Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author’s right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage. [http://researchspace.auckland.ac.nz/feedback](http://researchspace.auckland.ac.nz/feedback)

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.

Note : Masters Theses

The digital copy of a masters thesis is as submitted for examination and contains no corrections. The print copy, usually available in the University Library, may contain corrections made by hand, which have been requested by the supervisor.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Louise Angela Stubbing

A thesis submitted in fulfillment of the requirements for the degree of

Doctor of Philosophy in Chemistry

School of Chemical Sciences

The University of Auckland

August 2012
Abstract

This thesis is comprised of three parts, linked by the common thread of the synthesis of bioactive heterocycles.

PART ONE describes efforts towards the synthesis of the antimicrobial natural product platensimycin 1. Chapter 1 describes the isolation, biological activity and previously published syntheses of 1. Chapter 2 discusses the planned synthetic strategy towards 1 that centred on a tandem Rh(II)-catalysed cyclic carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition cascade to afford the tetracyclic framework of the platensimycin core. The substrate for this reaction, α-diazoketone 91, was expected to be obtained from the elaboration of a heavily functionalised Diels-Alder adduct 92. Studies towards a simplified model system 105 are described. The dienophile for the Diels-Alder cycloaddition was obtained from a Horner-Wadsworth-Emmons olefination of phosphonate 95 and chiral-pool derived aldehyde 96b. A high-pressure, high temperature Diels-Alder reaction with Danishefsky’s diene 93 successfully afforded the desired adduct 101. Functional group manipulation led to advanced intermediate 103; unfortunately, however, installation of the required diazo-moiety proved troublesome and all attempts to effect this transformation ultimately failed.

PART TWO describes a study of the proposed cycloaddition reactions of N-alkylsulfonylimines 202. The reaction of these unstable heterocumulenes with 1,3-dipoles is reported sporadically throughout the literature and much of their potential has yet to be explored. Additionally, the heterocyclic adducts proposed to derive from these cycloadditions have unusual and interesting structures that generally have yet to be described in the literature. Thus chapter 5 describes cycloadditions of 202 that were attempted with a variety of 1,3-dipoles including 1,3-dienes, azomethine ylides, donor-acceptor cyclopropanes, nitrones, azides, and nitrile oxides. A number of novel and interesting adducts were obtained from the reaction of 202 with 1,3-dienes, nitrones, and nitrile oxides. The conditions required for cycloaddition with donor-acceptor cyclopropanes and azides unfortunately appear to be incompatible with the generation of the unstable dipolarophiles 202. Preliminary antimicrobial screening of these compounds revealed that three of the adducts obtained (340a, 340c, and 340d) exhibit weak bacteriostatic activity against S. aureus.

PART THREE describes efforts towards the development of an asymmetric Mukaiyama-Michael addition of silyl enol ethers and/or silyl ketene acetals to chromones. Several C-2-substituted chromanones have been isolated from natural sources and exhibit a wide range of biological activities; yet asymmetric methods for the synthesis of this class of chromanones have only recently been described, and are summarised in chapter 7. Studies towards an asymmetric variant of the
Mukaiyama-Michael addition of silyl ketene acetal 550b to chromones based on chiral Cu(II)-bis(oxazoline) Lewis acid technology is described in chapter 8. A number of novel chromanones could be synthesised in variable yields using TMSOTf as the Lewis acid. The asymmetric variant of the conjugate addition, however, was unfortunately unsuccessful, providing chromanones 553b and 554c in low yields and with a total lack of stereoselectivity.
Acknowledgements

Firstly, I would like to thank my supervisors past and present, Dr Vittorio Caprio and Prof. Margaret Brimble, for the opportunities, support and guidance provided during this challenging endeavour. The advice of Dr David Barker and Dr Daniel Furkert has also been invaluable over the course of these (many) years.

For technical support, I would like to thank Mr Michael Walker and Mr Michael Schmidt for NMR; Ms Raisa Imatdieva and Dr Nicholas Lloyd for MS; Ms Tania Groutso for X-ray crystallographic analysis; and Mrs Anoma Ratnayake and Mr Tim Layt for general technical problem-solving.

Thanks also to Isabell Haym and Meder Kamalov for vital translations of German and Russian journal articles that would otherwise have remained incomprehensible, and Katrin Schuenemann for biological assays.

I am also grateful to all who have provided difficult to find and useful chemicals for the N-alkylsulfonylimine and chromone chapters – CSIRO, Kevin, Darcy, Christy, and Freda.

Finally, a huge thankyou to all labmates with which I have shared space, stories, and gripes, without which life would have been much duller. The list is much too long to reproduce here, but be assured that you have all made this experience enjoyable.

Louise Stubbing

February 2012.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu ) wave</td>
<td>microwave</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACP</td>
<td>acyl carrier protein</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionisation</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous (solution)</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>AS-RNA</td>
<td>antisense RNA</td>
</tr>
<tr>
<td>Aux</td>
<td>auxiliary</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>BOX</td>
<td>bis(oxazoline)</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>CAIMCP</td>
<td>catalytic asymmetric intramolecular cyclopropanation</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>CoA</td>
<td>coenzyme A</td>
</tr>
<tr>
<td>cod</td>
<td>cycloocta-1,5-diene</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>CSIRO</td>
<td>Commonwealth Scientific and Industrial Research Organisation</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>day(s)</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBNA</td>
<td>2,4-dinitrobenzoic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>d.e.</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarisation Transfer</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMAP</td>
<td>2-dimethylanilninepyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-dimethyl-N,N'-propylene urea</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ecFabF(C163Q)</td>
<td>mutant FabF enzyme derived from <em>E. coli</em> with cysteine residue #163 replaced with a glutamine residue in order to mimic the acyl-enzyme intermediate structure</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetate</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>ESI</td>
<td>electron spray ionisation</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>eV</td>
<td>electron volts</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>FAS</td>
<td>fatty acid synthesis</td>
</tr>
<tr>
<td>fod</td>
<td>6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HATU</td>
<td>N-[(dimethylamino)(3H-1,2,3-triazolo(4,5-b)pyridine-3-yloxy)methylene]-N-methylmethanaminium hexafluorophosphate</td>
</tr>
<tr>
<td>hfacac</td>
<td>hexafluoroacetylacetonato</td>
</tr>
<tr>
<td>HFIP</td>
<td>hexafluoroisopropanol</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple-Bond Correlation</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazide</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoric triamide</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear Single Quantum Correlation</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons (reaction)</td>
</tr>
<tr>
<td>iBu</td>
<td>isobutyl</td>
</tr>
<tr>
<td>IBX</td>
<td>iodoxybenzoic acid</td>
</tr>
<tr>
<td>IC\textsubscript{50}</td>
<td>median inhibition concentration</td>
</tr>
<tr>
<td>IndaBOX</td>
<td>2,2′-methylenebis[3a,8a-dihydro-8H-indeno[1,2-d]oxazole]</td>
</tr>
<tr>
<td>IndaPyBOX</td>
<td>2,6-bis[8-H-indeno[1,2-d]oxazolin-2-yl]pyridine</td>
</tr>
<tr>
<td>iPr, i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared (spectroscopy)</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenous</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>\textit{meta}-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>M</td>
<td>metal (generic)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td>MBC</td>
<td>minimum bactericidal concentration</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>med</td>
<td>medium</td>
</tr>
<tr>
<td>MEM</td>
<td>2-methoxyethoxymethyl</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl</td>
</tr>
<tr>
<td>MIC</td>
<td>minimum inhibitory concentration</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol%</td>
<td>molar percent</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MPO</td>
<td>4-methoxypyridine-(N)-oxide</td>
</tr>
<tr>
<td>MRSA</td>
<td>methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl, methanesulfonyl</td>
</tr>
<tr>
<td>NADH</td>
<td>nicotinamide adenine dinucleotide (reduced form)</td>
</tr>
<tr>
<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate (reduced form)</td>
</tr>
<tr>
<td>(n)-Bu</td>
<td>normal butyl</td>
</tr>
<tr>
<td>NCS</td>
<td>(N)-chlorosuccinimide</td>
</tr>
<tr>
<td>NFSI</td>
<td>(N)-fluorobenzenesulfonyimide</td>
</tr>
<tr>
<td>NMO</td>
<td>(N)-methylmorpholine-(N)-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NT</td>
<td>not tested</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>(o)</td>
<td><em>ortho</em></td>
</tr>
<tr>
<td>OTf</td>
<td>triflate, trifluoromethanesulfonate</td>
</tr>
<tr>
<td>(p)</td>
<td><em>para</em></td>
</tr>
<tr>
<td>(p)-ABSA</td>
<td><em>para</em>-acetamidobenzenesulfonyl azide</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetic(s)</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium <em>para</em>-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>PTSA</td>
<td><em>para</em>-toluenesulfonic acid</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>PyBOX</td>
<td>2,6-bis[4-phenyl-2-oxazolinyl]pyridine</td>
</tr>
<tr>
<td>quat.</td>
<td>quaternary</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>retention value</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>(R,R)-Et-DuPhos</td>
<td>(-)-1,2-bis((2R,5R)-2,5-diethylphospholano)benzene</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated (solution)</td>
</tr>
<tr>
<td>str</td>
<td>strong</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-<em>n</em>-butylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetra-<em>n</em>-butylammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td><em>tert</em>-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td><em>tert</em>-butyldimethylsilyl</td>
</tr>
<tr>
<td>Tbt&lt;sub&gt;s&lt;/sub&gt;</td>
<td>2,4,6-tris(bis(trimethylsilyl)methyl)benzyl</td>
</tr>
<tr>
<td>t-Bu, t-Bu</td>
<td><em>tert</em>-butyl</td>
</tr>
<tr>
<td>Tf</td>
<td>triflyl, trifluoromethanesulfonil</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>Tfacac</td>
<td>trifluoroacetylacetonato</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>t.l.c.</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Tol</td>
<td>toyl</td>
</tr>
<tr>
<td>Tr</td>
<td>trityl, triphenylmethyl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl ($p$-toluenesulfonyl)</td>
</tr>
<tr>
<td>VREF</td>
<td>vancomycin-resistant <em>Enterococcus faecium</em></td>
</tr>
<tr>
<td>wk</td>
<td>weak</td>
</tr>
</tbody>
</table>
PART ONE: Synthetic studies towards platensimycin

Chapter 1. Introduction and background

1.1 Introduction

1.1.1 Mode of action of platensimycin

1.2 Previous syntheses of platensimycin

1.2.1 First total synthesis of platensimycin – Nicolaou et al.

1.2.2 Subsequent formal syntheses of platensimycin

1.2.2.1 Syntheses towards Corey-Lalic dienone

1.2.2.2 Syntheses towards Snider’s deoxy intermediate

1.2.2.3 Friedel-Crafts cyclisation approach towards tetracyclic core

1.2.2.4 Lee’s carbonyl ylide/1,3-dipolar cycloaddition approach towards tetracyclic core

1.3 Aims

1.4 Methodology

1.4.1 Rhodium(II)-catalysed intramolecular cycloadditions

1.4.2 Trisubstituted dienophiles in the Diels-Alder reaction

Chapter 2. Discussion

1.5.1 Synthesis of starting materials

1.5.1.1 HWE partners – phosphonate and aldehyde

1.5.1.2 Synthesis of the dienophile – the HWE reaction

1.5.2 Synthesis of cyclohexenone: the Diels-Alder reaction

1.5.2.1 Attempted cycloaddition with model dienes

1.5.2.2 Cycloaddition with Danishefsky’s diene
1.5.2.3 Cycloaddition with Rawal’s diene 123 ........................................38

1.5.2.4 Modification of dienophile E-100 to enhance reactivity in the
Diels-Alder reaction .................................................................41

1.5.2.5 Optimisation of Diels-Alder reaction conditions ......................47

1.5.2.6 Lewis acid catalysis ..................................................................50

1.5.3 Elaboration to advanced ester 103 ..............................................52

1.5.3.1 Cleavage of the acetonide 101 ..............................................52

1.5.3.2 Elaboration of aldehyde 102 to advanced ester 103 ...............55

1.5.4 Attempted installation of the diazo moiety ..................................56

1.5.4.1 Attempted addition of lithiated ethyl diazoacetate 104 .............56

1.5.4.2 Revision of retrosynthesis I: addition of diazomethane ..........58

1.5.4.3 Revision of retrosynthesis II: protected α-diazoketone 188 ..........61

1.5.4.4 Revision of retrosynthesis III: C-4 carbonyl protection .............62

1.6 Conclusion ......................................................................................65

Chapter 3. Experimental Part One ..........................................................67

1.8 Experimental ....................................................................................68

1.8.1 Synthesis of HWE partners ..........................................................70

1.8.2 Synthesis of dienophiles ...............................................................74

1.8.3 Synthesis of dienes .......................................................................80

1.8.4 Diels-Alder cycloadditions ............................................................83

1.8.5 Deprotection of acetonide 101 .....................................................89

1.8.6 Elaboration to advanced ester 103 ..............................................92

1.8.7 Attempted installation of diazo-moiety ........................................94

1.8.8 Attempted TBS-protection of alcohol 190 .....................................97
PART TWO: *N*-Alkylsulfonylimines as heterodipolarophiles ........................................ 99

Chapter 4. Introduction and background ............................................................................. 101

2.1 Introduction ..................................................................................................................... 102

2.2 Preparation of *N*-alkylsulfonylimines ......................................................................... 103

2.3 Cycloaddition reactions of *N*-alkylsulfonylimines ............................................................ 105

2.3.1 Synthesis of 3-membered heterocycles ...................................................................... 105

2.3.2 Synthesis of 4-membered heterocycles ...................................................................... 105

2.3.3 Synthesis of 5-membered heterocycles ...................................................................... 110

2.3.4 Synthesis of 6-membered heterocycles ...................................................................... 110

2.3.5 Summary ....................................................................................................................... 113

2.4 Aims .................................................................................................................................. 114

Chapter 5. Discussion ............................................................................................................. 117

2.5 Synthesis of sulfamoyl chlorides ...................................................................................... 118

2.6 Reactions of *N*-alkylsulfonylimines with 1,3-dienes ....................................................... 120

2.6.1 Reactions of *N*-alkylsulfonylimines 202 with Danishefsky’s diene 93 ........... 120

2.6.2 Attempted cycloadditions of *N*-alkylsulfonylimines 202 with relatively unactivated dienes .......................................................................................... 124

2.6.3 Reaction of *N*-alkylsulfonylimines 202 with activated dienes: amino-substituted dienes ........................................................................................................... 126

2.6.4 Reaction of *N*-alkylsulfonylimines 202 with activated dienes: 2-silyloxydienes ......................................................................................................................... 132

2.6.5 Reaction of *N*-alkylsulfonylimines 202 with doubly activated dienes:
Chan’s diene 295 and Brassard’s diene 296 .................................................................. 138

2.6.6 Conclusion ....................................................................................................................... 143

2.7 Reactions of *N*-alkylsulfonylimines with 1,3-dipoles: azomethine ylides .............. 148
2.7.1 Synthesis of azomethine ylide precursors .............................................150

2.7.2 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with unstabilised azomethine ylide 393 .................................................................151

2.7.3 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with stabilised azomethine ylide 396a ..............................................................................152

2.7.4 Conclusion .................................................................................................153

2.8 Reactions of N-alkylsulfonylimines with 1,3-dipoles: donor-acceptor
cyclopropanes ....................................................................................................154

2.8.1 Synthesis of donor-acceptor cyclopropane 411 ...........................................155

2.8.2 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with
cyclopropane 411 .................................................................................................155

2.8.3 Conclusion ..................................................................................................156

2.9 Reactions of N-alkylsulfonylimines with 1,3-dipoles: nitrones ..................158

2.9.1 Synthesis of nitrone 421 ............................................................................159

2.9.2 Attempted cycloaddition of nitrone 421 with N-cyclohexyl-
sulfonylimine 202a ............................................................................................159

2.9.3 Conclusion ..................................................................................................161

2.10 Reactions of N-alkylsulfonylimines with 1,3-dipoles: azides .....................162

2.10.1 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with
azide 432 ..............................................................................................................162

2.10.2 Conclusion ................................................................................................163

2.11 Reactions of N-alkylsulfonylimines with 1,3-dipoles: nitrile oxides ..........164

2.11.1 Synthesis of nitrile oxides and their precursors .......................................166

2.11.2 Attempted cycloadditions of N-cyclohexylsulfonylimine 202a with
nitrile oxides 299a and 299b .............................................................................167
2.11.3 Investigation of alternative methods for the generation of nitrile oxides:
dehydration of a nitroalkane ................................................................. 174

2.11.4 Investigation of alternative methods for the generation of nitrile oxides:
dehydration of O-silylated hydroxamic acids ........................................ 176

2.11.5 Conclusion .................................................................................. 177

2.12 Conclusion .................................................................................... 179

Chapter 6. Experimental Part Two .............................................................. 181

2.13 Experimental .................................................................................. 182

2.13.1 Synthesis of sulfamoyl chlorides .................................................. 182

2.13.2 Synthesis of dienes ........................................................................ 184

2.13.3 Cycloadditions of N-alkylsulfonylimines 202a – 202e with dienes 93,
123, and 292 – 296 .................................................................................. 187

2.13.4 Synthesis of azomethine ylide precursor 395a ................................ 215

2.13.5 Synthesis of donor-acceptor cyclopropane 411 ............................ 215

2.13.6 Synthesis of nitrone 421 ............................................................... 217

2.13.7 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with
nitrone 421 ............................................................................................. 217

2.13.8 Synthesis of nitrile oxides ............................................................. 218

2.13.9 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with
nitrile oxides ......................................................................................... 222

PART THREE: Mukaiyama-Michael additions to chromones ....................... 225

Chapter 7. Introduction and background .................................................. 227

3.1 Chromones and their derivatives as privileged scaffolds ...................... 228

3.1.1 C-2-aromatic chromanones: flavanones ........................................ 228

3.1.2 C-2-aliphatic chromanones ............................................................ 229
3.1.3 2-γ-butyrolactone substituted chromanones ........................................... 230
3.2 Synthetic methods for the asymmetric synthesis of 2-substituted chromanones ...... 233
  3.2.1 Asymmetric intramolecular oxa-Michael addition ....................................... 233
  3.2.2 Asymmetric 1,4-additions to chromones .................................................. 236
3.3 Conjugate addition of silyl enol ethers and silyl ketene acetals to chromones .......... 239
3.4 Aims .............................................................................................................. 242
3.5 Methodology ................................................................................................. 246
Chapter 8. Discussion ......................................................................................... 249
3.6 Synthesis of chromones .................................................................................. 250
  3.6.1 Synthesis of unsubstituted chromone 474 .................................................. 250
  3.6.2 Synthesis of C-3 substituted chromones 547a-b and 547e-f ....................... 252
3.7 Model additions of silyl enol ethers to chromones ....................................... 255
  3.7.1 Synthesis of silyl enol ether 550a ................................................................ 255
  3.7.2 Addition of 550a to chromone 474 ............................................................. 256
  3.7.3 Investigation into the choice of Lewis acid ................................................. 259
  3.7.4 Investigation into an activating group at C-3: 3-acetylchromone 547a ......... 260
  3.7.5 Investigation into a removable activating group at C-3: 3-tert-
  butoxycarbonylchromone 547b .................................................................... 262
  3.7.6 Summary of addition of silyl enol ether 550a to chromones ...................... 264
3.8 Model additions of silyl ketene acetals to chromones .................................... 265
  3.8.1 Synthesis of silyl ketene acetal 550b ......................................................... 265
  3.8.2 Addition of silyl ketene acetal 550b to chromones 474 and 547a-c .......... 265
  3.8.3 Addition of silyl ketene acetal 550b to chromones 547d-g ....................... 266
  3.8.4 Conclusion ............................................................................................... 267
3.9 Chiral catalysis in the conjugate addition of silyl ketene acetals to chromones ........................................271

3.9.1 Attempted asymmetric addition of silyl ketene acetal 550b to chromone 474 ........................................................................................................271

3.9.2 Attempted asymmetric addition of silyl ketene acetal 550b to 3-acetylchromone 547a .................................................................................274

3.9.3 Conclusion ..........................................................................................275

3.10 Future work ...............................................................................................278

Chapter 9. Experimental Part Three ................................................................283

3.11 Experimental .........................................................................................284

3.11.1 Synthesis of chromones .......................................................................284

3.11.2 Conjugate additions to chromones .......................................................290

3.11.3 Chiral HPLC traces for attempted asymmetric conjugate additions ..........301

REFERENCES .....................................................................................................303

APPENDIX ........................................................................................................333

A1. Crystal data and structure refinement for exo-171 ........................................334

A2. Crystal data and structure refinement for 210a ............................................340
PART ONE

Synthetic studies towards platensimycin
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones
CHAPTER ONE

Introduction and background
1.1 Introduction

The advent and rise of bacterial species resistant to available therapy presents an alarming and ongoing challenge for clinicians and researchers alike. Moreover, antibiotics such as methicillin and particularly vancomycin, traditionally the drug of last resort for bacterial infection, are becoming increasingly ineffective as resistant bacterial strains emerge. The increased incidence of antibacterial resistance, coupled with the inability of existing therapies to efficiently treat and eradicate resistant strains, underscores the importance of continuing research into the discovery and development of novel and effective antibacterial drugs.

![Structure of platensimycin 1](image)

Figure 1.1.1. Structure of platensimycin 1.

Platensimycin is one such potential drug, recently discovered and characterised by Merck. Isolated from a strain of bacterium *Streptomyces platensis* found in soil samples, platensimycin shows potent, broad spectrum antibacterial activity against Gram positive organisms, including vancomycin-, linezolid- and methicillin-resistant strains, via inhibition of bacterial fatty acid synthesis (FAS).

Platensimycin was isolated from a fermentation broth of the MA7327 and MA7331 strains of *S. platensis* collected from South African and Spanish soil samples respectively, yielding between 2 and 4 mgL$^{-1}$ of product. Separation of the crude methanolic extract via sequential ion-exchange and reverse-phase HPLC was guided by bioassay to identify platensimycin-containing fractions.

1.1.1 Mode of action of platensimycin

Platensimycin has been shown to have broad-spectrum antibacterial activity against Gram-positive bacteria via inhibition of type II fatty acid biosynthesis (FASII). FAS is an integral process for the survival and therefore proliferation of microbial species, providing the building blocks for – among other essential processes – bacterial cell wall synthesis.

Fatty acid biosynthesis is an attractive target for antibacterial treatments due to two main factors. Firstly, bacterial (type II) FAS is carried out by a series of dissociated enzymes through a “ping-pong” mechanism, distinct from the mammalian (type I) FAS-complex, allowing specific targeting of the pathogenic organism without consequent toxicity. Secondly, FASII enzymes are highly
conserved across bacterial species, providing an opportunity for broad-spectrum antibacterial activity.⁷

![Figure 1.1.2. Type II fatty acid elongation cycle.](image)

Indeed, inhibition of bacterial fatty acid biosynthesis is hardly a novel mechanism of action; several antibacterial agents act by disrupting the synthesis of fatty acids essential to the survival of the organism. Examples of FASII inhibitors currently in use include isoniazid 2, an anti-tuberculosis agent, and triclosan 3, a widely-used antiseptic, which inhibit the enoyl-ACP reductase (FabI).⁹⁻¹² Platensimycin, however, inhibits the elongation condensing enzyme, β-ketoacyl-ACP synthase (FabF), and therein lies the novelty of its mechanism of action. Though other inhibitors of FabF are known – including thiolactomycin 4 and cerulenin 5¹³ – they, in contrast to platensimycin, exhibit poor in vivo efficacy. The more recently discovered phomallenic acids A-C, ⁶ – ⁸,¹⁴ and dual FabF/FabH inhibitor platencin ⁹,¹⁵ closely related to platensimycin, are further examples of FabF inhibitors whose potential therapeutic value has yet to be developed. Hence, as FabF inhibition is currently unexploited in the antibacterial drug market, it is expected that there will be no cross-resistance with existing multiresistant bacterial strains.
Recently, however, the validity of targeting FASII for potential antibacterial activity has been questioned. Brinster et al argued that the required fatty acids could instead be acquired from the bloodstream of the host when de novo synthesis was inhibited. However a subsequent publication has refuted this mechanism in the specific case of *Staphylococcus aureus*, and showed that FASII is indeed essential for this Gram-positive organism. Compellingly, they demonstrated that the MIC for platensimycin was unchanged in the presence of human serum containing fatty acids. This, in combination with the clinical success of FASII inhibitors such as 2 and 3 confirm that FASII inhibitors are not as generally impractical as Brinster et al had asserted, though it may be a concern in selected cases.

Platensimycin’s novel mechanism of action was initially discovered using an equally novel activity screening assay. The technique, known as whole-cell antisense differential sensitivity assay, involves the introduction of *fabF* antisense-mRNA (AS-RNA) into *S. aureus*, thereby decreasing expression of FabF/H; these cells then become hyper-sensitive to compounds that inhibit the enzyme. Inhibition can be quantified by comparison of the zone of inhibition on a *fabF* AS-RNA seeded plate to a control plate. Over 250,000 compounds were screened against plates of *fabF* AS-RNA modified *S. aureus*; upon comparison with control plates the researchers were able to discern which compounds had anti-FabF/H activity. In cell-free single-enzyme assays, platensimycin was shown to inhibit FabF with an IC$_{50}$ of 48 nM in *S. aureus* and 160 nM in *Escherichia coli*, while inhibition of
FabH was much weaker, with an IC\textsubscript{50} of 67 μM.\textsuperscript{4} Consequently, platensimycin can be said to inhibit FabF selectively.

Antibacterial activity was assessed against several genotypes across a number of organisms.\textsuperscript{4} Platensimycin \textbf{1} exhibited an impressive MIC of between 0.5-1 μg.mL\textsuperscript{-1} across all \textit{S. aureus} genotypes tested, including macrolide-, linezolid-, and vancomycin-resistant strains; moreover, platensimycin was active against macrolide-resistant \textit{Enterococcus faecalis}, vancomycin-intermediate-resistant \textit{Enterococcus faecium}, and \textit{Streptococcus pneumoniae}. Furthermore, \textbf{1} showed low mammalian toxicity, in both HeLa cytotoxicity assays and rodent studies. Though \textbf{1} exhibited some activity against efflux-negative \textit{E. coli}, subsequent lack of activity against the wild type suggests that platensimycin will prove to be ineffective against Gram-negative bacteria in general. In addition, therapeutic serum levels were only attainable \textit{via} continuous \textit{i.v.} infusion, which is hardly an ideal administration route. Platensimycin, therefore, is a useful lead compound and several synthetic studies that have been published to date in an attempt to improve PK properties and devise a clinically useful drug candidate.

Analysis of a co-crystal of platensimycin with a mutated form of FabF shows the active-site interactions that are essential for binding (Figure 1.1.4). The benzoic acid interacts with histidine active-site residues H340 and H303, in addition to an edge-to-face π-interaction with phenylalanine residue F400. These interactions are crucial for bioactivity, as both natural and synthetic analogues with modifications to the western aromatic hemisphere (e.g. platensimycin B series, \textbf{10} – \textbf{13} figure 1.1.5) exhibit dramatic losses in antimicrobial activity compared to \textbf{1}.\textsuperscript{20-26}

![Figure 1.1.4. Platensimycin 1 and interactions with mutated (to mimic the acyl-enzyme intermediate) ecFabF(C163Q).](image-url)
Modification to the eastern hemisphere of the molecule is tolerated to a much greater extent, though the activity of these analogues decreases by at least one order of magnitude in comparison to 1 (Table 1.1.1). In addition, retention of antibacterial activity appears to be dependent upon the conformation of the enone ring, affecting the positioning of the enone carbonyl group and thus interaction with alanine residue A309. The synthetic analogues 14 – 16 have been shown to exhibit antimicrobial activity comparable, though still inferior, to 1. To date, two analogues have been reported (7-phenylplatensimycin 17 and 11-methyl-7-phenylplatensimycin 18) that exhibit increased antimicrobial activity compared to platensimycin (Figure 1.1.6, table 1.1.2).
### Table 1.1.1. Comparison of MIC values (μg.mL⁻¹) of platensimycin 1, carbaplatensimycin 14, and adamantaplatensimycin 15 over a range of Gram-positive bacterial species.\(^{27}\)

<table>
<thead>
<tr>
<th>Bacterial strain</th>
<th>1</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>0.2-0.4</td>
<td>1.1-2.2</td>
<td>1.3-1.8</td>
</tr>
<tr>
<td>VREF</td>
<td>0.4-0.8</td>
<td>1.1-2.2</td>
<td>1.3-1.8</td>
</tr>
<tr>
<td>S. aureus</td>
<td>0.2-0.6</td>
<td>0.4-1.1</td>
<td>1.1-2.2</td>
</tr>
<tr>
<td>S. epidermis</td>
<td>&lt;0.2</td>
<td>0.2-0.5</td>
<td>0.5-1.1</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>2.2-4.4</td>
<td>17.6-22.0</td>
<td>8.8-11.1</td>
</tr>
<tr>
<td>Lysteria monocytogenes</td>
<td>&lt;0.2</td>
<td>1.1-2.2</td>
<td>3.3-4.4</td>
</tr>
</tbody>
</table>

### Table 1.1.2. Comparison of MIC values (μg.mL⁻¹) of platensimycin 1, 7-phenylplatensimycin 17, 11-methyl-7-phenylplatensimycin 18, and (-)-myrtamycin 16 over a range of Gram-positive bacterial species.\(^{33-35}\) NT = not tested.

<table>
<thead>
<tr>
<th>Bacterial strain</th>
<th>1</th>
<th>17</th>
<th>18</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA S. aureus</td>
<td>1</td>
<td>0.25</td>
<td>&lt;0.25</td>
<td>NT</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.25</td>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>16</td>
</tr>
<tr>
<td>VREF</td>
<td>0.4-0.8</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>B. subtilis (3160)</td>
<td>1</td>
<td>NT</td>
<td>NT</td>
<td>4</td>
</tr>
</tbody>
</table>
1.2 Previous syntheses of platensimycin

Over 20 approaches towards platensimycin 1 have been described since the first report of its isolation in 2006. Several reviews on the subject have also been published,\textsuperscript{36-40} the most recent of which covers not just synthesis of platensimycin, but also platencin and their respective analogues.\textsuperscript{40} For the purposes of this thesis, the first total synthesis from Nicolaou’s group,\textsuperscript{41} and the rhodium-catalysed cyclic carbonyl ylide/1,3-dipolar cycloaddition approach from E. Lee’s group,\textsuperscript{42} as well as any other syntheses not covered in the review mentioned above, will be discussed below.

1.2.1 First total synthesis of platensimycin – Nicolaou et al

The first total synthesis of platensimycin 1 was reported not long after the report of its isolation by Nicolaou and co-workers.\textsuperscript{41} Their retrosynthetic analysis – and indeed all others since – starts with the obvious disconnection of the amide bond to give the resorcylic acid-derived fragment 19 and platensic acid 20 (Figure 1.2.1). Platensic acid 20 can be further simplified to the key tetracyclic core 21 via double alkylation at C-4. Cleavage of the C-15 ether bond in 21 generates a tertiary carbocation synthon, and cleavage of the C-9 – C-10 bond in the secondary alcohol gives compound 22 as an advanced intermediate. Thus in the forward direction, sequential ketyl radical formation and stereoselective conjugate addition of aldehyde 23, followed by regioselective ether formation of the resultant alcohol gives the tetracyclic core 21. Aldehyde 23 can be accessed via cycloisomerisation of enyne 24.

![Figure 1.2.1. Retrosynthetic analysis of platensimycin by Nicolaou et al.\textsuperscript{41}](image)

Synthesis of aldehyde 23 began with double alkylation of 3-ethoxy-cyclohexen-2-one 25 (Scheme 1.2.1). Reduction of dialkylated enone 28 with DIBAL-H was followed by acidic hydrolysis. The
TBS-ether was then reintroduced to give enone 29. Treatment of 29 with Trost’s [CpRu(MeCN)₃]PF₆ catalyst in acetone afforded spirocyclic enone 30 as an inconsequential mixture of diastereomers. Formation of the trimethylsilyl enol ether and subsequent oxidation with Pd(OAc)₂ gave the dienone, and acidic hydrolysis of the TBS-ether furnished the required spirocyclic aldehyde 23.

Scheme 1.2.1. Reagents and conditions: a) LDA, 26, THF, -78 → 22 °C, 6 h, 92%; b) LDA, 27, THF, -78 → 22 °C, 13 h, 97%; c) (i) DIBAL-H, PhMe, -78 → -20 °C, 2 h; (ii) MeOH, 2 N aq. HCl, -20 → 22 °C, 2 h; d) TBSCI, imidazole, DMF, 22 °C, 20 min, 84% over two steps; e) [CpRu(MeCN)₃]PF₆, acetone, 22 °C, 1.5 h, 92%, d.r. 1:1; f) LiHMDS, TMSCl, THF, -78 °C, 2 h; g) Pd(OAc)₂, MeCN, 22 °C, 1.5 h, 68% over two steps; h) 1 N aq. HCl/THF (1:1), 22 °C, 2 h, 85%.

Elaboration to platensic acid 20 began with one-electron reduction of aldehyde 23 (Scheme 1.2.2). Etherification of the resulting inseparable mixture of diastereomeric alcohols 31 was effected with TFA. The undesired diastereomer of the alcohol was recovered unchanged. Sequential stereoselective double alkylation of tetracyclic core 21 using KHMDS with methyl iodide, followed by KHMDS and allyl iodide afforded substituted enone 34 in good yield and with minimal diastereomeric side-products. 34 was converted to carboxylic acid 20 via olefin cross-metathesis between 34 and boronate 35 under the influence of second generation Grubbs catalyst 36, giving vinyl boronate 37 as a 6:1 mixture of E:Z isomers. Oxidation with trimethylamine N-oxide produced aldehyde 38 in excellent yield. Further Pinnick oxidation of 38 completed synthesis of the eastern fragment 20 in 8.5% overall yield.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Scheme 1.2.2. Reagents and conditions: a) SmI₂, HFIP, THF/HMPA (10:1), -78 °C, 1 min, 46%, ca. 2:1 d.r.; b) TFA/CH₂Cl₂ (1.8:1), 0 °C, 1.5 h, 87%; c) KHMDS, MeI, THF/HMPA (5:1), -78 → -10 °C, 2 h, 88%; d) KHMDS, THF/HMPA (5:1), -78 → -10 °C, 2 h, 79%; e) 35, 36, CH₂Cl₂, 40 °C, 6 h, 85% ca. 6:1 E/Z; f) Me₃NO₃, THF, 65 °C, 2 h, 95%; g) NaOCl₂, 2-methyl-2-butene, NaH₂PO₄, t-BuOH/H₂O (1:1), 22 °C, 15 min, 95%.

Construction of the resorcylic acid fragment 19 began with protection of 2-nitroresorcinol 39 as the bis-MOM-ether (Scheme 1.2.3). Catalytic hydrogenation of 40, followed by Boc protection of the resulting amine gave 42. The methyl ester was installed through in situ silylation of amide 42, followed by lithiation of the aromatic ring, and subsequent addition of Mander’s reagent gave ester 43. Finally, deprotection of the Boc ester 43 provided amine 19 in 36% overall yield in preparation for the completion of the total synthesis.

Scheme 1.2.3. Reagents and conditions: a) NaH, MOMCl, THF, 0 → 22 °C, 1.5 h, 82%; b) H₂, 10% Pd/C, MeOH/EtOAc (10:1), 22 °C, 12 h, 99%; c) Boc₂O, 40 °C, 4 h, 99%; d) (i) n-BuLi, TMSCl, -78 °C, 15 min; (ii) n-BuLi, methyl cyanoformate, THF, -78 °C, 30 min; (iii) 1 N aq. HCl, 22 °C, 30 min, 54%; e) 1,2-dichlorobenzene, 205 °C (μwave), 5 min, 83%.

Union of the resorcylic acid-derived fragment 19 and platensic acid 20 was accomplished by treatment of the two fragments with HATU and triethylamine in good yield (Scheme 1.2.4).
Hydrolysis of the methyl ester, followed by deprotection of the MOM-ethers produced racemic platensimycin in excellent yield. Platensimycin 1 was therefore obtained in 6.5% over a longest linear sequence of 17 steps.

Scheme 1.2.4. Reagents and conditions: a) 19, 20, HATU, Et$_3$N, DMF, 22 °C, 26 h, 85%; b) LiOH, THF/H$_2$O (4:1), 45 °C, 2 h; then 2 N aq. HCl, THF/H$_2$O (3:1), 45 °C, 10 h, ca. 90% over 2 steps.

1.2.2 Subsequent formal syntheses of platensimycin

After publication of the first total synthesis, there was an explosion of formal syntheses reported in the literature – both racemic and enantioselective – employing a variety of different strategies. A summary of these is provided in figure 1.2.2. Of these, two methods published by Corey and Lalic,$^{43}$ and Snider et al,$^{44}$ provided the intermediates 46 and 47, respectively, that have themselves been the target of formal syntheses. The most popular target for the formal syntheses, however, remains the unadorned tetracyclic core 21.

In addition, Nicolaou et al had suggested, at the conclusion of their racemic total synthesis, that the sequence could be made enantioselective by using a chiral catalyst at the cycloisomerisation stage. Thus, methods towards the enantioselective synthesis of their spirocyclic dienone 23 have also been the subject of several studies.

The majority of these syntheses have been covered in either a comprehensive – and the most recent – review by Saleem et al,$^{40}$ or Kaliappan and Palanichamy’s review from early 2010.$^{38}$ However there remain four syntheses towards platensimycin 1 reported to date that are not covered in the aforementioned reviews; these will be discussed herein. In addition, E. Lee and coworkers’ tandem carbonyl ylide formation/1,3-dipolar cycloaddition approach$^{42}$ will also be discussed due to its similarity to our proposed synthetic strategy.
Figure 1.2.2: Summary of approaches towards platensimycin 1
1.2.2.1 Syntheses towards Corey-Lalic dienone 46

Two convergent approaches access the Corey-Lalic dienone 46 via the oxatropane 53 have been reported recently (Scheme 1.2.5).45,46 The first utilises a copper-catalysed vinyl oxirane rearrangement47 to give the ring-expanded product 53 from epoxide 61. The later report describes an alternative method for the synthesis of 53 via Lewis acid-catalysed intramolecular 1,3-dipolar cycloaddition of a donor-acceptor cyclopropane 62.46 The initial cycloadduct 63 can then be transformed directly to the common oxatropane 53 by monodecarboxylation, thereby constituting a formal synthesis of platensimycin 1.

![Scheme 1.2.5. Reagents and conditions:](image)

**Scheme 1.2.5. Reagents and conditions:** a) [Cu(hfacac)₂], PhMe, 150 °C, 0.5 h, 81%; b) LiEt₃BH, THF, -78 °C → r.t., 1.5 h, 97%; c) TsCl, Et₃N, CH₂Cl₂, 0 °C → r.t., 10 h, 96%; d) Et₃SiH, B(C₆F₅)₃, CH₂Cl₂, r.t., 1 h, 84%; e) TBAF, THF, 100 °C, 1 h, 91%; f) Sc(OTf)₃, DCE, r.t., 2 h, 87%; g) LiCl, wet DMSO, 160 °C, 10 h, 79%.

The most recent approach to advanced dienone 46 to be reported is based on an intramolecular Friedel-Crafts acylation and iodoetherification/intramolecular substitution (Scheme 1.2.6).48 Stobbe condensation of p-anisaldehyde 65 and dimethylsuccinate, followed by enantioselective reduction of the resulting alkene gave the free acid in excellent yield and enantioselectivity. The intramolecular Friedel-Crafts acylation then took place upon treatment with polyphosphoric acid, and the methoxy group was deprotected with HBr, giving tetralone 66. Formation of the enolate, and *in situ* methylation with methyllithium afforded the tertiary alcohol in excellent yield with minimal racemisation of the stereocentre. Dehydration of the alcohol was accomplished using Burgess’ reagent, and the ketone reduced with sodium borohydride to give the alcohol 67 with high diastereoselectivity. Iodoetherification of 67 efficiently constructed the third ring, and subsequent
treatment with potassium tert-butoxide in refluxing tert-butanol installed the final ring to give the
tetracyclic dienone 46 in 44.9% yield over 9 steps.

Scheme 1.2.6. Reagents and conditions: a) dimethyl succinate, KOtBu, t-BuOH, 100 °C, 0.5 h, 73%; b) [Rh(cod)2]BF4, (R,R)-Et-DuPhos, H2 (150 psi), CH2Cl2, r.t., 24 h, quant., e.e. 98%; c) PPA, 50 °C, 1 h, 83%; d) HBr, H2O, 90 °C, 2 h, 95%; e) (i) 2 eq. LiHMDS, THF, -78 °C, 0.5 h; (ii) MeLi, -78 °C → r.t., quant., e.e. 96%; f) Burgess reagent, THF, r.t., 2 h, 97%; g) NaBH4, MeOH, -10 °C, 1 h, 96%, d.r. 15:1; h) I2, NaHCO3, MeCN, r.t., 2 h, 95%, d.r. 9:1; i) KOtBu, t-BuOH, r.t. → reflux, overnight, 98%.

1.2.2.2 Syntheses towards Snider’s deoxy intermediate 47

Alternatively, a somewhat lengthy sequence, applied to the synthesis of both platensimycin 1 and
platencin 9, was reported recently by Hirai and Nakada (Scheme 1.2.7).49 Their approach builds
Snider’s intermediate 47 in an enantioselective manner through a catalytic asymmetric
intramolecular cyclopropanation (CAIMCP) of advanced α-diazo-β-keto sulfone 69. The α-diazo-β-
keto sulfone 69 itself is accessed in 10 steps from benzoic acid.49 The CAIMCP reaction with
bis(oxazoline) ligand 70 provided the cyclopropane 48 in good yield and enantioselectivity.
Regioselective ring-opening of the cyclopropane, followed by several functional group
manipulations, were required to convert 48 to 71. The sulfide was removed upon treatment with
Raney-nickel. Deprotection of the alcohol, oxidation, and subsequent Wittig reaction gave the enol
ether 72. Conversion to the enone via Nicolaou’s IBX-MPO protocol, and acid-catalysed cyclisation
afforded the tricyclic aldehyde 73. The aldehyde was converted to an exo-methylene by reduction to
the alcohol, iodination, and elimination with DBU. Stereoselective reduction of the alcohol with K-
Selectride® and subsequent TFA-induced etherification provided Snider’s intermediate 47 in 5.8%
overall yield and 29 steps from benzoic acid.
1.2.2.3 Friedel-Crafts cyclisation approach towards tetracyclic core 21

Lear and Eey have reported a route towards platensimycin 1 using a bismuth(III)-catalysed Friedel-Crafts cyclisation and stereoselective reduction to construct the tetracyclic core (Scheme 1.2.8).\(^\text{50}\) Sharpless epoxidation of allyl alcohol 74 (prepared in 81% yield from eugenol)\(^\text{50}\), followed by allyl Grignard addition and selective tosylation gave the tosyl alcohol 75. Dihydroxylation of the double bond and cyclisation of the resulting triol gave the lactol 56 in excellent yield. A large number of conditions were screened for the Friedel-Crafts cyclisation; ultimately, bismuth(III) triflate, in the presence of lithium perchlorate to overcome the Lewis basicity of the sulfonate group was the most successful. Deprotection of the benzyl group then afforded the tricycle 76. Intramolecular alkylative dearomatisation promoted by TBAF in xylene gave the tetracyclic dienone 77. Sequential stereoselective reduction of the dienone in the presence of D-phenylalanine derived-amine 78 and Hantzsch hydride donor 79 gave the methoxy-ketone 80 in good yield and in a 4:1 ratio in favour of the desired isomer. Demethylation, conversion to the mesylate, and subsequent elimination finally afforded the tetracyclic core of platensimycin 21 in 22% yield and 17 linear steps from eugenol.
Scheme 1.2.8. Reagents and conditions: a) L-(+)-DIPT, Ti(O\text{Pr})_4, t-BuOOH, CH_2Cl_2, -25 °C, 98%, e.e. 91%; b) allyl magnesium chloride, THF, -20 °C; c) TsCl, n-Bu_2SnO, Et_3N, CH_2Cl_2, 91% over 2 steps; d) (i) OsO_4, NMO; (ii) NaIO_4, THF/H_2O (2:1), 85%; e) 5 mol% Bi(OTf)_3, LiClO_4, CH_2Cl_2, 3.5 h, 94%; f) H_2, Pd/C, THF; g) TBAF, xylene, 130 °C, 4 h, 86% over 2 steps; h) 20 mol%, 78, 79, dioxane, 60 °C, Ar sealed, 130 h; i) H_2, Pd/C, EtOAc/ethanolic KOH (2:1), 73% over 2 steps, 80a:80b 4:1; j) AlCl_3, TBAI, MeCN/CH_2Cl_2 (2:1), 0 °C, 83%; k) MsCl, Et_3N, CH_2Cl_2, 0 °C → r.t.; l) LiBr\cdot H_2O, Li_2CO_3, DMSO, 150 °C, 72% over 2 steps.

1.2.2.4 Lee’s carbonyl ylide/1,3-dipolar cycloaddition approach towards tetracyclic core 21

Two separate routes towards 21 via tricyclic diketone 60 have been published; the first, by E. Lee et al, from early 2008 is unfortunately similar to the route which we ourselves have proposed. They had also identified the possibility of constructing the tricyclic ether through a rhodium catalysed, tandem cyclic carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition strategy. In their case, however, they constructed the tricyclic ether first and then appended the enone ring (Scheme 1.2.9).

Their synthesis began with reaction of isopropyl cyanoacetate 81 with (S)-propylene oxide 82, and subsequent reaction of the resulting lactone with (E)-iodoallyl iodide gave nitrile lactone 83 as the major product, with a small amount (13%) of the epimer also obtained. Conversion to the thioester, followed by oxidation with Dess-Martin periodinane afforded ketone 84. The thioester was then hydrolysed and converted to the corresponding α-diazoketone 85 via the isobutyl-mixed anhydride by treatment with diazomethane. Subjection of the α-diazoketone 85 to rhodium(II) acetate effected formation of the cyclic carbonyl ylide, and subsequent intramolecular 1,3-dipolar cycloaddition
afforded the desired tricyclic isomer 88 in 83% yield. A small amount of the isomeric tricycle 87 and cyclopropane 86 were also obtained (8% each).

Scheme 1.2.9. Reagents and conditions: a) 82, NaH, THF, reflux; (ii) (E)-I(CH)2CHI, 63%; b) t-BuSH, Me2Al, CH2Cl2, 0 °C; c) Dess-Martin periodinane, CH2Cl2, 0 °C, 92% over 2 steps; d) 1 N KOH, MeOH; e) (i) isobutyl chloroformate, Et3N, Et2O, 0 °C; (ii) CH3N2, Et2O, 0 °C → r.t., 88% over 2 steps; f) 3 mol% [Rh2(OAc)4], CH2Cl2, r.t., 86 8%, 87 8%, 88 83%; g) H3PO2, 1-ethylpiperidine, Et3B, MeOH, 0 °C, 94%; h) MeCOCH2PO(OMe)2, DIPEA, LiCl, MeCN, 90%; i) (i) Me2PhSiH, 2 mol% [RhCl(Ph3P)3], PhMe, 60 °C; (ii) DIBAL-H, PhMe, -40 °C; (iii) AcOH/H2O (1:1), 0 °C; j) 2 N HCl, THF, 0 °C, 59% over 2 steps; k) TsOH, PhMe, reflux, 96%.

With the tricyclic core 88 in hand, the authors then installed the required enone functionality through an intramolecular aldol reaction. Thus, reduction of the iodide 88 with hypophosphite and Horner-Wadsworth-Emmons reaction of the ketone gave enone 89. A one-pot hydrosilylation, reduction, and subsequent imine hydrolysis sequence then afforded the intramolecular aldol precursor 60, which was consequently converted to the tetracyclic core of platensimycin 21 upon treatment with p-toluenesulfonic acid in refluxing toluene in 20.3% overall yield from 81 and 82. This synthesis remains the best yielding preparation of tetracyle 21 reported to date.
1.3 Aims

Our approach to platensimycin 1 centres on the rhodium(II)-catalysed tandem carbonyl ylide formation-cycloaddition of a suitably substituted cyclohexenone 91 to construct the tetracyclic core (Figure 1.3.1).

Thus treatment of 91 with Rh$_2$(OAc)$_4$ should decompose the diazo moiety, leading to formation of a carbonyl ylide. Trapping of the ylide via an intramolecular 1,3-dipolar cycloaddition should then occur, providing the complex tetracyclic framework of platensimycin in one pot from 91. $\alpha$-Diazo ketone 91 can be accessed from enone 92, obtained in a stereoselective manner by the Diels-Alder reaction of Danishefsky’s diene 93 and trisubstituted olefin 94. Trisubstituted olefin 94 can be further simplified by way of a Wittig disconnection to give phosphonate 95 and (S)-glyceraldehyde acetonide 96a.

Allyl phosphonate 95 is obtained from the alkylation of triethyl phosphonoacetate 97 with allyl bromide (Scheme 1.3.1). (S)-Glyceraldehyde acetonide 96a is available from L-ascorbic acid in 3 steps; union of the two fragments via Horner-Wadsworth-Emmons olefination generates trisubstituted olefin 94. Diels-Alder cycloaddition with Danishefsky’s diene 93, followed by acidic workup selectively affords enone 92 from the initial endo-adduct. Oxidative cleavage of the...
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Acetonide reveals the aldehyde; hydrolysis of the ester and subsequent treatment with isobutyl chloroformate and diazoethane provides advanced α-diazoketone 91.

**Scheme 1.3.1. Reagents and conditions:** a) base, allyl bromide; b) base, 96a; c) 93, reflux; d) H\(^+[\), NaIO\(_4\); e) base; f) (i) Et\(_3\)N, isobutyl chloroformate; (ii) CH\(_3\)CHN\(_2\).

Treatment of 91 with Rh\(_2\)(OAc)\(_4\) generates intermediate carbonyl ylide 99, which should then undergo 1,3-dipolar cycloaddition with the pendant allyl moiety to give tetracyclic enedione 90 (Scheme 1.3.2). Advanced intermediate 90 may in turn be further elaborated to platensimycin 1. The inherent flexibility of the cyclisation-cycloaddition step also allows for the construction of tetracyclic analogues of platensimycin from a variety of substituted precursors.

**Scheme 1.3.2. Reagents and conditions:** a) Rh\(_2\)(OAc)\(_4\).

However insertion of rhodium into the aldehyde is a possible side process\(^{51,52}\) therefore synthesis of a model system, ketone 105, will be undertaken to investigate the feasibility of the cyclisation-cycloaddition. In the interest of rapid access to 105, (R)-glyceraldehyde 96b – available from D-mannitol in 2 steps – rather than 96a, will be used for the synthesis of model ketone 105 (Scheme 1.3.3).
Scheme 1.3.3. **Reagents and conditions:** a) base, 96b; b) H⁺, NaIO₄; c) MeMgBr; d) oxidation; e) (i) base; (ii) Et₃N, isobutyl chloroformate; (iii) n-BuLi, 104.

Model ketone 105 can be accessed via modification of aldehyde 102. Addition of methyl magnesium bromide affords the secondary alcohol, which is then oxidised to ketone 103. Hydrolysis of the ester and conversion to the carbonic mixed anhydride, followed by addition of lithiated ethyl diazoacetate 104 gives the α-diazo ester 105. α-Diazoester 105 will then be used to probe the experimental conditions required for successful Rh(II)-catalysed cyclisation-cycloaddition.
1.4 Methodology

1.4.1 Rhodium(II)-catalysed intramolecular cycloadditions

Our synthetic approach towards platensimycin relies upon a rhodium(II)-catalysed tandem cyclisation-cycloaddition of an appropriately substituted cyclohexenone to construct the tetracyclic core 21. Extensive studies by Padwa et al.,\textsuperscript{53,54} have shown that the tandem sequence is initiated by the rhodium(II)-catalysed decomposition of an α-diazo ketone to give the rhodium carbenoid 107. The carbenoid inserts into the carbonyl group to afford a carbonyl ylide 108, which may then be trapped by a wide range of dipolarophiles. In cases where the carbonyl moiety is tethered to the α-diazo ketone, a cyclic carbonyl ylide results.

![Figure 1.4.1. Generalised rhodium(II)-catalysed carbonyl ylide formation and subsequent trapping via 1,3-dipolar cycloaddition.](image)

The dipolarophile may be tethered or external. Intramolecular trapping, in particular, affords the prospect of assembling a complex polycyclic framework efficiently from rather more simple substrates in one step. In addition, the ability to not only construct, but also control stereochemistry of the newly formed C-C bonds increases the attractiveness of the process. The flexibility and synthetic utility of this methodology has been demonstrated by its application to several natural product syntheses.\textsuperscript{55} In particular, and of major significance to the approach proposed, Padwa et al.,\textsuperscript{56} have shown that α-diazo ketone 111 generates cyclic products 112 – 114 when treated with Rh\textsubscript{2}(OAc)\textsubscript{4} (Scheme 1.4.1). Tetracycle 112, especially, closely resembles the tetracyclic core of platensimycin.

![Scheme 1.4.1. Reagents and conditions: a) Rh\textsubscript{2}(OAc)\textsubscript{4}, 112 47%, 113 10%, 114 37%.](image)

Further, more complex, examples of the use of a rhodium-catalysed tandem cyclisation-cycloaddition in the synthesis of natural products, for instance pseudolaric acid\textsuperscript{57} and the aspidosperma alkaloids,\textsuperscript{58} are shown below (Scheme 1.4.2).
1.4.2 Trisubstituted dienophiles in the Diels-Alder reaction

The Diels-Alder reaction is a robust and powerful method for the formation of cyclic adducts in a highly regio- and stereospecific manner. Our synthesis towards platensimycin utilises the Diels-Alder cycloaddition of a trisubstituted dienophile with a highly reactive diene to construct a highly substituted cyclohexenone in one step. While extensive studies have been made on the reaction of highly substituted dienes, the corresponding reactions of highly substituted dienophiles have been neglected. In general, the conditions essential for successful cycloaddition are fairly harsh; high temperature, pressure, or extended reaction duration are often required. The use of Lewis acid catalysis is unfortunately not possible with dienophile 100 as the acetonide group is deprotected readily. Upon examination of the few examples of reactions of 3-silyloxydienes with trisubstituted dienophiles in the literature, the two most recent publications afford the most similar systems to our proposed synthesis.

During the course of the synthetic studies towards GKK1032s, Katoh et al prepared enone 122 via the Diels-Alder reaction of Danishefsky’s diene 93 and trisubstituted dienophile 121 (Scheme 1.4.3). 122 was obtained as a single diastereomer in good yield after heating 93 and 121 in a sealed tube at 150 °C for 3 d, followed by acidic workup.
Scheme 1.4.3. Reagents and conditions: a) (i) PhMe, 150 °C, 3 d; (ii) 0.05 M aq. HCl, r.t., 0.75 h, 66% over 2 steps.

Alternatively, Maier *et al.* used the more reactive Rawal diene 123 in their formal synthesis of dysidiolide (Scheme 1.4.4).\(^{66}\) Reaction of 123 and dienophile 124 in toluene at 115 °C for 5 days and subsequent treatment with aqueous HF afforded enone 125.

Scheme 1.4.4. Reagents and conditions: a) (i) PhMe, 115 °C, 5 d; (ii) 40% aq. HF, THF, 49% over 2 steps.

From these two examples it is apparent that Diels-Alder reaction of 100 and Danishefsky’s diene 93 will require both high temperature and extended reaction time.
CHAPTER TWO

Discussion
1.5.1 Synthesis of starting materials

1.5.1.1 HWE partners – phosphonate 95 and aldehyde 96b

Synthesis towards tetracyclic core 90 commenced with the synthesis of Horner-Wadsworth-Emmons partners, phosphonate 95 and (R)-glyceraldehyde acetonide 96b. The natural product requires use of the (S)-enantiomer of aldehyde 96a, however synthesis of 96a entails three steps, while its enantiomer 96b can be obtained in two. It was decided, therefore, to use 96b in the synthesis of enantiomeric model ketone 105, as its synthesis from D-mannitol would be more expedient (Figure 1.5.1).

Phosphonate 95 was obtained in relatively straightforward manner by simple alkylation of commercially available triethyl phosphonoacetate with allyl bromide (Scheme 1.5.1). Initial attempts to effect alkylation with sodium hydride in tetrahydrofuran only provided 95 in a disappointing 30% yield. Changing to the use of potassium carbonate as base in the presence of catalytic sodium iodide was more successful, providing phosphonate 95 in 74% yield. Extended reaction time resulted in formation of the Wittig-unreactive, dialkylated phosphonate 126 which required separation from desired allyl phosphonate 95 via careful flash column chromatography.

\[
\text{Scheme 1.5.1. Reagents and conditions: a) K}_2\text{CO}_3, \text{NaI, 60 °C, 4 d, 95 74%, 126 12%; b) NaH, THF, 0 °C, 95 30%}. 
\]

(R)-Glyceraldehyde acetonide 96b was prepared in a two-step sequence from D-mannitol 127 (Scheme 1.5.2). Initially preparation of 1,2-5,6-diisopropylidene-D-mannitol 128 was attempted through reaction of 2-methoxypropene with D-mannitol in N,N-dimethylformamide according to the
procedure of Horton, Debost, and Gelas. Though the reported yield was in excess of 90%, the amount of material obtained in our hands was unsatisfactory (<10%). Instead, simple acetalisation of the sugar was achieved using acetone catalysed by zinc chloride. Though the reaction was modest in yield, the reactants were all inexpensive, and the reaction could be scaled up to supply the bis(acetonide) in large amounts.

Scheme 1.5.2. Reagents and conditions: a) 2-methoxypropene, DMF, PTSA 0 °C to r.t., 7%; b) ZnCl₂, acetone, r.t., 3 h, 61%, c) NaIO₄, CH₂Cl₂, sat. aq. NaHCO₃, r.t., 3 h, 68%; d) NaIO₄, SiO₂, CH₂Cl₂, r.t., 1 h, 39%.

The second step of the synthetic sequence called for glycol cleavage to give two equivalents of (R)-glyceraldehyde 96b. Several options had been reported in the literature; sodium periodate was chosen as the most convenient and least toxic oxidant. Treatment with sodium periodate and silica in dichloromethane was successful; unfortunately the yield of 96b obtained was low. A detailed report from researchers at Eli Lilly found that the use of sodium periodate in dichloromethane in the presence of saturated sodium hydrogen carbonate solution gave 96b in reproducibly excellent yield and purity after distillation. Indeed, application of their procedure reliably gave 96b in 68% yield after distillation.

With both HWE partners 95 and 96b in hand, attention turned to their union.

1.5.1.2 Synthesis of dienophile – the HWE reaction

The Horner-Wadsworth-Emmons olefination has long been used in organic synthesis as an alternative to the Wittig olefination for the selective formation of E-olefins from aldehydes 129 and phosphonates 130. The selectivity is dependent on the substituents and tendency for interconversion between the intermediates 131 – 134 (Figure 1.5.2):
In addition, the use of phosphonates results in water-soluble byproducts that are easily removed during workup, in comparison to the often troublesome triphenylphosphine oxide obtained during a traditional Wittig olefination. Though unbranched phosphonates generally give excellent $E:Z$ ratios in the HWE olefination, the $E$ selectivity of substituted phosphonates is less assured and depends on the substituents.\(^\text{75}\) In order to maximise the ratio of desired $E$ olefin, several modifications to the original procedure have been published. Solvent, cation, and temperature effects influence the ratio of olefins obtained.\(^\text{76}\) For disubstituted olefins, the $E:Z$ ratio is maximised through:

a) DME rather than THF as solvent;

b) higher reaction temperatures;

c) Li$^+ >$ Na $>$ K as the metal cation;

d) increasing $\alpha$-substitution of the aldehyde coupling partner.

An important modification is the Masamune-Roush procedure, whereby using lithium chloride to chelate the phosphonate allows the use of much milder bases for deprotonation (Figure 1.5.3).\(^\text{77}\)

**Figure 1.5.2.** Mechanism of the Horner-Wadsworth-Emmons olefination. $Y$ = electron withdrawing group, e.g. CO$_2$R, CN, SO$_2$R, etc.

**Figure 1.5.3.** Masamune-Roush modification of the Horner-Wadsworth-Emmons reaction for base-sensitive compounds.\(^\text{77}\)
These conditions were selected initially, as the use of a relatively mild base should preclude epimisirisation of the chiral acetonide (Table 1.5.1, entry 1). While the olefination proceeded in good yield, the $E:Z$ selectivity was poor, in favour of the undesired $Z$-olefin. Furthermore, separation of the isomers via flash column chromatography proved difficult, requiring multiple repetitions to obtain sufficiently clean material.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>R</th>
<th>Yield (%)</th>
<th>Ratio $E:Z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 eq. DBU, LiCl, MeCN, r.t, 2 h</td>
<td>Et</td>
<td>77</td>
<td>1 : 2.2</td>
</tr>
<tr>
<td>2</td>
<td>1 eq. DBU, LiCl, DME, r.t., 4 h</td>
<td>Et</td>
<td>87</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td>3</td>
<td>1 eq. DBU, SiO$_2$, r.t., 5 h</td>
<td>Et</td>
<td>72</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td>4</td>
<td>1 eq. Et$_3$N, LiCl, MeCN, r.t., 4 h</td>
<td>Et</td>
<td>69</td>
<td>1.1 : 1</td>
</tr>
<tr>
<td>5</td>
<td>1.5 eq. NaH, THF, 0 °C, 4 h</td>
<td>Et</td>
<td>89</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>6</td>
<td>1.25 eq. $n$-BuLi, THF, -78 °C to r.t., 16 h</td>
<td>Et</td>
<td>88</td>
<td>1 : 2</td>
</tr>
<tr>
<td>7</td>
<td>1.05 eq. LDA, THF, -78 °C, 1 h; → r.t., 48 h</td>
<td>Et</td>
<td>91</td>
<td>1 : 2.5</td>
</tr>
<tr>
<td>8</td>
<td>2 eq. K$_2$CO$_3$, H$_2$O, 0 °C to r.t., 4 h</td>
<td>Et</td>
<td>41</td>
<td>2 : 1</td>
</tr>
<tr>
<td>9</td>
<td>2 eq. K$_2$CO$_3$, H$_2$O, 0 → 100 °C, 1 h</td>
<td>Et</td>
<td>36</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>10</td>
<td>2 eq. K$_2$CO$_3$, LiBr, MeCN, 0 °C → r.t., 180 h</td>
<td>Et</td>
<td>26</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>11</td>
<td>2 eq. K$_2$CO$_3$, LiBr, EtOH, r.t., 72 h</td>
<td>Et</td>
<td>34</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>12</td>
<td>2 eq. K$_2$CO$_3$, LiBr, MeOH, 0 °C → r.t., 180 h</td>
<td>Me</td>
<td>58</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>13</td>
<td>2 eq. K$_2$CO$_3$, LiCl, MeOH, 0 °C → r.t., 180 h</td>
<td>Me</td>
<td>56</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>14</td>
<td>2 eq. K$_2$CO$_3$, LiCl, EtOH, 0 → 45 °C, 96 h</td>
<td>Et</td>
<td>44</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>15</td>
<td>6 eq. K$_2$CO$_3$, EtOH, r.t., 120 h</td>
<td>Et</td>
<td>60</td>
<td>2.6 : 1</td>
</tr>
<tr>
<td>16</td>
<td>1.1 eq. KO'Bu, THF, -60 → -20 °C, 3 h</td>
<td>Et</td>
<td>77</td>
<td>2.2 : 1</td>
</tr>
<tr>
<td>17</td>
<td>1.1 eq. KO'Bu, THF, -78°C, 1 h</td>
<td>Et</td>
<td>70</td>
<td>2 : 1</td>
</tr>
<tr>
<td>18</td>
<td>1.1 eq. KO'Bu, THF, -78 → -45 °C, 3 h</td>
<td>Et</td>
<td>83</td>
<td>2.3 : 1</td>
</tr>
</tbody>
</table>

Table 1.5.1. Reaction conditions for the HWE union of phosphonate 95 and aldehyde 96b.
The E:Z ratio was determined by $^1$H-NMR spectroscopy based on the relative area of the signals assigned to H-1′. Designating the product as either the E or Z isomer was based on the chemical shift of the same signal; in the E-isomer, H-1′ is deshielded by proximity to the ester group, leading to a downfield shift compared to the same proton in the Z-isomer (Figure 1.5.4).

![Figure 1.5.4. Comparison of the chemical shifts of the H-1′ proton in the E- and Z-isomers of dienophile 100.](image)

Earlier work established that the yield of the E-olefin in a Horner-Wadsworth-Emmons reaction can be maximised by use of polar coordinating solvents such as dimethoxyethane. Application of this method to our reactants did, indeed, increase the proportion of E-olefin obtained; unfortunately the selectivity was still marginally in favour of the Z-olefin (Table 1.5.1, entry 2). Performing the reaction with all reagents adsorbed on silica again failed to provide the desired E-olefin in appreciable excess (entry 3). Use of stronger bases such as sodium hydride, n-BuLi, and LDA once again gave mixtures of 100 in excellent overall yield, but with stereoselectivity opposite to that required (entries 5 – 7).

Changing the choice of base to potassium carbonate gave the first indication of forming the desired E-selectivity. A variety of conditions (entries 8 – 15) were screened in attempts to improve the yield, with alcohol solvents (entries 11 – 15) giving the best yields. Use of elevated temperatures resulted in racemisation, in addition to loss of E:Z selectivity (entry 9). However, use of methanol as solvent gave rise to concurrent transesterification with the methyl ester of the dienophile being isolated (entries 12, 13). The most successful of the potassium carbonate protocols (entry 15) remained less than satisfactory, requiring extended reaction times to elevate the yield of dienophile 100 obtained. It was therefore decided to try a stronger base, potassium tert-butoxide, to improve yields while hopefully maintaining what little selectivity that had been established (entries 16 – 18). Screening of
different reaction conditions eventually resulted in an optimised protocol whereby addition of a solution of aldehyde 96b to a mixture of potassium tert-butoxide and phosphonate 95 in tetrahydrofuran at -78 °C, followed by slow warming to -45 °C, afforded olefin 100 in 83% overall yield and as a 2.3:1 mixture of E:Z isomers.

A range of one-pot protocols were also trialled (Table 1.5.2) with the hope of improving the yield over the two steps by eliminating the need for distillation of the aldehyde 96b, which when conducted on a small scale contributed to a significant reduction in yield. Disappointingly, the one-pot protocols failed to provide 100 in improved yield in comparison to the established stepwise approach.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
<th>Ratio E : Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 eq. DBU, Et₂O, r.t., 20 h</td>
<td>56</td>
<td>1 : 2</td>
</tr>
<tr>
<td>2</td>
<td>2 eq. LiOH, CH₂Cl₂, r.t., 20 h</td>
<td>9</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>3</td>
<td>11 eq. K₂CO₃, H₂O, r.t., 7 d</td>
<td>25</td>
<td>1.5 : 1</td>
</tr>
</tbody>
</table>

Table 1.5.2. One-pot glycol cleavage-HWE reaction attempts.

