The Enantioselective Total Synthesis of (-)-Hyperolactone C and Related Spirolactone Analogues Using a Diverted Metallocarbenoid O-H Insertion Strategy

Thesis for the degree of Doctor of Philosophy

Faculty of Science

School of Chemistry

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Submitted, September 2024

Abstract

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This thesis outlines and details the development of synthetic methodology achieving the enantioselective total synthesis of (-)-hyperolactone C, privileged spirolactone analogues and their related novel derivatives. The research described herein provides an elegant, accessible route to the particularly synthetically challenging spirocyclic hyperolactone topology, utilising a diverted metallocarbenoid O-H insertion transformation to enable the stereospecific assembly of densely functionalised spirolactones, from α-diazolactone and β-hydroxyketone precursors in a single step process. Chapter One introduces the hyperolactone natural product series, summarises previously reported research employed to synthesise the secondary metabolites and provides a summary of the key methodology used to construct the vicinal quaternary stereocentres of the mutually complex biologically active spirocyclic framework. Chapter Two documents the development of efficient enantioselective syntheses of suitably selected novel hyperolactone model systems from multiple synthetic strategies, enabling the direct access to, or late-stage diversification of, various hyperolactone analogues. Chapter Three discusses a devised chiral pool approach used to obtain enantioenriched α-diazolactone intermediates that were utilised to stereospecifically construct various spirolactones that were further functionalised to complete the enantioselective synthesis of (-)-hyperolactone C, and the divergent isolation of unnatural secondary metabolite variants. This chapter also details research towards an asymmetric transformation and the synthesis of novel spiro-pyranones through a ring expansion extension of the key methodology. Chapter Four reviews key findings and accomplishments of the provided research, and presents future work required for the continued advancement of this methodology. This thesis concludes with Chapter Five providing experimental procedures and full characterisation data for all synthesised compounds discussed.

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Declaration of Authorship

I, Kyran David Whymark, declare that this thesis and the work presented in it are my own and have been generated by me as the result of my own original research.

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I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this university;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this university or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
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6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. None of this work has been published before submission.

Acknowledgements

Firstly, I would like to acknowledge and thank my supervisor, Professor Christopher Hayes, for his time, expert support and guidance that he has given me throughout my research. I would also like to express my gratitude and thanks to my industrial supervisor, Dr Simon Nicolle, for organising and supporting me during my secondment at GlaxoSmithKline, and for allowing me to discuss and present my research at the EPSRC funded GlaxoSmithKline - University of Strathclyde - University of Nottingham Prosperity Partnership.

In addition to the above, I would like to recognise all those that I have had the pleasure of working alongside within the Hayes Research Group: Dr Michael Green, Reema Sadia, John Fox, Hannah Simpson, Dr Ephraim Okolo, Dr Jozef Park, Dr Sarah Memarzadeh, Benjamin Owen and the many project students who have been a delight to support. In addition, I thank all of the remaining members of laboratory C13, the GlaxoSmithKline Medicinal Chemistry Department and the wider University of Nottingham community who have made my time at Nottingham an enjoyable and worthwhile experience.

I would also like to thank members of staff from the Chemistry Department Analytical Services for their efficient technical support, in addition to Dr Stephen Argent and Dr Benjamin Weare for the x-ray crystallography structure determinations.

This research would not have been possible without the funding and support from the EPSRC Industrial Cooperative Awards in Science and Engineering (ICASE) studentship, in conjunction with GlaxoSmithKline and the University of Nottingham. My thanks and gratitude to all of these organisations.

Finally, I would like to give special thanks to my parents, family and friends who provided me with unceasing encouragement and support.

Definitions and Abbreviations

Ac	Acetyl-
API	Active pharmaceutical ingredient
Ar	Aryl-
ATR	Attenuated total reflection
BINOL	1,1′-Bi-2-naphthol
Bn	Benzyl-
BNP	(*R*)-(−)-1,1′-Binaphthalene-2,2′-diyl hydrogen phosphate
Boc	*tert*-Butyloxycarbonyl-
BOX	Bis(oxazoline)
CCDC	Cambridge Crystallographic Data Centre
CoA	Coenzyme A
COSY	Homonuclear correlation spectroscopy
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
decomp.	Decomposition
DEPT	Distortionless enhancement by polarization transfer
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dr	Diastereoisomeric ratio

DSC	Differential scanning calorimetry
EC_{50}	Half maximal effective concentration
ee	Enantiomeric excess
equiv.	Equivalents
Grubbs II	Dichloro[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](benzylidene)(tricyclohexylphosphine)ruthenium(II)
HMBC	Heteronuclear multiple bond correlation spectroscopy
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
h	Hours
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear spin quantum correlation spectroscopy
IBX	2-Iodoxybenzoic acid
IL-10	Interleukin 10
IR	Infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	Potassium bis(trimethylsilyl)amide
LCMV	Lymphocytic choriomeningitis mammarenavirus
LDA	Lithium diisopropylamide
lit.	Literature
m-CPBA	*meta*-Chloroperbenzoic acid
Met	Metal
min	Minutes
MOM	Methoxymethyl-
mp	Melting point
MPO	4-Methoxypyridine *N*-oxide hydrate
MS	Molecular sieves

MVK	Methyl vinyl ketone
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
- s	singlet
- d	doublet
- t	triplet
- q	quartet
- p	pentet
- m	multiplet
- app	apparent
- br	broad
NOESY	Nuclear overhauser effect spectroscopy
Oct	Octanoate
ORTEP	Oak ridge thermal ellipsoid plot
p-ABSA	4-Acetamidobenzenesulfonyl azide
Pd-AAA	Palladium catalysed asymmetric allylic alkylation
PG	Protecting group
PMB	*para*-Methoxybenzyl-
ppm	Parts per million
PPO	Diphosphate
Pr	Propyl-
PTSA	*para*-Toluenesulfonic acid
R_f	Retention factor
rr	Regiomeric ratio
rt	Room temperature
SAR	Structure activity relationship
SET	Single electron transfer

TBS	*tert*-Butyldimethylsilyl-
TBAI	Tetrabutylammonium iodide
TES	Triethylsilyl-
TFA	Trifluoracetic acid
Tf	Trifluoromethanesulfonyl-
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl-
TLC	Thin-layer chromatography
TMS	Trimethylsilyl-
TPP	Tetraphenylporphyrin
Ts	*para*-Toluenesulfonyl-
TsNIK	Potassium *N*-iodo *p*-toluenesulfonamide (Iodamine-T)
UV	Ultraviolet

Chapter 1: Introduction

1.1 *Hypericum* Derived Natural Products: Hyperolactone C, Biyouyanagin A and the Hyperolactone Series

Up until the 18th century, preparations of plant extracts or inorganic materials, identified by traditional folklore, were relied upon to treat the sick and vulnerable. These natural materials have often led to the discovery, isolation and characterisation of secondary metabolites that exhibit desirable biological responses within humans and animals, allowing these structurally diverse compounds to be applied as therapeutic treatments against numerous diseases and disorders. Plant species of the *Hypericum* genus, belonging to the family Hypericaceae, have provided an abundant source of various natural product classes that have been widely employed in traditional medicines across the world. Consisting of over five-hundred species distributed across all of the world's temperate climates, many *Hypericum* plants have been extensively studied by researchers, leading to the discovery of a plethora of synthetically challenging biologically active terpenoid and polyketide-based natural products, such as xanthones, flavonoids, naphthodianthrones and polyprenylated acylphloroglucinols.[1]

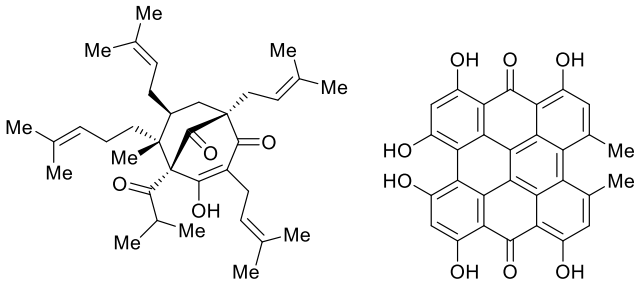


Figure 1-1: *Biologically active natural products isolated form Hypericum perforatum L.*

Attracting significant global interest, *Hypericum perforatum L.* (St. John's Wort) is the most renowned *Hypericum* species that has been used as a herbal panacea since the Ancient Greeks and Romans.[2] Oil extracts of *Hypericum perforatum L.* contain a broad range of natural products that exhibit various biological properties, such as antiviral, antioxidant and antimicrobial responses, with (+)-hyperforin **1** and

hypericin **2** being the most abundant active secondary metabolites (***Figure 1-1***).[3] Today, extracts of St. John's Wort are mainly used to treat depression, as well as other psychological disorders, although many clinical studies have indicated that the active pharmaceutical ingredients (APIs) can be harmful when taken alongside other medication.[4,5] Subsequently, many European countries have tight regulatory controls on the use of the botanical-based medicinal product, whereas St. John's Wort is currently considered a herbal/dietary supplement by the United States Food and Drug Administration with limited regulation.[6] The primary congener, (+)-hyperforin **1**, a terpenoid-based polycyclic polyprenylated acylphloroglucinol, has been demonstrated to possess antimalarial, antidepressant and human histone deacetylase inhibitory activities, in addition to displaying a potent induction activity for the cytochrome P450 enzyme 3A4.[7] The natural product's medicinal properties and synthetically challenging bicyclo[3.3.1]nonane core have inspired multiple successful enantioselective total syntheses of (+)-hyperforin **1**.[8,9] Hypericin **2**, a polyketide-based natural product, is another major biologically active constituent of *Hypericum perforatum L.* that possesses antiviral and antitumour properties, making this highly conjugated naphthodianthrone a highly attractive natural product target. With applications as a photodynamic therapy agent, hypericin **2** induces apoptosis of cancerous tissues through photoirradiation, motivating significant advances in the total synthesis, semi-synthesis and biosynthesis of the phenanthoperylene quinone.[10,11]

The broad range of characteristic natural products isolated from *Hypericum perforatum L.* has instigated studies into many other *Hypericum* species, leading to the discovery of additional secondary metabolites with remarkable properties. *Hypericum monogynum*, also referred to as *Hypericum chinense L. var. salicifolium*, is a closely related flowering evergreen shrub originating from China that has provided a rich source of specialised compounds containing highly diverse novel three-dimensional scaffolds with multiple stereocentres. The plant's roots are still used to treat rheumatic diseases and furuncles in China, whereas the stems and leaves have been used to treat various gynaecological disorders in Japan. Now grown as an ornamental plant in Japan, *Hypericum monogynum*, otherwise known in Japanese as Biyouyanagi, has led to the discovery of several natural product families that include: chipericumins A-D, chinesins I and II, biyoulactones A-E, merohyperins A-C and around fifty-xanthones that include biyouxanthones A-D.[1] These natural product

families have unique polycyclic ring systems with highly rich sp^3-hybridised carbon frameworks that give rise to their inherent biological activities.

Isolated from the stems and leaves of *Hypericum monogynum*, Tada *et al*. first isolated, characterised and assigned the relative stereochemistry of a highly strained spirocyclic lactone metabolite that was named 'hyperolactone' **3**.[12] Further investigations by Tada and co-workers later isolated and characterised an additional set of spirolactones, along with a related linear meroterpene, which were arbitrarily assigned as hyperolactones A-D **3**-**6** (***Figure 1-2***).[13] The biosynthesis of the common carbon skeleton was also speculated to be derived from isopentenyl pyrophosphate, with meroterpene **6** suspected to be a biosynthetic precursor of (-)-hyperolactone C **5**. Reporting the first total syntheses of hyperolactones A-C,[14,15] subsequent synthetic efforts from Kinoshita *et al*. permitted the absolute stereochemistry of the spirolactone framework to be confirmed, utilising X-ray crystallographic, spectroscopic and optical rotation data.

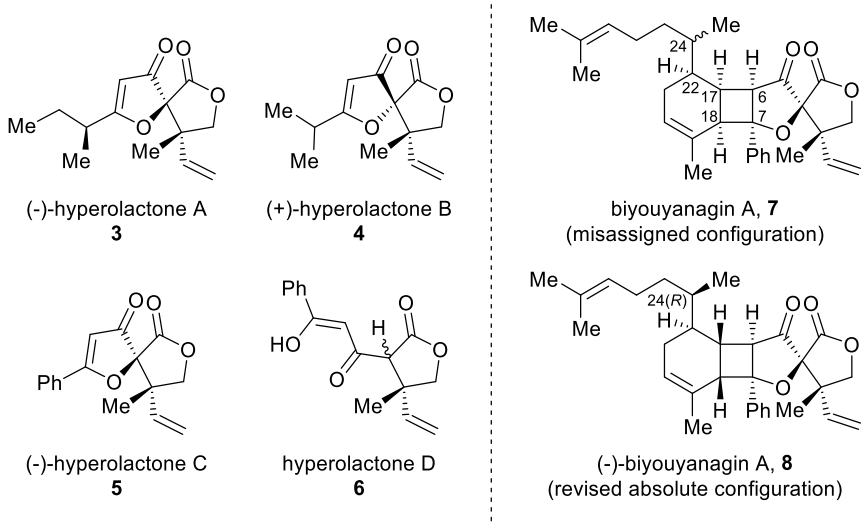


Figure 1-2: *(-)-Hyperolactone C, (-)-biyouyanagin A and the hyperolactone series.*

Aiming to discover further bioactive natural products from the dried leaves of *Hypericum monogynum*, Tanaka *et al.* extracted and isolated a novel hydrophobic meroterpene containing a sesquiterpene, cyclobutane and hyperolactone moiety, which was named biyouyanagin A **8** (***Figure 1-2***).[16] With the hyperolactone C motif incorporated into the six-four-five-five tetracyclic ring system, the stereochemical assignment was initially proposed with a *cis-syn-cis* configuration, with respect to the cyclobutane motif (**7**), which was deduced from key NOESY NMR correlations

between 6-*H* and 17-*H*, 22-*H* and Ar*H*, and 17-*H* and 18-*H*. Despite remaining ambiguity of the stereochemistry at the *C*24 position, biyouyanagin A **8** was biologically screened for antiviral activity against HIV, revealing an efficacious and selective inhibition of HIV replication in H9 lymphocytes (EC_{50} = 0.798 μg/mL) when compared to uninfected cells (EC_{50} >25 μg/mL), resulting in a therapeutic index (TI) value of >31.3. Additionally, biyouyanagin A **8** exhibited potent inhibition of lipopolysaccharide (LPS)-induced cytokine production (at 10 μg/mL: lL-10 = 0.03; IL-12 = 0.02; tumour necrosis factor-α (TNFα) = 0.48) from peripheral blood mononuclear cells.[16] Tanaka *et al.* also proposed that the biosynthetic pathway of **8** may involve the [2+2] photocyclisation of hyperolactone C **5**, also isolated from the leaves of *Hypericum monogynum*, with either *ent*-zingiberene **9** or *ent*-7-*epi*-zingiberene **10**, monocyclic terpenoids formed during the isoprenoid pathway (***Figure 1-3***).

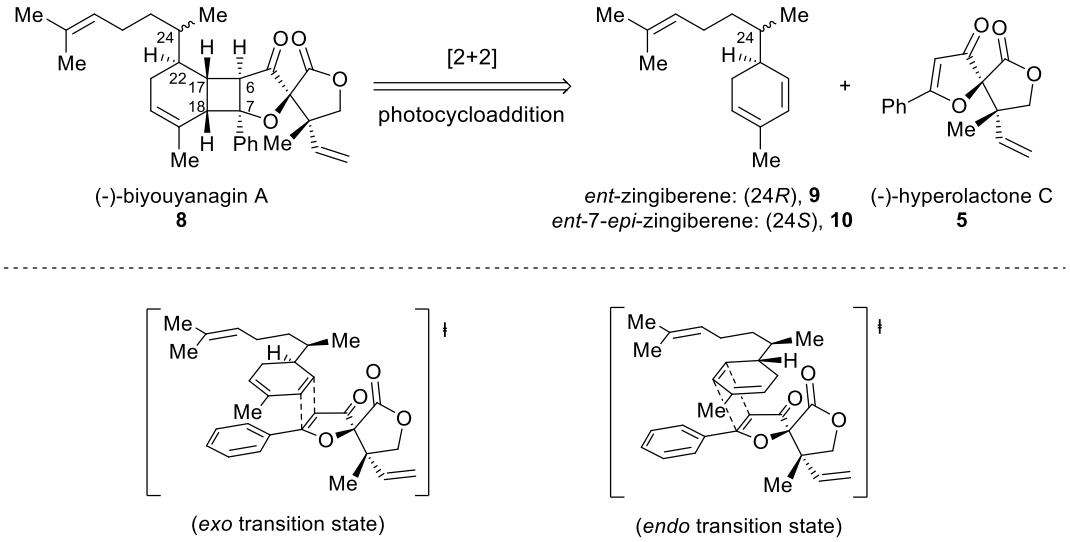


Figure 1-3: *Proposed retrosynthetic analysis of (-)-biyouyanagin A, highlighting the energetically favoured exo and sterically disfavoured endo transition states.*

With a strong therapeutic potential as a drug discovery lead, Nicolaou *et al.* reported the first total synthesis of (-)-biyouyanagin A **8**,[17,18] exploiting the previously proposed biosynthetic [2+2] photocycloaddition disconnection of the cyclobutane ring. Seeking to clarify the stereochemistry at the *C*24 position, Nicolaou and colleagues synthesised both the *C*24*R* and *C*24*S* epimers of biyouyanagin A through the photocycloaddition of (-)-hyperolactone C **5** with both *ent*-zingiberene **9** and *ent*-7-*epi*-zingiberene **10**, thus reporting the total syntheses of all of the natural product precursors utilising a chiral pool approach from (*S*)-malic acid, (*R*)- and (*S*)-citronellal

respectively. The photocycloadditions performed by the Nicolaou Group made it possible to determine the absolute configuration of (-)-biyouyanagin A **8**, which enabled the assignment of the *R*-configuration at the *C*24 position, as well as stereochemical revisions at the *C*17 and *C*18 positions. Rationalised through steric considerations between the cyclohexene and lactone ring components, the *exo* transition state of the [2+2] photocycloaddition was energetically favoured over the *endo* transition state, leading to the revised *cis-anti-cis* arrangement of the cyclobutane ring (***Figure 1-3***). With consistent spectroscopic and optical rotation data, the misassignment of the *C*17 and *C*18 positions may have occurred from the assumption that the key nOe correlation between 6-*H* and 17-*H* was incorrectly assumed to have a *syn*-relationship, as adjacent *trans* protons of a cyclobutane may still exhibit nOe correlations. Additionally, the absence of a strong correlation between 18-*H* and Ar*H* contradicted the original assignment (**7**), which was unambiguously confirmed by X-ray crystallographic analysis (***Figure 1-4***).

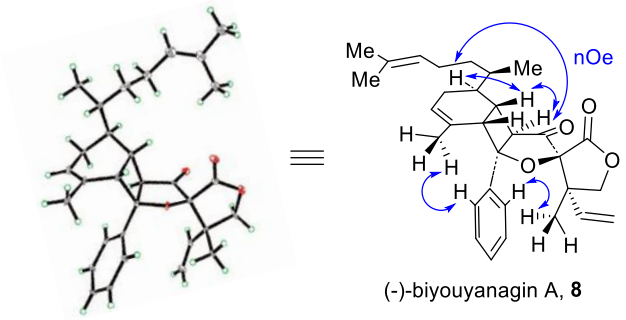


Figure 1-4: *ORTEP of (-)-biyouyanagin A, with displacement ellipsoids drawn at the 30% probability level [CCDC 706843],*[18] *depicted alongside several key nOe interactions.*

Having established an efficient convergent synthetic route to the biyouyanagin architecture, Nicolaou *et al.* then carried out structure activity relationship (SAR) studies in pursuit of an analogue with an enhanced pharmacological activity and a simplified molecular framework.[19] The Nicolaou Group constructed a biyouyanagin based compound library from the photocycloadditions of various synthesised hyperolactone derivatives with several olefin building blocks. The resulting biyouyanagin and hyperolactone analogues were then biologically screened in various assays for antiviral and anti-inflammatory activities against lymphocytic choriomeningitis mammarenavirus (LCMV), HIV and LPS-induced cytokine production. Using a previously outlined biological assay,[20] epifluorescence microscopy

determined (-)-biyouyanagin A **8**, along with a handful of biyouyanagin analogues, to have significant antiviral activity against LCMV at concentrations of 50 μM, with no noticeable toxicity observed for the utilised BHK-21 cell line. With an unknown mechanism of action, the active compounds were found to inhibit virus replication and gene expression rather than viral cell binding. Intriguingly, all tested hyperolactone compounds were found to have poor activities against LCMV, in direct contrast to their observed anti-HIV activities.

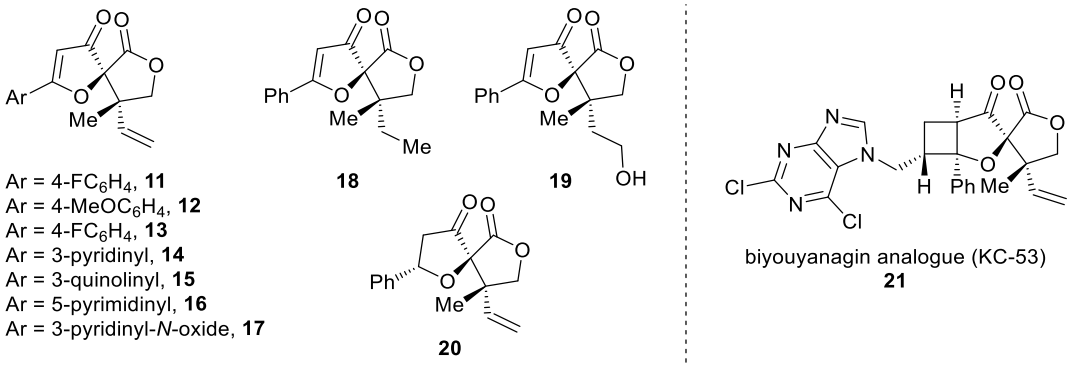


Figure 1-5: *Biologically screened hyperolactone derivatives and the chemical structure of potent biyouyanagin analogue KC-53.*

Many members of the synthesised biyouyanagin and hyperolactone compound libraries were found to have large degrees of inhibition for HIV-1 replication in MT-2 lymphocytes, as well as potent inhibitory effects across multiple inflammatory LPS-induced cytokines. SAR studies involving hyperolactone derivatives **11**-**20** indicated that aromatic substituent substitutions on the furan-3(2*H*)-one moiety had limited benefits within the biological assays but could be exploited to improve pharmacokinetic properties of importance. Modification of the vinyl bearing lactone ring, along with varying the olefin cycloaddition partner, revealed that the spirocyclic hyperolactone domain was the likely cause of the observed bioactivity and that all diastereoisomers of hyperolactone C significantly reduced LPS-stimulated inflammatory IL6 release in the human macrophage THP-1 cell line. Biyouyanagin analogue KC-53 **21** demonstrated the greatest potency in the HIV neutralisation assay (IC_{50} = 7.00 μM) and had the greatest anti-inflammatory performance, with a 90-96% inhibition of TNFα and interleukins IL6 and IL1β at 10 μM, across the chemical series. The nucleic acid base-biyouyanagin hybrid **21** also exhibited cytokine selectivity, as negligible effects for the production of IL1α or IL8 were observed. Demonstrating superior biological assay results, with respect to the other tested analogues, Nicolaou

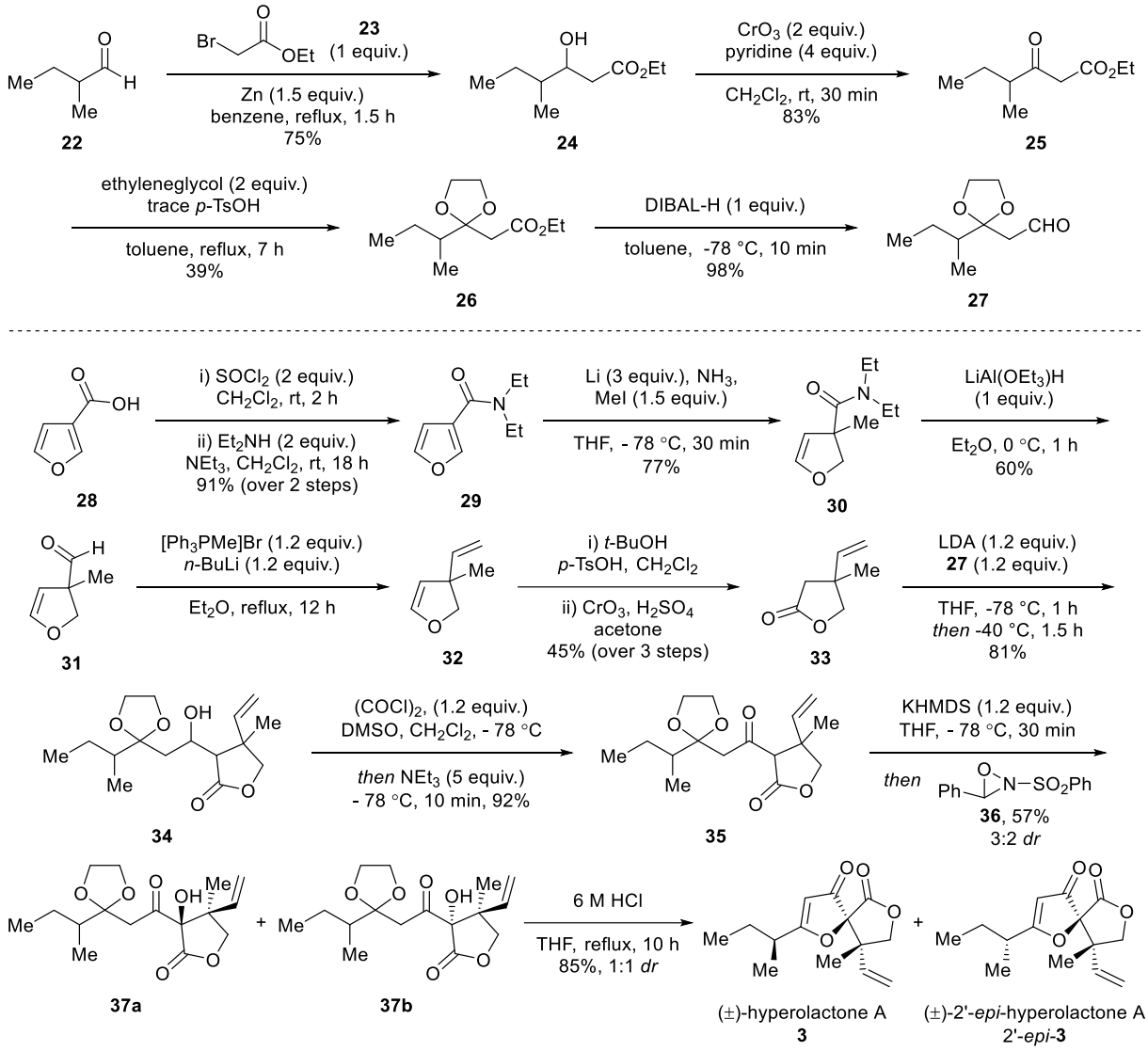
and co-workers did question whether KC-53's **21** properties were derived from the dichloronucleobase component or that of the biyouyanagin moiety. The post-photocycloaddition modified analogue was later the subject of further investigations of anticancer properties for a panel of cell lines by Constantinou *et al*.[21] Detailed studies of KC-53's **21** mechanism of action revealed the facilitation of apoptosis through both an extrinsic and intrinsic pathway. By promoting rapid irreversible apoptosis in leukemic cell lines at relatively low concentrations, KC-53 **21** has a highly promising application as a targeted therapeutic that could be particularly effective in treating acute leukemias that respond poorly to conventional chemotherapeutic agents that induce only the intrinsic apoptosis pathway.

Secondary metabolites remain critical contributors to the modern-day drug discovery process as project leads, with the pharmaceutical industry annually investing millions of pounds into the development of natural products inspired APIs that are efficacious, display limited adverse biological responses and possess favourable psychopharmacological profiles. With biyouyanagin and hyperolactone associated derivatives acting as valued chemical probes towards antiviral, anticancer and anti-inflammatory agents, synthetic methodologies that provide access to the challenging hyperolactone motif are extremely valuable. Subsequently, the therapeutically significant hyperolactone scaffold remains an attractive synthetic target, with the enantioselective construction of the vicinal quaternary stereocentres and complex spirocyclic topology, posing a major synthetic challenge.

1.2 Total Syntheses of Hyperolactone C

1.2.1 First Reported Total Syntheses of Hyperolactones A-C

Following the discovery of hyperolactones A-C by Tada *et al*.,[12,13] Kinoshita and colleagues reported the first total synthesis of (±)-hyperolactone A,[22] synthesising the spirocyclic core through an aldol addition between aldehyde **27** and lactone **33** (***Scheme 1-1***). Aldehyde **27** was prepared from a Reformatsky reaction, between 2-methylbutanal **22** and ethyl bromoacetate **23**, which was followed by a subsequent Collins oxidation, acetal protection, and DIBAL-H reduction sequence, affording the racemic aldehyde fragment in a moderate yield.



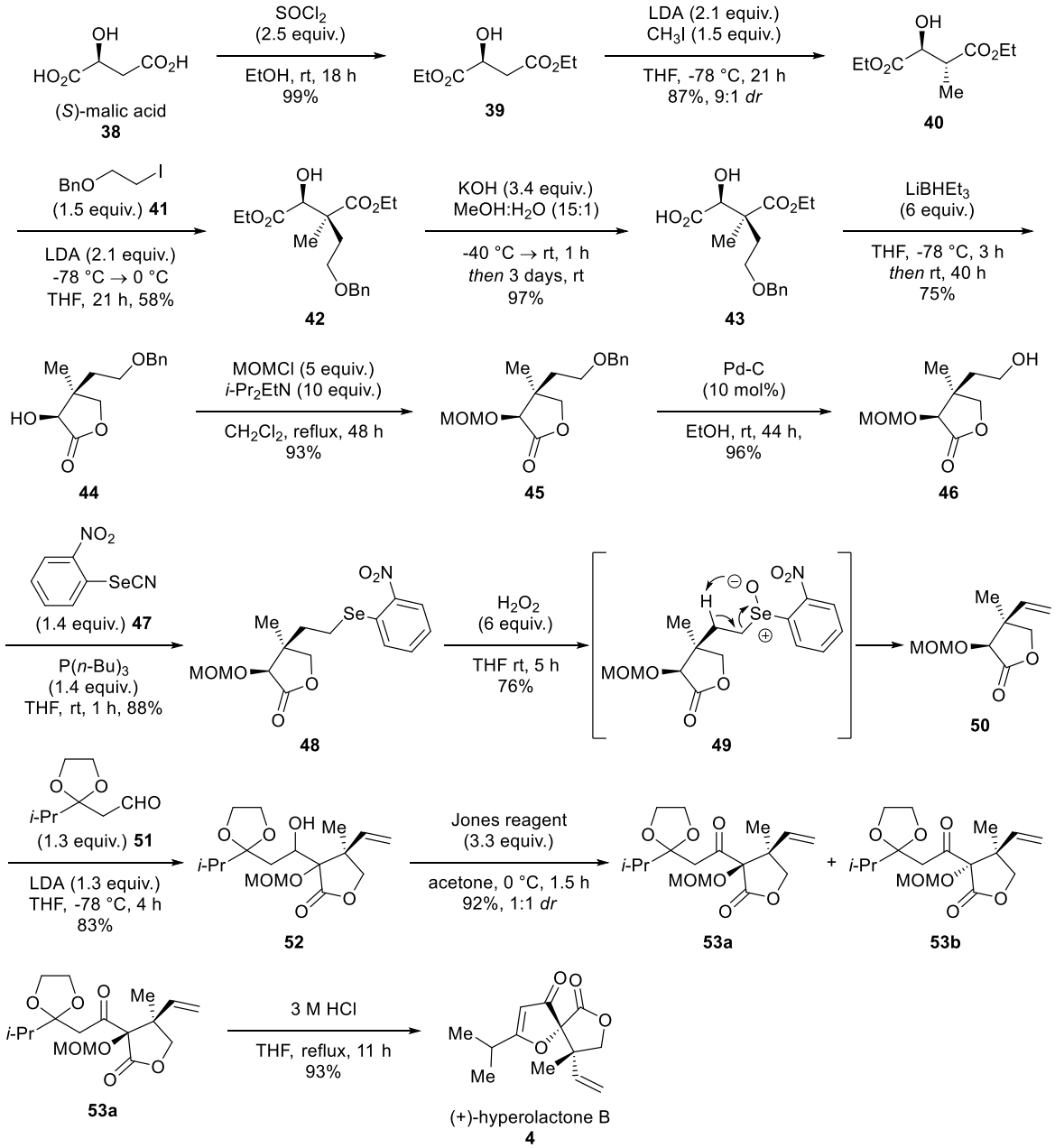
Scheme 1-1: *The first total synthesis of (±)-hyperolactone A.*

Lactone fragment **33** was synthesised from a seven-step sequence commencing with the conversion of 3-furoic acid **28** to *N*,*N*-diethylfuran-3-carboxamide **29**, *via* the corresponding acid chloride. Kinoshita *et al*. then utilised their previously developed and optimised Birch reduction-reductive alkylation procedure, affording *N*,*N*-dialkyl-3-alkyl-2,3-dihydro-3-furamides from 3-furamides,[23] to synthesise intermediate **30** in good yield. Unfortunately, the direct reductive alkylation of 3-furoic acid **28** to the resulting 3-alkyl-2,3-dihydro-3-furancarboxylic acid proceeded with an alternative ring opening decomposition of the *in situ* generated dianion. However, utilising the weaker anion-nitrogen lone pair interaction of furamides mitigated the competing facile ring opening, permitting the synthesis of **30**. Reducing intermediate **30** with lithium triethoxyaluminium hydride, freshly prepared by reacting lithium aluminium hydride

with three equivalents of ethanol, efficiently afforded aldehyde **31**. A three-step sequence involving a Wittig reaction with methyltriphenylphosphonium bromide, an acid-catalysed hydroxylation and a final Jones oxidation synthesised lactone **33**. An aldol addition of aldehyde **27** with the lithium enolate of lactone **33** furnished alcohol **34**, as a mixture of diastereoisomers, which was then converted to ketone **35** by employing a Swern oxidation. Affording chromatographically separatable α-hydroxyketones **37a-b**, a Davis oxidation, involving an oxygen atom transfer from 2-(phenylsulfonyl)-3-phenyloxaziridine **36** (Davis' reagent),[24] obtained **37a-b** (3:2 *dr*) in favour of the undesired diastereoisomer (**37a**). A final one-pot acid-catalysed procedure with minor diastereoisomer **37b**, involving a deprotection, cyclisation and elimination process, then installed the spirocyclic quaternary stereocentre, synthesising both (±)-hyperolactone A **3** and the unnatural epimer (1:1 *dr*), (±)-2'-*epi*-hyperolactone A 2'-*epi*-**3**, in ten-steps from the longest linear sequence, with overall yields of 1.1%. Despite exploiting an efficient one-pot procedure to directly construct the spirolactone moiety, utilising starting material and intermediate racemates established racemic stereocentres on both the hyperolactone core and the *sec*-butyl substituent. Furthermore, this lengthy synthetic route employs an aldol addition with no stereochemical control and a Davis oxidation that proceeds with an undesired diastereoselectivity.

Overcoming current enantioselectivity and diastereoselectivity issues, Kinoshita *et al*. then developed an enantioselective synthetic route to the hyperolactone motif, achieving the first total synthesis of (+)-hyperolactone B and confirming the natural product's presumed absolute configuration (***Scheme 1-2***).[14] Employing a chiral pool synthetic strategy to synthesise key aldol precursor **50**, (*S*)-malic acid first underwent a chemoselective thionyl chloride induced esterification to afford diethyl (*S*)-2-hydroxysuccinate **39**. Following a kinetically controlled Fráter-Seebach alkylation of the dianion of **39** with iodomethane,[25,26] hydroxysuccinate ester **40** was isolated as a mixture of diastereoisomers, in favour of the *erythro* diastereoisomer (9:1 *dr*), rationalised from the preferentially formed conformationally favoured *anti*-product. A successive diastereoselective alkylation of hydroxysuccinate ester **40**, with ((2-iodoethoxy)methyl)benzene **41**, then obtained **42** as a single enantiomer. Isolated from a chemoselective basic hydrolysis, the resultant hydroxysuccinate acid **43** was treated with lithium triethylborohydride (Super-Hydride®) to afford hydroxylactone **44**

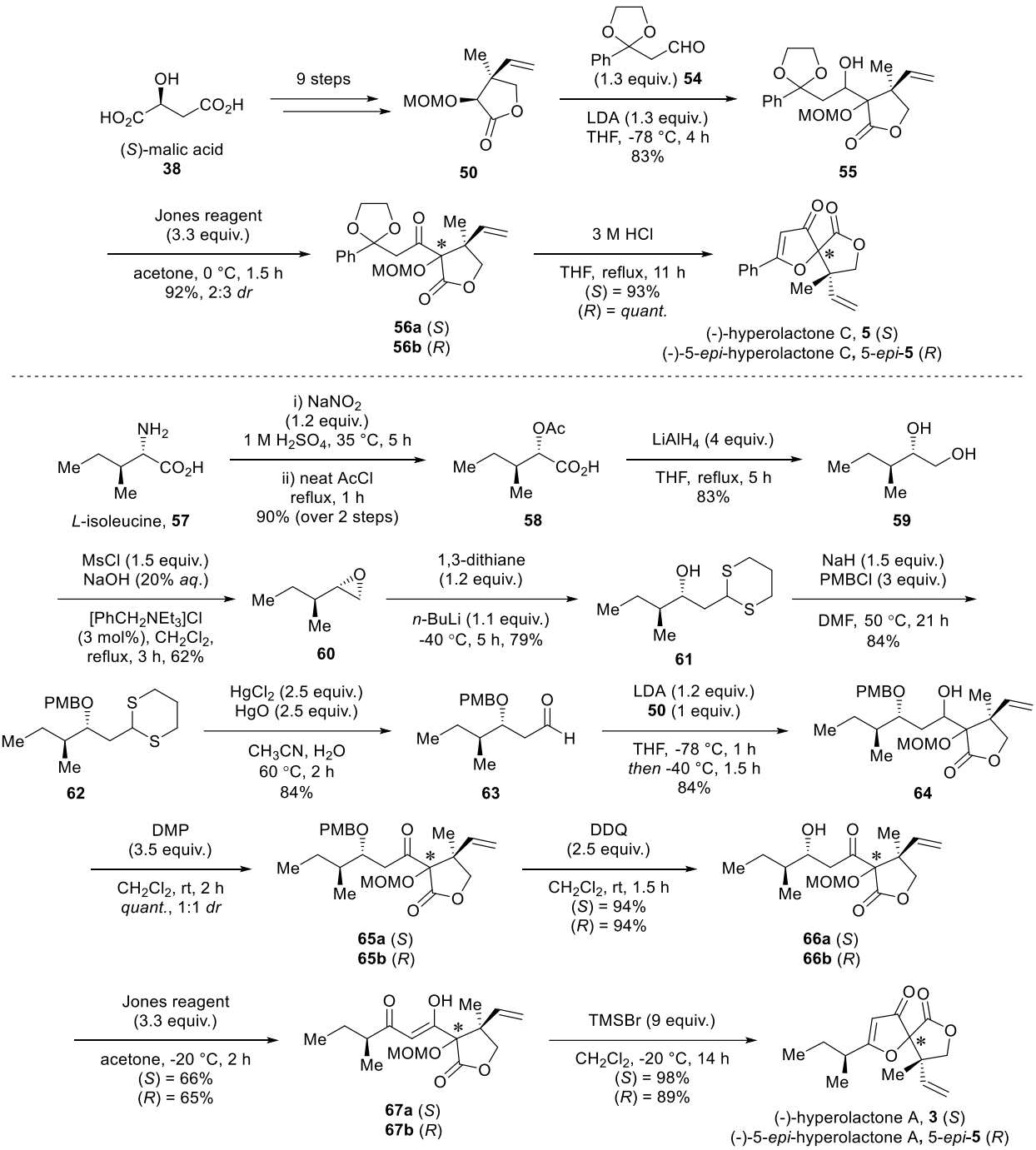
from a reductive cyclisation. Upon lactonisation, a methoxy ether alcohol protection and subsequent debenzylation then furnished primary alcohol **46** in excellent yield. Alcohol **46** then underwent a two-step Grieco elimination,[27] involving the formation of selenide **48** and a successive oxidative *syn*-elimination, to instal the vinyl substituent.



Scheme 1-2: *The first enantioselective total synthesis of (+)-hyperolactone B.*

With enantiopure lactone **50** to hand, an aldol addition with aldehyde **51**, synthesised from isobutyraldehyde utilising Kinoshita and co-worker's previously outlined four-step sequence (***Scheme 1-1***), produced alcohol **52** as an inseparable mixture diastereoisomers. A Jones oxidation then afforded chromatographically

separatable ketones **53a-b** with a diastereomeric ratio of 1:1, derived from the key aldol addition. Identifying the configurations of the resulting diastereoisomers from the nOe correlation between the methyl group of the lactone and the MOM methylene, the previously utilised key acid-catalysed spirocyclisation transformation of **53a** completed the enantioselective total synthesis of (+)-hyperolactone B in twelve-steps from the longest linear sequence, with an overall yield of 7.7%.



Scheme 1-3: *The first enantioselective total syntheses of (-)-hyperolactone C and (-)-hyperolactone A.*

Having developed an enantioselective route to the hyperolactone carbon skeleton, Kinoshita *et al*. then utilised the same aldol addition acid-catalysed spirocyclisation approach to complete the first total synthesis of (-)-hyperolactone C (***Scheme 1-3***).[15] The aldol addition between previously synthesised lactone **50** (***Scheme 1-2***) and aldehyde **54**, accessed from benzaldehyde using Kinoshita and co-worker's previously developed four-step sequence (***Scheme 1-1***), formed alcohol **55** as a mixture of diastereoisomers, which was treated with Jones reagent to obtain ketones **56a-b** (2:3 *dr*). With an unfortunate preferential diastereoselectivity for the undesired diastereoisomer, minor ketone **56a** underwent the key acid-catalysed spirocyclisation to afford (-)-hyperolactone C **5** (6.4% overall yield), whereas major ketone **56a** was reacted under the same conditions to yield (-)-5-*epi*-hyperolactone C 5-*epi*-**5** (9.0% overall yield) in twelve-steps from the longest linear sequence.

Utilising the same synthetic strategy to achieve the enantioselective total synthesis of (-)-hyperolactone A, Kinoshita *et al*. then developed a chiral pool approach to aldol precursor aldehyde **63** from *L*-isoleucine **57**. Performing an initial Van Slyke reaction, the resulting α-hydroxy carboxylic acid product was subsequently acetylated with acetyl chloride to afford **58** in 90% yield over two steps. The preliminary Van Slyke oxidation proceeds with complete stereochemical retention,[28,29] as the labile diazonium intermediate releases nitrogen gas through an intramolecular lactonization to form a reactive α-lactone species, which is then rapidly hydrolysed to the corresponding α-hydroxy carboxylic acid intermediate. A lithium aluminium hydride reduction of acid **58** then obtained diol **59**, which then underwent epoxide formation, in the presence of a phase-transfer catalyst, to afford epoxide **60**. Following this, a ring-opening alkylation installed the 1,3-dithiane functionality, with a successive *para*-methoxybenzyl alcohol protection and 1,3-dithiane deprotection synthesising desired aldehyde **63** over seven-steps. Applying the same synthetic approach, an aldol addition between aldehyde **63** and lactone **50** produced alcohol **64** as an inseparable mixture of diastereoisomers, where a successive Dess-Martin oxidation then produced chromatographically separatable ketones **65a-b** (1:1 *dr*). A DDQ induced *para*-methoxybenzyl cleavage and Jones oxidation then synthesised 1,3-diketones **67a-b**, where the predominantly formed enol tautomer was elucidated from NMR studies. Preventing the use of harsh acidic conditions under extended reflux durations, spirocyclisation of **67a-b** was achieved from a single-step procedure

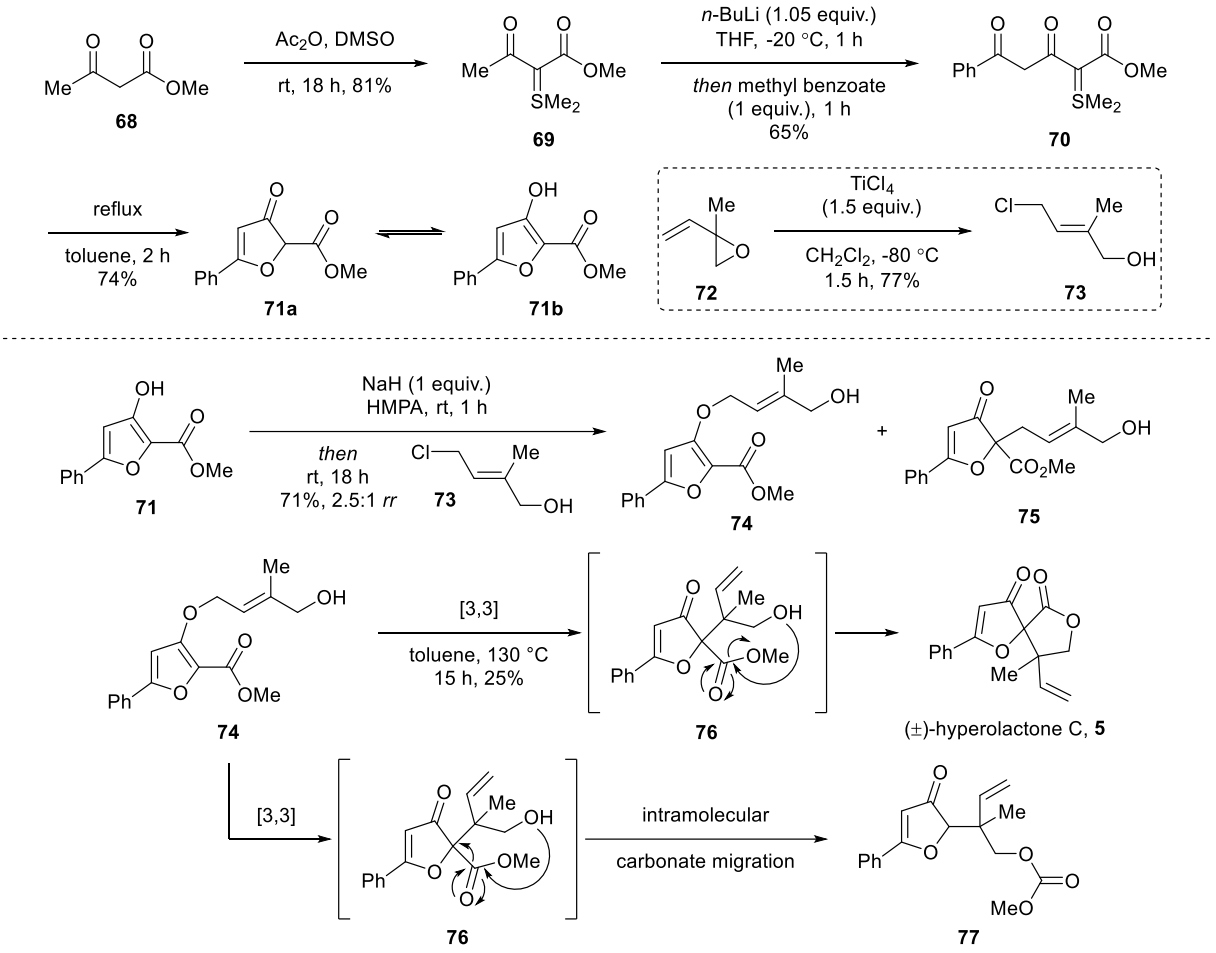
involving the treatment with trimethylbromosilane, completing the total syntheses of both (-)-hyperolactone A **3** and (-)-5-*epi*-hyperolactone A 5-*epi*-**3** in fourteen-steps with overall yields of 6.6% and 5.9% from the longest linear sequence.

Although entailing lengthy linear routes to the spirolactone motif, successful synthetic efforts by Kinoshita *et al.* established the enantioselective total syntheses of hyperolactones A-C and a variety of unnatural epimers, using readily available precursors and a late-stage spirocyclisation strategy, confirming the absolute configurations across the natural product series.

1.2.2 Total Synthesis of (±)-Hyperolactone C Applying a Tandem Claisen Rearrangement-Lactonisation Strategy

Developing a direct synthetic route that utilises a key tandem Claisen rearrangement-lactonisation transformation to construct the spirocyclic core, Kraus *et al*. reported the total synthesis of (±)-hyperolactone C **5** (***Scheme 1-4***).[30] Exploiting a synthetic strategy published by Yamamoto *et al.*,[31] substituted furanol **71** was obtained from methyl acetoacetate **68**, *via* a three-step synthesis. In the presence of excess amounts of acetic anhydride and dimethyl sulfoxide,[32,33] methyl acetoacetate **68** was converted to stabilised sulphonium ylide **69**, where an acylation with methyl benzoate and a successive thermal cyclisation, eliminating dimethyl sulphide, gave furan-3(2*H*)-one **71a**, which was isolated as the predominant furanol **71b** tautomer. Alkylation of furanol **71** with alcohol **73**, accessed from isoprene monoxide **72** through a $TiCl_4$-mediated stereoselective and regioselective epoxide opening,[34] formed a mixture of *O*-alkylated and *C*-alkylated regioisomers **74** and **75**. Unfortunately, the alkylation transformation was found to be highly solvent dependent, with DMF and acetonitrile having no effect on the regioselectivity (1:1 *rr*), whereas toluene was found to solely produce the *C*-alkylated regioisomer **75**. However, Kraus and colleagues found that by using HMPA as the solvent, the desired *O*-alkylated regioisomer **74** was favoured with a modest regiomeric ratio of 2.5:1. Although separable for analytical characterisation, the resulting mixture of regioisomers **74** and **75** underwent a heat induced [3,3]-sigmatropic rearrangement and successive intramolecular

transesterification to afford (±)-hyperolactone C **5** in a satisfactory 25% yield, based on the *O*-alkylated product.



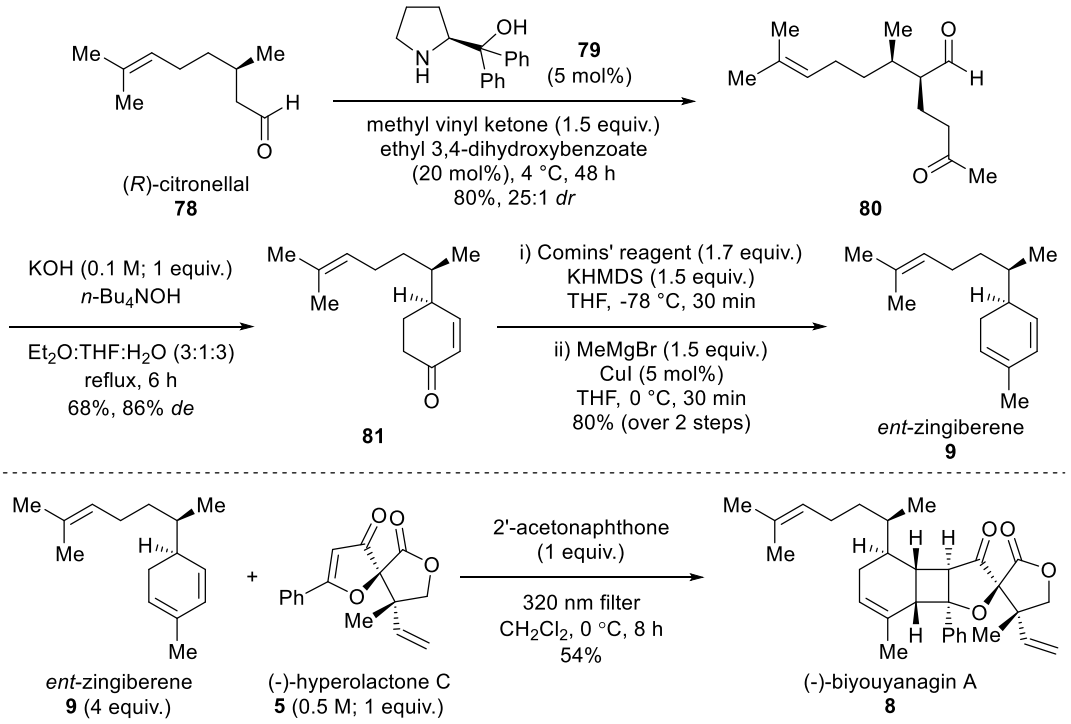
Scheme 1-4: *Total synthesis of (±)-hyperolactone C, using a tandem Claisen rearrangement-lactonisation transformation to construct the spirocyclic core*

Although successfully achieving the desired one-pot tandem Claisen rearrangement-spirocyclisation of furan **74** to (±)-hyperolactone C **5**, Kraus *et al*. also reported the isolation of a major by-product (**77**) from their key transformation, which was misassigned as a mixture of diastereomers of intermediate hydroxyester **76**. In an attempt to induce spirocyclisation, isolated by-product **77** was treated with either PTSA, *t*-BuOK, NaH or KH, and was even subjected to heat, however, none of these conditions failed to construct the hyperolactone motif. Subsequent research by Xie *et al*.,[35] employing a related palladium-catalysed asymmetric allylic alkylation (Pd-AAA) reaction to achieve the enantioselective total synthesis of (-)-hyperolactone C, isolated the same by-product from an identical late-stage lactonisation of intermediate **76**. Following the isolation and characterisation of intermediate hydroxyester **76**, Xie and

co-workers concluded, through thorough NMR analysis, that the formation of the two vicinal quaternary stereocentres had occurred, and that a competing intramolecular carbonate migration of the resultant hydroxyester **76** formed carbonate **77**, the major undesired product of this transformation. Although the poor yielding key transformation is largely affected by a competing intramolecular carbonate migration, and the overall yield of (±)-hyperolactone C **5** is satisfactory (6.9% in five-steps), the reported concise synthetic route provides a convenient strategy for the production of large quantities of the natural product.

1.2.3 Total Synthesis of (-)-Biyouyanagin A, (-)-Hyperolactone C and Related Analogues using a One-Pot Palladium-Catalysed Cascade Sequence

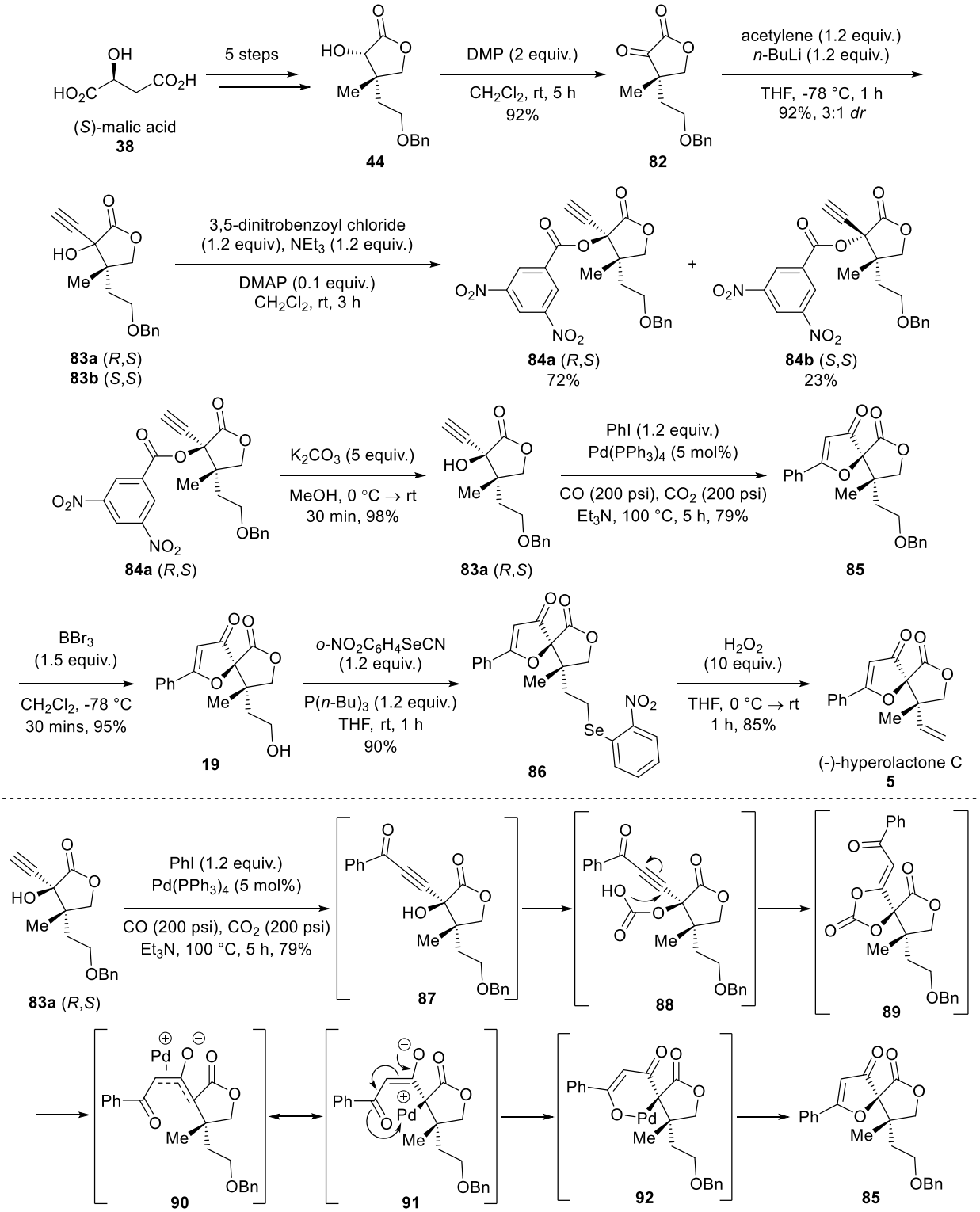
Following the isolation, characterisation and biological screening of (-)-biyouyanagin A **8** by Tanaka *et al.*,[16] Nicolaou and colleagues developed the first total synthesis of the secondary metabolite from a convergent synthetic strategy (***Scheme 1-5***),[17,18] involving a stereospecific chemoselective [2+2] photocycloaddition of (-)-hyperolactone C **5** with *ent*-zingiberene **9** (*vide supra*, ***Figure 1-3***).



Scheme 1-5: *Total synthesis of (-)-biyouyanagin A, from a chemoselective and stereoselective [2+2] photocycloaddition, highlighting the total synthesis of terpene precursor ent-zingiberene.*

Originally proposed as a plausible biosynthetic pathway of (-)-biyouyanagin A **8** by the natural product's discoverers,[16] Nicolaou and co-workers established a successful procedure for the photoinduced fusion of (-)-hyperolactone C **5** with *ent*-zingiberene **9**, involving irradiating the two terpenoid fragments with UV light (320 nm filter) in a quartz cell, while in the presence of the triplet sensitiser 2′-acetonaphthone.[36] The resulting [2+2] photocycloaddition formed the desired cyclobutane moiety of the six-four-five-five tetracyclic ring system in good yield (54%), proceeding with both excellent chemoselectivity and stereoselectivity, to form the *cis*-*anti*-*cis* configuration of the cyclobutane ring. Sterically unfavourable interactions between the lactone moiety of (-)-hyperolactone C **5** and the cyclohexene component of triene **9** in the *endo* transition state rationalises the observed stereochemical outcome (***Figure 1-3***), as the reaction occurs through the energetically favoured *exo* transition state. Carrying out the photocycloadditions of (-)-hyperolactone C **5** with both *ent*-zingiberene **9** and *ent*-7-*epi*-zingiberene **10** permitted the previously unknown absolute stereochemistry of the sesquiterpene domain to be unambiguously deduced. Additionally, Nicolaou and colleagues found that the cyclobutane configuration had been misassigned (*vide supra*, ***Figure 1-2***), leading to the stereochemical revision of (-)-biyouyanagin A **8**, which was indisputably confirmed from spectroscopic, melting point, optical rotation and X-ray crystallographic analysis.

Employing an enantioselective four-step synthetic route to achieve the total synthesis of *ent*-zingiberene **9** (***Scheme 1-5***), (*R*)-citronellal was converted to ketoaldehyde **80** from an organocatalysed asymmetric 1,4-addition of methyl vinyl ketone. The enamine-mediated Michael addition utilises ethyl 3,4-dihydroxybenzoate as a catechol-derived co-catalyst, which has been postulated to electrophilically activate the enone carbonyl *via* a hydrogen bond interaction,[37] and is facilitated by *L*-proline-based catalyst **79**.[38] Treating ketoaldehyde **80** with potassium hydroxide and tetrabutylammonium hydroxide, a basic phase-transfer catalyst, forms enone **81** from an intramolecular aldol condensation in 68% yield and 86% *de*. Resulting enone **81** is then efficiently converted to an intermediate vinyl triflate using Comins' reagent,[39] which then forms *ent*-zingiberene **9** from a copper(I) iodide-catalysed Kumada coupling with methyl magnesium iodide,[40] proceeding with an 80% yield over the two steps. Utilising the same chiral pool approach from (*S*)-citronellal, the total synthesis of *ent*-7-*epi*-zingiberene **10** was also achieved from the same four-step sequence.



Scheme 1-6: *Total synthesis of (-)-hyperolactone C, installing the spirocyclic carbon skeleton through a one-pot palladium-catalysed cascade sequence.*

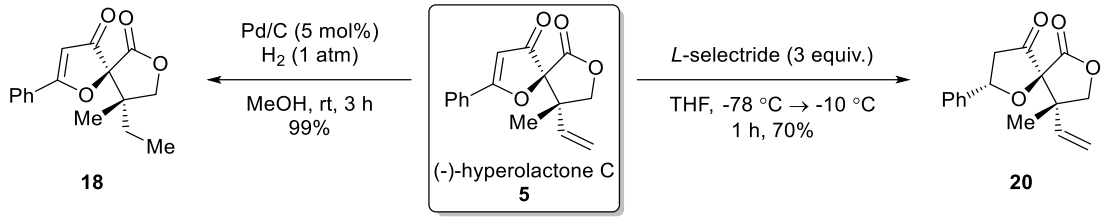
Replicating the initial stages of the first total synthesis of (-)-hyperolactone C **5** published by Kinoshita *et al.*,[15] Nicolaou and co-workers accessed α-hydroxylactone **44** from the previously developed five-step manipulation of (*S*)-malic acid **38** (***Scheme***

1-2). Undergoing an initial Dess-Martin oxidation to ketolactone **82**, a stereoselective nucleophilic addition of lithium acetylide at the electrophilic ketone furnished propargyl alcohols **83a-b** (3:1 *dr*), with the observed diastereoselectivity rationalised from a chelation between the benzyloxy and ketone functionalities, preferentially affording major diastereomer **83a**. Unfortunately, diastereoisomers **83a-b** were unable to be resolved chromatographically, and required a subsequent esterification transformation to their corresponding 4-nitrobenzoates **84a-b** (95% combined yield) to enable successful separation by flash column chromatography. Following purification and identification from X-ray crystallographic analysis, both 4-nitrobenzoate **84a** and **84b** were individually hydrolysed to afford enantiopure propargyl alcohols **83a** and **83b** in excellent yields (98% yield for each enantiomer). As a simplified alternative, propargyl alcohol **83a** was also separated from minor diastereomer **83b** through fractional crystallisation in 62% yield, using a CH_2Cl_2/hexanes solvent system.

With enantiopure propargyl alcohol **83a** to hand, hyperolactone **85** was then constructed in excellent yield from the direct installation of the furan-3(2*H*)-one ring system, utilising a one-pot palladium-catalysed spirocyclisation procedure under a mixed atmosphere of carbon dioxide and carbon monoxide. First developed by Inoue *et al*.,[41] the key palladium-catalysed cascade sequence commences with an oxidative addition of the aryl halide with the low valent metal complex, followed by a migratory insertion with carbon monoxide, with a successive Sonogashira-type process forming acetylenic ketone intermediate **87**. Addition of carbon dioxide to intermediate **87** then formed monocarbonate species **88** that rapidly reacts with the adjacent alkyne to afford cyclic carbonate **89**. The reaction mechanism is believed to proceed by a stereospecific palladium-catalysed decarboxylation to π-palladium complex **90**, that subsequently rearranges to palladacycle **92**, with a final reductive elimination regenerating the active catalyst and affording hyperolactone **85** with complete stereochemical retention. Having assembled the hyperolactone motif, a boron tribromide induced debenzylation and final two-step Grieco elimination then installed the required vinyl group to complete the total synthesis of (-)-hyperolactone C **5** in thirteen-linear steps with an impressive 12.5% overall yield.

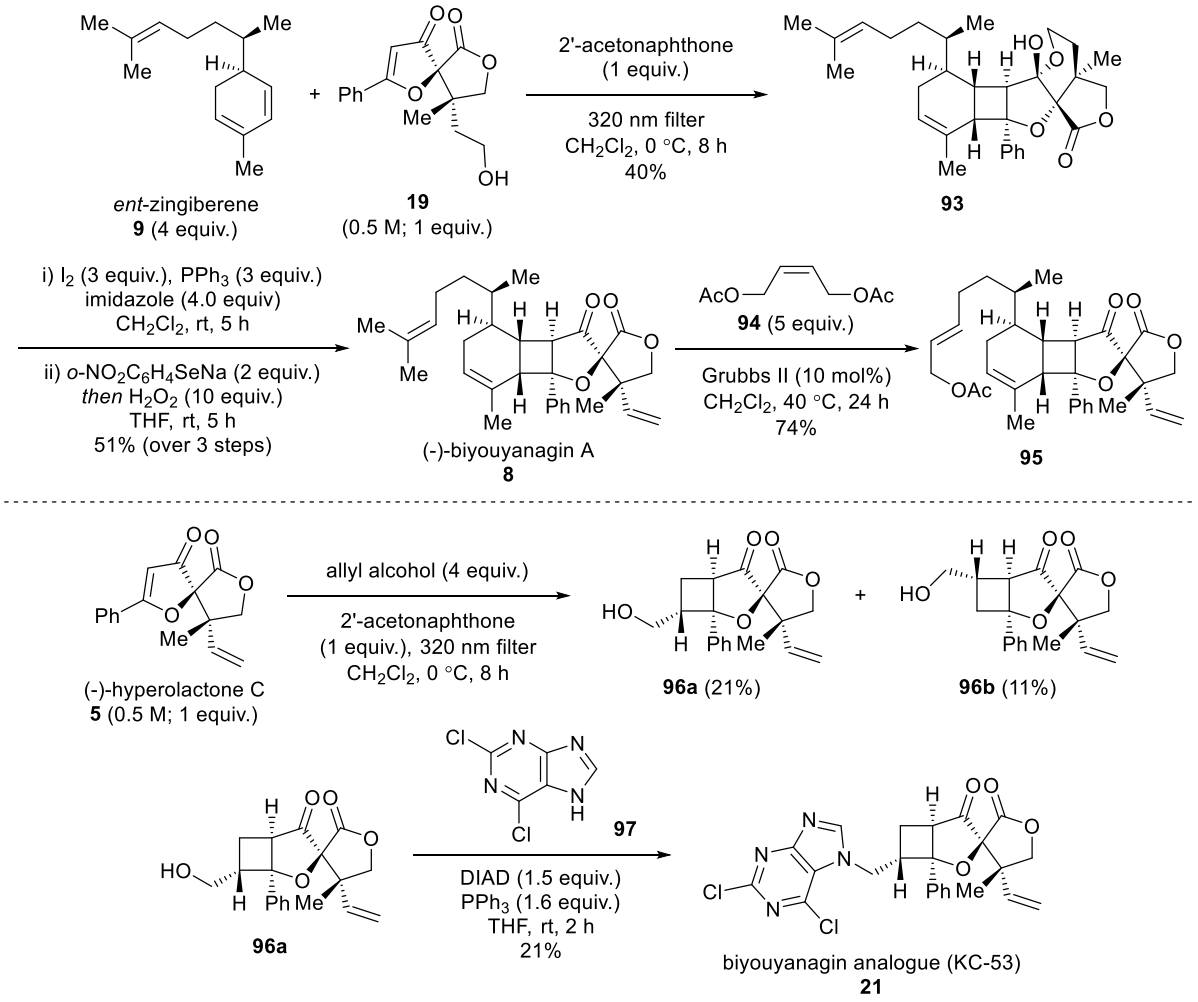
Having designed efficient synthetic methodologies for the successful total syntheses of *ent*-zingiberene **9**, (-)-hyperolactone C **5** and (-)-biyouyanagin A **8**, Nicolaou *et al*. then carried out further investigations into the synthesis of both

hyperolactone and biyouyanagin-based analogues. Building a large hyperolactone compound library,[19] a variety of aryl halides were reacted with propargyl alcohol **83a** in the palladium-catalysed spirocyclisation procedure to obtain numerous hyperolactones derivatives, all containing the hyperolactone A and C spirocyclic configuration (*vide supra*, ***Figure 1-5***). Alternatively, enantiopure propargyl alcohol **83b** was used to produce hyperolactones, with varying aryl substituents, possessing the inverse hyperolactone B spirocyclic configuration. In addition, Nicolaou and colleagues demonstrated that (-)-hyperolactone C **5** could be further functionalised by chemoselectively hydrogenating the vinyl functionality, using palladium on activated carbon, in the presence of the enone, to form hyperolactone **18** in a quantitative yield. Conversely, *L*-selectride was demonstrated to stereospecifically reduce the enone component of (-)-hyperolactone C **5**, *via* a facially selective hydride conjugate addition, affording spirocyclic dihydrofuranone **20**, as a single enantiomer.



Scheme 1-7: *Chemoselective hydrogenation and stereoselective 1,4-reduction of (-)-hyperolactone C.*

The constructed hyperolactone compound library was then reacted with a plethora of olefinic building blocks in the key [2+2] photocycloaddition transformation, to produce an array of biologically active biyouyanagin derivatives. Upon irradiating a mixture of hyperolactone **19** and *ent*-zingiberene **9**, a highly unique hexacyclic biyouyanagin analogue **93** was isolated, formed from a spontaneous intramolecular ring closure of the [2+2] adduct. Interestingly, the lactol form was not observed for precursor **19**, while X-ray crystallography confirmed that the lactol architecture of analogue **10** was favoured over the free alcohol. A second-generation route to (-)-biyouyanagin A **8** was then achieved from analogue **10** through a three-step Appel iodination and Grieco elimination sequence. Finally, a remarkably chemoselective cross metathesis of (-)-biyouyanagin A **8** with an excess of (*Z*)-2-butene-1,4-diol diacetate **94**,[42] in the presence of Grubbs' II catalyst, synthesised analogue **95** in a 73% yield, with no other by-products observed from the cross metathesis between **94** and the other olefinic bonds.

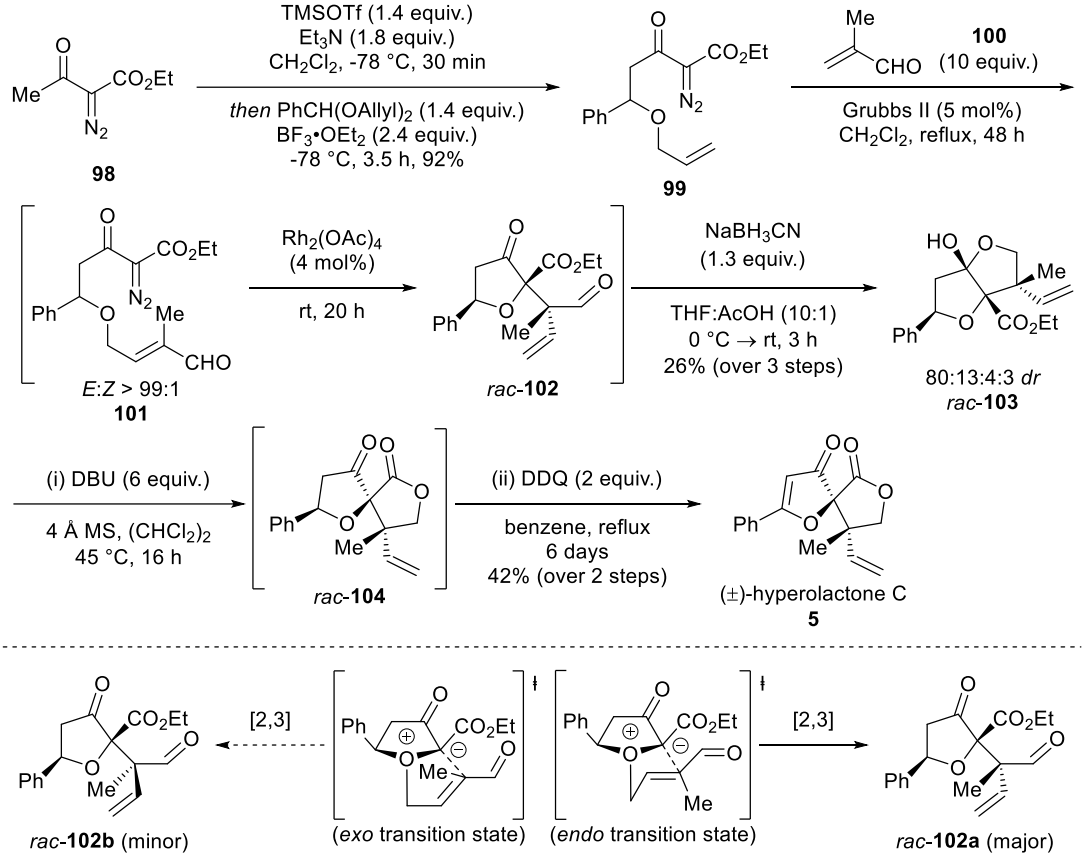


Scheme 1-8: *Second generation total synthesis of (-)-biyouyanagin A and the synthesis of biologically active biyouyanagin analogues.*

Having biologically screened the resulting biyouyanagin and hyperolactone compound libraries in various assays as part of SAR investigations,[19,21] Nicolaou *et al*. synthesised lead compound KC-53 **21**, which exhibited superior antiviral, anti-inflammatory and anticancer activities when compared with other synthesised analogues. Possessing a simplified molecular framework, the potent nucleic acid base-biyouyanagin hybrid **21** was synthesised from a [2+2] photocycloaddition between (-)-hyperolactone C **5** and allyl alcohol (***Scheme 1-8***), generating biyouyanagin analogues **96a** and **96b** in modest yields. A final Mitsunobu protocol of regioisomer **96a** with 2,6-dichloro-7*H*-purine **97** then furnished the highly potent biyouyanagin analogue KC-53 **21**, albeit in 4% yield over two steps. Uncovering the therapeutic potential of the hyperolactone and biyouyanagin scaffolds, research from the Nicolaou Group has provided efficient methodologies to the natural product carbon skeletons, enabling the generation of large numbers of biologically active derivatives.

1.2.4 Total Synthesis of Hyperolactone C *via* Tandem Oxonium Ylide Formation [2,3]-Sigmatropic Rearrangements

Developing a one-pot procedure for the generation of dihydrofuranones, involving the coupling of a ruthenium carbenoid-catalysed olefin cross-metathesis, a successive rhodium-catalysed oxonium ylide formation and a final diastereoselective [2,3]-sigmatropic rearrangement, Hodgson and co-workers applied their methodology to achieve the total synthesis of (±)-hyperolactone C **5** (***Scheme 1-9***).[43]

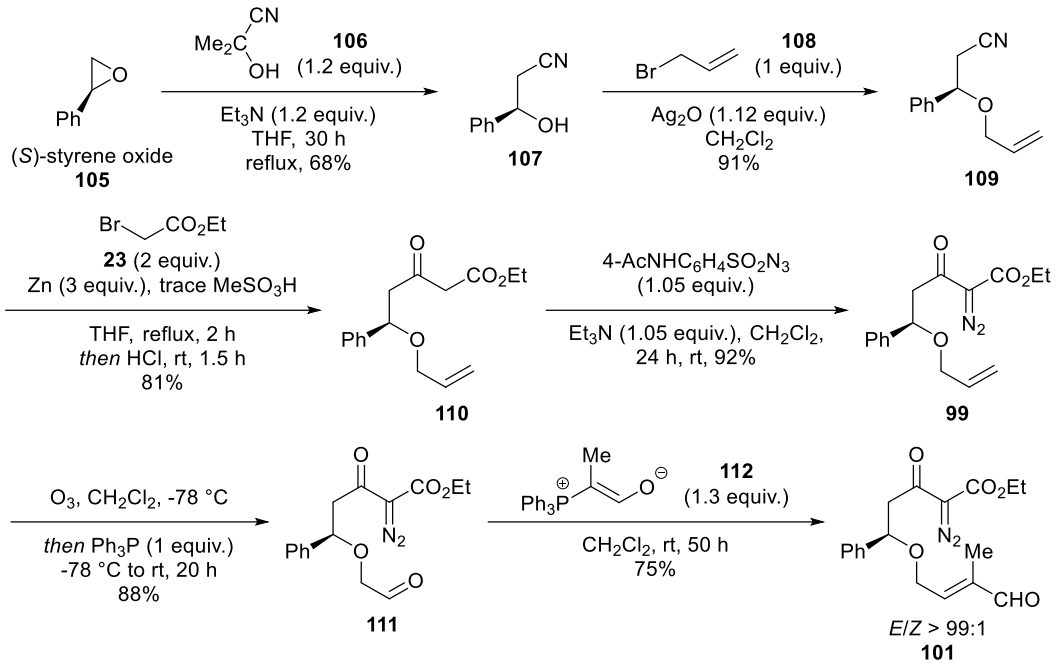


Scheme 1-9: *Total synthesis of (±)-hyperolactone C through a consecutive olefin cross metathesis/ oxonium ylide formation-rearrangement, highlighting the [2,3]-sigmatropic rearrangement transition states.*

Starting from commercially available ethyl diazoacetoacetate **98**, racemic α-diazo-β-ketoester **99** was prepared from a high yielding Lewis acid catalysed Mukaiyama-type aldol condensation with (bis(allyloxy)methyl)benzene. A subsequent cross-metathesis with methacrolein **100**, using Grubbs' II catalyst, stereoselectivity formed (*E*)-enal **101** (*E*:*Z* > 99:1), albeit in a poor 21% isolated yield. Despite achieving high cross-metathesis yields with many other substituted olefins from early substrate

scope studies, attempts to improve the yield of the initial cross-metathesis of allyl ether **99** with other *gem*-disubstituted oxygenated olefins (benzoyl- or trityl-protected methallyl alcohol) produced lower yields with only a modest *E*:*Z* selectivity. With other metathesis catalysts failing to improve the efficiency of the reaction, (*E*)-enal **101** was then subjected to a one-pot tandem $Rh_2(OAc)_4$ catalysed oxonium ylide formation [2,3]-sigmatropic rearrangement, producing unstable aldehyde **102**, that was found to decompose upon purification. Fortunately, crude aldehyde **102** was efficiently reduced by sodium cyanoborohydride to afford a mixture of chromatographically separable fused hemiketals **103** (80:13:4:3 *dr*, determined from ^{1}H NMR), in 69% yield over the two steps. The relative stereochemistry of the fused hemiketals **103** was assigned by nOe studies and can be rationalised from the diastereoselective intramolecular 1,3-dipolar cycloaddition, which proceeds *via* the *endo* transition state with the ylide and phenyl group located on opposing faces (***Scheme 1-9***). While the facial stereoselective is governed from the steric clash between the phenyl and resulting ylide, the origins of the *endo* selectivity is currently unknown, but is in accordance with other studies involving oxonium ylide rearrangements of α-diazoketones.[44] Improving the yield of the conversion of α-diazo-β-ketoester **99** to fused hemiketal **103**, a one-flask operation of the cross-metathesis and key tandem ylide formation-rearrangement transformation increased the overall yield of this sequence to 26%, over the three steps. Finally, a DBU-mediated spirolactonisation of major hemiketal **103**, followed by a successive DDQ-induced dehydrogenation, synthesised (±)-hyperolactone C **5** in 42% yield over two steps, completing the total synthesis of the racemic natural product with an overall yield of 8% over six-steps.

Aiming to improve upon the overall yield of the concise total synthesis and isolate (-)-hyperolactone C **5** as a single enantiomer, Hodgson *et al.* then developed a modified route to the spirolactone natural product.[45] Seeking to isolate key α-diazo-β-ketoester **101** enantioselectively, various asymmetric aldol approaches, involving both chiral ligands and auxiliaries, to diazo ether **99** proved challenging, directing Hodgson and colleagues to develop an alternative four-step synthetic route (***Scheme 1-10***).

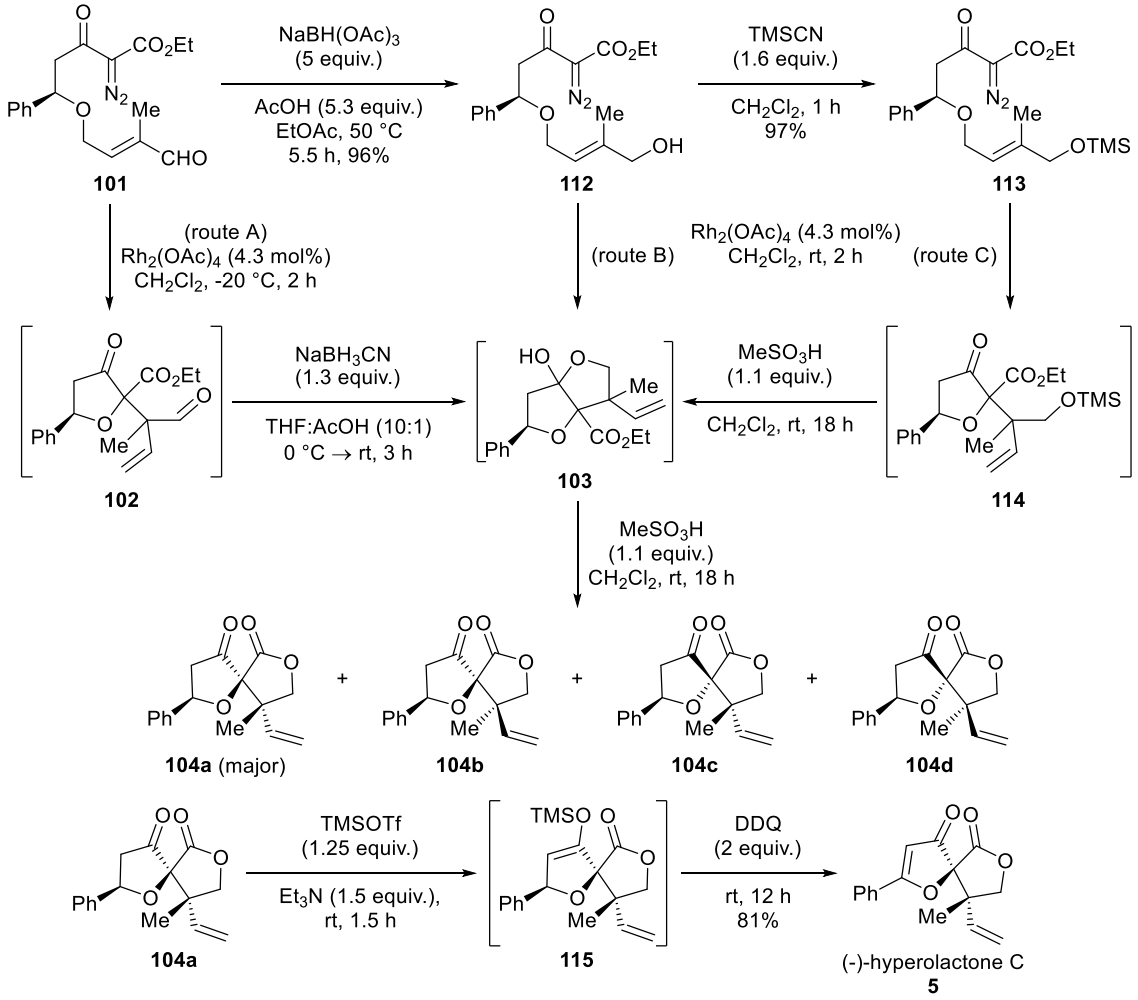


Scheme 1-10: *Optimised synthetic route to enantiopure α-diazo-β-ketoester* ***101****.*

Performing an initial regioselective ring-opening of readily available (*S*)-styrene oxide **105**,[46] resultant cyanohydrin **107** underwent an optimised alkylation with allyl bromide **108**, in the presence of silver(I) oxide, to afford nitrile **109** in good yield. Intermediate **109** was then converted to β-ketoester **110** through a Blaise reaction with ethyl bromoacetate **23**,[47] where a subsequent diazo transfer delivered α-diazo-β-ketoester **99**. Previously prepared from a challenging low yielding cross-metathesis using a large excess of methacrolein (***Scheme 1-9***), olefin **99** was subjected to an alternative ozonolysis Horner-Wadsworth-Emmons olefination sequence, synthesising desired (*E*)-enal **101** in an improved 66% yield over the two-steps.

Following the synthesis of (*E*)-enal **101**, Hodgson and co-workers then set out to optimise the key tandem rhodium-catalysed oxonium ylide formation [2,3]-sigmatropic rearrangement transformation (***Scheme 1-11***). Spectroscopic analysis of the crude spectra of unstable aldehyde **102** indicated significant side products from the key transformation, even when using alternative rhodium catalysts and conducting the reactions at -20 ºC. Due to their sensitivity on silica gel, the resulting by-products were unable to be characterised, however, preservation of the allyl aldehyde functionality in the crude ^{1}H NMR spectra of **102** indicates that an intramolecular [1,2]-sigmatropic rearrangement of the transient ylide, and/or a Buchner reaction,[48] may be competing. Even when utilising an alternative acid-catalysed spirocyclisation to

chromatographically separable spirolactones **104a-d**, the one-pot conversion of (*E*)-enal **101** to dihydrohyperolactones **104a-d** (79:13:6:2 *dr*) proceeded in 33% yield over the three steps (route A).

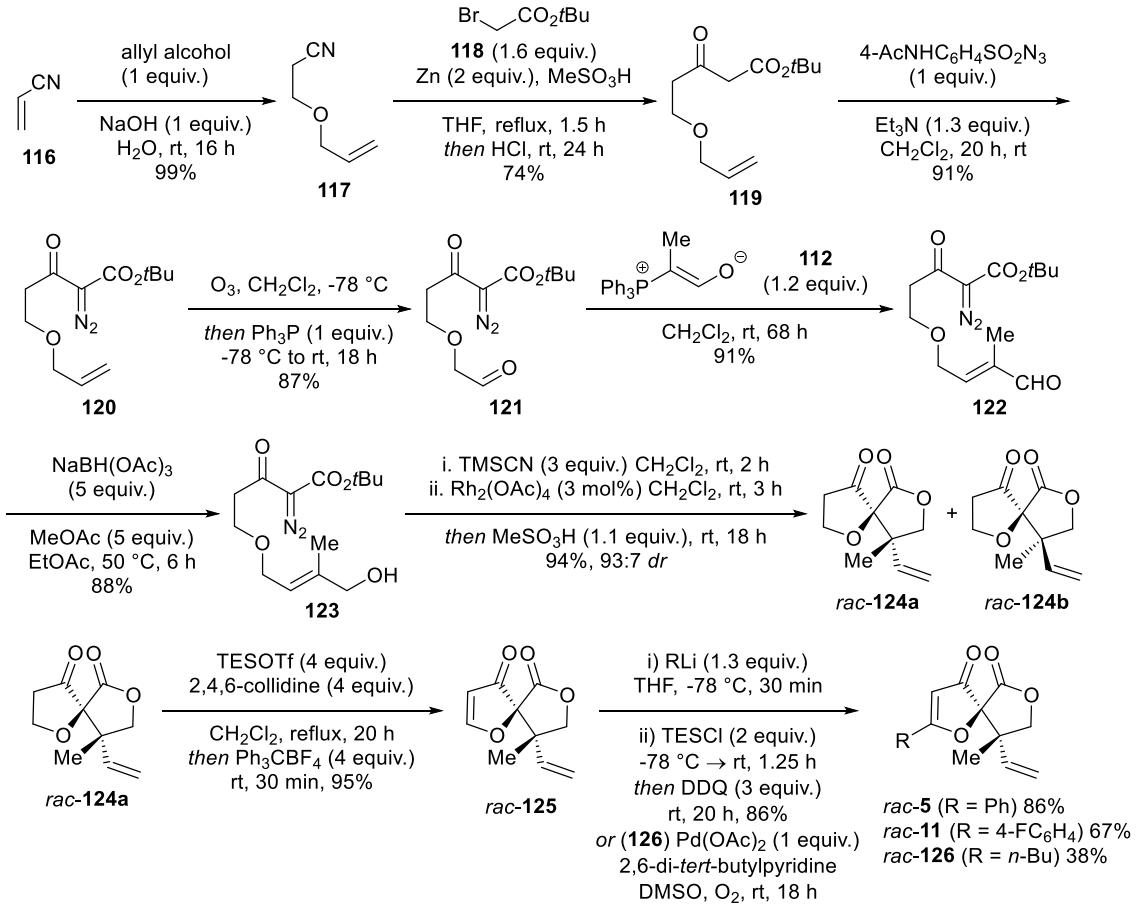


Scheme 1-11: *Total synthesis of (-)-hyperolactone C utilising an optimised oxonium ylide formation-rearrangement transformation.*

Exploring alternative routes to fused hemiketals **103**, exchanging the ordering of the one-pot multi-step procedure, by first carrying out a 1,2-reduction of (*E*)-enal **101** to allylic alcohol **112**, led to an improved 53% isolated yield for spirolactones **104a-d** (65:3:28:4 *dr*) (route B). Despite the enhanced yield, a reduction of diastereoselectivity for the intramolecular 1,3-dipolar cycloaddition was observed for allylic alcohol **112**, indicating that the rearrangement occurs with high *endo*-diastereoselectivity but with a greater tendency to take place on the undesired phenyl-bearing face. Temporarily protecting alcohol **112**, as its trimethylsilyl ether, was found to further enhance the isolated yield to 63% over the three steps, while also increasing the facial

diastereoselectivity of the key rearrangement (75:3:18:4 *dr*) (route C). Modifying the previously developed dehydrogenation procedure to involve the activation of spirolactone **104a** to its respective silyl enol ether **115**, a milder final DDQ-induced dehydrogenation then efficiently converted major diastereomer **104a** to (-)-hyperolactone C **5** in an improved yield of 81%, accessing the enantiopure natural product with an overall yield of 10.8% over ten-steps.

Utilising the optimised tandem oxonium ylide formation [2,3]-sigmatropic rearrangement chemistry, Hodgson *et al*. then developed their synthetic route further to allow for late-stage diversification of the spirolactone scaffold (***Scheme 1-12***).[49] Assembled from a Michael addition of allyl alcohol with acrylonitrile **116**, nitrile **117** was converted to (*E*)-enal **122** using Hodgson and colleagues' previously developed five-step sequence.

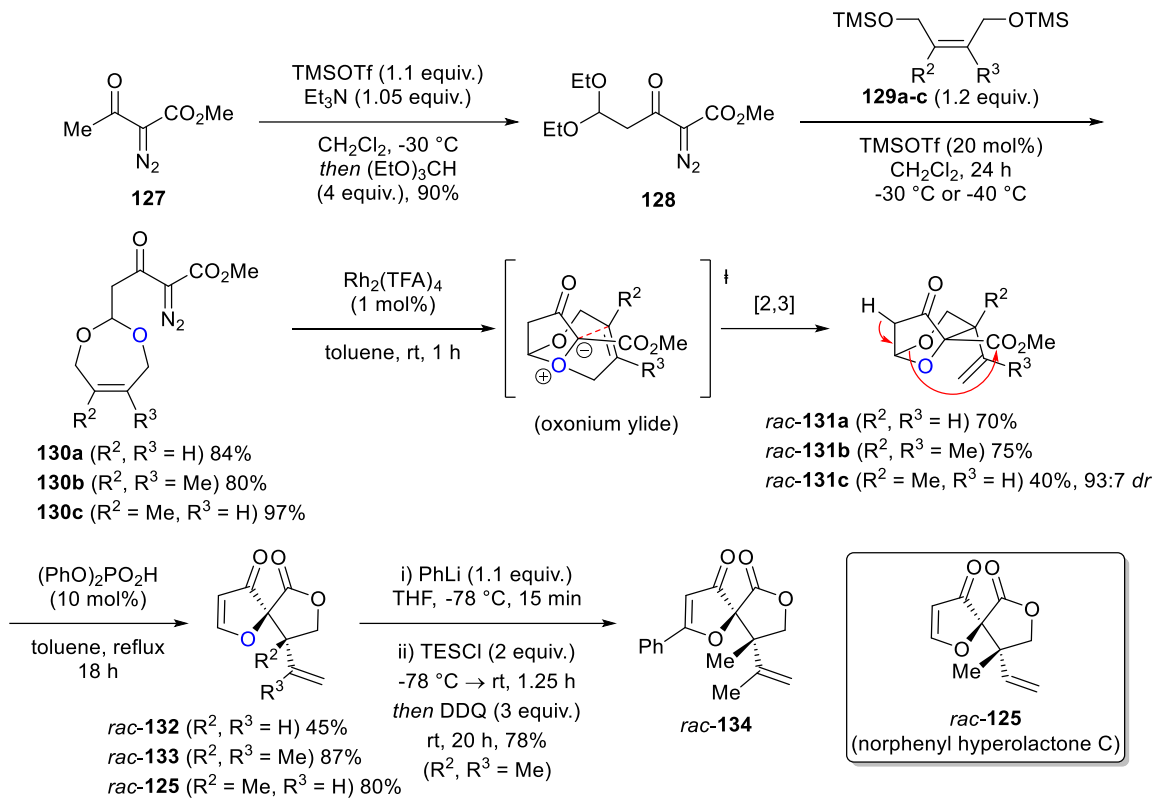


Scheme 1-12: *Total synthesis of (±)-hyperolactone C and analogues from a late-stage conjugate addition and tandem oxonium ylide-rearrangement strategy.*

Applying the optimised tandem oxonium ylide-rearrangement methodology to (*E*)-enal **122**, the resulting crude trimethylsilyl protected intermediate underwent a highly *endo*-diastereoselective [2,3]-sigmatropic rearrangement, with a successive acid-catalysed skeletal rearrangement furnishing spirolactones **124a-b** in an excellent 94% yield. Whilst factors influencing the stereoselectivity of [2,3]-sigmatropic oxonium ylide rearrangements are not well understood, increasing the steric bulk of the adjacent ester, by substituting the previously deployed methyl ester to a *tert*-butyl functionally, did slightly improve the *endo* selectivity (93:7 *dr*). Dehydrogenation was then achieved by reacting the *in situ* generated TES enol ether of major diastereomer **124a** with trityl fluoroborate, affording norphenyl hyperolactone C **125** in good yield. Several late-stage 1,4-conjugate additions with phenyllithium and 4-fluorophenyllithium, followed by a DDQ-mediated dehydrogenation of the activated TES enol ethers, efficiently produced both (±)-hyperolactone C **5** and (±)-4'-fluoro-hyperolactone C **11**. Addition of *n*-butyllithium proved challenging, due to the lack of a benzylic hydrogen, and required a Saegusa-Ito oxidation to afford hyperolactone **126**, albeit in 38% yield. Unfortunately, attempts to develop an enantioselective oxonium ylide formation-rearrangement transformation, using chiral dirhodium catalysts, resulted in unsatisfactory enantiomeric excesses, with the highest performing catalyst, Rh_2(*R*-BNP)$_4$, producing only modest levels of asymmetric induction (69:31 *er*). Despite this, Hodgson and co-worker's third-generation total synthesis of (±)-hyperolactone C **5** was achieved with an impressive overall yield of 33.2% over ten-steps, and allows late-stage access to hyperolactone analogues.

Aiming to gain full control of the relative stereochemistry of the intramolecular oxonium ylide formation 1,3-dipolar cycloaddition methodology, Hodgson *et al*. then developed a concise fourth-generation approach to the spirolactone motif, from substituted cyclic unsaturated acetals (***Scheme 1-13***).[50] Constraining the allylic ether as part of a cyclic acetal, acetals **130a-c** were synthesised from a Lewis acid-mediated condensation of triethyl orthoformate with the silyl enol ether of methyl diazoacetoacetate **127**,[51] followed by an additional acetal exchange with ditrimethylsilylated diols **129a-c**. Investigating the intramolecular oxonium ylide formation-rearrangement of symmetrical acetals **130a** and **130b**, the Rh_2(TFA)$_4$ catalysed transformation efficiently produced bicyclic acetals **131a-b** in high yields. Despite many trialled acid catalysts producing complex mixtures, a successive

diphenyl phosphate catalysed elimination-lactonisation process was then developed, furnishing spirofuranones **132** and **133** in moderate to good yields.

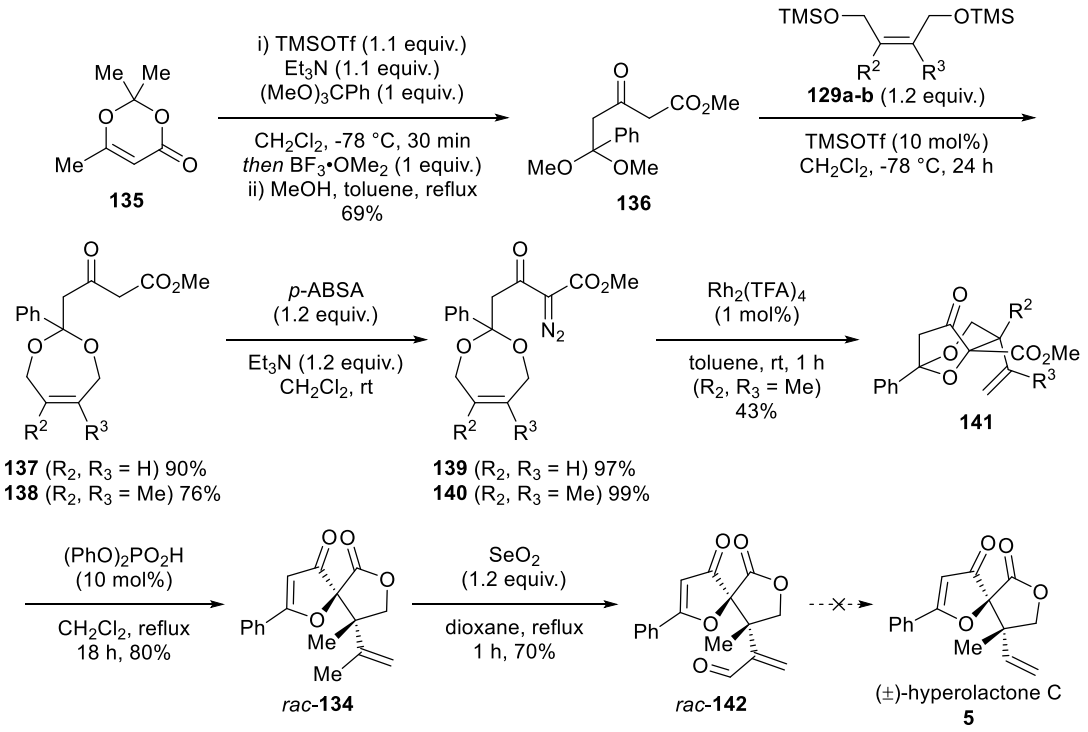


Scheme 1-13: *Formal Synthesis of (±)-hyperolactone C using a tandem intramolecular oxonium ylide formation [2,3]-sigmatropic rearrangement of cyclic acetals.*

Having accessed the spirocyclic carbon skeleton, Hodgson and co-workers then achieved the formal synthesis of (±)-hyperolactone C **5** by converting monomethylated acetal **130c** to norphenyl hyperolactone C **125**, using their key methodology. Asymmetric acetal **130c** was found to diastereoselectively form intermediate bicyclic acetal **131c** in moderate yield (43%, 73:27 *dr*), which was improved further when conducting the transformation at lower temperatures (-40 ºC, 40%, 93:7 *dr*). Rationalised from the +I effect exhibited from the methyl substituent, the observed diastereoselectivity arises from a preferential insertion of the highlighted acetal transient ylide forming oxygen atom (***Scheme 1-13***), where a final diphenyl phosphate mediated elimination-lactonisation affords norphenyl hyperolactone C **125**, achieving a concise formal synthesis of (±)-hyperolactone C **5**.

Synthesised with no diastereoselectivity issues from the key transformation, Hodgson *et al*. then postulated that spirofuranone **133** could be further manipulated to

achieve the total synthesis of (±)-hyperolactone C **5**. Introducing the phenyl functionality through their previously developed conjugate addition dehydrogenation methodology, hyperolactone analogue **134** was synthesised in high yield. Alternatively, analogue **134** was also accessed from phenyl-bearing bicyclic acetal **141**, that was obtained from a similar acetal exchange approach and an intramolecular oxonium ylide formation-rearrangement of intermediate diazo acetal **140** (***Scheme 1-14***).



