest challenges facing the modern era of medicinal chemistry.[25] The ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Psuedomonas aeruginosa, and Enterobacter* species) account for the majority of hospital-born infections and as such, are developing antibiotic resistance at an alarming rate.[26] To combat resistance, there is an increasing demand for new chemical structures which exhibit antimicrobial activity via novel mechanisms.

The CO-ADD (The Community for Antimicrobial Drug Discovery)[27] is an organisation which conducts widespread screening of novel chemical compounds for antimicrobial activity. Racemates of most β-lactones and their derivatives synthesized here were subjected to screening against 4 ESKAPE bacteria (*S. aureus, K. pneumoniae, A. baumannii and P. aeruginosa)* in addition to *E. coli* and the fungi *Candida albicans* and *Cryptociccus neoformans.* The pathogens were exposed to these compounds at a concentration of 32 μg/ml in whole cell growth inhibition assays.

Pleasingly, several of our compounds displayed promising activity. Specifically, β-lactones **220a** and **220d** in addition to cyclohexene **237**, effected almost 50% inhibition of bacterial growth against the Gram-negative bacteria *K. pneumonia* (Figure 3.4). Compounds **220a**, **220m**, and **239** were considerably more effective against another Gram-negative bacteria, *A. baumannii*, inhibiting 79%, 69%, and 70% of cell growth respectively. Finally, indole-derived β-lactone **220i** showed similar activity (76%) against *C. albicans.* All other screened compounds displayed almost no antimicrobial activity.

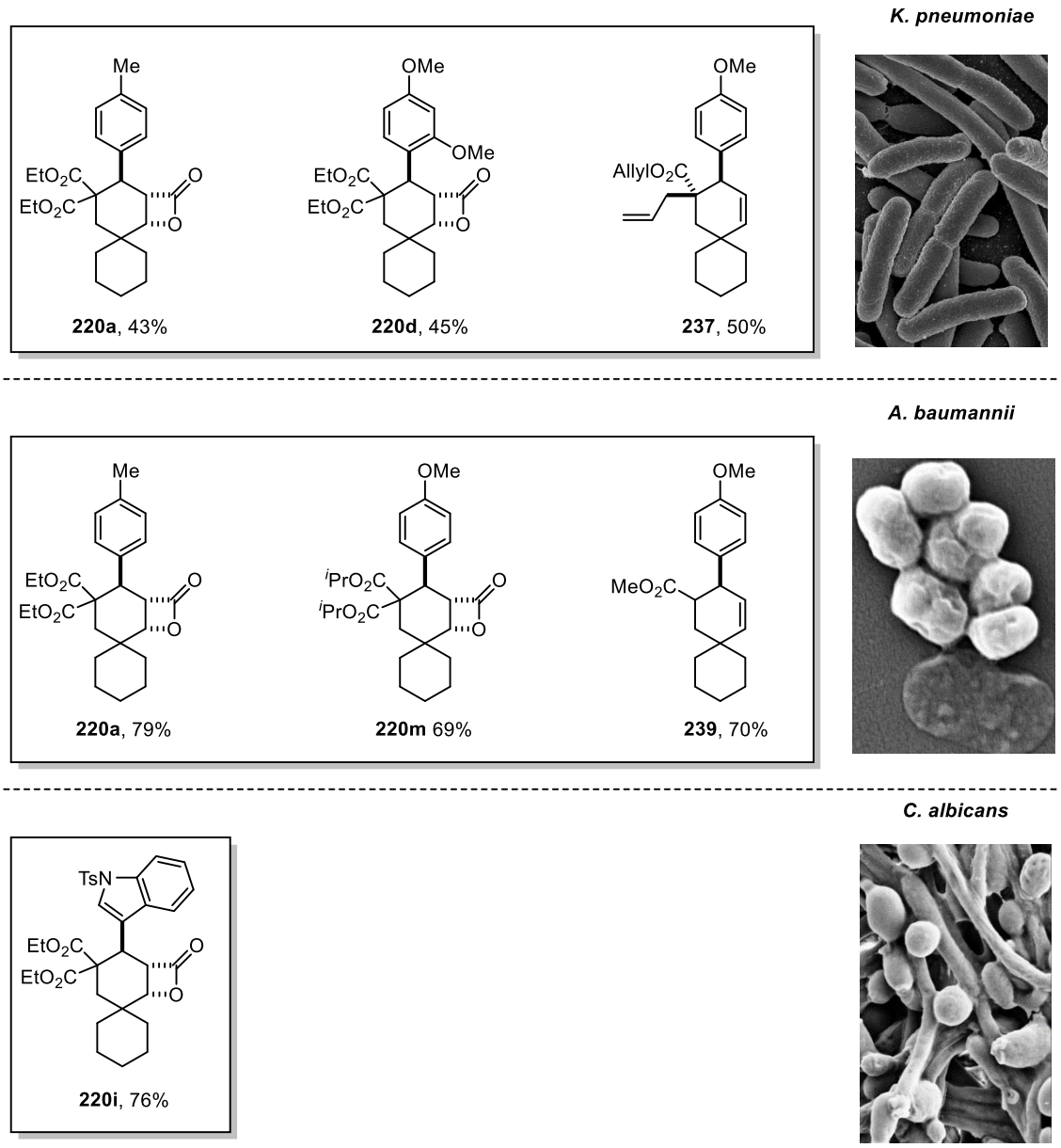
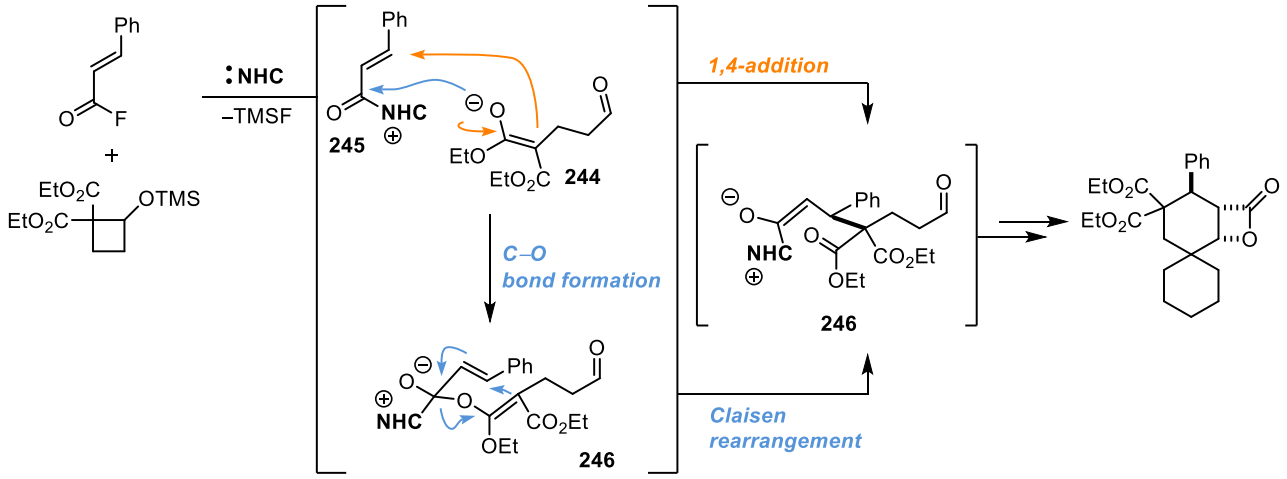


Figure 3.4. Antimicrobial activity of ß-lactones and derivatives represented as percentage inhibition at 32 µg/ml.

3.5 Mechanistic insights

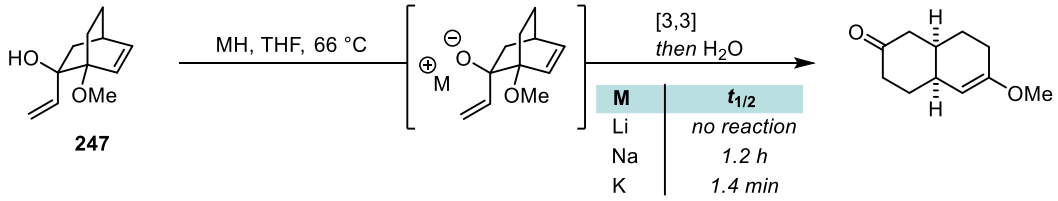
3.5 .1 Divergent mechanisms for initial C-C bond formation

While we envisage the (4+2) annulation to proceed *via O*-addition of enolate **244** to acyl azolium **245**, followed by anionic-oxy Claisen rearrangement (i.e. **246**→**247**), an alternate mechanistic scenario proceeding through *C*-centred 1,4-addition of enolate **244** to **245**, is plausible (Scheme 3.27).



Scheme 3.27. Plausible mechanisms for initial C-C bond construction.

To probe these mechanistic proposals, our attention turned to previous studies by Evans in which the effect of alkoxide counterions on the rate of the anionic oxy-Cope rearrangement was assessed (Scheme 3.28).[28] Evans demonstrated that a strongly coordinating lithium counterion failed to promote the reaction. When a sodium counterion was used, the rearrangement proceeded with a half-life ($t_{1/2}$) of 1.2 hours and finally, weakly coordinating potassium counterions allowed the rapid rearrangement of **247** ($t_{1/2}$= 1.4 minutes).

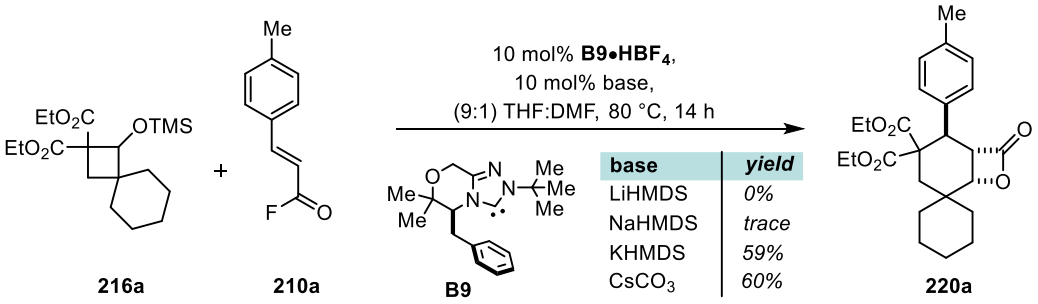


Scheme 3.28. Counterion effect on the rate of anionic oxy-Cope rearrangement.

With this in mind, the (4+2) annulation between **216a** and **210a** was carried out with variation of the counterion source,[29] and the reaction displayed a similar sensitivity to that observed in Evans' sigmatropic rearrangement. Tellingly, the reaction failed when lithium- and sodium-derived bases were used for carbene generation and when potassium and caesium derived bases were employed, the reaction proceeded smoothly (Scheme 3.29). We believe that these findings support a [3,3] sigmatropic rearrangement pathway, which is accelerated by weakly coordinating counterions.

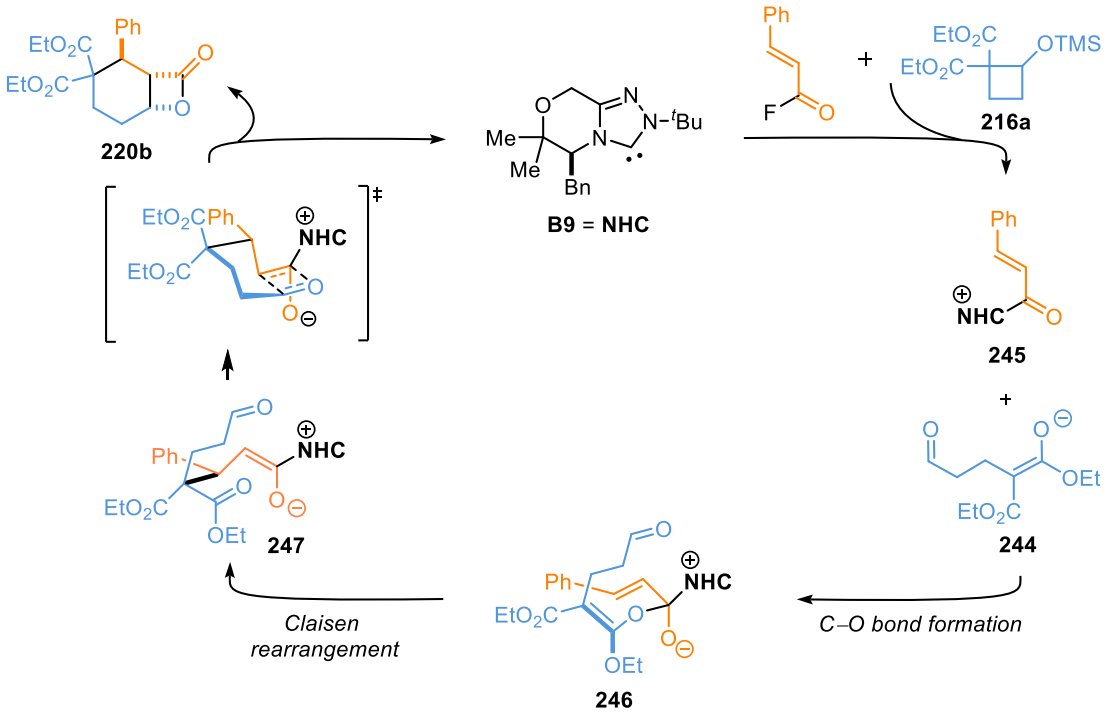
The effect of alkali metal counterions with respect to enolate reactivity[30] is in keeping with these mechanistic insights. Strongly associating counterions (i.e. lithium and sodium) sterically shield oxygen and therefore favour carbon-centred enolate reactivity. Conversely, weakly coordinating counterions (i.e. potassium and caesium) result in a more naked oxygen leading to increased reactivity at oxygen. Moreover, the reaction shows a preference for polar solvents which are capable of coordinating counterions and, therefore, would favour reaction at oxygen. Given that the reaction fails under conditions which would

support *C*-centred enolate reactivity and proceeds smoothly under conditions which support *O*-centered reactivity, we suspect that C-O bond formation and anionic oxy-Claisen rearrangement accounts for the initial C-C bond formation.



Scheme 3.29. Counterion effect on the yield of the (4+2) annulation.

Based on these observations, a complete mechanism for the (4+2) annulation is proposed (Scheme 3.30). The reaction is likely initiated by an NHC mediated desilylation/defluorination cascade which generates acyl azolium **245** and bifunctional enolate **244** upon retro-aldol opening of cyclobutane **216a**. Addition of the enolate **244** to the acyl azolium **245** then gives hemiacetal alkoxide **246** which undergoes anionic-oxy Claisen rearrangement, generating acyl azolium enolate **247**. Finally, an asynchronous (2+2) aldol/lacontonisation process[31] furnishes the β-lactone products **220** and regenerates the catalyst.

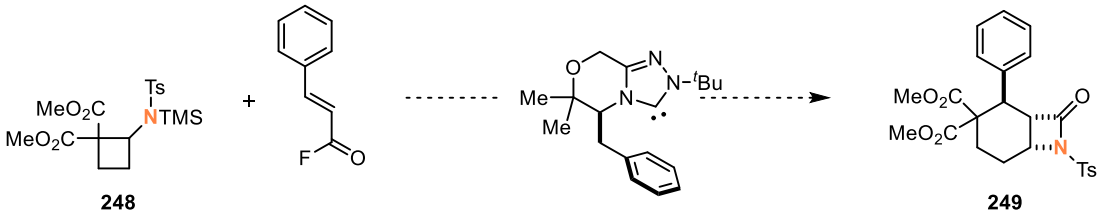


Scheme 3.30. Proposed mechanism of the (4+2) annulation.

3.6 Conclusions and outlook

Using a Lewis base approach, the first enantioselective (4+2) annulation of donor-acceptor cyclobutanes **216** has been realised. The NHC catalysed reaction with α,β-unsaturated acyl fluorides **210** generates densely functionalised cyclohexyl fused β-lactones **220** in excellent yield and with excellent stereochemical integrity (>20:1 d.r, most >98:2 d.r). The reaction is amenable to modest scale-up and the β-lactone products have extensive synthetic utility. Decarboxylative and ring-opening based derivatisations deliver heavily functionalised cyclohexanes, cyclohexenes, and quinolinones. Additionally, antimicrobial screening revealed some products and their derivatives exhibit promising activity against nosocomial pathogens *K. pneumoniae, A. baumannii and C. albicans.* Preliminary mechanistic investigations support the first *C-C* bond forming event proceeding through a *O-C* addition and anionic oxy-Claisen rearrangement pathway.

Future investigations will focus on translation of this reaction manifold to incorporate analogous nitrogen bearing DA-cyclobutanes (i.e. **248**) for the synthesis of β-lactams (i.e. **249**) (Scheme 3.31). If successful, we believe this methodology will provide access to a host of novel β-lactam products and thus support our research program surrounding the discovery of novel antimicrobial agents.



Scheme 3.31. Nitrogen bearing DA-cyclobutanes for the synthesis of β-lactams

Having developed a new NHC catalysed (4+2) annulation which offers remarkable utility, its application in total synthesis was pursued. Studies towards this end are detailed in the following chapters.

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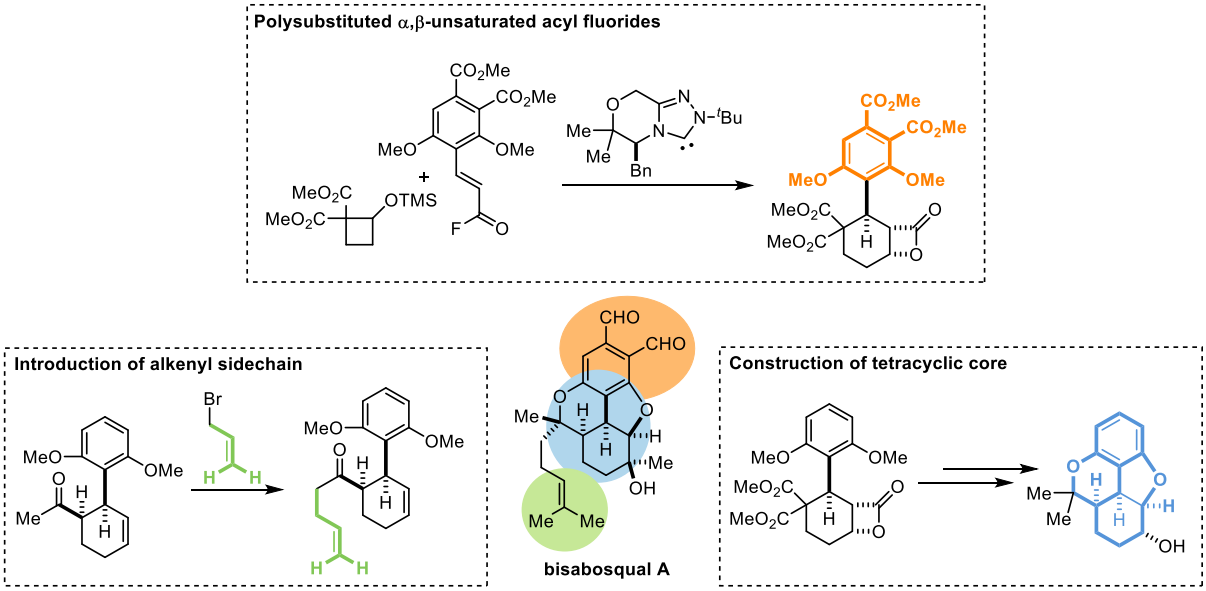
Chapter 4

Towards the synthesis of (+)-bisabosqual A

Examination of key strategies towards the synthesis of (+)-bisabosqual A are described in Chapter 3. The N-heterocyclic carbene catalysed (4+2) annulation of donor-acceptor cyclobutanes and α,β-unsaturated acyl fluorides is utilised to construct a cyclohexyl β-lactone which can be elaborated into the cis-cis fused tetracyclic core. Additionally, modification of the reaction substrates to facilitate incorporation of the penta-substituted aromatic motif and the alkenyl sidechain was examined.



4.1 Introduction

In 2001 Minagawa and co-workers isolated bisabosquals A-D from the culture broth of *Stachybotyrs* sp. RF-7260, a mould found growing on decaying tree leaves from coastal Japan (Figure 4.1).[1] Biological screening revealed that a suite of natural products that inhibit microsomal squalene synthases in *Saccharomyces cerevisiae* and *Candida albicans* (CA) were produced. Consequently, they exhibit broad spectrum anti-fungal activity *in vitro*, which is particularly true of bisabosqual A. Additionally, bisabosquals A-D inhibit mammalian squalene synthases from rat liver and HepG2 cells, and as such, have garnered interest for their use as antihypercholesteremic agents.

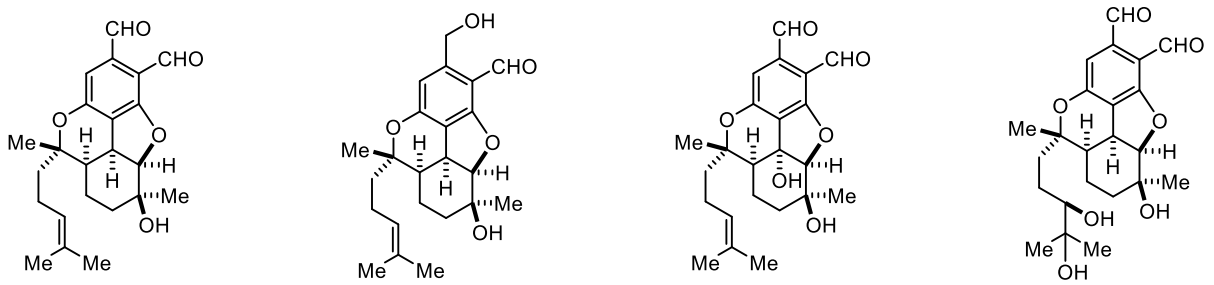
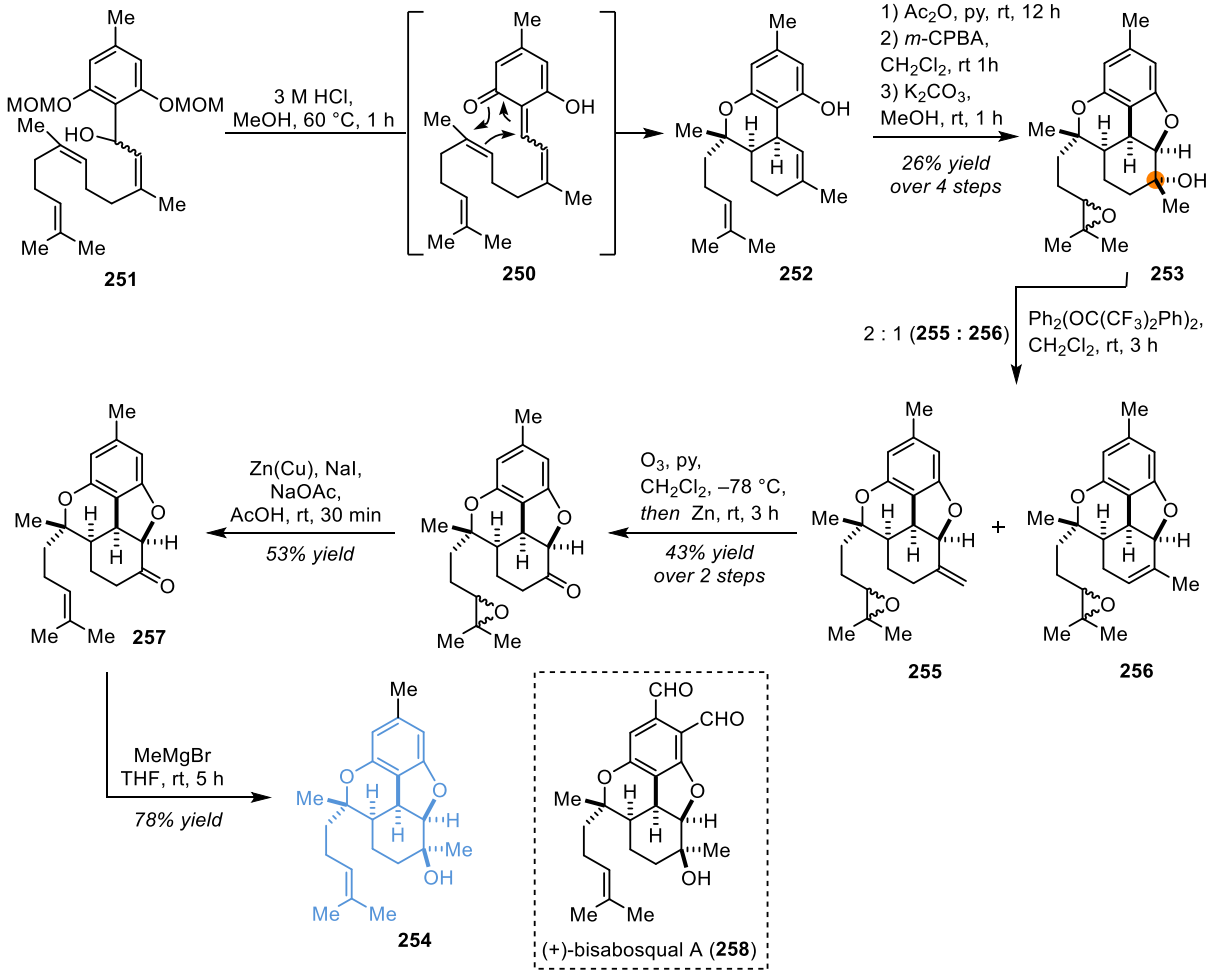


Figure 4.1. IC_{50} values against *Candida* albicans for bisabosquals A-D.

Structural elucidation was carried out using 2D NMR experiments and confirmed with crystallographic analysis of bisabosqual B.[2] The three fused 6-membered rings in the tetracyclic core of the bisabosquals resembles tetrahydrocannabinoids (THCs), however, in contrast to common THCs, the benzopyran and cyclohexane motifs are *cis*-fused. In fact, the entire hexahydrobenzofurobenzopyran architecture is unique to the bisabosqual natural products, although, several synthetic cannabinoid derivatives contain this motiff.[3] In terms of strategy, the tetracyclic core represents a significant synthetic challenge. Prospective routes must accommodate the formation of 5 contiguous stereocentres, including two challenging tertiary alcohols. To date, only one total synthesis of (±)-bisabosqual A has been reported, by Parker and co-workers in 2012,[4] however, a route for assembling the tetracyclic core has also been reported by the Snider group.[5]

4.1.1 Snider's synthesis of the tetracyclic core of the bisabosquals

In 2007, Snider and co-workers reported a biomimetic approach for the synthesis of the alkenyl substituted tetracyclic core of the bisabosquals (Scheme 4.1).[5] Notably, the synthesis utilises an inverse demand, hetereoatomic intramolecular Diels-Alder (IMDA) reaction of *ortho*-quinone methide **250**, accessed *via* hydrolysis and elimination of alcohol **251**. This powerful transformation forges the cyclohexane and fuses the benzopyran in a single step to give **252** with complete stereocontrol. Unfortunately, subsequent epoxidation occurred on the α-face, leading to the incorrect configuration of tertiary alcohol **253** after cyclisation of the pendant phenol. A series of functional group interconversions (**253**→**254**) were required to invert the tertiary alcohol stereocentre. Thus, elimination of alcohol **253** with Martin's sulfurane delivered exocyclic alkene **255** albeit as a 2:1 mixture of with regioisomer **256**. Next, ozonolysis of the required exocyclic alkene **255**, and subsequent reductive deoxygenation of the epoxide provided ketone **257**. Finally, addition of methylmagnesium bromide occurred with complete facial selectivity to furnish tertiary alcohol **254**, and in turn the tetracyclic core of the bisabosquals.



Scheme 4.1. Snider's synthesis of the tetracyclic core of the bisabosquals.

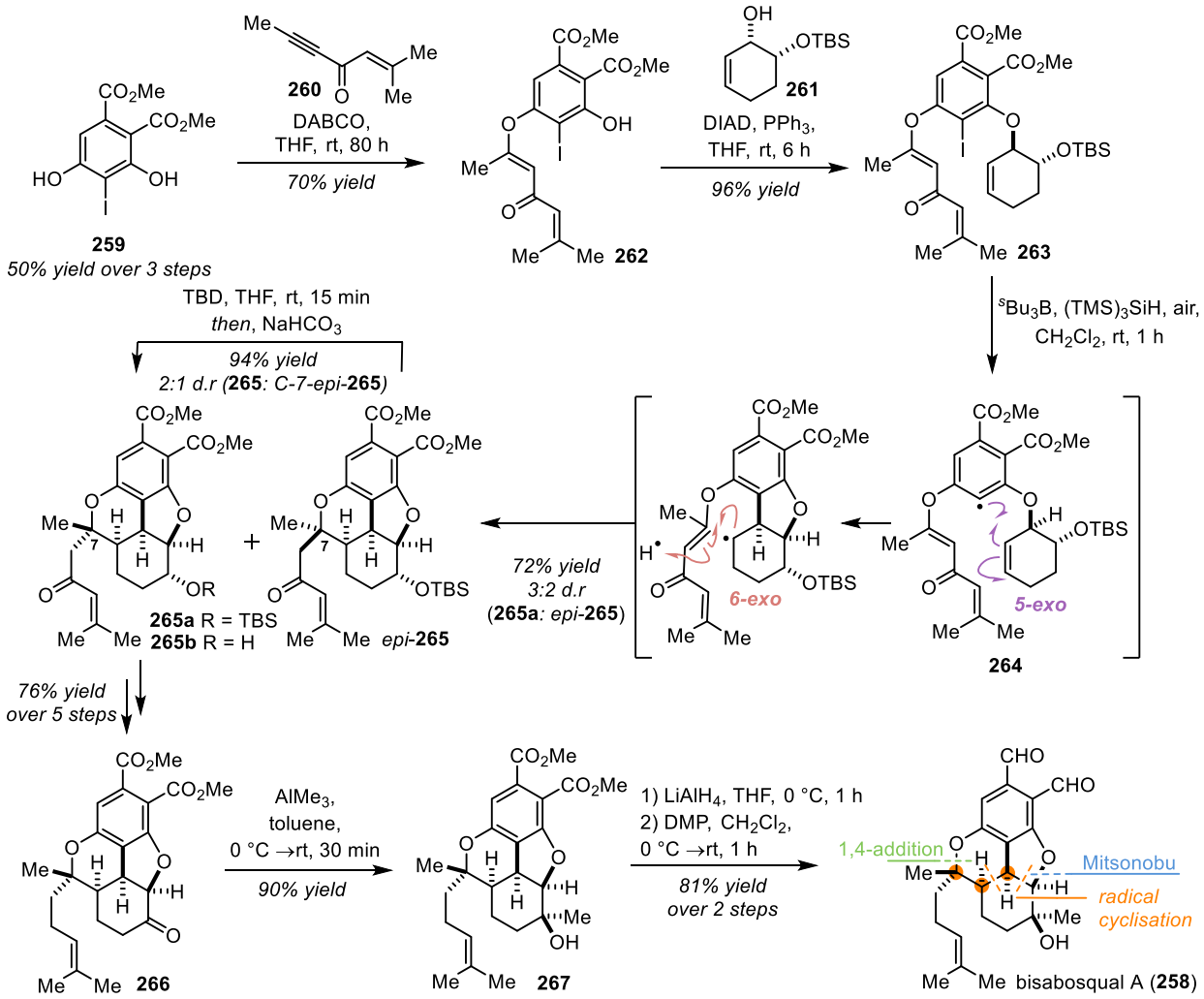
Despite a sequence of undesirable functional group interconversions to invert the tertiary alcohol stereocentre from **253**, Snider's strategy successfully generates the challenging tetracyclic core **254** with the correct stereochemical configuration It is probable that a total synthesis has not been realised through this strategy due to the potential challenges in achieving chemo- and, in particular, regioselectivity in the key IMDA reaction with the unsymmetrical and electron-poor aromatic fragment required for (+)-bisabosqual A (**258**).

4.1.2 Parker's total synthesis of (±)-bisabosqual A

Parker's reported synthesis of (±)-bisabosqual A (**258**) in 2012 represents the only successful total synthesis.[4] A convergent approach was employed, with fragments **259**, **260**, and **261** utilised to build the ether linkages and merge both the cyclohexane and aromatic motif (Scheme 4.2). Thus, a DABCO catalysed 1,4-addition of resorcinol **259** to ynone **260** provided phenol **262** before a Mitsonobu protocol with alcohol **261** furnished aryl iodide **263**. Next, aryl radical **264** is generated *via* treatment with tri-^{s}butylborane, which undergoes a tandem 5-*exo*-*trig*/6-*exo*-*trig* cyclisation cascade, thereby generating

the entire hexahydrobenzofurobenzopyran framework (i.e. **265**) in 72% yield after reductive trapping. Unfortunately, the desired isomer **265a** was formed alongside the C7 epimer *epi*-**265** in a 2:1 ratio, with limited epimerisation possible by treatment with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Next, a series of functional group interconversions to effect deprotection, oxidation, and deoxygenation were executed in excellent yield to provide ketone **266**. A diastereoselective addition of methyllithium then establishes the tertiary alcohol **267** with the correct configuration. Finally, global reduction of the phthalate esters followed by oxidation with Dess-Martin periodinane (DMP) provides the pthalaldehyde motif and ultimately, (±)-bisabosqual A (**258**).

Notably, Parker's synthesis features a powerful tandem radical cyclisation which constructs two rings and sets 3 stereogenic centres (two stereospecifically) in a single step. The authors suggest with simple adaptation, this sequence offers significant opportunity for an enantioselective synthesis and therefore analogue development. Despite this, no asymmetric variant or indeed any synthesis of the bisabosquals has been reported in the following 6 years.

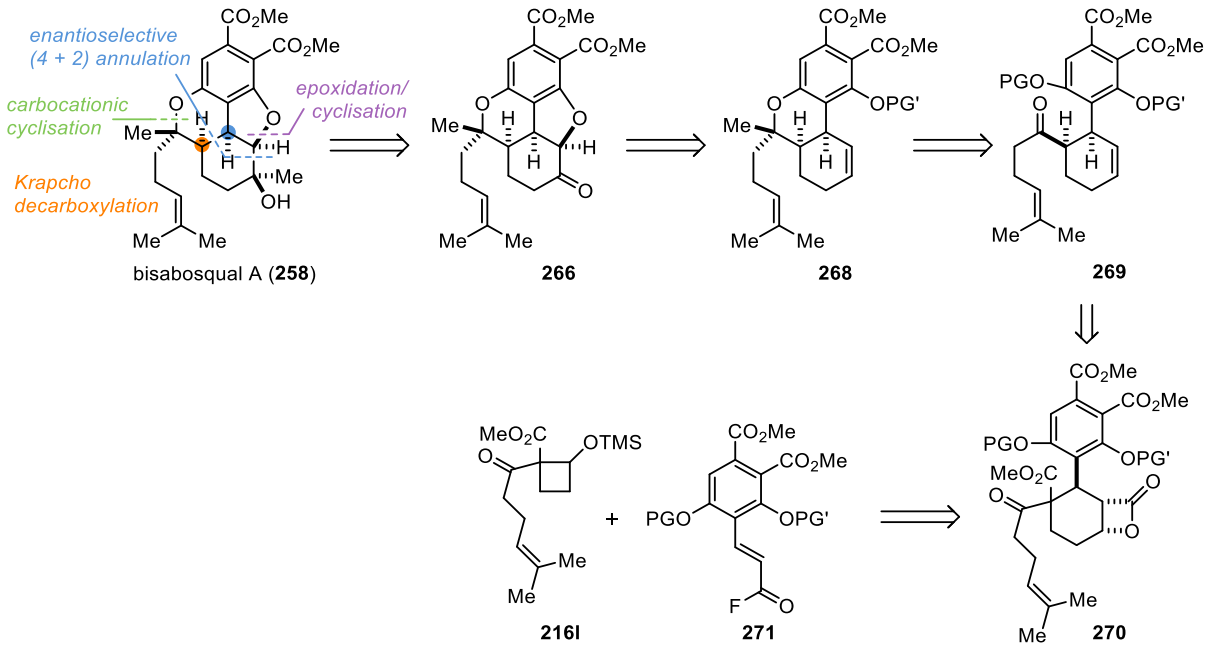


Scheme 4.2. Parker's total synthesis of (±)-bisabosqual A

4.2 Synthetic design and objectives

4.2.1 Retrosynthetic analysis of (±)-bisabosqual A

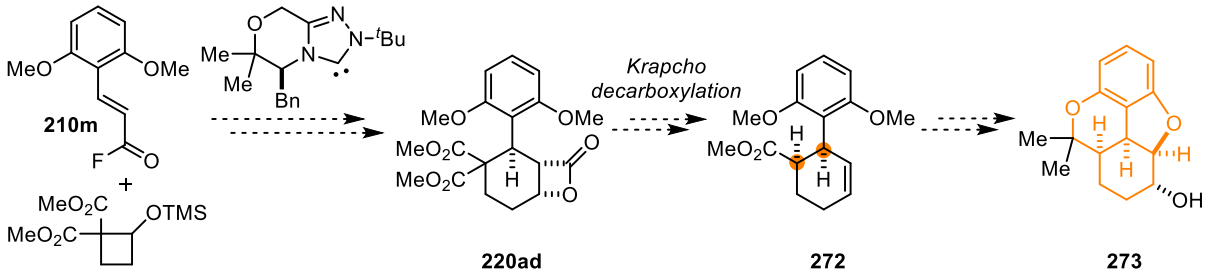
To address the lack of an enantioselective synthesis of (+)−bisabosqual A, and to showcase the previously introduced chemistry of NHCs with DA-cyclobutanes *(Chapter 3)*, a synthetic strategy to the natural product was developed. The approach stems from recognition that the previously developed (4+2) accesses highly enantioenriched and densely functionalised cyclohexyl β-lactones[6] which ,we believe, could be valuable substrates in the synthesis of the bisabosqual core. Thus, retrosynthetic analysis led us to propose a route to ketone **266**, a known precursor of bisabosqual A (**258**),[4] which would itself, be constructed *via* epoxidation and cyclisation from alkene **268** (Scheme 4.3).[5] In turn, alkene **268** could be obtained from ketone **269** exploiting Grignard addition/deprotection, and carbocationic cyclisation procedures reported by Trost[7] or Carreira.[8] Krapcho decarboxylation, as explored in *Chapter 3*, and concomitant thermal decarboxylation of β-lactone **270** was expected to provide ketone **269**.[9] Finally, the NHC catalysed (4+2) annulation would give access to β-lactone **270** after coupling of a suitable α,β-unsaturated acyl fluoride (i.e. **271**) and donor-acceptor (DA) cyclobutane **216l**.[6c] To enable the proposed enantioselective synthesis of (+)-bisabosqual A, we wished to first examine the viability of our general strategy through several model studies.



Scheme 4.3. Proposed retrosynthesis of (+)-bisabosqual A (**258**).

4.2.2 Model study 1: Construction of the cis-cis fused tetracyclic core

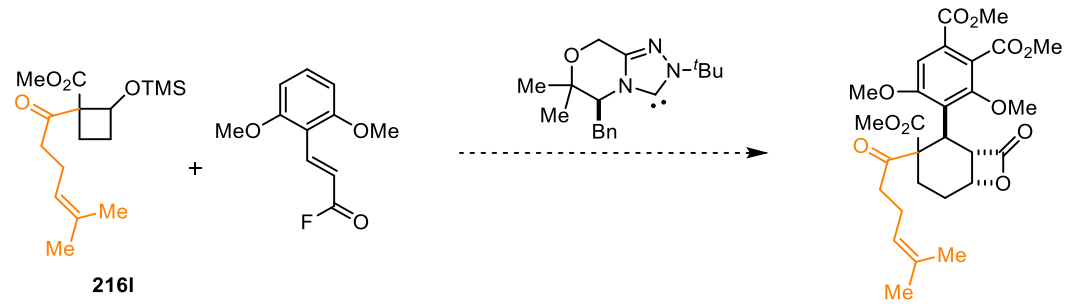
Our first endeavour aimed to establish a route for constructing the *cis-cis* fused tetracyclic core of the bisabosquals (Scheme 4.4). Given that our earlier methodological studies did not examine 2,6-disubstituted cinnamoyl fluorides (i.e. **210m**), their viability in the (4+2) annulation needed to assessed. Presuming the synthesis of proposed the proposed model β-lactone **220ad** is viable, its elaboration to the tetracyclic core **272** would be examined. Central to our strategy is a Krapcho decarboxylation which establishes the stereochemical configuration for the construction of *cis*-fused benzofuran ring. From **273** we anticipate the remaining rings and stereocentres can be formed by exploiting procedures established previously by Snider and Parker.



Scheme 4.4. Proposed construction of the tetracyclic core of the bisabosquals.

4.2.3 Model study 2: β-Keto ester derived DA-cyclobutanes

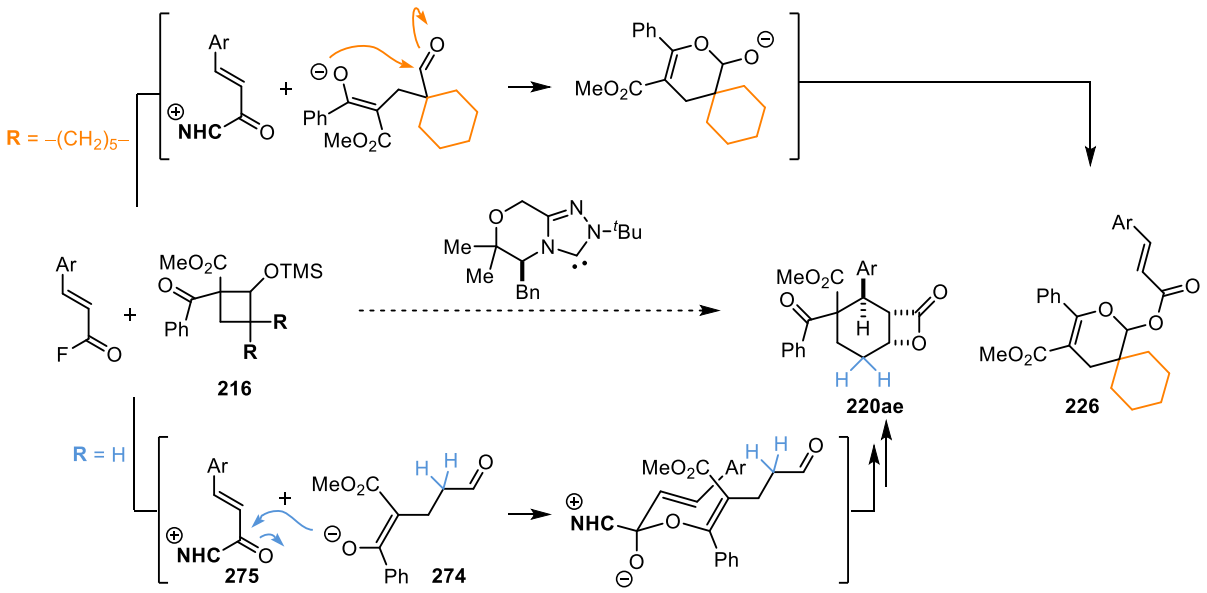
Central to our second investigation is assessing the suitability of β-keto ester derived DA-cylobutanes in the (4+2) annulation. If found to be valuable substrates, we anticipate that the application of an appropriate DA-cyclobutane (i.e. **216l**) would allow convenient early stage incorporation of the alkenyl side chain (Scheme 4.6).



Scheme 4.5. Examination of β-keto ester derived DA-cyclobutanes

Previously it was shown *(see Chapter 3, section 3.3.3)* that when β-ketoester derived DA-cylobutane **216** (R = $-(CH_2)_5-$) was employed in the reaction, lactol **226** was isolated as the sole product (Scheme 4.6).[10] Although this reaction pathway was non-productive, we reasoned that with DA-cylobutane **216** (R = H), the absence of Thorpe-Ingold effects, introduced by spirocyclic annulation, should disfavour lactolisation

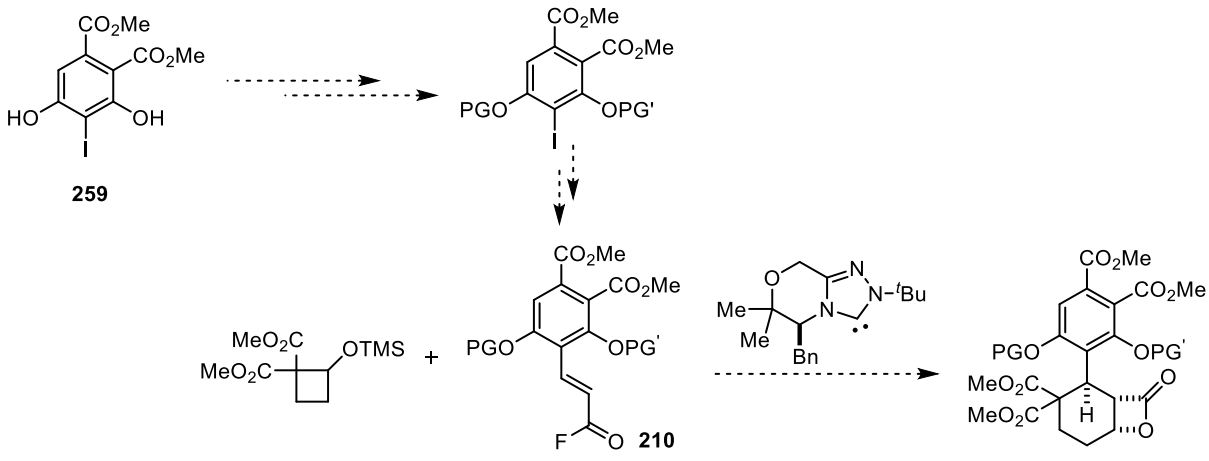
of bifunctional enolate **274**. Thus, *O*-addition of enolate **274** to acyl azolium **275** and subsequent anionic oxy Claisen (AOC) rearrangement would predominate, thereby leading to the desired β-lactone (i.e **220ae**)



Scheme 4.6. Lactolisation of vs *O*-addition and AOC.

4.2.4 Model study 3: Pentasubstituted α,β-unsaturated acyl fluorides

Two key enquires compose the final model investigation; the first relates to the viability of preparing unsymmetrical, pentasubstituted α,β-unsaturated acyl fluorides (i.e. **210**), while the second pertains to the suitability of such substrates in the requisite (4+2) annulation (Scheme 4.7). Resorcinol **259** utilised by Parker and co-workers, represents a potential source for the aromatic fragment. We anticipate that an orthogonal protecting group strategy may be required to enable regioselective formation of the benzopyran and benzofuran rings later in the prospective synthesis.

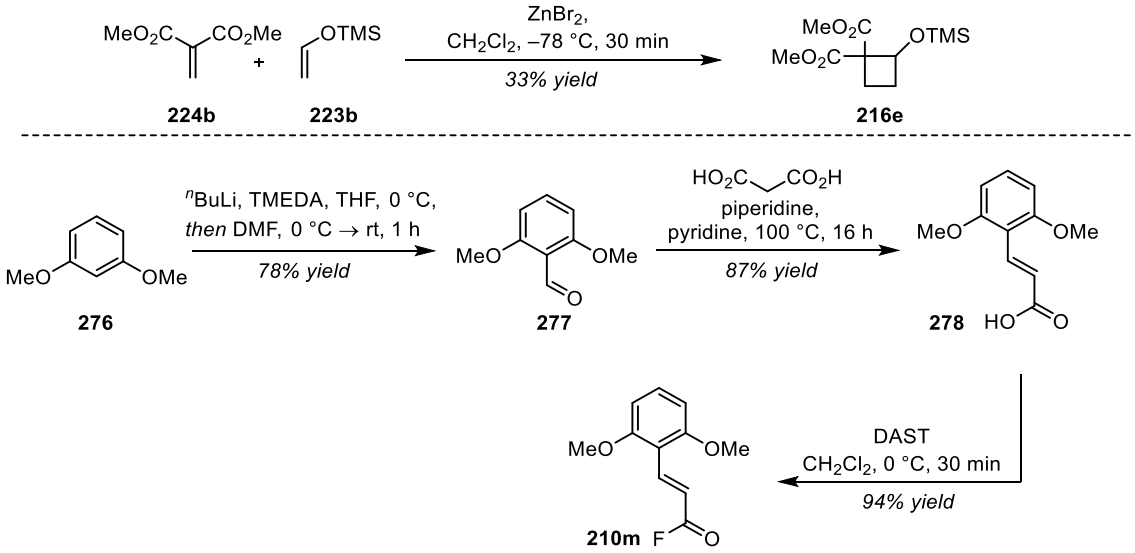


Scheme 4.7. Examination of pentasubstituted α,β-unsaturated acyl fluorides.

4.3 Model study 1: Assembly of the *cis-cis* fused tetracyclic core

4.3.1 Synthesis and reactivity of 2,6-disubstituted acyl fluorides

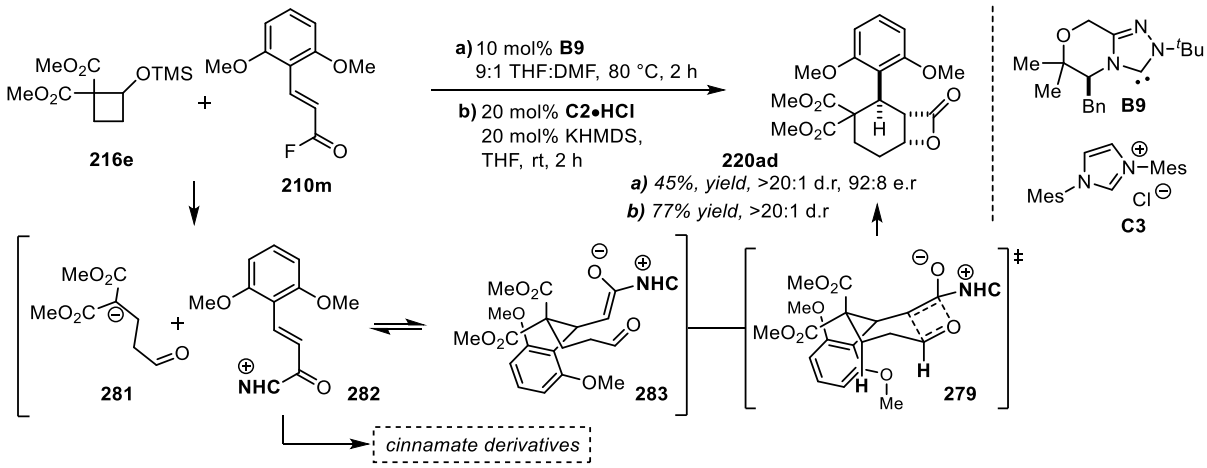
Studies commenced with the synthesis of model DA-cylobutane **216e** and α,β-unsaturated acyl fluoride **210m.** To this end, cyclobutane **216e** was prepared as described previously *(see Chapter 3, section 3.3.1)* from a (2+2) cycloaddition of methylene malonate **224b** and enol ether **223b** mediated by zinc bromide $ZnBr_2$ (Scheme 4.8).[11] In regards to the acyl fluoride, lithiation of 1,3-dimethoxybenzene (**276**) and subsequent formylation with *N,N*-dimethylformamide[12] gave access to 1,3-dimethoxybenzaldehyde (**277**) in 78% yield. Next, Doebner-modified Knoevenagel condensation provided α,β-unsaturated acid **278**[13] before fluorination with diethylaminosulfur trifluoride (DAST)[14] delivered the desired α,β-unsaturated acyl fluoride **210m** in 94% yield.



Scheme 4.8. Synthesis of DA-cyclobutane **216e** and α,β-unsaturated acyl fluoride **210m.**

With 2,6-dimethoxy substituted acyl fluoride **210m** in hand, its viability in the NHC catalysed step was assessed through annulation with DA-cyclobutane **216e.** When these substrates were exposed to NHC **B9**, β-lactone **220ad** was obtained in 45% yield, as a single diastereomer and with 92:8 e.r (Scheme 4.9a). In contrast, 2,4-dimethoxy-substituted acyl fluorides were shown to give the corresponding, β-lactone in comparatively greater yield (83%) and enantioselectivity (98:2 e.r) *(see Chapter 3, section 3.3.3)*, thus highlighting the sensitivity of the reaction to steric factors. In regard to the decreased yield observed here, ^{1}H NMR analysis of the crude reaction mixture indicated the presence of multiple cinnamate derived side-products.

It is possible that the 2,6-disubstituion of the aryl group introduces steric interactions in the transition state **279**, therefore slowing the asynchronous (2+2) aldol/lactonisation process (**283**→**220ad**).[15] Given that the *O*-addition and Claisen rearrangement sequence ([**281**+**282**]→**283**) is reversible, this scenario may favour side reactions of acyl azolium **282** which leads to unreactive cinnamate derived products and therefore erosion of yield. The reaction was also conducted with achiral catalyst **C3**, and a similar but less pronounced decrease in yield (73%) was observed (Scheme 4.9b). Due to the higher yield, and ready availability of the non-chiral NHC **C3**, racemic β-lactone **220ad** was used in the subsequent model investigations.



Scheme 4.9. (4+2) Annulation of α,β-unsaturated acyl fluoride **210m**.

The ^{1}H NMR spectrum of β-lactone **220ad** contained the three required methine signals between 5.2 and 3.8 ppm corresponding to H^a, H^b and H^c, however, the chemical shifts and coupling constants were, in part, inconsistent with analogous signals in 2-methoxy substituted β-lactone **220t** (Figure 4.2). The most downfield signal in **220t** corresponds to the β-lactone proton $H^{c'}$. In the case of 2,6-dimethoxy substituted **220ad**, the analogous H^c was assigned to the second most downfield methine signal at 4.85 ppm due to observed coupling to both methine signals and a methylene unit (as observed in COSY NMR). Given that the doublet of doublets at 3.85 ppm signal couples to H^c and additionally, a methylene unit, it was assigned as H^b. Consequently, H^a was assigned to the most downfield methine signal, a narrow doublet at 5.20 ppm. Data from ^{13}C NMR and IR analysis were also in agreement with this assignment and supported the presence of a β-lactone.

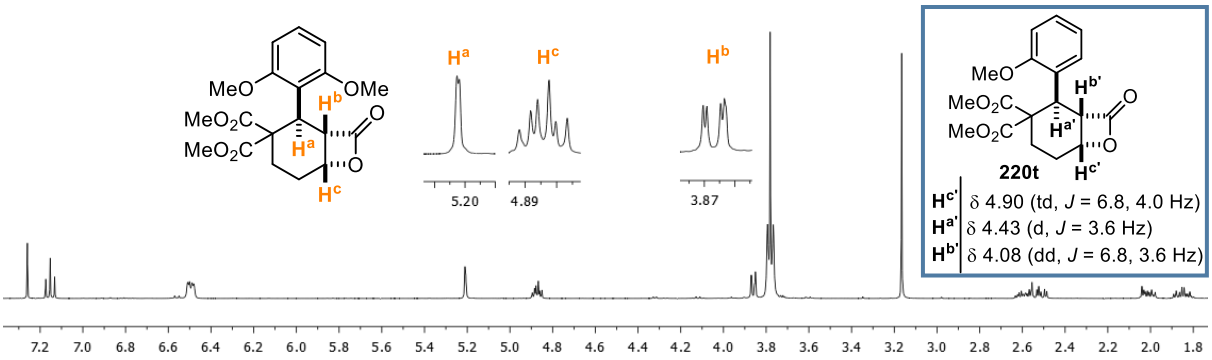


Figure 4.2. ^{1}H NMR spectrum of ß-lactone **220ad** in $CDCl_3$ (400 MHz) with **220t** shown for comparison.

In regard to β-lactone **220ad**, the significant downfield shift (δ 5.20 ppm) and decreased coupling constant (J = 1.5 Hz) of benzylic proton H^a compared to the related mono-methoxy substituted product **220t** ($H^{a'}$ δ 4.43 ppm, J = 3.6 Hz) prompted us to question the relative stereochemical arrangement between the β-lactone and aromatic substituent. Fortunately, crystals of **220ad** sufficient for X-ray diffraction analysis were grown, and the corresponding crystal structure was obtained (Figure 4.3), confirming that the structure and relative stereochemistry was consistent with previously prepared β-lactone products. Inspection of the crystal structure reveals the proximity of H^a to the neighbouring carbonyl and aromatic *p*-orbitals. It is probable that the steric bulk introduced by the 2,6-dimethoxy substituted aromatic forces the cyclohexane to adopt a conformation whereby H^a has greater overlap with these neighbouring *p*-orbitals. In this scenario, increased anisotropic deshielding of H^a then explains the unusually large chemical shift, while the dihedral angle between H^a and H^b is close to 90° (90.42(9)°), leading to the lower coupling constant.

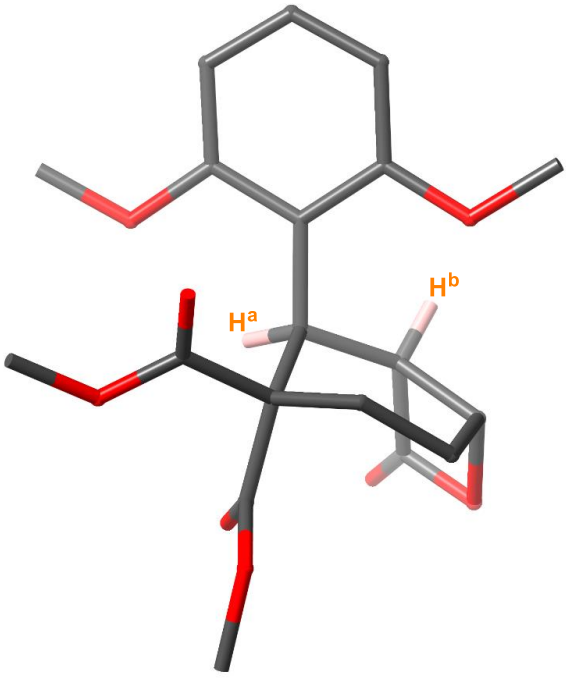
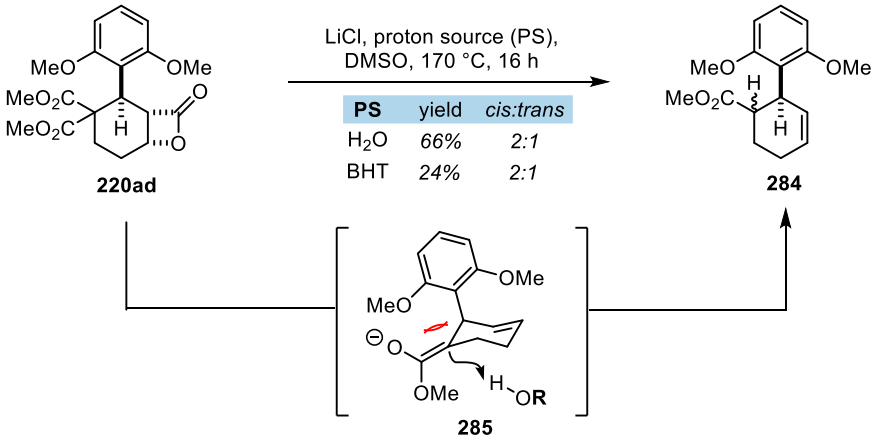


Figure 4.3. [1] X-ray crystal structure of ß-lactone **220ad**.

4.3.2 Decarboxylation of β-lactone 220ad

With β-lactone **220ad** in hand, it was treated with LiCl in DMSO at 170 °C following the procedures developed in *Chapter 3*[16] (Scheme 4.10). Both thermal and Krapcho decarboxylation proceeded as expected to give monoester **284** in 66% yield, albeit with modest diastereoselectivity (2:1) favouring the required *cis* configuration. In related work, Sugai and co-workers reported that diastereoselectivity of the Krapcho decarboxylation of cyclobutyl geminal diesters can be improved using phenol based proton sources.[17] We reasoned that a bulkier phenol should favour protonation of enolate **285** on the opposite face to the aryl substituent and therefore increase *cis* selectivity. Unfortunately, when butylated hydroxytoluene (BHT) was employed, the yield of monoester **284** decreased (24%) and the diasteroselectivity was unchanged (2:1).

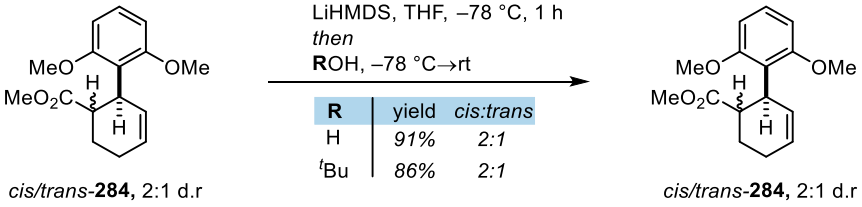


Scheme 4.10. Krapcho decarboxylation of β-lactone **220ad** with water and BHT.

It has been shown previously that closely related *cis*-monoesters (i.e. *cis*-**284**) are amenable to epimerisation to the *trans*-arrangement by treatment with NaOMe in refluxing methanol, [7,18] suggesting that *trans*-monoester **284** is the thermodynamic product and *cis*-monoester **284** is the kinetic product. These findings are consistent with the dealkoxycarbonylation of cyclohexyl *gem*-diesters reported by Krapcho and co-workers.[19]

Given these observations, we proposed that generation of enolate **285** and quenching at low temperature may enable epimerisation to the kinetic product. To probe this scenario, enolate **285** was generated directly from a *cis/trans* mixture of monoester **284** using lithium bis(trimethylsilyl)amide (LiHMDS) and subsequently quenched at low temperature (Scheme 4.11). In the event, this did not alter the diastereomeric ratio (2:1 *cis/trans*) of monoester **284** when either water (R = H) or the bulkier *tert*-butanol (R = ^{t}Bu) were used as the quenching agent. Despite modest diastereoselectivity, *cis*-monoester

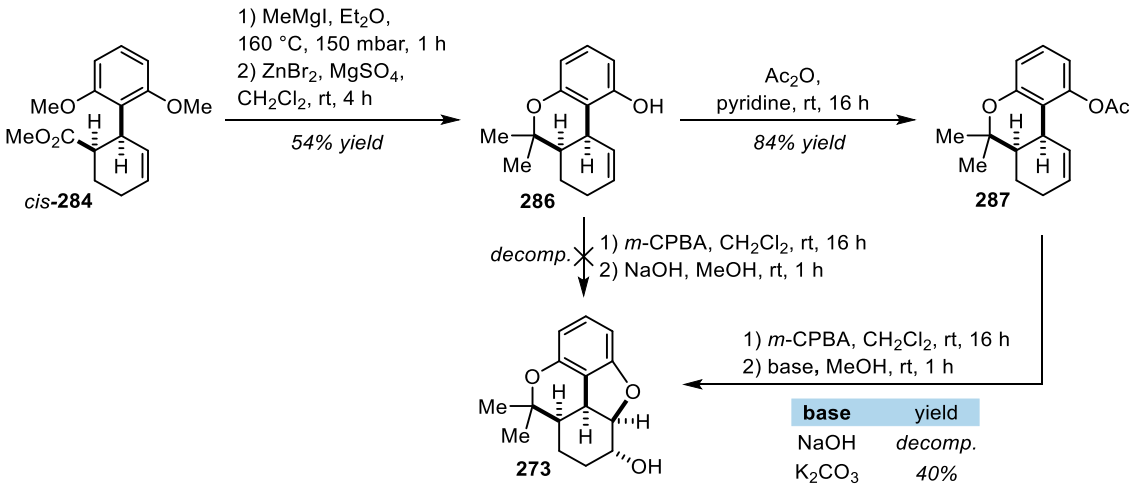
284 and *trans*-monoester **284** were separable by flash column chromatography, which was sufficient for the subsequent studies.



Scheme 4.11. Krapcho decarboxylation of ß-lactone **220ad**.

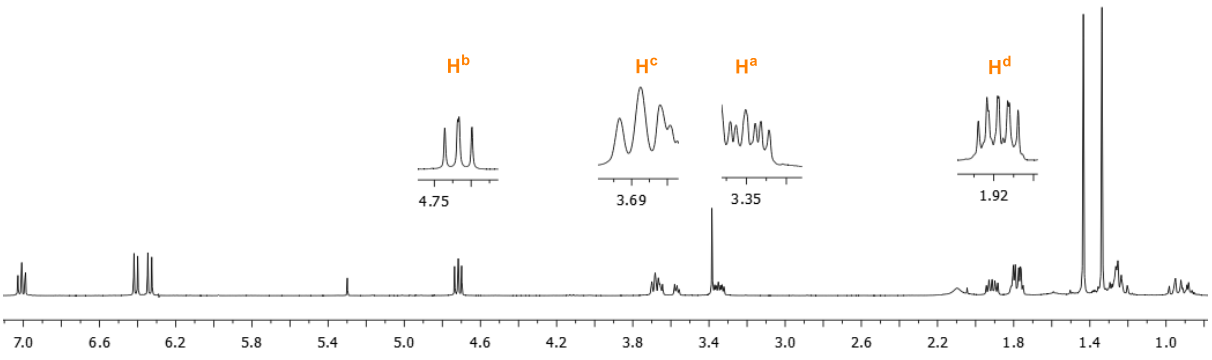
4.3.3 Synthesis of the tetracyclic core

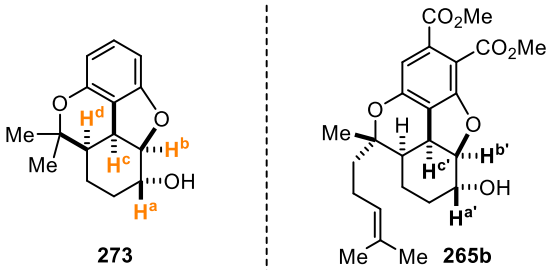
With *cis*-**284** in hand, it was subjected to a two-step procedure developed previously by Carriera[7] which effects methylation, aryl ether deprotection, and carbocationic cyclisation in the synthesis of Δ^9-tetrahydrocannabinol. Thus, after treatment of *cis*-**284** with methylmagnesium bromide and heating, followed by addition of zinc bromide, the benzopyran ring was formed and, *cis*-*cis*-fused hexahydrobenzopyran **286** was obtained in 54% yield (Scheme 4.12). Unfortunately, direct epoxidation and cyclisation of **286** with *meta*-chloroperbenzoic acid (*m*-CPBA) and sodium hydroxide (NaOH)[5] resulted in rapid decomposition. In Snider's synthesis of the tetracyclic core of bisabosqual A, instability and decomposition of similar materials was observed, an issue which could be resolved by acetylation of the phenol prior to epoxidation (see Scheme 4.1).[5] Thus, following Snider's procedures, acetylation of **286** with acetic anhydride provided acetate **287** in 84% yield, and epoxidation/cyclisation was attempted. Unfortunately, when NaOH was used to mediate the cyclisation step, decomposition was again observed. Concerned that hydroxide was leading to premature cleavage of the epoxide, the reaction was conducted with a milder base. Pleasingly, when potassium carbonate (K_2CO_3) was employed, closure of the benzofuran ring was successful, with the desired tetracyclic alcohol **273** isolated in 40% yield.



Scheme 4.12. Construction of hexahydrobenzofurobenzopyran **273**.

The structure of tetracycle **273** was confirmed by spectroscopic analysis and with comparison to Parker's related material **265b.** Comparison of the ^{1}H NMR spectrum of **273** to the starting cyclohexene **287** showed the loss of two alkene protons and the signal at 2.29 ppm corresponding to the acetate methyl group. Most tellingly, the ^{1}H NMR spectrum of the product contained 3 resonances between 4.8 and 3.3 ppm, each integrating to one proton which is indicative of the three labelled methine protons (Figure 4.4). The most downfield of these signals (4.72 ppm), has a chemical shift which is suggestive of deshielding by the adjacent ether oxygen in addition to ring strain in the benzofuran and, therefore, was assigned as H^{b}. This doublet of doublets couples (based on coupling constant and COSY NMR) to the triplet at 3.35 ppm in addition to a methine signal at 1.91 ppm, which were assigned as H^{b} and H^{d} respectively. This triplet in turn couples (based on COSY NMR) to the overlapping doublet of doublet of doublets at 3.35 ppm, which couples also to the methylene signal at 1.92 ppm, and was therefore assigned to H^{a}. The chemical shift of this signal is indicative of deshielding by the adjacent alcohol oxygen. Comparison of the ^{1}H NMR data for **273** to that derived from Parkers material **265b**, reveals a close relationship in both chemical shift, and coupling constant, between the related methine protons $H^{a}/H^{a'}$, $H^{b}/H^{b'}$, and $H^{c}/H^{c'}$ therefore supporting this assignment. In addition, the ^{13}C NMR data are entirely consistent with this assignment while IR analysis (br 3400 cm^{-1}), as well as the broad singlet at 2.10 ppm in the ^{1}H NMR, are supportive of the presence of a hydroxyl proton.





273 **265b**

Proton	This work		Parker's tetracycle	
	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)
H^{b} or $H^{b'}$	4.72	7.8, 7.1	4.90	8.2, 7.0
H^{c} or $H^{c'}$	3.68	7.1	3.65	7.2
H^{a} or $H^{a'}$	3.35	11.9, 6.8, 4.8	3.33	12.0, 7.1, 4.3

Figure 4.4. ^{1}H NMR of hexahydrobenzofurobenzopyran **273** and **265b** in $CDCl_3$ (400 MHz).

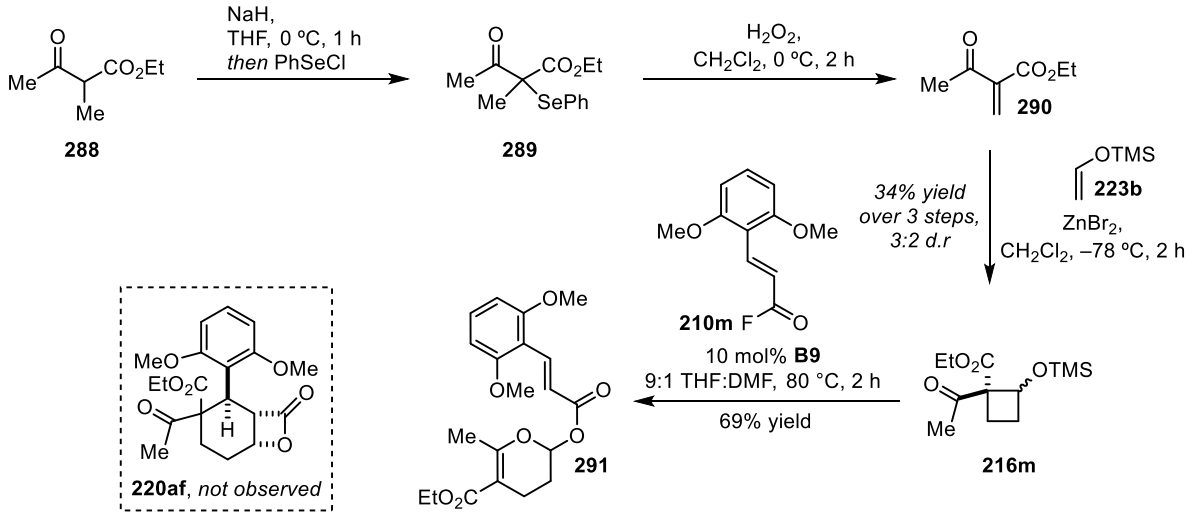
These model studies have demonstrated that 2,6-disbustituted cinnamoyl fluorides (i.e. **210m**) are valuable substrates for the NHC catalysed (4+2) annulation with DA-cyclobutane **216e**. Pleasingly, the β-lactone product **220ad** was utilised in the assembly of the hexahydrobenzofurobenzopyran core **273**, which was achieved in 10 steps from commercially available starting materials, therefore supporting the viability of a synthesis of the natural product. Inspired by the success of this sequence, our efforts focused next on establishing β-keto ester derived DA-cyclobutanes and examining their utility for installation the alkenyl side chain.

4.4 Model study 2: ß-Keto ester derived DA-cyclobutanes

4.4.1 Synthesis and reactivity of ß-ketoester derived DA-cyclobutane 216m

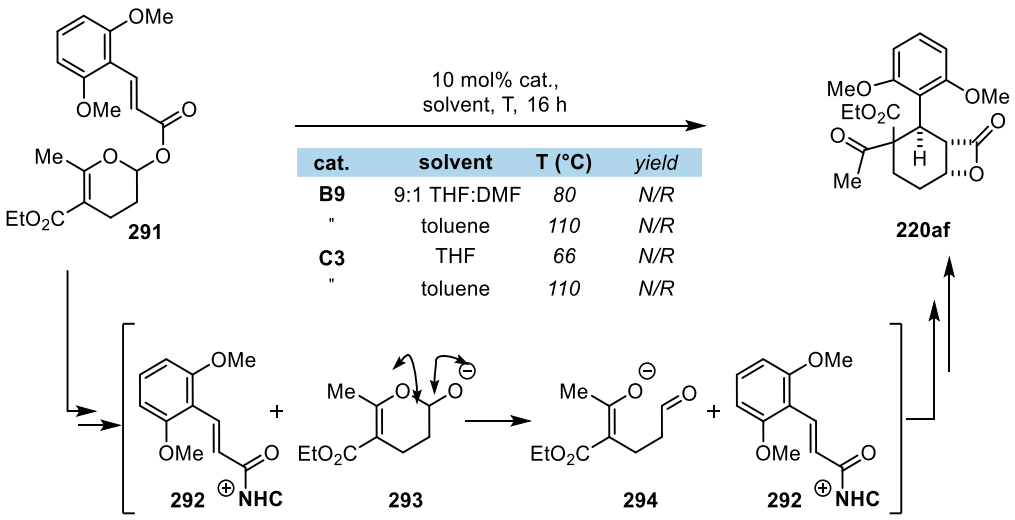
Studies commenced with identification of β-keto ester derived DA-cyclobutane **216m** as a suitable model substrate (Scheme 4.13). Although the required alkenyl sidechain is absent, **216m** serves as a suitable surrogate to investigate if the (4+2) annulation of β-keto ester-derived DA-cyclobutanes lacking spirocyclic annulation, can deliver β-lactone products. Starting from β-ketoester **288**, deprotonation with sodium hydride (NaH) and quenching with phenylselenium chloride (PhSeCl) provided selenide **289** which underwent selenoxide elimination to furnish methylene acetoacetate **290**.[20] Next, procedures described previously for the (2+2) cycloaddition with enol ether **223b** were transferred successfully, with a diastereomeric mixture of DA-cyclobutane **216m** obtained in 34% yield over 3 steps.