Thus, the optimum conditions for synthesis of dienophile E-100 were found to be the use of potassium tert-butoxide as base, in THF as solvent, at reduced temperature (-78 → -45 °C) over 3 h, providing 100 in 83% yield as a 2.3:1 mixture of E:Z isomers.
1.5.2 Synthesis of cyclohexenone 101: the Diels-Alder reaction

1.5.2.1 Attempted cycloaddition with model dienes

Initially it was decided to explore the Diels-Alder reaction of dienophile 100 with simple, inexpensive, and readily available 2,3-dimethyl-1,3-butadiene 138 (Table 1.5.3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Z-100</td>
<td>-</td>
<td>PhMe</td>
<td>reflux</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>E-100</td>
<td>BF₃·OEt₂</td>
<td>CH₂Cl₂</td>
<td>-78 to r.t.</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Z-100</td>
<td>BF₃·OEt₂</td>
<td>CH₂Cl₂</td>
<td>-78 to r.t.</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Z-100</td>
<td>BF₃·OEt₂</td>
<td>PhMe</td>
<td>225, μwave reactor</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1.5.3. Attempted Diels-Alder reaction of trisubstituted dienophile 100 with unactivated diene 138.

Both E and Z-dienophiles E-100 and Z-100 were used in order to minimise the amount of desired dienophile wasted through unsuccessful attempts. Simple reaction under thermal conditions failed to provide cycloadducts. Attempted activation through Lewis-acid catalysis with boron trifluoride diethyl etherate only afforded deprotected dienophile 140 (Figure 1.5.5).

Figure 1.5.5. Deprotected dienophile 140.

Changing to the singly-activated diene 141 also failed to give any cycloadduct under the conditions tested (Table 1.5.4). Both reflux (entry 1) and microwave heating (entry 2) methods were unsuccessful. Attention therefore turned to the more reactive diene 93 that would provide the desired enone 101 after elimination.
Table 1.5.4. Attempted Diels-Alder reaction of trisubstituted dienophile 100 with singly activated diene 141.

1.5.2.2 Cycloaddition with Danishefsky’s diene 93

As large quantities of Danishefsky’s diene 93 would be required for investigation of the Diels-Alder reaction, and 93 is relatively expensive, it was decided to prepare the diene in-house. The original procedure reported by Danishefsky and Kitahara,78 whereby triethylamine and zinc chloride are used to generate the enolate, which is then trapped with chlorotrimethylsilane, appears, at first, inferior to other procedures that claim much higher yields. The other methods feature aqueous workup conditions – to remove the troublesome triethylamine hydrochloride by byproduct – in contrast to the multiple filtrations required by Danishefsky’s procedure.
Table 1.5.5. Approaches towards Danishefsky’s diene 93.

Therefore we first attempted to synthesise 93 according to the method of Cazeau et al, in which iodontrimethylsilane is generated in situ and added to ketone 143 (Table 1.5.5). Unfortunately, only starting material 143 was obtained after workup and purification of the reaction mixture (entry 1). Hansson and Carlson’s method for the synthesis of silyloxydienes (LiBr/Et$_3$N/TMSCl) was attempted next, as the authors had reported that 93 could be obtained in >90% yield (entry 2). Unfortunately in our hands the yield of 93 obtained was poor (4%, as a 3:1 mixture of starting material:product). Therefore we returned to Danishefsky and Kitahara’s original conditions (entry 3, ZnCl$_2$/Et$_3$N/TMSCl) and were pleased to find that the procedure afforded silyloxydiene 93 in high yield. The Danishefsky-Kitahara procedure proved to be the most reliable, providing 93 in 75% yield after distillation (entry 3).

With highly reactive diene 93 in hand, simple thermal reaction with 100 in toluene, followed by acidic workup was initially attempted (Table 1.5.6). Unfortunately, as in earlier attempts, this approach failed to provide any product. Microwave irradiation at reflux for 2 h was also unsuccessful.
Table 1.5.6. Initial investigation of the Diels-Alder reaction of Danishefsky’s diene 93 with dienophile 100.

Reasoning that the high temperatures employed were leading to decomposition of the diene, rather than cycloaddition with the dienophile, we decided to increase the amount of 93 in the reaction. Doubling the equivalents of diene used under the same microwave conditions unfortunately still did not provide any of the desired adduct (entry 3). However, extending the reaction duration, in addition to an increase in the amount of diene, finally afforded the desired cycloadduct 144, albeit in low yield. Adduct 144 was unstable to silica, and flash column chromatography resulted in partial elimination to the desired enone 101. Treatment of the crude reaction mixture with mild aqueous acid facilitated full elimination to enone 101, whilst leaving the acetonide moiety intact. Unreacted dienophile E-100 was the major component of the remainder of the reaction mixture.

While this proof of concept was encouraging, the yield for the cycloaddition was unacceptably low. It was therefore decided to attempt to improve the yield by yet again increasing the reactivity of the diene component. Silyloxydienes have been shown to display increased reactivity in the Diels-Alder
reaction with a wide range of substrates, and 1-(dimethylamino)-3-(tert-butyldimethylsiloxy)-1,3-butadiene (Rawal’s diene 123), in particular, presented an ideal opportunity to improve the yield of 101.

1.5.2.3 Cycloaddition with Rawal’s diene 123

Rawal’s diene 123 is well-known for its increased reactivity in comparison to Danishefsky’s diene 93, due to an increase in the energy of the highest occupied molecular orbital (HOMO), leading to a reduction in the difference in energy between the HOMO(diene) and lowest unoccupied molecular orbital (LUMO) of the dienophile (Figure 1.5.7). Treatment of the initial cycloadduct with acid should effect elimination to give identical products to those obtained from cycloadditions with Danishefsky’s diene. It was decided to exploit this increased reactivity to improve yields of 101 (Scheme 1.5.6).

![Figure 1.5.6. Proposed cycloaddition of E-100 with Rawal’s diene 123.](image)
Figure 1.5.7. Comparison of HOMO values for Danishefsky’s diene 93 (black) and Rawal’s diene 123 (red). LUMO(diene) \( E-100 \) shown in blue. Energies calculated using ChemBio3D Ultra Hückel molecular orbital calculations.

Rawal’s diene 123 was obtained according to the procedure reported by Rawal et al.\textsuperscript{81} Vinylogous amide 146 was obtained in excellent yield from the same starting material as Danishefsky’s diene by treatment with dimethylamine hydrochloride and sodium hydroxide (Scheme 1.5.3).

Scheme 1.5.3. Reagents and conditions: a) Me\(_2\)NH\(\cdot\)HCl, NaOH, THF/H\(_2\)O, 0 °C → r.t., 5 h, 90%; b) KHMDS, THF, -78 → -30 °C, 4 h; then TBSCI, -78 °C → r.t., 1 h, ca. 60% (crude).

Slow addition of a solution of the vinylogous amide to a solution of KHMDS at -78 °C, followed by warming to -30 °C was essential for successful generation of the enolate. Subsequent quenching with a solution of TBSCI and warming to room temperature afforded the required diene 123 in good crude yield. Attempts to purify the diene only resulted in decomposition; thus the crude material was employed in excess in the Diels-Alder reaction with dienophile \( E-100 \) (Table 1.5.7).
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Table 1.5.7. Diels-Alder reactions of Rawal’s diene 123 and trisubstituted dienophile 100.

Though more reactive than Danishefsky’s diene 93, cycloadditions with 123 still required high temperature and pressure to afford adducts 145 or 147. Attempted reaction at room temperature or reflux (entries 1 and 2) did not afford 147. Yields of cycloadducts arising from the reaction of Rawal’s diene 123 with dienophile 100 were comparable to those obtained using Danishefsky’s diene 93. In contrast, elimination to the enone 101 unfortunately proved more troublesome, requiring much harsher conditions to effect elimination (Scheme 1.5.4).

Scheme 1.5.4. Reagents and conditions: a) BF₃:OEt₂, CH₂Cl₂, -78 °C → r.t., 5.5 h, 101 44%, 148 22%.

Use of boron trifluoride diethyl etherate did effect elimination; unfortunately there was concurrent deprotection of the acetonide in addition to loss of the distinctive enone olefinic protons in the ¹H-NMR spectrum. The product was later identified as 148, resulting from the intramolecular Michael addition of the newly liberated alcohol at C-2” to the newly formed enone (Figure 1.5.8). It was decided to persevere with Danishefsky’s diene, and try to improve the reactivity of the dienophile by altering the electron withdrawing group.
Figure 1.5.8. Mechanism of competing side reaction: the (Lewis) acid-catalysed intramolecular oxa-Michael reaction.

1.5.2.4 Modification of dienophile $E$-100 to enhance reactivity in the Diels-Alder reaction

Reduction of the ester group in dienophile $E$-100 to the aldehyde should enhance reactivity of the dienophile in the Diels-Alder reaction. By increasing the strength of this electron-withdrawing substituent, the $\text{LUMO}_{\text{dienophile}}$ will be lowered in energy (Figure 1.5.9). Thus, the gap between the $\text{HOMO}_{\text{diene}}$ and $\text{LUMO}_{\text{dienophile}}$ will be reduced, and cycloaddition between the two partners should occur more readily.
Figure 1.5.9. Comparison of HOMO and LUMO energies of Danishefsky’s diene 93 (black), Rawal’s diene 123 (red), aldehyde dienophile 154 (green), and disubstituted dienophile E-155 (blue). Energies calculated using ChemBio3D Ultra Hückel molecular orbital calculations.

Reduction of the ester with DIBAL-H (toluene, -78 °C) afforded mainly alcohol 153 (73%), as well as a small amount of aldehyde 154 (3%). Conversion of 153 to 154 was effected smoothly by treatment with buffered Dess-Martin periodinane in dichloromethane at room temperature (Scheme 1.5.5).

Scheme 1.5.5. Reagents and conditions: a) DIBAL-H, PhMe, -78 °C, 3.5 h, 153 73%, 154 3%; b) Dess-Martin periodinane, pyridine, CH₂Cl₂, r.t., 45 min, 86%.
In addition, it was decided to investigate the effect of disubstitution on the olefin. In contrast to the allyl-substituted phosphonate 95, HWE-union of triethylphosphonoacetate 97 and (R)-glyceraldehyde acetonide 96b afforded \textit{E}-155 in excellent yield and selectivity (Scheme 1.5.6).

![Scheme 1.5.6. Reagents and conditions: a) KOtBu, CH2Cl2, 0 °C, 2.5 h, \textit{E}-155 85%, \textit{Z}-155 8%.

First, aldehydic dienophile 154 was used in the Diels-Alder reaction (Table 1.5.7). Reaction of 154 with diene 93 appeared rapid, with disappearance of the dienophile indicated by t.l.c. analysis of the crude reaction mixture. Attempted elimination to the enone, however, afforded only a complex mixture that did not contain the expected enone 156 (entries 1-3). Reaction of 154 with Rawal’s diene 123 also failed to provide the desired adduct 156 (entry 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>Reaction conditions</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Danishefsky 93</td>
<td>Reflux</td>
<td>24</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Danishefsky 93</td>
<td>150 °C, pressure vessel</td>
<td>72</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Danishefsky 93</td>
<td>150 °C, pressure vessel</td>
<td>84</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>Rawal 123</td>
<td>150 °C, pressure vessel</td>
<td>16</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

\textit{Table 1.5.7. Attempted Diels-Alder reaction of dienophile 154 with dienes 93 and 123.}

Attention then turned to disubstituted dienophile \textit{E}-155 (Table 1.5.8). Reactivity was expected to be enhanced in comparison to reaction with trisubstituted dienophile \textit{E}-100 due to reduced steric crowding in the pericyclic transition state.
Table 1.5.8. Diels-Alder reaction of dienophile E-155 with dienes 93 and 123.

Reaction of E-155 with 93 was rapid in comparison to trisubstituted derivative E-100; elimination to enone 157, however, did not occur as cleanly, giving a mixture of the methoxy-ketone 158 and the desired adduct 157.

Danishefsky and coworkers had earlier reported difficulty in getting complete elimination to the enone from initial Dansishefsky diene adducts, and mixtures with the methoxy-ketones 160 were common (Scheme 1.5.7).\(^{83}\)

Scheme 1.5.7. Reagents and conditions: a) 2 N HCl/THF (1:4), 160:161 7:18.\(^{83}\)

The ratio of enone to methoxy-ketone products appeared to be dependent on the concentration of acid used for the elimination step; dilute acid (0.005 N HCl), in comparison to more concentrated
solutions (2 N HCl), minimised production of the methoxy-ketones. This could be overcome, however, through the use of TMSOTf as reported by Vorndam (Figure 1.5.10).

![Figure 1.5.10](image)

*Figure 1.5.10. Elimination of Danishefsky diene-derived Diels-Alder adducts with TMSOTf.*

However, due to the sensitivity of the acetonide to Lewis acids, this method would have, in all likelihood, induced deprotection and concurrent intramolecular Michael addition of the diol to give products of type 148. Other methods in the literature to induce elimination of Danishefsky diene adducts involved the use of fluoride sources (which gave mixtures of methoxy-ketone and enone) or weaker Lewis acids such as lanthanide triflates, as reported by Inokuchi et al. A mild method was desired to prevent hydrolysis and subsequent Michael addition of the acetonide moiety.

Thus, a small variety of methods were screened in order to determine the optimal elimination conditions (Table 1.5.9). The conditions used for adducts 144 where C-1 was a quaternary centre (dilute aqueous acid, entry 1), as stated earlier, proved unsuitable for 166. Stirring the crude reaction mixture with silica gel provided only a small quantity of the undesired methoxy-ketone 158, with the remainder of the material lost to decomposition (entry 2). Treatment with BF$_3$∙OEt$_2$ at reduced temperature, while successful in the case of 145, again proved unsuitable when applied to adduct 166 (entry 3). Fortunately, it was found that catalytic anhydrous zinc chloride in dichloromethane provided the best ratio of desired elimination product 157 to methoxy-ketone 158 (entry 4).
Table 1.5.9. Optimisation of the elimination of initial Diels-Alder adduct 166 to enone 157.

Another approach that has been used to good effect by many is to treat the crude mixture of methoxy-ketone and enone with a hindered base to effect elimination of the methoxy-ketone (Scheme 1.5.8).\textsuperscript{65,88} Attempted conversion of the methoxy-ketone 158 to the desired enone 157 using DBU in dichloromethane at room temperature was unsuccessful and only starting material 158 was recovered.

Scheme 1.5.8. Reagents and conditions: a) DBU, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 48 h.

In addition, 157 was quite unstable, undergoing isomerisation of the double bond to give 167 (Figure 1.5.11), due to the available proton at C-1. This isomerisation is analogous to that observed for the adducts arising from the Diels-Alder cycloaddition of Danishefsky’s diene with methyl vinyl ketone, reported earlier by Danishefsky et al.\textsuperscript{83} Treatment with silica catalysed the isomerisation to give the cyclohex-3-enone 169 as the major product.
Figure 1.5.11. Comparison of the isomerisation of Diels-Alder adduct 157 with 4-acetyl cyclohexenone 168.

Attention therefore turned to optimisation of the Diels-Alder reaction between dienophile \( E-100 \) with Danishefsky’s diene 93.

### 1.5.2.5 Optimisation of Diels-Alder reaction conditions

Efforts next concentrated on maximising the amount of enone 101 derived from the Diels-Alder cycloaddition between the original dienophile \( E-100 \) and readily available Danishefsky’s diene 93 (Table 1.5.10). In all cases, the enone 101 was obtained as a 7:1 mixture of \textit{endo}:\textit{exo}-derived adducts.
Table 1.5.10. Optimisation of reaction conditions for the Diels-Alder reaction of dienophile \( \text{E-100} \) and Danishefsky’s diene 93.

Initially, the yield could be improved by extending the duration of the reaction (entry 1). Moving to the use of a sealed pressure vessel – rather than the microwave – was an issue of convenience, the available microwave reactor at the time having maintenance issues. Increasing the molar equivalents of diene also had a positive effect (entries 2 – 5). This could be maximised by addition of three aliquots of 2 molar equivalents of diene at 48 h intervals – giving 101 in 75% yield, on average (entry 4). The remainder of the reaction mixture comprised of unreacted starting material, which could be recovered and recycled, and decomposed diene. Dilute acid-induced elimination of the initial Diels-Alder adducts was complete and the corresponding methoxy-ketone was not detected.

As methoxy-substituted dienophile \( \text{E-170} \) was available from earlier attempts to optimise the HWE step, we decided to use this in the Diels-Alder reaction as well (Table 1.5.11).
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Table 1.5.11. Optimisation of reaction conditions for the Diels-Alder reaction of dienophile \( E-170 \) and Danishefsky's diene 93.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. diene</th>
<th>Reaction conditions</th>
<th>Time (h)</th>
<th>Yield (%) ( a )</th>
<th>Recovered ( E-170 ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>150 °C, pressure vessel</td>
<td>72</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>150 °C, pressure vessel</td>
<td>120</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>150 °C, pressure vessel</td>
<td>144</td>
<td>65</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>3 x 2</td>
<td>150 °C, pressure vessel</td>
<td>120</td>
<td>69</td>
<td>22</td>
</tr>
</tbody>
</table>

\( a \) After elimination with 0.05 M aq. HCl, THF at r.t. for 1 h.

The change of the alkyl group to a methyl ester had little effect on selectivity, giving a 5:1 mixture of endo:exo-derived enones 171. The methyl ester adducts endo-171 and exo-171 could, however, be separated by careful flash column chromatography, while their ethyl ester counterparts 101 could not. In addition, the minor isomer exo-171 was obtained as a solid which enabled X-ray crystallographic analysis, thus confirming the structure (Figure 1.5.12).

Figure 1.5.12. ORTEP-structure of the minor stereoisomer exo-171, derived from the Diels-Alder reaction of methyl dienophile \( E-170 \) with Danishefsky’s diene 93.
The stereoselectivity of the cycloaddition was expected to be controlled by the bulky chiral acetonide substituent. The desired cycloadduct *endo*-144 is derived from approach of the diene from the *re* face of the dienophile, while approach of the diene from the *si* face is blocked by the steric bulk of the acetonide (Figure 1.5.13). The stereoselectivity observed was not 100%, and adduct *exo*-144 was also obtained, that was inseparable from the desired isomer. Presumably the high temperatures and extended duration of the reaction provides the additional energy required to overcome the steric barriers, and a mixture of stereoisomers is obtained.

**Figure 1.5.13.** Facial selectivity in the Diels-Alder reaction of dienophile *E*-100 with Danishefsky’s diene 93.

### 1.5.2.6 Lewis acid catalysis

Lewis acid catalysis of the Diels-Alder reactions of Danishefsky’s diene 93 have little representation in the literature due to the sensitivity of the diene to acid. Recently, Inokuchi and co-workers have found that the diene is, in fact, compatible with a range of lanthanide Lewis-acid catalysts, the most effective being ytterbium(III) triflate. Work that was carried out concurrently by colleagues on a similar system 172 found, however, that addition of Yb(OTf)₃ or Eu(fod)₃ to the cycloaddition mixture had no positive effect on yield, with the dienophile being recovered from the reaction in each case (Scheme 1.5.14).
Figure 1.5.14. Attempted Lewis acid-catalysed Diels-Alder reaction of diene 93 with closely related dienophile 172.\(^8\)

In addition, earlier attempts to catalyse the Diels-Alder cycloaddition of dienophile \(E-100\) with unactivated 2,3-dimethyl-1,3-butadiene 138 in the presence of boron trifluoride diethyl etherate as a Lewis acid catalyst resulted in deprotection of the acetonide moiety (Section 1.3.2.1.). Further investigation of Lewis acid catalysis on this system was therefore not pursued further.
1.5.3 Elaboration to advanced ester 103

1.5.3.1 Cleavage of the acetonide 101

A seemingly simple deprotection of acetonide 101 to give diol 149 was required. However, as had been noted earlier, use of acid catalysts was complicated by concurrent intramolecular Michael addition. In practice, the desired product could only be obtained in low yield after several conditions were investigated (Table 1.5.12).

Use of simple aqueous acids as the first attempt enabled isolation of diol 149 in low yield, but without recovery of any unreacted starting material (entry 1). Moving to a stronger acid (H$_2$SO$_4$, entry 2) had no positive effect. Use of milder acid conditions generally failed to effect deprotection of the acetonide, returning mainly unreacted starting material (entries 3 – 6). Where deprotection was successful, diol 149 reacted further under these conditions to give bicycle 148 in low yield. Attempted deprotection with boron trifluoride diethyl etherate as the Lewis acid failed to go to completion with 1 molar equivalent; addition of a second molar equivalent to the reaction mixture resulted in complete consumption of starting material with concomitant loss of 149, giving Michael adduct 148 as the major component (entry 8). Reaction with substoichiometric Lewis acid either failed to react or go to completion. Upon addition of extra acid, or an increase in temperature – in attempts to drive the process to completion – intramolecular oxa-Michael adduct 148 was obtained as the major product (entries 9 – 14).
### Table 1.5.12. Attempts to deprotect acetonide 101 to diol 149.

There is some evidence that protons may act as the catalyst in an oxa-Michael reaction, either by direct application of a Brønsted acid to the mixture, or provision of protons through hydrolysis of a metal salt. In this case, however, the absence of oxa-Michael adduct 148 when hydrolysis was performed with aqueous acid would seem to preclude a Brønsted acid mediated mechanism (Table 1.5.12).
1.5.12, entries 1, 2, and 6). Interestingly, an analogous reaction of a closely related system to give a 2-oxabicyclo[3.3.1]nonan-7-one has been reported recently (Figure 1.5.15).  

![Current work:](image1.png)

**Figure 1.5.15.** Comparison with similar intramolecular oxa-Michael additions from the literature.

While oxidative cleavage of the resultant diol 149 was accomplished easily under standard conditions (NaIO₄, aq. NaHCO₃, CH₂Cl₂, r.t., scheme 1.5.9), overall the transformation from 101 to 102 proved problematic – not only were yields of the desired diol 149 variable, they were unacceptably low. In addition, substantial amounts of material were lost to the oxa-Michael side reaction, with limited starting material recovered. Thus, an alternative pathway was sought.

Literature examples of alternative methods for the hydrolysis of an acetonide are numerous, but are largely based on the use of different Lewis acids. However, in a report from 1993, Wu and Wu showed that terminal acetonides could be transformed directly to the aldehyde using periodic acid in ethyl acetate. Gratefully, application of this procedure to acetonide 101 furnished key aldehyde 102 in excellent yield. This is presumably due to in situ oxidative cleavage of the diol as soon as it is formed, thereby preventing undesired intramolecular oxa-Michael reaction.

![Ghosh and Maity:](image2.png)

Scheme 1.5.9. **Reagents and conditions:** a) 2 M HCl, THF, r.t., 20 h, 13%; b) NaIO₄, aq. NaHCO₃, r.t., 1 h, 88%; c) H₃IO₆, EtOAc, 1.25 h, 71%.
1.5.3.2 Elaboration of aldehyde 102 to advanced ester 103

With a route to aldehyde 102 established, attention turned to conversion of this key intermediate to the model ketone. There was some concern that installation of the methyl group via Grignard addition could be complicated by the presence of the two additional reactive centres, namely an ester and an enone. A common strategy in similarly multifunctional systems has been to limit the molar equivalents of Grignard reagent employed in the transformation. In practice, limitation to slightly substoichiometric amounts of methyl magnesium bromide at reduced temperature was sufficient to guarantee selective addition at the aldehydic centre (Scheme 1.5.10).

Scheme 1.5.10. Reagents and conditions: a) MeMgBr, THF, -78 °C, 1 h, 90%; b) Dess-Martin periodinane, pyridine, CH₂Cl₂, r.t., 1.25 h, 94%.

A single diastereomer of 177 was recovered; however the absolute configuration of the resultant alcohol is inconsequential, as the subsequent oxidation step destroys this stereocentre. Nevertheless, the configuration is predicted to be that shown, based on the Felkin-Ahn model for nucleophilic attack at an aldehydic centre (Figure 1.5.16).

Figure 1.5.16. Predicted stereoselectivity of the Grignard addition to aldehyde 102.

Conversion of alcohol 177 to the methyl ketone 103 was effected cleanly with buffered Dess-Martin periodinane in excellent yield, thereby completing the synthesis of advanced ester 103 (Scheme 1.5.10). All that remained to obtain our desired model α-diazoester 105 was the installation of the diazo moiety.
1.5.4 Attempted installation of the diazo moiety

1.5.4.1 Attempted addition of lithiated ethyl diazoacetate

Initially it was planned to install the requisite diazo-functionality through addition of lithiated ethyl diazoacetate 104, as the reagent is considerably more stable and convenient to handle than diazoethane. Conversion of the ethyl ester to a suitable leaving group, followed by addition of the lithiate should give α-diazoester 105 (Figure 1.5.17).

![Figure 1.5.17. Retrosynthetic summary of the intended approach towards α-diazoester 105.](image)

The *in situ* generation and subsequent reaction of mixed anhydrides in this transformation is the most convenient method for synthesis of α-diazocarbonyl compounds from the corresponding acid.110 Thus, basic hydrolysis of the ester moiety gave the carboxylic acid 179 (aq. KOH/EtOH, 0 °C → r.t., 92%). Initially, a one-pot protocol for the conversion to desired α-diazoester 105 was attempted (Table 1.5.13). Standard conditions – whereby treatment of the carboxylic acid with triethylamine and isobutyl chloroformate, followed by addition of lithiated ethyl diazoacetate 104111 – failed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104, LDA, THF, -78 °C, 1 h</td>
<td>181 only recovered</td>
</tr>
<tr>
<td>2</td>
<td>104, LDA, THF, -90 °C, 1.5 h</td>
<td>181 only recovered</td>
</tr>
</tbody>
</table>

Table 1.5.13. Attempted one-pot conversion of acid 179 to α-diazoester 105.
Reasoning that the by-products of mixed anhydride formation (i.e. triethylamine hydrochloride) could be quenching the lithiate prior to addition to 181, we decided to attempt the same reactions in a stepwise manner, thereby allowing for purification and removal of any salts that may interfere in the lithiation. Thus, as previously described, basic hydrolysis of the ester 103 furnished 179, which was then converted to the mixed anhydride under standard conditions (Scheme 1.5.11). To our surprise, 181 survived silica chromatography intact, and could be isolated in excellent yield and purity.

![Scheme 1.5.11. Reagents and conditions:](image)

The structure of the mixed anhydride was confirmed by $^1$H- and $^{13}$C-NMR spectroscopy; the spectra show all the peaks associated with the parent acid (minus the OH resonance), in addition to an isobutyl group. The high resolution mass spectrum showed a molecular ion at $m/z$ 345.1301 corresponding to the required formula for the sodium adduct of 181, C$_{17}$H$_{22}$O$_6$Na.

Subsequent treatment of 181 with lithiated ethyl diazoacetate 104 however failed to supply diazoester 105 (Table 1.5.14). Changing the base from LDA to $n$-BuLi had no effect, as did decreasing the temperature. Purification of the reaction mixture revealed only unreacted starting material 181. The mixed anhydride turned out to be far more stable than anticipated, surviving column chromatography intact.

![Table 1.5.14. Attempted conversion of mixed anhydride 181 to α-diazoester 105.](image)
It was reasoned that if mixed anhydride 181, or ester 103, could be converted to β-ketoester 182, subsequent diazotransfer should supply α-diazoester 105. Disappointingly, attempted Claisen condensation of either 103 or 181 with ethyl acetate gave only unreacted starting material (Scheme 1.5.12). Use of excess ethyl acetate in the attempted Claisen condensation resulted in multiple additions to the ester carbonyl, C-4, and C-1′′.

Mixed anhydride 181 therefore was not labile enough to allow reaction with nucleophiles and revision of our synthetic strategy for the installation of the α-diazo moiety was required.

1.5.4.2 Revision of retrosynthesis I: addition of diazomethane

Abandoning the isobutyl mixed anhydride 181 as being too stable, attention turned to synthesis of derivatives with more labile leaving groups (Figure 1.5.18). Simultaneously, use of 104 as the diazo source was discarded, resorting to the use of more reactive diazomethane to furnish α-diazoketone 183 instead.
Several different leaving groups were evaluated in efforts towards the conversion of 179 to 183 (Table 1.5.15). These included the acid chloride (entry 1), acid fluoride (entry 2), and tosylate (entry 3). Formation of the symmetrical anhydride was also investigated (entries 4 – 6), although this method was not ideal, as two equivalents of the advanced intermediate 179 are required to generate one equivalent of product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Leaving group</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>(COCl)₂, cat. DMF, CH₂Cl₂, 0 °C, 1.5 h</td>
<td>184 trace; 185 32%</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Cyanuric fluoride, pyridine, MeCN, 0 °C, 1 h</td>
<td>184 64%; 185 0%</td>
</tr>
<tr>
<td>3</td>
<td>OTs</td>
<td>TsCl, Et₃N, CH₂Cl₂, 0 °C, 30 min</td>
<td>184 &gt;99%</td>
</tr>
<tr>
<td>4</td>
<td>OMs/symmetrical anhydride</td>
<td>MsCl, Et₃N, MeCN, 0 °C, 10 min</td>
<td>185 26%</td>
</tr>
<tr>
<td>5</td>
<td>Symmetrical anhydride</td>
<td>Methyl chloroformate, Et₃N, Et₂O, 0 °C, 1.5 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>Symmetrical anhydride</td>
<td>DCC, Et₃N, THF, 0 °C, 1 h</td>
<td>184 &gt;99%</td>
</tr>
</tbody>
</table>

Table 1.5.15. Attempted conversion of acid 179 to α-diazoketone 183 through a variety of methods.

Conversion of carboxylic acid 179 to the acid chloride and acid fluoride was accomplished using Vilsmeier reagent generated in situ, and cyanuric fluoride, respectively.¹¹²,¹¹³ Subsequent treatment of the reaction mixture with excess ethereal diazomethane¹¹⁴ unfortunately failed to deliver α-diazoketone 183, instead giving a mixture of methyl ester 184 (resulting from the reaction of diazomethane with unconverted acid 179) and acid lactol 185. Other measures to activate the
carboxylic acid were also unsuccessful, including DCC-mediated coupling (entry 6) and Nicolaou’s acyl mesylate/mixed anhydride protocol (entry 4). In the event that the activation step was unsuccessful, methyl ester 184 was recovered. If successful, however, intramolecular addition to the methyl ketone took place, providing lactol 185, which was inert to treatment with diazomethane.

Formation of the lactol 185 is supported by the spectral evidence. The $^1$H-NMR spectra of 179 and 185 are very similar; the chemical shift of the methyl ketone CH$_3$ is shifted downfield from $\delta$ 1.69 in the acid 179 to $\delta$ 2.02 in acid lactol 185 (Figure 1.5.19).

Figure 1.5.19. Comparison of the $^1$H-NMR spectra of carboxylic acid 179 (bottom, blue) and acid lactol 185 (red, top).

The $^{13}$C-NMR spectrum, however, was more informative, revealing that the quaternary carbon resonance of the methyl ketone (C-1’’), seen at $\delta$ 206.7 for 179, was missing in 185. Instead, the $^{13}$C-NMR spectrum for 185 contains a quaternary carbon at $\delta$ 104.8, corresponding to an acetal carbon (C-3).

Such compounds have been reported by Sommer et al, where the shift of the methyl ketone protons in $\alpha,\alpha,\beta$-substituted, $\gamma$-keto carboxylic acids (e.g. $\alpha,\alpha,\beta$-levulinic acid 186, Figure 1.5.20) is shifted upfield in the $^1$H-NMR spectrum due to the equilibrium between the acid and lactol forms. The extent of the shift towards the lactol form is determined by the substitution pattern.
Thus, in the case of 179, the α,α,β-substitution of the acid leads to an increased propensity for formation of the five-membered acid lactol 185.

**1.5.4.3 Revision of retrosynthesis II: protected α-diazoketone 188**

In an attempt to circumvent formation of 185, it was decided to protect secondary alcohol 190 as a TBS-ether, which could then be converted to the acid chloride. Consequent treatment with diazomethane would furnish α-diazoketone 188, which following deprotection of the TBS-ether could be transformed via oxidation to desired α-diazoketone 183 (Figure 1.5.21).

A TBS-ether was selected for the protecting group as it is stable to the conditions required to install the diazo moiety. In addition, the diazo functionality should then be stable to the conditions required for removal and oxidation of the resultant alcohol.

Unfortunately, protection of 190 was unsuccessful. When stirred with TBSCI and imidazole in N,N-dimethylformamide at room temperature over 3 d, no reaction occurred. When heated, the now familiar intramolecular oxa-Michael addition took place in preference to protection of the alcohol,
affording only 191 (Figure 1.5.22). As imidazole was employed in excess in this reaction, it is likely acting as base, rather than through an enamine-type mechanism.\textsuperscript{119}

![Chemical structures](image)

**Figure 1.5.22.** Attempted protection of alcohol 190 as a TBS-ether.

It had become apparent that the enone functionality, though present in the natural product, was obstructing desired transformations by participating in undesired intramolecular conjugate additions. It was decided to remove this undesired reactivity by protecting the C-4 carbonyl as either an oxo- or thioacetal.

### 1.5.4.4 Revision of retrosynthesis III: C-4 carbonyl protection

Protection of carbonyl groups in organic chemistry is generally limited to three strategies (Figure 1.5.23):

- a) protect the carbonyl group as a cyclic acetal (oxo-, thio-, or mixed);
- b) protect the carbonyl group by conversion to a methylene; or
- c) reduce the carbonyl group and protect the resultant alcohol.
Options b) and c) were discounted in this case, as an extra methylene group may cause later complications in the intramolecular 1,3-dipolar cycloaddition step, and reduction of the carbonyl group and subsequent protection of the alcohol introduces 4 additional steps to the synthesis. On the other hand, acetals as protecting groups introduce only 2 extra steps into the synthesis, and have been shown in an earlier formal synthesis of platensimycin to be removed readily at the conclusion of the synthesis.\textsuperscript{120}

Consequently, oxo- and thioacetals were considered for the protection of C-4 of the Diels-Alder adduct 101 (Figure 1.5.24):

Unfortunately, attempted protection of C-4 as a dioxolane under standard conditions (ethylene glycol and PTSA at reflux),\textsuperscript{121} only starting material 101 was obtained (Scheme 1.5.13). When more forcing conditions were used (i.e. extended reaction time), complex mixtures were obtained, in which
intermolecular conjugate addition of the diol to the enone occurred. Noyori's TMSOTf-catalysed procedure\textsuperscript{122} similarly afforded only a complex mixture lacking C-2 – C-3 unsaturation. Attempted protection as a dithiane\textsuperscript{123} likewise resulted in a complex mixture lacking C-2 – C-3 unsaturation.

Scheme 1.5.13. Reagents and conditions: a) (CH\textsubscript{2}OH\textsubscript{2}, PTSA, 3 \AA~mol. sieves, PhMe, reflux, 2 h; b) (CH\textsubscript{2}OH\textsubscript{2}, PTSA, PhMe, reflux, 16 h; c) HS(CH\textsubscript{2})\textsubscript{3}SH, cat. I\textsubscript{2}, THF, r.t., 24 h; d) (CH\textsubscript{2}OTMS\textsubscript{2}, TMSOTf, CH\textsubscript{2}Cl\textsubscript{2}, -78 → -20 °C, 4.5 h.

Being unable to install the requisite diazo-functionality without revising the entire retrosynthesis, work on this synthetic route was halted and attention turned to a new avenues of research.
1.6 Conclusion

In summary, a high pressure, thermal Diels-Alder cycloaddition between a trisubstituted olefin $E$-$\textbf{100}$ and activated silyloxydiene $\text{93}$ was developed to give highly functionalised enone $\textbf{101}$. The dienophile $E$-$\textbf{100}$ was itself derived from a Horner-Wadsworth-Emmons olefination between branched phosphonate $\textbf{95}$ and chiral pool-derived aldehyde $\textbf{96b}$ (Figure 1.5.25).

![Figure 1.5.25. Synthesis of dienophile $E$-$\textbf{100}$ and Diels-Alder cycloadduct $\textbf{101}$.

Deprotection of the acetonide proved to be more complex than anticipated; this seemingly trivial transformation was complicated by further intramolecular conjugate addition to the enone, giving the undesired $[3.3.1]$nonane $\textbf{148}$. Eventually, it was found that use of periodic acid – thereby bypassing the problematic intermediate diol – successfully provided the aldehyde $\textbf{102}$ in high yield in one step (Figure 1.5.26).

![Figure 1.5.26. Deprotection of acetonide moiety in cycloadduct $\textbf{101}$.

$$\text{HO}$$
Conversion of advanced intermediate 103 to the required $\alpha$-diazoester 105 or $\alpha$-diazoketone 183 was unsuccessful. Though a variety of techniques were attempted, 105 and 183 remained beyond our reach (Figure 1.5.27). Notably, the mixed carbonic anhydride 181 demonstrated remarkable stability, contributing to its lack of reactivity in attempted displacement with ethyl diazoacetate or diazomethane. This lack of reaction is postulated to be due to the steric crowding at the C-1 centre. Further complicating the transformation was the propensity for 178 to react intramolecularly to give the acid lactol 185.

Unfortunately our approach towards platensimycin was ultimately thwarted by our inability to install the requisite $\alpha$-diazocarbonyl functionality. Advanced intermediate 103 appears to contain too high a level of functionality for successful conversion to the desired $\alpha$-diazoketone 105 or $\alpha$-diazoester 183 under the conditions required. Attempts to overcome this by protection of the groups responsible for the undesired reactivity also met with failure. Being unable to install the requisite diazo-functionality without revising the entire retrosynthesis, work on this synthetic route was halted and attention turned to new avenues of research.
CHAPTER THREE

Experimental

Part One
1.8 Experimental

Tetrahydrofuran, diethyl ether, dimethoxyethane, and toluene were distilled from sodium-benzophenone ketyl under N\textsubscript{2} immediately prior to use. Anhydrous methanol and ethanol were obtained by distillation from the Grignard (Mg/I\textsubscript{2}/ROH) and stored over 4Å molecular sieves prior to use. Acetonitrile was distilled from CaH\textsubscript{2} under N\textsubscript{2} immediately prior to use. Dichloromethane was distilled from CaH\textsubscript{2} under N\textsubscript{2} immediately prior to use. N,N-Dimethylformamide was stirred over CaH\textsubscript{2} overnight, then decanted and distilled under reduced pressure and stored over 4Å molecular sieves prior to use. Acetone was distilled from calcium sulfate immediately prior to use. Triethylamine and diisopropylamine were distilled from calcium hydride; diisopropylamine was stored over 4Å molecular sieves, while triethylamine was stored over anhydrous KOH pellets under N\textsubscript{2}. DBU was fractionally distilled under reduced pressure and stored over KOH pellets under N\textsubscript{2}. Zinc chloride, lithium chloride, and lithium bromide were dried under high vacuum with heating before use. Sodium hydride was obtained from a 60% suspension in mineral oil by washing with anhydrous hexanes 3 times, followed by drying under vacuum. Chlorotrimethylsilane was distilled from calcium hydride prior to use. Dess-Martin periodinane was synthesised from 2-iodoxybenzoic acid according to the procedures of Santagostino\textsuperscript{124} and Ireland.\textsuperscript{125} NaHSO\textsubscript{4}∙SiO\textsubscript{2} was prepared according to the procedure of Breton.\textsuperscript{126} Diazomethane was prepared as an ethereal solution from Diazald\textsuperscript{®} according to the procedure of DeBoer and Backer.\textsuperscript{114} Ethyl diazoacetate was prepared according to the procedure of Clark et al.\textsuperscript{111} and was stored and used as a 10% (w/w) solution in toluene.

Analytical thin layer chromatography (t.l.c.) was performed using Kieselgel F254 0.2 mm (Merck) silica plates, and compounds visualised using ultraviolet irradiation (254 nm), followed by staining with vanillin or potassium permanganate stain. Flash column chromatography was performed using Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel.

NMR spectra were recorded on a Bruker Avance-300 or DRX-400 at the frequencies stated. Chemical shifts for compounds dissolved in deuterated chloroform were referenced to tetramethylsilane as internal standard for \textsuperscript{1}H spectra (δ 0.00), and residual solvent for \textsuperscript{13}C spectra (δ 77.0 ppm), respectively. Chemical shifts for compounds dissolved in deuterated methanol were referenced to residual solvent at δ 3.31 and 49.0 ppm for \textsuperscript{1}H and \textsuperscript{13}C spectra, respectively. The multiplicities of \textsuperscript{1}H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; td = triplet of doublets; ddd = doublet of doublet of doublets; br = broad. All \textsuperscript{13}C-NMR spectra were acquired using broadband decoupled mode, and assignments made using DEPT-135 and
DEPT-90 experiments. IR spectra were obtained using a PerkinElmer Spectrum100 UATR FT-IR spectrometer, using either a solid or thin film of the compound to be analysed. Mass spectra were obtained by fast atom bombardment (FAB), chemical ionisation (CI), or electron spray ionisation (ESI) using a VG70-SE spectrometer or microTOF-Q mass spectrometer. Melting points were determined using a hot-stage melting point apparatus and are uncorrected. Optical rotations were determined using a PerkinElmer 341 polarimeter using the sodium D line (589 nm); concentrations are reported in g/100 mL. High-performance liquid chromatography (HPLC) was performed on a Daicel Chiralpak\textsuperscript{TM} IC column using Dionex Ultimate 3000\textsuperscript{TM} HPLC kit with Chromelon software.
1.8.1 Synthesis of HWE partners

Ethyl 2-(diethoxyphosphoryl)pent-4-enoate 95

Method A: $K_2CO_3$/NaI/60 °C

Prepared according to the procedure of Kirschleger and Queignec.68

Triethyl phosphonoacetate 97 (10 g, 44.61 mmol) and allyl bromide 98 (6.476 g, 53.53 mmol) were added to a round-bottomed flask fitted with a reflux condenser and containing potassium carbonate (12.330 g, 89.21 mmol) and sodium iodide (3.343 g, 22.30 mmol) and the mixture stirred at 60 °C for 4 d. Water (15 mL) was added, and the mixture extracted with diethyl ether (3 x 70 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO$_4$, and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:3 to 1:2 as eluent) to give the title compound 95 (8.704 g, 74%) as a pale yellow oil, in addition to (1.630 g, 12%) of the dialkylated phosphonate 126.

Method B: NaH/THF/0 °C

Prepared according to the procedure of Minami et al.127

Triethyl phosphonoacetate 97 (89 μL, 0.45 mmol) was added slowly to a stirred suspension of sodium hydride (12 mg, 0.49 mmol) in tetrahydrofuran (3 mL) at 0 °C and stirred at this temperature for 30 min. Allyl bromide 98 (39 μL, 0.45 mmol) was then added and the mixture allowed to warm to room temperature and stirred for an additional 2 h. The reaction was quenched with sat. aq. NH$_4$Cl (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with water (15 mL), dried over MgSO$_4$, and concentrated under reduced pressure to give the crude as a pale yellow liquid. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:3 to 2:3 as eluent) to give the title compound 95 (35 mg, 30%) as a clear colourless liquid.
**Ethyl 2-(diethoxyphosphoryl)pent-4-enoate 95**

![Chemical Structure](Image)

R<sub>f</sub> (ethyl acetate:hexanes 3:2) = 0.43.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 5.66 (m, 1H, H-4), 5.02 (dq, 1H, J = 1.4, 17.1 Hz, H<sub>α</sub>-5), 4.94 (dd, 1H, 1.1, 10.2 Hz, H<sub>β</sub>-5), 4.08 (m, 6H, 2 x OEt, CO<sub>2</sub>Et), 2.93 (ddd, 1H, J = 3.9, 11.2, 22.3 Hz, H-1), 2.61 (m, 1H, H-2), 2.49 (m, 1H, H-2), 1.25 (td, 6H, J = 3.0, 7.0 Hz, 2 x OEt), 1.18 (t, 3H, J = 7.0 Hz, CO<sub>2</sub>Et).

Spectral data were in agreement with literature values.<sup>68</sup>

**Ethyl 2-allyl-2-(diethoxyphosphoryl)pent-4-enoate 126**

![Chemical Structure](Image)

R<sub>f</sub> (ethyl acetate:hexanes 3:2) = 0.51.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 5.87 (m, 2H, H-3), 5.10 (m, 4H, H-5), 4.17 (m, 6H, 2 x OEt, CO<sub>2</sub>Et), 2.67 (ddd, 4H, J = 0.7, 7.0, 15.3 Hz, H-3), 1.31 (m, 9H, 2 x OEt, CO<sub>2</sub>Et).

IR (thin film) cm<sup>-1</sup>: 2982 (=C–H), 2932, 2910, 1728 (str, C=O), 1639, 1443, 1367, 1319, 1236 (str), 1209 (str), 1162, 1096, 1048 (str), 1017 (str), 964 (str), 916 (str), 856, 792, 761, 673.

**1,2,5,6-Di-O-isopropylidene-D-mannitol 128**

![Chemical Structure](Image)
Method A: Acetone/ZnCl\textsubscript{2}

Prepared according to the procedure of Tipson and Cohen.\textsuperscript{70}

A solution of anhydrous zinc chloride (1.940 g, 19.2 mmol) in acetone (10 mL) was filtered into a round-bottomed flask containing D-mannitol (1 g, 5.49 mmol). The reaction was stirred for 3 h at room temperature, then poured into a beaker containing a solution of potassium carbonate (2.280 g, 16.5 mmol) in water (3 mL) and stirred vigorously for 15 min. The mixture was then filtered, and the filtrate extracted with dichloromethane (3 x 20 mL). The solids that had been removed via filtration were re-slurried with dichloromethane (2 x 20 mL) and the filtrate collected each time. The combined organic extracts were dried over MgSO\textsubscript{4} and the volatiles removed under reduced pressure to give the crude as a white solid. The crude was purified via recrystallisation from dichloromethane:hexanes 1:1 to give the title compound 128 (0.877 g, 61 %) as white needles.

Method B: 2-methoxypropene/PTSA

Prepared according to the procedure of Debost \textit{et al.}\textsuperscript{69}

2-Methoxypropene (0.1 mL, 1.08 mmol) was added to a solution of D-mannitol (100 mg, 0.55 mol) and calcium sulfate (2 mg, 0.01 mmol) in dimethylformamide (5 mL) at 0 °C. \textit{p}-Toluenesulfonic acid (ca. 2 mg) was then added, and the mixture stirred at this temperature for 4 h, then allowed to warm to room temperature and stirred overnight. Solid sodium carbonate (ca. 10 mg) was added, and the mixture allowed to stir for 1 h before filtering. The solids were washed with hexanes to give the title compound 128 (11 mg, 7%) as white needles.

\( R_f \) (ethyl acetate:hexanes 7:3) = 0.51.

\(^1\)H-NMR (400 MHz, CDCl\textsubscript{3}): δ 4.17 (q, 2H, \( J = 6.3 \) Hz, H\textsubscript{a}-1, H\textsubscript{a}-6), 4.12 (dd, 2H, \( J = 6.4, 8.6 \) Hz, H-2, H-5), 3.97 (dd, 2H, \( J = 5.5, 8.4 \) Hz, H\textsubscript{b}-1, H\textsubscript{b}-6), 3.75 (m, 2H, H-3, H-4), 2.57 (d, 2H, \( J = 6.7 \) Hz, 2 x OH), 1.42 (s, 6H, 2 x gem-dimethyl), 1.36 (s, 6H, 2 x gem-dimethyl).

Spectral data were in agreement with literature values.\textsuperscript{70}

\((R)\)-Glyceraldehyde acetonide 96b

![Diagram](image-url)
Method A:

Prepared according to the procedure of Schmid et al.\textsuperscript{73}

A saturated solution of sodium hydrogen carbonate (2.2 mL) was added to a vigorously stirred solution of 1,2-5,6-di-O-isopropylidene-D-mannitol 128 (6 g, 22.88 mmol) in dichloromethane (60 mL) in a water bath, and stirred for 15 min. Solid sodium periodate (9.785 g, 45.75 mmol) was then added portionwise over 20 min, and the suspension allowed to stir for 2.75 h. MgSO\textsubscript{4} was added, and the slurry filtered \textit{via} vacuum filtration. The solids were re-slurried with a further aliquot of dichloromethane (30 mL), stirred, and filtered. The combined filtrates were concentrated under reduced pressure to give a clear colourless oil. The crude was purified \textit{via} fractional vacuum distillation (Vigreux column, 60-64 °C, 40 mbar) to give the title compound 96b (4.073 g, 68%) as a clear colourless oil.

Method B:

Prepared according to the procedure of Voquang et al.\textsuperscript{72}

A solution of sodium periodate (4.240 g, 19.82 mmol) in water (30 mL) was added dropwise to a vigorously stirred suspension of silica (30 g) in dichloromethane (250 mL). A solution of 1,2-5,6-di-O-isopropylidene-D-mannitol 128 (4.00 g, 15.25 mmol) in dichloromethane (20 mL) was then added, and the mixture allowed to stir for 1 h. The mixture was then filtered through a sinter and the silica washed with dichloromethane (2 x 50 mL). The combined filtrates were concentrated under reduced pressure to give the crude as a yellow oil that become progressively more viscous on standing. The crude was purified in the same manner as method A to give the title compound 96b (1.536 g, 39%) as a clear, colourless oil.

R\textsubscript{f} (ethyl acetate:hexanes 1:1) = 0.23.

[\alpha]_{D}^{20} +74.3° (c = 3.76, chloroform).

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): δ 9.56 (d, 1H, J = 1.9 Hz, H-1'), 4.27 (m, 1H, H-4), 4.07 – 4.92 (m, 2H, H-5), 1.42 (s, 3H, gem-dimethyl), 1.37 (s, 3H, gem-dimethyl).

Spectral data were in agreement with literature values.\textsuperscript{73}
1.8.2 Synthesis of dienophiles

\((S,E)\)-Ethyl 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)pent-4-enoate \textit{E}-100 and \((S,Z)\)-Ethyl 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)pent-4-enoate \textit{Z}-100

Prepared according to the procedure of Oikawa \textit{et al.}^{128}

An ice-cold solution of potassium tert-butoxide (778 mg, 6.94 mmol) in tetrahydrofuran (20 mL) was added slowly to a solution of ethyl 2-(diethoxyphosphoryl)pent-4-enoate 95 (2.00 g, 7.57 mmol) in tetrahydrofuran (20 mL) at 0 °C, and the resulting bright yellow solution allowed to stir at this temperature for 15 min before cooling to -78 °C. A solution of \((R)\)-glyceraldehyde acetonide 96b (0.820 g, 6.31 mmol) was added, and the mixture allowed to stir at this temperature for 1 h. The cooling bath was removed and the reaction quenched with sat. aq. NH₄Cl (25 mL) and brine (10 mL). The aqueous was extracted with diethyl ether (3 x 75 mL) and the combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give the crude as a pale yellow oil. The crude was purified \textit{via} flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the title compounds \textit{E}-100 and \textit{Z}-100 (1.066 g, 70%) as a 2:1 mixture of \textit{E}:\textit{Z} isomers.

\((S,E)\)-Ethyl 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)pent-4-enoate \textit{E}-100

Colourless oil.

\([\alpha]_D^{20} +7.3^\circ \, (c = 1.23, \text{CH}_2\text{Cl}_2)\).

\(R_f\) (ethyl acetate:hexanes 1:4) = 0.6.
\[ ^1H-\text{NMR (400 MHz, CDCl}_3\]: \delta \ 6.76 \text{ (d, } 1\text{H, } J = 8.3 \text{ Hz, H-1'), 5.82 \text{ (m, } 1\text{H, H-4), 5.00 \text{ (m, } 2\text{H, H-5), 4.84 \text{ (m, } 1\text{H, H-2'), 4.21 \text{ (m, } 2\text{H, CO}_2\text{Et), 4.13 \text{ (dd, } 1\text{H, } J = 6.3, 8.3 \text{ Hz, H}_\beta\text{-6'), 3.63 \text{ (t, } 1\text{H, } J = 7.7 \text{ Hz, H}_\alpha\text{-6'), 3.15 \text{ (m, } 2\text{H, H-3), 1.46 \text{ (s, } 3\text{H, gem-dimethyl), 1.41 \text{ (s, } 3\text{H, gem-dimethyl), 1.30 \text{ (t, } 3\text{H, } J = 7.0 \text{ Hz, CO}_2\text{Et).}}
\]

\[ ^{13}\text{C-\text{NMR (100 MHz, CDCl}_3\]: } \delta \ 166.7 \text{ (quat., C-1), 139.5 \text{ (CH, C-1'), 135.3 \text{ (CH, C-4), 127.9 \text{ (quat., C-2), 115.7 \text{ (CH}_2\text{-C-5), 109.9 \text{ (quat., C-4), 72.5 \text{ (CH, C-2'), 68.8 \text{ (CH}_2\text{-C-6'), 61.0 \text{ (CH}_2\text{-CO}_2\text{Et), 31.2 \text{ (CH}_2\text{-C-3), 26.6 \text{ (CH}_3\text{, gem-dimethyl), 25.8 \text{ (CH}_3\text{, gem-dimethyl), 14.2 \text{ (CH}_3\text{-CO}_2\text{Et).}}}}
\]

\[ \text{IR (thin film) cm}^{-1}: \ 2985 \text{ (C–H), 2936, 2872, 1713 \text{ (str, C=O), 1653 \text{ (C=C), 1638 \text{ (C=C), 1617, 1479, 1438, 1370 \text{ (med), 1283, 1255 \text{ (str, C–O), 1207 \text{ (str, C–O), 1152 \text{ (med), 1095, 1056 \text{ (str, 1031 \text{ (med), 913 \text{ (med), 846 \text{ (med), 791, 762 \text{ (med), 712, 651.}}}}
\]

\[ \text{MS (FAB\textsuperscript{+}) m/z 241 [(M + H)\textsuperscript{+}, 13\%]; HRMS (FAB\textsuperscript{+}) m/z 241.14423 [(M + H)\textsuperscript{+}, calcd. for C}_{13}\text{H}_{21}\text{O}_4 \text{ 241.14398].}
\]

\((S,Z)\text{-Ethyl 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)pent-4-enoate Z-100}

![Z-100](image)

Colourless oil.

\([\alpha]_{D}^{20} \text{ +25.9}^\circ \text{ (c = 1.51, CH}_2\text{Cl}_2).\]

\(R_t \text{ (ethyl acetate:hexanes 1:4) = 0.66.}

\[ ^1H-\text{NMR (400 MHz, CDCl}_3\]: \delta \ 6.06 \text{ (dt, } 1\text{H, } J = 1.1, 6.9 \text{ Hz, H-1'), 5.81 \text{ (m, } 1\text{H, H-4), 5.25 \text{ (q, } 1\text{H, } J = 6.8 \text{ Hz, H-2'), 5.06 \text{ (m, } 2\text{H, H-5), 4.32 \text{ (dd, } 1\text{H, } J = 6.8, 8.2 \text{ Hz, H}_\beta\text{-6'), 4.20 \text{ (m, } 2\text{H, CO}_2\text{Et), 3.61 \text{ (dd, } 1\text{H, } J = 6.9, 8.2 \text{ Hz, H}_\alpha\text{-6'), 3.04 \text{ (m, } 2\text{H, H-3), 1.45 \text{ (s, } 3\text{H, gem-dimethyl), 1.38 \text{ (s, } 3\text{H, gem-dimethyl), 1.30 \text{ (t, } 3\text{H, } J = 7.1 \text{ Hz, CO}_2\text{Et).}}
\]

\[ ^{13}\text{C-\text{NMR (100 MHz, CDCl}_3\]: } \delta \ 166.5 \text{ (quat., CO}_2\text{Et), 142.2 \text{ (CH, C-1'), 135.0 \text{ (CH, C-4), 132.2 \text{ (quat., C-2), 116.9 \text{ (CH}_2\text{-C-5), 109.4 \text{ (quat., C-4'), 69.7 \text{ (CH}_2\text{-C-6'), 60.7 \text{ (CH}_2\text{-CO}_2\text{Et), 37.5 \text{ (CH}_2\text{-C-3), 26.6 \text{ (CH}_3\text{, gem-dimethyl), 25.4 \text{ (CH}_3\text{, gem-dimethyl), 14.1 \text{ (CH}_3\text{-CO}_2\text{Et).}}}}
\]

IR (thin film) cm\(^{-1}\): 2984 (C–H), 2936, 1712 (str, C=O), 1638 (C=C), 1432, 1370 (med), 1206 (str, C-O), 1145, 1054 (med), 1023 (med), 916, 849, 793.

MS (FAB\(^{+}\)) m/z 241 [(M + H\(^{+}\), 12%]; HRMS (FAB\(^{+}\)) m/z 241.14460 [(M + H\(^{+}\), calcd. for C\(_{13}\)H\(_{21}\)O\(_{4}\) 241.14398].

\((S,E)\)-Methyl 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)pent-4-enoate  \(E\)-170

![Chemical Structure](image)

Colourless oil.

\([\alpha]_{D}^{20}\) +15.8° (c = 1.02, CH\(_2\)Cl\(_2\)).

\(R_f\) (ethyl acetate:hexanes 1:4) = 0.54.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.78 (d, 1H, \(J = 8.4\) Hz, H-1'), 5.82 (m, 1H, H-4), 5.01 (m, 2H, H-5), 4.84 (m, 1H, H-2'), 4.13 (dd, 1H, \(J = 6.4, 8.2\) Hz, H\(_6\)-6'), 3.76 (s, 3H, CO\(_2\)Me), 3.63 (t, 1H, \(J = 7.9\) Hz, H\(_6\)-6'), 3.12 (m, 2H, H-3), 1.45 (s, 3H, gem-dimethyl), 1.41 (s, 3H, gem-dimethyl).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.2 (quat., CO\(_2\)Me), 140.0 (CH, C-1'), 135.3 (CH, C-4), 132.7 (quat., C-2), 115.7 (CH\(_2\), C-5), 110.0 (quat., C-4'), 72.5 (CH, C-2'), 68.8 (CH\(_2\), C-6'), 52.1 (CH\(_3\), CO\(_2\)Me), 31.2 (CH\(_2\), C-3), 26.6 (CH\(_3\), gem-dimethyl), 25.8 (CH\(_3\), gem-dimethyl).

IR (thin film) cm\(^{-1}\): 3081 (\(\equiv\)C–H), 2986 (C–H), 2951, 2935, 2874, 2255, 1715 (str, C=O), 1654 (C=C), 1638 (C=C), 1436 (med), 1371 (med), 1324, 1291, 1258 (str, C–H), 1214 (str), 1154 (med), 1062 (str), 1030 (med), 996, 916 (med), 853 (med), 836 (med), 794, 765, 734 (med).

MS (ESI) m/z 249 [(M + Na\(^{+}\), 100%]; HRMS (ESI) m/z 249.1097 [(M + Na\(^{+}\), calcd. for C\(_{12}\)H\(_{18}\)O\(_{4}\)Na 249.1097]
DIBAL-H (1 M in hexanes, 2.2 mL, 2.2 mmol) was added slowly dropwise to a solution of (S,E)-ethyl 2-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)pent-4-enoate E-100 (500 mg, 2.08 mmol) in toluene (20 mL) at -78 °C, and the mixture allowed to stir at this temperature for 2 h. T.l.c. analysis of the mixture revealed a significant amount of starting material present, so an additional portion of DIBAL-H (1 M in hexanes, 1 mL, 1 mmol) was added, and the mixture allowed to stir at -78 °C for a further 1.5 h. The mixture was allowed to warm to room temperature and sat. aq. NH₄Cl (30 mL) added. The aqueous was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were washed with brine (50 mL), dried over MgSO₄, and concentrated under reduced pressure to give the crude as a pale yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:19 to 1:1) to give the title compound 153 (303 mg, 73%) as a yellow oil. In addition, 116 mg of starting material E-100 was recovered, as well as a small amount (16 mg, 3%) of aldehyde 154.

Rᵢ (ethyl acetate:hexanes 1:4) = 0.14.

[α]ₐ²⁰ +32.4° (c = 1.24, CH₂Cl₂).

¹H-NMR (300 MHz, CDCl₃): δ 5.77 (m, 1H, H-4), 5.57 (d, 1H, J = 8.7 Hz, H-1’), 5.05 (m, 2H, H-5), 4.82 (m, 1H, H-2’), 4.06 (m, 3H, H-1, H₆-6’), 3.56 (t, 1H, J = 8.0 Hz, H₆-6’), 2.93 (m, 2H, H-3), 1.83 (br s, 1H, OH), 1.43 (s, 3H, gem-dimethyl), 1.40 (s, 3H, gem-dimethyl).

¹³C-NMR (75 MHz, CDCl₃): δ 142.1 (quat., C-2), 135.4 (CH, C-4), 123.7 (CH, C-1’), 116.0 (CH₂, C-5), 109.1 (quat., C-4’), 72.2 (CH, C-2’), 69.4 (CH₂, C-6’), 65.8 (CH₂, C-1), 32.7 (CH₂, C-3), 26.7 (CH₃, gem-dimethyl), 25.9 (CH₃, gem-dimethyl).

IR (thin film) cm⁻¹: 3320 (O–H), 2986 (=C–H), 2931 (C–H), 1602 (med, C=C), 1567 (med, C=C), 1432, 1326 (med), 1235 (med), 1121, 1052 (med), 998 (med), 887 (med), 823, 721, 656.
Dess-Martin periodinane (1.938 g, 4.57 mmol) was added to a solution of \((S,E)-2-((2,2\text{-dimethyl}-1,3\text{-dioxolan-4-yl})\text{methylene})\text{pent-4-en-1-ol} \) 153 (302 mg, 1.52 mmol) and pyridine (740 μL, 9.14 mmol) in dichloromethane (30 mL) and the mixture allowed to stir at room temperature for 45 min. Solid sodium disulfite (ca. 2 g) was added, followed by sat. aq. NaHCO\(_3\) (50 mL), and the resulting mixture allowed to stir for 20 min. The aqueous was extracted with dichloromethane (3 x 60 mL), and the combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the *title compound* 154 (256 mg, 86%) as a colourless oil.

R\(_f\) (ethyl acetate:hexanes 1:4) = 0.51.

\([\alpha]_D^{20}\) +16.8° (c = 0.86, CH\(_2\)Cl\(_2\)).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ 9.46 (s, 1H, H-1), 6.52 (d, 1H, \(J = 7.9\) Hz, H-1\'), 5.77 (m, 1H, H-4), 5.01 (m, 3H, H-5, H-2\'), 4.20 (dd, 1H, \(J = 6.4, 8.3\) Hz, H-6\'), 3.68 (dd, 1H, \(J = 7.3, 8.4\) Hz, H-6\'), 3.16 – 2.96 (m, 2H, H-3), 1.48 (s, 3H, gem-dimethyl), 1.43 (s, 3H, gem-dimethyl).

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): δ 193.5 (CH, C-1), 150.8 (CH, C-1\'), 142.2 (quat., C-2), 134.4 (CH, C-4), 116.0 (CH\(_2\), C-5), 110.3 (quat., C-4\'), 72.4 (CH, C-2\'), 68.8 (CH\(_2\), C-6\'), 28.3 (CH\(_2\), C-3), 26.6 (CH\(_3\), gem-dimethyl), 25.7 (CH\(_3\), gem-dimethyl).

IR (thin film) cm\(^{-1}\): 2968 (=C–H), 2955 (C–H), 2934, 1732 (str, C=O), 1635 (C=C), 1597 (C=C), 1458, 1447 (med), 1321, 1192 (str), 1113, 1056 (str), 1012, 987 (str), 954, 753, 742, 606.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

(S,E)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate  \(E\-155\) and (S,Z)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate  \(Z\-155\)

Prepared according to the procedure of Ortuño and Izquierdo.\(^{129}\)

Potassium tert-butoxide (1.552 g, 13.83 mmol) was added to an ice-cold solution of triethyl phosphonoacetate \(97\) (2.72 mL, 13.72 mmol) in dichloromethane (30 mL) and allowed to stir at 0 °C for 30 min. A solution of (R)-glyceraldehyde acetonide \(96b\) (1.5 g, 11.53 mmol) in dichloromethane (2 mL) was then added, and the mixture allowed to stir at 0 °C for an additional 2 h. The mixture was allowed to warm to room temperature and the volatiles removed under reduced pressure and the sticky residue diluted with ethyl acetate (40 mL). The solution was washed with sat. aq. NaHCO\(_3\) (2 x 50 mL) and then dried over MgSO\(_4\). The solvent was removed under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:19 as eluent) to give the title compounds \(E\-155\) (1.951 g, 85%) and \(Z\-155\) (0.187 g, 8%) as colourless oils.

(S,E)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate  \(E\-155\)

R\(_f\) (ethyl acetate:hexanes 1:4) = 0.56.

\([\alpha]_D^{20} +35.2^\circ\) (c = 1.25, CH\(_2\)Cl\(_2\)).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 6.88\) (dd, 1H, \(J = 15.6, 5.6\) Hz, H-3), \(6.10\) (dd, 1H, \(J = 15.8, 1.4\) Hz, H-2), \(4.67\) (m, 1H, H-4'), \(4.20\) (m, overlapping signals, 3H, CO\(_2\)Et, H\(_a\)-5'), \(3.68\) (dd, 1H, \(J = 8.3, 7.3\) Hz, H\(_b\)-5'), \(1.45\) (s, 3H, gem-dimethyl), \(1.41\) (s, 3H, gem-dimethyl), \(1.30\) (t, 3H, \(J = 7.1\) Hz, CO\(_2\)Et).

Spectral data were in agreement with literature values.\(^{130}\)
**1.8.3 Synthesis of dienes**

2-Trimethylsilyloxy-4-methoxy-1,3-butadiene (Danishefsky’s diene) 93

Prepared according to the procedure of Danishefsky and Kitahara.\textsuperscript{78}

Triethylamine (15.3 mL, 109.87 mmol) was added to a flask containing anhydrous zinc chloride (0.191 g, 1.40 mmol) and stirred at room temperature for ca. 30 min until the salt was fully suspended in the amine. A solution of trans-4-methoxy-3-buten-2-one 143 (5.1 mL, 49.94 mmol) in toluene (15 mL) was then added, followed by chlorotrimethylsilane (12.6 mL, 99.88 mmol). The ruby-red mixture was then allowed to stir at room temperature for 30 min, then heated at 40 °C for a further 23 h. The thick brown suspension was then allowed to cool to room temperature and freshly distilled diethyl ether (50 mL) was added. The mixture was then filtered twice through a pad of Celite\textsuperscript{®} and the volatiles removed under reduced pressure to give the crude as a dark brown oil.
crude was purified via fractional vacuum distillation (Vigreux column, 40 – 56 °C, 7 Torr) to give the title compound 93 (6.457 g, 75%) as a pale yellow liquid with a small amount of fluffy white solid (triethylamine hydrochloride) suspended within.

