Studies Towards the Total Synthesis of (+)-Lophotoxin and Site-selective Modification of the Thiopeptide Anticancer Natural Product Thiostrepton

A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of

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by

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Declaration

The work described in this thesis is entirely my own, except where I have acknowledged help from co-workers or given reference to a published source in the literature.

Johannes C. L. Walker

University of Oxford

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Acknowledgements

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J.C.L.W.
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Abstract

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Chapter 1: Introduction

The isolation, biological activity and importance of the furanocembranoid family of natural products is outlined and a review of synthetic efforts towards their total synthesis provided. Both classical and catalytic methods for the synthesis of polysubstituted furan heterocycles are summarised, with an emphasis on olefin metathesis methods and their impact on the field.

Chapter 2: Methodology Development and Model Studies Towards (+)-Lophotoxin

The development of a temporary-silicon-tether ring-closing metathesis approach to trisubstituted furans is described. The discovery of Brønsted acid and photochemical cyclisation conditions is discussed and the scope of all procedures evaluated. The results of model studies towards to a total synthesis of (+)-lophotoxin are also reported.

Chapter 3: Progress Towards the Total Synthesis of (+)-Lophotoxin

The development of the retrosynthetic strategy and current progress towards a total synthesis of (+)-lophotoxin is discussed. Asymmetric routes to two key fragments are described, along with their union, and the application of the photochemical aromatisation procedure to the furan core of (+)-lophotoxin is disclosed.

Chapter 4: Site-selective Modification of the Thiopeptide Anticancer Agent Thiostrepton

This chapter focusses on a separate project, which aimed to provide synthetic tools to assist in structure-activity investigations of the natural product Thiostrepton. The natural product and its biological activity are introduced along with previous examples of its modification. The development of a general site-selective acylation reaction and the synthesis of a library of analogues is discussed. The results of their biological evaluation is also reported.

Abbreviations and Acronyms

°	Degrees
18c6	1,4,7,10,13,16-hexaoxacyclooctadecane
9-BBN	9-Borabicyclo(3.3.1)nonane
Å	Angstrom
Ac	Acetyl
acac	Acetylacetone
AIBN	Azobisisobutyronitrile
All	Allyloxycarbonyl
app.	Apparent
aq.	Aqueous
atm	Atmospheric pressure
bar	Bar (unit of pressure)
BHT	Butylated hydroxytoluene
bis	Latin: the second instance of
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
bona fide	Latin: genuine
bpy	Bipyridine
Bu	Butyl
Bz	Benzoyl
C	Celcius
c	Concentration
ca. (*circa*)	Latin: approximately
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzoyl
CI	Chemical Ionisation
cm^{-1}	Wavenumber
conc.	Concentrated
Cp	Cyclopentadienyl
CSA	Camphor Sulfonic Acid

Cy	Cyclohexyl
Cys	Cysteine
D	Debye
Da	Dalton
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
De novo	Latin: starting from the beginning
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DIPT	Diisopropyl tartrate
DMAP	4-(Dimethylamino)pyridine
DMDO	Dimethyldioxirane
DME	Dimethyoxyethane
DMF	*N*,*N'*-Dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric Ratio
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
ee	Enantiomeric Excess
EI	Electron Impact Ionisation
eq.	Equivalent(s)
$ESI^{+/-}$	Electrospray Ionisation Positive/Negative Mode
EXSY	Exchange Spectroscopy
Et	Ethyl

FCC	Flash Column Chromatography
g	Gram(s)
h	Hour(s)
hfacac	Hexafluoroacetylacetone
HFIP	Hexafluoroisopropyl
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i-	Iso
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
in situ	Latin: in the original place
in vacuo	Latin: in a vacuum
in vitro	Latin: in the glass (outside a whole organism)
in vivo	Latin: in the living (inside a whole organism)
Pr	Propyl
IPr	1,3-*bis*(2,6-diisopropylphenyl)-imidazolium
J	Coupling constant (Hz)
k_{rel}	Relative rate constant
L	Litre(s)
LDA	Lithium Diispropylamide
m-	Meta
m	Metre(s)
M	Molar ($moldm^{-1}$)
*m*CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl (1,3,5-trimethylphenyl)
min	Minute(s)
MNBA	2-Methyl-6-nitrobenzoic anhydride
mol	Mole(s)

mol%	Mole percent
MOM	Methoxymethyl
MS	Molecular Sieves
n-	Normal
nbd	Norbornadiene
NBS	*N*-Bromosuccinimide
Bu	Butyl
NHC	Nucleophilic heterocyclic carbene
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
o-	Ortho
p-	Para
PDC	Pyridinium Dichromate
Ph	Phenyl
pH	$-\log_{10}[H^+]$
Pin	Pinacol
PMB	*para*-Methoxybenzyl
ppm	Parts per Million
PPTS	Pyridinium *para*-toluenesulfonate
pseudo	Latin: Not Genuine
PTSA	*para*-Toluenesulfonic acid
Py	Pyridyl
quant.	Quantitative
R	Generic Group
rpm	Rotations per Minute
RSM	Recovered Starting Material
rt	Room Temperature
sat.	Saturated
S_EAr	Electrophilic Aromatic Substitution
Ser	Serine

SET	Single Electron Transfer
t-	Tert
TBAF	Tetrabutylammonium Fluoride
TBAI	Tetrabutylammonium Iodide
TBDPS	*t*-Butyldiphenylsilyl
TBHDPBr	Tributylhexadecylphosphonium Bromide
TBHP	*t*-Butyl Hydroperoxide
TBS	*t*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
Thr	Threonine
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
Tol	Tolyl
Trp	Tryptophan
Ts	*para*-Toluenesulfonyl
Tyr	Tyrosine
UV	Ultraviolet
UV/Vis	Ultraviolet–Visible Spectroscopy
via	Latin: By way of
wrt.	With Respect To
wt%	Weight Percent
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
δ	Chemical Shift
λ_{max}	Ultraviolet Absorption Maximum
ν_{max}	Infrared Absorption Maximum

Chapter 1

Introduction

1.1 (+)-Lophotoxin and Related Natural Products

1.1.1 The Furanocembranoid Family of Natural Products

(+)-Lophotoxin (**1**) is a member of the furanocembranoid family of natural products, a large collection of diterpenoid compounds isolated exclusively from marine sources.[1] The family is characterised by a 14-membered carbon skeleton bearing a furan moiety across the *C*-3/6 positions and often a butenolide across the *C*-10/12 positions. Related natural product families, the pseudoteranes and gersolanes feature contracted 12- and 13-membered carbon skeletons respectively (Figure 1.1).

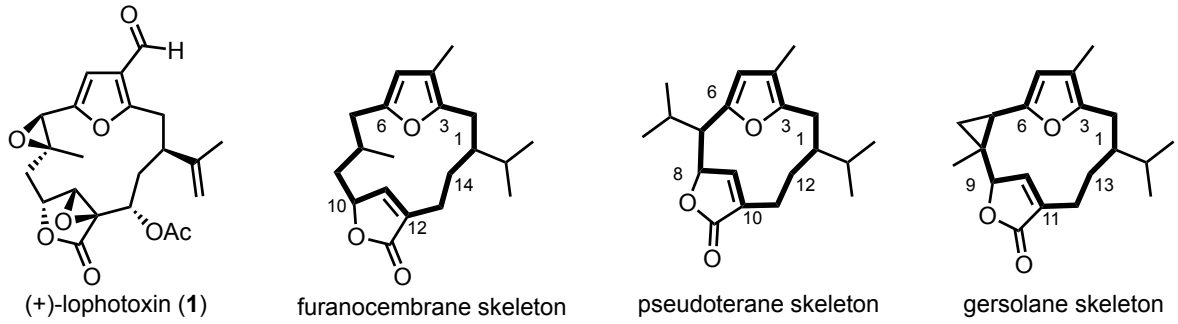


Figure 1.1 (+)-Lophotoxin (**1**) and pertinent natural product family skeletons

The shared carbon framework is diversely oxidised with both unsaturation and oxygenation to provide a plethora of richly functionalised compounds. Within the furanocembranoid cluster, oxygenation at *C*-2, *C*-13, and across the C-7/8 and C-11/12 double bonds are common derivatisations. The furan ring always bears a single-carbon unit either at the methyl, aldehyde or carboxylic acid oxidation state, and an isobutylene unit is ubiquitous at *C*-1, in differing states of oxygenation. The majority of isolated furanocembranoid natural products display (*R*) configuration at *C*-1 although a number are reported to have (*S*) configuration, including (+)-lophotoxin (**1**). However, it is yet to be confirmed whether this is indeed correct. The relative configurations of the compounds are identical in virtually all cases (Figure 1.2).

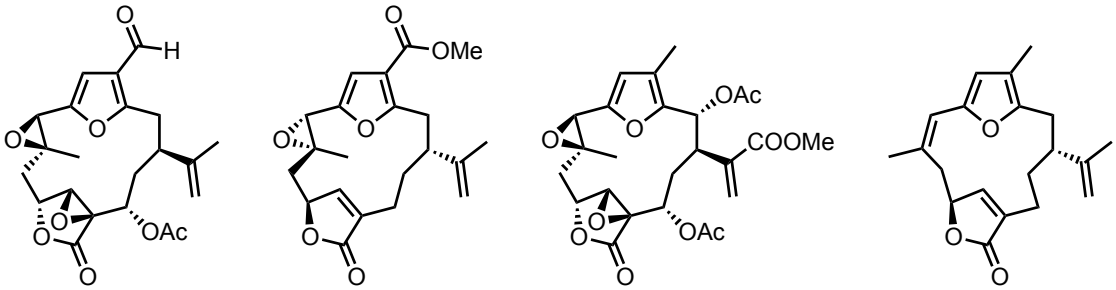


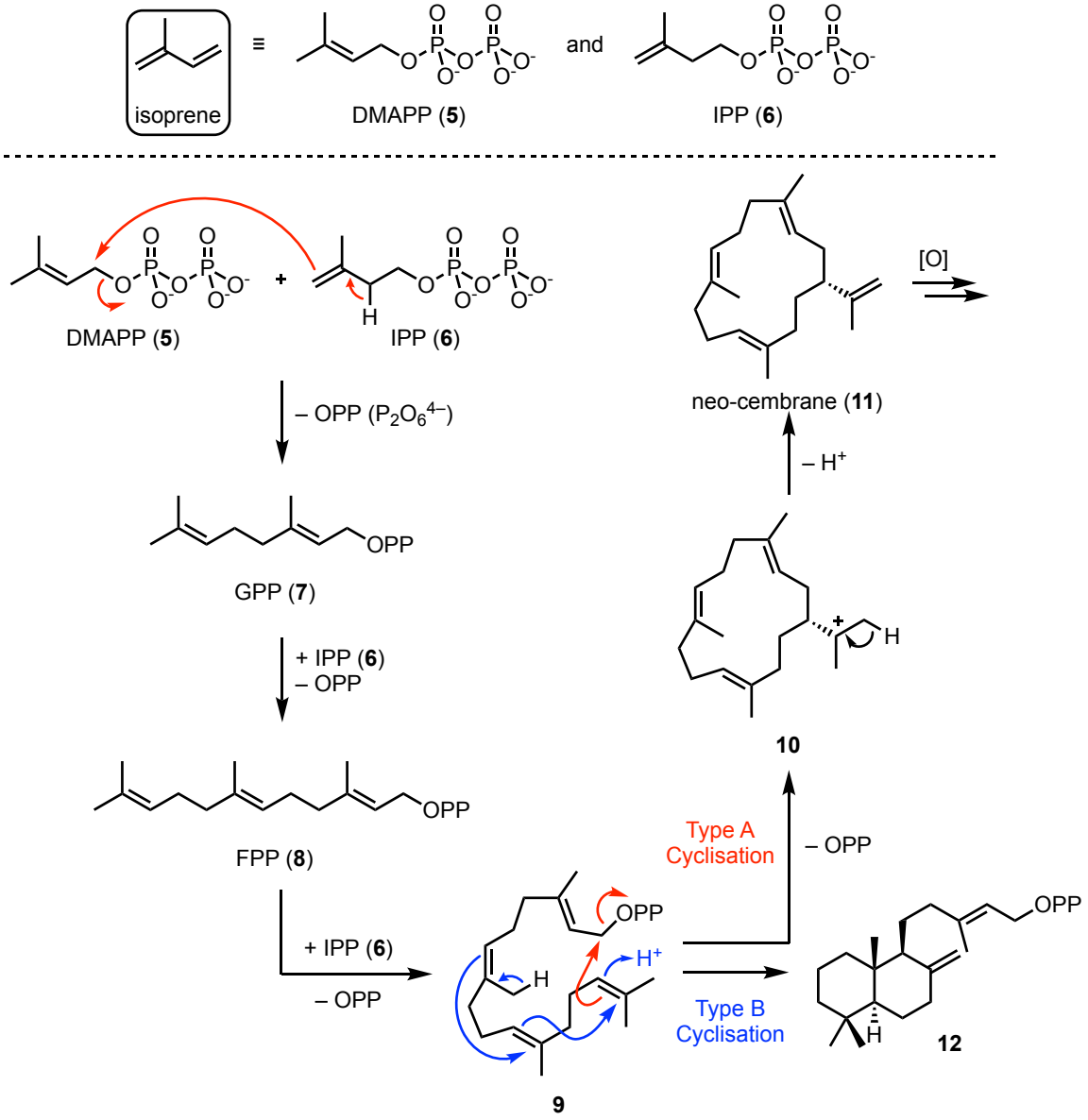
Figure 1.2 Representative examples of furanocembranoid natural products

(+)-Lophotoxin (**1**) itself is a highly oxidised member of the family, possessing epoxides at both *C*-7/8 and *C*-11/12 positions, an acetoxy group at *C*-13 and an aldehyde at *C*-4. It was first isolated by Fenical and co-workers in 1981 from the gorgonian pacific sea whips of the genus *Lophogorgia*.[2] Other notable furanocembranoid natural products include (+)-pukalide (**2**), the founding member of the family, isolated in 1957 by Schreuer and co-workers from the coral *Sinularia abrupta*[3] and (–)-bipinnatin A (**3**), isolated in 1989 from *Pseudopterogorgia bipinnata*.[4] (+)-Rubifolide (**4**), one of the simplest and least oxygenated examples, was isolated in 1987 from *Gersemia rubiformis*.[5]

1.1.2 Biosynthetic Origins of the Furanocembranoids

(+)-Lophotoxin (**1**) is derived from neo-cembrane (**11**, Cembrane A), the 14-membered carbon skeleton common to all furanocembranoid natural products. According to the isoprene rule proposed by Wallach in 1887, this monocyclic diterpene formally consists of four isoprene units.[6,7] Practically, these units take the form of electrophilic dimethylallyl pyrophosphate (**5**, DMAPP) and nucleophilic isopentenyl pyrophosphate (**6**, IPP). These sequentially combine to produce geranyl pyrophosphate (**7**, GPP), farnesyl pyrophosphate (**8**, FPP) and finally geranylgeranyl pyrophosphate (**9**). Macrocyclisation *via* a type A cyclisation transforms **9** into cation **10** and elimination then yields neo-cembrane (**11**). Site-selective enzymat-

ic oxidations furnish the fully elaborated natural product structures. Type B cyclisations typically form smaller rings such as those of labdane skeleton **12** (Scheme 1.1).[1]



Scheme 1.1 Furanocembranoid biosynthesis

1.1.3 Biological Activity of the Furanocembranoids

(+)-Lophotoxin (**1**) is the most well studied furanocembranoid due to its complex chemical structure and compelling biological activity. Fenical and co-workers reported a median lethal dose of 8.0 µg/g in mice and *in vitro* assays demonstrated its irreversible inhibition of voluntary nerve-stimulated muscular contractions.[2] Subsequent work by Fenical, Abramson and others verified that (+)-lophotoxin (**1**) is an irreversible antagonist of nicotinic acetylcholine

receptors.[8] These proteins reside at the neuromuscular junction and control communication between motor nerves and muscles. Unlike other inhibitors of these receptors, (+)-lophotoxin (**1**) neither contains a nitrogen atom nor is positively charged. Radiolabelled (+)-lophotoxin (**1**) was observed to bind covalently to the Tyr^{190} residue in the α-subunit of the receptors[9,10] and structure-activity studies by Abramson and co-workers suggested that the electrophilic *C*-7/8 epoxide could be responsible.[11] Structural alterations at other sites had a limited effect on activity although reduction of butenolide **13** to hemiacetal **14** also resulted in a loss of activity. On the basis of these observations, it was proposed that the binding mode of (+)-lophotoxin (**1**) was similar to that of acetylcholine, involving the Tyr^{190} and nearby Cys^{192} residues of the receptors. The salient interactions are between the electrophilic ester moieties and the thiol of Cys^{192}, and non-covalent bonding between the quaternary nitrogen of acetylcholine, or covalent bonding between the epoxide of (+)-lophotoxin (**1**), and the phenol of Tyr^{190} (Figure 1.3).

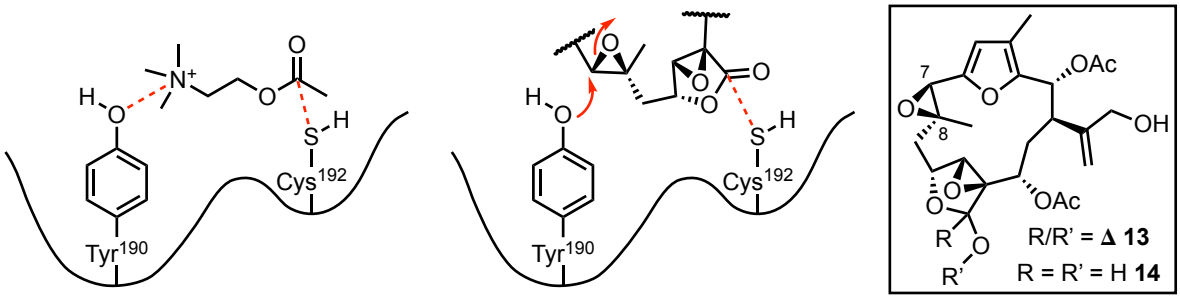


Figure 1.3 Proposed model of binding for acetylcholine and (+)-lophotoxin (**1**) in α-subunit. **Δ** = carbonyl

Other members of the furanocembranoid family have also displayed exciting biological activities. (–)-Lophodiol B has shown cytotoxic activity in human tumour cell lines MDA-MB-231, A-549 and HT-29[12] and (–)-bipinnatin A (**3**) in P-388 marine tumour cell lines.[4] Additionally, Kallolide A has demonstrated anti-inflammatory activity in a mouse ear assay[13] and bielschowskysin exhibited antimalarial activity against *Plasmodium falciparum* and cytotoxicity in non small cell lung and renal cancer cell lines.[14]

1.1.4 Synthetic Efforts Towards (+)-Lophotoxin (1) and Related Natural Products

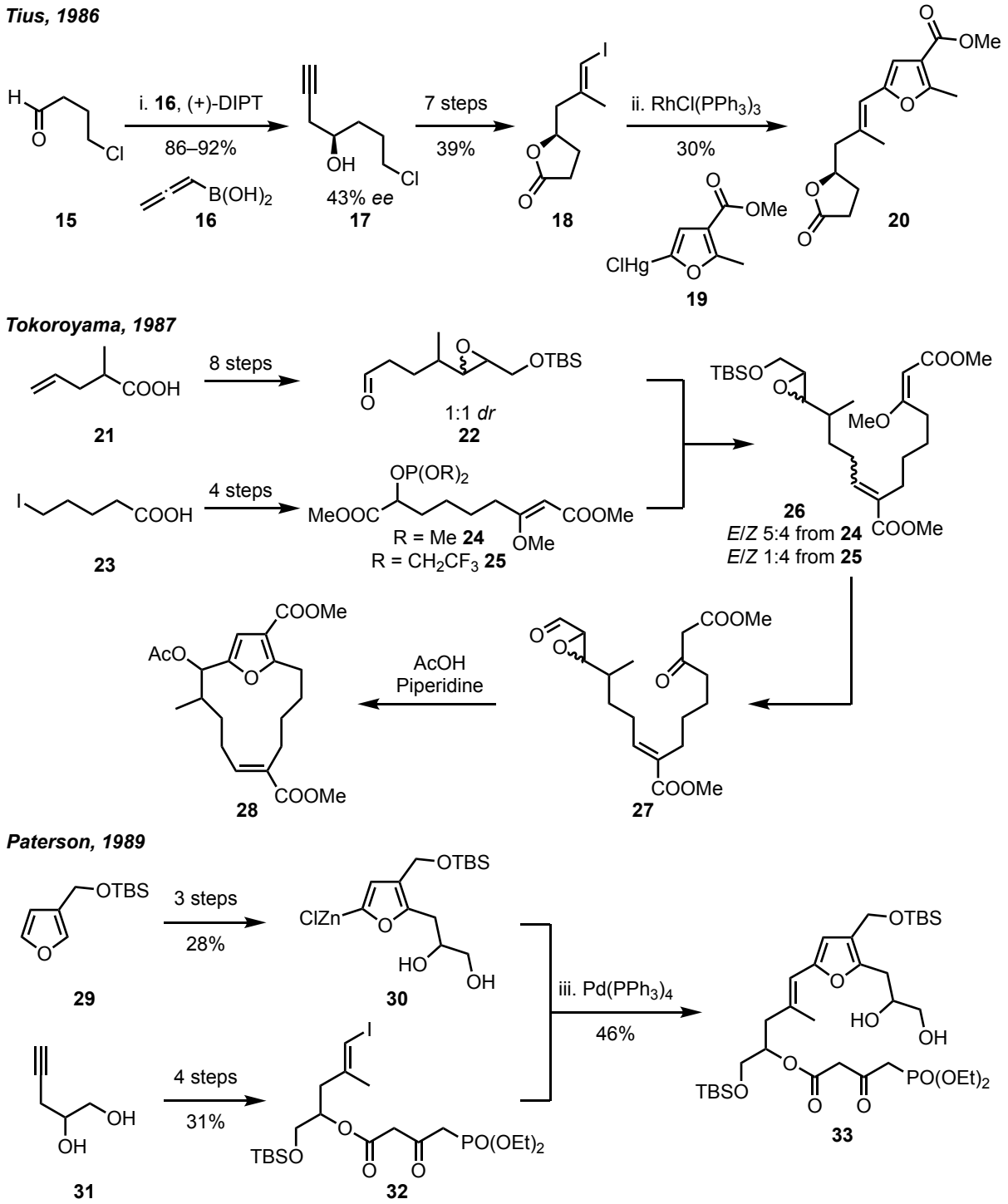
Inspired by its impressive biological activity and complex structure, a considerable amount of effort has been devoted to the total synthesis of (+)-lophotoxin (**1**), although its achievement has not yet been reported. However, a number of fragment syntheses have been disclosed and other furanocembranoid natural products have succumbed to synthesis. These efforts will be discussed in chronological order. Approaches to pseudoterane and gersolane natural products will not be covered to avoid interminable discussion.

1.1.4.1 Synthesis of (+)-Lophotoxin (1) Fragments, 1986–1989

Early work towards (+)-lophotoxin (**1**) focussed on the assembly of fragments that could be incorporated into future syntheses. In 1986, Tius and Trehan reported the first efforts in this area with the preparation of furan **20**.[15] Addition of allenylboronic acid (**16**) to aldehyde **15** produced alcohol **17** in 43% *ee* (unoptimised) which was subsequently elaborated to iodide **18** over 7 steps. The fragment was completed by rhodium(I) catalysed cross-coupling with mercuric furan **19** to give furan **20** in 30% yield.

Tokoroyama and co-workers published the first synthesis of a furanocembranoid like macrocycle in 1987.[16] Horner-Wadsworth-Emmons coupling of aldehyde **22** with phosphonate esters **24** or **25** produced enone **26** as a geometric mixture, the ratio of which was phosphonate dependent. Deprotection of (*E*)-**26** gave β-ketoester **27** and subjection of this to cyclisation conditions developed by Williams and co-workers furnished macrocycle **28**.[17]

In 1989, Paterson and Gardner disclosed the synthesis of a number of intermediates that could be applied to a total synthesis of (+)-lophotoxin (**1**).[18] Their route to furan **33** began from furan **29** and diol **31**. These building blocks were developed to produce furyl zinc **30** and iodide **32**. The furan core was formed using cross-coupling chemistry, this time employing a Negishi coupling to furnish furan **33** in 46% yield (Scheme 1.2).

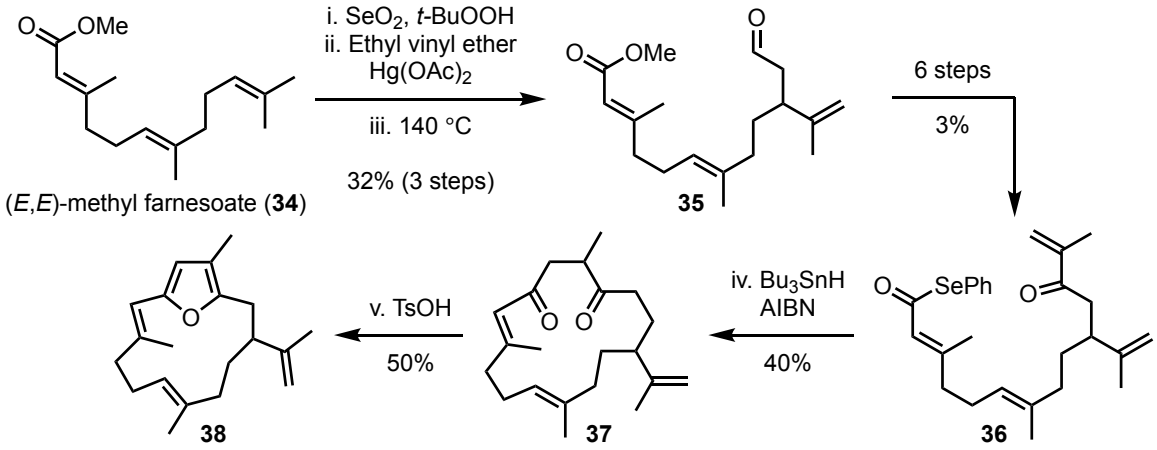


Scheme 1.2 Synthesis of (+)-lophotoxin (**1**) fragments. Selected reagents and conditions: i) **16**, (+)-DIPT, PhMe, –78 °C, 40 h, 86–92%; ii) **19**, $RhCl(PPh_3)_3$, LiCl, HMPA, 70 °C, 30%; iii) $Pd(PPh_3)_4$, THF, rt, 4 h, 46%. Detailed reaction conditions for Tokoroyama's route to **28** were not reported

1.1.4.2 Pattenden Synthesis of Furanocembranoid Carbon Skeleton 38, 1992

In 1992, Pattenden and Astley reported the development of an acyl radical macrocyclisation strategy to access furanocembrane skeleton **38**.[19,20] Starting from (*E*,*E*)-methyl farnesoate

(**34**), aldehyde **35** was synthesised over 3 steps *via* SeO_2 oxidation and a Claisen rearrangement. Six further steps provided key selenyl ester **36**. Formation of the acyl radical and macrocyclising conjugate addition gave diketone **37** and acid mediated condensation subsequently afforded furanocembrane skeleton **38** in 20% yield over two steps (Scheme 1.3).

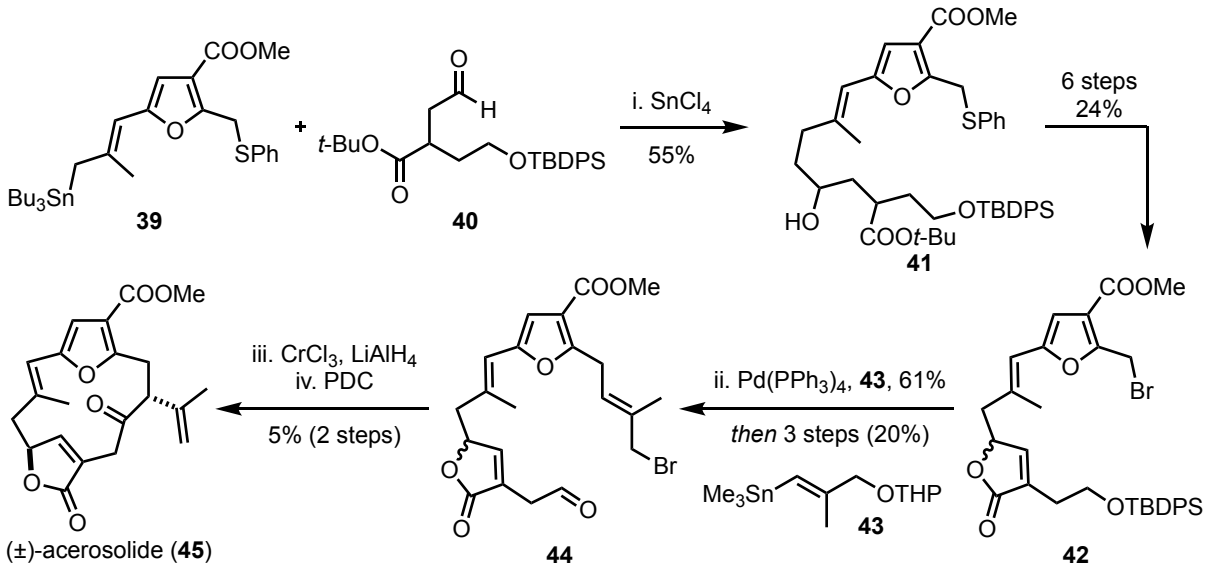


Scheme 1.3 Pattenden synthesis of furanocembrane skeleton **38**. Selected reagents and conditions: i) SeO_2, *t*-BuOOH, CH_2Cl_2, 0 °C to rt, 1 h, 42%; ii) Ethyl vinyl ether, $Hg(OAc)_2$, reflux, 16 h, 79%; iii) 140 °C, 2 h, 97%; iv) Bu_3SnH, AIBN, benzene, reflux, 5 h, 40%; v) TsOH, $CHCl_3$, reflux, 3.5 h, 50%

1.1.4.3 Paquette Synthesis of (±)-Acerosolide (45), 1993

The first furanocembranoid-like natural product to be prepared in the laboratory was the pseudoterane gorgiacerone, synthesised by Paquette and co-workers in 1992.[21] They subsequently disclosed the completed synthesis of (±)-acerosolide (**45**), the first 14-membered furanocembranoid to succumb to synthesis.[22] Their route began from allyl stannane **39**, used in the synthesis of gorgiacerone, and aldehyde **40**. Addition of $SnCl_4$ to **39** facilitated 1,3-transposition of the stannane group and subsequent addition into aldehyde **40** afforded alcohol **41** in 55% yield as an inconsequential mixture of diastereomers. The butenolide and alkyl bromide functionalities were then installed over 6 steps before completion of the carbon skeleton. Stille reaction with stannane **43** afforded furan **44** in 61% yield and subsequent deprotection of the primary alcohols and functional group interconversion set the stage for the key macrocyclising Nozaki coupling reaction. Using $CrCl_2$, formed *in situ* from $CrCl_3$ and $LiAlH_4$, in-

tramolecular metalloene addition of the allyl bromide into the aldehyde moiety and oxidation of the resulting diastereomeric mixture produced (±)-acerosolide (**45**) as a single diastereomer in 5% yield over 2 steps. The isobutylene group was assumed to isomerise to the more stable diastereomer under the oxidation conditions and the spectral data for this compound were identical to those reported for the authentic sample (Scheme 1.4).

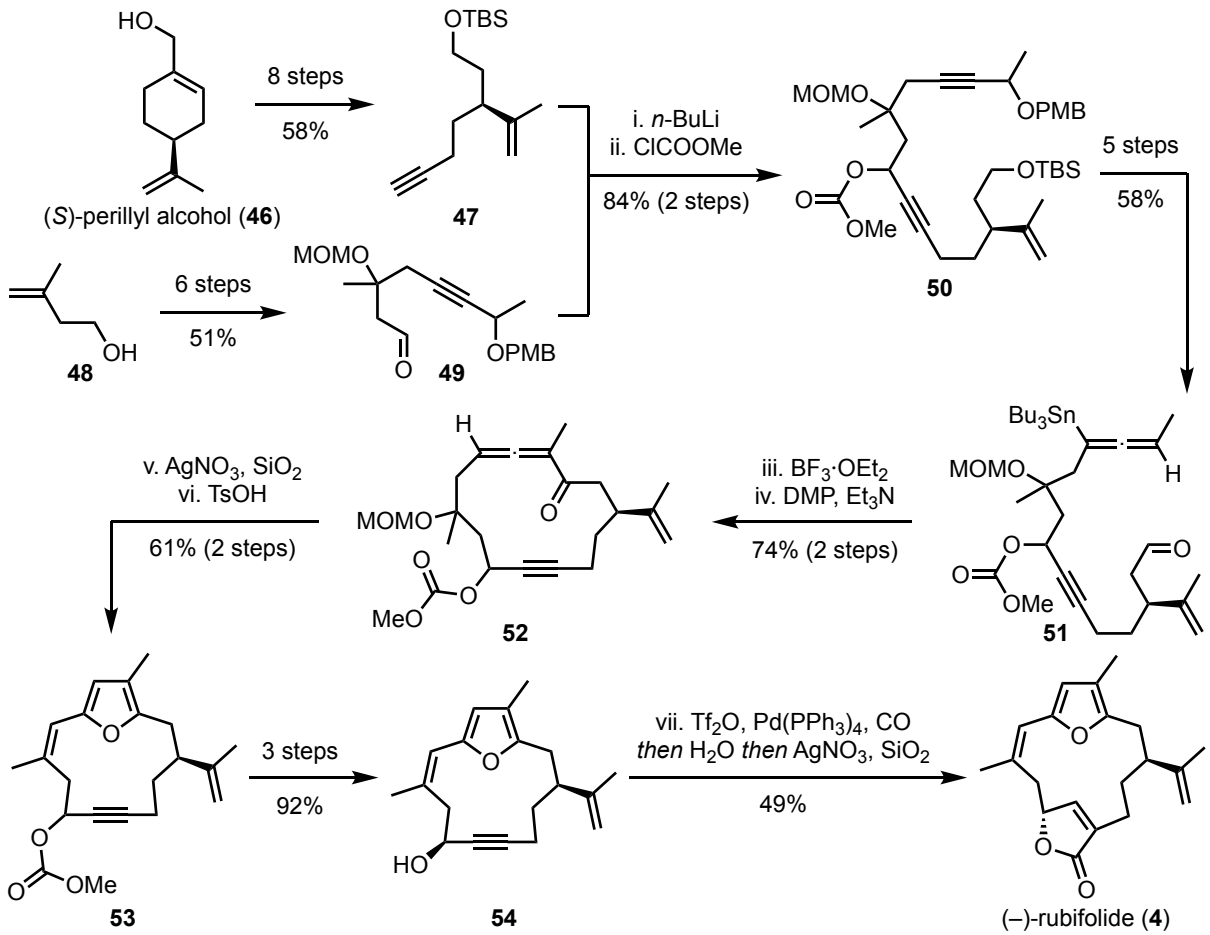


Scheme 1.4 Paquette synthesis of (±)-acerosolide (**45**). Selected reagents and conditions: i) $SnCl_4$, THF, –78 °C, 90 min, 55%; ii) **43**, $Pd(PPh_3)_4$, $CHCl_3$, reflux, 48 h, 65%; iii) $CrCl_3$, $LiAlH_4$, THF, 0 °C, 1 h *then* **44**, rt, 36 h, 20%; iv) PDC, 4Å MS, DMF, rt, 2 h, 25%

1.1.4.4 Marshall Synthesis of (–)-Rubifolide (4), 1997

Synthetic strategies towards pseudoteranes (–)-kallolide B[23] and (+)-kallolide A[24] were described by Marshall and co-workers in 1996 and 1998 respectively. In between these reports, they disclosed the first successful synthesis of the furanocembranoid (–)-rubifolide (**4**).[25] Key to their success was the "furan-last" approach employed, forming the macrocyclic skeleton prior to installation of the sensitive furan and butenolide moieties. Beginning from (*S*)-perillyl alcohol (**46**), alkyne **47** was accessed in 8 steps before being coupled with aldehyde **49** (6 steps from alcohol **48**). Protection of the propargyl alcohol which resulted from acetylide addition provided carbonate **50** in 84% yield over two steps. Transformation into allenylstannane **51** was then achieved in 58% yield over 5 steps. Macrocyclisation *via* intramolecular

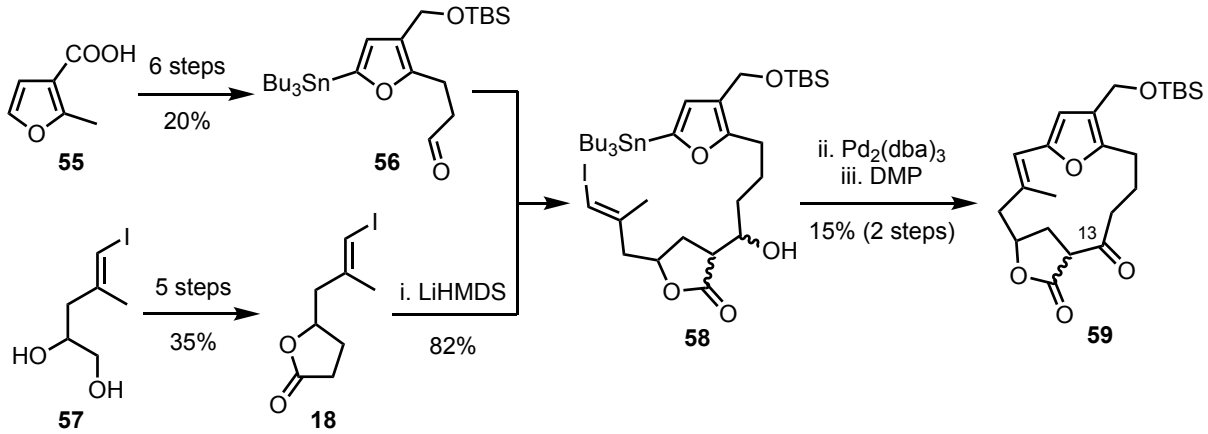
addition of the allenylstannane into the aldehyde moiety produced ketone **52** as a mixture of up to 8 diastereomers after oxidation and base mediated isomerisation to the allene. Treatment with $AgNO_3$ on silica effected the key intraannular furan formation, and subsequent elimination of the MOM protected alcohol was selective for the (*E*) olefin to give furan **53** in 61% over 2 steps. Carbonate deprotection and oxidation followed by facially selective reduction of the resulting ketone produced alcohol **54** as a single enantiomer. Butenolide formation was then achieved using a stereoselective Pd catalysed carbonylation to the allenic acid followed by lewis acid mediated cyclisation to provide (–)-rubifolide (**4**) in 49% yield. The specific rotation measured was equal but opposite to that reported, confirming the previously unknown absolute stereochemistry of the natural product (Scheme 1.5).



Scheme 1.5 Marhsall synthesis of (–)-rubifolide (**4**). Selected reagents and conditions: i) **47**, *n*-BuLi, THF, –78 °C, 1 h *then* **49**, rt, 10 min, 87%; ii) *n*-BuLi, ClCOOMe, THF, –78 °C to rt, overnight, 98%; iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, overnight; iv) DMP, CH_2Cl_2, rt, 30 min *then* Et_3N, rt, 6 h, 74% (2 steps); v) $AgNO_3$ on SiO_2, hexane, rt, 7 h, 84%; vi) TsOH, CH_2Cl_2, rt, 13 min, 73%; vii) $Pd(PPh_3)_4$, 2,6-lutidine, CO, THF, 0 °C *then* Tf_2O *then* H_2O, rt, 15 min *then* $AgNO_3$ on SiO_2, hexane, rt, 3 h, 49% (2 steps)

1.1.4.5 Paterson Synthesis of 14-Membered Furanocembranoid Skeleton 59, 1999

Building on their previous work, Paterson and co-workers published the synthesis of furan **59** in 1999, including oxygenation at *C*-13 for the first time.[26] Aldehyde **56** was synthesised from furan **55** in 6 steps and lactone **18** in 5 steps from diol **57**. An aldol reaction between lactone **18** and aldehyde **56** then furnished macrocycle precursor **58** in 82% yield. Macrocyclisation was effected using a Stille reaction; use of Farina conditions[27] followed by oxidation afforded furan **59** in 15% yield over two steps (Scheme 1.6).



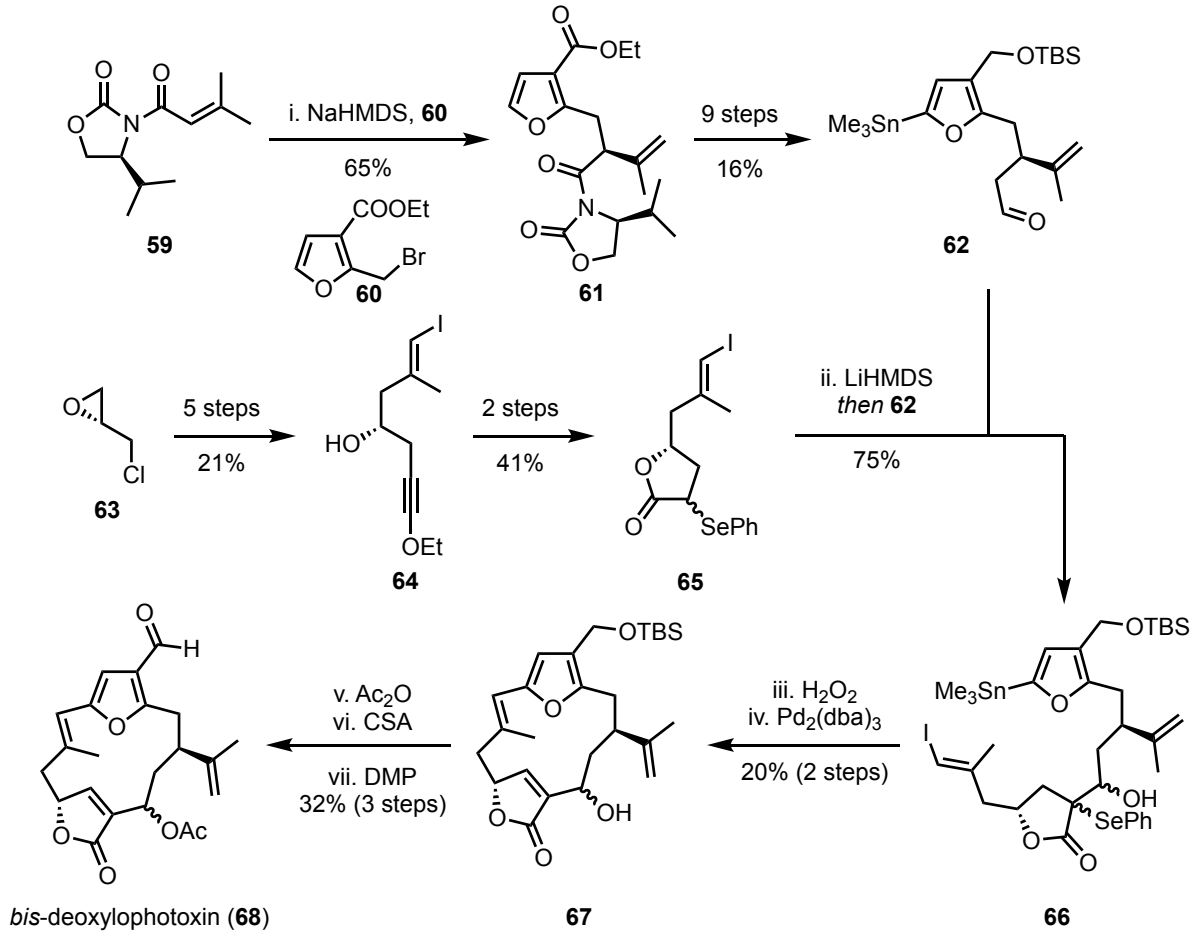
Scheme 1.6 Paterson synthesis of macrocycle **59**. Selected reagents and conditions: i) LiHMDS, THF, –78 °C, 5 min *then* **56**, 30 min, 82%; ii) $Pd_2(dba)_3$, $AsPh_3$, NMP, 40 °C, 24 h; iii) DMP, CH_2Cl_2, 40 min, 15% (2 steps)

1.1.4.6 Pattenden Synthesis of *bis*-Deoxylophotoxin (68), 2001

In 2001, Pattenden and co-workers reported the synthesis of *bis*-deoxylophotoxin (**68**), accessing for the first time a furanocembranoid skeleton at the equivalent oxidation state to (+)-lophotoxin (**1**).[28] Despite initially attempting to employ their acyl radical macrocyclisation strategy, they found this to be incompatible with the more functionally diverse framework and as such pursued an approach similar to that used by Paterson and co-workers, with sequential aldol and Stille reactions forging the macrocycle.[29] The left hand fragment was synthesised in 7 steps from (*R*)-epichlorohydrin (**63**) with the butyrolactone moiety being formed by hydrolysis of alkyne **64**. The right hand fragment was accessed in 10 steps from amide **59**. Deprotonation to the extended enolate and diastereoselective alkylation with bromide **60** set the *C*-1

stereocentre and gave furan **61** in 65% yield. After a further 9 steps, aldehyde **62** was produced in 16% overall yield.

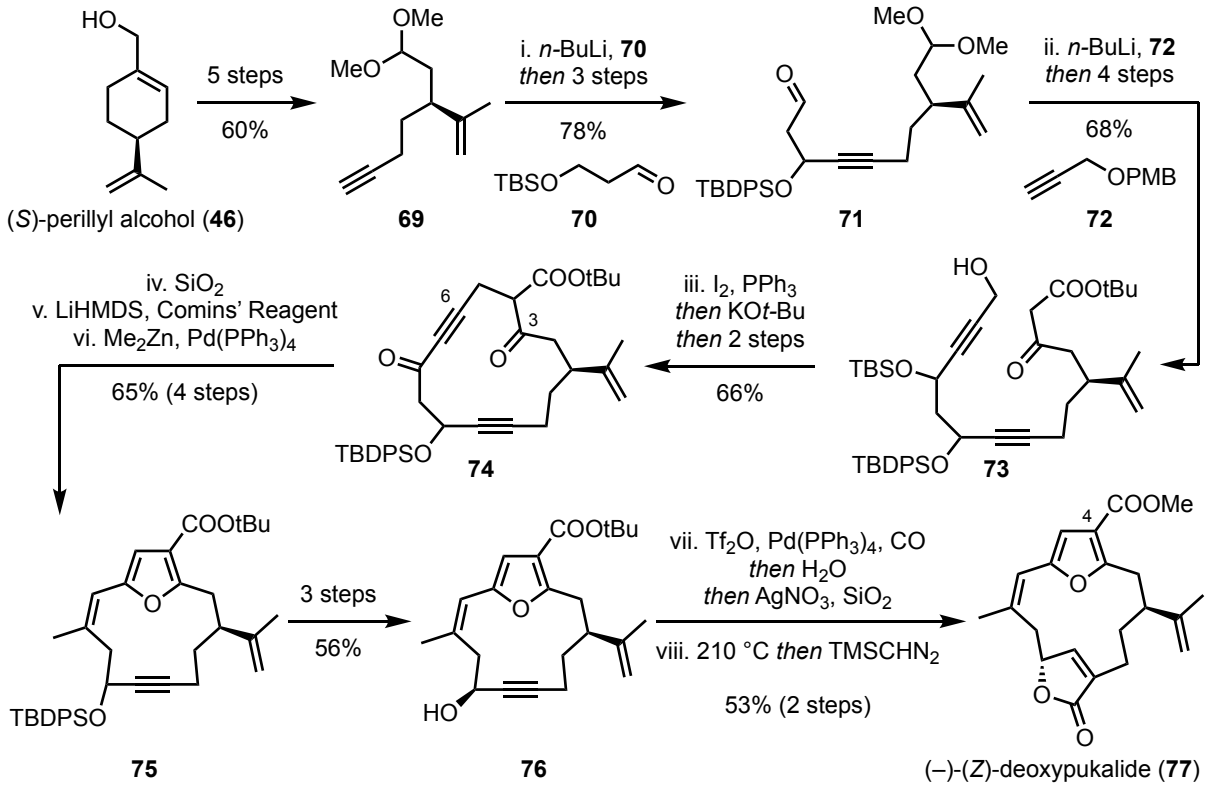
The two-stage macrocyclisation process began with an aldol reaction between lactone **65** and aldehyde **62** to provide aldol adduct **66** in 75% yield from which oxidative selenyl elimination afforded the butenolide moiety. Macrocyclisation was then accomplished using a Stille reaction (Farina conditions), producing macrocycle **67** in 20% yield over two steps as a mixture of diastereomers (revealed to be 2.3:1 after acylation). The synthesis was completed by deprotection of the TBS group and oxidation to afford *bis*-deoxylophotoxin (**68**) as a 2:1 mixture of diastereomers in 32% yield over 3 steps (Scheme 1.7).



Scheme 1.7 Pattenden synthesis of *bis*-deoxylophotoxin (**68**). Selected reagents and conditions: i) NaHMDS, THF, –78 °C, 1 h *then* **60**, –20 °C, 4 h, 65%; ii) LiHMDS, THF, –78 °C, 20 min *then* **62**, 50 min, 75%; iii) H_2O_2, CH_2Cl_2/pyridine, rt, 1 h; iv) $Pd_2(dba)_3$, $AsPh_3$, NMP, 40 °C, 16 h, 20% (2 steps); v) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 5 h, 40%; vi) CSA, MeOH:CH_2Cl_2, 0 °C, 3 h; vii) DMP, pyridine, CH_2Cl_2, 0 °C, 3 h, 80% (2 steps)

1.1.4.7 Marshall Synthesis of (–)-(*Z*)-Deoxypukalide (77), 2001

In another demonstration of their "furan-last" strategy, Marshall and co-workers disclosed the synthesis of (–)-(*Z*)-deoxypukalide (**77**).[30] This is structurally identical to their earlier target, (–)-rubifolide (**4**), with the exception of the methyl ester substituent, rather than methyl, at the *C*-4 position. Even this small structural difference necessitated a slight change in approach, with the allenyl intermediates used previously determined to be too unstable when substituted with an ester group. The synthesis began from (*S*)-perillyl alcohol (**46**), initially leading to alkyne **69** in 5 steps (60% yield). Alkylation with aldehyde **70** furnished internal alkyne **71** in 78% yield after protecting group manipulation. Addition of alkyne **72** followed by installation of the *t*-butyl ester then provided β-ketoester **73** in 68% yield (Scheme 1.8).



Scheme 1.8 Marshall synthesis of (–)-deoxypukalide (**77**). Selected reagents and conditions: i) *n*-BuLi, THF, –50 °C, 1 h *then* LiBr, –78 °C, **70**, 1 h, 84%; ii) **72**, *n*-BuLi, THF, –50 °C, 1 h *then* LiBr, –78 °C, **71**, 1 h, 88%; iii) I_2, PPh_3, imidazole, Et_2O:benzene (3:1), rt, 45 min *then* KO*t*-Bu, THF, –78 °C to rt, overnight, 83% (2 steps); iv) SiO_2, hexane, rt, 16 h, 96% (2 steps); v) LiHMDS, *N*-(5-Chloro-2-pyridyl)*bis*(trifluoromethanesulfonimide), THF:HMPA (5:1), –78 °C to rt, 1 h, 75%; vi) Me_2Zn, $Pd(PPh_3)_4$, THF, 0 °C to rt, overnight, 91%; vii) $Pd(PPh_3)_4$, 2,6-lutidine, CO, THF, 0 °C *then* Tf_2O *then* H_2O, rt, 1 h *then* $AgNO_3$ on SiO_2, hexane, rt, overnight, 58%; viii) 210 °C, 20 min *then* $TMSCHN_2$, MeOH, rt, 15 min, 92%

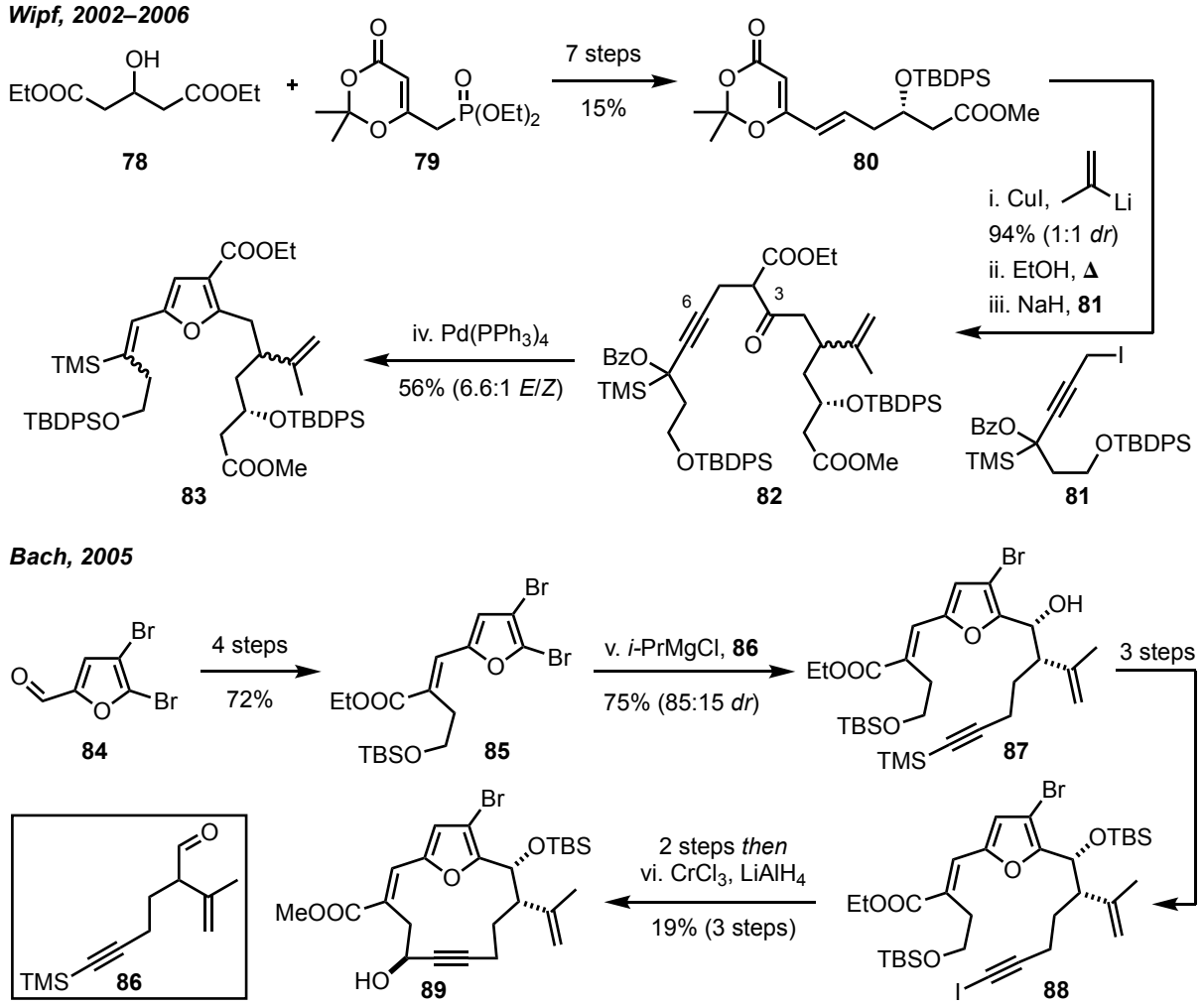
In the modified approach, macrocyclisation was effected by intramolecular alkylation of the β-ketoester. On treatment of ketone **74** with silica, the furan core could finally be installed in 96% yield *via* conjugate addition of the *C*-3 ketone to the *C*-6 position of the alkyne. Conversion of the resulting ketone to a vinyl triflate with Comins' reagent followed by Negishi coupling with Me_2Zn selectively provided the less strained, but unnatural, (*Z*) isomer of macrocycle **75**. The synthesis was completed by stereoselective Pd catalysed butenolide formation and subsequent transesterification *via* pyrolysis and methylation to produce (–)-(*Z*)-deoxypukalide (**77**) in 53% yield over two steps. The specific rotation was found to be equal, but opposite, to the natural product.

1.1.4.8 Model Studies by Wipf and Bach, 2002–2006

Across two reports, Wipf and co-workers disclosed their efforts in synthesising the furan core of (+)-lophotoxin (**1**) using their palladium catalysed synthesis of 2-alkenyl furans.[31,32] These investigations culminated in the synthesis of furan **83**.[33] Diester **78** was desymmetrised and elaborated to dienone **80** in 7 steps which included a Horner-Wadsworth-Emmons olefination with phosphonate ester **79**. The isopropene unit was installed without stereocontrol by 1,6-addition of isopropenyl cuprate. Following thermal unveiling of the β-ketoester, NaH deprotonation facilitated alkylation with iodide **81** to furnish alkyne **82** in 77% yield over two steps. The furan core was formed in a conceptually similar approach to that used by Marshall in the synthesis of (–)-deoxypukalide (**77**); palladium catalysis mediated the formal addition of the *C*-3 ketone to the *C*-6 alkyne giving furan **83** in 56% yield and as a 6.6:1 (*E*:*Z*) ratio of isomers.

In 2005, Bach and co-workers disclosed the first investigations towards the furanocembranoid bipinnatin J (**97**).[34] The key step involved regioselective *C*-2 Br–Mg exchange of furan **85** (4 steps from aldehyde **84**) followed by alkylation with aldehyde **86** to give alcohol **87** in 75% yield and 85:15 *dr* in favour of the *syn* diastereomer. Elaboration to iodide **88** was followed

by TBS removal and oxidation to set up the macrocylising Nozaki coupling reaction which afforded macrocycle **89** in 19% yield over 3 steps (Scheme 1.9)

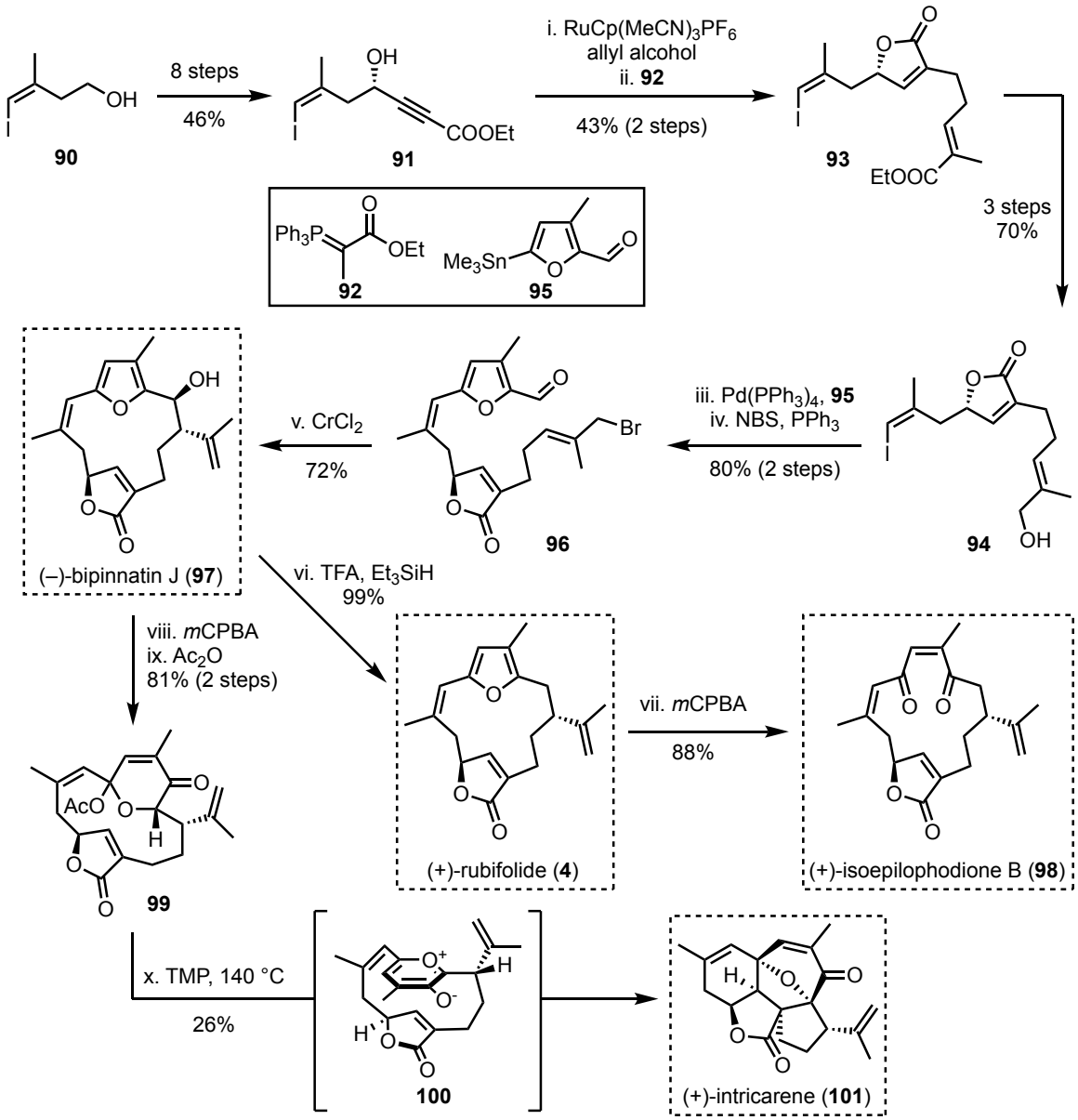


Scheme 1.9 Independent model studies by Wipf and Bach. Selected reagents and conditions: i) CuI, 2-lithiopropene, TMSCl, THF, –20 °C, 16 h, 94%; ii) EtOH, PhMe, reflux, 1.5 h; iii) NaH, THF, 0 °C, 20 min *then* **81**, 0 °C to rt, overnight, 77% (2 steps); iv) $Pd(PPh_3)_4$, $NaOAc{\cdot}3H_2O$, 2,6-lutidine, $MeCN{:}H_2O$ (10:1), 87 °C, 2 h, 56%; v) *i*-PrMgCl, THF, –35 °C *then* **86**, 75%; vi) $CrCl_3$, $LiAlH_4$, THF, 0 °C to rt, 3 h, 19%

1.1.4.9 Trauner Synthesis of (–)-Bipinnatin J (97), 2006

Trauner and co-workers successfully completed the synthesis of (–)-bipinnatin J (**97**) in 2006.[35] Starting from alcohol **90**, ester **91** was synthesised in 46% yield over 8 steps. A ruthenium catalysed Alder-ene type reaction enabled formation of the butenolide and subsequent Wittig olefination of the pendent aldehyde installed the acrylate moiety of ester **93**. Redox manipulations led to alcohol **94** and a Stille coupling with furyl stannane **95** then produced

furan **96**. Macrocyclisation was performed using a diastereoselective Nozaki reaction and (–)-bipinnatin J (**97**) was isolated as a single diastereomer in 72% yield (Scheme 1.10).



Scheme 1.10 Trauner syntheses of (–)-bipinnatin J (**97**), (+)-rubifolide (**4**), (+)-isoepilophodione B (**98**) and (+)-intricarene (**101**). Reagents and conditions: i) allyl alcohol, CSA, $RuCp(MeCN)_3PF_6$, THF:acetone (2:1), 50 °C, 1.5 h, 52%; ii) **92**, CH_2Cl_2, rt, 5 h, 84%; iii) **95**, $Pd(PPh_3)_4$, CuI, CsF, DMF, rt, 20 min, 92%; iv) NBS, PPh_3, CH_2Cl_2, –5 °C, 20 min, 87%; v) $CrCl_2$, 4Å MS, THF, rt, 16 h, 72%; vi) TFA, Et_3SiH, CH_2Cl_2, 0 °C, 20 min, 91%; vii) *m*CPBA, CH_2Cl_2, 0 °C, 88%; viii) *m*CPBA, CH_2Cl_2, 0 °C; ix) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 2 h, 81% (2 steps); x) TMP, DMSO, 140 °C, 16 h, 26%

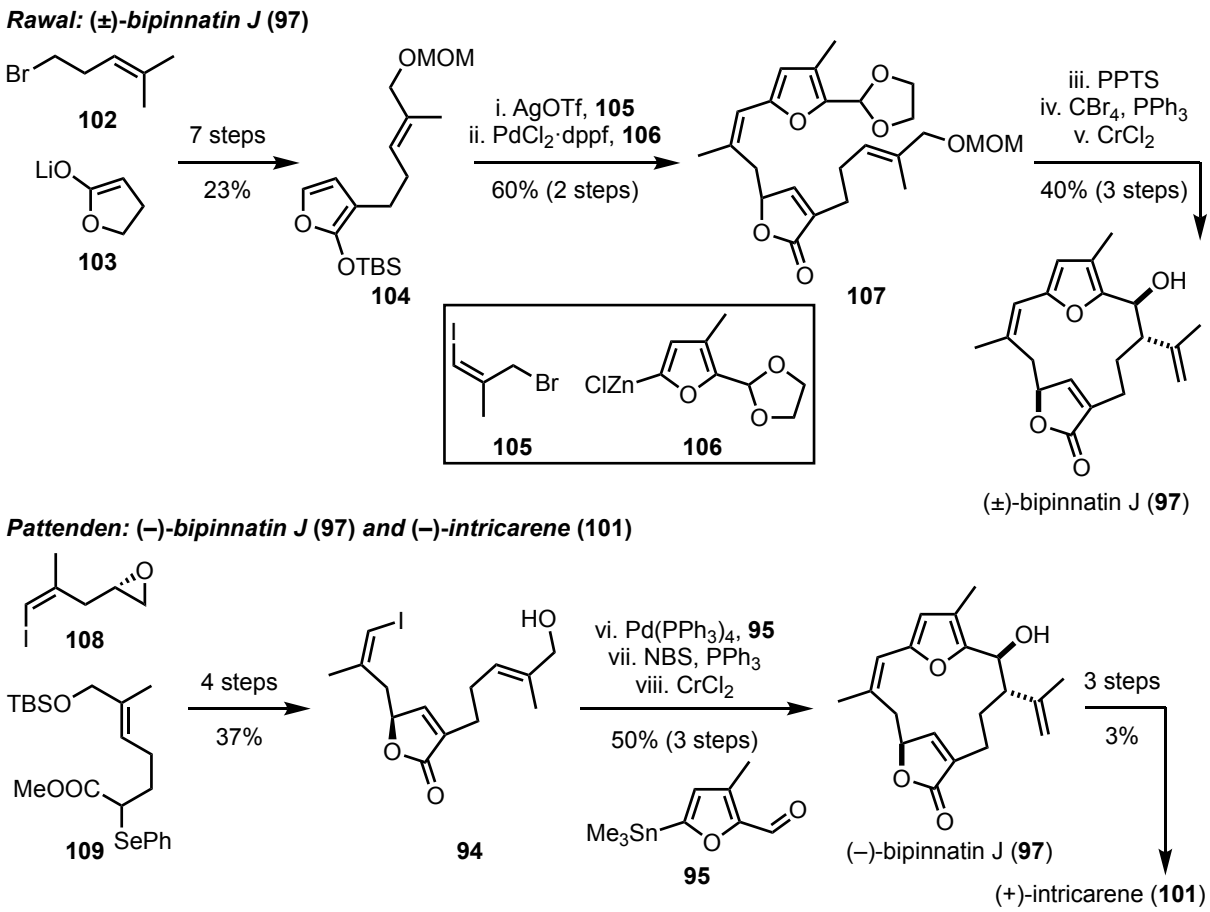
Further manipulation of **97** enabled the synthesis of additional natural products. Reduction of the *C*-2 alcohol produced (+)-rubifolide (**4**, natural enantiomer) and the susceptibility of the furan to oxidation was elegantly exploited to provide (+)-isoepilophodione (**98**) in 88% yield. In the same publication, a biomimetic approach to (+)-intricarene (**101**) was also described.

Oxidation of the furan moiety of (–)-bipinnatin J (**97**) and acylation of the resulting hemiacetal gave acetal **99**. Base mediated elimination then provided pyrilium ion **100** which underwent an *in situ* [5+2] dipolar cycloaddition to afford (+)-intricarene (**101**) in 26% yield. The authors later published further studies into modifications of the (+)-rubifolide (**4**) skeleton to access members of the coralloidolide sub-family of the furanocembranoids; many of these routes involved substantial rearrangement of the carbon skeleton and will not be discussed further.[36]

1.1.4.10 Rawal and Pattenden Syntheses' of Bipinnatin J (97), 2006

Similar approaches to (±)- and (–)-bipinnatin J (**97**) were reported in the same year by Rawal[37] and Pattenden respectively.[38] Rawal began from bromide **102** and lithium alkoxide **103**, initially forming furan **104** in 7 steps. Attachment of allyl bromide **105** *via* an S_N2 reaction and a Negishi coupling with furyl zinc **106** then provided macrocycle precursor **107**. A diastereoselective Nozaki reaction was again used to effect macrocyclisation with (±)-bipinnatin (**97**) successfully isolated as a single diastereomer in 40% yield over 3 steps.

In their route to (–)-bipinnatin J (**97**), Pattenden and co-workers began from epoxide **108**, used in their earlier synthesis of *bis*-deoxylophotoxin (**68**). Epoxide opening with the enolate generated from ester **109** and subsequent oxidative selenyl elimination furnished butenolide **94** in 37% over 4 steps. The final steps to (–)-bipinnatin J (**97**) mirrored those used previously and proceeded in 50% yield over 3 steps. Elaboration to (+)-intricarene (**101**) following the route established by Trauner was also achieved, but in much lower yield (Scheme 2.11).

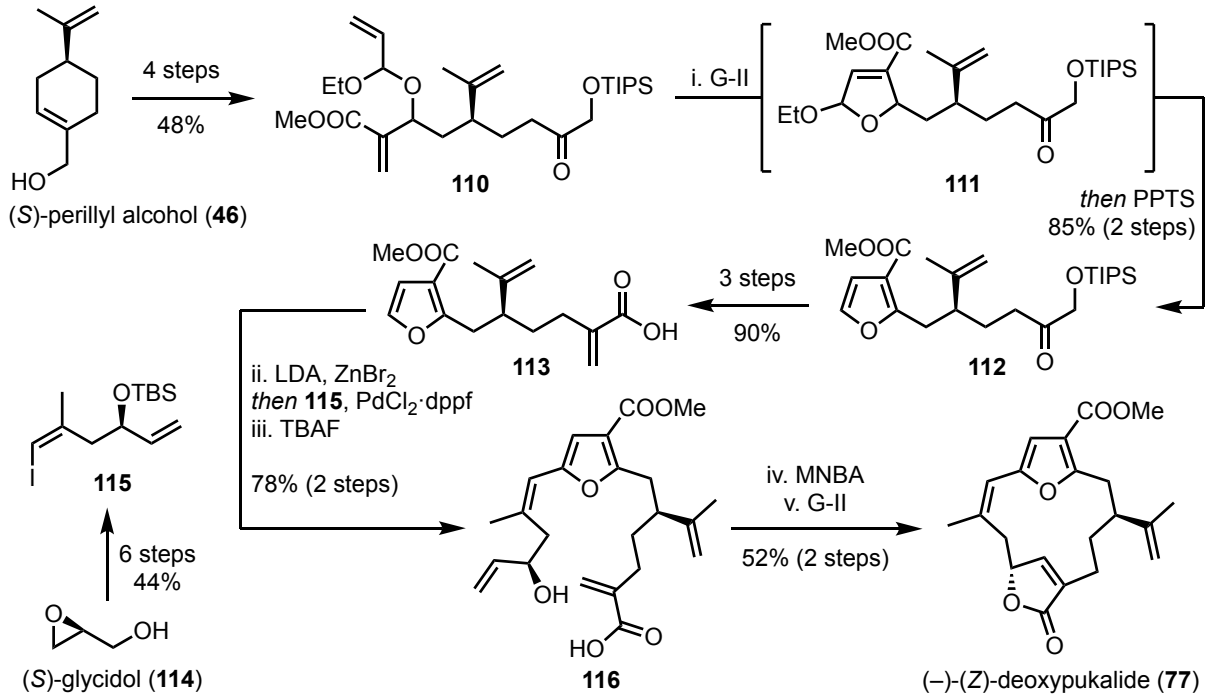


Scheme 1.11 Other syntheses of bipinnatin J (**97**) by Rawal and Pattenden. Reagents and conditions: i) **105**, AgOTf, CH_2Cl_2, –40 °C to rt, 4 h, 60%; ii) **106**, $PdCl_2$·dppf, THF, 0 °C to rt, 2 h, quant; iii) PPTS, *t*-BuOH, 90 °C, 18 h, 81%; iv) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 5 min, 68%; v) $CrCl_2$, 4Å MS, THF, rt, 16 h, 73%; vi) **95**, $Pd(PPh_3)_4$, CuI, CsF, DMF; vii) NBS, PPh_3, 72% (2 steps); viii) $CrCl_2$, 4Å MS, THF, 70%

1.1.4.11 Donohoe Synthesis of (–)-(*Z*)-Deoxypukalide (77), 2008

Donohoe and co-workers reported the synthesis of (–)-(*Z*)-deoxypukalide (**77**) in 2008, utilising their established RCM methodology to forge the furan core.[39] Beginning from (*S*)-perillyl alcohol (**46**), RCM precursor **110** was accessed in 48% yield over 4 steps. On treatment with G-II, RCM to acetal **111** proceeded smoothly and subsequent elimination of EtOH with PPTS provided furan **112** in 85% yield. Elaboration to acid **113** was achieved in 90% yield over 3 steps. The coupling partner iodide **115** could be accessed in 44% yield over 6 steps from (*S*)-glycidol (**114**). Deprotonation of furan **113** with LDA and transmetallation to zinc allowed for the Negishi coupling with iodide **115**. In a novel strategy for furanocembranoid macrocyclisation, TBS deprotection provided *seco*-acid **116** in 78% yield, enabling MNBA mediated

macrolactonisation. The synthesis was completed by RCM to furnish the butenolide moiety and provide (–)-(*Z*)-deoxypukalide (**77**) in 52% over 2 steps (Scheme 1.12).

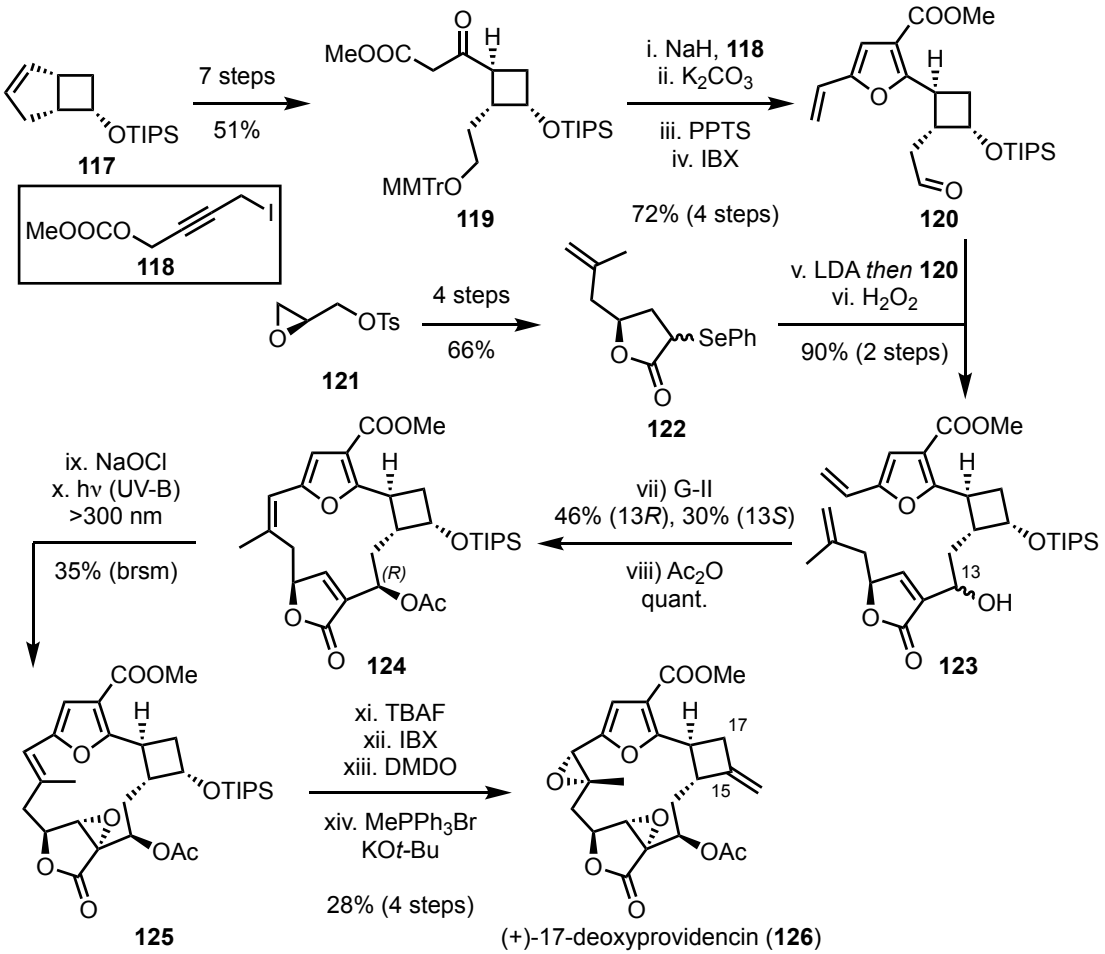


Scheme 1.12 Donohoe synthesis of (–)-(*Z*)-deoxypukalide (**77**). Reagents and conditions: i) G-II, CH_2Cl_2, reflux, 16 h *then* PPTS, reflux, 2 h, 85%; ii) LDA, THF, –78 °C, 1 h *then* $ZnBr_2$, 45 min –78 °C to 0 °C *then* **115**, $PdCl_2$·dppf, 50 °C, 4 h; iii) TBAF, THF, 50 °C, 2 h, 78% (2 steps); iv) MNBA, Et_3N, DMAP, CH_2Cl_2, rt, 19 h, 73%; v) G-II, PhMe, reflux, 16 h, 72%

1.1.4.12 Mulzer Synthesis of (+)-17-Deoxyprovidencin (126), 2014

In 2014, Mulzer and co-workers reported the synthesis of (+)-17-deoxyprovidencin (**126**), the most highly oxidised furanocembranoid synthesised to date.[40] The furan core **120** was accessed from cyclobutane **117** in 11 steps. Intermediate β-ketoester **119** was alkylated with iodide **118** and, in an approach related to that used by Marshall towards (–)-(*Z*)-deoxypukaldie (**77**), S_N2' delivered furan **120** after aromatisation in 74% yield. Aldol reaction between butyrolactone **122** (4 steps from chiral epoxide **121**) and aldehyde **120** followed by selenoxide elimination delivered diene **123** as a 1.5:1 mixture of diastereomers in 90% yield over 2 steps. The subsequent RCM was selective for the undesired (*Z*)-olefin but at this stage the *C*-13 diastereomers could be separated and acylation then afforded ester **124** in near quantitative yield as a single enantiomer. The undesired diastereomer could be epimerised using a Mitsunobu

inversion prior to acetylation. Substrate controlled diastereoselective epoxidation of the butenolide moiety was achieved using NaOCl and the (*Z*)-olefin could now be isomerised. The (*Z*)-isomer had a UV/Vis absorption maximum at 306 nm whereas the (*E*)-olefin absorbed below 300 nm. Performing the irradiation in a pyrex vessel (absorbs below *ca*. 300 nm) allowed partial conversion to natural (*E*)-isomer **125** which was isolated in 31% yield (34% recovered starting material). Epoxidation of the *C*-7/8 olefin was possible due to the masking of the *C*-15 exocyclic alkene; TIPS deprotection and oxidation to the ketone was followed by DMDO mediated epoxidation. Wittig methylenation then installed the *C*-15 olefin to provide (+)-17-deoxyprovidencin (**126**) in 28% yield over 4 steps (Scheme 1.13).

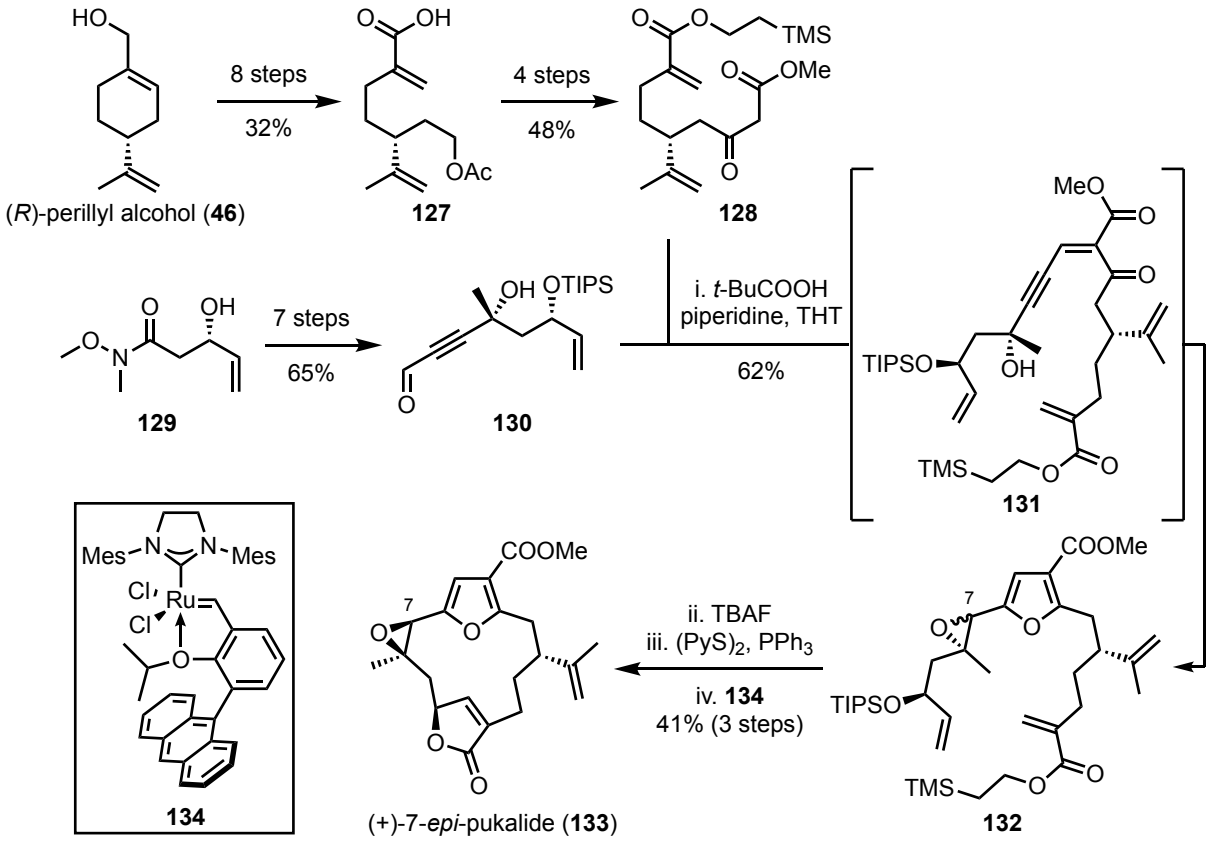


Scheme 1.13 Mulzer synthesis of (+)-17-deoxyprovidencin (**126**). Reagents and conditions: i) NaH, **118**, THF, 0 °C to rt, 40 min, 98%; ii) K_2CO_3, DMF, 90 °C, 2 h, 80%; iii) PPTS, CH_2Cl_2:MeOH (4:1), rt, 1 h, 93%; iv) IBX, EtOAc, reflux, 3 h, 97%; v) LDA, THF, –78°C, 30 min *then* **120**, –78°C, 1 h, 90%; vi) H_2O_2, CH_2Cl_2:$NH_4Cl_{(sat., aq.)}$ (4:1), 0°C, 1 h, quant; vii) G-II, benzene, reflux, 16 h, 46% (13*R*), 30% (13*S*); viii) Ac_2O, DIPEA, DMAP, CH_2Cl_2, 0 °C, 45 min, quant; ix) NaOCl, pyridine, –15 °C, 5 min, 84%; x) UV-B, 2 40 min, MeCN, rt, 31% and 34% RSM; xi) TBAF, THF, rt, 1 h, 79%; xii) IBX, THF:DMSO (10:1), rt, 15 h, 89%; xiii) DMDO, acetone, 0 °C, 18 h, 90%; xiv) $MePPh_3Br$, KO*t*-Bu, THF, 0 °C to rt, 15 min, 45%

The same strategy was also used by the authors to access the 14-membered macrocyclic precursor to the pseudoterane 11-gorgiacerol.[41] The carbon framework is nearly identical to (*Z*)-macrocycle **124**, with an isobutylene unit replacing the cyclobutane, and as such the route will not be discussed further.

1.1.4.13 Clark Synthesis of (+)-7-*epi*-Pukalide (133), 2017

Very recently, Clark and co-workers have reported the synthesis of (+)-7-*epi*-pukalide (**133**), using their Knoevenagel condensation methodology to furnish the furan core (see Section 1.2.3).[42] The right-hand fragment **128** was synthesised in 12 steps from (*R*)-perillyl alcohol (**46**) *via* acid **127**. The left hand fragment **130** was accessed in 7 steps from Weinreb amide **129**. Subjection of these two fragments to the cascade Knoevenagel condensation/aromatisation sequence furnished advanced furan **132** in 62% yield. This reaction occurs *via* the Knoevenagel adduct **131** from which tetrahydrothiophene (THT) mediates aromatisation to the furan. The adjacent tertiary alcohol then traps the sulfur ylid formed to furnish the epoxide *in situ* as a 1:1 mixture of diastereomers at *C*-7. Ester deprotection to the *seco*-acid and macrolactonisation using Corey-Nicolaou conditions was diastereoselective for the macrocycle with (*R*) stereochemistry at *C*-7, epimeric to that found in the natural product, which was produced in 46% yield over two steps. The diastereomer with (*S*) stereochemistry at *C*-7 did not react under any macrolactonisation conditions tested. The synthesis was completed by formation of the butenolide using RCM; modified catalyst **134** provided (+)-7-*epi*-pukalide (**133**) in 90% yield (Scheme 1.14).



Scheme 1.14 Clark synthesis of (+)-7-*epi*-pukalide (**133**). Reagents and conditions: i) *t*-BuOOH, piperidine, THT, 4Å MS, 35 °C, 16 h, 62%; ii) TBAF, THF, 10 °C, 3 h; iii) 2,2'-dipyridyl disulfide, PPh_3, PhMe, rt, 7 h *then* reflux, 14 h, 46%; iv) **134**, CH_2Cl_2, 40 °C, 17 h, 90%

1.2 Literature Routes to Furan Heterocycles

Furan heterocycles are the unifying structural feature of the furanocembranoids, but their influence extends far beyond natural product chemistry. These 5-membered 6π electron heteroaromatic compounds and their derivatives are ubiquitous within the fields of medicinal chemistry[43] and molecular electronics[44] and have found further application in surface coatings and resins. Furfuryl alcohol (**135**) was one component of the carbon based composite material used to protect NASA's Space Shuttle from thermal fluctuations on re-entry to Earth (Figure 1.4).[45]

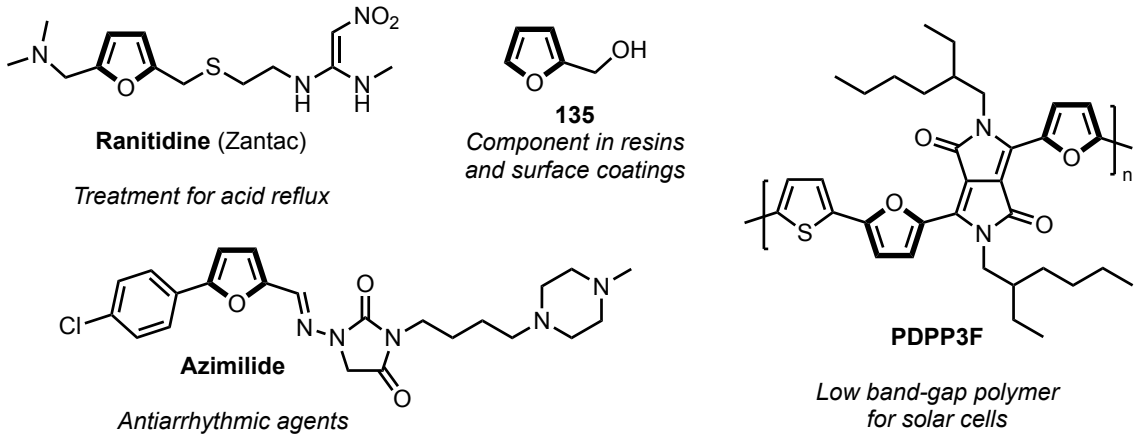
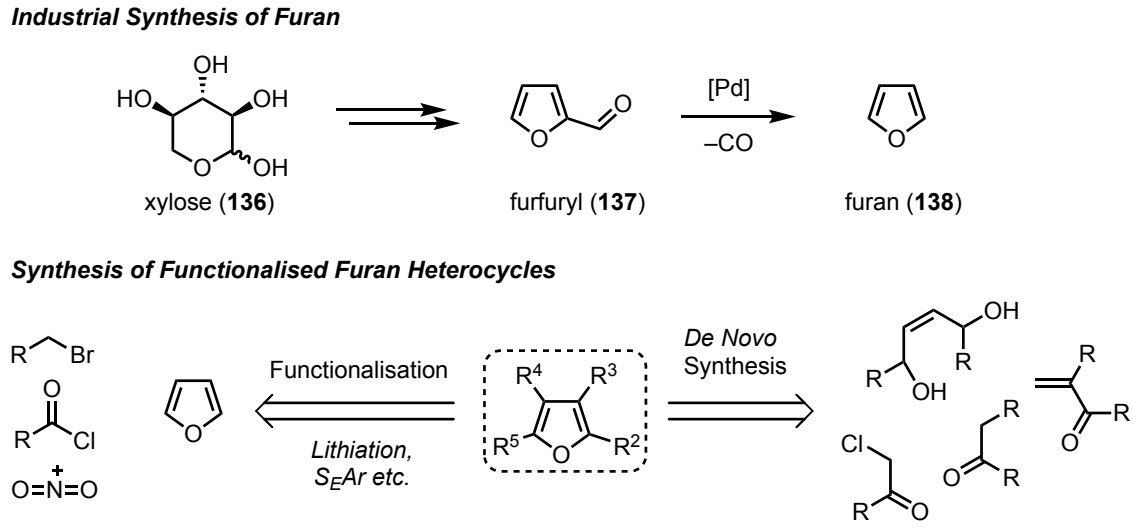


Figure 1.4 Examples of functionally useful furan heterocycles

Unfunctionalised furan (**138**) is produced industrially by palladium catalysed decarbonylation of furfural (**137**), which is itself formed from biomass derived xylose (**134**).[46] The synthesis of functionalised furans can be broadly grouped into two distinct categories: post-functionalisation of furan (**138**) or the *de novo* synthesis of decorated furans from simple building blocks.

Various methods exist for the functionalisation of furan (**138**) with common strategies including the deprotonation of the sp^2 C–H bonds and subsequent trapping with electrophiles, or exploitation of its electron-rich character in electrophilic aromatic substitution reactions.[47] More recently, transition-metal catalysed C–H functionalisation reactions that enable regioselective modification have been developed.[48]

De novo synthesis offers a complementary approach, providing access to polysubstituted furans directly from common building blocks, obviating the need to perform sequential functionalisation reactions. It allows chemists to override the intrinsic (electron-rich/nucleophilic) reactivity of furan (**138**) and construct heterocycles with substitution patterns that would otherwise be non-trivial to access. This strategy has been extensively investigated and a summary of commonly used methods will be presented, along with a closer examination of those that have relevance to furanocembranoid synthesis (Scheme 1.15).

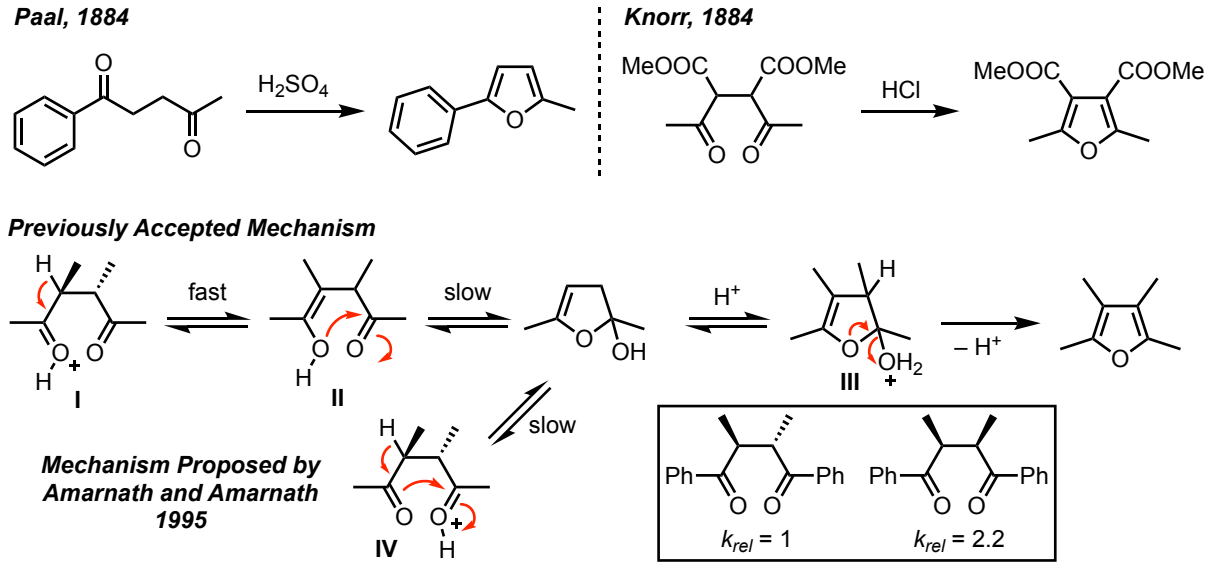


Scheme 1.15 Synthesis of furan (**138**) and synthetic strategies to furan derivatives

1.2.1 Classical Routes to Substituted Furans

The majority of known routes to furans are based on the acidic cyclising dehydration of 1,4-diketones described almost simultaneously by Paal[49] and Knorr[50] in 1884. Despite its long history, the mechanism for the Paal–Knorr synthesis, as it is more commonly known, was only rigorously delineated in 1995 by V. Amarnath and K. Amarnath when they showed that the rates of reaction for diastereomeric pairs of 3,4-disubstituted-2,5-hexane diones were different.[51] The previously accepted mechanism would have predicted no change in rate; enolisation (Scheme 1.16, **I**) was assumed to precede rate-determining enol addition into the adjacent ketone (**II**), followed by dehydration (**III**). Both *syn* and *anti* diastereomers were thus as-

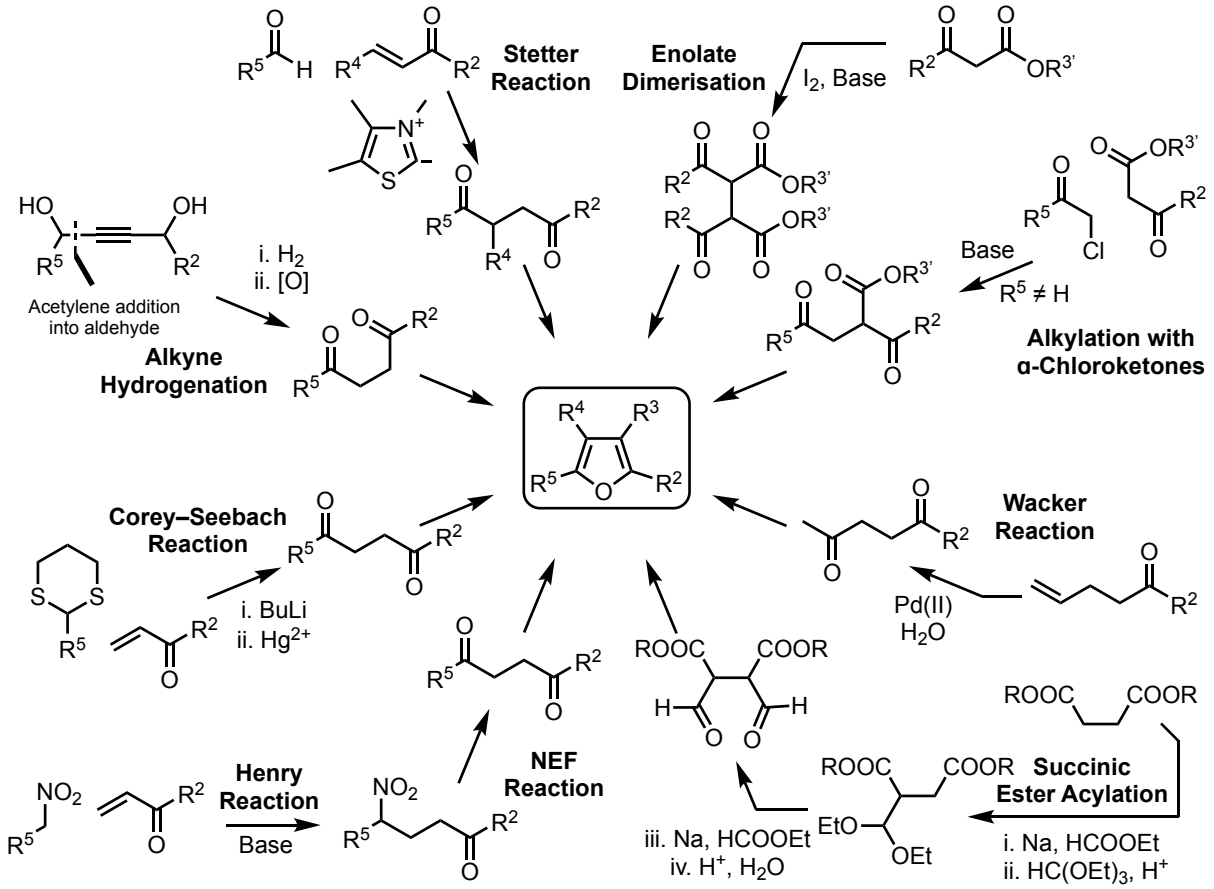
sumed to react *via* a common enol intermediate (**II**), negating the stereochemistry of the starting materials. To account for the observed rate difference, the authors proposed the addition of a *forming* enol into an already protonated ketone (**IV**), followed by dehydration to the furan. In this scenario, the relative stereochemistry would affect the population of the reactive conformation required for direct cyclisation. Further support for this mechanism was found in the lack of any observable degradation in the relative stereochemistry of unreacted starting material and the variation in rate with substituent size (Scheme 1.16).



Scheme 1.16 Paal–Knorr furan synthesis and mechanistic analysis

Since the seminal work of Paal and Knorr, the 1,4-diketone motif has become a key target *en route* to furans. Early routes relied on the fusion of two ketone containing species but this approach was complicated by the need to invert conventional carbonyl reactivity, either by making the carbonyl carbon nucleophilic or the α-position electrophilic. Umpolung reactivity was usually achieved through the use of α-halo carbonyls or masked carbonyl species, such as nitro alkanes and thioacetals, which behaved as nucleophilic carbonyl synthons. The use of succinic esters as scaffolds onto which carbonyls could be appended proved a useful, if lengthy, alternative, as did the hydrogenation of *bis*-hydroxy alkynes. The invention of the Stetter reac-

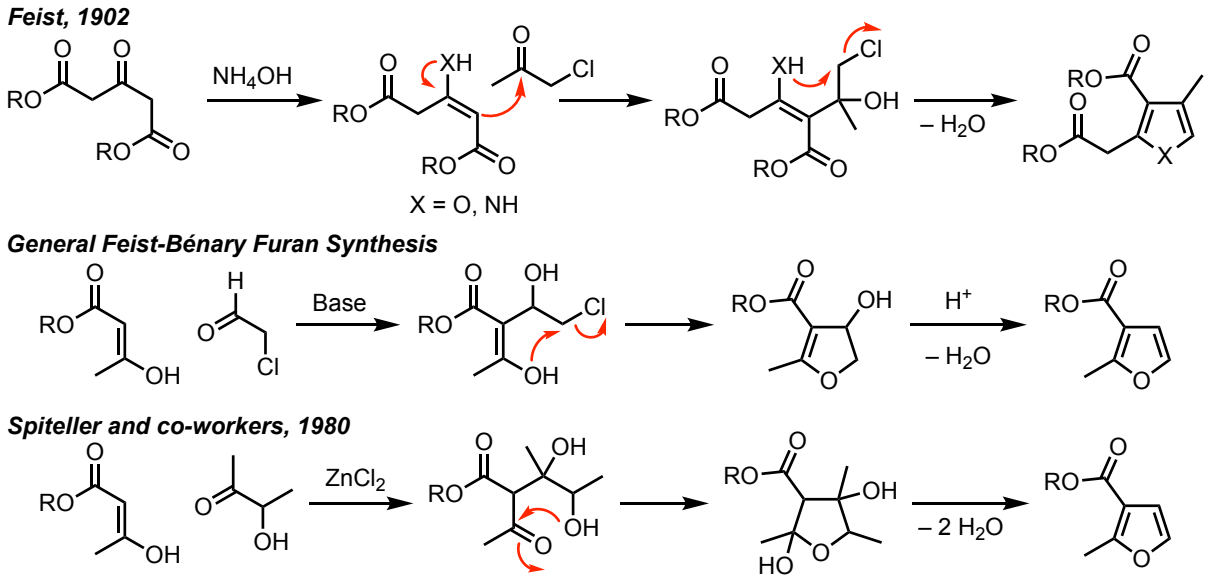
tion later provided a means to form the desired 1,4-diketones from conventional carbonyl species (Scheme 1.17).[52]



Scheme 1.17 Approaches to 1,4-dicarbonyls *en route* to furans

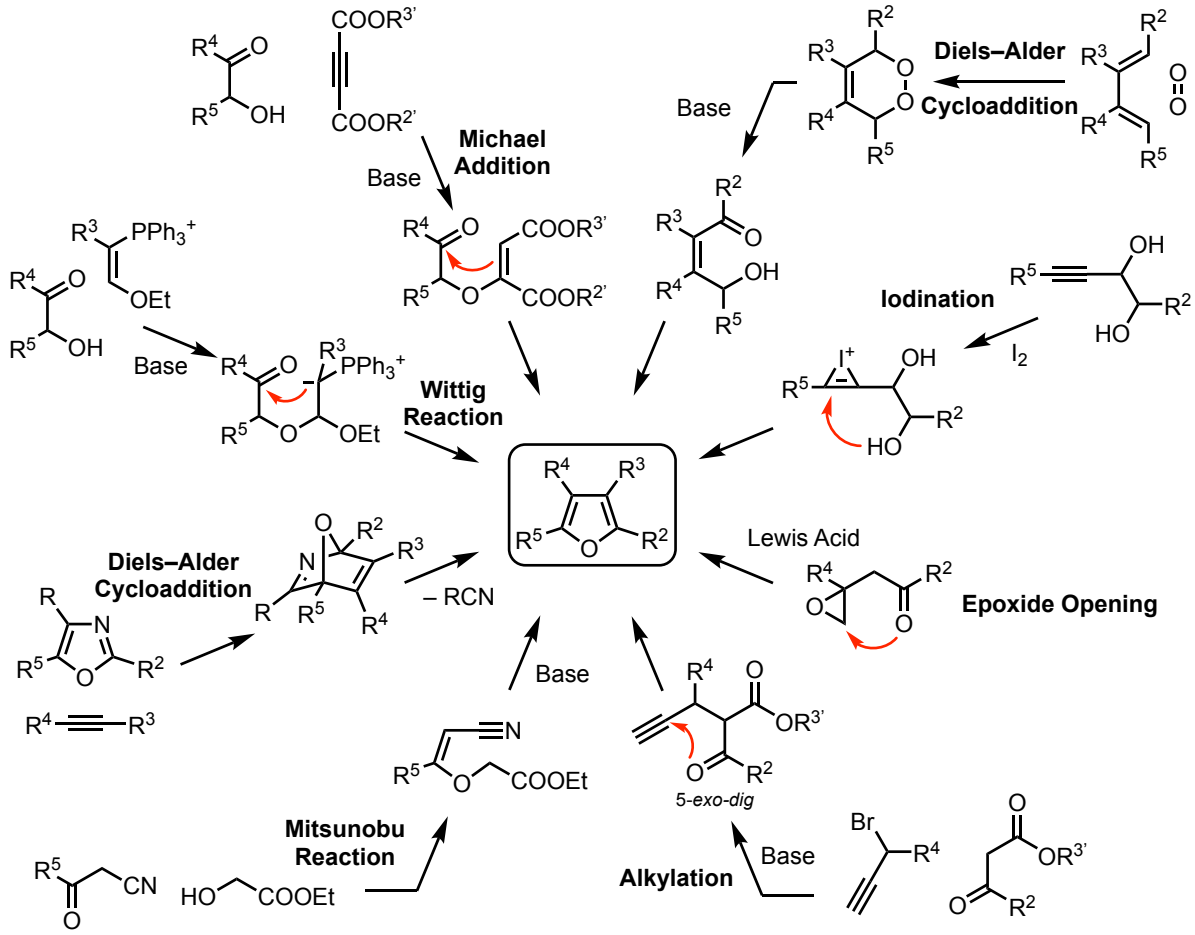
A related approach to furans, employing α-chloro carbonyls and 1,3-dicarbonyls, was described by Feist in 1902.[53] Reacting α-chloroacetone and 1,3-acetone dicarboxylic acid esters in aqueous ammonia, Feist isolated a mixture of pyrrole and furan derivatives. This method was later extended to the synthesis of pyridine derivatives by Bénary.[54] Mechanistically, the reaction occurs *via* an initial aldol reaction and is followed by S_N2 displacement of the α-chloro atom by the enolate oxygen. The Feist–Bénary furan synthesis is now most commonly performed under basic conditions using β-ketoesters and α-chloro aldehydes, for which selectivity for the aldol reaction is greater than C-alkylation (see Scheme 1.17 "Alkylation with α-Chloroketones"), followed by acid promoted dehydration. A modified procedure using the

more stable α-hydroxy carbonyls under lewis acidic conditions was later developed by Spiteller and co-workers (Scheme 1.18).[55]



Scheme 1.18 Feist–Bénary furan synthesis

The broad application of furan heterocycles has inspired the development of a gamut of other methods for their synthesis. The general principles of early approaches, involving fusion of two simple components followed by an intramolecular, C–O bond forming, thermodynamically driven aromatisation has largely been retained, along with an emphasis on exploiting acid or base mediated keto-enol tautomerism. In echos of the Paal–Knorr synthesis, functionality that can behave as carbonyl surrogates, such as epoxides, iodonium salts and alkynes, have sometimes been used. Alternatively, the initial coupling reaction has on occasion employed the oxygen atom directly with a C–C bond forming step completing the 5-membered ring, followed by dehydration. In these cases, C–C bond formation has occurred *via*, for example, enol or phosphorus ylid addition into ketones or enol addition into nitriles. A small number of methods utilising Diels–Alder cycloaddition have also been reported, to provide more unorthodox disconnections to the target compounds (Scheme 1.19).

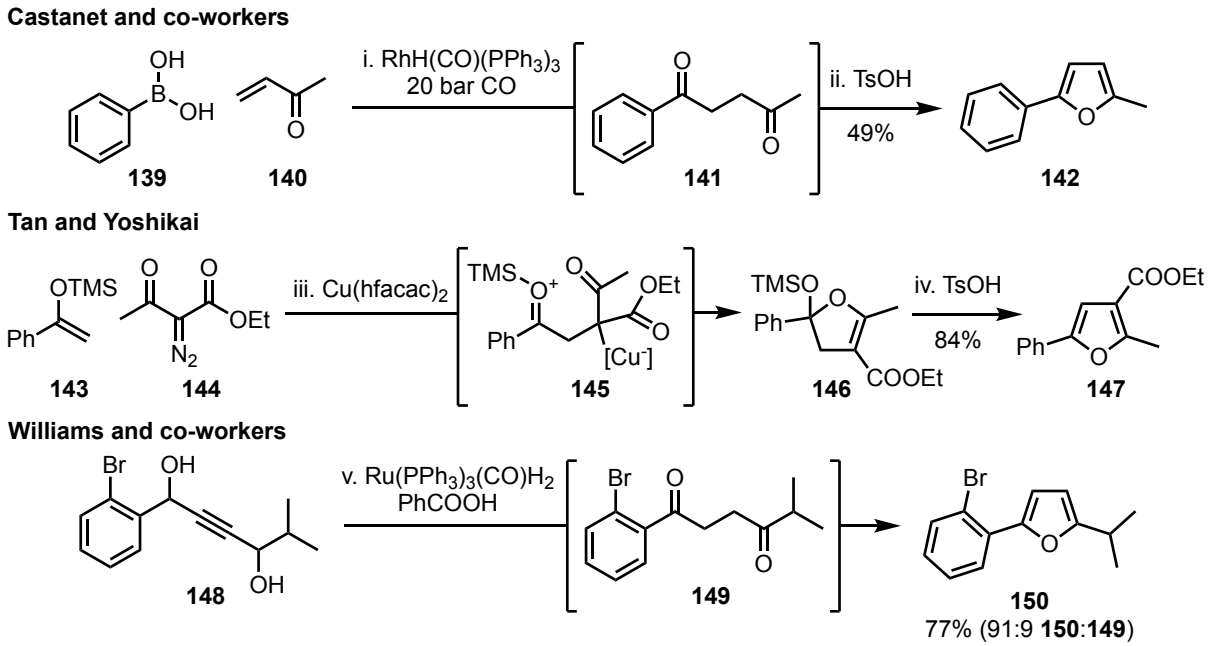


Scheme 1.19 Additional routes to functionalised furans

1.2.2 Transition-Metal Catalysed Routes to Substituted Furans

The advent of transition-metal catalysis initiated a paradigm shift in synthetic chemistry during the latter half of the 20th Century. New disconnections were made possible and milder, more general, conditions to compounds of potential value were developed.[56] An overview of the contributions transition-metal chemistry has made to the synthesis of furans will be presented. Examples where the catalysis has overcome difficulties associated with earlier approaches are emphasised, along with methods pertinent to the remainder of this thesis. The sub-class of olefin metathesis based routes to furans will be discussed separately (Section 1.3).

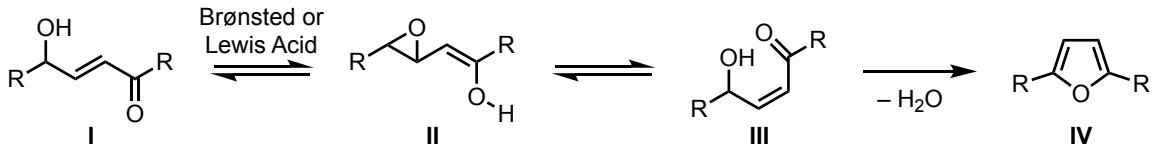
The development of new routes to the 1,4-dicarbonyl motif is one area in which transition-metal catalysis has contributed. Creative catalytic approaches to umpolung reactivity have provided modular routes to furans from more commonly used starting materials. In one such example, Castanet and co-workers utilised rhodium catalysis to effect the 1,4-carbonylative addition of aryl boronic acid **139** to methyl vinyl ketone (**140**) with aromatisation of the resulting 1,4-diketone **141** promoted under acidic conditions.[57] Alternatively, Tan and Yoshikai engaged copper catalysis to combine silyl enol ether **143** and diazo carbonyl **144**, producing hemiacetal **146** *via* 1,4-diketone **145**. Silanol elimination occurred on exposure to acid, providing furan **147**.[58] In a different approach, Williams and co-workers accessed the 1,4-diketone motif *via* ruthenium catalysed isomerisation of *bis*-hydroxy alkyne **148**. Acid mediated aromatisation of diketone **149** then afforded furan **150** (Scheme 1.20).[59]



Scheme 1.20 Transition-metal catalysed furan synthesis *via* 1,4-diketones. Reagents and conditions: RhH(CO)$(PPh_3)_3$, 20 bar CO, MeOH, 80 °C, 18 h; ii) TsOH, PhMe, reflux, overnight, 49% (2 steps); iii) $Cu(hfacac)_2$, CH_2Cl_2, 40 °C, 6 h; iv) TsOH, PhMe, 110 °C, 1.5 h, 84% (2 steps); v) $Ru(PPh_3)_3(CO)H_2$, Xantphos, PhCOOH, PhMe, reflux, 24 h, 77%

Transition-metal catalysis has also produced new and general motifs for furan synthesis. Of these, *trans*-ɣ-hydroxyenones **I** are one of the most widely used. These compounds exist at the same oxidation state as 1,4-diketones but with a different bonding constitution. They can

be efficiently transformed into the desired furans with mild acid. Isomerisation to their *cis*-form **III**, presumably *via* the intermediacy of epoxide **II**, precedes spontaneous condensation to furan **IV** (Scheme 1.21).[60] Interestingly, mechanistic experiments indicate that furan formation from *trans*-ɣ-hydroxyenone **I** is faster than from the corresponding 1,4-diketone.[61]

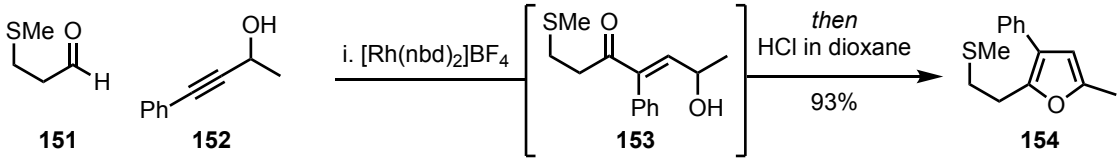


I II III IV

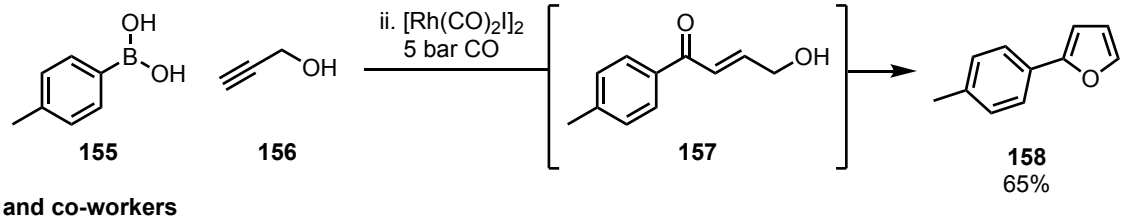
Scheme 1.21 ɣ-Hydroxyenones as general motifs to access furans

Willis and co-workers developed an efficient route to furans based on this concept, accessing the required intermediates *via* hydroacylation. Rhodium catalysed coupling of aldehyde **151**, bearing the chelating thioether group required for the reaction, with propargyl alcohol **152**, followed by aromatisation with HCl in dioxane (PTSA could also be used) afforded furan **154** in 93% yield.[62] Castanet and co-workers used a similar approach, effecting the formal hydroacylation of propargyl alcohol (**156**) with aryl boronic acid **155** under carbonylative conditions. Aromatisation to furan **158** occurred *in situ*, without the need for additional acid.[63] In a related approach, Hu and co-workers developed the conjugate addition of diazocarbonyl **159** to enone **160**. Deprotection of the product ketone **161** followed by oxidative reintroduction of the olefin provided the corresponding ɣ-hydroxyenone **162**. In this instance, direct condensation was not possible due to the tertiary nature of the ɣ-hydroxyl; aromatisation was instead achieved *via* ester decarboxylation under more forcing conditions (PhMe, reflux).[64] Larock and co-workers were able to access the *cis*-form of the ɣ-hydroxyenone motif directly, *via* regioselective s*yn* addition of mercuric chloride across alkyne **164**. Spontaneous aromatisation of ɣ-hydroxyenone **165** gave furan **166** in 63% yield. They were then able to employ the Hg–C bond in a palladium catalysed carbonylation reaction to afford ester **167** in 97% yield (Scheme 1.22).[65]

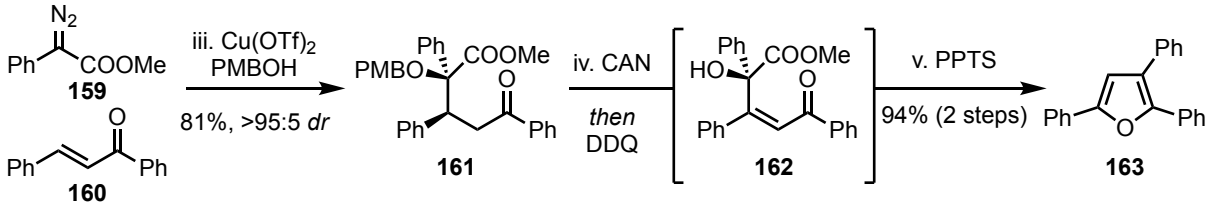
Willis and co-workers



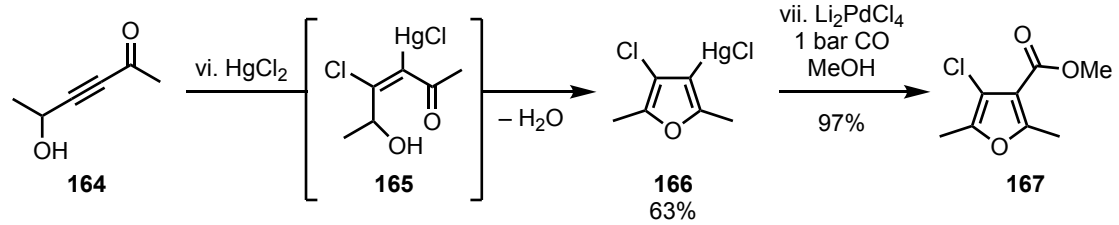
Castanet and co-workers



Hu and co-workers



Larock and co-workers

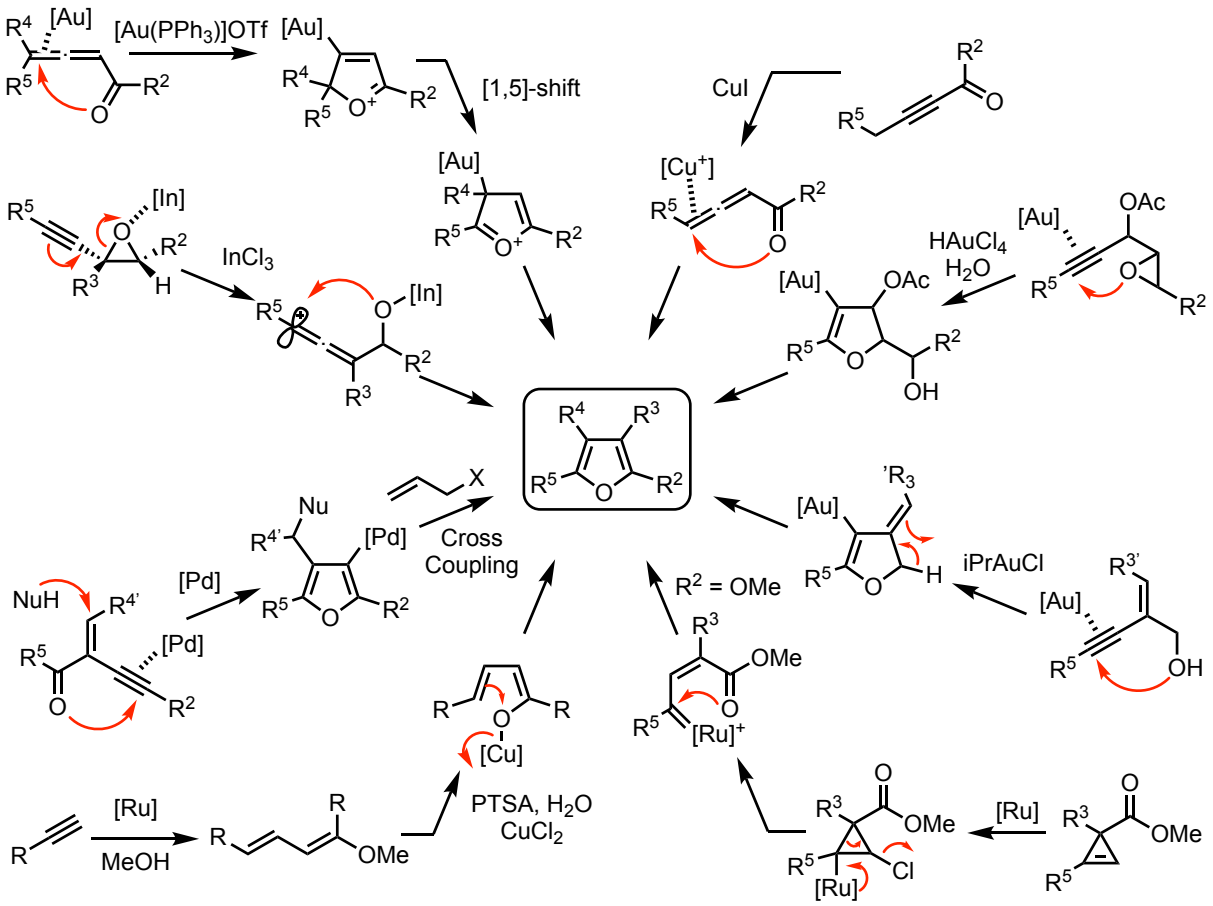


Scheme 1.22 Metal catalysed approaches to furans *via* ɣ-hydroxyenones. Reagents and conditions: i) $[Rh(nbd)_2]BF_4$, dppe, 1,2-DCE, 65 °C, 1 h *then* 1 M HCl in dioxane, 93%; ii) $[Rh(CO)_2I]_2$, LiI, 5 bar CO, MeOH, 90 °C, 18 h, 65%; iii) $Cu(OTf)_2$, CH_2Cl_2, 40 °C, 3 h, 81%; iv) CAN, CH_2Cl_2/H_2O, rt, 16 h *then* DDQ, CH_2Cl_2/H_2O, rt, 16 h; v) PPTS, PhMe, reflux, 6 h, 94% (2 steps); vi) $HgCl_2$, NaCl, MeOH, 5 °C, 12 h, 63%; vii) $PdCl_2$, LiCl, Et_3N, CO, MeOH, rt, 48 h, 97%

The use of transition-metal catalysis extends beyond the synthesis of general intermediates such as 1,4-dicarbonyls or ɣ-hydroxyenones. Innovative approaches to polysubstituted furans utilising novel mechanistic pathways are continually disclosed.[66,67] Skeletal rearrangements from pre-functionalised building blocks using indium[68] or ruthenium[69] catalysis have been reported as well as more complex palladium catalysed multicomponent processes, where the catalyst additionally behaves as a Lewis acid.[70] Ruthenium catalysed alkyne dimerisation has also provided access to symmetrically substituted furans.[71]

In other cases, catalysis has replaced the stronger Brønsted or inorganic Lewis acids (eg. $BF_3{\cdot}OEt_2$) of more traditional strategies, resulting in improved functional group tolerance.