As retro-aldol ring-opening of DA-cyclobutanes in the (4+2) annulation ablates any stereochemical information, **216m** was employed as a mixture of stereoisomers. Unfortunately, when **216m** was treated with NHC **B9** in the presence of acyl fluoride **210m**, only the previously observed lactolisation pathway occurred, with lactol **291** isolated in 69% yield. Furthermore, no evidence of desired the β-lactone **220af** could be observed by ^{1}H NMR analysis of the crude reaction mixture. Therefore, it is likely that for reasons discussed previously *(see Chapter 3, section 3.3.3)*, β-ketoester derived DA-cyclobutanes are not viable in this reaction.



Scheme 4.13. Synthesis and reactivity of DA-cyclobutane **216m**.

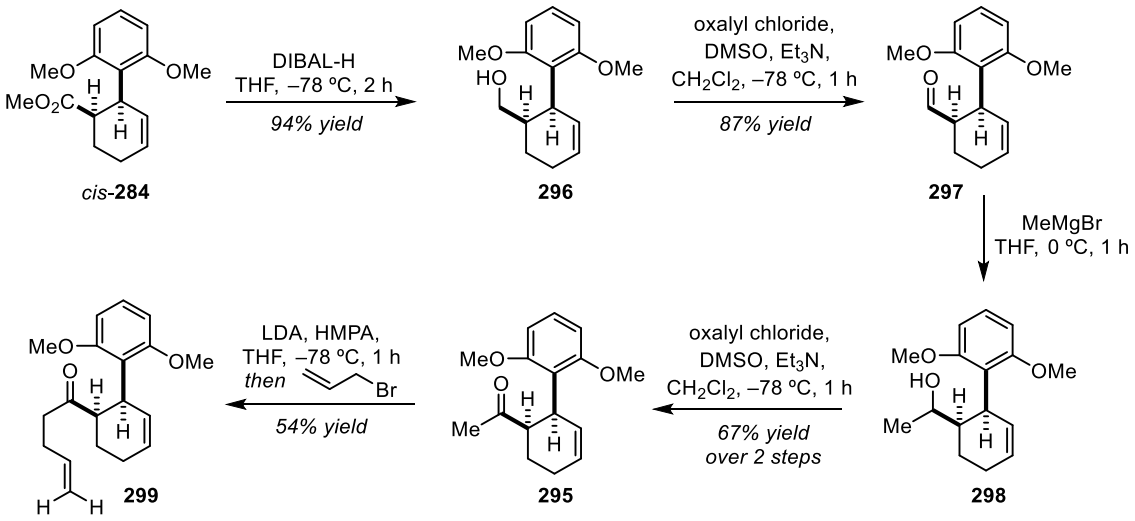
Whilst the desired reaction pathway could not be realised, we recognised that lactol **291** itself offers opportunity for NHC-mediated cyclisation, as activation of ester substrates by NHC addition is well studied.[21] Specifically, we proposed that NHC addition and fragmentation of lactol **291** could regenerate α,β-unsaturated acyl azolium **292** and hemiacetal alkoxide **292**, which may then reform enolate **294** (Scheme 4.14). Thus, it may be possible to effect the synthesis of β-lactone **220af** from lactol **291** using more forcing conditions. To investigate this scenario, lactol **291** was resubjected to the original conditions, however, no reaction was observed. To promote conversion of the substrate,, the reaction was conducted in refluxing toluene, however, again, the starting material was reisolated unchanged. Given the apparent stability of lactol **291**, we proposed that a more nucleophilic catalyst may be required to facilitate fragmentation, however, no reaction occurred upon treatment of this substrate with the more nucleophilic **C3** in either refluxing THF or toluene.



Scheme 4.14. NHC catalysed annulation of lactol **291**.

4.4.2 Alkylation strategy for incorporation of the alkenyl side-chain

Given the lack of viability of DA-cyclobutanes (and indeed lactols) containing β-ketoesters, a new strategy was required to install the alkenyl side chain. An alternate route was proposed, whereby a series of routine transformations using *cis*-monoester-**284** would provide access to ketone **295**, and subsequently allow incorporation of an alkenyl fragment through alkylation (Scheme 4.15). To this end, reduction of *cis*-**284** with DIBAL-H proceeded smoothly to give alcohol **296** before Swern oxidation gave the corresponding aldehyde **297**. Next, addition of methyl magnesium bromide (MeMgBr) provided the secondary alcohol **298** before a second Swern oxidation furnished the desired ketone **295**. To investigate the suitability of alkylation, ketone **295** was treated with lithium diisopropyl amide before the addition of a suitable alkenyl sidechain surrogate (allyl bromide).[22] To our delight, the alkylation proceeded without event, and ketone **299** was obtained in 54% yield.

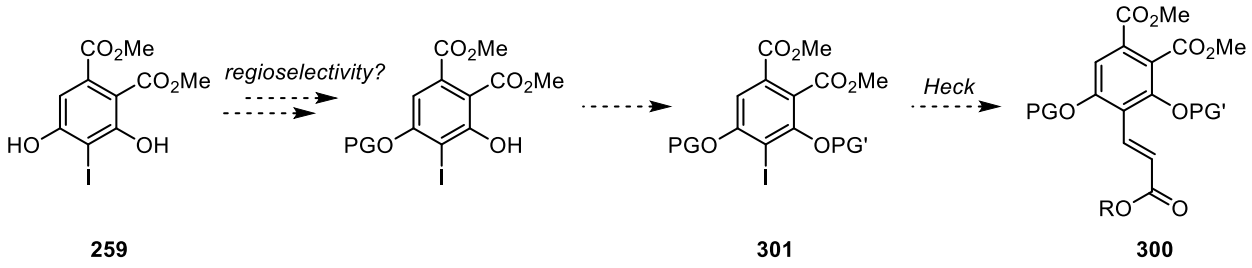


Scheme 4.15. Incorporation of the alkenyl sidechain.

Although attempts to implement β-ketoester derived DA-cyclobutane **210m** in the (4+2) annulation were unsuccessful, an alternate strategy to install the alkenyl sidechain was realised. While this strategy was quite step intensive, at this point no attempts to revise the sequence were made, although many obvious strategies to decrease the step count exist. After the success of the first two model studies, attention was directed to the synthesis of a suitably substituted α,β-unsaturated acyl fluoride and its reactivity in the NHC catalysed (4+2) annulation.

4.5 Model study 3: Pentasubstituted α,β-unsaturated acyl fluorides

Careful consideration of the aromatic fragment **259** used in Parkers synthesis of bisabosqual A, led to the development of a modified route to pentasubstituted α,β-unsaturated cinnamates (i.e. **300**, Scheme 4.16). Specifically, we envisaged Mizoroki-Heck coupling of an orthogonally protected aryl halide (i.e. **301**) to give the desired cinnamate.

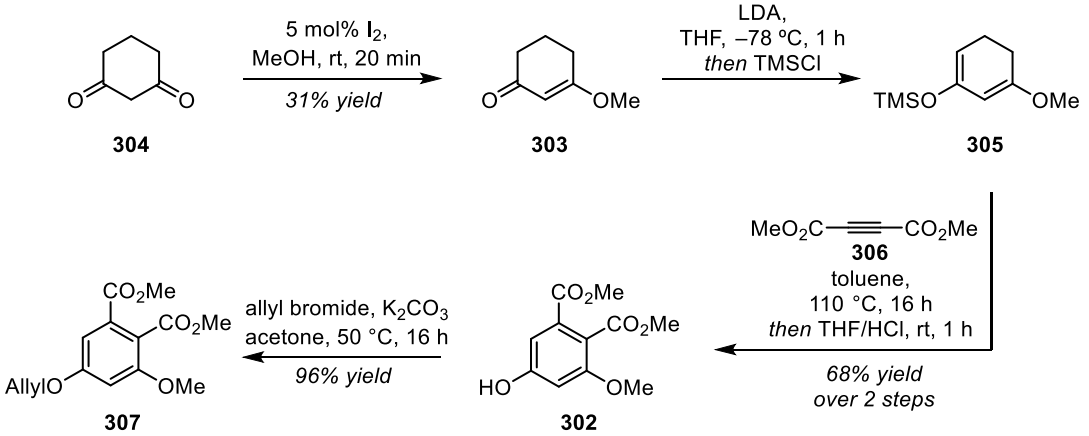


259 **301** **300**

Scheme 4.16. Proposed route to access pentasubstituted α,β-unsaturated cinnamates..

4.5.1 Synthesis of pentasubstituted α,β-unsaturated scaffolds

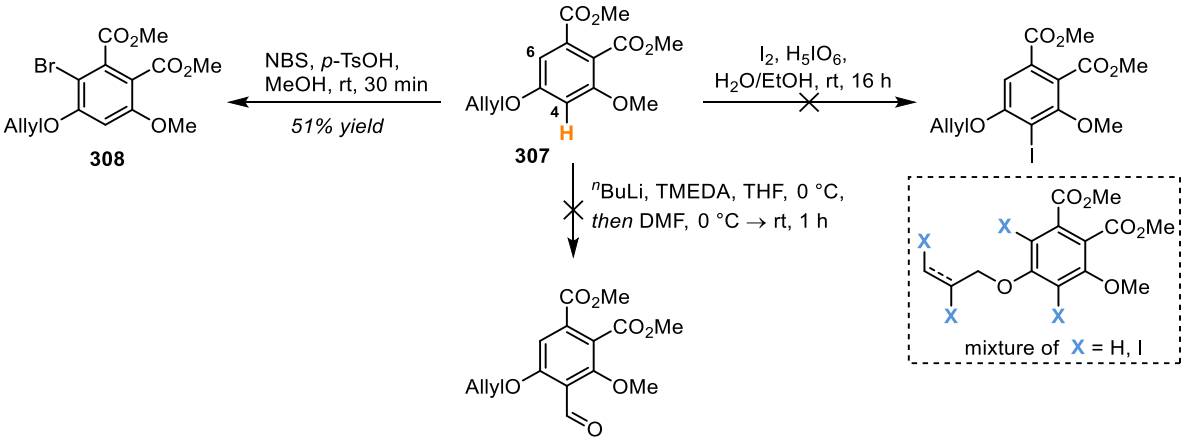
It was anticipated that installing orthogonal protecting groups from resorcinol **259** would be challenging, therefore, the synthesis commenced with the preparation of known phenol **302**,[23] an aromatic material which eliminates these difficulties (Scheme 4.17). To this end, commercially available methyl ether **303** was prepared in 31% yield after exposure of cyclohexanedione **304** to iodine (I_2) in methanol. Deprotonation of **303** with LDA and subsequent addition of trimethylsilyl chloride (TMSCl) generated diene **305** which was utilised directly in a Diels-Alder reaction with dimethylacetylene dicarboxylate (DMAD) (**306**). After expulsion of ethylene *via* a retro-Diels Alder mechanism followed by hydrolysis, the reaction generates pthalate **302** in 68% yield. Lastly, conversion of pthalate **303**, to the corresponding allyl ether **307** was achieved by treatment with potassium carbonate and allyl bromide.



304 **303** **305** **307** **302**

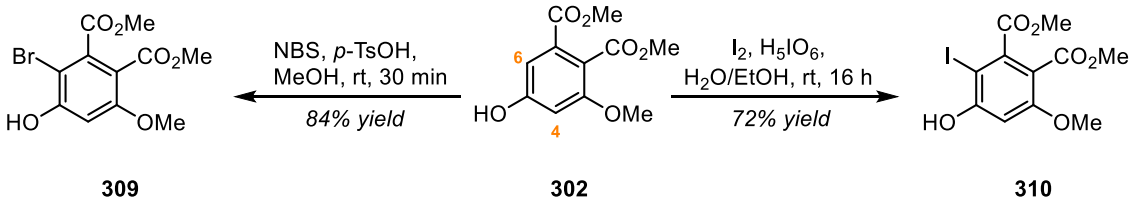
Scheme 4.17. Synthesis and protection of pentasubstituted aromatic scaffold **307**.

With phthalate **302** in hand, it was subjected to a range of conditions for selective functionalisation at C4. Unfortunately, treatment with I_2 and periodic acid, which effected regioselective iodination of the corresponding resorcinol in Parker's work,[4] gave a complex mixture of products (Scheme 4.18). ^{1}H NMR analysis of the crude reaction mixture indicated non-selective iodination of the aromatic positions, and the allyl group, leading to a mixture of regioisomers (i.e. X = H or I). Hoping that milder conditions would preclude reaction of the allyl group, **307** was treated with *N*-bromosuccinimide. This proceeded with chemo- and regioselectivity, however, bromination occurred at the undesired C6 position to give **308**. Finally, attempts to effect *ortho*-directed lithiation and subsequent formylation with DMF were unsuccessful, presumably due to competing lithiation of the allyl phenyl ether[24] and potential addition of *n*-butyl lithium (^{n}BuLi) to the phthalate esters.



Scheme 4.18. Attempted C4 functionalisation of benzene **307**.

Given the reactivity of the allyl ether in these attempted functionalisation's, and that phenols engender greater regioselectivity in the iodination reaction,[25] the halogenation was attempted prior to installation of the allyl group (Scheme 4.19). In these cases, both iodination and bromination of phthalate **302** proceeded to give a single regioisomer, however, single crystal X-ray diffraction of aryl bromide **309** determined C6 as the site of bromination and, iodination in the case of **310**, based on comparison of their ^{1}H NMR spectra (Figure 4.5).



Scheme 4.19. Halogenation of arene **302**.

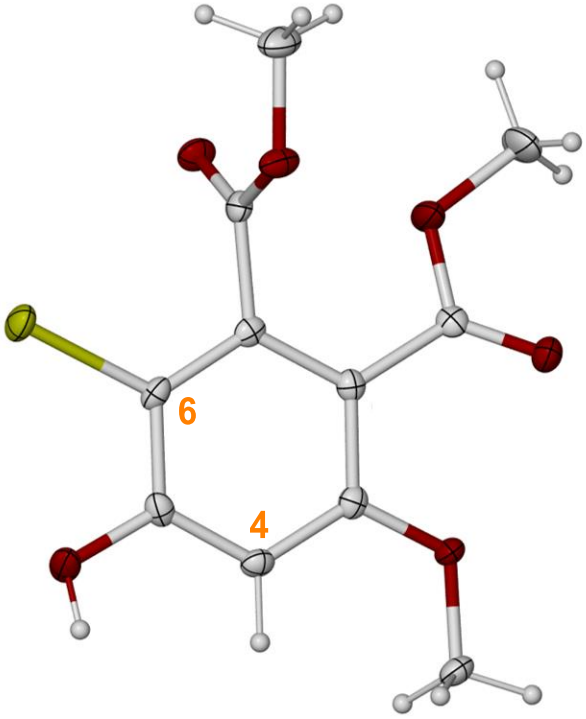
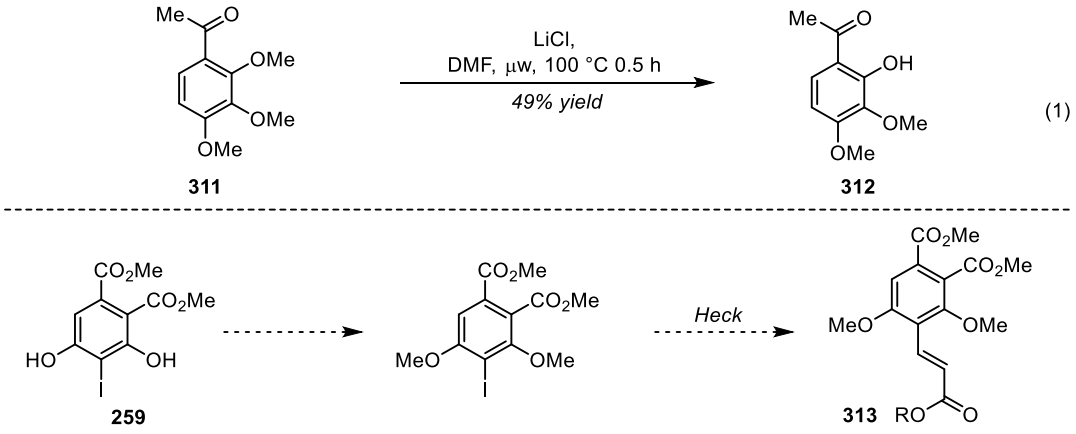


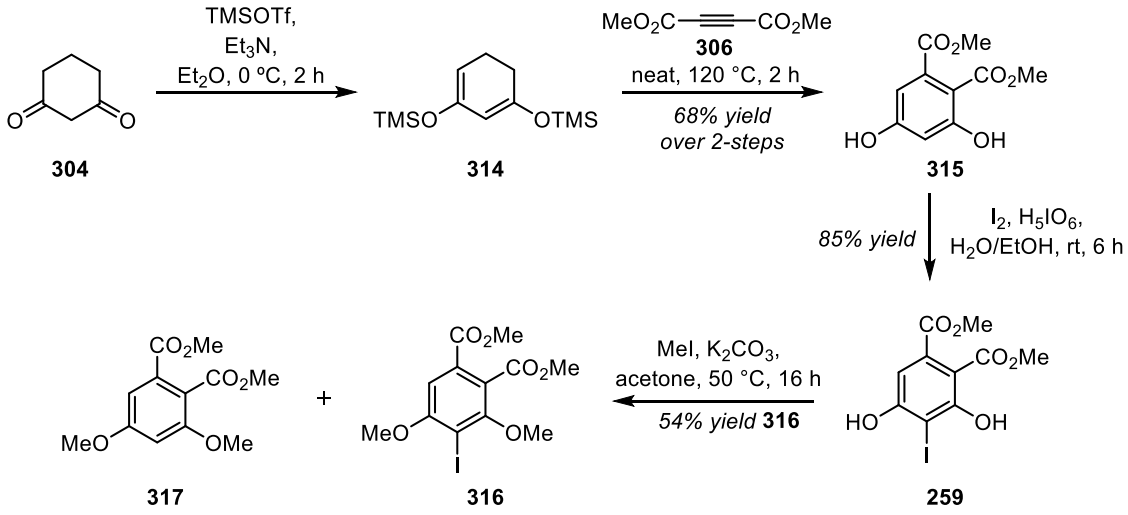
Figure 4.5. Crystal structure of aryl bromide **309**.

To achieve site-selective C4 functionalisation and ultimately access the required cinnamate scaffold a new route was devised. Closer inspection of the literature surrounding aromatic ether protecting group strategies revealed a host of procedures which enable selective mono-demethylation of electronically distinct *bis*-methylaryl ethers.[26] Notably, selective deprotection of methyl ethers with a neighbouring carbonyl group (i.e. **311**→**312**, Scheme 4.20, eq. 1)[26c] is possible, which is the case with the proposed aromatic fragment. With this in mind, we reasoned that selective demethylation of a *bis*-methyl ether would preclude the requirement for orthogonal protection and enable the synthesis of a suitable cinnamate (i.e. **313**) after methylation and Heck coupling from resorcinol **259**.



Scheme 4.21. Selective demethylation of aryl ether **311** and revised strategy for synthesis of **313**.

To this end, exposure of cyclohexanedione **304** to trimethylsilyltrifluoromethane sulfonate (TMSOTf) and triethylamine provided *bis*-silyl ether **314** which was used directly in a Diels-Alder reaction with DMAD (Scheme 4.21). After expulsion of ethylene and hydrolysis, resorcinol **315** was obtained in 68% yield over 2 steps.[27] Next, procedures reported by Hathaway[25] effected regioselective iodination at C4 to give aryl iodide **259** in 85% yield. Finally, treatment with iodomethane and K_2CO_3 delivered the corresponding aryl iodide **316** in 54% yield. Notably, upon exposure of **259** to K_2CO_3 the reaction mixture became increasingly yellow over time, suggesting the presence of free iodine. This observation, coupled with the isolation of the deiodinated arene **317** from the reaction mixture, is indicative of a base-mediated deiodination which provided a rationale for the moderate yield.



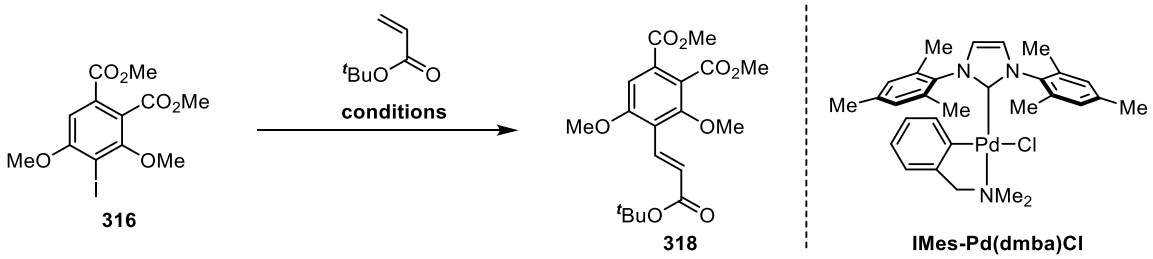
Scheme 4.21. Synthesis of aryl iodide **316**.

With aryl iodide **316** in hand, a Heck coupling with *tert*-butyl acrylate was explored. The *tert*-butyl derivative was selected initially to facilitate selective hydrolysis in the presence of methyl esters in the subsequent step. Traditional conditions utilising palladium acetate with or without a phosphine ligand or under aqueous conditions provided unsatisfactory yields of cinnamate **318**, with unreacted starting materials isolated (Table 4.1, entries 1-3).[28] These observations are indicative of catalyst decomposition, a consequence of the elevated temperatures required for oxidative addition to hindered aryl halides (i.e. **316**).[29]

Fortunately, Ying and co-workers have developed a new robust palladacycle IMes-Pd(dmba)Cl for catalysis of the Heck reaction, that is stable at high temperatures and tolerates hindered substrates.[30] When applied to the Heck coupling of aryl iodide **316** with *tert*-butyl acrylate, their conditions provided cinnamate **318** with an increased yield (19%), albeit with significant decomposition (Table 4.1, entry 4).

Pleasingly, by reducing the reaction time to 6 hours, decomposition was supressed and cinnamate **318** was isolated in 71% yield (Table 4.1, entry 5).

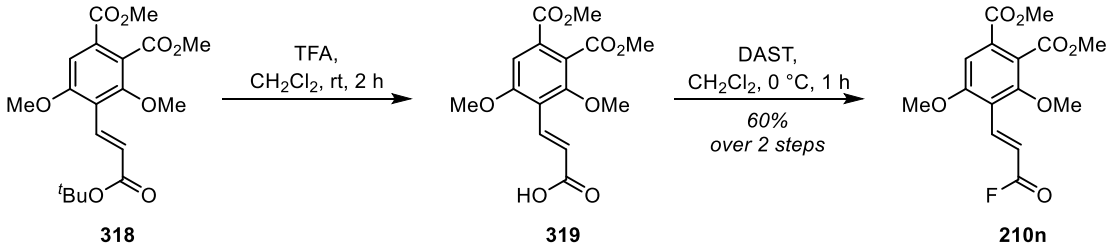
Table. 4.1: Heck coupling of aryl iodide **316** with *tert*-butyl acrylate.



entry	conditions	yield 318[a]
1	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Et_3N , DMF, 140 °C, 16 h	trace
2	10 mol% $Pd(OAc)_2$, Et_3N, DMF, 140 °C, 16 h	8%
3	10 mol% $Pd(OAc)_2$, TBAB, Na_2CO_3, H_2O, 100 °C, 16 h	4%
4	4 mol% IMes-Pd(dmba)Cl, K_2CO_3, NMP, 120 °C, 16 h	19%
5	4 mol% IMes-Pd(dmba)Cl, K_2CO_3, NMP, 120 °C, 6 h	71%

[a] Isolated yield following flash column chromatography.

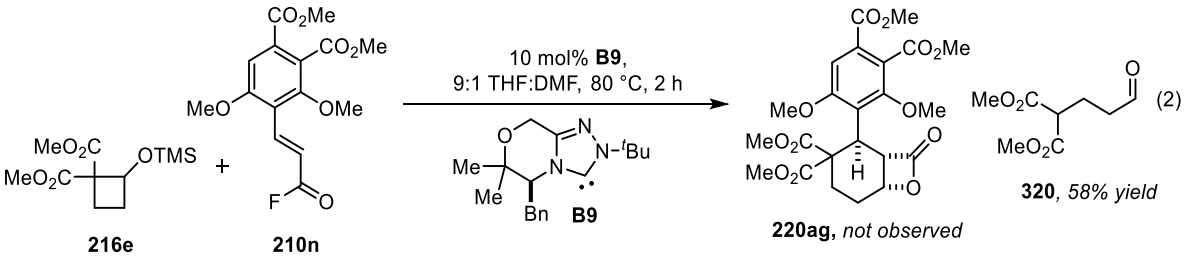
With cinnamate **318** in hand, all that remained was conversion to the corresponding acyl fluoride **210n**. Thus, selective hydrolysis of the *tert*-butyl ester using trifluoroacetic acid[31] provided carboxylic acid **319** before fluorination with DAST delivered the desired acyl fluoride **210n** in 60% yield over 2-steps (Scheme 4.22).



Scheme 4.22. Synthesis of α,β unsaturated cinnamoyl fluoride **210n**.

Unfortunately, when acyl fluoride **210n** was exposed to NHC **B9**in the presence of DA-cyclobutane **216e**, the desired β-lactone **220ag** was not observed. Instead, aldehyde **320** was isolated as the major reaction product (Scheme 4.23). Premature enolate quenching leading to aldehyde **320** is commonly observed when acyl fluorides bearing electron withdrawing β-aryl substituents are employed in the (4+2) annulation. However, in these reactions, the corresponding β-lactones were still isolated, albeit with reduced yields and enantioselectivity. Given that 2,6-disubstituted acyl fluorides have been established as viable, although

not ideal, substrates for (4+2) annulation, these results presumably relate to the highly electron withdrawing nature of the phthalate esters. In keeping with previous , and indeed later observations (see Scheme 4.9 and *Chapter 5, Scheme 5.10)*, we suspect that this substitution pattern slows the rate of the asynchronous (2+2) aldol/lactonisation process and allows non-productive pathways to dominate.

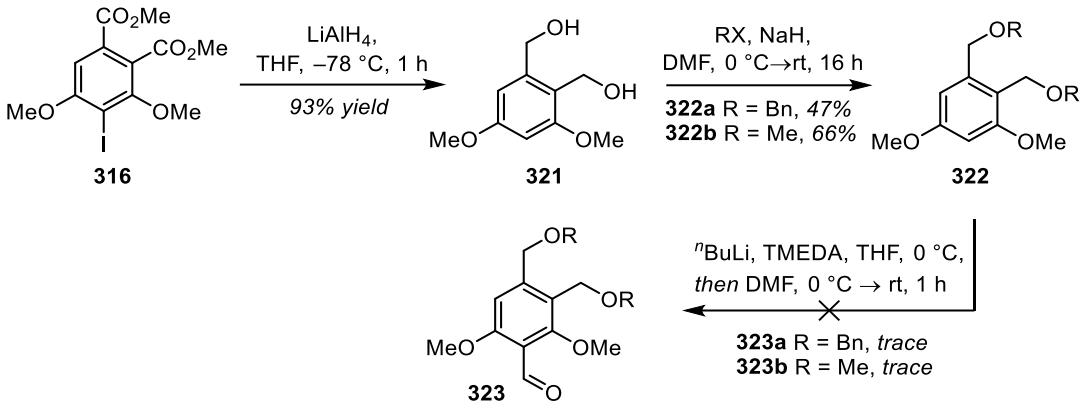


Scheme 4.23. (4+2) annulation of α,β-unsaturated cinnamoyl fluoride **210n**.

4.5.2 Acyl fluorides without electron withdrawing substituents

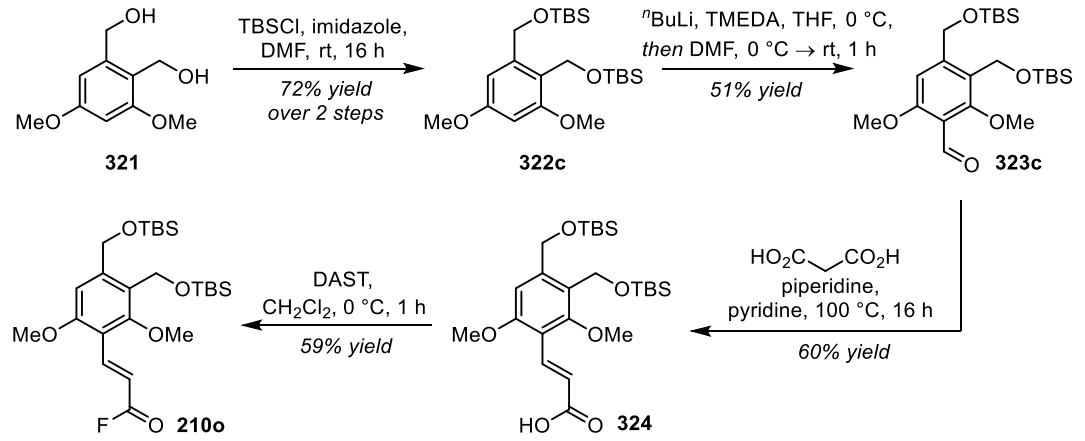
If the previously described reaction failed due to the presence of the two ester groups then we reasoned that global reduction of the phthalate esters and etherification would eliminate enable the synthesis of β-lactone suitable for elaboration to the natural product. Due to the presence of reducible functionality on both acid **319** and acyl fluoride **210n**, the synthesis of this material commenced with the previously prepared aryl iodide **316**. Upon treatment of **316** with lithium aluminium hydride ($LiAlH_4$), global reduction of the phthalate moiety proceeded, however, as an unforeseen consequence, this also resulted in complete reduction of the iodide to give diol **321** in 93% yield (Scheme 4.24).

In our previous studies, the presence of phthalate esters in addition to an allyl ether, complicated the lithiation and formylation of the C4 position (see Scheme 4.18). Given that the newly formed arene **321** is free of these functional groups, we proposed that with appropriate protection of the benzylic alcohols, lithiation and formylation may be possible. To investigate such a scenario, two derivatives **322a** and **322b** bearing benzyl and methyl ethers respectively, were prepared by treatment of diol **321** with benzyl bromide or iodomethane in the presence of sodium hydride. Unfortunately, subsequent formylation of **322a** and **322b** using ^{n}BuLi and DMF was not viable, with only trace amounts of the desired benzaldehydes **323a** and **323b** observed in addition to uncharacterisable decomposition products. It was suspected that in these cases, formylation is complicated by competing lateral lithiation at benzylic positions.[32]



Scheme 4.24. Attempted syntheses of benzaldehydes **323**.

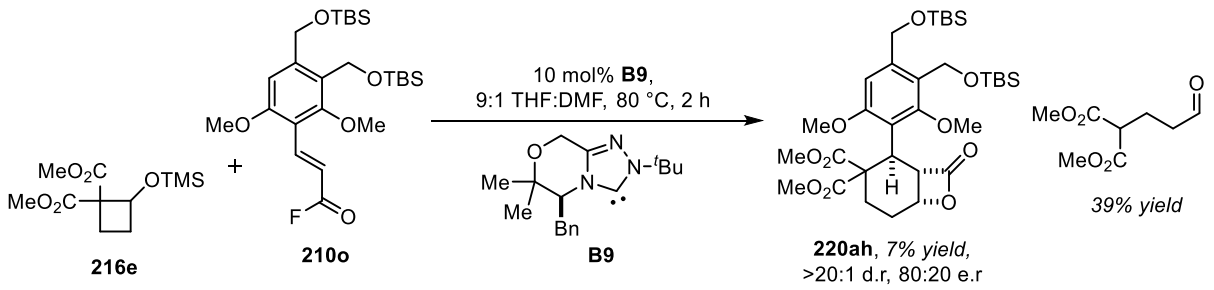
To suppress lithiation at the benzylic positions, sterically demanding *tert*-butyl dimethyl silyl (TBS) ether protection was examined. To this end, *bis*-silyl ether **322c** was synthesised from diol **321** by silylation with TBSCl mediated by imidazole[33] (Scheme 4.25). Gratifyingly, this strategy was successful and enabled the desired C4 formylation, with the corresponding benzaldehyde **323c** isolated in 51% yield. As described previously, the procedures for Doebner-modified Knovenagel condensation and fluorination with DAST were applied to deliver the desired α,β unsaturated acyl fluoride **210o** in 59% yield over two-steps from **323c**.



Scheme 4.25. Synthesis of α,β unsaturated acyl fluoride **210o**.

With α,β-unsaturated acyl fluoride **210i** in hand, its viability in the (4+2) annulation with DA-cyclobutane **216e** was assessed. Exposure of these substrates to NHC **B9** resulted in isolation of the desired β-lactone **220ah** with moderate enantioselectivity (80:20 e.r), however in poor chemical yield (7%) (Scheme 4.26). It is not clear what leads to the poor yield observed here, however, given that alkyl β-aryl substituents are well tolerated in the (4+2) annulation *(see Chapter 3, section 3.3.2)*, we suspect that the presence of *tert*-butyldimethyl silyl groups interferes with the concomitant defluorination/desilylation event which

initiates the reaction. While pleasing that the synthesis of β-lactone **220ah** in part supported to prospective synthesis of (+)-bisabosqual, due to time constraints, alternate protecting group strategies were not explored for this scaffold.

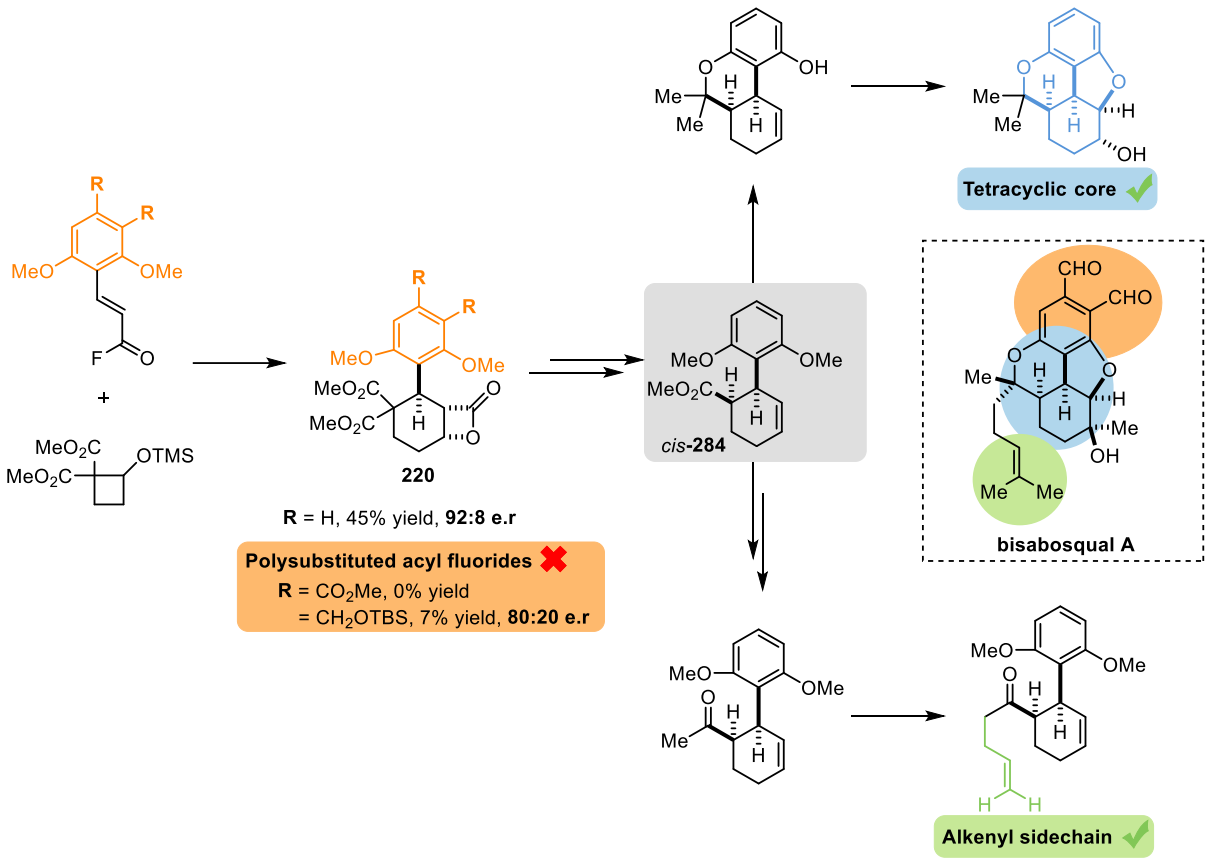


Scheme 4.26. (4+2) Annulation of acyl fluoride **210o** with DA-cyclobutane **216e**.

Our efforts to synthesise pentasubstituted α,β-unsaturated acyl fluorides (i.e. **210n** and **210o**) were ultimately successful, however, these were poor substrates for the NHC catalysed (4+2) annulation with DA-cyclobutane **216e**. Unfortunately, due to the challenges introduced in Model study 2 and 3, the pursuit of bisabosqual A was deemed unviable within the time constraints of these doctoral studies.

4.6 Conclusions and outlook

Model studies were carried out to determine the viability of the NHC catalysed (4+2) annulation of DA-cyclobutanes and α,β-unsaturated acyl fluorides toward the synthesis of bisabosqual A. It was shown that β-lactone **220ad** (R= H) , following dual decarboxylation to give *cis*-monoester **284** and subsequent cyclisations to close the benzopyran and benzofuran, gave the tetracyclic core of the bisabosquals (Scheme 4.27). Although β-ketoester derived DA-cyclobutanes did not provide β-lactone products, a route for the installation of the alkenyl sidechain was developed *via* a series of functional group interconversions from *cis*-monoester **284**. Finally, the synthesis of two pentasubstituted α,β-unsaturated acyl fluorides **210n** (R = CO_2Me) and **210o** (R = CH_2OTBS) and assessment of their reactivity, established that these were poor substrates for the (4+2) annulation. Unfortunately, as these acyl fluorides were not viable in the reaction, the synthesis of bisabosqual A was abandoned. Although the synthesis of bisabosqual A could not be realised, we recognised that *trans*-monoester **284** represented a valuable scaffold well-suited to the preparation of simpler, but related cannabinoid natural products. Studies towards this end are described in *Chapter 5*.



Scheme 4.27 Overview of model studies towards (+)-bisabosqual A

4.7 References

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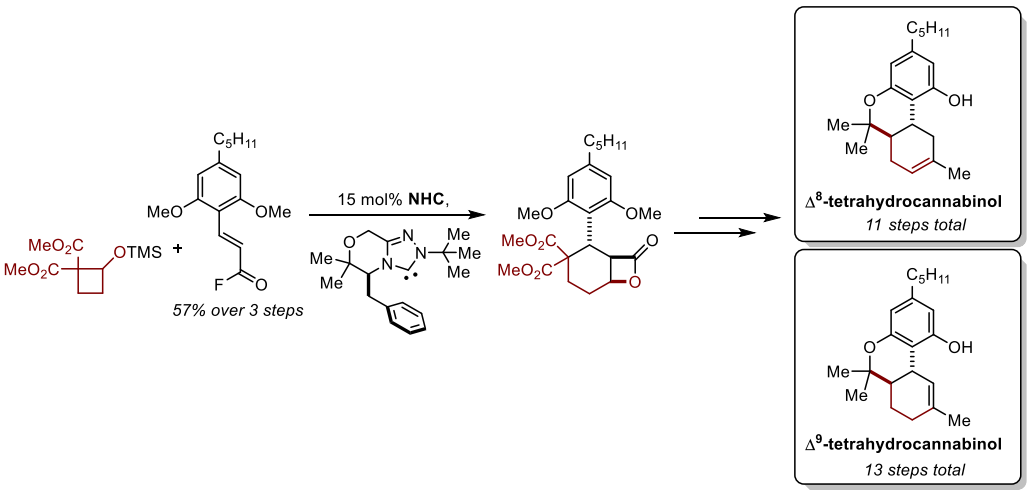
Chapter 5

Enantioselective total synthesis of Δ^8- and Δ^9-tetrahydrocannabinol

An enantioselective total synthesis of (−)-Δ⁸-tetrahydrocannbinol ((−)-Δ⁸-THC) and (−)-Δ⁹-tetrahydrocannbinol ((−)-Δ⁹-THC) has been enabled by the NHC-catalysed (4+2) annulation of donor-acceptor cyclobutanes and α,β-unsaturated acyl fluorides. The reaction provides a heavily functionalised cyclohexyl β-lactone in good yield and with excellent stereochemical integrity. Elaboration of the cyclohexane core into the natural products is achieved over an additional 8 and 10 steps for (−)-Δ⁸-THC and (−)-Δ⁹-THC respectively.



5.1 Introduction

The use of cannabis in traditional medicine dates back thousands of years.[1] Reports of analgesic and sedative properties, amongst others, saw its introduction to Western medicine in the 1830's,[2] before its eventual prohibition in the US (1970) amid concerns related to psychoactivity.[3] The isolation of cannabinoids from female *Cannabis sativa* in 1964[4], and elucidation of their structures, triggered intense synthetic and neurobiological investigations. (Figure 5.1). Discovery of the human endocannabinoid

system[5] revealed the bioactivity of cannabinoids is elicited through binding to G-coupled protein receptors CB_1 and CB_2. Surprisingly, only in the last 2 years has information regarding the mode of binding been elucidated.[6] These discoveries coupled with the relaxation of laws surrounding therapeutic and even recreational use of cannabinoids has sparked a modern era of synthetic chemistry and medicinal interest.[7]

Of the cannabinoids isolated from *Cannabis sativa*, (–)-Δ^9-THC (**325**) has received the most attention from the synthetic community, with over 30 total syntheses reported as of 2018.[8] The tricyclic structure consists of a tetra-substituted aromatic motif (A-ring) and a challenging tertiary alcohol-bearing benzopyran (B-ring) which is *trans*-fused to the final cyclohexene (C-ring).

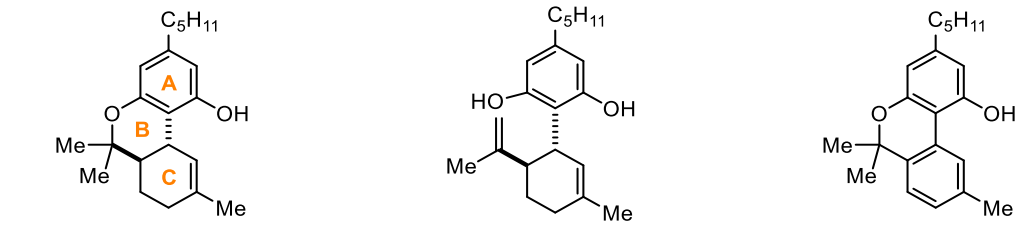


Figure 5.1. Cannabinoids of *Cannabis sativa*.

5.1.1 Synthetic strategies for the synthesis of (–)-Δ^9-THC

In almost all synthetic reports, the A-ring is derived from olivetol (**326**) with the syntheses diverging only with the source of the C-ring fragment and the strategy used to unify them. Early enantiospecific syntheses utilise a chiral pool strategy, with terpene derived C-ring precursors employed to access a hypothetical dication **327** (Figure 5.2a). Brønsted or Lewis acid catalysed condensation with olivetol then gives rise to (–)-Δ^9-THC (**325**).[9] C-ring fragments (i.e. **328**[10], **329**[11] and **330**[12]) derived from commercially available cyclohexenes have also found use is the synthesis of (–)-Δ^9-THC (**325**) through coupling with suitable olivetol derivatives (i.e. **331**, Figure 5.2b). Several syntheses employ acyclic materials to construct the C-ring (Figure 5.2c).[13] For instance, diol **332** is prepared through an enantioselective Diels-Alder reaction,[13a] while others construct the cyclohexene around the aromatic motif using ring closing metathesis (RCM).[13c-e] Of all enantiospecific syntheses reported for (–)-Δ^9-THC (**325**), only 5 employ enantioselective methods starting from achiral materials. These approaches are reviewed in detail herein.

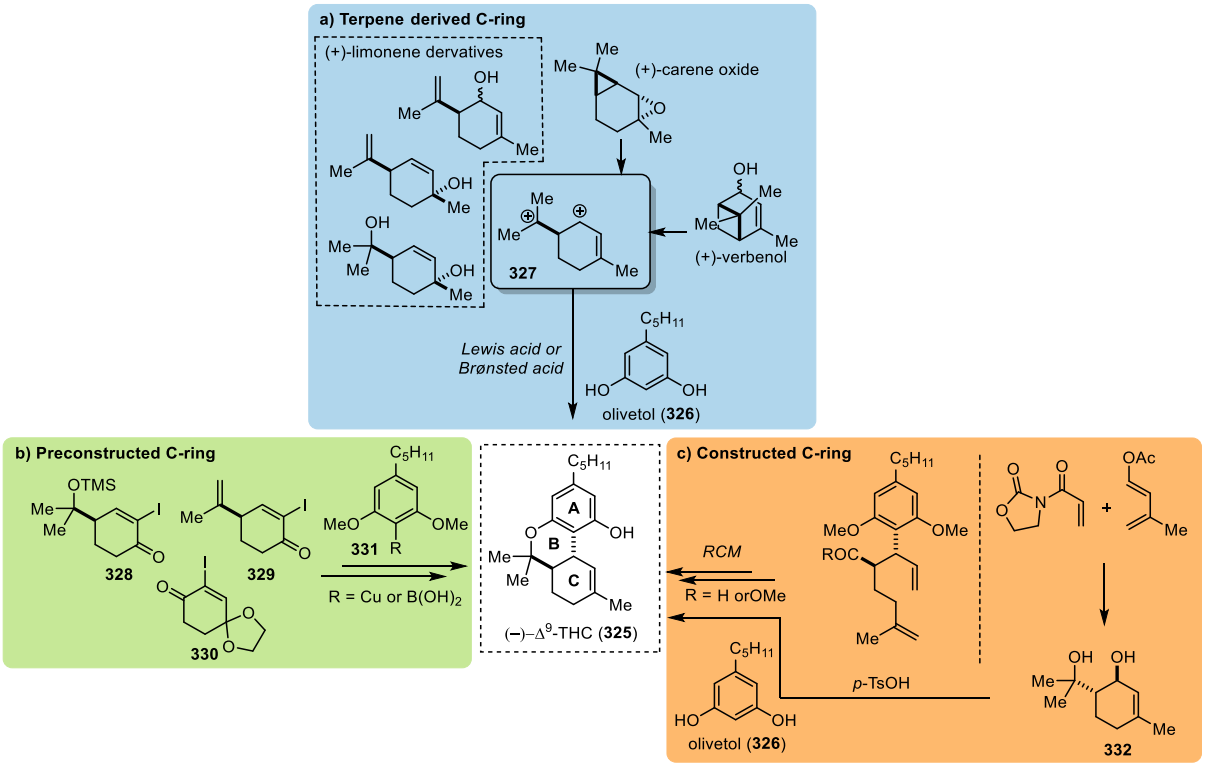
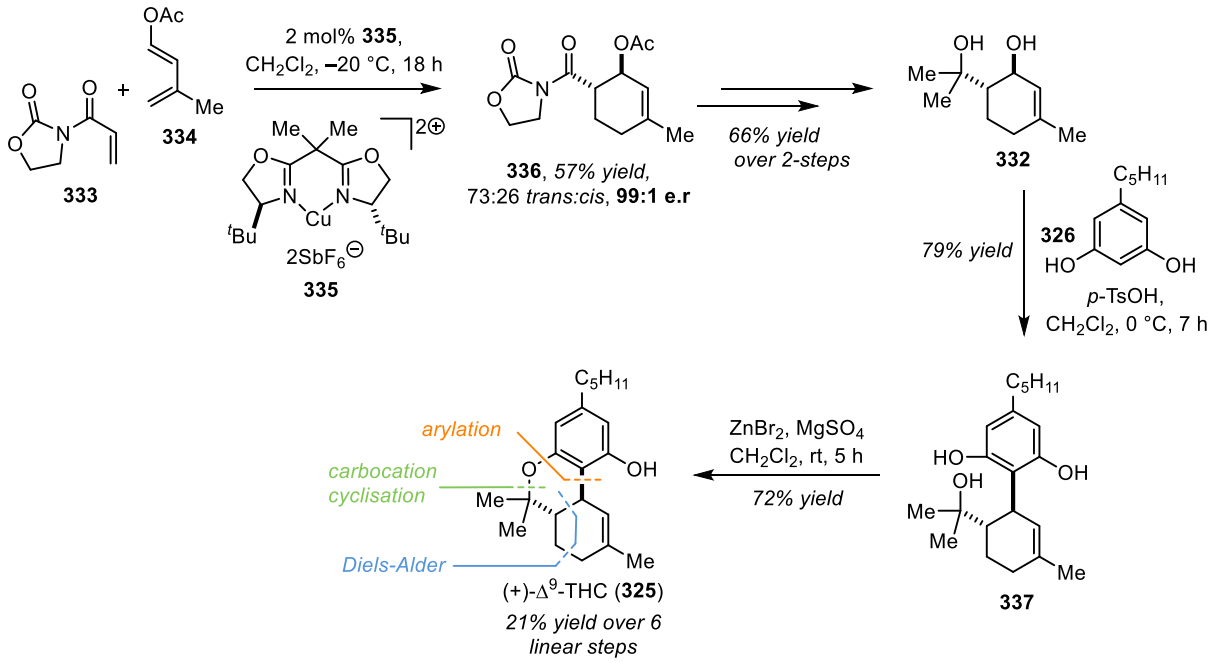


Figure 5.2. Overview of synthetic strategies for (−)-Δ^9-THC.

5.1.2 Evans' enantioselective Diels-Alder approach to Δ^9-THC

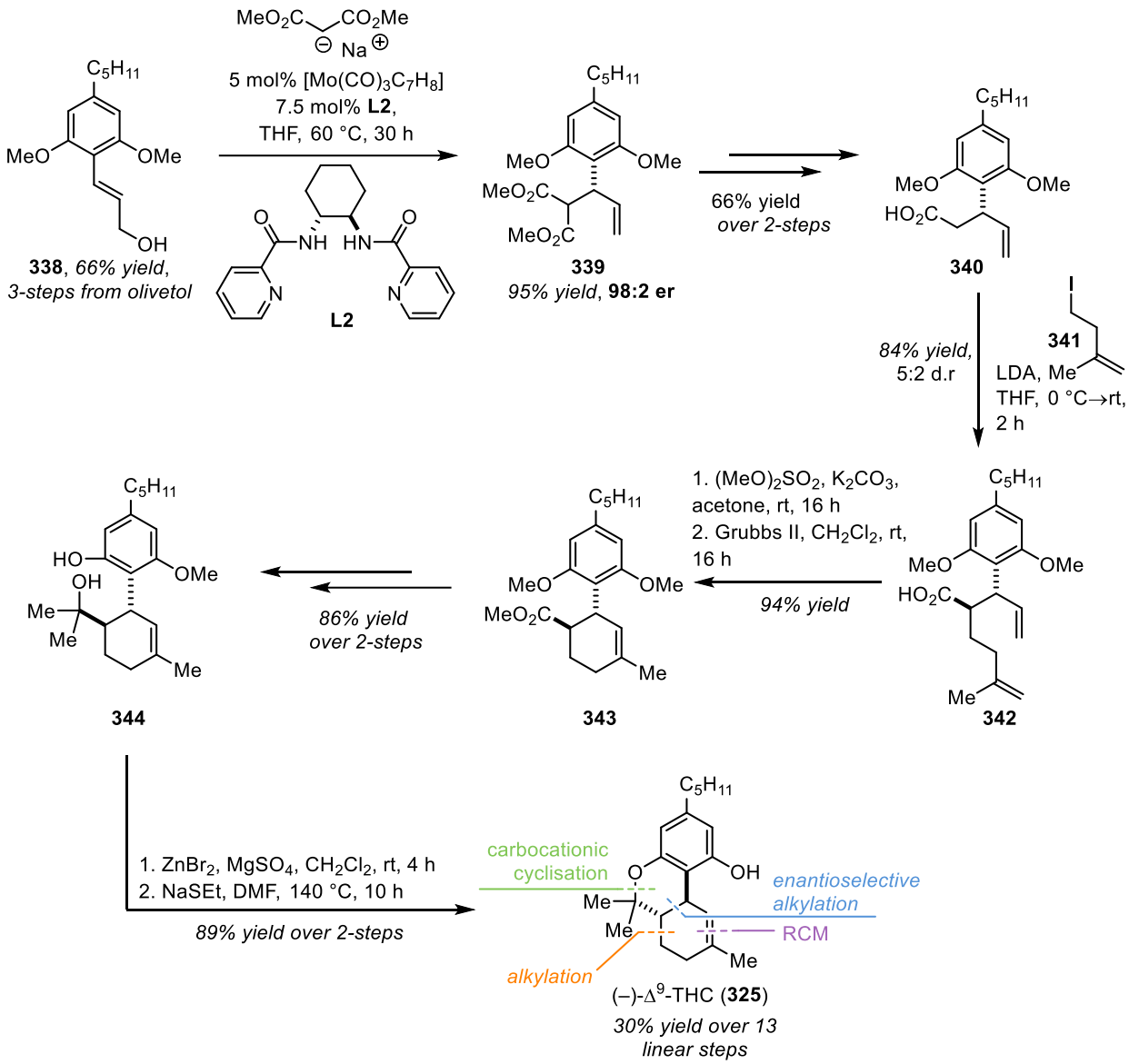
In 1997 Evans and co-workers reported the first enantioselective synthesis of Δ^9-THC from achiral materials (Scheme 5.1).[13a,b] Their strategy features three key disconnections. The first constructs the C-ring using a stereoselective Diels-Alder reaction between commercially available acrylamide **333** and diene **334**, catalysed by the Cu(II) BOX complex **335**. The cyclohexene adduct **336** was formed in 57% yield as a 73:26 ratio of diastereomers and with excellent enanatiopurity (99:1 e.r). Following functional group interconversion, diol **332** was united with olivetol *via* an acid catalysed alkylation, which delivered tertiary alcohol **337**. Finally, the B-ring was closed using a zinc bromide ($ZnBr_2$) mediated carbocationic cyclisation, which delivered the unnatural (+)-Δ^9-THC enantiomer. Evans' synthesis prepares enantiomerically pure (+)-Δ^9-THC (**325**) in 21% yield over 6 steps from commercially available starting materials. Importantly, no protecting group strategies were required and few functional group manipulations were performed.



Scheme 5.1. Evans' synthesis of (–)-Δ⁹-THC.

5.1.3 Trost's enantioselective allylic alkylation approach to (–)-Δ⁹-THC

Ten years separated Evans' Diels-Alder approach and the second enantioselective synthesis, in this case reported by Trost and Dogra (Scheme 5.2).[13d] Their synthesis commences with an enantioselective allylic alkylation of with dimethyl malonate with cinnamoyl alcohol (**338**) using a complex of molybdenum and chiral ligand **L2**. The resultant malonate **339** was prepared in 95% yield and with excellent regio- and enantioselectivity (98:2 e.r). Following conversion to the carboxylic acid **340**, alkylation with iodide **341** provided diene **342** in good yield, albeit with modest diastereoselectivity. Next, ring closing metathesis (RCM) introduces the C-ring, giving *trans*-ester **343** in excellent yield with subsequent functional group interconversion providing alcohol **344**. Finally, the carbocationic cyclisation developed by Evans was utilised to forge the benzopyran B-ring before deprotection furnished (–)-Δ⁹-THC (**325**). Despite the use of additional functional group manipulations and phenol protection strategies, enantiomerically pure (–)-Δ⁹-THC (**325**) was prepared with a higher overall yield (30%, *cf.* Evans 21%), however the step count was increased by 7 operations.

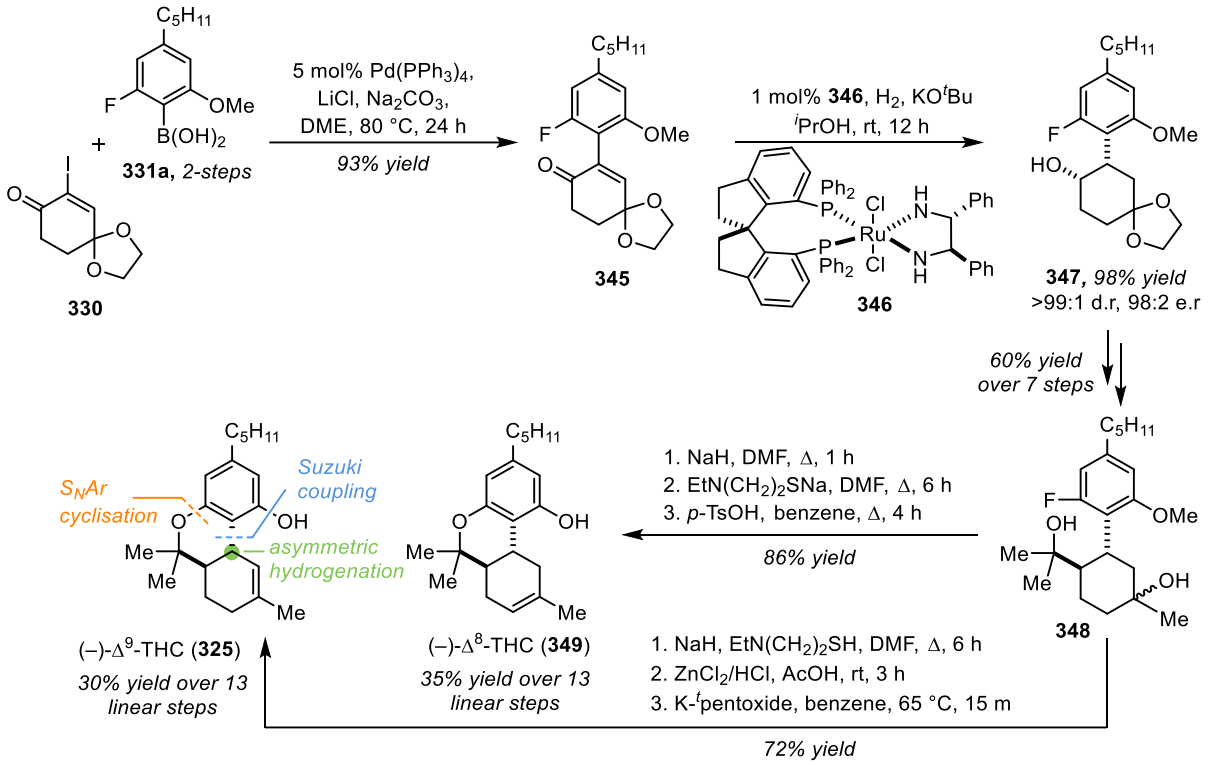


Scheme 5.2. Trost's synthesis of (–)-Δ⁹-THC.

5.1.4 Zhou's enantioselective hydrogenation approach to (–)-Δ⁹-THC

Unlike the previous syntheses, a 2013 report by Zhou and co-workers describes an approach whereby the C-ring was obtained from commercially available iodide **330** (Scheme 5.3).[12] Zhou's synthesis features two key disconnections. Firstly, Suzuki coupling of iodide **330** and boronic acid **331a** unified the C-ring and the aromatic motif to give enone **345** in 93% yield. Next, the enantioselective hydrogenation catalysed by ruthenium complex **346** delivered alcohol **347** in 98% yield with excellent selectivity (98:2 e.r). A series of functional group manipulations then generated diol **348**, an intermediate from which both (–)-Δ⁹-THC (**325**) and (–)-Δ⁸-THC (**349**) isomers are available. Thus, treatment with sodium hydride (NaH) facilitated intramolecular S_NAr cyclisation to form the B-ring before deprotection and elimination using *p*-TsOH furnished (–)-Δ⁸-THC (**349**). Alternatively, a one pot S_NAr/deprotection protocol followed by

chlorination and elimination with potassium *tert*-pentoxide provided the (−)-Δ⁹-THC (**325**) isomer. Despite a similar step count and yield (30%, 14 steps, *cf.* Trost 30%, 13 steps), Zhou's synthesis suffers from multiple protection/deprotection strategies and features a series of transformations that build little molecular complexity (i.e. **347**→**348**).

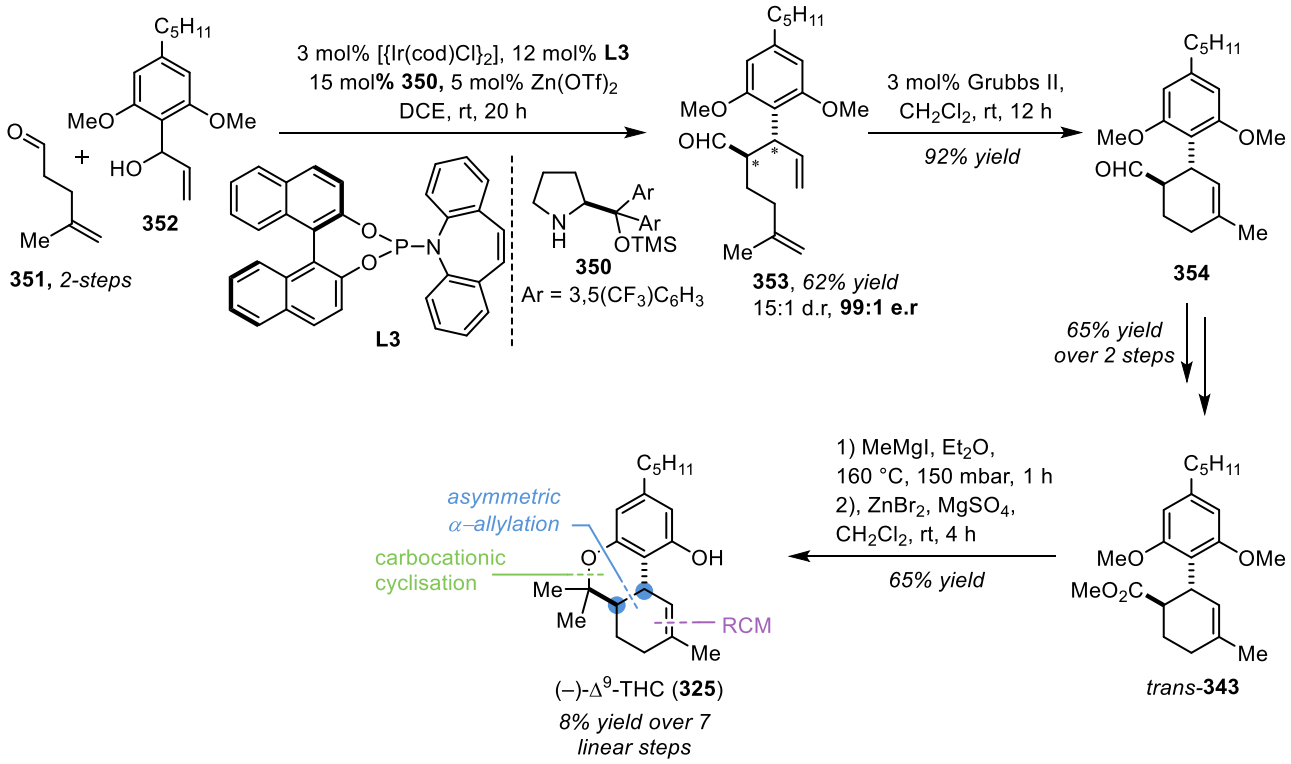


Scheme 5.3. Zhou's synthesis of (−)-Δ⁸-THC and (−)-Δ⁹-THC.

5.1.5 Carreira's stereodivergent approach to (−)-Δ⁹-THC

Inspired by the complex receptor interactions of cannabinoids,[14] Carreira and co-workers developed methodology to access all possible Δ⁹-THC stereoisomers.[13e] They hoped this would enable pharmacological examination of each isomer in earnest and in doing so, further our understanding of the bioactivity of these compounds. Carreira's approach features 3 key disconnections which resemble those of Trost (Scheme 5.4). Notably, a dual catalytic allylic alkylation with an iridium phosphoramidate complex and Jørgensen/Hayashi catalyst **350** enabled the α-allylation of aldehyde **351** with olivetol derived allyl alcohol **352**. The resultant aldehyde **353** was isolated in 62% yield and with excellent stereochemical integrity (15:1 d.r, 99:1 e.r). Remarkably, each chiral catalyst exerts independent control of one stereocentre, allowing for control of both stereocentres through the selection of the sense of each catalyst. Next, RCM with Grubbs II catalyst forged the cyclohexene **354** in 92% yield before functional group interconversion delivered the known *trans*-ester **343**. Finally, a two-step procedure was developed

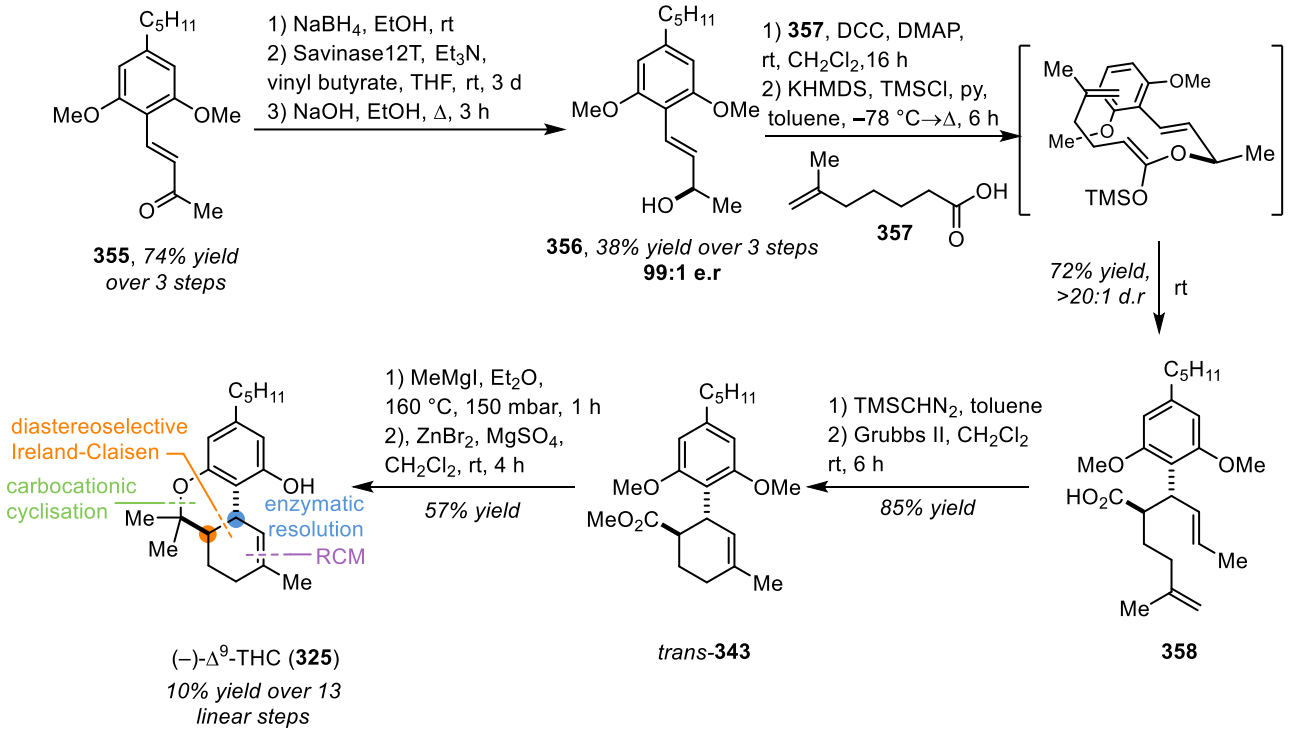
for the methylation, deprotection and carbocationic cyclisation which provided (–)-Δ⁹-THC (**325**) in 8% overall yield (7 steps). Despite lower overall yield, Carreira's synthesis improves upon Trost's studies through the development of a highly stereocontrolled α-allylation reaction.



Scheme 5.4. Carreira's synthesis of (–)-Δ⁹-THC.

5.1.6 Leahy's enzymatic resolution approach to (–)-Δ⁹-THC

The most recent enantioselective synthesis of (–)-Δ⁹-THC (**325**) was reported in 2018 by Leahy[13f] and co-workers and features key disconnections similar to Carreira. Starting with olivetol derived α,β-unsaturated ketone **355**, after reduction and enzymatic resolution with Savinase 12T alcohol, allylic alcohol **356** was obtained in 38% yield and 99:1 e.r (Scheme 5.5). Next, esterification of carboxylic acid **357** with **356** followed by silylketene acetal fromation allowed for a diastereoselective Ireland-Claisen rearrangement to occur, with carboxylic acid **358** obtained in 72% and with complete diasteroselectivity. After esterification using trimethylsilyl diazomethane, the RCM and cyclisation protocols developed by Carreira were applied to furnish (–)-Δ⁹-THC (**325**) in 10% yield over 13 steps.

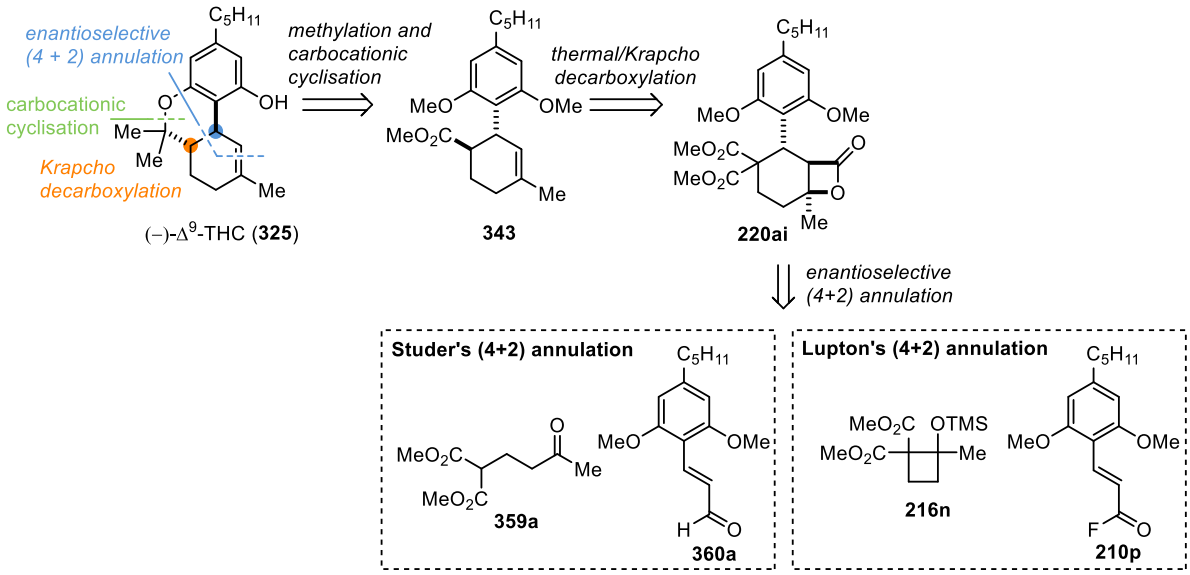


Scheme 5.5. Leahy's synthesis of (–)-Δ^9-THC.

5.2 Synthetic strategy for (–)-Δ^9-THC

5.2.1 Retrosynthetic analysis of (–)-Δ^9-THC

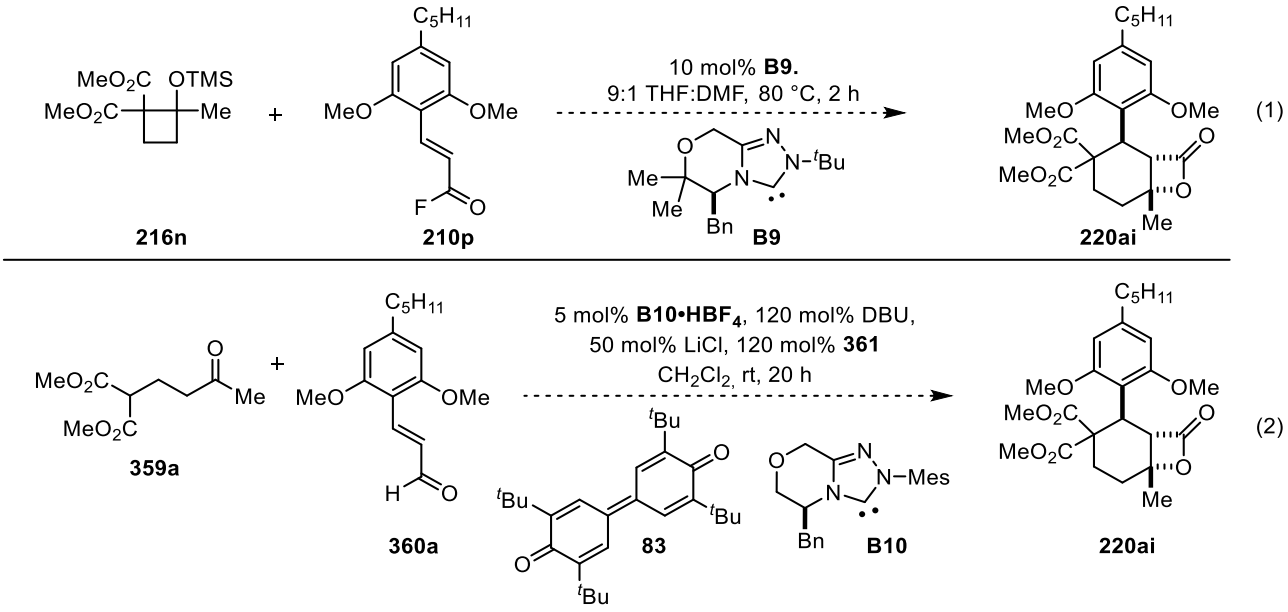
Our own approach to (–)-Δ^9-THC (**325**) stems from the recognition that NHC catalysis enables potentially valuable (4+2) annulations which generate highly enantioenriched cyclohexanes and, which we believe, are suitable C-ring precursors.[15] Retrosynthetic analysis of (–)-Δ^9-THC (**325**) led to the identification of *trans*-**343**, a known (–)-Δ^9-THC (**325**) precursor[13d, 13e] that we proposed is accessible through dual decarboxylation from β-lactone **220ai** (Scheme 5.6). Thermal decarboxylation of the β-lactone would introduce the alkene whilst concurrent Krapcho decarboxylation would provide the mono-ester and establish the diastereomeric configuration. Finally, the entire synthetic strategy is underpinned by the synthesis of enantiopure β-lactone **220ai**, which should be available through an enantioselective NHC catalysed (4+2) annulation with appropriate substrates (i.e. **216n** and **210p** or **359a** and **360a**).