$^1$H-NMR analysis showed the ratio of 93:143 to be 100:1.

$^1$H-NMR (400 MHz, CDCl$_3$): δ 6.83 (d, 1H, $J = 12.3$ Hz, H-4), 5.35 (d, 1H, $J = 12.3$ Hz, H-3), 4.09 (d, 2H, $J = 16.6$ Hz, H-1), 3.57 (s, 3H, OMe), 0.23 (s, 9H, OTMS).

Spectral data were in agreement with literature values.$^{78}$

(E)-4-Dimethylamino-3-buten-2-one 146

Prepared according to the procedure of Rawal et al.$^{81}$

Sodium hydroxide (2.996 g, 74.91 mmol) was added to a solution of dimethylamine hydrochloride (6.108 g, 74.91 mmol) in tetrahydrofuran:water (1:5, 60 mL) at 0 °C and stirred at this temperature for ca. 30 min until the solid had dissolved. Trans-4-methoxy-3-buten-2-one 143 (5.1 mL, 49.94 mmol) was then added dropwise and the solution allowed to stir at 0 °C for 30 min, before allowing to warm to room temperature and stirring for an additional 5 h. Water (50 mL) was then added, and the mixture extracted with dichloromethane (10 x 25 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure to give a yellow liquid. The crude was purified via fractional vacuum distillation (125 °C, 12 Torr) to give the title compound 146 (5.108 g, 90%) as a yellow liquid.

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.47 (d, 1H, $J = 12.8$ Hz, H-4), 5.05 (d, 1H, $J = 12.8$ Hz, H-3), 3.03 – 2.85 (br d, 6H, $J = 7.0$, HMe$_2$), 2.10 (s, 3H, H-1).

Spectral data were in agreement with literature values.$^{81}$
(E)-1-Dimethylamino-3-tert-butyldimethylsilyloxy-1,3-butadiene (Rawal’s diene) 123

Prepared according to the procedure of Rawal et al.\textsuperscript{81}

KHMDS (0.5 M in toluene, 56 mL, 27.84 mmol) was diluted with tetrahydrofuran (56 mL) and allowed to stir at room temperature for 5 min, before cooling the mixture to -78 °C. A solution of (E)-4-dimethylamino-3-buten-2-one 146 (3 g, 26.51 mmol) in tetrahydrofuran (7 mL) was added over 30 min via syringe pump. The cloudy yellow mixture was allowed to warm to -30 °C and stirred at this temperature for 4 h. The dark orange suspension was then re-cooled to -78 °C, and a solution of TBSCI (4.196 g, 27.84 mmol) in tetrahydrofuran (22 mL) was added slowly. The mixture was then allowed to warm to room temperature and the volatiles removed under reduced pressure. Freshly distilled diethyl ether (50 mL) was added, and the suspension filtered through cotton wool. The volatiles were removed under reduced pressure to give the title compound 123 (5.021 g, crude) as a dark red-brown oil.

\textsuperscript{1}H-NMR analysis of the crude showed it to be a mixture of 123:146 in a ration of 1:2. The material thus obtained was used without further purification.

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 6.57 (d, 1H, \(J = 13.2\) Hz, H-1), 4.78 (d, 1H, \(J = 13.2\) Hz, H-2), 3.92 (s, 1H, \(H_a\)), 3.84 (s, 1H, \(H_b\)), 2.70 (s, 6H, NMe\textsubscript{2}), 0.91 (s, 12H, OTBS), 0.05 (s, 6H, OTBS).

Spectral data were in agreement with literature values.\textsuperscript{81}
1.8.4 Diels-Alder cycloadditions

![Diels-Alder reaction scheme]

High-pressure Diels-Alder reaction: General procedure 1A.

Prepared according to the procedure of Asano et al.\(^\text{67}\)

Diene (2 mol. eq.) was added to a solution of the dienophile (1 mol. eq.) in toluene (1 mL/100 mg) in a sealed vessel, which was flushed with N\(_2\) and then heated at 150 °C for 48 h. The mixture was allowed to cool to room temperature and an additional aliquot of diene (2 mol. eq.) was added. The vessel was flushed with N\(_2\) and heated at 150 °C for an additional 48 h. Again, the mixture was allowed to cool and a final aliquot of diene (2 mol. eq.) added. The vessel was flushed with N\(_2\) and heated at 150 °C for a final 48 h. The mixture was allowed to cool to room temperature and the volatiles removed under reduced pressure to give an orange oil. The residue was diluted with tetrahydrofuran (3 mL/100 mg), and 0.05 M aq. HCl added (2 mL/100 mg). The mixture was allowed to stir vigorously at r.t. for 1 h, then extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with 2M NaOH (2 x 40 mL), brine (40 mL), dried over MgSO\(_4\), and concentrated under reduced pressure to give the crude as an orange oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 as eluent) to give the products as detailed in tables 1.5.6 – 1.5.11.

**(1R,6R)-Ethyl 6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxocyclohex-2-enecarboxylate**

157

Yellow oil.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

\[ R_f \text{ (ethyl acetate:hexanes 1:4)} = 0.33. \]

\[^1^H\text{-NMR (400 MHz, CDCl}_3\text{)}: \delta 6.81 (dd, 1H, } J = 3.1, 10.2 \text{ Hz, H-2), 6.11 (dd, 1H, } J = 1.2, 10.4 \text{ Hz, H-3), 4.25 (m, 3H, CO}_2\text{Et, H-4'), 4.05 (dd, 1H, } J = 7.1, 8.4 \text{ Hz, H}_5\text{-5'), 3.05 (m, 2H, H-1, H}_6\text{-5), 2.71 – 2.50 (m, 2H, H-6, H}_6\text{-5), 1.59 (s, 3H, gem-dimethyl), 1.41 (s, 3H, gem-dimethyl), 1.33 (t, 3H, } J = 7.1 \text{ Hz, CO}_2\text{Et).} \]

\[^{13}^C\text{-NMR (100 MHz, CDCl}_3\text{)}: \delta 206.9 \text{ (quat., C-4), 177.3 (quat., CO}_2\text{Et), 145.1 (CH, C-2), 130.3 (CH, C-3), 109.9 \text{ (quat., C-2'), 75.6 (CH, C-4'), 66.6 (CH}_2\text{, C-5'), 61.0 (CH}_2\text{, CO}_2\text{Et), 45.4 (CH, C-1), 39.1 (CH}_2\text{, C-5), 38.0 (CH, C-6), 24.8 (CH}_3\text{, gem-dimethyl), 24.4 (CH}_3\text{, gem-dimethyl), 14.2 (CH}_3\text{, CO}_2\text{Et).} \]

IR (thin film) cm\(^{-1}\): 2987 (=C–H), 2883 (C–H), 2874, 1774 (str, C=O), 1687 (str, C=C), 1642 (med), 1446, 1432 (med), 1352, 1348, 1229 (med), 1214 (med), 1027 (str), 1006 (med), 994 (med), 985 (med), 864 (med), 768 (med), 762.

MS (Cl) \( m/z \) 269 [(M + H)\(^+\), 28%]; HRMS (Cl) \( m/z \) 269.13915 [(M + H)\(^+\), calcd. for C\(_{14}\)H\(_{21}\)O\(_5\) 269.13890].

(1\(R\),6\(R\))-Ethyl 1-allyl-4-(tert-butyldimethylsilyloxy)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(dimethylamino)cyclohex-3-enecarboxylate 147

Yellow oil.

\[ R_f \text{ (ethyl acetate:hexanes 1:1)} = 0.57. \]

\[^1^H\text{-NMR (300 MHz, CDCl}_3\text{)}: \delta 5.68 (m, 1H, H-2'), 5.14 (m, 2H, H-3'), 4.81 (t, 1H, } J = 2.3 \text{ Hz, H-3), 4.38 (td, 1H, } J = 2.3, 7.1 \text{ Hz, H-4''), 4.15 – 4.03 (m, 2H, CO}_2\text{Et), 3.98 (dd, 1H, } J = 6.6, 8.1 \text{ Hz, H}_6\text{-5''), 3.62 (t, 1H, } J = 7.8 \text{ Hz, H}_6\text{-5''), 3.35 (m, 1H, H-2), 2.74 – 2.60 (m, 2H, H-5), 2.25 (s, 6H, 2-NMe\(_2\)), 1.95 (m, 2H, H-1'), 1.36 (s, 3H, gem-dimethyl), 1.29 (s, 3H, gem-dimethyl), 1.26 (t, 3H, } J = 7.2 \text{ Hz, CO}_2\text{Et), 0.95 (s, 9H, OTBS), 0.19 (s, 6H, OTBS).} \]
C-NMR (75 MHz, CDCl₃): δ 173.5 (quat., CO₂Et), 151.1 (quat., C-4), 134.1 (CH, C-2′), 119.1 (CH₂, C-3′), 108.9 (quat., C-2″), 99.5 (CH, C-3), 73.6 (CH, C-4″), 67.5 (CH₂, C-5″), 64.5 (CH, C-2), 60.1 (CH₂, CO₂Et), 50.8 (quat., C-1), 44.0 (2 x CH₃, 2-NMe₂), 38.4 (CH₂, C-1′), 36.1 (CH, C-6), 27.2 (CH₃, gem-dimethyl), 26.2 (CH₂, C-5), 25.7 (3 x CH₃, OTBS), 25.2 (CH₃, gem-dimethyl), 17.9 (quat., OTBS), 14.1 (CH₃, CO₂Et), -4.1 (CH₃, OTBS), -4.4 (CH₃, OTBS).

Yellow oil.

Rᵣ (ethyl acetate:hexanes 1:1) = 0.61.

H-NMR (400 MHz, CDCl₃): δ 6.41 (m, 1H, H-2′), 5.00 (m, 2H, H-3′), 4.79 (d, 1H, J = 5.6 Hz, H-3), 4.32 (ddd, 1H, J = 1.2, 6.4, 7.9 Hz, H-4″), 4.15 (m, 2H, CO₂Et), 4.12 (m, 1H, Hₐ-5″), 3.57 (t, 1H, J = 8.2 Hz, Hₕ₆-5″), 3.24 (d, 1H, J = 5.4 Hz, H-6), 2.63 (m, 1H, H-2), 2.42 (m, 1H, Hₐ-1′), 2.38 (m, 1H, Hₕ₆-5), 2.27 (m, 1H, Hₕ₆-1′), 2.20 (s, 6H, 2-NMe₂), 1.95 (dd, 1H, J = 6.6, 18.4 Hz, Hₕ₆-5), 1.38 (s, 3H, gem-dimethyl), 1.31 (s, 3H, gem-dimethyl), 1.28 (t, 3H, J = 7.1 Hz, CO₂Et), 0.94 (s, 9H, OTBS), 0.18 (s, 6H, OTBS).

C-NMR (100 MHz, CDCl₃): δ 175.0 (quat., CO₂Et), 152.5 (quat., C-4), 135.9 (CH, C-2′), 117.3 (CH₂, C-3′), 109.1 (quat., C-2″), 97.3 (CH, C-3), 75.6 (CH, C-4″), 69.2 (CH₂, C-5″), 65.5 (CH, C-2), 59.9 (CH₂, CO₂Et), 54.3 (quat., C-1), 44.0 (2 x CH₃, 2-NMe₂), 36.8 (CH₂, C-1′), 35.9 (CH, C-6), 26.3 (CH₃, gem-dimethyl), 26.0 (CH₂, C-3), 25.8 (quat., OTBS), 25.7 (CH₃, gem-dimethyl), 25.6 (3 x CH₃, OTBS), 14.1 (CH₃, CO₂Et), -4.3 (CH₃, OTBS), -4.4 (CH₃, OTBS).
**BF₃·OEt₂-induced elimination of (1S,6R)-ethyl 1-allyl-4-(tert-butyl-dimethylsilyloxy)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(dimethylamino)-cyclohex-3-enecarboxylate**

Boron trifluoride diethyl etherate (18 μL, 0.14 mmol) was added to a solution of (1S,6R)-ethyl 1-allyl-4-(tert-butyl-dimethylsilyloxy)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(dimethylamino)-cyclohex-3-enecarboxylate 145 (65 mg, 0.14 mmol) in dichloromethane (5 mL) at -78 °C and the mixture allowed to stir at this temperature for 0.5 h. The mixture was then allowed to warm to room temperature and stirred for an additional 5 h. Aq. NaHCO₃ (5 mL) was added, followed by ethyl acetate (10 mL). The organic layer was removed, and the aqueous extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 3:7 as eluent) to give the title compounds 101 (19 mg, 44%) as a pale yellow oil, and 148 (8 mg, 22%) as a pale yellow oil.

**Rf** (ethyl acetate:hexanes 3:7) = 0.50.

**1H-NMR (400 MHz, CDCl₃):** δ 6.77 (d, 1H, J = 10.3 Hz, H-2), 6.07 (d, 1H, J = 10.3 Hz, H-3), 5.82 (m, 1H, H-2′), 5.13 (m, 2H, H-3′), 4.43 (dt, 1H, J = 1.7, 7.3 Hz, H-4′), 4.21 (q, 2H, J = 7.1 Hz, CO₂Et), 4.03 (dd, 1H, J = 6.7, 8.2 Hz, H-5′), 3.58 (dd, 1H, J = 7.5, 8.0 Hz, H-6′), 2.84 (ddt, 1H, J = 1.2, 6.6, 13.9 Hz, H-6), 2.73 – 2.45 (m, 4H, H-5, H-1′), 1.36 (s, 3H, gem-dimethyl), 1.33 (s, 3H, gem-dimethyl), 1.28 (t, 3H, J = 7.2 Hz, CO₂Et).
13C-NMR (100 MHz, CDCl3): δ 198.2 (quat., C-4), 173.3 (quat., CO2Et), 149.7 (CH, C-2), 132.7 (CH, C-2′), 128.8 (CH, C-3), 119.6 (CH2, C-3′), 109.8 (quat., C-2′′), 73.7 (CH, C-4′), 67.8 (CH2, C-5′), 61.7 (CH2, CO2Et), 51.0 (quat., C-1), 42.1 (CH, C-6), 37.8 (CH2, C-1′), 34.5 (CH2, C-5), 25.9 (CH3, gem-dimethyl), 25.2 (CH3, gem-dimethyl), 14.2 (CH3, CO2Et).

IR (thin film) cm⁻¹: 3081, 2983 (―C–H), 2935 (C–H), 1784 (med), 1727 (str, C=O), 1683 (str, C=O), 1642 (med), 1453 (med), 1436 (med), 1382 (med), 1371 (med), 1223 (br, str, C-O), 1163 (str), 1091 (str), 1062 (str), 992 (med), 885 (med), 793 (med), 760.

MS (ESI) m/z 331 [(M + Na)+, 100%], HRMS (ESI) m/z 331.1504 [(M + Na)+, calcd. for C17H24O5Na 331.1516].

(1S,4R,5R,9S)-ethyl 9-allyl-4-hydroxy-7-oxo-2-oxabicyclo[3.3.1]nonane-9-carboxylate

Colourless oil.

Rf (ethyl acetate:hexanes 3:7) = 0.34.

1H-NMR (400 MHz, CDCl3): δ 5.77 (m, 1H, H-2′), 5.15 (m, 2H, H-3′), 4.42 (m, 1H, H-1), 4.20 (q, 2H, J = 7.2 Hz, CO2Et), 3.74 (m, 3H, H-3, H-4), 3.11 – 2.91 (m, 3H, H-1′, Ha-8), 2.75 – 2.67 (m, 3H, H-5, H-6), 2.42 (m, 1H, Hb-8), 1.97 (d, 1H, J = 2.4 Hz, OH), 1.29 (t, 3H, J = 7.3 Hz, CO2Et).

13C-NMR (100 MHz, CDCl3): δ 208.6 (quat., C-7), 173.1 (quat., CO2Et), 133.6 (CH, C-2′), 118.6 (CH2, C-3′), 71.7 (CH, C-1), 71.1 (CH, C-4), 64.2 (CH2, C-3), 60.9 (CH2, CO2Et), 48.4 (quat., C-9), 43.9 (CH2, C-6), 43.3 (CH2, C-8), 39.2 (CH2, C-1′), 38.8 (CH, C-5), 14.2 (CH3, CO2Et).

IR (thin film) cm⁻¹: 3434 (br, O–H), 3076 (=C–H), 2977 (C–H), 2955, 2925, 2871, 1718 (str, C=O), 1639 (C=C), 1463, 1417, 1398, 1367, 1351, 1289, 1215 (str, C–O), 1129 (med), 1109 (med), 1060 (med), 1043 (med), 996 (med), 966, 926 (med), 875, 857, 820, 804, 764, 736, 713, 663, 610, 588.

MS (ESI) m/z 269 [(M + H)+, 16%], 291 [(M + Na)+, 23%]; HRMS (ESI) m/z 269.1382 [(M + H)+, calcd. for C14H21O5 269.1384], 291.1200 [(M + Na)+, calcd. for C14H20O5Na 291.1203].
(1R,6R)-Methyl 1-allyl-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxocyclohex-2-enecarboxylate *endo*-171

Colourless oil.

$R_f$ (ethyl acetate:hexanes 3:7) = 0.4.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 6.78 (d, 1H, $J = 10.3$ Hz, H-2), 6.06 (d, 1H, $J = 10.3$ Hz, H-3), 5.79 (m, 1H, H-2'), 5.15 (m, 2H, H-3'), 4.42 (dd, 1H, $J = 1.1$, 7.1 Hz, H-4''), 4.04 (dd, 1H, $J = 7.0$, 8.2 Hz, H-5''), 3.75 (s, 3H, CO$_2$Me), 3.57 (t, 1H, $J = 7.8$ Hz, H$_a$-5''), 2.88 – 2.44 (m, 5H, H-5, H-6, H-1'), 1.36 (s, 3H, gem-dimethyl), 1.32 (s, 3H, gem-dimethyl).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 197.9 (quat., C-4), 173.7 (quat., CO$_2$Me), 149.3 (CH, C-2), 132.6 (CH, C-2'), 128.8 (CH, C-3), 119.5 (CH$_2$, C-3'), 109.7 (quat., C-2''), 73.6 (CH, C-4''), 67.8 (CH$_2$, C-5''), 52.6 (CH$_3$, CO$_2$Me), 51.2 (quat., C-1), 42.2 (CH, C-6), 37.7 (CH$_2$, C-1'), 34.5 (CH$_2$, C-5), 25.8 (CH$_3$, gem-dimethyl), 25.1 (CH$_3$, gem-dimethyl).

IR (thin film) cm$^{-1}$: 2987 (=C–H), 2942 (C–H), 1723 (str, C=O), 1681 (str, C=O), 1633, 1448 (med), 1431, 1387 (med), 1376 (med), 1228 (med, C–O), 1168 (med), 1142, 1038 (str), 1014, 997 (med), 885, 863, 792, 754.

MS (ESI) $m/z$ 317 [(M + Na)$^+$, 50%]; HRMS (ESI) $m/z$ 317.1370 [(M + Na)$^+$, calcd. for C$_{16}$H$_{22}$O$_3$Na 317.1359].

(1S,6S)-Methyl 1-allyl-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxocyclohex-2-enecarboxylate *exo*-171

White solid, melting point: 84 – 86 °C.
R_f (ethyl acetate:hexanes 3:7) = 0.43.

^1^H-NMR (400 MHz, CDCl_3): δ 6.65 (d, 1H, J = 10.2 Hz, H-2), 6.10 (d, 1H, J = 10.2 Hz, H-3), 5.93 (m, 1H, H-2'), 5.14 (m, 2H, H-4'', H_5-5''), 4.10 (m, 2H, H-4'', H_5-5''), 3.73 (s, 3H, CO_2Me), 3.58 (t, 1H, J = 7.3 Hz, H_5-5''), 2.95 (m, 2H, H_5-5', H-5), 2.53 (dd, 1H, J = 9.1, 13.9 Hz, H_5-5), 2.41 – 2.19 (m, 2H, H-6, H_5-5'). 1.33 (s, 6H, 2 x gem-dimethyl).

^13^C-NMR (100 MHz, CDCl_3): δ 196.5 (quat., C-4), 173.9 (quat., CO_2Me), 150.9 (CH, C-2), 133.5 (CH, C-2'), 128.6 (CH, C-3), 119.0 (CH_2, C-3'), 109.3 (quat., C-2''), 74.9 (CH, C-4''), 68.3 (CH_2, C-5''), 52.4 (CH_3, CO_2Me), 50.1 (quat., C-1), 44.5 (CH, C-6), 36.4 (CH_2, C-1'), 36.2 (CH_2, C-5), 26.2 (CH_3, gem-dimethyl), 25.6 (CH_3, gem-dimethyl).

IR (thin film) cm^{-1}: 3034, 2993 (=C–H), 2954 (C–H), 1731 (str, C=O), 1688 (str, C=C), 1653 (med), 1447 (med), 1428 (med), 1357, 1332 (med), 1296, 1231 (med, C–O), 1165 (med), 1154 (med), 1092 (str), 1062 (med), 994 (med), 887 (med), 854 (med), 753 (med).

MS (ESI) m/z 317 [(M + Na)^+, 50%]; HRMS (ESI) m/z 317.1370 [(M + Na)^+, calcd. for C_{16}H_{22}O_5Na 317.1359].

1.8.5 Deprotection of acetonide 101

(1R,6R)-Ethyl 1-allyl-6-((R)-1,2-dihydroxyethyl)-4-oxocyclohex-2-enecarboxylate 149

Table 1.5.12, entry 7. Prepared according to the procedure of Szarek et al.95

A solution of I_2 in methanol (1% w/v, 2 mL) was added to (1S,6R)-ethyl 1-allyl-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxocyclohex-2-enecarboxylate 101 (65 mg, 0.21 mmol) and the mixture allowed to stir at room temperature for 2 h. The reaction was quenched with sat. aq. Na_2S_2O_3 (5 mL), and the mixture extracted with chloroform (3 x 15 mL). The combined organic extracts were washed with brine, dried over MgSO_4, and concentrated under reduced pressure to give the crude as a pale yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 → 2:3 as eluent) to give the title compound 149 (11 mg, 19%) as a pale yellow oil, in addition to 148 (7 mg, 13%) as a pale yellow oil.
R_f (ethyl acetate:hexanes 1:1) = 0.14.

^1^H-NMR (400 MHz, CDCl\textsubscript{3}): δ 6.79 (d, 1H, J = 10.3 Hz, H-2), 6.06 (d, 1H, J = 10.2 Hz, H-3), 5.80 (m, 1H, H-2'), 5.16 (m, 2H, H-3'), 4.21 (q, 2H, J = 7.1 Hz, CO\textsubscript{2}Et), 4.11 (t, 1H, J = 5.8 Hz, H-1''), 3.56 (d, 2H, J = 6.1 Hz, H-2''), 2.87 (m, 1H, H-5'), 2.71 (m, 1H, H-5), 2.63 (m, 1H, H-1'), 2.58 (m, 1H, H-6), 2.45 (m, 1H, H-5), 1.28 (t, 3H, J = 7.1 Hz, CO\textsubscript{2}Et).

^1^C-NMR (100 MHz, CDCl\textsubscript{3}): δ 198.7 (quat., C-4), 173.4 (quat., CO\textsubscript{2}Et), 150.1 (CH, C-2), 132.9 (CH, C-2'), 128.7 (CH, C-3), 119.5 (CH\textsubscript{2}, C-3'), 69.8 (CH, C-1''), 65.3 (CH\textsubscript{2}, C-2''), 61.8 (CH\textsubscript{2}, CO\textsubscript{2}Et), 51.2 (quat., C-1), 41.5 (CH, C-6), 37.6, (CH\textsubscript{2}, C-1'), 35.0 (CH\textsubscript{2}, C-5), 14.2 (CH\textsubscript{3}, CO\textsubscript{2}Et).

IR (thin film) cm\textsuperscript{-1}: 3351 (br, O–H), 2984 (=C–H), 2867 (C–H), 1734 (str, C=O), 1648 (str, C=C), 1632, 1329 (med), 1314, 1295, 1254 (med), 1047 (str), 1019, 968 (str), 912 (med), 887, 768 (med), 669.

MS (ESI) m/z 269 [(M + H)^+], 6%; 291 [(M + Na)^+], 100%; HRMS (ESI) m/z 269.1378 [(M + H)^+ calcd. for C\textsubscript{14}H\textsubscript{21}O\textsubscript{5} 269.1384], 291.1202 [(M + Na)^+ calcd. for C\textsubscript{14}H\textsubscript{20}O\textsubscript{5}Na 291.1203].

(1\textit{R},6\textit{R})-Ethyl 1-allyl-6-formyl-4-oxocyclohex-2-enecarboxylate 102

Method A: Oxidative cleavage of the acetonide 101 with periodic acid

Prepared according to the procedure of Carda \textit{et al}.\textsuperscript{109}
Periodic acid (348 mg, 1.02 mmol) was added to a solution of (1R,6R)-ethyl 1-allyl-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxocyclohex-2-enecarboxylate 101 (314 mg, 1.02 mmol) in ethyl acetate (distilled, 20 mL) and allowed to stir at room temperature for 1.25 h. Solid sodium thiosulfate (ca. 200 mg) was added, and the mixture allowed to stir for 10 min. The mixture was then filtered through Celite®, and the Celite® washed with an additional 10 mL aliquot of ethyl acetate. The solvent was removed from the combined filtrates under reduced pressure to give the crude as a clear oil with yellow solids suspended within. The crude was purified via rapid flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 as eluent) to give the title compound 102 (172 mg, 71%) as a clear colourless oil.

**Method B: Oxidative cleavage of the diol 149 with sodium periodate**

Prepared according to the procedure of Schmid et al.73

Sodium periodate (14 mg, 0.07 mmol) was added to a vigorously stirred solution of (1R,6R)-ethyl 1-allyl-6-((R)-1,2-dihydroxyethyl)-4-oxocyclohex-2-enecarboxylate 149 (9 mg, 0.03 mmol) in dichloromethane (5 mL) and sat. aq. NaHCO₃ (0.8 mL). The mixture was allowed to stir at room temperature for 1 h, until t.l.c. analysis showed complete consumption of starting material. MgSO₄ was added, and the solids filtered and washed with dichloromethane (10 mL). The filtrates were concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 as eluent) to give the title compound 102 (7 mg, 88%) as a pale yellow oil.

R_f (ethyl acetate:hexanes 1:1) = 0.81.

^1H-NMR (400 MHz, CDCl₃): δ 9.37 (d, 1H, J = 1.1 Hz, H-1”), 6.87 (d, 1H, J = 10.3 Hz, H-2), 6.09 (d, 1H, J = 10.3 Hz, H-3), 5.74 (m, 1H, H-2’), 5.16 (m, 2H, H-3’), 4.28 (qd, 2H, J = 1.7, 7.2 Hz, CO₂Et), 3.54 (ddd, 1H, J = 1.0, 5.6, 8.6 Hz, H-6), 2.82 – 2.60 (4H, m, H-5, H-1’), 1.33 (t, 3H, J = 7.1 Hz, CO₂Et).

^13C-NMR (100 MHz, CDCl₃): δ 200.2 (CH, C-1”), 195.8 (quat., C-4), 171.9 (quat., CO₂Et), 148.3 (CH, C-2), 131.1 (CH, C-2’), 129.3 (CH, C-3), 120.8 (CH₂, C-3’), 62.3 (CH₂, CO₂Et), 50.8 (CH, C-6), 49.8 (quat., C-1), 38.8 (CH₂, C-1’), 34.4 (CH₂, C-5), 14.2 (CH₃, CO₂Et).

IR (thin film) cm⁻¹: 2947 (=C–H), 2873 (C–H), 1735 (str, C=O), 1682 (str, C=C), 1412, 1378 (med), 1357 (med), 1284 (med, C–O), 1183 (med), 1096 (med), 994 (med), 943 (med), 856, 823, 779 (med), 727 (med), 663 (med).
MS (ESI) \( m/z \) 237 [(M + H)\(^+\), 75%], 259 [(M + Na)\(^+\), 78%]; HRMS (ESI) \( m/z \) 237.1112 [(M + H)\(^+\)] calcd. for C\(_{13}\)H\(_{17}\)O\(_4\) 237.1121, 259.0931 [(M + Na)\(^+\)] calcd. for C\(_{13}\)H\(_{16}\)O\(_4\)Na 259.0941.

### 1.8.6 Elaboration to advanced ester 103

(1\(R\),6\(R\))-Ethyl 1-allyl-6-((R)-1-hydroxyethyl)-4-oxocyclohex-2-enecarboxylate 177

![Chemical Structure](image)

A solution of methylmagnesium bromide (3.0 M in diethyl ether, 40 \( \mu \)L, 0.12 mmol) was added to a solution of (1\(R\),6\(R\))-ethyl 1-allyl-6-formyl-4-oxocyclohex-2-enecarboxylate 102 (31 mg, 0.13 mmol) in tetrahydrofuran (5 mL) at -78 °C. The mixture was allowed to stir at this temperature for 30 min, then quenched with sat. aq. NH\(_4\)Cl (10 mL). The aqueous was extracted with diethyl ether (3 x 20 mL) and the combined organic extracts dried over MgSO\(_4\). The volatiles were removed under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 as eluent) to give the title compound 177 (27 mg, 90%) as a pale yellow oil. In addition, 5 mg of starting material 102 was also recovered.

\( R_f \) (ethyl acetate:hexanes 1:1) = 0.6; \( R_f \) (ethyl acetate:hexanes 3:7) = 0.20.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 6.77 (d, 1H, \( J = 10.1 \) Hz, H-2), 6.05 (d, 1H, \( J = 10.3 \) Hz, H-3), 5.80 (m, 1H, H-2\( ' \)), 5.15 (m, 2H, H-3\( ' \)), 4.28 (m, 1H, H-1\( ' \)), 4.21 (q, 2H, \( J = 7.0 \) Hz, CO\(_2\)Et), 2.92 – 2.87 (ddd, 1H, \( J = 0.6, 6.5, 14.0 \) Hz, H-1\( ' \)), 2.72 – 2.49 (m, 4H, H-5, H-6, H-6\( ' \)), 1.30 – 1.23 (m, 6H, H-2\( '' \) and CO\(_2\)Et).

\(^1\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 199.0 (quat., C-4), 173.5 (quat., CO\(_2\)Et), 150.4 (CH, C-2), 133.2 (CH, C-2\( ' \)), 128.9 (CH, C-3), 119.8 (CH\(_2\), C-3\( ' \)), 66.4 (CH, C-1\( ' \)), 62.4 (CH\(_2\), CO\(_2\)Et), 51.4 (quat., C-1), 46.0 (CH, C-6), 37.8 (CH\(_2\), C-1\( ' \)), 33.9 (CH\(_2\), C-5), 23.6 (CH\(_3\), C-2\( '' \)), 14.8 (CH\(_3\), CO\(_2\)Et).

IR (thin film) cm\(^{-1}\): 3444 (br, O–H), 3078 (=C–H), 2975 (C–H), 2928, 2853, 1725 (str, C=O), 1681 (str, C=C), 1446, 1416, 1390, 1367, 1285, 1257, 1222 (str, C–O), 1131, 1096, 1044, 1023, 917, 884, 860, 794, 733.

MS (ESI) \( m/z \) 253 [(M + H)\(^+\), 10%], 275 [(M + Na)\(^+\), 100%]; HRMS (ESI) \( m/z \) 253.1425 [(M + H)\(^+\)] calcd. for C\(_{14}\)H\(_{21}\)O\(_4\) 253.1434, 275.1242 [(M + Na)\(^+\)] calcd. for C\(_{14}\)H\(_{20}\)O\(_4\)Na 275.1254.
Dess-Martin periodinane (353 mg, 0.83 mmol) was added to a solution of (1R,6R)-ethyl 1-allyl-6-((R)-1-hydroxyethyl)-4-oxocyclohex-2-enecarboxylate 177 (70 mg, 0.28 mmol) and pyridine (135 μL, 1.66 mmol) in dichloromethane (15 mL) and stirred at room temperature for 1.25 h. Solid sodium disulfite (ca. 200 mg) was added, followed by sat. aq. NaHCO₃ (20 mL). The mixture was allowed to stir at room temperature for 30 min, then the aqueous was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 as eluent) to give the title compound 103 (65 mg, 94%) as a pale yellow oil.

R_f (ethyl acetate:hexanes 1:1) = 0.8; R_f (ethyl acetate:hexanes 3:7) = 0.4.

¹H-NMR (400 MHz, CDCl₃): δ 6.83 (d, 1H, J = 10.3 Hz, H-2), 6.06 (d, 1H, J = 10.3 Hz, H-3), 5.74 (m, 1H, H-2′), 5.12 (m, 2H, H-3′), 4.24 (q, 2H, J = 7.2 Hz, CO₂Et), 3.70 (dd, 1H, J = 5.8, 8.5 Hz, H-6), 2.79 – 2.59 (m, 4H, H-5, H-1′), 2.21 (s, 3H, H-2′′), 1.30 (t, 3H, J = 7.2 Hz, CO₂Et).

¹³C-NMR (100 MHz, CDCl₃): δ 206.7 (quat., C-1′′), 196.0 (quat., C-4), 172.4 (quat., CO₂Et), 149.1 (CH, C-2), 132.0 (CH, C-2′), 128.4 (CH, C-3), 119.9 (CH₂, C-3′), 61.9 (CH₂, CO₂Et), 51.1 (CH, C-6), 50.0 (quat., C-1), 38.4 (CH₂, C-1′), 36.7 (CH₂, C-5), 30.7 (CH₃, C-2′′), 14.0 (CH₃, CO₂Et).

IR (thin film) cm⁻¹: 3078 (=C–H), 2982 (C–H), 2926, 1713 (str, C=O), 1682 (str, C=O), 1641 (C=C), 1446, 1420, 1389, 1362, 1275, 1224 (str, C=O), 1097 (str, C=O), 1158, 1136, 1096, 1027 (med), 1004 (med), 923 (med), 885, 860, 840, 791, 763, 735, 701, 672, 634.

MS (ESI) m/z 251 [(M + H)⁺, 50%], 273 [(M + Na)⁺, 100%]; HRMS (ESI) m/z 251.1285 [(M + H)⁺, calcd. for C₁₄H₁₉O₄ 251.1278], 273.1104 [(M + Na)⁺, calcd. for C₁₄H₁₈O₄Na 273.1097].
A solution of aq. potassium hydroxide (1 M, 0.5 mL) was added dropwise to a solution of (1R,6R)-ethyl 6-acetyl-1-allyl-4-oxocyclohex-2-enecarboxylate 103 (14 mg, 0.056 mmol) in anhydrous ethanol (1 mL) at 0 °C and stirred for 10 min at room temperature. The solution was then re-cooled to 0 °C and aq. HCl (2 M, 0.25 mL) added. The mixture was allowed to stir for an additional 10 min, then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give the crude as a pale yellow oil. The crude was purified *via* flash column chromatography (silica gel, ethyl acetate:hexanes 1:1 as eluent) to give the *title compound* 179 (10 mg, 84%) as a pale yellow oil.

\[ \text{R}_f \text{ (ethyl acetate:hexanes 1:1) = 0.20.} \]

\[ ^1\text{H-NMR (400 MHz, CDCl}_3\text{): } \delta \ 6.60 \text{ (dd, 1H, } J = 1.2, 10.2 \text{ Hz, H-2}, 6.13 \text{ (d, 1H, } J = 10.2 \text{ Hz, H-3), 5.73 \text{ (m, 1H, H-2’}), 5.22 \text{ (m, 2H, H-3’), 3.84 \text{ (br s, 1H, OH), 2.76 \text{ (d, 1H, } J = 6.2 \text{ Hz, H-6), 2.63 – 2.46 \text{ (m, 4H, H-5, H-1’), 1.69 \text{ (s, 3H, H-2”).}}} \]

\[ ^{13}\text{C-NMR (100 MHz, CDCl}_3\text{): } \delta \ 195.6 \text{ (quat, C-1’), 195.6 \text{ (quat., C-4), 169.4 \text{ (quat., CO}_2\text{H), 145.6 \text{ (CH, C-2), 131.4 \text{ (CH, C-2’), 130.6 \text{ (CH, C-3), 120.8 \text{ (CH}_2\text{, C-3’), 45.8 \text{ (CH, C-6), 48.2 \text{ (quat., C-1), 41.2 \text{ (CH}_2\text{, C-1’), 33.1 \text{ (CH}_2\text{, C-5), 29.7 \text{ (CH}_3\text{, C-2”).}}} \]

IR (thin film) cm⁻¹: 3466 (br, wk, O–H), 2987 (=C–H), 2978 (C–H), 1734 (str, C=O), 1669 (str, C=C), 1435, 1398, 1332, 1254, 1218 (str, C–O), 1162, 1114, 1083 (str), 1016 (med), 978, 883, 769 (med), 679, 652.

MS (ESI) m/z 223 [(M + H)⁺, 11%), 245 [(M + Na)⁺, 90%]; HRMS (ESI) m/z 223.0973 [(M + H)⁺, calcd. for C₁₂H₁₅O₄ 223.0965], 245.0794 [(M + Na)⁺, calcd. for C₁₂H₁₄O₄Na 245.0784].
A solution of potassium hydroxide (1 M aq., 1 mL) was added dropwise to a solution of (1R,6R)-ethyl 6-acetyl-1-allyl-4-oxocyclohex-2-enecarboxylate 103 (14 mg, 0.055 mmol) in ethanol (4 mL) at 0 °C, then allowed to warm to room temperature and stirred for 15 min. The solution was re-cooled to 0 °C and aq. HCl (2 M, 0.5 mL) was added dropwise. The mixture was allowed to stir for 15 min, then brine (5 mL) was added, and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give the crude acid as a yellow oil. The carboxylic acid was dissolved in diethyl ether (5 mL), cooled to 0 °C, and triethylamine (10 μL, 0.072 mmol) was added. The mixture was allowed to stir at this temperature for 5 min, then isobutyl chloroformate (9 μL, 0.066 mmol) added, and the mixture allowed to stir for an additional 30 min. The suspension was filtered through Celite®, and the volatiles removed under reduced pressure to give the crude as a pale yellow oil. It was possible to purify the crude mixed anhydride via flash column chromatography (silica gel, ethyl acetate:hexanes 1:1 as eluent) to give the title compound 181 (15 mg, 83%) as a pale yellow oil.

\[ R_f \text{ (ethyl acetate:hexanes 1:1)} = 0.61. \]

\(^1\)H-NMR (400 MHz, CDCl₃): δ 7.13 (dd, 1H, J = 1.2, 10.5 Hz, H-2), 6.06 (d, 1H, J = 10.4 Hz, H-3), 5.73 (m, 1H, H-2’), 5.21 (m, 2H, H-3’), 4.06 (d, 2H, J = 6.6 Hz, CO₂CO₂i-Bu), 3.51 (td, 1H, J = 0.9, 6.4 Hz, H-6), 2.91 (d, 2H, J = 6.5 Hz, H-5), 2.69 (m, 2H, H-1’), 2.04 (m, 1H, CO₂CO₂i-Bu), 2.21 (s, 3H, H-2”), 0.96 (d, 6H, J = 6.8 Hz, CO₂CO₂i-Bu).
**Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones**

$^{13}$C-NMR (100 MHz, CDCl$_3$): δ 205.8 (quat., C-1’’), 194.3 (quat., C-4), 166.9 (quat., CO$_2$CO$_2$i-Bu), 149.1 (CH, C-2), 148.4 (quat., CO$_2$CO$_2$i-Bu), 131.1 (CH, C-2’), 129.2 (CH, C-3), 120.8 (CH$_2$, C-3’), 75.9 (CH$_2$, CO$_2$CO$_2$i-Bu), 53.5 (CH, C-6), 49.1 (quat., C-1), 41.7 (CH$_2$, C-1’), 35.7 (CH$_2$, C-5), 27.8 (CH$_3$, C-2’’), 27.6 (CH, CO$_2$CO$_2$i-Bu), 18.7 (2 x CH$_3$, CO$_2$CO$_2$i-Bu).

IR (thin film) cm$^{-1}$: 2966 (C–H), 2918, 2879, 2850, 1779 (str, C=O), 1758 (str, C=O), 1694 (str, C=C), 1473, 1441, 1415, 1383, 1341, 1300, 1282 (str, C=O), 1253 (str, C=O), 1238 (str, C=O), 1217 (str), 1180 (str), 1166 (str), 1132, 1111, 1074 (str), 1012 (str), 940 (str), 912 (str), 890 (str), 822, 793 (str), 782 (str), 740, 720, 671 (med), 654 (med).

MS (ESI) m/z 345 [(M + Na)$^+$, 100%], 361 [(M + K)$^+$, 18%]; HRMS (ESI) m/z 345.1301 [(M + Na)$^+$, calcd. for C$_{17}$H$_{22}$O$_6$Na 345.1309], 361.1031 [(M + K)$^+$, calcd. for C$_{17}$H$_{22}$O$_6$K 361.1048].

**1(R,6R)-Methyl 6-acetyl-1-allyl-4-oxocyclohex-2-enecarboxylate 184**

![184](image)

Colourles oil.

R$_f$ (ethyl acetate:hexanes 2:3) = 0.39.

$^1$H-NMR (300 MHz, CDCl$_3$): δ 7.16 (dd, 1H, J = 1.1, 10.3 Hz, H-2), 6.01 (d, 1H, J = 10.4 Hz, H-3), 5.68 (m, 1H, H-2’), 5.15 (m, 2H, H-3’), 3.73 (s, 3H, CO$_2$Me), 3.48 (td, 1H, J = 0.7, 6.3 Hz, H-6), 2.86 (d, 2H, J = 6.3 Hz, H-5), 2.62 (m, 2H, H-1’), 2.18 (s, 3H, H-2’’).

**3aR,7aR)-7a-Allyl-3-hydroxy-3-methyl-3a,4-dihydroisobenzofuran-1,5(3H,7aH)-dione 185**

![185](image)

Colourless oil.
R_f (ethyl acetate:hexanes 3:7) = 0.29.

^1^H-NMR (400 MHz, CDCl_3): δ 6.62 (dd, 1H, J = 1.5, 10.2 Hz, H-7), 6.24 (d, 1H, J = 10.3 Hz, H-6), 5.70 (m, 1H, H-2'), 5.27 (m, 2H, H-3'), 3.00 (dt, 1H, J = 1.1, 7.3 Hz, H-3a), 2.76 – 2.54 (m, 4H, H-1', H-4), 2.02 (s, 3H, H-1'').

^1^3^C-NMR (100 MHz, CDCl_3): δ 193.4 (quat., C-5), 174.1 (quat., C-1), 143.7 (CH, C-7), 131.5 (CH, C-6), 130.6 (CH, C-2'), 121.7 (CH_2, C-3'), 104.8 (quat., C-3), 48.9 (CH, C-3a), 47.5 (quat., C-7a), 41.9 (CH_2, C-1'), 34.1 (CH_2, C-4), 30.9 (CH_3, C-1'').

IR (neat) cm\(^{-1}\): 3214 (br, wk, O-H) 3081 (=C-H), 2984 (C-H), 2912, 1791 (str, C=O), 1685 (str, C=O), 1440 (med), 1408 (med), 1386 (med), 1354, 1294, 1246 (med), 1226 (str, C=O), 1163 (med), 1148 (med), 1071 (med), 1031 (str), 1008 (str), 983 (str), 946 (str), 846 (str), 785 (med), 760 (med).

MS (ESI) \(m/z\) 245 [(M + Na)^+ , 78%]; HRMS (ESI) \(m/z\) 245.0795 [(M + Na)^+ , calcd. for C_{12}H_{14}O_4Na 245.0784].

1.8.8 Attempted TBS-protection of alcohol 190

**[(1R,5S,8S)-Methyl 8-allyl-7-methyl-3-oxo-6-oxabicyclo[3.2.1]octane-8-carboxylate 191]**

Prepared according to the procedure of Corey and Venkateswarlu.\(^{131}\)

Imidazole (10 mg, 0.160 mmol) and tert-butyldimethylsilyl chloride (12 mg, 0.077 mmol) were added to a solution of \((1R,6R)-methyl 1-allyl-6-(1-hydroxyethyl)-4-oxocyclohex-2-ene-carboxylate 190\) (16 mg, 0.064 mmol) in dimethylformamide (1 mL) and heated at reflux for 16 h. Water (1 mL) was added, and the mixture extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over MgSO_4, and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 as eluent) to give the title compound 191 (7 mg, 44%) as a pale yellow oil.

R_f (ethyl acetate:hexanes 3:7) = 0.41.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 5.77 (m, 1H, H-2'), 5.15 (m, 2H, H-3'), 4.39 (m, 1H, H-7), 4.30 (br t, 1H, $J$ = 1.3 Hz, H-5), 3.74 (s, 3H, CO$_2$Me), 2.82 – 2.48 (m, 7H, H-2, H-4, H-1, H-1'), 1.19 (d, 3H, $J$ = 6.5 Hz, Me).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 209.6 (quat., C-3), 172.4 (quat., CO$_2$Me), 132.2 (CH, C-2'), 119.1 (CH$_2$, C-3'), 75.5 (CH, C-5), 59.2 (CH, C-7), 52.0 (CH$_3$, CO$_2$Me), 46.9 (CH$_2$, C-4), 41.8 (CH, C-1), 40.8 (CH$_2$, C-2), 38.4 (CH$_2$, C-1'), 17.7 (CH$_3$, Me).

IR (thin film) cm$^{-1}$: 3081 (=C–H), 2952 (C–H), 2929, 2853, 1725 (str, C=O), 1645 (C=C), 1436, 1416, 1388, 1339, 1321, 1285, 1264, 1217 (med, C–O), 1135, 1114, 1064, 1040, 1000, 923, 897, 864, 816, 797, 764, 632.

MS (ESI) m/z 239 [(M + H)$^+$, 50%], 261 [(M + Na)$^+$, 100%]; HRMS (ESI) m/z 239.1289 [(M + H)$^+$, calcd. for C$_{13}$H$_{19}$O$_4$ 239.1278], 261.1109 [(M + Na)$^+$, calcd. for C$_{13}$H$_{18}$O$_4$Na 261.1097].
PART TWO

N-Alkylsulfonylimines as heterodipolarophiles
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones
CHAPTER FOUR

Introduction and background
2.1 Introduction

*N-Alkylsulfonylimines* are unstable heterocumulenes that have been used as dipolarophiles with a variety of reactive dipoles. These compounds were first described by Atkins and Burgess in 1967, and their reaction with anilines and highly electron rich alkenes was reported.\(^\text{132}\) They are variously known throughout the literature as *N*-sulfonylamines,\(^\text{132}\) *N*-sulfonylalkylamines,\(^\text{133}\) *N*-alkylsulfonylimides,\(^\text{134}\) and *N*-alkylsulfonylimines,\(^\text{135}\) and are not to be confused with *N*-sulfonylimines.\(^\text{204}\) (Figure 2.1.1).

![Figure 2.1.1. *N*-Alkylsulfonylimines 202/203, *N*-sulfonylimines 204, and sulfenes 205.](image)

Their reactivity was proposed to mimic that of the closely related sulfenes 205. Sulfenes had been proposed as dipolarophiles in the early 60’s, based on their trapping reactions with enamines, 1,4-butadienes, ketene *N,N*-acetals, and vinylogous carboxamides.\(^\text{136-141}\) However both the syntheses and reactions of *N*-alkylsulfonylimines 202 are scattered throughout the literature and have not been reviewed at this time. A full report of the cycloaddition reactions of 202 with alkenes, enamines, ynamines, diazocompounds, azirines, silyloxydienes, azadienes, is therefore presented herein. The reactions have been ordered by the size of the heterocycle formed – from 3-membered thiaziridine 1,1-dioxides 206, through to the six-membered thiazinone 1,1-dioxides 210 and thiadiazine 1,1-dioxides 211 – 212 (Figure 2.1.2).
Figure 2.1.2. Examples of heterocycles available from cycloadditions with N-alkylsulfonylimines 202.

2.2 Preparation of N-alkylsulfonylimines

The reactive species 202 is usually generated and reacted in situ by the dehydrohalogenation of the corresponding N-alkylsulfonyl chloride (sulfamoyl chloride) 213 at reduced temperature in the presence of the trapping reagent (Scheme 2.2.1). Alternatively, a less common approach involves the fragmentation of an N-alkylsulfamoyl phthalimide 214, either thermally, or upon the action of base at room temperature.

Scheme 2.2.1. Reagents and conditions: a) Et₃N, THF, -78 °C; b) phthalimide, Et₃N, PhMe/THF, -40 °C; c) PhH, reflux; d) Et₃N, CH₂Cl₂, r.t.

The sulfamoyl chlorides themselves can be prepared using a wide variety of methods, as summarised below (Scheme 2.2.2):
Scheme 2.2.2. 

Reagents and conditions: a) ROH, hexanes; b) SO$_2$Cl$_2$, MeCN, 0 → 65 °C, 16 h; c) (i) HCl; (ii) SO$_2$Cl$_2$, Et$_2$O; d) (i) HCl; (ii) SO$_2$Cl$_2$, SbCl$_5$, MeCN, reflux; e) HSO$_3$Cl, CHCl$_3$; f) Py∙SO$_3$, H$_2$O; g) (i) 50% H$_2$SO$_4$∙SO$_3$, CH$_3$CHCl$_2$, 0 °C; (ii) 100% H$_2$SO$_4$, 80 °C, 2 h; h) H$_2$SO$_4$∙SO$_3$, MeNO$_2$; i) PCl$_5$, PhMe, reflux, 1 h.

The first approach involves gently warming an alcohol with chlorosulfonyl isocyanate 215 to give the acyl substituted sulfamoyl chloride 213, and this method has been used to prepare both tert-butoxy and benzhydryl derivatives.$^{143}$ An alternative option is to effect direct chlorosulfonylation of the amine that already contains the desired substitution. Several options for the reaction with sulfuryl chloride are reported in the literature, either from the amine directly$^{144}$ or via the hydrochloride salt, with$^{145-147}$ or without$^{148}$ Lewis acid catalysis, and these reactions have been performed on simple alkyl substrates. A process described in a Hungarian patent – itself an improvement on an earlier German process – involves the treatment of $N,N$-diisopropylurea 217 with oleum and sulfuric acid to access the sulfamic acid 219.$^{149}$ Lastly, sulfamoyl chlorides may be accessed via the corresponding sulfamic acid 219, which is itself available from either the isocyanate 218 upon treatment with fuming sulfuric acid,$^{150,151}$ or, in the case of incompatible R groups (e.g. aryl), from the amine 216 upon treatment with chlorosulfonic acid.$^{151,152}$ Treatment of the sulfamic acid with phosphorus pentachloride then gives the desired sulfamoyl chloride 213.$^{151}$
2.3 Cycloaddition reactions of N-alkylsulfonylimines

As described above, N-alkylsulfonylimines 202 and their precursors are readily prepared. The reactions of these heterocumulenes have been studied sporadically; however the most interesting of these reactions are the cycloadditions of 202 whereby novel sultams are generated. The cycloaddition reactions of N-alkylsulfonylimines 202 reported thus far are therefore described in this section.

2.3.1 Synthesis of 3-membered heterocycles

The reaction of N-alkylsulfonylimines with diazoalkanes 220 to give thiaziridine 1,1-dioxides 206 was studied by Quast and Kees (Scheme 2.3.1).\textsuperscript{155} A number of substituted thiaziridine 1,1-dioxides 206 were synthesized in this manner, including N-tert-butyl and –adamantyl derivatives.

\begin{equation}
\text{Scheme 2.3.1. Reagents and conditions: a) Et}_3\text{N, Et}_2\text{O, -78 °C, 2 h, 32 – 47% depending on substitution.}
\end{equation}

Similarly, the reaction of N-alkylsulfonylimines with a range of simple alkyl-substituted diazoalkanes has also been reported by Kidwai and Batra (Scheme 2.3.2).\textsuperscript{154} The thiaziridine 1,2-dioxides thus produced were all found to be unstable to prolonged storage.

\begin{equation}
\text{Scheme 2.3.2. Reagents and conditions: a) Et}_2\text{O, -30 °C. For R = Me, Pr, }^3\text{Pr, }^3\text{Bu, }^3\text{Bu.}
\end{equation}

2.3.2 Synthesis of 4-membered heterocycles

In their seminal 1967 paper, Burgess and Atkins demonstrated the reactions of N-alkylsulfonylimines in [2+2] cycloaddition reactions with electron rich olefins (Scheme 2.3.3).\textsuperscript{132} The reaction failed using less nucleophilic olefins; however modification of the R group to give an acyl derivative altered the electrophilicity such that reactions with less nucleophilic olefins were possible.

\begin{equation}
\text{Scheme 2.3.3. Reagents and conditions: a) Et}_3\text{N, Et}_2\text{O, r.t., quant.}
\end{equation}
Similarly, reactions of ‘inner salt’ compounds 225 to give 4-membered heterocycles were limited to strained or nucleophilic olefins. However THF-complexation of N-acylsulfonylimines enhanced the nucleophilicity of these compounds in comparison to the inner salts (Scheme 2.3.4). Subsequent addition to alkenes affords mixtures of 2-carbomethoxy-1,2-thiazetidines 228 and 2,3-dihydro-6-methoxy-1,4,5-oxathiazines 229, as well as vinyl sulfonamides 230. The product ratios obtained were dependent on the solvent and temperature. 4-membered rings formed via ring-closure of the zwitterion; 6-membered rings were more likely formed via a concerted process. A [2+2] cycloaddition mode was favoured with increasing nucleophilicity of the alkene.

Scheme 2.3.4. Reagents and conditions: a) NaH, -78 °C; b) THF, 30 °C; c) 226, 30 °C, THF or MeCN. Yields not given.

Heteroaromatic pi systems undergo initial [2+2] reactions with the THF-complex 226 at 30 °C, and the adducts then spontaneously fragment, losing sulfur trioxide in an overall “quasi Wittig reaction” (Figure 2.3.1). Benzaldehyde 231, for example, affords the imine 233 after treatment with THF-complex 226 at 30 °C.
Because the N-alkylsulfonylimines are only stable at reduced temperatures (forming homodimers and trimers on warming), generation of these intermediates at elevated temperatures would be more synthetically useful. In an extension of their earlier work, Burgess and Williams\textsuperscript{156} found that when acyl sulfamoyl chlorides were deprotonated with sodium hydride and the resulting salt 225 allowed to react with acetonitrile, six-membered 1,4,3,5-oxathiadiazines 238 formed (Scheme 2.3.5). These 6-membered heterocycles could then undergo a thermal [4+2] cycloreversion, and the N-sulfonylurethane 239 thus generated could be trapped \textit{in situ} with variously substituted alkenes in an analogous fashion to previous work. Again, product ratios were dependent on solvent and temperature. As an example of the more elevated temperature range, reaction of \textit{cis}-stilbene 240 with 238 at 105 °C gave the 6-membered adduct 241 exclusively.

\textbf{Scheme 2.3.5. Reagents and conditions:} a) MeCN, 30 °C, 75%; b) THF or MeCN, 30 – 60 °C; c) 227, THF or MeCN, 30 – 60 °C; d) 105 °C; yields not given.
Shingaki et al. reported the reactions of N-alkylsulfonylimines with enamines (Figure 2.3.2). The enamines were classified into three groups depending on substitution – those with a methylene group on the α-carbon; those with a hydrogen atom on the β-carbon; and those containing neither. Types A and B led only to acyclic products 245 – 247. Type C enamines 244, however, led to the unstable cyclic β-sultams 248, which hydrolysed to aldehydes 249 upon attempted chromatographic purification.

Figure 2.3.2. Reactions of N-alkylsulfonylimines 202 (R = Me, Et) with enamines 242 – 244.

These results suggested that the reaction pathway occurred via a zwitterionic intermediate, rather than a concerted mechanism (Figure 2.3.3). Electrophilic attack of the sulfur atom at the enamine β-carbon leads to the proposed zwitterionic intermediate 251, which, depending upon the enamine substitution pattern leads to either acyclic products 252 and 253, in the case of Type A and B, or cyclic products 254, as in the case of Type C enamines.
During an investigation into the reactions of N-alkylsulfonylimines with ynamines by Schaumann et al., it was found that, depending on the level of substitution of the ynamine, the initial [2+2] adducts underwent ring opening to an amidinosulfene species 257 that then underwent further reactions (Figure 2.3.4).

A representative example is the ring-opening and subsequent reactions of the derivative where R^1 = iPr, R^2 = Me, R^3 = Et (258, figure 2.3.5). The amidinosulfene 259 then dimerises or is trapped with either the remaining N-alkylsulfonylimine or the ynamine to give principally the 2H-1,5,2-dithiazane 1,1,5,5-tetraoxide 260.

Figure 2.3.3. Possible reaction pathways for the reaction of N-alkylsulfonylimines with enamines.

Figure 2.3.4. Reaction of N-alkylsulfonylimines 202 with ynamines 255. R^1 = 'Pr, iBu; R^2 = SiPh_3, SiMe_3, Me, Ph; R^3 = Me, Et.

Figure 2.3.5. Further reactions of 2H-1,2-thiazete 1,1-dioxides.
Dimerisation is not observed for the amidinosulfenes with bulkier substituents ($R^1 = \text{^iPr, } ^t\text{Bu; } R^2 = \text{Ph}$), and therefore only the [4+2] adducts are observed.

### 2.3.3 Synthesis of 5-membered heterocycles

Schaumann et al. have examined the reactions of $N$-alkylsulfonylimines with substituted azirines (Scheme 2.3.6). It was found that when simple alkyl-substituted $N$-alkylsulfonylimines 202 were reacted with 3-dimethylamino-2,2-diphenyl-$2H$-azirine 263, the expected 1,2,5-thiadiazole 1,1-dioxides 265 were produced. However when the substituent on the $N$-alkylsulfonylimine was electron-withdrawing, the reaction afforded the 1,2,3-oxathiazole 266. The oxathiazole 266 slowly isomerizes in solution to the thiadiazole 265 in solution; this can be accelerated by either heating the reaction mixture under reflux in ethyl acetate or stirring over silica gel in dichloromethane at room temperature.

![Scheme 2.3.6. Reagents and conditions: a) SiO$_2$, CH$_2$Cl$_2$, r.t.](image)

When the azirines 267 containing an alkyl residue with a hydrogen atom adjacent to the C-2 ring atom were treated with alkyl-substituted $N$-alkylsulfonylimines, acrylamidines 270 were obtained exclusively. However $N$-acylsulfonylimines, under the same conditions, gave mainly isomeric 1,2,5-thiadiazoles 269 and 1,2,3-oxathiazoles 268 (Figure 2.3.6).

![Figure 2.3.6. Reaction of $N$-alkylsulfonylimines 202 with azirine 267.](image)
2.3.4 Synthesis of 6-membered heterocycles

Following the work of Burgess et al., Kloek and Leschinsky further elaborated the chemistry of N-alkylsulfonylimines by investigating the reaction of these species with activated silyloxydienes. Novel 6-membered heterocycles 210 were obtained after acidic workup of the reaction mixture when N-alkylsulfonylimines were generated in the presence of the diene 93 at reduced temperature (Scheme 2.3.7).

Scheme 2.3.7. Reagents and conditions: a) (i) THF, -78 °C → r.t., 2 h; (ii) 10% aq. HCl, 0.75 h; R = Et, 60%, R = iPr, 71%.

When a more substituted diene 271 was used, a mixture of acyclic 272 and ring-closed products 210 was obtained (Scheme 2.3.8). In the case of the methyl-substituted sulfonamide 272, ring-closure occurred upon distillation, whereas the isopropyl-substituted sulfonamide required treatment with catalytic acid at reflux to effect formation of a similar product.

Scheme 2.3.8. Reagents and conditions: a) (i) THF, -78 °C → r.t., 2 h; (ii) 10% aq. HCl, 1 h; b) for R = Me, reflux, 57%; for R = iPr, H⁺/reflux, 39%.

The formation of the cyclic products 210 did require an acidic workup step, and the fact these products were also obtained with the related diene 271 suggested that the reaction proceeds via a stepwise rather than a concerted process.

Similarly, Schaumann and Tornus found that generation of N-alkylsulfonylimines from a phthalimide derivative 214 also resulted in formation of the [4+2] cycloaddition products using 2-trimethylsilyloxy-1,3-butadiene as the 4π component (Scheme 2.3.9).
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Scheme 2.3.9. Reagents and conditions: a) (i) 141, Et₃N, CH₂Cl₂, r.t., 12 h; (ii) 2 N aq. HCl, 0.5 h, 17%; b) 2 eq. 141, PhH, reflux, 274 trace, 275 21%.

When N-isopropylsulfonylimine is generated from 214 in the presence of the diene 141 at room temperature, the 2-isopropylthiazinan-5-one 1,1-dioxide 274 is produced after an acidic workup. On the other hand, when the N-isopropylsulfamoyl phthalimide 214 is heated with the diene 141 in the absence of base, the major product is cyclohexanone 275.

The authors have also shown that N-alkylsulfonylimines undergo [4+2] cycloaddition reactions with 2-aza-1,3-dienes 276 (R¹ = Me, Et) to give 2,3,3,5,6-pentasubstituted-3,6-dihydro-2H-1,2,4-thiadiazine 1,1-dioxides 277 as a diastereomeric mixture together with the corresponding N-H tautomer 278 (R¹ = Me). When bulky N-alkylsulfonylimines are used, bis-sulfamoylated dienes 279 are obtained (Scheme 2.3.10).

Scheme 2.3.10. Reagents and conditions: a) MeNHSO₂Cl or EtNHSO₂Cl, Et₃N, CH₂Cl₂, -78 °C → r.t., 1 h, R = Me, 277:278 28%, 2:1, R = Et, 277 53%; b) iPrNHSO₂Cl or tBuNHSO₂Cl, Et₃N, BF₃·OEt₂, CH₂Cl₂, -78 °C → r.t., 1 h, R = iPr, 37%, R = tBu, 11%.
However when bulky alkylsulfonylamines are generated from the phthalimide derivative, cycloadduct 277 is obtained (Scheme 2.3.11).

Scheme 2.3.11. Reagents and conditions: a) Et₃N, CH₂Cl₂, r.t., overnight, R¹ = Me, 26%, R¹ = Et, 21%.

2.3.5 Summary

The reactions of N-alkylsulfonylimines reported in the literature are sparse and fragmented. Their reactivity in cycloadditions is intermediate between sulfur trioxide and sulfenes, though this has not been fully explored in terms of the variety of 1,3- and 1,4-dipolar cycloaddition partners investigated. Cycloadditions with 1,3-dipoles, in particular, has yet to be investigated.

N-Alkylsulfonylimines however, have been used to prepare several novel heterocycles. These heterocycles have been formed by what appears to be cycloaddition of 202 with diazoalkanes, electron-rich olefins, azirines, enamines, ynamines, azadienes, and silyloxydienes. This may be a concerted or stepwise process, though evidence collected thus far supports the latter pathway rather than the former.
2.4 Aims

The aim of this study is to examine the scope of the reactivity of $N$-alkylsulfonylimines 202 with a variety of 1,4-dienes and 1,3-dipoles that have not been examined to date. Although the reaction of $N$-alkylsulfonylimines with azirines 281,133 and a small selection of activated dienes 275 and 280142,158 has been reported previously, several attractive options to extend the knowledge of their reactivity are available (Figure 2.4.1).

![Image of reactions of $N$-alkylsulfonylimines with 1,3- and 1,4-dipoles.](image)

**Figure 2.4.1.** Summary of reactions of $N$-alkylsulfonylimines 202 with 1,3- and 1,4-dipoles.

Firstly, the reactions of $N$-alkylsulfonylimines 202 with dienes has so far been limited to very reactive silyloxy dienes 93, 141, and 271 and aza-dienes 276.142,158 We propose to systematically investigate the cycloaddition of $N$-alkylsulfonylimines with a range of dienes, beginning with unactivated dienes 138 and 287 – 291, and working up to more reactive dienes 123 and 292 – 296 (Figure 2.4.2).
Secondly, reports of the reaction of 202 with 1,3-dipoles has been limited to azirines. Nitrones 297, azomethine ylides 298, nitrile oxides 299, azides 300, and donor-acceptor cyclopropanes 301, are also proposed to provide products of types 302 – 306 (Figure 2.4.3). Each of these possibilities will be systematically investigated in the current work.
Figure 2.4.3. Proposed cycloadditions of $N$-alkylsulfonylimines $202$ with nitrones $297$, azomethine ylides $298$, nitrile oxides $299$, azides $300$, and donor-acceptor cyclopropanes $301$. 
CHAPTER FIVE

Discussion
2.5 **Synthesis of sulfamoyl chlorides**

Examination of the literature suggested that the most robust method for the synthesis of simple alkyl-substituted sulfamoyl chlorides involved treatment of the corresponding isocyanate with fuming sulfuric acid. The resulting sulfamic acid could then be chlorinated with phosphorus pentachloride (Scheme 2.5.1).

![Scheme 2.5.1. Reagents and conditions: a) H$_2$SO$_4$∙SO$_3$, MeNO$_2$; b) PCl$_5$, PhMe, reflux, 1 h.](image)

However, the required isocyanates are sea-freight only items and were not in stock at the time. Due to the long lead time associated with sea freight, we had to turn to alternative methods for the synthesis of the desired sulfamoyl chlorides (Scheme 2.5.2). In addition, this method is not suitable for the synthesis of aryl-substituted sulfamic acids, as treatment with fuming sulfuric acid also leads to sulfonation of the aromatic ring.

Thus, commercially available *N*-cyclohexyl sulfamic acid 219a was converted to the sulfamoyl chloride 213a in routine fashion by treatment with phosphorus pentachloride in refluxing toluene.$^{160}$ Not only did this procedure furnish 213a as a conveniently handled solid, but use of the cyclohexyl substituted sulfamoyl chloride also allowed successful purification via vacuum distillation through a Vigreux column at 6 Torr. This process has been reported to result in decomposition of the product in the case of phenyl- and benzyl-substituted sulfamoyl chlorides. This was confirmed in practice, with formation of a black tar resulting upon attempted distillation of 213b – 213e.$^{151}$

The *tert*-butyl- and benzyl-substituted sulfamoyl chlorides were obtained by treatment of a cold (-10 °C) solution of the requisite amine with chlorosulfonic acid, giving the sulfamic acid as the parent amine salt in good yield. Chlorination with phosphorus pentachloride then gave the corresponding sulfamoyl chlorides 213b and 213d.$^{161}$

Application of this process to aniline, however, failed to provide the sulfamic acid, presumably due to sulfonation of the aromatic ring competing with reaction of the amine functionality. This problem, however, was overcome by following the method described by Kanetani,$^{162}$ whereby the amine was first converted to the *N*-trimethylsilylamine, and subsequent treatment with chlorosulfonic acid and phosphorus pentachloride then provided the sulfamoyl chloride. Treatment of aniline 216c with triethylamine and chlorotrimethylsilane afforded the *N*-trimethylsilylaniline in excellent yield. Sulfonation with chlorosulfonic acid proceeded as usual, and chlorination of the crude sulfamic acid
219c with phosphorus pentachloride in toluene at reflux finally provided the N-phenylsulfamoyl chloride 213c in reasonable yield.