Scheme 1-14: *Towards the total synthesis of (±)-hyperolactone C, via a phenyl-substituted cyclic acetal intermediate, attempting an allylic oxidation-deformylation strategy.*

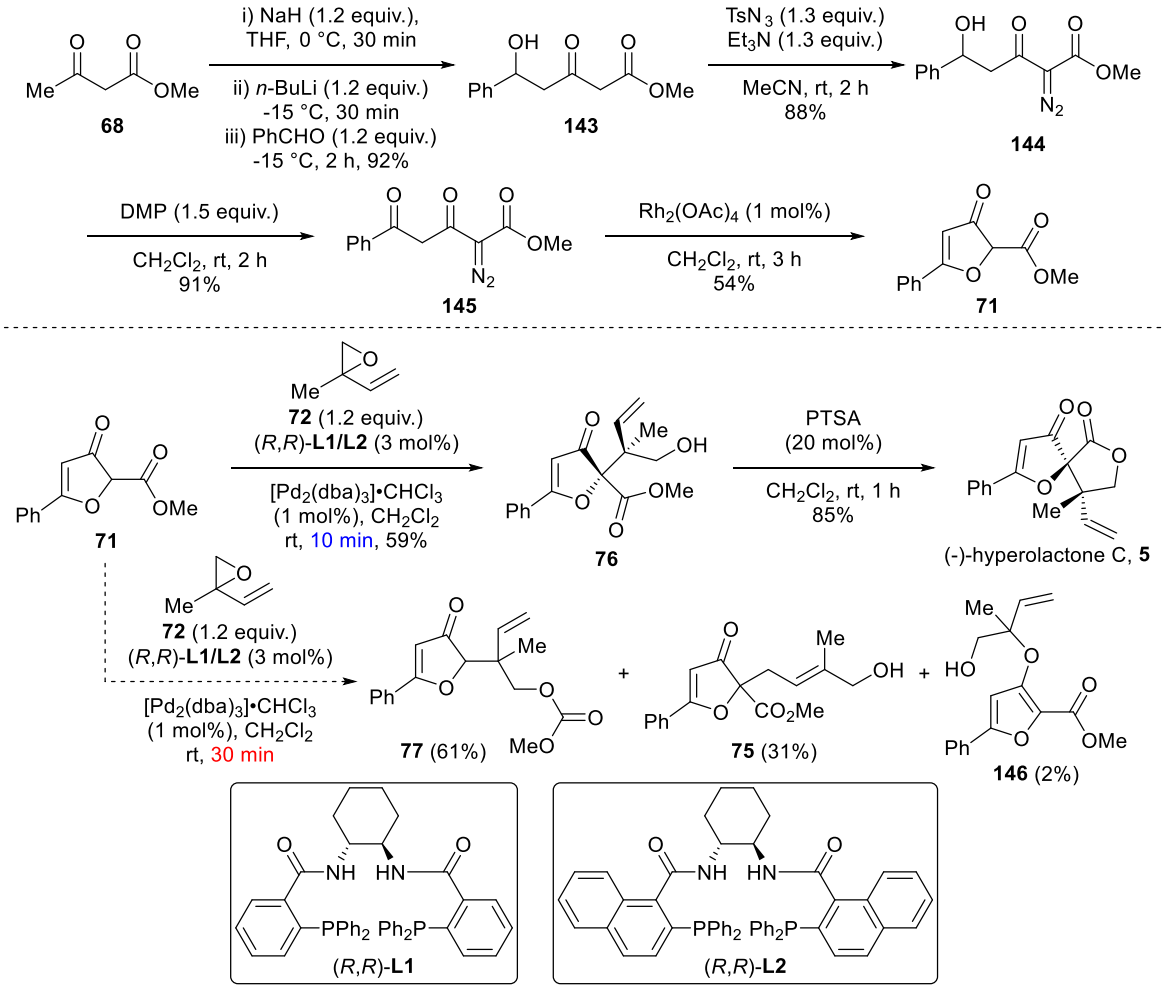
Unfortunately, attempts to complete the total synthesis of (±)-hyperolactone C **5** from a final allylic oxidation-deformylation strategy were unsuccessful. Despite the initial selenium dioxide induced allylic oxidation efficiently producing desired (*E*)-enal **142**, a final deformylation with either Wilkinson's catalyst, or other rhodium or iridium-based catalysts, that have been previously used in such transformations,[52,53] failed to obtain the natural product.

Having achieved multiple approaches to the hyperolactone motif and achieving numerous total syntheses of hyperolactone C and its related analogues, Hodgson's developed diastereoselective tandem oxonium ylide formation [2,3]-sigmatropic

rearrangement strategy has been firmly established as an efficient way of constructing the challenging vicinal quaternary stereocentres of the secondary metabolite.

1.2.5 Total Synthesis of (-)-Hyperolactone C Employing Palladium-Catalysed Asymmetric Allylic Alkylation (Pd-AAA) Strategies

Pioneered by Trost *et al.*,[54] palladium-catalysed asymmetric allylic alkylation (Pd-AAA) reactions have been widely exploited in natural product synthesis as a convenient synthetic strategy of installing quaternary stereocentres,[55] with excellent control over both the diastereoselectivity and enantioselectivity. Developing an enantioselective Tsuji-Trost reaction to install two vicinal quaternary carbon centres, Xie *et al.* devised a novel Pd-AAA approach to achieve the total synthesis of (-)-hyperolactone C **5** (***Scheme 1-15***).[35]

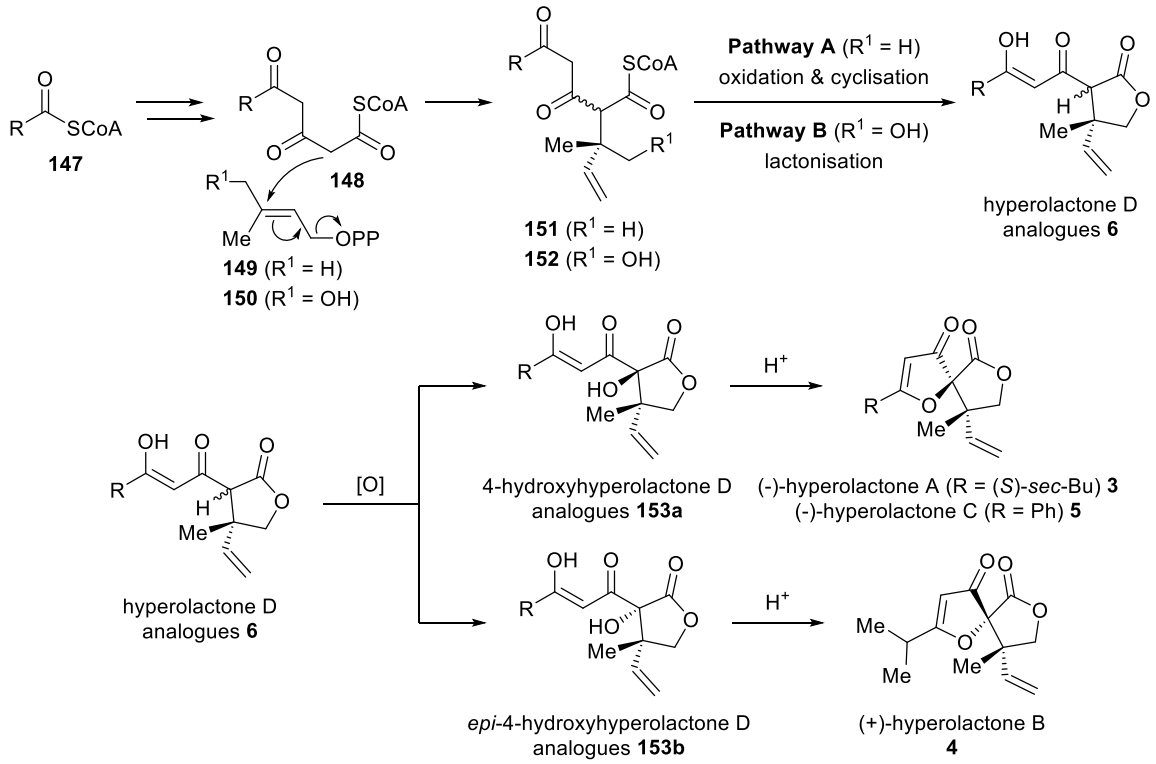


Scheme 1-15: *Enantioselective total synthesis of (-)-hyperolactone C employing a Pd-AAA approach.*

Adapting the synthesis of precursor β-ketoester **71** from Kraus and colleagues' total synthesis of racemic (±)-hyperolactone C **5** (***Scheme 1-4***), β-ketoester **71** was accessed from a four-step manipulation of methyl acetoacetate **68**. An initial aldol addition of benzaldehyde with the dianion of methyl acetoacetate **68** efficiently formed δ-hydroxy-β-oxo-pentanoate **143** under kinetic conditions, which was then converted to α-diazo-β-ketoester **95** from a diazo transfer with tosyl azide, and a successive Dess-Martin oxidation. A final $Rh_2(OAc)_4$ catalysed metallocarbenoid cyclisation of α-diazo-β-ketoester **95** then furnished desired Pd-AAA precursor **71** in good yield.

Unfortunately, early Pd-AAA reactions of β-ketoester **71** with isoprene monoepoxide **72**, involving $[Pd_2(dba)_3]$•$CHCl_3$ and chiral ligand (*R*,*R*)-**L1**, failed to produce desired product **76**. Having isolated and characterised the resultant products (**77**, **75** and **146**), Xie and co-workers deduced that the construction of desired hydroxyester **76** had occurred, but that a further intramolecular carbonate migration had resulted in the formation of by-product **77**, which was consistent with results obtained by Kraus *et al* (*vide supra*, ***Scheme 1-4***). With minor by-products **75** and **146** arising from competing alkylation reactions, it was postulated that major by-product **77** was formed upon prolonged reaction times. Reducing the reaction duration to ten-minutes, hydroxyester **76**, along with by-product **75** (31%), was obtained with an impressive isolated yield of 66%, producing only trace amounts of by-product **77**. Unstable at room temperature, hydroxyester **76** was found to slowly decompose to form both (-)-hyperolactone C **5** and carbonate **77**. Enabling Xie *et al.* to investigate the stereochemical outcome of the Pd-AAA reaction, unstable hydroxyester **76** was converted to its corresponding stable TBS ether, where subsequent chiral HPLC analysis discovered that the key transformation had occurred with high stereochemical control (8.7:1 *dr*, 95% *ee*). Enhancing the stereoselectivity further, alternative chiral ligand (*R*,*R*)-**L2** was found to increase both the diastereoselectivity and enantioselectivity of the Pd-AAA (26:1 *dr*, 99% *ee*), but was found to slightly reduce the yield for both desired hydroxyester **76** (59%) and by-product **75** (26%). Having optimised the key Pd-AAA procedure, hydroxyester **76** was then efficiently converted to (-)-hyperolactone C **5**, producing only trace amounts of carbonate **77**, through a final acid-catalysed lactonisation, completing the total synthesis of the spirocyclic natural product with an overall yield of 20% over six-steps.

With biomimetic syntheses of secondary metabolites providing many advantages over traditional synthetic designs, eliminating the reliance on protecting group strategies and enabling the oxidative modification of low oxidation state precursors to structurally diverse natural products, Xie *et al.* further developed their Pd-AAA methodology to enable the enantioselective biomimetic synthesis of the hyperolactone series. Expanding upon Tada and colleagues' suggested biosynthesis of the hyperolactone carbon skeleton,[13] Xie *et al.* proposed a detailed biogenetic synthesis of hyperolactones A-C (***Scheme 1-16***),[56] following the discovery and characterisation of linear meroterpene 4-hydroxyhyperolactone D (R = phenyl group) **153a** and additional spirolactone related derivatives isolated from methanolic extracts from dried leaves of *Hypericum monogynum*.[57]

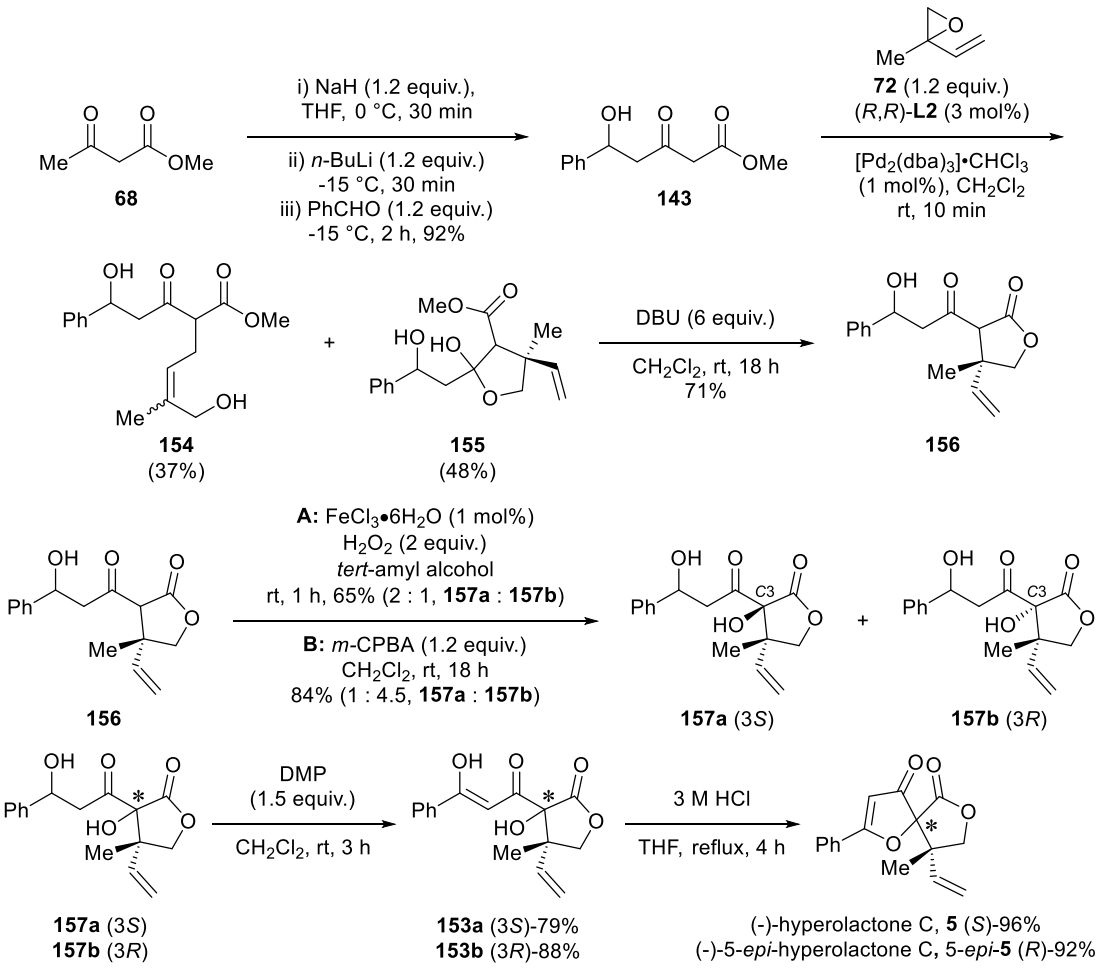


Scheme 1-16: *Postulated biogenetic pathway of the hyperolactones series.*

Synthesised from the polyketide pathway, β-ketoester **148** is thought to react with either dimethylallyl diphosphate **149**, or preferably hydroxy terpenoid **150**,[58] intermediates constructed through the isoprenoid pathway, to form polyketones **151-152**. These polyketides are then converted to hyperolactone D **6** (R = phenyl group) and its acyl analogues, from either an oxidation and progressive cyclisation process (pathway A), or *via* a direct lactonisation (pathway B). The resulting linear meroterpene

6 is then postulated to form 4-hydroxyhyperolactone D **153a** and *epi*-4-hydroxyhyperolactone D **153b** (R = phenyl group), along with their respective derivatives, through an α-hydroxylation, with a successive spirocyclisation producing the spirolactone motif, completing the biosynthesis of the hyperolactone series.

Having proposed a highly plausible biosynthetic pathway, Xie and co-workers then established a Pd-AAA synthetic strategy to achieve the enantioselective total synthesis of (-)-hyperolactone C **5**, using an adapted Pd-AAA approach (***Scheme 1-17***). Accessed from Xie and colleagues' previously utilised aldol addition between benzaldehyde and methyl acetoacetate **68**, β-ketoester **143** underwent the previously developed Pd-AAA transformation, in the presence of chiral ligand (*R*,*R*)-**L2**, to afford desired hemiketal **155** in good yield with high enantioselectivity (48%, 99% *ee*), along with linear side product **154** (37%).



Scheme 1-17: *Biomimetic synthesis of (-)-hyperolactone C using a Pd-AAA synthetic strategy.*

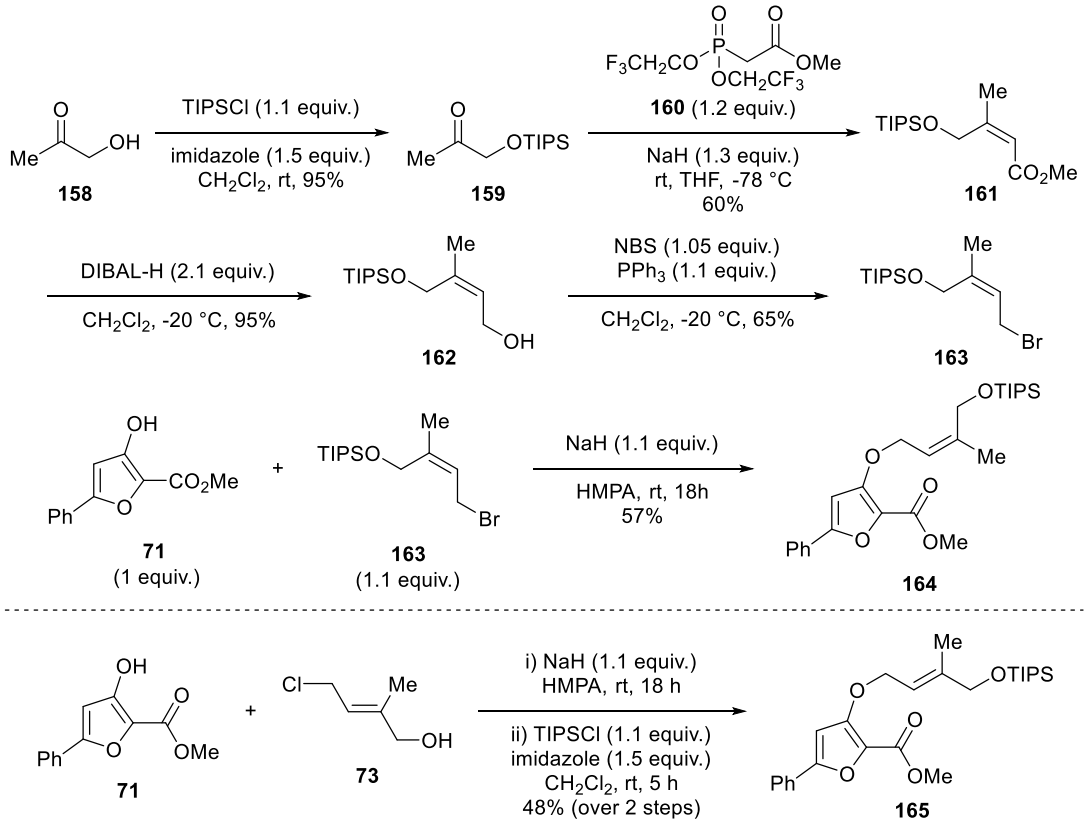
Although the key Pd-AAA transformation proceeds with high enantioselective control, attempts to improve the regioselectivity were unsuccessful, even with a wide range of conditions trialled. Despite the moderate regioselectivity, a subsequent DBU-catalysed lactonisation rearrangement effectively affords spirolactone **156**, as an inseparable diastereomeric mixture. Xie *et al.* then developed two key biomimetic oxidations with opposing diastereoselective control, converting intermediate **156** to chromatographically separatable hydroxy meroterpenes **157a-b**. Preferentially forming meroterpene **157a** with the spirocyclic configuration of 5-*epi*-hyperolactone C, a *m*-CPBA mediated α-hydroxylation successfully obtained intermediates **157a-b** (84%, 1:4.5 *dr*), while the use of hydrogen peroxide and $FeCl_3$•$6H_2O$ in *tert*-amyl alcohol was fortunately found to reverse the diastereoselectivity to favour the configuration of hyperolactone C (65%, 2:1 *dr*).[59] While the rationale behind the observed diastereoselectivity is currently unknown, individual Dess-Martin oxidations of epimers **157a** and **157b** synthesised 4-hydroxyhyperolactone D **153a** and *epi*-4-hydroxyhyperolactone D **153b**, which then underwent high yielding acid-catalysed spirocyclisations to afford (-)-hyperolactone C **5** (overall yield of 5.2%, over six-steps) and (-)-*epi*-hyperolactone C *epi*-**5** (overall yield of 17.5%, over six-steps).

Introducing the *iso*-propyl group to the hyperolactone framework, Xie *et al.* also achieved the total synthesis of (+)-hyperolactone B **4**, by substituting benzaldehyde for isobutyraldehyde in the initial aldol addition with the dianion of methyl acetoacetate **68**, and then performing their developed biomimetic synthetic strategy to the hyperolactone core. Demonstrating multiple concise approaches to the hyperolactone series, palladium-catalysed asymmetric allylic alkylations have been optimised to construct the synthetically challenging spirocyclic architecture with excellent enantioselectivities.

1.2.6 Stereodivergent Total Synthesis of (-)-Hyperolactone C Utilising an Enantioselective Dearomatisation Claisen Rearrangement Approach

Inspired by Karus and colleagues' total synthesis of racemic (±)-hyperolactone C **5**, achieved from their tandem Claisen rearrangement-lactonisation approach (*vide supra*, ***Scheme 1-4***),[30] Feng *et al.* devised a catalytic enantioselective

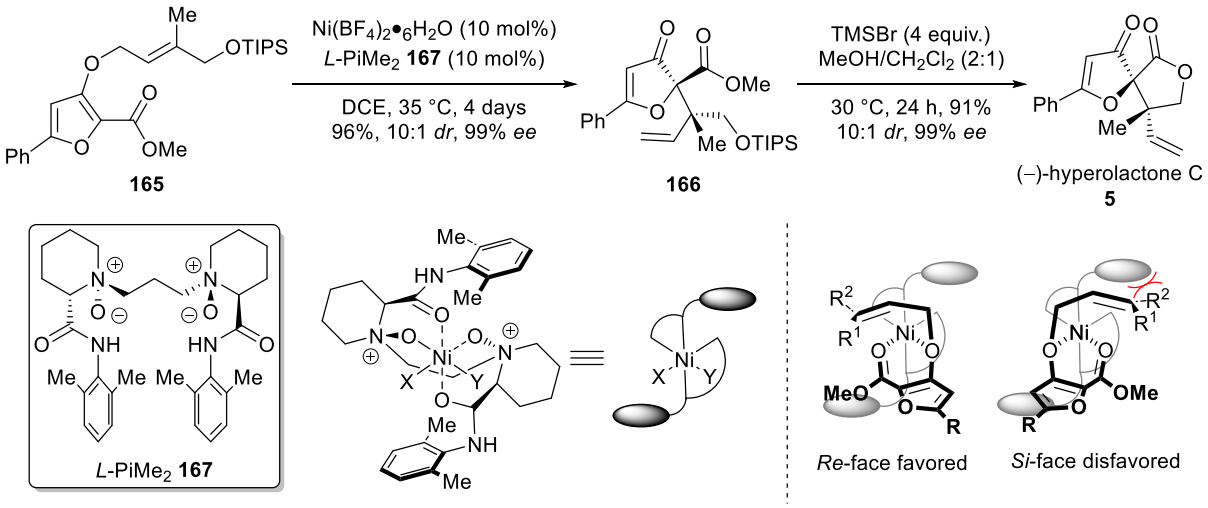
dearomatisation Claisen rearrangement of allyl furyl ethers, catalysed by chiral *N*,*N*'-dioxide-Ni(II) complexes, to assemble members and analogues of the hyperolactone series from a stereodivergent strategy.[60] Synthesising furanol **71** from Xie and co-worker's four-step manipulation of methyl acetoacetate **68** (*vide supra*, ***Scheme 1-15***), Feng *et al.* accessed (*E*)-substituted allyl furyl ether **165** exploiting Karus and co-worker's previously optimised regioselective furanol *O*-alkylation methodology, where the resultant crude underwent a subsequent TIPS alcohol protection, removing remaining *C*-alkylated by-products in the process (***Scheme 1-18***). (*Z*)-Substituted allyl furyl ether **164** was alternatively constructed from the *O*-alkylation of furanol **71** with (*Z*)-olefin **163**, which was synthesised from a developed four-step synthetic route from hydroxyacetone **158**, involving a TIPS protection, Still-Gennari olefination, DIBAL-H reduction and NBS mediated Appel sequence.



Scheme 1-18: *Synthetic procedures for (Z)- and (E)-substituted allyl furyl ethers precursors.*

With allyl furyl ethers **164-165** to hand, Feng and co-workers then investigated the key [3,3]-sigmatropic rearrangement with numerous combinations of Lewis acids and chiral ligands, revealing that nickel(II) complexes were considerably superior over ytterbium(III) and copper(II) complexes trialled in the Claisen rearrangement. Having

optimised the catalysis conditions, intermediate **166** was synthesised with both a high isolated yield (90%) in a highly stereoselective fashion (8:1 *dr*, 98% *ee*) when performed in DCE at 70 °C in the presence of nickel(II) tetrafluoroborate hexahydrate catalyst complexed with C_2-symmetric ligand *L*-PiMe$_2$ **167**, derived from *L*-pipecolic acid. Despite no improvements with other trialled *N*,*N*′-dioxide ligands or other silyl ether protecting groups, reducing the temperature and prolonging the reaction duration was found to increase both the yield (96%) and stereoselectivity (10:1 *dr*, 99% *ee*) of the formation of TIPS protected hydroxyester **166** (***Scheme 1-19***).

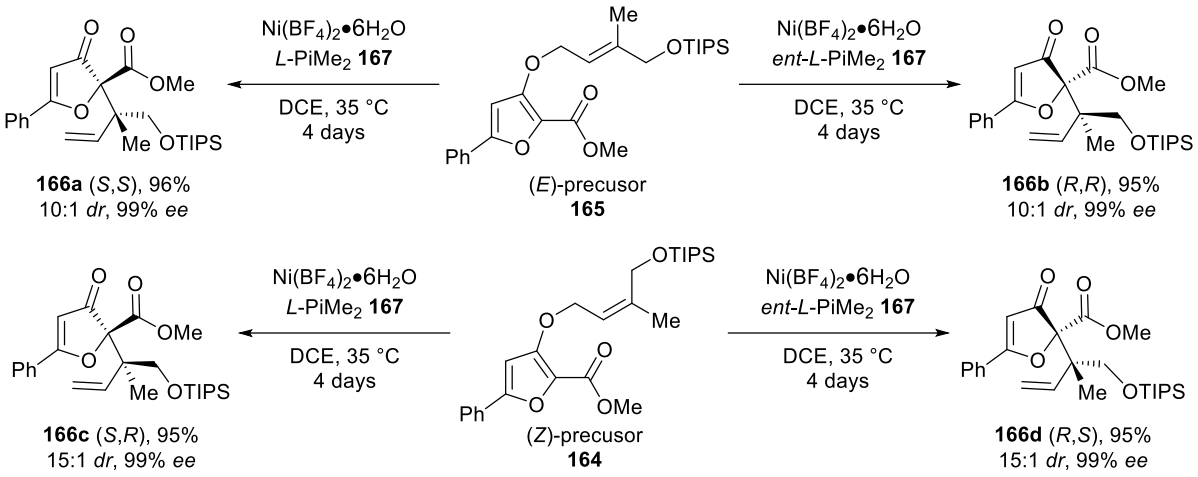


Scheme 1-19: *Total synthesis of (-)-hyperolactone C utilising an enantioselective dearomatisation Claisen rearrangement approach, highlighting the proposed stereochemical model.*[60]

Coordinating to the nickel(II) centre, tetradentate ligand *L*-PiMe$_2$ **167** first forms an octahedral complex, with the ether and carbonyl oxygen atoms of the allyl furyl ether substrate then coordinating to the Lewis acid catalyst in a bidentate manner. Due to a steric clash between the olefin substituent and the axillary aniline domain of *L*-PiMe$_2$ **167**, the allyl functionality has a preferential *Re*-face trajectory, with respect to the furan motif, enantioselectivity giving rise to (*S*,*S*)-vicinal quaternary stereocentres with (*E*)-olefin substrates and the inverse (*S*,*R*)-configuration with (*Z*)-olefin substrates.

Investigating the substrate scope of the Claisen rearrangement, Feng *et al.* found that the transformation retained its high yields and stereoselectivities for both electron-donating and electron-withdrawing substituents, in place of the previously utilised phenyl functionality. However, substitutions of bulky substituents on the alkene unit, such as phenyl and *iso*-butyl groups, were observed to reduce the diastereoselectivity,

while electron-donating functionalities in this position were found to dramatically decrease the enantioselectivity. Having built a large hyperolactone chemical library, Feng and colleagues then demonstrated that by utilising both *L*-PiMe$_2$ and *ent*-*L*-PiMe$_2$ **167** chiral ligands in the key transformation, while varying the olefin precursor's geometry, all four stereoisomers associated with intermediate **166** could be readily accessed, with complete control over the absolute stereochemistry (***Scheme 1-20***).



Scheme 1-20: *Stereodivergent synthesis to all four of the stereoisomers associated with hyperolactone C precursor* ***166****.*

Having synthesised all of the possible stereoisomers of TIPS protected hydroxyester **166**, a final one-pot trimethylbromosilane mediated silyl deprotection and lactonisation procedure then completed the enantioselective total synthesis of (-)-hyperolactone C **5**, with an overall yield of 16.7% over eight-steps from the longest linear chain (***Scheme 1-19***). Despite requiring a lengthy reaction duration and structurally diverse ligands complexed to a highly toxic nickel(II) catalyst, Feng *et al*. successfully demonstrated that their key enantioselective dearomatisation Claisen rearrangement methodology enabled the stereodivergent total synthesis of both hyperolactones B-C, and analogues thereof, along with their respective stereoisomers, by applying subtle variations to their synthetic route.

Although the biologically active hyperolactone series has inspired numerous synthetic approaches to successfully assemble the synthetically challenging spirolactone framework, the enantioselective construction of the vicinal quaternary stereocentres have been addressed by only a handful of developed methodologies. Many established approaches to the spirocyclic secondary metabolites have involved

lengthy linear routes, mediocre overall yields and stereoselectivity issues arising from the stereospecific configuration at the central quaternary spirocentre. Therefore, further novel procedures are critical for the continued advancement of biologically active hyperolactone and biyouyanagin based therapeutic agents.

1.3 Diverted O-H Insertion Reactions of Metallocarbenes to Highly Substituted Tetrahydrofuran Scaffolds

Ever since the discovery of ethyl diazoacetate by Curtius in 1883,[61] the diazo functional group has been extensively studied, leading to the development of a wide range of transformation classes and 'named reactions'. As versatile reagents in organic synthesis, the field of diazo chemistry has continued to rapidly expand and remains widely studied to date. With diazo compounds possessing a rich reactivity profile (***Figure 1-6***), significant research on their role as short lived reactive carbene precursors, generated photochemically or thermally, and as highly reactive metal-coordinated carbenes, referred to as metallocarbenes, has taken place since the 1970s.[62,63]

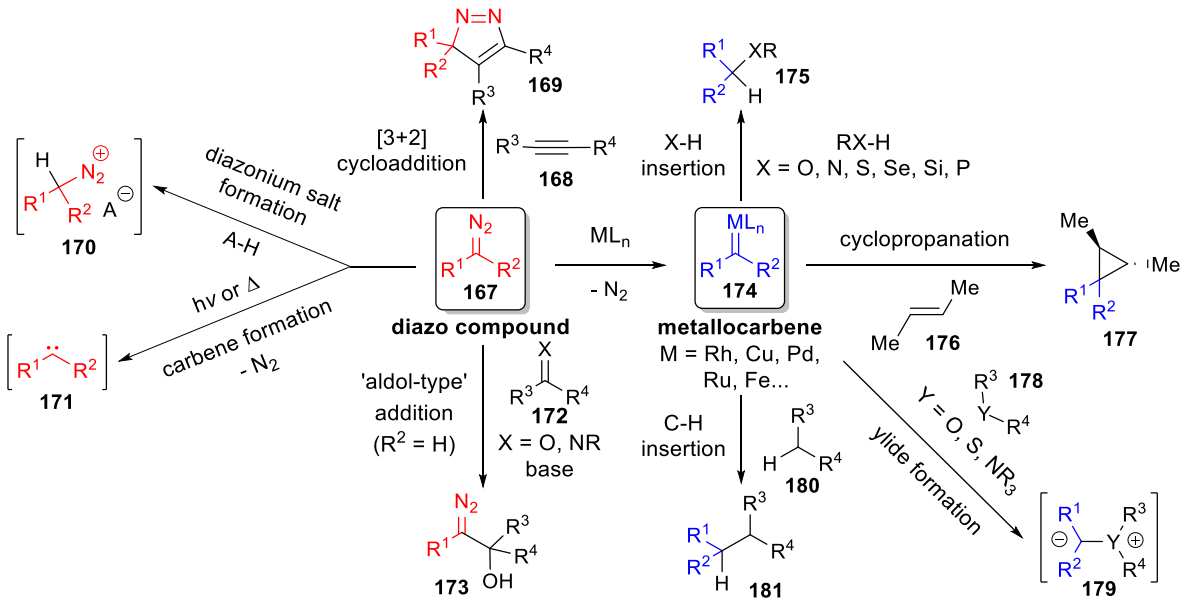


Figure 1-6: *General chemical transformations of diazo compounds and their respective metallocarbenoids.*

Due to the entropically favourable release of molecular nitrogen, diazo compounds are highly labile, with many transformations employing the use of stabilised diazo compounds, such as α-diazocarbonyls **182** that contain mesomerically stabilising electron-withdrawing groups in the α-position, rather than their unstabilised extremely explosive and toxic aliphatic counterparts.[64] Therefore, the process of generating reactive metallocarbenoids from α-diazocarbonyl compounds has been largely studied, with the catalytic process first initiated from the nucleophilic attack of the diazo bearing carbon to the Lewis acidic metal catalyst, forming a diazonium species **183** (***Figure 1-7***). Upon coordination, backdonation of electrons from the metal's d-orbitals into the adjacent σ^*-orbital irreversibly releases nitrogen gas and forms a highly reactive metal-bound carbene **184**. Electrophilic in nature, the Fischer carbene complex contains both a metal-carbon σ-bond and a π-bond, arising from the backbonding of electrons from the metal's d-orbitals into the vacant carbon p-orbital, which can subsequently react with a range of nucleophilic substates [Sub] in X-H insertions, C-H insertions, cyclopropanations and ylide formation reactions.

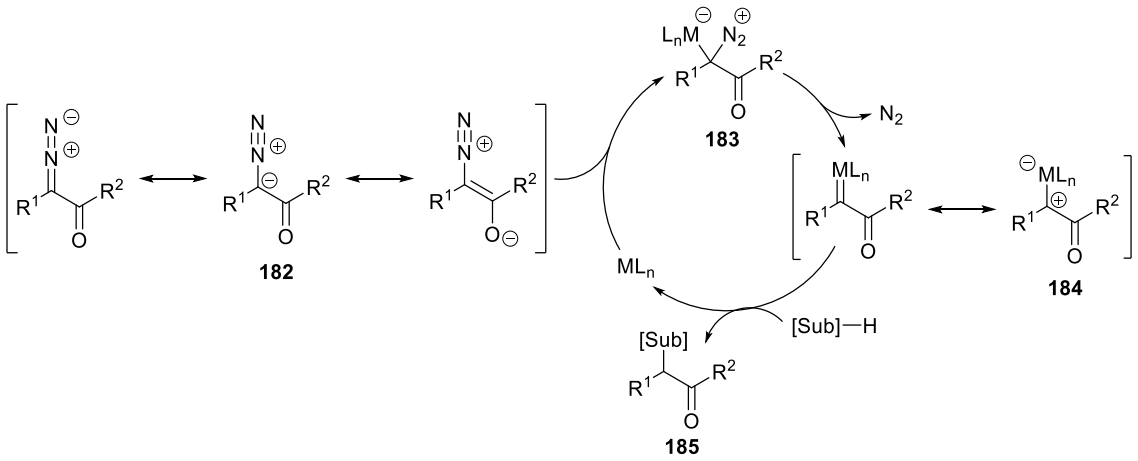


Figure 1-7: *Metal-catalysed α-diazocarbonyl decomposition ([Sub] = nucleophilic substrate).*

As a particularly powerful synthetic tool, the widely investigated X-H insertion reaction between nucleophiles and metallocarbenes has been demonstrated to form a plethora of synthetically challenging carbon-heteroatom bonds,[65,66] which has been utilised in a number of elegant total syntheses of biologically active complex natural products.[67,68] X-H insertion reactions are generally carried out in the presence of a metal catalyst or a Lewis acid, but can also undergo catalyst-free X-H insertions, where a diazo compound is thermally or photochemically activated to generate a free-carbene species **186** (***Figure 1-8***). In the presence of a nucleophile, such as an alcohol,

the free-carbene species undergoes an O-H insertion to generate an oxonium ylide intermediate **187** that then undergoes a formal [1,2]-hydride shift to form the O-H insertion product **188**. Due to the highly reactive nature of the free-carbene species, many competing detrimental side-processes may occur, which has led to the development of more efficient metal-catalysed, or Lewis acid induced, O-H insertions.

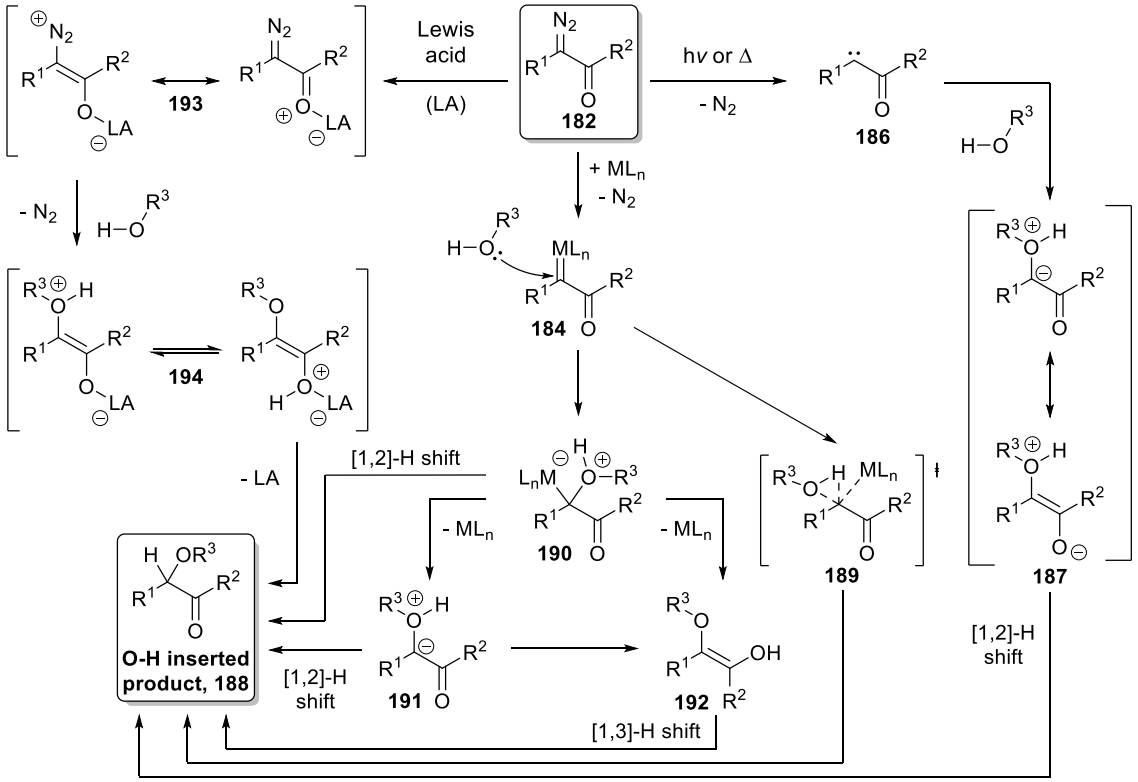


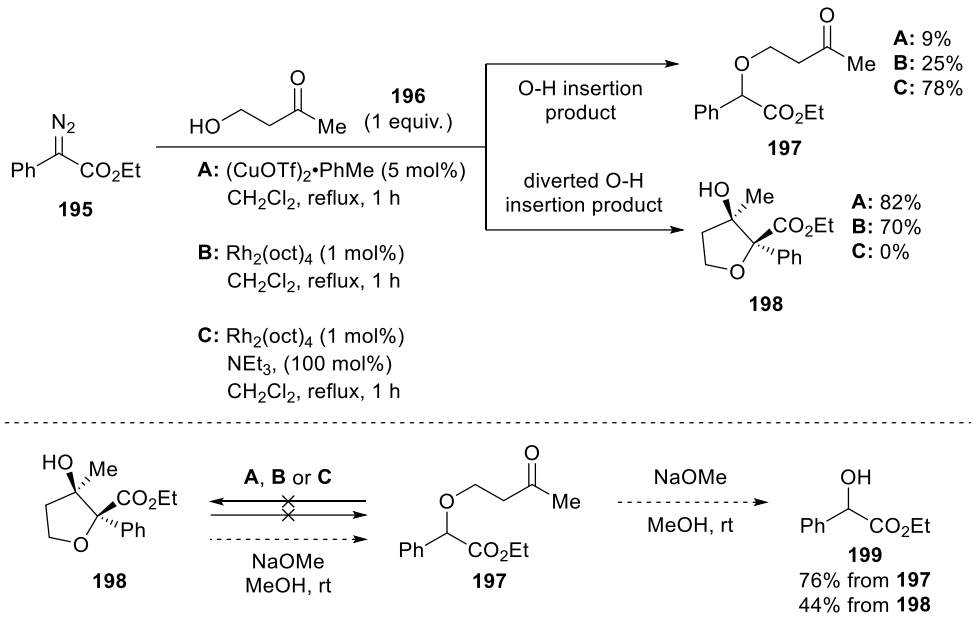
Figure 1-8: *Mechanistic understandings of the O-H insertion transformation of α-diazocarbonyls.*

Having been widely studied with copper(I), rhodium(II) and iron(III) complexes,[69,70] the metal-catalysed O-H insertion transformation involves the initial decomposition of the α-diazocarbonyl **182** to a metallocarbenoid species **184**. Although a concerted mechanism has been proposed (**189**),[71] it has generally been accepted that the reaction proceeds *via* a stepwise process, where the electrophilic metallocarbene reacts with Lewis bases, such as alcohols, to form a metal-bound ylide **190** that can be subsequently trapped with various electrophiles.[72] While the final stages of the reaction are not fully understood, metal-associated ylide **190** can either directly undergo a formal [1,2]-hydride shift, or form a metal-free ylide **191** through a metal-carbon bond cleavage that reacts in the same manner, to afford the corresponding O-H insertion product **188**. However, several computational calculations have suggested a high activation energy for the [1,2]-H shift of the

metal-free ylide **191**,[73,74] indicating that the reaction mechanism could proceed *via* an alternative intramolecular proton transfer to a free-(*Z*)-enol intermediate **192**, producing O-H insertion product **188** from a [1,3]-H shift. With asymmetric induction arising from metal-bound pathways, the transfer of chirality from a metal catalyst, complexed with chiral ligands, to the resulting product is governed through the [1,2]-H shift of metal-associated ylide **190**. Recent developments in enantioselective O-H insertion methodologies infer that copper(I) and iron(III) catalysts proceed *via* the metal-associated ylide, whereas rhodium(II) carboxylate catalysts follow a metal-free pathway *via* enol intermediate **192**.[75–78]

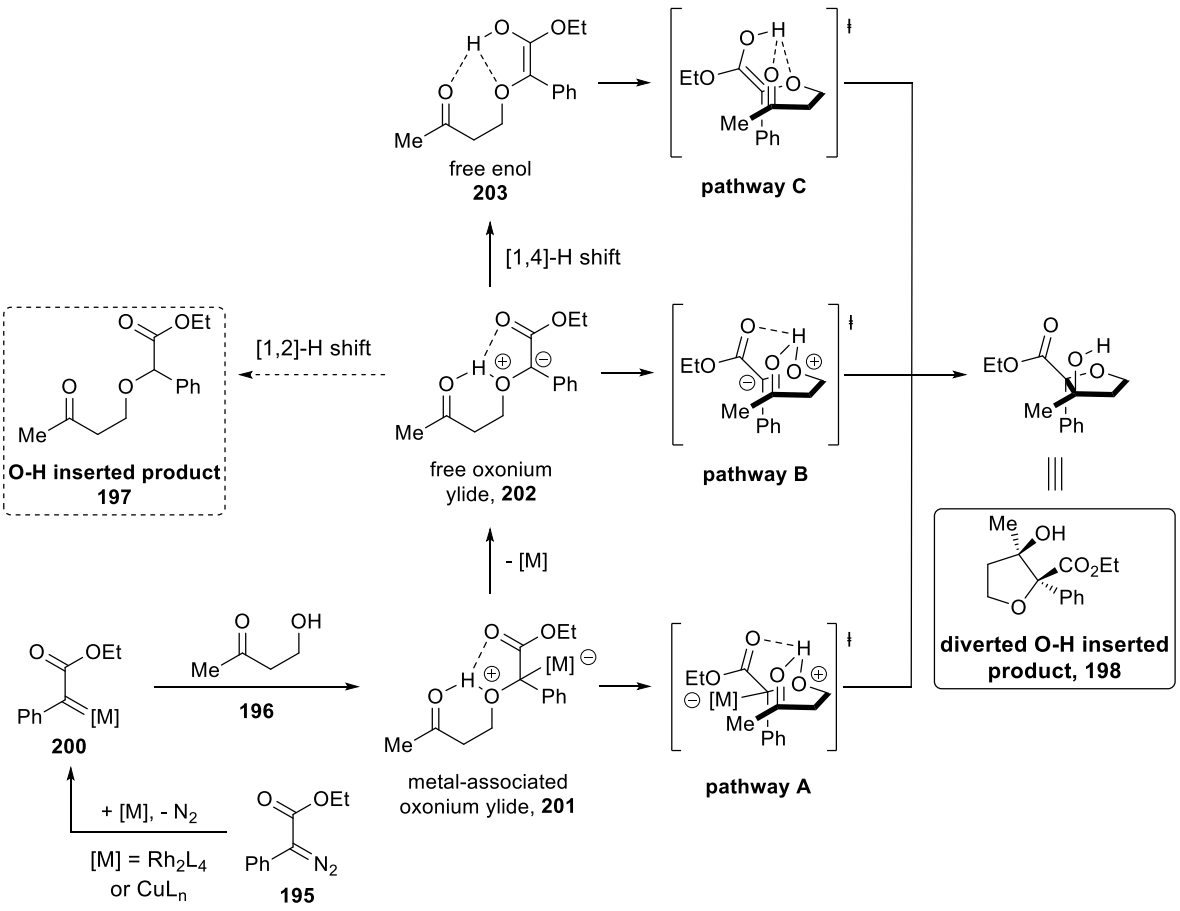
Having not been fully investigated, the Lewis acid induced O-H insertion pathway occurs from an unknown mechanism. Not considered to proceed through a carbene species, activation of either the carbonyl or diazo functionalities permits a nucleophilic alcohol addition,[79–81] where a successive proton shift and Lewis acid disassociation process then generates the desired O-H inserted product. With O-H, N-H and S-H insertions widely utilised in organic chemistry, along with possessing direct applications in chemical biology,[82,83] the development of novel metal-free and highly stereoselective metal-catalysed X-H insertions is of great significance.

Serendipitously discovered when investigating O-H insertions between the metallocarbenoid species of stabilised α-diazocarbonyl compounds with β-hydroxyketones, Moody and colleagues developed a single step seminal synthetic approach to highly substituted tetrahydrofurans, with excellent diastereoselectivity under mild conditions.[84] Initially exploring a range of alcohol substates, the metal-catalysed O-H insertion between ethyl 2-diazo-2-phenylacetate **195** and 4-hydroxybutanone **196**, led to the isolation of substituted tetrahydrofuran **198**, with only small amounts of the expected O-H insertion product **197** isolated (***Scheme 1-21***). Studying this transformation further, Moody *et al*. then trialled various reaction temperatures, concentrations and catalytic loadings, while varying reagent stochiometric ratios in the presence of numerous Lewis or Brønsted acids. Under optimal conditions tetrahydrofuran **198** was produced in 82% yield as a single diastereoisomer, confirmed from NOESY NMR experiments, with only trace amounts of the α-alkoxyester **197** isolated (<10%).



Scheme 1-21: *Serendipitous discovery of diverted metallocarbene O-H insertion of α-diazocarbonyl compounds with β-hydroxyketones.*

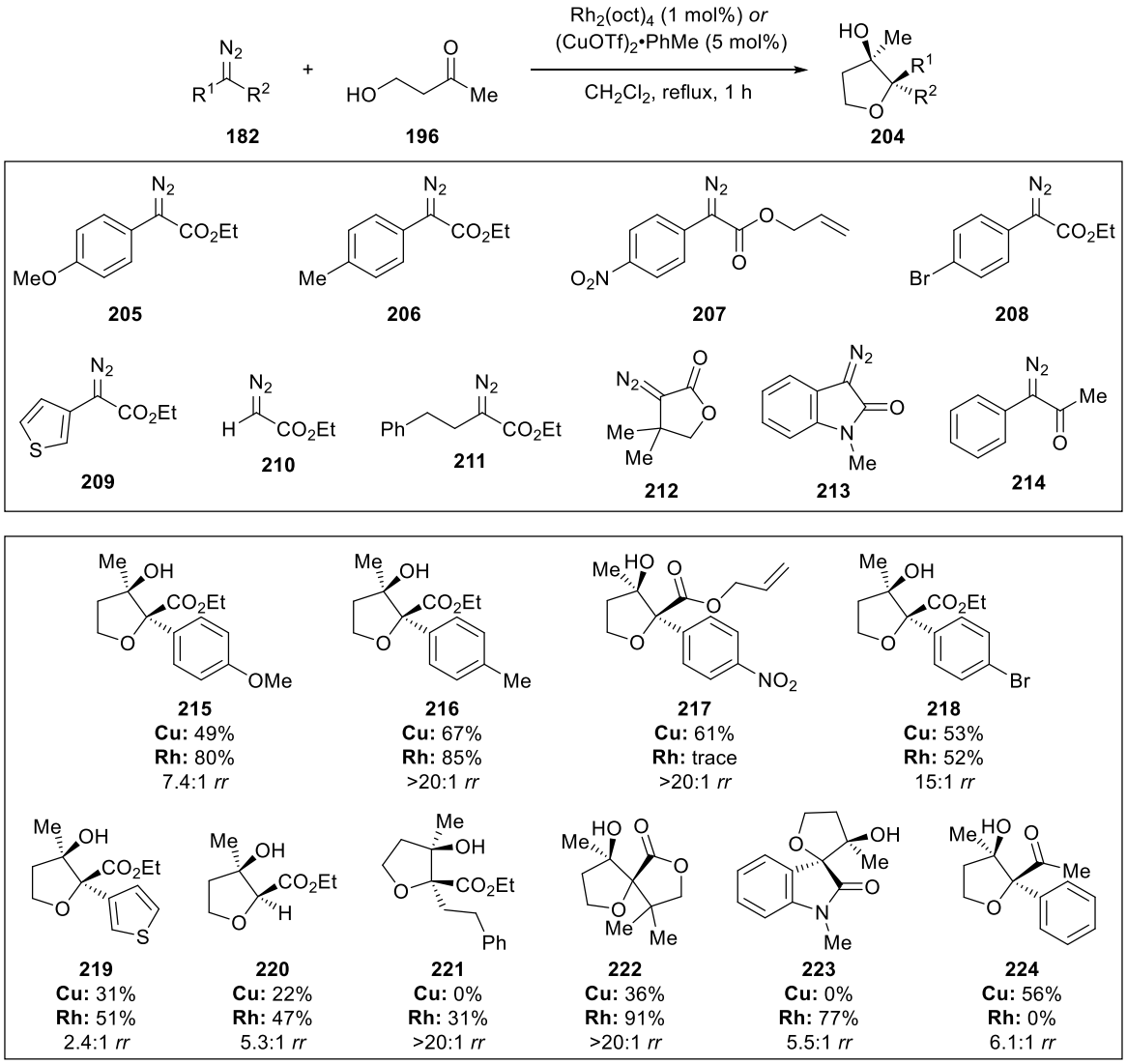
While traditionally applied O-H insertion catalysts, such as copper(I) iodide and copper(II) acetate, resulted in slow conversions to tetrahydrofuran **198**, Moody and co-workers observed that utilising either dirhodium(II) octanoate dimer, or copper(I) triflate toluene complex, was key for increasing the yield of the transformation. However, addition of triethylamine to this system led to the exclusive isolation of O-H insertion product **197**, while a slight excess of the α-diazocarbonyl was found to be essential. Establishing whether tetrahydrofuran **198** was formed through a stepwise initial O-H insertion reaction and subsequent intramolecular aldol cyclisation, ketoester **197** was subjected to the reaction conditions. Unable to be converted to tetrahydrofuran **198**, treatment with sodium methoxide led to the formation of methyl mandelate **199**, formed through a retro-Michael elimination of methyl vinyl ketone. Further control experiments demonstrated that tetrahydrofuran **198** was stable in the presence of metal catalysts and that a methyl mandelate **199** was again formed, presumably through a retro-aldol process, when treated with sodium methoxide. With O-H insertion product **197** not on the reaction pathway to tetrahydrofuran **198**, Moody and co-workers postulated that the reaction mechanism proceeds *via* a diverted carbene O-H insertion mechanism, where an intramolecular aldol cyclisation traps a transient oxonium ylide intermediate (***Scheme 1-22***).



Scheme 1-22: *Postulated diverted metallocarbene O-H insertion reaction mechanism, justifying the observed cis-cis stereochemistry.*

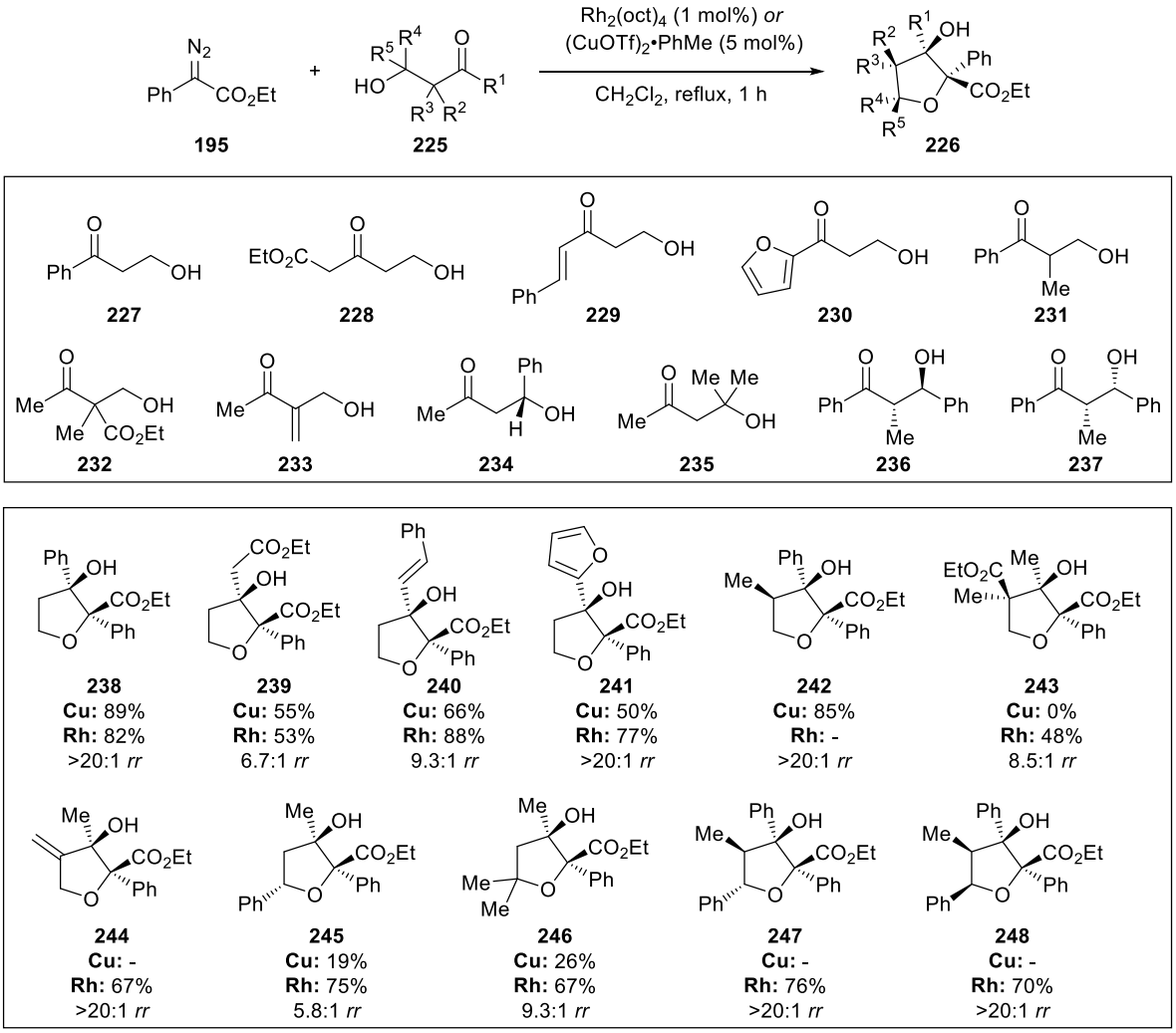
Initiated from a metal-catalysed decomposition of α-diazoester **195**, the nucleophilic O-H insertion of β-hydroxyketone **196** to electrophilic metallocarbene **200** affords metal-associated oxonium ylide **201**. The metal-bound ylide can disassociate generating metal-free oxonium ylide intermediate **202** that would be expected to undergo a formal [1,2]-hydride shift to the corresponding O-H insertion product **197**. However, it is proposed that intramolecular trapping of transient ylide intermediates **201** and **202**, through an aldol addition, produces tetrahydrofuran product **198**, *via* transition states A and B. Oxonium ylide **202** may also undergo an alternative proton transfer process to (*Z*)-enol intermediate **203**, that then affords the diverted O-H insertion product through the intramolecular aldol cyclisation, *via* transition state C. Proceeding with excellent diastereocontrol, the observed *cis-cis* conformation, with respect to the resultant hydroxy group and diazo derived ester functionality, can be rationalised from the stabilising hydrogen-bonding interactions observed in transition states A-C.

Having previously optimised the diverted metallocarbenoid O-H insertion transformation, detailed substrate scope studies were then performed (***Scheme 1-23***). Largely successful with numerous trialled α-diazocarbonyl substrates, Moody and co-workers found that dirhodium(II) octanoate dimer and copper(I) triflate toluene complex were complementary catalysts for their transformation with diazoacetates **205-208**. The rhodium-catalysed reaction of electron-rich diazoacetate **205** with β-hydroxyketone **196** obtained tetrahydrofuran **215** in high yield (80%), with only small amounts of the O-H inserted by-product isolated (7.4:1 *rr*). However, the same transformation with electron-deficient diazoacetate **207** was found to be more efficiently catalysed using copper catalysis, whereas both catalytic systems proceeded well with diazoacetate **208**.



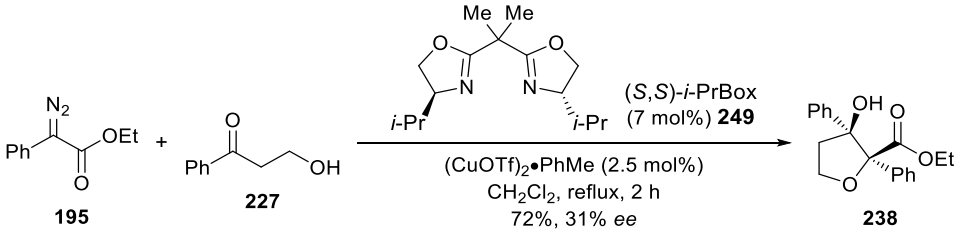
Scheme 1-23: *Stereospecific synthesis of 3-hydroxytetrahydrofurans from rhodium- and copper-catalysed diverted metallocarbene O-H insertion reactions.*

Lacking an adjacent aryl group, the diverted O-H insertion with commercially available ethyl diazoacetate **210** furnished desired tetrahydrofuran **220** in moderate yields, with the copper-catalysis system producing significant by-products, derived from carbene dimerisation. Interestingly, the same reaction with α-diazocarbonyl **211** was found to produce the desired tetrahydrofuran **221** in poor yields, due to an intramolecular [1,2]-hydride shift of the C-H bond in the α-position to the diazo group outcompeting the initial intermolecular alcohol insertion. Removing the α-C-H bond, cyclic diazocarbonyls **212** and **213** produced spirolactone **222** and spirolactam **223** in excellent yields using rhodium catalysis. However, the copper-catalysed diverted O-H insertion of diazoketone **214** led to the isolation of tetrahydrofuran **224** in moderate yield (56%), with the rhodium-catalysed transformation ineffective.



Scheme 1-24: *Stereospecific synthesis of polysubstituted tetrahydrofurans from rhodium- and copper-catalysed diverted metallocarbene O-H insertion reactions.*

Extending the substate scope further, the diverted O-H insertion of ethyl 2-diazo-2-phenylacetate **195** with a variety of β-hydroxyketones were evaluated, using both rhodium and copper-catalytic systems (***Scheme 1-24***). β-Hydroxyketone **227** and hydroxyketoester **228** proceeded well when subjected to both rhodium and copper catalysts, while the rhodium-catalysed reaction was superior for cinnamyl hydroxyethyl ketone **229** and furylketone **230** substates. Aldol **231**, containing an α-methyl substituent, efficiently produced desired tetrahydrofuran **242** with a high facial selectivity. Synthesised in a *cis*-*cis* configuration, the methyl substituent is located on the least sterically hindered ring face, demonstrating that the stereoselectivity could be extended to the four-position of the tetrahydrofuran. α-Disubstituted aldol **232** also produced a single diastereomer **243**, while allylic alcohol **233** formed tetrahydrofuran **244**, containing an exocyclic double bond, when subjected to rhodium catalysis. Enantioenriched aldol **234** underwent the diverted O-H insertion with no erosion of stereochemistry observed for the corresponding polysubstituted tetrahydrofuran **245**. Impressively, the transformation was also found to be relatively insensitive to steric bulk surrounding the inserting alcohol, as tertiary alcohol **235** produced its corresponding product **246** in 67%. Finally, α,β-disubstituted β-hydroxyketones **236** and **237** produced polysubstituted tetrahydrofurans **247** and **248** as single diastereoisomers, demonstrating that the methodology also provides stereocontrol to positions four and five of the heterocyclic framework, with the position four substituent having a greater influence on the stereocontrol when compared with substituents at position five.

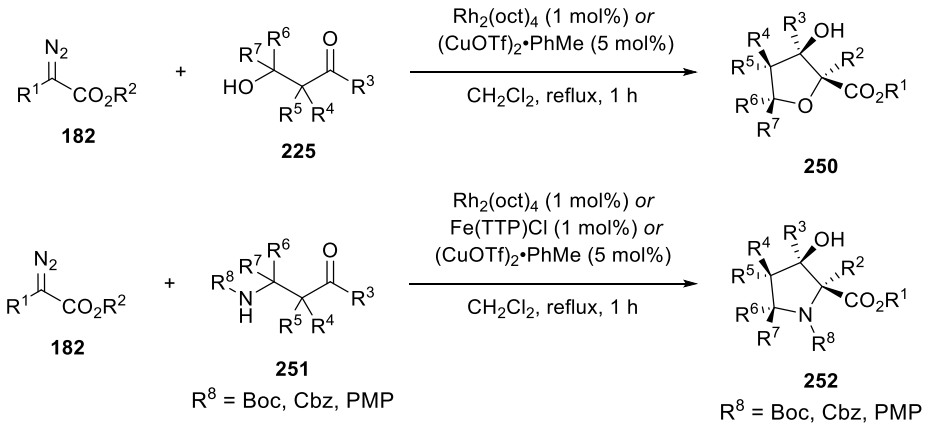


Scheme 1-25: *Enantioenriching asymmetric diverted metallocarbenoid diverted O-H insertion.*

Unfortunately, preliminary asymmetric diverted metallocarbene O-H insertion attempts, utilising rhodium and copper catalysts complexed to chiral ligands, were found to efficiently synthesise the desired tetrahydrofuran product but with limited chiral induction (***Scheme 1-25***). Rhodium-based systems proceeded with little to no enantioselective control (<7% *ee*), whereas BOX ligands coordinated to copper(I)

triflate toluene complex displayed encouraging enantiomeric excesses (31% *ee*). These early studies suggest that rhodium-based catalysts preferentially proceed through a metal free pathway, while copper-based catalysts remain, to a limited degree, associated to the ylide intermediate.

Only a handful of related metallocarbenoid synthetic strategies have been reported to stereospecifically synthesise the tetrahydrofuran heterocycle, based on an O-H insertion intramolecular Michael addition cascade and a carbonyl ylide formation-cycloaddition.[85,86] Moody and colleagues' developed diverted O-H insertion methodology provides a highly effective single step assembly of polysubstituted tetrahydrofurans, with excellent diastereoselectivity under mild conditions. Efficiently constructing synthetically challenging vicinal quaternary stereocentres with complete control over the relative stereochemistry across the entire tetrahydrofuran ring, expanding the utility of the transformation to β-aminoketone derivatives has also permitted the stereospecific synthesis of polysubstituted pyrrolidines, from a diverted metallocarbene N-H insertion variant.[87]

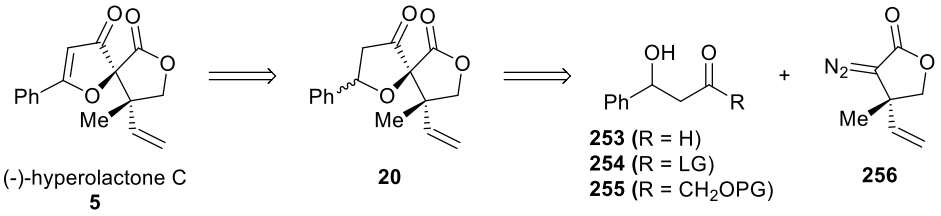


Scheme 1-26: *Developed diverted metallocarbene O-H and N-H insertions to polysubstituted tetrahydrofurans and pyrrolidines.*

Having been showcased to generate highly challenging heteroatom-infused spirocyclic frameworks from cyclic diazocarbonyl compounds, Moody and co-workers established that the diverted metallocarbene O-H insertion methodology may be utilised as a key synthetic strategy for the stereospecific assembly of challenging spirocycles. As an application of the developed methodology, this synthetic approach may be employed to achieve numerous total syntheses of biologically active and highly functionalised secondary metabolites.

1.4 Project Aims, Objectives and Previous Research

Seeking to enable the stereoselective synthesis of highly functionalised biologically active compounds through the continued development of the diverted carbene O-H insertion methodology, the Moody Research Group identified (-)-hyperolactone C **5** as an attractive natural product target that could be assembled from their key transformation. Retrosynthetic analysis identified the diverted O-H insertion between α-diazolactone **256** with β-hydroxycarbonyl compounds **253-255** as an effective strategy for the construction of the synthetically challenging spirolactone scaffold, where a late-stage dehydrogenation of hyperolactone precursor **20** would enable the synthesis of the secondary metabolite (***Scheme 1-27***).

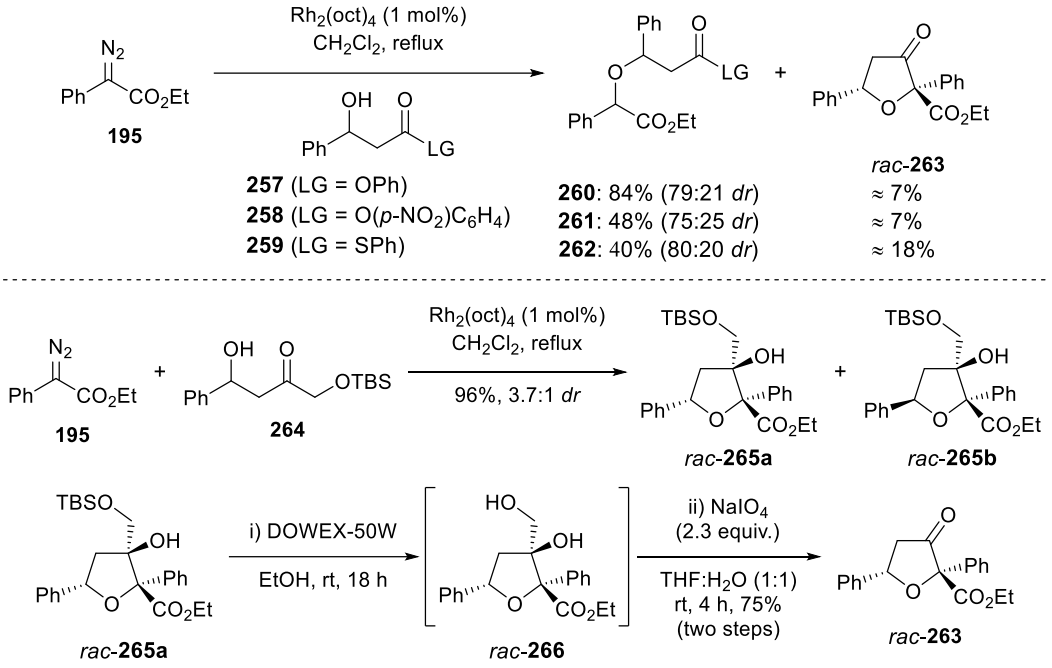


Scheme 1-27: *Initial retrosynthetic analysis of (-)-hyperolactone C using a diverted matallocarbene O-H insertion strategy.*

It was envisaged that the construction of spirocyclic dihydrofuranone **20** could be achieved from several diverted O-H insertion approaches that utilise either β-hydroxyaldehyde **253**, activated ester **254** or protected α-hydroxyketone **255**. These approaches either involve a diverted O-H insertion and successive oxidation, an alternative direct Claisen condensation diverted O-H insertion transformation, or a diverted O-H insertion oxidative cleavage sequence. With the absolute stereochemistry at the quaternary spirocyclic centre governed from the initial O-H insertion and subsequent intramolecular aldol ylide trapping, the diastereoselectivity of the key transformation has yet to be determined and may require the development of either an enantioselective procedure, or the inclusion of a directing functionality to achieve the desired configuration of the natural product scaffold.

Early studies carried out within the Moody Research Group were focused on establishing reaction conditions that would permit the synthesis of the dihydrofuranone framework.[88] Attempting a direct Claisen condensation diverted O-H insertion approach, the synthesis of dihydrofuranone **263** from α-diazocarbonyl **195** and

β-hydroxyester derivatives **257-259** were investigated (***Scheme 1-28***). Unfortunately, trialled reaction conditions using rhodium-catalysis furnished the linear O-H inserted products **260-262**, as a mixture of diastereoisomers, producing insignificant amounts of dihydrofuranone **263**.

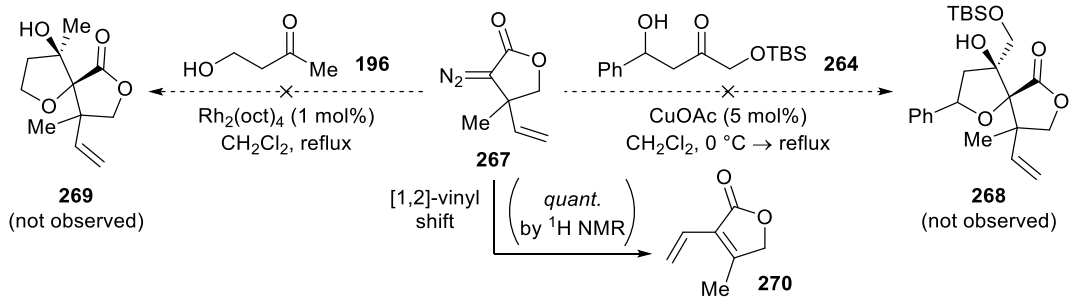


Scheme 1-28: *Accessing the dihydrofuranone moiety from a diverted O-H insertion approach.*

The alternative use of copper-catalysed systems produced complex mixtures and obtained low yields of both desired dihydrofuranone **263** and O-H inserted products **260-262**. Although dihydrofuranone **263** was identified, significant contamination with inseparable by-products, along with poor observed conversions to the desired motif, directed Moody *et al.* to alternative approaches.

Achieving the synthesis of dihydrofuranone **263**, the diverted O-H insertion between α-diazocarbonyl **195** and protected α-hydroxyketone **264** efficiently obtained chromatographically separable tetrahydrofurans **265a-b** in an exceptional yield with a moderate diastereoselectivity (3.7:1 *dr*). Confirmed through the nOe correlation between the methyl substituent and the methylene adjacent to the silylated alcohol, sterically favoured *cis*,*trans*-diastereoisomer **265a** was then converted to dihydrofuranone **263** through a two-step oxidative cleavage sequence in a good overall yield.

Having developed a diverted metallocarbene O-H insertion approach to the dihydrofuranone domain of the hyperolactone carbon skeleton, numerous attempts to access spirolactones **268** and **269**, from a diverted O-H insertion involving α-diazolactone **267**, primary aldol **264** and secondary aldol **196**, were then carried out (***Scheme 1-29***). Despite trialling a plethora of conditions, all performed reactions failed to produce the desired spirolactone framework. Instead of proceeding through the desired diverted O-H insertion pathway, the generated metallocarbenoid species underwent a rapid competing intramolecular [1,2]-vinyl migration to produce butanolide **270**.[89]



Scheme 1-29: *Attempted preparation of the spirolactone motif from a diverted O-H insertion strategy.*

Although these initial results confirm that α-diazocarbonyl compounds possessing vinyl groups in the α-position are incompatible with this transformation class, pursuing the synthesis of other functionalised spirocyclic dihydrofuranones, through a diverted O-H insertion approach that addresses the competing [1,2]-migratory shifts, may lead to an efficient strategy to the therapeutically active hyperolactone motif using easily accessible building blocks. Therefore, the primary aim of this research project is to develop an efficacious synthetic route to the spirocyclic hyperolactone topology, by exploiting the diverted metallocarbene O-H insertion methodology. Aiming to then achieve the total synthesis of (-)-hyperolactone C **5** by developing a stereospecific approach to the synthetically challenging vicinal stereocentres of the natural product, would permit the assembly of the absolute configuration at the quaternary spirocentre. With a view to developing an asymmetric procedure, the use of chiral ligands complexed to metal catalysts will be explored. Although diverted metallocarbenoid O-H insertions have been developed to diastereoselectively synthesise several heterocycles, this research also aims to expand the scope of this methodology to enable the synthesis of novel privileged spirolactone analogues, imperative for the advancement of this transformation.

Chapter 2: Assembling the Hyperolactone Scaffold *via* a Developed Diverted Carbene O-H Insertion Approach

2.1 Developed First-Generation Synthetic Strategy to the Spirocyclic Hyperolactone Framework

In order to validate the efficacy of a diverted O-H insertion approach to the spirocyclic hyperolactone motif and assess the stereochemical outcomes of the key transformation, novel hyperolactone **271** was selected as a suitable model system, differing by a vinyl group on the lactone domain with respect to the hyperolactone C molecular framework (***Figure 2-1***). Retrosynthetic analysis of hyperolactone **271** indicated that the diverted metallocarbene O-H insertion between α-diazolactone **212** and β-hydroxyketone **264** would lead to spirolactone **273**, that could be further manipulated through an oxidative cleavage sequence and final dehydrogenation to afford the hyperolactone scaffold. Therefore, initial synthetic efforts were directed at accessing diverted O-H insertion precursors **212** and **264**.

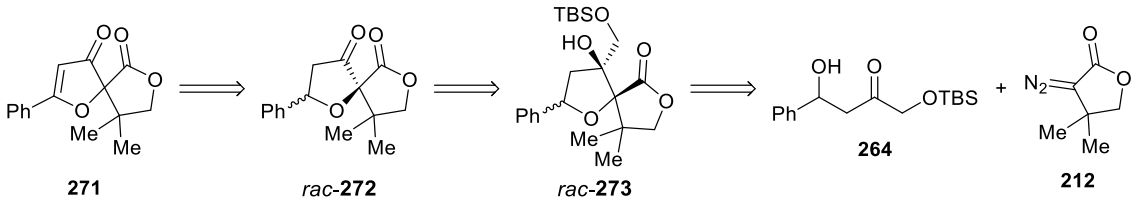
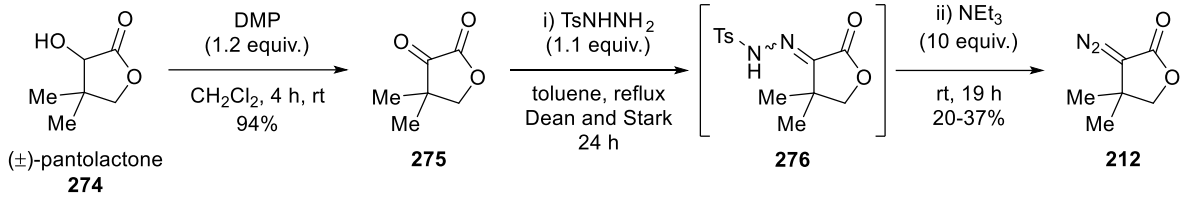


Figure 2-1: *Retrosynthetic analysis of model hyperolactone system **271** employing a diverted metallocarbene O-H insertion strategy.*

It was envisaged that the preparation of α-diazolactone **212** could be achieved by exploiting a previously reported Bamford-Stevens diazotisation of ketolactone **275**,[90,91] which may be subsequently synthesised *via* an oxidation of commercially available (±)-pantolactone **274** (***Scheme 2-1***). Attempting an initial Dess-Martin oxidation, poor isolated yields of desired ketolactone **275** were obtained, despite proceeding with a high consumption of (±)-pantolactone **274**, which was postulated to be the result of nucleophilic addition of water to the highly electrophilic ketone during an aqueous workup. Pleasingly, a modified procedure involving a filtration at -15 ºC with a successive chromatography purification, successfully removed remaining

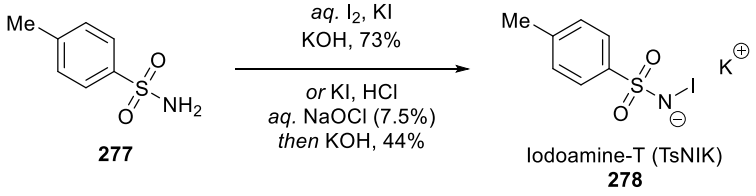
organoiodide impurities and prevented the detrimental formation of the corresponding diol, leading to the isolation of ketolactone **275** in excellent yield.



Scheme 2-1: *Initial preparation of α-diazoester **212** utilising a Bamford-Stevens diazotisation.*

Unfortunately, diazotisation of ketolactone **275**, involving the formation of tosylhydrazone intermediate **276** with a consecutive *in situ* base elimination, afforded α-diazolactone **212** in poor yields, ranging between 20-37%, consistent with results previously published.[90] Combatting the poor diazotisation yields, an alternative milder approach to α-diazolactone **212**, utilising the recently discovered hydrazone oxidative agent potassium *N*-iodo *p*-toluenesulfonamide **278** (TsNIK, iodamine-T) (***Scheme 2-2***), was then investigated.[92]

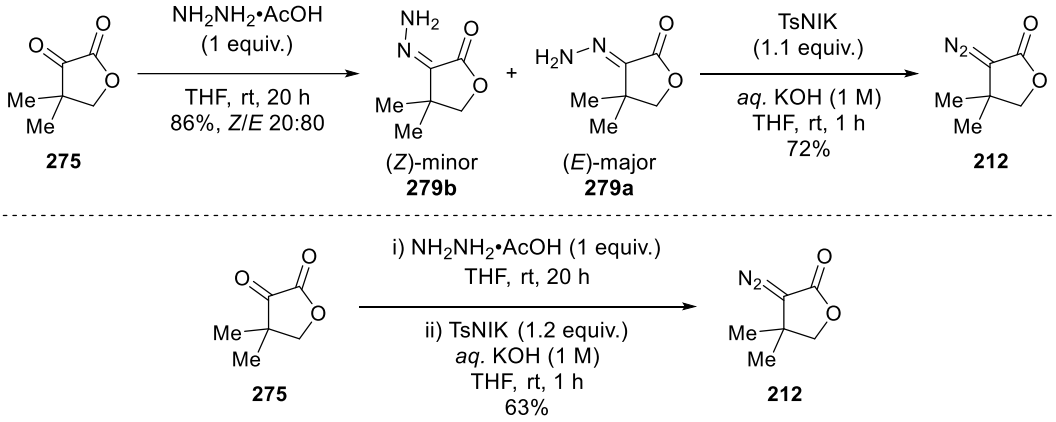
Developed by Moody *et al*., iodamine-T **278** has been demonstrated to oxidise numerous α-ketoester hydrazones, generated from the condensation of an α-ketoester with hydrazine hydrate in the presence of a weak Brønsted acid, or exclusively hydrazine acetate, to a range of α-diazocarbonyls in high yields. Although the reaction mechanism is not fully understood, Moody and colleagues suggest that the *in situ* reduction of iodamine-T produces potassium iodide, which is susceptible to oxidation, releasing an equivalent of iodine, which then reacts with potassium hydroxide to afford unstable potassium hypoiodite (KOI). Readily decaying through a disproportionation reaction to give potassium iodide and iodate, iodamine-T may act as a stable hypoiodite equivalent that permits the oxidation of α-ketoester hydrazones to their corresponding α-diazocarbonyl compounds.



Scheme 2-2: *Generation of iodamine-T **278** (TsNIK), a mild reagent for the oxidation of α-ketoester and α-ketoamide hydrazones to α-diazocarbonyl compounds.*

Iodamine-T **278** was rapidly synthesised by treating *p*-toluenesulfonamide **277** with iodine, in the presence of aqueous potassium iodide and hydroxide, which was purified *via* a simple filtration in excellent yield (***Scheme 2-2***). Due to the hazards and environmental toxicity properties iodine possesses, an additional TsNIK synthesis, involving the use of potassium iodide and bleach solution (NaOCl) to generate iodine *in situ*, was also developed by Moody *et al*., albeit in a reduced yield.

With iodamine-T efficiently synthesised, α-ketolactone **275** was treated with hydrazine acetate to chemoselectively obtain chromatographically separable hydrazones **279a-b** in excellent yield (***Scheme 2-3***). Utilising X-ray crystallographic studies (*vide infra*, ***Appendix B - Figure A***) and analysing the broadness of the ^{1}H NMR signals corresponding to the hydrazone functionality (C=N-N*H*$_2$), it was confirmed that under the applied reaction conditions, the least sterically hindered (*E*)-hydrazone **279a** configuration was favoured over the intramolecularly hydrogen bonded (*Z*)-hydrazone **279b** (*Z*/*E* 20:80). Mirroring the results acquired by Moody *et al*.,[92] steric factors were experimentally observed to have a preferential influence on the stereoselectivity when compared to electronic effects. Interestingly, Moody and colleagues observed the opposite stereoselectivity for linear α-ketoester hydrazones derived from α-ketoesters.

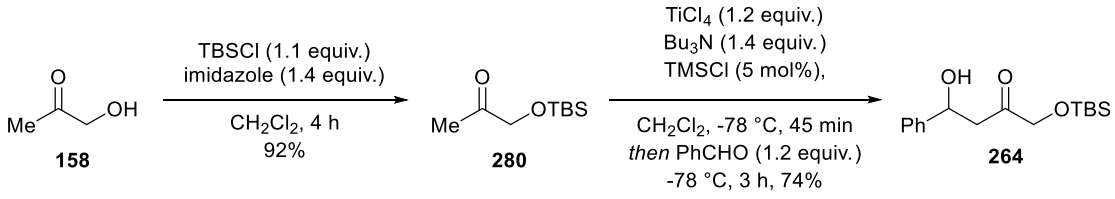


Scheme 2-3: *One-pot hydrazone formation and iodamine-T induced oxidation to α-diazolactone* ***212.***

Having efficiently synthesised hydrazones **279a-b**, purified (*E*)-hydrazone **297a** was then oxidised by iodamine-T, utilising Moody and co-workers' previously optimised diazotisation conditions to successfully afford α-diazolactone **212** in 72% (62% yield over two-steps), as a significant improvement from the initially obtained Bamford-Stevens diazotisation yields of 20-37%. Due to the fact that both the hydrazone formation and oxidation procedures are carried out using the same solvent,

Moody and colleagues also developed a one-pot hydrazone formation and oxidation procedure from α-ketoesters to their corresponding diazo compounds, giving comparable yields to those previously obtained over the two-steps, and even enhancing yields for α-diazocarbonyls obtained from labile hydrazones that were found to readily decompose upon storage. Applying this direct approach, α-ketolactone **275** was also successfully converted into α-diazolactone **212** without loss of yield. Having achieved an economical, efficient synthesis of α-diazolactone **212** from the direct hydrazone formation and oxidation process, this highly attractive synthetic methodology also involves a straightforward work-up purification procedure, removing the need for column chromatography. Furthermore, this 'green' diazotisation synthetic procedure was also demonstrated to have atom-economical flow chemistry applications for many complex diazo compounds, reducing its subsequent environmental impact and the requirement of extremely hazardous reagents used in other diazotisation procedures.[93]

Investigated in parallel to the synthesis of α-diazolactone **212**, it was envisaged that diverted O-H insertion precursor (±)-β-hydroxyketone **264** could be accessed from hydroxyacetone **158**, *via* a two-step silyl ether alcohol protection and a subsequent Mukaiyama aldol reaction with benzaldehyde (***Scheme 2-4***).[94] Selected for the ease of instalment, cleavage and steric bulk surrounding the hydroxy functionality, critical for ensuring the regioselective formation of the kinetic enolate in the Mukaiyama aldol reaction and chemoselectivity within the key diverted O-H insertion transformation, hydroxyacetone **158** was reacted with *tert*-butyldimethylsilyl chloride to furnish α-silyloxyketone **280**.



Scheme 2-4: *Preparation of β-hydroxyketone **264**, via a TBS silylation of hydroxyacetone **158** and a Mukaiyama aldol addition with benzaldehyde.*

Following a modified Mukaiyama aldol addition developed by Tanabe *et al*.,[95] tributylamine, a highly sterically hindered non-nucleophilic base, was employed under kinetic conditions to regioselectively form the kinetic enolate of α-silyloxyketone **280**, in the presence of titanium(IV) tetrachloride and catalytic amounts of trimethylsilyl

chloride. The successive addition and activation of benzaldehyde, from the Lewis acid coordination with titanium(IV) tetrachloride, promotes the aldol addition, resulting in the formation of racemic (±)-β-hydroxyketone **264** in high yield. Having developed an effective parallel synthetic strategy to α-diazolactone **212** and (±)-β-hydroxyketone **264**, the evaluation of the effectiveness and stereochemical outcomes of the key diverted metallocarbene O-H insertion transformation was then assessed and optimised (***Table 2-1***).

Having already been demonstrated to efficiently form spirolactone **222** from the diverted O-H insertion between the metallocarbene of α-diazolactone **212** and 4-hydroxybutanone **196**, in the presence of rhodium(II) octanoate dimer (*vide supra*, ***Scheme 1-23***), identical reaction conditions were trailed for the diverted O-H insertion reaction between α-diazolactone **212** and (±)-β-hydroxyketone **264** (entry 1, ***Table 2-1***). Unfortunately, poor yields (<10%) of the desired diverted O-H insertion product **273**, isolated as an inseparable mixture of diastereoisomers, were obtained along with butanolide **282**, which was isolated with additional minor contaminants. The main reaction component, butanolide **282**, was formed from a competing [1,2]-methyl group migration of the *in situ* generated metallocarbene **281**. With [1,2]-migrations of metallocarbenoids derived from similar cyclic α-diazocarbonyls previously reported,[96] attempts to mitigate this competing process by reducing the reaction temperature to ambient temperature, or to 0 ºC, were found to increase the yield of the key transformation, whereas the reaction was inhibited at -40 °C (entries 2-4). Exchanging rhodium(II) octanoate dimer for copper(I) triflate toluene complex did not prevent or reduce the significance of the competing [1,2]-methyl group migration, and also introduced an additional minor by-product, α,β-unsaturated ketone **283**, through a suspected copper induced dehydration process (entry 5). However, an initiation period, involving the addition of α-diazolactone **212** at 0 °C, was required to provide reproducible results, and was observed to slightly increase the yield of spirolactones **273a-b** (entry 6). Utilising THF as the reaction solvent reduced the reaction yield (entry 7) and thermal conditions, without the presence of a catalyst, resulted in only trace amounts of spirocyclisation (entry 8). Encouragingly, copper(I) acetate provided improved results as the formation of the major [1,2]-methyl migration product, butanolide **203**, was not observed, with only minor isolated yields of by-product α,β-unsaturated ketone **204** obtained (entry 9).

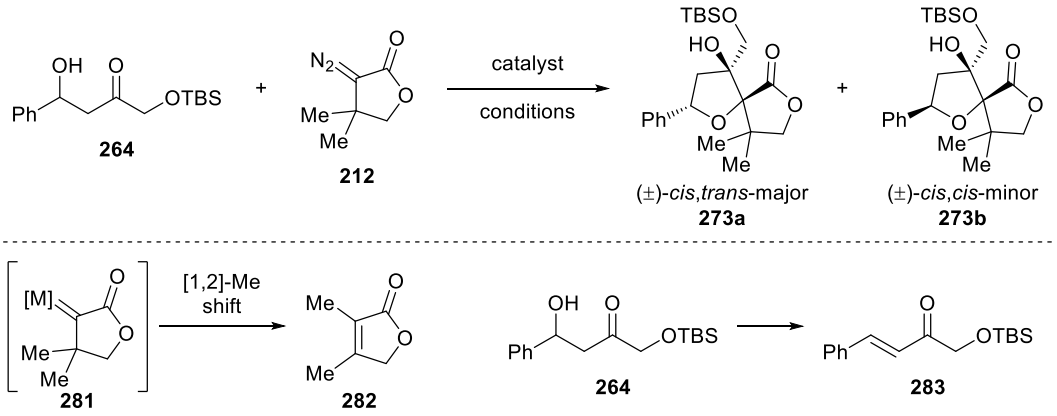


Table 2-1: *Diverted metallocarbene O-H insertion optimisation of α-diazolactone **212** with (±)-β-hydroxyketone **264**, to spirolactone diastereomeric mixture **273a-b**.*

Entry	Conditions[a]	212 / equiv.	Time / h	Yield[b] / %	*dr*[c] (273a:273b)	Recovered 264 / %
1	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	1	5[e]	90:10	90
2	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, rt	1.3	18	9[e]	88:12	82
3	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, 0 °C	1.3	1	20[e]	90:10	74
4	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, -40 °C	1.3	1	no rection[g]	/	/
5	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, 0 °C	1.3	1	19[d,e]	92:8	66
6	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, 0 °C→rt→reflux	1.3	1→1→1	22[d,e]	88:12	51
7	$(CuOTf)_2$•PhMe (5 mol%), THF, 0 °C	1.3	1	11[d,e]	92:8	70
8	no catalyst, CH_2Cl_2, reflux	1.3	1	trace[e,g]	/	/
9	CuOAc (5 mol%), CH_2Cl_2, 0 °C	1.3	1	34[d]	85:15	67
10	CuOAc (5 mol%), CH_2Cl_2, 0 °C→rt→reflux	1.3	2→2→16	38[d]	81:19	58
11	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, 0 °C→rt→reflux	1.3	2→2→16	21[e]	88:12	60
12	CuOAc (5 mol%), CH_2Cl_2, reflux	1.3	18	22[d]	83:17	68
13	CuOAc (5 mol%), DCE, 0 °C→rt→reflux	1.3	2→2→16	11[d,e]	78:22	66
14	CuOAc (5 mol%), CH_2Cl_2, rt	1.3	18	27[d]	80:20	67
15	CuOAc (5 mol%), CH_2Cl_2, rt→reflux	1.3	2→16	41[d]	86:14	43
16	CuOAc (10 mol%), CH_2Cl_2, rt→reflux	1.3	2→16	41[d]	82:18	40
17	CuOAc (5 mol%), CH_2Cl_2, rt→reflux	2	2→16	56[d]	86:14	20
18	CuOAc (5 mol%), CH_2Cl_2, rt→reflux (conc.)[f]	2	2→16	51[d]	85:15	18
19	CuOAc (5 mol%), CH_2Cl_2, 0 °C→rt→reflux	2	2→2→16	79[d]	84:16	10
20	CuOAc (5 mol%), CH_2Cl_2, 0 °C	2	2	60[d]	84:16	16
21	CuOAc (5 mol%), CH_2Cl_2, -40 °C	2	1	no reaction[g]	/	/

a = using a slow dropwise addition of α-diazolactone **212** to the reaction mixture over a 30 min period; b = isolated yield; c = the *dr* was determined by ^{1}H NMR analysis; d = α,β-unsaturated ketone **283** was detected; e = [1,2]-Me shift **282** product was observed; f = reaction concentration was increased from a 0.2 M to a 0.4 M solution; g = ^{1}H NMR analysis of the crude material.

Consequently, further optimisation efforts were directed towards the use of copper(I) acetate as the active catalyst, where extending the reflux duration from 1 h to 16 h was found to slightly increase the yield (entry 10). However, increasing the reflux temperature by substituting CH_2Cl_2 for DCE led to a dramatic loss in yield while also increasing the isolated yield of α,β-unsaturated ketone **283** and reintroducing butanolide **282** (entry 13). Increasing the catalytic loading from 5 mol% to 10 mol% (entry 16), as well as the concentration of the reaction system from 0.2 M to 0.4 M (entry 18), were found to have negligible effects (entry 18). However, a breakthrough was achieved when increasing the stoichiometry of α-diazolactone **212** from 1.3 equiv. to 2 equiv., as this adjustment greatly influenced the resulting yield of spirolactones **273a-b** (entry 17). Under optimised conditions (entry 19), a prolonged reflux duration, prior to an initiation period and an increased equivalent of α-diazolactone **212** slowly added to the reaction mixture at 0 °C, diastereoselectively produced the desired diverted O-H insertion products **273a-b** in 79% yield, in favour of the least sterically hindered *cis*,*trans*-configuration **273a** (84:16 *dr*). It is therefore postulated, for the case of α-diazolactone **212** and (±)-β-hydroxyketone **264**, that the sterically bulky phenyl group adjacent to the alcohol functionality decreases the rate of O-H insertion facilitating a competing [1,2]-methyl group migration from metallocarbene **281**, with the requirement of an initiation period suggesting that the key transformation is not a spontaneous process.

Exclusively forming a *syn*-configuration, with respect to the resultant hydroxy group and diazo derived lactone carbonyl functionality, the construction of the vicinal stereocenters proceeded with excellent diastereocontrol, rationalised from the stabilising hydrogen-bonding interactions observed in transition states A-D (***Figure 2-2***). Identifying the relative stereochemistry of the resulting diastereoisomers from the nOe correlations between the benzylic and aromatic protons with the methylene protons adjacent to the *tert*-butyldimethylsilyl group, the phenyl substituent located at the *C*2 position was found to preferentially reside on the opposite ring face to the lactone and hydroxyl functionalities. Therefore, the diastereoselectivity of the favoured *cis*,*trans*-configuration of major spirolactone **273a** can be rationalised from unfavourable 1,3-diaxial interactions between the phenyl and ketone functionalities observed in transition states B and D. Preferentially forming spirolactone enantiomers **273a** and **273c** over **273b** and **273d**, the phenyl substituent is located in a favourable

pseudo-equatorial position in transition states A and C, leading to the observed diastereoselectivity.

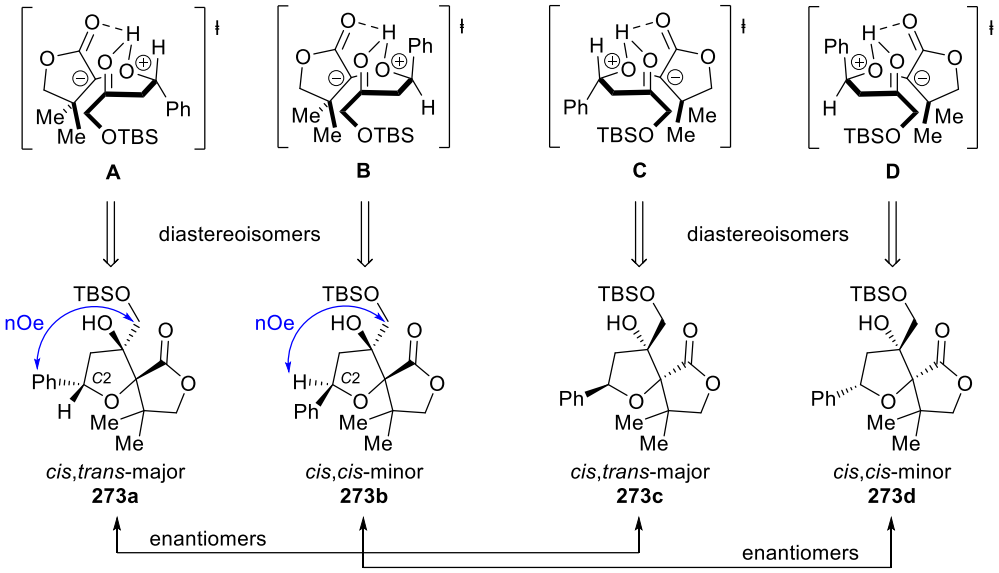
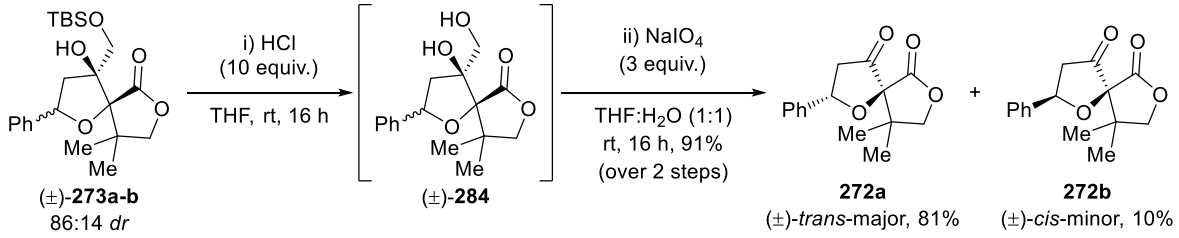


Figure 2-2: *Transition states of the diverted metallocarbene O-H insertion between α-diazolactone* ***212*** *and (±)-β-hydroxyketone* ***264****, leading to spirolactone products* ***273a-d****.*

Although racemic diastereoisomers **273a** and **273b** could not be separated by column chromatography at this stage, the inseparable diastereomeric mixture **273a-b** was subjected to an oxidative cleavage sequence, producing chromatographically separable spiro-dihydrofuranones **272a** and **272b** under mild conditions and in excellent yield (***Scheme 2-5***).

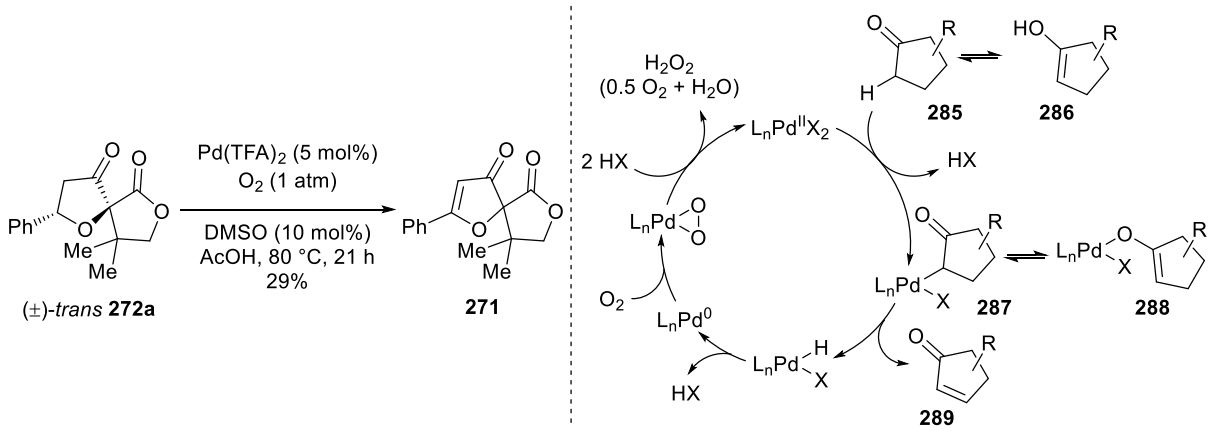


Scheme 2-5: *Oxidative cleavage of inseparable racemic spirolactone mixture* ***273a-b*** *to separable racemic spiro-dihydrofuranone diastereoisomers* ***272a-b****.*

Upon treatment with an acidic aqueous medium, diastereomeric spirolactone mixture **273** was readily converted to crude diol mixture **284**, that then underwent a sodium periodate mediated oxidative cleavage to spiroketolactones **272a** and **272b** in high yield. Chromatographically separable, *trans*-spiroketolactone **272a** was isolated in 81% yield, whereas the minor diastereomer *cis*-spiroketolactone **272b** was isolated

in 10% (91% yield over two steps). With a wide range of dehydrogenation approaches to cyclic enones known, emphasis was then focused on achieving the final furan-3(2*H*)-one domain of the hyperolactone framework.

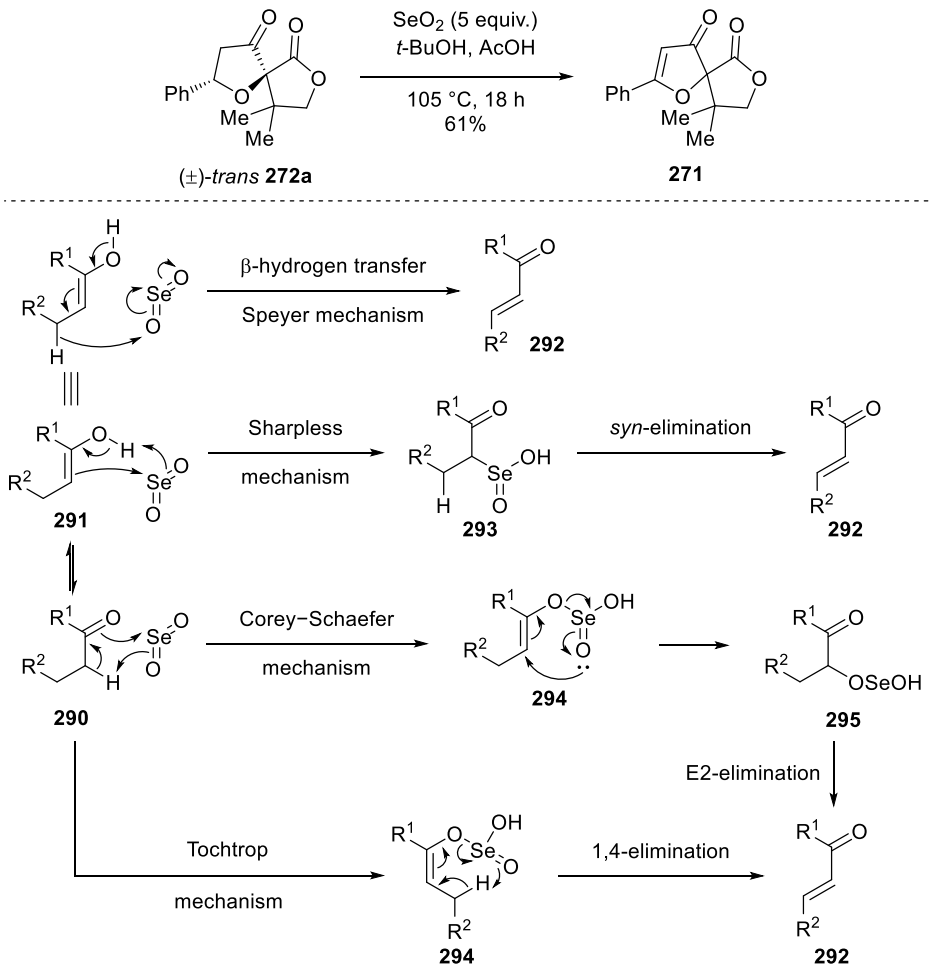
Although classical Saegusa-Ito oxidation conditions have permitted the efficient conversion of a diverse range of cyclic ketones, *via* their corresponding silyl enol ethers, to complex enone products,[97] the Pd(II)-mediated dehydrosilylation methodology requires stoichiometric equivalents of Pd(II) reagents, making this process highly expensive and unfavourable for scale-up procedures. Therefore, a modified Saegusa-Ito dehydrogenation, involving a direct aerobic Pd(II)-catalysed transformation developed by Stahl and co-workers,[98] was initially investigated.