Scheme 5.6. Proposed retrosynthesis of (−)-Δ^9-THC (**325**).

5.2.2 NHC catalysed (4+2) annulations

Specifically, two candidate NHC catalysed (4+2) annulations were targeted which generate cyclohexyl fused β-lactones (i.e. **220ai**).[15a] The first involves the coupling of donor-acceptor cyclobutane **216n** with α,β-unsaturated acyl fluoride **210p** using conditions discussed in *Chapter 3* (Scheme 5.7, eq. 1). The second is an analogous transformation reported by Studer[15b] utilising α,β-unsaturated aldehyde **360a** and methyl ketone **359a** in the presence of homochiral NHC **B10** and an oxidant **83** (Scheme 5.7, eq. 2). In Studer's reaction, only a single example was reported, with the viability of alternate substrates currently unknown.



Scheme 5.7. Related NHC catalysed (4+2) annulations.

5.2.3 Objectives

The ultimate objectives of this study are to implement the proposed enantioselective NHC catalysed (4+2) annulation reactions in the synthesis β-lactone **220ai**, and, if successful, to execute the synthesis of (–)-Δ^9-THC (**325**). In doing so, we hope to expand the scope of enantioselective syntheses of (–)-Δ^9-THC (**325**), in addition to the scope of complex targets available using NHC catalysed cascade reactions. Key to our investigation is the synthesis of methyl bearing DA-cyclobutane **216n** and acyl fluoride **210p**, and the application of these substrates in the subsequent coupling. The reaction must provide synthetically practical yields of enantioenriched β-lactone **220ai** to allow elaboration to the natural product. In an analogous fashion, the preparation and application of ketone **359a** and aldehyde **360a** for Studer's variant will be examined.

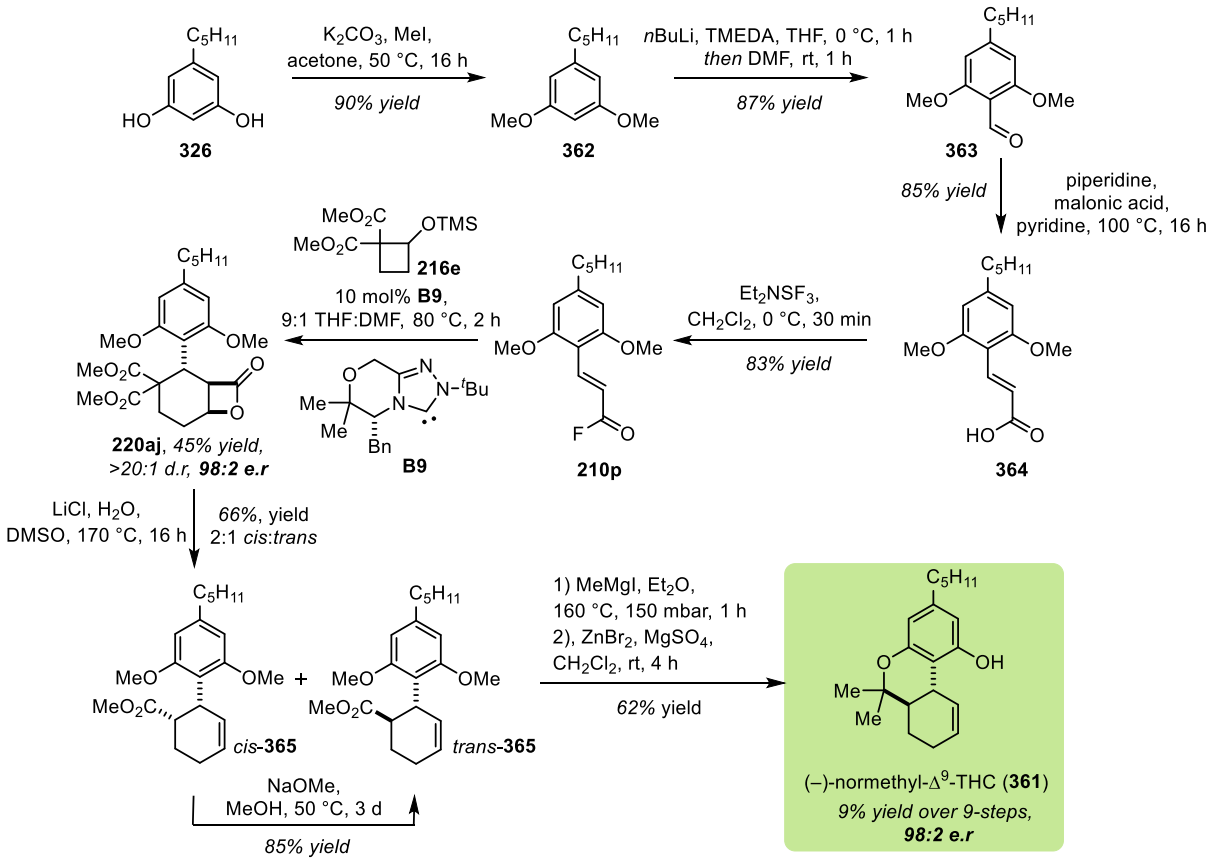
5.3 Preliminary investigations of the strategy

5.3.1 Synthesis of (–)-normethyl-Δ^9-THC (361)

Studies commenced by examining our general strategy with the synthesis of (–)-normethyl-Δ^9-THC (**361**). To enable this, the proposed α,β-unsaturated acyl fluoride **210p** was synthesised from olivetol (**326**), which could be sourced commercially ($8 USD per gram, Combi-Blocks). The synthesis commenced with protection of **326** as the known *bis* methyl ether **362**[13f] by treatment with iodomethane (MeI) under basic conditions (Scheme 5.8). Formylation with *n*-butyllithium and *N,N*-dimethylformamide then afforded aldehyde **363** which was subsequently converted to the corresponding carboxylic acid **364** following Doebner-modified Knovenagel condensation with malonic acid.[16] Finally, treatment with DAST delivered the desired α,β-unsaturated acyl fluoride **210p** in 83% yield.[17]

In contrast to previously synthesised polysubstituted acyl fluorides, which generated the expected products in 7% yield at best *(see Chapter 4, section 4.1)*, annulation of acyl fluoride **210p** with DA-cyclobutane **216e** proceeded smoothly to give β-lactone **220aj** in 45% yield and with 98:2 e.r. The modest yield of β-lactone **220aj** is consistent with the use of 2,6-dimethoxy substituted acyl fluorides as discussed in *Chapter 4 (section 4.3.1).*[18] Nevertheless, Krapcho decarboxylation[19] with concomitant decarboxylation of the β-lactone gave rise to cyclohexene *cis/trans*-**365** as a 2:1 *cis/trans* mixture. Pleasingly, *cis*-**365** could be converted to the desired *trans*-**365** using a base-mediated epimerisation as reported by Trost.[13d] Finally, conditions developed by Carreira effected exhaustive methylation, deprotection of the aryl methyl ethers, and carbocationic cyclisation to deliver enantiopure

(–)-normethyl-Δ^9-THC (**361**) in 9% overall yield (9-steps). This synthesis represents the only direct and regioselective route to **361**, with only two prior syntheses are reported; both generate **361** as a mixture of alkene isomers and, in one case, as an undesired side-product.[20]



Scheme 5.8. Synthesis of normethyl-Δ^9-THC (**361**).

With (–)-normethyl-Δ^9-THC (**361**) in hand, the spectroscopic data were compared with those found in the literature. Despite the compound appearing in several publications, only the report by Wilson and May[20b] contained spectral data. Pleasingly, the ^{1}H NMR spectrum derived from (–)-normethyl-Δ^9-THC (**361**) synthesised in these studies, matched closely with the partial ^{1}H NMR analysis detailed in this literature (Figure 5.3 and Table 5.1). The downfield area (δ 160-105 ppm) of the JMOD ^{13}C NMR spectrum contained the 8 required signals indicating the presence of an aromatic ring and an endocyclic olefin. Moreover, the phasing pattern (four positive and four negative signals) is indicative of four methine and four fully substituted carbon centres. The upfield region contains a peak at 77.4 ppm which is characteristic of deshielding by the adjacent benzopyran oxygen and the negative phasing supports a fully substituted carbon. Additionally, the required 11 aliphatic signals with correct phasing are present. Finally, the presence of the phenol is supported by a broad signal at 3300 cm^{-1} in the IR spectrum whilst the HRMS

is consistent with the proposed structure (*m/z* Found: $(M+H)^+$, $C_{20}H_{28}O_2$, 301.2159, requires 301.2162.)

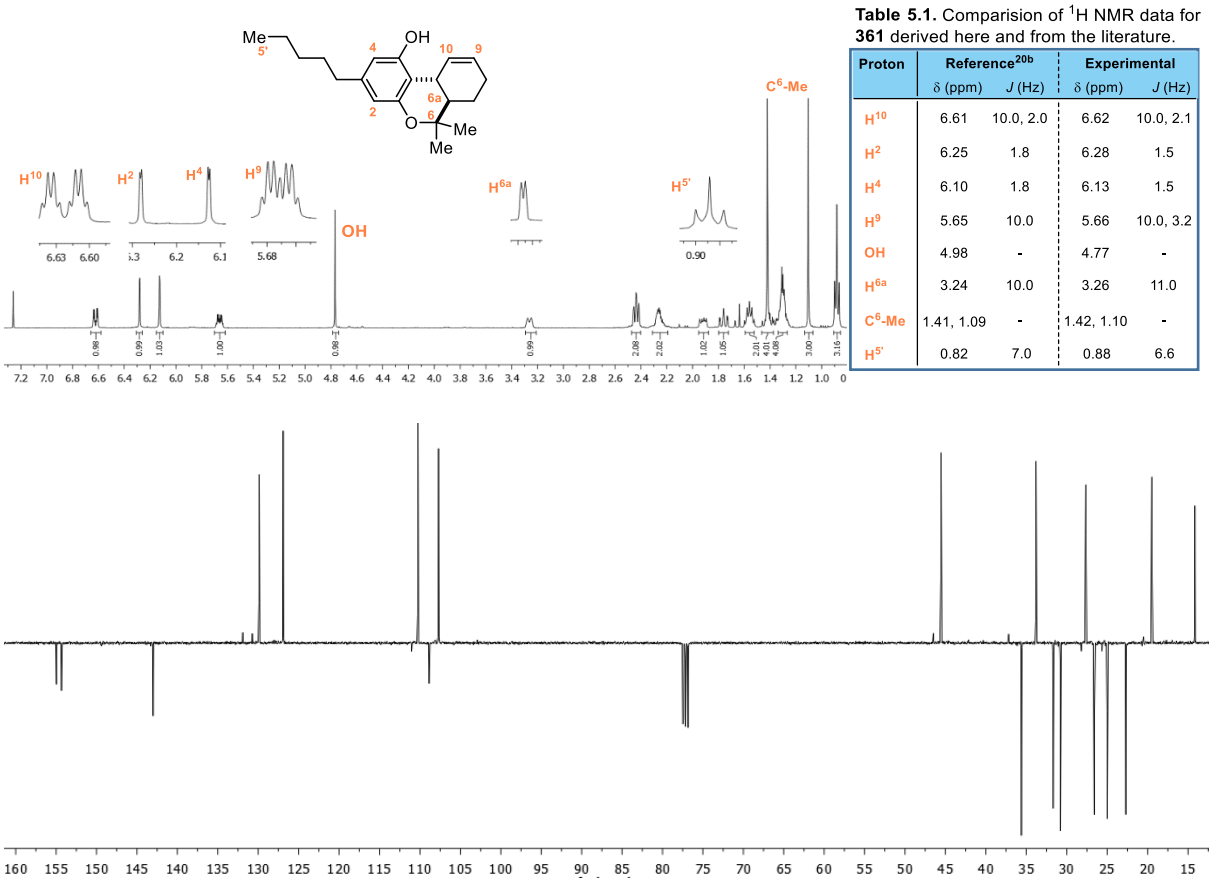


Table 5.1. Comparision of ^{1}H NMR data for **361** derived here and from the literature.

Proton	Reference[20b]		Experimental	
	δ (ppm)	*J* (Hz)	δ (ppm)	*J* (Hz)
H^{10}	6.61	10.0, 2.0	6.62	10.0, 2.1
H^{2}	6.25	1.8	6.28	1.5
H^{4}	6.10	1.8	6.13	1.5
H^{9}	5.65	10.0	5.66	10.0, 3.2
OH	4.98	-	4.77	-
H^{6a}	3.24	10.0	3.26	11.0
C^{6}-Me	1.41, 1.09	-	1.42, 1.10	-
$H^{5'}$	0.82	7.0	0.88	6.6

Figure 5.3. ^{1}H- and ^{13}C NMR spectra of normethyl-Δ^9-THC (**361**) in $CDCl_3$ (400 and 100 MHz)

5.4 Introduction of C9-methyl group via (4+2) annulation

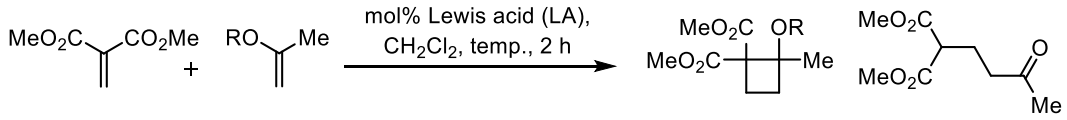
5.4.1 Synthesis of a methyl substituted DA-cyclobutane

Having demonstrated the viability of the general strategy, efforts were directed towards introduction of the C9-methyl group using methyl substituted DA-cyclobutane **216n** was targeted. To prepare this substrate, studies commenced with exposure of methylene malonate **224b** and enol ether **223g** to zinc bromide ($ZnBr_2$) at low temperature, conditions analogous to those used for the desmethyl variant (i.e. **216e**). Unfortunately, none of the desired DA-cyclobutane was observed and only malonate **359a** could be isolated from the reaction mixture (Table 5.2, entry 1).

The isolation of **359a** implicates the formation of the desired cyclobutane **216n** which is subsequently cleaved by $ZnBr_2$. When the reaction temperature or the catalyst loading were decreased to

supress this undesired cleavage, a similar outcome was observed (Table 5.2, entries 2 and 3).[21] Given the apparent propensity for ring opening, a more stable silyl ether was trialled. Unfortunately, even the slightly more stable TES enol ether **223h** failed to react with **224b** (Table 5.2, entry 4). Increasing reaction time to allow conversion of these substrates gave only trace amounts of the cleaved product **359a** (Table 5.2, entry 5). Finally, a range of Lewis acids known to promote related (2+2) cycloadditions[22] were also applied however, in these reactions, the desired cyclobutane was never observed under any circumstances (Table 5.2, entries 6-10).

Table 5.2. Attempted synthesis of DA-cyclobutane **216n**.



224b **223g** R = OTMS, **223h** R = OTES **216n** **359a**

entry	mol% LA	R	temp.(˚C)	result[a,b]
1	100 mol $ZnBr_2$	$SiMe_3$	–78	0% **216n**, 25% **359a**
2	100 mol $ZnBr_2$	"	–100	0% **216n**, 21% **359a**
3	50 mol% $ZnBr_2$	"	–78	0% **216n**, 17% **359a**
4	"	$SiEt_3$	"	N/R
5[c]	"	"	"	trace **359a**
6	10 mol% $FeCl_3$•Al_2O_3	$SiMe_3$	–78	"
7	5 mol% Tf_2NH	"	"	"
8	10 mol% $Yb(OTf)_2$	"	"	"
9	10 mol% $AlCl_3$	"	"	"
10	10 mol% $AlMe_3$	"	"	"

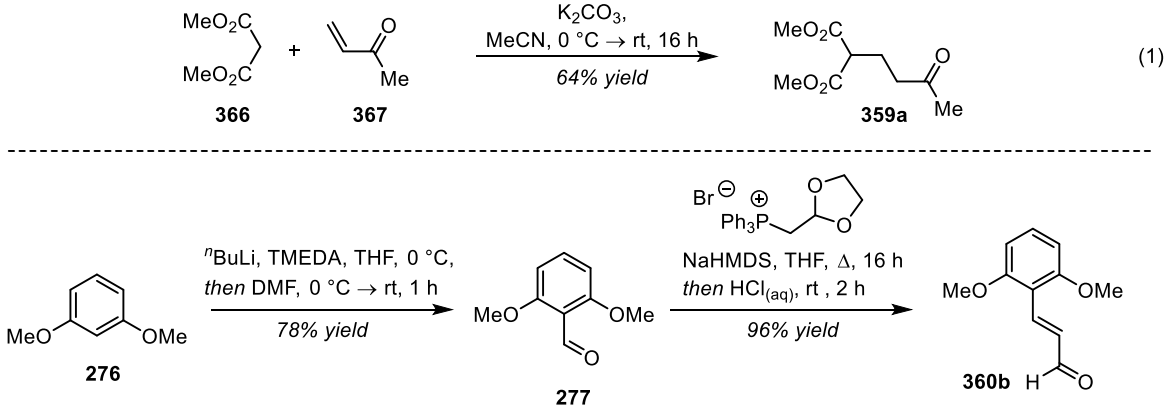
[a] Isolated yield of **359a** following flash column chromatography. [b] Trace quantities and complex mixtures observed in the ^{1}H NMR of the crude reaction mixture. [c] Reaction conducted for 6 h.

While product **359** potentially implicates formation of the desired cyclobutane, it could not be isolated or even observed by ^{1}H NMR analysis of the crude reaction mixture. Given these difficulties, attempts to install the C9-methyl group using this route were abandoned and attention was directed towards examining Studer's variant of the (4+2) annulation.

5.4.2 Aryl 2,6 disubstitution of in Studer's (4+2) annulation

To probe the viability of 2,6-disubstituted cinnamaldehydes in Studer's (4+2) annulation, methyl ketone **359** and α,β-unsaturated aldehyde **360b** were identified for model studies. Methyl ketone **359** was

prepared in 64% yield *via* potassium carbonate (K_2CO_3)-mediated 1,4-addition of dimethyl malonate (**366**) to methyl vinyl ketone (**367**) (Scheme 5.9, eq. 1).[23] After formylation of 1,3-dimethoxybenzene (**276**)[24], a one-pot Wittig/deprotection procedure was developed for the efficient conversion of benzaldehyde **277** to α,β-unsaturated aldehyde **360b** in 96% yield.

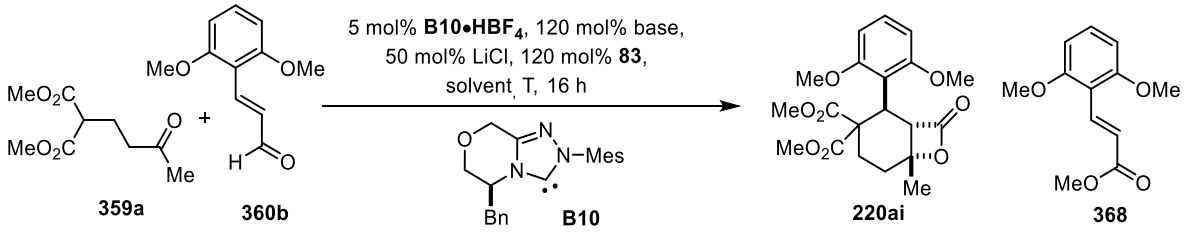


Scheme 5.9. Synthesis of model acyl fluoride **360b** and methyl ketone **359**.

With key substrates in hand, their viability in the proposed (4+2) annulation was examined. Exposure of **359a** and **360b** to conditions reported by Studer failed to produce the desired β-lactone. Instead, cinnamate ester **368** was the sole product (Table 5.3, entry 1). Given that the mechanism of Studer's annulation is likely to resemble our (4+2) annulation, we next trialled conditions which were found to be favourable in the latter reaction (*see Chapter 3, section 3.2).*

Unfortunately, when the reaction was conducted at higher temperatures, as used in our work, a similar outcome was observed (Table 5.3, entry 2). The reaction was also repeated using potassium hexamethyl disilazide to generate the NHC, however this did not improve the outcome (Table 5.3, entry 3). Finally, utilising the solvent system which was successful in our reaction was found to be incompatible, even at elevated temperatures, with substrates returned unchanged (Table 5.3, entries 4 and 5). In these cases, it is possible that solvation of lithium chloride (LiCl) by the solvent system prevents activation of the malonate to liberate methoxide, therefore supressing formation of cinnamate ester **368**.[15b]

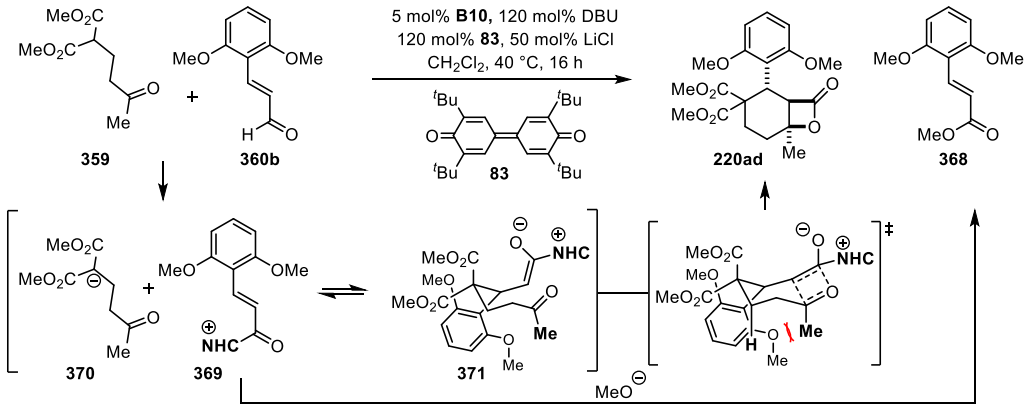
Table 5.3: Selected optimisations of Studer's (4+2) annulation.



entry	base	T (˚C)	solvent	result[a]
1	DBU	rt	CH_2Cl_2	20% **368**
2	"	40	"	23% **368**
3	KHMDS	"	"	14% **368**
4	"	"	9:1 THF:DMF	N/R
5	"	80	"	N/R

[a] Isolated yield of **368** following flash column chromatography.

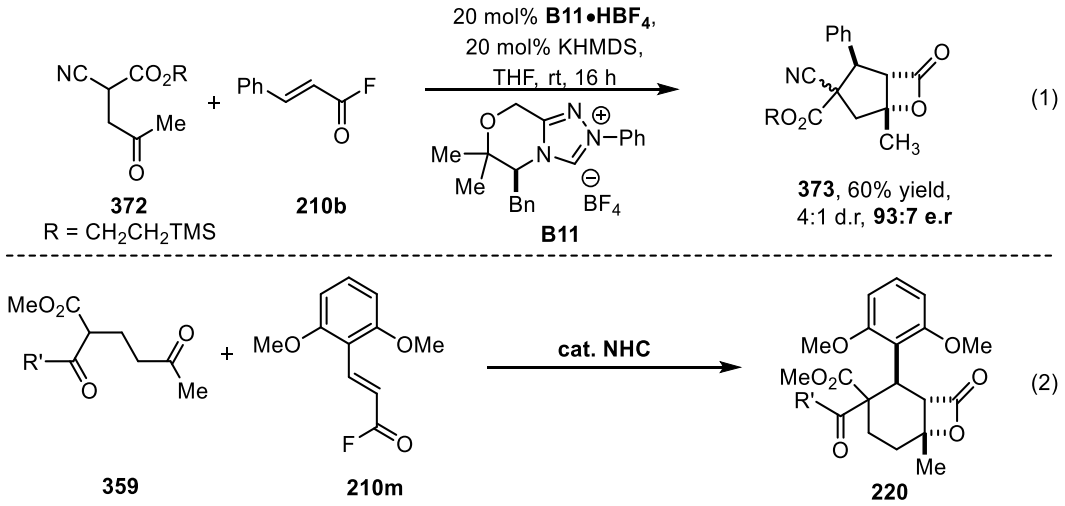
Isolation of cinnamate ester **368** from a number of reactions suggests that the α,β-unsaturated acyl azolium **369** intermediate is forming, however, it reacts through non-productive pathways (Scheme 5.10). Mechanistically, Studer proposes that 1,4-addition of enolate **370** to α,β-unsaturated acyl azolium **369** followed by an asynchronous (2+2) aldol/lactonisation process delivers the β-lactone products. Given that 1,4-addition is a reversible process, it is possible that unfavourable steric interactions slow the subsequent (2+2) process (**371**→**220ad**) an allow competing transesterification of the acyl azolium (**370**→**368**) to predominate. In this case, transesterification occurs *via* methoxide liberated from addition to the malonate esters. This is consistent with side-reactivity observed where 2,6-substituted α,β-unsaturated acyl azoliums were used in the analogous reaction of acyl fluorides and DA-cyclobutanes *(Chapter 4, Scheme 4.9)*.



Scheme 5.10. Application of Studer's (4+2) annulation.

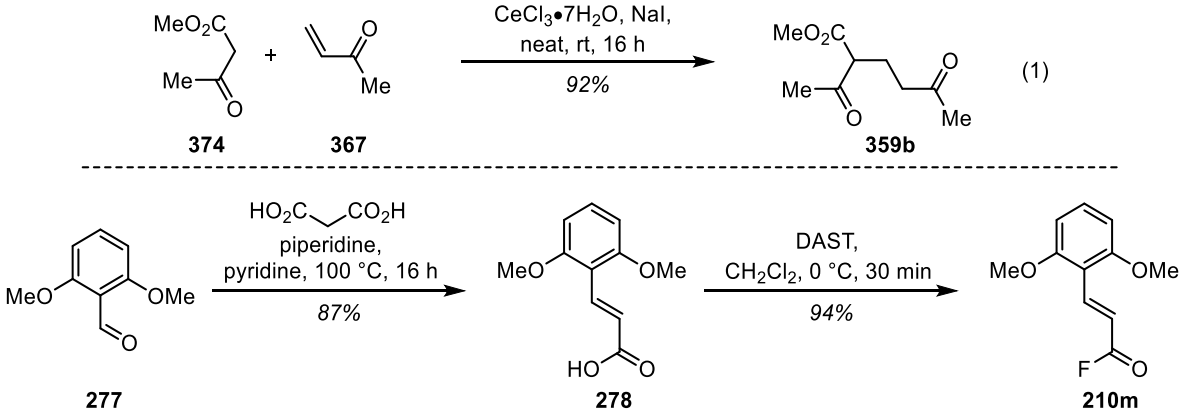
5.4.3 Silicon free acyl fluoride activation

Concurrent to these studies, research within our group revealed that α,β-unsaturated acyl fluorides can undergo NHC catalysed reactions with some 1,3-dicarbonyl substrates without silicon masking.[25] For example, malonitrile **372** and α,β-unsaturated acyl fluoride **210b** undergo a (3+2) annulation, providing cyclopentyl fused β-lactone **373** upon exposure to NHC **B11** (Scheme 5.11, eq. 1). This result suggested that it should be possible to exploit a ketone (i.e. **359**) in a direct annulation with the cinnamoyl fluoride **210m** to give access to the desired C9-methyl-bearing β-lactone scaffold (i.e. **220**) (Scheme 5.11, eq. 2).



Scheme 5.11. Silicon-free acyl fluoride activation

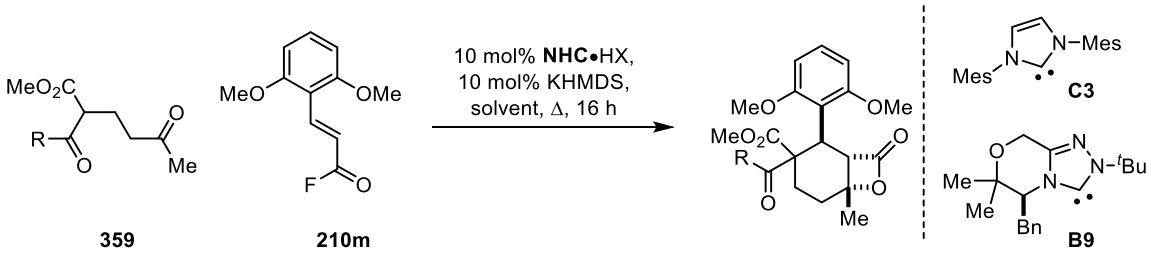
To investigate such a scenario, keto-ester **359b** was prepared by 1,4-addition of methylacetoacetate **374** to methyl vinyl ketone **367** in the presence of cerium chloride (Scheme 5.12, eq. 1).[26] This material, rather than the previously discussed malonate was initially examined due to its potential in approaches to other phytocannabinoids. As described previously in *Chapter 4*, Doebner-modified Knoevenagel condensation of benzaldehyde **277** followed by fluorination with DAST provided the model α,β-unsaturated acyl fluoride **220m**.



Scheme 5.12. Synthesis of ketoester **359b** and acyl fluoride **210m**.

With methyl ketones **359a** and **359b** in hand, their viability in the (4+2) annulation with acyl fluoride **210m** was examined. When keto ester-derived **359b** (R = Me) was exposed to either **B9** or achiral **C3** in the presence of unsaturated acyl fluoride **210m**, no reaction was observed (Table 5.4, entries 1 and 2). Similarly, when malonate derived **359a** (R = OMe) was subjected to the same conditions, the reaction also failed (Table 5.4, entries 3 and 4). To promote reactivity, and therefore conversion of the substrates, the series of reactions were repeated at increased temperatures using toluene, however, this did not change the outcome (Table 5.4, entry 5).

Table 5.4: Optimisation of silicon free (4+2) annulation



entry	NHC	R	solvent	result
1	**C3**	Me	THF	N/R
2	**B9**	"	"	N/R
3	**C3**	OMe	"	N/R
4	**B9**	"	"	N/R
5	**C3 or B9**	OMe or Me	toluene	N/R

5.5 Late stage introduction of C9-methyl group

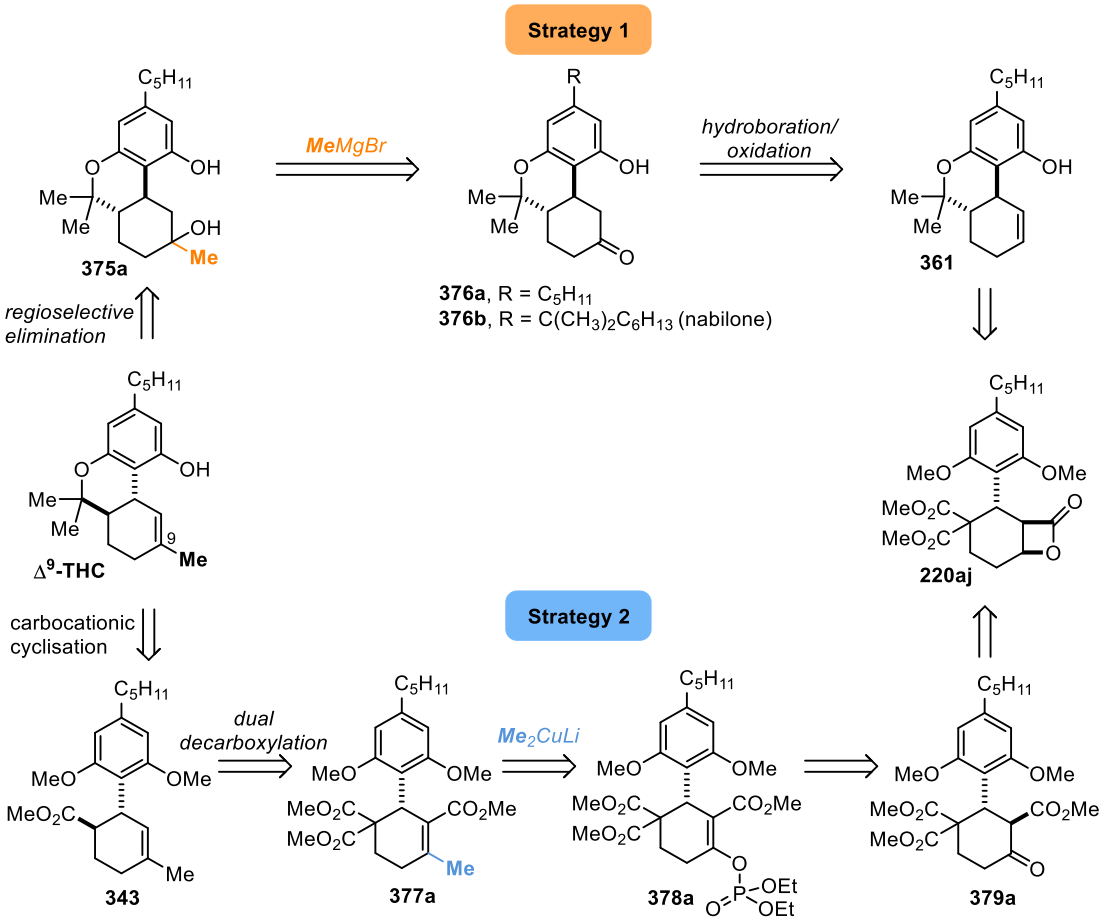
5.5.1 Design of alternate strategies for C9-methyl group installion

As all efforts to synthesise a methyl bearing β-lactone were not fruitful, alternate strategies to install the C9-methyl group were developed. Specifically, we revisited the synthesis of (–)-normethyl-Δ^9-THC (**361**) and recognised that with appropriate derivatisation of β-lactone **220aj**, the C9-methyl group could be introduced. In this regard, two strategies were proposed (Scheme 5.13).

The first strategy invokes a regioselective elimination of alcohol **375a**, a known precursor of (–)-Δ^9-THC (**325**),[9i,12] which in turn can be prepared *via* methylmagnesium bromide (MeMgBr) addition to ketone **376a**. The ketone **376a** should be accessible though oxidation of the alcohol generated by hydroboration/oxidation of (–)-normethyl-Δ^9-THC (**361**). If successful, appropriate modification of the

alkyl chain of the acyl fluoride, would also offer a route to pharmaceutical cannabinoid nabilone (**376b**, R = $C(CH_3)_2C_6H_{13}$).[27]

In the second route, the known Δ^9-THC precursor *trans*-**343**, which features in the initial strategy, could be synthesised *via* Krapcho decarboxylation of malonate **377a** with concomitant decarboxylation of the mono-ester. The C9-methyl group can then be introduced *via* cross-coupling of enol phosphate **378a** with lithium dimethyl cuprate (Me_2LiCu), itself available from β-keto ester **379a**. Finally, we envisaged reductive β-lactone cleavage of **220aj** and global oxidation of the resultant diol would provide the required β-keto ester **379a**.



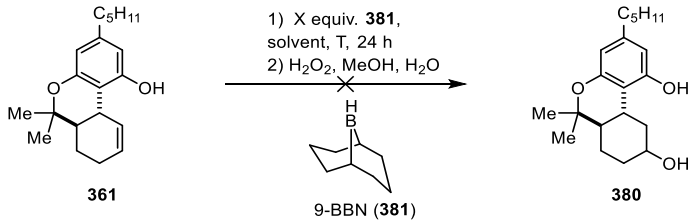
Scheme 5.13. Alternate strategies for synthesis of (–)-Δ^9-THC.

5.5.2 Hydroboration/oxidation strategy using (–)-normethyl-Δ^9-THC

With (–)-normethyl-Δ^9-THC (**361**) available through the previously developed route (Scheme 5.8), its viability in a hydroboration/oxidation protocol was examined. Initial experiments were conducted with 9-BBN (**381**) to enable the regioselective introduction of the alcohol. When **361** was exposed to one equivalent of 9-BBN in THF, no reaction was observed and the starting material was reisolated unchanged (Table 5.5, entry 1). It is possible that the phenolic functionality was either coordinating, or quenching the

borane reagent, hence two and four equivalents of 9-BBN were used, however this failed to promote the reaction (Table 5.5, entries 2 and 3). Repeating the reaction higher temperature to enable conversion of the substrate did not allow the synthesis of **380**, though some decomposition was observed (Table 5.5, entry 4). Conducting the reaction in toluene provided a similar outcome, with reflux inducing further decomposition (Table 5.5, entries 5 and 6). Finally, the sterically demanding 9-BBN was substituted with borane dimethylsulfide complex (BH_3•SMe_2), however no hydroboration products were observed (Table 5.5, entry 7).

Table 5.5: Attempted hydroboration of (–)-normethyl-Δ^9-THC (**361**)



entry	X equiv.	solvent	T (°C)	result[a]
1	1	THF	rt	**361** reisolated
2	2	"	"	"
3	4	"	"	"
4	"	"	66	90% **361** reisolated
5	"	toluene	"	85% **361** reisolated
6	"	"	110	70% **361** reisolated
7	4 equiv. BH_3•SMe_2	THF	rt	87% **361** reisolated

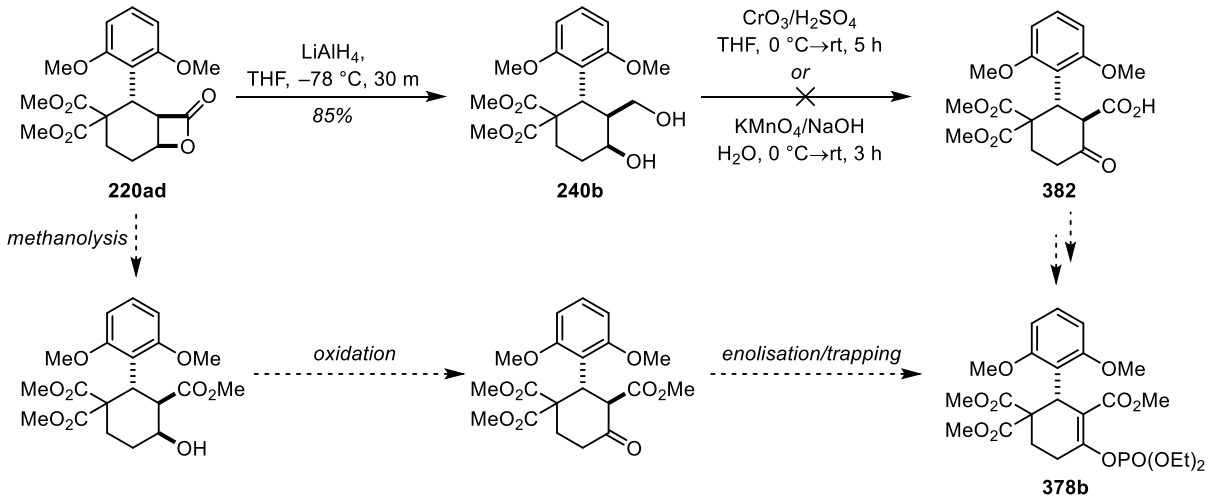
[a] Reisolation of **361** following flash column chromatography.

Upon closer review of the literature, the inert nature of the alkene in **361** toward hydroboration is unsurprising, with only few examples of the hydroboration of internal 3-phenylcyclohexene motifs reported. These reactions were sluggish, often requiring super-stoichiometric (>10 equivalents) of BH_3•SMe_2 and extended reaction times (>4 days).[28] In addition, the yields for these reactions are modest, hence, it was decided to examine the enol phosphate cross-coupling strategy.

5.5.3 Enol phosphate/cuprate cross-coupling strategy

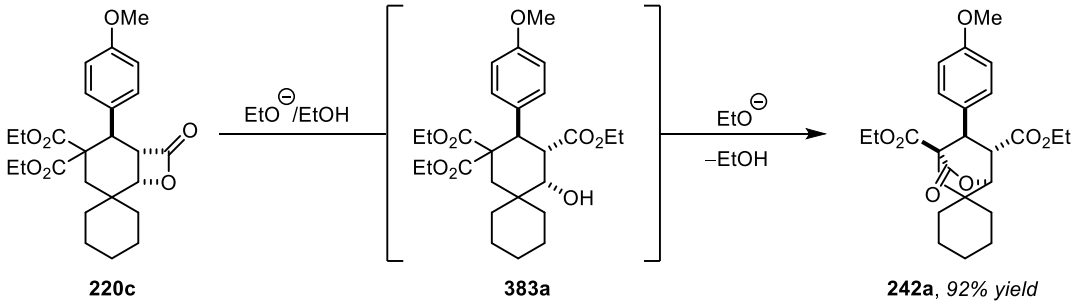
Investigations into our proposed cross-coupling strategy required the synthesis of a suitable enol phosphate **378b** (Scheme 5.14). Having prepared surplus β-lactone **220ad** during our studies towards (+)-bisabosqual A *(see Chapter 4, Scheme 4.9)*, studies here were conducted without 4-pentyl substitution on the aromatic ring. Thus, reductive β-lactone cleavage developed previously *(see Chapter*

3, Scheme 3.24) allowed conversion of β-lactone **220ad** to the corresponding diol **240b.** Unfortunately, global oxidation was not viable using either Jones reagent or potassium permanganate, with both procedures leading to complex mixtures. Although formation of acid **382** was suspected based upon ^{1}H NMR analysis of the crude residue, purification from the complex reaction mixture proved difficult. Given the difficulties in executing this oxidation, we envisaged an alternate synthesis of enol phosphate **378b** *via* methanolysis, oxidation and enolisation from β-lactone **220ad.**



Scheme 5.14. Attempted synthesis of enol phosphate **378b.**

In regard to subjecting **220ad** to methanolysis, derivatisation studies described in *Chapter 3* demonstrated that facile translactonisation occurs upon ethanolysis of β-lactone **220c** which results in bicyclic lactone **242a** (Scheme 5.15). Presumably this occurs by ethoxide opening of the β-lactone followed by transannular lactonisation however, it was proposed that if the second step in this process could be supressed then it should be possible to isolate alcohol **383a.**



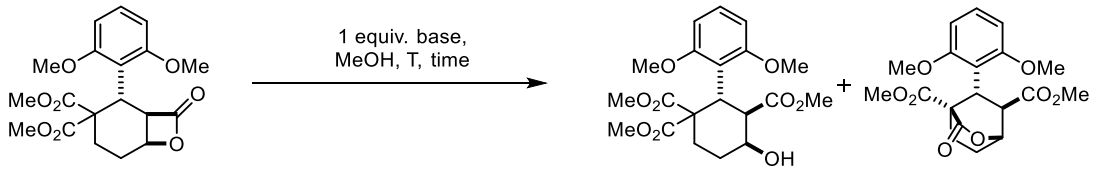
Scheme 5.15. Ethanolysis/translactonisation of ß-lactone **220c.**

Studies commenced with exposure of β-lactone **220ad** to sodium methoxide (NaOMe) for one hour, after which TLC analysis revealed the presence of 2 compounds. Pleasingly, analysis of the crude reaction mixture revealed desired the alcohol **383b** had indeed formed, albeit, as a minor product alongside the

bicyclic lactone **242b** (Table 5.6, entry 1). Upon purification, silica-mediated lactonisation converted the alcohol **383b** through the bicyclic lactone **242b**, highlighting the propensity for this reaction pathway. Further reduction of the reaction time increased the proportion of alcohol **383b** significantly although now incomplete consumption of the β-lactone was observed (Table 5.6, entry 2).

It was hoped that less basic sodium carbonate (Na_2CO_3) would suppress lactonisation, however, its poor solubility in MeOH prevented any reaction (Table 5.6, entry 3). Pleasingly, more soluble potassium carbonate (K_2CO_3) allowed the reaction to proceed and with improved selectivity (Table 5.6, entry 4). Given that alcohol/alkoxide reactivity can be affected by ion pairing,[29] we examined the effect of counterions on selectivity. Pleasingly, when the reaction was repeated with a larger caesium counterion, selectivity for alcohol **383b** was improved (Table 5.6, entry 5). Conversely, smaller counter-ions (i.e. lithium) resulted in rapid conversion to the lactone **242b** (Table 5.6, entry 6). Reducing the reaction temperature also improved the selectivity for **383b** (Table 5.6, entry 7), however, all further attempts to optimise using $CsCO_3$ were unsuccessful. Fortuitously, the reaction exhibited a particular sensitivity to the nature of the base, with potassium cyanide (KCN) providing optimal selectivity (Table 5.6, entry 7).

Table 5.6: Selected optimisations for methanolysis of β-lactone **220ad**.



220ad **383b** **242b**

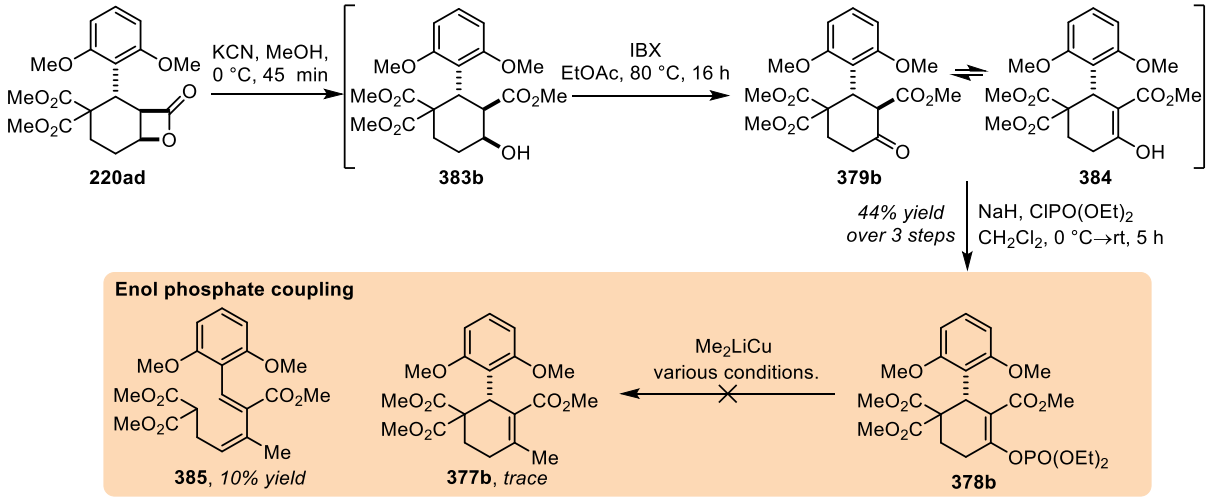
entry	base	T (°C)	time	ratio[a] 220a : 383b : 242b
1	NaOMe	rt	1 h	10 : 90 : 0
2	"	"	0.5 h	32 : 50 : 18
3[b]	Na_2CO_3	"	16 h	N/R
4[b]	K_2CO_3	"	1 h	55 : 43 : 2
5[b]	$CsCO_3$	"	1 h	60 : 38 : 2
6[b]	LiOMe	"	0.5 m	23 : 77 : 0
7[b]	$CsCO_3$	0	1.5 h	66 : 33 : 1
8[b]	KCN	0	0.75 h	74 : 23 : 3

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Monitored closely by TLC for consumption of **220ad** and quenched with H_2O immediately.

Due to the transannular lactonisation that occurs upon exposure to silica *(vide supra)*, purification was avoided, and the crude mixture of alcohol **383b** and lactone **242b** was immediately subjected to with 2-iodooxybenzoicacid (IBX). Unfortunately, purification was also hindered at this step due to the presence

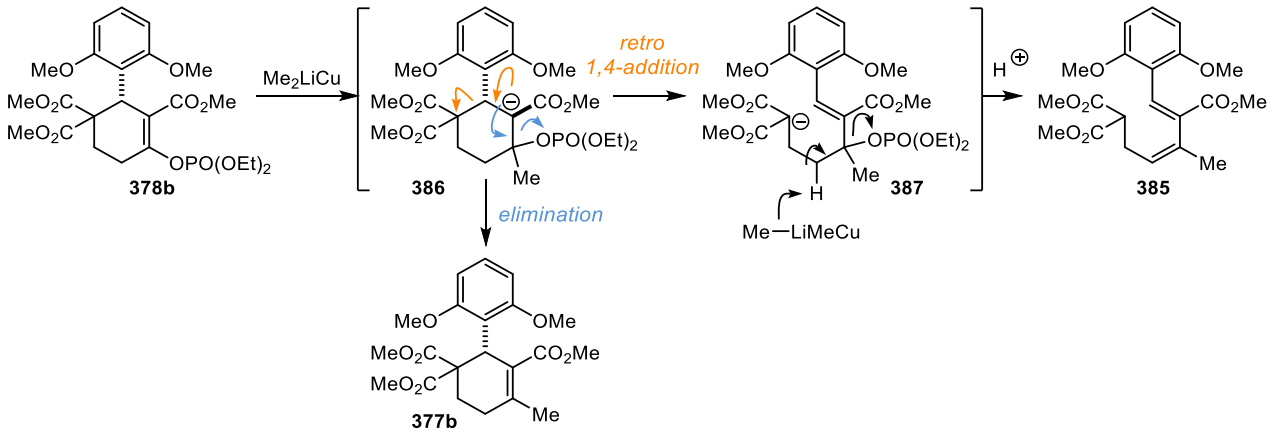
of lactone **242b** and a mixture of the keto and enol tautomers (**379b** and **384**, Scheme 5.16). In contrast enol phosphate **378b** was easily isolated in 44% yield by telescoping the methanolysis, oxidation, and enolisation and by finally introducing chlorodiethylphosphate to the reaction mixture.

Unfortunately, all attempts to cross-couple enol phosphate **378b** with Me_2LiCu were unsuccessful, with no reaction observed at low temperature whilst decomposition and competing side reactions leading to the formation of **385** predominated at elevated temperatures. Although the desired cross-coupled product **377b** was suspected based on LCMS analysis of the crude reaction mixture ($M+H^+ = 407.2$), it could not be isolated in synthetically viable yields.



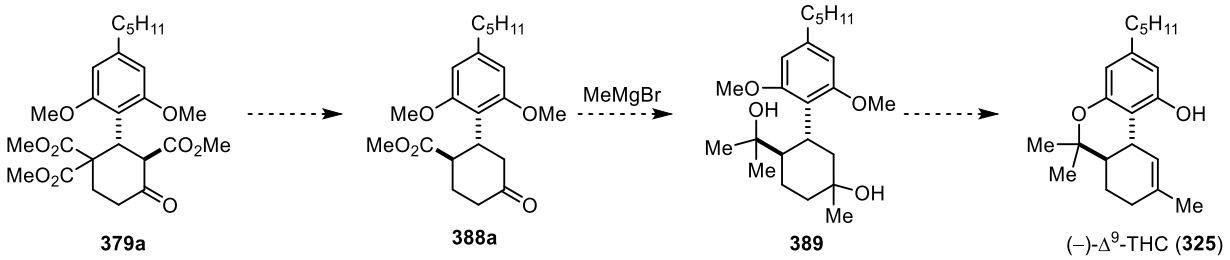
Scheme 5.16. Synthesis and cross-coupling of enol phosphate **378b**.

We propose that the formation of diene **385** proceeds through initial 1,4-addition of Me_2LiCu with enol phosphate **378b** to give enolate **386** (Scheme 5.17). Subsequent elimination of phosphate would provide the desired product **377b**, however, retro 1,4-addition predominates before base-mediated elimination gives the observed diene **385**. Stabilisation of carbanion **387** by the malonate and development of extended conjugation in diene **386** are likely key factors driving this pathway.



Scheme 5.17. Proposed formation of diene **385**.

Whilst it is disappointing that both of the revised strategies were not viable, we were encouraged by the formation of keto-ester **379b**. An alternate strategy using an intermediate of this type to access the natural product would exploit a dual Krapcho decarboxylation procedure of **379a** to generate ketone **389a**, with exhaustive methylation providing diol **389** and, after carbocationic cyclisation and elimination, (−)-Δ^9-THC (**325**) (Scheme 5.18).

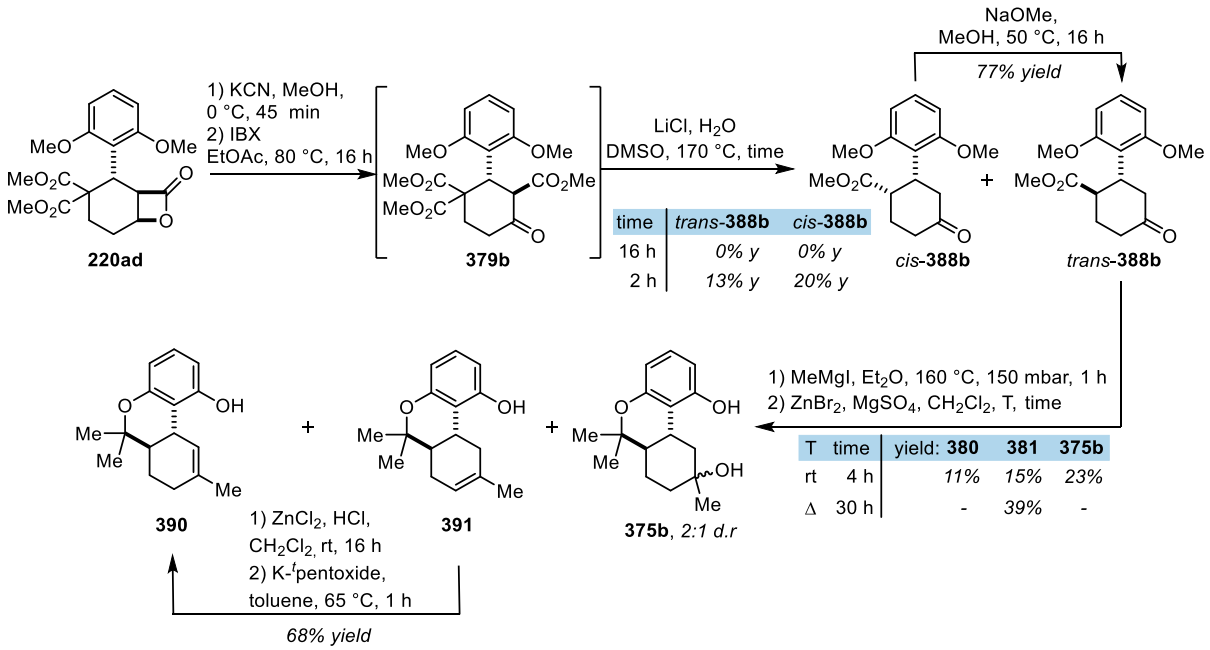


Scheme 5.18. Proposed strategy for synthesis of (−)-Δ^9-THC (**325**) from **379a**.

5.5.4 Dual Krapcho decarboxylation strategy

Using the model system, it seemed probable that model β-keto ester **379b**, bearing two 1,3-dicarbonyl motifs, could undergo dual Krapcho decarboxylation, thereby generating ketone **388b**. Unfortunately, when the β-keto ester **379b** was subjected to standard decarboxylation conditions, complete decomposition was observed after 16 h (Scheme 5.19). Fortuitously, simply reducing the reaction time to 2 hours allowed the isolation of ketone *cis*/trans-**388b** in 33% yield over 3-steps as a 2:1 (*cis* : *trans*) mixture. Intriguingly, the dual Krapcho procedure occurred at an enhanced rate compared to the mono-decarboxylation described previously, which required upwards of 12 hours reaction time. Potential reasons for this divergence are are discussed later (see Scheme 5.21).

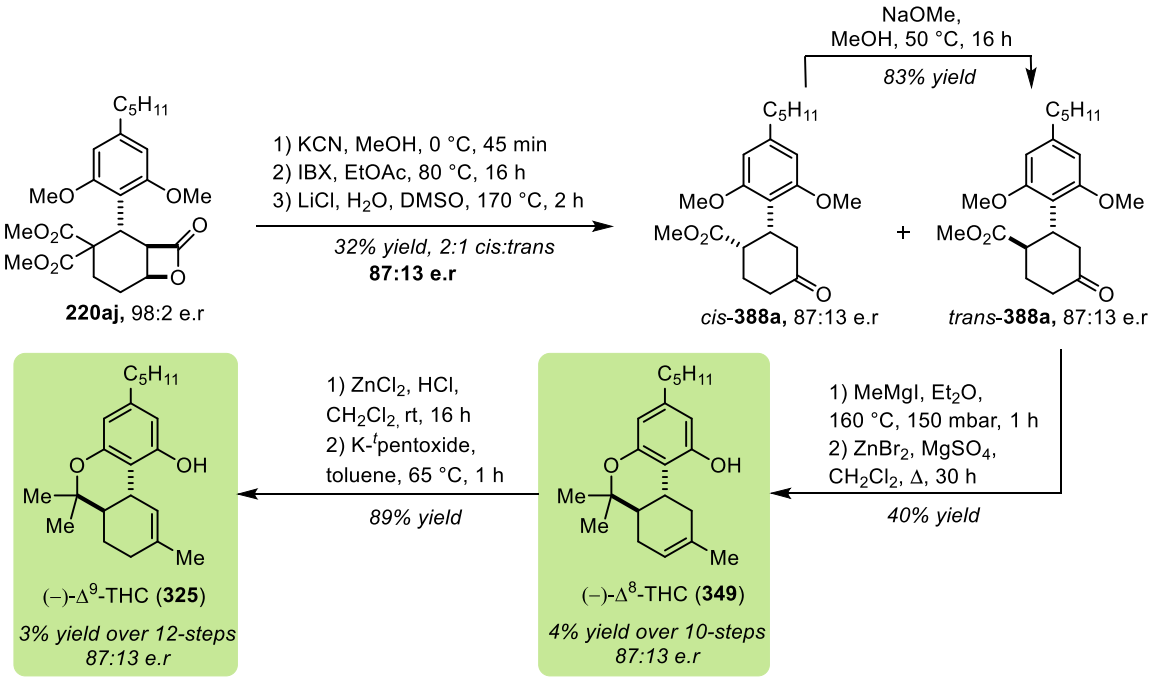
Pleasingly, the undesired *cis*-**388b** isomer was amenable to NaOMe-mediated epimerisation using conditions exploited previously for the synthesis of ester **365**. It was hoped that from *trans*-**388b**, application of the Grignard/carbocationic cyclisation procedure would then provide alcohol **375b** and subsequently both despentyl-Δ^9-THC (**390**) and despentyl-Δ^8-THC (**391**) following Zhous methods.[10] Under the standard conditions, facile elimination gave rise to a mixture of despentyl-Δ^9-THC (**390**) and despentyl-Δ^8-THC (**391**) isomers in addition to the desired alcohol **375b**. It was not possible to supress elimination, however, the reaction was rendered selective for despentyl-Δ^8-THC (**391**) by increasing the reaction temperatures and reaction time (30 h). Finally, conversion of despentyl-Δ^8-THC (**391**) to despentyl-Δ^8-THC (**390**) was achieved in 68% yield using a two-step procedure involving chlorination with gaseous HCl, and a regioselective elimination with potassium *tert*-amylate that is directed by the pendant phenolate.[9i]



Scheme 5.19. Dual Krapcho decarboxylation of **379a** and synthesis of **390** and **391**.

5.5.5 Synthesis of (−)-Δ⁸-THC and (−)-Δ⁹-THC

With the overall strategy established, all that remained was to employ enantioenriched β-lactone **220aj** bearing the 4-pentyl chain on the aromatic A ring in the developed sequence. Pleasingly, methanolysis, oxidation, dual Krapcho decarboxylation with this substrate proceeded without event to deliver ketone *trans*-**388a** in 27% yield after epimerisation, albeit with some erosion of enantiopurity (87:13 e.r) (Scheme 5.20). Nevertheless, Grignard addition, and $ZnBr_2$ mediated carbocationic cyclisation and elimination was viable with (−)-Δ⁸-THC (**3**) isolated in 40% yield. Finally, the isomerisation procedure described previously furnished (−)-Δ⁹-THC (**325**) in 89% yield over two subsequent steps.



Scheme 5.20. Synthesis of (−)-Δ^8-THC (**349**) and (−)-Δ^9-THC (**325**)

With (−)-Δ^9-THC (**325**) in hand, it was possible to compare the ^{1}H NMR (Figure 5.4) and ^{13}C NMR (Figure 5.5) data to those reported in the literature. Pleasingly, the spectroscopic data derived from the purified material matched in every respect, that described by Trost[13d] (see Table 5.7 for relevant comparison of ^{13}C NMR data). The specific rotation of (−)-Δ^9-THC (**325**) prepared here ($[\alpha]^{25} = -112.0°$) was accordingly lower compared to the enantiopure sample ($[\alpha]^{25} = -152.3°$) reported in the same literature and is consistent with the enantiomeric ratio (87:13) determined by chiral HPCL (87:13 e.r) analysis.

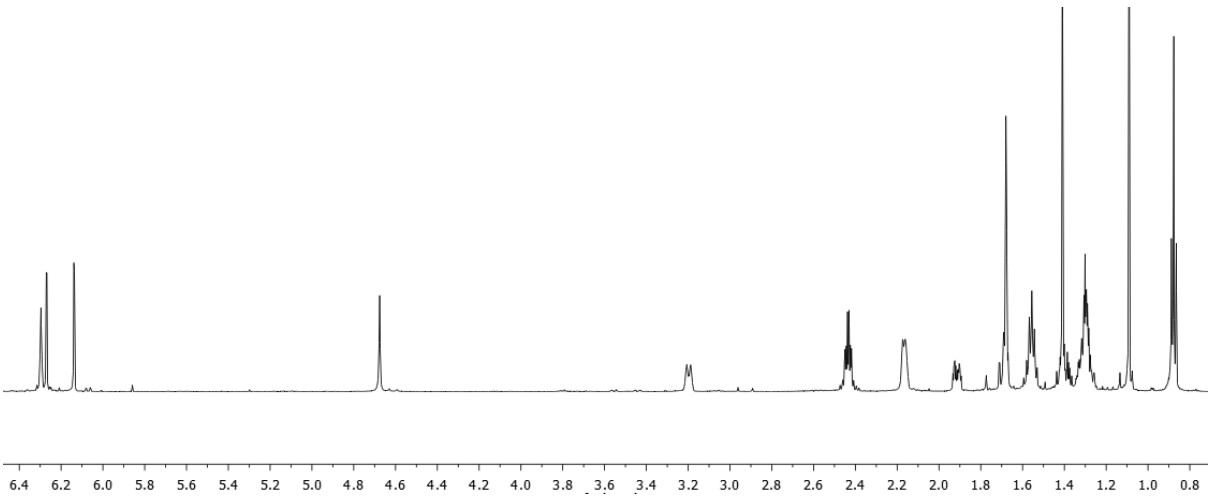


Figure 5.4. ^{1}H NMR spectra of Δ^9-THC (**325**) in $CDCl_3$ (400 MHz).

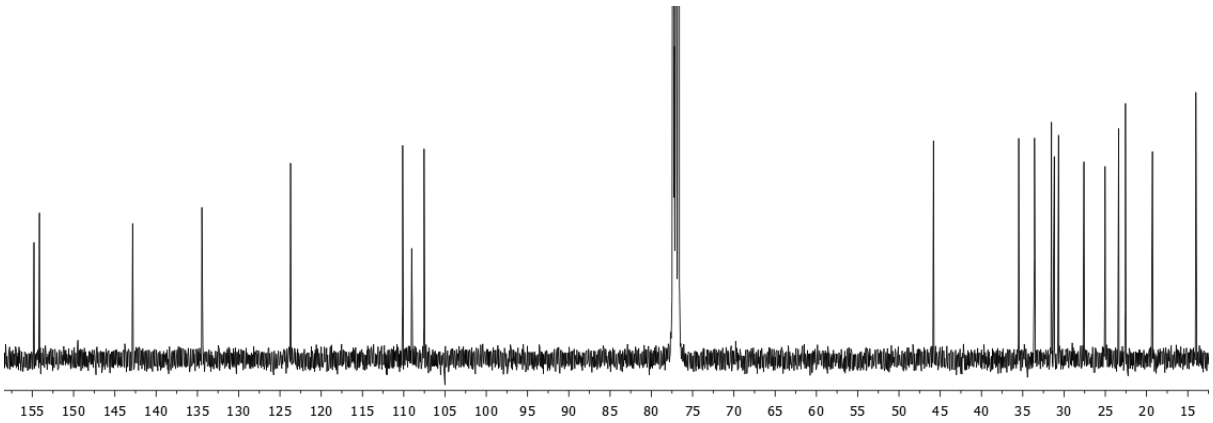
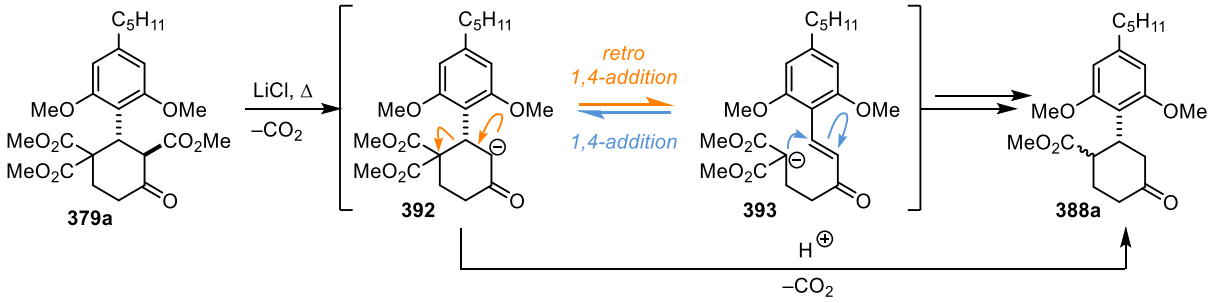


Figure 5.5. ^{13}C NMR spectra of Δ^9-THC (**325**) in $CDCl_3$ (100 MHz).

Table 5.7. Comparison of ^{13}C NMR signals from Δ^9-THC (**325**) derived from Trost's work and the present study.

δ >100 ppm		δ <100 ppm	
Trost's sample	**Experimental**	**Trost's sample**	**Experimental**
154.8	154.9	77.2	77.3
154.1	154.3	45.8	46.0
142.8	143.0	34.5	35.6
134.5	134.6	33.5	33.7
123.7	123.9	31.5	31.7
110.1	110.3	31.1	31.3
109.0	109.2	30.7	30.8
107.6	107.7	27.6	27.7
		25.0	25.2
		23.4	23.5
		22.5	22.7
		19.3	19.4
		14.0	14.2

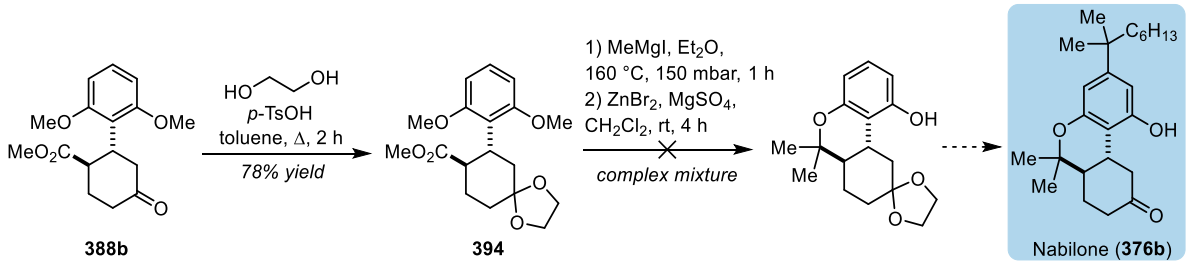
The decrease in enantiopurity in the conversion of **379a** to **388a** is potentially due to retro 1,4-addition chemistry akin to that proposed previously (Scheme 5.17) for the formation of diene **385**. Specifically, presuming dealkoxycarbonylation of β-keto ester **379a** generates enolate **392**, two pathways may prevail; firstly, protonation and a second dealkoxycarbonylation results in the desired ketone **388a**, while a second pathway invokes retro 1,4-addition to give enolate **393**, before 1,4-addition regenerates the enolate **392** and provides ketone **388a** after an additional decarboxylation event (Scheme 5.21). Through this mechanism, the benzylic stereocentre is becomes sp^2 hybridised (i.e. **393**), leading to some loss of enantiopurity. Additionally, this resonance between **392** and **393** may explain the rate enhancement observed for the dual Krapcho decarboxylation compared to that of the mono decarboxylation event.



Scheme 5.21. Proposed mechanism for enantioerosion.

5.5.6 Model studies toward the synthesis of Nabilone

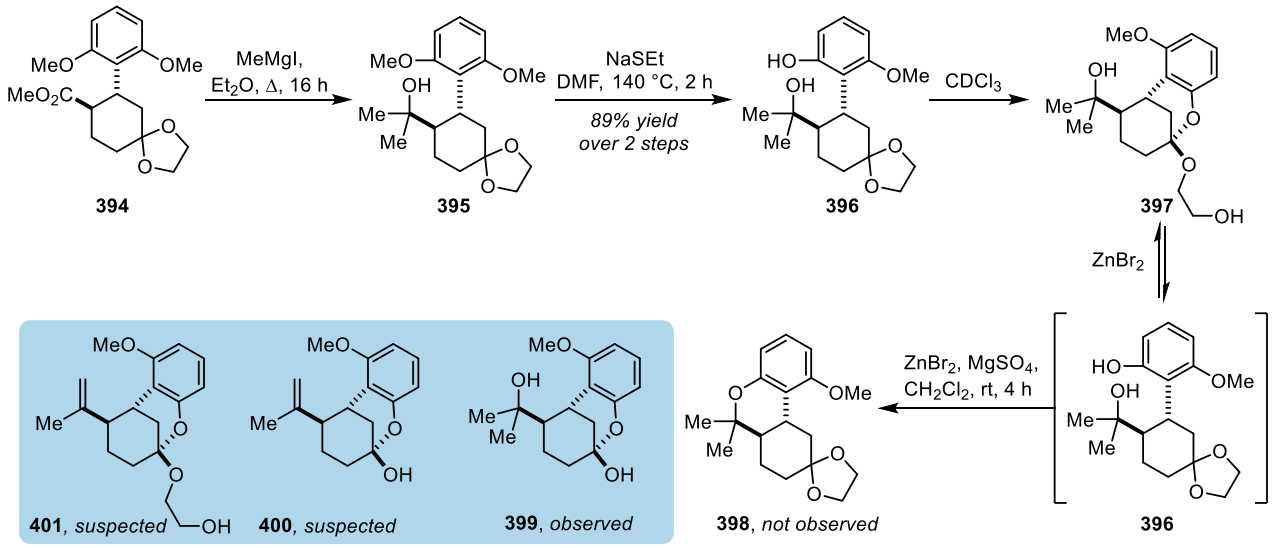
During studies to effect the hydroboration of (–)-normethyl-Δ^9-THC (**361**), a pharmaceutical cannabinoid analogue nabilone (**376b**) was also targeted. Although access to this scaffold through hydroboration was not possible, the route developed here which accesses β-ketoesters **388a and 388b** offered new opportunity to explore the synthesis of nabilone. Specifically, a ketal protection/deprotection strategy was envisaged (Scheme 5.22). Thus, protection of model β-ketoester **388b** with ethylene glyocol in the presence of *p*-TsOH provided ketal **394** in 78% yield. Unfortunately, when subjected to the forcing conditions for two step methylation, deprotection and carbocationic cyclisation, a complex mixture of products was obtained.



Scheme 5.22. Two-step methylation, deprotection and cyclisation of **394**

To overcome this, a stepwise sequence utilising milder conditions was assessed. Addition of MeMgI proceeded smoothly to provide tertiary alcohol **395** before methyl ether deprotection mediated by sodium ethyl thiolate (NaSEt), liberated phenol **396** in 89% yield over two steps (Scheme 5.23). Although the desired phenol **396** was initially isolated, rapid transketalisation in deuterated chloroform resulted in quantative conversion to diol **397**. It was hoped that an equilibrium could be established between ketals **396** and **397** and thereby allow *in situ* resolution to give pyran **398** however, when **387** was subjected to $ZnBr_2$, none of the desired product was observed. Instead, partial transketalisation and/or elimination resulted in the formation of hemiacetal **399** and suspected products **400** and **401**. It is probable a similar

transketalisation operates in the harsh two-step procedure described above, resulting in the complex mixture of products observed.