Scheme 2.5.2. Reagents and conditions: a) ClSO$_3$H, CH$_2$Cl$_2$, -10 °C, 2 – 4 h; b) Et$_3$N, TMSCl, hexanes, 5 °C → r.t., 16 h, 55%; c) PCl$_5$, PhMe, reflux, 2 h, yields as given.

N-Propylsulfamic acid 219e, kindly provided by researchers at CSIRO, was also converted to the sulfamoyl chloride 213e using the conditions already established.
2.6 Reactions of $N$-alkylsulfonylimines with 1,3-dienes

2.6.1 Reaction of $N$-alkylsulfonylimines 202 with Danishefsky’s diene 93

Initially it was planned to explore the reactions of $N$-alkylsulfonylimines as heterodienophiles in the Diels-Alder reaction prompted by the work of Kloek and Leschinsky, who reported that reaction of lower-alkyl substituted sulfamoyl chlorides with activated dienes 93 and 271 afforded thiazinone 1,1-dioxides 210 and 273 (Scheme 2.6.1).

![Scheme 2.6.1: Reagents and conditions](image)

*Scheme 2.6.1. Reagents and conditions:* a) (i) 202, THF, -78 °C → r.t., 3 h; (ii) 10% aq. HCl, r.t., 1 h, R = i-Pr, 60%, R = Et, yield not reported; b) (i) 202, THF, -78 °C → r.t., 2.75 h; (ii) 10% aq. HCl, r.t., 1 h, R = Me, 272:273 3:2; c) for R = Me: reflux or SiO$_2$, 57% over 2 steps; d) for R = i-Pr: PTSA, PhMe, reflux, 6 h, 39% over 2 steps.

With a variety of sulfamoyl chlorides in hand, it was decided to use the easily handled $N$-cyclohexylsulfonylimide chloride 213a as the first precursor to an $N$-alkylsulfonylimine (Table 2.6.1). A variety of conditions were evaluated, namely: changing the stoichiometry of the reagents, order of addition, temperature, and duration of the reaction. Each of these variations had little effect, in each case the thiazinone 1,1-dioxide 210a was only obtained in 40% yield at best (entries 2, 3).
Table 2.6.1. Optimisation conditions for the reaction of \(N\)-sulfonylimine \(202a\) and Danishefsky’s diene \(93\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. base</th>
<th>Eq. diene</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (210a) (%)</th>
<th>Yield (307) (%)</th>
<th>Yield (246a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-78</td>
<td>2</td>
<td>22</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.1</td>
<td>-78</td>
<td>2</td>
<td>40</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>-40</td>
<td>1</td>
<td>40</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>34</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1</td>
<td>-78</td>
<td>2</td>
<td>31</td>
<td>0</td>
<td>23</td>
</tr>
</tbody>
</table>

The moderate yield of product isolated is consistent with previous reactions of \(N\)-alkylsulfonylimines with activated dienes reported by Kloek and Leschinsky\(^{158}\) and Schaumann and Tornus,\(^{142}\) who reported yields ranging from 14 – 53%. The other major component of the reaction mixture was identified as the homodimer of \(202a\), namely dialkylsulfimide \(246a\), a common by-product observed in all subsequent cycloaddition reactions using \(N\)-alkylsulfonylimines.

The structure of the cyclic product, 2-cyclohexyl-1,2-thiazin-5(6\(H\))-one 1,1-dioxide \(210a\), was assigned using the \(^1\)H- and \(^{13}\)C-NMR, IR, and MS data. The \(^1\)H-NMR spectrum exhibited complex multiplets corresponding to the 10 CH protons of the cyclohexyl ring, in addition to a distinctive triplet of triplets further downfield (\(\delta \) 4.17 ppm) that was assigned to the CH proton \(\alpha\) to the nitrogen atom. A singlet at \(\delta \) 4.13 was assigned to the CH \(_2\) ring protons \(\alpha\) to the sulfonyl group. Finally, the two enone vinylic protons resonated as doublets at \(\delta \) 5.64, and \(\delta \) 7.27, respectively. Examination of the IR spectrum indicated the presence of a conjugated ketone (1647 cm\(^{-1}\) and 1583 cm\(^{-1}\)) and a sulfonyl group (two distinctive absorbances at 1338 cm\(^{-1}\) and 1156 cm\(^{-1}\)). Finally, the high resolution mass spectrum exhibited a molecular ion at \(m/z\) 230.0845, corresponding to a molecular formula of C\(_{10}\)H\(_{16}\)NO\(_3\)S, further confirming the proposed structure \(210a\).

The regiochemistry of the product obtained from the reaction of \(202a\) and \(93\) was confirmed by X-ray crystallographic analysis of \(210a\) (Figure 2.6.1).
In their work, Kloek and Leschinsky found that reactions of the methyl- and isopropyl-sulfamoyl chlorides with diene 93 gave the open-chain sulfonamides 272, suggesting that the thiazinone 1,1-dioxides were products of a stepwise, rather than a concerted process (Scheme 2.6.1, vide supra). These compounds could be converted to the corresponding thiazinone 1,1-dioxides under acidic and/or thermal conditions. For the N-cyclohexyl derivative 202a, the corresponding open-chain product 307 was only observed when the reaction was performed at 0 °C (Table 2.6.1, entry 4). This open-chain product was transient in nature and converted to the thiazinone 1,1-dioxide 210a upon gentle heating (40 °C) while being concentrated in a rotary evaporator.

Subjection of the remaining crude sulfamoyl chlorides to the same conditions provided a range of novel thiazinone 1,1-dioxides 210b – 210e in varying yields (Table 2.6.2).
Table 2.6.2. Preparation of variously substituted thiazinone 1,1-dioxides 210b – 210e.

*N*-benzyl derivative 210d is perhaps the most synthetically useful cycloadduct, in that the benzyl group could be removed *via* hydrogenolysis to obtain 308, thereby enabling further elaboration at nitrogen. Unfortunately, the yield of 210d obtained by this method was too low to allow for a practical synthesis of these types of compounds. Nevertheless, 210d was subjected to medium pressure hydrogenation conditions (10 bar, 10% Pd/C, H-cube, scheme 2.6.2).
Rather than deprotect the amine, in this case the enone double bond was selectively reduced, giving the sultam 309 in 63% yield. Use of either milder hydrogenolysis protocols, or alternative methods to remove the N-benzyl group, are required to obtain N-unsubstituted thiazinone 1,1-dioxides.

**2.6.2 Attempted cycloadditions of N-alkylsulfonylimines 202 with relatively unactivated dienes**

Given the initial success observed from the reaction of N-alkylsulfonylimines 202a – 202e with diene 93, extension of the above methodology using the more readily available N-cyclohexylsulfamoyl chloride 213a was next examined using several different dienes.

Our systematic investigation into the reactivity of N-alkylsulfonylimines with dienes (other than those already reported) began with all-carbon dienes cyclopentadiene 288, cyclohexa-1,3-diene 289, and 2,3-dimethylbutadiene 138 (Table 2.6.3). Thus, according to the previously established cycloaddition protocol, a solution of N-cyclohexylsulfamoyl chloride 213a in tetrahydrofuran was added to a solution of the diene and triethylamine.

Unfortunately dienes 138 and 288 – 289 failed to react – even at elevated temperatures – disappointingly giving only the homodimer 246a. Attempted use of the Lewis acid catalysts boron trifluoride diethyl etherate and titanium tetrachloride (Entries 8 and 9) also failed to afford the desired sultams when attempting reaction of 2,3-dimethylbuta-1,4-diene 138 with N-cyclohexylsulfonylimine 202a.
Table 2.6.3. Attempted cycloadditions of $N$-cyclohexylsulfonylimine 202a with unactivated dienes 138, 288, and 289.

Disappointingly, progressing to the use of the more activated 1-alkoxy-substituted diene 287 unfortunately also failed to produce the corresponding sultam upon attempted reaction with $N$-cyclohexylsulfonylimine 202a. Use of the cyclic dienes, furan 290 and 2-trimethylsiloxy derivative 291, also failed to provide any trace of cycloadduct (Table 2.6.4).

Again, performing the reaction at higher temperature (i.e. room temperature, entries 2, 5, and 7) did not promote cycloaddition, with sulfamide dimer 246a obtained in all cases. Attempted activation using the Lewis acid catalyst BF$_3$·OEt$_2$ (entry 3) was also unsuccessful.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Table 2.6.4. Attempted cycloadditions of N-cyclohexylsulfonylimine 202a with 1-alkoxy dienes 287, 290, and 291.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Catalyst</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcO</td>
<td>-78</td>
<td>1</td>
<td>-</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>r.t.</td>
<td>48</td>
<td>-</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>r.t.</td>
<td>4</td>
<td>BF₃OEt₂</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>-78</td>
<td>2</td>
<td>-</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>r.t.</td>
<td>2</td>
<td>-</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>-78</td>
<td>1</td>
<td>-</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>r.t.</td>
<td>2</td>
<td>-</td>
<td>dimer 246a only</td>
</tr>
</tbody>
</table>

It was therefore apparent that the reactivity of N-cyclohexylsulfonylimine 202a as a dienophile was limited, thus cycloaddition with 1,3-dienes necessitated activation of the diene component. Attention therefore turned to the use of more reactive dienes 123 and 294.

2.6.3 Reaction of N-alkylsulfonylimines 202 with activated dienes: amino-substituted dienes

As discussed earlier (Chapter 1, 1.5.2.3), Rawal’s diene 123 is synthetically equivalent to Danishefsky’s diene 93, but with enhanced reactivity due to an increase in the energy of the HOMO of the diene.⁸¹,⁸² N-Alkylsulfonylimines 202 have been shown to participate in the Diels-Alder cycloaddition with 93 (section 2.2.1); however the cycloadducts 210 were only obtained in low yield. It was hoped that yields could be improved by substitution of 93 with the more reactive Rawal’s diene 123 (Figure 2.6.3).
Figure 2.6.3. Proposed cycloaddition of Rawal’s diene 123 with N-alkylsulfonylimines 202.

Rawal’s diene 123 was synthesised according to the previously detailed procedure, whereby the enolate of (E)-4-(dimethylamino)but-3-en-2-one 146 was generated with KHMDS at reduced temperature (-78 → -30 °C), followed by trapping as the TBS-ether with a solution of TBSCl in tetrahydrofuran (Part 1, section 1.5.2.3). A solution of the sulfamoyl chloride was added dropwise to a solution of diene 123 and triethylamine at -78 °C, and the mixture allowed to stir at this temperature for 2 h. After warming to room temperature, the mixture was then allowed to stir for a further 16 h. The reaction was subjected to the same workup and purification steps as previous cycloadditions (Table 2.6.5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cy</td>
<td>1.5</td>
<td>84% 8%</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>1</td>
<td>18% 19%</td>
</tr>
</tbody>
</table>

Table 2.6.5. Reactions of N-cyclohexyl- and N-benzylsulfamoyl chloride with Rawal’s diene 123.

Reaction of Rawal’s diene 123 with N-cyclohexylsulfonylimine 202a and N-benzylsulfonylimine 202d in tetrahydrofuran gave sulfonamides 312 and 313 in good yield, rather than the expected
thiazinone 1,1-dioxides 210. These products presumably result from hydrolysis of the \( N,N \)-acetal present in the initial cycloadduct 311 (Figure 2.6.4).

![Figure 2.6.4. Proposed mechanism for the formation of open-chain sulfonamide 312a from initial cycloadduct 311a.](image)

Similar reactivity has been reported for the hetero-Diels-Alder reaction of Rawal’s diene 123 with aldehydes (Scheme 2.6.3).\(^{163}\) The \( N,O \)-acetal of adduct 314 is acid-labile and cleaves upon purification \textit{via} silica gel chromatography, affording 315 as the major (78\%) product. The desired dihydropyrone 316 was isolated instead by treatment of the crude adduct 314 with acetyl chloride. In the analogous aza-Diels-Alder reaction of 123 with imine 317, the \( N,N \)-acetal of the adduct is more stable – standard acidic workup (1 N HCl/THF, 4:1) afforded the dihydropyridone 318 in good (84\%) yield.

![Scheme 2.6.3. Reagents and conditions:](image)

The aza-Diels-Alder reaction of \( N \)-sulfinimines 319 with Rawal’s diene 123, like \( N \)-alkylsulfonylimines 202 also appears to proceed \textit{via} a stepwise mechanism (Scheme 2.6.4).\(^{164}\) The
expected N-sulfinyl cycloadducts were not isolated; the N-deprotected dihydropyridones 320 were obtained instead. However, when the R group on the sulfur atom was more difficult to remove (R = p-tol, t-Bu), the open-chain adducts 321 were isolated. Treatment of 321 with acid (conc. HCl) then triggered cyclisation, affording the corresponding dihydropyridones in moderate yields (for R = p-Tol, t-Bu: 40 – 50%).

![Scheme 2.6.4](image)

**Scheme 2.6.4. Reagents and conditions:** a) TMSOTf, CH₂Cl₂, -70 °C, 3.5 h, 61 – 98%; b) conc. HCl, MeOH, r.t., 5 h, 40 – 51%.

Additionally, small amounts of vinyl sulfonamides 313a and 313b were isolated from the reaction mixture. These were proposed to result from reaction of the N-alkylsulfonylimine with hydrolysed diene 146. Indeed, when a solution of N-cyclohexylsulfamoyl chloride 213a was added to a solution of E-4-(dimethylamino)but-3-en-2-one 146 and triethylamine in THF at -78 °C, the sulfonamide 313a was isolated in 17% yield (Scheme 2.6.5).

![Scheme 2.6.5](image)

**Scheme 2.6.5. Reagents and conditions:** a) Et₃N, THF, -78 °C → r.t., 1.5 h, 17%.

While this is consistent with the previously reported reaction of N-alkylsulfonylimines with a “type B” enamine (see section 2.3.2),¹³⁴ it is in contrast with that reported for the reaction of sulfenes 205 with enaminones.¹⁶⁵ When enaminones that were constrained in a cisoid configuration (i.e. those substituted with a phenyl group, 322) were treated with sulfene 205a, the cycloadducts 323 were obtained in moderate yield. However, the authors found that when the transoid rotamer of the
enaminone was the major conformer present (i.e. methyl substitution, 146), no reaction with 205a was observed (Scheme 2.6.5).

Figure 2.6.5. Reaction of enaminones 322 and 146 with sulfene 205a.

It was therefore decided to further investigate the reactions of \(N\)-alkylsulfonylimines with aminodienes using Oppolzer-Overman type \(N\)-carbamoyl diene 294 (Scheme 2.6.6).\(^{166-169}\) The cycloaddition of these dienes has not been extensively studied; existing reports only provide examples of intramolecular cycloaddition, or cycloaddition using very activated dienophiles (e.g. succinimides, acrolein).

Additionally, the hetero-Diels-Alder reactivity of this type of diene has not been reported to date. Thus, the proposed reaction of 294 with \(N\)-alkylsulfonylimines to give sultams of type 324 is hitherto unreported.

Scheme 2.6.6. Proposed cycloaddition of \(N\)-alkylsulfonylimines with Oppolzer-Overman type diene 294.

Fortuitously, diene 294 was available within our research group from unrelated studies. It can be synthesised in four steps from \(trans\)-4-methoxybuten-2-one 143 (Scheme 2.6.7).\(^{170}\)
Scheme 2.6.7. Reagents and conditions: a) BnNH$_2$, CH$_2$Cl$_2$, 2 h; b) Boc$_2$O, 1 mol% DMAP, CH$_2$Cl$_2$, 18 h, 93% over 2 steps; c) NaBH$_4$, MeOH, 0 °C, 3 h, quant.; d) MsCl, pyridine, MeCN, 4 Å mol. sieves, Et$_3$N, reflux, 2 h, 77%.

The cycloaddition of 294 with N-cyclohexylsulfonylimine 202a was performed under similar conditions to that previously described (Scheme 2.6.8). A solution of the diene 294 in tetrahydrofuran was added to a cold (-78 °C) tetrahydrofuran solution of N-cyclohexylsulfamoyl chloride 213a. Triethylamine was then added dropwise, the mixture stirred at -78 °C for 2 h, then warmed to room temperature. After aqueous workup, the mixture was subjected to flash column chromatography to afford a mixture of products.

Scheme 2.6.8. Reagents and conditions: a) Et$_3$N, THF, -78 °C → r.t., 2 h, 327 23%, 328 9%; b) SiO$_2$, 64%.

Rather than the desired sultam 324a, the open-chain adduct 327 was in fact isolated. Once again, this result is likely due to cleavage of the $N,N$-acetal in the initial cycloadduct 324a. 327 proved unstable and readily decomposed on silica to give 328.

These results illustrate the lower reactivity of $N$-alkylsulfonylimines 202 compared to sulfenes 205. Sulfene 205a has been shown to undergo cycloaddition with 1-dialkylamino-1,3-butadienes 329 to give a mixture of the [4+2] and [2+2] cycloadducts 331 and 333 (Scheme 2.6.6).
In the case of the reaction of \(202a\) with \(294\), no \([2+2]\) cycloaddition was observed. This is unsurprising, given that Burgess and Atkins have previously shown that only very electron-rich olefins participate in \([2+2]\) cycloadditions with \(N\)-alkylsulfonylimines (Section 2.3.2). \(^{132}\)

### 2.6.4 Reaction of \(N\)-alkylsulfonylimines 202 with activated dienes: 2-silyloxydienes

Addition of 2-silyloxy substituents to 1,4-dienes results in a more electron-rich diene. This translates to enhanced reactivity, which we hoped to exploit in the proposed cycloadditions of these activated dienes with \(N\)-alkylsulfonylimines. Two dienes were selected for this investigation: 2-triisopropylsilyloxypenta-1,3-diene \(292\) and 2-(trimethylsilyloxy)cyclohexa-1,3-diene \(293\).

2-Triisopropylsilyloxypenta-1,3-diene \(292\) was available in our labs from other unrelated work and has been used previously in hetero Diels-Alder reactions. \(^{173}\) It can be synthesised in a single step according to the procedure of Evans and Nelson starting from ethyl vinyl ketone \(334\) (Scheme 2.6.9).
Scheme 2.6.9. Evans and Nelson’s synthesis of diene 292. Reagents and conditions: a) TIPSOTf, KHMDS, THF, -78 °C → r.t., 1.5 h, 84%.

In an analogous manner to previous cycloaddition attempts with N-cyclohexylsulfonylimine 202a, a solution of the sulfamoyl chloride 213a was added dropwise to a solution of the diene 292 and triethylamine at room temperature (Scheme 2.6.10). Following workup and chromatographic purification, the novel sultam 335 was successfully obtained, albeit in low yield.

Scheme 2.6.10. Reagents and conditions: a) Et₃N, THF, r.t., 16 h, 25%.

With this success, attention next turned to the potential [4+2] cycloaddition between N-alkylsulfonylimines and a cyclic 2-silyloxy-1,3-diene.

Cyclic dienes, where the double bonds are fixed in a cisoid conformation, are inherently more reactive than their open-chain counterparts. The cyclohex-2-enone derived diene 293 was selected as a readily available example of this kind of diene. It was hoped that this enhanced reactivity would enable reaction with N-alkylsulfonylimines, thus providing access to the structurally novel 2-thia-3-azabicyclo[2.2.2]octan-6-one 2,2-dioxide ring system (Figure 2.6.7).

Figure 2.6.7. Proposed cycloaddition between cyclic silyloxy diene 293 and N-alkylsulfonylimines 202.

2-(Trimethylsilyloxy)cyclohexa-1,3-diene 293 was prepared in a straightforward manner according to the literature procedure reported by Rinderhagen and Mattay (Scheme 2.6.11).
Scheme 2.6.11. Reagents and conditions: a) (i) LDA, THF, -78 °C, 1 h; (ii) TMSCl, THF, -78 °C → r.t., 1 h, 83%.

Cyclohex-2-enone 338 was treated with LDA at reduced temperature (-78 °C) and the resulting enolate quenched with a solution of chlorotrimethylsilane in THF. Filtration and distillation at under vacuum (16 mbar) then provided the desired diene 293 in high yield and purity.

With diene 293 in hand, attention turned to its use in cycloadditions with N-alkylsulfonylimines 202a – 202d. Treatment of a solution of the diene 293 and N-cyclohexylsulfamoyl chloride 213a in THF with triethylamine at reduced temperature afforded a mixture of products (Table 2.6.6, entry 1). Under these conditions, the desired bicyclic sultam 337a was obtained as a crystalline solid, but only in trace quantity. The amount of 337a obtained could be increased by raising the reaction temperature (room temperature, entry 2). The yield of the [4+2]-derived product however remained low, and furthermore was only observed in the reaction of N-cyclohexylsulfonylimine 202a with diene 293.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield 337 (%)</th>
<th>Yield 339 (%)</th>
<th>Yield 340 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cy</td>
<td>-78</td>
<td>2</td>
<td>trace</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>r.t.</td>
<td>6</td>
<td>6</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu</td>
<td>-78 → r.t.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>-78 → r.t.</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>-78 → r.t.</td>
<td>2</td>
<td>0</td>
<td>34</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 2.6.6. Reaction of N-alkylsulfonyl chlorides 213a – 213d with diene 293.
Somewhat surprisingly, the remainder of the product mixture was found to consist of the 4,6-fused sultam 339. These novel sultams appear to be the result of [2+2] cycloaddition between diene 293 and the reactive N-alkylsulfonylimine. The structure of 339a was assigned based on $^1$H and $^{13}$C-NMR, IR, and MS data. Notably, in the $^1$H-NMR spectrum no N-H resonance is present, and the signal assigned to H-1′ resonates as a triplet of triplets at $\delta$ 3.34, indicating that 339a has a ring-closed structure. The high resolution mass spectrum exhibits a molecular ion at $m/z$ 352.1370, corresponding to a molecular formula of C$_{15}$H$_{27}$NO$_3$SSiNa. Both the initial [4+2] adduct 336a and [2+2] adduct 339a fit this molecular formula (Figure 2.6.8). However, the structure was assigned as 339a, rather than 336a, based on the chemical shifts for the resonances assigned to H-2 and H-3 in the $^1$H-NMR spectrum and the quaternary carbon resonance in the $^{13}$C-NMR spectrum assigned to C-1 in 339a.

Firstly, there are two resonances in the proton spectrum that fall in the olefinic region ($\delta$ 6.09 and $\delta$ 5.88), consistent with the proposed structure 339a, not 336a. The signal assigned to H-3 appears as a doublet of doublet of doublets, consistent with the structure proposed for 339a, where H-3 is split by coupling with H-2 ($J$ = 10.3 Hz) and H-4 ($J$ = 5.8, 3.2 Hz). This coupling pattern is inconsistent with that proposed for the corresponding proton H-5 in 336a. Furthermore, the quaternary carbon signal assigned to C-1 in 339a appears at $\delta$ 76.5 in the $^{13}$C-NMR spectrum, which is considerably lower (~30 ppm) than that expected for a quaternary carbon bearing the substitution as proposed for structure 336a (i.e. C-6, 336a).

![Figure 2.6.8. Structures proposed for the major product of the reaction of N-cyclohexylsulfonylimine 202a with diene 293.](image)

Sultams 339 were unstable and only isolated for the N-cyclohexyl (339a) and N-benzyl (339b) analogues (Table 2.6.6, entries 1, 2, and 5). Upon treatment with silica or dilute acid, 339a and 339b readily underwent ring-opening to give the enone sulfonamide products 340a and 340d. In the case of the N-phenyl and N-tert-butyl analogues (entries 3 and 4), the sulfonamides 340b and 340c were the only products isolated.

Similar mixtures of analogous products have been reported for an aza-Diels-Alder reaction of an N-tosyl imino-ester with 2-silyloxy-cyclohexa-1,3-dienes (Scheme 2.6.12). In these
communications, the authors reported that low temperatures favoured the formation of “open-chain” cyclohexenones 343 over the bicyclic products 342, the opposite selectivity to that observed in the present work using \(N\)-alkylsulfonylimines 202a – 202d.

![Scheme 2.6.12. Reagents and conditions: a) PhH, 5 \(\rightarrow\) 20 °C, 3 h; b) 0.0005 M aq. HCl in THF (1:4), 342a 47\%, 342b 18.5\%, 343a 6\%, 343b 2\%.](image)

A dual mechanistic pathway was proposed to explain the mixtures of products obtained (Figure 2.6.9). A \([4+2]\) cycloaddition mode would give the bicyclic intermediate 345, which upon hydrolysis gives the azabicyclo[2.2.2]octanone products 342. Additionally, intermediate 345 may undergo a retro-Michael reaction to give the silylated cyclohexenone species 346, which upon hydrolysis gives the open-chain cyclohexanones 343. Alternatively, a Mannich-type reaction between imine 341 and diene 293 would give intermediate 346 directly; once more, hydrolysis of this species gives the open-chain adducts 343, while intramolecular Michael addition, followed by hydrolysis would give the bicyclic intermediate 345. A \([2+2]\) addition mode was not considered but is nevertheless unlikely under these reaction conditions, given that the rare literature examples of \([2+2]\) cycloadditions between imines and enol ethers require high pressure (12 Kbar) and gentle heating (50 °C) to proceed.177

![Figure 2.6.9. Possible reaction mechanisms for the reaction of imine 341 with diene 293, giving product mixtures analogous to those obtained in this work from the reaction of \(N\)-alkylsulfonylimines 202 with 293.](image)
In addition, similar β-ketosulfonamide adducts 348 have been reported by Vega et al, resulting from the reaction of silyl enol ethers 347 with N-methylsulfonylimine 202f (Figure 2.6.10).\textsuperscript{135}

Figure 2.6.10. Reaction of N-methylsulfonylimine 202f with silyl enol ethers as described by Vega et al.\textsuperscript{135,178}

4-Membered [2+2] adducts were not observed in this reaction; however this does not preclude a [2+2] cycloaddition pathway, given the instability of the sultams 339a and 339b we have observed in the closely related reaction of diene 293 with N-alkylsulfonylimines 202a and 202d. Indeed, the isolation of both 2-thia-3-azabicyclo[2.2.2]octan-6-one 2,2-dioxide 337a and the 7-thia-8-azabicyclo[4.2.0]oct-2-ene 7,7-dioxides 339a and 339b suggests that N-alkylsulfonylimines react with 2-silyloxydienes via both [4+2] and [2+2] cycloaddition modes (Figure 2.6.11). In the case of diene 293, [2+2] cycloaddition is favoured, giving 339a and 339b and the ring-opened β-ketosulfonamides 340a – 340d as the major components of the reaction mixture.

Figure 2.6.11. Proposed mechanism for the reaction of N-alkylsulfonylimines 202a – 202d with diene 293.

These results are similar to those found by Burgess and Williams for the cycloaddition reactions of N-acysulfonylimine-THF complex 226 with alkenes (Section 2.3.2, scheme 2.3.4).\textsuperscript{155} While alkyl substituted N-alkylsulfonylimines 202 only gave cycloadducts with highly electron-rich olefins,\textsuperscript{132} recourse to the more reactive N-acyl derivative 224 or THF complex 226 allowed reaction with less nucleophilic olefins (e.g. 227a, 228a:229a 1:8, figure 2.6.12).
Extending this reactivity pattern to silyl enol ethers (e.g. 293), we would therefore expect [2+2] cycloaddition of N-alkylsulfonylimines 202a – 202d with 293 to be unfavourable. It is possible, however, that the enhanced reactivity of the N-alkylsulfonylimines observed in this work is due to in situ complexation of the reactive species with the THF used as solvent in the reaction (i.e. 350, vide supra).

2.6.5 Reaction of N-alkylsulfonylimines 202 with doubly activated dienes: Chan’s diene 295 and Brassard’s diene 296

The presence of additional electron-donating groups on a 1,4-diene further enhances the reactivity of the diene in [4+2] cycloadditions. Well known examples include Danishefsky’s diene 93 – whose reactivity with N-alkylsulfonylimines has already been examined – and the trisubstituted dienes Brassard’s diene 296, and Chan’s diene 295.

Chan’s diene 295\textsuperscript{179} and Brassard’s diene 296\textsuperscript{180} were both synthesised in two steps from methyl acetoacetate 351 following literature procedures (Scheme 2.6.13).\textsuperscript{181,182}

**Scheme 2.6.13.** Reagents and conditions: a) Et\textsubscript{3}N, TMSCl, hexanes, r.t., 18 h, 69%; b) LDA, TMSCl, -78 → 0 °C, 1.5 h, 52%; c) trimethyl orthoformate, cat. conc. H\textsubscript{2}SO\textsubscript{4}, r.t., 24 h, 75%; d) LDA, TMSCl, -78 °C → r.t., 1.5 h, 59%.
Reaction of N-cyclohexylsulfamoyl chloride 213a with Chan’s diene 295, provided sulfonamide 354 rather than the expected [4+2] cycloadduct, likely through a “Mukaiyama aldol-like” pathway (Scheme 2.6.14).

Scheme 2.6.14. Reagents and conditions: a) Et$_3$N, THF, -78 °C → r.t., 1.5 h, 65%.

This is not altogether unexpected, as Chan’s diene 295 is known to react relatively poorly in [4+2] cycloaddition reactions, giving Michael adducts preferentially. A [2+2] cycloaddition process, as observed for diene 293 is unlikely, as the N-alkylsulfonylimine 202a would be expected to react preferentially with the more electron-rich C-1 – C-2 olefinic bond, giving a product of type 356.

On the other hand, reaction with Brassard’s diene 296 afforded primarily the open-chain sulfonamides 357 as the major component, in addition to the desired [4+2] adducts 358 (Table 2.6.7).
Table 2.6.7. Reaction of N-alkylsulfamoyl chlorides 213a – 213d with Brassard’s diene 296.

357 and 358 were easily distinguishable upon analysis of their $^1$H-NMR spectra. In particular, the chemical shift and multiplicity of the H-1′ resonance proved to be a characteristic feature for the product 358 resulting from ring-closure. Notably, the signal assigned to H-1′ in 2-cyclohexyl-5-methoxy-1,2-thiazin-3(6$H$)-one 1,1-dioxide 358a appears as a triplet of triplets at $\delta$ 4.48 (Figure 2.6.13). In comparison the signal assigned to H-1′ of (E)-methyl 4-(N-cyclohexylsulfamoyl)-3-methoxybut-2-enoate 357a resonates as a multiplet at $\delta$ 3.31, due to further splitting from the N-H proton.
It was initially hoped that esters 357 could be converted to the desired thiazinones 358 by treatment with base. Work by Hanewacker et al on related 3-oxo-1,2,5-thiadiazolidine 1,1-dioxides suggested that treatment with base should effect cyclisation. Unfortunately, when 357a was treated with either sodium hydride or hydroxide, only starting material was recovered (Scheme 2.6.14).

**Figure 2.6.13.** Comparison of $^1$H-NMR spectra of open-chain adduct 357a and cyclic adduct 358a.

**Figure 2.6.14.** Attempted cyclisation of open-chain adducts from reaction of N-alkylsulfonylimines with Brassard’s diene 296.
It was thought that perhaps the double bond was restricting rotation and preventing cyclisation to 358a. Hydrogenation of the enol ether 357a to 361 was attempted in order to increase the flexibility of the resultant alkyl chain. The first attempt at this transformation was performed using a Parr hydrogenation apparatus, subjecting a solution of enol ether 357a to hydrogenation over 10% Pd/C at 3 bar overnight (Table 2.6.8, entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 bar, Parr</td>
<td>r.t.</td>
<td>19.5</td>
<td>Starting material 357a</td>
</tr>
<tr>
<td></td>
<td>hydrogenator</td>
<td></td>
<td></td>
<td>recovered</td>
</tr>
<tr>
<td>2</td>
<td>50 bar, H-cube</td>
<td>20</td>
<td>-</td>
<td>Starting material 357a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>recovered</td>
</tr>
<tr>
<td>3</td>
<td>80 bar, H-cube</td>
<td>20</td>
<td>-</td>
<td>Starting material 357a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>recovered</td>
</tr>
</tbody>
</table>

Table 2.6.8. Attempted reduction of the double bond in open-chain adduct 357a.

Unfortunately, this procedure failed to afford the desired product 361, and only starting material was recovered. It was decided to increase the pressure of hydrogen in an attempt to encourage reaction with the substrate. Using an H-cube continuous flow hydrogen generator, 357a was subjected to high pressure (50 bar) hydrogen over a 10 mol% Pd/C catalyst cartridge (entry 2). Again, this procedure only returned starting material. Increasing the hydrogen pressure to the maximum possible in the H-cube apparatus failed to provide any of the desired product 361, and this approach was abandoned.

Reconsidering our attempts to effect cyclisation of the methyl ester 357a to 358a, we postulated that the cyclisation was too slow. It was reasoned that increasing the length of time that 357 was exposed to base may result in the desired heterocycle. When exposure of 357 to aqueous sodium hydroxide was extended to a minimum of 24 h, however, only acids 362a – 362c were formed (Table 2.6.9). Cyclisation to the thiazinone 1,1-dioxides 358 could then be effected in high yield by treatment of the acids with thionyl chloride.
Table 2.6.9. Conversion of open-chain adducts 357 to thiazinone 1,1-dioxides 358.

The tert-butyl derivative 362b, however, gave the deprotected sultam 358b (where R = H) resulting from acid-catalysed dealkylation under these conditions.

2.6.6 Conclusion

In summary, a variety of novel sultams 210, 335, 337a, 339, and 358 and sulfonamides 312, 313, 327, 328, 340, 354, 357, and 362 have been synthesised via reaction of N-alkylsulfonylimines 202a – 202d with a variety of activated dienes (Figure 2.6.15).
Figure 2.6.15. Summary of novel compounds obtained from the reaction of $N$-alkylsulfonylimines 202 with dienes 93, 123, and 292 – 296.

There is considerable debate in the literature as to the exact nature of the mechanism of the so-called Diels-Alder reactions of silyloxydienes with heterodienophiles such as aldehydes$^{185-188}$ and imines.$^{189-192}$
In several cases this reaction appears to take place via a concerted process; however in cases using very reactive silyloxydienes (e.g. Danishefsky’s diene 93) intermediates have been isolated that support the theory that the reaction is not a concerted cycloaddition, but rather a stepwise process. When using aldehydes as the dienophile, the adducts 365 may arise either via a concerted Diels-Alder cycloaddition or a Mukaiyama aldol pathway (Figure 2.6.16). Use of imines in the aza-Diels-Alder reaction may give rise to adducts 369 via initial Mannich addition, followed by Michael ring-closure, or by a concerted Diels-Alder process (Figure 2.6.17). Reactions of these heterodienophiles with the more activated silyloxydienes occasionally give open-chain side products, thus suggesting that Mukaiyama or Mannich-Michael processes are operative.
Figure 2.6.17. Possible mechanistic pathways for aza-Diels-Alder reaction of Danishefsky’s diene 93 with imines 366.

In the current work, attempted cycloaddition with unactivated dienes was unsuccessful; only very activated dienes 93, 123, and 292 – 296 reacted with N-alkylsulfinimines 202a – 202d. A mixture of both cyclic and open chain adducts formed, lending support to the theory that these heterodienophiles react in cycloadditions via a stepwise, rather than a concerted process. However, [2+2] cycloadducts 339a and 339b have been isolated in the reaction of N-alkylsulfonylimines 202a and 202d with diene 293, in addition to [4+2] adduct 337a. This result indicates that in some cases the observed mixtures of products likely result from a combination of these processes operating simultaneously.

N-Alkylsulfonylimines 202 have also been proposed to be inferior heterodienophiles compared to the closely related sulfenes 205. This has been borne out in practice; sulfenes have been shown to participate in cycloadditions with a variety of dienes, including cyclopentadiene 288 (Scheme 2.6.15). The cycloadduct 371, however, was only obtained when the sulfene was generated via fluorodesilylation of the precursor 370.

Scheme 2.6.15. Reagents and conditions: a) CsF, MeCN, r.t., 2 h, 64%.
In the present work, N-alkylsulfonylimines 202a – 202d have only been demonstrated to react with very activated dienes – an observation also supported by others.\textsuperscript{155,158} This decrease in reactivity can be rationalised by the replacement of the carbon atom in sulfenes by a nitrogen atom in N-alkylsulfonylimines. The lone pair on the nitrogen atom donates its electrons to the sulfur atom, thereby decreasing its electrophilicity. This explains the decrease in reactivity towards dienes, especially given that these heterodienophiles appear to react via stepwise mechanisms.

Nevertheless, new adducts have been prepared in the present work that have not previously been reported in the literature (Figure 2.6.15, \textit{vide supra}). Preliminary antimicrobial testing against \textit{S. aureus} and \textit{E. coli} found that three of the compounds synthesised in this section have mild bacteriostatic activity against \textit{S. aureus} (Figure 2.6.18). This activity is presumably due to the presence of an enone moiety that can act as a Michael acceptor with nucleophilic biological molecules.

![Chemical structures](image)

\textbf{Figure 2.6.18.} Results of screening the novel adducts in this work in an antimicrobial assay.
2.7 Reactions of N-alkylsulfonylimines with 1,3-dipoles: Azomethine ylides

Given the success in Diels-Alder reactions of N-alkylsulfonylimines 202a – 202d with dienes 93, 123, and 292 – 296, we now sought to expand this methodology to the use of 1,3-dipoles.

Cycloaddition reactions of azomethine ylides with olefins have long been used for the synthesis of pyrrolidines, a biologically important motif.\(^\text{193-195}\) Unstabilised azomethine ylides of type 373 afford products of type 374 upon cycloaddition to a range of olefins that may be electron-rich, -poor, or unpolarised (Figure 2.7.1).\(^\text{196,197}\) Stabilised azomethine ylides of type 375 – 378, usually generated \textit{in situ} from the condensation of the corresponding amine and aldehyde, afford products of types 380 – 381; “W” and “U” shaped azomethine ylides 375 and 376 give the 2,5-\textit{syn} adducts, while “S” shaped azomethine ylides 377 and 378 afford the 2,5-\textit{anti} adducts 381.

![Reaction of azomethine ylides with olefins](image_url)

\textit{Unstabilised azomethine ylides:}

\begin{align*}
&\text{Unstabilised azomethine ylides:} \\
&\text{Stabilised azomethine ylides:}
\end{align*}

\textit{Stabilised azomethine ylides:}

![Cycloadducts of unstabilised azomethine ylides 373 and stabilised azomethine ylides 375 – 378 with olefins 372 and 379.](image_url)

Reaction of these dipoles with heterodipolarophiles, however, has been restricted to carbonyl compounds,\(^\text{198-204}\) their sulfur analogues,\(^\text{205-213}\) isocyanates,\(^\text{214}\) imines,\(^\text{198,205,215-222}\) and diazenes (Figure 2.7.2).\(^\text{223}\)
Figure 2.7.2. Examples of 5-membered heterocycles from reaction of a variety of heterodipolarophiles with azomethine ylides.

Cycloaddition of an azomethine ylide with an \( N \)-alkylsulfonylimine is proposed to give a 1,2,4-thiadiazolidine 1,1-dioxide 303 (Figure 2.7.3).

![Chemical structure](image)

Figure 2.7.3. Proposed cycloaddition of an azomethine ylide 298 with \( N \)-alkylsulfonylimine 202.

Few reports of this type of heterocycle exist; tetraphenyl-derivative 391 (Figure 2.7.4), synthesised through the cycloaddition of an azomethine ylide with \( \text{SO}_2 \), appears to be the only example in the literature.\(^{224}\) No biological activity for this heterocycle has been reported. The proposed adducts resulting from dipolar cycloaddition of \( N \)-alkylsulfonylimines with azomethine ylides therefore provide interesting synthetic targets, with their potential biological activity remaining unexplored.
2.7.1 Synthesis of azomethine ylide precursors

Azomethine ylides can be generated in a number of ways; for example the unstabilised azomethine ylide 393 is available via fluoride ion-\(^{198,225}\) or TFA-induced\(^{226}\) desilylation of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine 392 (Scheme 2.7.1).

Scheme 2.7.1. Reagents and conditions: a) LiF, MeCN, ultrasound; b) TFA, CH\(_2\)Cl\(_2\), 0 °C.

Alternatively, stabilised azomethine ylides can be generated via an imine tautomerisation method in which EWG-substituted imines are treated with base,\(^{227-229}\) which may be catalysed by addition of metal salts (Figure 2.7.5).

Figure 2.7.5. Generalised scheme for the reaction of an azomethine ylide 396 generated from an imine 395 with dipolarophiles.

Both approaches were considered for this work. Precursor 392 is commercially available, while imine 395 is available via the condensation of the hydrochloride salt of glycine ethyl ester 398 and benzaldehyde (Scheme 2.7.2):

Scheme 2.7.2. Reagents and conditions: a) Et\(_3\)N, Na\(_2\)SO\(_4\), CH\(_2\)Cl\(_2\), r.t., 6.5 h, 85%.
Thus, treatment of 398 with benzaldehyde 231 and triethylamine in the presence of Na$_2$SO$_4$ afforded the relatively unstable imine 395a in high yield.

2.7.2 Attempted cycloaddition of $N$-cyclohexylsulfonylimine 202a with unstabilised azomethine ylide 393

With both azomethine ylide precursors in hand, attention turned to their application in cycloadditions with $N$-cyclohexylsulfonylimine 202a.

The first method to be examined was the fluoride ion-induced desilylation of amine precursor 392. An acetonitrile suspension of lithium fluoride and 392 was treated with a solution of $N$-cyclohexylsulfamoyl chloride and triethylamine at -35 °C, and the reaction mixture stirred at this temperature for 4 h (Table 2.7.1, entry 1). The mixture was then allowed to warm to room temperature and stirred for an additional 2.5 d. After workup, only sulfamide dimer 246a, and not the proposed cycloadduct 394a was obtained.

Because the fluoride salt is only sparingly soluble in acetonitrile, sonication is required to solubilise it and induce desilylation of 392. An alternative method for the generation of the azomethine ylide was therefore attempted. Thus, a mixed solution of the sulfamoyl chloride 213a and azomethine ylide precursor 392 was treated with TFA at reduced temperature (-78 °C, entry 2). Unfortunately, only sulfamide dimer 246a was isolated. Reasoning that the reduced temperature was impeding formation of the azomethine ylide 393, the TFA-induced silylation procedure was performed again at 0 °C (entry 3). Unfortunately, again only dimer 246a was formed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiF, MeCN</td>
<td>-35 → r.t.</td>
<td>60</td>
<td>dimer 246a</td>
</tr>
<tr>
<td>2</td>
<td>TFA, CH$_2$Cl$_2$</td>
<td>-78 → 0</td>
<td>48</td>
<td>dimer 246a</td>
</tr>
<tr>
<td>3</td>
<td>TFA, CH$_2$Cl$_2$</td>
<td>0</td>
<td>48</td>
<td>dimer 246a</td>
</tr>
</tbody>
</table>

Table 2.7.1. Attempted reaction of $N$-cyclohexylsulfamoyl chloride with the unstabilised azomethine ylide derived from amine 392.
2.7.3 Attempted cycloaddition of \(N\)-cyclohexylsulfonylimine 202a with stabilised azomethine ylide 396a

The cycloaddition of \(N\)-cyclohexylsulfonylimine 202a with stabilised azomethine ylide 396a derived from the imine 395a, was next examined. It was hoped that because both reactive species 202a and 396a are generated under the same conditions, a one-pot protocol would afford the cyclised product 397a.

Thus, a cold (-78 °C) solution of \(N\)-cyclohexylsulfamoyl chloride 213a and imine 395a was treated with triethylamine, and allowed to stir at reduced temperature for 3 h (Table 2.7.2, entry 1). Warming to room temperature and subsequent workup only afforded sulfamide dimer 246a. It was thought that the temperature, while ideal for generation of the \(N\)-alkylsulfonylimine, was too low for successful generation of the azomethine ylide 396a. The reaction was therefore repeated at a higher temperature (-20 °C, entry 2) in the hope that the azomethine ylide would form more readily and then react with the \(N\)-cyclohexylsulfonylimine 202a as it formed. Unfortunately, in this case the reaction again only afforded the sulfamide dimer 246a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N, THF</td>
<td>-78 → r.t.</td>
<td>3</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N, THF</td>
<td>-20 → r.t.</td>
<td>2</td>
<td>dimer 246a only</td>
</tr>
<tr>
<td>3</td>
<td>Et₃N, AgSbF₆, (S)-BINAP, PhMe</td>
<td>-20 → r.t.</td>
<td>20</td>
<td>dimer 246a only</td>
</tr>
</tbody>
</table>

Table 2.7.2. Attempted reaction of \(N\)-cyclohexylsulfamoyl chloride with the stablised azomethine ylide derived from imine 395a.

Sansano and coworkers recently reported the use of BINAP-AgSbF₆ as a catalyst to effect cycloaddition of azomethine ylides to alkenes. Using these conditions, triethylamine was added to a mixed solution of the catalyst, sulfamoyl chloride, and imine in toluene at -20 °C, and the mixture
allowed to stir at this temperature for 4 h before warming to room temperature and stirring overnight. Unfortunately in this case only sulfamide dimer 246a was obtained.

2.7.4 Conclusion

 Attempted reactions of N-cyclohexylsulfamoyl chloride 213a to azomethine ylides was unsuccessful, affording only sulfamide dimer 246a. This result may be due to a mismatch in reactivity between the two components – the successful generation of the reactive azomethine ylides 393 and 396a from their respective precursors requires higher temperatures (-40 to -20 °C) than those tolerated by the N-alkylsulfonylimine (-78 °C). The heterocumulene therefore reacts with itself at lower temperature, giving homodimer 246a, before the 1,3-dipole can be generated. Attention therefore turned to the use of more stable, pre-formed dipoles in the hope that these, like the dienes examined in section 2.2, would react with 202a.
2.8 Reactions of N-alkylsulfonylimines with 1,3-dipoles: Donor-acceptor cyclopropanes

Donor-acceptor cyclopropanes 301 are 1,3-dipoles that can be unmasked with the assistance of appropriate Lewis-acids (Figure 2.8.1).\textsuperscript{231}

\begin{center}
\[ \text{ArCO}_2R^1 \quad \text{LA} \quad \text{Ar} \quad \text{CO}_2R^1 \quad \text{X} = \text{O, N; Y = C, N} \]
\end{center}

**Figure 2.8.1.** Overall schematic of the Lewis acid-promoted cycloaddition of donor-acceptor cyclopropanes with dipolarophiles. X = O, N; Y = C, N.

A variety of 5-membered heterocycles can be obtained upon reaction with different dipolarophiles. This technique has been exploited in the synthesis of substituted tetrahydrofurans 405 from aldehydes or ketones,\textsuperscript{232-235} pyrrolidines 406 from imines,\textsuperscript{236,237} and pyrazolidine derivatives 407 – 408 from diazenes\textsuperscript{238} (Figure 2.8.2).

\begin{center}
\begin{tikzpicture}
  \node (301) at (0,0) {\text{ArCO}_2\text{Me}}；
  \node (405) at (1.5,1) {\text{PhO}}；
  \node (406) at (1.5,2) {\text{MeO}_2\text{C}}；
  \node (402) at (3,1) {\text{PhN}}；
  \node (403) at (1.5,-1) {\text{CO}_2\text{Pr}}；
  \node (404) at (3,-1) {\text{CO}_2\text{Pr}}；
  \node (407) at (0,-1) {\text{PhN}}；
  \node (408) at (3,-2) {\text{CO}_2\text{Pr}}；
\end{tikzpicture}
\end{center}

**Figure 2.8.2.** 5-membered heterocycles from cycloadditions of donor-acceptor cyclopropanes with a variety of heterodipolarophiles.
It was decided to investigate the reaction of known donor-acceptor cyclopropane \(411\) with \(N\)-alkylsulfonylimines \(202\), which would potentially give dialkyl-3-aryl-1,2-thiazolidine-5,5-dicarboxylate 1,1-dioxides of type \(306\) (Figure 2.8.3).

![Figure 2.8.3. Proposed cycloaddition of a donor-acceptor cyclopropane 301 with N-alkylsulfonylimine 202.](image)

### 2.8.1 Synthesis of donor-acceptor cyclopropane 411

Knoevenagel condensation of diethyl malonate \(409\) with benzaldehyde afforded the alkene \(410\) in moderate yield.\(^{239}\) Corey-Chaykovsky cyclopropanation\(^{240}\) with trimethylsulfoxonium iodide and sodium hydride then afforded the cyclopropane diester \(411\) in low yield (Scheme 2.8.1).\(^{239}\)

![Scheme 2.8.1. Reagents and conditions: a) benzaldehyde, cat. piperidine, benzoic acid, PhMe, reflux, 16 h, 49%; b) trimethylsulfoxonium iodide, NaH, DMF, r.t., 16 h, 11%.](image)

### 2.8.2 Attempted cycloaddition of \(N\)-cyclohexylsulfonylimine 202a with cyclopropane 411

Initially, the \(N\)-cyclohexylsulfonylimine was generated in a separate vessel at reduced temperature – by treatment of a solution of the sulfamoyl chloride with triethylamine – this was then added to a suspension of the Lewis acid and cyclopropane \(411\) (Table 2.8.1).
Table 2.8.1. Attempted Lewis acid-catalysed donor-acceptor cyclopropane ring opening with \(N\)-cyclohexylsulfamoyl chloride 213a.

Unfortunately, the only products recovered were homodimer 246a (resulting from self-condensation of the \(N\)-alkylsulfonylimine), and unreacted starting material 411.

A one-pot procedure at room temperature, whereby the \(N\)-cyclohexylsulfonylimine 202a was generated in the presence of cyclopropane 411 and catalytic scandium(III) triflate, was also attempted. Again, the only compounds recovered were unreacted cyclopropane 411 and the cyclohexyl-homodimer 246a.

### 2.8.3 Conclusion

\(N\)-Alkylsulfonylimines have proven to be unreactive in attempted cycloadditions with donor-acceptor cyclopropanes such as 411. This result may be due to the lack of reactivity on the part of the heterodipolarophile. Alternatively, the lack of reaction could also be due to reduced formation of the dipole itself. As shown in figure 2.8.1 above, 1,3-dipole formation requires complexation of the cyclopropane with a Lewis acid; generation of the \(N\)-alkylsulfonylimine 202a, on the other hand, requires addition of triethylamine. The base may be sequestering the Lewis acid thereby preventing formation of the 1,3-dipole, and hence subsequent cycloaddition.
Attention therefore turned to the use of alternative 1,3-dipoles, such as nitrones and azides.
2.9 Reactions of N-alkylsulfonylimines with 1,3-dipoles: Nitrones

Nitrones participate in 1,3-dipolar cycloadditions with several heterodipolarophiles to form a variety of 5-membered heterocycles: thiones,\textsuperscript{241} germanium-heteroatom double bond species,\textsuperscript{242-245} and isocyanates at the N=C bond (Figure 2.9.1).\textsuperscript{246-248}

![Figure 2.9.1. 5-membered heterocycles from cycloadditions of nitrones with a variety of heterodipolarophiles.](image)

The reaction of nitrones with the related sulfenes has also been reported independently by Eloy and Van Overstraeten\textsuperscript{249} and Truce \textit{et al.}\textsuperscript{250} Rather than the expected 5-membered cycloadducts \textbf{418}, 1,2,5-benzoxathiazepines \textbf{419} were obtained (Figure 2.9.2). The authors proposed that initial cycloaddition of sulfene \textbf{205} to \textit{N}-aryl nitrone \textbf{412} afforded \textbf{419} after proton migration and ring enlargement. Subsequent work by others has confirmed the generality of this rearrangement.\textsuperscript{251-253}

![Figure 2.9.2. Reaction of sulfenes with \textit{N}-aryl nitrones.\textsuperscript{249,250}](image)

Based on similar cycloadditions, addition of a nitrone to an \textit{N}-alkylsulfonylimine is proposed to give a novel heterocyclic 1,2,3,5-oxathiadiazolidine \textbf{302}, and will be investigated in this work (Figure 2.9.3.).
2.9.1 **Synthesis of nitrone 421**

The dibenzylamine-derived nitrone 421 was selected for use in this study. The nitrone was obtained by oxidation of dibenzylamine with Oxone® according to the protocol described by Figueredo et al (Scheme 2.9.1)\(^{254}\).

\[
\text{Scheme 2.9.1. Reagents and conditions: a) Oxone}^\circledR, \text{aq. Na}_2\text{EDTA, NaHCO}_3, \text{MeCN:THF (4:1), 5 °C, 2 h, 85%}.\]

Thus, addition of 2.1 equivalents of Oxone® portionwise to a cold solution of dibenzylamine buffered with Na\(_2\)EDTA provided the desired nitrone 421 in 85% yield after purification by flash column chromatography.

2.9.2 **Attempted cycloaddition of nitrone 421 with N-cyclohexylsulfonylimine 202a**

Treatment of a mixed solution of N-cyclohexylsulfamoyl chloride 213a and nitrone 421 with triethylamine in THF at reduced temperature (-78 °C) for 2 h did not give the proposed product 302a; instead sulfamide 422 was obtained, along with a small amount of homodimer 246a (Table 2.9.1, entry 1).
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield 302a (%)</th>
<th>Yield 422 (%)</th>
<th>Yield 246a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78 → r.t.</td>
<td>2</td>
<td>0</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>r.t.</td>
<td>72</td>
<td>0</td>
<td>34</td>
<td>trace</td>
</tr>
</tbody>
</table>

Table 2.9.1. Attempted cycloaddition of nitrone 421 with N-cyclohexylsulfamoyl chloride 213a.

The structure of 422 was initially thought to be the O-sulfamic ester 423 in that the $^1$H- and $^{13}$C-NMR spectra exhibited resonances corresponding to a secondary N-cyclohexylamine in addition to those for a dibenzyl fragment. This was supported by the characteristic SO$_2$ absorptions in the IR-spectrum at 1329 and 1135 cm$^{-1}$. The structure was therefore proposed to be 422. Mass spectral analysis, however, revealed a molecular ion 16 mass units less than that required for this structure, suggesting that the product obtained lacks an oxygen atom. The structure of the product of the reaction of 213a with nitrone 421 was therefore revised to be sulfonamide 422.

Figure 2.9.4. Proposed and actual product of attempted cycloaddition of N-cyclohexylsulfamoyl chloride 213a with nitrone 421.
This unexpected product 422 may arise from the reaction of N-alkylsulfoximoyl chloride 213a with dibenzylamine 420 contaminating the nitrone 424 (Figure 2.9.5).

![Proposed mechanism for the formation of sulfonamide 422.](image)

Adding a solution of pre-prepared N-cyclohexylsulfonylimine to a solution of the nitrone at room temperature likewise failed to provide a cyclic product, giving 422 in slightly higher (34%) yield in comparison to the one-pot protocol (entry 2). This result suggests that unlike sulfenes, N-alkylsulfonylimines do not appear to undergo 1,3-dipolar cycloaddition with nitrones.

### 2.9.3 Conclusion

Reaction of N-cyclohexylsulfonylimine 202a and nitrone 421 did not afford the cyclic 1,2,3,5-oxathiadiazolidine product 302a. Disappointingly, only the open-chain sulfonamide 422 was isolated in low yield. It appears that N-alkylsulfonylimines are not reactive enough to take part in the [3+2] cycloaddition with nitrones, which is in contrast to reactions using sulfenes.

Attention next turned to the use of azides as 1,3-dipoles in cycloaddition reactions with heterodipolarophiles.
2.10 Reactions of N-alkylsulfonylimines with 1,3-dipoles: Azides

Although the so-called “click” cycloaddition of azides with acetylenes has been studied extensively,\textsuperscript{255} the corresponding reactions with heterodipolarophiles has been limited to isocyanates,\textsuperscript{256-259} alkylidene phosphoranes,\textsuperscript{260} aminophosphines,\textsuperscript{261} and iminoboranes (Figure 2.10.1).\textsuperscript{262}

Figure 2.10.1. 5-membered heterocycles from the reaction of azides with a variety of heterodipolarophiles.

The reaction of an azide 300 and N-alkylsulfonylimine 202 is proposed to give a novel 2,3-dihydro-1,2,3,4,5-thiatetrazole 1,1-dioxide of type 305 (Figure 2.10.2).

Figure 2.10.2. Proposed cycloaddition between an azide 300 and N-alkylsulfonylimines.

2.10.1 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with azide 432

Azide 432, kindly prepared by colleagues within our research group, was chosen as the cycloaddition partner for the reaction. 432 is available from dec-9-en-1-ol in 9 steps.\textsuperscript{263}
Scheme 2.10.1. **Reagents and conditions:** a) Et$_3$N, THF, -78 °C → r.t., 2 h.

Treatment of a solution of azide 432 and N-cyclohexylsulfamoyl chloride 213a in cold (-78 °C) tetrahydrofuran with triethylamine afforded only unreacted starting material and homodimer 246a (Scheme 2.10.1).

2.10.2 **Conclusion**

The proposed cycloaddition between azide 432 and N-cyclohexylsulfonylimine 202a did not proceed. It would appear then that N-alkylsulfonylimines are not reactive enough heterodipolarophiles to take part in [3+2] cycloadditions with azides. As [3+2] cycloadditions of heterodipolarophiles to azides are generally carried out under thermal conditions, it is perhaps not too surprising that the low temperature reaction (required to suppress self-condensation of 202a) of 202a and 432 failed.

This avenue of investigation was therefore not pursued further, and attention turned to the proposed cycloaddition of N-alkylsulfonylimines with nitrile oxides.
2.11 Reactions of N-alkylsulfonylimines with 1,3-dipoles: Nitrile oxides

Nitrile oxides have been used extensively in the synthesis of a wide variety of heterocycles. Cycloaddition of 299 with a dipolarophile gives products of type 437 – 442, and has been applied to a range of hetero-multiple bonds, including carbonyl groups and their sulfur analogues, selenoaldehydes, imines, nitriles, and alkylidene-phosphonanes (Figure 2.11.1).

![Figure 2.11.1. 5-membered heterocycles from the reaction of nitrile oxides 299 with a variety of heterodipolarophiles.](image1)

Reaction of a nitrile oxide 299 with a N-alkylsulfonylimine 202 is proposed to give 1,2,3,5-oxathiadiazole 2,2-dioxides 304 (Figure 2.11.2).

![Figure 2.11.2. Proposed cycloaddition between a nitrile oxide 299 and N-alkylsulfonylimines.](image2)

These heterocycles are not well represented in the literature, with only four examples reported, each synthesised in efforts directed towards the synthesis of biologically active molecules (Figure 2.11.3, compounds 443 – 445). 443 – 445 were prepared from their respective oximes through treatment with sulfuryl chloride. Our proposed cycloaddition is therefore a novel and interesting route to these interesting heterocycles. In addition, any bioactivity (or lack thereof) exhibited by these four compounds has not been reported. Hence, 1,2,3,5-oxathiadiazole 2,2-dioxides present an
attractive synthetic target due to their potential biological activity and rare occurrence in the literature.

Figure 2.11.3. Examples of 1,2,3,5-oxathiadiazole 2,2-dioxides in the literature, and their general synthesis.$^{288-290}$

The required nitrile oxides 299 in turn can be prepared by 3 main methods (Figure 2.11.4).$^{291}$

Figure 2.11.4. Different methods for the synthesis of nitrile oxides 299.

One of the most classical methods for synthesis of nitrile oxides is Mukaiyama’s procedure, whereby intermolecular dehydration of a nitroalkane 447 produces the nitrile oxide 299.$^{292}$ This method is generally used for synthesis of aliphatic nitrile oxides. Alternatively, Huisgen et al reported that dehydrohalogenation of a hydroximinoyl chloride 448 gives 299.$^{293}$ This method is generally used for the generation of aromatic nitrile oxides. Finally, a more recent procedure has been reported by Carreira et al whereby an O-silylated hydroxamic acid 449 is dehydrated upon treatment with triflic anhydride.$^{294}$ This last approach has only been used for the synthesis of aromatic nitrile oxides.

In the present work, all three approaches have been examined for the attempted cycloaddition of an \(N\)-alkylsulfonylimine to a nitrile oxide.
2.11.1 Synthesis of nitrile oxides and their precursors

Hydroximinoyl chlorides 448 appeared to be ideal reaction partners for N-alkylsulfonylimines, in that generation of both the dipolarophile and the nitrile oxide occurs via dehydrohalogenation of their respective precursors at reduced temperature, allowing for a one-pot procedure. The required hydroximinoyl chloride 448 is prepared from the corresponding aldehyde by conversion to the oxime, followed by chlorination with N-chlorosuccinimide (Figure 2.11.5). The nitrile oxides 299 could then be generated by treatment with triethylamine, either immediately prior to use, or in situ.

Figure 2.11.5. Generalised synthesis of nitrile oxides via Huisgen’s dehydrohalogenation from the parent aldehyde.

Initially, mesityl nitrile oxide 299a was selected for ease of handling, as this hindered nitrile oxide is relatively stable and can be pre-formed and stored under careful conditions.

Scheme 2.11.1. Reagents and conditions: a) NaOH, NH₂OH·HCl, EtOH, 5 °C → r.t., 1.5 h, 93%; b) NCS, DMF, r.t., 2 h, 91%; c) Et₃N, Et₂O, r.t., 1 h, quant.

Thus, oxime 451 was prepared from commercially available mesitaldehyde 450 by condensation with hydroxylamine hydrochloride in the presence of sodium hydroxide (Scheme 2.11.1). The crude oxime precipitated from the reaction mixture upon addition of water and was subjected to chlorination without further purification. Treatment with N-chlorosuccinimide in DMF, according to the procedure of Howe et al., required addition of gaseous HCl to initiate the reaction; nevertheless, hydroximinoyl chloride 448a was obtained in excellent yield without need for further purification. The nitrile oxide could then be generated from 448a upon treatment with triethylamine in diethyl ether; alternatively, the nitrile oxide could be generated in situ from 448a, conveniently under identical conditions required to generate the N-alkylsulfonylimine.

Hydroximinoyl chloride 448b was prepared in an analogous sequence from benzaldehyde 231, affording 448b in 84% overall yield (Scheme 2.11.2). Unlike the mesityl derivative, however, 448b
was much less stable than 448a, and was synthesised freshly from oxime 452 prior to each cycloaddition attempt.

\[
\begin{align*}
\text{phenyl oxime} & \quad \xrightarrow{a} \quad \text{phenyl oxime} \\
& \quad \xrightarrow{b} \quad \text{N-phenylsulfonylimine}
\end{align*}
\]

Scheme 2.11.2. Reagents and conditions: a) NaOH, NH₂OH·HCl, EtOH, 5 °C → r.t., 1.5 h, 95%; b) NCS, pyridine, CH₂Cl₂, r.t., 2 h, 88%.

### 2.11.2 Attempted cycloadditions of N-cyclohexylsulfonylimine with nitrile oxides 299a and 299b

Mesityl nitrile oxide 299a was first selected to investigate the proposed cycloaddition with N-cyclohexylsulfonylimine 202a, as its enhanced stability translated to convenience in handling. Cycloadditions were attempted with both pre-formed mesityl nitrile oxide 299a and by generation of both reactive partners in situ (Table 2.11.1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Additive</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>299a pre-formed</td>
<td>-78 → r.t.</td>
<td>2</td>
<td>-</td>
<td>dimer 246a</td>
</tr>
<tr>
<td>2</td>
<td>one-pot protocol; Et₃N added to a mixture of 448a and 213a</td>
<td>-40 → r.t.</td>
<td>1</td>
<td>-</td>
<td>dimer 246a</td>
</tr>
<tr>
<td>3</td>
<td>299a pre-formed</td>
<td>0 → r.t.</td>
<td>1</td>
<td>-</td>
<td>dimer 246a</td>
</tr>
<tr>
<td>4</td>
<td>299a pre-formed</td>
<td>40</td>
<td>1</td>
<td>-</td>
<td>dimer 246a</td>
</tr>
<tr>
<td>5</td>
<td>299a pre-formed</td>
<td>-78 → r.t.</td>
<td>4</td>
<td>MgBr₂</td>
<td>dimer 246a</td>
</tr>
</tbody>
</table>

Table 2.11.1. Attempted cycloaddition of mesityl nitrile oxide 299a with N-cyclohexylsulfamoyl chloride 213a.

Disappointingly, addition of triethylamine to a mixed solution of N-cyclohexylsulfamoyl chloride 213a and pre-formed nitrile oxide 299a at reduced temperature afforded only homodimer 246a.
Increasing the temperature of the reaction also failed to produce the proposed cycloadduct 304a (entries 3, 4). Options for optimisation were limited, as the N-alkylsulfonylimines are only stable at reduced temperatures, and polymerisation takes place at higher temperatures.\textsuperscript{298} Adopting a one-pot protocol was similarly unsuccessful (entry 2). Lewis acid catalysis also failed to provide the desired heterocycle 304a (entry 5).

Reasoning that perhaps the mesityl group was too bulky for cycloaddition to occur, use of phenyl nitrile oxide 299b was investigated. Once again, although a variety of reaction conditions were investigated none afforded the desired cycloadduct 304b (Table 2.11.2). One-pot protocols, whereby triethylamine was added to a mixture of the hydroximinoyl chloride 448b and N-cyclohexylsulfamoyl chloride in tetrahydrofuran, failed to provide the desired heterocycle 304b (entries 1, 3, 4), with only sulfamide homodimer 246a being recovered from these reactions.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield 304\textsubscript{b} (%)</th>
<th>Yield 453 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>One-pot protocol; Et\textsubscript{3}N added to a mixture of 448\textsubscript{b} and 213\textsubscript{a} in THF</td>
<td>-78 → r.t.</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>One-pot protocol</td>
<td>-40 → r.t.</td>
<td>2</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>One-pot protocol</td>
<td>0 → r.t.</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>One-pot protocol</td>
<td>r.t.</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Nitrile oxide 299\textsubscript{b} pre-formed; 213\textsubscript{a} and Et\textsubscript{3}N in THF then added</td>
<td>-78 → r.t.</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>448\textsubscript{b}, 213\textsubscript{a}, TBAF, THF</td>
<td>r.t.</td>
<td>0.5</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>448\textsubscript{b}, 213\textsubscript{a}, TBAF, THF</td>
<td>-40</td>
<td>2.5</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2.11.2. Attempted cycloaddition of phenyl nitrile oxide 448\textsubscript{b} with N-cyclohexylsulfamoyl chloride 213\textsubscript{a}.