Scheme 2-6: *Synthesis of hyperolactone* ***271*** *from a direct Pd(II)-catalysed dehydrogenation, highlighting the proposed mechanism by Stahl et al.*[98]

Generated *in situ*, the active Pd(II)-catalyst, $Pd(DMSO)_2(TFA)_2$, readily forms a Pd(II)-enolate that undergoes a successive β-hydride elimination to install the enone functionality and form a Pd(II)-hydride intermediate, which is ultimately re-oxidised to the active catalyst in an oxygen-rich environment (***Scheme 2-6***). Applying Stahl and colleagues' developed methodology, spiroketolactone **272a** was converted to desired hyperolactone **271**, albeit in an inadequate 29% yield. Although Stahl *et al*. achieved remarkable results for cyclohexanone systems, cyclopentanone motifs and ketones displaying a γ-phenyl group were also isolated with limited success, suggesting that the steric hinderance of the phenyl functionality limits either the formation of the Pd(II)-enolate intermediate or prevents the β-hydride elimination from efficiently occurring. Preventing the late-stage use of expensive toxic heavy metals, additional Saegusa-Ito based approaches were not investigated further.

Closely related to the Riley oxidation reaction mechanism,[99] selenium dioxide has also been demonstrated to effectively facilitate the dehydrogenation of ketones to α,β-unsaturated ketones, sparking many mechanistic studies.[100–103] With the true mechanistic nature of the selenium dioxide induced ketone dehydrogenation unknown, there have been a variety of plausible reaction pathways. These proposed pathways involve an enol tautomerisation and direct β-deprotonation (Speyer mechanism),[101] the formation and *syn*-elimination of an α-selenated species from the resulting enol tautomer (Sharpless mechanism)[102] or an E2-elimination of a selenous ester formed from a selenium dioxide-induced enolisation, where selenium dioxide acts as a Lewis acid (Corey-Schaefer mechanism) (***Scheme 2-7***).[100]

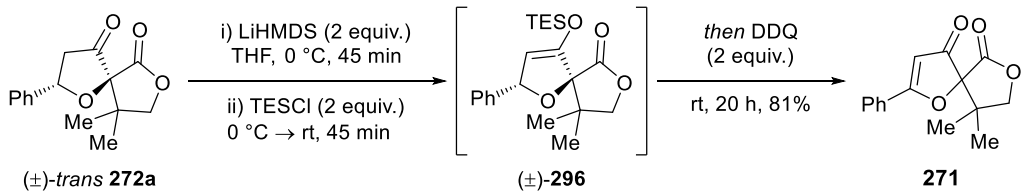


Scheme 2-7: *Preparation of hyperolactone* ***271*** *via a selenium oxide mediated dehydrogenation, highlighting postulated mechanisms.*

However, mechanistic studies carried out by Tochtrop *et al*. provide evidence that the reaction is initiated with the ketone tautomer, ruling out the Speyer and Sharpless mechanisms, and that the involvement of unstable selenous intermediate

295 is unlikely, as a more plausible rapid hydrolysis would prevent the proposed E2-elimination from occurring.[103] Therefore, Tochtrop and colleagues proposed an alternative mechanism involving a selenium dioxide-induced enolisation, forming a selenous ester intermediate that undergoes a subsequent 1,4-elimination to furnish the resultant α,β-unsaturated ketone. Having been successfully utilised to complete the total syntheses of other sterically hindered cyclic terpenoid-based natural products,[104] applying the same selenium dioxide induced dehydrogenation methodology to spiroketolactone **272a**, successfully produced desired hyperolactone **271** in an improved yield of 61%.

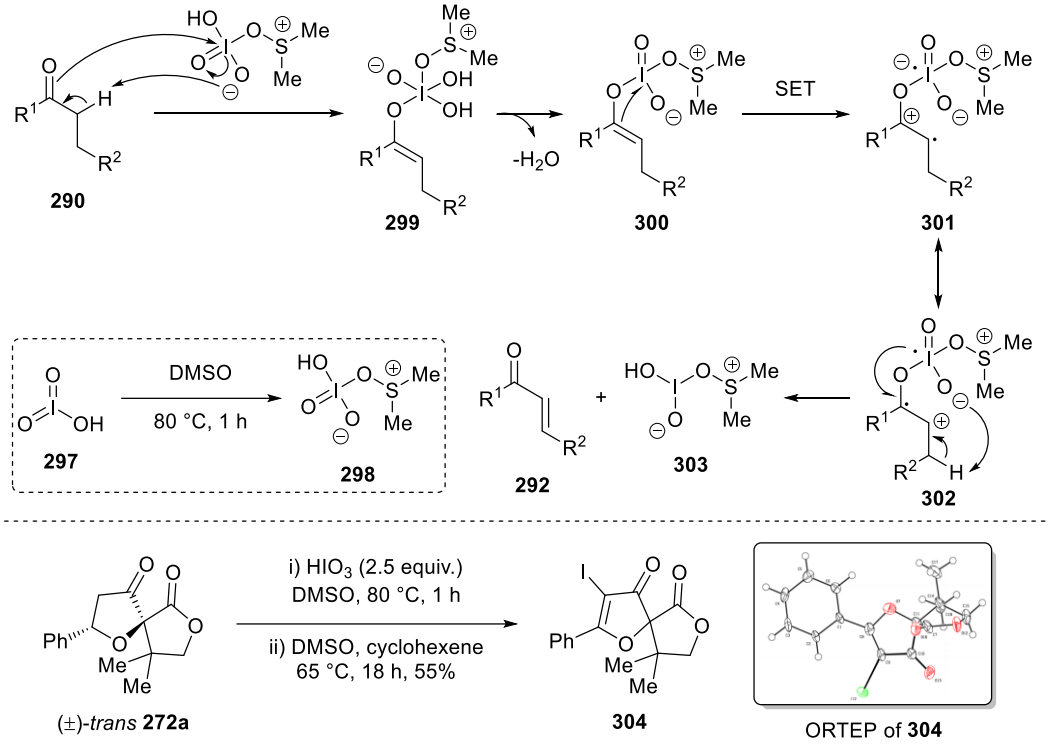
Aiming to further improve the efficiency of the final dehydrogenation reaction, Hodgson and co-workers' previously developed methodology, utilising a Lewis acid mediated silyl enol ether formation successive DDQ induced dehydrogenation to successfully achieve the total synthesis of (-)-hyperolactone C **5** (*vide supra*, ***Scheme 1-11***),[45] was then trialled. Unfortunately, hyperolactone **271** was obtained in disappointing yields (<30%), despite Hodgson and colleagues achieving impressive results for the conversion of an almost identical hyperolactone precursor. Suspecting that the use of highly labile moisture sensitive trimethylsilyl based reagents and intermediates may be lowering the desired conversion, a modified dehydrogenation procedure involving lithium bis(trimethylsilyl)amide and triethylchlorosilane to generate the corresponding triethylsilyl enol ether **296**, followed by the addition of DDQ at room temperature, led to the formation of hyperolactone analogue **271** in excellent yield (***Scheme 2-8***).



Scheme 2-8: *Generation of hyperolactone analogue **271**, utilising a DDQ induced dehydrogenation of silyl enol ether **296**.*

Despite having developed a modified silyl enol ether activated DDQ induced dehydrogenation to efficiently construct the desired hyperolactone motif, a final mild, atom-efficient iodic acid mediated dehydrogenation procedure, developed by Nicolaou *et al*., was then investigated (***Scheme 2-9***).[105]

Since the discovery of the direct IBX-mediated dehydrogenation of ketones and aldehydes to their corresponding enones,[106] extensive research has led to the development of cost-effective, commercially available iodine(V) dehydrogenation agents. Performing various mechanistic studies, the Nicolaou Group learnt that this transformation proceeded *via* a single electron transfer (SET) process and that ligands bonded to the iodine nucleus had a significant effect on the reaction's efficiency,[107] having experimentally observed a drastic reactivity shift from THF,[108] DMSO[106] and *N*-oxide-based ligands.[109] Modifying and removing the aromatic fragment of IBX, Nicolaou *et al.* uncovered that iodic acid and its anhydride, I_2O_5, were effective IBX surrogates that provided a mild, highly efficient, less toxic, chemoselective route to α,β-unsaturated ketones for a wide variety of substrates (***Scheme 2-9***).[105]



Scheme 2-9: *Iodic acid-DMSO complex **298** mediated dehydrogenation mechanism and the synthesis of iodo-hyperolactone **304**.*

Although Nicolaou and co-workers achieved remarkable results for a diverse range of cyclic ketones, the formation of hyperolactone **271** from spiroketolactone **272a**, utilising the iodic acid mediated dehydrogenation methodology, was unsuccessful. However, this procedure led to the unexpected isolation of iodo-hyperolactone **304**, confirmed from spectroscopic and X-ray crystallographic studies (*vide infra*, ***Appendix B - Figure B***). Proceeding through an unknown α-iodination

reaction mechanism, the dehydrogenation methodology required the addition of co-solvent cyclohexene, as the reaction conditions were reported to produce varying amounts of detrimental iodine as a by-product, which may have led to the formation of iodo-hyperolactone **304**. Although ineffective at furnishing the desired hyperolactone product, this transformation enables the construction of the hyperolactone framework and may permit the diversification of the enone functionality at the *C*3 hyperolactone position through the application of widely utilised cross-coupling methodologies. Alternative iodine(V) dehydrogenation agents or reaction conditions were not investigated.

Having achieved the synthesis of novel hyperolactone **271** from the development of a successful synthetic route, utilising a diverted carbene O-H insertion strategy, attention was then directed towards enantioselectively constructing the spirocyclic quaternary stereocentre of the hyperolactone motif. Having previously optimised and accessed the stereochemical outcomes of the diverted O-H insertion between the metallocarbene of α-diazolactone **212** and (±)-β-hydroxyketone **264**, it was postulated that utilising enantiomerically pure (*S*)-β-hydroxyketone **264** would govern the assembly of the vicinal quaternary stereocentres in the (-)-hyperolactone C configuration, leading to the enantioselective synthesis of the model hyperolactone (*S*)-**271** system (***Figure 2-3***).

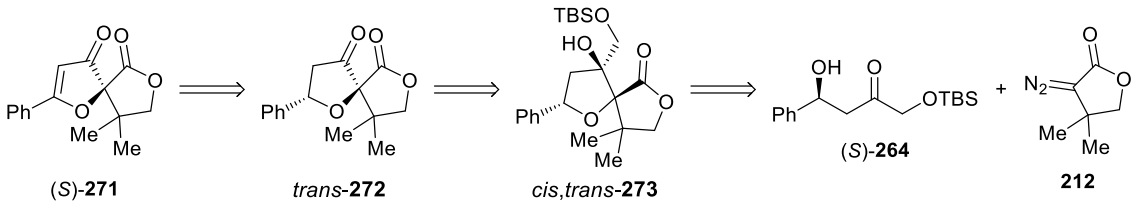
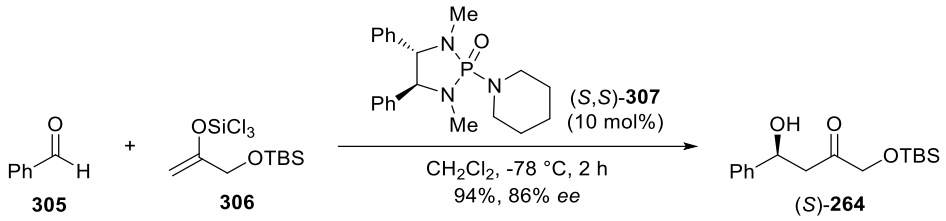


Figure 2-3: *Stereospecific retrosynthetic analysis of model hyperolactone system (S)-**271** employing a diverted metallocarbene O-H insertion strategy.*

Having synthesised (±)-β-hydroxyketone **264** from a two-step synthetic route, involving the silylation of hydroxyacetone and a subsequent Mukaiyama aldol addition with benzaldehyde, the development of an enantioselective aldol addition procedure was initially considered to directly enable the synthesis of the desired (*S*)-β-hydroxyketone **264** enantiomer. As a heavily researched transformation, catalytic asymmetric aldol additions, involving chiral organocatalysts, chiral ligands

complexed to metal catalysts and catalytic enzymatic reactions, have been developed to enable the synthesis of a wide variety of β-hydroxyketones.[110]

Applying an asymmetric aldol addition between benzaldehyde **305** and trichlorosilyl enolate **306**, Denmark *et al*. efficiently synthesised (*S*)-β-hydroxyketone **264** with a reasonable enantiomeric excess (94%, 86% *ee*), in the presence of a phosphoramide-based Lewis base (*S*,*S*)-**307** (***Scheme 2-10***).[111] Synthesising enoxytrichlorosilane **306** from a mercury(II)-catalysed trimethylsilyl to trichlorosilyl metathesis,[112] permitted by treating the corresponding trimethylsilyl enol ether with tetrachlorosilane in the presence of mercury(II) acetate, the subsequent aldol addition proceeds *via* an unknown mechanism. Denmark and co-workers postulate that the aldehyde component may initially coordinate to the Lewis acidic silicon centre to form a hexacoordinate diphosphoramide-bound silyl enolate complex that may react through a chair-like transition state. However, the aldolisation of trichlorosilyl enolates has also been suggested,[113] and computationally calculated,[114] to occur from a closed transition structure that resembles a boat.

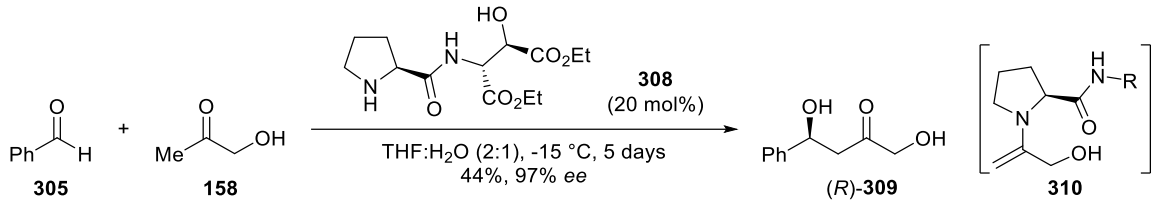


Scheme 2-10: *Preparation of (S)-β-hydroxyketone **264** from an enantioselective aldol addition.*

Although successfully demonstrating the synthesis of desired (*S*)-β-hydroxyketone **264** in high yield, the requirement of the commercially unavailable chiral phosphoramide ligand (*S*,*S*)-**307**, accessed from a lengthy linear synthetic route,[115] in addition to unsatisfactory levels of asymmetric induction (<90% *ee*), renders this methodology undesirable.

Unfortunately, trialling readily available chiral titanium(IV) isopropoxide and (*R*)-BINOL based Mukaiyama aldol reactions resulted in a dramatic loss of yield for the desired β-hydroxyketone product, despite being shown to enantioselectively synthesise a large number of related β-hydroxythioesters.[116,117] Choosing to investigate an organocatalysed aldol addition strategy, rather than examine alternative metal catalysts and chiral ligand systems, an adaptation of Chen and colleagues'

developed enantioselective aldolisation of hydroxyacetone in environmentally benign aqueous media was attempted.[118] Synthesising a range of 1,4-diols using a *L*-prolinamide derived organocatalyst **308**, Chen *et al.* synthesised (*R*)-1,4-diol **309** from hydroxyacetone in an exceptional enantiomeric excess (97% *ee*), with computational calculations suggesting that the transformation preferentially forms enamine **310**, over the competing enol enamine form, rationalised from stabilising hydrogen bonding interactions between solvent water molecules and the organocatalyst (***Scheme 2-11***).

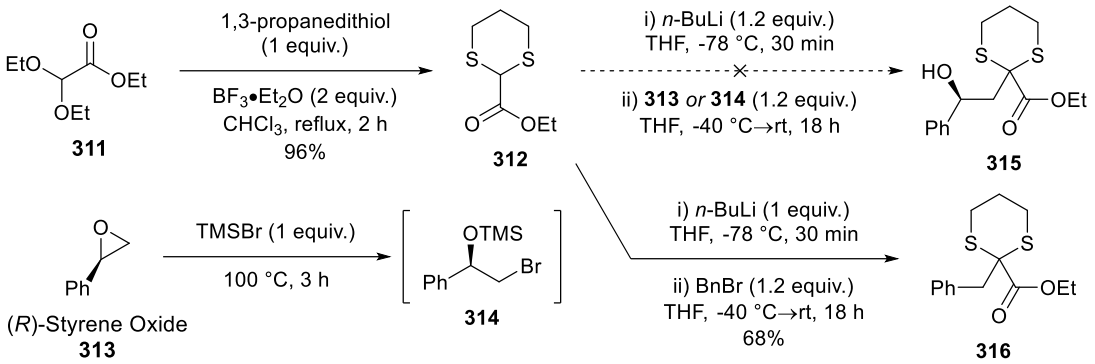


Scheme 2-11: *Preparation of (R)-1,4-diol **309** from an organocatalysed enantioselective aldol addition, highlighting the transient enamine intermediate.*

It was envisaged that the formation of (*S*)-1,4-diol **309** from a *D*-prolinamide organocatalysed enantioselective aldolisation of hydroxyacetone with benzaldehyde, followed by a successive chemoselective *tert*-butyldimethylsilyl protection of the primary alcohol, would enable the synthesis of (*S*)-β-hydroxyketone **264**. Disappointingly, desired (*S*)-1,4-diol **309** was only produced in trace amounts when reacted with *D*-prolinamide, even with prolonged reaction durations. With low optimised yields of 44%, the requirement of lengthy reaction durations (5 days) and the essential use of non-commercially available organocatalyst **308** for the synthesis of the undesired enantiomer, (*R*)-1,4-diol **309**, other organocatalysts and reaction conditions were not studied further.

Investigated in parallel to the direct aldolisation approach, the synthesis of (*S*)-β-hydroxyketone **264** *via* a Corey-Seebach umpolung strategy,[119] involving the alkylation of a 1,3-dithiane intermediate with (*R*)-styrene oxide to achieve the desired stereochemistry at the secondary alcohol, was examined. Commercially available (*R*)-styrene oxide, readily prepared from an epoxidation of styrene and a Jacobsen hydrolytic kinetic resolution to achieve the desired absolute stereochemistry,[120] was postulated to undergo an alkylation with 1,3-dithiane **312** to afford β-hydroxydithiane **315**, that could be further manipulated to (*S*)-β-hydroxyketone **264** (***Scheme 2-12***).

Having prepared 1,3-dithiane **312** from a Lewis acid induced condensation of ethyl diethoxyacetate **311** with 1,3-propanedithiol in excellent yield, subsequent alkylation attempts with (*R*)-styrene oxide, using both *n*-butyllithium and freshly prepared lithium diisopropylamide failed to afford β-hydroxydithiane **315**.

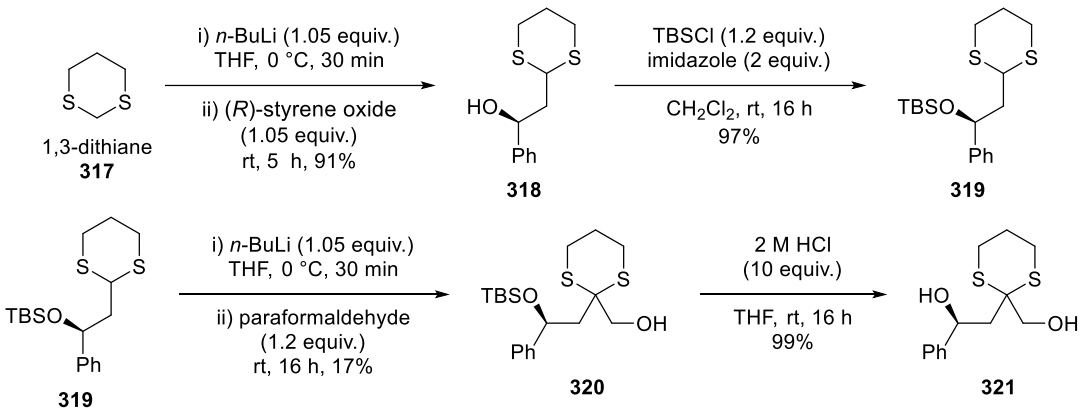


Scheme 2-12: *Attempted alkylations and synthesis of 1,3-dithiane **313**.*

Assessing the effectiveness of an alkylation approach from the *in situ* generated resonance stabilised anion of 1,3-dithiane **312**, an alternative electrophile, benzyl bromide, underwent a successful alkylation to furnish 1,3-dithiane **316** in high yield. Increasing the electrophilicity of (*R*)-styrene oxide **313**, it was subsequently postulated that an alternative alkylation with trimethylsilyl protected bromohydrin **314** may undergo an alkylation with 1,3-dithiane **312** to produce β-hydroxydithiane **315**, upon an acidic work-up. Despite Kricheldorf and co-workers achieving the synthesis of bromohydrin **314** from a trimethylbromosilane induced regioselective ring opening,[121] repeating their vacuum distillation purification conditions resulted in polymerisation and rapid degradation of the resulting bromohydrin. Unfortunately, subsequent alkylation attempts using the obtained crude material also failed to afford β-hydroxydithiane **315**.

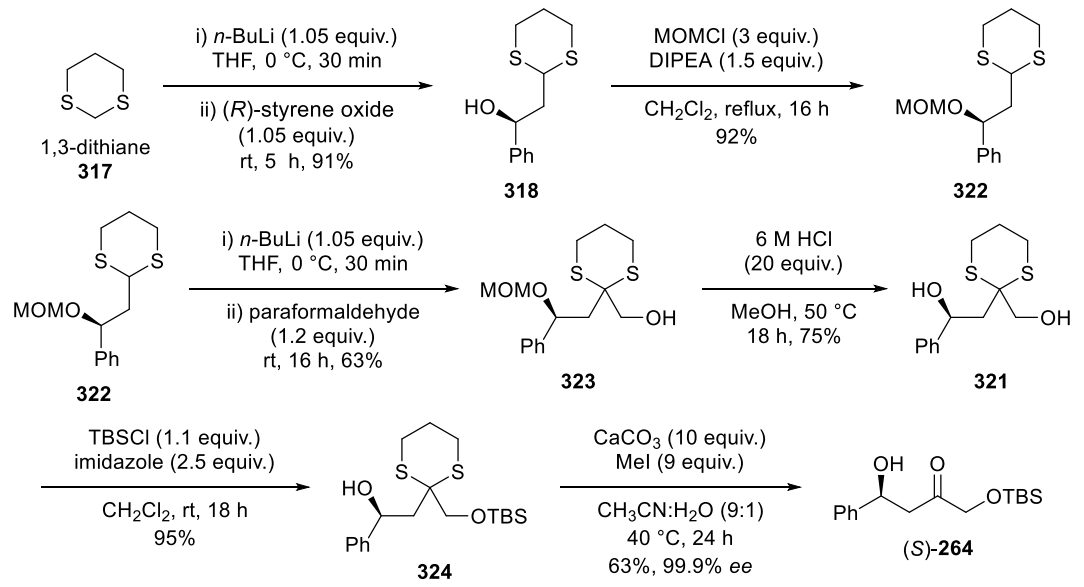
In spite of this, modification of the Corey-Seebach umpolung strategy led to the synthesis of 1,4-diol **321**, a precursor of (*S*)-β-hydroxyketone **264**, prepared from a developed four-step alkylation protecting group strategy (***Scheme 2-13***). Commencing from a high yielding alkylation between 1,3-dithiane **317** and (*R*)-styrene oxide, the synthesis of α-hydroxydithiane **320** was achieved from a subsequent alcohol *tert*-butyldimethylsilyl protection and successive alkylation with paraformaldehyde, where treatment with acidic aqueous media produced 1,4-diol **321**. Although an effective synthetic approach, the low yielding quaternary carbon forming alkylation between

1,3-dithiane **319** and paraformaldehyde was highly inefficient, indicating that the reaction may be retarded by the steric bulk of the *tert*-butyldimethylsilyl functionality.



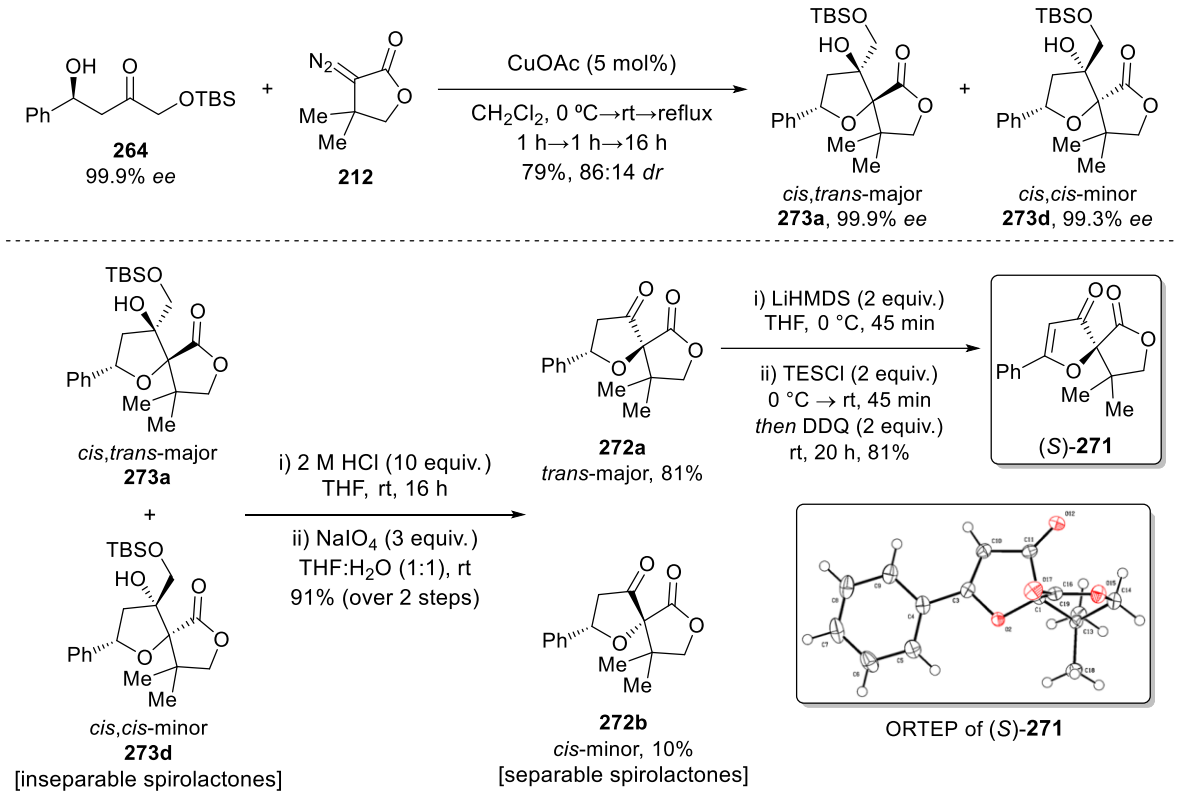
Scheme 2-13: *Initial preparation of 1,4-diol* ***321****.*

Attempting a direct paraformaldehyde alkylation with 1,3-dithiane **318**, using two equivalents of *n*-butyllithium under kinetic conditions, resulted in only small quantities of both the desired *C*-alkylated and disfavoured *O*-alkylated products. Therefore, substituting the sterically encumbered *tert*-butyldimethylsilyl functionality for the methoxymethyl ether protecting group, installed by the addition of chloromethyl methyl ether to a refluxing solution of alcohol **318** and Hünig's base, increased the efficiency of the paraformaldehyde alkylation, affording α-hydroxydithiane **323** in 63% yield (***Scheme 2-14***).



Scheme 2-14: *Preparation of (S)-β-hydroxyketone* ***264*** *from a developed Corey-Seebach umpolung synthetic strategy.*

Cleavage of the methoxymethyl ether protecting group proved challenging, where treating α-hydroxydithiane **323** with varying concentrations of aqueous hydrogen bromide produced complex mixtures. Under optimal conditions, hydrolysis of the methoxymethyl ether protecting group was achieved with a 6 M hydrogen chloride solution at 50 °C to generate 1,4-diol **321** in 75% yield. A subsequent high yielding chemoselective silylation at the primary alcohol, followed by a mild methyl iodide mediated dithiane cleavage,[122] avoiding the use of highly toxic mercuric reagents, afforded (*S*)-β-hydroxyketone **264** with an overall yield of 23.7% over six-steps as a single enantiomer (99.9% *ee*), confirmed from chiral HPLC.



Scheme 2-15: *Enantioselective total synthesis of model geminal dimethyl hyperolactone (S)-**271**.*

With both α-diazolactone **212** and (*S*)-β-hydroxyketone **264** to hand, applying the optimised diverted O-H insertion transformation successfully obtained an inseparable mixture of *cis*,*trans*-**273a** and *cis*,*cis*-**273d** spirolactones (79%, 86:14 *dr*), with chiral HPLC studies indicating that the stereospecific construction of the vicinal quaternary stereocentres proceeded without the loss of enantiomeric excess, derived from the phenyl substituent (***Scheme 2-15***). Utilising the previously developed oxidative cleavage sequence, ketolactones **272a** and **272b** were prepared in excellent yield and were chromatographically separated. The major *trans*-ketolactone enantiomer **272a** was

then subjected to the developed silyl enol ether activated DDQ induced dehydrogenation procedure to furnish (*S*)-hyperolactone **271**, with X-ray crystallography studies confirming that the spirocyclic configuration was in accordance with (-)-hyperolactone C **5** (*vide infra*, ***Appendix B - Figure D***), with an overall yield of 12.3% over ten-steps from the longest linear chain.

2.2 Developed Second-Generation Synthetic Strategy to the Spirocyclic Hyperolactone Framework

Having developed an enantioselective synthetic approach to the spirocyclic hyperolactone motif using a key diverted metallocarbenoid O-H insertion transformation, it was envisaged that an alternative retrosynthesis of model hyperolactone **271** would permit late-stage diversification at the *C*2 position. Applying a synthetic approach similar to that developed by Hodgson *et al* (*vide supra*, ***Scheme 1-12***),[49] spiroketolactone **327**, derived from the diverted carbene O-H insertion between α-diazolactone **212** and primary β-hydroxyketone **329**, may be converted to enone **326**, that could then be subjected to a 1,4-conjugate addition, dehydrogenation sequence to achieve the synthesis of both hyperolactones **271** and **325** (***Figure 2-4***).

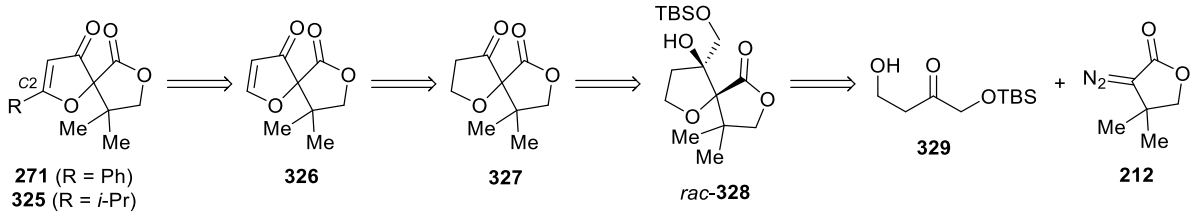
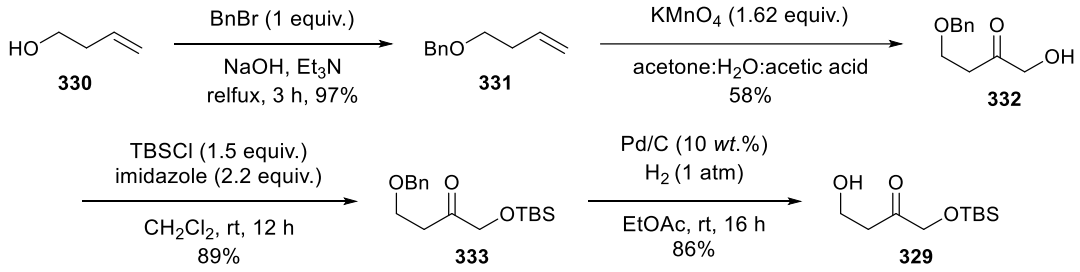


Figure 2-4: *Retrosynthetic analysis of model hyperolactone systems* ***271*** *and* ***325****, employing a diverted metallocarbene O-H insertion strategy that enables late-stage diversification.*

With the proposed retrosynthetic analysis having the ability of introducing both the phenyl and *iso*-propyl substituents through an advanced common intermediate, the synthesis of hyperolactone derivatives that are analogous to both the hyperolactone B and C natural products could be achieved utilising this divergent strategy.

Readily accessed from the benzylation of commercially available 3-buten-1-ol **330**, olefin **331** was converted to novel primary β-hydroxyketone **329** utilising a

subsequently developed three-step manipulation, involving a ketohydroxylation orthogonal protecting group approach (***Scheme 2-16***). Although it is plausible to access β-hydroxyketone **329** through a longer linear sequence, involving the dihydroxylation of terminal olefin **331**, a direct ketohydroxylation, utilising Plietker's developed mild ruthenium tetroxide-catalysed olefin to acyloin oxidation,[123,124] was initially investigated. Attempted ruthenium tetroxide-catalysed ketohydroxylations generated desired acyloin **332** in disappointing yields (<20%), along with a mixture of aldehyde and carboxylic acid scission products, despite Plietker achieving moderate to excellent yields, with mild conditions and short reaction durations, for a range of olefins.



Scheme 2-16: *Preparation of novel β-hydroxyketone* ***329****.*

With the ruthenium-catalysed ketohydroxylation methodology affording poor yields of desired acyloin **332**, an alternative potassium permanganate oxidation, reported and optimised by Bonini *et al*.,[125] was then trialled. Utilising stoichiometric amounts of potassium permanganate in aqueous acetone and catalytic acetic acid pleasingly generated α-ketol **332** in a moderate 58% yield, with only small quantities of the corresponding overoxidised carboxylic acid isolated. Although successful, it should be noted that scales above 30 mmol were found to erode the isolated yield of acyloin **332** and increase the yields of overoxidised by-products, despite trialling a range of reaction durations and stoichiometric equivalents of the oxidant. Having synthesised α-ketol **332**, the primary alcohol was then orthogonally protected with *tert*-butyldimethylsilyl chloride and a successive debenzylation, under an atmospheric pressure of hydrogen, successfully afforded β-hydroxyketone **329** in high yield.

Having efficiently synthesised primary β-hydroxyketone **329** from a high yielding four-step route, synthetic efforts were then directed towards the key diverted O-H insertion between the metallocarbenoid of α-diazolactone **212** and β-hydroxyketone **329**, for the preparation of spirolactone **328** (***Table 2-2***).

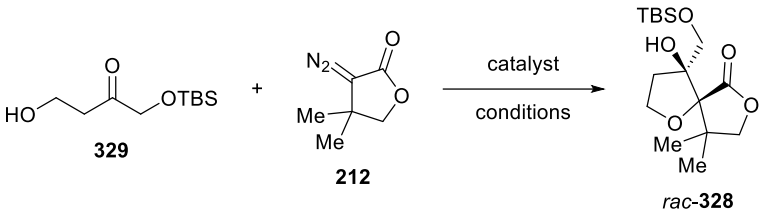
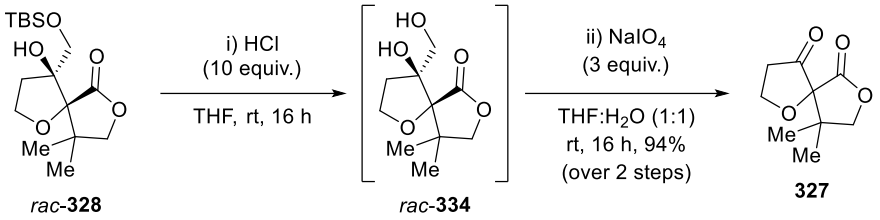


Table 2-2: *Diverted metallocarbene O-H insertion optimisation of α-diazolactone* ***212*** *with β-hydroxyketone* ***329*** *to afford spirolactone* ***328****.*

Entry	Conditions[a]	Diazo / equiv.	Time / h	Yield[b] %
1	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	1	62
2	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	2	1	93
3	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	0.5	1	55
4	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	1.3	1	21
5	CuOAc (5 mol%), CH_2Cl_2, reflux	1.3	1	12

a = using a slow dropwise addition of α-diazolactone **212** to the reaction mixture over a 30 min period; b = isolated yield.

Synthesising spirolactone **328** with an isolated yield of 62% using rhodium(II) octanoate dimer, the rhodium-catalysed diverted O-H insertion reaction was found to proceed with a much greater efficiency when compared to copper-based catalysts (entries 4 and 5). Moderate yields of the previously observed metallocarbenoid [1,2]-methyl rearrangement by-product was observed for all trialled catalytic systems, and that increasing the stoichiometry of α-diazolactone **212** to two equivalents was found to successfully mitigate the impact of this competing process (entries 1-3). Notably, only trace amounts of the linear O-H insertion product were detected and that substitution of the previously utilised secondary β-hydroxyketone **264** for β-hydroxyketone **329** removed the necessity of an initiation period at lower temperatures. This implies that the removal of the steric bulk around the inserting hydroxyl functionality increases the rate of the initial O-H insertion, thus reducing the influence of the competing metallocarbene rearrangement. Spirolactone **328** was then subjected to the established oxidative cleavage conditions, producing spiroketolactone **327**, *via* spirocyclic 1,2-diol intermediate **334** in excellent yield (***Scheme 2-17***).



Scheme 2-17: *Oxidative cleavage preparation of spiroketolactone* ***327****.*

Unfortunately, applying the previously developed silyl enol ether activated DDQ induced dehydrogenation procedure to spiroketolactone **327** led to the formation of only trace amounts of desired enone **326**, which may be rationalised from the absence of an essential γ-benzylic proton. Attempted selenium dioxide induced dehydrogenation conditions were also found to produce unsatisfactory yields of desired product **326** (<25%), leading to alternative investigations into the development of a mild IBX-mediated dehydrogenation approach (***Table 2-3***).

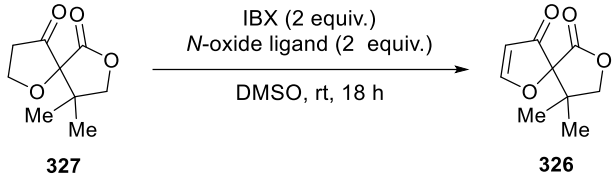


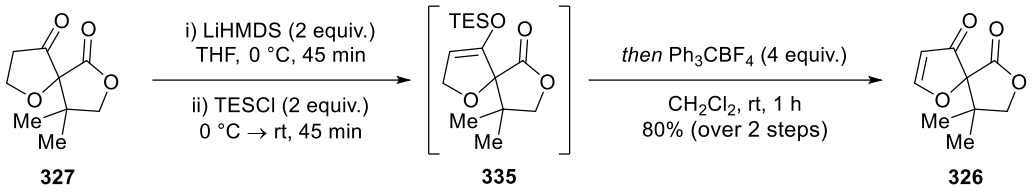
Table 2-3: *Conditions screened in the ambient temperature IBX•N-oxide dehydrogenation of* ***327****.*

Entry	*N*-Oxide Ligand[a]	Concentration / M	Isolated Yield / %	Recovered 327 / %
1	4-Methylmorpholine *N*-oxide (NMO)	2	16	59
2	4-Methylpyridine *N*-oxide	0.5	4	95
3	4-Methylmorpholine *N*-oxide (NMO)	0.5	20	79
4	4-Methoxypyridine *N*-oxide hydrate (MPO)	2	38	42
5	4-Methoxypyridine *N*-oxide hydrate (MPO)	0.5	16	74

With the Nicolaou Research Group performing extensive mechanistic studies of the IBX-mediated dehydrogenation transformation and uncovering the improved reactivity of IBX•*N*-oxide complexes,[126] a number of selected *N*-oxide ligand additives were trialled using their optimised methodology. Despite Nicolaou and colleagues generating a variety of cyclic enones, NMO, MPO and 4-methylpyridine *N*-oxide were all found to produce inadequate isolated yields of desired spirolactone **326** at concentrations of 0.5 M (<20%), albeit with a good starting material recovery.

Increasing the molarity to 2 M did increase the efficiency of the IBX•MPO induced dehydrogenation to 38% but was found to have a negligible effect with the IBX•NMO system (entry 4). With the solubility of all of the resultant *in situ* generated IBX•*N*-oxide complexes dramatically decreasing at higher concentrations, no further reaction conditions were trialled as limited success was observed across the series of *N*-oxide ligands assayed at various molarities.

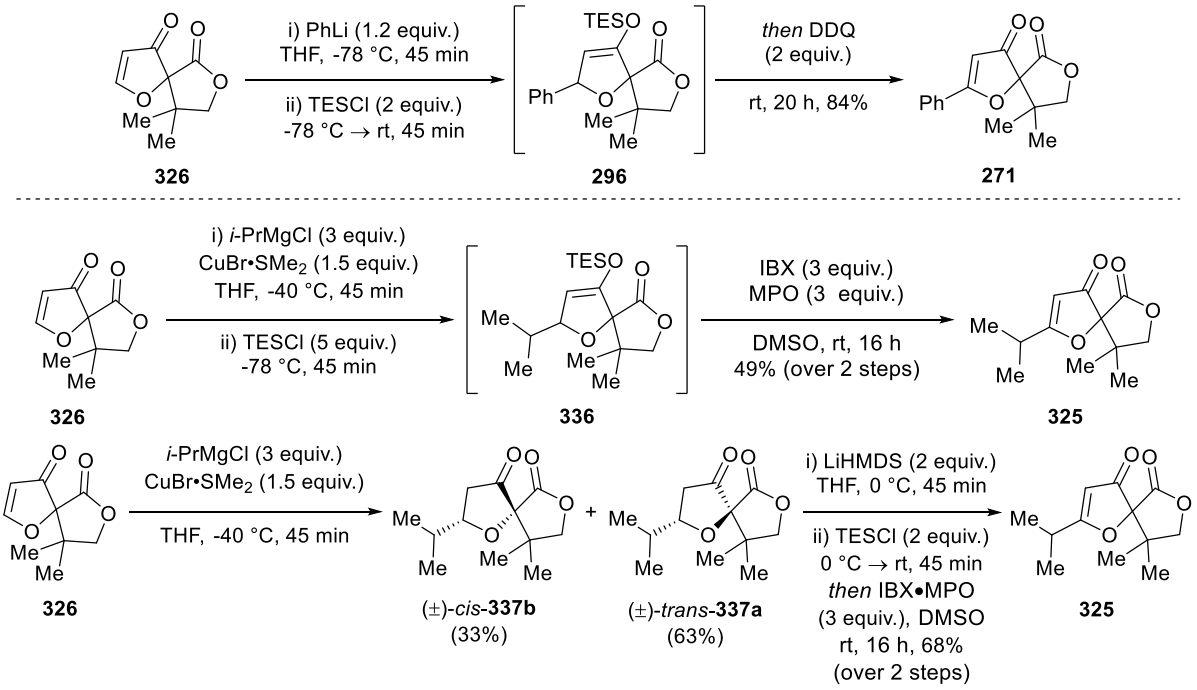
Pleasingly, a more successful dehydrogenation procedure was utilised to efficiently install the enone functionality (***Scheme 2-18***), involving the generation of triethylsilyl enol ether **335** using lithium bis(trimethylsilyl)amide and triethylchlorosilane, followed by a tritylium tetrafluoroborate mediated hydride abstraction,[127] obtaining spirocyclic enone **326** in 80% yield.



Scheme 2-18: *Preparation of spirocyclic enone **326** utilising a tritylium tetrafluoroborate mediated dehydrogenation procedure.*

Having developed an effective synthetic approach to norphenyl hyperolactone **326**, utilising Hodgson and co-workers' reported Michael addition dehydrogenation methodology efficiently introduced the phenyl substituent to the hyperolactone molecular framework (*vide supra*, ***Scheme 1-12***), synthesising *gem*-dimethyl hyperolactone **271** in 84% yield (***Scheme 2-19***), with an overall yield of 25.3% over ten-steps from the longest linear chain. Typically undergoing 1,2-additions to cyclic enone systems, Hodgson and colleagues found that the direct reaction of phenyllithium with a similar spirolactone chemoselectively underwent a 1,4-addition, which was rationalised by a sterically unfavourable trajectory to both of the carbonyl functionalities. Following the conjugate addition, triethylsilyl chloride trapping of the resulting enolate afforded intermediate silyl enol ether **296**, which was then treated with DDQ to assemble the hyperolactone C motif. Attempting to install an *iso*-propyl group to synthesise *gem*-dimethyl hyperolactone B variant **325**, treating enone **326** with isopropyllithium solution resulted in the formation of complex mixtures derived from a 1,2-addition at both the lactone and enone carbonyls. Overcoming the observed

chemoselectivity, reacting spirolactone **326** with the corresponding organocuprate, generated from isopropylmagnesium chloride solution and copper(I) bromide dimethyl sulphide complex, successfully led to the formation of triethylsilyl enol ether **336**, upon the addition of a large excess of triethylchlorosilane. Subjecting the resultant crude material to the previously utilised DDQ-mediated dehydrogenation methodology produced only trace amounts of hyperolactone **325**. Both the previously utilised tritylium tetrafluoroborate induced dehydrogenation procedure, as well as a range of trailed Saegusa-Ito conditions, failed to obtain yields greater than 15%, which may be due to the steric bulk associated with the adjacent *iso*-propyl substituent.

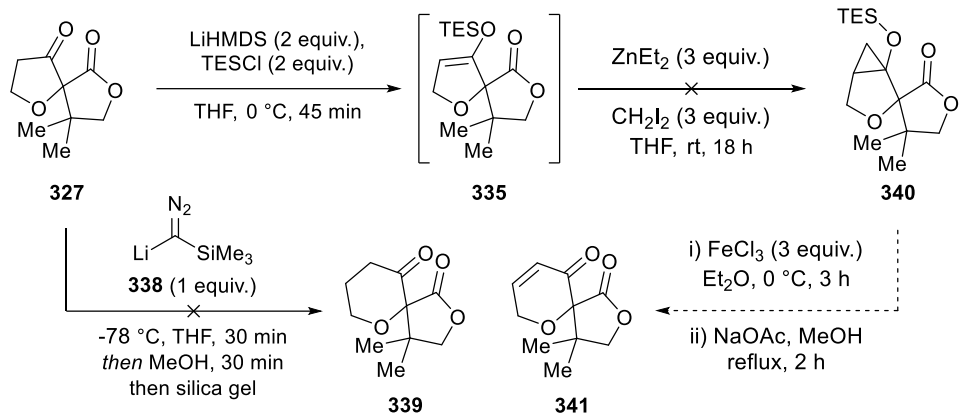


Scheme 2-19: *Late-stage conjugate addition diversification to the hyperolactone scaffold.*

Pleasingly, a mild IBX•MPO-mediated dehydrogenation of the crude triethylsilyl enol ether **336** furnished desired hyperolactone B analogue **325** in a moderate yield of 49% over two-steps. In addition to the isolation of hyperolactone **325**, *iso*-propyl bearing spiroketolactones **337a-b** were also isolated in 27%, derived from the hydrolysis of triethylsilyl enol ether **336**. Confirmed through nOe correlations between the *C*2 and *iso*-propyl protons with the geminal methyl groups of the lactone ring, the preferential diastereoselective formation of *trans*-**337a** (≈ 2:1 *dr*) indicates a conjugate addition trajectory on the same ring face as the all-carbon quaternary stereocentre. Isolating chromatographically separable spiroketolactones **337a** and **337b** from the organocuprate Michael addition in high yield (overall 96%), spirolactone **337a** was

converted into hyperolactone B analogue **325** from the IBX•MPO-mediated dehydrogenation of triethylsilyl enol ether **336** in an improved 68% yield (65% over three-steps). This implies that residue impurities remaining from the initial organocuprate conjugate addition may be lowering the efficiency of the final IBX dehydrogenation.

Having achieved the synthesis of both novel *gem*-dimethyl hyperolactone **325**, with an overall yield of 19.7% over twelve-steps from the longest linear chain, and hyperolactone analogue **271** from a common intermediate, attempts to enhance the utility of this synthetic route by trialling several ring expansion procedures were then investigated (***Scheme 2-20***), with the aim of converting the tetrahydrofuran domain of **327** to the corresponding pyranone. Unfortunately, the direct conversion of spiroketolactone **327** to spiro-tetrahydropyranone **339**, *via* a methylene homologation proceeding through a Tiffeneau-Demjanov rearrangement,[128] was unsuccessful, leading to complex mixtures. This reaction was suspected to undergo an undesired lactone cleavage, as well as an epoxide formation and degradation process, therefore, this approach was abandoned due to the lack of observed chemoselectivity between the carbonyl functionalities.

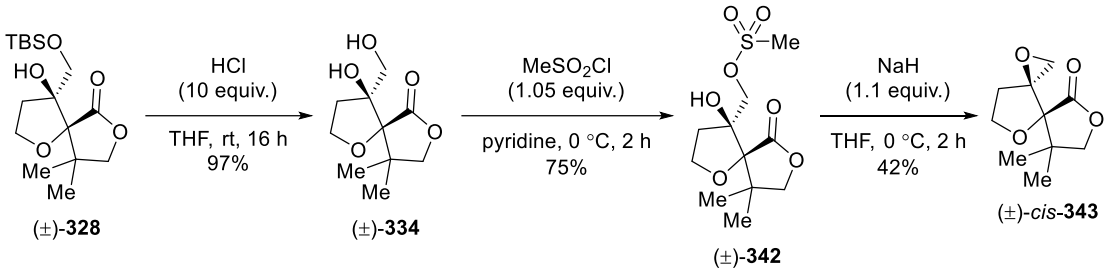


Scheme 2-20: *Attempted ring expansions of spiroketolactone **327**.*

Alternatively, it was envisioned that spiro-enone **341** could be accessed from the ring expansion of cyclopropane intermediate **340**, either from a two-step ferric chloride induced ring cleavage-dehydrochlorination sequence,[129] or through a one-pot ambiphilic base-mediated process.[130] However, the synthesis of intermediate **340** from an attempted Simmons-Smith cyclopropanation of triethylsilyl enol ether **335** was

ineffective, suspected to be thwarted by the steric bulk surrounding the congested silylated enol. No other protecting groups or cyclopropanation conditions were trialled.

Investigating the construction of novel pyranone-based hyperolactone derivates through an alternative type-one semipinacol rearrangement, mesylate **342** was efficiently synthesised by treating spirolactone **328** with acidic aqueous media to hydrolyse the *tert*-butyldimethylsilyl protecting group, which was followed by a chemoselective mesylation of the resultant primary alcohol of 1,2-diol **334** (***Scheme 2-21***).



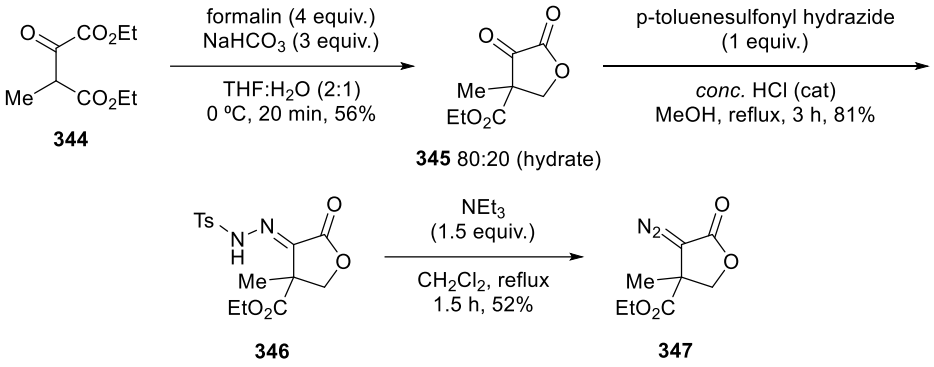
Scheme 2-21: *Attempted semipinacol ring expansion of mesylate **342**.*

Despite being a widely applied transformation for the synthesis of a variety of complex natural products,[131] an attempted base-mediated semipinacol rearrangement underwent an unprecedented epoxidation instead to form tricyclic spiroepoxide **343**, in an unoptimised 42% yield. With the structure and stereoconfiguration solved through X-ray crystallographic studies (*vide infra*, ***Appendix B - Figure N***), the generation of spirocyclic epoxide **343** implies that the close proximity of the hydroxy and adjacent mesylate prevents the desired skeletal rearrangement from occurring. Alternative leaving groups and semipinacol rearrangement conditions were not investigated further.

2.3 Diverted Metallocarbene O-H Insertion Stereochemical Evaluations and the Synthesis of Privileged Spirolactones

Having developed two synthetic approaches to the hyperolactone molecular framework that successfully permit late-stage diversification and the stereospecific construction of the spirocyclic quaternary stereocentre, attention was turned towards

the synthesis of α-diazolactone **347** to assess if a stereospecific diverted carbene O-H insertion transformation could lead to the synthesis of a hyperolactone analogue bearing an additional stereocentre on the lactone ring (***Scheme 2-22***). Accessing α-diazolactone **347** from commercially available diethyl 2-methyl-3-oxosuccinate **344**, a tandem aldol-lactonisation, achieved from the addition of sodium hydrogen carbonate and aqueous formaldehyde, afforded ketolactone **345**, and its corresponding hydrate (80:20 ratio), in moderate yield. Ketolactone **345** was then readily converted to α-diazolactone **347**, *via* tosylhydrazone **346**, from a Bamford-Stevens diazotisation sequence.



Scheme 2-22: *Preparation of α-diazolactone **347** utilising a Bamford-Stevens diazotisation.*

Having been previously synthesised by the Moody Research Group,[88] the diverted O-H insertion between the metallocarbenoid of α-diazolactone **347** and (±)-β-hydroxyketone **264** has been previously trialled with a number of selected catalysts, to generate inseparable mixtures of spirolactones **348a-d** (***Table 2-4***). Continuing the optimisation of this transformation, rhodium(II) octanoate dimer and copper(I) triflate toluene complex catalysts were evaluated for their diastereoselectivity and efficiency for the synthesis of single enantiomer spirolactone diastereoisomers **348a-d** (entries 6 and 7). Utilising various 2D-NMR experiments, the isomeric distribution was determined from the nOe correlations of the benzylic and methyl protons with the methylene protons adjacent to the *tert*-butyldimethylsilyl protected alcohol, which was later unambiguously confirmed from X-ray crystallographic studies of spirolactones obtained from subsequent transformations. Demonstrating a similar diastereoselectivity to copper(I) acetate (entry 1), copper(I) triflate toluene complex produced spirolactones **348a-d** with a 61% isolated yield, but with a poor facial selectivity for the formation of spirolactones **348a-b** over spirolactones **348c-d**

(**348a-b**:**348c-d** = 67:33, entry 6). In accordance with other rhodium-based catalysts (entries 2-5), rhodium(II) octanoate dimer displayed a moderate facial diastereoselectivity (**348a-b**:**348c-d** = 84:16, entry 7), preferentially constructing the vicinal stereocentres in the *cis*,*trans*-configuration, with respect to the phenyl substituent. This observed stereoselectivity can be rationalised from unfavourable 1,3-diaxial interactions between the phenyl and ketone functionalities, derived from (*S*)-β-hydroxyketone **264**, upon the formation of a transient oxonium ylide intermediate (*vide supra*, ***Figure 2-2***).

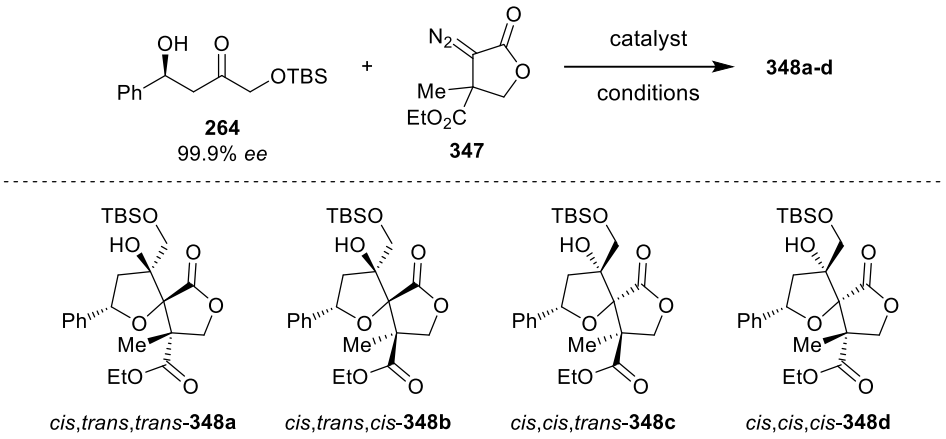


Table 2-4: *Diverted metallocarbene O-H insertion optimisation of α-diazolactone **347** with (S)-β-hydroxyketone **264** to afford spirolactones **348a-d**.*

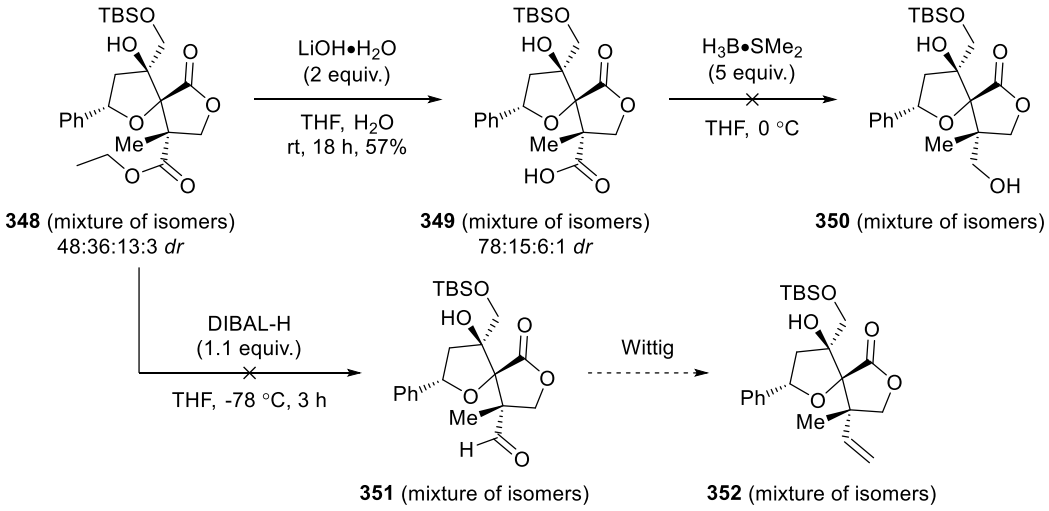
Entry	Conditions[b]	Yield[c] %	Ratio 348a : 348b : 348c : 348d
1[a]	CuOAc (5 mol%), CH_2Cl_2, reflux	67	33:33:14:20
2[a]	$Rh_2(OAc)_4$ (1 mol%), CH_2Cl_2, reflux	75	60:27:9:4
3[a]	$Rh_2(OPiv)_4$ (1 mol%), CH_2Cl_2, reflux	58	48:39:12:1
4[a]	$Rh_2(esp)_2$ (1 mol%), CH_2Cl_2, reflux	30	48:34:14:4
5[a]	Rh_2(*S*-DOSP)$_4$ (1 mol%), CH_2Cl_2, reflux	48	45:39:12:4
6	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	68	48:36:13:3
7	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	61	35:32:17:16

a = performed by Simon N. Nicolle,[88] using (±)-β-hydroxyketone **264** ; b = using a slow dropwise addition of α-diazolactone **347** to the reaction mixture over a 30 min period; c = isolated yield; esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionate; Rh_2(*S*-DOSP)$_4$ = dirhodium tetrakis((*S*)-*N*-(dodecylbenzenesulfonyl)prolinate).

Although preferentially forming spirolactone **348a**, possessing the same spirocyclic and lactone derived stereoconfiguration as (-)-hyperolactone C **5**, the experimentally observed diastereoselectivity for the rhodium(II) octanoate dimer

catalysed reaction also indicates a poor facial diastereoselectivity from the substituents of the lactone domain (**348a** and **348d**:**348b** and **348c** = 61:39, entry 7). With respect to the stereoconfiguration of the lactone substituents, the preferential generation of spirolactones **348a** and **348d** over **348b** and **348c** can be rationalised from the steric clash between the phenyl and ethyl ester functionalities, which are located on opposite ring faces for favoured spirolactones **348a** and **348d**. Pleasingly, only trace amounts of the undesired olefin, derived from a competing [1,2]-migration of the methyl group associated with the *in situ* generated dicarbonyl metallocarbenoid species, were detected. Although achieving moderate to good yields for the diverted O-H insertion transformation, the greatest isolated yield and diastereoselectivity was obtained using dirhodium(II) acetate dimer as the catalyst (entry 2). Heavily dependent on the choice of catalyst, the varying degree of diastereoselectivity indicates that this reaction may occur from a metal-bound mechanism.

Ambitiously attempting to chemoselectively reduce the ethyl ester functionality to an aldehyde and perform a successive Wittig reaction to install the vinyl substituent, present throughout the hyperolactone series, several attempts to reduce chromatographically inseparable spirolactones **348a-d** were carried out (***Scheme 2-23***).

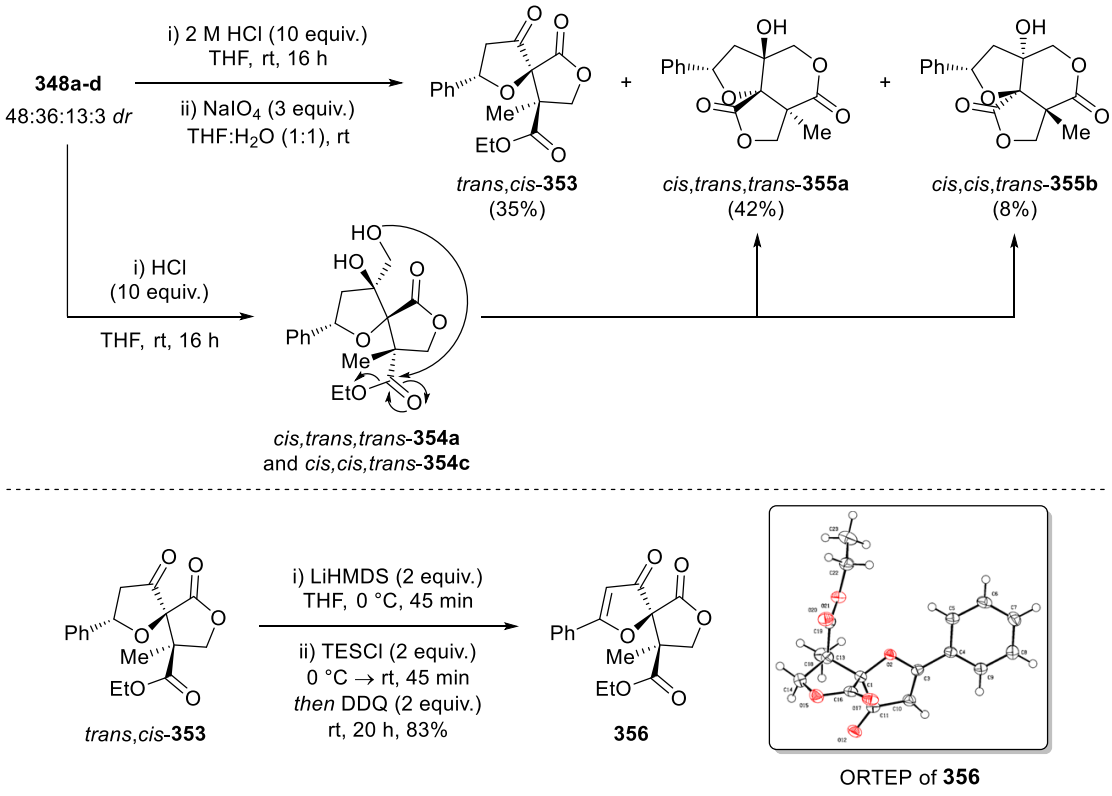


Scheme 2-23: *Attempted chemoselective reductions of spirolactones **348** and **349**.*

Unfortunately, numerous chemoselective DIBAL-H reduction attempts were unsuccessful. Failing to afford desired aldehyde **351**, a good recovery of spirolactones **348a-d** at both -78 °C and -40 °C in THF suggest that the sterically congested reduction of spirolactones **348a-d** is retarded by the use of a sterically bulky reducing

agent. Substituting the solvent to CH_2Cl_2 at -40 °C led to the partial formation of an inseparable complex mixture, suspected to contain the various stereoisomers of primary alcohol **350** and a related lactol by-product. Alternative lithium borohydride mediated reductions, as well as DIBAL-H reductions performed at 0 °C, led to the formation of complex mixtures from the reduction of both carbonyl functionalities.

Alternatively, it was envisioned that aldehydes **351** could be accessed from primary alcohols **350**, *via* a Dess-Martin oxidation. Hydrolysis of the ethyl ester functionality using lithium hydroxide monohydrate obtained carboxylic acids **349** in an unoptimised yield of 57%, although a successive chemoselective reduction of the carboxylic acid functionality with boron dimethyl sulphide complex and borane tetrahydrofuran complex led to only trace amounts of the desired alcohol product. Unable to access aldehydes **351** and alcohols **350** from a chemoselective reduction, and with chromatography resolution remaining an issue, this approach was not further investigated.



Scheme 2-24: *Formation of hyperolactone analogue* ***356*** *and the formation of tricyclic spirolactones* ***355a-b*** *through an intramolecular transesterification.*

Inseparable spirolactones **348a-d** were alternatively subjected to the previously utilised two-step deprotection-oxidative cleavage sequence to install the ketone functionality (***Scheme 2-24***). However, this transformation was found to unexpectedly generate tricyclic spirolactones **355a-b**, as well as expected spiroketolactone **353**. Derived from an intramolecular transesterification of 1,2-diol intermediates **354a** and **354c**, obtained from spirolactones **348a** and **348c**, this unforeseen acid mediated lactonisation process is rationalised from the close proximities of the ethyl ester and primary alcohol functionalities in the *cis*,*trans*,*trans*- and *cis*,*cis*,*trans*-configurations. Performing a basic tetra-*n*-butylammonium fluoride desilylation was also found to obtain tricyclic spirolactones **355a-b** and spiroketolactone **353** in an almost identical yield, with their structures solved from X-ray crystallographic studies (*vide infra*, ***Appendix B - Figure G-I***). Isolated *trans*,*cis*-ketolactone **353** was then converted into hyperolactone **356** in excellent yield, applying the previously developed silyl enol ether activated DDQ induced dehydrogenation methodology to furnish the enone moiety. Possessing the same spirocyclic configuration as (-)-hyperolactone C **5**, the adjacent quaternary stereocentre of the lactone domain displays the inverted *epi*-stereochemistry to the natural product, which was subsequently verified from X-ray crystallographic studies (*vide infra*, ***Appendix B - Figure J***).

Chapter 3: Enantioselective Total Synthesis of (-)-Hyperolactone C and Related Spirolactone Analogues

3.1 Enantioselective Total Synthesis of (-)-Hyperolactone C and Analogous Derivatives

Having successfully developed multiple synthetic strategies to the spirocyclic hyperolactone architecture, it was envisaged that the enantioselective total synthesis of (-)-hyperolactone C **5** could be directly achieved from the diverted O-H insertion reaction between (*S*)-β-hydroxyketone **264** and the metallocarbene of (*R*)-α-diazolactone **359**, which possesses a substituent that could be subsequently manipulated to install the vinyl functionality (***Figure 3-1***). Applying synthetic conditions conceived from the first-generation synthesis of model hyperolactone system **271** (*vide supra*, ***Scheme 2-15***), it was postulated that the configuration of the vicinal stereocentres of advanced spirolactone intermediate *cis*,*trans*,*trans*-**358** could be achieved from enantiopure precursors.

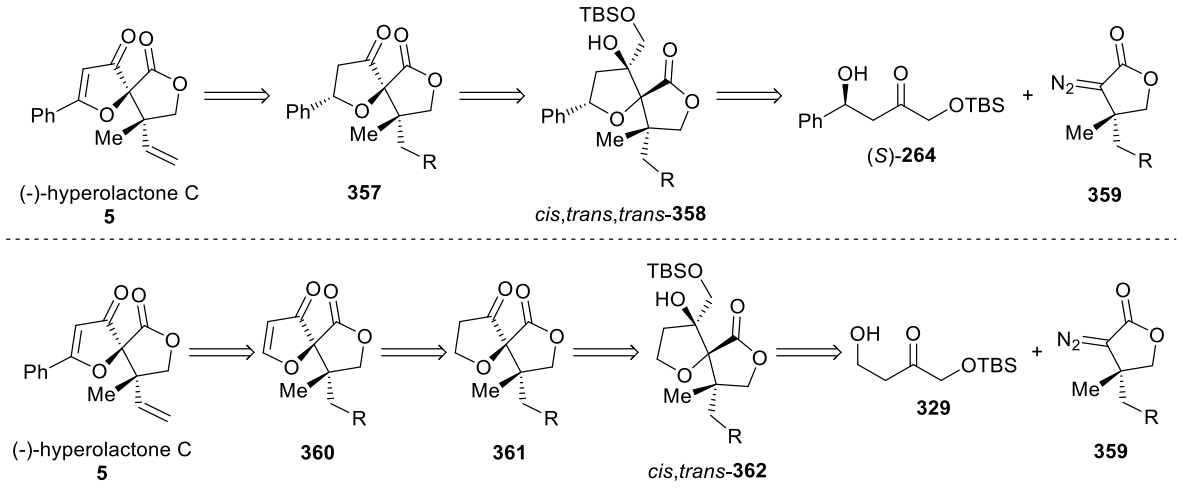
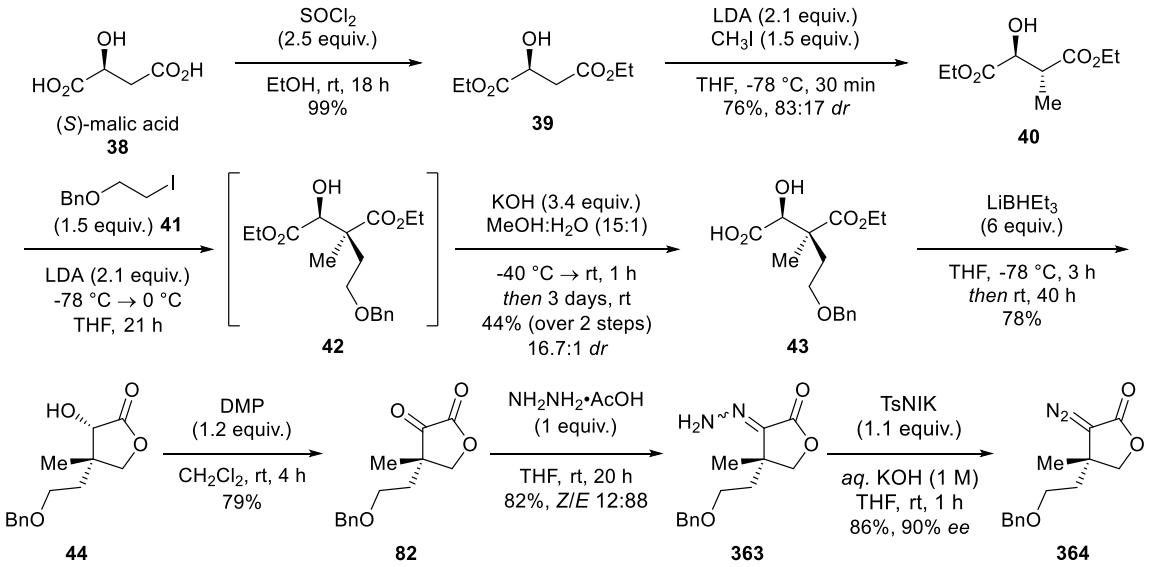


Figure 3-1: *Retrosynthetic analysis of (-)-hyperolactone C utilising first- and second-generation diverted metallocarbene O-H insertion approaches.*

Alternatively, applying a synthetic sequence inspired from the previously developed second-generation synthesis of model hyperolactone system **271** may achieve the enantioselective total synthesis of (-)-hyperolactone C **5** from *cis*,*trans*-spirolactone **362**. Derived from the diverted O-H insertion reaction between

(*R*)-α-diazolactone **359** and β-hydroxyketone **329**, the resulting stereoselectivity of the key transformation is governed by the diastereoselectivity exerted by the lactone substituents. With the absence of the directing phenyl substituent on the tetrahydrofuran domain, either the desired *cis*,*trans*- or undesired *cis*,*cis*-configuration would form. Despite previous investigations performed in the Moody Research Group revealing the incompatibility of metallocarbenoid species with vinyl substituents in the adjacent α-position (*vide supra*, ***Scheme 1-29***), substituting the vinyl group for a functionalised alkyl-based substituent, that could be later converted to the terminal olefin, may overcome the detrimental [1,2]-vinyl migration process.

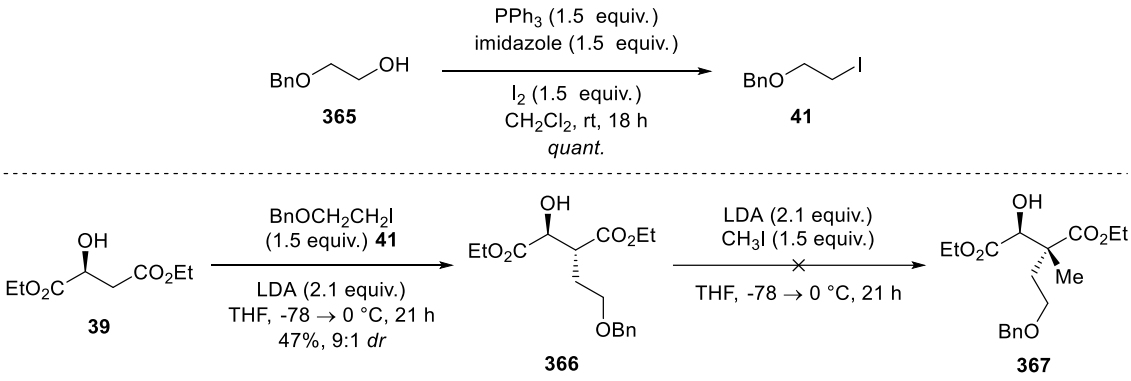
Selecting (*R*)-α-diazolactone **364** as a suitable diverted O-H insertion precursor target, the masked vinyl group can provide access to the desired vinyl functionality through a two-step Grieco elimination, which has been previously utilised by both the Kinoshita and Nicolaou Research Groups to achieve the enantioselective total synthesis of (-)-hyperolactone C **5**.[15,18] Adapting the initial stages of the reported total syntheses, ketolactone **82**, accessible from a chiral pool source, was identified as a suitable precursor for the synthesis of (*R*)-α-diazolactone **364** utilising the previously deployed highly successful iodamine-T diazotisation methodology.



Scheme 3-1: *Chiral pool approach to enantioenriched α-diazolactone **364**.*

Generating diethyl (*S*)-2-hydroxysuccinate **39** from (*S*)-malic acid **38**, utilising a near quantitative chemoselective thionyl chloride mediated esterification (***Scheme 3-8***), a kinetically controlled Fráter-Seebach alkylation of the dianion of **39** with iodomethane

furnished hydroxysuccinate ester **40** as a mixture of diastereoisomers,[25,26] in favour of the *erythro* stereoisomer (9:1 *dr*). Employing the use of a non-nucleophilic base, the experimentally observed stereochemistry at the newly formed quaternary centre is rationalised from the formation of a six-membered metal cation chelating transition state, with electrophilic addition occurring from a sterically favoured trajectory to preferentially form the conformationally favoured *anti*-product. Applying the same approach, a successive diastereoselective alkylation of hydroxysuccinate ester **40**, with ((2-iodoethoxy)methyl)benzene **41**, was then carried out to install the masked vinyl functionality. Unfortunately, the inefficient conversion to hydroxysuccinate ester **42** made isolation challenging, with various chromatographic techniques only partially separating unreacted starting material **40** from the desired product. Pleasingly, a subsequent chemoselective base-catalysed hydrolysis of the obtained crude successfully removed impurities associated with hydroxysuccinate ester **40**, affording hydroxysuccinate acid **43** in moderate yield (44%, 16.7:1 *dr*, over two-steps). Having diastereoselectively synthesised hydroxysuccinate acid **43**, it was postulated at this stage that the reversal of the alkylation sequence could allow access to the corresponding *epi*-α-diazolactone.



Scheme 3-2: *Investigated stereoselective LDA alkylation reactions, highlighting the synthesis of alkylating agent* ***41****.*

Performing an alternative alkylation of hydroxysuccinate ester **39** with ((2-iodoethoxy)methyl)benzene **41** (***Scheme 3-2***), accessed from primary alcohol **365** utilising a quantitative Appel transformation,[132] hydroxysuccinate ester **366** was generated in moderate yields, with an almost identical diastereoselectivity to the Fráter-Seebach alkylation with iodomethane (9:1 *dr*). Only partially separable from residual starting materials, a successive alkylation of hydroxysuccinate ester **366** with

iodomethane was found to produce inseparable mixtures of hydroxysuccinate esters **366** and **367**, while demonstrating a poor conversion to desired product **367**. These observations are in accordance with the results obtained by Auclair and co-workers for similar hydroxysuccinate esters with large substituents adjacent to the hydroxyl functionality,[133] suggesting that this substrate class is heavily influenced by steric factors that can result in lower than expected yields and diastereoselectivities, thus resulting in problematic purifications. Having observed similar detrimental issues, no further reaction conditions were trialled, and this approach to *epi*-α-diazolactone **364** was not investigated further.

In spite of this, focus was then returned towards the synthesis of (*R*)-α-diazolactone **364**, where hydroxysuccinate acid **43** was treated with lithium triethylborohydride (Super-Hydride®) solution to efficiently afford hydroxylactone **44** with an isolated yield of 78% (***Scheme 3-5***). Although efficiently producing the desired hydroxylactone motif, the reductive spontaneous *in situ* cyclisation transformation required a modified acidic work-up procedure to ensure reproducibility. Hydroxylactone **44** was then subjected to the previously developed modified Dess-Martin periodinane oxidation, hydrazine acetate induced hydrazone formation and iodamine-T diazotisation reaction sequence to efficiently afford enantioenriched (*R*)-α-diazolactone **364** in excellent yield with a high enantiopurity, calculated from chiral HPLC (90% *ee*).

Having developed and optimised a chiral pool approach to (*R*)-α-diazolactone **364**, the diverted O-H insertion between commercially available primary β-hydroxyketone **196** and the metallocarbene of (*R*)-α-diazolactone **364** was then investigated (***Table 3-1***). Evaluating the stereoselectivity and feasibility of this key transformation, an inseparable mixture of spirolactones **368a-b** were isolated in moderate yields (38-39%, 1:1 *dr*, 90% *ee*) when catalysed by rhodium(II) octanoate dimer and copper(I) triflate toluene complex (entries 1 and 2). Performing numerous NMR and chiral HPLC studies, this transformation was found to proceed with no facial diastereocontrol, revealing that the alkyl substituent on the lactone domain has no influence over the diastereoselectivity.

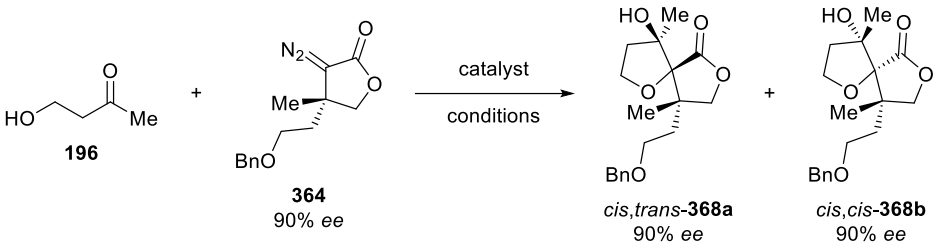
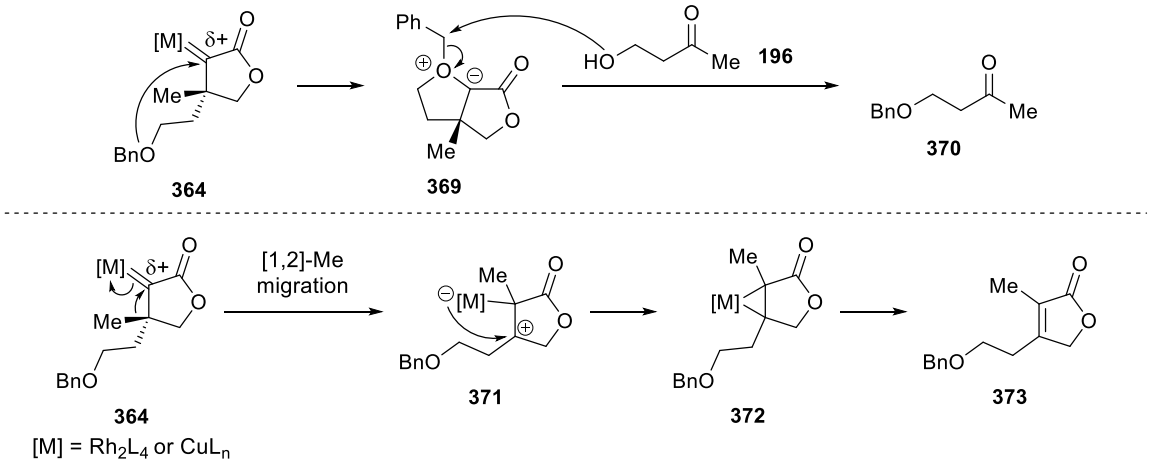


Table 3-1: *Diverted O-H insertion reaction of β-hydroxyketone* ***196*** *with (R)-α-diazolactone* ***364****.*

Entry	Conditions[a]	364 / equiv.	196 / equiv.	Time / h	Yield[b] %
1	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	1	1	38
2	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	1.3	1	1	39
3	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	2	1	1	70
4	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	2	1	1	40
5	CuOAc (5 mol%), CH_2Cl_2, 0 ºC→rt→reflux	2	1	2→2→16	trace
6	Fe(TPP)Cl (1 mol%), CH_2Cl_2, reflux	2	1	1	trace
7	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1	2	1	28

a = using a slow dropwise addition of α-diazoester **364** to the reaction mixture over a 30 min period; b = isolated yield (1:1 *dr*).

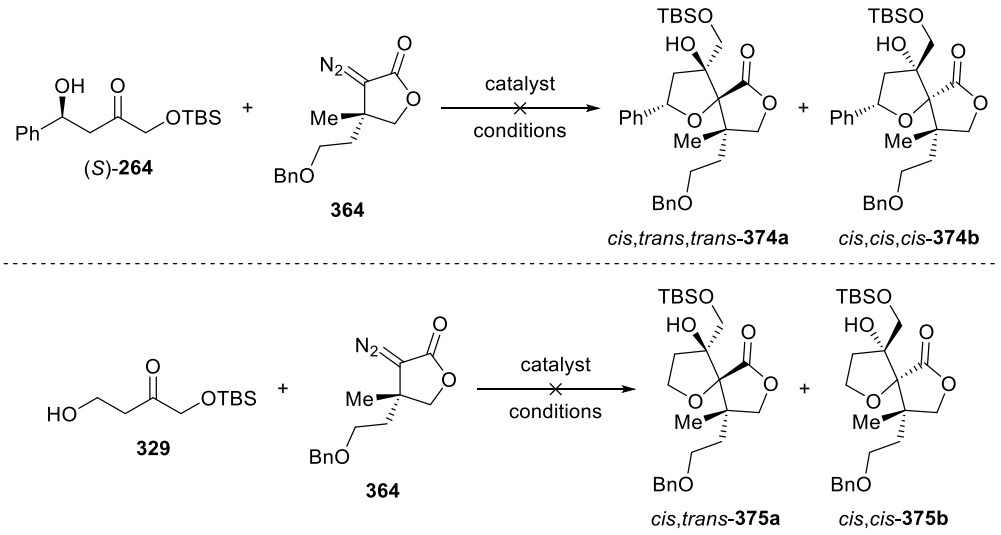
Unfortunately, the metallocarbenoid species was observed to undergo a competing [1,2]-methyl rearrangement, generating olefin **373** for all trialled catalytic systems (***Scheme 3-3***). Confirming the methyl migration regioselectivity through various 2D-NMR experiments, it was found that increasing the equivalents of (*R*)-α-diazolactone **364** mitigated the impact of this competing reaction for rhodium-based systems (entries 1, 3 and 7), whereas for copper-based systems this had no effect (entries 2 and 4).



Scheme 3-3: *Postulated formation of by-products* ***370*** *and* ***373****.*

The use of copper(I) acetate and iron(tetraporphyrinato) chloride failed to furnish desired spirolactones **368a-b**, as degradation of the metallocarbenoid species led to the formation of complex mixtures (entries 5 and 6). Only trace amounts of the corresponding undesired O-H inserted product were detected for all trialled catalytic systems, however, the introduction of a minor impurity (<15%), identified as ketone **370**, was solely isolated for copper-catalysed reactions (entries 2 and 4). It was therefore postulated that the formation of ketone **370** may be derived from an intramolecular benzyl oxygen insertion, generating bicyclic oxonium ylide species **369** that may then undergo a nucleophilic benzyl group transfer with β-hydroxyketone **196**.

Having successfully demonstrated the synthesis of spirolactones **368a-b**, synthetic effects were then directed towards the stereospecific assembly of (-)-hyperolactone C **5** precursor *cis*,*trans*,*trans*-**374a**, from the diverted carbene O-H insertion between (*S*)-β-hydroxyketone **264** and (*R*)-α-diazolactone **359** (***Scheme 3-4***). With the insertion of the secondary alcohol (*S*)-**264** directing the spirocyclic configuration towards the desired *cis*,*trans*,*trans*-configuration, and the lactone alkyl substituents previously displaying no facial diastereoselectivity, there was a strong precedence for the preferential generation of *cis*,*trans*,*trans*-spirolactone **374a** over *cis*,*cis*,*cis*-spirolactone **374b**.

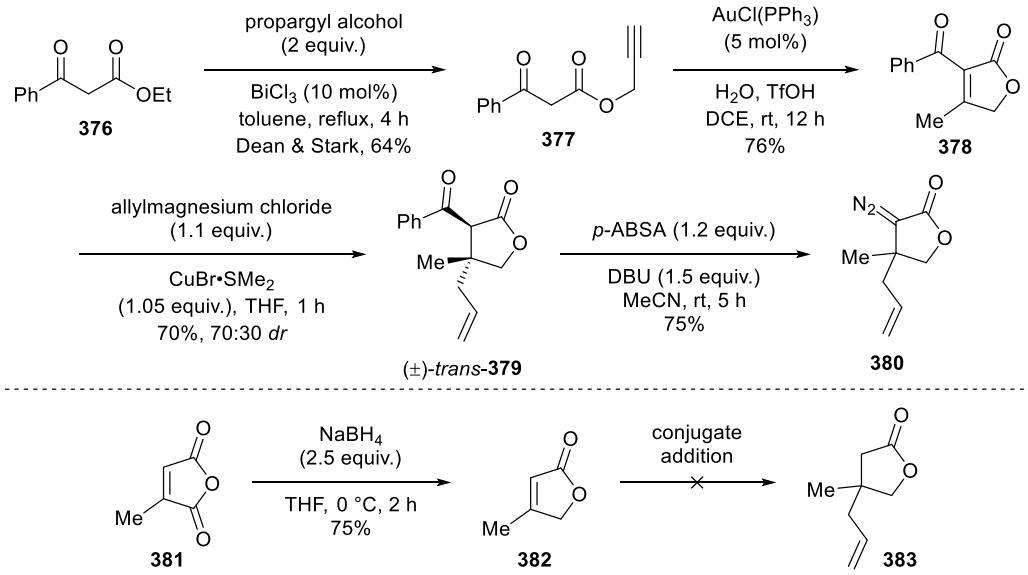


Scheme 3-4: *Attempted diverted metallocarbene O-H insertions with (R)-α-diazolactone **364**.*

Unfortunately, applying a variety of reaction conditions for a range of rhodium and copper-based catalysts failed to afford the desired diverted O-H inserted spirolactone products **374a-b**. With limited evidence of the initial O-H insertion process

occurring, the *in situ* generated metallocarbenoid species was found to undergo a rapid [1,2]-methyl migration to produce olefin **373**, completely out pacing the desired transformation. Previously deployed techniques, such as introducing an initiation period and increasing the stoichiometry of (*R*)-α-diazolactone **359**, failed to promote the spirocyclisation transformation. Disappointingly, alternative diverted carbene O-H insertions involving the use of primary β-hydroxyketone **329**, aiming to synthesise spirolactones **375a-b**, were also found to be unsuccessful, despite being previously found to efficiently form similar spirolactones. Unable to outcompete the detrimental [1,2]-methyl rearrangement, the synthesis of an alternative α-diazolactone, also bearing an alkyl-based masked vinyl functionality, was then investigated.

Postulating that the key transformation may access a functionalised spirolactone precursor to the hyperolactone motif through the application of an alternative masked vinyl group on the α-diazolactone reactant, that possesses a reduced steric bulk without the presence of a potentially inserting heteroatom, α-diazolactone **380** was selected as a suitable alternative. It was envisioned that the desired vinyl functional group could be accessed from an alternative allyl substituent, through an oxidative cleavage, chemoselective reduction and Grieco elimination sequence. Enabling the efficacy of the key transformation to be determined, a direct synthesis of racemic α-diazolactone **380** from commercially available ethyl benzoylacetate **376**, utilising a convenient four-step synthetic approach, was subsequently developed (***Scheme 3-5***).



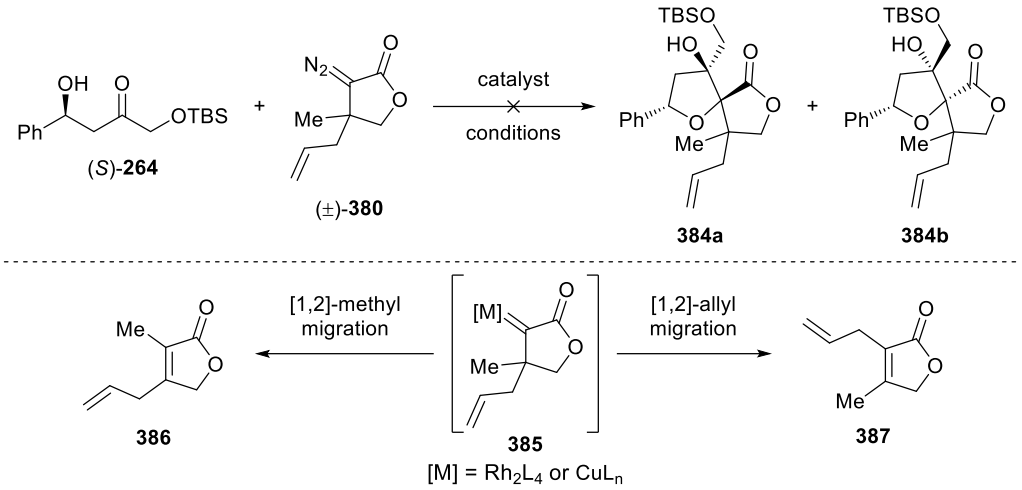
Scheme 3-5: *Preparation of α-diazolactone **380** from an organocuprate conjugate addition strategy.*

Although Depres and colleagues have reported the synthesis of β-ketoester **377** in a 97% yield from a direct transesterification of ethyl benzoylacetate **376** with propargyl alcohol,[134] involving equilibrium displacement without catalysis, lengthy reaction durations under reflux were deemed unfavourable. Alternatively, ethyl benzoylacetate **376** underwent a bismuth(III) chloride-catalysed transesterification to afford β-ketoester **377** in a 64% yield,[135] reducing the reflux duration to four-hours. β-Ketoester **377** was then treated with chloro(triphenylphosphine)gold(I) under acidic conditions to initiate an intramolecular annulation, synthesising lactone **378** in good yield.[136] A successive organocuprate conjugate addition then efficiently installed the allyl functionality, producing β-ketoester **379** as a diastereomeric mixture, with only insignificant amounts of undesired 1,2-addition by-products isolated (<10%). Rationalised from nOe correlations between the dicarbonyl α-proton and the alkyl substituents, the sterically favoured (±)-*trans*-β-ketoester **379** was preferentially formed (70:30 *dr*). Following this, a *p*-ABSA mediated debenzoylative diazo transfer then furnished desired α-diazolactone **380** in good yield, over the developed four-steps.[137]

Attempting to remove the necessity of an initial transesterification by performing a diazo transfer with lactone **383**, citraconic anhydride **381** was regioselectively reduced to lactone **382**, using a procedure described by Argade and co-workers.[138] However, attempts to introduce the allyl functionality *via* an organocuprate conjugate addition were unsuccessful, mirroring results obtained by Lin and colleagues.[139] Unfortunately, various rhodium-catalysed conjugate additions, involving the use of allylboronic acid or potassium allyltrifluoroborate,[140,141] were also found to be ineffective. Interestingly, the rhodium-catalysed conjugate addition of β-ketoester **378** was also found to be unsuccessful, despite trialling a range of conditions.

With (±)-α-diazolactone **380** to hand, the diverted O-H insertion between commercially available (*S*)-β-hydroxyketone **264** and the metallocarbene of (±)-α-diazolactone **380** was then investigated (***Scheme 3-6***). Disappointingly, both rhodium and copper-based catalysts were unsuccessful, with only copper(I) triflate toluene complex generating trace amounts of desired spirocyclic products **384a-b** when utilising two equivalents of the α-diazolactone reactant. Previously optimised conditions were found to be ineffective, as the *in situ* generated metallocarbenoid was

found to undergo an unprecedented [1,2]-allyl rearrangement, as well as a previously encountered [1,2]-methyl migration pathway, to afford olefins **386** and **387**.

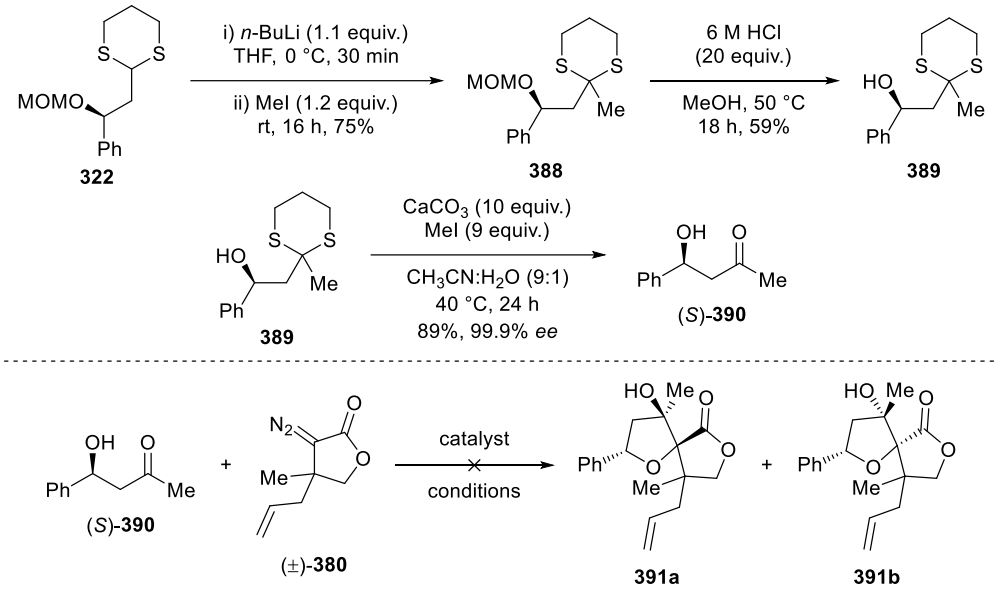


Scheme 3-6: *Attempted diverted O-H insertion with (S)-β-hydroxyketone **264** and (±)-α-diazolactone **380**, highlighting the detrimental formation of [1,2]-migration by-products **386** and **387**.*

Confirming the skeletal rearrangement through HMBC and nOe correlations between the lactone protons and the protons of the adjacent substituent, the preferential formation of [1,2]-allyl migration by-product **387**, over the corresponding [1,2]-methyl migration by-product **386**, indicates a higher migratory aptitude for the allyl substituent for the metallocarbenoid [1,2]-migration process, although the regioselectivity was found to be variable (≈1.5:1 **387**:**386**). With intramolecular migrations outcompeting the productive diverted O-H insertion transformation, the presence of sterically encumbered functionalities surrounding the ketone and inserting alcohol is postulated to dramatically reduce the rate of spirocyclisation.

Assessing whether the absence of the *tert*-butyldimethylsilyl functionality has an effect on the key transformation, the diverted O-H insertion between (±)-α-diazolactone **380** and (*S*)-β-hydroxyketone **390** was then attempted, thus enabling an evaluation of steric bulk surrounding the ketone functionality. Accessed from enantiopure 1,3-dithiane **322** (*vide supra*, ***Scheme 2-14***), (*S*)-β-hydroxyketone **390** was synthesised from a three-step alkylation and functional group cleavage sequence (***Scheme 3-7***). Identical to the results obtained with (*S*)-β-hydroxyketone **264**, the alternative use of (*S*)-β-hydroxyketone **390** led to the formation of olefins **386** and **387**, with only copper(I) triflate toluene complex generating trace amounts of desired spirocyclic products **391a-b**. Although unsuccessful, these control experiments

indicate that the *tert*-butyldimethylsilyl protecting group adjacent to the ketone functionality does not have a detrimental effect on the key transformation.



Scheme 3-7: *Unsuccessful diverted metallocarbene O-H insertions with (±)-α-diazolactone* ***380****, highlighting the synthesis of (S)-β-hydroxyketone* ***390****.*

Choosing to focus on the synthesis of spirolactones **392a-b**, the diverted O-H insertion between primary β-hydroxyketone **329** and the metallocarbene of (±)-α-diazolactone **380** was subsequently investigated, and accordingly optimised (***Table 3-2***). Pleasingly, the rhodium(II) octanoate dimer-catalysed reaction afforded spirolactones **392a-b** in a moderate 30% yield (entry 1), indicating that this transformation class was previously affected by the sterically hindering phenyl substituent adjacent to the inserting alcohol. The diastereoselectivity of the key transformation was determined from spectroscopic analysis of the inseparable mixture of spirolactones **392a-b**, with nOe correlations between protons associated with the lactone alkyl substituents and the methylene protons adjacent to the *tert*-butyldimethylsilyl protected alcohol determining the preferential formation of the *cis*,*cis*-configuration over the desired *cis*,*trans*-configuration, that is observed for (-)-hyperolactone C **5** (75:25 *dr*). The facial diastereoselectivity exerted from the lactone substituents reveals a steric clash between the protected alcohol and the allyl substituent, favouring the assembly of *cis*,*cis*-spirolactone **392b**. Although still being affected by competing [1,2]-migration side reactions, utilising copper(I) triflate toluene complex was found to increase the isolated yield of spirolactones **392a-b** to 37%, albeit with a negligible improvement to the diastereoselectivity (entry 2).