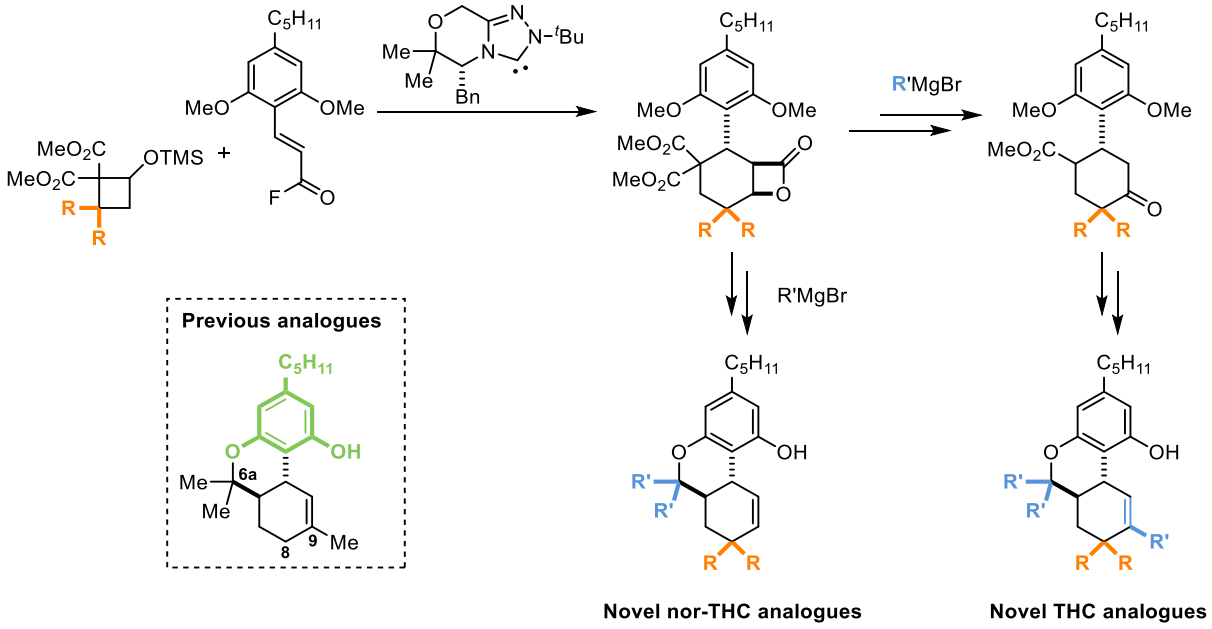


Scheme 5.23. Stepwise addition, deprotection and cyclisation of **394**.

5.6 Conclusions and outlook

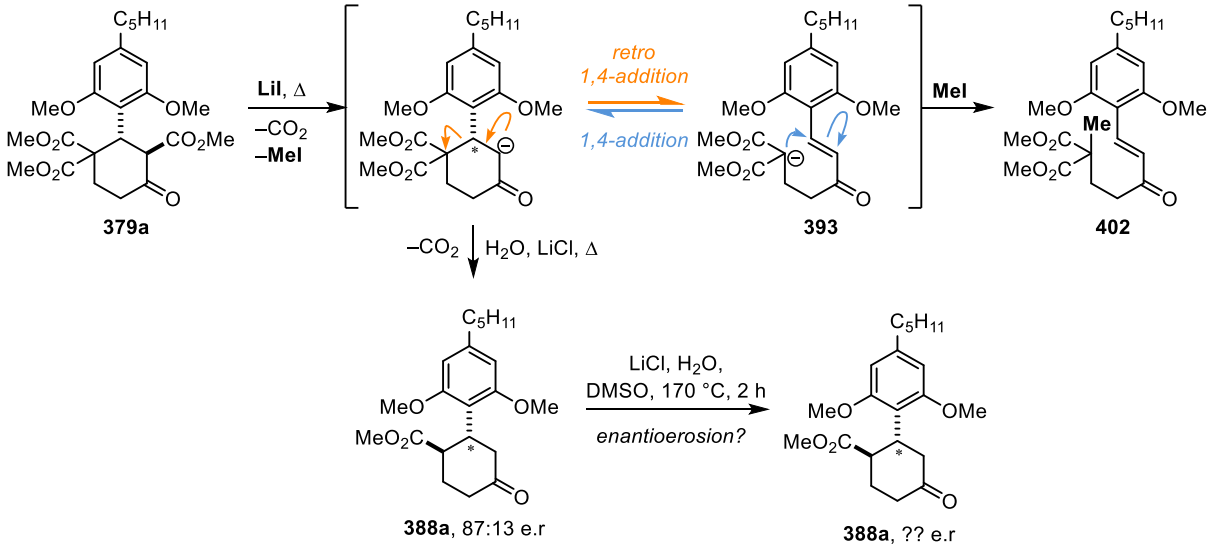
Several NHC catalysed (4+2) annulations were examined for the construction of the cyclohexyl core *en route* to (−)-Δ^8-THC (**349**) and (−)-Δ^9-THC (**325**). Of these, the enantioselective (4+2) annulation of donor-acceptor cyclobutane **216e** and α,β-unsaturated acyl fluoride **210p** was shown to be most valuable in realising the synthesis. After examination of several strategies to install the C9-methyl group, including use of methyl bearing DA-cyclobutane **216n**, hydroboration and enol phosphate coupling, a dual Krapcho decarboxylation procedure was established to access ketone **388a**. Subsequent methylation, and carbocationic cyclisation and elimination, generated (−)-Δ^8-THC (**349**) in 10-steps from commercially available olivetol, with isomerisation of the alkene providing (−)-Δ^9-THC (**325**) in two additional operations. In addition, studies toward the pharmaceutical cannabinoid nabilone were presented, however the proposed ketal protection strategy was found to be unviable due to problematic transketalisation.

The outlook of this study centres on analogue development for biological evaluation. Surprisingly, while significant attention has been given to substitution of the aromatic motif and C3, the biology of THC analogues possessing modification at C8 and C6a (Scheme 5.24) is far less studied.[7] We believe the sequence developed here offers opportunity for substitution of C8 and C6a for normethyl-Δ^9-THC analogues and C8, C6a, and C9 for Δ^9-THC analogues.



Scheme 5.24. Proposed normethyl-Δ^9-THC and Δ^9-THC analogue development

To enable the development of Δ^9-THC analogues, further optimisation of the sequence may be prudent. To address issues with enantioerosion, examination of its mechanism may inform future directions. By utilising lithium iodide (LiI), iodomethane (MeI) would be liberated upon dealkoxycarboxylation of β-keto ester **379a** (Scheme 5.25). If retro 1,4-addition operates, it may be possible to trap the cleaved enolate **393** with MeI under anhydrous conditions to give **402**. In addition, if enantioerosion of the product is occurring, this could be determined by resubjecting the ketone **388a** itself to the reaction conditions.



Scheme 5.25. Proposed studies for determining mechanism of enantioerosion.

5.7 References

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Chapter 6. Experimental Section

6.1 General experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DRX600 spectrometer operating at 150 MHz for carbon nuclei, a Bruker DRX400 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei or a Bruker DRX300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Infrared spectra (ν_{max}) were recorded on an Agilent Cary 630 FTIR Spectrometer. High resolution mass spectra (HRMS) (ESI) were recorded on a Bruker BioApex 47e FTMS fitted with an Analytical electrospray source using NaI for accurate mass calibration.

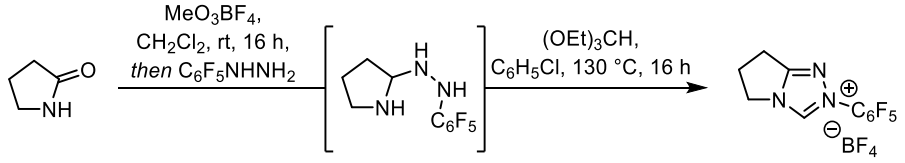
Analytical chiral HPLC was performed with an Agilent Technologies 1260 HPLC or a Perkin Elmer Series 200 HPLC using either a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. or using a RegisCell™ 5μm column (4.6 mm x 25 cm) obtained from Regis Technologies, Inc. with visualization at, 230, 220 or 210 nm.

Flash column chromatography was performed on silica gel (Davisil LC60A, 40-63 μm silica media) using compressed air. Thin layer chromatography (TLC) was performed using aluminum-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F254 plates). Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with potassium permanganate or vanillin stain followed by heating. Starting materials and reagents were purchased from Sigma-Aldrich, Merck, Oakwood, Combi-Blocks or Alfa-Aesar and were used as supplied. Diethyl ether (Et_2O) and tetrahydrofuran (THF) and 1,4-dioxane were dried over sodium benzphenone ketyl. Dichloromethane (CH_2Cl_2) was dried by passing over activated alumina. Toluene, acetonitrile and benzene were dried by passing over activated 3 Å molecular sieves. DMF was dried by stirring with calcium hydride overnight before being filtered and distilled under reduced pressure, and stored over 3 Å molecular sieves. DMSO was dried by stirring over activated 3 Å molecular sieves overnight and then distilled under reduced pressure and stored over 3Å molecular sieves. Methanol was dried over and distilled from magnesium methoxide. Anhydrous diglyme was purchased from Sigma-Aldrich and used as supplied. Unless otherwise stated, all reactions were conducted in flame-dried glassware under an atmosphere of nitrogen.

Compounds **210a**, **210f-l**, **216a**, **216f**, **216h**, **220a**, **220b**, **220d-j**, **220n-p**, **220y-aa**, **223g**, **223h** and **243** were prepared by Dr. Alison Levens.

6.1.1 Preparation of catalysts

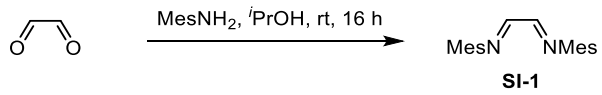
Tetrafluoro-l4-borane, 2-(6,6,6,6,6-pentafluoro-6l8-hexa-1,3,5-triyn-1-yl)-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium salt (B6•HBF$_4$)[1]



Following the procedure by Rovis,[1] a flame-dried RBF under N_2 was charged with 2-pyrrolidinone (10 mmol) and CH_2Cl_2 (50 mL) before trimethyloxonium tetrafluoroborate (10 mmol) was added in one portion. The suspension was stirred for 16 h at room temperature before pentafluorophenylhydrazine (10 mmol) was added and the mixture stirred for an additional 16 h at this temperature. The CH_2Cl_2 was removed under reduced pressure and the flask heated to 100 °C under vacuum for 2 h before chlorobenzene (50 mL) and triethylorthoformate (20 mmol) were added. The flask was heated to 130 °C for 16 h and then allowed to cool to room temperature before a second portion of triethylorthoformate (20 mmol) was added and the flask heated to 130 °C for an additional 16 h. After cooling to room temperature the mixture was poured into 50 mL of toluene, stirred for 30 minutes and filtered. The resulting solid was washed with toluene and hexanes and triturated (EtOAc and MeOH) to afford the title compound **B6•HBF$_4$** as an ivory solid in 26 % yield.

^{1}H NMR (300 MHz, acetone-D_6) δ 10.24 (s, 1H), 4.78 (dd, J = 7.5, 7.4 Hz, 2H), 3.42 (dd, J = 7.5, 7.4 Hz, 2H), 3.02 (ddd, J = 15.5, 8.1, 8.1 Hz, 2H) ppm

(1*Z*,2*E*)-N1,N2-Dimesitylethane-1,2-diimine (SI-1)[2]

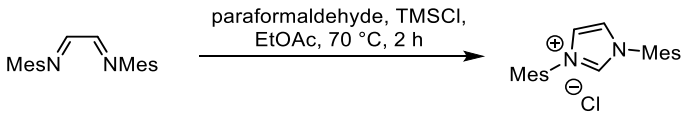


SI-1

Following the procedure of Delaude,[2] A round bottom flask was charged with 2,4,6-trimethylaniline (10.1 g, 75 mmol) and ispropanol (50 mL). With vigorous stirring, a solution of glyoxal (4.3 mL, 40% aqueous solution, 38 mmol) was added dropwise. After 16 h, the yellow slurry was filtered and the precipitate washed with water (2 x 50 mL). The solid was dried at 60 °C for 3 h under reduced pressure (0.1 mbar) to afford the title compound **SI-1** (12.0 g, 87% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 2H), 6.91 (s, 4H), 2.29 (s, 6H), 2.18 (s, 12 H) ppm

1,3-Dimesityl-1*H*-imidazol-3-ium chloride (C3•HCl)[2]

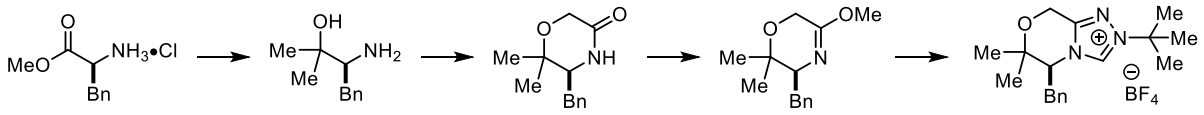


Following the procedure of Delaude,[2] a round bottom flask was charged with diimine **SI-1** (9.8 g, 33 mmol), paraformaldehyde (1.0 g, 33 mmol) and EtOAc (120 mL) and heated to 70 °C. A solution of chlorotrimethyl silane (4.2 mL, 33 mmol) in EtOAc (10 mL) was then added dropwise over 30 minutes and the suspension stirred at this temperature for 2 h. The mixture was then cooled to 0 °C before being filtered, and the white precipitate washed with EtOAc (2 x 50 mL) and Et_2O (50 mL). The solid was dried at 60 °C for 3 h under reduced pressure (0.1 mbar) to afford the title compound **C3•HCl** (9.5 g, 84% yield) as a white crystalline solid.

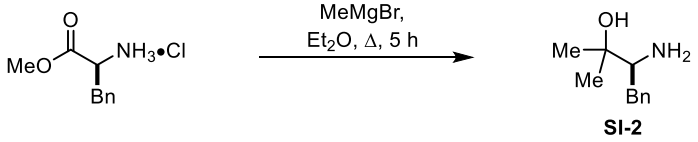
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1 H), 7.75 (s, 2H,), 6.99 (s, 4H), 2.33 (s, 6H), 2.13 (s, 12 H) ppm

Synthesis of B9•HBF_4

Catalyst **B9•HBF_4** was prepared according to the overall sequence shown in the scheme and procedures described below.



(*S*)-3-Amino-2-methyl-4-phenylbutan-2-ol (SI-2)[3]

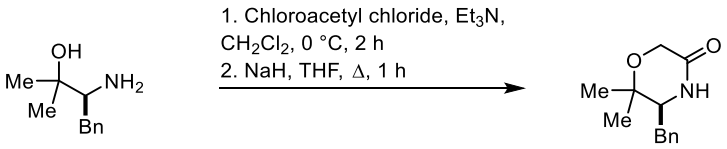


Following the procedure of Glorius,[4] a 2-necked round bottom flask was charged with methylmagnesium bromide (3.0 M in Et_2O, 131 mL, 391 mmol) and anhydrous diethyl ether (150 mL). L-phenylalanine methyl ester hydrochloride (12.1, 60 mmol) was added portionwise over 20 minutes and the mixture heated to reflux for 3 h. NaOH (1 M, 200 mL) was then added slowly, the slurry filtered through pad of celite and the filtrate was extracted with EtOAc (3 x 200 mL). The combined organics were washed with

brine, dried (Na_2SO_4), concentrated under reduced pressure to afford amino alcohol **SI-2** (9.5 g, 99% yield) which was used immediately without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 2H), 7.26-7.15 (m, 3H), 3.03 (dd, *J* = 13.6, 2.6 Hz, 1H, 6H), 2.81 (dd, *J* = 11.2, 2.6 Hz), 2.27 (dd, *J* = 13.6, 11.2 Hz, 1H), 1.31 (s, 3H), 1.21 (s, 3H) ppm

(*S*)-5-Benzyl-6,6-dimethylmorpholin-3-one (SI-3)[4]

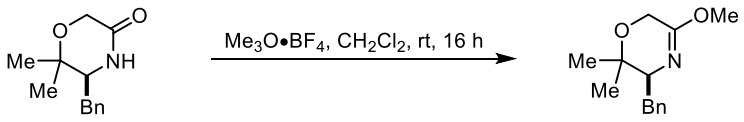


SI-3

Following the procedure of Glorius,[4] a round bottom flask was charged with amino alcohol **SI-2** (9.0 g, 53 mmol), Et_3N (9.5 mL, 71 mmol), CH_2Cl_2 and the mixture cooled to 0 °C. Chloroacetyl chloride (4.7 mL, 56 mmol) was added dropwise and the mixture stirred for 2 h before being quenched by the addition of NH_4Cl (40 mL of a saturated aqueous solution). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL), the combined organics dried (Na_2SO_4) and then concentrated under reduced pressure. The resultant purple residue was then dissolved in THF (250 mL), cooled to 0 °C and NaH (3.2 g, 60% in mineral oil, 79 mmol) added portionwise over 1 h. The mixture was heated to reflux for 1 h before being cooled and quenched by the addition of NH_4Cl (30 mL of a saturated aqueous solution). The aqueous layer was extracted with EtOAc (3 x 100 mL), the combined organics dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by flash column chromatography. The title compound **SI-3** was obtained in 45% yield as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 3H), 7.22-7.16 (m, 2H), 5.62 (bs, 1H), 4.16 (s, 2H), 3.59 (dd, *J* = 11.8, 2.9 Hz, 1H), 2.96 (dd, *J* = 13.5, 2.9 Hz, 1H), 2.40 (dd, *J* = 13.5, 11.8 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H) ppm

(*S*)-3-Benzyl-5-methoxy-2,2-dimethyl-3,6-dihydro-2*H*-1,4-oxazine (SI-4)[4]

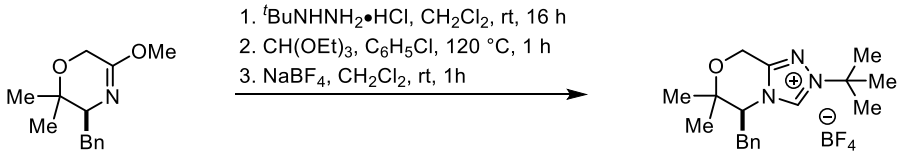


SI-4

Following the procedure of Glorius,[4] a round bottom flask was charged with morphilinone **SI-3** (800 mg, 3.7 mmol) and CH_2Cl_2 (20 mL). Trimethyloxonium tetrafluoroborate (650 mg, 4.5 mmol) was added in one portion, and the mixture stirred for 16 h at room temperature. The reaction was quenched by the slow addition of $NaHCO_3$ (25 mL of a saturated aqueous solution) before the being extracted with CH_2Cl_2 (3 x 25 mL). The combined organics were washed with water (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure, to afford the title compound **SI-4** as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 4H), 7.24-7.16 (m, 1H), 4.02 (d, J = 1.5 Hz, 2H), 3.65 (s, 3H), 3.47 (ddt, J = 10.1, 3.3, 1.5 Hz, 1H), 2.79 (dd, J = 13.2, 3.3 Hz, 1H), 2.51 (dd, J = 13.2, 10.1 Hz, 1H), 1.28 (s, 3H), 1.17 (s, 3H) ppm

(*S*)-5-Benzyl-2-(*tert*-butyl)-6,6-dimethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate (B9•HBF$_4$)[5]



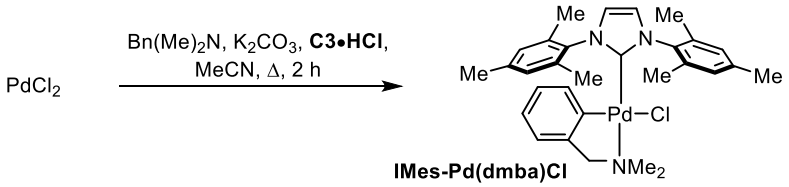
B9•HBF$_4$

Following the procedure of Lupton,[4] an RBF was charged with imidate **SI-4** (450 mg, 2 mmol), *tert*-butylhydrazine hydrochloride (250 mg, 2 mmol) and anhydrous methanol (10 mL). Anhydrous hydrogen chloride (50 μL, 4.0 M solution in 1,4-dioxane, 0.2 mmol) was then added and the mixture stirred for 12 h at room temperature before being concentrated to afford the crude amidrazone. The crude material was suspended in chlorobenzene and triethylorthoformate (2.6 mL, 16 mmol) and anhydrous hydrogen chloride (0.5 mL, 4.0 M solution in 1,4-dioxane, 2 mmol) were added. The vessel was sealed and heated to 120 °C for 1 h, before the solvent was removed under reduced pressure and the crude residue purified by flash column chromatography. The resulting residue of **B9•HCl** was then taken up in CH_2Cl_2 (5 mL) and sodium tetrafluoroborate (1.1 g, 10 mmol) was added. The suspension was stirred for 2 h at room temperature before being filtered, and the filtrate concentrated under reduced pressure. The resulting

white solid was recrystallised *via* trituration with CH_2Cl_2 and EtOAc to afford the title compound **B9•HBF$_4$** (412 mg, 46% yield) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.38-7.35 (m, 3H), 7.04-7.01 (m, 2H), 5.09 and 4.93 (ABq, J = 17.1 Hz, 2H), 4.89 (dd, J = 11.6, 4.7 Hz, 1H), 3.39 (dd, J = 13.5, 4.7 Hz, 1H), 2.83 (t, J = 13.5 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.41 (s, 9H) ppm

Synthesis of IMes-Pd(dmba)Cl[6]



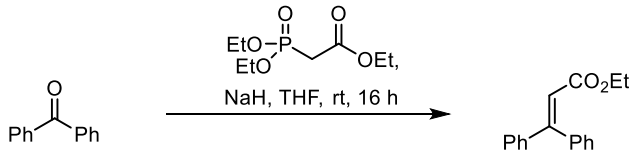
Following the procedure of Ying,[6] a two-necked RBF was charged with $PdCl_2$ (1.0 g, 5.6 mmol), N,N-dimethylbenzylamine (0.9 mL, 4 mmol) and acetonitrile (15 mL). The suspension was heated to reflux until the $PdCl_2$ had dissolved before finely powdered K_2CO_3 was added in one portion. The mixture was stirred for 20 min at reflux before **C3•HCl** (2.0 g, 4 mmol) was added in one portion and reflux continued for 1 h. The mixture was then cooled to room temperature, diluted with CH_2Cl_2 (20 mL), filtered, and the filtrate concentrated under reduced pressure. The crude residue was purified by recrystallization from acetonitrile to afford the title compound **IMes-Pd(dmba)Cl** (2.5 g, 75% yield) as an off white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11(s, 2H), 6.98 (s, 2H), 6.84-6.77 (m, 4H), 6.70 (td, J = 7.5, 1.2 Hz, 1H), 6.58 (dd, J = 7.5, 1.2 Hz, 1H), 3.53 (s, 2H), 2.45 (s, 6H), 2.43 (s, 6H), 2.29 (s, 6H), 2.22 (s, 6H) ppm

6.2 Experimental section for Chapter 2

6.2.1 Synthesis of α-cyclopropyl aldehydes 145

Ethyl 3,3-diphenylacrylate (155a)[7]

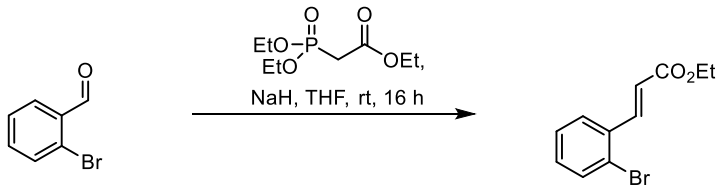


Following a modified procedure by Teichert,[7] a flame-dried RBF under N_2 was charged with NaH (0.60 g, 60% w/w in mineral oil, 15 mmol) and THF (20 mL). The suspension was cooled to 0 °C before triethylphosphonoacetate (2.98 mL, 15 mmol) was added dropwise and the mixture allowed to stir for 30 minutes at this temperature. Benzophenone (1.8 g, 10 mmol) in THF (10 mL) was added before the mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with the addition of NH_4Cl (20 mL, saturated aqueous solution), the phases separated and the aqueous extracted with EtOAc (3 x 15 mL). The combined organics were dried ($MgSO_4$), the solvent removed under reduced pressure and the crude material purified by flash chromatography to afford the title compound **155a** (1.9 g, 7.4 mmol) as a clear oil.

R_f 0.4 (3:7, v/v EtOAc : hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 8H), 7.24-7.20 (m, 2H), 6.37 (s, 1H), 4.05 (q, J = 7.2 Hz, 2H), 1.11 (t, J = 7.2 Hz, 3H) ppm

Ethyl (*E*)-3-(2-bromophenyl)acrylate (155b)[8]



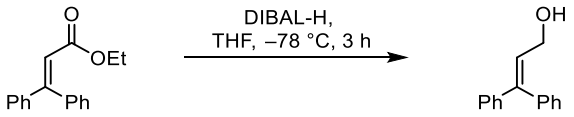
The title compound was prepared according to the representative procedure for **155a**. Following purification by flash column chromatography, the title compound **155b** (2.3 g, 70% yield) was isolated as a colourless oil.

R_f 0.5 (1:4, v/v EtOAc : hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 16.0 Hz, 1H), 7.60–7.57 (m, 2H), 7.34–7.29 (m, 1H), 7.24–7.17 (m, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.0 134.7, 133.5, 131.2, 127.8, 125.4, 121.2, 60.8, 14.4 ppm

3,3-Diphenylprop-2-en-1-ol (156a)[7]

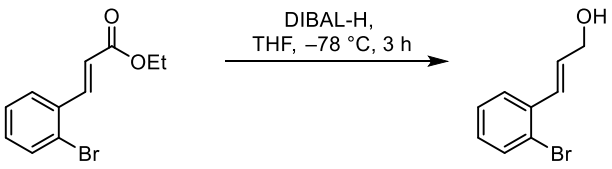


Following a modified procedure by Teichert,[7] a flame-dried RBF under N_2 was charged with acrylate **155a** (9.3 mmol) and THF (40 mL). The suspension was cooled to –78 °C before DIBAL-H (21.4 mL, 1 M solution in cyclohexane, 21.4 mmol) was added dropwise and the mixture allowed to stir for 3 h at this temperature. The reaction was quenched with the addition of MeOH (10 mL) and water (10 mL) and the mixture was allowed to warm to room temperature. NaOH (10 mL, 15% w/w) was added dropwise and the mixture filtered before the filtrate was concentrated under reduced pressure. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organics dried ($MgSO_4$), the solvent removed under reduced pressure and the crude material purified by flash by flash chromatography to afford the title compound **156a** (1.3 g, 99% yield) as a yellow oil.

R_f 0.2 (3:7, v/v EtOAc : hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2H), 7.37–7.24 (m, 4H), 7.21–7.17 (m, 2H), 7.15–7.12 (m, 2H), 6.19–6.16 (m, 1H), 4.80–4.76 (m, 1H), 4.00–3.96 (m, 2H) ppm

(*E*)-3-(2-Bromophenyl)prop-2-en-1-ol (156c)

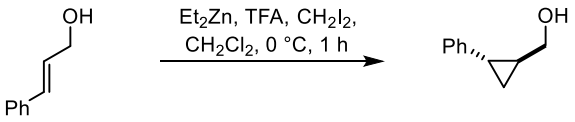


The title compound was prepared according to the representative procedure for **156a**. Following purification by flash column chromatography, the title compound **156c** (1.8 g, 76% yield) was isolated as a colourless oil.

R_f 0.3 (1:1, v/v EtOAc : hexanes)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.57 (m, 2H), 7.28–7.22 (m, 1H), 7.12–7.09 (m, 1H), 6.96 (dt, *J* = 15.8, 1.7 Hz 1H), 6.31 (dt, *J* = 15.8, 5.5 Hz 1H), (dd, *J* = 5.5, 1.7 Hz 2H), 4.36 (dd, *J* = 5.5, 1.7 Hz 2H), 1.68 (br s, 1 H) ppm

((1*S*,2*S*)-2-Phenylcyclopropyl)methanol (157a)[9]

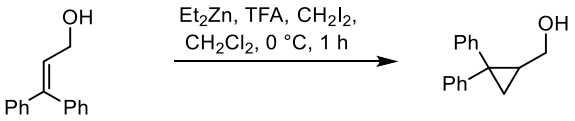


Following a modified procedure by Lorenz,[10] a flame-dried RBF under N_2 was charged with CH_2Cl_2 (20 mL). The flask was cooled to 0 °C and Et_2Zn (10 mmol, 1 M in hexanes) was added dropwise followed by the dropwise addition of TFA (5 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to stir for 20 minutes at this temperature before CH_2I_2 (20 mmol) in CH_2Cl_2 (10 mL) was added slowly. Upon stirring for 20 minutes, cinnamoyl alcohol (**156b**) (10 mmol) in CH_2Cl_2 (10 mL) was added slowly before the mixture was warmed to room temperature and allowed to stir for an additional 30 minutes. The reaction was quenched by the addition of HCl (50 mL of a 0.1 N solution), the layers were separated and the aqueous extracted with Et_2O (3 x 50 mL). The combined organics were washed with $NaHCO_3$ (50 mL of a saturated aqueous solution), water (50 mL) and brine (50 mL) before being dried ($MgSO_4$), concentrated under reduced pressure and the crude material purified by flash chromatography to afford the title compound **157a** (1.3 g, 87% yield) as a yellow oil.

R_f 0.3 (1:1 EtOAc : hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.22–7.17 (m, 1H), 7.09–7.01 (m, 2H), 3.63 (ABq, *J* = 11.2, 6.4 Hz, 1H), 3.59 (ABq, *J* = 11.2, 6.4 Hz, 1H), 1.82 (dt, *J* = 8.4, 4.6 Hz, 1H), 1.59–1.54 (s, 1H), 1.48–1.42 (m, 1H), 1.00–0.96 (m, 2H) ppm

(2,2-Diphenylcyclopropyl)methanol (157b)[11]

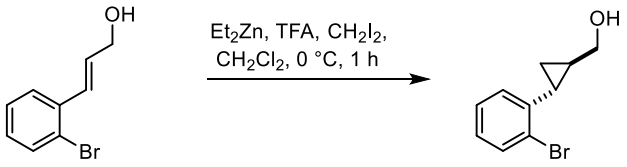


The title compound was prepared according to the representative procedure for **157a**. Following purification by flash column chromatography, the title compound **157b** (1.1 g, 59% yield) was isolated as a colourless oil

R_f 0.3 (1:1 EtOAc : hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.17 (m, 10H), 3.48 (dd, *J* = 11.8, 6.6 Hz, 1H), 3.38 (dd, *J* = 11.8, 7.8 Hz, 1H), 1.96–2.03 (m, 1H), 1.71 (bs, 1H), 1.40 (dd, *J* = 5.4, 4.8 Hz, 1H), 1.30 (dd, *J* = 8.6, 4.8 Hz, 1H) ppm

(2-(2-Bromophenyl)cyclopropyl)methanol (157c)



The title compound was prepared according to the representative procedure for **157a**. Following purification by flash column chromatography, the title compound **157c** (1.6 g, 68% yield) was isolated as a yellow oil.

R_f 0.3 (1:1 EtOAc : hexanes).

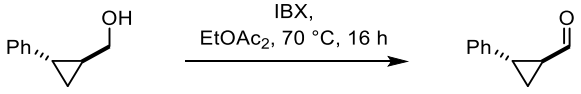
IR ν_{max} 3400, 2854, 1456, 1253 cm.$^{-1}$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.22 (td, *J* = 7.8, 1.2 Hz, 1H), 7.05 (td, *J* = 7.6, 1.6 Hz, 1H), 6.99 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.75–3.62 (m, 2H), 2.09–2.00 (m, 1H), 1.39–1.29 (m, 1H), 1.05 (dt, *J* = 8.5, 5.3 Hz, 1H), 0.95 (dt, *J* = 8.7, 5.3 Hz, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 132.6, 127.6(3), 127.6(0), 127.3, 126.2, 66.7, 24.9, 22.5, 11.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{10}H_{11}BrO$, 227.0063, requires 227.0066.

trans-2-Phenylcyclopropane-1-carbaldehyde (145a)[12]

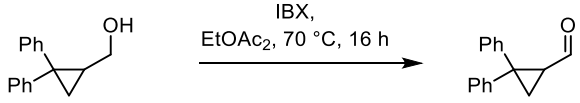


Following the procedure of Finney,[13] An RBF was charged with alcohol **157a** (2 mmol), IBX (0.84 g, 3 mmol) and EtOAc (15 mL). The suspension was heated to70 °C and stirred 16 h before it was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the crude material purified by flash chromatography to afford the title compound **145a** (111 mg, 38% yield) as a white solid.

R_f 0.3 (1:1 EtOAc : hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.25–7.20 (m, 1H), 7.13–7.10 (m, 2H), 2.63 (ddd, *J* = 10.6, 5.2, 4.0 Hz, 1H), 2.21–2.15 (dt, *J* = 9.2, 5.2 Hz, 1H), 1.56–1.51 (m, 2H) ppm

2,2-Diphenylcyclopropane-1-carbaldehyde (145b)[11]

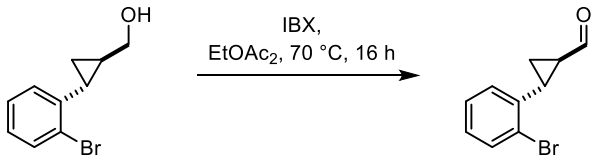


The title compound was prepared according to the representative procedure for **145a**. Following purification by flash column chromatography, the title compound **145b** (142 mg, 59 % yield) was isolated as a white solid.

R_f 0.3 (1:1 EtOAc : hexanes).

H^1 NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 6.8 Hz, 1H), 7.43–7.18 (m, 10H), 2.58–2.51 (m, 1H), 2.26 (t, *J* = 5.2 Hz, 1H), 1.88 (dd, *J* = 8.2, 5.2 Hz, 1H) ppm

***trans*-2-(2-Bromophenyl)cyclopropane-1-carbaldehyde (145c)**



The title compound was prepared according to the representative procedure for **145a**. Following purification by flash column chromatography, the title compound **145c** (323 mg, 85% yield) was isolated as a white solid.

R_f 0.5 (1:9 EtOAc : hexanes)

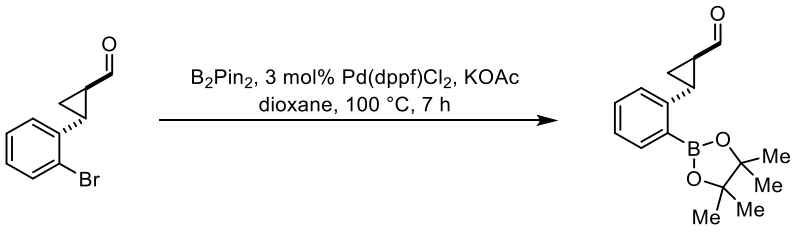
IR ν_{max} 2854, 1684, 1456, 1253 cm.$^{-}$

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (d, *J* = 4.6 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.25 (td, *J* = 7.6, 1.2 Hz, 1H), 7.15–7.08 (m, 1H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 1H), 2.78 (ddd, *J* = 11.2, 7.0, 4.2 Hz, 1H), 2.06–2.00 (m, 1H), 1.75 (dt, *J* = 9.0, 5.0 Hz, 1H), 1.54 (ddd, *J* = 12.0, 7.0, 5.0 Hz, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 138.1, 132.8, 128.7, 127.8, 127.6, 126.3, 32.5, 27.4, 15.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{10}H_9BrO$, 224.9913, requires 224.9910.

trans-2-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carbaldehyde (165)



Following a modified procedure of Miyaura,[14] an oven dried pressure tube was charged with $Pd(dppf)Cl_2$ (65 mg, 0.09 mmol), B_2pin_2 (0.83 g, 3.3 mmol) and KOAc (0.88 g, 9 mmol) before a septum was attached and the vessel flushed with argon. A solution of aldehyde **145c** (0.68 g, 3 mmol) in dioxane (10 mL) was then added and the vessel sealed and heated to 100 °C for 7 h. The mixture was cooled to room temperature, diluted with water (20 mL) and the mixture extracted with EtOAc (3 x 15 mL). The combined organics were dried ($MgSO_4$), the solvent removed under reduced pressure and the crude material purified by flash chromatography to afford the title compound **165** (0.5 g, 61% yield) as a yellow oil.

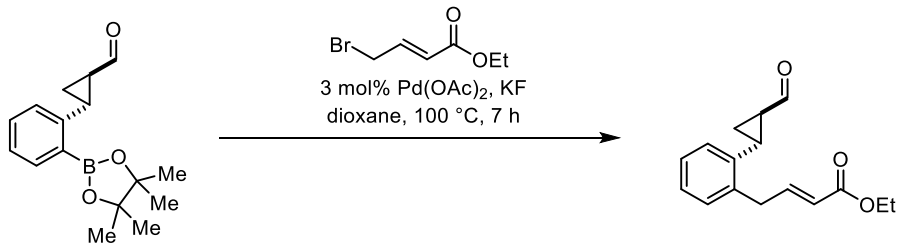
R_f 0.2 (1:9, v/v EtOAc : hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 5.4 Hz, 1H), 7.82 (dd, J = 7.4, 1.2 Hz, 1H), 7.37 (td, J = 7.6, 1.4 Hz, 1H), 7.23 (td, J = 7.4, 1.0 Hz, 2H), 7.02 (d, J = 7.6 Hz, 1H), 3.25 (ddd, J = 11.8, 7.6 Hz, 4.2 Hz 1H), 1.95–1.87 (m, 1H), 1.70–1.61 (m, 2H), 1.32 (d, J = 1.6 Hz, 12H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 145.0, 136.4, 131.4, 126.3, 125.0 83.9, 34.3, 26.6, 25.1, 24.9, 14.1 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{16}H_{21}BO_3$, 273.1654, requires 273.1657

Ethyl (*E*)-4-(2-(2-formylcyclopropyl)phenyl)but-2-enoate (162a)



Following a modified procedure of Wang,[15] an oven dried pressure tube under N_2 was charged with boronate **165** (0.5 g, 1.8 mmol), KF (0.47 g, 8.1 mmol) and dioxane (5 mL). The suspension was allowed to stir for 20 minutes followed by the addition of ethyl 4-bromocrotonate (0.70 g, 2.7 mmol) and

$Pd(OAc)_2$ (12 mg, 54 μmol) in dioxane (5 mL). The vessel was sealed and heated to 100 °C for 6 h. The mixture was then cooled to room temperature, diluted with water (20 mL) and the mixture extracted with EtOAc (3 x 15 mL). The combined organics were dried ($MgSO_4$), the solvent removed under reduced pressure and the crude material purified by flash chromatography to afford the title compound **162a** (255 mg, 55% yield) as a yellow oil.

R_f 0.2 (1:4, v/v EtOAc : hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, *J* = 4.6 Hz, 1H), 7.37–7.29 (m, 3H), 7.25–7.13 (m, 2H), 5.80 (dt, *J* = 15.6, 1.8 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.73 (dd, *J* = 6.4, 1.8 Hz, 2H), 2.71 (ddd, *J* = 9.2, 7.0, 4.6 Hz, 1H), 2.18 (dt, *J* = 12.8, 4.6 Hz, 1H), 1.85–1.75 (m, 1H), 1.64 (ddd, *J* = 8.2, 7.0, 4.8 Hz, 2H) 1.37 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 178.7, 145.0, 138.4, 135.2 132.3, 125.4, 125.0, 116.1, 65.2, 43.1, 34.3, 26.6, 25.1, 24.9, 14.1 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{18}O_3$, 259.1325, requires 259.1329

6.2.2 SET coupled NHC (4+2) annulation of a-cyclopropyl aldehydes 145

General procedure for the intermolecular NHC catalysed annulation of cyclopropyl aldehydes 145 with electrophiles

A flame-dried Schlenk flask was charged with **B6·BF$_4$** (0.2 mmol) and solvent (3 mL) followed by the addition of the appropriate base (0.2 mmol). The solution was allowed to stir for 30 min before being subjected to 3 x freeze-pump-thaw cycles. The cyclopropyl aldehydes **145a** (0.01 mmol), electrophile (0.1 mmol) and oxidant (0.2 mmol) were then added and the flask sealed and heated at the appropriate temperature and time. The solvent was removed under reduced pressure and the crude reaction mixture subjected to column chromatography.

General procedure for the intrammolecular NHC catalysed annulation of cyclopropyl aldehyde 162

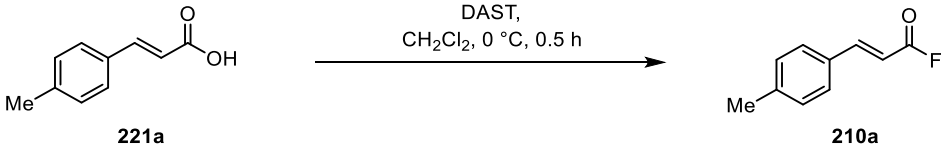
A flame-dried Schlenk flask was charged with **B6·BF$_4$** (0.2 mmol) and solvent (3 mL) followed by the addition of the appropriate base (0.2 mmol). The solution was allowed to stir for 30 min before being subjected to 3 x freeze-pump-thaw cycles. The cyclopropyl aldehyde **162a** (0.01 mmol) and oxidant (0.2 mmol) were then added and the flask sealed and heated at the appropriate temperature and time. The

solvent was removed under reduced pressure and the crude reaction mixture subject to column chromatography

6.3 Experimental section for Chapter 3

6.3.1 Synthesis of α,β-unsaturated acyl fluorides 210

(*E*)-3-(*p*-Tolyl)acryloyl fluoride (210a) [16]



221a **210a**

Following the procedure of Fu,[16] to a suspension of *trans*-4-methyl cinnamic acid **221a** (1.62 g, 10 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added diethylaminosulfur trifluoride (1.45 mL, 11 mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by slow addition of $NaHCO_3$ (10 mL of a saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 5 mL), the organic phase dried (Na_2SO_4), concentrated under reduced pressure to give a yellow oil. The crude material purified via flash column chromatography to afford the title compound **210a** (0.83 g, 50% yield) as a white solid.

R_f 0.5 (19:1, v/v hexanes : EtOAc)

MP 68-69 °C

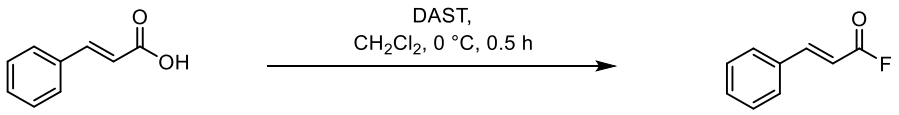
IR ν_{max} 2928, 1782, 1626, 1601, 1568, 1513, 1307, 1270, 1225 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 16.0 Hz, 1H), 7.46 (AA'BB', *J* = 8.4 Hz, 2H), 7.24 (AA'BB', *J* = 8.4 Hz, 2H), 6.32 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.41 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (d, *J* = 335.6 Hz), 151.5 (d, *J* = 6.1 Hz), 142.8, 130.5, 130.0, 128.9, 110.9 (d, *J* = 66.7 Hz), 21.7 ppm

HRMS (ESI) m/z Found: $(M-HF+H)^+$, $C_{10}H_9FO$, 145.0644, requires 145.0648

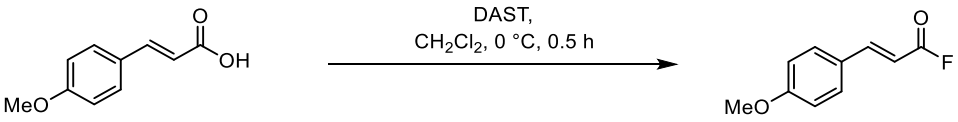
Cinnamoyl fluoride (210b)



The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210b** (0.81 g, 54% yield) was isolated as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 16.0 Hz, 1H), 7.58-7.56 (m, 2H), 7.48-7.43 (m, 2H), (dd, *J* = 16.0, 7.5 Hz, 1H).

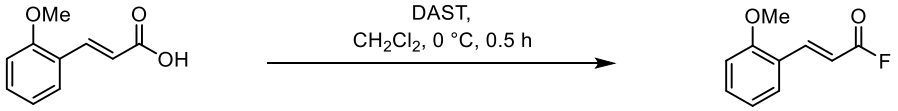
(*E*)-3-(4-Methoxyphenyl)acryloyl fluoride (210c)[17]



The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210c** (2.3 g, 62% yield) was isolated as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.0 Hz, 1H), 7.50 (AA'BB', *J* = 8.8 Hz, 2H), 6.93 (AA'BB', *J* = 8.8 Hz, 2H), 6.19 (dd, *J* = 16.0, 7.2 Hz, 1H), 3.85 (s, 3H) ppm

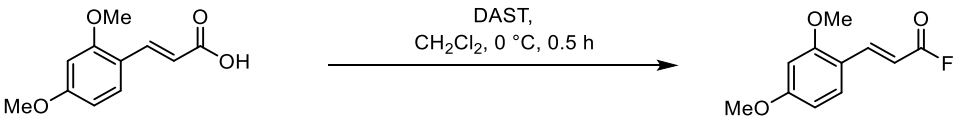
(*E*)-3-(2-Methoxyphenyl)acryloyl fluoride (210d)[17]



The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210d** (1.67 g, 96% yield) was isolated as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 16.0 Hz, 1H), 7.51-41 (m, 2H), 7.02-6.94 (m, 2H), 6.48 (dd, *J* = 16.0, 7.2 Hz, 1H), 3.90 (s, 3H) ppm

(*E*)-3-(2,4-Dimethoxyphenyl)acryloyl fluoride (210e)[18]



The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210e** (1.12 g, 81% yield) was isolated as a white solid.

R_f 0.5 (7:3, v/v hexanes : EtOAc)

MP 68-69 °C

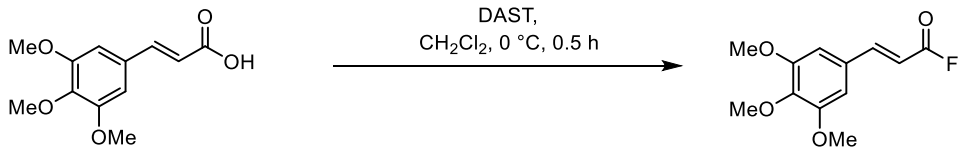
IR ν_{max} 2950, 1767, 1607, 1561, 1298, 1281, 1212 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 6.52 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.34 (dd, *J* = 16.0, 7.2 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 160.8, 158.5 (d, *J* = 333.9 Hz), 147.0 (d, *J* = 6.8 Hz), 131.8, 115.5, 109.2 (d, *J* = 65.7 Hz), 105.9, 98.4, 55.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{11}H_{11}FO_3$, 211.0759, requires 211.0765.

(*E*)-3-(3,4,5-Trimethoxyphenyl)acryloyl fluoride (210f)



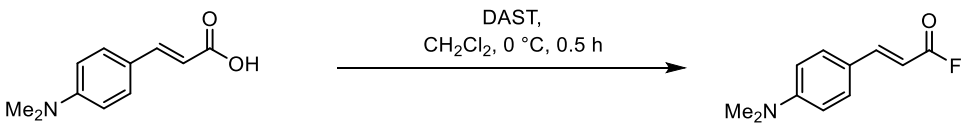
The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210f** (0.42 g, 63% yield) was isolated as a white solid.

IR ν_{max} 2940, 2839, 1778, 1578, 1454, 1327, 1199, 1117 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 15.8 Hz, 1H), 6.77 (s, 2H), 6.25 (dd, *J* = 15.8, 7.2 Hz, 1H), 3.90 (brs, 9 H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3 (d, *J* = 337.2 Hz), 153.7, 151.5 (d, *J* = 5.7 Hz), 141.6, 128.6, 111.2 (d, *J* = 67.2 Hz), 106.1, 61.1, 56.3 ppm

(*E*)-3-(4-(Dimethylamino)phenyl)acryloyl fluoride (210g)



The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210g** (0.12 g, 26% yield) was isolated as a yellow solid.

R_f 0.5 (4:1, v/v hexanes : EtOAc)

MP 164-165 °C

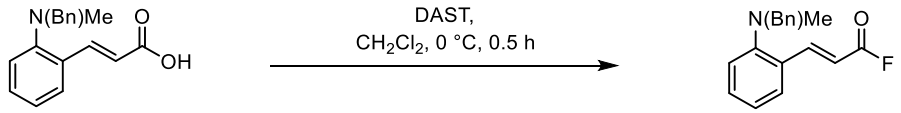
IR ν_{max} 2914, 1769, 1590, 1525, 1227 cm^{-1}

^{1}H NMR (400 MHz, CDCl3) δ 7.74 (d, *J* = 15.6 Hz, 1H), 7.43 (AA'BB', *J* = 8.8 Hz, 2H), 6.67 (AA'BB', *J* = 8.8 Hz, 2H), 6.06 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.06 (s, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (d, *J* = 331.5 Hz), 152.8, 152.1 (d, *J* = 6.7 Hz), 130.9, 120.9, 111.8, 105.0 (d, *J* = 66.3 Hz), 40.1 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{11}H_{12}FNO$, 194.0973, requires 194.0976

(*E*)-3-(2-(Benzyl(methyl)amino)phenyl)acryloyl fluoride (210h)



The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210h** (0.23 g, 30% yield) was isolated as a yellow solid.

R_f 0.4 (19:1, v/v hexanes : EtOAc)

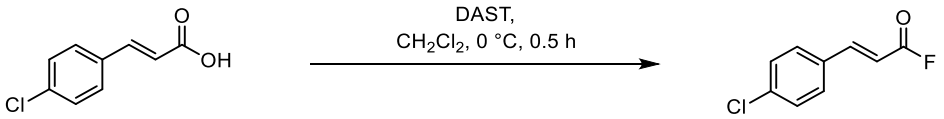
IR ν_{max} 3029, 2949, 1788, 1618, 1595, 1484, 1452, 1214 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 16.4 Hz, 1H), 7.57 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.40 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.36-7.31 (m, 2H), 7.30-7.25 (m, 3H), 7.12-7.07 (m, 2H), 6.34 (dd, *J* = 16.4, 8.0 Hz, 1H), 4.12 (s, 2H), 2.69 (s, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 157.8 (d, *J* = 336.0 Hz), 153.8, 149.4 (d, *J* = 5.7 Hz), 137.6, 132.4, 128.6(2), 128.5(8), 127.7, 127.6, 123.1, 120.7, 111.4 (d, *J* = 65.6 Hz), 62.2, 41.8 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{17}H_{16}FNO$, 270.1286, requires 270.1289

(*E*)-3-(4-Chlorophenyl)acryloyl fluoride (210i)



The title compound was prepared according to the representative procedure for **210a.** Following purification by flash column chromatography, the title compound **210ai** (0.92 g, 29% yield) was isolated as a white solid.

R_f 0.7 (4:1 v/v hexanes:EtOAc)

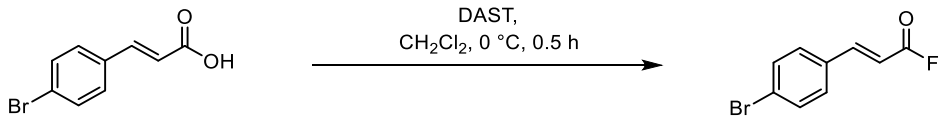
IR ν_{max} 2922, 1784, 1628, 1590, 1491, 1408, 1306, 1217 cm^{-1}

^{1}H NMR (400 MHz, $CDC1_3$) δ 7.75 (d, *J* = 16.0 Hz, lH), 7.46 (AA'BB', *J* = 8.4 Hz, 2H), 7.37 (AA'BB', *J* = 8.4 Hz, 2H), 6.32 (dd, *J* = 16.0, 6.8 Hz, lH) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (d, *J* = 336.6 Hz), 149.8 (d, *J* = 6.1 Hz), 137.9, 131.7, 129.9, 129.5, 112.7 (d, *J* = 67.5 Hz) ppm

HRMS (ESI) m/z Found: (M-HF+H) $C_9H_6{}^{35}CIFO$, 165.0107, requires 165.0102

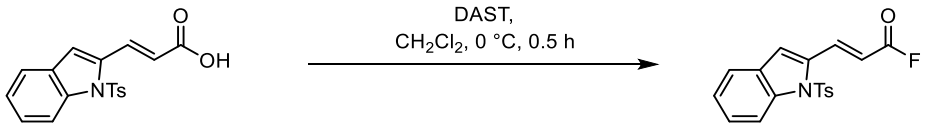
(*E*)-3-(4-Bromophenyl)acryloyl fluoride (210j)[16]



The title compound was prepared according to the representative procedure for **210a.** Following purification by flash column chromatography, the title compound **210j** (2.12 g, 55% yield) was isolated as a white solid.

^{1}H NMR (400 MHz, $CDC1_3$) δ 7.77 (d, *J* = 16.0 Hz, lH), 7.58 (AA'BB', *J* = 9.0 Hz, 2H), 7.43 (AA'BB', *J* = 9.0 Hz, 2H), 6.32 (dd, *J* = 16.0, 7.0 Hz, lH) ppm

(*E*)-3-(1-Tosyl-1H-indol-2-yl)acryloyl fluoride (210k)[19]



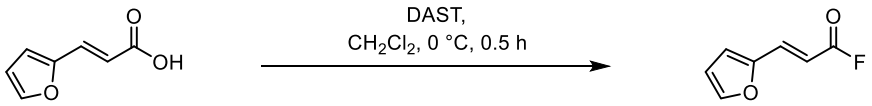
The title compound was prepared according to the representative procedure for **210a.** Following purification by flash column chromatography, the title compound **210k** (0.25 g, 61% yield) was isolated as a white solid.

IR νmax 3137, 2921, 1784, 1628, 1372, 1169, 1099, 972, 740, 658 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (brd, *J* = 8.2 Hz, 1H), 7.96 (s, 1H), 7.93 (d, *J* = 16.0 Hz, 1H), 7.82 (AA'BB', *J* = 8.4 Hz, 2H), 7.77 (brd, *J* = 7.6 Hz, 1H), 7.44-7.34 (m, 2H), 7.30-7.26 (m, 2H), 6.42 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.37 (s, 3H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 157.5 (d, *J* = 337.1 Hz), 146.1, 142.7 (d, *J* = 6.3 Hz), 135.7, 134.6, 130.7, 130.4, 127.6, 127.2, 126.1, 124.7, 120.7, 117.3, 114.1, 111.6 (d, *J* = 67.8), 21.7 ppm

(*E*)-3-(Furan-2-yl)acryloyl fluoride (210l)[16]

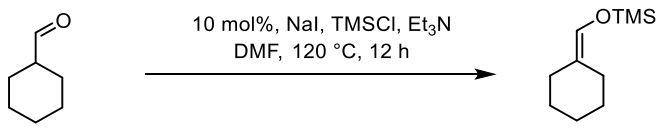


The title compound was prepared according to the representative procedure for **210a**. Following purification by flash column chromatography, the title compound **210l** (0.63 g, 41% yield) was isolated as a white solid.

^{1}H NMR (400 MHz, $CDC1_3$) δ 7.72-7.77 (m, 2H), 7.49-7.51 (m, lH), 6.64 (d, *J* = 2.0 Hz, lH), 6.08 (dd, *J* = 16.0 Hz, 7.8 Hz, lH)

6.3.2 Synthesis of DA-cyclobutanes 216

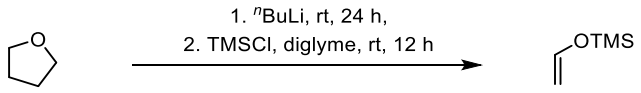
(Cyclohexylidenemethoxy)trimethylsilane (223a)[20]



Following the procedure of Reissig,[21] a round bottom flask was charged with sodium iodide (oven-dried, 0.45 g, 3 mmol), triethylamine (9.9 mL, 71 mmol) and dimethylformamide (15 mL). Chlorotrimethylsilane (4.5 mL, 35 mmol) was then added dropwise to the suspension, followed by the dropwise addition of cyclohexanecarboxaldehyde (3.6 mL, 30 mmol). The resulting mixture was then heated to 120 °C for 16 hours to give a brown slurry, which was cooled to room temperature and poured into $NaHCO_3$ (30 mL of a saturated aqueous solution). The mixture was extracted with hexanes (3 x 30 mL) and the combined organics washed with ice-cold HCl (4 x 30 mL, 1 M aqueous solution) and $NaHCO_3$ (30 mL of a saturated aqueous solution). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by short path distillation (70 °C, 1 mbar) to afford the title compound **223a** (5.1 g, 93% yield) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (m, 1 H), 2.18-2.15 (m, 2H), 1.95-1.92 (m, 2H), 1.55-1.45 (m, 6H), 0.16 (s, 9H) ppm

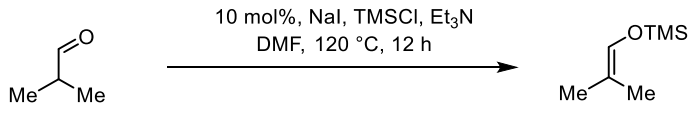
Trimethyl(vinyloxy)silane (223b)[22]



Following the procedure of Denmark,[22] a flame-dried Schlenk flask was charged with anhydrous THF (80 mL) and cooled to 0 °C. ^{n}Butyllithium (80 mL, 1.6 M solution in hexanes, 128 mmol) was added slowly and the mixture was stirred for 24 hours at room temperature before the solvent was removed under reduced pressure (inert under high vacuum). Anhydrous diglyme (24 mL) was then added slowly and the mixture was again concentrated under reduced pressure (high vacuum). Anhydrous diglyme (50 mL) was then added slowly, before the slow addition of chlorotrimethylsilane (12.2 mL, 96 mmol) to give a white suspension. The mixture was stirred for 12 h at room temperature before being subjected to bulb to bulb distillation, (10→0.1 mbar, with liquid N_2 cooling on the receiving flask). The distillate was purified by redistillation (short path, 100→120 °C oil bath, atmospheric pressure) to afford the title compound **223b** (9.41 g, 84% yield) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, J = 13.6, 5.6 Hz, 1 H), 4.44 (dd, J = 13.6, 0.8 Hz, 1H), 0.21 (s, 9H) ppm

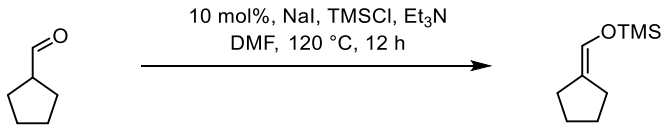
trimethyl((2-methylprop-1-en-1-yl)oxy)silane (223c)[23]



The title compound was prepared according to the representative procedure for **223a**. Following purification distillation (1 mar, short path, room temperature), the title compound **223c** (5.74 g, 80% yield) was isolated as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (sept, J = 1.6 Hz, 1H), 1.59 (dd, J = 1.6 Hz, 3H), 1.54 (dd, J = 1.6 Hz, 3H), 0.16 (s, 9H) ppm

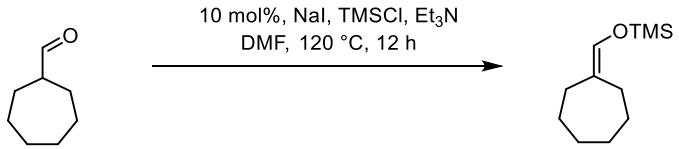
(Cyclopentylidenemethoxy)trimethylsilane (223d)[24]



The title compound was prepared according to the representative procedure for **223a**. Following purification distillation (2 mar, short path, 50 °C oil bath), the title compound **223d** (2.68 g, 79% yield) was isolated as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (p, J = 2.0 Hz, 1H), 2.25-2.22 (m, 2H), 1.66-1.56 (m, 4 H) 0.16 (s, 9H) ppm

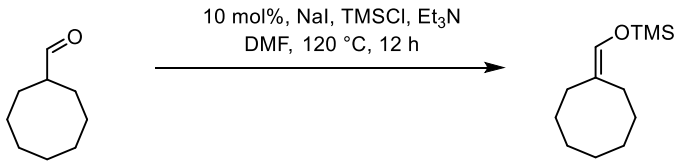
(Cycloheptylidenemethoxy)trimethylsilane (223e)



The title compound was prepared according to the representative procedure for **223a**. Following purification distillation (0.1 mbar, short path, 40 °C oil bath), the title compound **223e** (0.52 g, 55% yield) was isolated as colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.09-5.97 (m, 1H), 2.34-2.19 (m, 2H), 2.12-1.97 (m, 2H), 1.64-1.39 (m, 9H), 0.16 (s, 9H) ppm

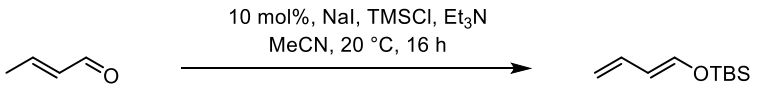
(Cyclooctylidenemethoxy)trimethylsilane (223f)



The title compound was prepared according to the representative procedure for **223a**. Following purification distillation (0.1 mar, short path, 50 °C oil bath), the title compound **223f** (0.45 g, 62% yield) was isolated as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07-5.94 (m, 1H), 2.25-2.12 (m, 2H), 2.05-1.97 (m, 2H), 1.65-1.41 (m, 10H) ppm

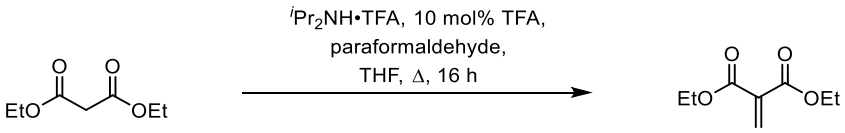
(*E*)-(Buta-1,3-dien-1-yloxy)(*tert*-butyl)dimethylsilane (233)[25]



Following the procedure of Pietruszka,[25] a round bottom flask was charged with crotonaldehyde (2.0 mL, 24 mmol), NaI (5.8 g, 39 mmol), Et_3N (5.4 mL, 39 mmol)and anhydrous acetonitrile (25 mL). The reaction vessel was sealed and stirred vigourously for 16 h at room temperature to give a brown slurry. The mixture was extracted with pentane (3 x 40 mL), the organics washed with $NaHCO_3$ (20 mL of a saturated aqueous solution) before being dried (Na_2SO_4). The organics were concentrated at atmospheric pressure on a rotaory evaporater (60 °C water bath, and the resultant oil purified by distillation (short path, 60 °C, 2 mbar) to afford the title compound **233** (2.3 g 52% yield) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.22 (ddd, *J* = 17.0, 10.8, 10.4 Hz, 1H), 5.73 (dd, *J* = 11.8, 10.8 Hz, 1H), 5.56 (d, *J* = 11.8 Hz, 1H), 4.98 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.81 (dd, *J* = 10.4, 2.0 Hz, 1H), 0.92 (s, 9H) 0.16 (s, 6H) ppm

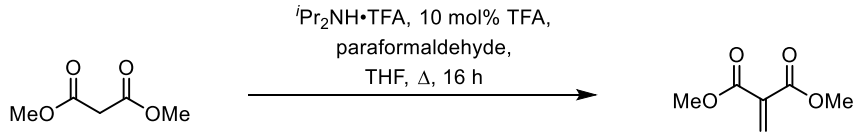
Diethyl 2-methylenemalonate (224a)[26]



Following the procedure of Waser,[27] a flamed dried RBF was charged with diethylmalonate (3.8 mL, 25 mmol), ^{i}Pr_2NH•TFA (5.4 g, 25 mmol), TFA (0.19 mL, 2.5 mmol), paraformaldehyde (1.5 g, 50 mmol) and THF (40 mL). The suspension was heated to reflux for 2 h, cooled to room temperature and an additional portion of paraformaldehyde (1.5 g, 50 mmol) was added. The suspension was again heated to reflux and stirred for additional 16 h, cooled to room temperature and the solvent removed under reduced pressure. The mixture was diluted with Et_2O (50 mL), filtered through cotton wool into a separating funnel and washed with HCl (2 x 20 mL, 1 $M_{(aq)}$). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure to afford crude **224a** (3.5 g) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 4H), 1.33 (t, *J* = 7.2 Hz, 6H) ppm

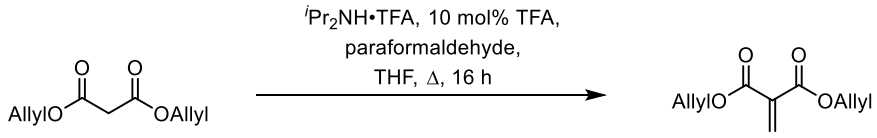
Dimethyl 2-methylenemalonate (224b)



The title compound **224n** was prepared according to the representative procedure for **224a** and was obtained crude as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 2H), 3.85 (s, 6H) ppm

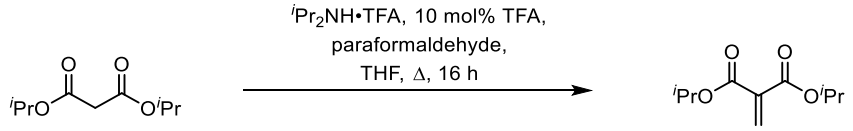
Diallyl 2-methylenemalonate (224c)



The title compound **224c** was prepared according to the representative procedure for **224a** and was obtained crude as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 2H), 6.00-5.90 (m, 2H), 5.40-5.35 (m, 2 H), 5.29-5.25 (m, 2H), 4.73 (dt, J = 5.7, 1.4 Hz, 4H) ppm

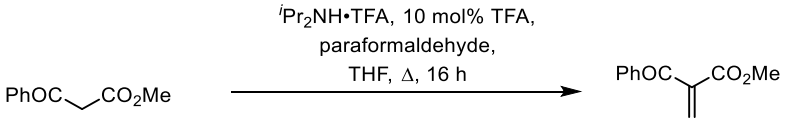
Diisoproypl 2-methylenemalonate (224d)



The title compound **225** was prepared according to the representative procedure for **224a** and was obtained crude as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 2H), 5.15, (hept, J = 6.3 Hz, 2H), 1.30, (d, J = 6.3 Hz, 12H) ppm

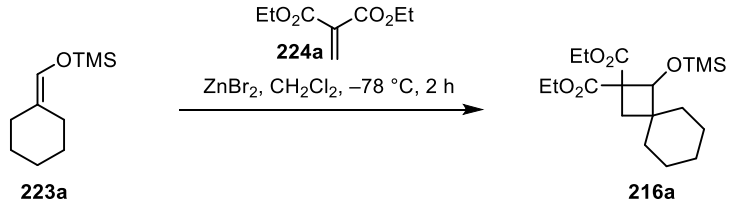
Methyl 2-benzoylacrylate (225)[28]



The title compound **225** was prepared according to the representative procedure for **224a** and was obtained crude as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.82 (m, 1H), 7.65–7.55 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 0.6 Hz, 1H), 6.06 (d, *J* = 0.5 Hz, 1H), 3.77 (s, 2H).

Diethyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216a)



Following a modification of the procedure of Roberts,[29] to a suspension of $ZnBr_2$ (2.73 g, 16 mmol) in anhydrous CH_2Cl_2 (30 mL) at –78 °C was added a solution of the methylenemalonate **224a** (3.57 g, 16 mmol) in CH_2Cl_2 (30 mL) followed by a solution of trimethylsilyl enol ether **223a** (3.51 g, 19 mmol) in CH_2Cl_2 (30 mL). After stirring at –78 °C for 2 hours, the reaction was quenched by the addition of a cold (–78 °C) solution of pyridine (15.1 mL, 63 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to warm to room temperature, then washed with Na_2EDTA (2 x 40 mL of a saturated aqueous solution), water (40 mL) and brine (40 mL) before the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude oil was purified by flash column chromatography on neutralized silica gel to afford the title compound **216a** (3.71 g, 66% yield) as a colourless oil.

R_f 0.3 (19:1, v/v hexanes : EtOAc)

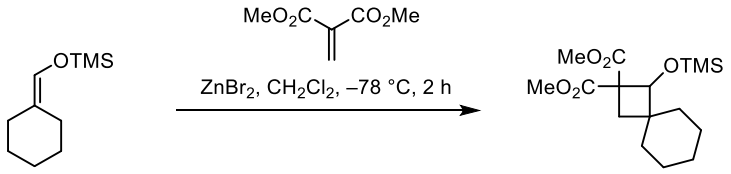
IR ν_{max} 2927, 2854, 1730, 1252 cm^{-1}

^{1}H NMR (400 MHz, CDC_3) δ 4.45 (brs, 1H), 4.28-4.07 (m, 4H), 2.61 (d, *J* = 12.4 Hz, 1H), 1.69-1.62 (m, 1H), 1.59-1.15 (m, 9H), 1.53 (d, *J* = 12.4 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.10 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.3, 76.6, 61.3, 61.2, 56.7, 41.6, 38.6, 33.9, 30.2, 26.2, 23.0, 22.2, 14.3, 14.2, 0.0 ppm

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{18}H_{32}O_5Si$, 379.1908, requires 379.1911

Dimethyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216b)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216b** (0.43 g, 31% yield) was obtained as a viscous oil.

R_f0.4 (9:1, v/v hexanes : EtOAc)

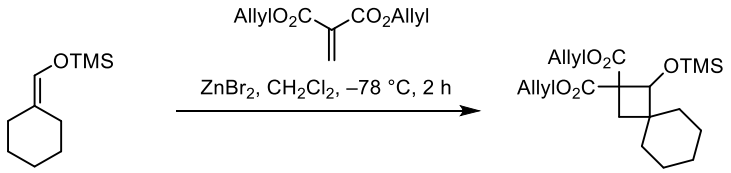
IR ν_{max} 2921, 2851, 1731, 1242 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (brs, 1H), 3.71 (s, 6H), 2.63 (d, *J* = 12.4 Hz, 1H), 1.70-1.60 (m, 1H), 1.56 (d, *J* = 12.4 Hz, 1H), 1.51-1.15 (m, 9H), 0.10 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 169.7, 76.8, 56.6, 52.5, 52.3, 41.7, 38.6, 34.0, 30.3, 26.1, 23.0, 22.2, -0.1 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{16}H_{28}O_5Si$, 329.1772 requires 329.1779

Diallyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216c)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216c** (0.36 g, 57% yield) was obtained as a viscous oil.

R_f0.8 (7:3, v/v hexanes : EtOAc)

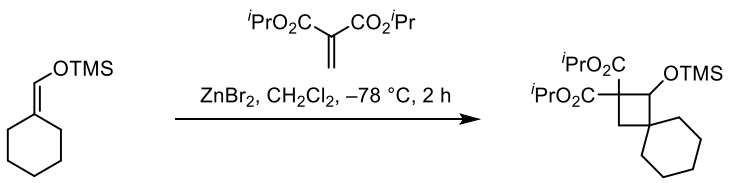
IR ν_{max} 3084, 2926, 2854, 1730, 1649, 1249 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.82 (m, 2H), 5.33-5.31 (m, 1H), 5.29-5.26 (m, 1H), 5.23-5.18 (m, 2H), 4.70 ($ABMX_2$, *J* = 14.8, 7.0, 1.4 Hz, 1H), 4.66-4.57 (m, 2H), 4.72-4.54 ($ABMX_2$, *J* = 14.8, 7.0, 1.4 Hz, 1H), 4.48 (brs, 1H), 2.65 (d, *J* = 12.4 Hz, 1H), 1.74- 1.62 (m, 1H), 1.57 (d, *J* = 12.4 Hz, 1H), 1.55-1.19 (m, 9H), 0.10 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.0, 132.2, 132.0, 118.5, 118.3, 76.7, 66.1, 65.9, 56.7, 41.8, 38.6, 34.0, 30.2, 26.2, 22.9, 22.2, 0.0 ppm

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{20}H_{32}O_5Si$, 403.1909, requires 403.1911

Diisopropyl 1-((trimethylsilyl)oxy)spiro[3.5]nonane-2,2-dicarboxylate (216d)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216d** (0.24 g, 22% yield) was obtained as a viscous oil.

R_f 0.2 (19:1, v/v hexanes : EtOAc)

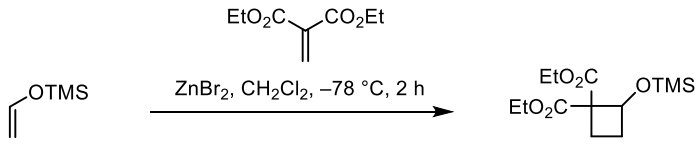
IR ν_{max} 2981, 2922, 2855, 1728, 1250 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (sept, *J* = 6.2 Hz, 1H), 5.03 (sept, *J* = 6.2 Hz 1H), 4.47 (brs, 1H), 2.60 (d, *J* = 12.4 Hz, 1H), 1.79-1.67 (m, 1H), 1.60-1.26 (m, 9H), 1.49 (d, *J* = 12.4 Hz, 1H), 1.26-1.20 (m, 12H), 0.11 (s, 9H) ppm

^{13}C-NMR (100 MHz, CDCl3) δ 171.2, 168.9, 76.4, 68.8, 68.4, 56.7, 41.6, 38.6, 33.7, 29.9, 26.2, 23.0, 22.2, 22.0, 21.8, 21.7, 0.0 ppm

HRMS (ESI) m/z Found: $(M+H)^+$,$C_{20}H_{36}O_5Si$, 385.2404, requires 385.2405

Diethyl 2-((trimethylsilyl)oxy)cyclobutane-1,1-dicarboxylate (216d)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216d** (1.41 g, 25% yield) was obtained as a colourless oil.

R_f 0.2 (19:1, v/v hexanes : EtOAc)

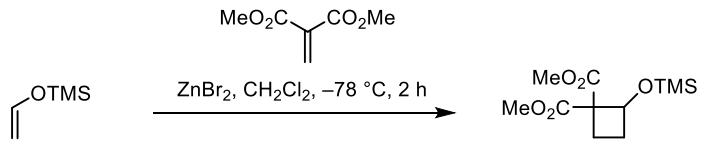
IR ν_{max} 2958, 2905, 1730, 1264, 1252, 1193 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (td, *J* = 8.0, 0.8 Hz, 1H), 4.29-4.13 (m, 4H), 2.50 (dddd, *J* = 11.6, 8.8, 4.4, 0.8 Hz, 1H), 2.20-2.09 (m, 2H), 1.68 (dt, *J* = 11.6, 9.6 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.10 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.7, 68.8, 61.7, 61.1, 60.9, 28.8, 21.0, 14.3, 14.1, -0.1 ppm

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{13}H_{24}O_5Si$, 311.1296, requires 311.1285

Dimethyl 2-((trimethylsilyl)oxy)cyclobutane-1,1-dicarboxylate (216e)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216d** (1.41 g, 38% yield) was obtained as a colourless oil.