However, when the reaction was conducted at -40 °C, a crystalline substance was isolated; its structure was identified as O-sulfamic ester 453 by comparison of the spectral data to the starting materials. Use of an alternative dehydrohalogenation reagent, TBAF\textsuperscript{299}, provided mainly homodimer 246\textsubscript{a}, together with small quantities of the novel product 453.
Reasoning that 453 arises from the reaction of N-cyclohexylsulfonylimine 202a with hydroximinoyl chloride 448b before it can be converted to the nitrile oxide, the TBAF-mediated dehydrohalogenation was performed at reduced temperature in an attempt to suppress this side reaction (entry 7). Unfortunately, this procedure only provided 453, in reduced yield compared to the reaction conducted at room temperature. The structure of the novel compound 453 was deduced from 1H-, 13C-NMR, IR, and mass spectra. Characteristically, the presence of a doublet at δ 5.50 in the 1H-NMR spectrum, assigned to a secondary amine proton, together with the cyclohexyl α-proton that resonated as a multiplet, indicated that cycloaddition had not taken place. In fact, the chemical shifts – in the carbon spectrum in particular – were virtually identical to those obtained for a mixture of both reactants (Table 2.11.3).
<table>
<thead>
<tr>
<th>No.</th>
<th>1’</th>
<th>2’</th>
<th>3’</th>
<th>4’</th>
<th>N-H</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>O-H</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>3.57</td>
<td>1.18 to 2.12</td>
<td></td>
<td>5.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>3.45</td>
<td>1.09 to 1.97</td>
<td></td>
<td>5.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>1’</th>
<th>2’</th>
<th>3’</th>
<th>4’</th>
<th>N-H</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>O-H</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4" alt="Chemical Structure 1" /></td>
<td>55.6</td>
<td>32.5</td>
<td>24.4</td>
<td>24.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure 2" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>139.9</td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure 3" /></td>
<td>54.1</td>
<td>33.2</td>
<td>24.4</td>
<td>24.9</td>
<td></td>
<td>146.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.11.3. Comparison of $^1$H- and $^{13}$C-NMR spectra of starting material 213a and 448b with novel product 453.
The presence of a secondary amine was confirmed in the IR spectrum by an N-H stretch at 3300 cm\(^{-1}\), and the mass spectrum revealed molecular ions at \(m/z\) 339 and 341 in a 3:1 ratio, corresponding to a molecular formula of C\(_{13}\)H\(_{17}\)N\(_2\)O\(_3\)SClNa, leading to assignment of the structure as the \(O\)-sulfamic ester 453. This result is analogous to the reaction of sulfenes with nitrile oxides (\textit{vide infra}). 453 was unable to be converted to 304b by addition of base (Table 2.11.4).

![Image](image_url)

**Table 2.11.4.** Attempted conversion of \(O\)-sulfamic ester 453 to desired heterocycle 304b.

In their studies on the reaction of the closely related sulfenes with nitrile oxides, Eloy and Overstraeten\(^{249}\), Talaty and Rajagopalan\(^{300}\), Truce and Naik\(^{301}\), and Durst and King\(^{302}\) all found that the reaction failed to provide cyclic adducts, with only the \(O\)-sulfonic esters 457 and 458 being isolated (Figure 2.11.6). Varying the order of addition of the reagents and the temperature of the reaction had little effect; resulting in derivatives 457 and 458 in each case. Use of mesityl nitrile oxide only afforded mesityl isocyanate.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Figure 2.11.6. Reaction of sulfenes 205 with nitrile oxides. \( R_1 = H, R_2 = Me; \) \( R_1 = H, p-Cl, m-NO_2, R_2 = Ph, Me; \) \( R_1 = H, R_2 = Me, Ph; \) \( R_1 = p-Cl, m-NO_2, m,p-di-Cl, H, R_2 = Me, Ph, Bn, p-NO_2Ph. \)

The authors were unable to determine the definitive mechanism for formation of 457 and 458, stating that the esters could result from either addition of the nitrile oxide to the sulfene with subsequent addition of HCl, or addition of the sulfene to unconverted hydroximinoyl chloride (Figure 2.11.7).

Figure 2.11.7. Possible mechanisms for the formation of the O-sulfonic ester 457 of hydroximinoyl chloride 448.
It would be reasonable to conclude that a similar mechanism is operating in the reaction of \( N \)-cyclohexylsulfamoyl chloride \textit{213a} with benzhydroximinoyl chloride \textit{448b}.

In attempts to avoid this side reaction, generation of the nitrile oxide using different methods were also investigated.

\textbf{2.11.3 Investigation of alternative methods for the generation of nitrile oxides: dehydration of a nitroalkane}

Often thought of as the classical method for the generation of nitrile oxides, intermolecular dehydration of a nitroalkane with phenyl isocyanate was first described by Mukaiyama and Hoshino in early 1960 (Figure 2.11.8).\(^{292}\) As the dehydration requires the presence of a catalytic amount of triethylamine, we expected this method to be compatible with, and even advantageous for, the concurrent dehydrohalogenation of a sulfamoyl chloride to generate the reactive \( N \)-alkylsulfonylimines.

![Figure 2.11.8. Mukaiyama conditions for the generation of a nitrile oxide from a nitroalkane: intermolecular dehydration.](image)

As (2-nitroethyl)benzene \textit{447a}\(^{303}\) was available in our lab from unrelated synthetic work, we decided to attempt dehydration of this nitroalkane under Mukaiyama’s conditions to generate the benzyl nitrile oxide \textit{299c}. The nitrile oxide should then undergo cycloaddition with \( N \)-cyclohexylsulfonylimine \textit{202a} to give 1,2,3,5-oxathiadiazole 2,2-dioxide \textit{304c} (Figure 2.11.9).
Figure 2.11.9. Proposed generation of benzyl nitrile oxide 299c via the intermolecular dehydration of nitroalkane 447a and subsequent cycloaddition with N-cyclohexylsulfonylimine 202a.

Initially, intermolecular dehydration of the nitroalkane with phenyl isocyanate and triethylamine, as described by Mukaiyama and Hoshino, only returned sulfamide dimer 246a and diphenylurea 466 (Scheme 2.11.2).

Scheme 2.11.2. Initial attempted cycloaddition of nitrile oxide 299c and N-cyclohexylsulfonylimine 202a under Mukaiyama’s conditions.

Postulating that the lack of reaction was due to incomplete generation of the nitrile oxide, we decided to alter the protocol, performing the dehydration step first, then adding a solution of the sulfamoyl chloride (Table 2.11.5, entry 2). In this case, however, only sulfamide dimer 246a and diphenylurea were afforded.
## 2.11.5. Attempted formation and reaction of nitrile oxide 299c via dehydration of nitroalkane 447a.

Alternative methods to effect dehydration of the nitroalkane have been described by Chen and Li\(^\text{304}\) and Cecchi et al.\(^\text{305}\). Attempted dehydration of 447a with thionyl chloride only returned 246a and 466 (entry 3); likewise, dehydration with DABCO at 60 °C was unsuccessful (entry 4).

Given the lack of evidence for reaction of N-alkylsulfonylimine 202 with nitrile oxide 299c, this avenue of investigation was not pursued further.

### 2.11.4 Investigation of alternative methods for the generation of nitrile oxides: dehydration of O-silylated hydroxamic acids

Recently, Carreira and coworkers described an alternative method for the generation of nitrile oxides from O-silylated hydroxamic acids (Figure 2.11.10).\(^\text{294}\) These precursors are stable, crystalline solids, and the reactive species is generated via dehydration at 0 °C upon addition of triflic anhydride.

![Figure 2.11.10. Generalised scheme for the generation of nitrile oxides 299 from O-silylated hydroxamic acids 449, and subsequent trapping with a dipolarophile.\(^\text{294}\)](image_url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dehydration method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>447a, 213a, PhNCO, Et3N, Et2O, r.t., 2 h</td>
<td>dimer 246a and diphenylurea 466</td>
</tr>
<tr>
<td>2</td>
<td>447a, PhNCO, Et3N, THF, r.t., 1 h; then 213a, THF, r.t., 16 h</td>
<td>dimer 246a and diphenylurea 466</td>
</tr>
<tr>
<td>3</td>
<td>447a, Et3N, CH2Cl2, r.t., 20 min; then 213a, Et3N, SOCl2, CH2Cl2, 0 °C, 2 h</td>
<td>dimer 246a and diphenylurea 466</td>
</tr>
<tr>
<td>4</td>
<td>447a, DABCO, CHCl3, 60 °C, 20 min; then 213a, CHCl3, 2 h.</td>
<td>dimer 246a and diphenylurea 466</td>
</tr>
</tbody>
</table>
The O-silylated hydroxamic acids 449 are readily accessed via transformation of the parent hydroxamic acid to the corresponding tert-butyldiphenylsilyl ether.

Scheme 2.11.3. Reagents and conditions: a) NH$_2$OH∙HCl, K$_2$CO$_3$, Et$_2$O/H$_2$O, 0 °C → r.t., 16 h, 29%; b) NaH, TBDPSCl, THF, 0 °C, 0.5 h, 43%.

Choosing the phenyl derivative as the most readily accessible, synthesis of the required O-silylated hydroxamic acid 449a began with amination of acetyl chloride with hydroxylamine hydrochloride and potassium carbonate to afford the hydroxamic acid 470 (Scheme 2.11.3). This acid was then converted to the TBDPS-ether in a straightforward manner using TBDPSCl with sodium hydride as base to provide the nitrile oxide precursor 449a as white needle-like crystals.

With the requisite precursor 449a in hand, its cycloaddition with N-cyclohexylsulfamoyl chloride was next attempted (Scheme 2.11.4). A cooled (-40°C) solution of 449a in dichloromethane was treated with triethylamine and triflic anhydride, then warmed to 0 °C to ensure complete formation of the nitrile oxide 299b. A solution of 213a was then added slowly and the reaction mixture maintained at 0 °C for an additional 2 hours. Unfortunately, these alternative dehydration conditions failed to provide the desired heterocycle 304b.

Scheme 2.11.4. Reagents and conditions: a) Tf$_2$O, CH$_2$Cl$_2$, Et$_3$N, -40 → 0 °C, 5 min; b) 213a, CH$_2$Cl$_2$, 0 °C, 2 h.

2.11.5 Conclusion

Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with nitrile oxides 299a – 299c was not successful. Similar to the attempted reaction of 202a with azomethine ylides (section 2.7), there appears to be a mismatch in the requirements for generation of the cycloaddition partners. This is exemplified by the isolation of O-sulfamic ester 453, resulting from reaction of the N-alkylsulfonylimine 202a with nitrile oxide precursor 448b prior to its conversion to the desired nitrile oxide 299b.
Whilst it was unfortunate that the desired 1,2,3,5-oxathiadiazole 2,2-dioxides 304 were not obtained, the O-sulfamic ester 453 obtained is interesting. The similar, sulfene-derived O-sulfonic esters 471 – 473 have been evaluated for antibacterial, fungicidal, and herbicidal activity (Figure 2.11.11). Unfortunately while 471 was active against *Candida albicans in vitro*, this activity did not translate to *in vivo* activity.\(^{307}\) *para*-Alkoxy derivatives 473 have been shown to display antifungal and antibacterial activity in an agricultural context,\(^{308}\) whereas the *o,o*-Cl derivatives 472 have been claimed as herbicides in a 1978 patent.\(^{309}\)

![Chemical structures](image)

**Figure 2.11.11.** Biological activity of some O-sulfonic esters derived from the reaction of hydroximinoyl chlorides with sulfenes.\(^{307-309}\)

In contrast, O-sulfamic esters like 453 have not previously been described, and as such their biological activity in similar assays will be evaluated in due course.

The experimental results described above suggest that *N*-alkylsulfonylimines exhibit similar reactivity towards nitrile oxides as the closely related sulfenes. Like sulfenes, *N*-cyclohexylsulfonylimine 202a forms the O-sulfamic ester 453 in the attempted 1,3-dipolar cycloaddition reaction with nitrile oxide 299b.
2.12 Conclusion

Attempted 1,3-dipolar cycloadditions of \(N\)-alkylsulfonylimines 202 with a range of 1,3-dipoles unfortunately met with little success. The proposed cyclic adducts were not isolated, and only the reactions with nitrones and nitrile oxides provided any novel products (Figure 2.12.1).

These results demonstrate that \(N\)-alkylsulfonylimines 202 do, indeed, exhibit reduced reactivity as heterodipolarophiles compared to the closely related sulfenes 205. Additionally, the conditions required to generate the reactive species 202 are often not conducive to successful reaction with dipoles 297 – 301. Generally 202 forms the homodimer 246 in preference to participating in the desired cycloaddition that requires higher temperatures to induce the cycloaddition reaction.

The biological activity of the novel compounds will be investigated in due course; however preliminary antibacterial screening of these compounds against \(S.\ aureus\) and \(E.\ coli\) showed no antibacterial activity.
CHAPTER SIX

Experimental

Part Two
2.13 Experimental

2.13.1 Synthesis of sulfamoyl chlorides 213

*N-Cyclohexylsulfamoyl chloride  213a*

Prepared according to the procedure of Olson *et al.*

Phosphorus pentachloride (11.618 g, 55.79 mmol) was added portionwise to a stirred suspension of *N*-cyclohexylsulfamic acid (10 g, 55.79 mmol) in toluene (140 mL) at room temperature. The bright yellow cloudy solution was then heated at reflux for 1.75 h. The mixture was allowed to cool to room temperature and filtered. The volatiles were removed under reduced pressure to give the crude as a dark orange-brown liquid. The crude was purified via vacuum distillation (150-154 °C, 8 Torr) to give the *title compound* 213a (6.419 g, 58%) as a pale yellow liquid that solidified in time to large colourless needles, m.p. 43 – 45 °C (lit. 43 – 47 °C).

1H-NMR (CDCl3, 300MHz): δ 5.90 (d, 1H, *J* = 5.5 Hz, N-H), 3.57 (m, 1H, H-1), 2.12 – 1.18 (m, 10H, H-2 to H-4).

13C-NMR (CDCl3, 75 MHz): δ 55.6 (CH, C-1), 32.5 (2 x CH2, C-2), 24.9 (CH2, C-4), 24.4 (2 x CH2, C-3).

Spectral data were in agreement with literature values.

*N-Propylsulfamoyl chloride  213e*

Prepared in an analogous manner to 213a from *N*-propylsulfamic acid 219e, according to the procedure of Olson *et al.* to give the *title compound* 213e (249 mg, 22%) as a brown liquid.

1H-NMR (CDCl3, 400MHz): δ 5.47 (br s, 1H, N-H), 3.31 (q, 2H, *J* = 7.1 Hz, H-1), 1.71 (sext, 2H, *J* = 7.4 Hz, H-2), 1.02 (t, 3H, *J* = 7.4 Hz, H-3).

IR (neat) cm\(^{-1}\): 3294 (N-H), 2972 (C–H), 2881, 1427 (med), 1365 (str, O=S=O), 1281, 1180 (str, O=S=O), 1066 (med, C–N), 1006 (med), 920, 841, 747.
**N-Benzyl sulfamoyl chloride 213d**

Prepared according to the procedures of Olson\textsuperscript{161} and Tait\textsuperscript{160} et al.

Chlorosulfonic acid (2.1 mL, 31.11 mmol) was added dropwise to a solution of benzylamine 216d (10.2 mL, 93.33 mmol) in dichloromethane (80 mL) at 0 °C and allowed to stir for 1.5 h at this temperature. The volatiles were removed under reduced pressure to give the crude sulfamate, a white solid, as the benzylamine salt. The residue was diluted with toluene (65 mL) and phosphorus pentachloride (6.478 g, 31.11 mmol) added portionwise to the slurry. The mixture was then heated at reflux for 2.5 h, then cooled to room temperature and filtered. The volatiles were removed under reduced pressure to give the crude **title compound 213d** (7.234 g, 38% crude) as an orange oil that was used without further purification.

\[ ^1 \text{H-NMR (CDCl}_3, 400\text{MHz): } \delta 7.41 – 7.15 (\text{m, 5H, H-3 to H-5}), 5.81 (\text{br s, 1H, N-H}), 4.47 (\text{d, 2H, } J = 5.8 \text{ Hz, H-1}). \]

IR (thin film) cm\textsuperscript{-1}: 3289 (N–H), 3035 (=C–H), 2881 (C–H), 1606 (wk), 1496 (C=C), 1456 (C=C), 1424 (C=C), 1370 (str, O=S=O), 1259, 1176 (str, O=S=O), 1082, 1048 (med), 1027 (med), 909, 846, 817, 744 (med), 696 (str).

**N-tert-Butylsulfamoyl chloride 213b**

Prepared in an analogous manner to N-benzylsulfamoyl chloride 213d from *tert*-butylamine 216b to give the **title compound 213b** (0.938 g, 8% crude) as a brown oil that was used without further purification.

\[ ^1 \text{H-NMR (CDCl}_3, 400\text{MHz): } \delta 5.98 (\text{br s, N-H}), 1.45 (\text{s, 9H, t-Bu}). \]

Spectra were consistent with those reported in the literature.\textsuperscript{312}
N-Phenylsulfamoyl chloride 213c

Prepared according to the procedures of Kanetani\textsuperscript{313} and Olson\textsuperscript{161} \textit{et al}.

Triethylamine (7.5 mL, 53.69 mmol) was added dropwise to a solution of chlorotrimethylsilane (6.8 mL, 53.69 mmol) in \textit{n}-hexanes (25 mL) at ca. 5 °C and the white suspension allowed to stir at this temperature for 1 h. Aniline 216c (4.9 mL, 53.69 mmol) was then added slowly and the mixture allowed to stir at ambient temperature overnight. The thick white suspension was filtered and the solids washed with hexanes (30 mL). The combined filtrates were concentrated under reduced pressure to give crude \textit{N}-trimethylsilylaniline (4.959 g, 30.00 mmol, 55%) as an orange oil. This was then diluted with dichloromethane (100 mL) and cooled to -20 °C. A solution of chlorosulfonic acid (2 mL, 30.00 mmol) in dichloromethane (20 mL) was then added dropwise via addition funnel over 30 min. The resulting pale pink suspension was allowed to stir at this temperature for 4 h, then warmed to room temperature and filtered. The white powdery solid was dried under vacuum to give \textit{N}-phenylsulfamic acid (4.491 g, 25.93 mmol, 86%). Toluene (55 mL) was added to the solids, and phosphorus pentachloride (5.400 g, 25.93 mmol) was added portionwise. The suspension was then heated at reflux for 2.75 h, then cooled and filtered. The volatiles were removed under reduced pressure to give the crude title compound 213c (4.368 g, 43% crude) as an orange-brown oil that was used without further purification.

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) 7.83 (s, 1H, N-H), 7.43 (m, 2H, H-3), 7.35 (m, 3H, H-2, H-4).

IR (thin film) cm\textsuperscript{-1}: 3276 (N–H), 3085, 3030, 1594 (med, C=C), 1494 (med, C=C), 1421 (med, C=C), 1367 (str, O=S=O), 1280 (med), 1169 (str, O=S=O), 1081, 1005, 932 (str), 752 (str), 731 (str), 692 (str).

2.13.2 Synthesis of dienes

(Cyclohexa-1,5-dien-1-yloxy)trimethylsilane 293

Prepared according to the procedure of Rinderhagen and Mattay.\textsuperscript{174}
n-BuLi (1.6 M in hexanes, 35.8 mL, 57.21 mmol) was added slowly to a solution of diisopropylamine (8.75 mL, 62.42 mmol) in tetrahydrofuran (85 mL) at 0 °C, and the resulting yellow solution allowed to stir at this temperature for 20 min before cooling to -78 °C. A solution of 2-cyclohexen-1-one 338 (5.04 mL, 52.01 mmol) in tetrahydrofuran (8 mL) was then added dropwise via cannula, and the mixture allowed to stir at -78 °C for 1 h. Chlorotrimethylsilane (9.85 mL, 78.02 mmol) was then added, and the pale yellow mixture allowed to warm to room temperature over 1 h. The solution was allowed to stir at r.t. for an additional 1 h, then the volatiles were removed under reduced pressure and the residue diluted with pentane (150 mL). The suspension was filtered through Celite® and concentrated under reduced pressure to give the crude as a yellow liquid. The crude was purified via fractional vacuum distillation (62-68 °C, 16 mbar) to give the title compound 293 (7.266 g, 83%) as a colourless, clear liquid.

\[ \text{1H-NMR (CDCl}_3, 300MHz): \delta 5.86 \text{ (m, 1H, H-6), 5.69 (m, 1H, H-5), 4.87 (m, 1H, H-2), 2.12 (m, 4H, H-3, H-4), 0.18 (s, 9H, OTMS).} \]

Spectral data were in agreement with literature values.\(^{174}\)

\((E)\)-Methyl 3-(trimethylsilyloxy)but-2-enoate 352

Prepared according to the procedure of Tamaru et al.\(^{182}\)

Chlorotrimethylsilane (7.0 mL, 55.00 mmol) was added dropwise to a solution of methyl acetoacetate 351 (5.4 mL, 50.00 mmol) and triethylamine (8.4 mL, 60.00 mmol) in hexanes (100 mL) and the white suspension allowed to stir at room temperature for 18 h. The thick suspension was filtered through Celite® and the volatiles removed under reduced pressure to give the crude as a dark yellow liquid. The crude was purified via distillation under reduced pressure (94-96 °C, 20 Torr) to give the title compound 352 (6.517 g, 69%) as a colourless liquid.

\[ \text{1H-NMR (CDCl}_3, 400MHz): \delta 5.14 \text{ (s, 1H, H-2), 3.66 (s, 3H, OMe), 2.27 (s, 3H, H-4), 0.27 (s, 9H, OTMS).} \]

Spectral data were in agreement with literature values.\(^{182}\)
(E)-Methyl 3-methoxybut-2-enoate 353

Prepared according to the procedure of Donner and Gill.\textsuperscript{181}

Conc. sulfuric acid (4 drops) was added to a mixture of methyl acetoacetate 351 (5.45 mL, 50.47 mmol) and trimethyl orthoformate (5.53 mL, 50.51 mmol), resulting initially in an exotherm, and the orange solution thus obtained was allowed to stir at room temperature for 24 h. Quinoline (6 drops) was added, and the mixture distilled under reduced pressure (110-112 °C, 115 Torr) to give the title compound 353 (4.915 g, 75\%) as a pale yellow liquid.

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400MHz): δ 5.03 (s, 1H, H-2), 3.68 (s, 3H, OMe), 3.63 (s, 3H, OMe), 2.30 (s, 3H, H-4).

Spectral data were in agreement with literature values.\textsuperscript{181}

1,3-Bis(trimethylsiloxy)-1-methoxybuta-1,3-diene 295 (Chan's diene)

Prepared according to the procedure of Tamaru et al.\textsuperscript{182}

n-BuLi (1.6 M in hexanes, 18.2 mL, 29.21 mmol) was added slowly to a solution of diisopropylamine (4.1 mL, 29.21 mmol) in tetrahydrofuran (30 mL) at 0 °C and allowed to stir at this temperature for 30 min before cooling to -78 °C. (E)-methyl 3-(trimethylsilyloxy)but-2-enoate 352 (5.00 g, 26.55 mmol) was added dropwise and the mixture allowed to stir at this temperature for 30 min. Chlorotrimethylsilane (4.5 mL, 35.85 mmol) was then added slowly, and the mixture allowed to warm to 0 °C over 1 h. The volatiles were removed under reduced pressure and the residue diluted with pentane (60 mL). The mixture was filtered through Celite\textsuperscript{®} and concentrated under reduced pressure to give the crude as a light orange liquid. The crude was purified via vacuum distillation (Vigreaux column, 107 – 110 °C, 10 Torr) to give the title compound 295 (3.584 g, 52\%) as a yellow liquid.

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400MHz): δ 4.48 (s, 1H, H-2), 4.15 (d, 1H, J = 1.3 Hz, H-4), 3.94 (d, 1H, J = 1.2 Hz, H-4), 3.56 (s, 3H, OMe), 0.25 (s, 9H, OTMS), 0.21 (s, 9H, OTMS).
Spectral data were in agreement with literature values.\textsuperscript{314}

\textbf{(E)-(1,3-Dimethoxybuta-1,3-dienyloxy)trimethylsilane 296 (Brassard's diene)}

![Chemical structure of (E)-(1,3-Dimethoxybuta-1,3-dienyloxy)trimethylsilane 296 (Brassard's diene)]

Prepared according to the procedure of Donner and Gill.\textsuperscript{181}

\(n\)-BuLi (1.6 M in hexanes, 20.2 mL, 32.27 mmol) was added slowly to a solution of diisopropylamine (4.5 mL, 32.27 mmol) in tetrahydrofuran (30 mL) at 0 °C and allowed to stir at this temperature for 30 min before cooling to -78 °C. \((E)\)-methyl 3-methoxybut-2-enoate \textsuperscript{353} (4 g, 30.74 mmol) was then added dropwise, and the resulting yellow solution allowed to stir at this temperature for 45 min. Chlorotrimethylsilane (4.7 mL, 36.88 mmol) was then added slowly, and the now cloudy yellow mixture allowed to warm to room temperature. The mixture was filtered and concentrated under reduced pressure to give a cloudy yellow residue that was diluted with pentane (50 mL) and filtered through Celite\textsuperscript{®}. The crude was purified via fractional vacuum distillation (90-98 °C, 10 Torr) to give the \textit{title compound} \textsuperscript{296} (3.692 g, 59\%) as a colourless liquid.

\(^1\)H-NMR (CDCl\textsubscript{3}, 400MHz): \(\delta\) 4.34 (d, 1H, \(J = 1.6\) Hz, H-2), 4.03 (d, 1H, \(J = 1.4\) Hz, H-4), 3.98 (t, 1H, \(J = 1.7\) Hz, H-4), 3.57 (s, 3H, OMe), 3.56 (s, 3H OMe), 0.26 (s, 9H, OTMS).

Spectral data were in agreement with literature values.\textsuperscript{181}

\textbf{2.13.3 Cycloadditions of N-alkylsulfonylimines 202a – 202e with dienes 93, 123, and 292 – 296}

\textbf{Reaction with Danishefsky's diene 93: General procedure 2A.}

![Chemical structure of Reaction with Danishefsky's diene 93: General procedure 2A.]

2-alkyl-1,2-thiazin-5(6H)-one 1,1-dioxides were prepared according to the procedure of Kloek and Leschinsky.\textsuperscript{158}

Triethylamine (1 mol eq.) was added to a solution of Danishefsky’s diene \textsuperscript{93} (1 mol eq.) in tetrahydrofuran (1.5 mL/mmol) at -78 °C, followed by a solution of the requisite sulfamoyl chloride \textsuperscript{213} (1 mol eq.) in tetrahydrofuran (1.5 mL/mmol). The white suspension was maintained at this temperature for 30 min before cooling to -78 °C. \(0.1 M\) HCl was then added slowly, and the mixture was allowed to warm to room temperature. The mixture was filtered and concentrated under reduced pressure to give the \textit{title compound} \textsuperscript{210} as a colourless solid.
temperature for 2 h, then allowed to warm to room temperature over 1 h. Aq. HCl (10% v/v, 1 mL/mmol) was added, and the biphasic mixture allowed to stir at room temperature for 1 h. Diethyl ether (1 mL) was added, and the organic layer removed. The aqueous was extracted with diethyl ether (2 x 3 mL), and the combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to give the crude product. The crude was purified via flash column chromatography (silica gel, dichloromethane: methanol 1:0 to 19:1 as eluent) to give the products.

2-Cyclohexyl-1,2-thiazin-5(6H)-one 1,1-dioxide 210a

Prepared according to general procedure 2A from N-cyclohexylsulfamoyl chloride 213a, to give the title compound 210a as a colourless crystalline solid, m.p. 80 – 82 °C.

R₇ (dichloromethane) = 0.43; R₇ (ethyl acetate:hexanes 3:7) = 0.34.

¹H-NMR (CDCl₃, 400MHz): δ 7.26 (d, 1H, J = 8.9 Hz, H-3), 5.64 (d, 1H, J = 8.8 Hz, H-4), 4.17 (m, 1H, H-1′), 4.13 (s, 2H, H-6), 2.01 – 1.10 (m, 10H, H-2′ to H-6′).

¹³C-NMR (CDCl₃, 100 MHz): δ 183.0 (quat., C-5), 143.5 (CH, C-3), 106.9 (CH, C-4), 61.7 (CH₂, C-6), 55.8 (CH, C-1′), 32.9 (2 x CH₂, C-2′, C-6′), 25.7 (2 x CH₂, C-3′, C-5′), 24.8 (CH₂, C-4′).

IR (solid) cm⁻¹: 3060 (=C–H), 1647 (str, C=O), 1583 (str, C=O), 1338 (str, O=S=O), 1156 (str, O=S=O), 1115 (med, C-N).

MS (ESI) m/z 230 [(M + H)⁺, 32%], 252 [(M + Na)⁺, 100]; HRMS (ESI) m/z 230.0845 [(M + H)⁺] calcd. for C₁₀H₁₆NO₃S 230.0845.

(Z)-4-(Cyclohexylamino)-2-oxobut-3-ene-1-sulfonic acid 307

Triethylamine (140 µL, 1.01 mmol) was added to a solution of Danishefsky’s diene 93 (200 µL, 1.01 mmol) in tetrahydrofuran (1.5 mL) at 0 °C, followed by a solution of N-cyclohexylsulfamoyl
chloride 213a (200 mg, 1.01 mmol) in tetrahydrofuran (1.5 mL). The mixture was allowed to stir at 0 °C for 1 h, then aq. HCl (10% v/v, ca. 2 mL) was added, and the mixture allowed to warm to room temperature over 1 h. The mixture was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts dried over MgSO\(_4\) and concentrated under reduced pressure to give the crude as an orange-yellow oil. The crude was purified via flash column chromatography (silica gel, dichloromethane as eluent) to give a mixture of 210a (79 mg, 34%) and the title compound 307 (23 mg, 25%) as a pale yellow oil. 307 underwent ring-closure to 210a under gentle heating while being concentrated in a rotary evaporator (water bath at 40 °C).

\(^1\)H-NMR (CDCl\(_3\), 400MHz): \(\delta\) 7.89 (d, 1H, \(J = 4.4\) Hz, H-4), 5.84 (d, 1H, \(J = 4.5\) Hz, H-3), 4.61 (d, 1H, \(J = 7.3\) Hz, N-H), 4.02 (s, 2H, H-1), 3.31 (m, 1H, H-1'), 3.2 (m, 1H, H-1), 2.02 – 1.24 (m, 10H, H-2' – H-6').

\(^13\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta\) 187.9 (quat., C-2), 175.5 (CH, C-4), 103.4 (CH, C-3), 61.6 (CH\(_2\), C-1), 53.5 (CH, C-1'), 34.1 (2 x CH\(_2\), C-2', C-6'), 25.1 (CH\(_2\), C-4'), 24.7 (2 x CH\(_2\), C-3', C-5').

**N,N-Dicyclohexylsulfamide 246a**

![Chemical Structure](Image)

White flaky crystals, m.p. 143 – 147 °C (lit.\(\textsuperscript{315}\) 154 – 155 °C).

R\(_f\) (ethyl acetate:hexanes 3:7) = 0.54.

\(^1\)H-NMR (CDCl\(_3\), 400MHz): \(\delta\) 4.31 (d, 2H, \(J = 7.7\) Hz, N-H), 3.18 (m, 2H, H-1), 2.02 – 1.24 (m, 20H, H-2 – H-4).

\(^13\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta\) 52.7 (2 x CH, C-1), 34.0 (4 x CH\(_2\), C-2), 25.3 (2 x CH\(_2\), C-4), 24.8 (4 x CH\(_2\), C-3).

MS (ESI) \(m/z\) 261 [(M + H)\(^+\), 100%], 283 [(M + Na)\(^+\), 62%], 299 [(M + K)\(^+\), 34%]; HRMS (ESI) \(m/z\) 261.1637 [(M + H)\(^+\), calcd. for C\(_{12}\)H\(_{25}\)N\(_2\)O\(_2\)S \ 261.1631], 283.1450 [(M + Na)\(^+\), calcd. for C\(_{12}\)H\(_{24}\)N\(_2\)O\(_2\)SNa \ 283.1451], 299.1195 [(M + K)\(^+\), calcd. for C\(_{12}\)H\(_{24}\)N\(_2\)O\(_2\)SK \ 299.1190].

Spectral data were in agreement with literature values.\(\textsuperscript{315}\)
2-tert-Butyl-1,2-thiazin-5(6H)-one 1,1-dioxide 210b

Prepared according to general procedure 2A from N-tert-butylsulfamoyl chloride 213b, to give the title compound 210b as a pale yellow crystalline solid, m.p. 161 – 164 °C.

R\(_f\) (ethyl acetate:hexanes 3:7) = 0.16.

\(^1\)H-NMR (CDCl\(_3\), 400MHz): \(\delta\) 7.41 (d, 1H, \(J = 9.0 \) Hz, H-3), 5.56 (d, 1H, \(J = 9.0 \) Hz, H-4), 4.11 (s, 2H, H-6), 1.66 (s, 9H, H-2' to H-4').

\(^13\)C-NMR (CDCl\(_3\), 100 MHz): \(\delta\) 183.6 (quat., C-5), 144.8 (CH, C-3), 106.3 (CH, C-4), 64.8 (quat., C-1'), 62.9 (CH\(_2\), C-6), 30.2 (3 x CH\(_3\), C-2' to C-4').

IR (solid) cm\(^{-1}\): 3303, 2983 (C–H), 2957, 2907, 2851, 1728, 1645 (str, C=O), 1565 (str, C=O), 1465, 1428, 1384, 1372, 1342 (str, O=S=O), 1292 (med), 1263 (med), 1247 (med), 1227 (med), 1183 (med), 1149 (str, O=S=O), 1132 (str), 1035 (med), 996 (med), 954 (med), 930, 895 (med), 842 (med), 823, 809, 792 (med), 697 (med), 609 (med).

MS (ESI) \(m/z\) 226 [(M + Na)\(^+\), 14%]; HRMS (ESI) \(m/z\) 226.0500 [(M + Na)\(^+\) calcd. for C\(_8\)H\(_{13}\)NO\(_3\)SNa 226.0508].

\(N,N\)-Di-tert-butylsulfamide 246b

Pale yellow solid.

R\(_f\) (ethyl acetate:hexanes 3:7) = 0.69.

\(^1\)H-NMR (CDCl\(_3\), 400MHz): \(\delta\) 4.05 (br s, 2H, N-H), 1.36 (s, 18H, H-2).

Spectral data were in agreement with literature values.\(^{316}\)
2-Phenyl-1,2-thiazin-5(6H)-one 1,1-dioxide 210c

Prepared according to general procedure 2A from N-phenylsulfamoyl chloride 213c, to give the title compound 210c as a yellow oil.

\[ R_f (\text{ethyl acetate:hexanes } 3:7) = 0.34. \]

\[ ^1\text{H-NMR (CDCl}_3, 400\text{MHz}: \delta 7.49 (m, 3H, H-3 to H-4'), 7.38 (m, 2H, H-2'), 7.29 (d, 1H, } J = 8.7 \text{ Hz, H-3'), 5.75 (d, 1H, } J = 8.6 \text{ Hz, H-4), 4.31 (s, 2H, H-6).} \]

\[ ^13\text{C-NMR (CDCl}_3, 100\text{MHz}: \delta 183.2 (\text{quat., C-5}), 147.2 (\text{CH, C-3}), 136.1 (\text{quat., C-1'}, 129.9 (2 \text{ x CH, C-3'}), 129.6 (\text{CH, C-4'}), 127.4 (2 \text{ x CH, C-2'}), 107.8 (\text{CH, C-4}), 61.8 (\text{CH}_2, \text{C-6}). \]

IR (solid) cm\(^{-1}\): 3063 (Ar C–H), 2984 (C–H), 2921, 2850, 1666 (str, C=O), 1626 (Ar C=C), 1585 (str), 1491 (str), 1455 (Ar C=C), 1406, 1352 (str, O=S=O), 1267 (str), 1250 (str), 1215, 1159 (str, O=S=O), 1062 (med), 895, 846, 760 (med), 695 (str).

MS (APCI) \text{m/z} 224 [\text{(M + H)}^+, 97%]; HRMS (APCI) \text{m/z} 224.0380 [\text{(M + H)}^+ \text{ calcd. for C}_{10}\text{H}_{10}\text{NO}_3\text{S 224.0376}].

2-Benzyl-1,2-thiazin-5(6H)-one 1,1-dioxide 210d

Prepared according to general procedure 2A from N-benzylsulfamoyl chloride 213d, to give the title compound 210d as a sticky yellow oil.

\[ R_f (\text{ethyl acetate:hexanes } 3:7) = 0.21. \]

\[ ^1\text{H-NMR (CDCl}_3, 400\text{MHz}: \delta 7.43 – 7.27 (m, 5H, H-3' – H-5'), 7.12 (d, 1H, } J = 8.6 \text{ Hz, H-3), 5.59 (d, 1H, } J = 8.6 \text{ Hz, H-4), 4.81 (s, 2H, H-1'), 4.20 (s, 2H, H-6).} \]
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ 183.1 (quat., C-5), 146.2 (CH, C-3), 134.2 (quat., C-2'), 129.0 (2 x CH, C-4'), 128.6 (CH, C-5'), 128.4 (2 x CH, C-3'), 107.5 (CH, C-4), 61.4 (CH$_2$, C-6), 50.2 (CH$_2$, C-1').

IR (thin film) cm$^{-1}$: 3272, 3087, 3063 (Ar C–H), 3035, 2986 (C–H), 2922, 2855, 1725, 1666 (str, C=O), 1594 (str, C=C), 1495, 1454 (med), 1413 (med), 1335 (str, O=S=O), 1238 (str), 1220 (str), 1156 (str, O=S=O), 1142 (str), 1085 (med), 1065 (med), 1040 (med), 1025 (med), 1011 (med), 908 (med), 932 (med), 891 (med), 843 (med), 816 (med), 764 (med), 729 (9str), 696 (str), 666 (str), 610 (med), 584 (med).

MS (ESI) m/z 260 [(M + Na)$^+$, 9%]; HRMS (ESI) m/z 260.0355 [(M + Na)$^+$, calcd. for C$_{11}$H$_{11}$NO$_3$SNa 260.0352].

**N,N-Dibenzylsulfamide 246d**

![Image of N,N-Dibenzylsulfamide 246d](image)

Pale yellow solid.

$R_f$ (ethyl acetate:hexanes 3:7) = 0.54.

$^1$H-NMR (CDCl$_3$, 400MHz): δ 7.37 – 7.26 (m, 10H, H-3 – H-5), 4.39 (br t, 2H, $J = 5.0$ Hz, N-H), 4.17 (d, 4H, $J = 6.0$ Hz, H-1).

Spectral data were in agreement with literature values.$^{315,317}$

**2-Propyl-1,2-thiazin-5(6H)-one 1,1-dioxide 210e**

![Image of 2-Propyl-1,2-thiazin-5(6H)-one 1,1-dioxide 210e](image)

Prepared according to general procedure 2A from N-propylsulfamoyl chloride 213e, to give the *title compound 210e* as an orange oil.

$R_f$ (dichloromethane) = 0.57


1H-NMR (CDCl$_3$, 400MHz): $\delta$ 7.18 (d, 1H, $J = 8.6$ Hz, H-3), 5.58 (d, 1H, $J = 8.5$ Hz, H-4), 4.15 (s, 2H, H-6), 3.64 (t, 2H, $J = 7.3$ Hz, H-1'), 1.77 (sextet, 2H, $J = 7.2$ Hz, H-2'), 1.00 (t, 3H, $J = 7.4$ Hz, H-3').

13C-NMR (CDCl$_3$, 100 MHz): $\delta$ 183.3 (quat., C-5), 147.3 (CH, C-3), 106.4 (CH, C-4), 61.2 (CH$_2$, C-6), 49.9 (CH$_2$, C-1'), 23.2 (CH$_2$, C-2'), 10.6 (CH$_3$, C-3').

IR (thin film) cm$^{-1}$: 3058 (=C–H), 2970 (C–H), 2926, 1662 (str, C=O), 1591 (str, C=C), 1467, 1336 (str, O=S=O), 1225 (str), 1140 (str, O=S=O), 1004, 837 (med), 768 (med).

MS (ESI) $m/z$ 190 [(M + H)$^+$, 87%], 212 [(M + Na)$^+$, 36%]; HRMS (ESI) $m/z$ 190.0530 [(M + H)$^+$, calcd. for C$_7$H$_{12}$NO$_3$S 190.0532], 212.0347 [(M + Na)$^+$, calcd. for C$_7$H$_{11}$NO$_3$SNa 212.0352].

2-Benzyl-1,2-thiazinan-5-one 1,1-dioxide 309

A solution of 2-benzyl 1,2-thiazin-5(6H)-one 1,1-dioxide 210d (8 mg, 0.03 mmol) in methanol (3 mL) was passed through an H-cube hydrogen generator equipped with a 10% Pd/C cartridge at 20 °C at a pump speed of 1 mLmin$^{-1}$ and pressure of 10 bar. The volatiles were removed under reduced pressure to give the crude as a pale orange solid. The crude was purified via flash column chromatography (silica gel, dichloromethane as eluent) to give the title compound 309 (5 mg, 63%) as a pale orange crystalline solid, m.p. 115 – 118 °C.

$R_f$ (ethyl acetate:hexanes 3:7) = 0.20.

1H-NMR (CDCl$_3$, 400MHz): $\delta$ 7.39 (m, 5H, H-3'–H-5'), 4.48 (s, 2H, H-1'), 4.00 (s, 2H, H-6), 3.40 (t, 2H, $J = 6.2$ Hz, H-3), 2.50 (t, 2H, $J = 6.3$ Hz, H-4).

13C-NMR (CDCl$_3$, 100 MHz): $\delta$ 195.1 (quat., C-5), 134.9 (quat., C-2'), 129.1 (2 x CH, C-4'), 128.8 (3 x CH, C-3' and C-5'), 63.5 (CH$_2$, C-6), 51.1 (CH$_2$, C-1'), 41.6 (CH$_2$, C-3), 37.6 (CH$_2$, C-4).

IR (solid) cm$^{-1}$: 2994, 2928 (C–H), 2852, 1709 (str, C=O), 1606 (wk), 1587 (wk), 1495, 1447 (C=C), 1413, 1347 (med), 1334 (str, O=S=O), 1297 (med), 1252, 1238, 1218 (med), 1189, 1142 (str, O=S=O), 1120 (str), 1097 (med), 1078 (med), 1054 (med), 1030, 989 (med), 961, 935, 881 (str), 798 (str), 766, 751 (str), 706 (str), 693 (str), 653 (str), 586 (str).
MS (ESI) m/z 262 [(M + Na)$^+$, 100%]; HRMS (ESI) m/z 262.0515 [(M + Na)$^+$, calcd. for C$_{11}$H$_{13}$NO$_3$SNa 262.0508].

**Reaction with Rawal’s diene 123: General procedure 2B.**

A solution of the sulfamoyl chloride 213 (1 mol. eq.) in tetrahydrofuran (1.5 mL/200 mg) was added dropwise to a solution of Rawal’s diene 123 (1.5 mol. eq.) and triethylamine (1 mol. eq.) in tetrahydrofuran (1.5 mL) at -78 °C. The resulting pink suspension was allowed to stir at this temperature for 2 h, then allowed to warm to room temperature and stirred overnight. The suspension was filtered through a plug of cotton wool and the volatiles removed under reduced pressure to give the crude. The crude was purified via flash column chromatography (silica gel, ethyl acetate: hexanes 1:4 to 1:1 to 1:0 as eluent) to give the products.

**Reaction with Rawal’s diene 123: General procedure 2C – inverse addition**

Triethylamine (1 mol. eq.) was added dropwise to a solution of the sulfamoyl chloride 213 (1 mol. eq.) in tetrahydrofuran (1.5 mL/100 mg) at -78 °C, followed by a solution of Rawal’s diene 123 (1.5 mol. eq.) in tetrahydrofuran (1.5 mL). The resulting pink suspension was allowed to stir at this temperature for 1.5 h, then allowed to warm to room temperature and diluted with diethyl ether (3 mL). The suspension was filtered through filter paper and the volatiles removed under reduced pressure to give the crude as a bright orange-red oil. The crude was purified via flash column chromatography (silica gel, dichloromethane:methanol 99:1 to 49:1 as eluent) to give the products.

**(E)-N-Cyclohexyl-4-(dimethylamino)-2-oxobut-3-ene-1-sulfonamide 312a**

Prepared according to general procedure 2B from N-cyclohexylsulfamoyl chloride 213a and Rawal’s diene 123, to give the title compound 312a (168 mg, 60%) as a thick, bright yellow oil that solidified
into bright yellow needles, m.p. 113 – 115 °C. When prepared according to general procedure 2C, 
312a was obtained in 84% yield.

Rf (dichloromethane:methanol 19:1) = 0.16.

$^1$H-NMR (CDCl$_3$, 400MHz): δ 7.66 (br d, 1H, J = 10.0 Hz, H-4), 5.14 (d, 1H, J = 12.4 Hz, H-3), 4.82 (d, 1H, J = 6.5 Hz, N-H), 3.97 (s, 2H, H-1), 3.31 (m, 1H, H-1'), 2.88 (s, 3H, NMe), 2.37 (s, 3H, NMe), 2.04 – 1.15 (m, 10H, H-2' – H-4').

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ 184.4 (quat., C-2), 154.5 (br, CH, C-4), 95.0 (br, CH, C-3), 62.1 (br, CH$_2$, C-1), 53.1 (CH, C-1'), 45.1 (CH$_3$, NMe), 37.2 (CH$_3$, NMe), 33.9 (2 x CH$_2$, C-2'), 25.1 (CH$_2$, C-4'), 24.6 (2 x CH$_2$, C-3').

IR (solid) cm$^{-1}$: 3158 (med, N–H), 2927 (C–H), 2859, 1646 (str, C=O), 1548 (med), 1453 (med), 1436 (str), 1425 (str), 1378 (med), 1338 (str, O=S=O), 1267 (str), 1250 (str), 1210, 1153 (str, O=S=O), 1091 (str), 1080 (str), 1064 (str), 1050 (str), 980 (str), 956 (med), 937 (med), 903 (med), 881 (str), 843 (med), 811 (str), 777 (med), 730 (med), 682 (med).

MS (ESI) m/z 275 [(M + H)$^+$, 61%], 297 [(M + Na)$^+$, 38%]; HRMS (ESI) m/z 275.1417 [(M + H)$^+$ calcd. for C$_{12}$H$_{23}$N$_2$O$_3$S 275.1424], 297.1236 [(M + Na)$^+$ calcd. for C$_{12}$H$_{22}$N$_2$O$_3$SNa 297.1243].

(Z)-N-Cyclohexyl-1-(dimethylamino)-3-oxobut-1-ene-2-sulfonamide 313a

Prepared according to general procedure 2B from N-cyclohexylsulfamoyl chloride 213a and Rawal’s diene 123, to give the title compound 313a (40 mg, 14%) as a yellow oil. When prepared according to general procedure 2C, 313a was obtained in 8% yield.

Rf (dichloromethane:methanol 19:1) = 0.26.

$^1$H-NMR (CDCl$_3$, 400MHz): δ 7.66 (s, 1H, H-1), 4.20 (br s, 1H, N-H), 3.08 (m, 7H, NMe$_2$, H-1'), 2.43 (s, 3H, H-4), 1.93 – 1.16 (m, 10H, H-2' – H-4').

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ 191.8 (quat., C-3), 156.6 (CH, C-1), 95.7 (quat., C-2), 52.4 (CH, C-1'), 45.6 (br, 2 x CH$_3$, NMe$_2$), 34.0 (2 x CH$_2$, C-2'), 29.7 (CH$_3$, C-4), 25.3 (CH$_2$, C-4'), 24.8 (2 x CH$_2$, C-3').
IR (thin film) cm$^{-1}$: 3290 (med, N–H), 2971, 2928 (med, C–H), 2853, 2821, 1716, 1646 (str, C=O), 1587 (str, C=C), 1482, 1446, 1427 (str), 1362 (str, O=S=O), 1304 (med), 1297 (med), 1285 (str), 1258 (med), 1233 (med), 1188 (med), 1130 (str, O=S=O), 1116 (med), 1084 (str), 1063 (med), 1038 (med), 991 (med), 943 (med), 910 (med), 889 (med), 880 (med), 841 (med), 747, 614 (str), 583, 543.

MS (ESI) m/z 275 [(M + H)$^+$, 67%], 297 [(M + Na)$^+$, 100%]; HRMS (ESI) m/z 275.1413 [(M + H)$^+$ calcd. for C$_{12}$H$_{23}$N$_2$O$_3$S 275.1424], 297.1234 [(M + Na)$^+$ calcd. for C$_{12}$H$_{22}$N$_2$O$_3$SNa 297.1243].

(E)-N-Benzyl-4-(dimethylamino)-2-oxobut-3-ene-1-sulfonamide 312b

\[ \begin{align*}
&\text{Prepared according to general procedure 2B from N-benzylsulfamoyl chloride 213d and Rawal’s diene 123, to give the title compound 312b (38 mg, 18%) as a dark yellow crystalline solid, m.p. 106–108 °C.} \\
&R_f \text{ (dichloromethane:methanol 19:1) = 0.23.} \\
^{1}H-NMR (CDCl$_3$, 400MHz): \delta 7.62 (br d, 1H, J = 9.9 Hz, H-4), 7.31 (m, 5H, H-3′–H-5′), 5.62 (t, 1H, J = 6.3 Hz, NH), 5.10 (d, 1H, J = 12.4 Hz, H-3), 4.31 (d, 2H, J = 6.3 Hz, H-1′), 3.94 (s, 2H, H-1), 3.11 (s, 3H, NMe), 2.84 (s, 3H, NMe).
\\
^{13}C-NMR (CDCl$_3$, 100 MHz): \delta 184.3 (quat., C-2), 154.8 (br, CH, C-4), 136.8 (quat., C-2′), 128.6 (2x CH, C-4′), 128.1 (2x CH, C-3′), 127.7 (CH, C-5′), 94.8 (br, CH, C-3), 61.1 (br, CH$_2$, C-1), 47.7 (CH$_2$, C-1′), 45.2 (CH$_3$, NMe), 37.3 (CH$_3$, NMe).
\\
IR (solid) cm$^{-1}$: 3129 (med, N–H), 2920 (med, C–H), 1640 (str, C=O), 1568 (str, C=C), 1426, 1370, 1317 (str, O=S=O), 1268, 1147 (str, O=S=O), 1076 (str), 1062 (str), 1030, 990, 958, 912, 872, 794, 721 (str).
\\
MS (ESI) m/z 283 [(M + H)$^+$, 37%], 305 [(M + Na)$^+$, 43%]; HRMS (ESI) m/z 283.1099 [(M + H)$^+$ calcd. for C$_{13}$H$_{19}$N$_2$O$_3$S 283.1111], 305.0917 [(M + Na)$^+$ calcd. for C$_{13}$H$_{18}$N$_2$O$_3$SNa 305.0930].
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

(Z)-N-Benzyl-1-(dimethylamino)-3-oxobut-1-ene-2-sulfonamide 313b

Prepared according to general procedure 2B from N-benzylsulfamoyl chloride 213d and Rawal’s diene 123, to give the title compound 313b (40mg, 19%) as an orange oil.

$R_f$ (dichloromethane:methanol 19:1) = 0.24.

$^1$H-NMR (CDCl$_3$, 400MHz): δ 7.51 (s, 1H, H-1), 7.30 (m, 5H, H-3′ – H-5′), 5.12 – 4.71 (br s, 1H, NH), 4.09 (d, 2H, $J$ = 6.1 Hz, H-1′), 3.05 (br s, 6H, NMe$_2$), 2.39 (s, 3H, H-4).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ 191.4 (quat., C-3), 157.0 (CH, C-1), 136.7 (quat., C-2′), 128.5 (2 x CH, C-4′), 128.1 (2 x CH, C-3′), 127.7 (CH, C-5′), 107.4 (br, quat., C-2), 47.2 (CH$_2$, C-1′), 45.6 (br, 2 x CH$_3$, NMe$_2$), 29.6 (CH$_3$, C-4).

IR (neat) cm$^{-1}$: 3268 (med, broad, N–H), 2929 (C–H), 1638 (str, C=O), 1581 (str, Ar), 1421, 1369 (str, O=S=O), 1292, 1237, 1197, 1134 (str, O=S=O), 1027 (med, C-N), 974, 946, 911

MS (ESI) $m/z$ 283 [(M + H)$^+$, 34%], 305 [(M + Na)$^+$, 100%]; HRMS (ESI) $m/z$ 283.1100 [(M + H)$^+$ calcd. for C$_{13}$H$_{19}$N$_2$O$_3$S 283.1111], 305.0920 [(M + Na)$^+$ calcd. for C$_{13}$H$_{18}$N$_2$O$_3$SNa 305.0930].

**Reaction with (E)-tert-butyl benzyl(1,3-dienyl)carbamate 294**

A solution of N-cyclohexylsulfamoyl chloride 213a (100 mg, 0.51 mmol) in tetrahydrofuran (1.5 mL) was added to a solution of (E)-tert-butyl benzyl(1,3-dienyl)carbamate (131 mg, 0.51 mmol) in tetrahydrofuran (1.5 mL) at room temperature. Triethylamine (70 μL, 0.51 mmol) was then added dropwise, and the resulting yellow suspension allowed to stir at room temperature for 3 h. Water (5 mL) was added, and the mixture extracted with diethyl ether (3 x 10 mL). The combined organic
extracts were washed with brine (30 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 3:17 as eluent) to give tert-Butyl benzyl((1$E$,3$Z$)-4-(N-cyclohexylsulfamoyl)buta-1,3-dienyl)carbamate 327 (49 mg, 23%) as a yellow oil, and (Z)-N-cyclohexyl-4-oxobut-2-ene-1-sulfonamide 328 (10 mg, 9%) as white needles.

327 slowly hydrolyses on silica gel to afford 328 in 64% yield.

tert-Butyl benzyl((1$E$,3$Z$)-4-(N-cyclohexylsulfamoyl)buta-1,3-dien-1-yl) carbamate 327

\[
\text{R}_f \text{ (ethyl acetate:hexanes 3:7) } = 0.53.
\]

$^1$H-NMR (CDCl$_3$, 400MHz): $\delta$ 7.55 (br d, 1H, $J = 4.3$ Hz, H-1), 7.32 (m, 3H, H-3′′ – H4′′), 7.16 (d, 2H, $J = 7.4$ Hz, H-2′′), 7.06 (dd, 1H, $J = 11.2$, 14.3 Hz, H-3), 5.96 (d, 1H, $J = 14.6$ Hz, H-4), 5.47 (t, 1H, $J = 12.5$ Hz, H-2), 4.78 (br s, 2H, H-1′′), 4.07 (d, 1H, $J = 7.4$ Hz, N-H), 3.11 (m, 1H, H-1′), 1.52 (s, 9H, t-Bu), 1.89 – 1.10 (m, 10H, H-2′–H-4′).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ 152.4 (quat., CO$_2$Bu), 140.9 (CH, C-3), 139.0 (CH, C-1), 136.3 (quat., C-2′′), 128.8 (2 x CH, C-4′′), 127.4 (CH, C-3), 126.2 (CH, C-5′′), 123.4 (2 x CH, C-3′′), 104.8 (CH, C-2), 83.2 (quat., t-Bu), 52.3 (CH, C-1′), 47.7 (br, CH$_2$, C-1′′), 34.3 (2 x CH$_2$, C-2′), 28.1 (3 x CH$_3$, t-Bu), 25.2 (CH$_2$, C-4′), 24.7 (2 x CH$_2$, C-3′).

IR (thin film) cm$^{-1}$: 3280 (N–H), 2931, 2858, 1717 (str, C=O), 1630 (str, C=O), 1496, 1453, 1385 (str, O=S=O), 1327 (str), 1281, 1266, 1151 (str, O=S=O), 1082, 989, 978, 926, 908, 883, 843, 770, 736, 712, 607, 570.

MS (ESI) $m/z$ 421 [(M + H)$^+$, 68%], 443 [(M + Na)$^+$, 22%]; HRMS (ESI) $m/z$ 421.2155 [(M + H)$^+$, calcd. for C$_{22}$H$_{33}$N$_2$O$_4$S 421.2156], 443.1980 [(M + Na)$^+$, calcd. for C$_{22}$H$_{32}$N$_2$O$_4$Na 443.1975].
(E)-N-Cyclohexyl-4-oxobut-2-ene-1-sulfonamide 328

\[ \text{\textsuperscript{1}H-NMR (CDCl}_3, 400\text{MHz}): \delta 9.62 (d, 1H, J = 7.7 \text{ Hz}, H-4), 6.83 (dt, 1H, J = 7.5, 15.4 \text{ Hz}, H-2), 6.33 (ddt, 1H, J = 1.3, 7.8, 15.7 \text{ Hz}, H-3), 4.33 (dd, 1H, J = 1.2, 7.9 \text{ Hz}, N-H), 4.00 (dd, 2H, J = 1.2, 7.6 \text{ Hz}, H-1), 3.32 (m, 1H, H-1'), 1.99 – 1.13 (m, 10H, H-2’–H-4’). \]

\[ \text{\textsuperscript{13}C-NMR (CDCl}_3, 100\text{ MHz}): \delta 192.4 (\text{CH}, C-4), 142.3 (\text{CH}, C-2), 138.1 (\text{CH}, C-3), 57.0 (\text{CH}_2, C-1), 53.3 (\text{CH}, C-1'), 34.6 (2 \times \text{CH}_2, C-2'), 25.0 (\text{CH}_2, C-4'), 24.8 (2 \times \text{CH}_2, C-3'). \]

IR (thin film) cm\(^{-1}\): 3283 (N–H), 2981 (C–H), 2856, 2746, 1692 (str, C=O), 1639 (C=C), 1453 (med), 1327 (str, O=S=O), 1263, 1239, 1142 (str, O=S=O), 1105 (med), 1077 (med), 998, 980, 922, 888, 729.

2-Cyclohexyl-6-methyl-5-((triisopropylsilyl)oxy)-3,6-dihydro-2H-1,2-thiazine 1,1-dioxide 335

A solution of N-cyclohexylsulfamoyl chloride 213a (200 mg, 1.01 mmol) in tetrahydrofuran (1.5 mL) was added to a solution of 3-(triisopropylsilyloxy)penta-1,3-diene 292 (291 mg, 1.21 mmol) and triethylamine (140 μL, 1.01 mmol) in tetrahydrofuran (1.5 mL) at room temperature. The resulting white suspension was allowed to stir for 16 h. Water (2 mL) was added, and the mixture extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, dry-load, ethyl acetate:hexanes 0:1 to 39:1 to 19:1 to 1:0 as eluent) to give the title compound 335 (101 mg, 25%) as a colourless oil.

\[ \text{R}_f \text{ (ethyl acetate:hexanes 1:4) = 0.79.} \]
\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400MHz): δ 4.88 (t, 1H, J = 3.5 Hz, H-4), 3.84 (tt, 1H, J = 11.7, 3.4 Hz, H-1'), 3.65 (dd, 2H, J = 3.5, 2.1 Hz, H-3), 3.52 (m, 1H, H-6), 1.83 – 1.77 (m, 5H, H-2' – H-4'), 1.52 (d, 3H, J = 6.9 Hz, 6-Me), 1.40 (m, 5H, H-2' – H-4'), 1.19 (m, 3H, OTIPS), 1.08 (dd, 18H, J = 7.2, 4.1 Hz, OTIPS).

\textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100 MHz): δ 146.7 (quat., C-5), 98.9 (CH, C-4), 58.5 (CH, C-6), 54.5 (CH, C-1'), 39.6 (CH\textsubscript{2}, C-3), 31.2 (2 x CH\textsubscript{2}, C-2'), 25.6 (CH\textsubscript{2}, C-4'), 25.2 (2 x CH\textsubscript{2}, C-3'), 17.6 (6 x CH\textsubscript{3}, OTIPS), 13.8 (CH\textsubscript{3}, 6-Me), 12.4 (3 x CH, OTIPS).

IR (neat) cm\textsuperscript{-1}: 2935 (=C–H), 2866 (C–H), 1677 (C=C), 1452 (med), 1384, 1369, 1316 (str, O=S=O), 1259 (med), 1244, 1203 (str), 1167, 1131 (str, O=S=O), 1082 (str), 1066 (str), 1030, 1015, 997, 970, 920, 881 (str), 868, 813, 757, 683, 664.

MS (ESI) m/z 402 [(M + H)\textsuperscript{+}, 100%], 424 [(M + Na)\textsuperscript{+}, 20%]; HRMS (ESI) m/z 402.2492 [(M + H)\textsuperscript{+}, calcd. for C\textsubscript{20}H\textsubscript{40}NO\textsubscript{3}SSi 402.2493], 424.2308 [(M + Na)\textsuperscript{+}, calcd. for C\textsubscript{20}H\textsubscript{39}NO\textsubscript{3}SSiNa 424.2312].

**Reaction with (cyclohexa-1,5-dien-1-yloxy)trimethylsilane 293: General procedure 2D.**

A solution of the sulfamoyl chloride 213 (1 mol. eq.) in tetrahydrofuran (1.5 mL/100 mg) was added dropwise to a solution of 2-trimethylsilyloxy-1,3-cyclohexadiene 293 (1.5 mol. eq.) and triethylamine (1 mol. eq.) in tetrahydrofuran (1.5 mL) at -78 °C, and the resulting suspension allowed to stir at this temperature for 2 h. The mixture was then allowed to warm to room temperature and filtered through a plug of cotton wool. The volatiles were removed under reduced pressure to give the crude. The crude was purified via flash column chromatography (silica gel, dry-load, ethyl acetate:hexanes 1:9 to 1:4 as eluent) to give the products.

**8-Cyclohexyl-1-((trimethylsilyl)oxy)-7-thia-8-azabicyclo[4.2.0]oct-2-ene 7,7-dioxide 339a**
Prepared according to general procedure 2D from \( N \)-cyclohexylsulfamoyl chloride 213a, to give the *title compound* 339a (223 mg, 67\%) as a colourless oil.

\[ R_f (\text{ethyl acetate:hexanes 3:7}) = 0.94. \]

\(^1\text{H}-\text{NMR (CDCl}_3, \text{400MHz): } \delta \ 6.09 \ (\text{ddd, 1H, } J = 3.2, 5.8, 10.3 \text{ Hz, H-3}), \ 5.88 \ (\text{dd, 1H, } J = 2.2, 10.4 \text{ Hz, H-2}), \ 4.24 \ (\text{dd, 1H, } J = 3.6, 6.9 \text{ Hz, H-6}), \ 3.34 \ (\text{tt, 1H, } J = 3.7, 9.9 \text{ Hz, H-1'}). 2.58 - 2.45 (m, 1H, \( H_{\alpha-4} \)), 2.36 - 2.29 (m, 1H, \( H_{\alpha-5} \)), 2.14 - 2.06 (m, 1H, \( H_{\alpha-5} \)), 2.05 - 1.84 (m, 2H, \( H_{\alpha-2}', H_{\alpha-5} \)), 1.80 - 1.71 (m, 2H, \( H_{\alpha-3}' \)), 1.58 - 1.47 (4H, m, \( H_{\beta-2}' \), H-4'), 1.33 - 1.24 (3H, m, \( H_{\beta-2}' \), H-3') 0.16 (s, 9H, OTMS).

\[^{13}\text{C}-\text{NMR (CDCl}_3, \text{100 MHz): } \delta \ 131.3 \ (\text{CH, C-3}), \ 128.0 \ (\text{CH, C-2}), \ 76.5 \ (\text{quat., C-1}), \ 75.4 \ (\text{CH, C-6}), \ 52.9 \ (\text{CH, C-1'}), \ 31.1 \ (\text{CH}_2, \text{C-2'}), \ 31.0 \ (\text{CH}_2, \text{C-2'}), \ 25.3 \ (\text{CH}_2, \text{C-4'}), \ 23.8 \ (2 \times \text{CH}_2, \text{C-3'}), \ 19.9 \ (\text{CH}_2, \text{C-4}), \ 19.6 \ (\text{CH}_2, \text{C-5}), \ 1.3 \ (3 \times \text{CH}_3, \text{OTMS}).\]

\[ \text{IR (thin film) cm}^{-1}: 2933 (\text{C–H}), 2856, 1449, 1392, 1373, 1351, 1309 (\text{str, O=S=O}), 1251 (\text{str}), 1203 (\text{med}), 1159 (\text{str, O=S=O}), 1125 (\text{med}), 1073 (\text{str}), 1005, 964 (\text{med}), 883 (\text{med}), 865 (\text{med}), 842 (\text{str}), 754 (\text{str}), 733 (\text{med}), 694 (\text{med}), 677 (\text{str}).\]

\[ \text{MS (ESI) } m/z \ 330 [(M + H)^+, 7\%], \ 352 [(M + Na)^+, 100\%], \ 368 [(M + K)^+, 9\%]; \text{HRMS (ESI) } m/z \ 330.1555 [(M + H)^+, \text{calcd. for } \text{C}_{15}\text{H}_{28}\text{NO}_{3}\text{Si } 330.1554], \ 352.1370 [(M + Na)^+, \text{calcd. for } \text{C}_{15}\text{H}_{27}\text{NO}_{3}\text{SiNa } 352.1373], \ 368.1111 [(M + K)^+, \text{calcd. for } \text{C}_{15}\text{H}_{27}\text{NO}_{3}\text{SiK } 368.1112].\]

**N-Cyclohexyl-2-oxocyclohex-3-ene-1-sulfonamide 340a**

\[ \text{Prepared according to general procedure 2D from } \text{N-cyclohexylsulfamoyl chloride 213a, to give the } \text{title compound 340a (138 mg, 53\%)} \text{ as fluffy white needles, m.p. 124 – 126 °C.}\]

Recrystallised from Et\(_2\)O/CH\(_2\)Cl\(_2\)/hexanes 1:1:1

\[ R_f (\text{ethyl acetate:hexanes 3:7}) = 0.21. \]

\[^{1}\text{H}-\text{NMR (CDCl}_3, \text{400MHz): } \delta \ 7.12 \ (\text{dt, 1H, } J = 10.2, 4.1 \text{ Hz, H-4}), \ 6.11 \ (\text{dt, 1H, } J = 10.2, 1.9 \text{ Hz, H-3}), \ 4.85 \ (\text{d, 1H, } J = 7.0 \text{ Hz, N-H}), \ 3.82 \ (\text{t, 1H, } J = 6.6 \text{ Hz, H-1}), \ 3.32 \ (\text{m, 1H, H-1'}), \ 2.73 \ (\text{m, 1H, } H_{\alpha-5}), \ 2.55 \ (\text{m, 2H, H-6}), \ 2.48 \ (\text{m, 1H, } H_{\alpha-5}), \ 2.04 - 1.17 (\text{m, 10H, H-2' – 4')).\]
C-NMR (CDCl₃, 100 MHz): δ 191.1 (quat., C-2), 152.3 (CH, C-4), 129.2 (CH, C-3), 65.7 (CH, C-1), 53.3 (CH, C-1'), 34.7 (CH₂, C-2'), 33.6 (CH₂, C-2'), 25.1 (CH₂, C-4'), 24.7 (CH₂, C-3'), 24.6 (CH₂, C-3'), 24.1 (CH₂, C-5), 23.8 (CH₂, C-6).

