Total Synthesis of Rubriflordilactone A

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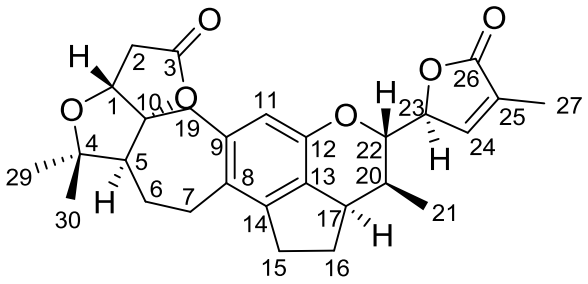
A thesis submitted for the degree of

Doctor of Philosophy in Chemistry

Trinity 2015



Rubriflordilactone A

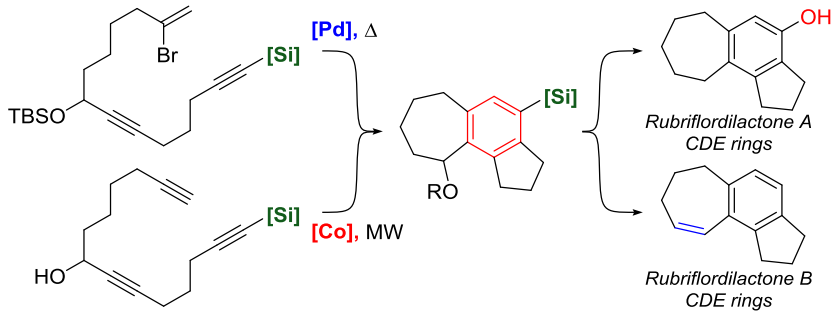
Abstract: Total Synthesis of Rubriflordilactone A

Doctor of Philosophy **Goh Simin, Shermin**

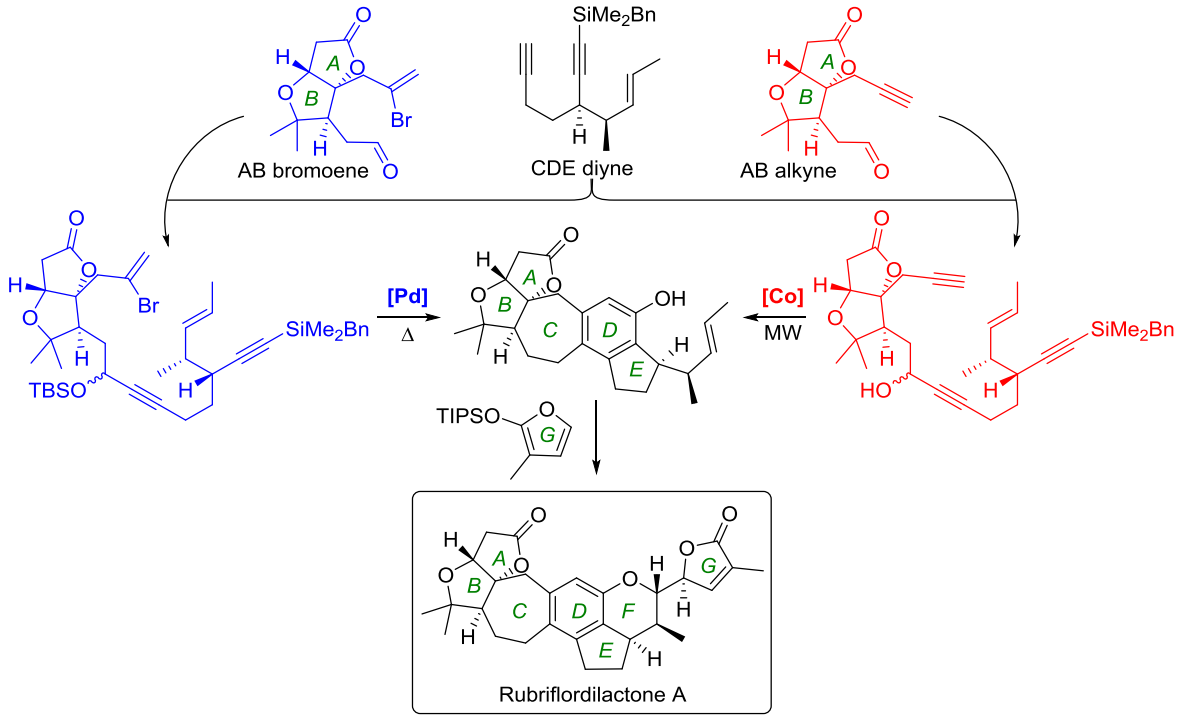
Trinity 2014 **Exeter College**

Rubriflordilactones A and B are highly oxygenated nortriterpenoid natural products isolated from *Schisandra rubriflora*. The latter is of particular biological interest as it shows significant anti-HIV activity.

Two transition metal-catalysed cascade cyclisation approaches for the formation of the CDE rings of the rubriflordilactones were developed. Palladium-catalysed cyclisation of bromoenediynes and cobalt-catalysed triyne cyclotrimerisation both transform acyclic precursors into 7,6,5-bisannelated arenes in a single step.



Two enantioselective syntheses of the AB ring fragment common to both rubriflordilactones, with bromoene or alkyne functional groups required for the respective cyclisation methods, are described; along with the refinement of a route to the CDE diyne fragment of rubriflordilactone A.



From these fully functionalised bromoenediyne and triyne substrates, both metal-catalysed cyclisation methods were successful; these strategies converged on a late-stage intermediate bearing the ABCDE ring system of rubriflordilactone A. Construction of the F ring, followed by attachment of the G ring by an intriguing oxo-carbenium ion addition reaction completed two enantioselective total syntheses of (+)-rubriflordilactone A.

Acknowledgements

I would like to extend my gratitude the following people who have made the four years of my DPhil experience an enjoyable process.

To Ed for accepting me into the group and entrusting me with the total synthesis rubriflordilactone A. It's been a long running project within the group, and I daresay we are happy to see it through! Thank you for your enthusiasm, guidance, support and understanding throughout this process.

To members of the EAA group past and present for their company and advice in the lab. A big thank you to those who have worked on the project – MC, Birgit, Hannah, Andrew, Polly, Guilhem and Mujji – and to the proofreaders of my thesis – Diane, Guilhem, Glenn and Yao. Special thanks to Diane, Glenn and Yao who have not only been great colleagues but also amazing friends.

To the NMR and Mass Spectrometry services in the CRL, and Mr. Stephen Boyer, who does our elemental analysis, for their support.

To the Agency for Science, Technology and Research (A*STAR) in Singapore for funding my studies in Oxford.

To my friends in Oxford, especially my badminton / table tennis / cooking buddies – Akash, Amogh, Amy, Fiona, Meijia, Jinquan and Yao – thank you for sharing this exciting chapter of my life.

And last but not least, to my parents, Sherwin and Jinquan for their unwavering support despite being 6761 miles away and 7-8 hours ahead in time, I owe a very big thank you!

Abbreviations

Å	Ångström
Ac	acetyl
AE	asymmetric epoxidation
AIBN	azobisisobutyronitrile
Ar	aryl or argon
app	apparent
aq.	aqueous
Bn	benzyl
BOP	bis(2-oxo-3-oxazolidinyl)phosphonic
bp	boiling point
br	broad
brsm	based on recovered starting material
Bu	butyl
°C	degrees celsius
calc.	calculated
cat.	catalytic
cm^{-1}	wavenumber(s)
CSA	*DL*-10-camphorsulfonic acid
δ	chemical shift
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EA	elemental analysis
ee	enantiomeric excess
equiv.	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
FI	field ionisation
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
IBX	2-iodoxybenzoic acid
imid.	imidazole
IPA	*iso*-propanol
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
m	meta
m	multiplet

M	molar
Me	methyl
mm Hg	milimetre of mercury
MS	molecular sieves
m/z	mass-to-charge ratio
n	*normal*
n.d.	not determined
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
n.r.	no reaction
o	*ortho*
o/n	overnight
p	*para*
Pet. Ether	petroleum ether
PG	protecting group
Ph	phenyl
PMBTCA	*para*-methoxybenzyl trichloroacetimidate
ppm	part(s) per million
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	isopropyl
py	pyridine
q	quartet
quant.	quantitative
quin	quintet
R	unspecified substituent
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
sept	septet
sext	sextet
t	*tert*
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethysilyl
temp.	temperature
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TS	transition state
Ts	tosyl (*p*-toluenesulfonyl)
ν_{max}	infrared absorption maximum
v/v	volume/volume percent
wt%	weight percent

Contents

1. Introduction

1.1. The *Schisandra* nortriterpenoids

Schinortriterpenoids, abbreviated from "*Schisandra* nortriterpenoids", are an exceptional class of terpenoid natural products with C_{26} to C_{29} frameworks that is exclusively found in plants of the *Schisandra* genus.[1] Their structures are distinguished from cycloartane-type triterpenoids by 3,4-oxidative cleavage, 9,10-cleavage with ring expansion, decarboxylation at C18 and / or C28, and a five- or six-membered lactone ring in the side chain (*see Section 1.1.1*).[1]

Micrandilactone A **1** was the first example of a schinortriterpenoid to be isolated by Sun *et al.* from the Chinese herbal plant *Schisandra micrantha* in 2003.[2] Since then, more than 200 schinortriterpenoids have been isolated, out of a total of more than 400 triterpenoid compounds isolated from plants of the *Schisandraceae* family, which includes both the *Schisandra* and *Kadsura* genus.[1]

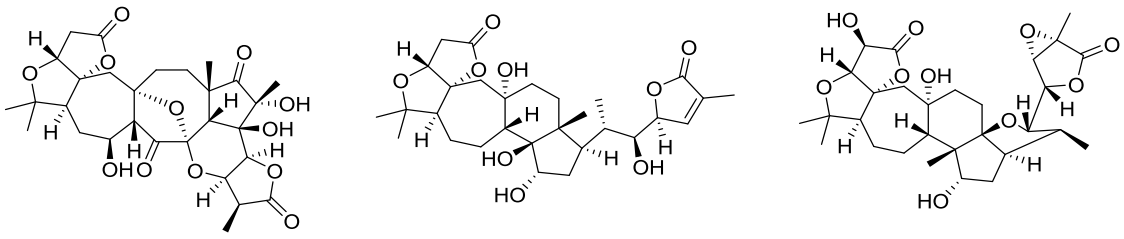


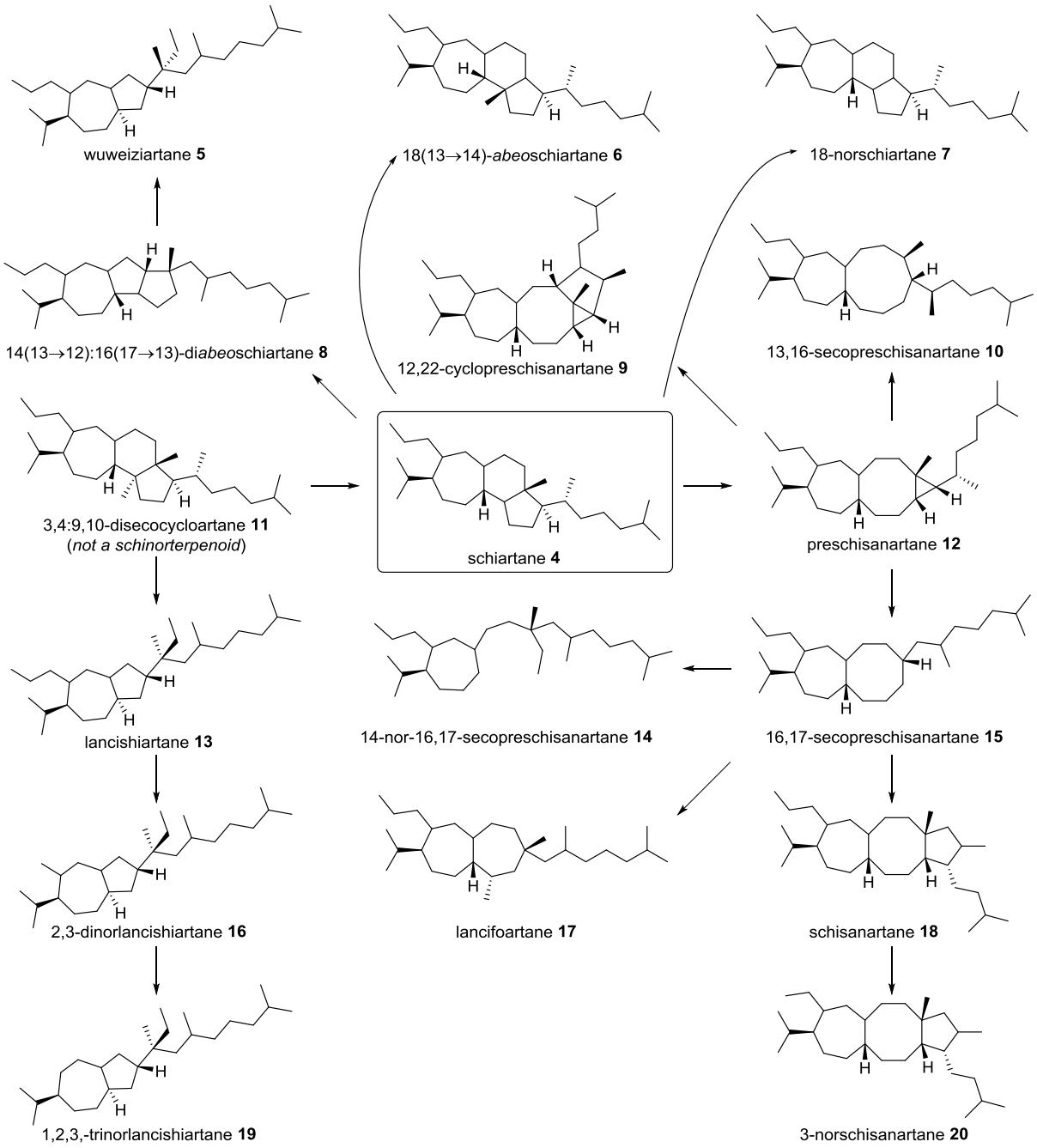
Figure 1-1 Selected examples of *Schisandra* nortriterpenoids

Researchers were not only intrigued by the interesting structural features of the *Schisandra* nortriterpenoids, but also by promising bioactivities. Extracts of the leaves and bark of plants of the genus *Schisandra* have been employed as folk medicines in China for thousands of years;[3] the dried mature fruits of *S. chinensis* and *S. sphenanthera*, known in Chinese traditional medicine as "wu wei zi" and "nan wu wei zi" respectively, have also been used to

treat hepatitis and insomnia.[4–6] Modern phytochemical and bioactivity investigations revealed that many schinortriterpenoids possess various beneficial pharmacological effects such as activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). Promising examples include micrandilactone C **2**, which exhibited anti-HIV activity with an EC_{50} value of 7.71 μg mL^{-1},[7] and propindilactone L **3**, which showed HBV inhibition against HBsAg and HBeAg with EC_{50} values of 0.480 and 1.185 μg mL^{-1} respectively.[8]

1.1.1. Classification

Schisandra nortriterpenoids have been classified into 16 sub-groups based on their carbon frameworks.[1] The schiartane skeleton **4** is considered to be the most basic schinortriterpenoid framework; it is thought to have biogenetically evolved into the other skeletons based on the proposed pathways shown in Scheme 1-1. The first six types of schinortriterpenoids to be identified were: schiartane **4**, wuweiziartane **5**, 18-(13→14)-*abeo*-schiartane **6**, 18-norschiartane **7**, pre-schisanartane **12** and schisanartane **18**;[9] but since then the discovery of more than a 100 new nortriterpenoids has led to the inclusion of more skeletal sub-groups.[1]



Scheme 1-1 The 16 skeletons of *Schisandra* nortriterpenoids and their biogenesis

1.1.2. Biosynthesis

The schiartane skeleton **4** itself is thought to have evolved from the cycloartane skeleton **21**, the representative structure of another group of triterpenoids from the *Schisandraceae* family (Figure 1-2).[10,11]

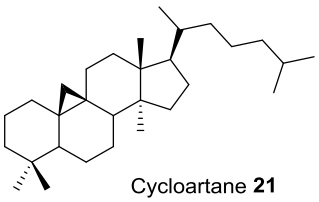
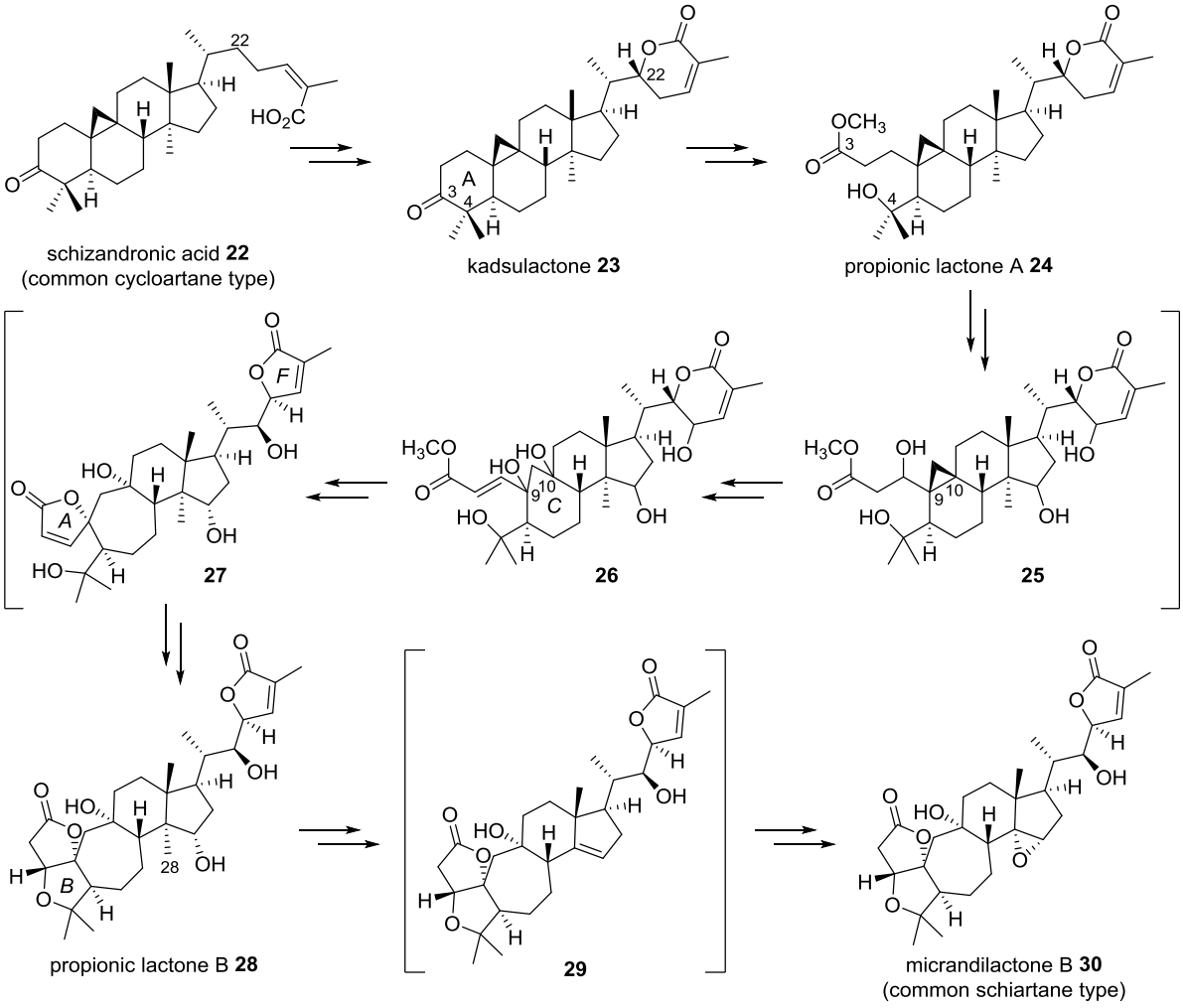


Figure 1-2 Basic skeleton of cycloartane

Sun and co-workers proposed a biosynthetic pathway (Scheme 1-2) in which schizandronic acid **22**, a cycloartane, evolves into the schiartane skeleton **4** featured in micrandilactone B.[11] In 2010, the discovery of two new triterpenoids propionic lactones A **24** and B **28**, isolated together with schizandronic acid **22** and micrandilactone B **30** and many other *Schisandra* nortriterpenoids from the stems of *Schisandra propinqua* var. *propinqua*, gave further support to this route; with the newly discovered triterpenoids acting as key intermediates.[11]



Scheme 1-2 Proposed biosynthetic pathway from schizandronic acid **25** to micrandilactone B **30** (Sun *et al.*, 2010) [11]

In the first steps, the α,β-unsaturated-δ-lactone **23** is formed by hydroxylation of schizandronic acid **22** at C22, followed by dehydration. Cleavage of the C3-C4 bond in kadsulactone's ring A, followed by methyl esterification at C3 and hydroxylation at C4 generates propionic lactone A **24**. After several hydroxylations to give **25**, intermediate **26**, bearing a seven-membered ring C is formed by bond cleavage at C9-C10. Transesterifications form the α,β-unsaturated-γ-lactone rings A and F in compound **27**; after which an intramolecular oxa-Michael addition to ring A constructs the furan ring B in propionic lactone B **28**. An oxidative decarboxylation of CH_3-28 gives compound **29**, from which micrandilactone B **30** is finally generated through an alkene epoxidation.

1.1.3. Our targets: rubriflordilactones A and B

Sun and co-workers isolated rubriflordilactones A **31** and B **32** (Figure 1-3) from the leaves and stems of *Schisandra rubriflora* in 2006.[12] They are classified in the 18-nor-schiartane group **7** of schinortriterpenoids.

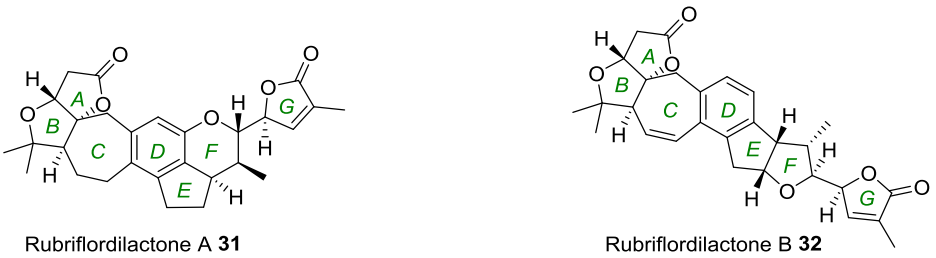


Figure 1-3 Rubriflordilactones A (**31**) and B (**32**)

Although related in structure and biosynthetic origin to other members of the *Schisandraceae* family, rubriflordilactones A and B are unique in their possession of an aromatic D ring. These molecules also share the same highly oxygenated [3.3.0] bicyclic lactone AB ring system, which is common to other schinortriterpenoids such as micrandilactone A **1**. Rubriflordilactones A and B possess very similar 7,6,5-CDE ring systems, differing only in the presence of unsaturation in the C ring of rubriflordilactone B **32**, and oxygenation in the D

ring of rubriflordilactone A **31**. Their highly unsaturated skeletons feature seven stereogenic centres in the case of rubriflordilactone A **31**, and eight in the case of rubriflordilactone B **32**.

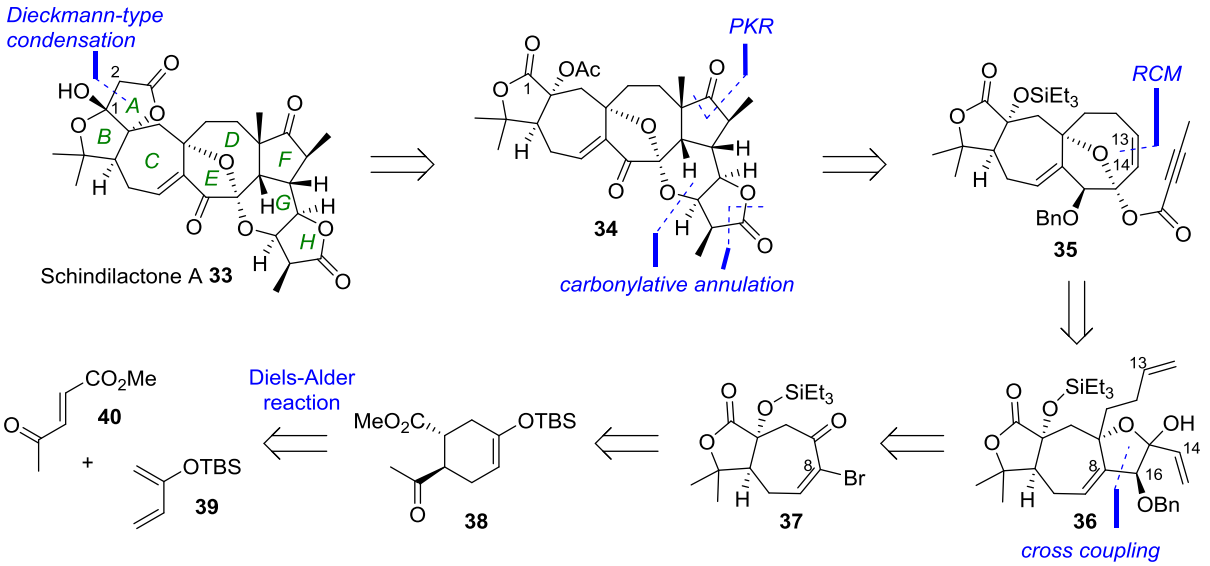
As with other compounds isolated from the *Schisandra* genus, rubriflordilactones A and B were tested for their bioactivities. Interestingly, while rubriflordilactone B **32** has moderate anti-HIV properties (EC_{50} = 9.75 µg mL^{-1} for inhibition of HIV-1_{IIIB}-induced syncytium formation), rubriflordilactone A **31** shows limited antiviral activity.[12]

1.2. Synthetic Approaches towards the *Schisandra* Natural Products

The *Schisandra* nortriterpenoid skeleton has attracted the attention of many synthetic chemists.[13–24] Nevertheless, most of publications describe only the synthesis of fragments of these natural products. In recent years, four total syntheses of *Schisandra* natural products have been achieved;[25–30] this section will review these syntheses.

1.2.1. Total synthesis of (±)-schindilactone A (Yang *et al.*, 2011)[25–28]

The first total synthesis of a schinortriterpenoid was achieved by Yang and co-workers in 2011 with the diastereoselective synthesis of (±)-schindilactone A **33** (**Scheme 1-3**).

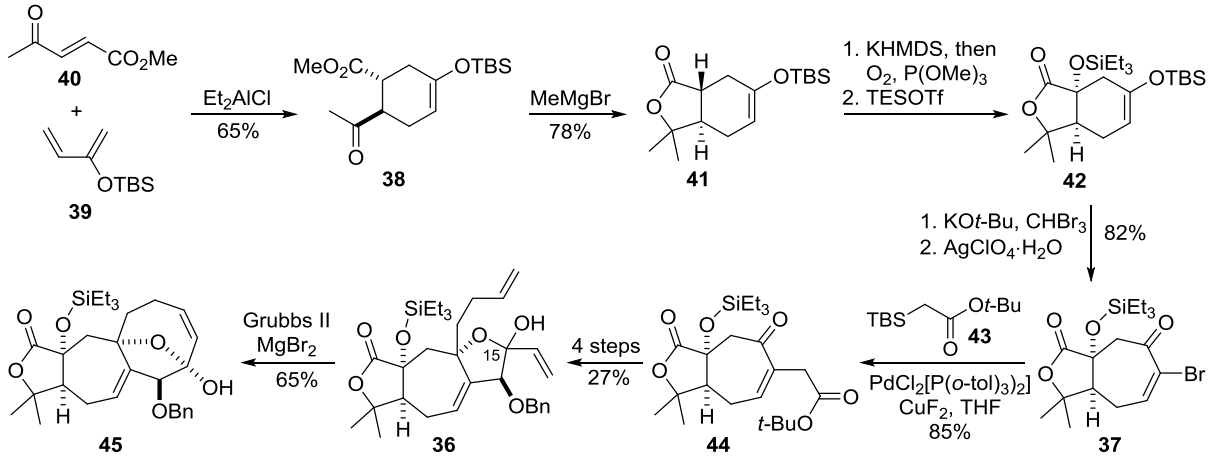


Scheme 1-3 Key disconnections to schindilactone A (Yang *et al.*, 2011) [25–28]

The retrosynthesis began with a disconnection of the C1-C2 bond (**Scheme 1-3**); the A ring would be the last to be installed by a Dieckmann-type condensation from acetate **34**. The FGH ring system in heptacycle **34** could be generated from enyne **35** first by a stereoselective Pauson-Khand reaction (PKR) to form the F ring, followed by a carbonylative annulation to install the GH ring system, a procedure which Yang and co-workers had previously developed in the synthesis of the right-hand side of micrandilactone A.[16] A

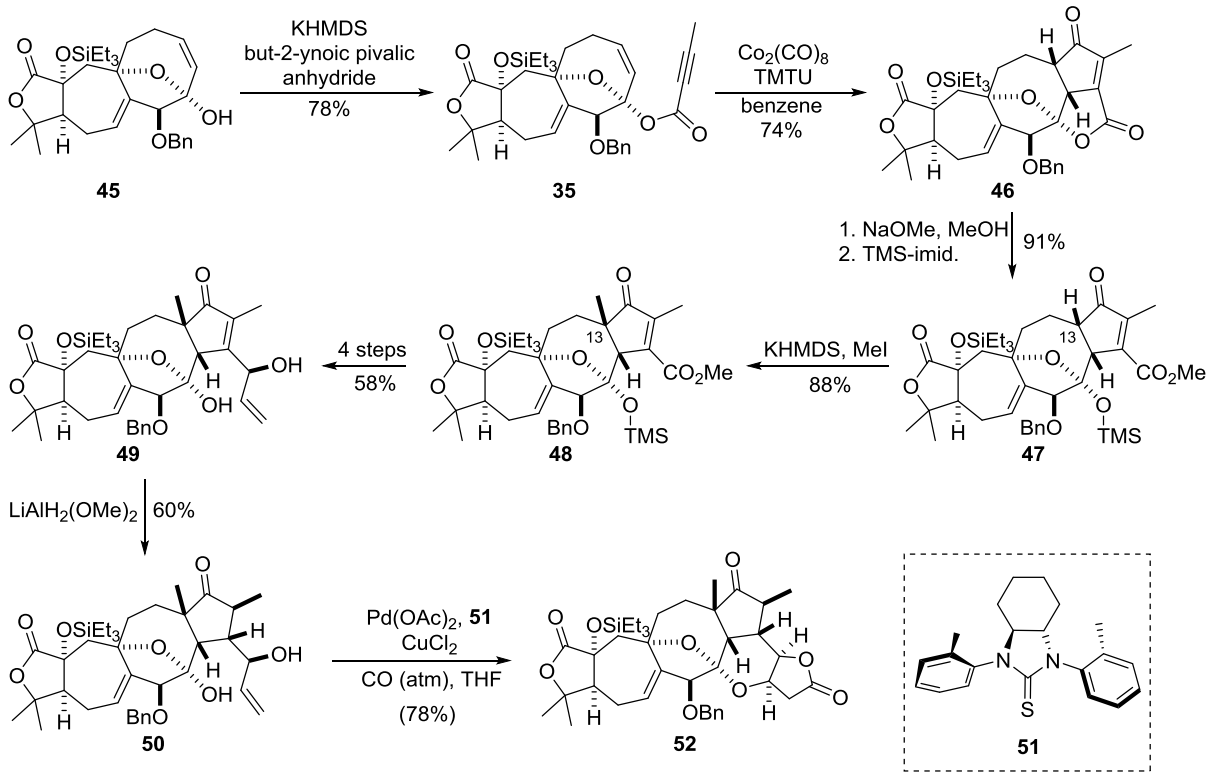
disconnection at the C13-C14 would lead to terminal diene **36**, from which the DE core could be constructed by a ring-closing metathesis reaction (RCM). The E ring in tricycle **36** could be installed by a cross-coupling reaction from vinyl bromide **37** to form the C8-C16 bond. The 6,8-bicycle **37** could be obtained from cyclohexene **38**, which could be synthesised *via* a Diels-Alder reaction from simple starting materials: diene **39** and dienophile **40**.

Yang and co-workers embarked on the forward synthesis (Scheme 1-4) with an intermolecular Diels-Alder reaction between diene **39** and dienophile **40,** catalysed by diethylaluminium chloride, to afford cyclohexene **38** as a single diastereomer in 65% yield.[23] Addition of methyl Grignard reagent to ketoester **38** and *in situ* transesterification gave lactone **41**. Oxidation of the α-position[31] and silyl protection of the resulting tertiary alcohol afforded intermediate **42**. Cyclopropanation[32,33] of alkene **42** and subsequent treatment with silver perchlorate[34] furnished vinyl bromide **37** in 82% yield over two steps. A palladium-catalysed coupling of vinyl bromide **37** with silane **43**[35] afforded ketoester **44** in an excellent 85% yield. This could be converted in four steps[36–38] to diene **36** (a 1:1 mixture of diastereomers at C15), the precursor for the ring-closing metathesis reaction to form the 8-membered ring. Utilising Grubbs II catalyst and magnesium bromide, which mediates an *in situ* hemiketal epimerisation,[39,40] **45** was obtained as a single diastereomer in 65% yield.



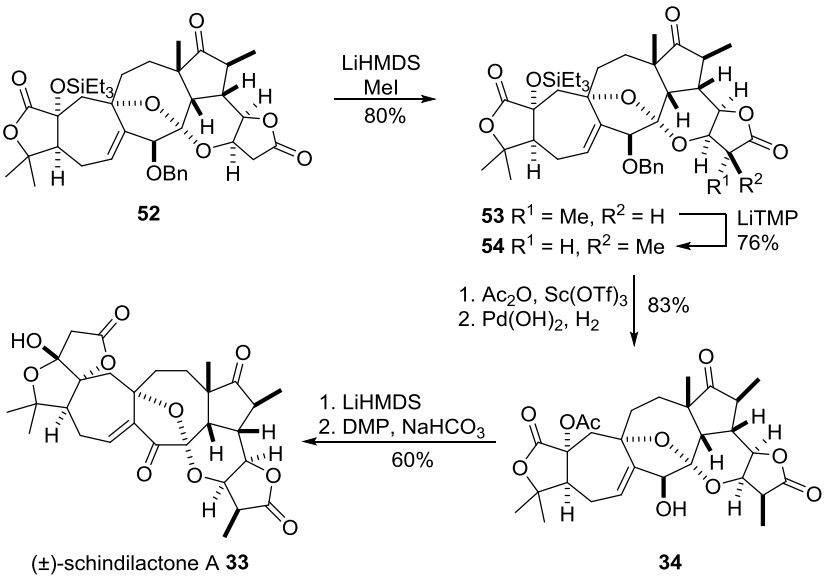
Scheme 1-4 Construction of the BC rings **45** of schindilactone A (Yang *et al.*, 2011)[25–28]

The next challenge was to construct the FGH ring system (Scheme 1-5). Based on precedent from Moyano *et al.* for the construction of *cis*-fused bicyclo[6.3.0]undecan-1-one through PKR,[41] Yang and co-workers planned to use a thiourea / cobalt-catalysed PKR[42] to form *cis*-fused, oxa-bridged bicyclo[6.3.0]undecan-2-one **46**. They started with the introduction of the yne ester moiety to alcohol **45** using but-2-ynoic pivalic anhydride to give enyne **35**. Subjecting enyne **35** to the optimised PKR conditions afforded the hexacyclic product **46** in 74% yield. Tranesterification and protection of the resulting alcohol gave intermediate **47**, which was selectively methylated at C13 to furnish compound **48** as a single diastereomer in 88% yield. Further transformations stereoselectively installed the allylic alcohol side chain observed in **49**. Hydroxyl-directed conjugate reduction of enone **49** with $LiAlH_2(OMe)_2$ then afforded ketone **50** in 60% yield.[24] Finally, a thiourea / palladium-catalysed carbonylative annulation reaction, which Yang and co-workers had previously developed in the synthesis of the right-hand side of micrandilactone A,[16] stereoselectively installed the GH rings to afford BCDEFGH ring system **52** in an excellent 78% yield.



Scheme 1-5 Synthesis of the BCDEFGH ring system **52** of schindilactone A (Yang *et al.*, 2011)[25–28]

Scheme 1-6 shows the route Yang and co-workers took to complete the synthesis of schindilactone A. Lactone **52** was selectively methylated[43] to give **53**, which was subsequently isomerised with LiTMP[44] to give the desired stereochemistry at C25 in compound **54**. In accordance with the retrosynthetic proposal, the final ring was to be generated by a Dieckmann-type condensation.[45,46] To accomplish this, the silyl protecting group in **54** was directly exchanged for an acetate group;[47,48] subsequent deprotection of the benzyl ether afforded acetate **34**. Treatment of acetate **34** with LiHMDS triggered the intramolecular Dieckmann-type condensation to form the A ring, and the D ring alcohol in the product was directly oxidised to give (±)-schindilactone A **33** in 60% yield over the last two steps.

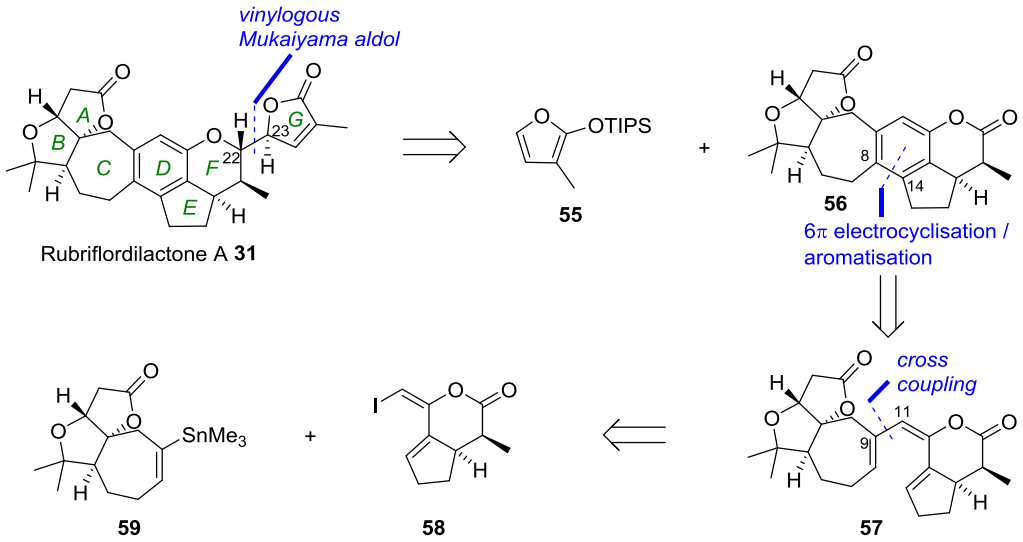


Scheme 1-6 Completion of the synthesis of (±)-schindilactone A (Yang *et al.*, 2011)[25–28]

In summary, the synthesis of (±)-schindilactone A consisted of 29 steps in its longest linear sequence with an overall yield of 0.2%, and represented the first total synthesis of a schinortriterpenoid.

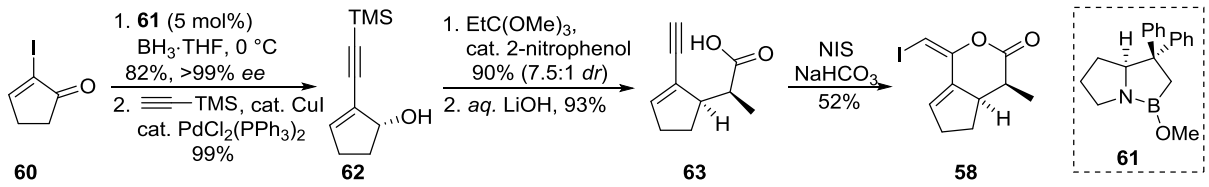
1.2.2. Total synthesis of rubriflordilactone A (Li *et al.*, 2014)[29]

The first total synthesis of rubriflordilactone A **31** was achieved by Li and co-workers in 2014. Their retrosynthesis started with a disconnection at the C22-C23 bond to ABCDEF ring system **56**; a vinylogous Mukaiyama aldol reaction of **56** with furan derivative **55** would install the G ring to form **31** (Scheme 1-7). The D ring in pentacycle **56** could be generated by a sequence of 6π-electrocyclisation and aromatisation from triene **57**. Further disconnection of triene **57** would lead to the EF fragment **58** and the ABC ring fragment **59**; the C9-C11 bond could be formed by a cross-coupling reaction.



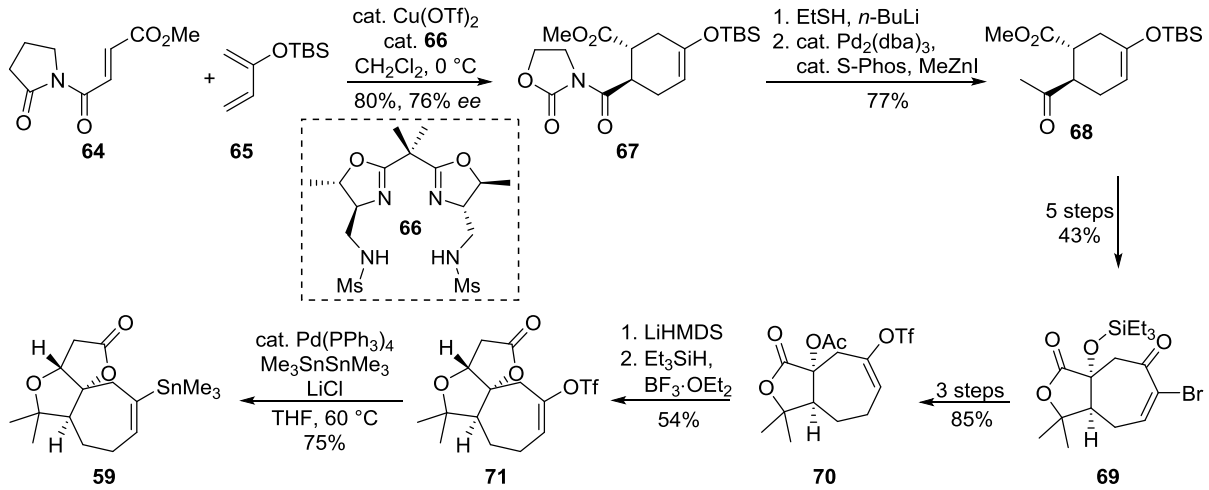
Scheme 1-7 Key disconnections to rubriflordilactone A (Li *et al.*, 2014)[29]

The forward synthesis began with the preparation of the EF ring fragment **58** (Scheme 1-8). 2-Iodo-2-cyclopentenone **60** was stereoselectively reduced using a Corey-Bakshi-Shibata protocol with oxazaborolidine **61**;[49] the resulting alcohol underwent Sonogashira coupling with TMS-acetylene to afford alkyne **62**.[50] A Johnson-Claisen rearrangement[51] of this alcohol **62**, followed by hydrolysis of the resulting methyl ester and deprotection of the TMS alkyne afforded acid **63** in good yields and diastereoselectivity. Finally, stereospecific iodolactonisation of acid **63** with NIS[52] gave the EF ring iodide coupling partner **58**.



Scheme 1-8 Synthesis of the EF ring fragment **58** of rubriflordilactone A (Li *et al.*, 2014)[29]

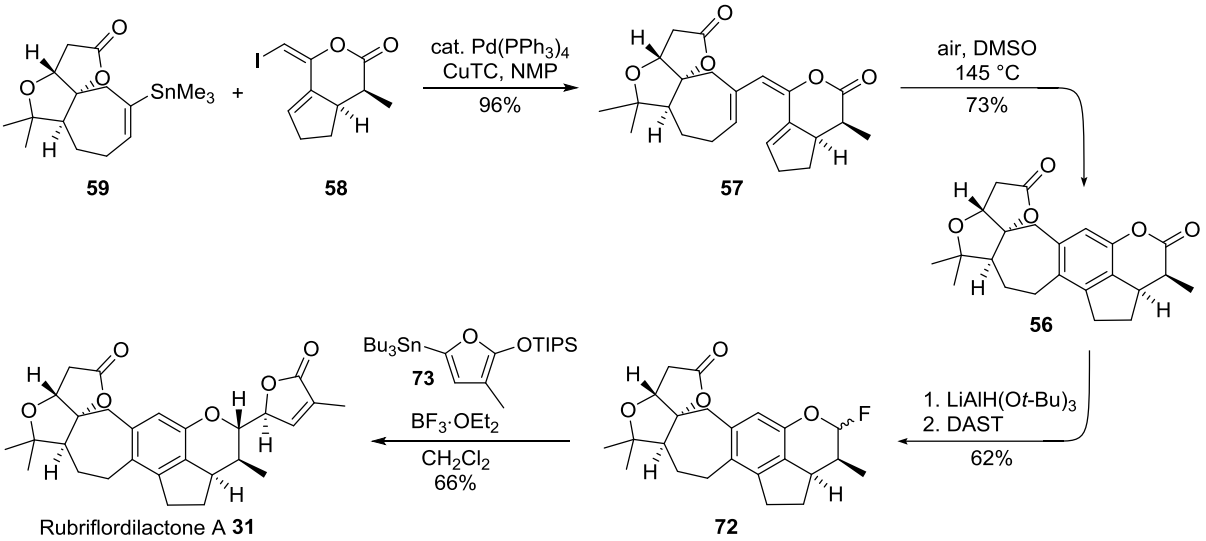
The synthesis of ABC fragment **59** would take advantage of Yang and co-workers' synthesis of the racemic BC ring system towards (±)-schindilactone A.[25–28] To prepare optically active **67**, Li *et al.* utilised a copper-catalysed asymmetric Diels-Alder reaction developed by Ishihara and co-workers (Scheme 1-9);[53,54] the cycloaddition of dienophile **64** and diene **65** afforded cyclohexene **67** in 80% yield and 76% *ee*. The oxazolidinone moiety in **67** was transformed into ketone **68**, which was then subjected to the five-step protocol developed by Yang *et al.* to afford BC ring bromoene **69**;[25–28] this product could be recrystallised to obtain enantiopurity of >99% *ee*. Intermediate **69** was converted to acetate **70**, which participated in an intramolecular Dieckmann condensation[25–28] and subsequent cationic deoxygenation[55,56] to form the A ring in ABC ring fragment **71**. Stannylation of **71** afforded the AB ring stannane coupling partner **59**.[57]



Scheme 1-9 Synthesis of the ABC ring fragment **59** of rubriflordilactone A (Li *et al.*, 2014)[29]

With both coupling partners iodide **58** and stannane **59** in hand, a late stage Stille-Migita reaction with Pd(0) / CuTC catalytic system[58–61] furnished triene **57** in an excellent 96% yield (Scheme 1-10). A one-pot thermal 6π-electrocyclisation and aromatisation process then

afforded a 73% yield of ABCDEF ring system **56**. The F ring lactone in **56** was selectively reduced to its corresponding lactol,[62,63] then treated with DAST to obtain fluoride **72**.[64] Li and co-workers attempted to attach the G ring butenolide with siloxyfuran **55**. However, they were unsuccessful and eventually resorted to using stannane **73**[65] in a C-glycosylation-type reaction[66] to afford rubriflordilactone A **31** in 66% yield.



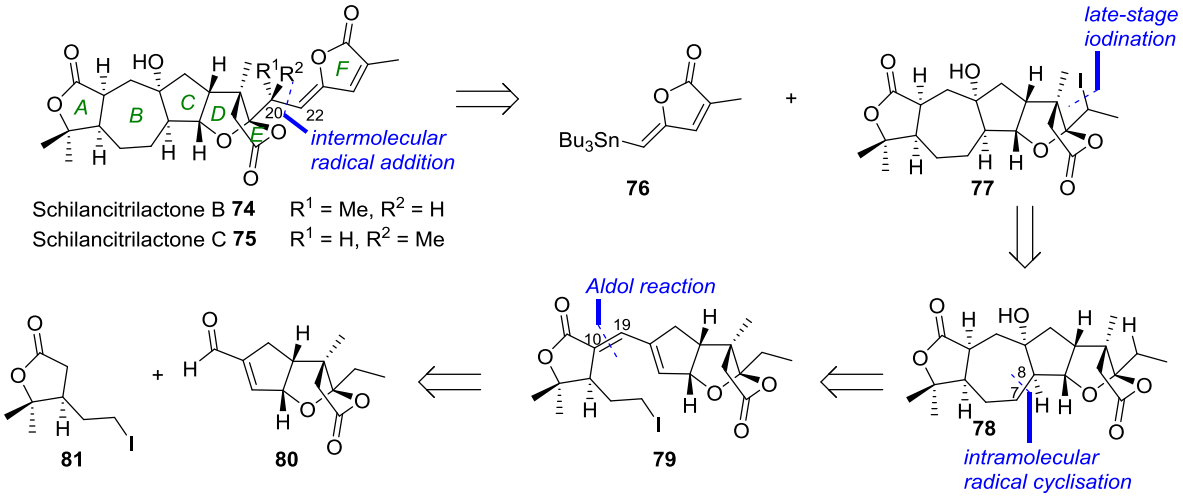
Scheme 1-10 Completion of rubriflordilactone A (Li *et al.*, 2014)[29]

In summary, the first total synthesis of rubriflordilactone A was achieved with 18 steps in its longest linear sequence from known compound **64** in 2.1% overall yield, with a one-pot 6π-electrocyclisation / oxidative aromatisation as the key step of the synthesis.

1.2.3. Total syntheses of schilancitrilactones B and C (Tang *et al.*, 2014)[30]

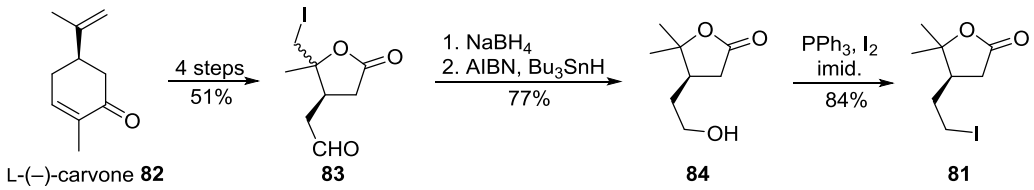
Most recently in 2015, Tang and co-workers completed the first total syntheses of schilancitrilactones B **74** and C **75**. Their retrosynthetic analysis began with a disconnection at the C20-C22 bond (Scheme 1-11); they hypothesised that both schilancitrilactones could be accessed by a radical addition reaction between the ABCDE ring alkyl iodide **77** and the F ring vinyl stannane **76**. The alkyl iodide **77** could be generated by a late-stage iodination at C20 from compound **78**. In turn, ring B in pentacycle **78** could be formed by intramolecular radical cyclisation reaction at C7-C8 from iodide **79**. A further disconnection at the C10-C19

bond would disassemble iodide **79** into the A ring lactone **81** and the CDE ring aldehyde **80**, which could be put together by an aldol reaction.



Scheme 1-11 Key disconnections to schilancitrilactones B and C (Tang *et al.*, 2015)[30]

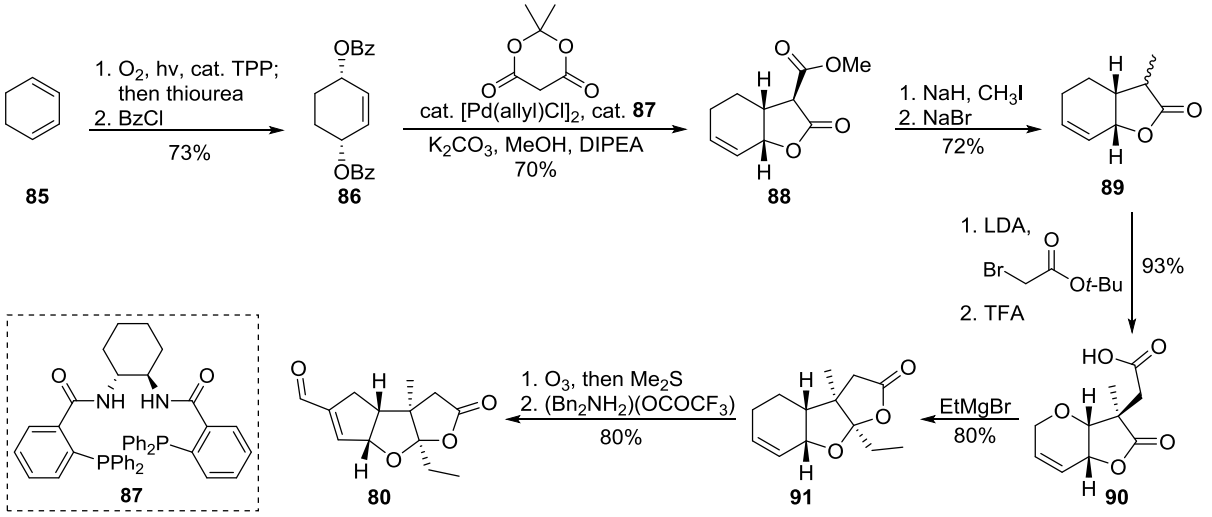
Tang and co-workers began their synthesis with the construction of the A ring fragment **81** (Scheme 1-12). L-carvone **82** was transformed to aldehyde **83** using a four step procedure reported by Fukuyama *et al*. with an overall yield of 51%.[67] This aldehyde was reduced and deiodinated to give alcohol **84**, which underwent nucleophilic substitution[68] to afford A ring lactone **81**.



Scheme 1-12 Synthesis of A ring iodide **81** (Tang *et al.*, 2015)[30]

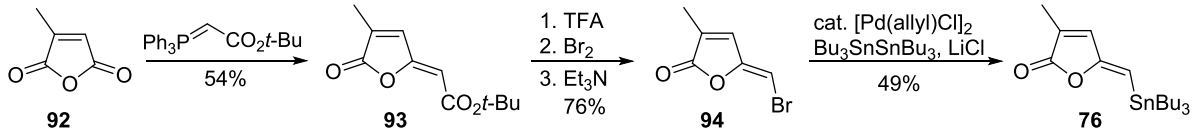
Synthesis of the CDE ring fragment **80** started with 1,3-cyclohexadiene **85** (Scheme 1-13). A three-step process developed by Trost *et al.* converted **85** into bicyclic lactone **88** in 51% overall yield.[69,70] This included an asymmetric palladium-catalysed allylic alkylation from cyclohexene **86** to bicycle **88**. Methylation of lactone **88**, followed by subsequent decarboxylation gave a 1:1 epimeric mixture of lactone **89**. Alkylation of this lactone **89** and ester hydrolysis furnished acid **90** as a single diastereomer in 93% yield. Addition of ethyl

magnesium bromide to lactone **90** followed by acidic workup afforded tricycle **91**, with the ethyl group selectively installed.[71] Finally, ozonolysis of the cyclohexene ring an intramolecular aldol condensation on the resulting aldehyde gave the CDE ring aldehyde **80** in 80% yield.[72,73]



Scheme 1-13 Synthesis of CDE ring aldehyde **80** (Tang *et al.*, 2015)[30]

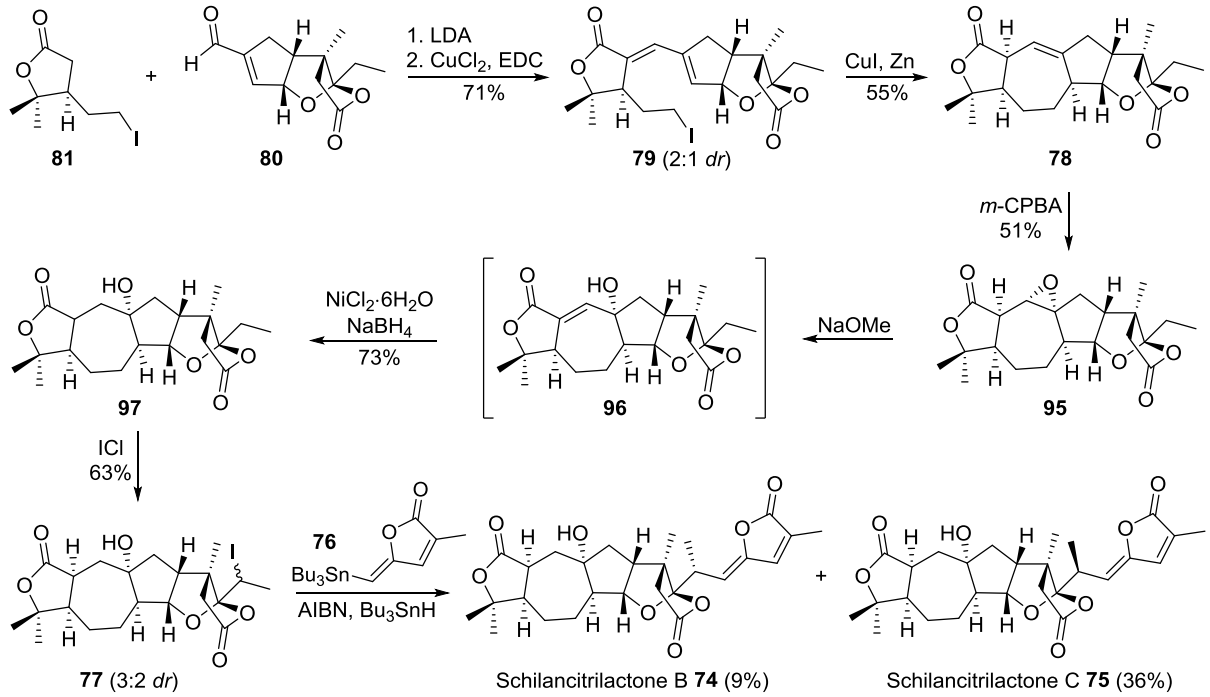
Next, synthesis of the F ring stannane **76** commenced with a Wittig reaction on citraconic anhydride **92** (Scheme 1-14). The reaction to give diene **93**, along with the next three steps have been described by Lönn-Stensrud *et al.*,[74] giving α,β,γ-unsaturated lactone **94** in an overall yield of 41% over four steps. This bromide **94** was then stannylated to obtain the F ring vinyl stannane **76** in a modest 49% yield, likely due to its instability to purification.[75]



Scheme 1-14 Synthesis of F ring stannane **76** (Tang *et al.*, 2015)[30]

With the key intermediates in hand, Tang and co-workers linked the A ring lactone **81** to the CDE ring aldehyde **80** (Scheme 1-15). Enolisation of lactone **81** and direct reaction with aldehyde **80** afforded an aldol adduct; dehydration of the newly formed alcohol furnished diene lactone **79** in 71% yield as a 2:1 mixture of diasteromers.[76,77] This iodide **79** was subjected to an intramolecular radical cyclisation utilising the method pioneered by Luche

and co-workers for conjugate additions[78] to close the 7-membered B ring, affording ABCDE ring system **78** in 55% yield. The alkene **78** was epoxidised to give epoxide **95**, which then underwent an E1cb reaction with NaOMe to give intermediate **96**, and then an *in situ* reduction with $NiCl_2$ / $NaBH_4$ to afford the ring opening product alcohol **97**.[79] Finally, treatment of pentacycle **97** with ICl generated iodide **77** in a 1.5:1 mixture of diastereomers at C20.[80,81] Reaction of iodide **77** with vinyl stannane **76** in the presence of AIBN and Bu_3SnH afforded schilancitrilactones B **74** (9%) and C **75** (36%) in an overall yield of 45%.



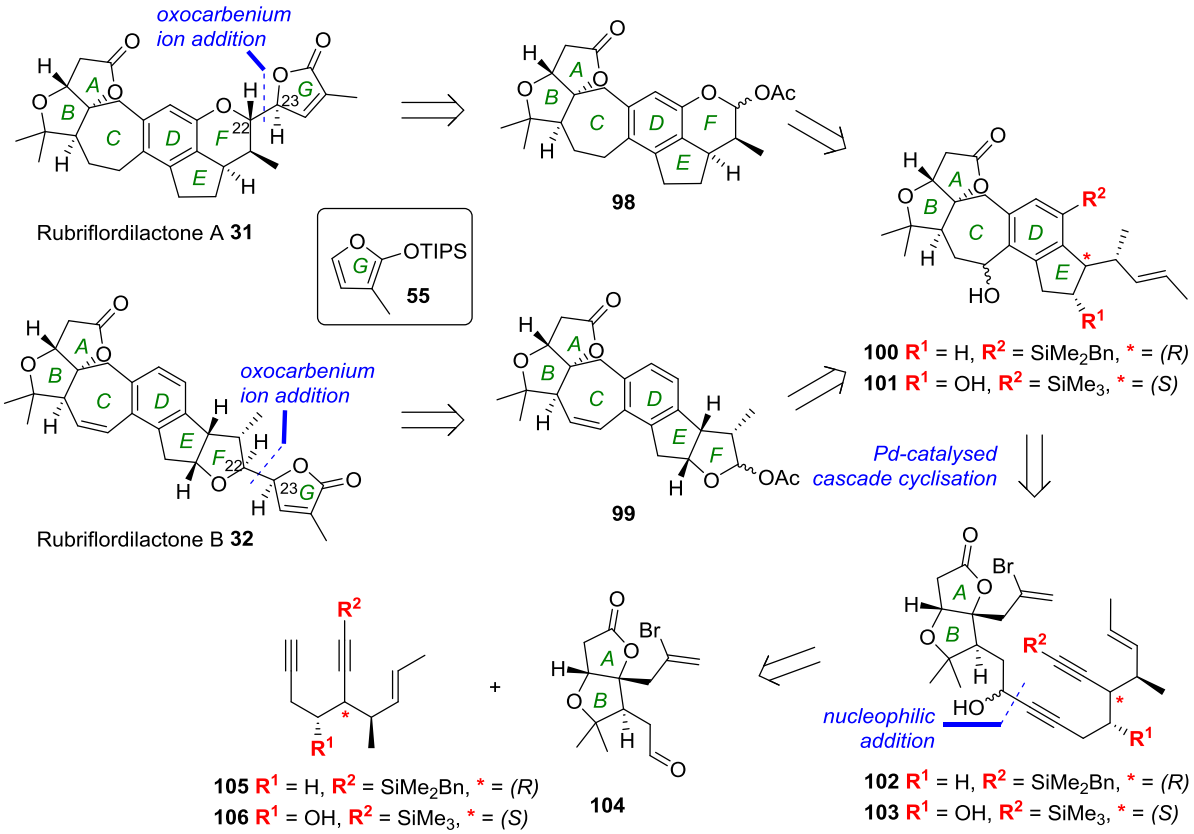
Scheme 1-15 Completion of schilancitrilactones A and B (Tang *et al.*, 2015)[30]

In summary, the first total synthesis of schilancitrilactones B and C has been achieved in 17 steps (longest linear sequence) with an overall combined yield of 1.0% from commercially available materials, with an intramolecular radical cyclisation and an intermolecular radical addition forming the key steps.

1.3. Our Approach towards Rubriflordilactones A and B

1.3.1. Proposed retrosynthesis

Our retrosynthetic strategy for both rubriflordilactones A **31** and B **32** began with a disconnection at the C22-C23 bond linking the G ring butenolide to the F ring (Scheme 1-16), similar to that proposed by Li and co-workers.[29] We envisaged that this bond could be formed by addition of G ring siloxyfuran analog **55** to the oxocarbenium ions formed by activation of the ABCDEF ring precursors **98** and **99**, for rubriflordilactone A and B respectively. These synthons would arise from the corresponding ABCDE ring pentacycles **100** and **101** through functional group interconversions and oxidative cleavage of the crotyl side chain to form the F ring.

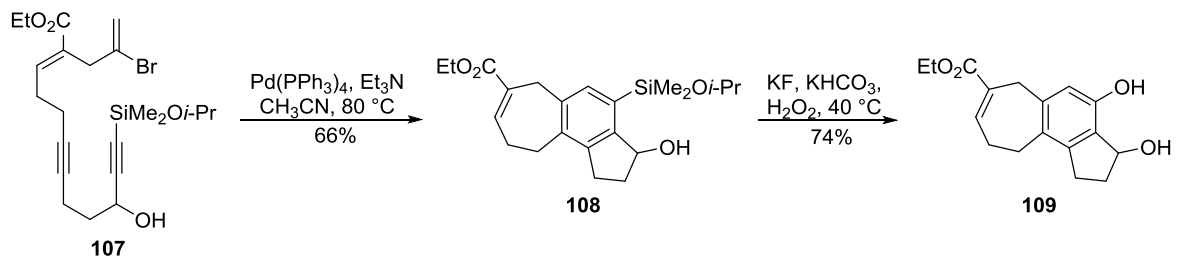


Scheme 1-16 Rubriflordilactones A and B retrosynthetic analysis

The core ABCDE ring systems could be formed in a single step under palladium catalysis from bromoenediynes **102** and **103** respectively. Our convergent strategy would enable us to synthesise both bromoenediynes from the same AB ring aldehyde **104** by addition of the appropriate CDE diyne fragment **105** or **106**.

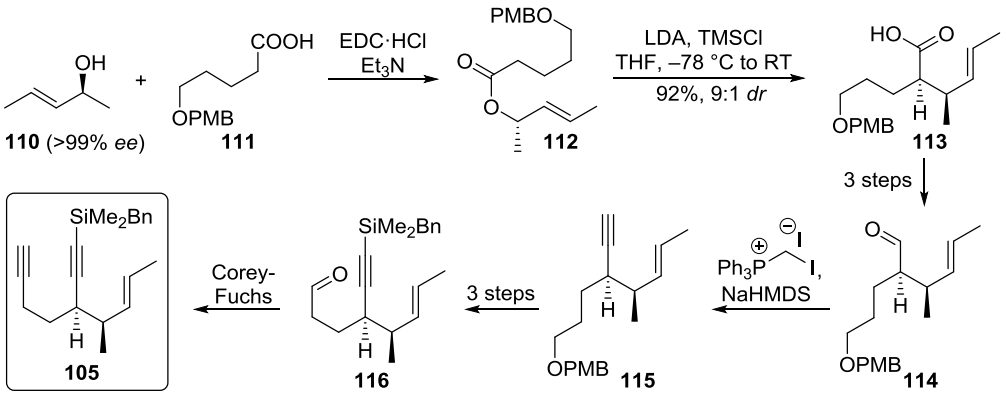
1.3.2. Previous work within the Anderson group

Rubriflordilactones A and B have been of interest to the Anderson group from when their structures were elucidated. Our interest lies in using a palladium-catalysed cascade cyclisation[82–84] to form the CDE ring system in a single step from an acyclic precursor. Although Negishi[85] and de Meijere[86–88] have both published elegant research on intramolecular cyclisations of bromoenediynes;[89] there is, to our knowledge, little precedent for cyclisation of substrates containing a 7-membered tether, or in application to natural product synthesis.[87,90] This research led the group to develop the first synthetic entry towards the CDE core of rubriflordilactone A in 2008 (Scheme 1-17).[91] The CDE ring system **108** was assembled in 66% yield in a single step from acyclic bromoenediyne **107** *via* a palladium-catalysed cascade cyclisation, after which a Tamao-Kumada oxidation[92] of the aromatic isopropoxydimethylarylsilane **108** revealed the free phenol **109**. More recent work in the group on the oxidation of aromatic silanes by Bracegirdle[93] and Rayment[94] has given us greater insight into the oxidation step. Further refinements to this palladium-catalysed cyclisation approach, and an alternative approach towards the CDE core, are reported in Chapter 2.



Scheme 1-17 Cyclisation to the CDE core of rubriflordilactone A (Anderson *et al.*, 2008)[91]

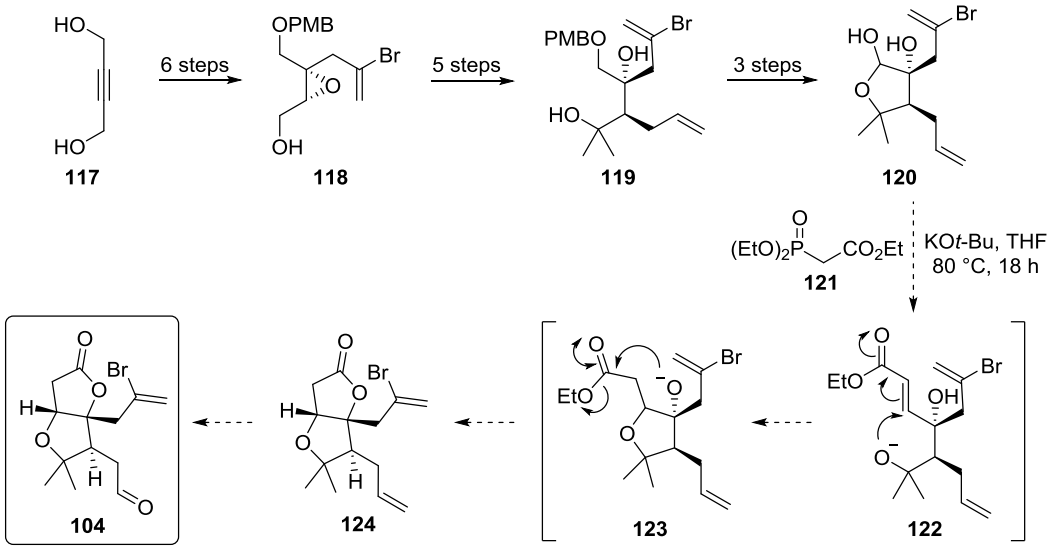
The success of the cascade cyclisation step prompted the group to begin work on the total synthesis of rubriflordilactone A. This culminated in an (unoptimised) synthesis of CDE diyne fragment **105** by Cordonnier, reported in her DPhil thesis in 2011, summarised in Scheme 1-18.[95] EDC-promoted coupling of enantioenriched alcohol **110** with acid **111** afforded ester **112**, which through an Ireland-Claisen rearrangement[96] furnished acid **113**. Acid **113** was reduced to aldehyde **114**, on which a Stork-Zhao olefination[97] / elimination procedure gave alkyne **115**. PMB ether **115** was transformed into aldehyde **116**, which then participated in a Corey-Fuchs alkynylation to afford CDE diyne fragment **105**. A refined synthetic route to diyne **105** is reported in Chapter 3.



Scheme 1-18 Current route to CDE diyne fragment **105**

The Anderson group also embarked on the synthesis of AB ring aldehyde fragment **104**. Scheme 1-19 summarises the most advanced route in the group at the outset of the work in this thesis, developed by Göckel and Puttock.[98] Butyn-1,4-diol **117** was converted in six steps to epoxide **118**, with key steps including a Stille coupling and a Sharpless asymmetric epoxidation. Epoxide **118** was then transformed in five steps to key intermediate tertiary alcohol **119**. From here, deprotection and oxidation of the PMB-protected alcohol **119** afforded lactol **120**. Based on previous studies by Yang *et al.* on the synthesis of the ABC ring unit of micrandilactone A,[23] it was expected that treatment of lactol **120** with HWE reagent **121** would afford AB ring alkene **124** *via* a cascade involving an oxa-Michael addition of the alkoxide to the enoate in **122**, followed by a lactonisation of **123**. Alkene **124** could then undergo oxidative cleavage to form desired AB ring aldehyde **104**. Unfortunately, this

effort was futile as lactol **120** could not be olefinated in productive yields. Work on an alternative route from tertiary alcohol **119** to AB ring aldehyde **104** is reported in Chapter 4.



Scheme 1-19 Current route towards AB ring aldehyde fragment **104**

1.4. Thesis Summary

Following the establishment of a general method for the synthesis of 7,6,5-rings by a palladium-catalysed cascade cyclisation of bromoenediynes,[91] this approach towards the CDE cores of rubriflordilactones A and B was further developed to increase its applicability to total synthesis. During the course of this thesis, Baars also investigated an alternative route to the CDE core of the rubriflordilactones *via* cobalt-catalysed triyne cyclotrimerisation,[99] which was instrumental in kick-starting our second route towards rubriflordilactone A. These studies have since been published[100] and are reported in Chapter 2.

In Chapter 3, a refinement of the established route[95] towards the CDE diyne fragment **105** of rubriflordilactone A is described. The successful application of the two transition metal-catalysed cyclisation approaches to this diyne, and of further transformations to form the CDEF core of rubriflordilactone A are also reported.

The enantioselective synthesis of the AB ring aldehyde fragment **104**, based on the partially developed route by Gockel and Puttock,[98] has been completed and has since been published.[101] In addition, the synthesis of a modified AB ring aldehyde which is compatible with the new cyclotrimerisation strategy, has also been accomplished and reported.[102] These syntheses are described in Chapter 4.

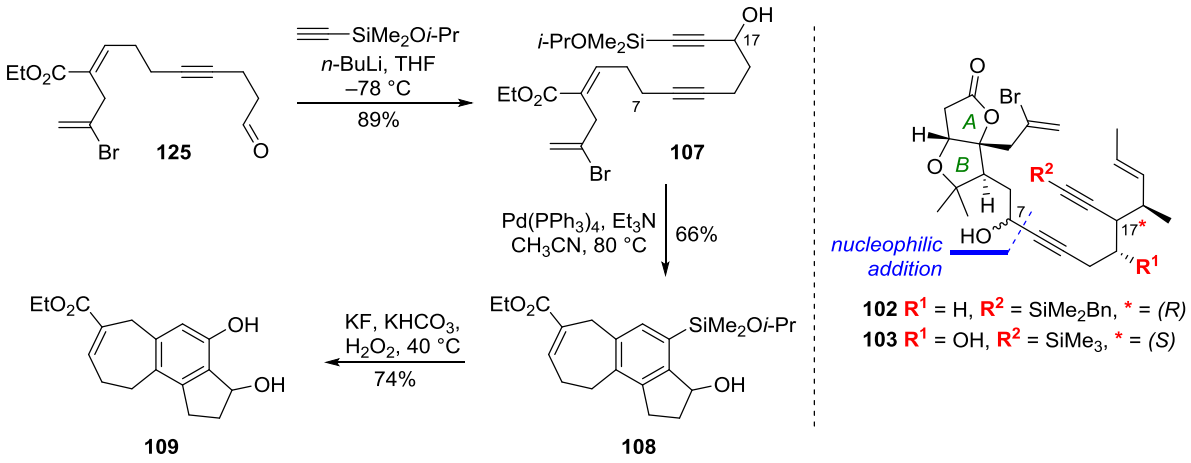
The remaining transformation to be investigated, the attachment of the G ring to the CDEF ring system is explored in Chapter 5. This chapter also describes an interesting study of the transformation of a lactol into a chloropyran, with some detail of the mechanism revealed using NMR spectroscopic techniques.

Finally, and undoubtedly the highlight of this thesis, two total syntheses of rubriflordilactone A have been concluded. Details of the syntheses, which were recently published,[102] and a comparison of our synthetic rubriflordilactone A with the natural product are described in Chapter 6.

2. The CDE Rings[100]

2.1. Retrosynthesis

In 2008, the group had developed the first synthetic entry towards the CDE core of rubriflordilactone A, with the 7,6,5-ring system **108** formed in a single step from acyclic precursor **107** in 66% yield (Scheme 2-1).[91] However, we felt that there was scope for improvement in this methodology. Firstly, the route to the cyclisation precursor differed from our retrosynthetic strategy towards the natural products, with the disconnection at C17 instead of C7 (rubriflordilactone A numbering) to aldehyde **125** and ethynyl(isopropoxy)dimethylsilane; this resulted in the different positioning of the hydroxyl group in bromoenediyne **107** from the natural product precursors **102** and **103**, which we later discovered had a huge impact on reactivity in the cyclisation step (*see Section 2.2.3*).

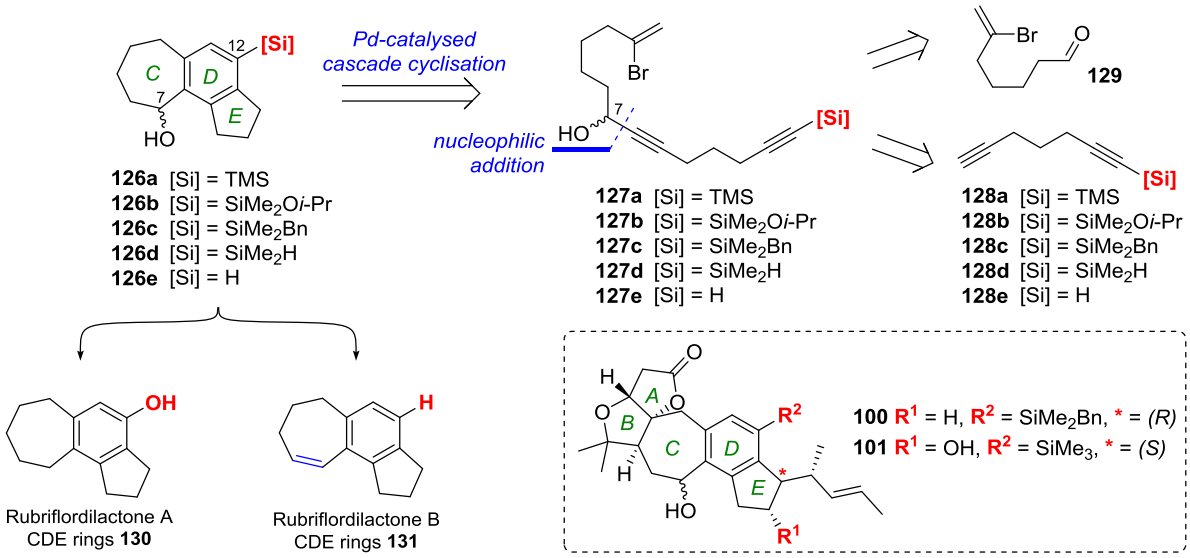


Scheme 2-1 Cyclisation to the CDE core of rubriflordilactone A **109** (Anderson *et al.*, 2008)[91]

Secondly, work by Cordonnier[95] has shown that the isopropoxydimethylsilane group was not amenable to several steps in the synthesis of the CDE diyne fragment of rubriflordilactone A due to its instability toward acidic or mild basic conditions; thus, it was decided to test its replacement with the more stable, but also oxidisable benzyldimethylsilane group.[103,104] More recent work in the group on the oxidation of aromatic silanes by Bracegirdle[93] and Rayment[94]

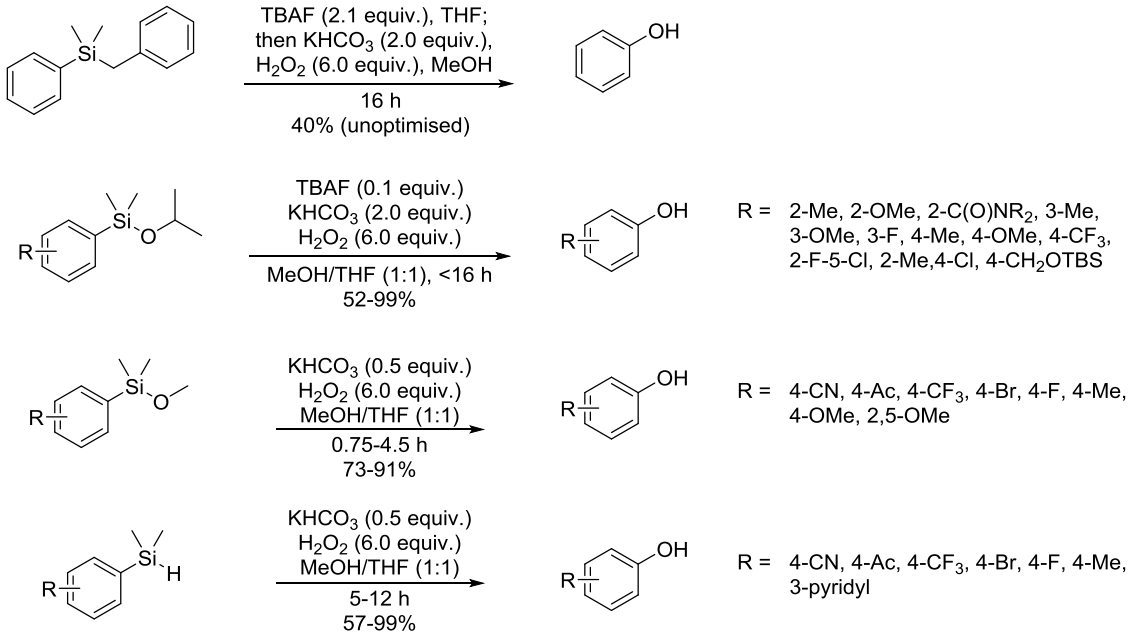
has also given us greater insight into oxidisable silicon groups, and we therefore aimed to investigate the compatibility of the benzyldimethylsilane group and other silicon groups in the cascade cyclisation protocol. Finally, we planned to study the derivatisation of the cyclised products towards the CDE cores of rubriflordilactones A and B so that these sequences could be applied to the total synthesis of the natural products.