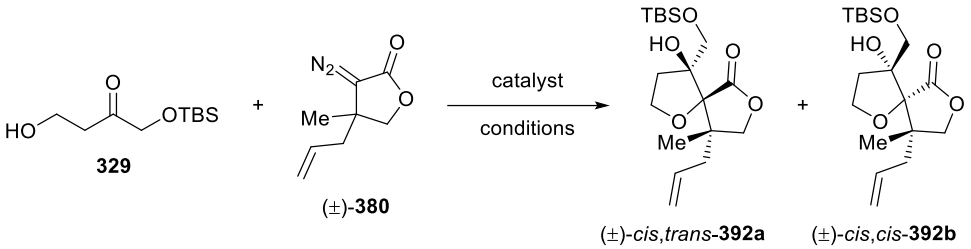


Table 3-2: *Diverted O-H insertion reaction of β-hydroxyketone* ***329*** *with (±)-α-diazolactone* ***380****.*

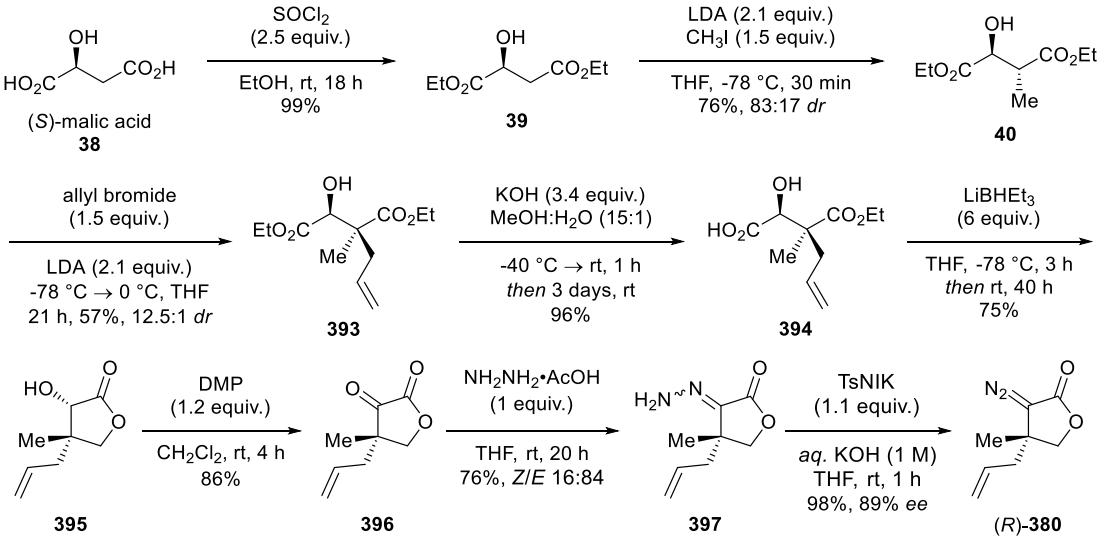
Entry	Conditions[a]	380 / equiv.	Time / h	Yield[b] %	*dr*[c] (392a:392b)
1	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	1	30	25:75
2	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	1.3	1	37	24:76
3	CuOAc (5 mol%), CH_2Cl_2, 0 ºC→rt→reflux	1.3	2→2→16	18	31:69
4	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	2	1	48	25:75
5	$(CuOTf)_2$•PhMe (5 mol%), (S,S)-*i*-PrBox (7 mol%), $NaBAr_F$ (6 mol%), CH_2Cl_2, 0 ºC→reflux	1.3	1→1	27	25:75

a = using a slow dropwise addition of α-diazoester **364** to the reaction mixture over a 30 min period; b = isolated yield; c = the *dr* was determined by ^{1}H NMR analysis; $NaBAr_F$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

Applying a previously beneficial initiation period with copper(I) acetate, both the diastereoselectivity (31:69 *dr*) and the efficiency of the desired spirocyclisation was found to dramatically decrease (18%, entry 3). However, increasing the stoichiometry of (±)-α-diazolactone **380**, while using the superior copper(I) triflate toluene complex catalyst, increased the isolated yield of spirolactones **392a-b** to 48% (entry 4), reducing the impact of [1,2]-allyl and methyl migrations of the metallocarbenoid species. Having been shown to exert modest levels of stereospecificity on tetrahydrofuran systems (*vide supra*, ***Scheme 1-25***), the addition of (*S*,*S*)-*i*-PrBOX and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, a mild cation stabilising non-coordinating anion additive that has been previously deployed in enantioselective O-H insertion reactions,[76,142] failed to improve the diastereoselectivity and decreased the efficiency of the transformation (entry 5).

Having developed and optimised a diverted O-H insertion approach to racemic hyperolactone precursors **392a-b**, synthetic efforts were directed towards the synthesis of (*R*)-α-diazolactone **380**. Although there has been significant research into copper-catalysed asymmetric conjugate additions of simple unsubstituted cyclic enones, with particular success involving chiral ferrocenyl-based diphosphine ligands,[143,144] the development of a challenging enantioselective procedure involving

expensive non-commercially available ligands was unfavourable. Having previously developed and optimised a chiral pool approach to enantioenriched (*R*)-α-diazolactone **364**, modification of this methodology provided efficient access to desired (*R*)-α-diazolactone **380** in high yield (***Scheme 3-8***).

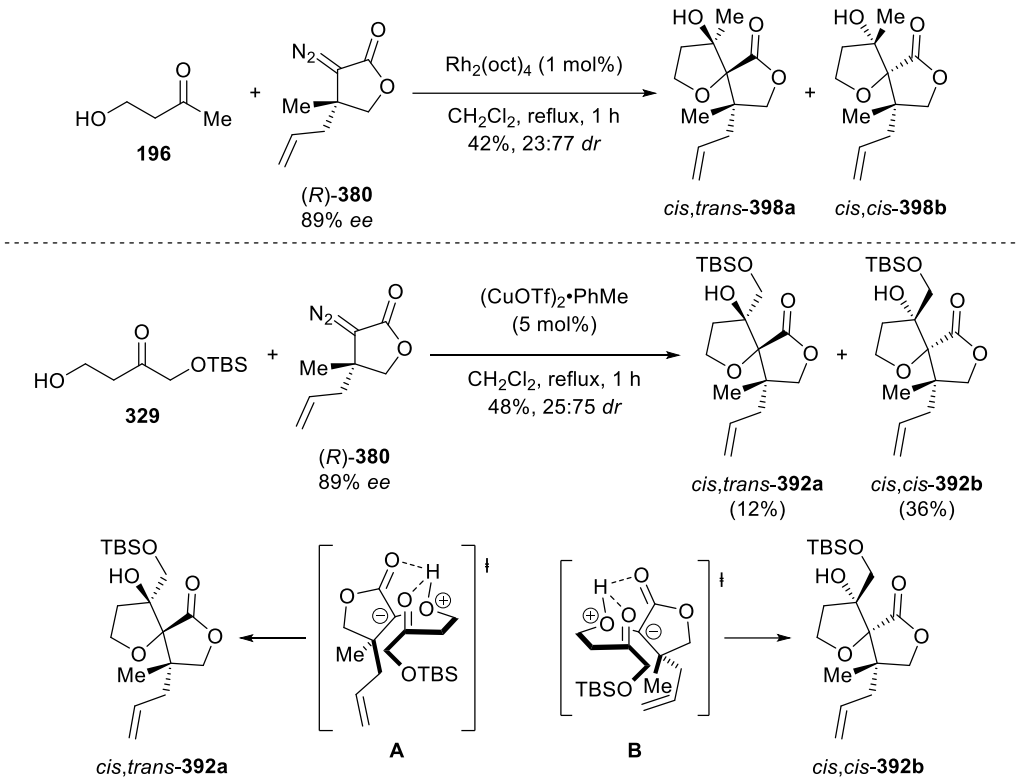


Scheme 3-8: *Chiral pool approach to enantioenriched (R)-α-diazolactone* ***380****.*

Performing an alternative diastereoselective alkylation of hydroxysuccinate ester **40** with allyl bromide, hydroxysuccinate ester **393**, bearing the desired methyl-allyl quaternary stereocentre, was obtained in moderate yield with an excellent diastereoselectivity (12.5:1 *dr*). Following this, hydroxysuccinate ester **393** was subjected to the previously utilised chemoselective base-catalysed hydrolysis and reductive lactonisation methodology to generate lactone **395** in excellent yield. Finally, a high yielding three-step oxidation, hydrazone formation and iodamine-T diazotisation reaction sequence synthesised desired enantioenriched (*R*)-α-diazolactone **380**, with a consistently high enantiopurity, calculated from chiral HPLC (89% *ee*).

Pleasingly, applying previously optimised reaction conditions for the diverted O-H insertion between primary β-hydroxyketone **329** and the metallocarbene of (*R*)-α-diazolactone **380** assembled spirolactones **392a-b** with a reproducible isolated yield and diastereoselectivity (***Scheme 3-9***). Although the purification of spirolactones **392a** and **392b** were challenging, chromatographic resolution provided access to both the *cis*,*trans*-stereoconfiguration, corresponding to (-)-hyperolactone C **5**, and the *cis*,*cis*-stereoconfiguration, associated with (-)-5-*epi*-hyperolactone C *epi*-**5**. Proceeding with the formation of a transient ylide intermediate, the facial

diastereoselectivity can be rationalised from a steric clash between the *tert*-butyldimethylsilyl and allyl functionalities in transition state **A**, with transition state **B** preferentially undergoing the spirocyclisation process with the two functional groups in a sterically favoured conformation, leading to the construction of *cis*,*cis*-spirolactone **392b**.

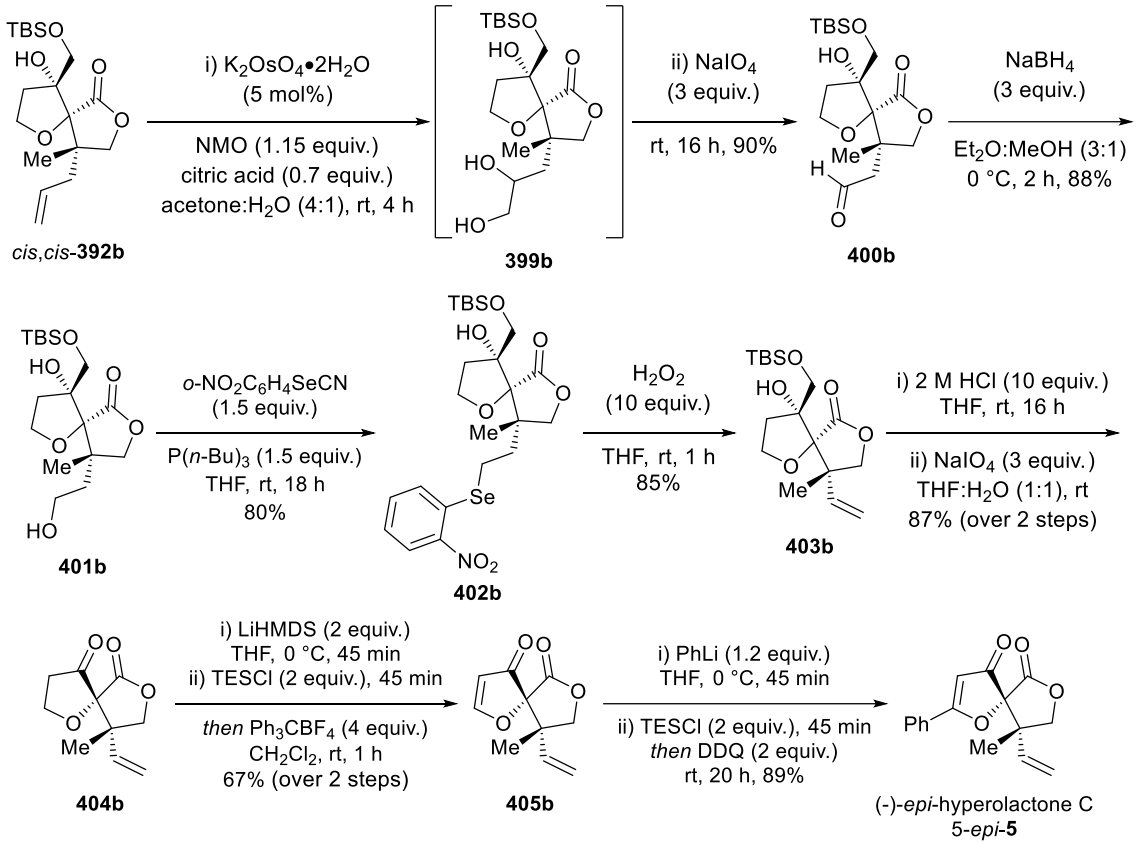


Scheme 3-9: *Key diverted metallocarbene O-H insertions with (R)-α-diazolactone **380**, highlighting the postulated transition states leading to the cis,trans- and cis,cis-stereoconfigurations.*

Assessing whether replacing the *tert*-butyldimethylsilyl functionality with a less sterically encumbered methyl substituent would alter the diastereoselectivity, the diverted O-H insertion between 4-hydroxybutan-2-one **196** and the metallocarbene of (*R*)-α-diazolactone **380** was also investigated. Spirolactones **398a-b** were subsequently obtained as an inseparable mixture, with an isolated yield of 42% using rhodium(II) octanoate dimer, favouring the *cis*,*cis*-stereoconfiguration (77:23 *dr*). Although isolating spirolactones **398a-b** with a lower yield of 38%, copper(I) triflate toluene complex was found to slightly improve the diastereoselectivity (80:20 *dr*). These investigations indicate that the substitution of less sterically bulky alcohol protecting groups to the β-hydroxyketone component may not improve the

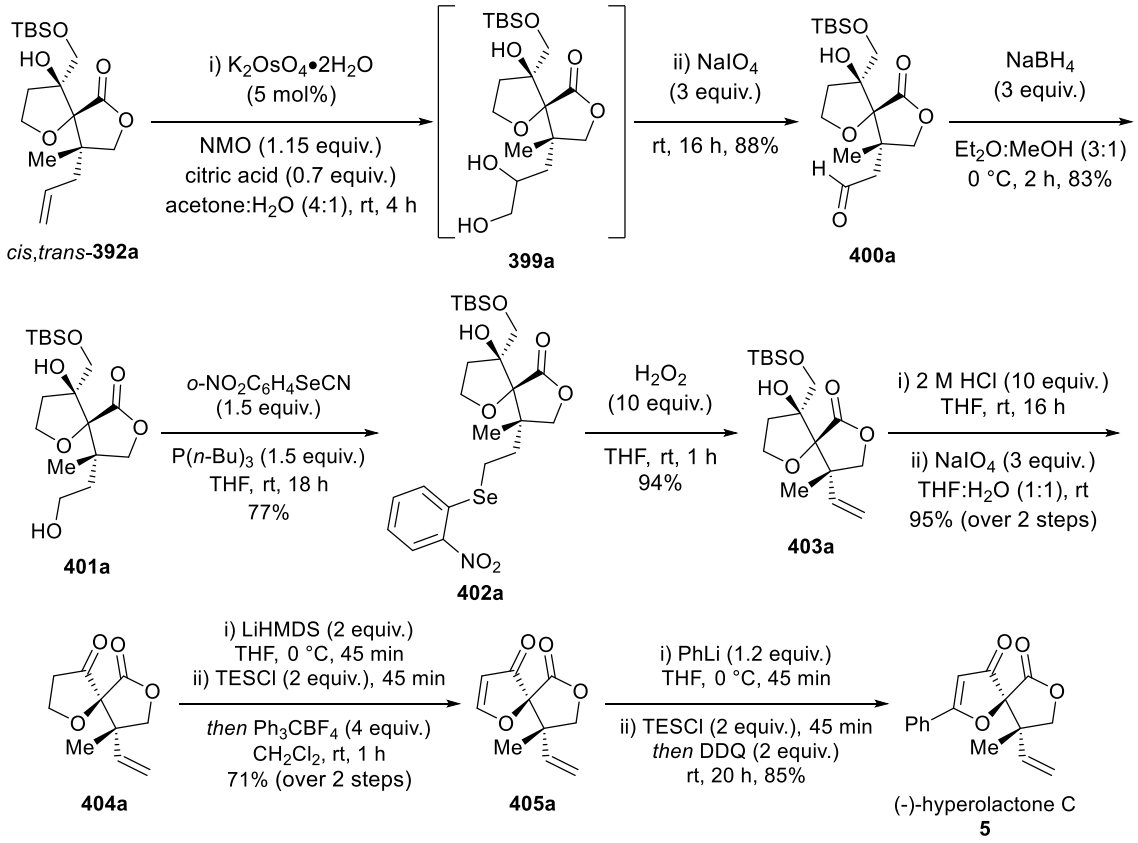
diastereoselectivity of the key transformation towards the desired hyperolactone C spirocyclic configuration.

With both *cis*,*trans*-spirolactone **392a** and *cis*,*cis*-spirolactone **392b** to hand, the allyl substituent of major diastereoisomer *cis*,*cis*-**392b** was then converted to spirolactone **403b**, utilising an optimised four-step sequence to furnish the desired vinyl functionality (***Scheme 3-10***). Generating osmium tetroxide *in situ* from the oxidation of potassium osmate with *N*-methyl morpholine-*N*-oxide (NMO), an Upjohn dihydroxylation was found to efficiently generate 1,2-diol intermediate **399b** from spirolactone **392b**,[145,146] where the successive addition of sodium periodate mediated an oxidative cleavage to afford aldehyde **400b** in 90% from a one-pot procedure. Performing a subsequent chemoselective reduction to afford primary alcohol **401b** in high yield, an optimised two-step Grecio elimination, involving the formation of selenide **402b** and its oxidative *syn*-elimination, efficiently generated spirolactone **403b**.



Scheme 3-10: *Total synthesis of (-)-epi-hyperolactone C 5-epi-**5** from cis,cis-spirolactone **392b**.*

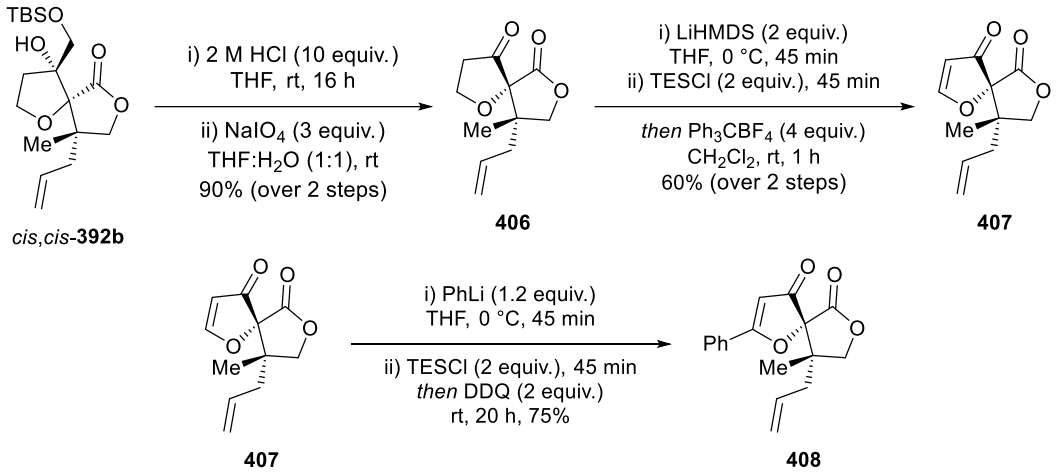
Confirming the absolute configuration of the three adjacent quaternary stereocentres of key spirocyclic intermediate **403b** from X-ray crystallographic studies (*vide infra*, ***Appendix B - Figure K***), a previously employed *tert*-butyldimethylsilyl deprotection and oxidative cleavage sequence then produced spiroketolactone **404b**. Having developed an efficient approach to the hyperolactone motif from similar spiroketolactone intermediates, a penultimate tritylium tetrafluoroborate mediated hydride abstraction of the corresponding triethylsilyl enol ether of spiroketolactone **404b** then produced norphenyl 5-*epi*-hyperolactone C **405b**. A final late-stage phenyllithium conjugate addition DDQ induced dehydrogenation of the trapped triethylsilyl enol ether was then performed with high yield, completing the enantioselective total synthesis of (-)-5-*epi*-hyperolactone C *epi*-**5** with an overall yield of 2% over eighteen-steps, from the longest linear chain.



Scheme 3-11: *Total synthesis of (-)-hyperolactone C* ***5*** *from cis,trans-spirolactone* ***392a****.*

Having now developed a nine-step total synthesis endgame strategy that successfully assembled the phenyl substituted furan-3(2*H*)-one moiety and converted the allyl lactone substituent to the desired vinyl functionality, minor diastereoisomer *cis*,*trans*-spirolactone **392a** was subjected to the optimised synthetic sequence to

achieve the enantioselective total synthesis of (-)-hyperolactone C **5** with an overall yield of 0.72% over eighteen-steps, from the longest linear chain (***Scheme 3-11***). Although the achieved total synthesis involves a lengthy developed route with a moderate overall yield, with respect to previously developed total syntheses, this methodology addresses the challenging enantioselective assembly of the vicinal stereocentres, while permitting late-stage diversification of the enone substituent. In addition, this developed diverted metallocarbenoid O-H insertion approach also provides the divergent construction of both spirocyclic stereoconfigurations and the isolation of unnatural hyperolactone analogues, bearing modifications at lactone core, through common advanced intermediates.

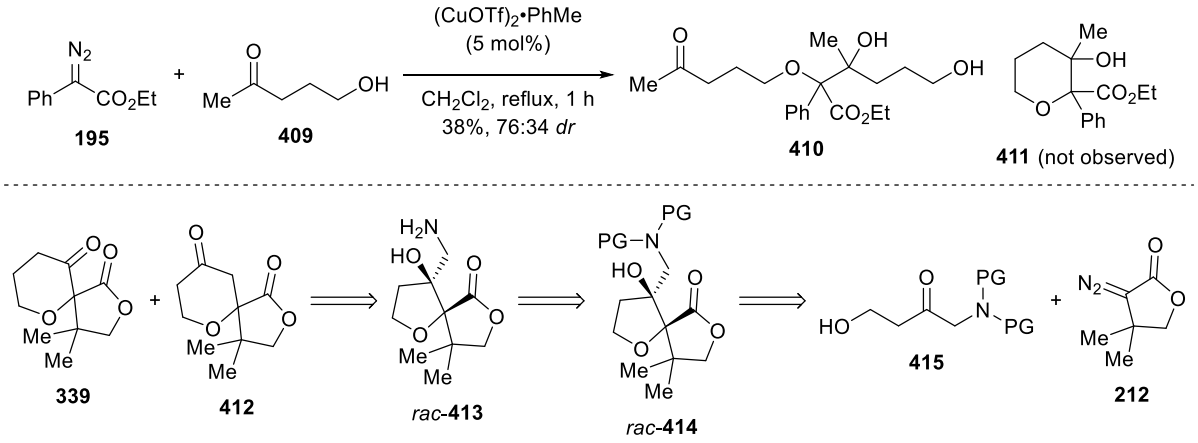


Scheme 3-12: *Total synthesis of unnatural hyperolactone analogue* ***408***

Demonstrating the utility of the developed diverted carbene O-H insertion approach, the direct deprotection-oxidative cleavage of *cis*,*cis*-spirolactone **392b** to spiroketolactone **406**, followed by the previously utilised dehydrogenation endgame sequence, furnished novel unnatural hyperolactone analogue **408**, with an overall yield of 2.9%, over fourteen-steps from the longest linear chain (***Scheme 3-12***). Through the application of alternative α-diazolactone components in the key diverted metallocarbene O-H insertion transformation, or by conducting further modifications to the spirocyclic scaffold, the synthesis of further privileged spirolactone precursors may be permitted. Ultimately, this may provide access to novel biologically active hyperolactones, critical for the continued advancement of hyperolactone-based therapeutic agents.

3.2 Advancement of the Diverted O-H Insertion Transformation and the Synthesis of Privileged Spirolactones

Having achieved the enantioselective total synthesis of (-)-hyperolactone C **5**, its spirocyclic epimer *epi*-**5**, and a number of unnatural hyperolactone analogues from a diverted metallocarbene O-H insertion approach, studies into the synthesis of spiro-pyranone variants of the natural product were then investigated. Unfortunately, previous studies conducted by the Moody Research Group discovered that the synthesis of tetrahydro-2*H*-pyran **411** from the diverted O-H insertion between δ-hydroxyketone **409** with the metallocarbenoid of α-diazoester **195** was unsuccessful (***Scheme 3-13***).[88] Affording complex mixtures, diol **410**, derived from an intermolecular ylide trapping process, was solely isolated as a diastereomeric mixture (38%, 76:34 *dr*), with no evidence of the desired trahydro-2*H*-pyran **411** generating intramolecular cyclisation occurring. Therefore, the direct synthesis of spiro-pyranones from δ-hydroxyketones, which partially exist in solution as their corresponding hemiacetal tautomer, was deemed unviable.

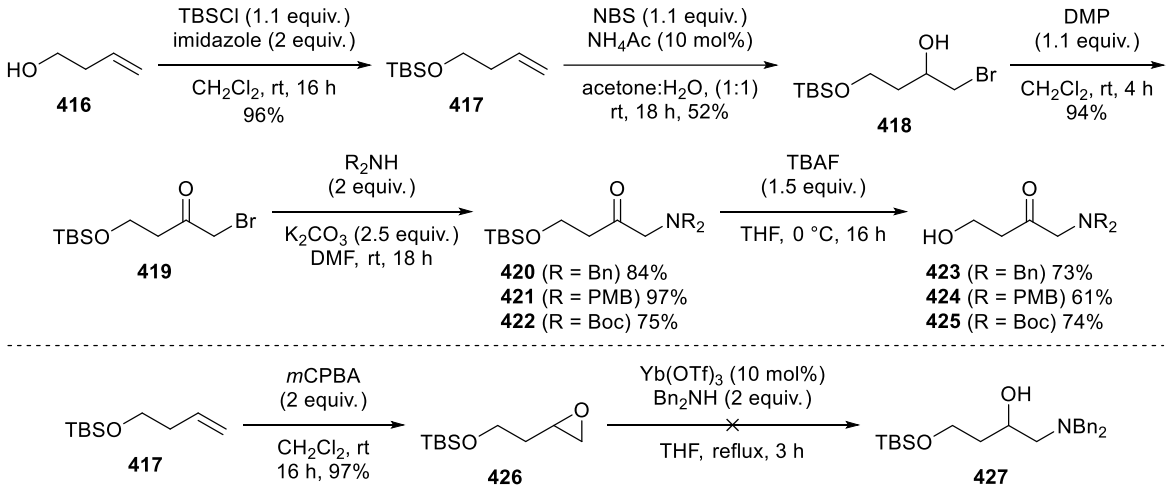


Scheme 3-13: *Retrosynthetic analysis of spiro-pyranones **399** and **412**.*

Having previously trialled several unsuccessful spiroketolactone and spirodiol ring expansion methodologies (*vide supra*, ***Scheme 2-20*** / ***Scheme 2-21***), it was alternatively envisaged that the synthesis of related hyperolactone spiro-pyranone derivatives **399** and **412** could be assembled from the Tiffeneau-Demjanov rearrangement of amino alcohol spirocycle **413**.[147] Proceeding with an unknown ring expansion regioselectivity, retrosynthetic analysis of spiro-pyranones **399** and **412** indicates that the key spirolactone intermediate **413** may be assembled from a diverted

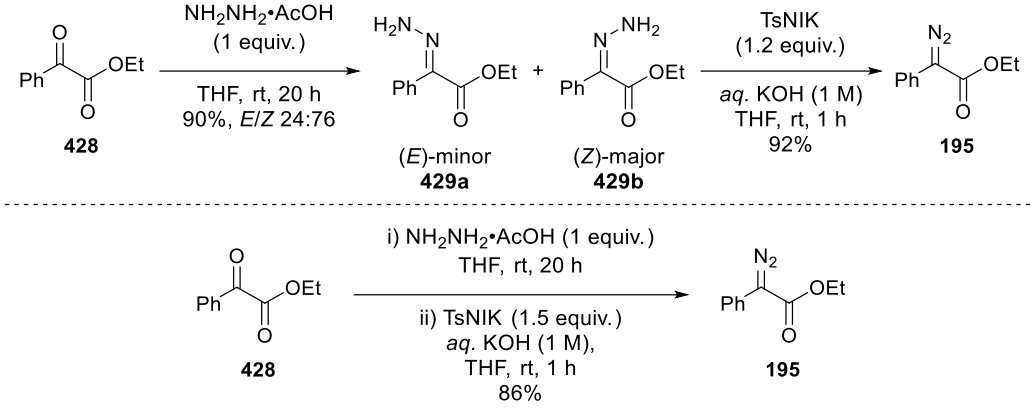
O-H insertion with an alternative β-hydroxyaminoketone reactant with the metallocarbene of α-diazolactone **212**.

Aiming to expand the value of this methodology by enabling the stereospecific synthesis of novel amino alcohol spirocycles, a general divergent five-step synthetic route to a range of β-hydroxyaminoketones, bearing a variety of amino protecting groups, was accordingly developed (***Scheme 3-14***). Accessed from commercially available 3-buten-1-ol **416**, initial route development involved the synthesis of *tert*-butyldimethylsilyl protected alkenol **417**, which was then efficiently converted to terminal epoxide **426**, upon treatment with *m*-CPBA (***Scheme 3-14***). Unfortunately, a subsequent ytterbium(III) trifluoromethanesulfonate-catalysed ring opening of **426** with dibenzylamine was unsuccessful despite Yamamoto and colleagues reporting high yields for similar epoxides.[148] Although many alternative Lewis acids have been reported to catalyse the ring opening of epoxides with amines to β-amino alcohols, the generation of **427** *via* this transformation was not investigated further.



Scheme 3-14: *Preparation of novel β-hydroxyaminoketones* ***423-425****.*

Alternatively, olefin **417** was regioselectivity converted to bromohydrin **418** in moderate yield, following the procedure described by Gotor and co-workers.[149] Following this, bromohydrin **418** was then treated with Dess-Martin periodinane to generate α-bromoketone **419**, where a subsequent mild S_N2 nucleophilic substitution with dibenzylamine and a final tetra-*n*-butylammonium fluoride induced desilylation efficiently synthesised novel β-hydroxyaminoketone **423** in excellent yield. Pleasingly, the alternative use of bis(4-methoxybenzyl)amine and di-*tert*-butyl iminodicarbonate led to the efficient syntheses of β-hydroxyaminoketones **424** and **425** in high yield.



Scheme 3-15: *Preparation of α-diazolactone* ***195****.*

Choosing to first evaluate the efficacy of the key diverted O-H insertion transformation between β-hydroxyaminoketones **423-425** and a simple α-diazoester, α-diazoester **195** was selected and prepared from readily available ethyl 2-oxo-2-phenylacetate **428**, utilising a highly successful hydrazone formation and iodamine-T diazotisation sequence (***Scheme 3-15***). Having synthesised the necessary precursors, the synthesis of amino alcohols **430-432**, utilising a key diverted metallocarbene O-H insertion transformation were then investigated (***Table 3-3***).

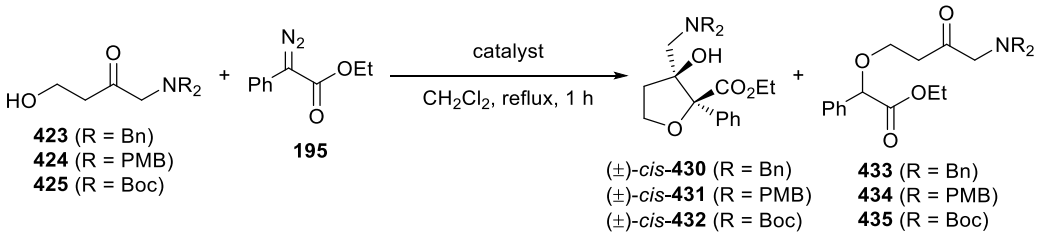


Table 3-3: *Diverted metallocarbene O-H Insertions between β-hydroxyaminoketones* ***423-425*** *and α-diazoester* ***195****.*

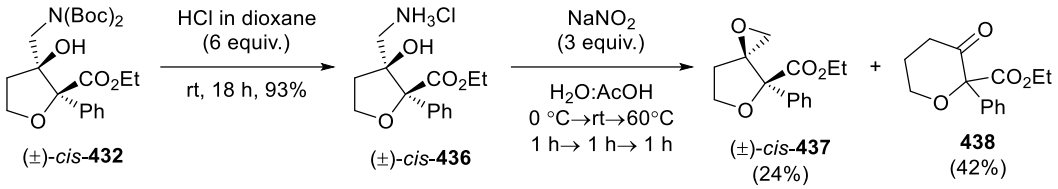
Entry	Conditions[a]	R	Diverted Yield[b] / % 430-432	Inserted Yield[b] / % 433-435	*dr*[c] (*cis*:*trans*) 430-432
1	$Rh_2(oct)_2$ (1 mol%), CH_2Cl_2, reflux	Bn	25	30	85:15
2	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	Bn	23	25	83:17
3	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	PMB	traces	43	/
4	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	PMB	traces	traces	/
5	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	Boc	63	traces	>20:1
6	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	Boc	traces	traces	/

a = using a slow dropwise addition of α-diazoester (1.3 equiv.) to the reaction mixture over a 30 min period; b = isolated yield; c = the *dr* was determined by ^{1}H NMR analysis.

Initially examining the formation of tetrahydrofuran **430** from dibenzylated β-hydroxyaminoketone **423**, attempted rhodium and copper-catalysed diverted O-H insertions afforded complex mixtures with poor isolated yields and a moderate facial diastereoselectivity for the desired amino alcohol **430** (entries 1 and 2). Interestingly, O-H inserted by-product **433** was isolated as the major product, indicating that the presence of the dibenzylated amino functionality reduces both the efficiency of the intramolecular cyclisation reaction and the diastereoselectivity. These results could imply that the available electron lone pair associated with the amino functionality disrupts the proposed hydrogen bonding network between the ketone and lactone functionalities, preferentially favouring the formation of O-H inserted product **433**, which is generally obtained in only trace amounts. The alternative use of β-hydroxyaminoketone **423**, containing the electron-rich 4-methoxybenzyl protecting group, only produced trace amounts of tetrahydrofuran **431** when using rhodium(II) octanoate dimer, solely isolating O-H insertion product **434** in a moderate 43% yield (entry 3). However, the use of copper(I) triflate toluene complex led to complex mixtures, which may be rationalised from either the electron-rich protecting group poisoning the active catalyst, or inserting into the electrophilic metallocarbenoid species, promoting the degradation of α-diazoester **195** (entry 4). Pleasingly, rhodium(II) octanoate dimer efficiently catalysed the diverted carbene O-H insertion reaction with β-hydroxyaminoketone **425**, furnishing desired tetrahydrofuran **432** in an improved yield of 62% as a single diastereoisomer (>20:1 *dr*) (entry 5). Only producing trace amounts of undesired O-H inserted by-product **435**, this result indicates a strong compatibility with the *tert*-butyloxycarbonyl protecting group, as the nitrogen's conjugated lone pair was unable to affect the desired transformation. Although tetrahydrofuran **432** was generated in high yield using rhodium-catalysis, copper(I) triflate toluene complex led to complex mixtures, however, this was postulated to be the result of *tert*-butyloxycarbonyl cleavage (entry 6).

Having assessed the compatibility of amino protecting groups in the diverted carbene O-H insertion transformation and confirmed the relative *cis*-stereoconfiguration from X-ray crystallographic studies (*vide infra*, ***Appendix B - Figure M***), tetrahydrofuran **432** was then converted to amino alcohol **436** in high yield, upon treatment with hydrogen chloride in dioxane (***Scheme 3-16***). Isolated as the corresponding hydrochloride salt, tetrahydrofuran **436** was then subjected to

Tiffeneau-Demjanov rearrangement conditions, involving the *in situ* generation of nitrous acid, which then mediates the diazotisation of the primary amine functionality, inducing the skeletal rearrangement. Although the exact mechanism of the Tiffeneau-Demjanov ring expansion has been historically debated, it is widely accepted that the alkyl shift and removal of the diazonium functionality occurs through a concerted process,[150] thus resulting in varying degrees of steric and electronic influences, making the regioselectivity challenging to predict.



Scheme 3-16: *Synthesis of pyranone* ***438*** *utilising a Tiffeneau-Demjanov rearrangement.*

The Tiffeneau-Demjanov ring expansion of amino alcohol **436** was found to generate both bicyclic epoxide **437** and pyranone **438** in moderate yields. The preferential formation of pyranone **438** indicates that the regioselectivity heavily favours the rearrangement of the less substituted *C*3-*C*4 bond, as the product corresponding to a *C*2-*C*3 bond migration was not observed. Although the migration of the higher substituted *C*2-*C*3 bond was assumed to be electronically favoured, the observed results indicate that this system is governed by additional steric or non-covalent interactions, which is in accordance with the results attained by Yoshikoshi and colleagues for an alternative five-membered natural product ring system.[151] Interestingly, the formation of bicycle **437** is the result of a competing epoxidation, obtained from the alcohol directly cleaving the *in situ* generated diazonium, which may be rationalised from the proximities of the adjacent functionalities.

Having successfully achieved the synthesis of pyranone **438**, the diverted O-H insertion transformation between α-diazolactone **212** and β-hydroxyaminoketones **423-425** were then investigated (***Table 3-4***). Firstly examining β-hydroxyaminoketone **423**, copper(I) triflate toluene complex and rhodium(II) octanoate dimer were both found to afford spirocyclic amino alcohol **439** in identical moderate yields, although rhodium(II) octanoate dimer was found to have a vastly superior diastereoselectivity (entries 1 and 2). As previously observed for diverted O-H insertions with α-diazoester **195**, the dibenzylated amino functionality was found to lower the facial

diastereoselectivity and promote the formation of O-H inserted by-product **442**. Although preferentially undergoing an O-H insertion, major product **442** was found to be heavily contaminated with chromatographically inseparable by-products, derived from the dimerisation and [1,2]-methyl shift of the *in situ* generated metallocarbenoid species. Trialling a range of catalysts, copper(I) acetate was found to promote the degradation of α-diazolactone **212** (entry 3), which may be the direct result of catalyst poisoning, while alternative rhodium-based catalysts were unable to improve the desired isolated yield of spirolactone **439** (entries 4-6). Unfortunately, increasing the stoichiometry of α-diazolactone **212** was also found to have a negligible effect (entry 4).

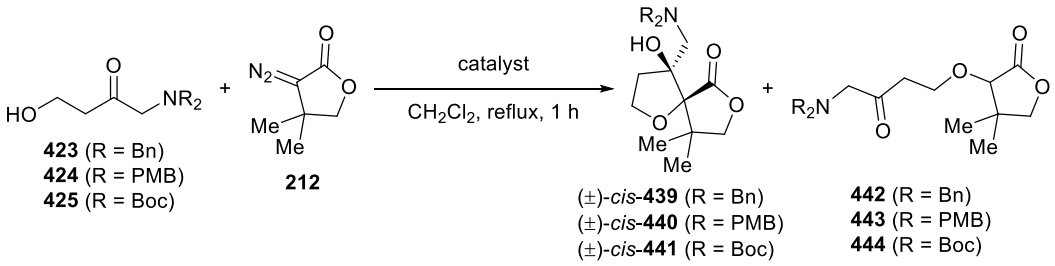


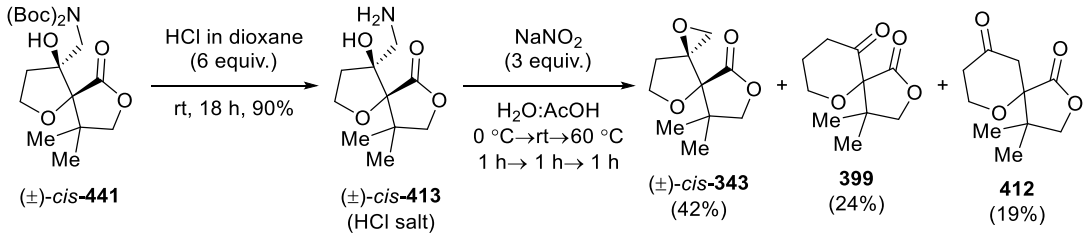
Table 3-4: *Diverted metallocarbene O-H Insertions between β-hydroxyaminoketones* ***423-425*** *and α-diazolactone* ***212****.*

Entry	Conditions[a]	Diazo / equiv.	R	Diverted Yield[b] /% 439-441	Inserted Yield[b] /% 442-444	*dr*[c] *cis*:*trans*) 439-441
1	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	1.3	Bn	36	N/A[d]	56:44
2	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	Bn	36	N/A[d]	86:14
3	CuOAc (5 mol%), CH_2Cl_2, reflux	1.3	Bn	/	/	/
4	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	2	Bn	34	N/A[d]	76:24
5	$Rh_2(OAc)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	Bn	34	N/A[d]	83:17
6	$Rh_2(esp)_2$ (1 mol%), CH_2Cl_2, reflux	1.3	Bn	25	N/A[d]	87:13
7	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	PMB	18	trace	66:33
8	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	1.3	PMB	10	trace	70:30
9	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1.3	Boc	31	30	>20:1
10	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	1.3	Boc	/	/	/
11	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	2	Boc	47	38	>20:1
12	CuOAc (5 mol%), CH_2Cl_2, reflux	1.3	Boc	/	/	/

a = using a slow dropwise addition of α-diazoester to the reaction mixture over a 30 min period; b = isolated yield; c = the *dr* was determined by ^{1}H NMR analysis; d = unable to be chromatically resolved; esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionate.

Alternatively, β-hydroxyaminoketone **424** was found to dramatically decrease both the diastereoselectivity and the efficiency of the spirocyclisation transformation, producing only trace amounts of the undesired O-H insertion by-product, with rhodium(II) octanoate dimer slightly outperforming copper(I) triflate toluene complex (entries 7 and 8). As expected, the key transformation between β-hydroxyaminoketone **425** and α-diazolactone **212** furnished desired diverted O-H insertion product **441** with exceptional diastereoselectivity, when catalysed by rhodium(II) octanoate dimer (entry 9). Although regioselectively favouring the formation of spirolactone **441**, significant isolated yields of O-H inserted by-product **444** were obtained, along with a contaminated fraction containing an olefin species, generated from the [1,2]-methyl migration of the metallocarbenoid of α-diazolactone **212**. Unfortunately, copper-catalysts were found to cleave the *tert*-butyloxycarbonyl protecting groups and produce complex mixtures (entries 10 and 12). However, increasing the stoichiometry of α-diazolactone **212** was found to greatly improve the efficiency of the desired rhodium-catalysed spirocyclisation transformation, furnishing spiro amino alcohol **441** with an isolated yield of 47% (entry 11).

Having evaluated a range of β-hydroxyaminoketones in the key diverted metallocarbene O-H insertion methodology and optimised the synthesis of spirolactone **441**, removal of the acid-labile *tert*-butyloxycarbonyl amino protecting groups afforded spiro amino alcohol **443** as the corresponding hydrochloride salt (***Scheme 3-17***). Performing a successive Tiffeneau-Demjanov ring expansion, spiro amino alcohol **443** was found to generate both spiro-pyranones **339** and **412**, along with tricyclic spiroepoxide **343**, which was isolated as the major product.



Scheme 3-17: *Synthesis of spiro-pyranones **399** and **412** via a Tiffeneau-Demjanov rearrangement.*

Unfortunately, the regioisomeric distribution indicates that there is little to no regioselectivity between the competing epoxidation and the desired Tiffeneau-Demjanov ring expansion, as the combined isolated yields of

spiro-pyranones **339** and **412** (43%) were found to approximately match the isolated yield for tricyclic spiroepoxide **343** (42%). These results demonstrate that the epoxidation process has a greater impact on spirocyclic systems, as the previously assessed Tiffeneau-Demjanov ring expansion for the corresponding tetrahydrofuran system **436** was found to isolate the resultant epoxide by-product with yields lower than 30% (*vide supra*, ***Scheme 3-16***). The enhanced epoxidation yield of **343** suggests that the proximity of the *in situ* generated diazonium and adjacent alcohol functionality are closer together, promoting the direct cleavage of the transient diazonium. In accordance with previous results, the Tiffeneau-Demjanov ring expansion favoured the rearrangement of the less substituted *C*3-*C*4 bond migration, preferentially affording spiro-pyranone **339** with an isolated yield of 24%. However, this transformation was also found to generate spiro-pyranone **412** with an isolated yield of 19%, derived from the migration of the electronically favoured more substituted *C*4-*C*5 bond, suggesting that electronic factors, or conformational effects, greatly alter the regioselectivity for spirolactone systems. Pleasingly, X-ray crystallographic studies were able to determine the relative stereoconfiguration of tricyclic spiroepoxide **343** and confirm the structures of both spiro-pyranones **339** and **412** (*vide infra*, ***Appendix B - Figure N-P***). Having developed, optimised and assessed the stereoselectivity of the key diverted carbene O-H insertion transformation between a variety of β-hydroxyaminoketones and α-diazocarbonyl compounds, the formation of spiro-pyranones **339** and **412** from a successive Tiffeneau-Demjanov ring expansion demonstrates the utility of the developed transformation, and may be further developed to access a number of pyranone-based hyperolactone analogues.

Having advanced the substrate scope of the diverted metallocarbene O-H insertion methodology to β-hydroxyaminoketones, synthetic efforts were then directed towards the development of an enantioselective transformation. Despite achieving limited asymmetric induction from a plethora of rhodium-based catalysts from previous studies performed in the Moody Research Group, it was found that copper-based catalysts were able to afford diverted O-H insertion products with moderate enantiomeric excesses (*vide supra*, ***Scheme 1-25***). Since these initial investigations there have been several seminal advancements in the field of enantioselective X-H insertions, that involve the use of chiral spiro bisoxazoline (spiroBOX) ligands and related chiral spiro phosphoric acid-based co-catalysts,[75–78] efficiently enabling

enantioselective induction from a tightly coordinated rigid spirocyclic chiral pocket. Aiming to apply these new ligand classes to achieve an enantioselective diverted metallocarbene O-H insertion reaction between α-diazoester **195** and β-hydroxyketone **227**, readily prepared from ethyl benzoylacetate **376**,[152] a number of catalysts, chiral ligands and reaction conditions were then trialled and evaluated (***Table 3-5*** and ***Scheme 3-18***).

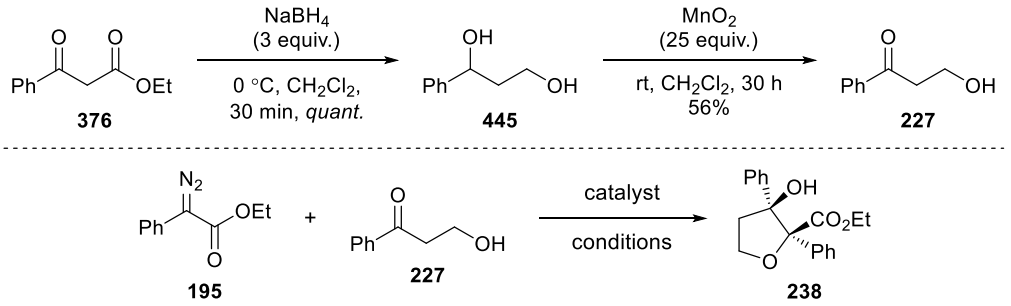
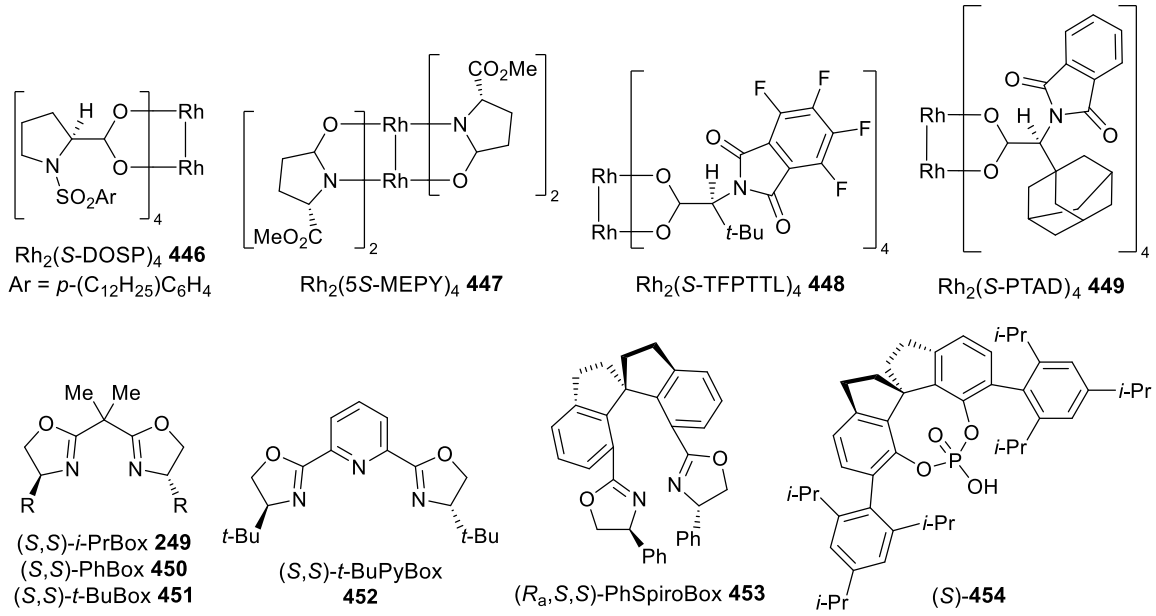


Table 3-5: *Attempted enantioselective diverted O-H insertions.*

Entry	Conditions[b]	Time / h	Yield / %[c]	*ee* / %[d]
1[a]	$(CuOTf)_2$•PhMe (5 mol%), CH_2Cl_2, reflux	1	89	*rac*
2[a]	$Rh_2(oct)_4$ (1 mol%), CH_2Cl_2, reflux	1	82	*rac*
3[a]	Rh_2(*S*-DOSP)$_4$ **446** (1 mol%), CH_2Cl_2, reflux	1	89	< 2
4[a]	Rh_2(*S*-DOSP)$_4$ **446** (1 mol%), pentane, 0 ºC	1	34	< 2
5[a]	Rh_2(5*S*-MEPT)$_4$ **447** (1 mol%), CH_2Cl_2, reflux	1	91	< 2
6[a]	Rh_2(*S*-TFPTTL)$_4$•2EtOAc **448** (1 mol%), CH_2Cl_2, reflux	1	95	< 2
7[a]	Rh_2(*S*-PTAD)$_4$ **449** (1 mol%), CH_2Cl_2, reflux	1	85	7
8[a]	$(CuOTf)_2$•PhMe (2.5 mol%), **249** (7 mol%), CH_2Cl_2, reflux	2	72	31
9[a]	$(CuOTf)_2$•PhMe (2.5 mol%), **452** (7 mol%), CH_2Cl_2, reflux	16	58	3
10	$(CuOTf)_2$•PhMe (2.5 mol%), **249** (7 mol%), CH_2Cl_2, reflux	2	71	24
11	$(CuOTf)_2$•PhMe (2.5 mol%), **249** (7 mol%), CH_2Cl_2, 0 ºC→rt→reflux	1→1→1	64	28
12	$(CuOTf)_2$•PhMe (2.5 mol%), **450** (7 mol%), CH_2Cl_2, reflux	2	56	8
13	$(CuOTf)_2$•PhMe (2.5 mol%), **451** (7 mol%), CH_2Cl_2, reflux	2	76	25
14	$FeCl_2$•$4H_2O$ (5 mol%), **453** (7 mol%), $NaBAr_F$ (7 mol%), CH_2Cl_2, reflux	18	37	< 2
15	$(CuOTf)_2$•PhMe (5 mol%), **453** (7 mol%), $NaBAr_F$ (7 mol%), CH_2Cl_2, reflux	1	91	6
16	$Rh_2(oct)_4$ (1 mol%), **454** (1 mol%), CH_2Cl_2, reflux	1	65	4
17	$Rh_2(TPA)_4$ (1 mol%), **454** (1 mol%), CH_2Cl_2, reflux	1	68	3

a = performed by Simon N. Nicolle;[88] b = using a slow dropwise addition of α-diazoester to the reaction mixture over a 30 min period; c = isolated yield; d = *ee* determined by chiral HPLC; $NaBAr_F$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.



Scheme 3-18: *Chiral ligands and rhodium-based catalysts investigated.*

Preliminary investigations for a number of rhodium-based catalysts, efficiently generated tetrahydrofuran **238** in high yields but with no asymmetric induction, suggesting that the rhodium-catalysed reaction mechanism proceeds through a metal free pathway (entries 3-7). However, copper-based catalysts were found to attain low levels of enantioselectivity in the presence of (*S*,*S*)-*i*-PrBOX ligand **249** (31% *ee*, entry 8), although (*S*,*S*)-*t*-BuPyBOX ligand **452** produced tetrahydrofuran **238** as a racemate (entry 9). This indicates that the copper-catalysed reaction mechanism may proceed, to a limited degree, *via* a metal-associated ylide intermediate, thus subsequent investigations were accordingly focused on the development of an enantioselective copper-catalysed transformation. Unfortunately, alternative BOX ligands were unable to improve the enantiomeric excess of tetrahydrofuran **238** (entries 10-13), with the introduction of an initiation period providing only a negligible effect on the enantioselectivity (entry 11). Despite achieving high levels of asymmetric induction in a number of metallocarbenoid X-H insertion reactions,[75,76] (*R*a,*S*,*S*)-PhsprioBOX ligand **453** mediated only low levels of asymmetric induction when coordinated to copper(I) triflate toluene complex (entry 15) and iron(II) chloride tetrahydrate (entry 14). However, it should be noted that the corresponding epimer, (*S*a,*S*,*S*)-PhsprioBOX, has been demonstrated to achieve superior enantiomeric excesses,[76] although this ligand is not commercially available, and was not investigated in this study. Alternatively, the recent development of a Brønsted acid

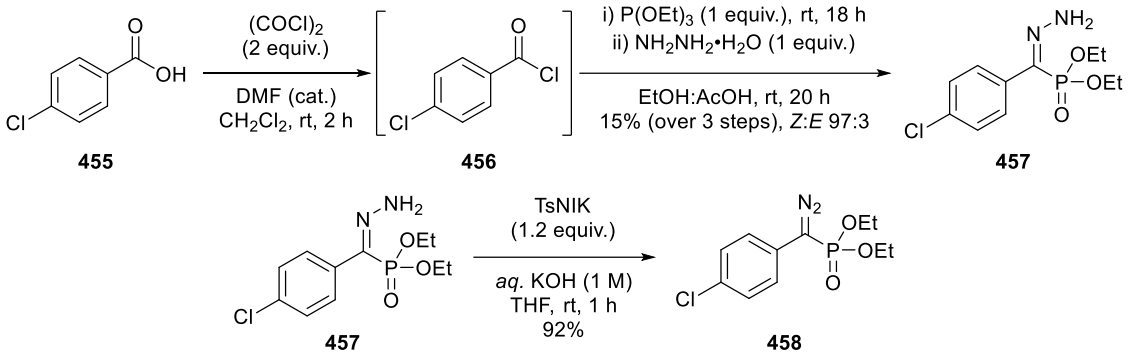
co-catalysed enantioselective α-diazoester O-H insertion has suggested that O-H insertions proceed *via* an alternative free-(*Z*)-enol intermediate,[77,78] furnishing O-H inserted products from a [1,3]-hydride shift, which is in accordance with computational calculations.[73,74] Having achieved excellent enantiomeric excesses from water inserting reactions with a number of α-diazoesters using chiral spiro phosphoric acid **454**, the presence of Brønsted acid co-catalyst **454** generated tetrahydrofuran **238** in reduced yields and disappointing low levels of asymmetric induction. Although unable to develop an enantioselective diverted O-H insertion transformation, these observations suggest that the reaction mechanism does not proceed *via* a free-(*Z*)-enol intermediate, the rhodium-catalysed pathway does not involve a metal-bound ylide intermediate and the copper-catalysed mechanism may occur from both a metal-associated and metal-free oxonium ylide.

Having investigated the development of an asymmetric diverted metallocarbene O-H insertion and expanded the substrate scope of the key transformation to β-hydroxyaminoketones, it was postulated that the application of alternative α-stabilised diazo compounds may afford novel heterocyclic scaffolds. Selecting α-diazophosphonates as a viable alternative to α-diazocarbonyl compounds, insertion reactions between α-diazophosphonates with alcohols and amines, have been widely investigated,[153–155] and has even been utilised as a key transformation in the total synthesis of (±)-maoecrystal V.[68] Although representing a diverse class of highly versatile reagents, only Che and co-workers have reported a three component diverted N-H insertion with α-diazophosphonates, anilines and aldehydes, which enabled the construction α-amino-β-hydroxyphosphonates with moderate yields and high enantioselectivities *via* a suspected metal-bound ammonium ylide.[156]

Despite achieving the synthesis of a variety of tetrahydrofurans and spirolactones from various diverted metallocarbenoid O-H insertions between a range of β-hydroxyketones with α-diazoesters, α-diazolactones and α-diazoketones, additional diazo compounds such as diphenyldiazomethane and diethyl α-phenyl diazophosphonate were found to afford complex mixture of products, with no clear evidence of O-H insertion.[84] While the Moody Research Group has only examined diethyl α-phenyl diazophosphonate, expanding the substrate scope by carrying out further investigations of aryl diazophosphonates with varying electronic properties,

may provide further mechanistic insights into the key transformation and result in the stereospecific assembly of phosphonate bearing tetrahydrofurans.

Selecting α-diazophosphonate **458** as a suitable model system, the desired aryl diazophosphonate diverted O-H insertion precursor was prepared from 4-chlorobenzoic acid **455**, applying a four-step synthetic strategy previously developed within the Hayes Research Group, which has also been demonstrated to have atom-economical flow chemistry applications.[157] (***Scheme 3-19***).

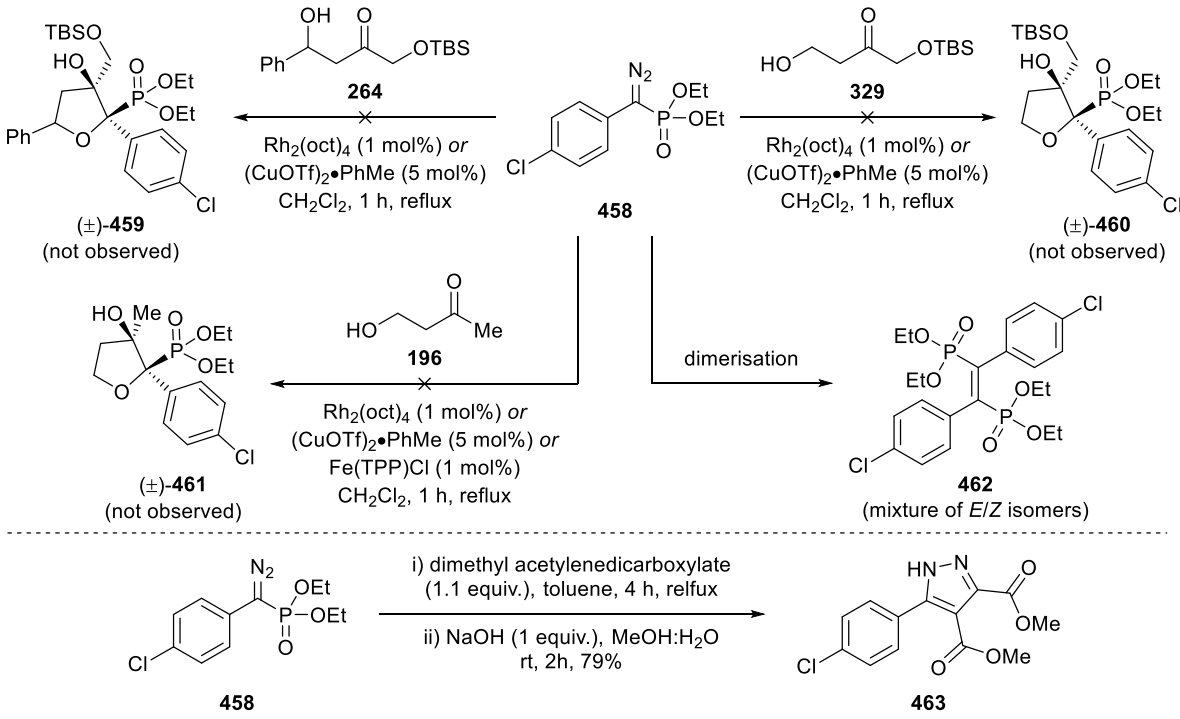


Scheme 3-19: *Preparation of α-diazophosphonate **458**.*

Upon treatment with oxalyl chloride, 4-chlorobenzoic acid was quantitatively converted to its respective acid chloride when activated with catalytic amounts of *N*,*N*-dimethylformamide. Related to the Michaelis-Arbuzov addition, successive treatment with triethylphosphite then furnished the corresponding α-ketophosphonate, which was then converted to hydrazonephosphonate **457** *via* a condensation with hydrazine monohydrate in the presence of acetic acid. Unfortunately, it was found that the formation of the α-ketophosphonate intermediate was inefficient with 4-chlorobenzoic acid and was unable to be improved from a 15% yield when trialling various reaction conditions, despite Hayes and colleagues achieving impressive yields for alternative acid chlorides. Completing the synthesis of α-diazophosphonate **458**, a final iodamine-T mediated diazotisation of hydrazonephosphonate **457** efficiently generated the desired diazo functionality in 92% yield. Despite affording α-diazophosphonate **458** in a moderate yield over four-steps, an alternative diazo transfer sequence, reported by Titanyuk and co-workers, may provide an improved synthesis to the desired precursor, however, this was not investigated.[158]

Having successfully synthesised α-diazophosphonate **458**, several diverted metallocarbene O-H insertion transformations, with a number of β-hydroxyketones,

were then investigated (***Scheme 3-20***). Unfortunately, all trialled reactions failed to afford the desired phosphonate bearing tetrahydrofurans, with no clear evidence of the initial O-H insertion occurring. The use of copper(I) triflate toluene complex, rhodium(II) octanoate dimer and iron(tetraporphyrinato) chloride were all unsuccessful, producing complex mixtures in all cases, with NMR and mass spectroscopy analysis implying that the degradation of α-diazophosphonate **458** was mainly occurring *via* a carbene dimerisation process.



Scheme 3-20: *Attempted diverted metallocarbene O-H insertions with α-diazophosphonate* ***458****, and the formation of pyrazole* ***463*** *utilising a 1,3-dipolar cycloaddition.*

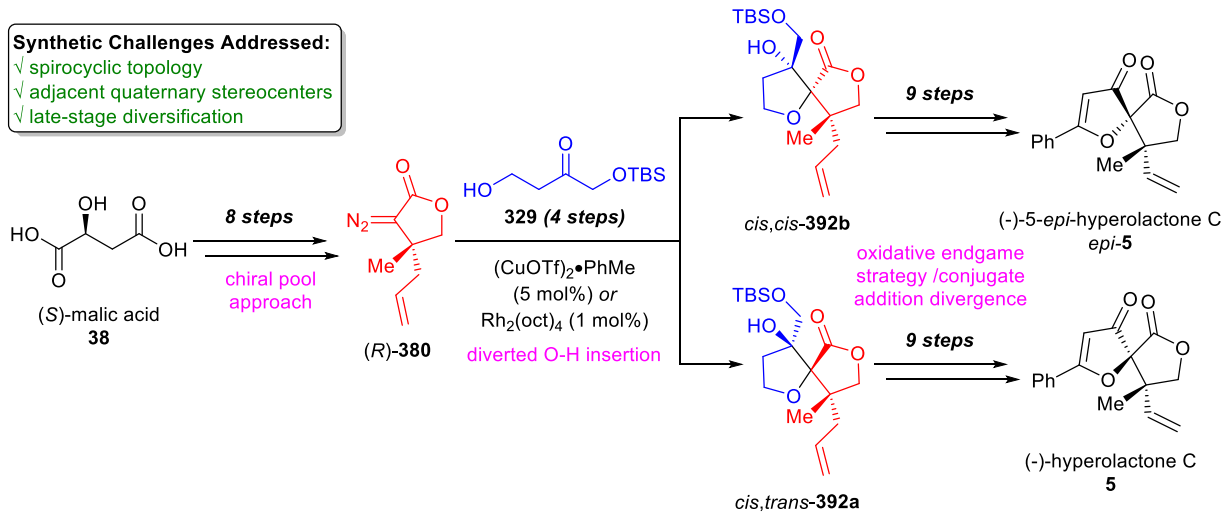
Although unsuccessful when applied in the key diverted carbene O-H insertion transformation, α-diazophosphonate **458** was found to efficiently undergo a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to efficiently afford a *N*-phosphorylpyrazole intermediate, involving a 1,5-sigmatropic migration of the phosphoryl group from the corresponding cycloadduct, that was then hydrolysed to pyrazole **463**. Having isolated pyrazole **463** in excellent yield, further cycloadditions involving alternative alkynes and dipolarophiles with α-diazophosphonates, surrogates for their highly unstable diazoalkane counterparts, are currently ongoing within the Hayes Research Group. These studies may efficiently provide access to therapeutically active functionalised pyrazoles that are abundant in many natural

product classes and various pharmaceutical agents. Furthermore, this transformation may also have biological applications, as appropriate water-compatible diazophosphonates may be applicable to bioorthogonal cycloaddition reactions.

Despite being unable to afford desired diverted O-H inserted products **459-461**, alternative α-diazophosphonates, with varying electronic substituents, may stereospecifically generate their corresponding phosphonate bearing tetrahydrofurans, that could then be manipulated to a range of diverse moieties. Additionally, continued development of the diverted O-H insertion transformation, by expanding the substrate scope to alternative stabilised diazo compounds and electrophiles, may enable the synthesis of further biologically active highly functionalised sp^3-rich heterocycles, which could have direct applications in the fields of natural product total synthesis and medicinal chemistry.

Chapter 4: Conclusions and Further Work

Having extended the scope of the diverted metallocarbene O-H insertion transformation between β-hydroxyketones and α-diazocarbonyl compounds to α-diazolactones, this developed methodology has enabled the stereospecific synthesis of a diverse range of privileged spirolactones. Achieving the initial objective of this project, several strategies to the synthetically challenging spirocyclic hyperolactone motif were attained from optimised diverted metallocarbene O-H insertion approaches. Enantioselectively synthesising numerous novel hyperolactone analogues, a direct convergent synthetic route, as well as an alternative second-generation parallel fragment-based approach, permitting late-stage diversification to the spirocyclic core, were successfully devised. Having established a viable route to the therapeutically active spirocyclic framework and evaluated the stereochemical assembly of the vicinal quaternary stereocentres of the natural product core, enantiopure diverted O-H insertion precursors were synthesised from chiral pool or readily available sources.



Scheme 4-1: *Summary of the enantioselective total synthesis of (-)-hyperolactone C* ***5*** *and related spirolactone analogues using a diverted metallocarbene O-H insertion approach.*

Achieving the primary research objective, the enantioselective total synthesis of (-)-hyperolactone C **5** and (-)-5-*epi*-hyperolactone C *epi*-**5** was achieved from a diverted metallocarbene O-H insertion approach (***Scheme 4-1***). Despite initial studies being affected by detrimental intramolecular [1,2]-sigmatropic rearrangements of

functionalities adjacent to the metallocarbenoid centre, employing the use of enantioenriched α-diazolactones bearing masked vinyl groups successfully enabled the stereospecific synthesis of advanced polysubstituted hyperolactone precursors. Although the achieved total synthesis details a lengthy developed route with a moderate overall yield, with respect to previous total syntheses, our methodology has addressed the enantioselective assembly of both spirocyclic stereoconfigurations, provides a stereospecific construction of the vicinal quaternary stereocentres and permits the late-stage diversification to analogues thereof. In addition, the divergent isolation of unnatural secondary metabolites bearing modifications to the lactone core were also attained from common intermediates.

As an extension of the developed methodology, the diverted metallocarbene O-H insertion transformation was extended to β-hydroxyaminoketones to efficiently generate amino alcohol spirocycles in excellent yields. Developing this approach further, subsequent Tiffeneau-Demjanov ring expansion rearrangements have provided access to novel spiro-pyranone scaffolds that may serve as valuable precursors to pyranone-based hyperolactone analogues. Although attempts to develop an enantioselective transformation and extend the substrate scope to α-diazophosphonates had limited success, future research should be directed towards the investigation of alternative stabilised diazo compounds and electrophiles, such as aldehydes and imines.

Enabling the stereospecific construction of synthetically challenging moieties, advancing the scope and understanding the limitations of this methodology is crucial to the development of privileged frameworks that could be readily applied in natural product synthesis or drug discovery. With a strong potential for facilitating the development of large diverse hyperolactone and biyouyanagin-based compound libraries, this synthetic methodology aims to inspire the synthesis of highly challenging spirocyclic natural products, as well as prospective hit-to-lead, and lead optimisation campaigns within drug discovery by deviating from highly sp^2-hybridised drug candidates, facilitating the exploration of unchartered chemical space.

Chapter 5: Experimental

5.1 General Experimental

Commercially available reagents were obtained from commercial suppliers and used without further purification, unless otherwise stated. Reactions were carried out in glassware, either flame-dried or oven dried overnight at 120 °C, cooled under an argon atmosphere. Anhydrous dichloromethane and triethylamine were distilled from calcium hydride, while anhydrous tetrahydrofuran and toluene were obtained from anhydrous solvent dispensers by filtration over activated alumina. Other anhydrous solvents and reagents used were obtained commercially. Petroleum ether refers to the petroleum ether fraction boiling between 40-60 °C. All aqueous solutions were prepared from water previously deionised. Saturated brine refers to an aqueous saturated solution of sodium chloride. Dess-Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX) were prepared following the procedures described by Ireland *et al*.[159] Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 GF254 aluminium backed plates and used to monitor reactions. They were visualised by exposure to UV light at 254 nm followed by chemical staining with either aqueous basic potassium permanganate or ethanolic vanillin. Column chromatography was carried out using a stationary phase of Merck silica gel 60, 35-70 μm particles, utilising solvents of analytical purity, with the applied eluent specified alongside R_f values, except where otherwise stated. Reverse phase chromatography was carried out using a Biotage Isolera Four flash chromatography system using prepacked reverse phase cartridges.

NMR spectra were recorded either using the Bruker AV500 (500 MHz ^{1}H frequency, 125 MHz ^{13}C frequency) or the Bruker AV400 (400 MHz ^{1}H frequency, 101 MHz ^{13}C frequency, 162 MHz ^{31}P frequency) instruments at 298 K as a dilute solution in the specified deuterated solvent. All chemical shifts were recorded on the δ scale, quoted in parts per million (ppm), using the residual solvent as an internal standard ($CDCl_3$: δ_H 7.26, δ_C 77.2; DMSO-d_6: δ_H 2.50, δ_C 39.5; acetone-d_6: δ_H 2.05, δ_C 206.3, 29.8; methanol-d_4: δ_H 3.31, δ_C 49.0). All coupling constants, *J*, were reported in Hertz (Hz) to one decimal place and the multiplicity of each signal is designated by

the following abbreviations: s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); hept (heptet), m (multiplet); br (broad) or combinations thereof. All assignments were made based on chemical shift, with the aid of DEPT sequences and correlation techniques (COSY, HMBC, HSQC, NOESY).

Infrared spectra were recorded using a Bruker ALPHA ATR-IR spectrometer over the range 4000-400 cm^{-1} or were recorded in solution from a PerkinElmer 1600 series FT-IR spectrometer, using NaCl cells over the range 4000-600 cm^{-1}. High resolution mass spectra were recorded using a Bruker MicrOTOF 61 spectrometer using an electrospray ionisation (ESI^+) technique. Melting points were measured on a Gallenkamp Griffin Education melting point apparatus and are uncorrected. Microanalytical data was obtained using an Exeter Analytical CE-440 Elemental Analyser on a dry homogeneous sample of material. Enantiopurity was determined from an Agilent 1260 or Agilent 1290 Infinity II HPLC, using solvents of analytical purity and an UV diode array detector pre-set at 210 and 254 nm for analyte detection. All specific rotations $[\alpha]_D$ were measured on a JASCO DIP-370 polarimeter at a wavelength of 589 nm, with a path length of 1 dm, and were calculated using Biot′s law: $\alpha = [\alpha]_D \ell c$, where the observed optical rotation α is measured. (Units for α, $[\alpha]_D$, c and ℓ are °, ° $cm^3\,g^{-1}\,dm^{-1}$, g cm^{-3}, and dm respectively, where concentrations are given in g/100 mL). Differential scanning calorimetry (DSC) and X-ray crystallographic data is contained within the accompanying appendices.

Compound nomenclature was generated using the ChemOffice® software package, which applies IUPAC official rules and recommendations. The atom numbering system used in the description of ^1H and ^{13}C NMR spectra intends to provide a clear description of the peak assignments and does not always reflect the systematic numbering given in the compound name. The use of the descriptors *cis*- and *trans*- refers to the relative stereochemistry substituent substitution of the ring system of interest.

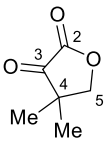
5.2 Chapter 2: Experimental

Lithium Diisopropylamide (LDA) Preparation

To a solution of anhydrous diisopropylamine (1.05 equiv.), freshly distilled from NaH, in anhydrous THF, cooled to 0 °C under argon, was added dropwise *n*-butyllithium (2.50 M in hexanes; 1 equiv.). The resultant light-yellow solution was stirred for 30 min at 0 °C before being used.

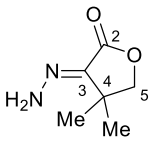
Before utilisation, the concentration of *n*-butyllithium was determined by titration. *n*-Butyllithium was added dropwise, under argon, to a prepared colourless 0.1 M solution of *N*-benzylbenzamide (211 mg, 1.00 mmol) in THF (10 mL) until the complete appearance of a deep blue colouration. Two additional titrations were then performed, and the concentration was then calculated on the averaged analyte volume added.

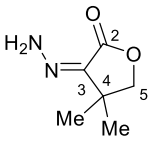
4,4-Dimethyldihydrofuran-2,3-dione 275



Dess-Martin periodinane (12.7 g, 30.0 mmol, 1.2 equiv.) was added to a stirred solution of (±)-pantolactone **274** (3.25 g, 25.0 mmol, 1 equiv.) in CH_2Cl_2 (140 mL), cooled to 0 °C, and was stirred for 10 min. The resulting reaction mixture was then warmed to room temperature and was left stirring for 4 h. The reaction solution was then cooled to -15 °C, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as an off-white crystalline solid (3.00 g, 23.4 mmol, 94%). $\mathbf{R_f}$ = 0.23 (33% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.45 (2 H, s, 5-CH_2), 1.31 (6 H, s, C(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 198.1 (3-*C*=O), 160.5 (2-*C*=O), 77.2 (5-*C*H_2), 42.0 (4-*C*), 22.3 (C(*C*H_3)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 3524, 2970, 2936, 2879, 1762 (C=O), 1459, 1393, 1276, 1176, 1040, 988, 940, 550, 477; **HRMS** (ESI$^+$) *m/z* found 129.0540 (M+H$^+$, $C_6H_9O_3$ requires 129.0546) and 151.0366 (M+Na$^+$, $C_6H_8O_3Na$ requires 151.0366); **mp** 66-68 °C, lit.[160] 66-68 °C. Spectroscopic data matched that previously reported.[160,161]

(*E*)- and (*Z*)-3-Hydrazono-4,4-dimethyldihydrofuran-2(3*H*)-one 279a and 279b


(*E*)-**279a**


(*Z*)-**279b**

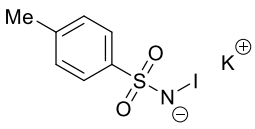
A solution of hydrazine acetate (91.1 mg, 1.00 mmol, 1 equiv.) and 4,4-dimethyldihydrofuran-2,3-dione **275** (128 mg, 1.00 mmol, 1 equiv.) in THF (4 mL) was left stirring at room temperature for 20 h, upon which (*E*)-3-hydrazono-4,4-dimethyldihydrofuran-2(3*H*)-one **279a** precipitates. Aqueous *sat.* sodium hydrogen carbonate solution (2.5 mL) was then added to the reaction mixture, causing the visible precipitate to dissolve completely. The resulting solution was then extracted with ethyl acetate (10 mL) and the organic phase was washed with brine (1 mL) and dried with $MgSO_4$. The dried organic phase was then concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 50 to 100% ethyl acetate in petroleum ether, affording the separated *title compounds*, in a *E*:*Z* 80:20 ratio, confirmed through X-ray crystallography studies.

(*E*)-3-Hydrazono-4,4-dimethyldihydrofuran-2(3*H*)-one 279a as a colourless solid (98.2 mg, 0.691 mmol, 69%). **R_f** = 0.18 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, DMSO-*d_6*): δ_H ppm 7.97 (2 H, s, N*H_2*), 3.95 (2 H, s, 5-C*H_2*), 1.32 (6 H, s, C(C*H_3*)$_2$); **^{13}C NMR** (101 MHz, DMSO-*d_6*): δ_C ppm 167.5 (2-*C*=O), 132.9 (3-*C*=N), 77.3 (5-*C*H_2), 36.4 (4-*C*), 21.2 (C(*C*H_3)$_2$); **IR** (ATR) v_{Max}/cm^{-1} 3410 (NH_2), 3296, 3233, 2966, 2930, 2873, 1726 (C=O), 1575 (C=N), 1477, 1460, 1376, 1314, 1263, 1143, 1054, 1014, 771, 741, 709, 524, 425; **HRMS** (ESI^+) *m/z* found 143.0816 ($M+H^+$, $C_6H_{11}N_2O_2$ requires 143.0815), 165.0631 ($M+Na^+$, $C_6H_{10}N_2O_2Na$ requires 165.0634) and 160.1077 ($M+NH_4^+$, $C_6H_{14}N_3O_2$ requires 160.1081); **mp** 158-159 °C, lit.[92] 159-160 °C; structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation). Spectroscopic data matched that previously reported.[92]

(*Z*)-3-Hydrazono-4,4-dimethyldihydrofuran-2(3*H*)-one 279b as a yellow oil (24.5 mg, 0.172 mmol, 17%). **R_f** = 0.45 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.97 (2 H, br s, N*H_2*), 4.16 (2 H, s, 5-C*H_2*), 1.26 (6 H, s, C(C*H_3*)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 165.0 (2-*C*=O), 134.7 (3-*C*=N), 79.5 (5-*C*H_2), 37.9 (4-*C*), 26.3 (C(*C*H_3)$_2$); **IR** (ATR) v_{Max}/cm^{-1} 3445 (NH_2), 3288, 2967, 2931, 2873, 1730 (C=O), 1596 (C=N), 1464, 1391, 1365, 1304, 1280, 1234, 1179, 1121, 1060, 1001, 867, 791, 666, 553, 457; **HRMS** (ESI^+) *m/z* found 143.0815 ($M+H^+$,

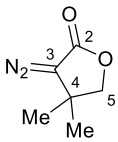
$C_6H_{11}N_2O_2$ requires 143.0815) and 165.0634 ($M+Na^+$, $C_6H_{10}N_2O_2Na$ requires 165.0634). Spectroscopic data matched that previously reported.[92]

Potassium *N*-iodo *p*-toluenesulfonamide (Iodamine-T) 278



A solution of *p*-toluenesulfonamide **277** (4.55 g, 26.6 mmol, 1 equiv.) in aqueous potassium hydroxide (10% *w*/*v*; 11.5 mL) was added to a solution of iodine (9.00 g, 35.5 mmol, 1.33 equiv.) and potassium iodide (18.0 g, 108 mmol, 4.08 equiv.) in water (20 mL). Aqueous potassium hydroxide (50% *w*/*v*; 6.00 mL) was then added, upon which the colouration associated with the iodine diminished and a yellow precipitate appeared. The yellow solid was filtered, washed with cold diethyl ether (20 mL) and dried *in vacuo*, affording the *title compound* as a yellow solid (6.53 g, 19.4 mmol, 73%).**^{1}H NMR** (400 MHz, DMSO-d_6): δ_H ppm 7.48 (2 H, d, *J* = 7.8 Hz, *ortho*-Ar*H*), 7.14 (2 H, d, *J* = 7.8 Hz, *meta*-Ar*H*), 2.31 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, DMSO-d_6): δ_C ppm 144.1 (*ipso-Ar*), 138.0 (*para-Ar*), 128.0 (*meta-Ar*H), 126.6 (*ortho-Ar*H), 20.8 (*C*H$_3$); **IR** (ATR) ν_{Max}/cm^{-1} 3056, 2978, 2954, 2918, 1560, 1497, 1443, 1396, 1188, 1136, 1107, 1063, 1022, 957, 816, 709, 663, 624, 568, 550, 407. Found: C, 24.82; H, 1.95; N, 4.09. $C_7H_7INO_2S$ requires C, 25.08; H, 2.11; N, 4.18%; **mp** 220 °C (decomp.), lit.[92] 220 °C (decomp.). Spectroscopic data matched that previously reported.[92]

3-Diazo-4,4-dimethyldihydrofuran-2(3*H*)-one 212

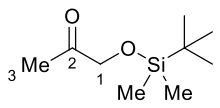


Method I: A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (370 mg, 1.10 mmol, 1.1 equiv.) and hydrazone **279a** (142 mg, 1.00 mmol, 1 equiv.) in THF (4 mL) was prepared. Aqueous potassium hydroxide (1 M; 1 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 5 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (30 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 5 mL),

brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (100 mg, 0.72 mmol, 72%).

Method II: A solution of hydrazine acetate (91.1 mg, 1.00 mmol, 1 equiv.) and 4,4-dimethyldihydrofuran-2,3-dione **275** (128 mg, 1.00 mmol, 1 equiv.) in THF (4 mL) was left stirring at room temperature for 20 h, upon which (*E*)-3-hydrazono-4,4-dimethyldihydrofuran-2(3*H*)-one **279a** precipitates. Aqueous potassium hydroxide (1 M; 1 mL) was then added to the reaction mixture (so that the final volume ratio 1 M KOH:THF was 1:4), causing the visible precipitate to dissolve completely. Potassium *N*-iodo *p*-toluenesulfonamide **278** (403 mg, 1.20 mmol, 1.2 equiv.) was then slowly added to the solution, causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 5 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (30 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 5 mL), brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (88.2 mg, 0.63 mmol, 63%). $\mathbf{R_f}$ = 0.22 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.05 (2 H, s, 5-CH_2), 1.41 (6 H, s, C(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 169.3 (2-*C*=O), 78.7 (5-*C*H_2), 39.0 (4-*C*), 26.0 (C(*C*H_3)$_2$), the signal due to 3-*C*N_2 was not observed; **IR** (ATR) ν_{Max}/cm^{-1} 2967, 2906, 2874, 2088 (CN_2), 1794 (C=O), 1727, 1463, 1396, 1373, 1345, 1273, 1142, 1050, 1008, 731; **HRMS** (ESI$^+$) *m/z* found 141.0655 (M+H$^+$, $C_6H_9N_2O_2$ requires 141.0659), 163.0479 (M+Na$^+$, $C_6H_8N_2O_2Na$ requires 163.0478), 158.0931 (M+NH_4^+, $C_6H_{12}N_3O_2$ requires 158.0924). Spectroscopic data matched that previously reported.[90,92]

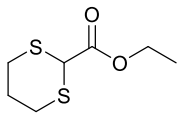
1-((*tert*-Butyldimethylsilyl)oxy)propan-2-one 280



Hydroxyacetone **158** (2.10 mL, 30.0 mmol, 1 equiv.) was added to a stirred solution of TBSCl (6.78 g, 45.0 mmol, 1.5 equiv.) and imidazole (4.49 g, 66.0 mmol, 2.2 equiv.) in CH_2Cl_2 (120 mL), cooled to 0 ºC, and was stirred for 10 min. The reaction mixture was then warmed to room temperature and stirred for 4 h. Brine (100 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 100 mL). The combined organic phases

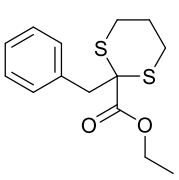
were then dried with $MgSO_4$, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (5.20 g, 27.6 mmol, 92%). **R_f** = 0.38 (10% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.14 (2 H, s, 1-C*H*$_2$), 2.17 (3 H, s, 3-C*H*$_3$), 0.92 (9 H, s, SiC(C*H*$_3$)$_3$), 0.09 (6 H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.4 (2-*C*=O), 69.7 (1-*C*H$_2$), 26.1 (3-*C*H$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 18.4 (Si*C*), -5.4 (Si(*C*H$_3$)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 2955, 2930, 2888, 2858, 1720 (C=O), 1472, 1354, 1253, 1114, 835, 777, 668, 505; **HRMS** (ESI$^+$) *m/z* found 189.1304 (M+H$^+$, $C_9H_{21}O_2Si$ requires 189.1305) and 211.1127 (M+Na$^+$, $C_9H_{20}O_2SiNa$ requires 211.1125). Spectroscopic data matched that previously reported.[162]

Ethyl 1,3-dithiane-2-carboxylate 312



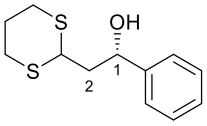
1,3-Propanedithiol (1.50 mL, 15.0 mmol, 1 equiv.), followed by ethyl diethoxyacetate **311** (2.64 g, 15.0 mmol, 1 equiv.) in chloroform (3 mL) was added, over successive 30 min periods, to a refluxing solution of boron trifluoride etherate (3.78 mL, 30 mmol, 2 equiv.) in chloroform (12 mL). The resulting solution was then heated for 30 min and was then cooled to room temperature. The reaction mixture was then quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were then washed with *sat.* aqueous sodium hydrogen carbonate solution (20 mL), brine (20 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (2.77 g, 14.4 mmol, 97%). **R_f** = 0.36 (10% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.23 (2 H, q, *J* = 7.1 Hz, CH$_3$C*H*$_2$), 4.16 (1 H, s, SC*H*S), 3.41 (2 H, ddd, *J* = 14.1, 11.4, 2.7 Hz, SC*H*$_{2A}$), 2.60 (2 H, dddd, *J* = 14.3, 5.6, 3.0, 0.8 Hz, SC*H*$_{2B}$), 2.15 (1 H, dttd, *J* = 14.1, 5.7, 2.7, 1.0 Hz, SCH$_2$C*H*$_{2A}$), 2.03 (1 H, dtt, *J* = 14.3, 11.4, 3.0 Hz, SCH$_2$C*H*$_{2B}$), 1.32 (3 H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 170.0 (*C*=O), 61.9 (CH$_3$*C*H$_2$), 40.2 (S*C*S), 26.2 (S*C*H$_2$), 25.2 (SCH$_2$*C*H$_2$), 14.2 (CH$_2$*C*H$_3$); **IR** (ATR) ν_{Max}/cm^{-1} 2979, 2932, 2902, 1722 (C=O), 1422, 1365, 1279, 1244, 1207, 1135, 1023, 913, 886, 816, 655, 534; the compound did not ionise under the ESI-HRMS conditions used. Spectroscopic data matched that previously reported.[163]

Ethyl 2-benzyl-1,3-dithiane-2-carboxylate 316



n-Butyllithium (2.27 M in hexanes; 0.28 mL, 624 µmol, 1 equiv.) was added dropwise, over the course of 10 min, to a solution of ethyl 1,3-dithiane-2-carboxylate **312** (120 mg, 624 µmol, 1 equiv.) in THF (2.5 mL) at -78 ºC. After stirring at -78 ºC for 10 min, the resulting reaction mixture was then warmed to -40 ºC and benzyl bromide (82.0 µL, 687 µmol, 1.1 equiv.) in THF (1.7 mL) was added. The resulting solution was then stirred at -40 ºC for 30 min, then warmed to room temperature and stirred for 18 h. The reaction mixture was then quenched with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (120 mg, 425 µmol, 68%). $\mathbf{R_f}$ = 0.26 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.33-7.24 (5 H, m, Ar*H*), 4.26 (2 H, q, *J* = 7.1 Hz, CH_3CH_2), 3.38 (2 H, s, $ArCH_2$), 3.23 (2 H, ddd, *J* = 13.5, 12.5, 2.6 Hz, SCH_{2A}), 2.72-2.65 (2 H, m, SCH_{2B}), 2.12 (1 H, ddt, *J* = 14.3, 4.5, 2.6 Hz, SCH_2CH_{2A}), 1.85 (1 H, ddt, *J* = 13.9, 12.5, 3.2 Hz, SCH_2CH_{2B}), 1.33 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 170.8 (*C*=O), 134.8 (*Ar*), 130.8 (*Ar*H), 128.1 (*Ar*H), 127.5 (*Ar*H), 62.2 (CH_3CH_2), 53.9 (S*C*S), 44.7 ($ArCH_2$), 28.3 (SCH_2), 24.6 (SCH_2CH_2), 14.3 (CH_2CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 3030, 2977, 2923, 1718 (C=O), 1495, 1453, 1423, 1364, 1279, 1247, 1200, 1181, 1079, 1028, 907, 857, 792, 753, 698, 586, 478, 462; **HRMS** (ESI$^+$) *m/z* found 283.0827 ($M+H^+$, $C_{14}H_{19}O_2S_2$ requires 283.0821), 305.0655 ($M+Na^+$, $C_{14}H_{18}O_2S_2Na$ requires 305.0640) and 300.1098 ($M+NH_4^+$, $C_{14}H_{22}NO_2S_2$ requires 300.1086).

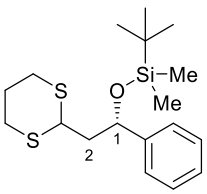
(*S*)-2-(1,3-Dithian-2-yl)-1-phenylethan-1-ol 318



n-Butyllithium (2 M in hexanes; 42.0 mL, 84.0 mmol, 1.05 equiv.) was added dropwise, over the course of 10 min, to a solution of 1,3-dithiane **317** (9.62 g, 80.0 mmol, 1 equiv.) in THF (240 mL) at 0 °C. After stirring for 30 min, (*R*)-styrene oxide (*R*)-**105** (9.60 mL, 84.0 mmol, 1.05 equiv.) was then added and the resulting solution stirred for an additional 30 min. The reaction mixture was then warmed to room temperature, stirred for 5 h, quenched with *sat.* aqueous ammonium chloride solution (100 mL) and then extracted with ethyl

acetate (3 x 100 mL). The combined organic phases were then washed with brine (100 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless viscous oil (19.0 g, 79.0 mmol, 99%). **R_f** = 0.43 (33% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.40-7.33 (4 H, m, Ar*H*), 7.31-7.27 (1 H, m, Ar*H*), 5.04-5.00 (1 H, m, 1-*H*), 4.18 (1 H, dd, *J* = 8.7, 5.8 Hz, SC*H*S), 2.93-2.82 (4 H, m, SCH_2), 2.28-2.20 (2 H, m, 2-H_A; O*H*), 2.16-2.05 (2 H, m, 2-H_B; SCH_2CH_{2A}), 1.96-1.86 (1 H, m, SCH_2CH_{2B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 143.8 (*Ar*), 128.7 (*Ar*H), 128.0 (*Ar*H), 126.0 (*Ar*H), 71.3 (1-*C*H), 44.5 (2-*C*H_2), 44.1 (*C*HS), 30.2 (SCH_{2A}), 30.0 (SCH_{2B}), 26.1 (SCH_2CH_2); **IR** (ATR) v_{Max}/cm^{-1} 3409 (OH), 3028, 2933, 2899, 2828, 1492, 1452, 1422, 1275, 1241, 1202, 1046, 1001, 909, 889, 762, 735, 700, 547; **HRMS** (ESI^+) *m/z* found 263.0542 ($M+Na^+$, $C_{12}H_{16}OS_2Na$ requires 263.0535); $[\alpha]_D^{17}$ = -13.2 (*c* 1.00, $CHCl_3$), lit.[122] (*R*)-**318**: $[\alpha]_D^{20}$ = +15.0 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[122]

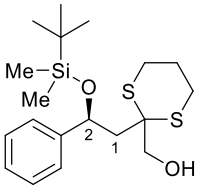
(*S*)-(2-(1,3-Dithian-2-yl)-1-phenylethoxy)(*tert*-butyl)dimethylsilane 319



TBSCl (1.13 g, 7.49 mmol, 1.2 equiv.) and imidazole (850 mg, 12.5 mmol, 2 equiv.) were added to a stirred solution of alcohol **318** (1.50 g, 6.24 mmol, 1 equiv.) in CH_2Cl_2 (15 mL), cooled to 0 °C, and was stirred for 10 min. The reaction mixture was warmed to room temperature and then stirred for 16 h. The resulting solution was then washed with *sat.* aqueous sodium hydrogen carbonate solution (25 mL), extracted with ethyl acetate (3 x 25 mL) and dried with $MgSO_4$. The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (2.14 g, 6.03 mmol, 97%). **R_f** = 0.40 (5% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.34-7.28 (4 H, m, Ar*H*), 7.26-7.22 (1 H, m, Ar*H*), 4.93 (1 H, dd, *J* = 9.0, 4.3 Hz, 1-*H*), 4.07 (1 H, dd, *J* = 9.5, 5.1 Hz, SC*H*S), 2.91-2.75 (4 H, m, SCH_2), 2.18-2.07 (2 H, m, 2-H_A; SCH_2CH_{2A}), 1.99-1.85 (2 H, m, 2-H_B; SCH_2CH_{2B}), 0.88 (9 H, s, $SiC(CH_3)_3$), 0.06 (3 H, s, $SiCH_{3A}$), -0.17 (3 H, s, $SiCH_{3B}$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 144.8 (*Ar*), 128.4 (*Ar*H), 127.5 (*Ar*H), 126.2 (*Ar*H), 71.6 (1-*C*H), 46.5 (2-*C*H_2), 44.0 (*C*HS), 30.3 (SCH_{2A}), 29.8 (SCH_{2B}), 26.2 (SCH_2CH_2), 26.0 ($SiC(CH_3)_3$), 18.3 (Si*C*), -4.4 ($SiCH_{3A}$), -4.9 ($SiCH_{3B}$); **IR** (ATR) v_{Max}/cm^{-1} 2951, 2928, 2895, 2855, 1493, 1471, 1422, 1361, 1250, 1205,

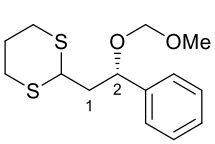
1088, 1068, 1005, 859, 834, 809, 776, 699, 670, 551; **HRMS** (ESI$^+$) *m/z* found 355.1581 (M+H$^+$, $C_{18}H_{31}OS_2Si$ requires 355.1580) and 377.1419 (M+Na$^+$, $C_{18}H_{30}OS_2SiNa$ requires 377.1400); $[\alpha]_D^{18}$ = -31.3 (*c* 1.00, $CHCl_3$), lit.[122] (*R*)-**319**: $[\alpha]_D^{20}$ = +27.0 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[122]

(*S*)-(2-(2-((*tert*-Butyldimethylsilyl)oxy)-2-phenylethyl)-1,3-dithian-2-yl)methanol 320



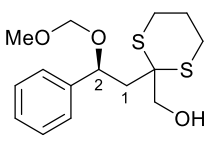
n-Butyllithium (2.27 M in hexanes; 0.75 mL, 1.69 mmol, 1.05 equiv.) was added dropwise, over the course of 10 min, to a solution of 1,3-dithiane **319** (570 mg, 1.61 mmol, 1 equiv.) in THF (5 mL) at 0 °C. After stirring for 1 h, paraformaldehyde (58.0 mg, 1.93 mmol, 1.2 equiv.) was then added and the resulting solution stirred for an additional 30 min. The reaction mixture was then warmed to room temperature, stirred for 16 h, quenched with *sat.* aqueous ammonium chloride solution (10 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic phases were then washed with brine (10 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a slowly crystallising colourless solid (107 mg, 0.277 mmol, 17%). **R$_f$** = 0.35 (15% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.33-7.18 (5 H, m, Ar*H*), 5.00 (1 H, dd, *J* = 9.0, 2.3 Hz, 2-*H*), 3.92 (1 H, dd, *J* = 12.0, 5.6 Hz, HOC*H*$_{2A}$), 3.78 (1 H, dd, *J* = 12.0, 8.7 Hz, HOC*H*$_{2B}$), 2.91-2.79 (3 H, m, SC*H*$_{2A}$; SC*H*$_{2A}$; O*H*), 2.62 (2 H, m, SC*H*$_{2B}$; SC*H*$_{2B}$), 2.41 (1 H, dd, *J* = 15.2, 9.0 Hz, 1-*H*$_A$), 2.05 (1 H, dd, *J* = 15.2, 2.3, Hz, 1-*H*$_B$), 2.01-1.94 (1 H, m, SCH_2CH_{2A}), 1.86 (1 H, dtt, *J* = 13.2, 9.7, 3.2 Hz, SCH_2CH_{2A}), 0.82 (9 H, s, SiC(C*H*$_3$)$_3$), 0.05 (3 H, s, SiC*H*$_{3A}$), -0.38 (3 H, s, SiC*H*$_{3B}$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 145.4 (*Ar*),128.5 (*Ar*H), 127.7 (*Ar*H), 126.3 (*Ar*H), 72.6 (2-*C*H), 65.3 (HO*C*H$_2$), 53.5 (S*C*S), 47.8 (1-*C*H$_2$), 26.1 (SiC(*C*H$_3$)$_3$), 25.9 (S*C*H$_2$), 25.3 (SCH$_2$*C*H$_2$), 18.1 (Si*C*), -4.1 (Si*C*H$_{3A}$), -4.5 (Si*C*H$_{3B}$); **IR** (ATR) v_{Max}/cm^{-1} 3446 (OH), 2952, 2928, 2856, 1493, 1463, 1421, 1277, 1059, 1005, 910, 882, 834, 809, 775, 732, 700, 599, 546; **HRMS** (ESI$^+$) *m/z* found 407.1491 (M+Na$^+$, $C_{19}H_{32}O_2S_2SiNa$ requires 407.1505); **mp** 28-31 °C; $[\alpha]_D^{20}$ = -37.3 (*c* 1.30, $CHCl_3$).

(*S*)-2-(2-(Methoxymethoxy)-2-phenylethyl)-1,3-dithiane 322



N,*N*-Diisopropylethylamie (3.80 mL, 21.8 mmol, 1.5 equiv.) and chloromethyl methyl ether (3.30 mL, 43.7 mmol, 3 equiv.) were successively added to a solution of alcohol **318** (3.50 g, 14.6 mmol, 1 equiv.) in CH_2Cl_2 (100 mL).The reaction mixture was then heated to reflux and stirred for 16 h. The resulting solution was then cooled to room temperature, quenched with *sat.* aqueous ammonium chloride solution (50 mL) and then extracted with ethyl acetate (3 x 100 mL). The combined organic phases were then dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (3.82 g, 13.4 mmol, 92%). **R_f** = 0.23 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.37-7.32 (4 H, m, Ar*H*), 7.32-7.27 (1 H, m, Ar*H*), 4.90 (1 H, dd, *J* = 9.0, 5.0 Hz, 2-*H*), 4.54 (1 H, d, *J* = 6.7 Hz, OCH_{2A}O), 4.52 (1 H, d, *J* = 6.7 Hz, OCH_{2B}O), 4.10 (1 H, dd, *J* = 9.0, 5.7 Hz, SC*H*S), 3.37 (3 H, s, OCH_3), 2.90-2.77 (4 H, m, SCH_2), 2.30 (1 H, ddd, *J* = 14.6, 9.0, 5.7 Hz, 1-H_A), 2.14-2.02 (2 H, m, 1-H_B; SCH_2CH_{2A}), 1.95-1.85 (1 H, m, SCH_2CH_{2B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 141.2 (*Ar*), 128.7 (*Ar*H), 128.1 (*Ar*H), 127.1 (*Ar*H), 94.4 (OCH_2O), 74.5 (2-*C*H), 56.0 (OCH_3), 43.70 (1-CH_2), 43.65 (S*C*HS), 30.1 (SCH_{2A}), 29.8 (SCH_{2B}), 26.2 (SCH_2CH_2); **IR** (ATR) ν_{Max}/cm^{-1} 3029, 2937, 2892, 2821, 1493, 1454, 1422, 1276, 1217, 1145, 1098, 1020, 983, 909, 755, 701, 666, 553; **HRMS** (ESI$^+$) *m/z* found 307.0806 (M+Na$^+$, $C_{14}H_{20}O_2S_2SiNa$ requires 307.0797) and 302.1256 (M+NH_4^+, $C_{14}H_{24}NO_2S_2$ requires 302.1243); $[\alpha]_D^{20}$ = -74.0 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[164]

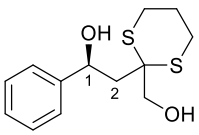
(*S*)-(2-(2-(Methoxymethoxy)-2-phenylethyl)-1,3-dithian-2-yl)methanol 323



n-Butyllithium (2.44 M in hexanes; 27.5 mL, 67.4 mmol, 1.05 equiv.) was added dropwise, over the course of 10 min, to a solution of 1,3-dithiane **322** (18.3 g, 64.2 mmol, 1 equiv.) in THF (225 mL) at 0 °C. After stirring for 1 h, paraformaldehyde (2.31 g, 77.0 mmol, 1.2 equiv.) was then added and the resulting solution stirred for an additional 30 min. The reaction mixture was then warmed to room temperature, stirred for 16 h, quenched with *sat.* aqueous ammonium chloride solution (500 mL) and then extracted with ethyl acetate (3 x 500 mL). The combined organic phases were then washed with brine (500 mL), dried with

$MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a viscous colourless oil (14.7 g, 46.8 mmol, 73%). **R_f** = 0.27 (30% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.37-7.26 (5 H, m, Ar*H*), 4.99 (1 H, dd, *J* = 9.2, 2.2 Hz, 2-*H*), 4.54 (1 H, d, *J* = 6.6 Hz, OCH_{2A}O), 4.48 (1 H, d, *J* = 6.6 Hz, OCH_{2B}O), 4.00 (1 H, dd, *J* = 12.0, 6.5 Hz, HOCH_{2A}), 3.87 (1 H, dd, *J* = 12.0, 7.9 Hz, HOCH_{2B}), 3.39 (3 H, s, OCH_3), 3.06 (1 H, dd, *J* = 7.9, 6.5 Hz, O*H*), 2.94-2.86 (2 H, m, SCH_{2A}; SCH_{2A}), 2.71-2.63 (2 H, m, SCH_{2B}; SCH_{2B}), 2.48 (1 H, dd, *J* = 15.4, 9.2 Hz, 1-H_A), 2.16 (1 H, dd, *J* = 15.4, 2.2 Hz, 1-H_B), 2.09-2.01 (1 H, m, SCH_2CH_{2A}), 1.91 (1 H, dtt, *J* = 13.5, 10.2, 3.2 Hz, SCH_2CH_{2B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 141.8 (*Ar*), 128.8 (*Ar*H), 128.1 (*Ar*H), 126.9 (*Ar*H), 94.8 (OCH_2O), 75.0 (2-*C*H), 65.2 ($HOCH_2$), 56.9 (OCH_3), 53.6 (S*C*S), 45.9 (1-CH_2), 26.2 (SCH_{2A}), 25.9 (SCH_{2B}), 25.2 (SCH_2CH_2); **IR** (ATR) v_{Max}/cm^{-1} 3462 (OH), 3029, 2897, 2824, 1493, 1453, 1420, 1374, 1277, 1241, 1210, 1150, 1097, 1015, 910, 763, 702, 540; **HRMS** (ESI^+) *m/z* found 315.1086 ($M+H^+$, $C_{15}H_{23}O_3S_2$ requires 315.1083), 337.0915 ($M+Na^+$, $C_{15}H_{22}O_3S_2Na$ requires 337.0903) and 332.1359 ($M+NH_4^+$, $C_{15}H_{26}NO_3S_2$ requires 332.1349); $[\alpha]_D^{19}$ = -70.0 (*c* 1.00, $CHCl_3$).

(*S*)-2-(2-(Hydroxymethyl)-1,3-dithian-2-yl)-1-phenylethan-1-ol 321

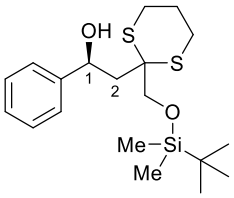


Method I: An aqueous solution of hydrochloric acid (2 M; 1.45 mL, 2.86 mmol, 10 equiv.) was added to a solution of silyl ether **320** (110 mg, 0.286 mmol, 1 equiv.) in THF (5 mL). The resulting reaction mixture was stirred at room temperature for 16 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (10 mL), brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the *title compound* as a colourless solid (76.8 mg, 0.284 mmol, 99%).