IR (solid) cm⁻¹: 3182 (med, N–H), 2933 (C–H), 2888, 2853, 1653 (str, C=O), 1458 (med), 1446 (med), 1402 (med), 1348, 1324 (str, O=S=O), 1256 (med), 1236, 1212, 1153 (str), 1143 (str), 1133 (str, O=S=O), 1076 (str), 1002 (med), 949 (med), 887 (str), 845 (med), 774 (med).

MS (ESI) m/z 258 [(M + H)⁺, 32%], 280 [(M + Na)⁺, 100%]; HRMS (ESI) m/z 258.1156 [(M + H)⁺ calcd. for C₁₂H₂₀NO₃S 258.1158]; 280.0982 [(M + Na)⁺ calcd. for C₁₂H₁₉NO₃SNa 280.0978].

(1R,4S)-3-Cyclohexyl-2-thia-3-azabicyclo[2.2.2]octan-6-one 2,2-dioxide 337

Prepared according to general procedure 2D from N-cyclohexylsulfamoyl chloride 213a to give the title compound 337 (16 mg, 6%) as a white solid, m.p. 124 – 126 °C.

R₉ (ethyl acetate:hexanes 3:7) = 0.13.

¹H-NMR (CDCl₃, 400MHz): δ 4.03 (pent., 1H, J = 3.0 Hz, H-4), 3.85 (dd, 1H, J = 3.3, 2.7 Hz, H-1), 3.68 (tt, 1H, J = 11.4, 3.6 Hz, H-1'), 2.77 (dt, 1H, J = 18.9, 3.0 Hz, H₂-5), 2.65 (m, 1H, H₆-7), 2.42 (dd, 1H, J = 18.7, 2.8 Hz, H₆-5), 2.26 – 2.11 (m, 2H, H₆-7 and H₆-8), 1.98 (m, 2H, 2 x H₆-2'), 1.86 – 1.74 (m, 3H, 2 x H₆-3', H₆-8), 1.67 (m, 1H, H₆-4'), 1.50 – 1.30 (m, 4H, 2 x H₆-2', 2 x H₆-3'), 1.09 (m, 1H, H₆-4').

¹³C-NMR (CDCl₃, 100 MHz): δ 199.6 (quat., C-6), 66.4 (CH, C-1), 53.4 (CH, C-1'), 49.5 (CH, C-4), 44.4 (CH₂, C-5), 31.7 (CH₂, C-2'), 31.5 (CH₂, C-2'), 25.7 (CH₂, C-3'), 25.6 (CH₂, C-3'), 25.3 (CH₂, C-8), 25.2 (CH₂, C-4'), 20.0 (CH₂, C-7).

IR (solid) cm⁻¹: 3234, 2927 (C–H), 2853, 1733 (str, C=O), 1694, 1651, 1597, 1492, 1445, 1393 (med), 1284 (br str, O=S=O), 1177 (str), 1148 (med), 1118 (str, O=S=O), 1106 (str), 1053, 1025 (med), 989 (med), 951, 919 (med), 895, 875 (med), 855, 844, 805, 749 (med), 717, 642, 586 (str), 559 (med).
MS (ESI) m/z 258 [(M + H)$^+$, 21%], 280 [(M + Na)$^+$, 100%], 296 [(M + K)$^+$, 6%]; HRMS (ESI) m/z 258.1161 [(M + H)$^+$, calcd. for C$_{12}$H$_{20}$NO$_3$S 258.1158], 280.0979 [(M + Na)$^+$, calcd. for C$_{12}$H$_{19}$NO$_3$SNa 280.0978], 296.0733 [(M + K)$^+$, calcd. for C$_{12}$H$_{19}$NO$_3$SK 296.0717].

**N-tert-Butyl-2-oxocyclohex-3-ene-1-sulfonamide 340b**

![Structure 340b]

Prepared according to general procedure 2D from N-tert-butylsulfamoyl chloride 213b to give the title compound 340b (24 mg, 18%) as a white crystalline solid, m.p. 93–96 °C.

R$_f$ (ethyl acetate:hexanes 3:7) = 0.37.

$^1$H-NMR (CDCl$_3$, 400MHz): δ 7.11 (dt, 1H, $J$ = 4.2, 10.2 Hz), 6.11 (dt, 1H, $J$ = 2.0, 10.4 Hz, H-3), 4.85 (s, 1H, N-H), 3.83 (dd, 1H, $J$ = 6.3, 7.8 Hz, H-1), 2.72 (m, 1H, H$_a$-5), 2.56 (m, 2H, H-6), 2.47 (m, 1H, H$_b$-5), 1.40 (s, 9H, H-2$'$).

$^{13}$C-NMR (CDCl$_3$, 100 MHz): δ 191.3 (quat., C-2), 152.2 (CH, C-4), 129.3 (CH, C-3), 67.9 (CH, C-1), 55.3 (quat., C-1$'$), 30.3 (3 x CH$_3$, C-2$'$), 24.2 (CH$_2$, C-5), 23.7 (CH$_2$, C-6).

IR (solid) cm$^{-1}$: 3224 (med, N–H), 2977 (C–H), 2925, 2880, 2853, 1715, 1665 (str, C=O), 1655 (str, C=C), 1447, 1393, 1320 (str, O=S=O), 1141 (str, O=S=O), 1082 (med, C-N), 997 (str), 861, 775, 636 (str).

MS (ESI) m/z 254 [(M + Na)$^+$, 100%]; HRMS (ESI) m/z 254.0810 [(M + Na)$^+$ calcd. for C$_{10}$H$_{17}$NO$_3$SNa 254.0821].

**2-Oxo-N-phenylcyclohex-3-ene-1-sulfonamide 340c**

![Structure 340c]

Prepared according to general procedure 2D from N-phenylsulfamoyl chloride 213c to give the title compound 340c (37 mg, 14%) as a pale peach crystalline solid, m.p. 123–125 °C.

R$_f$ (ethyl acetate:hexanes 3:7) = 0.31.
H-NMR (CDCl$_3$, 400 MHz): δ 7.34 (m, 4H, H-2′ – H-3′), 7.17 – 7.10 (m, 3H, H-4, H-4′, N-H), 6.15 (dd, 1H, J = 1.9, 10.2 Hz, H-3), 3.75 (t, 1H, J = 7.4 Hz, H-1), 2.67 (m, 1H, H$_a$-5), 2.48 (m, 2H, H-6), 2.40 (m, 1H, H$_b$-5).

13C-NMR (CDCl$_3$, 100 MHz): δ 190.8 (quat., C-2), 152.6 (CH, C-4), 136.4 (quat., C-1′), 129.5 (2 x CH, C-3′), 129.3 (CH, C-3), 126.2 (CH, C-4′), 122.8 (2 x CH, C-2′), 62.3 (CH, C-1), 24.1 (CH$_2$, C-5), 23.2 (CH$_2$, C-6).

IR (solid) cm$^{-1}$: 3221 (br, N–H), 3045 (=C–H), 2941 (C–H), 2923, 2894, 2855, 1732, 1651 (str, C=O), 1616 (C=C), 1596, 1544, 1489 (med), 1417 (str), 1392 (med), 1337 (str, O=S=O), 1305 (med), 1279, 1251, 122 (str), 1147 (str, O=S=O), 1125 (str), 1077 (med), 1019, 1003, 954 (med), 925 (str), 914 (med), 875, 843 (med), 816, 760 (str), 693 (str).

MS (ESI) m/z 252 [(M + H)$^+$, 10%], 274 [(M + Na)$^+$, 100%]; HRMS (ESI) m/z 252.0685 [(M + H)$^+$, calcd. for C$_{12}$H$_{14}$NO$_3$S 252.0689], 274.0507 [(M + Na)$^+$, calcd. for C$_{12}$H$_{13}$NO$_3$SNa 274.0508].

8-Benzyl-1-((trimethylsilyl)oxy)-7-thia-8-azabicyclo[4.2.0]oct-2-ene 7,7-dioxide 339b

Prepared according to general procedure 2D from N-benzylsulfamoyl chloride 213d to give the title compound 339b (113mg, 34%) as a colourless oil.

R$_f$ (ethyl acetate:hexanes 3:7) = 0.96.

1H-NMR (CDCl$_3$, 400MHz): δ 7.39 – 7.25 (m, 5H, H-3′ – H-5′), 6.02 (ddd, 1H, J = 10.3, 5.4, 3.4 Hz, H-3), 5.57 (dt, 1H, J = 10.5, 1.7 Hz, H-2), 4.37 (dd, 1H, J = 6.9, 4.6 Hz, H-6), 4.22 (s, 2H, H-1′), 2.53 – 2.43 (m, 1H, H$_a$-4), 2.39 – 2.32 (m, 1H, H$_b$-5), 2.14 – 2.05 (m, 1H, H$_a$-4), 2.01 – 1.93 (m, 1H, H$_b$-5), 0.08 (s, 9H, OTMS).

13C-NMR (CDCl$_3$, 100 MHz): δ 135.7 (quat., C-2′), 131.4 (CH, C-3), 128.3 (4 x CH, C-3′, C-4′), 127.5 (CH, C-5′), 127.0 (CH, C-2), 76.6 (CH, C-6), 44.3 (CH$_2$, C-1′), 20.1 (CH$_2$, C-4), 20.0 (CH$_2$, C-5), 1.40 (3 x CH$_3$, OTMS).

The sample decomposed to 340d during collection of $^1$H- and $^{13}$C-NMR spectra, and unfortunately before IR or MS spectra could be obtained.
**N-Benzyl-2-oxocyclohex-3-ene-1-sulfonamide 340d**

Prepared according to general procedure 2D from N-benzylsulfamoyl chloride 213d to give the title compound 340d (69 mg, 27%) as a pale yellow crystalline solid, m.p. 84 – 87 °C.

R<sub>f</sub> (ethyl acetate:hexanes 3:7) = 0.10.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400MHz): δ 7.37 – 7.28 (m, 5H, H-3′ – H-5′), 7.09 (dt, 1H, J = 4.1, 10.2 Hz, H-4), 6.06 (dt, 1H, J = 2, 10.2 Hz, H-3), 5.39 (t, 1H, J = 6.3 Hz, N-H), 4.36 (dd, 1H, J = 7.2, 14.0 Hz, H<sub>a</sub>-1′), 4.27 (dd, 1H, J = 5.6, 14.0 Hz, H<sub>b</sub>-1′), 3.69 (t, 1H, J = 7.0 Hz, H-1), 2.50 (m, 2H, H-6), 2.72 – 2.35 (m, 2H, H-5).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 100 MHz): δ 191.0 (quat., C-2), 152.5 (CH, C-4), 136.5 (quat., C-2′), 129.0 (CH, C-3), 128.6 (2 x CH, C-4′), 128.0 (2 x CH, C-3′), 127.9 (CH, C-5′), 64.8 (CH, C-1), 47.5 (CH<sub>2</sub>, C-1′), 24.0 (CH<sub>2</sub>, C-5), 23.4 (CH<sub>2</sub>, C-6).

IR (solid) cm<sup>-1</sup>: 3281, 3193 (br, N–H), 3031, 2927 (C–H), 2876, 1660 (str, C=O), 1650 (C=C), 1495, 1447 (med, Ar C=C), 1398 (med), 1323 (O=S=O), 1257 (str), 1236, 1212, 1144 (str, O=S=O), 1071 (str), 1057 (str), 968, 949 (str), 851 (med), 842 (med), 831 (med), 757 (str), 700 (str).

MS (ESI) m/z 266 [(M + H)<sup>+</sup>, 3%], 288 [(M + Na)<sup>+</sup>, 100%]; HRMS (ESI) m/z 266.0840 [(M + H)<sup>+</sup> calcd. for C<sub>13</sub>H<sub>16</sub>NO<sub>3</sub>S 266.0845], 288.0657 [(M + Na)<sup>+</sup> calcd. for C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub>SNa 288.0665].

**Methyl 4-(N-cyclohexylsulfamoyl)-3-oxobutanoate 354a and (Z)-methyl 4-(N-cyclohexylsulfamoyl)-3-hydroxybut-2-enoate 354b**

![Diagram of the synthesis and structures of 354a and 354b]
A solution of N-cyclohexylsulfamoyl chloride 213a (200 mg, 1.01 mmol) in tetrahydrofuran (1.5 mL) was added dropwise to a solution of Chan’s diene 295 (1.317 g, 5.06 mmol) and triethylamine (140 μL, 1.01 mmol) in tetrahydrofuran (1 mL) at -78 °C, and the resulting pale yellow suspension allowed to stir at this temperature for 1.5 h. The mixture was then allowed to warm to room temperature and water (2 mL) added. The aqueous was extracted with diethyl ether (3 x 8 mL), and the combined organic extracts dried over Na₂SO₄ and concentrated under reduced pressure to give the crude as an orange oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 3:17 to 3:7 as eluent) to give the title compound 354 (281 mg, 65%) as white needles, m.p. 98 – 100 °C.

Rf (ethyl acetate:hexanes 3:7) = 0.34.

Product ratio ca. 3:1, keto : enol.

¹H-NMR (CDCl₃, 400MHz): δ 12.09 (s, 1H, OH enol), 5.31 (s, 1H, H-2 enol), 4.56 (d, 1H, J = 7.5 Hz, N-H keto), 4.36 (d, 1H, J = 7.2 Hz, N-H enol), 4.25 (s, 2H, H-4 keto), 3.86 (s, 2H, H-4 enol), 3.77 (s, 3H, OMe enol), 3.76 (s, 3H, OMe keto), 3.74 (s, 2H, H-2 keto), 3.30 (m, 1H, H-1′), 2.03 – 1.15 (m, 10H, H-2′ – H-4′).

¹³C-NMR (CDCl₃, 100 MHz): δ 192.9 (quat., C-3 keto), 172.3 (quat., C-3 enol), 167.1 (quat., C-1 keto), 165.3 (quat., C-1 enol), 94.6 (CH, C-2 enol), 63.4 (CH₂, C-4 keto), 58.0 (CH₂, C-4 enol), 53.4 (CH, C-1′ enol), 53.3 (CH, C-1′ keto), 52.6 (CH₃, OMe keto), 51.6 (CH₃, OMe enol), 48.8 (CH₂, C-2 keto), 34.1 (2 x CH₂, C-2′ enol), 34.0 (2 x CH₂, C-2′ keto), 25.0 (CH₂, C-4′), 24.6 (2 x CH₂, C-3′).

IR (solid) cm⁻¹: 3284 (med, N–H), 2982 (C–H), 2933, 2857, 1738 (str, C=O), 1718 (str, C=O), 1456, 1441 (str), 1408, 1397 (med), 1317 (str, O=S=O), 1299 (str), 1268 (med), 1239 (str), 1180 (med), 1156 (str), 1141 (str, O=S=O), 1094, 1079 (str), 1063 (str), 1031, 1015 (str), 1004 (str), 948 (med), 929, 888 (med), 866 (med), 842, 773, 735 (str).

MS (ESI) m/z 278 [(M + H)⁺, 5%], 300 [(M + Na)⁺, 100%]; HRMS (ESI) m/z 278.1065 [(M + H)⁺, calcd. for C₁₁H₂₀NO₅S 278.1057], 300.0878 [(M + Na)⁺, calcd. for C₁₁H₁₉NO₅SNa 300.0876].
**Reaction with Brassard’s diene 296: General procedure 2E.**

A solution of the requisite sulfamoyl chloride (1 mol eq) in tetrahydrofuran (1.5 mL) was added to a solution of Brassard’s diene 296 (1.1 mol eq) and triethylamine (1 mol eq) in tetrahydrofuran (1.5 mL) at -78 °C. The resulting white suspension was allowed to stir at this temperature for 2 h, then allowed to warm to room temperature and stirred overnight. Water (2 mL) was added, and the mixture extracted with diethyl ether (3 x 7 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to give the crude. The crude was purified via flash column chromatography (silica gel, dichloromethane: methanol 1:0 to 49:1 as eluent) to give the products.

**(E)-Methyl 4-(N-cyclohexylsulfamoyl)-3-methoxybut-2-enoate 357a**

Prepared according to general procedure 2E from N-cyclohexylsulfamoyl chloride 213a, to give the **title compound 357a** as the major product (207 mg, 70%) as a white crystalline solid, m.p. 109 – 111 °C.

- Rf (ethyl acetate:hexanes 3:7) = 0.21.
- 1H-NMR (CDCl₃, 400MHz): δ 5.29 (s, 1H, H-2), 4.69 (m, 3H, H-4 and N-H), 3.73 (s, 3H, 3-OMe), 3.71 (s, 3H, CO₂Me), 3.31 (m, 1H, H-1'), 1.99 – 1.21 (m, 10H, H-2' – H-4').
- 13C-NMR (CDCl₃, 100 MHz): δ 167.2 (quat., C-1), 163.5 (quat., C-3), 95.4 (CH, C-2), 56.2 (CH₃, 3-OMe), 54.4 (CH₂, C-4), 53.0 (CH, C-1'), 51.3 (CH₃, CO₂Me), 34.1 (2 x CH₂, C-2'), 25.1 (CH₂, C-4'), 24.7 (2 x CH₂, C-3').
- IR (solid) cm⁻¹: 3332, 3264 (N–H), 3017 (=C–H), 2980 (C–H), 2936, 2856, 1747, 1713 (str, C=O), 1631 (str, C=C), 1489, 1443, 1431 (med), 1396, 1361, 1317 (str, O=S=O), 1300 (str), 1255, 1219,
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

1176, 1144 (str, O=S=O), 1126 (str), 1094, 1084, 1053 (med), 1021 (med), 995, 930 (med), 915 (med), 885, 842, 818 (med), 762 (med), 696, 652 (str), 615.

MS (ESI) m/z 292 [(M + H)⁺, 18%], 314 [(M + Na)⁺, 100%], 330 [(M + K)⁺, 4%]; HRMS (ESI) m/z 292.1216 [(M + H)⁺, calcd. for C₁₂H₂₂NO₅S 292.1213], 314.1035 [(M + Na)⁺, calcd. for C₁₂H₂₁NO₅SNa 314.1033], 330.0772 [(M + K)⁺, calcd. for C₁₂H₂₁NO₅SK 330.0772].

2-Cyclohexyl-5-methoxy-1,2-thiazin-3(6H)-one 1,1-dioxide 358a

Prepared according to general procedure 2E from N-cyclohexylsulfamoyl chloride 213a, to give the title compound 358a as the minor product (5 mg, 2%) as a colourless oil that solidified over time to a white crystalline solid, m.p. 107 – 109 °C.

Rᵣ (ethyl acetate:hexanes 1:1) = 0.34.

¹H-NMR (CDCl₃, 400MHz): δ 5.46 (s, 1H, H-4), 4.48 (m, 1H, H-1'), 4.04 (s, 2H, H-6), 3.78 (s, 3H, 5-OMe), 2.27 – 1.22 (m, 10H, H-2’ – H-4').

¹³C-NMR (CDCl₃, 100 MHz): δ 163.8 (quat., C-5), 160.8 (quat., C-3), 97.2 (CH, C-4), 56.7 (CH₃, 5-OMe), 55.6 (CH, C-1'), 53.4 (CH₂, C-6), 30.9 (2 x CH₂, C-2'), 26.6 (CH₂, C-4'), 25.0 (2 x CH₂, C-3').

IR (solid) cm⁻¹: 3082 (=C–H), 2977 (C–H), 2929, 2859, 1650 (str, C=O), 1629 (str, C=C), 1450 (med), 1440 (med), 1402, 1392, 1363 (med), 1354 (str, O=S=O), 1301 (med), 1262 (str), 1254 (str), 1234 (str), 1226 (str), 1193, 1165 (str, O=S=O), 1127 (str), 1081 (str), 1009, 983 (str), 931 (med), 886, (med), 857, 841,796, 761, 729, 606 (str), 583 (med).

MS (ESI) m/z 260 [(M + H)⁺, 10%], 282 [(M + Na)⁺, 50%]; HRMS (ESI) m/z 260.0947 [(M + H)⁺, calcd. for C₁₁H₁₈NO₄S 260.0951], 282.0768 [(M + Na)⁺, calcd. for C₁₁H₁₇NO₄SNa 282.0770].

(E)-Methyl 4-(N-tert-butylsulfamoyl)-3-methoxybut-2-enoate 357b
Prepared according to general procedure 2E from \( N\text{-}tert\text{-}butylsulfamoyl chloride \) \( 213b \) to give the \textit{title compound} \( 357b \) (54 mg, 23\%) as a pale yellow crystalline solid, m.p. 90 – 93 °C.

\[ R_f \text{ (ethyl acetate:hexanes 3:7) } = 0.30. \]

\( ^1H\text{-NMR (CDCl}_3, 400\text{MHz}) \): \( \delta \) 5.28 (s, 1H, H-2), 4.70 (s, 2H, H-4), 4.65 (s, 1H, N-H), 3.73 (s, 3H, 3-O\text{Me}), 3.71 (s, 3H, CO\text{2Me}), 1.38 (s, 9H, H-2').

\( ^{13}\text{C-NMR (CDCl}_3, 100\text{MHz}) \): \( \delta \) 167.2 (quat., C-1), 163.6 (quat., C-3), 95.3 (CH, C-2), 56.9 (CH\text{2}, C-4), 56.2 (CH\text{3}, 3-O\text{Me}), 55.0 (quat., C-1'), 51.2 (CH\text{3}, CO\text{2Me}), 30.1 (3 x CH\text{3}, C-2').

IR (solid cm\(^{-1}\)): 3286 (med, N–H), 2997 (C–H), 2977, 2947, 1742, 1709 (str, C=O), 1636 (str, C=C), 1442 (med), 1391 (med), 1364 (med), 1316 (str, O=S=O), 1198 (med), 1142 (str, O=S=O), 1128 (str), 1011 (str), 1054 (str), 935 (med), 827 (str), 642 (str).

MS (ESI) \( m/z \) 266 [(M + H)\(^+\), 12\%], 288 [(M + Na)\(^+\), 100\%]; HRMS (ESI) \( m/z \) 266.1053 [(M + H)\(^+\), calcd. for C\text{10}H\text{20}NO\text{5}S  266.1057], 288.0878 [(M + Na)\(^+\), calcd. for C\text{10}H\text{19}NO\text{5}SNa  288.0876].

\((E)\)-\textit{Methyl 3-methoxy-4-(N-phenylsulfamoyl)but-2-enoate}  \( 357c \)

Prepared according to the general procedure 2E from \( N\text{-}phenylsulfamoyl chloride \) \( 213c \) to give the \textit{title compound} \( 357c \) (80 mg, 30\%) as a yellow crystalline solid, m.p. 106 – 110 °C.

\[ R_f \text{ (ethyl acetate:hexanes 3:7) } = 0.27. \]

\( ^1H\text{-NMR (CDCl}_3, 400\text{MHz}) \): \( \delta \) 7.32 (m, 3H, H-3' and N-H), 7.25 (m, 2H, H-2'), 7.15 (m, 1H, H-4'), 5.23 (s, 1H, H-2), 4.75 (s, 2H, H-4), 3.64 (s, 3H, 3-O\text{Me}), 3.60 (s, 3H, CO\text{2Me}).

\( ^{13}\text{C-NMR (CDCl}_3, 100\text{MHz}) \): \( \delta \) 167.0 (quat., C-1), 162.4 (quat., C-3), 137.1 (quat., C-1'), 129.3 (2 x CH, C-3'), 125.0 (CH, C-4'), 120.5 (2 x CH, C-2'), 96.1 (CH, C-2), 56.3 (CH\text{3}, 3-O\text{Me}), 52.6 (CH\text{2}, C-4), 51.3 (CH\text{3}, CO\text{2Me}).

IR (solid cm\(^{-1}\)): 3237 (med, N–H), 3026, 2995 (C–H), 2956, 2939, 1738, 1710 (str, C=O), 1641 (str, C=C), 1593 (med), 1495, 1478 (med, Ar C=C), 1441 (med, Ar C=C), 1416 (med, Ar C=C), 1404, 1366, 1332 (str, O=S=O), 1148 (str, O=S=O), 1131 (str), 1057 (str), 1023 (str), 929 (str), 825 (med), 742 (str), 692 (str).
MS (ESI) m/z 308 [(M + Na)^+; 100%]; HRMS (ESI) m/z 308.0569 [(M + Na)^+; calcd. for C_{12}H_{15}NO_{5}SNa 308.0563].

**2-Benzyl-5-methoxy-1,2-thiazin-3(6H)-one 1,1-dioxide 358d**

![Structure of 358d](image)

Prepared according to general procedure 2E from N-benzylsulfamoyl chloride 213d, to give the title compound 358d (11 mg, 4%) as a colourless oil.

\[ R_f \text{ (ethyl acetate:hexanes 3:7) } = 0.16. \]

\[ ^1H-NMR \text{ (CDCl}_3\text{, 400MHz): } \delta 7.48 - 7.42 \text{ (m, 2H, H-4'), 7.33 - 7.25 \text{ (m, 3H, H-3', H-5')}, 5.51 \text{ (s, 1H, H-4)}, 4.95 \text{ (s, 2H, H-1')}, 4.09 \text{ (s, 2H, H-6)}, 3.79 \text{ (s, 3H, 5-OMe)}. \]

\[ ^{13}C-NMR \text{ (CDCl}_3\text{, 100 MHz): } \delta 163.3 \text{ (quat., C-5), 161.4 \text{ (quat., C-3), 136.2 \text{ (quat., C-2')}, 128.7 \text{ (2 x CH, C-4'), 128.5 \text{ (2 x CH, C-3'), 127.8 \text{ (CH, C-5')}, 96.4 \text{ (CH, C-4), 56.9 \text{ (CH3, 5-OMe), 53.0 \text{ (CH2, C-6)}, 43.5 \text{ (CH2, C-1')}}. \]

IR (thin film) cm\(^{-1}\): 3095 (Ar C–H), 3068 (=C–H), 3034, 2979 (C–H), 2928, 2854, 1668 (str, C=O), 1627 (str, C=C), 1497, 1455 (Ar C=C), 1440, 1358 (str), 1345 (str, O=S=O), 1294 (med), 1254 (med), 1227 (str), 1160 (str), 1130 (str, O=S=O), 1029 (med), 987 (str), 916 (med), 861 (str), 825 (str), 727 (str), 696 (str).

MS (ESI) m/z 268 [(M + H)^+; 20%], 290 [(M + Na)^+; 100%]; HRMS (ESI) m/z 268.0641 [(M + H)^+; calcd. for C_{12}H_{14}NO_{4}S 268.0638], 290.0457 [(M + Na)^+; calcd. for C_{12}H_{13}NO_{4}SNa 290.0457].

**Hydrolysis of Michael adducts 357: General procedure 2F.**

![Hydrolysis reaction](image)

Prepared according to the procedure of Unterhalt et al.\(^{184}\)

A solution of sodium hydroxide (aq. 4% w/v, 0.3 mL) was added to a stirred solution the requisite ester 357 (0.17 mmol) in dioxane/water (9:1, 5 mL) and the mixture allowed to stir for 24 h. A solution of HCl (aq., 5% v/v, 0.5 mL) and diethyl ether (5 mL) was added, and the mixture extracted.
with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, dry-load, ethyl acetate:hexanes 3:7 to 1:0 as eluent) to give the products.

**((E))-4-((N-Cyclohexylsulfamoyl)-3-methoxybut-2-enoic acid 362a**

![Chemical Structure](362a.png)

Prepared according to general procedure 2F from ((E))-methyl 4-((N-cyclohexylsulfamoyl)-3-methoxybut-2-enoate 357a to give the title compound 362a (25 mg, 82%) as colourless crystalline flakes, m.p. 152 – 154 °C.

R$_f$ (ethyl acetate:hexanes 1:1) = 0.14.

$^1$H-NMR (CD$_3$OD, 400MHz): δ 5.31 (s, 1H, H-2), 4.69 (s, 2H, H-4), 3.71 (s, 3H, 3-OMe), 3.17 (m, 1H, H-1’), 1.96 (m, 2H, H-2’), 1.73 (m, 2H, H-3’), 1.59 (m, 1H, H-4’), 1.38 – 1.20 (m, 5H, H-2’ – H-4’).

$^{13}$C-NMR (CD$_3$OD, 100 MHz): δ 170.0 (quat., C-1), 165.6 (quat., C-3), 96.5 (CH, C-2), 56.7 (CH$_3$, 3-OMe), 55.1 (CH$_2$, C-4), 54.3 (CH, C-1’), 35.4 (2 x CH$_2$, C-2’), 26.5 (CH$_2$, C-4’), 26.2 (2 x CH$_2$, C-3’).

IR (solid) cm$^{-1}$: 3273 (N–H), 3025 – 2500 (v br, O–H), 3025 (=C–H), 2933 (C–H), 2850, 2730, 2615, 1683 (C=O), 1669 (med, C=C), 1603 (str, C=C), 1443 (med), 1428 (med), 1390, 1354 (med), 1321 (str, O=S=O), 1201 (str), 1162 (str), 1149 (str, O=S=O), 1080 (med), 1069 (str), 1040 (med), 992 (med), 931 (med), 721 (str), 656 (str).

MS (ESI) m/z 300 [(M + Na)$^+$, 100%]; HRMS (ESI) m/z 300.0877 [(M + Na)$^+$, calcd. for C$_{11}$H$_{19}$NO$_5$SNa 300.0876].

**((E))-4-(N-tert-Butylsulfamoyl)-3-methoxybut-2-enoic acid 362b**

![Chemical Structure](362b.png)
Prepared according to general procedure 2F from (E)-Methyl 4-(N-tert-butylsulfamoyl)-3-methoxybut-2-enoate 357b to give the title compound 362b (30 mg, >99%) as white fluffy needles, m.p. 168 – 171 °C.

Rf (ethyl acetate:hexanes 3:7) = 0.07.

\(^1\)H-NMR (CD\(_3\)OD, 400MHz): δ 5.30 (s, 1H, H-2), 4.68 (s, 2H, H-4), 3.71 (s, 3H, 3-OMe), 1.34 (s, 9H, H-2').

\(^13\)C-NMR (CD\(_3\)OD, 100 MHz): δ 170.0 (quat., C-1), 165.5 (quat., C-3), 96.6 (CH, C-2), 57.8 (CH\(_2\), C-4), 56.7 (CH\(_3\), 3-OMe), 55.4 (quat., C-1'), 30.6 (3 x CH\(_3\), C-2').

IR (solid) cm\(^{-1}\): 3298 (N–H), 3200 – 2500 (v br, O–H), 3033 (=C–H), 2977 (C–H), 2915, 2880, 2857, 1678 (str, C=O), 1655, 1599 (str, C=C), 1458, 1469, 1443, 1428, 1392, 1366, 1352, 1318 (str, O=S=O), 1246, 1230, 1204 (str), 1186 (med), 1149 (str, O=S=O), 1128 (str), 1044 (med), 999 (med), 928, 907, 864, 839, 823 (str), 714 (str).

MS (ESI) m/z 252 [(M + H\(^+\), 4%), 274 [(M + Na\(^+\), 100%]; HRMS (ESI) m/z 252.0892 [(M + H\(^+\), calcd. for C\(_9\)H\(_{18}\)NO\(_5\)S 252.0900], 274.0710 [(M + Na\(^+\), calcd. for C\(_9\)H\(_{17}\)NO\(_5\)SNa 274.0720].

**(E)-3-Methoxy-4-(N-phenylsulfamoyl)but-2-enoic acid 362c**

Prepared according to general procedure 2F from (E)-Methyl 3-methoxy-4-(N-phenylsulfamoyl)but-2-enoate 357c to give the title compound 362c (46 mg, 78%) as a white crystalline solid, m.p. 155 – 158 °C.

Rf (ethyl acetate:hexanes 1:1) = 0.07.

\(^1\)H-NMR (CD\(_3\)OD, 400MHz): δ 7.27 (m, 4H, H-2' – H-3'), 7.09 (t, 1H, J = 7.1 Hz, H-4'), 5.24 (s, 1H, H-2), 4.71 (s, 2H, H-4), 3.59 (s, 3H, 3-OMe).

\(^13\)C-NMR (CD\(_3\)OD, 100 MHz): δ 169.8 (quat., C-1), 164.6 (quat., C-3), 139.5 (quat., C-1'), 130.2 (2 x CH, C-3'), 125.4 (CH, C-4'), 121.3 (2 x CH, C-2'), 97.0 (CH, C-2), 56.6 (CH\(_3\), 3-OMe), 53.5 (CH\(_2\), C-4).

IR (solid) cm\(^{-1}\): 3241 (N–H), 3098 – 2500 (br, O–H), 3021 (=C–H), 2939 (C–H), 2907, 2852, 1679 (str, C=O), 1606 (str, C=C), 1483 (str, Ar C=C), 1446 (med), 1419 (str), 1387, 1345 (str, O=S=O),
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

1307 (med), 1282, 1255, 1207 (str), 1161 (str), 1135 (str, O=S=O), 1079, 1044, 1032, 995, 927 (str), 905 (med), 852 (str), 838 (med), 752 (str), 723 (str).

MS (ESI) \( m/z \) 294 \([\text{M} + \text{Na}]^+, 100\%\); HRMS (ESI) \( m/z \) 294.0401 \([\text{M} + \text{Na}]^+, \text{calcd. for } \text{C}_{11}\text{H}_{13}\text{NO}_5\text{SNa} 294.0407\].

**Ring closure of sulfonamide acids 362: General procedure 2G.**

\[
\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{O} \\
\text{HO} \\
\text{N} \\
\text{SO} \\
\text{MeO} \\
\text{O} \\
\text{O} \\
\text{PhMe, 65 °C} \\
\text{362} \\
\rightarrow \\
\text{SOCl}_2 \\
\text{358} \\
\text{R} \\
\end{array}
\]

Prepared according to the procedure of Massarani *et al.*

Thionyl chloride (0.5 mL, excess) was added to a solution of the requisite acid 362 (1 mol eq) in toluene (3 mL), and the mixture heated to 65 °C for 3 h. The solution was allowed to cool to room temperature and the volatiles removed under reduced pressure to give the crude as a yellow oil. The crude was purified *via* filtration through a short plug of silica with dichloromethane as solvent, to give the products.

**2-Cyclohexyl-5-methoxy-1,2-thiazin-3(6H)-one 1,1-dioxide 358a**

Material prepared according to general procedure 2G from (E)-4-(N-cyclohexylsulfamoyl)-3-methoxybut-2-enoic acid 362a was identical to that prepared *via* general procedure 2E, in >99% yield.

**5-Methoxy-2H-1,2-thiazin-3(6H)-one 1,1-dioxide 358b**

 Prepared according to general procedure 2E from (E)-4-(N-tert-Butylsulfamoyl)-3-methoxybut-2-enoic acid 362b to give the *title compound* 358b (21 mg, >99%) as a yellow solid, mp 117 – 121 °C.

\[ \text{R}_f \text{ (ethyl acetate:hexanes 1:1) = 0.05.} \]

\[^{1}\text{H-NMR (CD}_3\text{OD, 400MHz): } \delta 5.49 \text{ (s, 1H, H-4), 4.29 (s, 2H, H-6), 3.84 (s, 3H, 5-OMe).} \]
C-NMR (CD$_3$OD, 100 MHz): $\delta$ 167.6 (quat., C-3), 166.9 (quat., C-5), 95.6 (CH, C-4), 57.8 (CH$_3$, 5-OMe), 53.0 (CH$_2$, C-6).

IR (thin film) cm$^{-1}$: 3168 (N–H), 2979 (=C–H), 2927 (C–H), 1670 (str, C=O), 1637 (str, C=C), 1614 (str), 1456 (med), 1370 (str), 1332 (str, O=S=O), 1262 (med), 1137 (str, O=S=O), 992 (med), 921 (str), 850 (str).

2-Phenyl-5-methoxy-1,2-thiazin-3(6H)-one 1,1-dioxide 358c

Prepared according to general procedure 2E from (E)-3-Methoxy-4-(N-phenylsulfamoyl)but-2-enoic acid 362c to give the title compound 358c (31 mg, 87%) as a pale brown oil.

R$_f$ (ethyl acetate:hexanes 3:7) = 0.04.

$^1$H-NMR (CDCl$_3$, 400MHz): $\delta$ 7.48 (m, 3H, H-3′, H-4′), 7.33 (m, 2H, H-2′), 5.64 (s, 1H, H-4), 4.27 (s, 2H, H-6), 3.86 (s, 3H, 5-OMe).

C-NMR (CDCl$_3$, 100 MHz): $\delta$ 163.5 (quat., C-5), 161.7 (quat., C-3), 130.6 (quat., C-1′), 130.1 (2 x CH, C-2′), 129.8 (CH, C-4′), 129.6 (2 x CH, C-3′), 96.5 (CH, C-4), 57.1 (CH$_3$, 5-OMe), 53.2 (CH$_2$, C-6).

IR (thin film) cm$^{-1}$: 3100 (=C–H), 2978 (C–H), 2929, 2850, 1675 (str, C=O), 1628 (str, C=C), 1596, 1489 (med, Ar C=C), 1455 (Ar C=C), 1443 (Ar C=C), 1362 (str, O=S=O), 1298 (med), 1263 (med), 1230 (str), 1162 (str), 1133 (str, O=S=O), 1076, 1022 (med), 994 (med), 960, 912, 885, 825 (med), 758, 728, 694 (str), 610 (str), 588.

MS (ESI) m/z 254 [(M + H)$^+$, 41%], 276 [(M + Na)$^+$, 1005] 292 [(M + K)$^+$, 23%]; HRMS (ESI) m/z 254.0490 [(M + H)$^+$, calcd. for C$_{11}$H$_{12}$NO$_4$S 254.0482], 276.0306 [(M + Na)$^+$, calcd. for C$_{11}$H$_{11}$NO$_4$SNa 276.0301], 292.0048 [(M + K)$^+$, calcd. for C$_{11}$H$_{11}$NO$_4$SK 292.0040].
2.13.4 Synthesis of azomethine ylide precursor 395a

(E)-Ethyl 2-(benzylideneamino)acetate 395a

\[
\begin{array}{c}
\text{H}_2\text{N} & \text{CO}_2\text{Et} \cdot \text{HCl} \\
\text{231} & \text{Et}_3\text{N} \\
\text{Na}_2\text{SO}_4, \text{CH}_2\text{Cl}_2 \\
\end{array}
\rightarrow
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{395a} \\
\end{array}
\]

Prepared according to the procedure of Weng et al.\textsuperscript{319}

Triethylamine (2 mL, 14.33 mmol) was added slowly to a solution of glycine ethyl ester hydrochloride 398 (1 g, 7.16 mmol) and benzaldehyde 231 (730 μL, 7.16 mmol) in dichloromethane (16 mL) containing sodium sulfate (0.509g, 3.58 mmol). The suspension was allowed to stir at room temperature for 6.5 h, then filtered. The filtrate was concentrated under reduced pressure (water bath at ambient temperature) to give a white solid. The residue was partitioned between diethyl ether and water (1:1, 50 mL) and the aqueous layer discarded. The organic layer was washed with brine (20 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure (water bath at ambient temperature) to give the crude title compound 395a (1.166g, 85% crude) as a pale yellow oil that was used without further purification.

\(^1\)H-NMR (CDCl\textsubscript{3}, 400 MHz): δ 8.30 (s, 1H, H-2\textsuperscript{′}), 7.78 (m, 2H, H-4\textsuperscript{′}), 7.43 (m, 3H, H-5\textsuperscript{′}, H-6\textsuperscript{′}), 4.40 (d, 2H, J = 1.1 Hz, H-2), 4.24 (q, J = 7.2 Hz, 2H, CO\textsubscript{2}Et), 1.31 (t, J = 6.9 Hz, 3H, CO\textsubscript{2}Et).

Spectral data were in agreement with literature values.\textsuperscript{320}

2.13.5 Synthesis of donor-acceptor cyclopropane 411

Diethyl 2-benzylidenemalonate 410

\[
\begin{array}{c}
\text{EtO}_2\text{C} & \text{CO}_2\text{Et} \\
\text{409} & \text{231} \\
\text{cat. piperidine, benzoic acid, PhMe} \\
\text{reflux} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{EtO}_2\text{C} & \text{CO}_2\text{Et} \\
\text{410} \\
\end{array}
\]

Prepared according to the procedure of Wood et al.\textsuperscript{239}

Piperidine (125 μL, 1.25 mmol) was added to a solution of benzoic acid (0.095 g, 0.78 mmol), diethyl malonate 409 (4.75 mL, 31.22 mmol), and benzaldehyde 231 (3.5 mL, 34.34 mmol) in toluene (10 mL). The flask was fitted with a Dean-Stark trap and heated with stirring at reflux...
overnight. The mixture was cooled to room temperature and washed with water (2 x 15 mL), 1 M aq. HCl (2 x 15 mL), sat. aq. Na₂CO₃ (15 mL), dried over Na₂SO₄, and concentrated under reduced pressure to give the crude as an orange oil. The crude was purified via fractional vacuum distillation (10 Torr, 180-182 °C) to give the title compound 410 (3.762 g, 49%) as a colourless liquid.

\[^1\text{H-NMR (CDCl}_3, 300MHz): \delta 7.74 (s, 1H, H-2), 7.52 – 7.35 (m, 5H, Ph), 4.32 (m, 4H, 2 x CO₂Et), 1.31 (m, 6H, 2 x CO₂Et).\]

Spectral data were in agreement with literature values.\(^ {239} \)

**Diethyl 2-phenylcyclopropane-1,1-dicarboxylate 411**

Prepared according to the procedure of Wood et al.\(^ {239} \)

Trimethylsulfoxonium iodide (0.886 g, 4.03 mmol) was added in one portion to a suspension of sodium hydroxide (0.097 g, 4.03 mmol) in dimethylformamide (5 mL), and the mixture allowed to stir at room temperature for 20 min. A solution of diethyl benzylidenemalonate 410 (1 g, 4.03 mmol) in dimethylformamide (1.5 mL) was then added slowly and the mixture allowed to stir at room temperature overnight. The dark brown-orange mixture was poured onto ice:2 M aq. HCl (1:1 mixture, 20 mL) and stirred for 10 min. The mixture was extracted with diethyl ether (4 x 15 mL), and the combined organic extracts washed with water (4 x 70 mL), dried over Na₂SO₄, and concentrated under reduced pressure to give the crude as an orange-brown oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 7:93 as eluent) to give the title compound 411 (115 mg, 11%) as a pale yellow oil.

\[^1\text{H-NMR (CDCl}_3, 400MHz): \delta 7.28 – 7.19 (m, 5H, Ph), 4.24 (m, 2H, CO₂Et), 3.84 (q, 2H, J = 7.0 Hz, CO₂Et), 3.22 (t, 1H, J = 8.7 Hz, H-2), 2.17 (dd, 1H, J = 5.2, 8.0 Hz, H₅-3), 1.70 (dd, 1H, J = 5.3, 9.3 Hz, H₆-3), 1.29 (t, 3H, J = 7.1 Hz, CO₂Et), 0.86 (t, 3H, J = 7.3 Hz, CO₂Et).\]

Spectral data were in agreement with literature values.\(^ {239} \)
2.13.6 Synthesis of nitrone 421

(Z)-N-Benzylidene-1-phenylmethanamine oxide 421

\[
\begin{align*}
\text{Oxone, aq. } \text{Na}_2\text{EDTA, } \\
\text{NaHCO}_3 & \rightarrow \\
\text{MeCN/THF, } 5^\circ \text{C} & \rightarrow \\
\end{align*}
\]

Prepared according to the procedure of Figueredo et al.\(^{254}\)

Solid NaHCO\(_3\) (426 mg, 5.07 mmol) was added to a vigorously stirred solution of dibenzylamine 420 (195 µL, 1.01 mmol) and aq. Na\(_2\)EDTA (0.01 M, 1.5 mL) in acetonitrile:tetrahydrofuran (4:1, 5 mL), cooled in an ice bath. Oxone\(^{®}\) (654 mg, 2.13 mmol) was then added portionwise over 2 h. The suspension was allowed to stir for a further 40 min, then ethyl acetate (5 mL) and brine (10 mL) were added. The organic layer was removed, and the aqueous extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure to give the crude as a pale yellow oil that solidified to a white solid. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:4 as eluent) to give the title compound 421 (182 mg, 85%) as a white crystalline solid.

\(^1\)H-NMR (CDCl\(_3\), 300MHz): \(\delta\) 8.21 (m, 1H, H-1), 7.51 – 7.33 (m, 10 H, 2 x Ph), 5.06 (s, 2H, H-2\(^{\prime}\)).

Spectral data were in agreement with literature values.\(^{254}\)

2.13.7 Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with nitrone 421

\(N\)-(Cyclohexylsulfamoyl)-\(N,\)\(N\)-dibenzylamine 422

\[
\begin{align*}
\text{Et}_3\text{N, THF, } -78^\circ \text{C} & \rightarrow \\
\end{align*}
\]

Triethylamine (70 µL, 0.51 mmol) was added dropwise to a solution of \(N\)-cyclohexylsulfamoyl chloride 213a (100 mg, 0.51 mmol) in tetrahydrofuran (2 mL) at -78°C, followed immediately by a solution of (Z)-N-benzylidene-1-phenylmethanamine oxide 421 (107 mg, 0.51 mmol) in tetrahydrofuran (1.5 mL). The mixture was allowed to stir at this temperature for 5 min, then
allowed to warm to room temperature over 2 h. Water (3 mL) was added, and the mixture extracted with ethyl acetate (3 × 7 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, and the volatiles removed under reduced pressure to give the crude as a pale yellow solid. The crude was purified via flash column chromatography (silica gel, dry-load, ethyl acetate:hexanes 1:9 to 1:1 as eluent) to give the title compound 422 (36 mg, 20%) as white needles, m.p. 102 – 105 °C.

Rₓ (ethyl acetate:hexanes 3:7) = 0.64.

¹H-NMR (CDCl₃, 400MHz): δ 7.36 – 7.27 (m, 10H, H-3 to H-5), 4.30 (s, 4H, H-1), 4.02 (d, J = 8.0 Hz, N-H), 3.10 (m, 1H, H-1'), 1.89 – 1.07 (m, 10H, H-2’–H-4').

¹³C-NMR (CDCl₃, 100 MHz): δ 136.1 (2 x quat., C-2), 128.8 (2 x CH, C-5), 128.6 (4 x CH, C-4), 127.8 (4 x CH, C-3), 52.6 (CH, C-1'), 50.4 (2 x CH₂, C-1), 34.0 (2 x CH₂, C-2'), 25.2 (CH₂, C-4'), 24.8 (2 x CH₂, C-3').

IR (solid) cm⁻¹: 3280 (N–H), 2925 (=C–H), 2854 (C–H), 1440 (str, C=C), 1329 (str, O=S=O), 1303 (str), 1283 (str), 1237 (med), 1135 (str, O=S=O), 1084 (str), 1027 (str), 950 (str), 884 (str), 744 (str).

MS (ESI) m/z 359 [(M + H)⁺, 69%], 381 [(M + Na)⁺, 100%], 397 [(M + K)⁺, 2%]; HRMS (ESI) m/z 359.1781 [(M + H)⁺, calcd. for C₂₀H₂₇N₂O₂S 359.1788], 381.1596 [(M + Na)⁺, calcd. for C₂₀H₂₆N₂O₂SNa 381.1607], 397.1347 [(M + K)⁺, calcd. for C₂₀H₂₆N₂O₂SK 397.1347].

2.13.8 Synthesis of nitrile oxides

Mesitaldehyde oxime 299a

Prepared according to the procedure of Cummins et al.²⁹⁷

A solution of sodium hydroxide (0.378 g, 9.45 mmol) in distilled water (0.5 mL) was added to a solution of hydroxylamine hydrochloride (0.563 g, 8.10 mmol) in distilled water (2.5 mL) at ca. 5 °C (ice-water bath). Mesitaldehyde 450 (0.99 mL, 6.75 mmol) was then added slowly, forming a white solid. Ethanol (2 mL) was added, and the mixture allowed to stir at 5 °C for 1 h, then warmed to room temperature over 30 min. Distilled water (3 mL) was added, and the white solid removed via
vacuum filtration. The solids were washed with distilled water (2 x 5 mL) and hexanes (2 x 5 mL), and dried under vacuum to give the *title compound 451* (1.027 g, 93% crude) as a white solid that was used without further purification.

$^1$H-NMR (CDCl$_3$, 400MHz): $\delta$ 8.41 (s, 1H, N=CH), 7.90 (s, 1H, N-OH), 6.88 (s, 2H, m-CH), 2.38 (s, 6H, o-Me), 2.29 (s, 3H, p-Me).

Spectral data were in agreement with literature values.$^{321}$

**Mesitylhydroximinoyl chloride 448a**

Prepared according to the procedure of Howe *et al.*$^{296}$

$N$-Chlorosuccinimide (ca. 80 mg) was added to a solution of mesitaldehyde oxime 451 (1 g, 6.13 mmol) in dimethylformamide (5 mL) and allowed to stir at room temperature for 10 min. No temperature increase was noted, so gaseous HCl (1 mL, taken from headspace of conc. HCl bottle) was bubbled through the solution to initiate the reaction, which was then allowed to stir for an additional 10 min. The remainder of the $N$-chlorosuccinimide (ca. 738 mg, 6.13 mmol in total) was then added portionwise, keeping the temperature of the solution below 30 °C (cooled intermittently with an ice-water bath), and the resulting solution allowed to stir at room temperature for 2 h. The mixture was then poured into ice water (20 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL) and brine (20 mL), dried over MgSO$_4$, and concentrated under reduced pressure to give the crude *title compound 448a* (1.100 g, 91% crude) as a white solid that was used without further purification.

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 7.72 (s, 1H, N-OH), 6.89 (s, 2H, m-CH), 2.30 (s, 3H, p-Me), 2.28 (s, 6H, o-Me).

Spectral data were in agreement with literature values.$^{296}$
Benzaldehyde oxime 452

Prepared according to the procedure of Cummins et al.\textsuperscript{297}

A solution of sodium hydroxide (1.055 g, 26.39 mmol) in distilled water (3 mL) was added to a solution of hydroxylamine hydrochloride (1.572 g, 22.62 mmol) in distilled water (7 mL) at ca. 5 °C (ice-water bath). Benzaldehyde 231 (1.91 mL, 18.85 mmol) was then added slowly. Ethanol (2 mL) was added, and the mixture allowed to stir at 5 °C for 1 h, then warmed to room temperature over 30 min. The mixture was extracted with dichloromethane (4 x 20 mL) and the combined organic extracts were dried over MgSO\textsubscript{4} and concentrated under reduced pressure to give the crude title compound 452 (2.169 g, 95% crude) as a pale yellow liquid that was used without further purification.

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 9.60 (br s, 1H, N-OH), 8.18 (s, 1H, H-1), 7.57 (m, 2H, H-4), 7.36 (m, 3H, H-3, H-5).

Spectral data were in agreement with literature values.\textsuperscript{297}

\textbf{N-Hydroxybenzimidoyl chloride 448b}

Prepared according to the procedure of Bialecki et al.\textsuperscript{322}

\(N\)-Chlorosuccinimide (1.102 g, 8.25 mmol) was added slowly to a solution of benzaldehyde oxime 452 (1 g, 8.25 mmol) and pyridine (200 μL, 2.48 mmol) in dichloromethane (10 mL) at room temperature. The orange reaction mixture was allowed to stir at this temperature for 2 h, during which time the mixture became paler in colour. Water (10 mL) was added, and the organic layer removed. The organic extract was dried over MgSO\textsubscript{4} and concentrated under reduced pressure to give the crude title compound 448b (1.132 g, 88% crude) as a sticky orange solid that was used without further purification.

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.99 (s, 1H, N-OH), 7.84 (m, 2H, \(o\)-H), 7.44 (m, 3H, m, \(p\)-H).Spectral data were in agreement with literature values.\textsuperscript{323}
**N-Hydroxybenzamide 470**

Prepared according to the procedure of Defoin et al.\textsuperscript{306}

Benzoyl chloride 469 (0.83 mL, 7.11 mmol) was added dropwise to a stirred suspension of potassium carbonate (1.179 g, 8.53 mmol) and hydroxylamine hydrochloride (0.692 g, 9.96 mmol) in diethyl ether:water (50:1, 5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed \textit{via} vacuum filtration, and the solids suspended in hot ethyl acetate (ca. 10 mL), then filtered while hot. This process was repeated a further 3 times. The combined ethyl acetate filtrates were concentrated under reduced pressure to give the crude as a white solid. The crude was purified \textit{via} recrystallisation from hot ethyl acetate to give the \textit{title compound} 470 (281 mg, 29%) as white crystalline flakes.

\[ ^1H-NMR\ (CDCl_3, \ 400\ MHz) \delta\ \text{8.14 (br s, 2H, N-H, O-H), 7.68 – 7.63 (m, 2H, H-3), 7.50 – 7.47 (m, 3H, H-4, H-5).}\]

Spectral data were in agreement with literature values.\textsuperscript{324}

**N-(tert-Butyldiphenylsilyloxy)benzamide 449a**

Prepared according to the procedure of Carreira et al.\textsuperscript{294}

A solution of \textit{N-hydroxybenzamide} 470 (200 mg, 1.46 mmol) in tetrahydrofuran (2 mL) was added slowly to a stirred suspension of sodium hydride (74 mg, 3.06 mmol) in tetrahydrofuran (4 mL) at 0 °C, and the cloudy white mixture allowed to stir at this temperature for 7 min. \textit{tert}-Butyldiphenylchlorosilane (380 µL, 1.46 mmol) was then added dropwise, and the mixture allowed to stir at 0 °C for an additional 20 min. Glacial acetic acid (0.4 mL) was then added dropwise, and the mixture allowed to warm to room temperature. Water (7 mL) was added, and the mixture extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with water (15 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure to give the crude as a pale
orange sticky solid. The crude was purified via recrystallisation from diethyl ether/hexanes to give the title compound 449a (236 mg, 43%) as pale yellow needles.

\[ ^{1}H-NMR \text{ (CDCl}_3, 400 \text{ MHz}) \delta 7.85 - 7.72 \text{ (m, 6H, Ar-H), 7.45 - 7.28 \text{ (m, 9H, Ar-H), 1.21 \text{ (s, 9H, OTBDPS)}.} \]

Spectral data were in agreement with literature values.$^{294}$

2.13.9 **Attempted cycloaddition of N-cyclohexylsulfonylimine 202a with nitrile oxides**

**(Z)-N-(N-Cyclohexylsulfamoyloxy)benzimidoyl chloride 453**

\[
\begin{align*}
\text{448b} & \quad \text{Et}_3\text{N, THF} \\
\text{-40 °C} & \quad \text{453}
\end{align*}
\]

A solution of N-cyclohexylsulfamoyl chloride 213a (200 mg, 1.01 mmol) in tetrahydrofuran (1 mL) was added to a solution of N-hydroxybenzimidoyl chloride 448b (157 mg, 1.01 mmol) in tetrahydrofuran (2 mL) at -40 °C. Triethylamine (282 µL, 2.02 mmol) was then added dropwise, and the resulting yellow suspension allowed to stir at -40 °C for 2 h. The mixture was allowed to warm to room temperature and filtered. The solvent was removed under reduced pressure to give the crude as an orange-red oil. The crude was purified via flash column chromatography (silica gel, dichloromethane as eluent) to give the main fraction consisting of 4 components (as analysed via t.l.c.), as a pale yellow crystalline solid. This fraction was then resubjected to flash column chromatography (silica gel, dry-load, ethyl acetate:hexanes 1:9 as eluent) to give the title compound 453 (147 mg, 46%) as a white crystalline solid, m.p. 109 – 112 °C.

\[ R_f \text{ (ethyl acetate:hexanes 1:9) = 0.09.} \]

\[ ^{1}H-NMR \text{ (CDCl}_3, 400 \text{ MHz}) \delta 7.93 \text{ (m, 2H, H-3), 7.52 \text{ (m, 1H, H-5), 7.44 \text{ (m, 2H, H-4), 5.50 \text{ (d, 1H,} J = 7.9 \text{ Hz, N-H), 3.45 \text{ (m, 1H, H-1}), 1.97 – 1.09 \text{ (m, 10H, H-2'-H-4').}} \]

\[ ^{13}C-NMR \text{ (CDCl}_3, 100 \text{ MHz}) \delta 146.8 \text{ (quat., C-1), 132.2 \text{ (CH, C-5), 130.6 \text{ (quat., C-2), 128.6 \text{ (2 x CH, C-4), 127.9 (2 x CH, C-3), 54.1 (CH, C-1'), 33.2 (2 x CH}_2, \text{ C-2'), 24.9 (CH}_2, \text{ C-4'), 24.4 (2 x CH}_2, \text{ C-3').}} \]
IR (solid) cm⁻¹: 3300 (N–H), 2937 (C–H), 2863, 1596, 1568 (C=N), 1446 (str), 1380 (str, O=S=O), 1360, 1348, 1315, 1306, 1257 (str), 1242, 1198 (str), 1180 (str, O=S=O), 1147, 1069 (str, C-N), 1055, 1030, 1002, 976, 927, 899 (str), 840, 779 (str), 760 (str), 691 (str), 684 (str).

MS (ESI) m/z 339 [(M + Na)⁺, 100%], 341 [(M+2 + Na)⁺, 34%] ; HRMS (ESI) m/z 339.0542 [(M + Na)⁺, calcd. for C₁₃H₁₇N₂O₃S³⁺ClNa 339.0541], 341.0514 [(M+2 + Na)⁺, calcd. for C₁₃H₁₇N₂O₃S³⁺ClNa) 341.0511].
PART THREE

*Mukaiyama-Michael additions to chromones*
CHAPTER SEVEN

Introduction and background
3.1 Chromones and their derivatives as privileged scaffolds

Chromones 474 – also known as 4H-chromenones and 1-benzopyran-4-ones – and their derivatives are a common motif in natural products, consisting of a benzo-fused pyran-4-one ring structure (Figure 3.1.1). They are isomeric with the related benzopyrones, coumarins 475.

![Figure 3.1.1. Core structures of chromones 474, coumarins 475, flavanones 476, and chromanones 477.](image)

Chromones 474 have been shown to display a wide variety of biological activities. These compounds can be divided into two broad categories: the flavanones 476, where C-2 substitution is aromatic, and chromanones 477, where the substituents at C-2 are aliphatic.

3.1.1 C-2-aromatic chromanones: flavanones

Flavanones 476 are a subdivision of the much larger flavonoid family of secondary metabolites (Figure 3.1.2). In general, where the stereochemistry has been determined, the C-2 centre is assigned as the (S)-enantiomer.

![Figure 3.1.2. Flavanoid and flavanone core structures.](image)

Flavanones are produced by a wide variety of plant species, and as mentioned earlier, display a variety of biological activities. Some of the most well-known flavanones include naringenin 479 and hesperidin 480, dietary antioxidants commonly found in citrus fruit. As such,
flavanones and the related C-2 aliphatic chromanones are interesting targets for synthesis. Enantioselective methods for the synthesis of these compounds however are rare.

### 3.1.2 C-2-aliphatic chromanones

The corresponding C-2-aliphatic chromanones are less well represented in the literature. Some recently described examples of C-2 aliphatic chromanones are presented below (Figure 3.1.3):

![Figure 3.1.3.](image)

**Figure 3.1.3.** Naturally occurring biologically active C-2 aliphatic chromanones 481 – 487, and synthetic 2-vinyl chromanones 488.

A rather complex example of a naturally occurring, biologically active C-2 aliphatic substituted chromanone is sanggenon C 481, isolated from the root bark of the white mulberry (*Morus alba*), which exhibits antitumour activity. Structurally simpler fungal metabolites phomochromones A 482 and B 483 have also shown good antibacterial, antifungal, and algicidal activity against a range of organisms. Also of interest are the aposphaerins A – C 484 – 486. Isolated from the fungi *Aposphaeria* sp. and *Paraphaeosphaeria quadrispata*, the family all contain a 2-pent-1′-enyl sidechain. The C-2 stereocentre is undefined in each case, presumably due to non-enzymatic ring-closure of the dihydropyranone. No bioactivity for these compounds has been reported to date. However the related 2-prop-1′-enyl chromanone 487, isolated from the deep sea fungus *Aspergillus*
*sydowi* YH11-2, displays antitumor activity in the low micromolar range, while its enantiomer is inactive.\(^{341}\) In addition, the synthetic 2-vinyl chromanones 488, with shorter C-2 alkyl chains, have also been shown to exhibit antimicrobial activity.\(^{329,342}\)

### 3.1.3 2-γ-butyrolactone substituted chromanones

Of particular interest in our research group are methods for the stereoselective synthesis of 2-γ-butyrolactone chromanones 489 that contain a quaternary stereogenic centre at the C-2 position. This family of chromanones is based on the core structure 489, which is present in a number of natural products (Figure 3.1.4).

*Figure 3.1.4. Monomeric naturally occurring 2-γ-butyrolactone substituted chromanones.*

Isolated from a species of the endophytic fungus *Microdiplodia*, microdiplodiasone 490 exhibited weak inhibitory activity against *Legionella pneumophila*;\(^{343}\) the lachnones 491 – 493, however, were inactive in antifungal, antimalarial, and cytotoxicity assays.\(^{344}\)
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Gonytolide C\textsuperscript{494,345} paecilin B\textsuperscript{495,346} and the blennolides D-F\textsuperscript{496 – 498,347} are all monomers of bioactive dimers; the monomers themselves have not been shown to exhibit biological activity.

Additionally, a number of dimeric 2-\(\gamma\)-butyrolactone chromanones have been isolated from a variety of sources (Figure 3.1.5).

![Chemical structures](image)

**Figure 3.1.5.** Homodimeric naturally occurring 2-\(\gamma\)-butyrolactone substituted chromanones.

Paecilin A\textsuperscript{499}, like the monomer paecilin B\textsuperscript{495}, has undefined stereochemistry and was inactive in the KB cell cytotoxicity assay.\textsuperscript{346} Related homodimer phomopsis-H76 A\textsuperscript{500} also possesses a C-2 quaternary centre in addition to a methyl substituent at the 3-position of the \(\gamma\)-butyrolactone, differing from paecilin A in the oxidation level of the 2-hydroxymethyl substituent and a 2,2'-biaryl linkage rather than the 2,4’-linkage in paecilin A.\textsuperscript{348} Though phomopsis-H76 A showed promising activity in preliminary biological evaluations,\textsuperscript{500} it was found to be inactive upon subsequent antimicrobial and cytotoxicity testing.

The monodictyochrome and gonytolide dimers, isolated from the marine algicolous fungus *Monodictys putredinis* and the fungal species *Gonytrichum*, respectively, are also formed from monomeric units that differ in their biaryl connectivity.\textsuperscript{345,349} Monodictyochrome A\textsuperscript{501} and its C-2 – C-2’ congener monodictyochrome B were examined for chemopreventative activity and were found to have moderate activity. Gonytolides A-C were assessed for potential promotion of innate immune activity; of the three, only gonytolide A\textsuperscript{502} showed activity in the assays examined.
Additionally, several heterodimers have been isolated from fungal fermentations (Figure 3.1.6).

**Figure 3.1.6.** Heterodimeric naturally occurring 2-γ-butyrolactone substituted chromanones.

Noduliprevenone 503 possesses the same framework as gonytolide B; however the γ-butyrolactone of one monomeric unit is ring opened to give an ester sidechain. Blennolide G 504 is comprised of the blennolide A and E monomers, connected by a 2,6′-biaryl linkage. The xanthoquinodins 505 and 506 have been shown to exhibit antibacterial activity against selected Gram-positive bacteria.

All these natural products possess a γ-butyrolactone at C-2 of the chromanone core; one can imagine the synthesis of this kind of scaffold via conjugate addition of a butenolide equivalent to an appropriately substituted chromone (Figure 3.1.7). Thus we are interested in methods for the stereoselective introduction of a substituent at C-2 of chromones.

**Figure 3.1.7.** General scheme for the synthesis of 2-γ-butyrolactone chromanones 507 via conjugate addition of 291 to chromone 505.
3.2 Synthetic methods for the asymmetric synthesis of 2-substituted chromanones

Methods for the asymmetric synthesis of flavanones are relatively rare; methods to prepare their C-2 aliphatic counterparts are even rarer. Methods for asymmetric control at this centre in chromanones have sparsely been reported on in the literature, with procedures mainly focussing on the use of lower order cuprates to effect stereoselective synthesis. The principal strategies for the asymmetric synthesis of chromanones fall into two categories: intramolecular oxa-Michael cyclisation of phenols promoted by chiral catalysts, and intermolecular asymmetric conjugate additions to chromones (Figure 3.2.1).

![Figure 3.2.1. Literature methods for the stereoselective synthesis of 2-substituted chromanones 474.](image)

3.2.1 Asymmetric intramolecular oxa-Michael addition

The first example of an asymmetric intramolecular oxa-Michael addition to construct a chromanone was reported in 1999 by Ishikawa et al en route to the synthesis of inophyllums A and E (Scheme 3.2.1). A number of chiral amines were screened as catalysts; the most successful of these was quinine, affording cis chromanone 512 preferentially in excellent enantiomeric excess.

![Scheme 3.2.1. Reagents and conditions: a) 2 eq. 513, PhCl, 4 °C, 23 h, yields as shown.](image)

The first catalytic version of an intramolecular conjugate addition was reported by Scheidt et al as part of their synthetic efforts towards a catalytic enantioselective synthesis of flavanones (Scheme 232 | Page)
The reaction was based upon an asymmetric intramolecular conjugate addition of alkylidene esters 508a. Incorporation of a tert-butyl ester substituent on the Michael acceptor increased the reactivity of the Michael acceptor and provided a second potential site for association with the catalyst. The conjugate addition was catalysed by quinine-derived thiourea 514. The undesired C-3 tert-butyl sidechain then underwent decarboxylation upon treatment with p-toluenesulfonic acid, affording the C-2 chiral chromanones 509 with good to excellent stereocontrol and yield (Scheme 3.2.2).

Scheme 3.2.2. Reagents and conditions: a) either: (i) 10 mol% 514, PhMe, -25 °C, 24 – 120 h; or (ii) 5 mol% 515/Ni(Tfâac)c(H2O, PhOMe, 30 °C, 12 - 24 h; b) p-TsOH, PhMe, 80 °C, 2 – 50 h, Scheidt et al: 65 – 97 % over 2 steps; Feng et al 90 – 99% over 2 steps.