To this end, we designed model systems **126a-e** (Scheme 2-2) which would have the same disconnections as the ones envisaged for rubriflordilactones A and B (*see Section 1.3.1*). The tricyclic CDE ring models **126a-e** are abridged versions of the pentacyclic ABCDE ring systems **100** and **101**, which would be key intermediates in the synthesis of rubriflordilactones A and B respectively. Although they lack the AB ring substituent at C5-C10, and the C17 substituent which would form the F ring (along with the C16 substituent for rubriflordilactone B), model systems **126a-e** have all the functionalities required to investigate the cascade cyclisation. The tricycles **126a-e** could be generated in a single step from the bromoenediyne precursors **127a-e** *via* a palladium-catalysed cascade cyclisation. These bromoenediynes **127a-e** in turn could be synthesised by a nucleophilic addition of diynes **128a-e** to bromoenal **129**. Diynes **128a-d** and bromoenal **129** could easily be synthesised from simple starting materials; the different silyl groups installed on diynes **128a-e** would enable investigation of the post-cyclisation modifications towards the CDE cores **130** and **131**, of rubriflordilactones A and B respectively.



Scheme 2-2 Retrosynthesis of the CDE ring system

The choice of silyl groups for diyne **128a-e** depended on the desired C12 substituent (rubriflordilactone A numbering) of the CDE rings. For rubriflordilactone A which bears a D ring phenol, we envisaged the installation of a suitably functionalised silane which could act as a "masked" phenol, to be subsequently revealed by an aromatic Tamao-Kumada oxidation.[92,105] Previous work in the group has shown the rate of arylsilane oxidation to be determined by the electron density on the silicon center, with ease of oxidation decreasing from $SiMe_2OR$ > $SiMe_2H$ > $SiMe_2Bn$ (Scheme 2-3).[93–95] Conditions catalytic in fluoride,[93] and even fluoride-free conditions, have been developed for alkoxyarylsilanes and hydroarylsilanes.[94] Hydroarylsilane **126d** is a particularly attractive target, as the corresponding alkynylhydrosilane **127d** is more stable than alkynylalkoxysilanes (e.g. **127b**), yet it provides a reactive oxidisable group.[94]



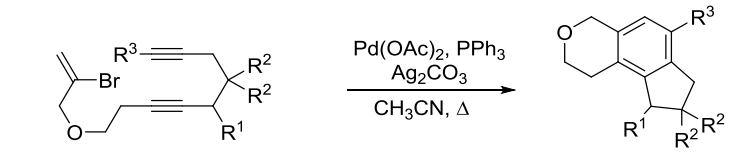
Scheme 2-3 Oxidation of arylsilanes to phenols (Anderson *et al.*, 2010, 2012 and Cordonnier, 2011)[95,93,94]

For rubriflordilactone B with no substituent at C12, unprotected bromoenediyne **127e** is the ideal substrate. However, work by de Meijere *et al.* showed that terminal bromoenediynes do not furnish the desired arenes in this reaction (*see Section 2.2.4*).[86] An alternative would be to install a simple alkylsilane (e.g. TMS, **127a**), which could conveniently undergo desilylation.[106]

2.2. Palladium-Catalysed Cascade Cyclisation

2.2.1. Methodology Background

One of the earliest examples of the use of bromoenediyne cascade cyclisations for the construction of polycyclic molecules was published by de Meijere and co-workers in 1991 (Scheme 2-4),[107] in which palladium-catalysed cyclisation of bromoenediynes **132a-b** afforded the aromatic tricycles **133a-b** in moderate yield (47-62%).

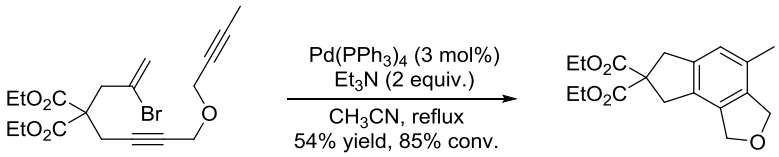


132a $R^1 = R^2 = H$, $R^3 = Me$
132b $R^1 = OBn$, $R^2 = Me$, $R^3 = CO_2Me$

133a: 62%
133b: 47%

Scheme 2-4 Cyclisation of bromoenediynes **132a-b** (de Meijere *et al.*, 1991)[107]

Similarly, Negishi reported the palladium-catalysed cascade cyclisation of bromoenediyne **134** to form 5,6,5-ring system **135** in 1992 (Scheme 2-5).[85]



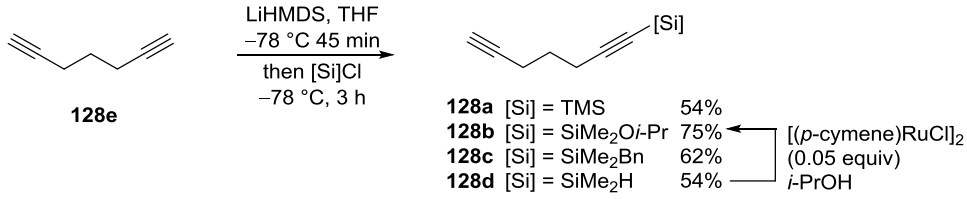
134 **135**

Scheme 2-5 Cyclisation of bromoenediyne **134** (Negishi *et al.*, 1992)[85]

Since then, many advances have been made,[87,88,86] including extensions to tricyclic aromatic azacycles,[108] chromans and isochromans,[109] chiral biphenyls,[110] strained aromatic polycycles[89], and dibenzopentafulvalenes.[111] Still, the palladium-catalysed intramolecular bromoenediyne cascade cyclisation had not been successfully applied in total synthesis.

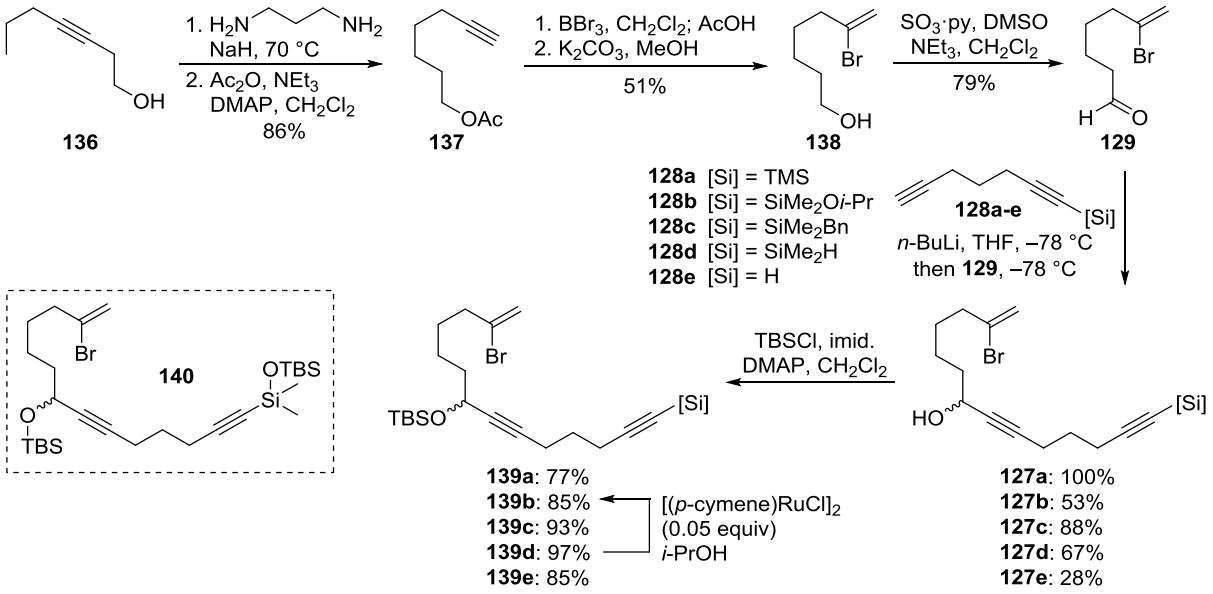
2.2.2. Synthesis of cyclisation precursors

The route began with the synthesis of the monoprotected diynes (Scheme 2-6). Trimethylsilyldiyne **128a**, benzyldimethylsilyldiyne **128c** and dimethylsilyldiyne **128d** were obtained by treatment of 1,6-heptadiyne **128e** with base and the appropriate chlorosilanes; the moderate yields (54-62%) could be explained by formation of the bissilylated diyne as a sideproduct. Isopropoxydimethylsilyldiyne **128b** was synthesised from hydrosilane **128d** by a ruthenium-catalysed dehydrogenative silyl ether formation.[112,113]



Scheme 2-6 Monosilylation of 1,6-heptadiyne **128e**

The synthesis of bromoenal **129** started from 3-heptyn-1-ol **136** (Scheme 2-7). An alkyne zipper reaction,[114] followed by protection of the alcohol afforded acetate **137** in 86% yield over two steps. Bromoboration[115] of terminal alkyne **137** and deprotection of the acetate then furnished bromoalkene **138** in 51% yield over two steps. A Parikh-Doering oxidation[116] of alcohol **138** gave a 79% yield of aldehyde **129**, a simplified analogue of the AB rings fragment **104**.



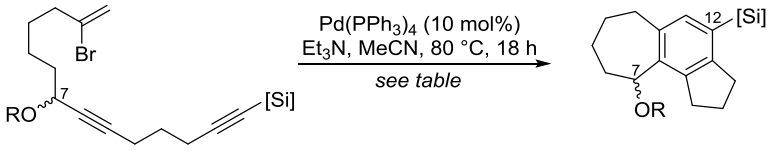
Scheme 2-7 Synthesis of bromoenediynes **139a-e**

Nucleophilic addition of a variety of lithiated silyldiynes **128a-d** and the unsubstituted diyne **128e** to aldehyde **129** gave their corresponding bromoenediynes **127a-e** in moderate to high yields (Scheme 2-7). The bromoenediynes bearing the trimethylsilane (**127a**) and benzyldimethylsilane (**127c**) groups were obtained in significantly better yields compared to their counterparts; the poor yield for unsubstituted bromoenediyne **127e** is likely to result from double coupling due to non-selective deprotonation. Finally, TBS protection of propargylic alcohols **127a-e** generated TBS ethers **139a-e** in good yields; with the exception of alcohol **127b**. Instead, TBS protection of isopropoxydimethylsilyldiynol **127b** surprisingly afforded disiloxane **140**, presumably due to the lability of the alkoxysilane. Gratifyingly, isopropoxydimethylsilane **139b** could be synthesised from hydrosilane **139d** by a ruthenium-catalysed dehydrogenative silyl ether formation.[112,113]

2.2.3. Cyclisation studies

With a range of bromoenediynes in hand, we investigated their palladium-catalysed cyclisation to tricyclic arylsilanes (Table 2-1). Unfortunately, propargylic alcohol **127a** decomposed under the reaction conditions (Entry 1, Table 2-1); combined with the good

result of its TBS-protected analogue **139a**, which gave tricycle **141a** in 62% yield (Entry 2, Table 2-1), this suggested that a free hydroxyl group at the C7 position (rubriflordilactone A numbering) was incompatible with the cyclisation conditions as previously reported.[86] Isopropoxysilane **139b** was cyclised in 41% yield to arylsilane **141b** (Entry 2, Table 2-1), while benzyldimethylsilane **139c** gave the best result, furnishing tricycle **141c** in an excellent 76% yield (Entry 4, Table 2-1). In contrast, hydrosilane **139d** decomposed under the reaction conditions (Entry 5, Table 2-1), possibly due to competitive oxidative addition into the Si-H bond. This result was unfortunate, since as mentioned above, previous studies in the group had shown that hydroarylsilanes could be most easily oxidised to phenols,[94] and until now this had been the preferred choice for direct access to the CDE ring system of rubriflordilactone A **130**. Likewise, terminal alkyne **139e** also did not survive the reaction conditions (Entry 6, Table 2-1), implying that a post-cyclisation desilylation modification would indeed be necessary to obtain the CDE ring system of rubriflordilactone B **131**.



127a (R = H)
139a-e (R = TBS)

126a (R = H)
141a-e (R = TBS)

Entry	Substrate	R	[Si]	Product	Yield / %
1	**127a**	H	TMS	-	dec.
2	**139a**	TBS	TMS	**141a**	62
3	**139b**	TBS	$SiMe_2O$*i*-Pr	**141b**	41
4	**139c**	TBS	$SiMe_2Bn$	**141c**	76
5	**139d**	TBS	$SiMe_2H$	-	dec.
6	**139e**	TBS	H	-	dec.

Reaction conditions: **Substrate** (30 mg, 1.0 equiv.) in MeCN (0.04 M) was degassed, then added to a flame-dried vial equipped with a stirrer bar and $Pd(PPh_3)_4$ (10 mol%), and degassed triethylamine (6.0 equiv.) was added; reaction mixture was stirred overnight under Ar atm at 80 °C.

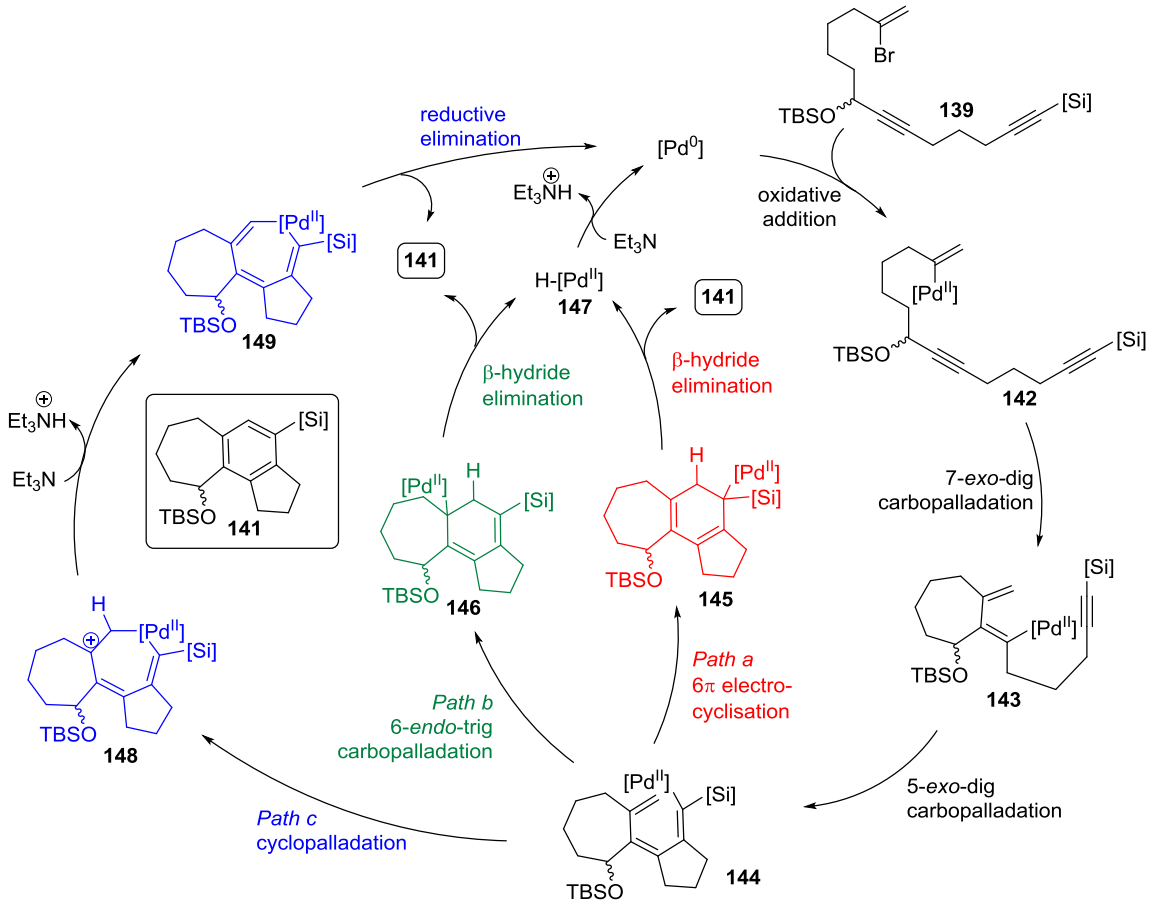
Table 2-1 Palladium-catalysed cyclisation of bromoenediynes to tricyclic aryl silanes

These results have revealed the scope of the palladium-catalysed cyclisation of bromoenediynes, especially the limitations of the alkyne substituent in **139a-e**. We remained

hopeful that the successfully cyclised arylsilanes **141a-c** could be converted into the CDE cores of the rubriflordilactones, which we will explore in Section 2.4.

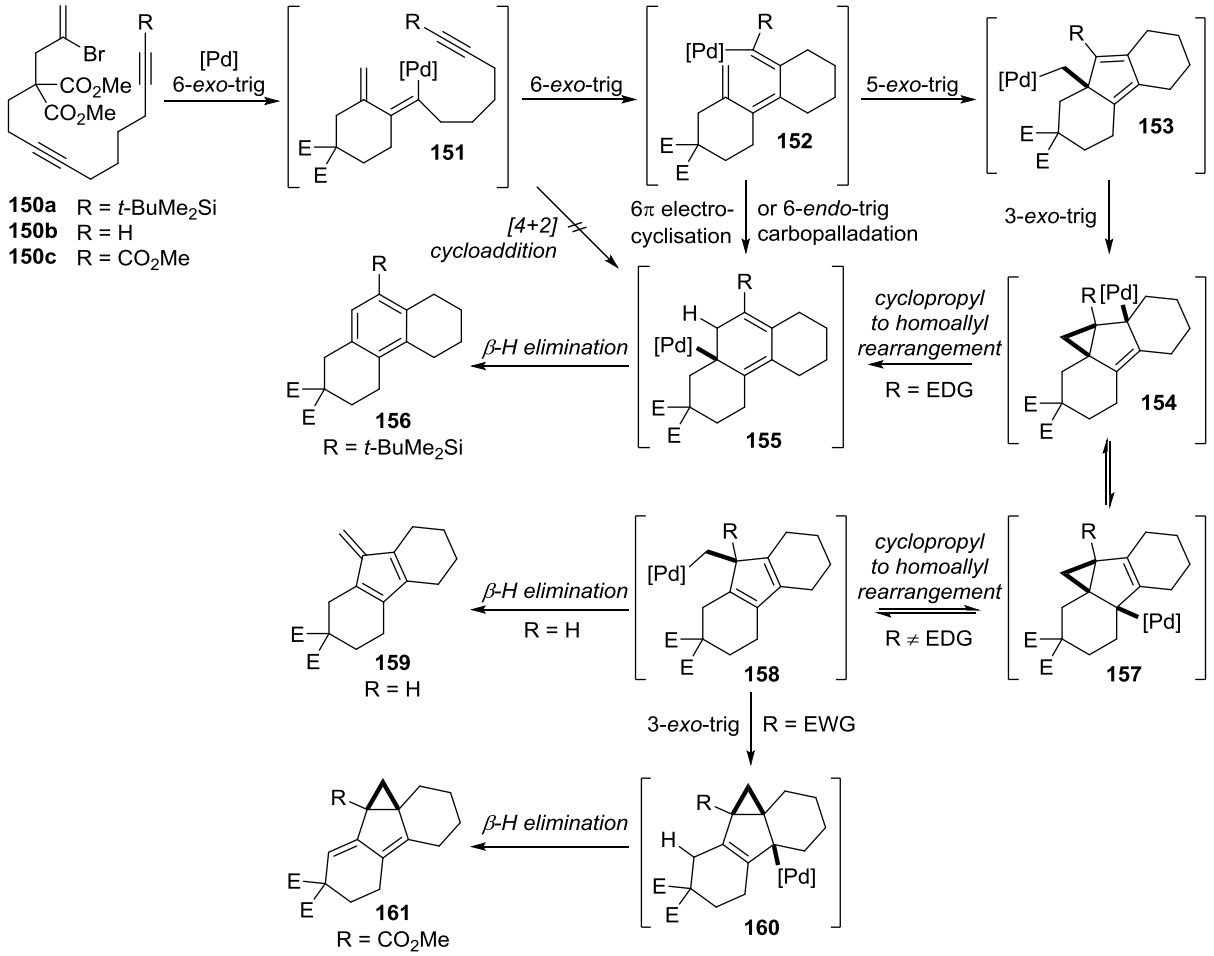
2.2.4. Mechanistic discussion

The proposed reaction mechanism (Scheme 2-8) of this palladium-catalysed cyclisation initiates with an oxidative addition of catalytically active palladium(0) species into the vinyl bromide **139**, formed by the dissociation of two triphenylphosphine ligands, to generate **142**.[86] An intramolecular 7-*exo*-dig *syn*-carbopalladation of **142** forms the 7-membered ring in dienyne **143**, after which a 5-*exo*-dig carbopalladation occurs to generate the 5-membered ring in triene-palladium complex **144**. Triene-palladium complex **144** could then form the product tricycle **141** and regenerate the palladium(0) active species by several routes. 6π-electrocyclisation (*Path a*) of triene-palladium complex **144** would generate palladated cyclohexadiene derivative **145**, while 6-*endo*-trig carbopalladation (*Path b*) would form a similar cyclohexadiene-palladium complex **146**. Both of these species undergo β-hydride elimination to furnish the product **141** and generate palladium-hydride species **147**, which is reduced by triethylamine to regenerate the palladium(0) active species. An alternative route involves cyclopalladation to form the 7-membered palladacycle **148**, which undergoes deprotonation to generate palladacycle **149**, and finally reductive elimination to afford the product (*Path c*).



Scheme 2-8 Mechanism for palladium-catalysed cascade cyclisation of bromoenediynes

However, work by de Mejiere and co-workers on the influence of tether length and alkyne substituent on the cyclisation outcome suggested that an alternative cyclisation mode is preferred when the peripheral rings are larger in size.[86–88] When 2-bromo-tetradec-1-ene-7,13-diynes **150a-e** were subjected to standard palladium-catalysis conditions, electron-rich alkynylsilane **150a** afforded 6,6,6-tricycle **156** in 79% yield, while terminal alkyne **150b** produced bisannelated fulvene **159** in 74% yield, and electron-deficient alkyne **150c** generated yet another product, tetracycle **161** in 54% yield. These results, along with the discovery by Negishi *et al.* that apparent 6-*endo*-trig carbopalladations actually occur as sequential 5- and 3-*exo*-trig carbopalladations with cyclopropylcarbinyl-to-homoallylpalladium rearrangement,[117] led de Meijere and co-workers to propose the mechanism shown in Scheme 2-9.



Scheme 2-9 Mechanism of palladium-catalysed cascade cyclisations of 2-bromo-tetradec-1-ene-7,13-diynes (de Meijere *et al.*)[86–88]

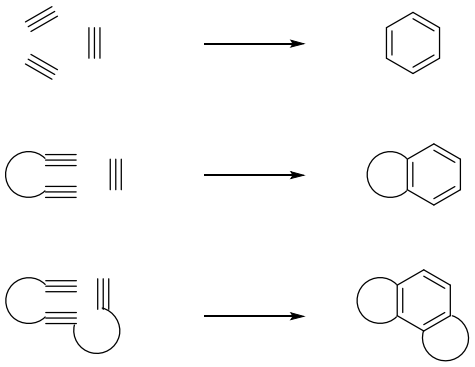
Upon oxidation addition to bromoenediynes **150a-e**, a 6-*exo*-trig carbopalladation first occurs to generate palladated intermediate **151** (Scheme 2-9), which undergoes a second carbopalladation to give hexatrienylpalladium complex **152**; a direct [4+2]-cycloaddition from **151** to form cyclohexadienylpalladium intermediate **155** is not possible due to the length of the tether linking the diene to the dienophile. They postulated that when the sizes of the peripheral rings are large, the geometry of the hexatrienylpalladium intermediate **152** favours carbopalladation over 6π-electrocyclisation. The above findings also suggested that instead of a 6-*endo*-trig carbopalladation to form complex **155**, a 5-*exo*-trig carbopalladation occurs to generate neopentyl-type intermediate **153**. Intermediate **153** then undergoes a 3-*exo*-trig carbopalladation to give tetracyclic species **154**, which equilibrates with **157** through an η^3-π-allyl palladium complex. The cyclopropane ring in **154** / **157** can undergo a

cyclopropylcarbinyl-to-homoallylpalladium rearrangement in two ways. If R is an electron-donating group, then the cyclopropyl bond which is substituted with the R group would break to generate cyclohexadienylpalladium species **155**, from which a β-hydride elimination would afford bisannelated benzene **156**. If R is not an electron-donating group, then the cyclopropyl bond which is not substituted with the R group would break to generate neopentyl-type intermediate **158**. If R is hydrogen, then β-hydride elimination from **158** would afford bisannelated fulvene **159**. However, if R is an electron-withdrawing group, another 3-*exo*-trig carbopalladation would occur to give tetracycle **160**. Finally, β-hydride elimination from **160** would generate tetracycle **161**.

2.3. Transition-Metal Catalysed [2+2+2] Cycloaddition

2.3.1. Methodology background

Cyclotrimerisation is the transition metal-catalysed formal [2+2+2] cycloaddition of three alkynes to form an arene.[118–120] An intermolecular reaction of three separate alkynes would form a polysubstituted benzene, while reactions in which two or three alkynes are tethered would result in fused ring aromatic systems (Scheme 2-10).

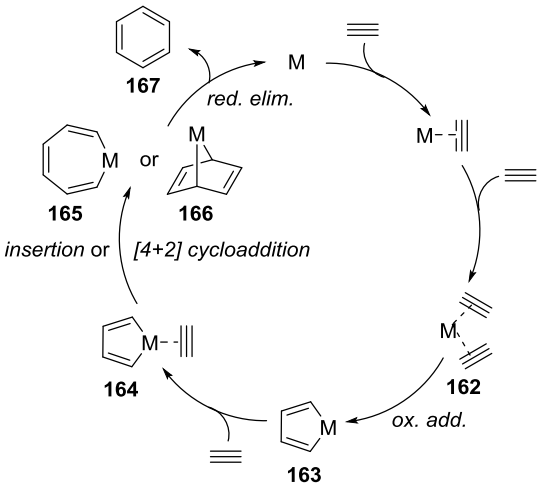


Scheme 2-10 Inter- and intramolecular cyclotrimerisation reactions

Reppe and co-workers first discovered the nickel-mediated intermolecular [2+2+2] cycloaddition reaction in 1948.[121] To date, various transition metal catalysts have been used in the cyclotrimerisation reaction, including nickel, chromium, cobalt, iridium, iron, niobium, palladium, rhodium, ruthenium, tantalum and zirconium. The scope has also been expanded to include other unsaturated compounds such as nitriles, isocyanates, olefins, carbonyls, imines, diimides, and even allenes, providing access to a diversity of products.

The cyclotrimerisation reaction may proceed by two mechanisms (Scheme 2-11). Both initiate with the coordination of two alkynes to the metal centre, forming complex **162**. Oxidative coupling of **162** generates metallacyclopentadiene **163**, which then coordinates the third alkyne to form complex **164**. Thereafter, the new alkyne either inserts directly into **164** to form metallacycle **165**, or undergoes a [4+2]-cycloaddition with the metallacyclopentadiene

164 to generate metallanorbornadiene **166**. Both complexes **165** and **166** undergo reductive elimination to generate the same product, benzene **167**.



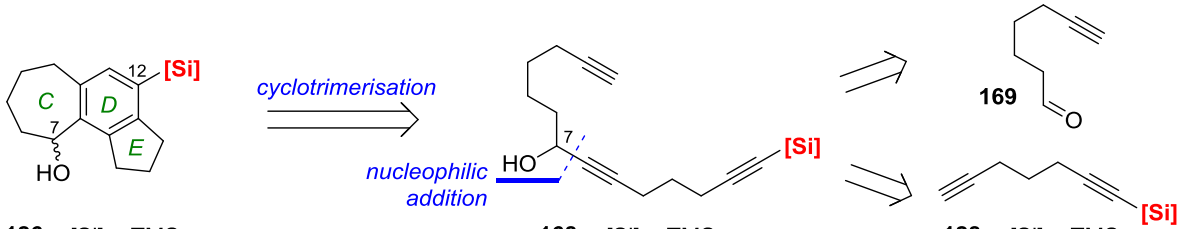
Scheme 2-11 Mechanism for the formation of benzene *via* cyclotrimerisation.

The reaction can be performed in a variety of solvents, but it usually heated. Although the [2+2+2] reaction is exothermic, it has a high activation energy because of large entropic and kinetic barriers.[122] As such, the use of transition metal catalysts is essential – the metal catalyst assembles the ring in a stepwise process, lowering the entropic barrier of each step by coordination of the reaction molecules in the appropriate orientation for reaction. In addition to the use of metal catalysts, conventional heating or microwave irradiation can aid in achieving activation. Empirical and theoretical studies on the benefits of microwave irradiation suggest that microwaves not only shorten the catalytic induction period by thermal effects, but also increase the lifetime of the triplet state of metallacyclopentadiene intermediate **163**, a key intermediate in this reaction, thus decreasing reaction times while increasing yields.[123,124]

2.3.2. Retrosynthesis

Although the palladium-catalysed cascade cyclisation of bromoenediynes proved to be highly effective for the formation of the 7,6,5-CDE ring model systems **141a-c**, we were concerned that the requirement for a vinyl bromide functional group would limit our synthetic strategy towards the rubriflordilactones. In this aspect, the cyclotrimerisation reaction from a triyne represented an attractive alternative for the construction of benzannulated rings. To the best of our knowledge, although intramolecular triyne cyclotrimerisation has previously been used in total synthesis,[125,120] it has never been applied to the formation of a 7-membered ring in natural products. These factors provided sufficient impetus for us to investigate the construction of 7,6,5-CDE ring model systems **126a-e** *via* cyclotrimerisation.

We envisaged that the same CDE ring model systems **126a-e** investigated above could be formed by the cyclotrimerisation of triynes **168a-e** (Scheme 2-12), instead of the cyclisation of bromoenediynes **127a-e** (*see Section 2.2*). In this investigation, the optimal catalyst system and also the influence of the silyl group on the cyclotrimerisation reaction would be studied. A similar disconnection at C7-C8 (rubriflordilactone A numbering) would generate the same diynes **128a-e**, and ynal **169**.



126a [Si] = TMS
126b [Si] = $SiMe_2O$*i*-Pr
126c [Si] = $SiMe_2Bn$
126d [Si] = $SiMe_2H$
126e [Si] = H

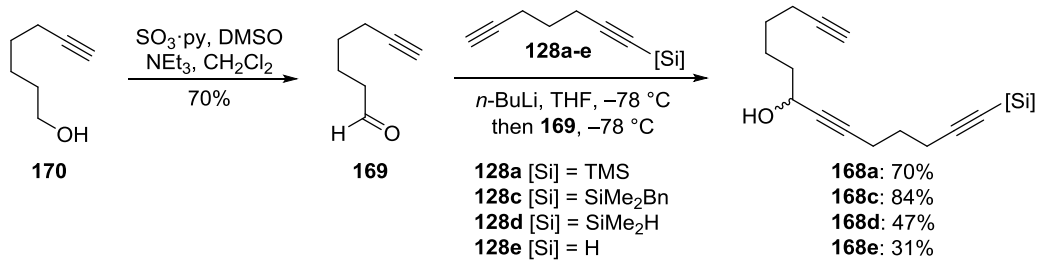
168a [Si] = TMS
168b [Si] = $SiMe_2O$*i*-Pr
168c [Si] = $SiMe_2Bn$
168d [Si] = $SiMe_2H$
168e [Si] = H

128a [Si] = TMS
128b [Si] = $SiMe_2O$*i*-Pr
128c [Si] = $SiMe_2Bn$
128d [Si] = $SiMe_2H$
128e [Si] = H

Scheme 2-12 Retrosynthesis of the CDE ring system by cyclotrimerisation

2.3.3. Synthesis of cyclisation precursors[100,99,i]

Synthesis of the triynes **168a-e** very closely mimicked the synthesis of the bromoenediynes **127a-e** (*see Section* 2.2). Ynal **169** was obtained from hept-6-yn-1-ol **170** in 70% yield using a Parikh-Doering oxidation (Scheme 2-13).[116]



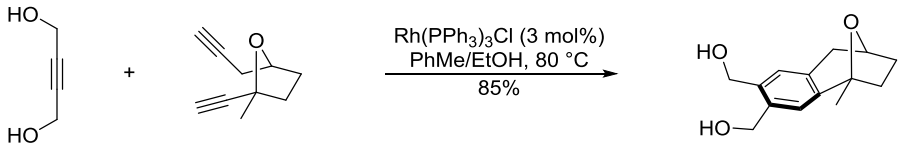
Scheme 2-13 Synthesis of triynes **168a-e**

Thereafter, nucleophilic addition of a variety of lithiated silyldiynes **128a-d** and the unsubstituted diyne **128e** to aldehyde **169** gave their corresponding triynes **168a-e** in moderate to high yields (Scheme 2-13). The triynes bearing the trimethylsilane (**168a**) and benzyldimethylsilane (**168c**) groups were again obtained in significantly better yields compared to their counterparts, as observed in the synthesis of their respective bromoenediyne analogues **127a-e** (*see Section 2.3.3*); the yields were also similar to that obtained from their corresponding bromoenediynes.

[i] These studies were conducted by Hannah Baars, a visiting Masters student in the Anderson group; the author's role in this study was limited to guidance and supervision. A summary of her work is presented here for continuity into the later chapters.

2.3.4. Cyclisation studies[100,99,ii]

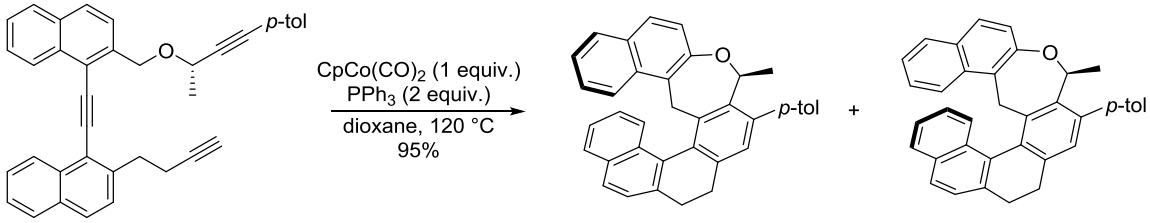
With acyclic precursors **168a-e** in hand, we proceeded to study the cyclotrimerisation reaction (Table 2-2). As we expected the formation of the 7-membered C ring to be the most challenging step in this reaction, the investigation focused on pre-existing methods in which 7-membered rings were constructed. Our screen of cyclotrimerisation conditions using triyne **168a** began with Wilkinson's catalyst,[126] which was used by Ramana and co-workers in the formation of benzannulated bridged 7-membered rings (Scheme 2-14).[127] Unfortunately, only decomposition was observed when their conditions were applied to triyne **168a** (Entries 1-2, Table 2-2).



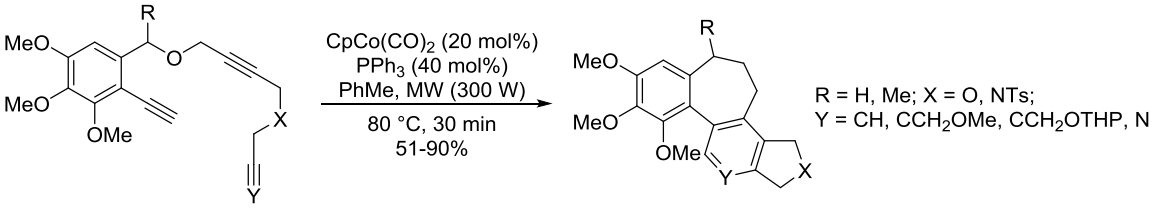
Scheme 2-14 Cyclotrimerisation to benzannulated rings (Ramana et al., 2007)[127]

The next metal screened was cobalt, starting with dicobalt octacarbonyl, first used as a catalyst in a cyclotrimerisation by Hübel and Hoogzand in 1960.[128] Small amounts of arene **126a** were isolated, albeit with only 30% conversion at reflux for 20 h (Entry 3, Table 2-2). The low conversion may be attributed to the formation of a stable alkyne-cobalt complex, akin to that in the Pauson Khand reaction,[129] prompting a switch to mononuclear cobalt catalysts. In recent years, cobalt catalysts of the type [$CpCoL_2$] (L = CO, PR_3, $R_2C{=}CR_2$) have been the most commonly used catalysts for cyclotrimerisation reactions due to their efficiency.[130–132] Stará and co-workers reported a protocol for the synthesis of [7]helicene-like molecules in 2005, using stoichiometric cyclopentadienylcobalt dicarbonyl with triphenylphosphine as ligand (Scheme 2-15).[133,134] Applying these conditions to substrate **168a** again gave low yields of the desired tricycle **126a** (Entries 4-5, Table 2-2).

[ii] These studies were conducted by Hannah Baars, a visiting Masters student in the Anderson group; the author's role in this study was limited to guidance and supervision. A summary of her work is presented here for continuity into the later chapters.

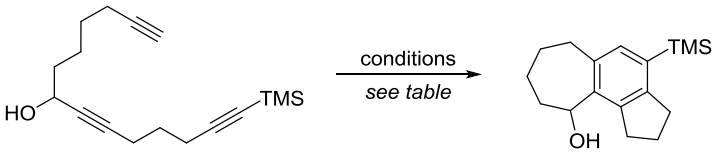


Scheme 2-15 Cyclotrimerisation to [7]helicene-like molecules (Stará *et al.*,2005)[133]



Scheme 2-16 Microwave-induced cobalt-catalysed cyclotrimerisation (Schmalz *et al.*,2009)[135]

Although disappointed with these results, we were cognisant of the use of microwave irradiation rather than conventional heating in cobalt-catalysed cyclotrimerisation.[123,124] Of particular interest were the conditions used by Schmalz and co-wokers to construct the 6,7,6,5-ring system in tetracyclic 6-oxa-allocolchicinoids from acyclic triynes (Scheme 2-16).[135] To our delight, significant improvement was observed when these conditions were applied, with the reaction proceeding to completion in 30 min using just 20 mol% of catalyst, affording **126a** in 67% yield (Entry 6, Table 2-2). Further optimisation showed that while varying the concentration did not lead to any improvement (Entries 7-8, Table 2-2), the reaction time was crucial - the reaction was incomplete after 15 min of irradiation (Entry 9, Table 2-2), but at an optimum irradiation period of 25 min, the desired product was generated in 89% yield (Entry 10, Table 2-2). With an aim to apply this reaction to total synthesis, we needed to prove the utility of this reaction on a larger scale. Unfortunately, both conversion and yield diminished on scale-up; gratifying, this problem was solved by simply doubling the microwave power to 300W, affording **126a** in 70% yield (Entries 11-12, Table 2-2).



168a **126a**

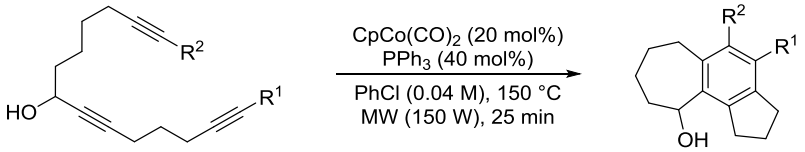
Entry	Catalyst / mol%	Solvent	Conc. / M	T / °C	time / min	Yield / %	Conversion / %
1	$Rh(PPh_3)_3Cl$ (3)	PhMe/EtOH (10:3)	0.05	80	5.5 h	dec.	n.d.
2	$Rh(PPh_3)_3Cl$ (10)	EtOH[b]	0.05	80	24 h	dec.	n.d.
3	$Co_2(CO)_8$ (10)	PhMe[b]	0.10	110	20 h	10	30
4	$CpCo(CO)_2/2PPh_3$ (100)	dioxane	0.04	100	48 h	10	67
5	$CpCo(CO)_2/2PPh_3$ (100)	PhMe	0.04	110	24 h	30	87
6	$CpCo(CO)_2/2PPh_3$ (20)	PhCl	0.04	150[a]	30	67	100
7	$CpCo(CO)_2/2PPh_3$ (20)	PhC	0.10	150[a]	30	55	100
8	$CpCo(CO)_2/2PPh_3$ (20)	PhCl	0.02	150[a]	30	53	100
9	$CpCo(CO)_2/2PPh_3$ (20)	PhCl	0.04	150[a]	15	63	73
10	**$CpCo(CO)_2/2PPh_3$ (20)**	**PhCl**	**0.04**	**150[a]**	**25**	**80**	**100**
11[b]	$CpCo(CO)_2/2PPh_3$ (20)	PhCl	0.04	150[a]	25	19	47
12[b]	**$CpCo(CO)_2/2PPh_3$ (20)**	**PhCl**	**0.04**	**150[c]**	**25**	**70**	**86**

Reaction conditions: To **168a** (30 mg) in degassed solvent (as indicated) was added catalyst (as indicated); reaction mixture was heated at temperature T (as indicated) for time t (as indicated);
[a] Microwave power: 150 W; [b] Performed using 210 mg of **168a**; [c] Microwave power: 300 W.

Table 2-2 Reaction optimisation for cyclotrimerisation of **168a** (Anderson *et al.*, 2012)[100,99,iii]

Having optimised the reaction on model substrate **168a**, we proceeded to examine the substrate scope (Table 2-3). This would determine if the nature of the silane had any effect on its reactivity. In a similar scenario to the palladium-catalysed cyclisation of bromoenediynes (*see Section 2.2.3*), benzyldimethylsilane **168c** delivered aromatic tricycle **126c** in an excellent 87% yield (Entry 2, Table 2-3), whereas hydrosilane **168d** and unsubstituted diyne **168e** both gave poor returns (Entries 3-4, Table 2-3). However, in contrast to the bromoenediyne cyclizations, protection of the propargylic alcohol was not necessary, or indeed beneficial.

[iii] These studies were conducted by Hannah Baars, a visiting Masters student in the Anderson group; the author's role in this study was limited to guidance and supervision. A summary of her work is presented here for continuity into the later chapters.



168a-f 126a-f

Entry	Substrate	R^1	R^2	Product	Yield / %
1	**168a**	**TMS**	**H**	**126a**	**80**
2	**168c**	**$SiMe_2Bn$**	**H**	**126c**	**87**
3	**168d**	$SiMe_2H$	H	**126d**	20
4	**168e**	H	H	**126e**	10
5	**168f**	H	TMS	**126f**	trace

Reaction conditions: To **substrate** (30 mg) and triphenyphosphine (40 mol%) in degassed PhCl (0.04 M) was added cyclopentadienylcobalt dicarbonyl (20 mol%); reaction mixture was heated at 150 °C in the microwave (150 W) for 25min.

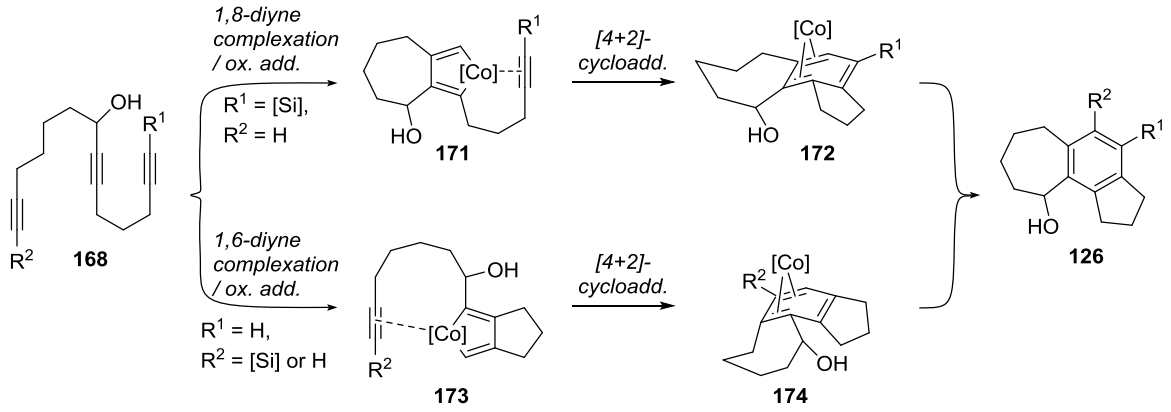
Table 2-3 Substrate scope for the cyclotrimerisation reaction (Anderson *et al.*, 2012)[100,99,iv]

Finally, we wondered if the position of the silyl substituent would affect the performance of the triyne in cyclotrimerisation. This conjecture was tested with triyne **168f**, in which the silyl substituent is installed at the 1,8-diyne terminus, where only a trace amount of arylsilane **126f** was obtained (Entry 5, Table 2-3). This implied that a sterically-demanding substituent was beneficial at the 1,6-diyne terminus, but detrimental at the 1,8-diyne terminus, shedding some light on the mechanism of the reaction.

[iv] These studies were conducted by Hannah Baars, a visiting Masters student in the Anderson group; the author's role in this study was limited to guidance and supervision. A summary of her work is presented here for continuity into the later chapters.

2.3.5. Mechanistic discussion

Two possible mechanistic pathways[136] are proposed based on the results of the above cyclotrimerisation investigation (Scheme 2-17). When the triyne is silylated at the 1,6-diyne terminus (i.e. $R^1 \neq H$) but not at the 1,8-diyne terminus (i.e. $R^2 \neq H$), as in **168a** or **168c**, complexation and oxidative addition into the 1,8-diyne is thermodynamically favoured on steric grounds (*Path a*). This leads to cobaltacycle **171**, with the seven-membered ring formed. In this complex **171**, the short tether length of the remote alkyne promotes rapid intramolecular cobalt-assisted [4+2]-cycloaddition, which outcompetes intermolecular processes to generate (η^4-arene)cobalt complex **172**. Dissociation of complex **172** then regenerates the cobalt catalyst and furnishes the product **126**.



Scheme 2-17 Proposed mechanism for cyclotrimerisation to 7,6,5-rings

In contrast, when the triyne is silylated at the 1,8-diyne terminus (i.e. $R^2 \neq H$) but not at the 1,6-diyne terminus (i.e. $R^1 = H$), as in **168f**, initiation of the reaction at the 1,6-diyne terminus is now thermodynamically favoured on steric grounds (*Path b*), generating cobaltacycle **173** with the five-membered ring installed. In this complex **173**, the intramolecular [4+2]-cycloaddition is slow since the longer tether length and steric bulk of the 1,8-diyne terminus raise the entropic barrier to organisation. As a result, competing intermolecular processes predominate and polymerisation occurs, lowering the yield of (η^4-arene)cobalt complex **174** and hence desired product **126**. In fact, in the case of **168f**, only trace amounts of **126f** were obtained (Entry 5, Table 2-3). Finally, when both the 1,8- and 1,6-diyne termini are

unsubstituted (i.e. $R^1 = R^2 = H$), as in **168e**, the reaction initiates at the 1,6-diyne terminus due to entropic factors (*Path b*), again forming cobaltacycle **173**. In this case, the intramolecular [4+2]-cycloaddition is less slow since the 1,8-diyne terminus is now unsubstituted; still, intermolecular processes are able to compete and the yield of tricycle **126** is low (10% for **126e**, Entry 4, Table 2-3).

2.3.6. Comparison of transition-metal catalysed cyclisations

Thus far, two methods for the synthesis of 7,6,5-rings in a single step from acyclic precursors have been described. Both routes worked best using benzyldimethylalkynylsilanes **139c** or **168c** to afford benzyldimethylarylsilanes **141c** or **126c**, precursors to the CDE core of rubriflordilactone A. Cyclisations to trimethylarylsilanes **141a** or **126a**, precursors to the CDE core of rubriflordilactone B, were also effective. While the palladium-catalysed cyclisation of bromoenediynes required the C7 hydroxyl to be protected (*see Section 2.2.3*), the cobalt-catalysed cyclotrimerisation could be performed with the free C7 hydroxyl, thus giving it the advantage of a shorter step count in synthesis (and possibly later in modification as well). Still, we felt that the two methods were complementary to each other, rather than competing, since they were compatible with different functional groups at C9 (rubriflordilactone A numbering). We continued with the elaboration of these cyclised products to the CDE cores of the rubriflordilactones.

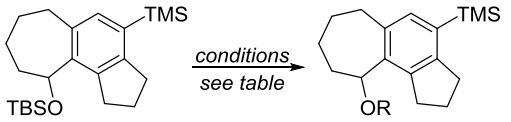
2.4. Functionalisation of the CDE Rings

Having prepared a range of tricyclic arylsilanes, we began our study on the divergent functionalisation of the C and D rings towards the cores of both rubriflordilactones A and B.

2.4.1. Towards the CDE rings of rubriflordilactone B

We envisaged that the CDE core of rubriflordilactone B **131** would arise from tricycles **141a** or **126a** by aromatic desilylation and elimination of the benzylic oxygen substituent.

Desilylation of **141a** was attempted with several standard conditions (Table 2-4). To our surprise and dismay, none of these conditions were able to desilylate the aryl TMS group. Even desilylation of the benzylic ether required refluxing conditions with an excess of the fluoride source to give alcohol **175a** (Entries 1-2, Table 2-4), no reaction was observed under mild heating conditions (Entry 3, Table 2-4). However, it was interesting to note that nucleophilic substitution occurred readily at the benzylic position under acidic conditions: stirring with trifluoroacetic acid afforded trifluoroacetate **175b**, which decomposed to alcohol **175a** on a silica column (Entry 4, Table 2-4), while heating with CSA in a methanol/THF mix gave methyl ether **175c** (Entry 5, Table 2-4). These results were encouraging as they suggested that benzylic elimination could be facile.



141a

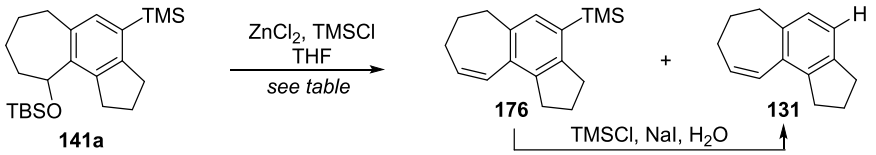
175a R = H
175b R = $C(O)CF_3$
175c R = CH_3

Entry	Conditions	Product	Yield / %
1	TBAF (5 equiv.), THF, 60 °C	**175a**	76
2	CsF (2 equiv.), DMF/H_2O (10:1), 150 °C, o/n	**175a**	n.d.
3	CsF (2 equiv.), DMF/H_2O (10:1), 70 °C, 2 days	-	n.r.
4	TFA, CH_2Cl_2, 0 °C, 3 min	**175b**	quant.[a]
5	CSA, MeOH/THF, 40 °C, o/n	**175c**	67

[a] Crude yield; product decomposed on silica column to afford **175a**.

Table 2-4 Failed desilylation of arylsilane **141a**

In view of these disappointing results, benzylic elimination was screened instead (Table 2-5). The reaction proceeded rapidly under Lewis acidic conditions to furnish an inseparable mixture of alkene **176** and a small amount of **131**, the CDE core of rubriflordilactone B, in an overall yield of 78% (Entry 1, Table 2-5).[137] Pleasingly, increasing the amount of zinc(II) chloride and the reaction time enabled the transformation of **176** directly into **131** (Entries 2-5, Table 2-5), although this never proceeded to completion. This turned out to be inconsequential as the mixtures of alkenes **176** and **131** could be desilylated by *in situ* generated trimethylsilyl iodide[138] to give only hydrocarbon **131** in quantitative yield. This sequence could also be applied to alcohol **126a**, affording **131** in an excellent 99% yield over two steps.



Entry	Substrate	$ZnCl_2$ equiv.	TMSCl equiv.	t / h	176:131[a]	Yield[b] / %
1	**141a**	1.5	2.0	2	90:10	78
2	**141a**	1.5	2.0	30	38: 62	n.d.
3	**141a**	1.5	3.0	30	29:71	n.d.
4	**141a**	1.5	5.0	20	45:55	87
5	**141a**	3.0	3.0	20	15:85	69
6	**126a**	1.5	2.0	2	100:0	99
7	**126a**	3.0	3.0	20	46:54	66

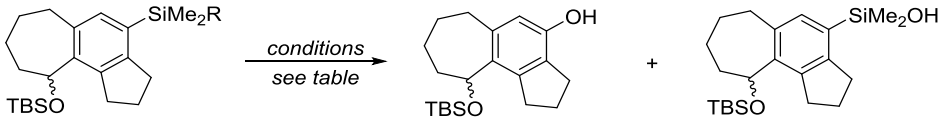
[a] Based on ^{1}H NMR integration of inseparable mixture of **176** and **131** after column chromatography;
[b] Overall yield for both **176** and **131**.

Table 2-5 Benzylic elimination to the rubriflordilactone B CDE core **131**

2.4.2. Towards the CDE rings of rubriflordilactone A

The route towards the CDE core of rubriflordilactone A **130** would require Tamao-Kumada oxidation[92] and benzylic reduction of tricyclic arylsilanes **141b-c** or **126c**.

Both aromatic silanes **141b** and **141c** could undergo Tamao-Kumada oxidation to reveal the "masked" phenol **177** (Table 2-6). For isopropoxydimethylarylsilane **141b**, oxidation was possible with catalytic amounts of TBAF, but the reaction necessitated heating and gave only moderate yield (Entry 1, Table 2-6).[93,94] For benzyldimethylarylsilane **141c**, oxidation had to be carried out in two stages,[139] with formation of silanol **178** with TBAF preceding the addition of H_2O_2; addition of all the reagents simultaneously[103,104] gave silanol **178** as the only product in low yield (Entry 2, Table 2-6). 2.1 equiv. of TBAF was essential for the reaction to proceed to completion in 92% yield, although increasing the amount of TBAF further decreases the reaction time (Entries 3-6, Table 2-6).



141b R = O*i*-Pr
141c R = Bn

177 **178**

Entry	Substrate	Conditions	178:177[a]	Yield / %
1	**141b**	TBAF (0.1 equiv.), H_2O_2 (6 equiv.), $KHCO_3$ (0.5 equiv.), MeOH/THF (1:1), 60 °C, 4 h	0:1	68
2	**141c**	TBAF (8 equiv.), H_2O_2 (10 equiv.), $KHCO_3$ (2 equiv.), MeOH/THF (1:1), 70 °C, 16 h	1:0	38
3	**141c**	TBAF (1.1 equiv.), 20 min; then H_2O_2 (6.0 equiv.), $KHCO_3$ (2 equiv.), MeOH, o/n	1:1	n.d.
4	**141c**	TBAF (2.1 equiv.), 20 min; then H_2O_2 (6.0 equiv.), $KHCO_3$ (0.5 equiv.) , MeOH, 3 h	1:2	n.d.
5	**141c**	**TBAF (2.1 equiv.), 20 min; then H_2O_2 (6.0 equiv.), $KHCO_3$ (0.5 equiv.) , MeOH, o/n**	**0:1**	**92**
6	**141c**	TBAF (10 equiv.), 20 min; then H_2O_2 (10 equiv.), $KHCO_3$ (2 equiv.), MeOH, 3 h	0:1	92

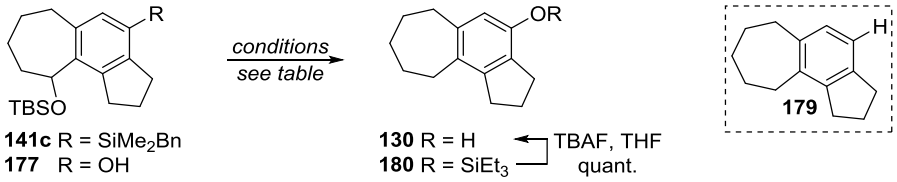
[a] Based on ^{1}H NMR integration of crude mixture

Table 2-6 Tamao-Kumada oxidation of aromatic silanes to phenol **177**

Overall, taking into consideration the sequence of transformations from diynes **128b-c** to phenol **177**, the benzyldimethylsilyl group was preferred to the isopropoxyldimethylsilyl group. This is because the benzyldimethylsilyl-substituted compounds displayed higher stability to column chromatography, and achieved higher yields for all steps of the reaction sequence, including the crucial cyclisation and oxidation steps.

Subsequently, reductive substitution of the benzylic TBS ether was investigated (Table 2-7). For arylsilane **141c**, ionic reduction with trifluoroacetic acid and triethylsilane substituted both the benzylic and the aromatic positions to afford octahydrocyclohepta[*e*]indene **179** (Entry 1, Table 2-7).[140] Gratifyingly, under the same conditions, phenol **177** afforded the desired product **130**, the tricyclic core of rubriflordilactone A, in 70% yield, with some aromatic ether **180** formed (Entry 2, Table 2-7). This aromatic ether **180** could be deprotected with TBAF to afford phenol **130**, thus increasing the overall yield to ~100% from phenol **177**. Following on from results for benzylic elimination (*see Section 2.4.1*), milder conditions using the Lewis

acid zinc(II) chloride to replace Brønsted acid TFA were screened; this proved successful as well, giving an 80% isolated yield of **130** with 19% of aromatic ether **180** (Entry 3, Table 2-7).



Entry	Substrate	Conditions	Product (Yield / %)
1	**141c**	TFA (4 equiv.), CH_2Cl_2, 0 °C, 3 min; then Et_3SiH (8 equiv.), RT, 2 h	**179** (84)
2	**177**	TFA (4 equiv.), CH_2Cl_2, 0 °C, 3 min; then Et_3SiH (8 equiv.), RT, 2 h	**130** (70) + **180** (30)
3	**177**	**Et_3SiH (2 equiv.), $ZnCl_2$ (1 equiv.), CH_2Cl_2, RT, 5 h**	**130 (80)** + **180 (19)**

Table 2-7 Reductive substitution of benzylic TBS ethers

In summary, we have developed two transition metal-catalysed routes to deliver tricyclic arylsilanes **141a-c** and **126a-c**, and also mild strategies to elaborate them into the CDE rings of rubriflordilactones A (**130**) and B (**131**). These methods would be applied to the synthesis of a more complex model of rubriflordilactone A (*see Chapter 3*) and thereafter to the total syntheses of this natural product.

3. The CDEF Ring System of Rubriflordilactone A

Having studied two complementary methodologies to the CDE core of the rubriflordilactones A and B, we moved on to apply them to the synthesis of a more advanced CDEF ring model system **181** (Figure 3-1).

3.1. Retrosynthesis

En route to the synthesis of the CDEF ring system, we would test the compatibility of our previously optimised palladium and cobalt-catalysed cyclisation strategies on the more complex bromoenediyne **183** and triyne **184** respectively (Figure 3-1). The products of these cyclisations would converge on the tricycle **182** using the Tamao oxidation / reductive substitution sequence that we have presented thus far, hence allowing us to investigate the construction of the F ring in **181** by oxidative cleavage of the crotyl side chain. This CDEF ring lactol **181** would then form an important starting point for our investigations into the attachment of the G ring as the final step(s) of the total synthesis of rubriflordilactone A.

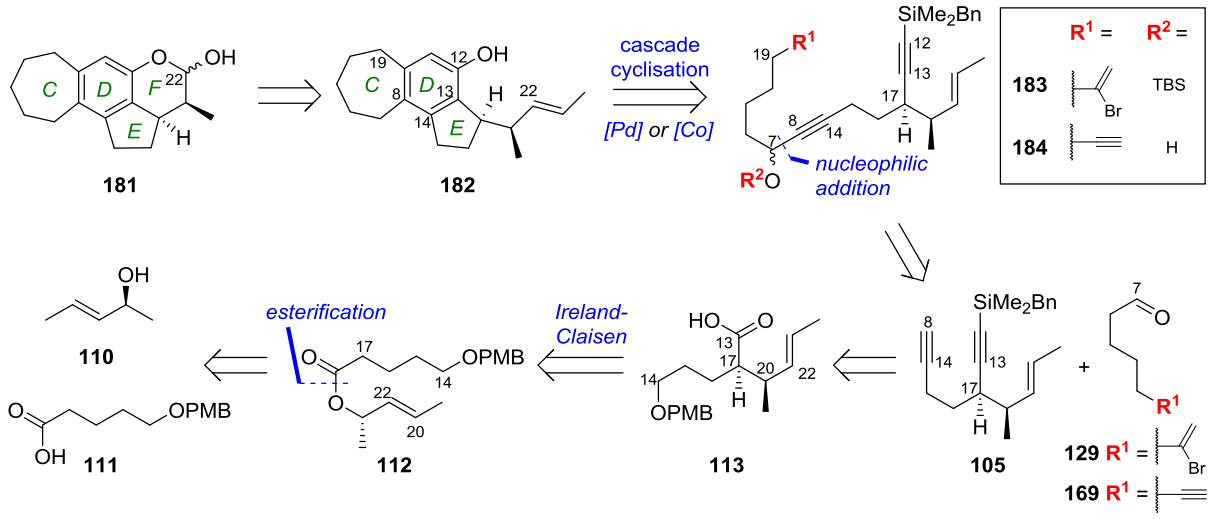


Figure 3-1 Retrosynthesis of CDEF ring system **181**

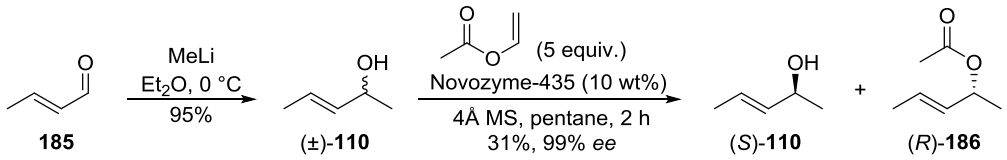
The cyclisation precursors **183** and **184** could be disconnected at the C7-C8 bond by nucleophilic addition of diyne **105** to the appropriate aldehyde **129** or **169** (*see Chapter 2*).

Diyne **105** could be generated by two aldehyde homologations at C14 and C13 from acid **113**, which could be obtained by an Ireland-Claisen rearrangement of ester **112**. A disconnection at the ester bond in **112** led to chiral alcohol **110** and carboxylic acid **111**.

3.2. Synthesis of the CDE Diyne Fragment 105[95,v]

3.2.1. Synthesis of carboxylic acid 113

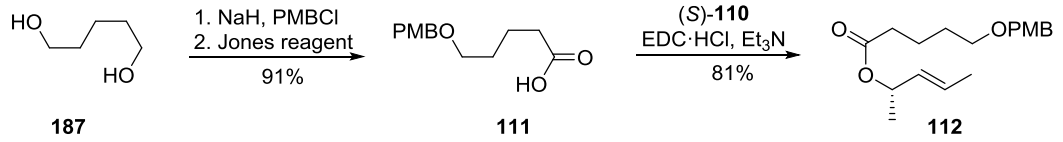
Our investigations began with the synthesis of the building blocks for ester **112**. Enantioenriched alcohol (*S*)-**110** was obtained from an enzymatic resolution of (±)-**110**, itself generated from the addition of methyllithium to crotonaldehyde **185** (Scheme 3-1). Novozyme-435 (10 mol%) and vinyl acetate was an effective means of achieving rapid resolution, affording enantioenriched desired alcohol (*S*)-**110** in 31% yield (with the maximum yield being 50%) with 99% *ee* in 2 h.[141] The (*R*)-enantiomer was consumed more rapidly in the acylation reaction as it is a better fit in the active site of the enzyme, forming acetate (*R*)-**186** which was removed.



Scheme 3-1 Synthesis of enantioenriched alcohol (*S*)-**110**

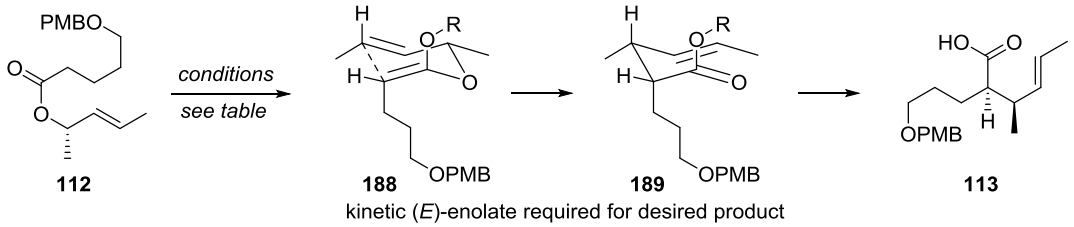
Carboxylic acid **111** was synthesised from 1,5-pentanediol **187** by mono-PMB protection, followed by Jones oxidation (Scheme 3-2).[142] Esterification of the two coupling partners, acid **111** and alcohol (*S*)-**110**, with EDC as coupling reagent proceeded smoothly to deliver ester **112** in 81% yield.[142]

[v] Synthesis of diyne **105** was previously accomplished by Dr. Marie-Caroline Cordonnier, a former DPhil student in the Anderson group. Reported here is a scale up and improvement of her procedure.



Scheme 3-2 Synthesis of ester **111**

We next investigated the Ireland-Claisen rearrangement [96,143–146] of the resultant ester **112** to give known carboxylic acid **113**,[142] a key reaction which would set the two adjacent stereocenters of the diyne fragment **105** (Scheme 3-3). The stereoselectivity of the Ireland-Claisen rearrangement hinges on the selectivity of enolisation.[6,146] Based on the 6-membered cyclic chair-like transition state **188** with the methyl group pseudo-equatorial (Scheme 3-3), the *E* / *Z* geometry of the ester enolate would control the relative *anti* / *syn* stereochemistry of the rearranged product **189**.



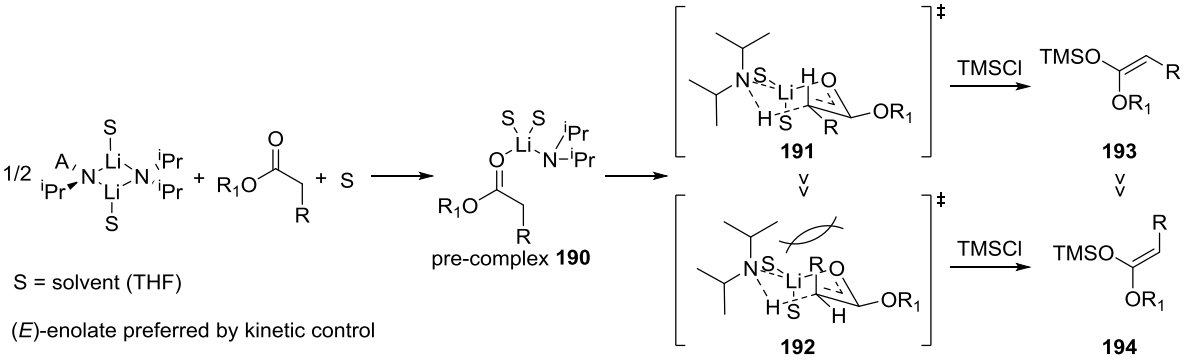
Scheme 3-3 Ireland-Claisen rearrangement of ester **112** to acid **113**

While the reaction proceeded *via* trapping of the silyl ketene acetal [142] to afford a 92% yield with a 9:1 *dr* (Table 3-1);[95] Collum's procedure *via* the free lithium enolate with LiHMDS / Et_3N in toluene[147] led to higher yield and diastereoselectivity (96%, >20:1 *dr*).

Entry	Conditions	Yield / %	dr
1	(i) LDA (3.0 equiv.), TMSCl / Et_3N (10 equiv.), THF, −78 °C to RT; (ii) 1N HCl	92	9:1
2	(i) LiHMDS (3.0 equiv.), Et_3N (30 equiv.), PhMe, −78 °C to RT; (ii) 5% *aq.* NaOH; (iii) conc. HCl, 0 °C	96	>20:1

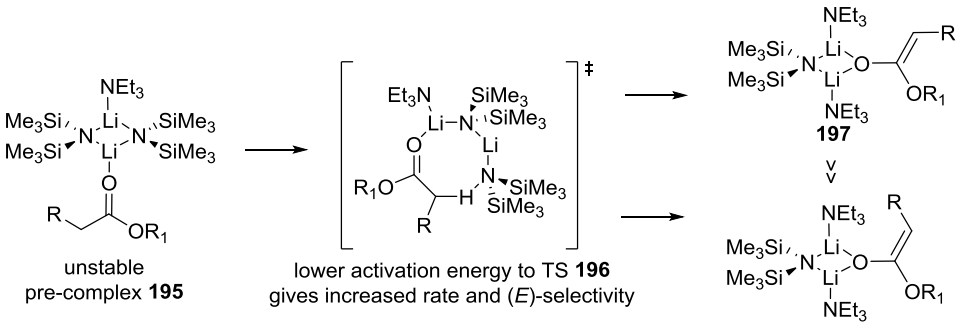
Table 3-1 Optimisation of the Ireland-Claisen rearrangement

In Ireland's model for enolisation *via* a monomeric transition state (Scheme 3-4),[96,143–145] the 1,3-diaxial interactions between the bulky isopropyl groups of LDA and the R group of the ester enolate favours the transition state **191** over **192**, thus leading to high selectivity for the (*E*)-enolate **193** over the (*Z*)-enolate **194**.



Scheme 3-4 Ireland model for enolisation [96,143–145]

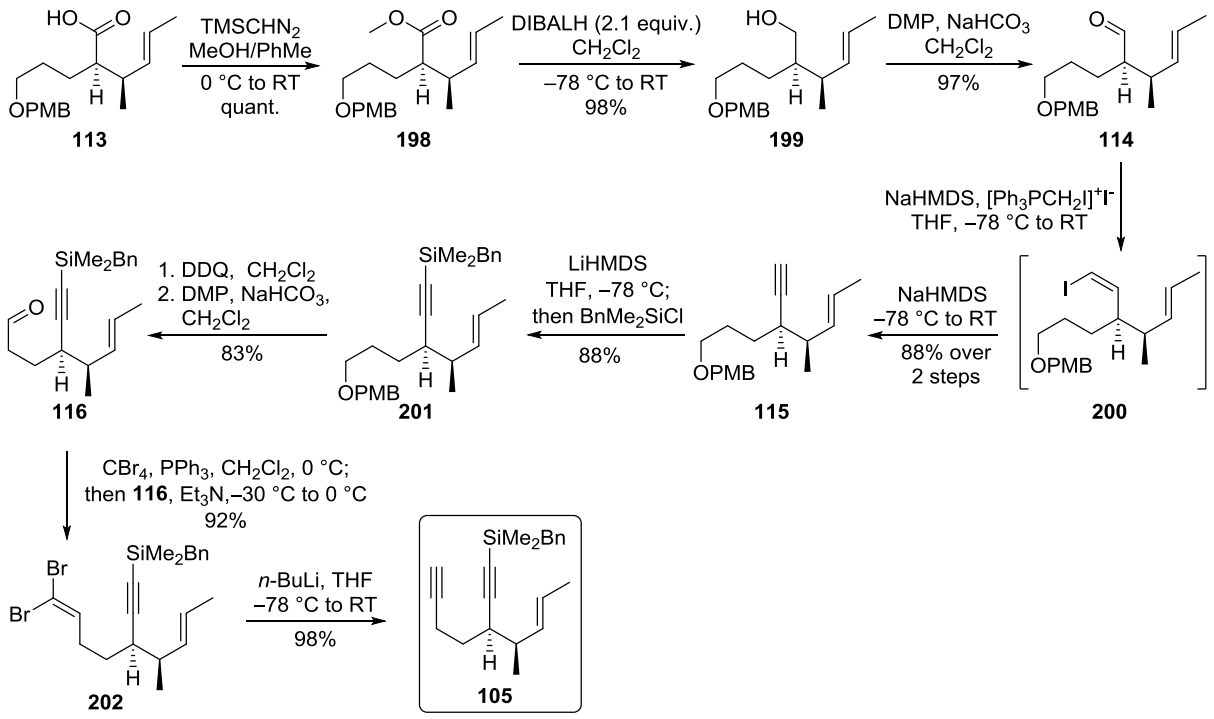
In the model proposed by Collum *et al.*, the enolisation proceeds *via* a dimeric transition state solvated by triethylamine (Scheme 3-5).[148,149,147] In this system, the steric demands of triethylamine destabilises the pre-complex **195** more than the transition state **196**, leading to a lower activation energy barrier as compared to the monomeric Ireland-type transition state (activation energy barrier between stable pre-complex **190** to transition state **191** in Scheme 3-4), leading to an increased rate of reaction as compared to the same reaction in THF. The dimeric transition state is also responsible for the improved selectivity for kinetic (*E*)-enolate **197**, which is optimal only when more than two equivalents of LiHMDS are used.



Scheme 3-5 Collum model for enolisation [148,149,147]

3.2.2. Completion of CDE diyne fragment 105

Acid **113** was reduced to aldehyde **114** in preparation for alkynylation (Scheme 3-6). Unfortunately, direct reduction from acid **113** to alcohol **199** with lithium aluminum hydride did not give reproducible results. As such methyl ester **198** was prepared from acid **113** with trimethylsilyldiazomethane, to facilitate the reduction. From ester **198**, we attempted a direct reduction to aldehyde **114** with 1.0 equiv. of DIBALH at −78 °C, but were disappointed to find that this consistently afforded mixtures of aldehyde **114** with alcohol **199**. Finally, we settled on a two step procedure from methyl ester **198**; DIBALH reduction (2.1 equiv.) of ester **198** to alcohol **199**, followed by DMP oxidation furnished aldehyde **114** in an overall yield of 95%.



Scheme 3-6 Synthesis of CDE diyne fragment **105**

A Stork-Zhao olefination[97] of aldehyde **114** furnished (*Z*)-vinyl iodide **200**, which underwent *in situ* elimination to afford alkyne **115** in an excellent 88% yield over 2 steps (Scheme 3-6). A benzyldimethylsilyl group was installed on the terminal alkyne to give internal alkyne **201**. DDQ protection of the *p*-methoxybenzyl ether **201** and subsequent oxidation of the resulting alcohol gave aldehyde **116**, ready for the next homologation step – this time a Corey-Fuchs

reaction. Ramirez olefination by an improved procedure of adding aldehyde **116** dropwise to the pre-formed ylide gave vinyl bromide **202** in a significantly improved yield of 92% as compared to Cordonnier's procedure.[95] Lithium-halogen exchange and rearrangement from dibromide **202** afforded the CDE diyne fragment **105** in an excellent 98% yield.

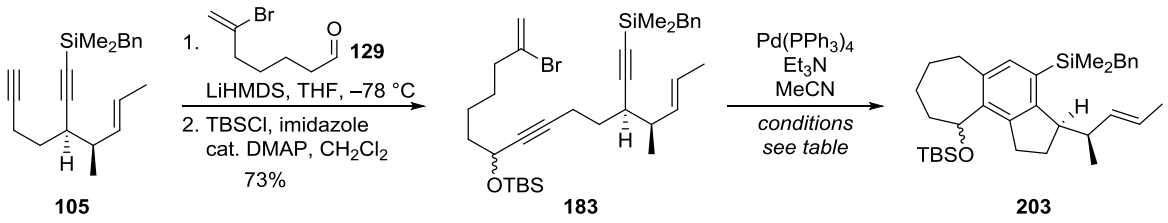
Overall, CDE diyne fragment **105** was synthesised on gram scale (3.5 g) with a 43% yield over 11 steps from enantioenriched alcohol (*S*)-**110** and carboxylic acid **111**. This successful synthesis served as the foundation for further investigations into the synthesis of the CDEF ring system **181**.

3.3. Investigation of the Cyclisation Methodologies

With diyne **105** in hand, we proceeded to investigate the compatibility of the transition metal-catalysed cyclisation methodologies on this more functionalised system.

3.3.1. Palladium-catalysed cascade cyclisation of the bromoenediyne

Nucleophilic addition of diyne **105** to bromoenal **129** and subsequent silyl protection furnished bromoenediyne **183** in 73% yield (Scheme 3-7). Starting from the previously optimised conditions for the palladium-catalysed cascade cyclisation of the CDE ring system **141c** (*see Section 2.2.3*) , we conducted a small optimisation survey for the cyclisation of bromoenediyne **183** to tricycle **203** (Table 3-2). Gratifyingly, our more complex substrate was compatible with palladium catalysis, affording tricycle **203** in 69% yield under our newly optimised conditions of 5 mol% tetrakis(triphenylphosphine)palladium(0) and 8 equiv. of triethylamine in acetonitrile (0.025 M) at 80 °C for 16 h.



Scheme 3-7 Synthesis of tricycle **203** *via* palladium-catalysed cascade cyclisation

Entry	$Pd(PPh_3)_4$ mol%	Et_3N equiv.	[Substrate] / M	T / °C	Yield / %
1	10	6	0.04	80	59
2	10	8	0.04	70	46
3	5	8	0.04	80	56
4	**5**	**8**	**0.025**	**80**	**69**
5	5	8	0.01	80	66

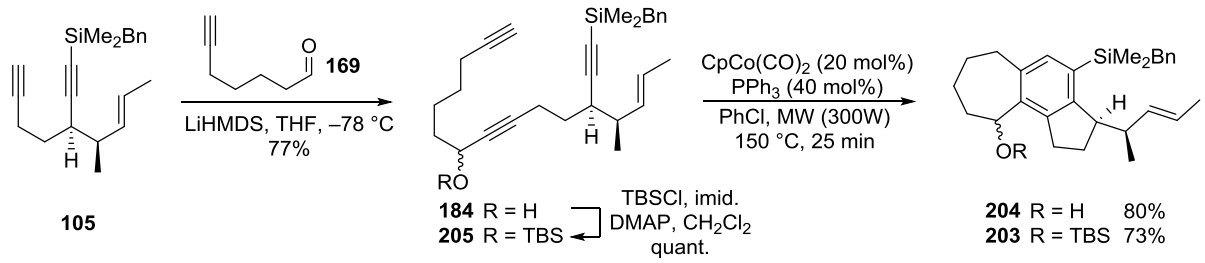
Reaction conditions: Bromoenediyne **183** (30 mg, 1.0 equiv.) in MeCN (as indicated) was degassed, then added to a flame-dried vial equipped with a stirrer bar and $Pd(PPh_3)_4$ (as indicated), and degassed triethylamine (as indicated) was added; reaction mixture was stirred overnight under Ar atm at temperature T (as indicated).

Table 3-2 Optimisation of the palladium-catalysed cascade cyclisation to tricycle **203**

Having established that the palladium-catalysed cascade cyclisation strategy worked well with the more complex diyne fragment **105** to give tricycle **203**, we questioned whether the cobalt-catalysed alternative would also stand up to the challenge.

3.3.2. Cobalt-catalysed triyne cyclotrimerisation

As an alternative to the palladium-catalysed cyclisation of bromoenediyne **183**, we set out to test the cyclotrimerisation reaction on its alkyne analog **184**. Addition of diyne **105** to ynal **169** gave triyne **184**. When subjected to our previously optimised cobalt catalysis conditions (*see Section 2.3.4*), we were delighted to obtain tricycle **204** in an excellent 80% yield. Alternatively, alcohol **184** could be TBS-protected before cyclotrimerisation (Scheme 3-8). Cyclotrimerisation of this TBS ether **205** delivered **203**, the same product as in the palladium-catalysed cascade cyclisation, in a 73% yield.