Method II: An aqueous solution of hydrochloric acid (6 M; 42.5 mL, 254 mmol, 20 equiv.) was added to a solution of methoxymethyl ether **323** (4.00 g, 12.7 mmol, 1 equiv.) in methanol (250 mL). The resulting reaction mixture was then heated to 50 °C and stirred for 18 h. Water (100 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 250 mL). The combined organic phases were then washed with brine (250 mL), dried with $MgSO_4$, concentrated *in*

vacuo and the crude product was purified by column chromatography, using the elution gradient 40 to 60% ethyl acetate in petroleum ether, affording the *title compound* as a colourless solid (2.99 g, 11.0 mmol, 87%). **R_f** = 0.24 (40% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.40-7.31 (4 H, m, Ar*H*), 7.29-7.25 (1 H, m, Ar*H*), 5.14 (1 H, dd, *J* = 8.0, 3.4 Hz, 1-*H*), 4.00 (1 H, d, *J* = 12.0 Hz, HOCH_{2A}), 3.87 (1 H, d, *J* = 12.0 Hz, HOCH_{2B}), 3.11 (2 H, br s, O*H*; O*H*), 2.99-2.88 (2 H, m, SCH_{2A}; SCH_{2A}), 2.73-2.65 (2 H, m, SCH_{2B}; SCH_{2B}), 2.28-2.19 (2 H, m, 2-H_2), 2.10 (1 H, dtt, *J* = 14.4, 5.9, 2.9 Hz, SCH_2CH_{2A}), 1.92 (1 H, dtt, *J* = 14.4, 11.0, 3.2 Hz, SCH_2CH_{2B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 144.4 (*Ar*), 128.7 (*Ar*H), 127.8 (*Ar*H), 125.8 (*Ar*H), 70.3 (1-*C*H), 65.1 ($HOCH_2$), 53.4 (S*C*S), 49.1 (2-*C*H_2), 26.3 (SCH_{2A}), 25.8 (SCH_{2B}), 25.1 (SCH_2CH_2); **IR** (ATR) ν_{Max}/cm^{-1} 3299 (OH), 2948, 2909, 2851, 1491, 1454, 1417, 1357, 1335, 1316, 1274, 1237, 1039, 1028, 1005, 904, 874, 834, 764, 703, 681, 650, 602, 543, 482; **HRMS** (ESI^+) *m/z* found 293.0642 ($M+Na^+$, $C_{13}H_{18}O_2S_2Na$ requires 293.00640); **mp** 139-141 °C; $[\alpha]_D^{18}$ = - 40.8 (*c* 1.00, $CHCl_3$).

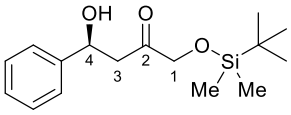
(*S*)-2-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1,3-dithian-2-yl)-1-phenylethan-1-ol 324



TBSCl (613 mg, 4.07 mmol, 1.1 equiv.) was added to a solution of diol **321** (1.00 g, 3.70 mmol, 1 equiv.) and imidazole (629 mg, 9.25 mmol, 2.5 equiv.) in CH_2Cl_2 (20 mL), cooled to 0 °C, and was stirred for 30 min. The reaction mixture was warmed to room temperature and then stirred for 18 h. The resulting solution was then washed with *sat.* aqueous sodium hydrogen carbonate solution (15 mL), extracted with ethyl acetate (3 x 15 mL) and dried with $MgSO_4$. The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (1.36 g, 3.53 mmol, 95%). **R_f** = 0.20 (5% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.43-7.38 (2 H, m, Ar*H*), 7.36-7.31 (2 H, m, Ar*H*), 7.28-7.22 (1 H, m, Ar*H*), 5.12 (1 H, dd, *J* = 9.5, 1.9 Hz, 1-*H*), 4.41 (1 H, br s, O*H*), 4.05 (1 H, d, *J* = 10.7 Hz, SiOCH_{2A}), 3.99 (1 H, d, *J* = 10.7 Hz, SiOCH_{2B}), 2.87-2.77 (4 H, m, SCH_2), 2.39 (1 H, dd, *J* = 15.2, 1.9 Hz, 2-H_A), 2.30 (1 H, dd, *J* = 15.2, 9.5 Hz, 2-H_B), 2.06-1.95 (2 H, m, SCH_2CH_2), 0.96 (9 H, s, $SiC(CH_3)_3$), 0.18 (6 H, br s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 144.9 (*Ar*), 128.5 (*Ar*H), 127.2

(*Ar*H), 125.8 (*Ar*H), 70.6 (1-*C*H), 68.4 (SiO*C*H_2), 53.3 (S*C*S), 49.0 (2-*C*H_2), 26.3 (S*C*H_{2A}), 25.9 (SiC(*C*H_3)$_3$), 25.8 (S*C*H_{2B}), 25.3 (SCH_2*C*H_2), 18.5 (Si*C*), -5.21 (Si*C*H_{3A}), -5.24 (Si*C*H_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3423 (OH), 2951, 2928, 2898, 2855, 1494, 1463, 1422, 1252, 1133, 1062, 1005, 908, 834, 777, 699, 537; **HRMS** (ESI$^+$) *m/z* found 385.1678 (M+H$^+$, $C_{19}H_{33}O_2S_2Si$ requires 385.1686) and 407.1503 (M+Na$^+$, $C_{19}H_{32}O_2S_2SiNa$ requires 407.1505); $[\alpha]_D^{18}$ = -13.4 (*c* 1.00, $CHCl_3$).

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-phenylbutan-2-one 264



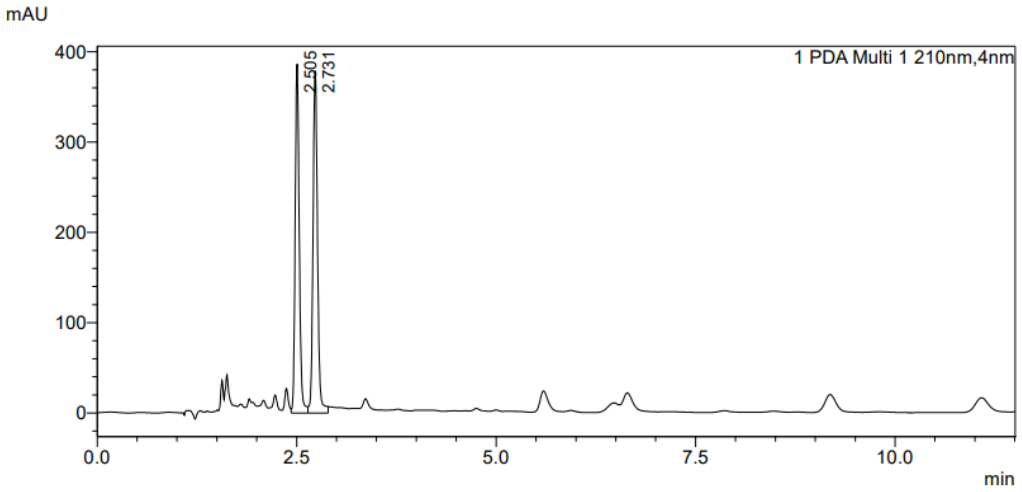
Methyl iodide (1.45 mL, 23.4 mmol, 9 equiv.) was added to a solution of alcohol **324** (1.00 g, 2.60 mmol, 1 equiv.) and calcium carbonate (2.60 g, 26.0 mmol, 10 equiv.) in acetonitrile:water (9:1; 26 mL), and was heated at 40 °C for 24 h. The resulting solution was then filtered through Celite® 545, extracted with ethyl acetate (3 x 50 mL), washed with brine (50 mL) and dried with $MgSO_4$. The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (482 mg, 1.64 mmol, 63%, 99% *ee*). **R$_f$** = 0.22 (15% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.38-7.27 (5 H, m, Ar*H*), 5.18 (1 H, dd, *J* = 8.8, 3.7 Hz, 4-*H*), 4.19 (2 H, br s, 1-H_2), 3.28 (1 H, br s, O*H*), 2.95 (1 H, dd, *J* = 17.2, 8.8 Hz, 3-H_A), 2.88 (1 H, dd, *J* = 17.2, 3.7 Hz, 3-H_B), 0.91 (9 H, s, SiC(CH_3)$_3$), 0.08 (6 H, br s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 211.1 (2-*C*=O), 143.0 (*Ar*), 128.7 (*Ar*H), 127.8 (*Ar*H), 125.8 (*Ar*H), 70.0 (1-*C*H_2), 69.8 (4-*C*H), 47.2 (3-*C*H_2), 25.9 (SiC(*C*H_3)$_3$), 18.4 (Si*C*), -5.37 (Si*C*H_3), -5.39 (Si*C*H_3); **IR** (ATR) v_{Max}/cm^{-1} 3452 (OH), 2953, 2929, 2887, 2857, 1720 (C=O), 1495, 1471, 1361, 1253, 1155, 1100, 1067, 835, 777, 699, 536; **HRMS** (ESI$^+$) *m/z* found 317.1547 (M+Na$^+$, $C_{16}H_{26}O_3SiNa$ requires 317.1543) and 312.1995 (M+NH_4^+, $C_{16}H_{30}NO_3Si$ requires 312.1989); $[\alpha]_D^{17}$ = -54.8 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[111]

(±)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-one (±)-**264** was prepared following a known procedure.[95]

NOTE: The product was observed to partially decompose, *via* a suspected dehydration process, when stored in the dark at room temperature for periods

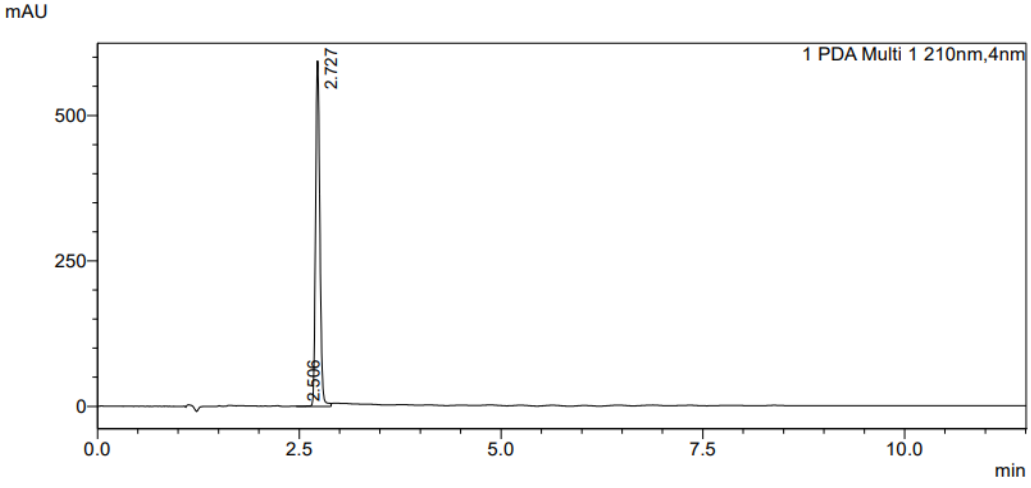
exceeding four-months. Acidic conditions were observed to rapidly increase the rate of decomposition.

(±)-**264** (*rac*) Chiral HPLC spectrum (Lux i-Amylose-3, 90:10 MeCN:MeOH, 1 mL/min, 210 nm, 40 °C).



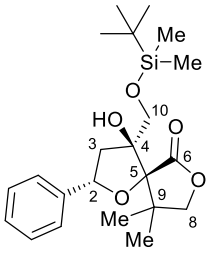
Peak	Retention Time / min	Relative Area	Area %
1	2.505	1391885	48.393
2	2.731	1484325	51.607

(*S*)-**264** (99.9% *ee*) Chiral HPLC spectrum (Lux i-Amylose-3, 90:10 MeCN:MeOH, 1 mL/min, 210 nm, 40 °C).

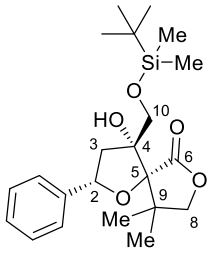


Peak	Retention Time / min	Relative Area	Area %
1	2.506	2191	0.100
2	2.727	2197291	99.900

(2*S*,4*S*,5*S*)- and (2*S*,4*R*,5*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9,9-dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonan-6-one 273a and 273d



cis,*trans*-**273a**

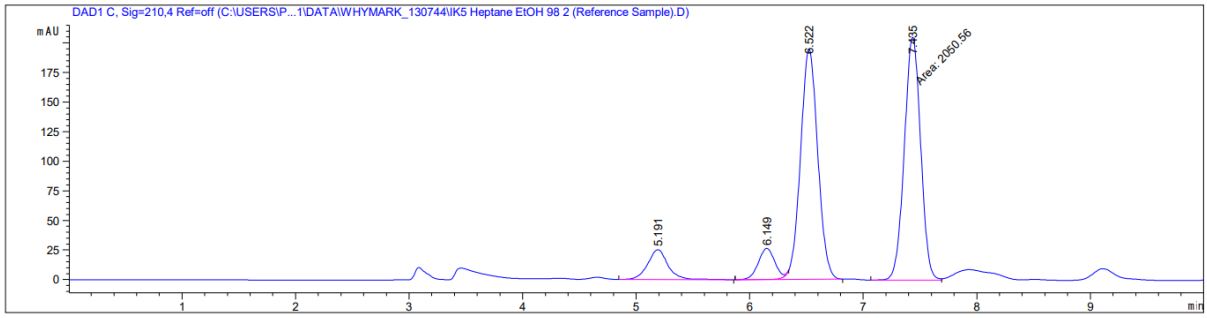


cis,*cis*-**273d**

A solution containing α-diazolactone **212** (56.1 mg, 0.40 mmol, 2 equiv.) in CH_2Cl_2 (2 mL) was added, over a 30 min period, to a solution of β-hydroxyketone (*S*)-**264** (58.9 mg, 0.20 mmol, 1 equiv.) and copper(I) acetate (1.2 mg, 10.0 μmol, 5 mol%) in CH_2Cl_2 (1 mL), cooled to 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for an additional 2 h before being heated to reflux for 16 h. The resulting reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compounds*, an inseparable mixture of diastereomers **273a** (**A**) and **273d** (**B**), as a colourless solid (ratio **273a**:**273d** 85:15, 64.2 mg, 0.158 mmol, 79%). The stereochemistry was inferred from key NOESY NMR correlations between Ar*H* and 10-H_2 (**A**); 2-*H* and 10-H_2 (**B**). $\mathbf{R_f}$ = 0.24 (10% ethyl acetate in pentane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H ppm 7.38-7.24 (5 H, m, Ar*H*, **A**; 5 H, m, Ar*H*, **B**), 5.24 (1 H, dd, *J* = 9.9, 5.4 Hz, 2-*H*, **A**), 5.10 (1 H, dd, *J* = 10.9, 6.2 Hz, 2-*H*, **B**), 4.18 (1 H, d, *J* = 7.9 Hz, 8-H_A, **A**), 4.15 (1 H, d, *J* = 8.0 Hz, 8-H_A, **B**), 3.92 (1 H, dd, *J* = 6.2, 1.0 Hz, 10-H_A, **B**), 3.90 (1 H, dd, *J* = 10.2, 1.6 Hz, 10-H_A, **A**), 3.81 (1 H, d, *J* = 7.9 Hz, 8-H_B, **A**), 3.77 (1 H, d, *J* = 8.0 Hz, 8-H_B, **B**), 3.57 (1 H, d, *J* = 10.2 Hz, 10-H_B, **A**), 3.18 (1 H, br s, O*H*, **B**), 3.08 (1 H, br s, O*H*, **A**), 2.89 (1 H, ddd, *J* = 13.1, 9.9, 1.6 Hz, 3-H_A, **A**), 2.87 (1 H, dd, *J* = 12.3, 6.2 Hz, 3-H_A, **B**), 2.70 (1 H, ddd, *J* = 12.3, 10.9, 1.0 Hz, 3-H_B, **B**), 2.53 (1 H, dd, *J* = 13.1, 5.4 Hz, 3-H_B, **A**), 1.33 (3 H, s, CH_{3A}, **A**), 1.30 (3 H, s, CH_{3A}, **B**), 1.24 (3 H, s, CH_{3B}, **A**), 1.18 (3 H, s, CH_{3B}, **B**), 0.96 (9 H, s, SiC(CH_3)$_3$, **B**), 0.84 (9 H, s, SiC(CH_3)$_3$, **A**), 0.16 (3 H, s, SiCH_{3A}, **B**), 0.07 (3 H, s, SiCH_{3B}, **B**), -0.01 (3 H, s, SiCH_{3A}, **A**), -0.05 (3 H, s, SiCH_{3B}, **A**), the signal due to 10-H_B, **B** was not observed; **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 177.2 (6-*C*=O, **B**), 174.9 (6-*C*=O, **A**), 142.3 (*Ar*, **A**), 141.6 (*Ar*, **B**), 128.7 (*Ar*H, **B**), 128.6 (*Ar*H, **A**), 128.0 (*Ar*H, **B**), 127.6 (*Ar*H, **A**), 126.3 *Ar*H, **B**), 125.5 (*Ar*H, **A**), 87.6 (5-*C*, **A**), 86.9 (5-*C*, **B**), 82.0 (4-*C*, **B**), 81.2 (4-*C*, **A**), 79.7 (8-*C*H_2, **B**), 78.91 (8-*C*H_2, **A**), 78.88 (2-*C*H, **B**), 76.6 (2-*C*H, **A**), 65.4 (10-*C*H_2, **A**), 64.3 (10-*C*H_2, **B**), 43.7 (3-*C*H_2, **B**), 43.1 (3-*C*H_2, **A**), 41.5 (9-*C*, **B**), 41.4 (9-*C*, **A**), 26.1 (SiC(*C*H_3)$_3$, **B**), 26.0 (SiC(*C*H_3)$_3$, **A**), 21.7 (*C*H_{3A}, **A**), 21.6 (*C*H_{3A}, **B**), 18.6 (Si*C*, **B**), 18.5 (Si*C*, **A**), 18.3 (*C*H_{3B}, **A**), 17.8 (*C*H_{3B}, **B**),

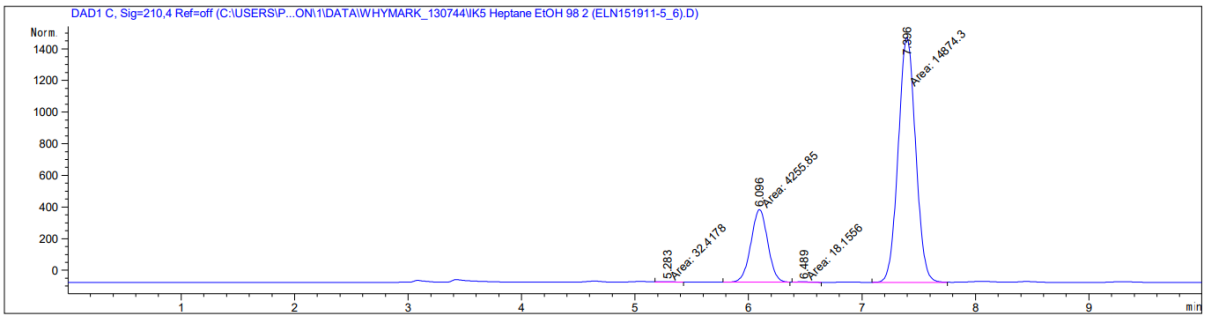
-5.1 (Si*C*H$_{3A}$, **B**), -5.27 (Si*C*H$_{3B}$, **B**), -5.30 (Si*C*H$_{3A}$, **A**), -5.5 (Si*C*H$_{3B}$, **A**); **IR** (ATR) ν_{Max}/cm^{-1} 3499 (OH), 3064, 2994, 2945, 2927, 2885, 2856, 1761 (C=O), 1606, 1494, 1462, 1396, 1370, 1307, 1252, 1222, 1171, 1093, 1067, 1016, 997, 951, 877, 833, 770, 751, 700, 514; **HRMS** (ESI$^+$) *m/z* found 407.2251 (M+H$^+$, $C_{22}H_{35}O_5Si$ requires 407.2248), 429.2070 (M+Na$^+$, $C_{22}H_{34}O_5SiNa$ requires 429.2070) and 424.2512 (M+NH$_4^+$, $C_{22}H_{38}NO_5Si$ requires 424.2514); **mp** 83-84 °C; $[\alpha]_D^{23}$ = -57.5 (*c* 1.00, $CHCl_3$).

(±)-**273a** and **273d** (*rac*, 87:13 *dr*) Chiral HPLC spectrum (Chiralpak IK, 98:2 *n*-heptane:EtOH, 1 mL/min, 210 nm, 25 °C).



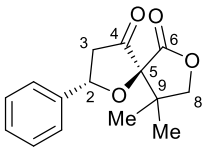
Peak	Retention Time / min	Relative Area	Area %
1	5.191	312.38693	6.6673
2	6.149	263.62708	5.6265
3	6.522	2058.79810	43.9410
4	7.435	2050.56030	43.7652

273a and **273d** (99% *ee*, 85:15 *dr*) Chiral HPLC spectrum (Chiralpak IK, 98:2 *n*-heptane:EtOH, 1 mL/min, 210 nm, 25 °C).

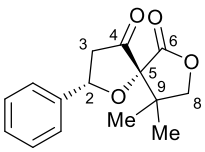


Peak	Retention Time / min	Relative Area	Area %
1	5.283	32.41782	0.1690
2	6.096	4255.85254	22.1882
3	6.489	18.15562	0.0947
4	7.396	1.48743e4	77.5481

(2*S*,5*S*)- and (2*S*,5*R*)-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 272a and 272b



trans-**272a**



cis-**272b**

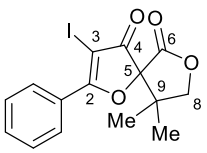
An aqueous solution of hydrochloric acid (2 M; 0.70 mL, 1.38 mmol, 5 equiv.) was added to a solution of silyl ethers **273a** and **273d** (ratio **273a**:**273d** 84:16, 112 mg, 0.275 mmol, 1 equiv.) in THF (2.5 mL). The resulting reaction mixture was stirred at room temperature for 16 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (5 mL), brine (5 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the crude diol which was then used in the next step without further purification. The resulting crude diol was then dissolved within a THF (1.5 mL) and water (1.5 mL) mixture. Sodium periodate (162 mg, 0.757 mmol, 2.75 equiv.) was then added and the resulting solution was stirred at room temperature for 18 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (5 mL), brine (5 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo*

and the crude product was purified by column chromatography affording the separated *title compounds.*

(2*S*,5*S*)-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 272a as a colourless oil (58.1 mg, 0.223 mmol, 81%). **R_f** = 0.50 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.44-7.34 (5 H, m, Ar*H*), 5.75 (1 H, dd, *J* = 11.0, 5.8 Hz, 2-*H*), 4.49 (1 H, d, *J* = 8.5 Hz, 8-H_A), 4.02 (1 H, d, *J* = 8.5 Hz, 8-H_B), 2.99 (1 H, dd, *J* = 17.9, 5.8 Hz, 3-H_A), 2.54 (1 H, dd, *J* = 17.9, 11.0 Hz, 3-H_B), 1.27 (3 H, s, CH_{3A}), 1.14 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.7 (4-*C*=O), 172.9 (6-*C*=O), 139.6 (*Ar*), 128.9 (*Ar*H), 128.8 (*Ar*H), 126.0 (*Ar*H), 89.8 (5-*C*), 77.2 (2-*C*H), 76.3 (8-*C*H_2), 45.7 (3-*C*H_2), 42.9 (9-*C*), 22.8 (*C*H_{3A}), 18.2 (*C*H_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3036, 2971, 2914, 1785 (C=O), 1749 (C=O), 1497, 1470, 1368, 1256, 1223, 1171, 1107, 1041, 1006, 991, 930, 769, 739, 699, 601, 485; **HRMS** (ESI^+) *m/z* found 261.1129 ($M+H^+$, $C_{15}H_{17}O_4$ requires 261.1121), 283.0948 ($M+Na^+$, $C_{15}H_{16}O_4Na$ requires 283.0941) and 278.1397 ($M+NH_4^+$, $C_{15}H_{20}NO_4$ requires 278.1387); $[\alpha]_D^{20}$ = -144 (*c* 1.00, $CHCl_3$).

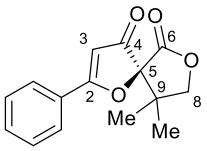
(2*S*,5*R*)-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 272b as a colourless oil (7.2 mg, 27.7 µmol, 10%). **R_f** = 0.31 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.58 (2 H, d, *J* = 7.5 Hz, Ar*H*), 7.45-7.40 (2 H, m, Ar*H*), 7.38-7.34 (1 H, m, Ar*H*), 5.39 (1 H, dd, *J* = 10.0, 6.5 Hz, 2-*H*), 4.42 (1 H, d, *J* = 8.5 Hz, 8-H_A), 4.00 (1 H, d, *J* = 8.5 Hz, 8-H_B), 2.99 (1 H, dd, *J* = 18.6, 6.5 Hz, 3-H_A), 2.75 (1 H, dd, *J* = 18.6, 10.0 Hz, 3-H_B), 1.25 (3 H, s, CH_{3A}), 1.23 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.1 (4-*C*=O), 171.5 (6-*C*=O), 140.1 (*Ar*), 129.0 (*Ar*H), 128.9 (*Ar*H), 126.4 (*Ar*H), 90.0 (5-*C*), 78.9 (2-*C*H), 75.7 (8-*C*H_2), 45.6 (3-*C*H_2), 43.3 (9-*C)*, 22.9 (*C*H_{3A}), 19.6 (*C*H_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3035, 2971, 2914, 1782 (C=O), 1747 (C=O), 1497, 1469, 1398, 1368, 1313, 1266, 1217, 1161, 1112, 1060, 1002, 941, 896, 840, 767, 733, 699, 581, 545, 500; **HRMS** (ESI^+) *m/z* found 261.1124 ($M+H^+$, $C_{15}H_{17}O_4$ requires 261.1121), 283.0945 ($M+Na^+$, $C_{15}H_{16}O_4Na$ requires 283.0941) and 278.1387 ($M+NH_4^+$, $C_{15}H_{20}NO_4$ requires 278.1387); $[\alpha]_D^{20}$ = +12.0 (*c* 1.00, $CHCl_3$).

(±)-3-Iodo-9,9-dimethyl-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 304



A 1 M solution of iodic acid (44.0 mg, 0.25 mmol, 2.5 equiv.) in DMSO (0.25 mL) was heated to 80 °C and was stirred for 1 h, with light excluded from the vessel. The resulting solution was cooled to room temperature, diluted with the co-solvent cyclohexene (25 µL) and added to spirolactone (±)-**272a** (26.0 mg, 0.10 mmol, 1 equiv.). The resulting reaction mixture was then further diluted with DMSO (100 µL), heated to 65 °C and stirred for 18 h, with light excluded from the vessel. The reaction solution was cooled to room temperature and aqueous *sat.* sodium hydrogen carbonate solution (5 mL) was then added to the reaction mixture. The resulting solution was then extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with aqueous *sat.* sodium hydrogen carbonate solution (5 mL), water (5 mL), brine (5 mL) and dried with $MgSO_4$. The dried organic phase was then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a pale-yellow solid (21.3 mg, 0.055 mmol, 55%). $\mathbf{R_f}$ = 0.28 (35% diethyl ether in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.28 (2 H, d, *J* = 7.7 Hz, Ar*H*), 7.67-7.62 (1 H, m, Ar*H*), 7.58-7.53 (2 H, m, Ar*H*), 4.75 (1 H, d, *J* = 8.5 Hz, 8-H_A), 4.12 (1 H, d, *J* = 8.5 Hz, 8-H_B), 1.40 (3 H, s, CH_{3A}), 1.16 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 194.6 (4-*C*=O), 182.9 (6-*C*=O), 168.1 (2-*C*), 133.8 (*Ar*H), 129.2 (*Ar*H), 128.9 (*Ar*H), 128.3 (*Ar*), 93.3 (5-*C*), 76.1 (8-CH_2), 65.1 (3-*C*), 44.2 (9-*C*), 22.9 (CH_{3A}), 18.2 (CH_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3065, 2982, 2965, 2921, 2853, 1794 (C=O), 1707 (C=O), 1601, 1584, 1559, 1488, 1469, 1446, 1365, 1332, 1303, 1284, 1254, 1223, 1171, 1117, 1093, 1044, 994, 908, 851, 776, 718, 690, 651, 595, 563, 520, 460; **HRMS** (ESI$^+$) *m/z* found 384.9948 (M+H$^+$, $C_{15}H_{14}O_4I$ requires 384.9931), 406.9760 (M+Na$^+$, $C_{15}H_{13}O_4INa$ requires 406.9751) and 402.0197 (M+NH_4^+, $C_{15}H_{18}NO_4I$ requires 402.0197); **mp** 107-109 °C; structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

(*S*)-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 271



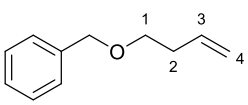
Method I: LiHMDS (1 M in THF; 270 µL, 0.27 mmol, 2 equiv.) was added dropwise to a solution of spirolactone **272a** (35.3 mg, 0.136 mmol, 1 equiv.) in THF (1 mL), cooled to 0 °C, and was stirred for 45 min. TESCl (45.5 µL, 0.27 mmol, 2 equiv.) was then added and the resulting solution was stirred for 45 min at 0 °C, then warmed to room temperature and stirred for 1 h. DDQ (61.6 mg, 0.27 mmol, 2 equiv.) was then added to the reaction mixture and the solution was stirred for 20 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (30 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic phases were washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless solid (28.7 mg, 0.111 mmol, 82%).

Method II: Phenyllithium (1.9 M in dibutyl ether; 95.0 µL, 0.18 mmol, 1.2 equiv.) was added dropwise to a solution of enone (±)-**326** (27.3 mg, 0.15 mmol, 1 equiv.) in THF (1.5 mL), cooled to -78 °C, and was stirred for 45 min. TESCl (50.0 µL, 0.30 mmol, 2 equiv.) was then added and the resulting solution was stirred for 30 min at -78 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h. DDQ (102 mg, 0.45 mmol, 2 equiv.) was then added to the reaction mixture and the solution was stirred for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (30 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic phases were washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the racemic *title compound* as a colourless solid (32.6 mg, 0.126 mmol, 84%).

R_f = 0.20 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.90-7.83 (2 H, m, Ar*H*), 7.64-7.59 (1 H, m, Ar*H*), 7.55-7.50 (2 H, m, Ar*H*), 6.01 (1 H, s, 3-*H*), 4.73 (1 H, d, *J* = 8.4 Hz, 8-H_A), 4.09 (1 H, d, *J* = 8.4 Hz, 8-H_B), 1.40 (3 H, s, CH_{3A}), 1.19 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 197.3 (4-*C*=O), 187.5 (2-*C*), 168.8 (6-*C*=O), 133.7 (*Ar*H), 129.2 (*Ar*H), 127.9 (*Ar*), 127.6 (*Ar*H), 100.4 (3-*C*H),

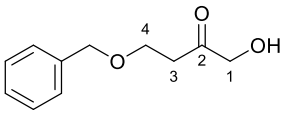
93.3 (5-*C*), 76.0 (8-*C*H_2), 43.8 (9-*C*), 23.4 (*C*H_{3A}), 18.2 (*C*H_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3112, 2972, 2916, 1792 (C=O), 1692, (C=O), 1605, 1592, 1568, 1491, 1469, 1450, 1374, 1347, 1258, 1167, 1098, 1042, 1001, 888, 772, 687, 650, 608, 574, 486, 452; **HRMS** (ESI$^+$) *m/z* found 259.0971 (M+H$^+$, $C_{15}H_{15}O_4$ requires 259.0965), 281.0792 (M+Na$^+$, $C_{15}H_{14}O_4Na$ requires 281.0784) and 276.1230 (M+NH_4^+, $C_{15}H_{18}NO_4$ requires 276.1230); **mp** 66-68 °C; $[\alpha]_D^{20}$ = -224 (*c* 1.00, $CHCl_3$); structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

((But-3-en-1-yloxy)methyl)benzene 331



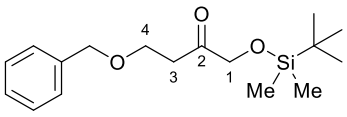
A solution of 3-buten1-ol **330** (11.7 g, 162 mmol, 1.08 equiv.), triethylamine (1.30 mL, 9.08 mmol, 0.06 equiv.) and sodium hydroxide (8.22 g, 206 mmol, 1.37 equiv.) in hexane (100 mL) was heated for 30 min at 50 °C. A solution of benzyl bromide (25.7 g, 150 mmol, 1 equiv.) in hexane (20 mL) was then added to the resulting reaction mixture over a 10 min period. The resulting solution was then heated to reflux and stirred for 3 h. After cooling, water (100 mL) was added, and the solution was extracted with diethyl ether (3 x 100 mL). The combined organic phases were then dried with $MgSO_4$, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (23.7 g, 146 mmol, 97%). $\mathbf{R_f}$ = 0.58 (5% diethyl ether in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.37-7.27 (5 H, m, Ar*H*), 5.85 (1 H, ddt, *J* = 17.0, 10.2, 6.8 Hz, C*H*=CH_2), 5.14-5.03 (2 H, m, CH=CH_2), 4.53 (2 H, s, ArCH_2), 3.54 (2 H, t, *J* = 6.8 Hz, 1-H_2), 2.39 (2 H, dt, *J* = 6.8, 6.8 Hz, 2-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 138.6 (*Ar*), 135.4 (3-*C*H), 128.5 (*Ar*H), 127.8 (*Ar*H), 127.7 (*Ar*H), 116.5 (4-*C*H_2), 73.1 (Ar*C*H_2), 69.8 (1-*C*H_2), 34.4 (2-*C*H_2); **IR** (ATR) v_{Max}/cm^{-1} 3066, 3030, 2979, 2855, 2790, 1641, 1495, 1454, 1361, 1270, 1203, 1097, 1028, 993, 912, 734, 696, 606, 459; the compound did not ionise under the ESI-HRMS conditions used. Spectroscopic data matched that previously reported.[165]

4-(Benzyloxy)-1-hydroxybutan-2-one 332



A solution of potassium permanganate (537 mg, 3.40 mmol, 1.62 equiv.) in acetone (6.4 mL) and water (2.1 mL) was added dropwise, over the course of a 10 min period, to a solution of ((but-3-en-1-yloxy)methyl)benzene **331** (441 mg, 2.10 mmol, 1 equiv.) in acetone (17 mL), water (3.8 mL) and acetic acid (0.8 mL). The resulting reaction mixture was stirred at room temperature for 2 h. The crude mixture was then filtered through a pad of Celite® 545 and washed with hexane (5 x 20 mL). The filtrate was concentrated *in vacuo*, diluted with diethyl ether (50 mL) and washed with saturated aqueous sodium hydrogen carbonate solution until pH = 8. The organic layer was then washed with brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a colourless oil (237 mg, 1.22 mmol, 58%). **R_f** = 0.30 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.37-7.27 (5 H, m, Ar*H*), 4.51 (2 H, s, ArCH_2), 4.29 (2 H, s, 1-H_2), 3.77 (2 H, t, *J* = 6.1 Hz, 4-H_2), 3.13 (1 H, br s, O*H*), 2.69 (2 H, t, *J* = 6.1 Hz, 3-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 208.6 (2-*C*=O), 137.8 (*Ar*), 128.6 (*Ar*H), 128.0 (*Ar*H), 127.8 (*Ar*H), 73.5 (Ar*C*H_2), 69.0 (1-*C*H_2), 65.1 (4-*C*H_2), 39.2 (3-*C*H_2); **IR** (ATR) ν_{Max}/cm^{-1} 3421 (OH), 3063, 3030, 2868, 1718 (C=O), 1495, 1453, 1364, 1274, 1205, 1075, 1002, 738, 698, 606, 460; **HRMS** (ESI$^+$) *m/z* found 217.0850 (M+Na$^+$, $C_{11}H_{14}O_3Na$ requires 217.0835) and 212.1276 (M+NH_4^+, $C_{11}H_{18}NO_3$ requires 212.1281). Spectroscopic data matched that previously reported.[166]

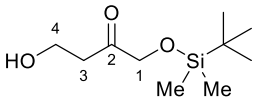
4-(Benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)butan-2-one 333



TBSCl (7.81 g, 51.8 mmol, 1.5 equiv.) and imidazole (5.17 g, 76.0 mmol, 2.2 equiv.) were added to a stirred solution of 4-(benzyloxy)-1-hydroxybutan-2-one **332** (6.71 g, 34.5 mmol, 1 equiv.) in CH_2Cl_2 (140 mL), cooled to 0 °C, and was stirred for 10 min. The reaction mixture was then warmed to room temperature and stirred for 12 h. The resulting solution was then washed with brine (100 mL), extracted with diethyl ether (3 x 100 mL) and dried with $MgSO_4$. The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (9.48 g, 30.7 mmol, 89%). **R_f** = 0.16

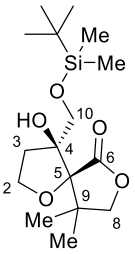
(5% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.36-7.27 (5 H, m, Ar*H*), 4.51 (2 H, s, ArC*H*$_2$), 4.20 (2 H, s, 1-*H*$_2$), 3.76 (2 H, t, *J* = 6.3 Hz, 4-*H*$_2$), 2.78 (2 H, t, *J* = 6.3 Hz, 3-*H*$_2$), 0.92 (9 H, s, SiC(C*H*$_3$)$_3$), 0.08 (6 H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.2 (2-*C*=O), 138.2 (*Ar*), 128.5 (*Ar*H), 127.9 (*Ar*H), 127.8 (*Ar*H), 73.4 (1-CH_2), 69.9 (Ar*C*H$_2$), 65.2 (4-*C*H$_2$), 39.0 (3-*C*H$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 25.8 (Si*C*), -5.4 (Si(*C*H$_3$)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 2953, 2929, 2885, 2856, 1721 (C=O), 1471, 1362, 1253, 1165, 1100, 835, 777, 735, 697, 669, 460; **HRMS** (ESI$^+$) *m/z* found 309.1879 (M+H$^+$, $C_{17}H_{29}O_3Si$ requires 309.1880), 331.1711 (M+Na$^+$, $C_{17}H_{28}O_3SiNa$ requires 331.1700) and 326.2139 (M+NH_4^+, $C_{17}H_{32}NO_3Si$ requires 326.2146). Spectroscopic data matched that previously reported.[167]

1-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxybutan-2-one 329



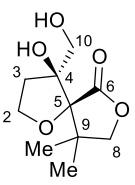
A solution of 4-(benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)butan-2-one **333** (7.95 g, 25.8 mmol, 1 equiv.) in ethyl acetate (130 mL) was treated with palladium on carbon (10 *wt*.%, activated carbon support, 795 mg) under an argon atmosphere. The resulting reaction mixture was then evacuated and flushed three times with argon, which was then repeated with hydrogen. The reaction mixture was then vigorously stirred under an atmosphere of hydrogen (1 atm, hydrogen balloon) at room temperature for 16 h. The resulting solution was then filtered through a pad of Celite® 545 and washed with ethyl acetate (3 x 100 mL). The filtrate was then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (4.83 g, 22.1 mmol, 86%). **R_f** = 0.40 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.18 (2 H, s, 1-*H*$_2$), 3.88 (2 H, dt, *J* = 6.2, 5.4 Hz, 4-*H*$_2$), 2.78 (2 H, t, *J* = 5.4 Hz, 3-*H*$_2$), 2.39 (1 H, t, *J* = 6.2 Hz, O*H*), 0.92 (9 H, s, SiC(C*H*$_3$)$_3$), 0.09 (6 H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 212.1 (2-*C*=O), 69.6 (1-*C*H$_2$), 57.7 (4-*C*H$_2$), 40.7 (3-*C*H$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 18.4 (Si*C*), -5.4 (Si(*C*H$_3$)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 3421 (OH), 2954, 2930, 2887, 2857, 1719 (C=O), 1471, 1361, 1254, 1159, 1104, 1057, 917, 834, 777, 732, 669; **HRMS** (ESI$^+$) *m/z* found 219.1414 (M+H$^+$, $C_{10}H_{23}O_3Si$ requires 219.1411), 241.1236 (M+Na$^+$, $C_{10}H_{22}O_3SiNa$ requires 241.1230) and 236.1686 (M+NH_4^+, $C_{10}H_{26}NO_3Si$ requires 236.1676).

(±)-*cis*-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one 328



A solution containing α-diazolactone **212** (565 mg, 4.03 mmol, 2 equiv.) in CH_2Cl_2 (12 mL) was added, over a 30 min period, to a refluxing solution of β-hydroxyketone **329** (440 mg, 2.02 mmol, 1 equiv.) and rhodium(II) octanoate dimer (15.7 mg, 20.2 µmol, 1 mol%) in CH_2Cl_2 (16 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (1.24 g, 3.77 mmol, 93%). **R_f** = 0.25 (20% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.06 (1 H, dd, *J* = 7.9 Hz, 8-H_A), 4.01 (1 H, ddd, *J* = 9.9, 8.4, 4.1 Hz, 2-H_A), 3.90 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.82 (1 H, dd, *J* = 10.3, 1.2 Hz, 10-H_A), 3.74 (1 H, d, *J* = 7.9 Hz, 8-H_B), 3.66 (1 H, dd, *J* = 10.3, 1.2 Hz, 10-H_B), 2.93 (1 H, d, *J* = 1.2 Hz, O*H*), 2.55 (1 H, dddd, *J* = 12.5, 9.9, 8.4, 1.2 Hz, 3-H_A), 2.47 (1 H, ddd, *J* = 12.5, 8.4, 4.1 Hz, 3-H_B), 1.26 (3 H, s, CH_{3A}), 1.10 (3 H, s, CH_{3B}), 0.92 (9 H, s, SiC(CH_3)$_3$), 0.11 (6 H, br s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.7 (6-*C*=O), 86.2 (5-*C*), 81.2 (4-*C*), 78.8 (8-*C*H_2), 65.2 (2-*C*H_2), 64.8 (10-*C*H_2), 41.1 (9-*C*), 35.1 (3-*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 21.5 (*C*H_{3A}), 18.5 (Si*C*), 18.1 (*C*H_{3B}), -5.2 (Si*C*H_{3A}), -5.3 (Si*C*H_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 3548 (OH), 2953, 2928, 2895, 2856, 1759 (C=O), 1463, 1363, 1255, 1098, 1073, 1014, 895, 836, 777, 735, 455; **HRMS** (ESI$^+$) *m/z* found 331.1942 (M+H$^+$, $C_{16}H_{31}O_5Si$ requires 331.1935), 353.1751 (M+Na$^+$, $C_{16}H_{30}O_5SiNa$ requires 353.1755) and 348.2197 (M+NH$_4^+$, $C_{16}H_{34}NO_5Si$ requires 348.2201).

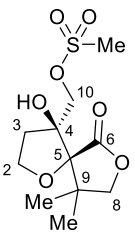
(±)-*cis*-4-Hydroxy-4-(hydroxymethyl)-9,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one 334



An aqueous solution of hydrochloric acid (2 M; 18.8 mL, 37.6 mmol, 10 equiv.) was added to a solution of silyl ether **328** (1.24 g, 3.76 mmol, 1 equiv.) in THF (30 mL). The resulting reaction mixture was stirred at room temperature for 16 h. Water (65 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 100 mL). The combined organic phases were then washed with water (100 mL), brine (100 mL) and

then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the *title compound* as a colourless solid (789 mg, 3.65 mmol, 97%). **R_f** = 0.27 (50% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.10 (1 H, d, *J* = 8.0 Hz, 8-H_A), 4.01 (1 H, ddd, *J* = 10.2, 8.4, 3.9 Hz, 2-H_A), 3.93 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.92-3.88 (1 H, m, 10-H_A), 3.75 (1 H, d, *J* = 8.0 Hz, 8-H_B), 3.47 (1 H, ddd, *J* = 11.4, 9.9, 2.0 Hz, 10-H_B), 3.03 (1 H, d *J* = 2.0 Hz, O*H*), 2.68 (1 H, ddd, *J* = 12.4, 8.4, 3.9 Hz, 3-H_A), 2.44 (1 H, dddd, 12.4, 10.2, 8.4, 2.0 Hz, 3-H_B), 2.25 (1 H, dd, *J* = 9.9, 3.5 Hz, O*H*), 1.25 (3 H, s, CH_{3A}), 1.08 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 176.2 (6-*C*=O), 85.7 (5-*C*), 81.5 (4-*C*), 79.2 (8-*C*H_2), 64.9 (2-*C*H_2), 63.4 (10-*C*H_2), 41.0 (9-*C*), 34.5 (3-*C*H_2), 21.4 (CH_{3A}), 17.5 (CH_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 3421 (OH), 2989, 2970, 2950, 2901, 1762 (C=O), 1466, 1456, 1370, 1305, 1257, 1179, 1156, 1143, 1075, 1051, 1006, 952, 929, 886, 730, 692, 463; **HRMS** (ESI^+) *m/z* found 217.1071 ($M+H^+$, $C_{10}H_{17}O_5$ requires 217.1071) and 239.0887 ($M+Na^+$, $C_{10}H_{16}O_5Na$ requires 239.0890), **mp** 112-114 °C; structure solved from X-ray crystallography studies (crystallisation from *n*-heptane).

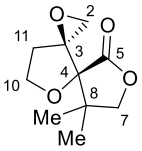
(±)-*cis*-4-Hydroxy-9,9-dimethyl-6-oxo-1,7-dioxaspiro[4.4]nonan-4-yl)methyl methanesulfonate 342



Methanesulfonyl chloride (19.0 µL, 0.243 mmol, 1.05 equiv.) was added to a solution of diol **334** (50.0 mg, 0.231 mmol, 1 equiv.) in pyridine (3.8 mL), cooled to 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was diluted with CH_2Cl_2 (30 mL). The resulting solution was then washed with aqueous *sat.* copper(II) sulphate (30 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were then washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless solid (51.1 mg, 0.174 mmol, 75%). **R_f** = 0.48 (50% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.50 (1 H, d, *J* = 10.9 Hz, 10-H_A), 4.18 (1 H, d, *J* = 10.9 Hz, 10-H_B), 4.10 (1 H, *J* = 8.0 Hz, 8-H_A), 4.06-3.93 (2 H, m, 2-H_2), 3.77 (1 H, *J* = 8.0 Hz, 8-H_B), 3.12 (3 H, s, SCH_3), 2.63-2.56 (2 H, m, 3-H_2), 1.26 (3 H, s, CH_{3A}), 1.10 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.2 (6-*C*=O), 85.9 (5-*C*), 80.3

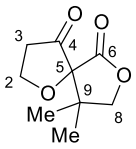
(4-*C*), 78.9 (8-*C*H$_2$), 69.4 (10-*C*H$_2$), 64.8 (2-*C*H$_2$), 40.9 (9-*C*), 38.2 (S*C*H$_3$), 34.6 (3-*C*H$_2$), 21.5 (*C*H$_{3A}$), 17.6 (*C*H$_{3B}$); **IR** (ATR) ν_{Max}/cm^{-1} 3526 (OH), 3004, 2970, 2942, 2909, 1760 (C=O), 1466, 1349, 1169, 1072, 1009, 984, 947, 894, 835, 755, 684, 524, 481, 459; **HRMS** (ESI$^+$) *m/z* found 295.0841 (M+H$^+$, $C_{11}H_{19}O_7S$ requires 295.0846), 317.0659 (M+Na$^+$, $C_{11}H_{18}O_7SNa$ requires 317.0665) and 312.1107 (M+NH$_4^+$, $C_{11}H_{22}NO_7S$ requires 312.1111); **mp** 78-79 °C.

(±)-*cis*-8,8-Dimethyl-1,6,9-trioxadispiro[2.0.44.33]undecan-5-one 343



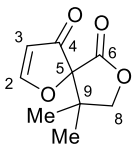
Sodium hydride (60% in mineral oil; 6.8 mg, 0.168 mmol, 1.1 equiv. was added to a solution of alcohol **342** (45.0 mg, 0.153 mmol, 1 equiv.) in THF (2 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and was then quenched with *sat.* aqueous ammonium chloride solution (5 mL). The resulting solution was then extracted with diethyl ether (3 x 15 mL) and the combined organic phases were washed with brine (15 mL) and dried with MgSO$_4$. The organic phase was concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless solid (12.8 mg, 64.6 µmol, 42%). **R$_f$** = 0.37 (50% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, CDCl$_3$): δ_H ppm 4.30 (1 H, ddd, *J* = 11.1, 8.4, 5.8 Hz, 10-*H$_A$*), 4.14 (1 H, app t, *J* = 8.4 Hz, 10-*H$_B$*), 3.88 (1 H, d, *J* = 9.5 Hz, 7-*H$_A$*), 3.85 (1 H, d, *J* = 9.5 Hz, 7-*H$_B$*), 3.20 (1 H, d, *J* = 3.5 Hz, 2-*H$_A$*), 3.16 (1 H, d, *J* = 3.5 Hz, 2-*H$_B$*), 2.39 (1 H, ddd, *J* = 13.3, 11.1, 8.4 Hz, 11-*H$_A$*), 1.81 (1 H, ddd, *J* = 13.3, 8.4, 5.8 Hz, 11-*H$_B$*), 1.14 (3 H, s, C*H$_{3A}$*), 1.12 (3 H, s, C*H$_{3B}$*); **^{13}C NMR** (101 MHz, CDCl$_3$): δ_C ppm 173.5 (5-*C*=O), 86.7 (4-*C*), 76.4 (7-*C*H$_2$), 67.2 (10-*C*H$_2$), 64.8 (3-*C*), 48.5 (2-*C*H$_2$), 41.4 (8-*C*), 33.8 (11-*C*H$_2$), 23.5 (*C*H$_{3A}$), 19.0 (*C*H$_{3B}$); **IR** (ATR) ν_{Max}/cm^{-1} 2982, 2918, 1778 (C=O), 1500, 1470, 1434, 1396, 1363, 1271, 1178, 1095, 1079, 998, 919, 901, 722, 685, 578, 457; **HRMS** (ESI$^+$) *m/z* found 199.0979 (M+H$^+$, $C_{10}H_{15}O_4$ requires 199.0965), 221.0801 (M+Na$^+$, $C_{10}H_{14}O_4Na$ requires 221.0784) and 216.1238 (M+NH$_4^+$, $C_{10}H_{18}NO_4$ requires 216.1230); **mp** 122-125 °C; structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

(±)-9,9-Dimethyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 327



An aqueous solution of hydrochloric acid (2 M; 2.90 mL, 5.82 mmol, 5 equiv.) was added to a solution of silyl ether **328** (384 mg, 1.16 mmol, 1 equiv.) in THF (10.6 mL). The resulting reaction mixture was stirred at room temperature for 16 h. Water (50 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 50 mL). The combined organic phases were then washed with water (50 mL), brine (50 mL) and dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the crude diol which was then used in the next step without further purification. The resulting crude diol was dissolved within a THF (6 mL) and water (6 mL) mixture. Sodium periodate (685 mg, 3.20 mmol, 2.75 equiv.) was then added and the resulting solution was stirred at room temperature for 18 h. Water (50 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 50 mL). The combined organic phases were then washed with water (50 mL), brine (50 mL) and dried with $MgSO_4$. The organic phase was concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless solid (202 mg, 1.10 mmol, 94%). **R_f** = 0.24 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.59 (1 H, ddd, *J* = 9.1, 9.1, 7.3 Hz, 2-H_A), 4.45 (1 H, d, *J* = 8.5 Hz, 8-H_A), 4.43 (1 H, ddd, *J* = 9.1, 9.1, 4.4 Hz, 2-H_B), 3.98 (1 H, d, *J* = 8.5 Hz, 8-H_B), 2.67 (1 H, ddd, *J* = 18.1, 7.3, 4.4 Hz, 3-H_A), 2.60 (1 H, ddd, *J* = 18.1, 9.1, 9.1 Hz, 3-H_B), 1.21 (3 H, s, CH_{3A}), 1.09 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 210.1 (4-*C*=O), 172.6 (6-*C*=O), 88.0 (5-*C*), 76.1 (8-CH_2), 65.2 (2-CH_2), 42.7 (9-*C*), 37.4 (3-CH_2), 22.7 (CH_{3A}), 18.3 (CH_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 2972, 2914, 1782 (C=O), 1746 (C=O), 1472, 1404, 1367, 1269, 1109, 1064, 999, 918, 816, 728, 521; **HRMS** (ESI^+) *m/z* found 207.0631 ($M+Na^+$, $C_9H_{12}O_4Na$ requires 207.0628) and 202.1079 ($M+NH_4^+$, $C_9H_{16}NO_4$ requires 202.1074); **mp** 46-48 °C.

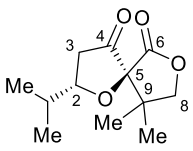
(±)-9,9-Dimethyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 326



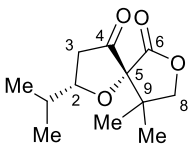
LiHMDS (1 M in THF; 2.50 mL, 2.50 mmol, 2 equiv.) was added dropwise to a solution of spirolactone **327** (230 mg, 1.25 mmol, 1 equiv.) in THF (9.5 mL), cooled to 0 °C, and was stirred for 45 min. TESCl (419 µL, 2.50 mmol, 2 equiv.) was then added and the resulting solution was stirred for 45 min at 0 °C. The

reaction mixture was then warmed to room temperature, quenched with water (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then washed with brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford the crude silyl ether, which was used in the next step without further purification. The resulting crude silyl ether was then dissolved in CH_2Cl_2 (100 mL). Ph_3CBF_4 (1.65 g, 4.99 mmol, 4 equiv.) was then added and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (50 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic phases were washed with brine (50 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless solid (181 mg, 0.996 mmol, 80%). $\mathbf{R_f}$ = 0.22 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.44 (1 H, d, *J* = 2.6 Hz, 2-*H*), 5.70 (1 H, d, *J* = 2.6 Hz, 3-*H*), 4.68 (1 H, d, *J* = 8.4 Hz, 8-H_A), 4.05 (1 H, d, *J* = 8.4 Hz, 8-H_B), 1.29 (3 H, s, CH_{3A}), 1.14 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 198.2 (4-*C*=O), 179.7 (2-*C*H), 168.0 (6-*C*=O), 107.0 (3-*C*H), 92.0 (5-*C*), 75.9 (8-*C*H_2), 43.5 (9-*C*), 23.2 (*C*H_{3A}), 18.0 (*C*H_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3155, 3119, 3084, 2974, 2916, 2849, 1792 (C=O), 1774 (C=O), 1697, 1562, 1469, 1355, 1265, 1215, 1146, 1085, 1000, 813, 794, 662, 609, 569, 523, 469; **HRMS** (ESI$^+$) *m/z* found 183.0656 (M+H$^+$, $C_9H_{11}O_4$ requires 183.0652), 205.0480 (M+Na$^+$, $C_9H_{10}O_4Na$ requires 205.0471) and 200.0910 (M+NH_4^+, $C_9H_{14}NO_4$ requires 200.0917); **mp** 46-48 °C.

(±)-*trans*- and (±)-*cis*-2-Isopropyl-9,9-dimethyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 337a and 337b



trans-**337a**



cis-**337b**

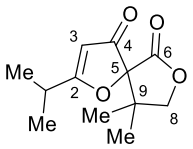
Isopropylmagnesium chloride solution (1.78 M in THF; 102 µL, 0.181 mmol, 1.1 equiv.) was added dropwise, over a 10 min period, to a solution of copper(I) bromide methyl sulphide complex (35.6 mg, 0.173 mmol, 1.05 equiv.) in THF (1.3 mL), cooled to -40 °C. After stirring for 45 min, the resulting reaction mixture was then cooled to -78 °C and enone **326** (30.0 mg, 0.165 mmol, 1 equiv.) in THF (0.65 mL) was added dropwise, over a 10 min period. The resulting solution was then stirred for 1 h, quenched with *sat.* aqueous ammonium chloride solution (10 mL),

warmed to room temperature and then extracted with diethyl ether (3 x 15 mL). The combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the separated *title compounds*.

(±)-*trans*-2-Isopropyl-9,9-dimethyl-1,7-dioxaspiro[4.4]nonane-4,6-dione **337a** as a colourless oil (23.5 mg, 0.104 mmol, 63%). The stereochemistry was inferred from the key NOESY NMR correlation between $(CH_3)_2CH$ and 9-C(CH_3)$_2$. **R_f** = 0.60 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.46 (1 H, ddd, *J* = 10.9, 6.7, 5.7 Hz, 2-*H*), 4.41 (1 H, d, *J* = 8.5 Hz, 8-H_A), 3.95 (1 H, d, *J* = 8.5 Hz, 8-H_B), 2.58 (1 H, dd, *J* = 17.9, 5.7 Hz, 3-H_A), 2.24 (1 H, dd, *J* = 17.9, 10.9 Hz, 3-H_B), 1.92 (1 H, hept, *J* = 6.7 Hz, $(CH_3)_2CH$), 1.18 (3 H, s, CH_{3A}), 1.04 (1 H, d, *J* = 6.7 Hz, CH(CH_{3A})$_2$), 1.02 (3 H, s, CH_{3B}), 0.96 (1 H, d, *J* = 6.7 Hz, CH(CH_{3B})$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 210.8 (4-*C*=O), 173.2 (6-*C*=O), 89.5 (5-*C*), 80.8 (2-*C*H), 76.2 (8-*C*H_2), 42.7 (9-*C*), 40.8 (3-*C*H_2), 33.3 $(CH_3)_2CH$), 22.7 (*C*H_{3A}), 18.4 (CH(*C*H_{3A})$_2$), 18.1 (*C*H_{3B}), 17.6 (CH(*C*H_{3B})$_2$); **IR** (ATR) v_{Max}/cm^{-1} 2964, 2913, 2878, 1787 (C=O), 1749 (C=O), 1469, 1395, 1368, 1265, 1225, 1159, 1113, 1041, 1000, 888, 733, 648, 548; **HRMS** (ESI$^+$) *m/z* found 227.1278 (M+H$^+$, $C_{12}H_{19}O_4$ requires 227.1278), 249.1097 (M+Na$^+$, $C_{12}H_{18}O_4Na$ requires 249.1097) and 244.1544 (M+NH_4^+, $C_{12}H_{22}NO_4$ requires 244.1543).

(±)-*cis*-2-Isopropyl-9,9-dimethyl-1,7-dioxaspiro[4.4]nonane-4,6-dione **337b** as a colourless oil (12.4 mg, 54.8 µmol, 33%). **R_f** = 0.48 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.33 (1 H, d, *J* = 8.5 Hz, 8-H_A), 4.06 (1 H, ddd, *J* = 8.8, 7.7, 6.6 Hz, 2-*H*), 3.94 (1 H, d, *J* = 8.5 Hz, 8-H_B), 2.58 (1 H, dd, *J* = 18.3, 6.6 Hz, 3-H_A), 2.48 (1 H, dd, *J* = 18.3, 8.8 Hz, 3-H_B), 2.04-1.94 (1 H, m $(CH_3)_2CH$), 1.18 (3 H, s, CH_{3A}), 1.12 (3 H, s, CH_{3B}), 1.09 (3 H, d, *J* = 6.7 Hz, CH(CH_{3A})$_2$), 0.95 (3 H, d, *J* = 6.7 Hz, CH(CH_{3B})$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 210.2 (4-*C*=O), 171.8 (6-*C*=O), 89.5 (5-*C*), 82.7 (2-*C*H), 75.5 (8-*C*H_2), 43.3 (9-*C*), 40.7 (3-*C*H_2), 33.7 $(CH_3)_2CH$), 22.6 (*C*H_{3A}), 19.5 (*C*H_{3B}), 18.7 (CH(*C*H_{3A})$_2$), 17.9 (CH(*C*H_{3B})$_2$); **IR** (ATR) v_{Max}/cm^{-1} 2964, 2915, 2877, 1785 (C=O), 1747 (C=O), 1469, 1367, 1266, 1162, 1112, 1004, 873, 738, 701, 585, 546; **HRMS** (ESI$^+$) *m/z* found 227.1277 (M+H$^+$, $C_{12}H_{19}O_4$ requires 227.1278), 249.1096 (M+Na$^+$, $C_{12}H_{18}O_4Na$ requires 249.1097) and 244.1543 (M+NH_4^+, $C_{12}H_{22}NO_4$ requires 244.1543).

(±)-2-Isopropyl-9,9-dimethyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 325

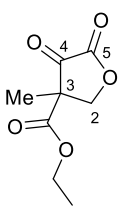


Method I: LiHMDS (1 M in THF; 0.44 mL, 0.44 mmol, 2 equiv.) was added dropwise to a solution of spirolactone **337a** (49.5 mg, 0.22 mmol, 1 equiv.) in THF (1.5 mL), cooled to 0 °C, and was stirred for 45 min. TMSCl (55.5 µL, 0.44 mmol, 2 equiv.) was then added and the reaction mixture was stirred for 45 min at 0 °C. The solution was then warmed to room temperature, quenched with water (2 mL) and then extracted with diethyl ether (3 x 5 mL). The combined organic phases were then washed with brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford the crude silyl enol ether, which was then used in the next step without further purification. A solution of 2-iodoxybenzoic acid 4-methoxypyridine *N*-oxide complex (0.4 M; 1.64 mL, 0.656 mmol, 3 equiv.), freshly prepared from the complete dissolution of 2-iodoxybenzoic acid (184 mg, 0.656 mmol, 3 equiv.) and 4-methoxypyridine *N*-oxide hydrate (94.0 mg, 0.656 mmol, 3 equiv.) in DMSO (1.64 mL) by vigorous stirring for 1 h at room temperature, was then added to the crude silyl enol ether. The resulting solution was stirred at room temperature for 16 h, then quenched with *sat.* aqueous sodium hydrogen carbonate solution (3 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were then washed with brine (10 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless solid (33.5 mg, 0.148 mmol, 68%).

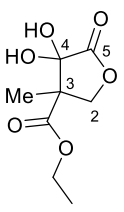
Method II: Isopropylmagnesium chloride solution (1.78 M in THF; 0.28 mL, 0.494 mmol, 3 equiv.) was added dropwise, over a 10 min period, to a solution of copper(I) bromide methyl sulphide complex (50.8 mg, 0.247 mmol, 1.5 equiv.) in THF (1.5 mL), cooled to -40 °C. After stirring for 45 min, the resulting reaction mixture was then cooled to -78 °C and enone **326** (30.0 mg, 0.165 mmol, 1 equiv.) in THF (0.65 mL) was added. After stirring for 45 min, TMSCl (105 µL, 0.823 mmol, 5 equiv.) was then added and the resulting solution was stirred for an additional 45 min at -78 °C. The reaction mixture was then warmed to room temperature, stirred for 30 min, then quenched with *sat.* aqueous sodium hydrogen carbonate solution (2 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were then washed with brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford the crude silyl enol ether, which was then used in the next step without further purification. A solution of 2-iodoxybenzoic acid 4-methoxypyridine *N*-oxide complex (0.4 M; 1.24 mL, 0.494

mmol, 3 equiv.), freshly prepared from the complete dissolution of 2-iodoxybenzoic acid (138 mg, 0.494 mmol, 3 equiv.) and 4-methoxypyridine *N*-oxide hydrate (70.7 mg, 0.494 mmol, 3 equiv.) in DMSO (1.24 mL) by vigorous stirring for 1 h at room temperature, was then added to the crude silyl enol ether. The resulting solution was stirred at room temperature for 16 h, then quenched with *sat.* aqueous sodium hydrogen carbonate solution (3 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were then washed with brine (10 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless solid (18.1 mg, 80.7 µmol, 49%), and another fraction containing spirolactones **337a** and **337b** (**337a**:**337b** ratio 2:1, 10.0 mg, 44.2 µmol, 27%). $\mathbf{R_f}$ = 0.36 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.40 (1 H, s, 3-*H*), 4.65 (1 H, d, *J* = 8.3 Hz, 8-H_A), 4.02 (1 H, d, *J* = 8.3 Hz, 8-H_B), 2.86 (1 H, hept, *J* = 7.0 Hz, $(CH_3)_2CH$), 1.31 (3 H, d, *J* = 7.0 Hz, $CH(CH_{3A})_2$), 1.30 (3 H, d, *J* = 7.0 Hz, $CH(CH_{3B})_2$), 1.28 (3 H, s, CH_{3A}), 1.12 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 201.3 (4-*C*=O), 198.1 (2-*C*), 168.7 (6-*C*=O), 101.2 (3-*C*H), 92.8 (5-*C*), 75.9 (8-CH_2), 43.3 (9-*C*), 30.5 $(CH_3)_2CH$), 23.2 (CH_{3A}), 19.8 ($CH(CH_{3A})_2$), 19.5 ($CH(CH_{3B})_2$), 18.1 (CH_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 2972, 2936, 2879, 1793 (C=O), 1691 (C=O), 1591, 1467, 1389, 1362, 1265, 1166, 1044, 1004, 938, 865, 762, 679, 599, 551, 489; **HRMS** (ESI$^+$) *m/z* found 225.1116 ($M+H^+$, $C_{12}H_{17}O_4$ requires 225.1121) and 247.0935 ($M+Na^+$, $C_{12}H_{16}O_4Na$ requires 247.0941); **mp** 49-50 °C; structure solved from X-ray crystallography studies (crystallisation from acetonitrile).

(±)-Ethyl 3-methyl-4,5-dioxotetrahydrofuran-3-carboxylate and (±)-Ethyl 4,4-dihydroxy-3-methyl-5-oxotetrahydrofuran-3-carboxylate 345a and 345b



345a

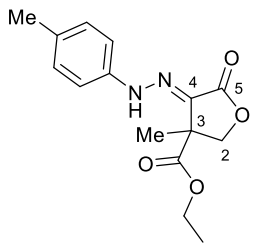


345b

Sodium hydrogen carbonate (25.2 g, 300 mmol, 3 equiv.) was added to a vigorously stirred solution of diethyl 2-methyl-3-oxosuccinate **344** (18.8 mL, 100 mmol, 1 equiv.) in THF (400 mL), cooled to 0 °C. Aqueous formaldehyde (31.5 mL, 35 *wt.*% solution), followed by water (200 mL) was then added and the resulting clear solution was stirred for 20 min. The reaction mixture was then poured into water (800 mL) and extracted with diethyl ether (3 x 600 mL). The combined organic phases were then washed with brine (400 mL), dried with $MgSO_4$ and

concentrated *in vacuo*. The resulting residue was purified by column chromatography affording the inseparable *title compounds* as a colourless oil (ratio **345a**:**345b** 80:20, 10.5 g, 56.5 mmol, 56%). $\mathbf{R_f}$ = 0.18 (50% diethyl ether in petroleum ether); Ketoester form **(14a)**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.05 (1 H, d, *J* = 9.9 Hz, 2-H_A), 4.44 (1 H, d, *J* = 9.9 Hz, 2-H_B), 4.21 (2 H, q, *J* = 7.2 Hz, CH_3CH_2), 1.54 (3 H, s, CH_3), 1.24 (3 H, t, *J* = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 190.7 (4-*C*=O), 167.5 (*C*=O), 158.7 (5-*C*=O), 73.7 (2-CH_2), 63.4 (CH_3CH_2), 51.8 (3-*C*), 17.8 (CH_3), 13.9 (CH_2CH_3); Hydrate form **(14b)**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.45 (1 H, d, *J* = 9.5 Hz, 2-H_A), 4.29 (2 H, br s, O*H*), 4.28-4.13 (2 H, m, CH_3CH_2), 4.06 (1 H, d, *J* = 9.5 Hz, 2-H_B), 1.35 (3 H, s, CH_3), 1.25 (3 H, t, *J* = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 173.9 (*C*=O), 171.3 (5-*C*=O), 94.4 (4-*C*), 72.8 (2-CH_2), 62.0 (CH_3CH_2), 52.7 (3-*C*), 16.6 (CH_3), 14.0 (CH_2CH_3); **IR** ($CHCl_3$) ν_{Max}/cm^{-1} 3431 (OH), 2986, 1799 (C=O), 1747 (C=O), 1268, 1249, 1002; **HRMS** (ESI$^+$) *m/z* found 241.0688 (M+MeOH+Na$^+$, $C_9H_{14}O_6Na$ requires 241.0689). Spectroscopic data matched that previously reported.[88]

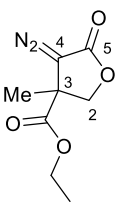
(±)-Ethyl (*E*)-3-methyl-5-oxo-4-(2-(*p*-tolyl)hydrazineylidene)tetrahydrofuran-3-carboxylate 346



p-Toluenesulfonyl hydrazide (10.5 g, 56.4 mmol, 1 equiv.) was added to a solution of ethyl 3-methyl-4,5-dioxotetrahydrofuran-3-carboxylate **345** (10.5 g, 56.4 mmol, 1 equiv.) in methanol (270 mL) and the resulting mixture was heated at reflux for 2 h. Concentrated hydrochloric acid (15 drops) was then added, and the resulting solution was heated at reflux for an additional 3 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography, using the elution gradient 20 to 40% ethyl acetate in petroleum ether, affording the *title compound* as a colourless solid (16.1 g, 45.4 mmol, 81%). $\mathbf{R_f}$ = 0.20 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 11.47 (1 H, s, N*H*), 7.87-7.76 (2 H, m, Ar*H*), 7.32 (2 H, d, *J* = 8.0 Hz, Ar*H*), 4.86 (1 H, d, *J* = 9.4 Hz, 2-H_A), 4.19 (1 H, d, *J* = 9.4 Hz, 2-H_B), 4.10 (2 H, q, *J* = 7.2 Hz, CH_3CH_2), 2.43 (3 H, s, ArCH_3), 1.52 (3 H, s, CH_3), 1.11 (3 H, t, *J* = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 170.6 (*C*=O), 163.0 (5-*C*=O),

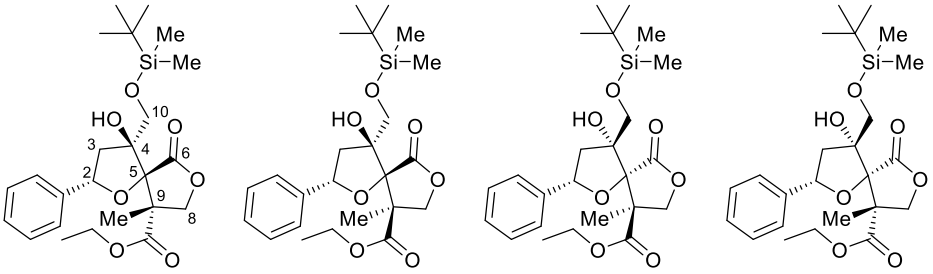
144.8 (4-*C*=N), 137.2 (*Ar*), 135.2 (*Ar*), 129.8 (*Ar*H), 128.0 (*Ar*H), 76.0 (2-*C*CH_2), 62.6 (CH_3CH_2), 48.3 (3-*C*), 21.7 (ArCH_3), 20.7 (CH_3), 13.9 (CH_2CH_3); **IR** ($CHCl_3$) ν_{Max}/cm^{-1} 3234 (NH), 3042, 2985, 1744 (C=O), 1599 (C=N), 1386, 1372, 1357, 1291, 1266, 1171, 1085, 981; **HRMS** (ESI^+) *m/z* found 377.0776 ($M+Na^+$, $C_{15}H_{18}N_2O_6SNa$ requires 377.0778); **mp** 115-116 °C. Spectroscopic data matched that previously reported.[88]

(±)-Ethyl 4-diazo-3-methyl-5-oxotetrahydrofuran-3-carboxylate 347



A solution of hydrazone **346** (3.58 g, 10.1 mmol, 1 equiv.) and triethylamine (1.55 mL, 15.2 mmol, 1.5 equiv.) in dichloromethane (30 mL) was heated at reflux for 90 min. Once cooled to room temperature, the reaction mixture was filtered through a silica plug, neutralised using 5% triethylamine in CH_2Cl_2, and eluted using CH_2Cl_2 affording the *title compound* as a yellow oil (1.05 g, 5.29 mmol, 52%). $\mathbf{R_f}$ = 0.30 (50% diethyl ether in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.79 (1 H, d, *J* = 9.3 Hz, 2-H_A), 4.18-4.33 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, CH_3CH_2), 4.04 (1 H, d, *J* = 9.3 Hz, 2-H_B), 1.66 (3 H, s, CH_3), 1.31 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 172.3 (*C*=O), 168.1 (5-*C*=O), 73.6 (2-*C*H_2), 62.8 (CH_3CH_2), 47.3 (3-*C*), 22.9 (CH_3), 14.2 (CH_2CH_3), the signal due to 4-*C*N_2 was not observed; **IR** ($CHCl_3$) ν_{Max}/cm^{-1} 2938, 2113 (CN_2), 1737 (C=O), 1389, 1375, 1253, 1109, 1014; **HRMS** (ESI^+) *m/z* found 221.0546 ($M+Na^+$, $C_8H_{10}N_2O_4Na$ requires 221.0533). Spectroscopic data matched that previously reported.[88]

Ethyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-6-oxo-2-phenyl-1,7-dioxaspiro[4.4]nonane-9-carboxylate (mixture of isomers) 348a-d

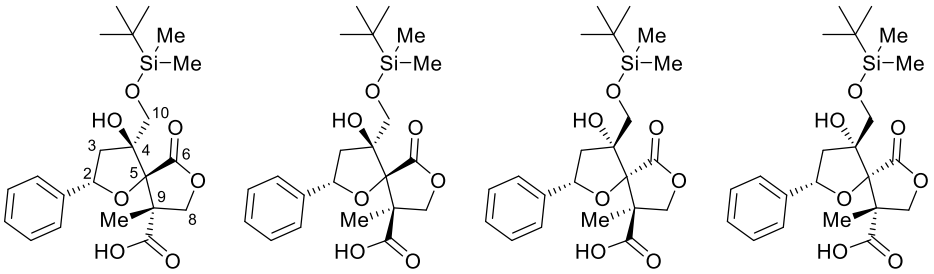


cis,*trans*,*trans*-**348a** *cis*,*trans*,*cis*-**348b** *cis*,*cis*,*trans*-**348c** *cis*,*cis*,*cis*-**348d**

A solution containing α-diazolactone **347** (90.0 mg, 454 μmol, 1.3 equiv.) in CH_2Cl_2 (1.75 mL) was added, over a 30 min period, to a refluxing solution of β-hydroxyketone

(*S*)-**264** (103 mg, 349 µmol, 1 equiv.) and rhodium(II) octanoate dimer (2.70 mg, 3.49 µmol, 1 mol%) in CH_2Cl_2 (2.60 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 10 to 20% ethyl acetate in petroleum ether, affording the inseparable *title compounds* as a colourless oil (ratio **348a**:**348b**:**348c**:**348d** 48:36:13:3, 101 mg, 237 µmol, 68%). The stereochemistry of these four products were inferred from various 2D-NMR experiments and from subsequent transformations; only the signals for the two major isomers **348a** (**A**) and **348b** (**B**) are reported herein: $\mathbf{R_f}$ = 0.36 (15% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.44-7.16 (5 H, m, Ar*H*, **A**; 5 H, m, Ar*H*, **B**), 5.45 (1 H, dd, *J* = 8.2, 7.5 Hz, 2-*H*, **A**), 5.35 (1 H, dd, *J* = 9.1, 6.0 Hz, 2-*H*, **B**), 4.85 (1 H, d, *J* = 8.6 Hz, 8-H_A, **B**), 4.50 (1 H, d, *J* = 9.1 Hz, 8-H_A, **A**), 4.15 (1 H, d, *J* = 10.7 Hz, 10-H_A, **B**), 4.12 (1 H, d, *J* = 9.1 Hz, 8-H_B, **A**), 4.34-4.07 (2 H, m, CH_3CH_2, **A**; 2 H, m, CH_3CH_2, **B**), 4.04 (1 H, d, *J* = 8.6 Hz, 8-H_B, **B**), 3.78 (1 H, d, *J* = 10.4 Hz, 10-H_A, **A**), 3.73 (1 H, br s, O*H*, **A**), 3.65 (1 H, br s, O*H*, **B**), 3.63 (1 H, d, *J* = 10.7 Hz, 10-H_B, **B**), 3.55 (1 H, d, *J* = 10.4 Hz, 10-H_B, **A**), 2.86 (1 H, ddd, *J* = 12.6, 9.1, 1.5 Hz, 3-H_A, **B**), 2.73 (1 H, dd, *J* = 13.0, 8.2 Hz, 3-H_A, **A**), 2.51 (1 H, dd, *J* = 12.6, 6.0 Hz, 3-H_B, **B**), 2.25 (1 H, dd, *J* = 13.0, 7.5 Hz, 3-H_B, **A**), 1.59 (3 H, s, CH_3, **B**), 1.54 (3 H, s, CH_3, **A**), 1.29 (3 H, t, *J* = 7.2 Hz, CH_2CH_3, **A**), 1.26 (3 H, t, *J* = 7.2 Hz, CH_2CH_3, **B**), 0.86 (9 H, s, $SiC(CH_3)_3$, **A**), 0.83 (9 H, s, $SiC(CH_3)_3$, **B**), 0.03 (3 H, s, $SiCH_{3A}$, **A**), 0.00 (3 H, s, $SiCH_{3B}$, **A**), −0.02 (3 H, s, $SiCH_{3A}$, **B**), −0.09 (3 H, s, $SiCH_{3B}$, **B**); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 173.5 (*C*=O, **A**), 172.8 (*C*=O, **B**), 172.6 (6-*C*=O, **A**), 170.3 (6-*C*=O, **B**), 141.9 (*Ar*, **B**), 141.4 (*Ar*, **A**), 128.6 (*Ar*H, **A**), 128.5 (*Ar*H, **B**), 127.8 (*Ar*H, **A**), 127.5 (*Ar*H, **B**), 125.9 (*Ar*H, **A**), 125.3 (*Ar*H, **B**), 87.9 (5-*C*, **B**), 87.7 (5-*C*, **A**), 82.0 (4-*C*, **B**), 81.8 (4-*C*, **A**), 78.11 (2-*C*H, **A**), 78.06 (2-*C*H, **B**), 74.3 (8-CH_2, **B**), 72.9 (8-CH_2, **A**), 66.1 (10-CH_2, **B**), 65.8 (10-CH_2, **A**), 62.0 (CH_3CH_2, **A**), 61.9 (CH_3CH_2, **B**), 52.2 (9-*C*, **B**), 51.4 (9-*C*, **A**), 44.4 (3-CH_2, **A**), 42.7 (3-CH_2, **B**), 26.0 ($SiC(CH_3)_3$, **A**), 25.9 ($SiC(CH_3)_3$, **B**), 18.59 (Si*C*, **A**), 18.57 (CH_3, **B**), 18.4 (Si*C*, **B**), 17.4 (CH_3, **A**), 14.1 (CH_2CH_3, **B**), 13.9 (CH_2CH_3, **A**), −5.3 ($SiCH_{3A}$, **A**), −5.4 ($SiCH_{3B}$, **A**; $SiCH_{3A}$, **B**), −5.5 ($SiCH_{3B}$, **B**); **IR** (ATR) v_{Max}/cm^{-1} 3502 (OH), 2953, 2929, 2885, 2856, 1782 (C=O), 1730 (C=O), 1462, 1450, 1389, 1363, 1286, 1252, 1220, 1145, 1024, 912, 837, 778, 734, 700; **HRMS** (ESI^+) *m/z* found 465.2280 ($M+H^+$, $C_{24}H_{37}O_7Si$ requires 465.2303) and 487.2138 ($M+Na^+$, $C_{24}H_{36}O_7SiNa$ requires 487.2123); $[\alpha]_D^{17}$ = -205 (*c* 1.00, $CHCl_3$).

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-6-oxo-2-phenyl-1,7-dioxaspiro[4.4]nonane-9-carboxylic acid (mixture of isomers) 349a-d

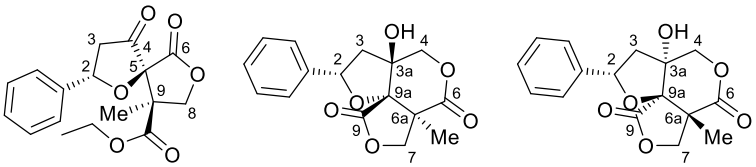


cis,*trans*,*trans*-**349a** *cis*,*trans*,*cis*-**349b** *cis*,*cis*,*trans*-**349c** *cis*,*cis*,*cis*-**349d**

Lithium hydroxide monohydrate (8.4 mg, 0.20 mmol, 2 equiv.) was added to a solution of spirolactones **348a-d** (ratio **348a**:**348b**:**348c**:**348d**, 48:36:13:3; 46.5 mg, 0.10 mmol, 1 equiv.) in THF (1 mL) and water (0.35 mL) at 0 °C. The resulting solution was then warmed to room temperature, stirred for 18 h, quenched with *sat.* aqueous ammonium chloride solution (3.00 mL) and then extracted with ethyl acetate (3 x 15 mL). The combined organic phases were then washed with brine (5 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the inseparable *title compounds* as a slowly crystallising colourless solid (approximate ratio **349a**:**349b**:**349c**:**349d**, 78:15:6:1; 25.0 mg, 57.3 µmol, 57%); The stereochemistry of these four products were inferred from various 2D-NMR experiments; only the signals for the two major isomers **349a** (**A**) and **349b** (**B**) are reported herein: $\mathbf{R_f}$ = 0.18 (5% MeOH in CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.40-7.28 (5 H, m, Ar*H*, **A**; 5 H, m, Ar*H*, **B**), 7.01 (1 H, br s, CO_2H, **A**; 1 H, br s, CO_2H, **B**), 5.39 (1 H, br t, *J* = 7.8 Hz, 2-*H*, **A**), 5.13 (1 H, dd, *J* = 10.7, 6.3 Hz, 2-*H*, **B**), 4.45 (1 H, d, *J* = 9.0 Hz, 8-H_A, **A**), 4.42 (1 H, d, *J* = 9.0 Hz, 8-H_A, **B**), 4.16 (1 H, d, *J* = 9.0 Hz, 8-H_B, **A**), 4.12 (1 H, d, *J* = 9.0 Hz, 8-H_B, **B**), 3.95 (1 H, d, *J* = 10.8 Hz, 10-H_A, **B**), 3.87 (1 H, d, *J* = 10.8 Hz, 10-H_A, **A**), 3.83 (1 H, d, *J* = 10.8 Hz, 10-H_B, **B**), 3.57 (1 H, d, *J* = 10.8 Hz, 10-H_B, **A**), 2.88 (1 H, dd *J* = 13.1, 8.6 Hz, 3-H_A, **A**), 2.78 (1 H, dd, *J* = 12.8, 10.7 Hz, 3-H_A, **B**), 2.60 (1 H, dd, *J* = 12.8, 6.3 Hz, 3-H_B, **B**), 2.11 (1 H, s, O*H*, **A**), 2.11-2.04 (1 H, m, 3-H_B, **A**), 2.05 (1 H, s, O*H*, **B**), 1.57 (3 H, s, CH_3, **A**), 1.49 (3 H, s, CH_3, **B**), 0.93 (9 H, s, SiC(CH_3)$_3$, **B**), 0.87 (9 H, s, SiC(CH_3)$_3$, **A**), 0.13 (3 H, s, SiCH_{3A}, **B**), 0.12 (3 H, s, SiCH_{3B}, **B**), 0.06 (3 H, s, SiCH_{3A}, **A**), 0.03 (3 H, s, SiCH_{3B}, **A**); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 177.9 (CO_2H, **A**), 177.5 (CO_2H, **B**), 174.4 (6-*C*=O, **B**), 172.9 (6-*C*=O, **A**), 141.3 (*Ar*, **A**), 140.8 (*Ar*, **B**), 128.74 (*Ar*H, **B**), 128.70 (*Ar*H, **A**), 128.2 (*Ar*H, **B**), 127.9 (*Ar*, **A**), 126.6 (*Ar*, **B**), 125.8 (*Ar*H, **A**), 86.7 (5-*C*, **A**), 86.5 (5-*C*,

B), 81.7 (4-*C*, **B**), 80.9 (4-*C*, **A**), 80.5 (2-*C*H_2, **B**), 77.4 (2-*C*H_2, **A**), 73.5 (8-*C*H_2, **A**), 73.1 (8-*C*H_2, **B**), 66.6 (10-*C*H_2, **A**), 65.5 (10-*C*H_2, **B**), 51.8 (9-*C*, **A**), 44.6 (3-*C*H_2, **A**), 44.2 (3-*C*H_2, **B**), 26.0 (SiC(*C*H_3)$_3$, **A**), 24.0 (SiC(*C*H_3)$_3$, **B**), 18.8 (Si*C*, **A**), 18.7 (Si*C*, **B**), 15.6 (*C*H_3, **A**), 15.5 (*C*H_3, **B**), -5.31 (Si*C*H_{3A}, **B**), -5.33 (Si*C*H_{3B}, **B**), -5.38 (Si*C*H_{3A}, **A**), -5.41 (Si*C*H_{3B}, **A**), the signal due to 9-*C*, **B** was not observed; **IR** (ATR) ν_{Max}/cm^{-1} 3474 (OH), 3253 (OH), 2954, 2929, 2857, 1771 (C=O), 1710 (C=O), 1462, 1380, 1362, 1255, 1212, 1101, 1052, 1025, 910, 835, 779, 754, 735, 680; **HRMS** (ESI$^+$) *m/z* found 437.1994 (M+H$^+$, $C_{22}H_{33}O_7Si$ requires 437.1990), 459.1812 (M+Na$^+$, $C_{22}H_{32}O_7SiNa$ requires 459.1810) and 454.2247 (M+NH_4^+, $C_{22}H_{36}NO_7Si$ requires 454.2256); **mp** 154-157 °C; $[\alpha]_D^{17}$ = +113 (*c* 1.00, $CHCl_3$).

Ethyl (2*S*,5*S*,9*R*)-9-methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]nonane-9-carboxylate 353, (2*S*,3a*S*,6a*S*,9a*S*)-3a-hydroxy-6a-methyl-2-phenylhexahydro-6*H*,9*H*-difuro[3,2-c:3',4'-d]pyran-6,9-dione 355a and (2*S*,3a*R*,6a*R*,9a*R*)-3a-hydroxy-6a-methyl-2-phenylhexahydro-6*H*,9*H*-difuro[3,2-c:3',4'-d]pyran-6,9-dione 355b



trans,*cis*-**353** *cis*,*trans*,*trans*-**355a** *cis*,*cis*,*trans*-**355b**

An aqueous solution of hydrochloric acid (2 M; 2.00 mL, 3.77 mmol, 5 equiv.) was added to a solution of silyl ethers **348a-d** (ratio **348a**:**348b**:**348c**:**348d**, 45:39:12:4; 350 mg, 753 µmol, 1 equiv.) in THF (6.3 mL). The resulting reaction mixture was stirred at room temperature for 17 h. Water (15 mL) was then added to the reaction mixture and the resulting solution was extracted with ethyl acetate (50 mL). The combined organic phases were then washed with brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the crude diol which was then used in the next step without further purification. The resulting crude diol was then dissolved within a THF (16.5 mL) and water (16.5 mL) mixture. Sodium periodate (484 mg, 2.26 mmol, 3 equiv.) was then added and the resulting solution was stirred at room temperature for 18 h. Water (20 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (40 mL). The combined organic phases were then washed with brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* and the crude product was purified by column chromatography,

using the elution gradient 25 to 50% ethyl acetate in petroleum ether, affording the separated *title compounds*.

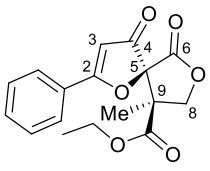
Ethyl (2*S*,5*S*,9*R*)-9-methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]nonane-9-carboxylate 353 as a colourless oil (83.6 mg, 263 µmol, 35%). **R_f** = 0.75 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.43-7.28 (5 H, m, Ar*H*), 5.64 (1 H, dd, *J* = 11.0, 5.9 Hz, 2-*H*), 4.65 (1 H, d, *J* = 9.3 Hz, 8-H_A), 4.27 (1 H, d, *J* = 9.3 Hz, 8-H_B), 4.11-4.36 (2 H, two overlapping dq, *J* = 10.7, 7.2 Hz, CH_3CH_2), 3.03 (1 H, dd, *J* = 17.8, 5.9 Hz, 3-H_A), 2.65 (1 H, dd, *J* = 17.8, 11.0 Hz, 3-H_B), 1.45 (3 H, s, CH_3), 1.23 (3 H, t, *J* = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 207.7 (4-*C*=O), 171.0 (*C*=O), 170.3 (6-*C*=O), 139.0 (*Ar*), 128.9 (*Ar*H), 128.8 (*Ar*H), 125.9 (*Ar*H), 86.3 (5-*C*), 77.9 (2-*C*H), 73.0 (8-CH_2), 62.3 (CH_3CH_2), 52.6 (9-*C*), 45.8 (3-CH_2), 15.6 (CH_3), 14.1 (CH_2CH_3); **IR** ($CHCl_3$) v_{Max}/cm^{-1} 2985, 2927, 1789 (C=O), 1757 (C=O), 1730 (C=O), 1290, 1155, 1113, 1010; **HRMS** (ESI$^+$) *m/z* found 341.1000 ($M+Na^+$, $C_{17}H_{28}O_6Na$ requires 341.0996); **mp** 78-80 °C; $[\alpha]_D^{18}$ = -144 (*c* 1.00, $CHCl_3$); structure solved from X-ray crystallography studies (crystallisation from *n*-heptane).

(2*S*,3a*S*,6a*S*,9a*S*)-3a-hydroxy-6a-methyl-2-phenylhexahydro-6*H*,9*H*-difuro[3,2-c:3',4'-d]pyran-6,9-dione 355a as a colourless solid (95.8 mg, 315 µmol, 42%). **R_f** = 0.40 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.41-7.26 (5 H, m, Ar*H*), 5.81 (1 H, dd, *J* = 7.9, 7.9 Hz, 2-*H*), 4.91 (1 H, d, *J* = 9.5 Hz, 7-H_A), 4.44-4.27 (2 H, m, 4-H_2), 4.15 (1 H, d, *J* = 9.5 Hz, 7-H_B), 3.84 (1 H, br s, O*H*), 2.84 (1 H, dd, *J* = 13.6, 7.9 Hz, 3-H_A), 2.09 (1 H, dd, *J* = 13.6, 7.9 Hz, 3-H_B), 1.59 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 174.2 (9-*C*=O), 171.5 (6-*C*=O), 140.0 (*Ar*), 128.9 (*Ar*H), 128.4 (*Ar*H), 125.5 (*Ar*H), 85.9 (9a-*C*), 79.9 (2-*C*H), 77.2 (3a-*C*), 74.0 (7-CH_2), 71.3 (4-CH_2), 46.8 (6a-*C*), 43.9 (3-CH_2), 18.4 (CH_3); **IR** ($CHCl_3$) v_{Max}/cm^{-1} 3042 (OH), 1756 (C=O), 1371, 1261, 1142, 1090, 1044; **HRMS** (ESI$^+$) *m/z* found 327.0640 ($M+Na^+$, $C_{16}H_{16}O_6Na$ requires 327.0845); **mp** 144-146 °C; $[\alpha]_D^{18}$ = +26.2 (*c* 1.00, $CHCl_3$); structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

(2*S*,3a*R*,6a*R*,9a*R*)-3a-hydroxy-6a-methyl-2-phenylhexahydro-6*H*,9*H*-difuro[3,2-c:3',4'-d]pyran-6,9-dione 355b as a colourless solid (18.7 mg, 61.5 µmol, 8%). **R_f** = 0.18 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.52-7.31 (5 H, m, Ar*H*), 5.16 (1 H, dd, *J* = 11.1, 5.5 Hz, 2-*H*), 5.10 (1 H, d, *J* =

9.5 Hz, 7-H_A), 4.57 (1 H, d, J = 12.3 Hz, 4-H_A), 4.50 (1 H, d, J = 12.3 Hz, 4-H_B), 4.06 (1 H, d, J = 9.5 Hz, 7-H_B), 3.16 (1 H, s, OH), 2.70 (1 H, dd, J = 13.2, 11.1 Hz, 3-H_A), 2.52 (1 H, dd, J = 13.2, 5.5 Hz, 3-H_B), 1.53 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 174.5 (9-C=O), 171.2 (6-C=O), 139.1 (*Ar*), 129.04 (*Ar*H), 128.97 (*Ar*H), 126.6 (*Ar*H), 85.1 (9a-C), 82.9 (2-CH), 78.2 (3a-C), 74.3 (7-CH$_2$), 70.4 (4-CH$_2$), 46.9 (6a-C), 45.0 (3-CH$_2$), 17.6 (CH$_3$); **IR** ($CHCl_3$) ν_{Max}/cm^{-1} 3691 (OH), 2927, 2854, 2602, 1757 (C=O), 1406, 1239; **HRMS** (ESI$^+$) *m/z* found 327.0638 (M+Na$^+$, $C_{16}H_{16}O_6Na$ requires 327.0845); **mp** 148-151 °C; $[\alpha]_D^{18}$ = -71.4 (*c* 1.00, $CHCl_3$); structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

Ethyl (5*S*,9*R*)-9-methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-9-carboxylate 356

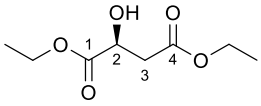


LiHMDS (1 M in THF; 314 µL, 0.314 mmol, 2 equiv.) was added dropwise to a solution of spirolactone **353** (50.0 mg, 0.157 mmol, 1 equiv.) in THF (3.2 mL), cooled to 0 °C, and was stirred for 45 min. TESCl (53.0 µL, 0.314 mmol, 2 equiv.) was then added and the resulting solution was stirred for 45 min at 0 °C, then warmed to room temperature and stirred for 1 h. DDQ (71.3 mg, 0.314 mmol, 2 equiv.) was then added to the reaction mixture and the solution was stirred for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (30 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic phases were then washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless solid (41.2 mg, 0.130 mmol, 83%). **R_f** = 0.26 (25% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.80-7.76 (2 H, m, ArH), 7.64-7.58 (1 H, m, ArH), 7.53-7.48 (2 H, m, ArH), 6.06 (1 H, s, 3-H), 4.60 (1 H, d, J = 9.1 Hz, 8-H_A), 4.56 (1 H, d, J = 9.1 Hz, 8-H_B), 4.36 (1 H, dq, J = 10.7, 7.1 Hz, CH_3CH_{2A}), 4.27 (1 H, dq, J = 10.7, 7.1 Hz, CH_3CH_{2B}), 1.44 (3 H, s, CH_3), 1.32 (3 H, t, J = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 195.8 (4-C=O), 187.6 (2-C), 170.3 (C=O), 167.5 (6-C=O), 134.0 (*Ar*H), 129.2 (*Ar*H), 127.5 (*Ar*H), 100.6 (3-CH), 90.1 (5-C), 72.1 (8-CH$_2$), 62.5 (CH_3CH_2), 52.0 (9-C), 14.3 (CH_2CH_3), 14.0 (CH$_3$), the signal due to *Ar* was not

observed; **IR** (ATR) v_{Max}/cm^{-1} 3109, 2983, 2967, 2943, 2905, 1777 (C=O), 1723 (C=O), 1685 (C=O), 1604, 1565, 1452, 1348, 1287, 1218, 1155, 1098, 1015, 999, 888, 778, 733, 682, 532, 493, 449; **HRMS** (ESI$^+$) *m/z* found 317.1029 (M+H$^+$, $C_{17}H_{17}O_6$ requires 317.1020), 339.0857 (M+Na$^+$, $C_{17}H_{16}O_6Na$ requires 339.0839) and 334.1292 (M+NH$_4^+$, $C_{17}H_{20}NO_6$ requires 334.1285); **mp** 62-64 °C; $[\alpha]_D^{17}$ = -210 (*c* 1.00, $CHCl_3$); structure solved from X-ray crystallography studies (crystallisation from *n*-heptane).