R_f 0.4 (7:3, v/v hexanes : EtOAc)

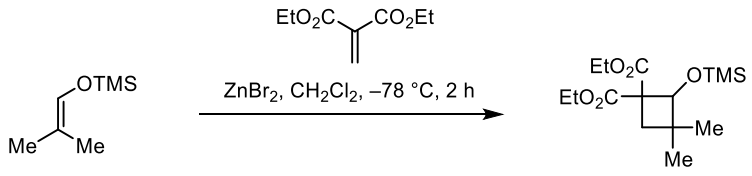
IR ν_{max} 2958, 2905, 1730, 1264, 1252, 1193 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (t, J = 8.1, Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.54-2.48 (m, 1H), 2.21-2.10 (m, 2H), 1.74-1.67 (m, 1H), 0.10 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 169.3, 69.2, 61.9, 52.4, 28.9, 21.2, 0.0 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{11}H_{20}O_5Si$, 261.1149, requires 261.1153

Diethyl 3,3-dimethyl-2-((trimethylsilyl)oxy)cyclobutane-1,1-dicarboxylate (216f)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216f** (0.83 g, 36% yield) was obtained as a viscous oil.

R_f 0.3 (19:1, v/v hexanes : EtOAc)

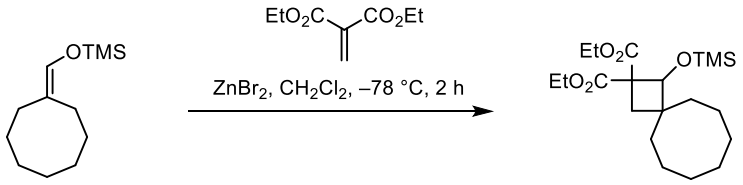
IR ν_{max} 2956, 2907, 1729, 1250, 1129 cm^{-1}

^{1}H NMR (400 MHz, CDC_3) δ 4.48 (brs, 1H), 4.26-4.09 (m, 4H), 2.55 (dd, J = 12.4, 0.8 Hz, 1H), 1.58 (d, J = 12.4 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.09 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.1, 76.2, 61.1(4), 61.1(1), 56.6, 37.5, 35.8, 29.0, 21.4, 14.3, 14.1, -0.2 ppm

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{15}H_{28}O_5Si$, 339.1596, requires 339.1598

Diethyl 1-((trimethylsilyl)oxy)spiro[3.7]undecane-2,2-dicarboxylate (216g)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216g** (0.34 g, 32% yield) was obtained as a colourless oil.

R_f0.7 (9:1, v/v hexanes : EtOAc)

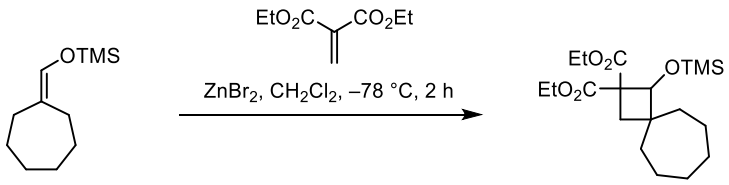
IR ν_{max} 2917, 2853, 1728, 1250 cm^{-1}

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.46 (brs, 1H), 4.30-4.06 (m, 4H), 2.55 (d, J = 12.4 Hz, 1H), 1.77-1.62 (m, 3H), 1.59-1.41 (m, 12H), 1.25 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.11 (s, 9H) ppm

^{13}**C NMR** (100 MHz, $CDCl_3$) δ 171.8, 169.3, 77.3, 61.3, 61.2, 56.5, 44.2, 37.3, 34.6, 28.9, 28.3, 27.8, 24.8, 22.7, 22.5, 14.3, 14.2, 0.0 ppm

LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{20}H_{36}O_5Si$, 407.1, requires 407.2

Diethyl 1-((trimethylsilyl)oxy)spiro[3.6]decane-2,2-dicarboxylate (216h)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216h** (0.15 g, 59% yield) was obtained as a colourless oil.

R_f 0.6 (9:1, v/v hexanes : EtOAc)

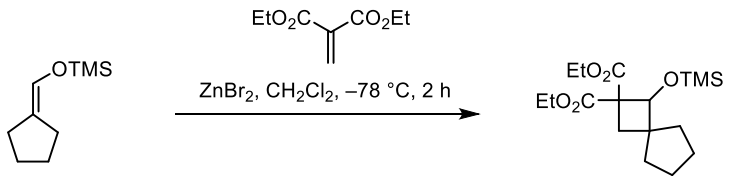
IR ν_{max} 2981, 2926, 2854, 1723, 1250 cm^{-1}

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.47 (brs, 1H), 4.28-4.17 (m, 2H), 4.16-3.08 (m, 2H), 2.61 (d, J = 12.4 Hz, 1H), 1.76-1.68 (m, 1H), 1.66-1.29 (m, 11H), 1.57 (d, J = 12.4 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.10 (s, 9H) ppm

^{13}**C NMR** (100 MHz, $CDCl_3$) δ 171.7, 169.3, 77.3, 61.3, 61.2, 59.7, 44.4, 42.2, 34.7, 32.4, 28.9, 28.4, 23.4, 22.8, 14.3, 14.2, 0.0 ppm

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{19}H_{34}O_5Si$, 393.2061, requires 393.2068

Diethyl 2-((trimethylsilyl)oxy)spiro[3.3]heptane-1,1-dicarboxylate (216i)



The title compound was prepared according to the representative procedure for **216a**. Following flash column chromatography the title compound **216i** (0.77 g, 32% yield) was obtained as a colourless oil.

R_f 0.3 (19:1, v/v hexanes : EtOAc)

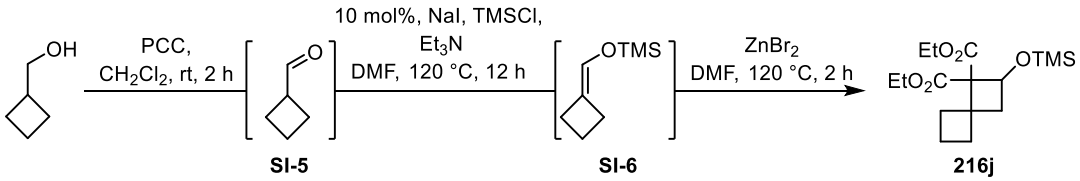
IR ν_{max} 2954, 2908, 1728, 1250 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (brs, 1H), 4.28-4.09 (m, 4H), 2.60 (d, J = 12.4 Hz, 1H), 2.04-1.96 (m, 1H), 1.72 (d, J = 12.4 Hz, 1H), 1.64-1.54 (m, 3H), 1.53-1.44 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.10 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.9, 76.1, 61.1, 61.0, 57.6, 48.7, 40.7, 35.1, 31.8, 25.1, 24.5, 14.2, 14.1, -0.1 ppm

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{17}H_{30}O_5Si$, 365.1758, requires 365.1755

Diethyl 2-((trimethylsilyl)oxy)spiro[3.3]heptane-1,1-dicarboxylate (216j)



A round bottom flask was charged with cyclobutane methanol (1.7 g, 20 mmol), pyridinium chlorochromate (8.6 g, 40 mmol), silica (8.6 g) and CH_2Cl_2 (30 mL). The brown suspension was stirred for 4 h at room temperature before it was filtered through a plug of silica (4 cm x 3 cm), and washed through with CH_2Cl_2 (20 mL). The organics were concentrated at atmospheric pressure on a rotary evaporator (50 °C water bath) to afford crude aldehyde **SI-5** which was used without further purification. A round bottom flask was charged with sodium iodide (oven-dried, 0.3 g, 2 mmol), triethylamine (6.6 mL, 47 mmol) and dimethylformamide (15 mL). Chlorotrimethylsilane (3.0 mL, 23 mmol) was then added dropwise to the suspension, followed by the dropwise addition of cyclobutanecarboxaldehyde **SI-5** prepared in the last step. The resulting mixture was then heated to 120 °C for 16 hours to give a brown slurry, which was cooled to room temperature and poured into $NaHCO_3$ (20 mL of a saturated aqueous

solution). The mixture was extracted with ^{n}pentane (3 x 20 mL) and the combined organics washed with ice-cold HCl (2 x 20 mL, 1 M aqueous solution) and $NaHCO_3$ (20 mL of a saturated aqueous solution). The organic phase was dried (Na_2SO_4) and concentrated at atmospheric pressure on a rotary evaporator (50 °C water bath) to afford crude enol ether **SI-6** which was used without further purification. The title compound was then prepared according to the representative procedure for **216a** (at 20 mmol scale). Following flash column chromatography the title compound **216j** (0.59 g, 9% yield over three steps) was obtained as a colourless oil.

R_f 0.3 (9:1, v/v hexanes : EtOAc)

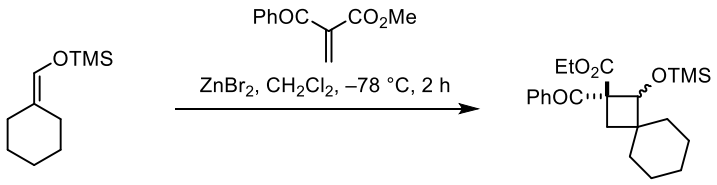
IR ν_{max} 2981, 2959, 2936, 1730, 1251, 1109 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (brs, 1H), 4.24-4.09 (m, 4H), 2.64 (dd, *J* = 12.0, 0.8 Hz, 1H), 2.44-2.35 (m, 1H), 2.00-1.86 (m, 3H), 1.84-1.65 (m, 2H), 1.71 (d, *J* = 12.0 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.16 (s, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.0, 75.2, 61.2, 61.1, 58.5, 45.7, 34.7, 32.9, 27.8, 16.7, 14.3, 14.2, 0.0 ppm

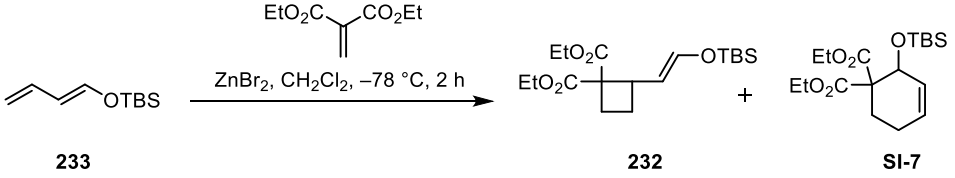
LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{16}H_{28}O_5Si$, 351.1, requires 351.2

Ethyl 2-benzoyl-1-((trimethylsilyl)oxy)spiro[3.5]nonane-2-carboxylate (216k)



The title compound was prepared according to the representative procedure for **216a.** Following flash column chromatography the title compound **216k** (0.39 g, 31% yield) was obtained as a white solid.

diethyl (E)-2-(2-((*tert*-butyldimethylsilyl)oxy)vinyl)cyclobutane-1,1-dicarboxylate (232)



233 **232** **SI-7**

The title compound was prepared according to the representative procedure for **216a**. DA-cyclobutane **232** (0.39 g, 14% yield) was formed alongside (4+2) cycloadduct **SI-7** which was only partially separable by flash column chromatography.

R_f 0.4 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2932, 2858, 1727, 1659, 1254 cm^{-1}

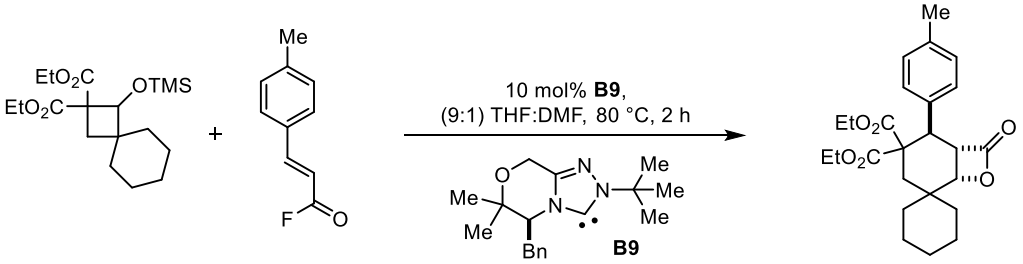
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 11.6, 0.8 Hz, 1H), 4.99 (dd, *J* = 11.6, 8.8 Hz, 1H), 4.21-4.13 (m, 4H), 3.56-3.48 (m, 1H), 2.60-2.53 (m, 1H), 2.13-1.93 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.2, 142.7, 110.0, 61.2, 61.1, 58.4, 39.8, 25.7, 23.5, 18.4, 14.4, 14.2, -5.1, -5.2 ppm

LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{18}H_{32}O_5Si$, 379.1, requires 379.2

6.3.4 Synthesis of β-lactones 220

Diethyl (1*S*,5*R*,6*S*)-7-oxo-5-(*p*-tolyl)-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220a)



A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane **216a** (36 mg, 0.1 mmol), α,β-unsaturated acyl fluoride **210a** (16 mg, 0.1 mmol), THF (0.65 mL) and DMF (0.15 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC **B9** (0.01 mmol) in THF (0.7 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound **220a** (37 mg, 86% yield, >20:1 d.r) as a viscous oil.

R_f 0.2 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2930, 2858, 1829, 1723, 1267, 1235 cm^{-1}

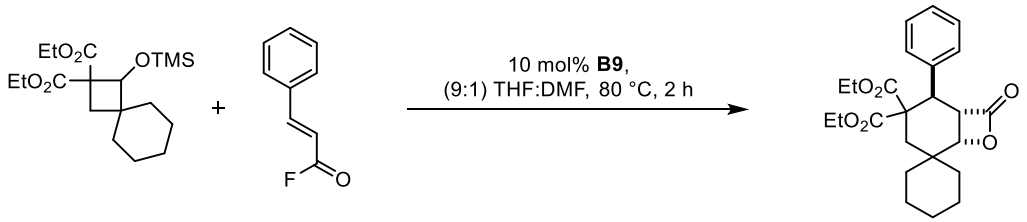
HPLC RegisCell™ 5μm, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 6.32 (major enantiomer) and 10.11 (minor enantiomer); er = 96:4

$[a]_D^{25}$ = +43.8° (c = 1.83, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (AA'BB', *J* = 8.4 Hz, 2H), 7.07 (AA'BB', *J* = 8.4 Hz, 2H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.18 (dd, *J* = 7.6, 6.4 Hz, 1H), 4.08 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.05 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.96 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.91 (d, *J* = 7.6 Hz, 1H), 3.85 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 2.30 (ABq, *J* = 15.2 Hz, 1H), 2.29 (s, 3H), 2.13 (ABq, *J* = 15.2 Hz, 1H), 1.84-1.75 (m, 1H), 1.66-1.30 (m, 9H), 1.10 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.6, 170.3, 137.6, 135.9, 129.2(0), 129.1(6), 76.5, 61.8, 61.4, 57.7, 53.5, 43.5, 39.7, 34.0, 33.7, 25.6, 22.2, 22.1, 21.2, 13.8(4), 13.7(7) ppm (1 peak missing or overlapping) HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{32}O_6$, 429.2264, requires 429.2272.

Diethyl (1*S*,5*R*,6*S*)-7-oxo-5-phenyl-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220b)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography, the title compound **220b** (40 mg, 93% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.2 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2936, 2863, 1830, 1723, 1269, 1236 cm^{-1}

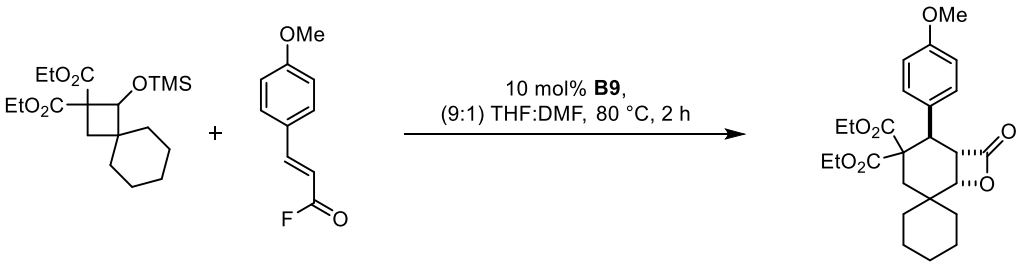
HPLC RegisCell™ 5μm, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 6.66 (major enantiomer) and 9.47 (minor enantiomer); er = 95:5 $[a]_D^{25}$ = +36.1° (c = 1.73, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.23 (m, 5H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.22 (dd, *J* = 8.0, 6.4 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.95 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 3.84 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 2.31 (ABq, *J* = 15.2 Hz, 1H), 2.15 (ABq, *J* = 15.2 Hz, 1H), 1.84-1.75 (m, 1H), 1.64-1.32 (m, 9H), 1.07 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.3, 170.5, 170.2, 138.9, 129.3, 128.5, 127.9, 76.5, 61.8, 61.4, 57.7, 53.3, 43.9, 39.6, 33.9, 33.7, 25.6, 22.2, 22.0, 13.8, 13.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{30}O_6$, 415.2101, requires 415.2115

Diethyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220c)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220c** (45 mg, 100% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.3 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2931, 2857, 1825, 1720, 1512, 1247, 1178 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 85:15, 1 mL/min, λ = 230 nm, fraction t_r = 8.03 (major enantiomer) and 11.10 (minor enantiomer); er = 97:3

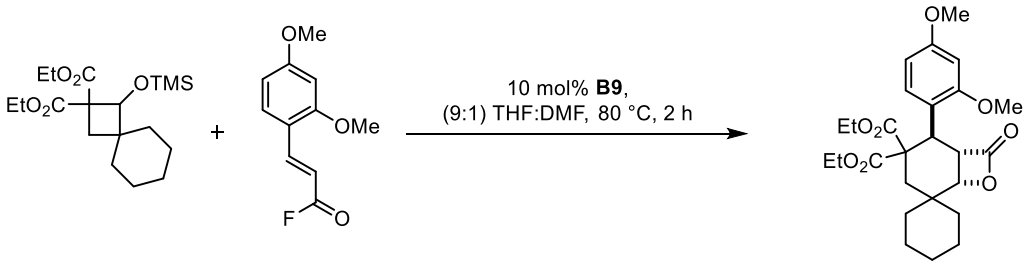
$[a]_D^{25}$ = +33.2° (c = 2.00, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (AA'BB', *J* = 8.8 Hz, 2H), 6.80 (AA'BB', *J* = 8.8 Hz, 2H), 4.59 (d, *J* = 6.4 Hz, 1H), 4.18 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.06 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.03 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.97 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.87 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 3H), 2.30 (ABq, *J* = 15.2 Hz, 1H), 2.15 (ABq, *J* = 15.2 Hz, 1H), 1.84-1.75 (m, 1H), 1.66-1.32 (m, 9H), 1.09 (t, *J* = 7.2 Hz, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.6, 170.4, 159.2, 130.8, 130.5, 113.9, 76.6, 61.8, 61.4, 57.9, 55.4, 53.5, 43.5, 39.4, 34.0, 33.7, 25.6, 22.2, 22.1, 13.9, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{32}O_7$, 445.2225, requires 445.2221

Diethyl (1*S*,5*R*,6*S*)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220d)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220d** (43 mg, 90% yield, >20:1 d.r) was obtained as a white solid.

^{1}H-NMR (>20:1 dr). R_f 0.2 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2932, 2853, 1827, 1730, 1235, 1210 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 238 nm, fraction t_r = 18.48 (minor enantiomer) and 20.76 (major enantiomer); er = 99:1

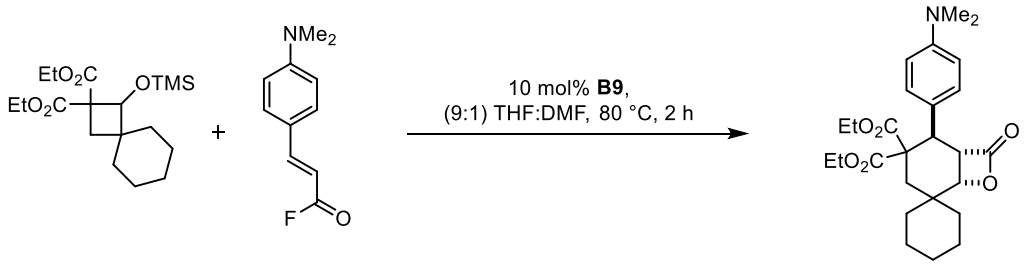
$[a]_D^{25}$ = +30.8° (c = 2.02, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 4.59 (d, *J* = 6.4 Hz, 1H), 4.26 (dd, *J* = 6.8, 6.4 Hz, 1H), 4.17 (d, *J* = 6.8 Hz, 1H), 4.08-3.85 (m, 4H), 3.77 (s, 3H), 3.73 (s, 3H), 2.25 (s, 2H), 1.82-1.74 (m, 1H), 1.66-1.28 (m, 9H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.4, 171.3, 170.6, 160.3, 158.7, 131.9, 119.8, 104.5, 98.6, 76.8, 61.5, 61.1, 57.0, 55.6, 55.4, 53.3, 39.3, 37.7, 34.3, 33.7, 31.1, 25.7, 22.3, 22.0, 13.9, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{34}O_8$, 475.2321, requires 475.2326.

Diethyl (1*S*,5*R*,6*S*)-5-(4-(dimethylamino)phenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220e)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220e** (44 mg, 97% yield, >20:1 d.r) was obtained as a viscous oil.

^{1}H-NMR (>20:1 dr). R_f 0.2 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2933, 2859, 1826, 1722, 1522, 1233 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 85:15, 1 mL/min, λ = 238 nm, fraction t_r = 8.20 (minor enantiomer) and 9.11 (major enantiomer); er = 99:1

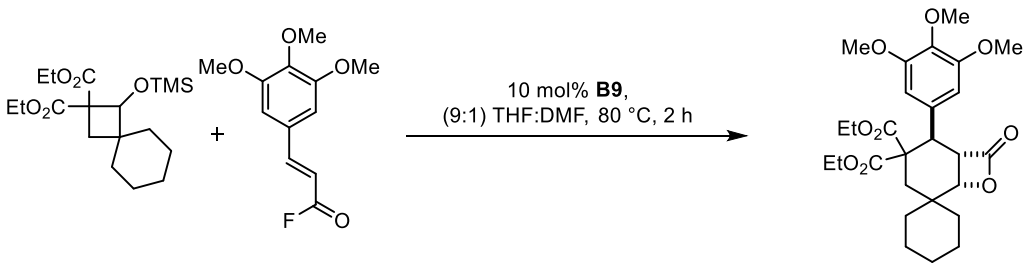
$[a]_D^{25}$ = +61.7° (c = 0.41, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (AA'BB', *J* = 8.8 Hz, 2H), 6.63 (AA'BB', *J* = 8.8 Hz, 2H), 4.55 (d, *J* = 6.4 Hz, 1H), 4.18 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.10 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.05 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.98 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.90 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 2.91 (s, 6H), 2.33 (ABq, *J* = 15.2 Hz, 1H), 2.17 (ABq, *J* = 15.2 Hz, 1H), 1.87-1.78 (m, 1H), 1.66-1.36 (m, 9H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.6, 170.4, 150.5, 130.2, 126.8, 112.7, 76.8, 61.6, 61.2, 58.4, 54.0, 43.6, 40.6, 39.8, 34.3, 33.9, 25.8, 22.4, 22.3, 13.8(4), 13.7(5) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{35}NO_6$, 458.2535, requires 458.2537

Diethyl (1*S*,5*R*,6*S*)-7-oxo-5-(3,4,5-trimethoxyphenyl)-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220f)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220f** (47 mg, 93% yield, >20:1 d.r) was obtained as viscous oil.

R_f 0.2 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2937, 2857, 1828, 1724, 1590, 1243, 1127 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 238 nm, fraction t_r = 14.39 (minor enantiomer) and 19.18 (major enantiomer); er = 96:4

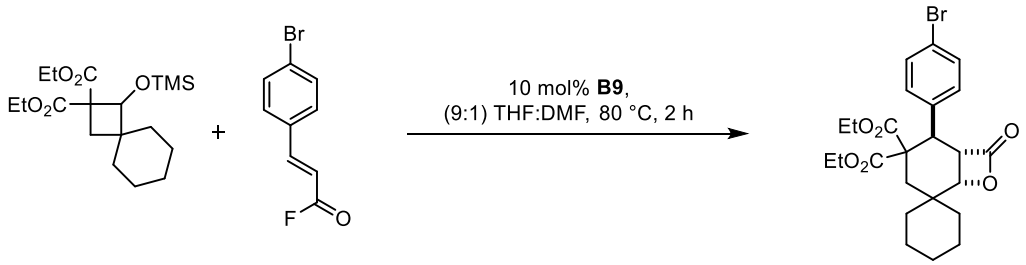
$[a]_D^{25}$ = +22.8° (c = 1.80, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.59 (d, *J* = 6.4 Hz, 1H), 4.27 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.04 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.00 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.97 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.90 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.83 (s, 6H), 3.81 (s, 3H), 3.74 (d, *J* = 9.6 Hz, 1H), 2.31 (ABq, *J* = 15.2 Hz, 1H), 2.21 (ABq, *J* = 15.2 Hz, 1H), 1.83-1.76 (m, 1H), 1.63-1.32 (m, 9H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.7, 170.6, 152.9, 137.7, 134.0, 106.8, 76.6, 61.8, 61.4, 60.9, 58.1, 56.2, 53.2, 45.0, 38.8, 34.0, 33.8, 25.6, 22.2, 22.1, 13.9, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{36}O_9$, 505.2439, requires 505.2432

Diethyl (1*S*,5*R*,6*S*)-5-(4-bromophenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220g)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220g** (40 mg, 80% yield, >20:1 d.r) was obtained as viscous oil.

R_f 0.3 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2933, 2859, 1827, 1722, 1267, 1235 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 15.25 (major enantiomer) and 18.14 (minor enantiomer); er = 92:8

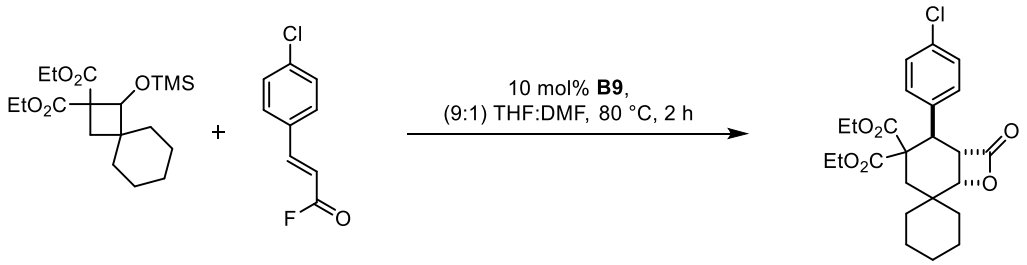
$[a]_D^{25}$ = +21.3° (c = 1.54, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (AA'BB', *J* = 8.8 Hz, 2H), 7.20 (AA'BB', *J* = 8.8 Hz, 2H), 4.59 (d, *J* = 6.4 Hz, 1H), 4.19 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.05 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.01 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.97 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.89 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.79 (d, *J* = 9.2 Hz, 1H), 2.30 (ABq, *J* = 15.2 Hz, 1H), 2.17 (ABq, *J* = 15.2 Hz, 1H), 1.83-1.74 (m, 1H), 1.66-1.32 (m, 9H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.1, 170.3(3), 170.3(2), 137.6, 131.6, 131.3, 122.2, 76.5, 61.9, 61.6, 57.8, 53.0, 44.2, 39.0, 34.1, 33.7, 25.6, 22.2, 22.1, 13.8(4), 13.7(7) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{29}{}^{79}BrO_6$, 493.1218, requires 493.1220

Diethyl (1*S*,5*R*,6*S*)-5-(4-chlorophenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220h)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220h** (36 mg, 81% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.3 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2933, 2857, 1828, 1723, 1266, 1235 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 12.56 (major enantiomer) and 14.35 (minor enantiomer); er = 87:13

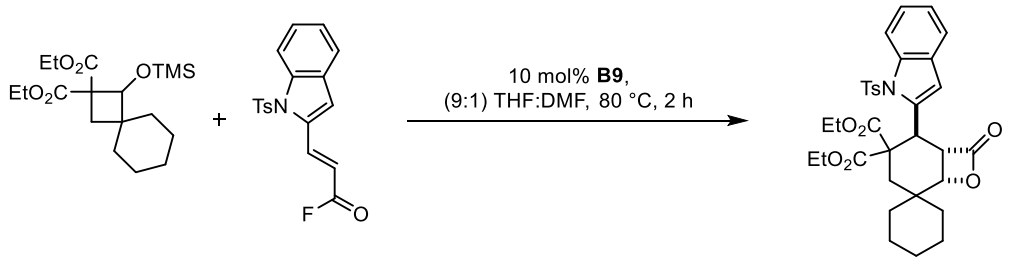
$[a]_D^{25}$ = +23.3° (c = 1.41, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 4H), 4.59 (d, *J* = 6.4 Hz, 1H), 4.19 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.05 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.00 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.97 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.89 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.81 (d, *J* = 9.2 Hz, 1H), 2.31 (ABq, *J* = 15.2 Hz, 1H), 2.17 (ABq, *J* = 15.2 Hz, 1H), 1.82-1.76 (m, 1H), 1.65-1.33 (m, 9H), 1.08(t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.3(4), 170.3(3), 137.1, 134.0 130.9. 128.6, 76.5, 61.9, 61.5, 57.8, 53.0, 44.1, 39.0, 34.1, 33.7, 25.6, 22.2, 22.0, 13.8(4), 13.7(7) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{29}{}^{35}ClO_6$, 449.1724, requires 449.1725

Diethyl (1*S*,5*S*,6*S*)-7-oxo-5-(1-tosyl-1*H*-indol-2-yl)-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220i)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220i** (50 mg, 83% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.2 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2935, 2861, 1824, 1719, 1448, 1370, 1175 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 70:30, 1 mL/min, λ = 238 nm, fraction t_r = 8.60 (minor enantiomer) and 17.31 (major enantiomer); er = 98:2

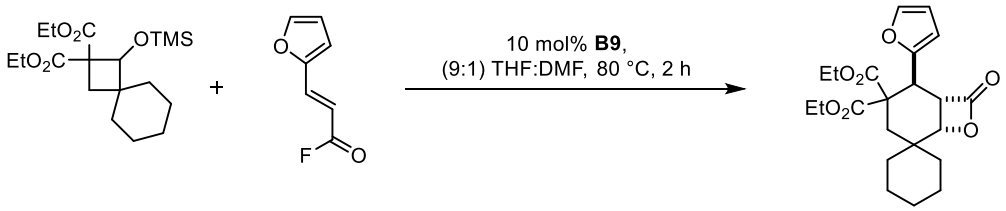
$[a]_D^{25}$ = +6.7° (c = 0.46, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.71 (AA'BB', *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.28-7.23 (m, 1H), 7.19 (AA'BB', *J* = 8.4 Hz, 2H), 7.20-7.17 (m, 1H), 4.61 (d, *J* = 6.0 Hz, 1H), 4.29 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.94 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.90 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.83 (d, *J* = 9.2 Hz, 1H), 3.70 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.40 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 2.32 (s, 3H), 2.32 (ABq, *J* = 15.2 Hz, 1H), 2.28 (ABq, *J* = 15.2 Hz, 1H), 1.86-1.77 (m, 1H), 1.67-1.31 (m, 9H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.52 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 170.4, 145.0, 135.3, 134.4, 130.8, 129.9, 127.0, 126.6, 124.9, 123.3, 120.3, 119.3, 113.6, 75.9, 61.8, 61.3, 56.6, 54.0, 37.6, 36.3, 34.7, 33.8, 25.6, 22.1, 21.9, 21.6, 13.7, 13.1 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{33}H_{37}NO_8S$, 608.2310, requires 608.2313

Diethyl (1*S*,5*S*,6*S*)-5-(furan-2-yl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220j)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220j** (29 mg, 72% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.2 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2933, 2859, 1827, 1725, 1448, 1239 cm^{-1}

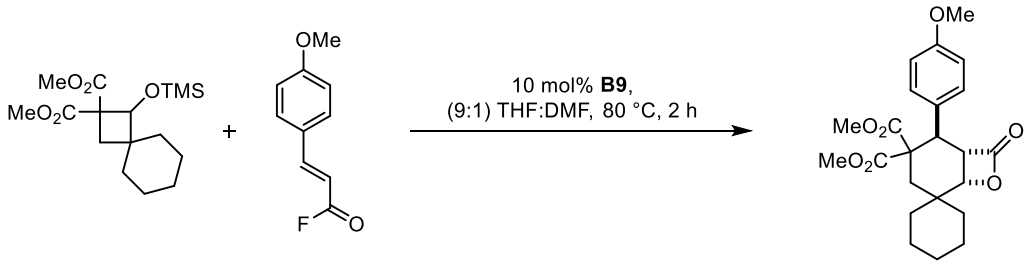
HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 12.32 (major enantiomer) and 17.91 (minor enantiomer); er = 92:8

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 2.0, 0.8 Hz, 1H), 6.29 (dd, *J* = 3.2, 2.0, Hz, 1H), 6.20 (brd, *J* = 3.2, Hz, 1H), 4.57 (d, *J* = 6.4 Hz, 1H), 4.24-4.12 (m, 4H), 4.04 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.93 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 2.33 (AB, *J* = 15.2 Hz, 1H), 2.12 (AB, *J* = 15.2 Hz, 1H), 2.33 (s, 3H), 1.78-1.72 (m, 1H), 1.62-1.30 (m, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.0, 169.9, 152.2, 142.3, 110.7, 108.8, 76.3, 62.1, 61.9, 56.7, 51.2, 39.7, 36.9, 34.0, 33.2, 25.6, 22.1, 22.0, 14.0, 13.9 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{22}H_{28}O_7$, 405.1911, requires 405.1908

Dimethyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220k)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220k** (32 mg, 84% yield, >20:1 d.r) was obtained as white solid.

R_f 0.2 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2941, 2915, 2856, 1824, 1734, 1256, 1239 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 85:85, 1 mL/min, λ = 230 nm, fraction t_r = 10.84 (major enantiomer) and 14.17 (minor enantiomer); er = 98:2

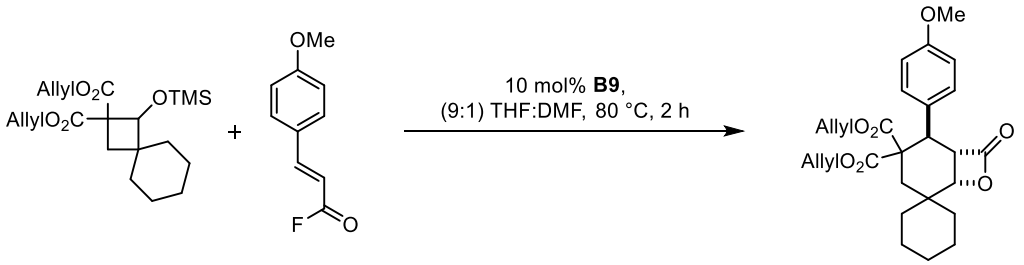
$[a]_D^{25}$ = +34.2° (c = 0.46, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (AA'BB', *J* = 8.8 Hz, 2H), 6.81 (AA'BB', *J* = 8.8 Hz, 2H), 4.60 (d, *J* = 6.4 Hz, 1H), 4.19 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.88 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 3H), 3.60 (s, 3H), 3.48 (s, 3H), 2.32 (ABq, *J* = 15.0 Hz, 1H), 2.16 (ABq, *J* = 15.0 Hz, 1H), 1.80-1.75 (m, 1H), 1.60-1.25 (m, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.8, 170.5, 159.3, 130.5, 130.3, 114.0, 76.4, 57.9, 55.3, 53.3, 52.7, 52.3, 43.4, 39.3, 33.9, 33.6, 25.6, 22.2, 22.0 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{23}H_{28}O_7$, 417.1902, requires 417.1908

Diallyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220l)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220l** (41 mg, 88% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.5 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2932, 2848, 1826, 1735, 1513, 1252, 1223 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 10.15 (major enantiomer) and 14.12 (minor enantiomer); er = 99:1

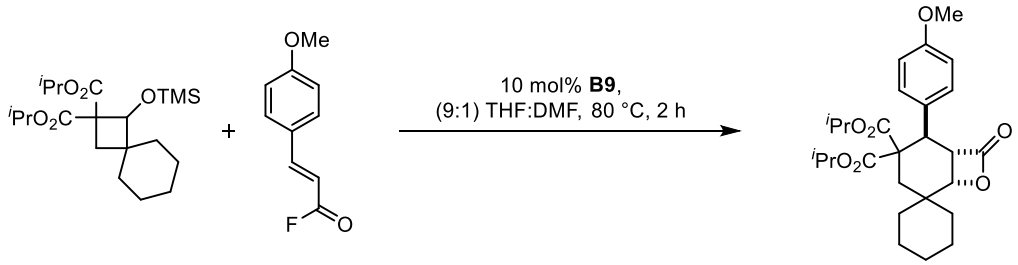
$[a]_D^{25}$ = +12.7° (c = 0.13, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (AA'BB', *J* = 8.8 Hz, 2H), 6.80 (AA'BB', *J* = 8.8 Hz, 2H), 5.78-5.62 (m, 2H), 5.25-5.19 (m, 1H), 5.20-5.16 (m, 2H), 5.16-5.14 (m, 1H) 4.60 (d, *J* = 6.4 Hz, 1H), 4.50 ($ABMX_2$, *J* = 13.0, 6.0, 1.2 Hz, 1H), 4.27 ($ABMX_2$, *J* = 13.0, 6.0, 1.2 Hz, 1H), 4.40 ($ABMX_2$, *J* = 14.4, 5.8, 1.2 Hz, 1H), 4.27 ($ABMX_2$, *J* = 14.4, 5.8, 1.2 Hz, 1H), 4.19 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.88 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 2.32 (ABq, *J* = 15.2 Hz, 1H), 2.16 (ABq, *J* = 15.2 Hz, 1H), 1.84-1.74 (m, 1H), 1.65-1.32 (m, 9H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.5, 169.9, 159.3, 131.2, 131.1, 130.6, 130.4, 119.2, 119.1, 113.9, 76.5, 66.5, 66.2, 58.0, 55.3, 53.4, 43.4, 39.5, 34.0, 33.7, 25.6, 22.2, 22.1 ppm (1 peak missing or overlapping)

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{32}O_7$, 469.2220, requires 469.2221

Diisopropyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220m)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220m** (41 mg, 86% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.3 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2975, 2934, 2872, 1828, 1732, 1514, 1236, 1217, 1105 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 7.48 (major enantiomer) and 9.09 (minor enantiomer); er = 94:6

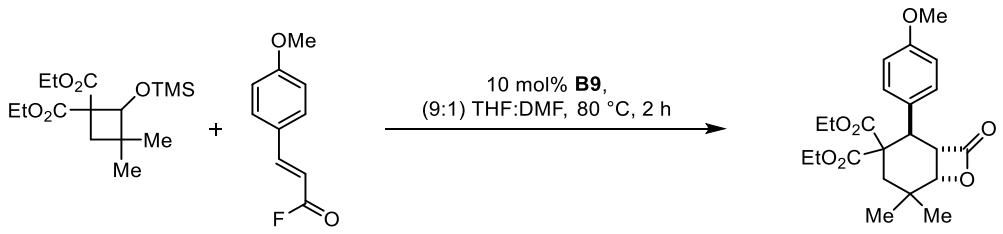
$[a]_D^{25}$ = +26.0° (c = 0.20, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (AA'BB', *J* = 8.8 Hz, 2H), 6.80 (AA'BB', *J* = 8.8 Hz, 2H), 4.89 (sept, *J* = 6.2 Hz, 1H), 4.74 (sept, *J* = 6.2 Hz, 1H), 4.59 (d, *J* = 6.2 Hz, 1H), 4.17 (dd, *J* = 8.8, 6.2 Hz, 1H), 3.79 (d, *J* = 8.8 Hz, 1H), 3.76 (s, 3H), 2.32 (ABq, *J* = 15.2 Hz, 1H), 2.16 (ABq, *J* = 15.2 Hz, 1H), 1.82-1.74 (m, 1H), 1.62-1.32 (m, 9H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.00 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.8, 170.1, 159.3, 130.9, 130.7, 113.9, 76.7, 69.7, 69.5, 57.8, 55.4, 53.7, 43.8, 39.5, 34.0, 33.9, 25.6, 22.3, 22.1, 21.7, 21.6, 21.5, 21.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{27}H_{36}O_7$, 473.2517, requires 473.2534

Diethyl (1*S*,2*R*,6*S*)-2-(4-methoxyphenyl)-5,5-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220n)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220n** (38 mg, 93% yield, >20:1 d.r) was obtained as a viscous oil.

R$_f$ 0.2 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2962, 2939, 1826, 1720, 1514, 1251 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 10.45 (major enantiomer) and 13.71 (minor enantiomer); er = 97:3

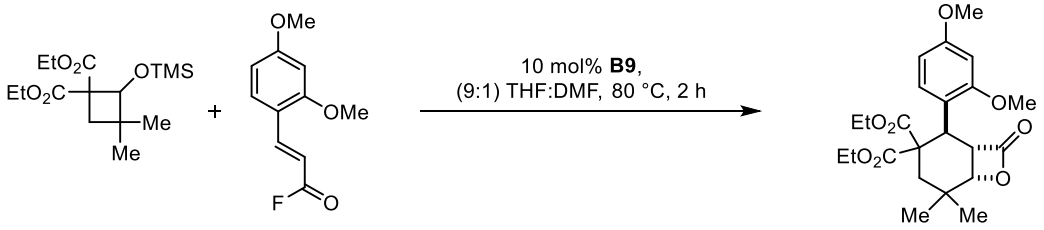
$[a]_D^{25}$ = +23.6° (c = 1.82, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (AA'BB', *J* = 8.8 Hz, 2H), 6.81 (AA'BB', *J* = 8.8 Hz, 2H), 4.49 (d, *J* = 6.4 Hz, 1H), 4.18 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.08 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.03 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.97 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.86 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.86 (d, *J* = 9.2 Hz, 1H), 3.77 (s, 3H), 2.24 (ABq, *J* = 15.2 Hz, 1H), 2.20 (ABq, *J* = 15.2 Hz, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.5, 170.4, 159.2, 130.5, 130.4, 113.8, 77.0, 61.8, 61.4, 58.5, 55.3, 53.3, 43.1, 41.9, 31.3, 31.1, 24.8, 13.9, 13.7 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{22}H_{28}O_7$, 427.1724, requires 427.1727.

Diethyl (1*S*,2*R*,6*S*)-2-(2,4-dimethoxyphenyl)-5,5-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220o)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220o** (43 mg, 100% yield, >20:1 d.r) was obtained as a viscous oil.

R$_f$ 0.3 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2975, 2941, 1827, 1729, 1612, 1507, 1210 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 230 nm, fraction t_r = 6.77 (minor enantiomer) and 7.59 (major enantiomer); er = 99:1

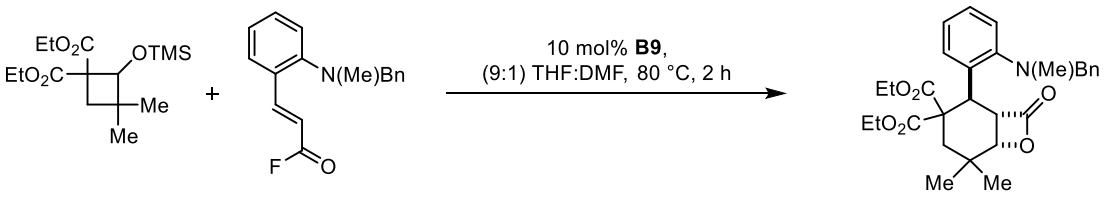
$[a]_D^{25}$ = +30.7° (c = 1.91, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 4.48 (d, *J* = 6.4 Hz, 1H), 4.25 (dd, *J* = 7.2, 6.4 Hz, 1H), 4.18 (d, *J* = 7.2 Hz, 1H), 4.10-3.84 (m, 4H), 3.78 (s, 3H), 3.74 (s, 3H), 2.29 (ABq, *J* = 14.8 Hz, 1H), 2.19 (ABq, *J* = 14.8 Hz, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2(4), 171.2(0), 170.5, 160.3, 158.7, 132.0, 119.7, 104.4, 98.5, 77.3, 61.6, 61.1, 57.5, 55.5, 55.4, 53.2, 41.7, 37.4, 31.4, 31.2, 25.6, 13.8(0), 13.7(7) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{23}H_{30}O_8$, 435.2007, requires 435.2013

Diethyl (1*S*,2*R*,6*S*)-2-(2-(benzyl(methyl)amino)phenyl)-5,5-dimethyl-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220p)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220p** (48 mg, 98% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.3 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2962, 1824, 1723, 1257 cm^{-1}

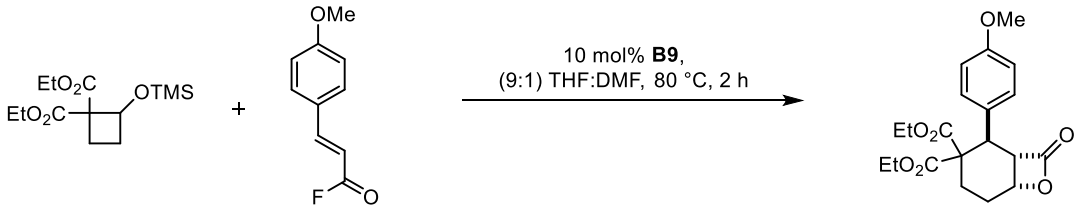
HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 238 nm, fraction t_r = 8.51 (major enantiomer) and 10.09 (minor enantiomer); er = 99:1

$[a]_D^{25}$ = -5.6° (c = 0.16, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.44-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.27-7.21 (m, 3H), 7.13 (ddd, *J* = 7.6, 6.4, 2.4 Hz, 1H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 1H), 4.39 (dd, *J* = 10.0, 6.0 Hz, 1H), 4.08 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.04 (d, *J* = 14.4 Hz, 1H), 4.00 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.94 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.78 (d, *J* = 14.4 Hz, 1H), 3.74 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 2.47 (s, 3H), 2.37 (ABq, *J* = 14.8 Hz, 1H), 2.26 (ABq, *J* = 14.8 Hz, 1H), 1.18 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.12 (s, 3H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.2, 170.6, 170.2, 154.1, 139.0, 135.7, 129.8, 128.6, 128.4, 128.3, 127.0, 125.0, 122.4, 77.1, 63.0, 61.3, 61.1, 58.1, 54.7, 44.9, 42.3, 36.9, 31.4, 30.8, 27.0, 13.8, 13.5 ppm **HRMS** (ESI) *m/z* Found: $(M+H)^+$, $C_{29}H_{35}NO_6$, 494.2535, requires 494.2537

Diethyl (1*S*,2*R*,6*R*)-2-(4-methoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220q)



The title compound was prepared according to the representative procedure for **220a** Following flash column chromatography the title compound **220q** (26 mg, 70% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.4 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2980, 2940, 1824, 1731, 1611, 1514, 1250, 1179 cm^{-1}

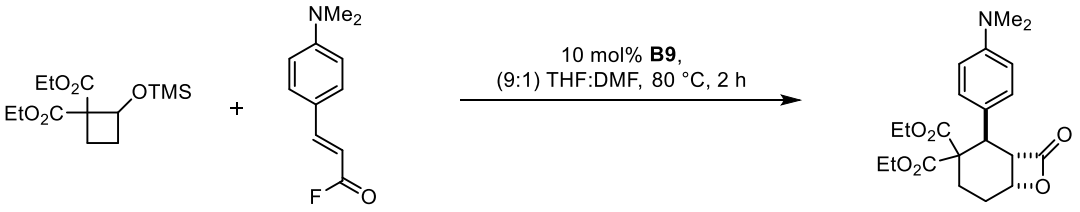
HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 238 nm, fraction t_r = 8.10 (minor enantiomer) and 9.48 (major enantiomer); er = 90:10

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (AA'BB, *J* = 8.8 Hz 2H), 6.80 (AA'BB, *J* = 8.8 Hz 2H), 4.91-4.87 (m, 1H), 4.17-4.07 (m, 3H), 4.02 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.91 (d, *J* = 4.8 Hz, 1H), 3.91 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.78 (d, *J* = 14.4 Hz, 1H), 3.37 (s, 3H), 2.28-2.17 (m, 3H), 2.07-1.97 (m, 1H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8,170.6, 169.8, 159.2, 131.8, 130.3, 113.9, 69.0, 61.9, 61.4, 58.1, 55.3, 53.5, 43.2, 26.2, 24.2, 13.9(4), 13.9(2) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{29}H_{35}NO_6$, 494.2535, requires 494.2537

Diethyl (1*S*,2*R*,6*R*)-2-(4-(dimethylamino)phenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220r)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220r** (35 mg, 90% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.2 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2981, 2903, 1824, 1733, 1614, 1523, 1248, 1224 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 238 nm, fraction t_r = 8.51 (minor enantiomer) and 10.09 (major enantiomer); er = 96:4

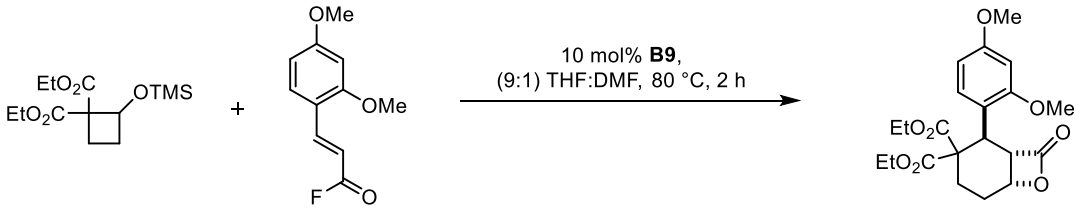
$[a]_D^{25}$ = +42.9° (c = 1.73, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (AA'BB', *J* = 8.8 Hz, 2H), 6.61 (AA'BB', *J* = 8.8 Hz, 2H), 4.92-4.87 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.08 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.01 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.93 (d, *J* = 4.8 Hz, 1H), 3.88 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 2.91 (s, 6H), 2.33-2.15 (m, 3H), 2.01-1.93 (m, 1H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.7, 169.9, 150.0, 129.7, 127.4, 112.3, 69.0, 61.9, 61.3, 58.2, 53.6, 42.7, 40.6, 25.7, 24.4, 14.0, 13.9 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{27}NO_6$, 390.1899, requires 390.1911

Diethyl (1*S*,2*R*,6*R*)-2-(2,4-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220s)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220s** (34 mg, 83% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.3 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2981, 2939, 1821, 1728, 1611, 1507, 1263, 1210 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 238 nm, fraction t_r = 7.49 (minor enantiomer) and 9.31 (major enantiomer); er = 97:3

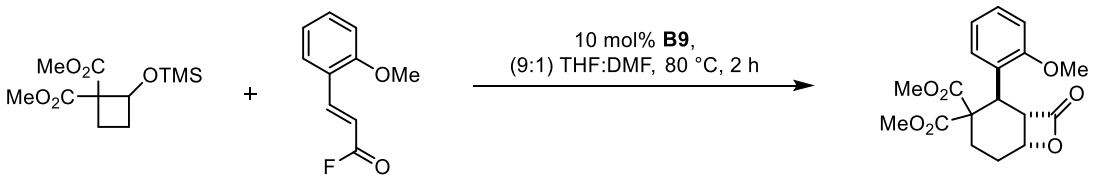
$[a]_D^{25}$ = +46.5° (c = 1.84, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 1H), 6.40 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 4.87 (td, *J* = 6.4, 4.0 Hz, 1H), 4.34 (d, *J* = 3.6 Hz, 1H), 4.17 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.14 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.04 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.93 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.77 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.75 (s, 3H), 2.41-2.32 (m, 2H), 2.17-2.09 (m, 1H), 2.00-1.92 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.0, 170.1, 160.4, 158.3, 132.1, 121.1, 104.3, 98.7, 70.0, 61.9, 61.2, 57.7, 55.5, 55.3, 53.1, 37.4, 25.6, 24.5, 14.0, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{26}O_8$, 407.1692, requires 407.1700

Diethyl (1*S*,2*R*,6*R*)-2-(2-methoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220t)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220t** (30 mg, 87% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.2 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2953, 2926, 1819, 1730, 1494, 1434, 1268, 1243 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 92:8, 1 mL/min, λ = 230 nm, fraction tr = 16.93 (minor enantiomer) and 18.02 (major enantiomer); er = 97:3

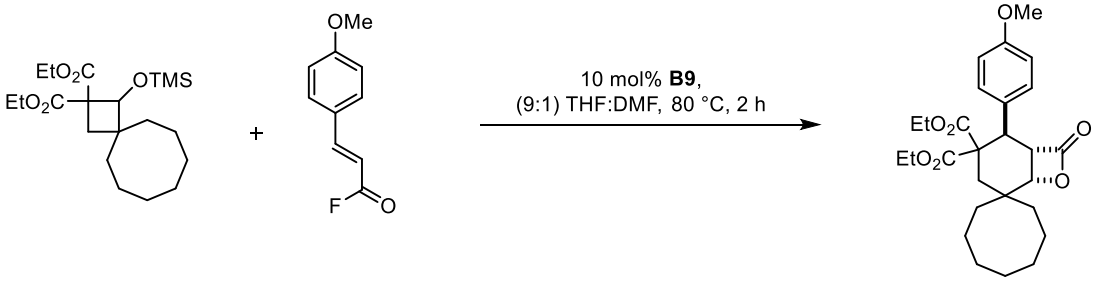
$[a]_D^{25}$ = +42.4° (c = 1.06, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20 (m, 2H), 6.89 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (brd, *J* = 7.6 Hz, 1H), 4.90 (td, *J* = 6.8, 4.0 Hz, 1H), 4.43 (d, *J* = 3.6 Hz, 1H), 4.08 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.35 (s, 3H), 2.44-2.36 (m, 2H), 2.17-2.10 (m, 1H), 2.01-1.92 (m, 1H) ppm

^{13}C NMR(100 MHz, $CDCl_3$) δ 171.4(1), 171.4(0), 170.3(8), 157.2, 131.5, 129.2, 128.4, 120.7, 110.9, 69.9, 57.7, 55.3, 52.9, 52.7, 52.1, 25.5, 24.6 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{18}H_{20}O_7$, 349.1279, requires 349.1282

Diethyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclooctane]-4,4-dicarboxylate (220u)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220u** (37 mg, 75% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.3 (4:1, v/vhexanes : EtOAc)

IR νmax 2919, 2854, 1823, 1719, 1610, 1513, 1248, 1180 cm-1

HPLC RegisCell™ 5μm, hexane : iPrOH 90:10, 1 mL/min, λ = 238 nm, fraction

tr = 10.21 (major enantiomer) and 16.59 (minor enantiomer); er = 98:2

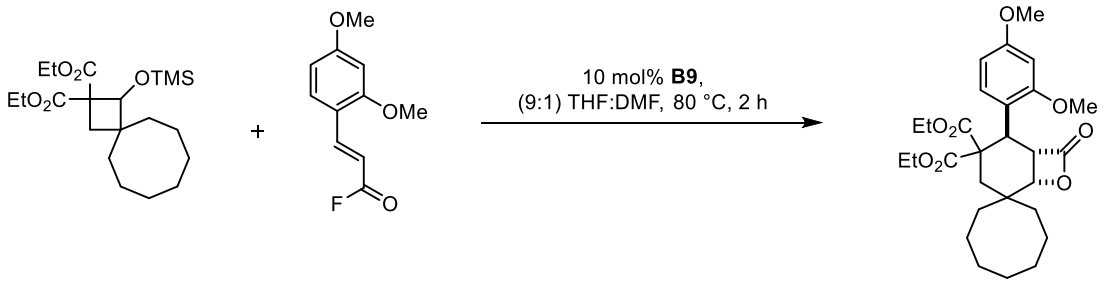
$[a]_D^{25}$ = +26.3° (c = 1.10, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (AA'BB', *J* = 8.8 Hz, 2H), 6.80 (AA'BB', *J* = 8.8 Hz, 2H), 4.51 (d, *J* = 6.4 Hz, 1H), 4.16 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.98-3.79 (m, 2H), 3.89 (d, *J* = 8.8 Hz, 1H), 3.76 (s, 3H), 2.27 (ABq, *J* = 15.2 Hz, 1H), 2.15 (ABq, *J* = 15.2 Hz, 1H), 1.93-1.83 (m, 1H), 1.73-1.41 (m, 13H), 1.10 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.6, 170.5, 159.2, 130.7, 130.5, 113.8, 77.4, 61.8, 61.4, 58.1, 55.4, 53.4, 43.0, 38.2, 37.4, 36.8, 29.0, 28.0, 25.5, 22.8, 22.2, 13.9, 13.8 ppm

LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{27}H_{36}O_7$, 495.1, requires 495.2

Diethyl (1*S*,5*R*,6*S*)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclooctane]-4,4-dicarboxylate (220v)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220v** (48 mg, 91% yield, >20:1 d.r) was obtained as a viscous oil.

R$_f$ 0.4 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2921, 2854, 1822, 1724, 1610, 1585, 1507, 1207, 1126 cm^{-1}

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 238 nm, fraction tr = 16.83 (minor enantiomer) and 22.63 (major enantiomer); er = 99:1

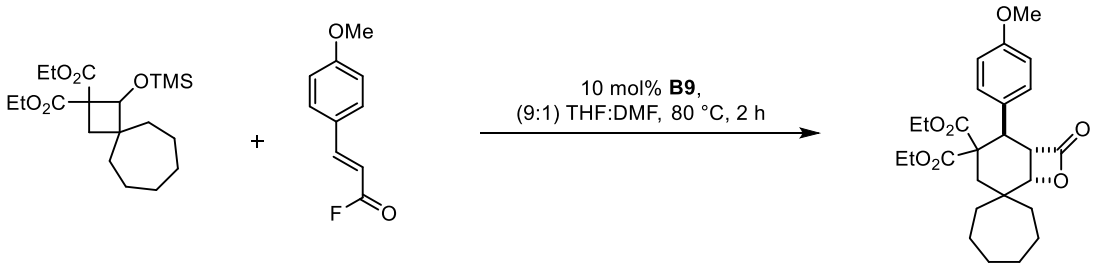
$[a]_D^{25}$ = +19.7° (c = 0.85, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 1H), 6.43 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 1H), 4.26 (dd, *J* = 7.6, 6.0 Hz, 1H), 4.17 (d, = 7.6 Hz, 1H), 4.07-3.85 (m, 4H), 3.77 (s, 3H), 3.72 (s, 3H), 2.28 (ABq, *J* = 15.2 Hz, 1H), 2.15 (ABq, *J* = 15.2 Hz, 1H), 1.91-1.85 (m, 1H), 1.68-1.46 (m, 13H),1.10 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2(8), 171.2(6), 170.7, 160.3, 158.7, 131.9, 119.7, 104.4, 98.5, 77.5, 61.5, 61.1, 57.1, 55.5, 55.4, 53.2, 38.6, 37.5, 37.1, 30.4, 28.9, 28.3, 25.6, 22.7, 22.4, 13.8(4), 13.8(0) ppm

LRMS (ESI) m/z Found: (M+Na)+, $C_{28}H_{38}O_8$, 525.3, requires 525.2

Diethyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cycloheptane]-4,4-dicarboxylate (220w)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220w** (43 mg, 94% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.2 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 2925, 2856, 1824, 1720, 1513, 1248, 1180, 1033 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 9.57 (major enantiomer) and 13.35 (minor enantiomer); er = 98:2

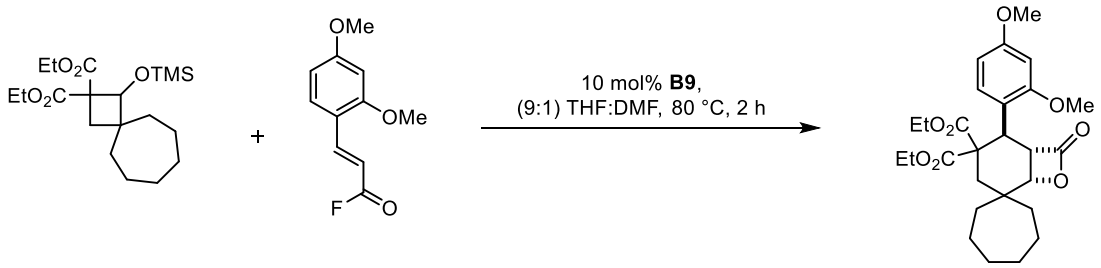
$[a]_D^{25}$ = +17.8° (c = 0.87, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (AA'BB', *J* = 8.8 Hz, 2H), 6.80 (AA'BB', *J* = 8.8 Hz, 2H), 4.50 (d, *J* = 6.4 Hz, 1H), 4.16-4.03 (m, 3H), 3.98-3.90 (m, 2H), 3.81-3.73 (m 1H), 3.77 (s, 3H), 2.35 (ABq, *J* = 14.8 Hz, 1H), 2.15 (ABq, *J* = 14.8 Hz, 1H), 1.91-1.85 (m, 1H), 1.79-1.73 (m, 1H), 1.63-1.43 (m, 10H), 1.13 (t, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 6.8 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.6, 170.5, 159.2, 130.5, 113.8, 78.0, 61.8, 61.5, 58.3, 55.4, 53.2, 42.4, 42.3, 40.8, 37.6, 34.5, 30.7, 30.6, 29.8, 23.0, 22.8, 14.0, 13.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{26}H_{34}O_7$, 459.2366, requires 459.2377

Diethyl (1*S*,5*R*,6*S*)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cycloheptane]-4,4-dicarboxylate (220x)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220x** (41 mg, 80% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.1 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2920, 2855, 1816, 1725, 1508, 1260, 1183, 1031 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 18.43 (minor enantiomer) and 24.09 (major enantiomer); er = 98:2

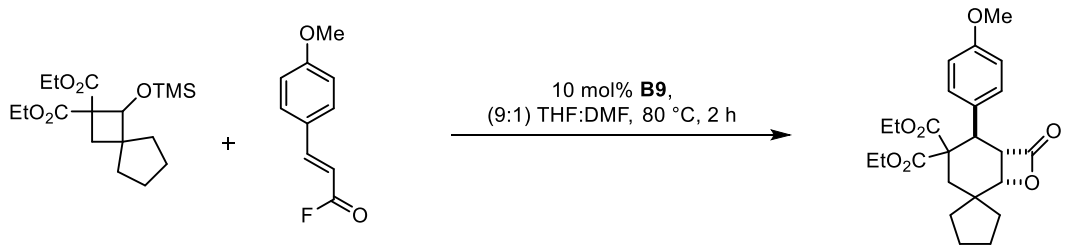
$[a]_D^{25}$ = +16.3° (c = 0.53, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 1H), 4.25 (dd, *J* = 8.2, 6.0 Hz, 1H), 4.19 (d, *J* = 8.2 Hz, 1H), 4.10-4.03 (m, 1H), 4.02-3.93 (m, 2H), 3.90-3.82 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.31 (ABq, *J* = 15.0 Hz, 1H), 2.26 (ABq, *J* = 15.0 Hz, 1H), 1.86-1.82 (m, 1H), 1.75-1.70 (m, 1H) 1.65-1.42 (m, 10H), 1.09 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.3, 170.7, 160.3, 158.7, 131.9, 119.7, 104.4, 98.4, 78.1, 61.6, 61.1, 57.2, 55.5, 55.4, 52.9, 41.9, 31.3, 37.3, 37.3(4), 37.2(7), 35.5, 30.8, 30.6, 22.8, 22.7 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{27}H_{36}O_8$, 511.2301, requires 511.2302.

Diethyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclopentane]-4,4-dicarboxylate (220y)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220y** (43 mg, 100% yield, >20:1 d.r) was obtained as a white solid.

R_f 0.3 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2957, 2878, 1828, 1722, 1612, 1514, 1253, 1182 cm^{-1}

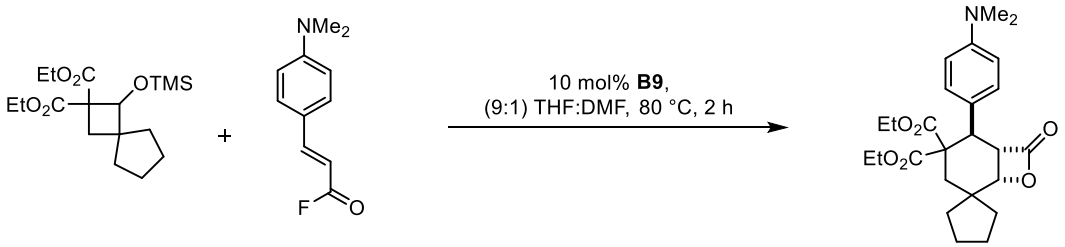
HPLC Daicel A-DH hexane : *i*PrOH 90:10, 1 mL/min, λ = 238 nm, fraction t_r = 16.95 (major enantiomer) and 18.52 (minor enantiomer); er = 89:11 e.r

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (AA'BB', *J* = 8.8 Hz, 2H), 6.81 (AA'BB', *J* = 8.8 Hz, 2H), 4.52 (d, *J* = 6.4 Hz, 1H), 4.17 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.08 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.03 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.99 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.89 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.81 (d, *J* = 9.6 Hz, 1H), 3.77 (s, 3H), 2.34 (ABq, *J* = 15.2 Hz, 1H), 2.29 (ABq, *J* = 15.2 Hz, 1H), 2.12-2.03 (m, 1H), 1.79-1.63 (m, 5H), 1.09 (t, *J* = 7.2 Hz, 6H), 1.06 (t, *J* = 7.2 Hz, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.6, 159.2, 130.5, 130.3, 113.8, 76.6, 61.7, 61.4, 58.8, 55.3, 53.2, 43.3, 43.0, 34.1, 24.5, 23.7, 13.9, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{24}H_{30}O_7$, 431.2067, requires 431.2064

Diethyl (1*S*,5*R*,6*S*)-5-(4-(dimethylamino)phenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclopentane]-4,4-dicarboxylate (220z)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220z** (44 mg, 98% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.3 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2957, 2877, 1828, 1722, 1615, 1523, 1244, 1225 cm^{-1}

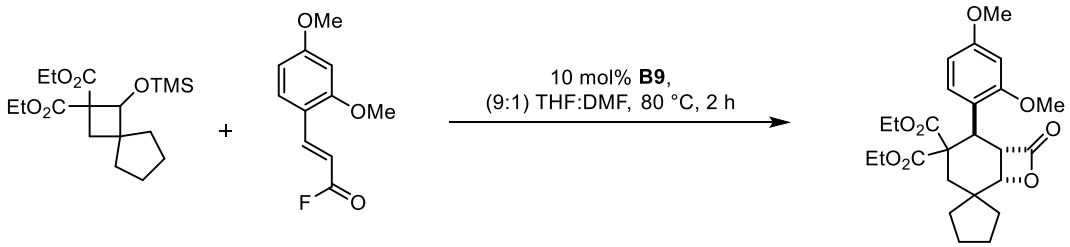
HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 238 nm, fraction t_r = 11.19 (major enantiomer) and 15.05 (minor enantiomer); er = 97:3

$[a]_D^{25}$ = +27.5° (c = 2.09, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (AA'BB', *J* = 8.8 Hz, 2H), 6.62 (AA'BB', *J* = 8.8 Hz, 2H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.16 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.09 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.08 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.00 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.89 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.81 (d, *J* = 8.8 Hz, 1H), 2.90 (s, 6H), 2.30 (s, 2H), 2.11-2.02 (m, 1H), 1.78-1.63 (m, 5H), 1.56-1.48 (m, 1H), 1.40-1.30 (m, 1H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.8, 170.6, 150.2, 129.9, 126.0, 112.4, 76.6, 61.6, 61.3, 58.8, 53.4, 43.0(1), 42.9(6), 41.5, 40.6, 39.9, 34.2, 24.5, 23.5, 13.9, 13.8 ppm HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{33}NO_6$, 444.2371, requires 444.2381.

Diethyl (1*S*,5*R*,6*S*)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclopentane]-4,4-dicarboxylate (220aa)



The title compound was prepared according to the representative procedure for **220a**. Following flash column chromatography the title compound **220aa** (46 mg, 99% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.2 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2958, 2875, 1825, 1726, 1507, 1239, 1209 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 238 nm, fraction t_r = 15.60 (minor enantiomer) and 18.31 (major enantiomer); er = 98:2

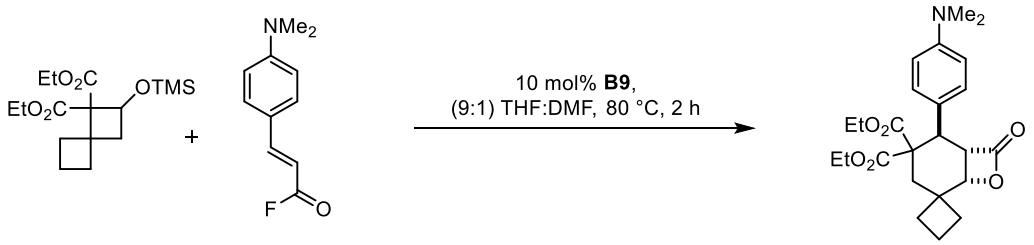
$[a]_D^{25}$ = +27.4° (c = 1.87, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.38 (d, *J* = 2.8 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 1H), 4.27 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.15 (d, *J* = 7.2 Hz, 1H), 4.10-3.88 (m, 4H), 3.78 (s, 3H), 3.74 (s, 3H), 2.36 (ABq, *J* = 14.8 Hz, 1H), 2.31 (ABq, *J* = 14.8 Hz, 1H), 2.12-2.04 (m, 1H), 1.79-1.63 (m, 5H), 1.54-1.44 (m, 1H), 1.41-1.32 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3(2), 171.3(0), 170.7, 160.3, 158.7, 131.8, 119.6, 104.4, 98.5, 76.8, 61.5, 61.1, 57.9, 55.5, 55.4, 53.1, 43.0, 41.5, 40.1, 37.4, 35.0, 24.1, 23.4, 13.9, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{25}H_{32}O_8$, 483.1984, requires 483.1989.

Diethyl (1*S*,5*R*,6*S*)-5-(4-(dimethylamino)phenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclobutane]-4,4-dicarboxylate (220ab)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220ab** (38 mg, 88% yield, >20:1 d.r) was obtained as a viscous oil.

R_f 0.3 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2981, 2941, 2874, 1826, 1720, 1614, 1523, 1268, 1240 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 238 nm, fraction t_r = 13.32 (major enantiomer) and 17.40 (minor enantiomer); er = 93:7

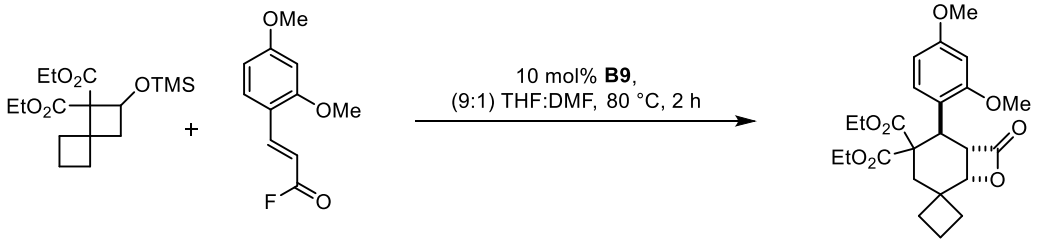
$[a]_D^{25}$ = +18.5° (c = 0.6, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (AA'BB', *J* = 8.8 Hz, 2H), 6.61 (AA'BB', *J* = 8.8 Hz, 2H), 4.69 (d, *J* = 6.4 Hz, 1H), 4.16 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.13-3.90 (m, 4H), 3.56 (d, *J* = 9.6 Hz, 1H), 2.90 (s, 6H), 2.47 (ABq, *J* = 14.8 Hz, 1H), 2.44-2.39 (m, 1H), 2.43 (ABq, *J* = 14.8 Hz, 1H), 2.10-1.83 (m, 5H), 1.09 (t, *J* = 7.2 Hz, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3(2), 171.3(0), 170.7, 160.3, 158.7, 131.8, 119.6, 104.4, 98.5, 76.8, 61.5, 57.9, 55.5, 53.1, 43.0, 41.5, 40.1, 37.4, 35.0, 24.1, 23.4, 13.9, 13.8 ppm

LRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{013}NO_6$, 430.1, requires 430.2

Diethyl (1*S*,5*R*,6*S*)-5-(2,4-dimethoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclobutane]-4,4-dicarboxylate (220ac)



The title compound was prepared according to the representative procedure for **220a.** Following flash column chromatography the title compound **220ac** (38 mg, 81% yield, >20:1 d.r) was obtained as a viscous oil.