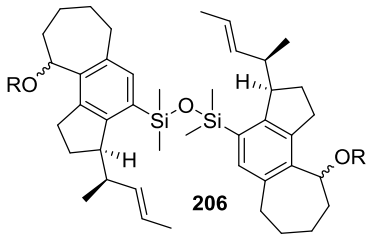


Scheme 3-8 Synthesis of tricycles **204** and **203** *via* cobalt-catalysed cyclotrimerisation

3.3.3. Functionalisation of the C and D rings

With tricycles **203** and **204** in hand, we proceeded to functionalise the C and D rings to attain phenol **182**. To do this, we would apply the protocol which we had developed for these transformations with the CDE ring system **141c**.[100]

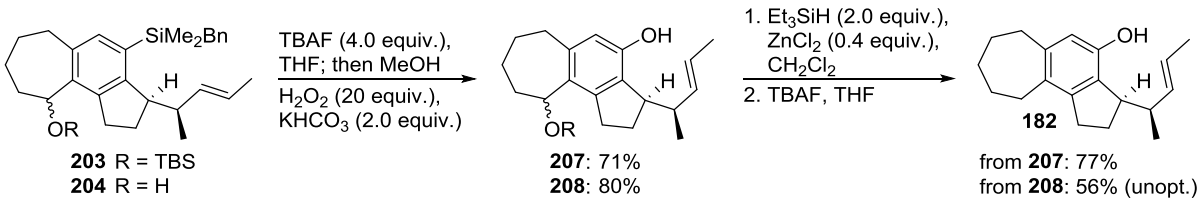
In this vein, the synthesis continued with the Tamao-Kumada oxidation[92] of benzyldimethylsilanes **203** and **204**. While the previously optimised procedure (*see Section 2.4.2*) worked for both systems, we noticed the formation of significant amounts of disiloxane **206** (Figure 3-2) during the first step of TBAF activation. Disiloxane **206** was unable to be oxidised in the subsequent step, resulting in lower yields of the desired phenol; the lack of reactivity of disiloxanes was also observed in studies by previous members of our group.[150] In a bid to decrease the formation of the disiloxane side product, we utilised the conditions which Kirschning *et al.* had used in their total synthesis of elansolid B1,[151] i.e. with increased amounts of reagents (4.0 equiv. of TBAF, 2.0 equiv. of potassium hydrogen carbonate and 20 equiv. of hydrogen peroxide). Indeed, the increased equivalents of TBAF suppressed the formation of disiloxane **206** in the first step. Thus, over two steps, the oxidation of benzyldimethylsilanes **203** and **204** afforded phenols **207** and **208** in 71% and 80% yield respectively (Scheme 3-9).



206

Figure 3-2 Disiloxane **206** formed in Tamao oxidation

This was followed by reductive substitution with triethylsilane[140] to give tricycle **182** (Scheme 3-9). The reaction with TBS ether **207** proceeded smoothly under our previously optimised conditions to give phenol **182** in 77% yield. In contrast, the free alcohol **208** only afforded 56% of desired product (unoptimised). This may be attributed to the consumption of triethylsilane for silylation of the free hydroxyl group, leading to less reagent available for the reductive substitution; increasing the amount of triethylsilane should improve the yield.



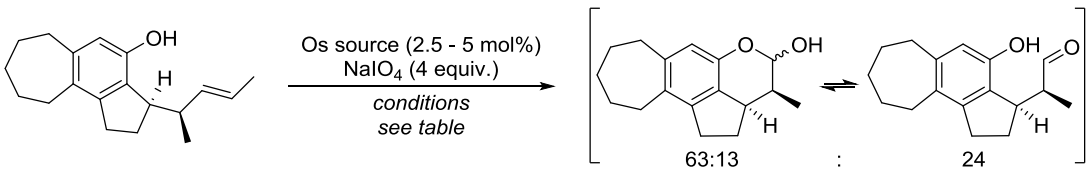
Scheme 3-9 Functionalisation of tricycles **203** and **204** to tricycle **182**

3.4. Construction of the F Ring

Having successfully established the efficacy of both our cyclisation methodologies to the synthesis of tricycle **182**, we now faced the challenging task of converting its crotyl side chain into the F ring.

3.4.1. One-pot oxidative cleavage methods

Our initial approach for oxidative cleavage of the pendent alkene was the Lemieux-Johnson oxidation (Table 3-3).[152] Using Jin's modified protocol with 2,6-lutidine,[153] oxidative cleavage of alkene **182** indeed gave us the CDEF ring lactol **181**, as a 63:13:24 mixture of two lactol diastereomers and the open-chain aldehyde form (in chloroform-*d*). Unfortunately, the yields were variable (Entry 1, Table 3-3). The reaction mixture did not contain any intermediate diol, suggesting that the slow step in this one-pot reaction was the dihydroxylation of alkene **182**. As such, the reaction conditions were modified in an attempt to improve the rate and yield of dihydroxylation,[154] but unfortunately to no avail (Entries 2-3, Table 3-3).



182

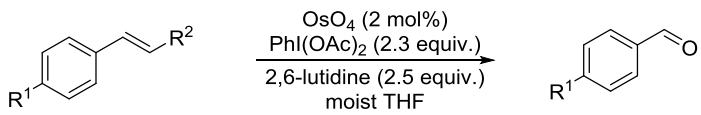
181 (equilibrium mixture of lactols and aldehyde)

Entry	Os source	Additive (equiv.)	Solvent	Yield / %	Recov. SM / %
1	OsO_4	2,6-lutidine (2)	dioxane / H_2O (3:1)	35-64	varied
2	$K_2OsO_2(OH)_4$	2,6-lutidine (2)	THF / H_2O (2:1)	46	15
3	OsO_4	citric acid (0.5)	*t*-BuOH / H_2O (1:1)	40	21

Table 3-3 Lemieux-Johnson oxidative cleavage of alkene **182**

Having failed to achieve consistently high yields with the Lemieux-Johnson oxidation, other methods for the oxidative cleavage of alkenes were investigated. We attempted another one-pot oxidative cleavage procedure using osmium(VIII) catalysis (2 mol%), this time with

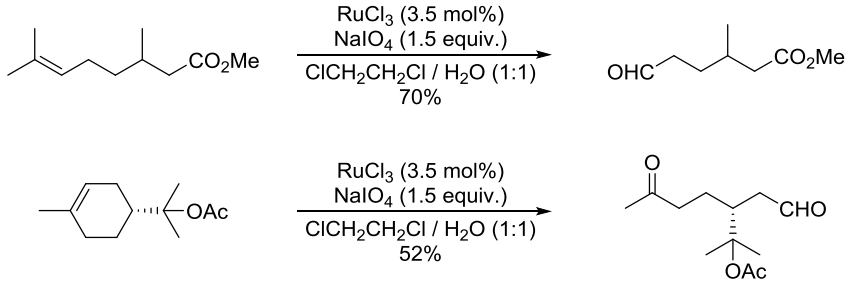
bis(acetoxy)iodobenzene as oxidant as described by Nicolaou *et al.* (Scheme 3-10).[155] Unfortunately, this failed to produce any desired product; likely due to the oxidation of the electron-rich phenol by bis(acetoxy)iodobenzene; the oxidation of phenols with bis(acetoxy)iodobenzene to cyclohexadienones and/or quinones has been documented.[156]



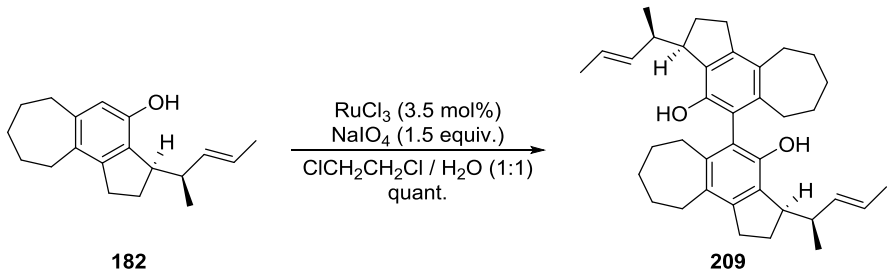
R^1	R^2	Yield/%
NO_2	Ph	98
OMe	Ph	97
OMe	H	98

Scheme 3-10 Oxidative cleavage of olefins with OsO_4–$PhI(OAc)_2$ system (Nicolaou *et al.*, 2010) [155]

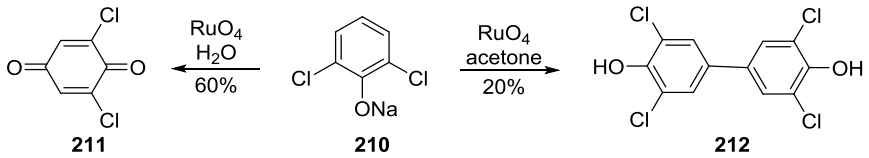
Catalytic ruthenium(III) chloride (3.5 mol%) with sodium periodate as oxidant was next trialed, following a report by Yang and Zhang on its utility in the oxidation of aliphatic olefins (Scheme 3-11).[157] Unfortunately, no desired product was obtained; NMR showed that the alkene functional group remained intact but the aromatic part of the molecule had altered, and high resolution mass spectrometry showed a molecular ion of mass 539.9886 (ESI^+ calc. for $C_{38}H_{51}O_2$ $[M+H]^+$ 539.3994), which corresponded to phenolic coupling product **209** (Scheme 3-12). Work by Ayres and Gopalan in 1976 showed that ruthenium tetroxide mediated the free radical oxidation of phenols (Scheme 3-13);[158] sodium 2,6-dichlorophenolate **210** was oxidised to 2,6-dichlorophenone **211** in aqueous solution, but gave the product of free radical phenolic coupling biphenyl **212** when the reaction was conducted in acetone.



Scheme 3-11 Oxidative cleavage of olefins with $RuCl_3$–$NaIO_4$ system (Yang and Zhang, 2001) [157]



Scheme 3-12 Attempted oxidative cleavage of alkene **182** with $RuCl_3$–$NaIO_4$ system

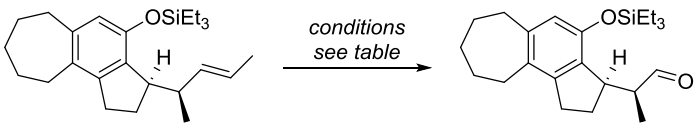


Scheme 3-13 Phenolic oxidation with ruthenium tetroxide (Ayres and Gopalan, 1976)[158]

Finally, we turned to ozonolysis in dichloromethane at −78 °C with a reductive work-up using dimethylsulfide; this unfortunately gave a complex mixture of products, likely because the electron-rich nature of the arene made it susceptible to attack by ozone. In 1961, Bernatek and Frengen studied the ozonolysis of phenol in ethyl acetate, which was cleaved into carbon dioxide, carbon monoxide, oxalic acid, glyoxal and formic acid.[159] Later studies on the ozonolysis of phenols in aqueous solutions (pH-dependent) have also yielded a variety of products; major products include hydroquinone, catechol, 1,4-benzoquinone and (*Z*),(*Z*)-muconic acid, while minor products observed were dimers of phenoxy radicals, such as 2,4'-dihyroxylbiphenyl and 2,4'-dihyroxylbiphenyl.[160,161] These studies suggested that the phenol moiety in **182** was again responsible for the issues with this reaction.

Since we suspected our problems were thus caused by oxidative cleavage of the phenol moiety, we decided to repeat some of these alkene cleavage reactions on the silyl ether of phenol **182**. Unfortunately, this alkene **213** was less reactive than the phenol **182**, only giving 15% of the desired aldehyde product **214**, with 57% of recovered starting material **213** under Lemieux-Johnson-Jin conditions (Entry 1, Table 3-4); we postulated that the steric bulk of the silyl ether hindered the attack of the alkene by osmium tetroxide. When we attempted the analogous ruthenium(III) chloride-sodium periodate oxidation, no reaction was observed

(Entry 2, Table 3-4); this suggested that ruthenium tetroxide was selective for oxidation of the phenol over the alkene functionality.



213 **214**

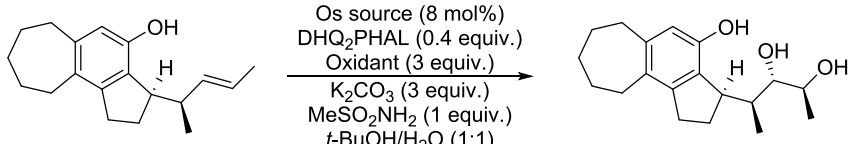
Entry	Metal (mol%)	$NaIO_4$ equiv.	Additive (equiv.)	Solvent	Results
1	OsO_4 (5)	4.0	2,6-lutidine (2.0)	dioxane / H_2O (3:1)	15% **214** + 57% **213**
2	$RuCl_3$ (3.5)	1.5	-	DCE / H_2O (1:1)	n.r.

Table 3-4 Attempted one-pot oxidative cleavage of alkene **213**

3.4.2. Dihydroxylation and diol cleavage

Having failed to achieve good yields for oxidative cleavage in one step, we resorted to the two step procedure of *syn*-dihydroxylation followed by diol cleavage.

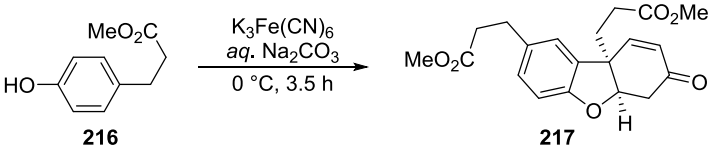
The investigations started with conditions for the Sharpless asymmetric dihydroxylation, since the use of chiral ligands would not only minimise the number of diastereomeric products from our substrate, but has also been shown to accelerate and improve the yield of the reaction.[162] First, one of the most commonly employed Sharpless asymmetric dihydroxylation conditions was employed, utilising catalytic potassium osmate(VI) dihydrate with DHQ_2PHAL as ligand, potassium ferricyanide as oxidant and methansulfonamide as additive (Entry 1, Table 3-5).[163,164] To our dismay, with alkene **182** we observed multiple spots on the TLC, with no desired product (2*S*,3S)-**215** formed. We later realised that phenols could undergo phenolic coupling under similar conditions in the absence any osmium source, mediated by potassium ferricyanide. One example is the oxidation of phenol **216** to the *ortho-para* coupled product **217** by Husson *et al.* in their synthesis of tetrahydrolunarine (Scheme 3-14).[165] As such, other oxidants and also osmium sources were trialed (Entries 2-4, Table 3-5). Unfortunately, none of these reactions were successful.



182 (2*S*,3*S*)-**215**

Entry	Os source	Oxidant	Observation
1	$K_2OsO_2(OH)_4$	$K_3Fe(CN)_6$	Multiple spots
2	$K_2OsO_2(OH)_4$	NMO	Multiple spots
3	OsO_4	NMO	Multiple spots
4	OsO_4	$NaIO_4$	Multiple spots

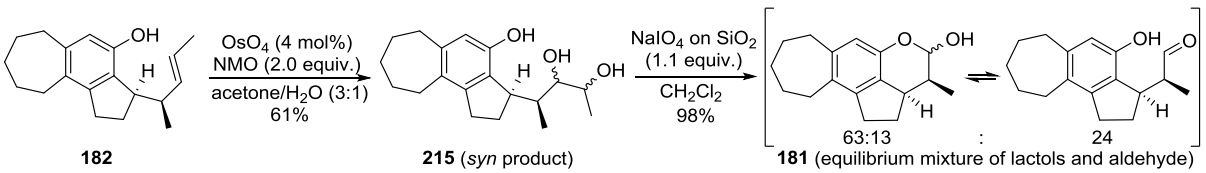
Table 3-5 Attempted asymmetric dihydroxylations of alkene **182**



216 **217**

Scheme 3-14 Oxidative phenolic coupling towards tetrahydrolunarine (Husson *et al.*, 1973)[165]

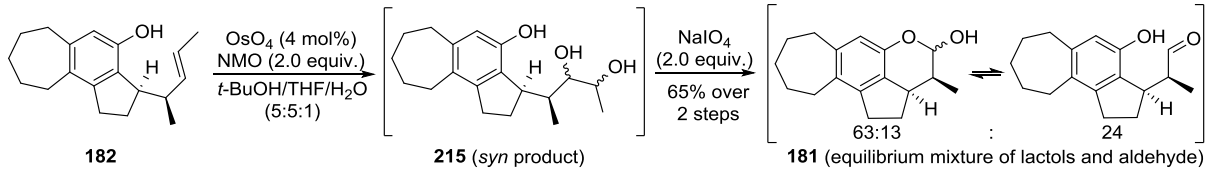
Finally, the Upjohn dihydroxylation conditions were tested.[166] To our delight, this dihydroxylation was successful, giving a diastereomeric mixture of *cis*-diol products **215** in 61% yield (Scheme 3-15). Diol **215** could undergo facile diol cleavage with silica-supported sodium periodate (10 min, 98% yield),[167] to afford lactol **181** in 60% yield over two steps.



182 **215** (*syn* product) **181** (equilibrium mixture of lactols and aldehyde)

Scheme 3-15 Two step dihydroxylation-diol cleavage of alkene **182** to lactol **181**

A one-pot, two step Upjohn dihydroxylation-diol cleavage procedure also gave a comparable 65% yield of lactol **181** over two steps (Scheme 3-16). However, we felt that isolation and purification of intermediate **215** was beneficial to the purity of lactol **181**, and hence preferred the two step procedure.



Scheme 3-16 One-pot two step dihydroxylation-diol cleavage of alkene **182** to lactol **181**

The successful construction of the CDEF rings lactol **181** marked a significant milestone in the project as it represented the completion of four out of the seven rings in rubriflordilactone A. We were hopeful that the methods discovered and the lessons learnt in this synthesis could be applied to the total synthesis of rubriflordilactone A. Lactol **181** would also serve as the starting point for investigations into the attachment of the G ring to the CDEF core.

4. Synthesis of the AB Rings

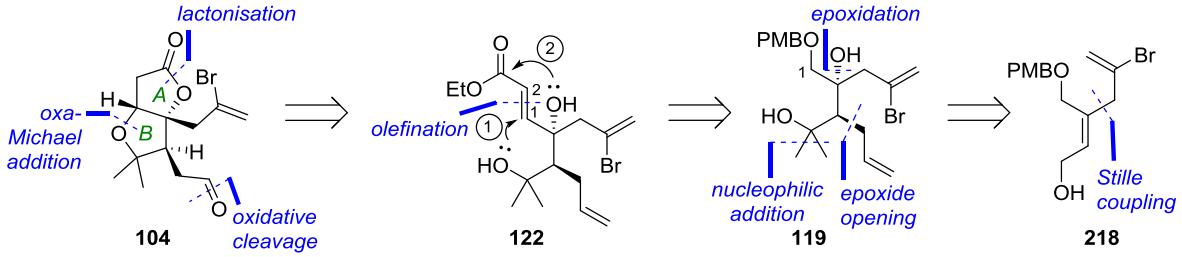
Thus far, efforts have been focused on the construction of the central CDEF core of rubriflordilactone A. However, the AB rings are of course just as important, and as much of a challenge, in the synthesis of rubriflordilactone A. Herein two syntheses of similar AB ring fragments are described.

4.1. The Bromoene AB Rings[101]

Based on disconnections of rubriflordilactones A and B, a pendent bromoalkene chain is necessary for the palladium-catalysed cascade cyclisation to proceed. Hence, we designed AB ring system **104** as shown in Scheme 4-1.

4.1.1. Retrosynthesis

It was envisaged that AB ring fragment **104** could be synthesised from key intermediate **122** *via* an oxidative cleavage of the terminal alkene moiety; and also a biomimetic[9] cascade reaction involving an oxa-Michael addition (①) with *in situ* lactonisation (②), in a similar manner to Yang and co-workers' construction of the ABC ring of micrandilactone A[23] and Mehta *et al.*'s synthesis of the ABC ring system of rubriflordilactone C[16] (Scheme 4-1). It is important to note that all previous syntheses of the ABC rings were achieved with a preformed C ring (or equivalent) as a template.[23,16,22,18,168,14] In contrast, our strategy would install the C ring at a later stage *via* a CDE cyclisation subsequent to AB ring formation; this would enable introduction of greater skeletal diversity.



Scheme 4-1 Retrosynthetic analysis of AB ring aldehyde **104**

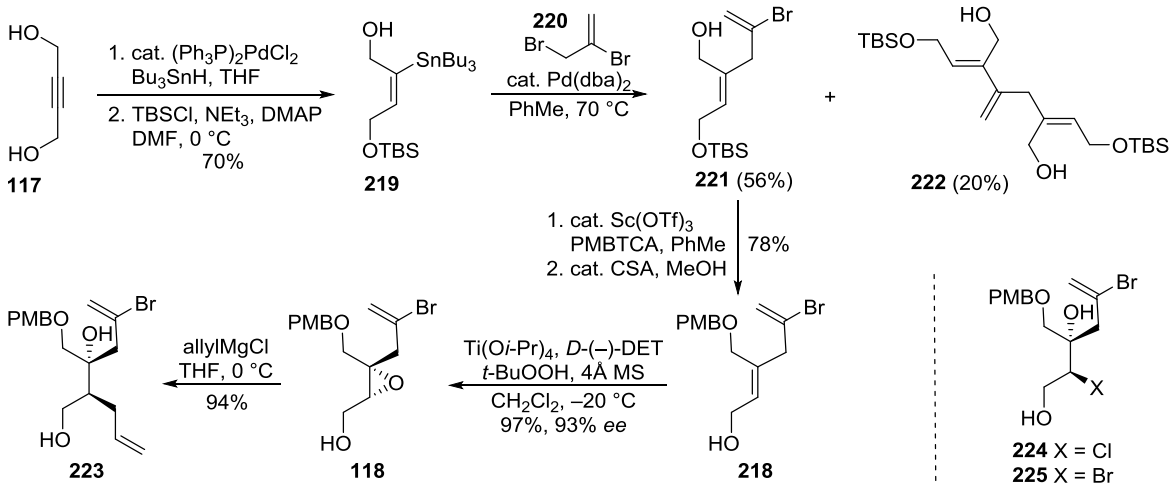
A disconnection at C1-C2 (rubriflordilactone A numbering) generated **119**; a Wittig or HWE reaction in the forward sequence would furnish α,β-unsaturated ester **122**, while a corresponding (*Z*)-selective olefination is expected to form an α,β-unsaturated lactone after *in situ* lactonisation. Alcohol **119** could be synthesised from alkene **218** by an asymmetric epoxidation with subsequent epoxide opening to set the two key stereocentres, as well as nucleophilic addition to install the *gem*-dimethyl moiety. Alkene **218** could be generated by a Stille coupling reaction from simple starting materials.

4.1.2. Synthesis of tertiary alcohol 119[98,vi]

The route to tertiary alcohol **119** started with a palladium-catalysed hydrostannylation[169] of but-2-yne-1,4-diol **117**, followed by regioselective monosilylation of the less hindered hydroxyl group to afford stannane **219** (Scheme 4-2). Stille coupling[170] of stannane **219** with 2,3-dibromopropene[171,172] **220** afforded vinyl bromide **221** in 56% yield. The relatively low yield of this desired vinyl bromide **221** can be partly attributed to the formation of byproduct **222** (21%), from successive Stille coupling reactions of one molecule of dibromopropene **220** with two molecules of stannane **219**. Despite the use of excess 2,3-dibromopropene (2.1 to 3.0 equiv.), the formation of byproduct **222** was not diminished, implying that the vinyl bromide moiety was competing with the allylic bromide functional group in the Stille reaction. Fortunately, these products were easily separable, affording a synthetically useful amount of

[vi] Synthesis of tertiary alcohol **119** was previously accomplished by Dr. Birgit Gockel, a former postdoctoral researcher, and Emma J. Puttock, a former Part II student, in the Anderson group. Reported here is a scale up and improvement of their procedure.

vinyl bromide **221** on multigram scale. Other electrophiles such as the allyl iodide,[170] acetate[173] and carbonate[174] were also tested,[vii] but these unfortunately did not improve the yield of vinyl bromide **221**.



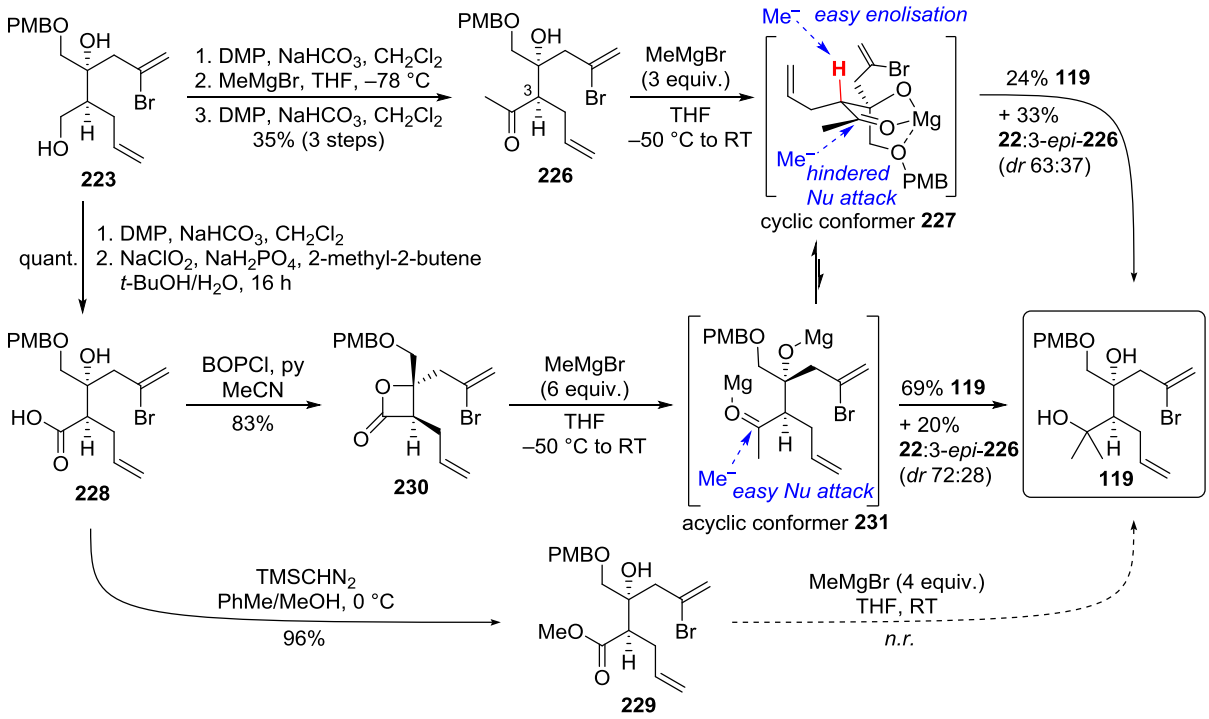
Scheme 4-2 Synthesis of primary alcohol **223**

From PMB ether **221**, a protecting group switch afforded alcohol **218** (Scheme 4-2), from which a Sharpless asymmetric epoxidation[175] delivered epoxide **118** in an excellent 97% yield with 93% *ee*, as determined by chiral HPLC. Ring opening of epoxide **118** with allylmagnesium chloride[176,177] proceeded regioselectively to afford diol **223**. The use of copper(I) cyanide as catalyst for ring opening[20] of epoxide **118** gave only chlorohydrin **224** in 61% yield with allylmagnesium chloride as reagent, and bromohydrin **225** in 81% yield with allylmagnesium bromide; similar results were obtained with other copper catalysts.[178–181]

The next challenge was to install the *gem*-dimethyl moiety to primary alcohol **223** (Scheme 4-3). We first attempted a repetitive stepwise oxidation / methylation sequence *via* intermediate ketone **226**.[98,viii] Ketone **226** was obtained in 35% yield after oxidation of the alcohol resulting from the first oxidation / methylation; however, the second addition of methylmagnesium bromide gave a low yield of tertiary alcohol **119** (24%), and the recovered ketone was partially epimerised at the allyl-bearing C3 stereocenter (**226**:3-*epi*-**226** = 63:37).

[vii] These investigations were conducted by Dr. Birgit Gockel, and Dr. Guilhem Chaubet, a current postdoctoral researcher, in the Anderson group; the author did not participate in these studies.
[viii] These investigations were conducted by Dr. Birgit Gockel and Emma Puttock in the Anderson group; the author did not participate in these investigations.

The formation of epimerised ketone **226** could be explained by a chelated bicyclic conformation **227**, in which attack of the Grignard nucleophile on the top face is disfavoured as it would have to proceed *via* a twist boat transition state, while attack on the bottom face is hindered by the concave face of this bicyclic complex; conversely, the α-proton of the ketone is easily accessible for enolisation to occur.[182] In contrast, the acyclic conformer **231** is more susceptible to attack by the Grignard nucleophile. However, as the equilibrium between these conformers likely lies towards the chelated form **227**, the overall conversion to tertiary alcohol **119** was low.



Scheme 4-3 Synthesis of tertiary alcohol **119**

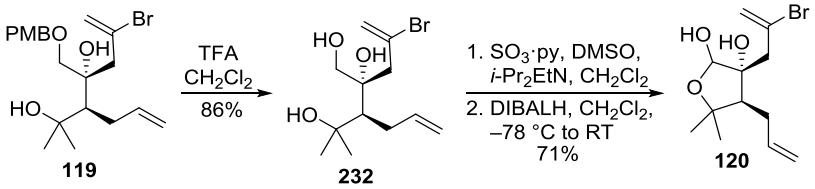
Next, primary alcohol **223** was oxidised to carboxylic acid **228** by sequential Dess-Marin oxidation / Pinnick oxidation in quantitative yield over two steps (Scheme 4-3). Esterification of acid **228** with trimethylsilyldiazomethane afforded methyl ester **229**, which unfortunately was completely unreactive to methylmagnesium bromide at room temperature,[98,ix] likely due to its preference for remaining in a chelated conformer analogous to bicyclic complex **227**.

[ix] These investigations were conducted by Dr. Birgit Gockel and Emma Puttock in the Anderson group; the author did not participate in these investigations.

An alternative esterification procedure using BOPCl serendipitously afforded β-lactone **230** in 83% yield, which to our delight could be double-methylated to generate tertiary alcohol **119** in 69% yield. This strained lactone **230** is initially incapable of forming the **227**-like chelate, and is rapidly attacked by methylmagnesium bromide to form acyclic ketone complex **231**. This complex **231** could either be attacked again by methylmagnesium bromide to form tertiary alcohol **119**, or undergo competing rearrangement to the chelated conformer **227**. In this case, it appears that the second Grignard addition is more rapid than the reaction from isolated ketone **226** (where initial alkoxide formation presumably promotes a rapid chelation), and thus the yield of tertiary alchol **119** was increased.

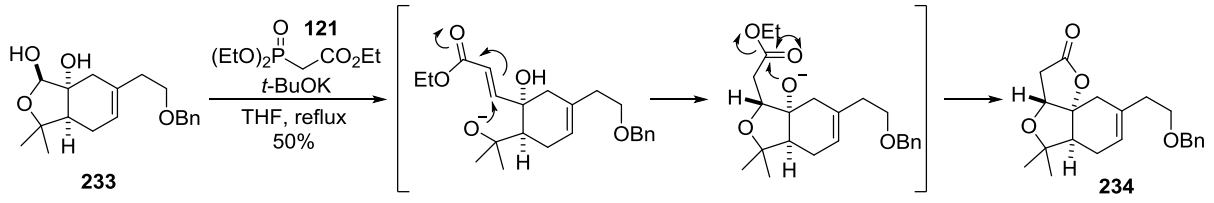
4.1.3. The closed lactol[x]

Deprotection of the PMB-protected alcohol **119** afforded triol **232**, which was converted by an oxidation / reduction sequence into lactol **120** (Scheme 4-4).



Scheme 4-4 Synthesis of lactol **120**

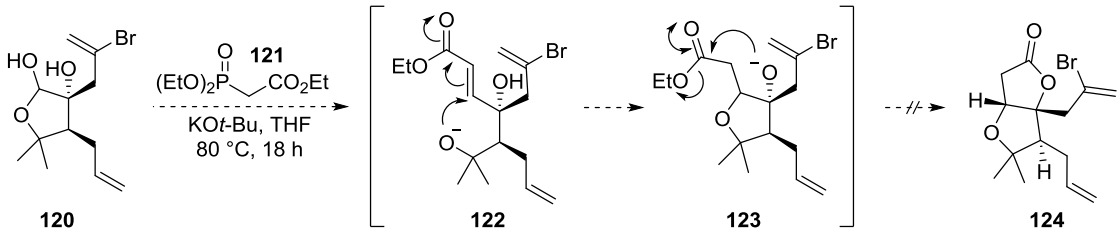
Previous studies by Yang *et al.* on the synthesis of the ABC ring unit of micrandilactone A **234** by a one-pot HWE olefination-*in situ* cascade cyclisation[23] from a similar lactol **233** (Scheme 4-5) suggested that the same could be applied to our system.



Scheme 4-5 Synthesis of the ABC ring unit **234** of micrandilactone A (Yang *et al.*, 2006)[23]

[x] Research on this route was conducted by Dr. Birgit Gockel in the Anderson group; the author did not participate in these investigations.

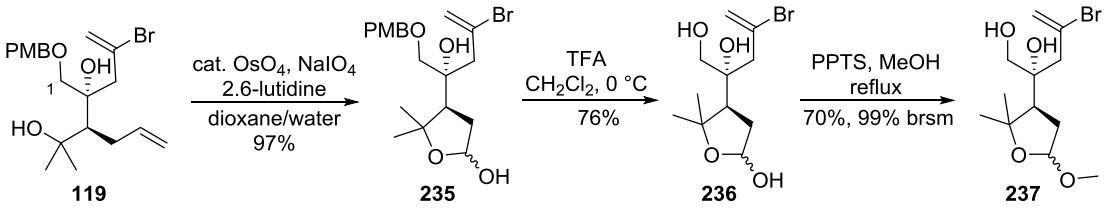
Based on the above precedent, we expected that treatment of lactol **120** with the same HWE reagent **121** would afford AB ring alkene **124** *via* a cascade reaction. First, the HWE olefination of lactol **120** would afford enoate **122**. This would undergo an intramolecular oxa-Michael attack by its alkoxide moiety to generate lactol **123**, which would then lactonise to give AB rings **124** (Scheme 4-6). Unfortunately, this effort was futile as lactol **120** could not be olefinated in productive yields. This suggested that in lactol **120**, Thorpe-Ingold effects from the *gem*-dimethyl moiety strongly disfavoured the equilibrium of the lactol with the open-chain aldehyde form which is reactive towards olefination; in contrast, the template C ring in **233** was instrumental in overcoming the Thorpe-Ingold effect, pushing the lactol-aldehyde equilibrium towards the open-chain aldehyde form, thereby generating the ABC ring unit of micrandilactone A. Since we lactol **120** was seemingly unreactive, an alternative route from tertiary alcohol **119** was necessary.



Scheme 4-6 Roadblock in route towards AB ring alkene **124**

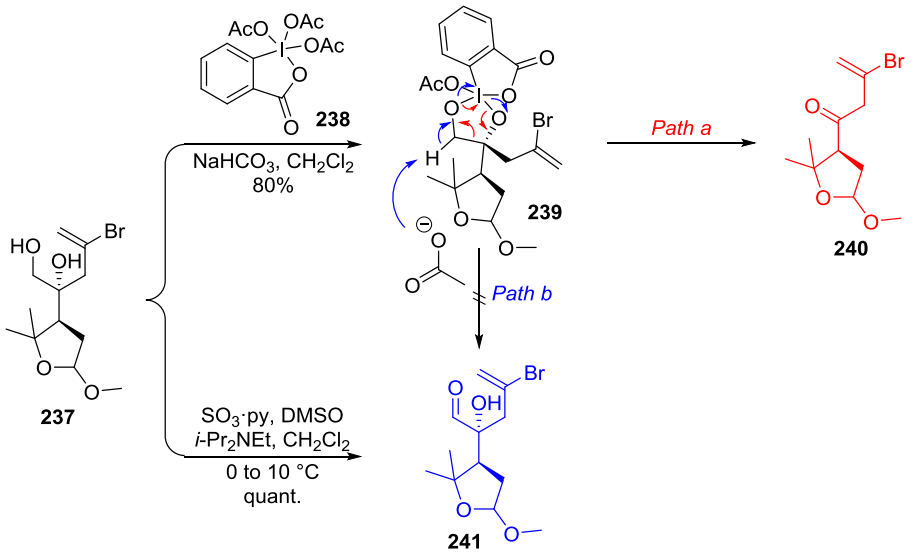
4.1.4. The reactive lactol

To avoid the formation of lactol **120**, we needed to protect the *gem*-dimethyl hydroxyl group so that it could not cyclise onto the aldehyde at C1 (rubriflordilactone A numbering). Our strategy was to protect this hydroxyl group as part of a different lactol or acetal **237**. To this end, oxidative cleavage of alkene **119** using the Lemieux-Johnson-Jin protocol[153] afforded lactol **235** in an excellent 97% yield (Scheme 4-7). The PMB ether was deprotected to give triol **236**, interestingly without any translactolisation, after which protection of the anomeric hydroxyl furnished methyl acetal **237**.



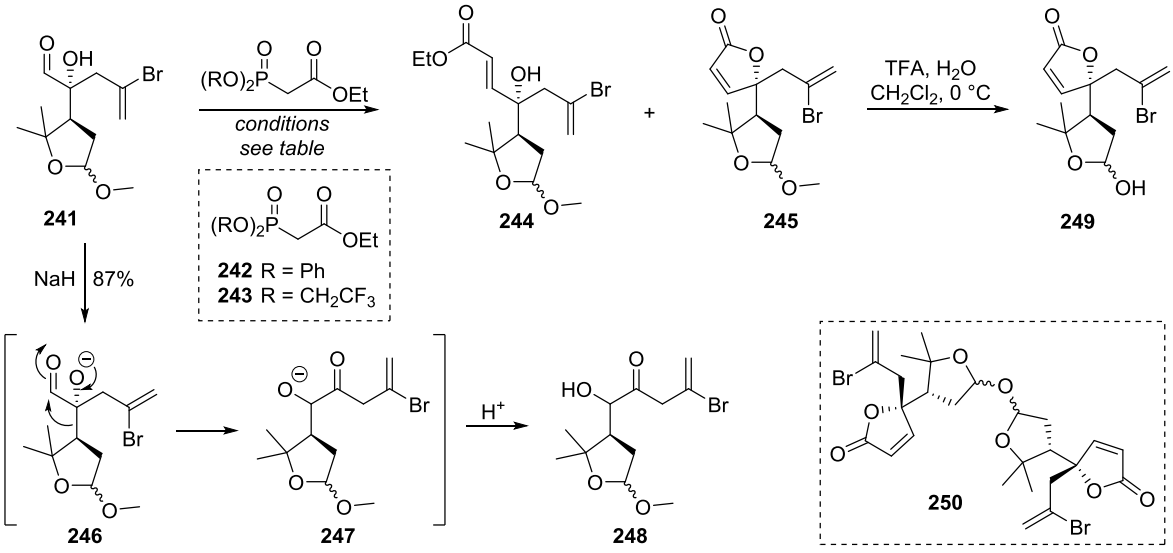
Scheme 4-7 Synthesis of lactol **237**

The next step required the oxidation of the primary alcohol in **237** in the presence of the adjacent tertiary alcohol to form aldehyde **241** (Scheme 4-8). With Dess-Martin periodinane (DMP) **238**,[183–186] only trace amounts of the desired aldehyde **241** were formed. Instead, the major product was ketone **240**, generated by oxidative cleavage of the diol with the hypervalent iodine reagent; this side reaction was precendented in Dess and Martin's own work,[15] and a mechanistic study by Santagostino *et. al.*[16] As illustrated in Scheme 4-8, diol **237** likely reacts with DMP **238** to form spirobicyclic iodoxolane **239**; this reactive intermediate could either break down to glycol C-C cleavage product **240** (*Path a*) or undergo proton abstraction to oxidation product **241** (*Path b*). In this case, the intramolecular pathway prevailed, delivering ketone **239**. Pleasingly, when we switched to Parikh-Doering[116] conditions (at low temperatures) for the oxidation of **237**, we obtained a quantitative yield of aldehyde **241**, as evidenced by the appearance of a singlet at 9.77 ppm (for the major diastereomer) in the ^{1}H NMR spectrum.



Scheme 4-8 Oxidation of primary alcohol **237**

Subsequently, aldehyde **241** would be olefinated by a (*Z*)-selective modified HWE reaction with either the Ando phosphonate[187] **242** or the Still-Gennari phosphonate[188] **243** (Scheme 4-9). We chose to use a (*Z*)-selective olefination so that *in situ* lactonisation would form the A ring in α,β-unsaturated lactone **245**; this would render the subsequent oxa-Michael cyclisation to form the B ring stereospecific.[14,18]



Scheme 4-9 Olefination of lactol **241**

Screening of reaction conditions with the Ando phosphonate **242** (Entries 1-2, Table 4-1) indicated that an excess of phosphonate reagent was necessary to drive the reaction to completion; otherwise the formation of α-hydroxyketone side product **248** was observed (Scheme 4-9). The α-hydroxyketone **248** was likely formed by a base-mediated α-ketol rearrangement[189] of α-hydroxyaldehyde **241**; deprotonation of tertiary alcohol leads to alkoxide **246**, which undergoes 1,2-alkyl shift to form alkoxide **247**, which upon protonation generates α-hydroxyketone **248**. Using Pihko and Salo's recommendation of excess sodium ions with sodium hydride as base and sodium iodide as additive,[190] instead of KHMDS, was detrimental to the reaction, resulting in complete conversion to side product **248** (Entry 3, Table 4-1). When Still-Gennari phosphonate **243** was utilised in the reaction, only moderate (*Z*)-selectivity was observed, with 16% of (*E*)-alkene **244** observed (Entry 4, Table 4-1), in contrast to the complete selectivity for the cyclised (*Z*)-alkene with the Ando phosphonate

242 (Entry 2, Table 4-1). The olefination product **245** could not be easily separated from the excess phosphonate reagent at this stage, but pleasingly lactol **249** could be isolated cleanly after deprotection of the methyl acetal **245** with TFA (Scheme 4-9). Addition of water in the deprotection step was essential to minimise the formation side product **250**, the oxy-bridged dimer of of lactol **249**.

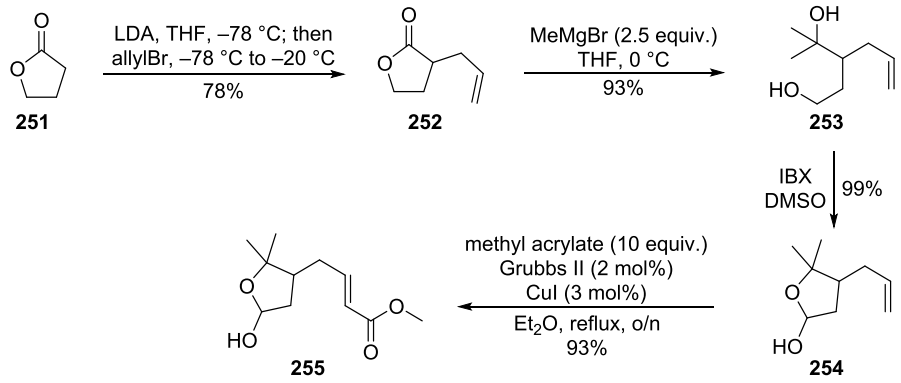
Entry	Reagents	Yield of 249[a] / %	Yield of 244 / %	Yield of 248 / %
1	**242** (1.1 equiv.), KHMDS (1.05 equiv.)	33	0	10
2	**242** (2.1 equiv.), KHMDS (2.0 equiv.)	55	0	0
3	**242** (1.3 equiv.), NaH (1.25 equiv.), NaI (1.0 equiv.)	0	0	87
4	**243** (2.1 equiv.), KHMDS (2.0 equiv.), 18-crown-6 (5.0 equiv.)[b]	46	16	0

Reaction conditions: A solution of phosphonate **242** or **243** (as indicated) and base (as indicated) in THF was stirred at 0 °C for 10 min, then added dropwise to a solution of **241** and additive in THF; reaction mixture was stirred between 0 °C and 10 °C for 2 h; [a] Yield over 2 steps; after TFA deprotection of methyl acetal **245**; [b] Reaction mixture was stirred from −78 °C to 0 °C.

Table 4-1 Olefination of lactol **241**

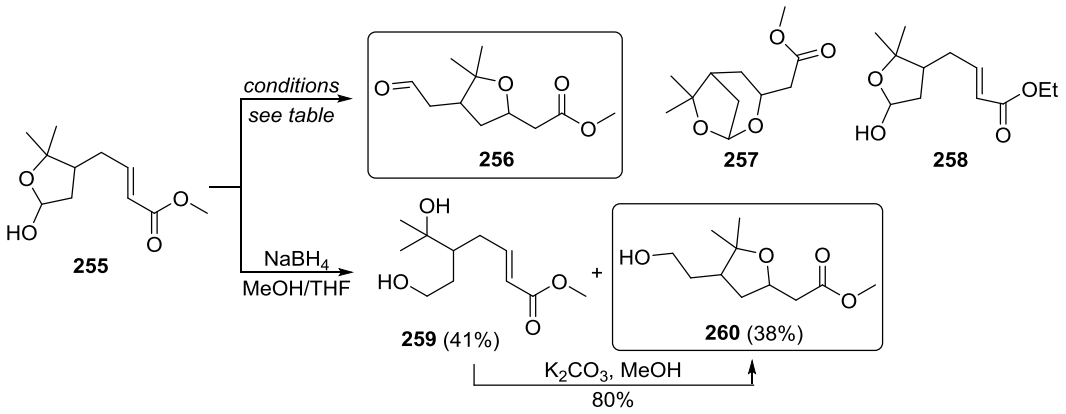
4.1.5. Model studies of the oxa-Michael addition

Completion of the AB ring aldehyde **104** from conjugated lactone **249** would involve ring opening of the lactol and subsequent oxa-Michael addition of the alkoxide generated onto the *α*,*β*-unsaturated lactone. To test the feasibility of a one-pot reaction, a model lactol-conjugated ester **255** was synthesised from γ-butyrolactone **251** in four steps *via* an allylation, double Grignard addition, oxidation and *in situ* lactol formation, and alkene metathesis (Scheme 4-10).



Scheme 4-10 Synthesis of model lactol-conjugated ester **255**

We screened several basic conditions to transform lactol **255** into aldehyde **256** (Table 4-2). Strong base sodium hydride gave a complex mixture of unidentified products, with no aldehyde **256** formed (Entry 1, Table 4-2). Alkoxide bases were more practical; potassium *tert*-butoxide effected the reaction at low temperatures (Entry 2, Table 4-2), while *in situ* generated ethoxide and methoxide bases required heating to 40 °C for the reaction to proceed; however, side products were observed in all of these reactions (Entries 2-5, Table 4-2). Non-nucleophilic amidine base DBU promoted a clean reaction, but this required elevated temperatures and did not reach completion (Entry 6, Table 4-2). The weak inorganic base potassium hydrogen carbonate was unable to effect any reaction (Entry 7, Table 4-2). These results suggest that the optimal bases fall within the pKa range of 10 < pKa < 20.



Entry	Conditions[a]	pKa	Yield of 256 / %	Recovered 255 / %	Side Product (Yield / %)
1	NaH, THF, 0 °C to RT, 2 h	37	0	0	complex mixture
2	KO^{t}Bu, THF, −78 °C to 0 °C, 5 h	19	21	11	**257** (9)
3	K_2CO_3, EtOH, 40 °C, 2 h	18	29	0	**258** (25)
4	**K_2CO_3, MeOH, 40 °C, 2 h**	**17**	**42**	**0**	**unknown**
5	Na_2CO_3, MeOH, 40 °C, 5 h	17	32	25	unknown
6	DBU, THF, 70 °C, 16 h	12	23	53	-
7	$KHCO_3$, MeOH, 40 °C, 5 h	7	n.r.	n.d.	-

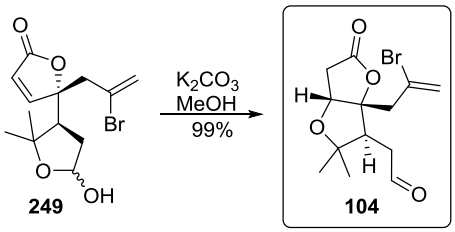
[a] All bases were used in 2.0 equiv.

Table 4-2 Screening of bases for conversion of lactol **255** to aldehyde **256**

Overall, this model study gave a positive indication that the one-pot reaction was viable, albeit in moderate yield. Similar conditions would be applied to intermediate **249** to hopefully arrive at AB ring aldehye **104**. As an alternative, after reduction of **255** with $NaBH_4$, the mixture of products (**259** and **260**) could be subjected to basic conditions to afford **260** in an overall yield of 71% over 2 steps.

4.1.6. Completion of the bromoene AB rings

Using our best conditions from the above model study on lactol **255**, we subjected AB ring precursor **249** to methanolic potassium carbonate. To our delight, these mildly conditions triggered the ring opening of lactol **249** and *in situ* oxa-Michael addition, even at room temperature, to afford the AB ring aldehyde **104** in 99% yield (Scheme 4-11).



Scheme 4-11 Completion of the bromoene AB rings **104**

The structure and stereochemistry of the AB ring aldehyde **104** were supported by NMR experiments, including ^{1}H NOE experiments (Figure 4-1). The NOE data showed that H5 is on the same face as H12', H9, H2 and H2', but on the opposite face from H12 and H3; supporting our assignment of stereochemistry.

500 MHz, $CDCl_3$, gradient NOE Tmix = 800 msec

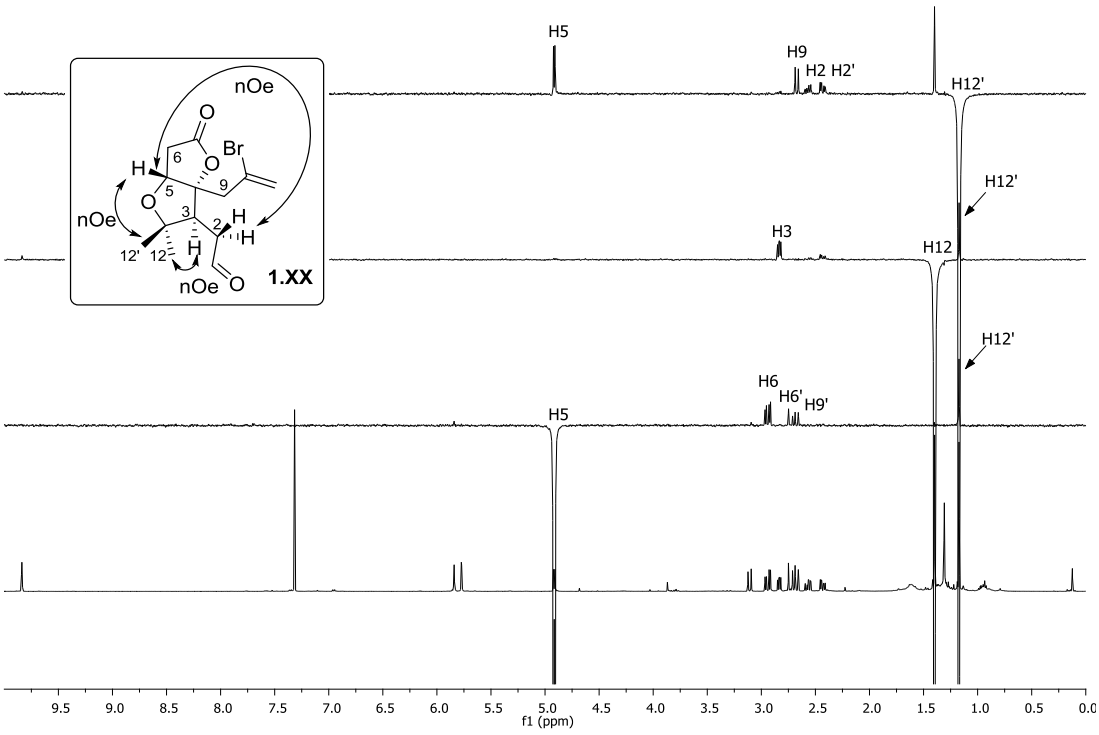


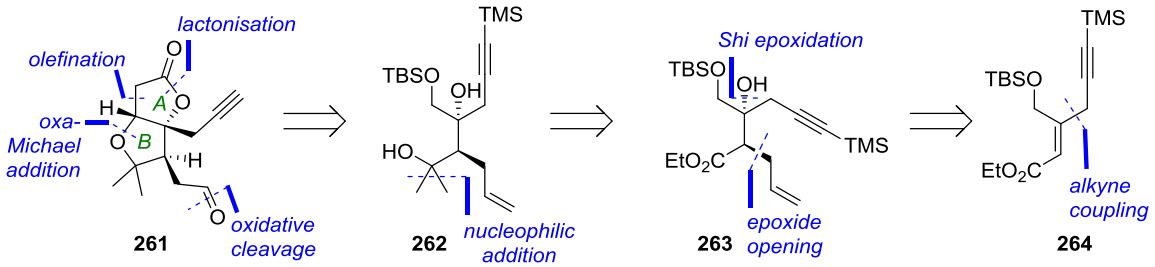
Figure 4-1 ^{1}H NOE NMR spectra of bromoene AB rings **104**

4.2. The Alkyne AB Rings[102]

With new insight into the applicability of the cobalt-catalysed cyclotrimerisation reaction in our synthesis (*see Section 2.3*), we needed to design an appropriate AB ring system for this ABCDE cyclisation reaction. Substituting the pendent bromoene chain for an alkyne gave the alkyne AB rings **261** (Scheme 4-12).

4.2.1. Retrosynthesis

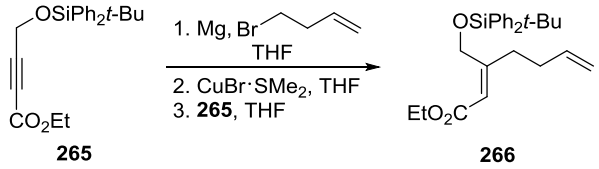
While it is reasonable to think that the alkyne AB rings **261** could be obtained from the bromoene AB rings **104** simply by elimination of HBr, we saw this new synthon as a chance to improve on our previous synthesis with a second-generation route. There were several drawbacks in our route to the bromoene AB rings **104** which we were keen to avoid. First, the use of stoichiometric amounts of toxic organotin reagents for Stille coupling reaction generates toxic byproducts and has safety implications on large scales, as well as being atom uneconomical; this is exacerbated by a low yield (56%) for the Stille reaction. Second, the need for a protecting group switch in the synthesis rendered it even more atom uneconomical. Finally, the multiple oxidation and reduction steps in the synthesis are also inefficient and "redox uneconomical".



Scheme 4-12 Retrosynthetic analysis of AB ring aldehyde **261**

Here, a new retrosynthesis is presented which aimed to overcome some of these drawbacks. The start of the retrosynthesis of alkyne AB rings **261** would be similar to that for the bromoene AB rings **104**, with the same disconnections leading to alcohol **262**. We envisaged

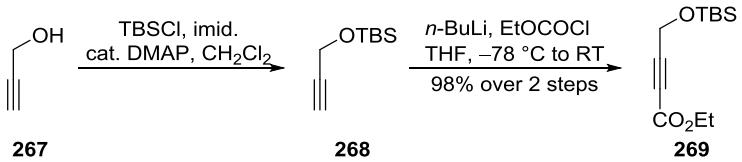
that the *gem*-dimethyl alcohol could be generated by double nucleophilic addition to ester **263**, itself synthesised by an asymmetric epoxidation of alkene **264** with subsequent epoxide opening to set the two key stereocenters. We proposed the use of the Shi epoxidation[191] instead of the Sharpless asymmetric epoxidation[175] here to eradicate the need for reduction of the ester before epoxidation, and later re-oxidation for the nucleophilic addition. Inspired by Barrett and co-workers' use of a *syn*-carbocupration of acetylenic ester **265** to form diene **266** in the total synthesis of *ent*-clavilactone B[192] (Scheme 4-13) and other precedent,[193] we envisaged that enyne **264** could be formed by a similar copper-mediated alkyne coupling from simple starting materials.



Scheme 4-13 Synthesis of diene **266** by cuprate addition (Barrett *et al.*, 2006)[192]

4.2.2. Investigation of the *syn*-carbocupration of acetylenic ester 269[99,194,xi]

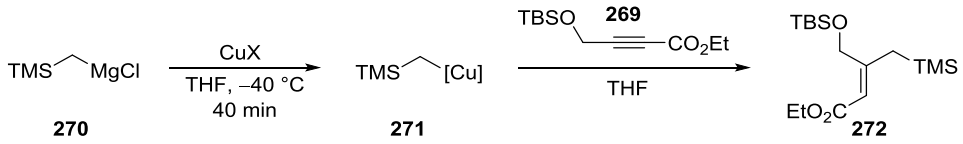
Our synthesis started from propargylic alcohol **267**, which smoothly underwent TBS protection to give alkyne **268** (Scheme 4-14). Addition of the lithiated alkyne **268** to ethyl chloroformate subsequently afforded ester **269** in 98% yield over 2 steps.



Scheme 4-14 Two step sequence to alkyne **269**

[xi] These steps were previously achieved by Hannah Baars and Andrew Phillips, a former Part II student, in the Anderson group under the supervision of the author. Reported here is a scale up and improvement of their procedure.

Next, we investigated the *syn*-carbocupration of acetylenic ester **269**, a key step in our synthesis. Preliminary studies by Baars[99,xii] with (trimethylsilyl)methylmagnesium chloride **270** using conditions published by Itoh and co-workers[195] showed that the choice of copper source was crucial: using copper(I) iodide for transmetalation did not effect any reaction (Entry 1, Table 4-3), while copper(I) bromide dimethylsulfide complex was observed to promote the reaction (Entry 2, Table 4-3). The amount of organocuprate **271** used also played an important role in achieving conversion to desired product **272** (Entries 4-6, Table 4-3), with a 1.5:1 ratio of organocuprate **272** to alkyne **269** giving the best results. The temperature of the reaction was also important: allowing the reaction temperature to warm up to 0 °C led to the formation of side products, and no desired product was obtained (Entry 2, Table 4-3).



270 **271** **272**

Entry	CuX	269 equiv.	T / °C	time / h	Results
1	CuI	1.2	−78	1	**269**:**272** = n.r.
2	$CuBr{\cdot}SMe_2$	1.2	−78	1	**269**:**272** = 5:1
3	$CuBr{\cdot}SMe_2$	1.2	0	5	No **272**
4	$CuBr{\cdot}SMe_2$	0.83	−40	2.5	**269**:**272** = 1:2
5	**$CuBr{\cdot}SMe_2$**	**0.67**	**−40**	**2.5**	**269:272** = **1:8**
6	$CuBr{\cdot}SMe_2$	0.5	−40	4	**272**:unknown = 6:1

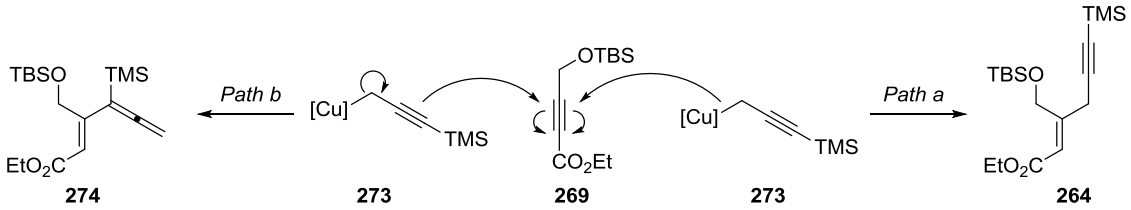
Reaction conditions: To a suspension of CuX (as indicated) in THF (0.15 M) was added dropwise a solution of $(TMS)CH_2MgCl$ (as indicated), then stirred at −40 °C for 40min; the reaction mixture was cooled to −78 °C before a solution of alkyne **269** (0.12 mmol) in THF (0.2 mL) was added. The reaction mixture was stirred warming to temperature T (as indicated) for time t (as indicated).

Table 4-3 Optimisation of alkyne coupling reaction with (trimethylsilyl)methylmagnesium chloride (Baars, 2012)[99,xiii]

[xii] This preliminary study was conducted by Hannah Baars in the Anderson group. The author's role in this study was limited to guidance and supervision.

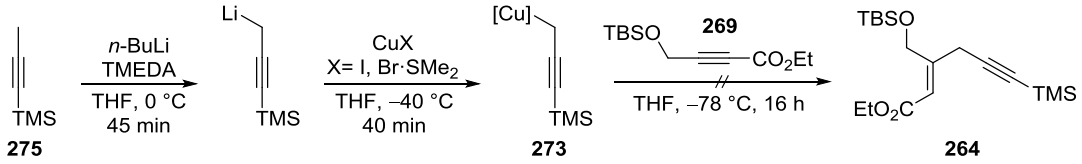
[xiii] This preliminary study was conducted by Hannah Baars in the Anderson group. The author's role in this study was limited to guidance and supervision.

Having experienced success in this preliminary study, we moved onto the use of propargylic cuprate **273** for the carbocupration of alkyne **269**. Unlike alkyl cuprate **271**, the propargylic cuprate **273** could react in two ways (Scheme 4-15), adding to the challenge. The cuprate could either attack the alkyne from the propargylic carbon to form desired enyne product **264** (*Path a*), or through the alkyne to form allene product **274** (*Path b*). Work by Ganem[196] and Jamison *et al.*[197] have shown that the desired selectivity could be achieved when the propargylic alcohol was protected with a sterically demanding group.



Scheme 4-15 Selectivity in cuprate addition

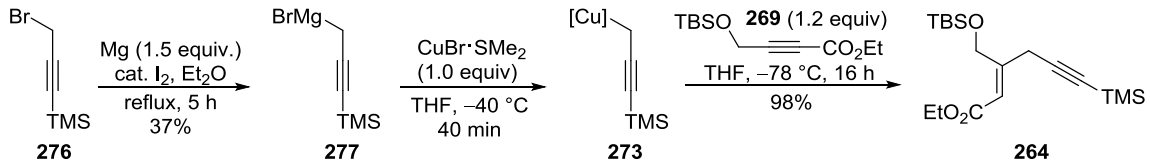
The reaction was initially attempted using Jamison and co-workers'[197] protocol to form the organocuprate **273**. Unfortunately, after lithiation of 1-(trimethylsilyl)propyne **275**, attempts at transmetalation and addition to alkyne **269** never afforded any desired product **264**, with only alkyne **269** recovered (Scheme 4-16).[99,xiv]



Scheme 4-16 Failed coupling of alkyne **264**

[xiv] This investigation was conducted by Hannah Baars in the Anderson group. The author's role in this study was limited to guidance and supervision.

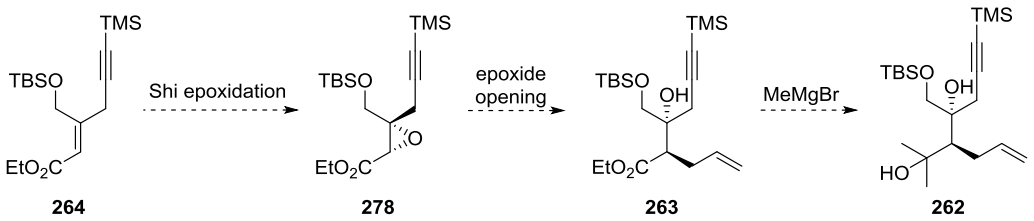
We hypothesised that the reactivity of the cuprate **273** would be affected by the exact nature of the copper species generated *in situ*, including its coordinating environment. In this vein, we decided instead to attempt to form organocuprate **273** from Grignard reagent **277**[198] (Scheme 4-17). Treatment of 3-bromo-1-(trimethylsilyl)-1-propyne **276** with magnesium turnings in refluxing diethylether generated Grignard reagent **277**, which was transmetalated with copper(I) bromide dimethylsulfide complex to form organocuprate **273**. Thereafter, addition of organocuprate **273** to acetylenic ester **269** (0.67 equiv.) using the previously optimised conditions afforded enyne **264** in 81% yield (from alkyne **269**). However, this protocol was inefficient since the Grignard reagent **273**, which required the greater synthetic effort, was being used in excess (1.5 times of alkyne **269**) and was of course not recoverable. Gratifyingly, we were able invert the ratio of organocuprate **273** to alkyne **269** from 1.5:1 to 1:1.2, a discovery which further enhanced the yield of enyne **264** from 81% to an excellent 98%.



Scheme 4-17 Copper-mediated coupling of alkyne **269** with cuprate **273**

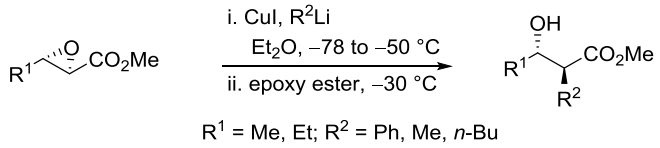
4.2.3. Synthesis of tertiary alcohol 262[194,xv]

We were keen to utilise the Shi epoxidation of alkene **264**, followed by ring opening of the resulting epoxide **278** and double methyl addition to ester **263** to obtain tertiary alcohol **262** (Scheme 4-18). This would minimise the number of redox manipulations and reduce the number of steps in the current route.



Scheme 4-18 Proposed route from ester **264** to tertiary alcohol **262**

Selective epoxide opening in the presence of an ester moiety is not unprecedented. Mulzer and Lammer used organocuprates to achieve this selectivity in 1986; transmetalation of organolithium reagents with copper(I) iodide afforded organocuprate reagents which effected ring opening of disubstitued epoxy esters to α-alkyl-β-hydroxyesters in good yields (~60%) with perfect regio- and stereocontrol (Scheme 4-19).[199] Unfortunately, preliminary studies by Baars showed that this protocol was not amenable to trisubstituted epoxides.[99,xvi]

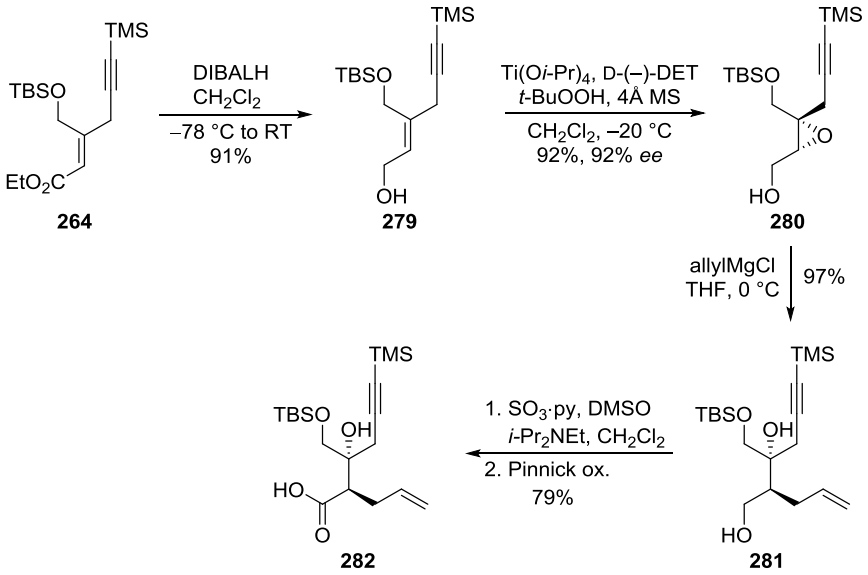


Scheme 4-19 Selective epoxide opening with organocuprates (Mulzer and Lammer, 1986)[199]

As such, we decided to return to our previously established route to the tertiary alcohol **119** en route to the bromoene AB rings **104** (*see Section 4.1.2*). DIBALH reduction of ester **264** gave alcohol **279** in 90% yield (Scheme 4-20). A Sharpless asymmetric epoxidation[175] of alkene **279** afforded epoxide **280** in with excellent yield and enantioselectivity, as determined

[xv] These steps were previously achieved by Andrew Phillips in the Anderson group under the supervision of the author. Reported here is a scale up and improvement of his procedure.
[xvi] This preliminary study was conducted on ethyl 3,3-dimethyloxirane-2-carboxylate by Hannah Baars in the Anderson group. The author's role in this study was limited to guidance and supervision.

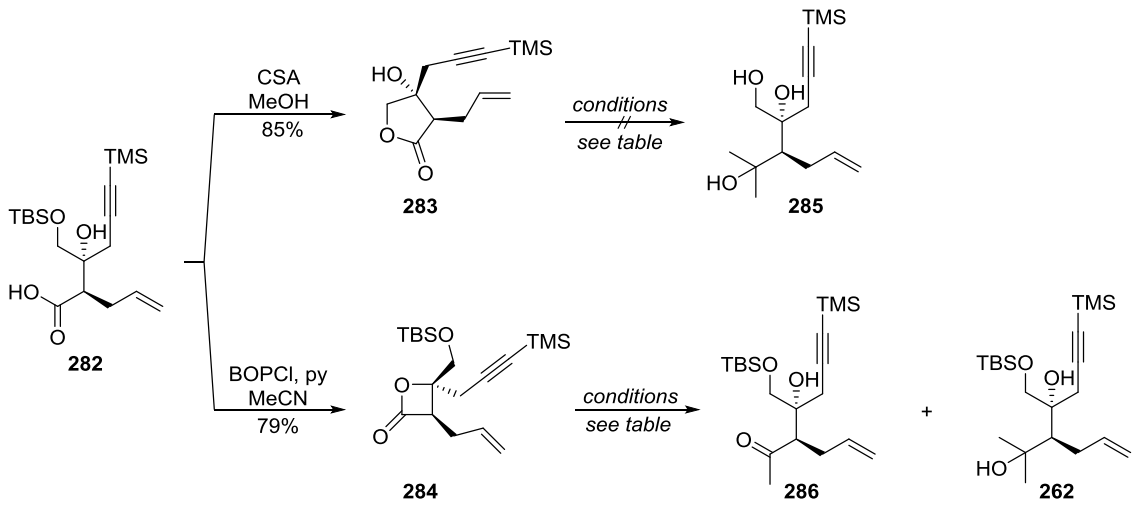
by chiral HPLC. Thereafter, ring opening of epoxide **280** with allylmagnesium chloride afforded diol **281** in 97% yield.[xvii] A two-step oxidation of the primary alcohol **281** gave acid **282** in 79% yield.



Scheme 4-20 Synthesis of acid **282**

We next proceeded to investigate the double methyl addition to form tertiary alcohol **262** *via* both the δ-lactone **283** and the β-lactone **284** (Scheme 4-21). Synthesis of both these lactones proceeded smoothly from acid **282**, with the δ-lactone **283** formed under acidic conditions in 85% yield, and the β-lactone **284** formed with coupling reagent BOPCl in 79% yield. Unfortunately, opening of the δ-lactone **283** proved difficult under a multitude of conditions, with only trace amounts of triol **285** observed at best. No reaction was observed when 2 equiv. of methylmagnesium bromide was added to δ-lactone **283** (Entry 1, Table 4-4), but when 6 equiv. of either methylmagnesium bromide or methyllithium was added **283**, multiple products were formed with only trace amounts of triol **285** detected (Entries 2-3, Table 4-4).

[xvii] These two steps were accomplished by Andrew Phillips and Guilhem Chaubet in the Anderson group. The author has not performed these steps herself.



Scheme 4-21 Synthesis of tertiary alcohol **262**

Entry	Substrate	Conditions	Yield of 286 / %	Yield of 262 / %
1	**283**	MeMgBr (2 equiv.), THF, −5 °C to 10 °C	n.r.	n.r.
2	**283**	MeMgBr (6 equiv.), THF, −5 °C to 10 °C	0	trace[a]
3	**283**	MeLi (6 equiv.), THF, −5 °C to 10 °C	0	0
4	**284**	**MeMgBr (6 equiv.), THF, −5 °C to 10 °C**	**32**	**67**
5	**284**	MeMgBr (6 equiv.), THF, −5 °C to 10 °C, inverse addition	38[b]	52
6	**284**	MeLi·LiBr (6 equiv.), Et_2O, 0 °C	64	34
7	**284**	MeLi·LiBr (6 equiv.), THF, 0 °C to 10 °C	60	12
8	**284**	MeLi·LiBr (6 equiv.), DMPU, THF, 0 °C	43	7
9	**284**	MeLi (6 equiv.), Et_2O, −5 °C to 10 °C	28[c]	11[c]
10	**286**	MeMgBr (3 equiv.), THF, −5 °C to RT	0	trace
11	**286**	**MeMgBr (3 equiv.), THF, −5 °C to 10 °C, inverse addition**	**55**	**37**
12	**286**	MeMgBr (3 equiv.), THF, RT, inverse addition	44[b]	39

[a] Yield of alcohol **285**; [b] Epimerisation of ketone **286** observed; [c] Alkyne desilylation observed.

Table 4-4 Screening of conditions for formation of tertiary alcohol **262**

Gratifyingly, the β-lactone **284** could be opened with methyl Grignard or methyllithium reagents, with methylmagnesium bromide giving the best yield of tertiary alcohol **262** at 67% (Entry 4, Table 4-4). In addition, the methyl ketone byproduct **286** was isolated in 32% yield;

and unlike the corresponding methyl ketone **226** of the bromoene AB rings route (*see Section 4.1.2*), no epimerisation was observed. We hypothesise that this difference in reactivity was due to the differing chelated conformations of intermediate methyl ketones **226** and **286**, which is likely influenced by the different substituents on the β-carbon. For methyl ketone **226** of the bromoene AB rings route, the PMB-protected hydroxyl group is capable of chelation to the magnesium cation. This, coupled with the preference for the bulky bromoene moiety to lie in an pseudo-equatorial position, locks the transition state in the chelated conformation **227** (Figure 4-2). While this conformation hinders nucleophilic attack on the ketone, it exposes the α-proton to attack by base. As such, further reaction of the ketone to form tertiary alcohol **119** was difficult, but enolisation of the α-proton was observed. In contrast, the TBS-protected hydroxyl group in methyl ketone **286** of the alkyne AB rings route is less able to chelate the magnesium cation. It also possesses greater steric bulk compared to the propargyl substituent and thus preferentially lies in the pseudo-equatorial position. In this chelated conformation **287** (Figure 4-2), both the ketone and α-proton are now shielded from attack. Thus methyl ketone **286** was isolated unepimerised from the reaction mixture.

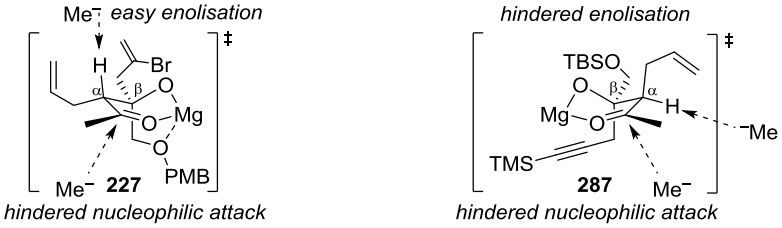
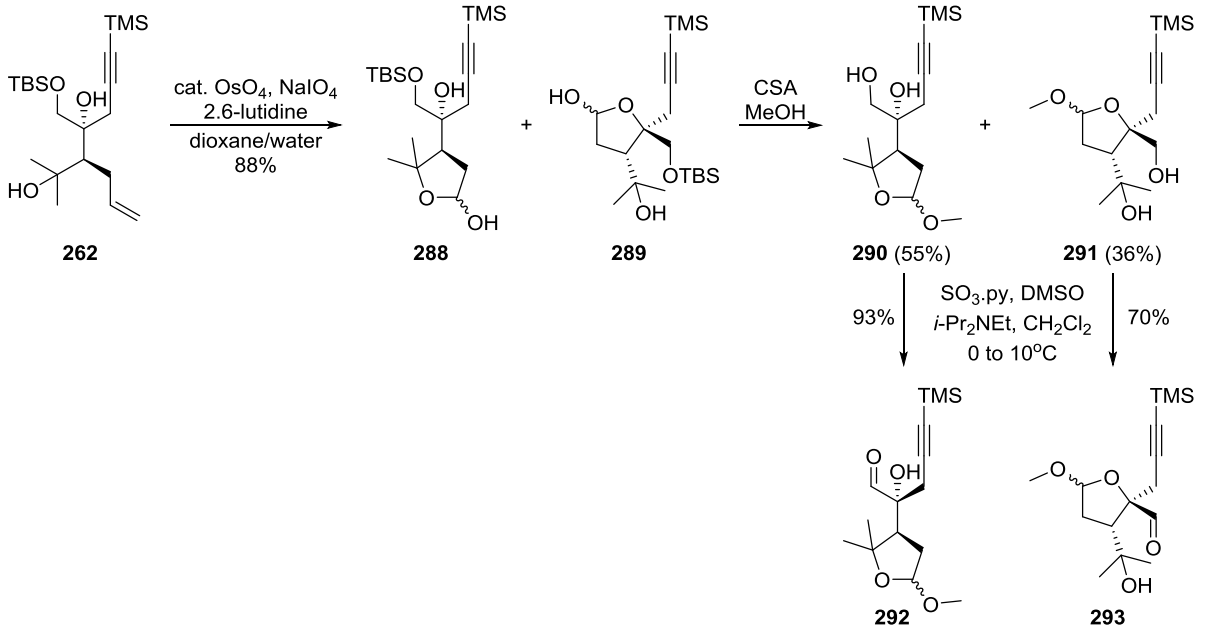


Figure 4-2 Proposed chelated conformations for methyl ketone intermediates **227** and **287**

Fortunately, inverse addition of methylmagnesium bromide to methyl ketone **286** at 0 °C could improve the yield of tertiary alcohol **262** to 75% over two iterations (Entry 11, Table 4-4), although the majority of ketone **262** remained unreacted (55%). Increasing the temperature at which inverse addition occurs did not improve the yield, and instead this time did cause epimerisation of the methyl ketone **286** (Entry 12, Table 4-4).

4.2.4. Too many lactols

A Lemieux-Johnson-Jin[153] oxidative cleavage of alkene **262** gave a mixture of inseparable regioisomeric lactols **288** and **289** (Scheme 4-22), arising from competing acetal formation by the two tertiary alcohols in **262**. The predominant regioisomer was **288** where the *gem*-dimethyl hydroxyl group is involved in acetal formation. Stirring in methanol under acidic conditions first protected the anomeric hydroxyl group, then cleaved the TBS protecing group on the primary lactol to yield the regioisomeric methyl lactols **290** (55%) and **291** (36%), which could be separated. Both of these primary alcohols **290** and **291** were oxidised under Parikh-Doering[116] conditions to aldehydes **292** and **293** respectively.



Scheme 4-22 From tertiary alcohol **262** to the lactols

This formation of the two methyl acetal regioisomers **290** and **291** was surprising since only regioisomer **237** was observed in the bromoene AB rings route (*see Section 4.1.4*). However, as we expected that both aldehyde regioisomers **292** and **293** could be transformed into the alkyne AB rings **261**, this observation was not too worrying. We attributed the difference in selectivity to the differing energies of the regioisomeric acetals, which would be affected by the size of the R group (bromoene vs alkyne). In solution, an equilibrium exists between the anomeric *gem*-dimethyl lactols **288α** and **288β**, the open-chain aldehyde form **294**, and their

regioisomeric lactols **289α** and **289β** (Figure 4-3). As shown in the envelope conformation, the 5-membered tetrahydrofuran ring of the *gem*-dimethyl lactol anomers **288α** and **288β** is formed by C1, C2, C3 and C7 (aldehyde **294** numbering), with C2 in the *endo* position. In these conformers, the tetrasubstituted C4 atom lies in a pseudo-equatorial position off C3. On the other hand, the regioisomeric hydroxymethyl lactol anomers **289α** and **289β** lie in the conformation with C1, C2, C3 and C4 forming the tetrahydrofuran ring, where C2 is still in the *endo* position. However, here the bulky C7 dimethylhydroxyl moiety lies in a pseudo-equatorial position off C3, forcing the C5 substituent to adopt a pseudo-axial position off C4. This results in 1,3-diaxial interactions between the C5 substituent and the axial C2 hydrogen. When the R group is an alkyne, since the C5 alkyne substituent is small, the 1,3-diaxial interactions raises the energy of hydroxymethyl lactol **289** when compared to the *gem*-dimethyl lactol **288** by a small amount, thus the observed ratio of lactols **288**:**289** was 67:33. Under acidic conditions, protonation of the anomeric hydroxyl transformed it into a good leaving group, thus forming oxocarbenium ions **295** and **296** from lactols **288** and **289** respectively. Attack of methanol on oxocarbenium ions then generated their corresponding methyl acetals – *gem*-dimethyl lactol **290** or hydroxymethyl lactol **291**. Should the reaction proceed by kinetic control, we would expect a similar ratio of methylated products as compared to the lactols; while thermodynamic control would afford a mixture of methyl acetals based on their energy profiles (which would also be analogous to that of the lactols). In this event, we used camphorsulphonic acid to achieve both methyl acetal formation and TBS deprotection simultaneously, affording a similar 61:39 mixture of methyl acetal regioisomers **290**:**291**.