Similarly, Feng et al have reported the use of an N,N'-dioxide nickel(II) complex 515 for the asymmetric intramolecular oxa-Michael addition to give chromanones 509 (Scheme 3.2.2). They also used the tert-butyl ester group to enhance the reactivity of the Michael acceptor, and the reaction, under the influence of 515, provided the flavanones 509 in excellent yield with good enantioselectivity.

Alternatively, the opposite enantiomer was obtained using catalysts 516 and 517, as found by Zhao and ShuLi et al respectively (Scheme 3.2.3). The former researchers incorporated a single alkyl rather than an aryl substituent, which required a three-fold increase in reaction time to obtain the resulting chromanone in high yield; however the N-triflyl phosphoramidate system 517 has only been used to effect the asymmetric synthesis of flavanones.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Scheme 3.2.3. Reagents and conditions: a) either: (i) 20 mol% 516, PhCF₃, r.t., 1 h; or (ii) 10 mol% 517, CCl₄, 60 °C; b) p-TsOH, PhMe, 80 °C, 2 h, Zhao et al 85 – >99% over 2 steps; ShuLi et al 82 – 95% over 2 steps.

Zhao and coworkers have also used the Cinchona-based catalyst 519 to effect a tandem intramolecular oxa-Michael/electrophilic fluorination reaction of phenols 508b (Scheme 3.2.4).³⁵⁵

Scheme 3.2.4. Reagents and conditions: a) 15 mol% 519, PhMe, r.t., 12 – 72 h; b) Na₂CO₃, NFSI, PhMe, r.t., 6 – 12 h, R = alkyl, 86 – 93%, R = aryl, 89 – 99 %. NFSI = N-fluorobenzenesulfonimide.

Chromanones 509, where R was an aryl group were generally obtained in excellent yield and enantioselectivity; when the R group was an ethyl group however, 509 was obtained in low enantiomeric excess, presumably due to more conformational flexibility in the transition state.

This asymmetric oxa-Michael approach has generally only been used to construct 2-aryl substituted flavanones in enantioenriched form; the few examples where substitution at C-2 is alkyl proceeded with much lower enantioselectivity, in addition to requiring longer reaction time to achieve higher conversions.
3.2.2 Asymmetric 1,4-additions to chromones

One of the earliest reports of asymmetric 1,4-additions to chromones came from the laboratory of Wallace and coworkers (Scheme 3.2.5). Use of a chiral sulfoxide auxiliary at the 3-position of the chromone (i.e. 520) both activated the Michael acceptor towards conjugate addition, and promoted asymmetric addition of a cuprate reagent.

A mixture of diastereomers was obtained however, and the relative ratio was not reported. This was rectified in a later paper where it was established that the trans-(2S)-chromanone 521b predominated. The sulfoxide could subsequently be removed by treatment with zinc and ammonium chloride to afford the chromanone 522 in high yield.

Hoyveda et al have reported the copper(II)-catalysed asymmetric conjugate addition of dialkylzinc reagents to unsaturated furanones and pyranones (Scheme 3.2.6). Asymmetry is induced in these reactions through the use of a chiral amino acid-derived phosphane ligand 524. Among the many examples investigated, the conjugate addition to chromone 474 is reported. The initial conjugate addition is performed in the presence of ligand 524, and the resulting enolate is trapped with benzaldehyde to give 523. The undesired C-3 substituent is then removed via a retro-aldol reaction. The C-2 ethyl- and isopropyl-chromanones 509 were obtained in high yield with excellent enantioselectivity.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Scheme 3.2.6. Reagents and conditions: a) 10 mol% 524, 4 mol% Cu(OTf)$_2$·PhH, [R$_2$Zn], PhCHO, PhMe, -30 °C, 24 h, yields as given; b) K$_2$CO$_3$, PhMe, 120 °C, 1 h, R = Et, 92%, R = i-Pr, 84%.

Recently, Liao et al have reported a rhodium-catalysed 1,4-addition of tetraarylborates to chromones 474 (Scheme 3.2.7).$^{359}$

Scheme 3.2.7. Reagents and conditions: a) 5 mol% [Rh(C$_2$H$_4$)$_2$Cl]$_2$/525, Ar$_4$BNa, CH$_2$Cl$_2$/H$_2$O (15:1), 40 °C, 24 h, 25 – 75% yield.

When treated with the rhodium-525 complex, flavanones 476a were obtained in moderate yield and excellent enantioselectivity. The relatively low yields reflect the reduced reactivity of the tetraarylborate in comparison to arylboronic acids. This has, however, been improved upon by the work of Korenaga and Sakai et al, in which Rh(II) based catalyst 526 was used with boronic acids to provide the flavanones 476b in high yield and excellent enantioselectivity (Scheme 3.2.8).$^{360}$
Like the intramolecular conjugate additions, these intermolecular conjugate additions to chromones have mainly been applied to the synthesis of flavanones, rather than the C-2 alkyl chromanones. In addition, the aliphatic substituents have been limited to simple lower order alkyl chains that lacked synthetic handles for future elaboration.
3.3 Conjugate addition of silyl enol ethers and silyl ketene acetals to chromones

The conjugate addition of silyl enol ethers and silyl ketene acetals to chromones has only been reported intermittently in the literature.

Akiba and coworkers described the addition of a range of nucleophiles to chromones based on the activation of the chromone as a benzopyrylium salt. The salt is generated by heating the chromone with neat tert-butyldimethylsilyl triflate (TBSOTf) at 80 °C for 1 h, and the resulting benzopyrylium salt was then reacted with a variety of nucleophiles (Figure 3.3.1).

Activated methylene compounds react with the benzopyrylium salt in the presence of 2,6-lutidine to give compounds of type and ; however when the nucleophile contained two strongly electron withdrawing groups, no products were obtained.

Similarly, reaction of the benzopyrylium salt with silyl enol ethers , again in the presence of 2,6-lutidine, afforded the C2-substituted silyl enol ethers in high to excellent yield (70 – 98%). These compounds could either be hydrolysed to their respective chromones by addition of acid, or reacted further with nucleophiles to give 2,3-disubstituted chromones.

The benzopyrylium salts also reacted with 3-(trimethylsilyl)-1-butene to give the tricyclic products, rather than the expected allylation product. Other annulation reactions were possible, either through double Michael addition reactions with a variety of unsaturated ketones, or [4+2] cycloaddition with butadienes.

Importantly, the authors found that addition of 2,6-lutidine to the reaction mixtures was essential to minimise side reactions; omission of the base resulted in very complex mixtures.
The conjugate addition of silyloxydienes 541 to chromones has also been examined by Langer and coworkers.\textsuperscript{363} Using the same benzopyrylium activation strategy, a variety of silyloxydienes 541 were added to chromone 474 giving the β-keto ester substituted chromanones 542 (Scheme 3.3.1).

\textbf{Scheme 3.3.1. Reagents and conditions:} a) TMSOTf, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C; b) (i) 541, 2,6-lutidine, CH\textsubscript{2}Cl\textsubscript{2}, 20 → 0 °C, 12 h; (ii) 10\% aq. HCl, 56 – 75\% over 3 steps.
Most recently, Porco et al have described the racemic conjugate addition of the masked butenolide equivalent 2-trimethylsiloxyfuran 291 to 5-hydroxychromones 543 (Scheme 3.3.2). Similar to the work of Akiba et al, the authors utilised the reactivity of siloxybenzopyrylium species 545, derived from the reaction of chromone 543 with diisopropylsilyl ditriflate 544. Consequent addition of 2-trimethylsiloxyfuran 291 to the salt at reduced temperature, followed by desilylation and reduction of the butenolide double bond afforded the 2-substituted γ-butyrolactone chromanone 546 in good yield. Again, the conjugate addition was not stereoselective, and afforded 546 as a 15:1 mixture of racemic diastereomers.

![Scheme 3.3.2. Reagents and conditions: a) 544, 2,6-lutidine, CH₂Cl₂, r.t., 0.5 h; b) 291, CH₂Cl₂, -78 °C, 1 h; c) Et₃N·3HF, CH₂Cl₂, -78 °C, 0.5 h, 93% over 3 steps d.r. 15:1; d) NiCl₂·6H₂O, NaBH₄, THF/MeOH, 0 °C, 10 min, 86%.](image)

An example of an asymmetric conjugate addition of 533 or 291 to chromones, however, has not been reported to date.
3.4 Aims

The aim of the present work is to investigate the asymmetric conjugate addition of silyl enol ethers and silyl ketene acetals to chromones. It is envisaged that asymmetry will be induced through the use of a chiral copper(II) catalyst of type 548 (Figure 3.4.1).

![Proposed method for asymmetric addition of silyl enol ethers and silyl ketene acetals to chromones](image)

Figure 3.4.1. Proposed method for asymmetric addition of silyl enol ethers and silyl ketene acetals 550 to chromones 547.

In order to establish the reactivity profile of the addition of silyl enol ethers/silyl ketene acetals to chromones, the addition of 550a in the absence of a chiral catalyst will serve as a starting point for this study (Figure 3.4.2).
Five avenues of further investigation will be pursued (Figure 3.4.3):

I. Firstly, the effect of substitution on the chromone ring will be examined. Electron-withdrawing substituents at C-3 should activate the chromone towards nucleophilic addition via the mesomeric effect. Substitution at C-2 should present a steric challenge for incoming nucleophiles; this effect, and whether it can be ameliorated through C-3 activation will also be examined. A number of chromones 547 will be synthesised in order to investigate these effects (Figure 3.4.3).

II. Next, the choice of Lewis acid will be investigated – is TMSOTf the optimal Lewis acid for the transformation, or will other metal ions, such as copper(II), catalyse the addition of 550a?

III. The reactivity of the nucleophile will also be examined – is silyl enol ether 550a sufficiently reactive to add to chromones 547? Can the yields be improved by using more reactive silyl ketene acetal 550b?
Once the reactivity pattern has been established in the absence of a chiral catalyst, we will examine the proposed chiral Lewis acid-catalysed conjugate addition of 550 with chromones 547. The parameters to be investigated are as follows (Figure 3.4.4):

I. The effect of different BOX-type ligands 555 – 558 will be examined – does one ligand confer superior enantioselectivity?

II. The effect of a second potential binding site for the catalyst will also be investigated – will asymmetric additions with, for example, 3-acetylchromone 547a result in higher enantioselectivity?
Figure 3.4.4. Proposed plan for investigation of the asymmetric conjugate addition of silyl enol ethers and silyl ketene acetals to chromones.
3.5 Methodology

The conjugate addition of silyl enol ethers and silyl ketene acetals to chromones has been partially investigated by Akiba et al., Langer et al., and Porco et al., as summarised in section 3.3 above.\textsuperscript{361-364} These studies, however, lack a systematic exploration of the steric and electronic factors that influence the yield of the adducts obtained.

Furthermore, a catalytic asymmetric variant of these additions has yet to be developed. Our proposed asymmetric catalytic method is based on the seminal work of Katsuki and Kitajima (Figure 3.5.1).\textsuperscript{365} Use of BOX-catalyst 562 in the Mukaiyama-Michael addition of TMS-furan derivative 559 to \( \alpha,\beta \)-unsaturated amide 560 gave the desired butenolide 561 in high yield and stereoselectivity. Later, Desimoni et al. also found that the PyBOX-derived catalyst 563 was also effective in achieving this transformation.\textsuperscript{366}

![Figure 3.5.1. Bis(oxazoline) catalysts used in the enantioselective Mukaiyama-Michael addition of TMS-furan derivatives 559 to an \( \alpha,\beta \)-unsaturated amide 560. \textsuperscript{365,366}](image)

Bernardi and coworkers had earlier reported the BOX-promoted Mukaiyama-Michael addition of silyl ketene acetals to activated cyclopentenones (Figure 3.5.2).\textsuperscript{367} The yields of adducts 566 obtained were low – the example shown represents the best result from the study, and required the use of a stoichiometric quantity of the Lewis acid. The enantioselectivity, likewise, was modest. A small increase (60 to 65\%) in enantiomeric excess could be achieved by decreasing the amount of Lewis acid used to 20 mol\%; however this drastically reduced the yield of 556 obtained.
Evans et al have also published the use of BOX catalyst 571 for the enantioselective conjugate addition of silyl ketene acetal 569 to alkylidene malonates 568 (Figure 3.5.3). A range of R groups were compatible, and use of 10 mol% of catalyst 571 provided the products 570 generally in high yield and enantioselectivity. Thus, there is literature precedence for bis(oxazoline) complex-catalysed Mukaiyama-Michael addition of silyl enol ethers and silyl ketene acetals to α,β-unsaturated ketones. The analogous reaction using chromones as the Michael acceptor will therefore be investigated in the present work.
CHAPTER EIGHT

Discussion
3.6 Synthesis of Chromones

Chromones substituted in a variety of positions were required to investigate their conjugate addition with silyl enol ether 550a and silyl ketene acetal 550b. The naturally occurring chromanones 490 – 506 contain substitution on both the aromatic ring (e.g. 5-hydroxyl) and the dihydropyranone (e.g. 2-methyl, figure 3.1.4). Hence, chromones 474 and 547a-b – 547e-f were synthesised to examine what effects these substituents may have. Fortuitously, 2-methylchromone 547d and the 5-methoxychromones 547c and 547g had been synthesised as part of an earlier study within our group and were already on hand.

![Figure 3.6.1. Chromones required for study of conjugate additions.](image)

3.6.1 Synthesis of unsubstituted chromone 474

The synthesis of chromones has received considerable attention in the literature, and a review was published recently detailing methods for their construction. We decided on a Kostanecki-Robinson acylation strategy for the construction of our desired chromones 547. Usually, Kostanecki acylation involves the use of an aliphatic anhydride for acylation of o-hydroxyaryl ketones, followed by cyclisation. However, this results in 2-substituted chromones, which does not provide access to 3-acetylchromone 547a. Instead, use of acetic formic anhydride allows the synthesis of 2-unsubstituted chromones (Figure 3.6.2).
Synthesis of the required diketo compounds 572, however, had earlier been found to be more complex than literature accounts would suggest (Scheme 3.6.1). Attempts to synthesise 572 via Baker-Venkataraman rearrangement of the ester 575 were unsuccessful. Under the conditions evaluated, hydrolysis of the ester rather than rearrangement took place. After extensive experimentation, however, it was found that diketone 572 could be synthesised in good yield via Claisen condensation of 2'-hydroxyacetophenone 574, according to the procedure of Patonay et al.

Scheme 3.6.1. Reagents and conditions: a) Ac₂O, DMAP, Et₃N, r.t., 16 h, 93%; b) base, see ref. 370 for details; c) NaH, EtOAc, THF, 5 min, r.t., 78%.

The remainder of the desired chromones 547a-b and 547e-f are also available from the common precursor, 2'-hydroxyacetophenone 574 (Schemes 3.6.2, 3.6.3, and 3.6.5). A one-pot procedure...
whereby condensation of 574 with ethyl formate in the presence of sodium hydride, followed by cyclisation of the resultant dicarbonyl compound 576 and subsequent dehydration using concentrated hydrochloric acid, gave rise to unsubstituted chromone 474.

Scheme 3.6.2. Reagents and conditions: a) HCO₂Et, NaH, 0 °C, 3.5 h; b) conc. HCl, r.t., 18 h, 92% over two steps.

Formation of the desired chromone 474 was confirmed by comparison of the ¹H-NMR data with the reported literature values. Characteristic resonances for chromone 474 were the doublets at δ 6.35 and 7.85 with a vicinal coupling constant of 6.0 Hz, assigned to protons H-3 and H-2, respectively.

### 3.6.2 Synthesis of C-3 substituted chromones 547a-b and 547e-f

The effect of an electron-withdrawing group at the 3-position of the chromone had previously been investigated by our group in the copper(II)-catalysed conjugate addition of 2-(trimethylsilyloxy)furan 291 with 3-acetylchromone 547a (Figure 3.6.3). The yield of adduct 578, compared to the product 577 resulting from addition of 291 to unsubstituted chromone 474, improved from 3% to 48%.

Figure 3.6.3. Effect of electron-withdrawing substituents at the 3-position of chromones in copper(II)-catalysed conjugate additions.

We also wished to examine this effect in our study. Consequently, attention turned to synthesis of 3-acetylchromones 547a and 547e via Kostanecki-Robinson acylation of the β-keto ester 572 (Scheme 3.6.3).

Accordingly, 547a and 547e were synthesised from diketone 572, itself available from 2′-hydroxyacetophenone 574. Once again, 572 was readily available within our research group.
Treatment of diketone 572 with acetic formic anhydride 573 in the presence of sodium formate at room temperature afforded 3-acetylchromone 547a, while use of acetic anhydride in the presence of sodium acetate under reflux provided its 2-methyl analogue 547e.

Additionally, earlier reports by Wallace et al.\textsuperscript{373} and later by Scheidt et al.\textsuperscript{351} demonstrated that ester substituents at C-3 on chromanones could be removed by simple decarboxylation under mildly acidic conditions. Thus, it was reasoned that an ester substituent at the 3-position would increase the reactivity of the Michael acceptor, which could subsequently be removed.

Synthesis of 3-(\textit{tert}-butoxycarbonyl)chromone 547b was first attempted via the acid chloride 582 (Scheme 3.6.4). Reaction of 2'-hydroxyacetophenone 574 with excess Vilsmeier reagent at 50 °C furnished 3-formylchromone 580 in good yield.\textsuperscript{374} Pinnick oxidation of the aldehyde with a biphasic mixture of sodium chlorite and sulfamic acid in dichloromethane/water provided the acid 581, in moderate yield.\textsuperscript{375} Addition of oxalyl chloride, and subsequent treatment of the resulting acid chloride with \textit{tert}-butanol and triethylamine in dichloromethane overnight unfortunately did not result in formation of the desired \textit{tert}-butyl ester 547b. Instead, analysis of the \textsuperscript{1}H-NMR spectrum of the bright yellow solid product obtained indicated the absence of the desired \textit{tert}-butyl group.
Scheme 3.6.4. Reagents and conditions: a) DMF, POCl₃, 50 °C, 4 h, 63%; b) NaClO₂, NH₄SO₃H, CH₂Cl₂/H₂O, 0 °C, 1 h, 50%; c) (COCl)₂, CH₂Cl₂, r.t., 5 h; then t-BuOH, Et₃N, CH₂Cl₂, r.t., 18 h.

An alternative synthesis of chromone 547b involved initial synthesis of β-keto ester 583 (Scheme 3.6.5). Formation of the enolate with lithium bis(trimethylsilyl)amide at -78 °C, followed by addition of a solution of Boc-anhydride afforded 583 in good yield. Treatment of 583 with acetic formic anhydride 573 (2.5 equivalents, prepared by reaction of acetyl chloride with sodium formate) at room temperature in the presence of sodium formate, followed by an additional aliquot of 573 afforded the desired chromone 547b in 55% yield after 4 h.

Scheme 3.6.5. Reagents and conditions: a) LiHMDS, THF, -78 °C, 2 h; then Boc₂O, THF, -78 °C to r.t., 18 h, 79%; b) 573, HCO₂Na, THF, r.t., 52 h, 55%.

The novel chromone 547b was obtained in moderate yield as white flaky crystals, and its structure confirmed by the molecular ion m/z 269.0778 in the high resolution mass spectrum, corresponding to the molecular formula of C₁₄H₁₄O₄Na. The ¹H-NMR spectrum exhibited five aromatic protons including a singlet at δ 8.58, corresponding to the newly installed H-2 proton and a nine proton singlet at δ 1.60, assigned to the tert-butyl ester.

Synthesis of the 2-methyl-3-(tert-butoxycarbonyl)chromone 547f was expected to be much more difficult. Work by Klutchko and Charlton et al had previously shown that the presence of an ester at C-3 made the cyclisation step less effective, the effect worsening as the size of the ester group increased. In addition, the basic conditions used may effect rearrangement to 3-acyl-4-hydroxycoumarins.
Nevertheless, it was decided to attempt simple cyclisation of 583 under the same conditions as used for the 3-acetyl derivative 547a, as the materials required were already at hand. Thus, a suspension of β-keto ester 583 and sodium acetate in acetic anhydride was heated at 110 °C for 3 h (Scheme 3.6.6). After workup and purification *via* flash column chromatography, 547f was obtained as white crystalline needles in 22% yield.

**Scheme 3.6.6. Reagents and conditions:** a) Ac₂O, NaOAc, 110 °C, 3 h, 22 %.
3.7 Model additions of silyl enol ethers to chromones

3.7.1 Synthesis of silyl enol ether 550a

The acetophenone-derived silyl enol ether 550a was first selected to study model conjugate additions of silyl enol ethers to chromones. Initially, synthesis of silyl enol ether 550a was attempted using \textit{in situ}-generated trimethylsilyl iodide to trap the enol generated by treatment of acetophenone 584 with triethylamine (Table 3.7.1).\textsuperscript{379}

![Diagram of silyl enol ether addition to chromone]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Workup</th>
<th>Results\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et\textsubscript{3}N, TMSCl, NaI, MeCN, r.t., 1 h</td>
<td>Dilution with pentane; wash of cold organic layer with ice-water.</td>
<td>Exotherm; 584 only present</td>
</tr>
<tr>
<td>2</td>
<td>Et\textsubscript{3}N, TMSCl, NaI, MeCN, r.t., 1.5 h</td>
<td>Dilution with pentane; filtration of crude mixture and distillation of filtrate at 34 Torr.</td>
<td>Black tar formation; no product present</td>
</tr>
<tr>
<td>3</td>
<td>LDA, THF, -78 °C, 1 h; then TMSCl, THF, -78 °C to r.t., 2 h</td>
<td>Dilution with pentane; filtration of crude mixture and distillation of filtrate at 20 Torr.</td>
<td>Product present in crude material; destroyed during attempted purification via fractional distillation</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS, THF, r.t., 20 min; then TMSCl, THF, r.t., 1.5 h</td>
<td>Concentration under reduced pressure; dilution with pentane; filtration and concentration under reduced pressure.</td>
<td>Product major component of crude material (90%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} As determined by \textsuperscript{1}H-NMR spectroscopy.

\textbf{Table 3.7.1.} Conditions evaluated for the synthesis of silyl enol ether 550a.
While the $^1$H-NMR spectrum of the crude reaction mixture indicated successful formation of 550a, separation of the silyl enol ether from the byproducts of the reaction mixture proved problematic. Aqueous workup to remove the byproducts was detrimental, causing an exothermic reaction in the organic phase – presumably due to hydrolysis of unreacted iodotrimethylsilane – and returning only acetophenone. Attempts to directly distill the desired silyl enol ether from the filtered reaction mixture resulted in formation of a black tar and only a small quantities of acetophenone were recovered.

Alternative methods were therefore sought that did not require the use of iodotrimethylsilane as the trapping reagent. Formation of the enol with LDA, followed by quenching with chlorotrimethylsilane was also attempted. Again, $^1$H-NMR analysis of the crude mixture revealed the desired product was present; however, distillation of the silyl enol ether 550a from the crude mixture proved difficult, returning only acetophenone and diisopropylamine. It was therefore decided that a method requiring minimal manipulation of the crude material to provide sufficiently pure silyl enol ether 550a was desired.

Thus, treatment of acetophenone 584 with a tetrahydrofuran solution of lithium bis(trimethylsilyl)amide, and subsequent trapping of the enolate with a solution of chlorotrimethylsilane in THF afforded crude silyl enol ether 550a in good yield. Attempts to purify crude 550a via fractional distillation under reduced pressure were unsuccessful; the crude material, however, was judged sufficiently pure to carry out the subsequent conjugate addition.

### 3.7.2 Addition of 550a to chromone 474

With crude silyl enol ether 550a in hand, attention turned to its use in conjugate additions to chromones. Work published by Akiba et al in the late 80’s/early 90’s had found it necessary to generate the benzoxopyrylium salt 528 in advance by heating the chromone 474 in neat TBSOTf, followed by addition of 584 at room temperature. Interestingly, the subsequent addition of silyl enol ethers, in particular, required addition of 2,6-lutidine to the reaction mixture in order to avoid formation of complex mixtures. However, the authors also found that addition of the TBS enol ether of 584, generated in situ, successfully provided the chromanone 553a in high yield (Scheme 3.7.1).
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Scheme 3.7.1. Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH₂Cl₂, r.t., 82%.

Furthermore, previous work within our research group studying the use of 2-(trimethylsilyloxy)furan 291 in reactions with chromones had found that use of strongly Lewis acidic TMSOTf in slight excess was required to effect the desired transformation (Scheme 3.7.2). A twofold excess of silyl enol ether was also required to provide the adducts 506 in good yield.

Scheme 3.7.2. Reagents and conditions: a) 1.1. eq. TMSOTf, 2.2 eq. 291, CH₂Cl₂, -78 °C, 1 h, 76 – 77%.

In order to establish the best possible reaction conditions for the addition of silyl enol ether 550a to chromone 474, a variety of parameters were investigated (Table 3.7.2).
**Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones**

Table 3.7.2. Investigation of the parameters for the addition of silyl enol ether 550a to unsubstituted chromone 474.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. TMSOTf</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temperature (°C)</th>
<th>Activation (min)</th>
<th>Time (h)</th>
<th>Yield 553a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>-78 to r.t.</td>
<td>10</td>
<td>1.5</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>THF</td>
<td>2,6-lutidine</td>
<td>-78 to r.t.</td>
<td>15</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>r.t.</td>
<td>10</td>
<td>4</td>
<td>25b</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>MeCN</td>
<td>-</td>
<td>r.t.</td>
<td>10</td>
<td>4</td>
<td>4b</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>MeCN</td>
<td>-</td>
<td>-20</td>
<td>15</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>-40</td>
<td>15</td>
<td>3.5</td>
<td>15b</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>-40</td>
<td>30</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>-40</td>
<td>60</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>0.5</td>
<td>THF</td>
<td>-</td>
<td>-40</td>
<td>15</td>
<td>4</td>
<td>11b</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>THF</td>
<td>-</td>
<td>-40</td>
<td>30</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>r.t.</td>
<td>0c</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

a The length of time the Lewis acid was allowed to stir with chromone 474.

b Impure – contains acetophenone

c Lewis acid added to a mixture of silyl enol ether 550a and chromone 474.

Initially, the reaction conditions established from earlier work within our group were used to effect the conjugate addition of silyl enol ether 550a to chromone 474. Thus, a solution of chromone 474 in tetrahydrofuran at -78 °C was treated with TMSOTf, and the mixture stirred for 10 min prior to addition of a solution of silyl enol ether 550a in THF. The mixture was stirred at reduced temperature for 1.5 h, then allowed to warm to room temperature. Subsequent workup and purification afforded known chromanone 553a in 26% yield. The structure was confirmed by comparison of its ¹H- and ¹³C-NMR data with literature values.

Encouraged by our initial success, we next attempted to increase the yield of 553a obtained from the reaction. T.l.c. analysis of the crude reaction mixture revealed the presence of three components –
the product 553a, acetophenone derived from the hydrolysis of 550a, and unreacted chromone 474. Akiba et al reported that addition of 2,6-lutidine to the reaction mixture was essential to reduce the complexity of the reaction mixture and increase the yield of the chromanone products. In our case, addition of 2,6-lutidine under the same conditions afforded none of the desired product 553a (entry 2).

Elevation of the reaction temperature to room temperature made no appreciable difference to the amount of product obtained; unfortunately the increased temperature also resulted in reaction of the Lewis acid with the solvent, leading to polymerisation and difficulty in extracting 553a from the resulting viscous reaction mixture. Changing the solvent to acetonitrile afforded a complex mixture with only a small amount of impure 553a able to be extracted from the crude mixture (entry 4). Reasoning that the complexity of the mixture was due to side reactions, the temperature was reduced to minimise the formation of the undesired by-products (entry 5). Unfortunately, no desired product 550a was obtained from the mixture. Use of dichloromethane as solvent at reduced temperature did provide 553a; however the yield was half that obtained using the original conditions.

Due to the large amount of unreacted starting materials recovered, we reasoned that perhaps the poor yield was due to destruction of silyl enol ether 550a by the Lewis acid in preference to its reaction with chromone 474. It was reasoned that leaving a mixture of 474 and TMSOTf to mix together for a longer period should improve formation of the benzopyrylium salt, facilitating subsequent reaction with 550a. Increasing this period to 30 (entry 7) and 60 (entry 8) minutes had the opposite effect, resulting in a reduced yield of 553a.

At this point, we thought that extended exposure of the chromone to the Lewis acid was resulting in decomposition of the starting material – therefore TMSOTf was added to a mixture of chromone and silyl enol ether in dichloromethane at room temperature (entry 11). In this case, t.l.c. analysis revealed a complex mixture of at least 8 products, none of which corresponded to chromanone 553a. Chromone 474 was the only identifiable component to be separated from the mixture.

Changing the equivalents of Lewis acid also made little difference to the amount of 553a recovered; reduction (0.5 eq., entry 9) and slight excess (1.5 eq., entry 10) of the equivalents of Lewis acid only returned 553a in poor yield.

3.7.3 Investigation into the choice of Lewis acid

The original conditions (1 eq. TMSOTf, THF, -78 °C → r.t., 1.5 h) therefore appeared to be the best to effect the desired transformation. The yield, however, was still poor. We sought to improve the
yield by screening a small selection of readily available Lewis acids in an attempt to increase reactivity of the chromone (Table 3.7.3).

The original conditions utilised TMSOTf as a Lewis acid, providing chromanone 553a in low yield. Boron and titanium-based Lewis acids (entries 2 and 3) failed to provide any product. Boron trifluoride diethyl etherate appeared to have no effect at all, while titanium(IV) chloride gave a complex mixture. Tin(II) triflate, on the other hand, was the only other Lewis acid to provide any product at all, affording 553a albeit in 2% yield. It was therefore decided that TMSOTf was the best possible Lewis acid for catalysis of these reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Reaction conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf</td>
<td>THF, -78 °C to r.t., 1.5 h</td>
<td>26% 553a</td>
</tr>
<tr>
<td>2</td>
<td>BF3 · OEt2</td>
<td>THF, -78 °C to r.t., 4 h</td>
<td>No product detected; starting material only recovered</td>
</tr>
<tr>
<td>3</td>
<td>TiCl4</td>
<td>CH2Cl2, -78 °C to r.t., 4 h</td>
<td>No product detected; starting material only recovered</td>
</tr>
<tr>
<td>4</td>
<td>Sn(OTf)2</td>
<td>CH2Cl2, r.t., 6 h</td>
<td>2% 553a</td>
</tr>
</tbody>
</table>

Table 3.7.3. Effect of varying Lewis acids on the conjugate addition of silyl enol ether 550a to chromone 474.

Thus, it appeared that the reaction of silyl enol ether 550a with unsubstituted chromone 474 provided chromanone 553a in a maximum yield of 26%.

### 3.7.4 Investigation into an activating group at C-3: 3-acetylchromone 547a

Another option to increase the reactivity of the conjugate addition involved activation of the chromone with electron-withdrawing substituents at C-3. Thus, 3-acetylchromone 547a was subjected to analogous reaction conditions as that described above for chromone 474 (Table 3.7.4).
Disappointingly, application of the best reaction conditions for chromone 474 to 3-acetylchromone 547a provided novel chromanone 554a in only trace amounts (entry 1). $^1$H- and $^{13}$C-NMR, IR-, and mass spectrometry were used to identify the product as a mixture of keto-enol tautomers. The protons attached to the newly generated C-2 sp$^3$ centres resonated at $\delta$ 5.99 for the (major) enol form and at $\delta$ 4.11 and 5.46 for the keto form.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq.</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temperature (°C)</th>
<th>Activation (min)$^a$</th>
<th>Time (h)</th>
<th>Yield 554a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>-78 to r.t.</td>
<td>10</td>
<td>1.5</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>THF</td>
<td>2,6-lutidine</td>
<td>-78 to r.t.</td>
<td>15</td>
<td>2, 16</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>r.t.</td>
<td>10</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>MeCN</td>
<td>-</td>
<td>r.t.</td>
<td>10</td>
<td>4</td>
<td>17$^b$</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>MeCN</td>
<td>-</td>
<td>-20</td>
<td>15</td>
<td>4</td>
<td>21$^b$</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>-40</td>
<td>15</td>
<td>3.5</td>
<td>7$^b$</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>-40</td>
<td>15</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
<td>THF</td>
<td>-</td>
<td>-40</td>
<td>15</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>THF</td>
<td>-</td>
<td>-40</td>
<td>30</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

$^a$ The length of time the Lewis acid was allowed to stir with chromone 547a.

$^b$ Impure – contains acetophenone

Table 3.7.4. Exploration of parameters for the addition of silyl enol ether 550a to 3-acetylchromone 547a.

Addition of 2,6-lutidine to the reaction mixture resulted in a slight increase in yield of the product. The most successful modification involved increasing the reaction temperature to -20 °C in acetonitrile. However, as for unsubstituted chromone 474, the maximum yield of desired product was a low 21%. Additionally, looking forward to potential asymmetric reactions, the presence of keto/enol tautomers would render analysis by chiral HPLC more difficult. Subsequent work thus focused on using the more promising 3-(tert-butoxycarbonyl)chromone 547b (Table 3.7.5).
3.7.5 Investigation into a removable activating group at C-3: 3-tert-butoxycarbonylchromone 547b

Application of the same reaction conditions as initially used for the addition of 550a to chromones 474 and 547a did not provide the expected 3-substituted chromanone 554b; rather an inseparable mixture of unreacted starting material and the 3-unsubstituted chromanone 553a was obtained.

Table 3.7.5. Exploration of parameters for the addition of silyl enol ether 550a to 3-(tert-butoxycarbonyl)chromone 547b.

Comparison of the $^1$H-NMR spectrum of the mixture with the starting material 547b and decarboxylated product 553a (obtained from earlier experiments, section 3.7.2) clearly established the presence of an inseparable mixture of both 547b and 553a (Figure 3.7.1).
Figure 3.7.1. Comparison of spectra. Inseparable mixture resulting from the addition of silyl enol ether 550a to chromone 547b (bottom, blue) compared to starting material 547b (top, red) and decarboxylated product 553a obtained in section 3.7.2 (middle, green).

It was unclear, however, whether 553a resulted from in situ decarboxylation of the expected chromanone 554b, or was a product of in situ decarboxylation of chromone 547b, followed by conjugate addition to the resulting unsubstituted chromone 474. In order to test whether the latter route was feasible, a solution of 3-(tert-butoxycarbonyl)chromone 547b in dichloromethane was treated with equimolar TMSOTf at room temperature for 1 h. The chromone appeared stable to these conditions, and was recovered unchanged without any unsubstituted chromone 474 being detected. This experiment suggested that 553a resulted from in situ decarboxylation of the expected chromanone 554b (Route B, Figure 3.7.2).

Figure 3.7.2. Formation of decarboxylated product 553a from 547b.
Additionally, it appeared that conducting the reaction at room temperature in dichloromethane was most favourable for addition of 550a and 547b, affording the 3-unsubstituted chromanone 553a in 20% yield. This is comparable to the yield of 553a obtained from the addition of 550a to unsubstituted chromone 474. The yield of chromanones 553a and 554a obtained from conjugate addition of 550a to 474, 547a, or 547b therefore remains unacceptably low.

3.7.6 Summary of addition of silyl enol ether 550a to chromones

Disappointingly, though silyl enol ether 550a did react with chromones 474 and 547a-b, the yields of chromanones 553a and 554a obtained were poor. In addition, 3-tert-butyl ester chromone 547b provided the decarboxylated chromanone 553a, rather than the expected product 554b. While this in situ removal of the ‘activating group’ is desirable, the tert-butyl ester moiety does not appear to confer enhanced reactivity in the conjugate addition compared to the unsubstituted chromone 474. Additionally, increased reactivity of 3-acetylchromone 547a was not observed.

TMSOTf appeared to be the optimal Lewis acid to effect these conjugate additions. Use of BF₃·OEt₂, TiCl₄, or Sn(OTf)₂ either failed to catalyse the conjugate addition, or provided the product chromanone 553a in very low yield.

Due to the low yields obtained for chromanones 553a and 554a, it was decided to replace silyl enol ethers with a more reactive nucleophile. Silyl ketene acetal 550b, derived from ethyl acetate, was proposed as the next nucleophile to investigate conjugate additions to chromones.
3.8 Model additions of silyl ketene acetalts to chromones

3.8.1 Synthesis of silyl ketene acetal 550b

Silyl ketene acetal 550b was able synthesised in excellent yield following the literature procedure reported by Jacobsen and Wenzel, by treatment of ethyl acetate with LDA and TBSCl in the presence of DMPU (Scheme 3.8.1). \(^{383}\)

\[
\begin{align*}
\text{Scheme 3.8.1. Reagents and conditions:} & \quad a) \text{LDA, } 585, \text{ THF, } -78^\circ \text{C, 0.5 h; then DMPU, TBSCl, THF, } -78^\circ \text{C to r.t., 1.5 h, 89% crude yield.}
\end{align*}
\]

Use of TBSCl, rather than TMSCl to trap the enol was rationalised anticipating that the resulting silyl ketene acetal would be more stable and less susceptible to hydrolysis, thus improving ease of handling. Indeed, unlike silyl enol ether 550a, an aqueous wash of a pentane solution of the crude reaction mixture did not result in appreciable decomposition of the product 550b, which was obtained as a yellow liquid. The successful formation of the silyl ketene acetal 550b was confirmed by examination of the \(^1\)H-NMR spectrum that exhibited two doublets at \(\delta\) 3.05 and 3.21 with a coupling constant of 2.3 Hz, assigned to the two vinylic protons. The crude material was judged sufficiently pure by \(^1\)H-NMR spectroscopy and was carried forward to the subsequent conjugate addition reactions without further purification.

3.8.2 Addition of silyl ketene acetal 550b to chromones 474 and 547a – 547c

Pleasingly, the postulated increase in reactivity of 550b compared to 550a was immediately validated in the conjugate addition of silyl ketene acetal 550b to unsubstituted chromone 474 (Table 3.8.1).

TMSOTf was added to a solution of chromone 474 in dichloromethane and the mixture allowed to stir at room temperature for 15 min, followed by addition of a solution of the silyl ketene acetal 550b in dichloromethane. The reaction mixture was allowed to stir at room temperature for 4 – 6 h before quenching with saturated aqueous sodium hydrogen carbonate. Purification by flash column chromatography then afforded the pure product 553b, a known compound, in dramatically increased yield (80%) compared to the reaction of 474 with 550a (26%). Comparison of the \(^1\)H- and \(^{13}\)C-NMR data with the literature data confirmed the structure of the desired product 553b. \(^{382}\)
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

![Chemical reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chromone</th>
<th>Product(s)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="474" /></td>
<td><img src="image" alt="553b" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="547a" /></td>
<td><img src="image" alt="554c" />, <img src="image" alt="554c" /></td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="547b" /></td>
<td><img src="image" alt="554d" /></td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="547c" /></td>
<td><img src="image" alt="554e" /></td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Table 3.8.1. Addition of silyl ketene acetal 550b to C2-unsubstituted chromones 474 and 547a – 547c.

Following this success, the reaction was next investigated using the full range of 2-\(H\) chromones on hand in order to probe the influence of the various substituents on the chromone. Thus, 3-acetylchromone 547a and 3-(\(t\)-butoxycarbonyl)chromone 547b provided the corresponding chromanones 554c and 554d in 10% and 2% yield, respectively (Table 3.8.1, entries 2 and 3). Characterisation by NMR-spectroscopy was complicated by the presence of both keto and enol tautomers, with the enol tautomer predominating.

5-Methoxychromone 547c, containing aryl substitution present in many of the \(\gamma\)-butyrolactone natural products, afforded the analogous 554e in >99% yield (entry 4).
3.8.3 Addition of silyl ketene acetal 550b to chromones 547d – 547g

Encouraged by the above results, we proceeded to investigate the addition of 550b to the 2-methyl analogues of the above chromones (Table 3.8.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chromone</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="547d" /></td>
<td><img src="image" alt="554f" /></td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="547e" /></td>
<td><img src="image" alt="554g" /></td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="547f" /></td>
<td><img src="image" alt="554h" /></td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="547g" /></td>
<td><img src="image" alt="554i" /></td>
<td>18</td>
</tr>
</tbody>
</table>

Table 3.8.2. Addition of silyl ketene acetal 550b to C-2 methyl substituted chromones 547d – 547g.

Expecting a dramatic drop in yield, we were gratified to discover only a modest decrease in the reactivity of 2-methylchromone 547d compared to 474 in reactions with 550b (Table 3.8.2, entry 1). This chromanone 554f has been reported previously in a patent; however the isolated yield was only 25%.\(^{384}\) Thus our procedure offers a significant improvement in the yield of 554f obtained. The 3-acetyl and 3-(tert-butoxycarbonyl)-derivatives, however, only provided 554g in 16% yield, and none of 554h (entries 2 and 3). The most dramatic result, however, was that the addition of silyl ketene acetal 550b to 2-methyl-5-methoxychromone 547g, only afforded 554i in 18% yield, compared to the quantitative quantity of 554e obtained from the addition of 550b to the 2-\(H\) analogue 547c (entry 4).
3.8.4 Conclusion

Conjugate addition of silyl ketene acetal $550b$ to a variety of C-2 and C-3 substituted chromones $474$, $547a$ – $547g$ met with some success (Figure 3.8.1).

![Figure 3.8.1. Summary of racemic conjugate addition of silyl enol ether $550a$ and silyl ketene acetal $550b$ to chromones $474$ and $547$.](image)

A number of novel chromanones have been prepared racemically in variable yield, depending on the substitution pattern of the starting chromone (Figure 3.8.2).
Figure 3.8.2. Summary of novel chromones (547b and 547f) and chromanones (554a, 554c-d, 554f-g, 554i) prepared in this work.

From the results obtained, it can be deduced that C-2 substitution negatively affects the addition of 550a and 550b, which is important given that the natural product scaffolds we wish to target are all quaternary at this centre. Contrary to our expectations, substitution at C-3 with an electron-withdrawing group does not enhance the reactivity, and in fact results in lower yields than those obtained with the corresponding C-3 unsubstituted chromones.

Unfortunately, the 3-tert-butoxycarbonylchromone 547b was unsatisfactory as a substrate in the conjugate additions; not only did additions to 547b provide an inseparable mixture of starting material and decarboxylated product 553a, the yield of 553a obtained was no higher than that afforded using the unsubstituted chromone 474. This result also suggests that the presence of electron-withdrawing groups at C-3 does not improve the reactivity of the pyranone ring. This is presumably due to the TMSOTf forming a benzopyrylium intermediate 540 as the reactive species (A, figure 3.8.3), rather than acting as a traditional Lewis-acid activator (B, figure 3.8.3).
Armed with this knowledge, we nevertheless decided to attempt an asymmetric variant of the conjugate addition catalysed by a chiral Lewis acid complex. Silyl ketene acetal 550b was selected as the nucleophile due to its superior reactivity profile. Chromone 474 and 3-acetyl chromone 547a were also selected to evaluate an asymmetric variant of these reactions.

474 was selected because we envisaged relatively facile addition of the silyl ketene acetal to the chromone, and furthermore the resulting chromanones 553 should be easily separated by chiral HPLC. 547a was also included in the study as the 3-acetyl group should provide a second site for complexation of the Lewis acid complex, which may confer enhanced stereoselectivity in the conjugate addition of 550b (Figure 3.8.5).
Figure 3.8.5. Use of 3-acetyl chromone 547a in a proposed asymmetric conjugate addition.
3.9 Chiral catalysis in the conjugate addition of silyl ketene acetals to chromones

3.9.1 Attempted asymmetric addition of silyl ketene acetal \(550b\) to chromone \(474\)

The degree of stereocontrol in the conjugate addition of silyl enol ether \(550b\) to chromones was next investigated. The racemic reaction conditions are also provided at the top of the table for comparison (entry 1, table 3.9.1).

DiPhBOX ligand \(555\) was the first of the bis(oxazoline) ligands to be screened in attempts to effect a catalytic, asymmetric conjugate addition of \(550b\) to chromone \(474\). A solution of ligand \(555\) and copper(II) triflate in dichloromethane was allowed to stir for 15 min at room temperature until a colour change to deep blue suggested successful complexation of the metal to the ligand. Addition of a solution of \(474\) followed, and the reaction mixture was allowed to stir with the complex for an additional 30 min to allow complexation to the chromone. Finally, a solution of the silyl ketene acetal \(550b\) was added, and the mixture allowed to stir for 4-6 h.

At 20 mol% loading of the chiral catalyst, the expected chromanone \(553b\) was obtained in ~20% yield. While the drop in yield is considerable compared to the uncatalysed version of the reaction, we decided to screen a series of BOX ligands to investigate whether asymmetric induction was possible through using a chiral Lewis acid.

Thus, 20 mol% PyBOX \(557\) and 20 mol% IndaPyBOX \(558\) were both used in the conjugate addition of \(550b\) to \(474\). Not unexpectedly, use of PyBOX ligand \(557\) afforded a lower yield of \(553b\) than use of DiPhBOX \(555\). However, use of IndaPyBOX ligand \(558\) improved the yield of \(553b\) obtained to 23% yield. Similarly, use of IndaBOX \(553\) resulted in 20% yield of \(553b\).

Reasoning that the low conversion may be improved using a stoichiometric quantity of the Lewis acid, we next attempted the conjugate addition using 100 mol% chiral catalyst loading. Disappointingly, this resulted in a further reduction in yield, providing \(553b\) in only 10% isolated yield.

Postulating that the reduction in reactivity may be due to a loss of Lewis acidity of the metal upon complexation with the ligand, we also tested the reaction in the presence of a stoichiometric quantity of copper(II) triflate. In this case, the desired chromanone \(553b\) was only obtained in a disappointingly low 21% yield.
Table 3.9.1. Conjugate addition of silyl ketene acetal 550b to chromone 474 with chiral Lewis acids.

Furthermore, chiral HPLC analysis of the products obtained from each reaction revealed a complete lack of asymmetric induction, with only racemic material being obtained in all cases.

Interestingly, when the reaction was performed in the absence of a ligand, with copper(II) triflate as the Lewis acid, a comparable amount of the chromanone 553b was obtained to the additions performed in the presence of the chiral ligands. The lack of stereoselectivity may therefore be due to
decomplexation of the metal centre from the chiral complex 548. The chromanone 553b isolated would then result from the copper(II) triflate-catalysed Mukaiyama-Michael addition of silyl ketene acetal 550b to chromone 474.
3.9.2 Attempted asymmetric addition of silyl ketene acetal 550b to 3-acetylchromone 547a

Similar reactions to those described above (section 3.9.2) were also performed for the conjugate addition of 550b to 3-acetylchromone 547a (Table 3.9.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Reaction conditions</th>
<th>Yield 554c (%)</th>
<th>αD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>TMSOTf, CH2Cl2, r.t., 4 h</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Ligand 555" /></td>
<td>20 mol% 555, Cu(OTf)2, CH2Cl2, r.t.,</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Ligand 555" /></td>
<td>20 mol% 555, CuCl2, AgSbF6, CH2Cl2, r.t., 3.5 h</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Ligand 555" /></td>
<td>20 mol% 555, Cu(OTf)2, TMSCl, CH2Cl2, r.t., 4.5 h</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Ligand 556" /></td>
<td>20 mol% 556, Cu(OTf)2, CH2Cl2, r.t., 5 h</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Ligand 557" /></td>
<td>20 mol% 557, Cu(OTf)2, CH2Cl2, r.t., 3.5 h</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Ligand 558" /></td>
<td>20 mol% 558, Cu(OTf)2, CH2Cl2, r.t., 5 h</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3.9.2. Conjugate addition of silyl ketene acetal 550b to 3-acetylchromone 547a with chiral Lewis acids.
Yields for the copper(II)-catalysed reactions of 550b to 547a, however, remained low. Evans and coworkers had earlier found that the counterion used for these Cu(II)-BOX complexes can have a large influence on the course of the reaction. Therefore we sought to increase the Lewis acidity of the Lewis-acid complex by using a less coordinating counterion such as [SbF$_6$]$^-$. Treatment of a Cu(II)-chloride/555 complex with AgSbF$_6$ and subsequent use of the resultant Lewis acid 586 in the conjugate addition slightly improved the yield of the product 554c from 10% to 16%. Unfortunately, the reaction was not clean, yielding 5% of a second product 589, presumably resulting from 1,2-addition of silyl ketene acetal 550b to the acetyl group of 547a (Figure 3.9.1).

![Side product from the reaction of 3-acetyl chromone 547a and silyl ketene acetal 550b in the presence of catalyst 586.](image)

Suspecting that the poor yields obtained may be due to irreversible binding of the catalyst to the chromone, we attempted to increase turnover of the metal centre by the addition of chlorotrimethylsilane to the reaction mixture (entry 4). While an improvement was seen compared to previous conditions, the overall yield of 554c obtained was still poor (22%). The reaction of chromone 547a with 550b using PyBOX 557 and IndaPyBOX 558 also resulted in low yields of product 554c (entries 6 and 7). Attempted resolution of the racemic mixture of product by chiral HPLC was unsuccessful; the specific rotation of each sample, however, suggests that once more, the reactions only resulted in racemic material.

### 3.9.3 Conclusion

An asymmetric variant of the Mukaiyama-Michael addition of silyl ketene acetal 550b to chromones 474 and 547a was attempted. Several BOX-type ligands were screened in this investigation; unfortunately no stereoselectivity was observed in the additions (Figure 3.9.2).
Figure 3.9.2. Summary of attempted asymmetric conjugate addition of chromones 474 or 547a with silyl ketene acetal 550b and ligands 555 – 558.

This lack of stereoselectivity may be due to several factors. Though the distinct colour changes observed during the reaction indicate that the chiral Lewis acid complexes did form, it is possible that upon addition of the chromone substrate the metal dissociates from the ligand and the conjugate addition proceeds via a pathway not involving the chiral ligand.

Furthermore, unsubstituted chromone 474, lacking a second oxygen site for complexation at C-3, presumably forms the monodentate copper-ligand complex 590 (Figure 3.9.3). The conformational flexibility of this complex effectively removes any preference for attack from one face or the other. This also may help to explain the total lack of stereoselectivity observed for conjugate additions of 550b to chromone 474.

Figure 3.9.3. Cu(II)-BOX-chromone complex 590.
However, the 3-acetyl substituted chromone 547a should form a bidentate complex with the chiral Lewis acid, conferring greater conformational rigidity to the complex (Figure 3.9.4). Preference for si facial attack (in the case of ligands 555 and 556) should therefore be observed to some extent.

![Figure 3.9.4. Cu(II)-BOX-chromone complex 591.](image)

Unfortunately, this was not the case, as the 3-acetyl adduct 554c was also only obtained as a racemate in all cases. This result suggests that the chiral complex may be binding to the substrate in a parallel, rather than a perpendicular fashion (Figure 3.9.5). The chiral ligand would therefore not cause any steric crowding in the transition state and thus nucleophilic attack at either face of the molecule is equally likely, and a racemic product is obtained.

![Figure 3.9.5. Perpendicular vs. parallel binding of the Cu(II)-BOX Lewis acid complex to chromone 547a.](image)
3.10 Future work

Successful asymmetric conjugate addition of silyl enol ethers and/or silyl ketene acetals to chromones may be effected by several strategies:

a) Use of a chiral ligand in the Lewis acid that will bind to the substrate in a perpendicular manner, allowing enantiofacial differentiation – there are several possible candidates that have yet to be explored (Figure 3.10.1).

![Possible ligands/catalysts for the conjugate addition of silyl enol ethers and silyl ketene acetals to chromones.](image)

Figure 3.10.1. Possible ligands/catalysts for the conjugate addition of silyl enol ethers and silyl ketene acetals to chromones.

Iminium catalysis could also be investigated, for which there are many amine catalysts available (e.g. Cinchona alkaloids 513 and 593). For example, chiral amine 596 was used in the first reported asymmetric catalytic Mukaiyama-Michael addition of siloxyfuran 291 to α,β-unsaturated aldehyde 594 (Figure 3.10.2). This has yet to be applied in Mukaiyama-Michael reactions using chromones as the Michael acceptor.

![Pioneering work by Macmillan et al on the iminium catalysed Mukaiyama-Michael addition of siloxyfurans to simple α,β-unsaturated aldehydes.](image)

Figure 3.10.2. Pioneering work by Macmillan et al on the iminium catalysed Mukaiyama-Michael addition of siloxyfurans to simple α,β-unsaturated aldehydes.
b) Incorporation of a chiral auxiliary into the chromone – this has been examined previously by Wallace et al.;\textsuperscript{356,390} however a thorough investigation of auxiliaries has not been reported. Earlier work by Brimble and McEwan had some success with asymmetric Mukaiyama-Michael addition of TMS-furan 291 to naphthoquinones bearing a chiral auxiliary (Scheme 3.10.1).\textsuperscript{391} However removal of the auxiliaries (597a – 597d) from the resultant furonaphthofurans 598 was unsuccessful due to the sensitive nature of the dihydronaphthofuran ring present in the adducts.

Scheme 3.10.1. Reagents and conditions: a) 100 mol\% Lewis acid, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C.

A similar approach, therefore, may be taken with chromones 599, whereby appending a chiral auxiliary such as an oxazolidinone (e.g. SuperQuat 601\textsuperscript{392}), pantolactone 602, N-methylsuccinimide 603, or camphorsultam 604 at C-3 may lead to sufficient facial differentiation in the conjugate addition, thereby affording the chromanone 554 in enantioenriched form after removal of the chiral auxiliary (Figure 3.10.3).
However, as with the furonaphthofurans 598, removal of the chiral auxiliary may prove problematic due to the base sensitivity of the adducts.

c) Introduction of a chiral auxiliary to the nucleophile – however care must be taken not to suppress the reactivity of the nucleophile as the chromones are relatively unreactive Michael acceptors. Only two examples of asymmetric additions of silyl ketene acetics substituted with chiral auxiliaries have been reported in the literature (Scheme 3.10.2).

The first example of the use of this strategy in the Mukaiyama-Michael addition was reported by Gennari et al.\textsuperscript{393} N-Methylephedrine 605-derived silyl ketene acetal 606 was added to ethyl or methyl vinyl ketone 607 under the influence of titanium(IV) tetrachloride in stoichiometric quantity as the Lewis acid catalyst. While the yields of 608 were low, good enantioselectivity was obtained with this system.

\textbf{Scheme 3.10.2. Reagents and conditions:} a) propionyl chloride, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C → r.t., 3 h, >99%; b) LDA, TMSCl, THF, -78 °C → r.t., 2 h, >95%, E:Z >95:5; c) 607, TiCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, -100 → -78 °C, 2 h, 60%; d) NaOH, H\textsubscript{2}O/MeOH (1:4), r.t., 15 h; e) CH\textsubscript{3}N\textsubscript{2}, Et\textsubscript{2}O/MeOH (9:1), yields as given.

Alternatively, Wicha and colleagues have reported the use of silyl ketene acetics 610 and 615 in an asymmetric conjugate addition to 2-methylcyclopentenone 611 (Scheme 3.10.3).\textsuperscript{394,395} Cyclic silyl
ketene acetal 610 was derived from chiral alcohol 609 in three steps, itself available in enantiopure form from the yeast reduction of 2,2-dimethylcyclohexa-1,3-dione. Trityl hexachloroantimonate (TrSbCl₆) was used as the Lewis acid catalyst at 5 mol% loading. Unlike Gennari’s silyl ketene acetal, the second example has the chiral component remote to the reactive centre. Good stereoselectivity was exhibited in both cases, but the stereoselectivity was opposite to the products obtained using an achiral silyl ketene acetal.

Scheme 3.10.3. Reagents and conditions: a) TBSCI; b) m-CPBA, NaHCO₃, CH₂Cl₂, 87% over 2 steps; c) LDA, TMSCl, 92%; d) 611, 5 mol% TrSbCl₆, CH₂Cl₂, yield as given; e) Sharpless AD-mix-α, 70%; f) 2,2-dimethoxypropane, TsOH; g) tBuSH, AlMe₃, 72%, over 2 steps, 96% e.e.; h) LDA, TMSCl, 95%; i) 611, then 617, cat. TrSbCl₆, CH₂Cl₂, -78 °C, yield as given.

Thus the analogous addition of, for example, an N-methylephedrine-derived silyl ketene acetal 606 to a chromone 547 may afford the C-2 stereocentre in a stereoselective manner (Figure 3.10.4).
Figure 3.10.4. Proposed addition of chiral auxiliary-based silyl ketene acetal 606 to chromones 547.
CHAPTER NINE

Experimental

Part Three
3.11 Experimental

3.11.1 Synthesis of chromones

Chromone 474

Prepared according to the one-pot procedure previously established within our group.\textsuperscript{370}

Sodium hydride (washed 3 x with hexanes, 1.058 g, 44.07 mmol) was added portion-wise to a solution of 2′-hydroxyacetophenone 574 (0.88 mL, 7.34 mmol) in ethyl formate (100 mL) at 0 °C over 2 h. The yellow mixture was allowed to stir at this temperature for 1.5 h, then quenched by addition of methanol (3.5 mL). Conc. HCl (11.5 mL) was then added, and the resulting white suspension allowed to warm to room temperature and stirred overnight. Water (50 mL) was added, and the mixture extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO\textsubscript{4}, and concentrated under reduced pressure to give the crude as a yellow oil. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the title compound 474 (990 mg, 92%) as a yellow oil that solidified over time to pale yellow plate-like crystals.

R\textsubscript{f} (ethyl acetate:hexanes 3:7): 0.29.

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): δ 8.22 (dd, 1H, J = 1.8, 8.0 Hz, H-5), 7.85 (d, 1H, J = 6.0 Hz, H-2), 7.67 (m, 1H, H-7), 7.46 (dd, 1H, J = 0.8, 8.4 Hz, H-8), 7.41 (td, 1H, J = 1.0, 8.1 Hz, H-6), 6.35 (d, 1H, J = 6.0 Hz, H-3).

Spectral data were in agreement with literature values.\textsuperscript{372}

3-Formyl chromone 580

Prepared according to the procedure of Khan et al.\textsuperscript{374}
POCl₃ (6.7 mL, 71.98 mmol) was added dropwise to anhydrous N,N-dimethylformamide (18 mL, 233.57 mmol) at 50 °C, and the resulting amber solution allowed to stir at this temperature for 2 h. A solution of 2'-hydroxyacetophenone 574 (1.77 mL, 14.69 mmol) in anhydrous N,N-dimethylformamide (4 mL) was added dropwise, and the mixture continued to stir at 45 – 55 °C for an additional 2 h. The heating was removed and the dark chocolate brown mixture allowed to stir at room temperature overnight. Ice (ca. ¾ c) was cautiously added and the resulting orange suspension allowed to stir for 3 h. The suspension was filtered via vacuum filtration and the crude tan solids recrystallised from hot ethanol and dried under vacuum to give the title compound 580 (1.599 g, 63%) as light tan crystals.

Rₕ (ethyl acetate:hexanes 3:7 as eluent): 0.27.

¹H-NMR (400 MHz, CDCl₃): δ 10.40 (s, 1H, H-1′), 8.55 (s, 1H, H-2), 8.31 (dd, 1H, J = 1.8, 7.9 Hz, H-5), 7.76 (ddd, 1H, J = 1.6, 7.2, 8.6 Hz, H-7), 7.52 (m, 2H, H-6, H-8).

Spectral data were in agreement with literature values.³⁹⁶,³⁹⁷

3-Carboxylic acid chromone 581

Prepared according to the procedure of Li et al.³⁷⁵

Rₕ (ethyl acetate:hexanes 1:1): 0.06.

A solution of sulfamic acid (4.139 g, 42.64 mmol) in water (50 mL) was added to a solution of 3-formylchromone 580 (1.5 g, 8.61 mmol) in dichloromethane (60 mL) at 0 °C. A solution of sodium chlorite (3.116 g, 34.45 mmol) in water (70 mL) was then added dropwise, and the mixture allowed to stir at 0 °C for 1 h. The organic layer was separated and the aqueous extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure to give the crude as a shiny, pale yellow solid. The crude was recrystallised from hot methanol to give the title compound 581 (812 mg, 50%) as fluffy off-white crystals.

¹H-NMR (400 MHz, CDCl₃): δ 13.40 (br s, 1H, O-H), 9.03 (s, 1H, H-2), 8.34 (dd, 1H, J = 1.8, 8.1 Hz, H-5), 7.88 (ddd, 1H, J = 1.6, 7.4, 8.7 Hz, H-7), 7.66 (d, 1H, J = 8.5 Hz, H-8), 7.61 (t, 1H, J = 7.6 Hz, H-6).
Spectral data were in agreement with literature values.\textsuperscript{398}

**tert-Butyl 3-(2-hydroxyphenyl)-3-oxopropanoate 583**

![Chemical structure]

Prepared according to a modification of the procedure of Geahlen \textit{et al.}\textsuperscript{399}

A solution of 2′-hydroxyacetophenone 574 (1.77 mL, 14.69 mmol) in tetrahydrofuran (40 mL) was added dropwise \textit{via} addition funnel to a solution of LiHMDS (1.0 M in THF, 44 mL, 44.07 mmol) at -78 °C. The mixture was allowed to stir at this temperature for 2 h, then a solution of di-\textit{tert}-butyl dicarbonate (3.6 mL, 15.86 mmol) in tetrahydrofuran (15 mL) was added quickly. The mixture was allowed to slowly warm to room temperature and stirred overnight. The mixture was then poured onto a mixture of ice (ca. ¾ c) and conc. HCl (10 mL). The resulting solution was extracted with dichloromethane (3 x 150 mL) and the combined organic extracts were washed with water (2 x 100 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure to give the crude as an orange oil. The crude was purified \textit{via} flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the title compound 583 (2.744 g, 79%) as a bright yellow oil.

R\textsubscript{f} (ethyl acetate:hexanes 3:7): 0.71.

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): δ 11.91 (s, 1H, OH), 7.67 (dd, 1H, \textit{J} = 1.6, 8.1 Hz, H-4′), 7.48 (m, 1H, H-6′), 6.99 (dd, 1H, \textit{J} = 1.0, 8.4 Hz, H-5′), 6.91 (m, 1H, H-3′), 3.91 (s, 2H, H-2), 1.46 (s, 9H, \textit{t}-Bu).

Spectral data were in agreement with literature values.\textsuperscript{351}

**Acetic formic anhydride 573**

![Chemical structure]

Prepared according to the procedure of Krimen.\textsuperscript{376}

Acetyl chloride (4.5 mL, 63.69 mmol) was added rapidly \textit{via} addition funnel to a vigorously stirred suspension of sodium formate (5.198 g, 76.43 mmol) in diethyl ether (5 mL). The mixture was allowed to stir at room temperature overnight. The solids were removed \textit{via} vacuum filtration and washed with dry diethyl ether (10 mL). The combined filtrates were concentrated under reduced
pressure to give the crude title compound 573 (5.203 g, crude) as a pale yellow liquid. The crude material was carried forward without further purification.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 9.10 (s, 1H, HCO$_2$), 2.28 (s, 3H, H$_3$CO$_2$).

Spectral data were in agreement with literature values.$^{376}$

3-Acetylchromone 547a

Prepared according to the procedure of Högberg et al.$^{400}$

$R_f$ (ethyl acetate:hexanes 3:7): 0.37.

Acetic formic anhydride 573 (ca. 1 g, 11.36 mmol) was added to a stirred suspension of 1-(2-hydroxyphenyl)butane-1,3-dione 572 (0.879 g, 4.94 mmol) and sodium formate (0.437 g, 6.42 mmol) in tetrahydrofuran (10 mL) and the mixture allowed to stir at room temperature for 20 h. The bright orange solution was poured into ice-water (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO$_4$, and concentrated under reduced pressure to give the crude as a bright red solid. The crude was purified via recrystallisation from hot ethanol to give the title compound 547a (326 mg, 35%), as pink needles.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.61 (s, 1H, H-2), 8.30 (dd, 1H, $J = 1.6$, 8.0 Hz, H-5), 7.72 (ddd 1H, $H-1.6$, 7.0, 8.6 Hz, H-7), 7.51 (m, 2H, H-6, H-8), 2.76 (s, 3H, H-2').

Spectral data were in agreement with literature values.$^{397}$

3-Acetyl-2-methyl-4H-chromen-4-one 547e

Acetic anhydride (6 mL) was added to a mixture of 1-(2-hydroxyphenyl)butane-1,3-dione 572 (0.700 g, 3.93 mmol) and sodium acetate (0.338 g, 4.13 mmol) and the mixture heated at reflux for 3
the mixture was allowed to cool to room temperature, whereupon it solidified to an orange mass. The mixture was diluted with toluene (30 mL) and filtered to remove undissolved salts. The filtrate was stirred with water (30 mL) for 1.5 h. The organic layer was then removed, dried over MgSO_4, and concentrated under reduced pressure to afford orange crystals. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:4 as eluent) to give the title compound 547e (0.382 g, 48%) as white crystals, m.p. 84 – 88 °C (lit. 89 – 90 °C).

R_f (ethyl acetate:hexanes 3:7): 0.40.

^1^H-NMR (400 MHz, CDCl_3): δ 8.14 (dd, 1H, J = 1.4, 8.0 Hz, H-5), 7.67 (ddd, 1H, J = 1.9, 7.4, 8.8 Hz, H-7), 7.41 – 7.37 (m, 2H, H-6, H-8), 2.63 (s, 3H, H-2'), 2.51 (s, 3H, 2-Me).

^1^C-NMR (100 MHz, CDCl_3): δ 200.1 (quat., C-1'), 175.5 (quat., C-4), 168.2 (quat., C-2), 155.0 (quat., C-8a), 133.8 (CH, C-7), 125.4 (CH, C-5), 125.2 (CH, C-6), 123.34 (quat., C-4a), 123.26 (quat., C-3), 117.4 (CH, C-8), 31.8 (CH_3, C-2'), 19.5 (CH_3, 2-Me).

IR (solid) cm^-1: 3038 (Ar C–H), 2924 (C–H), 1688 (str, C=O), 1636 (str, C=O), 1614 (str, C=C), 1560 (str, C=C), 1463 (str, C=C), 1383 (str), 1369 (str), 1346 (str), 1335 (str, C–C), 1219 (med, C–O), 1153 (med), 1126 (str), 1061 (med), 1029 (med), 995 (med), 951 (str), 864 (med), 846 (med), 757 (str), 700 (med), 650 (str), 631 (str), 569 (med).

MS (ESI) m/z 203 [(M + H)^+], 225 [(M + Na)^+], 100%; HRMS (ESI) m/z 203.0708 [(M + H)^+], calcd. for C_{12}H_{11}O_3 203.0703, 225.0529 [(M + Na)^+], calcd. for C_{12}H_{10}O_3Na 225.0522.

**tert-Butyl 4-oxo-4H-chromene-3-carboxylate 547b**

Prepared according to the procedure of Högberg *et al.*

R_f (ethyl acetate:hexanes 3:7): 0.71.