Gold has received particular attention in this regard owing to its proficiency as a π-acid. Numerous reports involving alkyne activation followed by intramolecular cyclisation with, for example, alcohol[72] or epoxide[73] functionality have been disclosed. Gold catalysed cascades incorporating post-cyclisation alkyl shifts have also been reported.[74] The Lewis acidity of copper has similarly been used to effect alkyne-allene isomerisation followed by intramolecular cyclisation (Scheme 1.23).[75]

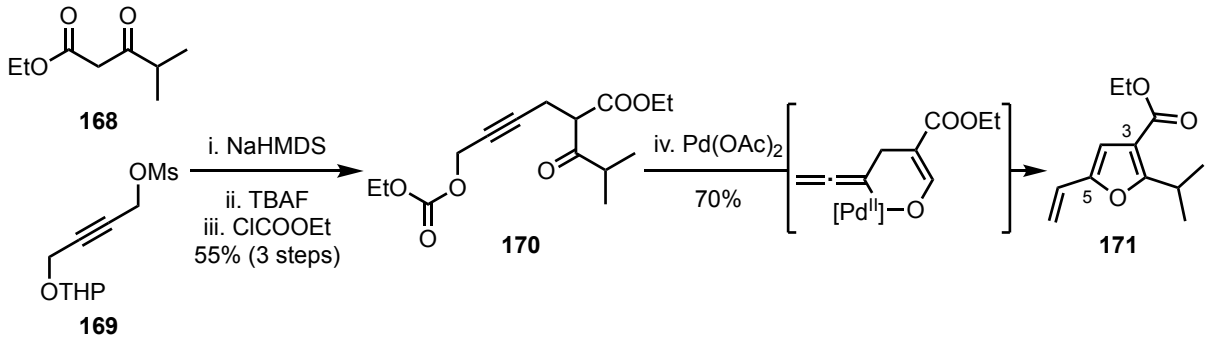


Scheme 1.23 Alternative transition-metal catalysed routes to furans

1.2.3 Routes to Trisubstituted Furans Relevant to Furanocembranoid Synthesis

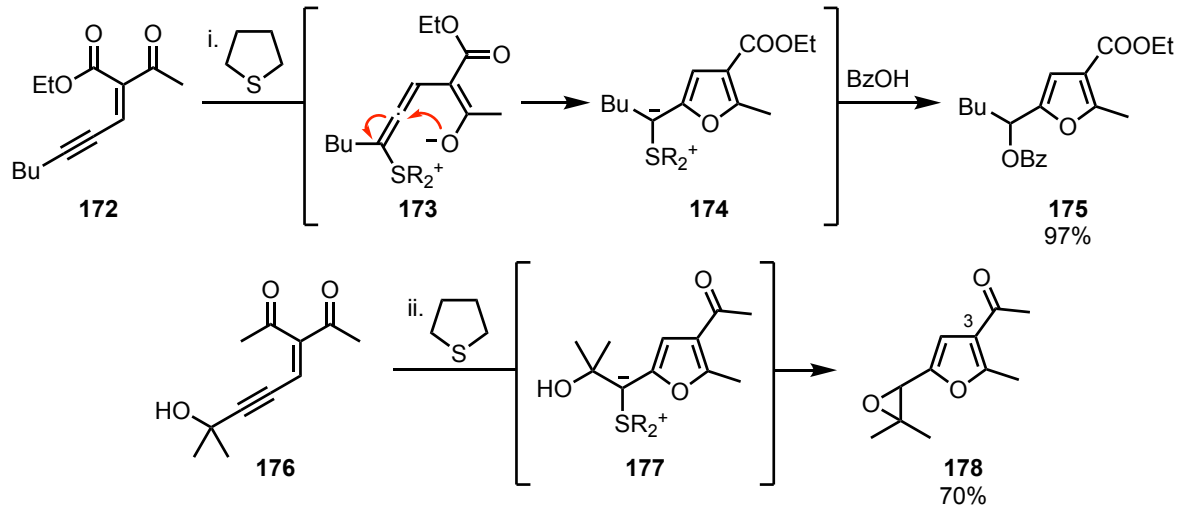
In addition to the methods discussed above, strategies to access furans of particular relevance to furanocembranoid synthesis have also been developed.

Wipf and co-workers disclosed the synthesis of alkenyl furans using palladium catalysed cycloelimination, directly installing both the *C*-3 ester and *C*-5 alkenyl substituents that would be required for furanocembranoid synthesis.[32] Alkylation of β-ketoester **168** with propargyl mesylate **169** and installation of the carbonate provided ketone **170** in 55% yield. On reaction with $Pd(OAc)_2$, furan **171** was formed in 70% yield. Mechanistically, the cyclisation is assumed to operate *via* a allenyl-Pd intermediate (Scheme 1.24).



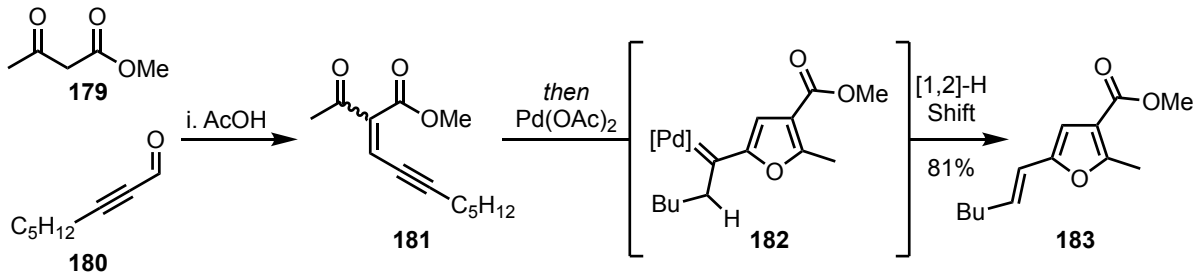
Scheme 1.24 Wipf cyclisation to alkenyl furans. Reagents and conditions: i) NaHMDS, THF, TBAI, –78 °C to 50 °C, 14 h; ii) TBAF, THF, rt, 15 min, 68% (2 steps); iii) ClCOOEt, pyridine, CH_2Cl_2, 0 °C to rt, 30 min, 82%; iv) $Pd(OAc)_2$, K_2CO_3, dppf, THF, reflux, 8 h, 70%

Nucleophilic catalysis was employed by Clark and co-workers to provide a route to epoxy furans.[76] Starting from ene-yne **172**, 1,6-addition of tetrahydrothiophene (THT, substoichiometric quantities) led to enolate **173**. Cyclisation then gave sulfur ylid **174** which could be trapped by benzoic acid to provide ester **175** in 97% yield. Alternatively, when ene-yne **176** was used, such that intramolecular trapping of the sulfur ylid was possible, epoxy furan **178** was formed in 70% yield. Although the *C*-3 ketone substituent is not present in any furanocembranoid natural product, the method does allow for installation of the crucial epoxide substituent directly (Scheme 1.25).



Scheme 1.25 Clark methodology to epoxy furans. Reagents and conditions: i) 50 mol% THT, BzOH, CH_2Cl_2, reflux, 18 h, 97%; ii) 20 mol% THT, CH_2Cl_2, reflux, 48 h, 70%

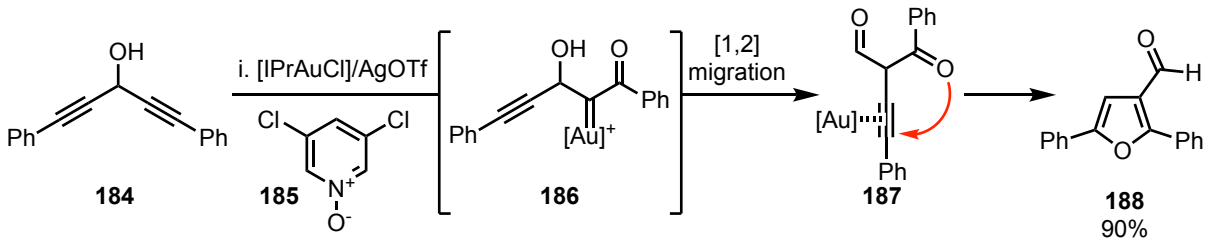
In a related approach, Cao and co-workers effected the formation of vinyl furan **183** *via* the Knoevenagel condensation of β-ketoester **179** and aldehyde **180**.[77] After consumption of the starting materials, $Pd(OAc)_2$ was added to the geometric mixture and catalysed both the cyclisation to the furan and the subsequent [1,2]-H shift to afford *C*-3 ester substituted furan **183** in 81% yield (Scheme 1.26).



Scheme 1.26 Cao approach to vinyl furans. Reagents and conditions: i) AcOH, MeOH, rt, 1 h *then* $Pd(OAc)_2$, rt, 6 h, 81%

A general route to 3-formyl furans has been provided by Hashmi and co-workers.[78] Subjection of diynol **184** to dual gold/silver catalysis in the presence of pyridine *N*-oxide **185** afforded gold carbene **186**. A [1,2]-alkynyl migration followed by π-acid assisted aromatisation then delivered furan **188** in 90% yield. The unusual migration is supported by isotopic labelling experiments and the selectivity for ketone derived cyclisation is attributed to the greater nucleophilicity of the ketone carbonyl compared to the aldehyde. A wide range of aryl sub-

stituents could be used, as well as a small number of alkyl groups. Unsymmetrical diynols were also tolerated with the regiochemical outcome dictated by the relative electron density of the alkynes; cationic gold preferentially binds to the more electron rich alkyne (Scheme 1.27).



Scheme 1.27 Hashmi synthesis of 3-formyl furans. Reagents and conditions: i) IPrAuCl, AgOTf, **185**, PhMe, rt, 30 min, 90%

1.3 Olefin Metathesis and its Application in Furan Synthesis

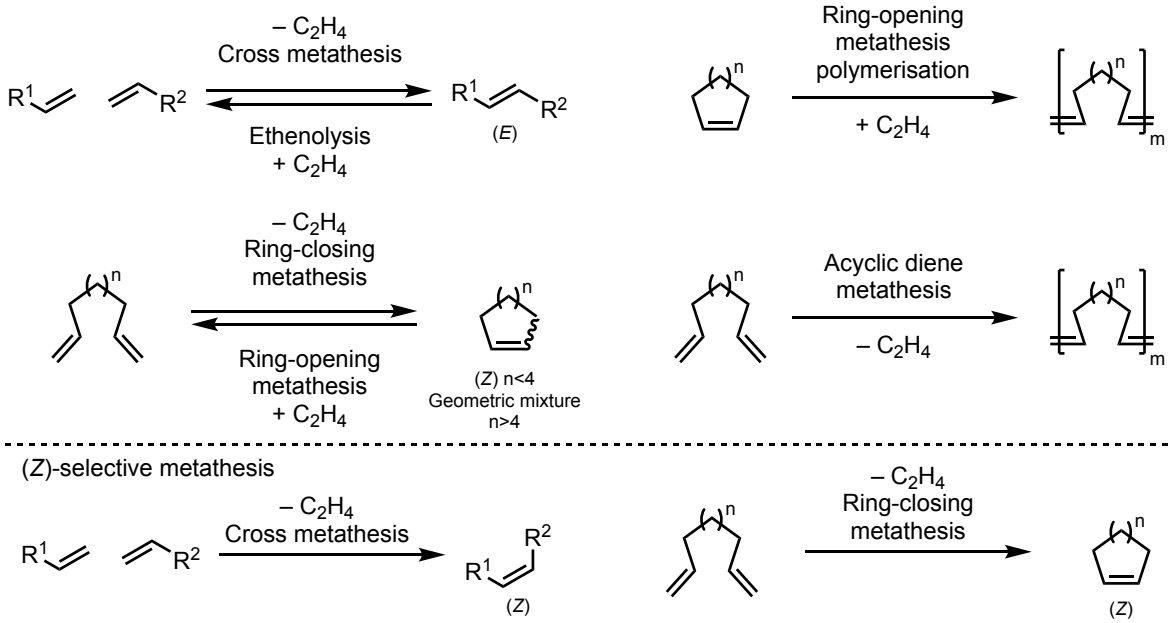
1.3.1 Olefin Metathesis: An Introduction

The synthesis of carbon-carbon double bonds is often achieved through the use of Wittig, Horner-Wadsmorth-Emmons, Julia or Peterson olefination reactions. In practical terms, however, these methods suffer from poor mass economy as a result of the high molecular weight phosphorus, sulfur or silicon groups required to activate the reaction partners.

Olefin metathesis can offer a more efficient approach to the stereoselective synthesis of alkenes. Through the sequential cleavage and recombination of two simple (often terminal) olefins a more highly substituted olefin may be furnished with ethylene the only byproduct. Since its popularisation in the early 1970's, olefin metathesis has become one of the most valuable methods in synthetic chemistry and its rise culminated in the award of the 2005 Nobel Prize in Chemistry. This was shared between Yves Chauvin, Robert Grubbs and Richard Schrock "for the development of the metathesis method in organic synthesis."[79]

Many different classes of olefin metathesis reaction have been described to date.[80] The most common is arguably cross metathesis (CM), the intermolecular coupling of two olefins. Ring-closing metathesis (RCM) is also well established, displaying the same reactivity as CM in an

intramolecular sense. It has been used both to construct small rings and to effect macrocyclisation. The reverse reactions of CM and RCM have also been described and are known as ethenolysis and ring-opening metathesis respectively. Olefin metathesis is widely used in polymer synthesis and in this regard ring-opening metathesis polymerisation (ROMP) and acyclic diene metathesis (ADMET) are the principle modes of reactivity. Olefin metathesis conventionally operates under thermodynamic control to afford the (*E*) or *trans* substituted alkenes. The main exception is RCM where the geometry (or geometric ratio) is dependent on the product ring size. Small rings (<8) typically display exclusive (*Z*) geometry on torsional and angle strain grounds and the proportion of the (*Z*) isomer then decreases as the ring size increases. Recently, catalysts that enable the kinetic formation of (*Z*) or *cis* substituted alkenes have been developed; (*Z*)-selective CM and RCM reactions are now becoming more widely used and have begun to be applied in natural product synthesis (Scheme 1.28).[81]



Scheme 1.28 Most common types of olefin metathesis reactivity

To facilitate these reactions, a family of metathesis catalysts have been developed.[80] The first well defined ruthenium complex capable of general metathesis chemistry was disclosed by Grubbs and co-workers in 1992.[82] This catalyst (**189**) showed some instability towards oxy-

gen and moisture and early development focussed on mitigating these properties. The diene substituent was soon replaced by a benzylidene group and this motif has been retained in the most commonly used catalysts today: Grubbs first and second generation and Hoveyda–Grubbs first and second generation catalysts. The second generation catalysts generally display higher activity and improved thermal stability due to the more tightly bound axial NHC ligand. The Hoveyda variants offer improved stability in solution on account of their *o*-isopropoxy vinyl benzene substituent. Fogg and co-workers showed that this ligand allows HG-II to operate under a "boomerang mechanism" whereby the extra coordinating ability of the isopropoxy motif facilitates more efficient recapture of the ligand by the active catalyst, reforming the stable catalyst complex and prolonging catalyst lifetime (Figure 1.5).[83]

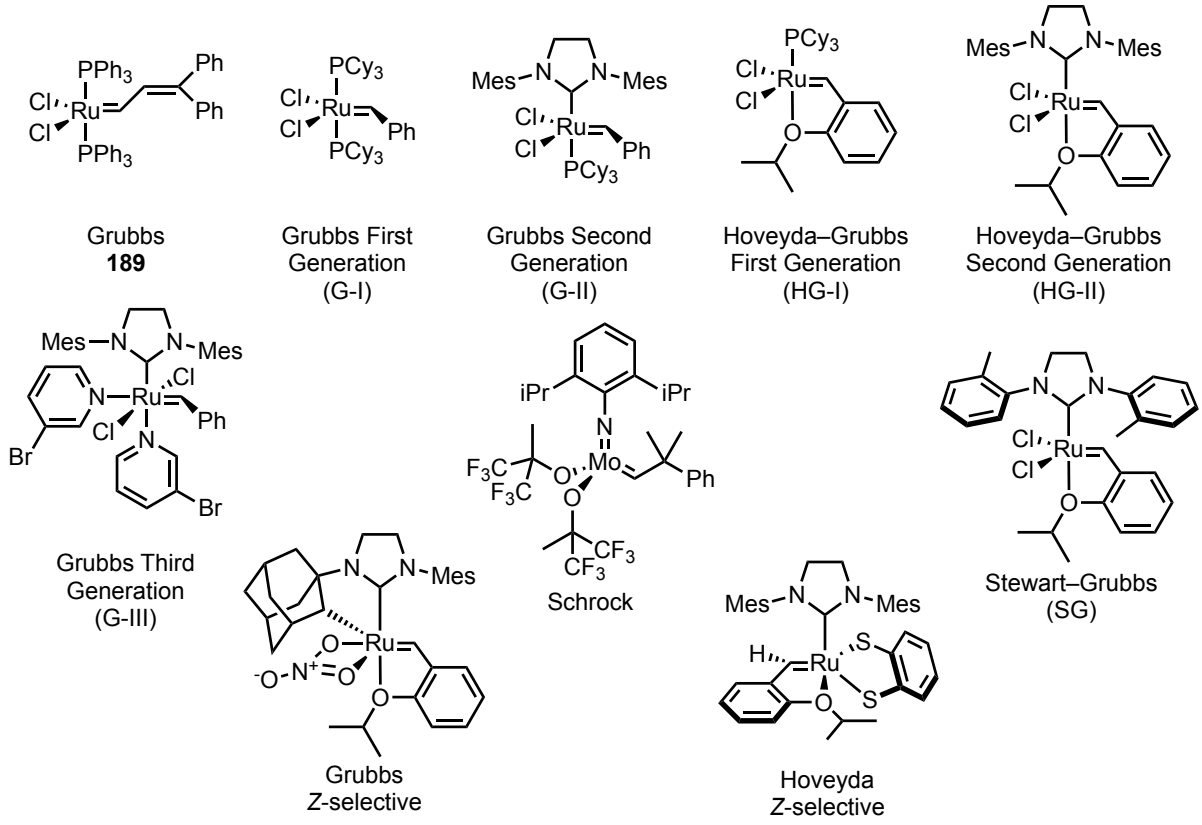


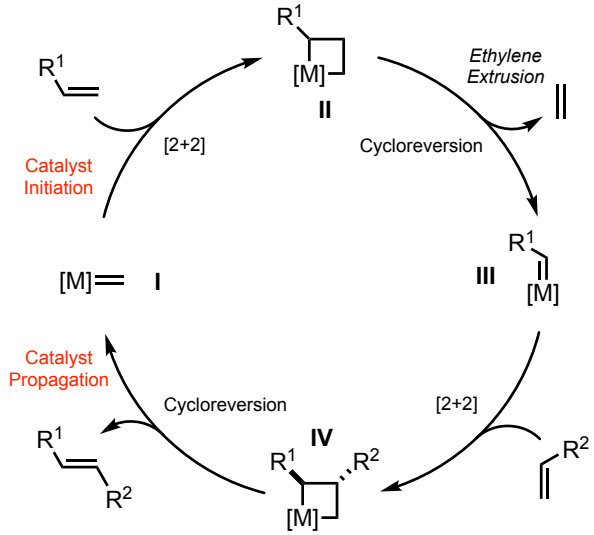
Figure 1.5 Commonly used catalysts for olefin metathesis

Grubbs third generation catalyst displays extremely fast activation in solution and has found use in ROMP production of polymers with narrow polydispersity.[84] Another commercial catalyst with a more specialist application is the Stewart-Grubbs catalyst; this is useful for steri-

cally demanding substrates and was the first known ruthenium catalyst to synthesise tetrasubstituted olefins with some reliability.[85] Schrock-alkylidene catalysts, containing a molybdenum active centre, are also well established and display some of the highest reactivity known. However, they are extremely oxygen and moisture sensitive and the requirement to work within a glove-box has limited their widespread use, despite the development of air-stable derivatives.[86] Additionally, they are known to be oxyphilic and are thus incompatible with many oxygen containing substrates. More recently, a number of catalysts capable of effecting the kinetic formation of (*Z*)-olefins have been developed. Both Grubbs and Hoveyda have disclosed ruthenium based systems where bidentate ligands have restricted the orientation of the reacting alkenes, encouraging their substituents away from the bulky NHC ligand to give the *cis* disposed products selectively.[87,88]

The mechanism for olefin metathesis was first proposed by Hérisson and Chauvin in 1971 and experimental investigations conducted since have corroborated their hypothesis.[89,90] The mechanism is believed to be conserved across all olefin metathesis reaction types and two phases of reactivity are generally considered; the initiation of the catalyst and its propagation through iterative catalytic cycles. Catalyst activation usually occurs during the first stage of the catalytic cycle when metal carbene **I** engages in a [2+2] cycloaddition with one of the olefin partners to give metallocyclobutane **II**. Cycloreversion then results in the transfer of the metal catalyst to the substrate (carbene **III**) and extrusion of ethylene. Ethylene is highly volatile (bp = –104 °C) and its entropically driven extrusion destabilises what is in principle an equilibrium process and encourages product formation. The second olefin partner then participates in a [2+2] cycloaddition with carbene **III** to provide metallocyclobutane **IV**. The substrate orientation is typically such that the largest substituents within **IV** are *trans* displaced to minimise their steric interaction. Cycloreversion then delivers the desired olefin

product as the *trans* geometric isomer and reforms active catalyst species **I**. The increased steric demand of the product disfavours its reintroduction into the catalytic cycle, additionally helping to drive the reaction to completion (Scheme 1.29).



Scheme 1.29 General mechanism of olefin metathesis reaction

1.3.2 Olefin Metathesis: Substrate Influence

The relative reactivity of different olefins in CM reactions has been evaluated by Grubbs and co-workers.[91] They established a system of categorising olefins on the basis of their propensity to homodimerise with G-I, G-II and Schrock type catalysts. Four 'types' of olefin were defined from most reactive to least reactive: Type I (fast homodimerisation), Type II (slow homodimerisation), Type III (no homodimerisation) and Type IV (spectators to CM). The homodimers of Type I olefins are generally able to participate in metathesis reactions themselves, re-entering the catalytic cycle after formation. In general they found than a slight excess of the less reactive metathesis partner was beneficial for efficient CM with olefins of different types and that when CM between two olefins of the same type was desired then a large excess of one partner was needed to prevent the formation of statistical product mixtures (Table 1.1).

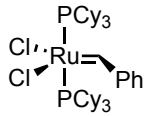
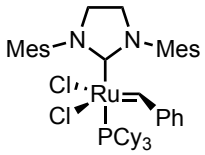
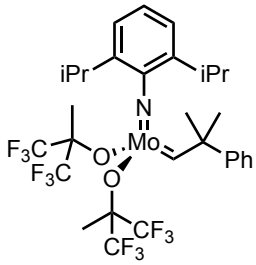
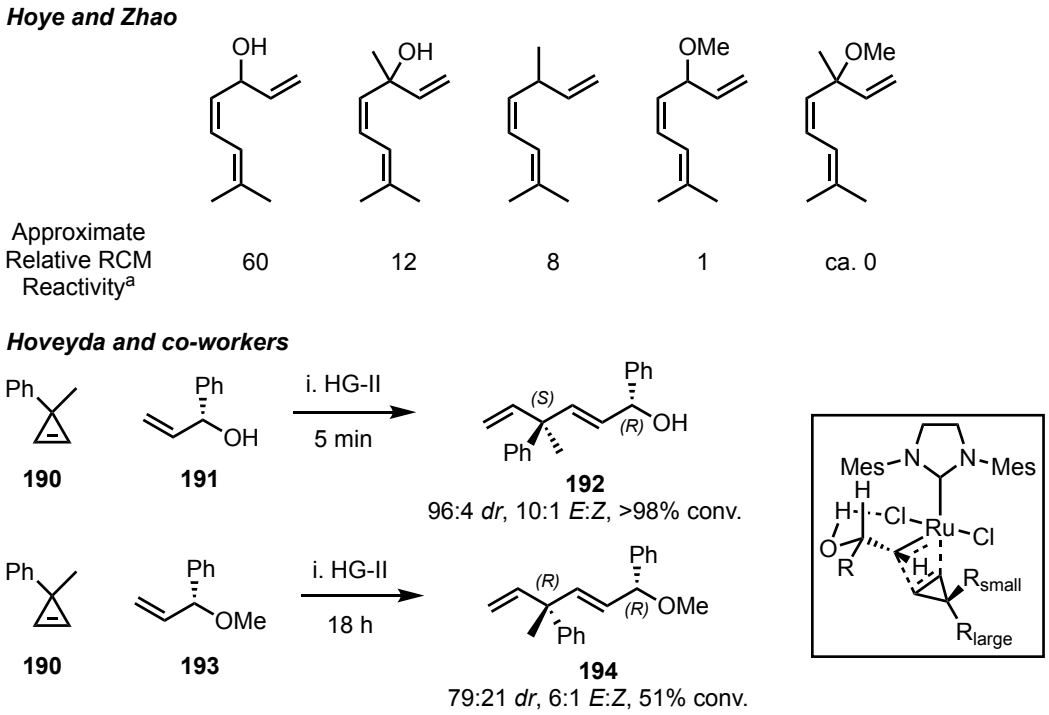
Olefin Type	 **G-I**	 **G-II**	 **Schrock**
Type I	terminal olefins, 1° allylic alcohols, allyl silanes	terminal olefins, 1° allylic alcohols, styrenes, allyl silanes	terminal olefins, allyl silanes
Type II	styrenes, 2° allylic alcohols, vinyl boronates	styrenes (large *ortho* substituent), α,β-unsaturated carbonyls, 2° allylic alcohols, unprotected 3° allylic alcohols	styrenes, allyl stannanes
Type III	vinyl siloxanes	1,1-disubstituted olefins, 4° allylic carbons, protected 3° allylic alcohols, non-bulky trisubstituted olefins	acrylonitrile
Type IV	1,1-disubstituted olefins, α,β-unsaturated carbonyls,	protected trisubstituted allyl alcohols, vinyl nitro olefins	1,1-disubstituted olefins

Table 1.1 Olefin categories in CM chemistry

Allylic alcohols, sulfides and selenides have been observed to display unusually high reactivity in metathesis chemistry, leading some to refer to them as "privileged substrates."[92] This allylic chalcogen effect was first observed by Hoye and Zhao.[93] In a series of competition experiments they estimated the relative reactivity of a library of dienes in RCM. Those that contained an allylic alcohol clearly reacted in preference to those without and even a quaternary allylic alcohol reacted in preference to a secondary allylic carbon in a direct competition experiment. Allyl ethers were not found to exhibit any heightened reactivity suggesting that hydrogen bonding may be the responsible interaction. Pre-association of the catalyst and substrate *via* a hydrogen bonding interaction between the alcohol and a halide ligand would seem reasonable and explain the favourable reactivity observed. Hoveyda and co-workers utilised this proposed hydrogen bonding interaction to effect the stereoselective ring-opening cross metathesis (ROCM) of cyclopropene **190**.[94] With allyl alcohol **191**, ROCM produced (*S*,*R*)-diene **192** in high yield and excellent stereoselectivity. When allyl ether **193** was used, the di-

astereomer (*R*,*R*)-diene **194** was produced instead, and in both lower yield and selectivity. A transition state for the reaction with (*S*,*R*)-diene **192** that is consistent with stereochemical outcome was proposed. With the allylic alcohol substituent in a *pseudo* equatorial position, intramolecular hydrogen bonding conformationally locks the intermediate metal carbene. Cyclopropene attack then occurs from the opposite face to the bulky NHC ligand (Scheme 1.30).

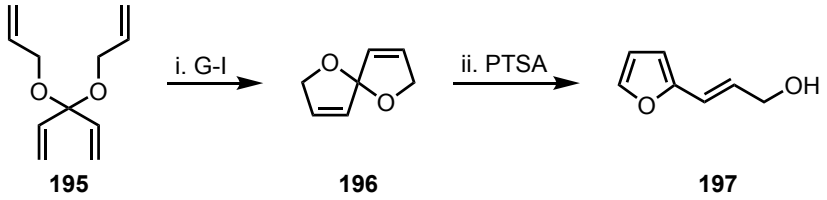


Scheme 1.30 Allylic chalcogen effect. [a]based on a series of competition experiments with the values representing a relative preference for reactivity (larger value ≡ greater propensity to react)

1.3.3 Metathesis Inspired Approaches to Furans

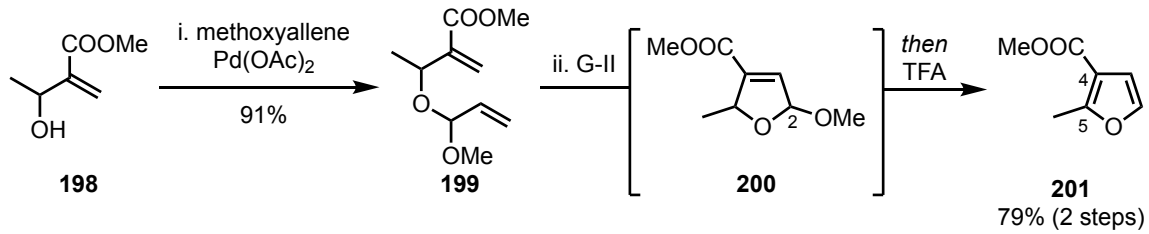
Olefin metathesis has found widespread application in the synthesis of heterocycles; creative approaches to saturated nitrogen and oxygen heterocycles using both CM and RCM have been developed.[95] More recently, the synthesis of heteroaromatics has also been accomplished with both CM and RCM being employed productively.[96,97]

The first example of an olefin metathesis approach to furans was reported by Harrity and co-workers in 1999. During investigations into the use of RCM to form spiroacetals, they observed the decomposition of acetal **196** to furan **197** on exposure to acid (Scheme 1.31).[98]



Scheme 1.31 Synthesis of furan **197** by Harrity and co-workers. Reagents and conditions: i) G-I, CH_2Cl_2, rt, 6 h; ii) PTSA, CH_2Cl_2, rt, 1 h

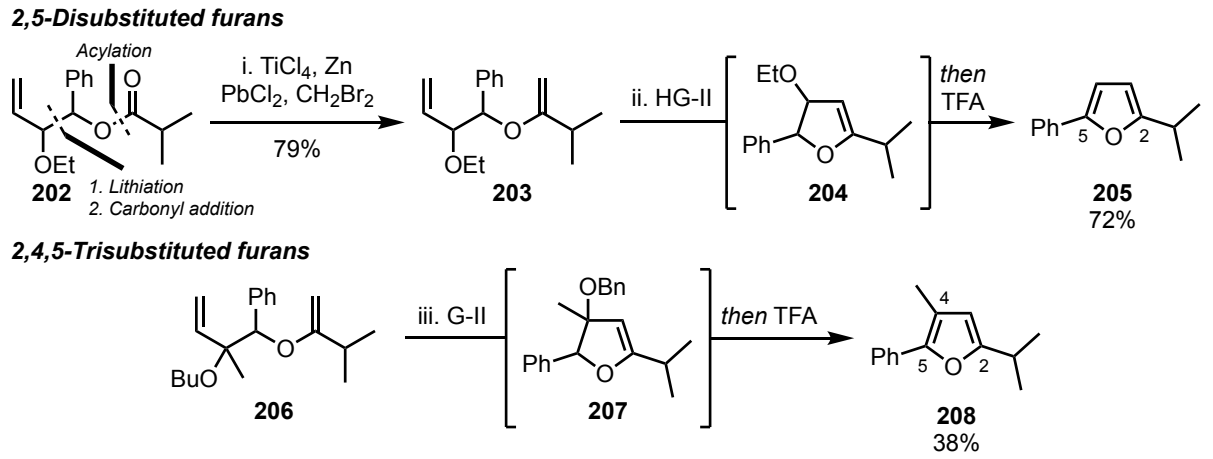
In 2005, Donohoe and co-workers published a study into the synthesis of furans and pyrroles using RCM.[99] Formation of mixed acetal **199** from allyl alcohol **198** preceded RCM to give cyclic acetal **200**. Elimination of MeOH from *C*-2 then provided furan **201** in 79% yield over two steps. Electron-rich and deficient aryl groups were tolerated at *C*-5 and aryl systems could also be incorporated into *C*-4 in place of the ester (Scheme 1.32).



Scheme 1.32 RCM approach to 4,5-disubstituted furans by Donohoe and co-workers. Reagents and conditions: i) methoxyallene, $Pd(OAc)_2$, dppe, Et_3N, MeCN, reflux, 91%; ii) G-II, CH_2Cl_2, reflux *then* TFA, 79% (2 steps)

In an extension of this work, Donohoe and co-workers later reported the synthesis of variously substituted furans from vinyl enol ethers; in this instance the alcohol leaving group was eliminated from the *C*-4 position of the furan.[100] Beginning from simple building blocks, es-

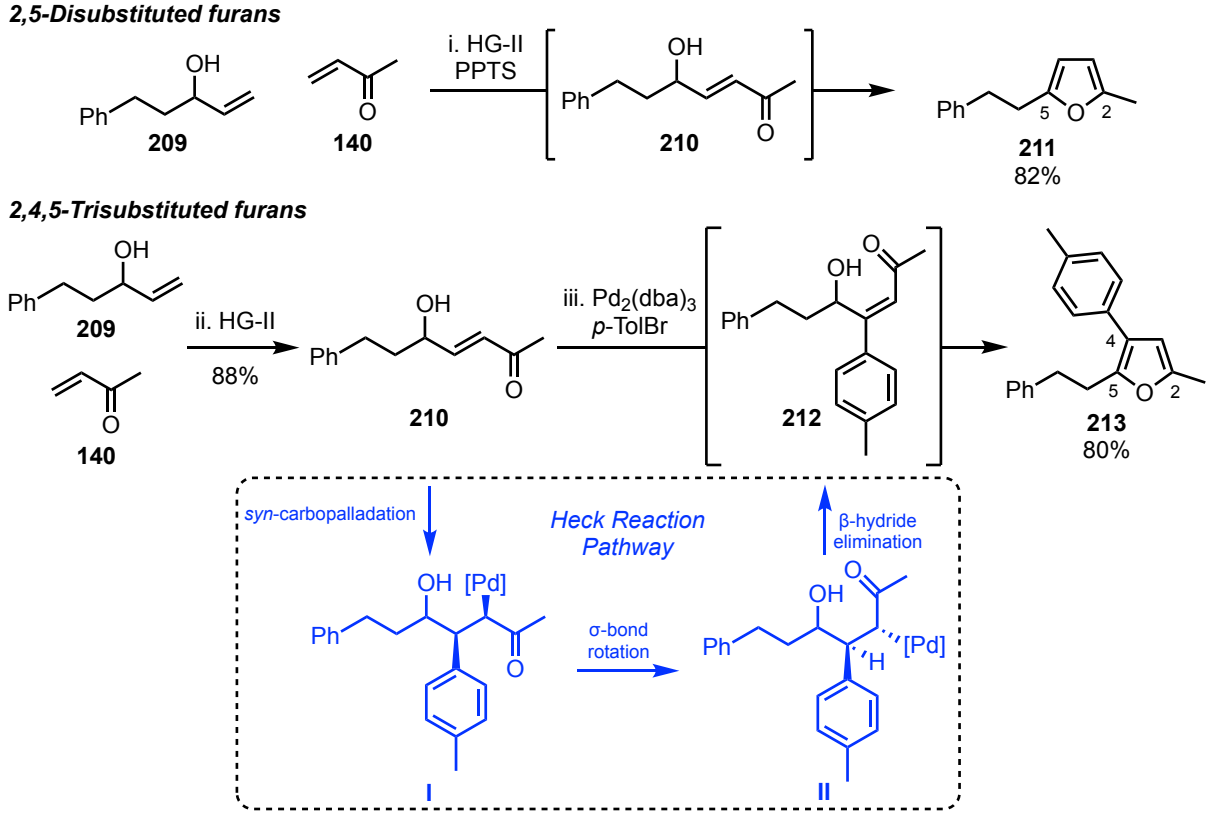
ter **202** was assembled and transformed into the required vinyl ether **203** using Takai–Utimoto methylenation. Treatment with HG-II catalyst provided cyclic enol ether **204** which underwent ethanol elimination on addition of acid to afford furan **205** in 72% yield. Aliphatic and electron deficient aromatic substituents were tolerated at both C-2 and C-5. The 2,4,5-trisubstituted furan **208** could also be synthesised although the yield for the RCM was lower, as might be expected with the increase in steric hindrance (Scheme 1.33).



Scheme 1.33 RCM approach to 2,5- and 2,4,5-substituted furans by Donohoe and co-workers. Reagents and conditions: i) $TiCl_4$, TMEDA, THF, 0 °C, 20 min *then* Zn, $PbCl_2$, rt, 30 min *then* **202**, CH_2Br_2, rt, 79%; ii) HG-II, PhMe, 60 °C *then* TFA, rt, 72%; iii) G-II, PhMe, 60 °C *then* TFA, rt, 38%

An alternative route employing ɣ-hydroxyenones was also devised by Donohoe and co-workers.[61] Subjection of allylic alcohol **209** and methyl vinyl ketone (**140**) to CM produced intermediate ɣ-hydroxyenone **210**. This could either be isomerised *in situ* with small quantities of PPTS to provide 2,5-disubstituted furan **211**, or isolated and subsequently aromatised using a Heck arylation reaction. In the latter case, σ bond rotation of Heck carbopalladation intermediate **I** is required to enable efficient β-hydride elimination from conformer **II**. This results in the (*E*) to (*Z*) olefin isomerisation of the ɣ-hydroxyenone and its direct condensation to 2,4,5-trisubstituted furan **213**. It is worth noting the beneficial impact of the allylic chalcogen effect on the efficiency of the CM, compensating for the lower reactivity of α,β-unsaturated carbonyls and delivering the desired ɣ-hydroxyenones in good yields. Additionally, aliphatic,

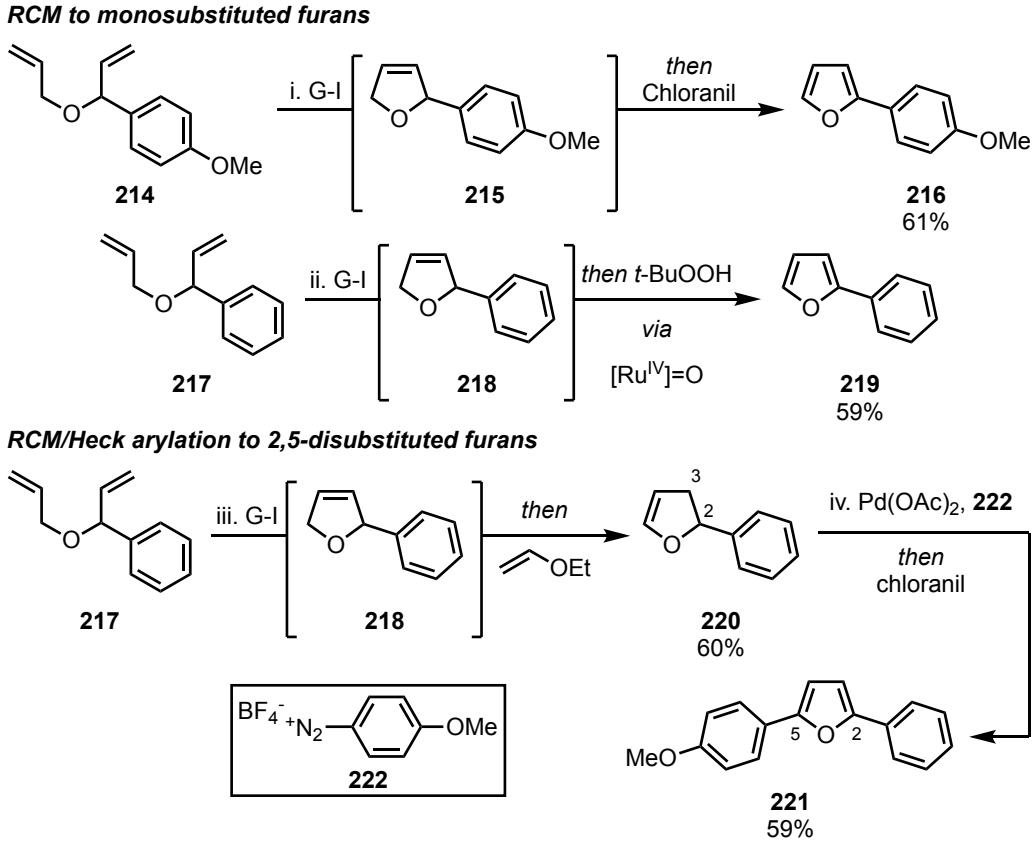
aromatic and heterocyclic substituents were tolerated at C-2 and C-5. Electron rich, electron poor and heterocyclic aromatic systems could be installed *via* the Heck reaction and one example of an intramolecular Heck reaction was also reported (Scheme 1.34).



Scheme 1.34 CM approach to 2,5- and 2,4,5-substituted furans by Donohoe and co-workers. Reagents and conditions: i) HG-II, PPTS, CH_2Cl_2, 40 °C, 24 h, 82%; ii) HG-II, CH_2Cl_2, 40 °C, 24 h, 88%; iii) *p*-TolBr, $Pd_2(dba)_3$, P*t*-Bu_3·HBF_4, Cy_2NMe, dioxane, 70 °C, 16 h, 80%

Recently, two further examples of the use of RCM in furan synthesis have been reported by Schmidt and co-workers.[101,102] Starting from allylic ether **214** they were able to effect the formation of 2,5-dihydrofuran **215**. In the absence of a leaving group, aromatisation to furan **216** was achieved *via* oxidation with DDQ or chloranil. Alternatively, *t*-BuOOH could be added, decomposing the ruthenium metathesis catalyst to the oxo-Ru(IV) species which mediated the required oxidation to monosubstituted furan **219**. The 2,5-dihydrofuran intermediate **218** could also be isomerised to the 2,3-dihydrofuran **220** by addition of vinyl ethyl ether. Once again, a catalyst decomposition product, a ruthenium hydride species, is proposed to have driven the transformation.[103] A Heck arylation then installed an aromatic group at C-5

and oxidation with chloranil or DDQ provided 2,5-disubstituted furan **221**. In all cases a number of aliphatic substituents were additionally tolerated along with a range of electron rich and electron poor aromatic substituents (Scheme 1.35).



Scheme 1.35 RCM approach to 2- and 2,5-substituted furans by Schmidt and co-workers. Reagents and conditions: i) G-I, PhMe, 50 °C, 1.5 h *then* chloranil, 90 °C, 20 h, 61%; ii) G-I, benzene, 20 °C, 30 min *then* *t*-BuOOH, 20 °C, 30 min, 59%; iii) G-I, PhMe, 40 °C, 1.5 h *then* $EtOCHCH_2$, 110 °C, 60%; iv) **222**, $Pd(OAc)_2$, NaOAc, MeCN, 20 °C, 15 min *then* chloranil, 80 °C, 20 h, 59%

1.4 Research Proposal

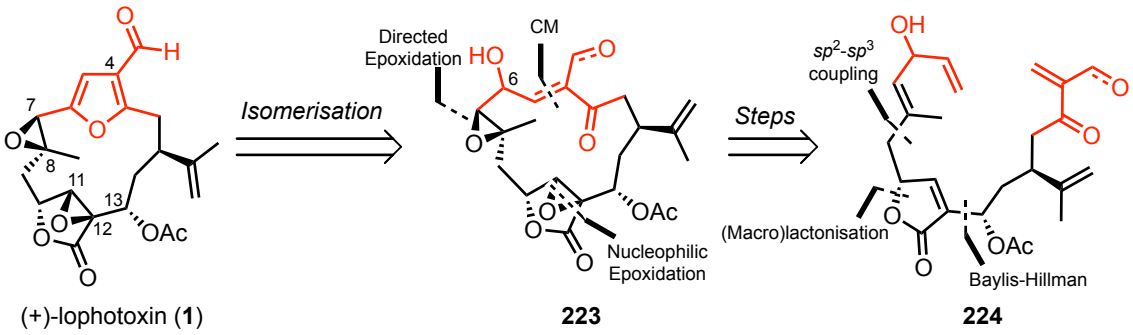
Although many synthetic approaches to furanocembranoid natural products have been disclosed, the completed synthesis of a more highly oxidised member of the family remains elusive. In particular, installation of the *C*-7/8 epoxide has proved challenging and prior to the recent report of (+)-17-deoxyprovidencin (**126**) by Mulzer and co-workers, no synthesis of a furanocembranoid derivative incorporating this moiety had been achieved. In their synthesis, masking of the additional exocyclic olefin was required to achieve selective epoxidation.

(+)-Lophotoxin (**1**) is often referred to as the flagship member of the furanocembranoid family, but despite its impressive biological activity it has not yet been synthesised in the laboratory. It is one of the most highly oxidised members of the family, bearing epoxides at *C*-7/8 and *C*-11/12, an acetate at *C*-13 and an aldehyde at *C*-4, and this complexity has supplemented the inherent synthetic challenge. Thus far only *bis*-deoxylophotoxin (**68**), with alkenes in place of the epoxides, has been synthesised with an otherwise similarly oxidised carbon framework.

The task of installing the crucial epoxides is further complicated by the instability of furan heterocycles to oxidising agents. Indeed, this reactivity has been exploited by Trauner and Pattenden in their approaches to (+)-isoepilophodione (**98**) and (+)-intricarene (**101**), oxidising the furan core to the corresponding 1,4-diketone.

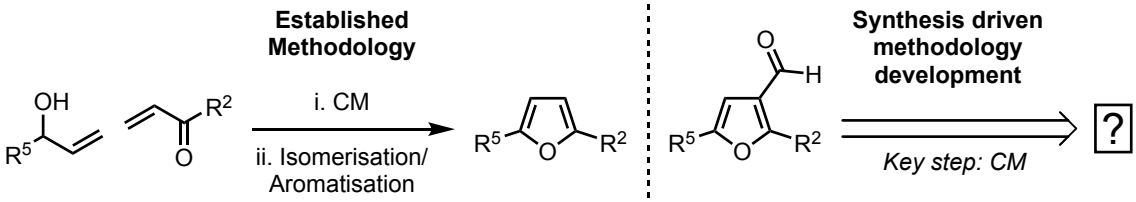
It was therefore determined that any synthesis of a highly oxidised furanocembranoid should be based on a 'furan-last' strategy, installing the epoxide prior to furan formation, thereby avoiding the use of strong epoxidising agents in the presence of the furan core. In this regard, the utility of the CM approach to furan heterocycles previously developed by the Donohoe group was identified. The ɣ-hydroxyenone metathesis products could be thought of as latent furan sources and a suitably functionalised derivative could be epoxidised prior to isomerisation to the furan at a late stage in the synthesis. The utility of the *C*-6 allylic alcohol as a di-

recting group for the *C*-7/8 epoxidation was also noted. (+)-Lophotoxin (**1**) was identified as a suitable target to test this hypothesis and further potential disconnections are highlighted; the final route would be designed once the exact methodology was established (Scheme 1.36).



Scheme 1.36 Metathesis approach to the furan core of (+)-lophotoxin (**1**) and potential disconnections

At the outset it was recognised that an extension to the CM approach to furans would have to be developed to facilitate installation of the single-carbon unit destined to be the *C*-4 aldehyde of (+)-lophotoxin (**1**). The realisation of an approach to synthetically useful trisubstituted furans would thus be the first goal of the investigation. Following the development of appropriate methodology, the synthesis of (+)-lophotoxin (**1**) would be attempted (Scheme 1.37).



Scheme 1.37 CM derived synthetic methodology to trisubstituted furans

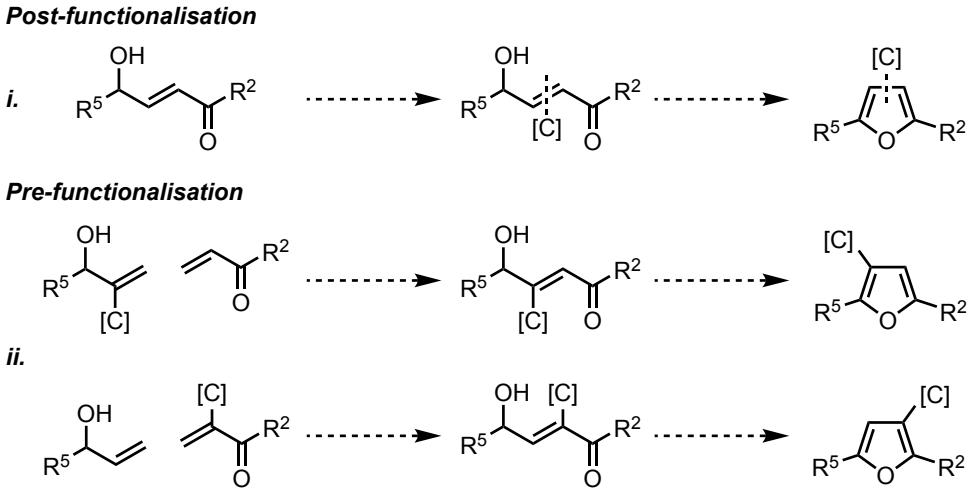
At this stage, the very recent disclosure of the synthesis of (+)-7-*epi*-pukalide (**133**) by Clark and co-workers should be acknowledged (see Section 1.1.4.13). They similarly highlighted the dearth of successful approaches to highly oxidised furanocembranoids and the difficulties associated with the installation of the *C*-7/8 epoxide. Using their own methodology they were able to effect the late stage formation of the *C*-7/8 epoxide and furan moieties in the same pot without resorting to potentially decomposing epoxidation conditions, although they were only able to produce the *C*-7 epimer of the natural product.

Chapter 2

Methodology Development and Model Studies towards (+)-Lophotoxin

2.1 Initial Research Aims

The design of a route towards (+)-lophotoxin (**1**) incorporating the reported CM protocol to form the furan required development of an extension to the methodology to allow for the installation of a single-carbon unit at the *C*-3 or *C*-4 position of the heterocycle. Two potential strategies towards this goal presented themselves at the outset; post-functionalisation of the CM products (Scheme 2.1, *i*) or pre-functionalisation of the CM precursors where both furan regioisomers would be accessible depending on whether the allylic alcohol or enone fragment was functionalised (Scheme 2.1, *ii*). Both approaches were investigated.



Scheme 2.1 Potential strategies towards trisubstituted furans

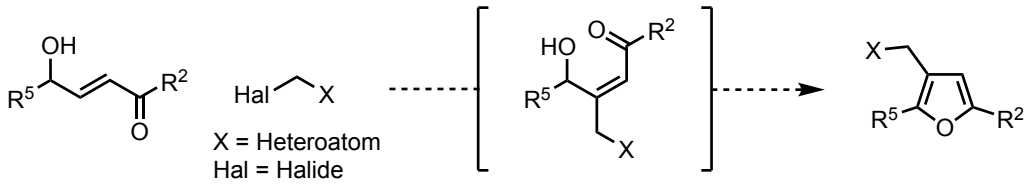
2.2 Attempted Development of a Cross Metathesis Protocol

2.2.1 Post-functionalisation of Cross Metathesis Products

Post-functionalisation of the CM products represented a highly attractive approach as a single intermediate could be transformed into furans incorporating either methyl, aldehyde or methyl ester substituents, providing access to the entire class of furanocembranoid cores. Both regioisomers of the trisubstituted furan could hypothetically be formed depending on the method of functionalisation. Previous work in the Donohoe group had already demonstrated the use of Heck reactions to furnish arylated furans from CM products.[61]

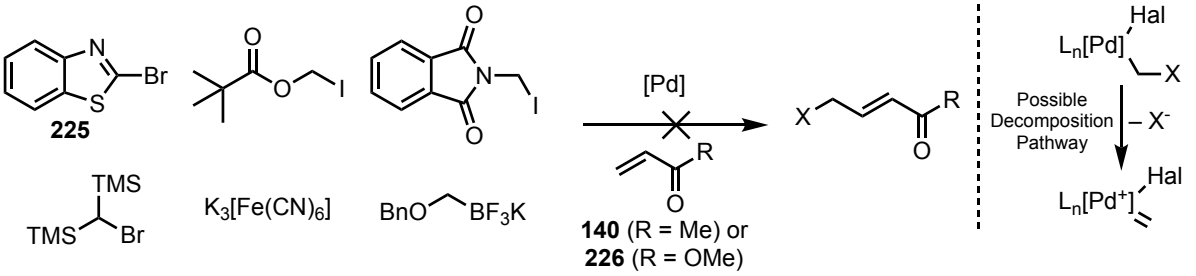
2.2.1.1 Single-carbon Units in Heck Reactions

Initial investigations in this area concentrated on the engagement of single-carbon organohalides or pseudohalides in Heck reactions, an as yet unknown transformation.[104] The inversion of olefin geometry inherent in the Heck reaction would facilitate *in situ* aromatisation of the intermediate to afford the 2,4,5-trisubstituted furans directly (Scheme 2.2).



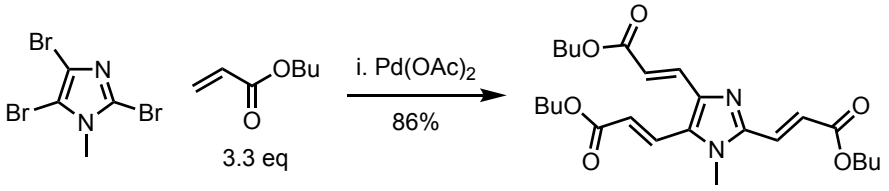
Scheme 2.2 Potential route to trisubstituted furans employing single-carbon units in Heck reactions

A number of potential single-carbon units were identified and screened in Heck reactions using ethyl acrylate (**226**) and methyl vinyl ketone (**140**) as model olefins. Unfortunately, no product formation was observed in any case. The single-carbon species was often consumed and it was proposed that the oxidative addition complex could be unstable for some substrates. Elimination from the complex is one plausible decomposition pathway (Scheme 2.3).



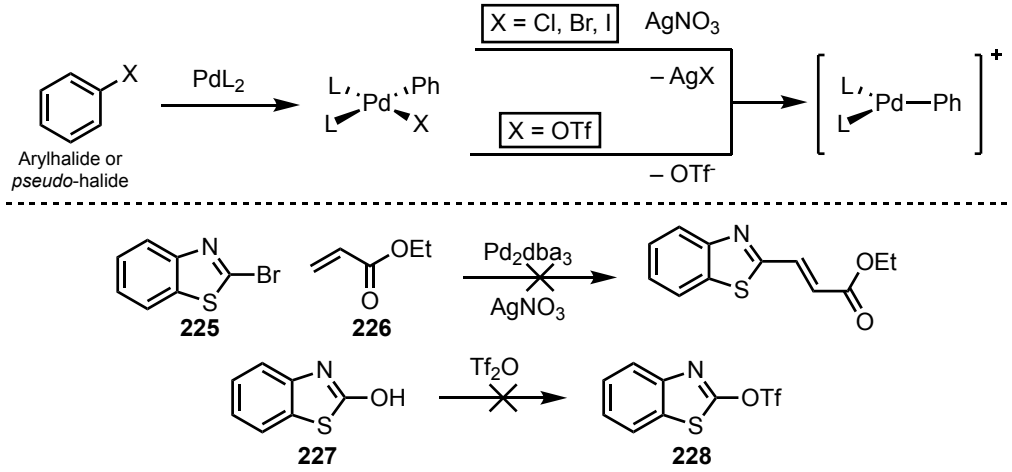
Scheme 2.3 Attempted use of single-carbon units in Heck reactions

Some substrates, including 2-bromobenzothiazole (**225**), were unreactive. It had been hoped to exploit the thiazole motif as an aldehyde surrogate, as conceived by Dondoni and co-workers.[105] 2-Bromobenzothiazoles have previously demonstrated competency in other cross-coupling reactions but only a small number of examples exist of their use in Heck reactions (in the patent literature). There is only one further example of any 1,3-azole exhibiting Heck reactivity with α,β-unsaturated carbonyls, disclosed by Toguem and Langer (Scheme 2.4).[106]



Scheme 2.4 Heck reaction of a 1,3-azole by Toguem and Langer. Reagents and conditions: i) $Pd(OAc)_2$, PCy_3, Et_3N, DMF, 100 °C, 24 h, 86%

One possible explanation for this lack of reactivity in Heck reactions is the increased σ donating ability of 1,3-azoles at their *C*-2 position. This likely decreases the electrophilicity of the oxidative addition complex, disfavouring coordination and migratory insertion of the formally nucleophilic olefin. The complex can be made more electrophilic through dissociation of the halide or pseudohalide substituent, forming a cationic Pd species. This is often referred to as the cationic Heck reaction pathway (Scheme 2.5).[107]

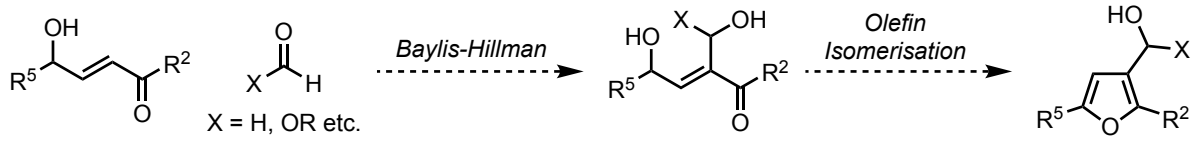


Scheme 2.5 Cationic Heck reactivity: Principles and attempted implementation

Cationic Heck reactivity is conventionally accessed by addition of $AgNO_3$ to reactions with aryl halides, where the formation of the silver halide salt is highly favourable, or use of the corresponding aryl organotriflate, as the triflate anion is weakly coordinating. Unfortunately, addition of $AgNO_3$ failed to induce product formation with 2-bromobenzothiazole (**225**); starting material decomposition was now evident in the ^1H NMR spectrum of the crude reaction mixture. Conversion of alcohol **227** to triflate **228** was also unsuccessful; no useful product could be isolated from the complex mixture formed.

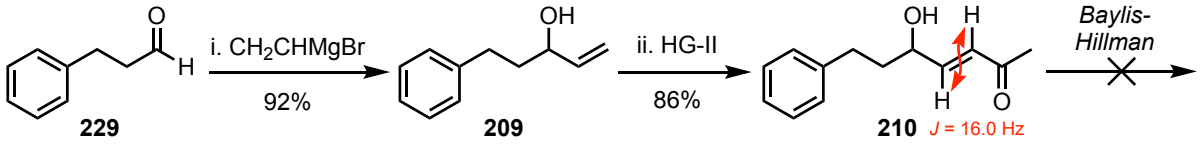
2.2.1.2 Baylis–Hillman Reactions

Baylis–Hillman reactions offer an alternative process whereby modification of an olefin can be achieved whilst leaving the original carbon framework intact. Use of a suitable single-carbon electrophile was envisaged to provide access to the functionalised trisubstituted olefin, or the trisubstituted furan if *in situ* isomerisation mediated by the nucleophilic catalyst occurred.



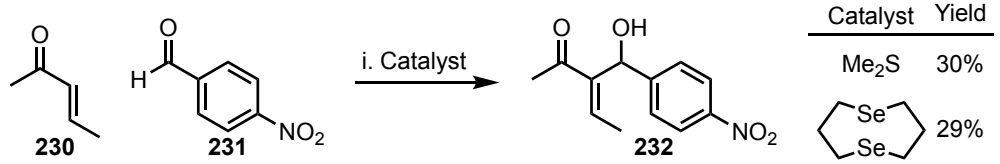
Scheme 2.6 Baylis–Hillman approach to functionalising CM products

Model enone **210** was synthesised in 79% yield from 3-phenylpropanal (**229**) by Grignard addition of a vinyl group and HG-II catalysed CM with methyl vinyl ketone (**140**). However, it was established by a co-worker that intermolecular Baylis–Hillman reactions of enone **210** with aldehydes were not feasible (Scheme 2.7).[153]



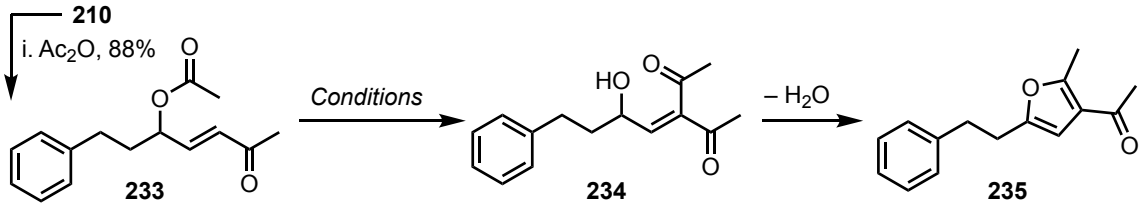
Scheme 2.7 Synthesis of enone **210** and its attempted use in Baylis–Hillman reactions. Reagents and conditions: i) 1.1 eq. vinylmagnesium bromide, THF, –78 °C, 2.5 h, 92%; ii) 5 eq. methyl vinyl ketone, 2.5 mol% HG-II, PhMe, rt, 24 h, N_2 flow, 86%

Once again, examples of this kind of reactivity are scarce in the literature with only two examples of linear internal α,β-unsaturated systems engaging in intermolecular Baylis–Hillman reactions reported. α,β-Unsaturated nitriles could be reacted at very high pressures in a mechanistic study[108] and unconventional (chalcogenide) catalysts effected the reaction of ketone **230** with aryl aldehyde **231** (Scheme 2.8).[109]



Scheme 2.8 Literature example of internal enones participating in Baylis–Hillman reactions. Reagents and conditons: i) 1 eq. **230**, 3 eq. **231**, 10 mol% catalyst, 1 eq. $TiCl_4$, CH_2Cl_2, rt, 6 h

It is generally assumed that the poor reactivity of linear internal α,β-unsaturated carbonyl systems in Baylis–Hillman reactions is due to the increase in steric hindrance at the β-position and the favourable release of the catalyst from the *trans* double bond.[110,111] Aside from the two isolated examples above, internal enones are only known to be effective substrates for Baylis–Hillman reactions in cyclic systems (eg. cyclohexenone), where geometric inversion is prohibited, or for intramolecular reactions where the close spatial displacement of the reactive centres helps overcome the poor inherent reactivity.[112,113] On the basis of the latter examples, acetate **233** was designed to allow for internal transfer of an acetate group. It was hoped that *in situ* condensation would then form furan **235**. Acetate **233** was synthesised by acylation of alcohol **210** in 88% yield and then subjected to a range of literature known Baylis–Hillman conditions.[114] Unfortunately, no desired reactivity was observed with acetate cleavage the only discernible outcome by ^{1}H NMR spectroscopy. It is possible that the acetate was not reactive enough to be trapped by the internal enolate; in literature examples of *intramolecular* Baylis–Hillman reactions the electrophile is either an aldehyde or an alkyl halide (Table 2.1).



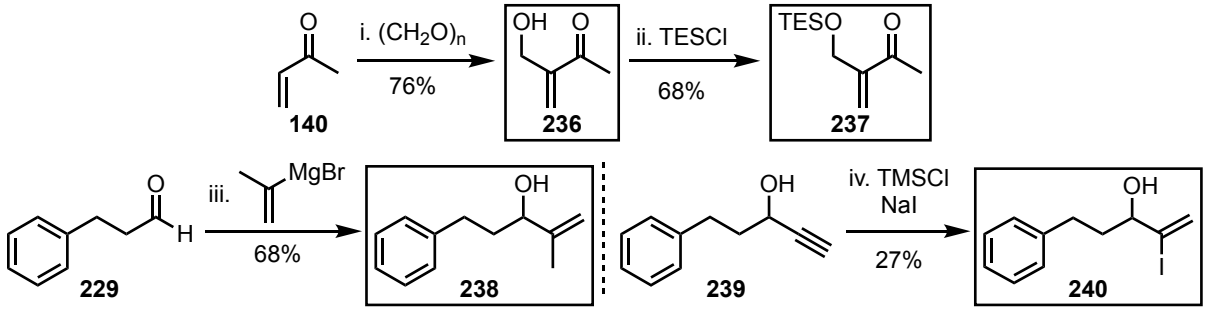
Entry	Conditions	Result
1	PPh_3, 4-nitrophenol, THF, rt to 50 °C	No reaction
2	Bu_3P, $BnEt_3NCl$, KOH(aq), *t*-BuOH:CH_2Cl_2, rt	Acetate cleavage
3	Bu_3P, PhMe, 85 °C	No reaction
4	$TiCl_4$, THF, rt	No reaction

Table 2.1 Synthesis of acetate **233** and screening of conditions for intramolecular Baylis–Hillman reactions. Reagents and conditions: i) 1.5 eq. Ac_2O, 2 eq. Et_3N, 10 mol% DMAP, $CHCl_3$, rt, 3 h, 88%

A number of other methods for functionalising the CM product were investigated including enone bromination and lithium amide conjugate addition/enolate trapping protocols.[115] These approaches were also unsuccessful and will not be discussed further.

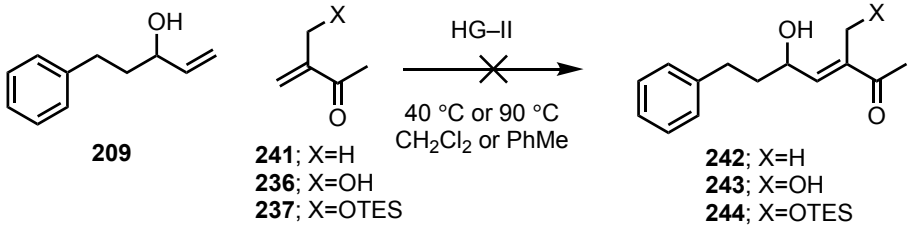
2.2.2 Pre-functionalisation of Cross Metathesis Precursors

With the failure of post-metathesis functionalisation, attention turned to the direct CM of substrates pre-functionalised with a single-carbon unit. Suitably functionalised model substrates were produced from commercial materials (**240** by a co-worker, Scheme 2.9).



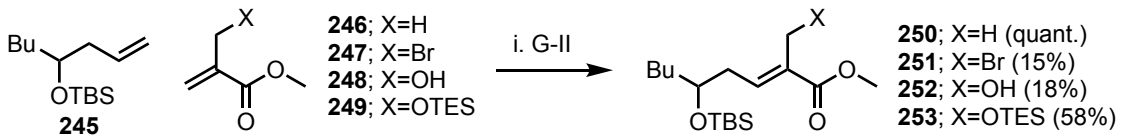
Scheme 2.9 Synthesis of building blocks. Reagents and conditions: i) 2 eq. $(CH_2O)_n$, 10 mol% DABCO, dioxane:H_2O (1:1), rt, 2 h, 76%; ii) 1.2 eq. TESCl, 2 eq. Et_3N, 1 eq. DMAP, CH_2Cl_2, 0 °C, 2 h, 68%; iii) 1.1 eq. isopropenylmagnesium bromide, THF, –78 °C to rt, 4 h, 68%; iv) 1.5 eq. TMSCl, 1.5 eq. NaI, 1.5 eq. H_2O, MeCN, rt, 24 h, 27%. Reaction iv performed by Simon Werrel

At the outset, 1,1-disubstituted enones **236**, **237** and **241** were separately subjected to CM with allyl alcohol **209**. Unfortunately, no product formation was observed in any case. Increasing the reaction temperature also failed to initiate the desired reactivity (Scheme 2.10).



Scheme 2.10 Failed CM with 1,1-disubstituted enones

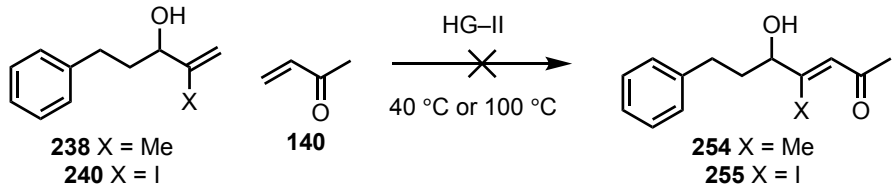
These results were somewhat surprising in the context of a report by Prunet and co-workers where similar 1,1-disubstituted acrylates **246**–**249** had been shown to react successfully with protected homoallylic alcohol **245** (Scheme 2.11).



Scheme 2.11 CM of 1,1-disubstituted enones by Prunet. Reagents and conditions: i) 3 eq. enone, 5 mol% G-II, CH_2Cl_2, 40 °C, 48 h

However, homoallylic alcohol **245** is less sterically demanding than allylic alcohol **209** and

acrylates are generally considered to be slightly more reactive than the corresponding enones in CM chemistry. According to the classifications proposed by Grubbs and co-workers, 1,1-disubstituted olefins are less reactive type III olefins that do not undergo homodimerisation.[91] The additional ketone substituent of enones **236**, **237** and **241** likely attenuates their reactivity further. Switching the single-carbon substituent to the allylic alcohol metathesis partner might be a productive strategy as the allylic chalcogen effect (see Chapter 1.3.1) could partially offset the increase in steric hindrance. Unfortunately, no reaction was observed between sterically less demanding methyl vinyl ketone (**140**) and 1,1-disubstituted allyl alcohols **238** or **240** at either 40 °C or 100 °C. Vinyl iodide **240** was chosen due to its potential for further derivatisation. These reactions were performed by a co-worker (Scheme 2.12).



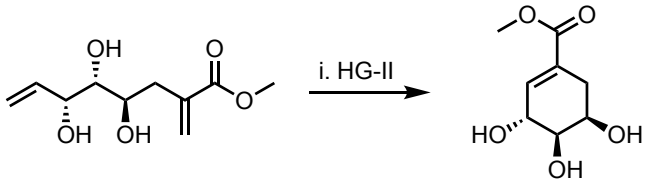
238 X = Me
240 X = I

140

254 X = Me
255 X = I

Scheme 2.12 Failed CM with 1,1-disubstituted allylic alcohols. Reactions performed by Simon Werrel

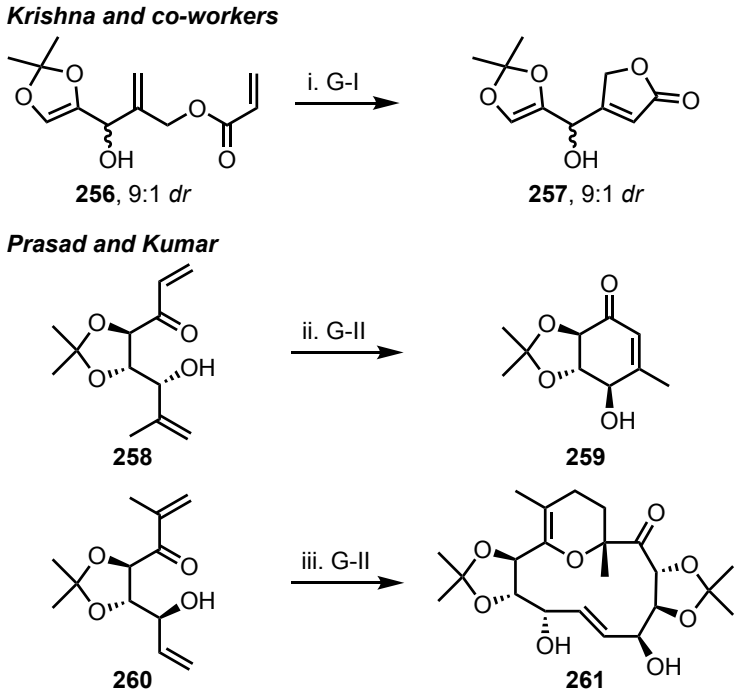
This general lack of reactivity is reflected in the fact that there are no literature examples of CM reactions with these substitution patterns. A single example of a RCM between a secondary allylic alcohol and a 1,1-disubstituted acrylate has been reported by Kiessling and co-workers, and was only made possible by using a high catalyst loading (Scheme 2.13).[116]



Scheme 2.13 Successful RCM reported by Kiessling. Reagents and conditions: i) 29 mol% HG-II, PhMe:CH_2Cl_2 (94:6), 50 °C, 5 h, 79%

Two examples exist of 1,1-disubstituted secondary allylic alcohols undergoing RCM with a terminal enone. Krishna and co-workers found ester **256** could be transformed into furanone **257** with G-I[117] and Prasad and Kumar showed that G-II enabled RCM of

acetonide **258** to cyclohexenone **259**.[118] Interestingly, acetonide **260**, where the 1,1 disubstitution had been switched from the allylic alcohol to the enone, did not engage in the expected RCM and instead underwent a homodimerising CM/Diels-Alder cascade to furnish macrocycle **261** (Scheme 2.14).



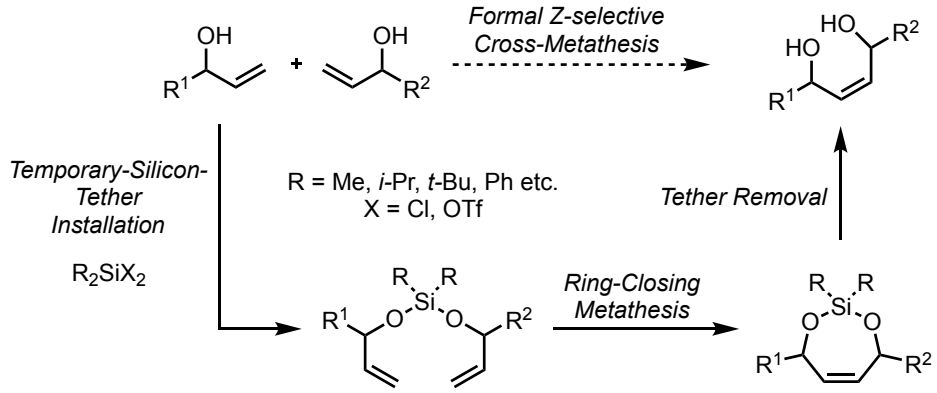
Scheme 2.14 Successful RCM reported by Krishna and Prasad. Reagents and conditions: i) 30 mol% G-I, CH_2Cl_2, reflux, 48 h, 62%; ii) 5 mol% G-II, CH_2Cl_2 (0.015 M), 50 °C, 6 h, 62%; iii) 5 mol% G-II, CH_2Cl_2 (0.015 M), 50 °C, 6 h, 69%

The success of both substitution patterns in RCM was encouraging and suggested that if the proposed CM reaction could be rendered intramolecular, a viable route to trisubstituted furans could be established.

2.3 Temporary-Silicon-Tether Ring-Closing Metathesis Approach

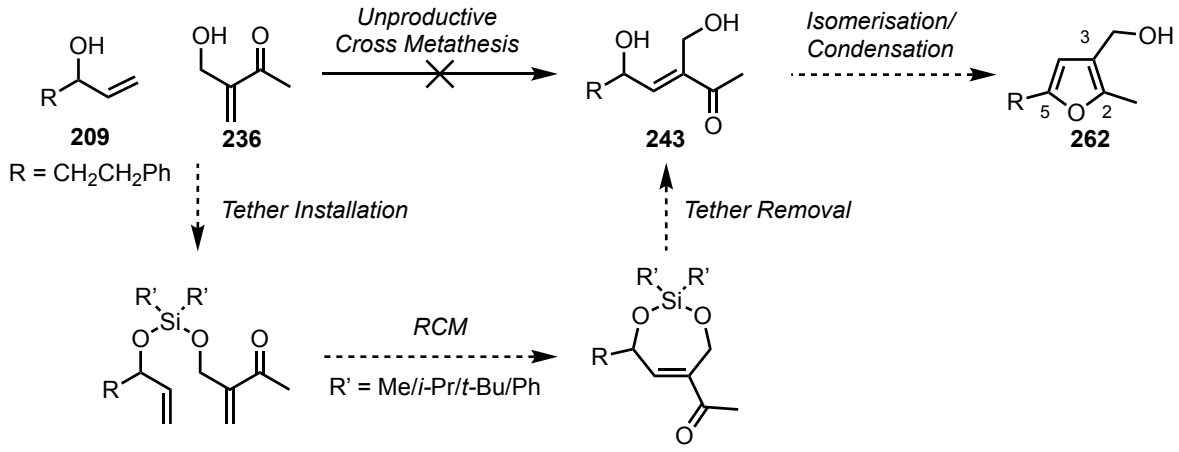
Prior to the recent advent of *Z*-selective CM catalysts, the synthesis of *cis*-disposed 1,2 disubstituted olefins through formal CM chemistry could only be achieved by use of temporary tethers. In this regard, temporary-silicon-tethers (TSTs) are the most prevalent and their application is well reviewed.[119] The olefins, usually bearing pendent alcohols, are bound together using a doubly electrophilic silicon source before RCM. The formal (*Z*)-CM product is then

unveiled by tether cleavage. This sequence is frequently described as temporary-silicon-tether ring-closing metathesis (TST-RCM) (Scheme 2.15).



Scheme 2.15 TST-RCM as a surrogate for *Z*-selective CM

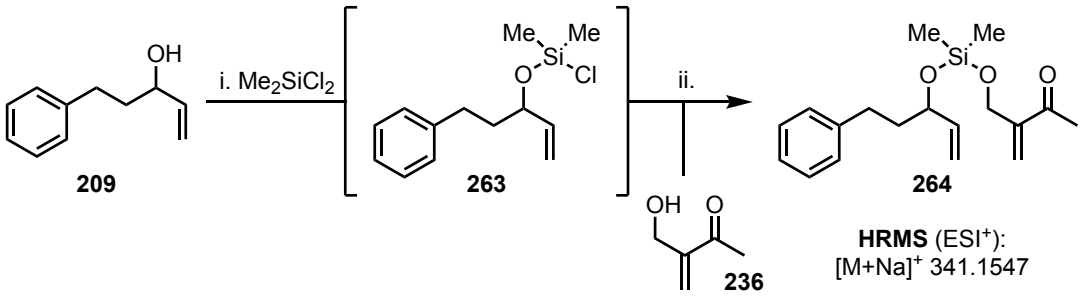
Of the metathesis partners already explored, allyl alcohols **209** and **236** were suitably substituted for incorporation into a TST-RCM sequence. Following TST formation and RCM, deprotection of the tether would lead to diol **243** which would be isomerised and undergo *in situ* condensation to trisubstituted furan **262** bearing a $–CH_2OH$ moiety at the *C*-3 position. In this way the unreactivity of the intermolecular CM reaction attempted earlier (see Scheme 2.10) would hopefully be overcome. The $–CH_2OH$ moiety could be modified to aldehyde, methyl or methyl ester functionalities, helping the methodology find broad application in furanocembranoid synthesis, beyond (+)-lophotoxin (**1**) (Scheme 2.16).



Scheme 2.16 Model system to investigate a TST-RCM route to trisubstituted furans

2.3.1 First Generation Temporary-Silicon-Tether

Efforts towards this goal began with the synthesis of TST **264**. Me_2SiCl_2 was selected as the electrophilic silicon source due to its ease of removal; it was hoped that tether removal in the presence of other silyl protecting groups might be possible and could prove useful in the context of multi-step natural product synthesis. Following the protocol established by Verdine and co-workers, alcohol **209** was added slowly to excess Me_2SiCl_2 in pyridine and was assumed to give silyl chloride **263**.[120] Excess Me_2SiCl_2 was required to prevent the formation of the symmetrical TST of alcohol **267** (see Scheme 2.20), but needed to be removed prior to the addition of alcohol **236** to ensure its selective silylation with silyl chloride **263**. The low boiling point of Me_2SiCl_2 (70 °C/atm) enabled its removal on a rotary evaporator. Addition of alcohol **236** to crude silyl chloride **263** then furnished TST **264** in 34% yield, along with unreacted alcohol **209** (Table 2.2, Entry 1).



Entry	Conditions: Step i	Conditions: Step ii	Yield 264
1	20 eq. Me_2SiCl_2, pyridine (0.1 M), rt, 2 h.[a]	1 eq. **236**, pyridine (0.15 M), rt, 2 h	34%[b]
2	20 eq. Me_2SiCl_2, 20 eq. pyridine, CH_2Cl_2 (0.1 M), 0 °C to rt, overnight.[a]	1.2 eq. **236**, 20 eq. pyridine, CH_2Cl_2 (0.1 M), rt, 3.5 h	40%
3	20 eq. Me_2SiCl_2, 20 eq. pyridine, CH_2Cl_2 (0.1 M), 0 °C to rt, overnight.[c]	As Entry 2 except: 1.25 h	63%
4	As Entry 3	As Entry 2 except: 2.75 h	57%
5	As Entry 3	As Entry 2 except: 45 min	67%
6	As Entry 3	As Entry 2 except: 15 min	77%

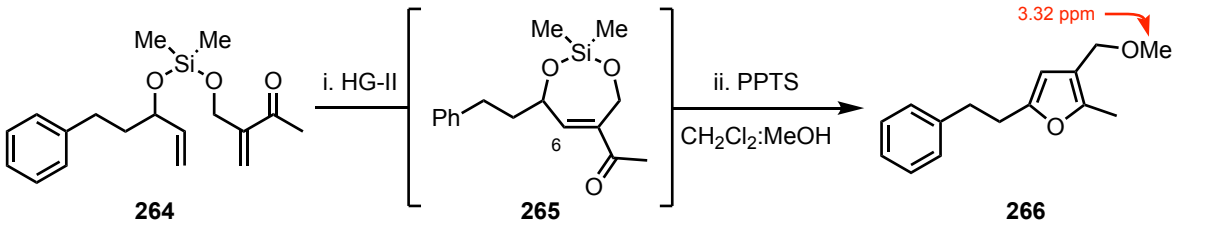
Table 2.2 Optimisation of formation of TST **264**. [a]Volatiles removed *via* rotary evaporator after Step i [b]Incomplete consumption of **209** [c]Volatiles removed *via* distillation under inert atmosphere after Step i

Changing the solvent to CH_2Cl_2 allowed for a reduction in the quantity of base whilst still

maintaining the reaction concentration. Stirring the initial silylation (Step i) overnight resulted in complete consumption of alcohol **209** and a slight increase in yield of TST **264** to 40% (Entry 2). The low yields were attributed to the practical aspect of removing volatiles after Step i; concentration on a rotary evaporator (in air atmosphere) likely led to the partial hydrolysis of silyl chloride **263**. White fumes suspected to be HCl could be observed on concentration. To enable concentration of the reaction mixture in an inert atmosphere, the reaction flask was fitted with a distillation bridge/receiver flask and connected to a high vacuum/dry N_2 manifold. After the initial silylation had been concluded under N_2 atmosphere, the system was slowly placed under vacuum and the volatiles condensed into the receiver flask. The reaction setup was then recharged with N_2 and additional solvent and base, and finally alcohol **236**, were added to the reaction flask through a rubber septum. In this way, exposure to air atmosphere was minimised and TST **264** could be furnished in 63% yield (Entry 3). The duration of the second silylation was found to be crucial to the performance of the reaction as the product apparently decomposed under the conditions; longer reaction times gave lower overall yields (Entries 3–5). Pleasingly, reducing the reaction time to 15 min afforded TST **264** in 77% yield on 100 mg scale. The reaction was scalable without any modification and yields of 76% (300 mg) and 75% (1 g) were achieved.

With TST **264** in hand, attention turned to the proposed RCM. Reaction of TST **264** with HG–II in CH_2Cl_2 at 40 °C was unsuccessful with only starting material observed by TLC after 4 days. However, increasing the temperature to 80 °C and performing the reaction in PhMe resulted in partial consumption of TST **264**. Silaketal **265** could be identified in the ^{1}H NMR spectrum of the crude reaction mixture (disappearance of methylene CH_2 protons and appearance of a signal at 6.59 ppm, consistent with *C*-6 enone) but could not be isolated by flash column chromatography (FCC), proving unstable to silica. Pleasingly, subjection of the crude

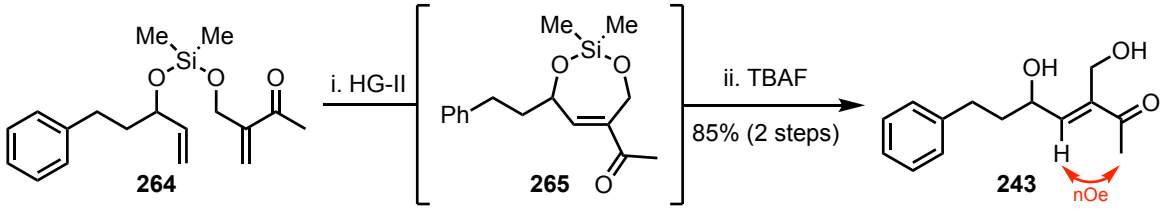
material to mild acid resulted in deprotection and cyclisation to furan **266** in 43% yield. Increasing the dilution of the RCM to 0.005 M provided furan **266** in an improved 84% yield (Scheme 2.17).



Reaction conc. step i	Yield (2 steps)
0.02 M	43%
0.005 M	84%

Scheme 2.17 RCM and cyclisation to furan **266**. Reagents and conditions: i) 10 mol% HG-II, PhMe, 80 °C, 24 h; ii) 4 eq. PPTS, CH_2Cl_2:MeOH (1:1, 0.05 M), 40 °C, 15 h

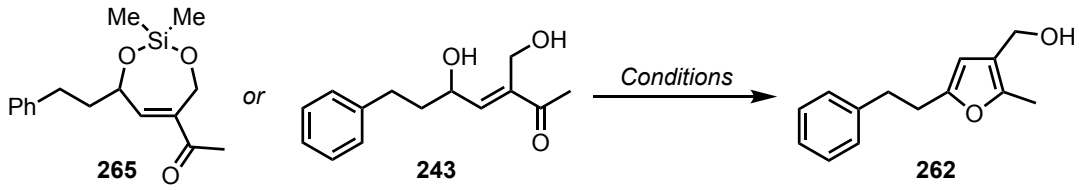
Modification of the methyl ether to functionalities pertinent to the furanocembranoids was briefly attempted. Unfortunately, deprotection, oxidation or substitution of the methyl ether moiety were all unsuccessful. Effecting cyclisation with alcohols other than MeOH also proved difficult with separation issues (prenol) or poor reactivity (*t*-BuOH, 15% yield) preventing this from being a useful strategy when small quantities of the furans were observed. However, TST deprotection under basic conditions could be performed without inducing cyclisation. Using TBAF, a co-worker was able to produce diol **243** in 85% yield (Scheme 2.18).



Scheme 2.18 Deprotection of silaketal **265**. Reagents and conditions: i) 10 mol% HG-II, PhMe, 80 °C, 24 h; ii) 2.5 eq. TBAF, THF, 0 °C, 3 h, 85% over 2 steps. Reactions performed by Simon Werrel

As methyl ether **266** could not be suitably transformed, a direct synthesis of furan **262**, incorporating the pendent -CH_2OH group, was required. Both the one-pot deprotection/isomerisation/cyclisation of crude silaketal **265** and the isomerisation/cyclisation of diol **243** were attempted. Starting from silaketal **265**, exchange of MeOH with H_2O in the conditions used to form methyl ether furan **266** led to a biphasic mixture and decomposition of the starting mate-

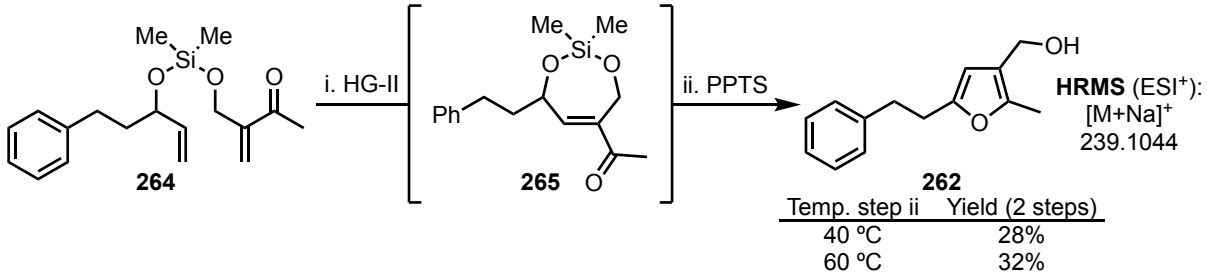
rial (Table 2.3, Entry 1), as did use of anhydrous HCl in dioxane (Entry 2). Tether deprotection was sometimes observed and in those cases diol **243** only was isolated. This reactivity was assumed to be the result of the increased miscibility of THF and H_2O (Entry 3) or the presence of a phase transfer catalyst (Entry 4). Diol **243** was unreactive under a range of acidic conditions (Entries 5–7). Increasing the acid strength was not found to have a beneficial effect; indeed, use of TFA resulted in decomposition of the starting material (Entry 8).



Entry	Starting Material	Conditions	Yield	
			243	**262**
1	**265**	1 eq. PPTS, CH_2Cl_2:H_2O (1:1, 0.02 M), 40 °C, 24 h	-	-
2	**265**	4 M HCl in Dioxane, 40 °C, 24 h	-	-
3	**265**	1 eq. PPTS, THF:H_2O (1:1, 0.02 M), 40 °C, 24 h	48%	-
4	**265**	4 eq. PPTS, 20 mol% $BnEt_3NCl$, CH_2Cl_2:H_2O (9:1, 0.05 M), 40 °C, 24 h	44%	-
5	**243**	1 eq. PPTS, $CHCl_3$ (0.03 M), 40 °C, 24 h	nd	-
6	**243**	5 eq. AcOH, THF, 40 °C, 24 h	nd	-
7	**243**	1 eq. PPTS, CH_2Cl_2:*t*-BuOH (1:1, 0.05 M), 40 °C, 24 h	nd	-
8	**243**	4 eq. TFA, CH_2Cl_2, rt	-	-

Table 2.3 Initial attempts to synthesise furan **262**. nd = not determined

Successful deprotection and isomerisation of silaketal **265** to furan **262** was eventually achieved in α,α,α-trifluorotoluene. Reaction with PPTS in the presence of a small quantity of H_2O afforded furan **262** in 28% yield at 40 °C and in 32% yield at 60 °C (Scheme 2.19).



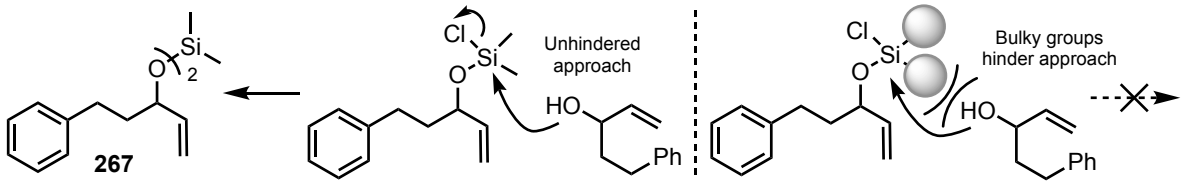
Scheme 2.19 RCM and cyclisation to furan **262**. Reagents and conditions: i) 10 mol% HG-II, PhMe, 80 °C, 24 h; ii) 4 eq. PPTS, α,α,α-trifluorotoluene:H_2O (9:1, 0.05 M), 40 °C, 18 h

Reducing the quantity of H_2O led to no improvement in yield and a 1:1 ratio of α,α,α-trifluorotoluene:H_2O to no reaction. Stronger acids (PTSA) or Lewis acids ($Yb(OTf)_3$) were unproductive and led to decomposition and formation of diol **243** in 12% yield respectively. Addition of 20 mol% $BnEt_3NCl$ or LiCl provided furan **262** in 30% and 24% yield. Further optimisation did not result in any improvement. The exact reasons for the relative success of α,α,α-trifluorotoluene in this reaction remain unknown. Ogawa and Curran have shown that CH_2Cl_2 can be replaced with α,α,α-trifluorotoluene in many common reactions such as acylation, silylation, oxidation and Lewis acid catalysed Friedel-Crafts and Diels-Alder reactions.[121] They note that the dielectric constants of both α,α,α-trifluorotoluene and CH_2Cl_2 are similar (9.18 and 9.04) but that the dipole moments are more disparate (2.86 and 1.60 D respectively). It is possible that the greater dipole moment assisted isomerisation by stabilising the formation of the proposed epoxide intermediate (Section 2.3.4, Scheme 2.30).

A number of difficulties had been encountered with the use of dimethysilyl TST **264**. Its synthesis was operationally complex and required a large excess of Me_2SiCl_2. Furthermore, optimisation of a one-pot deprotection/cyclisation sequence had been hampered by the instability of silaketal **265** and the consequent need to employ it crude. It was also observed to decompose over time, even when stored under inert atmosphere at –20 °C. It was therefore decided to identify a more robust alternative to the dimethylsilyl TST.

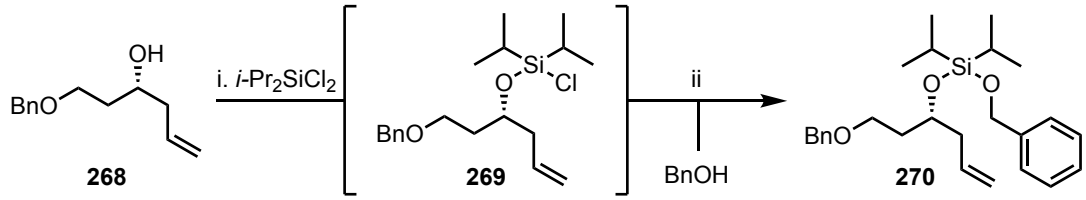
2.3.2 Second Generation Temporary-Silicon-Tether

A large excess of Me_2SiCl_2 had been needed to prevent formation of symmetrical TST **264**. It was proposed that the limited steric interaction between the small silane substituents and alcohol **209** lead to a high propensity for dimerisation. Larger silicon substituents might, therefore, make it might possible to form the TST with a near 1:1 ratio of alcohol **209** and chlorosilane. It was also hoped that a more bulky TST would display increased stability and enable product isolation (Scheme 2.20).



Scheme 2.20 Hypothesis for second generation tether with bulkier silicon substituents

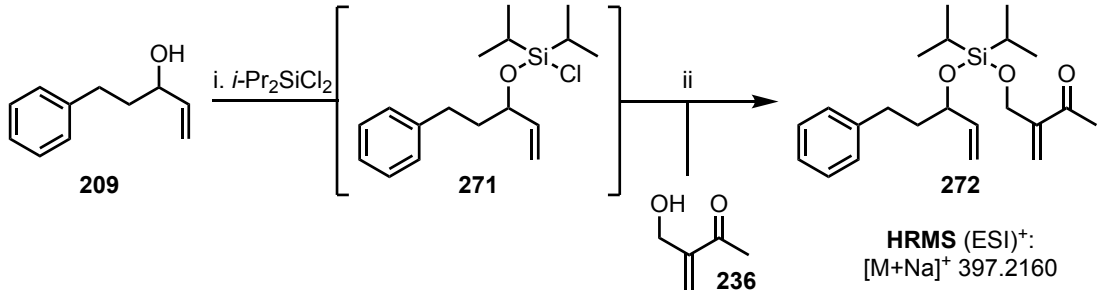
Paterson and co-workers had successfully employed an imidazole/*i*-Pr_2SiCl_2 system with alcohols of similar steric properties to that required in this investigation. Sequential addition of secondary alcohol **268** and benzyl alcohol to a single equivalent of *i*-Pr_2SiCl_2 had afforded TST **270** in 98% on 15 mmol scale (Scheme 2.21).[122]



Scheme 2.21 Paterson synthesis of sterically bulky TST **270**. Reagents and conditions: i) 1 eq. **268**, 1 eq. *i*-Pr_2SiCl_2, 5 eq. imidazole, CH_2Cl_2, 0 °C, 2 h; ii) 1 eq. BnOH, rt, overnight, 98%

Using the reported conditions, alcohol **209** was added to a suspension of imidazole and *i*-Pr_2SiCl_2 over 1 h *via* syringe pump. The slow addition supplemented the increased steric hindrance and further disfavoured formation of the symmetrical TST. Alcohol **236** was then added and consumption of chlorosilane **271** could be observed within 10 min by TLC analysis. Purification by FCC afforded TST **272** in 29% yield (Table 2.4, Entry 1). The irreversible conjugate addition of imidazole to enone **236** was identified as a possible side reaction con-

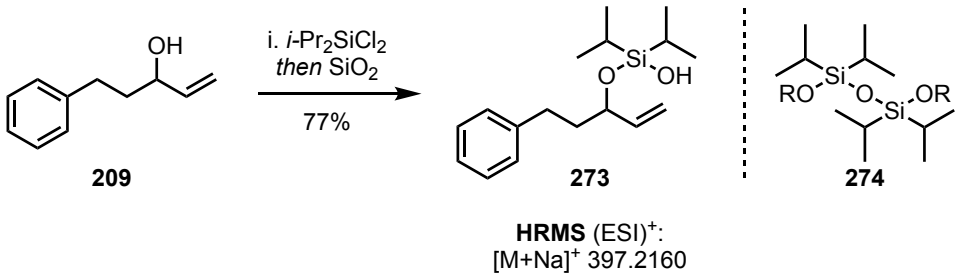
tributing to the low yield. Unfortunately, replacing imidazole with pyridine, which should be unable to add irreversibly, led to an even lower yield (16%, Entry 2). However, when only a slight excess of imidazole was used, TST **272** could be formed in 60% yield (Entry 3). Further increases were achieved by diluting the reaction, with TST **272** then isolated in 72% yield (Entry 4).



Entry	Reaction Concentration	eq. imidazole	eq. 236	Yield 272
1	0.3 M	5	1.05	29%
2	0.3 M	5[a]	1.2	16%
3	0.3 M	2.2	1.1	60%
4	0.1 M	2.2	1.1	72%

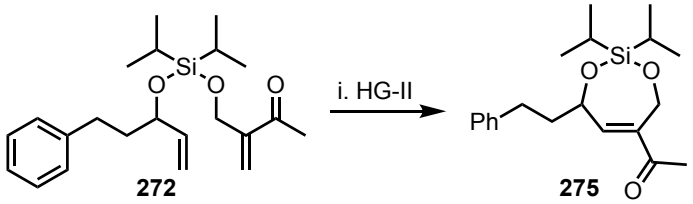
Table 2.4 Optimisation of second generation TST. General reagents and conditions: i) 1.05 eq. *i*-Pr_2SiCl_2, imidazole, then 1 eq. **236** over 1 h, then 20 min, CH_2Cl_2, 0 °C; ii) 1.1 eq. **236**, 10 min, 0 °C. [a]pyridine used

A common byproduct in these reactions was silanol **273**. This may have resulted from incomplete addition of alcohol **236** to chlorosilane **271** but prolonged reaction times for the second silylation failed to improve the overall yield. The structure of silanol **273** was verified by independent synthesis. Dry loading crude chlorosilane **271** directly onto SiO_2 followed by FCC afforded **273** in 77% yield. Its identity as the silanol rather than a polysilyl ether of type **274** was confirmed by HRMS (Scheme 2.22).



Scheme 2.22 Synthesis of silanol **273**. Reagents and conditions: 1.05 eq. *i*-Pr_2SiCl_2, 2.2 eq. imidazole, CH_2Cl_2, 0 °C, 3 h, 77%

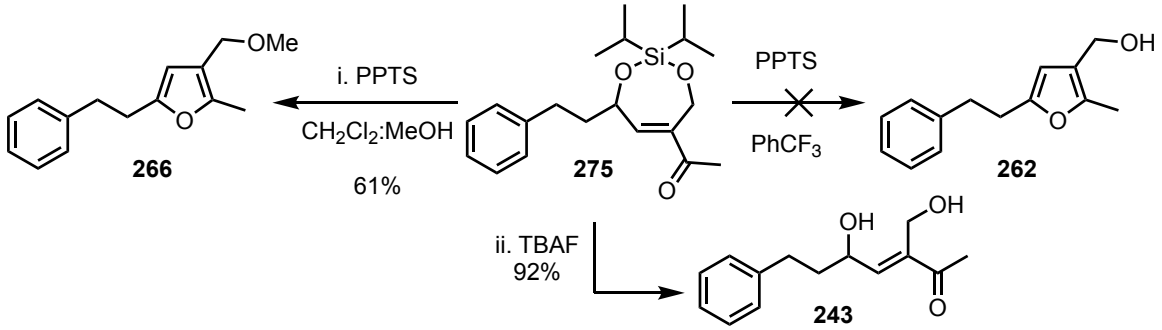
RCM of TST **272** using the conditions previously employed for the first generation TST produced silaketal **275** in 82% yield on the first attempt (Table 2.5, Entry 1). Importantly, this compound could be isolated by FCC, highlighting the improved stability of the diisopropyl TST. The catalyst loading could then be reduced with little detriment in yield (80%, Entry 2). The remainder of the mass balance was unreacted starting material and it was proposed that catalyst decomposition might occur at the high reaction temperatures required. However, dropwise addition of the catalyst led to no significant change (Entry 3). The reaction could also be performed on larger scale (400 mg) with no modification (Entry 4).



Entry	HG-II Loading	Comments	Yield 275
1	10%	-	82%
2	5%	-	80%
3	5%	Catalyst added dropwise over 6 h	81%
4	5%	400 mg scale	81%

Table 2.5 Optimisation of RCM of TST **275**. General reagents and conditions: HG-II, PhMe (0.005 M), 80 °C, 24 h

With silaketal **275** in hand, its reactivity in comparison to dimethyl silaketal **265** was assessed. Subjection to the acidic conditions previously used to access methyl ether furan **266** led to the expected deprotection and cyclisation, but in a lower yield of 61%. Unfortunately, formation of furan **262** in α,α,α-trifluorotoluene was not possible with no reaction observed after 18 h. The lower reactivity of silaketal **275** in these cases is consistent with the increased stability and steric demand of the diisopropyl tether. Silaketal **275** could be smoothly deprotected in 92% yield using TBAF as previously reported; this reaction was performed by a co-worker (Scheme 2.23).



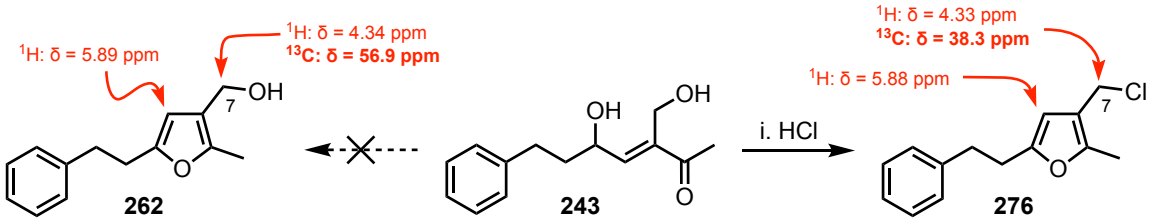
Scheme 2.23 Deprotection/cyclisation of silaketal **275** under established conditions. Reagents and conditions: i) 4 eq. PPTS, CH_2Cl_2:MeOH (1:1, 0.05 M), 40 °C, 16 h, 61%; ii) 2.5 eq. TBAF, THF, 0 °C, 1 h, 92%. Reaction ii performed by Simon Werrel

Serendipitously, resubmission of an NMR sample of diol **243** revealed a side-reaction had taken place after several days standing at room temperature in $CDCl_3$. Comparison with an authentic sample suggested that the additional peaks in the ^1H NMR spectrum corresponded to -CH_2OH substituted furan **262**. However, furan **262** could not be isolated by FCC, despite TLC analysis of the NMR sample corroborating its presence. If furan **262** had indeed been formed, the reaction was assumed to have been mediated by HCl (or DCl in $CDCl_3$); the decomposition of $CHCl_3$ to HCl and phosgene ($COCl_2$) is well established in the presence of UV light or O_2.[123,124]

2.3.3 Anhydrous HCl Promoted Isomerisation/Cyclisation

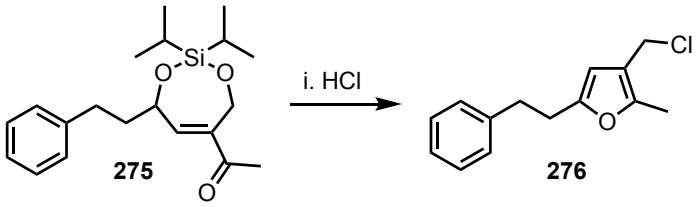
To improve on the partial conversion of diol **243** in $CDCl_3$, **243** was reacted with super-stoichiometric quantities of HCl in $CHCl_3$. A 1 M solution of HCl in $CHCl_3$ was prepared by adding equimolar quantities of acetyl chloride and MeOH to $CHCl_3$ at 0 °C. When diol **243** was added to this solution and stirred for 75 min, complete conversion to proposed furan **262** was observed by ^1H NMR. However, despite extensive efforts furan **262** could still not be isolated by FCC. Eventually, a much less polar compound was isolated which confusingly produced the same ^1H NMR spectrum as had been obtained from the crude reaction mixture. However, the ^{13}C NMR spectrum revealed the *C*-7 carbon signal to have a marked upfield shift relative to that observed for furan **262**. On the basis of data reported for related com-

pounds in the literature, the product was reassigned as -CH_2Cl substituted furan **276** (Scheme 2.24).[125]



Scheme 2.24 Formation of furan **276** under anhydrous HCl conditions. Reagents and Conditions: i) 1 M HCl in $CHCl_3$ (0.05 M), 0 °C, 75 min, full conversion by ^{1}H NMR

Silaketal **275** was also a suitable substrate for this transformation and its complete conversion to furan **276** was observed by ^{1}H NMR. Use of a biphasic mixture of $CHCl_3$ and H_2O led to no reaction, with HCl and substrate likely separated across the phase boundary. Only partial conversion was observed when the reaction was performed in aqueous 1 M HCl (Scheme 2.25). At present it is proposed that S_N2 at the primary alcohol of diol **243** (or the equivalent position in silaketal **275**) with chloride precedes furan formation; it is hypothesised that poor solvation of HCl under anhydrous conditions increases both the acidity of the proton and the nucleophilicity of the chloride anion. Further mechanistic discussion is in Section 2.3.4.

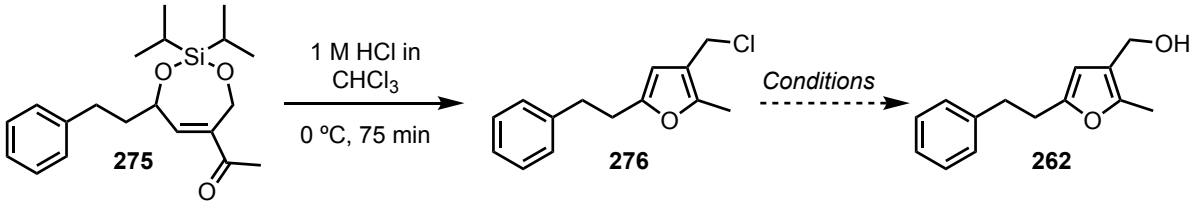


Solvent	Result (^{1}H NMR)
$CHCl_3$	Full Conversion
1:1 $CHCl_3$:H_2O	No Reaction
H_2O	Partial Conversion

Scheme 2.25 Effect of solvent on the deprotection/isomerisation of silaketal **275**. General reagents and conditions: 0 °C, 75 min

With a viable route to furan **276** in hand, conditions for its conversion to -CH_2OH substituted furan **262** were investigated. Silaketal **275** was transformed into furan **276** and the crude reaction mixture then submitted to a range of conditions after workup. Reaction of **276** with LiOH in THF did not lead to any of the desired product but use of K_2CO_3 in H_2O:DMF did result in partial conversion by ^{13}C NMR (Table 2.6, Entries 1 and 2). Finally, reaction with $AgNO_3$ led to complete consumption of **276** and furan **262** was isolated in 36% yield (Entry 3). The pre-

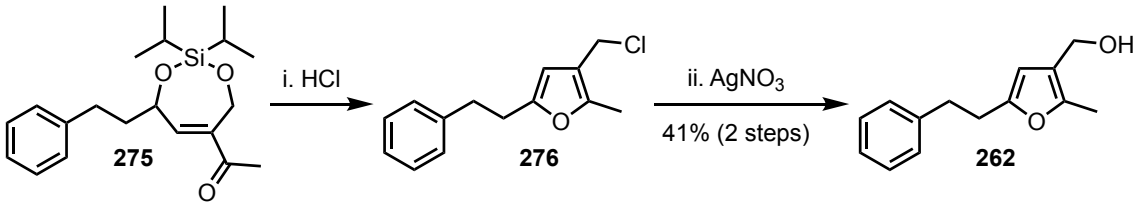
cipitation of AgCl is thought to help drive the reaction to completion.



Entry	Conditions	Result
1	3 eq. LiOH, drop H_2O, THF, rt	No Reaction
2	1 eq. K_2CO_3, H_2O:DMF (1:1), rt	Partial conversion to **262** by ^1H NMR
3	3 eq. $AgNO_3$, H_2O:Acetone (1:1), rt	36% **262**

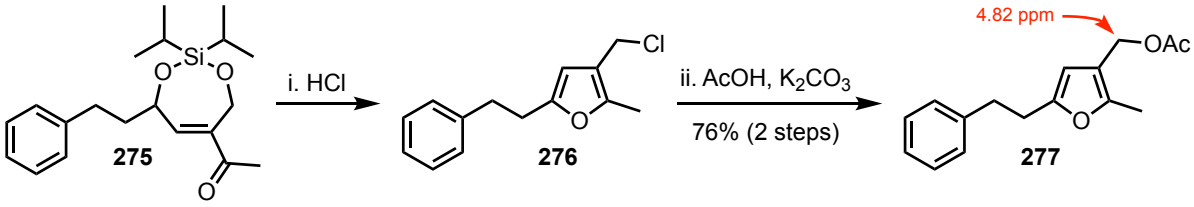
Table 2.6 Attempted conversion of furan **276** to furan **262**

Optimisation of this two-step process led to a small improvement in yield (41% over two steps). Importantly, the quantity of HCl could be reduced from 20 eq. (1 M HCl in $CHCl_3$ at 0.05 M) to 3 eq. In an operationally simpler protocol, HCl could also be generated *in situ* by adding acetyl chloride to a solution of silaketal **275** and methanol in $CHCl_3$ (Scheme 2.26).



Scheme 2.26 Two-step conversion of silaketal **275** to furan **262**. Reagents and conditions: i) 3 eq. MeOH, 5 eq. AcCl, $CHCl_3$ (0.05 M), 0 °C, 75 min; ii) 1.2 eq. $AgNO_3$, H_2O:Acetone (1:1, 0.05 M), rt, 4 h, 41%

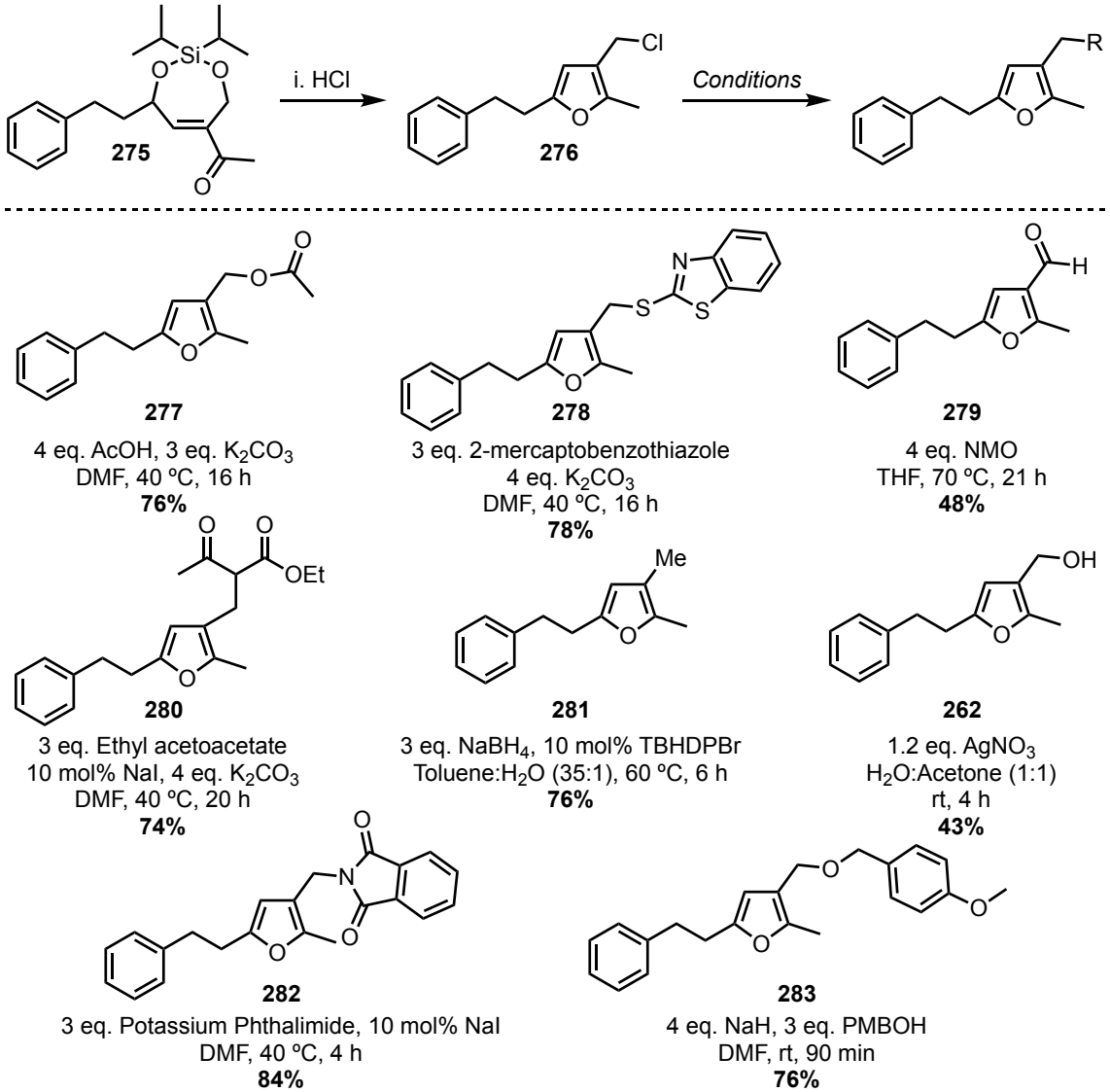
It was proposed that furyl chloride **276** might represent a synthetically useful electrophilic intermediate from which a range of *C*-3 substituted furans could be accessed. To test this hypothesis, furan **276** was dissolved in DMF, and AcOH and K_2CO_3 were added. Reaction at 40 °C smoothly furnished acetate **277** in 76% yield over two steps (Scheme 2.27).



Scheme 2.27 Synthesis of acetate **277**. Reagents and conditions: i) 3 eq. MeOH, 5 eq. AcCl, $CHCl_3$ (0.05 M), 0 °C, 75 min; ii) 4 eq. AcOH, 3 eq. K_2CO_3, DMF (0.1 M), 40 °C, 16 h, 76%

A series of nucleophiles was screened to provide a library of *C*-3 substituted furans. In addi-

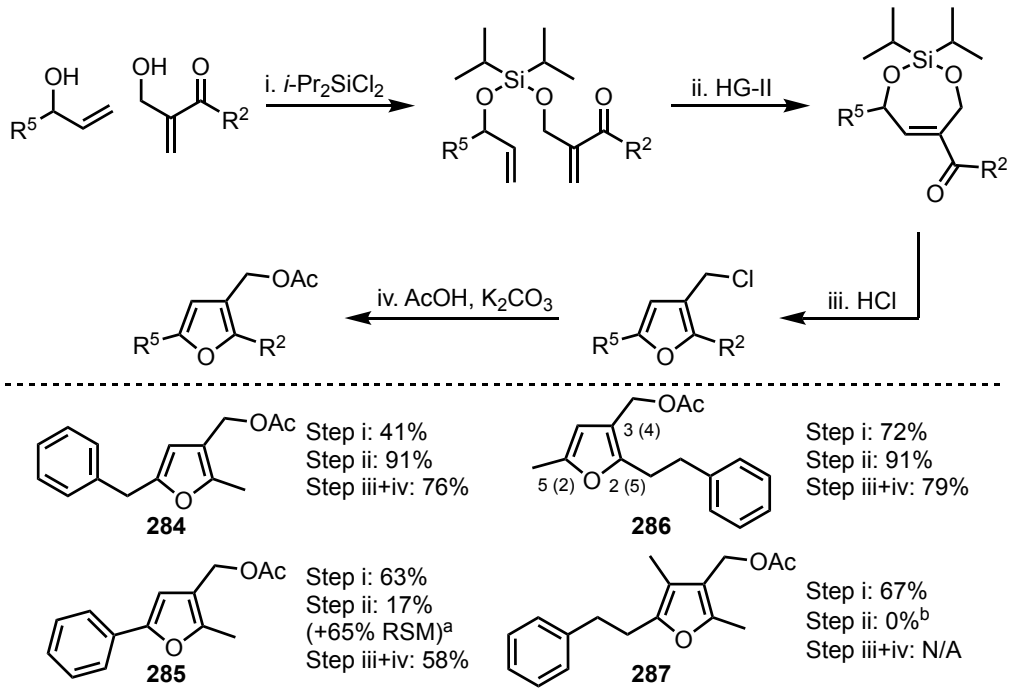
tion to acetate (**277**) and H_2O (**262**), heteroatomic nucleophiles including thiols (**278**), alcohols (**283**) and amides (**282**) were all tolerated. Carbon nucleophiles such as ethyl acetoacetate were also reactive (**280**) and hydride could be added to furnish the *C*-3 methyl substituent (**281**) using conditions reported by Rolla.[126] Reaction of furan **276** with NMO also provided access to the *C*-3 aldehyde substituent (**279**). The latter two examples are noteworthy as *C*-3 methyl and aldehyde substituted furans represent two of the major classes of furan cores present in the furanocembranoid family of natural products (Scheme 2.28).



Scheme 2.28 Scope at *C*-3. Reagents and conditions: i) 3 eq. MeOH, 5 eq. AcCl, $CHCl_3$ (0.05 M), 0 °C, 75 min

The scope with respect to *C*-2 and *C*-5 furan substituents was also investigated. The tolerance of increased steric hindrance at these positions was of particular interest owing to the chal-

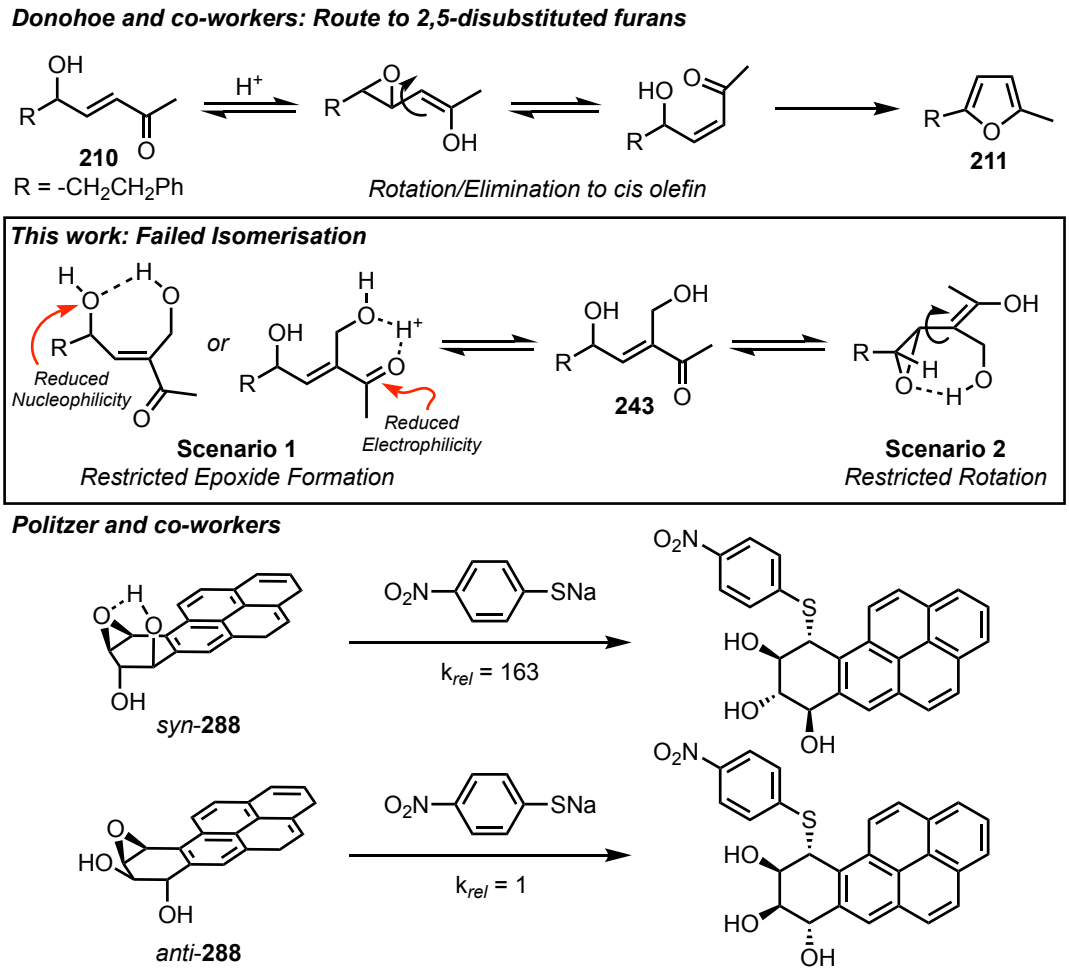
lenging nature of the RCM reaction. Furan **284** brought the phenyl substituent one carbon closer to the furan core. The lower yield of 41% for the TST forming reaction is unexplained but was consistent on repetition. Pleasingly, RCM efficiency was not affected and the subsequent deprotection/cyclisation/substitution sequence furnished furan **284** in 28% yield over 4 steps. For furan **285**, the phenyl group would be directly attached to the furan core. This time RCM proceeded in only 17% yield, although 65% unreacted starting material could be recovered. The remaining steps were not affected and furan **285** was formed in 17% (brsm) over 4 steps. Furan **286** can be viewed from two perspectives relative to model furan **277**, either as the 2,3,5-trisubstituted furan with the C-2 and C-5 substituents exchanged or the 2,4,5-trisubstituted furan retaining the substituents at *C*-2 and *C*-5. Its successful synthesis in 51% yield over 4 steps demonstrates that the same substituents may be tolerated on both fragments of the TST. The synthesis of tetrasubstituted furan **287** was unsuccessful as the substrate was too hindered for RCM, even at higher catalyst loadings and temperatures (Scheme 2.29).