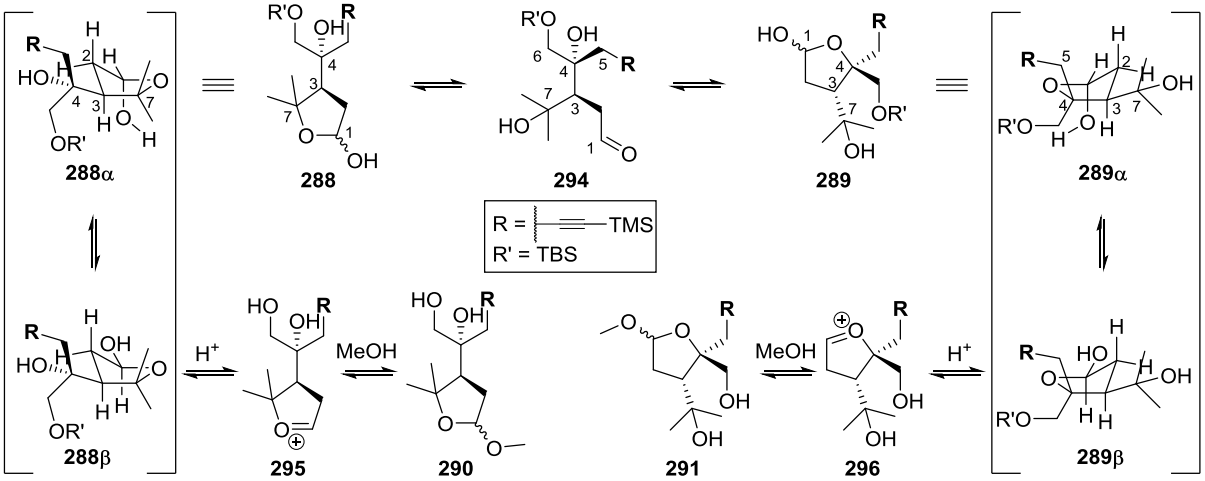
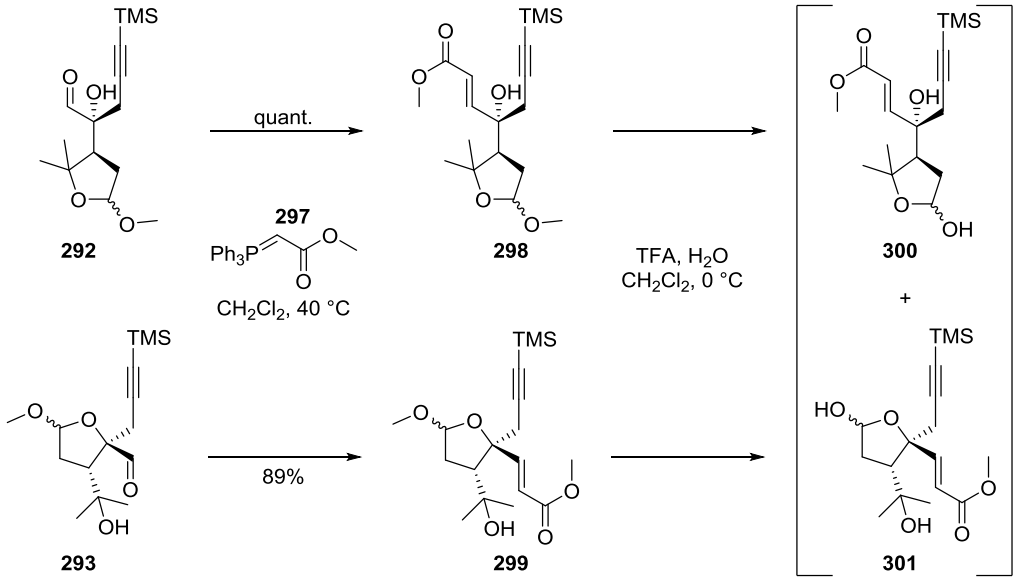


Figure 4-3 Proposed conformations for alkyne lactol regioisomers **288** and **289**

In contrast, when the C5 substituent is the bulky bromoene moiety, a stronger 1,3-diaxial repulsion would exist in the hydroxymethyl lactol. This increase in energy as compared to the *gem*-dimethyl lactol **236** is reflected in absence of the hydroxymethyl lactol regioisomer after deprotection of the PMB ether **235** under strong acid conditions (trifluoroacetic acid in dichloromethane, *see Section 4.1.4*). Thereafter, acetal protection (PPTS in refluxing methanol, *see Section 4.1.4*) afforded only methyl acetal **237**.

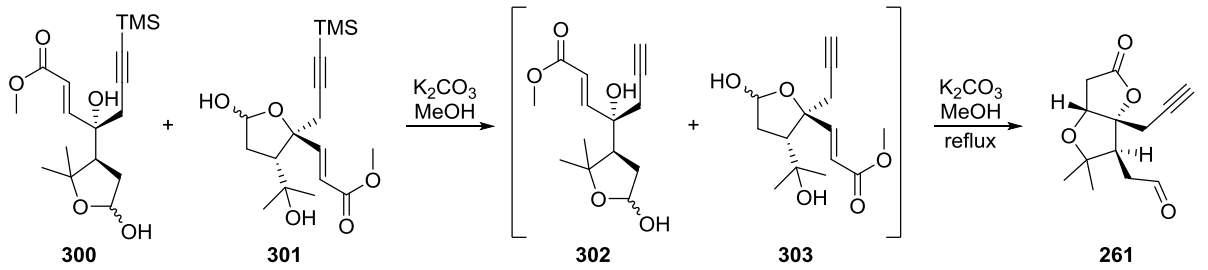
4.2.5. The (*E*)-olefination route

Based on our proposed retrosynthesis (*see Section 4.1.1*), both (*E*)- and (*Z*)-olefination should be able to lead to the formation of the AB rings. Since we had already explored (*Z*)-olefination en route to the bromoene AB rings **104** (*see Section 4.1.4*), we decided to investigate the alternative route *via* the (*E*)-alkene. In this vein, reaction of aldehydes **292** and **293** with Wittig phosphorane **297** afforded (*E*)-enoates **298** and **299** respectively (Scheme 4-23). Deprotection of each of the methyl acetal **298** and **299** led, once again, to a mixture of the two regioisomeric forms of the lactols **300** and **301**.



Scheme 4-23 (*E*)-olefination of aldehydes **292** and **293**

Finally, we attempted to form the AB rings and deprotect the alkyne from lactols **300** and **301** in a single step (Scheme 4-24). The same conditions employed for the synthesis of the bromoene AB rings **104** (methanolic potassium carbonate at room temperature, *see Section 4.1.6*) unfortunately only effected the deprotection of the alkyne to give a mixture of lactols **302** and **303**. However, upon heating the reaction mixture to 45 °C, formation of some alkyne AB rings **261** was observed, albeit in low conversion (unoptimised).



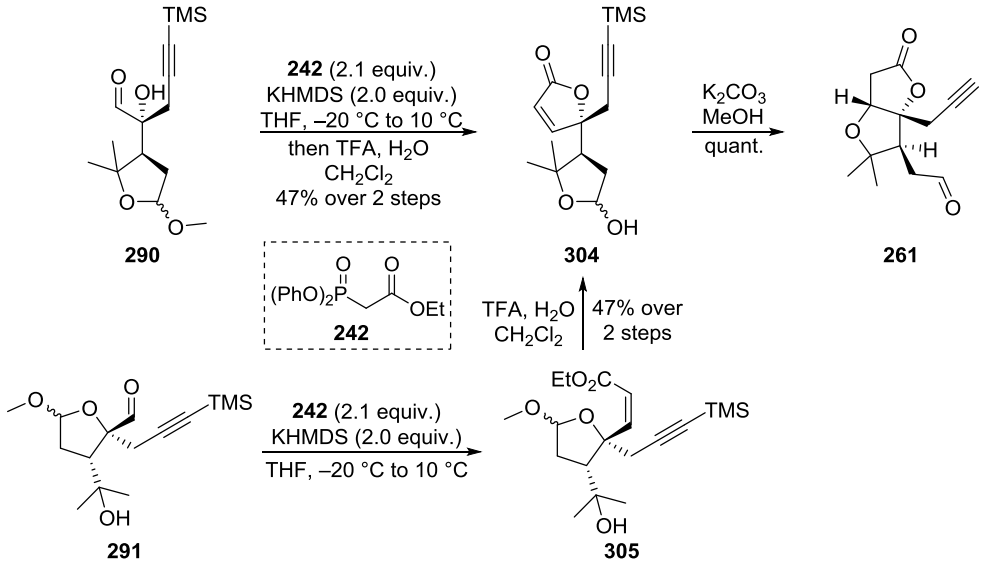
Scheme 4-24 From (*E*)-enoates to alkyne AB rings **261**

The yields from this route paled in comparison to the (Z)-enoate route which we had utilised for the synthesis of the bromoene AB rings **104** (*see Section 4.1.4*). We had postulated before that a pre-formed A ring would aid the subsequent construction of the B ring; but we did not expect that the difference in reactivity would be so great, since Yang and co-workers had synthesised the AB rings of micrandilactone A by a similar cascade cyclisation strategy.[23] These results again suggested that the presence of the C ring was extremely important to their strategy. Unsatisfied by the low yield of the alkyne AB rings **261** from this strategy, we returned to our previously established methodology using (*Z*)-olefination.

4.2.6. Completion of the alkyne AB rings[xviii]

By using Ando phosphonate **242** instead of the Wittig phosphorane **297** for the olefination of aldehyde **290**, we obtained butenolide **304** after methyl acetal deprotection in 47% yield over two steps (Scheme 4-25). This result is similar to the analogous route we established with the bromoene AB rings (*see Section 4.1.4*). Pleasingly, when regioisomeric aldehyde **291** was subjected to the same synthetic route, butenolide **304** was also obtained.[xix] This synthesis proceeded *via* enoate **305**, which rearranged upon treatment with TFA to afford butenolide **304** in 47% over two steps. Finally, a ring opening/oxa-Michael addition of lactol **304** afforded the alkyne AB rings **261** in quantitative yield.

[xviii] These steps were previously accomplished by Guilhem Chaubet in the Anderson group. Reported here is a scale up and improvement of his procedure.
[xix] These two steps were accomplished by Guilhem Chaubet in the Anderson group. The author has not performed these steps herself.



Scheme 4-25 Completion of alkyne AB rings **261**

Hitherto, we have presented two syntheses of AB ring aldehydes – bromoene **104** and alkyne **261**. Nucleophilic addition of the CDE diyne fragment **105** to each fragment would generate substrates which could be cyclised by different methodologies to the ABCDE pentacycles.

5. Attachment of the G Ring Butenolide

With the CDEF ring system of rubriflordilactone A in place, we turned our attention to attaching the G ring butenolide. As we envisaged that this would form the last step(s) of the total syntheses of rubriflordilactones A **31** and B **32**, a thorough investigation of this transformation was crucial for success.

5.1. Initial Forays into the Oxocarbenium Ion Addition Reaction

Our first disconnection for both rubriflordilactone A and B was the C22-C23 bond linking the G ring butenolide to the F ring (Figure 5-1). We envisaged that this bond could be formed by addition of an appropriate G ring siloxyfuran such as **55** to the oxocarbenium ions formed by activation of the ABCDEF ring precursors **98** and **99**, for rubriflordilactones A and B respectively.

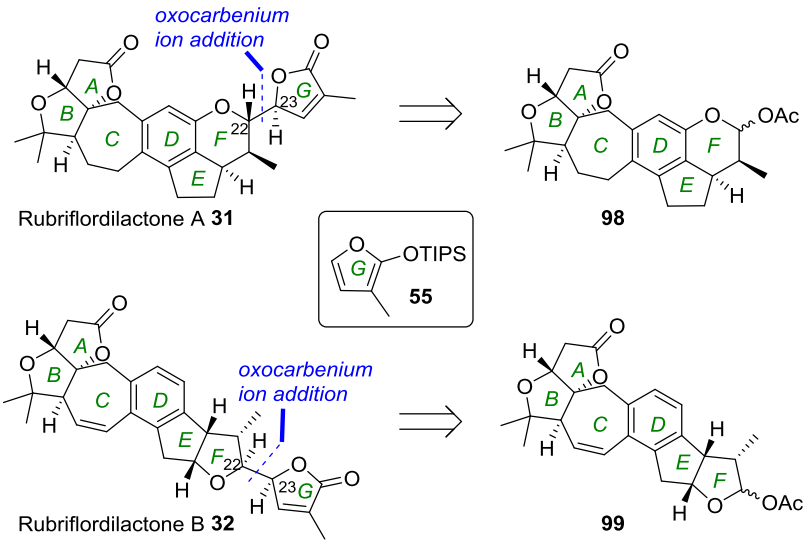


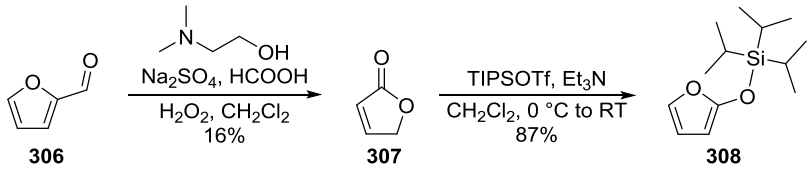
Figure 5-1 Disconnection of G ring in rubriflordilactones A and B

Oxocarbenium ions are important intermediates in the synthesis of complex natural products, particularly in the field of carbohydrate chemistry, where glycosylation is an important reaction. There have been numerous methods for Lewis acid-mediated substrate-controlled diastereoselective additions to substituted oxocarbenium ions,[200,201] and in recent years

studies into enantioselective addition reactions to prochiral oxocarbenium ions have emerged.[202–205]

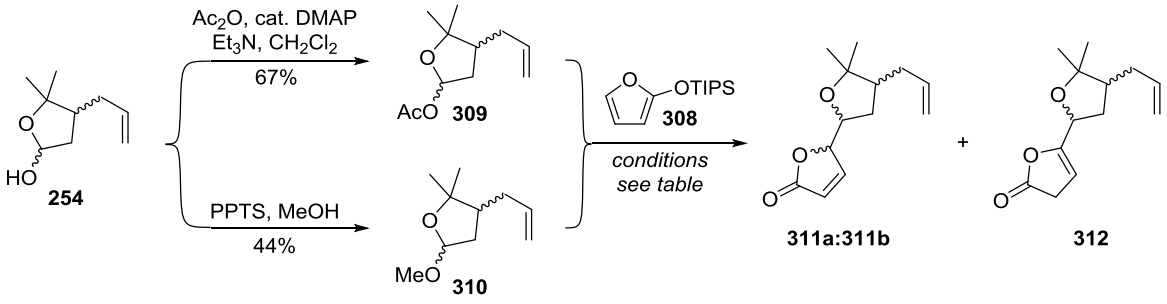
5.1.1. Investigations with a simple model system

We started our investigations with the synthesis of a simplified G ring butenolide precursor, siloxyfuran **308**, in two steps from furfural **306** (Scheme 5-1).[206,207]



Scheme 5-1 Synthesis of siloxyfuran **308**

Using the γ-lactol **254**, which we had previously synthesised as an intermediate to a model system for testing the AB rings formation, different routes to effect the attachment of the G ring were tested. The γ-lactol was first converted into different oxocarbenium precursors by activating the hydroxyl group of the hemiacetal (Scheme 5-2). Synthesis of acetate **309** proceeded smoothly, while methyl acetal **310** was obtained with more difficulty due to its instability. These oxocarbenium precursors were then reacted with siloxyfuran **308** under various conditions (Table 5-1).



Scheme 5-2 Investigating the oxocarbenium ion additon reaction from γ-lactol **254**

Pleasingly, all reactions with acetate **309** proceeded in excellent yields (Entries 1-6, Table 5-1), except for the reaction with TMSOTf, which gave significant amounts of side products (Entry 7, Table 5-1). There was also high selectivity for the desired conjugated enoate

product, obtained as a mixture of two diastereomers **311a** and **311b**, with some 1,4-enone side product **312**. It is interesting to note that while all transition metal-catalysed reactions gave a 1:1 ratio of the two conjugated enone epimers (Entries 1-4, Table 5-1), reactions catalysed by $BF_3{\cdot}OEt_2$ and TBSOTf gave different amounts of these epimers, each favouring a different epimer (Entries 5-6, Table 5-1).

Entry	Substrate	Lewis acid	Solvent	T / °C	Overall Yield / %	NMR Ratio (311a:311b:312)
1	**309**	$TiCl_4$[a]	CH_2Cl_2	−40	85[b] (66:34)	43:43:14
2	**309**	$ZnCl_2$	CH_2Cl_2	−40	quant.	41:41:18
3	**309**	$Sc(OTf)_3$	CH_2Cl_2	−40	81	42:42:16
4	**309**	$InCl_3$	CH_2Cl_2	−40	quant.	45:45:9
5	**309**	$BF_3.OEt_2$	Et_2O	−78	quant.	53:37:10
6	**309**	TBSOTf	Et_2O	−78	quant.	26:69:5
7	**309**	TMSOTf	Et_2O	−78	significant side products observed	
8	**310**	$ZnCl_2$	CH_2Cl_2	0 to RT	31[c]	34:39:26
9	**254**	$ZnCl_2$	CH_2Cl_2	−40 to RT	70	51:33:16

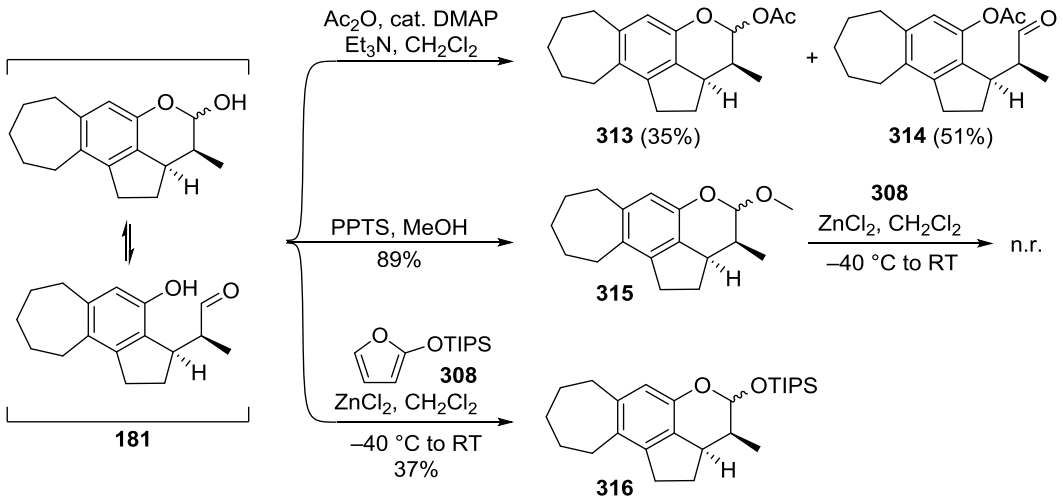
Reaction conditions: **Substrate** (20 mg, 1.0 equiv.) and siloxyfuran **308** (48.5 mg, 2.0 equiv.) in solvent (1 mL) under Ar atm at temperature T (as indicated) was added Lewis acid (0.4 equiv.), and stirred for 2 h; [a] Stoichiometric amount of $TiCl_4$ (1.0 equiv.) was used; [b] Yield of desired product only, no side product; [c] Starting material was unstable

Table 5-1 Oxocarbenium ion addition reaction optimisation on γ-lactol derivatives

Although indium(III) chloride afforded the best results for acetate **309**, we decided to extend the study to the other oxocarbenium precursors with zinc(II) chloride which is more readily available and less moisture sensitive. Methyl acetal **310** also underwent successful addition, albeit in a lower yield, likely a result of its instability (Entry 8, Table 5-1). To our surprise, even lactol **254** participated in the reaction to afford a good yield of enone products (Entry 9, Table 5-1). Following the encouraging results of the oxocarbenium ion addition reaction with the γ-lactol **254** and its derivatives **309** and **310**, we proceeded to the apply these conditions to the CDEF ring system.

5.1.2. Investigations with the CDEF ring system

In this vein, we began by activating the CDEF ring lactol **181**, which lies in equilibrium with the open-chain aldehyde form, to generate a good leaving group (Scheme 5-3).



Scheme 5-3 Attempted oxocarbenium ion addition reactions with CDEF ring system **181**

To our dismay, the same acetylation conditions that worked favourably for model system **254** gave a some of the desired lactol acetate **313** in 35% yield, but with open-chain phenyl acetate **314** as the major product in 51% yield. This result was also observed by Li *et al.*[29] in their attempts to acetylate the analogous rubriflordilactone A lactol under standard conditions. They surmised that this "ring-opening tendency may be attributable to the internal strain of the 6,5,6-tricyclic system and the good leaving ability of the phenoxide".

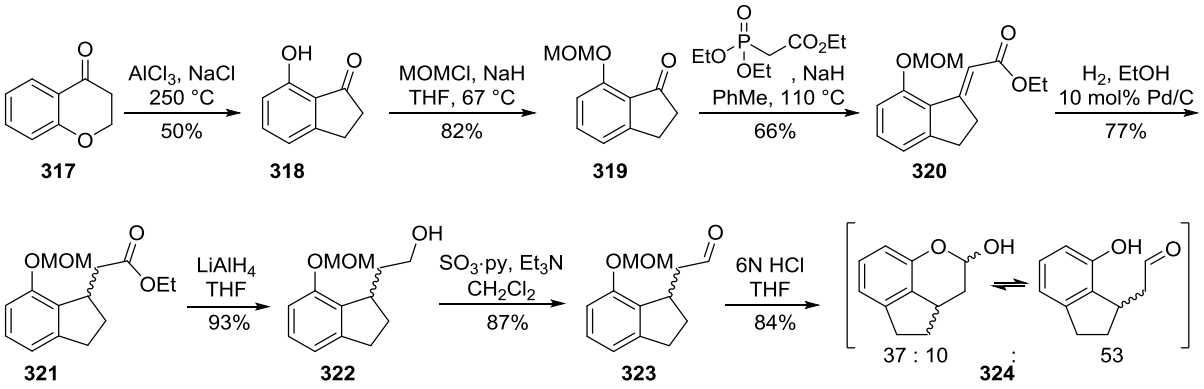
In a reversal of fates, transforming lactol **181** into its methyl acetal **315** was facile, and this may suggest that Lewis or Brønsted acid conditions are more conducive to this transformation than the mildly basic conditions of acetylation. Unfortunately, this leaving group proved to be ineffective under the oxocarbenium ion addition conditions optimised for the simple model system **310**. Under zinc(II) chloride catalysis, no reaction was observed with siloxyfuran **308**; and reaction with $BF_3 \cdot OEt_2$ merely led to deprotection of the lactol ether. Directly subjecting the lactol **181** to the zinc(II) chloride-catalysed reaction with siloxyfuran **308** was also ineffective, affording TIPS-protected lactol **316** instead of the desired product.

These unsuccessful attempts at attaching the G ring to the CDEF ring system suggested that a more comprehensive study of this transformation would need to be undertaken. Hence, we embarked on further studies with a DEF ring system.

5.1.3. Investigations with the DEF ring system

To gain a better understand of the intricacies involved in forming the C-C bond between the F and G rings in rubriflordilactone A, we decided to study the reaction on a readily available model system which more closely resembled the reactivity of the ABCDEF ring lactol precursor to rubriflordilactone A. The 6,5,6-DEF tricyclic system **324** is ideal for these purposes, since it offered a good balance between ease of synthesis and similarity in reactivity.

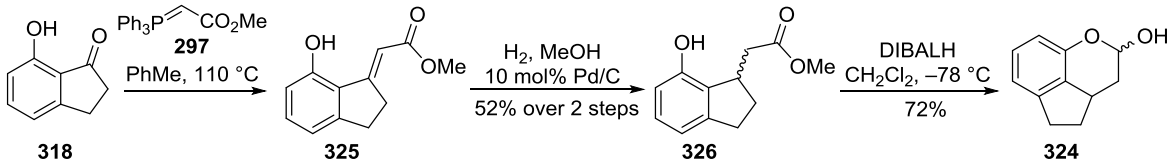
The first-generation synthesis of this DEF ring system **324** (in 7 steps) began with the thermal rearrangement of 4-chromenone **317** to give 7-hydroxyindanone **318** (Scheme 5-4).[208] This was followed by a HWE reaction and subsequent hydrogenation to give ester 3**21**, which was transformed by reduction and phenol deprotection into the DEF ring lactol **324**, obtained as a 53:37:10 equilibrium mixture of the open-chain aldehyde form to the two anomeric lactol forms (in chloroform-*d*).



Scheme 5-4 First-generation synthesis of DEF ring system **324**

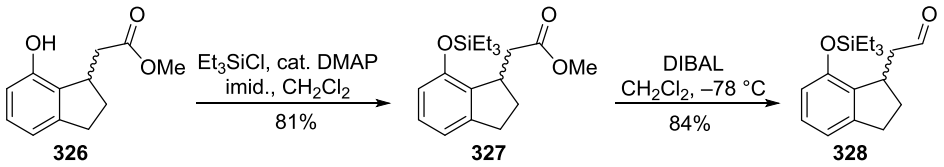
The synthesis was later refined to remove the need for protecting groups, reducing the number of steps (Scheme 5-5). This was achieved by substituting the HWE olefination with a

Wittig reaction using a pre-formed ylide to form the conjugated ester **325**, and also by reducing the subsequent alkyl ester **326** to the lactol **324** in one step, shortening the sequence to 4 steps from 4-chromenone.



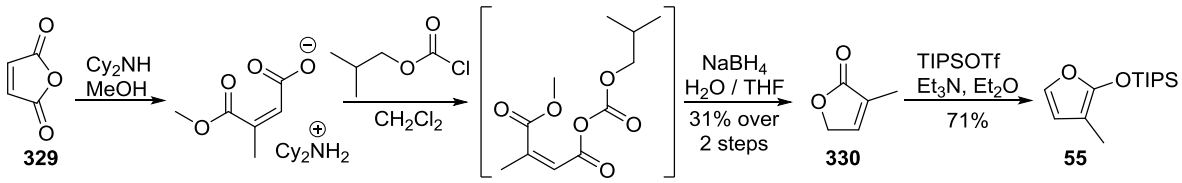
Scheme 5-5 Second-generation synthesis of DEF ring system **324**

For an alternative entry to the DEFG rings *via* a Mukaiyama Aldol reaction with the DEF aldehyde instead of the lactol-derived oxocarbenium cation, the phenol moiety in ester **326** was protected before DIBALH reduction, which afforded the corresponding aldehyde **328** (Scheme 5-6).



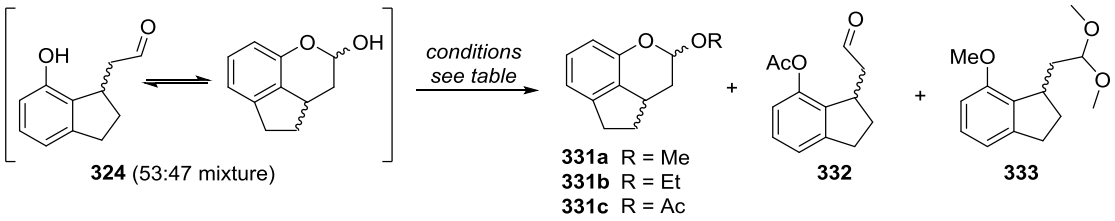
Scheme 5-6 Synthesis of aldehyde form of DEF ring system **328**

To better mimic the reaction in the real system, we also synthesised the desired G ring methyl siloxyfuran **55** from citraconic anhydride **329**, *via* 3-methyl-2(5*H*)-furanone **330** (Scheme 5-7).[209,210]



Scheme 5-7 Synthesis of G Ring siloxyfuran **55**

Once again, we started our investigation into the oxocarbenium ion addition by activating the lactol **322** to form more reactive oxocarbenium precursors (Table 5-2). Based on insight from our preliminary results for the CDEF ring system, we employed (Lewis) acidic methods for this transformation.[211–213] This enabled us to form the methyl acetal **331a** and the acetate **331c** in synthetically useful yields based on recovered starting material. As a comparison, we conducted the acetylation reaction under standard basic conditions, and this resulted in the formation of phenyl acetate **329** as the major product, as predicted (Entry 7, Table 5-2).



324 (53:47 mixture)

331a R = Me
331b R = Et
331c R = Ac

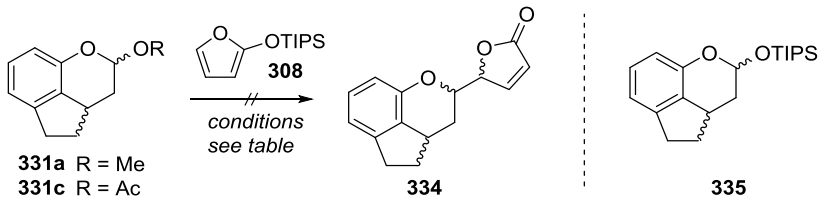
332

333

Entry	R	Conditions	Product (%)	Recov. 322 / %	Side product (%)
1	Me	PPTS, MeOH, reflux	**331a** (25)	0	**333** (4)
2	Me	$CH(OMe)_3$, TMSCl, CH_2Cl_2	**331a** (57)	35	-
3	Me	$CH_3C(OMe)_3$, TMSCl, CH_2Cl_2	**331a** (37)	45	-
4	Et	$CH_3C(OEt)_3$, TMSCl, CH_2Cl_2	**331b** (24)	0	complex mixture
5	Ac	Ac_2O, $BF_3{\cdot}OEt_2$, THF, 0 °C to RT	**331c** (54)	16	-
6	Ac	Ac_2O, TMSOTf, MeCN, 0 °C to RT	**331c** (8)	21	complex mixture
7	Ac	Ac_2O, py, DMAP, CH_2Cl_2	**332** (54)	0	**331c** (14)

Table 5-2 Functionalisation of DEF ring lactol **324** to oxocarbenium precursors

With the oxocarbenium precursors in hand, we proceeded with testing the oxocarbenium ion addition reaction with unsubstituted siloxyfuran **308**, in an attempt to form DEFG rings **334** (Table 5-3).



331a R = Me
331c R = Ac

334 **335**

Entry	Substrate	R	Conditions	Comments
1	**331a**	Me	$ZnCl_2$ (0.4 equiv.), CH_2Cl_2, −78 °C to 0 °C	n.r.
2	**331a**	Me	$BF_3{\cdot}OEt_2$ (0.4 equiv.), Et_2O, −78 °C to 0 °C	**324** recovered (28%)
3	**331c**	Ac	$ZnCl_2$ (0.4 equiv.), CH_2Cl_2, −78 °C to 0 °C	**335** observed
4	**331c**	Ac	$InCl_3$ (0.4 equiv.), CH_2Cl_2, −78 °C to 0 °C	**335** observed
5	**331c**	Ac	$BF_3{\cdot}OEt_2$ (0.4 equiv.), Et_2O, −78 °C to 0 °C	complex mixture

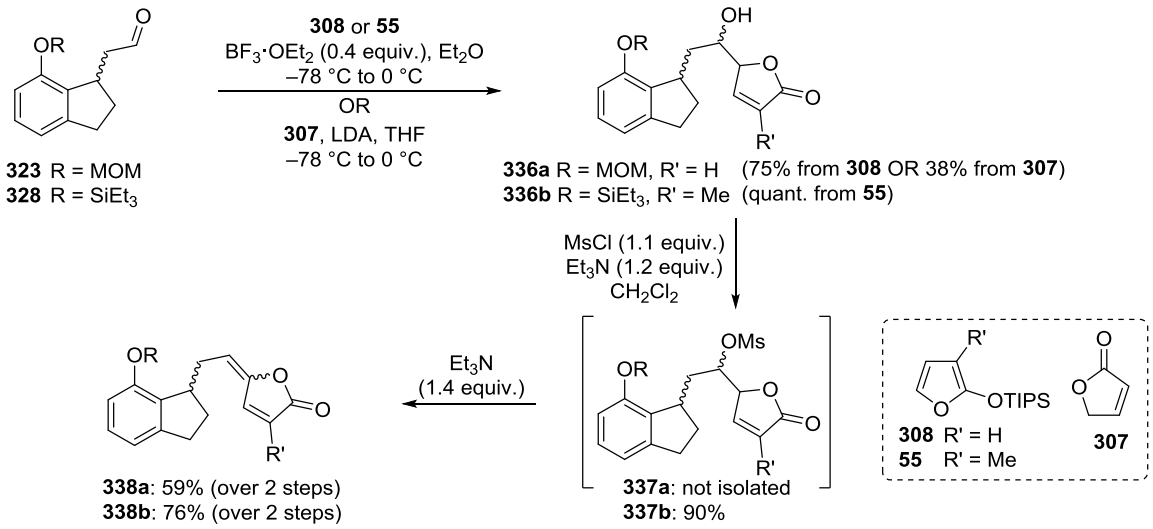
Table 5-3 Attempted oxocarbenium ion addition reactions with DEF ring lactol derivatives

Unfortunately, conditions which were successful for the simple γ-lactol once again failed to yield any desired product **334** with this ring-strained δ-lactol **324**. Following this setback, we decided to search for other methods of attaching the G ring to the DEF system.

5.2. Appending the G Ring, Followed by F Ring Formation

5.2.1. F ring formation by 1,6-oxa-Michael addition

Another route into the DEFG rings would first involve attachment of the G ring prior to cyclisation to form the F ring. This would proceed by C-C bond formation *via* addition of the G ring to the aldehyde **323** or **328** (Scheme 5-8), followed by *anti*-elimination of the resulting alcohol to give a γ-alkylidenebutenolide **338a-b**,[214] and finally an intramolecular 1,6-oxa-Michael addition of the phenol into this moiety.

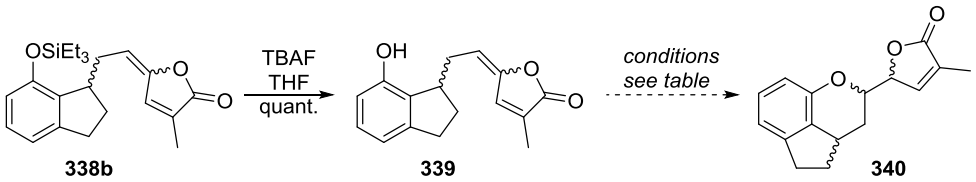


Scheme 5-8 Synthesis of γ-alkylidenebutenolide **338a-b**

Addition of the G ring could either proceed *via* a base-mediated nucleophilic addition reaction with the G ring butenolide **307** or **330** (Scheme 5-8), or a Lewis acid-catalysed vinylogous Mukaiyama aldol reaction with the G ring siloxyfuran **308** or **55**. When this was tested with aldehyde **323**, the vinylogous Mukaiyama aldol reaction of siloxyfuran **308** catalysed by $BF_3{\cdot}OEt_2$ afforded significantly higher yields of aldol adduct **336a** (75%) than the base-mediated addition of butenolide **307** (38%). Elimination of the newly formed hydroxyl group in **336a** could then be performed in a one-pot procedure with methanesulfonyl chloride and triethylamine to yield γ-alkylidenebutenolide **338a** *via* mesylate **337a**. This sequence also

achieved high yields for product **338b**, obtained by coupling of aldehyde **328** with methyl siloxyfuran **55**.

Deprotection of the silyl ether **338b** with TBAF smoothly afforded phenol **339**, the ideal substrate for our investigations on intramolecular oxa-Michael additions to γ-alkylidenebutenolides. Many conditions were attempted to effect this cyclisation step to give the DEFG rings **340**, ranging from base to acid, and even to ionic liquids or bifunctional organocatalysts (Table 5-4).



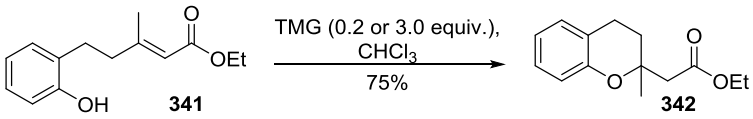
338b **339** **340**

Entry		Conditions	Comments
1	Bases	*t*-BuOK (0.4 equiv.), toluene	n.r.
2		*t*-BuOK (1.1 equiv.), toluene	Decomposed
3		*t*-BuOK (0.4 equiv.), THF, reflux	n.r.
4		NaH, THF, reflux	Full conversion; undesired products
5		KHMDS, toluene (0.9 equiv.)	n.r.
6		Cs_2CO_3, DMF, RT	n.r.
7		Cs_2CO_3, DMF, reflux	Decomposed
8	Lewis and Brønsted Acids	$InCl_3$ (0.4 equiv.), CH_2Cl_2	n.r.
9		$Sc(OTf)_3$ (0.4 equiv.), CH_2Cl_2, reflux	n.r.
10		$FeCl_3$ (0.4 equiv.) MeCN, reflux[215]	n.r.
11		$TiCl_4$ (0.4 equiv.), MeCN, reflux	n.r.
12		$La(NO_3)_3 \cdot 5H_2O$ (1.0 equiv.), MeCN[216]	Trace conversion; undesired product
13		*p*-TsOH, $Bu_3PEtOTs$[217]	Trace conversion; undesired product
14		TMG (3 equiv.), CH_2Cl_2[218]	Crude NMR shows only **339**

Table 5-4 Attempted intramolecular cyclisation of phenol onto 1,6-dienelactone **339**

When classic base-mediated conditions often employed for oxa-Michael additions were applied, no desired reaction was observed (Entries 1-7, Table 5-4). We postulated that the

reaction was suffering from the high stability and poor nucleophilicity of the phenoxide anion. Recognising this problem, we turned to the literature for examples of phenols involved in oxa-Michael additions. Many of these relied on activating the enone / α,β-unsaturated ester with Lewis acids instead.[215, 216] To our dismay, these reactions also failed to proceed (Entries 8-12, Table 5-4). In 2002, Karodia *et al.* reported a Brønsted acid-catalysed intermolecular conjugate addition of phenol into ethyl acrylate, performed in ionic liquid.[217] While this appeared promising, no desired reaction was observed with our system **339** (Entry 13, Table 5-4). Finally, we surmised that activation at both sites would be necessary for the reaction to proceed, and looked in the direction of bifunctional organocatalysts. Ishikawa and co-workers' demonstration of the use of tetramethylguanidine to effect the 6-*exo*-dig intramolecular oxa-Michael reaction of a very similar system **341** to give **342** in high yields [218] (Scheme 5-9) looked like the solution we needed. However, when these conditions were applied to our system **339**, we were unable to obtain any desired product **340**.

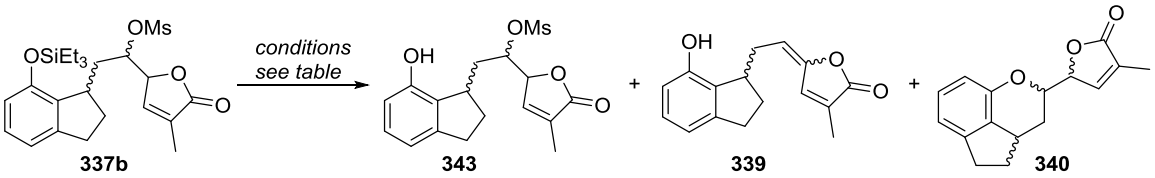


Scheme 5-9 6-*exo*-dig intramolecular oxa-Michael cyclisation to benzopyran (Ishikawa *et al.*, 2008) [218]

At this point, all of our attempts at the oxa-Michael addition of the phenol on the γ-alkylidenebutenolide had been unsuccessful. We attributed this to the inherent stability of both the phenol/phenoxide and the highly conjugated γ-alkylidenebutenolide moieties in the substrate **339**; the addition is possibly further disfavoured by the strain in the 5,6,5-tricyclic system in the product **340**. This prompted us to seek a different strategy which bypasses the formation of the γ-alkylidenebutenolide moiety.

5.2.2. F ring formation by nucleophilic substitution

In the hope of achieving nucleophilic substitution on the mesylate leaving group to give the DEFG rings in a one-pot strategy, we screened conditions for deprotection of phenol silyl ether **337b** (Table 5-5). However, under basic conditions and even TBAF (Entries 1-4, Table 5-5), the only product detected was **339**, once again supporting our hypothesis of the inherent stability of both phenol and butenolide. In an effort to prevent elimination of the mesylate, nucleophilic substitution under acidic conditions [219] was attempted; this time no elimination was observed, only desilylation to give **343**. No cyclisation was observed even upon isolation and resubmission of the phenolic intermediate to a longer reaction time (Entry 5, Table 5-5).



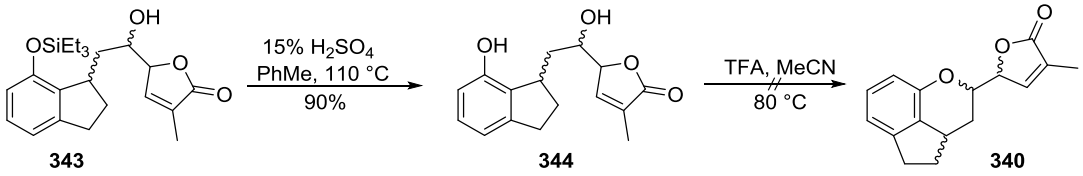
337b **343** **339** **340**

Entry	Conditions	Product (%)
1	K_2CO_3, DMF, RT	**339** (88)
2	K_2CO_3, DMF, reflux	**339** (69)
3	TBAF (2.1 equiv.), THF, RT	**339** (95)
4	TBAF (1.05 equiv.), THF, RT	**339** (100)
5	TFA, MeCN, 80 °C	**343** (82)

Table 5-5 Attempted one-pot phenol deprotection and cyclisation of **337b**

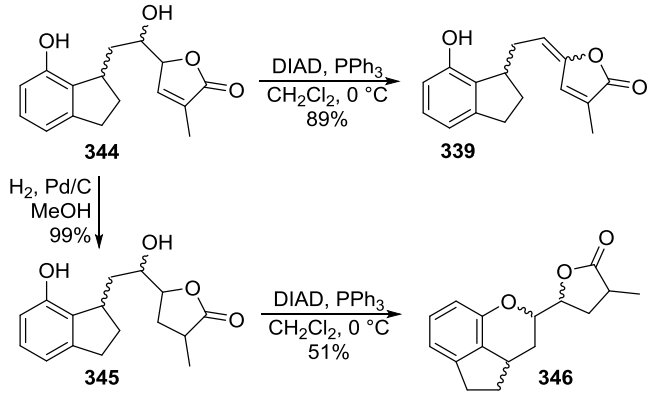
To increase the leaving group ability, we attempted to synthesise the triflate from **336b**. Disappointingly, despite adding the minimum amount of base required, elimination of the triflate was observed, along with desilylation.

Next, we tried methods to achieve cyclisation by direct substitution of the alcohol **343**. Dehydration under acidic conditions[220] only gave the desilylated product **344**, which would not react upon further heating with acid even after isolation (Scheme 5-10).



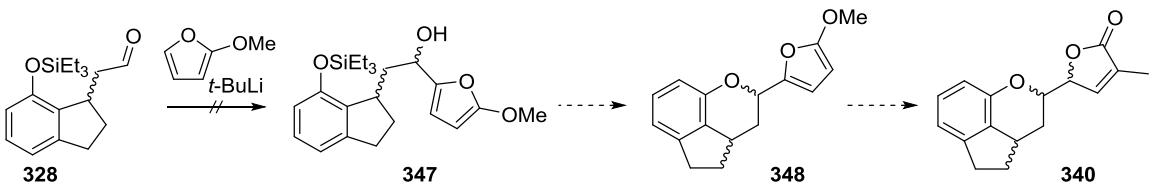
Scheme 5-10 Attempted dehydration of **344** under acidic conditions

Mitsunobu conditions that have previously been applied to intramolecular phenolic cyclisation to a 6-membered cyclic ether[221] were trialed on phenol **344** (Scheme 5-11). Unfortunately, elimination occurred yet again to give γ-alkylidenebutenolide **339**, even when the reaction was conducted at −78 °C.[222] We postulated that the opportunity for conjugation resulted in elimination in the Mitsunobu reaction, and to test this decided to attempt the Mitsunobu on hydrogenated substrate **345**. As predicted, the Mitsunobu reaction was successful to give DEFG ring system **346**, supporting our hypothesis.



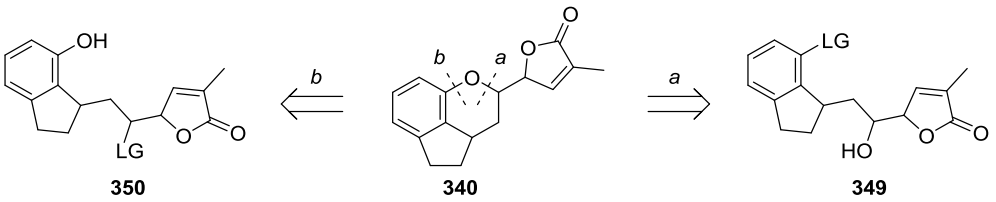
Scheme 5-11 Comparison of Mitsunobu reactions on alcohols **344** and **345**

This led us to consider installing a furan moiety as a "masked" G ring lactone. We expected that addition of lithiated 2-methoxyfuran to aldehyde **328** would give alcohol **347**, which could participate in the intramolecular Mitsunobu reaction to give 5,6,5-tricylic system **348** (Scheme 5-12). The furan moiety could then be deprotected to reveal the butenolide G ring **340**. To our dismay, addition of the lithiated furan to the aldehyde gave a mixture of products, which decomposed upon column chromatography to give γ-alkylidenebutenolide **339** among other products.



Scheme 5-12 Addition of 2-methoxyfuran to aldehyde **328** and planned outcome

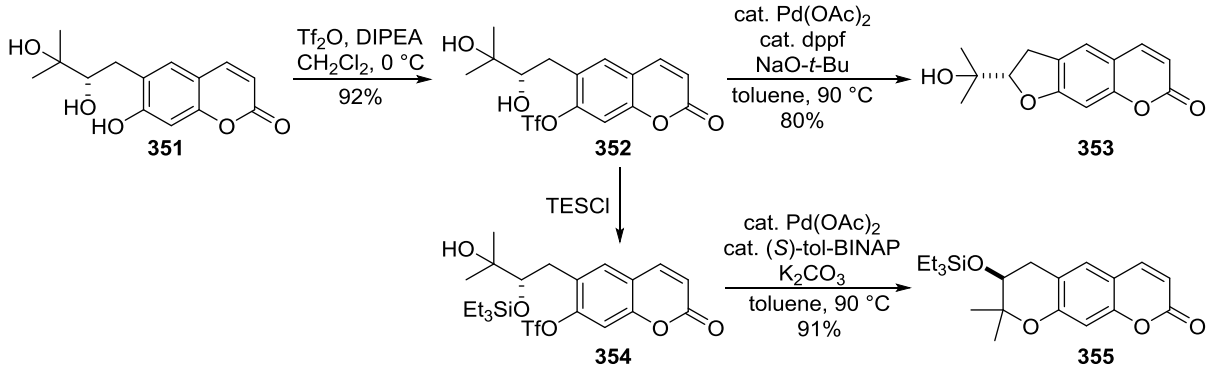
It was disheartening that all conditions attempted to date had failed to produce any trace of the DEFG rings **340**. This suggests that although the phenol functional group was the more obvious choice for nucleophile in these cyclisations (Disconnection *a* to phenol **349**, Scheme 5-13), its poor nucleophilicity should lead us to consider using the homoallylic alcohol as nucleophile instead (Disconnection *b* to alcohol **350**, Scheme 5-13).



Scheme 5-13 Choice of F ring disconnections from DEFG ring system **340**

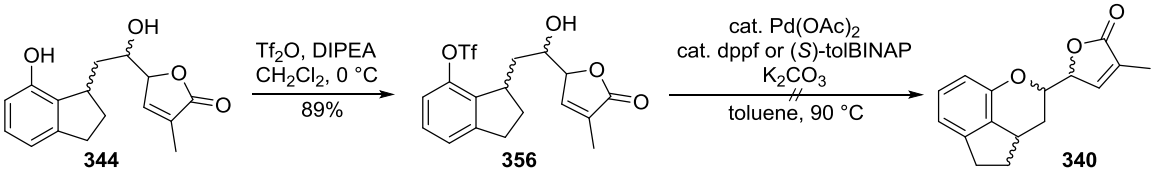
5.2.3. F ring formation by palladium-catalysed C-O cross coupling

With this in mind, we turned our attention to palladium-catalysed C-O coupling reactions, in which an aryl triflate could act as the electrophile, and the alkyl alcohol as the nucleophile. In 2003, Shibasaki *et al.* reported the enatioselective total synthesis of (+)-decursin and related compounds using a palladium-catalysed intramolecular C-O coupling strategy (Scheme 5-14).[223] Cyclisation of triflate **354** afforded dihydropyranocoumarin **355** in an excellent 91% yield, and this was later converted in two steps to (+)-decursin. Alvarez-Manzaneda *et al.* also applied this reaction to form a 6-membered cyclic phenol ether in their synthesis of puupehenol, the precursor of puupehenone-related metabolites, in 2009.[224]



Scheme 5-14 Pd-catalysed C-O coupling to form phenol ethers (Shibasaki *et al.*, 2003) [223]

Given the similarities of our system **344** to triol **351**, we decided to test this strategy in our synthesis. Selective triflation of the phenol was successful to yield triflate **356**, but this unfortunately did not give any DEFG rings **340** when exposed to cross-coupling conditions (Scheme 5-15).



Scheme 5-15 Synthesis of triflate **356** and attempted C-O coupling to the DEFG rings

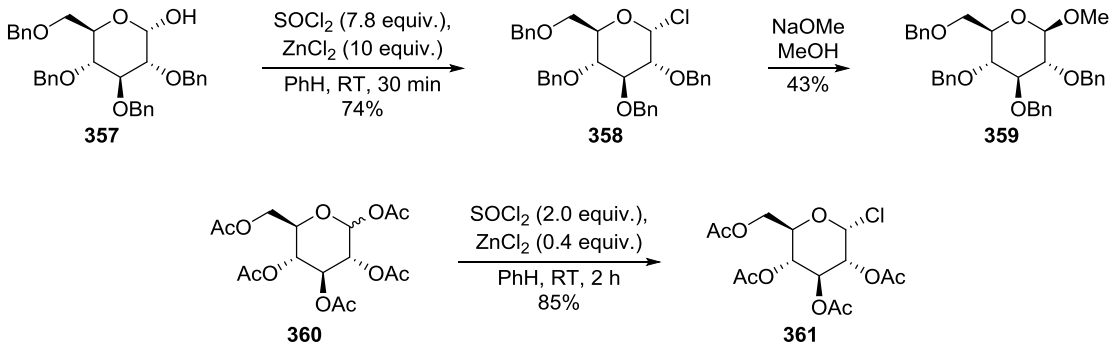
Having tried to no avail to achieve the cyclisation of the F ring after G ring attachment, we opted to return to the strategy of attaching the G ring to the pre-formed DEF rings **324**.

5.3. The Chloropyran Route

We returned to our original route towards the synthesis of the DEFG rings **340** feeling somewhat demoralised. However, we were now hopeful that by installing a better leaving group on the F ring, we could form the oxocarbenium cation with greater ease and thus achieve the oxocarbenium ion addition reaction. We were also now mindful of issues such as elimination of the phenol, and the likely need for strictly anhydrous conditions.

5.3.1. First success with the DEFG ring system

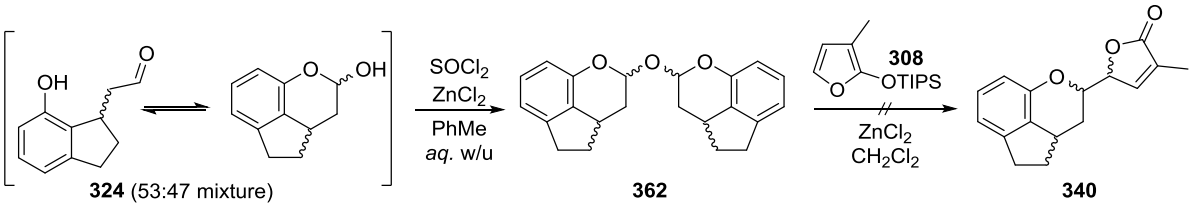
Having failed to perform the oxocarbenium ion addition reaction on the acetylated and methylated DEF lactols (**331c** and **331a** respectively), we looked into installing better leaving groups on the lactol fuctionality. In this vein, we were attracted to the work of Vercellotti *et al.*, who pioneered the use of zinc chloride–thionyl chloride in the synthesis of pyranosyl chlorides (Scheme 5-16). This was first demonstrated in 1969 on 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose **357**, which was converted into 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl choride **358** in good yield with 7.8 equiv. of thionyl chloride and 10 equiv. of zinc(II) chloride in benzene, and later transformed into methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **359**.[225]



Scheme 5-16 Preparation of pyranosyl chlorides (Vercellotti *et al.*, 1969, 1970) [225,226]

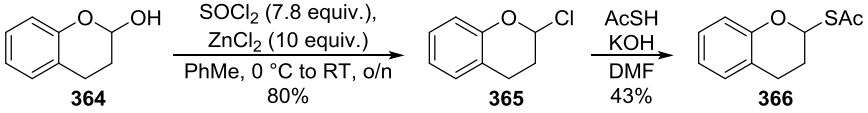
The group later (1970) extended this reaction to synthesise acetylated aldosyl chlorides from peracetylated pyranoses (Scheme 5-16), with decreased amounts of reagents (2.0 equiv. of thionyl chloride and 0.4 equiv. of zinc(II) chloride). [226] Notably, both anomers of 1,2,3,4,6-penta-*O*-acetyl-glucopyranose **360** were converted to the α-anomer of the glucopyranosyl chloride **361**, an observation which differs from that of previous investigations with aluminum(III) chloride and titanium(IV) chloride.[227] This reaction was also demonstrated on other fully acetylated monosaccharides – mannose, galactose and xylose – as well as the disaccharide lactose, with yields from 78-89%. These reactions were all monitored by TLC and were complete in less than 2 h.

When we applied the original conditions utilised by Vercellotti *et al.*,[225] but with toluene instead of benzene, we noticed complete conversion of our DEF ring lactol **324** to a less polar compound on the TLC plate. When this spot was isolated and purified by flash column chromatography on silica, we obtained an unknown compound **362**, as a 85:15 mixture of two diastereomers. This compound had ^{1}H and ^{13}C NMR chemical shifts which were similar to, but not the same, as the starting lactol **324**, albeit with no aldehyde form present (Table 5-6). Initially assuming that we had formed the chloropyran, we submitted this to the oxocarbenium ion addition reaction with siloxyfuran **55** and catalytic zinc(II) chloride. To our dismay, no reaction was observed and compound **362** was recovered (Scheme 5-17). Later, we realised that the mass spectrum for **362** was not congruent with the structure of the chloropyran **363** (theoretical mass 194.0498). In fact, the identified parent ion mass (HRMS (FI^+) calc. for $C_{22}H_{22}O_3$ $[M]^+$ 334.1569; found 334.1557) corresponded to an oxy-bridged dimer of lactol **324** (Table 5-6).



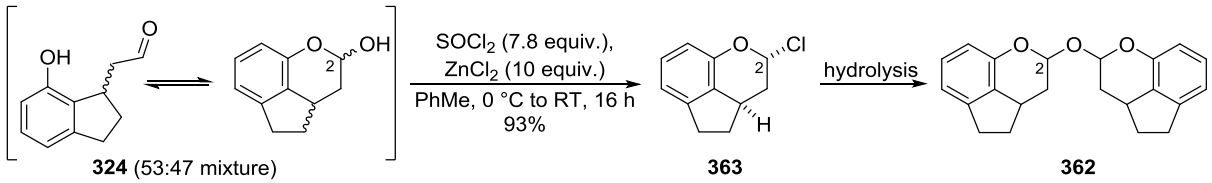
Scheme 5-17 Formation of DEF ring dimer **362**

In a system very similar to ours, Sipilä and Kansikas used a modification of Vercellotti's method to prepare chlorobenzyopyran **365** from benzopyranol **364** (Scheme 5-18).[228] They reported that the product was very sensitive and had to be used without further purification. Chlorobenzopyran **365** was isolated by filtration through celite, and subsequently used crude after removal of solvent in a nucleophilic substitution reaction to prepare thioacetate **366**.



Scheme 5-18 Preparation and utility of chlorobenzopyran **365** (Sipilä and Kansikas, 2002) [228]

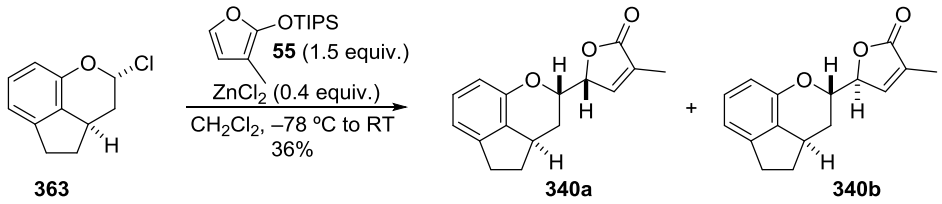
To our surprise, we obtained a different compound **363** by crude NMR when we applied this new work-up procedure to lactol **324**. This time, the product **363** was isolated as a single diastereomer, with its ^{13}C and ^{1}H NMR spectra showing a significant change in the chemical shifts of C2 and H2 respectively (Table 5-6). A hit by mass spectrometry (HRMS (FI^+) calc. for $C_{11}H_{11}OCl$ $[M]^+$ 194.0498; found 194.0495) confirmed that we had successfully synthesised the chloropyran **363**. As expected, upon purification by column chromatography, only dimer **362** and some starting material **324** were obtained, emphasising the instability of the chloropyran to hydrolysis e.g. with water or silica.



	Lactol 324	Chloropyran 363	Dimer 362
NMR Shift of H2 (δ_H / ppm)	5.76	6.53	5.91
NMR Shift of C2 (δ_C / ppm)	93.0	90.1	94.0

Table 5-6 Selected NMR data for lactol **324**, chloropyran **363** and dimer **362**

To our delight, crude chloropyran **363** reacted under Lewis acid catalysis in the presence of zinc(II) chloride with siloxyfuran **55** to afford DEFG ring system **340** in a 36% yield, as a 1:1 mixture of diastereomers (Scheme 5-19).

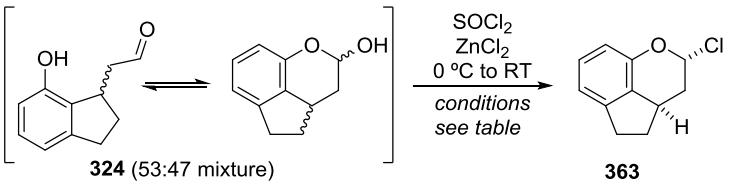


Scheme 5-19 Completion of the DEFG ring system **340**

5.3.2. Reaction optimisation with the DEFG ring system

Our spirits were lifted with this first synthesis of the DEFG ring system **340**. However, there was still much that needed to be optimised for the last two steps of the route from lactol **324** to DEFG rings **340**. In addition to improving the yield of each step, we were also hoping to turn the sequence into a one-pot reaction.

Conditions for the transformation of lactol **324** to chloropyran **363** were screened (Table 5-7). The results indicated that conversions and yields remained the same even when the equivalents of reagents were decreased to 2.0 equiv. of thionyl chloride and 0.4 equiv. of zinc(II) chloride (Entry 2, Table 5-7), akin to the conditions which Vercellotti *et al.* had used for their chlorination of peracetylated pyranoses.[226] We also wanted to emulate the short reaction times observed by Vercellotti *et al.* in their chlorination procedures. When a small aliquot was removed from the reaction mixture after 1 h, a 69% conversion to chloropyran **363** was observed, with dimer **362** accounting for the remaining 31% of material (Entry 3, Table 5-7). Since no starting material was present, at that time we attributed this observation to the accidental partial hydrolysis of the chloropyran **363** to the dimer **362**. It was even more pleasing to find that the amount of thionyl chloride could be reduced to 1.1 equiv. with negligible loss in yield of chloropyran **363** (Entry 4, Table 5-7), thus paving the way for a one-pot reaction. Unfortunately, yields for the reaction in dichloromethane were less promising that that in toluene (Entry 5, Table 5-7).



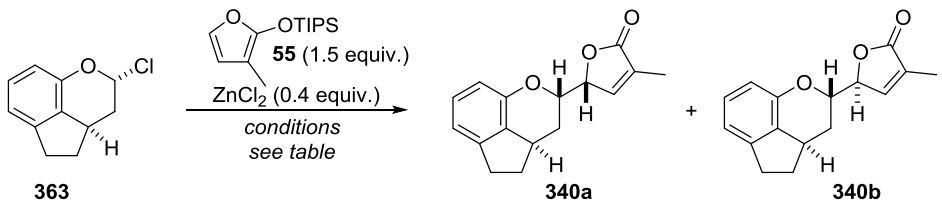
324 (53:47 mixture) **363**

Entry	$SOCl_2$ equiv.	$ZnCl_2$ equiv.	Solvent	Time / h	Conv. / %	Yield / %
1	7.8	10	PhMe	16	100	93
2	2.0	0.4	PhMe	16	100	92
3	2.0	0.4	PhMe	1	69 [a]	n.d.
4	1.1	0.4	PhMe	16	100	89
5	1.1	0.4	CH_2Cl_2	16	100	50

Reaction conditions: Lactol **324** (20 mg, 1.0 equiv.) in solvent (0.5 mL) and $SOCl_2$ (as indicated) was added to $ZnCl_2$ (as indicated) under Ar atm at 0 °C and stirred warming to RT for time (as indicated);
[a] A small aliquot was removed from the reaction mixture after 1 h; lactol **324** was fully consumed; dimer **362** accounted for remaining 31% of material.

Table 5-7 Optimisation of chloropyran **363** formation from lactol **324**

Similarly, conditions were screened for the oxocarbenium ion addition reaction. The reaction did not proceed without Lewis acid catalyst (Entry 2, Table 5-8), and gave poor yields with titanium(IV) chloride (Entry 3, Table 5-8). No reaction was observed at −78 °C with zinc(II) chloride (Entry 4, Table 5-8), which prompted us to raise the starting temperature to −40 °C with no observable change in the diastereomeric ratio. When the reaction was scaled from 20 mg to 50 mg of chloropyran **363**, the yield of our DEFG ring system **340** improved from 27% to 47% (Entry 5, Table 5-8). Finally, the addition reaction did not proceed in toluene, putting a dent in our hopes of constructing a one-pot reaction (Entry 6, Table 5-8).

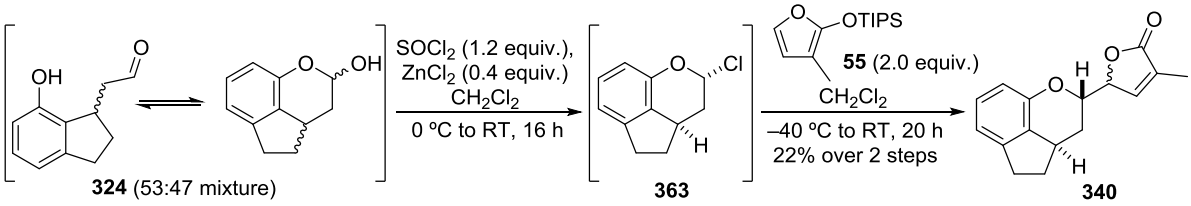


Entry	Lewis acid	Solvent	T / °C	Yield / %
1	$ZnCl_2$	CH_2Cl_2	−78 to RT	36
2	–	CH_2Cl_2	−78 to RT	n.r.
3	$TiCl_4$	CH_2Cl_2	−78 to RT	5
4	$ZnCl_2$	CH_2Cl_2	–78	n.r.
5[a]	$ZnCl_2$	CH_2Cl_2	−40 to RT	47
6	$ZnCl_2$	PhMe	−40 to RT	n.r.

Reaction conditions: Chloropyran **363** (20 mg, 1.0 equiv.) and siloxyfuran **55** (43 mg, 1.5 equiv.) in solvent (0.5 mL) was added to Lewis acid (0.4 equiv.) under Ar atm at temperature T (as indicated) and stirred warming to RT overnight; [a] 50 mg of Chloropyran **363** was used.

Table 5-8 Optimisation of the oxocarbenium ion addition reaction to the DEFG rings **340**

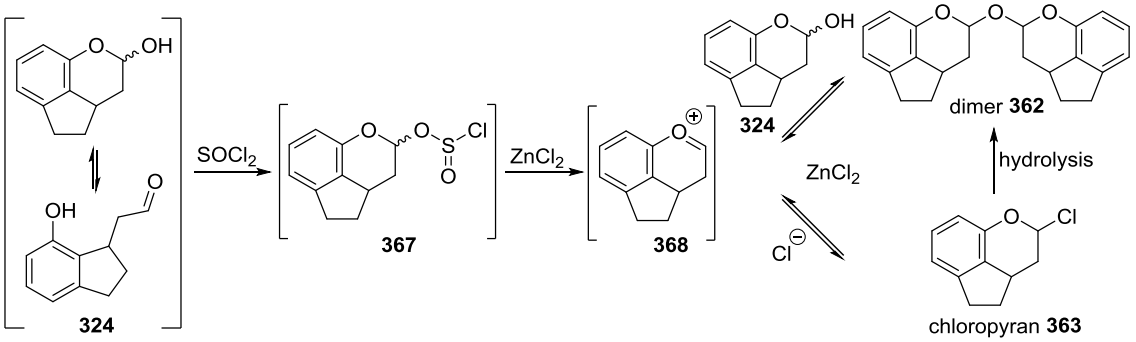
An attempt was made to convert the lactol **324** into the DEFG rings **340** in a one-pot process. Unfortunately, the oxocarbenium ion addition reaction would not proceed with toluene as solvent. We managed to achieve this with dichloromethane as solvent by cooling the reaction mixture containing the chloropyran down to −40 °C, then adding a pre-cooled solution of siloxyfuran **55** in dichloromethane (Scheme 5-20). However, the overall yield of 22% was significantly lower than the two step process.



Scheme 5-20 One-pot reaction from lactol **324** to DEFG ring system **340**

5.3.3. Chloropyran formation: NMR Studies with the DEF ring lactol

During our optimisation studies on the formation of the DEF ring chloropyran **363**, we had noticed some amounts of dimer **362** in the crude NMR of the chloropyran. We had initially attributed this to partial hydrolysis of the chloropyran **363** on accidental contact with moisture. In hindsight, there was a trend in which lower thionyl chloride loadings and shorter reaction times gave increased amounts of the dimer **362**. This suggested that the dimer **362** was perhaps instead formed during the reaction, and was converted to the chloropyran **363** over time (Scheme 5-21). Our proposed mechanism starts with activation of lactol **324** with thionyl chloride to form activated species **367**, which under zinc(II) chloride catalysis forms oxocarbenium ion **368**. The oxocarbenium ion **368** can either be attacked by another lactol molecule to form dimer **362**, which is more likely to occur at the start of the reaction since lactol concentration is high; or by a choride anion to form chloropyran **363**. This reaction is reversible since zinc(II) chloride can mediate formation of the oxocarbenium ion **368** from either of these two species. Thus, as the reaction progresses, the simultaneous decrease in concentration of lactol **324** and increase in chloride ion concentration causes dimer **362** to be transformed into chloropyran **363**.



Scheme 5-21 Proposed scheme for reversible formation of dimer **362** and chloropyran **363**

We set out to test this hypothesis. First, the role of zinc(II) chloride in the reaction was verified. Vercellotti *et al.* had observed in their studies of the chlorination of pyranoses that "thionyl chloride alone at room temperature does not effect complete reaction", while "zinc chloride in the presence of thionyl chloride considerably speeds up the chlorination reaction

with a minimum of side products".[225] In this experiment, DEF ring lactol **324** (30 mg, 1.0 equiv.) in toluene (0.5 mL, 0.4 M) was subjected to thionyl chloride (62 µL, 5.0 equiv.) only; and after stirring overnight at RT a 2:3 mixture of chloropyran **363** and dimer **362** was observed. This mixture was resubmitted to experimental conditions with thionyl chloride (25 µL, 2.0 equiv.), zinc(II) chloride (9.2 mg, 0.4 equiv.) and toluene (0.5 mL). To our delight, only chloropyran **363** was observed, indicating that interconversion between the dimer **362** and chloropyran **363** was possible, and was mediated by zinc(II) chloride.

In the same publication,[225] Vercellotti *et al.* noted that "optimum yield is obtained with roughly equimolar quantities" of zinc(II) chloride and thionyl chloride. They proposed that the reagents interact synergistically in a 1:1 ratio form a powerful Lewis acid, in analogy to studies with zinc(II) chloride and phosphoryl chloride.[229,230] We hypothesised that with increased zinc(II) chloride–thionyl chloride loading, then formation of the chloropyran would be more rapid than the dimer, and that there may be a loading at which no dimer was formed at all. Our starting point was to return to the original procedure from 1969.[225] We chose to conduct the reaction in chloroform-*d* in an NMR tube so we could monitor its progress by NMR. With 7.8 equiv. of thionyl chloride and 10 equiv. of zinc(II) chloride, the reaction of lactol **324** showed >90% conversion to chloropyran **363** in less than 20 min.

Herein, further NMR experiments designed to test this hypothesis are described, using the following procedure: To an argon-filled NMR tube equipped with dry zinc(II) chloride (variable) was added a solution of DEF ring lactol **324** (5.0 mg, 1.0 equiv.) in chloroform-*d* (0.5 mL). A solution of thionyl chloride (variable) in chloroform-*d* was added, and ^{1}H NMR spectra were periodically taken to determine the ratio of dimer to chloropyran. From the graph below (Figure 5-2), all conditions tested showed that the dimer **362** was the major species formed at the start of the reaction. Gratifyingly, it was converted over time to form the chloropyran **363**, giving further weight to our proposed mechanism (Scheme 5-21). As there was very little to differentiate between the effectiveness of the different conditions, other than

time, we decided to continue with an arbitrarily chosen loading of 4.0 equiv. of thionyl chloride and 5.0 equiv. of zinc(II) chloride for further experiments.

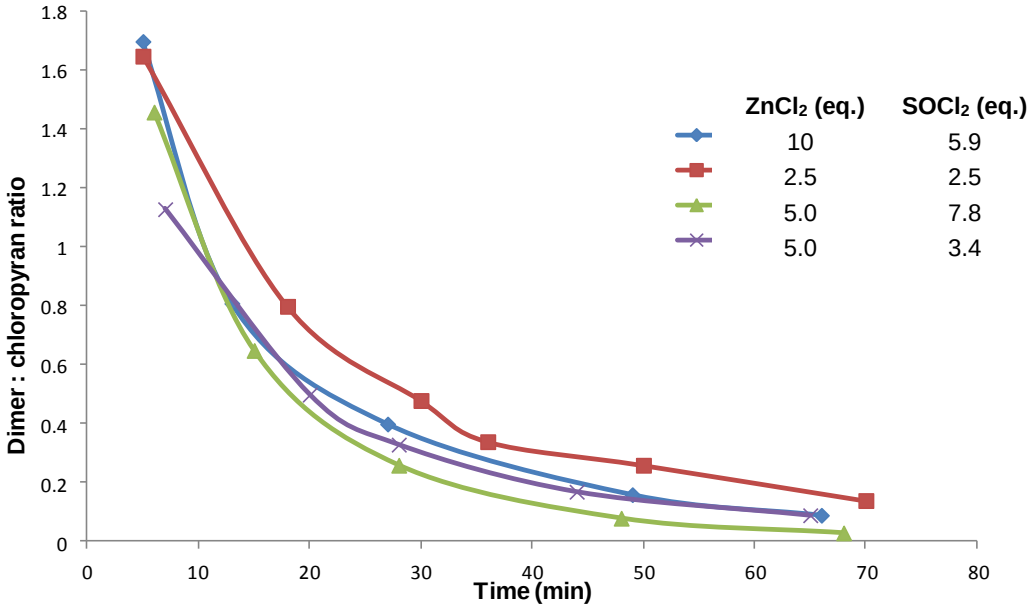


Figure 5-2 Dimer **362**-to-chloropyran **363** ratio over time in NMR study of chlorination of lactol **324**

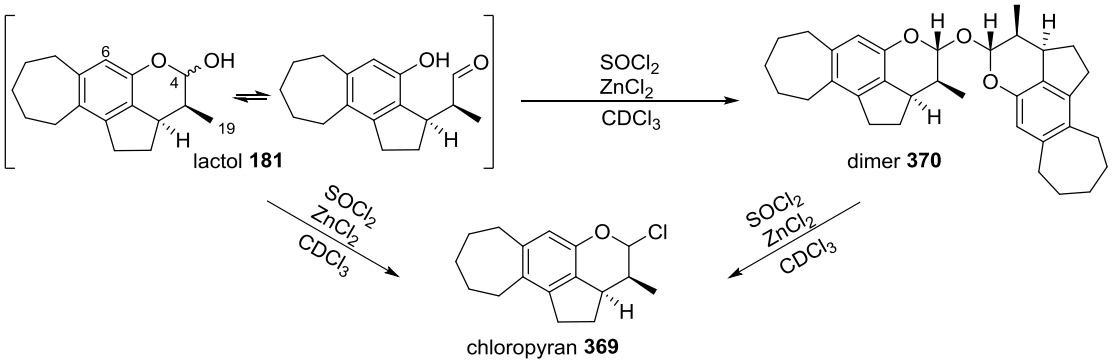
The results of our NMR study were encouraging enough for us to move on to investigating the same final steps with the CDEF ring system.

5.4. The CDEFG Ring Model

Having successfully attached the G ring to the DEF ring system, we now advanced to the more complex CDEF ring system **181**.

5.4.1. Chloropyran formation: NMR Studies with the CDEF ring lactol

First, we had to repeat our success with lactol chlorination. Once again, we conducted an NMR experiment to observe the kinetics of formation of chloropyran **369** and dimer **370** from CDEF ring lactol **181** (Scheme 5-22). The conditions for the NMR study were: CDEF ring lactol **181** (5.0 mg, 1.0 equiv.), thionyl chloride (4.0 equiv.) and zinc(II) chloride (5.0 equiv.) in chloroform-*d* (0.6 mL).



Scheme 5-22 NMR study for chlorination of **181** to form chloropyran **369**

As expected, this reaction proceeded through the dimer **370**. Figure 5-3 shows the ^{1}H NMR spectra of the reaction mixture before (t = 0 min) and after addition of thionyl chloride (t = 11 min, and thereafter until t = 47 min). The consumption of starting material **181** was easily monitored by the disappearance of its H6 (at 6.40 ppm) and H19 (at 0.73 ppm) peaks; these were replaced by the H6 peaks of the dimer **370** and chloropyran **369** (both at 6.45-6.46 ppm), and also their H19 peaks, at 0.69 ppm for dimer **370** and 0.85 ppm for chloropyran **369** respectively. Chloropyran **369** also exhibits a characteristic H4 peak (at 6.19 ppm), while dimer **370** has a more similar H4 shift (at 5.50 ppm) as compared to lactol **181** (at 5.38 ppm).

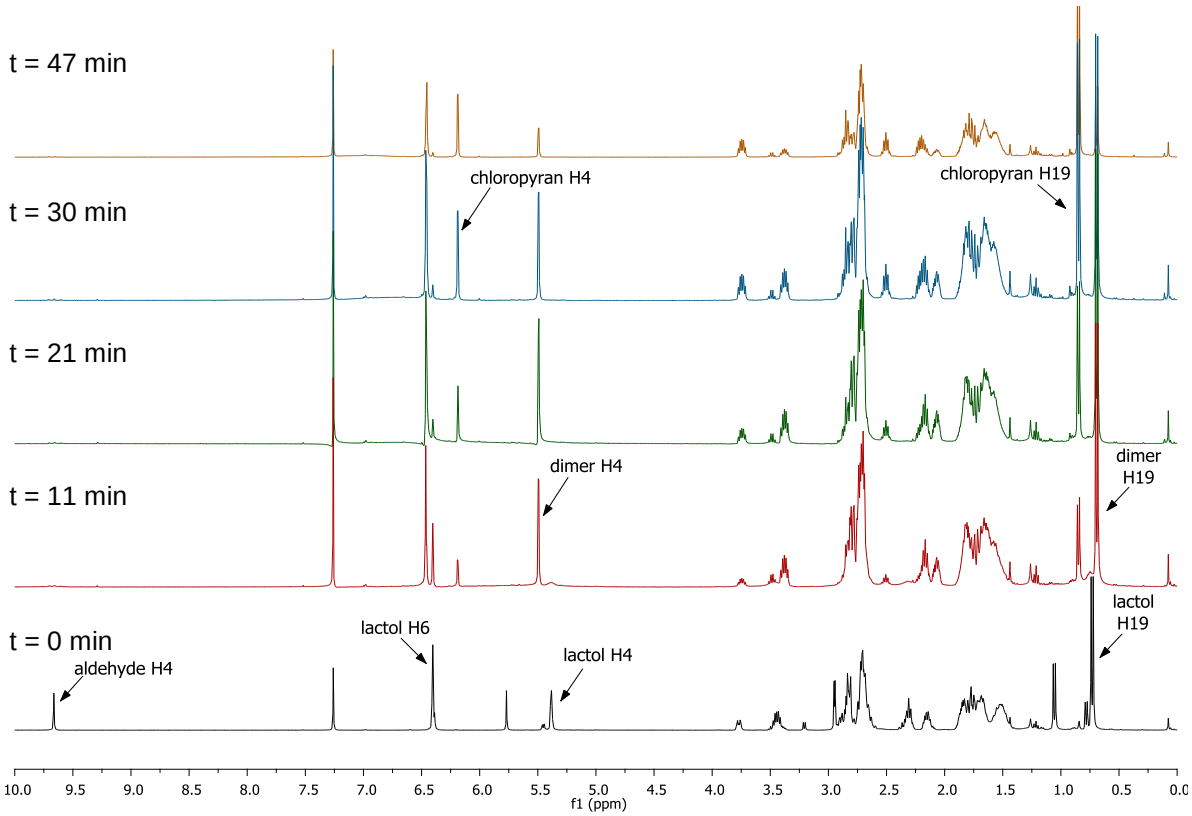


Figure 5-3 ^{1}H spectra of chlorination of CDEF ring lactol **181** in $CDCl_3$ over time

Gratifyingly, although the dimer **370** was initially formed in larger quantities than for the DEF ring system, it was still completely converted to the chloropyran **369** over time (Figure 5-4). It is important to note, though, that the chlorination proceeded much more slowly in toluene, and after stirring for 5 h at room temperature, the reaction mixture only showed a 1:1 ratio of chloropyran **369** to dimer **370**.