R_f0.3 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2980, 2941, 1825, 1725, 1612, 1507, 1264, 1237, 1208 cm^{-1}

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 238 nm, fraction

tr = 12.36 (minor enantiomer) and 15.82 (major enantiomer); er = 90:10

$[a]_D^{25}$ =+13.3° (c = 0.52, $CHCl_3$)

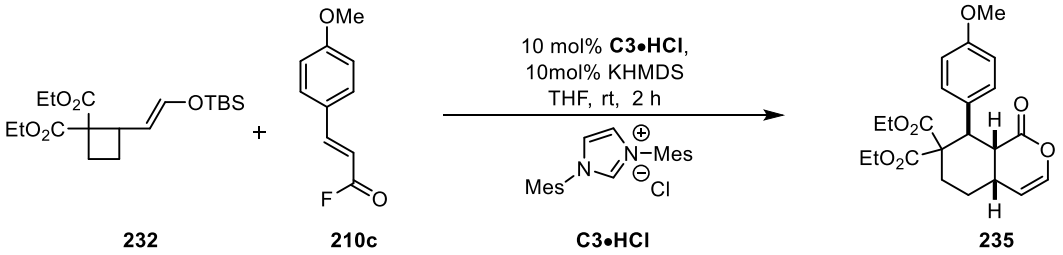
1H-NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.8 Hz, 1H), 6.42 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.72 (d, *J* = 6.4 Hz, 1H), 4.28 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.10- 3.88 (m, 5H), 3.77 (s, 3H), 3.70 (s, 3H), 2.52 (ABq, *J* = 14.8 Hz, 1H), 2.45-2.38 (m, 1H), 2.33 (ABq, *J* = 14.8 Hz, 1H), 2.07-1.86 (m, 5H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.9, 170.5, 160.2, 158.9, 131.5, 119.4, 104.4, 98.3, 77.0, 61.4, 61.1, 57.3, 55.5, 55.4, 52.8, 40.4, 38.5, 36.8, 34.4, 28.8, 16.1, 13.9, 13.8 ppm

LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{24}H_{30}O_8$, 469.1, requires 469.2

6.3.5 Synthesis of δ-lactone 235

Diethyl 8-(4-methoxyphenyl)-1-oxo-5,6,8,8a-tetrahydro-1*H*-isochromene-7,7(4aH)-dicarboxylate (235)



232 **210c** **C3•HCl** **235**

Potassium hexamethyldisilazide (0.02 mL of a 0.5 M solution in toluene, 0.01 mmol) was added to astirred solution of **C3•HCl** (3.4 mg, 0.01 mmol) in THF (2 mL) at room temperature. After 15 minutes, this solution was added in one portion to a stirred solution of donor-acceptor cyclobutane **232** (36 mg, 0.1 mmol) and α,β-unsaturated acyl fluoride **210c** (18 mg, 0.1 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred for 2 hours then concentrated under reduced pressure and purified *via* flash column chromatography to afford the title compound **235** (37 mg, 93% yield) as a single diastereoisomer as observed by ^{1}H NMR (>20:1 dr).

R$_f$ 0.3 (7:3, v/v hexanes : EtOAc)

IR ν$_{max}$ 2981, 2939, 1771, 1724, 1513, 1254, 1225, 1178 cm^{-1}

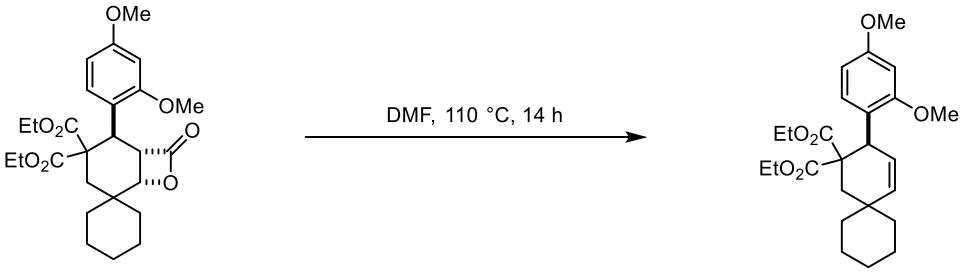
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (brs, 2H), 6.75 (brd, *J* = 9.2 Hz, 2H), 6.54 (dd, *J* = 6.0, 3.2 Hz, 1H), 5.05 (dm, *J* = 6.0 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.95-3.87 (m, 2H), 3.77-3.69 (m, 1H), 3.74 (s, 3H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.14-3.10 (m, 1H), 2.30-2.20 (m, 2H), 1.84-1.68 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.9, 168.1, 159.1, 141.8, 131.7, 128.7, 113.1, 108.5, 61.3, 61.0, 59.6, 55.2, 45.0, 42.4, 31.3, 29.9, 25.0, 14.1, 13.7 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{22}H_{26}O_7$, 403.1753, requires 403.1751.

6.3.5 Derivatisation studies

Diethyl (*R*)-3-(2,4-dimethoxyphenyl)spiro[5.5]undec-4-ene-2,2-dicarboxylate (236)



A solution of β-lactone **220d** (61.7 mg, 0.13 mmol) in DMF (2.5 mL) was heated at 110 °C for 14 hours. The mixture was allowed to cool to room temperature then water (3 mL) was added and the mixture was extracted with Et_2O (3 x 3 mL). The organic phase was washed with brine (1 x 5 mL), dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **236** (43 mg, 94%) yield as a white solid

R_f 0.4 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2931, 2853, 1732, 1504, 1208 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 238 nm, fraction t_r = 8.28 (minor enantiomer) and 9.24 (major enantiomer); er = 99:1

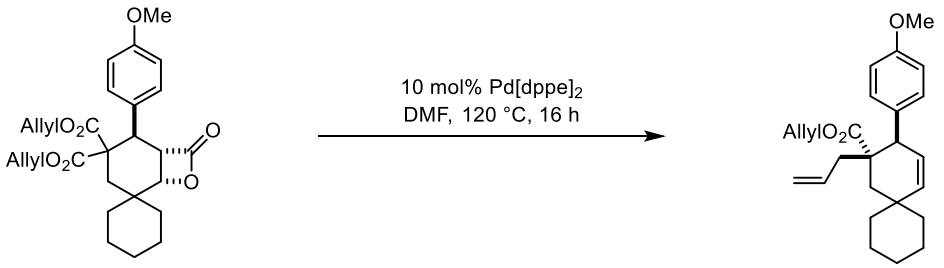
$[a]_D^{25}$ = +211° (c = 2.59, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 5.66 (brd, *J* = 10.0 Hz, 1H), 5.58 (dd, *J* = 10.0, 4.8 Hz, 1H), 4.84 (brd, *J* = 4.8 Hz, 1H), 4.22 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.07 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.96 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.66 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 2.47 (ABq, *J* = 14.8 Hz, 1H), 2.06 (ABq, *J* = 14.8 Hz, 1H), 1.65-1.18 (m, 10H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.9, 159.9, 158.2, 134.6, 131.8, 126.5, 119.9, 103.8, 98.3, 61.1, 60.8, 56.4, 55.4, 55.3, 41.4, 35.4, 33.9, 26.1, 21.8, 21.5, 14.0, 13.9 ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{25}H_{34}O_6$, 453.2246, requires 453.2248.

Allyl (2*S*,3*R*)-2-allyl-3-(4-methoxyphenyl)spiro[5.5]undec-4-ene-2-carboxylate (237)



In an oven-dried pressure tube, a solution of β-lactone **220l** (23.4 mg, 50 μmol) in DMF (0.5 mL) was heated at 120 °C under an atmosphere of argon for 6 hours. Upon cooling to room temperature, a solution of $Pd(dppe)_2$ (4.5 mg, 5 μmol) in DMF (0.5 mL) was added via cannula and the reaction mixture heated to 120 °C for 16 h. The mixture was allowed to cool to room temperature then water (3 mL) was added and the mixture was extracted with EtOAc (3 x 3 mL). The organic phase was washed with brine (1 x 5 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **235** (43 mg, 57%) as mixture of diastereoisomers as observed by ^{1}H NMR (3:1 dr).

Major diastereoisomer:

R_f 0.5 (19:1, v/v hexanes : EtOAc)

IR ν_{max} 3076, 3011, 2923, 2852, 1730, 1608, 1509, 1254, 1164, 1133 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 99:1, 1 mL/min, λ = 230 nm, fraction t_r = 3.89 (minor enantiomer) and 4.15 (major enantiomer); er = 99:1

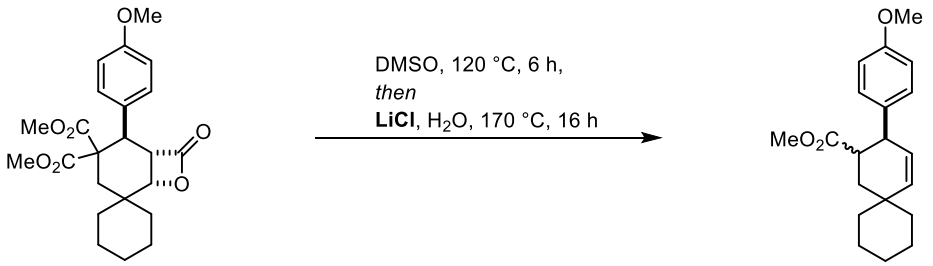
$[a]_D^{25}$ = +178.2° (c = 0.20, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) 7.14 (AA'BB', *J* = 8.7 Hz, 2H), 6.83 (AA'BB', *J* = 8.7 Hz, 2H), 5.92 (ddt, *J* = 17.0, 10.4, 6.0 Hz, 1H), 5.76-5.66 (m, 2H), 5.63-5.60 (m, 1H), 5.34 (ddt, *J* = 17.0 Hz, 1.5 Hz, 1.3 Hz, 1H), 5.23 (ddt, *J* = 10.4 Hz, 1.5 Hz, 1.3 Hz, 1H), 5.01-4.98 (m, 1H), 4.91-4.85 (m, 1H), 4.56 ($ABMX_2$, *J* = 13.0, 6.0, 1.3 Hz, 1H), 4.44 ($ABMX_2$, *J* = 13.0, 6.0, 1.3 Hz, 1H), 4.02 (d, *J* = 5.2 Hz 1H), 3.79 (s, 3H), 2.26 (ABq, *J* = 14.3 Hz, 1H), 2.07 (ABX, *J* = 14.1, 8.3, Hz, 1H), 1.75 (ABX, *J* = 14.1, 6.0 Hz, 1H), 1.60-1.37 (m, 10H), 1.50 (ABq, *J* = 14.3 Hz, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 158.6, 133.6, 132.4, 132.3, 131.6, 127.6, 118.7, 118.1, 113.5, 65.5, 55.4, 49.1, 44.4, 42.8, 41.3, 36.4, 35.0, 29.9, 26.1, 21.9, 21.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{32}O_3$, 381.2420, requires 381.2424

Methyl (3*S*)-3-(4-methoxyphenyl)spiro[5.5]undec-4-ene-2-carboxylate (239)



In a pressure tube, a solution of β-lactone **220k** (20.8 mg, 50 μmol) in DMSO (0.5 mL) was heated at 120 °C for 6 hours. Upon cooling to room temperature, lithium chloride (4 mg, 0.1 mmol) and water (1.8 μl, 50 μmol) were added and the reaction mixture heated to 170 °C for 16 hours. The mixture was allowed to cool to room temperature then water (3 mL) was added and the mixture was extracted with EtOAc (3 x 3 mL). The organic phase was washed with brine (1 x 5 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **239** (10 mg, 64% yield) as a mixture of diastereoisomers as observed by ^{1}H NMR (2:1 *cis/trans*).

***Trans*-isomer:**

R$_f$ 0.2 (19:1, v/v hexanes : EtOAc)

IR ν_{max} 2996, 2923, 2852, 1735, 1610, 1510, 1242, 1160, 1035 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 99:1, 0.5 mL/min, λ = 230 nm, fraction t_r = 13.23 (minor enantiomer) and 19.30 (major enantiomer); er = 98:2

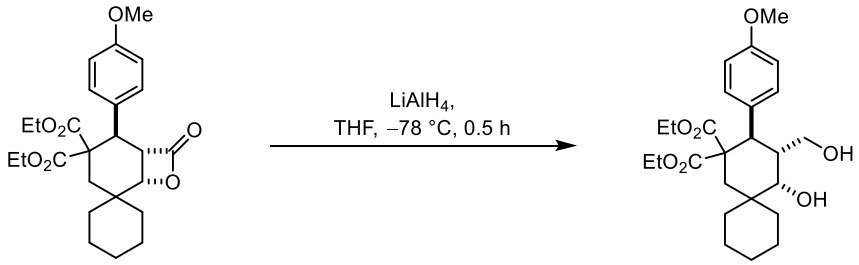
$[a]_D^{25}$ = +106.2° (c = 0.20, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (AA'BB', *J* = 8.4 Hz, 2H), 6.81 (AA'BB', *J* = 8.4 Hz, 2H), 5.74 (d, *J* = 10.4 Hz, 1H), 5.49 (dd, *J* = 10.4, 2.2 Hz, 1H), 3.78 (s, 3H), 3.61 (dt, *J* = 10.4, 2.2 Hz, 1H) 3.55 (s, 3H), 2.63 (ddd, *J* = 13.0, 10.4, 2.8, 1H), 2.01 (brd, *J* = 14.0 Hz, 1H), 1.60-1.37 (m, 11H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 158.4, 136.3, 129.0, 128.3, 114.0, 55.4, 51.7, 46.2, 44.7, 39.6, 37.9, 36.8, 34.9, 26.3, 22.0, 21.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{26}O_3$, 315.1957 requires 315.1955.

Diethyl (3*R*,4*R*,5*S*)-5-hydroxy-4-(hydroxymethyl)-3-(4-methoxyphenyl)spiro[5.5]undecane-2,2-dicarboxylate (240a)



Lithium aluminium hydride (0.2 mL of a 1 M aqueous solution, 0.2 mmol) was added dropwise to a solution of β-lactone **220c** (89 mg, 0.2 mmol) in THF (3 mL) at –78 °C. After 30 minutes, the reaction was quenched with water (0.2 mL) then sodium hydroxide (0.2 mL of a 1 M aqueous solution) and Et_2O (5 mL) were added sequentially. The reaction was allowed to warm to 0 °C in an ice-water bath, then magnesium sulfate was added and the mixture filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **240a** (78 mg, 83% yield) as a single diastereoisomer as observed by ^{1}H NMR (>20:1 dr).

R_f 0.3 (1:1, v/v hexanes : EtOAc)

IR ν_{max} 3443, 2929, 2857, 1721, 1610, 1511, 1241, 1176 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 230 nm, fraction tr = 11.52 (minor enantiomer) and 12.43 (major enantiomer); er = 96:4

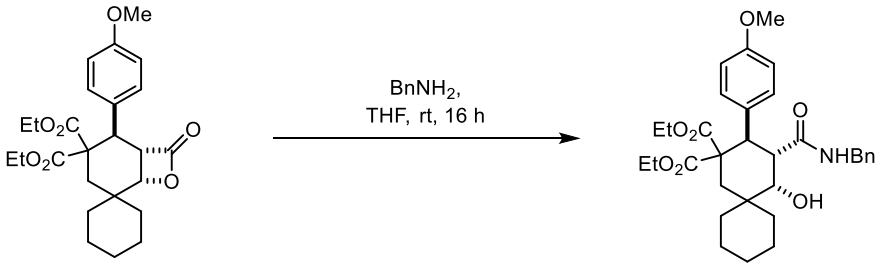
$[a]_D^{25}$ = -10.1° (c = 1.35, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (brs, 1H), 6.97 (brs, 1H), 6.78 (brs, 2H), 4.13 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.01-3.91 (m, 3H), 3.77 (s, 3H), 3.78-3.68 (m, 3H), 3.51 (d, *J* = 12.4 Hz, 1H), 3.10 (brs, 1H), 2.76 (dm, *J* = 12.4 Hz, 1H), 2.39 (d, *J* = 14.4 Hz, 1H), 2.24 (d, *J* = 14.4 Hz, 1H), 1.86 (brs, 1H), 1.57-1.24 (m, 10H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 172.0, 158.6, 130.9, 130.2, 114.0, 65.4, 61.2, 60.6, 59.1, 55.3, 44.1, 38.0, 37.5, 36.0, 32.8, 26.4, 21.7, 21.5, 13.9, 13.7 ppm

LRMS (ESI) m/z Found: $(M+Na)^+$, $C_{25}H_{36}O_7$, 471.3, requires 471.2

Diethyl (3*R*,4*S*,5*S*)-4-(benzylcarbamoyl)-5-hydroxy-3-(4-methoxyphenyl)spiro[5.5]undecane-2,2-dicarboxylate (241)



Benzylamine (44 μl, 0.4 mmol) was added to a solution of β-lactone **220c** (89 mg, 0.2 mmol) in THF (3 mL) at room temperature. After 24 hours, the mixture was concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **241** (99 mg, 86% yield) as a single diastereoisomer as observed by ^{1}H NMR (>20:1 dr).

R_f 0.3 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 3432, 3383, 2996, 2916, 1750, 1706, 1657, 1512, 1242 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 90:10, 1 mL/min, λ = 230 nm, fraction t_r = 7.08 (major enantiomer) and 7.97 (minor enantiomer); er = 95:5

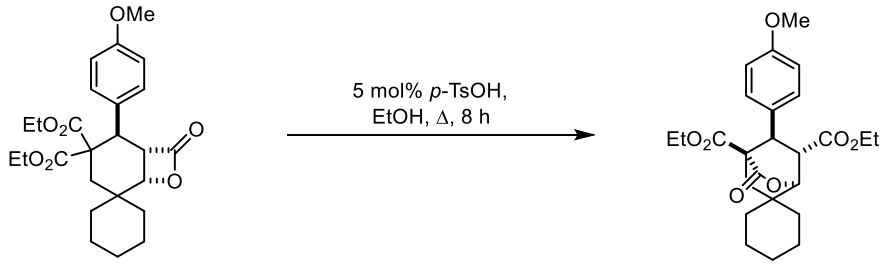
$[a]_D^{25}$ = +49.9° (c = 1.35, $CHCl_3$)

^{1}H NMR (400 MHz $CDCl_3$) δ 7.39-7.7.37 (m, 2H), 7.22-7.17 (m, 3H), 6.83-6.81 (m, 2H), 6.71-6.69 (m, 2H), 5.86 (brt, *J* = 5.4 Hz, 1H), 4.64 (brs, 1H), 4.29 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.18 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 4.03 (dd, *J* = 14.8, 5.4 Hz, 1H) 4.03-3.91 (m, 2H), 3.89 (brs, 1H), 3.78 (d, *J* = 12.4 Hz, 1H), 3.76 (s, 3H), 3.72 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.51 (dd, *J* = 12.4, 1.6 Hz, 1H), 2.51 (ABq, *J* = 14.4 Hz, 1H), 2.22 (ABq, *J* = 14.4 Hz, 1H), 1.64-1.31 (m, 10H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 172.4, 171.3, 158.7, 137.4, 132.1, 130.0, 128.6, 127.9, 127.5, 113.1, 61.2, 60.8, 58.7, 55.2, 45.9, 44.8, 43.6, 37.4, 36.3, 32.2, 26.4, 21.7, 21.5, 14.0, 13.7 ppm

HRMS (ESI) m/z Found: $(M+Na)^+$, $C_{32}H_{41}NO_7$, 574.2777, requires 574.2775

Diethyl (1*S*,4*S*,7*S*,8*R*)-8-(4-methoxyphenyl)-5-oxo-6-oxaspiro[bicyclo[2.2.2]octane-2,1'-cyclohexane]-4,7-dicarboxylate (242a)



A solution of β-lactone **220c** (89 mg, 0.2 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol) in EtOH (2 mL) was heated at reflux for 20 hours. The mixture was then concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **242a** (87mg, 98% yield) as a single diastereoisomer as observed by ^{1}H NMR (>20:1 dr).

R_f0.4 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2935, 2836, 1746, 1723, 1612, 1513, 1237, 1213, 1161, 1096 cm^{-1}

HPLC Daicel AD-H, hexane : iPrOH 90:10, 1 mL/min, λ = 230 nm, fraction tr = 15.65 (major enantiomer) and 23.49 (minor enantiomer); er = 95:5

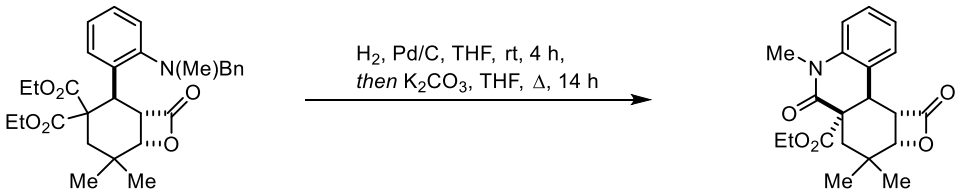
$[a]_D^{25}$ = -10.4° (c = 0.99, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (AA'BB', *J* = 8.8 Hz, 2H), 6.83 (AA'BB', *J* = 8.8 Hz, 2H), 4.71 (s, 1H), 4.24-4.09 (m, 4H), 4.03 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.17 (d, *J* = 7.6 Hz, 1H), 2.18 (ABq, *J* = 14.8 Hz, 1H), 2.02 (ABq, *J* = 14.8, 2.0 Hz, 1H), 1.80-1.57 (m, 5H), 1.53-1.28 (m, 5H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6(4), 171.5(8), 168.5, 159.2, 130.5, 129.3, 114.1, 85.1, 61.9, 61.7, 55.3, 54.0, 45.8, 42.8, 38.0, 35.4, 34.8, 25.5, 22.5, 21.2, 14.2, 14.0 ppm

HRMS (ESI) m/z Found: $(M+H)^+$, $C_{25}H_{32}O_7$, 445.2224, requires 445.2221

Ethyl (2a*S*,4a*S*,10b*R*,10c*S*)-3,3,6-trimethyl-1,5-dioxo-3,4,5,6,10b,10c-hexahydro-1H-oxeto[2,3-k]phenanthridine-4a(2a*H*)-carboxylate (243)



A suspension of β-lactone **220p** (30 mg, 60 μmol) and palladium on carbon (4.6 mg, 10 wt%) in THF (1.5 mL) was stirred at room temperature under an atmosphere of hydrogen for 4 hours. The mixture was then filtered through a pad of Celite, concentrated under reduced pressure and used immediately in the next step. The residue was dissolved in THF (1 mL), potassium carbonate (12.3 mg, 89 μmol) was added and the mixture was heated under reflux for 14 hours. The mixture was allowed to cool to room temperature then concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **243** (20 mg, 94% yield as a mixture of diastereoisomers as observed by ^{1}H NMR (5:1 *cis*/*trans*).

***cis*-isomer:**

R_f 0.3 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2977, 2962, 2934, 1825, 1732, 1676, 1472, 1367, 1278, 1243 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 80:20, 1 mL/min, λ = 238 nm, fraction t_r = 6.75 (minor enantiomer) and 9.71 (major enantiomer); er = 99:1

$[a]_D^{25}$ = +30.6° (c = 0.34, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 2H), 7.09 (td, *J* = 7.2, 1.2 Hz, 1H), 7.00 (brd, *J* = 8.4 Hz, 1H), 4.32 (d, *J* = 6.8 Hz, 1H), 4.02 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.99 (d, *J* = 11.2 Hz, 1H), 3.94 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.46 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.42 (s, 3H), 2.78 (ABq, *J* = 15.2 Hz, 1H), 2.01 (ABq, *J* = 15.2 Hz, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.1, 167.4, 138.2, 129.2, 129.1, 124.3, 124.0, 115.0, 76.6, 62.2, 52.6, 51.0, 38.6, 36.9, 32.0, 31.0, 30.9, 25.5, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{23}NO_5$, 358.1648, requires 358.1649.

***trans*-isomer:**

R_f 0.4 (7:3, v/v hexanes : EtOAc)

IR ν_{max} 2967, 2932, 1820, 1725, 1675, 1460, 1353, 1272, 1218 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 80:20, 1 mL/min, λ = 238 nm, fraction t_r = 7.04 (major enantiomer) and 9.20 (minor enantiomer); er = 99:1

$[a]_D^{25}$ = -132° (c = 0.19, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.35-7.30 (m, 1H), 7.15 (td, *J* = 7.6, 0.8 Hz, 1H), 7.01 (dd, *J* = 8.0, 0.8 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.53 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.91 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.82 (ABX_3, *J* = 10.8, 7.2 Hz, 1H), 3.64 (d, *J* = 11.2 Hz, 1H), 3.43 (s, 3H), 2.63 (ABq, *J* = 15.2 Hz, 1H), 2.03 (ABq, *J* = 15.2 Hz, 1H), 1.22 (s, 3H), 1.21 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm

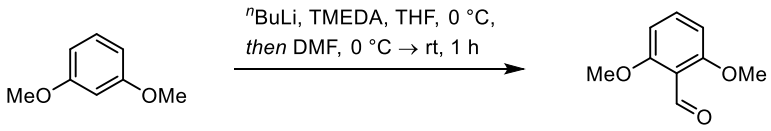
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8(6), 170.7(7), 168.1, 139.3, 128.5, 126.4, 125.1, 124.0, 115.0, 77.3, 61.8, 51.9, 49.7, 40.0, 36.1, 32.6, 31.2, 30.8, 25.9, 13.8 ppm

HRMS (ESI) *m/z* Found: $(M+CH_3OH+H)^+$, $C_{20}H_{23}NO_5$, 390.1914, requires 390.1911

6.4 Experimental section for Chapter 4

6.4.1 Synthesis of hexahydrobenzopyrobenzofuran 273

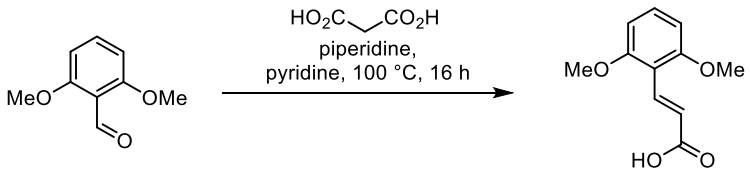
2,6-Dimethoxybenzaldehyde (277)[30]



Following a modified procedure of Krupadanam,[30] a round bottom flask was charged with 1,3-dimethoxybenzene (9.48 mL, 60 mmol), TMEDA (12.4 mL 82 mmol) and anhydrous THF (110mL). The mixture was cooled to 0 °C before ^{n}BuLi (1.6M in hexanes, 54 mL, 87 mmol) was added via syringe over 15 minutes. The reaction mixture was stirred at 0 °C for 60 minutes before anhydrous DMF (5.1 mL, 90 mmol) was added slowly. The solution was then stirred for 1 hour at 0 °C and quenched with the addition of NH_4Cl (60 mL of a saturated aquoues solution.) The yellow mixture was concentrated under reduced pressure before being extracted with EtOAc (3 x 60 mL) and washed with water (1 x 60 mL) and brine (1 x 60 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography to afford the title compound **277** (6.5 g, 72% yield) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 10.46 (s, 1H), 7.43 (t, *J* = 9.1 Hz, 1H), 6.55 (d, *J* = 9.1 Hz, 2H), 3.89 (s, 6H).

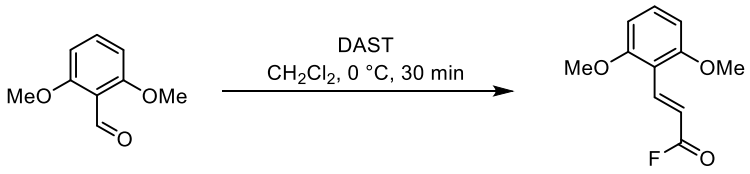
(*E*)-3-(2,6-dimethoxyphenyl)acrylic acid (278)[31]



Following a modified procedure of Diederich,[32] a round bottom flask was charged with aldehyde **277** (1.1 g, 6.4 mmol), malonic acid (1.33 g, 12.8 mmol), piperidine (0.5 mL) and pyridine (30 mL). The flask was sealed and heated to 100 °C for 16 h. After cooling to room temperature, the mixture was poured into ice cold water. Following acidification with concentrated HCl, the precipitate was washed with H_2O (500 mL) and hexanes (500 mL) before being dried at 60 °C *in vacuo*. The title compound **278** (1.2 g, 87%) was isolated as an off white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 16.3 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 16.3 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 3.90 (s, 6H) ppm

(*E*)-3-(2,6-dimethoxyphenyl)acryloyl fluoride (210m)



Following the procedure of Fu[16], to a suspension of α,β-unsaturated carboxylic acid **278** (0.84 g, 4 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added diethylaminosulfur trifluoride (0.58 mL, 4.4mmol mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by the slow addition of $NaHCO_3$ (20 mL of a saturated aqueous solution). The mixture was then extracted with CH_2Cl_2 (3 x 20 mL), and washed with $NaHCO_3$ (2 x 20 mL of a saturated aqueous solution). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **210m** (0.79 g, 94% yield) as an off white solid.

R_f 0.8 (1:1, v/v hexanes : EtOAc)

MP 90-92 °C

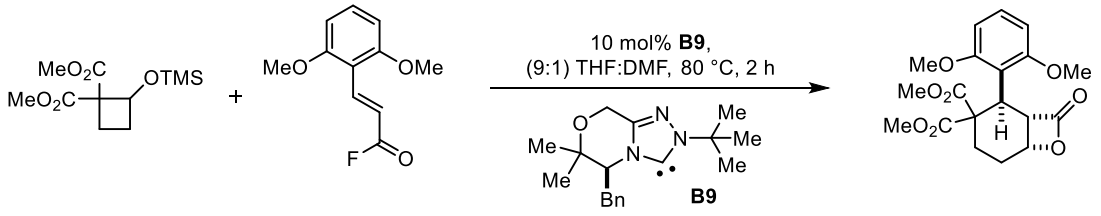
IR ν_{max} 2948, 2843, 1776, 1575, 1474, 1101 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 16.2 Hz, 2H), 7.34 (t, *J* = 8.4 Hz, 1H) 6.82 (dd, *J* = 16.2, 7.5 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 3.89 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.7, 157.4, 142.5, 133.3, 114.2, 113.6, 111.5, 56.0 ppm

HRMS (ESI) *m/z* Found: $(M-F)^+$, $C_{11}H_{11}FO_3$, 191.0708, requires 191.0699

Dimethyl (1*S*,2*R*,6*R*)-2-(2,6-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220ad)



A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane **216e** (3.6 g, 10 mmol), α,β-unsaturated acyl fluoride **210m** (2.1 g, 10 mmol), THF (65 mL) and DMF (1.5 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC **B9** (0.1 mmol) in THF (7 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound **220ad** (1.6 g, 45% yield, >20:1 d.r) as a yellow solid.

R_f 0.4 (1:1, v/v hexanes : EtOAc)

MP 117-119 °C

IR ν_{max} 2951, 2841, 1815, 1728, 1592, 1474, 1231, 1105 cm^{-1}

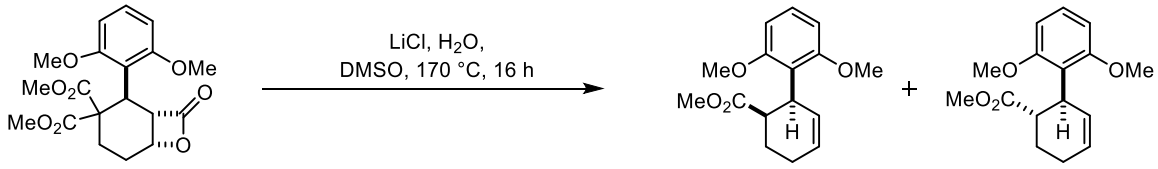
HPLC RegisCell™ 5μm, hexane : *i*PrOH 80:20, 1 mL/min, λ = 230 nm, fraction t_r = 10.09 (major enantiomer) and 11.09 (minor enantiomer); er = 92:8

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 8.3 Hz, 1H), 6.49 (dd, *J* = 8.3, 3.4 Hz, 2H), 5.21 (d, *J* = 1.3 Hz, 1H), 4.89-4.84 (m, 1H), 3.85 (dd, *J* = 6.9, 1.3 Hz, 1H), 3.79 (brs, 3H), 3.78 (s, 3H), 3.77 (brs, 3H), 3.16 (s, 3H), 2.60-2.48 (m, 2H), 2.03-1.98 (m, 1H), 1.89-1.81 (m, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.9, 158.2, 129.0, 118.0, 104.0, 103.9, 70.4, 57.4, 56.0 55.2, 52.9, 52.8, 51.7, 29.3, 25.0, 24.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{22}O_8$, 379.1381, requires 379.1387

cis-Methyl 2',6'-dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboxylate (_cis_-284) and _trans_-methyl 2',6'-dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboxylate (_trans_-284)



Following a modified procedure of Ban,[33] a round bottom flask was charged with β-lactone **220ad** (0.79 g, 2.1 mmol), LiCl (0.36 g, 8.6 mmol), water (77 μL, 4.3 mmol) and DMSO (8 mL). The flash was sealed and heated to 170 °C for 16 hours. The mixture was cooled to room temperture before water (10 mL) was added and the aqueous extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (1 x 20 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude material purified by flash column chromatography to afford the title compounds *cis*- and *trans*-**284** (0.38 g, 66% yield, 2:1 d.r *cis:trans*).

***cis*-isomer:**

R_f0.6 (2:1, v/v hexanes : EtOAc)

IR ν_{max} 2933, 2836, 1731, 1590, 1472, 1432, 1243, 1103 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 2H), 5.78-5.73 (m, 1H), 5.69-5.59 (m, 1H), 4.53-4.38 (m, 1H), 3.75 (s, 6H), 3.32 (s, 3H), 2.97 (ddd, *J* =9.3, 7.5, 3.8 Hz, 1H), 2.48-2.36 (m, 1H), 2.29-2.18 (m, 1H), 2.12-1.99 (m, 1H), 1.88-1.77 (m, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 159.2, 128.9, 127.9, 124.6, 118.4, 104.3, 55.8, 50.8, 43.1, 32.7, 23.4, 22.9 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{20}O_4$, 277.1437, requires 277.1434

***trans*-isomer:**

R_f0.6 (2:1, v/v hexanes : EtOAc)

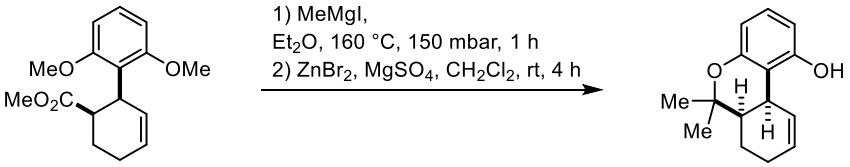
IR ν_{max} 2936, 2836, 1734, 1590, 1465, 1431, 1243, 1110 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 5.72-5.65 (m, 1H), 5.49-5.45 (m, 1H), 4.35-4.31 (m. 1H), 2.52-2.36 (m, 1H), 2.21-2.14 (m, 1H), 2.07-1.98 (m, 1H), 1.95-1.86 (m, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 159.1, 130.6, 127.8, 124.1, 119.7, 104.7, 56.1, 51.3, 43.5, 34.9, 26.8, 24.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{20}O_4$, 277.1437, requires 277.1434

6,6-Dimethyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (286)



Following the procedure of Carreira,[34] to a solution of *cis*-**284** (69 mg, 0.25 mmol) in Et_2O (2 mL) was added MeMgI (0.84 mL, 3.75 M in Et_2O, 2.5 mmol) dropwise. The mixture was stirred for 16 h at room temperature before the solvent was removed under reduced pressure. The residue was heated to 160 °C under reduced pressure (150 mbar) for 1 h before it was cooled to room temperature, diluted with Et_2O (3 mL) and quenched with NH_4Cl (3 mL of saturated aqueous solution). The mixture was extracted with Et_2O (3 x 3 mL), the organic phase dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was then taken up in CH_2Cl_2 (2 mL), and $ZnBr_2$ (86 mg, 0.4 mmol) and $MgSO_4$ (120 mg, 1 mmol) were added. The mixture was stirred for 4 h at room temperature before the reaction was quenched with the addition of NH_4Cl (3 mL of saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 2 mL), the organic phase dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **286** (31 mg, 54% yield) as a yellow oil.

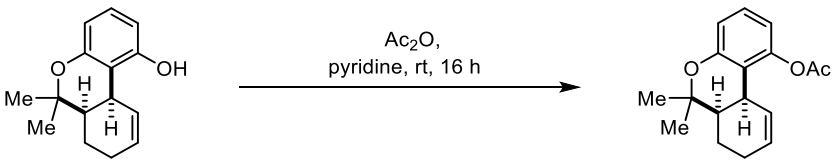
IR ν_{max} 3382, 2975, 2930, 2872, 1612, 1585, 1457, 1263, 1133, 1018 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98-6.89 (m, 1H), 6.60-6.54 (m, 1H), 6.47-6.39 (m, 1H), 6.27 (dd, *J* = 7.9, 1.0 Hz, 1H), 5.79 (ddd, *J* = 9.4, 5.1, 3.4 Hz, 1H), 5.81-5.77 (m, 1H), 4.97 (s, 1H), 3.63 (brs, 1H), 2.12-2.05 (m, 1H), 1.99-1.89 (m, 1H), 1.84-1.74 (m, 1H), 1.42 (s, 3H), 1.42-1.39 (m, 1H), 1.29 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 154.5, 129.7, 128.0, 127.3, 112.1, 110.5, 107.7, 70.7, 40.3, 31.6, 26.0, 25.3, 25.1, 20.4 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{15}H_{18}O_2$, 231.1380, requires 231.1383

6,6-Dimethyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-yl acetate (287)



Following the procedure of Snider,[35] a round bottom flask was charged with benzopyran **284** (31 mg, 0.13 mmol) and pyridine (0.5 mL). Acetic anhydride (0.25 mL) was then added dropwise and the mixture was

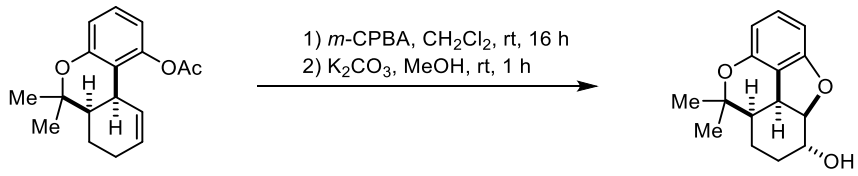
stirred for 16 h at room temperature. Et_2O (3 mL) was then added, and the mixture washed with water (2 x 3 mL), $NaHCO_3$ (2 x 3 mL of a saturated aqueous solution) and brine (3 mL). The combined organics were dried ($MgSO_4$), concentrated under reduced pressure and the crude material purified *via* flash column chromatography to afford the title compound **287** (31 mg, 85% yield) as a colourless oil.

IR ν_{max} 2978, 2933, 2839, 1763, 1459, 1369, 1203, 1027 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (td, J = 8.1, 0.7 Hz, 1H), 6.71 (td, J = 8.1, 1.2 Hz, 1H), 6.58 (dd, J = 8.1, 1.2 Hz, 1H), 6.21-6.15 (m, 1H), 5.84-5.76 (m, 1H), 3.51 (brs, 1H), 2.33 (s, 3H), 2.09-2.04 (m, 1H), 1.98-1.88 (m, 1H), 1.80-1.75 (m, 1H), 1.42 (s, 3H), 1.41-1.38 (m, 1H), 1.27 (s, 3H) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{17}H_{20}O_3$, 273.1490, requires 273.1485

9,9-Dimethyl-2,3,3a,3a1,9,9a-hexahydro-1*H*-benzofuro[4,3,2-cde]chromen-3-ol (273)



Following a modified procedure of Snider,[35] *m*-chloroperbenzoic acid (12 mg, 71 μmol) was added to a solution of acetate **287** (19 mg, 70 μmol) in CH_2Cl_2 (1 mL). The solution was stirred for 2 h at room temperature before the solvent was removed under reduced pressure. The residue was then taken up in EtOAc (3 mL) and washed with Na_2SO_3 (2 x 3 mL of a saturated aqueous solution), $NaHCO_3$ (2 x 3 mL of a saturated aqueous solution) and brine (3 mL). The combined organics were dried ($MgSO_4$), concentrated under reduced pressure to afford the crude epoxide which was used without further purification. The crude epoxide was taken up in MeOH (1 mL), and K_2CO_3 (10 mg, 71 μmol) was added. The mixture was stirred for 2 h at room temperature before being diluted with the addition of NH_4Cl (3 mL of a saturated aqueous solution). The aqueous layer was extracted with EtOAc (3 x 2 mL), and the combined organics dried ($MgSO_4$), concentrated under reduced pressure and purified *via* flash column chromatography to afford the title compound **273** (7 mg, 40% yield) as a yellow oil.

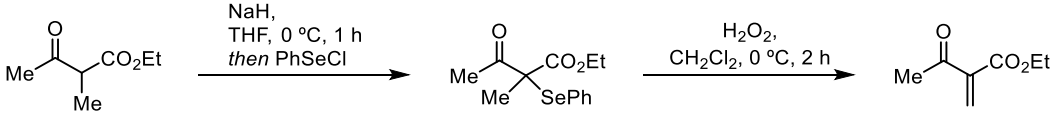
IR ν_{max} 2978, 2933, 2839, 1763, 1459, 1369, 1203, 1027

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (td, J = 8.1, 1.0 Hz, 1H), 6.41 (d, J = 8.1 Hz, 1H), 6.34 (d, J = 8.1 Hz, 1H), 4.72 (dd, J = 7.7, 7.0 Hz, 1H), 3.71-3.66 (m, 1H), 2.10 (brs, 1H) 3.37-3.31 (m, 1H), 1.96-1.86 (m, 1H), 1.84-1.73 (m, 2H), 1.43 (s, 3H), 1.34 (s, 3H) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{15}H_{18}O_3$, 247.1331, requires 247.1329

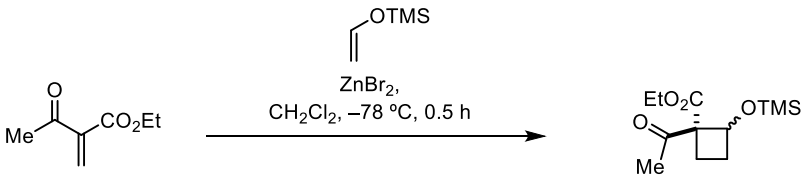
6.4.2 Synthesis of DA-cyclobutane 216m

Ethyl 2-methylene-3-oxobutanoate (290)



Following the procedure of Tardella,[36] a round bottom flask was charged with NaH (0.37 g, 60% in mineral oil 3 mmol) and THF (20 mL). The suspension was cooled to 0 °C and ethyl 2-methyl-3-oxobutanoate (0.28 mL, 2 mmol) was added dropwise over 15 minutes. After one hour of stirring at 0 °C, a solution of phenylselenium chloride (0.38 g, 2 mmol) was added dropwise and the mixture was warmed to room temperature and stirred for 30 minutes. Et_2O (30 mL) was added and the mixture was washed with $NaHCO_3$ (2 x 15 mL of a saturated aqueous solution). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude selenoxide which was used without further purification. The crude residue was taken up in CH_2Cl_2 (20 mL) and cooled to 0 °C before H_2O_2 (0.8 mL, 30% in H_2O) was added slowly. The biphasic mixture was stirred vigorously for 2 h at this temperature before being washed with $NaHCO_3$ (2 x 20 mL of a saturated aqueous solution) and brine (20 mL) The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound **290** which was used without further purification.

Ethyl 1-acetyl-2-((trimethylsilyl)oxy)cyclobutane-1-carboxylate (*cis*/*trans*-216m)



Following a modification of the procedure of Roberts,[29] to a suspension of $ZnBr_2$ (0.45 g, 2 mmol) in anhydrous CH_2Cl_2 (5 mL) at -78 °C was added a solution of the methylene acetoacetate **290** (2 mmol) in CH_2Cl_2 (5 mL) followed by a solution of trimethylsilyl enol ether **223b** (0.36 mL, 2.4 mmol) in CH_2Cl_2 (5 mL). After stirring at -78 °C for 30 minutes , the reaction was quenched by the addition of a cold (-78 °C) solution of pyridine (0.65 mL, 8 mmol) in CH_2Cl_2 (5 mL). The mixture was allowed to warm to room temperature, then washed with Na_2EDTA (2 x 10 mL of a saturated aqueous solution), water (10 mL) and brine (10mL) before the organic layer was dried (Na_2SO_4) and concentrated under reduced

pressure. The crude oil was purified by flash column chromatography on neutralized silica gel to afford the title compound **216m** (0.14 g, 26% yield) as a mixture of diastereomers (3:2 d.r) as observed by ^{1}H NMR analysis.

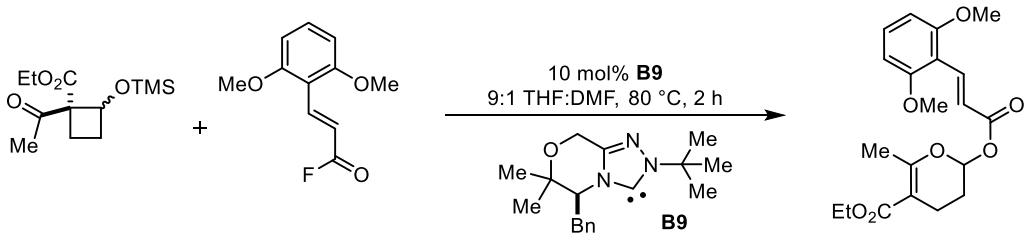
major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (t, *J* = 7.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.52-2.42 (m, 1H), 2.16-2.11 (m, 1H), 2.10 (s, 3H), 1.62-1.53 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.09 (s, 9H) ppm

minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (t, *J* = 7.6 Hz, 1H), 4.22-4.13 (m, *J* = 7.1 Hz, 2H), 2.62-2.56 (m, 1H), 2.17 (s, 3H), 1.94-1.82 (m, 1H), 1.62-1.53 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.11 (s, 9H) ppm

Ethyl (*E*)-2-((3-(2,6-dimethoxyphenyl)acryloyl)oxy)-6-methyl-3,4-dihydro-2*H*-pyran-5-carboxylate (291)



A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane **216m** (26 mg, 0.1 mmol), α,β-unsaturated acyl fluoride **210m** (21 mg, 0.1 mmol), THF (0.65 mL) and DMF (0.15 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC **B9** (0.01 mmol) in THF (0.7 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound **291** (26 mg, 69% yield) as a viscous oil.

IR ν_{max} 2938, 2841, 1705, 1618, 1594, 1476, 1255, 1107, 1017 cm^{-1}

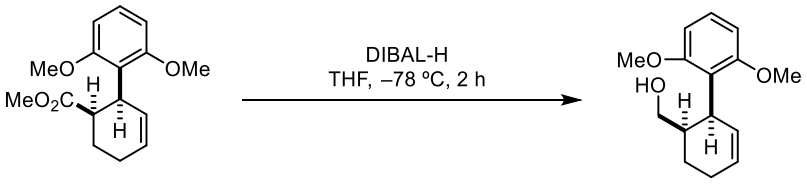
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 16.3 Hz, 1H), 7.28 (t, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 16.3 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 6.45 (dd, *J* = 3.5, 2.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 6H), 2.52-2.41 (m, 2H), 2.25 (s, 3H), 2.10-1.99 (m, 1H), 1.95-1.80 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.1, 161.5, 160.3, 137.4, 131.8, 119.5, 112.2, 103.8, 102.7, 89.9, 60.0, 55.9, 24.9, 20.0, 17.2, 14.5 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{27}O_7$, 377.1592, requires 377.1595

6.4.3 Synthesis of alkenyl side-chain bearing ketone 299

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)methanol (296)



A round bottom flask was charged with *cis*-ester **284** (0.23 g, 0.83 mmol) and THF (5 mL) and cooled to -78 °C. A solution of DIBAL-H (1.83 mL, 1.0 M, 1.83 mmol) was then added dropwise and the mixture stirred for 1.5 hours at this temperature. The reaction was then warmed to 0 °C and diluted with Et_2O (10 mL) before the sequential dropwise addition of water (80 μL), NaOH (80 μL of a 15 wt% solution in water) and again, water (0.18 mL). The suspension was allowed to warm to room temperature and stirred for 15 minutes before $MgSO_4$ was added and the mixture stirred for an additional 15 minutes. The cloudy suspension was filtered through a pad of celite, the filtrate was concentrated under reduced pressure and the crude material purified *via* flash column chromatography to afford the title compound **296** (0.19 g, 94% yield) as a clear oil.

R_f 0.3 (6:4, v/v hexanes : EtOAc)

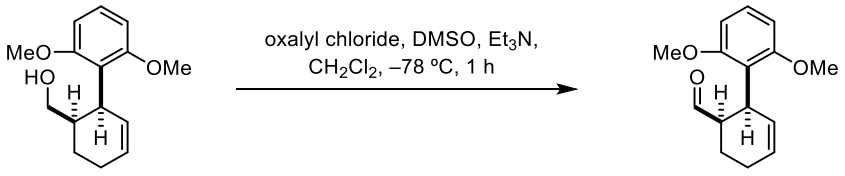
IR ν_{max} 3370, 3018, 2932, 2835, 1589, 1471, 1241, 1103 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 8.3 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 5.63-5.60 (m, 1H), 5.59-5.55 (m, 1H), 4.20-4.16 (m, 1H), 3.42 (dd, J = 11.3, 5.8 Hz, 1H), 3.32-3.26 (m, 1H), 2.12-1.96 (m, 4H), 1.88-1.81 (m, 1H), 1.72-1.65 (m, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 127.9, 124.6, 118.7, 104.9, 65.5, 55.9, 40.3, 33.5, 24.0, 23.5 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{15}H_{20}O_3$, 249.1485, requires

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde (297)



A round bottom flask was charged with dimethylsulfoxide (1.4 mL, 20 mmol) and CH_2Cl_2 (10 mL) and cooled to -78 °C. Oxalyl chloride (0.86 mL, 10 mmol) was then added slowly and the mixture stirred for 10 minutes before a solution of alcohol **296** (0.62 g, 2.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise.

The mixture was allowed to stir for 30 minutes at this temperature before triethylamine (7 mL, 50 mmol) was added slowly. The cloudy suspension was then placed in an ice bath for 10 minutes and then warmed to room temperature. Water (50 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified *via* flash column chromatography to afford the title compound **297** (0.54 g, 87% yield) as a yellow oil.

R_f 0.3 (4:1, v/v hexanes : EtOAc)

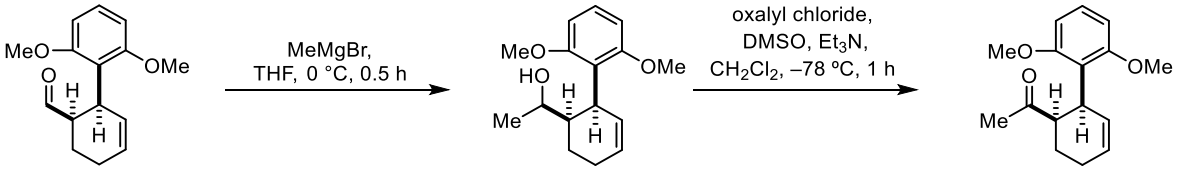
IR ν_{max} 3024, 2934, 2838, 2727, 1717, 1591, 1472, 1244, 1106 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 1.7 Hz, 1H), 7.18 (t, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 2H), 5.78-5.65 (m, 2H), 4.45 (brs, 1H), 3.76 (s,6H), 2.65 (brs, 1H), 2.35-2.39 (m 1H), 1.95-1.88 (m, 1H), 1.76-1.64 (m, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 158.7, 130.3, 128.3, 123.6, 117.7, 104.3, 55.6, 49.2, 33.1, 23.2, 22.0 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{15}H_{18}O_3$, 247.1331, requires 247.1329

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)ethan-1-one (295)



A round bottom flask was charged with aldehyde **297** (0.1 g, 0.73 mmol) and THF (5 mL) and cooled to 0 °C. A solution of MeMgBr (0.32 mL, 3.0 M in Et_2O, 0.94 mmol) was added slowly and the solution stirred for 1 hour at this temperature. The reaction was then quenched with the addition of NH_4Cl (10 mL of a saturated aqueous solution) and extracted with Et_2O (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the secondary alcohol **298** which was used immediately in the next step. A round bottom flask was charged with dimethylsulfoxide (0.41 mL, 5.8 mmol) and CH_2Cl_2 (5 mL) and cooled to –78 °C. Oxalyl chloride (0.25 mL, 2.9 mmol) was then added slowly and the mixture stirred for 10 minutes before a solution of alcohol **298** (0.73 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was allowed to stir for 30 minutes at this temperature before triethylamine (2.0 mL, 14.6 mmol) was added slowly. The cloudy suspension was then placed in an ice bath for 10 minutes and then warmed to room temperature. Water (20 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were dried (Na_2SO_4),

concentrated under reduced pressure and the crude material purified *via* flash column chromatography to afford the title compound **295** (0.13 g, 67% yield over two steps) as a yellow oil.

R_f 0.4 (1:1, v/v hexanes : EtOAc)

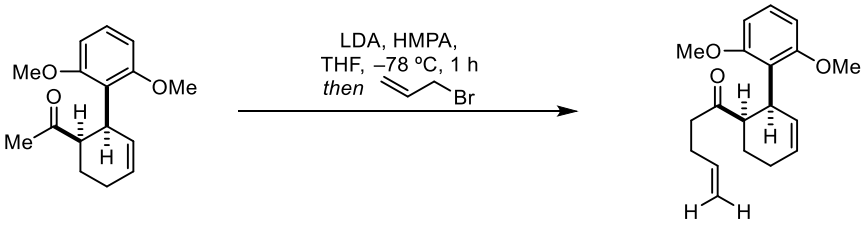
IR ν_{max} 3021, 2933, 2837, 1708, 1592, 1473, 1244, 1196 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 1H), 5.82-5.74 (m, 1H), 5.60 (brd, *J* = 9.9 Hz, 1H), 4.57 (brs, 1H), 3.74 (s, 6H), 3.03 (m, 1H), 2.34-2.23 (m, 2H) 2.09-2.04 (m, 1H), 1.85 (s, 3H), 1.76-1.67 (m, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 158.9, 128.9, 128.2, 125.4, 117.9, 104.5, 55.6, 51.7, 31.9, 29.4, 24.1, 21.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{20}O_3$, 261.1482, requires 261.1485

2',6'-Dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)pent-4-en-1-one (299)



Following a modified procedure of Shi,[37] to a freshly prepared solution of lithium diisopropylamide (0.4 mL, 0.4 M in THF, 0.4 mmol) at –78 °C was added methylketone **295** (25 mg, 0.1 mmol) in THF (1 mL). The mixture was stirred for 45 minutes at this temperature before hexamethylphosphoramide (35 μL, 0.2 mmol) was added followed by the addition of allyl bromide (17 μL, 0.2 mmol). The solution was then warmed to room temperature and stirred for 20 hours before the solvent was removed under reduced pressure. The residue was taken up in Et_2O (3 mL), and washed with water (2 mL) and brine (2 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the residue purified *via* flash column chromatography to afford the title compound **299** (16 mg, 54% yield) as a colourless oil.

R_f 0.4 (9:1, v/v hexanes : EtOAc)

IR ν_{max} 3020, 2932, 1836, 1709, 1591, 1472, 1243, 1106 cm^{-1}

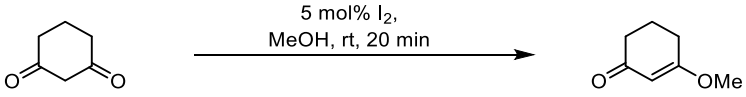
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 2H), 5.81-5.76 (m, 1H), 5.64-5.53 (m, 2H), 4.91-4.81 (m, 2H), 4.58-4.55 (m, 1H), 3.74 (s, 6H), 3.05 (ddd, *J* = 11.5, 8.0, 3.6 Hz, 1H), 2.41 (ddd, *J* = 17.1, 9.5, 5.7 Hz, 1H), 2.35-2.28 (m, 1H), 2.20 (ddd, *J* = 17.1, 9.5, 5.7 Hz, 2H), 2.12-1.99 (m, 2H), 1.83-1.73 (m, 1H), 1.67 (m, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 158.94, 138.1, 128.9, 128.3, 125.4, 118.0, 114.5, 104.5, 55.6, 50.8, 41.1, 31.8, 27.7, 24.1, 21.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{24}O_3$, 301.1800, requires 301.1798

6.4.4 Synthesis of α,β-unsaturated acyl fluoride 210n

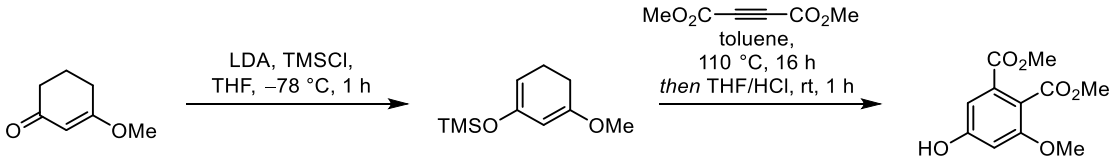
3-Methoxycyclohex-2-en-1-one (303)[38]



Following the procedure of Jadhav,[39] a round bottom flasked was charged with cyclohexadione (5.6 g, 50 mmol), iodine (0.63 g, 2.5 mmol) and MeOH (100 mL). The solution was stirred at room temperature for 20 minutes before the solvent was removed under reduced pressure. The residue was taken up in EtOAc (60 mL) and washed with Na_2SO_3 (3 x 50 mL, 10 wt% aqueous solution). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the residue purified *via* flash column chromatography to afford the title compound **303** (2.0 g, 31% yield) as colourless low melting solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 3.68 (s, 3H), 2.39 (t, J = 6.1 Hz, 2 H), 2.32 (t, J = 6.1 Hz, 2 H), 1.95 (m, 2 H)

Dimethyl 5-hydroxy-3-methoxyphthalate (302)[40]



To a freshly prepared solution of lithiumdiisopropylamide (11 mmol) in THF (10 mL) at – 78 °C was added a solution of enone **303** (1.26 g, 10 mmol) in THF (5 mL) over 20 minutes. The mixture was stirred for 1 hour at this temperature before chlorotrimethylsilane (1.46 mL, 11.5 mmol) was added slowly. After an additional 1 hour stirring at this temperature, the reaction mixture was poured into an ice cold solution of $NaHCO_3$ (50 mL of a saturated aqueous solution). The mixture was extracted with Et_2O (2 x 30 mL) and washed with brine, before the combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to afford the diene **305** as a colourless oil which was used immediately in the next reaction. Diene **305** was taken up in toluene (5 mL) and cooled to 0 °C before dimethyleacetylene

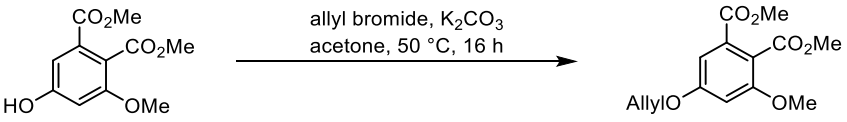
dicarboxylate (1.0 mL, 8 mmol) was added and the reaction vessel sealed and heated to 150 °C for 16 hours. After this time, the mixture was cooled to room temperature and THF (15 mL) and HCl (4 mL of a 2.0 M aqueous solution) were added. The orange solution was stirred for 1 h at room temperature and then extracted with Et_2O (3 x 20 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified *via* flash column chromatography to afford the title compound **302** (1.3 g, 68% yield) as a yellow solid.

R_f 0.3 (1:1, v/v hexanes : EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 5.98 (brs, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 165.9, 160.2, 157.9, 132.5, 130.0, 118.6, 118.4, 106.4, 103.8, 69.3, 56.4, 52.7, 52.7 ppm

Dimethyl 5-(allyloxy)-3-methoxyphthalate (307)



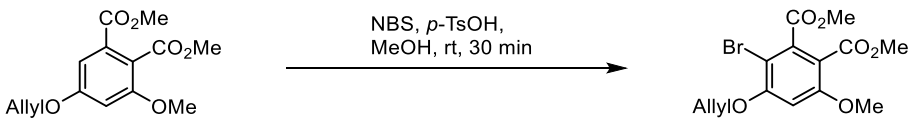
A round bottom flask was charged with phthalate **302** (1.31 g, 5.4 mmol), potassium carbonate (1.50 g, 10.8 mmol), allyl bromide (0.93 mL, 10.8 mmol) and acetone (40 mL). The flask was sealed and heated to 50 °C for 16 h, before being cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue purified *via* flash column chromatography to afford the title compound **307** (1.46 g, 96% yield) as an off white solid.

IR ν_{max} 2998, 2952, 2845, 1726, 1603, 1329, 1269, 1152, 1062 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 2.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 5.97 (m, 1H), 5.36 (brd, *J* = 17.3 Hz, 1H), 5.25 (brd, *J* = 10.4 Hz, 1H), 4.52 (d, *J* = 5.2 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H) ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{14}H_{26}O_6$, 281.1015, requires 281.1020

Dimethyl 4-(allyloxy)-3-bromo-6-methoxyphthalate (308)



A round bottom flask was charged with allyl ether **307** (1.40 g, 5 mmol), *p*-toluenesulfunic acid (95 mg, 0.5 mmol) and methanol (20 mL). A solution of *N*-bromosuccinimide (0.89 g, 5 mmol) in MeOH (10 mL) was then added over 20 minutes and the mixture stirred for an additional 10 minutes at room temperature. The reaction mixture was then concentrated under reduced pressure, and the residue purified *via* flash column chromatography (dry loaded) to afford the title compound **308** (1.49 g, 82% yield) as a white solid.

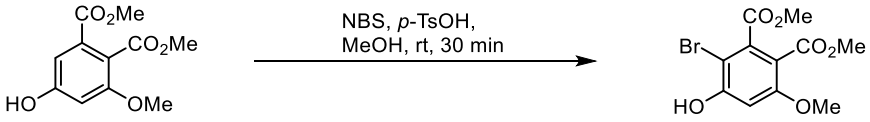
IR ν_{max} 2977, 2951, 2852, 1732, 1582, 1434, 1334, 1252, 1040 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.08-5.98 (m, 1H), 5.48 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.6 Hz, 1H), 4.66 (d, *J* = 4.1 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.09, 165.20, 159.07, 158.20, 138.33, 131.83, 118.58, 113.91, 101.26, 99.01, 70.32, 56.74, 52.92, 52.58 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{14}H_{15}BrO_6$, 359.0128, requires 359.0125

Dimethyl 3-bromo-4-hydroxy-6-methoxyphthalate (309)



The title compound was prepared according the representative procedure for compound **307**. The title compound **309** (1.24 g, 84% yield) was purified *via* flash column chromatography and isolated as a white solid.

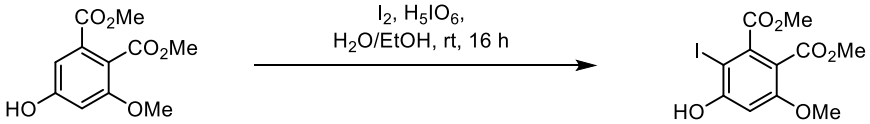
IR ν_{max} 3197, 2955, 2853, 1734, 1685, 1582, 1438, 1353, 1219, 1021 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.15 (s, 1H), 3.91 (s, 3H), 3.84 (s, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.3, 159.2, 155.9, 136.8, 114.8, 101.1, 99.2, 56.7, 53.1, 52.7 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{11}H_{12}BrO_6$, 318.9649 requires 318.9812

Dimethyl 4-hydroxy-3-iodo-6-methoxyphthalate (310)



Following the procedure of Parker, a round bottom flask was charged with phthalate **302** (0.28 g, 1 mmol), iodine (0.15 g, 0.6 mmol) and EtOH (7 mL). A solution of H_5IO_6 (46 mg, 0.2 mmol) in water (0.5 mL)

was then added in one portion and the solution stirred for 8 hours at room Temperature. After this time, the solvent was removed under reduced pressure, and the residue taken up in EtOAc (20 mL) and washed with $Na_2S_2O_3$ (3 x 10 mL of a saturated aqueous solution) and brine (20 mL). The organics layer was dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified *via* flash column chromatography to afford the title compound **310** (0.31 g, 72% yield) as a white solid.

R_f 0.2 (1:1, v/v hexanes : EtOAc)

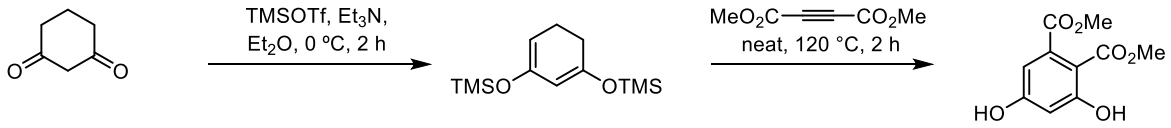
IR ν_{max} 3264, 2953, 1734, 1696, 1577, 1354, 1219, 1017 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.03 (brs, 1H), 3.92 (s, 3H), 3.84 (s, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 165.4, 160.3, 158.5, 140.9, 115.2, 103.4, 100.0, 56.6, 53.1, 52.8 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{11}H_{12}IO_6$, 366.9677 requires 366.9673

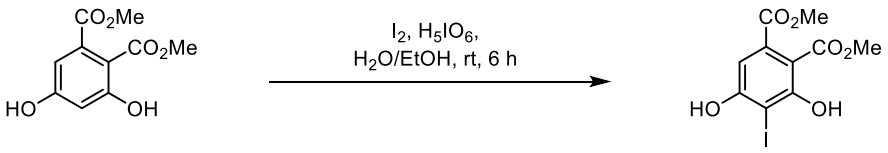
Dimethyl 3,5-dihydroxyphthalate (315)[41]



A flame-dried Schlenk flask was charged with cyclohexanedione (2.24 g, 20 mmol), triethylamine (5.70 mL, 40.8 mmol) and anhydrous Et_2O (40 mL). The flask was cooled to 0 °C and TMSOTf (7.16 mL, 39.6 mmol) was added dropwise before the solution was allowed to stir for 2 hours at this temperature. After this time, two distinct layers had formed and the top layer was transferred *via* syringe into a freshly dried Schlenk flask. The solvent was then removed under reduced pressure to afford bis TMS enol ether **314**. Dimethylacetylene dicarboxylate (2.40 mL, 15 mmol) was then added to the neat material and the vessel was sealed and heated to 120 °C for 2 hours to give an orange oil. The crude residue was purified *via* flash column chromatography to afford the title compound **315**(2.6 g, 64% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 7.25 (s, 1H), 6.45 (d, *J* =2.3 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 3.89 (s, 3H), 3.87 ppm (s, 3H) ppm

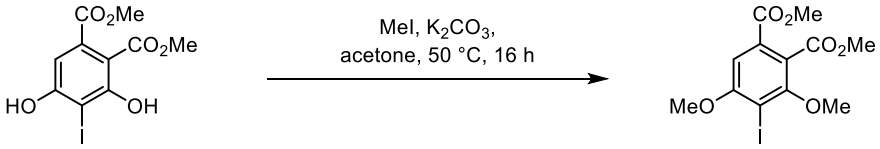
Dimethyl 3,5-dihydroxy-4-iodophthalate (259)[41]



The title compound was prepared according the representative procedure for compound **310**. The title compound **259** (0.55 g, 65% yield) was purified *via* flash column chromatography and isolated as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.01 (s, 1H), 6.63 (s, 1H), 6.19 (s, 1H), 3.90 (s, 3H), 3.88 ppm (s, 3H) ppm

Dimethyl 4-iodo-3,5-dimethoxyphthalate (316)



A round bottom flask was charged with phthalate **259** (0.55 g, 1.6 mmol), potassium carbonate (0.86 g, 6.2 mmol), iodomethane (0.39 mL, 6.2 mmol) and acetone (20 mL). The flask was sealed and heated to 50 °C for 16 h, before being cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue purified *via* flash column chromatography to afford the title compound **316** (0.32 g, 54% yield) as an off white solid.

R_f 0.5 (3:2, v/v hexanes : EtOAc)

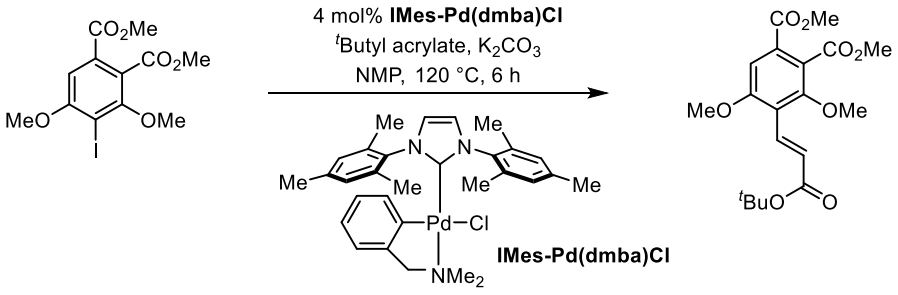
IR ν_{max} 2949, 2855, 1736, 1724, 1578, 1325, 1253, 1164, 1071 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.19 (s, 1H), 3.96 (s, 2H), 3.93 (s, 2H), 3.90 (s, 2H), 3.89 (s, 2H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 167.2, 165.4, 160.3, 158.8, 130.0, 123.8, 107.5, 90.6, 62.9, 57.1, 52.9(8), 52.9(5) ppm

HRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{12}H_{13}IO_6$, 402.1154 requires 402.9649

Dimethyl (*E*)-4-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-3,5-dimethoxyphthalate (318)



Following a modified procedure of Ying,[6] an oven dried pressure tube was charged with iodide **316** (380 mg, 1 mmol), ^{t}butyl acrylate, (175 μL, 1.2 mmol), potassium carbonate (275 mg, 2 mmol),

IMes-Pd(dmba)Cl (12 mg, 0.4 mmol) and *N*-methylpyrrolidine (1 mL). The flask was sealed and heated to 120 °C for 5 h to give a dark solution before being cooled to room temperature and diluted with Et_2O (20 mL). The mixture was then filtered through a pad of celite, concentrated under reduced pressure and the crude residue purified *via* flash column chromatography to afford the title compound **318** (270 mg, 71% yield) as a white solid.

R_f 0.2 (1:1, v/v hexanes : EtOAc)

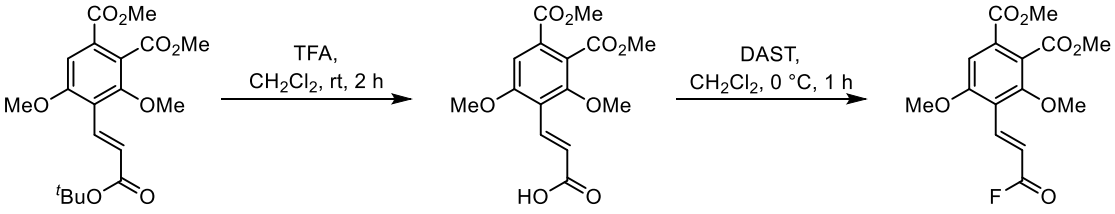
IR ν_{max} 2946, 2844, 1722, 1706, 1627, 1237, 1145, 1099, 1043

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 16.3 Hz, 1H), 7.26 (s, 1H), 6.83 (d, *J* = 16.3 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H), 1.48 (s, 9H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 167.8, 166.94, 165.3, 159.9, 157.8, 132.7, 129.4, 127.0, 123.93, 121.9, 108.22, 80.7, 63.4, 56.34, 52.9, 52.9, 28.3 ppm

LRMS (ESI) *m/z* Found: $(M+Na)^+$, $C_{19}H_{24}O_8$, 403.1 requires 403.1

Dimethyl (*E*)-4-(3-fluoro-3-oxoprop-1-en-1-yl)-3,5-dimethoxyphthalate (220n)



A round bottom flask was charged with cinnamate **318** (182 mg, 0.5 mmol) trifluoroacetic acid (1 mL) and CH_2Cl_2. The solution was stirred vigourously for 6 hours at room temperature before the solvent was removed under reduced pressure. Toluene (5 mL) was then added to the residue, and the solution subjected to rotary evaporation under reduced pressure. This was repeated an additional two times to remove the excess trifluoroacetic acid as an azeotrope which afforded the crude α,β-unsaturated carboxylic acid **319** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 16.3 Hz, 1H), 7.33 (s, 1H), 7.01 (d, *J* = 16.3 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 3.82 (s, 3H).

The crude acid **319** was taken up in anhydrous CH_2Cl_2 (2 mL) and diethylaminosulfurtrifluoride (79 μL, 0.6 mmol) was added dropwise at 0 °C. After 30 minutes of stirring at this temperature the reaction was quenched by slow addition of $NaHCO_3$ (1 mL of a saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 2 mL), the organic phase dried (Na_2SO_4) and concentrated under reduced pressure to

give a yellow oil. The crude material was purified *via* flash column chromatography to afford the title compound **220n** (100 mg, 60% yield over two-steps) as a white solid.

R_f 0.4 (1:1, v/v hexanes : EtOAc)

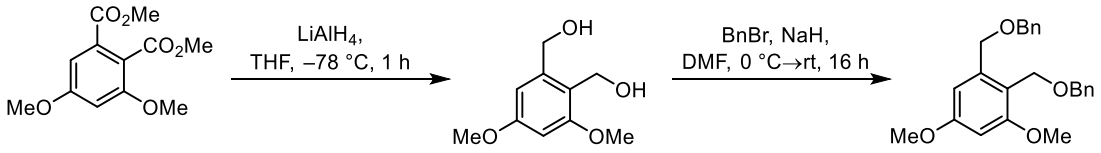
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 16.3 Hz, 1H), 7.34 (s, 1H), 6.95 (dd, *J* = 16.3, 7.0 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 2H), 3.91 (s, 3H), 3.83 (s, 3H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 167.3, 165.0, 160.4, 158.6, 157.9 (d, *J* = 338.3 Hz), 140.4 (d, *J* = 6.8 Hz), 131.5, 123.8, 120.2, 118.6 (*J* = 65.5 Hz), 108.4, 63.8, 56.6, 53.1, 53.0 ppm

HRMS (ESI) *m/z* Found: $(M-HF+H)^+$ $C_{15}H_{15}O_7F$, 327.0871 requires 327.0875

6.4.5 Synthesis of β-lactone 220ah

((((3,5-Dimethoxy-1,2-phenylene)bis(methylene))bis(oxy))bis(methylene))dibenzene (322a)



To a solution of phthalate **316** (0.86 g, 3.4 mmol) in THF at –78 °C was added $LiAlH_4$ (8.4 mL, 1.0 M in THF, 8.4 mmol) dropwise. The mixture was warmed to room temperature and stirred for 1 hour before it was diluted with Et_2O (20 mL). The reaction was then quenched by the sequential dropwise addition of water (0.33 mL), NaOH (0.33 m L of a 15 wt% solution in water) and again, water (3.4 mL). The suspension was stirred for 15 minutes before $MgSO_4$ was added and the mixture stirred for an additional 15 minutes. The cloudy suspension was then filtered through a pad of celite, the filtrate was concentrated under reduced pressure and to afford diol **321** which was used immediately in the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 4.78 (s, 2H), 4.71 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.55 (brs, 1H), 1.57 (brs, 1H) ppm

The diol **321** was taken up in THF (17 mL) and DMF (4 mL) and cooled to 0 °C before NaH (0.4 g, 60% in mineral oil, 10 mmol) was added in portions. The reaction mixture was warmed top room temperature and stirred for 16. After this time the reaction was quenched by the addition of water (10 mL) and the aqueous was extracted with EtOAc (3 x 10 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified *via* flash column chromatography to afford the title compound **322a** (0.61 g, 47% yield) as a viscous, colourless oil.