Scheme 2.29 Scope of TST-RCM sequence at *C*-2 and *C*-5. Reagents and conditions: i) 1 eq. allyl alcohol, 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, 1.5 h *then* 1.1 eq. enone, CH_2Cl_2, 0 °C, 15 min; ii) 5 mol% HG-II, PhMe (0.005 M), 80 °C, 24 h; iii) 3 eq. MeOH, 5 eq. AcCl, $CHCl_3$ (0.05 M), 0 °C, 75 min; iv) 4 eq. AcOH, 3 eq. K_2CO_3, DMF (0.1 M), 40 °C, 16 h. [a]10 mol% HG-II, 100 °C [b]10 mol% HG-II, 110 °C

2.3.4 Mechanistic Discussion

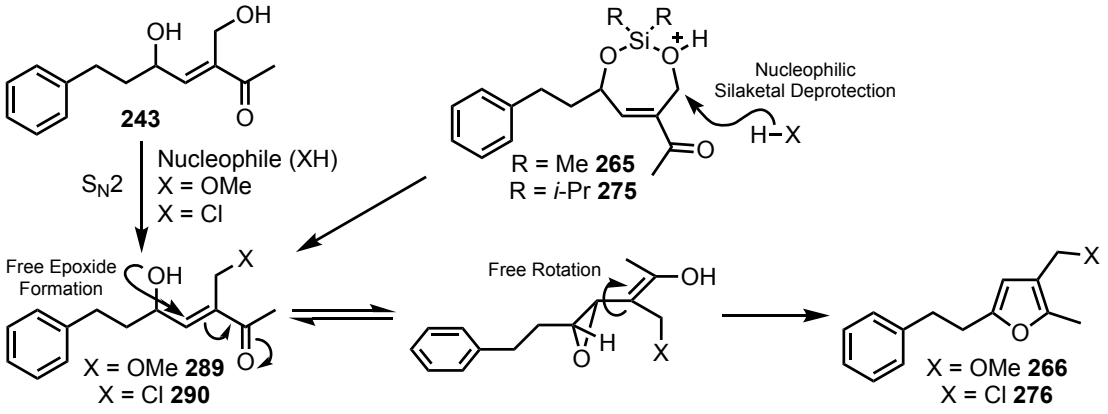
The success of only a small number of reaction conditions in isomerising and cyclising the diols to the corresponding trisubstituted furans was unexpected, particularly as the only structural modification from substrates successfully used to synthesise 2,5-disubstituted furans was the additional –CH_2OH moiety. Mechanistically, the Brønsted acid catalysed *trans* to *cis* isomerisation of allylic alcohol **210** *en route* to 2,5-disubstituted furan **211** had been assumed to operate *via* the intermediacy of the epoxide.[60,61] If this reaction manifold was now inoperable, it was assumed that the additional –CH_2OH moiety of **243** was restricting either the formation of the epoxide or the subsequent rotation/elimination to the *cis* olefin. Such hindrance might be caused by a hydrogen bonding interaction involving one or both hydroxyl groups (Scheme 2.30).



Scheme 2.30 Mechanistic hypotheses to explain the failed isomerisation of diol **243**

Intramolecular hydrogen bonding interactions with epoxides of the type proposed (Scenario 2, Scheme 2.30) have been reported in the literature. Politzer and co-workers described a computational investigation into the observed 163-fold increase in the rate of epoxide opening with sodium 4-nitrothiophenolate for *syn*-pyrene **288** over *anti*-pyrene **288**. They attributed the effect to epoxide activation by a transannular hydrogen bonding interaction.[127]

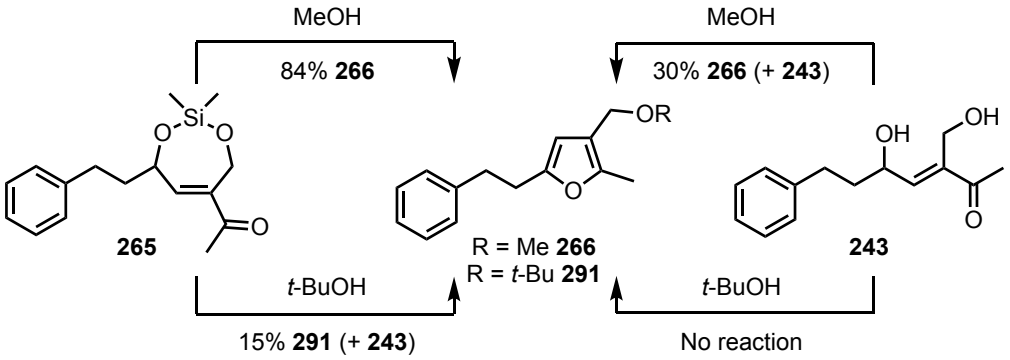
Of the conditions that did lead to successful isomerisation and cyclisation, both methanolic Brønsted acid and anhydrous HCl could potentially effect an S_N2 reaction between methanol or chloride and the primary hydroxyl of diol **243** to give intermediates **289** or **290** respectively. It seems reasonable to propose that removing this hydroxyl group from the system could reduce the hindrance towards epoxide formation or remove the intramolecular hydroxyl-epoxide hydrogen bonding interaction. Isomerisation and furan formation would therefore occur more readily, as observed. Additionally, both sets of conditions were able to effect the direct isomerisation and cyclisation from silaketals **265** and **275**. This might infer an alternative reaction pathway involving silaketal deprotection *via* S_N2 reaction with the nucleophile to afford intermediates **289** or **290** directly, bypassing the formation of diol **243** (Scheme 2.31).



Scheme 2.31 Mechanistic explanation for the success of methanolic acid and anhydrous HCl conditions

It is not yet possible to categorically distinguish between these two mechanistic possibilities. However, full conversion of diol **243** was not observed under the methanolic acid conditions. Additionally, substitution of *t*-BuOH for MeOH furnished furan **291** in just 15% yield from

silaketal **265** along with a large, but unquantified, amount of diol **243**. Resubjection of diol **243** to these conditions also led to no observed reactivity. These results suggest that nucleophilic silaketal deprotection plays some role in the mechanism when alcohols and Brønsted acid are used, otherwise at least partial conversion of diol **243** with *t*-BuOH would have been expected (Scheme 2.32).



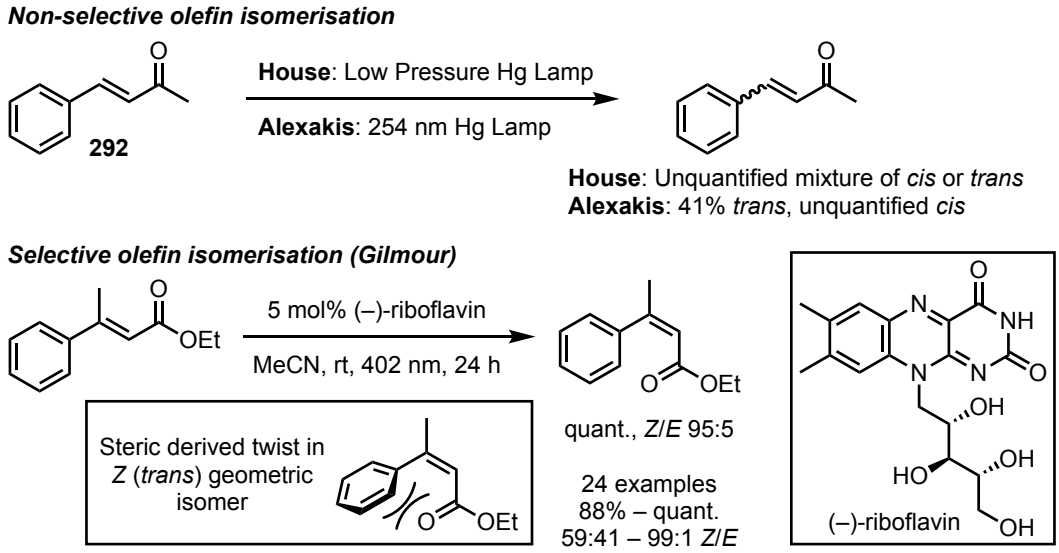
Scheme 2.32 Comparison of MeOH and *t*-BuOH in acidic cyclisation reactions. Reagents and conditions: 4 eq. PPTS, CH_2Cl_2:ROH (1:1, 0.05 M), 40 °C, 24 h

The means by which α,α,α-trifluorotoluene mediated the isomerisation and cyclisation of diol **243** is less clear. As previously discussed (see Section 2.3.1), α,α,α-trifluorotoluene has a similar dielectric constant to CH_2Cl_2 (9.18 and 9.04) but its dipole moment is much higher (2.86 D compared to 1.60 D). It is speculated that this may help stabilise either the epoxide intermediate on any polar transition state *en route*. The C–F bonds also give rise to the possibility of an interaction between the hydroxyl groups of diol **243** and the sigma-hole of a fluorine atom.[128] Such an interaction might interfere with hydrogen bonding and permit the isomerisation. No solvent system able to delineate the dipole moment and sigma-hole interactions has been identified.

The difficulties associated with effecting the *trans* to *cis* isomerisation of diol **243** to a synthetically useful intermediate for furanocembranoid synthesis in a high-yielding manner and without stoichiometric Brønsted acid meant that identification of an alternative reaction pathway that did not proceed *via* the epoxide intermediate was required.

2.3.5 Photochemical Isomerisation

The *trans* to *cis* isomerisation of olefins is disfavoured due to both the high energetic barrier to rotation about the double bond and the increased steric crowding in the *cis* isomer. Formation of a stable intermediate *en route*, such as the epoxide invoked earlier, is one strategy to circumvent this problem. Alternatively, a large energy input in the form of photochemical excitation can provide access to a twisted high energy intermediate from which relaxation to both *cis* and *trans* isomers occurs. The isomerisation of olefins using UV light has extensive literature precedence, in particular that of stilbene and its derivatives which have been studied for over 70 years.[129] With respect to α,β-unsaturated carbonyl systems, the isomerisation of *trans*-benzylideneacetone (**292**) was reported by House in 1959 using a low pressure mercury arc lamp[130] and Alexakis and co-workers subsequently accomplished the same transformation using a 254 nm mercury lamp.[131] In both cases a photostationary state was reached with both *cis* and *trans* isomers present in the reaction mixture. Both isomers were able to absorb at the irradiation wavelength and relaxation from the common high energy intermediate was not exclusively selective for one stereoisomer (Scheme 2.33).



Scheme 2.33 Literature examples of the photochemical isomerisation of olefins

While the current investigation was being carried out, Gilmour and co-workers reported the

selective *trans* to *cis* isomerisation of cinnamyl esters at 402 nm using (–)-riboflavin as an organic photocatalyst. Selectivity was elegantly achieved using the steric clash between the carbonyl and aromatic ring moieties in the *cis* form; this effected a change in the chromophore and prevented interaction between the *cis* isomer and the (–)-riboflavin photocatalyst.[132]

Measurement of the UV/Vis spectra of both diol **243** and furan **262** in different solvents revealed a strong π–π* absorbance for both species between 230 nm and 280 nm. Diol **243** displayed an additional n–π* absorbance between 290 nm and 380 nm, with furan **262** absorbing only extremely weakly in this range (Figure 2.2). Therefore, it was determined that irradiation with a 365 nm source (UVP PenRay, commercially available) might allow for isomerisation and cyclisation of diol **243** whilst ensuring that product absorbance was minimised. All optimisation of this reaction was conducted by a co-worker.

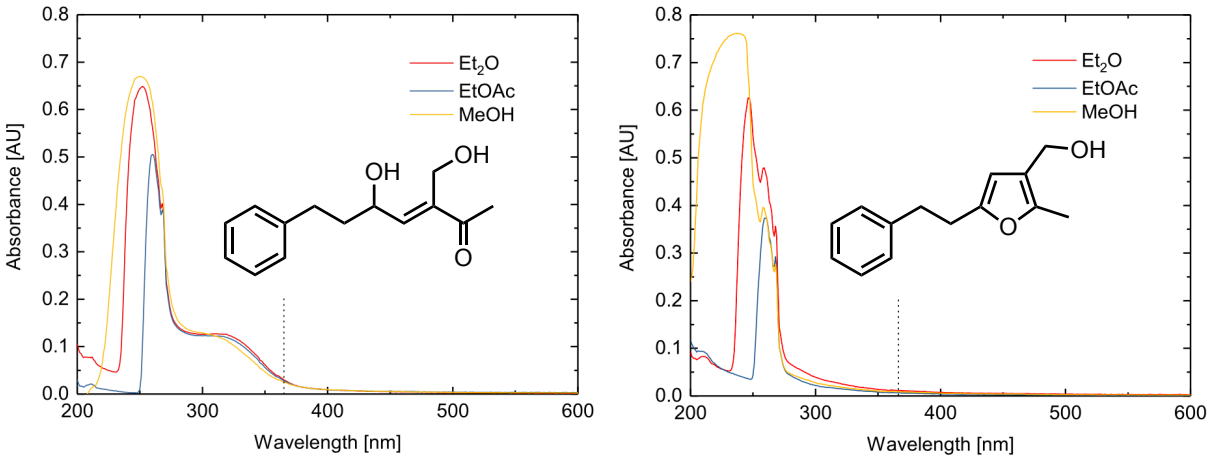
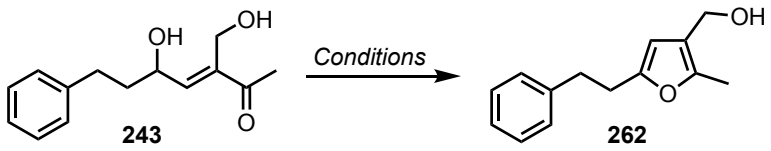


Figure 2.2 UV/Vis spectra of diol **243** and furan **262** (courtesy of Simon Werrel)

A custom made irradiation vessel which facilitated efficient irradiation of the reaction mixture was used for the photochemical reactions (see Table 2.7 and Chapter 5.3). On irradiation at 365 nm, diol **243** was smoothly converted to furan **262**, which was isolated in 70% yield (Table 2.7, Entry 1). Sparging the solvent with Argon for 10 min prior to use was necessary to achieve high yields but no extra benefit was had from freeze-pump-thaw degassing. A brief solvent screen indicated that EtOAc was the optimal solvent for the reaction (96% isolated

yield, Entries 2-3). This is consistent with the trend in product absorbance at 365 nm in the given solvents seen in the UV/Vis spectra (EtOAc<MeOH<Et_2O). Conducting the reaction at room temperature allowed for a faster reaction but furan **262** was isolated in a lower, although still acceptable, 79% yield (Entry 4). As expected, irradiation at 254 nm led to a much lower yield and shorter reaction time, reflecting the degree of absorbance of both furan **262** and diol **243** at the reaction wavelength (Entry 5).



Entry	Wavelength	Solvent	Temperature	Time	Yield 262
1	365 nm	Et_2O	0 °C	20 h	70%
2	365 nm	MeOH	0 °C	20 h	77%
3	365 nm	EtOAc	0 °C	20 h	96%
4	365 nm	EtOAc	rt	12 h	79%
5	254 nm	Et_2O	0 °C	2 h	26%

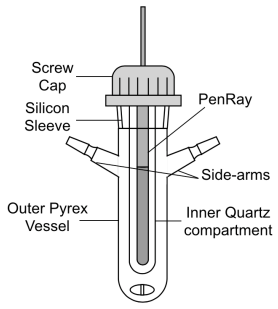
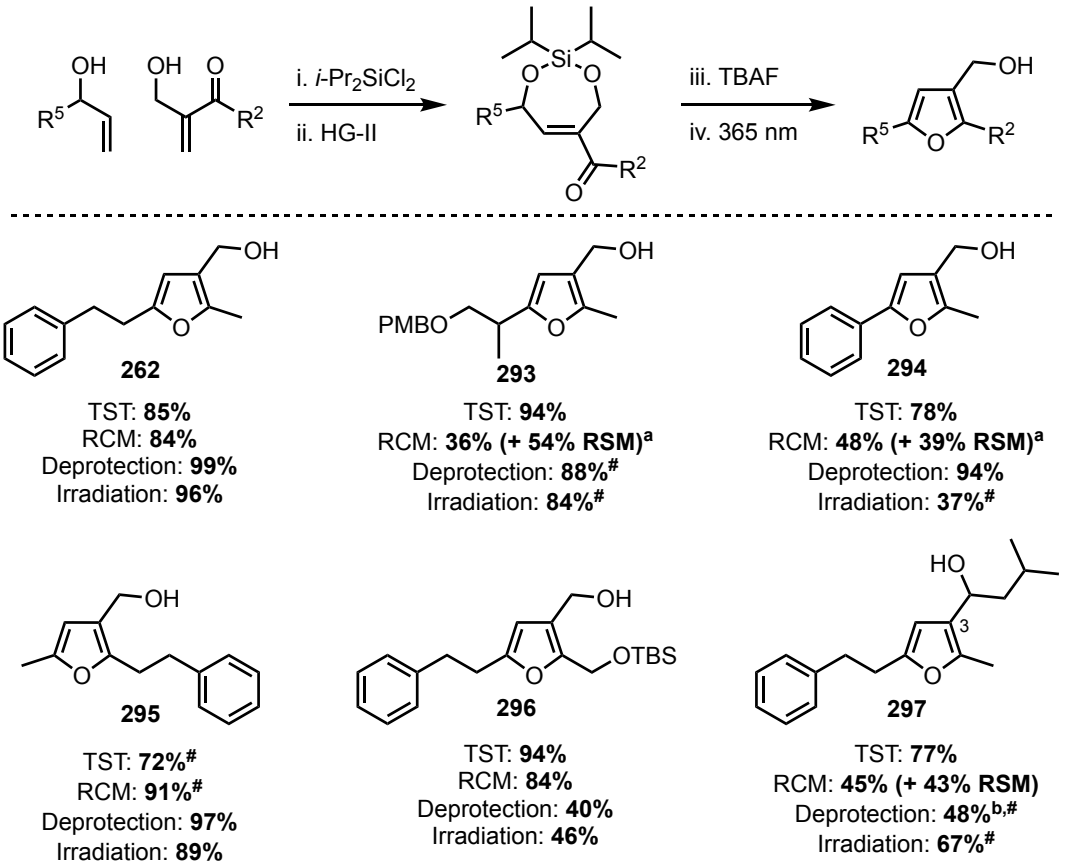


Table 2.7 Optimisation of irradiation of diol **243**. Reactions performed by Simon Werrel. Irradiation vessel custom-made by Terri Adams (University of Oxford). Image courtesy of Jack Hoffman

The scope of the procedure was then investigated, with emphasis placed on the degree of branching adjacent to the furan to assess its impact on the challenging RCM. All reactions were performed by a co-worker except where indicated.

All TST forming reactions proceeded in high yields, irrespective of additional functionality or branching. Increasing the branching of the allylic alcohol (*C*-5 furan substituent) reduced the efficiency of the RCM, as seen in the syntheses of furans **293** and **294**. In both cases, higher temperatures were required although increases in catalyst loading were not found to be beneficial. Much of the unreacted starting material could also be recovered. TST deprotections were performed using catalytic quantities of TBAF in a THF:pH 7 buffer solvent mixture, a protocol first reported by Phillips and co-workers.[133] This allowed for a degree of selectivity in the TST deprotection *en route* to furan **296**, where the relevant diol could be formed in the

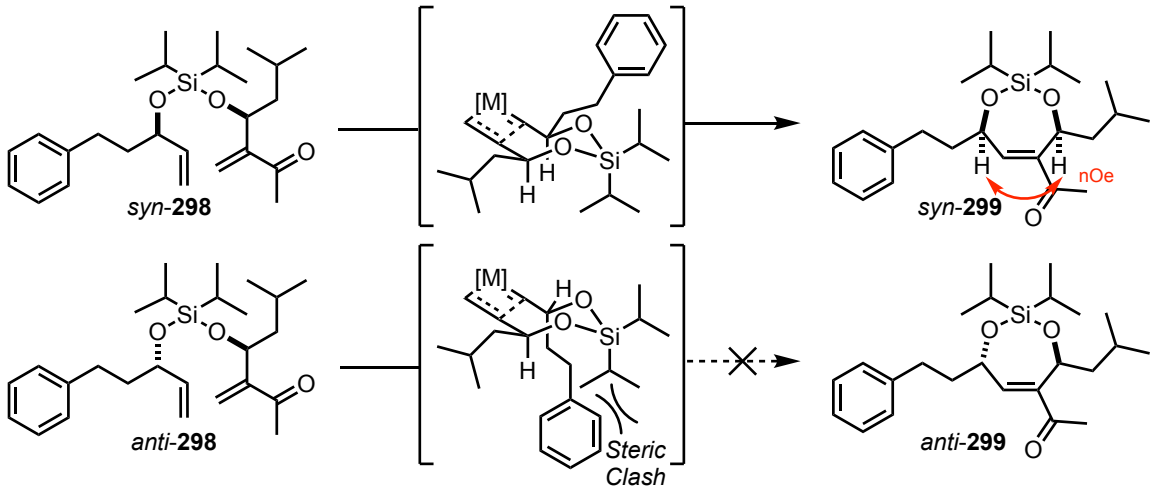
presence of a primary TBS group (48% yield). For almost all substrates the irradiations to the desired furans proceeded as expected. The lower yield for furan **294** is attributed to the extended chromophore of the furan core and adjacent aromatic ring; it is likely that this resulted in product absorption at the reaction wavelength with concomitant decomposition. The lower yield for TBS containing furan **296** is unexplained (Scheme 2.34).



Scheme 2.34 Scope of TST-RCM/irradiation route to trisubstituted furans. Reagents and conditions: i) As Table 2.d, Entry 5; ii) 5 mol% HG-II, PhMe (0.005 M), 80 °C, 24 h; iii) 0.1 eq. TBAF (1 M in THF), THF:pH 7 buffer (100:1), rt, 30 min; iv) 365 nm irradiation, EtOAc, 0 °C, 20 h. [a]24 h at 80 °C then 24 h at 100 °C [b]2.5 eq. TBAF used [#]Reactions performed by the author

The incorporation of a secondary alcohol at the *C*-3 position of the furan was also possible (furan **297**). In this case the RCM was found to be diastereoselective, with *syn*-TST **298** participating in metathesis and *anti*-TST **298** being reisolated. *Syn*-silaketal **299** was formed in 45% yield (from 1:1 *syn*:*anti*-**298**, max. 50% yield) and its relative stereochemistry was confirmed by nOe experiments. A similar phenomenon was observed by Evans and co-workers and the selectivity is believed to derive from the steric clash between the silicon and allylic

alcohol substituents in the transition state *en route* to the metallocyclobutane intermediate for the *anti* diastereomer (Scheme 2.35).[134] The deprotection required use of excess fluoride due to the increased steric demand of the secondary alcohol substituent.



Scheme 2.35 Proposed models to account for observed diastereoselectivity *en route* to furan **297**

It was then proposed that the photochemical isomerisation of enones followed by condensation might represent a general strategy to other heterocycle classes, such as 2,5-disubstituted furans and pyrroles. Photochemical conditions might tolerate sensitive functional groups that would have decomposed under the acidic conditions previously reported (see Chapter 1.3.3). Measurement of UV/Vis spectra for enone **210** and furan **211**, synthesised using the established methods, indicated that both systems had nearly identical photochemical properties to diol **243** and furan **262** (Figure 2.3).

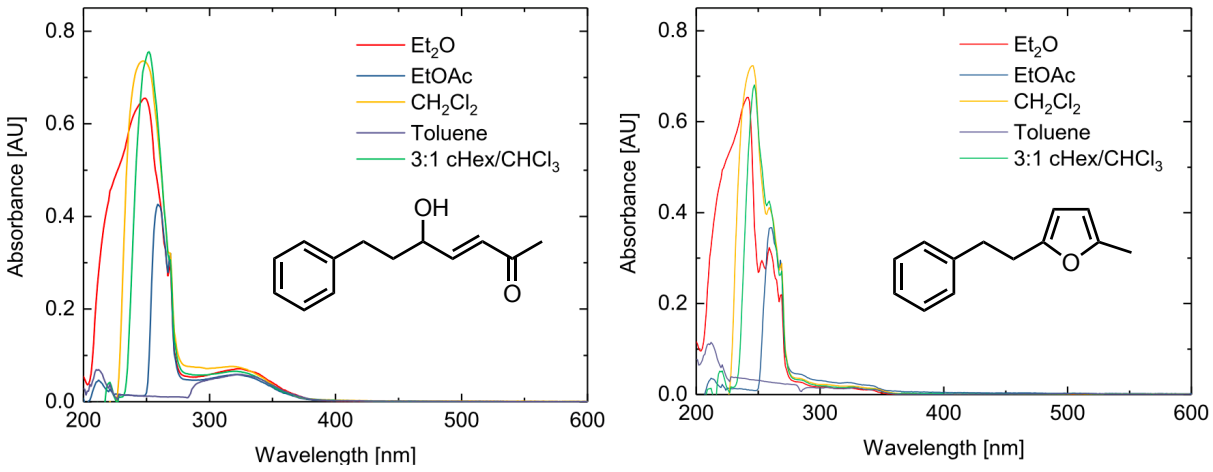
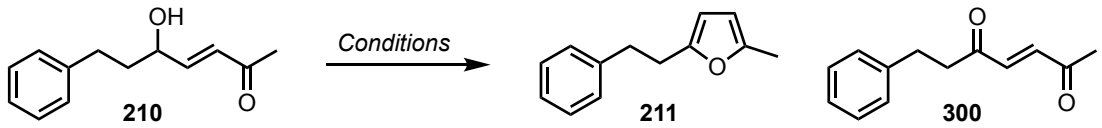


Figure 2.3 UV/Vis spectra for diol **210** and furan **211**

Irradiation at 365 nm was thus anticipated to provide access to the desired heterocycles. All optimisation was performed by a co-worker. As expected, irradiation of enone **210** at 365 nm in EtOAc provided furan **211** in 50% yield along with 18% enone **300** (Table 2.8, Entry 1). In other solvents furan **211** was formed exclusively and in high yield (Entries 2–4). It appeared that solvents of reduced polarity favoured formation of furan **211** and although cyclohexane alone was not efficient due to poor solubility of the starting material (Entry 5), a 3:1 mixture of cyclohexane:$CHCl_3$ provided furan **211** in near quantitative yield (Entry 6). In the absence of irradiation no reaction was observed, confirming that any trace HCl from the $CHCl_3$ was not catalysing the reaction (Entry 7). Irradiating the reaction at 254 nm led to a reduced yield due to product absorption at the reaction wavelength (Entry 8).

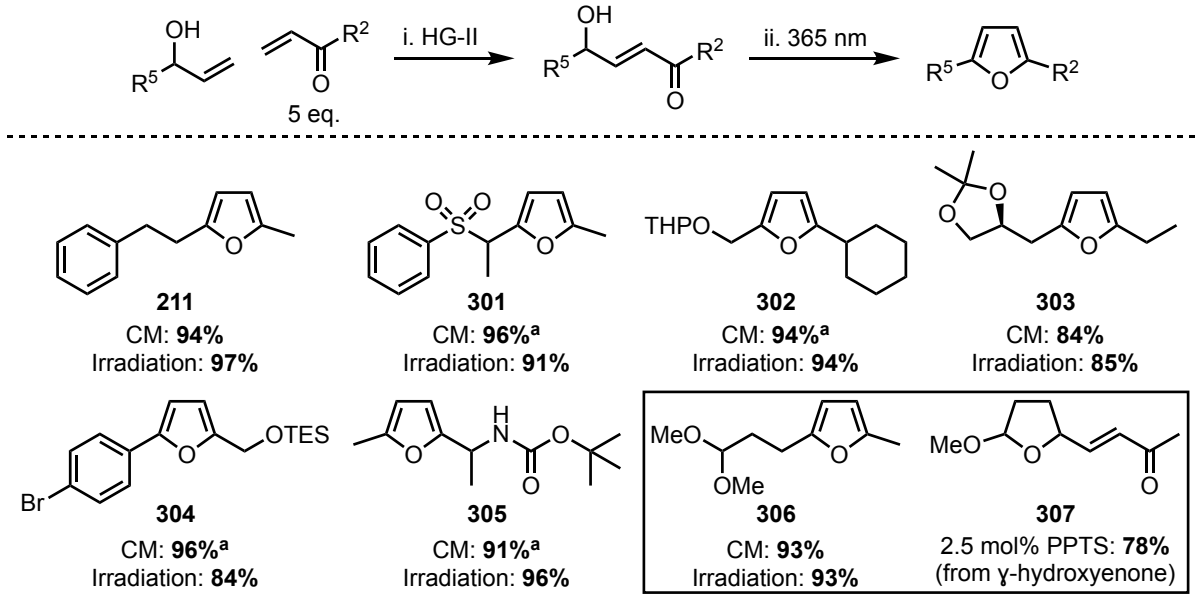


Entry	Wavelength	Solvent	Yield 211
1	365 nm	EtOAc	50%[a]
2	365 nm	Et_2O	85%
3	365 nm	CH_2Cl_2	88%
4	365 nm	PhMe	91%
5	365 nm	cyclohexane	22%
6	365 nm	cyclohexane:$CHCl_3$ (3:1)	97%
7	-	cyclohexane:$CHCl_3$ (3:1)	0%
8	254 nm	Et_2O	68%

Table 2.8 Optimisation of irradiation of enone **210**. General conditions: 0 °C, 8 h. [a]2 h, 18% **300** was also isolated. Reactions performed by Simon Werrel

Investigation of the scope revealed that UV irradiation indeed offered access to a range of substrates with acid sensitive functional groups. High yields could be achieved for all substrates in both CM and irradiation steps. Dimethyl acetal (**306**), THP (**302**) and cyclic acetal (**303**) functionalities were all tolerated. Attempted synthesis of dimethyl acetal substituted furan **306** from the corresponding γ-hydroxyenone intermediate under the previously reported

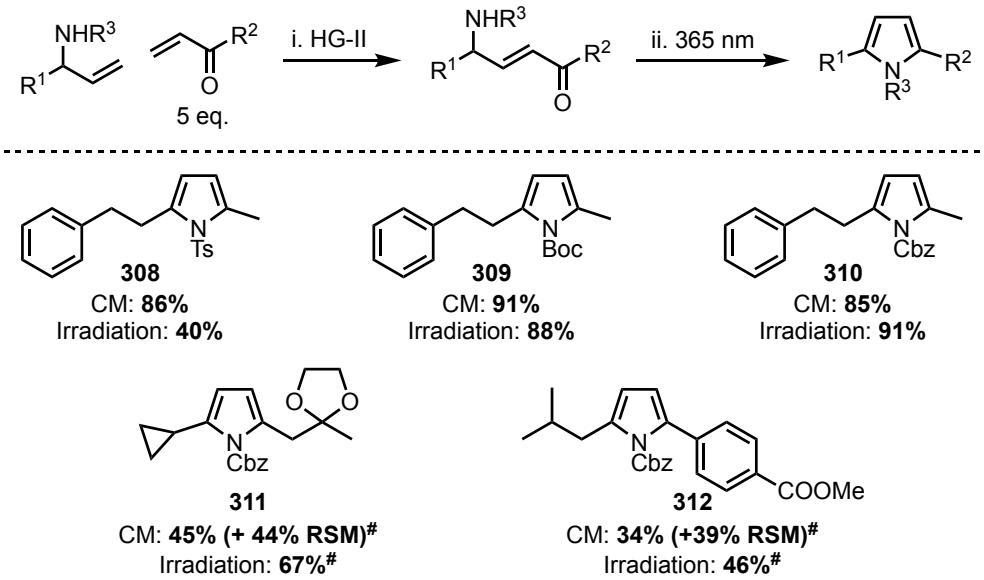
acidic conditions was unsuccessful and decomposition product THF **307** was formed in 78% yield instead, highlighting the improved substrate tolerance of the photochemical irradiation conditions. Protecting groups including TES (**304**) and Boc (**305**) also survived the reaction conditions. In contrast to the TST-RCM sequence to trisubstituted furans, increasing the branching at either the *C*-2 or *C*-5 positions of the furan was found to have no effect on the efficiency of the CM. All reactions in this investigation were performed by a co-worker (Scheme 2.36).



Scheme 2.36 Scope of 2,5-disubstituted furans. Reagents and conditions: i) 2.5 mol% HG-II, PhMe (0.25 M), rt, 24 h; ii) 365 nm, cyclohexane:$CHCl_3$ (3:1), 0 °C, 8 h. Reactions performed by Simon Werrel

Direct application of the irradiation conditions to the synthesis of 2,5-disubstituted pyrroles was also successful. In general, higher reaction temperatures were required for the CM due to the lower reactivity of allyl amines relative to allyl alcohols. Allyl amines bearing tosyl, Boc and Cbz protected groups were all still tolerated, however. Irradiation to give tosyl protected pyrrole **308** proceeded in lower yield than for Boc or Cbz protected pyrroles **309** and **310**. This is likely due to the absorbance of the tosyl group at the irradiation wavelength, as observed by Yonemitsu and co-workers.[135] The CMs of more hindered substrates *en route* to pyrroles **311** and **312** were more challenging, with lower isolated yields in both cases. Much

of the unreacted starting could be recovered, however. Cyclic acetal containing pyrrole **311** was isolated in 67% yield after irradiation. Some degradation of conjugated pyrrole **312** was observed (46% yield); product absorbance at the irradiation wavelength was once again likely responsible. All reactions were performed by a co-worker except where indicated (Scheme 2.37).

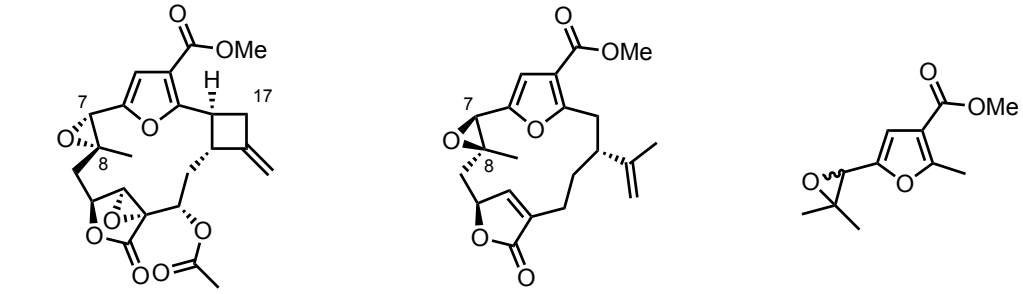


Scheme 2.37 Scope of 2,5-disubstituted pyrroles. Reagents and conditions: i) 2.5 mol% HG-II, PhMe (0.25 M), 40 °C, 24 h; ii) 365 nm, C_6H_{12}:$CHCl_3$ (3:1), 0 °C, 8 h. #Reactions performed by the author

With a high yielding, mild, approach to appropriately functionalised heterocycles successfully developed, attention turned to its application in systems similar to those that could be used in a total synthesis of (+)-lophotoxin (**1**). These model studies would aim to uncover which potentially useful functionalities could tolerated by the method and thus inform the eventual retrosynthetic plan towards the natural product.

2.4 Model Studies Towards a Retrosynthesis of (+)-Lophotoxin (1)

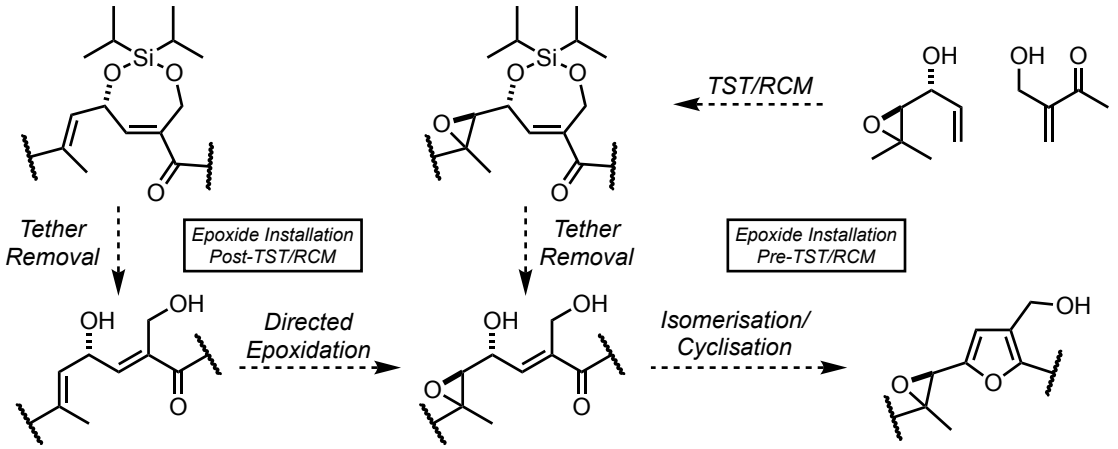
As previously discussed (see Chapter 1.4), the synthesis of furanocembranoids containing the *C*-7/8 epoxide has proved challenging, particularly when direct epoxidation of the corresponding alkene was attempted in the presence of the furan. The only successful reports are the total synthesis of (+)-17-deoxyprovidencin (**126**) by Mulzer and co-workers, where the exocyclic olefin was masked for the epoxidations,[40] and the non-stereoselective epoxide installations on related systems reported separately by Pattenden and Clark (Figure 2.4).[146,42]



(+)-17-deoxyprovidencin (**126**) Mulzer | (+)-7-*epi*-pukalide (**133**) Clark | **313** Pattenden

Figure 2.4 Examples of *C*-7/8 epoxide installation on relevant systems

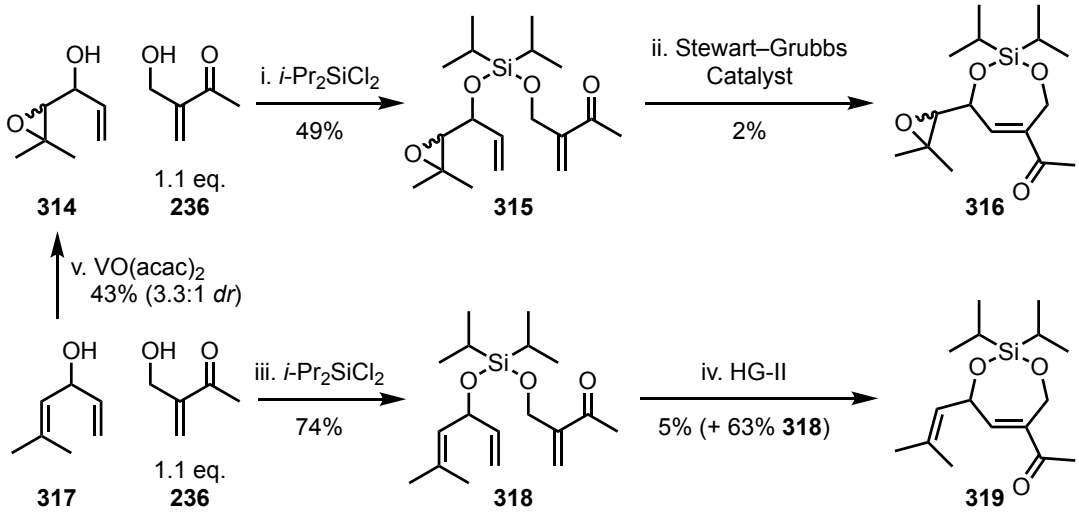
The TST-RCM approach to trisubstituted furans provided an opportunity to address both the stereoselectivity of, and substrate tolerance to, epoxidation. Deprotection of an alkenyl substituted silaketal would reveal an allylic alcohol which, if a single stereoisomer, could direct stereoselective epoxidation prior to isomerisation and furan formation (Scheme 2.38). Alternatively, the epoxide could be installed prior to the TST-RCM sequence and carried through.



Scheme 2.38 'Furan-last' strategy: Possible routes to install the *C*-7/8 epoxide

2.4.1 Synthesis of Silaketal 316 and 319 Model Systems

Relevant model systems were constructed to assess the viability of these two approaches. Directed epoxidation of alkene **317** was selective for the more electron rich olefin and epoxide **314** was isolated in 43% yield (3.3:1 *dr*). The relative stereochemistry of the diastereomers is undetermined. Both epoxide **314** and alkene **317** were subjected to the developed TST-RCM sequence with alcohol **236** (Scheme 2.39).

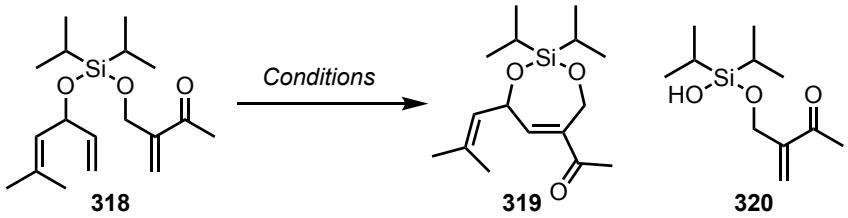


Scheme 2.39 Model studies for epoxide installation. Reagents and conditions: i) 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, CH_2Cl_2, 0 °C, 1.5 h *then* 1.1 eq. **236**, 0 °C, 10 min, 49%; ii) 5 mol% SG, PhMe, 80 °C, 24 h, 2%; iii) 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, CH_2Cl_2, 0 °C, 1.5 h *then* 1.1 eq. **236**, 0 °C, 10 min, 74%; iv) 5 mol% HG-II, PhMe, 80 °C, 24 h, 5%; v) 20 mol% $VO(acac)_2$, 2 eq. *t*-BuOOH, CH_2Cl_2, rt, overnight, 43%

Epoxide substituted TST **315** displayed extremely poor reactivity in the RCM. Only trace product was observed by TLC analysis under a range of conditions, employing both HG–II and Stewart–Grubbs catalyst (SG, designed for more sterically demanding substrates), and at higher temperatures. From one of these reactions silaketal **316** was isolated in 2% yield to confirm its identity. In an initial attempt, alkene substituted TST **318** was only slightly more reactive and silaketal **319** was isolated in 5% yield along with 63% unreacted TST **318**. Silanol **320** was also observed as a byproduct in the ^{1}H NMR of the crude reaction mixture (see Table 2.9). No byproduct related to the alcohol **317** derived portion of TST **318** could be identified by ^{1}H NMR analysis.

2.4.2 RCM Optimisation and Mechanistic Studies Related to TST 318

On the basis of its marginally higher reactivity, it was decided to attempt optimisation of the RCM with alkene substituted TST **318**. Reactions were analysed by measuring the molar ratio of TST **318**, silaketal **319** and silanol **320** in the ^{1}H NMR spectra of the crude reaction mixtures. Conversion to both silaketal **319** and silanol **320** increased with higher catalyst loadings (Table 2.9, Entries 2 and 3) but doubling the reaction concentration reduced the overall conversion (Entry 4). Using Zahn–1B catalyst, which displays faster activation in solution, led to greater consumption of TST **318** but this only served to increase the proportion of silanol **320** in the reaction mixture (Entry 5). Substituting 1,2-DCE for toluene increased the quantity of silanol **320** dramatically with silaketal **319** only making up 6% of the reaction mixture (Entry 6).

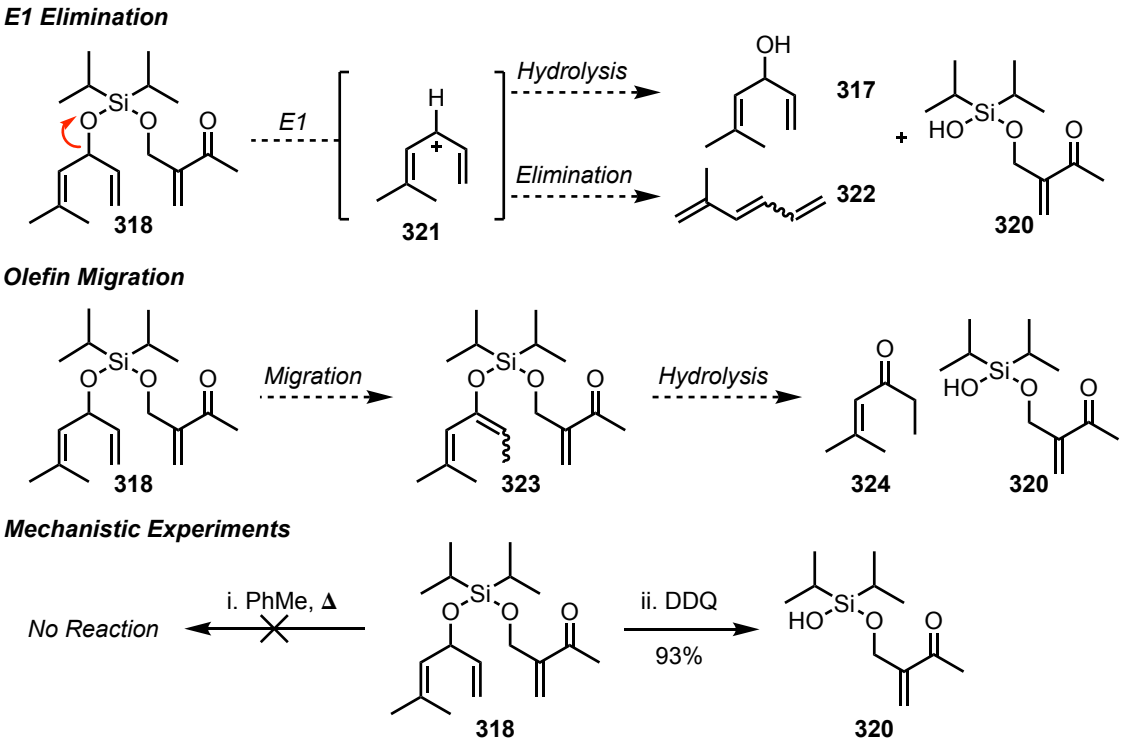


Entry	Catalyst	Temperature	Solvent	Concentration	Ratio (^{1}H NMR)		
					318	319	320
1	5 mol% HG–II	80 °C	PhMe	0.005 M	61	8	30
2	10 mol% HG–II	100 °C	PhMe	0.005 M	37	14	47
3	30 mol% HG–II	100 °C	PhMe	0.005 M	32	25	44
4	10 mol% HG–II	100 °C	PhMe	0.01 M	53	13	34
5	30 mol% Zahn–1B	100 °C	PhMe	0.005 M	18	26	55
6	30 mol% HG–II	100 °C	1,2-DCE	0.005 M	17	6	76

Table 2.9 Optimisation of RCM of TST **318**. General reaction conditions: 24 h

The formation of silanol **320** was unexpected; no similar byproduct had been observed in previous RCM reactions. Two potential mechanisms for its formation were postulated. Firstly, *via* direct E1 elimination of silanol **320** from TST **318** to form the doubly allylic stabilised cation **321** followed by hydrolysis to return alcohol **317**, or further elimination to triene **322**.

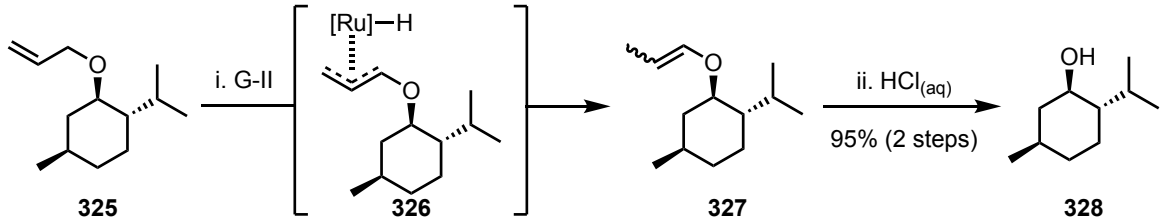
Secondly, *via* olefin migration and hydrolysis of silyl enol ether **323** to produce enone **324**. None of alcohol **317**, triene **322** or enone **324** were detected by ^{1}H NMR spectroscopy, although the latter two would likely have been volatile. Stirring TST **318** in toluene at the reaction temperature in the absence of HG-II led to no reaction, indicating that the decomposition is catalyst mediated. Together with the absence of alcohol **317** in the ^{1}H NMR of the reaction mixture, this might suggest that olefin migration is the more likely decomposition pathway. Conclusive evidence either way has not yet been obtained, however. This is an oft-noted side-reaction in metathesis chemistry and is mechanistically assumed to proceed *via* a Ru–H species (see Scheme 2.41). A number of strategies have been developed to prevent it, with addition of acetic acid or 1,4-quinone derivatives being the most successful.[136] Addition of acetic acid was thought to be unsuitable given the acid lability of the TST, and stirring TST **318** with 1 eq. DDQ in fact led to promotion of the side-reaction with silanol **320** formed in 93% yield (Scheme 2.40).



Scheme 2.40 Potential decomposition pathways of TST **318**

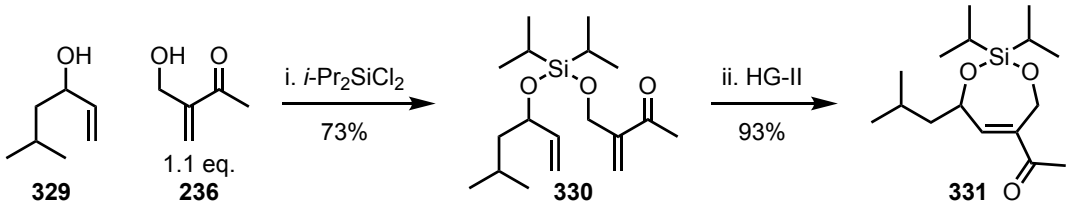
Oxidative deprotection of allyl ethers with DDQ has been reported by Yadav and co-workers

and was proposed to proceed *via* formal hydride removal to the allylic cation.[137] In 2002, Cossy and co-workers utilised olefin migration and disclosed the deprotection of allyl ethers such as ether **325** with G-II.[138] The mechanism is sometimes proposed to proceed *via* formation of a ruthenium-hydride/π-allyl complex such as intermediate **326** (Scheme 2.41). Since ruthenium-hydride formation could also be thought of as allylic oxidation by ruthenium, and the system has displayed incompatibility to oxidising reagents, a similar pathway might indeed be responsible for the formation of silanol **320**.



Scheme 2.41 Deprotection of allyl ethers by Cossy and co-workers. Reagents and conditions: i) 3 mol% G-II, CH_2Cl_2, reflux, 12 h; ii) 2 M $HCl_{(aq)}$, rt

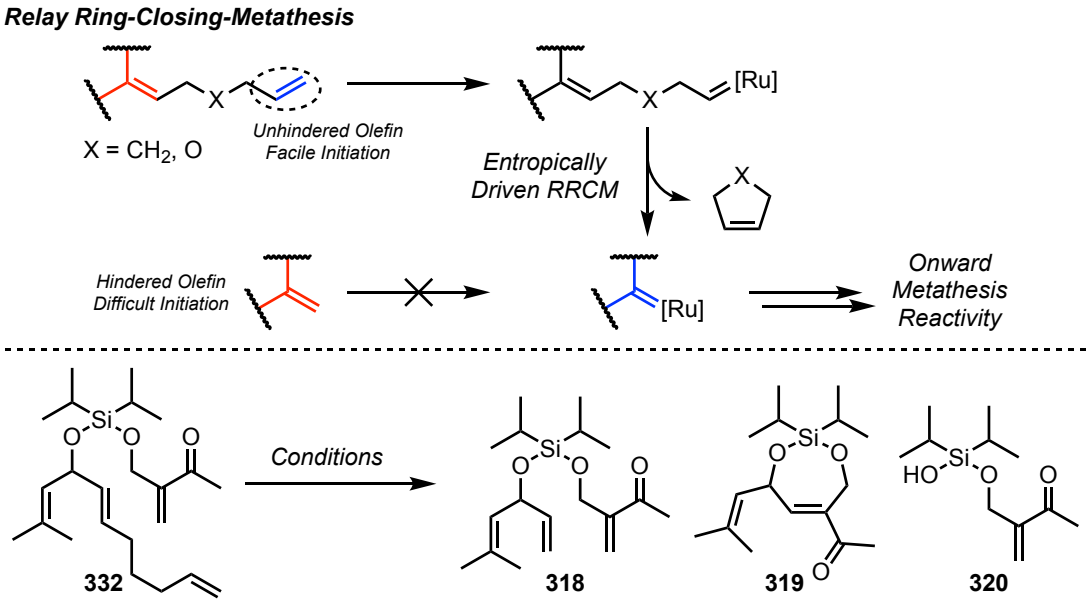
It was proposed that the electronic character of the pendent trisubstituted olefin, rather than an increase in steric hindrance, was responsible for the low yielding RCM. Reaction with saturated analogue **330** supported this as silaketal **331** could be obtained in 93% yield under unmodified RCM conditions (Scheme 2.42). These reactions were performed by a co-worker.



Scheme 2.42 TST-RCM of saturated silaketal **330**. Reagents and conditions: i) 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, CH_2Cl_2, 0 °C, 90 min *then* 1.1 eq **236**, 5 min, 73%; ii) 5 mol% HG-II, PhMe, 80 °C, 24 h, 93%. Reactions performed by Simon Werrel

To probe whether the pendent trisubstituted alkene was inhibiting catalyst initiation or onward reactivity of the resulting metal carbene, ring relay analogue TST **332** was prepared. Relay ring-closing metathesis (RRCM) is a strategy whereby an extended alkyl chain bearing a terminal unhindered olefin is added to an unreactive olefin.[139] Initiation occurs on the terminal alkene and entropically driven RCM then transfers the active metal species to the target

olefin, overcoming steric or electronic factors that would otherwise hinder the desired initiation. RRCM substrate TST **332** was prepared using the developed TST conditions (for synthetic details see Chapter 5.4) and subjected to RCM at two different temperatures and catalyst loadings. The distribution of products was then compared to that achieved without the relay chain (Table 2.10).



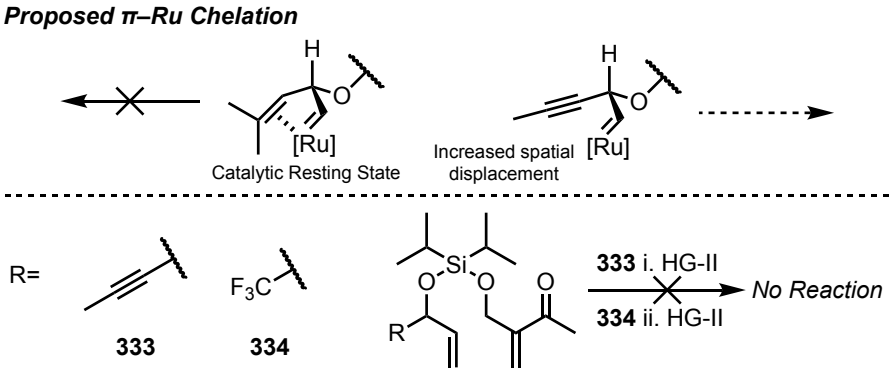
Entry	Conditions	Ratio (^{1}H NMR)			
		332	**318**	**319**	**320**
1	5 mol% HG-II, 80 °C	0	57	9	34
2	5 mol% HG-II, 80 °C	-[a]	61	8	30
3	10 mol% HG-II, 100 °C	0	52	18	30
4	10 mol% HG-II, 100 °C	-[a]	37	14	47

Table 2.10 RRCM. General reagents and conditions: PhMe, 24 h. [a]TST **318** used as starting material

Comparison between relay and non-relay substrates (Entries 1/2 and 3/4) revealed little change in product distribution when relay TST **332** was used. The consumption of starting material and presence of TST **318** in the ^{1}H NMR spectra indicated that the relay had successfully delivered the active catalyst to the desired olefin, but onward reactivity had been no more successful. At 100 °C, overall conversion to silaketal **319** and silanol **320** was slightly higher with relay TST **332**, but the product distribution was weighted even more in favour of

silanol **320** (Entry 4). As such, it appeared that the reaction was stalling after successful catalyst initiation, with the decomposition pathway occurring preferentially instead.

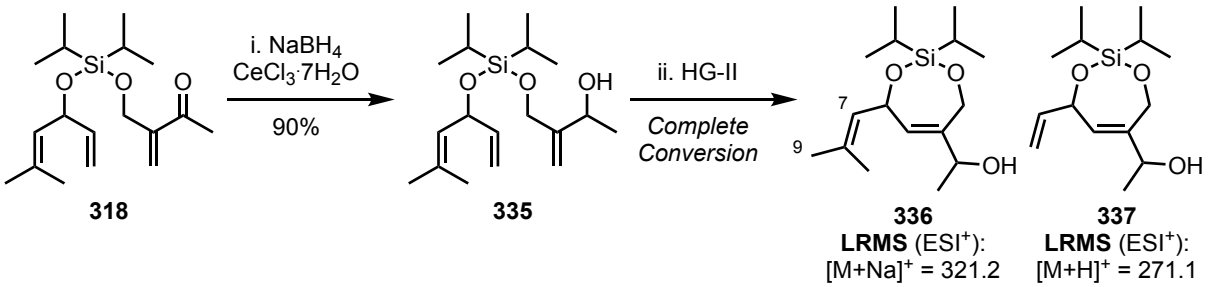
Poor metal carbene reactivity could have a number of causes and one early hypothesis was that the trisubstituted olefin was chelating the intermediate metal carbene, creating a resting state in the catalytic cycle. Alkyne substituted TST **333** was proposed as a synthetically useful system that might be spatially disposed to prevent chelation (for details of its synthesis see Chapter 5.4). However, **333** was even less reactive under the RCM conditions with no reaction observed after 24 h at 100 °C. It is possible that the increased electron withdrawing ability of the alkyne inhibited the reaction; complexation of the metal carbenoid and the enone moiety in the ring-closing step may become less favourable with reduced electron density. Trifluoromethyl substituted TST **334** (for details of its synthesis see Chapter 5.4) was also unreactive in the RCM, in line with this hypothesis (Scheme 2.43).



Scheme 2.43 Attempted RCM of TSTs **333** and **334**. Reagents and conditions: i) 10 mol% HG-II, PhMe, 100 °C, 24 h; ii) 5 mol% HG-II, PhMe, 80 °C, 24 h

Alternatively, modification of the enone fragment of the TST was proposed as a potential strategy to improve reaction efficiency; increasing the electron density of the alkene would make it more likely to participate in metathesis. Luche reduction offered a temporary method of activating the system as the alcohol formed could be re-oxidised post-RCM. Reduction of TST **319** afforded alcohol **335** in 90% yield as an approximately 1:1 mixture of diastereomers. Treating alcohol **335** with HG-II led to complete consumption of starting material but the

^{1}H NMR of the crude reaction mixture did not indicate clean conversion to desired silaketal **336**. Low resolution mass spectrometry returned two signals that were consistent with the formation of silaketals **336** ($[M+Na]^+$ = 321.2) and **337** ($[M+H]^+$ = 271.1) (Scheme 2.44).

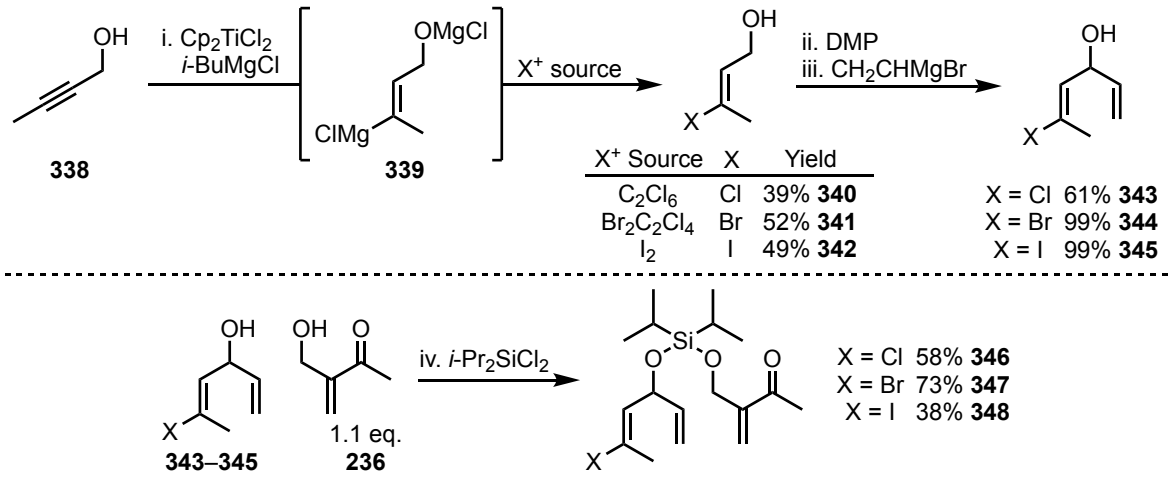


Scheme 2.44 Luche reduction and RCM of TST **318**. Reagents and conditions: i) 1.2 eq. $NaBH_4$, 1.1 eq. $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 1 h, 90%; ii) 5 mol% HG-II, PhMe, 80 °C, 24 h

The formation of primary olefin substituted silaketal **337** suggested at least a partial change in mechanism. Metathesis initiation was previously assumed to occur on the monosubstituted olefin but its presence in silaketal **337** indicated that this was unlikely to be the case here. Instead, the pendent hydroxyl group likely directed initiation onto the newly formed allylic alcohol (allylic chalcogen effect) with subsequent ring-closing to both the monosubstituted and trisubstituted olefins. It is conceivable that if this strategy were to be used in a synthesis of (+)-lophotoxin (**1**), the increased steric demand of the trisubstituted olefin (from the extended alkyl chain at *C*-9, see Scheme 1.36 and 2.44) would improve selectivity for the monosubstituted olefin.

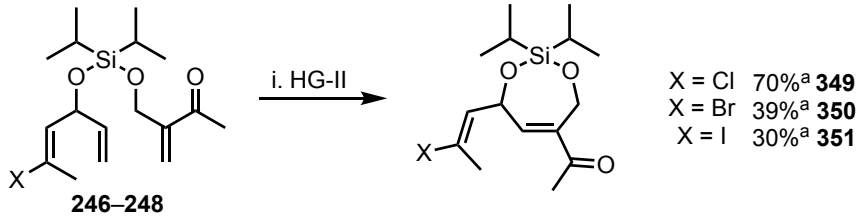
2.4.3 Vinyl Halide Substituted TSTs in RCM Reactions

In concurrent work, a co-worker investigated the use of vinyl halide substituted TSTs in RCM. It was thought that the halide substituent might temper olefin–catalyst coordination (see Scheme 2.43) due to its electron withdrawing nature and provide a useful synthetic handle. The (*E*) isomer would be required for furanocembranoid synthesis and titanium catalysed formation of vinyl Grignard **339** from alcohol **338** followed by quenching with the appropriate halide source provided an efficient route to (*E*)-vinyl halides **343**–**345**. Oxidation, Grignard addition and TST formation furnished TSTs **346**–**348** (Scheme 2.45).



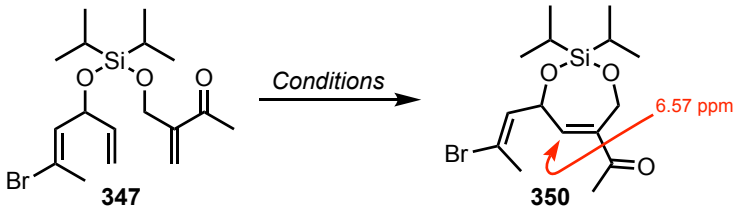
Scheme 2.45 Synthesis of geometrically pure halide substituted TSTs. Reagents and conditions: i) 5 mol% Cp_2TiCl_2, 2.64 eq. *i*-BuMgCl, Et_2O, 0 °C, 6 h *then* 3.5 eq. X^+ source; ii) 1.1 eq. DMP, CH_2Cl_2, 0 °C, 1 h; iii) 1.2 eq. $CH_2CHMgBr$ (1 M in THF), THF, –78 °C, 1.5 h; iv) 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, CH_2Cl_2, 0 °C, 1.5 h *then* 1.1 eq. **236**, 15 min. Reactions performed by Simon Werrel

RCM reactions of TSTs **346**–**348** were performed with 10 mol% HG-II at 100 °C. Vinyl chloride **346** proceeded to 70% conversion by ^{1}H NMR and reactivity decreased down the halide group. Interestingly, no silanol **320** formation was observed for any substrate; the halide substituents had switched off the decomposition pathway (Scheme 2.46).



Scheme 2.46 Screening of halide substituted TSTs in RCM. Reagents and conditions: i) 10 mol% HG-II, PhMe, 100 °C, 24 h. [a]Conversion by ^{1}H NMR. Reactions performed by Simon Werrel

Vinyl bromide **347** was judged to offer the best compromise between reactivity and synthetic utility and RCM optimisation was therefore continued on this substrate (Table 2.11). Increasing the reaction time led to no improvement in yield, suggesting catalyst degradation under the reaction conditions (Entry 2). However, portion-wise catalyst addition, either as discrete batches or with the second portion added dropwise as a solution in PhMe, did not appear to extend catalyst lifetime (Entries 3 and 4). Faster addition of the second portion of catalyst did, however, lead to an increase in yield (53%) with a corresponding reduction in TST **347** recovery (Entry 5). It appeared that a narrow window of catalyst activity existed and any additional catalyst needed to be added within this window before decomposition occurred.



347 **350**

Entry	Loading HG-II	Catalyst Addition Method	Reaction time	Yield	
				347	**350**
1	10 mol%	single batch	24 h	37%	34%
2	10 mol%	single batch	84 h	39%	30%
3	5+5 mol%	batchwise, second after 12 h	24 h	35%	37%
4	5+5 mol%	batch then dropwise over 5 h after 2 h	24 h	41%	37%
5	5+5 mol%	batch then dropwise over 2 h after 0.5 h	24 h	23%	53%
6	5+5 mol%	batch then dropwise over 2 h after 0.5 h[a]	24 h	7%	60%
7	5+5 mol%	batch then dropwise over 2 h after 0.5 h[a]	60 h	3%	67%

Table 2.11 Optimisation of RCM for TST **347**. General reagents and conditions: PhMe (0.005 M), 100 °C. [a]Constant gentle flow of N_2 over reaction mixture. Reactions performed by Simon Werrel

Given the unfavourability of the ring-closing step, increasing catalyst lifetime was of critical importance to the overall success of the reaction. Non-productive metathesis events, such as reaction with ethylene, were a possible source of catalyst decomposition.[83] In an effort to remove ethylene from the reaction mixture, whilst maintaining an otherwise inert atmosphere, the reaction was conducted under *pseudo* open-flask conditions. A dry N_2 inlet was attached to

the reaction flask and an outlet oil bubbler to the top of a reflux condenser. It was hoped that a constant gentle flow of N_2 would remove ethylene from the reaction surface and flush it out of the system through the bubbler, whilst still excluding oxygen from the reaction. Use of this setup did indeed increase the yield to 60% (Entry 6) and its effectiveness in extending catalyst lifetime can be seen in the 67% yield achieved after 60 h reaction time (Entry 7).

2.4.4 Attempted Cross-Coupling of Silaketal 350

With a productive route to silaketal **350** established, suitable conditions for the functionalisation of the vinyl bromide substituent needed to be identified. Due to the alkyl chain present at this position in the furanocembranoids, this would formally be an sp^2–sp^3 coupling reaction. Neutral conditions were deemed desirable as the TST would be vulnerable to acids and the ketone functionality would be prone to enolisation with bases. Strongly nucleophilic reagents were also likely to be unsuitable owing to the presence of the ketone and TST (Figure 2.5).

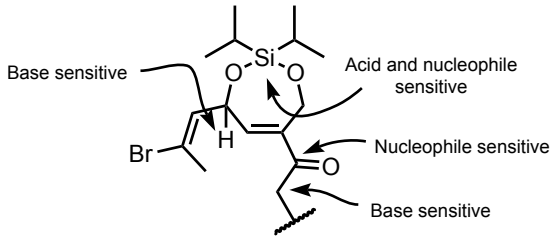


Figure 2.5 Substrate considerations for vinyl bromide functionalisation

Stille cross-coupling was considered potentially suitable; the absence of base and high reactivity of the organostannane provide ideal conditions for the proposed transformation and have led to its widespread application in natural product synthesis.[140] However, discrimination between the organostannane substituents was expected to be challenging as alkyl groups have the slowest rate of transmetallation and transfer of an sp^3 centre was required (Figure 2.6).

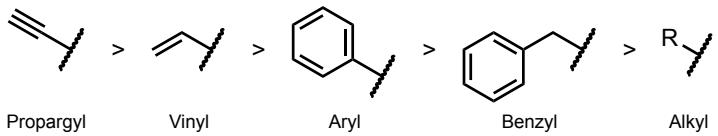
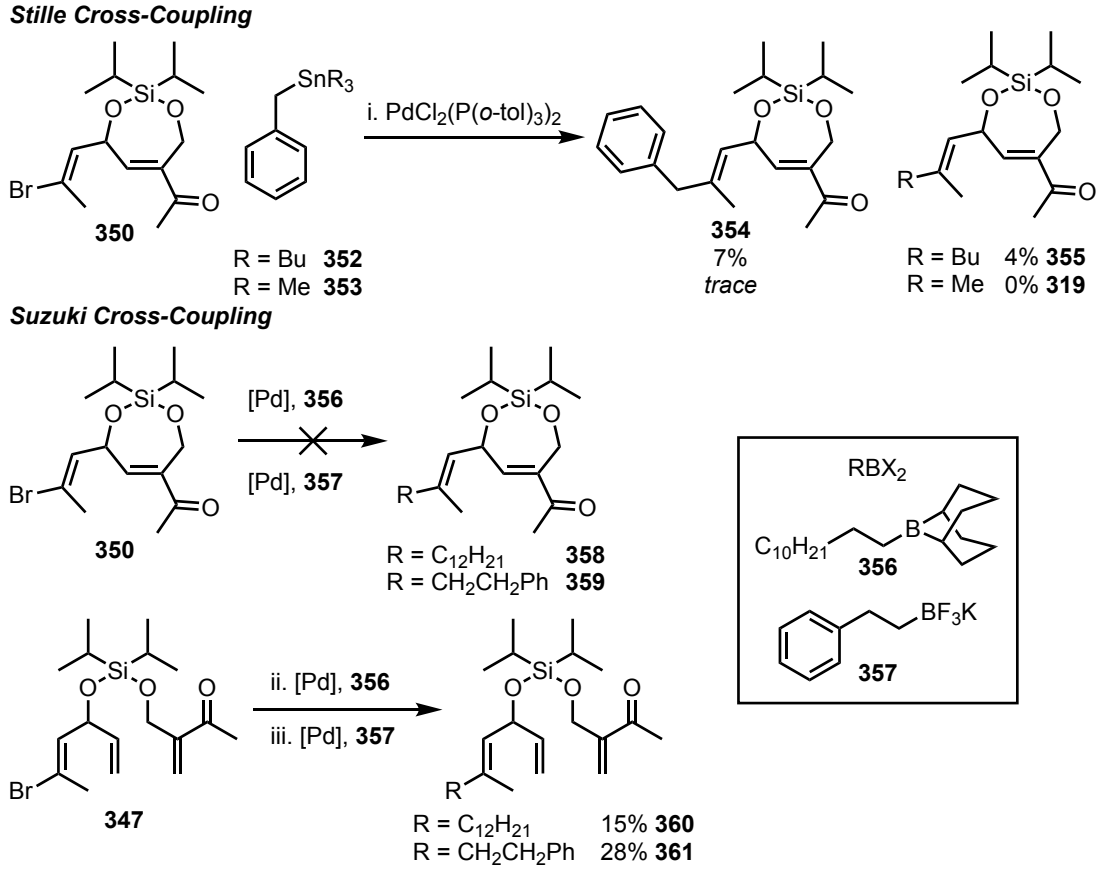


Figure 2.6 Organostannane rate of transmetallation

These concerns were confirmed when the reaction of silaketal **350** and tributyl(benzyl)-stannane (**352**) afforded a mixture of silaketals **354** and **355**, both in low yield. Use of trimethyl(benzyl)stannane (**353**) allowed for selective formation of silaketal **354**, but only in trace quantities (Scheme 2.47). Further optimisation of this procedure was unsuccessful.

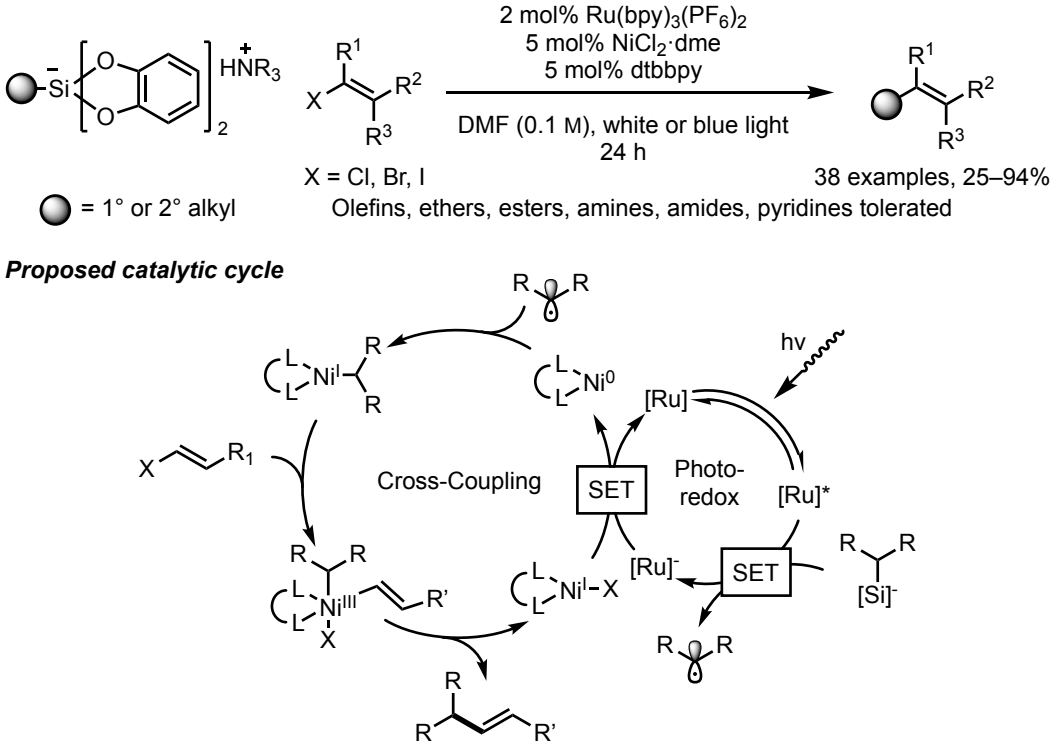


Scheme 2.47 Model cross-coupling reactions. Reagents and conditions: i) 3 eq. **352** or **353**, 5 mol% $PdCl_2(P(o\text{-tol})_3)_2$, 10 mol% CuI, NMP, 70 °C, 24 h; ii) 1.2 eq. **356**, 1.3 eq. K_3PO_4, 5 mol% $PdCl_2dppf{\cdot}CH_2Cl_2$, DMF:THF (4:1), 50 °C, 18 h, 15%; iii) 1.1 eq. **357**, 10 mol% $PdCl_2dppf{\cdot}CH_2Cl_2$, 3 eq. Cs_2CO_3, PhMe:H_2O (3:1), 50 °C, 18 h

Controlled transmetallation of a predetermined alkyl group would be possible from a boronic ester (or surrogate thereof). The use of Suzuki coupling was therefore investigated. Unfortunately, even with weak phosphate bases, silaketal **350** decomposed under the reaction conditions with both 9-BBN **356** and trifluoroborate **357**. Suzuki coupling was possible with TST **347**, albeit still in poor yield, but with the low reactivity of trialkyl olefin substituted TSTs in RCM still unresolved this was not a preferred strategy.

While the above investigations were being carried out, Molander and co-workers published

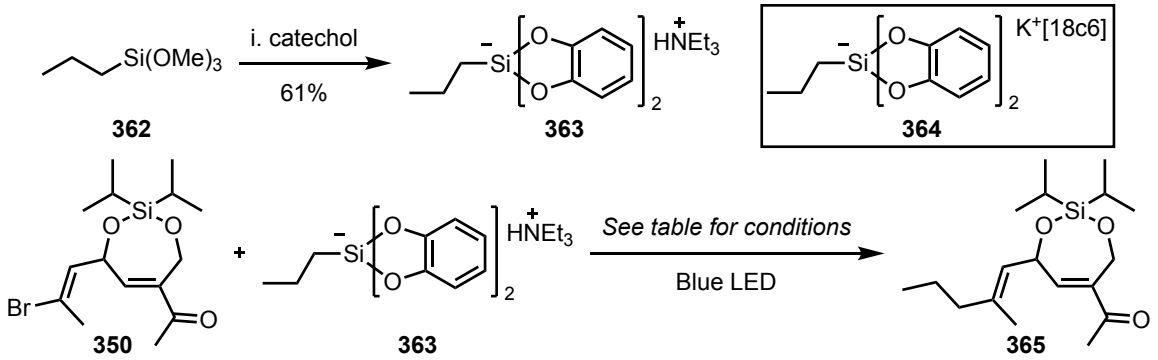
the cross-coupling of sp^3 alkyl silicates and vinyl halides. A range of vinyl halides could be reacted with the activated alkyl silicates under mild conditions using dual photoredox/Ni catalysis to afford alkylated olefins with retention of stereochemistry. The reaction proceeded at room temperature and in the absence of external Brønsted acid or base (Scheme 2.48).[141]



Scheme 2.48 Molander dual photoredox/Ni catalysed coupling of alkyl silicates and vinyl halides

These conditions were well suited to the required transformation and silicate **363** was therefore synthesised from trimethyoxy(propyl)silane (**362**) (61% yield) to enable investigations in this area. The reaction of silaketal **350** with silicate **363** under the reported conditions afforded desired silaketal **365** in 6% yield (Table 2.12, Entry 1). Increasing the $NiCl_2$·dme loading to 10 mol% improved the yield to 10% but further catalyst provided no benefit, ruling out catalyst turnover as the limiting step (Entries 2 and 3). The low amounts of recovered silaketal **350** suggested starting material degradation under the reaction conditions, possibly involving TST decomposition. The use of chloride anions to deprotect the TST was utilised earlier (see Chapter 2.3.3) but Ni sources containing less nucleophilic triflate or acetoacetate counterions did not improve mass recovery and indeed switched off the intended reactivity

(Entries 4 and 5). Acceptable reactivity had also been reported in THF and dioxane but no product was formed when reacting silaketal **350** under these conditions and only trace starting material remained (Entries 6 and 7). Product formation was also not observed when using alternative silicate sources[142] (Entry 8), lower intensity blue light (Entry 9) or vinyl chloride substituted silaketal **349** (Entry 10). Overall mass recovery improved when conducting the reaction at –20 °C, but silaketal **365** was still only formed in 10% yield (Entry 2 vs. 11).



Entry	Silicate	$NiCl_2$·dme	dtbbppy	$Ru(bpy)_3(PF_6)_2$	Solvent	Temp.	Yield 365	350
1	1.5 eq.	5 mol%	5 mol%	2 mol%	DMF	rt	6%	12%
2	1.5 eq.	10 mol%	10 mol%	2 mol%	DMF	rt	10%	12%
3	1.5 eq.	50 mol%	50 mol%	2 mol%	DMF	rt	8%	–
4	1.2 eq.	10 mol%[a]	10 mol%	2 mol%	DMF	rt	–	–
5	1.2 eq.	10 mol%[b]	10 mol%	2 mol%	DMF	rt	–	–
6	1.2 eq.	10 mol%	10 mol%	2 mol%	THF	rt	–	Trace
7	1.2 eq.	10 mol%	10 mol%	2 mol%	Dioxane	rt	–	Trace
8	1.2 eq.[c]	10 mol%	10 mol%	2 mol%	DMF	rt	–	Trace
9[d]	1.2 eq.	10 mol%	10 mol%	2 mol%	DMF	rt	–	Trace
10[e]	1.5 eq.	5 mol%	5 mol%	2 mol%	DMF	rt	–	–
11	1.2 eq.	10 mol%	10 mol%	2 mol%	DMF	–20 °C	10%	19%

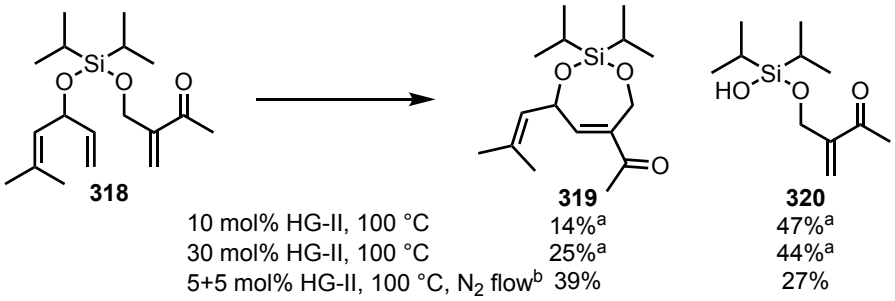
Table 2.12 Attempted optimisation of dual photoredox/Ni catalysed coupling of silaketal **350** and silicate **363**. Reagents and conditions: i) 1.9 eq. catechol, 1.2 eq. Et_3N, THF, reflux, 24 h. [a]$Ni(OTf)_2$, [b]$Ni(acac)_2$, [c]silicate **364**, [d]low intensity light, [e]silaketal **349**

Other strategies including lithium-halogen exchange and iron-catalysed cross-coupling with Grignard reagents[143] all failed to furnish any desired coupling product. On the basis of the general lack of reactivity of silaketal **350** in cross-coupling chemistry and the very low yields achieved using photoredox/Ni dual catalysis, a synthetic strategy towards (+)-lophotoxin (**1**)

incorporating vinyl bromides of type **350** was not deemed to be viable. However, these investigations had revealed more efficient, *pseudo* open-flask, conditions for RCM and application of these to the troublesome RCM of trialkyl olefin substituted TST **318** was attempted.

2.4.5 Diol 366 as an Advanced Model System

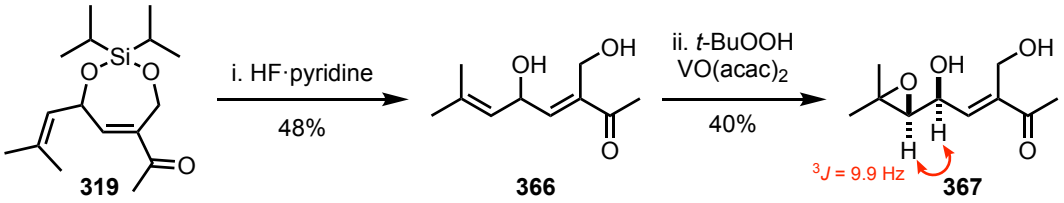
Previously, RCM with TST **318** using 10 mol% HG-II at 100 °C had resulted in 14% and 47% conversion to silaketal **319** and silanol **320** respectively by ^{1}H NMR. Use of 30 mol% HG-II had increased conversions to 25% and 44%. Applying the modified RCM conditions and using just 10 mol% HG-II, silaketal **319** could be isolated in a much improved 39% yield, along with 21% unreacted TST **318** and a reduced quantity of silanol **320** (27%, Scheme 2.49).



Scheme 2.49 RCM of TST **318** under modified reaction setup. General reagents and conditions: PhMe (0.005 M), 24 h. [a]conversion by ^{1}H NMR [b]Reaction performed by Simon Werrel

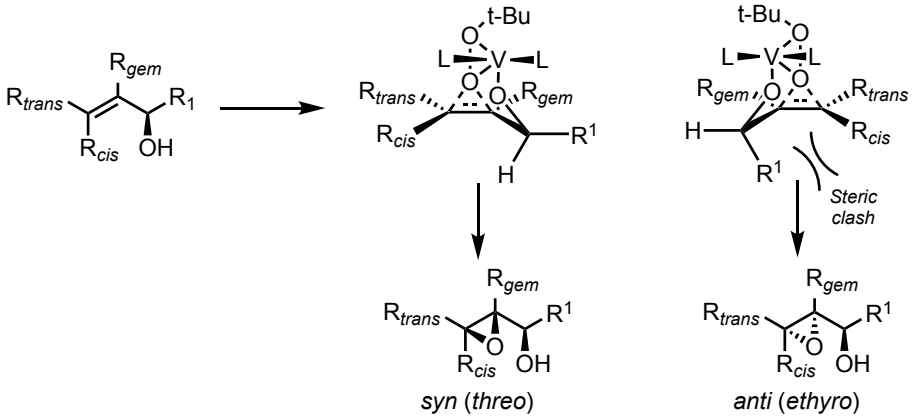
Although further optimisation would undoubtably be required, attention first turned to determining whether a furan incorporating an adjacent epoxide could be synthesised using photochemical irradiation. Silaketal **319** was deprotected using HF·pyridine to give diol **366** in 48% yield and after reaction with $VO(acac)_2$, epoxide **367** was isolated in 40% yield as a single diastereomer. As hoped, epoxidation had occurred on the more electron rich olefin. A relative stereochemistry of *syn* (*threo*) was assigned on the basis of the coupling constants reported for a series of related compounds by Mihelich.[144] *Threo* epoxy alcohols were reported to consistently have a ^3J coupling constant >5 Hz between the epoxide bound proton and the proton adjacent to the directing alcohol. Those with *ethyro* stereochemistry consistently showed a

coupling constant of *ca*. 3 Hz between the same protons (Scheme 2.50).



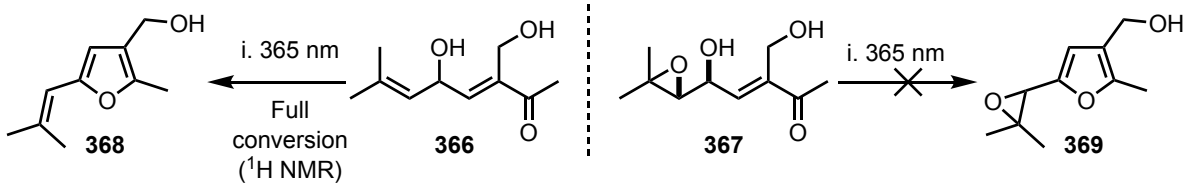
Scheme 2.50 Synthesis of epoxide **367**. Reagents and conditions: i) 2.5 eq. HF·pyridine, THF, 0 °C to rt, 3 h, 48%; ii) 1.2 eq. *t*-BuOOH, 20 mol% $VO(acac)_2$, CH_2Cl_2, 0 °C, 2.5 h, 40%

A model to account for the observed diastereoselectivity was proposed by Sharpless.[145] The dihedral angle between the alcohol and olefin is assumed to be *ca*. 40° for both *syn* and *anti* epoxidations. The crucial interaction is between R_{cis} and R^1 which favours epoxidation *via* the *syn* (*threo*) transition state to prevent steric clash when R_{cis} is a Me group (Scheme 2.51).



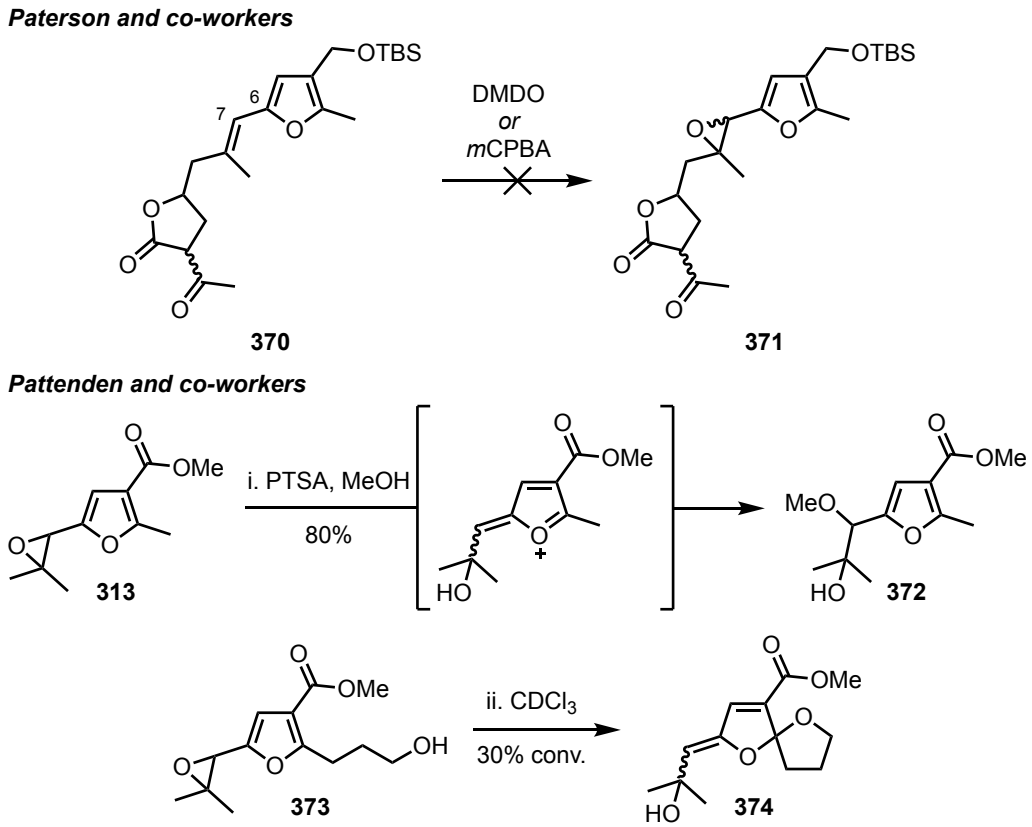
Scheme 2.51 Proposed model for the diastereoselectivity of $VO(acac)_2$ mediated epoxidation

With both diol **366** and epoxide **367** in hand, the photochemical isomerisation/cyclisation sequence was attempted. Irradiation of diol **366** at 365 nm resulted in complete conversion to furan **368** by ^{1}H NMR. Unfortunately, irradiation of epoxide **367** under the same conditions led to multiple unidentifiable products being formed and substantial decomposition of material. These reactions were performed by a co-worker (Scheme 2.52).



Scheme 2.52 Photochemical isomerisation of diol **366** and epoxide **367**. Reagents and conditions: i) 365 nm, EtOAc, 0 °C, 8 h. Reactions performed by Simon Werrel

The failure of epoxide **367** in the photochemical isomerisation was worrying as the key strategic disconnection towards (+)-lophotoxin (**1**) was the installation of the epoxide prior to furan formation. However, the literature contained a number of informative experiments. Paterson and co-workers had attempted the epoxidation of furan **370** with DMDO and *m*CPBA. In both cases decomposition was observed and epoxide **371** could not be isolated.[26] They suggested that the electron-rich furan destabilised the epoxide formed and decided to attempt the synthesis of a macrocyclic analogue where "rotation about the *C*-6/7 bond is constrained, thereby reducing epoxide destabilisation." Subsequent studies have not yet been communicated, however. Additionally, Pattenden and co-workers reported the reaction of more electron-poor epoxy furan **313** to furan **372** under acidic conditions and the partial conversion of furan **373** to spiroketal **374** on standing in $CDCl_3$ (Scheme 2.53).[146]

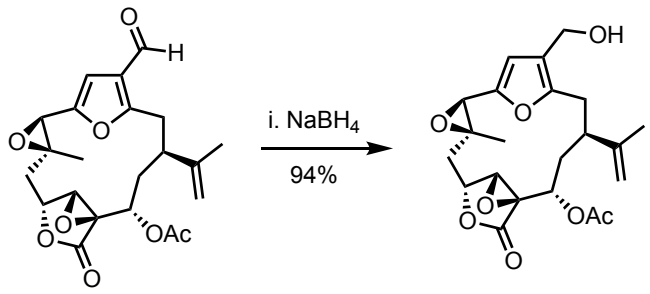


Scheme 2.53 Reactivity of furanocembranoid type furans. Reagents and conditions: i) PTSA, MeOH, rt, 30 min, 80%; ii) $CDCl_3$, rt, 30 min

It seems reasonable to suggest that donation from the furan π system into the epoxide C–O σ*

orbital is responsible for the decomposition of furans **369** and **371**, and the need for additional acid with less electron-rich furans **313** and **373** would be consistent with this hypothesis.

Crucially, Taylor and co-workers could reduce (+)-lophotoxin (**1**) to alcohol **375** in 94% yield as part of a structure-activity study (Scheme 2.54).[11] This indicates that the epoxide is stable next to the more electron rich furan when in the macrocyclic conformation. The crystal structure for (+)-lophotoxin (**1**) reported by Riguera and co-workers shows the epoxide lying out of the plane of the furan ring, providing an explanation for this stability that is consistent with the proposed decomposition pathway.[147] If irradiation were to be performed in the final stages of the synthesis, then the irradiation product would be almost identical to macrocycle **375**. It was therefore hoped that the original strategy could still be implemented.

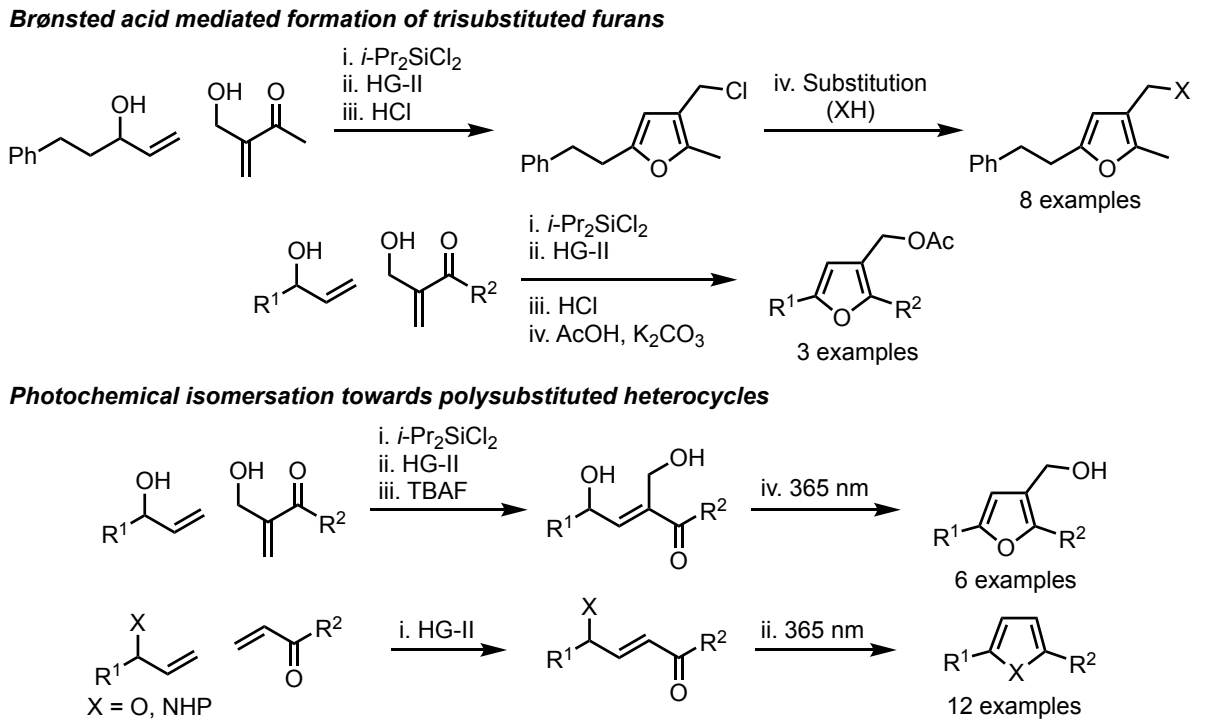


(+)-lophotoxin (**1**) **375**

Scheme 2.54 Synthesis of alcohol **375**. Reagents and conditions: i) 4.4 eq. $NaBH_4$, MeOH, 0 °C, 1 h, 94%

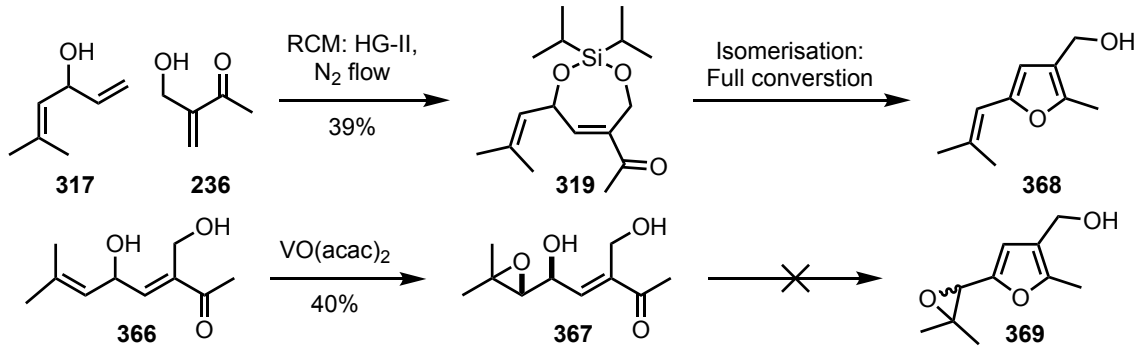
2.5 Conclusion

TST-RCM methodology for the synthesis of 2,3,5-trisubstituted furans was developed from simple allylic alcohol starting materials. Both acidic and neutral photochemical conditions that enable the isomerisation and cyclisation of the intermediate ɣ-hydroxyenones have been established and the scope of these procedures demonstrated. Extension of the photochemical isomerisation to the synthesis of 2,5-disubstituted furans and pyrroles was successful and a library of heterocyclic compounds was synthesised incorporating a number of acid sensitive functional groups that were not previously tolerated (Scheme 2.55).



Scheme 2.55 Development of TST-RCM methodology to polysubstituted heterocycles

Model studies pertaining to the furan core of the furanocembranoids established RCM conditions to access trialkyl substituted silaketal **319**, although the low yield of 39% required further optimisation. An alternative Luche reduction strategy for the RCM was also developed. Photochemical isomerisation furnished model trialkyl substituted furan **368**. Preliminary conditions for the required diastereoselective epoxidation were established although the isomerisation to epoxy furan **369** was unsuccessful. Literature reactions provided a plausible explanation for this observation and indicated that incorporation of the epoxide followed by isomerisation in a macrocyclic system remained a viable strategy (Scheme 2.56).



Scheme 2.56 Development of model conditions towards the furanocembranoid core

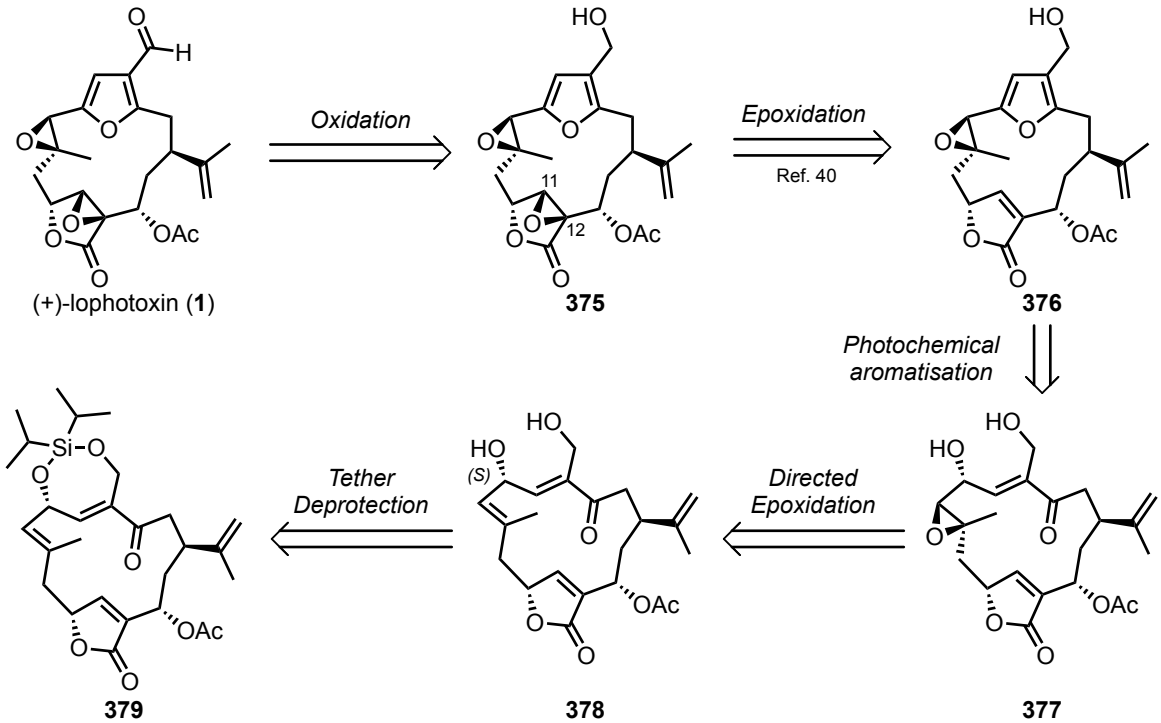
Chapter 3

Progress Towards the Total Synthesis of (+)-Lophotoxin

3.1 Retrosynthetic Analysis of (+)-Lophotoxin (1)

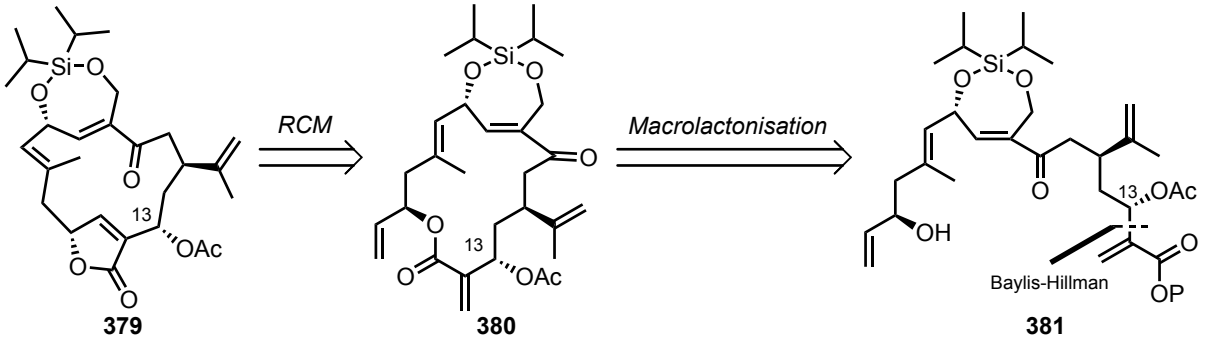
Our synthetic approach to (+)-lophotoxin (**1**) was informed by the preceding model studies, published synthetic efforts towards both (+)-lophotoxin (**1**) and related furanocembranoids, and some unpublished results pertaining to the total synthesis of (–)-(*Z*)-deoxypukalide (**77**) reported by Donohoe and co-workers.[39]

The end-game retrosynthesis is shown in Scheme 3.1. The *C*-11/12 epoxide would be installed after furan formation; nucleophilic epoxidation should be tolerated by the electron rich furan but reaction prior to its formation might lead to competitive epoxidation of the enone moiety.[40] The furan would be installed by photochemical aromatisation from epoxy diol **377** which would itself be formed *via* directed epoxidation of alkene **378**. $VO(acac)_2$ mediated epoxidation would likely operate with the stereocontrol observed for the acyclic model system due to the large ring size and so it was proposed that the alcohol with (*S*) stereochemistry in diol **378** would be required. Diol **378** would be unveiled by TST deprotection of silaketal **379**.



Scheme 3.1 End-game retrosynthesis

Butenolide synthesis is often accomplished using RCM. This strategy would enable the use of a macrolactonisation reaction to give **380** and in turn an asymmetric Baylis–Hillman reaction to forge the *C*-13 stereocentre (Scheme 3.2). Pattenden and co-workers had installed this alcohol with low stereocontrol (2.3:1) in their synthesis of *bis*-deoxylophotoxin (**68**),[29] as had Mulzer and co-workers (1.5:1) *en route* to (+)-17-deoxyprovidencin (**126**).[40] A route facilitating installation of the *C*-13 stereocentre with high stereocontrol has yet to be realised with the *C*-13 alcohol not present in any other furanocembranoid synthesised to date.

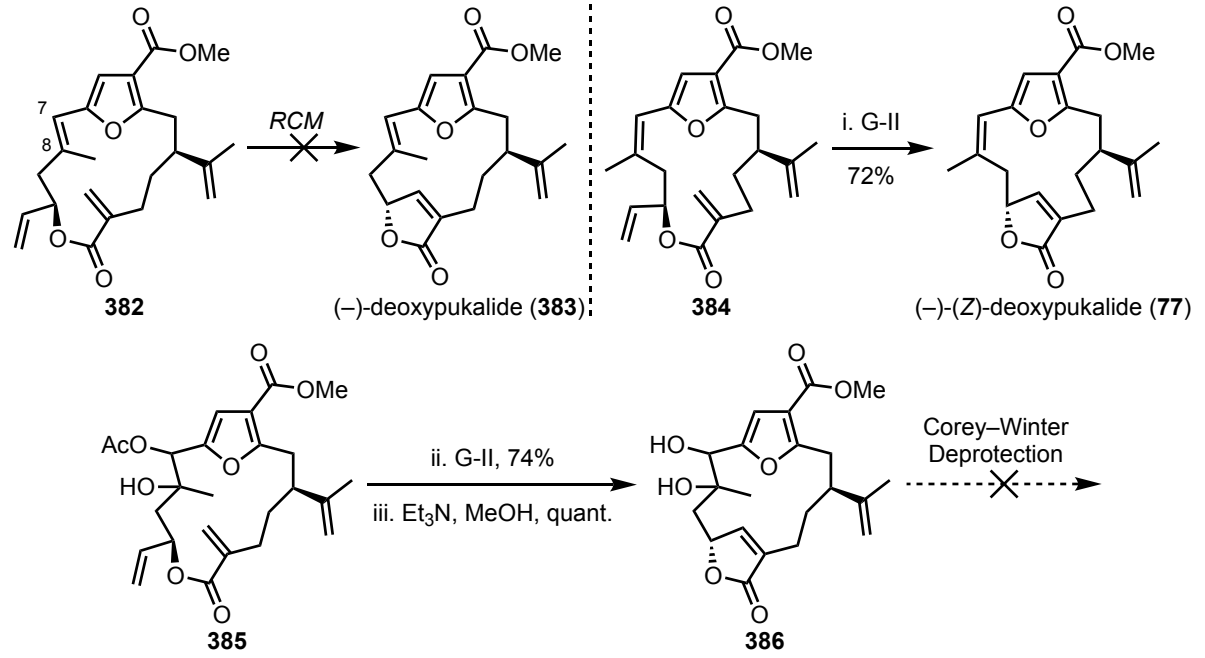


Scheme 3.2 Macrolactonisation of macrocycle **379** to silaketal **381**

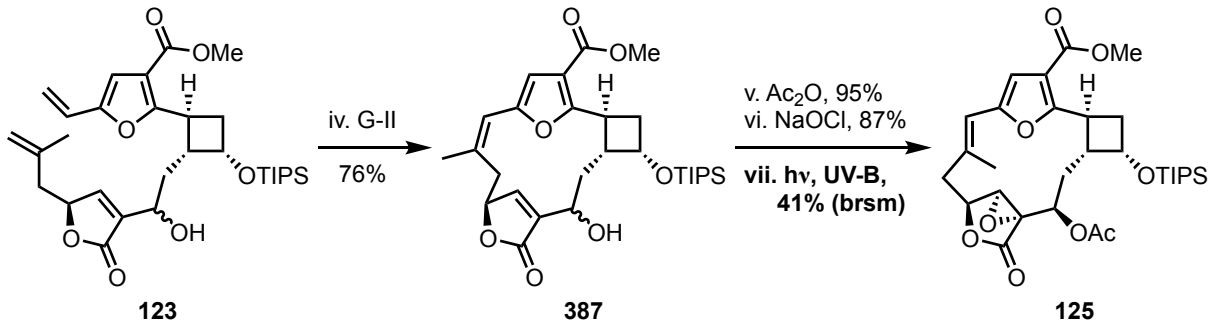
It was considered strategically important to synthesise the butenolide prior to furan formation. The failure of a related RCM with furan containing macrocycle **382** has previously been observed by Donohoe and co-workers in studies towards (–)-deoxypukalide (**383**).[148] This was ascribed to ring strain caused by the (*E*) *C*-7/8 olefin; the opposite (*Z*) olefin **384** underwent RCM in 72% yield. Increasing the flexibility of the macrocycle by dihydroxylating the (*E*) alkene had also led to efficient RCM from macrocycle **385** but a subsequent Corey-Winter reaction could not re-form the alkene. Similar effects involving (*E*) olefin derived ring strain have been reported by Mulzer, who noted a preference for the (*Z*) olefin when performing RCM to 13-membered macrocycle **387**. The geometry was later corrected using photochemical irradiation. Further, Clark and co-workers observed the selective macrolactonisation of the *pseudo* (*Z*) epoxide (1:1 epimeric ratio at *C*-7) to 14-membered macrocycle **389** *en route* to (+)-7-*epi*-pukalide (**133**, Scheme 3.3).[42] As such, it was planned to perform RCM prior to fu-

ran formation as the silaketal moiety (or deprotected diol) should improve flexibility and permit RCM with the required (*E*) alkene. The TST-RCM approach would thus have dual benefit, allowing for incorporation of the *C*-7/8 epoxide and RCM with the correct (*E*) olefin.

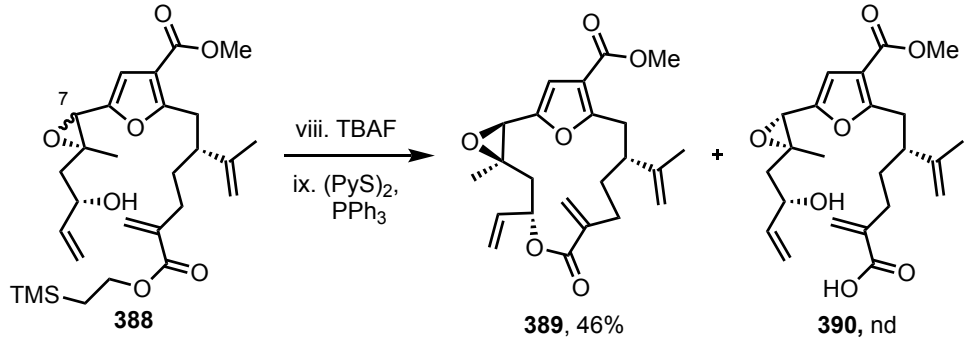
Donohoe: Difficulty in forming the butenolide moiety with an (E) olefin



Mulzer: (Z) selective RCM

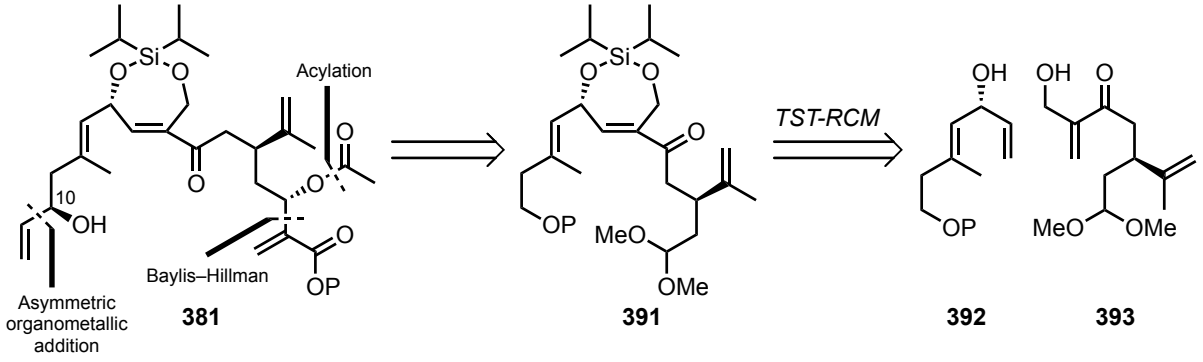


Clark: Resolution of pseudo (Z) stereoisomer by macrolactonisation



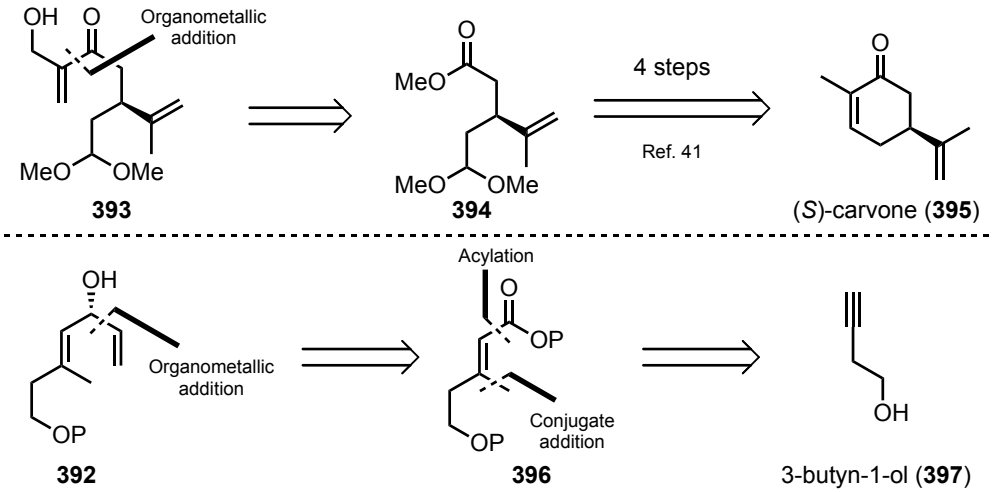
Scheme 3.3 Effect of *C*-7/8 olefin geometry on furanocembranoid synthesis. Reagents and conditions: i) 15 mol% G-II, PhMe, reflux, 16 h, 72%; ii) G-II, CH_2Cl_2, 74%; iii) Et_3N, MeOH, quant.; iv) 20 mol% G-II, benzene, reflux, 15 h, 76%, v) 1.05 eq. Ac_2O, 10 mol% DMAP, 1.1 eq. DIPEA, CH_2Cl_2, 0 °C, 45 min, >95%; vi) 5% NaOCl, pyridine, –15 °C, 5 min, 87%; vii) UV-B, MeCN, rt, 80 min, 31%; viii) 2 eq. TBAF (1 M in THF), THF, 10 °C, 3 h; ix) 1.4 eq. 2,2'-dipyridyl disulfide, 1.4 eq. PPh_3, PhMe, rt to reflux, 7 h, 46% (2 steps). nd = not determined

Asymmetric addition of a vinyl group would set the stereochemistry of the *C*-10 alcohol. Both asymmetric addition and Baylis–Hillman reactions would take place after the TST-RCM sequence. This was to avoid the use of fragments containing multiple hydroxyl groups in the TST formation step, which would require challenging regiochemical discrimination. Silaketal **391** would be formed using the developed TST-RCM methodology from allylic alcohols **392** and **393** (Scheme 3.4).



Scheme 3.4 Retrosynthesis of silaketal **381**

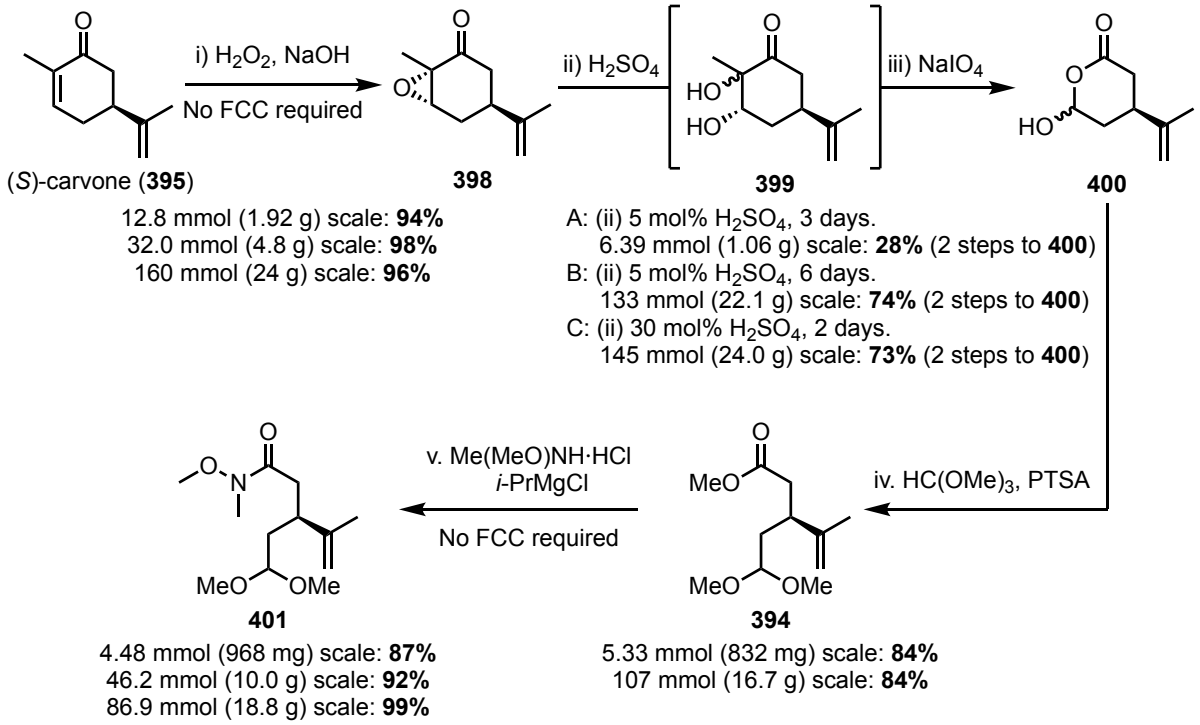
Alcohol **393** would be formed by addition of the appropriate organometallic into a Weinreb amide derived from known ester **394**.[41] The stereochemistry of (*R*)-alcohol **392** would be set by asymmetric organometallic addition or enzymatic resolution of the racemate. The latter route would provide access to both enantiomers. Ester **396** would be derived from 3-butyn-1-ol (**397**) by acylation of the alkyne and conjugate addition of a methyl group (Scheme 3.5).



Scheme 3.5 Retrosynthesis of alcohols **392** and **393**

3.2 Synthesis of Alcohol 393

The synthesis began by accessing known ester **394** from (*S*)-carvone (**395**) using the route previously reported by Mulzer and co-workers (Scheme 3.6).[41]

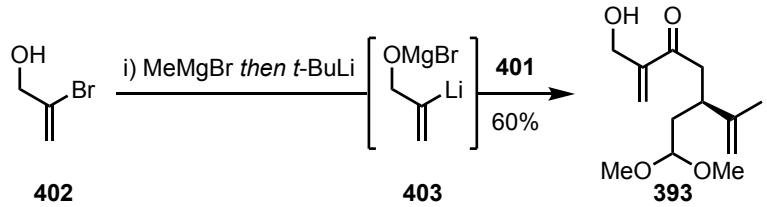


Scheme 3.6 Synthesis of amide **401**. Reagents and conditions: i) 2 eq. H_2O_2 (30% in H_2O), 30 mol% NaOH (4 M in H_2O), MeOH, –20 °C, 4 h, 96%; ii) 30 mol% H_2SO_4, THF:H_2O (20:1), 80 °C, 42 h; iii) 3 eq. $NaIO_4$, SiO_2, H_2O, CH_2Cl_2, 0 °C to rt, 12 h, 73% (2 steps); iv) 5 eq. $HC(OMe)_3$, 5 mol% PTSA·H_2O, MeOH, rt, 24 h, 84%; v) 1.5 eq. Me(MeO)NH·HCl, 3 eq. *i*-PrMgCl, THF, –20 °C, 3 h, 99%

Epoxidation of (*S*)-carvone (**395**) under basic conditions afforded epoxide **398** in 96% yield. Opening of the epoxide and diol cleavage were performed without purification of the intermediate diol **399** and using the reported conditions (A: 5 mol% H_2SO_4, 80 °C, 2 days followed by diol cleavage) hemiacetal **400** could be isolated in 28% yield over 2 steps, compared to the reported 70% yield. A higher yield could be obtained when either a longer reaction time was used for the epoxide opening (B: 6 days) or by increasing the amount of acid (C: 30 mol% H_2SO_4). One-pot esterification and acetalisation transformed hemiacetal **400** into ester **394** in 84% yield. Spectroscopic data for **394** matched that reported by Mulzer and co-workers. The methyl ester was then converted into Weinreb amide **401** using isopropylmagne-

sium chloride and MeO(Me)NH·HCl. This 5 step sequence required only two purification steps by FCC and provided 21.2 g of amide **401** in 58% yield from (*S*)-carvone (**395**).