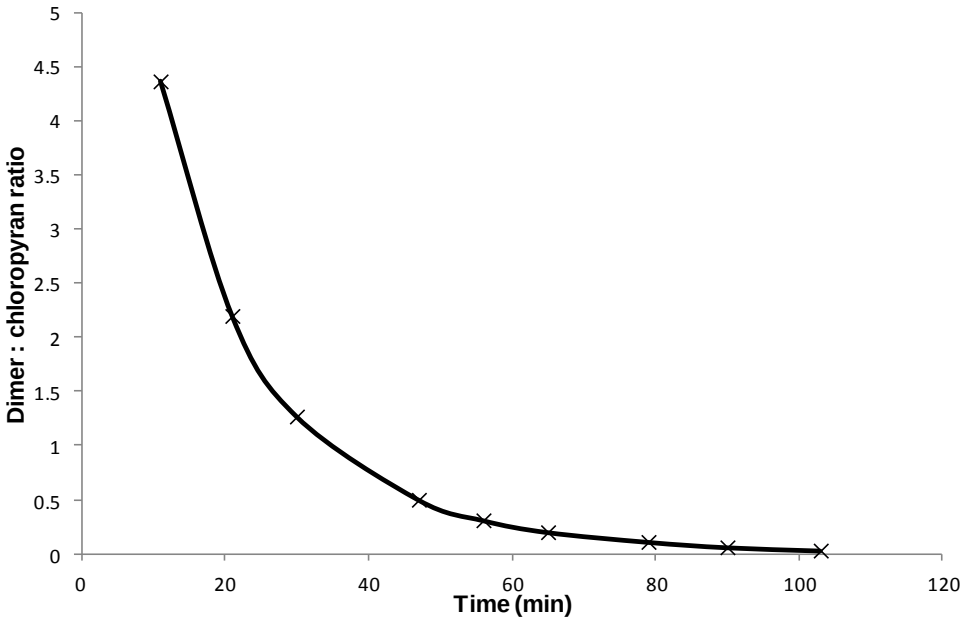


Figure 5-4 Dimer **370**-to-chloropyran **369** ratio over time in NMR study of chlorination of lactol **181**

To our delight, the NMR experiment could be repeated with some isolated CDEF ring dimer **370** (Figure 5-5). This was done at a lower concentration of CDEF ring dimer **370** (2.5 mg, 1.0 equiv.) in chloroform-*d* (0.6 mL), but with twice the amount of reagents thionyl chloride (8.0 equiv.) and zinc(II) chloride (10.0 equiv.). The time taken for full conversion was longer (> 5 h). In fact, the reaction mixture was left overnight in the NMR tube and on the next day showed full conversion to chloropyran **369** without observable degradation. This finding is of great importance since it means that any isolated dimer **370** formed after the two step reaction, arising for example by accidental partial hydrolysis of the chloropyran **369**, could be recycled to generate more chloropyran for subsequent usage.

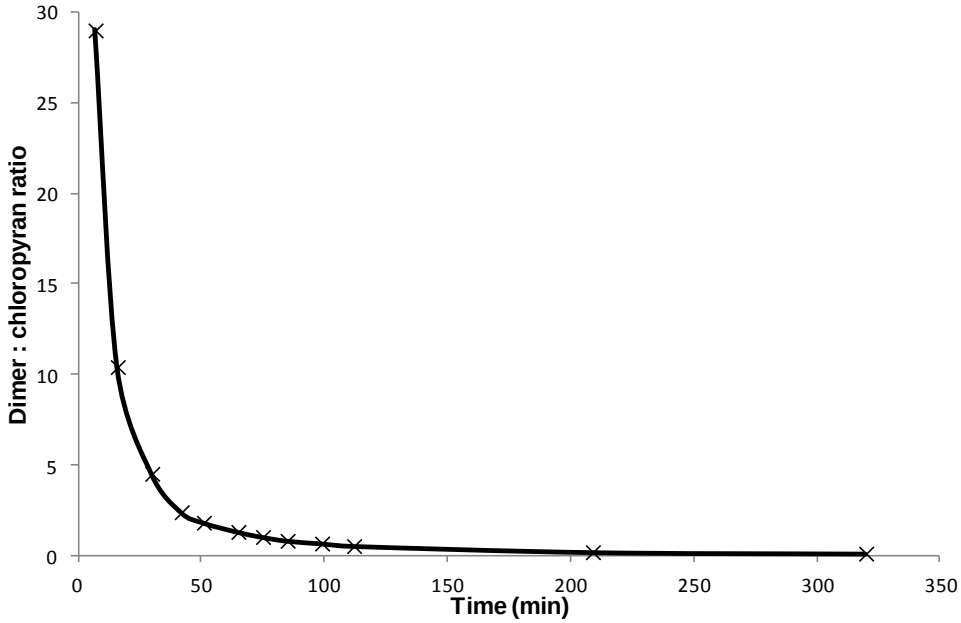
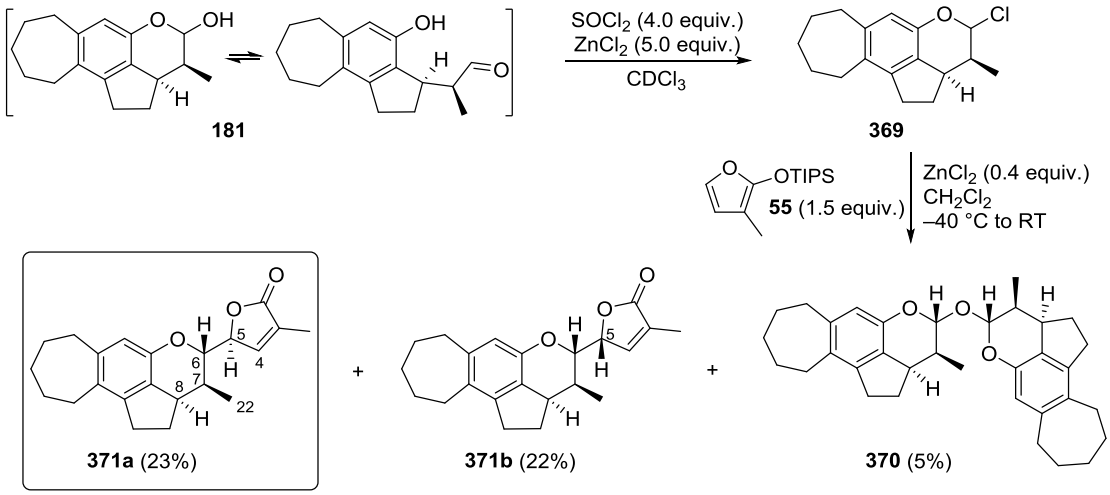


Figure 5-5 Dimer **370**-to-chloropyran **369** ratio over time in NMR study of chlorination of dimer **370**

5.4.2. Addition of the G ring to the CDEF ring chloropyran

As with the DEF ring chloropyran **363**, we subjected the crude sample of the CDEF ring chloropyran **369** to the oxocarbenium ion addition reaction (Scheme 5-23). Pleasingly, chloropyran **369** reacted under our previously optimised conditions to afford the desired CDEFG ring system diastereomer **371a** in a 23% yield over two steps. Side products obtained include its C5-epimer **371b** in 22% yield, and dimer **370** (5% yield).



Scheme 5-23 Synthesis of the CDEFG ring system **371a**

The stereochemical assignment of **371a** and **371b** was achieved by 2D NOESY NMR experiments and by comparison of the NMR spectra of both C5-epimers in pyridine-*d5* with that of the natural product.[12] The NOESY spectra showed that both compounds possessed the same stereochemistry in the F ring (Figure 5-6), with H6 showing through-space correlations with the hydrogen atoms of the C22 methyl group. However, differences in the through-space interactions of H4 and H5 with hydrogens on the F ring suggested a difference in stereochemistry at C5.

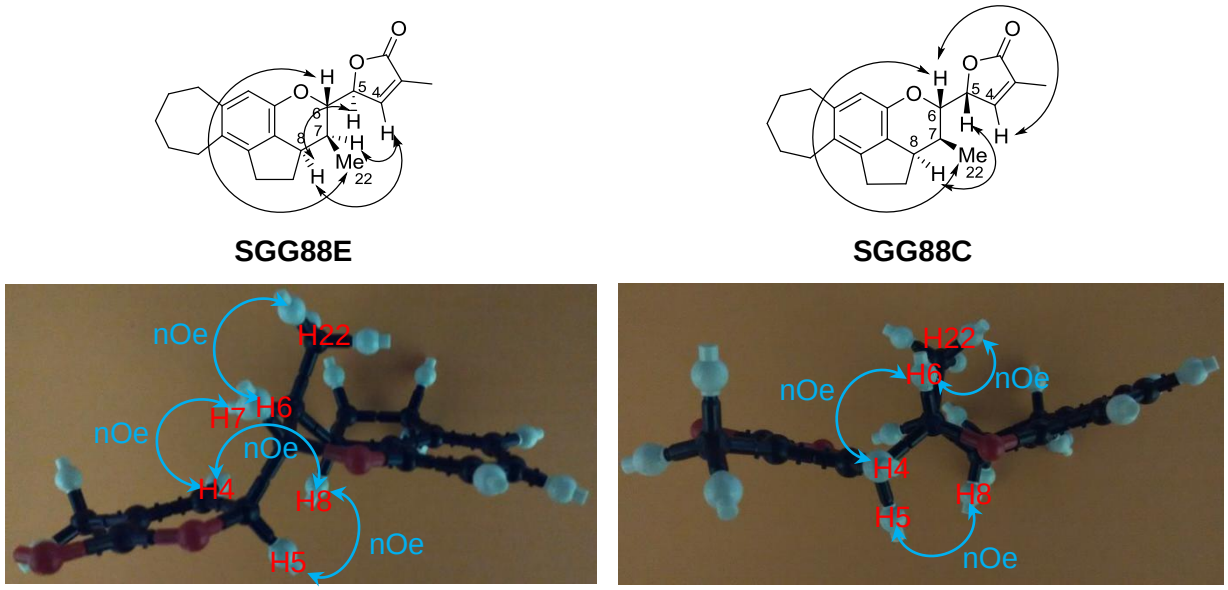
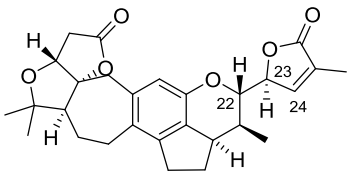


Figure 5-6 NOESY correlations for CDEFG rings C5-epimers **371a** and **371b**

For **371a**, the NOE correlations between H5 and H8, and from H4 to both H7 and H8 were consistent with the expected through-space interactions in the structure possessing (5*S*)-stereochemistry as shown in Figure 5-6 (left). Here, the model is orientated in a conformation in which H5 and H6 are anti-periplanar, where there is little steric overlap between the axial C22 methyl group and butenolide G ring substituents. In contrast, NOE correlations between H5 and C8, and from H4 to H6 observed for **371b** matched the structure of the (5*R*)-epimer. These through-space interactions are evident in the model (right, Figure 5-6) orientated in a preferred conformation where H5 is anticlinal to H6, and where there is little steric overlap between the equatorial C22 methyl group and butenolide G ring substituents. The structural information elucidated from these spectra indicated that **371a** was the desired C5-epimer.

To corroborate our assignment based on 2D NOESY NMR, a comparison of the key ^{13}C chemical shifts of both C5-epimers with rubriflordilactone A was conducted. Table 5-9 clearly shows a strong correlation between the ^{13}C NMR shifts of compound **371a** with rubriflordilactone A, supporting our assignment of this compound as the desired epimer. In contrast, compound **371b** showed large deviations in its ^{13}C NMR shifts from the natural product.



Rubriflordilactone A

Carbon No.	δ_C / ppm (C_5D_5N)		
	Rubriflorilactone A	**371a**[a]	**371b**[a]
22	83.5	83.3	82.4
23	82.2	82.8	79.4
24	145.1	145.9	149.6

[a] Data were recorded in C_5D_5N a on Bruker AVII 500 MHz spectrometer with a cryoprobe (^1H, ^{13}C, COSY, HSQC, HMBC).

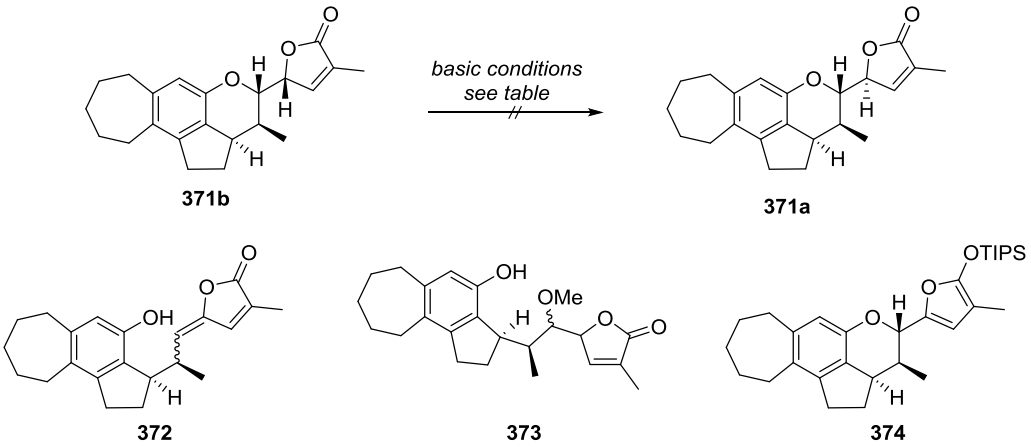
Table 5-9 Comparison of key ^{13}C signals for CDEFG rings C5-epimers **371a** and **371b** with rubriflordilactone A **31**

5.5. Epimerisation Studies

Completing the synthesis of the CDEFG ring system **317a** was an important achievement for us given our long struggle with the addition of the G ring. However, this result was rendered less impressive by the low yield and selectivity for the desired C5-epimer **371b**. This could be mitigated by C5-epimerisation of the undesired epimer **371b** to generate **371a**, which we set out to investigate.

5.5.1. Base-mediated epimerisations with CDEFG ring system C5-epimer

Investigations began with base-mediated epimerisations (Table 5-10). We predicted that deprotonation with a strong base (e.g. LiHMDS) at low temperature, followed by an acidic quench, would lead to a kinetic ratio of products in the protonation event. Unfortunately, only retro-Michael product **372** was isolated (Entry 1, Table 5-10). Thermodynamic conditions, which could be achieved by use of a weak base (e.g. potassium carbonate in methanol) at room or elevated temperatures, were next trialed. Phenol **372** was again the main product (51% conversion), albeit with an opposite *E*/*Z* preference, isolated alongside its methanol adduct **373** (Entry 2, Table 5-10). It appeared that γ-alkylidenebutenolide **372** was both the kinetic and thermodynamic product. Based on our previous studies with the DEFG system γ-alkylidenebutenolide **339** (*see Section 5.2.1*), this result, though not unexpected, signalled that further investigation into base-mediated epimerisation methods were likely to be futile.



Entry	Conditions	Product (%)[a]
1	(i) LiHMDS, THF, −78 °C, 30 min; (ii) AcOH, THF	**372** (34[b], *dr* 9:1)
2	K_2CO_3, MeOH, RT	**372** (51, *dr* 37:63) + **373** (49, *dr* 53:47)
3	TIPSOTf, Et_3N, CH_2Cl_2, 0 °C to RT	**374** (100[c])

[a] Based on NMR conversion; [b] Isolated yield; [c] Decomposed on flash column chromatography on silica to give **SGI31** (quant. isolated yield).

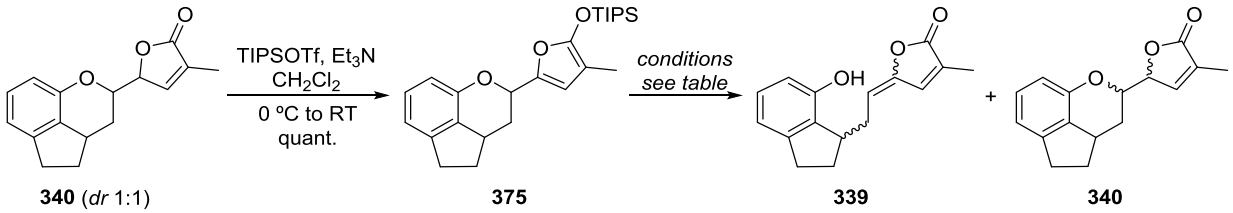
Table 5-10 Attempted base-mediated epimerisation of **371b** to **371a**

Our next course of action was a two-step procedure to epimerise the C5 centre *via* the formation of a siloxyfuran **374** (Entry 3, Table 5-10). Applying conditions we had used for the synthesis of G ring siloxyfurans **308** and **55**, we obtained a quantitative yield of crude **374**. Unfortunately, this decomposed on silica to give phenol **372** again.

5.5.2. Epimerisation *via* siloxyfuran with the DEFG ring system

We continued testing methods for epimerisation *via* a siloxyfuran with the DEFG rings **340** (Table 5-11). Both diastereomers of **340** were silylated to give a quantitative yield of siloxyfuran **375**. Several conditions were then investigated to remove the silyl group to regenerate the butenolide G ring, during which we hoped the desired diastereomer would form preferentially. Several fluoride sources were screened (Entries 1-3, Table 5-11); whilst TBAF gave the γ-alkylidenebutenolide product **339**, which we attributed it to its basicity, other fluoride sources did not promote any reaction. Acidic methods were next attempted; while catalytic CSA in methanol again entirely resulted in phenol **339** (Entry 5, Table 5-11), weaker

protic acids in an aqueous / mixed solvent system gave *small quantities* of desired DEFG rings **340** (Entries 5-6, Table 5-11) along with significantly larger quantities of phenol **339**.



340 (*dr* 1:1) **375** **339** **340**

Entry	Conditions	Product (%)[a]
1	TBAF, THF	**339** (100, *dr* 76:24)
2	$NaBF_4$, THF	n.r.
3	KF, THF	n.r.
4	CSA (0.25 equiv.), MeOH	**339** (100, *dr* 76:24)
5	1M citric acid / CH_2Cl_2 (1:1)	**339**(93, *dr* 86:14) + **340** (7, *dr* 57:43)
6	AcOH (1 equiv.) / THF / H_2O (0.1:1:1)	**339** (76, *dr* 72:28) + **340** (7, dr 71:29)

[a] Based on NMR conversion.

Table 5-11 Attempted hydrolysis of siloxyfuran **375** to DEFG ring system **340**

Due to time and material constraints we were unable to further investigate the epimerisation of the undesired epimer arising from the Mukaiyama Aldol-type reaction to the desired epimer in the DEFG ring system **340** and CDEFG ring system **371**. We instead decided to focus on applying what we have learnt from the attachment of the G ring in these model systems to the total synthesis of rubriflordilactone A.

6. Completion of Rubriflordilactone A[102]

At this point, we finally had all the methodology and materials in place to achieve the total synthesis of rubriflordilactone A.

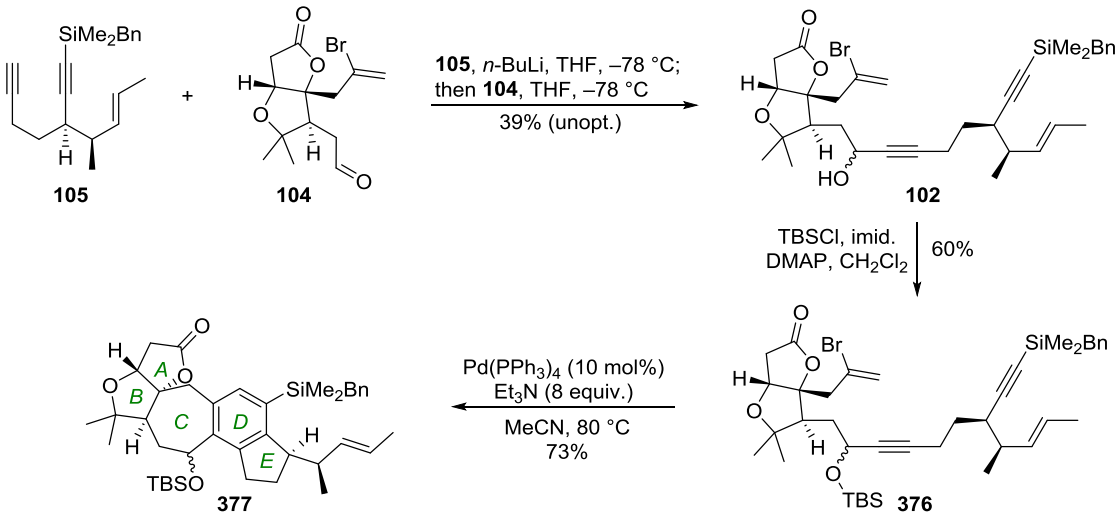
6.1. The ABCDE Rings

Our first step was to unite the AB and CDE fragments, followed by cyclisation to give the ABCDE rings of rubriflordilactone A. Again, we investigated both the palladium- and cobalt-catalysed cyclisation methodologies to achieve this transformation.

6.1.1. Palladium-catalysed cascade cyclisation

Nucleophilic addition of CDE diyne fragment **105** to the AB ring bromoenal **104**[101] gave bromoenediyne **102** (Scheme 6-1). This reaction was conducted on a small scale, so the yield of 39% represents an unoptimised yield.[xx] TBS protection of the resulting alcohol **102** afforded cyclisation precursor **376**. Gratifyingly, under our previously optimised palladium-catalysed conditions (*see Section 3.3.1*) the cascade cyclisation of precursor **376** afforded the ABCDE rings of rubriflordilactone A **377** in 73% yield.

[xx] While writing this thesis, this reaction was repeated on a larger scale by Dr. Guilhem Chaubet, achieving a better yield of 67%. This indicates that the low yield of the reaction reported here was due to scale sensitivity.

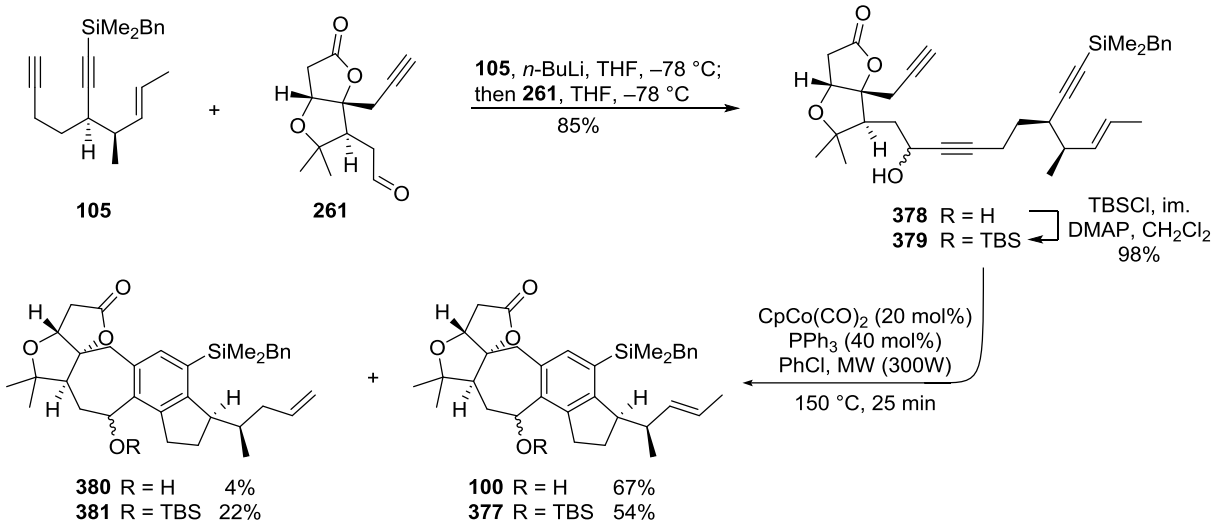


Scheme 6-1 Synthesis of the ABCDE rings **377** of rubriflordilactone A *via* palladium-catalysed cascade cyclisation

The successful synthesis of the ABCDE ring system **377** of rubriflordilactone A was a significant milestone in the project, since we finally obtained concrete proof that the key step in our proposed synthesis was feasible. With this delightful result in hand, we keenly awaited the outcome of the cobalt-catalysed cyclotrimerisation.

6.1.2. Cobalt-catalysed cyclotrimerisation

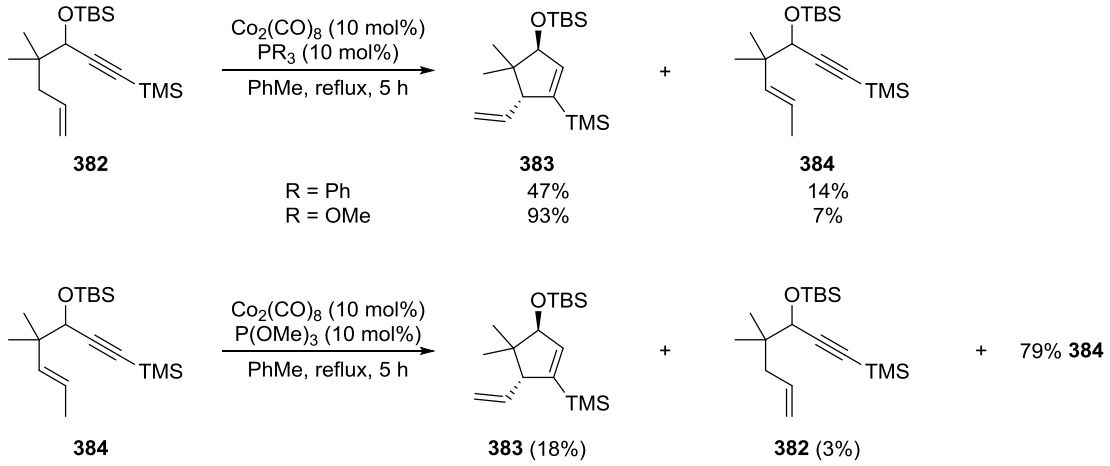
For this route, CDE diyne fragment **105** was instead added to the AB ring ynal **261** to give triyne **378** in 85% yield (Scheme 6-2). This triyne **378**, containing a free hydroxyl group, could be directly subjected to the cobalt-catalysed cyclotrimerisation (*see Section 3.3.2*) to give the corresponding ABCDE rings **100** in 67% yield. Alternatively, the alcohol could be TBS protected such that the resulting intermediate **379** would afford, after cyclotrimerisation, the same product **377** as from the palladium-catalysed cascade cyclisation; however, this reaction proceeded in only 54% yield.



Scheme 6-2 Synthesis of the ABCDE rings **100** and **377** of rubriflordilactone A *via* cobalt-catalysed cyclotrimerisation

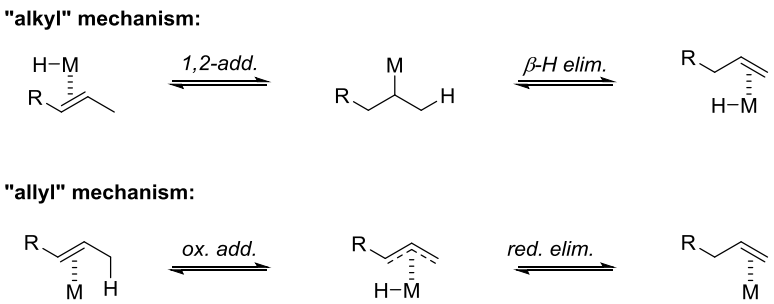
The diminished yields of the desired products **100** and **377**, as compared to that observed in the cyclotrimerisation of triyne **184** to CDE rings **204** (*see Chapter 3.3.2*), could be explained in part by the formation of terminal alkene side products **380** and **381**. This is especially prevalent for the TBS protected starting material **379**, which afforded 22% of terminal alkene **381**, as compared to a 4% yield of **380** when starting from the free alcohol substrate **378**. The side products are thought to be formed by cobalt-catalysed alkene isomerisation. Based on the above results, and also the absence of this side reaction in the cyclotrimerisation of **184** and **205**, we can infer that increasing the steric bulk of the substituents on the C ring

promotes alkene isomerisation in the crotyl side chain. This side reaction was also observed by Ajamian and Gleason in their study of cobalt-catalysed cycloisomerisation of 1,6-enynes (Scheme 6-3),[231] where cycloisomerisation of enyne **382** under cobalt catalysis with a phosphine ligand gave cyclopentene **383** along with side product 1,5-enyne **384**. The yields varied with the type of phosphine ligand used, proceeding with higher selectivity when using trimethylphosphite instead of triphenylphosphine. When the isolated internal 1,5-enyne **384** was subjected to the same catalytic conditions, it was transformed into the desired cyclopentene product **383** and starting 1,6-enyne **382**, albeit in low yields. The authors suggest that the slower rate of isomerisation of the 1,5-enyne **384** may imply that it acts a catalyst "sink", reducing efficiency.



Scheme 6-3 Cycloisomerisation of enynes **382** and **384** (Ajamian and Gleason, 2003) [231]

Transition metal-catalysed isomerisations of alkenes usually proceed through one of two mechanisms: the "alkyl" or the "allyl" mechanism. The "alkyl" mechanism refers to addition-elimination of a metal hydride species to the alkene; while the "allyl" mechanism proceeds *via* a π-allyl complex (Scheme 6-4).[232] In a previous communication, Dolaine and Gleason studied the cycloisomerisation of 1,6-enyne **382** with stoichiometric dicobalt octacarbonyl (with no ligand);[233] they proposed that both cycloisomerisation and alkene isomerisation occurred through an η^3-allylcobalt hydride ("allyl" mechanism), which was evidenced by deuterium labelling studies.

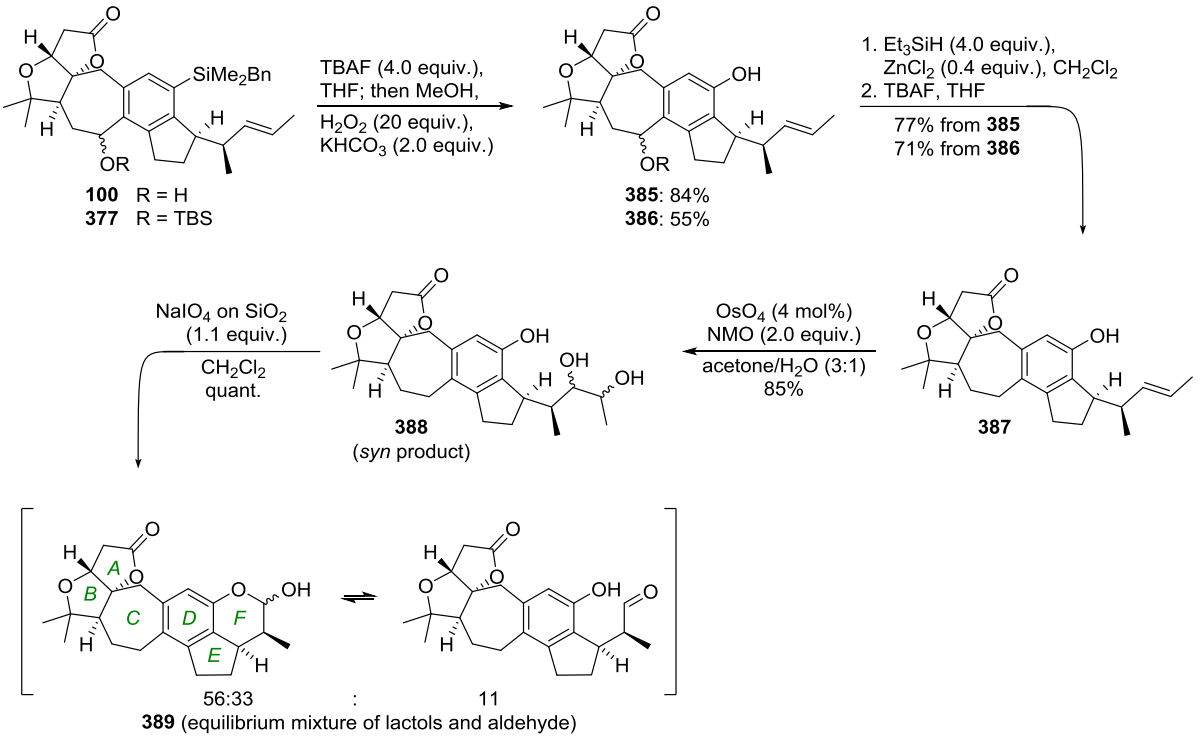


Scheme 6-4 Common mechanisms for transition metal-catalysed olefin migration

In spite of this isomerisation issue, the success of both the cyclisation methodologies provided a huge boost to our spirits as we continued implementing our strategy towards rubriflordilactone A.

6.2. The ABCDEF Rings

With the core infrastructure of rubriflordilactone set in place, we set about derivatisation of the two analogous ABCDE ring systems **100** and **377** so that they would converge on a common late-stage intermediate (Scheme 6-5). To achieve this, we employed the same steps which we had used to build the CDE ring system **182** (*see Chapter 3.3.3*). Firstly, the Tamao-Kumada oxidation[92] of arylsilanes **100** and **377** afforded the corresponding phenols **385** and **386**. Next in line was reductive substitution of the benzylic alcohol, a reaction that in model studies had been low yielding for the free alcohol **208** (unoptimised). We hypothesised that the low yield was a result of the consumption of triethylsilane to silylate the hydroxyl group. Pleasingly, with an increased amount of triethylsilane (4.0 equiv.), the reductive substitution was successful for both the free alcohol **385** (77%) and the TBS ether **386** (71%), such that the two routes converged at ABCDE rings **387**.

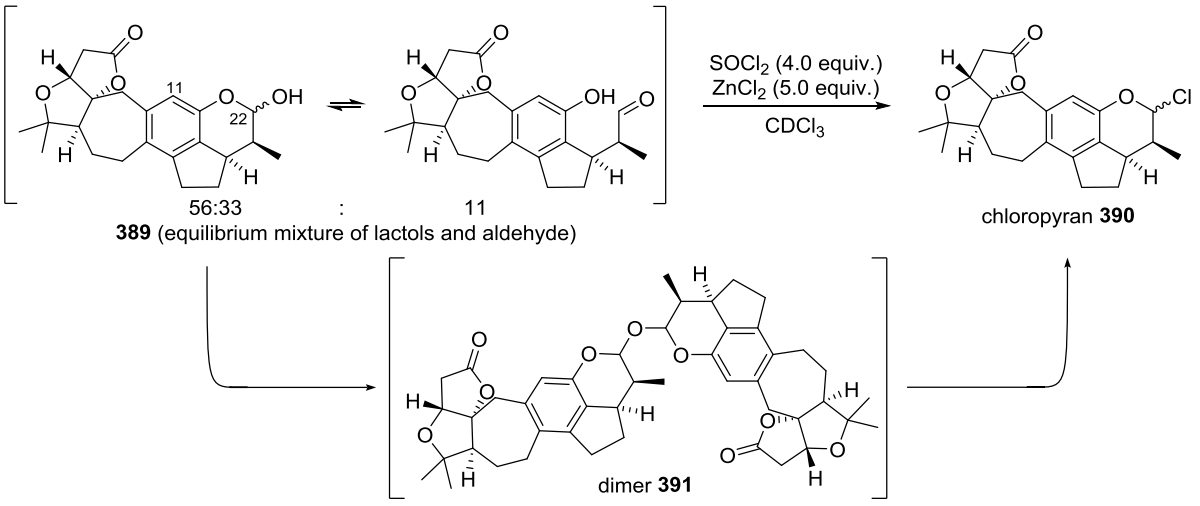


Scheme 6-5 Synthesis of the ABCDEF rings **389** of rubriflordilactone A

Osmium-catalysed dihydroxylation of alkene **387** afforded glycol **388** in an excellent 85% yield (Scheme 6-5), which was then cleaved[167] to give the ABCDEF ring lactol **389**, as a 56:33:11 mixture of two lactol diastereomers and the open-chain aldehyde form (in chloroform-*d*). At this point, we had achieved a formal synthesis of rubriflordilactone A as our route converged with that reported by Li *et al.* in 2014.[29] Yet, we were keen to complete our own total synthesis by attaching the G ring *via* the oxocarbenium ion addition methodology, which would also avoid the use of the tin-based nucleophile **73**.

6.3. Attachment of the G Ring

Having concluded Chapter 5 with a viable strategy to convert CDEF ring lactol **181** into the CDEFG ring system **371a-b**, we eagerly anticipated applying it to the total synthesis of rubriflordilactone A. In this vein, we started by monitoring the conversion of ABCDEF ring lactol **389** to its corresponding chloropyran **390** by ^{1}H NMR spectroscopy (Scheme 6-6).



Scheme 6-6 Formation of ABCDEF ring chloropyran **390** of rubriflordilactone A

As expected, this reaction proceeded through the dimer **391** (not isolated). Figure 6-1 shows the ^{1}H NMR spectra of the reaction mixture before (t = 0 min) and after addition of thionyl chloride (t = 5 min, and thereafter at 10 min intervals until t = 35 min). The consumption of starting material **389** could be easily monitored by the disappearance of the lactol H11 peak (at 6.24 ppm); this was replaced by the H11 peaks of the dimer **391** (at 6.29 ppm) and chloropyran **390** (at 6.32 ppm) in the aromatic region, as well as their respective H22 peaks (at 5.46 for dimer **390** and 6.15 ppm for chloropyran **391** respectively).

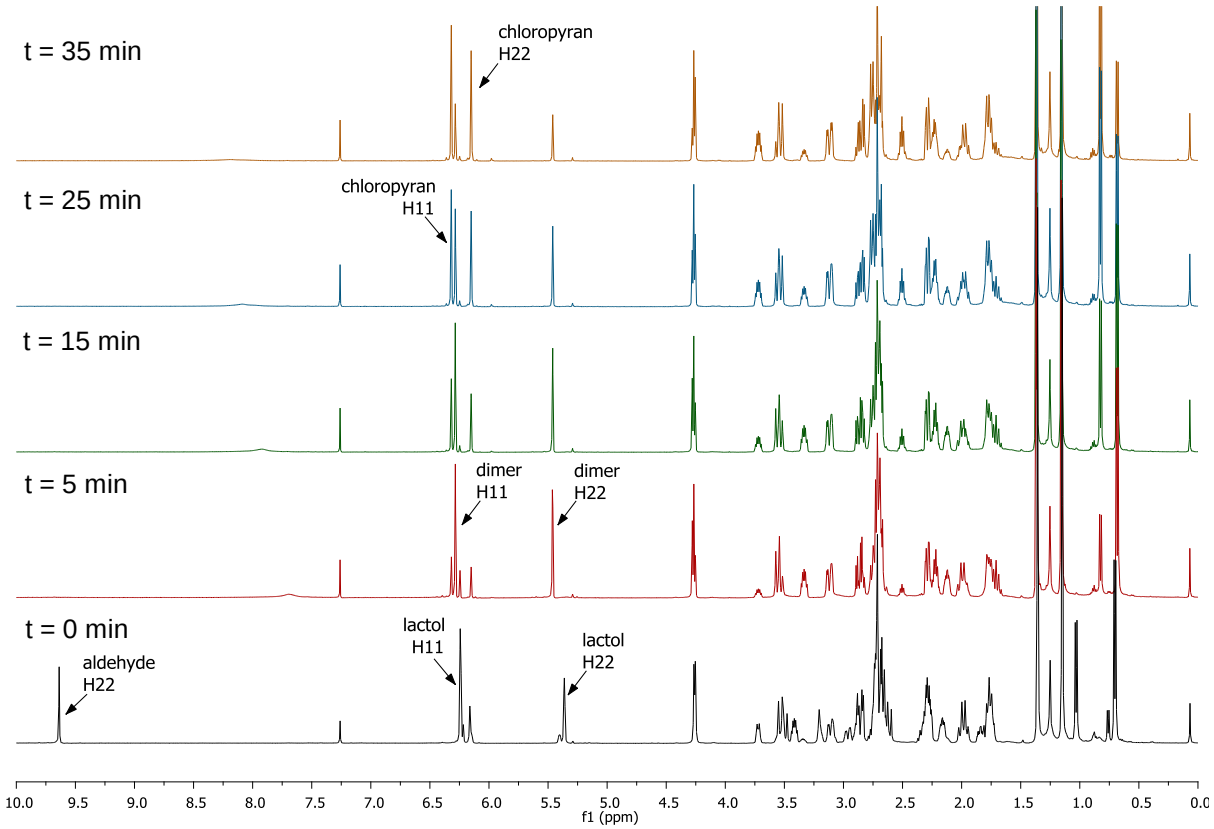


Figure 6-1 ^{1}H NMR spectra of chlorination of ABCDEF ring lactol **389** in $CDCl_3$ over time

Complete conversion to chloropyran **390** was achieved in 3 h (Figure 6-2). The consumption of lactol starting material **389** was also slower for this system as compared to the CDEF ring lactol **181**; allowing us to observe the exponential consumption of lactol **389** and intial rapid formation of dimer **391**, which was then slowly converted into chloropyran **390**.

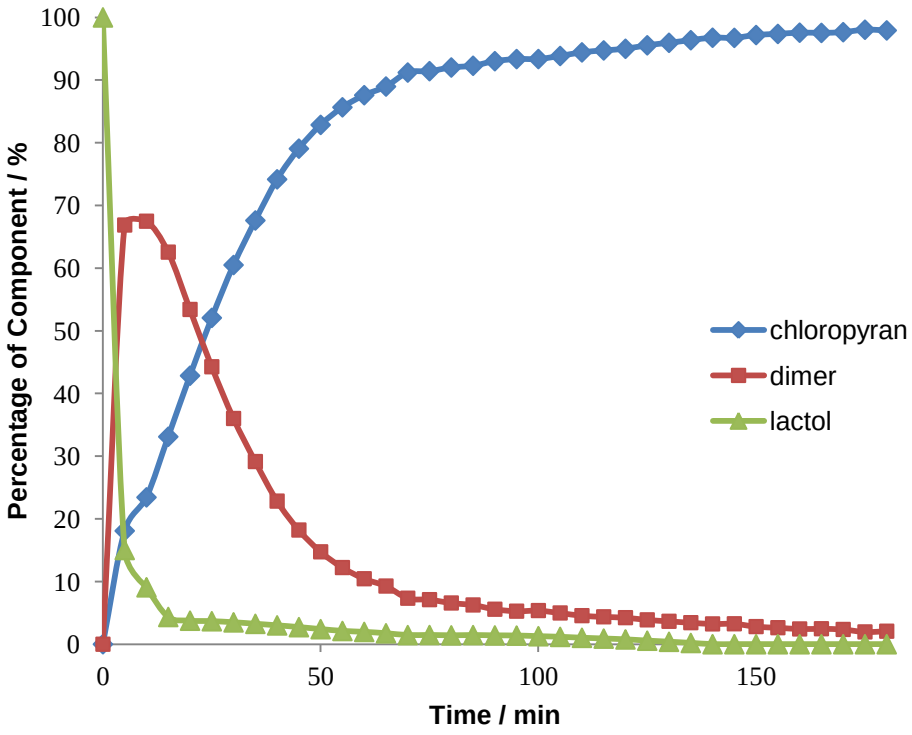
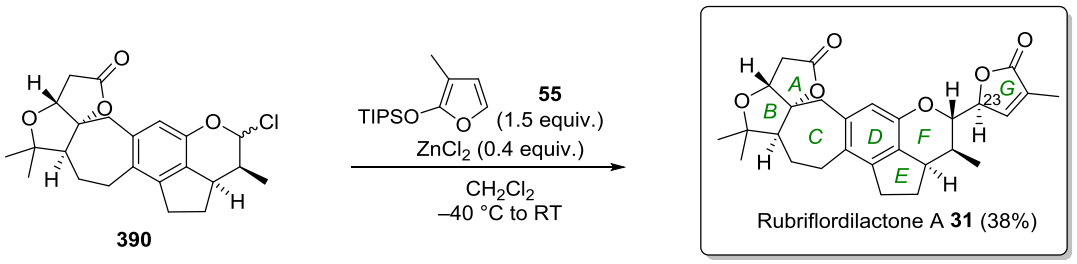


Figure 6-2 Reaction profile for chlorination of ABCDEF ring lactol **389** in $CDCl_3$

With the crude ABCDEF ring chloropyran **390** in hand, we carefully subjected this to the oxocarbenium addition reaction with the G ring siloxyfuran **55** (Scheme 6-7). To our absolute pleasure, rubriflordilactone A **31** was afforded in 38% yield over two steps, along with its C23-epimer **392** (in 33% yield).



Scheme 6-7 Completion of rubriflordilactone A **31**

6.4. Synthetic Rubriflordilactone A

6.4.1. Synthetic vs. natural rubriflordilactone A

A spectroscopic comparison of our synthetic rubriflordilactone A with the isolated natural product was conducted.[12] Figure 6-3 matches our ^{1}H NMR spectrum[xxi] with that of the isolated natural product.

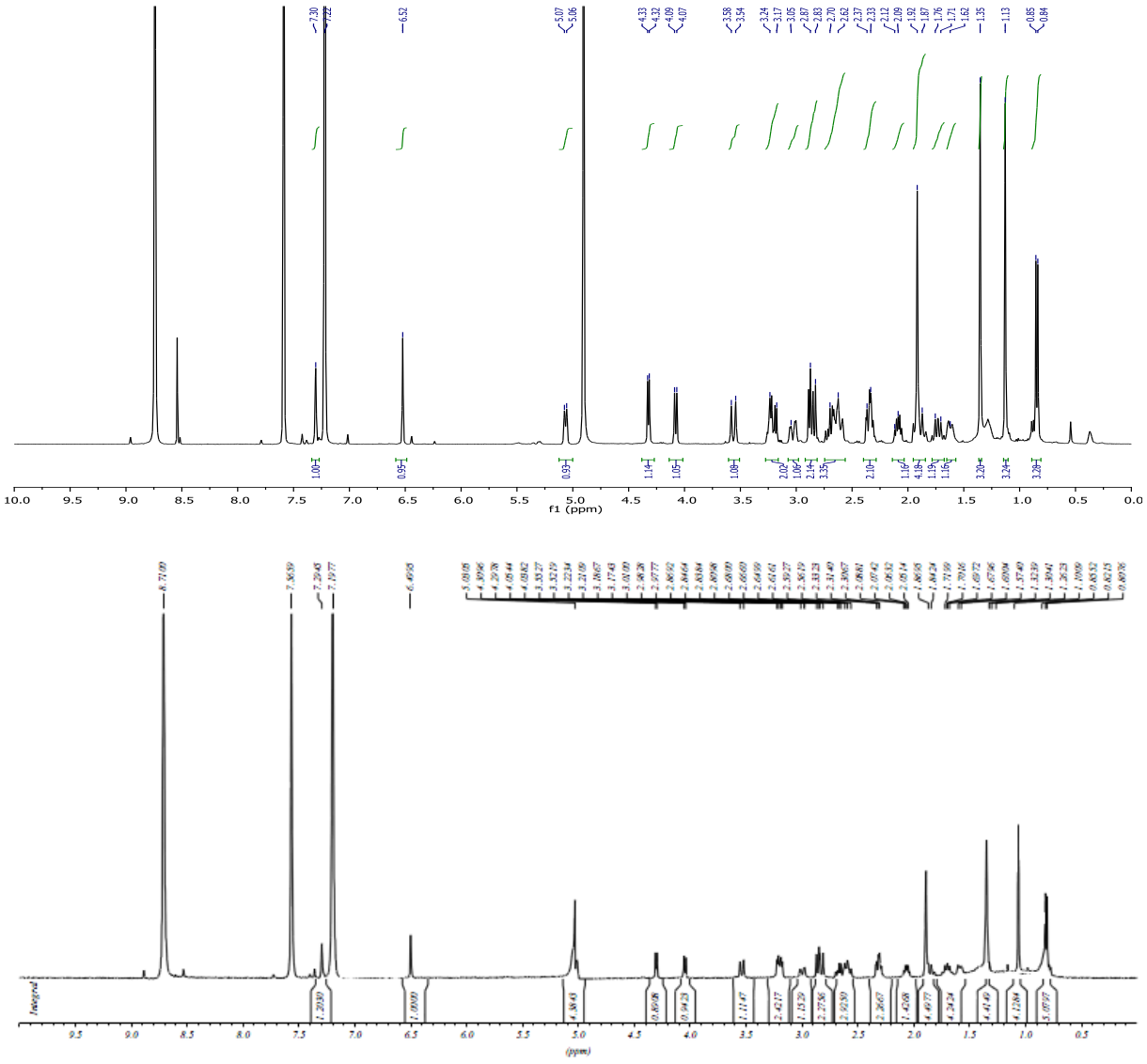


Figure 6-3 ^{1}H NMR spectra of synthetic (top, 500 MHz) and natural[12] (bottom, 400 MHz) rubriflordilactone A in pyridine-*d5*

[xxi] These NMR spectra was obtained after further purification of the synthetic natural product by Dr. Guilhem Chaubet.

Figure 6-4 compares our ^{13}C NMR spectrum[xxii] with the isolated natural product.

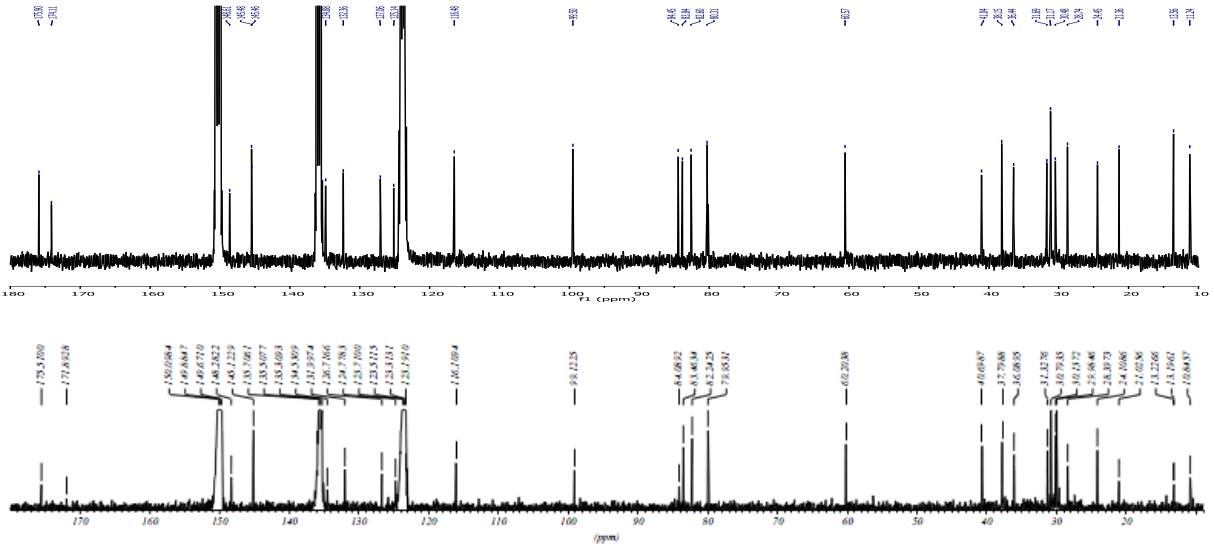
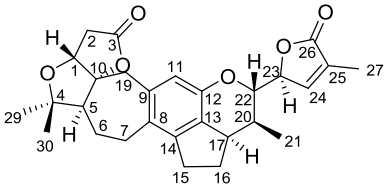


Figure 6-4 ^{13}C NMR spectra of synthetic (top, 126 MHz) and natural[12] (bottom, 101 MHz) rubriflordilactone A in pyridine-*d5*

In Table 6-1, we present a comparison of ^{1}H and ^{13}C NMR signals from our synthetic rubriflordilactone A to the isolated natural product by atom number. This comparison shows high correlation between our compound **31** and the natural product. The ^{1}H chemical shifts showed negligible difference (Δδ) of less than 0.06 ppm between the two compounds, except for H23 (Δδ = 0.11 ppm), in which the signal for the natural product was obscured by a huge water peak, and H15β/H16α, which we had reassigned based on our HSQC and COSY experiments.[xxiii] The ^{13}C chemical shifts showed a consistent, small difference between the two compounds (Δδ = 0.4 ppm), which may be attributed to calibration differences; the exceptions were C16 and C26, for which our chemical shifts were comparable to the reassigned values reported by Li *et al*.[29]

[xxii] These NMR spectra was obtained after further purification of the synthetic natural product by Dr. Guilhem Chaubet.

[xxiii] As Li *et al.* did not make any assignments in their reported data, we are unable to make a comparison by atom number even though their results are a closer match to our values.



Rubriflordilactone A **31**

	Natural δ ^{1}H (ppm, mult, J (Hz)) 400 MHz	**Synthetic**[a] δ ^{1}H (ppm, mult, J (Hz)) 500 MHz	**Δδ** (ppm)	**Natural** δ ^{13}C (ppm) 101 MHz	**Synthetic**[a] δ ^{13}C (ppm) 126 MHz	**Δδ** (ppm)
1	4.30 (d, 6.1)	4.33 (d, 6.1)	0.03	80.0	80.4	0.4
2α	2.83 (d, 18.3)	2.85 (d, 18.3)	0.02	36.1	36.5	0.4
2β	3.19 (dd, 18.3, 6.1)	3.21 (dd, 18.3, 6.1)	0.02			
3				175.5	175.9	0.4
4				84.1	84.5	0.4
5	2.32 (overlapped)	2.36 (dd, 12.5, 3.2)	0.04	60.2	60.6	0.4
6α	1.83 (m)	1.95-1.83 (m)	0.06	24.1	24.5	0.4
6β	1.58 (m)	1.66-1.57 (m)	0.04			
7α	2.99 (dd, 16.2, 2.6)	3.03 (dd, 17.3, 3.9)	0.04	30.8	31.2	0.4
7β	2.71 (overlapped)	2.70 (dd, 15.4, 8.5)	0.01			
8				134.5	134.9	0.4
9				126.7	127.1	0.4
10				99.1	99.5	0.4
11	6.50 (s)	6.52 (s)	0.02	116.1	116.5	0.4
12				148.3	148.7	0.4
13				124.8	125.2	0.4
14				145.1	145.5	0.4
15α	2.59 (overlapped)	2.67-2.56 (m)	0.02	31.3	31.7	0.4
15β	1.69 (m)	2.71 (dd, 15.3, 8.0) [c]	-			
16α	2.67 (m)	1.81-1.68 (m) [c]	-	31.3 (30.0) [b]	31.2	0.1
16β	2.06 (m)	2.09 (dt, 11.8, 6.3)	0.03			
17	3.21 (m)	3.26-3.20 (m)	0.02	37.8	38.2	0.4
19α	2.84 (d, 15.6)	2.87 (d, 15.6)	0.03	40.7	41.1	0.4
19β	3.54 (d, 15.6)	3.56 (d, 15.6)	0.02			
20	2.30 (m)	2.38-2.31 (m)	0.04	30.1	30.5	0.4
21	0.82 (3H, d, 7.1)	0.85 (3H, d, 7.0)	0.03	13.2	13.6	0.4
22	4.05 (dd, 7.8,1.3)	4.08 (d, 8.0)	0.03	83.5	83.9	0.4
23	4.96 (overlapped)	5.07 (d, 7.9)	0.11	82.2	82.6	0.4
24	7.29 (br s)	7.30 (br s)	0.01	145.1	145.5	0.4
25				132.0	132.4	0.4
26				174.2 (171.9) [b]	174.2	0
27	1.89 (3H, s)	1.92 (3H, s)	0.03	10.8	11.3	0.5
29	1.10 (3H, s)	1.13 (3H, s)	0.03	28.4	28.8	0.4
30	1.32 (3H, s)	1.35 (3H, s)	0.03	21.0	21.4	0.4

[a] Data were recorded in C_5D_5N on a Bruker AVII 500 MHz spectrometer with a cryoprobe (^{1}H, ^{13}C, COSY, HSQC, HMBC).

[b] δ ^{13}C (ppm) values obtained from Li *et al.*'s synthetic rubriflordilactone A;[29] misassigned values from natural rubriflordilactone A are in parentheses .

[c] The HSQC spectrum of our synthetic effort gave a different assignment of H15β/H16α to Sun *et al.*

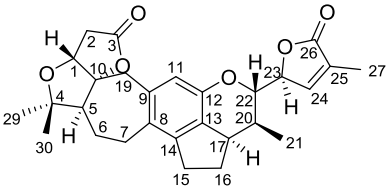
Table 6-1 NMR chemical shifts of natural[12] and synthetic rubriflordilactone A in pyridine-*d5*

High resolution mass spectrometry (ESI^+) showed the molecular ion to have a mass of 487.2092 (calc. for $C_{28}H_{32}NaO_6$ $[M+Na]^+$ 487.2091), again identical to the data reported by both the isolation team and previous synthetic work.

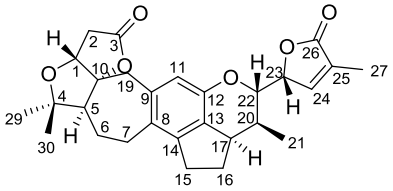
Thus far, all spectroscopic data of our synthetic rubriflordilactone A have been found to be identical to the natural product. However, one exception is the specific rotation, which showed an equal and opposite value, indicating that **31** is likely the unnatural enantiomer ($\propto_D^{25}$ +58.3 (*c* = 0.114, MeOH); lit. $\propto_D^{25}$ –58.1 (*c* = 0.114, MeOH)).[12] This specific rotation was also of the opposite sign to that reported by Li *et al.*, although both our efforts synthesised the same enantiomer. Personal communications with Prof. Li indicated that the (+)-value is correct, following a re-measurement of their synthetic sample; previous measurements may have been erroneous due to the fluctuations of the polarimeter at low sample concentration.

6.4.2. Rubriflordilactone A vs. C23-*epi*-rubriflordilactone A

We also compared the NMR chemical shifts for our synthetic rubriflordilactone A **31** with its C23-epimer **392** (Table 6-2), as established by 2D NOESY NMR experiments. As we would expect, there were significant changes in the ^1H and/or ^{13}C chemical shifts at and adjacent to the center of epimerisation. For example, the ^1H chemical shifts for H17, H20 and H22-24 showed a difference (Δδ) of more than 0.16 ppm between the two epimers. Similarly, the ^{13}C chemical shifts for C17, C20 and C23-25 showed a difference (Δδ) of more than 0.9 ppm between the two epimers. In particular, the ^{13}C chemical shift in chloroform-*d* for C23 is 81.6 ppm in rubriflordilactone A **31** and 78.4 ppm in C23-*epi*-rubriflordilactone A **392** (Δδ = 3.2 ppm); likewise, there was a significant difference in the ^{13}C chemical shifts of C24 in the two epimers at 144.3 ppm and 149.0 ppm for **31** and **392** respectively, (Δδ = 2.4 ppm).



Rubriflordilactone A **31**



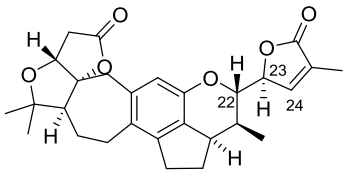
C23-*epi*-rubriflordilactone A **392**

	Rubriflordilactone A [a] δ ^{1}H (ppm, mult, J (Hz)) 500 MHz	**C23-epimer** [a] δ ^{1}H (ppm, mult, J (Hz)) 500 MHz	**Δδ** (ppm)	**31** [a] δ ^{13}C (ppm) 126 MHz	**392** [a] δ ^{13}C (ppm) 126 MHz	**Δδ** (ppm)
1	4.26 (d, 6.1)	4.27 (d, 6.0)	0.01	79.7	79.6	0.1
2α	2.87 (dd, 18.6, 6.3)	2.86 (dd, 18.6, 6.0)	0.01	36.0	36.0	0
2β	2.79-2.59 (m)	2.72 (d, 18.6)	0.03			
3				175.3	175.5	0.2
4				84.4	84.5	0.1
5	2.36-2.22 (m)	2.28 (dd, 12.5, 3.0)	0.01	59.6	59.2	0.4
6α	2.01 (dd, 19.0, 6.0)	2.06-1.95 (m),	0	24.1	24.1	0
6β	1.84-1.68 (m)	1.88-1.69 (m)	0.02			
7α	3.16-3.01 (m)	3.12 (ddd, 17.0, 5.3, 2.1)	0.04	30.5	30.5	0
7β	2.79-2.59 (m)	2.76-2.69 (m)	0.03			
8				133.6	133.3	0.3
9				126.6	126.5	0.1
10				98.9	99.2	0.3
11	6.35 (s)	6.25 (s)	0.10	115.9	115.3	0.6
12				147.9	147.9	0
13				124.2	124.8	0.6
14				144.8	145.3	0.5
15α	2.79-2.59 (m)	2.76-2.69 (m)	0.03	31.3	31.3	0
15β	2.79-2.59 (m)	2.76-2.69 (m)	0.03			
16α	2.16 (dt, 11.8, 6.1)	2.25-2.16 (m)	0.04	30.8	30.7	0.1
16β	1.84-1.68 (m)	1.88-1.69 (m)	0.02			
17	3.16-3.01 (m)	3.34 (dt, 10.9, 6.1)	0.25	37.8	36.7	1.1
19α	3.54 (d, 15.5)	3.56 (d, 15.4)	0.02	41.1	41.0	0.1
19β	2.79-2.59 (m)	2.64 (d, 15.4)	0.05			
20	2.36-2.22 (m)	2.69-2.61 (m)	0.34	29.5	28.6	0.9
21	0.85 (3H, d, 7.0)	0.83 (3H, d, 7.0)	0.02	13.7	12.9	
22	4.09 (d, 7.7)	3.79 (d, 9.8 Hz)	0.30	82.7	82.4	0.3
23	5.04 (dt, 7.4, 1.8)	4.88 (d, 9.8)	0.16	81.6	78.4	3.2
24	7.05 (s)	7.38 (s)	0.33	144.3	149.0	4.7
25				132.4	130.0	2.4
26				173.5	174.0	0.5
27	1.95 (3H, s)	1.94 (3H, s)	0.01	11.0	10.8	0.2
29	1.36 (3H, s)	1.37 (3H, s)	0.01	28.5	28.5	0
30	1.15 (3H, s)	1.16 (3H, s)	0.01	21.2	21.3	0.1

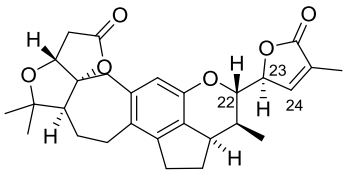
[a] Data were recorded in $CDCl_3$ on a Bruker AVII 500 MHz spectrometer with a cryoprobe (^{1}H, ^{13}C) and a AVIIIHD 400 MHz nanobay spectrometer (COSY, HSQC, HMBC, NOESY).

Table 6-2 Comparison of NMR shifts of synthetic rubriflordilactone A **31** and its C23-epimer **392** in chloroform-*d*

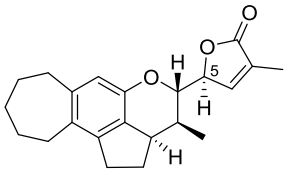
To further clarify this issue, a comparison of the key ^{13}C chemical shifts was made between synthetic rubriflordilactone A **31** and its C23-epimer **392**, and the previously synthesised CDEFG ring systems **371a** and **371b** (Figure 6-5; *see Section 5.4.2*). The ^{13}C NMR signals of CDEFG system **371a**, which possesses the same stereochemistry as rubriflordilactone A by analysis of 2D NOESY spectra, were in good agreement with the natural product (Table 6-3); while that of the C5-*epi*-CDEFG system **371b**, which is the epimer of **371a** at the C23-position of rubriflordilactone A, closely matched those of C23-*epi*-rubriflordilactone A **392**. For example, the ^{13}C chemical shift of C23 for rubriflordilactone A at 82.5 ppm, was consistent with the shift for its corresponding carbon in CDEFG system **371a** (C5) at 82.8 ppm. In contrast, the ^{13}C signal for C23 in C23-*epi*-rubriflordilactone A **392** at 79.3 ppm, closely matched the signal for C5 in C5-*epi*-CDEFG system **371b** at 79.4 ppm. This evidence confirmed our assignment of stereochemistry in compounds **31** and **392**.



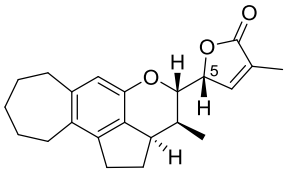
Rubriflordilactone A **31**



C23-*epi*-rubriflordilactone A **392**



CDEFG rings **371a**



C5-*epi*-CDEFG rings **371b**

Figure 6-5 Rubriflordilactone A **31** and its analogues

Carbon No.	**δ ^{13}C** (ppm) [a]			
	Rubriflordilactone A **31**	CDEFG rings **371a**	C23-*epi*-rubriflordi-lactone A **392**	C5-*epi*-CDEFG rings **371b**
22	83.8	83.3	82.5	82.4
23	82.5	82.8	79.3	79.4
24	145.4	145.9	149.6	149.6

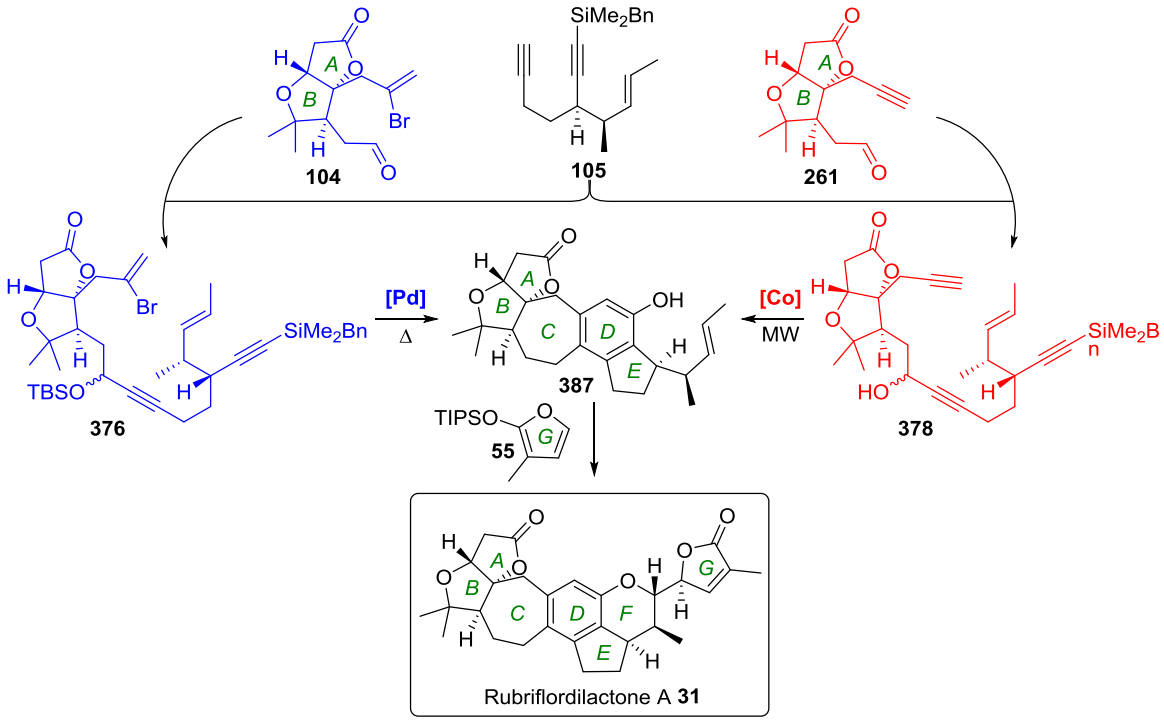
[a] Data were recorded in C_5D_5N on a Bruker AVII 500 MHz spectrometer with a cryoprobe (^1H, ^{13}C, COSY, HSQC, HMBC).

Table 6-3 Comparison of key ^{13}C NMR shifts of rubriflordilactone A **31** and its analogues in pyridine-*d5*

6.5. Conclusion and Future Work

6.5.1. Overview of synthesis

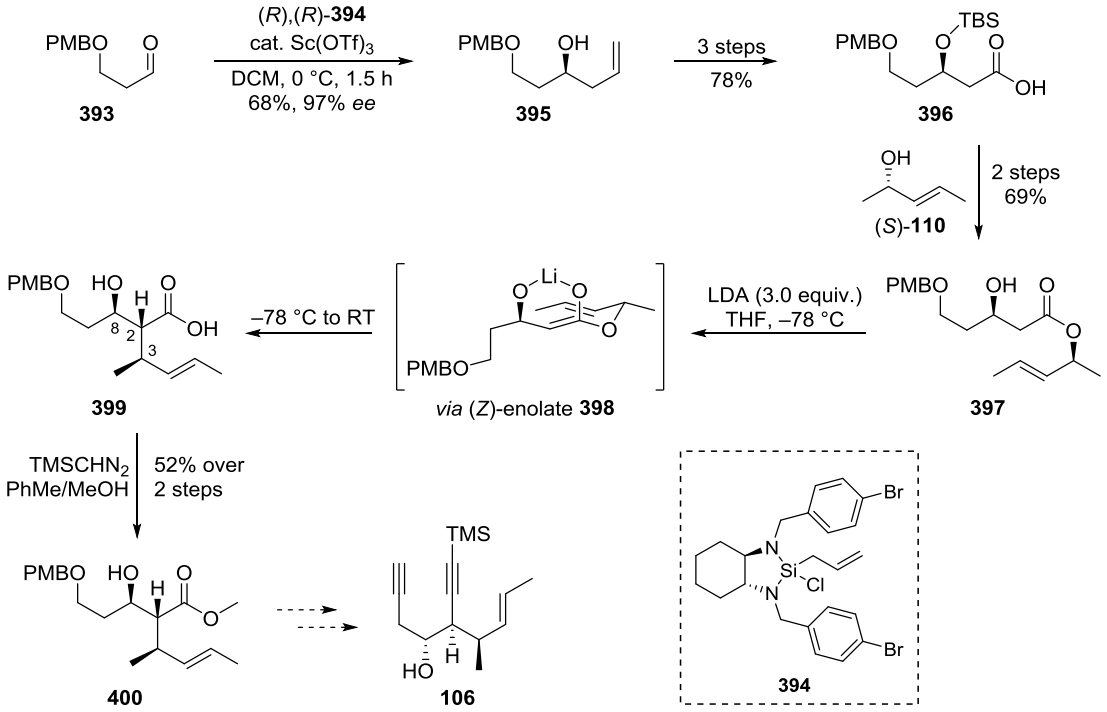
In summary, we have successfully established two synthetic strategies to achieve the enantioselective total synthesis of (+)-rubriflordilactone A (Scheme 6-8).[102] The key feature of these syntheses is the use of a transition metal-catalysed cyclisation to assemble the ABCDE ring system in a single step relatively late in the synthesis. The cobalt-catalysed cyclotrimerisation methodology enabled the more efficient synthesis of rubriflordilactone A, in 22 steps (longest linear sequence) with a 2.5% overall yield. The convergent nature of these routes, through coupling of the AB ring aldehydes with an appropriate CDE diyne fragment to assemble the key cyclisation substrates, enables a unified approach to other members of this natural product family and also their analogues.



Scheme 6-8 Summary of our total synthesis of (+)-rubriflordilactone A

6.5.2. Outlook to rubriflordilactone B and other *Schisandra* natural products

In particular, our total synthesis of rubriflordilactone A has set the stage for our group's approach towards rubriflordilactone B.[xxiv,234] As we envisaged using the same disconnections in the retrosynthesis of both rubriflordilactones A and B (*see Section 1.3.1*), our foremost challenge is to synthesise the CDE diyne fragment of rubriflordilactone B **32**. Similar to the synthesis of the corresponding fragment diyne **105** for rubriflordilactone A **31**, we also envisage an Ireland-Claisen rearrangement,[96,143–146] this time *via* the (*Z*)-enolate, as the key transformation leading to diyne **106**.



Scheme 6-9 Ireland-Claisen rearrangement towards CDE diyne fragment **106** of rubriflordilactone B

In this vein, the route[234] began with enantioselective allylation of aldehyde **393** using Leighton's reagent **394** to afford alkene **395** in excellent yield and enantioselectivity (Scheme 6-9).[235,236] Oxidative cleavage of alkene **395** resulted in acid **396**, which was coupled with

[xxiv] These studies towards the synthesis of diyne fragment **106** were initiated by Pollyanna Sanderson[234], a former Part II student, and are currently being advanced by Mujahid Muhammad, a current DPhil student, in the Anderson group. The author's role in this synthesis was limited to guidance and supervision, and the synthesis of allylation product **395**.

enantioenriched alcohol (*S*)-**110** to give β-hydroxyester **397**, the precursor for a dianionic Ireland-Claisen rearrangement.[237–240] The β-alkoxide functionality in **397** is essential for stereocontrol in enolate formation, since chelation of a metal cation by the β-alkoxide and (*Z*)-enolate functionalities forms a highly favourable 6-membered ring **398**. Enolate **398** is then in prime position to perform a [3,3]-sigmatropic rearrangement upon warming to afford *syn*-acid **399**. The acid could be protected *in situ* to afford its methyl ester **400** in 52% yield over two steps.

The stereochemistry of acid **399** was confirmed by NOESY NMR experiments on two cyclic derivatives (Figure 6-6). β-Lactone **401**, which was formed by lactonisation of β-hydroxyacid **399**, established the C2 stereochemistry of acid **399** relative to C8 (set by a Leighton allylation); while γ-lactone **402**, which was formed by iodolactonisation of acid **399**, established the C3 stereochemistry of acid **399** relative to C2.

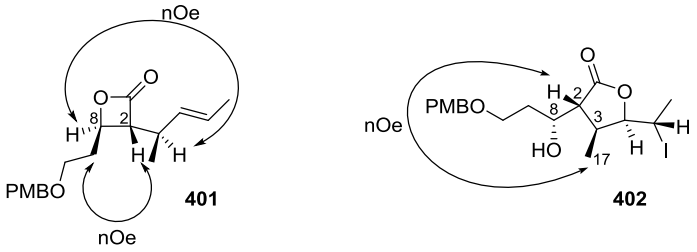


Figure 6-6 Determination of stereochemistry of acid **399**

Currently, efforts are underway to transform ester **400** into diyne **106** (Scheme 6-9), which would enable us to synthesise rubriflordilactone B **32** in a similar approach to our synthesis of rubrilfordilactone A **31**. This strategy could also likely be extended to other members of the schinortriterpenoid family.

Also of interest is the synthesis of natural product analogues, which are useful in the establishment structure-activity relationships in conjunction with biological activity testing. In the course of this thesis, we have already synthesised (+)-rubriflordilactone A **31** and its C23-epimer **392**, as well as the abridged CDEFG ring system of rubriflordilactone A **371a** and its C5-epimer **371b** (Figure 6-5). En route to the synthesis of rubriflordilactone B **32**, we would

also target the synthesis of similar analogues – the C23-epimer **403** of rubriflordilactone B, the abridged CDEFG ring system **404a** of rubriflordilactone B and its C5-epimer **404b** (Figure 6-7). The ABCDE ring systems **405** and **406** of rubriflordilactones A and B would also be attractive targets.

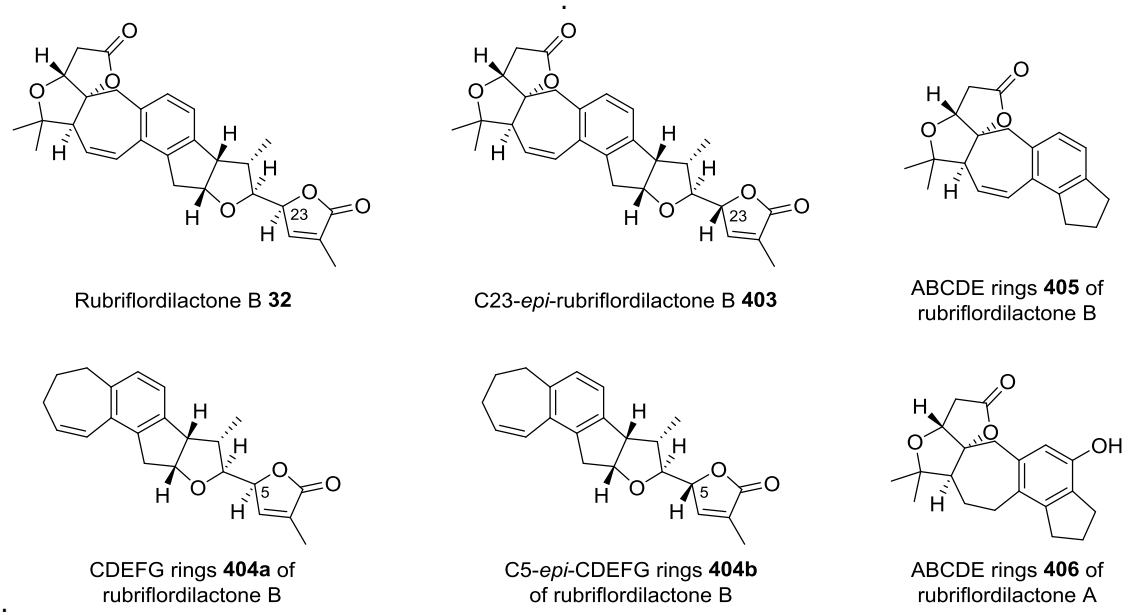
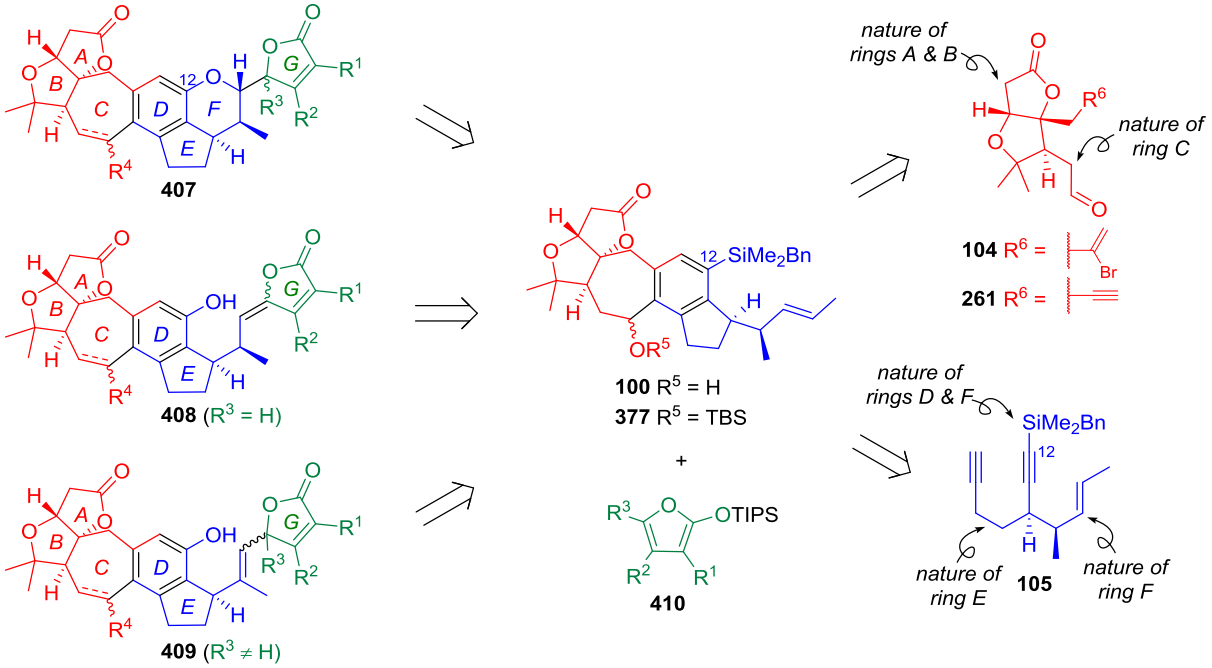


Figure 6-7 Rubriflordilactone B **32** and its analogues

Biological studies have shown that rubriflordilactone B **32** exhibits greater anti-HIV activity than rubriflordilactone A **31**.[12] Given that the rubriflordilactones share the same AB rings but not the CDEFG system, it would be interesting to compare the biological activities of the abridged CDEFG ring systems **371a** and **404a**, of rubriflordilactones A and B respectively, to each other, and also to their respective parent rubriflordilactone and its ABCDE ring system **405** or **406**. This would give us some insight into the influence of the AB rings on the bioactivities of these molecules. Another possible study would be to compare the biological activities of the epimers (e.g. C23-epi-rubriflordilactone A **392** vs. rubriflordilactone A **31**, C23-epi-rubriflordilactone B **403** vs. rubriflordilactone B **32**) to identify the influence, if any, of the C23-stereochemistry on their biochemistry; or of the enantiomers (e.g. (+)-rubriflordilactone A vs. the natural product). In the course of these biological studies, some

useful bioactivities of the compounds may possibly be unearthed, turning them into potential drug targets.