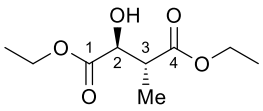
5.3 Chapter 3: Experimental

(*S*)-Diethyl 2-hydroxysuccinate 39

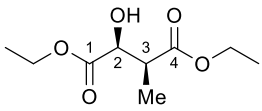


Thionyl chloride (100 mL, 1.38 mol, 2.3 equiv.) was added to a solution of *L*-(-)-malic acid **38** (80.5 g, 600 mmol, 1 equiv.) in EtOH (500 mL), cooled to 0 °C. The resulting reaction mixture was stirred at 0 °C for 30 min, was then heated to 35 °C and was stirred for 18 h. The reaction solution was then concentrated *in vacuo*, dissolved in ethyl acetate (1000 mL), washed with water (1000 mL), aqueous *sat.* sodium hydrogen carbonate solution (1000 mL) and dried with $MgSO_4$. The dried organic phase was then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (112 g, 591 mmol, 99%). $\mathbf{R_f}$ = 0.43 (10% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, acetone-d_6): δ_H ppm 4.49 (1 H, ddd, *J* = 6.9, 5.9, 4.9 Hz, 2-*H*), 4.40 (1 H, d, *J* = 5.9 Hz, O*H*), 4.21-4.14 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, 1-$CO_2CH_{2A,B}$), 4.11 (2 H, q, *J* = 7.1 Hz, 4-CO_2CH_2), 2.77 (1 H, dd, *J* = 15.8, 4.9 Hz, 3-H_A), 2.66 (1 H, dd, *J* = 15.8, 6.9 Hz, 3-H_B), 1.24 (3 H, t, *J* = 7.1 Hz, 1-$CO_2CH_2CH_3$), 1.22 (3 H, t, *J* = 7.1 Hz, 4-$CO_2CH_2CH_3$); **^{13}C NMR** (101 MHz, acetone-d_6): δ_C ppm 172.8 (1-*C*=O), 169.9 (4-*C*=O), 67.5 (2-*C*H), 60.7 (1-CO_2CH_2), 60.1 (4-CO_2CH_2), 39.0 (3-CH_2), 13.6 (1-$CO_2CH_2CH_3$), 13.5 (4-$CO_2CH_2CH_3$); **IR** (ATR) v_{Max}/cm^{-1} 3485 (OH), 2983, 2939, 2908, 1730 (C=O), 1468, 1447, 1372, 1351, 1264, 1164, 1098, 1024, 951, 858, 787, 671, 596; **HRMS** (ESI$^+$) *m/z* found 191.0914 (M+H$^+$, $C_8H_{15}O_5$ requires 191.0914), 213.0746 (M+Na$^+$, $C_8H_{14}O_5Na$ requires 213.0733) and 208.1181 (M+NH$_4^+$, $C_8H_{18}NO_5$ requires 208.1179); $[\alpha]_D^{22}$ = -15.1 (*c* 1.00, acetone), lit.[168] $[\alpha]_D^{22}$ = -16.3 (*c* 1.10, acetone). Spectroscopic data matched that previously reported.[168,169]

(2*S*,3*R*) and (2*R*,3*R*)-Diethyl 2-hydroxy-3-methylsuccinate 40a and 40b



anti-**40a**

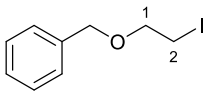


syn-**40b**

A freshly prepared solution of lithium diisopropylamine (1 M; 506 mmol, 506 mL, 2.3 equiv.) was added to a solution of (*S*)-diethyl 2-hydroxysuccinate **39** (41.8 g, 220 mmol, 1 equiv.), in THF (200 mL), cooled to -78 °C. The resulting reaction mixture was stirred for 3 h at -78 °C. Iodomethane (20.5 mL, 331 mmol, 1.5 equiv.) was then slowly added to the resulting reaction mixture over a 10 min period. The solution was then stirred at -78 °C for 8 h and gradually warmed to room temperature, over a 13 h period. The reaction mixture was then quenched with *sat.* aqueous ammonium chloride solution (500 mL) at 0 °C, stirred for 5 min, then warmed to room temperature and extracted with diethyl ether (3 x 1000 mL). The combined organic phases were then washed with brine (1000 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography, using the elution gradient 15 to 30% ethyl acetate in hexane, affording the *title compounds*, an inseparable mixture of diastereomers **40a** (**A**) and **40b** (**B**), as a pale-yellow oil (ratio **40a**:**40b** 83:17, 35.6 g, 177 mmol, 80%). $\mathbf{R_f}$ = 0.21 (20% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.59 (1 H, dd, *J* = 5.4, 3.6 Hz, 2-*H*, **B**), 4.32-4.22 (1 H, m, 2-*H*, **A**; 2 H, m, 1-CO_2CH_2, **A**; 2 H, m, 1-CO_2CH_2, **B**), 4.19 (2 H, q, *J* = 7.1 Hz, 4-CO_2CH_2, **B**), 4.18-4.10 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, 4-$CO_2CH_{2A,B}$, **A**), 3.15 (1 H, d, *J* = 6.3 Hz, O*H*, **A**), 3.06 (1 H, d, *J* = 5.4 Hz, O*H*, **B**), 3.01 (1 H, dq, *J* = 7.4, 3.6 Hz, 3-*H*, **A**), 2.91 (1 H, dq, *J* = 7.2, 3.6 Hz, 3-*H*, **B**), 1.31 (3 H, t, *J* = 7.1 Hz, 1-$CO_2CH_2CH_3$, **B**), 1.29 (3 H, t, *J* = 7.1 Hz, 1-$CO_2CH_2CH_3$, **A**), 1.29 (3 H, d, *J* = 7.4 Hz, $CHCH_3$, **A**), 1.24 (3 H, t, *J* = 7.1 Hz, 4-$CO_2CH_2CH_3$, **A**), 1.16 (3 H, d, *J* = 7.2 Hz, $CHCH_3$, **B**), the signal due to 4-$CO_2CH_2CH_3$, **B** was not observed; **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 173.44 (1-*C*=O, **A**), 173.38 (1-*C*=O, **B**), 173.37 (4-*C*=O, **B**), 173.0 (4-*C*=O, **A**), 72.6 (2-*C*H, **A**), 71.6 (2-*C*H, **B**), 62.2 (1-CO_2CH_2, **B**), 62.0 (1-CO_2CH_2, **A**), 61.1 (4-CO_2CH_2, **B**), 61.0 (4-CO_2CH_2, **A**), 43.3 (3-*C*H, **A**), 43.2 (3-*C*H, **B**), 14.30 (1-$CO_2CH_2CH_3$, **B**), 14.28 (4-$CO_2CH_2CH_3$, **B**), 14.26 (1-$CO_2CH_2CH_3$, **A**), 14.2 (4-$CO_2CH_2CH_3$, **A**), 13.1 ($CHCH_3$, **A**), 10.7 ($CHCH_3$, **B**); **IR** (ATR) v_{Max}/cm^{-1} 3496 (OH), 2982, 2941, 1729 (C=O), 1463, 1370, 1191, 1137, 1097, 1069, 1022, 913, 860, 790; **HRMS** (ESI^+) *m/z* found 205.1072 ($M+H^+$, $C_9H_{17}O_5$ requires 205.1071) and 227.0904 ($M+Na^+$, $C_9H_{16}O_5Na$ requires 227.0890); $[\alpha]_D^{20}$ = -8.3 (*c* 1.00, diethyl ether),

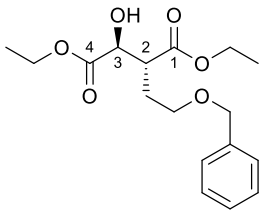
lit.[170] **40a**: $[\alpha]_D^{23}$ = -10.2 (*c* 1.14, diethyl ether) and **40b**: $[\alpha]_D^{23}$ = +2.8 (*c* 1.47, diethyl ether). Spectroscopic data matched that previously reported.[170–172]

((2-Iodoethoxy)methyl)benzene 41



To a solution of 2-(benzyloxy)ethanol **365** (5.00 g, 32.9 mmol, 1 equiv.) in CH_2Cl_2 (95 mL), cooled to 0 °C, triphenylphosphine (12.9 g, 49.3 mmol, 1.5 equiv.), imidazole (3.36 g, 49.3 mmol, 1.5 equiv.) and iodine (12.5 g, 49.3 mmol, 1.5 equiv.) were successively added. The resulting reaction mixture was warmed to room temperature and stirred for 18 h. Aqueous sodium thiosulfate solution (1 M; 100 mL) was then added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were then washed with brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless oil (8.59 g, 32.8 mmol, *quant.*). **R_f** = 0.25 (1% diethyl ether in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.39-7.28 (5 H, m, Ar*H*), 4.59 (2 H, s, ArOC*H_2*), 3.75 (2 H, t, *J* = 6.7 Hz, 1-*H_2*), 3.29 (2 H, t, *J* = 6.7 Hz, 2-*H_2*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 137.9 (*Ar*), 128.6 (*Ar*H), 128.0 (*Ar*H), 127.9 (*Ar*H), 73.0 (ArO*C*H_2), 70.9 (1-*C*H_2), 3.1 (2-*C*H_2); **IR** (ATR) ν_{Max}/cm^{-1} 3085, 3061, 3028, 2856, 1495, 1452, 1357, 1260, 1202, 1189, 1168, 1090, 1074, 1026, 982, 735, 696, 630, 592, 487, 459; the compound did not ionise under the ESI-HRMS conditions used. Spectroscopic data matched that previously reported.[132]

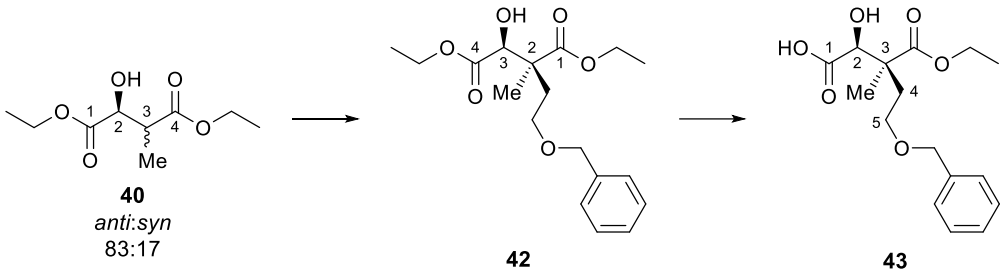
Diethyl (2*R*,3*S*)-2-(2-(benzyloxy)ethyl)-3-hydroxysuccinate 366



A freshly prepared solution of lithium diisopropylamine (1 M; 35.2 mmol, 35.2 mL, 2.3 equiv.) was added to a solution of (*S*)-diethyl 2-hydroxysuccinate **39** (2.90 g, 15.3 mmol, 1 equiv.), In THF (40 mL), cooled to -78 °C. The resulting reaction mixture was then stirred for 3 h at -78 °C. ((2-Iodoethoxy)methyl)benzene **41** (6.00 g, 22.9 mmol, 1.5 equiv.) was then slowly added to the resulting reaction mixture over a 10 min period. This solution was then stirred at -78 °C for 8 h and gradually warmed to room temperature, over a 13 h period. The reaction mixture was then quenched

with a solution of acetic acid (2.60 mL, 45.8 mmol, 3 equiv.) in diethyl ether (10 mL) at 0 °C, stirred for 5 min and was then warmed to room temperature. The resulting solution was then added to water (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic phases were then washed with *sat.* aqueous sodium hydrogen carbonate solution (100 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, using the elution gradient 20 to 50% diethyl ether in hexane, affording the *title compound* as a pale-yellow oil (997 mg, 3.07 mmol, 20%, 9:1 *dr*) and another fraction containing (*S*)-diethyl 2-hydroxysuccinate **39** and the *title compound* (1.34 g, 4.12 mmol, 27%, 7:1 *dr*) as a pale-yellow oil (ratio **366**:**39** 1.82:1). $\mathbf{R_f}$ = 0.22 (50% diethyl ether in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.36-7.26 (5 H, m, Ar*H*), 4.51 (2 H, s, ArCH_2), 4.29 (1 H, d, *J* = 3.2 Hz, 2-*H*), 4.30-4.22 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, 4-$CO_2CH_{2A,B}$), 4.17-4.06 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, 1-$CO_2CH_{2A,B}$), 3.65-3.54 (2 H, m, BnOCH_2), 3.28 (1 H, br s, O*H*), 3.17 (1 H, ddd, *J* = 7.1, 7.1, 3.2 Hz, 3-*H*), 2.21 (1 H, dddd, *J* = 14.3, 7.1, 7.1, 5.1 Hz, 2-CHCH_{2A}), 1.97 (1 H, dddd, *J* = 14.3, 7.1, 7.1, 5.1 Hz, 2-CHCH_{2B}), 1.31 (3 H, t, *J* = 7.1 Hz, 4-$CO_2CH_2CH_3$), 1.22 (3 H, t, *J* = 7.1 Hz, 1-$CO_2CH_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 173.5 (4-*C*=O), 172.5 (1-*C*=O), 138.4 (*Ar*), 128.5 (*Ar*H), 127.8 (*Ar*H), 73.1 (ArCH_2), 71.1 (3-*C*H), 67.7 (BnOCH_2), 62.0 (4-CO_2CH_2), 61.0 (1-CO_2CH_2), 45.6 (2-*C*H), 28.3 (2-CHCH_2), 14.3 (4-$CO_2CH_2CH_3$), 14.2 (1-$CO_2CH_2CH_3$), the signal due to *Ar*H was not observed; **IR** (ATR) ν_{Max}/cm^{-1} 3488 (OH), 2981, 2934, 2868, 1732 (C=O), 1454, 1370, 1209, 1180, 1096, 1026, 861, 737, 698, 610, 461; **HRMS** (ESI$^+$) *m/z* found 325.1653 ($M+H^+$, $C_{17}H_{25}O_6$ requires 325.1646), 347.1477 ($M+Na^+$, $C_{17}H_{24}O_6Na$ requires 347.1465) and 342.1901 ($M+NH_4^+$, $C_{17}H_{28}NO_6$ requires 342.1911); $[\alpha]_D^{25}$ = +12.2 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[173]

(2*S*,3*S*)-5-(Benzyloxy)-3-(ethoxycarbonyl)-2-hydroxy-3-methylpentanoic acid 43

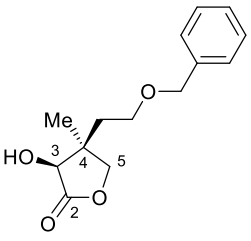


A freshly prepared solution of lithium diisopropylamine (1 M; 39.3 mmol, 39.3 mL, 2.3 equiv.) was added to a solution of hydroxysuccinate esters **40a-b** (ratio **40a**:**40b** 83:17, 3.50 g, 17.1 mmol, 1 equiv.) in THF (45 mL), cooled to -78 °C. The resulting reaction mixture was all stirred for 3 h at -78 °C. ((2-Iodoethoxy)methyl)benzene **41** (6.74 g, 25.7 mmol, 1.5 equiv.) was then slowly added to the resulting reaction mixture over a 10 min period. The resulting solution was stirred at -78 °C for 8 h and was then at gradually warmed to room temperature, over a 13 h period. The resulting reaction mixture was then left at 0 °C for 13 h. The reaction mixture was then quenched with a solution of acetic acid (2.90 mL, 51.4 mmol, 3 equiv.) in diethyl ether (5 mL) at 0 °C, stirred for 5 min and was then warmed to room temperature. The resulting solution was then added to water (50 mL) and extracted with diether ether (3 x 100 mL). The combined organic phases were then washed with *sat.* aqueous sodium hydrogen carbonate solution (100 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, using the elution gradient 10 to 25% ethyl acetate in hexane, affording an inseparable mixture of the starting material and the *title compound* as a pale-yellow oil (3.42 g, 16.7:1 *dr*). $\mathbf{R_f}$ = 0.19 (10% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.37-7.25 (5 H, m, Ar*H*), 4.47 (2 H, s, ArCH_2), 4.32 (1 H, br s, 3-C*H*), 4.22 (2 H, q, *J* = 7.1 Hz, 4-CO_2CH_2), 4.11 (2 H, q, *J* = 7.1 Hz, 1-CO_2CH_2), 3.66 (1 H, br s, O*H*), 3.54 (2 H, app t, *J* = 6.6 Hz, BnOC$H_{2A,B}$), 2.16 (1 H, ddd, *J* = 14.4, 6.6, 6.6 Hz, 2-CCH_{2A}), 1.92 (1 H, ddd, *J* = 14.4, 6.6, 6.6 Hz, 2-CCH_{2B}), 1.28 (3 H, t, *J* = 7.1 Hz, 4-$CO_2CH_2CH_3$), 1.23 (3 H, s, 2-CCH_3), 1.22 (3 H, t, *J* = 7.1 Hz, 1-$CO_2CH_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 174.7 (4-*C*=O), 172.7 (1-*C*=O), 138.1 (*Ar*), 128.5 (*Ar*H), 127.81 (*Ar*H), 127.77 (*Ar*H), 75.9 (3-*C*H), 73.2 (Ar*C*H_2), 66.5 (BnO*C*H_2), 61.9 (4-CO_2*C*H_2), 61.2 (1-CO_2*C*H_2), 48.8 (2-*C*), 34.5 (2-C*C*H_2), 18.2 (2-C*C*H_3), 14.3 (4-CO_2CH_2*C*H_3), 14.2 (1-CO_2CH_2*C*H_3); **HRMS** (ESI^+) *m/z* found 339.1807 ($M+H^+$, $C_{18}H_{27}O_6$ requires 339.1802), 361.1641 ($M+Na^+$,

$C_{18}H_{26}O_6Na$ requires 361.1622) and 356.2073 ($M+NH_4^+$, $C_{18}H_{30}NO_6$ requires 356.2068). Spectroscopic data matched that previously reported.[15]

A solution of potassium hydroxide (1.93 g, 34.3 mmol, 3.4 equiv.) in methanol (20 mL) and water (1.35 mL) was added to a solution of crude hydroxysuccinate ester **42** (3.42 g, 10.1 mmol, 1 equiv.) in methanol (27 mL) cooled to -40 °C. The resulting reaction mixture was stirred for 1 h at -40 °C, warmed to room temperature and stirred for 3 days. The resulting solution was then acidified by the addition of 2 M hydrochloric acid to pH-2 and the reaction mixture was extracted with diethyl ether (4 x 100 mL). The combined organic phases were then dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a yellow syrup (2.32 g, 7.46 mmol, 44% over two steps, 16.7:1 *dr*). **R_f** = 0.22 (5% MeOH in CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.41 (1 H, br s, CO_2H), 7.38-7.28 (5 H, m, Ar*H*), 4.58-4.50 (3 H, m, 2-*H*; ArCH_2), 4.18-4.09 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, $CH_3CH_{2A,B}$), 3.71-3.58 (2 H, m, 5-$H_{2A,B}$), 3.66 (1 H, s, O*H*), 2.13-2.01 (2 H, m, 4-$H_{2A,B}$), 1.28 (3 H, s, 3-CCH_3), 1.22 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.0 (*C*=O), 174.1 (1-*C*=O), 136.7 (*Ar*), 128.8 (*Ar*H), 128.4 (*Ar*H), 128.2 (*Ar*H), 74.1 (2-*C*H), 73.8 (ArCH_2), 66.6 (5-CH_2), 61.6 (CH_3CH_2), 49.3 (3-*C*), 35.4 (4-CH_2), 19.3 (3-CCH_3), 14.1 (CH_2CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 3424 (OH), 3031, 2980, 2937, 2872, 1720 (C=O), 1454, 1366, 1210, 1093, 1026, 942, 862, 737, 698, 609, 463; **HRMS** (ESI$^+$) *m/z* found 311.1498 ($M+H^+$, $C_{16}H_{23}O_6$ requires 311.1489), 333.1316 ($M+Na^+$, $C_{16}H_{22}O_6Na$ requires 333.1309) and 328.1766 ($M+NH_4^+$, $C_{16}H_{26}NO_6$ requires 356.2068); $[\alpha]_D^{22}$ = +7.6 (*c* 1.00, ethanol), lit.[15] $[\alpha]_D^{27}$ = +8.4 (*c* 0.71, ethanol). Spectroscopic data matched that previously reported.[15]

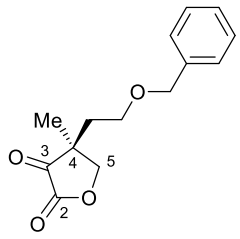
(3*S*,4*S*)-4-(2-(Benzyloxy)ethyl)-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one 44



Lithium triethylborohydride in THF (1 M; 37.8 mL, 37.8 mmol, 6 equiv.) was added, over a 10 min period, to a solution of carboxylic acid **43** (1.96 g, 6.31 mmol, 1 equiv.) in THF (75 mL) cooled to -78 °C. The resulting reaction mixture was stirred at -78 °C for 3 h, warmed to room temperature and stirred for 40 h. The resulting solution was then cooled to -10 °C, quenched with 2 M HCl (19 mL) and was stirred for 30 min. The solution was then warmed to room temperature and concentrated *in*

vacuo. The resulting aqueous solution was then extracted with diethyl ether (3 x 100 mL) and the combined organic phases were then washed with water (100 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a colourless viscous oil (1.23 g, 4.90 mmol, 78%). **R_f** = 0.20 (33% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.38-7.28 (5 H, m, Ar*H*), 4.59 (1 H, d, *J* = 11.7 Hz, ArCH_{2A}), 4.31 (1 H, d, *J* = 11.7 Hz, ArCH_{2B}), 4.19 (1 H, d, *J* = 9.5 Hz, 5-H_A), 4.09-4.03 (2 H, m, 3-*H*; O*H*), 3.97 (1 H, d, *J* = 9.5 Hz, 5-H_B), 3.62 (1 H, ddd, *J* = 10.1, 5.4, 3.4 Hz, BnOCH_{2A}), 3.48 (1 H, ddd, *J* = 10.1, 10.1, 2.3 Hz, BnOCH_{2B}), 1.94 (1 H, dddd, *J* = 15.2, 10.1, 3.4, 1.3 Hz, 4-CCH_{2A}), 1.62 (1 H, ddd, *J* = 15.2, 5.4, 2.3 Hz, 4-CCH_{2B}), 1.23 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 176.6 (2-*C*=O), 136.8 (*Ar*), 128.7 (*Ar*H), 128.5 (*Ar*H), 128.3 (*Ar*H), 75.7 (3-*C*H), 74.9 (5-*C*H_2), 73.5 (Ar*C*H_2), 66.2 (BnO*C*H_2), 42.9 (4-*C*), 34.4 (4-C*C*H_2), 24.1 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 3421 (OH), 3031, 2962, 2876, 1776 (C=O), 1456, 1366, 1207, 1103, 1000, 914, 875, 736, 698, 605, 458; **HRMS** (ESI$^+$) *m/z* found 251.1281 (M+H$^+$, $C_{14}H_{19}O_4$ requires 251.1278), 273.1096 (M+Na$^+$, $C_{14}H_{18}O_4Na$ requires 273.1097) and 268.1547 (M+NH_4^+, $C_{14}H_{22}NO_4$ requires 268.1543); $[\alpha]_D^{18}$ = +16.7 (*c* 1.00, $CHCl_3$), lit.[15] $[\alpha]_D^{27}$ = +6.0 (*c* 0.80, ethanol). Spectroscopic data matched that previously reported.[15]

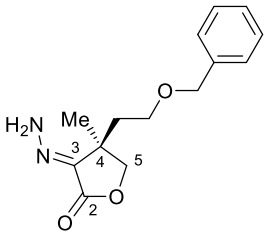
(*S*)-4-(2-(Benzyloxy)ethyl)-4-methyldihydrofuran-2,3-dione 82



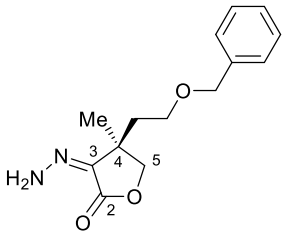
Dess-Martin periodinane (1.20 g, 2.83 mmol, 1.1 equiv.) was added to a solution of alcohol **44** (645 mg, 2.57 mmol, 1 equiv.) in CH_2Cl_2 (20 mL), cooled to 0 °C. The resulting reaction mixture was stirred at 0 °C for 10 min, warmed to room temperature and stirred for 5 h. The reaction solution was then cooled to -15 °C, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a colourless oil (503 mg, 2.03 mmol, 79%). **R_f** = 0.27 (33% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.36-7.23 (5 H, m, Ar*H*), 4.66 (1 H, d, *J* = 9.9 Hz, ArCH_{2A}), 4.40 (1 H, d, *J* = 12.2 Hz, 5-H_A), 4.35 (1 H, d, *J* = 12.2 Hz, 5-H_B), 4.34 (1 H, d, *J* = 9.9 Hz, ArCH_{2B}), 3.54-3.45 (2 H, m, BnOCH_2), 2.22 (1 H, ddd, *J* = 14.4, 10.0, 6.1 Hz, 4-CCH_{2A}), 1.80 (1 H, ddd, *J* = 14.4, 3.5, 3.5 Hz, 4-CCH_{2B}), 1.28 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 196.9 (3-*C*=O),

161.0 (2-*C*=O), 137.0 (*Ar*), 128.6 (*Ar*H), 128.13 (*Ar*H), 128.10 (*Ar*H), 74.9 (Ar*C*H_2), 73.3 (5-*C*H_2), 64.8 (BnO*C*H_2), 43.0 (4-*C*), 38.4 (4-C*C*H_2), 22.3 (*C*H_3); **IR** (ATR) v_{Max}/cm^{-1} 2919, 2869, 1785 (C=O), 1454, 1391, 1367, 1339, 1289, 1230, 1134, 1095, 990, 829, 737, 699, 604, 537, 488, 462; **HRMS** (ESI^+) *m/z* found 271.0942 ($M+Na^+$, $C_{14}H_{16}O_4Na$ requires 271.0941) and 266.1389 ($M+NH_4^+$, $C_{14}H_{20}NO_4$ requires 266.1387); $[\alpha]_D^{20}$ = -0.21 (*c* 1.00, $CHCl_3$), lit.[18] $[\alpha]_D^{25}$ = -0.19 (*c* 2.70, $CHCl_3$). Spectroscopic data matched that previously reported.[18]

(*R*,*E*)- and (*R*,*Z*)-4-(2-(Benzyloxy)ethyl)-3-hydrazineylidene-4-methyldihydrofuran-2(3*H*)-one 363a and 363b



(*R*,*E*)-**363a**



(*R*,*Z*)-**363b**

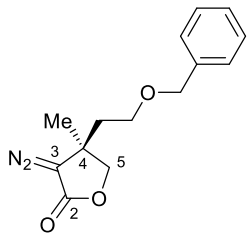
A solution of hydrazine acetate (267 mg, 2.90 mmol, 1 equiv.) and ketolactone **82** (719 mg, 2.90 mmol, 1 equiv.) in THF (20 mL) was left stirring at room temperature for 20 h, upon which hydrazone **363a** precipitates. Aqueous *sat.* sodium hydrogen carbonate solution (10 mL) was then added to the reaction mixture, causing the visible precipitate to dissolve completely. The resulting solution was then extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (5 mL) and dried with $MgSO_4$. The dried organic phase was then concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 50 to 100% ethyl acetate in hexane, affording the separated *title compounds*, in a *E*:*Z* 88:12 ratio.

(*R*,*E*)-4-(2-(Benzyloxy)ethyl)-3-hydrazineylidene-4-methyldihydrofuran-2(3*H*)-one 363a as a colourless solid (548 mg, 2.09 mmol, 72%). $\mathbf{R_f}$ = 0.12 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.38-7.27 (5 H, m, Ar*H*), 6.58 (2 H, br s, N*H*$_2$), 4.50 (1 H, d, *J* = 11.7 Hz, ArC*H*$_{2A}$), 4.44 (1 H, d, *J* = 11.7 Hz, ArC*H*$_{2B}$), 4.27 (1 H, d, *J* = 9.0 Hz, 5-*H*$_A$), 3.94 (1 H, d, *J* = 9.0 Hz, 5-*H*$_B$), 3.62-3.51 (2 H, m, BnOC*H*$_2$), 2.12 (1 H, ddd, *J* = 14.9, 8.3, 5.0 Hz, 4-CC*H*$_{2A}$), 1.97 (1 H, ddd, *J* = 14.9, 5.7, 4.3 Hz, 4-CC*H*$_{2B}$), 1.50 (3 H, s, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 167.9 (2-*C*=O), 137.4 (3-*C*=N), 136.6 (*Ar*), 128.7 (*Ar*H), 128.2 (*Ar*), 127.9 (*Ar*H), 77.2 (5-*C*H_2), 73.6 (Ar*C*H_2), 67.4 (BnO*C*H_2), 40.8 (4-*C*), 36.7 (4-C*C*H_2), 20.9 (*C*H_3); **IR**

(ATR) v_{Max}/cm^{-1} 3412 (NH_2), 3286, 3233, 2964, 2911, 2871, 1724 (C=O), 1575 (C=N), 1455, 1377, 1363, 1319, 1272, 1115, 1007, 729, 695, 532, 426; **HRMS** (ESI^+) *m/z* 263.1396 ($M+H^+$, $C_{14}H_{19}N_2O_3$ requires 263.1390) and 285.1219 ($M+Na^+$, $C_{14}H_{18}N_2O_3Na$ requires 285.1210); **mp** 136-138 °C; $[\alpha]_D^{21}$ = +149 (*c* 0.50, $CHCl_3$).

(*R*,*Z*)-4-(2-(Benzyloxy)ethyl)-3-hydrazineylidene-4-methyldihydrofuran-2(3*H*)-one 363b as a yellow oil (75.6 mg, 0.288 mmol, 10%). $\mathbf{R_f}$ = 0.53 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.00 (2 H, br s, N*H*$_2$), 7.36-7.27 (5 H, m, *Ar*H), 4.49-4.42 (3 H, m, ArC*H*$_2$; 5-*H*$_A$), 4.15 (1 H, d, *J* = 9.3 Hz, 5-*H*$_B$), 3.60-3.56 (2 H, m, BnOC*H*$_2$), 1.96 (1 H, ddd, *J* = 14.3, 7.0, 7.0 Hz, 4-CC*H*$_{2A}$), 1.85 (1 H, ddd, *J* = 14.3, 5.2, 5.2 Hz, 4-CC*H*$_{2B}$), 1.24 (3 H, s, *C*H$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 165.2 (2-*C*=O), 138.2 (3-*C*=N), 134.2 (*Ar*), 128.5 (*Ar*H), 127.79 (*Ar*), 127.76 (*Ar*H), 78.5 (5-*C*H$_2$), 73.4 (Ar*C*H$_2$), 66.8 (BnO*C*H$_2$), 40.2 (4-*C*), 38.6 (4-C*C*H$_2$), 24.6 (*C*H$_3$); **IR** (ATR) v_{Max}/cm^{-1} 3440 (NH_2), 3284, 2965, 2924, 2865, 1728 (C=O), 1585 (C=N), 1454, 1367, 1268, 1206, 1101, 999, 912, 790, 735, 697, 453; **HRMS** (ESI^+) *m/z* found 263.1389 ($M+H^+$, $C_{14}H_{19}N_2O_3$ requires 263.1390) and 285.1216 ($M+Na^+$, $C_{14}H_{18}N_2O_3Na$ requires 285.1210); $[\alpha]_D^{21}$ = +14.3 (*c* 0.55, $CHCl_3$).

(*R*)-4-(2-(Benzyloxy)ethyl)-3-diazo-4-methyldihydrofuran-2(3*H*)-one 364

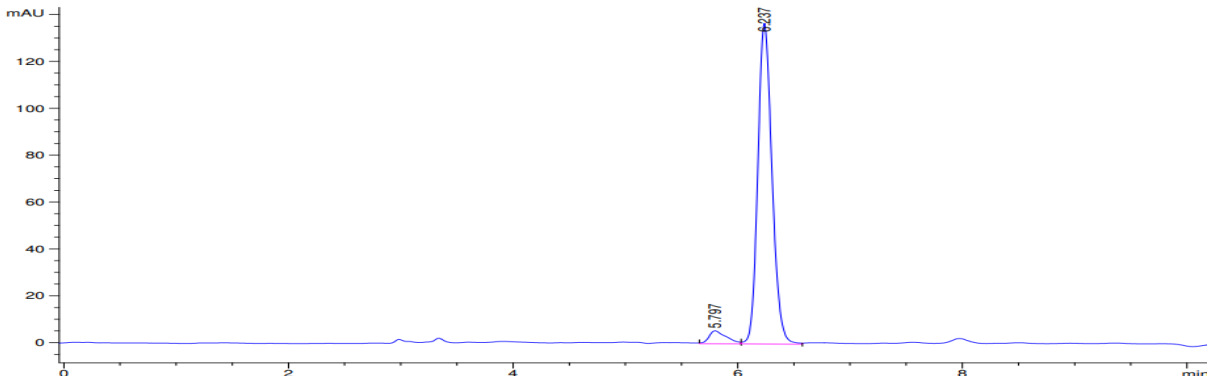


Method I: A solution of hydrazine acetate (14.1 mg, 0.153 mmol, 1 equiv.) and ketolactone **82** (38.0 mg, 0.153 mmol, 1 equiv.) in THF (1 mL) was left stirring at room temperature for 20 h, upon which hydrazone **363a** precipitates. Aqueous potassium hydroxide (1 M; 0.2 mL) was then added to the reaction mixture (so that the final volume ratio 1 M KOH:THF was 1:4), causing the visible precipitate to dissolve completely. Potassium *N*-iodo *p*-toluenesulfonamide **278** (77.2 mg, 0.23 mmol, 1.5 equiv.) was then slowly added to the solution, causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 1 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (30 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 1 mL), brine (1 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (31.1 mg, 0.12 mmol, 78%, 90% *ee*).

Method II: A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (129 mg, 0.384 mmol, 1.2 equiv.) and hydrazone **363b** (84.0 mg, 0.320 mmol, 1 equiv.) in THF (1.28 mL) was prepared. Aqueous potassium hydroxide (1 M; 0.32 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 1.6 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (10 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 1.6 mL), brine (1.6 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (71.0 mg, 0.273 mmol, 85%, 90% *ee*).

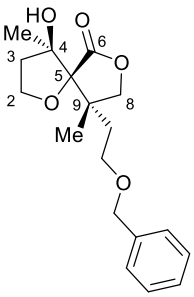
Method III: A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (545 mg, 1.62 mmol, 1.2 equiv.) and hydrazone **363a** (354 mg, 1.35 mmol, 1 equiv.) in THF (5.4 mL) was prepared. Aqueous potassium hydroxide (1 M; 1.35 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 6.75 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (40 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 6.75 mL), brine (6.75 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (301 mg, 1.16 mmol, 86%, 90% *ee*). $\mathbf{R_f}$ = 0.53 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.38-7.29 (5 H, m, Ar*H*), 4.48 (2 H, s, ArC*H*$_2$), 4.25 (1 H, d, *J* = 8.9 Hz, 5-*H*$_A$), 4.01 (1 H, d, *J* = 8.9 Hz, 5-*H*$_B$), 3.59 (2 H, app t, *J* = 5.8 Hz, BnOC*H*$_2$), 1.96 (2 H, app t, *J* = 5.8 Hz, 4-CC*H*$_2$), 1.40 (3 H, s, C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 169.9 (2-*C*=O), 137.7 (*Ar*), 128.6 (*Ar*H), 128.0 (*Ar*), 78.1 (5-*C*H$_2$), 73.5 (Ar*C*H$_2$), 66.3 (BnO*C*H$_2$), 41.6 (4-*C*), 38.8 (4-C*C*H$_2$), 23.9 (*C*H$_3$), the signals due to 3-*C*N$_2$ and *Ar*H were not observed; **IR** (ATR) ν_{Max}/cm^{-1} 2964, 2906, 2864, 2091 (CN$_2$), 1728 (C=O), 1454, 1389, 1375, 1344, 1249, 1218, 1123, 1099, 1055, 1010, 731, 699, 603, 531, 463; **HRMS** (ESI$^+$) *m/z* found 283.1051 (M+Na$^+$, $C_{14}H_{16}N_2O_3Na$ requires 283.1053) and 278.1494 (M+NH$_4^+$, $C_{14}H_{20}N_3O_3$ requires 278.1499); $[\alpha]_D^{21}$ = +12.4 (*c* 1.00, $CHCl_3$).

(*R*)-**364** (90% *ee*) Chiral HPLC spectrum (Chiralcel OJ-H, 90:10 *i*-hexane:*i*-PrOH, 1 mL/min, 254 nm, ambient temperature).

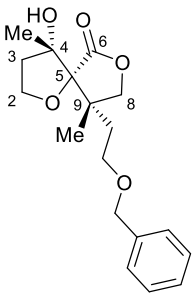


Peak	Retention Time / min	Relative Area	Area %
1	5.797	58.90127	4.6738
2	6.237	1201.33997	95.3262

(4*R*,5*S*,9*S*)- and (4*S*,5*R*,9*S*)-9-(2-(Benzyloxy)ethyl)-4-hydroxy-4,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one 368a and 368b



cis,*trans*-**368a**

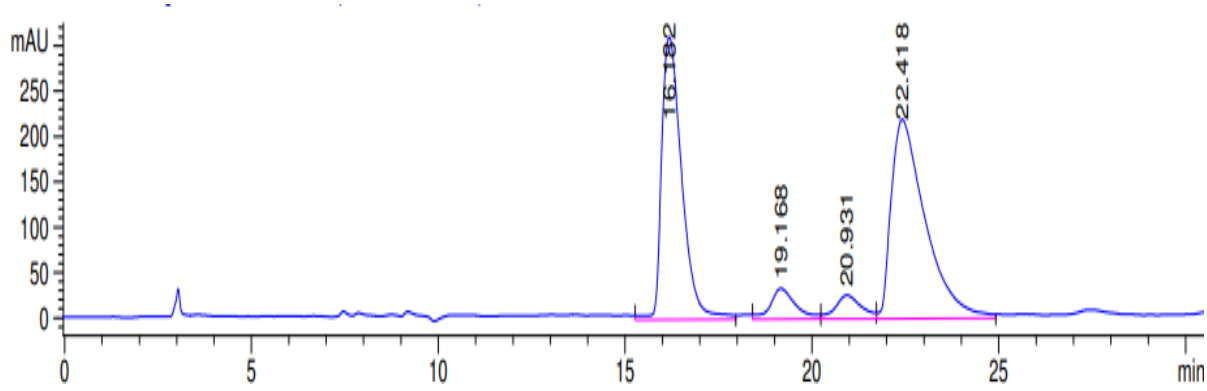


cis,*cis*-**368b**

A solution containing α-diazolactone **364** (78.1 mg, 0.30 mmol, 2 equiv.) in CH_2Cl_2 (1 mL) was added, over a 30 min period, to a refluxing solution of 4-hydroxy-2-butanone **196** (13.0 µL, 0.15 mmol, 1 equiv.) and rhodium(II) octanoate dimer (1.2 mg, 1.50 µmol, 1 mol%) in CH_2Cl_2 (1.5 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compounds*, an inseparable mixture of diastereoisomers **368a** and **368b**, as a colourless oil (ratio **368a**:**368b** 1:1, 33.6 mg, 105 µmol, 70%, 90% *ee*). Stereochemical assessments for diastereoisomers **368a** and **368b** could not be distinguished using NOSEY NMR studies. $\mathbf{R_f}$ = 0.37 (33% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.38-7.27 (10 H, m, Ar*H*), 4.48 (4 H, br s, ArCH_2), 4.33 (1 H, d, *J* = 8.3 Hz, 8-H_A), 4.32 (1 H, d, *J* = 8.6 Hz, 8-H_A), 4.02-3.85 (2 H, m, 8-H_B; 4 H, m, 2-H_2), 3.63-3.58 (2 H, m, BnOCH_{2A}), 3.57-3.53 (2 H, m, BnOCH_{2B}), 3.03 (2 H, br s, O*H*), 2.79-2.70 (2 H, m,

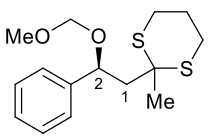
3-H_A), 2.28 (1 H, dt, J = 14.5, 7.4 Hz, 9-CCH_{2A}), 2.07-2.00 (2 H, m, 3-H_B), 1.99-1.87 (2 H, m, 9-CCH_2), 1.75 (1 H, dt, J = 14.5, 5.2 Hz, 9-CCH_{2B}), 1.41 (6 H, br s, 9-CCH_3), 1.27 (s, 3 H, 4-CCH_3), 1.14 (s, 3 H, 4-CCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 177.0 (6-*C*=O), 176.8 (6-*C*=O), 138.2 (*Ar*), 138.1 (*Ar*), 128.60 (*Ar*H), 128.56 (*Ar*H), 127.9 (*Ar*H), 127.8 (*Ar*H), 127.74 (*Ar*H), 127.72 (*Ar*H), 86.5 (5-*C*), 85.7 (5-*C*), 78.6 (8-*C*H_2), 78.3 (4-*C*), 78.1 (4-*C*), 75.3 (8-*C*H_2), 73.4 (Ar*C*H_2), 73.2 (Ar*C*H_2), 66.7 (BnO*C*H_2), 66.3 (BnO*C*H_2), 64.9 (2-*C*H_2), 64.8 (2-*C*H_2), 44.0 (9-*C*), 43.6 (9-*C*), 41.8 (3-*C*H_2), 41.7 (3-*C*H_2), 31.4 (9-C*C*H_2), 30.4 (9-C*C*H_2), 23.7 (4-C*C*H_3), 23.4 (4-C*C*H_3), 17.9 (9-C*C*H_3), 14.7 (9-C*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 3540 (OH), 2976, 2893, 1754 (C=O), 1453, 1366, 1272, 1205, 1177, 1098, 1075, 1011, 940, 738, 698, 663, 461; **HRMS** (ESI$^+$) *m/z* found 321.1709 (M+H$^+$, $C_{18}H_{25}O_5$ requires 321.1697), 343.1530 (M+Na$^+$, $C_{18}H_{24}O_5Na$ requires 343.1516) and 338.1966 (M+NH_4^+, $C_{18}H_{28}NO_5$ requires 338.1962); $[\alpha]_D^{17}$ = -67.0 (*c* 0.50, $CHCl_3$).

368a-b (90% *ee*, 1:1 *dr*) Chiral HPLC spectrum (Chiralcel OJ-H, 90:10 *i*-hexane:*i*-PrOH, 1 mL/min, 210 nm, ambient temperature).



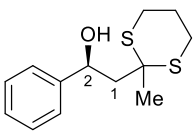
Peak	Retention Time / min	Relative Area	Area %
1	16.182	1.17881e4	41.1431
2	19.168	1599.25464	5.5818
3	20.931	1264.64624	4.4139
4	22.418	1.39995e4	48.8612

(*S*)-2-(2-(Methoxymethoxy)-2-phenylethyl)-2-methyl-1,3-dithiane 388



n-Butyllithium (2.27 M in hexanes; 5.40 mL, 12.2 mmol, 1.2 equiv.) was added dropwise, over the course of 10 min, to a solution of 1,3-dithiane **322** (2.90 g, 10.2 mmol, 1 equiv.) in THF (36 mL) at 0 °C. After stirring for 1 h, methyl iodide (0.76 mL, 12.2 mmol, 1.2 equiv.) was then added and the resulting solution stirred for an additional 30 min. The reaction mixture was then warmed to room temperature, stirred for 16 h, quenched with *sat.* aqueous ammonium chloride solution (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic phases were then washed with brine (20 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (2.27 g, 7.60 mmol, 75%). $\mathbf{R_f}$ = 0.19 (15% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.36-7.32 (4 H, m, Ar*H*), 7.31-7.25 (1 H, m, Ar*H*), 4.90 (1 H, dd, *J* = 7.6, 3.5 Hz, 2-*H*), 4.52 (1 H, d, *J* = 6.7 Hz, OCH_{2A}O), 4.48 (1 H, d, *J* = 6.7 Hz, OCH_{2B}O), 3.36 (3 H, s, OCH_3), 2.90 (1 H, ddd, *J* = 14.4, 9.9, 3.1 Hz, SCH_{2A}), 2.83-2.72 (3 H, m, SCH_2; SCH_{2B}), 2.48 (1 H, dd, *J* = 15.1, 7.6 Hz, 1-H_A), 2.37 (1 H, dd, *J* = 15.1, 3.5 Hz, 1-H_B), 2.00 (1 H, dtt, *J* = 13.8, 6.3, 3.1 Hz, SCH_2CH_{2A}), 1.89 (1 H, dtt, *J* = 13.8, 9.9, 3.6 Hz, SCH_2CH_{2B}), 1.65 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 142.8 (*Ar*), 128.7 (*Ar*H), 127.8 (*Ar*H), 127.1 (*Ar*H), 94.7 (OCH_2O), 76.4 (2-*C*H), 56.5 (OCH_3), 48.7 (1-*C*H_2), 48.4 (S*C*S), 28.7 (CH_3), 26.8 (SCH_{2A}), 26.7 (SCH_{2B}), 25.1 (SCH_2CH_2); **IR** (ATR) ν_{Max}/cm^{-1} 3061, 3028, 2928, 2903, 2821; **HRMS** (ESI^+) *m/z* found 321.0957 (M+Na, $C_{15}H_{22}O_2S_2Na$ requires 321.0953); $[\alpha]_D^{17}$ = -78.7 (*c* 1.00, $CHCl_3$).

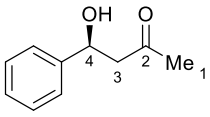
(*S*)-2-(2-Methyl-1,3-dithian-2-yl)-1-phenylethan-1-ol 389



An aqueous solution of hydrochloric acid (6 M; 6.33 mL, 38.0 mmol, 20 equiv.) was added to a solution of methoxymethyl ether **388** (567 mg, 1.90 mmol, 1 equiv.) in methanol (30 mL). The resulting reaction mixture was then heated to 50 °C and stirred for 18 h. Water (30 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 30 mL). The combined organic phases were then washed with brine (30 mL), dried with $MgSO_4$, concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 10 to 20% ethyl acetate in petroleum ether,

affording the *title compound* as a colourless oil (282 mg, 1.11 mmol, 59%). **R_f** = 0.46 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.40-7.33 (4 H, m, Ar*H*), 7.29-7.25 (1 H, m, Ar*H*), 5.05 (1 H, ddd, *J* = 9.6, 2.0, 2.0 Hz, 2-*H*), 3.62 (1 H, d, *J* = 2.0 Hz, OH), 3.06 (1 H, ddd, *J* = 13.9, 10.7, 2.9 Hz, SCH_{2A}), 2.96 (1 H, ddd, J = 13.9, 10.7, 2.9 Hz, SCH_{2A}), 2.87-2.72 (2 H, m, SCH_{2B}; SCH_{2B}), 2.61 (1 H, dd, *J* = 15.1, 9.6 Hz, 1-H_A), 2.14 (1 H, dd, *J* = 15.1, 2.0 Hz, 1-H_B), 2.10-2.02 (1 H, m, SCH_2CH_{2A}), 1.90 (1 H, dtt, *J* = 13.8, 10.7, 3.2 Hz, SCH_2CH_{2B}), 1.73 (3 H, s, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 144.6 (*Ar*), 128.6 (*Ar*H), 127.5 (*Ar*H), 125.8 (*Ar*H), 71.7 (2-*C*H), 49.8 (1-*C*H_2), 47.8 (S*C*S), 28.6 (*C*H_3), 26.9 (S*C*H_{2A}), 26.7 (S*C*H_{2B}), 24.7 (SCH_2CH_2); **IR** (ATR) ν_{Max}/cm^{-1} 3413 (OH), 3060, 3026, 2905; **HRMS** (ESI$^+$) *m/z* found 277.0692 (M+Na, C13H18NaOS2 requires 277.0691); $[\alpha]_D^{18}$ = -67.0 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[174]

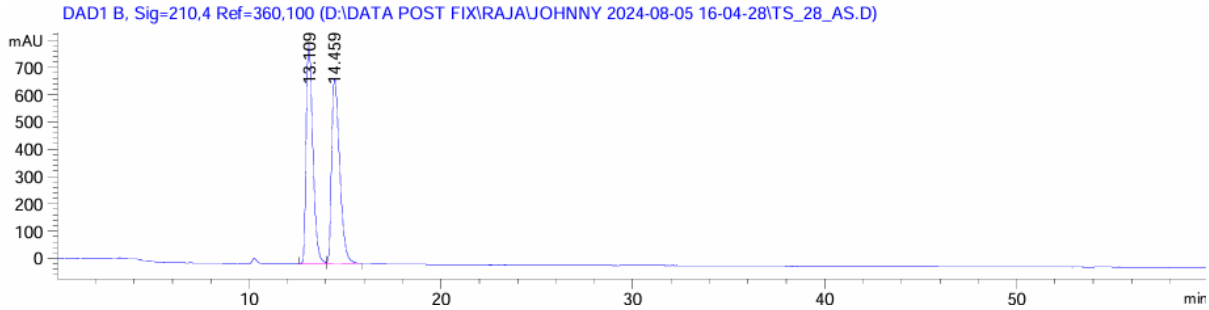
(*S*)-4-Hydroxy-4-phenylbutan-2-one 390



Methyl iodide (220 µL, 3.51 mmol, 9 equiv.) was added to a solution of 1,3-dithiane **389** (100 mg, 0.39 mmol, 1 equiv.) and calcium carbonate (2.60 g, 26.0 mmol, 10 equiv.) in acetonitrile:water (9:1; 2.6 mL), and was heated at 40 °C for 24 h. The resulting solution was then filtered through Celite® 545, extracted with ethyl acetate (3 x 10 mL), washed with brine (10 mL) and dried with $MgSO_4$. The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (56.8 mg, 0.34 mmol, 89%, 99% *ee*). **R_f** = 0.47 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.37-7.31 (4 H, m, Ar*H*), 7.30-7.26 (1 H, m, Ar*H*), 5.15 (1 H, dd, *J* = 9.0, 3.4 Hz, 4-*H*), 3.28 (1 H, br s, O*H*), 2.89 (1 H, dd, *J* = 17.6, 9.0 Hz, 3-H_A), 2.81 (1 H, dd, *J* = 17.6, 3.4 Hz, 3-H_B), 2.19 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.2 (2-*C*=O), 142.9 (*Ar*), 128.7 (*Ar*H), 127.8 (*Ar*H), 125.8 (*Ar*H), 70.0 (4-*C*H), 52.1 (3-*C*H_2), 30.9 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 3412 (OH), 3063, 3031, 2917, 1703 (C=O); **HRMS** (ESI$^+$) *m/z* found 187.0740 (M+Na, $C_{10}H_{12}O_2Na$ requires 187.0730); $[\alpha]_D^{17}$ = -99.0 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[175]

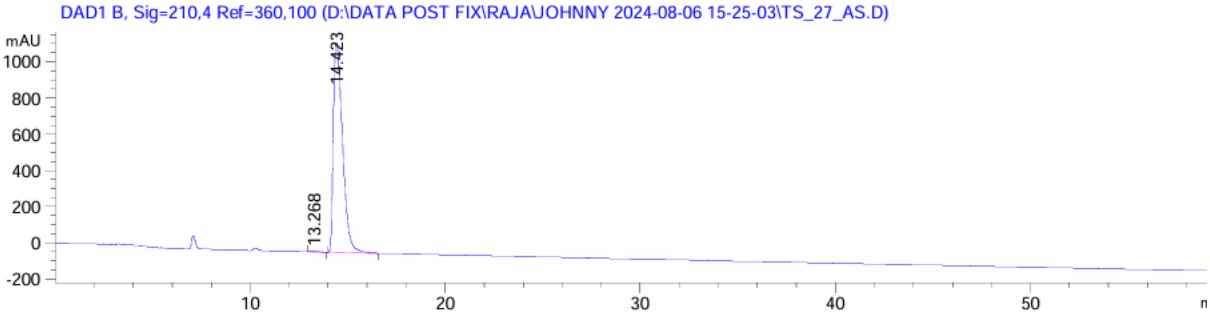
(±)-4-hydroxy-4-phenylbutan-2-one (±)-**390** was prepared following a known procedure.[176]

(±)-**390** (*rac*) Chiral HPLC spectrum (Chiralpak AS-H, 90:10 MeCN:*i*-PrOH, 1 mL/min, 210 nm, ambient temperature).



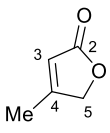
Peak	Retention Time / min	Relative Area	Area %
1	13.109	19628.7	49.7224
2	14.459	19847.9	50.2776

(*S*)-**390** (99% *ee*) Chiral HPLC spectrum (Chiralpak AS-H, 90:10 MeCN:*i*-PrOH, 1 mL/min, 210 nm, ambient temperature).



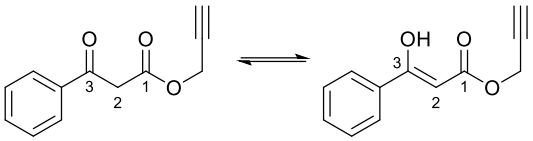
Peak	Retention Time / min	Relative Area	Area %
1	13.268	117.39691	0.3071
2	14.423	38111.5	99.6929

4-Methylfuran-2(5*H*)-one 382



Sodium borohydride (3.78 g, 100 mmol, 2.5 equiv.) was added to a solution of citraconic anhydride **381** (4.48 g, 40.0 mmol, 1 equiv.) in THF (85 mL), cooled to 0 °C, and was stirred for 2 h. The reaction mixture was then quenched with water, acidified with dilute hydrochloric acid, extracted with ethyl acetate (3 x 100 mL) and dried with $MgSO_4$. The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (2.96 g, 30.2 mmol, 75%). $\mathbf{R_f}$ = 0.16 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.83 (1 H, q, *J* = 1.7 Hz, 3-*H*), 4.70 (2 H, dd, *J* = 1.7 Hz, 0.9 Hz, 5-H_2), 2.12 (3 H, dd, *J* = 1.7, 0.9 Hz, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 174.3 (2-*C*=O), 166.1 (4-*C*), 116.6 (3-*C*H), 74.0 (5-*C*H_2), 14.2 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 3024, 2936, 1765 (C=O), 1728, 1664, 1406, 1271, 1156, 1070, 1009, 966, 928, 867, 759, 718, 497; **HRMS** (ESI^+) *m/z* found 99.0429 ($M+H^+$, $C_5H_7O_2$ requires 99.0441) and 121.0264 ($M+Na^+$, $C_5H_6O_2Na$ requires 121.0260). Spectroscopic data matched that previously reported.[138]

Prop-2-yn-1-yl 3-oxo-3-phenylpropanoate and Prop-2-yn-1-yl (*Z*)-3-hydroxy-3-phenylacrylate 377a and 377b

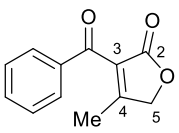


377a **377b**

Propargyl alcohol (3.75 mL, 65.0 mmol, 2.5 equiv.) and $BiCl_3$ (820 mg, 2.60 mmol, 10 mol%) were added to a solution of ethyl benzoylacetate **376** (5.00 g, 26.0 mmol, 1 equiv.) in toluene (45 mL) and heated to reflux in a Dean and Stark apparatus for 4 h. The resulting solution was cooled to room temperature, filtered, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compounds*, an interconverting mixture of tautomers **377a** (**A**) and **377b** (**B**), as an orange oil (ratio **377a**:**377b** 76:24, 3.36 g, 16.6 mmol, 64%). $\mathbf{R_f}$ = 0.23 (10% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 12.27 (1 H, s, O*H*, **B**), 7.94-7.91 (2 H, m, Ar*H*, **A**), 7.79-7.76 (2 H, m, Ar*H*, **B**), 7.62-7.57 (1 H, m, Ar*H*, **A**; 1 H, m, Ar*H*, **B**), 7.50-7.45 (2 H, m, Ar*H*, **A**), 7.44-7.39 (2 H, m, Ar*H*, **B**), 5.72 (1 H, s, 2-*H*, **B**), 4.81 (2 H, d, *J* = 2.5 Hz, OCH_2, **B**), 4.75 (2 H, d, *J* = 2.5 Hz, OCH_2, **A**), 4.05 (2 H, s, 2-H_2, **A**), 2.52 (1 H, t, *J* = 2.5 Hz, OCH_2CCH, **B**), 2.49 (1 H, t, *J* = 2.5 Hz, OCH_2CCH,

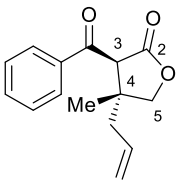
A); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 192.0 (3-*C*=O, **A**), 172.5 (*C*OH, **B**), 172.2 (1-*C*=O, **B**), 166.8 (1-*C*=O, **A**), 135.9 (*A*r, **A**), 134.0 (*Ar*H, **A**), 133.2 (*Ar*, **B**), 131.7 (*Ar*H, **B**), 128.9 (*Ar*H, **A**), 128.7 (*Ar*H, **B**), 128.6 (*Ar*H, **A**), 126.3 (*Ar*H, **B**), 86.7 (2-*C*H, **B**), 77.7 (OCH_2*C*CH, **A**), 77.4 (OCH_2*C*CH, **B**), 75.5 (OCH_2C*C*H, **A**), 75.2 (OCH_2C*C*H, **B**), 52.9 (O*C*H_2, **A**), 51.9 (O*C*H_2, **B**), 45.6 (2-*C*H_2, **A**); **IR** (ATR) v_{Max}/cm^{-1} 3289 (OH), 3064, 2941, 2130, 1744 (C=O), 1684 (C=O), 1617, 1597, 1580, 1450, 1409, 1370, 1325, 1264, 1210, 1180, 1139, 1080, 987, 938, 757, 686, 645, 533; **HRMS** (ESI^+) *m/z* found 203.0710 ($M+H^+$, $C_{12}H_{11}O_3$ requires 203.0703) and 225.0533 ($M+Na^+$, $C_{12}H_{10}O_3Na$ requires 225.0522). Spectroscopic data matched that previously reported.[134,135]

3-Benzoyl-4-methylfuran-2(5*H*)-one 378

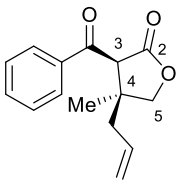


$AuCl(PPh_3)$ (367 mg, 0.74 mmol, 5 mol%), water (2.70 mL, 148 mmol, 10 equiv.) and triflic acid (13.0 mL, 148 mmol, 10 equiv.) were added to a solution of tautomers **377a-b** (ratio **377a**:**377b** 76:24, 3.00 g, 14.8 mmol, 1 equiv.) in DCE (185 mL). The reaction mixture was then stirred at room temperature for 18 h and was then concentrated *in vacuo*. The resulting residue was purified by column chromatography affording the *title compound* as a beige solid (2.28 g, 11.3 mmol, 76%). **R_f** = 0.23 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.87-7.83 (2 H, m, Ar*H*), 7.64-7.59 (1 H, m, Ar*H*), 7.50-7.46 (2 H, m, Ar*H*), 4.87 (2 H, s, 5-H_2), 2.20 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 189.8 (*C*=O), 170.6 (2-*C*=O), 169.1 (4-*C*), 136.2 (*Ar*), 134.3 (*Ar*H), 129.7 (*Ar*H), 128.8 (*Ar*H), 127.6 (3-*C*), 73.0 (5-*C*H_2), 14.0 (*C*H_3); **IR** (ATR) v_{Max}/cm^{-1} 2931, 1748 (C=O), 1655 (C=O), 1594, 1578, 1447, 1434, 1383, 1323, 1253, 1164, 1090, 1043, 1006, 942, 891, 769, 699, 678, 562, 521, 451; **HRMS** (ESI^+) *m/z* found 203.0707 ($M+H^+$, $C_{12}H_{11}O_3$ requires 203.0703) and 225.0531 ($M+Na^+$, $C_{12}H_{10}O_3Na$ requires 225.0522); **mp** 45-48 °C. Spectroscopic data matched that previously reported.[136]

(±)-*trans*- and (±)-*cis*-4-Allyl-3-benzoyl-4-methyldihydrofuran-2(3*H*)-one 379a and 379b



trans-**379a**

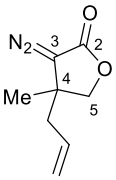


cis-**379b**

Allylmagnesium chloride solution (2 M in THF; 1.44 mL, 2.88 mmol, 1.1 equiv.) was added dropwise, over a 10 min period, to a solution of copper(I) bromide methyl sulphide complex (566 mg, 2.75 mmol, 1.05 equiv.) in THF (20 mL), cooled to -40 °C. After stirring for 45 min, the resulting reaction mixture was then cooled to -78 °C and enone **378** (530 mg, 2.62 mmol, 1 equiv.) in THF (10 mL) was added dropwise, over a 10 min period. The resulting solution was stirred for 1 h, then quenched with *sat.* aqueous ammonium chloride solution (50 mL), warmed to room temperature and extracted with ethyl acetate (3 x 150 mL). The combined organic phases were then washed with brine (150 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compounds*, an inseparable mixture of diastereomers **379a** (**A**) and **379b** (**B**), as a colourless oil (ratio **379a**:**379b** 70:30, 451 mg, 1.85 mmol, 70%). The stereochemistry was inferred from key NOESY NMR correlations between 3-*H* and C*H*$_2$CH=CH$_2$ (**A**); 3-*H* and C*H*$_3$ (**B**). **R$_f$** = 0.36 (25% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.97-7.90 (2 H, m, Ar*H*, **A**; 2 H, m, Ar*H*, **B**), 7.66-7.59 (1 H, m, Ar*H*, **A**; 1 H, m, Ar*H*, **B**), 7.52-7.47 (2 H, m, Ar*H*, **A**; 2 H, m, Ar*H*, **B**), 5.86 (1 H, dddd, *J* = 17.4, 10.1, 7.4, 7.4 Hz, C*H*=CH$_2$, **A**), 5.56 (1 H, dddd, *J* = 17.4, 10.1, 7.4, 7.4 Hz, C*H*=CH$_2$, **B**), 5.32-5.23 (2 H, m, CH=C*H*$_2$, **A**), 5.01-4.94 (2 H, m, CH=C*H*$_2$, **B**), 4.48 (1 H, d, *J* = 8.7 Hz, 5-*H*$_A$, **B**), 4.41 (1 H, s, 3-*H*, **A**), 4.28 (1 H, s, 3-*H*, **B**), 4.23 (1 H, d, *J* = 8.7 Hz, 5-*H*$_A$, **A**), 4.16 (1 H, d, *J* = 8.7 Hz, 5-*H*$_B$, **A**), 4.01 (1 H, d, *J* = 8.7 Hz, 5-*H*$_B$, **B**), 2.38-2.33 (2 H, m, C*H*$_{2A,B}$CH=CH$_2$, **A**), 2.25 (1 H, dd, *J* = 13.8, 7.4 Hz, C*H*$_A$CH=CH$_2$, **B**), 2.14 (1 H, dd, *J* = 13.8, 7.4 Hz, C*H*$_B$CH=CH$_2$, **B**), 1.34 (3 H, s, C*H*$_3$, **B**), 1.00 (3 H, s, C*H*$_3$, **A**); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 195.4 (*C*=O, **A**), 195.0 (*C*=O, **B**), 174.3 (2-*C*=O, **A**), 173.7 (2-*C*=O, **B**), 137.0 (*Ar*, **A**), 136.9 (*Ar*, **B**), 134.29 (*Ar*H, **A**), 134.26 (*Ar*H, **B**), 132.09 (*C*H=CH$_2$, **A**), 132.05 (*C*H=CH$_2$, **B**), 129.10 (*Ar*H, **A**), 129.08 (*Ar*H, **B**), 129.0 (*Ar*H, **B**), 128.9 (*Ar*H, **A**), 121.1 (CH=*C*H$_2$, **A**), 119.9 (CH=*C*H$_2$, **B**), 77.7 (5-*C*H$_2$, **B**), 77.1 (5-*C*H$_2$, **A**), 58.7 (3-*C*H, **B**), 57.0 (3-*C*H, **A**), 44.8 (4-*C*, **B**), 44.7 (*C*H$_2$CH=CH$_2$, **A**), 44.6 (4-*C*, **A**), 38.7 (*C*H$_2$CH=CH$_2$, **B**), 25.1 (*C*H$_3$, **B**), 19.1 (*C*H$_3$, **A**); **IR** (ATR) v_{Max}/cm^{-1} 3070, 2937, 2909, 1772 (C=O), 1667 (C=O), 1596, 1580, 1474, 1448, 1328, 1301, 1213, 1187, 1156, 1025, 1000, 924, 886, 846, 770,

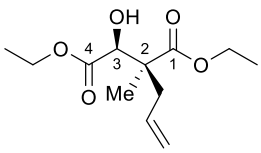
688, 591; **HRMS** (ESI$^+$) *m/z* found 245.1172 (M+H$^+$, $C_{15}H_{17}O_3$ requires 245.1172), 267.0988 (M+Na$^+$, $C_{15}H_{16}O_3Na$ requires 267.0992) and 262.1437 (M+NH$_4^+$, $C_{15}H_{20}NO_3$ requires 262.1438).

(±)-4-Allyl-3-diazo-4-methyldihydrofuran-2(3*H*)-one 380



1,8-Diazabicycloundec-7-ene (0.45 mL, 2.99 mmol, 1 equiv.) was added over a 30 min period to a solution of 4-acetamidobenzenesulfonyl azide (862 mg, 3.59 mmol, 1.2 equiv.) and lactones **379a-b** (ratio **379a**:**379b** 70:30, 730 mg, 2.99 mmol, 1 equiv.) in acetonitrile (15 mL) at 0 °C. After 10 min, additional DBU (0.22 mL, 1.49 mmol, 0.5 equiv.) was added and the resulting reaction mixture was then warmed to room temperature. The solution was then stirred for 5 h, quenched with water (20 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic phases were washed with water (25 mL), brine (25 mL), then dried with MgSO$_4$, concentrated *in vacuo* and purified by reverse phase column chromatography, using the elution gradient 5 to 100% acetonitrile in water, affording the *title compound* as a clear yellow oil (370 mg, 2.23 mmol, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.84-5.74 (1 H, m, C*H*=CH$_2$), 5.25-5.20 (2 H, m, CH=C*H$_2$*), 4.16 (1 H, d, *J* = 8.8 Hz, 5-*H$_A$*), 3.98 (1 H, d, *J* = 8.8 Hz, 5-*H$_B$*), 2.47-2.36 (2 H, m, 4-CC*H$_2$*), 1.42 (3 H, s, C*H$_3$*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 169.5 (*C*=O), 131.8 (*C*H=CH$_2$), 120.9 (CH=*C*H$_2$), 76.6 (5-*C*H$_2$), 44.1 (4-C*C*H$_2$), 41.9 (4-*C*), 23.9 (*C*H$_3$), the signal due to *C*N$_2$ was not observed; **IR** (ATR) ν_{Max}/cm^{-1} 2955, 2915, 2848, 2090 (CN$_2$), 1730 (C=O), 1458, 1389, 1376, 1225, 1117, 1071, 1044, 1004, 922, 815, 731, 637, 531; **HRMS** (ESI$^+$) *m/z* found 167.0818 (M+H$^+$, $C_8H_{11}N_2O_2$ requires 167.0815) and 189.0639 (M+Na$^+$, $C_8H_{10}N_2O_2Na$ requires 189.0634).

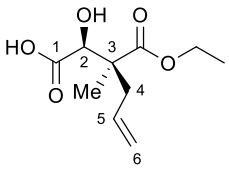
Diethyl (2*S*,3*S*)-2-allyl-3-hydroxy-2-methylsuccinate 393



A freshly prepared solution of lithium diisopropylamine (1 M; 45.1 mmol, 45.1 mL, 2.3 equiv.) was added to a solution of hydroxysuccinate esters **40a-b** (ratio **40a**:**40b** 83:17, 4.00 g, 19.6 mmol, 1 equiv.), in THF (55 mL), cooled to -78 °C. The resulting reaction mixture was then stirred for 5 min, warmed to -40 °C and then stirred for 3 h at -78 °C. Allyl bromide

(2.60 mL, 29.4 mmol, 1.5 equiv.) was then slowly added to the resulting reaction mixture over a 10 min period. This solution was then stirred at -40 °C for 8 h and gradually warmed to room temperature, over a 13 h period. The reaction mixture was then quenched with *sat.* aqueous ammonium chloride solution (250 mL) at 0 °C, stirred for 5 min, then warmed to room temperature and extracted with diethyl ether (3 x 500 mL). The combined organic phases were then washed with brine (500 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography, using the elution gradient 30 to 50% diethyl ether in hexane, affording the *title compound* as a yellow oil (2.71 g, 11.1 mmol, 57%, 12.5:1 *dr*). $\mathbf{R_f}$ = 0.35 (50% diethyl ether in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.75 (1 H, dddd, *J* = 17.1, 10.3, 7.8, 7.0 Hz, C*H*=CH_2), 5.13-5.06 (2 H, m, CH=CH_2), 4.25 (1 H, d, *J* = 7.7 Hz, 3-*H*), 4.29-4.21 (2 H, two overlapping dq, *J* = 10.8, 7.2 Hz, 4-$CO_2CH_{2A,B}$), 4.17 (2 H, q, *J* = 7.2 Hz, 1-$CO_2CH_{2A,B}$), 3.37 (1 H, d, *J* = 7.7 Hz, O*H*), 2.53 (1 H, dd, *J* = 13.7, 7.0 Hz, 2-CCH_{2A}), 2.33 (1 H, dd, *J* = 13.7, 7.8 Hz, 2-CCH_{2B}), 1.31 (3 H, t, *J* = 7.2 Hz, 4-$CO_2CH_2CH_3$), 1.26 (3 H, t, *J* = 7.2 Hz, 1-$CO_2CH_2CH_3$), 1.18 (3 H, s, 2-CCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 174.5 (4-*C*=O), 173.0 (1-*C*=O), 133.2 (*C*H=CH_2), 119.1 (CH=*C*H_2), 75.4 (3-*C*H), 62.0 (4-CO_2CH_2), 61.1 (1-CO_2CH_2), 50.0 (2-*C*), 39.7 (2-C*C*H_2), 18.0 (2-C*C*H_3), 14.3 (4-$CO_2CH_2CH_3$; 1-$CO_2CH_2CH_3$); **IR** (ATR) v_{Max}/cm^{-1} 3499 (OH), 3078, 2981, 2939, 1727 (C=O), 1641, 1447, 1368, 1210, 1091, 1021, 918, 862, 797, 651, 598; **HRMS** (ESI^+) *m/z* found 245.1383 ($M+H^+$, $C_{12}H_{21}O_5$ requires 245.1384), 267.1220 ($M+Na^+$, $C_{12}H_{20}O_5Na$ requires 267.1203) and 262.1640 ($M+NH_4^+$, $C_{12}H_{24}NO_5$ requires 262.1649); $[\alpha]_D^{22}$ = +18.7 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[133]

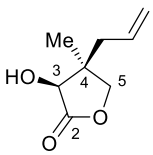
(2*S*,3*S*)-3-(Ethoxycarbonyl)-2-hydroxy-3-methylhex-5-enoic acid 394



A solution of potassium hydroxide (7.11 g, 127 mmol, 3.4 equiv.) in methanol (53.4 mL) and water (3.55 mL) was added to a solution of diethyl (2*S*,3*S*)-2-allyl-3-hydroxy-2-methylsuccinate **393** (9.10 g, 37.3 mmol, 1 equiv.) in methanol (71.3 mL) cooled to -40 °C. The resulting reaction mixture was stirred for 1 h at -40 °C, warmed to room temperature and stirred for 3 days. The resulting solution was then acidified by the addition of 2 M hydrochloric acid to pH-2 and the reaction mixture was extracted with diethyl ether

(4 x 150 mL). The combined organic phases were then dried with $MgSO_4$ and concentrated *in vacuo*, affording the *title compound* as a brown syrup (7.70 g, 35.6 mmol, 96%). **R_f** = 0.20 (5% MeOH in CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.20 (1 H, br s, CO_2H), 5.74 (1 H, dddd, *J* = 17.4, 10.2, 7.3, 7.3 Hz, C*H*=CH_2), 5.16-5.10 (2 H, m, CH=CH_2), 4.35 (1 H, s, 2-*H*), 4.20 (2 H, q, *J* = 7.2 Hz, CH_3CH_2), 3.73 (1 H, s, O*H*), 2.58 (1 H, dd, *J* = 13.7, 7.3 Hz, 4-H_A), 2.43 (1 H, dd, *J* = 13.7, 7.3 Hz, 4-H_B), 1.28 (3 H, t, *J* = 7.2 Hz, CH_2CH_3), 1.26 (3 H, s, 3-CCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 176.1 (*C*=O), 175.4 (1-*C*=O), 132.7 (5-*C*H), 119.6 (6-CH_2), 74.6 (2-*C*H), 61.6 (CH_3CH_2), 50.2 (3-*C*), 39.8 (4-CH_2), 18.2 (3-CCH_3), 14.2 (CH_2CH_3); **IR** (ATR) v_{Max}/cm^{-1} 3446 (OH), 3078, 2982, 2917, 1714 (C=O), 1641, 1442, 1383, 1368, 1216, 1086, 1020, 996, 918, 861, 742, 653; **HRMS** (ESI^+) *m/z* found 217.1072 ($M+H^+$, $C_{10}H_{17}O_5$ requires 217.1071) and 239.0901 ($M+Na^+$, $C_{10}H_{16}O_5Na$ requires 239.0890); $[\alpha]_D^{20}$ = +13.4 (*c* 1.00, $CHCl_3$).

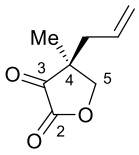
(3*S*,4*S*)-4-Allyl-3-hydroxy-4-methyldihydrofuran-2(3*H*)-one 395



Lithium triethylborohydride in THF (1 M; 222 mL, 222 mmol, 6 equiv.) was added, over a 10 min period, to a solution of carboxylic acid **394** (8.00 g, 37.0 mmol, 1 equiv.) in THF (440 mL) cooled to -78 °C. The resulting reaction mixture was stirred at -78 °C for 3 h, warmed to room temperature and stirred for 40 h. The resulting solution was then cooled to -10 °C, quenched with 2 M HCl (111 mL) and stirred for 30 min. The solution was then warmed to room temperature and concentrated *in vacuo*. The resulting aqueous solution was then extracted with diethyl ether (3 x 200 mL) and the combined organic phases were then washed with water (200 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a colourless viscous oil (4.51 g, 28.9 mmol, 78%). **R_f** = 0.22 (33% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.82-5.72 (1 H, m, C*H*=CH_2), 5.17-5.12 (2 H, m, CH=CH_2), 4.23 (1 H, d, *J* = 9.3 Hz, 5-H_A), 4.17 (1 H, s, 3-*H*), 3.84 (1 H, d, *J* = 9.3 Hz, 5-H_B), 2.81 (1 H, br s, O*H*), 2.25 (1 H, ddd, *J* = 14.1, 6.8, 1.3 Hz, 4-CCH_{2A}), 2.13 (1 H, dd, *J* = 14.1, 8.1 Hz, 4-CCH_{2B}), 1.21 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 177.7 (2-*C*=O), 132.9 (*C*H=CH_2), 119.8 (CH=*C*H_2), 76.0 (3-*C*H), 73.5 (5-CH_2), 43.7 (4-*C*), 36.2 (4-CCH_2), 21.3 (CH_3); **IR** (ATR) v_{Max}/cm^{-1} 3425 (OH), 3078, 2965, 2910, 1773

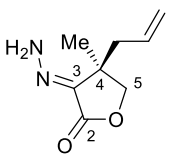
(C=O), 1640, 1458, 1383, 1304, 1183, 1107, 998, 915, 879, 729, 656, 625, 543, 507; **HRMS** (ESI$^+$) *m/z* found 157.0864 (M+H$^+$, $C_8H_{13}O_3$ requires 157.0859), 179.0681 (M+Na$^+$, $C_8H_{12}O_3Na$ requires 179.0679) and 174.1123 (M+NH$_4^+$, $C_8H_{16}NO_3$ requires 174.1125); $[\alpha]_D^{23}$ = +9.1 (*c* 1.00, $CHCl_3$).

(*S*)-4-Allyl-4-methyldihydrofuran-2,3-dione 396

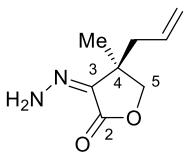


Dess-Martin periodinane (15.6 g, 36.8 mmol, 1.15 equiv.) was added to a stirred solution of alcohol **395** (5.00 g, 32.0 mmol, 1 equiv.) in CH_2Cl_2 (225 mL), cooled to 0 °C. The resulting reaction mixture was stirred at 0 °C for 10 min, warmed to room temperature and stirred for 18 h. The reaction solution was then cooled to -15 °C, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a colourless oil (4.61 g, 29.9 mmol, 93%). **R$_f$** = 0.28 (33% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.68 (1 H, dddd, *J* = 17.5, 10.2, 7.4, 7.4 Hz, C*H*=CH$_2$), 5.25-5.16 (2 H, m, CH=C*H$_2$*), 4.62 (1 H, d, *J* = 9.7 Hz, 5-*H$_A$*), 4.37 (1 H, d, *J* = 9.7 Hz, 5-*H$_B$*), 2.43 (1 H, dddd, *J* = 13.9, 7.4, 1.1, 1.1 Hz, 4-CC*H$_{2A}$*), 2.33 (1 H, dddd, *J* = 13.9, 7.4, 1.1, 1.1 Hz, 4-CC*H$_{2B}$*), 1.30 (3 H, s, C*H$_3$*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 198.0 (3-*C*=O), 160.4 (2-*C*=O), 130.4 (*C*H=CH$_2$), 121.5 (CH=*C*H$_2$), 74.9 (5-*C*H$_2$), 45.1 (4-*C*), 40.5 (4-CCH$_2$), 20.6 (*C*H$_3$); **IR** (ATR) v_{Max}/cm^{-1} 3081, 2981, 2919, 1775 (C=O), 1641, 1455, 1389, 1322, 1299, 1235, 1161, 1136, 1076, 992, 951, 927, 731, 549, 475, 421; **HRMS** (ESI$^+$) *m/z* found 155.0705 (M+H$^+$, $C_8H_{11}O_3$ requires 155.0703) and 177.0527 (M+Na$^+$, $C_8H_{10}O_3Na$ requires 177.0522); $[\alpha]_D^{21}$ = +0.60 (*c* 1.00, $CHCl_3$).

(*R*,*Z*)- and (*R*,*E*)-4-Allyl-3-hydrazineylidene-4-methyldihydrofuran-2(3*H*)-one 397a and 397b



(*R*,*E*)-**397a**



(*R*,*Z*)-**397b**

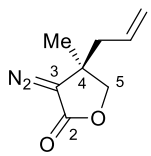
A solution of hydrazine acetate (134 mg, 1.46 mmol, 1 equiv.) and ketolactone **396** (225 mg, 1.46 mmol, 1 equiv.) in THF (10 mL) was left stirring at room temperature for 20 h, upon which hydrazone **397a** precipitates. Aqueous *sat.* sodium hydrogen carbonate solution (5 mL) was then added to the reaction mixture, causing the visible precipitate to dissolve completely.

The resulting solution was then extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (5 mL) and dried with $MgSO_4$. The dried organic phase was then concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 50 to 100% ethyl acetate in hexane, affording the separated *title compounds*, in a *E*:*Z* 84:16 ratio.

(*R*,*E*)-4-Allyl-3-hydrazineylidene-4-methyldihydrofuran-2(3*H*)-one 397a as a colourless solid (156 mg, 0.929 mmol, 64%). **R_f** = 0.13 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 6.43 (2 H, s, NH_2), 5.74 (2 H, dddd, *J* = 16.7, 10.3, 7.3, 7.3 Hz, C*H*=CH_2), 5.26-5.21 (2 H, m, CH=CH_2), 4.22 (1 H, d, *J* = 9.1 Hz, 5-H_A), 3.96 (1 H, d, *J* = 9.1 Hz, 5-H_B), 2.57 (1 H, dddd, *J* = 14.1, 7.3, 1.2, 1.2 Hz, 4-CCH_{2A}), 2.43 (1 H, dddd, *J* = 14.1, 7.3, 1.2, 1.2 Hz, 4-CCH_{2B}), 1.47 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 167.5 (2-*C*=O), 136.9 (3-*C*=N), 132.0 (*C*H=CH_2), 120.8 (CH=*C*H_2), 75.1 (5-*C*H_2), 41.4 (4-*C*), 40.7 (4-C*C*H_2), 20.6 (*C*H_3); **IR** (ATR) v_{Max}/cm^{-1} 3406 (NH_2), 3289, 3229, 3197, 2965, 2925, 2871, 1727 (C=O), 1575 (C=N), 1476, 1456, 1397, 1377, 1327, 1308, 1263, 1159, 1121, 1052, 1009, 923, 741, 709, 517; **HRMS** (ESI^+) *m/z* found) 169.1011 ($M+H^+$, $C_8H_{13}N_2O_2$ requires 169.0977) and 191.0829 ($M+Na^+$, $C_8H_{12}N_2O_2Na$ requires 191.0796); **mp** 176-179 °C; $[\alpha]_D^{18}$ = +161 (*c* 0.10, $CHCl_3$).

(*R*,*Z*)-4-Allyl-3-hydrazineylidene-4-methyldihydrofuran-2(3*H*)-one 397b as a yellow oil (29.9 mg, 0.178 mmol, 12%). **R_f** = 0.74 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.01 (br s, 2 H, NH_2), 5.75 (1 H, dddd, *J* = 16.8, 10.3, 7.3, 7.3 Hz, C*H*=CH_2), 5.16-5.09 (2 H, m, CH=CH_2), 4.32 (1 H, d, *J* = 9.1 Hz, 5-H_A), 4.06 (1 H, d, *J* = 9.1 Hz, 5-H_B), 2.35 (1 H, dddd, *J* = 13.7, 7.3, 1.2, 1.2 Hz, 4-CCH_{2A}), 2.27 (1 H, dddd, *J* = 13.7, 7.3, 1.2, 1.2 Hz, 4-CCH_{2B}), 1.25 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 165.1 (2-*C*=O), 133.6 (3-*C*=O), 133.0 (*C*H=CH_2), 119.5 (CH=*C*H_2), 77.4 (5-*C*H_2), 44.2 (4-C*C*H_2), 40.8 (4-*C*), 24.3 (*C*H_3); **IR** (ATR) v_{Max}/cm^{-1} 3448 (NH_2), 3287, 2968, 2915, 1730 (C=O), 1584 (C=N), 1454, 1386, 1370, 1113, 1000, 921, 791; **HRMS** (ESI^+) *m/z* found 169.1005 ($M+H^+$, $C_8H_{13}N_2O_2$ requires 169.0977) and 191.0830 ($M+Na^+$, $C_8H_{12}N_2O_2Na$ requires 191.0796); $[\alpha]_D^{18}$ = +13.2 (*c* 0.18, $CHCl_3$).

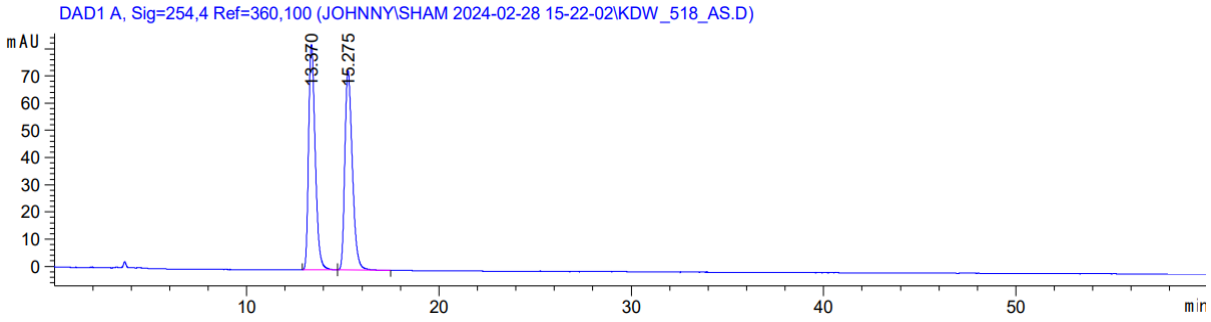
(*R*)-4-Allyl-3-diazo-4-methyldihydrofuran-2(3*H*)-one 380



Method I: A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (24.0 mg, 71.3 μmol, 1.2 equiv.) and hydrazone **397b** (10.0 mg, 59.5 μmol, 1 equiv.) in THF (0.2 mL) was prepared. Aqueous potassium hydroxide (1 M; 0.05 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 0.25 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (1.5 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 0.25 mL), brine (0.25 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (9.7 mg, 58.4 μmol, 98%, 80% *ee*).

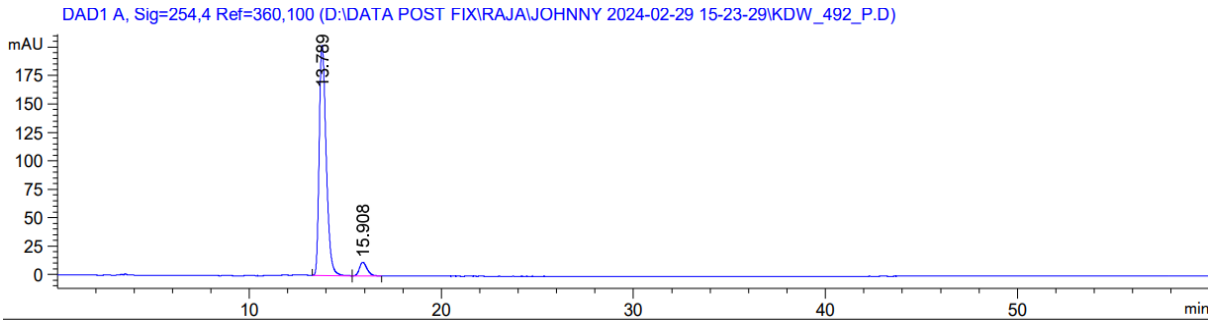
Method II: A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (331 mg, 0.985 mmol, 1.2 equiv.) and hydrazone **397a** (138 mg, 0.821 mmol, 1 equiv.) in THF (3.2 mL) was prepared. Aqueous potassium hydroxide (1 M; 0.8 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 4 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (25 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 4 mL), brine (4 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (134 mg, 0.805 mmol, 98%, 80% *ee*). $\mathbf{R_f}$ = 0.36 (50% diethyl ether in petroleum ether); $[\alpha]_D^{19}$ = +85.4 (*c* 0.40, $CHCl_3$); See earlier for characterisation data.

(±)-**380** (*rac*) Chiral HPLC spectrum (Chiralpak AS-H, 90:10 MeCN:*i*-PrOH, 1 mL/min, 254 nm, ambient temperature).



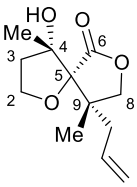
Peak	Retention Time / min	Relative Area	Area %
1	13.370	1985.03284	49.88668
2	15.275	1994.03918	50.1132

(*R*)-**380** (89% *ee*) Chiral HPLC spectrum (Chiralpak AS-H, 90:10 MeCN:*i*-PrOH, 1 mL/min, 254 nm, ambient temperature).

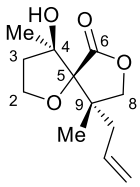


Peak	Retention Time / min	Relative Area	Area %
1	13.801	1766.08032	94.5813
2	15.936	101.18032	5.4187

(4*S*,5*R*,9*S*)- and (4*R*,5*S*,9*S*)-9-Allyl-4-hydroxy-4,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one 398b and 398a



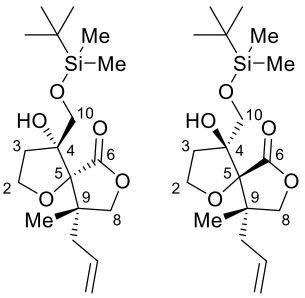
cis,*cis*-**398b**



cis,*trans*-**398a**

A solution containing α-diazolactone (*R*)-**380** (64.8 mg, 0.39 mmol, 1.3 equiv.) in CH_2Cl_2 (2.5 mL) was added, over a 30 min period, to a refluxing solution of 4-hydroxy-2-butanone **196** (26.4 mg, 0.30 mmol, 1 equiv.) and rhodium(II) octanoate dimer (2.3 mg, 3.00 µmol, 1 mol%) in CH_2Cl_2 (2 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compounds*, an inseparable mixture of diastereomers **398b** (**B**) and **398a** (**A**), as a colourless oil (ratio **398b**:**398a** 77:23, 37.2 mg, 164 µmol, 42%). The stereochemistry was inferred from key NOESY NMR correlations between 4-CH_3 and 9-CH_3 (**B**); 4-CH_3 and 9-CCH_2 (**A**). $\mathbf{R_f}$ = 0.38 (25% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.76 (1 H, dddd, *J* = 16.7, 10.2, 8.5, 6.4 Hz, C*H*=CH_2, **B**), 5.69 (1 H, ddt, *J* = 17.4, 10.0, 7.5 Hz, C*H*=CH_2, **A**), 5.18-5.09 (2 H, m, CH=CH_2, **A**; 2 H, m, CH=CH_2, **B**), 4.20 (1 H, d, *J* = 8.3 Hz, 8-H_A, **A**), 4.07 (1 H, d, *J* = 8.3 Hz, 8-H_A, **B**), 4.01-4.87 (2 H, m, 2-H_2, **A**; 2 H, m, 2-H_2, **B**, 1 H, m, 8-H_B, **B**), 3.73 (1 H, d, *J* = 8.3 Hz, 8-H_B, **A**), 2.98 (1 H, s, O*H*, **A**), 2.94 (1 H, s, O*H*, **B**), 2.79-2.65 (1 H, m, 3-H_A, **A**; 1 H, m, 9-CCH_{2A}, **A**; 1 H, m, 3-H_A, **B**), 2.46 (1 H, dd, *J* = 14.4, 6.4 Hz, 9-CCH_{2A}, **B**), 2.23-2.16 (1 H, m, 9-CCH_{2B}, **B**), 2.19 (1 H, dd, *J* = 13.7, 7.5 Hz, 9-CCH_{2B}, **A**), 2.07-2.01 (1 H, m, 3-H_B, **B**), 2.03 (1 H, ddd, *J* = 12.3, 7.7, 3.1 Hz, 3-H_B, **A**), 1.43 (3 H, s, 9-CCH_3, **B**), 1.41 (3 H, s, 9-CCH_3, **A**), 1.25 (3 H, s, 4-CCH_3, **A**), 1.09 (3 H, s, 4-CCH_3, **B**); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 177.0 (6-*C*=O, **B**), 176.8 (6-*C*=O, **A**), 132.4 (*C*H=CH_2, **A**), 120.1 (CH=*C*H_2, **B**), 119.3 (CH=*C*H_2, **A**), 86.2 (5-*C*, **A**), 85.7 (5-*C*, **B**), 78.12 (4-*C*, **A**), 78.07 (4-*C*, **B**), 77.8 (8-*C*H_2, **A**), 73.8 (8-*C*H_2, **B**), 64.9 (2-*C*H_2, **A**), 44.4 (9-*C*, **B**), 43.8 (9-*C*, **A**), 41.7 (3-*C*H_2, **B**), 41.6 (3-*C*H_2, **A**), 36.2 (9-C*C*H_2, **A**), 35.9 (9-C*C*H_2, **B**), 23.6 (4-C*C*H_3, **A**), 23.4 (4-C*C*H_3, **B**), 17.8 (9-C*C*H_3, **A**), 14.6 (9-C*C*H_3, **B**), the signals due to (*C*H=CH_2, **B**) and (2-*C*H_2, **B**) were not observed; **IR** (ATR) v_{Max}/cm^{-1} 3547 (OH), 2979, 2899, 1754 (C=O), 1639, 1459, 1420, 1298, 1261, 1205, 1163, 1124, 1075, 989, 921, 759, 660, 620, 477; **HRMS** (ESI$^+$) *m/z* found 227.1272 (M+H$^+$, $C_{12}H_{19}O_4$ requires 227.1278) and 249.1095 (M+Na$^+$, $C_{12}H_{18}O_4Na$ requires 249.1097); $[\alpha]_D^{24}$ = -36.3 (*c* 1.00, $CHCl_3$).

(4*R*,5*R*,9*S*)- and (4*S*,5*S*,9*S*)-9-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-1,7-dioxaspiro[4.4]nonan-6-one 392b and 392a



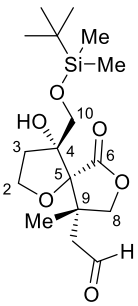
cis,*cis*-**392b** *cis*,*trans*-**392a**

A solution containing α-diazolactone (*R*)-**380** (63.8 mg, 384 µmol, 2 equiv.) in CH_2Cl_2 (2 mL) was added, over a 30 min period, to a refluxing solution of β-hydroxyketone **329** (42.0 mg, 192 µmol, 1 equiv.) and copper(I) triflate toluene complex (5.0 mg, 9.62 µmol, 5 mol%) in CH_2Cl_2 (1.5 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the separated *title compounds*.

(4*R*,5*R*,9*S*)-9-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-1,7-dioxaspiro[4.4]nonan-6-one 392b as a colourless solid (24.9 mg, 69.8 µmol, 36%). The stereochemistry was inferred from the key NOESY NMR correlation between 10-CH_2 and 9-CH_3. **R_f** = 0.21 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.70 (1 H, dddd, *J* = 17.4, 10.0, 7.6, 7.6 Hz, C*H*=CH_2), 5.18-5.09 (2 H, m, CH=CH_2), 4.19 (1 H, d, *J* = 8.1 Hz, 8-H_A), 4.01 (1 H, ddd, *J* = 10.2, 8.4, 4.0 Hz, 2-H_A), 3.91 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.81 (1 H, d, *J* = 10.3 Hz, 10-H_A), 3.74 (1 H, d, *J* = 8.1 Hz, 8-H_B), 3.67 (1 H, d, *J* = 10.3 Hz, 10-H_B), 3.00 (1 H, s, O*H*), 2.65 (1 H, dd, *J* = 13.7, 7.6 Hz, 9-CCH_{2A}), 2.61-2.52 (1 H, m, 3-H_A), 2.43 (1 H, ddd, *J* = 12.4, 8.4, 4.0 Hz, 3-H_B), 2.15 (1 H, dd, *J* = 13.7, 7.6 Hz, 9-CCH_{2B}), 1.27 (3 H, s, CH_3), 0.92 (9 H, s, SiC(CH_3)$_3$), 0.11 (6 H, br s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.6 (6-*C*=O), 132.5 (*C*H=CH_2), 119.3 (CH=*C*H_2), 86.5 (5-*C*), 81.1 (4-*C*), 77.4 (8-*C*H_2), 65.19 (2-*C*H_2), 65.15 (10-*C*H_2), 43.8 (9-*C*), 36.3 (9-C*C*H_2), 35.5 (3-*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.5 (Si*C*), 18.3 (*C*H_3), -5.2 (Si*C*H_{3A}), -5.3 (Si*C*H_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3547 (OH), 2953, 2929, 2893, 2856, 1757 (C=O), 1472, 1390, 1363, 1320, 1202, 1126, 1097, 1074, 1006, 937, 893, 777, 757, 716, 553, 458; **HRMS** (ESI$^+$) *m/z* found 357.2098 (M+H$^+$, $C_{18}H_{33}O_5Si$ requires 357.2092), 379.1916 (M+Na$^+$, $C_{18}H_{32}O_5SiNa$ requires 379.1911) and 374.2360 (M+NH_4^+, $C_{18}H_{36}NO_5Si$ requires 374.2357); $[\alpha]_D^{17}$ = -58.2 (*c* 1.00, $CHCl_3$).

(4*S*,5*S*,9*S*)-9-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-1,7-dioxaspiro[4.4]nonan-6-one 392a as a colourless solid (7.9 mg, 22.2 µmol, 12%). The stereochemistry was inferred from the key NOESY NMR correlation between 10-CH_2 and 9-CCH_2. **R_f** = 0.23 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.77 (1 H, dddd, *J* = 16.5, 10.1, 8.6, 6.1 Hz, C*H*=CH_2), 5.20-5.08 (2 H, m, CH=CH_2), 4.06 (1 H, d, *J* = 8.3 Hz, 8-H_A), 4.00 (1 H, ddd, *J* = 10.2, 8.4, 3.8 Hz, 2-H_A), 3.91 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.90-3.83 (2 H, m, 8-H_B; 10-H_A), 3.67 (1 H, d, *J* = 10.3 Hz, 10-H_B), 2.91 (1 H, br s, O*H*), 2.63-2.42 (3 H, m, 3-H_2; 9-CCH_{2A}), 2.24 (1 H, dd, *J* = 14.4, 8.6 Hz, 9-CCH_{2B}), 1.07 (3 H, s, CH_3), 0.92 (9 H, s, SiC(CH_3)$_3$), 0.11 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.7 (6-*C*=O), 132.6 (*C*H=CH_2), 120.0 (CH=*C*H_2), 86.0 (5-*C*), 81.1 (4-*C*), 73.6 (8-*C*H_2), 65.1 (2-*C*H_2), 64.8 (10-*C*H_2), 44.3 (9-*C*), 36.3 (9-C*C*H_2), 35.2 (3-*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.5 (Si*C*), 14.8 (*C*H_3), -5.2 (Si*C*H_{3A}), -5.3 (Si*C*H_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 3547 (OH), 2953, 2929, 2894, 2856, 1757 (C=O), 1471, 1384, 1364, 1293, 1251, 1199, 1125, 1098, 1055, 1007, 895, 837, 777, 756, 683, 667, 456; **HRMS** (ESI$^+$) *m/z* found 357.2091 (M+H$^+$, $C_{18}H_{33}O_5Si$ requires 357.2092), 379.1900 (M+Na$^+$, $C_{18}H_{32}O_5SiNa$ requires 379.1911) and 374.2350 (M+NH_4^+, $C_{18}H_{36}NO_5Si$ requires 374.2357); $[\alpha]_D^{17}$ = +32.6 (*c* 1.00, $CHCl_3$).

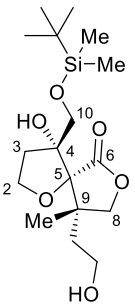
2-((4*R*,5*R*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-6-oxo-1,7-dioxaspiro[4.4]nonan-9-yl)acetaldehyde 400b



N-Methylmorpholine (117 mg, 1.00 mmol, 1.15 equiv.), citric acid monohydrate (128 mg, 609 µmol, 0.7 equiv.) and potassium osmate dihydrate (16.0 mg, 43.5 µmol, 5 mol%) were added to a solution of spirolactone **329b** (310 mg, 869 µmol, 1 equiv.) in acetone (27 mL) and water (6.75 mL). The resulting solution was then stirred for 4 h at room temperature. Sodium periodate (558 mg, 2.61 mmol, 3 equiv.) was then added and the reaction mixture was stirred at room temperature for 16 h. The resulting solution was then quenched with *sat.* sodium thiosulphate (15 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic phases were then washed with brine (20 mL), dried with $MgSO_4$, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil

(280 mg, 780 µmol, 90%). **R_f** = 0.38 (25% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 9.75 (1 H, dd *J* = 1.5, 1.5 Hz, C*H*O), 4.30 (2 H, two overlapping d observed as a br s, 8-H_2), 3.97 (1 H, ddd, *J* = 10.3, 8.4, 3.9 Hz, 2-H_A), 3.87 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.78 (1 H, d, *J* = 10.5 Hz, 10-H_A), 3.72 (1 H, d, *J* = 10.5 Hz, 10-H_B), 3.03 (1 H, s, O*H*), 3.01 (1 H, br d, *J* = 17.9 Hz, 9-CCH_{2A}), 2.75 (1 H, dd, *J* = 17.9, 1.5 Hz, 9-CCH_{2B}), 2.60 (1 H, ddd, *J* = 12.6, 10.3, 8.4 Hz, 3-H_A), 2.33 (1 H, ddd, *J* = 12.6, 8.4, 3.9 Hz, 3-H_B), 1.38 (3 H, s, CH_3), 0.92 (9 H, s, SiC(CH_3)$_3$), 0.12 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 199.6 (*C*HO), 174.8 (6-*C*=O), 86.2 (5-*C*), 80.7 (4-*C*), 77.0 (8-*C*H_2), 65.4 (10-*C*H_2), 65.3 (2-*C*H_2), 46.6 (9-C*C*H_2), 43.1 (9-*C*), 36.1 (3-*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.8 (*C*H_3), 18.5 (Si*C*), -5.24 (Si*C*H_{3A}), -5.27 (Si*C*H_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 3530 (OH), 2954, 2927, 2852, 1761 (C=O), 1722 (C=O), 1461, 1366, 1254, 1173, 1094, 1073, 1006, 836, 777, 732, 527; **HRMS** (ESI$^+$) *m/z* found 359.1878 (M+H$^+$, $C_{17}H_{31}O_6Si$ requires 359.1884), 381.1708 (M+Na$^+$, $C_{17}H_{30}O_6SiNa$ requires 381.1704) and 376.2151 (M+NH$_4^+$, $C_{17}H_{34}NO_6Si$ requires 376.2150); $[\alpha]_D^{18}$ = -19.8 (*c* 1.00, $CHCl_3$).

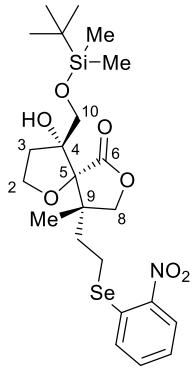
(4*R*,5*R*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-(2-hydroxyethyl)-9-methyl-1,7-dioxaspiro[4.4]nonan-6-one 401b



Sodium borohydride (87.1 mg, 2.30 mmol, 3 equiv.) was slowly added to a solution of aldehyde **400b** (275 mg, 767 µmol, 1 equiv.) in diethyl ether (4.7 mL), cooled to 0 °C. MeOH (1.6 mL) was then added dropwise, over a 15 min period, and the resulting solution was then warmed to room temperature and stirred for 2 h. The reaction mixture was then quenched with *sat.* aqueous ammonium chloride solution (15 mL) and the resulting solution was extracted with diethyl ether (3 x 25 mL). The combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (243 mg, 675 µmol, 88%). **R_f** = 0.20 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.33 (1 H, d, *J* = 8.4 Hz, 8-H_A), 4.00 (1 H, ddd, *J* = 10.2, 8.4, 3.8 Hz, 2-H_A), 3.94 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.90 (1 H, d, *J* = 8.4 Hz, 8-H_B), 3.83-3.75 (1 H, m, HOCH_{2A}), 3.80 (1 H, d, *J* = 10.3 Hz, 10-H_A), 3.74-3.65 (1 H, m, HOCH_{2B}), 3.68 (1 H, d, *J* = 10.3 Hz, 10-H_B), 3.04 (1 H, br s, O*H*),

2.62-2.52 (1 H, m, 3-H_A), 2.43 (1 H, ddd, J = 12.4, 8.4, 3.8 Hz, 3-H_B), 2.16 (1 H, ddd, J = 14.6, 8.6, 6.4 Hz, 9-CCH_{2A}), 1.69 (1 H, ddd, J = 14.6, 5.4, 5.4 Hz, 9-CCH_{2B}), 1.31 (3 H, s, CH_3), 0.91 (9 H, s, SiC(CH_3)$_3$), 0.10 (6 H, s, Si(CH_3)$_2$), the signal due to OH was not observed; **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.4 (6-C=O), 86.8 (5-C), 81.2 (4-C), 78.0 (8-CH$_2$), 65.2 (2-CH$_2$), 65.1 (10-CH$_2$), 58.9 (HOCH$_2$), 43.6 (9-C), 35.6 (3-CH$_2$), 34.4 (9-CCH$_2$), 26.0 (SiC(CH$_3$)$_3$), 18.8 (CH$_3$), 18.5 (SiC), -5.2 (SiCH$_{3A}$), -5.3 (SiCH$_{3B}$); **IR** (ATR) ν_{Max}/cm^{-1} 3469 (OH), 2952, 2928, 2894, 2855, 1756 (C=O), 1471, 1365, 1253, 1171, 1095, 1073, 1005, 836, 777, 688, 666, 454; **HRMS** (ESI$^+$) *m/z* found 361.2055 (M+H$^+$, $C_{17}H_{33}O_6Si$ requires 361.2041), 383.1868 (M+Na$^+$, $C_{17}H_{32}O_6SiNa$ requires 383.1860) and 378.2326 (M+NH$_4^+$, $C_{17}H_{36}NO_6Si$ requires 378.2306); $[\alpha]_D^{18}$ = -73.7 (*c* 1.00, $CHCl_3$).

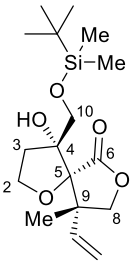
(4*R*,5*R*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-9-(2-((2-nitrophenyl)selanyl)ethyl)-1,7-dioxaspiro[4.4]nonan-6-one 402b



To a solution of alcohol **401b** (155 mg, 430 µmol, 1 equiv.) and 2-nitrophenyl selenocyanate **47** (137 mg, 600 µmol, 1.4 equiv.) in THF (6 mL) was added P(*n*-Bu)$_3$ (150 µL, 600 µmol, 1.4 equiv.) (Caution: toxic gas liberated). The resulting reaction mixture was stirred for 18 h at room temperature, then quenched with *sat.* aqueous ammonium chloride solution (6 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic phase was then washed with brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, using the elution gradient 15 to 25% ethyl acetate in pentane, affording the *title compound* as a dark yellow oil (212 mg, 389 µmol, 91%). **R_f** = 0.30 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.30 (1 H, dd, J = 8.3, 1.4 Hz, ArH), 7.55 (1 H, ddd, J = 8.3, 7.1, 1.4, ArH), 7.47 (1 H, dd, J = 8.3, 1.4 Hz, ArH), 7.34 (1 H, dd, J = 8.3, 7.1, 1.4 Hz, ArH), 4.30 (1 H, d, J = 8.0 Hz, 8-H_A), 4.00 (1 H, ddd, J = 10.3, 8.4, 4.0 Hz, 2-H_A), 3.99 (1 H, d, J = 8.0 Hz, 8-H_B), 3.90 (1 H, ddd, J = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.75 (1 H, d, J = 10.4 Hz, 10-H_A), 3.66 (1 H, d, J = 10.4 Hz, 10-H_B), 3.02 (1 H, br s, OH), 2.96 (1 H, ddd, J = 12.9, 11.1, 4.6 Hz, ArSeCH_{2A}), 2.67 (1 H, ddd, J = 12.9, 11.1, 4.9 Hz, ArSeCH_{2B}), 2.57 (1 H, ddd, J = 12.6, 10.3, 8.4 Hz, 3-H_A), 2.43-2.33 (2 H, m, 3-H_B; 9-CCH_{2A}), 1.88 (1 H, ddd, J = 13.9, 12.9, 4.6 Hz,

9-CC*H*$_{2B}$), 1.38 (3 H, s, C*H*$_3$), 0.87 (9 H, s, SiC(C*H*$_3$)$_3$), 0.07 (3 H, s, SiC*H*$_{3A}$), 0.05 (3 H, s, SiC*H*$_{3B}$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.2 (6-*C*=O), 147.0 (*Ar*), 133.9 (*Ar*H), 133.1 (*Ar*), 128.8 (*Ar*H), 126.7 (*Ar*H), 125.8 (*Ar*H), 86.7 (5-*C*), 81.0 (4-*C*), 76.8, (8-*C*H$_2$), 65.35 (10-*C*H$_2$), 65.33 (2-*C*H$_2$), 45.0 (9-*C*), 35.8 (3-*C*H$_2$), 30.7 (9-C*C*H$_2$), 26.0 (SiC(*C*H$_3$)$_3$), 20.1 (ArSe*C*H$_2$), 18.4 (Si*C*), 18.2 (*C*H$_3$), -5.27 (Si*C*H$_{3A}$), -5.32 (Si*C*H$_{3B}$); **IR** (ATR) v_{Max}/cm^{-1} 3545 (OH), 2952, 2928, 2894, 2855, 1756 (C=O), 1590, 1566, 1511, 1461, 1331, 1303, 1252, 1097, 1070, 989, 837, 779, 730, 479; **HRMS** (ESI$^+$) *m/z* found 546.1417 (M+H$^+$, $C_{23}H_{36}NO_7SeSi$ requires 546.1421) and 568.1229 (M+Na$^+$, $C_{23}H_{35}NO_7SeSiNa$ requires 568.1240); $[\alpha]_D^{17}$ = -26.8 (*c* 1.00, $CHCl_3$).