Addition of vinyl lithium **403**, originally reported by Corey and Widiger,[149] into amide **401** then furnished alcohol **393** in 60% yield. Vinyl lithium **403** was prepared according to the procedure developed by Hegde and Myles involving sequential deprotonation of alcohol **402** with MeMgBr followed by treatment with *t*-BuLi (Scheme 3.7).[150]

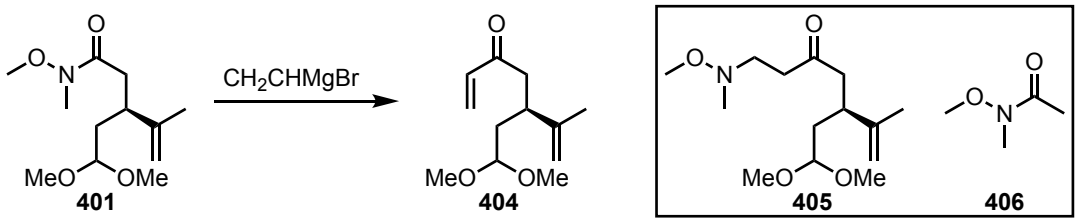


Scheme 3.7 Attempted direct synthesis of alcohol **393**. Reagents and conditions: i) 3 eq. **402**, 3 eq. MeMgBr (3 M in Et_2O), 6 eq. *t*-BuLi (1.67 M in hexanes), 0 °C, 3 h *then* 1 eq. **401**, 0 °C to rt, 3 h, 60%

Unfortunately, the reaction was found to be capricious and incomplete conversion was frequently observed. Purification was then further complicated as amide **401** and alcohol **393** co-eluted on FCC. It was therefore decided to attempt the addition of vinylmagnesium bromide followed by a Baylis–Hillman reaction with paraformaldehyde.

Addition of vinylmagnesium bromide to amide **401** formed enone **404** in 81% on 1.27 mmol scale (Table 3.1, Entry 1). Unfortunately, increases in reaction scale led to concomitant decreases in isolated yield, with the mass balance consisting mostly of amine conjugate addition product **405** (Entries 2 and 3). It was proposed that inefficient quenching of the reaction was allowing deprotonated *N*,*O*-dimethylhydroxylamine to add into enone **404**.[151] Due to the presence of the dimethyl acetal, quenching with stronger acids was not appropriate. Miller and co-workers reported the use of a sequential acetic anhydride and methanol quench (forming amide **406**) to address this problem. Application of their conditions produced enone **404** in >81% yield on both 1.65 and 20.4 mmol scales (Entries 4 and 5).[152] Stirring the reaction mixture for an extended period of time after quenching allowed for easier isolation of enone **404**

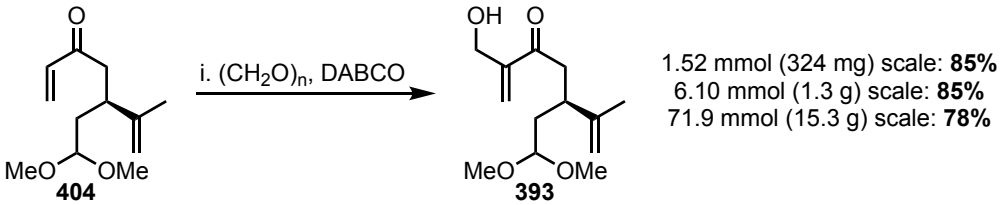
as it minimised formation of acetic acid, which co-eluted with the product, and **404** was finally isolated on 83% yield on 86 mmol scale (Entry 6).



Entry	Scale	Quench	Yield 404
1	1.27 mmol (310 mg)	NH_4Cl (sat., aq.)	81%
2	11.9 mmol (2.91 g)	NH_4Cl (sat., aq.)	63%
3	41.0 mmol (10.0 g)	NH_4Cl (sat., aq.)	12%
4	1.65 mmol (405 mg)	Ac_2O (K_2CO_3 filtered), 5 min *then* MeOH, 1 min	81%
5	20.4 mmol (5 g)	Ac_2O (K_2CO_3 filtered), 5 min *then* MeOH, 1 min	84%
6	86.3 mmol (21.2 g)	Ac_2O (K_2CO_3 filtered), 10 min *then* MeOH, 30 min	83%

Table 3.1 Synthesis of enone **404**. General reagents and conditions: 2 eq. $CH_2CHMgBr$, THF, –5 °C, 2 h

The Baylis–Hillman reaction between enone **404** and paraformaldehyde then led to smooth formation of alcohol **393** which could be isolated on 85% yield on 1.52 mmol scale. Scale up to 71 mmol resulted in only a slightly reduced yield of 78% (Scheme 3.8).

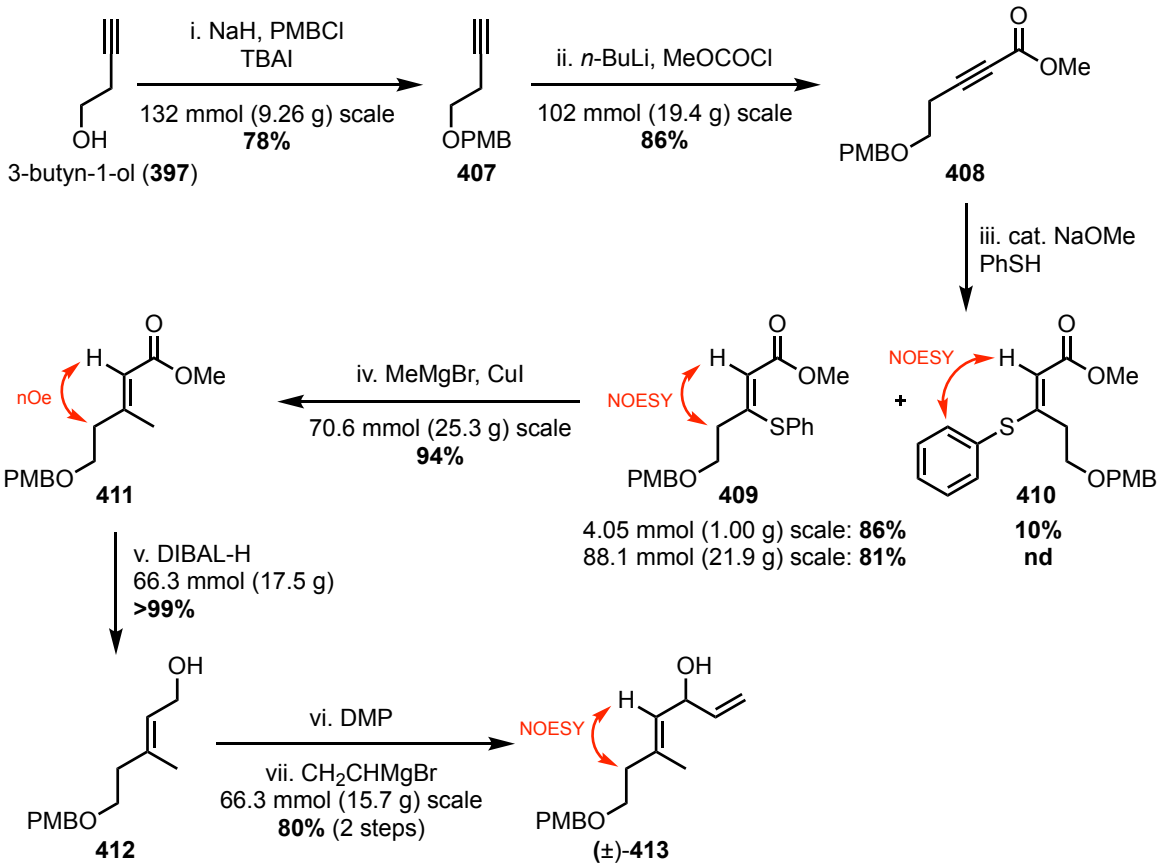


Scheme 3.8 Synthesis of alcohol **393**. Reagents and conditions: i) 3 eq. $(CH_2O)_n$, 10 mol% DABCO, dioxane:H_2O (1:1), rt, 18 h, 78%

Overall, alcohol **393** was synthesised in 37% yield over 7 steps from commercially available (*S*)-carvone (**395**). The route proved scalable with 13.7 g (56.6 mmol) of alcohol **393** brought through in a single pass. Attention then turned to the synthesis of an alcohol of type **392** (see Scheme 3.5). The PMB protecting group was chosen for **392** as deprotection in the presence of the acid sensitive TST and base sensitive Baylis-Hillman ester might be required (see Scheme 3.4). Oxidative PMB deprotection conditions would likely be tolerated, however.

3.3 Synthesis of (±)-Allylic Alcohol 413

Following the route developed by a co-worker, (±)-alcohol **413** was synthesised in 40% yield over 7 steps (Scheme 3.9).[153] Deprotonation of 3-butyn-1-ol (**397**) with 1 eq. NaH and quenching with *p*-methoxybenzyl chloride afforded ether **407** in 78% yield. The strict use of 1 eq. NaH was found to be crucial to avoid formation of inseparable allenyl byproducts. Acylation of alkyne **407** with methyl chloroformate then produced alkynoate **408** in 86% yield.



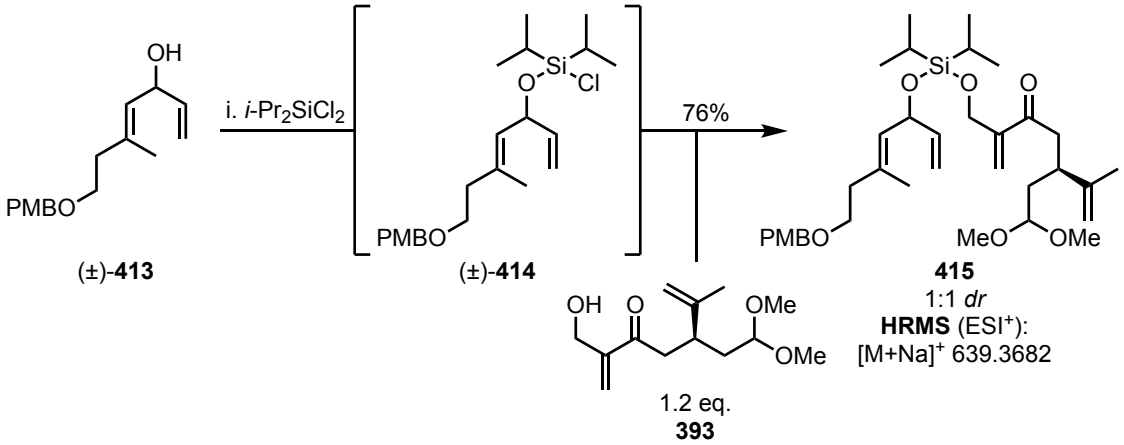
Scheme 3.9 Synthesis of (±)-alcohol **413**. Reagents and conditions: i) 1 eq. NaH, 1.1 eq. PMBCl, 10 mol% TBAI, THF, 0 °C, overnight, 78%; ii) 1.05 eq. *n*-BuLi, 1.2 eq. ClCOOMe, THF, –78 °C, 2.5 h, 86%; iii) 5 mol% NaOMe, 1.1 eq. PhSH, MeOH, rt, 2.5 h, 81%; iv) 3.7 eq. MeMgBr (3 M in Et_2O), 1.9 eq. CuI, THF, –78 °C, 2 h, 94%; v) 2.5 eq. DIBAL-H (1 M in hexanes), THF, –78 °C, 2.5 h, quant.; vi) 1.2 eq. DMP, CH_2Cl_2, 0 °C to rt, 90 min; vii) 2.5 eq. $CH_2CHMgBr$ (1 M in THF), THF, –78 °C, 1 h, 80% (2 steps)

Stereoselective conjugate addition of thiophenol produced a separable 8.6:1 mixture of thiols **409** and **410**.[154] The identity of each geometric isomer was confirmed by NOESY NMR with the major isomer being the desired (*Z*) olefin. Reaction on 88 mmol scale furnished (*Z*)-thiol **409** in 81% yield. Mukaiyama and co-workers showed that the stereospecific copper

mediated addition-elimination of alkyl Grignard reagents into such thiol species was possible with retention of configuration.[155] Use of stoichiometric CuI allowed smooth formation of enone **411** in 94% yield; the retention of double bond geometry was confirmed by nOe enhancements. Excess DIBAL-H effected the quantitative reduction of the ester moiety to alcohol **412** which could then be oxidised to the corresponding aldehyde with DMP. Addition of vinylmagnesium bromide furnished (±)-alcohol **413** in 80% yield over two steps. This 7 step sequence was also scalable; the largest single batch of (±)-alcohol **413** synthesised was 14.0 g. Although an asymmetric synthesis of (*R*)-alcohol **413** would eventually be required, it was decided to continue with the racemic mixture in order to optimise the RCM reaction.

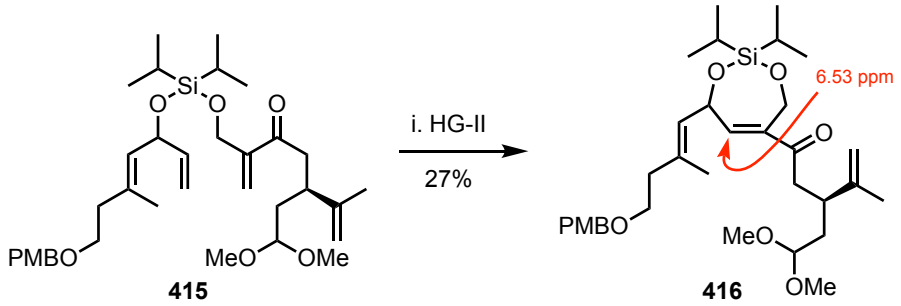
3.4 Synthesis of Silaketal 416

With (±)-alcohol **413** and alcohol **393** in hand, the TST-RCM sequence was investigated. Silylation of (±)-alcohol **413** with *i*-Pr_2SiCl_2 produced silyl chloride **414** which was quenched by addition of alcohol **393** to afford TST **415** in 76% yield (Scheme 3.10).



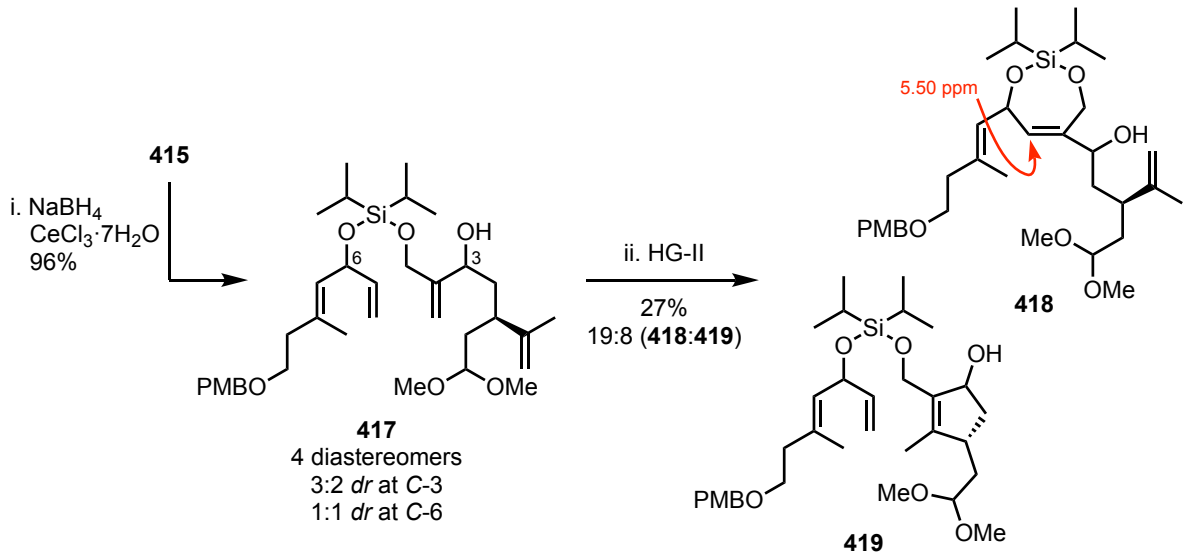
Scheme 3.10 Synthesis of silaketal **415**. Reagents and conditions: 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, CH_2Cl_2, 0 °C, 90 min *then* 1.2 eq **393**, 5 min, 76%

In model studies, the RCM of TST **318**, bearing a pendent trialkyl substituted olefin, had produced silaketal **319** in 39% yield (see Chapter 2.4.5). Subjection of TST **415** to these conditions furnished silaketal **416** in only 27% yield and optimisation by a co-worker did not provide any improvement (Scheme 3.11).



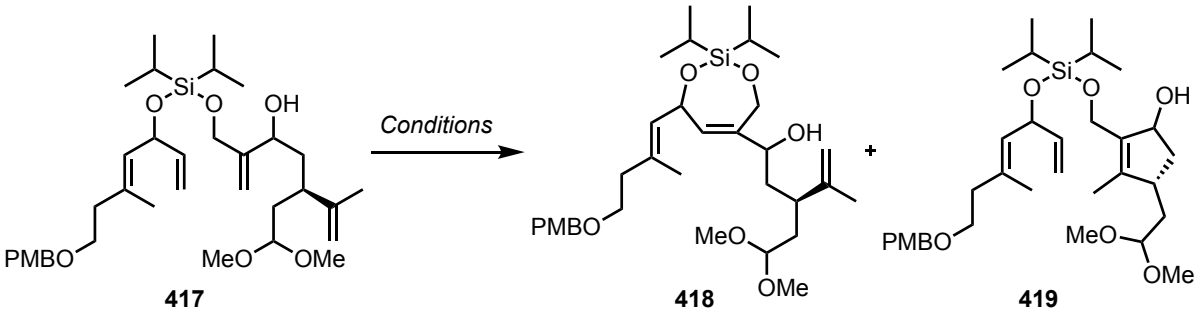
Scheme 3.11 RCM to TST **416**. Reagents and conditions: i) 5+5 mol% HG-II, PhMe, 100 °C, 24 h, N_2 flow, 27%. Reaction performed by Simon Werrel

The low reactivity of **415** would be consistent with the intramolecular chelate resting state invoked earlier; the more electron rich nature of the olefin in TST **415** would impart a stronger π–[Ru] bonding interaction, further disfavouring ring-closing. To circumvent this, the Luche reduction/RCM sequence was attempted as initiation would then preferentially occur on the allylic alcohol. Luche reduction afforded alcohol **417** in 96% yield (3:2 *dr* at *C*-3) which was subjected to RCM with HG-II. Silaketal **418** and cyclopentene **419** were then isolated as a 19:8 inseparable mixture in 27% yield. Although cyclopentene **419** could not be separated and rigorously characterised, its formation was inferred from the loss of both allylic alcohol and isobutylene methylene (CH_2) signals in the ^{1}H NMR spectrum (Scheme 3.12).



Scheme 3.12 Luche reduction and RCM of TST **415**. Reagents and conditions: i) 1.1 eq. $CeCl_3 \cdot 7H_2O$, 1.2 eq. $NaBH_4$, MeOH, 0 °C, 2 h, 96%; ii) 5 mol% HG-II, PhMe, 80 °C, 24 h

Although the formation of 5-membered rings is usually favoured over 7-membered rings in RCM, the crowded tetrasubstituted olefin of cyclopentene **419** likely prevented it from being the major product and allowed the synthesis of silaketal **418**. It was hoped that by reducing the reaction temperature the formation of cyclopentene **419** could be further inhibited.



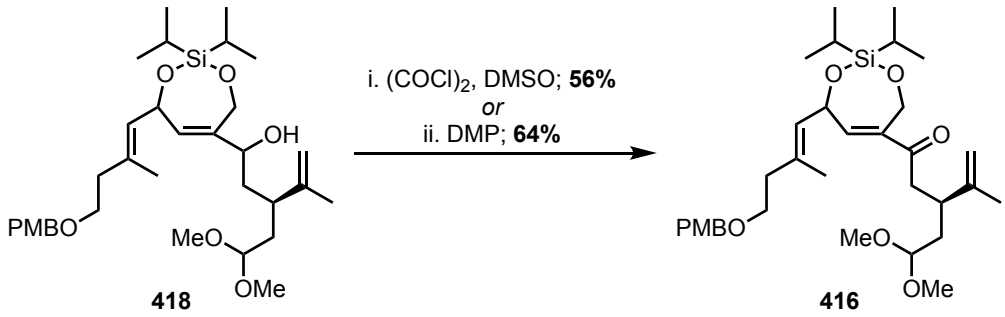
Entry	HG-II Loading	PhMe conc.	Temp.	Time	Combined Yield	Ratio (418:419)
1	5 mol%	0.005 M	80 °C	24 h	27%	19:8
2	5 mol%	0.005 M	60 °C	48 h	51%	46:5
3	10 mol%	0.005 M	60 °C	24 h	51%	46:5
4	**10 mol%**	**0.005 M**	**60 °C**	**48 h**	**55%**	**1:trace**
5	5+5 mol%	0.005 M	60 °C	54 h	41%	39:2
6	5 mol%	0.01 M	60 °C	45 h	57%	53:4
7	5 mol%	0.02 M	60 °C	48 h	42%	1:trace
8	5 mol%[a]	0.01 M	60 °C	42 h	52%	1:trace
9	10 mol%	0.01 M	60 °C	42 h	43%	1:trace
10	5 mol%	0.01 M[b]	60 °C	48 h	–	–

Table 3.2 Optimisation of RCM of alcohol **417**. [a]Zahn 1B [b]1,2-DCE

Pleasingly, reducing the temperature to 60 °C and extending the reaction time led to an increase in combined yield to 51% and a reduction in the proportion of cyclopentene **419** present (Table 3.2, Entries 1 and 2). The same result was seen within 24 h when increasing the catalyst loading to 10 mol% (Entry 3). The best set of conditions was found when both catalyst loading and reaction time were increased with silaketal **418** then isolated as essentially a single compound in 55% yield (Entry 4). Portionwise addition of the catalyst was not found to be beneficial (Entry 5). Doubling the reaction concentration allowed for a reduced catalyst

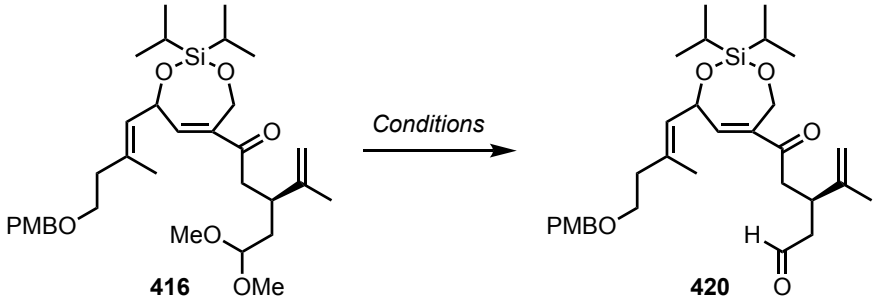
loading and provided a combined yield of 57% (Entry 6) but further increases in reaction concentration were not worthwhile (Entry 7). Substituting Zahn-1B for HG-II had minimal impact (Entry 8) and combining increased concentration and catalyst loading had a detrimental effect with silaketal **418** being isolated in 43% yield (Entry 9). As previously observed, performing the reaction in 1,2-DCE led to decomposition of the starting material (Entry 10).

Initial attempts at oxidising silaketal **418** using Parikh–Doering conditions were unsuccessful whilst PCC led to decomposition of **418**. However, both Swern (56%) and Dess–Martin Periodinane (64%) conditions provided ketone **416** in good yield (Scheme 3.13).



Scheme 3.13 Oxidation of silaketal **418**. Reagents and conditions: i) 20 eq. $(COCl)_2$, 40 eq. DMSO, 67 eq. Et_3N, CH_2Cl_2, –78 °C to rt, 1 h, 56%; ii) 2.5 eq. DMP, 10 eq. $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 18 h, 64%

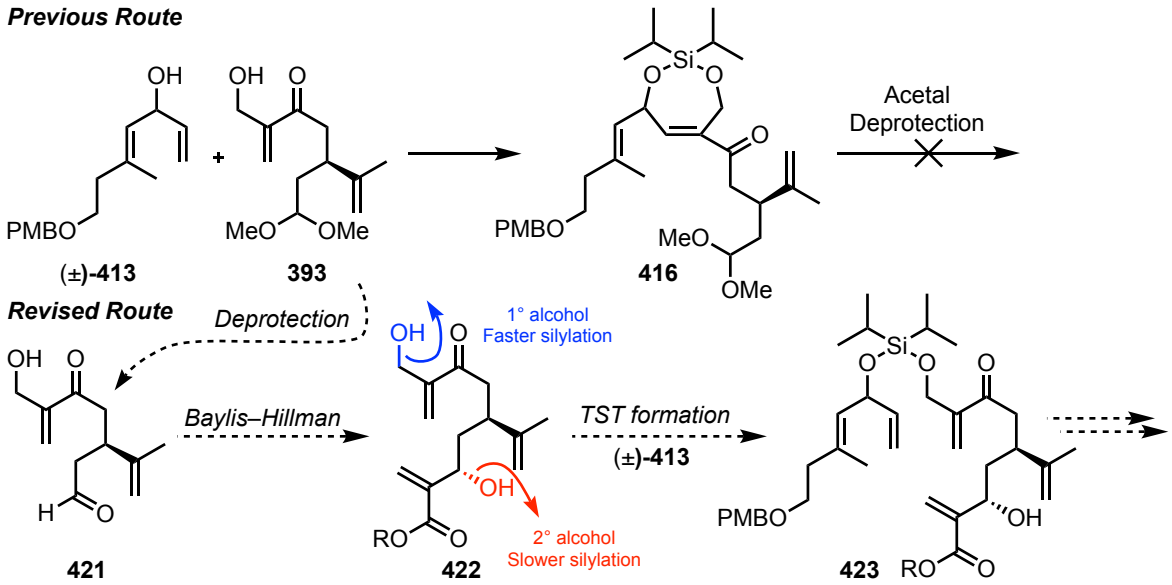
Dimethyl acetal deprotection of **416** in the presence of the TST was expected to the challenging given the lability of both groups to acidic conditions. Surprisingly, treatment with PPTS led to no reaction, with both groups remaining intact (Table 3.3, Entry 1). Substituting PPTS for $Sc(OTf)_2$ or other Lewis acids led to decomposition of acetal **416** (Entries 2–4), as did $PdCl_2(MeCN)_2$ in acetone, conditions first reported by Lipschutz and co-workers (Entry 5).[156] The acetal moiety was also untouched after reaction with silica gel in predominantly aqueous solvent and acetal **416** was recovered (98%, Entry 6). The lack of success with acidic conditions prompted a search for alternatives. Fujioka and co-workers have demonstrated the deprotection of dimethyl acetals using TESOTf and 2,4,6-collidine. They reported that trityl and TBS groups, cyclic acetals and thioacetals all tolerated the reaction conditions.[157] Unfortunately, no reaction was observed with acetal **416** under these conditions (Entry 7).



Entry	Conditions	Result
1	1 eq. PPTS, acetone, rt, 24 h	N/R
2	1 eq. $Sc(OTf)_2$, acetone, rt, 24 h	Decomposition
3[a]	$FeCl_3 \cdot 6H_2O$, CH_2Cl_2, rt, 15 min	Decomposition
4	15 mol% NaI, 1.5 eq. $CeCl_3 \cdot 7H_2O$, MeCN, rt, 18 h	Decomposition
5	30 mol% $PdCl_2(MeCN)_2$, Acetone, rt, 2.5 h	Decomposition
6[a]	silica gel, H_2O/CH_2Cl_2 (9;1), rt, 20 h	98% **416**
7	2 eq. TESOTf, 3 eq. collidine, CH_2Cl_2, 0 °C, 1 h	N/R

Table 3.3 Attempted deprotection of acetal **416**. [a]Reaction performed by Simon Werrel. N/R = no reaction

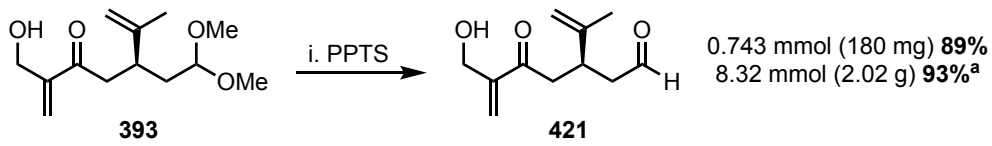
The failure of acetal deprotection prompted a reassessment of our synthetic strategy. Despite reservations over performing the asymmetric Baylis–Hillman prior to TST formation there was the possibility that the fast reaction times observed for TST formation (<5 min) would allow kinetic discrimination between the primary and secondary alcohols of unprotected Baylis–Hillman adducts **422**. This would facilitate the direct synthesis of TST **423** and obviate the need to perform the acetal deprotection in the presence of the TST (Scheme 3.14).



Scheme 3.14 Revised synthetic plan: Baylis–Hillman prior to TST formation

3.5 Synthesis of Asymmetric Baylis–Hillman Adduct 427

The synthesis of a Baylis–Hillman adduct of type **423** began with deprotection of the dimethyl acetal group present in alcohol **393**. Exposure to PPTS in acetone:H_2O (1:1) led to consumption of **393** with aldehyde **421** being isolated in 89% yield following aqueous work up (Scheme 3.15).



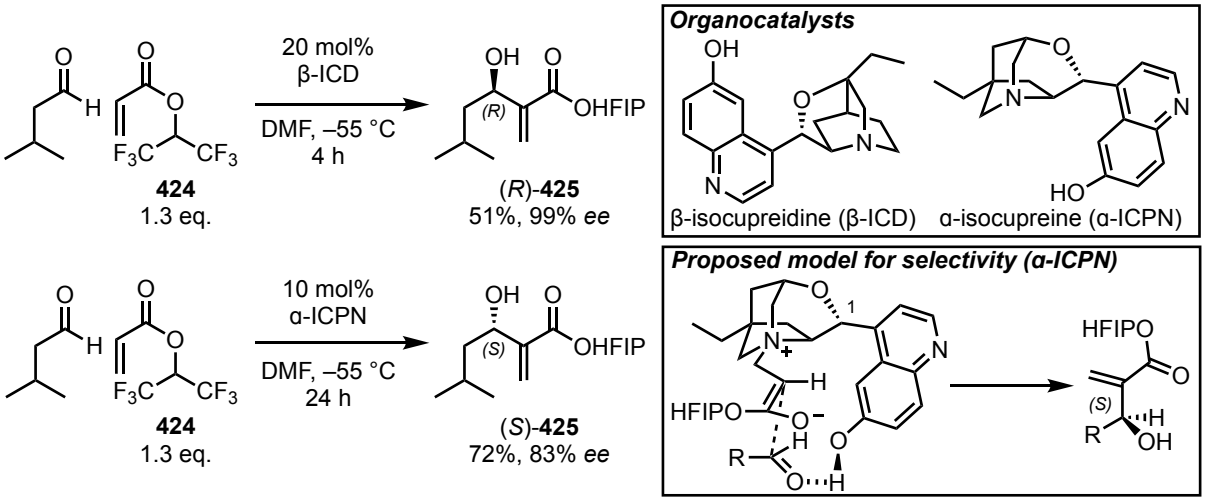
393 **421**

Scheme 3.15 Synthesis of aldehyde **421**. Reagents and conditions: 10 mol% PPTS, acetone:H_2O (1:1), 50 °C, 18 h, 89%. [a]additional hydration or polymerisation peaks present in ^{1}H NMR spectrum

The reaction was scalable although additional peaks were often present in the ^{1}H NMR spectrum, for example in the 9–10 ppm region, indicating that the material could become contaminated. It is possible that aldehyde hydration or polymerisation occurred during the period of time required to remove larger quantities of solvent using a rotary evaporator. Despite this, no discernible effect on later Baylis–Hillman reactivity could be observed; both clean and apparently contaminated samples behaved similarly.

A literature search revealed that asymmetric Baylis–Hillman reactions between acrylates and aliphatic aldehydes are extremely rare. Only a single class of quinine derived organocatalysts, reported by Hatakeyama and co-workers, have demonstrated the ability to promote this reaction (Scheme 3.16). The naturally occurring β-isocupreidine (β-ICD) was shown to catalyse formation of the Baylis–Hillman adduct (*R*)-**425**[158] and enantiocomplementary α-isocupreine (α-ICPN, accessible in one pot from quinine) the (*S*)-enantiomer.[159] In the proposed stereochemical model for α-ICPN, the aldehyde is held below the enolate by a hydrogen bonding interaction, with the facial (and therefore enantio) selectivity dictated by the spatial disposition of the quinoline moiety and bicyclic core, and the *C*-1 stereochemistry. To overcome the conventional low reactivity of the acrylate and aliphatic aldehyde combination, electron with-

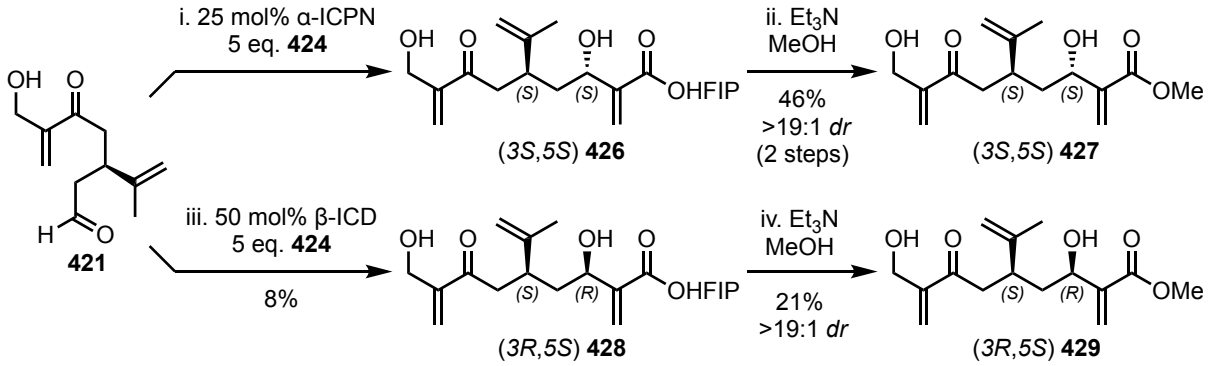
drawing hexafluoroisopropyl acrylate (**424**) was used. This ester is thought to encourage catalyst addition into the acrylate, thereby increasing the effective concentration of the enolate formed. Due to the lability of hexafluoroisopropyl esters, transesterification to the more stable methyl esters is often performed. Additionally, this reaction has already been successfully applied in natural product synthesis.[160]



Scheme 3.16 Hatakeyama asymmetric Baylis–Hillman methodology

As the Baylis–Hillman reaction would set the (*S*) stereochemistry of the *C*-13 alcohol in (+)-lophotoxin (**1**), reaction with the α-ICPN catalyst was required. Despite the long reaction time (2 days), aldehyde **421** could be transformed into (3*S*,5*S*)-HFIP ester **426** in *ca.* 58% yield. The diastereoselectivity of the reaction could not be accurately determined due to the presence of multiple side products in the crude reaction mixture and complete purification of **426** was additionally hampered by the co-elution of some of these byproducts. Fortunately, after transesterification of the partially purified material with MeOH, purification by FCC was possible and (3*S*,5*S*)-methyl ester **427** was isolated in *ca.* 78% yield (46% over two steps) as a single diastereomer by ^{1}H and ^{13}C NMR. Small quantities of a byproduct, assumed to be the (3*R*, 5*S*)-diastereomer **428**, were also isolated. For comparison, β-ICD was used to synthesise the diastereomeric (3*R*,5*S*)-methyl ester **429** directly, which was isolated as a single diastereomer in 2% yield over two steps after transesterification. The low yield was consistent on repetition

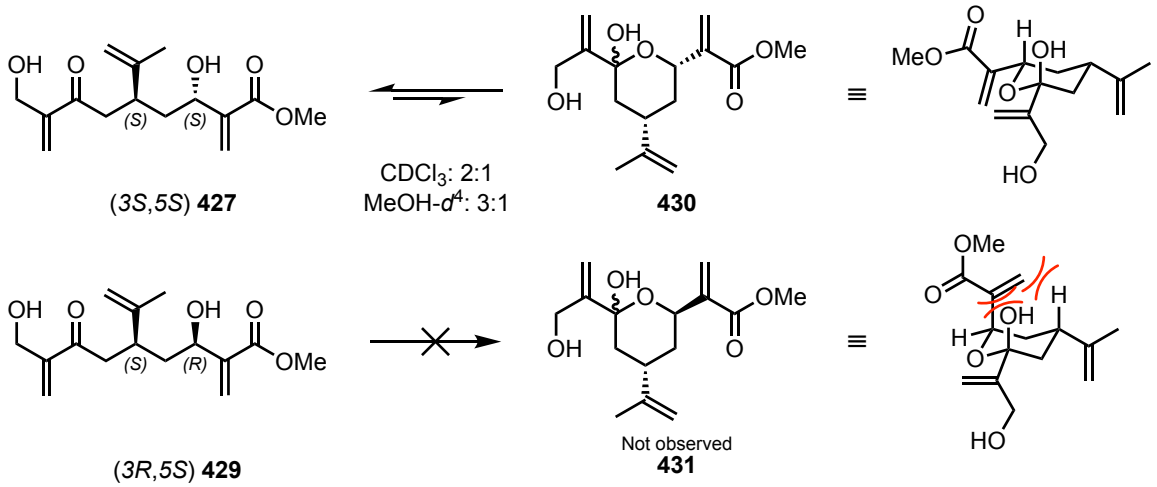
and is unexplained. Comparison of the ^{1}H and ^{13}C NMR spectra of both (3*S*,5*S*)-methyl ester **427** and (3*R*,5*S*)-methyl ester **429** revealed the two compounds to be non-identical, as expected. Additionally, the spectral data for (3*R*,5*S*)-methyl ester **429** matched those of the byproduct isolated from the reaction with α-ICPN (Scheme 3.17).



Scheme 3.17 Baylis–Hillman with both β-ICD and α-ICPN. Reagents and conditions: i) 5 eq. **424**, 25 mol% α-ICPN, DMF (0.1 M), –55 °C, 2 days; ii) 5 eq. Et_3N, MeOH, 25 °C, 12 h, 46% (2 steps); iii) 5 eq. **424**, 50 mol% β-ICD, DMF (0.33 M), –55 °C, 2 days, 8%; iv) 5 eq. Et_3N, MeOH, rt, 75 min, 21%

The absolute stereochemistry of these products was assigned on the basis of that reported for similar compounds synthesised with the respective catalysts in the literature (see Scheme 3.s) and the immediately following observations (see Scheme 3.18). Despite extensive efforts, attempted verification using Mosher's esters or through derivatisation was not successful.

NMR analysis of (*3S*,*5S*)-ester **427** revealed that it existed in both linear **427** and hemiacetal **430** forms in solution, with the ratio dependent on the solvent employed. Interconversion between the two forms was confirmed by EXSY NMR. In contrast, the hemiacetal (**431**) form of (*3R*,*5S*)-ester **429** could not be detected by ^{1}H NMR; its formation is likely disfavoured by multiple 1,3-diaxial interactions with the now necessary axial substituent. The chair conformation of hemiacetal **430** provides further evidence for the relative (and by extension absolute) stereochemistry of both methyl esters **427** and **429** and is also consistent with the determined stereochemical outcome of the reported asymmetric Baylis–Hillman reactions (Scheme 3.18).



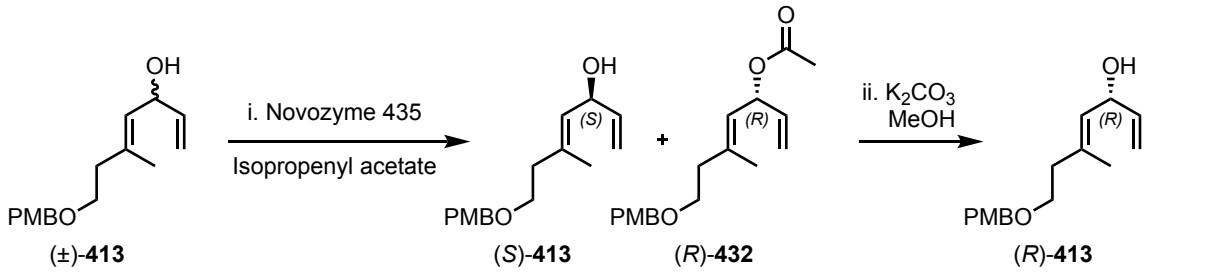
Scheme 3.18 Partial cyclisation of ester **427**

With a sequence to (3*R*,5*S*)-ester **427** established, an asymmetric synthesis of (*R*)-alcohol **413** was now required to enable a fully asymmetric synthesis of (+)-lophotoxin (**1**).

3.6 Synthesis of (*R*)-Alcohol 413

Although the (*R*) enantiomer of alcohol **413** was likely required for the planned late-stage directed allylic epoxidation (see Chapter 3.1), access to both enantiomers was desirable at this stage in case the substrate stereocontrol of the macrocyclic system was unexpectedly different. It was therefore decided to resolve (±)-alcohol **413** into its two enantiomers by enzymatic resolution.

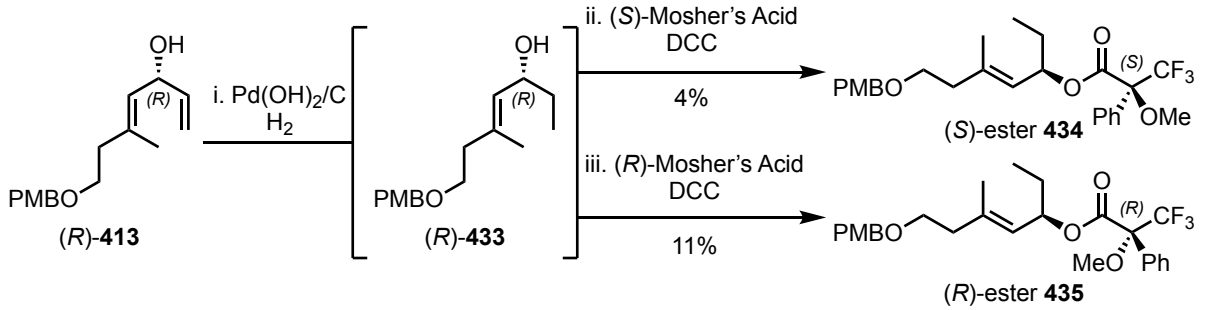
Following the procedure reported by Bäckvall and co-workers, (±)-alcohol **413** was resolved using Novozyme 435 (*Candida antarctica* lipase B, CALB) and freshly distilled isopropenyl acetate to afford both (*S*)-alcohol **413** and (*R*)-acetate **432** in 44% yield.[161] (*R*)-Acetate **432** was found to be unstable, with E1 elimination of acetate the likely cause, and the acetate group was therefore cleaved immediately under basic conditions to provide (*R*)-alcohol **413** in quantitative yield. The reaction scale could be increased to 11.4 mmol (3.00 g) of (±)-alcohol **413** without compromising the yield. HPLC analysis in comparison to a racemic standard indicated that (*S*)-alcohol **413** had been formed in 89% *ee* and the required (*R*)-alcohol **413** in 95% *ee* (Scheme 3.19).



Scheme 3.19 Enzymatic Resolution of (±)-alcohol **413**. Reagents and conditions: Novozyme 435 (30 mg/mmol **413**), 1.5 eq. isopropenyl acetate, PhMe, rt, 24 h, 48% (*S*), 48% (*R*); ii) 10 eq. K_2CO_3, MeOH, rt, 18 h, 92%

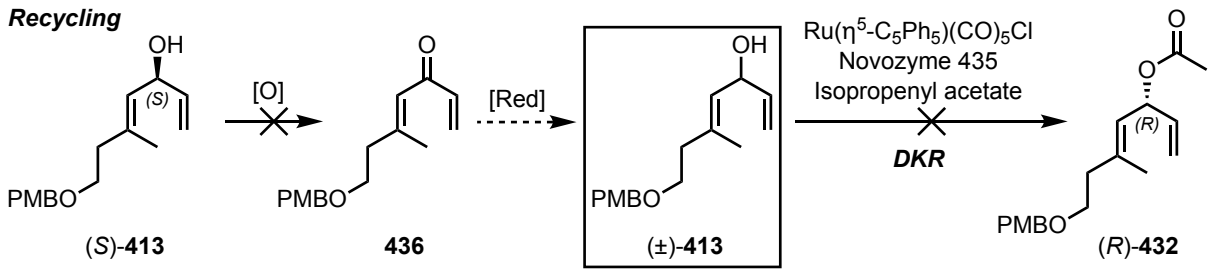
Attempted formation of Mosher's esters from (*R*)-alcohol **413** was unsuccessful, in line with the observed instability of (*R*)-acetate **432**. Instead, hydrogenation of the primary olefin using Pearlman's catalyst ($Pd(OH)_2/C$) and direct acylation of crude (*R*)-alcohol **433** provided (*S*)-

ester **434** and (*R*)-ester **435**. Low isolated yields were still observed but were high enough to rule out isolation of the minor enantiomer and sufficient material could be isolated for the required analysis (Scheme 3.20). Using the protocol reported by Hoye and co-workers, ^{1}H NMR analysis confirmed the expected (*R*) stereochemistry (for detailed analysis see Chapter 5.5).[162]



Scheme 3.20 Hydrogenation and Mosher's ester analysis. Reagents and conditions: i) 10 wt% $Pd(OH)_2/C$, EtOAc, rt, H_2; ii) 3 eq. (*S*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 3 eq. DCC, 3 eq. DMAP, CH_2Cl_2, rt, 15 h, 4%; iii) 3 eq. (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 3 eq. DCC, 3 eq. DMAP, CH_2Cl_2, rt, 15 h, 11%

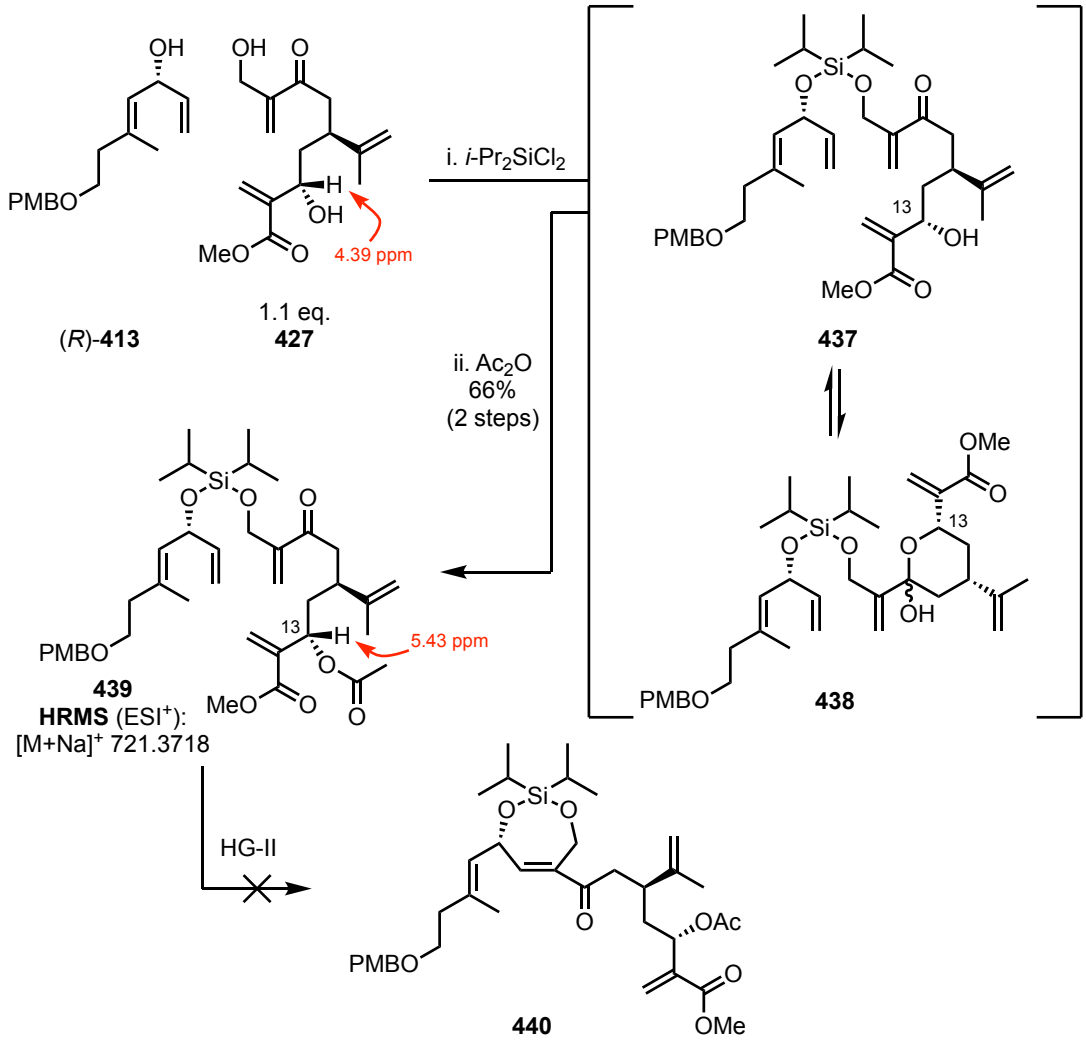
Bäckvall and co-workers have also reported the dynamic kinetic resolution (DKR) of allylic alcohols by continuous racemisation of the allylic alcohol (oxidation/reduction *via* the ketone) under ruthenium catalysis and selective enzymatic acylation of one enantiomer.[161] However, subjection of (±)-alcohol **413** to these conditions led only to decomposition. Attempted recycling of (*S*)-alcohol **413** *via* stepwise oxidation and reduction was also unsuccessful with alcohol oxidation using DMP producing a complex mixture of products. These results suggest that the intermediate ketone **436** is unstable and an alternative strategy would be needed to access either enantiomer in >50% yield (Scheme 3.21).



Scheme 3.21 Attempted recycling and DKR of (*S*)-alcohol **413**

3.7 Asymmetric Synthesis of Silaketal 443

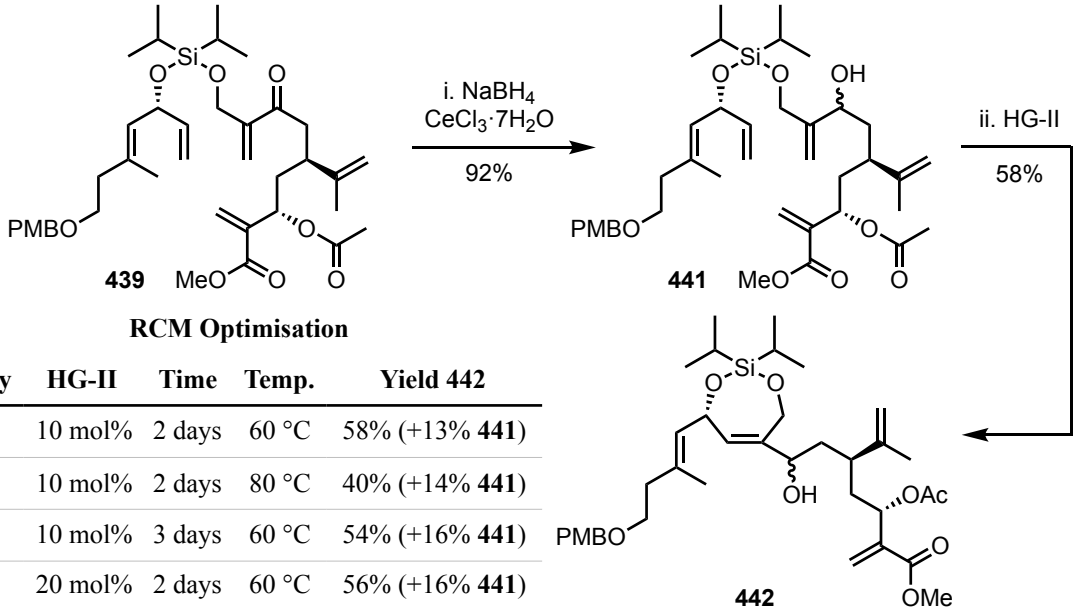
With both (*R*)-alcohol **413** and (*3S,5S*)-ester **427** in hand, the TST-RCM sequence could be performed. Subjection of **413** and **427** to the TST forming sequence provided what was assumed to be TST **437**. However, its purification was hampered by equilibration between its linear (**437**) and hemiacetal (**438**) forms and partial co-elution of these with other, silicon based, byproducts. As a result, it was decided to install the *C*-13 acetyl group present in (+)-lophotoxin (**1**) at this stage to prevent equilibration. Pleasingly, acetylation of the crude mixture of TST **437** and hemiacetal **438** resulted in smooth formation of ester **439** in 66% yield over two steps (from 1.35 mmol, 355 mg, (*R*)-alcohol **413**) (Scheme 3.22).



Scheme 3.22 Synthesis of TST **439**. Reagents and conditions: i) 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, CH_2Cl_2, 0 °C, 90 min *then* 1.1 eq **427**, 0 °C, 20 min; ii) 5 eq. Ac_2O, 20 eq. pyridine, 10 mol% DMAP, CH_2Cl_2, 0 °C, 2 h, 66% (2 steps)

As might be expected from the lability of hexafluoroisopropyl esters, attempted incorporation of (*3S*,*5S*)-HFIP ester **426** into the TST sequence was unsuccessful with multiple products observed after acylation. Direct RCM of TST **439** was also briefly investigated. Although ^{1}H NMR analysis of the crude reaction mixture suggested formation of silaketal **440**, TLC analysis did not corroborate its presence. On FCC (100% EtOAc), a polar compound was collected whose ^{1}H NMR spectrum was consistent with TST deprotection. As such, the Luche reduction/RCM approach was pursued.

Reduction of TST **439** proceeded in 92% yield (3:2 *dr*, undetermined stereochemistry) and treatment of the resulting alcohol **441** with 10 mol% HG-II afforded silaketal **442** in 58% yield along with 13% recovered **441** (Scheme 3.23, Entry 1). Interestingly, no RCM with the isobutylene unit was observed, in contrast to earlier results (see Chapter 3.4). It seems reasonable to suggest that the added steric bulk of the nearby acetylated alcohol prevented ring-closing to the isobutylene. Increasing the reaction temperature reduced the isolated yield to 40% although RCM with the isobutylene unit was still not observed (Entry 2). Conversion could not be further improved by increasing the reaction time or catalyst loading (Entries 3 and 4).

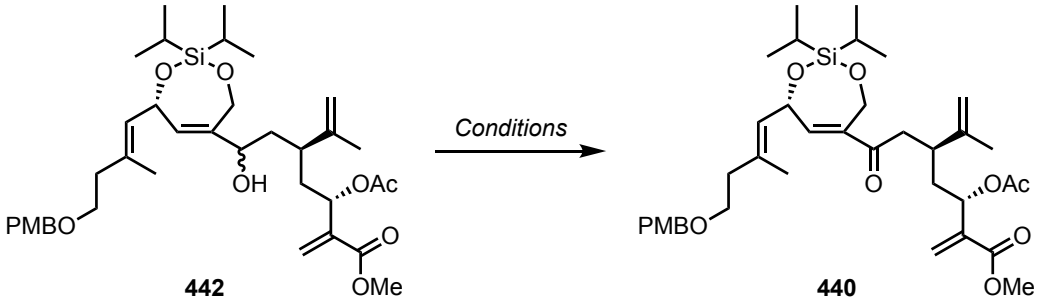


RCM Optimisation

Entry	HG-II	Time	Temp.	Yield 442
1	10 mol%	2 days	60 °C	58% (+13% **441**)
2	10 mol%	2 days	80 °C	40% (+14% **441**)
3	10 mol%	3 days	60 °C	54% (+16% **441**)
4	20 mol%	2 days	60 °C	56% (+16% **441**)

Scheme 3.23 Luche reduction and RCM of TST **439**. Reagents and conditions: i) 1.1 eq. $CeCl_3 \cdot 7H_2O$, 1.2 eq. $NaBH_4$, MeOH, 0 °C, 2 h, 92%; ii) General Conditions: PhMe (0.005 M)

Oxidation of silaketal **442** was now required to re-establish the correct oxidation state. As before, no reaction was observed using Parikh–Doering oxidation conditions, but $NaHCO_3$ buffered Dess–Martin Periodinane effected the desired oxidation in 56% yield (Table 3.4, Entry 1). Use of a stronger base led to longer reaction times and a reduction in yield to 34% (Entry 2) but performing the reaction in the absence of base led to formation of ketone **440** in 72% yield after just 2.5 h (Entry 3). Increasing the reaction concentration was found to reduce the isolated yield to 63% (Entry 4). Meyer and Schreiber showed that Dess–Martin Periodinane is more reactive in the presence of water.[163] It is possible that the desiccating properties of sodium bicarbonate and, in particular, sodium carbonate had slowed the oxidation, allowing decomposition under the reaction conditions. Reaction without base led to a faster reaction time and the product could then be isolated before any significant product degradation occurred.



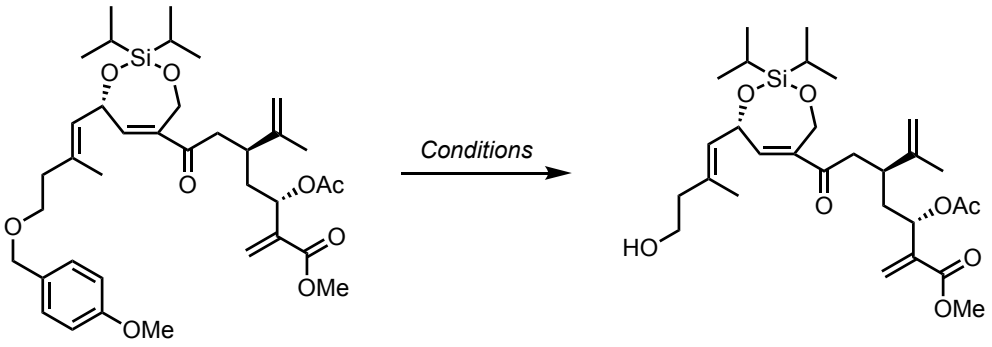
442 **440**

Entry	Conditions	Yield 440
1	1.5 eq. DMP, 10 eq. $NaHCO_3$, CH_2Cl_2 (0.05 M), 0 °C, 18 h	56%
2	1.5 eq. DMP, 10 eq. Na_2CO_3, CH_2Cl_2 (0.05 M), 0 °C, 24 h	34%
3	2 eq. DMP, CH_2Cl_2 (0.05 M), 0 °C, 2.5 h	72%
4	2 eq. DMP, CH_2Cl_2 (0.1 M), 0 °C, 2 h	63%

Table 3.4 Oxidation of silaketal **442**

The removal of the PMB protecting group was now required. Oxidative cleavage is often used and it was hoped that these conditions would be compatible with the framework of silaketal **440**. Due to the acidic nature of DDQ in solution, a buffered reaction solvent was required and alcohol **443** was then isolated in 30% yield (Table 3.5, Entries 1 and 2). A number of unidentified byproducts were also formed but the use of fewer equivalents of DDQ was

not possible; very slow conversion was observed and a further seven equivalents were required to effect full consumption of **440** (Entry 3). Increasing the quantity of DDQ and careful monitoring of the reaction was more successful with alcohol **443** isolated in 58% yield after 50 min (Entry 4).

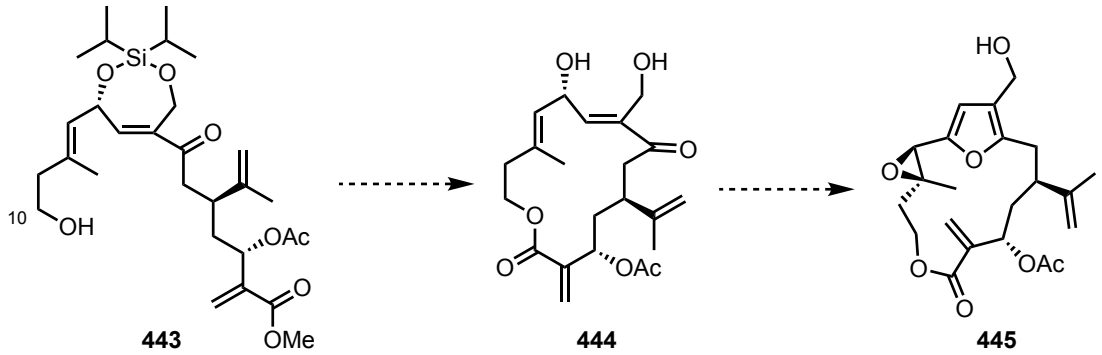


440 **443**

Entry	DDQ	Solvent	Temp.	Time	Yield 443
1	5 eq.	CH_2Cl_2 0.005 M	0 °C to rt	18 h	–
2	5 eq.	CH_2Cl_2:pH 7 buffer (6:1) 0.01 M	0 °C	2 h	30%
3	2+5+2 eq.	CH_2Cl_2:pH 7 buffer (6:1) 0.01 M	0 °C	3 h	55%
4	10 eq.	CH_2Cl_2:pH 7 buffer (6:1) 0.01 M	0 °C	50 min	58%

Table 3.5 Deprotection of ether **440**

The next steps towards (+)-lophotoxin (**1**) would involve forging the *C*-10 stereocentre by asymmetric addition of a vinyl group. However, alcohol **443** also represented an advanced intermediate from which the proposed epoxidation/isomerisation sequence could be tested. It was decided to investigate this prior to further scaffold manipulation (Scheme 3.24).

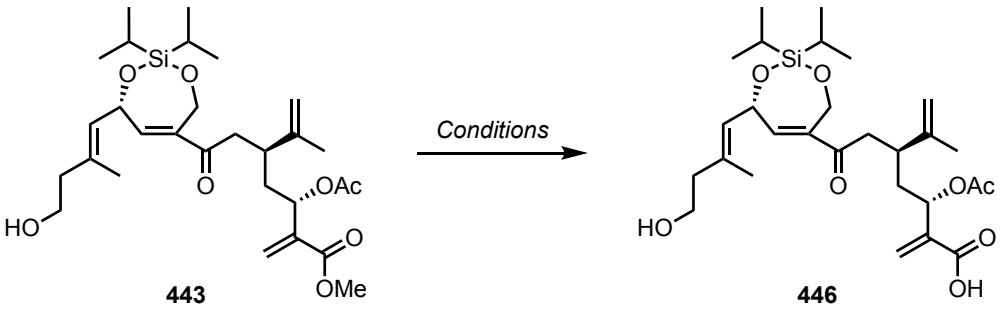


443 **444** **445**

Scheme 3.24 Planned synthesis of model macrocycle **445**

3.8 Attempted Cleavage of Methyl Ester 443

To enable macrolactonisation, conversion of the ester **443** to *seco*-acid **446** was required. Unfortunately, subjection of ester **443** to K_2CO_3 in wet MeOH did not cleave the methyl ester and resulted in other unidentifiable side reactions (Table 3.6, Entry 1). The methyl ester was also untouched by NaOH although in this case partial TST deprotection may have occurred; a peak consistent with the hydrolysis of a single Si–O bond was observed by mass spectrometry whilst signals corresponding to protons adjacent to the TST were shifted in the ^{1}H NMR spectrum of the crude reaction mixture (Entry 2). Additionally, LiOH in THF/H_2O led to complete decomposition of ester **443** (Entry 3) and no reaction was observed with LiI in refluxing EtOAc (Entry 4).



443 **446**

Entry	Conditions	Result
1	K_2CO_3, MeOH, 0 °C, 2 h	Ester untouched Unknown byproduct
2	NaOH, THF:H_2O (1:1), 0 °C, 4 h	Ester untouched Partial TST removal
3	LiOH, THF:H_2O (1:1), 0 °C, 4 h	Decomposition
4	LiI, EtOAc, reflux, 15 h	No reaction
5	$Ba(OH)_2 \cdot 8H_2O$, THF:CH_2Cl_2:pH 7 buffer, rt, 18 h	Decomposition
6	KOTMS, THF, rt, 12 h	Decomposition
7	Me_3SnOH, 1,2-DCE, 80 °C, 24 h	Decomposition
8	Me_3SnOH, 1,2-DCE, 80 °C, 24 h[a]	Ester untouched Partial TST removal

Table 3.6 Attempted deprotection of methyl ester **443**. [a]Et_3N added during work up

Paterson and co-workers have reported the use of $Ba(OH)_2 \cdot 8H_2O$ for the cleavage of methyl esters in the context of complex molecule synthesis but with ester **443** only decomposition

occurred (Entry 5).[164] Similarly, KOTMS resulted only in degradation of ester **443** (Entry 6).[165] Nicolaou and co-workers have reported the selective cleavage of methyl esters with Me_3SnOH.[166] Exquisite selectivity was observed in a range of highly complex natural product examples and when ester **443** was reacted with Me_3SnOH under the reported conditions conversion to a single species was evident by TLC. Unfortunately, this compound decomposed on work up (Entry 7). Suspecting that the carboxylic acid, if present, might facilitate decomposition of the TST, Et_3N was added to the work up to form the triethylammonium salt. The product now survived work up but, as for NaOH hydrolysis, the methyl ester had remained intact with suspected partial TST cleavage observed by ^1H NMR.

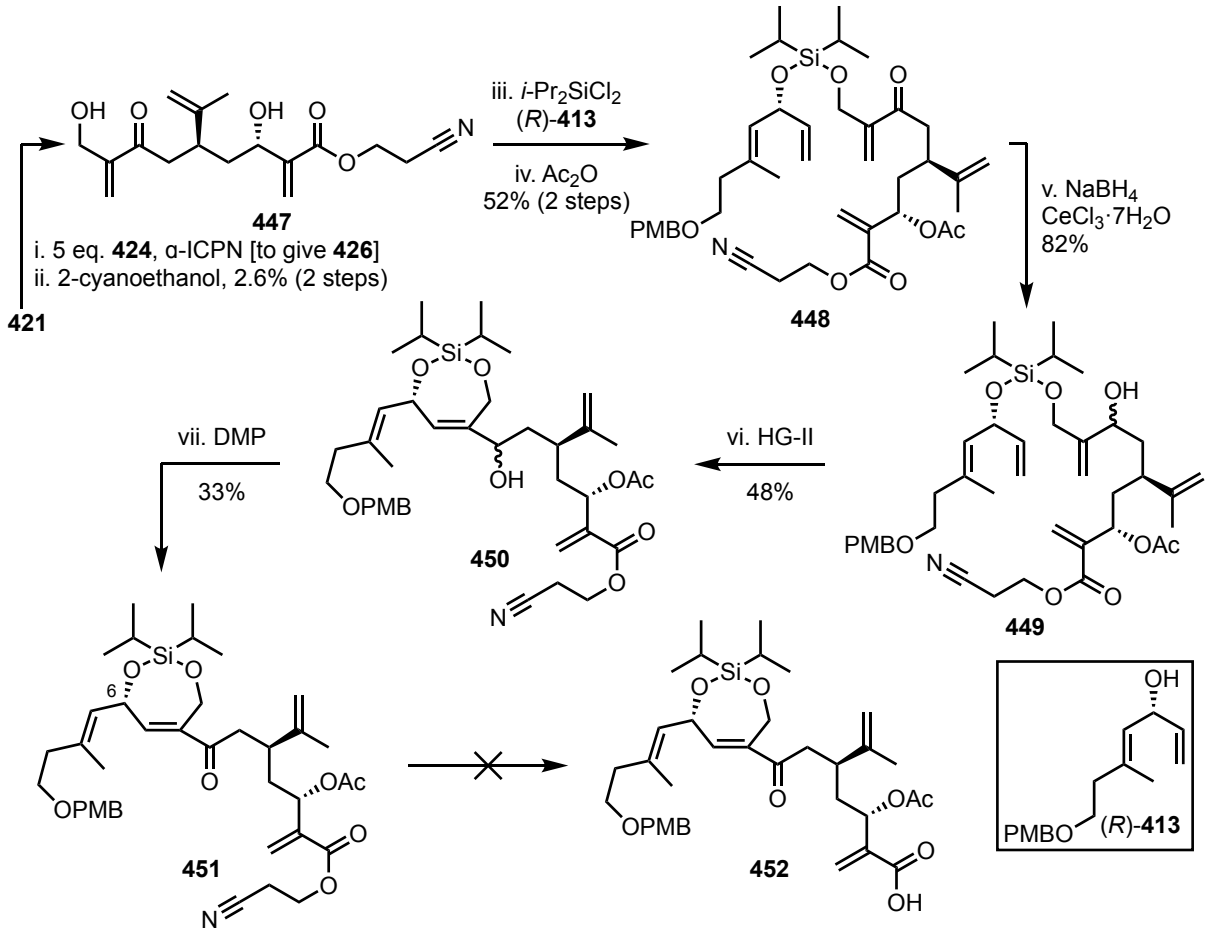
The failure to realise any methyl ester cleavage meant that the identity of the carboxylic acid protecting group would have to be changed.

3.9 Alternative Protecting Groups for the *C*-20 Carboxylic Acid

In selecting an alternative carboxylic acid protecting group, the reaction conditions of the preceding sequence and any steps involved in forging the *C*-10 stereocentre had to be considered. Groups susceptible to degradation by Luche reduction, olefin metathesis, oxidation and organometallic reagents were therefore unlikely to be suitable. Activated esters (HFIP, *p*-nitrophenol etc.) and allyl esters were all discarded based on these assumptions.

In searching for a suitable protecting group, 2-cyanoethyl esters were considered. These groups are frequently used in oligonucleotide synthesis as phosphotriester protecting groups, and were developed by the groups of Letsinger[167] and Reese.[168] Removal is typically conducted under basic conditions with DBU or piperidine at room temperature. These conditions appeared suitable for the current system and the incorporation of the 2-cyanoethyl ester moiety was attempted.

Transesterification of the Baylis–Hillman product (3*S*,5*S*)-HFIP ester **426** with 2-cyanoethanol was complicated by the high boiling point of 2-cyanoethanol (228 °C) and the resulting need to remove excess alcohol by FCC. Multiple attempts at purification with significant loss of material eventually provided 2-cyanoethyl ester **447** in sufficient purity (2.6% yield over 2 steps from aldehyde **421**). TST formation and acylation provided TST **448** in 52% yield over two steps and subsequent Luche reduction provided alcohol **449** in 82% yield. Subjection of **449** to RCM with HG-II afforded silaketal **450** in 48% yield and oxidation of the alcohol then gave ketone **451** in 33% yield. The low yield is unexplained and due to the low quantities of material at this point the reaction could not be repeated. With ester **451** in hand the required deprotection was attempted (Scheme 3.25).



Scheme 3.25 Synthesis of silaketal **451** and attempted ester deprotection. Reagents and conditions: i) 5 eq. **424**, 25 mol% α-ICPN, DMF (0.1 M), –55 °C, 2 days; ii) 5 eq. Et_3N, 2-cyanoethanol (0.4 M), rt, 18 h, 2.6% (2 steps); iii) 1.05 eq. *i*-Pr_2SiCl_2, 2.5 eq. imidazole, CH_2Cl_2, 0 °C, 90 min *then* 1.1 eq (*R*)-**413**, 20 min; iv) 5 eq. Ac_2O, 20 eq. pyridine, 10 mol% DMAP, CH_2Cl_2, rt, 2 h, 52% (2 steps); v) 1.1 eq. $CeCl_3 \cdot 7H_2O$, 1.2 eq. $NaBH_4$, MeOH, 0 °C, 2 h, 82%; vi) 10 mol% HG-II, PhMe, 60 °C, 24 h, Ar flow, 48%; vii) 2 eq. DMP, CH_2Cl_2, rt, 2 h, 33%

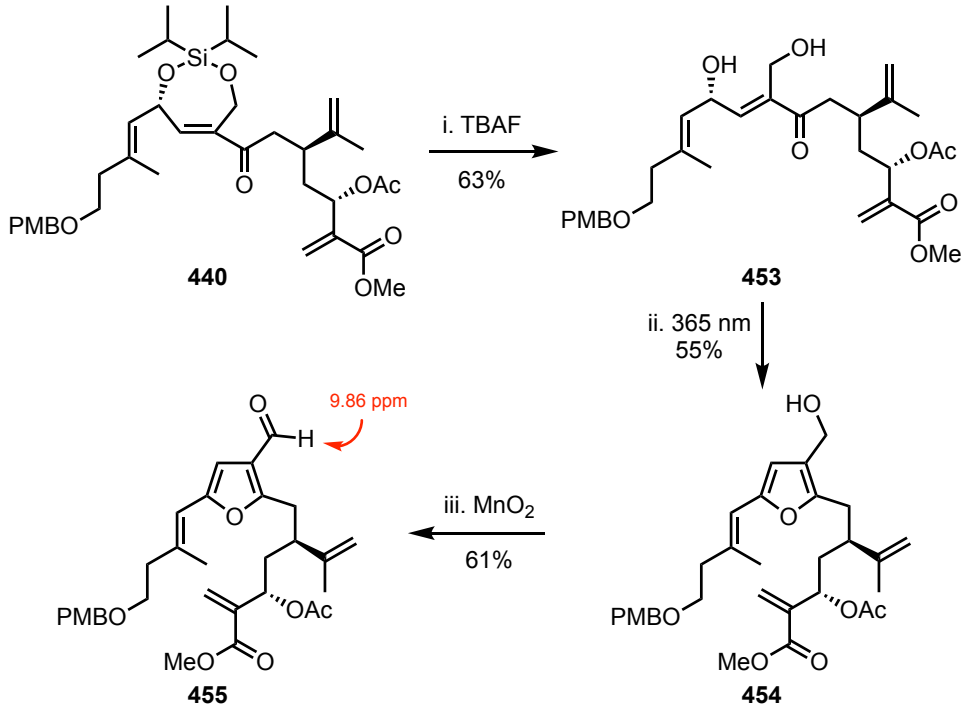
On treating ester **451** with DBU, conversion to predominantly one compound was observed by TLC. However, decomposition was observed on concentration of the reaction mixture. After aqueous work up, ^{1}H NMR revealed formation of a species very similar to the starting material **451**. Unfortunately, the 2-cyanoethyl ester moiety appeared to remain intact and there was evidence of other side reactions. However, conducting the reaction in CD_2Cl_2 allowed for direct observation of acrylonitrile formation by ^{1}H NMR (ca. 25% after 1 h), indicating that ester deprotection under these conditions was occurring. Unfortunately, other side reactions were again evident and apparently occurred at a much faster rate than ester deprotection.

Fearing that deprotonation of the *C*-6 proton might have led to some of the observed side reactivity, the reaction was repeated with Cy_2NMe, a weaker but bulkier base. However, no reaction was observed, even when heated to 100 °C. Use of quinuclidine resulted in decomposition of ester **451**. In light of these difficulties, the identification of suitable deprotection conditions is ongoing.

3.10 Synthesis of Furan 455

Concurrently to the above investigations into ester cleavage, it was decided to confirm that photochemical aromatisation to the furan core of (+)-lophotoxin (**1**) would be possible, particularly in the presence of the acrylate moiety and other olefin functionality.

To this end, silaketal **440** was deprotected with excess TBAF to afford diol **453** in 63% yield. Irradiation at 365 nm proceeded smoothly with near complete conversion evident by ^{1}H NMR spectroscopy. Furan **454** was isolated in 55% yield with losses attributed to FCC on small scale (12 mg). Oxidation with MnO_2 proceeded cleanly, but slowly, to provide aldehyde **455** in 61% yield (Scheme 3.26).

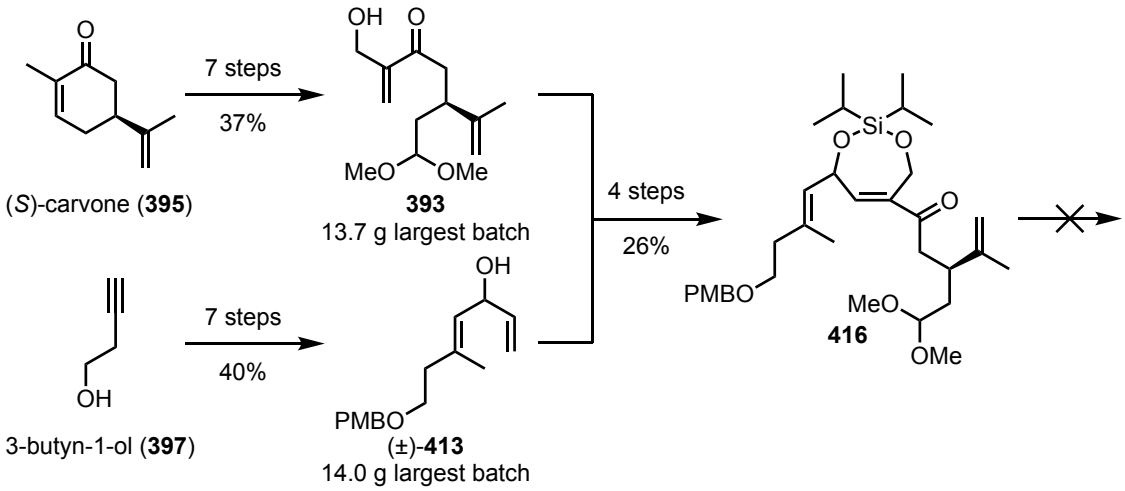


Scheme 3.26 Synthesis of furan **455**. Reagents and conditions: i) 3 eq. TBAF (1 M in THF), THF, 0 °C, 2 h, 63%; ii) 365 nm, EtOAc, 0 °C, 21 h, 55%; iii) 4 × 20 eq. MnO_2, CH_2Cl_2, 0 °C to rt, 54 h, 61%

The synthesis of aldehyde **455** confirms the compatibility of the molecular framework to the developed photochemical aromatisation. It is the culmination of 27 steps (18 steps longest linear sequence) and was achieved in 0.8% overall yield from (*S*)-carvone (**395**).

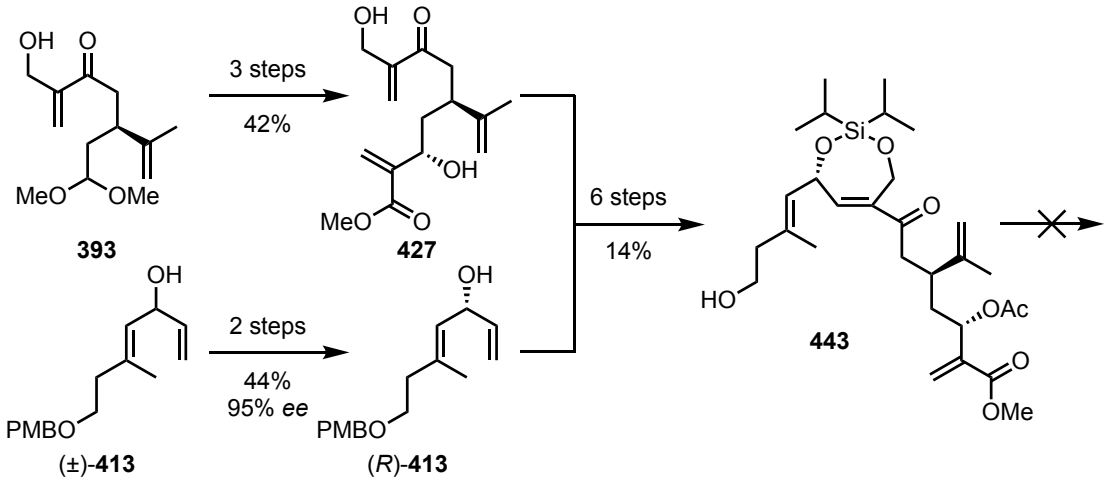
3.11 Conclusions and Future Work

High yielding routes to alcohols **393** and (±)-**413** have been developed and provided *ca.* 14 g of each compound. Incorporation into the TST-RCM sequence afforded advanced intermediate silaketal **416** in 9% yield over 11 steps from (*S*)-carvone (**395**). Unfortunately, dimethyl acetal deprotection did not prove possible (Scheme 3.27).



Scheme 3.27 Synthesis of silaketal **416**

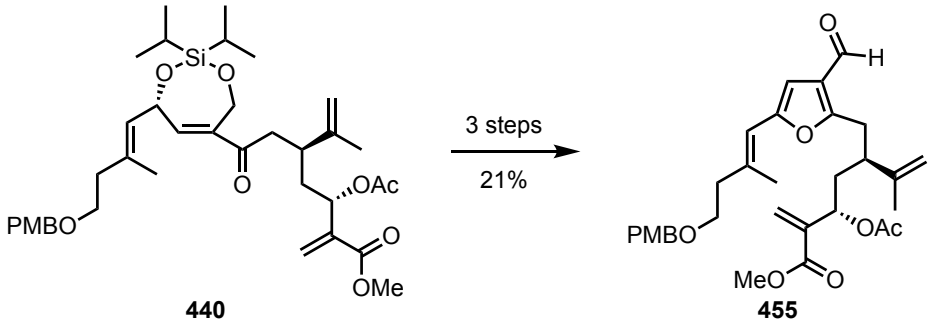
The synthesis was therefore redesigned to include the acetal deprotection and asymmetric Baylis–Hillman reactions prior to TST formation. Alcohols **393** and (±)-**413** were elaborated to (*3S*,*5S*)-ester **427** and (*R*)-alcohol **413** respectively. These fragments were submitted to the TST-RCM sequence to afford silaketal **443** in 2% yield over 16 steps from (*S*)-carvone (**395**). Methyl ester deprotection was then attempted but was ultimately unsuccessful (Scheme 3.28).



Scheme 3.28 Synthesis of silaketal **443**

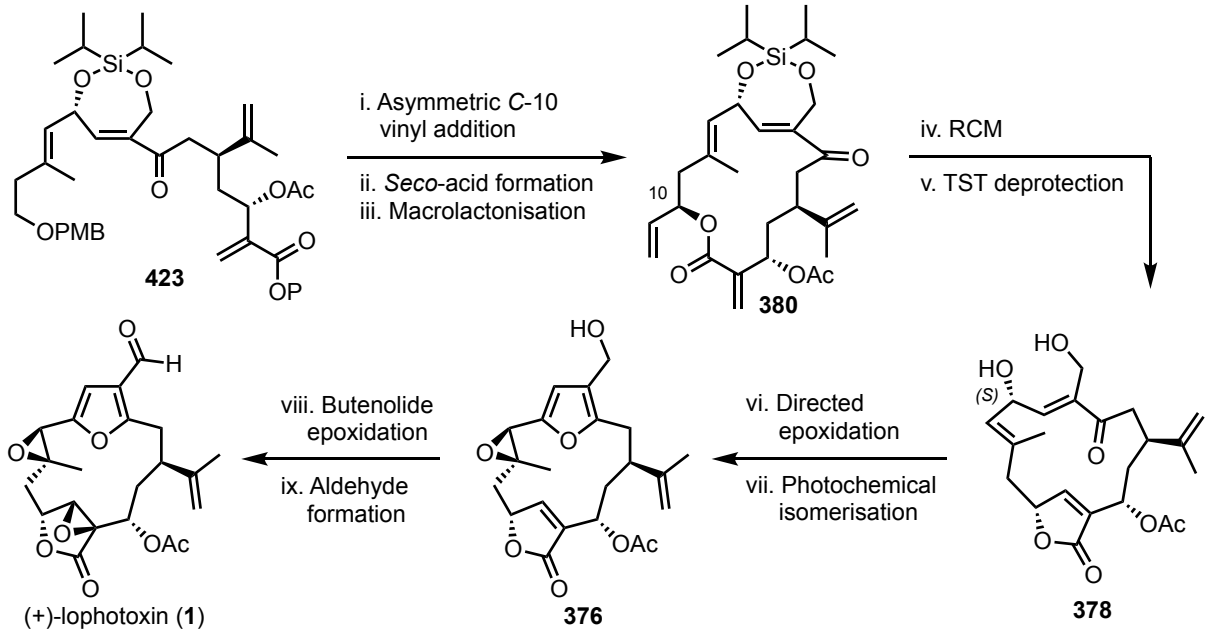
2-Cyanoethyl ester containing silaketal **451** was also synthesised but its deprotection has not been achieved with any selectivity. Future work will include further investigations into the deprotection of **451**. Should this be unsuccessful, other ester derivatives such as 2,2,2-trichloroethyl esters, or ester surrogates such as thioesters, will be tested.

Concurrently, the photochemical araomatisation of advanced intermediate diol **453** confirmed the functional group compatibility to this procedure and furan **455** was synthesised in 0.8% yield in 27 steps (18 steps longest linear sequence) from (*S*)-carvone (**395**) (Scheme 3.29).



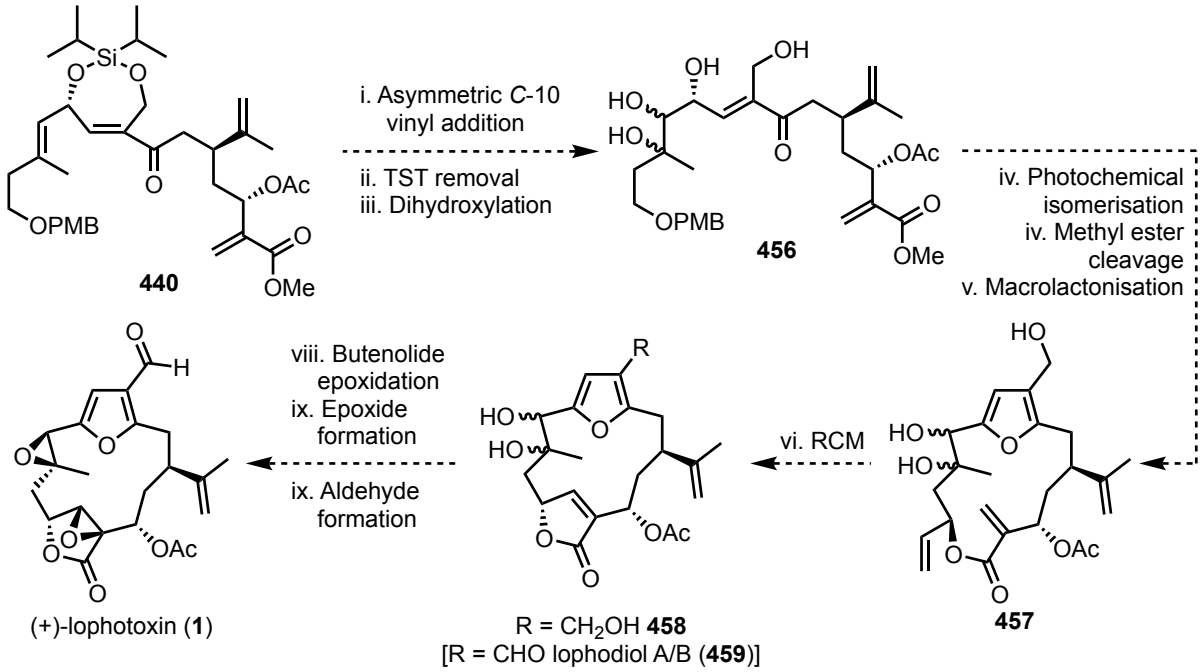
Scheme 3.29 Synthesis of furan **455**

Once a suitable protecting group strategy has been established, the *C*-10 stereocentre will be set and the required *seco*-acid unveiled prior to macrolactonisation to give **380**. The planned end-game will then realise the first total synthesis of (+)-lophotoxin (**1**) (Scheme 3.30).



Scheme 3.30 Planned route to (+)-lophotoxin (**1**)

An alternative strategy involving earlier directed dihydroxylation has also been devised. From advanced polyol **456**, furan formation should allow for deprotection of the methyl ester and macrolactonisation to ester **457**. Previous unpublished work by Donohoe and co-workers has shown that RCM mediated butenolide formation within carbon skeletons of type **457** is possible (see Scheme 3.3). Attempts will then be made to convert the diol moiety to the corresponding epoxide, again strategically forming it late stage without the use of strong oxidisation agents in the presence of the furan moiety. This route would also result in the synthesis of lophodiol A and/or B (**459**), increasing the number of highly oxidised furanocembranoid natural products accessible (Scheme 3.31).



Scheme 3.31 Alternative strategy to furanocembranoid natural products

Chapter 4

Site-selective Modifications of the Thiopeptide Anticancer Agent Thiostrepton

4.1 Introduction

4.1.1 Thiostrepton (460) and its Biosynthetic Origin

Thiostrepton (**460**, sometimes referred to as Thiostrepton A) was first isolated in 1954 from *Streptomyces azureus* by Donovick[169] and further extractions from *Streptomyces hawaiiensis* and *Streptomyces laurentii* were reported in 1955.[170,171] Its structure was unambiguously determined by Hodgkin in 1970 through X-ray crystal structure analysis.[172] It is considered the central member of the thiopeptide family of natural products whose complex macrocyclic and bicyclic structures contain a rich diversity of functionality including heteroaryl, partially saturated heterocyclic and amino acid derived residues. All possess a 6-membered nitrogen containing heterocycle at their core, in differing oxidation states.[173] Thiostrepton (**460**) itself comprises a core bicyclic structure and a 'tail' region containing one thiazole and two dehydroalanine (DHA) residues (Figure 4.1).

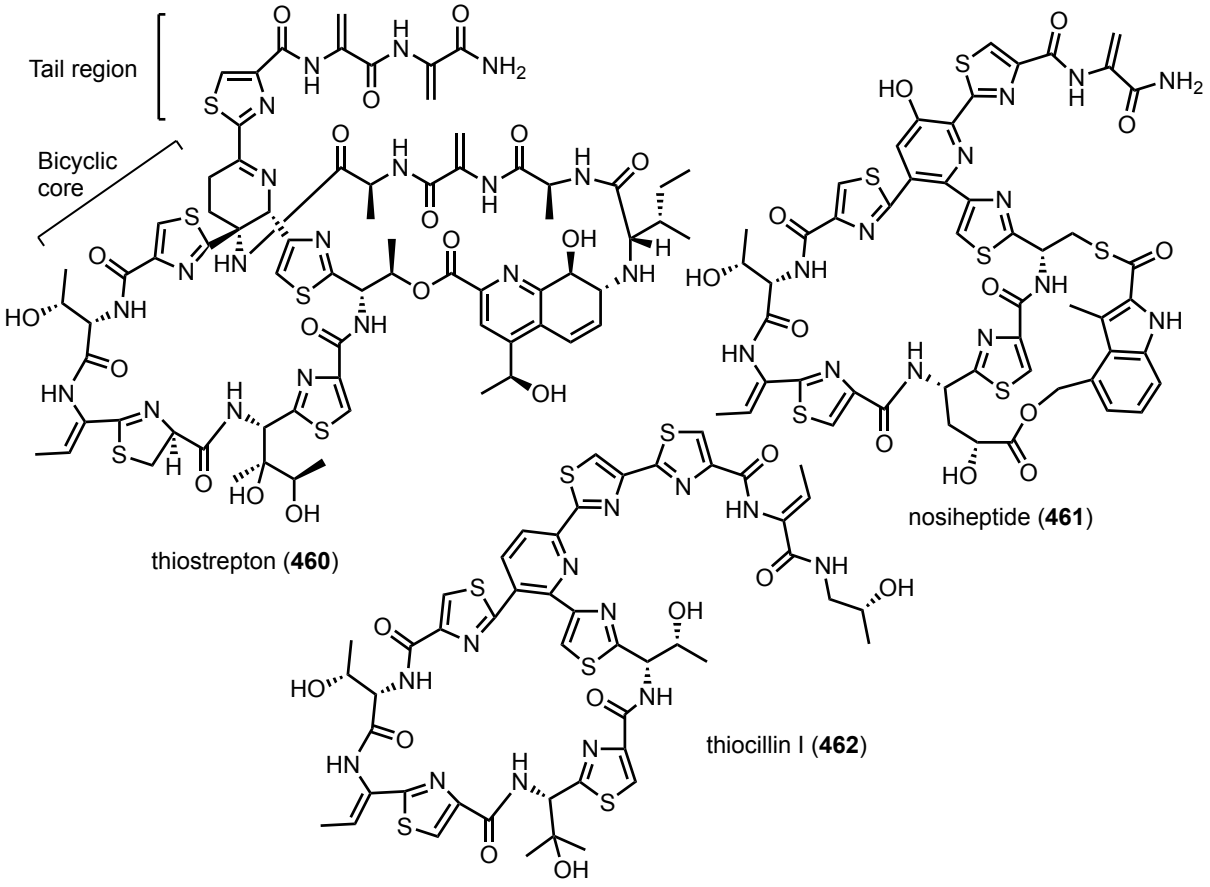
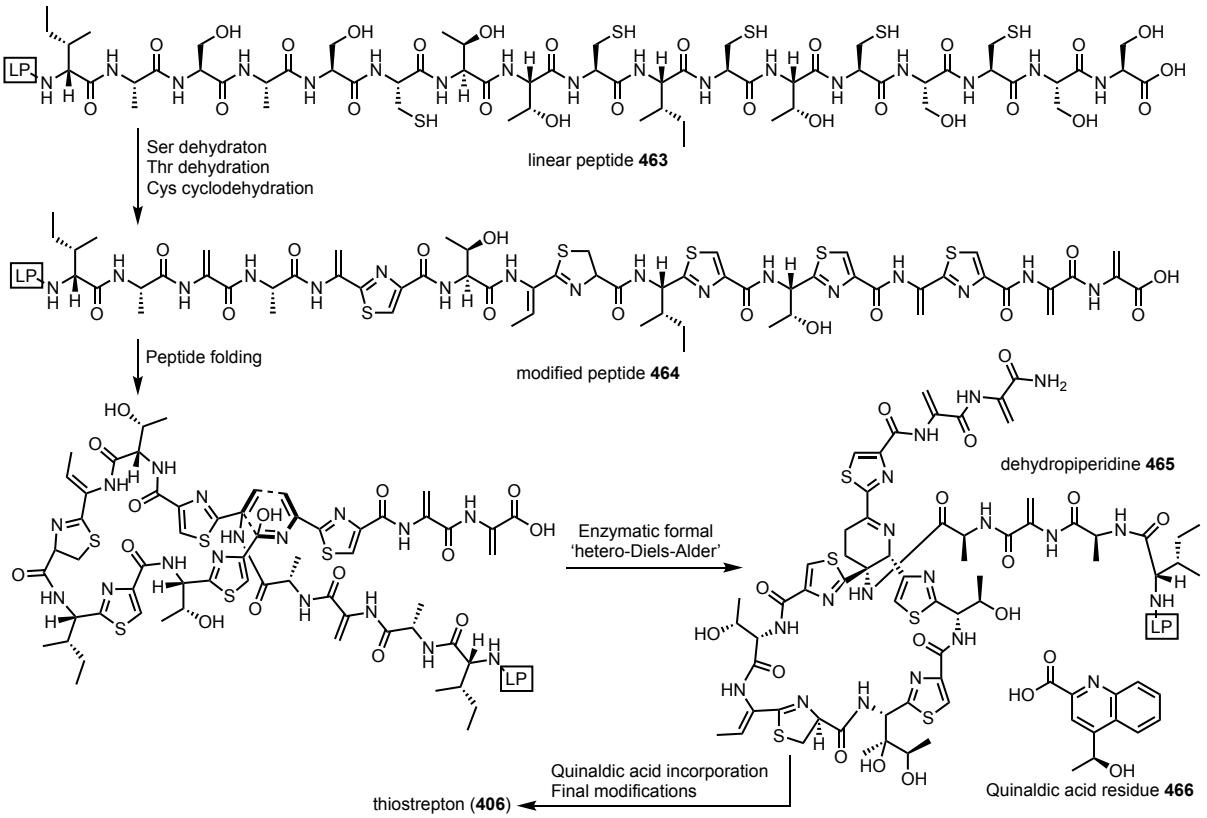


Figure 4.1 Selected members of the thiopeptide family of natural products

The biosynthetic origin of thiostrepton (**460**) has only recently been elucidated.[174] Four nearly simultaneous reports indicated that it is formed from linear peptide **463**, which is itself ribosomally synthesised and genetically encoded.[175,176,177,178] Post-translational modification of **463** provides modified peptide **464**: Ser residues are eliminated to DHAs, Thr resides to butyrines and Cys undergo cyclodehydration to thiazolines and onward oxidation to thiazoles. In 1978, Bycroft and Gowland proposed the subsequent enzymatic formal hetero-Diels-Alder reaction to access the dehydropiperidine **465** and this is not discounted by the recent reports. Kelly and co-workers postulated an alternative mechanism involving enamine addition into DHA derived resides.[177] Discrimination between these two scenarios has not yet been achieved. Quinaldic acid residue **466** is Trp derived although whether it too is ribosomally synthesised is still in doubt. Additional enzymes within the *tsr* gene cluster, including P450s sited at tsrI and tsrK, are proposed to effect the final modifications towards thiostrepton (**460**) (Scheme 4.1).



Scheme 4.1 Biosynthesis of thiostrepton (**460**). LP = leading peptide

4.1.2 Biological Activity of Thiostrepton (460)

The thiopeptide family of natural products are best known as antibiotics. Thiostrepton (**460**) has shown activity again Gram-positive bacterial pathogens, with potency comparable to the penicillins. Protein biosynthesis is inhibited through binding of thiostrepton (**460**) to the GT-Pase-associated centre of the 70S ribosome.[179] In common with other thiopeptide antibiotics, thiostrepton's clinical usage has been hampered by poor aqueous solubility. Notably, Novartis recently developed a thiopeptide inspired antibiotic, LFF571, installing additional carboxylic acid residues to improve pharmacokinetics. It has demonstrated non-inferior activity compared to Vancomycin and is currently in Phase II trials.[180,181]

In addition to antibacterial activity, thiostrepton (**460**) has shown efficacy as an antimalarial[182,183] and is used in veterinary medicine to treat Gram-negative derived mastitis and in dermatological creams.

In 2005, Nicolaou and co-workers reported the micromolar activity of thiostrepton (**460**) in lung, colon, ovarian, breast and leukemia cell lines.[184] Lam and co-workers subsequently disclosed efficacy in breast cancer cells and importantly observed inhibition of MCF-7 carcinoma cells but minimal toxicity to non-cancerous, healthy, MCF-10A cells.[185] Gartel and co-workers later demonstrated *in vitro* micromolar activity against neuroblastoma, leukemia and liver cell lines[186] and melanoma cells.[187] They were also able to establish activity again breast cancer cells *in vivo*.[188] The mode of action of thiostrepton (**460**) with regard to this anticancer activity is still to be definitively established but inhibition of transcription factor Forkhead Box M1 (FoxM1) and the proteasome have both been implicated.

4.1.2.1 FoxM1 Inhibition

Forkhead Box M1 (FoxM1) is a transcription factor of the Forkhead family, characterised by their winged-helix/forkhead DNA binding motif (Figure 4.2). It is involved in cell cycle regu-

lation and is expressed in embryonic and proliferating cells but not in regular, non-proliferating, cells. Upregulation may be initiated in otherwise healthy cells by tissue injury, oxidative stress or, importantly, mitogenic stimuli.[189] It has been implicated in tumour development (oncogenesis) and knockdown in cancer cells resulted in reduced levels of proliferation.[190] As such, it has become a sought after target for anticancer therapies with the potential to provide treatment across a spectrum of cancer types.

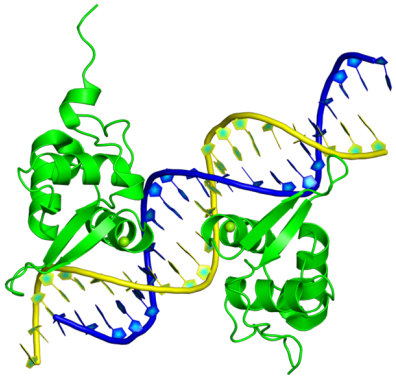


Figure 4.2 FoxM1–DNA binding (PDB: 3g73)[191]

Lam and co-workers showed that thiostrepton (**460**) induced downregulation of FoxM1 as little as four hours after treatment. FoxM1 is needed for cell proliferation, migration and transformation, and all stages of the cell-cycle were inhibited by thiostrepton (**460**).[185] Gartel and co-workers also reported the reduced expression of FoxM1 in neuroblastoma, leukemia and liver cells,[186] and melanoma on treatment with thiostrepton (**460**).[187] Balasubramanian and co-workers were able to confirm the direct binding of thiostrepton (**460**) to FoxM1 though pull-down experiments using a biotinylated analogue, where the biotin moiety was bound *via* a thioether linkage to the internal DHA residue of the tail fragment. The thiostrepton-biotin analogue was found to have reduced bioactivity compared to thiostrepton (**460**) but the biotin-linker alone showed no effect, indicating that residual activity was derived from the thiostrepton fragment (see Section 4.1.3).[192]

4.1.2.2 Proteasome Inhibition

Proteasomes are large protein complexes responsible for maintaining homeostasis in single cell organisms, eukaryotes and bacteria by removing unwanted or degraded proteins.[193] The most common variety found in mammals is the 26S proteasome (*ca.* 2000 kDa), made up of a 20S barrel-like core structure with two 19S capping units. Proteins destined for removal are marked with ubiquitin, a small (8.5 kDa) protein, which is recognised by the 19S units. Protease enzymes in the catalytically active 20S core break down the proteins to smaller polypeptides (seven or eight amino acids) which can then be recycled.

Proteasome inhibition has been shown to effect cell death in human cancer cell lines and the first proteasome inhibitor to be approved, Bortezomib (**467**, marketed as Velcade by Millenium Pharmaceuticals), is used to treat multiple myeloma. Inhibition was proposed to occur *via* reversible covalent binding between the boronic acid moiety and terminal threonine residues within the proteasome.[194] Other proteasome inhibitors likely operate *via* a similar mechanism; MG132 (**468**) was designed to incorporate an aldehyde residue that facilitates binding. The downstream pathway to apoptosis on proteasome inhibition has yet to be fully elucidated, however (Figure 4.3).

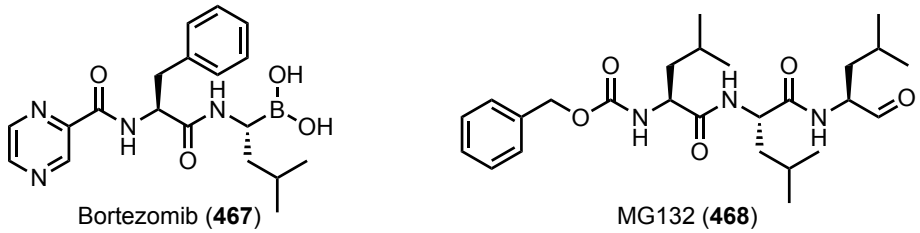


Figure 4.3 Proteasome inhibitors

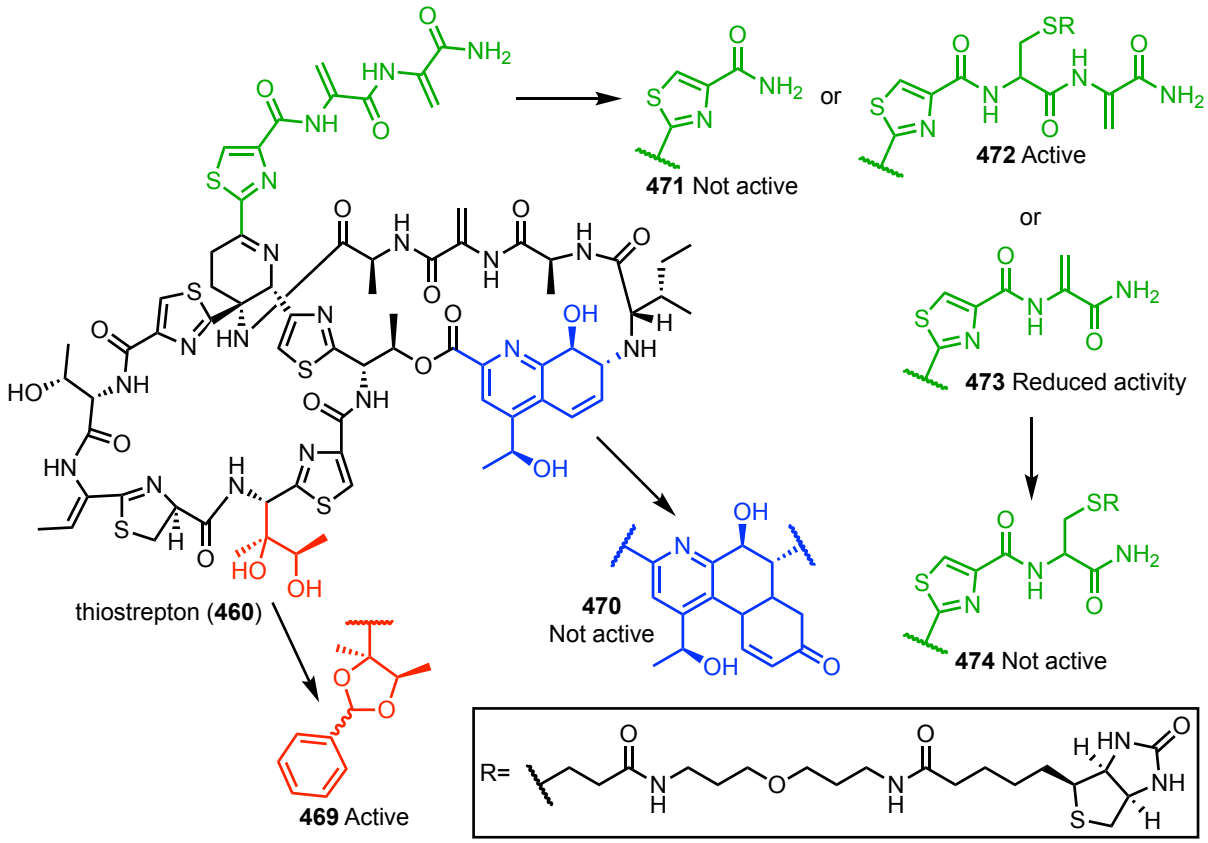
Thiostrepton (**460**) was first identified as a proteasome inhibitor by Gartel and co-workers[195] and this was later validated by Ardnt and co-workers.[183] Gartel also disclosed the downregulation of FoxM1 by MG132, a *bona fide* proteasome inhibitor, hinting that the two mechanisms may in fact be interlinked. Dual action treatment with thiostrepton (**460**) and bortezomib

(**467**) was shown to offer improved tumour suppression *in vivo* compared to treatment with either individual compound.[196] In support of the potential presence of two modes of action, the pull-down experiments performed by Balasubramanian and co-workers also identified direct binding to the 26S proteasome, in addition to that with FoxM1.[192] Additionally, recent work by Stellar and co-workers showed that thiostrepton (**460**) binds covalently to the cysteine residues within Rpt subunits of the 19S proteasome unit.[197]

4.1.3 Derivatisation of Thiostrepton (460)

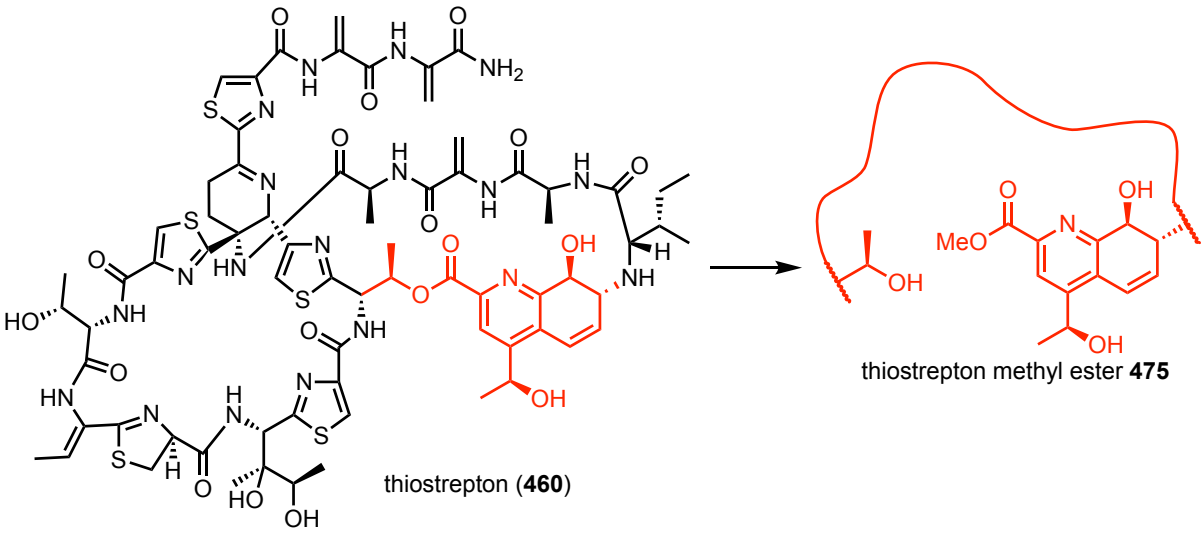
The potent *in vitro* and *in vivo* activity against cancer cell lines exhibited by thiostrepton (**460**), particularly in the context of its reduced toxicity in healthy cells, has precipitated a growing body of synthetic work aimed at elucidating its structure-activity relationships.

Balasubramanian and co-workers synthesised a number of analogues and measured their relative ability to modulate FoxM1 levels in MCF-7 cells (Scheme 4.2).[192]



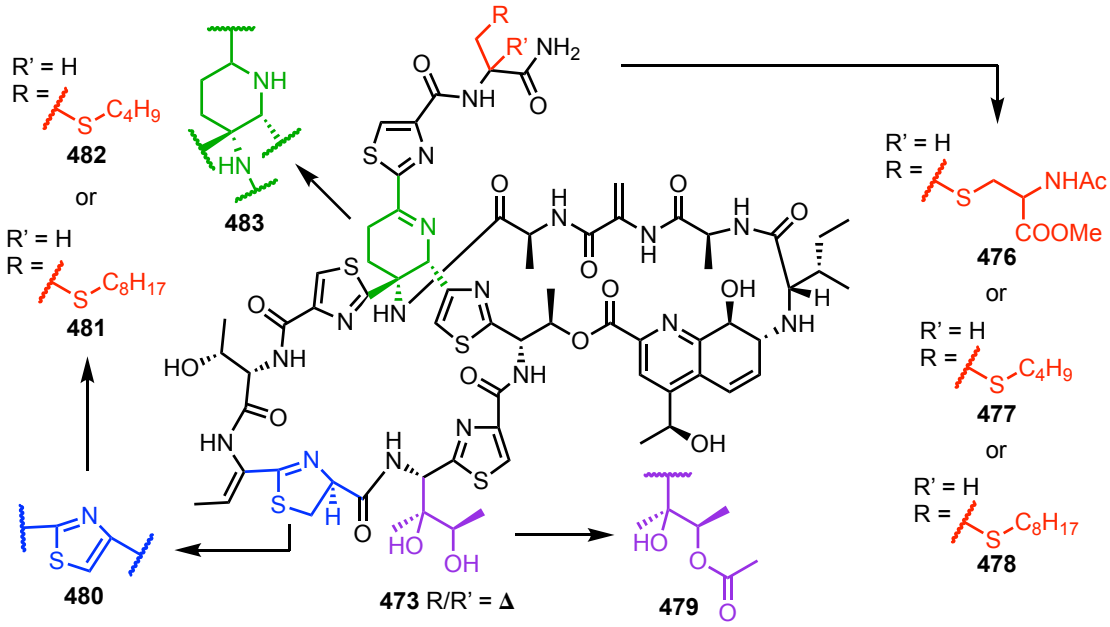
Scheme 4.2 Thiostrepton analogues synthesised by Balasubramanian and co-workers

Acetal **469** demonstrated biological activity but enone **470**, accessed *via* a Diels-Alder reaction of the quinaldic acid with Danishefsky's diene, did not possess any ability to modulate FoxM1 levels. Truncation of the DHA tail was possible and thiols, including a biotin appended thiol used for pull-down experiments, could also be added into the DHA residues. However, only species that preserved at least one DHA moiety retained the parent biological activity. Gartel and co-workers reported the synthesis of macrolactone cleavage product **475** on treatment of thiostrepton (**460**) with NaOMe. They found that all proteasome inhibition activity was lost on cleavage and that **475** was also unable to inhibit FoxM1 expression. Additionally, no apoptosis was observed in human osteosarcoma U-2IS C3 cells (Scheme 4.3).[198]



Scheme 4.3 Thiostrepton methyl ester **475** reported by Gartel and co-workers

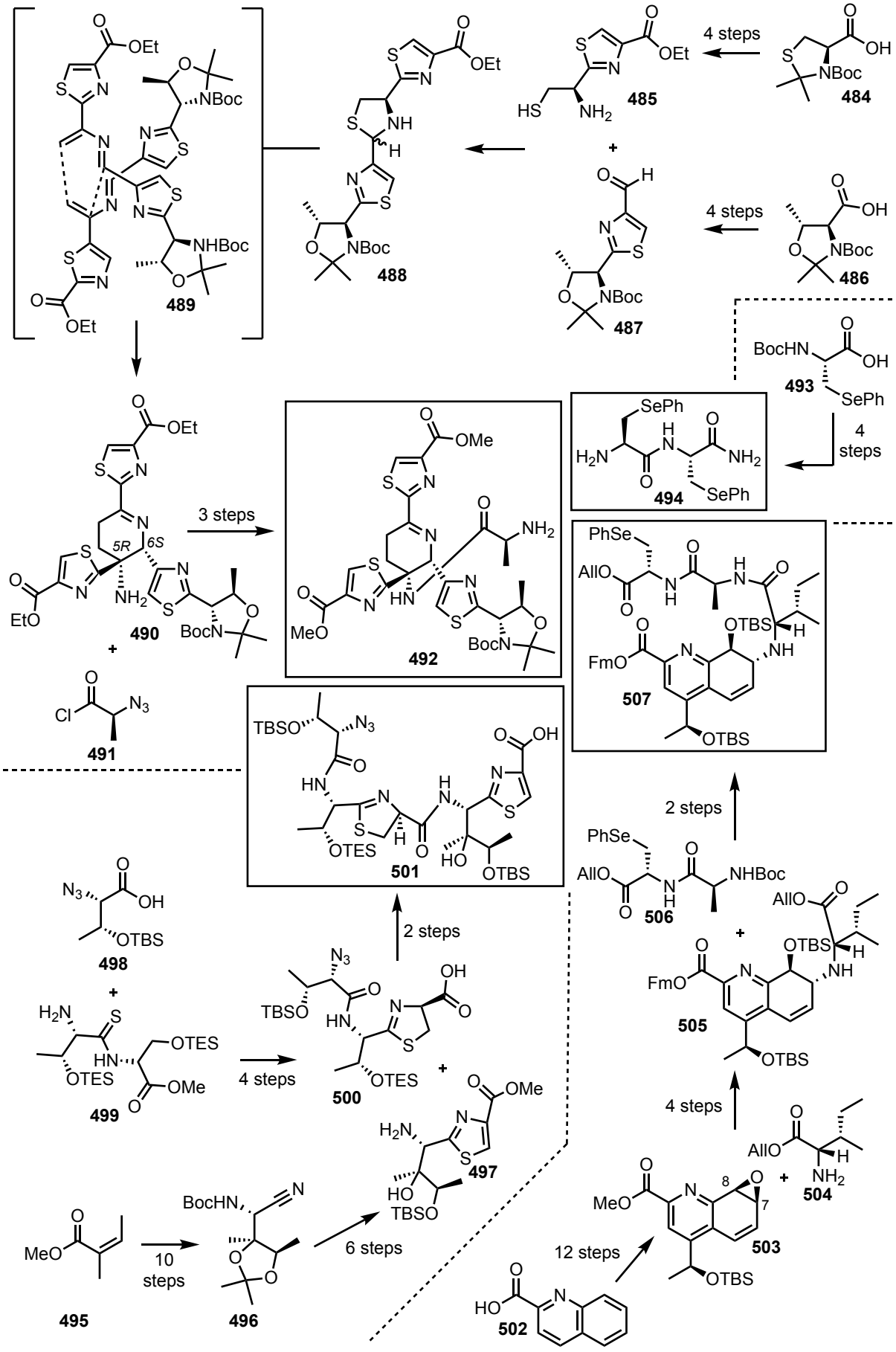
Arndt and co-workers synthesised a small library of analogues shown in two publications, addressing both proteasome inhibition and the identity of the ribosomal binding site.[183,199] They reported improved proteasome inhibition on oxidation of the thiazoline ring to thiazole **480** and further reductions in IC_{50} (up to 20 fold) were observed on conjugate addition of long chain alkyl thiols to form thioethers **476**–**478**, **481** and **482**. The most active analogues were thioether **478** and **481** which both exhibited nanomolar proteasome inhibition. Piperidine **483** and ester **479** were also formed but their biological activity was not assessed (Scheme 4.4).



Scheme 4.4 Thiostrepton analogues synthesised by Arndt and co-workers. **Δ** = methylidene

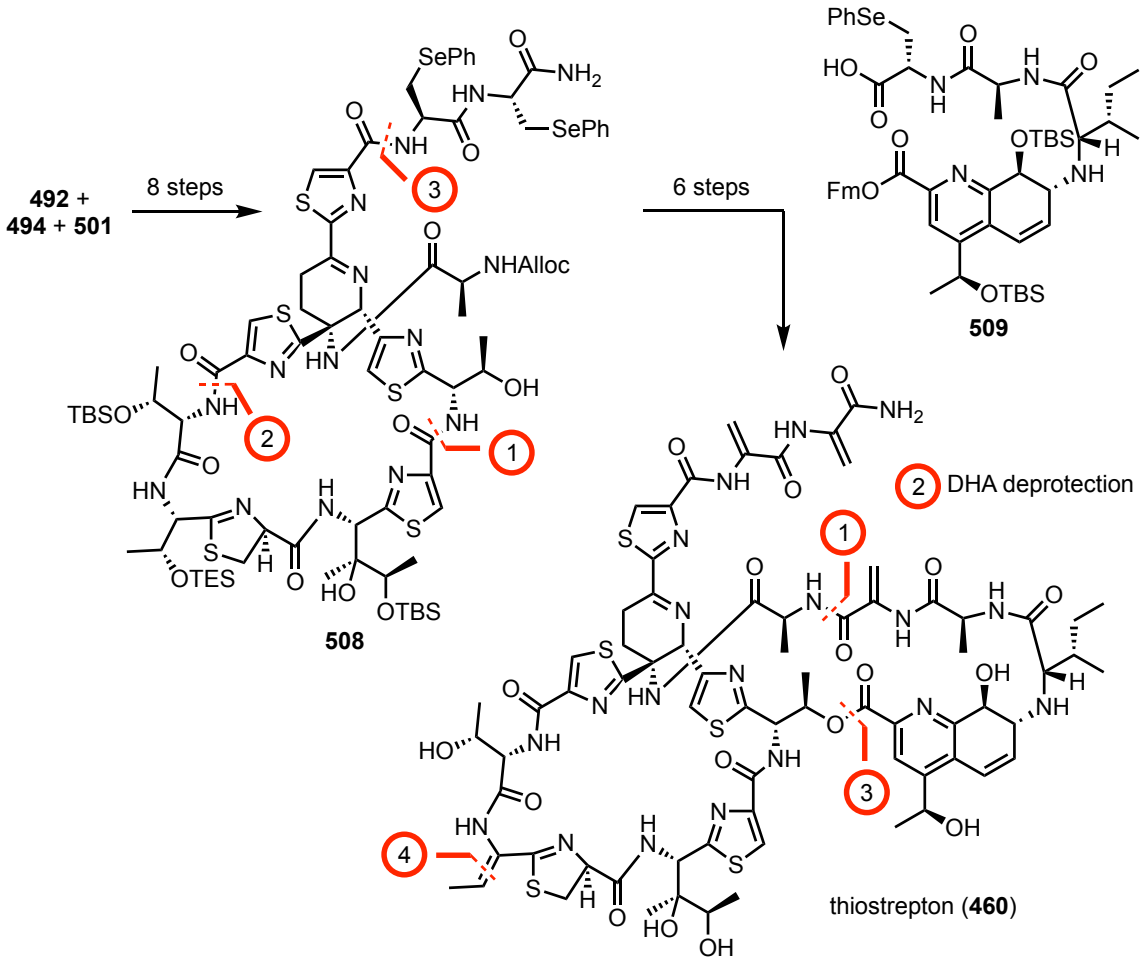
4.1.4 Nicolaou Total Synthesis of Thiostrepton (460), 2004

In addition to work probing the structural features required for bioactivity, Nicolaou and co-workers disclosed the total synthesis of thiostrepton (**460**) in 2004.[200,201] The key aspects of their approach will be discussed. A convergent route incorporating both natural and *de novo* unnatural amino acids was developed and began with the synthesis of four building block fragments; dehydropiperidine **492**, thiazole-thiazoline **501**, quinaldic acid **507** and amide **494**.[202,203] The route to dehydropiperidine **492** began from known carboxylic acids **484** and **486**. Elaboration to thiol **485** and aldehyde **487** followed by condensation provided thiazolidine **488** as an inconsequential mixture of stereoisomers. Base induced formation of azadiene **489** enabled a biosynthetically inspired hetero Diels–Alder dimerisation, constructing amine **490**. The reaction was not stereoselective and both desired (*5R*,*6S*)-**490** and undesired (*5S*,*6R*)-**490** dehydropiperidines were formed as an inseparable 1:1 mixture. Acylation with azide **491** and azide reduction led to dehydropiperidine **492**, at which stage the stereoisomers could be separated. Amide **494**, the precursor to the 'tail' region of thiostrepton (**460**), was synthesised in four steps by amide coupling of two acid **493** units (Scheme 4.5).