Of course, other analogues of the rubriflordilactones could also be synthesised. Our highly convergent synthesis enables easy manipulation of the rubriflordilactone structure. For example, Scheme 6-10 shows that a huge amount of diversity can already be achieved from the post-cyclisation steps to rubriflordilactone A **31** alone. From the previously synthesised pentacycles **100** or **377** (*see Section 6.1*), analogues of type **407**, similar in structure to rubriflordilactone A but bearing different substituents R^1 to R^4, or types **408** and **409**, which do not bear the F ring, could be synthesised. Substituents R^1 to R^3 would be determined by the substitution of siloxyfuran **410**, while substitutent R^4 would depend on the post-cyclisation modification to the C ring. Given the importance of the CDEFG rings to the bioactivities of the rubriflordilactones, variation of the butenolide and this region could be highly effective.



Scheme 6-10 Possible post-cyclisation diversification to rubriflordilactone A analogues

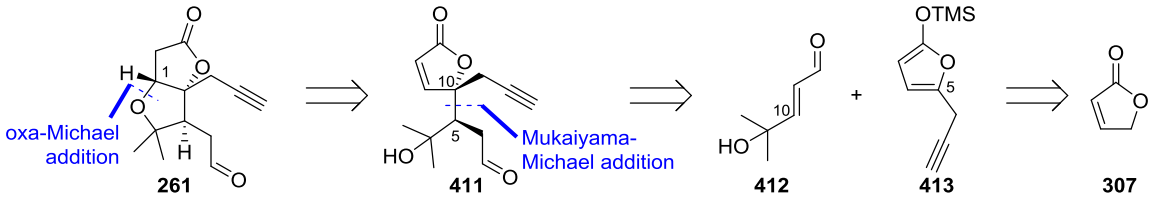
Scheme 6-10 also indicates how modification of the pre-cyclisation fragments could affect the nature of the rings in rubriflordilactone A. For example, the AB ring aldehydes **104** or **261** could be re-designed to alter not only rings A and B, but also ring C (e.g. by changing the

length or substitution of the pendent aldehyde chain). Similarly, modifications the CDE enediyne fragment **105** could affect the nature of the D, E and/or F rings. The length and substitution of the terminal alkyne tether in enediyne **105** would decide the nature of the E ring, while the same paramenters on the alkene tether in enediyne **105** would decide the nature of the F ring; the silyl substituent would affect the C12 substituent (rubriflordilactone A numbering), which would in turn determine the nature of rings D and F (or lack thereof). This method of design could strategically target other *Schisandra* nortriterpenoids and analogues of these natural products, thus yielding a diversity of molecules bearing schinortriterpenoid-like scaffolds, with potentially beneficial bioactivities.

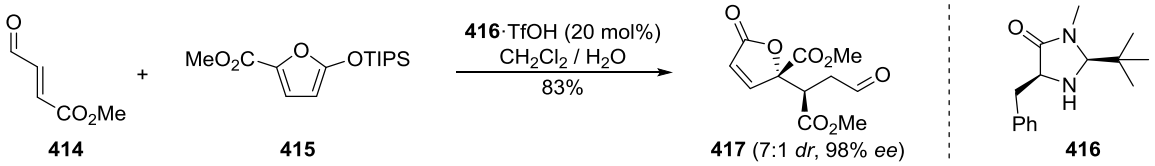
6.5.3. Proposed second-generation synthesis of rubriflordilactone A

Having established a viable route to rubriflordilactone A, we seeked to increase the efficiency of the synthesis. This could be done by decreasing the step count to the separate fragments of rubriflordilactone A **31**. Herein, proposed second-generation syntheses of the AB ring aldehyde fragment **261** and the CDE diyne fragment **105** are described.

Scheme 6-11 illustrates a more concise retrosynthesis of the AB ring fragment **261**. As with our current synthesis, the first disconnection would be the C-O bond at C1 (rubriflordilactone A numbering), leading to butenolide **411**. In the forward synthesis, an intramolecular oxa-Michael addition from alcohol **411** (or its lactol form) would produce AB ring fragment **261**. A second disconnection at the C5-C10 bond would generate known enal **412**[241] and oxyfuran **413**. These two fragments could be put together by an asymmetric Mukaiyama-Michael addition reaction to form butenolide **411**. MacMillan and co-workers[242] showed that chiral amine **416** could enantioselectively catalyse the reaction of enal **412** with oxyfuran **415** (Scheme 6-12), providing important precedent for our proposed strategy. Oxyfuran **413** could be synthesised from butenolide **307** in two steps.

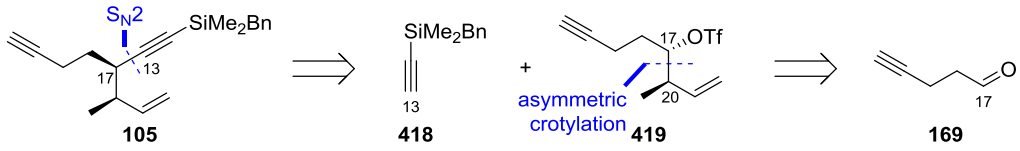


Scheme 6-11 Second-generation retrosynthesis of AB ring aldehyde **261**



Scheme 6-12 Enantioselective Mukaiyama-Michael reaction (MacMillan *et. al*, 2003)[242]

Similarly, we proposed a more succinct retrosynthesis of CDE diyne fragment **105** (Scheme 6-13). A C13-C17 disconnection (rubriflordilactone A numbering) would lead to silylalkyne **418** and triflate **419**; a direct S_N2 displacement of the triflate with alkyne **418** would give diyne **105** in the forward sequence. Another disconnection at C17-C20 in the triflate would lead to aldehyde **169**, which we have previously synthesised. An enantioselective crotylation of this aldehyde, followed by reaction with triflic anhydride, would generate triflate **419**. The asymmetric crotylation step could be easily achieved by using chiral boron reagents e.g. Brown crotylation[243,244] or silicon reagents e.g. Leighton crotylation.[245–247]



Scheme 6-13 Second-generation retrosynthesis of CDE diyne fragment **105**

The success of these second-generation syntheses would not only streamline the total synthesis of rubriflordilactone A, but would also benefit the syntheses of other *Schisandra* natural products and their analogues.

7. Experimental

7.1. General Experimental Considerations

Nuclear Magnetic Resonance Spectroscopy: ^{1}H NMR spectra were acquired on Bruker DRX500, AVII500 (500 MHz, with cryoprobe) or AVIII400 (400 MHz) spectrometers and were referenced to residual non-deuterated solvent peaks in $CDCl_3$ (δ = 7.26) or C_5D_5N (δ = 8.74, 7.58, 7.22). Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), and multiplet (m); *app* = apparent. Coupling constants (*J*) are measured to the nearest 0.1 Hz and are presented as observed. ^{13}C NMR spectra were obtained on Bruker AVII500 (126 MHz, with cryoprobe) or AVIII400 (101 MHz) spectrometers and were referenced to solvent peaks in $CDCl_3$ (δ = 77.16) or C_5D_5N (150.35, 135.91, 123.87).

Mass Spectrometry: Low-resolution mass spectra (*m/z*) were recorded on a Waters LCT Premier EX mass spectrometer, using electrospray ionization (ESI). High resolution mass spectra (**HRMS**) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Bruker MicroTOF (resolution = 5000 FWHM) using electrospray ionisation (ESI), elecron ionisation (EI) or field ionisation (FI). The parent ion $[M]^+$, $[M+H]^+$, $[M+Na]^+$ or $[M-H]^-$ is calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Infrared Spectroscopy: Absorption spectra were obtained in $CHCl_3$ as solvent on a Bruker Tensor 27 FT-IR spectrometer. The sample was prepared as a thin film on a diamond/ZnSe PIKE Miracle ATR module. Wavelengths of maximum absorbance (ν_{max}) are quoted in wavenumbers (cm^{-1}). Only selected, characteristic IR absorption data are provided for each compound.

Specific rotations: Optical rotations were recorded on a Perkin Elmer 241 or 341 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). Specific rotations ($[\alpha]_D$) are reported in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are reported in g/100 mL. Temperatures are reported in °C (typically 25 °C).

Melting Points: Melting points were obtained using a Reichert-Koffler block and are uncorrected.

Elemental Analysis: Samples were analysed by Mr Stephen Boyer, Science Centre, London, Metropolitan University.

Microwave reactions: Microwave reactions (CEM Discover microwave reactor) were conducted in sealed glass vessels (10 mL or 40 mL)

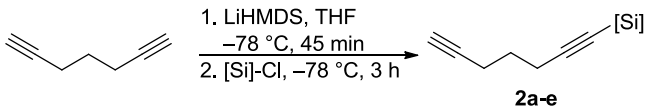
Chromatography: Flash chromatography refers to normal phase column chromatography on silica gel using a head pressure of N_2, using either Merck Geduran® Silicagel 60 (40 - 63 μm) or Macherey-Nagel Silica 60 M (40 - 63 μm). Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet light (254 nm) and/or heating the plate after staining with vanillin or $KMnO_4$. High performance liquid chromatography (HPLC) was performed on an Agilent 1200 Series running in normal phase under UV detection using a ZORBAX RX-SIL (150 mm x 4.6 mm ID) as the analytical column. Chiral analysis was carried out using DAICEL CHIRALPAK-IA, IB or IC (250 mm x 4.6 mm ID).

Materials: Unless otherwise stated, all reactions were carried out in oven-dried glassware under an atmosphere of argon, using anhydrous reaction solvents. Et_2O, dichloromethane, THF and toluene were dried over activated alumina before use. All other commercially available reagents and solvents were either used as received, and/or dried and purified before use using standard procedures. Pet. Ether refers to the fraction of light Pet. Ether boiling at 40-60 °C unless stated otherwise.

7.2. Procedures and Characterisations for Synthesis of the CDE Rings

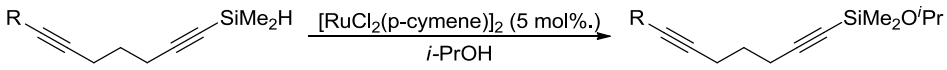
7.2.1. General procedures

GP 1: *Monoprotection of diynes*



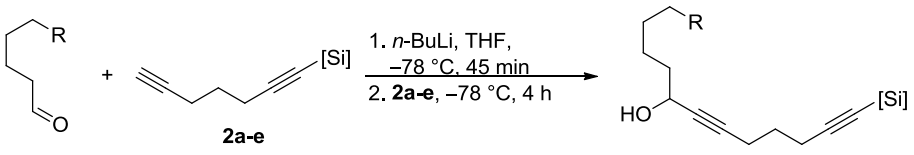
To a stirred solution of 1,6-heptadiyne (1.0 equiv.) in dry THF (0.18 M) under argon at –78 °C was added LiHMDS (1 M in THF, 1.0 equiv.). After stirring for 45 min, a solution of chlorosilane (1.2 equiv.) in dry THF (3.5 M) was added. The reaction mixture was stirred for 3 h at –78 °C before it was quenched with sat. *aq.* NH_4Cl solution. After warming to RT the layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with Na_2SO_4 and the solvent removed *in vacuo*.

GP 2: *Etherification of hydrosilanes*



To a stirred solution of hydrosilane (1.0 equiv.) in 2-propanol (2.0 equiv.) was added $[RuCl_2(p\text{-cymene})]_2$ (5 mol %). The reaction mixture was stirred for 2 h before it was filtered through a short plug of Celite® and the solvent removed *in vacuo*.[113]

GP 3: *Coupling of aldehyde with diyne*



To a stirred solution of diyne **2** (1.5 equiv.) in dry THF (0.25 M) under argon at –78 °C was added *n*-BuLi (2.5 M in hexane, 1.3 equiv.). After stirring for 45 min a solution of aldehyde

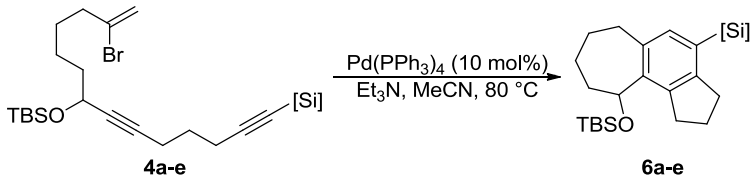
(1.0 equiv.) in dry THF (1 M) was added. The reaction mixture was stirred for 2 h at –78 °C before being quenched with sat. *aq.* NH_4Cl solution. After warming to RT the mixture was filtered through a pad of Celite® and the solvent removed *in vacuo*.

GP 4: *TBS protection of alcohols*

3a-e **4a-e**

To a stirred solution of alcohol **3** (1.0 equiv.) in dry dichloromethane (0.25 M) under argon at 0 °C was added sequentially imidazole (1.5 equiv.), DMAP (0.1 equiv.) and TBSCl (1.1 equiv.). The reaction mixture was warmed to RT and stirred for 2 h before being quenched with sat. *aq.* $NaHCO_3$ solution, the layers separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with Na_2SO_4 and the solvent removed *in vacuo*.

GP 5: *Palladium-catalysed cyclisation of bromoenediynes*

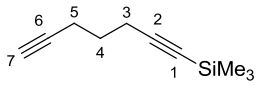


4a-e **6a-e**

Bromoendiyne **4** (1.0 equiv.) was dissolved in dry acetonitrile (0.04 M), and the solution degassed withargonbubbling for 30 min. Triethylamine was separately degassed with argon bubbling for 30 min. A vial equipped with a stirrer bar was charged with tetrakis(triphenylphosphine)palladium(0) (10 mol %)) in the glovebox, and subsequently degassed with argon bubbling for 15 min. The degassed solution of starting material was added to the catalyst by syringe, followed by the degassed triethylamine (6.0 equiv.). The reaction mixture was stirred at 80 °C overnight, then cooled to RT and the solvent carefully removed *in vacuo*.[95]

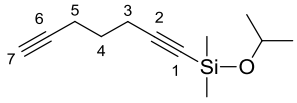
7.2.2. Synthesis of Cyclisation Precursors

(Hepta-1,6-diynyl)trimethylsilane (128a)



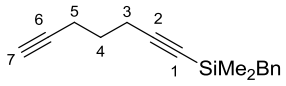
Prepared by **GP1** using 1,6-heptadiyne (0.82 mL, 7.16 mmol) and chlorotrimethylsilane (1.10 mL, 8.60 mmol). Kughelrohr distillation (80-100 °C at 11 mbar) afforded trimethylsilane **128a** (0.638 g, 54%) as a colourless oil. $\mathbf{R_f}$ 0.79 (Pet. Ether/ Et_2O (19:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.39-2.32 (2H, m, H3), 2.34-2.27 (2H, td, *J* = 2.6 Hz, H5), 1.96 (1H, t, *J* = 2.6 Hz, H7), 1.76-1.69 (2H, m, H4), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 106.2, 85.4, 83.7, 68.9, 27.7, 19.1, 17.7, –0.3. Data in accordance with literature.[95]

Hepta-1,6-diyn-1-yl(isopropoxy)dimethylsilane (128b)



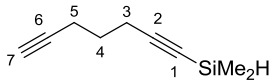
Prepared by **GP3** using hydrosilane **128d** (200 mg, 1.33 mmol). Flash column chromatography on a short plug of silica gel (9:1 Pet. Ether/ Et_2O) afforded alkoxysilane **128b** (209 mg, 75%) as a colourless oil. $\mathbf{R_f}$ 0.16 (Pet. Ether); **IR** (thin film, ν_{max} / cm^{-1}) 3310 (m), 2970 (s), 2936 (m), 2175 (m), 1254 (m), 1123 (m), 1027 (s), 822 (s), 790 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.13 (1H, sept, *J* = 6.1 Hz, $OCH(CH_3)_2$), 2.40-2.34 (2H, t, *J* = 7.1 Hz, H3), 2.32 (2H, td, *J* = 7.1, 2.6 Hz, H5), 1.96 (1H, t, *J* = 2.6 Hz, H7), 1.75 (2H, quin, *J* = 7.1 Hz, H4), 1.19 (6H, d, *J* = 6.1 Hz, $OCH(CH_3)_2$), 0.23 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 106.1, 83.9, 83.6, 69.0, 66.0, 27.5, 25.6, 18.9, 17.7, 0.9; **HRMS** (FI^+) calc. for $C_{12}H_{21}OSi$ $[M+H]^+$ 209.1362, found 209.1367.

Benzyl(hepta-1,6-diynyl)dimethylsilane (128c)



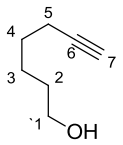
Prepared by **GP1** using 1,6-heptadiyne (500 mg, 5.26 mmol) and benzylchlorodimethylsilane (1.15 mL, 6.32 mmol). Flash column chromatography on silica gel (30:1 Pet. Ether/ EtOAc) afforded an inseparable 1:0.4 mixture of the monoprotected diyne **128c** (62%) and the bisprotected diyne (25%) as a colourless oil (1.33 g). $\mathbf{R_f}$ 0.25 (Pet. Ether ×2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24-7.20 (2H, m, H_{Ar}), 7.10-7.08 (3H, m, H_{Ar}), 2.35 (2H, t, *J* = 7.1 Hz, H3), 2.33-2.27 (2H, td, *J* = 7.1, 2.7 Hz, H5), 2.18 (2H, s, $SiCH_2$), 1.97 (1H, t, *J* = 2.7 Hz, H7), 1.76-1.69 (2H, m, H4), 0.11 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.3, 128.5, 128.2, 124.4, 107.6, 83.8, 83.6, 68.9, 27.5, 26.6, 19.0, 17.6, –1.7. Data in accordance with literature.[248]

(Hepta-1,6-diynyl)dimethylsilane (128d)



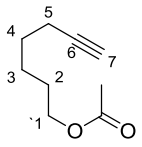
Prepared by **GP1** using 1,6-heptadiyne (500 mg, 5.43 mmol) and chlorodimethylsilane (0.63 mL, 5.70 mmol). Flash column chromatography on silica gel (9:1 Pet. Ether/ Et_2O), followed by Kughelrohr distillation (69 °C at 8 mbar) afforded diyne **128d** (403 mg, 49%) as a colourless oil. $\mathbf{R_f}$ 0.29 (Pet. Ether ×2); **IR** (thin film, ν_{max} / cm^{-1}) 2925 (s), 2854 (m), 2153 (m), 1463 (m), 1142 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.16-4.06 (1H, m, SiH), 2.38 (2H, td, *J* = 7.1, 1.0 Hz, H3), 2.32 (2H, td, *J* = 7.1, 2.6 Hz, H5), 1.97 (1H, t, *J* = 2.6 Hz, H7), 1.76 (2H, quin, *J* = 7.1 Hz, H4), 0.22 (6H, d, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 107.8, 83.6, 82.4, 69.0, 27.5, 19.1, 17.7, –2.6; **HRMS** (FI^+) Mass not found. Characterization of **127d** confirms identity of this compound, together with analogy to other silanes.

Hept-6-yn-1-ol



To sodium hydride (2.67 g, 66.9 mmol, 3.0 equiv.) under argon was added slowly 1,3-diaminopropane (36 mL). The reaction mixture was heated to 70 °C for 30 min before it was cooled to RT. 3-heptyn-1-ol (2.50 g, 22.3 mmol, 1.0 equiv.) was added dropwise and the reaction was stirred for a further 40 min before the reaction mixture was quenched by careful addition of an ice/water mixture. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were washed with water, 1 N HCl, water and brine, and dried with Na_2SO_4. The solvent was removed *in vacuo* to yield hept-6-yn-1-ol contaminated with small amounts of 1,3-diaminopropane (2.94 g, >100%) as a colourless oil. The crude product was used without further purification in the next step. $\mathbf{R_f}$ 0.4 (Pet. Ether / Et_2O (1:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.65 (2H, t, *J* = 6.4 Hz, H1), 2.20 (2H, dt, *J* = 6.9, 2.6 Hz, H5), 1.94 (1H, t, *J* = 2.6 Hz, H7), 1.62-1.52 (4H, m, H2 and H4), 1.51-1.45 (2H, m, H3), 1.38 (1H, bs, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) 84.5, 68.4, 62.9, 32.3, 28.3, 25.0, 18.5. Data in accordance with literature.[249]

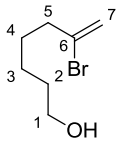
Hept-6-ynyl acetate (137)



To a stirred solution of crude hept-6-yn-1-ol (22.3 mmol, 1 equiv.) in dry dichloromethane (330 mL) under argon at 0 °C was added DMAP (290 mg, 2.32 mmol, 0.1 equiv.), dry triethylamine (6.2 mL, 44.6 mmol, 2 equiv.) and acetic anhydride (4.2 mL, 44.6 mmol, 2 equiv.). The reaction mixture was stirred for 16 h at RT before the solvent was removed carefully *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 to 1:1 Pet. Ether/ Et_2O) to yield acetate **137** (3.44 g, quant over 2 steps) as a

colourless oil. **R_f** 0.45 (Pet. Ether / EtOAc (4:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.06 (2H, t, *J* = 6.7 Hz, H1), 2.20 (2H, dt, *J* = 6.7 Hz, *J* = 2.6 Hz, H5), 2.04 (3H, s, OCH_3), 1.94 (1H, t, *J* = 2.6 Hz, H7), 1.68-1.60 (2H, m, H2), 1.59-1.51 (2H, m, H4), 1.51-1.43 (2H, m, H3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.3, 84.3, 68.5, 64.4, 28.2, 28.1, 25.2, 21.1, 18.4. Data in accordance with literature.[248]

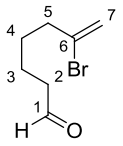
6-Bromohept-6-en-1-ol (138)



Boron tribromide (1 M in dichloromethane, 11.0 mL, 11.0 mmol, 0.5 equiv.) was cooled under argon to –78 °C before hept-6-ynyl acetate (3.44 g, 22.0 mmol, 1.0 equiv.) was added dropwise. The reaction was warmed to RT quickly and stirred for 5 h before it was quenched with acetic acid (22 mL). After stirring for 1 h water was added, the layers separated and the aqueous layer extracted twice with dichloromethane. The combined organic layers were dried with Na_2SO_4 and the solvent removed carefully *in vacuo*. The crude 6-bromohept-6-enyl acetate was used in the next step without further purification.

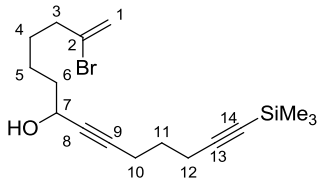
To a solution of the crude acetate in wet methanol (220 mL) was added potassium carbonate (9.14 g, 66.1 mmol, 3.0 equiv.). The reaction mixture was stirred for 2 h before it was concentrated carefully *in vacuo*. Water was added, the layers separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with Na_2SO_4 and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 to 2:1 Pet. Ether/ Et_2O) to yield bromoalkene **138** (2.19 g, 51% over 2 steps) as a pale yellow oil. **R_f** 0.32 (Pet. Ether/ EtOAc (4:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.56-5.55 (1H, m, H7), 5.39 (1H, d, *J* = 1.6 Hz, H7), 3.67-3.63 (2H, m, H1), 2.43 (2H, t, *J* = 7.3 Hz, H5), 1.63-1.55 (4H, m, H2 and H4), 1.42-1.34 (2H, m, H3), 1.28 (1H, bs, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.7, 116.7, 62.9, 41.5, 32.5, 27.7, 24.6. Data in accordance with literature.[95]

6-Bromohept-6-enal (129)



To a stirred solution of 6-bromohept-6-en-1-ol (2.15 g, 11.1 mmol) in dichloromethane (56 mL) under argon was added triethylamine (10.8 mL, 77.7 mmol ,7.0 equiv.) and DMSO (7.5 mL, 106 mmol, 9.5 equiv.). The reaction mixture was cooled to 0 °C and sulfur trioxide pyridine complex (5.30 g, 33.3 mmol, 3.0 equiv.) was added portionwise. The reaction mixture was stirred for 1 h at 0 °C before being allowed to warm to RT and stirred for a further 1 h. The reaction mixture was quenched by addition of 1 N HCl. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with Na_2SO_4 and the solvent removed *in vacuo*. Flash column chromatography on silica gel (6:1 Pet. Ether/ Et_2O) afforded aldehyde **129** (1.75 g, 82%) as a pale yellow oil. $\mathbf{R_f}$ 0.46 (Pet. Ether/ EtOAc (9:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.77 (1H, t, *J* = 3.2 Hz, H1), 5.58-5.57 (1H, m, H7), 5.40 (1H, d, *J* = 1.6 Hz, H7), 2.48-2.42 (4H, m, H2 and H5), 1.69-1.55 (4H, m, H3 and H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.3, 134.0, 117.0, 43.6, 41.2, 27.4, 20.9. Data in accordance with literature.[95]

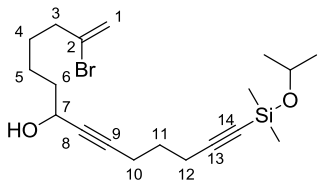
14-(Trimethylsilyl)-2-bromotetradeca-1-en-8,13-diyn-7-ol (127a)



Prepared by **GP3** using diyne **128a** (258 mg, 1.57 mmol) and aldehyde **129** (200 mg, 1.05 mmol). Flash column chromatography on silica gel (9:1 Pet. Ether/ Et_2O) afforded alcohol **127a** (372 mg, quant) as a colourless oil. $\mathbf{R_f}$ 0.29 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3343 (br, OH), 2941 (s), 2863 (m), 2174 (m), 1630 (m), 1249 (m), 842 (s), 760 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.59-5.55 (1H, m, H1), 5.41 (1H, d, *J* = 1.5 Hz, H1),

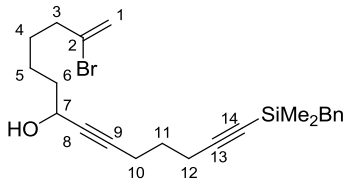
4.41-4.32 (1H, m, H7), 2.45 (2H, t, *J* = 7.2 Hz, H3), 2.37-2.30 (4H, m, H10 and H12), 1.76-1.66 (5H, m, H6, H11 and OH), 1.66-1.56 (2H, m, H4), 1.53-1.44 (2H, m, H5), 0.16 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.6, 116.7, 106.3, 85.4, 84.7, 81.9, 62.7, 41.4, 37.9, 27.9, 27.6, 24.1, 19.2, 18.0, 0.28; **HRMS** (ES^+) calc. for $C_{17}H_{27}OSiBrNa$ $[M+Na]^+$ 377.0912, found 377.0907.

2-Bromo-14-(isopropoxydimethylsilyl)tetradeca-1-en-8,13-diyn-7-ol (127b)



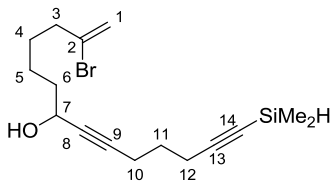
Prepared by **GP3** using diyne **128b** (82 mg, 0.392 mmol) and aldehyde **129** (530 mg, 0.262 mmol). Flash column chromatography on silica gel (6:1 Pet. Ether/ Et_2O) afforded alcohol **127b** (551 mg, 53%) as a colourless oil. **R_f** 0.12 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3379 (br, OH), 2938 (s), 2865 (m), 2174 (m), 1629 (m), 1253 (m), 1026 (s), 883 (s), 822 (s), 790 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.58-5.56 (1H, m, H1), 5.40 (1H, d, *J* = 1.5 Hz, H1), 4.41-4.31 (1H, m, H7), 4.12 (1H, sept, *J* = 6.1 Hz, $SiOC\underline{H}(CH_3)_2$), 2.44 (2H, t, *J* = 7.2 Hz, H3), 2.39-2.29 (4H, m, H10 and H12), 1.78-1.65 (5H, m, H6, H11 and OH), 1.65-1.55 (2H, m, H4), 1.52-1.33 (2H, m, H5), 1.19 (6H, d, *J* = 6.1 Hz, $SiOCH(C\underline{H}_3)_2$), 0.23 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.6, 116.7, 106.2, 84.6, 83.9, 82.0, 66.0, 62.7, 41.4, 37.9, 27.7, 27.6, 25.6, 24.1, 19.1, 18.0, 0.9; **HRMS** (ES^+) calc. for $C_{19}H_{31}O_2SiBrNa$ $[M+Na]^+$ 421.1169, found 421.1173.

14-(Benzyldimethylsilyl)-2-bromotetradeca-1-en-8,13-diyn-7-ol (127c)



Prepared by **GP3** using diyne **128c** (1.57 mmol) and aldehyde **129** (200 mg, 1.05 mmol). Flash column chromatography on silica gel (4:1 Pet. Ether/ Et_2O) afforded alcohol **127c** (399 mg, 88%) as a colourless oil. $\mathbf{R_f}$ 0.21 (Pet. Ether/ Et_2O (4:1)); **IR** (thin film, v_{max} / cm^{-1}) 3358 (br, OH), 2938 (s), 2862 (m), 2174 (m), 1629 (m), 1600 (m), 1493 (m), 1250 (m), 832 (s), 699 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23-7.20 (2H, m, H_{Ar}), 7.10-7.06 (3H, m, H_{Ar}), 5.57 (1H, d, *J* = 1.5 Hz, H1), 5.40 (1H, d, *J* = 1.5 Hz, H1), 4.42-4.33 (1H, m, H7), 2.45-2.42 (2H, t, *J* = 6.9 Hz, H3), 2.37-2.29 (4H, m, H10 and H12), 2.18 (2H, s, $SiCH_2$), 1.74-1.67 (5H, m, H6, H11 and OH), 1.63-1.58 (2H, m, H4), 1.50-1.44 (2H, m, H5), 0.10 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.3 (×, C_{Ar}), 134.6 (×, C2), 128.5 (+, C_{Ar}), 128.3 (+, C_{Ar}), 124.4 (+, C_{Ar}), 116.7 (–, C1), 107.7 (×, C14), 84.7 (×, C8), 83.8 (×, C13), 81.9 (×, C9), 62.7 (+, C7), 41.4 (–, C3), 37.9 (–, C6), 27.7 (–, C11), 27.7 (–, C4), 26.6 (–, $SiCH_2$), 24.1 (–, C5), 19.2 (–, C10), 17.9 (–, C12), –1.8 (+, $Si(CH_3)_2$); **HRMS** (ES^+) calc. for $C_{23}H_{31}OSiBrNa$ $[M+Na]^+$ 453.1220, found 453.1218.

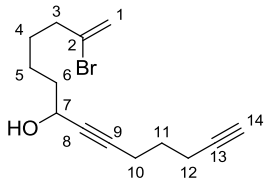
2-Bromo-14-(dimethylsilyl)tetradeca-1-en-8,13-diyn-7-ol (127d)



Prepared by **GP3** using diyne **128d** (100 mg, 0.662 mmol) and aldehyde **129** (84.3 mg, 0.441 mmol). Flash column chromatography on silica gel (6:1 Pet. Ether/ Et_2O) afforded alcohol **127d** (101 mg, 67%) as a colourless oil. $\mathbf{R_f}$ 0.32 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, v_{max} / cm^{-1}) 3345 (br, OH), 2939 (m), 2863 (m), 2176 (m), 2135 (m), 1629 (m), 1290 (m), 881 (s), 839 (m), 771 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.59-5.57 (1H, m, H1), 5.40 (1H, d, *J*

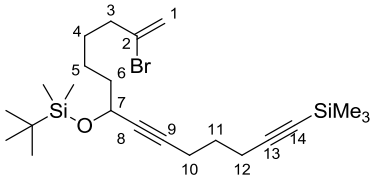
= 1.5 Hz, H1), 4.37 (1H, tt, *J* = 6.6, 2.0 Hz, H7), 4.14-4.08 (1H, m, SiH), 2.45 (2H, t, *J* = 7.2 Hz, H3), 2.37-2.30 (4H, m, H10 and H12), 1.82-1.66 (5H, m, H6, H11 and OH), 1.65-1.55 (2H, m, H4), 1.54-1.41 (2H, m, H5), 0.22 (6H, *J* = 3.8 Hz, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.6 (×, C2), 116.7 (–, C1), 107.9 (×, C14), 84.6 (×, C8), 82.4 (×, C13), 82.0 (×, C9), 62.7 (+, C7), 41.4 (–, C3), 37.9 (–, C6), 27.7 (–, C11), 27.6 (–, C4), 24.1 (–, C5), 19.2 (–, C10), 18.0 (–, C12), –2.6 (+, $Si(CH_3)_2$); **HRMS** (ES^+) calc. for $C_{16}H_{25}OSiBrNa$ $[M+Na]^+$ 363.0750, found 363.0749.

2-Bromotetradeca-1-en-8,13-diyn-7-ol (127e)



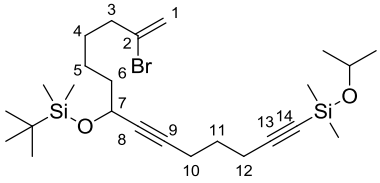
Prepared by **GP3** using hepta-1,6-diyne **128e** (197 µL, 1.72 mmol) and aldehyde **129** (219 mg, 1.15 mmol). Flash column chromatography on silica gel (9:1 Pet. Ether/ Et_2O) afforded alcohol **127e** (90 mg, 28%) as a colourless oil. **R_f** 0.35 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3320 (br, OH), 3928 (s), 2940 (s), 2862 (m), 2174 (m), 1739 (m), 1630 (m), 1431 (m), 1017 (m), 887 (m), 641 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.58-5.56 (1H, m, H1), 5.40 (1H, d, *J* = 1.8 Hz, H1), 4.41-4.31 (1H, m, H7), 2.49-2.41 (2H, m, H3), 2.35 (2H, td, *J* = 7.0, 2.0 Hz, H10), 2.30 (2H, td, *J* = 7.0, 2.7 Hz, H12), 1.96 (1H, t, *J* = 2.7 Hz, H14), 1.77-1.65 (5H, m, H11, H6 and OH), 1.65-1.56 (2H, m, H4), 1.51-1.41 (2H, m, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.6 (×, C2), 116.7 (–, C1), 85.4 (×, C8), 83.6 (×, C13), 82.0 (×, C9), 69.1 (+, C14), 62.7 (+, C7), 41.4 (–, C3), 37.9 (–, C6), 27.7 (–, C11), 27.6 (–, C4), 24.1 (–, C5), 17.9 (–, C10), 17.8 (–, C12); **HRMS** (FI^+) calc. for $C_{14}H_{20}OBr$ $[M+H]^+$ 283.0698, found 283.0854.

((2-Bromo-14-(trimethylsilyl)tetradeca-1-en-8,13-diyn-7-yl)oxy)(*tert*-butyl)dimethylsilane (139a)



Prepared by **GP4** using alcohol **127a** (166 mg, 0.468 mmol). Flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) afforded TBS ether **139a** (170 mg, 77%) as a colourless oil. $\mathbf{R_f}$ 0.79 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2952 (m), 2931 (m), 2858 (m), 2176 (m), 1630 (m), 1249 (m), 1091 (m), 836 (s), 776 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.59-5.53 (1H, m, H1), 5.39 (1H, d, *J* = 1.5 Hz, H1), 4.36-4.29 (1H, m, H7), 2.43 (2H, t, *J* = 7.2 Hz, H3), 2.35-2.27 (4H, m, H10 and H12), 1.76-1.66 (2H, m, H11), 1.61-1.67 (2H, m, H6), 1.61-1.55 (2H, m, d, H4), 1.50-2.38 (2H, m, H5), 0.90 (9H, s, $SiC(CH_3)_3$), 0.15 (9H, s, $Si(CH_3)_3$), 0.11 (6H, d, *J* = 7.8 Hz, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.8 (×, C2), 116.6 (–, C1), 106.5 (×, C14), 85.2 (×, C8), 83.6 (×, C13), 82.6 (×, C9), 63.1 (+, C7), 41.5 (–, C3), 38.7 (–, C6), 27.9 (–, C11), 27.7 (–, C4), 26.0 (+, $SiC(\underline{C}H_3)_3$), 24.3 (–, C5), 19.2 (–, C10), 18.4 (+, $Si\underline{C}(CH_3)_3$), 18.0 (–, C12), 0.3 (+, $Si(CH_3)_3$), –4.3 (+, $Si(CH_3)_2$), –4.8 (+, $Si(CH_3)_2$); **HRMS** (ES^+) calc. for $C_{23}H_{41}OSi_2BrNa$ $[M+Na]^+$ 491.1777, found 491.1772.

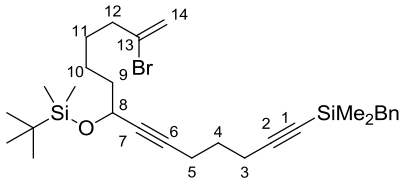
5-(5-Bromohex-5-en-1-yl)-2,2,3,3,13,13,15-heptamethyl-4,14-dioxa-3,13-disilahexadeca-6,11-diyne (139b)



Prepared by **GP3** using hydrosilane **139d** (87 mg, 0.19 mmol) to yield alkoxysilane **139b** (83 mg, 85%) as a colourless oil, which was used without further purification in the next step. $\mathbf{R_f}$ 0.74 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2932 (s), 2858 (m), 2175 (m), 1630 (m), 1463 (m), 1253 (s), 1093 (s), 1030 (s), 836 (s), 790 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H

5.57-5.55 (1H, m, H1), 5.39 (1H, d, *J* = 1.5 Hz, H1), 4.37-4.27 (1H, m, H7), 4.13 (1H, sept, *J* = 6.1 Hz, SiOC<u>H</u>$(CH_3)_2$), 2.43 (2H, t, *J* = 7.2 Hz, H3), 2.37-2.28 (4H, m, H10 and H12), 1.76-1.67 (2H, m, H11), 1.67-1.61 (2H, m, H6), 1.61-1.53 (2H, m, H4), 1.48-1.39 (2H, m, H5), 1.19 (6H, d, *J* = 6.1 Hz, SiOCH(C<u>H</u>$_3)_2$), 0.90 (9H, s, SiC$(CH_3)_3$), 0.23 (6H, s, Si$(CH_3)_2$), 0.11 (6H, d, *J* = 7.6 Hz, OSi$(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.6 (×, C2), 116.6 (–, C1), 106.4 (×, C14), 83.8 (×, C8), 83.4 (×, C13), 82.7 (×, C9), 66.0 (+, SiO<u>C</u>H$(CH_3)_2$), 63.1 (+, C7), 41.5 (–, C3), 38.7 (–, C6), 27.7 (–, C11), 27.7 (–, C4), 26.0 (+, OSiC(<u>C</u>$H_3)_3$), 25.6 (+, SiOCH(<u>C</u>$H_3)_2$), 24.3 (–, C5), 19.0 (–, C10), 18.4 (+, OSi<u>C</u>$(CH_3)_3$), 18.0 (–, C12), 0.9 (+, Si$(CH_3)_2$), –4.3 (+, OSi$(CH_3)_3$), –4.8 (+, OSi$(CH_3)_3$); **HRMS** (ES^+) calc. for $C_{25}H_{45}O_2Si_2BrNa$ $[M+Na]^+$ 535.2034, found 535.2039.

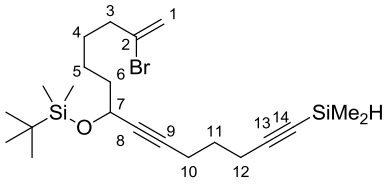
Benzyl(13-bromo-8-((*tert*-butyldimethylsilyl)oxy)tetradeca-13-en-1,6-diyn-1-yl)dimethylsilane (139c)



Prepared by **GP4** using alcohol **127c** (460 mg, 1.07 mmol). Flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) afforded TBS ether **139c** (545 mg, 93%) as a colourless oil. **R_f** 0.80 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2950 (m), 2930 (m), 2857 (m), 2174 (m), 1629 (m), 1601 (m), 1493 (m), 1207 (m), 835 (s), 699 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.19 (2H, m, H_{Ar}), 7.11-7.04 (3H, m, H_{Ar}), 5.57-5.55 (1H, m, H14), 5.39 (1H, d, *J* =1.3 Hz, H14), 4.38-4.29 (1H, m, H8), 2.43 (2H, t, *J* =7.2 Hz, H12), 2.24 - 2.36 (4H, m, H5 and H7), 2.18 (2H, s, $SiCH_2$), 1.74-1.62 (4H, m, H9 and H4), 1.61-1.55 (2H, m, H11), 1.51-1.38 (2H, m, H10), 0.91 (9H, s, SiC$(CH_3)_3$), 0.13 (3H, s, OSi$(CH_3)_2$), 0.11 (3H, s, OSi$(CH_3)_2$), 0.10 (6H, s, SiBn$(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.4 (×, C_{Ar}), 134.8 (×, C13), 128.5 (+, C_{Ar}), 128.3 (+, C_{Ar}), 124.4 (+, C_{Ar}), 116.6 (–, C14), 107.9 (×, C1), 83.7 (×, C7), 83.5 (×, C2), 82.7 (×, C6), 63.1 (+, C8), 41.5 (–, C12), 38.7 (–, C9), 27.8 (–, C4), 27.7 (–, C11), 26.6

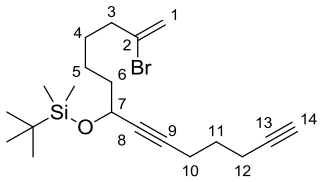
(–, $SiCH_2$), 26.0 (+, $SiC(\underline{C}H_3)_3$), 24.3 (–, C10), 19.2 (–, C5), 18.4 (×, $Si\underline{C}(CH_3)_3$), 18.0 (–, C3), –1.8 (+, $Si(CH_3)_2$), –4.3 (+, $OSi(CH_3)_2$), –4.9 (+, $OSi(CH_3)_2$); **HRMS** (FI^+) calc. for $C_{29}H_{45}OSi_2Br$ $[M]^+$ 544.2192, found 544.2249

((2-bromo-14-(dimethylsilyl)tetradeca-1-en-8,13-diyn-7-yl)oxy)(*tert*-butyl)dimethylsilane (139d)



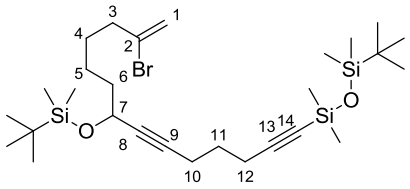
Prepared by **GP4** using alcohol **127d** (137 mg, 0.402 mmol). Flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) afforded TBS ether **139d** (178 mg, 97%) as a colourless oil. $\mathbf{R_f}$ 0.89 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2931 (s), 2858 (m), 2177 (m), 2137 (m), 1630 (m), 1251 (m), 1092 (m), 882 (s), 837 (s), 774 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.57-5.55 (1H, m, H1), 5.39 (1H, d, *J* = 1.9 Hz, H1), 4.32 (1H, tt, *J* = 6.4, 2.1 Hz, H7), 4.10 (1H, sept, *J* = 3.7 Hz, SiH), 2.43 (2H, t, *J* = 7.1 Hz, H3), 2.36-2.28 (4H, m, H10 and H12), 1.75-1.68 (2H, m. H11), 1.68-1.60 (2H, m, H6), 1.60-1.58 (2H, m, H4), 1.49-1.36 (2H, m, H5), 0.90 (9H, s. $SiC(CH_3)_3$), 0.21 (6H, d, *J* = 3.8 Hz, $OSi(CH_3)_2$), 0.11 (6H, d, *J* = 9.8 Hz, $SiH(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 134.8 (×, C2), 116.6 (–, C1), 108.4 (×, C14), 83.4 (×, C8), 82.7 (×, C13), 82.2 (×, C9), 63.1 (+, C7), 41.5 (–, C3), 38.7 (–, C6), 27.7 (–, C11), 27.7 (–, C4), 26.0 (+, $SiC(\underline{C}H_3)_3$), 24.3 (–, C5), 19.2 (–, C10), 18.4 (×, $Si\underline{C}(CH_3)_3$), 18.0 (–, C12), –2.6 (+, $Si(CH_3)_2$), –4.3 (+, $OSi(CH_3)_2$), –4.8 (+, $OSi(CH_3)_2$); **HRMS** (ES^+) calc. for $C_{22}H_{39}OSi_2BrNa[M+Na]^+$ 477.1615, found 477.1611.

((2-Bromotetradeca-1-en-8,13-diyn-7-yl)oxy)(*tert*-butyl)dimethylsilane (139e)



Prepared by **GP4** using alcohol **127e** (85 mg, 0.300 mmol). Flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) afforded TBS ether **139e** (101 mg, 85%) as a colourless oil. $\mathbf{R_f}$ 0.77 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3310 (m), 2932 (s), 2858 (m), 1630 (m), 1463 (m), 1253 (m), 1092 (m), 885 (s), 837 (s), 777 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.57-5.55 (1H, m, H1), 5.39 (1H, d, *J* = 1.8 Hz, H1), 4.33 (1H, tt, *J* = 3.5, 1.8 Hz, H7), 2.43 (2H, t, *J* = 7.3 Hz, H3), 2.35-2.27 (4H, m, H10 and H12), 1.96 (1H, t, *J* = 2.7 Hz), 1.76-1.67 (2H, m, H11), 1.67-1.60 (2H, m, H6), 1.60-1.52 (2H, m, H4), 1.51-1.36 (2H, m, H5), 0.90 (9H, s, $SiC(CH_3)_3$), 0.11 (6H, d, *J* = 7.8 Hz, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 134.8, 116.6, 83.7, 83.4, 82.7, 68.9, 63.1, 41.5, 38.7, 27.7 (2C), 26.0, 24.3, 18.4, 17.9, 17.7, −4.3, −4.8; **HRMS** (ES^+) calc. for $C_{20}H_{33}OSiBrNa$ $[M+Na]^+$ 419.1376, found 419.1382.

1-(13-Bromo-8-((*tert*-butyldimethylsilyl)oxy)tetradeca-13-en-1,6-diyn-1-yl)-3-(*tert*-butyl)-1,1,3,3-tetramethyldisiloxane (140)

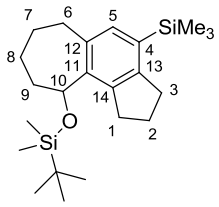


To a stirred solution of alcohol **127e** (370 mg, 0.926 mmol, 1.0 equiv.) in dry dichloromethane (3.8 mL) under argon at 0 °C was added sequentially imidazole (94 mg, 1.39 mmol, 1.5 equiv.), 4-dimethylaminopyridine (11 mg, 0.093 mmol, 0.1 equiv.) and TBSCl (154 mg, 1.02 mmol, 1.1 equiv.). The reaction mixture was warmed to RT and stirred for 2 h before being quenched with sat. *aq.* $NaHCO_3$ solution, the layers separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was purified by flash

column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) to yield disiloxane **140** (101 mg, 19%) as a colourless oil. **R_f** 0.87 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2929 (s), 2857 (m), 2177 (m), 1630 (m), 1254 (m), 1066 (s br), 835 (s), 791 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.57-5.55 (1H, m, H1), 5.39 (1H, d, *J* = 1.6 Hz, H1), 4.33 (1H, tt, *J* = 6.3, 1.9 Hz, H7), 2.47-2.37 (2H, m, H3), 2.34-2.28 (4H, m, H10 and H12), 1.74-1.67 (2H, m, H11), 1.67-1.60 (2H, m, H6), 1.60-1.55 (2H, m, H4), 1.49-1.38 (2H, m, H5), 0.90 (9H, s, $SiC(CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.19 (6H, s, $SiOSi(CH_3)_2$), 0.11 (6H, d, *J* = 9.8 Hz, $OSi(CH_3)_2$), 0.05 (6H, s, $CSi(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 134.8, 116.6, 105.2, 85.4, 83.5, 82.6, 63.1, 41.5, 38.7, 27.8, 27.7, 26.0, 25.8, 24.3, 19.0, 18.4, 18.2, 18.0, 2.6, –2.9, –4.3, –4.8; **HRMS** (ES^+) calc. for $C_{28}H_{53}O_2Si_3BrNa$ $[M+Na]^+$ 607.2429, found 607.2442; **EA** calc. for $C_{28}H_{53}O_2Si_3Br$: C, 57.40; H, 9.12. Found: C, 57.29; H, 8.95.

7.2.3. Palladium-catalysed cyclisation of bromoenediynes

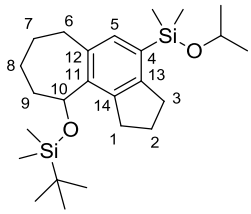
tert-Butyldimethyl((4-(trimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-10-yl)oxy)silane (141a)



Prepared by **GP5** using bromoendiyne **139a** (30 mg, 0.0639 mmol). Flash column chromatography on silica gel (99:1 Pet. Ether/ Et_2O) afforded tricycle **141a** (15.4 mg, 62%) as a white solid. **mp** 64-66 °C; **R_f** 0.50 (Pet. Ether); **IR** (thin film, ν_{max} / cm^{-1}) 2927 (s), 2851 (m), 1462 (m), 1246 (m), 1082 (m), 831 (s), 770 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.97 (1H, s, H5), 5.09 (1H, d, *J* = 6.8 Hz, H10), 3.34 (1H, t, *J* = 13.3 Hz, H6), 3.00-2.80 (4H, m, H1 and H3), 2.54 (1H, dd, *J* = 13.3, 6.7 Hz, H6), 2.31-2.16 (1H,m, H8), 2.09-1.97 (3H, m, H9 and H2), 1.97-1.87 (1H, m, H7), 1.69 (1H, dt, *J* = 13.5, 3.6 Hz, H8), 1.63-1.52 (1H, m, H9), 1.42-1.28 (1H, m, H7), 0.89 (9H, s, $SiC(CH_3)_3$), 0.27 (9H, s, $Si(CH_3)_3$), 0.07 (3H, s, $Si(CH_3)$), –0.18 (3H,

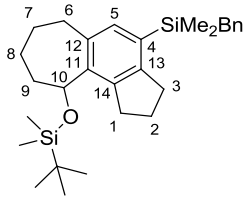
s, $Si(CH_3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.2, 140.5, 140.4, 140.3, 134.2, 133.3, 71.6, 35.5, 34.6, 34,0, 31.3, 29.3, 26.1, 25.3, 25.2, 18.4, –0.4, –4.6, –4.8; **HRMS** (FI^+) calc. for $C_{23}H_{40}OSi_2$ $[M]^+$ 388.2618, found 388.2624; **EA** calc. for $C_{23}H_{40}OSi_2$: C, 71.06; H, 10.37. Found: C, 70.92; H, 10.30.

tert-Butyl((4-(isopropoxydimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-10-yl)oxy)dimethylsilane (141b)



Prepared by **GP5** using bromoendiyne **139b** (82.9 mg, 0.161 mmol). Flash column chromatography on silica gel (99:1 Pet. Ether/ Et_2O) afforded tricycle **141b** (28.9 mg, 41%) as a colourless oil. **R_f** 0.50 (Pet. Ether/ Et_2O (19:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2928 (s), 2855 (m), 1739 (m), 1367 (m), 1251 (s), 1087 (s), 1023 (s), 833 (s), 755 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.04 (1H, s, H5), 5.10 (1H, d, *J* = 6.6 Hz, H10), 3.95 (1H, sept, *J* = 6.1 Hz, $SiOC\underline{H}(CH_3)_2$), 3.35 (1H, t, *J* = 13.4 Hz, H6), 3.05-2.96 (2H, m, H12), 2.93 (1H, dd, *J* = 8.2, 6.6 Hz, H10), 2.89-2.81 (1H, m, H10), 2.55 (1H, dd, *J* = 13.4, 6.6 Hz, H6), 2.30-2.19 (1H, m, H8), 2.10-1.97 (3H, m, H9 and H2), 1.96-1.87 (1H, m, H7), 1.70 (1H, dt, *J* = 13.6, 3.6 Hz, H8), 1.56 (1H, td, *J* = 13.2, 3.2 Hz, H9), 1.40-1.29 (1H, m, H7), 1.14 (3H, d, *J* = 6.1 Hz, $SiOCH(C\underline{H}_3)_2$), 1.10 (3H, d, *J* = 6.1 Hz, $SiOCH(C\underline{H}_3)_2$), 0.88 (9H, s, $OSiC(CH_3)_3$), 0.38 (6H, d, *J* = 4.7 Hz, $Si(CH_3)_2$), 0.06 (3H, s, $OSi(CH_3)_2$), –0.22 (3H, s, $OSi(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 147.5, 141.1, 140.5 (2C), 134.5, 131.5, 71.7, 62.3, 35.5, 34.6, 33.9, 31.3, 29.3, 26.0, 25.8, 25.7, 25.4, 25.3, 18.3, –0.2, –0.6, –4.7, –4.8; **HRMS** (ESI^+) calc. for $C_{25}H_{44}O_2Si_2Na$ $[M+Na]^+$ 455.2772, found 455.2771.

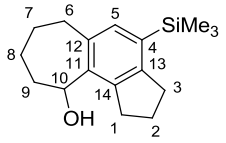
Benzyl(10-((*tert*-butyldimethylsilyl)oxy)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)dimethylsilane (141c)



Prepared by **GP5** using bromoendiyne **139c** (150 mg, 0.275 mmol). Flash column chromatography on silica gel (99:1 Pet. Ether/ Et_2O) afforded tricycle **141c** (97 mg, 76%) as a colourless oil. $\mathbf{R_f}$ 0.42 (Pet. Ether); **IR** (thin film, ν_{max} / cm^{-1}) 2930 (s), 2855 (m), 1600 (m), 1493 (m), 1250 (s), 1087 (m), 833 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.14 (2H, t, *J* = 7.6 Hz, H_{Ar}), 7.05 (1H, t, *J* = 7.3 Hz, H_{Ar}), 6.94 (1H, s, H5), 6.88 (2H, d, *J* = 7.6 Hz, H_{Ar}), 5.11 (1H, d, *J* = 6.6 Hz, H10), 3.35 (1H, t, *J* = 13.4 Hz, H6), 2.99-2.90 (1H, m, H3), 2.89-2.79 (2H, m, H1 and H3), 2.69 (1H, ddd, *J* = 15.1, 8.4, 6.1 Hz, H1), 2.53 (1H, dd, *J* = 13.4, 6.6 Hz, H6), 2.35-2.27 (2H, m, $SiCH_2$), 2.27-2.20 (1H, m, H8), 2.08-1.90 (4H, m, H9, H2 and H7), 1.71 (1H, dt, *J* = 13.5, 3.2 Hz, H8), 1.62-1.53 (1H, m, H9), 1.35 (1H, q, *J* = 12.9 Hz, H7), 0.91 (9H, s, $SiC(CH_3)_3$), 0.26 (6H, s, $SiBn(CH_3)_2$), 0.08 (3H, s, OSi $(CH_3)_2$), –0.17 (3H, s, $OSi(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 147.7, 140.7, 140.7, 140.4, 140.2, 134.6, 131.5, 128.4, 128.1, 124.0, 71.6, 35.5, 34.6, 34.2, 31.3, 29.3, 26.5, 26.1, 25.4, 25.2, 18.4, –2.5, –2.6, –4.7, –4.8; **HRMS** (FI^+) calc. for $C_{29}H_{44}OSi_2$ $[M]^+$ 464.2931, found 464.2949.

7.2.4. Derivatisation of aromatic tricycles

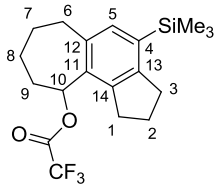
4-(Trimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-10-ol (175a)



To a stirred solution of TBS ether **141a** (20.0 mg, 0.0514 mmol, 1.0 equiv.) in THF (0.5 mL) was added TBAF (1 M in THF, 260 µL, 0.260 mmol, 5.0 equiv.). The reaction mixture was

stirred at 60 °C overnight, then cooled to RT. The reaction was quenched with sat. *aq.* $NaHCO_3$ solution, the layers separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 Pet. Ether/ Et_2O) to yield alcohol **175b** (11 mg, 76%) as a white solid. **mp** 125-127 °C; $\mathbf{R_f}$ 0.31 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3296 (br, OH), 2931 (m), 2849 (m), 1438 (m), 1245 (m), 1034 (m), 833 (s), 759 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.05 (1H, s, H5), 5.25-5.15 (1H, m, H10), 3.23 (1H, *app* t, *J* = 13.0 Hz, H6), 3.08-2.85 (4H, m, H1 and H3), 2.69 (1H, dd, *J* = 14.4, 6.8 Hz, H6), 2.28-2.12 (2H, m, H8 and H9), 2.12-2.00 (2H, m, H2), 2.00-1.93 (1H, m, H7), 1.82-1.74 (1H, m, H8), 1.74-1.67 (1H, m, H9), 1.64 (1H, d, *J* = 3.0 Hz, OH), 1.52-1.37 (1H, m, H7), 0.28 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.9, 141.9, 140.0, 139.4, 134.7, 134.6, 71.5, 35.8, 34.0, 33.1, 31.3, 28.9, 25.1, 25.0, -0.5; **HRMS** (ESI^+) calc. for $C_{17}H_{26}OSiNa$ $[M+Na]^+$ 297.1645, found 297.1634.

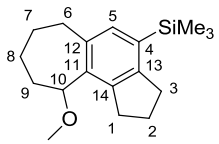
4-(Trimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-10-yl 2,2,2-trifluoroacetate (175b)



To a stirred solution of TBS ether **141a** (20.0 mg, 0.0514 mmol, 1.0 equiv.) in dichloromethane (0.1 mL) at 0 °C was added TFA (2.5 M in THF, 100 µL, 0.250 mmol, 5.0 equiv.) was added. The reaction mixture was stirred at 0 °C for 3 min before being quenched with sat. *aq.* $NaHCO_3$ solution. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was passed through a short plug of Celite® (19:1 Pet. Ether/ Et_2O) to yield trifluroacetate ester **175b** (19.1 mg, quant.) as a colourless oil. **mp** 72-74 °C; $\mathbf{R_f}$ 0.34 (Pet. Ether/ Et_2O (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2934

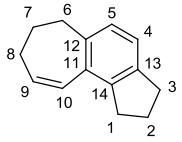
(m), 2855 (m), 1781 (s), 1444 (m), 1220 (m), 1165 (s), 1146 (s), 836 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.06 (1H, s, H5), 6.32 (1H, d, *J* = 6.6 Hz, H10), 3.21-3.09 (2H, m, H6 and H1), 2.96 (2H, t, *J* = 7.5 Hz, H3), 2.91 (1H, dd, *J* = 15.6, 7.5 Hz, H1), 2.72 (1H, dd, *J* = 14.5, 6.9 Hz, H6), 2.40-2.29 (1H, m, H9), 2.09 (2H, *app* quin, *J* = 7.5 Hz, H2), 2.06-1.98 (2H, m, H7 and H8), 1.94-1.83 (1H, m, H8), 1.83-1.74 (1H, m, H9), 1.55-1.45 (1H, m, H7), 0.29 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 156.9, 148.1, 143.0, 140.5, 136.4, 134.6, 133.3, 114.9 (q), 78.7, 35.4, 34.1, 31.1, 31.0, 28.4, 25.4, 25.0, –0.6;; **HRMS** (FI^+) calc. for $C_{19}H_{25}F_3O_2Si$ $[M]^+$ 370.1576, found 370.1576; **EA** calc. for $C_{19}H_{25}F_3O_2Si$: C, 61.70; H, 6.80. Found: C, 61.78; H, 6.85.

(10-Methoxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)trimethylsilane (175c)



To a stirred solution of TBS ether **141a** (76.4 mg, 0.197 mmol, 1.0 equiv.) in methanol (4.9 mL) was added CSA (91.3 mg, 0.393 mmol, 2.0 equiv.). The reaction mixture was stirred at 40 °C overnight, then cooled to RT. The reaction mixture was quenched with triethylamine (55 µL, 0.393 mmol, 2.0 equiv.) and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (99:1 Pet. Ether/ Et_2O) to yield methyl ether **175c** (38.2 mg, 67%) as a colourless oil. **R_f** 0.61 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2922 (s), 1737 (m), 1440 (m), 1247 (m), 1091 (s), 835 (s), 732 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.01 (1H, s, H5), 4.63 (1H, d, *J* = 6.3 Hz, H10), 3.24-3.17 (4H, m, OCH_3 and H6), 3.00-2.86 (4H, m, H1 and H3), 2.59 (1H, dd, *J* = 13.7, 6.8 Hz, H6), 2.23 (1H, ddt, *J* = 14.1, 6.7, 3.6 Hz, H9), 2.13-2.07 (1H, m, H8), 2.07-2.01 (2H, m, H2), 1.96-1.87 (1H, m, H7), 1.77-1.69 (1H, m, H8), 1.66-1.58 (1H, m, H9), 1.43-1.33 (1H, m, H7), 0.27 (6H, s, $Si(CH_3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.3, 142.6, 140.4, 137.2, 134.3, 134.2, 79.7, 56.2, 35.4, 34.0, 31.6, 31.5, 28.9, 25.3, 25.1, –0.5; **HRMS** (ESI^+) calc. for $C_{18}H_{28}OSiNa$ $[M+Na]^+$ 311.1802, found 311.1794.

1,2,3,6,7,8-hexahydrocyclohepta[*e*]indene (131)

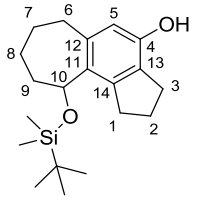


To a stirred solution of TBS ether **141a** (12.0 mg, 0.031 mmol, 1.0 equiv.) in dry THF (1.0 mL) was added zinc(II) chloride (6.3 mg, 0.046 mmol, 1.5 equiv.) and chlorotrimethylsilane (8.0 µL, 0.062 mmol, 2.0 equiv.).[137] The reaction mixture was stirred for 2 h before it was cooled to 0 °C, diluted with diethyl ether and quenched with sat. *aq.* NH_4Cl solution and warmed to RT. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$, and the solvent removed carefully *in vacuo*. The residue was diluted with Pet. Ether/ Et_2O (19:1) and filtered through a short plug of silica, then concentrated to yield a mixture of hydrocarbon **131** (10%) and its TMS-protected counterpart **176** (90%), which was used in the next step without further purification.

To a solution of the crude mixture of **131** and **176** (0.031 mmol, 90% silylated, 1.0 equiv.) in acetonitrile (0.4 mL) was added sodium iodide (3.4 mg, 0.026 mmol, 1.0 equiv.), distilled water (0.5 µL, 0.031 mmol, 1.0 equiv.) and chlorotrimethylsilane (3.3 µL, 0.031 mmol, 1.0 equiv.).[138] The reaction mixture was stirred at RT for 30 min, then quenched with sat. *aq.* $NaHCO_3$ solution. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether), to yield hydrocarbon **131** (3.8 mg, 70%) as a colourless oil. $\mathbf{R_f}$ 0.54 (Pet. Ether); **IR** (thin film, ν_{max} / cm^{-1}) 3016 (m), 2925 (s), 2851 (m), 1443 (m), 813 (w), 772 (w); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.99 (1H, d, J = 7.6 Hz, H5), 6.91 (1H, d, J = 7.6 Hz, H4), 6.48 (1H, dt, J = 12.1, 2.2 Hz, H10), 5.97 (1H, dt, J = 12.1, 4.7 Hz, H9), 2.90 (4H, *app* q, J = 6.7 Hz, H1 and H3), 2.81-2.74 (2H, m, H6), 2.38 (2H, tdd, J = 6.8, 4.7, 2.2 Hz, H8), 2.07 (2H, *app* quin, J = 7.5 Hz, H2), 2.02-1.91 (2H, m, H7); **^{13}C NMR** (126 MHz, $CDCl_3$)

δ_C 143.6, 141.9, 139.9, 132.7, 132.5, 127.2, 127.1, 122.6, 35.4, 33.0, 32.0 (2C), 28.8, 25.1; **HRMS** (FI^+) calc. for $C_{14}H_{16}$ 184.1252, found 184.1249.

10-((*tert*-Butyldimethylsilyl)oxy)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-ol (177)



To arylsilane **141c** (10.0 mg, 0.0215 mmol, 1.0 equiv.) was added TBAF (1 M in THF, 45 µL, 0.0451 mmol, 2.1 equiv.). The reaction mixture was stirred for 30 min, then hydrogen peroxide (30% w/v in water, 15 µL, 0.129 mmol, 6.0 equiv.) in methanol (0.1 mL) and potassium hydrogen carbonate (1.1 mg, 0.0108 mmol, 0.5 equiv.) was added.[139] The reaction mixture was stirred at RT overnight before being quenched with sat. *aq.* $Na_2S_2O_3$ solution. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 Pet. Ether/ EtOAc) to yield phenol **177** (6.6 mg, 92%) as a white solid. **mp** 118-120 °C; $\mathbf{R_f}$ 0.44 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3381 (br, OH), 2926 (s), 2853 (m), 1595 (m), 1448 (m), 1154 (m), 832 (s), 771 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.38 (1H, s, H5), 5.01 (1H, d, *J* = 6.6 Hz, H10), 4.55 (1H, br s, OH), 3.37-3.27 (1H, m, H6), 3.03-2.83 (2H, m, H1), 2.81 (2H, t, *J* = 7.5 Hz, H3), 2.43 (1H, dd, *J* = 13.6, 6.6 Hz, H6), 2.30-2.16 (1H, m, H8), 2.12-2.04 (2H, m, H2), 2.04-1.98 (1H, m, H9), 1.98-1.86 (1H, m H7), 1.75-1.64 (1H, m, H8), 1.51 (1H, td, *J* = 13.3, 3.2 Hz, H9), 1.39-1.28 (1H, m, H7), 0.88 (9H, s, $SiC(CH_3)_3$), 0.05 (3H, s, $Si(CH_3)_2$), –0.20 (3 H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 150.2, 144.3, 143.8, 132.6, 125.6, 115.3, 71.3, 35.4, 35.1, 32.3, 29.3, 28.7, 26.0, 25.2, 25.2, 18.3, –4.7, –4.8; **HRMS** (ESI^-) calc. for $C_{20}H_{31}O_2Si$ $[M-H]^-$ 331.2099, found 331.2104.

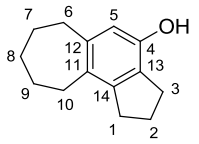
1,2,3,6,7,8,9,10-Octahydrocyclohepta[*e*]inden-4-ol (130) and triethyl((1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)oxy)silane (180)

To a stirred solution of TBS ether **177** (13.0 mg, 0.0391 mmol, 1.0 equiv.) in dichloromethane (1.3 mL) at 0 °C was added TFA (2.5 M in dichloromethane, 62 µL, 0.156 mmol, 4.0 equiv.). The reaction mixture was stirred for 3 min, then triethysilane (50 µL, 0.313 mmol, 8.0 equiv.) was added.[140] The reaction mixture was stirred for at RT 3 h before being quenched with sat. *aq.* $NaHCO_3$ solution, the layers separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (Pet. Ether/ EtOAc (19:1)) to yield phenol **130** (5.6 mg, 70%) as a white solid and its corresponding triethylsilylaryl ether **180** (3.8 mg, 30%) as a colourless oil.

OR

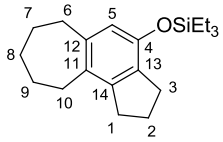
To a stirred solution of TBS ether **177** (5.0 mg, 0.015 mmol, 1.0 equiv.) in dry dichloromethane was added zinc(II) chloride (2.0 mg, 0.015 mmol, 1.0 equiv.) and triethylsilane (4.9 µL, 0.030 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 3 h before being quenched with sat. *aq.* NH_4Cl solution and diluted with diethyl ether. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether/ EtOAc (19:1)) to yield phenol **130** (2.4 mg, 80%) as a white solid and its corresponding triethylsilylaryl ether **180** (0.9 mg, 19%) as a colourless oil.

1,2,3,6,7,8,9,10-Octahydrocyclohepta[*e*]inden-4-ol (130)



mp 86-88 °C; **R_f** 0.50 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3387 (br), 2920 (s), 2849 (m), 2174 (m), 1597 (m), 1448 (m), 1075 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.44 (1H, s, H5), 4.34 (1H, br s, OH), 2.89 (2H, t, *J* = 7.6 Hz, H1), 2.84 (2H, t, *J* = 7.6 Hz, H3), 2.73-2.67 (4H, m, H6 and H10), 2.10 (2H, *app* quin, J_{HH} = 7.6 Hz, H2), 1.85-1.78 (2H, m, H8), 1.66-1.53 (4H, m, H7 and H9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 149.4, 144.7, 143.9, 131.7, 126.1, 114.1, 36.4, 33.0, 32.4, 31.3, 29.1, 28.7, 28.1, 25.0; **HRMS** (ESI^-) calc. for $C_{14}H_{17}O$ $[M-H]^-$ 201.1285, found 201.1287.

Triethyl((1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)oxy)silane (180)

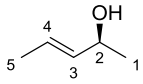


R_f 0.86 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2939 (s), 2862 (m), 1629 (m), 1431 (m), 1025 (m), 887 (m), 639 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.38 (1H, s, H5), 2.84 (4H, *app* dt, *J* = 11.7, 7.5 Hz, H1 and H3), 2.70-2.66 (4H, m, H6 and H10), 2.01 (2H, quin, *J* = 7.5 Hz, H2), 1.80 (2H, *app* dt, *J* = 11.7, 5.8 Hz, H8), 1.64-1.55 (4H, m, H7 and H8), 1.00 (9H, t, *J* = 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.73 (6H, q, *J* = 8.0 Hz $Si(C\underline{H}_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 149.3, 144.2, 143.1, 132.0, 131.2, 118.0, 36.6, 33.0, 32.5, 31.4, 30.2, 28.9, 28.1, 24.9, 6.9, 5.5; **HRMS** (FI^+) calc. for $C_{20}H_{32}OSi$ $[M]^+$ 316.2223, found 316.2215.

7.3. Procedures and Characterisations for Synthesis of the CDEF Rings

7.3.1. Synthesis of the CDE diyne fragment

(*S*,*E*)-pent-3-en-2-ol ((*S*)-110)

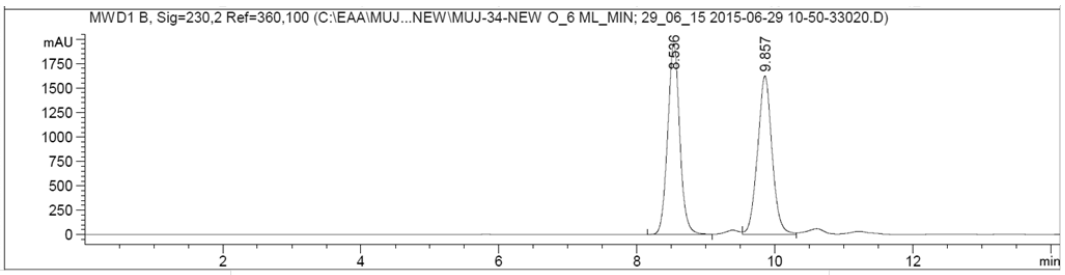


To a stirred solution of crotonaldehyde (2.0 mL, 24.1 mmol, 1.0 equiv.) in Et_2O (10 mL) under argon at 0 °C was added methyllithium (1.5 M in diethyl ether, 19.3 mL, 29.0 mmol, 1.2 equiv.) dropwise. The reaction mixture was warmed to RT and stirred for 1.5 h, then the reaction was quenched by addition of NH_4Cl (sat. *aq.*). The layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography on a short plug of silica gel (3:1→1:1 30-40 Pet. Ether / Et_2O), to give (±)-**110** (1.97 g, 22.9 mmol, 95%) as a colourless oil.

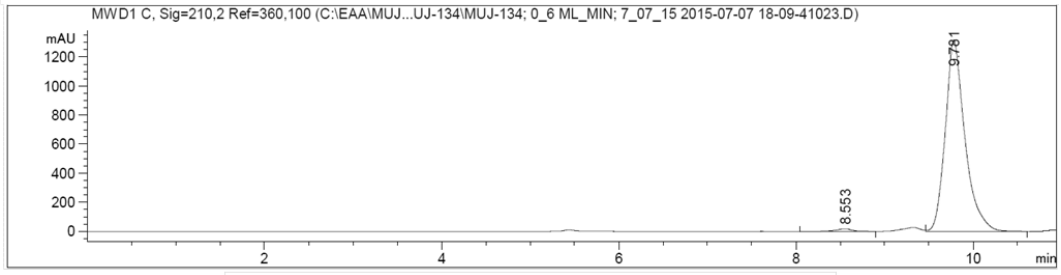
Kinetic Resolution: To a stirred solution of racemic pent-3-en-2-ol (5.54 g, 64.3 mmol, 1.0 equiv.) in anhydrous pentane (33 mL) under argon was added vinyl acetate (29.7 mL, 322 mmol, 5.0 equiv.), activated 4 Å molecular sieves (crushed, 2.72 g, 50 wt%) and Novozyme 435 (554 mg, 10 wt%). The reaction mixture was stirred for 2.5 h at RT, then it was filtered through a pad of Celite®, and the filtrate was concentrated. The product was purified by flash chromatography on a short plug of silica (3:1→1:1 30-40 Pet. Ether / Et_2O), to give (*S*)-**110** (2.16 g, 25.1 mmol, 39%) as a colourless oil. $\mathbf{[\alpha]_D^{25}}$ –10.5 (*c* = 1.00, $CHCl_3$); $\mathbf{R_f}$ 0.45 (1:1, 30-40 Pet. Ether / Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.64 (1H, dqd, *J* = 15.2, 6.4 and 0.7 Hz, H4), 5.52 (1H, ddq, *J* = 15.2, 6.4 and 1.2 Hz, H3), 4.24 (1H, quin, *J* = 6.4 Hz, H2), 1.67 (3H, dd, *J* = 6.4 and 1.2 Hz, H5), 1.24 (3H, d, *J* = 6.4 Hz, H1); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 135.5, 125.9, 69.1, 23.5, 17.7; Data in accordance with literature.[141,250]

ee: **99% *ee*** as determined by chiral HPLC: CHIRALPAK IA, 0.6 mL/min, 0.5% IPA/hexanes, t_R (*R*) = 8.54 min, t_R (*S*) = 9.86 min.

The enantiomeric excess was determined as follows: To a solution of the enantioenriched alcohol (20 mg) in dichloromethane (0.5 mL) was added benzoyl chloride (33 mg), Et_3N (46 µL) and DMAP (1 mg). The reaction was stirred for 3 h at RT, then it was quenched with NH_4Cl (sat. *aq.*). The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated; the product was purified via flash chromatography (4:1 30-40 Pet. Ether / Et_2O) to yield the corresponding benzoate ester, which was used for HPLC analysis.

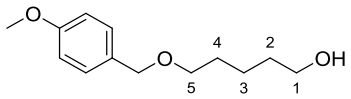


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.536	VV	0.1845	2.38733e4	1954.12146	50.1369
2	9.857	VV	0.2164	2.37429e4	1625.66553	49.8631
Totals :				4.76162e4	3579.78699	



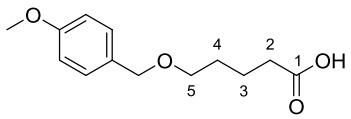
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.553	VV	0.1735	260.37378	19.04672	1.2658
2	9.781	VV	0.2197	2.03101e4	1318.34253	98.7342
Totals :				2.05704e4	1337.38925	

5-((4-methoxybenzyl)oxy)pentan-1-ol



To a stirred suspension of NaH (60% dispersion in mineral oil, 5.20 g, 130 mmol, 2.2 equiv.) in THF (150 mL) under argon at 0 °C was added a solution of 1,5-pentanediol (43.6 mL, 395 mmol, 6.7 equiv.) in THF. The reaction mixture was heated to reflux for 3 h, then allowed to cool to RT before TBAI (1.10 g, 2.00 mmol, 0.05 equiv.) and PMBCl (8.0 mL, 59.0 mmol, 1.0 equiv.) were added. The reaction mixture was again heated to reflux (12 h), then allowed to cool to RT, quenched with water, and filtered through a short pad of Celite®. The filtrate was concentrated, and the residue was taken up in dichloromethane and water. The layers were separated and the aqueous phase extracted three times with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on a short plug of silica (2:1→1:1 Pet. Ether / EtOAc eluent), to afford alcohol 5-((4-methoxybenzyl)oxy)pentan-1-ol (13.2 g, 58.8 mmol, quant.) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 4.43 (2H, s, C$\underline{H}_2$Ar), 3.80 (3H, s, OMe), 3.64 (2H, t, *J* = 6.6 Hz, H1), 3.45 (2H, t, *J* = 6.5 Hz, H5), 1.70-1.52 (4H, m, H2 and H4), 1.49-1.37 (3H, m, H3 and OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.3, 130.8, 129.4, 113.6, 72.7, 70.1, 63.0, 55.4, 32.7, 29.6, 22.5. Data in accordance with literature.[251]

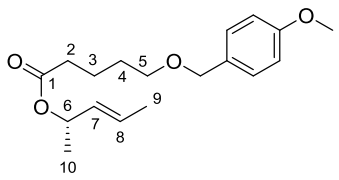
5-((4-methoxybenzyl)oxy)pentanoic acid (111)



To a stirred solution of 5-((4-methoxybenzyl)oxy)pentan-1-ol (14.0 g, 62.1 mmol, 1.0 equiv.) in acetone (120 mL) at 0 °C was added Jones' reagent (2.5 M CrO_3 / H_2SO_4, 37.4 mL, 94 mmol, 1.5 equiv.). The reaction mixture was stirred at 0 °C for 1 h, then the reaction was quenched by addition of propan-2-ol (15 mL), and then carefully neutralised with $NaHCO_3$.