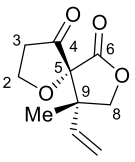
(4*R*,5*R*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-9-vinyl-1,7-dioxaspiro[4.4]nonan-6-one 403b



Hydrogen peroxide (30% *aq.*, 6.1 mL, 1.84 mmol, 10 equiv.) was added to a solution of selenide **402b** (100 mg, 184 µmol, 1 equiv.) in THF (2.1 mL) cooled to 0 °C. The resulting reaction mixture was stirred for 1 h, then quenched with *sat.* aqueous sodium bisulphate solution (20 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase was then washed with brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a slowly crystallising colourless solid (53.6 mg, 156 µmol, 85%). **R_f** = 0.44 (10% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 6.17 (1 H, dd, *J* = 18.1, 10.6 Hz, C*H*=CH$_2$), 5.30-5.24 (2 H, m, CH=C*H*$_2$), 4.24 (1 H, d, *J* = 8.1 Hz, 8-*H*$_A$), 4.03 (1 H, ddd, *J* = 8.4, 8.4, 5.5 Hz, 2-*H*$_A$), 3.91 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-*H*$_B$), 3.72 (1 H, dd, *J* = 10.6, 1.1 Hz, 10-*H*$_A$), 3.69 (1 H, d, *J* = 8.1 Hz, 8-*H*$_B$), 3.51 (1 H, dd, *J* = 10.6, 1.1 Hz, 10-*H*$_B$), 2.89 (1 H, s, O*H*), 2.56-2.48 (2 H, m, 3-*H*$_2$), 1.39 (3 H, s, C*H*$_3$), 0.90 (9 H, s, SiC(C*H*$_3$)$_3$), 0.07 (6 H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 174.6 (6-*C*=O), 136.1 (*C*H=CH$_2$), 117.1 (CH=*C*H$_2$), 86.5 (5-*C*), 81.3 (4-*C*), 77.1 (8-*C*H$_2$), 65.6 (2-*C*H$_2$), 64.5 (10-*C*H$_2$), 46.3 (9-*C*), 34.5 (3-*C*H$_2$), 26.1 (SiC(*C*H$_3$)$_3$), 18.5 (Si*C*), 17.3 (*C*H$_3$), -5.2 (Si*C*H$_{3A}$), -5.3 (Si*C*H$_{3B}$); **IR** (ATR) v_{Max}/cm^{-1} 3540 (OH), 2953, 2928, 2901, 2883, 2855, 1752 (C=O), 1468, 1364, 1321, 1275, 1248, 1198, 1131, 1070, 1040, 984, 965, 945, 891, 834, 776, 712, 694, 518, 457; **HRMS** (ESI$^+$) *m/z* found 343.1940 (M+H$^+$, $C_{17}H_{31}O_5Si$ requires 343.1935), 365.1756 (M+Na$^+$, $C_{17}H_{30}O_5SiNa$

requires 365.1755) and 360.2195 ($M+NH_4^+$, $C_{17}H_{34}NO_5Si$ requires 360.2210); **mp** 44-46 °C; $[\alpha]_D^{20}$ = -79.0 (*c* 1.00, $CHCl_3$); structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

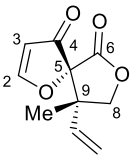
(5*R*,9*S*)-9-Methyl-9-vinyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 404b



An aqueous solution of hydrochloric acid (2 M; 0.58 mL, 1.17 mmol, 10 equiv.) was added to a solution of silyl ether **403b** (40.0 mg, 117 µmol, 1 equiv.) in THF (1.00 mL). The resulting reaction mixture was stirred at room temperature for 16 h. Water (2.50 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (10 mL), brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the crude diol which was then used in the next step without further purification. The resulting crude diol was then dissolved within a THF (2.60 mL) and water (2.60 mL) mixture. Sodium periodate (74.9 mg, 350 µmol, 3 equiv.) was then added and the resulting solution was stirred at room temperature for 18 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (10 mL), brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (20.0 mg, 102 µmol, 87%). $\mathbf{R_f}$ = 0.21 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.93 (1 H, dd, *J* = 17.5, 10.9 Hz, C*H*=CH_2), 5.28 (1 H, *J* = 10.9 Hz, CH=CH_{2A}), 5.23 (1 H, *J* = 17.5 Hz, CH=CH_{2B}), 4.54 (1 H, ddd, *J* = 9.2, 9.2, 7.3 Hz, 2-H_A), 4.46 (1 H, d, *J* = 8.8 Hz, 8-H_A), 4.42 (1 H, ddd, *J* = 9.2, 9.2, 4.4 Hz, 2-H_B), 4.26 (1 H, d, *J* = 8.8 Hz, 8-H_B), 2.70 (1 H, ddd, *J* = 18.1, 7.3, 4.4 Hz, 3-H_A), 2.63 (1 H, ddd, *J* = 18.1, 9.2, 9.2 Hz, 3-H_B), 1.19 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.5 (4-*C*=O), 172.0 (6-*C*=O), 137.1 (*C*H=CH_2), 115.7 (CH=*C*H_2), 87.5 (5-*C*), 73.6 (8-*C*H_2), 65.2 (2-*C*H_2), 48.0 (9-*C*), 37.4 (3-*C*H_2), 15.7 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 2916, 2849, 1783 (C=O), 1748 (C=O), 1478, 1461, 1404, 1382, 1368, 1262, 1175, 1144, 1102, 1063, 1004, 927, 807, 734, 663, 568, 512; **HRMS** (ESI^+) *m/z* found 197.0811 ($M+H^+$, $C_{10}H_{13}O_4$ requires 197.0808), 219.0631 ($M+Na^+$, $C_{10}H_{12}O_4Na$ requires 219.0628) and 214.1073 ($M+NH_4^+$, $C_{10}H_{16}NO_4$ requires

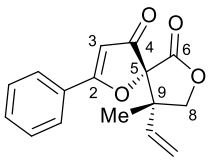
214.1074); $[\alpha]_D^{20}$ = +156 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[49]

(5*R*,9*S*)-9-Methyl-9-vinyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 405b



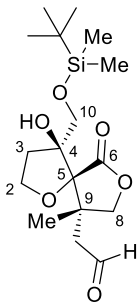
LiHMDS (1 M in THF; 408 µL, 408 µmol, 2 equiv.) was added dropwise to a solution of spirolactone **404b** (40.0 mg, 204 µmol, 1 equiv.) in THF (1.6 mL), cooled to 0 °C, and was stirred for 45 min. TESCl (68.4 µL, 408 µmol, 2 equiv.) was then added and the resulting solution was stirred for 45 min at 0 °C. The reaction mixture was then warmed to room temperature, quenched with water (8.5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford the crude silyl ether, which was then used in the next step without further purification. The resulting crude silyl ether was then dissolved in CH_2Cl_2 (8.5 mL). Ph_3CBF_4 (269 mg, 815 µmol, 4 equiv.) was then added and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (15 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless oil (26.7 mg, 137 µmol, 67%). $\mathbf{R_f}$ = 0.28 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.43 (1 H, d, *J* = 2.6 Hz, 2-*H*), 5.94 (1 H, dd, *J* = 17.5, 10.9 Hz, C*H*=CH_2), 5.73 (1 H, d, *J* = 2.6 Hz, 3-*H*), 5.32 (1 H, *J* = 10.9 Hz, CH=CH_{2A}), 5.29 (1 H, d, *J* = 17.5 Hz, CH=CH_{2B}), 4.72 (1 H, d, *J* = 8.7 Hz, 8-H_A), 4.34 (1 H, d, *J* = 8.7 Hz, 8-H_B), 1.25 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 197.6 (4-*C*=O), 179.7 (2-*C*H), 167.5 (6-*C*=O), 136.5 (*C*H=CH_2), 116.5 (CH=*C*H_2), 107.2 (3-*C*H), 91.2 (5-*C*), 73.4 (8-*C*H_2), 48.7 (9-*C*), 15.4 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 3085, 2979, 2916, 1787 (C=O), 1699 (C=O), 1565, 1417, 1354, 1182, 1140, 1078, 1045, 1003, 932, 831, 815, 732, 665, 572; **HRMS** (ESI^+) *m/z* found 217.0475 ($M+Na^+$, $C_{10}H_{10}O_4Na$ requires 217.0471); $[\alpha]_D^{19}$ = +204 (*c* 1.00, $CHCl_3$).

(+)-5-*epi*-Hyperolactone C *epi*-5



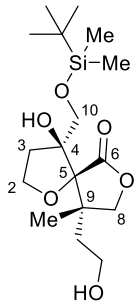
Phenyllithium (1.75 M in dibutyl ether; 22.0 µL, 38.0 µmol, 1.25 equiv.) was added dropwise to a solution of enone **405b** (5.9 mg, 30.4 µmol, 1 equiv.) in THF (0.5 mL), cooled to -78 °C, and was stirred for 45 min. TESCl (10.0 µL, 61.0 µmol, 2 equiv.) was then added and the resulting solution was stirred for 30 min at -78 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h. DDQ (13.8 mg, 61.0 µmol, 2 equiv.) was then added to the reaction mixture and the solution was stirred for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (1 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (1 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases were then washed with brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless solid (7.3 mg, 27.0 µmol, 89%). $\mathbf{R_f}$ = 0.32 (25% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.86-7.83 (2 H, m, Ar*H*), 7.63-7.59 (1 H, m, Ar*H*), 7.54-7.49 (2 H, m, Ar*H*), 6.06 (1 H, dd, *J* = 17.5, 10.9 Hz, C*H*=CH_2), 6.04 (1 H, s, 3-*H*), 5.37 (1 H, *J* = 10.9 Hz, CH=CH_{2A}), 5.34 (1 H, d, *J* = 17.5 Hz, CH=CH_{2B}), 4.79 (1 H, d, *J* = 8.7 Hz, 8-H_A), 4.38 (1 H, d, *J* = 8.7 Hz, 8-H_B), 1.30 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 196.8 (4-*C*=O), 187.6 (2-*C*H), 168.3 (6-*C*=O), 137.0 (*C*H=CH_2), 133.8 (Ar*H*), 129.2 (Ar*H*), 127.8 (*Ar*), 127.6 (Ar*H*), 116.4 (CH=*C*H_2), 100.5 (3-*C*H), 93.5 (5-*C*), 74.5 (8-*C*H_2), 49.0 (9-*C*), 15.6 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 2951, 2929, 1789 (C=O), 1692 (C=O), 1605, 1592, 1592, 1491, 1474, 1451, 1346, 1181, 1151, 1091, 1046, 1015, 998, 888, 772, 733, 688, 651, 574; **HRMS** (ESI$^+$) *m/z* found 271.0969 (M+H$^+$, $C_{16}H_{15}O_4$ requires 271.0965), 293.0782 (M+Na$^+$, $C_{16}H_{14}O_4Na$ requires 293.0784) and 288.1229 (M+NH_4^+, $C_{16}H_{18}NO_4$ requires 288.1230); **mp** 98-99 °C, lit.[18] 97-98 °C; $[\alpha]_D^{20}$ = +387 (*c* 0.25, ethanol), lit.[15] $[\alpha]_D^{22}$ = +283 (*c* 0.054, ethanol), lit.[18] $[\alpha]_D^{25}$ = +364 (*c* 0.14, ethanol). Spectroscopic data matched that previously reported.[15,18,56,60]

2-((4*S*,5*S*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-6-oxo-1,7-dioxaspiro[4.4]nonan-9-yl)acetaldehyde 400a



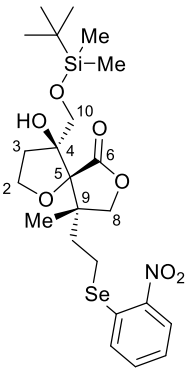
N-Methylmorpholine (64.2 mg, 548 µmol, 1.15 equiv.), citric acid monohydrate (70.1 mg, 334 µmol, 0.7 equiv.) and potassium osmate dihydrate (8.8 mg, 23.8 µmol, 5 mol%) were added to a solution of spirolactone **392a** (170 mg, 477 µmol, 1 equiv.) in acetone (14.8 mL) and water (3.7 mL). The resulting solution was then stirred for 4 h at room temperature. Sodium periodate (306 mg, 1.43 mmol, 3 equiv.) was then added and the reaction mixture was stirred at room temperature for 16 h. The resulting solution was then quenched with *sat.* sodium thiosulphate (10 mL) and then extracted with ethyl acetate (3 x 15 mL). The combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (150 mg, 420 µmol, 88%). **R_f** = 0.39 (25% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 9.77 (1 H, dd *J* = 1.4, 1.4 Hz, C*H*O), 4.34 (2 H, d, *J* = 8.7 Hz, 8-H_A), 4.07 (2 H, dd, *J* = 8.7, 1.9 Hz, 8-H_B), 3.99 (1 H, ddd, *J* = 10.4, 8.5, 3.8 Hz, 2-H_A), 3.89 (1 H, ddd, *J* = 8.5, 8.5, 8.5 Hz, 2-H_B), 3.80 (1 H, d, *J* = 10.6 Hz, 10-H_A), 3.64 (1 H, d, *J* = 10.6 Hz, 10-H_B), 3.17 (1 H, app dt, *J* = 17.9, 1.9 Hz, 9-CCH_{2A}), 2.93 (1 H, s, O*H*), 2.70 (1 H, br d, *J* = 17.9 Hz, 9-CCH_{2B}), 2.60 (1 H, ddd, *J* = 12.4, 10.4, 8.5 Hz, 3-H_A), 2.31 (1 H, ddd, *J* = 12.4, 8.5, 3.8 Hz, 3-H_B), 1.29 (3 H, s, CH_3), 0.91 (9 H, s, SiC(CH_3)$_3$), 0.12 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 199.9 (*C*HO), 175.0 (6-*C*=O), 85.7 (5-*C*), 80.7 (4-*C*), 74.5 (8-*C*H_2), 65.2 (10-*C*H_2), 65.0 (2-*C*H_2), 45.1 (9-C*C*H_2), 43.2 (9-*C*), 35.7 (3-*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.5 (Si*C*), 14.5 (*C*H_3), -5.3 (Si(*C*H_3)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 3526 (OH), 2953, 2929, 2895, 2856, 1762 (C=O), 1720 (C=O), 1462, 1363, 1253, 1097, 1063, 1013, 837, 778, 736; **HRMS** (ESI$^+$) *m/z* found 359.1882 (M+H$^+$, $C_{17}H_{31}O_6Si$ requires 359.1884), 381.1713 (M+Na$^+$, $C_{17}H_{30}O_6SiNa$ requires 381.1704) and 376.2143 (M+NH_4^+, $C_{17}H_{34}NO_6Si$ requires 376.2150); $[\alpha]_D^{20}$ = +64.8 (*c* 1.00, $CHCl_3$).

(4*S*,5*S*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-(2-hydroxyethyl)-9-methyl-1,7-dioxaspiro[4.4]nonan-6-one 401a



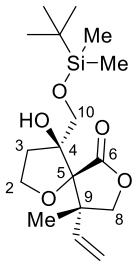
Sodium borohydride (41.2 mg, 1.09 mmol, 3 equiv.) was slowly added to a solution of aldehyde **400a** (130 mg, 363 µmol, 1 equiv.) in diethyl ether (2.2 mL), cooled to 0 °C. MeOH (0.75 mL) was then added dropwise, over a 15 min period, and the resulting solution was then warmed to room temperature and stirred for 2 h. The reaction mixture was then quenched with *sat.* aqueous ammonium chloride solution (5 mL) and the resulting solution was extracted with diethyl ether (3 x 15 mL). The combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (109 mg, 301 µmol, 83%). $\mathbf{R_f}$ = 0.20 (30% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.26 (1 H, d, *J* = 8.4 Hz, 8-H_A), 3.99 (1 H, ddd, *J* = 10.1, 8.3, 3.9 Hz, 2-H_A), 3.95 (1 H, d, *J* = 8.4 Hz, 8-H_B), 3.94 (1 H, ddd, *J* = 8.3, 8.3, 8.3 Hz, 2-H_B), 3.83 (1 H, d, *J* = 10.3 Hz, 10-H_A), 3.77 (2 H, app t, *J* = 6.8 Hz, HOCH_2), 3.64 (1 H, d, *J* = 10.3 Hz, 10-H_B), 3.13 (1 H, br s, O*H*), 2.59-2.51 (1 H, m, 3-H_A), 2.43 (1 H, ddd, *J* = 12.3, 8.3, 3.9 Hz, 3-H_B), 1.99-1.92 (1 H, m, 9-CCH_{2A}), 1.86 (1 H, ddd, *J* = 14.5, 6.8, 6.8 Hz, 9-CCH_{2B}), 1.12 (3 H, s, CH_3), 0.90 (9 H, s, SiC(CH_3)$_3$), 0.09 (6 H, s, Si(CH_3)$_2$), the signal due to O*H* was not observed; **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.6 (6-*C*=O), 86.1 (5-*C*), 81.1 (4-*C*), 74.7 (8-*C*H$_2$), 65.0 (2-*C*H$_2$), 64.8 (10-*C*H$_2$), 59.0 (HO*C*H$_2$), 43.8 (9-*C*), 35.2 (3-*C*H$_2$), 34.1 (9-C*C*H$_2$), 26.0 (SiC(*C*H$_3$)$_3$), 18.5 (Si*C*), 15.6 (*C*H$_3$), -5.3 (Si*C*H$_{3A}$), -5.4 (Si*C*H$_{3B}$); **IR** (ATR) ν_{Max}/cm^{-1} 3437 (OH), 2953, 2929, 2890, 2857, 1757 (C=O), 1463, 1363, 1254, 1097, 1070, 1014, 837, 777, 734; **HRMS** (ESI$^+$) *m/z* found 361.2045 (M+H$^+$, $C_{17}H_{33}O_6Si$ requires 361.2041) and 383.1874 (M+Na$^+$, $C_{17}H_{32}O_6SiNa$ requires 383.1860); $[\alpha]_D^{20}$ = +73.8 (*c* 1.00, $CHCl_3$).

(4*S*,5*S*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-9-(2-((2-nitrophenyl)selanyl)ethyl)-1,7-dioxaspiro[4.4]nonan-6-one 402a



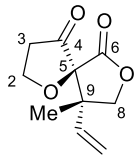
To a solution of alcohol **401a** (50.0 mg, 139 µmol, 1 equiv.) and 2-nitrophenyl selenocyanate **47** (44.1 mg, 194 µmol, 1.4 equiv.) in THF (2 mL) was added P(*n*-Bu)$_3$ (48.5 µL, 194 µmol, 1.4 equiv.) (Caution: toxic gas liberated). The resulting reaction mixture was stirred for 18 h at room temperature, then quenched with *sat.* aqueous ammonium chloride solution (2 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic phase was then washed with brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, using the elution gradient 15 to 25% ethyl acetate in pentane, affording the *title compound* as a dark yellow oil (58.3 mg, 107 µmol, 77%). **R_f** = 0.36 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.29 (1 H, dd, *J* = 8.4, 1.6 Hz, Ar*H*), 7.55-7.48 (2 H, m, Ar*H*), 7.32 (1 H, ddd, *J* = 8.4, 6.8, 1.6 Hz, Ar*H*), 4.14 (1 H, d, *J* = 8.8 Hz, 8-H_A), 4.05 (1 H, d, *J* = 8.8 Hz, 8-H_B), 4.02 (1 H, ddd, *J* = 10.3, 8.4, 3.7 Hz, 2-H_A), 3.92 (1 H, ddd, *J* = 8.4, 8.4, 8.4 Hz, 2-H_B), 3.80 (1 H, d, *J* = 10.3 Hz, 10-H_A), 3.64 (1 H, d, *J* = 10.3 Hz, 10-H_B), 3.04-2.97 (1 H, m, ArSeCH_{2A}), 2.91 (1 H, s, O*H*), 2.88-2.81 (1 H, m, ArSeCH_{2B}), 2.60 (1 H, *J* = 12.3, 10.3, 8.4 Hz, 3-H_A), 2.43 (1 H, ddd, *J* = 12.3, 8.4, 3.7 Hz, 3-H_B), 2.16-2.07 (2 H, m, 9-CCH_2), 1.18 (3 H, s, CH_3), 0.91 (9 H, s, SiC(CH_3)$_3$), 0.09 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.0 (6-*C*=O), 146.9 (*Ar*), 133.9 (*Ar*H), 133.2 (*Ar*), 128.9 (*Ar*H), 126.7 (*Ar*H), 125.8 (*Ar*H), 85.7 (5-*C*), 81.0 (4-*C*), 74.0 (8-*C*H$_2$), 65.1 (2-*C*H$_2$), 64.9 (10-*C*H$_2$), 45.5 (9-*C*), 35.3 (3-*C*H$_2$), 31.7 (9-C*C*H$_2$), 26.0 (SiC(*C*H$_3$)$_3$), 20.6 (ArSe*C*H$_2$), 18.5 (Si*C*), 15.7 (*C*H$_3$), -5.2 (Si*C*H$_{3A}$), -5.3 (Si*C*H$_{3B}$); **IR** (ATR) ν_{Max}/cm^{-1} 3545 (OH), 2952, 2928, 2894, 2856, 1759 (C=O), 1591, 1566, 1511, 1462, 1331, 1303, 1251, 1062, 1036, 1017, 836, 778, 754, 729, 647; **HRMS** (ESI$^+$) *m/z* found 546.1418 (M+H$^+$, $C_{23}H_{36}NO_7SeSi$ requires 546.1421); $[\alpha]_D^{22}$ = +76.7 (*c* 1.00, $CHCl_3$).

(4*S*,5*S*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-9-vinyl-1,7-dioxaspiro[4.4]nonan-6-one 403a



Hydrogen peroxide (30% *aq.*, 3.10 mL, 0.92 mmol, 10 equiv.) was added to a solution of selenide **402a** (50.0 mg, 91.8 µmol, 1 equiv.) in THF (1 mL) cooled to 0 °C. The resulting reaction mixture was stirred for 1 h, then quenched with *sat.* aqueous sodium bisulphate solution (15 mL) and was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was then washed with brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a colourless oil (29.7 mg, 86.7 µmol, 94%). $\mathbf{R_f}$ = 0.60 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 6.18 (1 H, dd, *J* = 17.5, 11.0 Hz, C*H*=CH_2), 5.23 (1 H, d, *J* = 11.0 Hz, CH=CH_{2A}), 5.19 (1 H, d, *J* = 17.5 Hz, CH=CH_{2B}), 4.13 (1 H, ddd, *J* = 8.2, 7.4, 7.4 Hz, 2-H_A), 4.09 (2 H, two overlapping d observed as a br s, 8-H_2), 3.95 (1 H, ddd, *J* = 8.2, 8.2, 8.2 Hz, 2-H_B), 3.83 (1 H, d, *J* = 10.2 Hz, 10-H_A), 3.62 (1 H, d, *J* = 10.2 Hz, 10-H_B), 3.10 (1 H, s, O*H*), 2.39 (2 H, app t, *J* = 7.4 Hz, 3-H_2), 1.22 (3 H, s, CH_3), 0.90 (9 H, s, SiC(CH_3)$_3$), 0.07 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 175.4 (6-*C*=O), 138.0 (*C*H=CH_2), 114.8 (CH=*C*H_2), 86.7 (5-*C*), 82.0 (4-*C*), 76.3 (8-*C*H_2), 66.0 (2-*C*H_2), 64.7 (10-*C*H_2), 47.4 (9-*C*), 35.1 (3-*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.5 (Si*C*), 16.8 (*C*H_3), -5.26 (Si*C*H_{3A}), -5.32 (Si*C*H_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 3544 (OH), 2954, 2929, 2895, 2857, 1762 (C=O), 1472, 1321, 1254, 1096, 1067, 1008, 835, 776, 736, 702; **HRMS** (ESI$^+$) *m/z* found 343.1937 (M+H$^+$, $C_{17}H_{31}O_5Si$ requires 343.1935), 365.1746 (M+Na$^+$, $C_{17}H_{30}O_5SiNa$ requires 365.1755) and 360.2198 (M+NH_4^+, $C_{17}H_{34}NO_5Si$ requires 360.2210); $[\alpha]_D^{21}$ = +63.7 (*c* 1.00, $CHCl_3$).

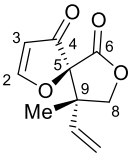
(5*S*,9*S*)-9-Methyl-9-vinyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 404a



An aqueous solution of hydrochloric acid (2 M; 0.37 mL, 0.73 mmol, 10 equiv.) was added to a solution of silyl ether **403a** (25.0 mg, 73.0 µmol, 1 equiv.) in THF (0.76 mL). The resulting reaction mixture was stirred at room temperature for 18 h. Water (3.3 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (10 mL), brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the

crude diol which was then used in the next step without further purification. The resulting crude diol was then dissolved within a THF (0.42 mL) and water (0.42 mL) mixture. Sodium periodate (46.8 mg, 219 µmol, 3 equiv.) was then added and the resulting solution was stirred at room temperature for 18 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (10 mL), brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (13.6 mg, 69.3 µmol, 95%). **R_f** = 0.35 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.82 (1 H, dd, *J* = 17.5, 10.9 Hz, C*H*=CH_2), 5.30 (1 H, *J* = 10.9 Hz, CH=CH_{2A}), 5.28 (1 H, *J* = 17.5 Hz, CH=CH_{2B}), 4.66 (1 H, d, *J* = 8.7 Hz, 8-H_A), 4.55-4.49 (1 H, m, 2-H_A), 4.35 (1 H, ddd, *J* = 8.8, 8.8, 5.1 Hz, 2-H_B), 4.00 (1 H, d, *J* = 8.7 Hz, 8-H_B), 2.64 (1 H, ddd, *J* = 18.2, 7.6, 5.1 Hz, 3-H_A), 2.55 (1 H, ddd, *J* = 18.2, 8.8, 8.8 Hz, 3-H_B), 1.32 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.3 (4-*C*=O), 171.8 (6-*C*=O), 135.3 (*C*H=CH_2), 119.2 (CH=*C*H_2), 88.6 (5-*C*), 74.2 (8-*C*H_2), 65.5 (2-*C*H_2), 48.3 (9-*C*), 37.0 (3-*C*H_2), 19.2 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 2969, 2916, 2851, 1783 (C=O), 1749 (C=O), 1474, 1366, 1271, 1156, 1102, 1002, 935, 814, 727, 661, 526; **HRMS** (ESI^+) *m/z* found 197.0807 ($M+H^+$, $C_{10}H_{13}O_4$ requires 197.0808), 219.0627 ($M+Na^+$, $C_{10}H_{12}O_4Na$ requires 219.0628) and 214.1080 ($M+NH_4^+$, $C_{10}H_{16}NO_4$ requires 214.1074); $[\alpha]_D^{18}$ = -156 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[49]

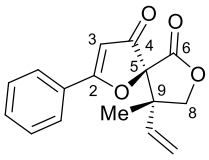
(5*S*,9*S*)-9-Methyl-9-vinyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 405a



LiHMDS (1 M in THF; 163 µL, 163 µmol, 2 equiv.) was added dropwise to a solution of spirolactone **404a** (16.0 mg, 81.5 µmol, 1 equiv.) in THF (0.65 mL), cooled to 0 °C, and was stirred for 45 min. TESCl (27.5 µL, 163 µmol, 2 equiv.) was then added and the resulting solution was stirred for 45 min at 0 °C. The reaction mixture was then warmed to room temperature, quenched with water (3.5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were then washed with brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford the crude silyl ether, which was then used in the next step without further purification. The resulting crude silyl ether was then dissolved in CH_2Cl_2 (3.5

mL). Ph_3CBF_4 (108 mg, 326 µmol, 4 equiv.) was then added and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (5 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases were then washed with brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless solid (11.3 mg, 58.2 µmol, 71%). **R_f** = 0.30 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.40 (1 H, d, *J* = 2.6 Hz, 2-*H*), 5.91 (1 H, dd, *J* = 17.4, 10.9 Hz, C*H*=CH_2), 5.67 (1 H, d, *J* = 2.6 Hz, 3-*H*), 5.30 (1 H, *J* = 10.9 Hz, CH=CH_{2A}), 5.26 (1 H, d, *J* = 17.4 Hz, CH=CH_{2B}), 4.92 (1 H, d, *J* = 8.5 Hz, 8-H_A), 4.08 (1 H, d, *J* = 8.5 Hz, 8-H_B), 1.43 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 197.6 (4-*C*=O), 179.6 (2-*C*H), 167.5 (6-*C*=O), 134.0 (*C*H=CH_2), 119.4 (CH=*C*H_2), 107.1 (3-*C*H), 91.9 (5-*C*), 74.2 (8-*C*H_2), 48.7 (9-*C*), 19.6 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 2982, 2955, 2916, 2849, 1772 (C=O), 1703 (C=O), 1566, 1464, 1416, 1369, 1350, 1267, 1203, 1144, 1086, 1003, 977, 947, 814, 720, 696, 663, 578, 522, 409; **HRMS** (ESI^+) *m/z* found 217.0473 ($M+Na^+$, $C_{10}H_{10}O_4Na$ requires 217.0471) and 212.0921 ($M+NH_4^+$, $C_{10}H_{10}NO_4$ requires 212.0917); $[\alpha]_D^{20}$ = -158 (*c* 1.00, $CHCl_3$). Spectroscopic data matched that previously reported.[49]

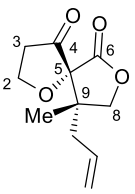
(-)-Hyperolactone C 5



Phenyllithium (1.75 M in dibutyl ether; 35.5 µL, 61.8 µmol, 1.25 equiv.) was added dropwise to a solution of enone **405a** (10.0 mg, 51.5 µmol, 1 equiv.) in THF (0.5 mL), cooled to -78 °C, and was stirred for 45 min. TESCl (17.5 µL, 103 µmol, 2 equiv.) was then added and the resulting solution was stirred for 30 min at -78 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h. DDQ (23.4 mg, 103 µmol, 2 equiv.) was then added to the reaction mixture and the solution was stirred for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (1 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (1 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases were then washed with brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude

product was purified by column chromatography affording the *title compound* as a colourless solid (11.9 mg, 44.0 µmol, 85%). **R_f** = 0.32 (25% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.87-7.84 (2 H, m, Ar*H*), 7.63-7.59 (1 H, m, Ar*H*), 7.54-7.49 (2 H, m, Ar*H*), 5.99 (1 H, dd, *J* = 17.5, 10.9 Hz, C*H*=CH_2), 5.98 (1 H, s, 3-*H*), 5.27 (1 H, *J* = 10.9 Hz, CH=CH_{2A}), 5.26 (1 H, d, *J* = 17.5 Hz, CH=CH_{2B}), 4.97 (1 H, d, *J* = 8.5 Hz, 8-H_A), 4.11 (1 H, d, *J* = 8.5 Hz, 8-H_B), 1.53 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 196.7 (4-*C*=O), 187.4 (2-*C*H), 168.2 (6-*C*=O), 134.4 (*C*H=CH_2), 133.7 (Ar*H*), 129.2 (Ar*H*), 127.9 (*Ar*), 127.6 (Ar*H*), 119.2 (CH=*C*H_2), 100.4 (3-*C*H), 93.3 (5-*C*), 74.3 (8-*C*H_2), 49.0 (9-*C*), 19.7 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 2955, 2917, 2850, 1779 (C=O), 1701 (C=O), 1604, 1591, 1567, 1449, 1343, 1272, 1168, 1097, 1037, 998, 975, 934, 773, 691, 573, 488; **HRMS** (ESI^+) *m/z* found 271.0973 ($M+H^+$, $C_{16}H_{15}O_4$ requires 271.0965), 293.0788 ($M+Na^+$, $C_{16}H_{14}O_4Na$ requires 293.0784) and 288.1235 ($M+NH_4^+$, $C_{16}H_{18}NO_4$ requires 288.1230); **mp** 105-106 °C, lit.[13] 104 °C, lit.[15,18] 105-106 °C, lit.[35] 104-105 °C; $[\alpha]_D^{22}$ = -244 (*c* 0.50, $CHCl_3$), lit.[13] $[\alpha]_D^{20}$ = -356 (*c* 0.02, ethanol), lit.[15] $[\alpha]_D^{25}$ = -390 (*c* 0.02, ethanol), lit.[18] $[\alpha]_D^{25}$ = -273 (*c* 0.69, $CHCl_3$), lit.[35] $[\alpha]_D^{20}$ = -218 (*c* 0.10, $CHCl_3$), lit.[60] $[\alpha]_D^{25}$ = -281 (*c* 0.33, CH_2Cl_2); structure solved from X-ray crystallography studies (crystallisation from *n*-heptane). Spectroscopic data matched that previously reported.[13,15,18,30,35,45,56,60]

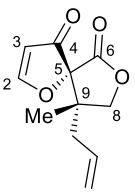
(5*R*,9*S*)-9-Allyl-9-methyl-1,7-dioxaspiro[4.4]nonane-4,6-dione 406



An aqueous solution of hydrochloric acid (2 M; 1.1 mL, 2.24 mmol, 10 equiv.) was added to a solution of silyl ether **392b** (80.0 mg, 224 µmol, 1 equiv.) in THF (2.3 mL). The resulting reaction mixture was stirred at room temperature for 18 h. Water (5 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The combined organic phases were then washed with water (10 mL), brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the crude diol which was then used in the next step without further purification. The resulting crude diol was then dissolved within a THF (1.3 mL) and water (1.3 mL) mixture. Sodium periodate (144 mg, 673 µmol, 3 equiv.) was then added and the resulting solution was stirred at room temperature for 18 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 10 mL). The

combined organic phases were then washed with water (10 mL), brine (10 mL) and then dried with $MgSO_4$. The organic phase was concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (42.2 mg, 201 µmol, 90%). **R_f** = 0.32 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.73 (1 H, dddd, *J* = 16.3, 10.6, 7.4, 7.4 Hz, C*H*=CH_2), 5.19-5.12 (2 H, m, CH=CH_2), 4.55 (1 H, ddd, *J* = 9.0, 9.0, 7.4 Hz, 2-H_A), 4.41 (1 H, ddd, *J* = 9.0, 9.0, 4.6 Hz, 2-H_B), 4.27 (1 H, d, *J* = 8.9 Hz, 8-H_A), 4.16 (1 H, d, *J* = 8.9 Hz, 8-H_B), 2.67 (1 H, ddd, *J* = 18.3, 7.4, 4.6 Hz, 3-H_A), 2.61 (1 H, ddd, *J* = 18.3, 9.0, 9.0 Hz, 3-H_B), 2.28-2.18 (2 H, m, 9-CCH_2), 1.03 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 210.2 (4-*C*=O), 172.7 (6-*C*=O), 132.1 (*C*H=CH_2), 120.5 (CH=*C*H_2), 87.7 (5-*C*), 72.7 (8-*C*H_2), 65.3 (2-*C*H_2), 45.5 (9-*C*), 38.9 (9-C*C*H_2), 37.4 (3-*C*H_2), 16.4 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 2958, 2916, 2849, 1781 (C=O), 1748 (C=O), 1463, 1376, 1289, 1254, 1178, 1106, 1002, 922, 813, 733, 701, 524; **HRMS** (ESI$^+$) *m/z* found 211.0972 (M+H$^+$, $C_{11}H_{15}O_4$ requires 211.0965) and 233.0783 (M+Na$^+$, $C_{11}H_{14}O_4Na$ requires 233.0784); $[\alpha]_D^{20}$ = +185 (*c* 1.00, $CHCl_3$).

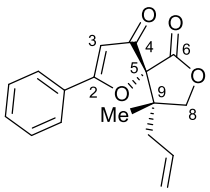
(5*R*,9*S*)-9-Allyl-9-methyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 407



LiHMDS (1 M in THF; 0.38 mL, 381 µmol, 2 equiv.) was added dropwise to a solution of spirolactone **406** (40.0 mg, 190 µmol, 1 equiv.) in THF (1.5 mL), cooled to 0 °C, and was stirred for 45 min. TESCl (63.9 µL, 381 µmol, 2 equiv.) was then added and the resulting solution was stirred for 45 min at 0 °C. The reaction mixture was then warmed to room temperature, quenched with water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were then washed with brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford the crude silyl ether, which was then used in the next step without further purification. The resulting crude silyl ether was then dissolved in CH_2Cl_2 (10 mL). Ph_3CBF_4 (251 mg, 761 µmol, 4 equiv.) was then added and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (10 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases were then washed with brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column

chromatography affording the *title compound* as a slowly crystallising colourless solid (23.6 mg, 113 µmol, 60%). **R_f** = 0.27 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.45 (1 H, d, *J* = 2.7 Hz, 2-*H*), 5.82-5.71 (1 H, m, C*H*=CH_2), 5.27 (1 H, d, *J* = 2.7 Hz, 3-*H*), 5.25-5.17 (2 H, m, CH=CH_2), 4.55 (1 H, d, *J* = 8.8 Hz, 8-H_A), 4.27 (1 H, d, *J* = 8.8 Hz, 8-H_B), 2.40-2.28 (2 H, m, 9-CCH_2), 1.12 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 198.2 (4-*C*=O), 179.6 (2-*C*H), 168.1 (6-*C*=O), 131.5 (*C*H=CH_2), 121.1 (CH=*C*H_2), 107.1 (3-*C*H), 91.8 (5-*C*), 72.5 (8-*C*H_2), 46.3 (9-*C*), 39.6 (9-C*C*H_2), 16.1 (*C*H_3); **IR** (ATR) ν_{Max}/cm^{-1} 2916, 2850, 1783 (C=O), 1692 (C=O), 1563, 1462, 1374, 1244, 1183, 1092, 1027, 966, 863; **HRMS** (ESI$^+$) *m/z* found 209.0807 (M+H$^+$, $C_{11}H_{13}O_4$ requires 209.0808), 231.0628 (M+Na$^+$, $C_{11}H_{12}O_4Na$ requires 231.0628) and 226.1072 (M+NH_4^+, $C_{11}H_{16}NO_4$ requires 226.1074); **mp** 40-43 °C; $[\alpha]_D^{24}$ = +108 (*c* 1.00, $CHCl_3$).

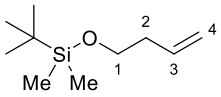
(5*R*,9*S*)-9-Allyl-9-methyl-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 408



Phenyllithium (1.75 M in dibutyl ether; 30.0 µL, 51.9 µmol, 1.2 equiv.) was added dropwise to a solution of enone **407** (9.0 mg, 43.2 µmol, 1 equiv.) in THF (0.5 mL), cooled to -78 °C, and was stirred for 45 min. TESCl (14.5 µL, 86.4 µmol, 2 equiv.) was then added and the resulting solution was stirred for 30 min at -78 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h. DDQ (19.6 mg, 86.4 µmol, 2 equiv.) was then added to the reaction mixture and the solution was stirred for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and washed with aqueous *sat.* sodium hydrogen carbonate solution (5 mL). The resulting aqueous phase was then extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases were then washed with brine (5 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by column chromatography affording the *title compound* as a colourless solid (9.6 mg, 33.8 µmol, 78%). **R_f** = 0.36 (25% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.89-7.85 (2 H, m, Ar*H*), 7.65-7.60 (1 H, m, Ar*H*), 7.56-7.51 (2 H, m, Ar*H*), 6.03 (1 H, s, 3-*H*), 5.90-5.78 (1 H, m, C*H*=CH_2), 5.28-5.22 (2 H, m, CH=CH_2), 4.61 (1 H, d, *J* = 8.7 Hz, 8-H_A), 4.30 (1 H, d, *J* = 8.7 Hz, 8-H_B), 2.52-2.40 (2 H, m, 9-CCH_2), 1.17 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 197.3 (4-*C*=O), 187.4 (6-*C*=O), 168.8 (2-*C*), 133.8 (*Ar*H), 131.8 (*C*H=CH_2), 129.2 (*Ar*H),

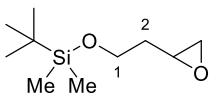
127.9 (*Ar*), 127.6 (*Ar*H), 121.0 (CH=CH_2), 100.4 (3-*C*H), 93.1 (5-*C*), 72.7 (8-CH_2), 46.6 (9-*C*), 39.9 (9-CCH_2), 16.3 (CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 2973, 2915, 1784 (C=O), 1692 (C=O), 1605, 1592, 1568, 1491, 1471, 1451, 1346, 1154, 1093, 997, 925, 887, 805, 773, 733, 688, 652, 568; **HRMS** (ESI^+) *m/z* found 285.1122 ($M+H^+$, $C_{17}H_{17}O_4$ requires 285.1121) and 307.0946 ($M+Na^+$, $C_{17}H_{16}O_4Na$ requires 307.0941); **mp** 47-49 °C; $[\alpha]_D^{19}$ = +164 (*c* 1.00, $CHCl_3$).

(But-3-en-1-yloxy)(*tert*-butyl)dimethylsilane 417



TBSCl (9.95 g, 66.0 mmol, 1.1 equiv.) and imidazole (8.17 g, 120 mmol, 2 equiv.) were added to a stirred solution of 3-buten1-ol **416** (4.33 g, 60.0 mmol, 1 equiv.) in CH_2Cl_2 (155 mL), cooled to 0 °C, and was stirred for 10 min. The reaction mixture was warmed to room temperature and then stirred for 16 h. The resulting solution was then washed with *sat.* aqueous sodium hydrogen carbonate solution (50 mL), extracted with ethyl acetate (3 x 100 mL) and dried with $MgSO_4$. The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (10.7 g, 57.6 mmol, 96%). $\mathbf{R_f}$ = 0.80 (5% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 5.82 (1 H, ddt, *J* = 17.1, 10.2, 6.8 Hz, C*H*=CH_2), 5.10-5.00 (2 H, m, CH=CH_2), 3.66 (2 H, t, *J* = 6.8 Hz, 1-H_2), 2.28 (2 H, dt, *J* = 6.8, 6.8 Hz, 2-H_2), 0.89 (9 H, s, SiC(CH_3)$_3$), 0.05 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 135.6 (3-*C*H), 116.4 (4-CH_2), 63.0 (1-CH_2), 37.6 (2-CH_2), 26.1 (SiC(CH_3)$_3$), 18.5 (Si*C*), -5.1 (Si(CH_3)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 2955, 2929, 2896, 2858, 1642, 1472, 1254, 1097, 986, 909, 834, 774, 626; the compound did not ionise under the ESI-HRMS conditions used. Spectroscopic data matched that previously reported.[177]

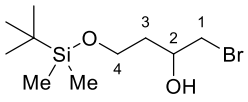
(±)-*tert*-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane 426



m-CPBA (≤77%; 14.4 g, 64.4 mmol, 2 equiv.) was added to a stirred solution of olefin **417** (6.00 g, 32.2 mmol, 1 equiv.) in CH_2Cl_2 (110 mL) at 0 °C and was stirred for 10 min. The resulting solution was then warmed to room temperature was stirred for 16 h. The reaction mixture was then quenched by *sat.* aqueous sodium hydrogen carbonate solution (65 mL) and *sat.* aqueous sodium

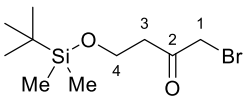
sulphite solution (65 mL). The reaction mixture was then vigorously stirred for an additional 15 min and extracted with pentane (150 mL). The organic layer was then washed with aqueous sodium hydrogen carbonate solution (20 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (6.30 g, 31.2 mmol, 97%). **R_f** = 0.32 (5% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 3.77 (2 H, dd, *J* = 7.3, 5.4 Hz, 1-H_2), 3.07-3.02 (1 H, m, OC*H*), 2.78 (1 H, dd, *J* = 5.1, 4.0 Hz, OCH_{2A}), 2.51 (1 H, dd, *J* = 5.1, 2.7 Hz, OCH_{2B}), 1.82-1.65 (2 H, m, 2-H_2), 0.90 (9 H, s, SiC(CH_3)$_3$), 0.06 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 60.2 (1-CH_2), 50.2 (O*C*H), 47.3 (OCH_2), 36.0 (2-CH_2), 26.0 (SiC(CH_3)$_3$), 18.4 (Si*C*), -5.3 (Si(CH_3)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 2954, 2929, 2886, 2857, 1471, 1412, 1387, 1253, 1098, 1006, 830, 774, 661; the compound did not ionise under the ESI-HRMS conditions used. Spectroscopic data matched that previously reported.[178]

(±)-1-Bromo-4-((*tert*-butyldimethylsilyl)oxy)butan-2-ol 418



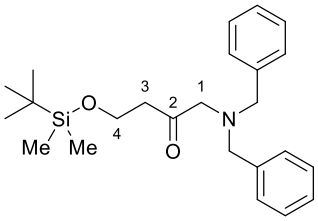
Ammonium acetate (168 mg, 2.17 mmol, 0.1 equiv.) and NBS (4.25 g, 23.9 mmol, 1.1 equiv.) was added to a solution of olefin **417** (4.05 g, 21.7 mmol, 1 equiv.) in acetone (22 mL) and water (22 mL). The resulting reaction mixture was stirred at room temperature for 18 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were then dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (3.20 g, 11.3 mmol, 52%). **R_f** = 0.19 (50% CH_2Cl_2 in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.03 (1 H, ddq, *J* = 7.6, 5.4, 3.6 Hz, 2-*H*), 3.89 (1 H, ddd, *J* = 10.4, 5.9, 4.4 Hz, 4-H_A), 3.82 (1 H, ddd, *J* = 10.4, 7.5, 4.4 Hz, 4-H_B), 3.51 (1 H, d, *J* = 3.6 Hz, O*H*), 3.48-3.40 (2 H, m, 1-H_2), 1.87-1.74 (2 H, m, 3-H_2), 0.89 (9 H, s, SiC(CH_3)$_3$), 0.08 (6 H, br s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 71.1 (2-*C*H), 61.6 (4-CH_2), 38.7 (1-CH_2), 36.6 (3-CH_2), 26.0 (SiC(CH_3)$_3$), 18.3 (Si*C*), -5.39 (SiCH_{3A}), -5.41 (SiCH_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 3410 (OH), 2954, 2928, 2883, 2857, 1471, 1254, 1089, 938, 831, 774, 729, 662; **HRMS** (ESI$^+$) *m/z* found 283.0726 (M+H$^+$, $C_{10}H_{24}BrO_2Si$ requires 283.0723) and 305.0544 (M+Na$^+$, $C_{10}H_{23}BrO_2SiNa$ requires 305.0543).

1-Bromo-4-((*tert*-butyldimethylsilyl)oxy)butan-2-one 419



Dess-Martin periodinane (3.59 g, 8.47 mmol, 1.1 equiv.) was added to a stirred solution of bromohydrin **418** (2.18 g, 7.70 mmol, 1 equiv.) in CH_2Cl_2 (140 mL), cooled to 0 °C, and was stirred for 10 min. The resulting reaction mixture was then warmed to room temperature and was left stirring for 4 h. The reaction solution was then cooled to -15 °C, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography affording the *title compound* as a colourless oil (3.00 g, 23.4 mmol, 94%). $\mathbf{R_f}$ = 0.27 (5% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 3.96 (2 H, s, 1-H_2), 3.91 (2 H, t, *J* = 6.0 Hz, 4-H_2), 2.81 (2 H, t, *J* = 6.0 Hz, 3-H_2), 0.87 (9 H, s, SiC(CH_3)$_3$), 0.05 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 201.1 (2-*C*=O), 59.2 (4-*C*H_2), 43.0 (3-*C*H_2), 35.6 (1-*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 18.3 (Si*C*), -5.4 (Si(CH_3)$_2$); **IR** (ATR) ν_{Max}/cm^{-1} 2954, 2929, 2856, 1717 (C=O), 1471, 1390, 1254, 1087, 936, 834, 777, 664; **HRMS** (ESI$^+$) *m/z* found 281.0561 (M+H$^+$, $C_{10}H_{22}BrO_2Si$ requires 281.0567) and 303.0389 (M+Na$^+$, $C_{10}H_{21}BrO_2SiNa$ requires 303.0386).

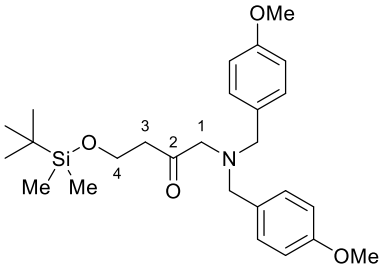
4-((*tert*-Butyldimethylsilyl)oxy)-1-(dibenzylamino)butan-2-one 420



Dibenzylamine (1.15 mL, 5.94 mmol, 1.05 equiv.) was added to a solution of α-bromoketone **419** (1.59 g, 5.65 mmol, 1 equiv.) and potassium carbonate (1.95 g, 14.1 mmol, 2.5 equiv.) in DMF (10 mL) and the resulting reaction mixture was stirred at room temperature for 18 h. Water (50 mL) was then added to the reaction mixture and the resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then washed with brine (2 x 20 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (1.89 g, 4.75 mmol, 84%). $\mathbf{R_f}$ = 0.40 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.40-7.23 (10 H, m, Ar*H*), 3.82 (2 H, t, *J* = 6.3 Hz, 4-H_2), 3.67 (4 H, s, N(CH_2Ar)$_2$), 3.24 (2 H, s, 1-H_2), 2.61 (2 H, t, *J* = 6.3 Hz, 3-H_2), 0.83 (9 H, s, SiC(CH_3)$_3$), 0.00 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.7 (2-*C*=O), 138.9 (*Ar*), 129.1 (*Ar*H), 128.5 (*Ar*H), 127.3 (*Ar*H), 63.7 (1-*C*H_2), 58.8 (4-*C*H_2), 58.7 (N(*C*H_2Ar)$_2$), 43.2 (3-*C*H_2), 26.0 (SiC(CH_3)$_3$), 18.4 (Si*C*), -5.4 (Si(CH_3)$_2$); **IR** (ATR)

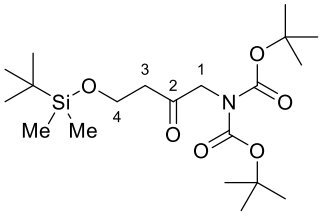
v_{Max}/cm^{-1} 3063, 3028, 2953, 2927, 2883, 2855, 2801, 1717 (C=O), 1494, 1454, 1373, 1253, 1090, 1028, 834, 777, 744, 698, 497, 470; **HRMS** (ESI^+) *m/z* found 398.2522 ($M+H^+$, $C_{24}H_{36}NO_2Si$ requires 398.2510) and 420.2333 ($M+Na^+$, $C_{24}H_{35}NO_2SiNa$ requires 420.2329).

1-(Bis(4-methoxybenzyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)butan-2-one 421



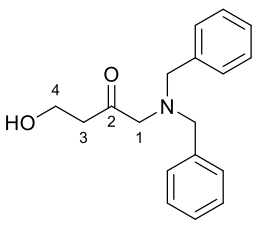
Bis(4-methoxybenzyl)amine (1.92 g, 7.47 mmol, 1.05 equiv.) was added to a solution of α-bromoketone **419** (2.00 g, 7.11 mmol, 1 equiv.) and potassium carbonate (2.46 g, 17.8 mmol, 2.5 equiv.) in DMF (12.0 mL) and the resulting reaction mixture was stirred at room temperature for 18 h. Water (20 mL) was then added to the reaction mixture and the resulting solution was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were then washed with brine (2 x 20 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a pale-yellow oil (3.17 g, 6.92 mmol, 97%). $\mathbf{R_f}$ = 0.23 (10% ethyl acetate in cyclohexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.32-7.26 (4 H, m, Ar*H*) 6.90-6.84 (4 H, m, Ar*H*), 3.83 (2 H, t, *J* = 6.4 Hz, 4-H_2), 3.82 (6 H, s, N(BnOCH_3)$_2$) 3.60 (4 H, s, N(CH_2Ar)$_2$) 3.21 (2 H, s, 1-H_2), 2.62 (2 H, t, *J* = 6.4 Hz, 3-H_2) 0.85 (9 H, s, SiC(CH_3)$_3$) 0.02 (6 H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.7 (2-*C*=O), 158.8 (*Ar)*, 130.7 (*Ar*), 130.1 (*Ar*H), 113.7 (*Ar*H), 63.4 (1-*C*H$_2$), 58.7 (4-*C*H$_2$), 57.8 (N(*C*H$_2$Ar)$_2$), 55.2 (N(BnO*C*H$_3$)$_2$), 43.0 (3-*C*H$_2$), 25.8 (SiC(*C*H$_3$)$_3$), 18.2 (Si*C*), -5.5 (Si(CH_3)$_2$); **IR** (ATR) v_{Max}/cm^{-1} 2953, 2929, 2855, 2835, 1715 (C=O), 1611, 1510, 1463, 1301, 1245, 1171, 1087, 1035, 831, 776, 733, 522; **HRMS** (ESI^+) *m/z* found 458.2731 ($M+H^+$, $C_{26}H_{39}NO_4Si$ requires 458.2727).

tert-Butyl (*tert*-butoxycarbonyl)(4-((*tert*-butyldimethylsilyl)oxy)-2-oxobutyl)carbamate 422



Di-*tert*-butyl iminodicarbonate (1.57 g, 7.23 mmol, 1.05 equiv.) was added to a solution of α-bromoketone **419** (1.94 g, 6.88 mmol, 1 equiv.) and potassium carbonate (2.34 g, 17.2 mmol, 2.5 equiv.) in DMF (15 mL) and the resulting reaction mixture was stirred at room temperature for 18 h. Water (50 mL) was then added to the reaction mixture and the resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then washed with brine (2 x 20 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a colourless oil (2.16 g, 5.16 mmol, 75%). $\mathbf{R_f}$ = 0.30 (10% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.40 (2 H, s, 1-H_2), 3.90 (2 H, t, J = 6.4 Hz, 4-H_2), 2.61 (2 H, t, J = 6.4 Hz, 3-H_2), 1.48 (18 H, s, $N(CO_2C(CH_3)_3)_2$), 0.88 (9 H, s, $SiC(CH_3)_3$), 0.05 (6 H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 203.3 (2-*C*=O), 152.2 ($N(CO_2C(CH_3)_3)_2$), 83.0 ($N(CO_2C(CH_3)_3)_2$), 58.3 (4-CH_2), 55.4 (1-CH_2), 43.0 (3-CH_2), 28.1 ($N(CO_2C(CH_3)_3)_2$), 26.0 ($SiC(CH_3)_3$), 18.4 (Si*C*), -5.3 ($Si(CH_3)_2$); **IR** (ATR) ν_{Max}/cm^{-1} 2955, 2930, 2885, 2857, 1759 (C=O), 1729 (C=O), 1696 (C=O), 1472, 1366, 1338, 1254, 1230, 1142, 1110, 836, 777; **HRMS** (ESI^+) *m/z* found 418.2638 ($M+H^+$, $C_{20}H_{40}NO_6Si$ requires 418.2619) and 440.2456 ($M+Na^+$, $C_{20}H_{39}NO_6SiNa$ requires 440.2439).

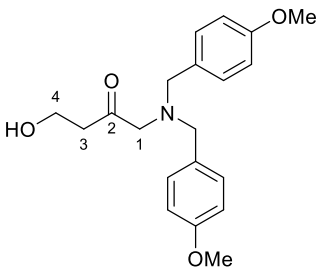
1-(Dibenzylamino)-4-hydroxybutan-2-one 423



Tetra-*n*-butylammonium fluoride (1 M in THF, 642 µL, 6.42 mmol, 1.5 equiv.), was added to a solution of amine **420** (1.70 g, 4.28 mmol, 1 equiv.) in THF (40 mL) at 0 °C, and the resulting reaction mixture was stirred at 0 °C for 18 h. Water (50 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 50 mL). The combined organic phases were then washed with brine (50 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography, using the elution gradient 20 to 50% ethyl acetate in petroleum ether, affording the *title compound* as a yellow syrup (888 mg, 3.13 mmol, 73%). $\mathbf{R_f}$ = 0.40

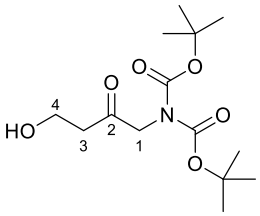
(50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.40-7.26 (10 H, m, Ar*H*), 3.77 (2 H, t, *J* = 5.4 Hz, 4-H_2), 3.67 (4 H, s, N(CH_2Ar)$_2$), 3.22 (2 H, s, 1-H_2), 2.68 (2 H, t, *J* = 5.4 Hz, 3-H_2), 2.45 (1 H, br s, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 211.8 (2-*C*=O), 138.4 (*Ar*), 129.1 (*Ar*H), 128.6 (*Ar*H), 127.5 (*Ar*H), 63.5 (1-*C*H$_2$), 59.1 (N(*C*H$_2$Ar)$_2$), 57.9 (4-*C*H$_2$), 42.3 (3-*C*H$_2$); **IR** (ATR) v_{Max}/cm^{-1} 3412 (OH), 3084, 3061, 3027, 2884, 2803, 1710 (C=O), 1494, 1453, 1371, 1248, 1050, 1027, 975, 914, 746, 699, 497, 473; **HRMS** (ESI$^+$) *m/z* found 284.1639 (M+H$^+$, $C_{18}H_{22}NO_2$ requires 284.1645) and 306.1447 (M+Na$^+$, $C_{18}H_{21}NO_2Na$ requires 306.1464).

1-(Bis(4-methoxybenzyl)amino)-4-hydroxybutan-2-one 424



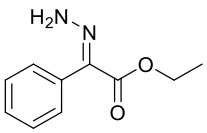
Tetrabutylammonium fluoride (1 M; 124 µL, 12.4 mmol, 1.4 equiv.) was added to a solution of amine **421** (4.06 g, 8.87 mmol, 1 equiv.) in THF (80 mL) at 0 °C, and the resulting reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 16 h. Water (50 mL) was then added to the reaction mixture and the resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then washed with brine (50 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography, using the elution gradient 20 to 50% ethyl acetate in cyclohexane, affording the *title compound* as a brown syrup (1.95 g, 5.39 mmol, 61%). **R_f** = 0.20 (50% ethyl acetate in cyclohexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.30-7.26 (4 H, m, Ar*H*), 6.89-6.86 (4 H, m, Ar*H*), 3.81 (6 H, s, N(BnOCH_3)$_2$), 3.76 (2 H, t, *J* = 5.4 Hz, 4-H_2), 3.58 (4 H, s, N(CH_2Ar)$_2$), 3.17 (2 H, s, 1-H_2), 2.85 (1 H, br s, O*H*), 2.66 (2 H, t, *J* = 5.4 Hz, 3-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 211.8 (2-*C*=O), 158.9 (*Ar*), 130.21 (*Ar*H), 130.18 (*Ar*), 113.8 (*Ar*H), 63.1 (1-*C*H$_2$), 58.2 (N(*C*H$_2$Ar)$_2$), 57.8 (4-*C*H$_2$), 55.3 (N(BnO*C*H$_3$)$_2$), 42.3 (3-*C*H$_2$); **IR** (ATR) v_{Max}/cm^{-1} 3436 (OH), 2935, 2906, 2836, 1712 (C=O), 1611, 1510, 1463, 1372, 1301, 1240, 1172, 1105, 1032, 815, 761, 521; **HRMS** (ESI$^+$) *m/z* found 344.1870 (M+H$^+$, $C_{20}H_{25}NO_4$ requires 343.1783).

Di-*tert*-butyl (4-hydroxy-2-oxobutyl)iminodicarbonate 425

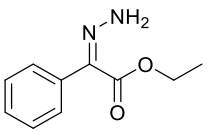


Tetra-*n*-butylammonium fluoride (1 M in THF, 647 µL, 6.47 mmol, 1.5 equiv.), was added to a solution of amine **422** (1.80 g, 4.31 mmol, 1 equiv.) in THF (45 mL) at 0 °C, and the resulting reaction mixture was stirred at 0 °C for 18 h. Water (50 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 x 50 mL). The combined organic phases were then washed with brine (50 mL), dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography, using the elution gradient 20 to 50% ethyl acetate in petroleum ether, affording the *title compound* as a yellow syrup (963 mg, 3.18 mmol, 74%). **R_f** = 0.38 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.40 (2 H, s, 1-H_2), 3.88 (2 H, t, *J* = 5.5 Hz, 4-H_2), 2.65 (2 H, t, *J* = 5.5 Hz, 3-H_2), 2.31 (1 H, br s, O*H*), 2.19 (18 H, s, $N(CO_2C(CH_3)_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 205.6 (2-*C*=O), 152.3 ($N(CO_2C(CH_3)_3)_2$), 83.4 ($N(CO_2C(CH_3)_3)_2$), 58.0 (4-CH_2), 55.1 (1-CH_2), 41.8 (3-CH_2), 28.1 ($N(CO_2C(CH_3)_3)_2$); **IR** (ATR) ν_{Max}/cm^{-1} 3502 (OH), 2979, 2936, 1756 (C=O), 1722 (C=O), 1692 (C=O), 1479, 1366, 1341, 1228, 1137, 1108, 1051, 853, 777, 703; **HRMS** (ESI^+) *m/z* found 304.1744 ($M+H^+$, $C_{14}H_{26}NO_6$ requires 304.1755) and 326.1584 ($M+Na^+$, $C_{14}H_{25}NO_6Na$ requires 326.1574).

(*E*)- and (*Z*)-Ethyl 2-hydrazineylidene-2-phenylacetate 429a and 429b



(*E*)-**429a**



(*Z*)-**429b**

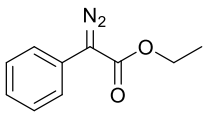
A solution of hydrazine acetate (461 mg, 5.00 mmol, 1 equiv.) and ethyl 2-oxo-2-phenylacetate **428** (891 mg, 5.00 mmol, 1 equiv.) in THF (30 mL) was left stirring at room temperature for 20 h, upon which hydrazone **492a** precipitates. Aqueous *sat.* sodium hydrogen carbonate solution (10 mL) was then added to the reaction mixture, causing the visible precipitate to dissolve completely. The resulting solution was then extracted with ethyl acetate (3 x 25 mL) and the combined organic phases were washed with brine (10 mL) and dried with $MgSO_4$. The dried organic phase was then concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 20 to 50%

ethyl acetate in petroleum ether, affording the separated *title compounds*, in a *Z*:*E* 76:24 ratio.

(*E*)-Ethyl 2-hydrazineylidene-2-phenylacetate 429a as a light-yellow solid (212 mg, 1.10 mmol, 22%). **R_f** = 0.30 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.52-7.7.46 (2 H, m, Ar*H*), 7.45-7.40 (1 H, m, Ar*H*), 7.32-7.28 (2 H, m, Ar*H*), 6.19 (2 H, br s, NH_2), 4.31 (2 H, q, *J* = 7.1 Hz, CH_3CH_2), 1.34 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 164.6 (*C*=O), 137.8 (*C*=N), 129.7 (*Ar*), 129.5 (*Ar*H), 129.3 (*Ar*H), 129.0 (*Ar*H), 61.5 (CH_3CH_2), 14.5 (CH_2CH_3); **IR** (ATR) v_{Max}/cm^{-1} 3409 (NH_2), 3280, 3061, 2983, 2908, 2874, 1697 (C=O), 1563 (C=N), 1492, 1446, 1369, 1329, 1311, 1229, 1141, 1114, 1076, 1047, 1026, 996, 781, 757, 692, 467; **HRMS** (ESI^+) *m/z* found 193.0976 ($M+H^+$, $C_{10}H_{13}N_2O_2$ requires 193.0972) and 215.0806 ($M+Na^+$, $C_{10}H_{12}N_2O_2Na$ requires 215.0791); **mp** 94-96 ºC, lit.[92] 96-97 ºC. Spectroscopic data matched that previously reported.[92]

(*Z*)-Ethyl 2-hydrazineylidene-2-phenylacetate 429b as a yellow oil (653 mg, 3.40 mmol, 68%). **R_f** = 0.74 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.38 (2 H, br s, NH_2), 7.54-7.49 (2 H, m, Ar*H*), 7.36-7.27 (3 H, m, Ar*H*), 4.31 (2 H, q, *J* = 7.1 Hz, CH_3CH_2), 1.33 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 163.1 (*C*=O), 136.8 (*C*=N), 131.3 (*Ar*), 128.3 (*Ar*H), 128.0 (*Ar*H), 127.7 (*Ar*H), 60.8 (CH_3CH_2), 14.3 (CH_2CH_3); **IR** (ATR) v_{Max}/cm^{-1} 3451 (NH_2), 3282, 2980, 2936, 2904, 1685 (C=O), 1564 (C=N), 1519, 1493, 1445, 1368, 1261, 1145, 1019, 843, 797, 758, 697, 668, 519; **HRMS** (ESI^+) *m/z* found 193.0978 ($M+H^+$, $C_{10}H_{13}N_2O_2$ requires 193.0972) and 215.0800 ($M+Na^+$, $C_{10}H_{12}N_2O_2Na$ requires 215.0791). Spectroscopic data matched that previously reported.[92]

Ethyl 2-diazo-2-phenylacetate 195



Method I: A solution of hydrazine acetate (461 mg, 5.00 mmol, 1 equiv.) ethyl 2-oxo-2-phenylacetate **428** (891 mg, 5.00 mmol, 1 equiv.) in THF (30 mL) was left stirring at room temperature for 20 h. Aqueous potassium hydroxide (1 M; 7.5 mL) was then added to the reaction mixture (so that the final volume ratio 1 M KOH:THF was 1:4), causing the visible precipitate to dissolve completely. Potassium *N*-iodo *p*-toluenesulfonamide **278** (2.02 g, 6.00

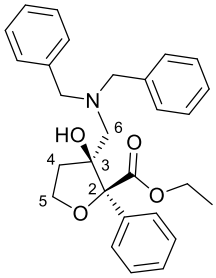
mmol, 1.5 equiv.) was then slowly added to the solution, causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 37.5 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (150 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 37.5 mL), brine (37.5 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (817 mg, 4.29 mmol, 86%).

Method II: A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (1.39 g, 4.14 mmol, 1.2 equiv.) and hydrazone **429a** (663 mg, 3.45 mmol, 1 equiv.) in THF (13.8 mL) was prepared. Aqueous potassium hydroxide (1 M; 3.45 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 17.2 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (100 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 17.2 mL), brine (17.2 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (592 mg, 3.11 mmol, 90%).

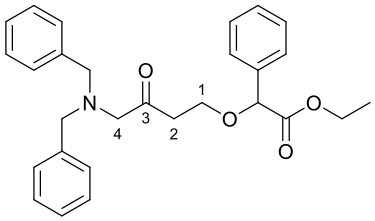
Method III: A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (441 mg, 1.31 mmol, 1.2 equiv.) and hydrazone **429b** (210 mg, 1.09 mmol, 1 equiv.) in THF (4.40 mL) was prepared. Aqueous potassium hydroxide (1 M; 1.10 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 5.50 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (35 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 5.50 mL), brine (5.50 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (190 mg, 1.00 mmol, 92%). $\mathbf{R_f}$ = 0.60 (50% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.51-7.47 (2 H, m, Ar*H*), 7.41-7.36 (2 H, m, Ar*H*), 7.21-7.15 (1 H, m, Ar*H*), 4.34 (2 H, q, *J* = 7.1 Hz, CH_3CH_2), 1.35 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 165.4 (*C*=O), 129.1 (*Ar*H),

125.9 (*Ar*H), 125.8 (*Ar*), 124.1 (*Ar*H), 61.1 (CH_3CH_2), 14.6 (CH_2CH_3), the signal due to CN_2 was not observed; **IR** (ATR) v_{Max}/cm^{-1} 2981, 2935, 2081 (CN_2), 1699 (C=O), 1498, 1370, 1337, 1286, 1244, 1152, 1050, 1028, 755, 691, 666, 497; the compound did not ionise under the ESI-HRMS conditions used. Spectroscopic data matched that previously reported.[92]

(±)-Ethyl *cis*-3-((dibenzylamino)methyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate 430 and (±)-Ethyl 2-(4-(dibenzylamino)-3-oxobutoxy)-2-phenylacetate 433



cis-**430**



433

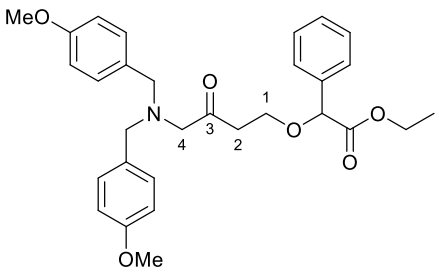
A solution containing ethyl 2-diazo-2-phenylacetate **195** (49.5 mg, 0.26 mmol, 1.3 equiv.) in CH_2Cl_2 (1.5 mL) was added, over a 30 min period, to a refluxing solution of β-hydroxyketone **423** (56.7 mg, 0.20 mmol, 1 equiv.) and rhodium(II) octanoate dimer (1.6 mg, 2.00 μmol, 1 mol%) in CH_2Cl_2 (1 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 5 to 20% ethyl acetate in cyclohexane, affording the separated *title compounds.*

(±)-Ethyl *cis*-3-((dibenzylamino)methyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate 430 (22.6 mg, 0.05 mmol, 25%, 85:15 *dr*) as a colourless oil; only the signals for the major diastereoisomer are reported herein: $\mathbf{R_f}$ = 0.26 (10% ethyl acetate in cyclohexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.38-7.23 (15 H, m, Ar*H*), 4.47 (1 H, br s, O*H*), 4.24-4.14 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, CH_3CH_2), 4.12-4.05 (1 H, m, 5-H_A), 3.80 (2 H, d, *J* = 13.5 Hz, $N(CH_{2A}Ar)_2$), 3.70-3.65 (1 H, m, 5-H_B), 3.37 (2 H, d, *J* = 13.5 Hz, $N(CH_{2B}Ar)_2$), 2.74 (1 H, d, *J* = 13.8 Hz, 6-H_A), 2.25-2.20 (1 H, m, 4-H_A), 2.17 (1 H, d, *J* = 13.8 Hz, 6-H_B), 1.90 (1 H, ddd, *J* = 12.3, 7.6, 5.0 Hz, 4-H_B), 1.17 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 172.5 (*C*=O), 139.1 (benzyl *Ar*), 137.1 (phenyl *Ar*), 129.2 (benzyl *Ar*H), 128.3 (benzyl *Ar*H), 127.93 (phenyl *Ar*H), 127.87 (phenyl *Ar*H), 127.1 (benzyl *Ar*H),

125.9 (phenyl *Ar*H), 88.7 (2-*C*), 83.2 (3-*C*), 66.4 (5-*C*H_2), 61.5 (CH_3CH_2), 59.7 (N(*C*H_2Ar)$_2$), 57.1 (6-*C*H_2), 36.3 (4-*C*H_2), 14.0 (CH_2CH_3); **IR** (ATR) v_{Max}/cm^{-1} 3469 (OH), 3062, 3028, 2980, 2892, 2837, 2799, 1730 (C=O), 1494, 1448, 1368, 1256, 1205, 1095, 1061, 1026, 858, 741, 697, 508; **HRMS** (ESI$^+$) *m/z* found 446.2336 (M+H$^+$, $C_{28}H_{32}NO_4$ requires 446.2326) and 468.2167 (M+Na$^+$, $C_{28}H_{31}NO_4Na$ requires 468.145).

(±)-Ethyl 2-(4-(dibenzylamino)-3-oxobutoxy)-2-phenylacetate 433 (27.0 mg, 0.06 mmol, 30%) as a colourless oil. **R$_f$** = 0.20 (10% ethyl acetate in cyclohexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.40-7.24 (15 H, m, Ar*H*), 4.82 (1 H, s, ArC*H*), 4.22-4.10 (2 H, two overlapping dq, *J* = 10.8, 7.4 Hz, CH_3CH_2), 3.80-3.74 (1 H, m, 1-H_A), 3.70-3.64 (1 H, m, 1-H_B), 3.66 (4 H, br s, N(CH_2Ar)$_2$, 3.24 (2 H, br s, 4-H_2), 2.86-2.72 (2 H, m, 2-H_2), 1.20 (3 H, t, *J* = 7.4 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 208.7 (3-*C*=O), 170.7 (*C*=O), 138.6 (benzyl *Ar*), 136.4 (phenyl *Ar*), 129.0 (benzyl *Ar*H), 128.54 (phenyl *Ar*H), 128.48 (phenyl *Ar*H), 128.4 (benzyl *Ar*H), 127.2 (phenyl *Ar*H), 127.1 (benzyl *Ar*H), 81.5 (Ar*C*H), 64.9 (1-*C*H_2), 63.4 (4-*C*H_2), 61.1 (CH_3CH_2), 58.7 (N(*C*H_2Ar)$_2$), 40.2 (2-*C*H_2), 14.1 (CH_2CH_3); **IR** (ATR) v_{Max}/cm^{-1} 3063, 3030, 2981, 2930, 2880, 2805, 1730 (C=O), 1494, 1454, 1368, 1254, 1205, 1178, 1114, 1072, 1027, 733, 697, 481; **HRMS** (ESI$^+$) *m/z* found 446.2323 (M+H$^+$, $C_{28}H_{32}NO_4$ requires 446.2326).

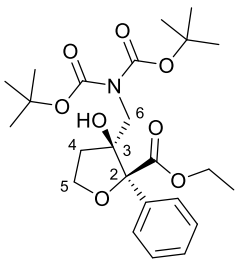
(±)-Ethyl 2-(4-(bis(4-methoxybenzyl)amino)-3-oxobutoxy)-2-phenylacetate 434



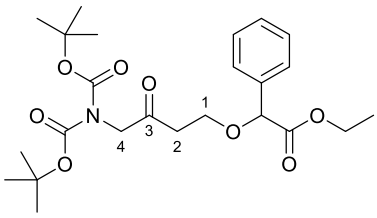
A solution containing ethyl 2-diazo-2-phenylacetate **195** (49.5 mg, 0.26 mmol, 1.3 equiv.) in CH_2Cl_2 (1.5 mL) was added, over a 30 min period, to a refluxing solution of β-hydroxyketone **424** (68.7 mg, 0.20 mmol, 1 equiv.) and rhodium(II) octanoate dimer (1.6 mg, 2.00 μmol, 1 mol%) in CH_2Cl_2 (1 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and purified by column chromatography affording the *title compound* as a pale-yellow oil (51.3 mg, 85.0 μmol, 43%). **R$_f$** = 0.19 (20% ethyl acetate in cyclohexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.39-7.36 (2 H, m, phenyl Ar*H*), 7.33-7.29 (3 H, m, phenyl Ar*H*), 7.27-7.23 (4 H,

m, *para*-methoxybenzyl Ar*H*), 6.86-6.82 (4 H, m, *para*-methoxybenzyl Ar*H*), 4.80 (1 H, s, ArC*H*), 4.17-4.10 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, CH_3CH_2), 3.79 (6 H, s, N(BnOCH_3)$_2$), 3.73-3.63 (2 H, m, 1-H_2), 3.55 (4 H, br s, N(CH_2Ar)$_2$), 3.17 (2 H, br s, 4-H_2), 2.81-2.71 (2 H, m, 2-H_2), 1.19 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 209.0 (3-*C*=O), 170.7 (*C*=O), 158.8 (*para*-methoxybenzyl *Ar*), 136.4 (phenyl *Ar*), 130.6 (*para*-methoxybenzyl *Ar*), 130.1 (*para*-methoxybenzyl *Ar*H), 129.4 (phenyl *Ar*H), 128.5 (phenyl *Ar*H), 127.1 (phenyl *Ar*H), 113.7 (*para*-methoxybenzyl *Ar*H), 81.5 (Ar*C*H), 64.9 (4-*C*H_2), 63.2 (CH_3CH_2), 61.1 (1-*C*H_2), 57.9 (N(CH_2Ar)$_2$), 55.2 (N(BnOCH_3)$_2$), 40.2 (2-*C*H_2), 14.0 (CH_2CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 2934, 2836, 1739 (C=O), 1731 (C=O), 1611, 1510, 1455, 1368, 1301, 1245, 1175, 1094, 1030, 814, 731, 697, 664, 522; **HRMS** (ESI$^+$) *m/z* found 506.2547 (M+H$^+$, $C_{30}H_{35}NO_6$ requires 506.2543).

(±)-*cis*-Ethyl 3-((bis(*tert*-butoxycarbonyl)amino)methyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate 432 and (±)-Ethyl 2-(4-(bis(*tert*-butoxycarbonyl)amino)-3-oxobutoxy)-2-phenylacetate 435



cis-**432**



435

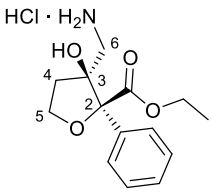
A solution containing ethyl 2-diazo-2-phenylacetate **195** (74.2 mg, 0.39 mmol, 1.3 equiv.) in CH_2Cl_2 (1.5 mL) was added, over a 30 min period, to a refluxing solution of β-hydroxyketone **425** (91.0 mg, 0.30 mmol, 1 equiv.) and rhodium(II) octanoate dimer (2.4 mg, 3.00 μmol, 1 mol%) in CH_2Cl_2 (1 mL). The resulting reaction mixture stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 10 to 25% ethyl acetate in petroleum ether, affording the separated *title compounds*.

(±)-*cis*-Ethyl 3-((bis(*tert*-butoxycarbonyl)amino)methyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate 432 as colourless solid (87.4 mg, 0.188 mmol, 63%). **R_f** = 0.23 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.61-7.57 (2 H, m, Ar*H*), 7.36-7.27 (3 H, m, Ar*H*), 4.50 (1 H, d, *J* = 1.6 Hz, O*H*), 4.37-4.25 (4 H, m, 5-H_2; CH_3CH_2), 4.15 (1 H, d, *J* = 14.8 Hz, 6-H_A), 3.41 (1 H, d, *J* =

14.8 Hz, 6-H_B), 2.09 (1 H, dtd, J = 12.6, 9.6, 1.6 Hz, 4-H_A), 1.93 (1 H, ddd, J = 12.6, 5.3, 3.4 Hz, 4-H_B), 1.45 (18 H, s, N($CO_2C(CH_3)_3)_2$), 1.29 (3 H, t, J = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 171.4 (*C*=O), 154.2 (N($CO_2C(CH_3)_3)_2$), 138.0 (*Ar*), 128.4 (*Ar*H), 128.3 (*Ar*H), 126.1 (*Ar*H), 91.9 (2-*C*), 84.7 (3-*C*), 83.3 (N($CO_2C(CH_3)_3)_2$), 67.9 (5-CH_2), 61.8 (CH_3CH_2), 51.2 (6-CH_2), 35.3 (4-CH_2), 28.1 (N($CO_2C(CH_3)_3)_2$), 14.2 (CH_2CH_3); **IR** (ATR) v_{Max}/cm^{-1} 3411 (OH), 2979, 2934, 2895, 1728 (C=O), 1718 (C=O), 1676 (C=O), 1442, 1424, 1390, 1348, 1289, 1277, 1262, 1241, 1219, 1167, 1130, 1081, 1066, 1031, 957, 887, 854, 758, 735, 703, 629, 494, 420; **HRMS** (ESI^+) *m/z* found 466.2446 ($M+H^+$, $C_{24}H_{36}NO_8$ requires 466.2435) and 488.2272 ($M+Na^+$, $C_{24}H_{35}NO_8Na$ requires 488.2255); **mp** 74-76 °C; structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

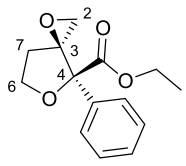
(±)-Ethyl 2-(4-(bis(*tert*-butoxycarbonyl)amino)-3-oxobutoxy)-2-phenylacetate 435 as colourless oil (23.9 g, 51.3 μmol, 17%). **R_f** = 0.20 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.43-7.20 (2 H, m, Ar*H*), 7.36-7.31 (3 H, m, Ar*H*), 4.88 (1 H, s, ArC*H*), 4.42 (2 H, br s, 4-H_2), 4.23-4.09 (2 H, two overlapping dq, J = 10.8, 7.1 Hz, CH_3CH_2), 3.83 (1 H, ddd, J = 9.4, 6.5, 6.5 Hz, 1-H_A), 3.75 (1 H, ddd, J = 9.4, 6.5, 6.5 Hz, 1-H_B), 2.78 (2 H, app t, J = 6.5 Hz, 2-H_2), 1.46 (18 H, s, N($CO_2C(CH_3)_3)_2$), 1.20 (3 H, t, J = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 202.7 (3-*C*=O), 170.8 (*C*=O), 152.1 (N($CO_2C(CH_3)_3)_2$), 136.4 (*Ar*), 128.8 (*Ar*H), 128.8 (*Ar*H), 127.4 (*Ar*H), 83.1 (N($CO_2C(CH_3)_3)_2$), 81.7 (Ar*C*H), 64.4 (1-CH_2), 61.4 (CH_3CH_2), 55.2 (4-CH_2), 40.0 (2-CH_2), 28.1 (N($CO_2C(CH_3)_3)_2$), 14.2 (CH_2CH_3); **IR** (ATR) v_{Max}/cm^{-1} 2980, 2935, 1795 (C=O), 1728 (C=O), 1455, 1393, 1366, 1340, 1230, 1174, 1141, 1107, 1029, 914, 895, 855, 776, 730, 697; **HRMS** (ESI^+) *m/z* found 466.2426 ($M+H^+$, $C_{24}H_{36}NO_8$ requires 466.2435), 488.2279 ($M+Na^+$, $C_{24}H_{35}NO_8Na$ requires 488.2255) and 483.2708 ($M+NH_4^+$, $C_{24}H_{39}N_2O_8$ requires 483.2701).

(±)-*cis*-Ethyl 3-(aminomethyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate Hydrochloride 436

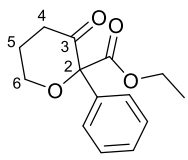


A solution of hydrochloric acid in dioxane (4 M; 3.45 mL, 13.7 mmol, 6 equiv.) was added to tetrahydrofuran **432** (947 mg, 2.28 mmol, 1 equiv.) and was stirred at room temperature for 18 h. The resulting solution was then concentrated *in vacuo* affording the *title compound* as a light brown gum (634 mg, 2.12 mmol, 93%). **^{1}H NMR** (400 MHz, methanol-d_4): δ_H ppm 7.65-7.61 (2 H, m, Ar*H*), 7.44-7.35 (3 H, m, Ar*H*), 4.41-4.36 (2 H, m, 5-H_2), 4.33-4.20 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, CH_3CH_2), 3.15 (1 H, d, *J* = 13.1 Hz, 6-H_A), 2.70 (1 H, d, *J* = 13.1 Hz, 6-H_B), 2.22-2.11 (2 H, m, 4-H_2), 1.28 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, methanol-d_4): δ_C ppm 172.4 (*C*=O), 138.3 (*Ar*), 129.8 (*Ar*H), 129.7 (*Ar*H), 127.1 (*Ar*H), 92.7 (2-*C*), 82.0 (3-*C*), 67.4 (5-CH_2), 63.1 (CH_3CH_2), 45.3 (6-CH_2), 35.7 (4-CH_2), 14.3 (CH_2CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 3184 (NH_4Cl), 3023 (OH), 2979, 2899, 1725 (C=O), 1446, 1369, 1294, 1267, 1096, 1071, 1021, 858, 754, 733, 701, 643, 614; **HRMS** (ESI^+) *m/z* found 266.1395 ($M+H^+$, $C_{14}H_{20}NO_4$ requires 266.1387) and 288.1214 ($M+Na^+$, $C_{14}H_{19}NO_4Na$ requires 288.1206).

(±)-Ethyl *cis*-4-phenyl-1,5-dioxaspiro[2.4]heptane-4-carboxylate 437 and (±)-Ethyl 3-oxo-2-phenyltetrahydro-2*H*-pyran-2-carboxylate 438



cis-**437**



438

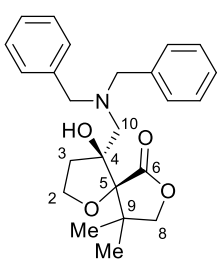
A solution of sodium nitrite (414 mg, 6.00 mmol, 3 equiv.) in water (2.3 mL), cooled to 0 °C, was added to a solution of amino alcohol **436** (600 mg, 2.00 mmol, 1 equiv.) in water (17 mL) and acetic acid (4.2 mL), cooled to -5 °C. The reaction mixture was stirred at -5 °C for 1 h, then warmed to room temperature and stirred for an additional 1 h before being heated to 60 °C for 1 h. The resulting reaction mixture was then cooled to room temperature and aqueous *sat.* sodium hydrogen carbonate solution (40 mL) was added to the reaction mixture. The resulting solution was then extracted with diethyl ether (3 x 40 mL) and the combined organic phases were washed brine (40 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by reverse phase column chromatography,

using the elution gradient 5 to 100% acetonitrile in water, affording the separated *title compounds*.

(±)-Ethyl *cis*-4-phenyl-1,5-dioxaspiro[2.4]heptane-4-carboxylate 437 as a colourless oil (120 mg, 483 µmol, 24%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.56-7.53 (2 H, m, Ar*H*), 7.39-7.30 (3 H, m, Ar*H*), 4.35 (1 H, ddd, *J* = 8.8, 8.8, 7.5 Hz, 6-H_A), 4.26-4.13 (2 H, two overlapping dq, *J* = 10.8, 7.1 Hz, CH_3CH_2), 4.06 (1 H, ddd, *J* = 8.8, 8.8, 3.9 Hz, 6-H_B), 3.45 (1 H, d, *J* = 4.4 Hz, 2-H_A), 3.17 (1 H, d, *J* = 4.4 Hz, 2-H_B), 2.41 (1 H, ddd, *J* = 13.6, 8.8, 8.8 Hz, 7-H_A), 1.92 (1 H, ddd, *J* = 13.6, 7.5, 3.9 Hz, 7-H_B), 1.25 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 168.7 (*C*=O), 138.4 (*Ar*), 128.6 (*Ar*H), 128.5 (*Ar*H), 126.4 (*Ar*H), 86.3 (4-*C*), 67.0 (3-*C*), 65.9 (6-CH_2), 61.9 (CH_3CH_2), 48.7 (2-CH_2), 31.6 (7-CH_2), 14.2 (CH_2CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 2982, 2889, 1752 (C=O), 1730 (C=O), 1448, 1198, 1090, 1067, 1030, 901, 860, 729, 699, 637, 509; **HRMS** (ESI^+) *m/z* found 249.1126 ($M+H^+$, $C_{14}H_{17}O_4$ requires 249.1121), 271.0944 ($M+Na^+$, $C_{14}H_{16}O_4Na$ requires 271.0941) and 266.1401 ($M+NH_4^+$, $C_{14}H_{20}NO_4$ requires 266.1387).

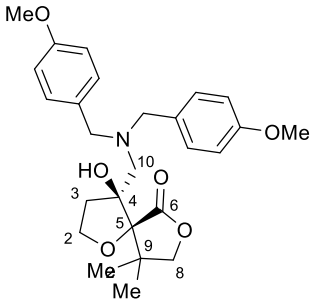
(±)-Ethyl 3-oxo-2-phenyltetrahydro-2*H*-pyran-2-carboxylate 438 as a colourless oil (207 mg, 834 µmol, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.45-7.32 (5 H, m, Ar*H*), 4.32-4.24 (2 H, two overlapping q, *J* = 7.1 Hz, CH_3CH_2), 4.12-4.03 (2 H, m, 6-H_2), 2.71-2.59 (2 H, m, 4-CH_2), 2.26-2.11 (2 H, m, 5-H_2), 1.26 (3 H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 202.1 (3-*C*=O), 168.6 (*C*=O), 134.7 (*Ar*), 128.7 (*Ar*H), 128.4 (*Ar*H), 126.6 (*Ar*H), 88.8 (2-*C*), 63.5 (6-CH_2), 62.4 (CH_3CH_2), 37.6 (4-CH_2), 27.0 (5-CH_2), 14.2 (CH_2CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 2965, 2873, 1731 (C=O), 1423, 1242, 1218, 1099, 1079, 1022, 961, 852, 751, 728, 698, 561; **HRMS** (ESI^+) *m/z* found 249.1121 ($M+H^+$, $C_{14}H_{17}O_4$ requires 249.1121), 271.0940 ($M+Na^+$, $C_{14}H_{16}O_4Na$ requires 271.0941) and 266.1382 ($M+NH_4^+$, $C_{14}H_{20}NO_4$ requires 266.1387).

(±)-*cis*-4-((Dibenzylamino)methyl)-4-hydroxy-9,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one 439

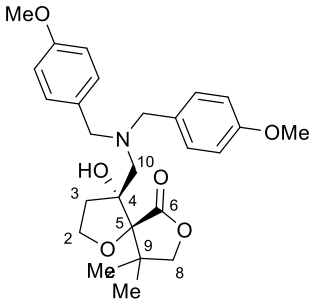


A solution containing 3-diazo-4,4-dimethyldihydrofuran-2(3*H*)-one **212** (36.4 mg, 0.26 mmol, 1.3 equiv.) in CH_2Cl_2 (1.5 mL) was added, over a 30 min period, to a refluxing solution of 1-(dibenzylamino)-4-hydroxybutan-2-one **423** (56.7 mg, 0.20 mmol, 1 equiv.) and rhodium(II) octanoate dimer (1.6 mg, 2.00 µmol, 1 mol%) in CH_2Cl_2 (1 mL). The resulting reaction mixture stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (28.5 mg, 72.0 µmol, 36%, 82:18 *dr*); only the signals for the major diastereoisomer are reported herein: $\mathbf{R_f}$ = 0.39 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.41-7.26 (10 H, m, Ar*H*), 4.21 (2 H, d, *J* = 13.2 Hz, N(CH_{2A}Ar)$_2$), 3.98 (1 H, d, *J* = 7.8 Hz, 8-H_A), 3.70-3.66 (2 H, m, 2-H_A; 8-H_B), 3.30 (2 H, d, *J* = 13.2 Hz, N(CH_{2B}Ar)$_2$), 3.00 (1 H, ddd, *J* = 11.2, 7.8, 2.6 Hz, 3-H_A), 2.85-2.79 (2 H, m, 2-H_B; O*H*), 2.70 (1 H, dd, *J* = 13.5, 2.1 Hz, 10-H_A), 2.58 (1 H, d, *J* = 13.5 Hz, 10-H_B), 2.48-2.38 (1 H, m, 3-H_B), 1.27 (3 H, s, CH_{3A}), 1.00 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 176.5 (6-*C*=O), 139.7 (*Ar*), 129.4 (*Ar*H), 128.4 (*Ar*H), 127.2 (*Ar*H), 86.2 (5-*C*), 83.2 (4-*C*), 78.7 (8-*C*H$_2$), 64.9 (2-*C*H$_2$), 60.3 (N(*C*H$_2$Ar)$_2$), 53.3 (10-*C*H$_2$), 40.9 (9-*C*), 34.8 (3-*C*H$_2$), 21.5 (*C*H$_{3A}$), 18.1 (*C*H$_{3B}$); **IR** (ATR) v_{Max}/cm^{-1} 3545 (OH), 3062, 3027, 2957, 2925, 2852, 2798, 1759 (C=O), 1585, 1452, 1412, 1366, 1320, 1261, 1069, 1014, 924, 749, 699, 470; **HRMS** (ESI$^+$) *m/z* found 396.2184 (M+H$^+$, $C_{24}H_{30}NO_4$ requires 396.2169) and 418.1993 (M+Na$^+$, $C_{24}H_{29}NO_4Na$ requires 418.1989).

(±)-*cis*- and (±)-*trans*-4-((Bis(4-methoxybenzyl)amino)methyl)-4-hydroxy-9,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one 440a and 440b



cis-**440a**

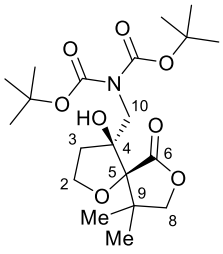


trans-**440b**

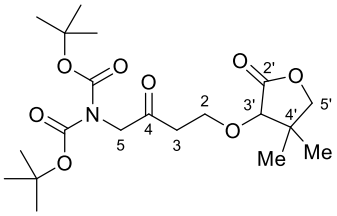
A solution containing α-diazolactone **212** (36.4 mg, 0.26 mmol, 1.3 equiv.) in CH_2Cl_2 (1.5 mL) was added, over a 30 min period, to a refluxing solution of β-hydroxyketone **424** (68.7 mg, 0.20 mmol, 1 equiv.) and rhodium(II) octanoate dimer (1.6 mg, 2.00 μmol, 1 mol%) in CH_2Cl_2 (1 mL). The resulting reaction mixture was stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography, using the elution gradient 10 to 20% ethyl acetate in cyclohexane, affording the *title compounds*, an inseparable mixture of diastereomers **440a** (**A**) and **440b** (**B**), as a colourless gum (ratio **440a**:**440b** 66:33, 16.5 mg, 40.0 μmol, 18%). $\mathbf{R_f}$ = 0.30 (20% ethyl acetate in cyclohexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.25 (4 H, d, *J* = 8.6 Hz, Ar*H*, **B**), 7.20 (4 H, d, *J* = 8.6 Hz, Ar*H*, **A**), 6.84-6.70 (4 H, m, Ar*H*, **A**; 4 H, m, Ar*H*, **B**), 4.75 (1 H, br s, O*H*, **A**; 1 H, br s, O*H*, **B**), 4.09 (2 H, d, *J* = 13.2 Hz, N(CH_{2A}Ar)$_2$, **B**), 4.05-3.96 (1 H, m, 8-H_A, **A**; 1 H, m, 8-H_A, **B**; 2 H, m, 2-H_2, **A**), 3.89 (2 H, d, *J* = 13.2 Hz, N(CH_{2A}Ar)$_2$, **A**), 3.81 (6 H, s, N(BnOCH_3)$_2$, **B**), 3.81 (6 H, s, N(BnOCH_3)$_2$, **A**), 3.71-3.67 (1 H, m, 2-H_A, **B**), 3.66 (1 H, d, *J* = 8.1 Hz, 8-H_B, **B**), 3.60 (1 H, d, *J* = 8.1 Hz, 8-H_B, **A**), 3.35 (2 H, d, *J* = 13.2 Hz, N(CH_{2B}Ar)$_2$, **A**), 3.12 (2 H, d, *J* = 13.2 Hz, N(CH_{2B}Ar)$_2$, **B**), 3.05-2.96 (2 H, m, 10-H_2, **A**), 2.94-2.85 (1 H, m, 3-H_A, **B**; 1 H, m, 2-H_B, **B**), 2.67-2.26 (1 H, m, 10-H_A, **B**), 2.56-2.52 (1 H, m, 10-H_B, **B**), 2.46-2.38 (1 H, m, 3-H_A, **A**; 1 H, m, 3-H_B, **B**), 2.12 (1 H, ddd, *J* = 12.0, 5.7, 2.1 Hz, 3-H_B, **A**), 1.38 (3 H, s, CH_{3A}, **B**), 1.07 (3 H, s, CH_{3A}, **A**), 0.99 (3 H, s, CH_{3B}, **B**), 0.53 (3 H, s, CH_{3B}, **A**); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 176.4 (6-*C*=O, **B**), 175.0 (6-*C*=O, **A**), 159.1 (*Ar*, **A**), 158.6 (*Ar*, **B**), 131.7 (*Ar*, **A**), 130.40 (*Ar*H, **A**), 130.37 (*Ar*H, **B**), 128.3 (*Ar*, **B**), 114.0 (*Ar*H, **A**), 113.6 (*Ar*H, **B**), 90.0 (5-*C*, **A**), 86.0 (5-*C*, **B**), 83.0 (4-*C*, **B**), 79.2 (4-*C*, **A**), 79.1 (8-*C*H_2, **A**), 78.6 (8-*C*H_2, **B**), 67.2 (2-*C*H_2, **A**), 64.8 (2-*C*H_2, **B**), 59.2 (N(*C*H_2Ar)$_2$, **B**), 58.7 (N(*C*H_2Ar)$_2$, **A**), 56.7 (10-*C*H_2, **A**), 55.31 (N(BnO*C*H_3)$_2$, **A**), 55.25 (N(BnO*C*H_3)$_2$, **B**), 52.9 (10-*C*H_2, **B**), 43.3 (9-*C*, **A**), 40.7 (3-*C*H_2, **A**), 36.6 (9-*C*, **B**), 34.7 (3-*C*H_2, **B**), 21.4 (*C*H_{3A}, **B**), 21.1 (*C*H_{3A}, **A**), 18.5 (*C*H_{3B}, **A**), 18.0 (*C*H_{3B}, **B**); **IR** (ATR)

v_{Max}/cm^{-1} 3542 (OH), 2955, 2932, 2915, 2836, 1764 (C=O), 1611, 1585, 1569, 1511, 1464, 1365, 1301, 1248, 1174, 1101, 1052, 1034, 1013, 945, 821, 758, 521; **HRMS** (ESI$^+$) *m/z* found 456.2391 (M+H$^+$, $C_{26}H_{34}NO_6$ requires 456.2386).

(±)-*cis*-*tert*-Butyl (*tert*-butoxycarbonyl)((4-hydroxy-9,9-dimethyl-6-oxo-1,7-dioxaspiro[4.4]nonan-4-yl)methyl)carbamate 441 and (±)-*tert*-Butyl (*tert*-butoxycarbonyl)(4-((4,4-dimethyl-2-oxotetrahydrofuran-3-yl)oxy)-2-oxobutyl)carbamate 444



cis-**441**



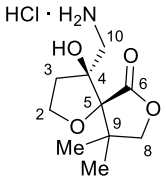
444

A solution containing 3-diazo-4,4-dimethyldihydrofuran-2(3*H*)-one **212** (112 mg, 0.80 mmol, 2 equiv.) in CH_2Cl_2 (2 mL) was added, over a 30 min period, to a refluxing solution of 1-(dibenzylamino)-4-hydroxybutan-2-one **425** (121 mg, 0.40 mmol, 1 equiv.) and rhodium(II) octanoate dimer (3.1 mg, 4.00 µmol, 1 mol%) in CH_2Cl_2 (1.5 mL). The resulting reaction mixture stirred at reflux for 1 h. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the separated *title compound*s.

(±)-*cis*-*tert*-Butyl (*tert*-butoxycarbonyl)((4-hydroxy-9,9-dimethyl-6-oxo-1,7-dioxaspiro[4.4]nonan-4-yl)methyl)carbamate 441 as a colourless oil (77.4 mg, 0.186 mmol, 47%). **R_f** = 0.45 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.04-3.93 (5 H, m, 8-H_A; 2-H_2; 10-H_2), 3.72 (1 H, d, *J* = 7.9 Hz, 8-H_B), 3.63 (1 H, s, O*H*), 2.67 (1 H, dtd, *J* = 12.2, 9.7, 1.9 Hz, 3-H_A), 2.21 (1 H, ddd, *J* = 12.2, 6.7, 3.5 Hz, 3-H_B), 1.51 (18 H, s, $N(CO_2C(CH_3)_3)_2$), 1.32 (3 H, s, CH_{3A}), 1.15 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 174.9 (6-*C*=O), 154.5 ($N(CO_2C(CH_3)_3)_2$), 85.9 (5-*C*), 83.4 ($N(CO_2C(CH_3)_3)_2$), 82.2 (4-*C*), 78.4 (8-CH_2), 65.4 (2-CH_2), 48.1 (10-CH_2), 40.9 (9-*C*), 34.2 (3-CH_2), 28.1 ($N(CO_2C(CH_3)_3)_2$), 21.6 (CH_{3A}), 18.4 (CH_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3423 (OH), 2977, 2932, 1753 (C=O), 1700 (C=O), 1585, 1392, 1366, 1238, 1169, 1127, 1068, 1015, 850, 792, 757, 732, 694, 457, 435; **HRMS** (ESI$^+$) *m/z* found 438.2101 (M+Na$^+$, $C_{20}H_{33}NO_8Na$ requires 438.2098).

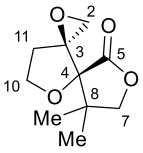
(±)-*tert*-Butyl (*tert*-butoxycarbonyl)(4-((4,4-dimethyl-2-oxotetrahydrofuran-3-yl)oxy)-2-oxobutyl)carbamate 444 as a colourless oil (61.1 mg, 0.147 mmol, 38%). $\mathbf{R_f}$ = 0.23 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.44 (1 H, d, *J* = 18.0 Hz, 5-H_A), 4.39 (1 H, d, *J* = 18.0 Hz, 5-H_B), 4.20 (1 H, ddd, *J* = 9.7, 5.4, 5.4 Hz, 2-H_A), 3.99-3.93 (1 H, m, 2-H_B), 3.95 (1 H, d, *J* = 8.9 Hz, 5'-H_A), 3.97 (1 H, d, *J* = 8.9 Hz, 5'-H_B), 3.74 (1 H, s, 3'-*H*), 2.82 (1 H, ddd, *J* = 17.1, 8.2, 5.4 Hz, 3-H_A), 2.64 (1 H, ddd, *J* = 17.1, 5.4, 5.4 Hz, 3-H_B), 1.47 (18 H, s, $N(CO_2C(CH_3)_3)_2$), 1.17 (3 H, s, CH_{3A}), 1.04 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 202.6 (4-*C*=O), 175.3 (2'-*C*=O), 152.1 ($N(CO_2C(CH_3)_3)_2$), 83.1 (3'-*C*H), 83.0 ($N(CO_2C(CH_3)_3)_2$), 76.4 (5'-CH_2), 66.3 (2-CH_2), 55.1 (5-CH_2), 40.6 (4'-*C*), 40.0 (3-CH_2), 28.1 ($N(CO_2C(CH_3)_3)_2$), 23.4 (CH_{3A}), 19.3 (CH_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 2978, 2929, 1749 (C=O), 1683 (C=O), 1446, 1367, 1325, 1231, 1141, 1122, 1079, 1030, 887, 855, 759, 733, 661, 577, 479; **HRMS** (ESI$^+$) *m/z* found 438.2105 ($M+Na^+$, $C_{20}H_{33}NO_8Na$ requires 438.2098).

(±)-*cis*-4-(Aminomethyl)-4-hydroxy-9,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one Hydrochloride 413

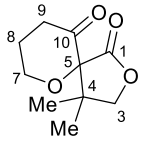


A solution of hydrochloric acid in dioxane (4 M; 1.25 mL, 5.06 mmol, 6 equiv.) was added to spirolactone **441** (350 mg, 0.842 mmol, 1 equiv.) and was stirred at room temperature for 18 h. The resulting solution was then concentrated *in vacuo* affording the *title compound* as a pale-yellow gum (190 mg, 0.754 mmol, 90%). **^{1}H NMR** (400 MHz, methanol-d_4): δ_H ppm 4.06-3.99 (3 H, m, 8-H_A; 2-H_2), 3.84 (1 H, d, *J* = 8.2 Hz, 8-H_B), 3.28 (1 H, dd, *J* = 12.6, 2.3 Hz, 10-H_A), 3.10 (1 H, d, *J* = 12.6 Hz, 10-H_B), 2.81 (1 H, dtd, *J* = 11.9, 9.4, 2.3 Hz, 3-H_A), 2.40-2.30 (1 H, m, 3-H_B), 1.28 (3 H, s, CH_{3A}), 1.13 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, methanol-d_4): δ_C ppm 175.4 (6-*C*=O), 87.3 (5-*C*), 79.4 (8-CH_2), 79.1 (4-*C*), 65.5 (2-CH_2), 44.0 (10-CH_2), 41.7 (9-*C*), 34.2 (3-CH_2), 21.2 (CH_{3A}), 18.0 (CH_{3B}); **IR** (ATR) v_{Max}/cm^{-1} 3151 (NH_4Cl), 3044 (OH), 2966, 2907, 2849, 1774 (C=O), 1603, 1523, 1455, 1375, 1307, 1215, 1139, 1096, 1076, 1057, 1039, 1008, 979, 882, 763, 711, 691, 539; **HRMS** (ESI$^+$) *m/z* found 216.1236 ($M+H^+$, $C_{10}H_{18}NO_4$ requires 216.1230) and 238.1064 ($M+Na^+$, $C_{10}H_{17}NO_4Na$ requires 238.1050).