Scheme 4.5 Nicolaou's total synthesis: synthesis of building blocks

The synthesis of thiazole-thiazoline **501** began from methyl angelate (**495**). The corresponding (–)-menthol ester enabled the key diastereoselective dihydroxylation to provide the diol motif of ester **496**. Synthesis of thiazoline **500** began from threonine derived acid **498**. Amide coupling with dipeptide **499** followed by deprotection of the primary TES group and activation of the resulting alcohol as the alkyl fluoride with DAST facilitated intramolecular S_N2 with the thiocarbonyl to furnish the thiazoline fragment of acid **500**. Amide coupling of acid **500** and amine **497** afforded thiazole-thiazoline **501**. Quinaldic acid fragment **507** was accessed from quinaldic acid (**502**). Reduction of the benzenoid ring followed by reintroduction of the *C*-7/8 olefin and stereoselective epoxidation gave epoxide **503**. Epoxide opening with amine **504** in the presence of $LiClO_4$ provided ester **505**; amide coupling with dipeptide **506** then afforded the completed quinaldic acid fragment **507**.



Scheme 4.6 Nicolaou's total synthesis: completion of synthesis

The union of dehydropiperidine **492** and thiazole-thiazoline **501** was achieved by first coupling the acid moiety of thiazole-thiazoline **501** with the secondary amine of dehydropiperidine **492** (unveiled by acetonide and Boc deprotection). Macrocyclisation was effected by reduction of the thiazole-thiazoline **501** derived azide and subsequent amide coupling. Amide **494** (representing the 'tail' region) was then connected to afford macrocycle **508**. Quinaldic acid fragment **507** was deprotected to give acid **509** which was then coupled to macrocycle **508**. At this stage it was necessary to unveil all DHA residues; macrolactonisation was not possible with the selenyl ethers in place. Macrolactonisation under Yamaguchi conditions afforded the required bicyclic structure and HF·pyridine then effected both global deprotection and installation of the propene unit by stereospecific E2 elimination to provide thiostrepton (**1**) (Scheme 4.6).

Nicolaou and co-workers also assessed the biological activity of a number of intermediates used in their synthesis.[184] Species derived from quinaldic acid **507** or the 'tail' region were inactive; the latter is surprising in the context of the loss of activity reported by Balasubramanian and co-workers when DHA residues were removed. Dehydropiperidine **510** and piperidine **511** both exhibited micromolar activity against a wide range of cancer cell lines. Thiazole-thiazoline **512** showed both single and double-digit micromolar activity, depending on cancer type. Interestingly, neither an analogue of dehydropiperidine **510** where both primary amines were protected nor the (*5S,6R*) isomer of piperidine **511** were active (Figure 4.4).

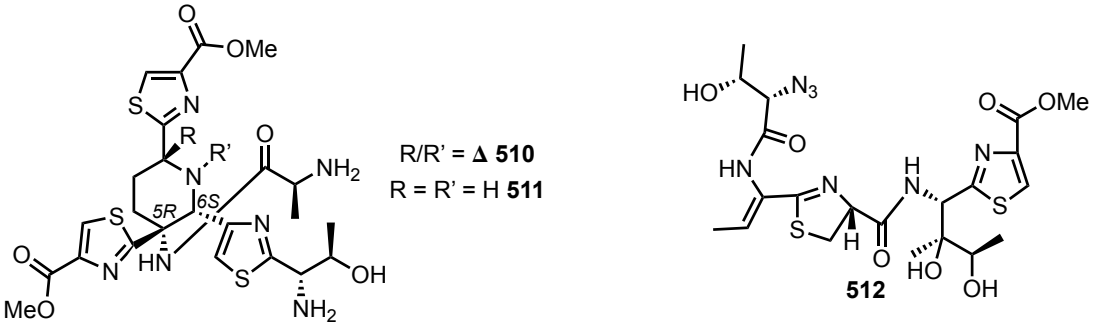


Figure 4.4 Biologically active thiostrepton fragments. **Δ** = methylidene

4.2 Research Proposal

Thiostrepton's broad spectrum activity against a range of cancer types as well as multiple reports of its non-toxicity to healthy cells represent an exciting starting point from which to design a future therapeutic. At the same time, a number of potential issues are well documented. Poor water solubility creates challenges with respect to absorption into the bloodstream and the micromolar potency, although acceptable as a lead compound, would ideally be improved. The design of simplified analogues that exhibit improved solubility and activity would be greatly aided by a more precise understanding of the structural features responsible for its activity, either as a FoxM1 or proteasome inhibitor. Although initial investigations into the structure-activity relationships of thiostrepton (**460**) have already been reported, some of the results appear contradictory, particularly with respect to the influence of the DHA containing 'tail' region.

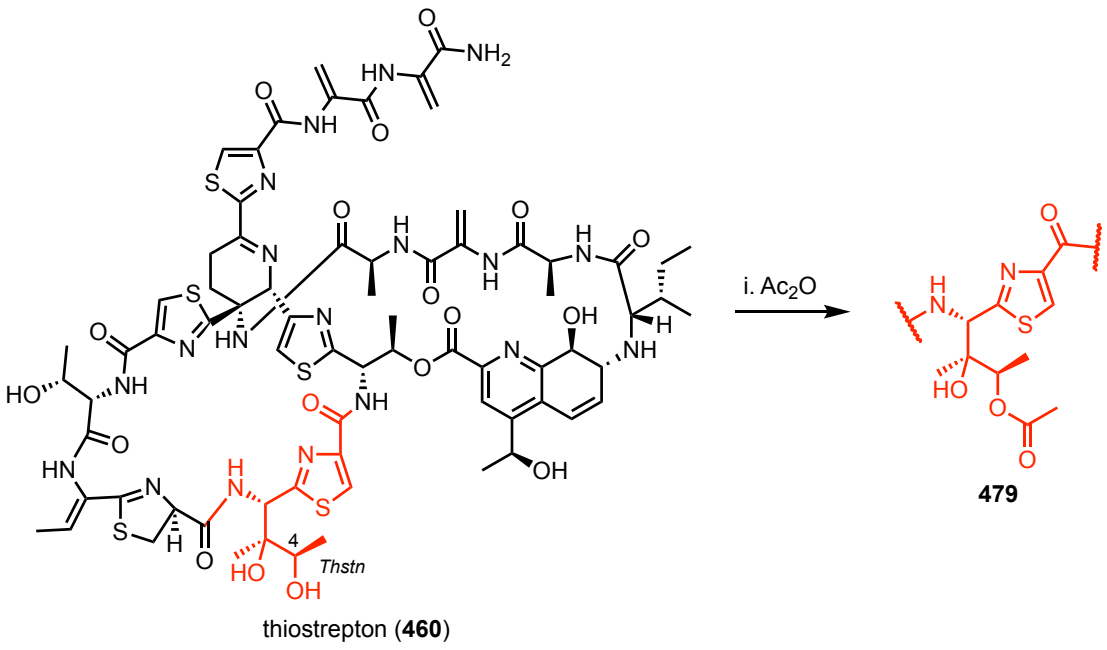
In was envisaged that a general tagging protocol would enable the attachment of a range of functional probes, enabling a detailed investigation into the exact mode of action and biophysical interactions (binding site) with both FoxM1 and the proteasome. Functionalities that would enable fluorescence imaging and cross-linking were amongst probes considered.

Despite the previous use of an alkyl thiol as a carrier for biotin, the disruption of the DHA residues was considered undesirable given the ambiguity over their biological role. However, the report by Balasubramanian and co-workers had indicated that protection of the diol motif did not disrupt the biological activity.[192] Additionally, Arndt and co-workers had shown that that site-selective acetylation of the secondary alcohol of this diol was possible.[199] It was thus decided to develop a general site-selective acylation protocol that would facilitate incorporation of the range of probes required for further investigation.

4.3 Results and Discussion

4.3.1 A General Approach to Site-selective Acylation

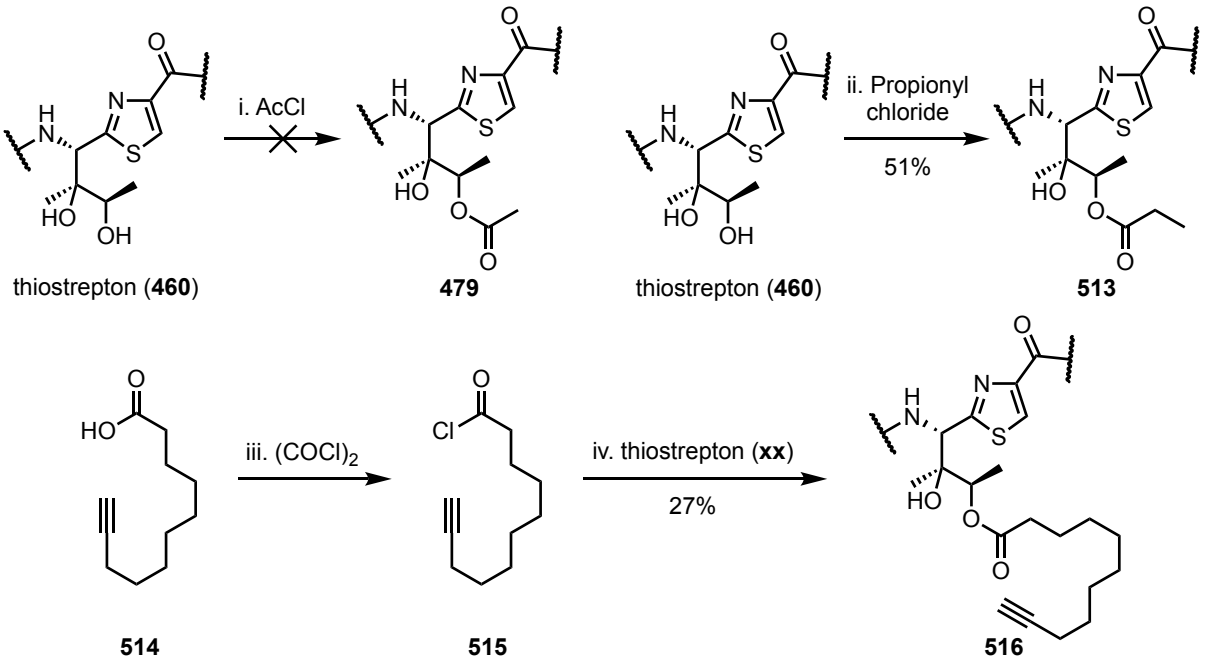
Before commencing development of a general acylation protocol, the reported acetylation of the Thstn *C*-4 alcohol was attempted. Arndt and co-workers had shown that use of a small excess of acetic anhydride in conjunction with catalytic quantities of DMAP in THF led to formation of ester **479** in 33% yield.[199] Unfortunately, replication of these conditions was unsuccessful and thiostrepton (**460**) was completely recovered. Use of a large excess of acetic anhydride and stoichiometric DMAP in $CHCl_3$ at high dilution did, however, lead to formation of the desired ester **479** in 82% yield. The site of acetylation could be clearly seen from the change in chemical shift of the Thstn H-4 proton from 3.80 to 5.02 ppm. The remainder of the ^1H NMR spectrum was essentially unchanged from that of thiostrepton (**460**). It was crucial to use amylenes (1-pentene) stabilised $CHCl_3$ as EtOH stabilised $CHCl_3$ resulted in quenching of acetic anhydride and formation of EtOAc at the reaction concentration used (Scheme 4.7).



Scheme 4.7 Acetylation of thiostrepton (**460**). Reagents and conditions: i) 10 eq. Ac_2O, 20 eq. Et_3N, 1 eq. DMAP, $CHCl_3$ (6.2 mM), rt, 21 h, 82%

To maximise the potential applicability of a general acylation protocol, a widely available class of acyl donors was required. Carboxylic acids were selected due to their prevalence (ca. 190,000 commercially available according to a Reaxys search) and their ease of activation as either the acid chloride or anhydride. Both activation strategies were investigated.

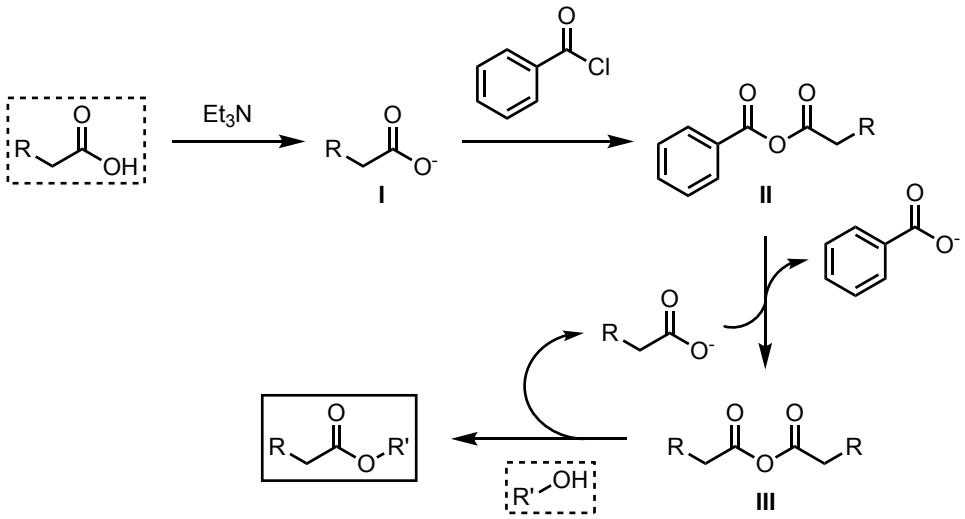
Reaction of thiostrepton (**460**) with acetyl chloride was unexpectedly unsuccessful, even when excess reagents were used. However, propionyl chloride and acid chloride **515** (prepared from 10-undecynoic acid (**514**) and oxalyl chloride) did react with thiostrepton (**460**) to afford esters **513** and **516** in 51% and 27% yield respectively. In both cases, products resulting from polyacylation were observed by mass spectrometry but could not be identified in the ^{1}H NMR of isolated material (Scheme 4.8).



Scheme 4.8 Acylation of thiostrepton (**460**) with acid chlorides. Reagent and conditions: i) 10 eq. AcCl, 20 eq. pyridine, 1 eq. DMAP, $CHCl_3$, rt, 24 h; ii) 10 eq. C_2H_5COCl, 20 eq. Et_3N, 1.5 eq. DMAP, $CHCl_3$, rt, 24 h, 51%; iii) $(COCl)_2$, rt, 30 min; iv) 10 eq. **515**, 20 eq. Et_3N, 1.5 eq. DMAP, rt, 24 h, 27%

Turning to acid anhydrides, Dhimitruka and SantaLucia have developed a protocol for the acylation of alcohols with unhindered aliphatic carboxylic acids *via in situ* activation as the mixed anhydride using benzoyl chloride.[204] The authors propose the following mechanism to

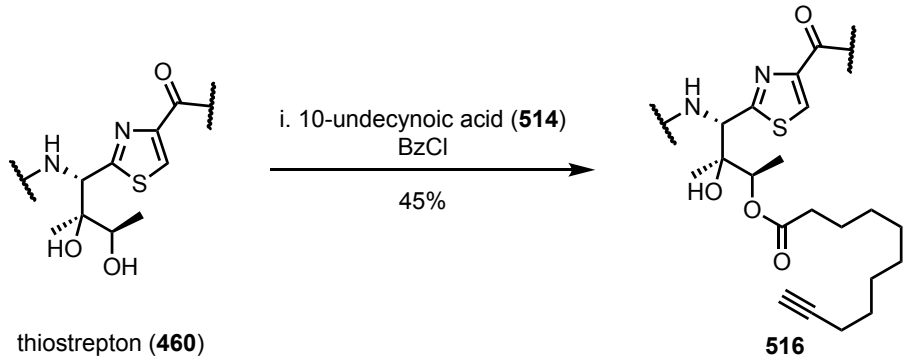
account for the chemoselective acylation of alcohols R′OH with aliphatic carboxylic acids RCH_2COOH in the presence of the aromatic acid chloride (Scheme 4.9).



Scheme 4.9 Postulated mechanism for Dhimitruka and SantaLucia esterification

Deprotonation of the aliphatic acid leads to carboxylate **I** which reacts with the aromatic acid chloride to form mixed anhydride **II**. The authors propose that the increased nucleophilicity of aliphatic carboxylates compared to aromatic carboxylates or alcohols, and the increased electrophilicity of the aliphatic portion of mixed anhydride **II** (on both steric and electronic grounds), leads to formation of symmetrical anhydride **III**. Acylation of R′OH with **III** then gives the desired product. In principle, however, the differing electrophilicity in mixed anhydride **II** would also allow for the regioselective acylation of R′OH directly. Indeed, they note that when more sterically hindered aliphatic carboxylic acids are used, acylation products derived from both aliphatic and aromatic portions of mixed anhydride **II** form, which would be consistent with acylation from mixed anhydride **II**.

Application of these conditions to the acylation of thiostrepton (**460**) with 10-undecynoic acid (**514**) led to selective monoacylation and formation of ester **516** in 45% yield on 500 mg scale. No polyacylation products were observed by either ^{1}H NMR or mass spectrometry (Scheme 4.10).

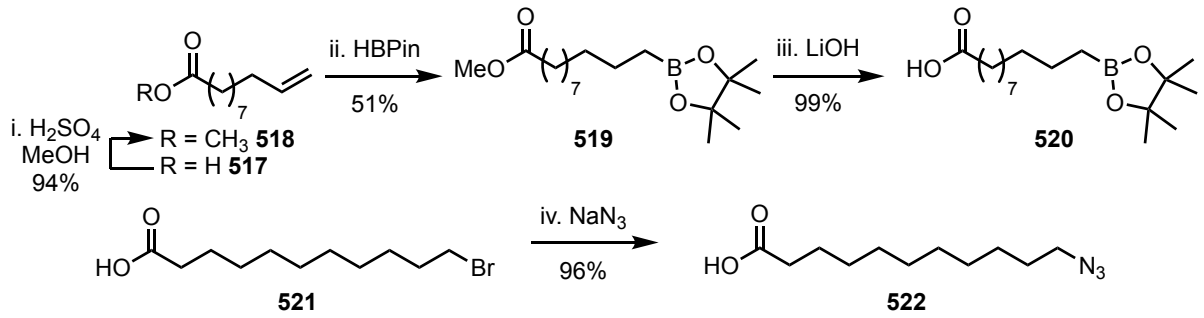


Scheme 4.10 Yamaguchi esterification of thiostrepton (**460**). Reagents and conditions: i) 5.1 eq. **514**, 10 eq. BzCl, 10 eq. Et_3N, 1.25 eq. DMAP, $CHCl_3$, 0 °C, 2.5 h, 45%

The modified Yamaguchi esterification conditions had a number of benefits over the use of acid chlorides. Only monoacylation products could be observed by both ^1H NMR spectroscopy and mass spectrometry, and the procedure also enabled the one-pot acylation with ubiquitous carboxylic acids directly, rather than requiring acid activation *via* the acid chloride. The scope of the acylation reaction was therefore explored using this procedure.

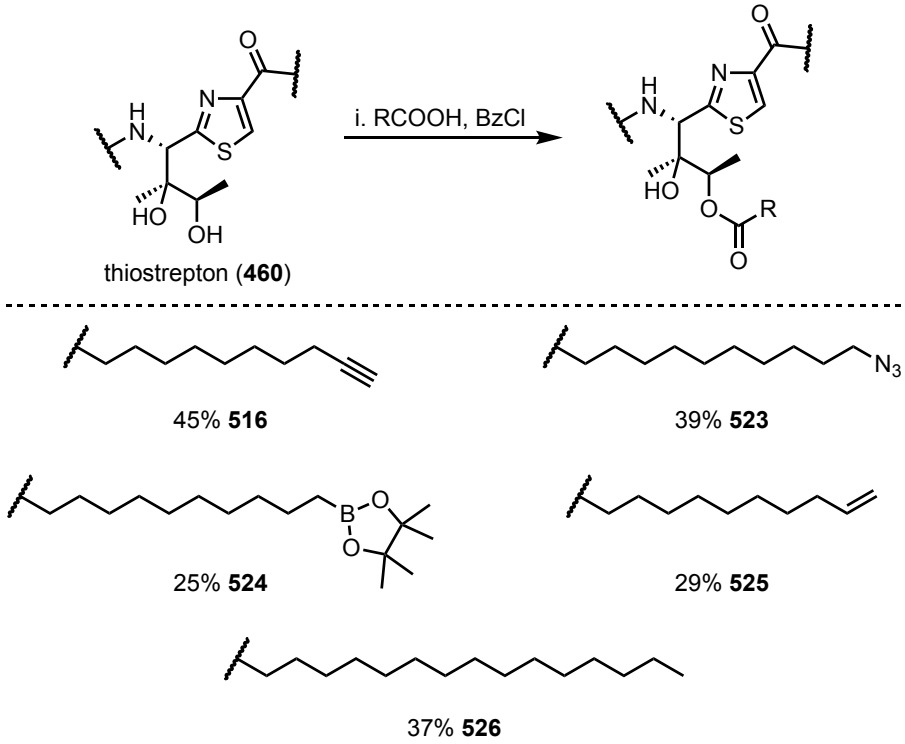
4.3.2 Scope of Site-selective Acylation

A collection of carboxylic acids was assembled for the investigation, either from commercial suppliers or *via* synthesis. Special emphasis was placed on acids containing residues that would facilitate further modification or attachment of biological probes. Boronic acid **520** was synthesised in 47% yield over 3 steps from 10-undecenoic acid (**517**) *via* Rh(I) catalysed hydroboration and azide **522** could be accessed by nucleophilic substitution of 11-bromoundecanoic acid (**521**) in 96% yield (Scheme 4.11).



Scheme 4.11 Synthesis of carboxylic acids. Reagents and conditions: i) H_2SO_4, MeOH, reflux, 24 h, 94%; ii) 1.2 eq. HBPin, 10 mol% $RhCl(PPh_3)_3$, THF, 0 °C to rt, 48 h, 51%; iii) 15 eq. $LiOH{\cdot}H_2O$, H_2O:THF (1:1), 0 °C to rt, 16 h, 99%; iv) 1.1 eq. NaN_3, DMF, 65 °C, 24 h, 96%

Subjection of the carboxylic acids to the acylation protocol led to selective formation of the monoacylated thiostrepton derivatives in all cases. In addition to alkyne **516**, thiostrepton analogues incorporating azide (**523**), boronate ester (**524**) and alkene functionalities (**525**) could all be accessed. These groups might facilitate the attachment of functional probes using click, Suzuki or olefin metathesis reactions. A thiostrepton derivative bearing an extended alkyl chain (**526**) was also synthesised (Scheme 4.12).

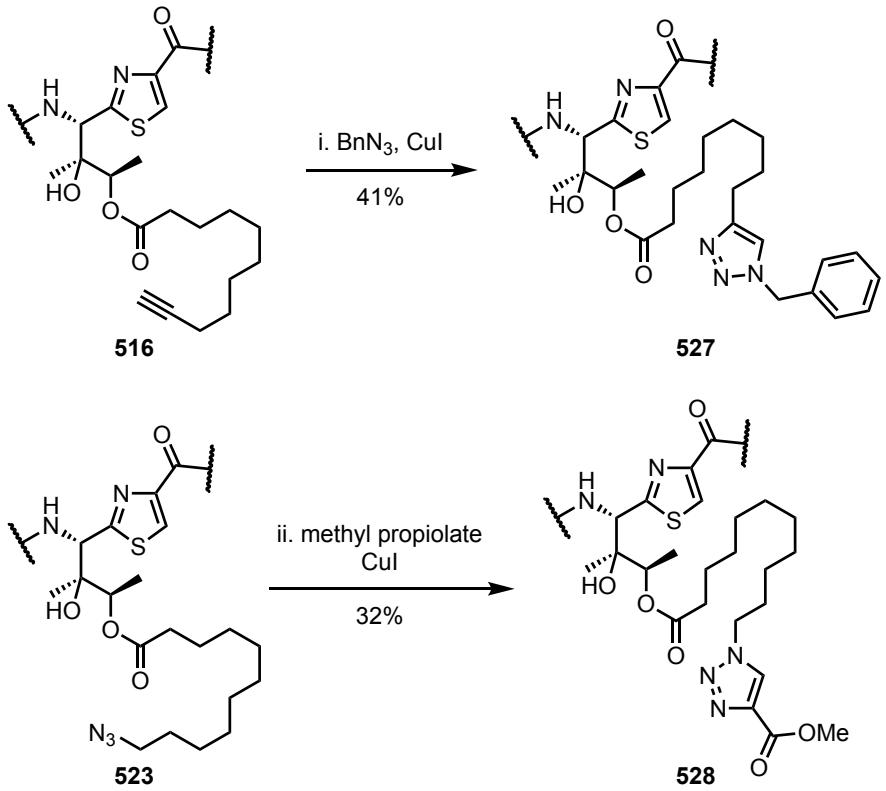


Scheme 4.12 Scope of acylation reaction with carboxylic acids. Reagents and conditions: i) 5.1 eq. carboxylic acid, 10 eq. PhCOCl, 10 eq. Et_3N, 1.25 eq. DMAP, $CHCl_3$, 0 °C, 2.5 h

With this small library in hand, modification of the appended functionality was attempted.

4.3.3 Further Derivatisation of Thiostrepton Analogues

The [3+2] cycloaddition of alkynes with azides, commonly known as the 'click reaction,' has found widespread use in chemical biology as a means of attaching probes and markers to biologically active molecules in an effort to better understand their behaviour or to induce a biochemical response.[205] The ability to use alkyne **516** and azide **523** in click chemistry would thus represent a powerful approach to answering many of the questions regarding the mode of action and binding site of thiostrepton (**460**). As a proof-of-concept, **516** and **523** were reacted with benzyl azide and methyl propiolate under conventional click conditions providing triazoles **527** and **528** in 41% and 32% yield respectively (Scheme 4.13).

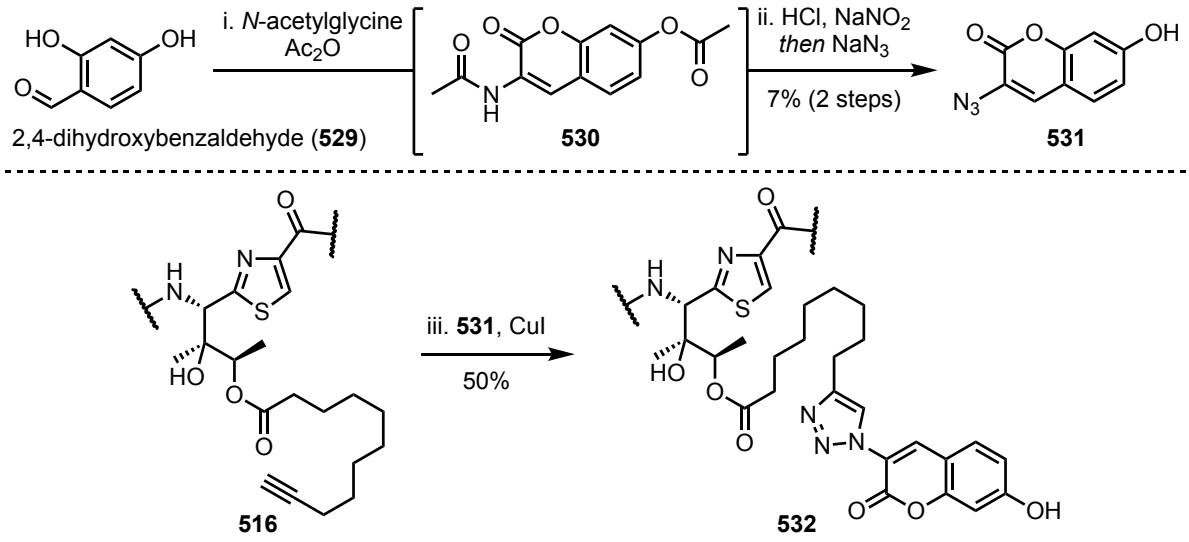


Scheme 4.13 Click reaction of thiostrepton derivatives. Reagents and conditions: i) 7 eq. BnN_3, 2 eq. CuI, 20 eq. DIPEA, $CHCl_3$, 60 °C, 1 h, 41%; ii) 5 eq. methyl propiolate, 2 eq. CuI, 20 eq. DIPEA, $CHCl_3$, 60 °C, 2 h, 32%

One established application of click chemistry is the tagging of biologically active compounds with fluorescent moieties *in vivo*, facilitating the imaging of their cellular distribution or binding efficiency. Once the molecule has reached its target site, the fluorescent species may be introduced, whereupon a click reaction will link the two compounds and imaging of their cel-

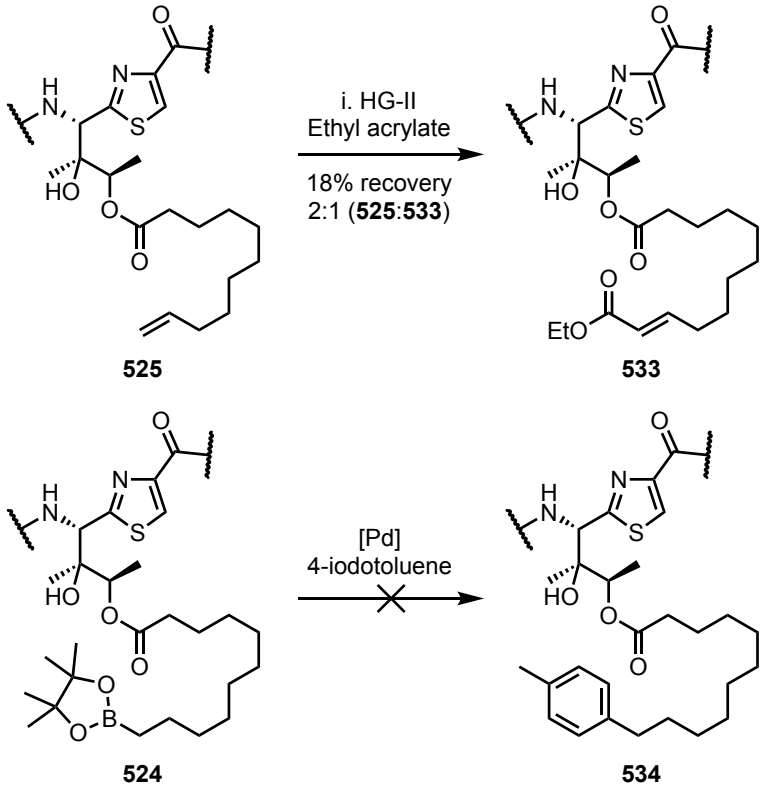
lular distribution can be performed. This strategy allows for the incorporation of the fluorescent species with minimal impact on the initial biological activity; alkyne functionalities in particular are small and less likely to disrupt ligation compared to the fluorescent moiety itself. Wang and co-workers have developed a series of fluorogenic 3-azidocoumarins for this purpose.[206] The fluorogenic approach allows use of excess reagent without contributing to background fluorescence as only once the click reaction has occurred does the probe fluoresce. In this way the exact location or distribution of the active molecule can be determined.

Using the reported procedure, 3-azidocoumarin **531** was synthesised from 2,4-dihydroxybenzaldehyde (**529**) in 7% yield over 2 steps. It is reported to fluoresce strongly at 490–499 nm once reacted.[206] Click reaction with alkyne **516** in a $CHCl_3$:EtOH solvent mixture facilitated dissolution of both species and triazole **532** was isolated in 50% yield (Scheme 4.14).



Scheme 4.14 Synthesis and reaction of 3-azidocoumarin **531**. Reagents and conditions: i) 1 eq. *N*-acetylglycine, Ac_2O, reflux, 6 h *then* Et_2O, –78 °C; ii) EtOH, $HCl_{(aq)}$, reflux 1 h *then* $NaNO_2$, 0 °C, 15 min *then* NaN_3, 0 °C, 80 min, 7% (2 steps); iii) 3 eq. **531**, 2 eq. CuI, 20 eq. DIPEA, $CHCl_3$:EtOH (1:1), rt, 4.5 h, 50%

Modification of other thiostrepton analogues was also attempted. After CM of alkene **525** with ethyl acrylate, a 2:1 mixture of alkene **525** and acrylate **533** could be isolated by FCC in 18% combined yield. Separation of these two species was not possible. The Suzuki coupling of boronate ester **524** was also attempted but no reaction was observed (Scheme 4.15).



Scheme 4.15 Cross metathesis and attempted Suzuki coupling of thiostrepton derivatives. Reagents and conditions: i) 10 eq. ethyl acrylate, 10 mol% HG-II, $CHCl_3$, 50 °C, 18 h, 18% mass recovery

4.4 Biological Data

A total of seven compounds were submitted for biological evaluation as proteasome inhibitors. This work was undertaken by Dr. Heidi Olzscha and Prof. Nicholas La Thangue (Department of Oncology, University of Oxford). The compounds submitted were azide **523**, thiostrepton (**460**), boronate ester **524**, amide **471**,[192] coumarin **532**, alkane **526** and alkyne **516**. Known proteasome inhibitors Bortezomib (**467**) and MG132 (**468**) were additionally tested to allow for comparison.

4.4.1 MTT Assay to Measure IC_{50}

For the purposes of IC_{50} measurement, Hek293T cells were treated with the compounds in DMSO solutions for the times indicated. Both a blank experiment, in the absence of cells, and a control (DMSO only) were run in parallel. After incubation, conversion of MTT into purple formazan was measured at 570 nm; this correlates with the numbers of cells present and their

viability. All experiments were carried out in three independent biological replicates and, for thiostrepton derivatives, in triplicate. The IC_{50} was calculated from the dose response curves of the MTT assay (Table 4.1).

Time	Azide **523**	Thiostrepton (**460**)	Boronate **524**	Amide **471**	Coumarin **532**	Alkane **526**	Alkyne **516**	Bortezomib (**467**)	MG132 (**468**)
1 day	29.8	41.0	27.7	98.5	98.0	50.4	17.0	0.699	2.61
2 days	8.33	3.97	9.69	38.1	50.8	26.3	3.69	0.0663	0.520
3 days	5.07	2.29	5.02	27.9	45.1	29.9	2.54	0.0293	0.319

Table 4.1 MTT assay for IC_{50} measurement. Values in mM

Varying levels of cytotoxicity were observed; after 3 days, IC_{50} values for azide **523**, thiostrepton (**460**), boronate **524** and alkyne **516** were all single digit mM. Those for amide **471**, coumarin **532** and alkane **526** were all double digit mM. Bortezomib (30 nM) and MG132 (300 nM) both displayed high levels of cytotoxicity, as expected.

4.4.2 Flow Cytometry to Measure Proteasome Inhibition

Proteasome inhibition was measured on a Ub-EGFP (Ubiquitin/Green Fluorescent Protein) cell line. This is based on Hek293T cells and expresses Ub-EGFP which is degraded by the proteasome under normal conditions. When the proteasome is inhibited it accumulates, however, and the degree of fluorescence from GFP can be measured and correlated to inhibition. The concentrations of compounds used for this experiment were chosen according to the IC_{50} values obtained after three days of treatment and are as follows: azide **523**, thiostrepton (**460**), boronate **524** and alkyne **526** (5 μM); amide **471**, coumarin **532** and alkane **526** (25 μM); Bortezomib (**467**, 25 nM); MG132 (**468**, 5 μM). All experiments were carried out in three independent biological replicates and in triplicate and the results are graphically represented; note the logarithmic scale on the y-axis (Figure 4.5). Thiostrepton (**460**), Bortezomib (**467**) and MG132 (**468**) all inhibited the proteasome as expected. The relative activity of thiostrep-

ton (**460**) should be viewed in the context of the increased concentration used, however. Azide **523**, Boronate **524** and alkyne **516** were all able to inhibit the proteasome to a small degree with amide **471**, coumarin **532** and alkane **526** producing essentially no response. These results approximately correlate with IC_{50}.

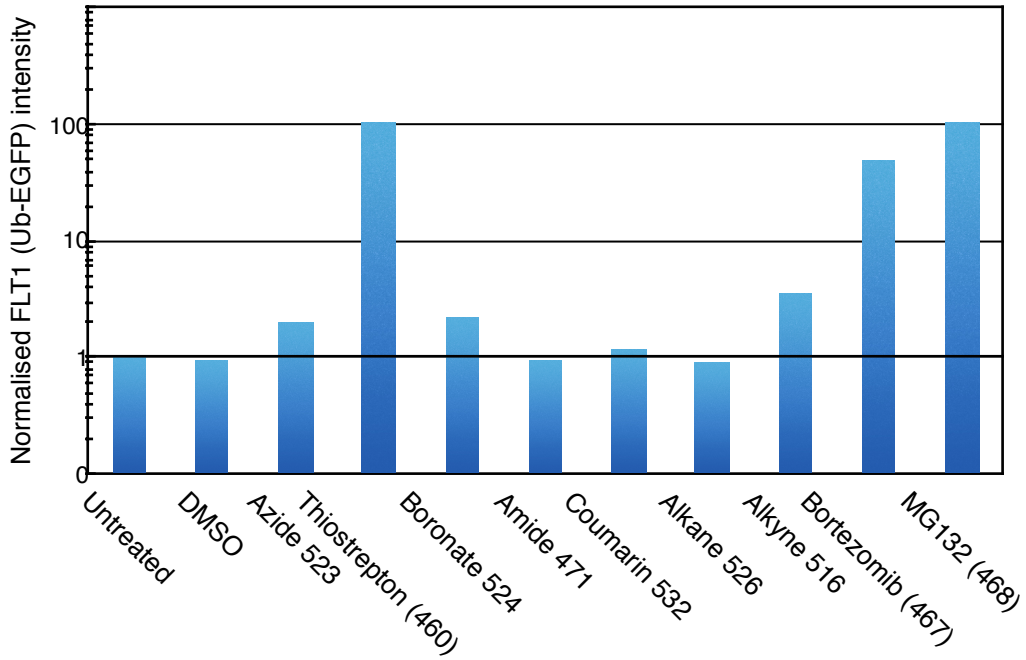


Figure 4.5 Flow cytometry experiment for proteasome inhibition

4.4.3 Fluorescence Microscopy

Fluorescence microscopy provided the opportunity to assess the fate of coumarin **532** on application to whole cells. A background lambda scan was performed between 400–800 nm to measure autofluorescence from the Hek293T cells (Figure 4.6, *i*, observed intensity maximum at 482 nm). Cells pre-treated with coumarin **532** were then evaluated at 482 nm. The coumarin moiety is known to fluoresce strongly with a maximum between 490–499 nm and the scan successfully enabled visualisation of both the cells and coumarin **532**, revealing aggregation of **532**, unfortunately outside of the cell walls. This aggregation can be seen in the strong point emissions of **532** in Figure 4.6, *ii*. This aggregation outside the cell walls might explain the lack of cytotoxicity and proteasome inhibitory activity exhibited by coumarin **532**.

It seem reasonable to suggest that similar aggregation might also explain the lack of activity shown by amide **471** and alkane **526**.

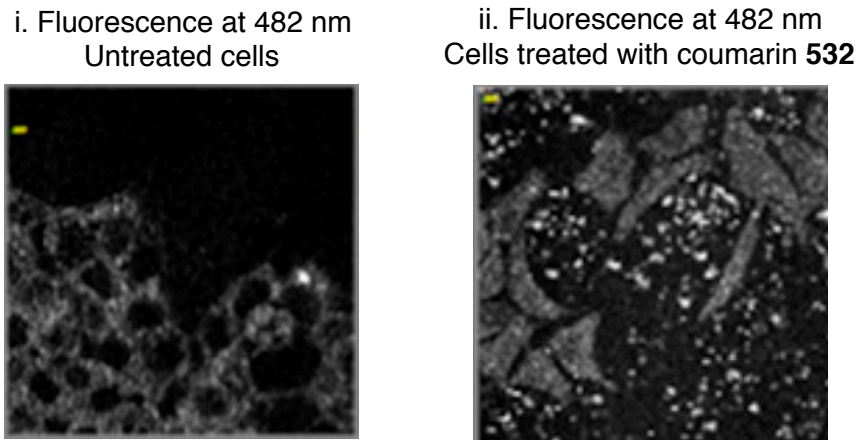


Figure 4.6 Fluorescence microscopy experiments with coumarin **532**

Imaging at 488 nm allowed for visualisation of GFP after treatment of the Ub-EGFP expressing cell line with the library of compounds. Differential interference contrast (DIC) spectroscopy was used to visualise the cells prior to analysis and comparison between the two images clearly shows the liberation of GFP from Ub-EGFP within cell walls only (Figure 4.7).

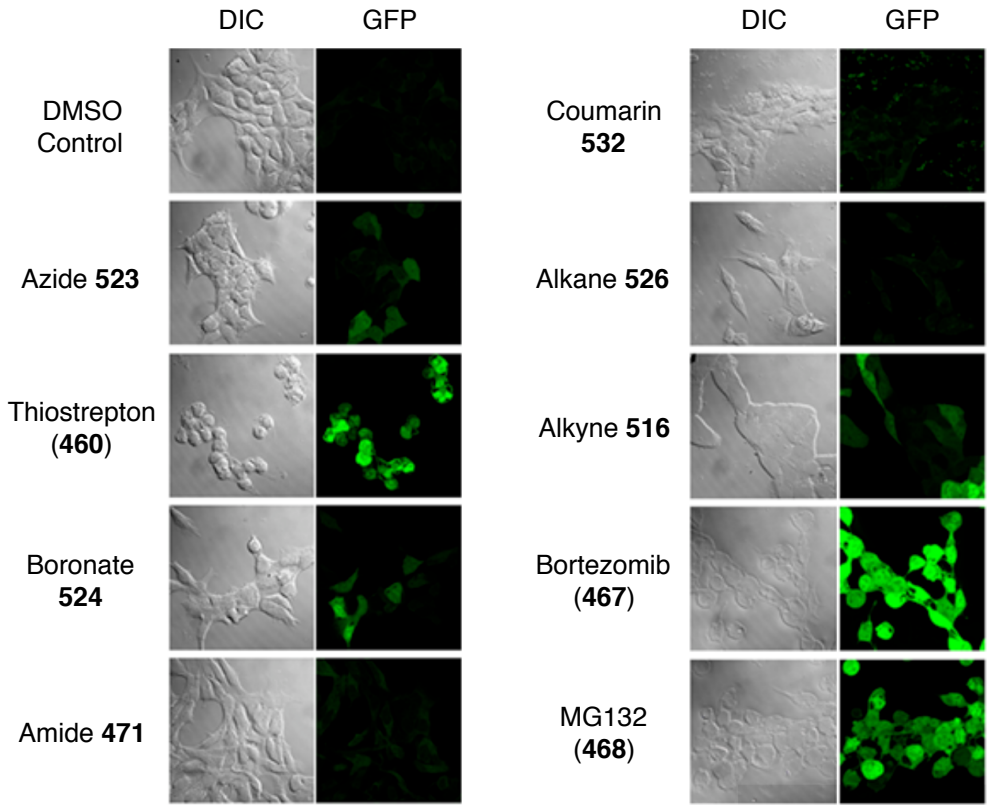


Figure 4.7 Fluorescence microscopy experiments to visualise GFP

The highest intensities of GFP fluorescence are seen for thiostrepton (**460**), Bortezomib (**467**) and MG132 (**468**). Some fluorescence is seen for azide **523**, boronate **524** and alkyne **516**. Minimal fluorescence is seen for amide **471**, coumarin **532** and alkane **526**. These results are consistent with those obtained earlier in flow cytometry experiments.

4.4.4 Discussion of Biological Data

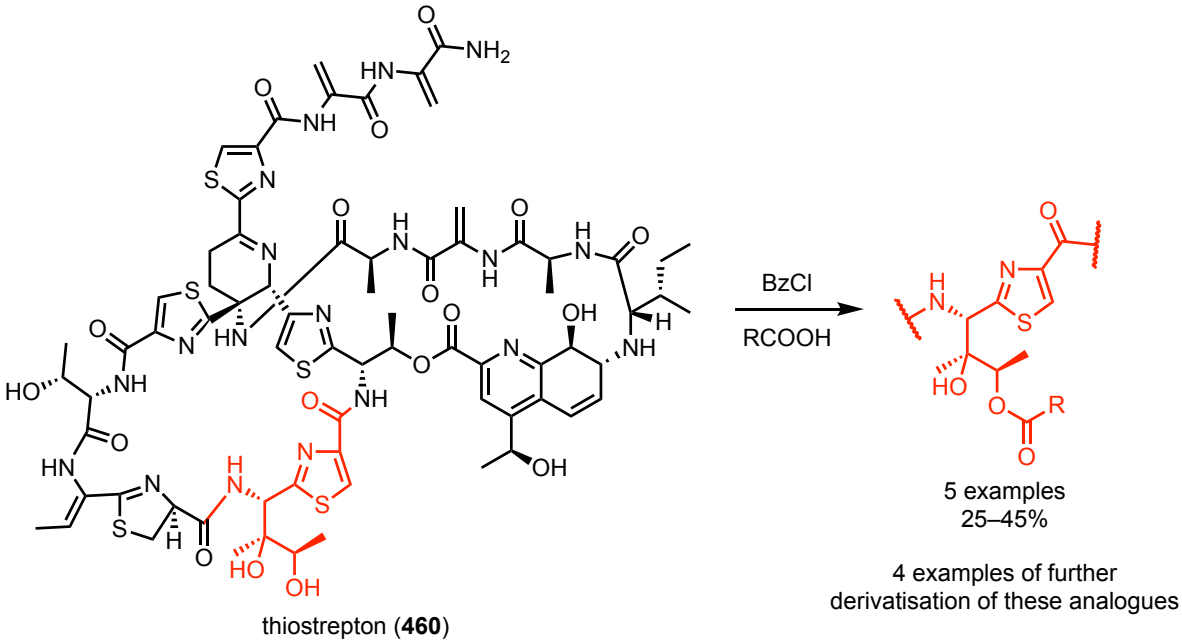
Three of the analogues were able to retain some of the activity of thiostrepton (**460**) itself. In general, cytotoxicity and proteasome inhibition activity were correlated in the following order: thiostrepton (**460**) ≫ alkyne **516** > boronate **524** > azide **523**. Thiostrepton (**460**) was similarly active to known proteasome inhibitors Bortezomib (**467**) and MG132 (**468**).

The lack of activity shown by coumarin **532** could be explained by compound aggregation outside the cell walls, as shown by fluorescence microscopy. That alkane **526** is also ineffective is more surprising given that structurally similar alkyne **516** showed some ability as a proteasome inhibitor. Amide **471** has previously been investigated by Balasubramanian and Arndt as a thiostrepton analogue. In both cases, removal of the dehydroalanine units led to an almost complete loss of activity and this is corroborated by the present results.

It is difficult to draw conclusions in terms of a structure-activity relationship due to the small changes in biological activity for those compounds that did provide a response and the structural similarity between compounds that both did and did not display activity. However, many of the compounds did retain some of the parent biological activity, crucially including alkyne **516** and azide **523** which can facilitate click chemistry. This suggests that site-selective acylation might represent a viable strategy towards the incorporation of assorted probes and markers.

4.5 Conclusions and Future Work

In conclusion, a general method for the site-selective acylation of thiostrepton (**460**) with aliphatic carboxylic acids has been developed. Many of the compounds synthesised could be further modified and a small library of analogues was produced. Selected examples from this library were submitted for testing to assess their cytotoxicity and activity as proteasome inhibitors (Scheme 4.16).



Scheme 4.16 Summary of synthetic modifications of thiostrepton (**460**)

The retention of biological activity in some cases suggests that this strategy could be used to study the behaviour of thiostrepton (**460**). However, issues surrounding cell permeability may be more general than that observed for coumarin **532**. *In vitro* assays will be able to establish the fundamental activity of all compounds and will be performed before proceeding further. The reactivity of both alkyne **516** and azide **523** in click chemistry will then be exploited to attach a range of other probes. Functionality that will enable cross-linking,[207] pull-down experiments, or alternative imaging experiments will all be incorporated to enable the detailed studies of thiostrepton's mode of action required.

Chapter 5

Experimental Procedures and Supporting Information

5.1 General Information

Reagents and Solvents

All solvents and reagents were obtained from Acros, Alfa Aesar, Fischer Scientific, Fluorochem, Sigma-Aldrich, Strem or Tokyo Chemical Industry (TCI). Thiostrepton (**460**) was purchased from Merck Millipore. All reagents were used as received or were purified using standard laboratory techniques according to Armarego and Chai.[208] CH_2Cl_2, tetrahydrofuran (THF), diethyl ether (Et_2O) and toluene (PhMe) were dried over activated 3Å molecular sieves for 2 days and then filtered through an activated alumina purification column prior to use. Anhydrous *N*,*N*,-dimethylformamide (DMF) and anhydrous chloroform ($CHCl_3$, amylene stabilised) were used directly from Sure/Seal® bottles purchased from Sigma-Aldrich. Dioxane (99+% stabilised with BHT) was purchased from Alfa Aesar and used as received. Brine refers to a saturated solution of NaCl in de-ionised H_2O. pH7 Buffer refers to a solution made from OXOID phosphate buffered saline (Dulbecco A) tablets according to the manufacturers instructions.

Reactions

All glassware was flame-dried under vacuum and reactions performed in an argon atmosphere unless otherwise stated. All reactions were stirred with magnetic followers unless otherwise stated. All stated temperatures refer to external bath temperatures unless an internal reaction temperature is explicitly stated. Internal reaction temperatures were measured using a glass mercury thermometer inserted into the reaction mixture through a Quickfit® thermometer adaptor fitted with a silicone ring seal.

Chromatography

Flash column chromatography was performed with Merck Kieselgel 60 (0.040–0.063 mm) silica gel performed according to the method reported by W. C. Still and co-workers.[209] All solvents used for chromatographic purification were HPLC grade or equivalent and supplied by Sigma-Aldrich or Fischer Scientific. TLC analyses were performed on Merck Kieselgel 60 F_{254} precoated aluminium-backed plates with layer thickness between 175 and 225 μm. Product spots were visualised under UV light (λ_{max} = 254 nm) and/or by staining with a potassium permanganate, vanillin or phosphomolybdic acid solution.

Nuclear Magnetic Resonance (NMR) Spectroscopy

All spectra were recorded on a Bruker DPX200, Bruker AVIII HD 400, Bruker AVIII HD 500 or Bruker AVII 500 (equipped with a He cryoprobe) instruments, with the deuterated solvent acting as internal deuterium lock. ^{1}H NMR spectra were recorded at 200, 400 or 500 MHz, ^{13}C NMR spectra at 101 or 126 MHz with broadband proton decoupling and ^{19}F NMR spectra at 377 MHz without proton decoupling as stated. The residual protic solvent signal acted as an internal reference for ^{1}H NMR and the deuterated solvent carbon signal acted as an internal reference for ^{13}C NMR ($CDCl_3$: ^{1}H NMR = 7.26 ppm, ^{13}C NMR = 77.16 ppm; MeOH-d_4: ^{1}H NMR = 3.31 ppm, ^{13}C NMR = 49.00 ppm; DMSO-d_6: ^{1}H NMR = 2.50 ppm, ^{13}C NMR = 39.52 ppm). ^{19}F NMR spectra were not externally referenced. Where NMR spectra have been recorded in $CDCl_3$:MeOH-d_4 solvent mixtures, the residual MeOH solvent signal acted as an internal reference for ^{1}H NMR and the deuterated MeOH-d_4 solvent carbon signal acted as an internal reference for ^{13}C NMR (^{1}H NMR = 3.31 ppm, ^{13}C NMR = 49.00 ppm). Chemical shifts are reported to 0.01 ppm for ^{1}H NMR spectra except in cases where two distinguishable peaks are within 0.01 ppm, in which case the shifts are reported to 0.001 ppm. Chemical shifts are reported to 0.1 ppm for ^{13}C NMR spectra except in cases where two distinguishable peaks

are within 0.1 ppm, in which case the shifts are reported to 0.01 ppm. Where diastereomers (or similar) are isolated together but full characterisation of each isomer is still possible, chemical shifts for each isomer will be reported separately. Diastereomeric (or similar) peaks that are within 0.01 ppm for ^{1}H NMR or 0.1 ppm for ^{13}C NMR but are still distinguishable will be reported according to the above guidelines but each isomer may be reported separately. Coupling constants are quoted to the nearest 0.1 Hz for ^{1}H NMR. The multiplicity of a signal is reported as such: s–singlet, d–doublet, t–triplet, q–quartet, quint.–quintet, sext.–sextet, sept.–septet, oct.–octet, non.–nonet, m–multiplet, br.–broad, app.–apparent, or combinations thereof. Structural assignments were made with the aid of DEPT135, COSY, HSQC, HMBC, 1-D nOe and 2-D NOESY experiments.

Infrared Spectroscopy

Fourier-transform infrared (FTIR) spectra were recorded from evaporated films or neat samples on a Bruker Tensor 27 spectrometer equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Selected absorption maxima are given in wavenumbers (cm^{-1}).

Mass Spectrometry

Electrospray ionisation (ESI) high resolution mass spectrometry (HMRS) spectra were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass. The error is calculated with reference to the values given.

Chemical ionisation (CI) and electron impact ionisation (EI) HRMS were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. The reagent gas used for CI was either ammonia (NH_3) or methane (CH_4) and the source conditions were adjusted to maximise sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration (as used for these experiments). The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass. The error is calculated with reference to the values given.

Melting Points

Melting points (M.P.) were obtained using a Leica VMTG heated-stage microscope equipped with a Testo 720 thermometer and are uncorrected. The solvent systems used for recrystallisation are quoted in parentheses.

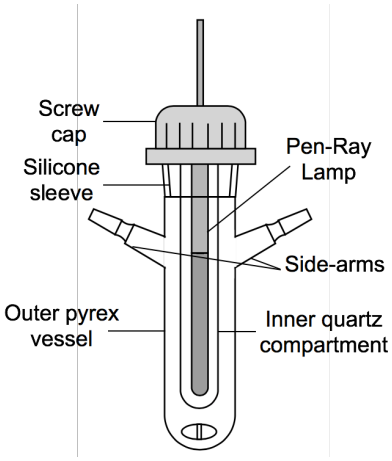
Optical Rotations

Optical rotations were recorded on a Perkin Elmer 241 Polarimeter (using the sodium D line, 589 nm). The $[\alpha]_D^{25}$ (specific rotation) values are reported in degrees ° (formal unit $deg dm^{-1} cm^3 g^{-1}$). The concentration of the sample in g/100 mL and the solvent are given in parentheses.

Photochemical Irradiations

Photochemical irradiations were performed using a UVP Pen-Ray lamp (11SC-1L) with the principle emission centred around 365 nm. Reactions were performed in a 10 mL irradiation vessel which was made by Terri Adams at the University of Oxford. The outer compartment was made of pyrex glass and fitted with inlet and outlet side-arms. The removable inner glass compartment was made of fused quartz. A silicone ring placed at the connection of the two

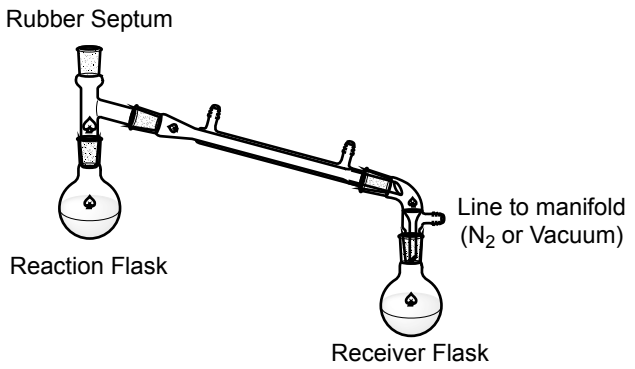
compartments served as a seal and a ring screw cap held the assembly together, allowing the UV lamp to be held within the inner compartment (Image courtesy of Jack Hoffman). Reactions on all scales were performed with 7–8 mL of solvent to ensure efficient irradiation of the reaction mixture by the Pen-Ray.



5.2 Special Experimental Setups

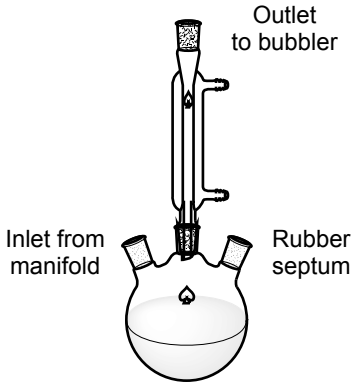
Setup A

This setup was used for the formation of temporary silicon tethers when dimethyl-dichlorosilane was employed.



Setup B

This setup was used for some olefin metathesis reactions and this will be identified where applicable.



5.3 Compound Numbering

General compounds are named and numbered according to the rules established by the International Union of Pure and Applied Chemistry (IUPAC). Alternative numbering is sometimes used to ensure consistency across compound classes. Compounds synthesised *en route* to (+)–lophotoxin (**1**) are named according to the rules established by the IUPAC and numbered according to the system reported by Fenical and co-workers (Figure 5.1).[2]

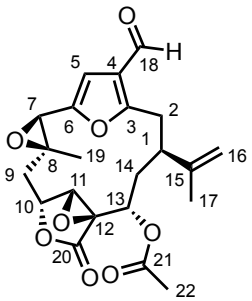


Figure 5.1 (+)-Lophotoxin (**1**) numbering scheme

Thiostrepton (**460**) derivatives are numbered according to the system reported by Henses and Albers-Schönberg. The relevant fragments are differentially coloured below for clarity (Figure 5.2).[210]

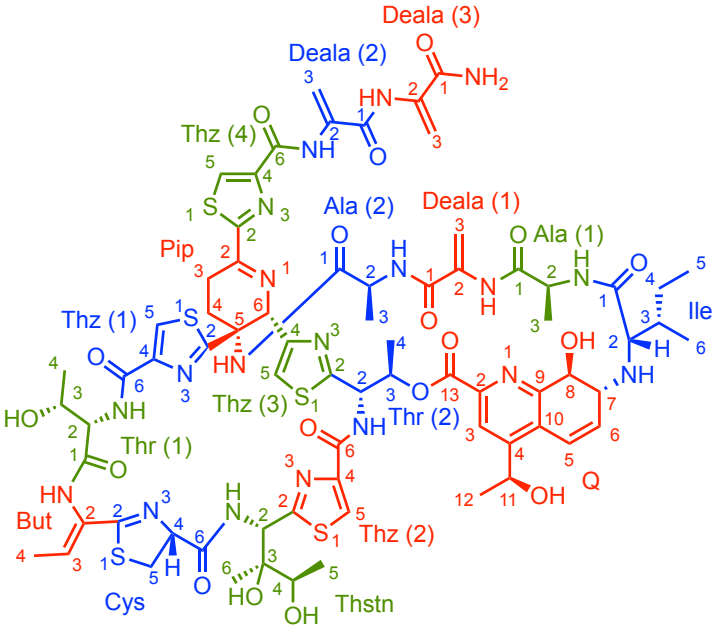
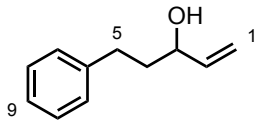


Figure 5.2 Thiostrepton (**460**) numbering scheme

5.4 Experimental Procedures

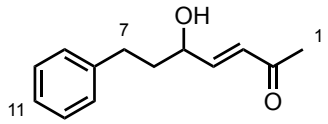
5-Phenylpen-1-en-3-ol (**209**)



3-Phenylpropanal (**229**, 12.0 mL, 91.2 mmol) was added dropwise *via* syringe pump over 2 h to a solution of vinylmagnesium bromide (1 M in THF, 100 mL, 100 mmol) in THF (200 mL, 0.3 M) at –78 °C (dry ice/acetone bath). The reaction was removed from the cold bath and stirred for 2.5 h, warming slowly to rt. The reaction was quenched at rt by dropwise addition of NH_4Cl (sat., aq., 100 mL) and diluted with H_2O (100 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:EtOAc) to afford alcohol **209** as a colourless oil (13.5 g, 92%). Data is consistent with that reported in the literature.[211]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.09 (m, 5 H, 2 × H-7, 2 × H-8 and H-9), 5.84 (ddd, *J* = 16.7, 10.4, 6.1 Hz, 1 H, H-2), 5.18 (dt, *J* = 17.2, 1.4 Hz, 1 H, H-1$_{trans}$), 5.07 (dt, *J* = 10.4, 1.3 Hz, 1 H, H-1$_{cis}$), 4.06 (q, *J* = 6.1 Hz, 1 H, H-3), 2.75–2.57 (m, 2 H, 2 × H-5) and 1.85–1.74 ppm (m, 2 H, 2 × H-4); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 141.9 (C-6), 141.0 (C-2), 128.5 (2 C, 2 × C-7 or 2 × C-8), 128.4 (2 C, 2 × C-7 or 2 × C-8), 125.9 (C-9), 115.0 (C-1), 72.5 (C-3), 38.5 (C-4) and 31.7 ppm (C-5).

(E)-5-Hydroxy-7-phenylhept-3-en-2-one (**210**)

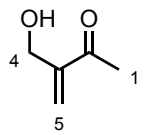


Notes: Experimental setup B (Section 5.3) was used for this reaction. Glassware was not flame dried but was charged with N_2 and kept under a positive N_2 pressure *via* a manifold line prior to use. Dry PhMe was sparged with N_2 for *ca*. 10 min prior to use.

Methyl vinyl ketone (4.06 mL, 50.0 mmol) was added to a solution of alcohol **209** (1.62 g, 10.0 mmol) in PhMe (40 mL, 0.25 M) at rt. Hoveyda–Grubbs second generation catalyst (157 mg, 0.250 mmol) was added under a positive N_2 pressure and the reaction then stirred at rt for 22 h under a gentle flow of N_2. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (1:1–2:3 pentane:Et_2O) to afford enone **210** as a yellow oil (1.76 g, 86%). Data is consistent with that reported in the literature.[61]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26–7.10 (m, 5 H, 2 × H-9, 2 × H-10 and H-11), 6.69 (dd, *J* = 16.0, 5.0 Hz, 1 H, H-4), 6.21 (dd, *J* = 16.0, 1.6 Hz, 1 H, H-3), 4.32–4.23 (m, 1 H, H-5), 2.80–2.61 (m, 2 H, 2 × H-7), 2.19 (s, 3 H, 3 × H-1) and 1.91–1.83 ppm (m, 2 H, 2 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.6 (C-2), 148.7 (C-4), 141.3 (C-8), 129.3 (C-3), 128.7 (2 C, 2 × C-9 or 2 × C-10), 128.6 (2 C, 2 × C-9 or 2 × C-10), 126.3 (C-11), 70.6 (C-5), 38.2 (C-6), 31.6 (C-7) and 27.6 ppm (C-1).

3-(Hydroxymethyl)but-3-en-2-one (**236**)

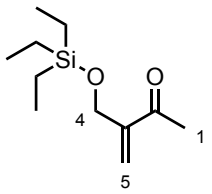


Paraformaldehyde (2.59 g, 86.3 mmol) and DABCO (484 mg, 4.31 mmol) were sequentially added as single portions to a solution of methyl vinyl ketone (3.50 mL, 43.2 mmol) in diox-

ane:H_2O (1:1, 0.1 M, 430 mL) at rt and the reaction then stirred at rt for 2 h. The reaction was diluted with EtOAc (200 mL) and brine (200 mL). The layers were separated and the aqueous phase extracted with EtOAc (5 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (2:1 pentane:EtOAc) to afford alcohol **236** as a pale yellow oil (3.30 g, 76%). Data is consistent with that reported in the literature.[212]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.12 (s, 1 H, H-5), 6.04 (t, *J* = 1.4 Hz, 1 H, H-5), 4.32–4.30 (m, 2 H, 2 × H-4) and 2.37 ppm (s, 3 H, 3 × H-1); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 200.5 (C-2), 147.3 (C-3), 126.3 (C-5), 62.6 (C-4) and 26.1 ppm (C-1).

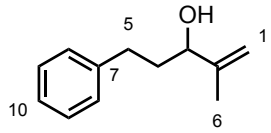
3-(((Triethylsilyl)oxy)methyl)but-3-en-2-one (**237**)



DMAP (24.4 mg, 0.200 mmol) was added to a solution of alcohol **236** (200 mg, 2.00 mmol) in CH_2Cl_2 (8 mL, 0.25 M) at 0 °C (ice/H_2O bath). Et_3N (0.560 mL, 4.00 mmol) and triethylchlorosilane (0.400 mL, 2.40 mmol) were sequentially added dropwise and the reaction then stirred at 0 °C for 2 h. The reaction was quenched at 0 °C by addition of $NaHCO_3$ (sat., aq., 10 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1–19:1 pentane:Et_2O) to afford silyl ether **237** as a colourless oil (292 mg, 68%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.16–6.11 (m, 2 H, 2 × H-5), 4.37 (t, *J* = 2.0 Hz, 2 H, 2 × H-4), 2.35 (s, 3 H, 3 × H-1), 0.95 (t, *J* = 7.9 Hz, 9 H, 3 × $SiCH_2C\underline{H}_3$) and 0.62 ppm (q, *J* = 7.9 Hz, 6 H, 3 × $SiC\underline{H}_2CH_3$), **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.4 (C-2), 147.9 (C-3), 124.4 (C-5), 60.7 (C-4), 26.3 (C-1), 6.9 (3 C, 3 × $SiCH_2\underline{C}H_3$) and 4.5 ppm (3 C, 3 × $Si\underline{C}H_2CH_3$); **FTIR** ν_{max} (thin film): 1677, 1389, 1085 and 728 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{11}H_{22}O_2NaSi^+$ $[M+Na]^+$ 237.1281; found 237.1283 (Δ 0.84 ppm).

2-Methyl-5-phenylpent-1-en-3-ol (**238**)

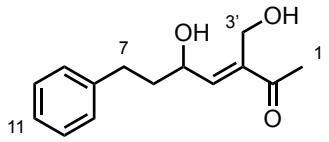


3-Phenylpropionaldehyde (**229**, 2.00 mL, 14.4 mmol) was added dropwise *via* syringe pump over 2 h to a solution of isopropenylmagnesium bromide (0.5 M in THF, 31.6 mL, 15.8 mmol) in THF (16.4 mL, 0.3 M final concentration) at –78 °C (dry ice/acetone bath). The reaction was removed from the cold bath and stirred for 4 h, warming slowly to rt. The reaction was quenched at rt by dropwise addition of NH_4Cl (sat., aq., 20 mL) and diluted with H_2O (20 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before bring purified by flash column chromatography (4:1 pentane:Et_2O) to afford alcohol **238** as a pale yellow oil (1.76 g, 69%). Data is consistent with that reported in the literature.[213]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.18 (m, 5 H, 2 × H-8, 2 × H-9 and H-10), 5.01–4.97 (m, 1 H, H-1), 4.90–4.88 (m, 1 H, H-1), 4.10 (t, *J* = 6.5 Hz, 1 H, H-3), 2.78–2.61 (m, 2 H, 2 × H-5), 1.95–1.84 (m, 2 H, 2 × H-4) and 1.76 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$,

101 MHz): δ = 147.5 (C-2), 142.1 (C-7), 128.6 (2 C, 2 × C-8 or 2 × C-9), 128.5 (2 C, 2 × C-8 or 2 × C-9), 125.9 (C-10), 111.4 (C-1), 75.4 (C-3), 36.7 (C-4), 32.0 (C-5) and 17.7 (C-6) ppm.

(E)-5-Hydroxy-3-(hydroxymethyl)-7-phenylhept-3-en-2-one (**243**)



Method A:

Hoveyda–Grubbs second generation catalyst (9.0 mg, 14 μmol) was added to a two-necked round-bottomed flask fitted with a reflux condenser and the flask then evacuated and charged with Ar (× 3). PhMe (6 mL) and a solution of TST **264** (45.4 mg, 0.143 mmol) in PhMe (1.0 mL + 0.2 mL rinse, 20 mM final concentration) were added rt and the reaction then stirred at 80 °C for 24 h. The reaction was cooled to rt and directly concentrated *in vacuo* before being redissolved in THF:H_2O (1:1, 7.2 mL, 20 mM). Pyridinium *p*-toluenesulfonic acid (36.0 mg, 0.143 mmol) was added at rt and the reaction then stirred at 40 °C overnight. The reaction was cooled to rt, quenched by addition of $NaHCO_3$ (sat., aq., 5 mL) and diluted with EtOAc (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (1:1 pentane:EtOAc) to afford diol **243** as a yellow oil (16 mg, 48%).

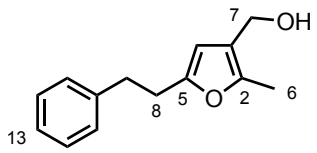
Method B:

Tetrabutylammonium fluoride (1 M in THF, 1.40 mL, 1.40 mmol) was added to a solution of silaketal **275** (98.0 mg, 0.283 mmol) in THF (2.8 mL, 0.1 M) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 1 h. The reaction was warmed to rt and dry loaded directly onto SiO_2 before being purified by flash column chromatography (7:3:0–14:6:1

pentane:EtOAc:MeOH) to afford diol **243** as a colourless oil (51.1 mg, 77%). The geometry was confirmed by NOESY NMR (Section 5.5.3).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.15 (m, 5 H, 2 × H-9, 2 × H-10 and H-11), 6.62 (d, *J* = 7.9 Hz, 1 H, H-4), 4.63 (q, *J* = 7.2 Hz, 1 H, H-5), 4.34 (dd, *J* = 12.6, 4.0 Hz, 1 H, H-3′), 4.23 (dd, *J* = 12.5, 5.3 Hz, 1 H, H-3′), 2.87–2.66 (m, 3 H, 2 × H-7, C-3′ OH), 2.59 (br. s, 1 H, C-5 OH), 2.32 (s, 3 H, 3 × H-1), 2.09–1.99 (m, 1 H, H-6) and 1.94–1.84 ppm (m, 1 H, H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 201.0 (C-2), 147.0 (C-4), 141.0 (C-3 or C-8), 139.8 (C-3 or C-8), 128.6 (2 C, 2 × C-9 or 2 × C-10), 128.4 (2 C, 2 × C-9 or 2 × C-10), 126.2 (C-11), 67.6 (C-5), 56.9 (C-3′), 38.1 (C-6), 31.4 (C-7) and 25.6 ppm (C-1); **FTIR** ν_{max} (thin film): 3391, 2926, 2341, 1667, 1496, 1356, 1027 and 700 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{14}H_{19}O_3^+$ $[M+H]^+$ 235.1329; found 235.1330 (Δ 0.43 ppm).

(2-Methyl-5-phenethylfuran-3-yl)methanol (**262**)



Method A:

Note: dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (9.3 mg, 15 μmol) was added to a two-necked round-bottomed flask fitted with a reflux condenser and the flask then evacuated and charged with Ar (× 3). PhMe (28 mL) and a solution of TST **264** (47.4 mg, 0.149 mmol) in PhMe (1.5 mL + 0.5 mL rinse, 5 mM final concentration) were added at rt and the reaction then stirred at 80 °C for 24 h. The reaction was cooled to rt and directly concentrated *in vacuo* before being redissolved in α,α,α-trifluorotoluene:H_2O (9:1, 3 mL, 50 mM). Pyridinium *p*-toluenesulfonic acid (150 mg, 0.597 mmol) was added at rt and the reaction then stirred at 60 °C

for 18 h. The reaction mixture cooled to rt and diluted with H_2O (5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (7:3 pentane:EtOAc) to afford furan **262** as a yellow oil (10.3 mg, 32%).

Method B:

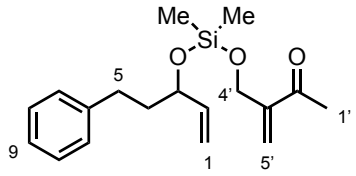
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm prior to use.

Acetyl chloride (54 μL, 0.46 mmol) was added dropwise to a solution of silaketal **275** (52.8 mg, 0.152 mmol) and MeOH (19 μL, 0.50 mmol) in $CHCl_3$ (3 mL, 50 mM) at 0 °C (ice/ H_2O bath). The reaction was removed from the cold bath and stirred for 2 h, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford furan **276** which was used directly without further purification. Furan **276** was redissolved in acetone:H_2O (1:1, 3 mL, 50 mM) and $AgNO_3$ (51.8 mg, 0.305 mmol) was added at rt. The reaction flask was covered in aluminium foil and the reaction then stirred at rt overnight. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (3:1 pentane:EtOAc) to afford furan **262** as a yellow oil (13.4 mg, 41%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.18 (m, 2 H, 2 × H-12), 7.16–7.10 (m, 3 H, 2 × H-11 and H-13), 5.89 (s, 1 H, H-4), 4.34 (s, 2 H, 2 × H-7), 2.91–2.74 (m, 4 H, 2 × H-8 and 2 ×

H-9), 2.19 (s, 3 H, 3 × H-6) and 1.27 ppm (br. s, 1 H, OH); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 153.6 (C-5), 147.5 (C-2), 141.4 (C-10), 128.51 (2 C, 2 × C-11 or 2 × C-12), 128.46 (2 C, 2 × C-11 and 2 × C-12), 126.2 (C-13), 119.4 (C-3), 106.4 (C-4), 56.9 (C-7), 34.5 (C-9), 30.0 (C-8) and 11.7 ppm (C-6); **FTIR** ν_{max} (thin film): 3341, 2921, 1580, 1496, 1454, 1213, 1001, 937, 749 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{14}H_{16}O_2Na^+$ $[M+Na]^+$ 239.1043; found 239.1044 (Δ 0.42 ppm).

3-(((Dimethyl((5-phenylpent-1-en-3-yl)oxy)silyl)oxy)methyl)but-3-en-2-one (**264**)



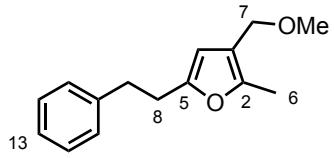
Notes: Experimental setup A (Section 5.3) was used for this reaction. Glassware was flame dried under vacuum, charged with N_2 and kept under a positive N_2 pressure *via* a manifold line prior to use.

The reaction flask was sequentially charged with CH_2Cl_2 (15.8 mL), pyridine (3.04 mL, 37.6 mmol) and Me_2SiCl_2 (4.56 mL, 37.6 mmol) and the mixture cooled to 0 °C (ice/H_2O bath). A solution of alcohol **209** (305 mg, 1.88 mmol) in CH_2Cl_2 (2.8 mL + 0.2 mL rinse, 0.1 M final concentration) was added at 0 °C *via* syringe pump over *ca*. 30 min. The reaction was removed from the cold bath and stirred overnight, warming slowly to rt. The reaction flask was subsequently placed in a rt water bath and the receiver flask in a –78 °C bath (dry ice/acetone). The reaction was slowly placed under vacuum *via* a manifold to remove CH_2Cl_2 and pyridine from the reaction mixture [CAUTION: to prevent bumping vacuum must be applied very slowly. The risk of bumping is higher once almost all solvent has been removed]. Once all CH_2Cl_2 and pyridine was removed from the reaction flask the reaction setup was re-

moved from the cold bath and placed under high vacuum for 10 min. The reaction setup was charged with N_2 and kept under a positive N_2 pressure *via* a manifold line. The reaction flask was charged with dry CH_2Cl_2 (16.8 mL) and pyridine (1.52 mL, 18.8 mmol). A solution of alcohol **236** (226 mg, 2.26 mmol) in CH_2Cl_2 (1.5 mL + 0.5 mL rinse, 0.1 M final concentration) was added at rt *via* syringe over 1–2 min and the reaction then stirred at rt for 10 min. The reaction was directly concentrated *in vacuo* in air atmosphere before being diluted with Et_2O (20 mL) and $NaHCO_3$ (sat., aq., 20 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford TST **264** as a colourless oil (453 mg, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.22 (m, 2 H, 2 × H-8), 7.22–7.13 (m, 3 H, 2 × H-7 and H-9), 6.11 (td, *J* = 1.8, 0.8 Hz, 1 H, H-5′), 6.10 (td, *J* = 2.1, 0.8 Hz, 1 H, H-5′), 5.85 (ddd, *J* = 16.9, 10.3, 6.3 Hz, 1 H, H-2), 5.18 (dt, *J* = 17.1, 1.5 Hz, 1 H, H-1_{trans}), 5.08 (ddd, *J* = 10.3, 1.7, 1.1 Hz, 1 H, H-1_{cis}), 4.43 (t, *J* = 2.0 Hz, 2 H, 2 × H-4′), 4.30–4.20 (m, 1 H, H-3), 2.73–2.57 (m, 2 H, 2 × H-5), 2.35 (s, 3 H, 3 × H-1′), 1.94–1.73 (m, 2 H, 2 × H-4), 0.16 (s, 3 H, $SiCH_3$) and 0.16 ppm (s, 3 H, $SiCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.2 (C-2′), 147.4 (C-3′), 142.2 (C-6), 140.8 (C-2), 128.5 (2 C, 2 × C-7 or 2 × C-8), 128.5 (2 C, 2 × C-7 or 2 × C-8), 125.9 (C-9), 124.5 (C-5′), 114.7 (C-1), 73.5 (C-3), 60.6 (C-4′), 39.5 (C-4), 31.7 (C-5), 26.2 (C-1′), –2.4 ($SiCH_3$) and –2.5 ppm ($SiCH_3$); **FTIR** ν_{max} (thin film): 2922, 1676, 1258, 1086, 867 and 798 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{18}H_{26}NaO_3Si^+$ $[M+Na]^+$ 341.1543; found 341.1547 (Δ 1.17 ppm).

3-(Methoxymethyl)-2-methyl-5-phenethylfuran (**266**)

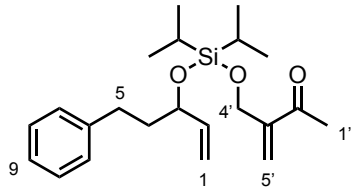


Note: dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (12.0 mg, 19.2 μmol) was added to a two-necked round-bottomed flask fitted with a reflux condenser and the flask then evacuated and charged with Ar (× 3). PhMe (36.4 mL) and a solution of TST **264** (61.0 mg, 0.192 mmol) in PhMe (1.5 mL + 0.5 mL rinse, 5 mM final concentration) were added at rt and the reaction then stirred at 80 °C for 24 h. The reaction was cooled to rt and directly concentrated *in vacuo* before being redissolved in CH_2Cl_2:MeOH (1:1, 3.8 mL, 50 mM). Pyridinium *p*-toluenesulfonate (193 mg, 0.768 mmol) was added at rt and the reaction then stirred at 40 °C overnight. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (3:2 CH_2Cl_2:pentane) to afford furan **266** as a yellow oil (34.3 mg, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.25 (m, 2 H, 2 × H-12), 7.22–7.18 (m, 3 H, 2 × H-11 and H-13), 5.93 (s, 1 H, H-4), 4.19 (s, 2 H, 2 × H-7), 3.32 (s, 3 H, OCH_3), 2.97–2.89 (m, 2 H, 2 × H-9), 2.89–2.83 (m, 2 H, 2 × H-8) and 2.26 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 153.4 (C-5), 148.2 (C-2), 141.5 (C-10), 128.50 (2 C, 2 × C-11 or 2 × C-12), 128.48 (2 C, 2 × C-11 or 2 × C-12), 126.1 (C-13), 116.6 (C-3), 106.9 (C-4), 66.1 (C-7), 57.7 (OCH_3), 34.6 (C-9), 30.1 (C-8) and 11.7 ppm (C-6); **FTIR** ν_{max} (thin film): 2922, 1579, 1454, 1191, 1089, 749 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{15}H_{19}O_2^+$ $[M+H]^+$ 231.1380; found 231.1382 (Δ 0.87 ppm).

3-(((Diisopropyl((5-phenylpent-1-en-3-yl)oxy)silyl)oxy)methyl)but-3-en-2-one (**272**)

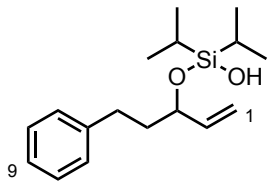


Note: Alcohol **209** was azeotroped with PhMe (× 3) and dried under high vacuum prior to use. *i*-Pr_2SiCl_2 (0.188 mL, 1.04 mmol) was added dropwise to a solution of imidazole (169 mg, 2.48 mmol) in CH_2Cl_2 (10.5 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **209** (161 mg, 0.993 mmol) in CH_2Cl_2 (1.8 mL + 0.2 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (109 mg, 1.09 mmol) in CH_2Cl_2 (1.1 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **272** as a colourless oil (262 mg, 70%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.24 (m, 2 H, 2 × H-8), 7.20–7.14 (m, 3 H, 2 × H-7 and H-9), 6.13 (app. dtd, *J* = 12.7, 2.1, 1.0 Hz, 2 H, 2 × H-5′), 5.86 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1 H, H-2), 5.19 (dt, *J* = 17.2, 1.5 Hz, 1 H, H-1$_{trans}$), 5.09 (ddd, *J* = 10.4, 1.8, 1.1 Hz, 1 H, H-1$_{cis}$), 4.49 (t, *J* = 2.1 Hz, 2 H, 2 × H-4′), 4.35 (q, *J* = 6.2 Hz, 1 H, H-3), 2.68–2.62 (m, 2 H, 2 × H-5), 2.34 (s, 3 H, 3 × H-1′), 1.93–1.78 (m, 2 H, 2 × H-4) and 1.07–1.04 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.1 (C-2′), 147.5 (C-3′), 142.3 (C-6), 140.8 (C-2), 128.4 (2 C, 2 × C-7 or 2 × C-8), 128.3 (2 C, 2 × C-7 or 2 × C-8), 125.7 (C-9), 124.1 (C-5′), 114.5 (C-1), 73.3 (C-3), 60.8 (C-4′), 39.7 (C-4), 31.1 (C-5), 26.1 (C-1′), 17.50 ($SiCH\underline{C}H_3$), 17.45 ($SiCH\underline{C}H_3$), 17.44 ($SiCH\underline{C}H_3$), 17.40 ($SiCH\underline{C}H_3$), 12.4 ($Si\underline{C}HCH_3$) and 12.3 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2867, 1677, 1087, 1031, 884, 750

and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{22}H_{34}NaO_3Si^+$ $[M+Na]^+$ 397.2169; found 397.2160 (Δ 2.27 ppm).

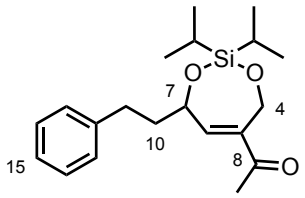
Diisopropyl((5-phenylpent-1-en-3-yl)oxy)silanol (**273**)



i-Pr_2SiCl_2 (0.166 mL, 0.667 mmol) was added dropwise to a solution of imidazole (95.0 mg, 1.40 mmol) in CH_2Cl_2 (6.7 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **209** (103 mg, 0.635 mmol) in CH_2Cl_2 (1.2 mL + 0.1 mL rinse) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 3 h. The reaction mixture was dry loaded directly onto SiO_2 and purified by flash column chromatography (CH_2Cl_2) to afford silanol **273** as a colourless oil (144 mg, 77%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.15 (m, 5 H, 2 × H-7, 2 × H-8 and H-9), 5.91 (ddd, *J* = 17.0, 10.3, 6.4 Hz, 1 H, H-2), 5.23 (dt, *J* = 17.2, 1.6 Hz, 1 H, H-1*trans*), 5.11 (dt, *J* = 10.4, 1.5 Hz, 1 H, H-1*cis*), 4.38 (q, *J* = 6.2 Hz, 1 H, H-3), 2.76–2.59 (m, 2 H, 2 × H-5), 2.01–1.76 (m, 3 H, 2 × H-4 and SiOH) and 1.17–0.90 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 142.4 (C-6), 141.5 (C-2), 128.5 (2 C, 2 × C-7 or 2 × C-8), 128.5 (2 C, 2 × C-7 or 2 × C-8), 125.9 (C-9), 114.5 (C-1), 73.2 (C-3), 39.8 (C-4), 31.4 (C-5), 17.4 (2 C, 2 × $SiCH\underline{C}H_3$), 17.31 ($SiCH\underline{C}H_3$), 17.27 ($SiCH\underline{C}H_3$), 12.8 ($Si\underline{C}HCH_3$) and 12.7 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 3460, 2944, 2866, 1085, 1032, 992, 921, 884, 807, 747 and 697 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{17}H_{28}O_2NaSi^+$ $[M+Na]^+$ 315.1751; found 315.1751 (Δ 0.00 ppm).

1-(2,2-Diisopropyl-7-phenethyl-4,7-dihydro-1,3,2-dioxasilepin-5-yl)ethanone (**275**)

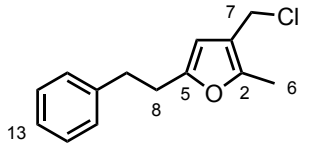


Note: dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (35.1 mg, 56.0 μmol) was added to a round-bottomed flask fitted with a reflux condenser and the system then evacuated and charged with N_2 (× 3). PhMe (220 mL) and a solution of TST **272** (420 mg, 1.12 mmol) in PhMe (3 mL + 1 mL rinse, 5 mM final concentration) were added at rt and the reaction then heated to 80 °C for 24 h under N_2 atmosphere supplied *via* a manifold. The reaction mixture was cooled to rt and directly concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford silaketal **275** as a yellow oil (315 mg, 81%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.17 (m, 5 H, 2 × H-13, 2 × H-14 and H-15), 6.59 (dd, *J* = 3.1, 1.8 Hz, 1 H, H-6), 4.91–4.85 (m, 1 H, H-7), 4.83 (dd, *J* = 15.3, 1.1 Hz, 1 H, H-4), 4.70 (ddd, *J* = 15.3, 2.7, 1.9 Hz, 1 H, H-4), 2.95–2.72 (m, 2 H, 2 × H-11), 2.25 (s, 3 H, 3 × H-9), 2.10–1.96 (m, 2 H, 2 × H-10), 1.12–1.08 (m, 7 H, $SiCH(CH_3)_2$) and 1.07–1.03 ppm (m, 7 H, $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.6 (C-8), 146.0 (C-6), 141.8 (C-5 or C-12), 141.6 (C-5 or C-12), 128.5 (2 C, 2 × C-13 or 2 × C-14), 128.5 (2 C, 2 × C-13 or 2 × C-14), 126.0 (C-15), 70.3 (C-7), 59.4 (C-4), 39.3 (C-10), 31.7 (C-11), 25.9 (C-9), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.22 ($SiCH\underline{C}H_3$), 17.17 ($SiCH\underline{C}H_3$), 12.2 ($Si\underline{C}HCH_3$) and 12.1 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2866, 1669, 1464, 1242, 1130, 1105, 1032, 993, 885, 788, 748 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{20}H_{30}NaO_3Si^+$ $[M+Na]^+$ 369.1856; found 369.1855 (Δ 0.27 ppm).

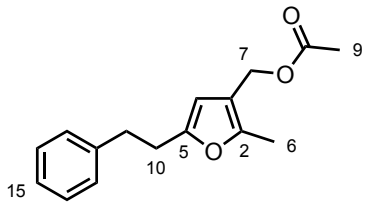
3-(Chloromethyl)-2-methyl-5-phenethylfuran (**276**)



Acetyl chloride (0.213 mL, 3.00 mmol) was added to a solution of MeOH (0.121 mL, 3.00 mmol) in $CHCl_3$ (3 mL, 1 M) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. Silaketal **275** (51.4 mg, 0.141 mmol) was dissolved in this solution (3.0 mL, 50 mM, transferred *via* syringe) and the reaction then stirred for 1 h, warming slowly to rt. The reaction was directly concentrated *in vacuo*, redissolved in Et_2O (10 mL) and washed with NaOH (1 M, aq., 10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (97:3 pentane:Et_2O) to afford furan **276** as a yellow oil (18.7 mg, 53%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.09 (m, 5 H, 2 × H-11, 2 × H-12 and H-13), 5.88 (s, 1 H, H-4), 4.33 (s, 2 H, 2 × H-7), 2.90–2.72 (m, 4 H, 2 × H-8 and 2 × H-9) and 2.19 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 153.8 (C-5), 148.4 (C-2), 141.2 (C-10), 128.4 (2 C, 2 × C-11 or 2 × C-12), 128.3 (2 C, 2 × C-11 or 2 × C-12), 126.1 (C-13), 116.8 (C-3), 106.5 (C-4), 38.3 (C-7), 34.3 (C-9), 29.9 (C-8) and 11.5 ppm (C-6). **HRMS**: Not found using any ionisation method.

(2-Methyl-5-phenethylfuran-3-yl)methyl acetate (**277**)



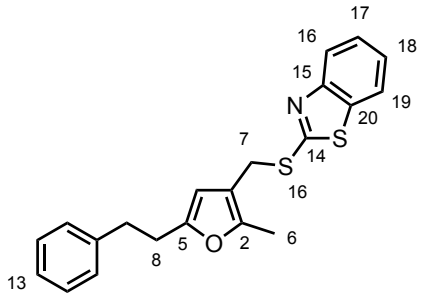
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (60.0 µL, 0.837 mmol) was added dropwise to a solution of silaketal **275** (58.0 mg, 0.167 mmol) and MeOH (21.0 µL, 0.502 mmol) in $CHCl_3$ (3.3 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford furan **276** which was used directly without further purification. Furan **276** was redissolved in DMF (1.7 mL, 0.1 M) at rt and anhydrous K_2CO_3 (69.4 mg, 502 mmol) and AcOH (38.0 µL, 0.664 mmol) were added at rt. The reaction was stirred at 40 °C for 16 h. The reaction was cooled to rt, quenched by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (15:1 pentane:Et_2O) to afford ester **277** as a colourless oil (33.0 mg, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.20 (m, 2 H, 2 × H-14), 7.19–7.13 (m, 3 H, 2 × H-13 and H-15), 5.90 (s, 1 H, H-4), 4.82 (s, 2 H, 2 × H-7), 2.93–2.78 (m, 4 H, 2 × H-10 and 2 × H-11), 2.24 (s, 3 H 3 × H-6) and 2.02 ppm (s, 3 H, 3 × H-9); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 171.2 (C-8), 153.6 (C-5), 149.2 (C-2), 141.4 (C-12), 128.52 (2 C, 2 × C-13 or 2 × C-14),

128.46 (2 C, 2 × C-13 or 2 × C-14), 126.2 (C-15), 114.9 (C-3), 107.0 (C-4), 58.4 (C-7), 34.0 (C-11), 30.0 (C-10), 21.2 (C-9) and 11.7 ppm (C-6); **FTIR** ν_{max} (thin film): 3028, 2923, 1738, 1454, 1372, 1232, 1022, 949, 750 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{16}H_{18}O_3Na^+$ $[M+Na]^+$ 281.1148; found 281.1149 (Δ 0.36 ppm).

2-(((2-Methyl-5-phenethylfuran-3-yl)methyl)thio)benzo[d]thiazole (**278**)



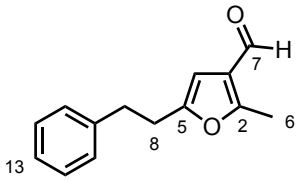
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (55.0 μL, 0.776 mmol) was added dropwise to a solution of silaketal **275** (53.2 mg, 0.154 mmol) and MeOH (19.0 μL, 0.460 mmol) in $CHCl_3$ (3.1 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford furan **276** which was used directly without further purification. Anhydrous K_2CO_3 (85.0 mg, 0.614 mmol) and 2-mercaptobenzothiazole (77.0 mg, 0.460 mmol) were sequentially added to a solution of furan **276** in DMF (1.5 mL, 0.1 M) at rt and the reaction then stirred at 40 °C for 16 h. The reaction was cooled to rt and diluted with $NaHCO_3$ (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous

$MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford thiazole **278** as a colourless oil (44.0 mg, 78%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.87–7.83 (m, 1 H, H-16), 7.74–7.70 (m, 1 H, H-19), 7.41–7.36 (m, 1 H, H-17), 7.29–7.19 (m, 3 H, 2 × H-12 and H-18), 7.17–7.10 (m, 3 H, 2 × H-11 and H-13), 5.92 (s, 1 H, H-4), 4.30 (s, 2 H, 2 × H-7), 2.90–2.84 (m, 2 H, 2 × H-9), 2.82–2.76 (m, 2 H, 2 × H-8) and 2.27 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 166.7 (C-14), 153.6 (C-5 or C-15), 153.3 (C-5 or C-15), 148.2 (C-2), 141.3 (C-10), 135.5 (C-20), 128.5 (2 C, 2 × C-11 or 2 × C-12), 128.5 (2 C, 2 × C-11 or 2 × C-12), 126.2 (2 C, C-13 and C-17), 124.4 (C-18), 121.6 (C-16), 121.1 (C-19), 114.4 (C-3), 107.1 (C-4), 34.5 (C-9), 30.1 (C-8), 29.0 (C-7) and 11.9 ppm (C-6); **FTIR** ν_{max} (thin film): 1455, 1426, 993, 754, 726 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{21}H_{20}NOS_2^+$ $[M+H]^+$ 366.0981; found 366.0981 (Δ 0.00 ppm).

2-Methyl-5-phenethylfuran-3-carbaldehyde (**279**)



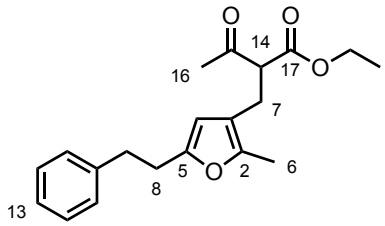
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (55.0 μL, 0.776 mmol) was added dropwise to a solution of silaketal **275** (53.8 mg, 0.153 mmol) and MeOH (19.0 μL, 0.460 mmol) in $CHCl_3$ (3.1 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to

afford furan **276** which was used directly without further purification. *N*-methylmorpholine-*N*-oxide (72.7 mg, 0.621 mmol) was added to a solution of furan **276** in THF (1.5 mL, 0.1 M) at rt and the reaction then stirred at 70 °C for 21 h. The reaction was cooled to rt and diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (17:3 pentane:Et_2O) to afford aldehyde **279** as a colourless oil (16.0 mg, 48%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.81 (s, 1 H, H-7), 7.26–7.19 (m, 2 H, 2 × H-12), 7.19–7.09 (m, 3 H, 2 × H-11 and H-13), 6.21 (s, 1 H, H-4), 2.92–2.86 (m, 2 H, 2 × H-9), 2.86–2.81 (m, 2 H, 2 × H-8) and 2.49 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 184.9 (C-7), 161.1 (C-2), 155.3 (C-5), 140.7 (C-10), 128.6 (2 C, 2 × C-11 or 2 × C-12), 128.4 (2 C, 2 × C-11 or 2 × C-12), 126.4 (C-13), 123.5 (C-3), 103.3 (C-4), 34.1 (C-9), 29.6 (C-8) and 12.7 ppm (C-6); **FTIR** ν_{max} (thin film): 1678, 1578, 1418, 821 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{14}H_{15}O_2^+$ $[M+H]^+$ 215.1067; found 215.1067 (Δ 0.00 ppm).

Ethyl 2-((2-methyl-5-phenethylfuran-3-yl)methyl)-3-oxobutanoate (**280**)



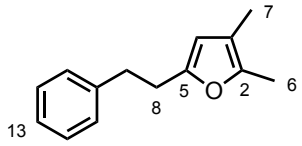
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (54.0 μL, 0.766 mmol) was added dropwise to a solution of silaketal **275** (53.1 mg, 0.153 mmol) and MeOH (19.0 μL, 0.460 mmol) in $CHCl_3$ (3.1 mL, 50 mM) at 0 °C

(ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford furan **276** which was used directly without further purification. NaI (2.3 mg, 15 μmol), anhydrous K_2CO_3 (84.7 mg, 613 mmol) and ethyl acetoacetate (59.0 μL, 0.460 mmol) were sequentially added to a solution of furan **276** in DMF (1.5 mL, 0.1 M) at rt and the reaction then stirred at 40 °C for 20 h. The reaction was cooled to rt and diluted with $NaHCO_3$ (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (CH_2Cl_2) to afford furan **280** as a colourless oil (37.2 mg, 74%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.23 (m, 2 H, 2 × H-12), 7.21–7.12 (3 H, 2 × H-11 and H-13), 5.70 (s, 1 H, H-4), 4.14 (q, *J* = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.58 (t, *J* = 7.6 Hz, 1 H, H-14), 2.92–2.75 (m, 6 H, 2 × H-7, 2 × H-8 and 2 × H-9), 2.17 (s, 3 H, 3 × H-6), 2.16 (s, 3 H, 3 × H-16) and 1.22 ppm (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 203.0 (C-15), 169.4 (C-17), 153.1 (C-5), 146.7 (C-2), 141.4 (C-10), 128.5 (4 C, 2 × C-11, 2 × C-12), 126.1 (C-13), 115.5 (C-3), 106.8 (C-4), 61.6 ($O\underline{C}H_2CH_3$), 60.2 (C-14), 34.5 (C-9), 30.0 (C-8), 29.9 (C-16), 23.9 (C-7), 14.2 ($OCH_2\underline{C}H_3$) and 11.5 ppm (C-6); **FTIR** ν_{max} (thin film): 2923, 1740, 1716, 1209, 1181, 1146 and 700 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{20}H_{25}O_4^+$ $[M+H]^+$ 329.1747; found 329.1748 (Δ 0.30 ppm).

2,3-Dimethyl-5-phenethylfuran (**281**)



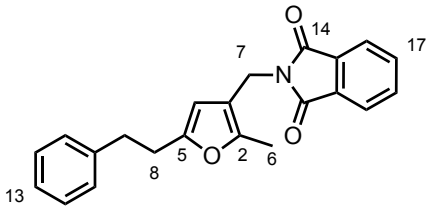
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (59.0 μL, 0.833 mmol) was added dropwise to a solution of silaketal **275** (57.7 mg, 0.167 mmol) and MeOH (21.0 μL, 0.500 mmol) in $CHCl_3$ (3.3 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford furan **276** which was used directly without further purification. H_2O (50 μL, 2.6 μL/ 1 mg $NaBH_4$), $NaBH_4$ (19.0 mg, 0.500 mmol) and tributylhexadecylphosphonium bromide (8.5 mg, 17 μmol) were sequentially added to a solution of furan **276** in PhMe (1.7 mL, 0.1 M) at rt and the reaction then stirred at 40 °C. After 4 h additional $NaBH_4$ (19.0 mg, 0.500 mmol) was added and the reaction then stirred at 60 °C for a further 2 h. The reaction was cooled to rt and diluted with H_2O (10 mL) and EtOAc (10 mL). The layers were separated and the organic phase washed with brine (10 mL). The combined aqueous layers were extracted with EtOAc (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (pentane) to afford furan **281** as a colourless oil (24.3 mg, 73%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.19 (m, 5 H, 2 × H-11, 2 × H-12 and H-13), 5.78 (s, 1 H, H-4), 2.98–2.91 (m, 2 H, 2 × H-9), 2.86 (m, 2 H, 2 × H-8), 2.20 (s, 3 H, 3 × H-6) and

1.92 ppm (s, 3 H, 3 × H-7); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 152.5 (C-5), 145.5 (C-2), 141.7 (C-10), 128.5 (4 C, 2 × C-11 and 2 × C-12), 126.1 (C-13), 114.3 (C-3), 108.4 (C-4), 34.7 (C-9), 30.1 (C-8), 11.4 (C-6) and 10.0 ppm (C-7); **FTIR** ν_{max} (thin film): 1767, 1453, 934, 747 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{14}H_{17}O^+$ $[M+H]^+$ 201.1274; found 201.1276 (Δ 0.99 ppm).

2-((2-Methyl-5-phenethylfuran-3-yl)methyl)isoindoline-1,3-dione (**282**)



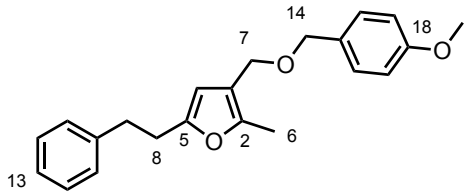
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (55.0 μL, 0.776 mmol) was added dropwise to a solution of silaketal **275** (53.8 mg, 0.153 mmol) and MeOH (19.0 μL, 0.460 mmol) in $CHCl_3$ (3.1 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford furan **276** which was used directly without further purification. NaI (2.3 mg, 15 μmol) and phthalimide potassium salt (86.3 mg, 0.466 mmol) were sequentially added to a solution of furan **276** in DMF (1.5 mL, 0.1 M) at rt and the reaction then stirred at 40 °C for 4 h. The reaction was cooled to rt and diluted with $NaHCO_3$ (10 mL) and Et_2O (10 ml). The layers were separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concen-

trated *in vacuo* before being purified by flash column chromatography (17:3 pentane:Et_2O) to afford amide **282** as a white solid (45.0 mg, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.83 (dd, *J* = 5.4, 3.0 Hz, 2 H, 2 × H-17), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2 H, 2 × H-16), 7.28–7.12 (m, 5 H, 2 × H-11, 2 × H-12 and H-13), 5.99 (s, 1 H, H-4), 4.56 (s, 2 H, 2 × H-7), 2.92–2.84 (m, 2 H, 2 × H-9), 2.84–2.75 (m, 2 H, 2 × H-8) and 2.39 ppm (3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 168.2 (2 C, 2 × C-14), 153.3 (C-5), 148.5 (C-2), 141.4 (C-10), 134.0 (2 C, 2 × C-16), 132.4 (2 C, 2 × C-15), 128.5 (2 C, 2 × C-11 or 2 × C-12), 128.4 (2 C, 2 × C-11 or 2 × C-12), 126.1 (C-13), 123.4 (2 C, 2 × C-17), 115.2 (C-3), 107.4 (C-4), 34.5 (C-9), 32.8 (C-7), 30.1 (C-8) and 11.7 ppm (C-6); **FTIR** ν_{max} (thin film): 1710, 1392, 934, 730, 712 and 700 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{22}H_{20}O_3N^+$ $[M+H]^+$ 346.1438; found 346.1439 (Δ 0.29 ppm); **M.P.** 123–125°C ($CHCl_3$).

3-(((4-Methoxybenzyl)oxy)methyl)-2-methyl-5-phenethylfuran (**283**)



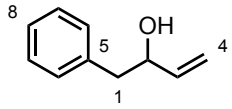
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (53.0 µL, 0.743 mmol) was added dropwise to a solution of silaketal **275** (51.5 mg, 0.149 mmol) and MeOH (18.0 µL, 0.446 mmol) in $CHCl_3$ (3 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to

afford furan **276** which was used directly without further purification. Concurrently, *p*-methoxybenzyl alcohol (55.0 μL, 336 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 24.0 mg, 594 mmol) in DMF (1 mL) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 15 min. A solution of furan **276** in DMF (1 mL + 0.5 mL rinse) was added dropwise at 0 °C, the reaction removed from the cold bath and stirred for 90 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of H_2O (2 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford ether **283** as a colourless oil (38.0 mg, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.20 (m, 7 H, 2 × H-11, 2 × H-12, H-13 and 2 × H-16), 6.92 (d, *J* = 8.6 Hz, 2 H, 2 × H-17), 5.99 (s, 1 H, H-4), 4.46 (s, 2 H, 2 × H-14), 4.29 (s, 2 H, 2 × H-7), 3.85 (s, 3 H, OCH_3), 3.01–2.94 (m, 2 H, 2 × H-9), 2.94–2.85 (m, 2 H, 2 × H-8) and 2.26 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.3 (C-18), 153.3 (C-5), 148.2 (C-2), 141.5 (C-10), 130.6 (C-15), 129.5 (2 C, 2 × C-16), 128.5 (4 C, 2 × C-11 and 2 × C-12), 126.1 (C-13), 116.7 (C-3), 113.9 (2 C, 2 × C-17), 107.1 (C-4), 71.3 (C-14), 63.3 (C-7), 55.4 (OCH_3), 34.6 (C-9), 30.1 (C-8) and 11.8 ppm (C-6); **FTIR** ν_{max} (thin film): 2920, 2856, 1512, 1246, 1067, 1035, 818 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{22}H_{25}O_3^+$ $[M+H]^+$ 337.1798; found 337.1800 (Δ 0.59 ppm).

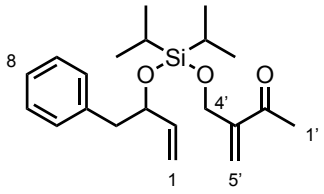
1-Phenylbut-3-en-2-ol (**S1**)



Phenylacetaldehyde (2.00 mL, 17.0 mmol) was added dropwise over 1 h *via* syringe pump to a solution of vinylmagnesium bromide (1 M in THF, 18.7 mL, 18.7 mmol) in THF (56 mL, 0.3 M) at 0 °C (ice/water bath). The reaction was stirred at 0 °C for 4 h. The reaction was quenched at 0 °C by dropwise addition of NH_4Cl (sat., aq., 20 mL), removed from the cold bath and warmed slowly to rt. The mixture was diluted with H_2O (20 mL) and the layers separated. The aqueous phase was extracted with Et_2O (20 mL) and the combined organic layers dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (4:1 pentane:EtOAc) to afford alcohol **S1** as a colourless oil (1.41 g, 53%). Data is consistent with those reported in the literature.[214]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.29 (m, 2 H, 2 × H-7), 7.28–7.22 (m, 3 H, 2 × H-6 and H-8), 5.94 (ddd, *J* = 17.3, 10.5, 5.8 Hz, 1 H, H-3), 5.26 (dt, *J* = 17.3, 1.4 Hz, 1 H, H-4$_{trans}$), 5.14 (dt, *J* = 10.5, 1.3 Hz, 1 H, H-4$_{cis}$), 4.39–4.32 (m, 1 H, H-2), 2.89 (dd, *J* = 13.6, 5.1 Hz, 1 H, H-1), 2.80 (dd, *J* = 13.6, 7.9 Hz, 1 H, H-1) and 1.69 ppm (br. s, 1 H, OH); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 140.5 (C-3), 137.8 (C-5), 129.7 (2 C, 2 × C-6), 128.6 (2 C, 2 × C-7), 126.7 (C-8), 115.1 (C-4), 73.8 (C-2) and 44.0 ppm (C-1).

3-(((Diisopropyl((1-phenylbut-3-en-2-yl)oxy)silyl)oxy)methyl)but-3-en-2-one (**S2**)



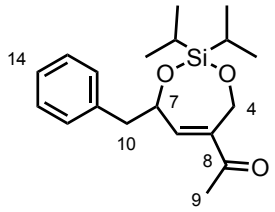
Note: Alcohol **S1** was azeotroped with PhMe (× 3) and dried under high vacuum for 1 h prior to use.

i-Pr_2SiCl_2 (0.453 mL, 2.51 mmol) was added dropwise to a solution of imidazole (407 mg, 5.98 mmol) in CH_2Cl_2 (25 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **S1** (354 mg, 2.39 mmol) in CH_2Cl_2 (4.4 mL + 0.4 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 45 min. A solution of alcohol **236** (263 mg, 2.63 mmol) in CH_2Cl_2 (2.6 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **S2** as a colourless oil (353 mg, 41%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.22 (m, 2 H, 2 × H-7), 7.22–7.14 (m, 3 H, 2 × H-6 and H-8), 6.13–6.09 (m, 2 H, 2 × H-5′), 5.81 (ddd, *J* = 16.9, 10.4, 6.4 Hz, 1 H, H-2), 5.09 (dt, *J* = 17.2, 1.5 Hz, 1 H, H-1$_{trans}$), 5.00 (ddd, *J* = 10.3, 1.7, 1.1 Hz, 1 H, H-1$_{cis}$), 4.47 (qt, *J* = 6.5, 1.1 Hz, 1 H, H-3), 4.44–4.30 (m, 2 H, 2 × H-4′), 2.88 (dd, *J* = 13.3, 6.6 Hz, 1 H, H-4), 2.77 (dd, *J* = 13.3, 6.5 Hz, 1 H, H-4), 2.34 (s, 3 H, 3 × H-1′) and 1.24–0.82 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.2 (C-2′), 147.7 (C-3′), 140.6 (C-2), 138.2 (C-5), 130.0 (2 C, 2 × C-6 or 2 × C-7), 128.2 (2 C, 2 × C-6 or 2 × C-7), 126.3 (C-8), 124.1 (C-5′), 114.4 (C-1), 75.0 (C-3), 60.8 (C-4′), 45.3 (C-4), 26.3 (C-1′), 17.54 (2 C, 2 × $SiCH\underline{C}H_3$), 17.48 ($SiCH\underline{C}H_3$), 17.45 ($SiCH\underline{C}H_3$), 12.5 ($Si\underline{C}HCH_3$) and 12.3 ppm ($Si\underline{C}HCH_3$);

FTIR ν_{max} (thin film): 2944, 2867, 1677, 1086, 1031, 884, 750 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{21}H_{32}NaO_3Si^+$ $[M+Na]^+$ 383.2013; found 383.2011 (Δ 0.52 ppm).

1-(7-Benzyl-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-5-yl)ethanone (**S3**)



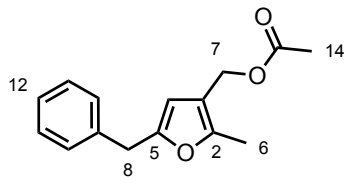
Note: dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (21.8 mg, 34.7 μmol) was added to a round-bottomed flask fitted with a reflux condenser and the system then evacuated and charged with N_2 (× 3). PhMe (140 mL) and a solution of TST **S2** (250 mg, 0.694 mmol) in PhMe (1.8 mL + 0.2 mL rinse, 5 mM final concentration) were sequentially added at rt and the reaction then heated to 80 °C for 24 h under N_2 atmosphere supplied *via* a manifold. The reaction mixture was cooled to rt and directly concentrated *in vacuo* before being purified by flash column chromatography (17:3 pentane:Et_2O) to afford silaketal **S3** as a yellow oil (210 mg, 91%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.16 (m, 5 H, 2 × H-12, 2 × H-13 and H-14), 6.68 (dd, *J* = 3.1, 1.9 Hz, 1 H, H-6), 5.04–4.97 (m, 1 H, H-7), 4.77 (dd, *J* = 15.6, 1.2 Hz, 1 H, H-4), 4.60 (ddd, *J* = 15.7, 2.8, 2.0 Hz, 1 H, H-4), 2.97 (app. qd, *J* = 13.3, 6.8 Hz, 2 H, 2 × H-10), 2.24 (s, 3 H, 3 × H-9) and 1.05–0.78 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.8 (C-8), 145.1 (C-6), 142.2 (C-5), 138.0 (C-11), 129.8 (2 C, 2 × C-12 or 2 × C-13), 128.4 (2 C, 2 × C-12 or 2 × C-13), 126.8 (C-14), 71.8 (C-7), 60.0 (C-4), 44.2 (C-10), 26.1 (C-9), 17.5 ($SiCH(\underline{C}H_3)_2$), 17.3 ($SiCH(\underline{C}H_3)_2$), 17.2 ($SiCH(\underline{C}H_3)_2$), 17.1 ($SiCH(\underline{C}H_3)_2$), 12.1 ($Si\underline{C}H(CH_3)_2$) and 12.0 ppm ($Si\underline{C}H(CH_3)_2$); **FTIR** ν_{max} (thin film): 2944, 2866, 1669,

1241, 1104, 885, 789, 763 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{19}H_{28}O_3Si^+$ $[M+H]^+$ 333.1880; found 333.1881 (Δ 0.30 ppm).

(5-Benzyl-2-methylfuran-3-yl)methyl acetate (**284**)

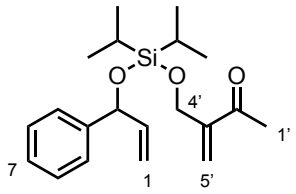


Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (76.0 μL, 1.07 mmol) was added dropwise to a solution of silaketal **S3** (71.4 mg, 0.215 mmol) and MeOH (26.0 μL, 0.644 mmol) in $CHCl_3$ (4.3 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding furan which was used directly without further purification. The furan was redissolved in DMF (2.1 mL, 0.1 M), anhydrous K_2CO_3 (89.0 mg, 0.644 mmol) and AcOH (49.0 μL, 0.859 mmol) were sequentially added at rt, and the reaction then stirred at 40 °C for 16 h. The reaction was cooled to rt, quenched by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford ester **284** as a colourless oil (40.3 mg, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39–7.22 (m, 5 H, 2 × H-10, 2 × H-11 and H-12), 5.96 (s, 1 H, H-4), 4.87 (s, 2 H, 2 × H-7), 3.92 (s, 2 H, 2 × H-8), 2.29 (s, 3 H, 3 × H-6) and 2.08 ppm (s, 3 H, 3 × H-14); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 171.2 (C-13), 152.8 (C-5), 149.9 (C-2), 138.1 (C-9), 128.9 (2 C, 2 × C-10 or 2 × C-11), 128.9 (2 C, 2 × C-10 or 2 × C-11), 126.9 (C-12), 115.1 (C-3), 108.1 (C-4), 58.3 (C-7), 34.6 (C-8), 21.2 (C-14) and 11.7 ppm (C-6); **FTIR** ν_{max} (thin film): 1737, 1372, 1230, 1022, 958, 757 and 704 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{15}H_{16}NaO_3^+$ $[M+Na]^+$ 267.0992; found 267.0992 (Δ 0.00 ppm).

3-(((Diisopropyl((1-phenylallyl)oxy)silyl)oxy)methyl)but-3-en-2-one (**S4**)

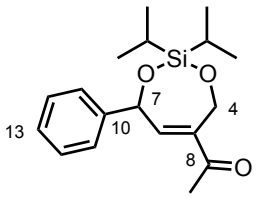


Note: 1-Phenyl-2-propen-1-ol was azeotroped with PhMe (× 3) and dried under high vacuum prior to use.

i-Pr_2SiCl_2 (0.433 mL, 2.40 mmol) was added dropwise to a solution of imidazole (389 mg, 5.71 mmol) in CH_2Cl_2 (24 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of 1-phenyl-2-propen-1-ol (0.300 mL, 2.28 mmol) in CH_2Cl_2 (4.2 mL + 0.4 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (251 mg, 2.51 mmol) in CH_2Cl_2 (2.5 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **S4** as a colourless oil (499 mg, 63%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.20 (m, 5 H, 2 × H-5, 2 × H-6 and H-7), 6.07–6.03 (m, 2 H, 2 × H-5′), 5.93 (ddd, *J* = 17.0, 10.2, 5.8 Hz, 1 H, H-2), 5.33–5.31 (m, 1 H, H-3), 5.28 (dt, *J* = 17.0, 1.5 Hz, 1 H, H-1$_{trans}$), 5.05 (dt, *J* = 10.2, 1.5 Hz, 1 H, H-1$_{cis}$), 4.43–4.29 (m, 2 H, 2 × H-4′), 2.29 (s, 3 H, 3 × H-1′) and 1.12–0.95 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.1 (C-2′), 147.5 (C-3′), 143.5 (C-4), 141.4 (C-2), 128.4 (2 C, 2 × C-5 or 2 × C-6), 127.3 (C-7), 126.1 (2 C, 2 × C-5 or 2 × C-6), 124.0 (C-5′), 113.4 (C-1), 75.7 (C-3), 60.9 (C-4′), 26.2 (C-1′), 17.6 (2 C, 2 × $SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 12.4 ($Si\underline{C}HCH_3$) and 12.4 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2945, 2867, 1677, 1086, 1062, 1029, 884, 859, 752 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{20}H_{30}NaO_3Si^+$ $[M+Na]^+$ 369.1856; found 369.1854 (Δ 0.54 ppm).

1-(2,2-Diisopropyl-7-phenyl-4,7-dihydro-1,3,2-dioxasilepin-5-yl)ethanone (**S5**)

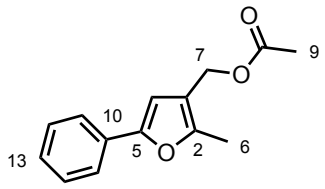


Note: dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (90.4 mg, 0.144 mmol) was added to a round-bottomed flask fitted with a reflux condenser and the system evacuated and charged with N_2 (× 3). PhMe (280 mL) and a solution of TST **S4** (500 mg, 1.44 mmol) in PhMe (6 mL + 2 mL rinse, 5 mM final concentration) were sequentially added at rt and the reaction then heated to 100 °C for 24 h under N_2 atmosphere supplied *via* a manifold. The reaction mixture was cooled to rt and directly concentrated *in vacuo* before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford silaketal **S5** as a yellow oil (81.3 mg, 17%). TST **S4** (328 mg, 65%) was also recovered.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.48–7.30 (m, 5 H, 2 × H-11, 2 × H-12 and H-13), 6.79 (ddd, *J* = 3.5, 1.8, 0.6 Hz, 1 H, H-6), 6.00–5.92 (m, 1 H, H-7), 4.97–4.80 (m, 2 H, 2 × H-4), 2.27 (s, 3 H, 3 × H-9) and 1.14–1.06 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.8 (C-8), 146.2 (C-6), 142.6 (C-5 or C-10), 141.7 (C-5 or C-10), 128.9 (2 C, 2 × C-11 or 2 × C-12), 128.0 (2 C, 2 × C-11 or 2 × C-12), 126.1 (C-13), 73.1 (C-7), 60.1 (C-4), 26.2 (C-9), 17.6 ($SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.3 ($SiCH\underline{C}H_3$), 12.4 ($Si\underline{C}HCH_3$) and 12.2 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2945, 2867, 1671, 1238, 1104, 1036, 886, 786 and 699 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{18}H_{26}O_3NaSi^+$ $[M+Na]^+$ 341.1543; found 341.1545 (Δ 0.59 ppm).

(2-Methyl-5-phenylfuran-3-yl)methyl acetate (**285**)



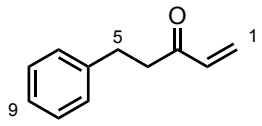
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (48.0 μL, 0.670 mmol) was added dropwise to a solution of silaketal **S9** (42.7 mg, 0.134 mmol) and MeOH (17.0 μL, 0.401 mmol) in $CHCl_3$ (2.7 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding furan which was used directly without further purification. The furan was redissolved in DMF (1.35 mL, 0.1 M), anhydrous K_2CO_3 (55.5 mg, 0.402 mmol) and AcOH (31.0 μL, 0.536 mmol) were sequentially added at rt, and the reaction then stirred at

40 °C for 16 h. The reaction was cooled to rt, quenched by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford ester **285** as a colourless oil (18.0 mg, 58%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67–7.58 (m, 2 H, 2 × H-11), 7.36 (dd, *J* = 8.5, 7.0 Hz, 2 H, 2 × H-12), 7.30–7.19 (m, 1 H, H-13), 6.61 (s, 1 H, H-4), 4.94 (s, 2 H, 2 × H-7), 2.38 (s, 3 H, 3 × H-6) and 2.08 ppm (s, 3 H, 3 × H-9); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 171.2 (C-8), 152.1 (C-2 or C-5), 150.7 (C-2 or C-5), 130.8 (C-10), 128.8 (2 C, 2 × C-12), 127.2 (C-13), 123.6 (2 C, 2 × C-11), 116.7 (C-3), 106.9 (C-4), 58.2 (C-7), 21.2 (C-9) and 11.9 ppm (C-6); **FTIR** ν_{max} (thin film): 2923, 1734, 1372, 1234, 1023, 760 and 693 cm^{-1}; **HRMS** (CH_4 CI^+): Calculated for $C_{14}H_{15}O_3^+$ $[M+H]^+$ 231.1016; found 231.1019 (Δ 1.30 ppm).

5-Phenylpent-1-en-3-one (**S6**)

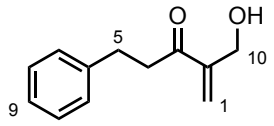


(Diacetoxyiodo)benzene (3.46 g, 10.7 mmol) and TEMPO (280 mg, 1.79 mmol) were sequentially added to a solution of alcohol **209** (1.45 g, 8.94 mmol) in CH_2Cl_2 (18 mL, 0.5 M) at rt and the reaction then was stirred at rt for 18 h. The reaction was quenched at rt by addition of $Na_2S_2O_3$ (sat., aq., 10 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column

chromatography (3:2 pentane:CH_2Cl_2) to afford ketone **S6** as a colourless oil (1.07 g, 75%). Data is consistent with that reported in the literature.[211]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.28 (m, 2 H, 2 × H-8), 7.27–7.20 (m, 3 H, 2 × H-7 and H-9), 6.39 (dd, *J* = 17.7, 10.5 Hz, 1 H, H-2), 6.25 (dd, *J* = 17.1, 1.1 Hz, 1 H, H-1$_{trans}$), 5.87 (dd, *J* = 10.5, 1.1 Hz, 1 H, H-1$_{cis}$) and 3.04–2.92 ppm (m, 4 H, 2 × H-4 and 2 × H-5); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.9 (C-3), 141.2 (C-6), 136.6 (C-1), 128.6 (2 C, 2 × C-7 or 2 × C-8), 128.5 (2 C, 2 × C-7 or 2 × C-8), 128.4 (C-2), 126.3 (C-9), 41.4 (C-4) and 29.9 ppm (C-5).