The solution was then diluted with EtOAc and washed with 3N NaOH (100 mL). The layers were separated, and the aqueous phase was acidified with conc. HCl, then extracted three times with EtOAc (3 x 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give acid **111** (14.0 g, 56.8 mmol, 91%) as a white solid. $\mathbf{R_f}$ 0.15 (2:1 petroelum ether / Et_2O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, ArH), 6.88 (2H, d, *J* = 8.5 Hz, ArH), 4.43 (2H, s, C$\underline{H}_2$Ar), 3.80 (3H, s, OMe), 3.46 (2H, t, *J* = 6.1 Hz, H5), 2.37 (2H, t, *J* = 7.3 Hz, H2), 1.77-1.69 (2H, m, H4), 1.69-1.62 (2H, m, H3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 179.3, 159.3, 130.6, 129.4, 113.9, 72.7, 69.6, 55.4, 33.7, 29.1, 21.7. Data in accordance with literature.[142]

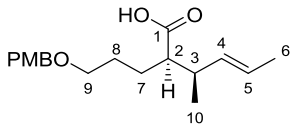
(*S*,*E*)-pent-3-en-2-yl 5-((4-methoxybenzyl)oxy)pentanoate (112)



To a stirred solution of alcohol (*S*)-**110** (2.78 g, 32.3 mmol, 1.0 equiv.) and acid **111** (8.46 g, 35.5 mmol, 1.1 equiv.) in THF (28 mL) was added EDC•HCl (9.28 g, 48.4 mmol, 1.5 equiv.), triethylamine (8.97 mL, 64.6 mmol, 2.0 equiv.) and DMAP (394 mg, 3.23 mmol, 0.1 equiv.). The reaction mixture was stirred at RT for 16 h, then it was quenched with water. The layers were separated and the aqueous layer extracted three times with EtOAc. The combined organic phases were washed with 1N HCl, then dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography on a short plug of silica (4:1 Pet. Ether / EtOAc), to give ester **112** (7.97 g, 26.0 mmol, 81%) as a colourless oil. $\mathbf{[\alpha]_D^{25}}$ –52.86 (*c* = 0.19, $CHCl_3$); $\mathbf{R_f}$ 0.27 (2:1 Pet. Ether / Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 5.71 (1H, dqd, *J* = 15.4, 6.5 and 0.8 Hz, H8), 5.46 (1H, ddq, *J* = 15.4, 6.8 and 1.5 Hz, H7), 5.30 (1H, quin, *J* = 6.5 Hz, H6), 4.42 (2H, s, C$\underline{H}_2$Ar), 3.80 (3H, s, O$\underline{Me}$), 3.45 (2H, t, *J* = 6.2 Hz, H5), 2.30 (2H, t, *J* = 7.1 Hz, H2), 1.75-1.70 (2H, m, H3), 1.68 (2H, dd, *J* = 6.5 and 0.7 Hz, H9), 1.67-1.60 (2H, m, H4), 1.27 (3H, d, *J* = 6.6 Hz,

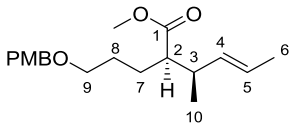
H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.0, 159.3, 131.0, 130.8, 129.4, 128.2, 113.9, 72.7, 71.1, 69.7, 55.4, 34.5, 29.3, 21.9, 20.5, 17.8. Data in accordance with literature.[142]

(2*R*,3*R*,*E*)-2-(3-((4-methoxybenzyl)oxy)propyl)-3-methylhex-4-enoic acid (113)



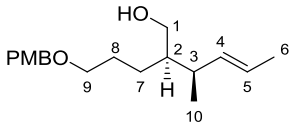
To a stirred solution of LiHMDS (1M in toluene, 36.9 mL, 36.9 mmol, 3.0 equiv.) and triethylamine (51.3 mL, 369 mmol, 30 equiv.) in toluene (150 mL) under argon at –78 °C was added dropwise a solution of ester **112** (3.77 g, 12.3 mmol, 1.0 equiv.) in toluene (5.2 mL).[147] The reaction was warmed to RT over 5 h, then poured into 5% NaOH (*aq.*) (370 mL). Et_2O was added and the layers were separated. The aqueous layer was cooled to 0 °C, then acidified with conc. HCl. Et_2O was added, the layers were separated and the aqueous phase extracted three times with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography on a short plug of silica (5:1 Pet. Ether / EtOAc +1% AcOH) to afford acid **113** (3.63 g, 11.8 mmol, 96%) as a colourless oil. **$[\alpha]_D^{25}$** +2.4 (*c* = 0.24, $CHCl_3$); **R_f** 0.43 (1:1 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 11.06 (1H, br s, COOH), 7.26 (2H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 5.47 (1H, dq, *J* = 15.1 and 6.3 Hz, H5), 5.23 (1H, ddd, *J* = 15.1, 8.6 and 1.3 Hz, H4), 4.43 (2H, s, C$\underline{H_2}$Ar), 3.81 (3H, s, O$\underline{Me}$), 3.53-3.38 (2H, m, H9), 2.41-2.29 (1H, m, H3), 2.22-2.11 (1H, m, H2), 1.67 (3H, d, *J* = 6.6 Hz, H6), 1.66-1.60 (2H, m, H8), 1.60-1.53 (2H, m, H7), 1.03 (3H, d, *J* = 6.6 Hz, H10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 181.8, 159.2, 134.0, 130.6, 129.4, 125.9, 113.9, 72.5, 69.7, 55.3, 51.5, 39.8, 27.8, 27.0, 19.3, 18.0. Data in accordance with literature.[142]

(2*R*,3*R*,*E*)-Methyl 2-(3-((4-methoxybenzyl)oxy)propyl)-3-methylhex-4-enoate (198)



To a stirred solution of acid **113** (593 mg, 1.94 mmol, 1.0 equiv.) in 5:1 toluene / methanol (55 mL) under argon at 0 °C was slowly added $TMSCHN_2$ (1.16 mL, 2.13 mmol, 1.1 equiv.). The reaction mixture was stirred at RT for 30 min before being quenched with acetic acid (0.5 mL), then it was diluted with water and extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (9:1 Pet. Ether / Et_2O) to afford methyl ester **198** (549 mg, 1.71 mmol, 88%) as a colourless oil. $\mathbf{[\alpha]_D^{25}}$ +15.0 (*c* = 0.12, $CHCl_3$); $\mathbf{R_f}$ 0.38 (7:3 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 2951, 1733, 1513, 1248, 1036, 821; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.24 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 5.43 (1H, dq, *J* = 15.1 and 6.3 Hz, H5), 5.20 (1H, ddd, *J* = 15.1, 8.7 and 1.6 Hz, H4), 4.41 (2H, s, C$\underline{H_2}$Ar), 3.80 (3H, s, O$\underline{Me}$), 3.66 (3H, s, $CO_2\underline{Me}$), 3.45-3.35 (2H, m, H9), 2.35-2.26 (1H, m, H3), 2.15 (1H, td, *J* = 9.5 and 3.5 Hz, H2), 1.65 (3H, dd, *J* = 6.3 and 1.3 Hz, H6), 1.63-1.56 (2H, m, H8), 1.54-1.48 (2H, m, H7), 0.94 (3H, d, *J* = 6.9 Hz, H10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 176.3, 159.3, 134.3, 130.8, 129.4, 125.7, 113.7, 72.6, 69.8, 55.4, 51.7, 51.4, 40.1, 28.0, 27.3, 19.3, 18.0; **HRMS** (ES^+) calc. for $C_{19}H_{28}NaO_4$ $[M+Na]^+$ 343.1880; found 343.1873. Data in accordance with literature.[95]

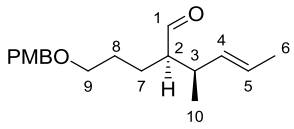
(2*R*,3*R*,*E*)-2-(3-((4-Methoxybenzyl)oxy)propyl)-3-methylhex-4-en-1-ol (199)



To a stirred solution of methyl ester **198** (4.80 g, 15.0 mmol, 1.0 equiv.) in dichloromethane (45 mL) under argon at –78 °C was added a solution of DIBALH (1.0 M in hexane, 37.5 mL, 37.5 mmol, 2.5 equiv.). The solution was warmed to –30 °C over 2 h, then the reaction was quenched by addition of sodium potassium tartrate (sat. *aq.*), and the mixture was stirred

vigorously for a further 1 h. The layers were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$), then filtered through Celite® and the filtrate was concentrated. The product was purified by flash chromatography (2:1 Pet. Ether / Et_2O) to yield the alcohol **199** (4.23 g, 14.5 mmol, 97%) as a colourless oil. $[\alpha]_D^{25}$ +17.4 (*c* = 1.00, $CHCl_3$); R_f 0.23 (1:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 3647, 3385, 2933, 2359, 1513, 1248; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.8 Hz, ArH), 6.88 (2H, d, *J* = 8.8 Hz, ArH), 5.48-5.40 (1H, dq, *J* = 15.1 and 6.0 Hz, H5), 5.40-5.34 (1H, m, H4), 4.43 (2H, s, C$\underline{H_2}$Ar), 3.80 (3H, s, O$\underline{Me}$), 3.58 (2H, *app* t, *J* = 5.2 Hz, H1), 3.44 (2H, t, *J* = 6.5 Hz, H9), 2.37-2.25 (1H, m, H3), 1.72-1.66 (1H, m, H8), 1.65 (3H, d, *J* = 6.0 Hz, H6), 1.63-1.53 (1H, m, H8), 1.49 (1H, br s, OH), 1.48-1.44 (1H, m, H7), 1.44-1.39 (1H, m, H2), 1.32-1.23 (1H, m, H7), 0.98 (3H, d, *J* = 6.9 Hz, H10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 159.3, 135.4, 130.8, 129.4, 124.6, 113.9, 72.7, 70.5, 64.1, 55.4, 45.8, 37.8, 27.9, 24.4, 18.2, 17.7; **HRMS** (ES^+) calc. for $C_{18}H_{28}NaO_3$ $[M+Na]^+$ 315.1931; found 315.1925. Data in accordance with literature.[95]

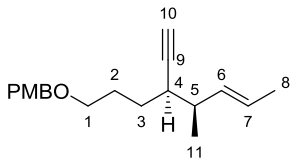
(2*R*,3*R*,*E*)-2-(3-((4-methoxybenzyl)oxy)propyl)-3-methylhex-4-enal (114)



To a stirred solution of alcohol **199** (4.60 g, 15.7 mmol, 1.0 equiv.) in dichloromethane (480 mL) under argon at 0 °C was added Dess-Martin periodinane (8.67 g, 20.5 mmol, 1.3 equiv.) and $NaHCO_3$ (1.33 g, 15.7 mmol, 1.0 equiv.). The reaction mixture was stirred at RT for 1 h before being quenched by addition of $Na_2S_2O_3$ (100 mL, sat. *aq.*) and $NaHCO_3$ (100 mL, sat. *aq.*). The mixture was stirred for 30 min, then the layers were separated and the aqueous phase extracted three times with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (2:1 Pet. Ether / Et_2O) to yield aldehyde **114** (4.10 g, 14.1 mmol, 90%) as a colourless oil. $[\alpha]_D^{25}$ +8.3 (*c* = 1.00, $CHCl_3$); R_f 0.45 (7:3 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 2933, 1722, 1513,

1247, 1098, 411; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.56 (1H, d, *J* = 3.8 Hz, H1), 7.25 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 5.46 (1H, dqd, *J* = 15.2, 6.3 and 1.2 Hz, H5), 5.28 (1H, ddq, *J* = 15.2, 8.1 and 1.6 Hz, H4), 4.41 (2H, s, C$\underline{H_2}$Ar), 3.80 (3H, s, O$\underline{Me}$), 3.42 (2H, t, *J* = 5.4 Hz, H9), 2.45 (1H, *app* sext, *J* = 7.1 Hz, H3), 2.22-2.01 (1H, m, H2), 1.66 (3H, dd, *J* = 6.3 and 1.2 Hz, H6), 1.64-1.51 (4H, m, H7 and H8), 1.00 (3H, d, *J* = 6.9 Hz, H10); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 205.7, 159.3, 133.5, 130.7, 129.4, 126.0, 113.9, 72.6, 69.7, 57.3, 55.4, 37.4, 27.8, 23.5, 18.6, 18.0; **HRMS** (ES^+) calc. for $C_{18}H_{26}NaO_3$ $[M+Na]^+$ 313.1774; found 313.1774. Data in accordance with literature.[95]

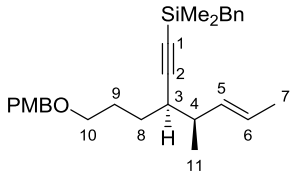
1-((((4*R*,5*R*,*E*)-4-Ethynyl-5-methyloct-6-en-1-yl)oxy)methyl)-4-methoxybenzene (115)



To a stirred suspension of (iodomethyl)triphenylphosphonium iodide (183 mg, 0.344 mmol, 2.0 equiv.) in THF (1.5 mL) under argon at RT was added NaHMDS (2.0 M in hexane, 172 µL, 0.344 mmol, 2.0 equiv.). After stirring for 20 min, the solution was cooled to –78 °C and a solution of aldehyde **114** (50.0 mg, 0.172 mmol, 1.0 equiv.) in THF (0.3 mL) was added. After 15 min, the reaction mixture was warmed to RT over 30 min until TLC showed complete formation of the *cis*-vinyl iodide derivative. The reaction mixture was then cooled to –78 °C, and additional NaHMDS (2.0 M in hexane, 172 µL, 0.344 mmol, 2.0 equiv.) was added. The reaction mixture was warmed to RT over 30 min and stirred for a further 10 min before being quenched with NH_4Cl (sat. *aq.*). Et_2O was added, the layers were separated, and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (9:1 Pet. Ether / Et_2O) to yield alkyne **115** (41.4 mg, 0.144 mmol, 84%) as a colourless oil. **$[\alpha]_D^{25}$** –22.8 (*c* = 1.00, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3260, 2987, 2876, 1613, 1580, 1215, 1090, 694; **R_f** 0.36 (19:1 Pet. Ether / Et_2O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.26 (3H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 5.45 (1H, dq, *J* = 15.1 and 6.0 Hz, H7), 5.30 (1H, dqd, *J* = 15.1,

7.9 and 1.4 Hz, H6), 4.43 (2H, d, *J* = 2.5 Hz, C<u>H</u>$_2$Ar), 3.81 (3H, s, O<u>Me</u>), 3.53-3.36 (2H, m, H1), 2.26-2.20 (1H, m, H4), 2.15 (1H, *app* sextet, *J* = 6.8 Hz, H5), 2.06 (1H, d, *J* = 2.5 Hz, H10), 1.92-1.79 (1H, m, H2), 1.70-1.64 (1H, m, H2), 1.66 (3H, dd, *J* = 6.1, 0.9 Hz, H8), 1.64-1.55 (1H, m, H3), 1.46-1.37 (1H, m, H3), 1.07 (3H, d, *J* = 6.6 Hz, H11); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 159.3, 135.2, 130.9, 129.4, 124.9, 113.9, 86.4, 72.6, 70.6, 69.9, 55.4, 40.7, 37.7, 29.5, 27.8, 18.1, 17.7; **HRMS** (ES^+) calc. for $C_{19}H_{28}NaO_2$ $[M+Na]^+$ 309.1825; found 309.1823. Data in accordance with literature.[95]

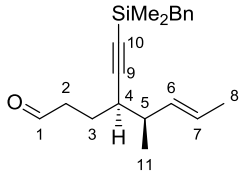
Benzyl((3*R*,4*R*,*E*)-3-(3-((4-methoxybenzyl)oxy)propyl)-4-methylhept-5-en-1-yn-1-yl)dimethylsilane (201)



To a stirred solution of alkyne **115** (500 mg, 1.75 mmol, 1.0 equiv.) in THF (8.0 mL) under argon at –78 °C was added LiHMDS (1 M in THF, 2.4 mL, 2.4 mmol, 1.4 equiv.). The mixture was stirred for 30 min at –78 °C, followed by addition of a solution of $BnMe_2SiCl$ (451 mg, 2.4 mmol, 1.4 equiv.) in THF (0.7 mL). The mixture was stirred for a further 30 min at –78 °C, then warmed to RT and stirred for 3 h before being quenched with NH_4Cl (sat. *aq.*). Et_2O was added, the layers were separated, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (19:1 Pet. Ether / Et_2O) to yield the alkynylsilane **201** (741 mg, 1.70 mmol, 98%) as a colourless oil. $\mathbf{[\alpha]_D^{25}}$ +17.8 (*c* = 1.00, $CHCl_3$); $\mathbf{R_f}$ 0.57 (9:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 2165, 1728, 1612, 1247, 1097, 828; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.27 (2H, d, *J* = 8.3 Hz, PMB-ArH), 7.20 (2H, d, *J* = 8.5 Hz, Bn-ArH), 7.08 (3H, *app* d, *J* = 6.8 Hz, Bn-ArH), 6.88 (2H, d, *J* = 8.3 Hz, PMB-ArH), 5.41 (1H, dq, *J* = 15.2 and 6.1 Hz, H6), 5.32 (1H, ddd, *J* = 15.2, 8.1 and 1.3 Hz, H5), 4.43 (2H, d, *J* = 1.9 Hz , C<u>H</u>$_2$Ar), 3.80 (3H, s, O<u>Me</u>), 3.49-3.40 (2H, m, H10), 2.25-2.19 (1H, m, H3), 2.17 (2H, s,

SiC<u>H</u>$_2$Ph), 2.12 (1H, *app* q, *J* = 7.0 Hz, H4), 1.88-1.79 (1H, m, H9), 1.65 (3H, dd, *J* = 6.1 and 1.3 Hz, H7), 1.65-1.62 (1H, m, H8), 1.61-1.52 (1H, m, H9), 1.37 (1H, dtd, *J* = 13.0, 10.0 and 4.7 Hz, H9), 1.04 (3H, d, *J* = 6.8 Hz, H11), 0.10 (6H, s, Si(C<u>H</u>$_3$)$_2$Bn); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 159.3, 139.5, 135.3, 130.9, 129.4, 128.5, 128.2, 124.7, 124.3, 113.9, 110.7, 85.1, 72.5, 70.0, 55.4, 40.9, 38.9, 29.4, 27.8, 26.7, 18.1, 17.9, –1.6; **HRMS** (ES^+) calc. for $C_{28}H_{38}NaO_2Si$ $[M+Na]^+$ 457.2533; found 457.2532. Data in accordance with literature.[95]

(4*R*,5*R*,*E*)-4-((Benzyldimethylsilyl)ethynyl)-5-methyloct-6-enal (116)

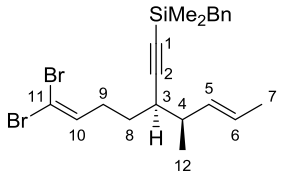


To a stirred solution of PMB ether **201** (209 mg, 0.48 mmol, 1.0 equiv.) in dichloromethane (3.9 mL) and water (0.9 mL) under argon was added DDQ (164 mg, 0.72 mmol, 1.5 equiv.). The reaction mixture was stirred for 1 h, then it was quenched by addition of $NaHCO_3$ (3 mL sat. *aq.*). The layers were separated and the aqueous phase extracted three times with dichloromethane (3 x 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude alcohol was used in the next step without further purification.

To a stirred solution of this alcohol in dichloromethane (4.0 mL) under argon at 0 °C was added Dess-Martin periodinane (286 mg, 0.68 mmol, 1.4 equiv.) and $NaHCO_3$ (41 mg, 0.48 mmol, 1.0 equiv.). The reaction mixture was stirred for 1 h at RT before being quenched by addition of $Na_2S_2O_3$ (2 mL, sat. *aq.*) and $NaHCO_3$ (2 mL, sat. *aq.*). The mixture was stirred for 30 min, then the layers were separated and the aqueous phase extracted three times with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (19:1 Pet. Ether / Et_2O) to afford aldehyde **116** (125 mg, 0.40 mmol, 83%) as a colourless oil. $\mathbf{[\alpha]_D^{25}}$ +68.6 (*c* = 0.99, $CHCl_3$); $\mathbf{R_f}$ 0.43 (9:1 Pet. Ether / Et_2O); **IR** (thin film / ν_{max} / cm^{-1}) 2960, 2165, 1726, 1493, 1250, 836, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.76 (1H, s, H1), 7.23-7.19 (2H, m, ArH), 7.10-7.06 (3H, m, ArH), 5.45

(1H, dq, *J* = 15.3 and 6.2 Hz, H7), 5.29 (1H, ddd, *J* = 15.3, 8.2 and 1.3 Hz, H6), 2.63-2.55 (1H, m, H2), 2.52-2.44 (1H, m, H2), 2.23 (1H, ddd, *J* = 10.7, 7.0 and 4.3 Hz, H4), 2.17 (2H, s, SiC$\underline{H}_2$Ph), 2.16-2.08 (1H, m, H5), 1.82 (1H, dddd, *J* = 13.4, 9.1, 6.5 and 4.3 Hz, H7), 1.66 (3H, d, *J* = 6.3 Hz, H8), 1.62-1.52 (1H, m, H7), 1.07 (3H, d, *J* = 6.8 Hz, H11), 0.12 (6H, s, Si(C$\underline{H}_3$)$_2$Bn); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.5, 139.4, 134.7, 128.5, 128.2, 125.4, 124.4, 109.7, 86.2, 42.2, 41.2, 38.4, 26.6, 25.1, 18.4, 18.1, –1.7; **HRMS** (ES^+) calc. for $C_{20}H_{28}NaOSi$ $[M+Na]^+$ 335.1802; 335.1795. Data in accordance with literature.[95]

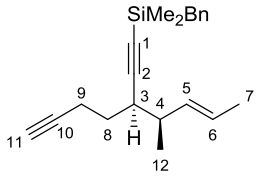
Benzyl((3*R*,4*R*,*E*)-3-(4,4-dibromobut-3-en-1-yl)-4-methylhept-5-en-1-yn-1-yl)dimethylsilane (202)



To a stirred solution of CBr_4 (565 mg, 1.70 mmol, 2.0 equiv.) in dry dichloromethane (4.2 mL) under argon at 0 °C was added powdered PPh_3 (895 mg, 3.41 mmol, 4.0 equiv.). After stirring for a further 10 min, the reaction mixture was cooled to –30 °C and a solution of aldehyde **116** (266 mg, 0.852 mmol, 1.0 equiv.) and triethylamine (1.2 mL, 8.52 mmol, 10 equiv.) in dichloromethane (4.3 mL) was added dropwise. The reaction mixture was stirred for 1 h, warming from –30 °C to 0 °C, before being quenched by addition of water. The layers were separated and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (49:1 Pet. Ether / Et_2O) to yield vinyl dibromide **202** (340 mg, 0.726 mmol, 85%) as a colourless oil. $\mathbf{[\alpha]_D^{25}}$ +22.3 (*c* = 1.00, $CHCl_3$); $\mathbf{R_f}$ 0.83 (19:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 3025, 2960, 2167, 1601, 1493, 1250, 837; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24-7.22 (2H, m, ArH), 7.12-7.08 (3H, m, ArH), 6.41 (1H, t, *J* = 7.5 Hz, H10), 5.46 (1H, dq, *J* = 15.2 and 6.3 Hz, H6), 5.30 (1H, ddd, *J* = 15.2, 8.1 and 1.3 Hz, H5), 2.34-2.26 (1H, m, H9), 2.25-2.21 (1H, m, H4), 2.19 (2H, s, SiC$\underline{H}_2$Ph), 2.8-2.10 (2H, m, H9

and H3), 1.68 (3H, dd, *J* = 6.3 and 1.5 Hz, H7), 1.61-1.53 (1H, m, H8), 1.49-1.40 (1H, m, H8), 1.06 (3H, d, *J* = 6.7 Hz, H12), 0.13 (6H, s, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.4, 138.4, 134.9, 128.5, 128.3, 125.3, 124.4, 109.8, 89.1, 85.9, 41.0, 38.6, 31.3, 30.8, 26.7, 18.3, 18.1, –1.8; **HRMS** (EI/FI) calc. for $C_{21}H_{28}Br_2Si$ $[M]^+$ 468.0307; found 468.0810. Data in accordance with literature.[95]

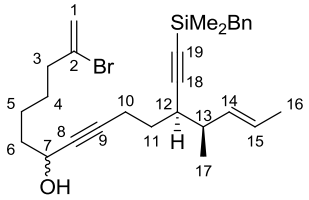
Benzyl((*3R*,*4R*,*E*)-3-(but-3-ynyl)-4-methylhept-5-en-1-ynyl)dimethylsilane (105)



To a solution of vinyl dibromide **202** (55.0 mg, 0.117 mmol, 1.0 equiv.) in THF (2.0 mL) at –78 °C was added *n*-BuLi (2.5 M in hexane, 105 µL, 0.258 mmol, 2.2 equiv.) dropwise. The mixture was warmed to RT, and stirred for 40 min, then quenched with NH_4Cl (sat. *aq.*). The layers were separated and the aqueous phase extracted three times with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (49:1 Pet. Ether / Et_2O) to afford diyne **105** (35.6 mg, 0.115 mmol, 98%) as a colourless oil. **$[\alpha]_D^{25}$** +98.0 (*c* = 1.00, $CHCl_3$); **R_f** 0.70 (19:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 2929, 2165, 1728, 1612, 1247, 1097, 828; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.21 (2H, m, ArH), 7.11-7.08 (3H, m, ArH), 5.45 (1H, dq, *J* = 15.2 and 6.3 Hz, H6), 5.32 (1H, dd, *J* = 15.2 and 8.1 Hz, H5), 2.42-2.34 (2H, m, H3 and H9), 2.25 (1H, ddd, *J* = 16.7, 8.3 and 2.3 Hz, H9), 2.18 (2H, s, Si$\underline{C}H_2$Ph), 2.14 3 (1H, q, *J* = 7.1 Hz, H4), 1.97 (1H, t, *J* = 2.6 Hz, H11), 1.75-1.69 (1H, m, H8), 1.67 (3H, d, *J* = 6.3 Hz, H7), 1.58-1.49 (1H, m, H8), 1.07 (3H, d, *J* = 6.8 Hz, H12), 0.12 (6H, s, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.4, 134.9, 128.5, 128.2, 125.2, 124.4, 109.6, 85.8, 84.4, 68.5, 40.8, 38.2, 31.8, 26.6, 18.2, 18.1, 16.8, –1.7; **HRMS** (ES^+) calc. for $C_{19}H_{28}NaSi$ $[M+Na]^+$ 331.1858; found 331.1860. Data in accordance with literature.[95]

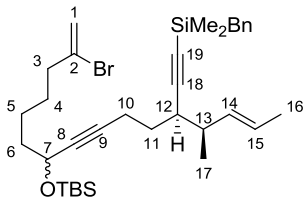
7.3.2. Synthesis of the CDEF rings

(12*R*,13*R*,*E*)-12-((Benzyldimethylsilyl)ethynyl)-2-bromo-13-methylhexadeca-1,14-dien-8-yn-7-ol



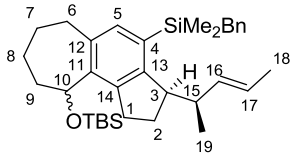
To a stirred solution of diyne **105** (871 mg, 2.82 mmol, 1.0 equiv.) in dry THF (21 mL) under argon at –78 °C was added *n*-BuLi (2.5 M in hexane, 1.13 mL, 2.82 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred for 30 min before a solution of aldehyde **129** (908 mg, 4.75 mmol, 1.7 equiv.) in dry THF (1.2 mL) was added. The reaction mixture was stirred for 3 h from –78 °C to –20 °C before being quenched with NH_4Cl solution (2 mL, sat. *aq.*) and warmed to RT. The mixture was filtered through a plug of Celite® and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) to yield the title bromoenediynol (1.30 g, 92%) as a colourless oil. **R_f** 0.17 (Pet. Ether/ Et_2O (17:3)); **IR** (thin film, ν_{max} / cm^{-1}) 3370 (br), 2935 (m), 2167 (m), 1630 (m), 1601 (m), 1494 (m), 1452 (m), 1250 (m), 1208 (m), 968 (m), 837 (s), 670 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.24-7.19 (2H, m, ArH), 7.11-7.05 (3H, m, ArH), 5.56 (1H, d, *J* = 1.5 Hz, H1), 5.44 (1H, dq, *J* = 15.1, 6.4 Hz, H15), 5.39 (1H, d, *J* = 1.5 Hz, H1), 5.31 (1H, ddq, *J* = 15.1, 8.1, 1.3 Hz, H14), 4.41-4.32 (1H, m, H7), 2.44 (2H, t, *J* = 7.3 Hz, H3), 2.42-2.36 (1H, m, H10), 2.33 (1H, ddd, *J* = 10.6, 6.5, 4.4 Hz, H12), 2.29-2.21 (1H, m, H10), 2.17 (2H, s, SiC$\underline{H_2}$Ph), 2.14 (1H, q, *J* = 7.0 Hz, H13), 1.74-1.68 (2H, m, H6), 1.67 (3H, dd, *J* = 6.4, 1.3 Hz, H16), 1.66-1.64 (1H, m, H11), 1.62 (2H, *app* t, *J* = 7.6 Hz, H4), 1.56-1.44 (3H, m, H11 and H5), 1.05 (3H, d, *J* = 7.0 Hz, H17), 0.11 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 139.4, 134.9, 134.6, 128.5, 128.2, 125.1, 124.4, 116.7, 109.7, 85.8, 85.4, 81.5, 62.7, 41.4, 40.8, 38.3, 37.9, 31.9, 27.7, 26.7, 24.1, 18.1, 18.1, 17.1, –1.6; **HRMS** (ESI^+) calc. for $C_{28}H_{39}BrOSiNa$ $[M+Na]^+$ 521.1846, found 521.1835.

Benzyl((3*R*)-13-bromo-8-((*tert*-butyldimethylsilyl)oxy)-3-((*R*,*E*)-pent-3-en-2-yl)tetradeca-13-en-1,6-diyn-1-yl)dimethylsilane (183)



To a stirred solution of the above alcohol (1.30 g, 2.60 mmol, 1.0 equiv.) in dry dichloromethane (33 mL) under argon at 0 °C was added sequentially imidazole (266 mg, 3.90 mmol, 1.5 equiv.), 4-dimethylaminopyridine (31.8 mg, 0.260 mmol, 0.1 equiv.) and TBSCl (510 mg, 3.38 mmol, 1.5 equiv.). The reaction mixture was warmed to RT and stirred for 2 h before being quenched with $NaHCO_3$ solution (30 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 30 mL). The combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) to yield TBS ether **183** (1.58 g, 99%) as a colourless oil. $\mathbf{R_f}$ 0.76 (Pet. Ether/ Et_2O (19:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2955 (s), 2859 (s), 2172 (m), 1494 (m), 1452 (m), 1250 (m), 1142 (m), 837 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.24-7.19 (2H, m, ArH), 7.11-7.25 (3H, m, ArH), 5.55 (1H, d, *J* = 1.5 Hz, H1), 5.43 (1H, dq, *J* = 15.1, 6.3 Hz, H15), 5.38 (1H, d, *J* = 1.5 Hz, H1), 5.31 (1H, dqd, *J* = 15.1, 8.0, 1.3 Hz, H14), 4.34 (1H, t, *J* = 6.3 Hz, H7), 2.43 (2H, *app* t, *J* = 7.3 Hz, H3), 2.40-2.32 (2H, m, H5 and H12), 2.29-2.20 (1H, m, H5), 2.17 (2H, s, SiC$\underline{H}_2$Ph), 2.16-2.07 (1H, m, H13), 1.69-1.61 (3H, m, H10 and H6), 1.66 (3H, dd, *J* = 6.3, 1.3 Hz, H16), 1.58 (2H, *app* dt, *J* = 15.3, 7.8 Hz, H4), 1.53-1.39 (3H, m, H6 and H11), 1.05 (3H, d, *J* = 6.9 Hz, H17), 0.91 (9H, s, $SiC(CH_3)_3$), 0.13 (3H, s, $Si(CH_3)_2$), 0.11 (9H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 139.4, 135.0, 134.8, 128.5, 128.2, 125.1, 124.4, 116.6, 109.8, 85.6, 84.2, 82.2, 63.2, 41.5, 40.8, 38.8, 38.2, 32.0, 27.7, 26.7, 26.0, 24.3, 18.5, 18.1, 18.1, 17.1, –1.6, –1.6, –4.3, –4.8; **HRMS** (EI^+) calc. for $C_{30}H_{44}BrOSi_2$ $[M-^tBu]^+$ 555.2114, found 555.2233.

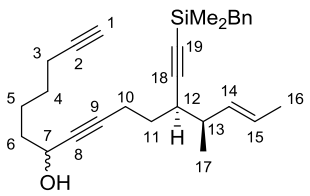
Benzyl((3*R*)-10-((*tert*-butyldimethylsilyl)oxy)-3-((*R*,*E*)-pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)dimethylsilane (203)



Bromoenediyne **183** (30 mg, 0.049 mmol, 1.0 equiv.) was dissolved in dry acetonitrile (1.95 mL), and the solution degassed with argon bubbling for 30 min. Triethylamine was separately degassed with argon bubbling for 30 min. A vial equipped with a stirrer bar was charged with tetrakis(triphenylphosphine)palladium(0) (2.8 mg, 0.002 mmol, 5 mol%) in the glovebox, and subsequently degassed with argon bubbling for 15 min. The degassed solution of starting material was added to the catalyst by syringe, followed by the degassed triethylamine (54 µL, 0.39 mmol, 8.0 equiv.). The reaction mixture was stirred at 80 °C overnight, then cooled to rt and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (99:1 Pet. Ether/ Et_2O) to yield tricycle **203** (17.9 mg, 69%, inseparable 1:1 mixture of diastereomers) as a yellow oil. These diastereomers were generally not readily separated by chromatography, and they were generally carried forward to deoxygenated intermediate **182**; the data presented below was obtained for the purpose of characterization by careful chromatography. $\mathbf{R_f}$ 0.86 (Pet. Ether/ Et_2O (19:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2928 (s), 2855 (m), 1493 (m), 1451 (m), 1250 (m), 1154 (m), 1088(m), 1056 (m), 833 (s); **HRMS** (EI^+) calc. for $C_{34}H_{52}OSi_2$ $[M]^+$ 532.3557, found 532.3568. **Diastereomer 1:** **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.15 (2H, t, *J* = 7.3 Hz, $SiCH_2\underline{Ph}$), 7.04 (1H, t, *J* = 7.3 Hz, $SiCH_2\underline{Ph}$), 6.91 (1H, s, H5), 6.91-6.89 (2H, m, $SiCH_2\underline{Ph}$), 5.26 (1H, dqd, *J* = 15.4, 6.3, 1.3 Hz, H17), 5.13 (1H, ddq, *J* = 15.4, 5.7, 1.3 Hz, H16), 5.06-5.00 (1H, m, H10), 3.40-3.33 (1H, m, H6), 3.24-3.19 (1H, m, H3), 2.81-2.74 (2H, m, H1), 2.49-2.39 (2H, m, H12 and H15), 2.32 (2H, s, $SiC\underline{H_2}Ph$), 2.31-2.19 (1H, m, H8), 2.05-1.96 (1H, m, H9), 1.96-1.89 (3H, m, H2 and H7), 1.73-1.64 (1H, m, H8), 1.55-1.52 (1H, m, H9), 1.52 (3H, d, *J* = 6.3 Hz, H18), 1.35-1.26 (1H, m, H2), 1.10 (3H, d, *J* = 6.6 Hz, H19), 0.92 (9H, s, $SiC(CH_3)_3$), 0.30 (3H, s, $Si(CH_3)_2$),

0.24 (3H, s, $Si(CH_3)_2$), 0.07 (3H, s, $Si(CH_3)_2$), –0.18 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 150.6 (C14), 141.1 (C11), 140.8 (C13), 140.5 (C12), 140.1 (C4), 136.1 (C5), 131.9 (C16), 131.6 ($SiCH_2\underline{Ph}$), 128.6 ($SiCH_2\underline{Ph}$), 128.1 ($SiCH_2\underline{Ph}$), 124.2 (C17), 124.1 ($SiCH_2\underline{Ph}$), 71.5 (C10), 50.7 (C3), 41.8 (C15), 35.3 (C6), 34.4 (C9), 30.9 (C1), 29.4 (C2), 27.5 ($Si\underline{C}H_2Ph$), 26.1 ($SiC(\underline{C}H_3)_3$), 25.1 (C8), 24.9 (C7), 19.0 (C19), 18.5 (C18), 18.3 ($Si\underline{C}(CH_3)_3$), –1.3 ($Si(CH_3)_2$), –1.7 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), –4.9 ($Si(CH_3)_2$). **Diastereomer 2: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.15 (2H, t, *J* = 7.3 Hz, $SiCH_2\underline{Ph}$), 7.04 (1H, t, *J* = 7.4 Hz, $SiCH_2\underline{Ph}$), 6.92 (1H, s, H5), 6.90-6.88 (2H, m, $SiCH_2\underline{Ph}$), 5.07-5.01 (2H, m, H16 and H10), 4.94 (1H, dqd, *J* = 15.5, 6.3, 0.6 Hz, H17), 3.40-3.33 (1H, m, H6), 3.03 (1H, d, *J* = 15.5 Hz, H3), 2.83-2.79 (1H, m, H1), 2.61 (1H, dt, *J* = 15.8, 9.3 Hz, H1), 2.50-2.46 (1H, m, H6), 2.31-2.28 (1H, m, H15), 2.30 (2H, s, $SiC\underline{H}_2Ph$), 2.27-2.20 (2H, m, H8), 2.04-1.99 (1H, m, H9), 1.95-1.84 (3H, m, H2 and H7), 1.71-1.67 (1H, m, H8), 1.45 (3H, d, *J* = 6.0 Hz, H18), 1.44-1.40 (1H, m, H9), 1.35-1.26 (1H, m, H2), 1.11 (3H, d, *J* = 6.9 Hz, H19), 0.90 (9H, s, $SiC(CH_3)_3$), 0.31 (3H, s, $Si(CH_3)_2$), 0.26 (3H, s, $OSi(CH_3)_2$), 0.08 (3H, s, $OSi(CH_3)_2$), –0.15 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 151.0 (C14), 140.5 (C11), 140.4 (C13), 140.2 (C12), 140.2 (C4), 135.5 (C5), 132.0 (C16), 130.9 ($SiCH_2\underline{Ph}$), 128.5 ($SiCH_2\underline{Ph}$), 128.1 ($SiCH_2\underline{Ph}$), 124.1 (C17), 124.0 ($SiCH_2\underline{Ph}$), 71.5 (C4), 51.2 (C3), 42.6 (C15), 35.4 (C6), 35.0 (C9), 31.2 (C1), 29.4 (C2), 27.6 ($Si\underline{C}H_2Ph$), 26.1 ($SiC(\underline{C}H_3)_3$), 25.3 (C8), 25.2 (C7), 19.0 (C19), 18.4 ($Si\underline{C}(CH_3)_3$), 18.3 (C18), –1.2 ($Si(CH_3)_2$), –1.5 ($Si(CH_3)_2$), –4.6 ($OSi(CH_3)_2$), –4.7 ($OSi(CH_3)_2$).

(12*R*,13*R*,*E*)-12-((Benzyldimethylsilyl)ethynyl)-13-methylhexadeca-14-en-1,8-diyn-7-ol (184)

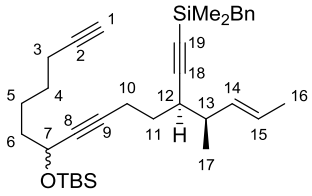


To a stirred solution of diyne **105** (343 mg, 1.11 mmol, 1.0 equiv) in dry THF (6.9 mL) under argon at –78 °C was added *n*-BuLi (2.5 M in hexane, 0.44 mL, 0.440 mmol, 0.99 equiv)

dropwise. The reaction mixture was stirred for 30 min before a solution of hept-6-ynal **169** (147 mg, 1.33 mmol, 1.2 equiv) in dry THF (2.3 mL) was added. The reaction mixture was stirred for 3 h from –78 °C to –20 °C before being quenched with NH_4Cl (0.6 mL, sat. *aq.*) and warmed to rt. The mixture was filtered through a plug of Celite® and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 Pet. Ether/ Et_2O) to yield the triyne **184** (356 mg, 77%, 97% brsm) as a colourless oil, and some diyne **105** (71 mg, 21%) was recovered.

R_f 0.47 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3380 (br), 3307 (m), 2933 (m), 2166 (w), 1601 (m), 1494 (m), 1250 (m), 969 (m), 837 (s), 763 (m), 699 (m), 633 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.22 (2H, t, *J* = 7.7 Hz, ArH), 7.11-7.06 (3H, m, ArH), 5.44 (1H, dq, *J* = 15.1, 6.2 Hz, H15), 5.31 (1H, ddd, *J* = 15.1, 8.1, 1.3 Hz, H14), 4.37 (1H, *app* q, *J* = 6.4 Hz, H7), 2.40 (1H, dddd, *J* = 16.5, 8.5, 4.5, 1.9, H10), 2.33 (1H, ddd, *J* = 10.5, 6.5, 4.5 Hz, H12), 2.29-2.24 (1H, m, H10), 2.24-2.19 (2H, m, H3), 2.17 (2H, s, SiC$\underline{H_2}$Ph), 2.13 (1H, dqd, *J* = 8.1, 6.8, 6.5 Hz, H13), 1.95 (1H, t, *J* = 2.6 Hz, H1), 1.73 (1H, *app* dd, *J* = 5.4, 1.2 Hz, H6), 1.72- 1.68 (2H, m, H11), 1.67 (3H, dd, *J* = 6.2, 1.3 Hz, H16), 1.60- 1.56 (4H, m, H4 and H5), 1.55-1.49 (1H, m, H11), 1.05 (3H, d, *J* = 6.8 Hz, H17), 0.11 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 139.4, 134.9 , 128.5, 128.2, 125.1, 124.4, 109.7, 85.6, 85.3, 84.5, 81.5, 68.5, 62.7, 40.7, 38.3, 37.7, 31.9, 28.3, 26.6, 24.5, 18.5, 18.1, 18.1, 17.1, −1.6; **HRMS** (ESI^+) calc. for $C_{28}H_{38}NaO_{Si}$ $[M+Na]^+$ 441.2584, found 441.2583.

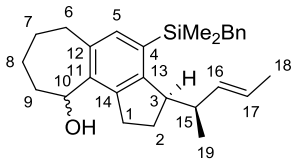
Benzyl((3*R*)-13-bromo-8-((*tert*-butyldimethylsilyl)oxy)-3-((*R*,*E*)-pent-3-en-2-yl)tetradeca-13-en-1,6-diyn-1-yl)dimethylsilane (205)



To a stirred solution of the triynol **184** (20.0 mg, 0.048mmol, 1.0 equiv.) in dry dichloromethane (0.5 mL) under argon at 0 °C was added sequentially imidazole (4.9 mg,

0.072 mmol, 1.5 equiv.), 4-dimethylaminopyridine (0.6 mg, 0.005 mmol, 0.1 equiv.) and TBSCl (8.6 mg, 0.057 mmol, 1.2 equiv.). The reaction mixture was warmed to RT and stirred for 2 h before being quenched with $NaHCO_3$ solution (0.5 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 0.5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) to yield TBS ether **205** (25.3 mg, 99%) as a colourless oil. $\mathbf{R_f}$ 0.74 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2951 (s), 2858 (s), 2171 (w), 1494 (w), 1452 (w), 1250 (m), 1097 (m), 837 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 (2H, dd, *J* = 10.0, 5.3 Hz, ArH), 7.14- 7.03 (3H, m, ArH), 5.43 (1H, dq, *J* = 15.2, 6.2 Hz, H15), 5.31 (1 H, ddq, *J* = 15.2, 8.1, 1.2 Hz, H1), 4.34 (1H, dd, *J* = 8.3, 4.2 Hz, H7), 2.43-2.31 (2H, m, H6 and H12), 2.27 (1H, td, *J* = 8.1, 1.7 Hz, H6), 2.24-2.19 (2H, m, H10), 2.17 (2H, s, SiC$\underline{H}_2$Ph), 2.11 (1H, *app* sextet, *J* = 6.8 Hz, H13), 1.94 (1H, t, *J* = 2.6 Hz, H1), 1.71-1.60 (3H, m, H3 and H11), 1.66 (3H, dd, *J* = 6.2, 1.2 Hz, H16), 1.60-1.44 (5H, m, H4, H5 and H11), 1.05 (3H, d, *J* = 6.8 Hz, H17), 0.91 (9H, s, $SiC(CH_3)_3$), 0.13 (3H, s, $Si(CH_3)_2$), 0.11 (9H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.4, 135.0, 128.5, 128.2, 125.1, 124.4, 109.8, 85.6, 84.6, 84.2, 82.2, 68.4, 63.2, 40.8, 38.6, 38.3, 38.2, 32.0, 28.4, 26.7, 26.0, 24.70, 18.5, 18.4, 18.1, 17.1, −1.6, −4.3, −4.8; **HRMS** (EI^+) calc. for $C_{34}H_{52}OSi_2$ $[M]^+$ 532.3557, found 532.3568.

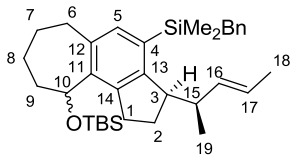
(3*R*)-4-(Benzyldimethylsilyl)-3-((*R*,*E*)-pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-10-ol (204)



To a solution of triyne **184** (37.1 mg, 0.089 mmol, 1.0 equiv) in chlorobenzene (2.3 mL, 0.04 M) in a microwave tube was added triphenylphosphine (9.3 mg, 0.035 mmol, 40 mol%) and the mixture was degassed with argon bubbling for 30 min. Cyclopentadienyl cobalt dicarbonyl (3.2 mg, 0.018 mmol, 20 mol%) was added and the reaction mixture was heated

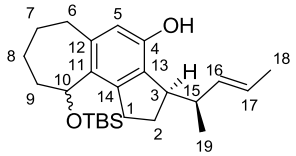
in a microwave (300 W) at 150 °C for 25 min. Upon cooling, the solvent was removed *in vacuo*.The crude product was purified by flash column chromatography on silica gel (9:1 Pet. Ether/ Et_2O) to yield two CDE ring system diastereomers **204a** (14.5 mg, 39%) and **204b** (17.2 mg, 46%), as colourless oils. **IR** (thin film, ν_{max} / cm^{-1}) 3308 (br), 2929 (s), 1493 (m), 1452 (m), 1248 (m), 1231 (m), 1148 m), 870 (m), 833 (m); **HRMS** (ESI^+) calc. for $C_{28}H_{38}NaOSi$ $[M+Na]^+$ 441.2584, found 441.2583. **Diastereomer a: R_f** 0.27 (9:1 Pet. Ether/ EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.20 (2H, t, *J* = 7.4 Hz, ArH), 7.07 (1H, t, *J* = 7.4 Hz, ArH), 7.04 (1H, s, H5), 6.97 (2H, d, *J* = 7.4 Hz, ArH), 5.14 (1H, d, *J* = 5.3 Hz, H10), 5.13-5.09 (1H, m, H16), 5.09-5.02 (1H, dqd, *J* = 15.4, 6.1, 0.6 Hz, H17), 3.24 (1H, *app* t, *J* = 9.8 Hz, H1), 3.21 (1H, dt, *J* = 6.7, 3.1 Hz, H3), 2.84-2.72 (2H, m, H6), 2.64 (1H, dd, *J* = 14.1, 6.7 Hz, H1), 2.40-2.36 (1H, m, H15), 2.35 (2H, d, *J* = 4.7 Hz, $SiCH_2Bn$), 2.23-2.12 (2H, m, H9 and H8), 2.01-1.88 (3H, m, H2 and 2 × H7), 1.82-1.73 (1H, m, H9), 1.70 (1H, td, *J* = 14.4, 3.0 Hz, H8), 1.51 (3H, d, *J* = 6.1 Hz, H18), 1.48 (d, *J* = 3.1 Hz, OH), 1.47-1.37 (1H, *app* qdd, *J* = 12.3, 3.2, 1.6 Hz, H2), 1.11 (3H, d, *J* = 6.9 Hz, H19), 0.29 (3H, s, $Si(CH_3)_2$), 0.25 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 151.4 (C14), 142.4 (C11), 140.1 (C13), 140.1 (C4), 139.3 (C12), 136.2 (C5), 132.7 ($SiCH_2$Ph), 131.8 (C16), 128.5 ($SiCH_2$Ph), 128.2 ($SiCH_2$Ph), 124.3 (C17), 124.2 ($SiCH_2$Ph), 71.5 (C10), 51.1 (C3), 42.2 (C15), 35.9 (C1), 33.0 (C8), 31.0 (C6), 28.9 (C2), 27.3 ($SiCH_2Ph$), 25.0 (C7), 24.9 (C9), 19.1 (C19), 18.4 (C18), −1.3 ($Si(CH_3)_2$), −1.6 ($Si(CH_3)_2$). **Diastereomer b: R_f** 0.19 (9:1 Pet. Ether/ EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.19 (2H, t, *J* = 7.4 Hz, ArH), 7.07 (1H, t, *J* = 7.4 Hz, ArH), 6.99 (1H, s Hz, H5), 6.96 (2H, d, *J* = 7.4 Hz, ArH), 5.15-5.11 (1H, m, H10), 5.08 (1H, dqd, *J* = 15.3, 6.6, 1.6 Hz, H16), 4.95 (1H, dqd, *J* = 15.3, 6.0, 0.6 Hz, H17), 3.22 (1H, *app* t, *J* = 12.9 Hz, H1), 3.16 (1H, *app* dt, *J* = 7.3, 3.5 Hz, H3), 2.86 (1H, ddd, *J* = 15.8, 8.6, 2.2 Hz, H6), 2.72-2.64 (1H, m, H6), 2.61 (1H, dd, *J* = 14.3, 6.8 Hz, H1), 2.38-2.33 (1H, m, H15), 2.34 (2H, d, *J* = 3.0 Hz, $SiCH_2Bn$), 2.24- 2.15 (2H, m, H8 and H9), 2.01-1.89 (3H, m, 2 × H7 and H2), 1.76 (1H, *app* dt, *J* = 14.2, 4.7 Hz, H9), 1.61 (1H, d, *J* = 2.8 Hz, OH), 1.60-1.53 (1H, m, H8), 1.46 (3H, dt, *J* = 6.3, 1.3 Hz, H18), 1.45-1.36 (1H, m, H2), 1.11 (3H, d, *J* = 6.9 Hz, H19), 0.30 (3H, s, $Si(CH_3)_2$), 0.24 (3H, s, $Si(CH_3)_2$).

Benzyl((3*R*)-10-((*tert*-butyldimethylsilyl)oxy)-3-((*R*,*E*)-pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)dimethylsilane (203)



To a solution of triyne **205** (14.0 mg, 0.026 mmol, 1.0 equiv) in chlorobenzene (0.7 mL, 0.04 M) in a microwave tube was added triphenylphosphine (2.8 mg, 0.011 mmol, 40 mol%) and the mixture was degassed with argon bubbling for 30 min. Cyclopentadienyl cobalt dicarbonyl (1.0 mg, 0.005 mmol, 20 mol%) was added and the reaction mixture was heated in a microwave (300 W) at 150 °C for 25 min. Upon cooling, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (99:1 Pet. Ether/ Et_2O) to yield tricycle **203** (9.8 mg, 70%, inseparable 1:1 mixture of diastereomers) as a yellow oil. The data for this compound was identical to that recorded for **23** derived from the Pd-catalyzed route (see above).

(3*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-3-((*R*,*E*)-pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-ol (207)

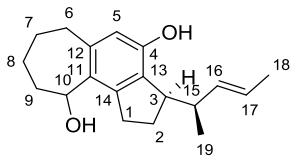


To a solution of benzyldimethylarylsilane **203** (56.5 mg, 0.106 mmol, 1.0 equiv.) in THF (0.95 mL) was added TBAF (1 M in THF, 223 µL, 0.223 mmol, 2.1 equiv.). The reaction mixture was stirred for 30 min, then hydrogen peroxide (30% w/v in water, 72 µL, 0.636 mmol, 6 equiv.) in methanol (0.95 mL) and potassium hydrogen carbonate (5.3 mg, 0.0530 mmol, 0.5 equiv.) were added.[151] The reaction mixture was stirred at RT overnight, then quenched with $Na_2S_2O_3$ (1 mL, sat. *aq.*), the layers separated and the aqueous layer extracted three times with diethyl ether (3 x 1 mL). The combined organic layers were dried with Na_2SO_4 and the

solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (19:1 Pet. Ether/ Et_2O) to yield phenol **207** (29.4 mg, 69%, inseparable 1:1 mixture of diasteromers) as a colourless oil. These diastereomers were generally not readily separated by chromatography, and they were generally carried forward to deoxygenated intermediate **182**; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.38 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3387 (br), 2920 (s), 2849 (m), 2174 (m), 1597 (m), 1439 (m), 1373 (m), 1297 (s), 1088 (s), 1053 (s), 1022 (s), 834 (s), 801 (s); **HRMS** (EI^+) calc. for $C_{25}H_{40}O_2Si$ $[M]^+$ 400.2798, found 400.2798. **Diastereomer 1: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.37 (1H, s, H5), 5.59-5.36 (2H, m, H16 and H17), 4.98 (1H, *J* = 6.3 Hz, H10), 4.82 (1H, s, OH), 3.38-3.24 (2H, m, H3 and H6), 2.90 (1H, *app* dt, *J* = 16.0, 8.2 Hz, H1), 2.78 (1H, tdd, *J* = 16.3, 9.5, 2.7 Hz, H1), 2.69-2.59 (1H, m, H15), 2.42 (1H, dd, *J* = 13.6, 6.6 Hz, H6), 2.28-2.18 (1H, m, H8), 2.16-2.05 (1H, m, H2), 2.03-1.87 (3H, m, H9, H2 and H7), 1.74-1.65 (1H, m, H8), 1.63 (2H, d, *J* = 5.7 Hz, H18), 1.52-1.46 (1H, m, H9), 1.34-1.27 (1H, m, H7), 0.98 (2H, d, *J* = 6.9 Hz, H19), 0.87 (9H, s, $SiC(CH_3)_3$), 0.03 (3H, s, $Si(CH_3)_2$), –0.23 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 150.9 (C4), 144.7 (C12), 144.3 (C14), 135.3 (C16), 132.3 (C11), 126.9 (C13), 125.7 (C17), 116.1 (C5), 71.1 (C10), 48.7 (C3), 39.8 (C15), 35.4 (C6), 34.9 (C9), 31.5 (C1), 29.3 (C7), 28.5 (C2), 26.0 ($SiC(\underline{C}H_3)_3$), 25.1 (C8), 18.3 (C18), 18.3 ($Si\underline{C}(CH_3)_3$), 16.7 (C19), –4.6 ($Si(CH_3)_2$), –5.0 ($Si(CH_3)_2$). **Diastereomer 2: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.35 (1H, s, H5), 5.59-5.36 (2H, m, H16 and H17), 4.97 (1H, d, *J* = 6.6 Hz, H10), 4.79 (1H, s, OH), 3.35-3.26 (1H, m, H6), 3.26-3.20 (1H, m, H3), 2.81 (2H, *app* dd, *J* = 9.0, 5.6 Hz, H1), 2.59-2.51 (1H, m, H15), 2.42 (1H, dd, *J* = 13.6, 6.6 Hz, H6), 2.28-2.18 (1H, m, H8), 2.16-2.05 (1H, m, H2), 2.03-1.87 (3H, m, H9, H2 and H7), 1.74-1.65 (1H, m, H8), 1.64 (2H, d, *J* = 4.4 Hz, H18), 1.52-1.46 (1H, m, H9), 1.34-1.27 (1H, m, H7), 0.99 (2H, d, *J* = 6.9 Hz, H19), 0.87 (9H, s, $SiC(CH_3)_3$), 0.03 (3H, s, $Si(CH_3)_2$), –0.20 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 150.7 (C4), 144.2 (C12), 144.2 (C14), 135.7 (C16), 132.3 (C11), 126.9 (C13), 125.6 (C17), 115.9 (C5), 71.2 (C10), 48.6 (C3), 40.0 (C15), 35.4 (C6), 35.2 (C9), 31.4 (C1), 29.2 (C7),

29.1 (C2), 26.0 (SiC($\underline{C}H_3)_3$), 25.3 (C8), 18.3 (C18), 18.2 (Si$\underline{C}(CH_3)_3$), 17.0 (C19), –4.7 ($Si(CH_3)_2$), –4.7 ($Si(CH_3)_2$).

(3*R*)-3-((*R*,*E*)-Pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]indene-4,10-diol (208)



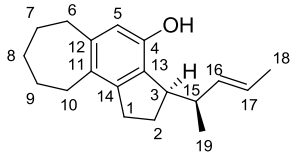
To a stirred solution of arylsilane **204** (27.7 mg, 0.0662 mmol, 1.0 equiv.) in THF (0.7 mL) was added TBAF (0.26 mL, 1M in THF, 0.260 mmol, 4.0 equiv.), and the reaction mixture was stirred for 15 min. Upon disappearance of silane by TLC, MeOH (0.7 mL), $KHCO_3$ (13.2 mg, 0.132 mmol, 2.0 equiv.) and H_2O_2 (0.17 mL, 30 w/w in H_2O, mmol, 20 equiv.) were added sequentially.[151] The reaction mixture was stirred at RT overnight before being quenched with $Na_2S_2O_3$ (0.5 mL, sat. *aq*.) and NH_4Cl (0.5 mL, sat. *aq*.). The layers were separated and the aqueous layer extracted three times with diethyl ether (3 x 1 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (9:1 Pet. Ether/ EtOAc), then concentrated to yield phenol **208** (15.1 mg, 80%, as a 46:54 mixture of diastereomers) as a colourless oil. These diastereomers were generally carried forward to deoxygenated intermediate **182**; the data presented below was obtained for the purpose of characterization. **IR** (ν_{max} (thin film) /cm^{-1}) 3308 (br), 2927 (s), 2854 (m), 1719 (m), 1648 (m), 1596 (m), 1449 (s), 1376 (m), 1254 (m), 1084 (s), 970 (s); **HRMS** (ESI^+) calc. for $C_{19}H_{25}NaO_2$ $[M+Na]^+$: 285.1860; found: 285.1861. **Diastereomer a: R_f** 0.55 (Pet. Ether/ EtOAc (4:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.34 (1H, s, H5), 5.47-5.42 (2H, dd, H16 and H17), 5.02 (1H, d, *J* = 6.0 Hz, H10), 4.90 (1H, s, ArOH), 3.22 (1H, dt, *J* = 8.5, 4.2 Hz, H3), 3.12 (1H, *app* tt, *J* = 13.0, 2.0 Hz), 2.88 (1H, dt, *J* = 16.0, 8.1 Hz, H1), 2.71 (1H, ddd, *J* = 16.0, 9.4, 4.3 Hz, H1), 2.59-2.52 (1H, m, H15), 2.49 (1H, ddt, *J* = 14.2, 6.7, 1.6 Hz, H6), 2.11-2.01 (3H, m, H9, H8 and H2), 1.91-1.82 (2H, m, H2 and H7), 1.71-1.63 (1H, m, H8), 1.60 (3H, dd, *J* = 4.5, 1.3 Hz,

H18), 1.55-1.49 (1H, m, H9), 1.38-1.31 (1H, m, H7), 0.92 (3H, d, *J* = 6.9 Hz, H19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.5 (C4), 146.1 (C12), 143.9 (C14), 135.8 (C16), 131.1 (C11), 127.4 (C13), 126.0 (C17), 116.5 (C5), 71.1 (C10), 49.0 (C3), 39.6 (C15), 35.8 (C6), 33.5 (C9), 31.2 (C1), 29.3 (C2), 28.9 (C7), 24.9 (C8), 18.3 (C18), 16.6 (C19). **Diastereomer b: R_f** 0.35 (Pet. Ether/ EtOAc (4:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.40 (1H, s, H5), 5.55-5.39 (2H, m, H16 and H17), 5.08 (1H, d, *J* = 5.5 Hz, H10), 4.90 (1H, s, ArOH), 3.25 (1H, ddd, *J* = 8.6, 4.2, 3.2 Hz, H3), 3.16 (1H, t, *J* = 13.0 Hz, H6), 2.87 (2H, *app* dd, *J* = 9.1, 5.8 Hz), 2.62-2.51 (m, H6 and H15), 2.25-2.03 (3H, m, H9, H2 and H8), 2.03-1.83 (2H, m, H2 and H7), 1.79-1.70 (1H, m, H8), 1.65 (3H, dd, *J* = 4.5, 0.8 Hz, H18), 1.63-1.55 (1H, m, H9), 1.55-1.38 (2H, m, H7 and OH), 0.99 (3H, d, *J* = 6.9 Hz, H19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.4 (C4), 146.0 (C12), 143.7 (C14), 135.7 (C16), 131.1 (C11), 127.6 (C13), 125.9 (C17), 116.3 (C5), 71.1 (C10), 48.8 (C3), 40.1 (C15), 35.8 (C6), 33.7 (C9), 31.4 (C1), 29.2 (C2), 28.7 (C7), 25.0 (C8), 18.2 (C18), 16.9 (C19).

(*R*)-3-((*R*,*E*)-Pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[e]inden-4-ol (182) and triethyl(((*R*)-3-((*R*,*E*)-pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)oxy)silane (213)

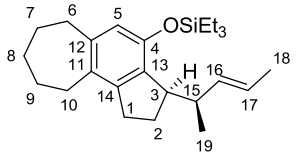
To a stirred solution of TBS ether **207** (167 mg, 0.417 mmol, 1.0 equiv.) in dry dichloromethane (18.5 mL) was added zinc(II) chloride (85 mg, 0.625 mmol, 1.50 equiv.) and triethylsilane (0.13 mL, 0.834 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 3 h before being quenched with NH_4Cl (18 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 18 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether/ EtOAc (49:1)) to yield phenol **182** (74 mg, 66%) as a colourless oil and the corresponding triethylsilylaryl ether **213** (48 mg, 30%) as a colourless oil.

(*R*)-3-((*R*,*E*)-Pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-ol (182)



[α]$_D^{25}$ +18.0 (*c* = 0.968, $CHCl_3$); **R_f** 0.36 (Pet. Ether / EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3427 (br), 2921 (s), 2849 (m), 1600 (m), 1447 (m), 1298 (m), 1261 (m), 1077 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.41 (1H, s, H5), 5.51-5.46 (2H, m, H16 and H17), 4.80 (1H, s, OH), 3.35-3.24 (1H, m, H3), 2.82 (1H, dt, *J* = 16.6, 8.4 Hz, H1), 2.77-2.72 (1H, m, H1), 2.72-2.68 (2H, m, H6), 2.67-2.61 (2H, m, H10), 2.60-2.50 (1H, m, H15), 2.19-2.04 (1H, m, H2), 1.93 (1H, ddt, *J* = 11.9, 8.3, 3.4 Hz, H2), 1.89-1.80 (1H, m, H8), 1.80-1.73 (1H, m, H8), 1.71-1.68 (1H, m, H7), 1.66 (3H, dd, *J* = 4.7, 1.3 Hz, H18), 1.64-1.59 (1H, m, H9), 1.54-1.51 (1H, m, H7), 1.51-1.45 (1H, m, H9), 0.98 (3H, d, *J* = 6.9 Hz, H19); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 150.0 (C4), 145.1 (C14), 144.0 (C12), 136.0 (C16), 131.4 (C11), 127.2 (C13), 125.7 (C17), 114.8 (C5), 49.2 (C3), 40.1 (C15), 36.4 (C6), 33.0 (C8), 31.4 (C1), 31.1 (C10), 29.3 (C2), 28.7 (C7), 28.1 (C9), 18.2 (C18), 16.6 (C19); **HRMS** (EI^+) calc. for $C_{19}H_{26}O$ $[M]^+$ 270.1984, found 270.1987.

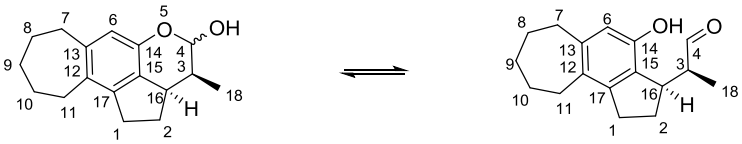
Triethyl(((*R*)-3-((*R*,*E*)-pent-3-en-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl)oxy)silane (213)



[α]$_D^{25}$ +7.5 (*c* = 0.1648, $CHCl_3$); **R_f** 0.85 (Pet. Ether / EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2955 (s), 2920 (s), 1589 (m), 1481 (m), 1456 (m), 1297 (m), 1111 (m), 1086 (m), 1009 (m), 807 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.36 (1H, s, H5), 5.26-5.13 (2H, m, H16 and H17), 3.22-3.13 (1H, m, H3), 2.72- 2.61 (7H, m, H1, H15, H6 and H10), 1.98-1.85 (2H, m, H2), 1.79 (2H, *app* td, *J* = 12.1, 6.8, H8), 1.57-1.53 (2H, m, H7 and H9), 1.54 (3H, dd, *J* = 5.0, 1.0 Hz, H18), 1.04 (3H, d, *J* = 6.9 Hz, H19), 1.00 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.75 (6H, dd, *J* =

7.9, 1.5 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$; **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 149.7 (C4), 144.6 (C14), 143.1 (C12), 134.2 (C16), 133.2 (C13), 131.6 (C11), 123.7 (C17), 117.5 (C5), 49.3 (C3), 38.6 (C15), 36.6 (C6), 33.0 (C8), 31.5 (C1), 31.2 (C10), 28.8 (C7), 28.1 (C9), 26.4 (C2), 19.1 (C19), 18.3 (C18), 7.0 (Si(CH$_2$<u>C</u>H$_3$)), 5.6 (Si(<u>C</u>H$_2$CH$_3$)); **HRMS** (FI$^+$) calc. for $C_{25}H_{40}OSi$ $[M]^+$ 384.2849, found 384.2867.

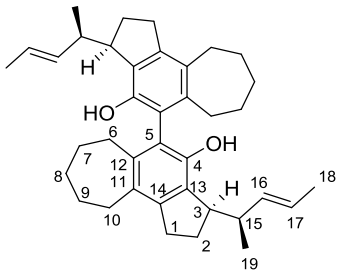
Equilibrium mixture of lactols (2a*R*,3*S*)-3-Methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromen-4-ol and aldehyde (S)-2-((R)-4-hydroxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[e]inden-3-yl)propanal (181)



To a stirred solution of alkene **182** (9.1 mg, 0.0337 mmol, 1.0 equiv.) in 1,4-dioxane (0.4 mL) and water (0.1 mL) was sequentially added 2,6-lutidine (8 µL, 0.07 mmol, 2.0 equiv.), osmium(VII) tetroxide (2.5% wt in *tert*-butanol, 7 µL, 0.0007 mmol, 0.02 equiv.) and sodium periodate (23.4 mg, 0.135 mmol, 4.0 equiv.).[153] The reaction mixture was stirred at RT overnight before being diluted with water and diethyl ether. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (9:1 Pet. Ether/ Et_2O), then concentrated to yield lactol **181** (5.6 mg, 64%, 74% brsm, as a 63:13:24 inseparable mixture of epimers and open-chain aldehyde form) as a colourless oil, and some alkene **182** (1.3 mg, 14%) was recovered. **R_f** 0.15 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2918 (s), 2849 (m), 1739 (s), 1610 (m), 1453 (m), 1366 (m), 1261 (m), 1092 (m), 1017 (m), 966 (s), 798 (m); **HRMS** (ESI$^+$) calc. for $C_{17}H_{22}NaO_2$ $[M+Na]^+$ 281.1512, found 281.1516. **^{1}H NMR** (500 MHz, $CDCl_3$; note that shifts for the minor lactol diastereomer are not reported) δ_H 9.66 (0.24H, s, H4^{ald}), 6.42 (0.24H, s, H6^{ald}), 6.40 (0.63H, s, H6^{maj}), 5.81 (0.24H, s, OH^{ald}), 5.38 (0.63H, dd, *J* = 2.6, 2.1 Hz, H4^{maj}), 3.77 (0.24H, dt, *J* = 9.1, 3.5 Hz, H16^{ald}), 3.51-3.35 (0.63H, m, H16^{maj}),

2.93-2.92 (0.24H, m, $H3^{ald}$), 2.91-2.85 (0.24H, m, $H1^{ald}$), 2.85-2.80 (2.52H, m, H1 and H7), 2.74-2.68 (3H, m, H7 and H11), 2.33-2.29 (0.63H, m, $H3^{maj}$), 2.18-2.12 (1H, m, H2), 1.92-1.81 (0.24H, m, $H10^{ald}$),1.87-1.82 (0.63H, m, $H9^{maj}$), 1.80-1.73 (2H, m, H2, $H9^{maj}$ and $H10^{ald}$), 1.73-1.65 (2, m, H8, $H10^{maj}$ and $H9^{ald}$), 1.56-1.45 (0.48H, m, $H8^{ald}$ and $H9^{ald}$), 1.50 (1.26H, *app* ddd, J = 12.3, 8.9, 5.1 Hz, $H8^{maj}$ and $H10^{maj}$), 1.06 (0.72H, d, J = 7.6 Hz, $H18^{ald}$), 0.73 (1.89H, d, J = 7.2 Hz, $H18^{maj}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 207.4 ($C4^{ald}$), 150.0 ($C5^{ald}$), 146.5 ($C14^{maj}$), 144.9 ($C14^{ald}$), 144.8 ($C13^{ald}$), 144.4 ($C17^{maj}$), 143.2 ($C13^{maj}$), 131.9 ($C12^{maj}$), 131.4 ($C12^{ald}$), 125.1 ($C14^{ald}$), 124.1 ($C15^{maj}$), 115.1 ($C6^{ald}$), 113.0 ($C6^{maj}$), 97.4 ($C4^{maj}$), 36.9 ($C7^{maj}$), 51.6 ($C3^{ald}$), 42.3 ($C16^{ald}$), 36.3 ($C7^{ald}$), 35.3 ($C16^{maj}$), 33.0 ($C9^{maj}$), 32.3 ($C3^{maj}$), 32.0 ($C9^{ald}$), 31.4 ($C1^{ald}$), 31.3 ($C1^{maj}$), 31.2 ($C11^{maj}$), 31.1 ($C11^{ald}$), 30.8 ($C2^{ald}$), 29.9 ($C2^{maj}$), 28.7 ($C8^{maj}$), 28.6 ($C8^{ald}$), 28.2 ($C10^{maj}$), 28.1 ($C10^{ald}$), 11.0 ($C18^{maj}$), 10.5 ($C18^{ald}$).

(3*R*,3'*R*)-3,3'-di((*R*,*E*)-pent-3-en-2-yl)-1,1',2,2',3,3',6,6',7,7',8,8',9,9',10,10'-hexadecahydro-[5,5'-bi(cyclohepta[*e*]indene)]-4,4'-diol 209



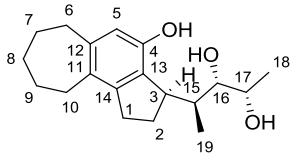
To a stirred solution of alkene **182** (5.0 mg, 0.0185 mmol, 1.0 equiv.) in 1,2-dichloroethane (0.1 mL) and water (80 µL) was sequentially added a solution of ruthenium (III) chloride in water (12.9 µL, 0.05 M in H_2O, 0.6 µmol, 3.5 mol%) and sodium periodate (7.9 mg, 0.0370 mmol, 2.0 equiv.). The reaction mixture was stirred at RT overnight before being quenched with $Na_2S_2O_3$ (1 mL, sat. *aq.*) and diluted with ethyl acetate (1 mL). The layers were separated and the aqueous layer extracted three times with ethyl acetate (1 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (99:1 Pet. Ether/ Et_2O), then concentrated to yield lactol **209** (5.0 mg, quant.) as a colourless

oil. **$[\alpha]_D^{25}$** +16.9 (*c* = 0.455, $CHCl_3$); **R_f** 0.85 (Pet. Ether/ Et_2O (19:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3512 (2), 2954 (s), 2920 (s), 2849 (s), 1616 (m), 1437 (m), 1310 (m), 1075 (m), 966 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.29-5.19 (4H, m, 2 x H16 and 2 x H17), 4.47 (2H, s, 2 x OH), 3.32 (2H, dt, *J* = 8.7, 4.2 Hz, 2 x H3), 2.90-2.78 (6H, m, 4 x H1 and 2 x H15), 2.78-2.63 (4H, m, 4 x H10), 2.50-2.32 (4H, m, 4 x H6), 2.06 (2H, dq, *J* = 13.0, 8.7 Hz, 2 x H2), 2.00-1.93 (2H, m, 2 x H2), 1.82-1.69 (4H, m, 4 x H8), 1.65-1.55 (4H, m, 4 x H9), 1.53 (6H, d, *J* = 4.4 Hz, H18), 1.48-1.39 (4H, m, 4 x H7), 1.05 (6H, d, *J* = 6.9 Hz, H19); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 148.1, 145.1, 142.6, 134.1, 131.7, 128.9, 124.3, 117.8, 49.6, 38.6, 32.8, 31.7, 31.6, 31.4, 28.3, 28.0, 26.2, 19.2, 18.3; **HRMS** (ESI^+) calc. for $C_{38}H_{51}O_2$ $[M+H]^+$ 539.3884, found 539.3886.

(2*R*,3*R*,4*S*)-4-((*R*)-4-hydroxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-3-yl)pentane-2,3-diol (215a) and (2*S*,3*S*,4*S*)-4-((*R*)-4-hydroxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-3-yl)pentane-2,3-diol (215b)

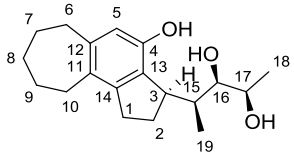
To a stirred solution of alkene **182** (49.0 mg, 0.181 mmol, 1.0 equiv.) in acetone (1.3 mL) and water (0.45 mL) was sequentially added osmium(VII) tetroxide (4% wt in water, 46 µL, 0.007 mmol, 0.04 equiv.) and NMO (50% wt in water, 88 µL, 0.362 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 2 h before being quenched with $Na_2S_2O_3$ (1.2 mL, sat. *aq*.). The layers were separated and the aqueous layer extracted three times with ethyl acetate (3 x 1.5 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (4:1 Pet. Ether/ EtOAc→3:1 Pet. Ether/ EtOAc), then concentrated to yield triols **215a** (16.8 mg, 30%) and **215b** (16.9 mg, 31%) as colourless oil. **IR** (ν_{max} (thin film) /cm^{-1}) 3442 (br), 2920 (s), 2848 (m), 1587 (m), 1449 (m), 1360 (m), 1279 (m), 1050 (m); **HRMS** (ESI^+) calc. for $C_{19}H_{28}NaO_3$ $[M+Na]^+$: 327.1931; found: 327.1928.

(2*S*,3*R*,4*S*)-4-((*R*)-4-hydroxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-3-yl)pentane-2,3-diol (215a)



R_f 0.21 (Pet. Ether/ EtOAc (7:3)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.20 (1H, br s, ArOH), 6.48 (1H, s, H5), 3.98 (1H, qd, *J* = 6.4, 3.2 Hz, H17), 3.69 (1H, ddd, *J* = 9.2, 2.8, 1.7 Hz, H3), 3.16 (1H, dd, *J* = 8.6, 3.2 Hz, H16), 2.92 (1H, ddd, *J* = 16.2, 10.3, 8.7 Hz, H1), 2.77 (1H, ddd, *J* = 16.2, 9.8, 2.0 Hz, H1), 2.73-2.58 (4H, m, H6 and H10), 2.37 (1H, *app* dq, *J* = 13.0, 9.7 Hz, H2), 2.06 (1H, dqd, *J* = 8.6, 6.9. 2.8 Hz, H15), 1.89-1.81 (2H, m, H2 and H8), 1.81-1.65 (2H, m, H8 and OH), 1.65-1.46 (4H, m, H7 and H9), 1.29 (3H, d, *J* = 6.4 Hz, H18), 0.76 (3H, d, *J* = 6.9 Hz, H19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.6 (C4), 145.4 (C12), 144.5 (C14), 130.4 (C11), 124.6 (C12), 115.2 (C5), 78.6 (C17), 67.6 (C16), 42.3 (C15), 41.6 (C3), 36.4 (C6), 33.0 (C2), 32.9 (C8), 32.1 (C1), 31.2 (C10), 28.7 (C7), 28.3 (C9), 21.0 (C18), 12.6 (C19);

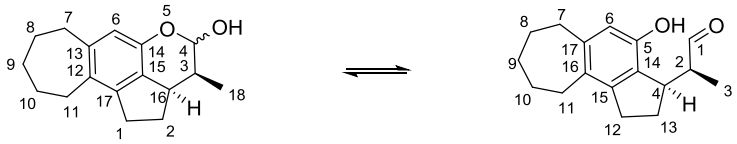
(2*S*,3*S*,4*S*)-4-((*R*)-4-hydroxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-3-yl)pentane-2,3-diol (215b)



R_f 0.15 (Pet. Ether/ EtOAc (7:3)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.47 (1H, s, H5), 4.58 (2H, br s, OH), 3.74 (1H, dq, *J* = 8.3, 6.2 Hz, H17), 3.58 (1H, dd, *J* = 8.3, 2.2 Hz, H16), 3.36 (1H, ddd, *J* = 8.9, 3.2, 2.2, H3), 2.87 (1H, dt, *J* = 16.5, 8.4, H1), 2.80-2.56 (5H, m, H1, H6 and H10), 2.36 (1H, dq, *J* = 12.7, 8.9 Hz, H2), 1.96 (1H, qt, *J* = 7.2, 2.2 Hz, H15), 1.85 (2H, m, H2 and H8), 1.80-1.60 (3H, m, H8, H7 and H9), 1.57 (2H, m, H7 and H9), 1.22 (3H, d, *J* = 6.2 Hz, H18), 0.72 (3H, d, *J* = 7.3 Hz, H19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.2 (C4), 145.0 (C12), 144.2 (C14), 130.7 (C11), 126.7 (C13), 115.8 (C5), 81.3 (C16), 69.6 (C17), 47.3 (C3),

40.5 (C15), 36.4 (C6), 35.8 (C2), 33.0 (C8), 31.3 (C10), 31.2 (C1), 28.7 (C7), 28.3 (C9), 19.9 (C18), 9.7 (C19).

Equilibrium mixture of lactols (2a*R*,3*S*)-3-Methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromen-4-ol and aldehyde (S)-2-((R)-4-hydroxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[e]inden-3-yl)propanal (181)

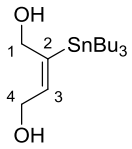


To a stirred solution of diols **215** (33.7 mg, 0.111 mmol, 1.0 equiv.) in dichloromethane (1.7 mL) at 0 °C was added 10 wt% sodium periodate on silica (308 mg, 0.144 mmol, 1.3 equiv.).[167] The suspension was stirred for a further 15 min at 0 °C before being loaded onto a short plug of silica and purified by flash column chromatography (9:1 Pet. Ether/ Et_2O), then concentrated to yield lactol **181** (27.9 mg, 98%, as a 63:13:24 inseparable mixture of epimers and open-chain aldehyde form) as a colourless oil. The data for this mixture of compounds was identical to that recorded for **181** derived from Johnson-Lemieux-Jin protocol (see above).

7.4. Procedures and Characterisations for Synthesis of the AB Rings

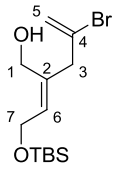
7.4.1. Synthesis of the AB bromoene rings

(*E*)-2-(Tributylstannyl)but-2-ene-1,4-diol



To a stirred solution of but-2-yne-1,4-diol (1.30 g, 15.1 mmol, 1.0 equiv.) in dry THF (45 mL) under argon was added $PdCl_2(PPh_3)_2$ (212 mg, 0.30 mmol, 2 mol%). Tributyltin hydride (4.9 mL, 18.1 mmol, 1.2 equiv.) was added slowly, and the reaction mixture was stirred for 20 min. The solvent was then removed *in vacuo,* and the residue was purified by flash chromatography (4:1→1:1 Pet. Ether / EtOAc) to afford (*E*)-2-(tributylstannyl)but-2-ene-1,4-diol (4.80 g, 12.7 mmol, 84%) as light brown oil. **R_f** 0.43 (1:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3330 (br, OH), 2956 (s), 2924 (s), 2871 (s), 2853 (s), 1614 (w, C=C), 1462 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.79 (1H, tt, J_{HH} = 5.9 and 2.1 Hz; J_{SnH} = 66.7 Hz, H3), 4.38 (2H, m; J_{SnH} = 36.3 Hz, H1), 4.20 (2H, *app* t, *J* = 5.4 Hz, H4), 1.74 (1H, t, *J* = 4.9 Hz, OH), 1.65 (1H, t, *J* = 4.7 Hz, OH), 1.53-1.27 (12H, m, $SnCH_2C\underline{H}_2C\underline{H}_2CH_3$, OH), 0.96-0.85 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 149.4, 138.2, 63.6, 59.8, 29.3, 27.5, 13.8, 10.1; **HRMS** (ESI^+) calc. for $C_{16}H_{34}O_2SnNa$ $[M+Na]^+$ 401.1473, found 401.1476. Data in accordance with literature.[169]

(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-(tributylstannyl)but-2-en-1-ol (219)



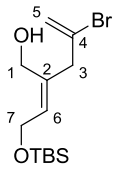
To a stirred solution of (*E*)-2-(tributylstannyl)but-2-ene-1,4-diol (13.9 g, 36.8 mmol, 1.0 equiv.) in dry DMF (77 mL) under argon at 0°C was added imidazole (2.51 g, 36.8 mmol, 1.0 equiv.) and TBSCl (5.54 g, 36.8 mmol, 1 equiv.). The reaction mixture was stirred for 60 min, then it was quenched with water. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (10:1 Pet. Ether / EtOAc) to yield stannane **219** (15.0 g, 30.5 mmol, 83%) as a light brown oil. **R_f** 0.57 (4:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3443 (br, O-H), 2956 (s), 2928 (s), 2856 (s), 1930 (w), 1614 (w, C=C), 1463 (s), 1256 (s), 1079 (s), 837 (s). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.70 (1H, tt, J = 5.4 and 2.1 Hz; J_{SnH} = 68.2 Hz, H3) 4.34 (2H, br d with unresolved fine coupling, J = 5.5; J_{SnH} = 37.0 Hz, H1), 4.25–4.16 (2H, m, H4) 1.81 (1H, t, J = 5.4 Hz, OH), 1.55-1.46 (6H, m, $SnCH_2C\underline{H}_2CH_2CH_3$), 1.37-1.27 (6H, m, $SnCH_2CH_2C\underline{H}_2CH_3$), 0.94–0.85 (15H, m, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$ and Si*t*-Bu), 0.09 (6H, s, $SiMe_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.1, 139.0, 63.9, 60.9, 29.3, 27.5, 26.0, 13.8, 10.1, –5.0; **HRMS** (ESI^+) calc. for $C_{22}H_{48}O_2SiSnNa$ $[M+Na]^+$ 515.2338; found 515.2341. Data in accordance with literature.[98]

(*Z*)-4-Bromo-2-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)pent-4-en-1-ol (221) and (2*Z*,5*Z*)-2,5-bis(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)-3-methylenehexane-1,6-diol (222)

To a stirred solution of stannane 2**19** (5.00 g, 8.14 mmol, 1.0 equiv.) in dry degassed toluene (61 mL) under argon was added $Pd(dba)_2$ (187 mg, 0.33 mmol, 4 mol%). The solution was degassed (Ar purge) for a further 30 min, then 2,3-dibromopropene **220** (2.40 mL, 24.4

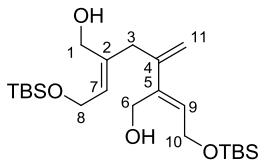
mmol, 3.0 equiv.) was added and the reaction was heated to 70°C overnight. The reaction was cooled to RT, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 Pet. Ether / EtOAc) to afford **221** (1.46 g, 4.54 mmol, 56%) as yellow oil, along with byproduct **222** (724 mg, 1.71 mmol, 21%) as a light yellow oil.