Acetic formic anhydride 573 (crude, 1.400 g, ca. 15.90 mmol), was added to a solution of *tert*-butyl 3-(2-hydroxyphenyl)-3-oxopropanoate 583 (1.500 g, 6.35 mmol) and sodium formate (0.561 g, 8.25 mmol) in tetrahydrofuran (15 mL) at room temperature and the mixture allowed to stir for 4 h. T.L.C. analysis of the reaction mixture at this time revealed a substantial amount of starting material present, so a further aliquot of acetic formic anhydride 573 (1.000 g, ca. 11.36 mmol) was added and
the mixture allowed to stir at room temperature for 72 h. The mixture was then poured onto ice-water (ca. 70 mL) and the aqueous extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried over Na₂SO₄, and concentrated under reduced pressure to give the crude as a yellow crystalline solid. The crude was purified via flash column chromatography (silica gel, ethyl acetate:hexanes 3:17 as eluent) to give the title compound 547b (857 mg, 55 %) as white crystalline flakes, mp 101 – 105 °C.

¹H-NMR (400 MHz, CDCl₃): δ 8.58 (s, 1H, H-2), 8.28 (dd, 1H, J = 1.5, 8.0 Hz, H-5), 7.69 (ddd, 1H, J = 1.8, 7.2, 8.7 Hz, H-7), 7.45 (m, 2H, H-6, H-8), 1.60 (s, 9H, t-Bu).

¹³C-NMR (100 MHz, CDCl₃): δ 173.7 (quat., C-4), 162.2 (quat., CO₂t-Bu), 161.2 (CH, C-2), 155.6 (quat., C-8a), 134.0 (CH, C-7), 126.6 (CH, C-5), 126.0 (CH, C-6), 125.3 (quat., C-4a), 118.1 (CH, C-8), 117.5 (quat., C-3), 82.3 (quat., t-Bu), 28.2 (3 x CH₃, t-Bu).

IR (solid) cm⁻¹: 3094, 3011 (Ar C–H), 2969 (med, C–H), 2932, 1728 (str, ester C=O), 1648 (str, C=O), 1615 (str, Ar C=C), 1570 (med), 1562 (med), 1487, 1463 (str, Ar C=C), 1392 (str), 1362 (str), 1349 (str), 1313 (str), 1289 (str), 1259, 1237 (str), 1211, 1164 (str, ester C–O), 1147 (str), 1117 (str), 1089 (str), 1043 (med), 1026 (med), 949, 934 (med), 917 (med), 866 (med), 847 (str), 807 (str), 752 (str), 711 (med), 679 (med), 617 (med).

MS (ESI) m/z 269 [(M + Na)⁺, 100%]; HRMS (ESI) m/z 269.0778 [(M + Na)⁺, calcd. for C₁₄H₁₄O₄Na 269.0784].

**tert-Butyl 2-methyl-4-oxo-4H-chromene-3-carboxylate  547f**

Prepared according to a modification of the procedure reported by Charlton et al.⁴⁷⁷

Rₚ (ethyl acetate:hexanes 3:7): 0.59.

Sodium acetate (anhydrous, 182 mg, 2.22 mmol) was added to a solution of tert-butyl 3-(2-hydroxyphenyl)-3-oxopropanoate 583 (500 mg, 2.11 mmol) in acetic anhydride (2.8 mL) and the mixture heated at 100 – 110 °C for 3 h. The mixture was allowed to cool and diluted with toluene (5 mL). The mixture was filtered through cotton wool to remove the salt and the filtrate stirred with water (30 mL) for 3 h. The organic layer was removed, dried over MgSO₄, and concentrated under reduced pressure to give the crude as an orange oil. The crude was purified via flash column chromatography...
chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the title compound 547f (122 mg, 22%) as white needles, mp 70 – 76 °C.

$^1$H-NMR (400 MHz, CDCl$_3$): δ 8.18 (dd, 1H, $J = 1.4, 8.0$ Hz, H-5), 7.64 (m, 1H, H-7), 7.41 – 7.36 (m, 2H, H-6, H-8), 2.48 (s, 3H, 2-Me), 1.61 (s, 9H, CO$_2$Bu).

$^{13}$C-NMR (100 MHz, CDCl$_3$): δ 174.4 (quat., C-4), 165.2 (quat., C-1’), 164.3 (quat., C-2), 155.7 (quat., C-8a), 133.7 (CH, C-7), 126.0 (CH, C-5), 125.3 (CH, C-6), 123.5 (quat., C-4a), 119.7 (quat., C-3), 117.7 (CH, C-8), 82.7 (quat., t-Bu), 28.1 (3 x CH$_3$, CO$_2$Bu), 19.1 (CH$_3$, 2-Me).

IR (thin film) cm$^{-1}$: 2978 (C–H), 2934, 1769, 1723 (str, C=O), 1647 (str, C=C), 1617 (str, Ar C=C), 1575 (med), 1464 (str, Ar C=C), 1400 (str), 1366 (str), 1299 (med), 1254 (med), 1222 (med), 1169 (str), 1150 (str), 1129 (str), 1073 (str), 1037, 995 (med), 908, 847 (med), 812 (med), 762 (str), 693, 659, 612.

MS (ESI) m/z 283 [(M + Na)$^+$, 91%]; HRMS (ESI) m/z 283.0938 [(M + Na)$^+$, calcd. for C$_{15}$H$_{16}$O$_4$Na 283.0941].

3.11.2 Conjugate additions to chromones

Trimethyl(1-phenylvinyloxy)silane 550a

Prepared according to the procedure of Watts et al.$^{381}$

A solution of acetophenone 584 (1.94 mL, 16.65 mmol) in tetrahydrofuran (25 mL) was added dropwise to a solution of LiHMDS (1.0 M in THF, 18.3 mL, 18.31 mmol) at room temperature and the resulting orange mixture allowed to stir for 20 min. A solution of chlorotrimethylsilane (2.1 mL, 16.65 mmol) in tetrahydrofuran (25 mL) was then added dropwise, and the mixture allowed to stir at r.t. for 1.5 h. The volatiles were removed under reduced pressure and the residue diluted with pentane (40 mL). The resulting suspension was filtered through cotton wool and the filtrate concentrated under reduced pressure to give the crude title compound 550a (4.927 g, crude) as an orange liquid. Crude 550a was carried forward without further purification.

$^1$H-NMR (300 MHz, CDCl$_3$): δ 7.60 (m, 2H, H-2’), 7.30 (m, 3H, H-3’, H-4’), 5.04 (d, 1H, $J = 2.2$ Hz, H$_{3'2}$), 4.78 (d, 1H, $J = 2.2$ Hz, H$_{3'2}$), 0.16 (s, 9H, OTMS).
Spectral data were in agreement with literature values.\textsuperscript{380}

**tert-Butyl(1-ethoxyvinyl)dimethylsilane 550b**

![Chemical structure of tert-Butyl(1-ethoxyvinyl)dimethylsilane 550b]

Prepared according to the procedure of Jacobsen and Wenzel.\textsuperscript{383}

\(n\)-BuLi (1.6 M in hexanes, 7.8 mL, 12.48 mmol) was added slowly to a solution of diisopropylamine (1.9 mL, 13.62 mmol) in tetrahydrofuran (25 mL) at 0 °C, and the resulting pale yellow solution allowed to stir at this temperature for 20 min, then cooled to -78 °C. Ethyl acetate (1.1 mL, 11.35 mmol) was then added dropwise, and the mixture allowed to stir at -78 °C for 30 min. DMPU (2 mL) was added, followed by a solution of TBSCl (2.053 g, 13.62 mmol) in tetrahydrofuran (3 mL) added slowly. The mixture was allowed to stir at -78 °C for an additional 30 min before allowing to warm to room temperature. The volatiles were removed under reduced pressure and the residue diluted with pentane (30 mL). The solution was washed with sat. aq. CuSO\(_4\) (30 mL), sat. aq. NaHCO\(_3\) (30 mL), and brine (30 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure to give the crude title compound 550b (2.053 g, 89% crude) as a yellow oil. This material was judged sufficiently pure (by \(^1\)H-NMR analysis) to carry through without further purification.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 3.74 (q, 2H, J = 7.0 Hz, OEt), 3.21 (d, 1H, J = 2.3 Hz, H\(_a\)-2), 3.05 (d, 1H, J = 2.3 Hz, H\(_b\)-2), 1.29 (t, 3H, J = 7.0 Hz, OEt), 0.92 (s, 9H, OTBS), 0.17 (s, 6H, OTBS).

Spectral data were in agreement with literature values.\textsuperscript{383}

**General procedure 3A: Preparation of chromanones 553a-b and 554a-g via TMSOTf-catalysed conjugate addition of 550a or 550b.**

![General procedure 3A: Preparation of chromanones 553a-b and 554a-g via TMSOTf-catalysed conjugate addition of 550a or 550b]
TMSOTf (1 eq.) was added to a solution of the chromone (1 eq.) in dichloromethane (1 mL/0.1 mmol chromone) at room temperature, and the mixture allowed to stir for 15 min. A solution of silyl enol ether 550a (1.5 eq.) or silyl ketene acetal 550b (1.2 eq.) in dichloromethane (1 mL/0.1 mmol) was then added dropwise, and the resulting mixture allowed to stir for an additional 4 – 6 h. Sat. aq. NaHCO₃ was added, and the mixture extracted with dichloromethane 3 times. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated under reduced pressure to afford the crude adducts. See tables 3.7.2 – 3.7.5 and 3.8.1 – 3.8.2 for yields of adducts obtained.

**General procedure 3B: Asymmetric Lewis acid-catalysed conjugate addition of silyl ketene acetal 550b to chromones 474 and 547a.**

![Diagram of the reaction](image)

Cu(OTf)₂ (0.2 eq.) was added to a solution of the ligand (0.2 eq.) in dichloromethane (5 mL) and the resulting brightly coloured solution allowed to stir at room temperature for 10 min. A solution of the chromone (1 eq.) in dichloromethane (0.5 mL/0.1 mmol) was then added dropwise, and the mixture allowed to stir for 30 min. A solution of silyl ketene acetal 550b (1.2 eq.) in dichloromethane (1 mL/0.1 mmol) was then added dropwise, and the mixture allowed to stir for a further 4 – 6 h. Water (10 mL) was added, and the mixture extracted with dichloromethane 3 times. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated under reduced pressure to afford the crude adducts. See tables 3.9.1 – 3.9.2 for yields of adducts obtained.

**2-(2-Oxo-2-phenylethyl)chroman-4-one 553a**

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the **title compound 553a** as a yellow crystalline solid, m.p. 85-92 °C (lit. 99-102 °C).

Rᵣ (ethyl acetate:hexanes 3:7): 0.56.
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

\[ \delta \text{ H-NMR (400 MHz, CDCl}_3\text{): } \delta 7.98 \text{ (m, 2H, H-4'), 7.90 (dd, 1H, } J = 1.7, 7.9 \text{ Hz, H-5), 7.63 - 7.59 (m, 1H, H-7), 7.52 - 7.44 (m, 3H, H-5', H-6'), 7.03 (td, 1H, } J = 0.7, 7.9 \text{ Hz, H-6), 6.93 (d, 1H, } J = 8.3 \text{ Hz, H-8), 5.18 (m, 1H, H-2), 3.70 (dd, 1H, } J = 6.4, 16.9 \text{ Hz, H-a-1'}, 3.29 (dd, 1H, } J = 6.0, 17.0 \text{ Hz, H-b-1'), 2.92 (dd, 1H, } J = 3.3, 16.8 \text{ Hz, H-a-3), 2.80 (dd, 1H, } J = 12.2, 16.8 \text{ Hz, H-b-3).} \]

MS (ESI\(^+\)) \text{ m/z 289 [(M + Na)]}, 29\%; HRMS (ESI\(^+\)) \text{ m/z 289.0840 [(M + Na)] calcd. for C}_{17}\text{H}_{14}\text{O}_3\text{Na 289.0835].}

Spectral data were in agreement with literature values.\(^{362,382}\)

3-Acetyl-2-(2-oxo-2-phenylethyl)chroman-4-one \textit{keto}-554a and (Z)-3-(1-Hydroxyethylidene)-2-(2-oxo-2-phenylethyl)chroman-4-one \textit{enol}-554a

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the \textit{title compound} 554a as a yellow oil.

\[ R_f \text{ (ethyl acetate:hexanes 3:7): 0.59.} \]

Ratio \textit{keto}:\textit{enol} = 1:8 by \(^1\text{H-NMR.}\)

\[ \delta \text{ H-NMR (400 MHz, CDCl}_3\text{): } \delta 7.88 \text{ (dd, 1H, } J = 1.6, 7.8 \text{ Hz, H-5), 7.83 \text{ (m, 2H, H-5'), 7.56 (m, 1H, H-6'), 7.44 - 7.36 (m, 3H, H-4', H-7), 7.06 (td, 1H, } J = 0.8, 8.0 \text{ Hz, H-6), 6.76 (dd, 1H, } J = 0.6, 8.4 \text{ Hz, H-8 enol), 5.99 (dd, 1H, } J = 4.0, 8.8 \text{ Hz, H-2 enol), 5.46 (m, 1H, H-2 keto), 4.11 (d, 1H, } J = 9.9 \text{ Hz, H-3 keto), 3.79 (dd, 1H, } J = 8.8, 16.2 \text{ Hz, H-a-1' enol), 2.93 (dd, 1H, } J = 4.0, 16.3 \text{ Hz, H-b-1' enol), 2.45 (s, 3H, H-2'' keto), 2.24 (s, 3H, H-2'' enol).} \]

\[ \delta \text{ C-NMR (100 MHz, CDCl}_3\text{): } \delta 196.7 \text{ (quat., C-2' enol), 188.0 \text{ (quat., C-1'' enol), 176.1 \text{ (quat., C-4 enol), 156.7 \text{ (quat., C-8a enol), 136.7 \text{ (quat., C-3' enol), 135.1 \text{ (CH, C-7 enol), 133.6 \text{ (CH, C-6' enol), 128.7 \text{ (2 x CH, C-4' enol), 128.3 \text{ (2 x CH, C-5' enol), 126.2 \text{ (CH, C-5 enol), 121.9 \text{ (CH, C-6 enol), 119.3 \text{ (quat., C-4a enol), 118.1 \text{ (CH, C-8 enol), 105.5 \text{ (quat., C-3 enol), 72.3 \text{ (CH, C-2 enol), 62.9 \text{ (CH, C-2 keto), 43.6 \text{ (CH}_2, C-1' enol), 31.3 \text{ (CH}_3, C-2'' keto), 22.1 \text{ (CH}_3, C-2'' enol).} }\]}

IR (neat) cm\(^{-1}\): 3065 (Ar C–H), 2964 (C–H), 2923, 2855, 1718 (C=O), 1682 (str, C=O), 1604 (str, Ar C=C), 1463 (str, Ar C=C), 1448 (str), 1419 (str), 1359 (str), 1302 (str), 1282 (str), 1216 (str), 1181
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

MS (ESI$^+$) m/z 331 [(M + Na)$^+$, 53%]; HRMS (ESI$^+$) m/z 331.0937 [(M + Na)$^+$, calcd. for C$_{19}$H$_{16}$O$_4$Na 331.0941].

**Ethyl 2-(4-oxochroman-2-yl)acetate 553b**

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the title compound 553b as a colourless oil.

R$_f$ (ethyl acetate:hexanes 3:7): 0.53.

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.88 (dd, 1H, $J = 1.7$, 7.9 Hz, H-5), 7.47 (m, 1H, H-7), 7.03 (m, 1H, H-6), 6.97 (dd, 1H, $J = 0.7$, 8.5 Hz, H-8), 4.92 (m, 1H, H-2), 4.21 (q, 2H, $J = 7.1$ Hz, CO$_2$Et), 2.92 (dd, 1H, $J = 7.3$, 15.8 Hz, H$_a$-1'), 2.79 (m, 2H, H-3), 2.72 (dd, 1H, $J = 5.6$, 15.7 Hz, H$_b$-1'), 1.29 (t, 3H, $J = 7.3$ Hz, CO$_2$Et).

MS (ESI) m/z 257 [(M + Na)$^+$, 100%]; HRMS (ESI) m/z 257.0772 [(M + Na)$^+$, calcd. for C$_{13}$H$_{14}$O$_4$Na 257.0784].

Spectral data were in agreement with literature values.$^{382}$

**Ethyl 2-(5-methoxy-4-oxochroman-2-yl)acetate 554e**

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 3:7 as eluent) to give the title compound 554e as a pale yellow oil.

R$_f$ (ethyl acetate:hexanes 3:7): 0.10.

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.36 (t, 1H, $J = 8.4$ Hz, H-7), 6.57 – 6.51 (m, 2H, H-6, H-8), 4.86 (m, 1H, H-2), 4.21 (q, 2H, $J = 7.0$ Hz, CO$_2$Et), 3.91 (s, 3H, 5-OMe), 2.87 (dd, 1H, $J = 7.4$, 15.8 Hz, H$_a$-
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

3), 2.74 (d, 2H, J = 7.6 Hz, H-1’), 2.69 (dd, 1H, J = 5.6, 15.8 Hz, H-5,3), 1.29 (t, 3H, J = 7.0 Hz, CO₂Et).

Spectral data were in agreement with literature values.³⁸²

**Ethyl 2-(3-acetyl-4-oxochroman-2-yl)acetate keto-554c and (Z)-Ethyl 2-(3-(1-hydroxyethylidene)-4-oxochroman-2-yl)acetate enol-554c**

Purified *via* flash column chromatography (silica gel, ethyl acetate:hexanes 7:93 as eluent) to give the *title compound 554c* as a pale yellow oil.

Rᵣ (ethyl acetate:hexanes 3:7): 0.54.

Ratio keto : enol = 1:9 by ¹H-NMR.

¹H-NMR (400 MHz, CDCl₃): δ 7.84 (dd, 1H, J = 1.7, 7.8 Hz, H-5 enol), 7.44 (m, 1H, H-7 enol), 7.05 (m, 1H, H-6 enol), 6.89 (dd, 1H, J = 0.8, 8.4 Hz, H-8 enol), 5.72 (dd, 1H, J = 4.2, 9.6 Hz, H-2 enol), 5.18 (pent, 1H, J = 5.5 Hz, H-2 keto), 4.17 (m, 2H, CO₂Et), 2.91 (dd, 1H, J = 9.7, 15.3 Hz, H₃-1’), 2.47 (dd, 1H, J = 4.2, 15.1 Hz, H₆-1’), 2.43 (s, 3H, H-2” keto), 2.21 (s, 3H, H-2” enol), 1.27 (t, 3H, J = 7.1 Hz, OEt).

¹³C-NMR (100 MHz, CDCl₃): δ 187.9 (quat., C-1” enol), 176.1 (quat., C-4 enol), 169.8 (quat., CO₂Et enol), 156.6 (quat., C-8a enol), 135.2 (CH, C-7 enol), 126.1 (CH, C-5 enol), 122.0 (CH, C-6 enol), 119.2 (quat., C-4a enol), 118.0 (CH, C-8 enol), 104.9 (quat., C-3 enol), 74.8 (CH, C-2 keto), 72.5 (CH, C-2 enol), 60.9 (CH₂, CO₂Et), 40.7 (CH₂, C-1’), 22.0 (CH₃, C-2” enol), 14.2 (CH₃, CO₂Et).

IR (thin film) cm⁻¹: 3064 (Ar C–H), 2980 (C–H), 2931, 2876, 2855, 1731 (str, C=O), 1684, 1606 (str, Ar C=C), 1464 (str, Ar C=C), 1420 (med), 1369 (str), 1302 (str), 1218 (med), 1164 (str), 1120, 1088, 1034 (med), 952, 903, 839, 759 (str), 711.

MS (ESI) m/z 299 [(M + Na)⁺, 80%]; HRMS (ESI) m/z 299.0877 [(M + Na)⁺, calcd. for C₁₅H₁₆O₅Na 299.0890].
Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:19 as eluent) to give the title compound \(554d\) as a colourless oil.

\[ R_f (\text{ethyl acetate:hexanes 3:7}): \text{Ratio keto : enol} = 3:5 \text{ by } ^1\text{H-NMR}. \]

\[ ^{1}\text{H-NMR (400 MHz, CDCl}_3\text{): } \delta12.24 \text{ (br s, 1H, OH enol)}, 7.89 \text{ (dd, 1H, } J = 1.7, 7.9 \text{ Hz, H-5, keto)}, \]
\[ 7.65 \text{ (dd, 1H, } J = 1.6, 7.7 \text{ Hz, H-5, enol)}, 7.49 \text{ (m, 1H, H-7, keto)}, 7.32 \text{ (m, 1H, H-7, enol)}, 7.06 - 6.96 \text{ (m, 3H, H-6, H-8 keto, H-6 enol)}, 6.84 \text{ (m, 1H, H-8 enol)}, 5.64 \text{ (dd, 1H, } J = 3.0, 10.0 \text{ Hz, H-2 enol)}, 5.12 \text{ (ddd, 1H, } J = 3.5, 8.0, 11.4 \text{ Hz, H-2 keto)}, 4.24 - 4.13 \text{ (m, 4H, CO}_2\text{Et)}, 3.69 \text{ (d, 1H, } J = 11.4 \text{ Hz, H-3 keto)}, 2.88 - 2.72 \text{ (m, 3H, H-1' keto, H}_{\alpha}-1' \text{ enol)}, 2.46 \text{ (dd, 1H, } J = 3.0, 14.8 \text{ Hz, H}_{\beta}-1' \text{ enol)}, 1.55 \text{ (s, 9H, CO}_2\text{Bu enol)}, 1.51 \text{ (s, 9H, CO}_2\text{Bu keto)}, 1.28 \text{ (m, 6H, CO}_2\text{Et)}. \]

\[ ^{13}\text{C-NMR (100 MHz, CDCl}_3\text{): } \delta 187.7 \text{ (quat., C-4 keto)}, 170.1 \text{ (quat., CO}_2\text{Et enol)}, 169.3 \text{ (quat., CO}_2\text{Et keto)}, 166.3 \text{ (quat., CO}_2\text{Bu enol)}, 165.6 \text{ (quat., CO}_2\text{Bu keto)}, 161.9 \text{ (quat., C-8a keto)}, 160.4 \text{ (quat., C-4 enol)}, 154.9 \text{ (quat., C-8a enol)}, 136.5 \text{ (CH, C-7 keto)}, 133.1 \text{ (CH, C-7 enol)}, 127.3 \text{ (CH, C-5 keto)}, 125.5 \text{ (CH, C-6 keto)}, 124.3 \text{ (CH, C-5 enol)}, 121.9 \text{ (CH, C-6 enol)}, 120.1 \text{ (quat., C-4a keto)}, 117.9 \text{ (CH, C-8 keto)}, 117.5 \text{ (quat., C-4a enol)}, 117.4 \text{ (CH, C-8 enol)}, 95.8 \text{ (quat., C-3 enol)}, 83.0 \text{ (quat., CO}_2\text{Bu enol)}, 82.5 \text{ (quat., CO}_2\text{Bu keto)}, 75.6 \text{ (CH, C-2 keto)}, 71.4 \text{ (CH, C-2 enol)}, 61.1 \text{ (CH}_2\text{, CO}_2\text{Et keto)}, 60.6 \text{ (CH}_2\text{, CO}_2\text{Et enol)}, 58.2 \text{ (CH, C-3 keto)}, 40.2 \text{ (CH}_2\text{, C-1' enol)}, 38.5 \text{ (CH}_2\text{, C-1' keto)}, 28.5 \text{ (3 x CH}_3\text{, CO}_2\text{Bu enol)}, 28.1 \text{ (3 x CH}_3\text{, CO}_2\text{Bu keto)}, 14.2 \text{ (CH}_3\text{, CO}_2\text{Et enol)}, 14.1 \text{ (CH}_3\text{, CO}_2\text{Et keto)}. \]

IR (thin film) cm\(^{-1}\): 2922 (=C–H), 2849 (C–H), 1736 (str, C=O), 1694 (med, C=C), 1652 (str, C=C), 1629 (str, C=C), 1610 (med, Ar C=C), 1579, 1476 (med Ar C=C), 1463 (med), 1306 (med), 1290 (med), 1273 (med), 1226 (med), 1140 (str), 1118, 1097 (med), 1035, 985, 835, 761 (str), 740 (str).

MS (ESI) \(m/z\) 335 [(M + H)^\(+\), 11\%], 357 [(M + Na)^\(+\), 100\%]; HRMS (ESI) \(m/z\) 335.1486 [(M + H)^\(+\), calcd. for C\(_{18}\)H\(_{22}\)O\(_6\) 335.1489], 357.1302 [(M + Na)^\(+\), calcd. for C\(_{18}\)H\(_{22}\)O\(_6\)Na 357.1309].
Ethyl 2-(2-methyl-4-oxochroman-2-yl)acetate 554f

![Structure](554f)

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the title compound 554f as a colourless oil.

R_f (ethyl acetate:hexanes 3:7): 0.42.

^1^H-NMR (400 MHz, CDCl_3): δ 7.86 (dd, 1H, J = 1.8, 7.8 Hz, H-5), 7.48 (m, 1H, H-7), 7.00 (m, 1H, H-6), 6.93 (m, 1H, H-8), 4.15 (q, 2H, J = 7.2 Hz, CO_2Et), 3.08 (d, 1H, J = 16.7 Hz, H_2-3), 2.82 – 2.72 (m, 3H, H_2-3, H-1'), 1.56 (s, 3H, 2-Me), 1.26 (t, 3H, J = 7.3 Hz, CO_2Et).

^1^3C-NMR (100 MHz, CDCl_3): δ 191.5 (quat, C-4), 169.2 (quat., CO_2Et), 159.1 (quat., C-8a), 136.2 (CH, C-7), 126.4 (CH, C-5), 121.1 (CH, C-6), 120.1 (quat., C-4a), 118.3 (CH, C-8), 79.1 (quat., C-2), 60.7 (CH_2, CO_2Et), 46.8 (CH_2, C-3), 43.9 (CH_2, C-1'), 24.5 (CH_3, 2-Me), 14.1 (CH_3, CO_2Et).

IR (thin film) cm^-1: 2979, 2940 (C–H), 1733 (str, C=O), 1693 (str, C=O), 1609 (str, Ar C=C), 1581, 1464 (str, Ar C=C), 1375, 1326 (str), 1309 (str), 1241, 1199, 1154, 1115, 1054, 923, 899, 805, 765 (str).

MS (ESI) m/z 271 [(M + Na)^+], 76%; HRMS (ESI) m/z 271.0941 [(M + Na)^+], calcd. for C_{14}H_{16}O_4Na 271.0941.

Ethyl 2-(3-acetyl-2-methyl-4-oxochroman-2-yl)acetate keto-554g and ethyl 2-(3-acetyl-4-hydroxy-2-methyl-2H-chromen-2-yl)acetate enol-554g

![Structure](keto-554g, enol-554g)

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:19 as eluent) to give the title compound 554g as a yellow oil.

R_f (ethyl acetate:hexanes 3:7): 0.50.
H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (dt, 1.6H, $J = 2.1$, 7.9 Hz, H-5), 7.53 – 7.45 (m, 1.6H, H-6), 7.04 – 6.98 (m, 1.8H, $J = 3.4$ Hz, H-1$'$ keto), 6.95 (br d, 1.6H, $J = 8.6$ Hz, H$_{a}$-1$'$, enol), 2.82 (d, 2H, $J = 3.4$ Hz, H-1$''$ keto), 2.40 (s, 3H, H-2$''$ keto), 2.32 (s, 2H, H-2$''$ enol), 1.60 (s, 3H, 2-Me keto), 1.54 (s, 2H, 2-Me keto), 1.30 – 1.24 (overlapping t, 6.5H, $J = 7.0$ Hz, CO$_2$Et).

C-NMR (100 MHz, CDCl$_3$): $\delta$ 203.4 (quat., C-1$''$ keto), 201.8 (quat., C-1$''$ enol), 189.8 (quat., C-4 keto), 187.9 (quat., C-4 enol), 158.8 (quat., C-8a keto), 158.7 (quat., C-8a enol), 137.0 (CH, C-7 enol), 136.6 (CH, C-7 keto), 126.9 (CH, C-5 enol), 126.5 (CH, C-5 keto), 121.33 (CH, C-6 enol), 121.28 (CH, C-6 keto), 120.6 (quat., C-4a enol), 118.9 (quat., C-4a enol), 118.49 (CH, C-8 enol), 118.46 (CH, C-8 keto), 98.8 (quat., C-3 enol), 81.0 (quat., C-2 keto), 79.8 (quat., C-2 enol), 64.1 (CH, C-3 keto), 60.84 (CH$_2$, CO$_2$Et keto), 60.79 (CH$_2$, CO$_2$Et enol), 43.2 (CH$_2$, C-1$'$ keto), 41.2 (CH$_2$, C-1$'$$'$ enol), 33.1 (CH$_3$, C-2$''$ keto), 31.9 (CH$_3$, C-2$''$ enol), 23.9 (CH$_3$, 2-Me enol), 21.2 (CH$_3$, 2-Me keto), 14.16 (CH$_3$, CO$_2$Et keto), 14.12 (CH$_3$, CO$_2$Et enol).

IR (thin film) cm$^{-1}$: 2981, 2931 (C–H), 2907, 2876, 2852, 1723 (str, C=O), 1685 (str, C=O), 1607 (str, Ar C=C), 1584 (med), 1463 (str, Ar C=C), 1420, 1375 (med), 1357 (med), 1320 (str), 1234 (str), 1187 (str), 1148 (med), 1108 (str), 1084 (med), 1030 (med), 960, 939, 917 (med), 899, 762 (str), 675.

MS (ESI$^+$) m/z 291 [(M + H)$^+$, 10%], 313 [(M + Na)$^+$, 88%]; HRMS (ESI$^+$) m/z 291.1225 [(M + H)$^+$, calcd. for C$_{16}$H$_{19}$O$_5$ 291.1227, 313.1044 [(M + Na)$^+$, calcd. for C$_{16}$H$_{18}$O$_5$Na 313.1046].

Ethyl 2-(5-methoxy-2-methyl-4-oxochroman-2-yl)acetate 554i

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 3:7 as eluent) to give the title compound 554i as a pale yellow oil.

R$_f$ (ethyl acetate:hexanes 3:7): 0.16.

H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.37 (t, 1H, $J = 8.4$ Hz, H-7), 6.54 – 6.49 (m, 2H, H-6, H-8), 4.15 (q, 2H, $J = 7.1$ Hz, OEt), 3.91 (s, 3H, 5-OMe), 3.02 (d, 1H, $J = 16.1$ Hz, H$_{a}$-3), 2.77 – 2.73 (m, 3H, H-1$'$, H$_b$-3), 1.54 (s, 3H, 2-Me), 1.26 (t, 3H, $J = 7.3$ Hz, OEt).
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 190.3 (quat., C-4), 169.3 (quat., CO$_2$Et), 160.8 (quat., C-8a), 160.3 (quat., C-5), 136.0 (CH, C-7), 110.6 (quat., C-4a), 110.5 (CH, C-8), 103.6 (CH, C-6), 78.6 (quat., C-2), 60.7 (CH$_2$, CO$_2$Et), 56.1 (CH$_3$, 5-OMe), 48.4 (CH$_2$, C-3), 44.0 (CH$_2$, C-1'), 24.3 (CH$_3$, 2-Me), 14.1 (CH$_3$, CO$_2$Et).

IR (thin film) cm$^{-1}$: 2979, 2920 (C–H), 2852, 1732 (str, C=O), 1686 (str, C=O), 1601 (str, Ar C=C), 1576 (med), 1473 (str, Ar C=C), 1429 (med), 1370 (med), 1338 (med), 1256 (str), 1211 (med), 1175 (med), 1157 (med), 1129 (med), 1105 (med), 1087 (str), 1034 (med), 984, 951, 894, 824, 790 (med), 730.

MS (ESI) m/z 301 [(M + Na)$^+$, 100%], HRMS (ESI) m/z 301.1023 [(M + Na)$^+$, calcd. for C$_{15}$H$_{18}$O$_5$Na 301.1046].

**Changing the counterion:**

![Chemical structure diagram]

Procedure carried out according to the method of Evans *et al.*$^{385}$

A mixture of CuCl$_2$ (4 mg, 0.03 mmol), AgSbF$_6$ (22 mg, 0.06 mmol), and ligand 555 (15 mg, 0.03 mmol) was diluted with dichloromethane (5 mL) and the mixture allowed to stir at room temperature for 1 h, becoming yellow-green in colour. A solution of 547a (30 mg, 0.16 mmol) in dichloromethane (1.5 mL) was then added and the resulting pale blue mixture allowed to stir for 0.5 h. A solution of 550b (39 mg, 0.19 mmol) in dichloromethane (1.5 mL) was then added dropwise and the resulting green-yellow mixture allowed to stir for an additional 3.5 h. Water (10 mL) was added, and the organic layer removed. The aqueous was extracted with dichloromethane (2 x 10 mL) and the combined organic extracts dried over MgSO$_4$ and concentrated under reduced pressure to afford a yellow-brown solid. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 1:9 as eluent) to give 554c (7 mg, 16%) as a colourless oil. Spectral data were identical with material prepared according to general procedure 3A. In addition, 5% of 1,2-adduct 589 was obtained as a yellow oil.
**Ethyl 3-((tert-butyldimethylsilyl)oxy)-3-(4-oxo-4H-chromen-3-yl)butanoate 589**

Purified via flash column chromatography (silica gel, ethyl acetate:hexanes 1:9 as eluent) to give the **title compound 589** as a yellow oil.

\[ \text{Rf (ethyl acetate:hexanes 3:7): 0.70.} \]

\[ ^1\text{H-NMR (400 MHz, CDCl}_3\text{): } \delta 8.22 \text{ (dd, 1H, } J = 1.5, 8.0 \text{ Hz, H-5)}, \ 8.18 \text{ (s, 1H, H-2)}, \ 7.64 \text{ (ddd, 1H, } J = 1.6, 7.0, 8.6 \text{ Hz, H-7)}, \ 7.44 \text{ (d, 1H, } J = 8.3 \text{ Hz, H-8)}, \ 7.38 \text{ (ddd, 1H, } J = 1.0, 7.2, 8.0 \text{ Hz, H-6)}, \]
\[ 4.01 \text{ (m, 1H, H}_2O\text{-OEt)}, \ 3.88 \text{ (m, 1H, H}_2O\text{-OEt)}, \ 3.65 \text{ (d, 1H, } J = 14.4 \text{ Hz, } H_2O^{-2}'), \ 2.74 \text{ (d, 1H, } J = 14.3 \text{ Hz, } H_2O^{-2}'), \ 1.77 \text{ (s, 3H, H-4')}, \ 1.06 \text{ (t, 3H, } J = 7.1 \text{ Hz, OEt)}, \ 0.96 \text{ (s, 9H, OTBS)}, \ 0.27 \text{ (s, 3H, OTBS)}, \ 0.20 \text{ (s, 3H, OTBS).} \]

\[ ^{13}\text{C-NMR (100 MHz, CDCl}_3\text{): } \delta 176.7 \text{ (quat., C-4)}, \ 170.2 \text{ (quat., C-1')}, \ 156.3 \text{ (quat., C-8a)}, \ 153.9 \text{ (CH, C-2)}, \ 133.3 \text{ (CH, C-7)}, \ 128.8 \text{ (quat., C-3)}, \ 126.0 \text{ (CH, C-5)}, \ 124.8 \text{ (CH, C-6)}, \ 124.3 \text{ (quat., C-4a)}, \ 117.9 \text{ (CH, C-8)}, \ 74.6 \text{ (quat., C-3')}, \ 59.8 \text{ (CH}_2\text{, CO}_2\text{Et)}, \ 45.2 \text{ (CH}_2\text{, C-2')}, \ 28.6 \text{ (CH}_3\text{, C-4')}, \ 26.0 \text{ (3 x CH}_3\text{, OTBS)}, \ 18.5 \text{ (quat., OTBS)}, \ 14.0 \text{ (CH}_3\text{, CO}_2\text{Et)}, \ -1.7 \text{ (CH}_3\text{, OTBS)}, \ -2.0 \text{ (CH}_3\text{, OTBS).} \]

\[ \text{IR (thin film) cm}^{-1}: \ 2955, \ 2926 \text{ (C–H)}, \ 2854, \ 1736 \text{ (str, C=O)}, \ 1644 \text{ (str, C=O)}, \ 1611 \text{ (med, Ar C=C)}, \ 1574, \ 1466 \text{ (str, Ar C=C)}, \ 1381 \text{ (str)}, \ 1372 \text{ (str)}, \ 1339 \text{ (str)}, \ 1312 \text{ (str)}, \ 1287 \text{ (med)}, \ 1257 \text{ (str)}, \ 1214 \text{ (str)}, \ 1184 \text{ (str)}, \ 1157 \text{ (str)}, \ 1132 \text{ (str)}, \ 1100 \text{ (str)}, \ 1072 \text{ (str)}, \ 1036 \text{ (str)}, \ 1001 \text{ (str)}, \ 899 \text{ (str)}, \ 837 \text{ (str)}, \ 808 \text{ (Str)}, \ 778 \text{ (str)}, \ 761 \text{ (str)}, \ 703 \text{ (str)}, \ 663 \text{ (med).} \]

\[ \text{MS (ESI^{+}) m/z 391 [(M + H)^{+}, 2\%], 413 [(M + Na)^{+}, 100\%]; HRMS (ESI^{+}) m/z 391.1941 [(M + H)^{+}, calcd. for C}_{21}H_{31}O_{5}Si 391.1935], 413.1752 [(M + Na)^{+}, calcd. for C}_{21}H_{30}O_{5}SiNa 413.1755]. \]

**Increasing metal turnover:**
A mixture of Cu(OTf)$_2$ (12 mg, 0.03 mmol) and ligand 555 (15 mg, 0.03 mmol) was diluted with dichloromethane (5 mL) and allowed to stir at room temperature for 15 min until the solution became deep blue in colour. A solution of chromone 547a (31 mg, 0.16 mmol) in dichloromethane (1.5 mL) was added, and the resulting green solution allowed to stir for 30 min. A solution of silyl ketene acetal 550b (40 mg, 0.20 mmol) in dichloromethane (1.5 mL) was added dropwise, followed by TMSCl (25 μL, 0.20 mmol). The resulting brown solution was allowed to stir for an additional 4.5 h at room temperature, then water (10 mL) added and the organic layer removed. The aqueous was extracted further with dichloromethane (2 x 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over MgSO$_4$, and concentrated under reduced pressure to afford a yellow solid. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes 7:93 as eluent) to give 554c (10 mg, 22%) as a colourless oil. Spectral data were identical with material prepared according to general procedure 3A.
3.11.3 Chiral HPLC traces for attempted asymmetric conjugate additions

Racemic; TMSOTf-catalysed.
Stoichiometric Lewis acid complex

556

558
References


(22) Krauss, J.; Knorr, V.; Manhardt, V.; Scheffels, S.; Bracher, F. *Arch. Pharm. (Weinheim, Ger.)* **2008**, *341*, 386.


Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones


310 | Page
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones


Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones


Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

(144) Weiss, G.; Schulze, G. *Amidosulfonic acid derivatives*, DE1493486, 1973
(145) Schulze, G.; Weiss, G. *N-Alkylsulfamoyl chlorides*, BE667311, 1966
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones


(206) Beugelmans, R.; Chastanet, J.; Roussi, G. Heterocycles 1987, 26, 3197.


(224) Krasnov, V. L.; Bodrikov, I. V.; Vasyanina, G. I.; Matyukov, E. V. *Substituted 1,2,4-thiadiazolidine 1,1-dioxides*, SU1118641, 1984.


(229) Tsuge, O.; Uneo, K.; Oe, K. *Chem. Lett.* 1979, 1407.


(254) Gella, C.; Ferrer, E.; Alibes, R.; Busque, F.; de March, P.; Figueredo, M.; Font, J. J.
(257) Smets, G. J.; Vandensavel, J. M. 1-Arylsulfonyl-4-butyl-2-tetrazolin-5-ones as
(258) Chung, J. Y. L.; Ho, G.-J.; Chartrain, M.; Roberge, C.; Zhao, D.; Leazer, J.; Farr, R.;
Robbins, M.; Emerson, K.; Mathre, D. J.; McNamara, J. M.; Hughes, D. L.; Grabowski, E. J. J.;
(262) Paetzold, P.; Eleftheriadis, E.; Minkwitz, R.; Woelfel, V.; Gleiter, R.; Bischof, P.;
(263) Atkinson, D. J.; Sperry, J.; Brimble, M. A. Synlett 2011, 99.
(266) Nicolaides, D. N.; Fylaktakidou, K. C.; Litinas, K. E.; Papaageorgiou, G. K.;
(269) Toma, L.; Quadrelli, P.; Perrini, G.; Gandolfi, R.; Di Valentini, C.; Corsaro, A.;
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones


(310) Koenig, K. H.; Hamprecht, G. Sulfamoyl halides, DE2513997, 1976
(320) Sin, N.; Venables, B. L.; Scola, P. M.; Wang, A. X. Preparation of proline-containing tripeptides as hepatitis C virus inhibitors, EP2265606, 2009
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones


(384) Kabbe, H. J. *4-Chromanones, 1977*
APPENDIX
A.1 Crystal data and structure refinement for exo-171

Table A1. Crystal data and structure refinement for exo-171.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{16}H_{22}O_{5}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>294.34</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.41970(10) Å  alpha = 90 deg.</td>
</tr>
<tr>
<td></td>
<td>b = 25.4719(4) Å  beta = 113.8020(10) deg.</td>
</tr>
<tr>
<td></td>
<td>c = 7.49690(10) Å  gamma = 90 deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>1471.07(3) Å^{3}</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4, 1.329 Mg/m^{3}</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.098 mm^{-1}</td>
</tr>
<tr>
<td>F(000)</td>
<td>632</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.39 x 0.28 x 0.2 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.60 to 27.84 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-8&lt;=h&lt;=11, -33&lt;=k&lt;=33, -9&lt;=l&lt;=9</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>18584 / 3488 [R(int) = 0.0211]</td>
</tr>
<tr>
<td>Completeness to theta</td>
<td>27.84 99.9 %</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^{2}</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3488 / 0 / 193</td>
</tr>
<tr>
<td>Goodness-of-fit on F^{2}</td>
<td>1.041</td>
</tr>
</tbody>
</table>
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Final R indices [I>2sigma(I)]  \( R_1 = 0.0343 \), \( wR2 = 0.0889 \)

R indices (all data)  \( R_1 = 0.0389 \), \( wR2 = 0.0925 \)

Largest diff. peak and hole  0.407 and -0.228 e.A\(^{-3}\)

Table 2. Atomic coordinates (x 10\(^4\)) and equivalent isotropic displacement parameters (A\(^2\) x 10\(^3\)) for exo-171. \( U(eq) \) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>( U(eq) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>9685(1)</td>
<td>649(1)</td>
<td>9807(1)</td>
<td>14(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>11462(1)</td>
<td>859(1)</td>
<td>10539(2)</td>
<td>16(1)</td>
</tr>
<tr>
<td>C(2')</td>
<td>7037(1)</td>
<td>1822(1)</td>
<td>2131(1)</td>
<td>13(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>12141(1)</td>
<td>1059(1)</td>
<td>9358(1)</td>
<td>15(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>11163(1)</td>
<td>1104(1)</td>
<td>7163(1)</td>
<td>12(1)</td>
</tr>
<tr>
<td>C(4')</td>
<td>8028(1)</td>
<td>1202(1)</td>
<td>4550(1)</td>
<td>13(1)</td>
</tr>
<tr>
<td>C(5')</td>
<td>6118(1)</td>
<td>1320(1)</td>
<td>4125(1)</td>
<td>15(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>9198(1)</td>
<td>1159(1)</td>
<td>6713(1)</td>
<td>12(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>8598(1)</td>
<td>706(1)</td>
<td>7645(1)</td>
<td>13(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>11817(1)</td>
<td>1602(1)</td>
<td>6516(1)</td>
<td>14(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>12050(2)</td>
<td>2523(1)</td>
<td>6834(2)</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>11536(1)</td>
<td>619(1)</td>
<td>6138(2)</td>
<td>15(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>13428(1)</td>
<td>505(1)</td>
<td>6667(2)</td>
<td>19(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>14243(2)</td>
<td>87(1)</td>
<td>7653(2)</td>
<td>22(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>7170(2)</td>
<td>2407(1)</td>
<td>1900(2)</td>
<td>20(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>6815(1)</td>
<td>1519(1)</td>
<td>296(1)</td>
<td>16(1)</td>
</tr>
<tr>
<td>O(1')</td>
<td>5606(1)</td>
<td>1714(1)</td>
<td>2646(1)</td>
<td>18(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>9120(1)</td>
<td>434(1)</td>
<td>10887(1)</td>
<td>17(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>11558(1)</td>
<td>2026(1)</td>
<td>7412(1)</td>
<td>19(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>12531(1)</td>
<td>1610(1)</td>
<td>5410(1)</td>
<td>20(1)</td>
</tr>
<tr>
<td>O(3')</td>
<td>8535(1)</td>
<td>1652(1)</td>
<td>3756(1)</td>
<td>15(1)</td>
</tr>
</tbody>
</table>

Table 3. Bond lengths [\( \text{A} \)] and angles [deg] for exo-171.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [( \text{A} )]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-O(1)</td>
<td>1.2229(12)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.4697(14)</td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.5127(13)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.3342(14)</td>
</tr>
<tr>
<td>C(2)-H(2)</td>
<td>0.9300</td>
</tr>
<tr>
<td>C(2')-O(3')</td>
<td>1.4218(12)</td>
</tr>
</tbody>
</table>
### Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2')-O(1')</td>
<td>1.4317(12)</td>
</tr>
<tr>
<td>C(2')-C(12)</td>
<td>1.5100(14)</td>
</tr>
<tr>
<td>C(2')-C(13)</td>
<td>1.5214(13)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.5182(13)</td>
</tr>
<tr>
<td>C(3)-H(3)</td>
<td>0.9300</td>
</tr>
<tr>
<td>C(4)-C(7)</td>
<td>1.5364(13)</td>
</tr>
<tr>
<td>C(4)-C(9)</td>
<td>1.5529(14)</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.5558(13)</td>
</tr>
<tr>
<td>C(4')-O(3')</td>
<td>1.4323(11)</td>
</tr>
<tr>
<td>C(4')-C(5)</td>
<td>1.5236(13)</td>
</tr>
<tr>
<td>C(4')-C(5')</td>
<td>1.5381(14)</td>
</tr>
<tr>
<td>C(4')-H(4')</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(5')-O(1')</td>
<td>1.4263(12)</td>
</tr>
<tr>
<td>C(5')-H(5'1)</td>
<td>0.9700</td>
</tr>
<tr>
<td>C(5')-H(5'2)</td>
<td>0.9700</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.5364(13)</td>
</tr>
<tr>
<td>C(5)-H(5)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(6)-H(6A)</td>
<td>0.9700</td>
</tr>
<tr>
<td>C(6)-H(6B)</td>
<td>0.9700</td>
</tr>
<tr>
<td>C(7)-O(3)</td>
<td>1.2045(13)</td>
</tr>
<tr>
<td>C(7)-O(2)</td>
<td>1.3370(13)</td>
</tr>
<tr>
<td>C(8)-O(2)</td>
<td>1.4504(13)</td>
</tr>
<tr>
<td>C(8)-H(8A)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(8)-H(8B)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(8)-H(8C)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.5061(14)</td>
</tr>
<tr>
<td>C(9)-H(9A)</td>
<td>0.9700</td>
</tr>
<tr>
<td>C(9)-H(9B)</td>
<td>0.9700</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.3194(16)</td>
</tr>
<tr>
<td>C(10)-H(10)</td>
<td>0.9300</td>
</tr>
<tr>
<td>C(11)-H(11A)</td>
<td>0.9300</td>
</tr>
<tr>
<td>C(11)-H(11B)</td>
<td>0.9300</td>
</tr>
<tr>
<td>C(12)-H(12A)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(12)-H(12B)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(12)-H(12C)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(13)-H(13A)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(13)-H(13B)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(13)-H(13C)</td>
<td>0.9600</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)</td>
<td>121.65(9)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(6)</td>
<td>121.58(9)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(6)</td>
<td>116.77(8)</td>
</tr>
<tr>
<td>Bond</td>
<td>Angle (°)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>C(3) - C(2) - C(1)</td>
<td>122.33 (9)</td>
</tr>
<tr>
<td>C(3) - C(2) - H(2)</td>
<td>118.8</td>
</tr>
<tr>
<td>C(1) - C(2) - H(2)</td>
<td>118.8</td>
</tr>
<tr>
<td>O(3') - C(2') - O(1')</td>
<td>105.23 (7)</td>
</tr>
<tr>
<td>O(3') - C(2') - C(12)</td>
<td>108.53 (8)</td>
</tr>
<tr>
<td>O(1') - C(2') - C(12)</td>
<td>109.26 (8)</td>
</tr>
<tr>
<td>O(3') - C(2') - C(13)</td>
<td>111.27 (8)</td>
</tr>
<tr>
<td>O(1') - C(2') - C(13)</td>
<td>109.73 (8)</td>
</tr>
<tr>
<td>C(12) - C(2') - C(13)</td>
<td>112.54 (8)</td>
</tr>
<tr>
<td>C(2) - C(3) - C(4)</td>
<td>123.93 (9)</td>
</tr>
<tr>
<td>C(2) - C(3) - H(3)</td>
<td>118.0</td>
</tr>
<tr>
<td>C(4) - C(3) - H(3)</td>
<td>118.0</td>
</tr>
<tr>
<td>C(3) - C(4) - C(7)</td>
<td>107.39 (8)</td>
</tr>
<tr>
<td>C(3) - C(4) - C(9)</td>
<td>110.24 (8)</td>
</tr>
<tr>
<td>C(7) - C(4) - C(9)</td>
<td>109.24 (8)</td>
</tr>
<tr>
<td>C(3) - C(4) - C(5)</td>
<td>107.85 (8)</td>
</tr>
<tr>
<td>C(7) - C(4) - C(5)</td>
<td>110.05 (8)</td>
</tr>
<tr>
<td>C(9) - C(4) - C(5)</td>
<td>111.97 (8)</td>
</tr>
<tr>
<td>O(3') - C(4') - C(5)</td>
<td>109.10 (8)</td>
</tr>
<tr>
<td>O(3') - C(4') - C(5')</td>
<td>102.68 (7)</td>
</tr>
<tr>
<td>C(5) - C(4') - C(5')</td>
<td>114.03 (8)</td>
</tr>
<tr>
<td>O(3') - C(4') - H(4')</td>
<td>110.3</td>
</tr>
<tr>
<td>C(5) - C(4') - H(4')</td>
<td>110.3</td>
</tr>
<tr>
<td>C(5') - C(4') - H(4')</td>
<td>110.3</td>
</tr>
<tr>
<td>O(1') - C(5') - C(4')</td>
<td>105.13 (8)</td>
</tr>
<tr>
<td>O(1') - C(5') - H(5'1)</td>
<td>110.7</td>
</tr>
<tr>
<td>C(4') - C(5') - H(5'1)</td>
<td>110.7</td>
</tr>
<tr>
<td>O(1') - C(5') - H(5'2)</td>
<td>110.7</td>
</tr>
<tr>
<td>C(4') - C(5') - H(5'2)</td>
<td>110.7</td>
</tr>
<tr>
<td>H(5'1) - C(5') - H(5'2)</td>
<td>108.8</td>
</tr>
<tr>
<td>C(4') - C(5) - C(6)</td>
<td>110.38 (8)</td>
</tr>
<tr>
<td>C(4') - C(5) - C(4)</td>
<td>114.30 (8)</td>
</tr>
<tr>
<td>C(6) - C(5) - C(4)</td>
<td>110.48 (8)</td>
</tr>
<tr>
<td>C(4') - C(5) - H(5)</td>
<td>107.1</td>
</tr>
<tr>
<td>C(6) - C(5) - H(5)</td>
<td>107.1</td>
</tr>
<tr>
<td>C(4) - C(5) - H(5)</td>
<td>107.1</td>
</tr>
<tr>
<td>C(1) - C(6) - C(5)</td>
<td>113.03 (8)</td>
</tr>
<tr>
<td>C(1) - C(6) - H(6A)</td>
<td>109.0</td>
</tr>
<tr>
<td>C(5) - C(6) - H(6A)</td>
<td>109.0</td>
</tr>
<tr>
<td>C(1) - C(6) - H(6B)</td>
<td>109.0</td>
</tr>
<tr>
<td>C(5) - C(6) - H(6B)</td>
<td>109.0</td>
</tr>
<tr>
<td>H(6A) - C(6) - H(6B)</td>
<td>107.8</td>
</tr>
</tbody>
</table>
Symmetric transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å² x 10³) for exo-171.

The anisotropic displacement factor exponent takes the form:
-2 \pi^2 \left[ h^2 a^* U_{11} + \ldots + 2 h k a^* b^* U_{12} \right]

<table>
<thead>
<tr>
<th></th>
<th>U_{11}</th>
<th>U_{22}</th>
<th>U_{33}</th>
<th>U_{23}</th>
<th>U_{13}</th>
<th>U_{12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>15(1)</td>
<td>12(1)</td>
<td>15(1)</td>
<td>2(1)</td>
<td>8(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>15(1)</td>
<td>20(1)</td>
<td>12(1)</td>
<td>2(1)</td>
<td>4(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(2')</td>
<td>13(1)</td>
<td>14(1)</td>
<td>13(1)</td>
<td>2(1)</td>
<td>5(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>12(1)</td>
<td>17(1)</td>
<td>13(1)</td>
<td>1(1)</td>
<td>3(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>11(1)</td>
<td>14(1)</td>
<td>12(1)</td>
<td>1(1)</td>
<td>5(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(4')</td>
<td>12(1)</td>
<td>13(1)</td>
<td>13(1)</td>
<td>1(1)</td>
<td>5(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(5')</td>
<td>13(1)</td>
<td>16(1)</td>
<td>16(1)</td>
<td>3(1)</td>
<td>5(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>11(1)</td>
<td>12(1)</td>
<td>12(1)</td>
<td>1(1)</td>
<td>5(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>12(1)</td>
<td>14(1)</td>
<td>14(1)</td>
<td>1(1)</td>
<td>6(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>11(1)</td>
<td>17(1)</td>
<td>13(1)</td>
<td>2(1)</td>
<td>3(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>44(1)</td>
<td>17(1)</td>
<td>26(1)</td>
<td>-3(1)</td>
<td>20(1)</td>
<td>-13(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>13(1)</td>
<td>17(1)</td>
<td>16(1)</td>
<td>-1(1)</td>
<td>7(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>16(1)</td>
<td>20(1)</td>
<td>23(1)</td>
<td>0(1)</td>
<td>11(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>17(1)</td>
<td>20(1)</td>
<td>27(1)</td>
<td>-1(1)</td>
<td>9(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>31(1)</td>
<td>14(1)</td>
<td>16(1)</td>
<td>1(1)</td>
<td>10(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>20(1)</td>
<td>15(1)</td>
<td>14(1)</td>
<td>0(1)</td>
<td>7(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>O(1')</td>
<td>15(1)</td>
<td>23(1)</td>
<td>19(1)</td>
<td>8(1)</td>
<td>9(1)</td>
<td>6(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>20(1)</td>
<td>18(1)</td>
<td>19(1)</td>
<td>5(1)</td>
<td>12(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>28(1)</td>
<td>15(1)</td>
<td>17(1)</td>
<td>-3(1)</td>
<td>12(1)</td>
<td>-9(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>20(1)</td>
<td>22(1)</td>
<td>23(1)</td>
<td>7(1)</td>
<td>14(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>O(3')</td>
<td>12(1)</td>
<td>18(1)</td>
<td>13(1)</td>
<td>5(1)</td>
<td>3(1)</td>
<td>-2(1)</td>
</tr>
</tbody>
</table>
Crystal data and structure refinement for 210a

Table 1. Crystal data and structure refinement for 210a.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{20}H_{30}N_{2}O_{6}S_{2}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>458.58</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 13.435(5) Å, alpha = 90.000(5) deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>2199(2) Å³</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4, 1.385 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.281 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>976</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.36x 0.23 x 0.20 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.10 to 27.97 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-17 &lt;= h &lt;= 17, -8 &lt;= k &lt;= 5, -34 &lt;= l &lt;= 34</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>27855 / 5291 [R(int) = 0.0361]</td>
</tr>
</tbody>
</table>
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

Completeness to theta = 27.97° 99.7%

Refinement method Full-matrix least-squares on $F^2$

Data / restraints / parameters 5291 / 0 / 391

Goodness-of-fit on $F^2$ 1.006

Final R indices [I>2sigma(I)] R1 = 0.0335, wR2 = 0.0847

R indices (all data) R1 = 0.0429, wR2 = 0.0903

Largest diff. peak and hole 0.467 and -0.372 e.A$^{-3}$

Table 2. Atomic coordinates (x10$^4$) and equivalent isotropic displacement parameters (A$^2$ x 10$^3$) for 210a.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1')</td>
<td>2222(1)</td>
<td>1931(2)</td>
<td>9051(1)</td>
<td>15(1)</td>
</tr>
<tr>
<td>C(2')</td>
<td>1200(1)</td>
<td>914(3)</td>
<td>8921(1)</td>
<td>21(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>2828(1)</td>
<td>3336(2)</td>
<td>8225(1)</td>
<td>18(1)</td>
</tr>
<tr>
<td>C(3')</td>
<td>612(1)</td>
<td>855(3)</td>
<td>9401(1)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(3A)</td>
<td>6161(1)</td>
<td>4712(2)</td>
<td>8887(1)</td>
<td>18(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>3343(1)</td>
<td>3293(2)</td>
<td>7801(1)</td>
<td>22(1)</td>
</tr>
<tr>
<td>C(4')</td>
<td>543(1)</td>
<td>3054(3)</td>
<td>9647(1)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(4A)</td>
<td>5293(1)</td>
<td>4491(2)</td>
<td>9112(1)</td>
<td>20(1)</td>
</tr>
<tr>
<td>C(5')</td>
<td>1568(1)</td>
<td>4109(3)</td>
<td>9742(1)</td>
<td>21(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>4056(1)</td>
<td>1649(2)</td>
<td>7702(1)</td>
<td>20(1)</td>
</tr>
<tr>
<td>C(5A)</td>
<td>5165(1)</td>
<td>3100(2)</td>
<td>9542(1)</td>
<td>18(1)</td>
</tr>
<tr>
<td>C(6')</td>
<td>2112(1)</td>
<td>4194(2)</td>
<td>9249(1)</td>
<td>18(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>4383(1)</td>
<td>240(3)</td>
<td>8159(1)</td>
<td>20(1)</td>
</tr>
<tr>
<td>C(6A)</td>
<td>6108(1)</td>
<td>2001(3)</td>
<td>9777(1)</td>
<td>19(1)</td>
</tr>
<tr>
<td>C(7')</td>
<td>7929(1)</td>
<td>3825(2)</td>
<td>8709(1)</td>
<td>17(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>7806(1)</td>
<td>2663(3)</td>
<td>8194(1)</td>
<td>21(1)</td>
</tr>
<tr>
<td>C(9')</td>
<td>8764(1)</td>
<td>2841(3)</td>
<td>7916(1)</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(9A)</td>
<td>9063(1)</td>
<td>5155(3)</td>
<td>7847(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(10')</td>
<td>9153(1)</td>
<td>6342(3)</td>
<td>8358(1)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(11')</td>
<td>8194(1)</td>
<td>6168(3)</td>
<td>8640(1)</td>
<td>25(1)</td>
</tr>
<tr>
<td>N(2)</td>
<td>2869(1)</td>
<td>1837(2)</td>
<td>8611(1)</td>
<td>15(1)</td>
</tr>
<tr>
<td>N(2A)</td>
<td>7033(1)</td>
<td>3583(2)</td>
<td>9010(1)</td>
<td>16(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>2674(1)</td>
<td>-1666(2)</td>
<td>8123(1)</td>
<td>23(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>3622(1)</td>
<td>-1549(2)</td>
<td>8962(1)</td>
<td>24(1)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [deg] for 210a.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length  [Å] (E)</th>
<th>Angle  [deg] (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1')-N(2)</td>
<td>1.4947 (17)</td>
<td></td>
</tr>
<tr>
<td>C(1')-C(6')</td>
<td>1.522 (2)</td>
<td></td>
</tr>
<tr>
<td>C(1')-C(2')</td>
<td>1.529 (2)</td>
<td></td>
</tr>
<tr>
<td>C(2')-C(3')</td>
<td>1.533 (2)</td>
<td></td>
</tr>
<tr>
<td>C(3')-C(4)</td>
<td>1.351 (2)</td>
<td></td>
</tr>
<tr>
<td>C(3)-N(2)</td>
<td>1.3787 (18)</td>
<td></td>
</tr>
<tr>
<td>C(3')-C(4')</td>
<td>1.527 (2)</td>
<td></td>
</tr>
<tr>
<td>C(3A)-C(4A)</td>
<td>1.351 (2)</td>
<td></td>
</tr>
<tr>
<td>C(3A)-N(2A)</td>
<td>1.3869 (18)</td>
<td></td>
</tr>
<tr>
<td>C(4)–C(5)</td>
<td>1.443 (2)</td>
<td></td>
</tr>
<tr>
<td>C(4')–C(5')</td>
<td>1.531 (2)</td>
<td></td>
</tr>
<tr>
<td>C(4A)–C(5A)</td>
<td>1.445 (2)</td>
<td></td>
</tr>
<tr>
<td>C(5')–C(6')</td>
<td>1.532 (2)</td>
<td></td>
</tr>
<tr>
<td>C(5)–O(3)</td>
<td>1.2248 (18)</td>
<td></td>
</tr>
<tr>
<td>C(5)–C(6)</td>
<td>1.526 (2)</td>
<td></td>
</tr>
<tr>
<td>C(5A)–O(6)</td>
<td>1.2235 (18)</td>
<td></td>
</tr>
<tr>
<td>C(5A)–C(6A)</td>
<td>1.530 (2)</td>
<td></td>
</tr>
<tr>
<td>C(6)–S(1)</td>
<td>1.7540 (15)</td>
<td></td>
</tr>
<tr>
<td>C(6A)–S(2)</td>
<td>1.7595 (15)</td>
<td></td>
</tr>
<tr>
<td>C(7')–N(2A)</td>
<td>1.4949 (18)</td>
<td></td>
</tr>
<tr>
<td>C(7')–C(12')</td>
<td>1.526 (2)</td>
<td></td>
</tr>
<tr>
<td>C(7')–C(8')</td>
<td>1.530 (2)</td>
<td></td>
</tr>
<tr>
<td>C(8')–C(9')</td>
<td>1.529 (2)</td>
<td></td>
</tr>
<tr>
<td>C(9')–C(10')</td>
<td>1.520 (3)</td>
<td></td>
</tr>
<tr>
<td>C(10')–C(11')</td>
<td>1.528 (3)</td>
<td></td>
</tr>
<tr>
<td>C(11')–C(12')</td>
<td>1.534 (2)</td>
<td></td>
</tr>
<tr>
<td>N(2)–S(1)</td>
<td>1.6704 (16)</td>
<td></td>
</tr>
<tr>
<td>N(2A)–S(2)</td>
<td>1.6713 (16)</td>
<td></td>
</tr>
<tr>
<td>O(1)–S(1)</td>
<td>1.4341 (11)</td>
<td></td>
</tr>
<tr>
<td>O(2)–S(1)</td>
<td>1.4316 (11)</td>
<td></td>
</tr>
<tr>
<td>O(4)–S(2)</td>
<td>1.4334 (12)</td>
<td></td>
</tr>
</tbody>
</table>
Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

O(5)-S(2) 1.4342(11)

N(2) - C(1') - C(6') 111.96(11)
N(2) - C(1') - C(2') 112.05(11)
C(6') - C(1') - C(2') 110.95(12)
C(1') - C(2') - C(3') 109.62(12)
C(4) - C(3) - N(2) 126.37(14)
C(4') - C(3') - C(2') 111.94(13)
C(4A) - C(3A) - N(2A) 126.06(14)
C(3) - C(4) - C(5) 123.20(14)
C(3') - C(4') - C(5') 112.19(13)
C(3A) - C(4A) - C(5A) 123.79(13)
C(4') - C(5') - C(6') 110.89(12)
O(3) - C(5) - C(4) 125.03(14)
O(3) - C(5) - C(6) 119.41(14)
O(6) - C(5A) - C(4A) 124.45(13)
O(6) - C(5A) - C(6A) 119.21(13)
C(4A) - C(5A) - C(6A) 116.26(12)
C(1') - C(6') - C(5') 108.48(12)
C(5) - C(6) - S(1) 110.26(10)
C(5A) - C(6A) - S(2) 111.40(10)
N(2A) - C(7') - C(12') 111.35(12)
N(2A) - C(7') - C(8') 112.09(12)
C(12') - C(7') - C(8') 111.54(13)
C(9') - C(8') - C(7') 110.01(13)
C(10') - C(9') - C(8') 111.44(14)
C(9') - C(10') - C(11') 111.45(14)
C(10') - C(11') - C(12') 111.77(14)
C(7') - C(12') - C(11') 109.64(13)
C(3) - N(2) - C(1') 122.93(12)
C(3) - N(2) - S(1) 117.23(10)
C(1') - N(2) - S(1) 116.36(9)
C(3A) - N(2A) - C(7') 121.65(12)
C(3A) - N(2A) - S(2) 115.96(10)
C(7') - N(2A) - S(2) 116.64(9)
O(2) - S(1) - O(1) 118.10(8)
O(2) - S(1) - N(2) 107.07(7)
O(1) - S(1) - N(2) 109.95(7)
O(2) - S(1) - C(6) 112.32(7)
O(1) - S(1) - C(6) 107.86(7)
N(2) - S(1) - C(6) 100.02(8)
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å² × 10³) for 210a.

The anisotropic displacement factor exponent takes the form:

\[-2 \pi^2 [ h^2 a^* U_{11} + \ldots + 2 h k a^* b^* U_{12} ]\]
## Synthetic studies towards bioactive heterocycles: platensimycin, sultams, and chromones

<table>
<thead>
<tr>
<th></th>
<th>O(6)</th>
<th>20(1)</th>
<th>24(1)</th>
<th>28(1)</th>
<th>0(1)</th>
<th>5(1)</th>
<th>-1(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)</td>
<td>21(1)</td>
<td>11(1)</td>
<td>16(1)</td>
<td>1(1)</td>
<td>2(1)</td>
<td>3(1)</td>
<td></td>
</tr>
<tr>
<td>S(2)</td>
<td>16(1)</td>
<td>13(1)</td>
<td>19(1)</td>
<td>3(1)</td>
<td>0(1)</td>
<td>1(1)</td>
<td></td>
</tr>
</tbody>
</table>