2-(Hydroxymethyl)-5-phenylpent-1-en-3-one (**S7**)

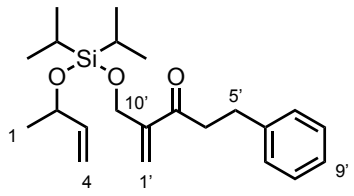


Paraformaldehyde (112 mg, 3.74 mmol) and DABCO (21.0 mg, 0.187 mmol) were sequentially added to a solution of ketone **S6** (295 mg, 1.87 mmol) in dioxane:H_2O (1:1, 19 mL, 0.1 M) at rt and the reaction then stirred at rt for 90 min. The reaction was diluted with Et_2O (20 mL) and brine (20 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (1:1 pentane:Et_2O) to afford alcohol **S7** as a colourless oil (322 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.25 (m, 2 H, 2 × H-8), 7.24–7.18 (m, 3 H, 2 × H-7 and H-9), 6.10 (s, 1 H, H-1), 6.00 (t, *J* = 1.3 Hz, 1 H, H-1), 4.33 (s, 2 H, 2 × H-10), 3.08–3.02 (m, 2 H, 2 × H-4) and 2.99–2.91 ppm (m, 2 H, 2 × H-5); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 201.6 (C-3), 146.9 (C-2), 141.1 (C-6), 128.7 (2 C, 2 × C-7 or 2 × C-8), 128.5 (2 C, 2 × C-7 or 2 × C-8), 126.3 (C-9), 125.4 (C-1), 62.8 (C-10), 39.8 (C-4) and 30.1 ppm (C-5); **FTIR**

ν_{max} (thin film): 3422, 2928, 1670, 1453, 1030, 994, 751 and 700 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{12}H_{14}O_2Na^+$ $[M+Na]^+$ 213.0886; found 213.0886 (Δ 0.00 ppm).

2-((((But-3-en-2-yloxy)diisopropylsilyl)oxy)methyl)-5-phenylpent-1-en-3-one (**S8**)

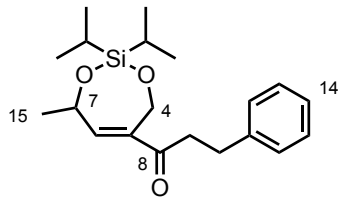


i-Pr_2SiCl_2 (0.240 mL, 1.33 mmol) was added dropwise to a solution of imidazole (216 mg, 3.17 mmol) in CH_2Cl_2 (13.3 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of 3-buten-2-ol (0.110 mL, 1.27 mmol) in CH_2Cl_2 (2.4 mL + 0.2 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **S7** (265 mg, 1.40 mmol) in CH_2Cl_2 (1.4 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **S8** as a colourless oil (346 mg, 72%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.13 (m, 5 H, 2 × H-7′, 2 × H-8′ and H-9′), 6.12–6.09 (m, 2 H, 2 × H-1′), 5.84 (ddd, *J* = 17.2, 10.4, 5.5 Hz, 1 H, H-3), 5.15 (dt, *J* = 17.1, 1.5 Hz, 1 H, H-4$_{trans}$), 4.96 (dt, *J* = 10.4, 1.5 Hz, 1 H, H-4$_{cis}$), 4.49 (t, *J* = 2.0 Hz, 2 H, 2 × H-10′), 4.48–4.40 (m, 1 H, H-2), 3.07–2.98 (m, 2 H, 2 × H-4′), 2.97–2.87 (m, 2 H, 2 × H-5′), 1.23 (d, *J* = 6.4 Hz, 3 H, 3 × H-1), 1.04 (app. s, 7 H, $SiCH(CH_3)_2$) and 1.03 ppm (app. s, 7 H, $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 200.3 (C-3′), 147.3 (C-2′), 142.6 (C-3), 141.3 (C-6′), 128.6 (2 C, 2 × C-7′ or 2 × C-8′), 128.5 (2 C, 2 × C-7′ or 2 × C-8′), 126.3 (C-9′), 123.2 (C-1′), 112.8 (C-4), 69.5 (C-2), 61.0 (C-10′), 39.9 (C-4′), 30.2 (C-5′), 24.5 (C-1), 17.6

(2 C, 2 × SiCH<u>C</u>H$_3$), 17.5 (2 C, 2 × SiCH<u>C</u>H$_3$), 12.42 (Si<u>C</u>HCH$_3$) and 12.38 ppm (Si<u>C</u>HCH$_3$); **FTIR** ν_{max} (thin film): 2945, 2867, 1675, 1122, 1081, 1058, 1031, 992, 884 and 698 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{22}H_{34}NaO_3Si^+$ $[M+Na]^+$ 397.2169; found 397.2167 (Δ 0.50 ppm).

1-(2,2-Diisopropyl-7-methyl-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-3-phenylpropan-1-one (**S9**)



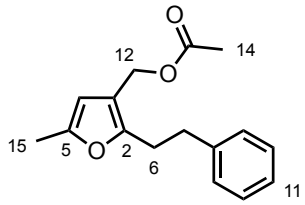
Note: dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (25.4 mg, 40.6 μmol) was added to a round-bottomed flask fitted with a reflux condenser and the system then evacuated and charged with N_2 (× 3). PhMe (160 mL) and a solution of TST **S8** (303 mg, 0.811 mmol) in PhMe (1.5 mL + 0.5 mL rinse, 5 mM final concentration) were sequentially added at rt and the reaction then heated to 80 °C for 24 h under N_2 atmosphere supplied *via* a manifold. The reaction mixture was cooled to rt and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford silaketal **S9** as a yellow oil (256 mg, 91%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.26 (m, 2 H, 2 × H-13), 7.23–7.17 (m, 3 H, 2 × H-12 and H-14), 6.63–6.54 (m, 1 H, H-6), 5.05–4.96 (m, 1 H, H-7), 4.83 (ddd, *J* = 15.7, 1.3, 0.7 Hz, 1 H, H-4), 4.74, (ddd, *J* = 15.7, 2.6, 1.7 Hz, 1 H, H-4), 3.02–2.86 (m, 4 H, 2 × H-9 and 2 × H-10), 1.39 (d, *J* = 6.8 Hz, 3 H, 3 × H-15) and 1.09–1.01 ppm (m, 14 H, 2 × SiCH(CH_3)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 200.0 (C-8), 145.9 (C-6), 141.3 (C-5 or C-11), 141.2 (C-5 or C-11), 128.7 (2 C, 2 × C-12 or 2 × C-13), 128.5 (2 C, 2 × C-12 or 2 × C-13), 126.3 (C-14), 67.0 (C-7), 60.3 (C-4), 39.8 (C-9), 30.6 (C-10), 24.2 (C-15), 17.6 (SiCH<u>C</u>H$_3$), 17.5

($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 12.2 ($Si\underline{C}HCH_3$) and 12.1 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2866, 1669, 1138, 1102, 1057, 885, 787, 750 and 687 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{20}H_{30}NaO_3Si^+$ $[M+Na]^+$ 369.1856; found 369.1855 (Δ 0.27 ppm).

(5-Methyl-2-phenethylfuran-3-yl)methyl acetate (**286**)



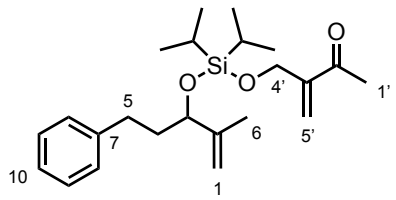
Note: Acetyl chloride was freshly distilled from quinoline (10:1 acetyl chloride:quinoline) at 52 °C/1 atm. prior to use.

Acetyl chloride (75.0 µL, 0.638 mmol) was added dropwise to a solution of silaketal **S9** (73.7 mg, 0.213 mmol) and MeOH (26.0 µL, 0.638 mmol) in $CHCl_3$ (4.3 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the corresponding furan which was used directly without further purification. The furan was redissolved in DMF (2.1 mL, 0.1 M), anhydrous K_2CO_3 (86.3 mg, 0.638 mmol) and AcOH (49.0 µL, 0.851 mmol) were sequentially added at rt, and the reaction then stirred at 40 °C for 16 h. The reaction was cooled to rt, quenched by dropwise addition of $NaHCO_3$ (sat., aq., 2 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being puri-

fied by flash column chromatography (19:1 pentane:Et_2O) to afford ester **286** as a colourless oil (43.4 mg, 79%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.10 (m, 5 H, 2 × H-9, 2 × H-10 and H-11), 5.91 (s, 1 H, H-4), 4.67 (s, 2 H, 2 × H-12), 2.90 (s, 4 H, 2 × H-6 and 2 × H-7), 2.26 (s, 3 H, 3 × H-15) and 2.01 ppm (s, 3 H, 3 × H-14); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 171.1 (C-13), 151.9 (C-2 or C-5), 150.6 (C-2 or C-5), 141.2 (C-8), 128.6 (2 C, 2 × C-9 or 2 × C-10), 128.5 (2 C, 2 × C-9 or 2 × C-10), 126.2 (C-11), 115.5 (C-3), 107.3 (C-4), 58.0 (C-12), 32.3 (C-7), 28.4 (C-6), 21.2 (C-14) and 13.6 ppm (C-15); **FTIR** ν_{max} (thin film): 1737, 1374, 1228, 1022 and 700 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{16}H_{18}NaO_3^+$ $[M+Na]^+$ 281.1148; found 281.1149 (Δ 0.36 ppm).

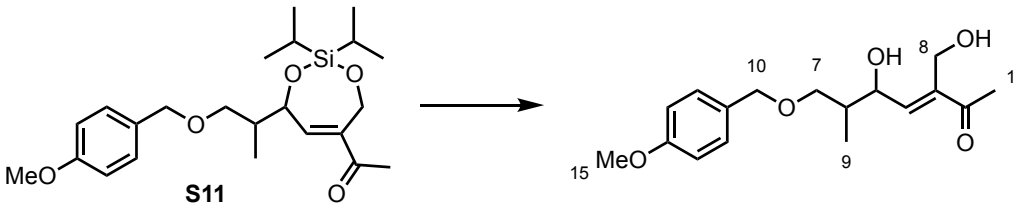
3-(((Diisopropyl((2-methyl-5-phenylpent-1-en-3-yl)oxy)silyl)oxy)methyl)but-3-en-2-one (**S10**)



Note: Alcohol **238** was azeotroped with PhMe (× 3) and dried under high vacuum prior to use. *i*-Pr_2SiCl_2 (0.304 mL, 1.91 mmol) was added dropwise to a solution of imidazole (272 mg, 3.99 mmol) in CH_2Cl_2 (19 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **238** (319 mg, 1.81 mmol) in CH_2Cl_2 (3.4 mL + 0.2 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (200 mg, 2.00 mmol) in CH_2Cl_2 (2 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **S10** as a colourless oil (475 mg, 67%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.26 (m, 2 H, 2 × C-9), 7.23–7.16 (m, 3 H, 2 × C-8 and C-10), 6.19–6.16 (m, 1 H, H-5′), 6.15–6.12 (m, 1 H, H-5′), 4.96–4.93 (m, 1 H, H-1), 4.88–4.85 (m, 1 H, H-1), 4.51 (t, *J* = 2.1 Hz, 2 H, 2 × H-4′), 4.33 (t, *J* = 6.2 Hz, 1 H, H-3), 2.62–2.54 (m, 2 H, 2 × H-5), 2.37 (s, 3 H, 3 × H-1′), 1.94–1.84 (m, 2 H, 2 × H-4), 1.75 (t, *J* = 1.1 Hz, 3 × H-6), 1.09 (app. s, 7 H, $SiCH(CH_3)_2$) and 1.07 ppm (app. s, 7 H, $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.3 (C-2′), 147.7 (C-2), 146.6 (C-3′), 142.5 (C-7), 128.5 (2 C, 2 × C-8 or 2 × C-9), 128.4 (2 C, 2 × C-8 or 2 × C-9), 125.8 (C-10), 124.2 (C-5′), 111.7 (C-1), 76.2 (C-3), 60.9 (C-4′), 37.7 (C-4), 31.5 (C-5), 26.2 (C-1′), 17.63 (C-6 or $SiCH\underline{C}H_3$), 17.60 (C-6 or $SiCH\underline{C}H_3$), 17.58 (C-6 or $SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 12.42 ($Si\underline{C}HCH_3$) and 12.39 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2945, 2867, 1677, 1389, 1087, 899, 885, 750 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{23}H_{36}O_3Na^+$ $[M+Na]^+$ 411.2326; found 411.2324 (Δ 0.49 ppm).

(E)-5-Hydroxy-3-(hydroxymethyl)-7-((4-methoxybenzyl)oxy)-6-methylhept-3-en-2-one (**S12**)



Note: Silaketal **S11** was provided by Simon Werrel.

Tetrabutylammonium fluoride (1 M in THF, 32 μL, 32 μmol) was added to a solution of silaketal **S11** (100 mg, 0.238 mmol) in THF:pH 7 buffer (100:1, 0.1 M, 2.4 mL) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 50 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (45:4:1 CH_2Cl_2:acetone:MeOH) to afford diol **S12** as a colourless oil and an inseparable 3:2 ratio of diastereomers (64.5 mg, 88%). The diastereomeric ratio was calculated on the basis of the in-

tegrals of the two H-4 peaks in the ^{1}H NMR spectrum (6.62 and 6.58 ppm). Contains trace quantities of diisopropylsilanediol (^{1}H NMR peaks at 1.25 and 1.05 ppm and ^{13}C-NMR peaks at 29.9 and 17.0 ppm).

^{1}H NMR (Major Diastereomer, $CDCl_3$, 400 MHz): δ = 7.28–7.22 (m, 2 H, 2 × H-12), 6.92–6.87 (m, 2 H, 2 × H-13), 6.62 (d, *J* = 7.7 Hz, 1 H, H-4), 4.74 (dt, *J* = 7.4, 3.6 Hz, 1 H, H-5), 4.52–4.39 (m, 2 H, 2 × H-10), 4.39–4.26 (m, 2 H, 2 × H-8), 3.81 (s, 3 H, 3 × H-15), 3.56 (dd, *J* = 9.3, 4.0 Hz, 1 H, H-7), 3.49–3.43 (m, 1 H, H-7), 3.34 (d, *J* = 4.4 Hz, 1 H, C-5 OH), 2.87–2.77 (m, 1 H, C-8 OH), 2.29 (s, 3 H, 3 × H-1), 2.13–1.99 (m, 1 H, H-6) and 0.97 ppm (d, *J* = 7.1 Hz, 3 H, 3 × H-9).

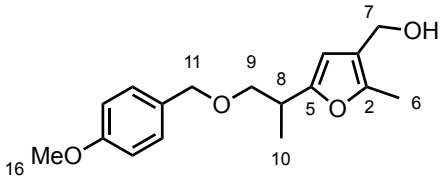
^{13}C NMR (Major Diastereomer, $CDCl_3$, 101 MHz): δ = 201.1 (C-2), 159.59 (C-14), 145.7 (C-4), 140.6 (C-3), 129.68 (C-11), 129.64 (2 C, 2 × C-12), 114.08 (2 C, 2 × C-13), 73.40 (C-10), 73.38 (C-7), 71.6 (C-5), 57.2 (C-8), 55.4 (C-15), 39.2 (C-6), 25.89 (C-1) and 11.9 ppm (C-9).

^{1}H NMR (Minor Diastereomer, $CDCl_3$, 400 MHz): δ = 7.28–7.22 (m, 2 H, 2 × H-12), 6.92–6.87 (m, 2 H, 2 × H-13), 6.58 (d, *J* = 8.3 Hz, 1 H, H-4), 4.54 (td, *J* = 8.1, 2.5 Hz, 1 H, H-5), 4.52–4.39 (m, 2 H, 2 × H-10), 4.39–4.26 (m, 2 H, 2 × H-8), 3.92 (d, *J* = 3.3 Hz, 1 H, C-5 OH), 3.81 (s, 3 H, 3 × H-15), 3.61 (dd, *J* = 9.4, 3.9 Hz, 1 H, H-7), 3.49–3.43 (m, 1 H, H-7), 2.87–2.77 (m, 1 H, C-8 OH), 2.32 (s, 3 H, 3 × H-1), 2.13–1.99 (m, 1 H, H-6) and 0.90 ppm (d, *J* = 7.0 Hz, 3 H, 3 × H-9).

^{13}C NMR (Minor Diastereomer, $CDCl_3$, 101 MHz): δ = 201.3 (C-2), 159.61 (C-14), 145.6 (C-4), 140.9 (C-3), 129.66 (2 C, 2 × C-12), 129.5 (C-11), 114.09 (2 C, 2 × C-13), 74.2 (C-7), 73.40 (C-10), 73.0 (C-5), 57.3 (C-8), 55.4 (C-15), 38.8 (C-6), 25.85 (C-1) and 13.7 ppm (C-9).

FTIR ν_{max} (thin film): 3429, 2935, 1670, 1513, 1248, 1032 and 1010 cm^{-1}; **HRMS** (ESI^{+}): Calculated for $C_{17}H_{24}NaO_5^{+}$ $[M+H]^{+}$ 331.1516; found 331.1515 (Δ 0.30 ppm).

(5-(1-((4-Methoxybenzyl)oxy)propan-2-yl)-2-methylfuran-3-yl)methanol (**293**)

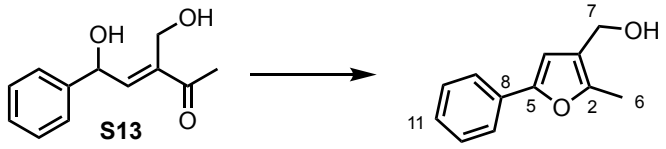


Note: EtOAc was sparged with Ar for *ca.* 10 min prior to use.

A solution of diol **S12** (31.2 mg, 0.101 mmol) in EtOAc (7 mL) was added to the irradiation vessel. The insert was added, screw cap fitted and the vessel flushed with Ar for 10 min. The vessel was placed under a gentle flow of Ar *via* a manifold for the remainder of the reaction. The reaction was cooled to 0 °C (cryostat-cooled acetone bath), a 365 nm UVP Pen-Ray placed in the insert and switched on, and the reaction then stirred at 0 °C for 20 h. The Pen-Ray was switched off and the reaction then allowed to warm to rt. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (7:3 pentane:EtOAc) to afford furan **293** as a colourless oil (24.8 mg, 84%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.25–7.21 (m, 2 H, 2 × H-13), 6.89–6.85 (m, 2 H, 2 × H-14), 6.01 (s, 1 H, H-4), 4.45 (d, *J* = 1.6 Hz, 2 H, 2 × H-11), 4.42 (s, 2 H, 2 × H-7), 3.80 (s, 3 H, 3 × H-16), 3.63 (dd, *J* = 9.2, 5.9 Hz, 1 H, H-9), 3.42 (dd, *J* = 9.2, 7.4 Hz, 1 H, H-9), 3.05 (sext., *J* = 6.9 Hz, 1 H, H-8), 2.24 (s, 3 H, 3 × H-6) and 1.25 ppm (d, *J* = 7.0 Hz, 3 H, 3 × H-10); **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 159.3 (C-15), 156.0 (C-5), 147.6 (C-2), 130.7 (C-12), 129.3 (2 C, 2 × C-13), 119.3 (C-3), 113.9 (2 C, 2 × C-14), 105.8 (C-4), 73.6 (C-9), 72.8 (C-11), 56.9 (C-7), 55.4 (C-16), 34.0 (C-8), 16.2 (C-10) and 11.7 ppm (C-6); **FTIR** ν_{max} (thin film): 3401, 2935, 2877, 1612, 1513, 1248 and 1035 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{17}H_{22}NaO_4^+$ $[M+H]^+$ 313.1410; found 313.1410 (Δ 0.00 ppm).

(2-Methyl-5-phenylfuran-3-yl)methanol (**294**)

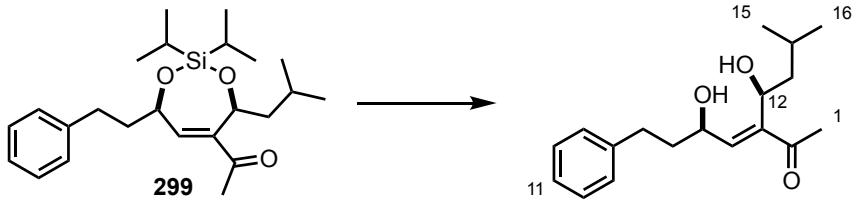


Notes: EtOAc was sparged with Ar for *ca.* 10 min prior to use. Diol **S13** was provided by Simon Werrel.

A solution of diol **S13** (30.8 mg, 0.149 mmol) in EtOAc (7 mL) was added to the irradiation vessel. The insert was added, the screw cap fitted and the vessel flushed with Ar for 10 min. The vessel was placed under a gentle flow of Ar *via* a manifold for the remainder of the reaction. The reaction was cooled to 0 °C (cryostat-cooled acetone bath), a 365 nm UVP Pen-Ray placed in the insert and switched on, and the reaction then stirred at 0 °C for 21 h. The Pen-Ray was switched off and the reaction then allowed to warm to rt. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (3:1 pentane:EtOAc) to afford furan **294** as a colourless oil (10.5 mg, 37%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.64–7.59 (ddd, *J* = 8.3, 1.8, 1.0 Hz, 2 H, 2 × H-10), 7.40–7.32 (m, 2 H, 2 × H-9), 7.25–7.19 (m, 1 H, H-11), 6.64 (s, 1 H, H-4), 4.51 (s, 2 H, 2 × H-7), 2.37 (s, 3 H, 3 × H-6) and 1.45 ppm (s, 1 H, OH); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 152.0 (C-2 or C-5), 149.1 (C-2 or C-5), 130.9 (C-8), 128.8 (2 C, 2 × C-9), 127.2 (C-11), 123.5 (2 C, 2 × C-10), 121.1 (C-3), 106.3 (C-4), 56.9 (C-7) and 11.9 ppm (C-6); **FTIR** ν_{max} (thin film): 3337, 2919, 1876, 1602, 1555, 1487, 1448, 997, 759 and 692 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{12}H_{13}O_2^+$ $[M+H]^+$ 189.0910; found 189.0911 (Δ 0.53 ppm).

(E)-5-Hydroxy-3-(1-hydroxy-3-methylbutyl)-7-phenylhept-3-en-2-one (**S14**)

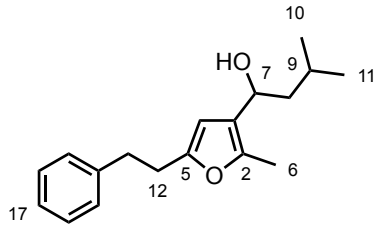


Note: Silaketal **299** was provided by Simon Werrel.

Tetrabutylammonium fluoride (1 M in THF, 27 μL, 27 μmol) was added to a solution of silaketal **299** (107 mg, 0.266 mmol) in THF:pH 7 buffer (100:1, 0.1 M, 2.7 mL) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 1 h before being warmed to rt. Tetrabutylammonium fluoride (1 M in THF, 0.670 mL, 0.670 mmol) was added at rt and the reaction then stirred at rt for a further 4 h. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (9:1 CH_2Cl_2:acetone) to afford diol **S14** as a colourless oil (35.5 mg, 45%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.25 (m, 2 H, 2 × H-10), 7.23–7.16 (m, 3 H, 2 × H-9 and H-11), 6.47 (d, *J* = 8.2 Hz, 1 H, H-4), 4.57 (td, *J* = 8.4, 4.1 Hz, 1 H, H-5), 4.52–4.44 (m, 1 H, H-12), 3.92 (d, *J* = 9.3 Hz, 1 H, C-12 OH), 3.79 (br. s, 1 H, C-5 OH), 2.83 (ddd, *J* = 14.3, 9.2, 5.3 Hz, 1 H, H-7), 2.70 (ddd, *J* = 13.8, 8.9, 7.3 Hz, 1 H, H-7), 2.29 (s, 3 H, 3 × H-1), 1.96 (dtd, *J* = 14.0, 8.8, 5.3 Hz, 1 H, H-6), 1.84–1.67 (m, 3 H, H-6, H-13 and H-14), 1.09 (ddd, *J* = 13.3, 8.4, 4.0 Hz, 1 H, H-13), 0.87 (d, *J* = 6.5 Hz, 3 H, 3 × H-15) and 0.82 ppm (d, *J* = 6.4 Hz, 3 H, 3 × H-16); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 203.1 (C-2), 145.9 (C-4), 141.5 (C-3 or C-8), 141.3 (C-3 or C-8), 128.6 (2 C, 2 × C-10), 128.5 (2 C, 2 × C-9), 126.2 (C-11), 68.0 (C-12), 66.4 (C-5), 46.0 (C-13), 38.0 (C-6), 31.5 (C-7), 26.9 (C-1), 24.8 (C-14), 23.5 (C-15) and 21.7 ppm (C-16); **FTIR** ν_{max} (thin film): 3394, 2954, 1657, 1455, 1230, 1062, 980, 747, 699 and 653 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{18}H_{27}O_3^+$ $[M+H]^+$ 291.1955; found 291.1956 (Δ 0.34 ppm).

3-Methyl-1-(2-methyl-5-phenethylfuran-3-yl)butan-1-ol (**297**)

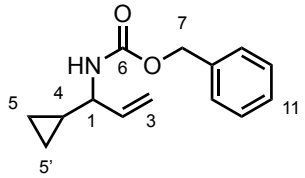


Note: EtOAc was sparged with Ar for *ca.* 10 min prior to use.

A solution of diol **S14** (24.9 mg, 85.7 μmol) in EtOAc (7 mL) was added to the irradiation vessel. The insert was added, screw cap fitted and the vessel flushed with Ar for 10 min. The vessel was placed under a gentle flow of Ar *via* a manifold for the remainder of the reaction. The reaction was cooled to 0 °C (cryostat-cooled acetone bath), a 365 nm UVP Pen-Ray placed in the insert and switched on, and the reaction then stirred at 0 °C for 19 h. The Pen-Ray was switched off and the reaction then allowed to warm to rt. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:EtOAc) to afford furan **297** as a colourless oil (15.8 mg, 67%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.25 (m, 2 H, 2 × H-16), 7.23–7.16 (m, 3 H, 2 × H-15 and H-17), 5.93 (s, 1 H, H-4), 4.63 (t, *J* = 7.1 Hz, 1 H, H-7), 2.98–2.90 (m, 2 H, 2 × H-13), 2.89–2.82 (m, 2 H, 2 × H-12), 2.27 (s, 3 H, 3 × H-6), 1.69 (dt, *J* = 12.9, 7.2 Hz, 1 H, H-8), 1.59 (dquint., *J* = 13.2, 6.5 Hz, 1 H, H-9), 1.53–1.43 (m, 2 H, H-8 and OH), 0.93 (d, *J* = 2.1 Hz, 3 H, 3 × H-10) and 0.91 ppm (d, *J* = 2.0 Hz, 3 H, 3 × H-11); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 153.5 (C-5), 146.4 (C-2), 141.4 (C-14), 128.5 (4 C, 2 × C-15 and 2 × C-16), 126.2 (C-17), 123.0 (C-3), 104.1 (C-4), 65.0 (C-7), 46.8 (C-8), 34.6 (C-13), 30.2 (C-12), 24.9 (C-9), 22.9 (C-10), 22.8 (C-11) and 11.9 ppm (C-6); **FTIR** ν_{max} (thin film): 3366, 2954, 2923, 2868, 1454, 997, 749 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{18}H_{25}O_2^+$ $[M+H]^+$ 273.1849; found 273.1849 (Δ 0.00 ppm).

Benzyl (1-cyclopropylallyl)carbamate (**S15**)

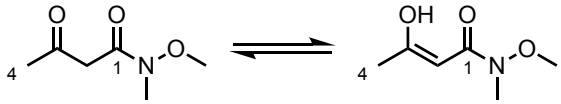


Cyclopropanecarboxaldehyde (0.410 mL, 5.50 mmol) and formic acid (1.20 mL, 31.8 mmoL) were sequentially added to a solution of benzyl carbamate (756 mg, 5.00 mmol) and benzenesulfinic acid sodium salt (821 mg, 5.00 mmol) in THF (2.2 mL, 2.5 M wrt. cyclopropanecarboxaldehyde) and H_2O (5.5 mL, 1 M wrt. cyclopropanecarboxaldehyde) at rt and the reaction then stirred vigorously at rt for 4 days. The suspension was filtered and the solids then washed sequentially with H_2O (10 mL) and pentane (10 mL) before being dried under high vacuum to afford the intermediate sulfinate as a white solid (973 mg) which was used without further purification. The intermediate sulfinate was dissolved in THF (20 mL, 0.125 M) and cooled to –20 °C (cryostat-cooled acetone bath). Vinylmagnesium bromide (1 M in THF, 5.00 mL, 5.00 mmol) was added dropwise over 15 min. The reaction was removed from the cold bath, placed in a 0 °C (ice/H_2O) bath and stirred for 2 h, warming slowly to 0 °C. The reaction was quenched at 0 °C by dropwise addition of NH_4Cl (sat., aq., 20 mL), diluted with H_2O (20 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford allyl amine **S15** as a viscous clear oil (200 mg, 34%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43–7.29 (m, 5 H, 2 × H-9, 2 × H-10 and H-11), 5.82 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1 H, H-2), 5.22 (d, *J* = 17.2 Hz, 1 H, H-3$_{trans}$), 5.14–5.09 (m, 3 H, H-3$_{cis}$ and 2 × H-7), 4.86 (s, 1 H, NH), 3.70–3.60 (m, 1 H, H-1), 0.93–0.84 (m, 1 H, H-4),

0.57–0.46 (m, 2 H, H-5 and H-5′), 0.43–0.36 (m, 1 H, H-5) and 0.28 ppm (dq, J = 9.1, 4.8 Hz, 1 H, H-5′); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 155.9 (C-6), 137.3 (C-2), 136.7 (C-8), 128.7 (2 C, 2 × C-10), 128.3 (3 C, 2 × C-9 and C-11), 115.0 (C-3), 66.9 (C-7), 57.2 (C-1), 15.7 (C-4), 3.1 (C-5′) and 2.9 ppm (C-5); **FTIR** ν_{max} (thin film): 3324, 1694, 1522, 1235, 1023, 992, 920, 738 and 697 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{14}H_{18}NO_2^+$ $[M+H]^+$ 232.1332; found 232.1334 (Δ 0.86 ppm); **M.P.** 41–42 °C ($CHCl_3$).

N-Methoxy-N-methyl-3-oxobutanamide (**S16**)



Et_3N (7.86 mL, 56.4 mmol) was added to a suspension of *N,O*-dimethylhydroxylamine hydrochloride (5.00 g, 51.3 mmol) and 2,2,6-trimethyl-1,3-dioxin-4-one (10.0 mL, 76.9 mmol) in PhMe (150 mL, 0.33 M) at rt and the reaction then stirred at 90 °C for 20 h. The reaction was cooled to rt and quenched by addition of HCl (1 M, aq., 180 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (1:1 pentane:Et_2O) to afford amide **S16** as a pale yellow oil and a 5:1 ratio of keto:enol tautomers (4.60 g, 61%). The tautomeric ratio is calculated based on the integrals of the NCH_3 peaks in the ^{1}H NMR (3.21 and 3.18 ppm). Data is consistent with that reported in the literature.[215]

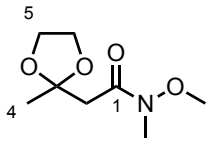
^{1}H NMR (Keto Tautomer, $CDCl_3$, 400 MHz): δ = 3.666 (s, 3 H, OCH_3), 3.57 (s, 2 H, 2 × H-2), 3.21 (s, 3 H, NCH_3) and 2.25 ppm (s, 3 H, 3 × H-4).

^{13}C NMR (Keto Tautomer, $CDCl_3$, 101 MHz): δ = 201.8 (C-3), 168.0 (C-1), 61.4 (OCH_3), 48.6 (C-2), 32.1 (NCH_3) and 30.2 ppm (C-4).

^{1}H NMR (Enol Tautomer, $CDCl_3$, 400 MHz): δ = 13.71 (s, 1 H, OH), 5.38 (s, 1 H, H-2), 3.672 (s, 3 H, OCH_3), 3.18 (s, 3 H, NCH_3) and 1.96 ppm (s, 3 H, 3 × H-4).

^{13}C NMR (Enol Tautomer, $CDCl_3$, 101 MHz): δ = 175.3 (C-1 or C-3), 172.5 (C-1 or C-3), 86.6 (C-2), 61.3 (OCH_3), 31.7 (NCH_3) and 21.9 ppm (C-4).

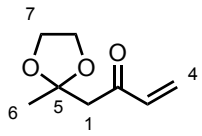
N-Methoxy-N-methyl-2-(2-methyl-1,3-dioxolan-2-yl)acetamide (**S17**)



p-Toluenesulfonic acid monohydrate (200 mg, 1.05 mmol) and ethylene glycol (1.64 mL, 29.4 mmol) were sequentially added to a solution of ketone **S16** (3.05 g, 21.0 mmol) in benzene (47 mL, 0.45 M) at rt. The reaction flask was fitted with a Dean–Stark distillation head and the reaction then refluxed in an oil bath preheated to 100 °C for 24 h. The reaction was cooled to rt and diluted with H_2O (50 mL). The layers were separated and the aqueous phase extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with $NaHCO_3$ (sat., aq., 2 × 50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (1:1 pentane:EtOAc) to afford amide **S17** as a pale yellow oil (2.43 g, 62%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.97 (s, 4 H, 4 × H-5), 3.69 (s, 3 H, OCH_3), 3.19 (s, 3 H, NCH_3), 2.82 (s, 2 H, 2 × H-2) and 1.51 ppm (s, 3 H, 3 × H-4); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ = 170.4 (C-1), 108.5 (C-3), 64.9 (2 C, 2 × C-5), 61.3 (OCH_3), 40.8 (C-2), 32.1 (NCH_3) and 24.8 ppm (C-4); **FTIR** ν_{max} (thin film): 2941, 2888, 1655, 1376, 1180, 1045 and 1002 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_8H_{15}NNaO_4^+$ $[M+Na]^+$ 212.0893; found 212.0894 (Δ 0.47 ppm).

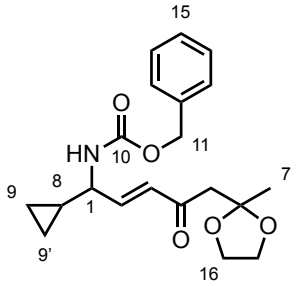
1-(2-Methyl-1,3-dioxolan-2-yl)but-3-en-2-one (**S18**)



Vinylmagnesium bromide (1 M in THF, 24.0 mL, 24.0 mmol) was added dropwise over 20 min to a solution of amide **S17** (2.22 g, 12.0 mmol) in THF (60 mL, 0.2 M) at –78 °C (dry ice/acetone bath). The reaction was removed from the cold bath and placed in a 0 °C bath (ice/H_2O) and stirred for 2 h, warming slowly to 0 °C. The reaction was cooled to –78 °C (dry ice/acetone bath) and quenched by fast addition of HCl (2 M, aq., 50 mL) before being removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous layer extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (7:3 pentane:Et_2O) to afford the enone **S18** as a colourless oil (988 mg, 54%). Data is consistent with that reported in the literature.[216]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.45 (dd, *J* = 17.5, 10.6 Hz, 1 H, H-3), 6.22 (dd, *J* = 17.5, 1.2 Hz, 1 H, H-4$_{trans}$), 5.80 (dd, *J* = 10.5, 1.1 Hz, 1 H, H-4$_{cis}$), 3.97–3.91 (m, 4 H, 4 × H-7), 2.91 (s, 2 H, 2 × H-1) and 1.41 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 197.4 (C-2), 137.0 (C-3), 128.8 (C-4), 108.2 (C-5), 64.8 (2 C, 2 × C-7), 49.3 (C-1) and 24.8 ppm (C-6).

Benzyl (E)-(1-cyclopropyl-5-(2-methyl-1,3-dioxolan-2-yl)-4-oxopent-2-en-1-yl)carbamate (**S19**)



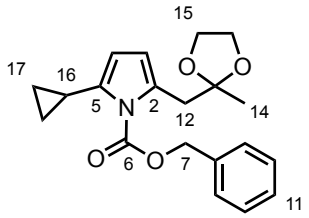
Notes: Experimental setup B (Section 5.3) was used for this reaction. Glassware was not flame dried but was charged with Ar and kept under a positive Ar pressure *via* a manifold line prior to use. PhMe was sparged with Ar for *ca.* 10 min prior to use.

Amide **S15** (231 mg, 1.00 mmol) was added to a solution of enone **S18** (760 mg, 5.00 mmol) in PhMe (4 mL, 0.25 M) at rt. Hoveyda–Grubbs second generation catalyst (31.3 mg, 25.0 μmol) was added under a positive Ar pressure and the reaction then stirred at 40 °C for 22 h under a gentle flow of Ar. The reaction was cooled to rt and directly concentrated *in vacuo* before being purified by flash column chromatography (1:1–2:3 pentane:Et_2O) to afford enone **S19** as a yellow oil (164 mg, 45%). Amide **S15** (104 mg, 44%) could also be recovered.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.28 (m, 5 H, 2 × H-13, 2 × H-14 and H-15), 6.77 (dd, *J* = 15.9, 5.2 Hz, 1 H, H-2), 6.32 (d, *J* = 15.8 Hz, 1 H, H-3), 5.09 (s, 2 H, 2 × H-11), 5.06–4.99 (m, 1 H, NH), 3.99–3.86 (m, 4 H, 4 × H-16), 3.80–3.67 (m, 1 H, H-1), 2.90 (s, 2 H, 2 × H-5), 1.41 (s, 3 H, 3 × H-7), 0.90 (quint.t, *J* = 15.9, 5.2 Hz, 1 H, H-8), 0.66–0.51 (m, 2 H, H-9 and H-9′), 0.47–0.38 (m, 1 H, H-9) and 0.32 ppm (dq, *J* = 8.9, 4.7 Hz, 1 H, H-9′); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 196.9 (C-4), 155.7 (C-10), 145.5 (C-2), 136.3 (C-12), 129.6 (C-3), 128.7 (2 C, 2 × C-13 or 2 × C-14), 128.4 (C-15), 128.3 (2 C, 2 × C-13 or 2 × C-14), 108.2 (C-6), 67.1 (C-11), 64.78 (C-16), 64.76 (C-16), 56.4 (C-1), 50.2 (C-5), 24.9 (C-7), 15.4 (C-8), 3.6

(C-9′) and 4.3 ppm (C-9); **FTIR** ν_{max} (thin film): 3326, 2985, 2889, 1693, 1522, 1234, 1045 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{20}H_{25}NNaO_5^+$ $[M+H]^+$ 382.1625; found 382.1624 (Δ 0.26 ppm).

Benzyl 2-cyclopropyl-5-((2-methyl-1,3-dioxolan-2-yl)methyl)-1H-pyrrole-1-carboxylate (**311**)



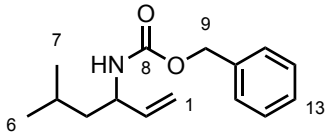
Note: Benzene and $CHCl_3$ were separately sparged with Ar for *ca.* 10 min prior to use.

A solution of enone **S19** (89.9 mg, 0.250 mmol) in benzene:$CHCl_3$ (3:1, 8 mL) was added to the irradiation vessel. The insert was added, screw cap fitted and the vessel flushed with Ar for 10 min. The vessel was placed under a gentle flow of Ar *via* a manifold for the remainder of the reaction. The reaction was cooled to 0 °C (cryostat-cooled acetone bath), a 365 nm UVP Pen-Ray placed in the insert and switched on, and the reaction then stirred at 0 °C for 8 h. The Pen-Ray was switched off and the reaction then allowed to warm to rt. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (17:3 pentane:Et_2O) to afford pyrrole **311** as a colourless oil (57.7 mg, 67%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.48–7.44 (m, 2 H, 2 × H-9), 7.41–7.34 (m, 3 H, 2 × H-10 and H-11), 5.90 (d, *J* = 3.3 Hz, 1 H, H-3), 5.75 (dd, *J* = 3.3, 1.1 Hz, 1 H, H-4), 5.36 (s, 2 H, 2 × H-7), 3.81–3.73 (m, 2 H, 2 × H-15), 3.53–3.46 (m, 2 H, 2 × H-15), 3.18 (s, 2 H, 2 × H-12), 2.06 (dddd, *J* = 13.6, 6.3, 5.3, 2.7 Hz, 1 H, H-16), 1.26 (s, 3 H, 3 × H-14), 0.72–0.66 (m, 2 H, 2 × H-17) and 0.54–0.48 ppm (m, 2 H, 2 × H-17); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ = 152.5 (C-6), 138.7 (C-5), 135.2 (C-8), 129.7 (C-2), 129.0 (2 C, 2 × C-9), 128.76 (C-11), 128.75 (2 C, 2 × C-10), 112.6 (C-3), 109.3 (C-13), 108.1 (C-4), 69.1 (C-7), 65.1 (2 C, 2 × C-15), 37.8

(C-12), 25.1 (C-14), 9.7 (C-16) and 6.7 ppm (2 C, 2 × C-17); **FTIR** ν_{max} (thin film): 1741, 1396, 1308, 1293, 1213, 1117, 1047, 783 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{20}H_{23}NNaO_4^+$ $[M+Ma]^+$ 364.1519; found 364.1519 (Δ 0.00 ppm).

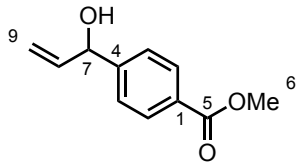
Benzyl (5-methylhex-1-en-3-yl)carbamate (**S20**)



Isovaleraldehyde (0.590 mL, 5.50 mmol) and formic acid (1.20 mL, 31.8 mmol) were sequentially added to a solution of benzyl carbamate (756 mg, 5.00 mmol) and benzenesulfinic acid sodium salt (821 mg, 5.00 mmol) in THF (2.2 mL, 2.5 M wrt. isovaleraldehyde) and H_2O (5.5 mL, 1 M wrt. isovaleraldehyde) at rt and the reaction then stirred vigorously at rt for 4 days. The suspension was filtered and the solids then washed sequentially with H_2O (10 mL) and pentane (10 mL) before being dried under high vacuum to afford the corresponding sulfinate as a white solid (1.54 g) which was used without further purification. The sulfinate was redissolved in THF (30 mL, 0.15 M) and cooled to –20 °C (cryostat-cooled acetone bath). Vinylmagnesium bromide (1 M in THF, 10.7 mL, 10.7 mmol) was added dropwise over 15 min. The reaction was removed from the cold bath and placed in a 0 °C (ice/H_2O) bath and stirred for 2 h, warming slowly to 0 °C. The reaction was quenched at 0 °C by dropwise addition of NH_4Cl (sat., aq., 20 mL), diluted with H_2O (20 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1–4:1 pentane:Et_2O) to afford carbamate **S20** as a viscous clear oil (549 mg, 44%).

^{1}H NMR (DMSO-d^6, 400 MHz): δ = 7.41–7.25 (m, 5 H, 2 × H-11, 2 × H-12 and H-13), 5.73 (ddd, *J* = 16.6, 9.7, 6.3 Hz, 1 H, H-2), 5.13–4.95 (m, 5 H, 2 × H-1, 2 × H-9 and NH), 4.03 (quint., *J* = 7.6 Hz, 1 H, H-3), 1.59 (sept., *J* = 6.8 Hz, 1 H, H-5), 1.42–1.30 (m, 1 H, H-4), 1.30–1.17 (m, 1 H, H-4) and 0.86 ppm (app. d, *J* = 6.7 Hz, 6 H, 3 × H-6 and 3 × H-7); **^{13}C NMR** (DMSO-d^6, 101 MHz): δ = 155.5 (C-8), 140.0 (C-2), 137.3 (C-10), 128.3 (2 C, 2 × C-11 or 2 × C-12), 127.73 (C-13), 127.66 (2 C, 2 × C-11 or 2 × C-12), 113.7 (C-1), 65.1 (C-9), 51.2 (C-3), 43.4 (C-4), 24.2 (C-5), 22.8 (C-6 or C-7) and 22.0 ppm (C-6 or C-7); **FTIR** ν_{max} (thin film): 3326, 2956, 1693, 1527, 1247, 1222, 919, 736 and 696 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{15}H_{22}NO_2^+$ $[M+H]^+$ 270.1465; found 270.1465 (Δ 0.00 ppm).

Methyl 4-(1-hydroxyallyl)benzoate (**S21**)

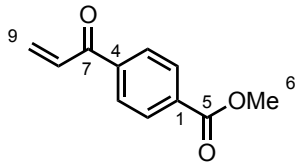


Vinylmagnesium bromide (1 M, in THF, 18.0 mL, 18.0 mmol) was added dropwise over 10 min to a solution of methyl 4-formylbenzoate (2.46 g, 15.0 mmol) in THF (38 mL, 0.4 M) at –78 °C (dry ice/acetone bath) and the reaction then stirred at –78 °C for 75 min. The reaction was quenched at –78 °C by fast addition of HCl (2 M, aq., 20 mL) before being removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (7:3–1:1 pentane:Et_2O) to afford alcohol **S21** as a colourless oil (2.28 g, 79%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.03–7.97 (m, 2 H, 2 × H-2), 7.46–7.39 (m, 2 H, 2 × H-3), 5.99 (ddd, *J* = 17.2, 10.3, 6.2 Hz, 1 H, H-8), 5.37–5.31 (m, 1 H, H-9$_{trans}$), 5.23 (d, *J* = 5.7 Hz,

1 H, H-7), 5.22–5.18 (m, 1 H, H-9$_{cis}$), 3.89 (s, 3 H, 3 × H-6) and 2.49 ppm (br. s, 1 H, OH).; **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.1 (C-5), 147.7 (C-1), 139.8 (C-8), 129.9 (2 C, 2 × C-2), 129.4 (C-4), 126.3 (2 C, 2 × C-3), 116.0 (C-9), 75.0 (C-7) and 52.3 ppm (C-6); **FTIR** ν_{max} (thin film): 3435, 1719, 1703, 1276, 1110 and 712 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{11}H_{12}NaO_3^+$ $[M+H]^+$ 215.0679; found 215.0680 (Δ 0.46 ppm).

Methyl 4-acryloylbenzoate (**S22**)

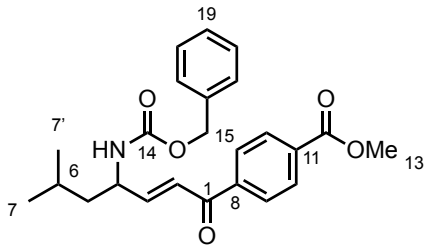


$NaHCO_3$ (9.24 g, 110 mmol) and Dess–Martin Periodinane (7.00 g, 16.5 mmol) were sequentially added as single portions to a solution of alcohol **S21** (2.11 g, 11.0 mmol) in CH_2Cl_2 (55 mL, 0.2 M) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 16 h, warming slowly to rt. The reaction was quenched at rt by addition of a 1:1:1 solution of $NaHCO_3$ (sat., aq.), $Na_2S_2O_3$ (sat., aq.) and H_2O (75 mL total), and the biphasic mixture then stirred vigorously at rt until clear on standing. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford ketone **S22** as a white solid (1.55 g, 74%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.16–8.13 (m, 2 H, 2 × H-2), 8.00–7.97 (m, 2 H, 2 × H-3), 7.14 (dd, *J* = 17.2, 10.6 Hz, 1 H, H-8), 6.46 (dd, *J* = 17.1, 1.5 Hz, 1 H, H-9$_{trans}$), 6.00 (dd, *J* = 10.6, 1.5 Hz, 1 H, H-9$_{cis}$) and 3.96 ppm (s, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 190.8 (C-7), 166.4 (C-5), 140.8 (C-1), 133.9 (C-4), 132.4 (C-8), 131.3 (C-9), 130.0 (2 C, 2 × C-2), 128.7 (2 C, 2 × C-3) and 52.6 ppm (C-6); **FTIR** ν_{max} (thin film): 1722, 1689, 1410,

1276, 1223, 1108, 993 and 737 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{11}H_{11}O_3^+$ $[M+H]^+$ 191.0703; found 191.0705 (Δ 1.05 ppm); **M.P.** 49–51 °C ($CHCl_3$).

Methyl (E)-4-(4-(((benzyloxy)carbonyl)amino)-6-methylhept-2-enoyl)benzoate (**S23**)



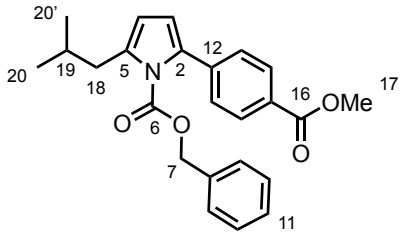
Notes: Experimental setup B (Section 5.3) was used for this reaction. Glassware was not flame dried but was charged with Ar and kept under a positive Ar pressure *via* a manifold line prior to use. Dry PhMe was sparged with Ar for *ca.* 10 min prior to use.

Enone **S22** (950 mg, 5.00 mmol) was added to a solution of amide **S20** (247 mg, 1.00 mmol) in PhMe (4 mL, 0.25 M) at rt. Hoveyda–Grubbs second generation catalyst (15.7 mg, 25.0 μmol) was added under a positive Ar pressure the reaction then stirred at rt for 24 h under a gentle flow of Ar. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (9:1–3:2 pentane:Et_2O) to afford enone **S23** as a pale yellow solid (141 mg, 34%). Amide **S20** (97.0 mg, 39%) was also recovered.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.11 (d, *J* = 8.0 Hz, 2 H, 2 × H-10), 7.93 (d, *J* = 8.0 Hz, 2 H, 2 × H-9), 7.42–7.30 (m, 5 H, 2 × H-17, 2 × H-18 and H-19), 7.03–6.85 (m, 2 H, H-2 and H-3), 5.12 (d, *J* = 2.9 Hz, 2 H, 2 × H-15), 4.91–4.77 (m, 1 H, NH), 4.57–4.47 (m, 1 H, H-4), 3.95 (s, 3 H, 3 × H-13), 1.81–1.65 (m, 1 H, H-6), 1.47 (t, *J* = 7.4 Hz, 2 H, 2 × H-5), 0.96 (s, 3 H, 3 × H-7) and 0.94 ppm (s, 3 H, 3 × H-7′); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 190.2 (C-1), 166.3 (C-12), 155.8 (C-14), 149.4 (C-3), 141.1 (C-11), 136.4 (C-16), 133.7 (C-8), 129.9 (2 C, 2 × C-10), 128.7 (2 C, 2 × C-17 or 2 × C-18), 128.6 (2 C, 2 × C-9), 128.4 (C-19), 128.3 (2 C, 2 × C-17 or 2 × C-18), 124.7 (C-2), 67.1 (C-15), 52.6 (C-13), 51.1 (C-4), 43.8 (C-5), 24.9 (C-

6), 22.9 (C-7) and 22.3 ppm (C-7′); **FTIR** ν_{max} (thin film): 3326, 2985, 2889, 1693, 1522, 1234, 1045 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{24}H_{27}NNaO_5^+$ $[M+Na]^+$ 432.1781; found 432.1775 (Δ 1.39 ppm); **M.P.** 117–118 °C ($CHCl_3$).

Benzyl 2-isobutyl-5-(4-(methoxycarbonyl)phenyl)-1H-pyrrole-1-carboxylate (**312**)



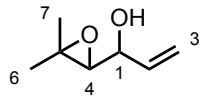
Note: Benzene and $CHCl_3$ were separately sparged with Ar for *ca.* 10 min prior to use.

A solution of enone **S23** (102 mg, 0.250 mmol) in benzene:$CHCl_3$ (3:1, 8 mL) was added to the irradiation vessel. The insert was added, screw cap fitted and the vessel flushed with Ar for 10 min. The vessel was placed under a gentle flow of Ar *via* a manifold for the remainder of the reaction. The reaction was cooled to 0 °C (cryostat-cooled acetone bath), a 365 nm UVP Pen-Ray placed in the insert and switched on, and the reaction then stirred at 0 °C for 8 h. The Pen-Ray was switched off and the reaction then allowed to warm to rt. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford pyrrole **312** as a colourless oil (45.0 mg, 46%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79–7.74 (m, 2 H, 2 × H-14), 7.17–7.07 (m, 5 H, 2 × H-10, H-11 and 2 × H-13), 6.89–6.85 (m, 2 H, 2 × H-9), 6.09 (d, *J* = 3.3 Hz, 1 H, H-3), 5.88 (d, *J* = 3.4 Hz, 1 H, H-4), 4.99 (s, 2 H, 2 × H-7), 3.80 (s, 3 H, 3 × H-17), 2.56 (dd, *J* = 7.0, 0.7 Hz, 2 H, 2 × H-18), 1.77 (non., *J* = 6.7 Hz, 1 H, H-19), 0.80 (s, 3 H, 3 × H-20) and 0.78 ppm (s, 3 H, 3 × H-20′); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.0 (C-16), 151.7 (C-6), 139.2 (C-2 or C-15), 138.2 (C-2 or C-15), 134.1 (C-8 or C-12), 134.0 (C-8 or C-12), 129.4 (2 C, 2 × C-14), 128.8 (2 C, 2 × C-9), 128.7 (C-11), 128.5 (2 C, 2 × C-10), 128.0 (C-5), 127.6

(2 C, 2 × C-13), 114.1 (C-3), 111.7 (C-4), 69.3 (C-7), 52.2 (C-17), 37.7 (C-18), 28.3 (C-19) and 22.6 ppm (2 C, C-20 and C-20′); **FTIR** ν_{max} (thin film): 1743, 1718, 1274, 1147, 1101, 768 and 698 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{24}H_{26}NO_4^+$ $[M+H]^+$ 392.1856; found 392.1854 (Δ 0.51 ppm).

1-(3,3-Dimethyloxiran-2-yl)prop-2-en-1-ol (**314**)



A solution of alcohol **317** (1.04 g, 9.26 mmol) in CH_2Cl_2 (2 mL + 0.5 mL rinse) was added to a solution of vanadyl acetylacetonate (491 mg, 1.85 mmol) in CH_2Cl_2 (90 mL, 0.1 M) at 0 °C (ice/H_2O bath). *t*-Butyl hydroperoxide (*ca.* 5.5 M in decane, 3.4 mL, 18.6 mmol) was added dropwise and the reaction then removed from the cold bath and stirred for 18 h, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $Na_2S_2O_3$ (sat., aq., 20 mL), the layers separated and the aqueous phase extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (2:1 pentane:Et_2O) to afford epoxide **314** as a colourless oil and an inseparable 3.3:1 mixture of diastereomers (513 mg, 43%). The diastereomeric ratio was calculated on the basis of the integrals of the two H-2 peaks in the ^1H NMR spectrum (6.02 and 5.89 ppm). The stereochemical identities of the isomers are unconfirmed. Data for the major diastereomer is consistent with that reported for an unspecified stereoisomer in the literature.[217]

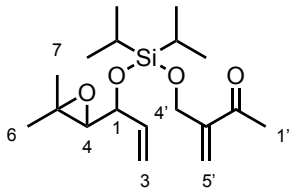
^1H NMR (Major Diastereomer, $CDCl_3$, 400 MHz): δ = 5.89 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H, H-2), 5.37 (dt, *J* = 17.3, 1.5 Hz, 1 H, H-3$_{trans}$), 5.25 (dt, *J* = 10.6, 1.4 Hz, 1 H, H-3$_{cis}$), 4.07–3.97 (m, 1 H, H-1), 2.77 (d, *J* = 7.8 Hz, 1 H, H-4), 2.29–2.21 (m, 1 H, OH), 1.35 (s, 3 H, 3 × H-6 or 3 × H-7) and 1.34 ppm (s, 3 H, 3 × H-6 or 3 × H-7).

^{13}C NMR (Major Diastereomer, $CDCl_3$, 101 MHz): δ = 136.1 (C-2), 116.8 (C-3), 72.0 (C-1), 66.9 (C-4), 59.4 (C-5), 25.02 (C-6 or C-7) and 19.4 ppm (C-6 or C-7).

^{1}H NMR (Minor Diastereomer, $CDCl_3$, 400 MHz): δ = 6.02 (ddd, *J* = 17.3, 10.5, 5.7 Hz, 1 H, H-2), 5.38 (dt, *J* = 17.3, 1.4 Hz, 1 H, H-3$_{trans}$), 5.26 (dt, *J* = 10.5, 1.3 Hz, 1 H, H-3$_{cis}$) 4.07–3.97 (m, 1 H, H-1), 2.74 (d, *J* = 7.7 Hz, 1 H, H-4), 1.84 (s, 1 H, OH), 1.42 (s, 3 H, 3 × H-6 or 3 × H-7) and 1.36 ppm (s, 3 H, 3 × H-6 or 3 × H-7).

^{13}C NMR (Minor Diastereomer, $CDCl_3$, 101 MHz): δ = 137.6 (C-2), 116.7 (C-3), 71.3 (C-1), 65.4 (C-4), 59.4 (C-5), 24.95 (C-6 or C-7) and 18.9 ppm (C-6 or C-7).

3-(((((1-(3,3-Dimethyloxiran-2-yl)allyl)oxy)diisopropylsilyl)oxy)methyl)but-3-en-2-one (**315**)



i-Pr_2SiCl_2 (0.390 mL, 2.45 mmol) was added dropwise to a solution of imidazole (349 mg, 5.13 mmol) in CH_2Cl_2 (25 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **314** (299 mg, 2.33 mmol) in CH_2Cl_2 (4.4 mL + 0.2 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (257 mg, 2.57 mmol) in CH_2Cl_2 (2.6 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford TST **315** as a colourless oil and an inseparable 5:1 mixture of diastereomers (388 mg, 49%). The diastereomeric ratio was calculated on the basis of the integrals of the two H-2 peaks in the ^{1}H NMR spectrum (5.95 and 5.83 ppm). The stereochemical identities of the isomers are undetermined.

^{1}H NMR (Major Diastereomer, $CDCl_3$, 400 MHz): δ = 6.19–6.10 (m, 2 H, 2 × H-5′), 5.83 (ddd, *J* = 17.2, 10.5, 5.2 Hz, 1 H, H-2), 5.34 (dt, *J* = 17.2, 1.6 Hz, 1 H, H-3$_{trans}$), 5.17 (dt, *J* = 10.5, 1.5 Hz, 1 H, H-3$_{cis}$), 4.59–4.47 (m, 2 H, 2 × H-4′), 4.15–4.07 (m, 1 H, H-1), 2.73 (d, *J* = 7.8 Hz, 1 H, H-4), 2.34 (s, 3 H, 3 × H-1′), 1.294 (s, 3 H, 3 × H-6 or 3 × H-7), 1.287 (s, 3 H, 3 × H-6 or 3 × H-7) and 1.12–1.08 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

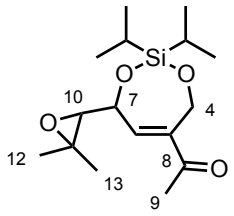
^{13}C NMR (Major Diastereomer, $CDCl_3$, 101 MHz): δ = 199.1 (C-2′), 147.6 (C-3′), 136.5 (C-2), 124.0 (C-5′), 115.68 (C-3), 73.3 (C-1), 67.2 (C-4), 60.9 (C-4′), 57.8 (C-5), 26.2 (C-1′), 24.9 (C-6 or C-7), 19.6 (C-6 or C-7), 17.38 ($SiCH\underline{C}H_3$), 17.36 ($SiCH\underline{C}H_3$), 17.31 ($SiCH\underline{C}H_3$), 17.26 ($SiCH\underline{C}H_3$), 12.4 ($Si\underline{C}HCH_3$) and 12.28 ppm ($Si\underline{C}HCH_3$).

^{1}H NMR (Minor Diastereomer, $CDCl_3$, 400 MHz): δ = 6.19–6.10 (m, 2 H, 2 × H-5′), 5.95 (ddd, *J* = 17.2, 10.4, 5.7 Hz, 1 H, H-2), 5.32 (dt, *J* = 17.2, 1.5 Hz, 1 H, H-3$_{trans}$), 5.19 (dt, *J* = 10.4, 1.4 Hz, 1 H, H-3$_{cis}$), 4.59–4.47 (m, 2 H, 2 × H-4′), 4.15–4.07 (m, 1 H, H-1), 2.72 (d, *J* = 7.9 Hz, 1 H, H-4), 2.36 (s, 3 H, 3 × H-1′), 1.34 (s, 3 H, 3 × H-6 or 3 × H-7), 1.32 (s, 3 H, 3 × H-6 or 3 × H-7) and 1.12–1.08 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Minor Diastereomer, $CDCl_3$, 101 MHz): δ = 199.0 (C-2′), 147.3 (C-3′), 137.9 (C-2), 124.1 (C-5′), 115.71 (C-3), 71.2 (C-1), 66.2 (C-4), 60.8 (C-4′), 59.4 (C-5), 26.1 (C-1′), 24.5, (C-6 or C-7), 19.1 (C-6 or C-7), 17.38 ($SiCH\underline{C}H_3$), 17.36 ($SiCH\underline{C}H_3$), 17.31 ($SiCH\underline{C}H_3$), 17.26 ($SiCH\underline{C}H_3$), 12.4 ($Si\underline{C}HCH_3$) and 12.32 ppm ($Si\underline{C}HCH_3$).

FTIR ν_{max} (thin film): 2946, 2868, 1678, 1148, 1091, 1034 and 858 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{18}H_{32}O_4NaSi^+$ $[M+Na]^+$ 363.1962; found 363.1952 (Δ 2.75 ppm).

1-(7-((S)-3,3-Dimethyloxiran-2-yl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-5-yl)ethanone (**316**)

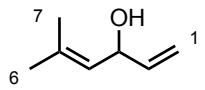


Note: dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Stewart–Grubbs catalyst (8.2 mg, 14 μmol) was added to a round-bottomed flask fitted with a reflux condenser and the system then evacuated and charged with N_2 (× 3). PhMe (55.4 mL) and a solution of TST **315** (97.6 mg, 0.287 mmol) in PhMe (1.5 mL + 0.5 mL rinse, 5 mM final concentration) were sequentially added at rt and the reaction then heated to 80 °C for 24 h under N_2 atmosphere supplied *via* a manifold. The reaction mixture was cooled to rt and directly concentrated *in vacuo* before being purified by flash column chromatography (17:3 pentane:Et_2O) to afford silaketal **316** as a yellow oil and as a single diastereomer (1.8 mg, 2%). The relative stereochemistry is undetermined.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.64–6.59 (m, 1 H, H-6), 4.85 (dt, *J* = 16.4, 1.3 Hz, 1 H, H-4), 4.77 (ddd, *J* = 16.4, 2.8, 1.9 Hz, 1 H, H-4), 4.70–4.65 (m, 1 H, H-7), 3.03 (d, *J* = 7.9 Hz, 1 H, H-10), 2.34 (s, 3 H, 3 × H-9), 1.39 (s, 3 H, 3 × H-12 or 3 × H-13), 1.37 (s, 3 H, 3 × H-12 or 3 × H-13) and 1.11–1.04 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.4 (C-8), 144.0 (C-5), 140.2 (C-6), 71.2 (C-7), 66.6 (C-10), 61.0 (C-4), 58.2 (C-11), 26.3 (C-9), 25.1 (C-12 or C-13), 19.7 (C-12 or C-13), 17.49 ($SiCH\underline{C}H_3$), 17.46 ($SiCH\underline{C}H_3$), 17.3 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 12.2 ($Si\underline{C}HCH_3$) and 12.1 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2946, 2868, 1673, 1247, 1094, 1031, 887 and 789 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{16}H_{28}O_4NaSi^+$ $[M+Na]^+$ 335.1649; found 335.1651 (Δ 0.60 ppm).

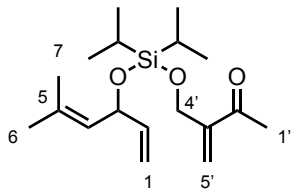
5-Methylhexa-1,4-dien-3-ol (**317**)



3-Methylcrotonaldehyde (2.00 mL, 20.7 mmol) was added dropwise *via* syringe pump over 1 h to a solution of vinylmagnesium bromide (1 M in THF, 22.8 mL, 22.8 mmol) and THF (18.6 mL, 0.5 M final concentration) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 2.5 h, warming slowly to rt. The reaction was quenched at rt by dropwise addition of NH_4Cl (sat., aq., 20 mL) and diluted with H_2O (20 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before bring purified by flash column chromatography (4:1 pentane:Et_2O) to afford alcohol **317** as a pale yellow oil (1.63 g, 71%). Data is consistent with that reported in the literature.[218]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.88 (ddd, *J* = 17.2, 10.4, 5.8 Hz, 1 H, H-2), 5.23 (dt, *J* = 17.2, 1.5 Hz, 1 H, H-1$_{trans}$), 5.19 (sept., *J* = 1.4 Hz, 1 H, H-4), 5.09 (dt, *J* = 10.3, 1.4 Hz, 1 H, H-1$_{cis}$), 4.90–4.81 (m, 1 H, H-3), 1.74 (s, 3 H, 3 × H-7), 1.71 (s, 3 H, 3 × H-6) and 1.51 ppm (br. s, 1 H, OH); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 140.2 (C-2), 136.0 (C-5), 126.1 (C-4), 114.3 (C-1), 70.2 (C-3), 26.0 (C-6) and 18.4 ppm (C-7).

3-(((Diisopropyl((5-methylhexa-1,4-dien-3-yl)oxy)silyl)oxy)methyl)but-3-en-2-one (**318**)

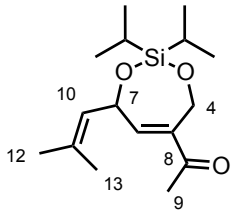


i-Pr_2SiCl_2 (0.430 mL, 2.38 mmol) was added dropwise to a solution of imidazole (386 mg, 5.66 mmol) in CH_2Cl_2 (24 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **317** (254 mg, 2.27 mmol) in CH_2Cl_2 (4.1 mL + 0.4 mL

rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (250 mg, 2.49 mmol) in CH_2Cl_2 (2.5 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **318** as a colourless oil (544 mg, 74%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.16 (td, *J* = 2.2, 1.0 Hz, 1 H, H-5′), 6.12 (td, *J* = 2.0, 1.0 Hz, 1 H, H-5′), 5.80 (ddd, *J* = 17.1, 10.3, 5.2 Hz, 1 H, H-2), 5.21–5.11 (m, 2 H, H-1 and H-4), 5.01–4.94 (m, 2 H, H-1 and H-3), 4.47 (t, *J* = 2.1 Hz, 2 H, 2 × H-4′), 2.35 (s, 3 H, 3 × H-1′), 1.68 (d, *J* = 1.4 Hz, 3 H, 3 × H-6 or 3 × H-7), 1.62 (d, *J* = 1.3 Hz, 3 H, 3 × H-6 or 3 × H-7) and 1.07–1.02 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.2 (C-2′), 147.8 (C-3′), 140.3 (C-2), 132.5 (C-5), 127.4 (C-4), 124.0 (C-5′), 112.7 (C-1), 70.6 (C-3), 60.9 (C-4′), 26.3 (C-1′), 25.8 (C-6 or C-7), 18.4 (C-6 or C-7), 17.6 ($SiCH\underline{C}H_3$), 17.5 (2 C, 2 × $SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 12.5 ($Si\underline{C}HCH_3$) and 12.4 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2867, 1678, 1090, 1042 and 885 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{18}H_{32}NaO_3Si^+$ $[M+Na]^+$ 347.2013; found 347.2014 (Δ 0.29 ppm).

1-(2,2-Diisopropyl-7-(2-methylprop-1-en-1-yl)-4,7-dihydro-1,3,2-dioxasilepin-5-yl)ethanone (**319**)

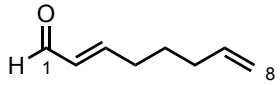


Note: Experimental setup B (Section 5.3) was used for this reaction. Dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (19.5 mg, 31.1 μmol) was added to a round-bottomed flask fitted with a reflux condenser and the system then evacuated and charged with N_2 (× 3). PhMe (57 mL) and a solution of TST **318** (102 mg, 0.313 mmol) in PhMe (1.8 mL + 0.2 mL rinse, 5 mM final concentration) were sequentially added at rt and the flask then placed in an oil bath pre-heated to 60 °C. The reaction was immediately heated to 100 °C and stirred for a further 30 min once the temperature was reached (*ca.* 30 min). A solution of Hoveyda–Grubbs second generation catalyst (19.5 mg, 31.1 μmol) in PhMe (4 mL, 5 mM final concentration) was then added over 2 h *via* syringe pump. The reaction was stirred at 100 °C for 22 h under N_2 atmosphere supplied *via* a manifold. The reaction mixture was cooled to rt and directly concentrated *in vacuo* before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford silaketal **319** as a yellow oil (20.5 mg, 22%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.60 (ddd, *J* = 3.7, 1.7, 0.8 Hz, 1 H, H-6), 5.58–5.52 (m, 1 H, H-7), 5.38 (dsept., *J* = 8.7, 1.4 Hz, 1 H, H-10), 4.83 (ddd, *J* = 15.6, 1.3, 0.8 Hz, 1 H, H-4), 4.75 (ddd, *J* = 15.7, 2.3, 1.7 Hz, 1 H, H-4), 2.30 (s, 3 H, 3 × H-9), 1.78 (d, *J* = 1.4 Hz, 3 H, 3 × H-12 or 3 × H-13), 1.74 (d, *J* = 1.4 Hz, 3 H, 3 × H-12 or 3 × H-13) and 1.08–1.03 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.9 (C-8), 146.1 (C-6), 141.6 (C-5), 135.4 (C-11), 125.8 (C-10), 68.3 (C-7), 60.1 (C-4), 26.2 (C-9), 25.9 (C-12 or C-13), 18.4 (C-12 or C-13), 17.6 ($SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 12.40 ($Si\underline{C}HCH_3$) and 12.38 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2867, 1671, 1240, 1127, 1102, 1043, 1011, 885, 789 and 695 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{16}H_{29}O_3Si^+$ $[M+H]^+$ 297.1881; found 297.1882 (Δ 0.34 ppm).

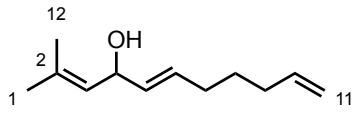
(E)-Octa-2,7-dienal (**S24**)



Celite (3.34 g, 1 g per 1 g pyridinium chlorochromate) and pyridinium chlorochromate (3.34 g, 15.5 mmol) were added sequentially as single portions to a solution of 2,7-octadienol (1.50 mL, 10.3 mmol) in CH_2Cl_2 (50 mL, 0.2 M) at rt with vigorous stirring. The reaction was stirred at rt for 1.5 h before being filtered through a pad of silica. The solids were then washed several times with EtOAc. Fractions containing product were concentrated *in vacuo* before being purified by flash column chromatography (17:3 pentane:Et_2O) to afford aldehyde **S24** as a pale yellow oil (820 mg, 64%). Data is consistent with that reported in the literature.[219]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.50 (d, *J* = 7.9 Hz, 1 H, H-1), 6.85 (dt, *J* = 15.6, 6.8 Hz, H-3), 6.12 (ddt, *J* = 15.6, 7.9, 1.6 Hz, 1 H, H-2), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H, H-7), 5.07–4.96 (m, 2 H, 2 × H-8), 2.41–2.29 (m, 2 H, 2 × H-4), 2.15–2.06 (m, 2 H, 2 × H-6) and 1.61 ppm (quint., *J* = 7.5 Hz, 2 H, 2 × H-5); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 194.2 (C-1), 158.6 (C-3), 137.8 (C-7), 133.3 (C-2), 115.5 (C-8), 33.2 (C-6), 32.1 (C-4) and 27.1 ppm (C-5).

(E)-2-Methylundeca-2,5,10-trien-4-ol (**S25**)

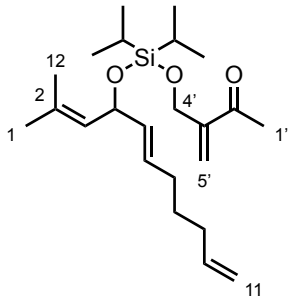


t-BuLi (1.68 M in hexanes, 1.92 mL, 3.23 mmol) was added dropwise to a solution of 1-bromo-2-methyl-1-propene (0.165 mL, 1.61 mmol) in Et_2O (5.4 mL, 0.3 M wrt. bromide) at –78 °C (dry ice/acetone bath) and the reaction then stirred –78 °C for 20 min. In a separate round-bottomed flask, $MgCl_2$ (154 mg, 1.62 mmol) was suspended in Et_2O (1 mL) at rt. The vinyllithium solution was transferred directly to the $MgCl_2$ suspension *via* cannula and the

reaction then stirred at rt for 2.5 h. A solution of aldehyde **S24** (102 mg, 0.823 mmol) in Et_2O (1 mL) was added dropwise and the reaction then stirred at rt for a further 1.5 h. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 5 mL), the layers separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (4:1 pentane:Et_2O) to afford alcohol **S25** as a yellow oil (108 mg, 73%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H, H-10), 5.66 (dtd, *J* = 15.5, 6.6, 1.0 Hz, 1 H, H-6), 5.51 (ddt, *J* = 15.3, 6.6, 1.3 Hz, 1 H, H-5), 5.21 (dquint., *J* = 8.6, 1.4 Hz, 1 H, H-3), 5.00 (dq, *J* = 17.1, 1.7 Hz, 1 H, H-11$_{trans}$), 4.95 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1 H, H-11$_{cis}$), 4.85–4.77 (m, 1 H, H-4), 2.10–1.99 (m, 4 H, 2 × H-7 and 2 × H-9), 1.73 (d, *J* = 1.4 Hz, 3 H, 3 × H-1 or 3 × H-12), 1.70 (d, *J* = 1.4 Hz, 3 H, 3 × H-1 or 3 × H-12), 1.48 (quint., *J* = 7.5 Hz, 2 H, 2 × H-8) and 1.41 ppm (br. s, 1 H, OH); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 138.8 (C-10), 135.3 (C-2), 132.2 (C-5), 131.4 (C-6), 126.7 (C-3), 114.7 (C-11), 70.0 (C-4), 33.4 (C-9), 31.7 (C-7), 28.5 (C-8), 26.0 (C-1 or C-12) and 18.4 ppm (C-1 or C-12); **FTIR** ν_{max} (thin film): 2975, 2927, 2856, 1441, 968 and 910 cm^{-1}; **HRMS** (CH_4 CI$^+$): Calculated for $C_{12}H_{21}O^+$ $[M+H]^+$ 181.1587; found 181.1592 (Δ 2.76 ppm).

(E)-3-(((Diisopropyl((2-methylundeca-2,5,10-trien-4-yl)oxy)silyl)oxy)methyl)but-3-en-2-one (**332**)

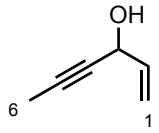


i-Pr_2SiCl_2 (66 μL, 0.36 mmol) was added dropwise to a solution of imidazole (59.0 mg, 0.867 mmol) in CH_2Cl_2 (3.6 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **S25** (62.5 mg, 0.347 mmol) in CH_2Cl_2 (0.5 mL + 0.2 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (38.2 mg, 0.381 mmol) in CH_2Cl_2 (0.4 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford TST **329** as a colourless oil (82.0 mg, 60%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.16 (td, *J* = 2.2, 1.0 Hz, 1 H, H-5′), 3.12 (td, *J* = 2.1, 1.1 Hz, 1 H, H-5′), 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H, H-10), 5.55 (dtd, *J* = 15.3, 6.6, 1.1 Hz, 1 H, H-6), 5.42 (ddt, *J* = 15.3, 5.9, 1.3 Hz, 1 H, H-5), 5.15 (dquint., *J* = 8.3, 1.4 Hz, 1 H, H-3), 4.98 (ddt, *J* = 17.1, 2.2, 1.6 Hz, 1 H, H-11$_{trans}$), 4.96–4.89 (m, 2 H, H-4 and H-11$_{cis}$), 4.46 (t, *J* = 2.1 Hz, 2 H, 2 × H-4′), 2.35 (s, 3 H, 3 × H-1′), 2.09–1.96 (m, 4 H, 2 × H-7 and 2 × H-9), 1.68 (d, *J* = 1.4 Hz, 3 H, 3 × H-1 or 3 × H-12), 1.60 (d, *J* = 1.3 Hz, 3 H, 3 × H-1 or 3 × H-12), 1.44 (quint., *J* = 7.5 Hz, 2 H, 2 × H-8) and 1.06–1.01 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.2 (C-2′), 147.9 (C-3′), 138.9 (C-10),

132.5 (C-5), 131.8 (C-2), 129.3 (C-6), 128.0 (C-3), 124.0 (C-5′), 114.6 (C-11), 70.4 (C-4), 60.9 (C-4′), 33.4 (C-9), 31.7 (C-7), 28.6 (C-8), 26.3 (C-1′), 25.8 (C-1 or C-12), 18.3 (C-1 or 12), 17.59 (SiCH<u>C</u>H$_3$), 17.56 (SiCH<u>C</u>H$_3$), 17.55 (SiCH<u>C</u>H$_3$), 17.4 (SiCH<u>C</u>H$_3$), 12.51 (Si<u>C</u>HCH$_3$) and 12.46 ppm (Si<u>C</u>HCH$_3$); **FTIR** ν_{max} (thin film): 2928, 2867, 1678, 1090, 1045, 971 and 885 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{23}H_{40}O_3NaSi^+$ $[M+Na]^+$ 415.2639; found 415.2630 (Δ 2.17 ppm).

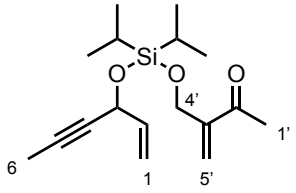
Hex-1-en-4-yn-3-ol (**S26**)



Propyne (*ca.* 7.5 mL) was condensed into a round-bottomed flask at –78 °C (dry ice/acetone bath) using a cold-finger dry ice condenser (dry/ice acetone filled). Under a positive flow of N_2 the condenser was removed and replaced with a stopper. Et_2O (50 mL) was added followed by dropwise addition of *n*-BuLi (2.27 M in THF, 15.0 mL, 34.1 mmol) over 10 min at –78 °C. THF (20 mL) was added and the reaction then stirred at –78 °C for 15 min. Acrolein (2.67 mL, 31.0 mmol) was added dropwise over 10 min and the reaction then stirred at –78 °C for 30 min. The reaction was quenched at –78 °C by dropwise addition of NH_4Cl (sat,. aq., 40 mL) before being diluted with brine (40 mL), acidified to <pH 4 by addition of HCl (1 M, aq.), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with Et_2O (2 × 40 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (4:1 CH_2Cl_2:pentane) to afford alcohol **S26** as a colourless oil (286 mg, contains THF and CH_2Cl_2, *ca.* 75% **S26** by mass).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.95 (ddd, *J* = 17.0, 10.1, 5.5 Hz, 1 H, H-2), 5.42 (dt, *J* = 17.1, 1.4 Hz, 1 H, H-1$_{trans}$), 5.18 (dt, *J* = 10.1, 1.3 Hz, 1 H, H-1$_{cis}$), 4.87–4.78 (m, 1 H, H-3), 2.02 (d, *J* = 6.2 Hz, 1 H, OH) and 1.87 ppm (d, *J* = 2.2 Hz, 3 H, 3 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 137.6 (C-2), 116.1 (C-1), 82.8 (C-5), 78.3 (C-4), 63.5 (C-3) and 3.7 ppm (C-6); **FTIR** ν_{max} (thin film): 3338, 2921, 1644, 1423, 1404, 1270, 1145 and 1010 cm^{-1}; **HRMS** (CH_4 CI$^+$): Calculated for $C_6H_9O^+$ $[M+H]^+$ 97.0648; found 97.0646 (Δ 2.06 ppm).

3-((((Hex-1-en-4-yn-3-yloxy)diisopropylsilyl)oxy)methyl)but-3-en-2-one (**333**)

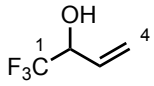


i-Pr_2SiCl_2 (0.278 mL, 1.54 mmol) was added dropwise to a solution of imidazole (250 mg, 3.69 mmol) in CH_2Cl_2 (15.4 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **S26** (75 wt% in THF/CH_2Cl_2, 188 mg, 1.47 mmol) in CH_2Cl_2 (2.8 mL + 0.2 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h via syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (162 mg, 1.62 mmol) in CH_2Cl_2 (1.6 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **333** as a colourless oil (119 mg, 26%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.22–6.10 (m, 2 H, 2 × H-5′), 5.89 (ddd, *J* = 16.8, 10.1, 5.1 Hz, 1 H, H-2), 5.36 (dt, *J* = 17.0, 1.6 Hz, 1 H, H-1$_{trans}$), 5.11 (dq, *J* = 10.1, 1.1 Hz, 1 H, H-1$_{cis}$), 4.98 (dq, *J* = 5.6, 1.9 Hz, 1 H, H-3), 4.62–4.47 (m, 2 H, 2 × H-4′), 2.35 (s, 3 H, 3 ×

H-1′), 1.82 (d, J = 2.2 Hz, 3 H, 3 × H-6) and 1.12–1.02 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.2 (C-2′), 147.6 (C-3′), 138.1 (C-2), 124.1 (C-5′), 114.7 (C-1), 81.8 (C-5), 78.7 (C-4), 63.5 (C-3), 61.1 (C-4′), 26.2 (C-1′), 17.5 ($SiCH\underline{C}H_3$), 17.42 ($SiCH\underline{C}H_3$), 17.40 ($SiCH\underline{C}H_3$), 17.35 ($SiCH\underline{C}H_3$), 12.5 ($Si\underline{C}HCH_3$), 12.3 ($Si\underline{C}HCH_3$) and 3.7 ppm (C-6); **FTIR** ν_{max} (thin film): 2945, 2868, 1678, 1391, 1149, 1090, 930, 885 and 854 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{17}H_{28}O_3NaSi^+$ $[M+Na]^+$ 331.1700; found 331.1700 (Δ 0.00 ppm).

1,1,1-Trifluorobut-3-en-2-ol (**S27**)

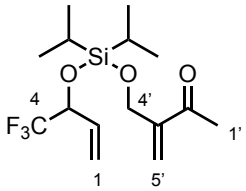


H_2SO_4 (5.5 mL) was added to a two-necked round-bottomed flask fitted with a reflux condenser. Vinylmagnesium bromide (1 M in THF, 8.6 mL, 8.6 mmol) and THF (13.4 mL, 0.4 M total) were added to a second round-bottomed flask fitted with a cold-finger dry ice condenser (dry ice/acetone filled). The dry ice condenser was connected to the top of the reflux condenser by clean rubber tubing. The flask containing H_2SO_4 was heated to 100 °C and the flask containing the vinylmagnesium bromide solution cooled to –78 °C (dry ice/acetone bath). Trifluoroacetaldehyde hydrate (72% in H_2O, 4.00 mL, 17.2 mmol) was added dropwise to the conc. H_2SO_4 over 30 min. Trifluoroacetaldehyde was observed to condense slowly into the vinylmagnesium bromide solution and the reaction then stirred at –78 °C for 2.5 h. The reaction was quenched at –78 °C by dropwise addition of NH_4Cl (sat,. aq., 10 mL), acidified to <pH1 by addition of HCl (3 M, aq., 5 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure (40 °C/300 mbar) until only a small volume

of excess THF remained before being purified by flash column chromatography (3:1 pentane:Et_2O) to afford alcohol **S27** as a colourless oil (1.15 g, 1:1.1 **S27**:THF, 63% **S27** by mass). Data is consistent with that reported in the literature.[220]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.91 (ddd. *J* = 16.7, 10.5, 5.7 Hz, 1 H, H-3), 5.59 (dt, *J* = 17.3, 1.2 Hz, 1 H, H-4$_{trans}$), 5.48 (d, *J* = 10.7 Hz, 1 H, H-4$_{cis}$) and 4.54–4.38 ppm (m, 1 H, H-2); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 130.4 (C-3), 121.2 (C-4) and 71.6 ppm (q, *J* = 31.7 Hz, C-2). A carbon signal for C-1 could not be identified; **^{19}F NMR** ($CDCl_3$, 377 MHz): δ = –79.4 ppm (d, *J* = 6.5 Hz, 3 F, 3 × F-1).

3-(((Diisopropyl((1,1,1-trifluorobut-3-en-2-yl)oxy)silyl)oxy)methyl)but-3-en-2-one (**334**)

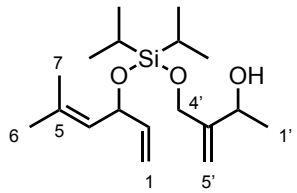


i-Pr_2SiCl_2 (0.295 mL, 1.63 mmol) was added dropwise to a solution of imidazole (265 mg, 3.89 mmol) in CH_2Cl_2 (16 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of alcohol **S27** (63%, 311 mg, 1.56 mmol) in CH_2Cl_2 (2.9 mL + 0.2 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (171 mg, 1.71 mmol) in CH_2Cl_2 (1.7 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (23:2 pentane:Et_2O) to afford TST **334** as a colourless oil (179 mg, 34%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.17–6.11 (m, 2 H, 2 × H-5′), 5.86 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1 H, H-2), 5.50 (dd, *J* = 17.2, 1.3 Hz, 1 H, H-1$_{trans}$), 5.41 (d, *J* = 10.4 Hz, 1 H, H-1$_{cis}$),

4.65–4.53 (m, 1 H, H-3), 4.50 (td, *J* = 2.0, 0.6 Hz, 2 H, 2 × H-4′), 2.36 (s, 3 H, 3 × H-1′) and 1.12–1.01 ppm (m, 14 H, 2 × SiCH(CH_3)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.1 (C-2′), 147.3 (C-3′), 131.7 (C-2), 124.3 (C-5′), 120.9 (C-1), 72.4 (q, *J* = 32.3 Hz, C-3), 61.2 (C-4′), 26.2 (C-1′), 17.2 (SiCH<u>C</u>H$_3$), 17.2 (SiCH<u>C</u>H$_3$), 17.2 (SiCH<u>C</u>H$_3$), 17.1 (SiCH<u>C</u>H$_3$), 12.3 (Si<u>C</u>HCH$_3$) and 12.2 ppm (Si<u>C</u>HCH$_3$). A peak corresponding to C-4 could not be identified; **^{19}F NMR** ($CDCl_3$, 377 MHz): δ = –78.7 ppm (d, *J* = 6.3 Hz, 3 F, 3 × F-4); **FTIR** ν_{max} (thin film): 2950, 2871, 1679, 1270, 1175, 1129 and 1091 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{15}H_{25}O_3F_3NaSi^+$ $[M+Na]^+$ 361.1417; found 361.1417 (Δ 0.00 ppm).

3-(((Diisopropyl((5-methylhexa-1,4-dien-3-yl)oxy)silyl)oxy)methyl)but-3-en-2-ol (**335**)

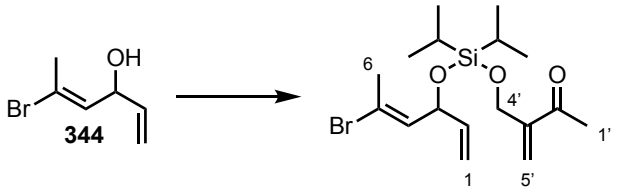


$CeCl_3 \cdot 7H_2O$ (253 mg, 0.678 mmol) was added to a solution of TST **318** (200 mg, 0.616 mmol) in MeOH (3 mL, 0.2 M) at rt and the suspension then cooled to 0 °C (ice/H_2O bath). $NaBH_4$ (25.6 mg, 0.678 mmol) was added in one portion (CAUTION: effervescence of H_2) and the reaction then stirred at 0 °C for 1 h. The reaction was quenched at 0 °C by drop-wise addition of acetone (3 mL) and the solution directly concentrated *in vacuo*. The residue was redissolved in EtOAc (5 mL), potassium sodium tartrate tetrahydrate (sat., aq., 5 mL) added at rt and the mixture stirred vigorously at rt overnight. The mixture was diluted with NH_4Cl (sat., aq., 5 mL) and H_2O (5 mL), the layers separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (4:1 pentane:Et_2O) to afford alcohol **335** as a colourless oil and an inseparable *ca.* 1:1 ratio of di-

astereomers (181 mg, 90%). The diastereomeric ratio was estimated on the basis of peak heights of the two C-3′ peaks in the ^{13}C NMR spectrum (69.49 and 69.45 ppm). Diastereomeric peaks are not distinguishable in the ^{1}H NMR spectrum. ^{13}C NMR diastereomeric peaks are reported together where distinguishable.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.82 (ddd, *J* = 17.2, 10.2, 5.2 Hz, 1 H, H-2), 5.21 (dt, *J* = 17.2, 1.7 Hz, 1 H, H-1*trans*), 5.16 (dt, *J* = 8.3, 1.5 Hz, 1 H, H-4), 5.07 (q, *J* = 1.2 Hz, 2 H, 2 × H-5′), 5.04–4.98 (m, 2 H, H-1*cis* and H-3), 4.45–4.29 (m, 3 H, 2 × H-4′ and H-2′), 2.47 (d, *J* = 4.7 Hz, 1 H, OH), 1.71 (d, *J* = 1.3 Hz, 3 H, 3 × H-6 or 3 × H-7), 1.65 (d, *J* = 1.3 Hz, 3 H, 3 × H-6 or 3 × H-7), 1.34 (d, *J* = 6.5 Hz, 3 H, 3 × H-1′) and 1.10–0.99 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 150.83 (C-3′), 150.82 (C-3′), 140.29 (C-2), 140.27 (C-2), 132.6 (C-5), 127.34 (C-4), 127.33 (C-4), 112.8 (C-1), 109.94 (C-5′), 109.92 (C-5′), 70.7 (C-3), 69.49 (C-2′), 69.45 (C-2′), 64.5 (C-4′), 25.8 (C-6 or C-7), 22.0 (C-1′), 18.4 (C-6 or C-7), 17.6 ($SiCH\underline{C}H_3$), 17.53 ($SiCH\underline{C}H_3$), 17.51 ($SiCH\underline{C}H_3$), 17.50 ($SiCH\underline{C}H_3$), 12.5 ($Si\underline{C}HCH_3$) and 12.4 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 3367, 2944, 2867, 1464, 1069, 885 and 692 cm^{-1}; **HRMS** (ESI^{+}): Calculated for $C_{18}H_{34}O_3NaSi^{+}$ $[M+Na]^{+}$ 349.2169; found 349.2170 (Δ 0.29 ppm).

(E)-3-(((((5-Bromohexa-1,4-dien-3-yl)oxy)diisopropylsilyl)oxy)methyl)but-3-en-2-one (**347**)



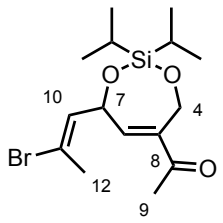
Note: Alcohol **344** was provided by Simon Werrel.

i-Pr_2SiCl_2 (0.404 mL, 2.24 mmol) was added dropwise to a solution of imidazole (363 mg, 5.33 mmol) in CH_2Cl_2 (22 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then

stirred for 5 min. A solution of alcohol **344** (377 mg, 2.13 mmol) in CH_2Cl_2 (3.5 mL + 0.4 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 15 min. A solution of alcohol **236** (235 mg, 0.235 mmol) in CH_2Cl_2 (2.3 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (19:1 pentane:Et_2O) to afford TST **347** as a colourless oil (584 mg, 70%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.15 (app. tq, *J* = 1.9, 1.0 Hz, 2 H, 2 × H-5′), 5.84 (dq, *J* = 8.6, 1.3 Hz, 1 H, H-4), 5.78 (ddd, *J* = 17.1, 10.3, 5.2 Hz, 1 H, H-2), 5.23 (dt, *J* = 17.0, 1.5 Hz, 1 H, H-1$_{trans}$), 5.08 (dt, *J* = 10.3, 1.4 Hz, 1 H, H-1$_{cis}$), 4.91 (ddt, *J* = 8.3, 5.2, 1.5 Hz, 1 H, H-3), 4.47 (t, *J* = 2.1 Hz, 2 × H-4′), 2.36 (s, 3 H, 3 H, 3 × H-1′), 2.24 (d, *J* = 1.3 Hz, 3 H, 3 × H-6) and 1.05 ppm (app. d, *J* = 1.5 Hz, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.2 (C-2′), 147.5 (C-3′), 138.5 (C-2), 134.1 (C-4), 124.2 (C-5′), 121.1 (C-5), 114.3 (C-1), 70.9 (C-3), 61.0 (C-4′), 26.3 (C-1′), 24.1 (C-6), 17.47 ($SiC\underline{C}H_3$), 17.46 ($SiC\underline{C}H_3$), 17.4 ($SiC\underline{C}H_3$), 17.3 ($SiC\underline{C}H_3$), 12.4 ($Si\underline{C}CH_3$) and 12.3 ppm ($Si\underline{C}CH_3$); **FTIR** ν_{max} (thin film): 2946, 2868, 1678, 1390 and 1090 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{17}H_{29}O_3{}^{79}Br$-$NaSi^+$ $[M+Na]^+$ 411.0962; found 411.0964 (Δ 0.49 ppm).

(E)-1-(7-(2-Bromoprop-1-en-1-yl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-5-yl)ethan-one (**350**)



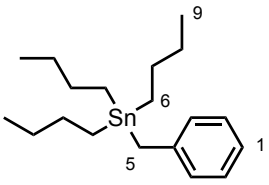
Notes: Experimental setup B (Section 5.3) was used for this reaction. Glassware was flame dried under vacuum, charged with N_2 and kept under a positive N_2 pressure *via* a manifold line prior to use. Dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (16.1 mg, 25.7 μmol) was added to the flask and the system then evacuated and charged with N_2 (× 3). PhMe (96 mL) and a solution of TST **347** (200 mg, 0.514 mmol) in PhMe (3 mL + 1 mL rinse, 5 mM final concentration) were sequentially added at rt and the flask then placed in an oil bath at rt. The reaction was immediately heated to 100 °C and stirred for a further 30 min once the temperature was reached (*ca.* 30 min) under a gentle flow of N_2. A solution of Hoveyda–Grubbs second generation catalyst (16.1 mg, 25.7 μmol) in PhMe (4 mL, 5 mM final concentration) was added over 2 h *via* syringe pump and the reaction then stirred at 100 °C for 22 h under a gentle flow of N_2. The reaction mixture was cooled to rt and directly concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford silaketal **350** as a yellow oil (103 mg, 56%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.57 (ddd, *J* = 3.8, 1.8, 1.0 Hz, 1 H, H-6), 6.10 (dq, *J* = 8.9, 1.4 Hz, 1 H, H-10), 5.47 (dddd, *J* = 8.9, 3.8, 2.3, 1.4 Hz, 1 H, H-7), 4.88–4.70 (m, 2 H, 2 × H-4), 2.36 (d, *J* = 1.4 Hz, 3 H, 3 × H-12), 2.32 (s, 3 H, 3 × H-9), 1.02 (app. s, 7 H, $SiCH(CH_3)_2$) and 0.99 ppm (app. s, 7 H, $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.6 (C-8), 143.3 (C-6), 142.6 (C-5), 132.6 (C-10), 124.0 (C-11), 68.5 (C-7), 60.6 (C-4), 26.3 (C-9), 24.1

(C-12), 17.5 (SiCH<u>C</u>H$_3$), 17.41 (SiCH<u>C</u>H$_3$), 17.36 (SiCH<u>C</u>H$_3$), 17.1 (SiCH<u>C</u>H$_3$) and 12.3 ppm (2 C, 2 × Si<u>C</u>HCH$_3$); **FTIR** ν_{max} (thin film): 2946, 2868, 2341, 1672, 1238, 1102, 885 and 788 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{15}H_{25}O_3{}^{79}BrNaSi^+$ $[M+Na]^+$ 383.0649; found 383.0649 (Δ 0.00 ppm).

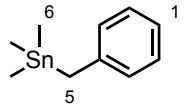
Benzyltributylstannane (**352**)



Zinc powder (260 mg, 3.98 mmol) was added to a round-bottomed flask fitted with a reflux condenser and the system then evacuated and charged with Ar (× 3). THF (2 mL, 1 M), NH_4Cl (sat., aq., 4 mL, 0.5 M) and tributyltin chloride (0.540 mL, 1.99 mmol) were sequentially added at rt. Benzyl bromide (K_2CO_3 filtered, 0.480 mL, 4.04 mmol) was then slowly added dropwise and the reaction then stirred at rt for 24 h. The reaction was diluted with pentane (5 mL) and the layers separated. The organic phase was concentrated *in vacuo* before being purified by flash column chromatography (10% KF doped SiO_2, pentane) to afford stannane **352** as a colourless oil (655 mg, 86%). Data is consistent with that reported in the literature.[221]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.16 (t, *J* = 7.6 Hz, 2 H, 2 × H-2), 7.04–6.92 (m, 3 H, H-1 and 2 × H-3), 2.39–2.22 (m, 2 H, 2 × H-5), 1.52–1.32 (m, 6 H, 6 × H-7), 1.32–1.20 (m, 6 H, 6 × H-8), 0.87 (t, *J* = 7.3 Hz, 9 H, 9 × H-9) and 0.83–0.77 ppm (m, 6 H, 6 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 143.9 (C-4), 128.4 (2 C, 2 × C-2), 127.1 (2 C, 2 × C-3), 123.0 (C-1), 29.2 (3 C, 3 × C-7), 27.5 (3 C, 3 × C-8), 18.3 (C-5), 13.8 (3 C, 3 × C-9) and 9.4 ppm (3 C, 3 × C-6).

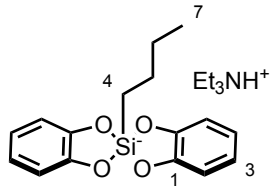
Benzyltrimethylstannane (**353**)



Zinc powder (735 mg, 11.2 mmol) was added to a round-bottomed flask fitted with a reflux condenser and the system then evacuated and charged with Ar (× 3). Trimethyltin chloride (1.12 g, 5.62 mmol, CAUTION: Toxic) was weighed into to a pre-weighed snap cap vial, transferred to the reaction flask in THF (5.6 mL, 1 M) and NH_4Cl (sat., aq., 11.2 mL, 0.5 M) added at rt. Benzyl bromide (K_2CO_3 filtered, 1.34 mL, 11.2 mmol) was slowly added drop-wise and the reaction then stirred at rt for 24 h. The reaction was diluted with pentane (10 mL) and the layers separated. The organic phase was concentrated *in vacuo* before being purified by flash column chromatography (10% KF doped SiO_2, pentane) to afford stannane **353** as a colourless oil (775 mg, 54%). Data is consistent with that reported in the literature.[222]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22–7.15 (m, 2 H, 2 × H-2), 7.03–6.95 (m, 3 H, H-1 and 2 × H-3), 2.31 (s, 2 H, 2 × H-5) and 0.05 ppm (s, 9 H, 9 × H-6); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 143.3 (C-4), 128.4 (2 C, 2 × C-2), 126.9 (2 C, 2 × C-3), 123.2 (C-1), 20.3 (C-5) and –9.93 ppm (3 C, 3 × C-6).

Triethylammonium bis(catecholato)butylsilicate (**363**)

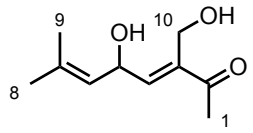


Et_3N (0.390 mL, 2.81 mmol) was added to a solution of catechol (412 mg, 2.34 mmol) in THF (4.7 mL, 0.5 M) at rt and the reaction then stirred at rt for 5 min. Trimethoxy(propyl)sil-ane (**362**, 0.412 mL, 2.34 mmol) was added at rt and the reaction then stirred at 70 °C for

24 h. The reaction was cooled to rt and directly concentrated *in vacuo.* The residue was redissolved in CH_2Cl_2 (10 mL) and pentane slowly added at rt with stirring to facilitate precipitation. The resulting suspension was filtered and dried under high vacuum to afford silicate **363** as an off-white solid (560 mg, 61%). Contains *ca.* 20 wt% unreacted catechol.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.75–6.71 (m, 4 H, 4 × H-2), 6.68–6.62 (m, 4 H, 4 × H-3), 3.15 (q, *J* = 7.4 Hz, 6 H, 3 × $NC\underline{H}_2CH_3$), 1.37–1.22 (m, 13 H, 2 × H-5, 2 × H-6 and 3 × $NCH_2C\underline{H}_3$), 0.77 (t, *J* = 7.3 Hz, 3 H, 3 × H-7) and 0.70–0.64 ppm (m, 2 H, 2 × H-4); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 149.8 (4 C, 4 × C-1), 118.7 (4 C, 4 × C-3), 110.8 (4 C, 4 × C-2), 46.2 (3 C, 3 × $N\underline{C}H_2$), 19.8 (C-4), 18.2 (C-7), 18.1 (C-5 or C-6) and 9.1 ppm (3 C, 3 × $NCH_2\underline{C}H_3$). A signal for C-5 or C-6 could not be resolved.

(E)-5-Hydroxy-3-(hydroxymethyl)-7-methylocta-3,6-dien-2-one (**366**)

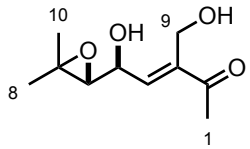


HF·pyridine (70% HF basis, 4.5 μL, 0.17 mmol) was added *via* micropipette to a solution of silaketal **319** (20.5 mg, 69.1 μmol) in THF (6.9 mL, 0.01 M) in an Eppendorf tube at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 3 h, warming slowly to rt. The reaction was diluted with $NaHCO_3$ (sat., aq., 5 mL), the layers separated and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (20:20:1 pentane:EtOAc:MeOH) to afford diol **366** as a colourless oil (6.1 mg, 48%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.65 (d, *J* = 7.6 Hz, 1 H, H-4), 5.36 (dd, *J* = 8.8, 7.6 Hz, 1 H, H-5), 5.32–5.24 (m, 1 H, H-6), 4.36 (q, *J* = 12.5 Hz, 2 H, 2 × H-10), 2.83 (br. s, 1 H,

C-10 OH), 2.36 (s, 3 H, 3 × H-1), 2.32 (br. s, 1 H, C-5 OH), 1.764 (s, 3 H, 3 × H-8 or H-9) and 1.761 ppm (s, 3 H, 3 × H-8 or H-9); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 201.4 (C-2), 146.1 (C-4), 139.2 (C-3), 138.1 (C-7), 124.4 (C-6), 65.6 (C-5), 57.2 (C-10), 26.1 (C-8 or C-9), 25.8 (C-1) and 18.6 ppm (C-8 or C-9); **FTIR** ν_{max} (thin film): 3372, 2917, 1667, 1026 and 984 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{10}H_{16}NaO_3^+$ $[M+Na]^+$ 207.0992; found 207.0993 (Δ 0.48 ppm).

(E)-5-(3,3-Dimethyloxiran-2-yl)-5-hydroxy-3-(hydroxymethyl)pent-3-en-2-one (**367**)

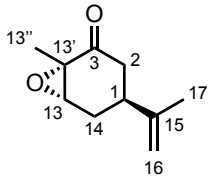


t-Butyl hydroperoxide (*ca.* 5.5 M in decane, 10 μL, 55 μmol) was added to a solution of diol **364** (8.4 mg, 46 μmol) and vanadyl acetylacetoacetate (2.4 mg, 9.1 μmol) in CH_2Cl_2 (0.450 mL, 0.1 M) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 2.5 h. The reaction was quenched at 0 °C by addition of $Na_2S_2O_3$ (sat., aq., 1 mL), removed from the cold bath and warmed slowly to rt. The reaction mixture extracted with EtOAc (3 × 5 mL) and the combined organic layers washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (12:8:1 pentane:EtOAc:MeOH) to afford epoxide **367** as a colourless oil and as a single diastereomer (3.6 mg, 40%). The relative stereochemistry is assigned on the basis of that reported for similar compounds in the literature. The pertinent value is the coupling constant between H-5 and H-6 which is 9.9 Hz; it is reported that the *threo* isomer gives a coupling constant of >5 Hz whereas the *ethyro* isomer gives a couple constant of *ca.* 3 Hz.[144]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.78 (t, *J* = 2.1 Hz, 1 H, H-4), 4.68 (ddt, *J* = 9.8, 3.6, 1.9 Hz, 1 H, H-5), 4.49 (ddd, *J* = 17.6, 2.0, 0.7 Hz, 1 H, H-9), 4.32 (ddd, *J* = 17.6, 3.2, 2.3 Hz,

1 H, H-9), 3.56 (d, J = 9.9 Hz, 1 H, H-6), 2.77 (br. s, 1 H, OH), 2.60 (br. s, 1 H, OH), 2.32 (s, 3 H, 3 × H-1), 1.36 (s, 3 H, 3 × H-8 or 3 × H-10) and 1.24 ppm (s, 3 H, 3 × H-8 or 3 × H-10); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 198.4 (C-2), 144.1 (C-4), 141.8 (C-3), 78.1 (C-6), 77.0 (C-7), 68.5 (C-5), 60.1 (C-9), 25.8 (C-1), 23.7 (C-8 or C-10) and 21.8 ppm (C-8 or C-10); **FTIR** ν_{max} (thin film): 2976, 2939, 1668, 1239 and 1073 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{10}H_{16}O_4Na^+$ $[M+Na]^+$ 223.0941; found 223.0943 (Δ 0.90 ppm).

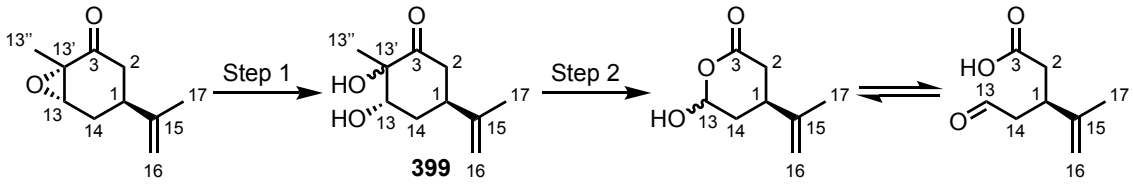
(1S,4S,6S)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (**398**)



(*S*)-(+)-Carvone (**395**, 25.0 mL, 160 mmol) was dissolved in MeOH (375 mL, 0.43 M) and cooled to –20 °C (cryostat-cooled acetone bath). NaOH (4 M, aq., 12.0 mL, 48.0 mmol) and H_2O_2 (30% w/w in H_2O, 32.6 mL, 320 mmol) were sequentially added dropwise and the reaction then stirred at –20 °C for 30 min. The cryostat temperature control was then adjusted to 0 °C and the reaction then stirred for 5 h, warming slowly to 0 °C. After 5 h the reaction was judged to have reached completion (TLC, 7:3 pentane:Et_2O) and was quenched at 0 °C by dropwise addition of HCl (3 M, aq., 16 mL, 48 mmol) and $Na_2S_2O_3$ (sat., aq., 250 mL). The mixture was diluted with H_2O (150 mL) and Et_2O (500 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with Et_2O (2 × 500 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* until only a small quantity of MeOH remained. The residue was redissolved in Et_2O (200 mL) and washed sequentially with H_2O (100 mL) and brine (2 × 200 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford epoxide **398** as a pale yellow oil (25.7 g, 96%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.80–4.77 (m, 1 H, H-16), 4.72–4.70 (m, 1 H, H-16), 3.44 (dd, *J* = 3.2, 1.1 Hz, 1 H, H-13), 2.71 (td, *J* = 11.3, 5.7 Hz, 1 H, H-1), 2.58 (ddd, *J* = 17.5, 4.7, 1.4 Hz, 1 H, H-2), 2.42–2.31 (m, 1 H, H-14), 2.02 (dd, *J* = 17.6, 11.6 Hz, 1 H, H-2), 1.90 (ddd, *J* = 14.8, 11.1, 1.2 Hz, 1 H, H-14), 1.74–1.68 (m, 3 H, 3 × H-17) and 1.41 ppm (s, 3 H, 3 × H-13″); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 205.6 (C-3), 146.5 (C-15), 110.6 (C-16), 61.5 (C-13), 59.0 (C-13′), 41.9 (C-2), 36.2 (C-1), 28.9 (C-14), 20.7 (C-17) and 15.4 ppm (C-13″); **FTIR** ν_{max} (thin film): 2978, 2936, 1707, 1440, 1119, 891 and 815 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{10}H_{15}O_2^+$ $[M+H]^+$ 167.1067; found 167.1068 (Δ 0.60 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ –87.4° (c = 1.00, CH_2Cl_2)

(4S)-6-Hydroxy-4-(prop-1-en-2-yl)tetrahydro-2H-pyran-2-one (**400**)



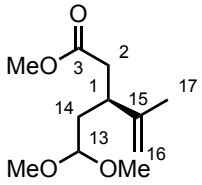
Step 1: Epoxide **398** (24.0 g, 145 mmol) was dissolved in THF (686 mL). H_2SO_4 (4.25 g, 43.3 mmol) was dissolved in H_2O (34 mL) and added dropwise to the reaction at rt (final solvent mixture 20:1 THF:H_2O, 0.2 M). A reflux condenser was fitted and reaction stirred at 80 °C for 2 days. The reaction was cooled to rt and diluted with pentane (300 mL), Et_2O (300 mL) and H_2O (300 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with brine (3 × 250 mL) before being dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford crude diol **399** as a yellow oil which was used directly without further purification.

Step 2: $NaIO_4$ (92.7 g, 434 mmol) and SiO_2 (92.7 g, 1 g per 1 g $NaIO_4$) were suspended in CH_2Cl_2 (960 mL, 0.15 M wrt. epoxide **398**) and cooled to 0 °C (ice/H_2O bath) with vigorous stirring. H_2O (120 mL, 1.2 M wrt. epoxide **398**) was added *via* dropping funnel over 1 h to

give a fine suspension. Crude diol **399** was redissolved in CH_2Cl_2 (145 mL, 1 M) and added to the reaction *via* pipette. The reaction was stirred overnight, warming slowly to rt in the cold bath. The suspension was filtered through a pad of cotton wool and the solids then washed several times with CH_2Cl_2. The filtrate was concentrated *in vacuo* before bring purified by flash column chromatography (CH_2Cl_2–9:1 CH_2Cl_2:MeOH) to afford hemiacetal **400** as a yellow oil (16.7 g, 73%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.61 (br. s, 1 H, H-13), 4.86–4.80 (m, 2 H, 2 × H-16), 3.11 (quint., *J* = 7.3 Hz, 1 H, H-1), 2.61–2.39 (m, 4 H, 2 × H-2 and 2 × H-14) and 1.74–1.68 ppm (m, 3 H, 3 × H-17); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 201.6 (C-13), 177.7 (C-3), 145.0 (C-15), 112.7 (C-16), 46.5 (C-14), 38.1 (C-2), 37.2 (C-1) and 20.0 ppm (C-17); **FTIR** ν_{max} (thin film): 2918, 1709, 1230, 1160 and 898 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_8H_{11}O_3^-$ $[M–H]^-$ 155.0714; found 155.0712 (Δ 1.29 ppm).

(S)-Methyl 3-(2,2-dimethoxyethyl)-4-methylpent-4-enoate (**394**)

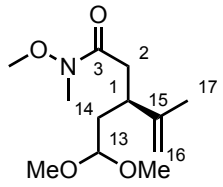


Hemiacetal **400** (16.7 g, 107 mmol) was dissolved in dry MeOH (10 mL) and added *via* pipette, under a positive pressure of N_2, to a solution of *p*-toluenesulfonic acid monohydrate (1.02 g, 5.34 mmol) in dry MeOH (200 mL, 0.5 M final concentration) at rt. Trimethyl orthoformate (58.4 mL, 534 mmol) was added at rt and the reaction then stirred at rt for 24 h. The reaction mixture was quenched at rt with $NaHCO_3$ (sat., aq., 200 mL) and diluted with EtOAc (200 mL) and H_2O (200 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (2 × 200 mL),

dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography to afford ester **394** as a pale yellow oil (19.4 g, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.79 (app. q, *J* = 1.4 Hz, 2 H, 2 × H-16), 4.32 (dd, *J* = 7.4, 4.2 Hz, 1 H, H-13), 3.64 (s, 3 H, $COOCH_3$), 3.30 (s, 3 H, OCH_3), 3.29 (s, 3 H, OCH_3), 2.78–2.69 (m, 1 H, H-1), 2.42–2.39 (m, 2 H, 2 × H-2) and 1.77–1.60 ppm (m, 5 H, 2 × H-14 and 3 × H-17); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 172.8 (C-3), 146.0 (C-15), 112.5 (C-16), 102.9 (C-13), 52.9 (OCH_3), 52.7 (OCH_3), 51.6 ($COO\underline{C}H_3$), 39.8 (C-1), 39.1 (C-2), 35.8 (C-14) and 19.0 ppm (C-17); **FTIR** ν_{max} (thin film): 2951, 1738, 1437, 1189, 1158, 1125, 1053 and 895 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{11}H_{20}O_4Na^+$ $[M+H]^+$ 239.1254; found 239.1254 (Δ 0.00 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +4.7° (c = 1.00, CH_2Cl_2).

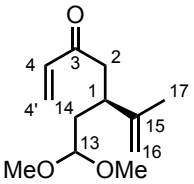
(S)-3-(2,2-Dimethoxyethyl)-N-methoxy-N,4-dimethylpent-4-enamide (**401**)



N,*O*-dimethylhydroxylamine hydrochloride (12.7 g, 130 mmol) was added to a solution of ester **394** (18.8 g, 86.9 mmol) in THF (174 mL, 0.5 M) at rt and cooled to –20 °C (cryostat-cooled acetone bath). Isopropylmagnesium chloride (2 M in THF, 130 mL, 260 mmol) was added dropwise *via* cannula over 90 min and the reaction then stirred at –20 °C for a further 3 h. The reaction was quenched at –20 °C by dropwise addition of NH_4Cl (sat., aq., 130 mL). The mixture was diluted with H_2O (100 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford amide **401** as a yellow oil (21.2 g, 99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.82–4.78 (m, 2 H, 2 × H-16), 4.35 (dd, *J* = 7.6, 4.0 Hz, 1 H, H-13), 3.67 (s, 3 H, $NOCH_3$), 3.30 (s, 3 H, OCH_3), 3.29 (s, 3 H, OCH_3), 3.16 (s, 3 H, NCH_3), 2.81 (dtd, *J* = 9.5, 7.3, 5.3 Hz, 1 H, H-1), 2.57–2.43 (m, 2 H, 2 × H-2), 1.77 (ddd, *J* = 14.0, 7.7, 5.3 Hz, 1 H, H-14), 1.71 (dd, *J* = 1.5, 0.8 Hz, 3 H, 3 × H-17) and 1.63 ppm (ddd, *J* = 13.8, 9.5, 4.0 Hz, 1 H, H-14); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 173.2 (C-3), 146.8 (C-15), 112.0 (C-16), 102.9 (C-13), 61.3 ($NOCH_3$), 53.0 (OCH_3), 52.3 (OCH_3), 38.9 (C-1), 36.7 (C-2), 35.9 (C-14), 32.3 (NCH_3) and 19.5 ppm (C-17); **FTIR** ν_{max} (thin film): 2939, 1664, 1644, 1384, 1127, 1062, 1050 and 1001 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{12}H_{23}O_4NNa^+$ $[M+Na]^+$ 268.1519; found 268.1517 (Δ 0.37 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +2.8° (c = 1.00, CH_2Cl_2).

(S)-5-(2,2-Dimethoxyethyl)-6-methylhepta-1,6-dien-3-one (**404**)

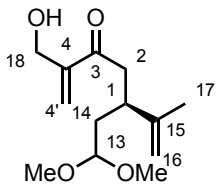


Amide **401** (21.2 g, 86.3 mmol) was dissolved in dry THF (173 mL, 0.5 M) and cooled to –10 °C (internal thermometer, cryostat-cooled aceteone bath). Vinylmagnesium bromide (1 M in THF, 173 mL, 173 mmol) was added dropwise *via* cannula over 1 h and the reaction then stirred at –10 °C for a further 90 min. The reaction was quenched at –10 °C by dropwise addition of acetic anhydride (K_2CO_3 filtered, 49.0 mL, 518 mmol; CAUTION: exotherm) over 10 min and then stirred for 10 min. MeOH (49.0 mL, 1.21 mol) was added dropwise at –10 °C (CAUTION: exotherm) over 5 min, the reaction flask removed from the cold bath and the mixture then stirred for 30 min, warming slowly to rt. The mixture was diluted with NH_4Cl (sat., aq., 100 mL), the layers separated and the aqueous phase extracted with EtOAc (3 ×

200 mL). The combined organic layers were washed with Na_2CO_3 (sat., aq., 2 × 100 mL) and brine (200 mL), dried over anhydrous $MgSO_4$ and anhydrous K_2CO_3, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1–4:1 pentane:Et_2O) to afford enone **404** as a pale yellow oil (15.3 g, 83%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.34 (dd, *J* = 17.6, 10.6 Hz, 1 H, H-4), 6.20 (dd, *J* = 17.7, 1.1 Hz, 1 H, H-4′*trans*), 5.80 (dd, *J* = 10.6, 1.2 Hz, 1 H, H-4′*cis*), 4.79–4.76 (m, 2 H, 2 × H-16), 4.33 (dd, *J* = 7.6, 4.0 Hz, 1 H, H-13), 3.29 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 2.87–2.79 (m, 1 H, H-1), 2.70–2.59 (m, 2 H, 2 × H-2), 1.76–1.70 (m, 1 H, H-14), 1.69 (t, *J* = 1.1 Hz, 3 H, 3 × H-17) and 1.67–1.60 ppm (m, 1 H, H-14); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.5 (C-3), 146.4 (C-15), 136.7 (C-4), 128.2 (C-4′), 112.2 (C-16), 102.9 (C-13), 52.8 (OCH_3), 52.6 (OCH_3), 44.4 (C-2), 38.8 (C-1), 36.0 (C-14) and 19.4 ppm (C-17); **FTIR** ν_{max} (thin film): 2946, 1681, 1126, 1056 and 961 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{12}H_{20}O_3Na^+$ $[M+Na]^+$ 235.1305; found 235.1300 (Δ 2.13 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ –1.6° (c = 1.00, CH_2Cl_2).

(S)-5-(2,2-Dimethoxyethyl)-2-(hydroxymethyl)-6-methylhepta-1,6-dien-3-one (**393**)

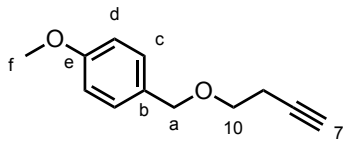


Paraformaldehyde (6.47 g, 216 mmol) and DABCO (811 mg, 7.19 mmol) were sequentially added as single portions to a solution of enone **404** (15.3 g, 71.9 mmol) in dioxane:H_2O (1:1, 720 mL, 0.1 M) at rt and the reaction then stirred at rt for 24 h. The reaction was diluted with EtOAc (700 mL) and brine (500 mL). The layers separated and the aqueous phase extracted with EtOAc (4 × 350 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (1:1 pentane:Et_2O) to afford alcohol **393** as a yellow oil (12.6 g). Mixed fractions were re-purified

by flash column chromatography (3:2 pentane:Et_2O) to afford additional alcohol **393** as a yellow oil (1.07 g; 13.7 g total, 78%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.09 (s, 1 H, H-4′), 6.00 (t, *J* = 1.3 Hz, 1 H, H-4′), 4.80–4.75 (m, 2 H, 2 × H-16), 4.34 (dd, *J* = 7.5, 4.0 Hz, H-13), 4.30 (d, *J* = 5.8 Hz, 2 H, 2 × H-18), 3.30 (s, 3 H, OCH_3), 3.29 (s, 3 H, OCH_3), 2.87–2.72 (m, 3 H, H-1 and 2 × H-2), 2.31 (t, *J* = 6.5 Hz, 1 H, OH), 1.76–1.71 (m, 1 H, H-14), 1.70 (t, *J* = 1.1 Hz, 3 H, 3 × H-17) and 1.64 ppm (ddd, *J* = 14.3, 8.7, 4.1 Hz, 1 H, H-14); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 201.5 (C-3), 147.1 (C-4), 146.4 (C-15), 125.3 (C-4′), 112.3 (C-16), 102.9 (C-13), 62.9 (C-18), 52.81 (OCH_3), 52.79 (OCH_3), 42.4 (C-2), 39.2 (C-1), 36.0 (C-14) and 19.4 ppm (C-17); **FTIR** ν_{max} (thin film): 3434, 2943, 1672, 1378, 1127 and 1056 cm^{-1}; **HRMS** (NH_3 CI^+): Calculated for $C_{13}H_{23}O_4^+$ $[M+H]^+$ 243.1596; found 243.1591 (Δ 2.06 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ –3.7° (c = 1.00, CH_2Cl_2).