R_f 0.6 (4:1, v/v hexanes : EtOAc)

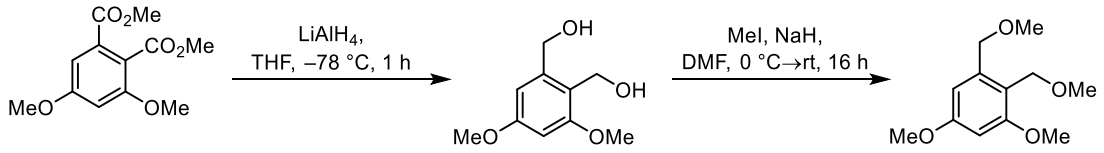
IR ν_{max} 3029, 2937, 2839, 1604, 1453, 1316, 1199, 1147, 1057 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.26 (m, 10H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.61 (s, 2H), 4.58 (s, 2H), 4.52 (s, 2H), 4.48 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 160.7, 159.5, 140.9, 138.90, 138.5, 128.5, 128.4, 128.1, 127.97, 127.8, 127.6, 117.0, 105.0, 97.9, 72.6, 72.2, 69.7, 62.20, 55.9, 55.5 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{26}O_4$, 379.1900 requires 379.1904

1,5-Dimethoxy-2,3-bis(methoxymethyl)benzene (322b)



The title compound was prepared according the representative procedure for compound **322a**, however using iodomethane in place of benzyl bromide. The title compound **322b** (0.15 g, 66% yield) was purified *via* flash column chromatography and isolated as a white solid.

R_f 0.3 (7:3, v/v hexanes : EtOAc)

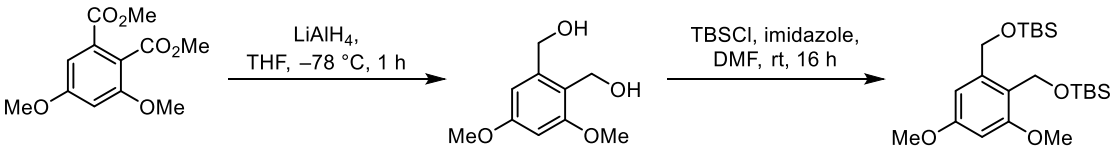
IR ν_{max} 2925, 2889, 2820, 1603, 1459, 1303, 1199, 1145, 1076 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 4.54 (s, 2H), 4.50 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.42 (s, 3H), 3.34 (s, 3H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 160.7, 159.5, 140.7, 116.8, 104.6, 97.9, 72.0, 64.4, 58.5, 58.0, 55.9, 55.5 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{12}H_{18}O_4$, 227.1270 requires 227.1278

(((3,5-Dimethoxy-1,2-phenylene)bis(methylene))bis(oxy))bis(*tert*-butyldimethylsilane) (322c)



To a solution of phthalate **316** (0.25 g, 3.4 mmol) in THF at -78 °C was added $LiAlH_4$ (2.5 mL, 1.0 M in THF, 2.5 mmol) dropwise. The mixture was warmed to room temperature and stirred for 1 hour before it was diluted with Et_2O (20 mL). The reaction was then quenched by the sequential dropwise addition of water (0.08 mL), NaOH (0.08 mL of a 15 wt% solution in water) and again, water (0.8 mL). The suspension was stirred for 15 minutes before $MgSO_4$ was added and the mixture stirred for an additional

15 minutes. The cloudy suspension was then filtered through a pad of celite, the filtrate was concentrated under reduced pressure and to afford diol **321** which was used immediately in the next reaction. The residue was taken up in DMF (3 mL) and TBSCl (0.45 g, 3 mmol) and imidazole (0.19 g, 3mmol) were added. The solution was stirred for 16 h at room temperature before water (10 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined roganics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified *via* flash column chromatography to afford the title compound **322c** (0.26 g, 62% yield) as a colourless oil.

R_f 0.3 (7:3, v/v hexanes : EtOAc)

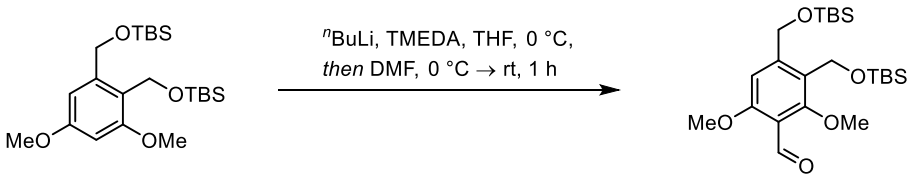
IR ν_{max} 2953, 2929, 2856, 1605, 1462, 1253, 1146, 1064 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 1.7 Hz, 1H), 6.35 (d, *J* = 1.7 Hz, 1H), 4.90 (s, 2H), 4.70 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 0.97 (s, 9H), 0.89 (s, 9H), 0.12 (s, 6H), 0.03 (s, 6H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 160.3, 158.0, 144.1, 117.9, 102.8, 97.0, 62.4, 55.8, 55.5, 55.3, 26.1, 26.1, -5.1, -52 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{12}H_{18}O_4$, 227.1270 requires 227.1278

3,4-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxybenzaldehyde (323c)



Following a modified procedure of Krupadanam,[30] a round bottom flask was charged with arene **322c** (0.91 g, 2.1 mmol), TMEDA (0.40 mL, 2.6 mmol) and anhydrous THF (10 mL). The mixture was cooled to 0 °C before ^{n}BuLi (1.6 mL, 1.6 M in hexanes, 2.6 mmol) was added via syringe over 15 minutes. The reaction mixture was stirred at 0 °C for 60 minutes before anhydrous DMF (0.20 mL, 2.7 mmol) was added slowly. The solution was then stirred for 1 hour at 0 °C and quenched with the addition of NH_4Cl (60 mL of a saturated aquoues solution.) The yellow mixture was concentrated under reduced pressure before being extracted with EtOAc (3 x 10 mL) and washed with water (1 x 10 mL) and brine (1 x 10mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography to afford the title compound **323c** (0.54 g, 57% yield) as a colourless oil.

R_f 0.2 (4:1, v/v hexanes : EtOAc)

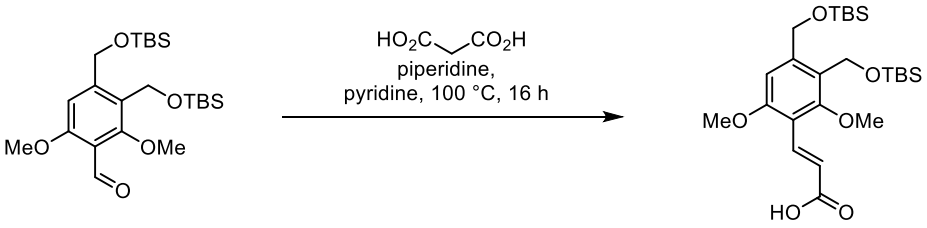
IR ν_{max} 2953, 2930, 2857, 1689, 1599, 1462, 1253, 1111, 1051 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.15 (s, 1H), 4.92 (s, 2H), 4.65 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 0.97 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H), 0.10 (s, 6H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 189.3, 162.0, 160.54, 151.4, 122.6, 116.6, 105.0, 64.3, 62.2, 56.0, 55.4, 26.0, 26.0, -5.2, -5.3 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{23}H_{42}O_5Si_2$, 469.2761 requires 469.2644

(*E*)-3-(3,4-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)acrylic acid (324)



Following a modified procedure of Diederich,[32] a round bottom flask was charged with aldehyde **323c**(0.46 g, 1 mmol), malonic acid (0.21 g, 2 mmol), piperidine (0.1 mL) and pyridine (3 mL). The flask was sealed and heated to 100 °C for 16 h. After cooling to room temperature, the mixture was poured into ice cold water. Following acidification (pH = 4) with concentrated HCl, the precipitate was washed with H_2O (50 mL) and hexanes (50 mL) before being dried at 60 °C *in vacuo*. The α,β-unsaturated acid **324** (0.30 g, 60%) was isolated as an off white solid.

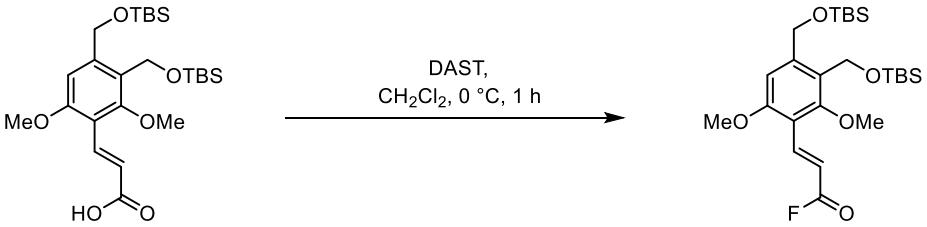
IR ν_{max} 2953, 2930, 2857, 1684, 1601, 1463, 1255, 1130, 1050, 842 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 16.2 Hz, 1H), 7.42 (s, 1H), 7.09 (d, *J* = 16.2 Hz, 1H), 5.07 (s, 2H), 4.83 (s, 2H), 4.08 (s, 3H), 3.91 (s, 3H), 1.14 (s, 9H), 1.06 (s, 9H), 0.29 (s, 6H), 0.27 (s, 6H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 173.3, 159.9, 159.1, 146.8, 122.3, 120.3, 119.7, 114.5, 104.7, 63.8, 62.8, 56.1, 26.2, 25.8, -5.5, -5.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{25}H_{44}O_6Si_2$, 469.2617 requires 496.2676

(*E*)-3-(3,4-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)acryloyl fluoride (210o)



Following the procedure of Fu,[16] to a suspension of α,β-unsaturated acid **324** (1.0 g, 2 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added diethylaminosulfur trifluoride (0.29 mL, 2.2 mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by slow addition of $NaHCO_3$ (30 mL of a saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), the organic phase dried (Na_2SO_4), concentrated under reduced pressure to give a yellow oil. The crude material purified via flash column chromatography to afford the title compound **210o** (0.59 g, 59% yield) as a white solid.

R_f 0.6 (4:1, v/v hexanes : EtOAc)

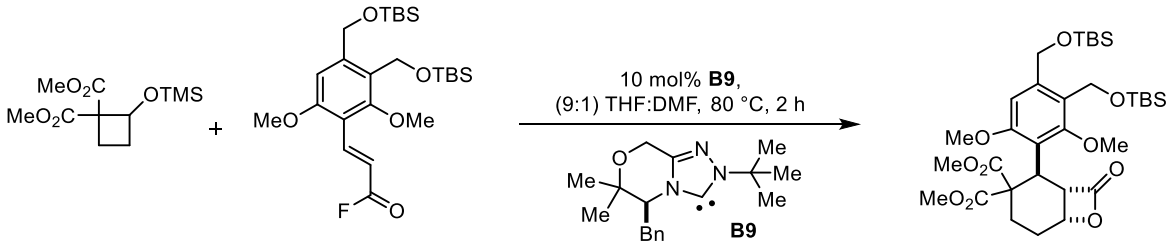
IR ν_{max} 2955, 2932, 2858, 1796, 1618, 1464, 1258, 1133, 835 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 16.2 Hz, 1H), 7.13 (s, 1H), 6.86 (dd, *J* = 16.2, 7.3 Hz, 1H), 4.91 (s, 2H), 4.66 (s, 2H), 3.93 (s, 3H), 3.76 (s, 3H), 0.98 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H), 0.11 (s, 6H) ppm

^{13}CNMR (100 MHz, $CDCl_3$) δ 160.3, 159.5, 159.0 (d, *J* = 337.9 Hz), 148.4, 143.0, 142.9 (d, *J* = 7.3 Hz), 122.5, 114.5 (d, *J* = 64.6 Hz), 113.9, 105.0, 63.2, 62.1, 5615, 55.8, 26.0, 26.0, 18.5, 18.4, -5.2, -5.3 ppm

HRMS (ESI) *m/z* Found: $(M-HF+H)^+$, $C_{25}H_{44}O_6Si_2$, 479.2627 requires 496.2649

Diethyl (1*S*,2*R*,6*R*)-2-(3,4-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220ah)



A two-neck flask equipped with a reflux condenser and septum was charged with donor-acceptor cyclobutane **216e** (52 mg, 0.2 mmol), α,β-unsaturated acyl fluoride **210o** (100 mg, 0.2 mmol), THF (1.3 mL) and DMF (0.3 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC **B9** (0.02 mmol) in THF (1.4 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at reflux for 2 hours. The mixture was then allowed to cool to room temperature, concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the title compound **220ah** (9 mg, 7% yield, >20:1 d.r) as a viscous oil.

R_f 0.4 (4:1, v/v hexanes : EtOAc)

IR ν_{max} 2953, 2857, 1824, 1735, 1258, 1126, 1050, 836 cm^{-1}

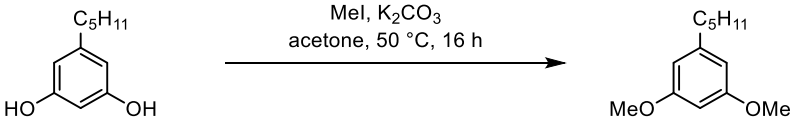
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 4.98 (d, *J* = 1.2 Hz, 1H), 4.82-4.71 (m, 2H), 4.73 (d, *J* = 1.6 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 3.75 (d, *J* = 1.7 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.99 (s, 3H), 2.57-2.41 (m, 2H), 1.96-1.86 (m, 1H), 1.78-1.70 (m, 1H), 0.85 (s, 9H), 0.79 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), 0.00 (s, 43) ppm

HRMS (ESI) *m/z* Found: $(M-HF+H)^+$, $C_{33}H_{55}O_{10}Si_2$, 668.3335 requires 667.3328

6.5 Experimental section for Chapter 5

6.5.1 Synthesis of (−)-normethyl-Δ⁹-THC (36)

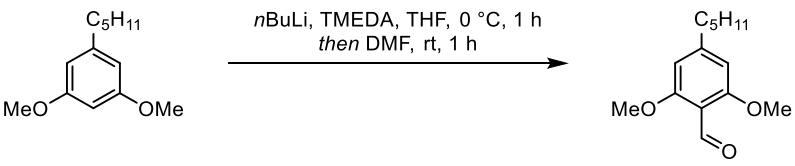
1,3-Dimethoxy-5-pentylbenzene (362)[42]



Following the procedure of Vanek,[43] a round bottom flask was charged with olivetol (**326**) (3.6 g, 20 mmol), potassium carbonate (13.8 g, 100 mmol), iodomethane (6.2 mL, 100 mmol) and acetone (60 mL). The flask was sealed and heated to 50 °C for 16 h, before being cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue purified *via* flash column chromatography to afford the title compound **362** (3.83 g, 90% yield) as a viscous yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, *J* = 2.2 Hz, 2 H), 6.30 (t, *J* = 2.2 Hz, 1 H), 3.78 (s, 6 H), 2.54 (t, *J* = 7.4 Hz, 2 H), 1.66-1.57 (m, 2 H), 1.37-1.28 (m, 4 H), 0.90 (t, *J* = 6.6 Hz, 3 H) ppm

2,6-Dimethoxy-4-pentylbenzaldehyde (363)[42]

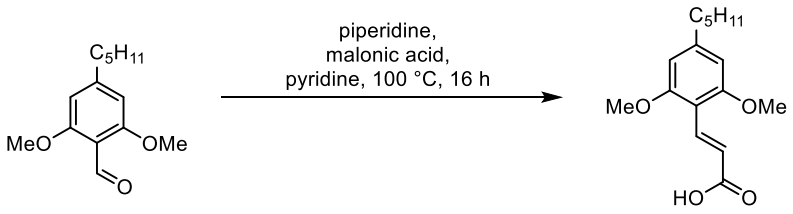


Following a modified procedure of Krupadanam,[30] a round bottom flask was charged with arene **362** (3.1 g mL, 15 mmol), TMEDA (2.5 mL 16.5 mmol) and anhydrous THF (30). The mixture was cooled to 0 °C before ^{n}BuLi (10.3 mL, 1.6 M in hexanes, 16.5 mmol) was added via syringe over 15 minutes. The

reaction mixture was stirred at 0 °C for 60 minutes before anhydrous DMF (1.3 mL, 16.5 mmol) was added slowly. The solution was then stirred for 1 hour at 0 °C and quenched with the addition of NH_4Cl (30 mL of a saturated aquoues solution.) The yellow mixture was concentrated under reduced pressure before being extracted with EtOAc (3 x 30 mL) and washed with water (30 mL) and brine (60 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography to afford the title compound **363** (2.72 g, 77% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 6.38 (s, 2H), 3.89 (s, 6H), 2.63 (t, J = 7.6 Hz, 2H), 1.56-1.47 (m, 2H), 1.41-1.28 (m, 4H), 0.91 (t, J = 6.592 Hz, 3H) ppm

(*E*)-3-(2,6-Dimethoxy-4-pentylphenyl)acrylic acid (364)



Following a modified procedure of Ling,[44] a 250 mL RBF was charged with aldehyde **363** (19.2 g, 81 mmol), malonic acid (16.9 g, 162 mmol), piperidine (6.5 mL), and pyridine (100 mL). The flask was sealed and heated to 100 °C for 16 h. After cooling to room temperature, the mixture was poured into ice cold water. Following acidification with concentrated HCl, the precipitate was washed with H_2O (500 mL) and hexanes (500 mL) before being dried at 60 °C *in vacuo*. The title compound **364** (18.7 g, 83%) was isolated as an off-white solid.

R_f 0.1 (1:1, v/v hexanes : EtOAc)

MP 180-182 °C

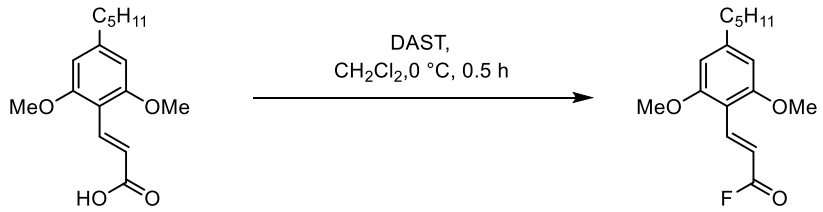
IR ν_{max} 2930, 2862, 2688, 1675, 1599, 1563, 1409 1201, 1121 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 16.2 Hz, 1H), 7.86 (d, J = 16.2 Hz, 1H), 6.38 (s, 2H), 3.87 (s, 3H), 2.60-2.57 (m, 2H), 1.67-1.59 (m, 2H), 1.36-1.33 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 160.3, 148.0, 138.0, 118.5, 109.9, 104.0, 55.8, 37.1, 31.7, 31.0, 22.7, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{22}O_4$, 279.1591, requires 279.1591

(*E*)-3-(2,6-Dimethoxy-4-pentylphenyl)acryloyl fluoride (210p)



Following the procedure of Georg, to a suspension of α,β-unsaturated carboxylic acid **364** (8.4 g, 30 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added diethylaminosulfur trifluoride (6.0 mL, 45 mmol). After stirring at 0 °C for 30 minutes, the reaction was quenched by slow addition of $NaHCO_3$ (200 mL of a saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the organic phase dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound **210p** (7.3 g, 83%) was isolated as an off-white solid.

R_f 0.8 (10:3, v/v hexanes : EtOAc)

MP 30-32 °C

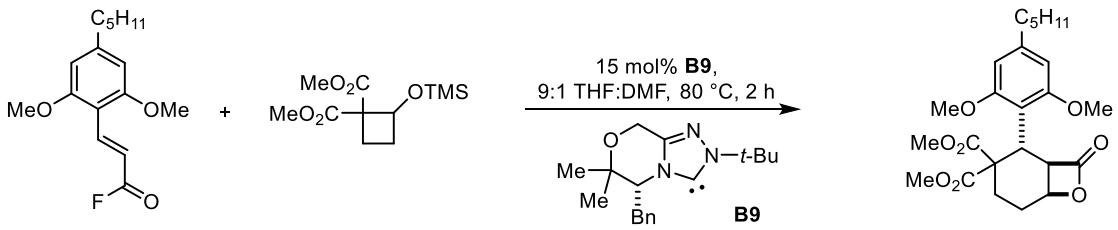
IR ν_{max} 2932, 2858, 1781, 1602, 1565, 1459, 1118, 1089 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 16.2 Hz, 1H), 6.77 (dd, *J* = 16.2, 7.6 Hz, 1H), 6.39 (s, 2H), 3.89 (s, 6H), 2.62-2.58 (m, 2H), 1.67-1.60 (m, 2H), 1.38-1.30 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 159.8 (d, *J* = 334.4 Hz), 149.8, 142.6 (d, *J* = 7.4 Hz), 112.4 (d, *J* = 63.9 Hz), 112.0, 109.2, 104.0, 55.8, 37.1, 31.6, 30.8, 22.6, 14.1 ppm

HRMS (ESI) *m/z* Found: $(M-H)^-$, $C_{16}H_{21}FO_3$, 279.1398, requires 279.1396

Dimethyl (1*R*,2*S*,6*S*)-2-(2,6-dimethoxy-4-pentylphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220aj)



A two-neck flask equipped with a reflux condenser and septum was charged with DA-cyclobutane **216e** (2.1 g, 10.7. mmol), α,β-unsaturated acyl fluoride **210p** (3.0 g, 10.7 mmol), THF (85 mL) and DMF (10 mL). The solution was placed in an 80 °C oil bath, then a solution of NHC **B9** (0.58 g, 1.6 mmol) in THF (5 mL) was added. The septum was replaced with a stopper and the reaction mixture was stirred at 80 °C

for 2 hours. The mixture was then allowed to cool to room temperature, before being concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound **X** (7.3 g, 45%) was isolated as a yellow oil and as a single diastereoisomer as observed by ^{1}H-NMR (>20:1 dr).

R_f 0.3 (10:3, v/v hexanes : EtOAc)

HPLC RegisCell™ 5 μm, hexane : *i*PrOH 95:5, 1 mL/min, λ = 230 nm, fraction t_r = 16.82 min (major enantiomer) and 20.30 min (minor enantiomer); er = 98:2

$[a]_D^{25}$ = –129.8° (c = 0.03 $CHCl_3$)

MP 95-97 °C;

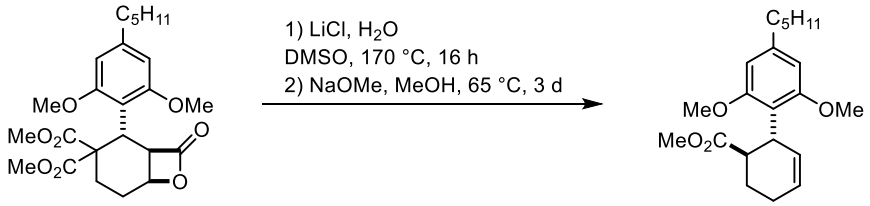
IR ν_{max} 2932, 1857, 1819, 1731, 1608, 1230, 1118 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 1H); 6.29 (s, 1H) 5.14 (d, *J* = 1.1 Hz, 1H), 4.88-4.83 (m, 1H), 3.85 (dd, *J* = 6.9, 1.1 Hz, 1H), 3.77 (s, 6H), 3.75 (brs, 3H), 3.16 (s, 3H) 2.61-2.48 (m, 4H), 2.02-1.96 (m, 1H), 1.86-1.77 (m, 1H), 1.61-1.53 (m, 2H), 1.37-1.25 (m, 4H) 0.88 (t, *J* = 6.8 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1(1), 172.0(7), 170.9 158.0, 157.7, 144.3, 115.3, 104.1(3), 104.0(5), 70.5, 57.5, 56.0, 55.1, 53.0, 52.9, 51.7, 36.6, 31.6, 31.1 29.3, 25.0, 24.7, 22.6, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{24}H_{32}O_8$, 449.2170, requires 449.2167

Methyl (1*R*,2*R*)-2',6'-dimethoxy-4'-pentyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboxylate (*trans*-365)



A solution of β-lactone **220aj** (0.96 g, 2.1 mmol), LiCl (0.36 g, 8.6 mmol) and H_2O (77 μL, 4.3 mmol) in DMSO (8 mL) was heated to 170 °C for 16 hours. The mixture was cooled to rt, H_2O (10 mL) added and the mixture extracted with EtOAc (3 x 15 mL). The organic phase was washed with brine (1 x 20 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude material passed through a silica plug (2:10, v/v hexanes : EtOAc). The crude residue was dissolved in a freshly prepared solution of NaOMe (10 mL, 1 M, 10 mmol) and heated to 65 °C for 3 d. The mixture was cooled to rt, neutralized with HCl (0.1 M) and extracted with Et_2O (3 x 3 mL). The organic phase was washed with H_2O (2 x 10 mL), dried

(Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound *trans*-**365** in 54% yield.

R_f 0.3 (20:1, v/v hexanes : EtOAc)

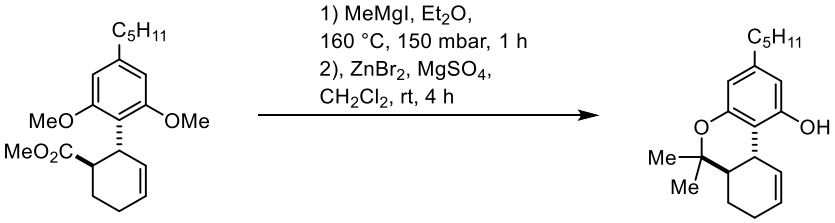
IR ν_{max} 2933, 2836, 1731, 1590, 1472, 1243, 1103 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 2H), 5.71-5.65 (m, 1H), 5.47 (d, *J* = 9.9 Hz, 1H), 4.28 (brd, *J* = 9.9 Hz, 1H), 3.76 (s, 6H), 3.47 (s, 3H), 3.25-3.19 (m, 1H), 2.56-2.53 (m, 2H), 2.23-2.11 (m, 2H), 2.10-1.98 (m, 1H), 1.94-1.83 (m, 1H), 1.65-1.58 (m, 2H), 1.38-1.27 (m, 4H), 0.91 (t, *J* = 6.6 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 158.8, 142.9, 130.9, 123.9, 116.8, 104.9, 56.0, 51.2, 43.7, 36.6, 34.8, 31.8, 31.1, 26.9, 24.6, 22.7, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{30}O_4$, 347.2216, requires 347.2217

(6a*R*,10aR)-6,6-Dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (normethyl-(-)-Δ^9-THC (361))



Following the procedure of Carreira,[34] to a solution of *trans*-**365** (88 mg, 0.25 mmol) in Et_2O (2 mL) was added MeMgI (0.84 mL, 3.75 M in Et_2O, 2.5 mmol) dropwise. The mixture was stirred for 16 h at rt before the solvent was removed under reduced pressure. The residue was heated to 160 °C under reduced pressure (150 mbar) for 1 h before it was cooled to room temperature, diluted with Et_2O (3 mL) and quenched with NH_4Cl (3 mL of saturated aqueous solution). The mixture was extracted with Et_2O (3 x 3 mL), the organic phase dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was taken up in CH_2Cl_2 (2 mL), and $ZnBr_2$ (86 mg, 0.4 mmol) and $MgSO_4$ (120 mg, 1 mmol) were added. The mixture was stirred for 4 h at rt before the reaction was quenched by the addition of NH_4Cl (3 mL of saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 2 mL), the organic phase dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography to afford the title compound **361** in 62% yield.

R_f 0.2 (10:1, v/v hexanes : EtOAc)

IR ν_{max} 3405, 2928, 2859, 1703, 1621, 1578, 1425, 1046 cm^{-1}

HPLC RegisCell™ 5μm, hexane : *i*PrOH 95:5, 1 mL/min, λ = 230 nm, fraction t_r = 15.83 (minor enantiomer) and 18.39 (major enantiomer); er = 98:2

$[a]_D^{25}$ = –56.3° (c = 0.03, $CHCl_3$)

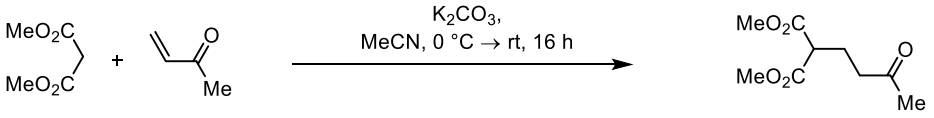
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dq, *J* = 10.0, 2.1 Hz 1H), 6.28 (d, *J* = 1.5 Hz, 1H), 6.13 (d, *J* = 1.5 Hz, 1H), 5.66 (dq, *J* = 10.0, 3.2 Hz 1H), 4.77 (s, 1H) 3.26 (d, *J* = 11.0, Hz, 1H), 2.45-2.42 (m, 2H), 2.31-2.19 (m, 2H), 1.96-1.88 (m, 1H), 1.79-1.73 (m, 1H), 1.60-1.52 (m, 2H), 1.43-1.40 (m, 1H), 1.42 (s, 3H) 1.34-1.26 (m, 4H), 1.10 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 154.3, 143.0, 129.9, 126.9, 110.2, 108.9, 107.7, 77.5, 45.6, 35.6, 33.8, 31.7, 30.8, 27.6, 26.6, 25.0, 22.7, 19.5, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{20}H_{28}O_2$, 301.2159, requires 301.2162

6.5.2 Alternate (4+2) annulations for introduction of the C9 methyl group

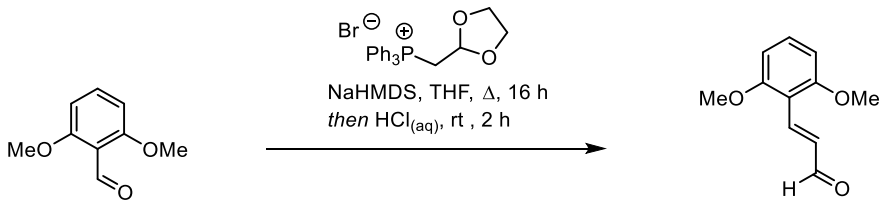
Dimethyl 2-(3-oxobutyl)malonate (359a) [45]



Following the procedure of Campeau,[45] a round bottom flask was charged with methylacetoacetate (1.27 mL, 10 mmol), 3-buten-2-one (0.82 mL, 11 mmol) and $FeCl_3$ (16 mg, 0.1 mmol). The neat mixture was stirred for 16 h at room temperature and the resulting residue purified *via* flash column chromatography to afford the title compound **359a** (0.93 g, 53% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 6H), 3.38 (t, *J* = 7.3 Hz, 1H), 2.48 (t, *J* = 7.3 Hz, 1H), 2.09 (d, *J* = 7.4 Hz, 2H), 2.07 (s, 3H)

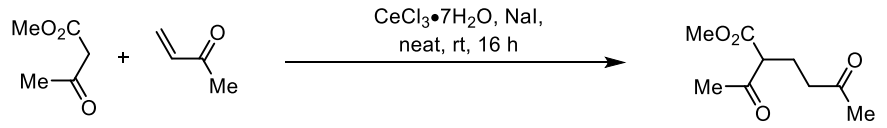
(*E*)-3-(2,6-Dimethoxyphenyl)acrylaldehyde (360b)[46]



A round bottom flask was charged with ((1,3-dioxolan-2-yl)methyl)triphenylphosphonium bromide (2.58 g, 6 mmol) and THF (40 mL) before NaHMDS (6 mL, 1.0 M solution in toluene, 6 mmol) was added over 1 minute. The resulting yellow suspension was allowed to stir for 30 minutes before aldehyde **277** (0.71 g, 3 mmol) in THF (10 mL) was added. The suspension was heated to reflux for 16 hours before being cooled to room temperature, and HCl (50 mL of a 10% aqueous solution) was added. The suspension was stirred for an additional 2 h at this temperature before being extracted with EtOAc (3 x 60 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified *via* flash column chromatography (dry loaded) to afford the title compound **360b** (0.76 g, 96% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 16.2 Hz, 1H), 7.33 (t, *J* = 8.3 Hz, 2H), 7.18 (dd, *J* = 16.2, 8.0 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1 H), 3.89 (s, 6H).

Methyl 2-acetyl-5-oxohexanoate (374)[47]

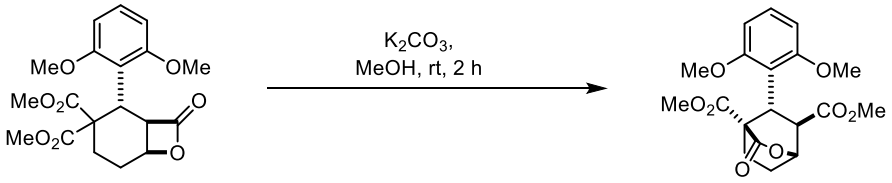


The title compound was prepared according to the representative procedure for compound **359a.** The title compound **374** (0.53 g, 51% yield) was purified *via* flash column chromatography and was isolated as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.45 (t, *J* = 7.3 Hz, 1H), 2.46-2.42 (m, 2H), 2.18 (s, 3H), 2.07 (s, 3H), 2.04-2.00 (m, 2H) ppm

6.5.3 Revised strategies to install the C9 methyl group

Dimethyl 5-(2,6-dimethoxyphenyl)-3-oxo-2-oxabicyclo[2.2.2]octane-4,6-dicarboxylate (2242b)



To a solution of β-lactone **220ad** (1.81 g, 5 mmol) in MeOH (20 mL) was added K_2CO_3 (1.4 g, 10 mmol) in one portion. The mixture was stirred at room temperature for 2 h before the solvent removed under reduced pressure. H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organic phase was dried, concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound **242b** (1.64 g, 87%) was isolated as a yellow oil and as a single diastereomer as observed by ^{1}H-NMR.

R_f 0.5 (5:2, v/v hexanes : EtOAc)

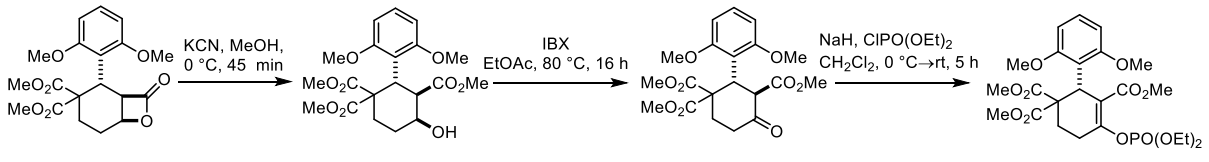
IR ν_{max} 2951, 2843, 1755, 1732, 15793, 1474, 1242, 1116 cm^{-1}

^{1}H NMR (400MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 2H), 5.15 (d, *J* = 3.9 Hz, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 6H), 3.65 (s, 3H), 3.61 (d, *J* = 7.5 Hz, 1H), 3.53 (s, 3H), 2.80 (ddd, *J* = 13.9, 11.2, 5.3 Hz, 1H), 2.19-2.13 (m, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 172.1, 169.3, 159.2, 129.5, 112.7, 104. 6, 78.0, 54.1, 52.4, 52.0, 45.2, 33.7, 25.9, 22.1 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{19}H_{22}O_8$, 379.1384, requires 379.1387

Trimethyl (*R*)-5-((diethoxyphosphoryl)oxy)-2',6'-dimethoxy-3,4-dihydro-[1,1'-biphenyl]-2,2,6(1*H*)-tricarboxylate (378b)



To a suspension of the β-lactone **220ad** (0.76 g, 2 mmol) in MeOH (10 mL) at 0 °C was added KCN (0.13 g, 2 mmol) in one portion. The mixture was stirred at this temperature until consumption of the starting material (monitored carefully by TLC) after which ice cold H_2O (15 mL) was added immediately. The mixture was extracted with EtOAc (3 x 15 mL), the organic phase dried (Na_2SO_4) and concentrated under

reduced pressure to afford the crude alcohol **383b** which was used immediately without further purification.

^{1}H NMR of **383b** (400MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.3 Hz, 1H), 6.54 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.41 (d, *J* = 8.3 Hz, 1H), 4.80 (d, *J* = 12.4 Hz, 1H), 4.23 (dd, *J* = 5.0, 3.0 Hz, 1H), 3.86 (s, 3H), 3.82 (dd, *J* = 12.4, 1.9 Hz, 1H), 3.72 (s, 3H), 3.58 (s, 3H), 3.52 (s, 3H), 3.24 (s, 3H), 2.54-2.38 (m, 1H), 2.29-2.16 (m, 2H), 1.86 (ddd, *J* = 14.1, 7.4, 4.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 1H) ppm

The crude alcohol **383b** was dissolved in EtOAc (20 mL), IBX (1.12 g, 4 mmol) added and the suspension heated under reflux for 16 h. The suspension was cooled to room temperature, filtered through a pad of Celite and the solvent removed under reduced pressure to afford the crude β-ketoester **379b** which was used immediately in the next step.

^{1}H NMR of **383b** (400MHz, $CDCl_3$) δ 7.15 (t, *J* = 8.3 Hz, 1H), 6.56-6.44 (m, 2H), 5.42 (d, *J* = 6.4 Hz, 1H), 4.04 (d, *J* = 6.5 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.25 (s, 3H), 2.98 (m, 1H), 2.66-2.55 (m, 1H), 2.42-2.24 (m, 2H) ppm

The crude ester **379b** was taken up in CH_2Cl_2 (20 mL) and sodium hydride (75 mg, 3 mmol) was added portion wise at 0 °C. The mixture was allowed to stir for 45 minutes at this temperature before chlorodiethyphosphate (0.35 mL, 2.4 mmol) was added dropwise. After this, the reaction was warmed to room temperature and stirred for an additional 2 hours before being quenched by the addition of $NaHCO_3$ (10 mL of a saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and washed with water (10 mL) and brine (10 mL). The combined organics were dried (Na_2SO_4), concentrated under reduced pressure, and the crude residue purified *via* flash column chromatography to afford the title compound **378b** (0.48 g, 44% yield over 3 steps) as a viscous, colourless oil.

R_f 0.2 (3:2, v/v hexanes : EtOAc)

IR ν_{max} 2955, 2841, 2366, 1736, 1435, 1258, 1031 cm^{-1}

^{1}H NMR (400MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 2H), 5.62 (brs, 1H), 4.27-4.10 (m, 4H), 3.76 (s, 9H), 3.51 (s, 3H), 3.32 (s, 3H), 2.87 (m, 1H), 2.70 (dd, *J* = 19.1, 6.8 Hz, 1H), 2.43-2.29 (m, 1H), 2.28-2.19 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR (100MHz, $CDCl_3$) δ 170.7, 170.0, 165.3, 165.2, 151.03 (d, *J* = 7.6 Hz), 128.7, 116.6, 116.5, 114.0(3), 114.0(1), 67.5, 64.2 (d, *J* = 6.0 Hz), 64.1 (d, *J* = 6.0 Hz), 57.6, 55.7, 52.4, 51.5 (d, *J* = 1.6 Hz), 50.9 (d, *J* = 1.6 Hz), 34.6, 25.8, 25.2, 25.0, 15.72 (d, *J* = 6.0 Hz) ppm

cis-Methyl (1*R*,2*R*)-2-(2,6-dimethoxyphenyl)-4-oxocyclohexane-1-carboxylate (_cis_-388b) and _trans_-methyl (1*R*,2*R*)-2-(2,6-dimethoxyphenyl)-4-oxocyclohexane-1-carboxylate and (_trans_-388b)

To a suspension of the β-lactone **220ad** (1.9 g, 5 mmol) in MeOH (20 mL) at 0 °C was added KCN (0.32 g, 5 mmol) in one portion. The mixture was stirred at this temperature until consumption of the starting material (monitored carefully by TLC) after which ice cold H_2O (30 mL) was added immediately. The mixture was extracted with EtOAc (3 x 30 mL), the organic phase dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was dissolved in EtOAc (20 mL), IBX (2.8 g, 10 mmol) added and the suspension heated under reflux for 16 h. The suspension was cooled to rt, filtered through a pad of Celite and the solvent removed under reduced pressure. The crude residue was dissolved in DMSO (10 mL), LiCl (10 mmol) and H_2O (7.5 mmol) were added, and the vessel sealed and heated to 170 °C for 2 h. The mixture was cooled to rt, H_2O (20 mL) added and the mixture extracted with EtOAc (3 x 20 mL). The organic phase was washed with brine (1 x 20 mL), dried ($MgSO_4$), concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound **338** (0.48 g, 33%) was isolated as a yellow oil as a separable mixture of a diastereomers as observed by ^{1}H NMR (3:2 *cis/trans*).

cis-isomer:

R_f 0.5 (1:1, v/v hexanes : EtOAc)

IR ν_{max} 2931, 2857, 1732, 1709, 1579, 1454, 1119 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 2H), 4.24-4.20 (m, 1H), 3.70 (s, 6H), 3.55 (s, 3H), 3.04 (ddd, *J* = 16.2, 6.1, 1.5 Hz, 1H), 2.97-2.95 (m, 1H), 2.82-2.78 (m, 1H), 2.50 (ddd, *J* = 16.2, 6.1, 0.8 Hz, 1H), 2.33-2.15. (m, 2H), 1.92-1.85 (m, 1H) ppm **^{13}C NMR** (100 MHz, $CDCl_3$) δ 209.0, 174.5, 158.7, 128.6, 116.7, 106.1, 104.1, 55.0, 51.3, 44.9, 43.8, 39.1, 34.3, 25.4 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{20}O_5$, 293.1380, requires 293.13843

trans-isomer:

R_f 0.6 (1:1, v/v hexanes : EtOAc)

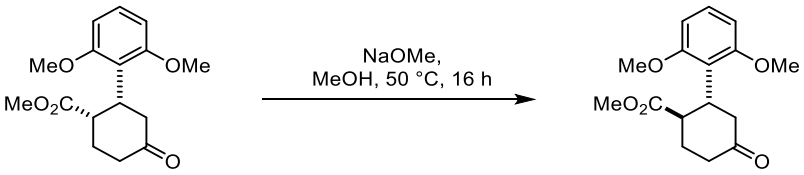
IR ν_{max} 2950, 2840, 1734, 1716, 1593, 1474, 1245, 1108 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 2H), 4.07-4.03 (m, 1H) 3.80 (s, 6H), 3.54 (td, *J* = 11.0, 3.6 Hz 1H), 3.43 (s, 3H), 3.02 (dd, *J* = 15.1, 12.0, 1H), 2.50-2.39 (m, 3H), 2.24-2.20 (m, 1H), 2.04-1.97 (m, 1 H) ppm

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.3, 175.0, 128.3, 117.6, 104.5, 55.8, 51.5, 44.7, 44.0, 39.9, 35.8, 28.3 ppm

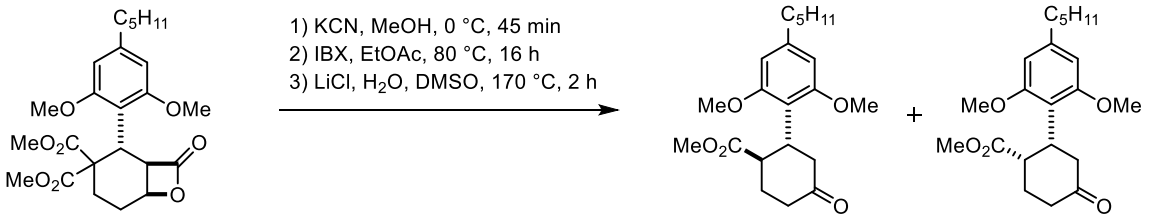
HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{20}O_5$, 293.1384, requires 293.1384

Methyl (1*R*,2*R*)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate (*trans*-388b)



Following a modification of the procedure of Trost,[42] a solution of *cis*-**388b** (181 mg, 0.5 mmol) in freshly prepared NaOMe (2.5 mL, 1 M, 2.5 mmol) was heated to 50 °C for 16 h. The mixture was cooled to rt, neutralized with HCl (0.1 M) and the mixture extracted with Et_2O (3 x 3 mL). The organic phase was washed with H_2O (2 x 10 mL), dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography afford *trans*-**388b** in 83% yield.

Methyl (1*S*,2*R*)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate and methyl (1*R*,2*R*)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate (*cis*-388a and *trans*-388a)



The title compound was prepared according to the representative procedure for **388b**. Following flash column chromatography the title compound **388a** (0.48 g, 33%) was obtained as a separable mixture of a diastereomers as observed by ^{1}H NMR (3:2 *cis*/*trans*).

***cis*-isomer:**

R_f 0.4 (5:2, v/v hexanes : EtOAc);

IR ν_{max} 2931, 2857, 1732, 1709, 1579, 1226, 1119 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 2H), 4.19-4.15, (m, 1H), 3.69 (s, 6H) , 3.54 (s, 3H), 3.01 (ddd, *J* = 16.3, 5.9, 1.4 Hz, 1H), 2.96-2.92 (m, 1H), 2.82-2.75 (m, 1H), 2.56-2.52 (m, 2H), 2.48 (dd, *J* = 16.3, 6.8 Hz, 1H), 2.32-2.14 (m, 2H), 1.90-1.83 (m, 1H), 1.64-1.57 (m, 2H), 1.37-1.30 (m, 4H) 0.90 (t, *J* = 7.0 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 174.6, 158.5, 143.8, 113.7, 104.2, 54.9, 51.3, 45.0, 43.9, 39.2, 36.6, 34.2, 31.8, 31.1, 25.3, 22.7, 14.2 ppm; HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{30}O_5$, 363.2163, requires 363.2166.

***trans*-isomer:**

R_f 0.3 (10:3, v/v hexanes : EtOAc);

IR ν_{max} 2931, 2857, 1735, 1713, 1580, 1454, 1120 cm^{-1};

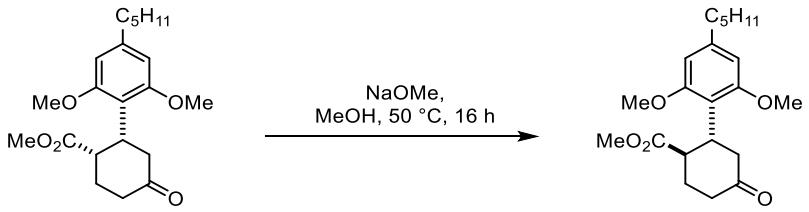
$[a]_D^{25} = -190.5°$ (c = 0.05 $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 2H), 4.00 (ddd, *J* = 11.8, 11.0, 5.0 Hz, 1H), 3.79 (s, 6H), 3.51 (td, *J* = 11.0, 3.7 Hz, 1H) 3.44 (s, 3H), 3.00 (dd, *J* = 14.5, 11.8 Hz, 1H), 2.55-2.51 (m, 2H), 2.48-2.37 (m, 3H), 2.25-2.18 (m, 1H), 2.05-1.95 (m, 1H), 1.63-1.56 (m, 2H), 1.37-1.29 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 175.1, 158.4, 143.6, 114.9, 104.7, 55.8, 51.5, 44.9, 44.2, 39.9, 36.6, 35.8, 31.8, 31.1, 28.3, 22.7, 14.2 ppm

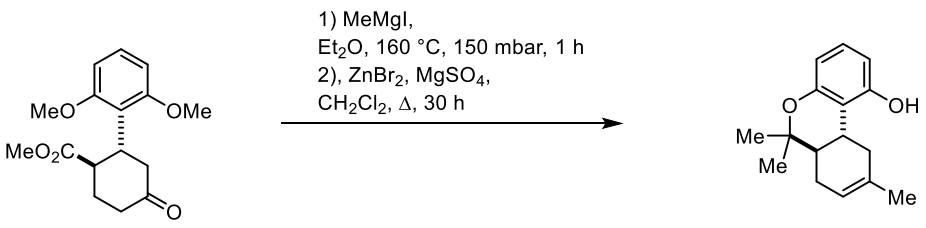
HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{30}O_5$, 363.2141, requires 363.2166

Methyl (1*R*,2*R*)-2-(2,6-dimethoxy-4-pentylphenyl)-4-oxocyclohexane-1-carboxylate (*trans*-388a)



Following a modification of the procedure of Trost,[42] a solution of *cis*-**388a** (181 mg, 0.5 mmol) in freshly prepared NaOMe (2.5 mL, 1 M, 2.5 mmol) was heated to 50 °C for 16 h. The mixture was cooled to rt, neutralized with HCl (0.1 M) and the mixture extracted with Et_2O (3 x 3 mL). The organic phase was washed with H_2O (2 x 10 mL), dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography afford *trans*-**388a** in 83% yield.

6,6,9-Trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol ((despentyl-Δ^8-THC (390))



Following a modified procedure of Carreira,[34] to a solution of *trans*-**388b** (29 mg, 0.1 mmol) in Et_2O (1 mL) was added MeMgI (0.33 mL, 3.0 M in Et_2O, 1 mmol) dropwise. The yellow suspension was stirred for 16 h at rt before the solvent was removed under reduced pressure. The residue was heated to 160 °C under reduced pressure (150 mbar) for 1 h before it was cooled to room temperature, diluted with Et_2O (3 mL) and quenched with NH_4Cl (3 mL of saturated aqueous solution). The mixture was extracted with Et_2O (3 x 3 mL), the organic phase dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (2 mL), and $ZnBr_2$ (113 mg, 0.5 mmol) and $MgSO_4$ (120 mg, 1 mmol) were added. The flask was sealed and heated to reflux for 30 h before the reaction was quenched by the addition of NH_4Cl (3 mL of saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 x 2 mL), the organic phase dried (Na_2SO_4), concentrated under reduced pressure and the crude material purified via flash column chromatography. The title compound **390** (10 mg, 40%) was isolated as a yellow oil.

R_f 0.3 (9:1, v/v hexanes : EtOAc)

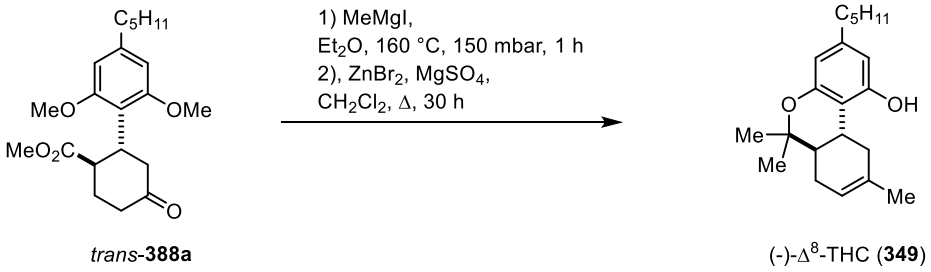
IR ν_{max} 3435, 2972, 2919, 2850, 1612, 1584, 1459, 1184, 1025 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (td, *J* = 8.1, 0.8 Hz, 1H), 6.43 (td, *J* = 8.1, 1.1 Hz, 1H), 6.26 (td, *J* = 8.1, 1.1 Hz, 1H), 5.44 (d, *J* = 4.3 Hz, 1H, 3.23-3.19 (m, 1H), 2.74 (td, *J* = 10.7, 4.7 Hz, 1H), 2.18-2.13 (m, 1H), 1.89-1.80 (m, 3H), 1.71 (s, 3H), 1.39 (s, 3H), 1.10 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 155.2, 134.9, 127.5, 119.5, 113.5, 110.6, 107.4, 45.1, 36.1, 31.9, 28.1, 27.7, 23.6, 18.6 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{16}H_{20}O_2$, 245.1531, requires 245.1536.

(–)-trans-Δ⁸-Tetrahydrocannabinol ((–)-Δ⁸-THC (349))



trans-**388a** (-)-Δ⁸-THC (**349**)

The title compound was prepared according to the representative procedure for **390**. Following flash column chromatography the title compound **349** (0.48 g, 33%) was obtained as a yellow oil.

R_f 0.5 (10:1, v/v hexanes : EtOAc)

IR ν_{max} 3443, 2957, 2929, 2857, 1624, 1579, 1426, 1183, 1033 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 95:5, 1 mL/min, λ = 220 nm, fraction t_r = 9.25 (minor enantiomer) and 11.05 (major enantiomer); er = 83:17

$[a]_D^{25}$ = –220.3° (c = 0.05, $CHCl_3$); lit.[48] $[a]_D^{25}$ = –232.3° (c = 0.96, $CHCl_3$)

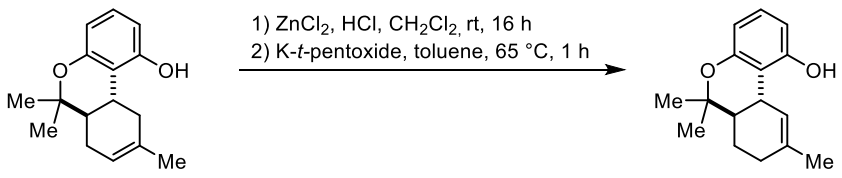
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 1H), 6.11 (s, 1H), 5.43, (d, *J* = 4.1 Hz, 1H), 4.70, (s, 1H), 3.21-3.17, (m, 1H), 2.73-2.67 (m, 1H), 2.46-2.42 (m, 2H), 2.16-2.10 (m, 1H), 1.89-1.75, (m, 3 H), 1.70 (s, 3H), 1.61-1.53 (m, 2H), 1.38 (s, 3H), 1.35-1.26 (m, 4H), 1.11 (s, 3H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 154.9, 142.9, 134.9, 119.5, 110.7, 110.3, 107.8, 76.8, 45.1, 36.2, 35.6, 31.7(4), 31.7(3), 30.7, 28.1, 27.7, 23.6, 22.7, 18.7, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{30}O_2$, 314.2315, requires 314.2319

6.5.4 Synthesis of (–)-Δ⁹-THC 325

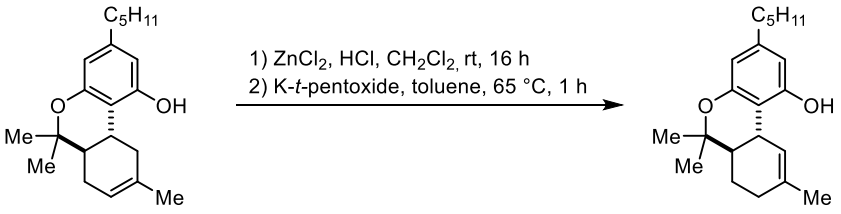
(6a*R*,10a*R*)-6,6,9-Trimethyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol



Following a modified procedure of Petrzilka,[49] dry hydrogen chloride was bubbled through a solution of chromene **390** (14 mg, 0.044 mmol) and $ZnCl_2$ (7.6 mg, 0.031 mmol) in CH_2Cl_2 (2 mL) for 2 h. Ice water (3 mL) was added, and the mixture extracted with CH_2Cl_2 (3 x 3 mL) before the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was taken up in toluene (2 mL)

and a solution of potassium *tert*-amylate (0.7 mL, 0.5 M) added. The mixture was heated to 65 °C for 1 h before ice cold water (3 mL) was added. The mixture was extracted with EtOAc (3 x 3 mL), the organic phase dried (Na_2SO_4), concentrated under reduced pressure, and the crude material purified via flash column chromatography. The title compound **391** (5.2 mg, 68% yield) as a yellow oil.

(–)-Δ^8-tetrahydrocannabinol ((–)-Δ^9-THC (325))



The title compound was prepared according to the representative procedure for **391**. Following flash column chromatography the title compound **325** (12.3 mg, 89% yield) was obtained as a yellow oil.

R_f 0.5 (10:1, v/v hexanes : EtOAc)

IR ν_{max} 3391, 2957, 2928, 2858, 1624, 1578, 1426, 1184, 1035 cm^{-1}

HPLC Daicel AD-H, hexane : *i*PrOH 95:5, 1 mL/min, λ = 214 nm, fraction t_r = 11.9 (major enantiomer) and 22.6 (minor enantiomer); er = 84:16 $[a]_D^{25}$ = –112.0° (c = 0.01, $CHCl_3$)

$[a]_D^{25}$ = –112.0° (c = 0.01, $CHCl_3$); lit.[42] $[a]_D^{25}$ = –152.3° (c = 0.79, $CHCl_3$)

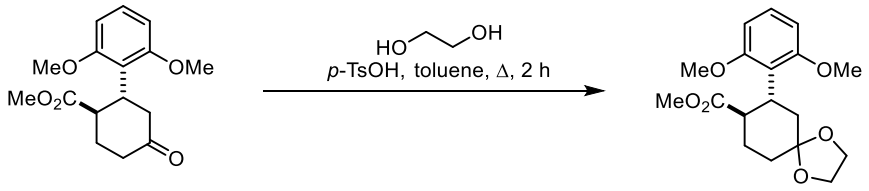
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31-6.29 (m, 1H), 6.27 (d, *J* = 1.5 Hz, 1H), 6.14 (d, *J* = 1.5 Hz, 1H), 4.68 (s, 1H) 3.20 (d, *J* = 10.9, Hz, 1H), 2.45-2.42 (m, 2H), 2.18-2.15 (m, 2H), 1.93-1.89 (m, 1H), 1.71-1.67 (m, 4H), 1.58-1.53 (m, 2H), 1.45-1.37 (m, 1H), 1.41 (s, 3H) 1.33-1.27 (m, 4H), 1.09 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.3, 143.0, 134.6, 123.9, 110.3, 109.2, 107.7, 77.3, 46.0, 35.6, 33.7, 31.7, 31.3, 30.8, 27.7, 25.2, 23.5, 22.7, 19.4, 14.2 ppm

HRMS (ESI) *m/z* Found: $(M+H)^+$, $C_{21}H_{30}O_2$, 314.2314, requires 314.2319

6.5.5 Studies into the synthesis of Nabilone 376b

Methyl (7*R*,8*R*)-7-(2,6-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (394)



A round bottom flask was charged with ketoester *trans*-**388b** (53 mg, 0.18 mmol), ethylene glycol (12 μL, 0.22 mmol, *p*-toluenesulfonic acid (2 mg) and toluene (3 mL). A Dean-Stark appartus was attached and the solution was heated to 130 °C for 2 hours. After this time, the reaction was cooled to room temperature, the solvent removed under reduced pressure, and the crude residue purified *via* flash column chromatography. The title compound **394** (20 mg, 78% yield) was isolated as a clear oil.

R_f 0.3 (7:3, v/v hexanes : EtOAc)

^{1}H NMR(400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 4.09-3.85 (m, 5H), 3.80 (s, 6H), 3.36 (s, 3H), 3.29 (td, *J* = 11.6, 4.7 Hz, 1H), 2.32 (t, *J* = 13.1 Hz, 1H), 1.98-1.90 (m, 2H), 1.90 - 1.81 (m, 1H), 1.72 – 1.63 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.80, 159.8, 158.2, 127.7, 118.8, 108.8, 104.7, 64.5, 64.3, 56.5, 55.5, 51.1, 45.3, 37.7, 34.3, 34.1, 27.5 ppm

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Appendix 1

X-Ray Crystal Structures

Diallyl (1*S*,5*R*,6*S*)-5-(4-methoxyphenyl)-7-oxo-8-oxaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexane]-4,4-dicarboxylate (220l)

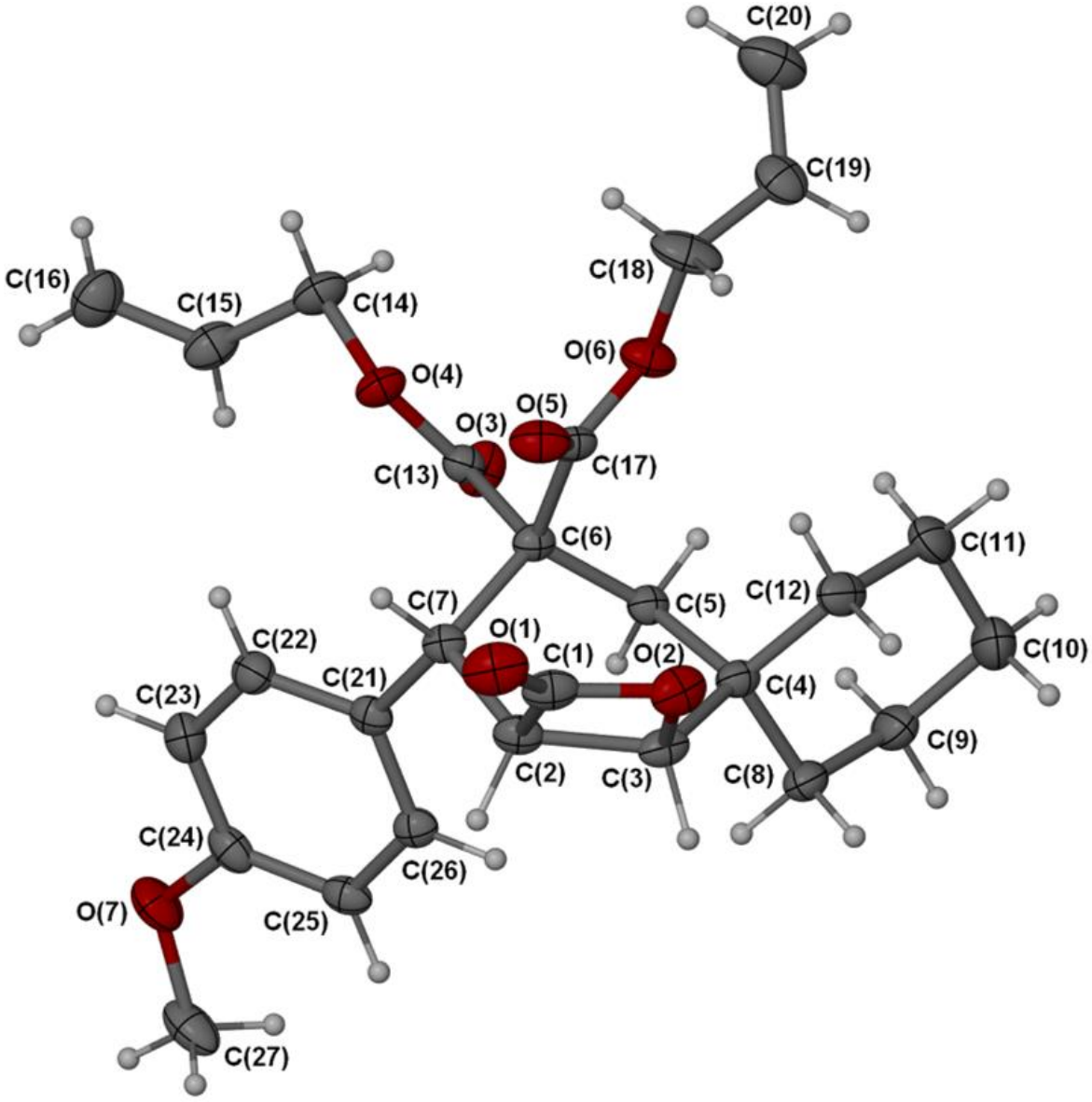

Figure A1. Molecular diagram of **220l**

Table A1. Crystal data and structure refinement for **220l**

Identification code	MX21_16
Empirical formula	C27 H32 O7
Formula weight	468.52
Temperature	123(2) K
Wavelength	1.54184 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 9.6963(2) A alpha = 90 deg. b = 11.8962(3) A beta = 90 deg. c = 21.2475(4) A gamma = 90 deg.
Volume	2450.88(9) A^3
Z, Calculated density	4, 1.270 Mg/m^3
Absorption coefficient	0.747 mm^-1
F(000)	1000
Crystal size	0.25 x 0.20 x 0.20 mm
Theta range for data collection	4.161 to 66.939 deg.
Limiting indices	-11<=h<=11, -10<=k<=14, -24<=l<=25
Reflections collected / unique	15316 / 4353 [R(int) = 0.0321]
Completeness to theta = 66.939	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.49288
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4353 / 2 / 327
Goodness-of-fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0800
R indices (all data)	R1 = 0.0341, wR2 = 0.0813
Absolute structure parameter	-0.01(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.191 and -0.175 e.A^-3

Table A2. Bond lengths (A) and bond angles (°) for **220l**

O(1)-C(1)	1.194(3)
O(2)-C(1)	1.362(3)
O(2)-C(3)	1.500(2)
O(3)-C(13)	1.193(3)
O(4)-C(13)	1.341(3)
O(4)-C(14)	1.463(3)
O(5)-C(17)	1.199(3)
O(6)-C(17)	1.344(3)
O(6)-C(18')	1.459(2)
O(6)-C(18)	1.459(2)
O(7)-C(24)	1.366(3)
O(7)-C(27)	1.430(3)
C(1)-C(2)	1.518(3)
C(2)-C(7)	1.540(3)
C(2)-C(3)	1.552(3)
C(3)-C(4)	1.538(3)
C(4)-C(8)	1.547(3)
C(4)-C(12)	1.548(3)
C(4)-C(5)	1.549(3)
C(5)-C(6)	1.532(3)
C(6)-C(17)	1.533(3)
C(6)-C(13)	1.538(3)
C(6)-C(7)	1.561(3)
C(7)-C(21)	1.522(3)
C(8)-C(9)	1.526(3)
C(9)-C(10)	1.522(4)
C(10)-C(11)	1.522(4)
C(11)-C(12)	1.530(4)
C(14)-C(15)	1.476(4)
C(15)-C(16)	1.316(4)
C(18)-C(19)	1.446(4)
C(18')-C(19')	1.307(14)
C(19)-C(20)	1.290(6)
C(19')-C(20')	1.30(2)
C(21)-C(26)	1.393(3)
C(21)-C(22)	1.397(3)
C(22)-C(23)	1.384(3)
C(23)-C(24)	1.386(3)
C(24)-C(25)	1.393(3)
C(25)-C(26)	1.395(3)
C(1)-O(2)-C(3)	91.63(16)
C(13)-O(4)-C(14)	116.27(16)
C(17)-O(6)-C(18')	115.69(17)
C(17)-O(6)-C(18)	115.69(17)
C(24)-O(7)-C(27)	117.6(2)
O(1)-C(1)-O(2)	127.2(2)
O(1)-C(1)-C(2)	137.3(2)
O(2)-C(1)-C(2)	95.32(17)
C(1)-C(2)-C(7)	117.67(17)
C(1)-C(2)-C(3)	84.01(16)
C(7)-C(2)-C(3)	120.16(17)
O(2)-C(3)-C(4)	114.32(17)
O(2)-C(3)-C(2)	88.57(15)
C(4)-C(3)-C(2)	122.47(17)
C(3)-C(4)-C(8)	107.19(16)
C(3)-C(4)-C(12)	110.21(17)
C(8)-C(4)-C(12)	107.22(17)

C(3)-C(4)-C(5)	111.08(17)
C(8)-C(4)-C(5)	108.16(16)
C(12)-C(4)-C(5)	112.73(16)
C(6)-C(5)-C(4)	115.98(16)
C(5)-C(6)-C(17)	112.34(17)
C(5)-C(6)-C(13)	108.62(16)
C(17)-C(6)-C(13)	103.35(15)
C(5)-C(6)-C(7)	110.96(16)
C(17)-C(6)-C(7)	111.00(16)
C(13)-C(6)-C(7)	110.28(16)
C(21)-C(7)-C(2)	110.98(16)
C(21)-C(7)-C(6)	112.19(16)
C(2)-C(7)-C(6)	110.67(16)
C(9)-C(8)-C(4)	113.80(18)
C(10)-C(9)-C(8)	110.5(2)
C(9)-C(10)-C(11)	110.8(2)
C(10)-C(11)-C(12)	111.7(2)
C(11)-C(12)-C(4)	112.66(18)
O(3)-C(13)-O(4)	124.64(18)
O(3)-C(13)-C(6)	125.28(18)
O(4)-C(13)-C(6)	110.06(16)
O(4)-C(14)-C(15)	112.18(19)
C(16)-C(15)-C(14)	122.7(2)
O(5)-C(17)-O(6)	124.64(19)
O(5)-C(17)-C(6)	126.00(19)
O(6)-C(17)-C(6)	109.34(16)
C(19)-C(18)-O(6)	108.7(2)
C(19')-C(18')-O(6)	115.8(6)
C(20)-C(19)-C(18)	126.4(4)
C(20')-C(19')-C(18')	142(2)
C(26)-C(21)-C(22)	117.35(19)
C(26)-C(21)-C(7)	122.09(18)
C(22)-C(21)-C(7)	120.53(18)
C(23)-C(22)-C(21)	121.3(2)
C(22)-C(23)-C(24)	120.6(2)
O(7)-C(24)-C(23)	115.9(2)
O(7)-C(24)-C(25)	124.7(2)
C(23)-C(24)-C(25)	119.4(2)
C(24)-C(25)-C(26)	119.25(19)
C(21)-C(26)-C(25)	122.04(19)

Dimethyl (1*S*,2*R*,6*R*)-2-(2,6-dimethoxyphenyl)-8-oxo-7-oxabicyclo[4.2.0]octane-3,3-dicarboxylate (220ad)

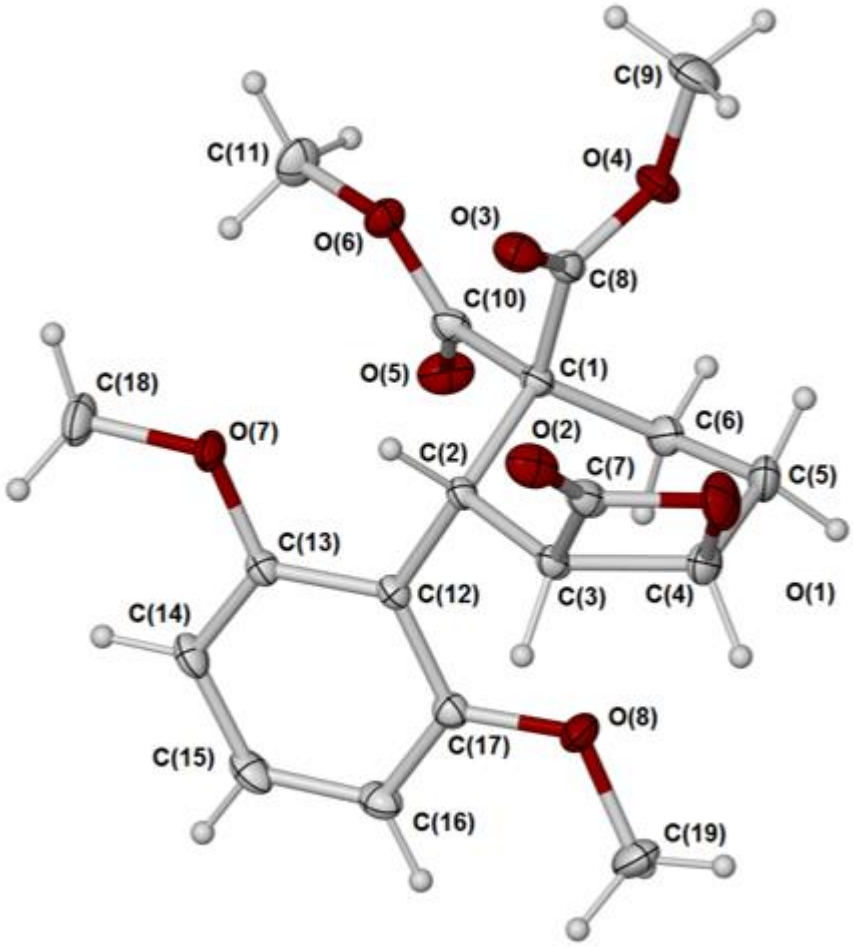

Figure A2. Molecular diagram of **220ad**

Table A3. Crystal data and structure refinement for **220ad**

Identification code	MX30_18
Empirical formula	C19 H22 O8
Formula weight	378.36
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 9.9485(8) A alpha = 90 deg. b = 8.1713(7) A beta = 93.276(3) deg. c = 21.8254(18) A gamma = 90 deg.
Volume	1771.3(3) A^3
Z, Calculated density	4, 1.419 Mg/m^3
Absorption coefficient	0.111 mm^-1
F(000)	800
Crystal size	0.34 x 0.25 x 0.25 mm
Theta range for data collection	3.116 to 30.532 deg.
Limiting indices	-14<=h<=14, -11<=k<=11, -30<=l<=30
Reflections collected / unique	32116 / 5387 [R(int) = 0.0251]
Completeness to theta = 25.242	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7460 and 0.6827
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5387 / 0 / 248
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0949
R indices (all data)	R1 = 0.0408, wR2 = 0.0996
Extinction coefficient	n/a
Largest diff. peak and hole	0.446 and -0.223 e.A^-3

Table A4. Bond lengths (A) and bond angles (°) for **220ad**

O(1)-C(7)	1.3588(12)
O(1)-C(4)	1.4894(13)
O(2)-C(7)	1.1845(13)
O(3)-C(8)	1.1942(11)
O(4)-C(8)	1.3319(11)
O(4)-C(9)	1.4383(12)
O(5)-C(10)	1.1942(11)
O(6)-C(10)	1.3273(11)
O(6)-C(11)	1.4420(11)
O(7)-C(13)	1.3613(11)
O(7)-C(18)	1.4125(11)
O(8)-C(17)	1.3594(11)
O(8)-C(19)	1.4203(11)
C(1)-C(10)	1.5227(12)
C(1)-C(8)	1.5244(12)
C(1)-C(6)	1.5280(12)
C(1)-C(2)	1.5601(12)
C(2)-C(12)	1.5169(11)
C(2)-C(3)	1.5244(11)
C(2)-H(2)	1.0000
C(3)-C(7)	1.5114(13)
C(3)-C(4)	1.5263(13)
C(3)-H(3)	1.0000
C(4)-C(5)	1.5135(14)
C(4)-H(4)	1.0000
C(5)-C(6)	1.5158(14)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-C(17)	1.3948(12)
C(12)-C(13)	1.3950(12)
C(13)-C(14)	1.3815(12)
C(14)-C(15)	1.3759(14)
C(14)-H(14)	0.9500
C(15)-C(16)	1.3698(14)
C(15)-H(15)	0.9500
C(16)-C(17)	1.3889(12)
C(16)-H(16)	0.9500
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(7)-O(1)-C(4)	91.87(7)
C(8)-O(4)-C(9)	115.28(8)
C(10)-O(6)-C(11)	115.11(7)
C(13)-O(7)-C(18)	117.12(7)
C(17)-O(8)-C(19)	117.84(8)
C(10)-C(1)-C(8)	107.74(7)