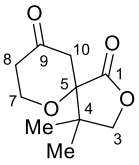
(±)-*cis*-8,8-Dimethyl-1,6,9-trioxadispiro[2.0.44.33]undecan-5-one 343, (±)-4,4-Dimethyl-2,6-dioxaspiro[4.5]decane-1,10-dione 399 and (±)-4,4-Dimethyl-2,6-dioxaspiro[4.5]decane-1,9-dione 412



cis-**343**



399



412

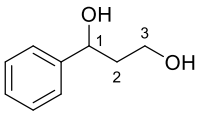
A solution of sodium nitrite (152 mg, 2.21 mmol, 3 equiv.) in water (0.85 mL), cooled to 0 °C, was added to a solution of amino alcohol **413** (185 mg, 735 µmol, 1 equiv.) in water (6.2 mL) and acetic acid (1.55 mL), cooled to -5 °C. The reaction mixture was stirred at -5 °C for 1 h, then warmed to room temperature and stirred for an additional 1 h before being heated to 60 °C for 1 h. The resulting reaction mixture was then cooled to room temperature and aqueous *sat.* sodium hydrogen carbonate solution (15 mL) was added to the reaction mixture. The resulting solution was then extracted with diethyl ether (3 x 15 mL) and the combined organic phases were washed brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, using the elution gradient 20 to 50% ethyl acetate in pentane, affording the separated *title compounds*.

(±)-*cis*-8,8-Dimethyl-1,6,9-trioxadispiro[2.0.44.33]undecan-5-one 343 as a colourless solid (62.0 mg, 313 µmol, 42%). See earlier for characterisation data.

(±)-4,4-Dimethyl-2,6-dioxaspiro[4.5]decane-1,10-dione 399 as a colourless solid (34.4 mg, 174 µmol, 24%). $\mathbf{R_f}$ = 0.18 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.38 (1 H, ddd, *J* = 12.1, 7.4, 5.1 Hz, 7-H_A), 4.18 (1 H, d, *J* = 8.4 Hz, 3-H_A), 3.99 (1 H, dt, *J* = 12.1, 5.8 Hz, 7-H_B), 3.91 (1 H, d, *J* = 8.4 Hz, 3-H_B), 2.68 (1 H, dt, *J* = 16.6, 6.4 Hz, 9-H_A), 2.56 (1 H, dt, *J* = 16.6, 7.9 Hz, 9-H_B), 2.27-2.10 (2 H, m, 8-CH_2), 1.19 (3 H, s, CH_{3A}), 1.13 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 207.1 (10-*C*=O), 173.3 (1-*C*=O), 89.3 (5-*C*), 76.5 (3-CH_2), 62.8 (7-CH_2), 44.6 (4-*C*), 37.6 (9-CH_2), 23.4 (8-CH_2), 22.6 (CH_{3A}), 20.1 (CH_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 2973, 2931, 2894, 2871, 1777 (C=O), 1707 (C=O), 1476, 1368, 1314, 1276, 1109, 1038, 1016, 1001, 962, 819, 704, 597, 524, 487, 426; **HRMS** (ESI$^+$) *m/z* found 199.0975 ($M+H^+$, $C_{10}H_{15}O_4$ requires 199.0965), 221.0800 ($M+Na^+$, $C_{10}H_{14}O_4Na$ requires 221.0784) and 216.1237 ($M+NH_4^+$, $C_{10}H_{18}NO_4$ requires 216.1230); **mp** 48-50 °C; structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

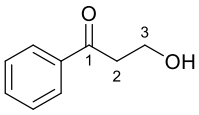
(±)-4,4-Dimethyl-2,6-dioxaspiro[4.5]decane-1,9-dione 412 as a colourless solid (27.0 mg, 136 µmol, 19%). **R_f** = 0.27 (20% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 4.25 (1 H, d, *J* = 8.2 Hz, 3-H_A), 4.21-4.14 (1 H, m, 7-H_A), 3.99 (1 H, dt, *J* = 11.7, 3.4 Hz, 7-H_B), 3.89 (1 H, d, *J* = 8.2 Hz, 3-H_B), 2.57 (1 H, ddd, *J* = 15.6, 11.6, 7.7 Hz, 8-H_A), 2.47-2.40 (1 H, m, 8-H_B), 2.41 (1 H, d, *J* = 15.1 Hz, 10-H_A), 2.32 (1 H, d, *J* = 15.1 Hz, 10-H_B), 1.14 (3 H, s, CH_{3A}), 0.99 (3 H, s, CH_{3B}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 203.5 (9-*C*=O), 174.3 (1-*C*=O), 82.0 (5-*C*), 78.0 (3-*C*H_2), 62.9 (7-*C*H_2), 43.2 (4-*C*), 40.7 (8-*C*H_2), 40.2 (10-*C*H_2), 22.1 (*C*H_{3A}), 16.9 (*C*H_{3B}); **IR** (ATR) ν_{Max}/cm^{-1} 2974, 2917, 2896, 2850, 1762 (C=O), 1715 (C=O), 1466, 1368, 1292, 1259, 1226, 1156, 1070, 1023, 998, 982, 967, 856, 816, 740, 685, 493, 439; **HRMS** (ESI$^+$) *m/z* found 199.0982 (M+H$^+$, $C_{10}H_{15}O_4$ requires 199.0965), 221.0805 (M+Na$^+$, $C_{10}H_{14}O_4Na$ requires 221.0784) and 216.1244 (M+NH_4^+, $C_{10}H_{18}NO_4$ requires 216.1230); **mp** 51-53 °C; structure solved from X-ray crystallography studies (crystallisation from acetonitrile evaporation).

(±)-1-Phenylpropane-1,3-diol 445



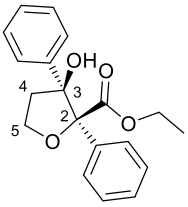
Sodium borohydride (3.40 g, 90.0 mmol, 3 equiv.) was slowly added to a solution of ethyl benzoylacetate **376** (5.77 g, 30.0 mmol, 1 equiv.) in CH_2Cl_2 (55 mL), cooled to 0 ºC, over the course of 30 min. The resulting reaction mixture was then neutralised using 2 M HCl and the solution was concentrated *in vacuo*. The resulting solution was then added to *sat.* aqueous sodium hydrogen carbonate solution (50 mL), extracted with ethyl acetate (3 x 50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to afford a viscous colourless oil (4.55 g, 29.9 mmol, *quant.*). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.37-7.26 (5 H, m, Ar*H*), 4.96 (1 H, dd, *J* = 8.7, 3.8 Hz, 1-*H*), 3.88-3.82 (2 H, m, 3-H_2), 2.95 (1 H, br s, O*H*), 2.51 (1 H, br s, O*H*), 2.06-1.90 (2 H, m, 2-H_2); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 144.4 (*Ar*), 128.7 (*Ar*H), 127.8 (*Ar*H), 125.8 (*Ar*H), 74.6 (1-*C*H), 61.7 (3-*C*H_2), 40.6 (2-*C*H_2); **IR** (ATR) ν_{Max}/cm^{-1} 3324 (OH), 3062, 3030, 2944, 2885, 1492, 1421, 1335, 1280, 1046, 916, 752, 699, 561; **HRMS** (ESI$^+$) *m/z* found **HRMS** (ESI$^+$) *m/z* found 175.0728 (M+Na$^+$, $C_9H_{12}O_2Na$ requires 175.0730). Spectroscopic data matched that previously reported.[179]

3-Hydroxy-1-phenylpropan-1-one 227



Manganese dioxide (28.6 g, 329 mmol, 25 equiv.) was added to a solution of diol **445** (2.00 g, 13.1 mmol, 1 equiv.) in CH_2Cl_2 (135 mL) and the reaction mixture was stirred at room temperature for 30 h. The resulting solution was then filtered through a pad of Celite, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as colourless oil (1.10 g, 7.31 mmol, 56%). $\mathbf{R_f}$ = 0.25 (40% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.98-7.95 (2 H, m, Ar*H*), 7.62-7.56 (1 H, m, Ar*H*), 7.51-7.45 (2 H, m, Ar*H*), 4.04 (2 H, t, *J* = 5.3 Hz, 3-H_2), 3.23 (2 H, t, *J* = 5.3 Hz, 2-H_2), 2.60 (1 H, br s, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 200.7 (1-*C*=O), 136.8 (*Ar*), 133.7 (*Ar*H), 128.8 (*Ar*H), 128.2 (*Ar*H), 58.2 (3-*C*H_2), 40.5 (2-*C*H_2); **IR** (ATR) v_{Max}/cm^{-1} 3404 (OH), 2923, 1676 (C=O), 1596, 1580, 1448, 1361, 1253, 1211, 1178, 1036, 1000, 975, 927, 871, 746, 689, 571, 487; **HRMS** (ESI^+) *m/z* found 151.0764 ($M+H^+$, $C_9H_{11}O_2$ requires 151.0754) and 173.0580 ($M+Na^+$, $C_9H_{10}O_2Na$ requires 173.0573). Spectroscopic data matched that previously reported.[152]

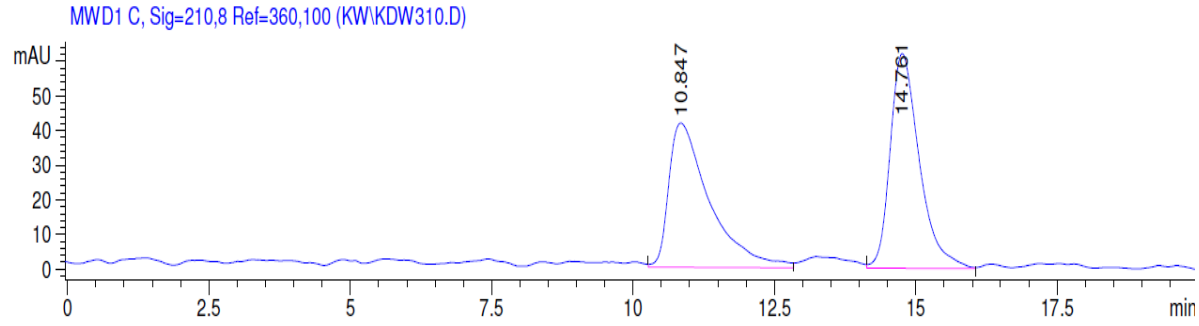
Ethyl (2*S*,3*S*)-3-hydroxy-2,3-diphenyltetrahydrofuran-2-carboxylate 238



A solution of copper(I) triflate toluene complex (5.2 mg, 10.0 µmol, 5 mol%) and (*S*,*S*)-*i*-PrBOX (3.7 mg, 14.0 µmol, 7 mol%) in CH_2Cl_2 (1 mL) was stirred at room temperature for 4 h, and was then cooled to 0 °C. A solution containing β-hydroxyketone **227** (30.0 mg, 0.20 mmol, 1 equiv.) in CH_2Cl_2 (0.5 mL) was then added and the resulting reaction mixture was stirred for 20 min. A solution of α-diazolactone **195** (49.5 mg, 0.26 mmol, 1.3 equiv.) in CH_2Cl_2 (1 mL) was then added, over a 30 min period, to the reaction mixture. The resulting solution was then stirred at 0 °C for 1 h, then warmed to room temperature and stirred for an additional 1 h before being heated to reflux for 1 h. The resulting reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless oil (39.8 mg, 0.127 mmol, 64%). $\mathbf{R_f}$ = 0.33 (20% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.17-7.03 (10 H, m, Ar*H*), 4.66 (1 H, s, O*H*), 4.47 (2 H, dd, *J* = 8.9, 5.5 Hz, 5-H_2), 4.30-4.22 (2 H, two overlapping dt, *J* = 10.6, 7.1 Hz, CH_3CH_2), 2.69 (1 H, dt, *J* = 13.0, 8.9 Hz, 4-H_A), 2.29 (1 H, ddd, *J* = 13.0, 6.0,

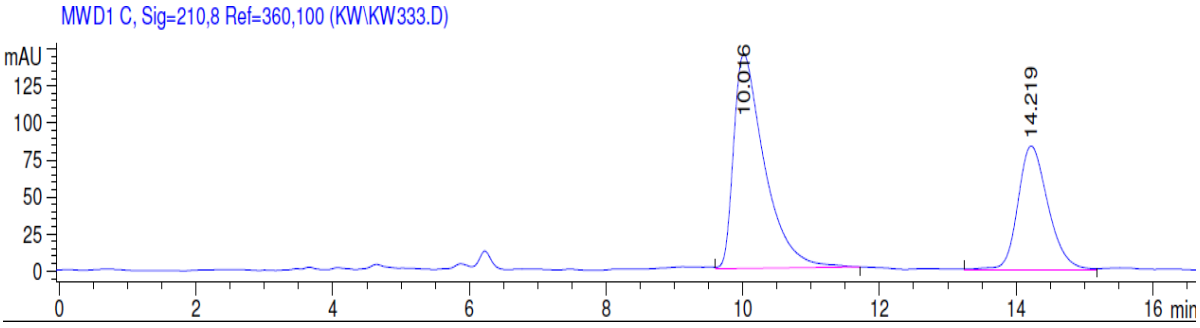
5.1 Hz, 4-H_B), 1.25 (3 H, t, J = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 173.3 (*C*=O), 140.7 (*Ar*), 137.4 (*Ar*), 127.8 (*Ar*H), 127.5 (*Ar*H), 127.32 (*Ar*H), 127.29 (*Ar*H), 126.8 (*Ar*H), 126.0 (*Ar*H), 90.8 (2-*C*), 85.9 (3-*C*), 66.9 (5-CH_2), 62.2 (CH_3CH_2), 39.6 (4-CH_2), 14.1 (CH_2CH_3); **IR** (ATR) ν_{Max}/cm^{-1} 3450 (OH), 3060, 2981, 2895, 1730 (C=O), 1493, 1447, 1367, 1256, 1132, 1095, 1066, 1030, 909, 730, 697; **HRMS** (ESI^+) *m/z* found 335.1270 ($M+H^+$, $C_{19}H_{20}O_4Na$ requires 335.1254) and 330.1698 ($M+Na^+$, $C_{19}H_{24}NO_4$ requires 330.1700). Spectroscopic data matched that previously reported.[84]

(±)-**238** (*rac*) Chiral HPLC spectrum (Chiralpak AD-H, 90:10 *i*-hexane:*i*-PrOH, 1 mL/min, 210 nm, ambient temperature).



Peak	Retention Time / min	Relative Area	Area %
1	10.847	2094.54980	48.4316
2	14.761	2230.20679	51.5684

(*S*,*S*)-**238** (28% *ee*) Chiral HPLC spectrum (Chiralpak AD-H, 90:10 *i*-hexane:*i*-PrOH, 1 mL/min, 210 nm, ambient temperature).



Peak	Retention Time / min	Relative Area	Area %
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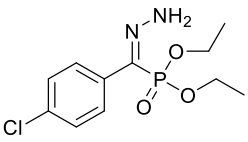
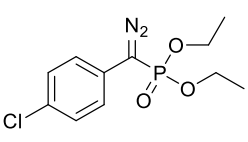
2	14.219	2532.28589	35.7741

Diethyl (*Z*)-((4-chlorophenyl)(hydrazineylidene)methyl)phosphonate 457



Oxalyl chloride (1.70 mL, 20.0 mmol, 2 equiv.) was added to a solution of 4-chlorobenzoic acid **455** (1.57 g, 10.0 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) at 0 °C, followed by the addition of 10 drops of DMF. The resulting solution was stirred at room temperature for 3 h before being concentrated *in vacuo* to afford the corresponding acid chloride as a colourless oil that was used in the next step without further purification. Triethyl phosphite (1.70 mL, 10.0 mmol, 1 equiv.) was then added and the solution was stirred at room temperature for 18 h, before the addition of ethanol (5 mL). The resulting reaction mixture was then added to a solution of hydrazine hydrate (0.50 mL, 10 mmol, 1 equiv.) in ethanol and acetic acid (10:1, 11 mL). The resulting solution was stirred at room temperature for 18 h, diluted with water (20 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a yellow oil (427 mg, 1.47 mmol, 15%, *Z*:*E* 97:3). **R_f** = 0.24 (50% ethyl acetate in hexane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 8.24 (2 H, br s, NH_2), 7.58-7.54 (2 H, m, Ar*H*), 7.30-7.27 (2 H, m, Ar*H*), 4.20-3.99 (4 H, m, P(OC$H_2$$CH_3$)$_2$), 1.28 (6 H, t, *J* = 7.1 Hz, P(OCH_2CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 135.8 (d, J_{CP} = 27.5 Hz, *Ar*H),133.4 (*Ar*), 128.7 (d, J_{CP} = 152.7 Hz, *C*=N), 128.5 (*Ar*H), 127.7 (d, J_{CP} = 3.2 Hz, *Ar*H), 62.6 (d, J_{CP} = 4.7 Hz, P(OC$H_2$$CH_3$)$_2$), 16.3 (d, J_{CP} = 6.3 Hz, P(OCH_2CH_3)$_2$); **^{31}P NMR** (162 MHz, $CDCl_3$): δ_P ppm 9.08; **IR** (ATR) ν_{Max}/cm^{-1}; 3394 (NH_2), 3192, 2924, 2854, 1593 (C=N), 1511, 1490, 1463, 1225, 1092, 1010, 961, 830, 792, 618, 493, 462; **HRMS** (ESI$^+$) *m/z* found 291.0671 (M+H$^+$, $C_{11}H_{17}ClN_2O_3P$ requires 291.0660) and 313.0488 (M+Na$^+$, $C_{11}H_{16}ClN_2O_3PNa$ requires 313.0479).

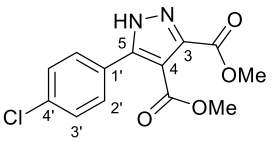
Diethyl ((4-chlorophenyl)(diazo)methyl)phosphonate 458



A suspension of potassium *N*-iodo *p*-toluenesulfonamide **278** (224 mg, 0.67 mmol, 1.2 equiv.) and hydrazone **457** (162 mg, 0.56 mmol, 1 equiv.) in THF (2.2 mL) was prepared. Aqueous potassium hydroxide (1 M; 0.55 mL) was slowly added to the THF suspension (so that the final volume ratio 1 M KOH:THF was 1:4), causing the dissolution of the potassium salt and the appearance of a yellow colouration. The resulting reaction mixture was

left stirring at room temperature for 1 h. Aqueous potassium hydroxide (1 M; 2.8 mL) was then added to the reaction mixture and the resulting solution was extracted with diethyl ether (20 mL). The organic phase was then washed with aqueous potassium hydroxide (1 M; 2.8 mL), brine (2.8 mL), dried with $MgSO_4$ and concentrated *in vacuo* affording the *title compound* as a bright yellow oil (146 mg, 0.507 mmol, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 7.33-7.30 (2 H, m, Ar*H*), 7.13-7.09 (2 H, m, Ar*H*), 4.26-4.08 (4 H, m, P(OC*H*$_2$CH$_3$)$_2$), 1.33 (6 H, t, *J* = 7.0 Hz, P(OCH$_2$C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 130.9 (*Ar*), 129.5 (*Ar*H), 125.6 (d, J_{CP} = 9.8 Hz, *Ar*), 124.0 (d, J_{CP} = 4.5 Hz, *Ar*H), 63.2 (d, J_{CP} = 5.1 Hz, P(O*C*H$_2$CH$_3$)$_2$), 16.3 (d, J_{CP} = 6.9 Hz, P(OCH$_2$*C*H$_3$)$_2$), the signal due to *C*N$_2$ was not observed; **^{31}P NMR** (162 MHz, $CDCl_3$): δ_P ppm 16.5; **IR** (ATR) ν_{Max}/cm^{-1} 2982, 2908, 2075 (C=N), 1492, 1392, 1297, 1256, 1185, 1163, 1095, 1012, 969, 820, 729, 591, 499; **HRMS** (ESI$^+$) *m/z* found 289.0516 (M+H$^+$, $C_{11}H_{15}ClN_2O_3P$ requires 289.0503), 311.0331 (M+Na$^+$, $C_{11}H_{14}ClN_2O_3PNa$ requires 311.0323) and 306.0783 (M+NH$_4^+$, $C_{11}H_{18}ClN_3O_3P$ requires 306.0769. Spectroscopic data matched that previously reported.[158]

Dimethyl 5-(4-chlorophenyl)-1*H*-pyrazole-3,4-dicarboxylate 463



A solution of α-diazophosphonate **458** (116 mg, 0.40 mmol, 1 equiv.) and dimethyl acetylenedicarboxylate (54.0 µL, 0.44 mmol, 1.1 equiv.) in toluene (0.8 mL) was heated at reflux for 4 h. Once cooled to room temperature, the reaction mixture was then concentrated *in vacuo* and the resulting residue was dissolved in MeOH (0.8 mL). Sodium hydroxide (16.0 mg, 0.4 mmol, 1 equiv.) in water (0.32 mL) was then added and the resulting solution was stirred at room temperature for 2 h. Water (10 mL) was then added to the reaction mixture and the resulting solution was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were then washed with brine (10 mL) and dried with $MgSO_4$. The organic phase was concentrated *in vacuo* and the crude product was purified by column chromatography affording the *title compound* as a colourless solid (93.4 mg, 0.317 mmol, 79%). **R$_f$** = 0.40 (40% ethyl acetate in pentane); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H ppm 10.76 (1 H, br s, N*H*), 7.58 (2 H, d, *J* = 8.5 Hz, 2'-Ar*H*), 7.43 (2 H, d, *J* = 8.5 Hz, 3'-Ar*H*), 3.96 (3 H, s, 4-CCO$_2$C*H*$_3$), 3.85 (3 H, s, 3-CCO$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C ppm 164.2 (4-C*C*=O), 160.8 (3-C*C*=O), 146.6 (4'-*Ar*),

140.4 (4-*Ar*), 135.9 (5-*Ar*), 129.5 (2'-*Ar*H), 129.1 (3'-*Ar*H), 127.3 (1'-*Ar*), 52.73 (3-CCO_2CH_3), 52.70 (4-CCO_2CH_3), the signal due to 3-*Ar* was not observed; **IR** (ATR) v_{Max}/cm^{-1} 3264 (NH), 3014, 2957, 1734 (C=O), 1544, 1487, 1449, 1307, 1288, 1227, 1159, 1091, 1060, 985, 955, 838, 822, 800, 743, 664, 540, 402; **HRMS** (ESI^+) m/z found 317.0298 ($M+Na^+$, $C_{13}H_{11}ClN_2O_4Na$ requires 317.0300); **mp** 147-148 °C.

References

1 N. Tanaka and Y. Kashiwada, *J. Nat. Med.*, 2021, **75**, 423–433.

2 G. Di Carlo, F. Borrelli, E. Ernst and A. A. Izzo, *Trends Pharmacol. Sci.*, 2001, **22**, 292–297.

3 E. C. Tatsis, S. Boeren, V. Exarchou, A. N. Troganis, J. Vervoort and I. P. Gerothanassis, *Phytochemistry.*, 2007, **68**, 383–393.

4 J. Barnes, L. A. Anderson and J. D. Phillipson, *J. Pharm. Pharmacol.*, 2001, **53**, 583–600.

5 Q. X. Ng, N. Venkatanarayanan and C. Y. X. Ho, *J. Affect. Disord.*, 2017, **210**, 211–221.

6 S. Nicolussi, J. Drewe, V. Butterweck and H. E. Meyer zu Schwabedissen, *Br. J. Pharmacol.*, 2020, **177**, 1212–1226.

7 Y. Shimizu, S. L. Shi, H. Usuda, M. Kanai and M. Shibasaki, *Angew. Chem. Int. Ed.*, 2010, **49**, 1103–1106.

8 B. A. Sparling, D. C. Moebius and M. D. Shair, *J. Am. Chem. Soc.*, 2013, **135**, 647.

9 Y. Ji, B. Hong, I. Franzoni, M. Wang, W. Guan, H. Jia and H. Li, *Angew. Chem. Int. Ed.*, 2022, **61**, e202116136.

10 J. Motoyoshiya, Y. Masue, Y. Nishi and H. Aoyama, *Nat. Prod. Commun.*, 2007, **2**, 67–70.

11 L. F. Huang, Z. H. Wang and S. L. Chen, *Chin. J. Nat. Med.*, 2014, **12**, 81–88.

12 M. Tada, M. Nagai, C. Okumura, Y. Osano and T. Matsuzaki, *Chem. Lett.*, 1989, **18**, 683–686.

13 Y. Aramaki, K. Chiba and M. Tada, *Phytochemistry.*, 1995, **38**, 1419–1421.

14 T. Ueki, D. Ichinari, K. Yoshihara, Y. Morimoto and T. Kinoshita, *Tetrahedron Lett.*, 1998, **39**, 667–668.

15 T. Ueki, M. Doe, Y. Morimoto, T. Kinoshita, R. Tanaka and K. Yoshihara, *J. Heterocycl. Chem.*, 2001, **38**, 165–172.

16 N. Tanaka, M. Okasaka, Y. Ishimaru, Y. Takaishi, M. Sato, M. Okamoto, T. Oshikawa, S. U. Ahmed, L. M. Consentino and K. H. Lee, *Org. Lett.*, 2005, **7**, 2997–2999.

17 K. C. Nicolaou, D. Sarlah and D. M. Shaw, *Angew. Chem. Int. Ed.*, 2007, **46**, 4708–4711.

18 K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe and D. R. Burton, *J. Am. Chem. Soc.*, 2008, **130**, 11114–11121.

19 K. C. Nicolaou, S. Sanchini, D. Sarlah, G. Lu, T. R. Wu, D. K. Nomura, B. F. Cravatt, B. Cubitt, J. C. De La Torre, A. J. Hessell and D. R. Burton, *Proc. Nat. Acad. Sci.*, 2011, **108**, 6715–6720.

20 S. F. Emonet, L. Garidou, D. B. McGavern and J. C. De La Torre, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 3473–3478.

21 C. G. Savva, S. Totokotsopoulos, K. C. Nicolaou, C. M. Neophytou and A. I. Constantinou, *BMC Cancer.*, 2016, **16**, 1–14.

22 D. Ichinari, T. Ueki, K. Yoshihara and T. Kinoshita, *Chem. Commun.*, 1997, **18**, 1743–1744.

23 T. Kinoshita, D. Ichinari and J. Sinya, *J. Heterocycl. Chem.*, 1996, **33**, 1313–1317.

24 F. A. Davis, L. C. Vishwakarma, J. M. Billmers and J. Finn, *J. Org. Chem.*, 1984, **49**, 3241–3243.

25 D. Seebach and D. Wasmuth, *Helv. Chim. Acta.*, 1980, **63**, 197–200.

26 G. Fráter, U. Müller and W. Günther, *Tetrahedron.*, 1984, **40**, 1269–1277.

27 P. A. Grieco, S. Gilman and M. Nishizawa, *J. Org. Chem.*, 1976, **41**, 1485–1486.

28 D. D. van Slyke, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 3170–3181.

29 D. Pleissner, R. Wimmer and N. T. Eriksen, *Anal. Chem.*, 2011, **83**, 175–181.

30 G. A. Kraus and J. Wei, *J. Nat. Prod.*, 2004, **67**, 1039–1040.

31 J. C. S. Perkin and M. Yamamoto, *J. Chem. Soc. Perkin Trans. 1.*, 1976, 1688–1691.

32 A. Hochrainer and F. Wessely, *Monatsh. Chem.*, 1966, **97**, 1–9.

33 S. Katayama, T. Watanabe and M. Yamauchi, *Chem. Pharm. Bull.*, 1990, **38**, 3314–3316.

34 S. Hecht, S. Amslinger, J. Jauch, K. Kis, V. Trentinaglia, P. Adam, W. Eisenreich, A. Bacher and F. Rohdich, *Tetrahedron Lett.*, 2002, **43**, 8929–8933.

35 C. Du, L. Li, Y. Li and Z. Xie, *Angew. Chem. Int. Ed.*, 2009, **48**, 7853–7856.

36 G. O. Schenck, J. Kuhls and C. H. Krauch, *Justus Liebigs Ann. Chem.*, 1966, **693**, 20–43.

37 Y. Chi and S. H. Gellman, *Org. Lett.*, 2005, **7**, 4253–4256.

38 D. Enders, H. Kipphardt, P. Gerdes, L. J. Breña-Valle and V. Bhushan, *Bull. Soc. Chim. Belg.*, 1988, **97**, 691–704.

39 D. L. Comins and A. Dehghani, *Tetrahedron Lett.*, 1992, **33**, 6299–6302.

40 A. S. E. Karlström, M. Rönn, A. Thorarensen and J. E. Bäckvall, *J. Org. Chem.*, 1998, **63**, 2517–2522.

41 Y. Inoue, K. Ohuchi, I. F. Yen and S. Imaizumi, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 3518–3522.

42 A. K. Chatterjee, T. L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370.

43 D. M. Hodgson, D. Angrish, S. P. Erickson, J. Kloesges and C. H. Lee, *Org. Lett.*, 2008, **10**, 5553–5556.

44 J. S. Clark, T. C. Fessard and C. Wilson, *Org. Lett.*, 2004, **6**, 1773–1776.

45 D. M. Hodgson and S. Man, *Chem. Eur. J.*, 2011, **17**, 9731–9737.

46 D. Mitchell and T. M. Koenig, *Tetrahedron Lett.*, 1992, **33**, 3281–3284.

47 H. Shin, B. S. Choi, K. K. Lee, H. W. Choi, J. H. Chang, K. W. Lee, D. H. Nam and N. S. Kim, *Synthesis.*, 2004, **16**, 2629–2632.

48 E. Buchner and T. Curtius, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 2371–2377.

49 D. M. Hodgson, E. Moreno-Clavijo, S. E. Day and S. Man, *Org. Biomol. Chem.*, 2013, **11**, 5362–5369.

50 D. M. Hodgson, S. Man, K. J. Powell, Z. Perko, M. Zeng, E. Moreno-Clavijo, A. L. Thompson and M. D. Moore, *J. Org. Chem.*, 2014, **79**, 9728–9734.

51 M. A. Calter and P. M. Sugathapala, *Tetrahedron Lett.*, 1998, **39**, 8813–8816.

52 M. Kreis, A. Palmelund, L. Bunch and R. Madsen, *Adv. Synth. Catal.*, 2006, **348**, 2148–2154.

53 T. Iwai, T. Fujihara and Y. Tsuji, *Chem. Commun.*, 2008, **11**, 6215–6217.

54 B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, 1973, **95**, 292–294.

55 B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921−2943.

56 Y. Wu, C. Du, C. Hu, Y. Li and Z. Xie, *J. Org. Chem.*, 2011, **76**, 4075–4081.

57 N. Tanaka, Y. Kashiwada, Y. K. Sang, W. Hashida, M. Sekiya, Y. Ikeshiro and Y. Takaishi, *J. Nat. Prod.*, 2009, **72**, 1447–1452.

58 F. Rohdich, F. Zepeck, P. Adam, S. Hecht, J. Kaiser, R. Laupitz, T. Gräwert, S. Amslinger, W. Eisenreich, A. Bacher and D. Arigoni, *Proc. Natl. Acad. Sci. U.S.A.*, 2003, **100**, 1586–1591.

59 D. Li, K. Schröder, B. Bitterlich, M. K. Tse and M. Beller, *Tetrahedron Lett.*, 2008, **49**, 5976–5979.

60 H. Zheng, Y. Wang, C. Xu, X. Xu, L. Lin, X. Liu and X. Feng, *Nat. Commun.*, 2018, **9**, 1–7.

61 T. Curtius, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2230–2231.

62 A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981–10080.

63 J. Wang, *Tetrahedron Lett.*, 2022, **108**, 154135.

64 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67–84.

65 D. Gillingham and N. Fei, *Chem. Soc. Rev.*, 2013, **42**, 4918–4931.

66 X. Zhao, Y. Zhang and J. Wang, *Chem. Commun.*, 2012, **48**, 10162–10173.

67 T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6161–6163.

68 J. Gong, G. Lin, W. Sun, C. C. Li and Z. Yang, *J. Am. Chem. Soc.*, 2010, **132**, 16745–16746.

69 Y. Liang, H. Zhou and Z.-X. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 17783–17785.

70 I. Aviv and Z. Gross, *Chem. Eur. J.*, 2008, **14**, 3995–4005.

71 Z. Qu, W. Shi and J. Wang, *J. Org. Chem.*, 2004, **69**, 217–219.

72 G. K. Murphy, C. Stewart and F. G. West, *Tetrahedron.*, 2013, **69**, 2667–2686.

73 Z. Z. Xie, W. J. Liao, J. Cao, L. P. Guo, F. Verpoort and W. Fang, *Organometallics.*, 2014, **33**, 2448–2456.

74 H. K. Kisan and R. B. Sunoj, *Chem. Commun.*, 2014, **50**, 14639–14642.

75 B. Liu, S. F. Zhu, W. Zhang, C. Chen and Q. L. Zhou, *J. Am. Chem. Soc.*, 2007, **129**, 5834–5835.

76 S. F. Zhu, Y. Cai, H. X. Mao, J. H. Xie and Q. L. Zhou, *Nat. Chem.*, 2010, **2**, 546–551.

77 Y. Y. Ren, S. F. Zhu and Q. L. Zhou, *Org. Biomol. Chem.*, 2018, **16**, 3087–3094.

78 Y. Li, Y. T. Zhao, T. Zhou, M. Q. Chen, Y. P. Li, M. Y. Huang, Z. C. Xu, S. F. Zhu and Q. L. Zhou, *J. Am. Chem. Soc.*, 2020, **142**, 10557–10566.

79 S. Pétursson, *Carbohydr. Res.*, 2001, **331**, 239–245.

80 S. V. Pansare, R. P. Jain and A. Bhattacharyya, *Tetrahedron Lett.*, 1999, **40**,

5255–5258.

81 H. H. San, S. J. Wang, M. Jiang and X. Y. Tang, *Org. Lett.*, 2018, **20**, 4672–4676.

82 S. Chamni, Q. L. He, Y. Dang, S. Bhat, J. O. Liu and D. Romo, *ACS Chem. Biol.*, 2011, **6**, 1175–1181.

83 K. Tishinov, K. Schmidt, D. Häussinger and D. G. Gillingham, *Angew. Chem.*, 2012, **124**, 12166–12170.

84 S. M. Nicolle, W. Lewis, C. J. Hayes and C. J. Moody, *Angew. Chem. Int. Ed.*, 2015, **54**, 8485–8489.

85 X. Xu, X. Han, L. Yang and W. Hu, *Chem. – A Eur. J.*, 2009, **15**, 12604–12607.

86 Y. Hashimoto, K. Itoh, A. Kakehi, M. Shiro and H. Suga, *J. Org. Chem.*, 2013, **78**, 6182–6195.

87 S. M. Nicolle, W. Lewis, C. J. Hayes and C. J. Moody, *Angew. Chem. Int. Ed.*, 2016, **55**, 3749–3753.

88 S. M. Nicolle, PhD Thesis, University of Nottingham, 2015.

89 W. Kirmse and S. Kopannia, *J. Org. Chem.*, 1998, **63**, 1178–1184.

90 R. T. Buck, D. M. Coe, M. J. Drysdale, L. Ferris, D. Haigh, C. J. Moody, N. D. Pearson and J. B. Sanghera, *Tetrahedron Asymmetry.*, 2003, **14**, 791–816.

91 B. W. R Bamford and T. S. Stevens, *J. Chem. Soc.*, 1952, 4735–4740.

92 S. M. Nicolle and C. J. Moody, *Chem. Eur. J.*, 2014, **20**, 4420–4425.

93 S. M. Nicolle, C. J. Hayes and C. J. Moody, *Chem. Eur. J.*, 2015, **21**, 4576–4579.

94 T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1973, **2**, 1011–1014.

95 Y. Yoshida, N. Matsumoto, R. Hamasaki and Y. Tanabe, *Tetrahedron Lett.*, 1999, **40**, 4227–4230.

96 L. L. Rodina, J. J. Medvedev, O. S. Galkina and V. A. Nikolaev, *Eur. J. Org.*

Chem., 2014, **2014**, 2993–3000.

97 Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011–1013.

98 T. Diao and S. S. Stahl, *J. Am. Chem. Soc.*, 2011, **133**, 14566–14569.

99 H. L. Riley, J. F. Morley and N. A. C. Friend, *J. Chem. Soc.*, 1932, 1875–1883.

100 J. P. Schaefer, *J. Am. Chem. Soc.*, 1962, **84**, 713–716.

101 R. A. Jerussi and D. Speyer, *J. Org. Chem.*, 1966, **31**, 3199–3203.

102 K. B. Sharpless and K. M. Gordon, *J. Am. Chem. Soc.*, 1976, **98**, 300–301.

103 Q. Li and G. P. Tochtrop, *Org. Lett.*, 2014, **16**, 1382–1385.

104 W. Zhang, H. Yao, J. Yu, Z. Zhang and R. Tong, *Angew. Chem. Int. Ed.*, 2017, **56**, 4787–4791.

105 K. C. Nicolaou, T. Montagnon and P. S. Baran, *Angew. Chem. Int. Ed.*, 2003, **42**, 3981–3981.

106 K. C. Nicolaou, Y. L. Zhong and P. S. Baran, *J. Am. Chem. Soc.*, 2000, **122**, 7596–7597.

107 K. C. Nicolaou, P. S. Baran, R. Kranich, Y.-L. Zhong, K. Sugita and N. Zou, *Angew. Chem.*, 2001, **113**, 208–212.

108 K. C. Nicolaou, P. S. Baran, Y. L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich and J. A. Vega, *J. Am. Chem. Soc.*, 2002, **124**, 2233–2244.

109 K. C. Nicolaou, D. L. F. Gray, T. Montagnon and S. T. Harrison, *Angew. Chem. Int. Ed.*, 2002, **41**, 996–1000.

110 Y. Yamashita, T. Yasukawa, W. J. Yoo, T. Kitanosono and S. Kobayashi, *Chem. Soc. Rev.*, 2018, **47**, 4388–4480.

111 S. E. Denmark and R. A. Stavenger, *J. Am. Chem. Soc.*, 2000, **122**, 8837–8847.

112 S. E. Denmark, R. A. Stavenger, S. B. D. Winter, K. T. Wong and P. A. Barsanti, *J. Org. Chem.*, 1998, **63**, 9517–9523.

113 S. E. Denmark, B. D. Griedel, D. M. Coe and M. E. Schnute, *J. Am. Chem. Soc.*, 1994, **116**, 7026–7043.

114 B. W. Gung, Z. Zhu and R. A. Fouch, *J. Org. Chem.*, 1995, **60**, 2860–2864.

115 S. E. Denmark, X. Su, Y. Nishigaichi, D. M. Coe, K. T. Wong, S. B. D. Winter and J. Y. Choi, *J. Org. Chem.*, 1999, **64**, 1958–1967.

116 G. E. Keck, L. S. Geraci, D. Krishnamurthy, M. C. Grier, K. Mikami, M. Terada, T. Nakai and S. Narisawa, *J. Am. Chem. Soc.*, 1995, **117**, 3949.

117 R. Zimmer, A. Peritz, R. Czerwonka, L. Schefzig and H.-U. Reißig, *Eur. J. Org. Chem.*, 2002, **20**, 3419–3428.

118 X. H. Chen, S. W. Luo, Z. Tang, L. F. Cun, A. Q. Mi, Y. Z. Jiang and L. Z. Gong, *Chem. Eur. J.*, 2007, **13**, 689–701.

119 B. T. Gröbel and D. Seebach, *Synthesis.*, 1977, **6**, 357–402.

120 S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307–1315.

121 H. R. Kricheldorf, G. Moerber and W. Regel, *Synth. Commun.*, 1981, **1**, 383–384.

122 B. Zhang, Z. Yang, J. Yang, G. Zhao, B. Ma, X. Xie and X. She, *Synlett.*, 2012, **23**, 2129–2131.

123 B. Plietker, *J. Org. Chem.*, 2003, **68**, 7123–7125.

124 B. Plietker, *J. Org. Chem.*, 2004, **69**, 8287–8296.

125 C. Bonini, L. Chiummiento, M. Funicello, P. Lupattelli and M. Pullez, *Eur. J. Org. Chem.*, 2006, **2006**, 80–83.

126 K. C. Nicolaou, T. Montagnon, P. S. Baran, T. Montagnon and P. S. Baran, *Angew. Chem. Int. Ed.*, 2002, **114**, 1035–1038.

127 M. E. Jung, Y. G. Pan, M. W. Rathke, D. F. Sullivan and R. P. Woodbury, *J. Org. Chem.*, 1977, **42**, 3961–3963.

128 H. Liu, C. Sun, N. K. Lee, R. F. Henry and D. Lee, *Chem. – A Eur. J.*, 2012, **18**, 11889–11893.

129 Y. Ito, S. Fujii and T. Saegusa, *J. Org. Chem.*, 1976, **41**, 2073.

130 M. Jida and J. Ollivier, *European J. Org. Chem.*, 2008, **2008**, 4041–4049.

131 Z.-L. Song, C.-A. Fan and Y.-Q. Tu, *Chem. Rev.*, 2011, **111**, 7523–7556.

132 T. Huber, T. A. Preuhs, C. K. G. Gerlinger and T. Magauer, *J. Org. Chem.*, 2017, **82**, 7410–7419.

133 T. O. Akinnusi, K. Vong and K. Auclair, *Bioorg. Med. Chem.*, 2011, **19**, 2696–2706.

134 C. Mottet, O. Hamelin, G. Garavel, J. P. Depres and A. E. Greene, *J. Org. Chem.*, 1999, **64**, 1380–1382.

135 G. Sabitha, R. Srinivas, P. Gopal, M. Bhikshapathi and J. S. Yadav, *Helv. Chim. Acta.*, 2011, **94**, 119–121.

136 H. Sun, H. Huang, D. Zhang, E. Feng, W. Qian, L. Zhang, K. Chen and H. Liu, *Adv. Synth. Catal.*, 2011, **353**, 1413–1419.

137 D. F. Taber, R. B. Sheth and P. V Joshi, *J. Org. Chem.*, 1992, **57**, 2851–2854.

138 S. Gogoi and N. P. Argade, *Tetrahedron.*, 2006, **62**, 2715–2720.

139 L. Shi, X. Lei, J. Zhang and G. Lin, *Helv. Chim. Acta.*, 2010, **93**, 555–564.

140 Y. Luo, H. B. Hepburn, N. Chotsaeng and H. W. Lam, *Angew. Chem. Int. Ed.*, 2012, **51**, 8309–8313.

141 B. Gopula, S. H. Yang, T. S. Kuo, J. C. Hsieh, P. Y. Wu, J. P. Henschke and H. L. Wu, *Chem. Eur. J.*, 2015, **21**, 11050–11055.

142 H. Nishida, N. Takada, M. Yoshimura, T. Sonoda and H. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2600–2604.

143 C. Vila, V. Hornillos, M. Fañanás-Mastral and B. L. Feringa, *Chem. Commun.*, 2013, **49**, 5933–5935.

144 B. L. Feringa, R. Badorrey, D. Peña, S. R. Harutyunyan and A. J. Minnaard, *Proc. Natl. Acad. Sci.*, 2004, **101**, 5834–5838.

145 P. Dupau, R. Epple, A. A. Thomas, V. V Fokin and K. B. Sharpless, *Adv. Synth. Catal.*, 2002, **344**, 219–451.

146 A. A. Hussein, N. N. A. Jafar and Y. Ma, *J. Org. Chem.*, 2024, **89**, 6892–6902.

147 S. M. Kohlbacher, V. S. Ionasz, L. Ielo and V. Pace, *Monatsh. Chem.*, 2019, **150**, 2011–2019.

148 M. Meguro, N. Asao and Y. Yamamoto, *J. Chem. Soc.,* 1994, 2597–2601.

149 F. R. Bisogno, A. Cuetos, A. A. Orden, M. Kurina-Sanz, I. Lavandera and V. Gotor, *Adv. Synth. Catal.*, 2010, **352**, 1657–1661.

150 C. N. Cooper, P. J. Jenner, N. B. Perry, J. Russell-King, H. J. Storesund and M. C. Whiting, *J. Chem. Soc. Perkin Trans. 2.*, 1982, 605–611.

151 M. Miyashita and A. Yoshikoshi, *J. Am. Chem. Soc.*, 1974, **96**, 1917–1925.

152 T. Aoyama, N. Sonoda, M. Yamauchi, K. Toriyama, M. Anzai, A. Ando and T. Shioiri, *Synlett.*, 1998, **29**, 35–36.

153 M. Marinozzi, F. Pertusati and M. Serpi, *Chem. Rev.*, 2016, **116**, 13991–14055.

154 E. Aller, R. T. Buck, M. J. Drysdale, L. Ferris, D. Haigh, C. J. Moody, N. D. Pearson and J. B. Sanghera, *J. Chem. Soc. Perkin Trans. 1.*, 1996, 2879–2884.

155 M. J. Davies, C. J. Moody and R. J. Taylor, *J. Chem. Soc. Perkin Trans. 1.*, 1991, 1–7.

156 C.-Y. Zhou, J.-C. Wang, J. Wei, Z.-J. Xu, Z. Guo, K.-H. Low, C.-M. Che, J.-C. Wang, Z.-J. Xu, C.-M. Che, S.-H. Kong, C.-Y. Zhou, J. Wei, Z. Guo and K.-H. Low, *Angew. Chem. Int. Ed.*, 2012, **51**, 11376–11380.

157 K. Ruffell, F. R. Smith, M. T. Green, S. M. Nicolle, M. Inman, W. Lewis, C. J. Hayes and C. J. Moody, *Eur. J. Org. Chem.*, 2021, **27**, 13703–13708.

158 I. P. Beletskaya and I. D. Titanyuk, *J. Org. Chem.*, 2022, **87**, 2748–2757.

159 R. E. Ireland and L. Liu, *J. Org. Chem.*, 1993, **58**, 2899.

160 R. E. C. Brown, K. J. Coulston and M. J. Irvine, *Aust. J. Chem.*, 1991, **44**, 87–101.

161 H. Yamaoka, N. Moriya and M. Ikunaka, *Org. Process Res. Dev.*, 2004, **8**, 931–938.

162 M. S. Davey, R. Malde, R. C. Mykura, A. T. Baker, T. E. Taher, C. S. Le Duff, B. E. Willcox and Y. Mehellou, *J. Med. Chem.*, 2018, **61**, 2111–2117.

163 B. David and F. Schuber, *Bioorganic Med. Chem. Lett.*, 1996, **6**, 1673–1676.

164 X. Liu, J. Jia, Y. Jia, H. Gu, J. Luo and X. Chen, *Org. Lett.*, 2018, **20**, 1945–1948.

165 Y. C. Xu, D. T. Kohlman, S. X. Liang and C. Erikkson, *Org. Lett.*, 1999, **1**, 1599–1602.

166 J. Lehmann and U. P. Weitzel, *Carbohydr. Res.*, 1996, **294**, 65–94.

167 L. Jin Liu and J. Hee Hong, *Bull. Korean Chem. Soc.*, 2011, **32**, 411.

168 R. Belibel and C. Barbaud, *J. Polym. Sci. Part A Polym. Chem.*, 2015, **53**, 2586–2597.

169 X. Li, K. Zhou, H. He, Q. Zhou, Y. Sun, L. Hou, L. Shen, X. Wang, Y. Zhou, Z. Gong, S. He, H. Jin, Z. Gu, S. Zhao, L. Zhang, C. Sun, S. Zheng, Z. Cheng, Y. Zhu, M. Zhang, J. Li and S. Chen, *ACS Med. Chem. Lett.*, 2017, **8**, 969–974.

170 K. Iseki, S. Oishi and Y. Kobayashi, *Tetrahedron.*, 1996, **52**, 71–84.

171 J. S. Bajwa and M. J. Miller, *J. Org. Chem.*, 1983, **48**, 1114–1116.

172 A. Sokolsky, X. Wang and A. B. Smith, *Tetrahedron Lett.*, 2015, **56**, 3160–3164.

173 A. Chiba, T. Aoyama, R. Suzuki, T. Eguchi, T. Oshima and K. Kakinuma, *J. Org. Chem.*, 1999, **64**, 6159–6165.

174 B. I. Stahl, F. Wrabletz, J. Gosselck, L. Stahl, F. Wrabletz and J. Gosselck, *Chem. Ber.*, 1989, **122**, 371–375.

175 H. N. Genc and A. Sirit, *Tetrahedron Asymmetry.*, 2016, **27**, 201–207.

176 D. Acetti, E. Brenna, C. Fuganti, F. G. Gatti and S. Serra, *Eur. J. Org. Chem.*, 2010, **2010**, 142–151.

177 S. Johnson, R. Rahmani, D. R. Drew, M. J. Williams, M. Wilkinson, Y. H. Tan, J. X. Huang, C. J. Tonkin, J. G. Beeson, J. Baum, B. J. Smith and J. B. Baell, *J. Med. Chem.*, 2016, **59**, 10994–11005.

178 B. J. Albert and K. Koide, *J. Org. Chem.*, 2008, **73**, 1093–1098.

179 Y. Lee, S. Shabbir, Y. Jeong, J. Ban and H. Rhee, *Bull. Korean Chem. Soc.*, 2015, **36**, 2885–2889.

180 F. Stoessel, *Thermal Safety of Chemical Processes: Risk Assessment and Process Design*, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2008.

181 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.

182 G. M. Sheldrick, *Acta Cryst.*, 2015, **A71**, 3–8.

183 G. M. Sheldrick, *Acta Cryst.*, 2015, **C71**, 3–8.

Appendices

Appendix A - Differential Scanning Calorimetry (DSC) Studies

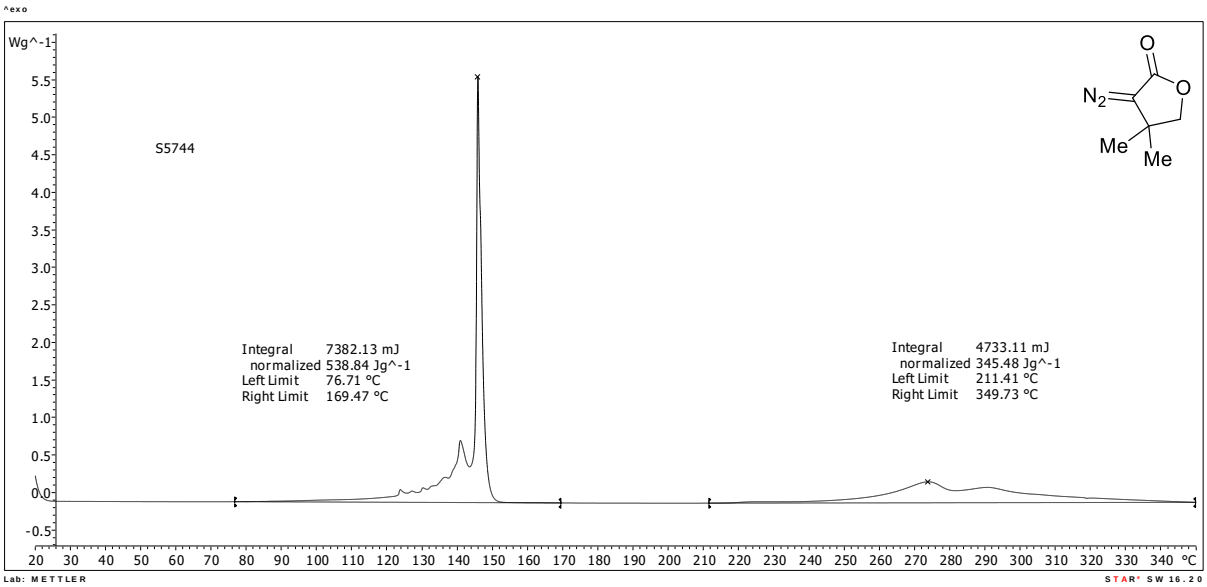
Although we have not experienced any issues in the handling of diazo chemicals, care should be taken when manipulating them due to their potentially explosive nature. A thorough risk assessment should always be carried out prior to the isolation and manipulation of diazo compounds, with cooling and safety measures applied throughout. DSC analysis was performed using a Mettler Toledo DSC 3+. 10.0-20.0 mg of the specified sample was accurately weighed to 1 d.p. into a Mettler Toledo ME-26731 gold-plated 40 µL high-pressure crucible, with a seal insert and lid rated to 150 bar, and sealed under air with the appropriate sealing press. After equilibrating at 20 °C, samples were heated at 2 °C min^{-1} to a maximum temperature of 350 °C. Data analysis was conducted using Mettler Toledo STARe software version 16.20.

The onset temperature (T_{onset}) is defined as the temperature at which the heat flow is measured to be >0.01 W g^{-1} from the baseline. To estimate the maximum recommended process temperature to avoid hazardous thermal decomposition (T_{D24}) the formula given in (1, developed by Stoessel,[180] was used. T_{D24} is defined as the temperature at which the time to maximum rate under adiabatic conditions (TMR_{ad}) becomes 24 h.

$$T_{D24} = 0.7(T_{onset}) - 46 \textbf{ (1)}$$

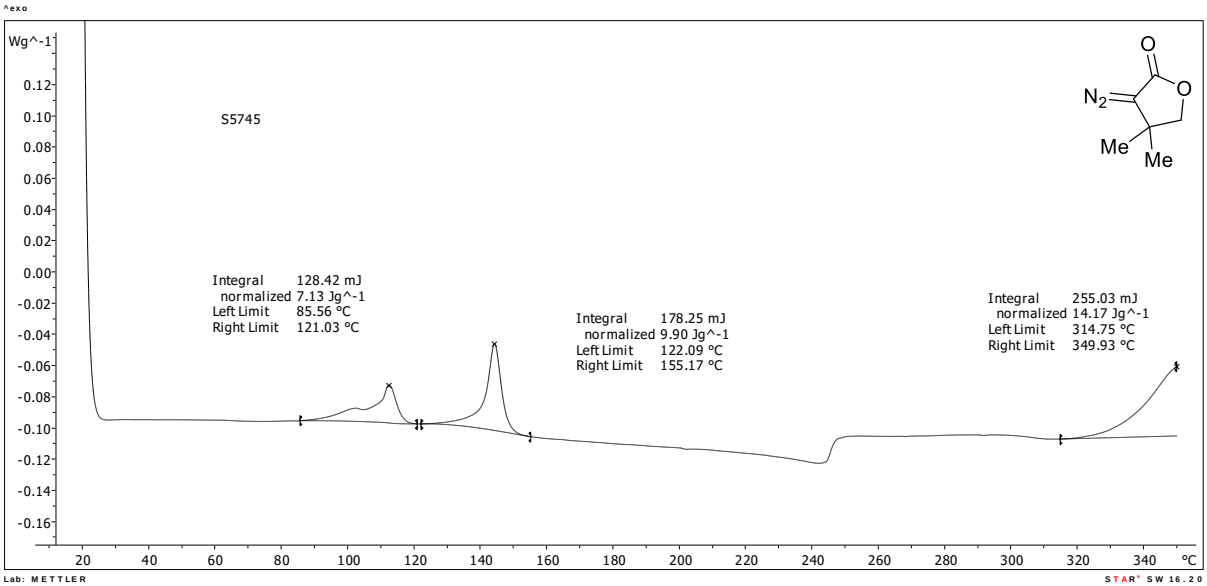
This formula was developed using the assumption that at the detection limit of an exotherm in the DSC experiment (T_{onset}), the conversion is close to zero and thus the heat release rate is equal to the detection limit. Additionally, a detection limit of 0.01 W g^{-1}, a specific heat capacity of 1 kJ kg^{-1} K^{-1}, as well as conservative approximations of a relatively low activation energy (50 kJ mol^{-1}) and zero-order kinetics for the decomposition are assumed. Due to the limited sensitivity of performed DSC experiments, values are reported to the nearest 5 °C.

DSC Thermogram of Isolated 3-Diazo-4,4-dimethyldihydrofuran-2(3*H*)-one (212)



T_{onset} = 90 °C; T_{D24} = 10 °C.

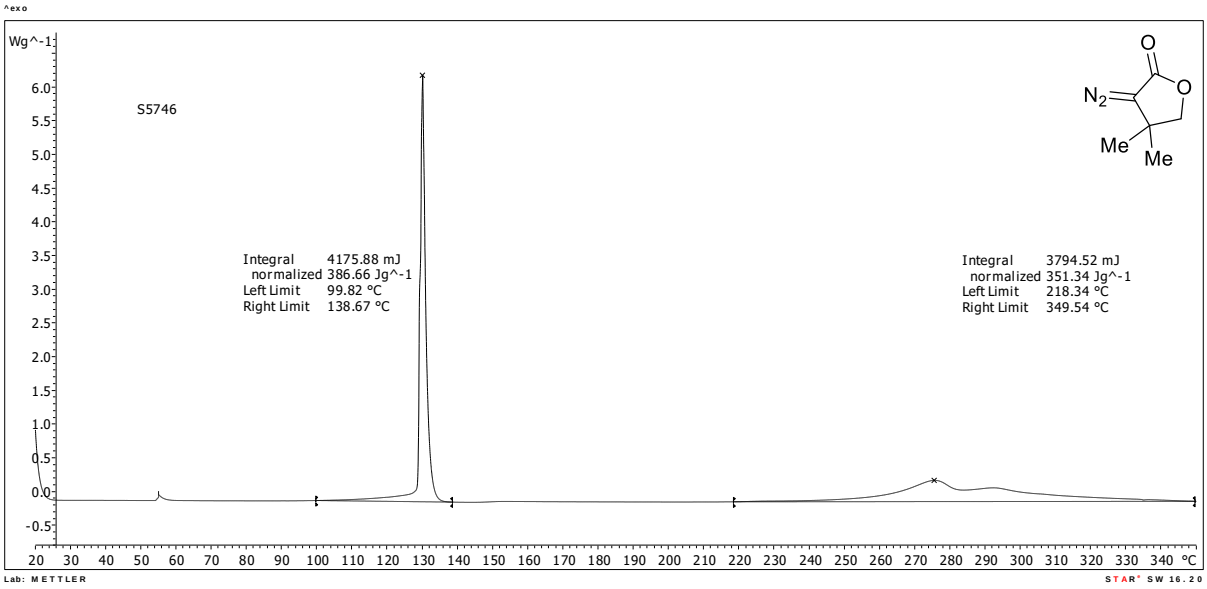
DSC Thermogram of 0.2 M 3-Diazo-4,4-dimethyldihydrofuran-2(3*H*)-one (212) in Dichloromethane

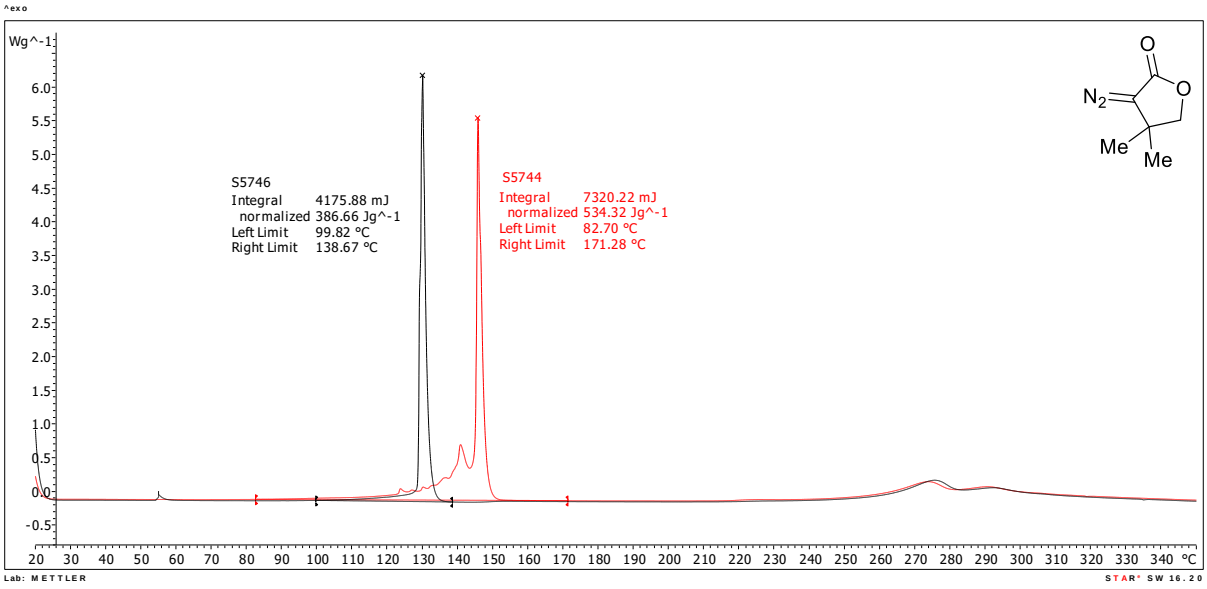


T_{init} = 350 °C; T_{D24} = 200 °C.

(NOTE: Only exotherms that are >40 J g^{-1} have been used to calculate T_{D24}, with anything below considered to be non-hazardous).

DSC Thermogram of 3-Diazo-4,4-dimethyldihydrofuran-2(3*H*)-one (212) with Isothermal Ageing at 55 °C





The maximum recommended processing temperature of isolated 3-diazo-4,4-dimethyldihydrofuran-2(3*H*)-one **212** (T_{D24} = 10 °C) indicates that heat should not be applied during preparation, or upon use. Therefore, α-diazolactone **212** should be stored in the dark, under inert conditions, using a refrigerator or freezer appliance. Dilution in CH_2Cl_2 (0.2 M) was found to significantly reduce the overall energy of decomposition and increase the maximum recommended processing temperature

(T_{D24} = 200 °C) associated with heating the solution, as the respective solvent acts as a heat sink. However, alternative solvents and concentrations should be tested prior to use.

The isothermal ageing DSC experiment (method: 20 to 55 °C at 2 °C min^{-1}, held at 55 °C for 20 hours, 55 to 350 °C at 2 °C min^{-1}) of isolated α-diazolactone **212** lowered the main peak temperature as well as the overall energy of decomposition (approx. 30% lower), suggesting that partial decomposition occurs during the ageing period. Repeating the isothermal ageing experiment at 40 °C for 1 hour resulted in a similar onset temperature, main peak temperature, and energy of decomposition to that observed for the DSC thermogram of isolated α-diazolactone **212**. Therefore, cooling and safety measures, small reaction scales and dilute solutions were utilised throughout all associated diverted O-H insertion reactions, with heating to a maximum of 40 °C for a 1 hour period carried out during the isolation α-diazolactone **212**.

Appendix B - X-Ray Crystallographic Data

X-ray diffraction measurements were generated from either a SuperNova Titan S2 diffractometer, or a dectris-CrysAlisPro-abstract goniometer imported dectris images diffractometer, from a single crystalline sample of the specified compound. Using Olex2,[181] the structures were solved with either the SHELXL[182] or XT[182] structure solution program using Intrinsic Phasing and were refined with the SHELXL[183] refinement package, applying Least Squares minimisation. Data collection and refinement parameters are reported for each crystal, while structures are displayed with displacement ellipsoids drawn at the 50% probability level.

(*E*)-3-Hydrazono-4,4-dimethyldihydrofuran-2(3*H*)-one 279a

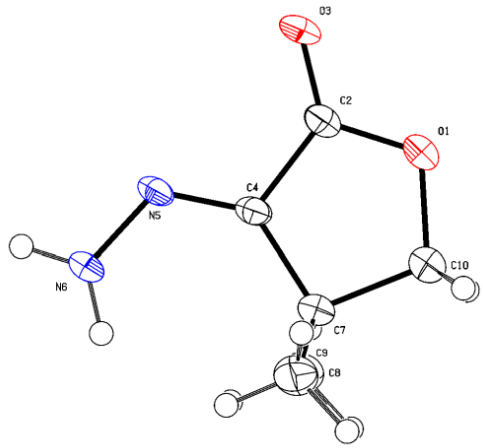


Figure A: *ORTEP of compound* ***279a****.*

Empirical formula	$C_6H_{10}N_2O_2$
Formula weight ($gmol^{-1}$)	142.16
Temperature (K)	120(2)
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.7198(3) Å α = 90 º b = 9.3177(5) Å β = 90 º c = 11.8486(7) Å γ = 90 º
Volume, V ($Å^3$)	741.88(7)
Cell formula units, Z	4
Density (*calc*), D_x (g/cm^3)	1.273

Absorption coefficient, μ (mm^{-1})	0.809
$F(000)$	304.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.321 × 0.018 × 0.017
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	12.084 to 144.924
Index ranges	-5≤ h ≤8 -9≤ k ≤11 -14≤ l ≤8
Reflections collected	2734
Independent reflections	1413 [R_{int} = 0.0218, R_{σ} = 0.0291]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.968, 0.781
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1413 / 2 / 99
Goodness-of-fit on F^2	1.080
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0317, wR_2 = 0.0779
Final R indexes (all data)	R_1 = 0.0349, wR_2 = 0.0799
H-atom treatment	H-atoms treated with a combination of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0424P)^2 + 0.0499P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.14, -0.16

(±)-3-Iodo-9,9-dimethyl-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 304

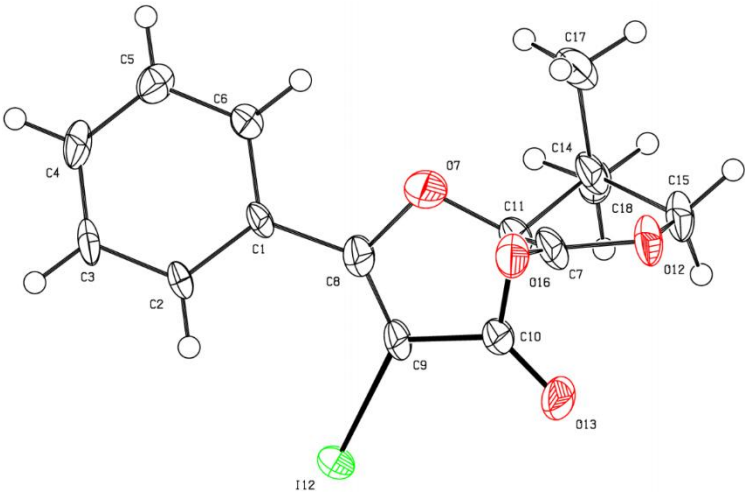


Figure B: *ORTEP of compound* ***304****.*

Empirical formula	$C_{15}H_{13}IO_4$
Formula weight (gmol^{-1})	384.15
Temperature (K)	100(2)
Crystal system, space group	Orthorhombic, Cccm
Unit cell dimensions	a = 9.88923(18) Å α = 90 º b = 36.0442(5) Å β = 90 º c = 7.95886(20) Å γ = 90 º
Volume, V (Å^3)	2836.93(10)
Cell formula units, Z	8
Density (*calc*), D_x (g/cm^3)	1.799
Absorption coefficient, μ (mm^{-1})	2.101
$F(000)$	1504
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.035 x 0.01 x 0.005
Radiation source and wavelength, λ (Å)	Synchrotron (λ = 0.6889)
2θ range for data collection (º)	4.14 to 54.674
Index ranges	-13≤ h ≤13 -48≤ k ≤48 -10≤ l ≤10
Reflections collected	19399
Independent reflections	1886 [R_{int} = 0.1009, R_σ = 0.0597]

Absorption correction	Symmetry-related measurements
Max. and min. transmission [T_{Max}, T_{Min}]	0.990, 0.930
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1886 / 333 / 150
Goodness-of-fit on F^2	1.331
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0690, wR_2 = 0.1821
Final R indexes (all data)	R_1 = 0.0712, wR_2 = 0.1830
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + 75.5274P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	1.010, -1.750

(±)-*cis*-4-Hydroxy-4-(hydroxymethyl)-9,9-dimethyl-1,7-dioxaspiro[4.4]nonan-6-one 334

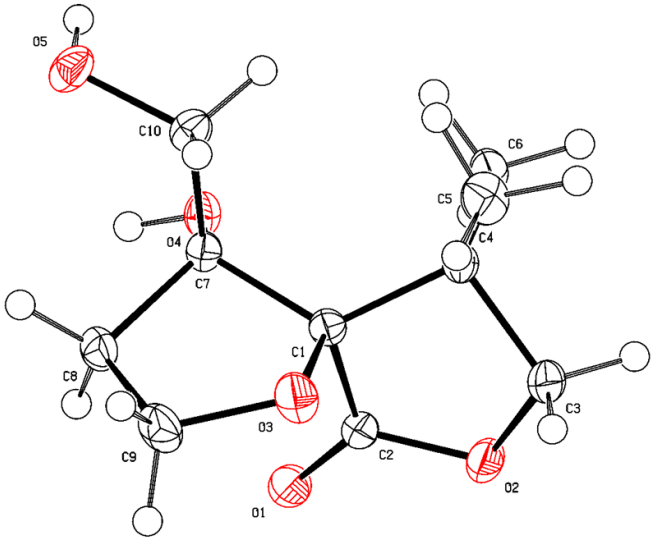


Figure C: *ORTEP of compound* ***334****.*

Empirical formula	$C_{10}H_{16}O_5$
Formula weight (gmol^{-1})	216.23
Temperature (K)	120(2)
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 6.78280(10) Å α = 90 º b = 14.8720(2) Å β = 93.0660(10) º

	c = 10.49320(10) Å γ = 90 º
Volume, V (Å^3)	1056.97(2)
Cell formula units, Z	4
Density (*calc*), D_x (g/cm^3)	1.359
Absorption coefficient, μ (mm^{-1})	0.919
$F(000)$	464.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.54 x 0.15 x 0.09
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	10.328 to 145.576
Index ranges	-7≤ h ≤8 -18≤ k ≤18 -12≤ l ≤12
Reflections collected	15189
Independent reflections	2088 [R_{int} = 0.0289, R_σ = 0.0155]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.922, 0.637
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2088 / 0 / 140
Goodness-of-fit on F^2	1.026
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0307, wR_2 = 0.0767
Final R indexes (all data)	R_1 = 0.0322, wR_2 = 0.0778
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0363P)^2 + 0.4119P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.29, -0.20

(±)-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 271

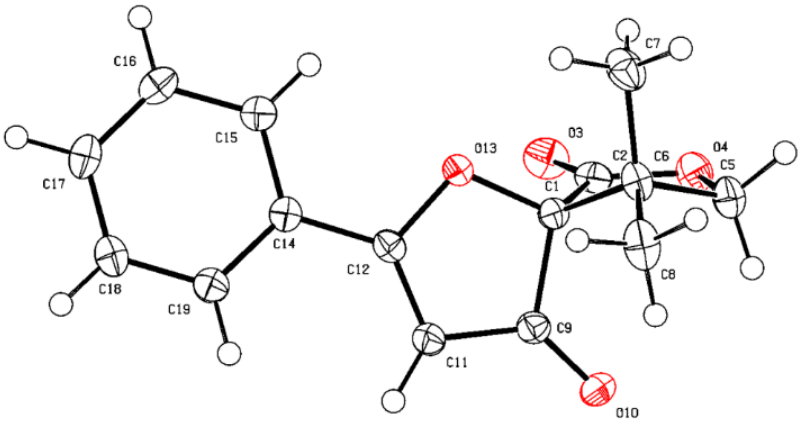


Figure D: *ORTEP of compound* ***271****.*

Empirical formula	$C_{15}H_{14}O_4$
Formula weight (gmol^{-1})	258.26
Temperature (K)	120(2)
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 7.29990(10) Å α = 90 º b = 18.1952(2) Å β = 90 º c = 18.9609(2) Å γ = 90 º
Volume, V (Å^3)	2518.45(5)
Cell formula units, Z	8
Density (*calc*), D_x (g/cm^3)	1.362
Absorption coefficient, μ (mm^{-1})	0.818
$F(000)$	1088.0
Crystal appearance, colouration	Block, colourless
Crystal size (mm)	0.245 x 0.111 x 0.088
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	9.328 to 147.794
Index ranges	-9≤ h ≤9 -19≤ k ≤22 -23≤ l ≤23
Reflections collected	43527
Independent reflections	2547 [R_{int} = 0.0253, R_σ = 0.0086]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.932, 0.825

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2547 / 0 / 174
Goodness-of-fit on F^2	1.040
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0311, wR_2 = 0.0812
Final R indexes (all data)	R_1 = 0.0320, wR_2 = 0.0820
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0435P)^2 + 0.8294P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.26, -0.23

(*S*)-9,9-Dimethyl-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (*S*)-271

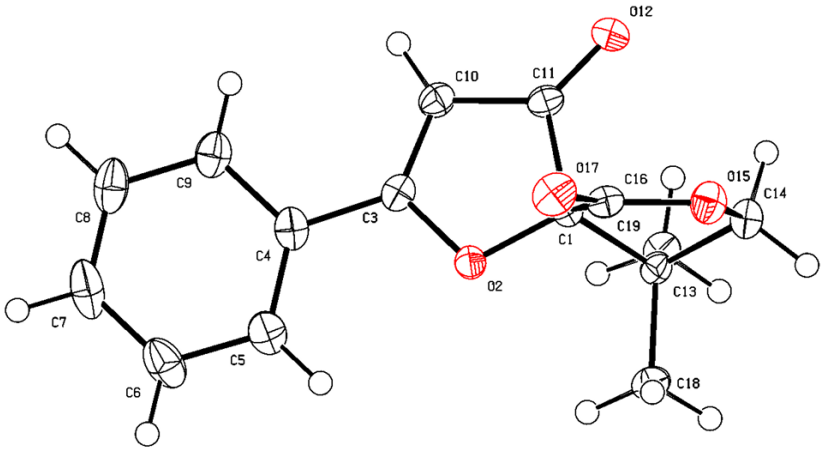


Figure E: *ORTEP of compound (S)-**271**.*

Empirical formula	$C_{15}H_{14}O_4$
Formula weight (gmol^{-1})	258.26
Temperature (K)	120(2)
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.71190(10) Å α = 90 º b = 12.39440(10) Å β = 90 º c = 15.52850(10) Å γ = 90 º
Volume, V (Å^3)	1291.82(2)
Cell formula units, Z	4
Density (*calc*), D_x (g/cm^3)	1.328
Absorption coefficient, μ (mm^{-1})	0.797

$F(000)$	544.0
Crystal appearance, colouration	Block, colourless
Crystal size (mm)	0.16 x 0.143 x 0.071
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	9.13 to 144.822
Index ranges	-8≤ h ≤8 -15≤ k ≤15 -19≤ l ≤19
Reflections collected	20783
Independent reflections	2555 [R_{int} = 0.0224, R_{σ} = 0.0111]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.946, 0.883
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2555 / 0 / 175
Goodness-of-fit on F^2	1.047
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0236, wR_2 = 0.0610
Final R indexes (all data)	R_1 = 0.0241, wR_2 = 0.0614
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0339P)^2 + 0.2235P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.20, -0.12

(±)-2-Isopropyl-9,9-dimethyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione 325

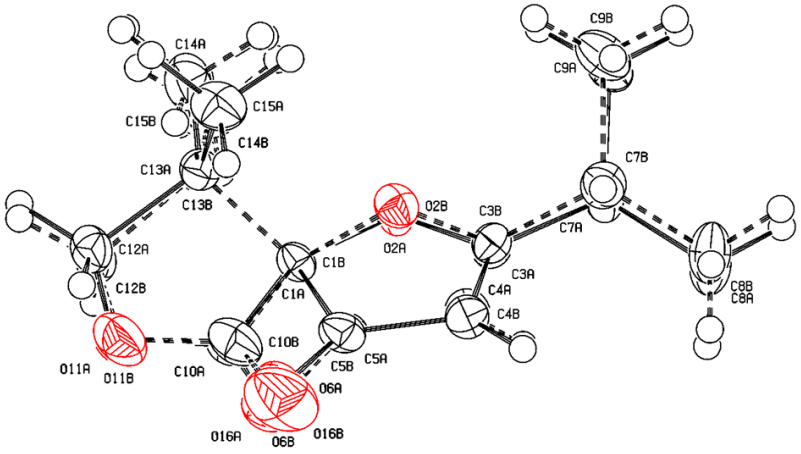


Figure F: *ORTEP of compound* ***325****.*

Empirical formula	$C_{12}H_{16}O_4$
Formula weight (gmol^{-1})	224.25
Temperature (K)	120(2)
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 10.5633(3) Å α = 90 º b = 9.41180(10) Å β = 114.089(3) º c = 12.8903(3) Å γ = 90 º
Volume, V (Å^3)	1169.94(5)
Cell formula units, Z	4
Density (*calc*), D_x (g/cm^3)	1.273
Absorption coefficient, μ (mm^{-1})	0.788
$F(000)$	480.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.14 × 0.119 × 0.102
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	9.17 to 144.628
Index ranges	-12≤ h ≤12 -11≤ k ≤11 -15≤ l ≤15
Reflections collected	17825
Independent reflections	2293 [R_{int} = 0.0243, R_σ = 0.0124]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.924, 0.898

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2293 / 825 / 268
Goodness-of-fit on F^2	1.087
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0336, wR_2 = 0.0925
Final R indexes (all data)	R_1 = 0.0359, wR_2 = 0.0947
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0491P)^2 + 0.2436P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.24, -0.16

Ethyl (2*S*,5*S*,9*R*)-9-methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]nonane-9-carboxylate 353

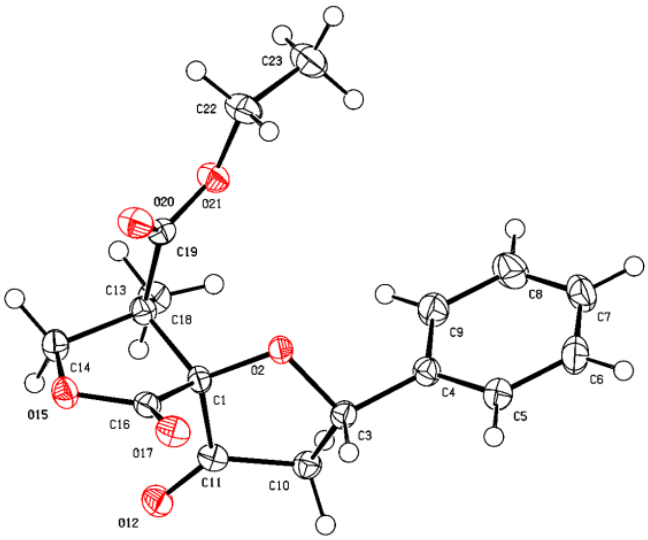


Figure G: *ORTEP of compound* ***353****.*

Empirical formula	$C_{17}H_{18}O_6$
Formula weight (gmol^{-1})	318.31
Temperature (K)	120(2)
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.32600(10) Å α = 90 º b = 11.87040(10) Å β = 90 º c = 20.5417(2) Å γ = 90 º
Volume, V (Å^3)	1542.52(3)
Cell formula units, Z	4

Density (*calc*), D_x (g/cm^3)	1.371
Absorption coefficient, μ (mm^{-1})	0.872
$F(000)$	672.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.277 × 0.035 × 0.027
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	8.604 to 158.666
Index ranges	-8≤ h ≤8 -14≤ k ≤7 -26≤ l ≤26
Reflections collected	14992
Independent reflections	3227 [R_{int} = 0.0259, R_σ = 0.0208]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.977, 0.794
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3227 / 0 / 210
Goodness-of-fit on F^2	1.109
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0292, wR_2 = 0.0728
Final R indexes (all data)	R_1 = 0.0321, wR_2 = 0.0801
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0345P)^2 + 0.4715P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.21, -0.18

(2*S*,3a*S*,6a*S*,9a*S*)-3a-hydroxy-6a-methyl-2-phenylhexahydro-6*H*,9*H*-difuro[3,2-c:3',4'-d]pyran-6,9-dione 355a

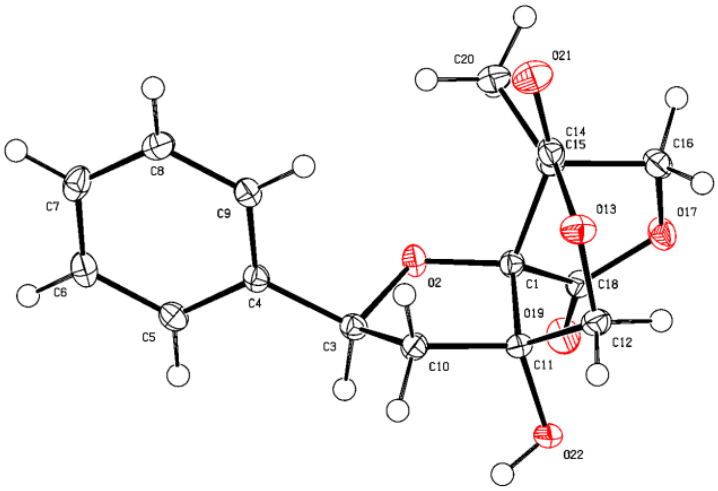


Figure H: *ORTEP of compound* ***355a****.*

Empirical formula	$C_{16}H_{16}O_6$
Formula weight (gmol^{-1})	304.29
Temperature (K)	120(2)
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 8.65280(10) Å α = 90 º b = 11.44110(10) Å β = 90 º c = 13.8754(2) Å γ = 90 º
Volume, V (Å^3)	1373.63(3)
Cell formula units, Z	4
Density (*calc*), D_x (g/cm^3)	1.471
Absorption coefficient, μ (mm^{-1})	0.953
$F(000)$	640.0
Crystal appearance, colouration	Block, colourless
Crystal size (mm)	0.117 × 0.077 × 0.062
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	10.02 to 140.126
Index ranges	-10≤ h ≤10 -13≤ k ≤13 -16≤ l ≤16
Reflections collected	23443
Independent reflections	2613 [R_{int} = 0.0271, R_σ = 0.0123]
Absorption correction	Gaussian from crystal shape

Max. and min. transmission [T_{Max}, T_{Min}]	0.943, 0.897
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2613 / 1 / 203
Goodness-of-fit on F^2	1.064
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0228, wR_2 = 0.0574
Final R indexes (all data)	R_1 = 0.0233, wR_2 = 0.0580
H-atom treatment	H-atoms treated with a combination of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0314P)^2 + 0.2864P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.20, -0.16

(2*S*,3a*R*,6a*R*,9a*R*)-3a-hydroxy-6a-methyl-2-phenylhexahydro-6*H*,9*H*-difuro[3,2-c:3',4'-d]pyran-6,9-dione 355b

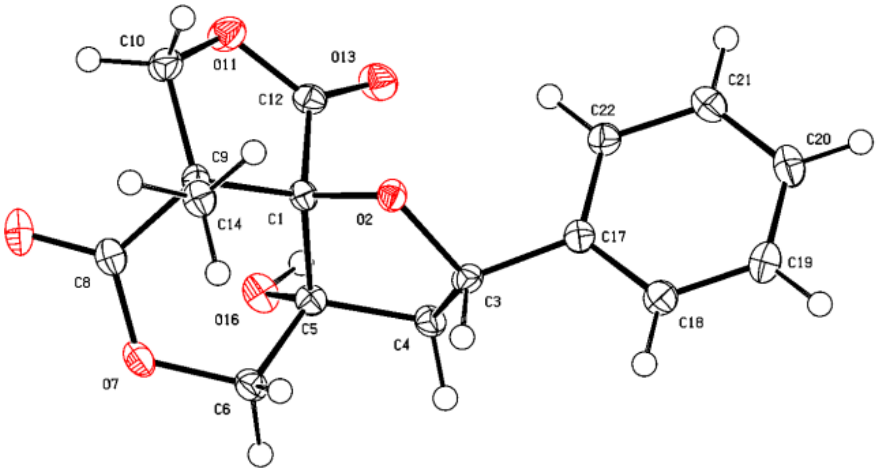


Figure I: *ORTEP of compound* ***355b****.*

Empirical formula	$C_{16}H_{16}O_6$
Formula weight (gmol^{-1})	304.29
Temperature (K)	120(2)
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.39260(10) Å α = 90 º b = 12.2879(2) Å β = 90 º c = 17.2320(2) Å γ = 90 º
Volume, V (Å^3)	1353.60(3)
Cell formula units, Z	4

Density (*calc*), D_x (g/cm^3)	1.493
Absorption coefficient, μ (mm^{-1})	0.967
$F(000)$	640.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.136 × 0.07 × 0.019
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	8.838 to 150.858
Index ranges	-8≤ h ≤8 -15≤ k ≤13 -21≤ l ≤20
Reflections collected	12751
Independent reflections	2703 [R_{int} = 0.0210, R_σ = 0.0166]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.982, 0.880
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2703 / 1 / 203
Goodness-of-fit on F^2	1.072
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0255, wR_2 = 0.0661
Final R indexes (all data)	R_1 = 0.0274, wR_2 = 0.0681
H-atom treatment	H-atoms treated with a combination of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0336P)^2 + 0.3914P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.18, -0.17

Ethyl (5*S*,9*R*)-9-methyl-4,6-dioxo-2-phenyl-1,7-dioxaspiro[4.4]non-2-ene-9-carboxylate 356

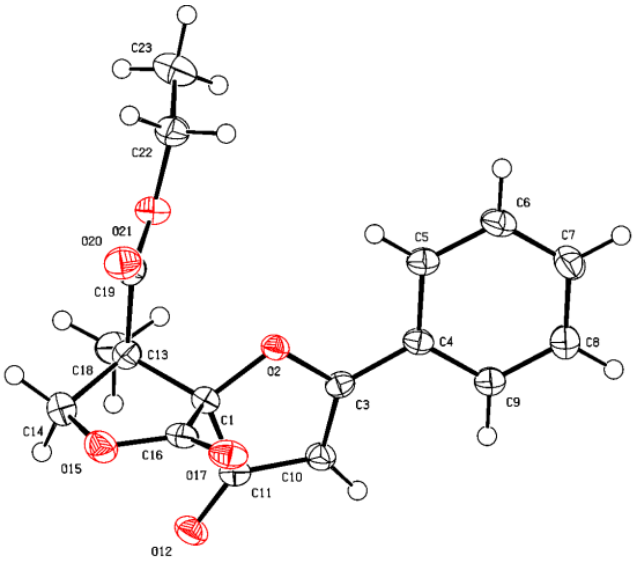


Figure J: *ORTEP of compound* ***356****.*

Empirical formula	$C_{17}H_{16}O_6$	
Formula weight ($gmol^{-1}$)	316.30	
Temperature (K)	120(2)	
Crystal system, space group	Monoclinic, $P2_1$	
Unit cell dimensions	a = 7.83240(10) Å b = 11.7097(2) Å c = 8.8052(2) Å	α = 90 º β = 107.548(2) º γ = 90 º
Volume, V ($Å^3$)	769.99(3)	
Cell formula units, Z	2	
Density (*calc*), D_x (g/cm^3)	1.364	
Absorption coefficient, μ (mm^{-1})	0.873	
$F(000)$	332.0	
Crystal appearance, colouration	Needles, colourless	
Crystal size (mm)	0.249 × 0.087 × 0.046	
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)	
2θ range for data collection (º)	10.538 to 140.152	
Index ranges	-9≤ h ≤9 -14≤ k ≤11 -10≤ l ≤10	
Reflections collected	14409	

Independent reflections	2795 [R_{int} = 0.0254, R_σ = 0.0180]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.958, 0.811
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2795 / 1 / 210
Goodness-of-fit on F^2	1.052
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0225, wR_2 = 0.0566
Final R indexes (all data)	R_1 = 0.0230, wR_2 = 0.0570
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0302P)^2 + 0.0981P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.15, -0.13

(4*R*,5*R*,9*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-9-methyl-9-vinyl-1,7-dioxaspiro[4.4]nonan-6-one 403b

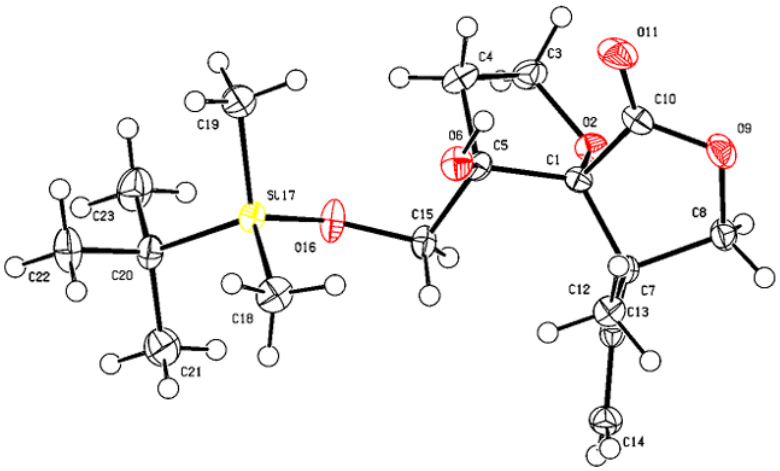


Figure K: *ORTEP of compound* ***403b****.*

Empirical formula	$C_{17}H_{30}O_5Si$
Formula weight (gmol^{-1})	342.50
Temperature (K)	120(2)
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.10120(10) Å α = 90 º b = 7.14460(10) Å β = 90 º c = 43.1076(7) Å γ = 90 º

Volume, V (Å^3)	1879.09(5)
Cell formula units, Z	4
Density (*calc*), D_x (g/cm^3)	1.211
Absorption coefficient, μ (mm^{-1})	1.285
$F(000)$	744.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.278 × 0.118 × 0.098
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	8.204 to 144.968
Index ranges	-7≤ h ≤7 -8≤ k ≤8 -53≤ l ≤52
Reflections collected	29610
Independent reflections	3719 [R_{int} = 0.0319, R_σ = 0.0157]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.882, 0.715
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3719 / 1 / 217
Goodness-of-fit on F^2	1.044
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0237, wR_2 = 0.0619
Final R indexes (all data)	R_1 = 0.0244, wR_2 = 0.0625
H-atom treatment	H-atoms treated with a combination of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0354P)^2 + 0.3413P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.22, -0.13

(-)-Hyperolactone C 5

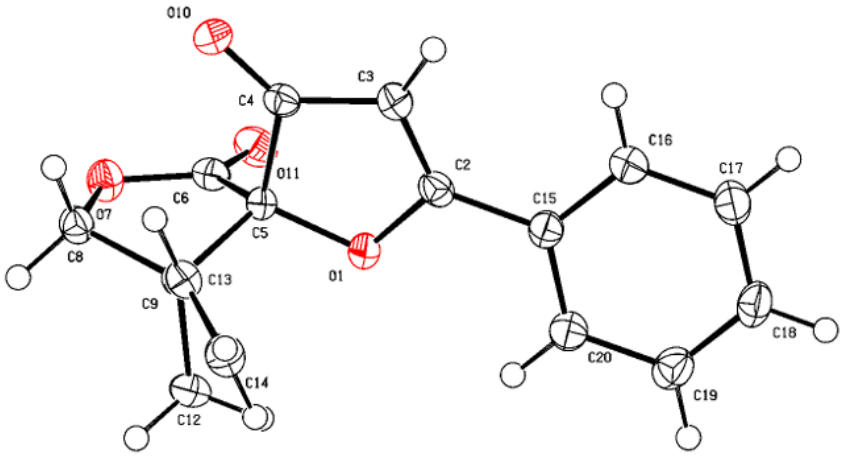


Figure L: *ORTEP of compound* ***5****.*

Empirical formula	$C_{16}H_{14}O_4$
Formula weight ($gmol^{-1}$)	270.27
Temperature (K)	120(2)
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	a = 6.19050(10)Å α = 90 º b = 7.4854(2) Å β = 98.619(2) º c = 14.4453(3) Å γ = 90 º
Volume, V ($Å^3$)	661.81(3)
Cell formula units, Z	2
Density (*calc*), D_x (g/cm^3)	1.356
Absorption coefficient, μ (mm^{-1})	0.805
$F(000)$	284.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.115 × 0.044 × 0.009
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	6.188 to 151.506
Index ranges	-7≤ h ≤7 -9≤ k ≤8 -18≤ l ≤18
Reflections collected	11482
Independent reflections	2549 [R_{int} = 0.0305, R_σ = 0.0236]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.993, 0.913

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2549 / 1 / 182
Goodness-of-fit on F^2	1.100
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0331, wR_2 = 0.0864
Final R indexes (all data)	R_1 = 0.0337, wR_2 = 0.0868
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0430P)^2 + 0.1922P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.22, -0.15

(±)-*cis*-Ethyl 3-((bis(*tert*-butoxycarbonyl)amino)methyl)-3-hydroxy-2-phenyltetrahydrofuran-2-carboxylate 432

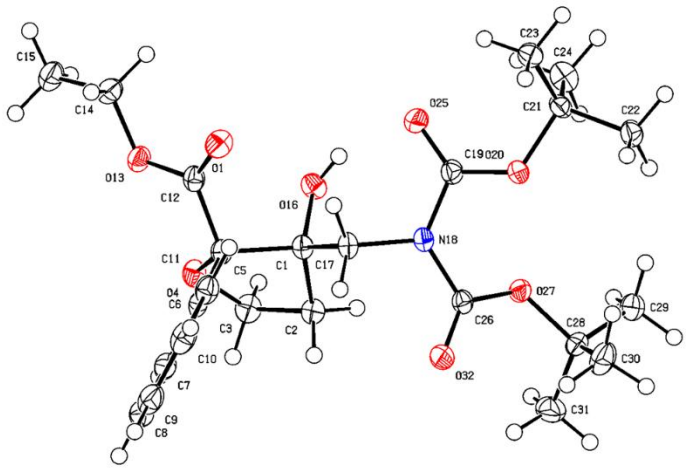


Figure M: *ORTEP of compound* ***432****.*

Empirical formula	$C_{24}H_{35}NO_8$	
Formula weight (gmol^{-1})	465.53	
Temperature (K)	120(2)	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 9.2429(3) Å b = 12.0039(3) Å c = 12.3500(4) Å	α = 75.782(2) º β = 70.269(3) º γ = 74.620(2) º
Volume, V (Å^3)	1225.08(7)	
Cell formula units, Z	2	
Density (*calc*), D_x (g/cm^3)	1.262	

Absorption coefficient, μ (mm^{-1})	0.781
$F(000)$	500.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.772 x 0.156 x 0.111
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	9.328 to 144.736
Index ranges	-11≤ h ≤11 -14≤ k ≤14 -15≤ l ≤15
Reflections collected	19330
Independent reflections	4765 [R_{int} = 0.0240, R_{σ} = 0.0188]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.918, 0.877
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4765 / 1 / 308
Goodness-of-fit on F^2	1.036
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0321, wR_2 = 0.0842
Final R indexes (all data)	R_1 = 0.0364, wR_2 = 0.0883
H-atom treatment	H-atoms treated with a combination of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0481P)^2 + 0.2979P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.35, -0.21

(±)-*cis*-8,8-Dimethyl-1,6,9-trioxadispiro[2.0.44.33]undecan-5-one 343

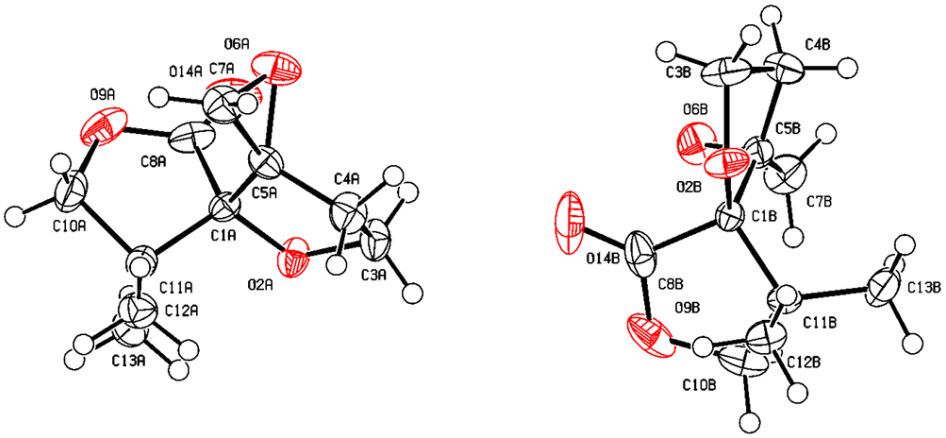


Figure N: *ORTEP of compound* ***343****.*

Empirical formula	$C_{10}H_{14}O_4$
Formula weight (gmol^{-1})	198.21
Temperature (K)	120(2)
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 12.5656(4) Å α = 90 º b = 11.1188(4) Å β = 108.771(3) º c = 14.6628(4) Å γ = 90 º
Volume, V (Å^3)	1939.64(11)
Cell formula units, Z	8
Density (*calc*), D_x (g/cm^3)	1.358
Absorption coefficient, μ (mm^{-1})	0.876
$F(000)$	848.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.161 x 0.109 x 0.05
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	7.43 to 158.608
Index ranges	-15≤ h ≤15 -13≤ k ≤13 -18≤ l ≤18
Reflections collected	41064
Independent reflections	4157 [R_{int} = 0.0354, R_σ = 0.0165]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.958, 0.873

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4157 / 479 / 257
Goodness-of-fit on F^2	1.120
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0894, wR_2 = 0.2878
Final R indexes (all data)	R_1 = 0.0938, wR_2 = 0.2895
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0862P)^2 + 10.6593P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.52, -0.43

(±)-4,4-Dimethyl-2,6-dioxaspiro[4.5]decane-1,10-dione 399

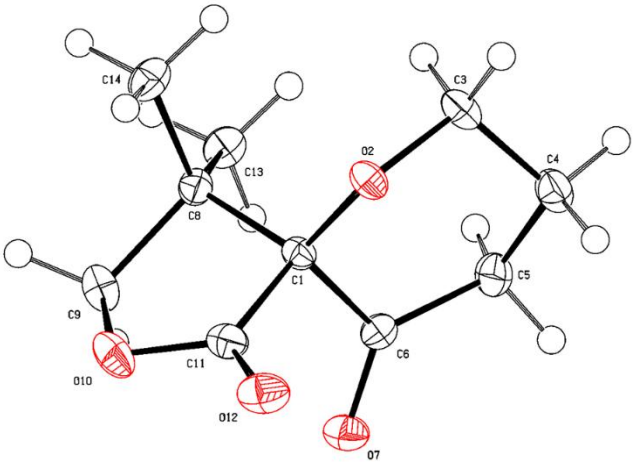


Figure O: *ORTEP of compound* ***399****.*

Empirical formula	$C_{10}H_{14}O_4$
Formula weight (gmol^{-1})	198.21
Temperature (K)	120(2)
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 6.8951(2) Å α = 90 º b = 12.8544(4) Å β = 104.743(4) º c = 10.9405(4) Å γ = 90 º
Volume, V (Å^3)	937.76(6)
Cell formula units, Z	4
Density (*calc*), D_x (g/cm^3)	1.404
Absorption coefficient, μ (mm^{-1})	0.906

$F(000)$	424.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.306 x 0.152 x 0.028
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	10.83 to 144.66
Index ranges	-8≤ h ≤8 -15≤ k ≤15 -13≤ l ≤13
Reflections collected	13559
Independent reflections	1836 [R_{int} = 0.0292, R_{σ} = 0.0146]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.973, 0.766
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1836 / 0 / 129
Goodness-of-fit on F^2	1.048
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0334, wR_2 = 0.0823
Final R indexes (all data)	R_1 = 0.0369, wR_2 = 0.0854
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0400P)^2 + 0.4512P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.34, -0.22

(±)-4,4-Dimethyl-2,6-dioxaspiro[4.5]decane-1,9-dione 412

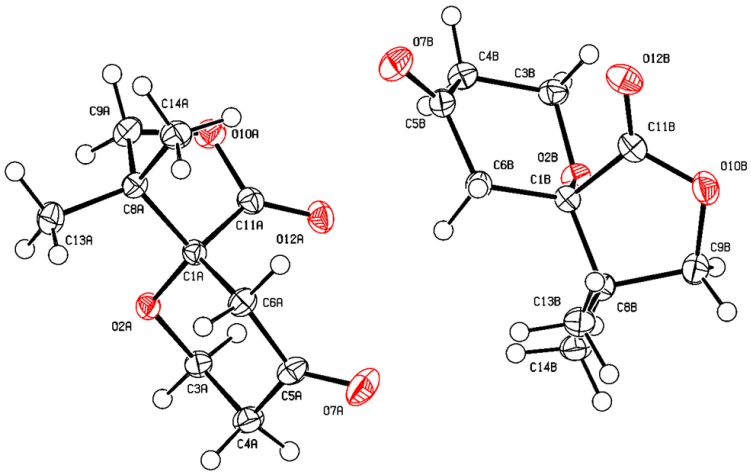


Figure P: *ORTEP of compound* ***412****.*

Empirical formula	$C_{10}H_{14}O_4$
Formula weight (gmol^{-1})	198.21
Temperature (K)	120(2)
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 8.60390(10) Å α = 90 º b = 21.8944(2) Å β = 95.0210(10) º c = 10.59120(10) Å γ = 90 º
Volume, V (Å^3)	1987.49(3)
Cell formula units, Z	8
Density (*calc*), D_x (g/cm^3)	1.325
Absorption coefficient, μ (mm^{-1})	0.855
$F(000)$	848.0
Crystal appearance, colouration	Needles, colourless
Crystal size (mm)	0.1 x 0.1 x 0.02
Radiation source and wavelength, λ (Å)	Cu Kα (λ = 1.54184)
2θ range for data collection (º)	8.076 to 158.466
Index ranges	-10≤ h ≤10 -27≤ k ≤27 -13≤ l ≤13
Reflections collected	25595
Independent reflections	4160 [R_{int} = 0.0337, R_σ = 0.0205]
Absorption correction	Gaussian from crystal shape
Max. and min. transmission [T_{Max}, T_{Min}]	0.983, 0.919

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4160 / 0 / 257
Goodness-of-fit on F^2	1.050
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0329, wR_2 = 0.0837
Final R indexes (all data)	R_1 = 0.0378, wR_2 = 0.0884
H-atom treatment	H-atom parameters constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0396P)^2 + 0.6989P]$ where $P = (F_o^2 + 2Fc^2)/3$
Largest diff. peak and hole (e/Å^3)	0.27, -0.20