1-((But-3-yn-1-yloxy)methyl)-4-methoxybenzene (**407**)

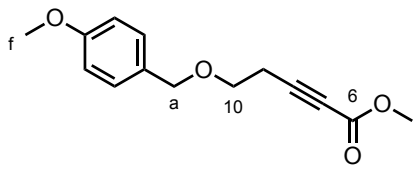


p-Methoxybenzyl alcohol (50 mL) was added dropwise to HCl (37%, aq., 100 mL) at rt and the reaction then stirred at rt for 1 h. The reaction was diluted with Et_2O (100 mL) and the layers separated. The organic phase was washed sequentially with $NaHCO_3$ (sat., aq., 100 mL) and brine (100 mL), dried over anhydrous $CaCl_2$ for 1 h, filtered and concentrated *in vacuo* to afford *p*-methoxybenzyl chloride which was kept over K_2CO_3 and used within a few hours. 3-Butyn-1-ol (10.0 mL, 132 mmol) was added to dry THF (260 mL, 0.5 M) at rt and cooled to 0 °C (ice/H_2O bath). NaH (60% dispersion in mineral oil, 5.29 g, 132 mmol) was added portionwise over 10 min (CAUTION: effervescence) and the reaction then stirred at

0 °C for 30 min. *p*-Methoxybenzyl chloride (19.8 mL, 145 mmol) was added dropwise over 10 min and tetrabutylammonium iodide (4.89 g, 13.2 mmol) then added in one portion. The reaction was removed from the cold bath and stirred overnight, warming slowly to rt. The reaction was quenched at rt by dropwise addition of H_2O (100 mL). The layers were separated and the aqueous phase extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (pentane–19:1 pentane:Et_2O) to afford alkyne **407** as a colourless oil (19.8 g, 78%). Data is consistent with that reported in the literature.[223]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.24 (m, 2 H, 2 × H-c), 6.93–6.86 (m, 2 H, 2 × H-d), 4.49 (s, 2 H, 2 × H-a), 3.81 (s, 3 H, 3 × H-f), 3.58 (t, *J* = 7.0 Hz, 2 H, 2 × H-10), 2.49 (td, *J* = 7.0, 2.7 Hz, 2 H, 2 × H-9) and 1.99 ppm (t, *J* = 2.7 Hz, 1 H, H-7); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.4 (C-e), 130.2 (C-b), 129.5 (2 C, 2 × C-c), 114.0 (2 C, 2 × C-d), 81.5 (C-8), 72.8 (C-a), 69.4 (C-7), 68.0 (C-10), 55.4 (C-f) and 20.0 ppm (C-9).

Methyl 5-((4-methoxybenzyl)oxy)pent-2-ynoate (**408**)



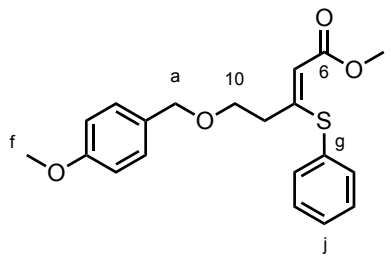
Note: *n*-BuLi was titrated with 2,6-di-*tert*-butyl-4-methylphenol and 2,2'-dipyridyl prior to use.

Alkyne **407** (19.4 g, 102 mmol) was dissolved in dry THF (204 mL, 0.5 M) and cooled to –78 °C (dry ice/acetone bath). *n*-BuLi (2.3 M, 46.6 mL, 107 mmol) was added dropwise at –78 °C *via* syringe over 40 min (internal reaction temperature remained below –75 °C) and the reaction then stirred at –78 °C for 40 min. Methyl chloroformate (9.47 mL, 123 mmol)

was added dropwise at –78 °C (internal reaction temperature remained below –70 °C) and the reaction then stirred at –78 °C for 2.5 h. The reaction was quenched at –78 °C by dropwise addition of NH_4Cl (sat., aq., 50 mL), diluted with H_2O (100 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (4:1–7:3 pentane:Et_2O) to afford ester **408** as a pale yellow oil (21.9 g, 86%). Data is consistent with that reported in the literature.[223]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.24 (m, 2 H, 2 × H-c), 6.91–6.85 (m, 2 H, 2 × H-d), 4.48 (s, 2 H, 2 × H-a), 3.80 (s, 3 H, 3 × H-f), 3.75 (s, 3 H, $COOCH_3$), 3.60 (t, *J* = 6.9 Hz, 2 H, 2 × H-10) and 2.62 ppm (t, *J* = 6.9 Hz, 2 H, 2 × H-9); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.4 (C-e), 154.1 (C-6), 129.9 (C-b), 129.5 (2 C, 2 × C-c), 114.0 (2 C, 2 × C-d), 86.6 (C-8), 73.7 (C-7), 72.9 (C-a), 66.8 (C-10), 55.4 (C-f), 52.7 ($COO\underline{C}H_3$) and 22.3 ppm (C-9).

Methyl (Z)-5-((4-methoxybenzyl)oxy)-3-(phenylthio)pent-2-enoate (**409**)

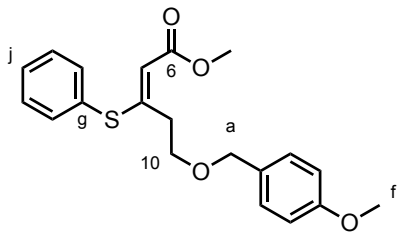


Sodium methoxide (240 mg, 4.41 mmol) and thiophenol (9.89 mL, 96.9 mmol, CAUTION: stench) were sequentially added to MeOH (330 mL) at rt and the reaction then stirred at rt for 5 min. A solution of ester **408** (21.9 g, 88.1 mmol) in MeOH (10 mL + 2 × 5 mL rinses, 0.25 M final concentration) was added dropwise and the reaction then stirred at rt for 2.5 h. The reaction was quenched at rt by addition of NH_4Cl (sat., aq., 100 mL) and diluted with brine (200 mL) and EtOAc (400 mL). The layers were separated and the aqueous phase ex-

tracted with EtOAc (2 × 300 mL). The combined organic layers were washed with $NaHCO_3$ (sat., aq., 200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (pentane–7:3 pentane:Et_2O, slow gradient) to afford ester **409** as a yellow oil (25.7 g, 81%). The geometry was assigned by NOESY NMR (Section 5.5.3).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.47 (m, 2 H, 2 × H-h), 7.42–7.31 (m, 3 H, 2 × H-i and H-j), 7.18–7.12 (m, 2 H, 2 × H-c), 6.88–6.83 (m, 2 H, 2 × H-d), 5.92 (t, *J* = 0.9 Hz, 1 H, H-7), 4.27 (s, 2 H, 2 × H-a), 3.79 (s, 3 H, 3 × H-f), 3.75 (s, 3 H, $COOCH_3$), 3.40 (t, *J* = 6.8 Hz, 2 H, 2 × H-10) and 2.41 ppm (td, *J* = 6.8, 1.0 Hz, 2 H, 2 × H-9); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 166.5 (C-6), 159.3 (C-e), 158.1 (C-8), 135.9 (2 C, 2 × C-h), 130.6 (C-g), 130.0 (C-b), 129.5 (C-j), 129.33 (2 C, 2 × C-i), 129.28 (2 C, 2 × C-c), 113.8 (2 C, 2 × C-d), 112.7 (C-7), 72.6 (C-a), 68.2 (C-10), 55.3 (C-f), 51.3 ($COO\underline{C}H_3$) and 36.7 ppm (C-9); **FTIR** ν_{max} (thin film): 1702, 1582, 1512, 1246, 1178, 1090, 1134, 821 and 753 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{20}H_{22}O_4NaS^+$ $[M+Na]^+$ 381.1131; found 381.1129 (Δ 0.52 ppm).

Methyl (E)-5-((4-methoxybenzyl)oxy)-3-(phenylthio)pent-2-enoate (**410**)

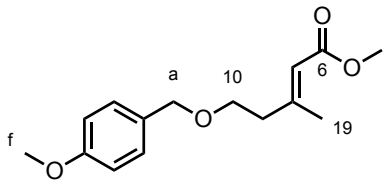


Sodium methoxide (10.9 mg, 0.202 mmol) and thiophenol (0.454 mL, 4.45 mmol, CAUTION: stench) were sequentially added to MeOH (16 mL) at rt and the reaction then stirred at rt for 5 min. A solution of ester **408** (1.00 g, 4.05 mmol) in MeOH (1 + 1 mL, 0.25 M final concentration) was added dropwise and the reaction then stirred at rt for 3.5 h. The reaction was quenched at rt by addition of NH_4Cl (sat., aq., 10 mL) and diluted with brine (10 mL) and

EtOAc (20 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (sat., aq., 20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (pentane–9:1 pentane:EtOAc, slow gradient) to afford ester **410** as a yellow oil (149 mg, 10%). The geometry was assigned by NOESY NMR (Section 5.5.3).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51–7.46 (m, 2 H, 2 × H-h), 7.46–7.40 (m, 3 H, 2 × H-i and H-j), 7.33–7.29 (m, 2 H, 2 × H-c), 6.91–6.86 (m, 2 H, 2 × H-d), 5.23 (s, 1 H, H-7), 4.52 (s, 2 H, 2 × H-a), 3.80 (s, 3 H, 3 × H-f), 3.76 (t, *J* = 7.0 Hz, 2 H, 2 × H-10), 3.59 (s, 3 H, $COOCH_3$) and 3.22 ppm (t, *J* = 7.0 Hz, 2 H, 2 × H-9); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 165.3 (C-6), 161.7 (C-8), 159.2 (C-e), 135.6 (2 C, 2 × C-h), 130.7 (C-b), 130.0 (C-j), 129.9 (2 C, 2 × C-i), 129.6 (C-g), 129.3 (2 C, 2 × C-c), 113.8 (2 C, 2 × C-d), 111.4 (C-7), 72.5 (C-a), 69.1 (C-10), 55.4 (C-f), 51.0 ($COO\underline{C}H_3$) and 33.9 ppm (C-9); **FTIR** ν_{max} (thin film): 2947, 1709, 1600, 1513, 1433, 1342, 1247, 1173, 1089 and 1036 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{20}H_{22}O_4NaS^+$ $[M+Na]^+$ 381.1131; found 381.1117 (Δ 3.67 ppm).

Methyl (E)-5-((4-methoxybenzyl)oxy)-3-methylpent-2-enoate (**411**)

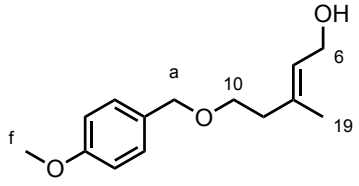


MeMgBr (3 M in Et_2O, 87.0 mL, 261 mmol) was added dropwise *via* syringe over 40 min to a suspension of CuI (25.5 g, 134 mmol) in dry THF (260 mL) at –78 °C (dry ice/acetone bath) and the reaction then stirred at –78 °C for 15 min. The reaction was removed from the cold bath for 10 min (internal temperature rose to *ca.* –20 °C) and then re-cooled to –78 °C. A solution of ester **409** (25.3 g, 70.6 mmol) in THF (10 mL + 2 × 5 mL rinses, 0.25 M final concen-

tration) was added dropwise and the reaction then stirred at –78 °C for 2 h. The reaction was quenched at –78 °C by dropwise addition of NH_4Cl (sat., aq., 500 mL, 7 mL/mmol) and NH_4OH (35% solution, 250 mL, 3.5 mL/mmol), removed from the cold bath and stirred for 10 min. The resulting suspension was filtered through a pad of celite and the solids then washed several times with EtOAc. The layers of the filtrate were separated and the aqueous phase extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1–4:1 pentane:Et_2O) to afford ester **411** as a pale yellow oil (17.5 g, 94%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.20 (m, 2 H, 2 × H-c), 6.91–6.84 (m, 2 H, 2 × H-d), 5.75–5.69 (m, 1 H, H-7), 4.44 (s, 2 H, 2 × H-a), 3.79 (s, 3 H, 3 × H-f), 3.68 (s, 3 H, $COOCH_3$), 3.57 (t, *J* = 6.6 Hz, 2 H, 2 × H-10), 2.43 (td, *J* = 6.6, 1.1 Hz, 2 H, 2 × H-9) and 2.17 ppm (t, *J* = 1.0 Hz, 3 H, 3 × H-19); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 167.1 (C-6), 159.3 (C-e), 157.2 (C-8), 130.2 (C-b), 129.4 (2 C, 2 × C-c), 116.6 (C-7), 113.9 (2 C, 2 × C-d), 72.8 (C-a), 67.5 (C-10), 55.3 (C-f), 50.9 ($COO\underline{C}H_3$), 40.9 (C-9) and 19.0 ppm (C-19); **FTIR** ν_{max} (thin film): 1716, 1651, 1613, 1513, 1436, 1357, 1247, 1225, 1173, 1150, 1096, 1034 and 821 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{15}H_{20}O_4Na^+$ $[M+Na]^+$ 287.1254; found 287.1253 (Δ 0.35 ppm).

(E)-5-((4-Methoxybenzyl)oxy)-3-methylpent-2-en-1-ol (**412**)

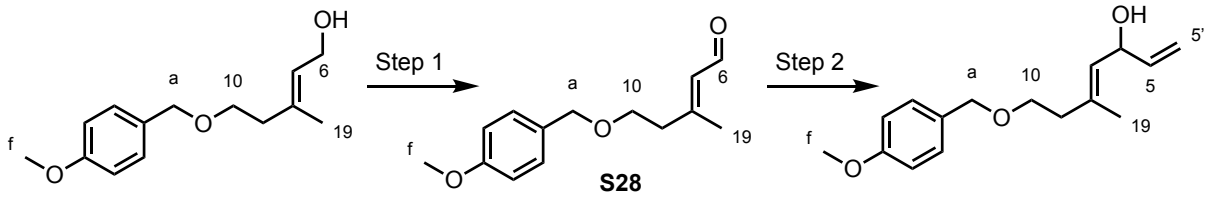


Diisobutylaluminium hydride (1 M in hexanes, 166 mL, 166 mmol) was added dropwise *via* cannula over 40 min to a solution of ester **411** (17.5 g, 66.3 mmol) in CH_2Cl_2 (200 mL,

0.33 M) at –78 °C (dry ice/acetone bath). The reaction was removed from the cold bath and stirred for 2.5 h, warming slowly to rt. The reaction was quenched at 0 °C (ice/H_2O bath) by sequential dropwise addition of H_2O (6.6 mL, 0.04 mL/mmol Al), NaOH (15 wt% in H_2O, 6.6 mL, 0.04 mL/mmol Al) and H_2O (16.6 mL, 0.1 mL/mmol Al). The reaction was removed from the cold bath and the mixture then stirred vigorously (>1000rpm) for 15 min, warming slowly to rt. Anhydrous $MgSO_4$ (100 g) was added at rt and the mixture then stirred vigorously at rt for a further 15 min. The suspension was filtered through a pad of celite and the solids then washed several times with EtOAc. The filtrate was concentrated *in vacuo* to afford alcohol **412** as a yellow oil (15.7 g, quant.).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.22 (m, 2 H, 2 × H-c), 6.91–6.84 (m, 2 H, 2 × H-d), 5.44 (t, *J* = 6.9 Hz, 1 H, H-7), 4.43 (s, 2 H, 2 × H-a), 4.12 (dd, *J* = 7.2, 3.0 Hz, 2 H, 2 × H-6), 3.79 (s, 3 H, 3 × H-f), 3.53 (t, *J* = 6.8 Hz, 2 H, 2 × H-10), 2.32 (t, *J* = 6.8 Hz, 2 H, 2 × H-9) and 1.67 ppm (s, 3 H, 3 × H-19); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.2 (C-e), 136.6 (C-8), 130.5 (C-b), 129.4 (2 C, 2 × C-c), 125.2 (C-7), 113.9 (2 C, 2 × C-d), 72.6 (C-a), 68.4 (C-10), 59.3 (C-6), 55.4 (C-f), 39.5 (C-9) and 16.6 ppm (C-19); **FTIR** ν_{max} (thin film): 3393, 2859, 1512, 1245, 1173, 1088, 1033 and 819 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{14}H_{20}O_3Na^+$ $[M+Na]^+$ 259.1305; found 259.1302 (Δ 1.17 ppm).

(±,E)-7-((4-Methoxybenzyl)oxy)-5-methylhepta-1,4-dien-3-ol (**413**)



Step 1: Dess–Martin periodinane (33.8 g, 79.6 mmol) was added in one portion to a solution of alcohol **412** (15.7 g, 66.3 mmol) in CH_2Cl_2 (265 mL, 0.25 M) at 0 °C (ice/H_2O bath) and

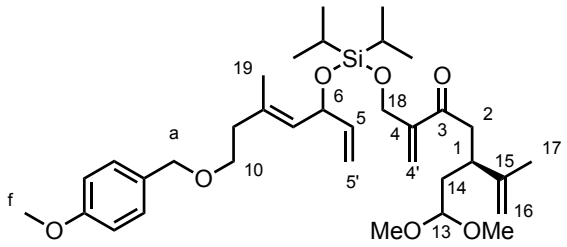
the reaction then stirred at 0 °C for 5 min. The reaction was removed from the cold bath and stirred for 90 min, warming slowly to rt. The reaction was quenched at rt by addition of a 1:1:1 solution of $Na_2S_2O_3$ (sat., aq.), $NaHCO_3$ (sat., aq.) and H_2O (390 mL total), and the biphasic mixture then stirred vigorously at rt until clear on standing. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed sequentially with $NaHCO_3$ (sat., aq., 2 × 200 mL) and brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford crude aldehyde **S28** which was used directly without further purification.

Step 2: A solution of crude aldehyde **S28** in THF (20 mL + 5 mL rinse) was added dropwise over 30 min to a solution of vinylmagnesium bromide (1 M in THF, 133 mL, 133 mmol) in THF (240 mL, 0.25 M final concentration) at –78 °C (dry ice/acetone bath) and the reaction then stirred at –78 °C for 1 h. The reaction was quenched at –78 °C by dropwise addition of NH_4Cl (sat., aq., 200 mL) and diluted with H_2O (200 mL). The reaction was removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with Et_2O (3 × 200 mL). The combined organic layers were washed sequentially with $NaHCO_3$ (sat., aq., 200 mL) and brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (2:1–1:1 pentane:Et_2O) to afford (±)-alcohol **413** as a yellow oil (14.0 g, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.22 (m, 2 H, 2 × H-c), 6.89–6.84 (m, 2 H, 2 × H-d), 5.87 (ddd, *J* = 17.2, 10.3, 5.7 Hz, 1 H, H-5), 5.26–5.19 (m, 2 H, H-5′$_{trans}$ and H-7), 5.08 (dt, *J* = 10.3, 1.4 Hz, 1 H, H-5′$_{cis}$), 4.85 (t, *J* = 7.1 Hz, 1 H, H-6), 4.43 (s, 2 H, 2 × H-a), 3.79 (s, 3 H, 3 × H-f), 3.54 (td, *J* = 6.9, 1.1 Hz, 2 H, 2 × H-10), 2.32 (td, *J* = 6.6, 1.0 Hz, 2 H, 2 × H-9), 1.90 (s, 1 H, OH) and 1.71 ppm (d, *J* = 1.4 Hz, 3 H, 3 × H-19).; **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.2 (C-e), 139.9 (C-5), 136.1 (C-8), 130.5 (C-b), 129.3 (2 C, 2 × C-c), 127.5

(C-7), 114.3 (C-5′), 113.9 (2 C, 2 × C-d), 72.6 (C-a), 69.9 (C-6), 68.4 (C-10), 55.4 (C-f), 39.6 (C-9) and 17.0 ppm (C-19); **FTIR** ν_{max} (thin film): 3404, 2859, 1613, 1513, 1247, 1093, 1034, 991 and 821 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{16}H_{22}O_3Na^+$ $[M+Na]^+$ 285.1461; found 285.1461 (Δ 0.00 ppm).

(15S,E)-9,9-Diisopropyl-17-methoxy-1-(4-methoxyphenyl)-5-methyl-12-methylene-15-(prop-1-en-2-yl)-7-vinyl-2,8,10,18-tetraoxa-9-silanonadec-5-en-13-one (**415**)



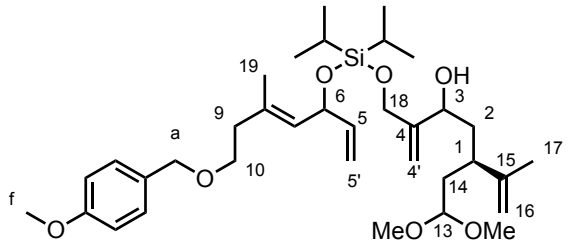
Note: Alcohols (±)-**413** and **393** were azeotroped with PhMe (× 3) and dried under high vacuum prior to use.

i-Pr_2SiCl_2 (0.220 mL, 1.22 mmol) was added dropwise to a solution of imidazole (198 mg, 2.91 mmol) in CH_2Cl_2 (12.2 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of (±)-alcohol **413** (306 mg, 1.16 mmol) in CH_2Cl_2 (2.0 mL + 0.5 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 20 min. A solution of alcohol **393** (331 mg, 1.37 mmol) in CH_2Cl_2 (1.3 mL, 1 M) was added dropwise at 0 °C over 5 min and the reaction then stirred at 0 °C for 10 min. The reaction mixture was filtered and the solution dry loaded directly onto SiO_2 before being purified by flash column chromatography (6:1–4:1 pentane:Et_2O) to afford TST **415** as a colourless oil and an inseparable *ca.* 1:1 mixture of diastereomers (548 mg, 76%). The diastereomeric ratio was estimated on the basis of peak heights of the two C-8 peaks in the ^{13}C NMR spectrum (133.13 and 133.11 ppm). Diastereomeric peaks are not dis-

tinguishable in the ^{1}H NMR spectrum. ^{13}C NMR diastereomeric peaks are reported together where distinguishable.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26–7.23 (m, 2 H, 2 × H-c), 6.89–6.84 (m, 2 H, 2 × H-d), 6.11 (q, *J* = 1.9 Hz, 1 H, H-4′), 6.09 (q, *J* = 1.6 Hz, 1 H, H-4′), 5.79 (ddd, *J* = 17.0, 10.1, 5.2 Hz, 1 H, H-5), 5.22–5.15 (m, 2 H, H-5′*trans* and H-7), 5.02–4.96 (m, 1 H, H-5′*cis*), 4.76 (app. dd, *J* = 3.3, 1.7 Hz, 2 H, 2 × H-16), 4.45 (dt, *J* = 4.5, 2.1 Hz, 2 H, 2 × H-18), 4.42 (s, 2 H, 2 × H-a), 4.33 (dd, *J* = 7.6, 4.0 Hz, 1 H, H-13), 3.80 (s, 3 H, 3 × H-f), 3.51 (t, *J* = 7.1 Hz, 2 H, 2 × H-10), 3.30 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 2.86–2.71 (m, 3 H, H-1 and 2 × H-2), 2.35–2.23 (m, 2 H, 2 × H-9), 1.76 (m, 1 H, H-14), 1.69 (s, 3 H, 3 × H-17), 1.67–1.59 (m, 4 H, H-14 and 3 × H-19) and 1.03 ppm (app. d, *J* = 8.0 Hz, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 200.01 (C-3), 199.99 (C-3), 159.2 (C-e), 147.6 (C-4), 146.6 (C-15), 140.0 (C-5), 133.13 (C-8), 133.11 (C-8), 130.8 (C-b), 129.4 (2 C, 2 × C-c), 128.7 (C-7), 122.9 (C-4′), 113.9 (2 C, 2 × C-d), 113.0 (C-5′), 112.2 (C-16), 102.9 (C-13), 72.6 (C-a), 70.46 (C-6), 70.44 (C-6), 68.9 (C-10), 61.1 (C-18), 55.4 (C-f), 52.8 (OCH_3), 52.6 (OCH_3), 42.6 (C-2), 39.6 (C-9), 39.1 (C-1), 36.0 (C-14), 19.4 (C-17), 17.6 ($SiCH\underline{C}H_3$), 17.5 (2 C, C-19 and $SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 12.5 ($Si\underline{C}HCH_3$) and 12.4 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2866, 1673, 1514, 1248, 1126, 1055 and 1037 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{35}H_{56}O_7NaSi^+$ $[M+Na]^+$ 639.3688; found 639.3682 (Δ 0.94 ppm).

(15R,E)-9,9-Diisopropyl-17-methoxy-1-(4-methoxyphenyl)-5-methyl-12-methylene-15-(prop-1-en-2-yl)-7-vinyl-2,8,10,18-tetraoxa-9-silanonadec-5-en-13-ol (**417**)

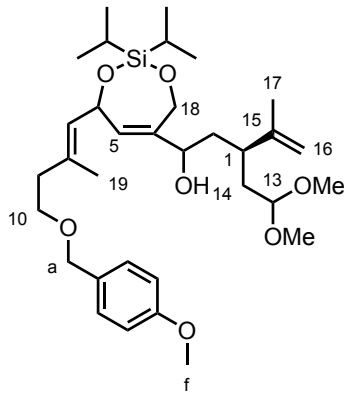


$CeCl_3 \cdot 7H_2O$ (227 mg, 0.609 mmol) was added to a solution of TST **415** (342 mg, 0.554 mmol) in MeOH (5.5 mL, 0.1 M) at rt and the suspension then cooled to 0 °C (ice/H_2O bath). $NaBH_4$ (25.1 mg, 0.665 mmol) was added in one portion (CAUTION: effervescence of H_2) and the reaction then stirred at 0 °C for 2 h. The reaction was quenched at 0 °C by dropwise addition until the cloudy precipitate persisted and then faster addition of NH_4Cl (sat., aq., 5 mL total). The reaction mixture was diluted with H_2O (5 mL), removed from the cold bath and warmed slowly to rt. The mixture was extracted with Et_2O (2 × 20 mL) and the combined organic layers washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (4:1 pentane:EtOAc) to afford alcohol **417** as a colourless oil and an inseparable mixture of diastereomers (320 mg, 94%). An epimeric ratio of 3:2 at C-3 was calculated on the basis of the two H-3 peaks in the ^{1}H NMR spectrum (5.12 and 5.09–5.07 ppm). An epimeric ratio of 1:1 at C-6 is assumed on the basis of the ratio of the preceding compound, TST **415**, as it could not be determined from either ^{1}H or ^{13}C NMR spectra. ^{1}H and ^{13}C NMR diastereomeric peaks are distinguished where possible (up to four) but are reported together as it was not possible to assign any stereoisomer completely. Major and minor refers to the epimers at C-3 and are assigned where possible. ^{1}H NMR integrals are reported such that 1 H refers to the total integral of a single proton summed across all stereoisomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26–7.21 (m, 2 H, 2 × H-c), 6.90–6.83 (m, 2 H, 2 × H-d), 5.81 (app. dddd, *J* = 17.1, 10.1, 5.4, 2.8 Hz, 1 H, H-5), 5.26–5.18 (m, 2 H, H-5′$_{trans}$ and H-7), 5.12 (major, q, *J* = 1.6 Hz, 0.6 H, H-4′), 5.09–5.07 (minor, m, 0.4 H, H-4′), 5.06–4.99 (m, 3 H, H-4′, H-5′$_{cis}$ and H-6), 4.86–4.75 (m, 2 H, 2 × H-16), 4.42 (s, 2 H, 2 × H-a), 4.42–4.26 (m, 3 H, H-13 and 2 × H-18), 4.17–4.06 (m, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.52 (tq, *J* = 7.0, 1.3 Hz, 2 H, 2 × H-10), 3.31–3.27 (m, 6 H, 2 × OCH_3), 2.67 (major, dd, *J* = 5.1, 1.7 Hz, 0.6 H, OH), 2.58 (minor, tt, *J* = 7.6, 5.5 Hz, 0.4 H, H-1), 2.37–2.36 (m, 3 H, H-1 [major], 2 × H-9 and OH [minor]), 1.77–1.55 (m, 10 H, 2 × H-2, 2 × H-14, 3 × H-17 and 3 × H-19) and 1.09–0.98 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.3 (C-e), 150.45 (minor, C-4), 150.42 (minor, C-4), 148.85 (major, C-4), 148.83 (major, C-4), 147.20 (major, C-15), 147.19 (major, C-15), 146.33 (minor, C-15), 146.32 (minor, C-15), 140.04 (C-5), 140.02 (C-5), 133.22 (major, C-8), 133.20 (major, C-8), 133.20 (minor, C-8), 133.20 (minor, C-8), 130.7 (C-b), 129.4 (2 C, 2 × C-c), 128.70 (minor, C-7), 128.68 (major, C-7), 128.66 (minor, C-7), 128.65 (major, C-7), 113.9 (2 C, 2 × C-d), 113.33 (minor, C-16), 113.32 (minor, C-16), 113.02 (C-5′), 113.00 (C-5′), 112.65 (major, C-16), 112.64 (major, C-16), 111.78 (major, C-4′), 111.75 (major, C-4′), 110.2 (minor, C-4′), 103.2 (minor, C-13), 103.1 (major, C-13), 72.61 (C-a), 72.60 (C-a), 72.59 (major, C-3), 72.5 (major, C-3), 71.13 (minor, C-3), 71.06 (minor, C-3), 70.5 (C-6), 70.48 (C-6), 68.72 (major, C-10), 68.71 (minor, C-10), 68.683 (major, C-10), 68.677 (minor, C-10), 64.21 (major and minor, C-18), 64.15 (minor, C-18), 64.06 (major, C-18), 55.4 (C-f), 53.09 (OCH_3), 53.07 (OCH_3), 53.0 (OCH_3), 52.9 (OCH_3), 52.72 (OCH_3), 52.71 (OCH_3), 40.2 (major, C-1), 39.86 (C-1 [minor] or C-2 [minor]), 39.82 (C-1 [minor] or C-2 [minor]), 39.5 (C-9), 39.38 (major, C-2), 39.36 (major, C-2), 36.7 (minor, C-14), 36.0 (major, C-14), 18.4 (C-17), 18.0 ($SiCH\underline{C}H_3$), 17.58 ($SiCH\underline{C}H_3$), 17.56 ($SiCH\underline{C}H_3$), 17.53 ($SiCH\underline{C}H_3$), 17.52 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.19 (C-19), 17.17

(C-19), 12.46 (Si<u>C</u>HCH$_3$), 12.43 (Si<u>C</u>HCH$_3$), 12.42 (Si<u>C</u>HCH$_3$) and 12.41 ppm (Si<u>C</u>HCH$_3$); **FTIR** ν_{max} (thin film): 2943, 2866, 1514, 1248, 1125, 1056 and 1039 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{35}H_{58}O_7NaSi^+$ $[M+Na]^+$ 641.3844; found 641.3837 (Δ 1.09 ppm).

(3R)-1-(2,2-Diisopropyl-7-((E)-4-((4-methoxybenzyl)oxy)-2-methylbut-1-en-1-yl)-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-3-(2,2-dimethoxyethyl)-4-methylpent-4-en-1-ol (**418**)



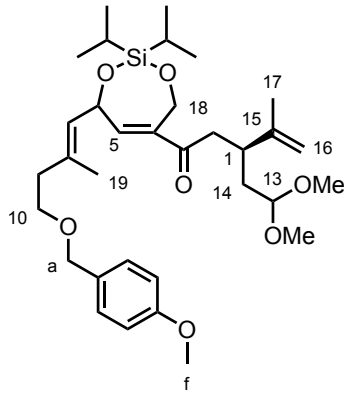
Notes: Experimental setup B (Section 5.3) was used for this reaction. Glassware was flame dried under vacuum, charged with N_2 and kept under a positive N_2 pressure *via* a manifold line prior to use. Dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (2.3 mg, 3.7 μmol) was added to the reaction flask under a positive N_2 pressure and dissolved in PhMe (5 mL). A solution of alcohol **417** (20.8 mg, 33.6 μmol) in PhMe (1 mL + 0.7 mL rinse, 5 mM final concentration) was added at rt and the reaction then stirred at 60 °C for 24 h under a gentle flow of N_2. Additional PhMe (3 mL) was added and the reaction then continued for 24 h. The reaction was cooled to rt and concentrated *in vacuo* before being purified by flash column chromatography (3:2–1:1 pentane:Et_2O) to afford silaketal **418** as a yellow oil and an inseparable unquantifiable mixture of diastereomers (11.0 mg, 55%). Additionally, an unknown byproduct is present (*ca.* <2 wt%). ^{1}H and ^{13}C NMR diastereomeric peaks are distinguished where possible (up to four) but are reported together as it was not possible to assign any stereoisomer completely.

^{1}H NMR integrals are reported such that 1 H refers to the total integral of a single proton summed across all stereoisomers.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28–7.21 (m, 2 H, 2 × H-c), 6.91–6.83 (m, 2 H, 2 × H-d), 5.56–5.45 (m, 1 H, H-5), 5.44–5.34 (m, 2 H, H-6 and H-7), 4.86–4.73 (m, 2 H, 2 × H-16), 4.64–4.53 (m, 1 H, H-18), 4.44 (s, 2 H, 2 × H-a), 4.42–4.27 (m, 2 H, H-13 and H-18), 4.04–3.85 (m, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.55 (td, *J* = 7.1, 1.9 Hz, 2 H, 2 × H-10), 3.30 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 2.58–2.48 (m, 0.4 H, H-1), 2.39–2.25 (m, 3 H, H-1, 2 × H-9 and OH), 1.96–1.88 (m, 0.5 H, OH), 1.77–1.45 (m, 10 H, 2 × H-2, 2 × H-14, 3 × H-17 and 3 × H-19) and 1.11–1.00 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 159.1 (C-e), 147.24 (C-15), 147.15 (C-15), 146.14 (C-15), 146.05 (C-15), 144.3 (C-4), 143.9 (C-4), 142.71 (C-4), 142.67 (C-4), 134.0 (C-8), 133.91 (C-8), 134.87 (C-8), 131.3 (C-5), 131.2 (C-5), 130.5 (C-b), 129.7 (C-5), 129.6 (C-5), 129.3 (2 C, 2 × C-c), 128.8 (C-7), 128.69 (C-7), 128.67 (C-7), 128.6 (C-7), 113.8 (2 C, 2 × C-d), 113.3 (C-16), 112.68 (C-16), 112.66 (C-16), 103.0 (C-13), 102.92 (C-13), 102.90 (C-13), 75.1 (C-3), 74.7 (C-3), 73.4 (C-3), 72.8 (C-3), 72.5 (C-a), 68.6 (C-10), 68.48 (C-10), 68.46 (C-10), 68.3 (C-6), 68.23 (C-6), 68.22 (C-6), 68.0 (C-6), 61.5 (C-18), 61.4 (C-18), 60.8 (C-18), 60.7 (C-18), 55.3 (C-f), 53.2 (OCH_3), 53.1 (OCH_3), 52.93 (OCH_3), 52.89 (OCH_3), 52.60 (OCH_3), 52.57 (OCH_3), 40.5 (C-1), 40.4 (C-1), 39.90 (C-1), 39.84 (C-1), 39.5 (C-9), 39.4 (C-9), 39.3 (C-2), 38.8 (C-2), 36.37 (C-14), 36.34 (C-14), 35.9 (C-14), 18.2, 17.98, 17.95, 17.53, 17.50, 17.47, 17.41, 17.38, 17.3, 17.2, 17.1, 16.9 (peaks correspond to C-17, C-19 and $SiCH\underline{C}H_3$), 12.6 ($Si\underline{C}HCH_3$), 12.53 ($Si\underline{C}HCH_3$), 12.51 ($Si\underline{C}HCH_3$), 12.45 ($Si\underline{C}HCH_3$) and 12.4 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 3451, 2943, 2866, 1513, 1464, 1248, 1126, 1064 and 886 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{33}H_{54}O_7NaSi^+$ $[M+Na]^+$ 613.3531; found 613.3530 (Δ 0.16 ppm).

(3S)-1-(2,2-Diisopropyl-7-((E)-4-((4-methoxybenzyl)oxy)-2-methylbut-1-en-1-yl)-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-3-(2,2-dimethoxyethyl)-4-methylpent-4-en-1-one (**416**)

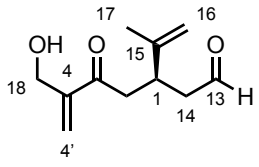


Dess–Martin Periodinane (15.4 mg, 36.4 μmol) and $NaHCO_3$ (12.1 mg, 0.146 mmol) were added to a solution of silaketal **418** (8.6 mg, 15 μmol) in CH_2Cl_2 (1 mL, 15 mM) at 0 °C (ice/ H_2O bath). The reaction was removed from the cold bath and stirred for 18 h, warming slowly to rt. The reaction was quenched at rt by addition of a 1:1:1 solution of $Na_2S_2O_3$ (sat., aq.), $NaHCO_3$ (sat., aq.) and H_2O (3 mL total), and the biphasic mixture then stirred vigorously at rt until clear on standing. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed sequentially with $NaHCO_3$ (sat., aq., 5 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (4:1 pentane:EtOAc) to afford ketone **416** as a colourless oil and an inseparable approximately 1:1 mixture of diastereomers (5.5 mg, 64%). The diastereomeric ratio was estimated on the basis of peak heights of the two C-7 peaks in the ^{13}C NMR spectrum (127.13 and 127.06 ppm). Diastereomeric peaks are not distinguishable in the ^{1}H NMR spectrum. ^{13}C NMR diastereomeric peaks are reported together where distinguishable.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.28–7.23 (m, 2 H, 2 × H-c), 6.90–6.84 (m, 2 H, 2 × H-d), 6.56–6.51 (m, 1 H, H-5), 5.59–5.53 (m, 1 H, H-6), 5.43 (app. tq, *J* = 8.7, 1.4 Hz, 1 H, H-7),

4.81–4.71 (m, 4 H, 2 × H-16 and 2 × H-18), 4.45 (s, 2 H, 2 × H-a), 4.31 (app. ddd, *J* = 7.5, 4.0, 2.4 Hz, 1 H, H-13), 3.80 (s, 3 H, 3 × H-f), 3.57 (app. td, *J* = 6.9, 1.9 Hz, 2 H, 2 × H-10), 3.29 (app. d, *J* = 1.2 Hz, 3 H, OCH_3), 3.27 (app. d, *J* = 1.0 Hz, 3 H, OCH_3), 2.78 (app. dt, *J* = 14.7, 6.8 Hz, 1 H, H-1), 2.73–2.61 (m, 2 H, 2 × H-2), 2.37 (app. tq, *J* = 7.0, 2.0 Hz, 2 H, 2 × H-9), 1.75 (app. t, *J* = 1.6 Hz, 3 H, 3 × H-19), 1.72–1.64 (m, 4 H, H-14 and 3 × H-17), 1.65–1.55 (m, 1 H, H-14) and 1.10–0.99 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 199.9 (C-3), 199.8 (C-3), 159.3 (C-e), 146.58 (C-15), 146.55 (C-15), 144.4 (C-5), 141.6 (C-4), 141.5 (C-4), 135.88 (C-8), 135.86 (C-8), 130.6 (C-b), 129.4 (2 C, 2 × C-c), 127.13 (C-7), 127.06 (C-7), 113.9 (2 C, 2 × C-d), 112.21 (C-16), 112.18 (C-16), 102.9 (C-13), 102.8 (C-13), 72.7 (C-a), 68.42 (C-10), 68.41 (C-10), 68.3 (C-6), 68.2 (C-6), 60.5 (C-18), 60.4 (C-18), 55.4 (C-f), 52.84 (OCH_3), 52.82 (OCH_3), 52.7 (OCH_3), 52.6 (OCH_3), 42.38 (C-2), 42.36 (C-2), 39.6 (C-9), 39.4 (C-1), 39.3 (C-1), 36.1 (C-14), 36.0 (C-14), 19.54 (C-17), 19.50 (C-17), 17.58 ($SiCH\underline{C}H_3$), 17.57 ($SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.20 ($SiCH\underline{C}H_3$), 17.18 (C-19), 17.16 (C-19), 12.5 ($Si\underline{C}HCH_3$), 12.44 ($Si\underline{C}HCH_3$) and 12.42 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2866, 1668, 1514, 1248, 1144, 1096 and 886 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{33}H_{52}O_7NaSi^+$ $[M+Na]^+$ 611.3375; found 611.3372 (Δ 0.49 ppm).

(S)-6-(Hydroxymethyl)-5-oxo-3-(prop-1-en-2-yl)hept-6-enal (**421**)

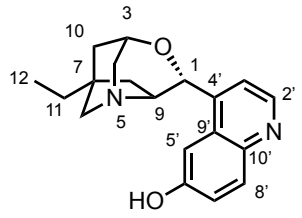


p-Toluenesulfonic acid (18.7 mg, 74.3 μmol) was added to a solution of acetal **393** (180 mg, 0.743 mmol) in acetone:H_2O (1:1, 7.5 mL, 0.1 M) at rt. A reflux condenser was fitted and the reaction then stirred at 50 °C for 18 h. The reaction was cooled to rt and the majority of the

acetone removed under reduced pressure (*ca.* 300 mbar). The reaction mixture was diluted with $NaHCO_3$ (sat., aq., 10 mL) and EtOAc (10 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with HCl (1 M, aq., 3 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford aldehyde **421** as a colourless oil (130 mg, 89%) which was used without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.69 (t, *J* = 2.1 Hz, 1 H, H-13), 6.15 (d, *J* = 0.8 Hz, 1 H, H-4′), 6.05 (t, *J* = 1.3 Hz, 1 H, H-4′), 4.85–4.74 (m, 2 H, 2 × H-16), 4.30 (d, *J* = 5.6 Hz, 2 H, 2 × H-18), 3.28–3.20 (m, 1 H, H-1), 2.93–2.76 (m, 2 H, 2 × H-2), 2.60–2.47 (m, 2 H, 2 × H-14), 2.28 (t, *J* = 6.4 Hz, 1 H, OH) and 1.73 ppm (dd, *J* = 1.4, 0.8 Hz, 3 H, 3 × H-17); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 201.5 (C-13), 200.8 (C-3), 147.0 (C-4), 145.8 (C-15), 125.7 (C-4′), 112.5 (C-16), 62.6 (C-18), 47.2 (C-14), 41.7 (C-2), 37.0 (C-1) and 20.2 ppm (C-17); **FTIR** ν_{max} (thin film): 3422, 2920, 1719, 1670, 1647, 1377, 1131, 1102, 1022, 945 and 895 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{11}H_{17}O_3^+$ $[M+H]^+$ 197.1172; found 197.1173 (Δ 0.51 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ –3.4° (c = 1.00, CH_2Cl_2).

4-((1R,3S,5R,7R,9S)-7-Ethylhexahydro-1H-3,7-methanopyrrolo[2,1-c][1,4]oxazin-1-yl)quinolin-6-ol (α-*Isocupreine*)

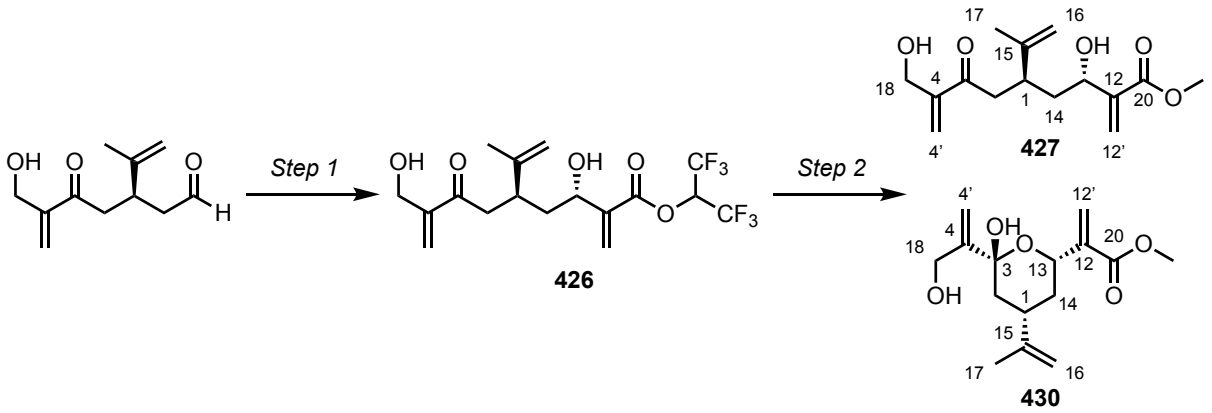


Quinine (2.00 g, 6.16 mmol) was added in one portion to trifluoromethanesulfonic acid (15 mL, 0.4 M) at 0 °C (ice/H_2O bath). A reflux condenser was fitted and the reaction then stirred at 0 °C for 10 min. The reaction was removed from the cold bath and stirred for

10 min, warming slowly to rt. The reaction was stirred at 50 °C for 24 h and then 80 °C for a further 24 h. The reaction was cooled to rt, diluted by dropwise addition of ice-water (40 mL) and quenched at rt by portionwise addition of Na_2CO_3 (10 g, CAUTION: effervescence). The resulting suspension was diluted with $CHCl_3$ (100 mL), the layers separated and the aqueous layer extracted with $CHCl_3$ (100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous K_2CO_3, filtered and concentrated *in vacuo* before partial purification by flash column chromatography (100:2:1–100:5:1 $CHCl_3$:MeOH:Et_3N). Fractions containing product were concentrated *in vacuo* before being redissolved in $CHCl_3$ (amylene stabilised to prevent crystallisation with ethanol, *ca.* 24 mL). The solution was added in one portion to hexane (7 × volume $CHCl_3$, 170 mL) and the resulting suspension filtered. The precipitate was dried under high vacuum to afford α-isocupreine as a pale brown solid (1.22 g, 63%). Data is consistent with that reported in the literature.[224]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.07 (br. s, 1 H, OH), 8.71 (d, *J* = 4.5 Hz, 1 H, H-2′), 7.96 (d, *J* = 9.0 Hz, 1 H, H-8′), 7.81 (d, *J* = 2.6 Hz, 1 H, H-5′), 7.54 (dd, *J* = 4.5, 0.9 Hz, 1 H, H-3′), 7.24 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-7′), 5.88 (d, *J* = 1.4 Hz, 1 H, H-1), 4.43 (d, *J* = 2.6 Hz, 1 H, H-3), 4.16–4.00 (m, 2 H, H-4 and H-9), 3.06–2.80 (m, 3 H, H-4 and 2 × H-6), 2.07–1.95 (m, 1 H, H-10), 1.95–1.81 (m, 2 H, H-8 and H-10), 1.42 (qd, *J* = 7.4, 5.4 Hz, 2 H, 2 × H-11), 1.31–1.14 (m, 1 H, H-8) and 0.88 ppm (t, *J* = 7.6 Hz, 3 H, 3 × H-12); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 156.6 (C-6′), 147.1 (C-2′), 143.2 (C-4′ or C-10′), 142.7 (C-4′ or C-10′), 131.5 (C-8′), 126.9 (C-9′), 122.1 (C-7′), 118.5 (C-3′), 105.9 (C-5′), 69.7 (C-3), 68.2 (C-1), 66.8 (C-6), 64.3 (C-9), 53.2 (C-4), 43.0 (C-7), 41.7 (C-10), 37.1 (C-8), 29.2 (C-11) and 9.5 ppm (C-12); **M.P.** >200 °C ($CHCl_3$); **Specific Rotation:** $[\alpha]_D^{25}$ –95.4° (c = 1.00, CH_2Cl_2).

Methyl (3S,5S)-3-hydroxy-8-(hydroxymethyl)-2-methylene-7-oxo-5-(prop-1-en-2-yl)non-8-enoate (**427**)



Step 1: A solution of aldehyde **421** (655 mg, 3.34 mmol) in DMF (5 mL + 3 mL rinse) was added to a solution of α-isocupreine (259 mg, 0.834 mmol) in DMF (25 mL, 0.1 M final concentration) at rt and the mixture then cooled to –55 °C (cryostat-cooled acetone bath). 1,1,1,3,3,3-hexafluoroisopropyl acrylate (2.80 mL, 16.8 mmol) was added dropwise *via* syringe pump over 1 h and the reaction then stirred at –55 °C for 2 days. The reaction was quenched at –55 °C by addition of HCl (1 M, aq., 6 mL), diluted with EtOAc (20 mL) and brine (20 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (sat., aq., 20 mL) and brine (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before partial purification by flash column chromatography (4:1:0–40:10:1 pentane:EtOAc:MeOH). Fractions containing product were collected and concentrated *in vacuo* to afford crude ester **426** (821 mg).

Step 2: Crude ester **426** was redissolved in dry MeOH (9.8 mL, 0.2 M) and cooled to 0 °C (ice/H_2O bath). Et_3N (1.36 mL, 9.76 mmol) was added at 0 °C and the reaction then removed from the cold bath and stirred at 25 °C (oil bath temperature) for 12 h. The reaction was quenched at 25 °C by addition of DOWEX 50WX8-200 ion-exchange resin and the suspen-

sion then filtered through celite, washing several times with EtOAc. The filtrate was concentrated *in vacuo* before being purified by flash column chromatography (40:10:1 pentane:EtOAc:MeOH) to afford (*3S*,*5S*)-ester **427** as a pale yellow oil (435 mg, 46% over 2 steps). The compound exists in equilibrium with hemiacetal **430** in a 2:1 (**427**:**430**) ratio in $CDCl_3$ and 10:3 (**427**:**430**) in CD_3OD. The ratio in CD_3OD was calculated on the basis of the integrals of the two H-12′ peaks in the ^{1}H NMR spectrum (5.92 and 5.91 ppm).

^{1}H NMR (Linear form **427**, CD_3OD, 500 MHz): δ = 6.20 (app. dt, *J* = 2.4, 1.3 Hz, 2 H, H-4′ and H-12′), 6.05 (t, *J* = 1.8 Hz, 1 H, H-4′), 5.91 (t, *J* = 1.5 Hz, 1 H, H-12′), 4.82–4.80 (m, 2 H, 2 × H-16), 4.39 (ddt, *J* = 10.4, 2.4, 1.1 Hz, 1 H, H-13), 4.31–4.17 (m, 2 H, 2 × H-18), 3.74 (s, 3 H, $COOCH_3$), 3.06 (dddd, *J* = 10.9, 8.0, 6.8, 4.0 Hz, 1 H, H-1), 2.85–2.73 (m, 2 H, 2 × H-2), 1.77 (ddd, *J* = 13.6, 11.0, 2.3 Hz, 1 H, H-14), 1.74–1.71 (m, 3 H, 3 × H-17) and 1.36 ppm (ddd, *J* = 14.1, 10.3, 4.0 Hz, 1 H, H-14).

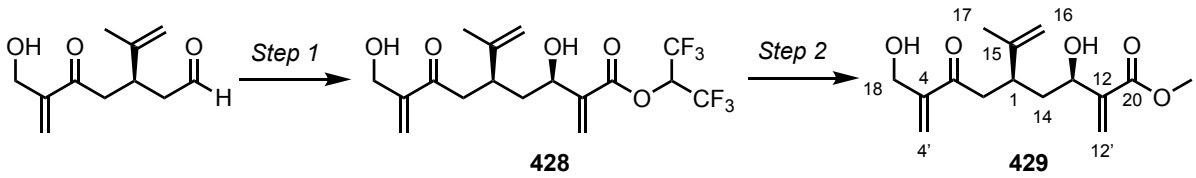
^{13}C NMR (Linear form **427**, CD_3OD, 126 MHz): δ = 202.6 (C-3), 168.1 (C-20), 149.3 (C-4), 147.2 (C-15), 146.3 (C-12), 124.5 (C-4′), 124.2 (C-12′), 113.7 (C-16), 68.5 (C-13), 61.2 (C-18), 52.2 ($COO\underline{C}H_3$), 44.0 (C-2), 42.3 (C-1), 41.3 (C-14) and 18.4 ppm (C-17).

^{1}H NMR (Hemiacetal form **430**, CD_3OD, 500 MHz): δ = 6.24 (t, *J* = 1.3 Hz, 1 H, H-12′), 5.92 (t, *J* = 1.6 Hz, 1 H, H-12′), 5.41 (q, *J* = 1.5 Hz, 1 H, H-4′), 5.24 (q, *J* = 1.7 Hz, 1 H, H-4′), 4.89–4.87 (m, 1 H, H-13), 4.73 (quint., *J* = 1.7 H, 1 H, H-16), 4.70 (dt, *J* = 2.0, 1.0 Hz, 1 H, H-16), 4.31–4.17 (m, 2 H, 2 × H-18), 3.76 (s, 3 H, $COOCH_3$), 2.69 (tt, *J* = 12.6, 3.6 Hz, 1 H, H-1), 2.00 (ddt, *J* = 12.7, 3.7, 2.0 Hz, 1 H, H-14), 1.84–1.80 (m, 1 H, H-2), 1.74–1.71 (m, 3 H, 3 × H-17), 1.48 (t, *J* = 12.8 Hz, 1 H, H-2) and 1.09 ppm (td, *J* = 12.5, 11.3 Hz, 1 H, H-14).

^{13}C NMR (Hemiacetal form **430**, CD_3OD, 126 MHz): δ = 167.9 (C-20), 154.4 (C-4), 149.9 (C-15), 143.7 (C-12), 124.9 (C-12′), 110.4 (C-4′), 109.6 (C-16), 98.5 (C-3), 69.5 (C-13), 62.3 (C-18), 52.3 ($COO\underline{C}H_3$), 40.7 (C-2), 39.1 (C-1), 37.9 (C-14) and 20.9 ppm (C-17).

FTIR ν_{max} (thin film): 3420, 2952, 2921, 1716, 1670, 1439, 1274, 1151, 1071 and 1014 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{15}H_{22}O_5Na^+$ $[M+Na]^+$ 305.1359; found 305.1359 (Δ 0.00 ppm).

Methyl (3R,5S)-3-hydroxy-8-(hydroxymethyl)-2-methylene-7-oxo-5-(prop-1-en-2-yl)non-8-enoate (**429**)



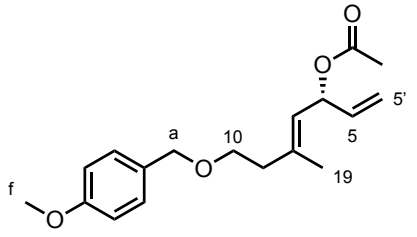
428 **429**

Step1: 1,1,1,3,3,3-hexafluoroisopropyl acrylate (0.132 mL, 0.791 mmol) was added to a solution of aldehyde **421** (31.0 mg, 0.158 mmol) in DMF (0.260 mL) at rt and the solution then cooled to –55 °C (cryostat-cooled acetone bath). A solution of β-isocupreidine (24.5 mg, 78.9 μmol) in DMF (0.200 mL, 0.33 M final concentration) was cooled to –55 °C (cryostat-cooled acetone bath) and added to the reaction solution *via* cannula. The reaction was stirred at –55 °C for 2 days. The reaction was quenched at –55 °C by addition of HCl (1 M, aq., 1 mL), diluted with EtOAc (5 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with $NaHCO_3$ (sat., aq., 5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before partial purification by flash column chromatography (2:1 pentane:EtOAc). Fractions containing product were collected and concentrated *in vacuo* to afford crude ester **428** (5.7 mg).

Step 2: Crude ester **428** (5.7 mg) was azeotroped with benzene (× 3) and dried under high vacuum for 1 h before being redissolved in dry MeOH (0.150 mL, 0.1 M) at rt and cooled to 0 °C (ice/H_2O bath). Et_3N (10 μL, 73 μmol) was added at 0 °C and the reaction then was then removed from the cold bath and stirred for 75 min, warming slowly to rt. The reaction was quenched at rt by addition of DOWEX 50WX8-200 ion-exchange resin and the suspension then filtered through celite, washing several times with EtOAc. The filtrate was concentrated *in vacuo* before being purified by flash column chromatography (1:1 pentane:EtOAc) to afford (*3R*,*5S*)-ester **429** as a pale yellow oil and as a single diastereomer (0.9 mg, 2% over 2 steps). The stereochemistry was assigned on the basis of the model reported in the literature.[224]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.25 (d, *J* = 1.2 Hz, 1 H, H-12′), 6.12 (s, 1 H, H-4′), 6.02 (t, *J* = 1.3 Hz, 1 H, H-4′), 5.87 (t, *J* = 1.2 Hz, 1 H, H-12′), 4.79 (quint., *J* = 1.5 Hz, 1 H, H-16), 4.75 (s, 1 H, H-16), 4.34 (q, *J* = 6.8 Hz, 1 H, H-13), 4.30 (s, 2 H, 2 × H-18), 3.79 (s, 3 H, $COOCH_3$), 3.01 (d, *J* = 6.7 Hz, 1 H, C-13 OH), 2.90–2.78 (m, 3 H, H-1 and 2 × H-2), 2.28 (br. s, 1 H, C-18 OH), 1.79–1.74 (m, 2 H, 2 × H-14) and 1.73–1.71 ppm (m, 3 H, 3 × H-17); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 202.0 (C-3), 167.1 (C-20), 147.1 (C-4), 147.1 (C-15), 141.7 (C-12), 125.8 (C-12′), 125.6 (C-4′), 112.2 (C-16), 70.1 (C-13), 62.8 (C-18), 52.1 ($COO\underline{C}H_3$), 42.2 (C-2), 39.9 (C-1), 39.6 (C-14) and 19.7 ppm (C-17).

(R,E)-7-((4-Methoxybenzyl)oxy)-5-methylhepta-1,4-dien-3-yl acetate (*R*)-(**432**)



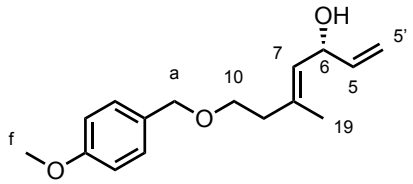
Notes: Isopropenyl acetate was stirred at rt over anhydrous K_2CO_3 for 3 h and then distilled directly at 92 °C/1 atm. prior to use. No magnetic follower was used for the reaction.

Lipase acrylic resin from *Candida antarctica* (Novozyme 435, 229 mg, 30 mg/mmol) was added to a solution of (±)-alcohol **413** (2.00 g, 7.62 mmol) and isopropenyl acetate (1.26 mL, 11.4 mmol) in PhMe (51 mL, 0.15 M) at rt. The flask was capped and sealed with plastic paraffin film before being placed in an orbital incubator at 25 °C with a rotation rate of 200 rpm for 24 h. The reaction mixture was filtered through a plug of cotton wool and concentrated *in vacuo* before being purified by flash column chromatography (20:10:1–25:25:1 pentane:Et_2O:Et_3N) to afford (*R*)-acetate **432** as a colourless oil (1.02 g, 44%). (*S*)-alcohol **413** was also recovered as a colourless oil (992 mg, 49%). The enantiopurity of (*S*)-alcohol **413** was measured to be 89% *ee* by HPLC.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28–7.21 (m, 2 H, 2 × H-c), 6.91–6.84 (m, 2 H, 2 × H-d), 5.95 (ddt, *J* = 8.6, 5.6, 1.4 Hz, 1 H, H-6), 5.82 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1 H, H-5), 5.28–5.19 (m, 2 H, H-5′$_{trans}$, H-7), 5.15 (dt, *J* = 10.4, 1.3 Hz, 1 H, H-5′$_{cis}$), 4.43 (s, 2 H, 2 × H-a), 3.80 (s, 3 H, 3 × H-f), 3.54 (t, *J* = 6.9 Hz, 2 H, 2 × H-10), 2.40–2.28 (m, 2 H, 2 × H-9), 2.05 (s, 3 H, $COCH_3$) and 1.74 ppm (d, *J* = 1.4 Hz, 3 H, 3 × H-19); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 170.3 ($\underline{C}OCH_3$), 159.3 (C-e), 138.3 (C-8), 136.0 (C-5), 130.6 (C-b), 129.4 (2 C, 2 × C-c), 123.2 (C-7), 116.4 (C-5′), 113.9 (2 C, 2 × C-d), 72.7 (C-a), 72.0 (C-6), 69.4 (C-10), 55.4 (C-f), 39.7 (C-9), 21.5 ($CO\underline{C}H_3$) and 17.2 ppm (C-19); **FTIR** ν_{max} (thin film): 1734, 1513, 1238,

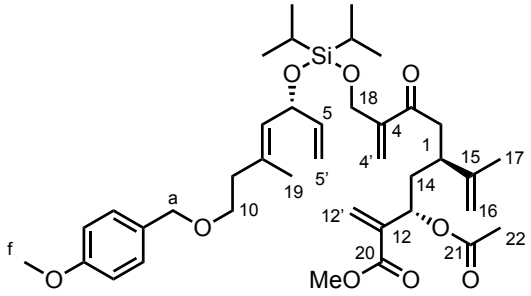
1095 and 1035 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{18}H_{24}O_4Na^+$ $[M+Na]^+$ 327.1572; found 327.1574 (Δ 0.61 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +17.2° (c = 1.00, CH_2Cl_2).

(R,E)-7-((4-Methoxybenzyl)oxy)-5-methylhepta-1,4-dien-3-ol (*R*)-(**413**)



Anhydrous K_2CO_3 (4.63 g, 76.2 mmol) was added in one portion to a solution of (*R*)-acetate **432** (1.02 g, 3.37 mmol) in MeOH (13.5 mL, 0.25 M) at rt and the reaction then stirred at rt overnight. The reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL), the layers separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (1:1 pentane:Et_2O) to afford (*R*)-alcohol **413** as a colourless oil (861 mg, 97%). The enantiopurity of (*R*)-alcohol **413** was measured to be 95% *ee* by HPLC. Data is consistent with that reported for (±)-**413**. Additionally: **Specific Rotation:** $[\alpha]_D^{25}$ +30.6° (c = 1.00, CH_2Cl_2).

Methyl (7R,15S,17S,E)-17-acetoxy-9,9-diisopropyl-1-(4-methoxyphenyl)-5-methyl-12,18-dimethylene-13-oxo-15-(prop-1-en-2-yl)-7-vinyl-2,8,10-trioxa-9-silanonadec-5-en-19-oate (**439**)



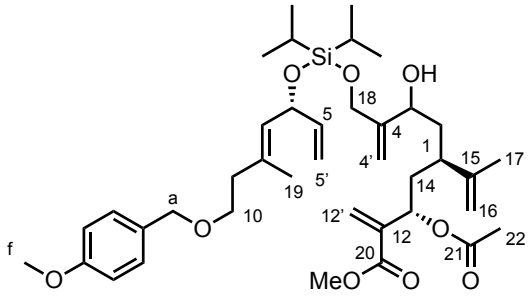
Note: Alcohols (*R*)-**413** and (*3S*,*5S*)-**427** were azeotroped with PhMe (× 3) and dried under high vacuum prior to use.

i-Pr_2SiCl_2 (0.256 mL, 1.42 mmol) was added dropwise to a solution of imidazole (230 mg, 3.38 mmol) in CH_2Cl_2 (14 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of (*R*)-alcohol **413** (355 mg, 1.35 mmol) in CH_2Cl_2 (2.2 mL + 0.5 mL rinse, 0.5 M) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 30 min. A solution of alcohol (*3S*,*5S*)-**427** (421 mg, 1.49 mmol) in CH_2Cl_2 (2.5 mL + 0.5 mL rinse, 0.5 M) was added dropwise at 0 °C over 3 min and the reaction then stirred at 0 °C for 20 min. The reaction mixture was filtered through a short plug of silica, eluting with EtOAc, concentrated *in vacuo* and dried under high vacuum for 15 min. The residue was redissolved in CH_2Cl_2 (13.5 mL, 0.1 M) and pyridine (2.20 mL, 27.0 mmol) and DMAP (16.5 mg, 0.147 mmol) were then sequentially added at rt. The reaction was cooled to 0 °C (ice/H_2O bath) and acetic anhydride (K_2CO_3 filtered, 0.640 mL, 6.76 mmol) added dropwise. The reaction was removed from the cold bath and stirred for 2 h, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 5 mL), the layers separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous $MgSO_4$,

filtered and concentrated *in vacuo* before being purified by flash column chromatography (7:3 pentane:Et_2O) to afford TST **439** as a colourless oil (639 mg, 66%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.26–7.22 (m, 2 H, 2 × H-c), 6.89–6.83 (m, 2 H, 2 × H-d), 6.23 (s, 1 H, H-12′), 6.12 (t, *J* = 2.1 Hz, 1 H, H-4′), 6.08 (t, *J* = 2.1 Hz, 1 H, H-4′), 5.79 (ddd, *J* = 17.1, 10.2, 5.3 Hz, 1 H, H-5), 5.71 (t, *J* = 1.0 Hz, 1 H, H-12′), 5.43 (dd, *J* = 10.6, 2.4 Hz, 1 H, H-13), 5.23–5.14 (m, 2 H, H-5′ and H-7), 5.02–4.96 (m, 2 H, H-5′ and H-6), 4.81 (t, *J* = 1.7 Hz, 1 H, H-16), 4.73 (d, *J* = 1.9 Hz, 1 H, H-16), 4.45 (t, *J* = 1.8 Hz, 2 H, 2 × H-18), 4.42 (s, 2 H, 2 × H-a), 3.80 (s, 3 H, 3 × H-f), 3.75 (s, 3 H, $COOCH_3$), 3.51 (t, *J* = 7.1 Hz, 2 H, 2 × H-10), 2.90 (dtd, *J* = 11.0, 7.1, 4.1 Hz, 1 H, H-1), 2.81 (dd, *J* = 15.8, 6.9 Hz, 1 H, H-2), 2.68 (dd, *J* = 15.9, 7.3 Hz, 1 H, H-2), 2.34–2.22 (m, 2 H, 2 × H-9), 2.08 (s, 3 H, 3 × H-22), 1.84 (ddd, *J* = 13.8, 10.9, 2.6 Hz, 1 H, H-14), 1.72 (s, 3 H, 3 × H-17), 1.71–1.64 (m, 1 H, H-14), 1.63 (s, 3 H, 3 × H-19) and 1.06–1.01 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 199.8 (C-3), 169.9 (C-21), 165.7 (C-20), 159.2 (C-e), 147.7 (C-4), 145.0 (C-15), 140.6 (C-12), 140.0 (C-5), 133.1 (C-8), 130.7 (C-b), 129.3 (2 C, 2 × C-c), 128.7 (C-7), 124.6 (C-12′), 123.0 (C-4′), 113.9 (2 C, 2 × C-d), 113.6 (C-16), 113.0 (C-5′), 72.6 (C-a), 70.4 (C-6), 70.1 (C-13), 68.8 (C-10), 61.0 (C-18), 55.4 (C-f), 52.1 ($COO\underline{C}H_3$), 42.4 (C-2), 40.0 (C-1), 39.5 (C-9), 37.8 (C-14), 21.1 (C-22), 18.4 (C-17), 17.53 ($SiCH\underline{C}H_3$), 17.49 (2 C, 2 × $SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.1 (C-19), 12.44 ($Si\underline{C}HCH_3$) and 12.41 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2945, 2866, 1748, 1721, 1514, 1245, 1146, 1092, 1060, 1037, 886 and 819 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{39}H_{58}O_9NaSi^+$ $[M+Na]^+$ 721.3742; found 721.3718 (Δ 3.33 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +27.2° (c = 1.00, CH_2Cl_2).

Methyl (7R,15R,17S,E)-17-acetoxy-13-hydroxy-9,9-diisopropyl-1-(4-methoxyphenyl)-5-methyl-12,18-dimethylene-15-(prop-1-en-2-yl)-7-vinyl-2,8,10-trioxa-9-silanonadec-5-en-19-oate (**441**)



$CeCl_3 \cdot 7H_2O$ (358 mg, 0.962 mmol) was added to a solution of TST **439** (611 mg, 0.874 mmol) in MeOH (8.7 mL, 0.1 M) at rt and the suspension then cooled to 0 °C (ice/H_2O bath). $NaBH_4$ (39.8 mg, 1.05 mmol) was added in one portion (CAUTION: effervescence of H_2) and the reaction then stirred at 0 °C for 2 h. The reaction was quenched at 0 °C by drop-wise addition until the cloudy precipitate persisted and then faster addition of NH_4Cl (sat., aq., 10 mL total). The reaction was removed from the cold bath, warmed slowly to rt and diluted with H_2O (10 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (3:2 pentane:Et_2O) to afford alcohol **441** as a colourless oil and an inseparable 3:2 ratio of diastereomers (567 mg, 92%). The diastereomeric ratio was calculated on the basis of the integrals of the two H-16 peaks in the ^1H NMR spectrum (4.89 and 4.84 ppm).

^1H NMR (Major Diastereomer, $CDCl_3$, 500 MHz): δ = 7.26–7.22 (m, 2 H, 2 × H-c), 6.89–6.84 (m, 2 H, 2 × H-d), 6.23 (s, 1 H, H-12′), 5.86–5.76 (m, 1 H, H-5), 5.69 (t, *J* = 1.1 Hz, 1 H, H-12′), 5.44–5.37 (m, 1 H, H-13), 5.25–5.18 (m, 2 H, H-5′ and H-7), 5.12 (q, *J* = 1.6 Hz, 1 H, H-4′), 5.06–4.99 (m, 3 H, H-4′, H-5′ and H-6), 4.84 (quint., *J* = 1.4 Hz, 1 H, H-16), 4.69 (d, *J* = 2.1 Hz, 1 H, H-16), 4.42 (s, 2 H, 2 × H-a), 4.41–4.25 (m, 2 H, 2 × H-18), 4.16–4.08 (m,

1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.758 (s, 3 H, $COOCH_3$), 3.55–3.50 (m, 2 H, 2 × H-10), 2.57 (d, *J* = 5.0 Hz, 1 H, OH), 2.47–2.39 (m, 1 H, H-1), 2.35–2.24 (m, 2 H, 2 × H-9), 2.06 (s, 3 H, 3 × H-22), 1.83 (dddd, *J* = 14.1, 11.4, 4.6, 2.4 Hz, 1 H, H-14), 1.77–1.69 (m, 4 H, H-2 and 3 × H-17), 1.67–1.64 (m, 3 H, 3 × H-19), 1.63–1.52 (m, 2 H, H-2 and H-14) and 1.08–1.01 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Major Diastereomer, $CDCl_3$, 126 MHz): δ = 169.8 (C-21), 165.7 (C-20), 159.3 (C-e), 149.0 (C-4), 146.0 (C-15), 140.92 (C-12), 140.03 (C-5), 133.23 (C-8), 130.6 (C-b), 129.4 (2 C, 2 × C-c), 128.6 (C-7), 124.38 (C-12′), 113.9 (2 C, 2 × C-d), 113.8 (C-16), 113.02 (C-5′), 111.6 (C-4′), 72.61 (C-a), 72.5 (C-3), 70.50 (C-6), 70.2 (C-13), 68.7 (C-10), 64.10 (C-18), 55.4 (C-f), 52.07 ($COO\underline{C}H_3$), 41.2 (C-1), 39.54 (C-2), 39.48 (C-9), 38.0 (C-14), 21.05 (C-22), 17.57 (C-17), 17.52 ($SiCH\underline{C}H_3$), 17.47 ($SiCH\underline{C}H_3$), 17.39 ($SiCH\underline{C}H_3$), 17.2 (C-19), 17.1 ($SiCH\underline{C}H_3$), 12.42 ($Si\underline{C}HCH_3$) and 12.40 ppm ($Si\underline{C}HCH_3$).

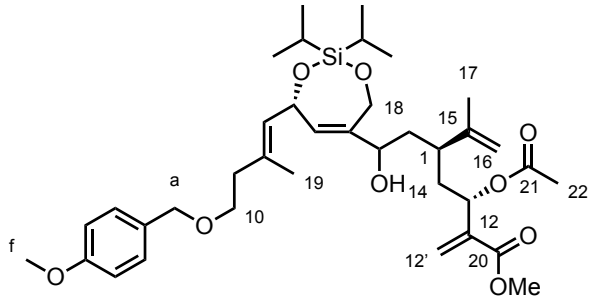
^{1}H NMR (Minor Diastereomer, $CDCl_3$, 500 MHz): δ = 7.26–7.22 (m, 2 H, 2 × H-c), 6.89–6.84 (m, 2 H, 2 × H-d), 6.23 (s, 1 H, H-12′), 5.86–5.76 (m, 1 H, H-5), 5.70 (t, *J* = 1.3 Hz, 1 H, H-12′), 5.44–5.37 (m, 1 H, H-13), 5.25–5.18 (m, 2 H, H-5′ and H-7), 5.08 (q, *J* = 1.6 Hz, 1 H, H-4′), 5.06–4.99 (m, 3 H, H-4′, H-5′ and H-6), 4.89 (dt, *J* = 2.9, 1.5 Hz, 1 H, H-16), 4.78 (d, *J* = 2.3 Hz, 1 H, H-16), 4.42 (s, 2 H, 2 × H-a), 4.41–4.25 (m, 2 H, 2 × H-18), 4.16–4.08 (m, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.756 (s, 3 H, $COOCH_3$), 3.55–3.50 (m, 2 H, 2 × H-10), 2.71–2.63 (m, 1 H, H-1), 2.37 (d, *J* = 5.2 Hz, 1 H, OH), 2.35–2.24 (m, 2 H, 2 × H-9), 2.07 (s, 3 H, 3 × H-22), 1.83 (dddd, *J* = 14.1, 11.4, 4.6, 2.4 Hz, 1 H, H-14), 1.77–1.69 (m, 1 H, H-2), 1.67 (s, 3 H, 3 × H-17), 1.67–1.64 (m, 3 H, 3 × H-19), 1.63–1.52 (m, 2 H, H-2 and H-14) and 1.08–1.01 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Minor Diastereomer, $CDCl_3$, 126 MHz): δ = 169.9 (C-21), 165.8 (C-20), 159.3 (C-e), 150.5 (C-4), 144.9 (C-15), 140.94 (C-12), 139.99 (C-5), 133.17 (C-8), 130.6 (C-b), 129.4

(2 C, 2 × C-c), 128.7 (C-7), 124.41 (C-12′), 114.6 (C-16), 113.9 (2 C, 2 × C-d), 113.00 (C-5′), 110.2 (C-4′), 72.59 (C-a), 71.0 (C-3), 70.48 (C-6), 70.3 (C-13), 68.6 (C-10), 64.06 (C-18), 55.4 (C-f), 52.06 ($COO\underline{C}H_3$), 40.8 (C-1), 39.6 (C-2), 39.47 (C-9), 38.7 (C-14), 21.09 (C-22), 17.55 (C-17), 17.52 ($SiCH\underline{C}H_3$), 17.50 ($SiCH\underline{C}H_3$), 17.39 ($SiCH\underline{C}H_3$), 17.13 (C-19 or $SiCH\underline{C}H_3$), 17.11 (C-19 or $SiCH\underline{C}H_3$), 12.5 ($Si\underline{C}HCH_3$) and 12.42 ppm ($Si\underline{C}HCH_3$).

FTIR ν_{max} (thin film): 2944, 2866, 2341, 1748, 1723, 1514, 1247, 1089 and 1038 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{39}H_{60}O_9NaSi^+$ $[M+Na]^+$ 723.38988; found 723.38947 (Δ 0.57 ppm).

Methyl (3S,5R)-3-acetoxy-5-(2-((S)-2,2-diisopropyl-7-((E)-4-((4-methoxybenzyl)oxy)-2-methylbut-1-en-1-yl)-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-2-hydroxyethyl)-6-methyl-2-methyl-enehept-6-enoate (**442**)



Notes: Experimental setup B (Section 5.3) was used for this reaction. Glassware was flame dried under vacuum, charged with Ar and kept under a positive Ar pressure *via* a manifold line prior to use. Dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (101 mg, 0.162 mmol) was added to the reaction flask under a positive Ar pressure and dissolved in PhMe (150 mL). A solution of alcohol **441** (567 mg, 0.809 mmol) in PhMe (8 mL + 2 mL rinse, 5 mM final concentration) was added at rt and the reaction then stirred at 60 °C for 24 h under a gentle flow of Ar. The reaction was cooled to rt and concentrated *in vacuo* before being purified by flash column chromatography

(4:1–7:3 pentane:EtOAc) to afford silaketal **442** as a yellow oil and an inseparable 9:5 ratio of diastereomers (307 mg, 56%). The diastereomeric ratio was measured from the integrals of H-16 in the ^{1}H NMR spectrum (4.77–4.75 and 4.69 ppm).

^{1}H NMR (Major Diastereomer, $CDCl_3$, 500 MHz): δ = 7.28–7.20 (m, 2 H, 2 × H-c), 6.91–6.82 (m, 2 H, 2 × H-d), 6.24–6.21 (m, 1 H, H-12′), 5.69 (q, *J* = 1.2 Hz, 1 H, H-12′), 5.47 (d, *J* = 2.2 Hz, 1 H, H-5), 5.44–5.35 (m, 3 H, H-6, H-7 and H-13), 4.84 (dd, *J* = 2.3, 1.4 Hz, 1 H, H-16), 4.69 (d, *J* = 2.3 Hz, 1 H, H-16), 4.65–4.56 (m, 1 H, H-18), 4.44 (s, 2 H, 2 × H-a), 4.38 (d, *J* = 14.7 Hz, 1 H, H-18), 4.01 (td, *J* = 6.7, 2.7 Hz, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.759 (s, 3 H, $COOCH_3$), 3.55 (td, *J* = 6.9, 1.3 Hz, 2 H, 2 × H-10), 2.47–2.37 (m, 1 H, H-1), 2.34 (sept., *J* = 7.1 Hz, 2 H, 2 × H-9), 2.06 (s, 3 H, 3 × H-22), 1.86–1.78 (m, 1 H, H-14), 1.75–1.65 (m, 8 H, H-2, H-14, 3 × H-17 and 3 × H-19), 1.65–1.52 (m, 1 H, H-2) and 1.11–1.00 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Major Diastereomer, $CDCl_3$, 126 MHz): δ = 169.8 (C-21), 165.7 (C-20), 159.2 (C-e), 146.1 (C-15), 142.6 (C-4), 140.8 (C-12), 134.0 (C-8), 131.4 (C-5), 130.7 (C-b), 129.4 (2 C, 2 × C-c), 128.7 (C-7), 124.5 (C-12′), 114.1 (C-16), 113.9 (2 C, 2 × C-d), 75.4 (C-3), 72.6 (C-a), 70.1 (C-13), 68.58 (C-10), 68.5 (C-6), 60.9 (C-18), 55.4 (C-f), 52.1 ($COO\underline{C}H_3$), 41.7 (C-1), 39.5 (C-9), 38.9 (C-2), 38.2 (C-14), 21.0 (C-22), 17.69 ($SiCH\underline{C}H_3$), 17.5–17.2 (4 C, C-17 and 3 × $SiCH\underline{C}H_3$), 17.01 (C-19), 12.67 ($Si\underline{C}HCH_3$) and 12.64 ppm ($Si\underline{C}HCH_3$).

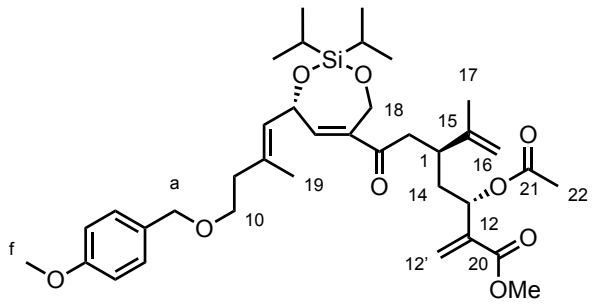
^{1}H NMR (Minor Diastereomer, $CDCl_3$, 500 MHz): δ = 7.28–7.20 (m, 2 H, 2 × H-c), 6.91–6.82 (m, 2 H, 2 × H-d), 6.24–6.21 (m, 1 H, H-12′), 5.69 (q, *J* = 1.2 Hz, 1 H, H-12′), 5.54 (d, *J* = 3.5 Hz, 1 H, H-5), 5.44–5.35 (m, 3 H, H-6, H-7 and H-13), 4.89 (dd, *J* = 2.3, 1.4 Hz, 1 H, H-16), 4.77–4.75 (m, 1 H, H-16), 4.65–4.56 (m, 1 H, H-18), 4.44 (s, 2 H, 2 × H-a), 4.32 (d, *J* = 14.8 Hz, 1 H, H-18), 3.92–3.84 (m, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.756 (s, 3 H, $COOCH_3$), 3.55 (td, *J* = 6.9, 1.3 Hz, 2 H, 2 × H-10), 2.62 (ddd, *J* = 11.0, 6.8, 4.1 Hz, 1 H,

H-1), 2.34 (sept., J = 7.1 Hz, 2 H, 2 × H-9), 2.07 (s, 3 H, 3 × H-22), 1.86–1.78 (m, 1 H, H-14), 1.75–1.65 (m, 8 H, H-2, H-14, 3 × H-17 and 3 × H-19), 1.65–1.52 (m, 1 H, H-2) and 1.11–1.00 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Minor Diastereomer, $CDCl_3$, 126 MHz): δ = 169.8 (C-21), 165.8 (C-20), 159.2 (C-e), 144.8 (C-15), 144.4 (C-4), 140.9 (C-12), 134.1 (C-8), 130.7 (C-b), 129.8 (C-5), 129.4 (2 C, 2 × C-c), 128.9 (C-7), 124.5 (C-12′), 114.7 (C-16), 113.9 (2 C, 2 × C-d), 72.9 (C-3), 72.6 (C-a), 70.3 (C-13), 68.61 (C-10), 68.1 (C-6), 61.8 (C-18), 55.4 (C-f), 52.1 ($COO\underline{C}H_3$), 40.9 (C-1), 39.6 (C-9), 39.1 (C-2), 38.6 (C-14), 21.1 (C-22), 17.63 ($SiCH\underline{C}H_3$), 17.5–17.2 (4 C, C-17 and 3 × $SiCH\underline{C}H_3$), 17.16 (C-19), 12.60 ($Si\underline{C}HCH_3$) and 12.5 ppm ($Si\underline{C}HCH_3$).

FTIR ν_{max} (thin film): 3457, 2944, 2866, 1747, 1722, 1514, 1246, 1146, 1093, 1037 and 886 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{37}H_{56}O_9NaSi+$ $[M+Na]^+$ 695.3586; found 695.3582 (Δ 0.58 ppm).

Methyl (3S,5S)-3-acetoxy-5-(2-((S)-2,2-diisopropyl-7-((E)-4-((4-methoxybenzyl)oxy)-2-methylbut-1-en-1-yl)-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-2-oxoethyl)-6-methyl-2-methylene-hept-6-enoate (**440**)

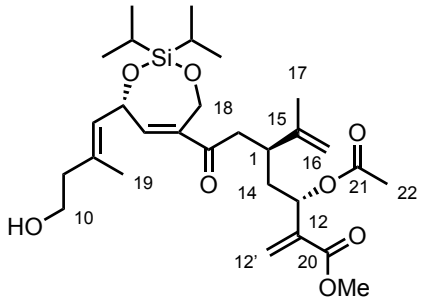


Dess–Martin Periodinane (82.9 mg, 0.196 mmol) was added to a solution of silaketal **442** (65.8 mg, 97.8 μmol) in CH_2Cl_2 (2 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 3.5 h, warming slowly to rt. The reaction was quenched at rt by addition of a 1:1:1 solution of $Na_2S_2O_3$ (sat., aq.), $NaHCO_3$ (sat., aq.) and

H_2O (3 mL total), and the biphasic mixture then stirred vigorously at rt until clear on standing. The layers were separated and the aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (2:1 pentane:Et_2O) to afford ketone **440** as a colourless oil (47.0 mg, 71%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.26–7.22 (m, 2 H, 2 × H-c), 6.89–6.84 (m, 2 H, 2 × H-d), 6.53 (dt, *J* = 3.8, 1.2 Hz, 1 H, H-5), 6.22 (s, 1 H, H-12′), 5.71 (t, *J* = 1.1 Hz, 1 H, H-12′), 5.56 (ddt, *J* = 8.8, 3.6, 1.7 Hz, 1 H, H-6), 5.46–5.39 (m, 2 H, H-7 and H-13), 4.83–4.70 (m, 4 H, 2 × H-16 and 2 × H-18), 4.45 (s, 2 H, 2 × H-a), 3.79 (s, 3 H, 3 × H-f), 3.75 (s, 3 H, $COOCH_3$), 3.57 (t, *J* = 6.9 Hz, 2 H, 2 × H-10), 2.86 (dtd, *J* = 11.0, 7.0, 4.0 Hz, 1 H, H-1), 2.74 (dd, *J* = 15.8, 6.8 Hz, 1 H, H-2), 2.56 (dd, *J* = 15.8, 7.2 Hz, 1 H, H-2), 2.42–2.31 (m, 2 H, 2 × H-9), 2.08 (s, 3 H, 3 × H-22), 1.81 (ddd, *J* = 13.9, 11.0, 2.6 Hz, 1 H, H-14), 1.74 (d, *J* = 1.3 Hz, 3 H, 3 × H-19), 1.69 (dd, *J* = 1.4, 0.7 Hz, 3 H, 3 × H-17), 1.67–1.62 (m, 1 H, H-14) and 1.08–1.01 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 199.6 (C-3), 169.9 (C-21), 165.7 (C-20), 159.3 (C-e), 145.0 (C-15), 144.6 (C-5), 141.7 (C-4), 140.6 (C-12), 135.9 (C-8), 130.6 (C-b), 129.3 (2 C, 2 × C-c), 127.1 (C-7), 124.6 (C-12′), 113.9 (2 C, 2 × C-d), 113.6 (C-16), 72.7 (C-a), 70.1 (C-13), 68.4 (C-10), 68.2 (C-6), 60.4 (C-18), 55.4 (C-f), 52.1 ($COO\underline{C}H_3$), 42.1 (C-2), 40.1 (C-1), 39.6 (C-9), 37.8 (C-14), 21.1 (C-22), 18.5 (C-17), 17.6 ($SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 17.1 (C-19), 12.5 ($Si\underline{C}HCH_3$) and 12.4 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2947, 2867, 1718, 1720, 1669, 1513, 1274, 1248, 1231, 1173, 1146, 1122, 1098, 1066, 1038 and 1012 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{37}H_{54}O_9NaSi+$ $[M+Na]^+$ 693.3429; found 693.3425 (Δ 0.58 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +17.1° (c = 1.00, CH_2Cl_2).

Methyl (3S,5S)-3-acetoxy-5-(2-((S)-7-((E)-4-hydroxy-2-methylbut-1-en-1-yl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-2-oxoethyl)-6-methyl-2-methylenehept-6-enoate (**443**)

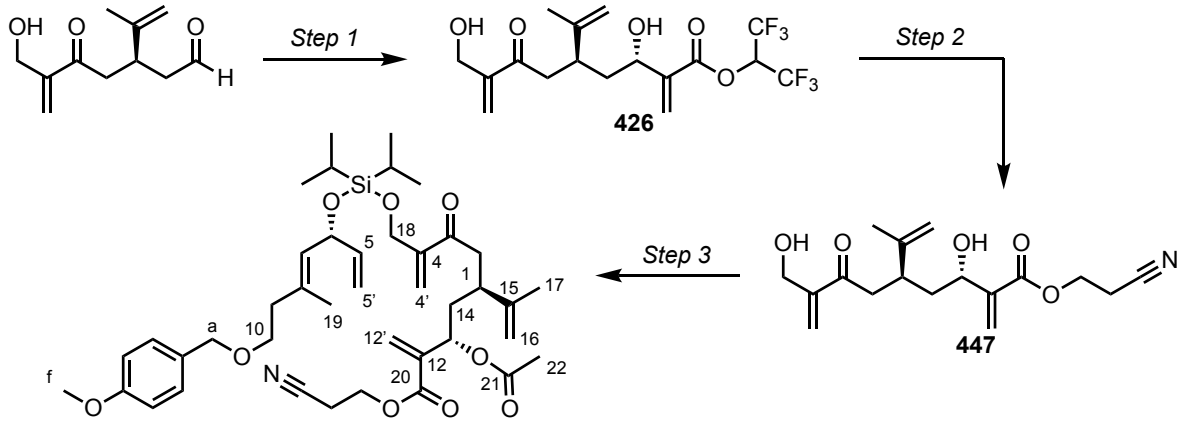


2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (164 mg, 0.724 mmol) was added in one portion to a solution of ether **440** (48.6 mg, 72.4 μmol) in CH_2Cl_2:pH 7 buffer (6:1, 7 mL, 0.01 M) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 50 min. The reaction was quenched at 0 °C by dropwise addition of $Na_2S_2O_3$ (sat., aq., 3 mL), diluted with H_2O (3 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (7:3 pentane:EtOAc) to afford alcohol **443** as a yellow oil (23.3 mg, 58%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.53 (d, *J* = 3.6 Hz, 1 H, H-5), 6.23 (s, 1 H, H-12′), 5.72 (d, *J* = 1.1 Hz, 1 H, H-12′), 5.60–5.55 (m, 1 H, H-6), 5.48 (dq, *J* = 8.4, 1.4 Hz, 1 H, H-7), 5.45–5.40 (m, 1 H, H-13), 4.84–4.70 (m, 4 H, 2 × H-16 and 2 × H-18), 3.75 (app. s, 5 H, 2 × H-10 and $COOCH_3$), 2.85 (dtd, *J* = 11.0, 7.0, 4.1 Hz, 1 H, H-1), 2.73 (dd, *J* = 15.8, 6.9 Hz, 1 H, H-2), 2.61 (dd, *J* = 15.8, 7.3 Hz, 1 H, H-2), 2.33 (t, *J* = 6.4 Hz, 2 H, 2 × H-9), 2.08 (s, 3 H, 3 × H-22), 1.82 (ddd, *J* = 13.7, 10.7, 2.7 Hz, 1 H, H-14), 1.77 (d, *J* = 1.4 Hz, 3 H, 3 × H-19), 1.70 (dd, *J* = 1.3, 0.7 Hz, 3 H, 2 × H-17), 1.69–1.63 (m, 1 H, H-14) and 1.08–1.03 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 199.6 (C-3), 169.9 (C-21), 165.8 (C-20),

145.1 (C-15), 144.3 (C-5), 141.9 (C-4), 140.5 (C-12), 135.3 (C-8), 128.3 (C-7), 124.8 (C-12′), 113.5 (C-16), 70.1 (C-13), 68.2 (C-6), 60.44 (C-10 or C-18), 60.41 (C-10 or C-18), 52.1 ($COO\underline{C}H_3$), 42.6 (C-9), 42.1 (C-2), 40.2 (C-1), 37.8 (C-14), 21.1 (C-22), 18.6 (C-17), 17.6 ($SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 16.8 (C-19), 12.42 ($Si\underline{C}HCH_3$) and 12.41 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 3486, 2946, 2868, 1747, 1721, 1668, 1233, 1147, 1119, 1041, 994 and 886 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{29}H_{46}O_8NaSi^+$ $[M+Na]^+$ 573.2854; found 573.2854 (Δ 0.00 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +26.5° (c = 1.00, CH_2Cl_2).

2-Cyanoethyl (7R,15S,17S,E)-17-acetoxy-9,9-diisopropyl-1-(4-methoxyphenyl)-5-methyl-12,18-dimethylene-13-oxo-15-(prop-1-en-2-yl)-7-vinyl-2,8,10-trioxa-9-silanonadec-5-en-19-oate (**448**)



Step 1: A solution of aldehyde **421** (2.98 g, 15.2 mmol) in DMF (25 mL + 5 mL rinse) was added to a solution of α-isocupreine (1.18 g, 3.90 mmol) in DMF (122 mL, 0.1 M final concentration) at rt and the mixture then cooled to –55 °C (cryostat-cooled acetone bath). 1,1,1,3,3,3-hexafluoroisopropyl acrylate (12.7 mL, 76.0 mmol) was added dropwise *via* syringe pump over 1 h and the reaction then stirred at –55 °C for 2 days. The reaction was quenched at –55 °C by addition of HCl (1 M, aq., 38 mL), diluted with EtOAc (150 mL) and

brine (150 mL), removed from the cold bath and warmed slowly to rt. The layers were separated and the aqueous phase extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (2 × 150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before partial purification by flash column chromatography (4:1:0–40:10:1 pentane:EtOAc:MeOH). Fractions containing product were collected and concentrated *in vacuo* to afford crude ester **426** (3.31 g, contains *ca.* 23 mol% aldehyde **421** ie. *ca.* 2.90 g **426**).

Step 2: Crude ester **426** was redissolved 2-cyanoethanol (17.3 mL, 0.4 M) at rt. Et_3N (4.83 mL, 34.7 mmol) was added and the reaction then stirred at rt for 18 h. The reaction was diluted with EtOAc (500 ml) and H_2O (500 mL). The layers were separated and the organic phase washed sequentially with H_2O (3 × 250 mL) and brine (250 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before partial purification by flash column chromatography (40:10:1–20:5:1 pentane:EtOAc:MeOH) to afford crude 2-cyanoethyl ester **447** as a pale yellow oil (171.5 mg, *ca.* 75 mol% by ^{1}H NMR).

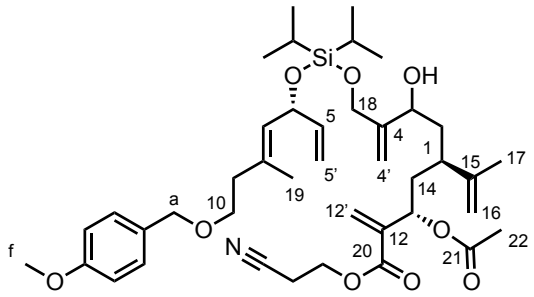
Step 3: *i*-Pr_2SiCl_2 (66 μL, 0.37 mmol) was added dropwise to a solution of imidazole (60 mg, 0.88 mmol) in CH_2Cl_2 (3.7 mL, 0.1 M wrt. silane) at 0 °C (ice/H_2O bath) and the reaction then stirred for 5 min. A solution of (*R*)-alcohol **413** (92 mg, 0.35 mmol) in CH_2Cl_2 (1 mL + 0.5 mL rinse) was added dropwise at 0 °C over 1 h *via* syringe pump and the reaction then stirred at 0 °C for 30 min. A solution of crude 2-cyanoethyl ester **447** (75 mol% by ^{1}H NMR, 165 mg, 0.386 mmol) in CH_2Cl_2 (1 mL + 0.5 mL rinse) was added dropwise at 0 °C over 1 min and the reaction then stirred at 0 °C for 40 min. The reaction mixture was filtered through a short plug of silica, eluting with EtOAc, concentrated *in vacuo* and dried under high vacuum for 15 min. The residue was redissolved in CH_2Cl_2 (3.5 mL, 0.1 M) and pyridine (0.568 mL, 7.02 mmol) and DMAP (4.3 mg, 35 μmol) were then sequentially added at rt. The

reaction was cooled to 0 °C (ice/H_2O bath) and acetic anhydride (K_2CO_3 filtered, 0.166 mL, 1.76 mmol) added dropwise. The reaction was removed from the cold bath and stirred for 2 h, warming slowly to rt. The reaction was quenched at rt by dropwise addition of $NaHCO_3$ (sat., aq., 5 mL), the layers separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (3:1 pentane:EtOAc) to afford TST **448** as a colourless oil (135 mg, 1.2% over 3 steps from aldehyde **421**).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24 (d, *J* = 8.3 Hz, 2 H, 2 × H-c), 6.86 (d, *J* = 8.3 Hz, 2 H, 2 × H-d), 6.32 (s, 1 H, H-12'), 6.12 (s, 1 H, H-4'), 6.09 (s, 1 H, H-4'), 5.83–5.73 (m, 2 H, H-5 and H-12'), 5.41 (dd, *J* = 10.5, 2.6 Hz, 1 H, H-13), 5.21–5.19 (m, 1 H, H-7), 5.17 (d, *J* = 11.3 Hz, H-5'$_{cis}$), 5.03–4.95 (m, 2 H, H-5'$_{trans}$ and H-6), 4.81 (s, 1 H, H-16), 4.73 (s, 1 H, H-16), 4.45 (t, *J* = 2.1 Hz, 2 H, 2 × H-18), 4.41 (s, 2 H, 2 × H-a), 4.40–4.30 (m, 2 H, OCH_2CH_2CN), 3.79 (s, 3 H, 3 × H-f), 3.51 (t, *J* = 7.1 Hz, 2 H, 2 × H-10), 2.90 (dtd, *J* = 10.9, 7.0, 4.1 Hz, 1 H, H-1), 2.85–2.64 (m, 4 H, 2 × H-2 and OCH_2CH_2CN), 2.29 (oct., *J* = 7.0 Hz, 2 H, 2 × H-9), 2.08 (s, 3 H, 3 × H-22), 1.84 (ddd, *J* = 13.8, 10.8, 2.9 Hz, 1 H, H-14), 1.75–1.66 (m, 4 H, H-14 and 3 × H-17), 1.62 (s, 3 H, 3 × H-19), 1.03 (app. s, 7 H, $SiCH(CH_3)_2$) and 1.02 ppm (app. s, 7 H, $SiCH(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.8 (C-3), 169.9 (C-21), 164.6 (C-20), 159.2 (C-e), 147.6 (C-4), 145.0 (C-15), 139.9 (C-5), 139.8 (C-12), 133.1 (C-8), 130.7 (C-b), 129.3 (2 C, 2 × C-c), 128.6 (C-7), 126.2 (C-12'), 123.2 (C-4'), 116.8 (OCH_2CH_2CN), 113.8 (2 C, 2 × C-d), 113.6 (C-16), 113.0 (C-5'), 72.6 (C-a), 70.4 (C-6), 69.8 (C-13), 68.8 (C-10), 61.0 (C-18), 59.3 (OCH_2CH_2CN), 55.4 (C-f), 42.3 (C-2), 39.7 (C-1), 39.5 (C-9), 37.7 (C-14), 21.0 (C-22), 18.6 (C-17), 18.1 (OCH_2CH_2CN), 17.51 ($SiCHCH_3$), 17.47 (2 C, 2 × $SiCHCH_3$), 17.4 ($SiCHCH_3$), 17.1 (C-19), 12.41 ($SiCHCH_3$) and

12.38 ppm (Si<u>C</u>HCH$_3$); **FTIR** ν_{max} (thin film): 2944, 2866, 1744, 1673, 1514, 1245, 1142, 1097, 1034, 886 and 819 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{41}H_{59}O_9NNaSi^+$ $[M+Na]^+$ 760.3851; found 760.3845 (Δ 0.79 ppm).

2-cyanoethyl (7R,15R,17S,E)-17-acetoxy-13-hydroxy-9,9-diisopropyl-1-(4-methoxyphenyl)-5-methyl-12,18-dimethylene-15-(prop-1-en-2-yl)-7-vinyl-2,8,10-trioxa-9-silanonadec-5-en-19-oate (**449**)



$CeCl_3 \cdot 7H_2O$ (72.7 mg, 0.195 mmol) was added to a solution of TST **448** (131 mg, 0.177 mmol) in MeOH (1.8 mL, 0.1 M) at rt and the suspension then cooled to 0 °C (ice/H_2O bath). $NaBH_4$ (8.1 mg, 0.21 mmol) was added in one portion (CAUTION: effervescence of H_2) and the reaction then stirred at 0 °C for 2 h. The reaction was quenched at 0 °C by drop-wise addition until the cloudy precipitate persisted and then faster addition of NH_4Cl (sat., aq., 2 mL total). The reaction was removed from the cold bath, warmed slowly to rt and diluted with H_2O (2 mL). The mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (7:3 pentane:Et_2O) to afford alcohol **449** as a colourless oil and an inseparable 2:1 ratio of diastereomers (107 mg, 82%). The diastereomeric ratio was calculated on the basis of the integrals of the two H-16 peaks in the ^{1}H NMR spectrum (4.89 and 4.86–4.61 ppm).

^{1}H NMR (Major Diastereomer, $CDCl_3$, 400 MHz): δ = 7.25–7.20 (m, 2 H, 2 × H-c), 6.89–6.83 (m, 2 H, 2 × H-d), 6.31 (s, 1 H, H-12'), 5.88–5.75 (m, 2 H, H-5 and H-12'), 5.38 (dd, *J* = 10.2, 2.3 Hz, 1 H, H-13), 5.25–5.18 (m, 2 H, H-5' and H-7), 5.12 (q, *J* = 1.6 Hz, 1 H, H-4'), 5.06–4.99 (m, 3 H, H-4', H-5' and H-6), 4.86–4.81 (m, 1 H, H-16), 4.69 (d, *J* = 2.2 Hz, 1 H, H-16), 4.42 (s, 2 H, 2 × H-a), 4.39–4.33 (m, 3 H, $OC\underline{H}_2CH_2CN$ and C-18), 4.32–4.25 (m, 1 H, H-18), 4.17–4.07 (m, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.52 (td, *J* = 6.9, 1.0 Hz, 2 H, 2 × H-10), 2.74 (t, *J* = 6.3 Hz, 2 H, $OCH_2C\underline{H}_2CN$), 2.58 (d, *J* = 5.1 Hz, 1 H, OH), 2.47–2.40 (m, 1 H, H-1), 2.29 (t, *J* = 6.8 Hz, 2 H, 2 × H-9), 2.06 (s, 3 H, 3 × H-22), 1.87–1.74 (m, 2 H, H-2 and H-14), 1.72 (s, 3 H, 3 × H-17), 1.66–1.63 (m, 3 H, 3 × H-19), 1.63–1.53 (m, 2 H, H-2 and H-14) and 1.06–1.01 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Major Diastereomer, $CDCl_3$, 101 MHz): δ = 169.85 (C-21), 164.6 (C-20), 159.3 (C-e), 149.0 (C-4), 146.0 (C-15), 140.17 (C-12), 140.02 (C-5), 133.23 (C-8), 130.6 (C-b), 129.4 (2 C, 2 × C-c), 128.6 (C-7), 126.0 (C-12'), 116.7 ($OCH_2CH_2\underline{C}N$), 113.9 (2 C, 2 × C-d), 113.8 (C-4'), 113.01 (C-5'), 111.6 (C-4'), 72.59 (C-a), 72.4 (C-3), 70.50 (C-6), 69.9 (C-13), 68.7 (C-10), 64.1 (C-18), 59.2 ($O\underline{C}H_2CH_2CN$), 55.4 (C-f), 41.1 (C-1), 38.54 (C-2), 39.47 (C-9), 37.9 (C-14), 21.0 (C-22), 18.1 ($OCH_2\underline{C}H_2CN$), 17.6 (C-17), 17.515 (2 C, 2 × $SiCH\underline{C}H_3$), 17.509 ($SiCH\underline{C}H_3$), 17.39 ($SiCH\underline{C}H_3$), 17.2 (C-19), 12.42 ($Si\underline{C}HCH_3$) and 12.40 ppm ($Si\underline{C}HCH_3$).

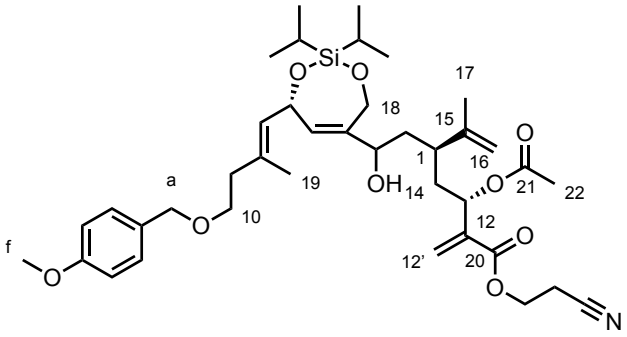
^{1}H NMR (Minor Diastereomer, $CDCl_3$, 400 MHz): δ = 7.25–7.20 (m, 2 H, 2 × H-c), 6.89–6.83 (m, 2 H, 2 × H-d), 6.31 (s, 1 H, H-12'), 5.88–5.75 (m, 2 H, H-5 and H-12'), 5.42–5.37 (m, 1 H, H-13), 5.25–5.18 (m, 2 H, H-5' and H-7), 5.08 (q, *J* = 1.8 Hz, 1 H, H-4'), 5.06–4.99 (m, 3 H, H-4', H-5' and H-6), 4.89 (t, *J* = 1.8 Hz, 1 H, H-16), 4.78 (d, *J* = 2.3 Hz, 1 H, H-16), 4.42 (s, 2 H, 2 × H-a), 4.39–4.33 (m, 3 H, $OC\underline{H}_2CH_2CN$ and C-18), 4.32–4.25 (m, 1 H, H-18), 4.17–4.07 (m, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.52 (td, *J* = 7.0, 0.8 Hz, 2 H, 2 × H-10), 2.74

(t, *J* = 6.3 Hz, 2 H, $OCH_2C\underline{H}_2CN$), 2.70–2.62 (m, 1 H, H-1), 2.39 (d, *J* = 5.2 Hz, 1 H, OH), 2.32–2.29 (m, 2 H, 2 × H-9), 2.07 (s, 3 H, 3 × H-22), 1.87–1.74 (m, 2 H, H-2 and H-14), 1.68 (s, 3 H, 3 × H-17), 1.66–1.63 (m, 3 H, 3 × H-19), 1.63–1.53 (m, 2 H, H-2 and H-14) and 1.06–1.01 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Minor Diastereomer, $CDCl_3$, 101 MHz): δ = 169.94 (C-21), 164.7 (C-20), 159.3 (C-e), 150.5 (C-4), 144.9 (C-15), 140.21 (C-12), 139.99 (C-5), 133.16 (C-8), 130.6 (C-b), 129.4 (2 C, 2 × C-c), 128.7 (C-7), 126.1 (C-12'), 116.7 ($OCH_2CH_2\underline{C}N$), 114.6 (C-4'), 113.9 (2 C, 2 × C-d), 113.00 (C-5'), 110.2 (C-4'), 72.57 (C-a), 71.0 (C-3), 70.48 (C-6), 70.1 (C-13), 68.6 (C-10), 64.1 (C-18), 59.2 ($O\underline{C}H_2CH_2CN$), 55.4 (C-f), 40.7 (C-1), 39.54 (C-2), 39.47 (C-9), 38.6 (C-14), 21.1 (C-22), 18.1 (OCH_2CH_2CN), 17.53 (C-17), 17.509 ($SiCH\underline{C}H_3$), 17.49 ($SiCH\underline{C}H_3$), 17.38 ($SiCH\underline{C}H_3$), 17.3 ($SiCH\underline{C}H_3$), 17.1 (C-19), 12.44 ($Si\underline{C}HCH_3$) and 12.41 ppm ($Si\underline{C}HCH_3$).

FTIR ν_{max} (thin film): 3514, 2942, 2866, 1724, 1513, 1245, 1142, 1088, 1035, 886 and 819 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{41}H_{61}O_9NNaSi^+$ $[M+Na]^+$ 762.4008; found 762.3997 (Δ 1.44 ppm).

2-Cyanoethyl (3S,5R)-3-acetoxy-5-(2-((S)-2,2-diisopropyl-7-((E)-4-((4-methoxybenzyl)oxy)-2-methylbut-1-en-1-yl)-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-2-hydroxyethyl)-6-methyl-2-methyl-enehept-6-enoate (**450**)



Notes: Experimental setup B (Section 5.3) was used for this reaction. Glassware was flame dried under vacuum, charged with Ar and kept under a positive Ar pressure *via* a manifold line prior to use. Dry PhMe was sparged with N_2 for *ca.* 10 min prior to use.

Hoveyda–Grubbs second generation catalyst (5.3 mg, 8.4 μmol) was added to the reaction flask under a positive Ar pressure and dissolved in PhMe (15 mL). A solution of alcohol **449** (62 mg, 84.3 μmol) in PhMe (1 mL + 0.9 mL rinse, 5 mM final concentration) was added at rt and the reaction then stirred at 60 °C for 24 h under a gentle flow of Ar. The reaction was cooled to rt and concentrated *in vacuo* before being purified by flash column chromatography (7:3–3:2 pentane:EtOAc) to afford silaketal **450** as a yellow oil and an inseparable 3:2 ratio of diastereomers (28.9 mg, 48%). The diastereomeric ratio was measured from the integrals of H-16 in the ^{1}H NMR spectrum (4.90 and 4.85 ppm).

^{1}H NMR (Major Diastereomer, $CDCl_3$, 400 MHz): δ = 7.26 (d, *J* = 8.1 Hz, 2 H, 2 × H-c), 6.87 (d, *J* = 8.1 Hz, 2 H, 2 × H-d), 6.32 (s, 1 H, H-12'), 5.81 (s, 1 H, H-12'), 5.48 (s, 1 H, H-5), 5.45–5.34 (m, 3 H, H-6, H-7 and H-13), 4.85 (s, 1 H, H-16), 4.70 (s, 1 H, H-16), 4.65–4.56 (m, 1 H, H-18), 4.44 (s, 2 H, 2 × H-a), 4.42–4.33 (m, H-18 and OC$\underline{H_2}CH_2CN$), 4.02 (t, *J* = 6.6 Hz, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.56 (t, *J* = 7.0 Hz, 2 H, 2 × H-10), 2.76 (t,

J = 6.3 Hz, 2 H, $OCH_2C\underline{H}_2CN$), 2.48–2.38 (m, 1 H, H-1), 2.34 (oct., *J* = 7.2 Hz, 2 H, $OCH_2C\underline{H}_2CN$), 2.07 (s, 3 H, 3 × H-22), 1.88–1.39 (m, 10 H, 2 × H-2, 2 × H-14, 3 × H-17 and 3 × H-19) and 1.11–1.02 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

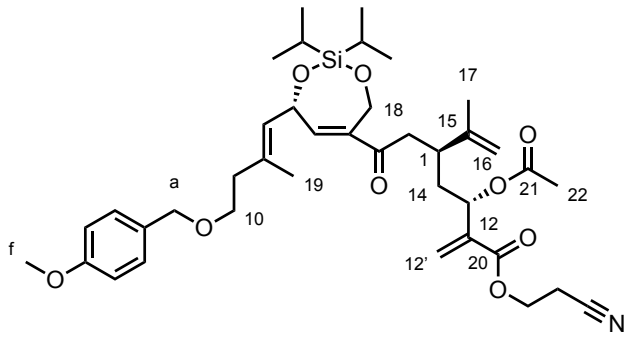
^{13}C NMR (Major Diastereomer, $CDCl_3$, 101 MHz): δ = 169.8 (C-21), 164.6 (C-20), 159.2 (C-e), 146.0 (C-15), 142.6 (C-4), 140.05 (C-12), 134.0 (C-8), 131.4 (C-5), 130.6 (C-e), 129.37 (2 C, 2 × C-c), 128.7 (C-7), 126.1 (C-12'), 116.8 ($OCH_2CH_2\underline{C}N$), 114.0 (C-16), 113.9 (2 C, 2 × C-d), 75.2 (C-3), 72.6 (C-a), 69.9 (C-13), 68.55 (C-10), 68.5 (C-6), 60.9 C-18), 59.2 (C-a), 55.4 (C-f), 41.5 (C-1), 39.5 (C-9), 38.9 (C-2), 38.0 (C-14), 21.0 (C-22), 18.1 ($OCH_2\underline{C}H_2CN$), 17.72–17.70 (5 C, C-17 and 4 × $SiCH\underline{C}H_3$), 17.0 (C-19), 12.64 ($Si\underline{C}HCH_3$) and 12.63 ppm ($Si\underline{C}HCH_3$).

^{1}H NMR (Minor Diastereomer, $CDCl_3$, 400 MHz): δ = 7.26 (d, *J* = 8.1 Hz, 2 H, 2 × H-c), 6.87 (d, *J* = 8.1 Hz, 2 H, 2 × H-d), 6.32 (s, 1 H, H-12'), 5.81 (s, 1 H, H-12'), 5.55 (d, *J* = 3.5 Hz, 1 H, H-5), 5.45–5.34 (m, 3 H, H-6, H-7 and H-13), 4.90 (s, 1 H, H-16), 4.77 (s, 1 H, H-16), 4.65–4.56 (m, 1 H, H-18), 4.44 (s, 2 H, 2 × H-a), 4.42–4.33 (m, H-18 and $OC\underline{H}_2CH_2CN$), 3.89 (d, *J* = 10.0 Hz, 1 H, H-3), 3.80 (s, 3 H, 3 × H-f), 3.56 (t, *J* = 7.0 Hz, 2 H, 2 × H-10), 2.76 (t, *J* = 6.3 Hz, 2 H, $OCH_2C\underline{H}_2CN$), 2.63 (ddd, *J* = 14.5, 10.3, 3.7 Hz, 1 H, H-1), 2.34 (oct., *J* = 7.2 Hz, 2 H, $OCH_2C\underline{H}_2CN$), 2.08 (s, 3 H, 3 × H-22), 1.88–1.39 (m, 10 H, 2 × H-2, 2 × H-14, 3 × H-17 and 3 × H-19) and 1.11–1.02 ppm (m, 14 H, 2 × $SiCH(CH_3)_2$).

^{13}C NMR (Minor Diastereomer, $CDCl_3$, 101 MHz): δ = 169.9 (C-21), 164.7 (C-20), 159.2 (C-e), 144.8 (C-15), 144.4 (C-4), 140.10 (C-12), 134.1 (C-8), 130.6 (C-e), 129.8 (C-5), 129.35 (2 C, 2 × C-c), 128.9 (C-7), 126.1 (C-12'), 116.8 ($OCH_2CH_2\underline{C}N$), 114.7 (C-16), 113.9 (2 C, 2 × C-d), 72.9 (C-3), 72.6 (C-a), 70.0 (C-13), 68.59 (C-10, 68.1 (C-6), 61.7 (C-18), 59.2 (C-a), 55.4 (C-f), 40.8 (C-1), 39.6 (C-9), 39.1 (C-2), 38.5 (C-14), 21.1 (C-22), 18.1 ($OCH_2\underline{C}H_2CN$), 17.72–17.70 (6 C, C-17, C-19 and 4 × $SiCH\underline{C}H_3$), 12.58 ($Si\underline{C}HCH_3$) and 12.5 ($Si\underline{C}HCH_3$).

FTIR ν_{max} (thin film): 3467, 2942, 2866, 1724, 1245, 1144, 1090, 1036 and 886 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{39}H_{57}O_9NNaSi^+$ $[M+Na]^+$ 734.3695; found 734.3690 (Δ 0.68 ppm).

2-Cyanoethyl (3S,5S)-3-acetoxy-5-(2-((S)-2,2-diisopropyl-7-((E)-4-((4-methoxybenzyl)oxy)-2-methylbut-1-en-1-yl)-4,7-dihydro-1,3,2-dioxasilepin-5-yl)-2-oxoethyl)-6-methyl-2-methylene-hept-6-enoate (**451**)

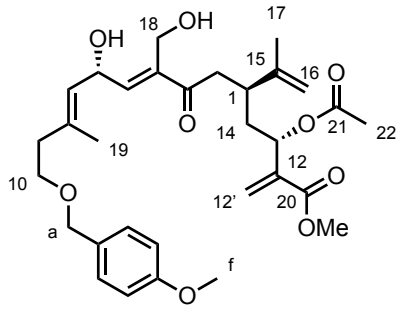


Dess–Martin Periodinane (34.5 mg, 81.3 μmol) was added to a solution of silaketal **450** (28.9 mg, 40.6 μmol) in CH_2Cl_2 (0.81 mL, 50 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 2 h, warming slowly to rt. The reaction was quenched at rt by addition of a 1:1:1 solution of $Na_2S_2O_3$ (sat., aq.), $NaHCO_3$ (sat., aq.) and H_2O (1.2 mL total), and the biphasic mixture then stirred vigorously at rt until clear on standing. The mixture was diluted with EtOAc (5 mL) and H_2O (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (3:1 pentane:EtOAc) to afford ketone **451** as a colourless oil (9.6 mg, 33%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.21 (m, 2 H, 2 × H-c), 6.89–6.84 (m, 2 H, 2 × H-d), 6.53 (d, *J* = 3.9 Hz, H-5), 6.32 (s, 1 H, H-12'), 5.82 (s, 1 H, H-12'), 5.55 (ddd, *J* = 7.4, 3.7, 1.7 Hz, 1 H, H-6), 5.45–5.38 (m, 2 H, H-7 and H-13), 4.84–4.70 (m, 4 H, 2 × H-16 and 2 × H-18), 4.45 (s, 2 H, 2 × H-a), 4.36 (td, *J* = 6.4, 3.1 Hz, 2 H, $OC\underline{H}_2CH_2CN$), 3.80 (s, 3 H, 3 × H-

f), 3.57 (t, *J* = 6.9 Hz, 2 H, 2 × H-10), 2.92–2.86 (m, 1 H, H-1), 2.80–2.68 (m, 3 H, H-2 and $OCH_2C\underline{H}_2CN$), 2.57 (dd, *J* = 15.9, 7.3 Hz, 1 H, H-2), 2.36 (t, *J* = 6.9 Hz, 2 H, 2 × H-9), 2.09 (s, 3 H, 3 × H-22), 1.81 (ddd, *J* = 13.8, 10.8, 2.8 Hz, 1 H, H-14), 1.74 (d, *J* = 1.4 Hz, 3 H, 3 × H-19), 1.71–1.64 (m, 4 H, H-14 and 3 × H-17), 1.06 (s, 7 H, $SiCHCH_3$) and 1.07 ppm (s, 7 H, $SiCHCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 199.6 (C-3), 169.9 (C-21), 164.6 (C-20), 159.3 (C-e), 145.1 (C-15), 144.7 (C-5), 141.7 (C-4), 139.9 (C-12), 136.0 (C-8), 130.6 (C-b), 129.4 (2 C, 2 × C-c), 127.0 (C-7), 126.3 (C-12'), 116.8 ($OCH_2CH_2\underline{C}N$), 113.9 (2 C, 2 × C-d), 113.6 (C-16), 72.7 (C-a), 69.9 (C-13), 68.4 (C-10), 68.3 (C-6), 60.4 (C-18), 59.3 ($O\underline{C}H_2CH_2CN$), 55.4 (C-f), 42.1 (C-2), 39.9 (C-1), 39.6 (C-9), 37.7 (C-14), 21.0 (C-22), 18.8 (C-17), 17.9 ($OCH_2\underline{C}H_2CN$), 17.6 ($SiCH\underline{C}H_3$), 17.5 ($SiCH\underline{C}H_3$), 17.4 ($SiCH\underline{C}H_3$), 17.2 ($SiCH\underline{C}H_3$), 17.1 (C-19), 12.5 ($Si\underline{C}HCH_3$) and 12.4 ppm ($Si\underline{C}HCH_3$); **FTIR** ν_{max} (thin film): 2944, 2866, 1744, 1724, 1514, 1246, 1144, 1098 and 1036 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{39}H_{55}O_9NNaSi^+$ $[M+Na]^+$ 732.3538; found 732.3535 (Δ 0.41 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +15.9° (c = 0.50, CH_2Cl_2).

Methyl (3S,5S,8E,10S,11E)-3-acetoxy-10-hydroxy-8-(hydroxymethyl)-14-((4-methoxybenzyl)oxy)-12-methyl-2-methylene-7-oxo-5-(prop-1-en-2-yl)tetradeca-8,11-dienoate (**453**)

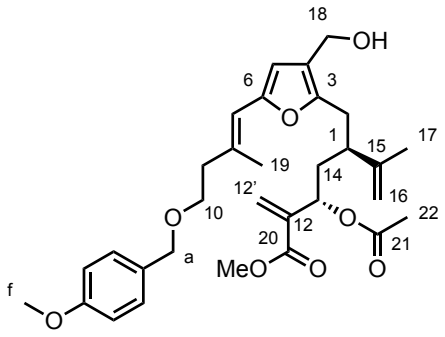


Tetrabutylammonium fluoride (1 M in THF, 10 µL, 10 µmol) was added to a solution of silaketal **440** (63.6 mg, 94.5 µmol) in THF:pH 7 buffer (10:1, *ca.* 0.1 M, 1.1 mL) (ice/H_2O bath).

The reaction was stirred at 0 °C for 1 h and then removed from the cold bath. Additional tetrabutylammonium fluoride (1 M in THF, 0.280 mL, 0.280 mmol) was added and the reaction then stirred for 1 h, warming slowly to rt. The reaction mixture was dry loaded directly onto SiO_2 before being purified by flash column chromatography (1:1 pentane:EtOAc) to afford diol **453** as a colourless oil (33.6 mg, 63%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.20 (m, 2 H, 2 × H-c), 6.90–6.83 (m, 2 H, 2 × H-d), 6.62 (d, *J* = 6.9 Hz, 1 H, H-5), 6.24 (t, *J* = 0.7 Hz, 1 H, H-12′), 5.73 (t, *J* = 1.1 Hz, 1 H, H-12′), 5.46–5.40 (m, 1 H, H-13), 5.40–5.30 (m, 2 H, H-6 and H-7), 4.81 (t, *J* = 1.7 Hz, 1 H, H-16), 4.73 (dd, *J* = 1.9, 1.0 Hz, 1 H, H-16), 4.42 (s, 2 H, 2 × H-a), 4.32 (app. qd, *J* = 12.5, 6.4 Hz, 2 H, 2 × H-18), 3.80 (s, 3 H, 3 × H-f), 3.76 (s, 3 H, $COOCH_3$), 3.53 (t, *J* = 6.7 Hz, 2 H, 2 × H-10), 2.88 (ddd, *J* = 10.7, 8.9, 5.7 Hz, 1 H, H-1), 2.81–2.72 (m, 3 H, 2 × H-2 and C-18 OH), 2.36–2.30 (m, 3 H, 2 × H-9 and C-6 OH), 2.09 (s, 3 H, 3 × H-22), 1.83 (ddd, *J* = 14.3, 10.5, 2.8 Hz, 1 H, H-14), 1.76 (d, *J* = 1.3 Hz, 3 H, 3 × H-19) and 1.73–1.64 ppm (m, 4 H, H-14 and 3 × H-17); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 201.8 (C-3), 170.0 (C-21), 165.8 (C-20), 159.4 (C-e), 145.1 (C-5 or C-15), 145.0 (C-5 or C-15), 140.4 (C-12), 139.4 (C-4 or C-8), 138.4 (C-4 or C-8), 130.3 (C-b), 129.5 (2 C, 2 × C-c), 125.9 (C-7), 124.9 (C-12′), 113.9 (2 C, 2 × C-d), 113.6 (C-16), 72.7 (C-a), 70.0 (C-13), 67.9 (C-10), 65.5 (C-6), 57.3 (C-18), 55.4 (C-f), 52.1 ($COO\underline{C}H_3$), 41.7 (C-2), 40.0 (C-1), 39.7 (C-9), 37.7 (C-14), 21.1 (C-22), 18.5 (C-17) and 17.1 ppm (C-19); **FTIR** ν_{max} (thin film): 3420, 2951, 1744, 1719, 1514, 1246 and 1035 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{31}H_{42}O_9Na^+$ $[M+Na]^+$ 581.2721; found 581.2718 (Δ 0.52 ppm); **Specific Rotation:** $[\alpha]_D^{25}$ +33.1° (c = 1.00, CH_2Cl_2).