C(10)-C(1)-C(6)	108.31(7)
C(8)-C(1)-C(6)	111.14(7)
C(10)-C(1)-C(2)	110.39(7)
C(8)-C(1)-C(2)	109.33(7)
C(6)-C(1)-C(2)	109.90(7)
C(12)-C(2)-C(3)	111.68(7)
C(12)-C(2)-C(1)	113.56(7)
C(3)-C(2)-C(1)	110.81(7)
C(12)-C(2)-H(2)	106.8
C(3)-C(2)-H(2)	106.8
C(1)-C(2)-H(2)	106.8
C(7)-C(3)-C(2)	120.90(7)
C(7)-C(3)-C(4)	84.81(7)
C(2)-C(3)-C(4)	120.78(8)
C(7)-C(3)-H(3)	109.4
C(2)-C(3)-H(3)	109.4
C(4)-C(3)-H(3)	109.4
O(1)-C(4)-C(5)	111.98(8)
O(1)-C(4)-C(3)	88.81(7)
C(5)-C(4)-C(3)	119.38(8)
O(1)-C(4)-H(4)	111.6
C(5)-C(4)-H(4)	111.6
C(3)-C(4)-H(4)	111.6
C(4)-C(5)-C(6)	113.98(8)
C(4)-C(5)-H(5A)	108.8
C(6)-C(5)-H(5A)	108.8
C(4)-C(5)-H(5B)	108.8
C(6)-C(5)-H(5B)	108.8
H(5A)-C(5)-H(5B)	107.7
C(5)-C(6)-C(1)	111.96(8)
C(5)-C(6)-H(6A)	109.2
C(1)-C(6)-H(6A)	109.2
C(5)-C(6)-H(6B)	109.2
C(1)-C(6)-H(6B)	109.2
H(6A)-C(6)-H(6B)	107.9
O(2)-C(7)-O(1)	126.07(9)
O(2)-C(7)-C(3)	139.01(9)
O(1)-C(7)-C(3)	94.51(8)
O(3)-C(8)-O(4)	123.81(8)
O(3)-C(8)-C(1)	125.12(8)
O(4)-C(8)-C(1)	111.07(7)
O(4)-C(9)-H(9A)	109.5
O(4)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
O(4)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
O(5)-C(10)-O(6)	124.31(9)
O(5)-C(10)-C(1)	123.88(8)
O(6)-C(10)-C(1)	111.80(7)
O(6)-C(11)-H(11A)	109.5
O(6)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
O(6)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(17)-C(12)-C(13)	116.74(8)
C(17)-C(12)-C(2)	124.90(8)

C(13)-C(12)-C(2)	118.31(7)
O(7)-C(13)-C(14)	122.46(8)
O(7)-C(13)-C(12)	115.52(7)
C(14)-C(13)-C(12)	122.02(8)
C(15)-C(14)-C(13)	119.05(9)
C(15)-C(14)-H(14)	120.5
C(13)-C(14)-H(14)	120.5
C(16)-C(15)-C(14)	121.32(8)
C(16)-C(15)-H(15)	119.3
C(14)-C(15)-H(15)	119.3
C(15)-C(16)-C(17)	118.88(9)
C(15)-C(16)-H(16)	120.6
C(17)-C(16)-H(16)	120.6
O(8)-C(17)-C(16)	121.57(8)
O(8)-C(17)-C(12)	116.45(8)
C(16)-C(17)-C(12)	121.98(8)
O(7)-C(18)-H(18A)	109.5
O(7)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(7)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
O(8)-C(19)-H(19A)	109.5
O(8)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
O(8)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Dimethyl 3-bromo-4-hydroxy-6-methoxyphthalate (309)

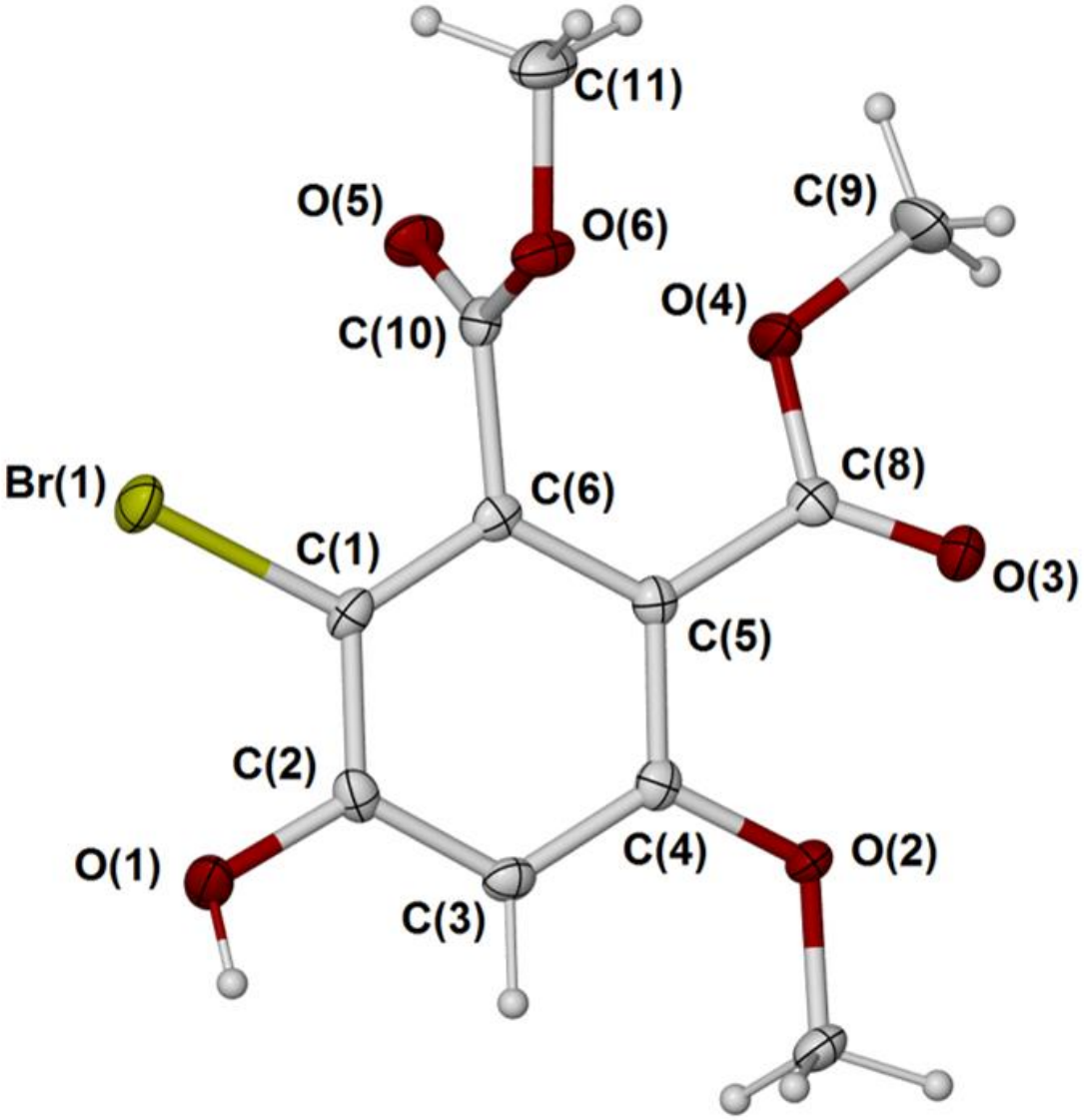

Figure A3. Molecular diagram of **309**

Table A5. Crystal data and structure refinement for **309**

Identification code	MX16_18
Empirical formula	C11 H11 Br O6
Formula weight	319.11
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 11.5781(6) A alpha = 90 deg. b = 12.7450(7) A beta = 110.050(4) deg. c = 8.6125(4) A gamma = 90 deg.
Volume	1193.86(11) A^3
Z, Calculated density	4, 1.775 Mg/m^3
Absorption coefficient	3.460 mm^-1
F(000)	640
Crystal size	0.35 x 0.30 x 0.25 mm
Theta range for data collection	3.028 to 27.226 deg.
Limiting indices	-14<=h<=14, -16<=k<=8, -11<=l<=11
Reflections collected / unique	9530 / 2647 [R(int) = 0.0424]
Completeness to theta = 25.242	99.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.1506 and 0.0810
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2647 / 0 / 170
Goodness-of-fit on F^2	1.015
Final R indices [I>2sigma(I)]	R1 = 0.0274, wR2 = 0.0564
R indices (all data)	R1 = 0.0405, wR2 = 0.0598
Extinction coefficient	n/a
Largest diff. peak and hole	0.340 and -0.507 e.A^-3

Table A6. Bond lengths (A) and bond angles (°) for **309**

Br(1)-C(1)	1.892(2)
O(1)-C(2)	1.348(2)
O(2)-C(4)	1.346(2)
O(2)-C(7)	1.437(3)
O(3)-C(8)	1.205(2)
O(4)-C(8)	1.332(3)
O(4)-C(9)	1.446(3)
O(5)-C(10)	1.201(2)
O(6)-C(10)	1.330(3)
O(6)-C(11)	1.447(3)
C(1)-C(6)	1.386(3)
C(1)-C(2)	1.395(3)
C(2)-C(3)	1.375(3)
C(3)-C(4)	1.394(3)
C(4)-C(5)	1.404(3)
C(5)-C(6)	1.408(3)
C(5)-C(8)	1.482(3)
C(6)-C(10)	1.504(3)
C(4)-O(2)-C(7)	118.50(16)
C(8)-O(4)-C(9)	116.22(18)
C(10)-O(6)-C(11)	114.69(17)
C(6)-C(1)-C(2)	120.39(19)
C(6)-C(1)-Br(1)	121.20(16)
C(2)-C(1)-Br(1)	118.40(15)
O(1)-C(2)-C(3)	122.4(2)
O(1)-C(2)-C(1)	117.69(19)
C(3)-C(2)-C(1)	119.90(19)
C(2)-C(3)-C(4)	120.5(2)
O(2)-C(4)-C(3)	122.3(2)
O(2)-C(4)-C(5)	117.19(18)
C(3)-C(4)-C(5)	120.50(19)
C(4)-C(5)-C(6)	118.40(19)
C(4)-C(5)-C(8)	120.24(18)
C(6)-C(5)-C(8)	121.35(19)
C(1)-C(6)-C(5)	120.4(2)
C(1)-C(6)-C(10)	117.53(18)
C(5)-C(6)-C(10)	122.09(18)
O(3)-C(8)-O(4)	121.05(19)
O(3)-C(8)-C(5)	127.1(2)
O(4)-C(8)-C(5)	111.84(18)
O(5)-C(10)-O(6)	124.8(2)
O(5)-C(10)-C(6)	123.8(2)
O(6)-C(10)-C(6)	111.29(17)

Appendix 2

Publications from Doctoral Studies

NHC Catalysis

International Edition: DOI: 10.1002/anie.201609330
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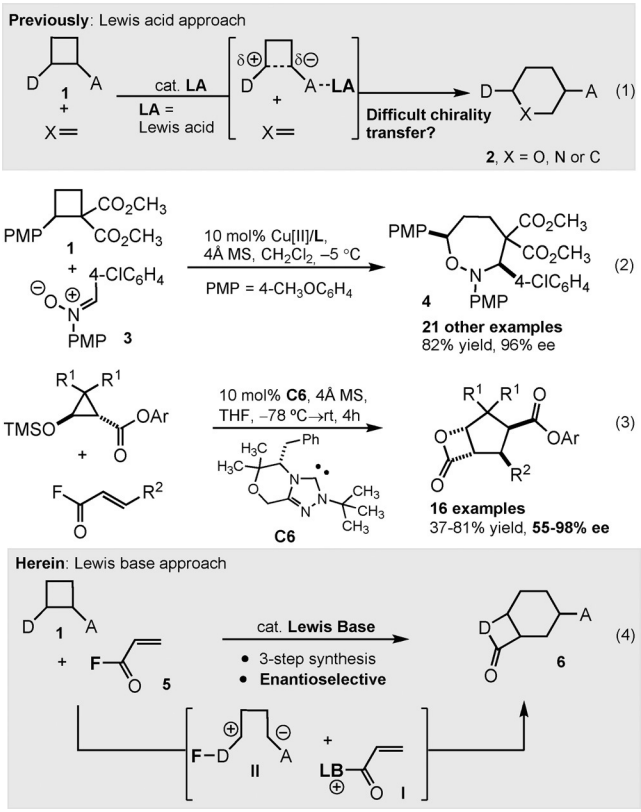
Enantioselective (4+2) Annulation of Donor–Acceptor Cyclobutanes by N-Heterocyclic Carbene Catalysis

*Alison Levens, Adam Ametovski, and David W. Lupton**

Abstract: *Herein we report the enantioselective (4+2) annulation of donor–acceptor cyclobutanes and unsaturated acyl fluorides using N-heterocyclic carbene catalysis. The reaction allows a 3-step synthesis of cyclohexyl β-lactones (25 examples) in excellent chemical yield (most ≥90%) and stereochemical integrity (all >20:1 d.r., most ≥97:3 e.r.). Mechanistic studies support ester enolate Claisen rearrangement, while derivatizations provide functionalized cyclohexenes and dihydroquinolinones.*

Release of ring-strain provides a powerful driving force for reaction discovery. Perhaps nowhere is this more evident than in the ring-opening annulation of vicinal donor–acceptor (DA) cyclopropanes.[1] Interestingly, while analogous DA-cyclobutanes (i.e. **1**) possess similar strain energy, their application in organic synthesis is significantly more limited (Scheme 1).[2] For example, only within the last decade have studies building on the pioneering work of Saigo[3] delivered general Lewis acid catalyzed approaches to the (4+2) annulation of DA-cyclobutanes [Eq. (1)].[4] These reactions define a concise route to tetrahydropyrans, piperidines and cyclohexanes (**2**) with excellent diastereoselectivity. Despite important advances in catalysis with DA-cyclobutanes, to the best of our knowledge, enantioselective variants of the (4+2) annulation are yet to be discovered. Indeed the only example of enantioselective catalysis using DA-cyclobutanes was reported last year by Xie and Tang with the Lewis acid catalyzed (4+3) annulation of nitrone **3** to afford oxazepane **4** [Eq. (2)].[5] Previously, we have had success with the annulation of DA cyclopropanes to give enantioenriched cyclopentanes [Eq. (3)].[6] Based on these experiences, we envisioned a Lewis base approach to enable the first enantioselective (4+2) annulation of DA-cyclobutanes.

The challenge with enantioselective Lewis acid catalysis using DA-cyclobutanes likely relates to oxocarbenium ion formation from the 1,4-ylide intermediate.[7] Such a scenario allows bond formation remote to the catalyst, thereby limiting chirality transfer [Eq. (1)]. In contrast, a dual activation Lewis base approach would concurrently activate both coupling partners (i.e. **I** and **II**), covalently linking the catalyst to the π-system. Their subsequent union in a stepwise (4+2) annulation[8] (**I** + **II** → **6**) should proceed with enantioselective bond construction [Eq. (4)]. Mechanistically related (4+2) annulations exploiting non-cyclobutane substrates have been realized by Romo and Studer, although in both cases only a single example was reported.[9] More generally, dual activation strategies to enable enantioselective catalysis have been reported by ourselves and others using electron rich pyridyl,[10] isothiourea[11] and N-heterocyclic carbene (NHC)[12] catalysts. Herein we communicate the enantioselective (4+2) annulation of DA cyclobutanes using a Lewis base approach, which provides a range of enantioenriched cyclohexyl β-lactones[13] (25 examples, most ≥97:3 e.r.).



Scheme 1. Background.

Preliminary studies focused on DA-cyclobutanes bearing a single ester. While some opening and annulation occurred, these substrates are less reactive than their cyclopropyl analogs. To address this, the more reactive malonate derived DA-cyclobutane **1a** was targeted.[14] Gratifyingly, in the presence of acyl fluoride **5a** a trace of β-lactone **6a** was observed with Fu's pyridyl catalyst, although isothiourea **B** gave no product (Table 1, entries 1 and 2). In contrast, NHC[15] **C1** gave cyclohexyl β-lactone **6a** in 18% yield as a 67:33 ratio of enantiomers (Table 1, entry 3). Alternate

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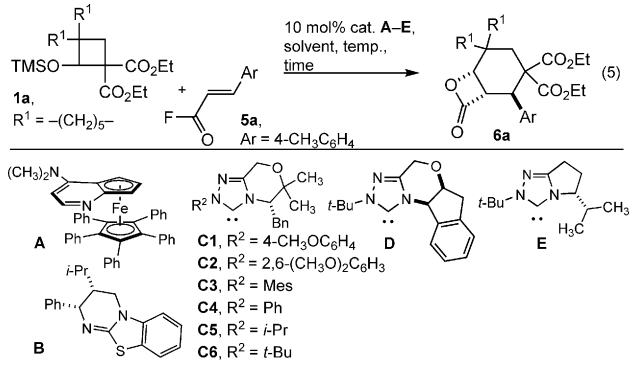
Table 1: Selected optimizations.



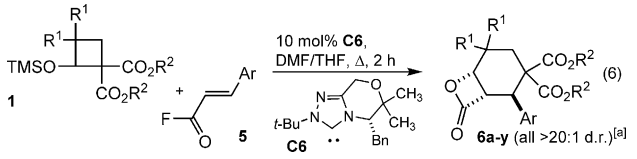
Entry	Cat.[a]	T [°C]	Solvent/Time	Yield [%][b]	d.r.[c]	e.r.[d]
1	**A**	rt	THF/12 h	trace	–	–
2	**B**	rt	THF/12 h	–	–	–
3[e]	**C1**	rt	THF/12 h	18	>20:1	67:33
4[e]	**C2-5**	rt	THF/12 h	trace	–	–
5[e]	**C6**	rt	THF/12 h	44	>20:1	96:4
6[e]	**D**	rt	THF/12 h	40	>20:1	15:85
7[e]	**E**	rt	THF/12 h	31	>20:1	78:22
8	**C6**	−78	THF/12 h	62	>20:1	92:8
9	**C6**	Δ	THF/12 h	59	>20:1	97:3
10	**C6**	Δ	toluene/11 h	21	>20:1	93:7
11	**C6**	Δ	DMF/13 h	86	>20:1	92:8
12	**C6**	Δ	1:9 DMF:THF/12 h	73	>20:1	96:4
13	**C6**[f]	**Δ**	**1:9 DMF:THF/2 h**	**93**	**>20:1**	**96:4**
14	**C6**[g]	Δ	1:9 DMF:THF/2 h	93	>20:1	96:4

[a] NHCs generated with KHMDS [b] Isolated yield. [c] Diastereomeric ratio by ^{1}H-NMR analysis. [d] Enantiomeric ratio by HPLC over chiral stationary phases. [e] 20 mol% catalyst. [f] KBF_4 and HMDS free, see experimental section. [g] 10 mol% HMDS, KBF_4 free.

morpholine catalysts **C2–C5** bearing various N-substituents[16] were not viable (Table 1, entry 4), however *t*-butyl NHC **C6** gave a 44% yield of enantioenriched β-lactone **6a** (96:4 e.r.) as a single diastereoisomer (>20:1 d.r.) (Table 1, entry 5). Indanol and pyrrolidine *t*-butyl catalysts **D** and **E** were viable, albeit less enantioselective (Table 1, entries 6 and 7). Enantioselectivity was poorer at lower temperature, while it increased when heated to reflux (97:3 e.r.) (Table 1, entries 8 and 9). The reaction tolerated toluene and DMF, with the later increasing yield but decreasing enantioselectivity (Table 1, entries 10 and 11). A compromise between yield and enantioselectivity was realized, with a 1:9 DMF/THF mixture providing β-lactone **6a** in 73% yield and 96:4 e.r. (Table 1, entry 12). Finally a "salt"[17] and HMDS-free version of the reaction increased the yield to 93% without affecting enantioselectivity (Table 1, entry 13). Reintroduction of HMDS had no impact on the reaction (Table 1, entry 14), thus removal of KBF_4 is key to this improvement (see below).

Reaction generality was examined with the coupling of unsaturated acyl fluorides **5** and DA-cyclobutanes **1**. While electron poor, neutral, and rich acyl fluorides reacted with good yields (≥80%), enantioselectivity was sensitive to β-aryl electronics. Thus, substrates containing the 4-BrC_6H_4 group gave β-lactone **6b** in 92:8 e.r. (Table 2, entry 1), while electron rich 2,4-$(CH_3O)_2C_6H_3$ and 4-$(CH_3)_2NC_6H_4$ gave **6e** and **6f** in 99:1 e.r. (Table 2, entries 6 and 7). The reaction

Table 2: Scope.

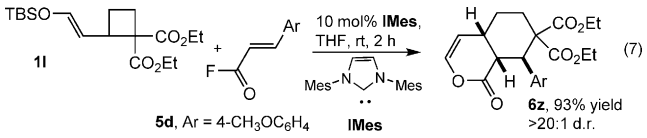


Entry	Ar	R^2	**6**	Yield [%][b]	e.r.[c]
1	4-BrC_6H_4	Et	**b**	80	92:8
2	C_6H_5	Et	**c**	86	95:5
3	4-$CH_3C_6H_4$	Et	**a**	93	96:4
4	4-$CH_3OC_6H_4$	Et	**d**	100	97:3
5[d]	4-$CH_3OC_6H_4$	Et	**d**	73	96:4
6	2,4-$(CH_3O)_2C_6H_3$	Et	**e**	90	99:1
7	4-$(CH_3)_2NC_6H_4$	Et	**f**	97	99:1
8	3,4,5-$(CH_3O)_3C_6H_2$	Et	**g**	93	96:4
9	3-Ts-indolyl	Et	**h**	83	98:2
10	4-$CH_3OC_6H_4$	CH_3	**i**	84	98:2
11	4-$CH_3OC_6H_4$	*i*-Pr	**j**	86	94:6
12	4-$CH_3OC_6H_4$	allyl	**k**	88	99:1
13	4-$(CH_3)_2NC_6H_4$	Et	**l**	90	96:4
14	2,4-$(CH_3O)_2C_6H_3$	Et	**m**	83	97:3
15	2-$CH_3OC_6H_4$	CH_3	**n**	87	97:3
16	4-$CH_3OC_6H_4$	Et	**o**	93	97:3
17	2,4-$(CH_3O)_2C_6H_3$	Et	**p**	100	99:1
18	2-BnN$(CH_3)C_6H_4$	Et	**q**	98	99:1
19	4-$(CH_3)_2NC_6H_4$	Et	**r**	88	93:7
20	2,4-$(CH_3O)_2C_6H_3$	Et	**s**	81	90:10
21	4-$(CH_3)_2NC_6H_4$	Et	**t**	98	97:3
22	2,4-$(CH_3O)_2C_6H_3$	Et	**u**	99	98:2
23	4-$CH_3OC_6H_4$	Et	**v**	94	98:2
24	2,4-$(CH_3O)_2C_6H_3$	Et	**w**	80	98:2
25	4-$CH_3OC_6H_4$	Et	**x**	75	98:2
26	2,4-$(CH_3O)_2C_6H_3$	Et	**y**	91	99:1

[a] Determined by ^{1}H-NMR analysis of crude residue. [b] Isolated yield. [c] Enantiomeric ratio by HPLC over chiral stationary phases. [d] 3 mol% **C6**.

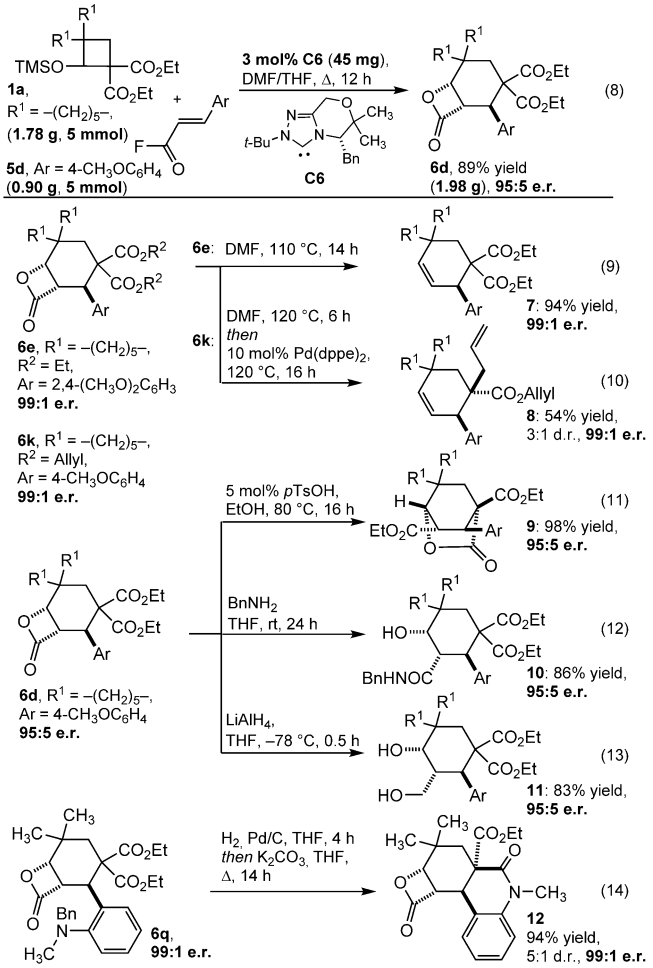
tolerated N-heterocycles with indole-containing β-lactone **6h** prepared in 83% yield and 98:2 e.r. (Table 2, entry 9). Unfortunately, β-alkyl acyl fluorides were not compatible with the reaction, potentially due to acyl azolium dienolate formation as developed by Chi and others with related substrates.[18] Variation of the ester was examined with methyl, isopropyl, and allyl esters (**6i**, **6j** and **6k**) prepared with excellent enantiopurity (98:2, 94:6 and 99:1 e.r.)

(Table 2, entries 10–12). The later was analyzed by single-crystal X-ray diffraction to determine absolute stereochemistry.[19] Absence of substitution about the cyclobutane was tolerated with cyclohexyl β-lactones **6l**, **6m** and **6n** prepared in ≥ 96:4 e.r. (Table 1, entries 13–15). Similarly dimethyl DA-cyclobutane gave β-lactones **6o**, **6p** and **6q** in excellent yield and enantiopurity (97:3, 99:1 and 99:1 e.r.) (Table 1, entries 16–18). The synthesis of spirocyclic cyclobutanes **6r** and **6s** occurred with decreased enantioselectivity, 93:7 and 90:10 respectively, (Table 2, entries 19 and 20) while cyclopentyl, heptyl, and octyl β-lactones **6t–6y** all formed in ≥ 97:3 e.r. (Table 2, entries 21–26). Finally, a vinylogous variant of the reaction was possible using TBS ether **1l** and acyl fluoride **5d** to give δ-lactone **6z** [Eq. (7)]. NHC-catalyzed approaches to related products have recently been report by Studer, Ye and Chi, all with high enantioselectivity.[20] While the synthesis of **6z** was viable with IMes, suitable chiral catalysts are yet to be identified, presumably due to the enhanced stability of the TBS (cf. TMS) requiring more nucleophilic catalysts.



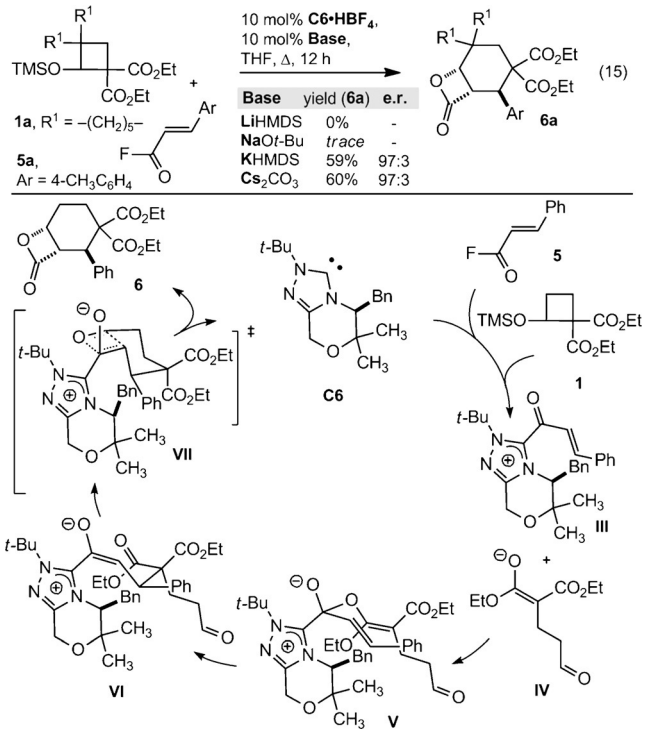
To allow larger scale (4+2) annulations lower catalyst loadings were examined. Pleasingly, 3 mol% **C6** provided the expected product in good yield and similar enantioselectivity (Table 2, entry 5), allowing a 5 mmol reaction, producing 1.98 grams of β-lactone **6d** in 89% yield and 95:5 e.r. (cf. 100% yield; 97:3 e.r.), to be realized [Eq. (8)] (Scheme 2). Derivatization studies commenced with the decarboxylation of β-lactone **6e** to afford cyclohexene **7** in 94% yield and 99:1 e.r. [Eq. (9)]. Coupling β-lactone decarboxylation with decarboxylative allylation of diallyl malonate **6k** allowed diene **8** to be prepared as a 3:1 mixture of diastereoisomers [Eq. (10)]. Opening of the β-lactone with ethanol triggered desymmetrization of the malonate to afford [2.2.2]-bicyclic δ-lactone **9** [Eq. (11)]. Benzylamine, under milder conditions, opened the β-lactone to afford amide **10** in 86% isolated yield [Eq. (12)], while chemoselective reductive opening of the β-lactone led to formation of diol **11** in 83% yield [Eq. (13)]. Finally, hydrogenolysis of β-lactone **6q** followed by cyclization provided quinolinone **12** in 94% yield as a 5:1 mixture of separable diastereomers [Eq. (14)]. Relative stereochemistry, and structural confirmation, were performed by single-crystal X-ray analysis.[19]

Mechanistically, the early stages of this reaction likely involve NHC mediated defluorination–desilylation to afford acyl azolium **III** and enolate **IV**[21] (Scheme 3). The viability of such a process is supported by the fluoride mediated opening of cyclobutane **1a** with TBAF which gives protonated **IV** in 88% yield (see the Supporting Information). Unfortunately, re-subjection of this material to the reaction conditions leads to complex mixtures, presumably as a result of acyl anion formation. In related work of Studer this is avoided by exploiting the methyl ketone variant of **IV** and a related acyl



Scheme 2. Scale-up and derivatization studies.

azolium[9b] in a reaction likely to proceed by either Michael addition or C–O bond formation followed by Claisen rearrangement.[22] To investigate these scenarios the reaction was performed using various bases for NHC generation bearing different counterions [Eq. (15)]. Tellingly, the reaction fails with strongly coordinating lithium and sodium bases, which favor Michael addition of the enolate. Similarly adding LiCl (0.5 equiv) to a reaction with Cs_2CO_3 causes the reaction to fail. In contrast, potassium and cesium salts favor ionic structures, and subsequent C–O bond formation, giving good yields of **6a**. Further support for a [3,3]-rearrangement is derived from the known acceleration of such reactions by poorly coordinating counterions.[23] Thus, we propose that C–O bond formation gives hemiacetal **V** that undergoes [3,3]-sigmatropic rearrangement to afford **VI**, which after asynchronous (2+2)[24] and loss of the NHC, then delivers β-lactone **6**. A striking observation in the optimization was the enhanced enantioselectivity at higher temperatures. Although less common than enhancement at low temperature it has been observed in reactions with large entropic contributions to the diastereomeric transition state energies in the enantiodetermining step (i.e. $\Delta\Delta S^{+}_{S/R}$ significant cf. $\Delta\Delta H^{+}_{S/R}$).[25] Although further studies are needed to fully appreciate this interesting observation it seems probable that



Scheme 3. Mechanistic studies.

reaction volume is gained in the conversion of **V** to **VI** that allows the $\Delta\Delta S^{\ddagger}$ term to make a significant contribution to the overall activation energy.

Donor–acceptor cyclobutanes are exceptional substrates for reaction design. Beyond documented ring-strain, they are readily accessible, with all substrates prepared in 2 steps. Thus, the enantioselective (4+2) annulation allows a 3-step synthesis of densely functionalized cyclohexyl β-lactones. This sequence compares favorably to the state-of-the-art in enantioselective β-lactone synthesis.[13] The ability of this reaction to rapidly deliver molecular complexity is currently being examined as a vehicle to drive studies in total synthesis and medicinal chemistry.

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Keywords: cyclohexanes · donor–acceptor cyclobutanes · enantioselective catalysis · N-heterocyclic carbenes · organocatalysis

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Angew. Chem. **2016**, *128*, 16370–16374

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Biomimetic and Biocatalytic Synthesis of Bruceol

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Abstract: *The first total synthesis of bruceol has been achieved using a biomimetic cascade cyclization initiated by a stereoselective Jacobsen–Katsuki epoxidation (and kinetic resolution) of racemic protobruceol-I. A bacterial cytochrome P450 monooxygenase was also found to catalyze the conversion of protobruceol-I into bruceol. The first full analysis of the NMR data of natural bruceol suggested that "isobruceol" was a previously unrecognized natural product also isolated from Philotheca brucei. This was confirmed by the re-isolation, synthesis, and X-ray analysis of isobruceol. In total, eight stereoisomers and structural isomers of bruceol have been synthesized in a highly divergent approach.*

The meroterpenoid bruceol (**1**) was first isolated from the Western Australian shrub *Philotheca brucei* (formerly known as *Eriostemon brucei*) by Jefferies and co-workers at the University of Western Australia in 1963 (Figure 1).[1] The compact, pentacyclic structure of **1** consists of a 5,7-dioxycoumarin fused to a so-called "citran" ring system that is biosynthetically derived from cyclization of a geranyl group. The relative configuration of **1** was determined by X-ray crystallography of 8-bromobruceol, but given the era of the study, no detailed NMR analysis was conducted.[1] The absolute configuration of natural (−)-**1** was later determined by X-ray studies of chloroacetate and iodoacetate derviatives.[2] In 1992 Waterman and co-workers re-investigated natural products from *Philotheca brucei*, and they published full NMR data of what they believed was re-isolated **1**.[3] However, based on the synthetic and isolation work described herein, we report that Waterman actually isolated isobruceol (**2**), which has an opposite orientation of the dioxycoumarin to the "citran" ring system compared to bruceol. There is also some confusion in the literature between structures **3** and **4**, with both compounds being previously referred to as deoxybruceol. Henceforth, we propose that **3** is deoxybruceol and **4** is deoxyisobruceol. (±)-**4** was first synthesized by Crombie and Ponsford in 1968 in a remarkable work of both biomimetic synthesis and natural product anticipation.[4,5] The isolation of **4** from *Philotheca brucei* was reported in 1981 by Jefferies and co-workers[2] (as a racemate) and again in 1992 by Waterman and co-workers[3] (as a single enantiomer). To date, **3** has not been isolated as a natural product.

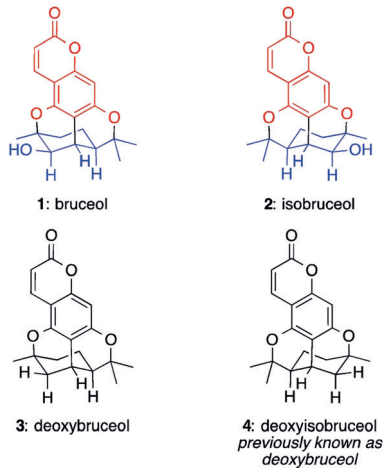

Figure 1. Bruceol-type natural products isolated from *Philotheca brucei*. Note the variation in the orientation of the dioxycoumarin rings (red) to the "citran" ring systems (blue) of bruceol and isobruceol.

Given that bruceol (**1**) and deoxyisobruceol (**4**) have different carbon skeletons, with opposite orientations of the upper dioxycoumarin with respect to the lower tricyclic "citran" ring system, they are clearly not biosynthetically related by a direct enzymatic C–H oxidation. However, both **1** and **4** may be derived from the geranylated dihydroxycoumarin **5** (Scheme 1). In the biosynthesis of **4**, Crombie proposed that oxidation and oxa-6π-electrocyclization of **5** gives chromene **6**.[5] Tautomerization (and dearomatization) of **6** to give *ortho*-quinone methide[6] **7** followed by an intramolecular hetero-Diels–Alder reaction would then give deoxyisobruceol (**4**). Alternatively, and as previously proposed by Trauner,[7] oxidative cyclization of **5** could give protobruceol-I (**8**), a naturally occurring chromene and structural isomer of **6**.[8] Stereoselective epoxidation of **8** (on the opposite face to the bulky homoprenyl substituent) would give the labile epoxide **9**, which could ring open (and dearomatize) to give *ortho*-quinone methide **10**, and then form **1** via an intramolecular hetero-Diels–Alder reaction. We speculate that a monooxygenase enzyme might catalyze this epoxidation–cyclization cascade reaction in vivo, either enantioselectively (i.e. kinetic resolution of a racemic chromene **8**) or diastereoselectively (if chromene **8** is enantiopure in nature).[9]

Crombie and Ponsford's landmark two-step total synthesis of (±)-**4** was reported over 50 years ago.[4] 5,7-Dihydroxycoumarin (**11**) was first synthesized in one step from phloroglucinol,[10] and then condensed with citral (**12**) in

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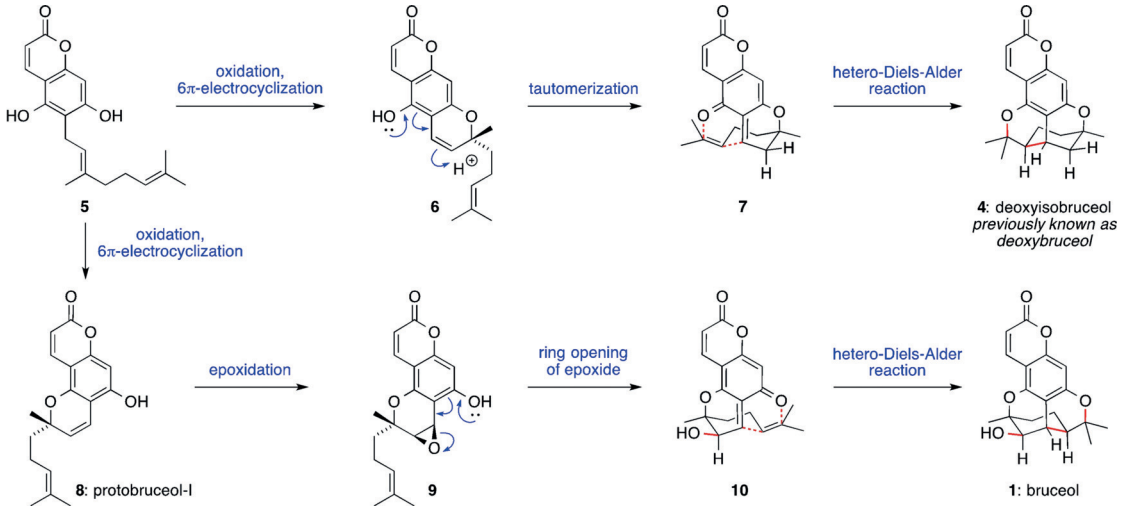
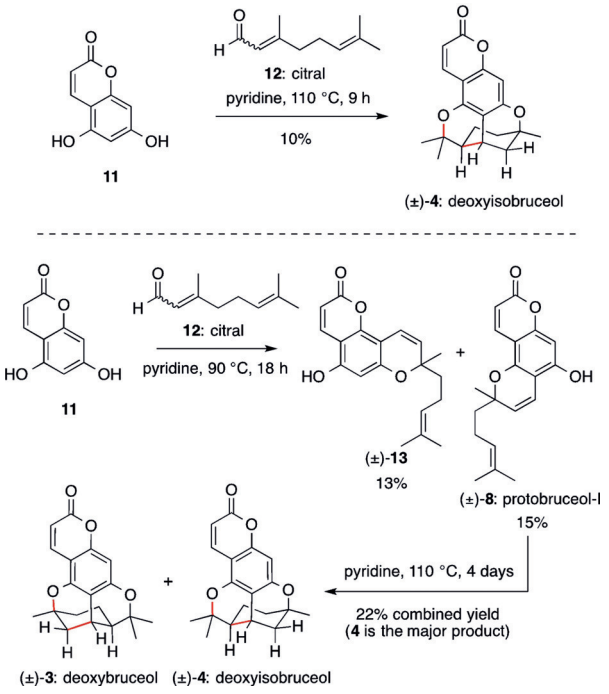


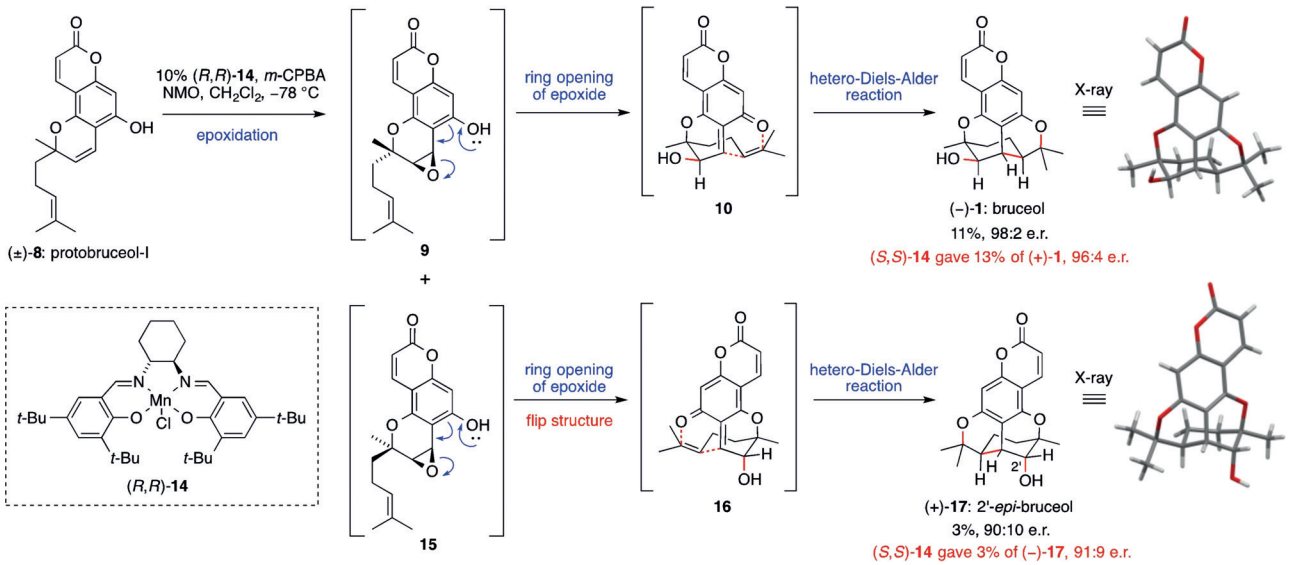
Scheme 1. Proposed biosynthesis of bruceol and deoxyisobruceol.

pyridine at 110 °C to give (±)-**4** in 10 % yield (Scheme 2). The product of this reaction was initially incorrectly assigned as (±)-**3** by analogy to bruceol (**1**), until later X-ray studies by Crombie led to a structure revision to (±)-**4**.[5] The mechanism of the cascade reaction involves initial condensation of **11** with **12** to give chromene (±)-**6**, followed by tautomerization and intramolecular cycloaddition to give (±)-**4**, thus closely mirroring the proposed biosynthetic pathway. Later studies by Crombie showed that condensation of **11** with **12** in pyridine at the lower temperature of 90 °C gave the isomeric chromenes (±)-**8** and (±)-**13** in modest yields.[5] Then, heating (±)-**8** in pyridine at 110 °C formed a mixture of (±)-**3** and (±)-**4** in 22 % combined yield, indicating that some interconversion of chromenes (±)-**8** and (±)-**6** must occur under these conditions via reversible retro-oxa-6π-electrocyclization and oxa-6π-electrocyclization reactions, prior to the irreversible intramolecular hetero-Diels–Alder reactions. More recently, an improved synthesis of (±)-**4** in 45 % yield has been achieved by Lee and Kim, who condensed **11** with **12** in the presence of catalytic ethylenediamine diacetate in DMF at 100 °C.[11]



Scheme 2. A summary of Crombie's synthetic work on deoxybruceol and deoxyisobruceol.

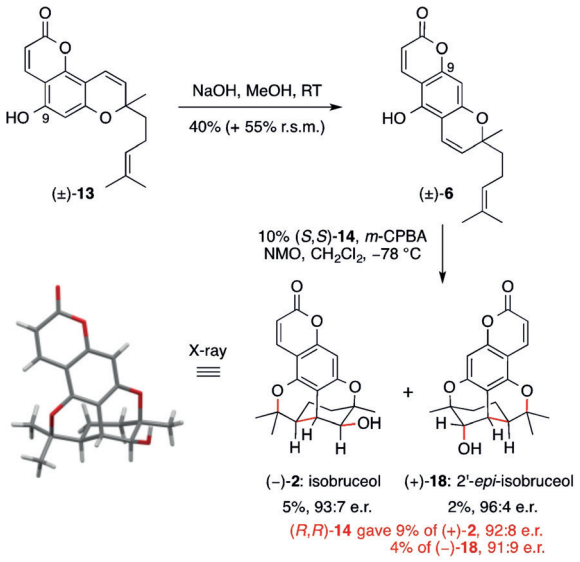
Our biomimetic synthesis of both enantiomers of bruceol is outlined in Scheme 3. (±)-**8** was first synthesized according to a modified version of Crombie's procedure (Scheme 2, and see the Supporting Information for full details). We then mimicked the proposed biosynthetic epoxidation of protobruceol-I with a stereoselective Jacobsen–Katsuki epoxidation.[12] Jacobsen-type chiral (salen)manganese(III)-complexes are known to efficiently catalyze the epoxidation of (*Z*)-1,2-disubstituted alkenes in preference to tri-substituted alkenes (as required in our synthesis), and chromenes have been reported to be good substrates for the reaction.[13] Furthermore, Jacobsen has used his epoxidation as a method for the kinetic resolution of chiral, racemic chromenes, which was applied in an asymmetric synthesis of a chromene natural product, (+)-teretifolione B.[14] High catalyst-induced selectivity, but moderate substrate-induced selectivity, was observed in Jacobsen's kinetic resolution of chromenes, and similar selectivity was observed in our biomimetic synthesis of (−)-**1** (Scheme 3). Thus, treatment of (±)-**8** with 10 mol % of Jacobsen's catalyst (*R*,*R*)-**14** with *m*-CPBA and NMO as stoichiometric oxidants gave (−)-**1** (11 % yield, 98:2 e.r.), alongside 2′-*epi*-bruceol (+)-**17** (3 % yield, 90:10 e.r.). Both enantiomers of (±)-**8** therefore undergo epoxidation to some extent (i.e. low substrate selectivity), but the facial selectivity is good, with addition to the top face (as drawn) of the alkene strongly preferred in each case (i.e. high catalyst-selectivity). A similar result was obtained using (*S*,*S*)-**14** to give (+)-**1** (13 % yield, 96:4 e.r.) and (−)-**17** (3 % yield, 91:9 e.r.). We believe that the low yield for the epoxidation–cyclization cascades of (±)-**8** to give (−)-



Scheme 3. Biomimetic synthesis of (−)-bruceol using a stereoselective Jacobsen–Katsuki epoxidation of (±)-protobruceol-I. *m*-CPBA = *meta*-chloroperoxybenzoic acid, NMO = 4-methylmorpholine *N*-oxide.

1 and (+)-**1** is due to over-oxidation of the electron-rich dioxycoumarin ring system to form some polar, uncharacterized by-products. However, these low yields are partially offset by the significant increase in molecular complexity (three stereocentres, three bonds, and two rings are formed in the cascade) and by the fact that the reactions are kinetic resolutions.

Our synthetic bruceol (**1**) correlated with the low resolution NMR data that was published in Jefferies' original 1963 isolation paper alongside their X-ray crystallographic data.[1] However, close comparison of our ^{1}H and ^{13}C NMR spectra of synthetic **1** with those of the natural "bruceol" reported by Waterman in 1992 revealed slight discrepancies.[3] We postulated that Waterman had in fact isolated isobruceol (**2**), partly due to its co-isolation with deoxyisobruceol (**4**), and related *Philotheca brucei* natural products such as eriobrucinol and hydroxyeriobrucinol,[15] that share the same orientation of the dioxycoumarin with respect to the chromene-derived ring system. To prove our conjecture, we intended to re-isolate both **1** and the suspected **2** from *Philotheca brucei*, so we contacted natural product chemists at the University of Western Australia for advice on obtaining this plant. To our surprise, we were given several grams of Jefferies' original, crystalline sample of **1** from the University of Western Australia's library of natural products. The first detailed NMR analysis of this 55-year-old sample conclusively showed that it matched our synthetic **1**, but not Waterman's re-isolated "bruceol" NMR data. We also obtained an X-ray crystal structure of synthetic **1**.[16] Next, we obtained 5 kg of dried *Philotheca brucei* from the Koolyanobbing Range (500 km east of Perth, WA). Extraction of the dried plant material with Et_2O followed by flash column chromatography on silica gel gave multi-gram quantities of a 11:1 mixture of **1** (major component) and a similar compound with ^{1}H NMR spectra that matched Waterman's "bruceol". Purification of the unknown compound via selective crystallization to remove **1**, followed by preparative HPLC, gave a few milligrams of crystalline material that was identified by X-ray analysis as isobruceol (**2**) (Scheme 4). NMR data for this compound fully agreed with Waterman's data, thus proving that he isolated isobruceol, not bruceol.

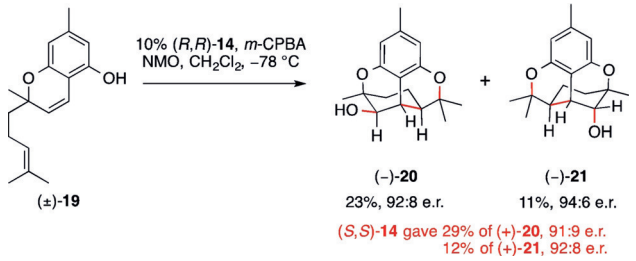


Scheme 4. Biomimetic synthesis of (−)-isobruceol.

We then conducted a stereoselective synthesis of isobruceol to determine its absolute configuration. This first required the synthesis of chromene (±)-**6** (Scheme 4), which is presumably an undiscovered natural product ("protoisobruceol"). Treatment of chromene (±)-**13** (a previously undesired by-product in the synthesis of (±)-**8**) with NaOH in MeOH gave a separable equilibrium mixture of (±)-**13** and (±)-**6** via methoxide-induced opening of the lactone ring followed by cyclization of the methyl ester intermediate at the C-9 phenol.[17] Jacobsen–Katsuki epoxidation of (±)-**6** with

10 mol% (*S*,*S*)-**14** gave (−)-**2** (5% yield, 93:7 e.r.), which matched the sign of the optical rotation of natural isobruceol, thereby confirming that the absolute configuration of (−)-**2** is as shown in Scheme 4. A 2% yield of 2′-*epi*-isobruceol (+)-**18** (96:4 e.r.) was also obtained, and a similar result was obtained using the (*R*,*R*)-**14** catalyst to give (+)-**2** (9% yield, 92:8 e.r.) and (−)-**18** (4% yield, 91:9 e.r.).

The low yields obtained in our biomimetic syntheses of **1** and **2** are, to some extent, due to over-oxidation of the electron-rich dioxycoumarin ring systems under the Jacobsen–Katsuki reaction conditions. Jacobsen has also observed that tricyclic chromenes similar to **6** and **8** are poor substrates for stereoselective epoxidation.[14] We therefore demonstrated a more efficient epoxidation–cyclization cascade of the simpler bicyclic chromene (±)-**19**.[18] Thus, Jacobsen–Katsuki epoxidation of (±)-**19** with 10 mol% (*R*,*R*)-**14** gave the bruceol analogue (−)-**20** (23% yield, 92:8 e.r.), alongside the epimer (−)-**21** (11% yield, 94:6 e.r.) (Scheme 5). The use of (*S*,*S*)-**14** gave (+)-**20** (29% yield, 91:9 e.r.) and (+)-**21** (12% yield, 92:8 e.r.). Chromene (±)-**19** is therefore a much better substrate for the epoxidation–cyclization cascade than (±)-**8** or (±)-**6**.



Scheme 5. Synthesis of simplified bruceol analogues **20** and **21**.

To gain further insight into the biosynthesis of bruceol and isobruceol, chromenes (±)-**8**, (±)-**6** and, (±)-**19** were screened against a small library of bacterial cytochrome P450 monooxygenase enzymes.[19] A variant of $P450_{BM3}$, A74G/F87V/L188Q (GVQ) converted ≥80% of (±)-**19** into two products (see Figure S1 in the Supporting Information).[19a] Co-elution of synthetic standards using chiral phase HPLC and GC-MS, and analysis of the MS spectra enabled their characterization as the bruceol analogue (+)-**20** and an epoxide[20] formed by oxidation of the prenyl side chain (Supporting Information, Scheme S1 and Figure S2). Given the larger size of (±)-**8** and (±)-**6**, a series of $P450_{BM3}$ variants, which had been designed to increase the size of the substrate binding pocket, were screened for oxidation activity (Supporting Information, Table S1). While oxidation of these substrates was less efficient and selective, chiral phase HPLC co-elution experiments of the enzyme turnovers, using the variant KSK19/I263A/A328I,[19b–d] with synthetic standards revealed the formation of (+)-**1** and (−)-**2** as single enantiomers (Figure 2). Therefore, the P450 monooxygenases could catalyze the enantioselective chromene epoxidation–cyclization cascade proposed in Scheme 1 to form the "citran" ring system of bruceol natural products. The identity of the natural monooxygenase enzyme that catalyzes this cascade reaction in *Philotheca brucei* remains to be determined.

In summary, we have mimicked the epoxidation–cyclization cascade proposed to occur in the biosynthesis of bruceol by using a Jacobsen–Katsuki epoxidation of an electron-rich chromene. The first full NMR analysis of bruceol, including the original sample isolated by Jefferies in 1963, revealed that isobruceol had been isolated and mistaken for bruceol by Waterman in 1992. This hypothesis was confirmed by the re-isolation and synthesis of isobruceol, thus highlighting the roles that biosynthetic speculation and biomimetic synthesis continue to play in the revision of natural product assignments.[21] Finally, we have shown that bacterial cytochrome P450 monooxygenases are capable of catalyzing the bruceol cascade in a complex example of a P450-mediated oxidative cyclization.[9]

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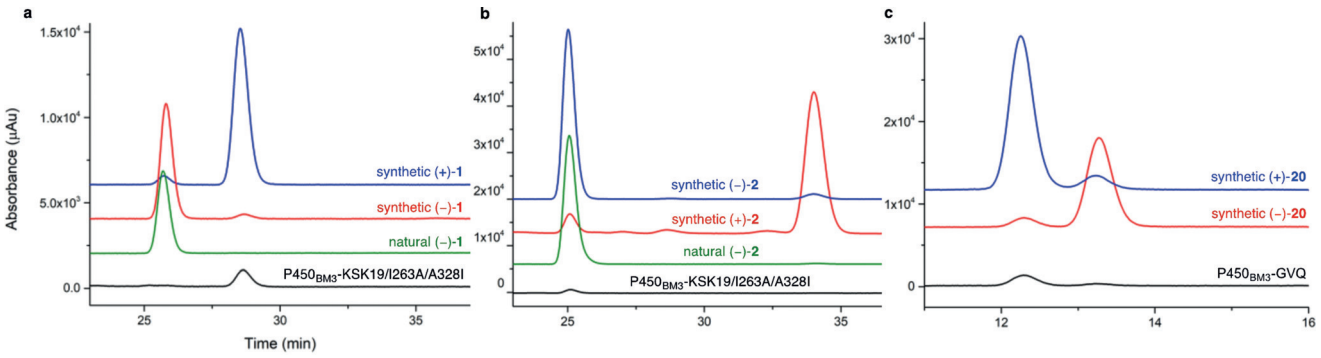

Figure 2. Chiral phase HPLC co-elution experiments of the products of enzymatic oxidative cyclizations of chromenes **8**, **6**, and **19** with synthetic standards. a) $P450_{BM3}$-KSK19/I263A/A328I produced bruceol (+)-**1** from protobruceol-I (±)-**8** and b) this enzyme also produced isobruceol (−)-**2** from protoisobruceol (±)-**6**. c) $P450_{BM3}$-GVQ produced the bruceol analogue (+)-**20** after oxidation of the chromene analogue (±)-**19**. Note the chromatograms have been offset along the *y* axis for clarity.

Prof. Emilio Ghisalberti at the same institution. We thank Dr. Carole Elliott and Dr. Wolfgang Lewandrowski (Kings Park Science, Department of Biodiversity, Conservation, and Attractions) for the collection of *Philotheca brucei* under licence (SW018739). We thank Prof. Luet-Lok Wong (University of Oxford, UK) for the gene constructs of $P450_{BM3}$.

Conflict of interest

The authors declare no conflict of interest.

Keywords: biomimetic synthesis · biosynthesis · cascade reactions · natural products · total synthesis

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Enantioselective Total Synthesis of (−)-Δ⁹-Tetrahydrocannabinol via N-Heterocyclic Carbene Catalysis

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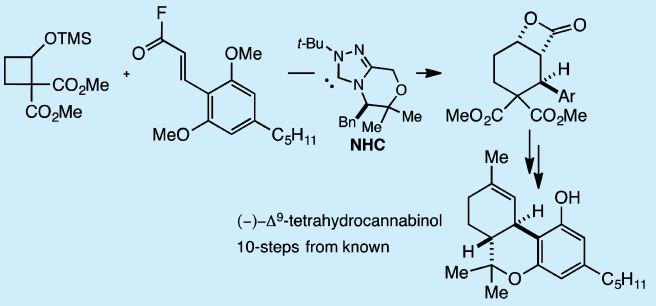
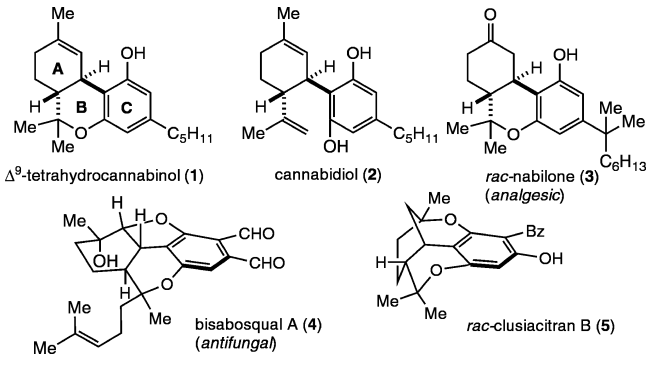
Supporting Information

ABSTRACT: Enantioselective syntheses of (−)-Δ⁸-tetrahydrocannabinol ((−)-Δ⁸-THC) and (−)-Δ⁹-THC have been achieved in eight and 10 steps, respectively, from a known cinnamic acid. The syntheses take advantage of an enantioselective N-heterocyclic carbene (NHC)-catalyzed (4 + 2) annulation between donor−acceptor cyclobutanes and cinnamoyl fluorides to construct the highly enantioenriched cycloxyl β-lactone shown. Having constructed this A-ring precursor, elaboration to (−)-Δ⁸-THC is achieved through β-lactone alcoholysis followed by oxidation, dual decarboxylation, trimethylation, and cationic cyclization. Finally, the conversion to (−)-Δ⁹-THC is achieved with established chemistry.



While over 200 phytocannabinoids are known,[1] within popular culture their zeitgeist remains strongly linked to (−)-Δ⁹-tetrahydrocannabinol ((−)-Δ⁹-THC, **1**) and cannabidiol (**2**). The bioactivity of the former is elicited through binding to the G protein-coupled receptors CB_1 and CB_2,[2] with structural information regarding the mode of binding emerging in 2017.[2a] While these compounds have captured significant attention, other phytocannabinoids (i.e., **3**−**5**) can have distinct bioactivities and unusual molecular structures.[3]



The chemical synthesis of Δ⁹-THC has been extensively examined over the last 50 years,[4−7] and a number of enantiospecific approaches and syntheses of racemic Δ⁹-THC have been developed. Many have been achieved through terpenylation of olivetol (**6**), as typified by the enantioselective synthesis from (−)-verbenol (**7**) reported by Mechoulam and Gaoni (Scheme 1a).[4a] In contrast, enantioselective routes are far more limited.[5−7] In 1997 Evans reported the enantioselective total synthesis of (+)-Δ⁹-THC via a bis(oxazoline)-copper-catalyzed Diels−Alder reaction (**8** + **9** → **10**).[5] Subsequent coupling to **6** and cyclization gave the unnatural enantiomer of THC in an efficient manner. In 2007 Trost and Dogra reported the enantioselective synthesis of **1**[6a] through ring-closing metathesis (RCM) to introduce the A ring. Enabled by stereodivergent access to 1,7-diene **11**, a related RCM approach was used by Carreira in his elegant synthesis of all stereoisomers of Δ⁹-THC.[6b] Finally, Leahy recently developed a synthesis enabled by sigmatropic rearrangement followed by RCM,[6c] while Zhou exploited high-pressure enantioselective ketone reduction in his approach to **1** and (−)-Δ⁸-THC (**12**).[7]

In 2016 we reported the enantioselective N-heterocyclic carbene (NHC)-catalyzed synthesis of cyclohexyl β-lactones (i.e., **13**) from donor−acceptor cyclobutanes (i.e., **14**) and cinnamoyl fluorides (i.e., **15a**).[8a,9] The reaction displays broad generality, and we envisioned that it could provide materials (such as **13a** or **13b**) suited to the preparation of **1** (Scheme 1b). To realize this, decarboxylation and/or decarbonylation would yield cyclohexene **16** or cyclohexanone **17**, after which exhaustive methylation and cationic cyclization would give **1**. This sequence should define a concise entry to **1** while being amenable to the preparation of materials with a modified A ring by the use of alternate cyclobutanes. Strikingly, modification of the A ring has received limited attention in studies of the bioactivity of (−)-Δ⁹-THC analogues.[1] Herein we report the enantioselective total syntheses of normethyl-(−)-Δ⁹-THC (**18**), (−)-Δ⁸-THC (**12**), and (−)-Δ⁹-THC (**1**) in six, eight, and 10 steps, respectively, from commercial cinnamate **15b** (X = OH),[10] which itself can be derived from **6** in three steps.[6c,10b]

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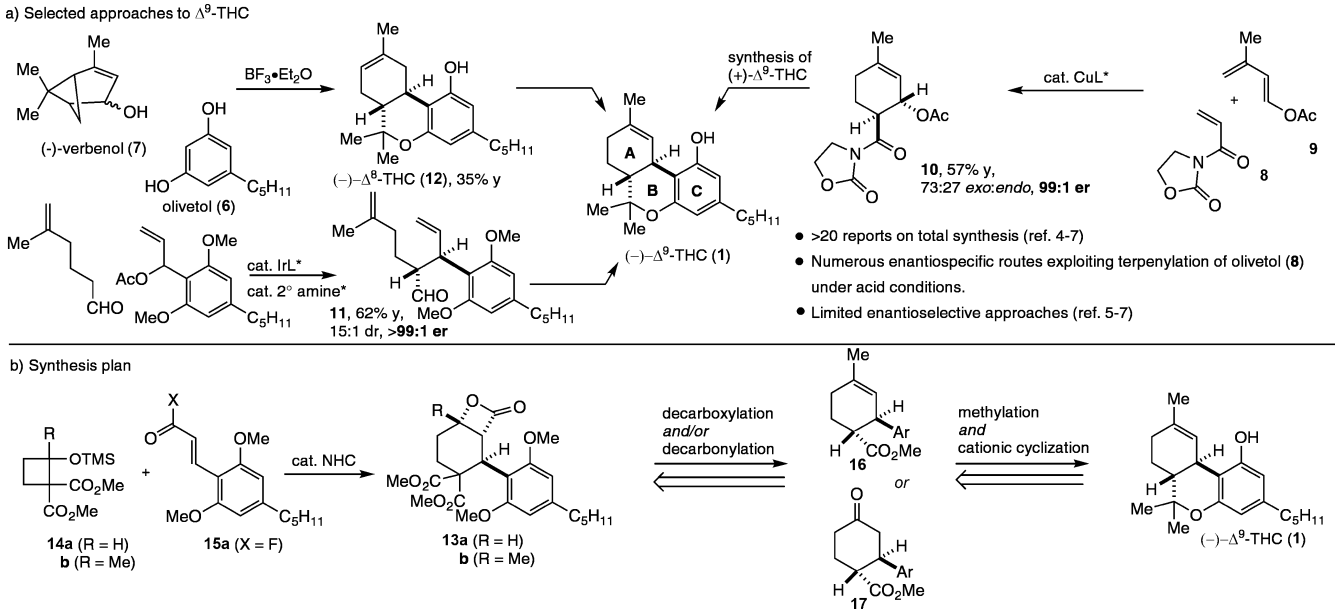
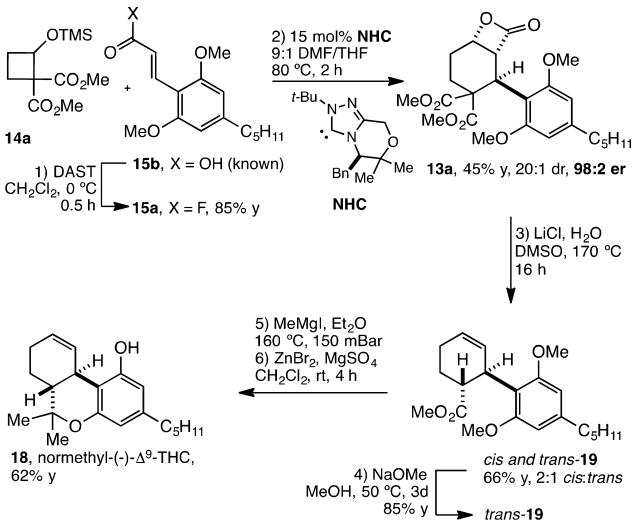
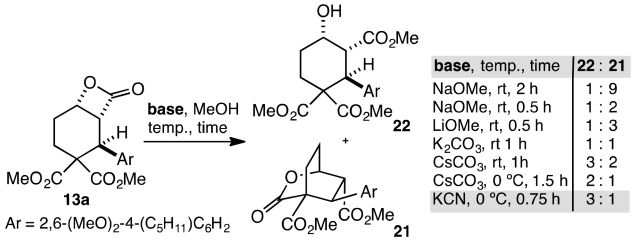
Scheme 1. (a) Selected Previous Approaches to Δ^9-THC; (b) Our Synthesis Plan



Scheme 2. Synthesis of Normethyl-(−)-Δ^9-THC (18)



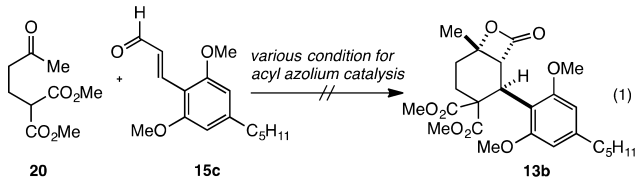
Scheme 3. Optimization of the Opening of β-Lactone 13a



base, temp., time	22 : 21
NaOMe, rt, 2 h	1 : 9
NaOMe, rt, 0.5 h	1 : 2
LiOMe, rt, 0.5 h	1 : 3
K_2CO_3, rt 1 h	1 : 1
$CsCO_3$, rt, 1h	3 : 2
$CsCO_3$, 0 °C, 1.5 h	2 : 1
KCN, 0 °C, 0.75 h	3 : 1

Studies commenced by establishing the viability of the general strategy through the preparation of **18** (Scheme 2). In our methodological studies,[8a] 2,6-disubstituted cinnamoyl fluorides (i.e., **15a**) were not examined, and hence, their viability in NHC catalysis needed to be determined. Following conversion of commercially available and readily accessible cinnamate **15b** (X = OH)[10] to acyl fluoride **15a** (X = F),[11] the annulation of **15a** was examined. Gratifyingly, reaction with the known donor−acceptor cyclobutane **14a** (R = H)[12] proceeded without event to provide cyclohexyl β-lactone **13a** in 45% yield as a single diastereoisomer with excellent enantioselectivity (98:2 er). While the yield was modest, this result is in keeping with reactions of heavily substituted α,β-unsaturated acyl azoliums.[9j] Krapcho decarboxylation[13] of malonate **13a** with concomitant decarboxylation of the β-lactone provided a 2:1 mixture of *cis*- and *trans*-cyclohexenes **19** in 66% yield. Conversion of the diastereomeric mixture to the desired *trans*-**19** was achieved in 85% yield using the conditions reported by Trost and Dogra.[6a] Finally, two-step conversion of *trans*-**19** to normethyl-(−)-Δ^9-THC (**18**) using conditions described by Carreira[6b] closed the B ring and provided the desired product in 62% isolated yield.

Having demonstrated the key reactions necessary for the overall strategy, attention was directed toward the 9-methyl group. Our preferred approach would exploit donor−acceptor cyclobutane **14b** (R = Me). However, all attempts to prepare this material proved unsuccessful. An alternate approach exploiting methyl ketone **20**, a substrate used by Studer in a related (4 + 2) annulation, was envisaged.[8b] Unfortunately, union of ketone **20** with enal **15c** under oxidative NHC catalysis failed to give the desired cyclohexanone **13b** (eq 1), as only cinnamic acid derivatives were isolated.



An alternate strategy to install the 9-methyl group involved the preparation of ketone **17** by methanolysis of β-lactone **13a**, oxidation, and dual Krapcho decarboxylation (Scheme 1, **13a** → **17**). Global methylation followed by cationic cyclization and elimination would then provide the cannabinoid targets. This approach was initially met with difficulties due to the facile formation of bicyclic lactone **21** upon cleavage of the β-lactone (Scheme 3). Fortuitously, the reaction was sensitive to the base, with KCN favoring the formation of the desired

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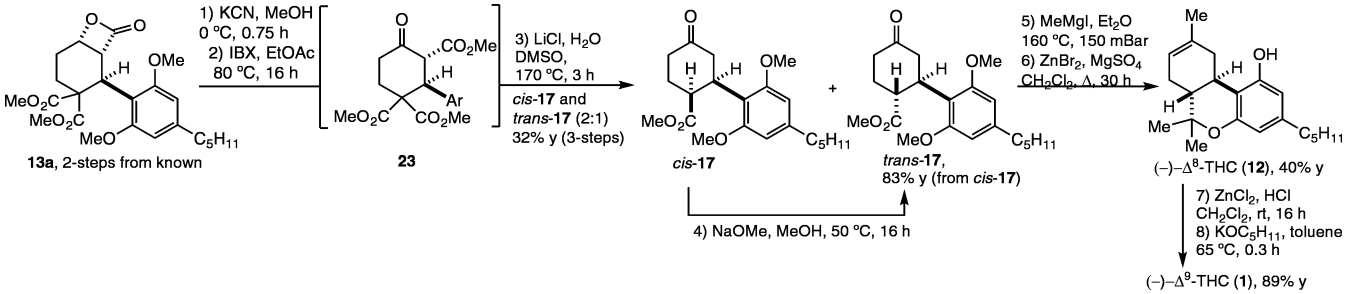
Scheme 4. Synthesis of (−)-Δ⁸ THC (12) and (−)-Δ⁹ THC (1)



alcohol **22**. Using these conditions and immediately subjecting alcohol **22** to oxidation with IBX gave *β*-keto ester **23** (Scheme 4). This material underwent dual Krapcho decarboxylation to give cyclohexanone **17** in 32% isolated yield over the three steps as a 2:1 mixture of diastereoisomers. Epimerization as previously described then gave *trans*-**17** in 83% isolated yield. Finally, using modified conditions of Carreira, global methylation followed by elimination and cyclization gave (−)-Δ⁸-THC (**12**) in 40% isolated yield over the two steps. Conversion of **12** to (−)-Δ⁹-THC (**1**) was achieved in two steps using reported conditions.[14]

Methodological discoveries have the potential to enable new approaches in multistep target-oriented synthesis. The studies herein exploited an NHC-catalyzed (4 + 2) annulation to provide cyclohexyl *β*-lactone **13a**, which could be elaborated to (−)-Δ⁸-THC (**12**) in six steps and (−)-Δ⁹-THC (**1**) in eight steps. Overall, a concise approach to these cannabinoids has been developed. In addition, by exploiting alternate cyclobutane starting materials, access to A-ring analogues of the cannabinoids should be possible. The impact of modifications in this region of **1** on CB_1 and CB_2 selectivity will be examined in subsequent studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00198.

Experimental procedures, ^1H and ^{13}C NMR spectra of new materials, and HPLC traces of chiral materials (PDF)

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Notes

The authors declare no competing financial interest.

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