Methyl (3S,5S)-3-acetoxy-5-((3-(hydroxymethyl)-5-((E)-4-((4-methoxybenzyl)oxy)-2-methyl-but-1-en-1-yl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoate (**454**)



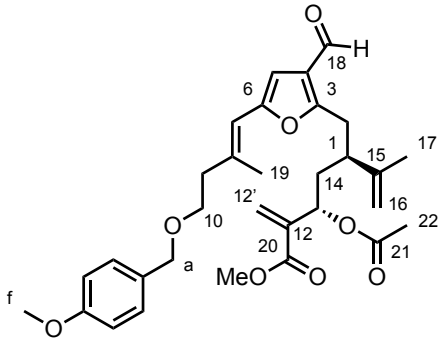
Note: EtOAc was sparged with Ar for *ca.* 10 min prior to use.

A solution of diol **453** (12.1 mg, 22.5 μmol) in EtOAc (7 mL) was added to the irradiation vessel. The insert was added, screw cap fitted and the vessel flushed with Ar for 10 min. The vessel was placed under a gentle flow of Ar *via* a manifold for the remainder of the reaction. The reaction was cooled to 0 °C (cryostat-cooled acetone bath), a 365 nm UVP Pen-Ray placed in the insert and switched on, and the reaction then stirred at 0 °C for 21 h. The Pen-Ray was switched off and the reaction then allowed to warm to rt. The reaction was directly concentrated *in vacuo* before being purified by flash column chromatography (3:2 pentane:EtOAc) to afford furan **454** as a colourless oil (6.5 mg, 55%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.22 (m, 2 H, 2 × H-c), 6.91–6.84 (m, 2 H, 2 × H-d), 6.24 (s, 1 H, H-12′), 6.17 (s, 1 H, H-5), 6.04 (s, 1 H, H-7), 5.70 (s, 1 H, H-12′), 5.46–5.40 (m, 1 H, H-13), 4.81 (t, *J* = 1.8 Hz, 1 H, H-16), 4.66 (d, *J* = 2.0 Hz, 1 H, H-16), 4.46 (s, 2 H, 2 × H-a), 4.41 (d, *J* = 5.5 Hz, 2 H, 2 × H-18), 3.80 (s, 3 H, 3 × H-f), 3.75 (s, 3 H, $COOCH_3$), 3.58 (t, *J* = 6.9 Hz, 2 H, 2 × H-10), 2.73–2.62 (m, 3 H, H-1 and 2 × H-2), 2.45 (t, *J* = 6.8 Hz, 2 H, 2 × H-9), 2.05 (s, 3 H, 3 × H-22), 1.97 (d, *J* = 1.2 Hz, 3 H, 3 × H-19), 1.95–1.85 (m, 1 H, H-14), 1.71 (d, *J* = 4.1 Hz, 4 H, H-14 and 3 × H-17) and 1.43 ppm (t, *J* = 5.7 Hz, 1 H, OH); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 169.9 (C-21), 165.8 (C-20), 159.3 (C-e), 152.0 (C-6),

149.4 (C-3), 145.7 (C-15), 140.5 (C-12), 134.9 (C-8), 130.6 (C-b), 129.4 (2 C, 2 × C-c), 125.0 (C-12′), 121.8 (C-4), 115.5 (C-7), 113.9 (2 C, 2 × C-d), 113.4 (C-16), 109.1 (C-5), 72.8 (C-a), 70.4 (C-13), 68.6 (C-10), 56.7 (C-18), 55.4 (C-f), 52.1 (COO$\underline{C}$H$_3$), 43.5 (C-1), 41.0 (C-9), 37.6 (C-14), 31.2 (C-2), 21.1 (C-22), 18.9 (C-19) and 18.4 ppm (C-17); **FTIR** ν_{max} (thin film): 3466, 2951, 1743, 1721, 1514, 1245, 1095 and 1036 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{31}H_{40}O_8Na^+$ $[M+Na]^+$ 563.2615; found 563.2612 (Δ 0.53 ppm).

Methyl (3S,5S)-3-acetoxy-5-((3-formyl-5-((E)-4-((4-methoxybenzyl)oxy)-2-methylbut-1-en-1-yl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoate (**455**)

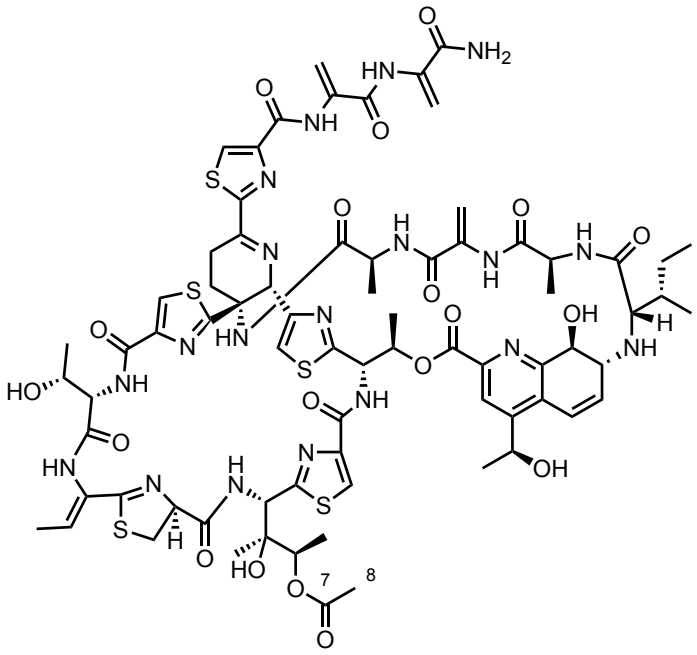


Note: Furan **454** was azeotroped with PhMe (× 3) and dried under high vacuum prior to use. MnO_2 (10.9 mg, 0.126 mmol) was added to a solution of furan **454** (3.4 mg, 6.4 μmol) in CH_2Cl_2 (1.3 mL, 5 mM) at 0 °C. The reaction was removed from the cold bath and stirred, warming slowly to rt. Additional batches of MnO_2 (10.9 mg, 0.126 mmol) were added after 24, 36 and 48 h. The reaction was stirred for 60 h in total. The reaction mixture was filtered through a plug of silica, eluting with EtOAc, and concentrated *in vacuo* before being purified by flash column chromatography (7:3 pentane:EtOAc) to afford aldehyde **455** as a yellow oil (2.1 mg, 61%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.86 (s, 1 H, H-18), 7.27–7.24 (m, 2 H, 2 × H-c), 6.90–6.84 (m, 2 H, 2 × H-d), 6.44 (s, 1 H, H-5), 6.25 (s, 1 H, H-12′), 6.07 (d, *J* = 1.4 Hz, 1 H, H-7), 5.71 (t, *J* = 1.0 Hz, 1 H, H-12′), 5.47–5.42 (m, 1 H, H-13), 4.81 (t, *J* = 1.6 Hz, 1 H, H-16), 4.68–

4.65 (m, 1 H, H-16), 4.47 (s, 2 H, 2 × H-a), 3.80 (s, 3 H, 3 × H-f), 3.77 (s, 3 H, $COOCH_3$), 3.59 (t, J = 6.7 Hz, 2 H, 2 × H-10), 3.02 (dd, J = 14.6, 8.5 Hz, 1 H, H-2), 2.94 (dd, J = 14.6, 6.6 Hz, 1 H, H-2), 2.82–2.74 (m, 1 H, H-1), 2.47 (t, J = 6.6 Hz, 2 H, 2 × H-9), 2.06 (s, 3 H, 3 × H-22), 2.00–1.92 (m, 4 H, H-14 and 3 × H-19) and 1.74–1.65 ppm (m, 4 H, H-14 and 3 × H-17); **^{13}C NMR** ($CDCl_3$, 126 MHz): δ = 184.9 (C-18), 169.8 (C-21), 165.7 (C-20), 162.0 (C-3), 159.4 (C-e), 153.3 (C-6), 144.1 (C-15), 140.5 (C-12), 138.3 (C-8), 130.5 (C-b), 129.4 (2 C, 2 × C-c), 124.8 (C-12′), 124.7 (C-4), 114.6 (C-7), 114.5 (C-16), 113.9 (2 C, 2 × C-d), 105.1 (C-5), 72.8 (C-a), 70.1 (C-13), 68.2 (C-10), 55.4 (C-f), 52.2 ($COO\underline{C}H_3$), 43.8 (C-1), 40.9 (C-9), 37.7 (C-14), 31.8 (C-2), 21.0 (C-22), 19.0 (C-19) and 18.0 ppm (C-17); **FTIR** ν_{max} (thin film): 1746, 1719, 1677, 1514, 1246, 1233 and 1094 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{31}H_{38}O_8Na^+$ $[M+Na]^+$ 561.2459; found 561.2455 (Δ 0.71 ppm).

Thiostrepton-O-acetate (**479**)



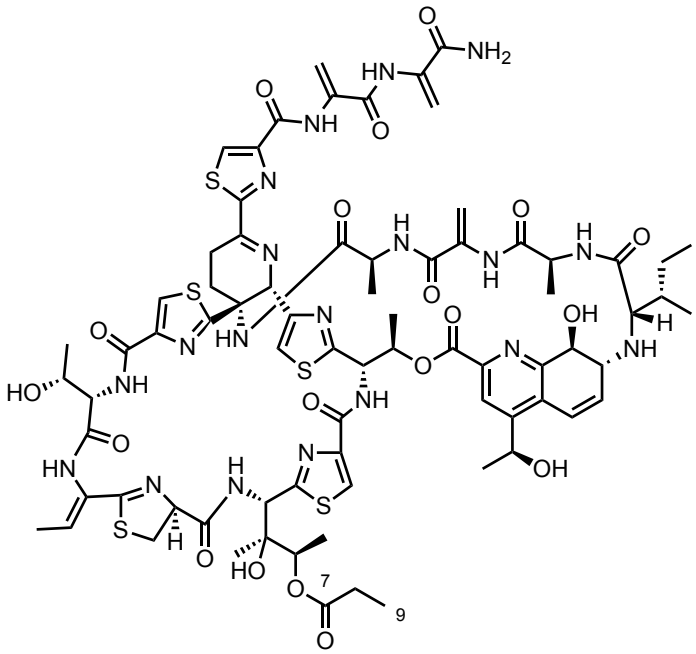
Pyridine (30.0 µL, 0.371 mmol) was added to a solution of thiostrepton (**460**) (31.0 mg, 18.6 µmol) in $CHCl_3$ (3.0 mL, 6.2 mM) at rt and the mixture then cooled to 0 °C (ice/H_2O bath). Acetic anhydride (18.0 µL, 0.190 mmol) was added dropwise at 0 °C and the reaction

then removed from the cold bath and stirred for 4 h, warming slowly to rt. DMAP (2.0 mg, 18 μmol) was added at rt and the reaction then stirred at rt for a further 20 h. The reaction was quenched at rt by addition of H_2O (1 mL), diluted with HCl (1 M, aq., 5 mL) and the mixture extracted with $CHCl_3$ (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1 $CHCl_3$:MeOH) to afford ester **479** as an off-white solid (26.0 mg, 82%). Data is consistent with that reported in the literature.[199]

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.97 (s, 1 H, Deala(2) NH), 9.88 (s, 1 H, Pip NH), 9.09 (s, 1 H, Deala(3) NH), 8.78 (d, *J* = 8.8 Hz, 1 H, Thr(2) NH), 8.62 (s, 1 H, But NH), 8.27 (s, 1 H, Thz(4) H-5), 8.26 (s, 1 H, Thz(2) H-5), 8.14 (s, 1 H, Thz(1) H-5), 7.78 (d, *J* = 5.5 Hz, 1 H, Ala(1) NH), 7.57 (d, *J* = 10.4 Hz, 1 H, Deala(3) NH_2), 7.52 (s, 1 H, Thz(3) H-5), 7.28 (s, 1 H, Q H-3), 7.10 (d, *J* = 7.8 Hz, 1 H, Ala(2) NH), 7.02 (d, *J* = 7.7 Hz, 1 H, Thr(1) NH), 6.87 (d, *J* = 9.9 Hz, 1 H, Q H-5), 6.68 (d, *J* = 2.4 Hz, 1 H, Deala(2) H-3), 6.51 (d, *J* = 1.9 Hz, 1 H, Deala(3) H-3), 6.40–6.31 (m, 2 H, Q H-6 and Thr(2) H-3), 6.19 (q, *J* = 7.0 Hz, 1 H, But H-3), 5.81 (d, *J* = 2.2 Hz, 1 H, Deala(1) H-3), 5.76 (s, 1 H, Thr(2) H-2), 5.68–5.64 (m, 2 H, Thstn H-2 and Deala(3) H-3), 5.58 (d, *J* = 2.4 Hz, 1 H, Deala(2) H-3), 5.34–5.25 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.02 (q, *J* = 6.3 Hz, 1 H, Thstn H-4), 4.89 (dd, *J* = 12.4, 9.2 Hz, 1 H, Cys H-4), 4.71 (q, *J* = 6.5 Hz, 1 H, Ala(2) H-2), 4.43–4.37 (m, 2 H, Q H-8 and Thr(1) H-2), 3.78 (q, *J* = 6.8 Hz, 1 H, Ala(1) H-2), 3.62–3.52 (m, 2 H, Cys H-5 and Q H-7), 3.46 (dd, *J* = 19.4, 5.3 Hz, 1 H, Pip H-3), 3.19 (t, *J* = 12.0 Hz, 1 H, Cys H-5), 2.94 (d, *J* = 4.4 Hz, 1 H, Ile H-2), 2.93–2.87 (m, 1 H, Pip H-3), 2.34–2.22 (m, 1 H, Pip H-4), 2.09 (s, 3 H, 3 × Thstn H-8), 1.92–1.83 (m, 1 H, Ile H-3), 1.70 (d, *J* = 6.5 Hz, 3 H, 3 × Thr(2) H-4), 1.56 (d, *J* = 7.1 Hz, 3 H, 3 × But H-4), 1.54–1.48 (m, 1 H, Thr(1) H-3), 1.41 (d, *J* = 6.5 Hz, 3 H, 3 × Ala(2) H-3), 1.35 (d, *J* = 6.6 Hz, 3 H, 3 × Q H-12), 1.32 (d, *J* = 6.3 Hz,

3 H, 3 × Thstn H-5), 1.26 (s, 3 H, 3 × Thstn H-6), 1.23–1.20 (m, 1 H, Ile H-4), 1.16 (d, J = 6.7 Hz, 3 H, 3 × Ala(1) H-3), 1.11–1.03 (m, 1 H, Ile H-4), 0.97 (d, J = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, J = 7.3 Hz, 3 H, 3 × Ile H-5) and 0.80 ppm (d, J = 6.3 Hz, 3 H, 3 × Thr(1) H-4). A signal at *ca.* 4.10 ppm (1 H, Pip H-4) is obscured by a solvent peak; **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 174.1, 174.0, 171.4, 171.3, 170.8, 170.4, 169.6, 169.6, 169.0, 167.2, 166.8, 166.2, 163.4, 162.8, 162.7, 162.5, 162.4, 161.4, 160.3, 157.8, 155.2, 154.4, 150.7, 150.5, 147.0, 144.2, 134.8, 133.6, 133.5, 132.7, 130.7, 129.1, 128.4, 127.9, 126.4, 125.7, 123.9, 123.1, 118.9, 105.4, 104.0, 100.5, 79.7, 76.6, 72.6, 70.4, 68.2, 66.9, 66.1, 65.1, 64.8, 59.5, 58.2, 56.4, 56.2, 52.6, 52.5, 50.2, 39.0, 34.7, 30.1, 30.0, 25.5, 24.8, 23.3, 21.7, 20.2, 19.7, 19.7, 19.6, 16.4, 16.0, 14.4 and 12.2 ppm.

Thiostrepton-O-propanoate (**513**)



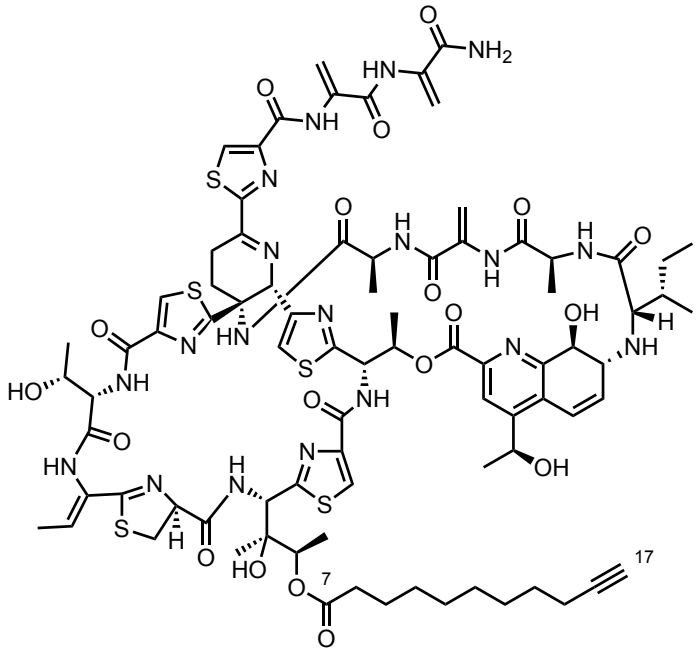
Propionyl chloride (25.0 µL, 0.288 mmol) was added to a solution of Et_3N (70.0 µL, 0.502 mmol) and thiostrepton (**460**) (42.0 mg, 25.2 µmol) in $CHCl_3$ (2.0 mL, 13 mM) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 1 h, warming slowly to rt. DMAP (4.2 mg, 37 µmol) was added at rt and the reaction then stirred at rt for a

further 23 h. The reaction was quenched at rt by addition of H_2O (1 mL) and the mixture extracted with $CHCl_3$ (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1 $CHCl_3$:MeOH) to afford ester **513** as an off-white solid (22.0 mg, 51%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.98 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.12 (s, 1 H, Deala(3) NH), 8.79 (d, *J* = 8.8 Hz, 1 H, Thr(2) NH), 8.65 (s, 1 H, But NH), 8.27 (s, 1 H, Thz(4) H-5), 8.25 (s, 1 H, Thz(2) H-5) 8.15 (s, 1 H, Thz(1) H-5), 8.00 (s, 1 H, Deala(1) NH), 7.80 (d, *J* = 5.5 Hz, 1 H, Ala(1) NH), 7.71 (br. s, 1 H, Thstn NH), 7.56 (d, *J* = 10.6 Hz, 1 H, Deala(3) NH_2), 7.53 (s, 1 H, Thz(3) H-5), 7.28 (s, 1 H, Q H-3), 7.15 (d, *J* = 8.2 Hz, 1 H, Ala(2) NH), 7.04 (d, *J* = 6.9 Hz, 1 H, Thr(1) NH), 6.87 (d, *J* = 10.0 Hz, 1 H, Q H-5), 6.67 (d, *J* = 2.3 Hz, 1 H, Deala(2) H-3), 6.50 (d, *J* = 1.9 Hz, 1 H, Deala(3) H-3), 6.41–6.31 (m, 2 H, Q H-6 and Thr(2) H-3), 6.19 (q, *J* = 7.1 Hz, 1 H, But H-3), 5.81 (d, *J* = 2.2 Hz, 1 H, Deala(1) H-3), 5.76 (s, 1 H, Thr(2) H-2), 5.70–5.57 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.36–5.26 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.04 (q, *J* = 6.3 Hz, 1 H, Thstn H-4), 4.89 (dd, *J* = 12.4, 9.2 Hz, 1 H, Cys H-4), 4.71 (q, *J* = 6.6 Hz, 1 H, Ala(2) H-2), 4.44–4.37 (m, 2 H, Q H-8 and Thr(1) H-2), 4.10–4.02 (m, 1 H, Pip H-4), 3.78 (q, *J* = 6.7 Hz, 1 H, Ala(1) H-2), 3.63–3.58 (m, 1 H, Cys H-5), 3.52 (dd, *J* = 11.5, 9.1 Hz, 1 H, Q H-7), 3.19 (t, *J* = 11.9 Hz, 1 H, Cys H-5), 2.95 (d, *J* = 4.4 Hz, 1 H, Ile H-2), 2.92–2.88 (m, 1 H, Pip H-3), 2.65 (app. t, *J* = 7.6 Hz, 2 H, 2 × Thstn H-8), 2.39–2.25 (m, 1 H, Pip H-4), 1.92–1.84 (m, 1 H, Ile H-3), 1.70 (d, *J* = 6.6 Hz, 3 H, 3 × Thr(2) H-4), 1.57 (d, *J* = 7.0 Hz, 3 H, 3 × But H-4), 1.41 (d, *J* = 6.5 Hz, 3 H, 3 × Ala(2) H-3), 1.36 (d, *J* = 6.6 Hz, 3 H, 3 × Q H-12), 1.33–1.19 (m, 11 H, Ile H-4, Thr(1) H-3, 3 × Thstn H-5, 3 × Thstn H-6 and 3 × Thstn H-9), 1.16 (d, *J* = 6.8 Hz, 3 H, 3 × Ala(1) H-3), 1.12–1.04 (m, 1 H, Ile H-4), 0.97 (d, *J* = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, *J* = 7.3 Hz, 3 H, 3 × Ile H-5) and 0.80 ppm (d,

J = 6.2 Hz, 3 H, 3 × Thr(1) H-4). A signal at *ca.* 3.30 ppm (1 H, Pip H-3) is obscured by a solvent peak; **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 173.6, 173.4, 173.3, 170.7, 170.2, 169.9, 169.0, 168.5, 166.8, 166.3, 165.7, 162.9, 162.3, 162.2, 162.1, 161.8, 160.9, 159.8, 157.3, 154.6, 153.7, 150.1, 150.0, 148.6, 146.4, 134.6, 134.3, 133.0, 132.2, 130.2, 129.0, 128.7, 127.9, 127.4, 125.8, 125.1, 123.3, 122.5, 118.4, 104.6, 103.5, 79.2, 76.1, 72.1, 69.5, 68.1, 67.7, 66.4, 65.6, 64.6, 59.0, 57.6, 55.9, 55.7, 54.1, 52.1, 51.9, 49.6, 38.5, 34.4, 34.1, 31.8, 25.3, 24.6, 24.3, 22.8, 22.6, 19.7, 19.1, 19.0, 18.2, 15.8, 15.4, 13.9 and 11.6 ppm; **FTIR** ν_{max} (thin film): 3353, 2364, 1731, 1650, 1487, 1420, 1206, 895, 752 and 666 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{75}H_{89}N_{19}NaO_{19}S_5^+$ $[M+Na]^+$ 1742.5078; found 1742.5094 (Δ 0.92 ppm); **M.P.** 210−230 °C (decomposition).

Thiostrepton-O-10-undecynoate (**516**)

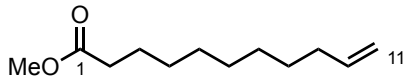


Benzoyl chloride (0.170 mL, 1.50 mmol) was added to a solution of Et_3N (0.410 mL, 2.94 mmol), 10-undecynoic acid (274 mg, 1.50 mmol) and thiostrepton (**460**) (491 mg, 0.295 mmol) in $CHCl_3$ (25 mL, 12 mM) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 2 min. DMAP (41.0 mg, 0.366 mmol) was added at 0 °C and the reaction then stirred

at 0 °C for a further 2.5 h. The reaction was quenched at 0 °C by addition of EtOH (20 mL), removed from the cold bath and allowed to warm to rt. The mixture was diluted with H_2O (20 mL) and extracted with $CHCl_3$ (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1 $CHCl_3$:MeOH) to afford ester **516** as an off-white solid (245 mg, 45%). **^{1}H NMR** (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.96 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.09 (s, 1 H, Deala(3) NH), 8.78 (d, *J* = 8.9 Hz, 1 H, Thr(2) NH), 8.62 (s, 1 H, But NH), 8.26 (s, 1 H, Thz(4) H-5), 8.25 (s, 1 H, Thz(2) H-5) 8.13 (s, 1 H, Thz(1) H-5), 7.97 (s, 1 H, Deala(1) NH), 7.78 (d, *J* = 5.4 Hz, 1 H, Ala(1) NH), 7.60 (br. s, 1 H, Thstn NH), 7.54 (d, *J* = 10.3 Hz, 1 H, Deala(3) NH_2), 7.51 (s, 1 H, Thz(3) H-5), 7.27 (s, 1 H, Q H-3), 7.11 (d, *J* = 7.8 Hz, 1 H, Ala(2) NH), 7.01 (d, *J* = 7.7 Hz, 1 H, Thr(1) NH), 6.87 (d, *J* = 10.0 Hz, 1 H, Q H-5), 6.68 (d, *J* = 2.4 Hz, 1 H, Deala(2) H-3), 6.51 (d, *J* = 1.9 Hz, 1 H, Deala(3) H-3), 6.43 (d, *J* = 2.0 Hz, 1 H, Deala(3) NH_2), 6.40–6.28 (m, 2 H, Q H-6 and Thr(2) H-3), 6.18 (q, *J* = 7.0 Hz, 1 H, But H-3), 5.80 (d, *J* = 2.1 Hz, 1 H, Deala(1) H-3), 5.76 (d, *J* = 8.9 Hz, 1 H, Thr(2) H-2), 5.67–5.55 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.36–5.24 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.03 (q, *J* = 6.3 Hz, 1 H, Thstn H-4), 4.89 (dd, *J* = 12.4, 9.3 Hz, 1 H, Cys H-4), 4.71 (quint., *J* = 6.7 Hz, 1 H, Ala(2) H-2), 4.44–4.37 (m, 2 H, Q H-8 and Thr(1) H-2), 3.84–3.74 (m, 1 H, Ala(1) H-2), 3.58 (dd, *J* = 5.8, 2.0 Hz, 1 H, Cys H-5), 3.56–3.49 (m, 1 H, Q H-7), 3.45 (dd, *J* = 19.2, 4.8 Hz, 1 H, Pip H-3), 3.20 (t, *J* = 12.0 Hz, 1 H, Cys H-5), 2.94 (d, *J* = 4.5 Hz, 1 H, Ile H-2), 2.92–2.85 (m, 1 H, Pip H-3), 2.39–2.23 (m, 3 H, Pip H-4 and 2 × Thstn H-8), 2.14 (td, *J* = 7.1, 2.7 Hz, 2 H, 2 × Thstn H-15), 1.95 (t, *J* = 2.6 Hz, 1 H, Thstn H-17), 1.92–1.82 (m, 1 H, Ile H-3), 1.69 (d, *J* = 6.5 Hz, 3 H, 3 × Thr(2) H-4), 1.56 (d, *J* = 7.0 Hz, 3 H, 3 × But H-4), 1.64–1.53 (m, 2 H, 2 × Thstn H-9), 1.52–1.19 (m, 24 H, 3 × Ala(2) H-3, Ile H-4, 3 × Q H-12, Thr(1) H-3, 3 ×

Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12, 2 × Thstn H-13 and 2 × Thstn H-14), 1.15 (d, J = 6.6 Hz, 3 H, 3 × Ala(1) H-3), 1.12–1.01 (m, 1 H, Ile H-4), 0.97 (d, J = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, J = 7.3 Hz, 3 H, 3 × Ile H-5) and 0.80 ppm (d, J = 6.2 Hz, 3 H, 3 × Thr(1) H-4). A signal at *ca.* 4.10 ppm (1 H, Pip H-4) is obscured by a solvent peak; **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 207.0, 206.4, 176.6, 173.6, 173.4, 170.6, 170.3, 169.9, 169.4, 169.1, 168.8, 168.5, 166.6, 166.2, 165.7, 162.8, 162.2, 162.1, 161.8, 160.8, 159.8, 157.3, 154.6, 153.8, 150.2, 150.0, 146.4, 143.7, 134.3, 133.1, 133.0, 132.2, 130.1, 128.5, 127.8, 127.4, 125.8, 125.2, 123.4, 122.5, 118.4, 104.5, 103.4, 100.0, 84.6, 79.2, 75.9, 72.1, 68.2, 67.7, 66.4, 65.6, 64.6, 64.2, 59.0, 58.4, 58.1, 57.6, 55.9, 55.7, 52.1, 51.9, 38.5, 34.4, 34.2, 29.6, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5, 28.4, 28.3, 27.5, 27.3, 24.8, 24.6, 24.3, 23.4, 23.3, 22.8, 19.6, 19.1, 19.0, 15.8, 15.4, 13.7, 13.5 and 11.6 ppm; **FTIR** ν_{max} (thin film): 3356, 2932, 2361, 1731, 1642, 1516, 1485, 1417, 1207, 1054, 926, 752 and 645 cm^{-1}; **HRMS** (ESI$^+$): Calculated for $C_{83}H_{101}N_{19}NaO_{19}S_5^+$ $[M+Na]^+$ 1851.6095; found 1851.6167 (Δ 3.89 ppm); **M.P.** 200−220 °C (decomposition). 94 ^{13}C carbon signals are observed when 83 are expected. The discrepancy is ascribed to the presence of conformational isomers of the appended alkyl chain.

Methyl undec-10-enoate (**518**)

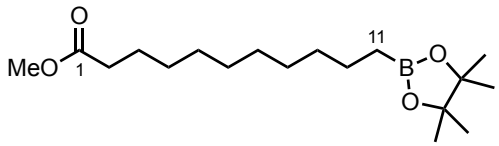


H_2SO_4 (0.5 mL) was added dropwise to a solution of 10-undecenoic acid (**517**, 2.05 g, 11.1 mmol) in MeOH (20 mL, 0.56 M) at rt and the reaction then stirred at reflux for 24 h. The reaction mixture was cooled to rt, diluted with pentane (50 mL) and washed with $NaHCO_3$ (sat., aq., 50 mL) and brine (50 mL). The organic phase was dried over anhydrous Mg-

SO_4, filtered and concentrated *in vacuo* to afford ester **518** as a colourless oil (2.08 g, 94%). Data is consistent with that reported in the literature.[225]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H, H-10), 4.99 (dq, *J* = 17.1, 1.7 Hz, 1 H, H-11$_{trans}$), 4.92 (ddt, *J* = 10.2, 2.4, 1.2 Hz, 1 H, H-11$_{cis}$), 3.66 (s, 3 H, OCH_3), 2.30 (t, *J* = 7.5 Hz, 2 H, 2 × H-2), 2.07–1.98 (m, 2 H, 2 × H-9), 1.66–1.56 (m, 2 H, 2 × H-3) and 1.41−1.24 ppm (m, 10 H, 2 × H-4, 2 × H-5, 2 × H-6, 2 × H-7 and 2 × H-8); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 174.3 (C-1), 139.2 (C-10), 114.1 (C-11), 51.5 (OCH_3), 34.1 (C-2), 33.8 (C-9), 29.3, 29.24, 29.18, 29.1, 28.9 (C-4, C-5, C-6, C-7 and C-8) and 25.0 ppm (C-3).

Methyl 11-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecanoate (**519**)

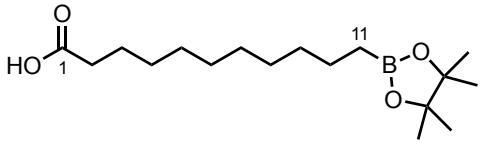


Pinacolborane (1.78 mL, 12.3 mmol) was added dropwise to a solution of ester **518** (2.02 g, 10.2 mmol) and tris(triphenylphosphine)rhodium (I) chloride (94.0 mg, 0.102 mmol) in THF (10 mL, 1.2 M) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 48 h, warming slowly to rt. The reaction was cooled to 0 °C and quenched by dropwise addition of MeOH and H_2O (1:1, 4 mL) (CAUTION: exotherm). The layers were separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford borane **519** as a colourless oil (1.69 g, 51 %). Data is consistent with that reported in the literature.[226]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.66 (s, 3 H, OCH_3), 2.30 (t, *J* = 7.6 Hz, 2 H, 2 × H-2), 1.61 (quint., *J* = 7.4 Hz, 2 H, 2 × H-3), 1.45–1.34 (m, 2 H, 2 × H-10), 1.33–1.21 (m, 24 H, 2 × H-4,

2 × H-5, 2 × H-6, 2 × H-7, 2 × H-8, 2 × H-9 and 2 × $C(CH_3)_2$) and 0.76 ppm (t, J = 7.8 Hz, 2 H, 2 × H11); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 169.0 (C-1), 83.0 (2 C, 2 × $\underline{C}(CH_3)_2$), 51.6 ($COO\underline{C}H_3$), 34.3 (C-2), 32.6, 29.64, 29.59, 29.5, 29.4, 29.3 (C-4, C-5, C-6, C-7, C-8 and C-9), 25.1 (C-3), 25.0 (4 C, 4 × CH_3) and 24.2 ppm (C-10). No ^{13}C signal for C-11 could be identified.

11-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)undecanoic acid (**520**)

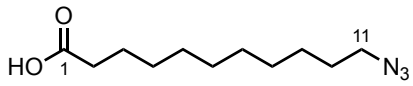


A solution of $LiOH{\cdot}H_2O$ (3.10 g, 73.9 mmol) in H_2O (50 mL) was cooled to 0 °C (ice/H_2O bath) and added dropwise to a solution of borane **519** (1.61 g, 4.93 mmol) in THF (50 mL, 0.1 M) at 0 °C (ice/H_2O bath). The reaction was removed from the cold bath and stirred for 16 h, warming slowly to rt. HCl (3 M, aq.) was added until the reaction was determined to be approximately pH 0 (monitoring with litmus paper) and the resulting mixture then diluted with brine (50 mL). The layers were separated and the aqueous phase extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford acid **520** as an orange oil (1.58 g, 4% THF by mass, 99%). A small quantity was purified by flash column chromatography to enable characterisation.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.30 (br. s, 1 H, COOH), 2.33 (t, J = 7.5 Hz, 2 H, 2 × H-2), 1.61 (quint., J = 7.5 Hz, 2 H, 2 × H-3), 1.43–1.33 (m, 2 H, 2 × H-10), 1.33–1.20 (m, 24 H, 2 × H-4, 2 × H-5, 2 × H-6, 2 × H-7, 2 × H-8, 2 × H-9 and 2 × $C(CH_3)_2$) and 0.75 ppm (t, J = 7.8 Hz, 2 H, 2 × H-11); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 180.1 (C-1), 83.0 (2 C, 2 × $\underline{C}(CH_3)_2$), 34.2 (C-2), 32.5, 29.6, 29.52, 29.47, 29.4, 29.2 (C-4, C-5, C-6, C-7, C-8 and C-9), 24.8 (4 C, 4 × CH_3), 24.7 (C-3), 24.0 (C-10) and 11.1 ppm (br., C-11); **FTIR** ν_{max} (thin film):

2927, 2855, 1710, 1378, 1319, 1146 and 625 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{17}H_{32}BO_4^-$ $[M-H]^-$ 310.2435; found 310.2437 (Δ 0.64 ppm).

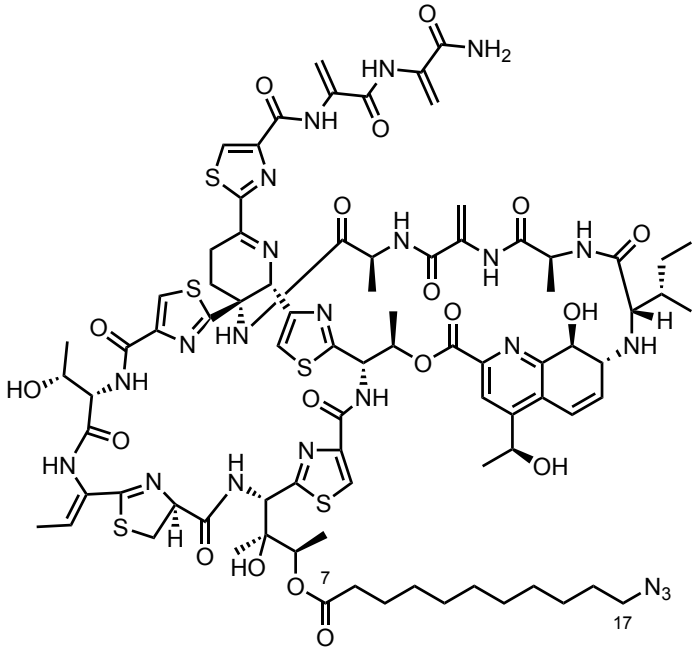
11-Azidoundecanoic acid (**522**)



Sodium azide (270 mg, 4.15 mmol) was added in one portion to a solution of 11-bromoundecanoic acid (**521**, 1.00 g, 3.77 mmol) in DMF (5.0 mL, 0.75 M) at rt and the reaction then stirred at 65 °C for 24 hr. The reaction was cooled to rt and diluted with HCl (3 M, aq.) until the reaction was determined to be approximately pH 0 (monitored by litmus paper) [CAUTION: Hydrozoic acid is toxic and explosive in concentrated solutions]. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford azide **522** as a yellow oil (825 mg, 96 %). Data is consistent with that reported in the literature.[227]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.66 (br. s, 1 H, COOH), 3.25 (t, *J* = 7.0 Hz, 2 H, 2 × H-11), 2.35 (t, *J* = 7.5 Hz, 2 H, 2 × H-2), 1.68–1.55 (m, 4 H, 2 × H-3 and 2 × H-10) and 1.42–1.23 ppm (m, 12 H, 2 × H-4, 2 × H-5, 2 × H-6, 2 × H-7, 2 × H-8 and 2 × H-9); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ = 179.7 (C-1), 51.5 (C-11), 34.0 (C-2), 29.4, 29.3, 29.2, 29.1, 29.0 (C-5, C-6, C-7, C-8 and C-9), 28.8 (C-10), 26.7 (C-4) and 24.7 ppm (C-3).

Thiostrepton-O-11-azidoundecanoate (**523**)



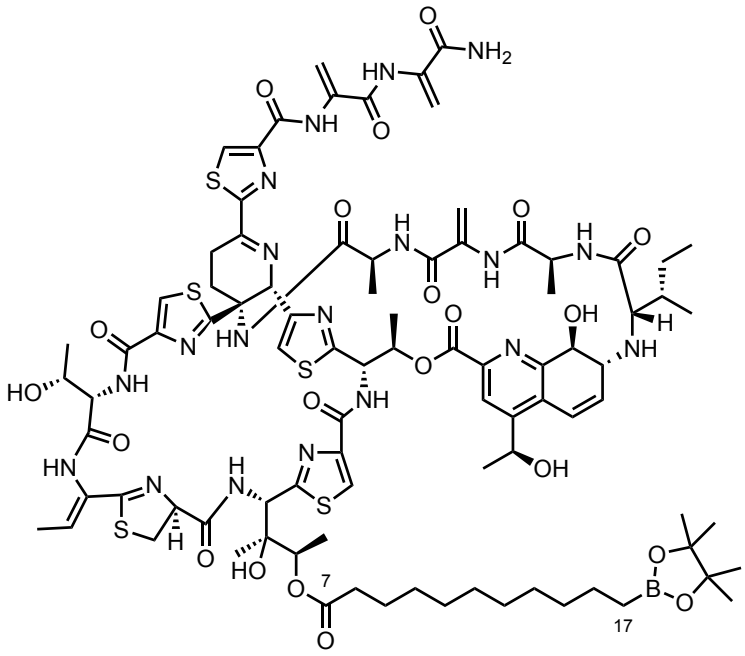
Benzoyl chloride (75.0 μL, 0.662 mmol) was added to a solution of Et_3N (0.184 mL, 1.32 mmol), azide **522** (153 mg, 0.673 mmol) and thiostrepton (**460**) (220 mg, 0.132 mol) in $CHCl_3$ (11 mL, 12 mM) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 2 min. DMAP (18.5 mg, 0.165 mmol) was added at 0 °C and the reaction then stirred at 0 °C for a further 2.5 h. The reaction was quenched at 0 °C by addition of EtOH (10 mL), removed from the cold bath and allowed to warm to rt. The mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1 $CHCl_3$:MeOH) to afford ester **523** as an off-white solid (96.0 mg, 39%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.97 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.11 (s, 1 H, Deala(3) NH), 8.79 (d, *J* = 8.8 Hz, 1 H, Thr(2) NH), 8.63 (s, 1 H, But NH), 8.27 (s, 1 H, Thz(4) H-5), 8.25 (s, 1 H, Thz(2) H-5) 8.14 (s, 1 H, Thz(1) H-5), 8.02–7.97 (m, 1 H, Deala(1) NH), 7.79 (d, *J* = 5.4 Hz, 1 H, Ala(1) NH), 7.66 (s, 1 H, Thstn NH), 7.56 (d, *J* = 10.4 Hz, 1 H, Deala(3) NH_2), 7.52 (s, 1 H, Thz(3) H-5), 7.27 (s, 1 H, Q H-3), 7.17–7.13

(m, 1 H, Ala(2) NH), 7.03 (d, *J* = 7.7 Hz, 1 H, Thr(1) NH), 6.87 (d, *J* = 10.0 Hz, 1 H, Q H-5), 6.68 (d, *J* = 2.3 Hz, 1 H, Deala(2) H-3), 6.50 (d, *J* = 1.9 Hz, 1 H, Deala(3) H-3), 6.41–6.30 (m, 2 H, Q H-6 and Thr(2) H-3), 6.19 (q, *J* = 7.0 Hz, 1 H, But H-3), 5.80 (d, *J* = 2.2 Hz, 1 H, Deala(1) H-3), 5.76 (s, 1 H, Thr(2) H-2), 5.70–5.57 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.36–5.25 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.04 (q, *J* = 6.4 Hz, 1 H, Thstn H-4), 4.90 (dd, *J* = 12.4, 9.3 Hz, 1 H, Cys H-4), 4.72 (q, *J* = 6.6 Hz, 1 H, Ala(2) H-2), 4.43–4.39 (m, 2 H, Q H-8 and Thr(1) H-2), 4.09–4.03 (m, 1 H, Pip H-4), 3.79 (q, *J* = 6.8 Hz, 1 H, Ala(1) H-2), 3.59 (dd, *J* = 5.7, 2.0 Hz, 1 H, Cys H-5), 3.53 (dd, *J* = 11.5, 9.1 Hz, 1 H, Q H-7), 3.46 (dd, *J* = 18.7, 4.4 Hz, 1 H, Pip H-3), 3.27–3.16 (m, 3 H, Cys H-5 and 2 × Thstn H-17), 2.94 (d, *J* = 4.6 Hz, 1 H, Ile H-2), 2.93–2.88 (m, 1 H, Pip H-3), 2.42–2.22 (m, 3 H, Pip H-4 and 2 × Thstn H-8), 1.91–1.81 (m, 1 H, Ile H-3), 1.70 (d, *J* = 6.5 Hz, 3 H, 3 × Thr(2) H-4), 1.64–1.48 (m, 5 H, 3 × But H-4 and 2 × Thstn H-9), 1.41 (d, *J* = 6.6 Hz, 3 H, 3 × Ala(2) H-3), 1.38–1.19 (m, 25 H, Ile H-4, 3 × Q H-12, Thr(1) H-3, 3 × Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12, 2 × Thstn H-13, 2 × Thstn H-14, 2 × Thstn H-15 and 2 × Thstn H-16), 1.16 (d, *J* = 6.8 Hz, 3 H, 3 × Ala(1) H-3), 1.13–1.04 (m, 1 H, Ile H-4), 0.97 (d, *J* = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, *J* = 7.4 Hz, 3 H, 3 × Ile H-5) and 0.81 ppm (d, *J* = 6.3 Hz, 3 H, 3 × Thr(1) H-4); **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 176.6, 173.8, 173.5, 173.4, 173.3, 170.7, 170.3, 169.8, 169.0, 168.5, 166.8, 166.2, 165.7, 162.9, 162.2, 162.2, 162.1, 161.9, 161.8, 160.9, 159.8, 157.3, 154.6, 153.7, 150.1, 150.0, 146.5, 143.6, 134.3, 134.2, 133.1, 132.9, 130.2, 129.7, 128.5, 128.2, 127.9, 127.3, 125.8, 125.1, 123.3, 122.5, 118.3, 104.6, 103.5, 103.4, 79.2, 76.1, 72.1, 69.6, 67.6, 66.4, 65.7, 64.6, 64.2, 59.1, 57.6, 55.9, 55.7, 52.1, 51.9, 51.4, 49.6, 38.5, 34.4, 29.6, 29.4, 29.3, 29.2, 29.1, 28.8, 26.6, 24.6, 24.4, 22.8, 19.7, 19.1, 19.0, 15.8, 15.4, 14.0, 13.9 and 11.6 ppm; **FTIR** ν_{max} (thin film): 3354, 2928, 2361, 2096, 1731, 1643, 1518, 1415, 1206, 1054, 898, 752 and

667 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{83}H_{105}N_{22}NaO_{19}S_5^+$ $[M+Na]^+$ 1896.6422; found 1896.6476 (Δ 2.85 ppm); **M.P.** 210−230 °C (decomposition).

Thiostrepton-O-11-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecanoate (**524**)



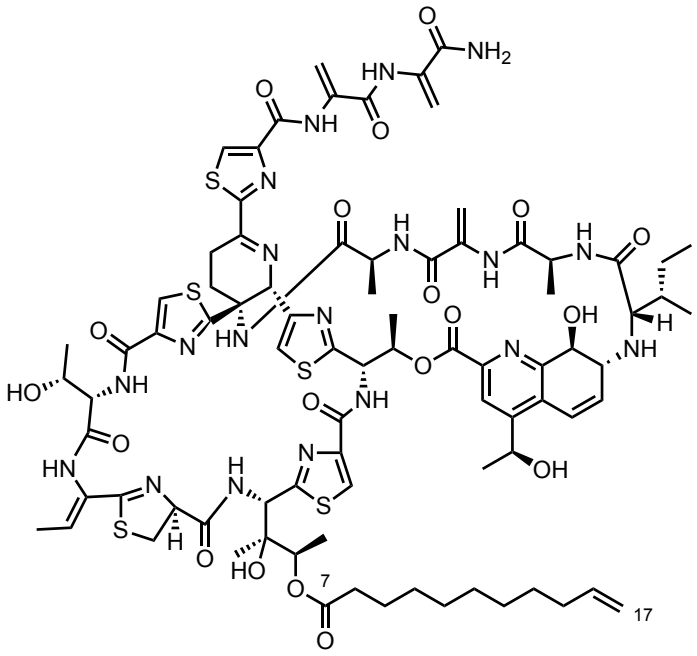
Benzoyl chloride (81.0 μL, 0.715 mmol) was added to a solution of Et_3N (0.198 mL, 1.42 mmol), acid **520** (223 mg, 0.714 mmol) and thiostrepton (**460**) (237 mg, 142 μmol) in $CHCl_3$ (12 mL, 12 mM) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 2 min. DMAP (20.0 mg, 0.178 mmol) was added at 0 °C and the reaction then stirred at 0 °C for a further 2.5 h. The reaction was quenched at 0 °C by addition of EtOH (10 mL), removed from the cold bath and allowed to warm to rt. The mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1 $CHCl_3$:MeOH) to afford ester **524** as an off-white solid (33.0 mg, 12%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.96 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.10 (s, 1 H, Deala(3) NH), 8.78 (d, *J* = 9.0 Hz, 1 H, Thr(2) NH), 8.63 (s, 1 H, But NH), 8.27 (s, 1 H, Thz(4) H-5), 8.25 (s, 1 H, Thz(2) H-5) 8.14 (s, 1 H, Thz(1) H-5), 7.98 (s, 1 H,

Deala(1) NH), 7.80–7.75 (m, 1 H, Ala(1) NH), 7.54 (d, J = 10.7 Hz, 1 H, Deala(3) NH_2), 7.52 (s, 1 H, Thz(3) H-5), 7.27 (s, 1 H, Q H-3), 7.15–7.08 (m, 1 H, Ala(2) NH), 7.02 (d, J = 7.7 Hz, 1 H, Thr(1) NH), 6.87 (d, J = 10.0 Hz, 1 H, Q H-5), 6.68 (d, J = 2.4 Hz, 1 H, Deala(2) H-3), 6.51 (d, J = 1.9 Hz, 1 H, Deala(3) H-3), 6.39–6.30 (m, 2 H, Q H-6 and Thr(2) H-3), 6.18 (q, J = 6.8 Hz, 1 H, But H-3), 5.80 (d, J = 2.2 Hz, 1 H, Deala(1) H-3), 5.76 (s, 1 H, Thr(2) H-2), 5.69–5.55 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.36–5.23 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.04 (q, J = 6.2 Hz, 1 H, Thstn H-4), 4.89 (dd, J = 12.3, 9.4 Hz, 1 H, Cys H-4), 4.74–4.68 (m, 1 H, Ala(2) H-2), 4.44–4.37 (m, 2 H, Q H-8 and Thr(1) H-2), 3.81–3.76 (m, 1 H, Ala(1) H-2), 3.61–3.57 (m, 1 H, Cys H-5), 3.53 (t, J = 10.3 Hz, 1 H, Q H-7), 3.45 (dd, J = 18.8, 4.6 Hz, 1 H, Pip H-3), 3.20 (t, J = 12.0 Hz, 1 H, Cys H-5), 2.94 (d, J = 4.5 Hz, 1 H, Ile H-2), 2.93–2.87 (m, 1 H, Pip H-3), 2.39–2.22 (m, 3 H, Pip H-4 and 2 × Thstn H-8), 1.93–1.82 (m, 1 H, Ile H-3), 1.69 (d, J = 6.5 Hz, 3 H, 3 × Thr(2) H-4), 1.56 (d, J = 7.1 Hz, 3 H, 3 × But H-4), 1.54–1.49 (m, 2 H, 2 × Thstn H-9), 1.41 (d, J = 6.6 Hz, 3 H, 3 × Ala(2) H-3), 1.35 (d, J = 6.6 Hz, 3 H, 3 × Q H-12), 1.33–1.19 (m, 34 H, Ile H-4, Thr(1) H-3, 3 × Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12, 2 × Thstn H-13, 2 × Thstn H-14, 2 × Thstn H-15, 2 × Thstn H-16 and 2 × BOC($C\underline{H}_3$)$_2$), 1.16 (d, J = 6.7 Hz, 3 H, 3 × Ala(1) H-3), 1.11–1.03 (m, 1 H, Ile H-4), 0.97 (d, J = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, J = 7.3 Hz, 3 H, 3 × Ile H-5), 0.80 (d, J = 6.0 Hz, 3 H, 3 × Thr(1) H-4) and 0.73 ppm (t, J = 7.7 Hz, 2 H, 2 × Thstn H-17). A signal at *ca.* 4.10 ppm (1 H, Pip H-4) is obscured by a solvent peak; **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 173.6, 173.5, 173.4, 173.3, 170.7, 170.3, 169.8, 169.0, 168.5, 166.8, 166.2, 165.7, 162.8, 162.2, 162.2, 162.1, 161.9, 161.8, 160.8, 159.8, 157.3, 154.6, 153.8, 150.1, 150.0, 146.5, 143.6, 134.2, 133.0, 132.9, 132.2, 130.2, 128.5, 127.9, 127.4, 125.8, 125.1, 123.3, 122.5, 118.3, 106.3, 106.1, 104.5, 103.5, 103.4, 83.1, 79.9, 79.8, 79.2, 76.1, 74.9, 72.1, 69.5, 68.0,

68.0, 67.9, 67.6, 66.9, 66.4, 65.6, 64.6, 64.6, 64.2, 59.0, 57.7, 57.6, 55.9, 55.7, 52.1, 52.0, 51.9, 49.6, 38.5, 34.4, 34.2, 34.1, 32.4, 29.6, 29.4, 29.3, 29.2, 29.1, 24.7, 24.6, 24.4, 24.3, 23.9, 22.9, 19.7, 19.1, 19.0, 15.8, 15.4, 13.9 and 11.6 ppm; **FTIR** ν_{max} (thin film): 3357, 2927, 2495, 1731, 1644, 1415, 1207, 1146, 1054, 926 and 754 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{89}H_{117}{}^{11}BN_{19}O_{21}S_5^+$ $[M+H]^+$ 1958.7477; found 1958.7460 (Δ 0.87 ppm); **M.P.** 210−220 °C (decomposition). 95 ^{13}C carbon signals are observed when 89 are expected. The discrepancy is ascribed to the presence of conformational isomers of the appended alkyl chain.

Thiostrepton-O-undecenoate (**525**)



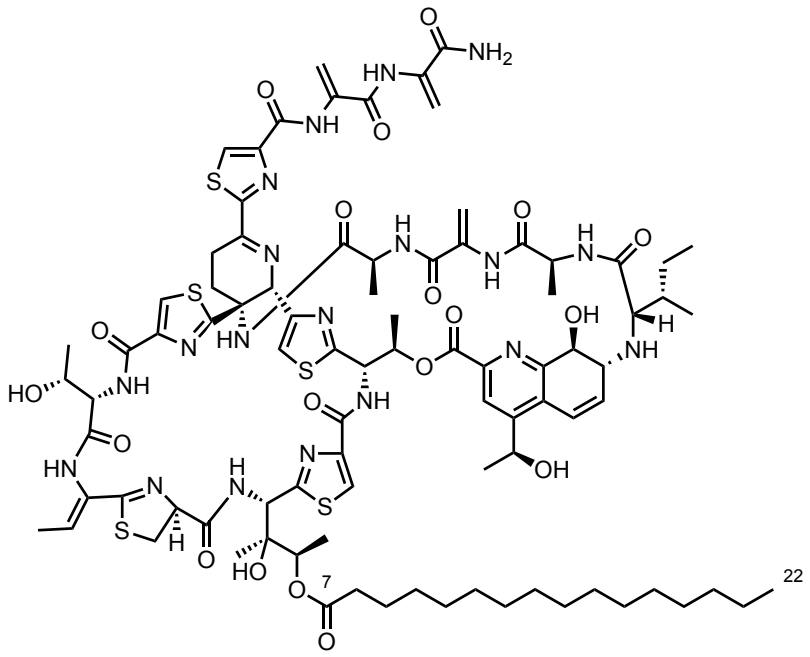
Benzoyl chloride (66.0 μL, 0.569 mmol) was added to a solution of Et_3N (0.159 mL, 1.14 mmol), 10-undecenoic acid (**517**, 107 mg, 0.581 mmol) and thiostrepton (**460**) (190 mg, 0.114 mmol) in $CHCl_3$ (9.5 mL, 12 mM) at 0 °C (ice/H_2O bath) and the reaction then stirred at 0 °C for 2 min. DMAP (16.0 mg, 0.143 mmol) was added at 0 °C and the reaction then stirred at 0 °C for a further 2.5 h. The reaction was quenched at 0 °C by addition of EtOH (10 mL), removed from the cold bath and allowed to warm to rt. The mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried over

anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1 $CHCl_3$:MeOH) to afford ester **525** as an off-white solid (91.0 mg, 44%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.96 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.10 (s, 1 H, Deala(3) NH), 8.78 (d, *J* = 9.0 Hz, 1 H, Thr(2) NH), 8.63 (s, 1 H, But NH), 8.26 (s, 1 H, Thz(4) H-5), 8.25 (s, 1 H, Thz(2) H-5) 8.14 (s, 1 H, Thz(1) H-5), 8.00 (s, 1 H, Deala(1) NH), 7.78 (d, *J* = 5.5 Hz, 1 H, Ala(1) NH), 7.61 (br. s, 1 H, Thstn NH), 7.54 (d, *J* = 10.3 Hz, 1 H, Deala(3) NH_2), 7.52 (s, 1 H, Thz(3) H-5), 7.27 (s, 1 H, Q H-3), 7.13 (d, *J* = 7.8 Hz, 1 H, Ala(2) NH), 7.03 (d, *J* = 7.7 Hz, 1 H, Thr(1) NH), 6.87 (d, *J* = 10.0 Hz, 1 H, Q H-5), 6.68 (d, *J* = 2.4 Hz, 1 H, Deala(2) H-3), 6.50 (d, *J* = 1.9 Hz, 1 H, Deala(3) H-3), 6.41–6.31 (m, 2 H, Q H-6 and Thr(2) H-3), 6.27 (d, *J* = 6.9 Hz, 1 H, Deala(3) NH_2), 6.19 (q, *J* = 7.0 Hz, 1 H, But H-3), 5.83–5.72 (m, 3 H, Deala(1) H-3, Thr(2) H-2 and Thstn H-16), 5.68–5.57 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.36–5.25 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.04 (q, *J* = 6.3 Hz, 1 H, Thstn H-4), 4.98–4.84 (m, 3 H, Cys H-4 and 2 × Thstn H-17), 4.71 (q, *J* = 6.6 Hz, 1 H, Ala(2) H-2), 4.44–4.37 (m, 2 H, Q H-8 and Thr(1) H-2), 4.06 (ddd, *J* = 13.2, 6.5, 3.3 Hz, 1 H, Pip H-4), 3.80 (q, *J* = 6.7 Hz, 1 H, Ala(1) H-2), 3.62–3.57 (m, 1 H, Cys H-5), 3.56–3.49 (m, 1 H, Q H-7), 3.49–3.41 (m, 1 H, Pip H-3), 3.20 (t, *J* = 12.0 Hz, 1 H, Cys H-5), 2.95 (d, *J* = 4.5 Hz, 1 H, Ile H-2), 2.93–2.86 (m, 1 H, Pip H-3), 2.41–2.21 (m, 3 H, Pip H-4 and 2 × Thstn H-8), 2.06–1.94 (m, 2 H, 2 × Thstn H-15), 1.92–1.83 (m, 1 H, Ile H-3), 1.69 (d, *J* = 6.5 Hz, 3 H, 3 × Thr(2) H-4), 1.64–1.50 (m, 2 H, 2 × Thstn H-9), 1.57 (d, *J* = 7.0 Hz, 3 H, 3 × But H-4), 1.41 (d, *J* = 6.5 Hz, 3 H, 3 × Ala(2) H-3), 1.35 (d, *J* = 6.5 Hz, 3 H, 3 × Q H-12), 1.33–1.19 (m, 18 H, Ile H-4, Thr(1) H-3, 3 × Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12, 2 × Thstn H-13 and 2 × Thstn H-14), 1.16 (d, *J* = 6.7 Hz, 3 H, 3 × Ala(1) H-3), 1.11–1.02 (m, 1 H, Ile H-4),

0.97 (d, *J* = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, *J* = 7.4 Hz, 3 H, 3 × Ile H-5) and 0.80 ppm (d, *J* = 6.2 Hz, 3 H, 3 × Thr(1) H-4); **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 176.6, 173.6, 173.3, 170.7, 170.3, 169.8, 169.0, 168.5, 166.8, 166.2, 166.2, 165.7, 162.9, 162.9, 162.3, 162.2, 162.1, 161.9, 160.8, 159.7, 157.3, 154.6, 153.8, 150.2, 150.1, 146.5, 143.6, 139.1, 134.3, 133.1, 133.0, 132.9, 130.2, 128.5, 127.9, 127.3, 125.8, 125.1, 123.3, 122.6, 118.3, 114.0, 114.0, 104.5, 103.4, 79.2, 76.1, 72.1, 69.6, 67.7, 66.4, 65.6, 64.6, 64.2, 59.0, 57.6, 55.9, 55.8, 55.7, 52.1, 38.5, 34.4, 34.1, 33.7, 29.3, 29.2, 29.1, 29.0, 29.0, 28.8, 28.8, 24.9, 24.6, 24.3, 22.8, 19.7, 19.2, 19.1, 19.0, 15.8, 15.5, 14.0 and 11.7 ppm; **FTIR** ν_{max} (thin film): 3359, 2926, 2361, 1731, 1645, 1486, 1416, 1288, 1207, 1054, 899, 753 and 668 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{83}H_{103}N_{19}NaS_5^+$ $[M+Na]^+$ 1853.6252; found 1853.6312 (Δ 3.24 ppm); **M.P.** 200−220 °C (decomposition).

Thiostrepton-O-hexadecanoate (**526**)



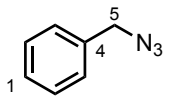
Benzoyl chloride (70.0 μL, 0.618 mmol) was added to a solution of Et_3N (0.172 mL, 1.23 mmol), palmitic acid (162 mg, 0.632 mmol) and thiostrepton (**460**) (206 mg, 0.124 mmol) in $CHCl_3$ (10 mL, 12 mM) at 0 °C (ice/H_2O bath) and the reaction then stirred at

0 °C for 2 min. DMAP (17.3 mg, 0.154 mmol) was added at 0 °C and the reaction then stirred at 0 °C for a further 2.5 h. The reaction was quenched at 0 °C by addition of EtOH (10 mL), removed from the cold bath and allowed to warm to rt. The mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1 $CHCl_3$:MeOH) to afford ester 526 as an off-white solid (88.0 mg, 37%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.98 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.12 (s, 1 H, Deala(3) NH), 8.80 (d, *J* = 8.8 Hz, 1 H, Thr(2) NH), 8.66 (s, 1 H, But NH), 8.27 (s, 1 H, Thz(4) H-5), 8.26 (s, 1 H, Thz(2) H-5) 8.14 (s, 1 H, Thz(1) H-5), 8.01 (s, 1 H, Deala(1) NH), 7.81 (d, *J* = 5.4 Hz, 1 H, Ala(1) NH), 7.69 (s, 1 H, Thstn NH), 7.57 (d, *J* = 10.5 Hz, 1 H, Deala(3) NH_2), 7.53 (s, 1 H, Thz(3) H-5), 7.27 (s, 1 H, Q H-3), 7.19 (d, *J* = 7.7 Hz, 1 H, Ala(2) NH), 7.04 (d, *J* = 7.7 Hz, 1 H, Thr(1) NH), 6.87 (d, *J* = 10.0 Hz, 1 H, Q H-5), 6.68 (d, *J* = 2.4 Hz, 1 H, Deala(2) H-3), 6.49 (d, *J* = 1.8 Hz, 1 H, Deala(3) H-3), 6.44–6.28 (m, 2 H, Q H-6 and Thr(2) H-3), 6.20 (q, *J* = 7.0 Hz, 1 H, But H-3), 5.80 (d, *J* = 2.2 Hz, 1 H, Deala(1) H-3), 5.76 (s, 1 H, Thr(2) H-2), 5.69–5.55 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.35 (d, *J* = 2.1 Hz, 1 H, Deala(1) H-3), 5.33–5.26 (m, 2 H, Pip H-6 and Q H-11), 5.05 (q, *J* = 6.3 Hz, 1 H, Thstn H-4), 4.91 (dd, *J* = 12.2, 9.4 Hz, 1 H, Cys H-4), 4.72 (q, *J* = 6.6 Hz, 1 H, Ala(2) H-2), 4.45–4.38 (m, 2 H, Q H-8 and Thr(1) H-2), 4.10–4.01 (m, 1 H, Pip H-4), 3.80 (q, *J* = 6.8 Hz, 1 H, Ala(1) H-2), 3.63–3.57 (m, 1 H, Cys H-5), 3.54 (dd, *J* = 11.5, 9.1 Hz, 1 H, Q H-7), 3.45 (dd, *J* = 20.0, 5.3 Hz, 1 H, Pip H-3), 3.20 (t, *J* = 12.0 Hz, 1 H, Cys H-5), 2.95 (d, *J* = 4.6 Hz, 1 H, Ile H-2), 2.96–2.86 (m, 1 H, Pip H-3), 2.43–2.21 (m, 3 H, Pip H-4 and 2 × Thstn H-8), 1.91–1.81 (m, 1 H, Ile H-3), 1.70 (d, *J* = 6.6 Hz, 3 H, 3 × Thr(2) H-4), 1.58 (d, *J* = 7.2 Hz, 3 H, 3 × But H-4), 1.64–1.50 (m, 2 H, 2

× Thstn H-9), 1.41 (d, *J* = 6.6 Hz, 3 H, 3 × Ala(2) H-3), 1.38–1.19 (m, 35 H, Ile H-4, 3 × Q H-12, Thr(1) H-3, 3 × Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12, 2 × Thstn H-13, 2 × Thstn H-14, 2 × Thstn H-15, 2 × Thstn H-16, 2 × Thstn H-17, 2 × Thstn H-18, 2 × Thstn H-19, 2 × Thstn H-20 and 2 × Thstn H-21), 1.16 (d, *J* = 6.7 Hz, 3 H, 3 × Ala(1) H-3), 1.13–1.05 (m, 1 H, Ile H-4), 0.97 (d, *J* = 6.8 Hz, 3 H, 3 × Ile H-6) and 0.90–0.79 ppm (m, 9 H, 3 × Ile H-5, 3 × Thr(1) H-4 and 3 × Thstn H-22); **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 176.7, 173.8, 173.4, 170.7, 170.6, 170.3, 169.8, 169.0, 168.5, 166.8, 166.2, 165.7, 163.0, 162.9, 162.3, 162.2, 162.1, 161.9, 161.8, 160.9, 159.8, 157.3, 154.6, 153.7, 150.1, 150.0, 146.5, 146.4, 143.6, 134.3, 133.2, 132.9, 132.2, 130.2, 128.6, 128.5, 127.9, 127.3, 125.7, 125.2, 123.3, 122.5, 118.3, 104.6, 103.5, 103.4, 79.2, 76.1, 72.1, 69.6, 67.6, 66.4, 65.7, 64.6, 64.2, 59.1, 57.6, 55.9, 55.7, 52.1, 52.0, 51.9, 38.5, 34.4, 34.2, 34.1, 31.9, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 29.1, 24.9, 24.7, 24.4, 22.8, 22.6, 19.6, 19.1, 19.1, 19.0, 18.9, 15.8, 15.4, 13.9 and 11.6 ppm; **FTIR** ν_{max} (thin film): 2926, 2361, 1731, 1645, 1417, 1207, 1119, 975, 908, 730 and 647 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{88}H_{115}N_{19}O_{19}NaS_5^+$ $[M+Na]^+$ 1925.7191; found 1925.7266 (Δ 3.89 ppm); **M.P.** 190−210 °C (decomposition).

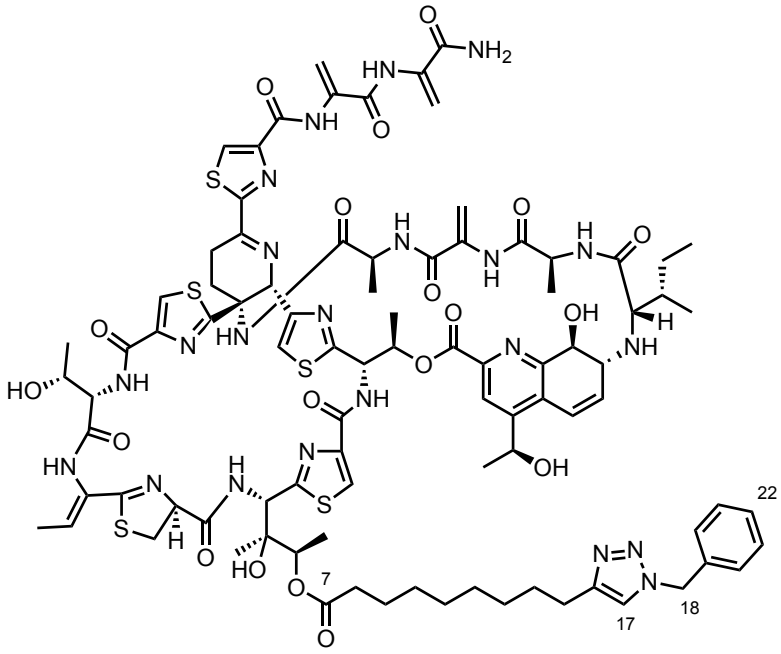
(Azidomethyl)benzene (**S29**)



Sodium azide (123 mg, 1.89 mmol) was added to a solution of benzyl bromide (0.150 mL, 1.26 mmol) in acetone:H_2O (4:1, 25 mL, 50 mM) at rt and the reaction then stirred at rt for 24 h. The reaction was diluted with HCl (3 M, aq., 5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic

layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford azide **S29** as a pale yellow oil (119 g, 71 %). Data is consistent with that reported in the literature.[227] **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 7.46–7.29 (m, 5 H, H-1, 2 × H-2 and 2 × H-3) and 4.34 ppm (s, 2 H, 2 × H-5); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ = 135.8 (C-4), 129.3 (2 C, 2 × C-2), 128.8 (C-1), 128.7 (2 C, 2 × C-3) and 55.3 ppm (C-5).

Thiostrepton-O-9-(1-benzyl-1H-1,2,3-triazol-4-yl)nonanoate (**527**)



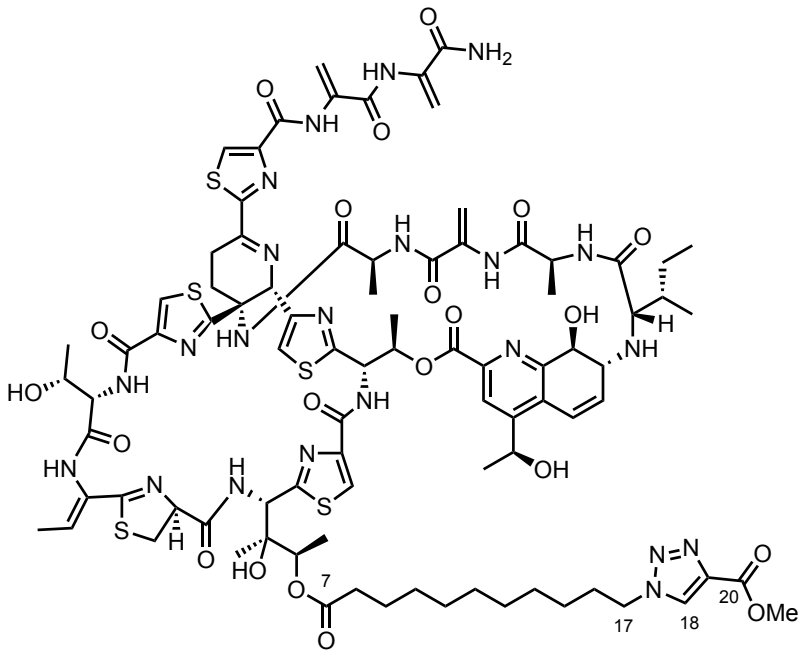
N,*N*-Diisopropylethylamine (20.0 μL, 0.115 mmol) was added to a mixture of alkyne **516** (10.0 mg, 5.47 μmol), benzyl azide (**S29**) (5.0 mg, 38 μmol) and copper iodide (2.3 mg, 12 μmol) in $CHCl_3$ (0.50 mL, 11 mM) at rt and the reaction then stirred at 60 °C for 1 h. The reaction was cooled to rt, quenched by addition of H_2O (2 mL) and the mixture extracted with $CHCl_3$ (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (39:1 $CHCl_3$:MeOH) to afford triazole **527** as an off-white solid (4.4 mg, 41%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 9.97 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.11 (s, 1 H, Deala(3) NH), 8.79 (d, *J* = 9.3 Hz, 1 H, Thr(2) NH), 8.63 (s, 1 H, But NH),

8.27 (s, 1 H, Thz(4) H-5), 8.25 (s, 1 H, Thz(2) H-5) 8.14 (s, 1 H, Thz(1) H-5), 8.00 (s, 1 H, Deala(1) NH), 7.58–7.50 (m, 2 H, Thstn H-22 and Thz(3) H-5), 7.36–7.31 (m, 3 H, Thstn H-17 and 2 × Thstn H-21), 7.28 (s, 1 H, Q H-3), 7.26–7.23 (m, 2 H, 2 × Thstn H-20), 7.12 (d, J = 10.5 Hz, 1 H, Ala(2) NH), 7.04 (d, J = 7.6 Hz, 1 H, Thr(1) NH), 6.87 (d, J = 10.0 Hz, 1 H, Q H-5), 6.68 (d, J = 2.3 Hz, 1 H, Deala(2) H-3), 6.50 (d, J = 2.3 Hz, 1 H, Deala(3) H-3), 6.41–6.30 (m, 2 H, Q H-6 and Thr(2) H-3), 6.19 (q, J = 7.1 Hz, 1 H, But H-3), 5.81 (d, J = 2.2 Hz, 1 H, Deala(1) H-3), 5.76 (s, 1 H, Thr(2) H-2), 5.68–5.57 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.48 (s, 2 H, 2 × Thstn H-18), 5.35–5.25 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.04 (q, J = 6.2 Hz, 1 H, Thstn H-4), 4.88 (dd, J = 12.1, 9.4 Hz, 1 H, Cys H-4), 4.71 (q, J = 6.3 Hz, 1 H, Ala(2) H-2), 4.43–4.37 (m, 2 H, Q H-8 and Thr(1) H-2), 4.09–4.00 (m, 1 H, Pip H-4), 3.78 (q, J = 6.6 Hz, 1 H, Ala(1) H-2), 3.64–3.56 (m, 1 H, Cys H-5), 3.51 (dd, J = 11.5, 9.2 Hz, 1 H, Q H-7), 3.47–3.42 (m, 1 H, Pip H-3), 3.18 (t, J = 12.0 Hz, 1 H, Cys H-5), 2.95 (d, J = 4.3 Hz, 1 H, Ile H-2), 2.93–2.87 (m, 1 H, Pip H-3), 2.64 (t, J = 7.8 Hz, 2 H, 2 × Thstn H-15), 2.40–2.22 (m, 3 H, Pip H-4 and 2 × Thstn H-8), 1.94–1.83 (m, 1 H, Ile H-3), 1.70 (d, J = 6.5 Hz, 3 H, 3 × Thr(2) H-4), 1.65–1.51 (m, 2 H, 2 × Thstn H-9), 1.56 (d, J = 7.0 Hz, 3 H, 3 × But H-4), 1.41 (d, J = 6.6 Hz, 3 H, 3 × Ala(2) H-3), 1.35 (d, J = 6.6 Hz, 3 H, 3 × Q H-12), 1.34–1.19 (m, 18 H, Ile H-4, Thr(1) H-3, 3 × Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12, 2 × Thstn H-13 and 2 × Thstn H-14), 1.16 (d, J = 6.7 Hz, 3 H, 3 × Ala(1) H-3), 1.12–1.02 (m, 1 H, Ile H-4), 0.97 (d, J = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, J = 7.3 Hz, 3 H, 3 × Ile H-5) and 0.79 ppm (d, J = 6.2 Hz, 3 H, 3 × Thr(1) H-4); **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 173.4, 173.3, 170.7, 170.2, 169.9, 169.04, 169.00, 168.5, 166.8, 166.3, 165.7, 162.9, 162.3, 162.2, 162.1, 161.8, 160.8, 159.8, 157.3, 154.6, 153.8, 150.1, 150.0, 148.6, 146.4, 143.6, 134.5, 134.3, 133.0, 132.9, 132.2, 130.2, 129.0, 128.7, 128.5, 127.92, 127.85, 127.4,

125.8, 125.1, 123.4, 122.5, 121.3, 119.1, 118.4, 104.6, 103.5, 79.2, 76.1, 72.1, 69.5, 67.7, 66.4, 65.6, 64.6, 64.2, 62.4, 59.0, 57.7, 57.6, 55.8, 55.7, 54.2, 52.1, 51.9, 49.6, 38.5, 34.4, 34.1, 31.8, 29.6, 29.3, 29.2, 29.12, 29.08, 29.0, 28.9, 25.3, 24.6, 24.3, 22.8, 19.7, 19.1, 19.05, 19.04, 19.0, 15.8, 15.4, 13.9 and 11.6 ppm; **FTIR** ν_{max} (thin film): 3360, 2361, 2342, 1734, 1653, 1490, 1366, 1216 and 669 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{90}H_{109}N_{22}O_{19}S_5^+$ $[M+H]^+$ 1961.6837; found 1961.6942 (Δ 5.35 ppm); **M.P.** 210−220 °C (decomposition).

Thiostrepton-O-11-(4-methoxycarbonyl)-1H-1,2,3-triazol-1-yl)undecanoate (**528**)

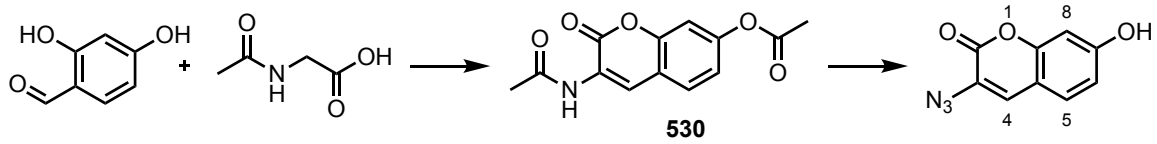


Methyl propiolate (6.0 μL, 67 μmol) and *N,N*-diisopropylethylamine (46 μL, 26 μmol) were sequentially added to a solution of azide **523** (25.0 mg, 13.3 μmol) and copper iodide (5.0 mg, 26 μmol) in $CHCl_3$ (1.3 mL, 10 mM) at rt and the reaction then stirred at 60 °C for 2 h. The reaction was cooled to rt, quenched by addition of H_2O (1 mL) and the mixture extracted with $CHCl_3$ (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column chromatography (49:1–19:1 $CHCl_3$:MeOH) to afford triazole **528** as a pale yellow solid (8.4 mg, 32%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 400 MHz): δ = 9.97 (s, 1 H, Deala(2) NH), 9.87 (s, 1 H, Pip NH), 9.11 (s, 1 H, Deala(3) NH), 8.79 (d, *J* = 8.9 Hz, 1 H, Thr(2) NH), 8.63 (s, 1 H, But NH), 8.27 (s, 1 H, Thz(4) H-5), 8.25 (s, 1 H, Thz(2) H-5), 8.18 (s, 1 H, Thstn H-18), 8.14 (s, 1 H, Thz(1) H-5), 7.99 (s, 1 H, Deala(1) NH), 7.79 (d, *J* = 5.6 Hz, 1 H, Ala(1) NH), 7.55 (d, *J* = 10.5 Hz, 1 H, Deala(3) NH_2), 7.52 (s, 1 H, Thz(3) H-5), 7.27 (s, 1 H, Q H-3), 7.03 (d, *J* = 7.7 Hz, 1 H, Thr(1) NH), 6.87 (d, *J* = 10.0 Hz, 1 H, Q H-5), 6.68 (d, *J* = 2.3 Hz, 1 H, Deala(2) H-3), 6.50 (d, *J* = 1.9 Hz, 1 H, Deala(3) H-3), 6.41–6.30 (m, 2 H, Q H-6 and Thr(2) H-3), 6.19 (q, *J* = 7.0 Hz, 1 H, But H-3), 5.81 (d, *J* = 2.2 Hz, 1 H, Deala(1) H-3), 5.77 (s, 1 H, Thr(2) H-2), 5.69–5.57 (m, 3 H, Deala(2) H-3, Deala(3) H-3 and Thstn H-2), 5.35–5.25 (m, 3 H, Deala(1) H-3, Pip H-6 and Q H-11), 5.04 (q, *J* = 6.4 Hz, 1 H, Thstn H-4), 4.89 (dd, *J* = 12.4, 9.3 Hz, 1 H, Cys H-4), 4.71 (q, *J* = 6.5 Hz, 1 H, Ala(2) H-2), 4.44–4.36 (m, 4 H, Q H-8, Thr(1) H-2 and 2 × Thstn H-17), 4.09–4.00 (m, 1 H, Pip H-4), 3.91 (s, 3 H, Thstn C-20 OCH_3), 3.84–3.74 (m, 1 H, Ala(1) H-2), 3.62–3.47 (m, 2 H, Cys H-5 and Q H-7), 3.19 (t, *J* = 12.0 Hz, 1 H, Cys H-5), 2.94 (d, *J* = 4.5 Hz, 1 H, Ile H-2), 2.40–2.20 (m, 3 H, Pip H-4 and 2 × Thstn H-8), 1.94–1.83 (m, 3 H, Ile H-3 and 2 × Thstn H-16), 1.70 (d, *J* = 6.5 Hz, 3 H, 3 × Thr(2) H-4), 1.65–1.49 (m, 2 H, 2 × Thstn H-9), 1.56 (d, *J* = 7.1 Hz, 3 H, 3 × But H-4), 1.41 (d, *J* = 6.6 Hz, 3 H, 3 × Ala(2) H-3), 1.35 (d, *J* = 6.6 Hz, 3 H, 3 × Q H-12), 1.33–1.20 (m, 20 H, Thr(1) H-3, Ile H-4, 3 × Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12, 2 × Thstn H-13, 2 × Thstn H-14 and 2 × Thstn H-15), 1.16 (d, *J* = 6.7 Hz, 3 H, 3 × Ala(1) H-3), 1.12–1.02 (m, 1 H, Ile H-4), 0.97 (d, *J* = 6.9 Hz, 3 H, 3 × Ile H-6), 0.86 (t, *J* = 7.3 Hz, 3 H, 3 × Ile H-5) and 0.80 ppm (d, *J* = 6.3 Hz, 3 H, 3 × Thr(1) H-4); **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 194.8, 189.3, 188.6, 179.6, 176.9, 173.9, 171.2, 171.1, 170.4, 169.7, 166.2, 161.8, 154.4, 150.7, 147.0, 144.2, 1460.1, 133.5, 130.7, 129.0, 128.1, 126.4, 124.0, 118.9, 109.5, 107.7, 105.0, 104.0, 72.6, 70.0, 66.0,

59.5, 54.8, 52.7, 51.3, 43.0, 34.9, 32.4, 30.6, 30.1, 30.0, 29.8, 29.6, 29.4, 26.8, 25.2, 23.1, 19.6, 18.8, 17.5, 16.4, 14.5, 12.6 and 12.2 ppm; **FTIR** ν_{max} (thin film): 3356, 2921, 2850, 2362, 2342, 2158, 1732, 1650, 1520, 1425, 1208, 777, 669, 632 and 613 cm^{-1}. **HRMS** (ESI^+): Calculated for $C_{87}H_{108}N_{22}NaO_{21}S_5^+$ $[M+Na]^+$ 1979.6555; found 1979.6626 (Δ 3.59 ppm); **M.P.** 210−220 °C (decomposition). 54 ^{13}C carbon signals are observed when 87 are expected. The discrepancy is ascribed to the low mass obtained and the consequent difficulty of measuring a ^{13}C spectrum of sufficient intensity to visualise all the signals.

3-Azido-7-hydroxy-2H-chromen-2-one (**531**)

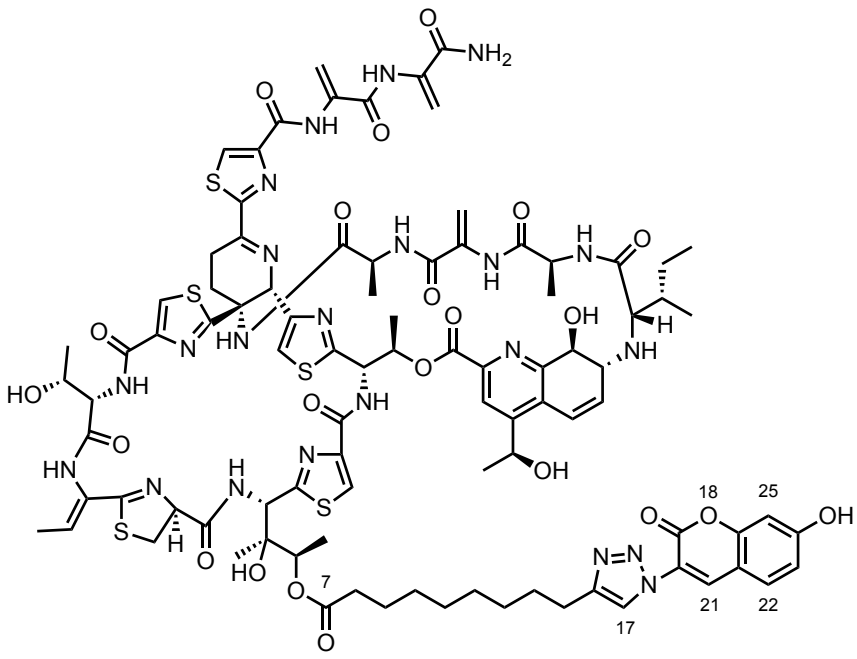


A solution of 2,4-dihydroxybenzaldehyde (2.76 g, 20.0 mmol), *N*-acetylglycine (2.34 g, 20.0 mmol) and sodium acetate (5.22 g, 64.0 mmol) in acetic anhydride (100 mL, 0.2 M) was stirred at reflux for 6 h. The reaction was cooled to rt and concentrated *in vacuo*. The residue was redissolved in Et_2O (20 mL) and cooled to –78 °C (dry ice/acetone bath). The precipitate formed was filtered and the solids then washed with cold H_2O before being dried *in vacuo* to afford crude coumarin **530** (572 mg). Crude coumarin **530** (572 mg) was redissolved in EtOH (10 mL) and HCl (37%, aq., 20 mL) added dropwise to the solution at rt. The reaction was heated to reflux for 1 h. The reaction was cooled to rt and ice (40 g) added in a single portion. The reaction mixture was cooled to 0 °C (ice/H_2O bath) and $NaNO_2$ (2.76 g, 40.0 mmol) added portionwise. The reaction mixture was stirred at 0 °C for 15 min and NaN_3 (3.90 g, 60.0 mmol) then added portionwise at 0 °C over 1 h [CAUTION: Toxic and potentially explosive]. The reaction mixture was stirred at 0 °C for a further 20 min after which it was

filtered. The solids were washed with H_2O before being dried *in vacuo* to afford coumarin **531** as a brown solid (250 mg, 6%). Data is consistent with that reported in the literature.[206]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.54 (s, 1 H, OH), 7.60 (s, 1 H, H-4), 7.48 (d, *J* = 8.5 Hz, 1 H, H-5), 6.81 (dd, *J* = 8.5, 2.3 Hz, 1 H, H-6) and 6.76 ppm (d, *J* = 2.3 Hz, 1 H, H-8); **^{13}C NMR** (DMSO-d_6, 101 MHz): δ = 160.3 (C-2 or C-7 or C-9), 157.3 (C-2 or C-7 or C-9), 152.8 (C-2 or C-7 or C-9), 129.1 (C-6), 127.8 (C-8), 121.1 (C-3 or C-10), 113.8 (C-5), 111.3 (C-3 or C-10) and 102.0 ppm (C-4). **M.P.** >250 °C (EtOH).

Thiostrepton-O-9-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazol-4-yl)nonanoate (**532**)



N,*N*-Diisopropylethylamine (0.177 mL, 1.02 mmol) was added to a mixture of alkyne **516** (93.0 mg, 50.8 μmol), coumarin **531** (29.0 mg, 0.143 mmol) and copper iodide (20.0 mg, 0.105 mmol) in $CHCl_3$ (2.5 mL, 20 mM) and EtOH (2.5 mL, 20 mM) at rt and the reaction then stirred at rt for 4.5 h. The reaction was quenched at rt by addition of H_2O (5 mL) and the mixture extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* before being purified by flash column

chromatography (39:1 to 19:1 $CHCl_3$:MeOH) to afford triazole **532** as a yellow solid (52.0 mg, 50%).

^{1}H NMR (4:1 $CDCl_3$:CD_3OD, 500 MHz): δ = 10.04 (s, 1 H, Thstn C-24 OH), 9.97 (s, 1 H, Deala(2) NH), 9.85 (s, 1 H, Pip NH), 8.81 (d, *J* = 8.9 Hz, 1 H, Thr(2) NH), 8.67 (s, 1 H, But NH), 8.43 (s, 1 H, Thstn H-17), 8.27–8.26 (m, 3 H, Thstn H-21, Thz(2) H-5 and Thz(4) H-5), 8.15 (s, 1 H, Thz(1) H-5), 8.02 (s, 1 H, Deala(1) NH), 7.82 (d, *J* = 5.2 Hz, 1 H, Ala(1) NH), 7.74, (br. s, 1 H, Thstn NH), 7.57 (d, *J* = 10.3 Hz, 1 H, Deala(3) NH_2), 7.54 (s, 1 H, Thz(3) H-5), 7.51 (d, *J* = 8.5 Hz, 1 H, Thstn H-22), 7.27 (s, 1 H, Q H-3), 7.24–7.20 (m, 1 H, Ala(2) NH), 7.05 (d, *J* = 7.6 Hz, 1 H, Thr(1) NH), 6.89–6.86 (m, 2 H, Q H-5 and Thstn H-23), 6.83 (d, *J* = 2.2 Hz, 1 H, Thstn H-25), 6.66 (s, 1 H, Deala(2) H-3), 6.60 (d, *J* = 1.8 Hz, 1 H, Deala(3) H-3), 6.39 (dd, *J* = 9.8, 5.7 Hz, 1 H, Q H-6), 6.34 (q, *J* = 6.7 Hz, 1 H, Thr(2) H-3), 6.27 (d, *J* = 7.3 Hz, 1 H, Deala(3) NH_2), 6.20 (q, *J* = 7.0 Hz, 1 H, But H-3), 5.80 (d, *J* = 2.1 Hz, 1 H, Deala(1) H-3), 5.78–5.69 (m, 2 H, Thr(2) H-2 and Thstn H-2), 5.67–5.62 (m, 2 H, Deala(2) H-3 and Deala(3) H-3), 5.35 (s, 1 H, Deala(1) H-3), 5.33−5.26 (m, 2 H, Pip H-6 and Q H-11), 5.05 (q, *J* = 6.4 Hz, 1 H, Thstn H-4), 4.91 (dd, *J* = 12.3, 9.4 Hz, 1 H, Cys H-4), 4.72 (q, *J* = 6.7 Hz, 1 H, Ala(2) H-2), 4.43–4.36 (m, 2 H, Q-8 and Thr(1) H-2), 4.10–3.94 (m, 1 H, Pip H-4), 3.80 (q, *J* = 6.8 Hz, 1 H, Ala(1) H-2), 3.65–3.50 (m, 2 H, Cys H-5 and Q H-7), 3.48–3.38 (m, 1 H, Pip H-3), 3.20 (t, *J* = 12.0 Hz, 1 H, Cys H-5), 2.95 (d, *J* = 4.5 Hz, 1 H, Ile H-2), 2.93–2.83 (m, 1 H, Pip H-3), 2.76 (t, *J* = 7.7 Hz, 2 H, 2 × Thstn H-15), 2.36 (q, *J* = 7.2 Hz, 2 H, 2 × Thstn H-8), 2.34–2.23 (m, 1 H, Pip H-4), 1.91–1.83 (m, 1 H, Ile H-3), 1.76–1.67 (m, 5 H, 3 × Thr(2) H-4 and 2 × Thstn H-9), 1.65–1.53 (m, 5 H, 3 × But H-4 and 2 × Thstn H-14), 1.44–1.20 (m, 22 H, 3 × Ala(2) H-3, Ile H-4, 3 × Q H-12, Thr(1) H-3, 3 × Thstn H-5, 3 × Thstn H-6, 2 × Thstn H-10, 2 × Thstn H-11, 2 × Thstn H-12 and 2 × Thstn H-13), 1.16 (d, *J* = 6.7 Hz, 3 H, 3 × Ala(1) H-3), 1.14–1.05 (m, 1 H, Ile H-4),

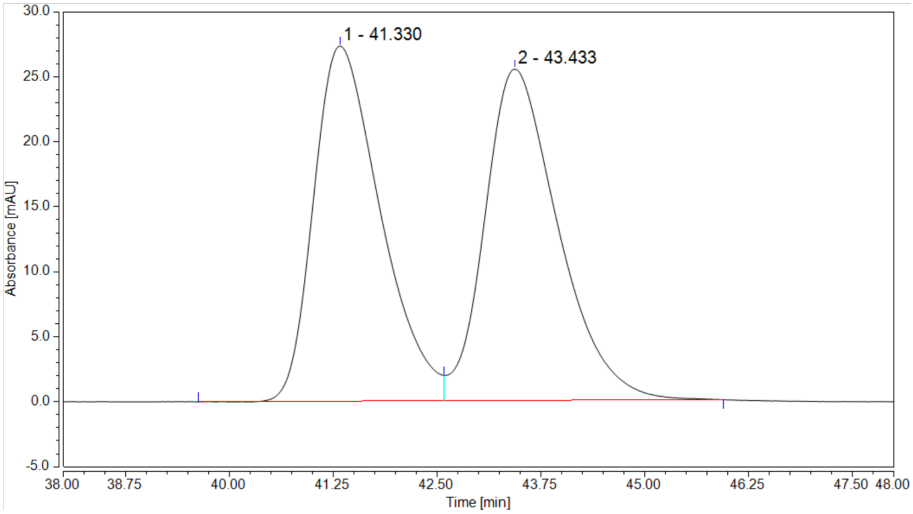
0.97 (d, *J* = 6.8 Hz, 3 H, 3 × Ile H-6), 0.87 (t, *J* = 7.3 Hz, 3 H, 3 × Ile H-5) and 0.81 ppm (d, *J* = 6.2 Hz, 3 H, 3 × Thr(1) H-4).; **^{13}C NMR** (4:1 $CDCl_3$:CD_3OD, 126 MHz): δ = 173.8, 173.0, 172.5, 171.1, 169.9, 169.4, 169.0, 168.1, 167.6, 165.9, 165.6, 164.9, 162.4, 162.0, 161.8, 161.4, 161.3, 161.0, 160.0, 158.9, 156.5, 156.0, 154.0, 153.8, 152.8, 149.2, 147.4, 145.5, 142.7, 134.2, 132.5, 132.1, 131.4, 129.4, 127.6, 126.9, 126.5, 124.9, 124.3, 122.3, 121.6, 121.3, 118.5, 117.5, 113.9, 109.7, 103.3, 102.5, 101.8, 84.1, 78.3, 75.2, 71.6, 71.2, 68.8, 66.7, 65.5, 64.8, 63.7, 63.3, 58.2, 57.8, 56.7, 55.0, 54.8, 51.5, 51.2, 51.0, 48.7, 37.7, 33.5, 33.3, 28.7, 28.5, 28.3, 28.18, 28.17, 24.5, 24.1, 23.7, 23.5, 21.9, 21.7, 18.8, 18.1, 18.2, 18.1, 14.9, 14.5, 14.2, 13.1 and 10.7 ppm; **FTIR** ν_{max} (thin film): 3350, 2361, 1731, 1645, 1417, 1208, 1118, 1054, 908, 752, 731 and 667 cm^{-1}; **HRMS** (ESI^+): Calculated for $C_{92}H_{107}N_{22}O_{22}S_5^+$ $[M+H]^+$ 2031.6528; found 2031.6630 (Δ 5.02 ppm); **M.P.** 210−220 °C (decomposition).

5.5 Additional Experimental Data

5.5.1 HPLC Traces

HPLC traces were measured by John Jolliffe, University of Oxford. Separation was performed on a Chiralpak 1A column with a mobile phase of 2% IPA/hexane eluting at a rate of 1 mL/min. Absorbances at 275 nm were measured to facilitate peak integration.

(±)-alcohol **413**

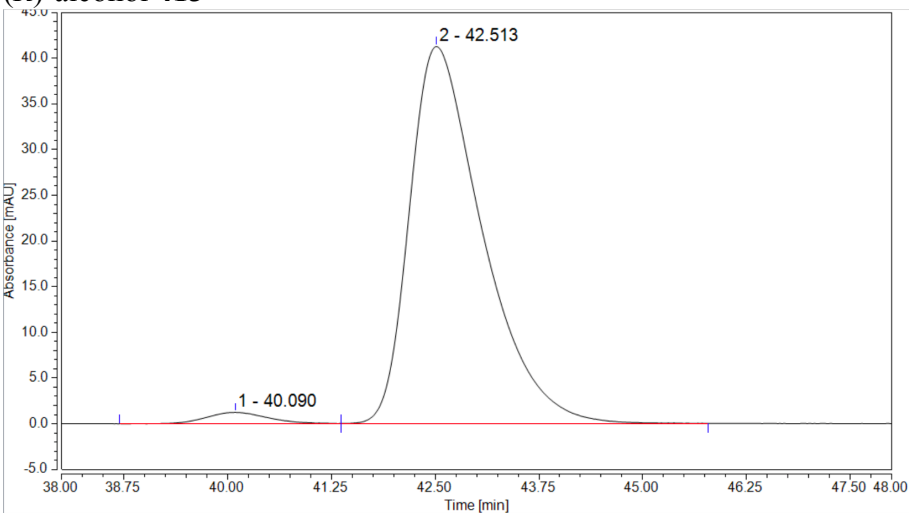


Integration Results

No.	Retention Time (min)	Area (mAU*min)	Height (mAU)	Relative Area (%)
1	41.330	25.493	27.324	49.39
2	43.433	26.125	25.490	50.61
Total		51.618	52.814	100.00

Figure 5.3 HPLC trace for (±)-alcohol **413**

(*R*)-alcohol **413**

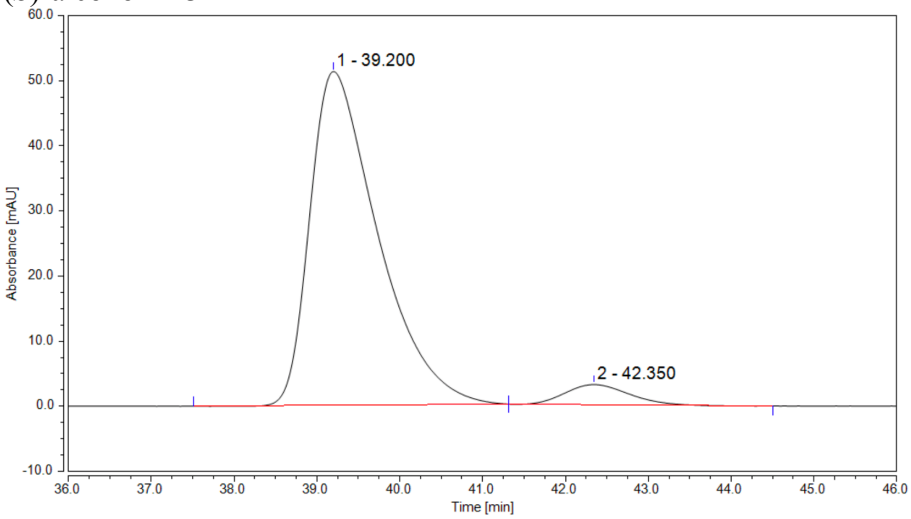


Integration Results

No.	Retention Time (min)	Area (mAU*min)	Height (mAU)	Relative Area (%)
1	40.090	1.026	1.225	2.39
2	42.513	41.899	41.234	97.61
Total		42.925	42.459	100.00

Figure 5.4 HPLC trace for (*R*)-alcohol **413**

(*S*)-alcohol **413**



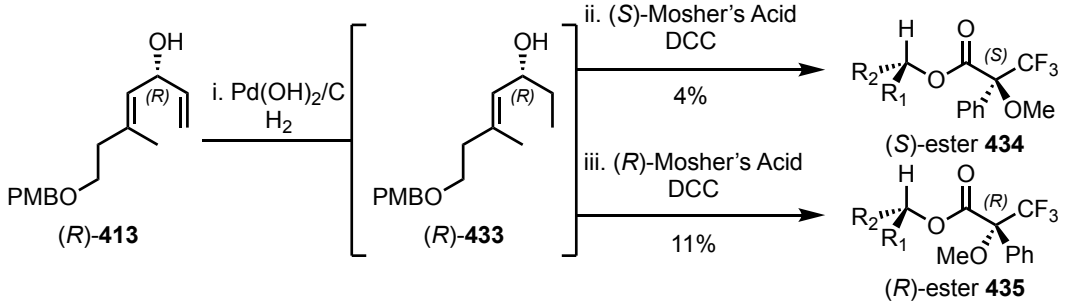
Integration Results

No.	Retention Time (min)	Area (mAU*min)	Height (mAU)	Relative Area (%)
1	39.200	48.653	51.268	94.64
2	42.360	2.756	3.104	5.36
Total		42.925	42.459	100.00

Figure 5.5 HPLC trace for (*S*)-alcohol **413**

5.5.2 Mosher's Ester Analysis

Confirmation of stereochemistry for (*R*)-alcohol **413** was performed in accordance with the protocol reported by Hoye and co-workers.[162]



Scheme 5.1 Mosher's ester analysis. Reagents and conditions: i) 10 wt% $Pd(OH)_2/C$, EtOAc, rt, H_2; ii) 3 eq. (*S*)-(–)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid, 3 eq. DCC, 3 eq. DMAP, CH_2Cl_2, rt, 15 h, 4%; iii) 3 eq. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid, 3 eq. DCC, 3 eq. DMAP, CH_2Cl_2, rt, 15 h, 11%

Mosher's Ester Analysis

Proton	(S)-ester **434** (ppm)	(*R*)-ester **435** (ppm)	**Δ**δ ($\delta_S - \delta_R$) (ppm)
1	5.60	5.66	–0.06
2	1.79–1.70 1.67–1.57	1.75–1.62 1.62–1.50	+ve
3	0.91	0.82	+0.09
4	5.06	5.22	–0.16
5	1.79	1.79	0
6	2.30	2.33	–0.02
7	3.49	3.55–3.47	–ve

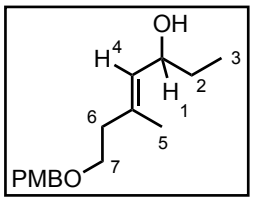


Table 5.1 Mosher's ester analysis for alcohol **433**

The **Δ**δ ($\delta_S - \delta_R$) values for protons H-2 and H-3 are positive. The **Δ**δ ($\delta_S - \delta_R$) values for protons H-4, H-6 and H-7 are negative. Protons with positive **Δ**δ ($\delta_S - \delta_R$) values reside in the R_1 environment above and those with negative **Δ**δ ($\delta_S - \delta_R$) values reside in R_2 (see Scheme 5.1 for R_1 and R_2). This correlates with (*R*) stereochemistry for alcohol (*R*)-**433** and by extension (*R*)-**413**, as expected.

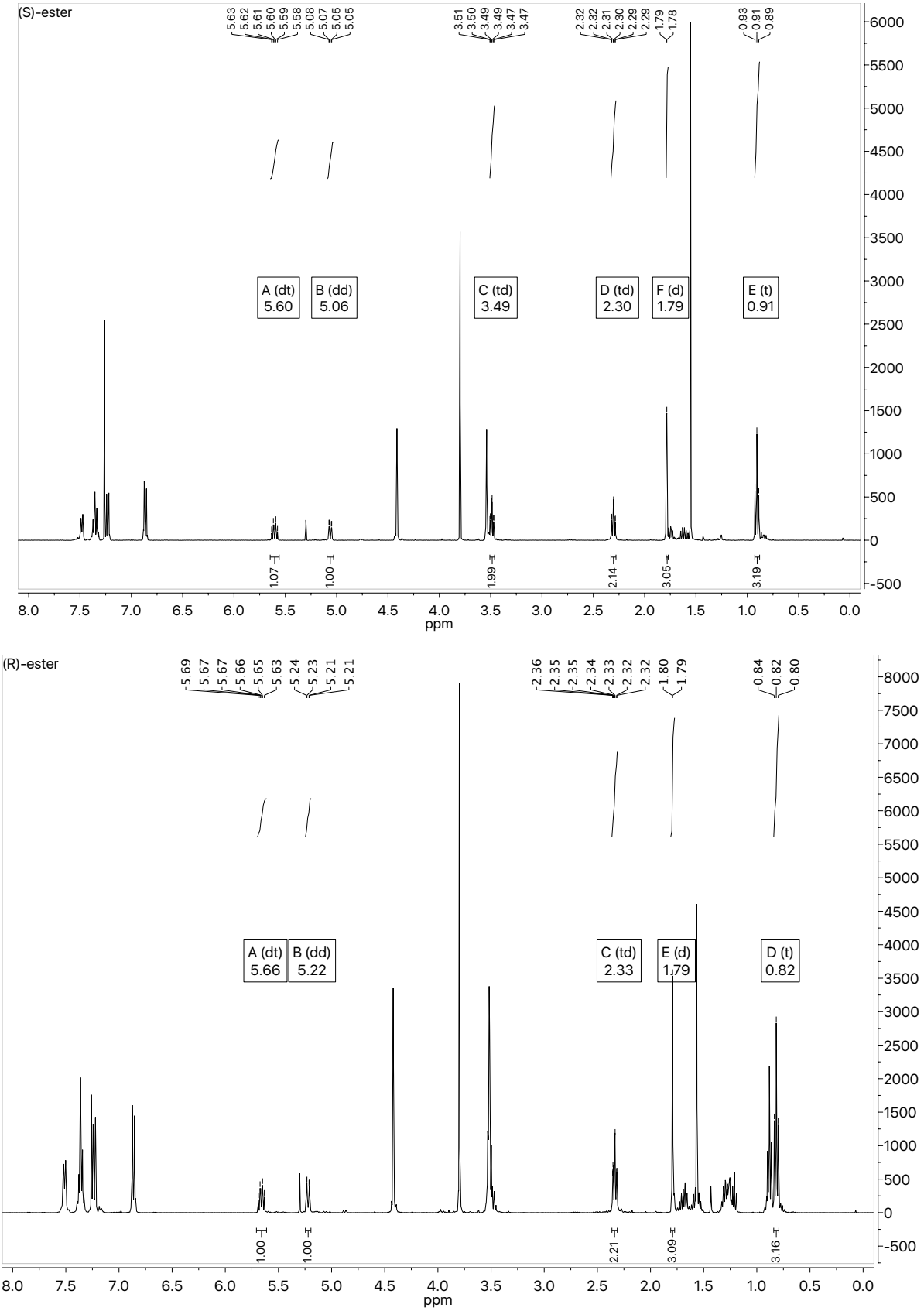
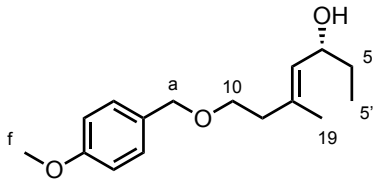


Figure 5.6 ^{1}H NMR spectra of (*S*)-ester **434** and (*R*)-ester **435**

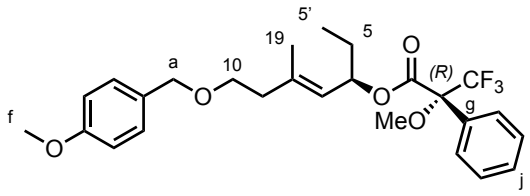
(R,E)-7-((4-Methoxybenzyl)oxy)-5-methylhept-4-en-3-ol (**433**)



$P(OH)_2/C$ (2.2 mg, 10 wt%) was added to a solution of (*R*)-alcohol **413** (22.0 mg, 83.9 μmol) in EtOAc (8.4 mL, 0.01 M) at rt. The flask was evacuated and filled with H_2 (balloon) three times before being stirred (1000 rpm) in a H_2 atmosphere at rt. The reaction was monitored by TLC analysis (every 5 minutes) and once consumption of starting material was observed (1 h) the reaction mixture was directly filtered through a pad of Celite, washing several times with EtOAc. The filtrate was concentrated *in vacuo* to afford (*R*)-alcohol **433** which was used directly.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.22 (m, 2 H, 2 × H-c), 6.91–6.84 (m, 2 H, 2 × H-d), 5.20 (dq, *J* = 8.7, 1.3 Hz, 1 H, H-7), 4.44 (s, 2 H, 2 × H-a), 4.28 (q, *J* = 7.1 Hz, 1 H, H-6), 3.80 (s, 3 H, 3 × H-f), 3.54 (td, *J* = 6.9, 1.2 Hz, 2 H, 2 × H-10), 2.35–2.27 (m, 2 H, 2 × H-9), 1.69 (d, *J* = 1.4 Hz, 3 H, 3 × H-19), 1.61 (dqd, *J* = 13.7, 7.4, 6.3 Hz, 1 H, H-5), 1.49–1.38 (m, 1 H, H-5) and 0.88 ppm (t, *J* = 7.4 Hz, 3 H, 3 × H-5′).

(*R*,*E*)-7-((4-Methoxybenzyl)oxy)-5-methylhept-4-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**434**)

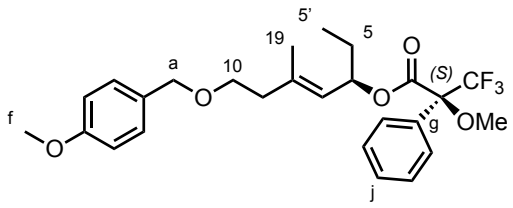


Note: (*R*)-Alcohol **433** was azeotroped with PhMe (× 3) and dried under high vacuum for 1 h prior to use.

(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (25.3 mg, 0.108 mmol), *N*,*N*'-dicyclohexylcarbodiimide (22.3 mg, 0.108 mmol) and DMAP (13.2 mg, 0.108 mmol) were sequentially added to a solution of (*R*)-Alcohol **433** (9.5 mg, 36 μmol) in CH_2Cl_2 (0.72 mL, 0.05 M) at rt and the reaction then stirred at rt for 15 h. The reaction mixture was filtered through a plug of cotton wool and concentrated *in vacuo* before being purified by flash column chromatography (9:1–2:3 pentane:Et_2O) to afford (*R*)-ester **434** as a colourless oil (2.0 mg, 11%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57–7.47 (m, 2 H, 2 × H-i), 7.41–7.31 (m, 3 H, 2 × H-h and H-j), 7.26–7.21 (m, 2 H, 2 × H-c), 6.89–6.84 (m, 2 H, 2 × H-d), 5.66 (dt, *J* = 9.3, 6.7 Hz, 1 H, H-6), 5.22 (dq, *J* = 9.4, 1.4 Hz, 1 H, H-7), 4.42 (s, 2 H, 2 × H-a), 3.80 (s, 3 H, 3 × H-f), 3.55–3.47 (m, 5 H, 2 × H-10 and OC<u>H</u>$_3$), 2.33 (td, *J* = 6.8, 1.1 Hz, 2 H, 2 × H-9), 1.79 (d, *J* = 1.3 Hz, 3 H, 3 × H-19), 1.75–1.62 (m, 1 H, H-5), 1.62–1.50 (m, 1 H, H-5) and 0.82 ppm (t, *J* = 7.4 Hz, 3 H, 3 × H-5′).

(*R*,*E*)-7-((4-Methoxybenzyl)oxy)-5-methylhept-4-en-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**435**)



Note: (*R*)-Alcohol **433** was azeotroped with PhMe (× 3) and dried under high vacuum for 1 h prior to use.

(*S*)-(–)-α-Methoxy-α-trifluoromethylphenylacetic acid (19.1 mg, 81.8 μmol), *N*,*N*'-dicyclohexylcarbodiimide (16.9 mg, 81.8 μmol) and DMAP (10.0 mg, 81.8 μmol) were sequentially added to a solution of (*R*)-Alcohol **433** (7.2 mg, 27 μmol) in CH_2Cl_2 (0.55 mL, 0.05 M) at rt and the reaction then stirred at rt for 15 h. The reaction mixture was filtered through a plug of

cotton wool and concentrated *in vacuo* before being purified by flash column chromatography (9:1 pentane:Et_2O) to afford (*S*)-ester **435** as a colourless oil (0.6 mg, 4%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.44 (m, 2 H, 2 × H-i), 7.42–7.29 (m, 3 H, 2 × H-h and H-j), 7.27–7.19 (m, 2 H, 2 × H-c), 6.93–6.82 (m, 2 H, 2 × H-d), 5.60 (dt, *J* = 9.3, 6.8 Hz, 1 H, H-6), 5.06 (dq, *J* = 9.3, 1.3 Hz, 1 H, H-7), 4.41 (s, 2 H, 2 × H-a), 3.80 (s, 3 H, 3 × H-f), 3.54 (q, *J* = 1.2 Hz, 3 H, OC$\underline{H}_3$), 3.49 (td, *J* = 7.0, 1.6 Hz, 2 H, 2 × H-10), 2.30 (td, *J* = 6.9, 1.1 Hz, 2 H, 2 × H-9), 1.79 (d, *J* = 1.4 Hz, 3 H, 3 × H-19), 1.79–1.70 (m, 1 H, H-5), 1.67–1.57 (m, 1 H, H-5) and 0.91 ppm (t, *J* = 7.4 Hz, 3 H, 3 × H-5′).

5.5.3 2D NMR Spectra

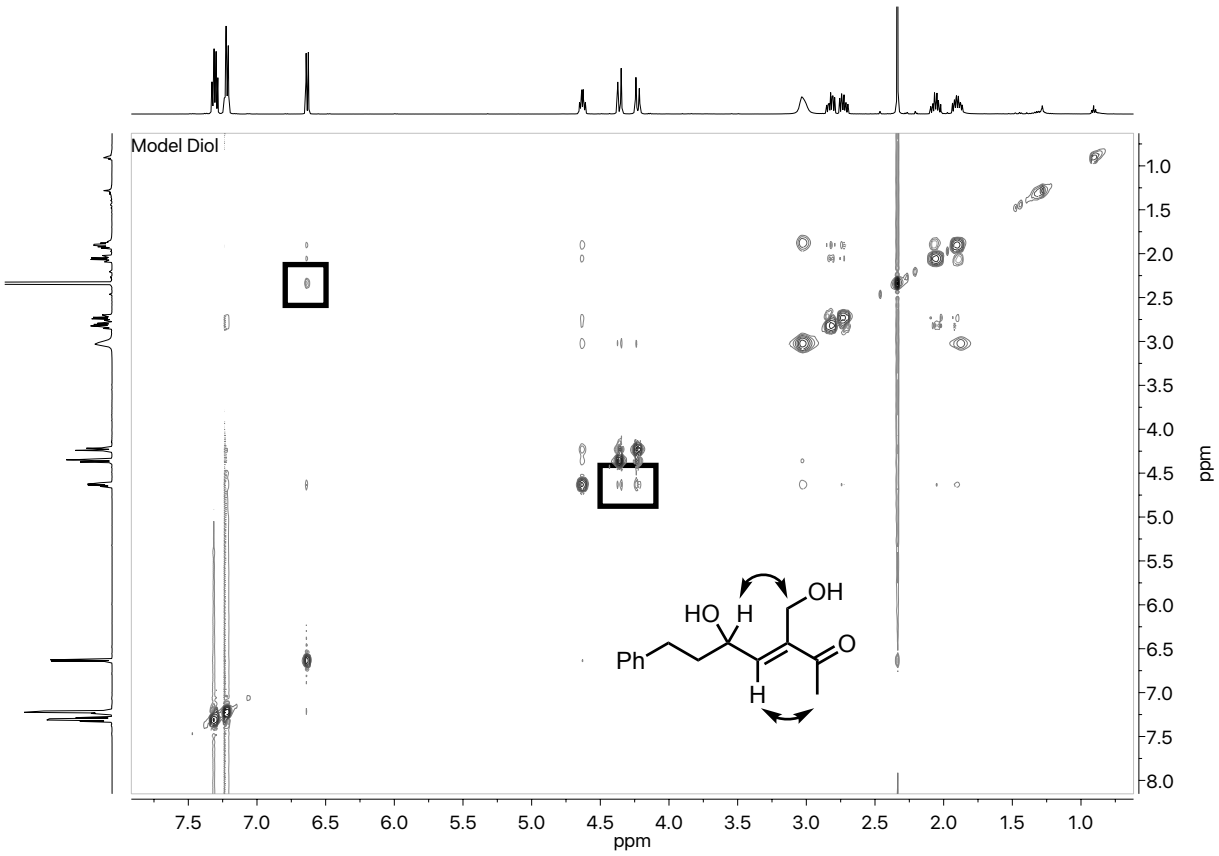


Figure 5.7 NOESY for diol **243**. Key correlations are boxed

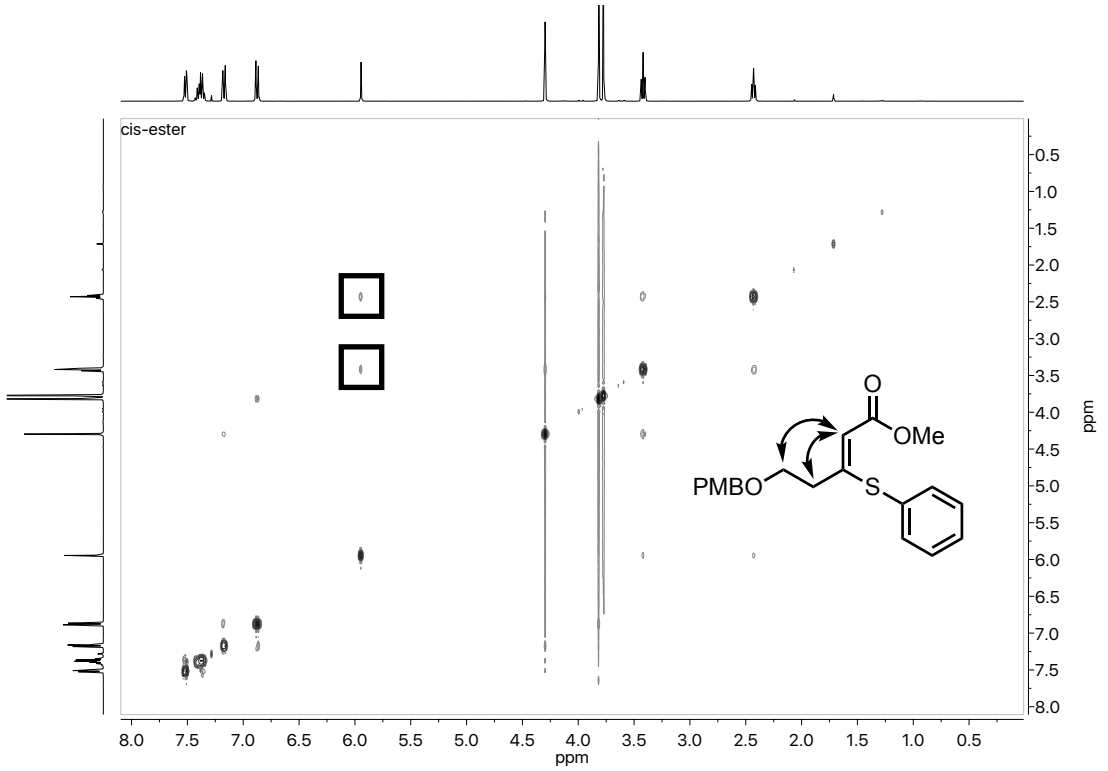


Figure 5.8 NOESY for *trans*-ester **409**. Key correlations are boxed

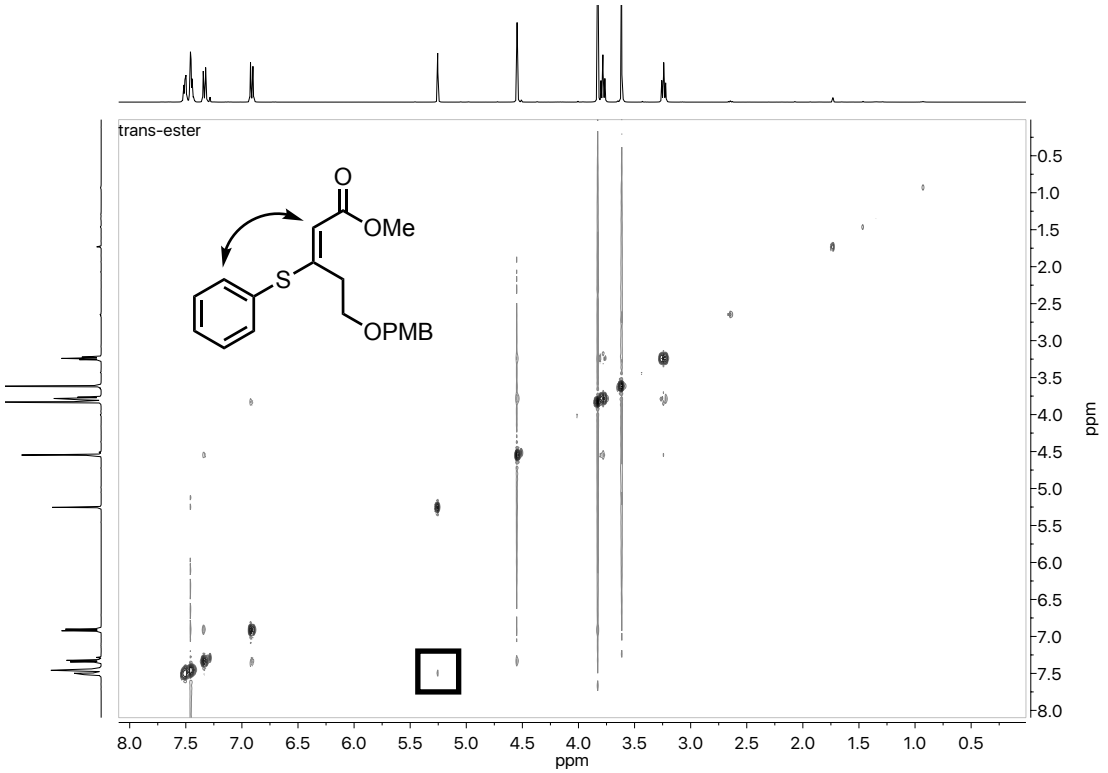


Figure 5.9 NOESY for *trans*-ester **410**. Key correlation is boxed

Chapter 6

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