(*Z*)-4-Bromo-2-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)pent-4-en-1-ol (221)



R_f 0.30 (4:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3377 (br, O-H), 2930 (s), 2857 (s), 1626 (w, C=C), 1471 (s), 1100 (s), 1061 (s), 836 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.69 (1H, *app* q, *J* = 1.3 Hz, H6), 5.65 (1H, t, *J* = 6.1 Hz, H2), 5.52 (1H, d, *J* = 1.6 Hz, H6), 4.29 (2H, d, *J* = 6.1 Hz, H1), 4.14 (2H, s, H7), 3.25 (2H, s, H4), 2.20 (1H, s, OH), 0.91 (9H, s, Si*t*-Bu), 0.10 (6H, s, $SiMe_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 137.5, 131.8, 131.0, 118.9, 60.1, 59.6, 47.7, 26.0, 18.4, –5.1; **HRMS** (ESI^+) calc. for $C_{13}H_{25}O_2BrSiNa$ $[M+Na]^+$ 343.0699; found 343.0697. Data in accordance with literature.[98]

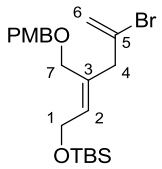
(2*Z*,5*Z*)-2,5-bis(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)-3-methylenehexane-1,6-diol (222)



R_f 0.07 (4:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3378 (br, OH), 3085 (m), 3052 (s), 2955 (s), 2930 (s), 2885 (s), 2857 (s), 2306 (w), 1720 (m), 1606 (m), 1472 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.83 (1H, t, *J* = 6.3 Hz, H9), 5.56 (1H, t, *J* = 6.3 Hz, H7), 5.29 (1H, d, *J* = 0.8 Hz, H11), 5.06 (1H, d, *J* = 0.8 Hz, H11), 4.32 (2H, d, *J* = 6.3 Hz, H10), 4.29 (2H, s, H6), 4.24 (2H, d, *J* = 6.3 Hz, H8), 4.09 (2H, s, H1), 3.10 (2H, s, H3), 2.48 (1H, s, OH), 1.63 (1H, s, OH), 0.90 (9H, s, Si*t*-Bu), 0.89 (9H, s, Si*t*-Bu), 0.08 (6H, s, $SiMe_2$), 0.07 (6H, s, $SiMe_2$); **^{13}C NMR**

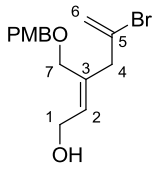
(126 MHz, $CDCl_3$) δ_C 144.9, 141.0, 140.1, 130.1, 129.3, 115.1, 60.6, 59.9, 59.6, 58.9, 41.0, 26.0 (2C), 18.4 (2C), –5.0, –5.1; **HRMS** calc. for $C_{23}H_{46}O_4SiNa$ $[M+Na]^+$ 465.2827; found 465.2826. Data in accordance with literature.[98]

(*Z*)-((5-Bromo-3-(((4-methoxybenzyl)oxy)methyl)hexa-2,5-dien-1-yl)oxy)(*tert*-butyl)dimethylsilane



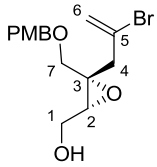
To a stirred solution of alcohol **221** (1.82 g, 5.67 mmol, 1 equiv.) in toluene (115 mL) under argon was added PMBTCA (2.40 g, 8.50 mmol, 1.5 equiv.) and $Sc(OTf)_3$ (139 mg, 0.28 mmol, 5 mol%). After stirring for 5 min, sat. $NaHCO_3$ solution (50 mL) was added and the layers were separated. The aqueous layer was extracted three times with diethyl ether (50 mL × 3), the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 Pet. Ether / EtOAc) to yield the title PMB ether (2.50 g, 5.66 mmol, 100%) as light yellow oil. $\mathbf{R_f}$ 0.52 (4:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 2954 (s), 2932 (s), 2903 (s), 2856 (s), 1738 (m), 1613 (s), 1586 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, Ar), 6.87 (2H, d, *J* = 8.5 Hz, Ar), 5.65 (1H, t, *J* = 6.2 Hz, H2), 5.62 (1H, d, *J* = 1.3 Hz, H6), 5.48 (1H, d, *J* = 1.3 Hz, H6), 4.38 (2H, s, C$\underline{H}_2$Ar), 4.23 (2H, d, *J* = 6.2 Hz, H1), 3.97 (2H, s, H7), 3.80 (3H, s, OMe), 3.23 (2H, s, H4), 0.89 (9H, s, Si*t*-Bu), 0.06 (6H, s, $SiMe_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 159.3, 133.1, 132.7, 131.7, 130.4, 129.5, 118.8, 113.9, 71.9, 65.9, 59.7, 55.4, 46.9, 26.0, 18.4, –4.9; **HRMS** (ESI^+) calc. for $C_{21}H_{33}O_3BrSiNa$ $[M+Na]^+$ 463.1275; found 463.1274. Data in accordance with literature.[98]

(*Z*)-5-Bromo-3-(((4-methoxybenzyl)oxy)methyl)hexa-2,5-dien-1-ol (218)



To a stirred solution of the above TBS ether (3.71 g, 8.40 mmol, 1.0 equiv.) in methanol (210 mL) was added camphorsulfonic acid (195 mg, 0.84 mmol, 0.1 equiv.). The reaction mixture was stirred for 20 min, then Et_3N (116 µL, 0.84 mmol, 0.1 equiv.) was added and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 Pet. Ether / EtOAc) to afford alcohol **218** (2.15 g, 6.57 mmol, 78%) as a light yellow oil. $\mathbf{R_f}$ 0.43 (1:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3406 (br, OH), 2909 (s), 2862 (s), 2837 (s), 1625 (s), 1612 (s), 1513 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.7 Hz, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 5.79 (1H, t, *J* = 6.8 Hz, H2), 5.62 (1H, d, *J* = 1.5 Hz, H6), 5.49 (1H, d, *J* = 1.5 Hz, H6), 4.42 (2H, s, C$\underline{H_2}$Ar), 4.18 (2H, d, *J* = 6.4 Hz, H1), 4.00 (2H, s, H7), 3.80 (3H, s, OMe), 3.23 (2H, s, H4), 1.78 (1H, t, *J* = 5.9 Hz, OH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 159.4, 135.4, 132.0, 131.3, 129.9, 129.6, 119.1, 114.0, 72.3, 66.3, 58.9, 55.4, 47.5; **HRMS** (ESI^+) calc. for $C_{15}H_{19}O_3BrNa$ $[M+Na]^+$ 349.0410; found 349.0406. Data in accordance with literature.[98]

((2*R*,3*S*)-3-(2-Bromoallyl)-3-((4-methoxybenzyloxy)methyl)oxiran-2-yl)methanol (118)



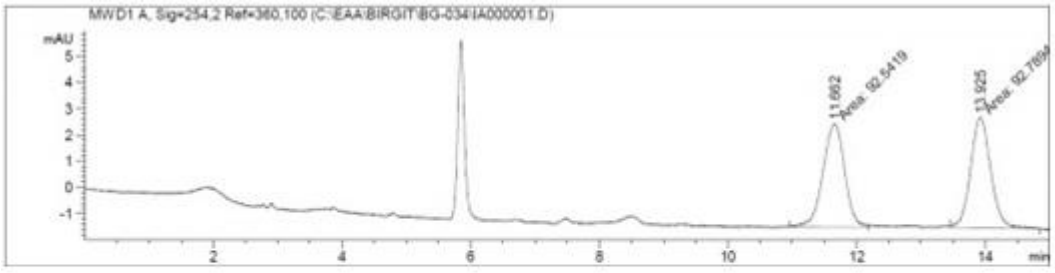
Activated 4 Å molecular sieves (645 mg, 30 w/w%) were heated under vacuum for 5 min in a Schlenk tube and cooled down under argon. Dichloromethane (20 mL) and Ti(O*i*-Pr)$_4$ (2.00 mL, 6.57 mmol, 1.0 equiv.) was added and the solution was cooled to –30°C, then D-(–)-diethyl tartrate (1.40 mL, 7.88 mmol, 1.2 equiv.) was added dropwise.[192] After stirring the reaction mixture for 30 min at –30 °C, a solution of **218** (2.15 g, 6.57 mmol, 1.0 equiv.) in dichloromethane (7 mL) was added dropwise, followed again by stirring for 30 min at –30 °C.

Tert-butyl hydroperoxide (5.5 M in hexanes, 3.60 mL, 19.7 mmol, 3.0 equiv.) was added dropwise and the reaction flask was placed in a freezer at –20 °C. After 19 h the reaction was cooled down to –30 °C and a solution of tartaric acid (2.96 g, 19.7 mmol, 3 equiv.) and $FeSO_4$•7H_2O (16.4 g, 59.1 mmol, 9.0 equiv.) in water (20 mL) was poured in with vigorous stirring of the reaction mixture. After warming slowly to RT (~1 h), some water (10 mL) was added, the layers were separated and the aqueous layer was extracted three times with dichloromethane (25 mL × 3). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Et_2O (26 mL) was added to the crude product, which was cooled to 0 °C, then a solution of NaOH (0.75 M in brine, 32 mL) was added dropwise. After stirring for 1.5 h at 0 °C, water (10 mL) was added, the layers were separated and the aqueous layer was extracted three times with Et_2O (40 mL × 3). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 Pet. Ether / EtOAc) to afford epoxide **118** (2.19 g, 6.38 mmol, 97%) as highly viscous yellow oil. **R_f** 0.38 (1:1 Pet. Ether / EtOAc); **$[\alpha]_D^{25}$** +9.3 (c 1.04, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3454 (br, OH), 3053 (m), 2962 (s), 2906 (s), 1612 (m), 1513 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 (2H, d, *J* = 8.5 Hz, Ar), 6.87 (2H, d, *J* = 8.5 Hz, Ar), 5.68 (1H, s, H6), 5.53 (1H, d, *J* = 1.3 Hz, H6), 4.50 (1H, d, *J* = 11.4 Hz, CH_2Ar), 4.40 (1H, d, *J* = 11.4 Hz, CH_2Ar), 3.79 (3H, s, OMe), 3.72-3.66 (2H, m, H1), 3.61 (1H, d, *J* = 10.9 Hz, H7), 3.59 (1H, d, *J* = 10.9 Hz, H7), 3.19 (1H, t, *J* = 5.8 Hz, H2), 3.02 (1H, d, *J* = 14.9 Hz, H4), 2.60 (1H, d, *J* = 14.9 Hz, H4), 2.32-2.27 (1H, m, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 129.7, 129.5, 127.8, 120.8, 114.1, 73.3, 69.1, 61.5, 61.0, 60.9, 55.4, 45.9; **HRMS** (ESI^+) calc. for $C_{15}H_{19}O_4BrNa$ $[M+Na]^+$ 365.0359; found 365.0360. Data in accordance with literature.[98]

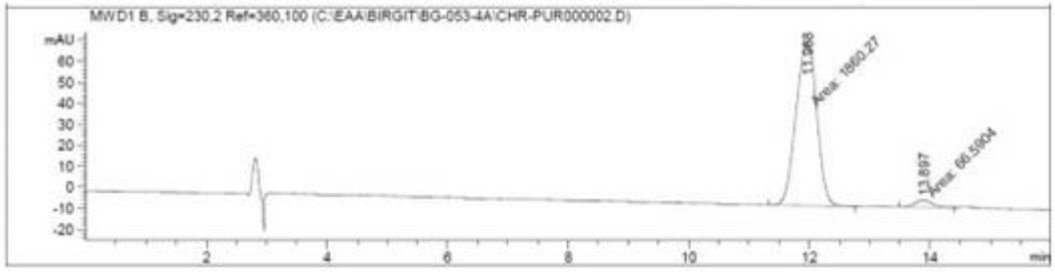
ee: 93% as determined by chiral HPLC: CHIRALPAK IA, 5 mL/min, 10% IPA/hexane; t_R (2*R*,3*S*) = 12.14 min, t_R (2*S*,3*R*) = 13.53 min.

Preparation of ***rac*-118**: To a stirred solution of **218** (135 mg, 0.42 mmol, 1.0 equiv.) in dichloromethane (8 mL) at 0 °C was added *m*-CPBA (70 wt% in water, 254 mg, 1.03 mmol, 2.5 equiv.). The reaction was warmed to RT and stirred for 4 h, before being quenched with

$NaHCO_3$ (8 mL, sat. *aq.*). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were then washed with $Na_2S_2O_3$ (2 x 5 mL, sat. *aq.*) before being dried ($MgSO_4$) and concentrated, to yield epoxide ***rac*-118** (134 mg 0.39 mmol, 94%) as a colourless oil. Data identical to the epoxide **(+)-118** prepared using Sharpless AE.

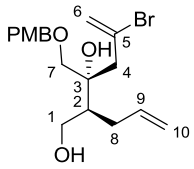


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.662	FM	0.3907	92.54185	3.94794	49.9332
2	13.925	FM	0.3665	92.78944	4.21927	50.0668
Totals :				185.33129	8.16721	



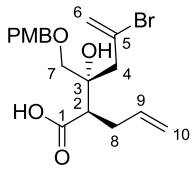
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.968	MM	0.3974	1860.26794	78.02112	96.5441
2	13.897	MM	0.3303	66.59045	3.36038	3.4559
Totals :				1926.85839	81.38150	

(2*S*,3*R*)-2-Allyl-5-bromo-3-((4-methoxybenzyloxy)methyl)hex-5-ene-1,3-diol (223)



To a stirred solution of epoxide **118** (1.08 g, 3.15 mmol, 1.0 equiv.) in THF (31 mL) at 0 °C was added allylmagnesium chloride (1.7 M in THF, 7.40 mL, 12.6 mmol, 4.0 equiv.) dropwise. The reaction mixture was stirred for 10 min, then it was quenched with NH_4Cl (2 mL, sat. *aq.*). The resulting suspension was filtered through a pad of celite, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on (1:1 Pet. Ether / EtOAc) to afford diol **223** (1.14 g, 2.96 mmol, 94%) as a slightly yellow, highly viscous oil. $\mathbf{R_f}$ 0.47 (1:1 Pet. Ether / EtOAc); $\mathbf{[\alpha]_D^{25}}$ –4.9 (*c* 1.05, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3531 (br, OH), 3054 (s), 2985 (s), 2936 (s), 2305 (m), 1613 (s), 1514 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.5 Hz, Ar), 6.89 (2H, d, *J* = 8.5 Hz, Ar), 5.83-5.73 (1H, m, H9), 5.71 (1H, s, H6), 5.63 (1 H, s, H6), 5.05 (1H, d, *J* = 16.9 Hz, H10), 5.03 (1H, d, *J* = 11.6 Hz, H10), 4.49 (1H, d, *J* = 11.6 Hz, CH_2Ar), 4.48 (1H, d, *J* = 11.6 Hz, CH_2Ar), 3.81 (3H, s, OMe), 3.82-3.77 (1H, m, H1), 3.74-3.69 (1H, m, H1), 3.53 (1H, d, *J* = 9.3 Hz, H7), 3.43 (1H, d, *J* = 9.3 Hz, H7), 3.13 (1H, s, OH-3), 3.10-3.07 (1H, m, H2), 2.91 (1H, d, *J* = 15.0 Hz, H4), 2.81 (1H, d, *J* = 15.0 Hz, H4), 2.25-2.16 (1H, m, H8), 2.02-1.93 (2H, m, H8 and OH-1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 159.5, 137.1, 129.6, 129.5, 127.5, 121.9, 116.7, 114.0, 77.0, 73.3, 72.0, 61.6, 55.4, 47.3, 45.0, 30.8; **HRMS** (ESI^+) calc. for $C_{18}H_{25}O_4BrNa$ $[M+Na]^+$ 407.0828; found 407.0827. Data in accordance with literature.[98]

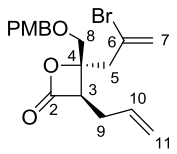
(2*R*,3*R*)-2-Allyl-5-bromo-3-hydroxy-3-(((4-methoxybenzyl)oxy)methyl)hex-5-enoic acid (228)



To a stirred solution of alcohol **223** (1.02 g, 2.65 mmol, 1.0 equiv.) in dichloromethane (80 mL) was added $NaHCO_3$ (222 mg, 2.52 mmol, 0.95 equiv.), followed by Dess-Martin periodinane (1.69 g, 3.40 mmol, 1.5 equiv.). The reaction mixture was stirred for 1 h, then it was quenched with $NaHCO_3$ (40 mL, sat. *aq.*) and $Na_2S_2O_3$ (40 mL, sat. *aq.*). The mixture was stirred vigorously until the layers became clear (~15 min). The layers were then separated, and the aqueous layer was extracted three times with dichloromethane (70 mL × 3). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was used without purification in the following Pinnick oxidation. The crude aldehyde (2.65 mmol, 1 equiv.) was dissolved in *t*-BuOH (40 mL) and 2-methyl-2-butene (8.4 mL, 79.5 mmol, 30 equiv.) was added. Into the reaction mixture was poured a solution of sodium chlorite (80%, 2.99 g, 26.5 mmol, 10 equiv.) and NaH_2PO_4 (3.38 g, 21.2 mmol, 8 equiv.) in water (16 mL). After stirring overnight, the reaction was diluted with brine, and the layers were separated. The aqueous layer was extracted four times with EtOAc. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 Pet. Ether / EtOAc) to yield acid **228** (1.06 g, 2.65 mmol, 100%) as a colourless highly viscous oil. $\mathbf{R_f}$ 0.35 (1:1 Pet. Ether / EtOAc); $\mathbf{[\alpha]_D^{25}}$ –2.1 (c 1.04, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3412 (br, OH), 3077 (s), 2979 (s), 2957 (s), 2933 (s), 2874 (s), 1707 (s), 1613 (s), 1514 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.24 (2H, d, *J* = 9.1 Hz, Ar), 6.88 (2H, d, *J* = 9.1 Hz, Ar), 5.80-5.71 (1H, m, H9), 5.70 (1 H, s, H6), 5.63 (1H, d, *J* = 1.5 Hz, H6), 5.09 (1 H, dd, *J* = 17.0 and 1.5 Hz, H10), 5.03 (1H, d, *J* = 10.2 Hz, H10), 4.48 (1H, d, *J* = 11.7 Hz, CH_2Ar), 4.42 (1H, d, *J* = 11.7 Hz, CH_2Ar), 3.80 (3H, s, OMe), 3.57 (1H, d, *J* = 9.4 Hz, H7), 3.46 (1H, d, *J* = 9.4 Hz, H7), 3.19 (1H, s, OH), 2.99 (1H,

d, *J* = 14.9 Hz, H4), 2.91-2.88 (1H, m, H2), 2.72 (1H, d, *J* = 14.9 Hz, H4), 2.40-2.37 (2H, m, H8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 177.6, 159.4, 134.9, 129.6, 129.5, 126.4, 122.3, 117.3, 113.8, 74.3, 73.0, 70.9, 55.3, 51.0, 46.6, 31.1; **HRMS** (ESI^+) calc. for $C_{18}H_{23}O_5BrNa$ $[M+Na]^+$ 421.0621; found 421.0623. Data in accordance with literature.[98]

(3*R*,4*R*)-3-Allyl-4-(2-bromoallyl)-4-((4-methoxybenzyloxy)methyl)oxetan-2-one (230)

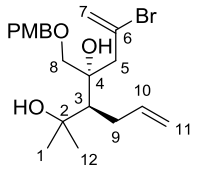


To a stirred solution of acid **228** (2.46 g, 6.15 mmol, 1 equiv.) in dry acetonitrile (50 mL) was added dry pyridine (37 mL) and *bis*-(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP-Cl) (4.70 g, 18.5 mmol, 3.0 equiv.). The reaction mixture was stirred for 2.5 h before it was quenched with water. The layers were separated and the aqueous layer was extracted four times with EtOAc. The combined organic layers were dried with (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 Pet. Ether / EtOAc) to yield lactone **230** (1.95 g, 5.11 mmol, 83%) as light yellow oil. **R_f** 0.66 (1:1 Pet. Ether / EtOAc); **$[\alpha]_D^{25}$** –2.7 (c 1.05, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3418 (br, OH), 3079 (m), 2918 (s), 2851 (s), 2358 (w), 2254 (m), 1835 (s), 1722 (m), 1612 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.24 (2 H, d, *J* = 8.6 Hz, ArH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 5.88-5.80 (1H, m, H10), 5.77 (1H, s, H7), 5.65 (1H, d, *J* = 1.7 Hz, H7), 5.13 (1H, ddd, *J* = 17.1, 2.8 and 1.5 Hz, H11), 5.09 (1H, dq, *J* = 10.2, 2.6 and 1.5 Hz, H11), 4.52 (1H, d, *J* = 11.6 Hz, CH_2Ar), 4.49 (1H, d, *J* = 11.6 Hz, CH_2Ar), 3.81 (3H, s, OMe), 3.77-3.69 (3H, m, 2 x H8 and H3), 3.21 (1H, d, *J* = 14.9 Hz, H5), 2.93 (1H, d, *J* = 14.9 Hz, H5), 2.60-2.49 (2H, m, H9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 170.0, 159.5, 134.0, 129.6, 129.4, 125.0, 123.0, 117.6, 114.0, 80.5, 73.6, 69.3, 56.1, 55.4, 46.4, 28.3; **HRMS** (ESI^+) calc. for $C_{18}H_{21}O_4BrNa$ $[M+Na]^+$ 403.0515; found 403.0512.

(3*S*,4*R*)-3-Allyl-6-bromo-4-((4-methoxybenzyloxy)methyl)-2-methylhept-6-ene-2,4-diol (119) and (4*R*)-3-Allyl-6-bromo-4-hydroxy-4-((4-methoxybenzyloxy)methyl)hept-6-en-2-one (226)

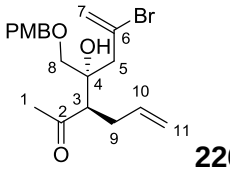
To a stirred solution of **25** (400 mg, 1.05 mmol, 1 equiv.) in THF (10.5 mL) at –50°C was added dropwise MeMgBr (3 M in Et_2O, 2.1 mL, 6.30 mmol, 6.0 equiv.). The reaction mixture was warmed slowly to RT (6 h) and was then quenched with NH_4Cl (1 mL, sat. *aq.*). The resulting suspension was filtered through a pad of celite, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (10:1→4:1 Pet. Ether / EtOAc) to yield tertiary alcohol **119** (300 mg, 0.73 mmol, 69%) as colourless oil, along with the ketone **226** (86 mg, 21%, mixture of C3-epimers, ratio of **226** : **3-*epi*-226** = 72:28) as a light yellow oil.

(3*S*,4*R*)-3-Allyl-6-bromo-4-((4-methoxybenzyloxy)methyl)-2-methylhept-6-ene-2,4-diol (119)

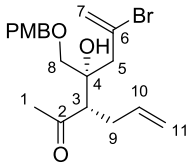


R_f 0.58 (1:1 Pet. Ether/ EtOAc); **$[\alpha]_D^{25}$** –20.4 (c 1.01, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}) 3358 (br, OH), 3074 (m), 2972 (s), 2934 (s), 2873 (s), 2836 (s), 1613 (s), 1513 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.6 Hz, Ar), 6.89 (2H, d, *J* = 8.6 Hz, Ar), 5.85-5.77 (1H, m, H10), 5.75 (1H, s, H7), 5.63 (1H, d, *J* = 1.4 Hz, H7), 5.00-4.95 (2H, m, H11), 4.51 (1H, d, *J* = 11.3 Hz, CH_2Ar), 4.46 (1H, d, *J* = 11.3 Hz, CH_2Ar), 4.22 (1H, br, OH), 3.81 (3H, s, OMe), 3.80 (1H, d, *J* = 9.3 Hz, H8), 3.53 (1H, d, *J* = 9.3 Hz, H8), 2.94 (1H, d, *J* = 15.1 Hz, H5), 2.72 (1H, d, *J* = 15.1 Hz, H5), 2.18-2.04 (3H, m, H3 and H9), 1.26 (3H, s, H1), 1.23 (3H, s, H12); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 159.5, 139.6, 129.6, 129.5, 127.8, 121.8, 115.4, 114.0, 78.1, 74.9, 73.3, 72.3, 55.4, 52.9, 49.7, 32.5, 32.2, 26.8; **HRMS** (ESI^+) calc. for $C_{20}H_{29}O_4BrNa$ $[M+Na]^+$ 435.1141; found 435.1130.

(3*R*,4*R*)-3-Allyl-6-bromo-4-hydroxy-4-(((4-methoxybenzyl)oxy)methyl)hept-6-en-2-one (226) and (3*S*,4*R*)-3-Allyl-6-bromo-4-hydroxy-4-(((4-methoxybenzyl)oxy)methyl)hept-6-en-2-one (3-*epi*-226)



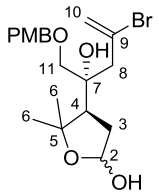
226



3-*epi*-226

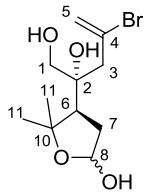
The data here is reported as a 72:28 mixture of C3-diastereoisomers (major = * = **226**; minor = no* = **3-*epi*-226**); **R_f** 0.67 (1:1 Pet. Ether/ EtOAc); **IR** (thin film, v_{max} / cm^{-1}) 3531 (br, OH), 3054 (s), 2985 (s), 2936 (s), 2305 (m), 1613 (s), 1514 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.23-7.21 (4H, m, H*$_{Ar}$ and H_{Ar}), 6.88-6.86 (4H, m, H*$_{Ar}$ and H_{Ar}), 5.73-5.74 (4H, m, H10*, H7*, H10 and H7), 5.60 (1H, d, *J* = 1.5 Hz, H7*), 5.59 (1H, d, *J* = 1.3 Hz, H7), 5.05-4.97 (4H, m, H11* and H11), 4.47-4.37 (4H, m, CH_2*Ar and CH_2Ar), 3.79 (6H, s, OCH_3* and OCH_3), 3.55 (1H, s, OH), 3.53-3.44 (2H, m, H8* and H8), 3.38 (1H, d, *J* = 9.4 Hz, H8*), 3.34 (1H, *J* = 9.6 Hz, H8), 3.25 (1H, s, OH*), 3.09 (1H, dd, *J* = 9.5 and 5.0 Hz, H3*), 3.05 (1H, dd, *J* = 9.8 and 5.0 Hz, H3), 2.96 (1H, d, *J* = 14.9 Hz, H5*), 2.84 (1H, d, *J* = 14.7 Hz, H5), 2.69 (1H, d, *J* = 14.7 Hz, H5), 2.65 (1H, d, *J* = 14.9 Hz, H5*), 2.40-2.24 (4H, m, H9* and H9), 2.17 (3H, s, H1*), 2.12 (3H, s, H1); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 214.6 (C2), 213.6 (C2*), 159.4 (C_{Ar}* and C_{Ar}), 135.4 (C_{Ar}* and C_{Ar}), 135.2 (C10*), 129.8 (C_{Ar}* and C_{Ar}), 129.7 (C-10), 129.6 (C_{Ar}* and C_{Ar}), 127.2 (C6*), 127.0 (C6), 122.1 (C7), 121.9 (C7*), 117.5 (C11), 117.2 (C11*), 113.9 (C_{Ar}*) 113.8 (C_{Ar}), 75.2 (C4*), 73.5 (C8), 73.1 (C4), 73.0 ($C_{Ar}\underline{C}H_2$* and $C_{Ar}\underline{C}H_2$), 71.3 (C8*), 55.6 (C3*), 55.3 (OCH_3* and OCH_3), 55.1 (C3), 46.7 (C5*) 45.9 (C5), 34.3 (C1*) 33.9 (C1), 31.8 (C9), 31.6 (C9*); **HRMS** (ESI^+) calc. for $C_{19}H_{25}O_4BrNa$ $[M+Na]^+$ 419.0828; found 419.0827.

(4*R*)-4-((*R*)-4-bromo-2-hydroxy-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)-5,5-dimethyltetrahydrofuran-2-ol (235)



To a stirred solution of alkene **226** (150 mg, 0.363 mmol, 1.0 equiv.) in 1,4-dioxane (3.9 mL) and water (0.9 mL) was sequentially added 2,6-lutidine (87 µL, 0.726 mmol, 2.0 equiv.), osmium(VII) tetroxide (2.5% wt in *tert*-butanol, 90 µL, 0.0073 mmol, 0.02 equiv.) and sodium periodate (309 mg, 1.45 mmol, 4.0 equiv.).[153] The reaction mixture was stirred at RT for 2 h before being diluted with water (4 mL) and diethyl ether (5 mL). The layers were separated and the aqueous layer extracted three times with diethyl ether (5 mL × 3). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was filtered through a short plug of silica (7:3 Pet. Ether/ EtOAc), then concentrated to yield lactol **235** (147 mg, 97%, inseparable mixture of epimers and some regional isomers) as a colourless oil, which was used in the next step without further purification. $\mathbf{R_f}$ 0.36 (Pet. Ether/ EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3422 (br), 2932 (m), 1613 (m), 1514 (s), 1463 (m), 1368 (m), 1249 (2), 1090 (s), 1034 (s), 818 (m); **HRMS** (ESI^+) calc. for $C_{19}H_{27}O_5BrNa$ $[M+Na]^+$ 437.0934, found 437.0921.

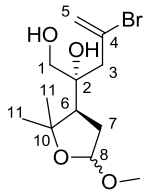
(*2R*)-4-Bromo-2-((3*R*)-5-hydroxy-2,2-dimethyltetrahydrofuran-3-yl)pent-4-ene-1,2-diol (236)



To a stirred solution of PMB ether **235** (147 mg, 0.354 mmol) in dichloromethane (18 mL) at 0 °C was added TFA (2.0 mL) dropwise. The reaction mixture was stirred for 15 min at 0 °C

before being quenched with $NaHCO_3$ solution (10 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (15 mL × 3). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (7:3 Pet. Ether/ EtOAc), to yield diol **236** (79.8 mg, 76%) as a colourless oil. $\mathbf{R_f}$ 0.54 (Pet. Ether/ EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3428 (br), 2927 (m), 1738 (w), 1624 (m), 1468 (m), 1292 (m), 1119 (m), 1089 (s), 1030 (s), 881 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.76 (1H, t, *J* = 1.6 Hz, H5), 5.70 (1H, d, *J* = 1.6 Hz, H5), 5.28 (1H, d, *J* = 3.2 Hz, H8), 4.01 (1H, d, *J* = 11.3 Hz, H1), 3.75 (1H, br s, OH), 3.53 (1H, d, *J* = 11.3 Hz, H1), 3.23 (1H, d, *J* = 15.1 Hz, H3), 2.75 (1H, dd, *J* = 15.1, 1.0 Hz, H3), 2.39 (1H, s, OH), 2.24 (1H, ddd, *J* = 12.6, 5.0, 3.2 Hz, H7), 2.17 (1H, d, *J* = 5.0 Hz, H6), 1.89 (1H, d, *J* = 12.6 Hz, H7), 1.69 (3H, s, H11), 1.28 (3H, s, H11); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 127.6 (×, C-4), 122.5 (–, C-5), 98.3 (+, C-8), 84.2 (×, C-10), 72.4 (×, C-2), 68.4 (–, C-1), 50.9 (–, C-3), 48.4 (+, C-6), 36.0 (–, C-7), 30.5 (+, C-11), 25.0 (+, C-11); **HRMS** (FI^+) Mass not found. Characterization of **237** confirms identity of this compound.

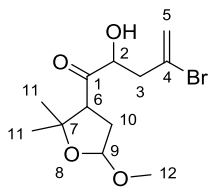
(2*R*)-4-Bromo-2-((3*R*)-5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)pent-4-ene-1,2-diol (237)



To a stirred solution of the lactols **236** (76 mg, 0.258 mmol, 1.0 equiv.) in methanol (9.4 mL) was added PPTS (2.5 mg, 0.0103 mmol, 0.04 equiv.). The reaction mixture was heated at reflux for 5 h, then cooled to RT and quenched with $NaHCO_3$ (1 mL, sat. *aq.*). The solvent was removed carefully *in vacuo*, and the residue was diluted with Et_2O. Water was added (5 mL), the layers separated and the aqueous layer extracted three times with Et_2O (5 mL × 3). The combined organic layers were dried with $MgSO_4$, and concentrated. The crude product

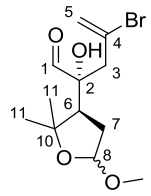
was purified by flash chromatography using a short plug of SiO_2 (7:3→3:2 Pet. Ether / EtOAc), to yield the methyl acetals **237** (56 mg, 0.181 mmol, 70%, as a 62:38 mixture of acetal epimers) as a colourless oil, together with recovered lactol starting material (23 mg, 0.078 mmol, 29%). These anomers were generally not readily separated by chromatography, and they were generally carried forward bromoene AB rings **104**; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.37 (Pet. Ether/ EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3455 (br), 2971 (m), 1739 (m), 1625 (m), 1371 (m), 1229 (m), 1103 (m), 1042 (s), 979 (m); **HRMS** (ESI^+) calc. for $C_{12}H_{21}O_4BrNa$ $[M+Na]^+$ 331.0508; found 331.0515. **Major epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.77 (1H, br s, H5), 5.68 (1H, d, *J* = 1.3 Hz, H5), 4.86 (1H, d, *J* = 5.0 Hz, H8), 3.65 (1H, dd, *J* = 18.0 and 11.0 Hz, H1), 3.58-3.51 (1H, m, H1), 3.31 (3H, s, OCH_3), 2.93 (1H, d, *J* = 14.8 Hz, H3), 2.84 (1H, d, *J* = 14.8 Hz, H3), 2.48 (1H, dd, *J* = 12.6 and 6.6 Hz, H6), 2.40 (1H, s, OH), 2.18 (1H, *app* td, *J* = 12.6 and 5.0 Hz, H7), 1.96 (1H, dd, *J* = 12.6 and 6.6 Hz, H7), 1.43 (3H, s, H11), 1.32 (3H, s, H11'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 127.6, 122.4, 102.0, 83.7, 74.4, 66.0, 54.2, 50.1, 47.3, 34.6, 32.7, 25.8. **Minor epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.77 (1H, br s, H5), 5.67 (1H, d, *J* = 1.3 Hz, H5), 4.94 (1H, dd, *J* = 6.1 and 3.9 Hz, H8), 3.65 (1H, dd, *J* = 18.0 and 11.0 Hz, H1), 3.58-3.51 (1H, m, H1), 3.35 (3H, s, OCH_3), 2.89 (1H, d, *J* = 14.8 Hz, H3), 2.85 (1H, d, *J* = 14.8 Hz, H3), 2.67 (1H, s, OH), 2.36 (1H, ddd, *J* = 13.2, 8.8 and 6.1 Hz, H7), 2.27 (1H, *app* t, *J* = 9.3 Hz, H6), 2.10 (1H, ddd, *J* = 13.2, 9.8 and 3.9 Hz, H7), 1.43 (3H, s, H11), 1.36 (3H, s, H11); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 127.9, 122.2, 103.2, 83.3, 74.4, 66.0, 55.3, 52.0, 47.8, 34.6, 31.2, 25.6.

4-Bromo-2-hydroxy-1-(5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)pent-4-en-1-one (240)



IR (thin film, ν_{max} / cm^{-1}) 3429 (br), 2976 (m), 2930 (m), 1712 (s), 1632 (sm), 1447 (m), 1368 (m), 1224 (m), 1101 (s), 1038 (s); **HRMS** (ESI^+) calc. for $C_{12}H_{19}BrNaO_4$ $[M+Na]^+$ 329.0359, found 329.0359. **Major epimer: R_f** 0.29 (Pet. Ether/ EtOAc (3:2)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.76 (1H, s, H5), 5.61 (1 H, d, *J* = 1.4 Hz, H5), 5.02-4.99 (1H, m, H9), 4.42 (1H, dd, *J* = 9.5, 2.9 Hz, H2), 3.60 (1 H, dd, *J* = 11.1, 7.2 Hz, H6), 3.30 (3H, s, H12) 2.92 (1H, dd, *J* = 14.5, 2.9 Hz, H3), 2.51 (1H, dd, *J* = 14.5, 9.5 Hz, H3), 2.43 (1 H, ddd, *J* = 12.8, 11.1, 4.9 Hz, H10), 2.12 (1H, dd, *J* 12.8, 7.2 Hz, H10), 1.69 (1H, br s, OH), 1.56 (3H, s, H11), 1.12 (3H, s, H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.4, 128.5, 121.2, 103.7, 84.0, 74.9, 54.5, 53.4, 45.5, 37.5, 31.4, 25.6. **Minor epimer: R_f** 0.21 (Pet. Ether/ EtOAc (3:2)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.73 (1H, s, H5), 5.58 (1 H, d, *J* = 1.8 Hz, H5), 5.02-4.99 (1H, m, H9), 4.48 (1H, dd, *J* = 8.1, 3.8 Hz, H2), 3.53 (1 H, dd, *J* = 11.1, 6.9 Hz, H6), 3.30 (3H, s, H12), 3.05 (1H, br s, OH), 2.94-2.90 (1H, m, H3), 2.66-2.54 (2H, m, H3 and H10), 1.98 (1H, dd, *J* = 13.1, 6.9 Hz, H10), 1.59 (3H, s, H11), 1.03 (3H, s, H11); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 209.6, 128.5, 121.1, 103.8, 84.0, 74.8, 54.3, 53.4, 46.3, 35.8, 31.7, 25.5.

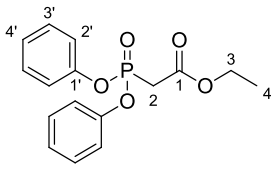
(2*R*)-4-Bromo-2-hydroxy-2-((3*R*)-5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)pent-4-enal (241)



Dry DMSO (190 µL, 2.72 mmol, 42 equiv.) was added to SO_3•py (83.4 mg, 0.524 mmol, 8.1 equiv.) under argon, and the suspension was stirred at RT for 15 min. Dichloromethane (1.2 mL) was added, then the mixture was cooled to 0 °C and stirred for a further 10 min. A solution of diol **237** (20.0 mg, 0.065 mmol, 1.0 equiv.) in dry dichloromethane (1.2 mL), and *i*-$PrEt_2N$ (0.22 mL, 1.33 mmol, 20 equiv.) were added simultaneously, and the resulting mixture stirred for 1 h between 0 and 10 °C. The reaction was then quenched with NH_4Cl (sat. *aq.*). The reaction was then quenched with NH_4Cl (1 mL, sat. *aq.*). Et_2O (4 mL) and

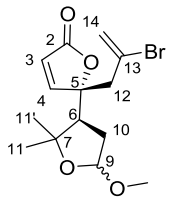
water (2 mL) was added, the phases were separated, and the aqueous layer extracted three times with Et_2O (3 mL × 3). The combined organic layers were washed sequentially with $NaHCO_3$ (sat. *aq.*), followed by brine. The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography through a short plug of silica (5:1 Pet. Ether / EtOAc), to afford aldehyde **241** (19.8 mg, 99%, 62:38 mixture of C8-epimers) as a white solid. These epimers were generally not readily separated by chromatography, and they were generally carried forward bromoene AB rings **104**; the data presented below was obtained for the purpose of characterization by careful chromatography. **IR** (thin film, ν_{max} / cm^{-1}) 3485 (br), 2976 (m), 1729 (s), 1627 (m), 1368 (m), 1327 (m), 1226 (m), 1103 (s), 1045 (s), 978 (m), 813 (m); **HRMS** (ESI^+) calc. for $C_{12}H_{19}O_4BrNa$ $[M+Na]^+$ 329.0359; found 329.0363. **Major epimer:** $\mathbf{R_f}$ 0.39 (7:3 Pet. Ether / EtOAc); $^{\mathbf{1}}$**H NMR** (500 MHz, $CDCl_3$) δ_H 9.77 (1H, s, H1), 5.70 (1H, s, H5), 5.59 (1H, d, *J* = 1.9 Hz, H5), 4.86 (1H, d, *J* = 4.7 Hz, H8), 3.51 (1H, br s, OH), 3.31 (3H, s, OCH_3), 3.11 (1H, d, *J* = 14.8 Hz, H3), 3.02 (1H, d, *J* = 14.8 Hz, H3), 2.59 (1H, dd, *J* = 13.2 and 6.4 Hz, H6), 2.11 (1H, *app* td, *J* = 12.9 and 4.7 Hz, H7), 1.74 (1H, dd, *J* = 12.6 and 6.4 Hz, H7), 1.49 (3H, s, H11), 1.22 (3H, s, H11'); $^{\mathbf{13}}$**C NMR** (126 MHz, $CDCl_3$) δ_C 202.2, 124.7, 123.2, 102.1, 83.8, 79.7, 54.2, 50.5, 48.6, 34.3, 32.7, 25.8. **Minor epimer:** $\mathbf{R_f}$ 0.58 (7:3 Pet. Ether / EtOAc); $^{\mathbf{1}}$**H NMR** (500 MHz, $CDCl_3$) δ_H 9.88 (1H, s, H1), 5.71 (1H, s, H5), 5.59 (1H, d, *J* = 1.9 Hz, H5), 4.97-4.95 (1H, m, H8), 3.73 (1H, br s, OH), 3.34 (3H, s, OCH_3), 3.05 (1H, d, *J* = 14.5 Hz, H3), 2.99 (1H, d, *J* = 14.5 Hz, H3), 2.33-2.25 (2H, m, H7 and H6), 2.14-2.07 (1H, m, H7), 1.40 (3H, s, H11),1.28 (3H, s, H11'); $^{\mathbf{13}}$**C NMR** (126 MHz, $CDCl_3$) δ_C 201.8, 124.6, 123.2, 103.2, 83.2, 79.8, 55.3, 53.0, 49.0, 34.6, 30.9, 25.5.

Ethyl 2-(diphenoxyphosphoryl)acetate[252] (242)



To a stirred solution of diphenyl phosphite (1.13 mL, 85-90%, ~5.0 mmol, 1.0 equiv.) in dry dichloromethane (5.0 mL) at 0 °C under argon was added ethyl bromoacetate (0.58 mL, 5.0 mmol, 1.0 equiv.) and triethylamine (0.99 mL, 7.0 mmol, 1.4 equiv.) sequentially. After stirring for 15 min at 0 °C, the reaction mixture was stirred at RT for 1 h before being hydrolysed with water (5 mL), and extracted with EtOAc/ Pet. Ether (3:1) (15 mL). The organic layer was washed with water (10 mL) followed by NaCl solution (10 mL, sat. *aq.*), dried with $MgSO_4$ and concentrated *in vacuo* to a pale yellow residue. The crude product was purified by flash column chromatography on a short plug of silica (5:1 Pet. Ether/ EtOAc) to yield Ando phosphonate **242** (844 mg, 53%) as a colourless oil. $\mathbf{R_f}$ 0.16 (Pet. Ether/ EtOAc (7:3)); **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 7.39-7.30 (4H, m, H_{Ar}), 7.26-7.15 (6H, m, H_{Ar}), 4.23 (2H, q, J_{HH} = 7.1 Hz, H-3), 3.27 (2H, d, J_{HP} = 21.6 Hz, H-4), 1.28 (3H, t, J_{HH} = 7.1 Hz, H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.9 (d), 150.1 (d), 130.0, 125.7, 120.8 (d), 62.1, 34.4 (d), 14.2; **^{31}P NMR** (170 MHz, $CDCl_3$) δ_P 12.9. Data in accordance with literature.[252,253]

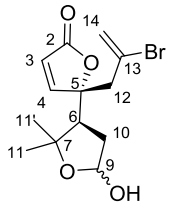
(5*S*)-5-(2-Bromoallyl)-5-((3*S*)-5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)furan-2(5*H*)-one (246)



To a stirred solution of ethyl 2-(diphenoxyphosphoryl)acetate **121** (24 mg, 0.073 mmol, 1.7 equiv.) in THF (0.75 mL) under argon at 0 °C was added KHMDS (0.7 M in THF, 100 µL, 0.070 mmol, 1.6 equiv.) and the resulting mixture was stirred at 0 °C for 20 min. This solution was then added dropwise to a solution of aldehyde **241** (13 mg, 0.043 mmol, 1.0 equiv.) in THF (0.4 mL) under argon at –20 °C, and the reaction mixture was stirred for 2 h between –20 and 0 °C, before being quenched with NH_4Cl (2 mL, sat. *aq.*). Et_2O (1 mL) was added, the layers were separated, and the aqueous layer was extracted three times with Et_2O (2 mL × 3). The combined organic layers were dried ($MgSO_4$) and concentrated. The product was

purified by flash chromatography through a short plug of silica gel (6:1→4:1 Pet. Ether / EtOAc), to afford lactone **246** as a colourless oil which co-eluted with the excess phosphonate ester. This mixture was used in the next step without further purification. For the purposes of characterization, a small amount of each epimer of **246** could be obtained pure by careful chromatography. **IR** (thin film, ν_{max} / cm^{-1}) 2976 (m), 1729 (s), 1627 (m), 1368 (m), 1327 (m), 1226 (m), 1103 (s), 1045 (s), 978 (m), 813 (m); **HRMS** (ESI^+) calc. for $C_{14}H_{19}O_4BrNa$ $[M+Na]^+$ 353.0359; found 353.0358. **Major epimer:** $\mathbf{R_f}$ 0.44 (7:3 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.49 (1H, d, *J* = 5.7 Hz, H4), 6.09 (1H, d, *J* = 5.7 Hz, H3), 5.66 (1H, d, *J* = 1.5 Hz, H14), 5.59 (1H, d, *J* = 1.5 Hz, H14), 4.84 (1H, d, *J* = 4.7 Hz, H8), 3.39 (1H, d, *J* = 14.5 Hz, H12), 3.31 (3H, s, OCH_3), 2.87 (1H, d, *J* = 14.5 Hz, H12), 2.63 (1H, dd, *J* = 12.6 and 6.3 Hz, H6), 1.89 (1H, *app* td, *J* = 12.6 and 5.0 Hz, H7), 1.78 (1H, dd, *J* = 12.6 and 6.3 Hz, H7), 1.49 (3H, s, H11), 1.27 (3H, s, H11'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 172.1, 157.7, 124.1, 123.8, 121.5, 101.7, 88.5, 83.2, 54.3, 51.3, 48.3, 35.2, 32.3, 25.6. **Minor epimer:** $\mathbf{R_f}$ 0.40 (7:3 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.55 (1H, d, *J* = 5.7 Hz, H4), 6.11 (1H, d, *J* = 5.7 Hz, H3), 5.68 (1H, d, *J* = 1.6 Hz, H14), 5.60 (1H, d, *J* = 1.6 Hz, H14), 4.96 (1H, dd, *J* = 5.8 and 4.3 Hz, H8), 3.33 (3H, s, OCH_3), 3.29 (1H, d, *J* = 14.5 Hz, H12), 2.83 (1H, d, *J* = 14.5 Hz, H12), 2.38-2.28 (2H, m, H6 and H7), 1.92-1.82 (1H, m, H7), 1.39 (3H, s, H11), 1.25 (3H, s, H11'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 172.4, 156.8, 124.3, 123.7, 122.0, 102.8, 88.7, 82.4, 55.5, 53.8, 49.4, 35.7, 30.2, 25.4.

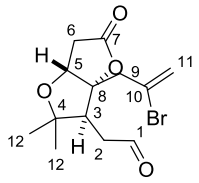
(5*S*)-5-(2-Bromoallyl)-5-((3*S*)-5-hydroxy-2,2-dimethyltetrahydrofuran-3-yl)furan-2(5*H*)-one (249)



To a stirred solution of the crude methyl acetal **246** (*ca.* 0.043 mmol from previous reaction) in dichloromethane (2.1 mL) at 0 °C was added distilled water (10 µL) and TFA (0.2 mL)

dropwise. The reaction mixture was stirred for 15 min at 0 °C before being quenched with $NaHCO_3$ (2 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (2 mL × 3). The combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography through a short plug of silica gel (7:3→1:1 Pet. Ether / EtOAc), to afford lactol **249** (7.4 mg, 55% over 2 steps, as a 73:27 mixture of C8-epimers) as a white solid. These epimers were generally not readily separated by chromatography, and they were generally carried forward bromoene AB rings **104**; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.15 (7:3 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3469 (br), 3002 (w), 2944 (m), 1749 (s), 1437 (m), 1367 (s), 1230 (m), 1216 (s), 1203 (m); **HRMS** (ESI^+) calc. for $C_{13}H_{17}BrNaO_4$ $[M+Na]^+$ 339.0202; found 339.0212. **Major epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.51 (1H, d, *J* = 5.7 Hz, H4), 6.10 (1H, d, *J* = 5.7 Hz, H3), 5.67 (1H, d, *J* = 1.6 Hz, H14), 5.60 (1H, d, *J* = 1.6 Hz, H14), 5.38 (1H, dd, *J* = 4.8 and 2.5 Hz, H8), 3.39 (1H, d, *J* = 14.6 Hz, H12), 2.89 (1H, d, *J* = 14.6 Hz, H12), 2.71 (1H, *J* = 12.9, 6.5 Hz, H6), 2.50 (1H, t, *J* = 1.9 Hz, OH), 1.92 (1H, tdd, *J* = 12.9, 4.8 and 1.6 Hz, H7), 1.81 (1H, dd, *J* = 12.9 and 6.5 Hz, H7), 1.52 (3H, s, H11), 1.24 (3 H, s, H11'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 172.4, 157.7, 124.2, 123.8, 121.5, 95.3, 88.4, 83.6, 51.0, 48.4, 35.8, 32.4, 25.5. **Minor epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.55 (1H, d, *J* = 5.7 Hz, H4), 6.12 (1H, d, *J* = 5.7 Hz, H3), 5.68 (1H, d, *J* = 1.8 Hz, H13), 5.61 (1H, d, *J* = 1.8 Hz, H13), 5.48 (1H, ddd, *J* = 6.2, 4.7 and 3.5 Hz, H9), 3.30 (1H, d, *J* = 14.5 Hz, H11), 2.84 (1H, d, *J* = 14.5 Hz, H11), 2.70 (1H, d, *J* = 3.5 Hz, OH), 2.39 (1H, dd, *J* = 12.0 and 8.2 Hz, H6), 2.31 (1H, ddd, *J* = 13.2, 8.2 and 6.2 Hz, H10), 1.87 (1H, m, H10), 1.39 (3H, s, H14), 1.32 (3H, s, H14); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 172.1, 156.9, 124.3, 123.7, 122.0, 96.1, 88.5, 82.6, 54.3, 49.3, 36.6, 30.3, 25.9.

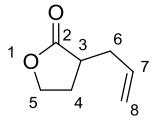
2-((3*S*,3a*R*,6a*R*)-3a-(2-bromoallyl)-2,2-dimethyl-5-oxohexahydrofuro[3,2-*b*]furan-3-yl)acetaldehyde (104)



To a stirred solution of lactol **249** (13.5 mg, 0.043 mmol, 1.0 equiv.) in MeOH (1.7 mL) was added K_2CO_3 (11.8 mg, 0.085 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 2 h before being quenched with NH_4Cl (1.5 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with EtOAc (1.5 x 3 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo*. The product was purified by flash chromatography through a short plug of silica (2:1 Pet. Ether / EtOAc), to give AB ring aldehyde **104** (13.4 mg, 0.043 mmol, 99%) as a white solid. $\mathbf{R_f}$ 0.38 (3:2 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 2971 (m), 1774 (s), 1740 (s), 1723 (s), 1624 (m), 1437 (m), 1375 (m), 1231 (m), 1215 (s), 1175 (m), 1021 (m), 927 (m); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 9.78 (1H, t, *J* = 1.9 Hz, H1), 5.79 (1H, d, *J* = 1.3 Hz, H11), 5.72 (1H, d, *J* = 1.3 Hz, H11), 4.86 (1H, d, *J* = 6.6 Hz, H4), 3.05 (1H, d, *J* = 14.8 Hz, H9), 2.89 (1H, dd, *J* = 18.6 and 6.6 Hz, H6), 2.78 (1H, dd, *J* = 9.1 and 6.0 Hz, H3), 2.67 (1H, d, *J* = 18.6 Hz, H6), 2.62 (1H, d, *J* = 14.8 Hz, H9), 2.51 (1H, ddd, *J* = 16.7, 9.1 and 1.9 Hz, H2), 2.38 (1H, ddd, *J* = 16.7, 6.0 and 1.9 Hz, H2), 1.34 (3H, s), 1.12 (3H, s); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ_C 199.4 (C1), 175.2 (C7), 125.1 (C11), 123.4 (C10), 94.6 (C8), 82.7 (C4), 77.0 (C5), 53.6 (C3), 45.7 (C9), 40.8 (C2), 37.3 (C6), 27.7 (C12), 21.1 (C12); **HRMS** (ESI^+) calc. for $C_{13}H_{17}BrO_2Na$ $[M+Na]^+$ 339.0202; found 339.020.

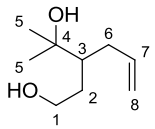
7.4.2. Oxa-Michael Model System

3-Allyldihydrofuran-2(3*H*)-one[254] (252)



To a stirred solution of diisopropylamine (4.2 mL, 30 mmol, 1.2 equiv.) in dry THF (35 mL) under argon at -78 °C was added *n*-BuLi (2.5 M in hexane, 12 mL, 30 mmol, 1.2 equiv.) dropwise. The resulting mixture was stirred at –78 °C for 40 min, after which a solution of γ-butyrolactone (1.9 mL, 25 mmol, 1.0 equiv.) in dry THF (25 mL) was added. The reaction mixture was sitrred at –78 °C for 1 h, after which neat allyl bromide (7.5 mL, 75 mmol, 3.0 equiv.) was added. The reaction mixture was stirred, warming gradually to –20 °C over 6 h before being quenched with NH_4Cl solution (3 mL, sat. *aq.*) and water (7 mL). The layers were separated and the aqueous layer extracted two times with ethyl acetate (2 x 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (7:3 Pet. Ether/ EtOAc) to yield allyldihyrofuranone **252** (2.46 g, 78%) as a colourless oil. $\mathbf{R_f}$ 0.58 (Pet. Ether/ EtOAc (3:2)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.78 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, H7), 5.15-5.09 (2H, m, H8), 4.33 (1H, td, *J* = 9.0, 3.0 Hz, H5), 4.20 (1H, td, *J* = 9.0, 7.0 Hz, H5), 2.71-2.54 (2H, m, H3 and H-6), 2.36 (1H, ddt, *J* = 15.6, 9.0, 3.0 Hz, H4), 2.30-2.22 (1H, m, H6), 2.04-1.94 (1H, m, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.0, 134.5, 117.9, 66.7, 39.0, 34.5, 27.9. Data in accordance with literature.[254]

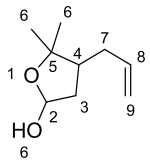
3-Allyl-4-methylpentane-1,4-diol (253)



To a stirred solution of lactone **252** (2.46 g, 19.5 mmol, 1.0 equiv.) in dry THF (30 mL) under argon at 0 °C was added methylmagnesium bromide (3 M in Et_2O, 16.2 mL, 48.8 mmol, 2.5

equiv.) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h before being quenched with NH_4Cl solution (2 mL, sat. *aq.*). The suspension was filtered through a pad of Celite® and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 to 1:1 Pet. Ether/ EtOAc) to yield diol **253** (2.86 g, 93%) as a colourless oil. $\mathbf{R_f}$ 0.11 (Pet. Ether/ EtOAc (3:2)); **IR** (thin film, ν_{max} / cm^{-1}) 3320 (br), 2974 (s), 1640 (m), 1440 (m), 1382 (m), 1154 (m), 1048(m), 909 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.88-5.70 (1H, m, H7), 5.10-4.98 (2H, m, H8), 3.79-3.74 (1H, m, H1), 3.61-3.55 (1H, m, H1), 2.59 (2H, br s, OH), 2.32 (1H, d, *J* = 13.9 Hz, H6), 1.95-1.87 (1H, m, H6), 1.80-1.71 (1H, m, H2), 1.68-1.56 (2H, m, H2 and H-3), 1.28 (3H, s, H5), 1.18 (3H, s, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 116.3, 73.3, 62.2, 47.4, 36.1, 32.3, 29.3, 26.1; **HRMS** (ESI^+) calc. for $C_9H_{18}O_2Na$ $[M+Na]^+$ 181.1199, found 181.1193; **EA** calc. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.20; H, 11.52.

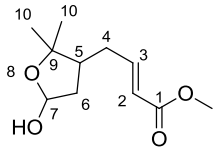
4-Allyl-5,5-dimethyltetrahydrofuran-2-ol (254)



To a stirred suspension of 2-iodoxybenzoic acid (1.06 g, 3.8 mmol, 1.2 equiv.) in dry DMSO (9.5 mL) under argon was added diol **253** (500 mg, 3.2 mmol, 1.0 equiv.). The reaction mixture was stirred at RT for 2 h before being quenched with water (30 mL). The suspension was filtered through a pad of Celite®, washing with diethyl ether and water. The layers were separated and the aqueous layer extracted four times with diethyl ether (4 x 15 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo* to yield lactol **254** (487 mg, 99%, as a 65:35 mixture of diastereomers) as a colourless oil. The crude product was used in the next step without further purification. For the purposes of characterization, a small amount of each epimer of **254** could be obtained pure by careful chromatography. $\mathbf{R_f}$ 0.54 (Pet. Ether/ EtOAc (3:2)); **IR** (thin film, ν_{max} / cm^{-1}) 3407 (br), 2974 (m), 1641 (m), 1437 (m), 1368 (m), 1143 (m), 1022 (s), 911 (m); **HRMS** (ESI^+) calc. for

$C_9H_{16}O_2Na$ $[M+Na]^+$ 179.1043, found 179.1039. **Major epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.84-5.70 (1H, tt, *J* = 17.0, 6.9 Hz, H8), 5.39 (1H, d, *J* = 4.7 Hz, H2), 5.06 (1H, dq, *J* = 17.0, 1.6 Hz, H9), 5.00 (1H, dd, *J* = 10.2, 1.7 Hz, H9), 2.75 (1H, br s, OH) 2.31-2.22 (1H, m, H4), 2.22-2.14 (1H, m, H7), 2.05 (1H, dd, *J* = 12.7, 6.6 Hz, H3), 2.03-1.94 (1H, m, H7), 1.73 (1H, td, *J* = 12.7, 4.9 Hz, H3), 1.37 (3H, s, H6), 1.03 (3H, s, H6); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 137.3, 115.9, 96.7, 84.2, 45.1, 39.8, 34.5, 30.1, 23.5 . **Minor diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.84-5.70 (1H, m, H8), 5.47 (1H, t, *J* = 5.5 Hz, H2), 5.05 (1H, dq, *J* = 17.0, 1.6 Hz, H9), 4.99-4.96 (1H, m, H9), 2.98 (1H, br s, OH), 2.42 (1H, ddd, *J* = 13.5, 7.8, 6.1 Hz, H4), 2.14-2.11(1H, m, H7), 2.05 (1H, dd, *J* = 12.7, 6.6 Hz, H3), 2.03-1.94 (1H, m, H7), 1.65 (1H, ddd, *J* = 13.6, 11.0, 5.0 Hz, H3), 1.24 (1H, s, H6), 1.21 (1H, s, H6); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 137.3, 115.7, 97.6, 83.2, 48.5, 40.3, 34.8, 28.3, 23.8.

(*E*)-Methyl 4-(5-hydroxy-2,2-dimethyltetrahydrofuran-3-yl)but-2-enoate (255)

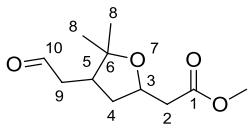


To a stirred solution of alkene **254** (359 mg, 2.30 mmol, 1.0 equiv.) in dry diethyl ether (23 mL) was added copper(I) iodide (12.9 mg, 0.069 mmol, 3 mol%) and methyl acrylate (2.05 mL, 23.0 mmol, 10 equiv.), and the suspension degassed with argon bubbling for 30 min.[255] Grubbs' 2nd generation catalyst (38.8 mg, 0.046 mmol, 2 mol%) was added, and the reaction was stirred at 40 °C overnight before the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3:2 Pet. Ether/ EtOAc) to yield cross metathesis product **255** (457 mg, 93%) as a colourless oil. These epimers were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography.

R_f 0.21 (Pet. Ether/ EtOAc (3:2)); **IR** (thin film, ν_{max} / cm^{-1}) 3403 (br), 2973 (m), 1722 (s), 1657 (m), 1437 (m), 1326 (m), 1030(s), 987 (m); **HRMS** (ESI^+) calc. for $C_{11}H_{18}O_4Na$ $[M+Na]^+$ 237.1097, found 237.1098; **EA** calc. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.50; H,

8.58. **Major epimer: ^{1}H NMR** (400 MHz, $CDCl_3$) 7.00-6.82 (1H, m, H3), 5.87 (1H, dt, *J* = 15.7, 1.5 Hz, H2), 5.41 (1H, d, *J* = 2.8 Hz, H7), 3.73 (3H, s, OCH_3), 3.42 (1H, br s, OH), 2.38-2.21 (3H, m, H5 and H-4), 2.06 (1H, dd, *J* = 12.6, 6.3 Hz, H6), 1.73 (1H, td, *J* = 12.6, 4.8 Hz, H6), 1.36 (3H, s, H10), 1.03 (3H, s, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.9, 147.5, 122.3, 96.5, 83.9, 51.6, 44.6, 39.6, 32.8, 29.9, 23.5. **Minor epimer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.00-6.82 (1H, m, H3), 5.87 (1H, dt, *J* = 15.7, 1.5 Hz, H2), 5.52-5.44 (1H, m, H7), 3.73 (3H, s, OCH_3), 2.45-2.39 (1H, m, H6), 2.23-2.11 (2H, m, H4), 2.03-1.92 (1H, m, H7), 1.84 (1H, br s, OH), 1.69-1.60 (1H, m, H6), 1.23 (3H, s, H10), 1.22 (3H, s, H10); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.0, 147.6, 122.2, 97.4, 83.1, 51.6, 47.6, 39.9, 33.2, 28.3, 23.8.

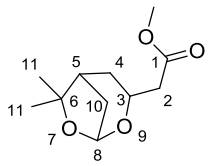
Methyl 2-(5,5-dimethyl-4-(2-oxoethyl)tetrahydrofuran-2-yl)acetate (256)



To a stirred solution of lactol **255** (20.0 mg, 0.093 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added potassium carbonate (25.8 mg, 0.187 mmol, 2.0 equiv.). The reaction mixture was stirred at 40 °C overnight, then cooled to RT before being quenched with NH_4Cl (2.0 mL, sat. *aq.*). The solvent was removed carefully *in vacuo*, and the residue was diluted with diethyl ether (4 mL). Water was added (4 mL), the layers separated and the aqueous layer extracted three times with diethyl ether (3 x 4 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (4:1 Pet. Ether/ EtOAc), to yield aldehyde **256** (8.3 mg, 42%) as a colourless oil. $\mathbf{R_f}$ 0.53 (Pet. Ether/ EtOAc (3:2)); **IR** (thin film, ν_{max} / cm^{-1}) 2972 (m), 1774 (m), 1726 (s), 1438 (s), 1370 (m), 1267 (m), 1201 (m), 1053 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.79 (1H, s, H10), 4.38-4.30 (1H, m, H3), 3.68 (3H, s, OCH_3), 2.65 (1H, dd, *J* = 15.2, 6.5 Hz, H2), 2.54 (1H, dq, *J* = 15.8, 1.8 Hz, H9), 2.47 (1H, dd, *J* = 15.2, 6.6 Hz, H2), 2.44-2.33 (3H, m, H5, H4 and H-9), 1.42 (1H, q, *J* = 10.6 Hz, H4), 1.26 (3H, s, H8), 1.05 (3H, s, H8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 201.1, 171.7, 82.0, 73.3, 51.8,

45.0, 42.9, 41., 38.2, 28.1, 24.8; **HRMS** (ESI^+) calc. for $C_{11}H_{18}O_4Na$ $[M+Na]^+$ 237.1097, found 237.1091.

Methyl 2-(6,6-dimethyl-2,7-dioxabicyclo[3.2.1]octan-3-yl)acetate (257)

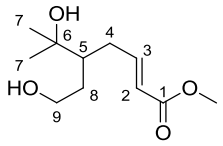


To a stirred solution of lactol **255** (21.8 mg, 0.102 mmol, 1.0 equiv.) in dry THF (1.0 mL) at –78 °C was added potassium *tert*-butoxide (22.8 mg, 0.203 mmol, 2.0 equiv.). The reaction mixture was stirred warming to 0 °C for 4 h before being quenched with NH_4Cl (1 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with diethyl ether (3 x 1 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (9:1 to 2:1 Pet. Ether/ EtOAc) to yield dioxabicycle **257** (1.9 mg, 9%) as a colourless oil and aldehyde **256** (4.5 mg, 21%), and some lactol **255** (2.3 mg, 11%) was recovered. $\mathbf{R_f}$ 0.65 (Pet. Ether/ EtOAc (3:2)); **IR** (thin film, ν_{max} / cm^{-1}) 2968 (m), 1740 (s), 1438 (m), 1368 (m), 1315 (m), 1178 (m), 1067 (s), 886 (m); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 5.33 (1H, d, *J* = 3.8 Hz, H8), 4.52-4.44 (1H, m, H3), 3.69 (3H, s, OCH_3), 2.55 (1H, dd, *J* = 14.9, 6.9 Hz, H2), 2.44 (1H, dd, *J* = 14.9, 6.1 Hz, H2), 2.20-2.12 (1H, m, H10), 2.10-2.06 (1H, m, H5), 1.97-1.90 (1H, m, H4), 1.73 (1H, d, *J* = 11.7 Hz, H10), 1.56-1.51 (1H, m, H4), 1.50 (3H, s, H11), 1.22 (3H, s, H11); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ_C 171.7, 99.6, 82.9, 66.3, 51.9, 41.8, 40.2, 38.4, 33.8, 28.7, 22.7; **HRMS** (ESI^+) calc. for $C_{11}H_{18}O_4Na$ $[M+Na]^+$ 237.1097, found 237.1095.

(*E*)-Methyl 6-hydroxy-5-(2-hydroxyethyl)-6-methylhept-2-enoate (259) and methyl 2-(5,5-dimethyl-4-(2-hydroxyethyl)tetrahydrofuran-2-yl)acetate (260)

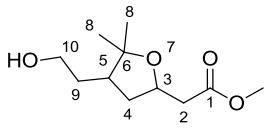
To a stirred solution of lactol **255** (20.0 mg, 0.093 mmol, 1.0 equiv.) in MeOH (0.8 mL) and THF (0.8 mL) was added sodium borohydride (3.5 mg, 0.093 mmol, 1.0 equiv.). The reaction mixture was stirred at RT for 1 h before being quenched with NH_4Cl solution (1 mL, sat. *aq.*). The solvent was removed carefully *in vacuo*, and the residue diluted with diethyl ether (2 mL). Water was added (1 mL), the layers were separated and the aqueous layer extracted three times with diethyl ether (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (2:1 to 1:2 Pet. Ether/ EtOAc), to yield diol **259** (8.3 mg, 41%) as a colourless oil, tetrahydrofuran 2**60** (7.7 mg, 37%) as a colourless oil, and some lactol **62** (4.3 mg, 22%) was recovered.

(*E*)-Methyl 6-hydroxy-5-(2-hydroxyethyl)-6-methylhept-2-enoate (259)



R_f 0.27 (Pet. Ether/ EtOAc (3:7)); **IR** (thin film, ν_{max} / cm^{-1}) 3363 (br), 2972 (s), 1720 (s), 1705 (s), 1654 (m), 1437 (m), 1323 (m), 1166 (s), 1046 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.93 (1H, ddd, *J* = 15.6, 9.0, 6.1 Hz, H3), 5.83 (1H, dt, *J* = 15.6, 1.5 Hz, H2), 3.74-3.68 (1H, m, H9), 3.70 (3H, s, OCH_3), 3.59-3.51 (1H, m, H9), 3.43 (1H, br s, OH), 2.48-2.38 (1H, m, H4), 2.15-2.00 (1H, m, H4), 1.80-1.70 (1H, m, H8), 1.70-1.63 (1H, m, H5), 1.61-1.52 (1H, m, H8), 1.25 (3H, s, H7), 1.17 (3H, s, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.1, 149.2, 122.1, 72.7, 61.3, 51.6, 47.0, 34.2, 32.4, 28.9, 26.2; **HRMS** (ESI^+) calc. for $C_{11}H_{20}O_4Na$ $[M+Na]^+$ 239.1254, found 239.1249; **EA** calc. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.95; H, 9.40.

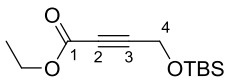
Methyl 2-(5,5-dimethyl-4-(2-hydroxyethyl)tetrahydrofuran-2-yl)acetate (260)



To a stirred solution of diol **66** (20.0 mg, 0.093 mmol, 1.0 equiv.) in MeOH (2.0 mL) was added potassium carbonate (25.8 mg, 0.187 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 3 h before being quenched with NH_4Cl (2 mL, sat. *aq.*). The solvent was removed carefully *in vacuo* and the residue diluted with diethyl ether (4 mL). Water was added (2 mL), the layers were separated and the aqueous layer extracted three times with diethyl ether (3 x 4 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (3:2 Pet. Ether/ EtOAc) to yield tetrahydrofuran **60** (15.9 mg, 80%) as a colourless oil. $\mathbf{R_f}$ 0.40 (Pet. Ether/ EtOAc (3:7)); **IR** (thin film, ν_{max} / cm^{-1}) 3439 (br), 2969 (m), 1738 (s), 1438 (m), 1382 (m), 1263 (m), 1200 (m), 1053 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.34-4.22 (1H, m, H3), 3.75-3.69 (1H, m, H10), 3.68 (3H, s, OCH_3), 3.67-3.62 (1H, m, H10), 2.66 (1H, dd, *J* = 15.1, 6.3 Hz, H2), 2.46 (1H, dd, *J* = 15.1, 6.9 Hz, H2), 2.27 (1H, dt, *J* = 12.0, 5.9 Hz, H4), 2.03 (1H, dddd, *J* = 12.0, 10.8, 6.6, 3.8 Hz. H-5), 1.68 (1H, dtd, *J* = 13.4, 7.5, 3.8 Hz, H9), 1.57 (1H, br s, OH), 1.50-1.41 (1H, m, H9), 1.42 (1H, td, *J* = 12.0, 10.2 Hz, H4), 1.25 (3H, s, H8), 1.03 (3H, s, H8); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 171.9, 82.6, 73.4, 62.3, 51.8, 46.0, 41.8, 38.3, 33.2, 28.3, 24.6; **HRMS** (ESI^+) calc. for $C_{11}H_{20}O_4Na$ $[M+Na]^+$ 239.1254, found 239.1255; **EA** calc. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.93; H, 9.43.

7.4.3. Synthesis of the AB alkyne rings

Ethyl 4-((*tert*-butyldimethylsilyl)oxy)but-2-ynoate (269)

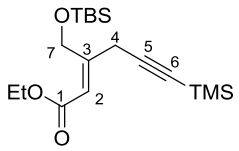


To a stirred solution of propargyl alcohol (5.5 mL, 93.1 mmol, 1.0 equiv.) in dry dichloromethane (370 mL) under argon at 0 °C was added imidazole (9.53 g, 140 mmol, 1.5 equiv.), DMAP (1.14 g, 3.579.31 mmol, 10 mol%) and TBSCl (15.5 g, 102 mmol, 1.1 equiv.). The reaction mixture was warmed to RT and stirred for 3 h before being quenched with $NaHCO_3$ (sat. *aq.*). The layers were separated and the aqueous phase extracted three times with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated to yield *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane, which was used crude in the next step.

The crude alkyne (1.0 equiv.) was dissolved in dry THF (400 mL) under argon, and to this stirred solution at –78 °C was added *n*-BuLi (2.5M in hexanes, 37.2 mL, 102 mmol, 1.1 equiv.). After stirring the reaction mixture for 1 h at this temperature, ethyl chloroformate (9.9 mL, 102 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred for 3 h while slowly warming to RT, then the reaction was quenched by addition of NH_4Cl (200 mL, sat. *aq.*). The layers were separated and the aqueous phase extracted three times with Et_2O (3 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (9:1Pet. Ether / Et_2O) to yield alkyne **269** (22.0 g, 90.8 mmol, 98%) as a colourless oil.

R_f 0.20 (20:1 Pet. Ether / EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.42 (2H, s, H4), 4.23 (2H, q, *J* = 7.1 Hz, $C\underline{H}_2CH_3$), 1.30 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$), 0.90 (9H, s, $SiC(C\underline{H}_3)_3$), 0.13 (6H, s, $Si(C\underline{H}_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 153.5, 85.8, 76.8, 62.2, 51.5, 25.9, 18.4, 14.1, –5.1. Data in accordance with literature.[256]

Ethyl (*Z*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(trimethylsilyl)hex-2-en-5-ynoate (264)

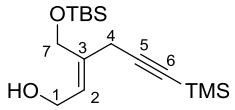


To an oven-dried two-necked flask equipped with a stirrer bar and a reflux condensor under argon was added acid-washed magnesium turnings (1.79 mg, 73.7 mmol, 1.5 equiv.) and a few crystals of iodine. To the stirred mixture was simultaneously added dropwise diethyl ether (48 mL) and (3-bromoprop-1-yn-1-yl)trimethylsilane **276** (9.39 g, 49.1 mmol, 1.0 equiv.) until reaction initiation was observed as evidenced by a gentle reflux. Dropwise addition continued to maintain this reflux; upon complete addition, the reaction mixture was refluxed for a further 5 h, then allowed to cool to RT. The solution of Grignard reagent **277** was titrated against salicylaldehyde diphenylhydrazone[257] (29.1 mg) in THF (5 mL) to reveal a concentration of 0.38 M (18.1 mmol, 37%).

To a suspension of copper(I) bromide dimethyl sulfide complex (4.44 g, 21.6 mmol, 1.2 equiv.) in THF (70 mL) under argon at –78 °C was added the above Grignard solution *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane **277** (0.38 M, 47.1 mL, 18.0 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred at –40 °C for 40 min before recooling to –78 °C, upon which alkyne **269** (5.24 mg, 21.6 mmol, 1.2 equiv.) was added. The reaction mixture was stirred overnight at –78 °C, before being quenched with NH_4Cl (100 mL, sat. *aq.*). The layers were separated and the aqueous phase extracted three times with Et_2O (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was passed through a short pad of silica (49:1 Pet. Ether / Et_2O eluent) to yield the crude α,β-unsaturated ester **264** as a colourless oil, which was used directly in the next step but could be purified by further chromatography for the purpose of characterization. $\mathbf{R_f}$ 0.45 (20:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 2931, 2898, 2858, 2180, 1716, 1651, 1472, 1382, 1363, 1286, 1250, 1208, 1129, 1093, 1040, 1006, 939, 918, 836, 777, 760, 699, 670,

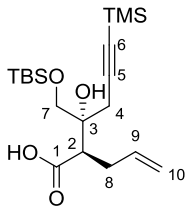
651; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.07 (1H, *app* quin, *J* = 1.8 Hz, H2), 4.80-4.81 (2H, m, H7), 4.16 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.31 (2H, br s, H4), 1.29 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 0.89 (9H, s, $OSiC(C\underline{H}_3)_3$), 0.18 (9H, s, $Si(C\underline{H}_3)$), 0.07 (6H, s, $Si(C\underline{H}_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 166.3, 157.2, 115.9, 102.4, 89.4, 61.8, 60.0, 26.0, 25.1, 18.4, 14.4, 0.2, –5.4; **HRMS** (ES^+) calc. for $C_{18}H_{34}NaO_3Si_2$ $[M+Na]^+$ 377.1939, found 377.1932. Data in accordance with literature.[99,194]

(*Z*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-(trimethylsilyl)hex-2-en-5-yn-1-ol (279)



To a stirred solution of the crude α,β-unsaturated ester **264** in dry dichloromethane (100 mL) under argon at –78 °C was added DIBALH (1M in THF, 39.6 mL, 39.6 mmol, 2.2 equiv.) dropwise. The reaction mixture was stirred for 3 h at this temperature before being quenched by dropwise addition of water (1.6 mL), then 2M NaOH (1.6 mL). The reaction flask was placed in a 0 °C bath, then further water (3.9 mL) was added and the mixture was allowed to stir for 30 min. The layers were separated and the aqueous phase was extracted three times with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (4:1 Pet. Ether / Et_2O eluent) to yield alcohol **279** (5.04 g, 16.1 mmol, 90% over 2 steps) as a white crystalline solid. **mp** 41-43 °C; **R_f** 0.37 (4:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 3362, 2957, 2930, 2898, 2857, 2360, 2177, 1727, 1472, 1251, 1084, 1005, 840, 777, 760; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.84 (1H, t, *J* = 6.8 Hz, H2), 4.23 (2H, s, H7), 4.21 (2H, *app* t, *J* = 6.1 Hz, H1), 3.08 (2H, s, H4), 1.84 (1H, t, *J* = 5.8 Hz, OH), 0.90 (9H, s, $OSiC(C\underline{H}_3)_3$), 0.16 (9H, s, $Si(C\underline{H}_3)_3$), 0.08 (6H, s , $OSi(C\underline{H}_3)_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 137.1, 126.8, 103.6, 87.9, 60.8, 58.8, 26.0, 25.7, 18.4, 0.2, –5.3; **HRMS** (ES^+) calc. for $C_{16}H_{32}NaO_2Si_2$ $[M+Na]^+$ 335.1833; found 335.1827. Data in accordance with literature.[194]

(2*R*,3*R*)-2-Allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxy-6-(trimethylsilyl)hex-5-ynoic acid (282)

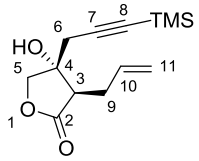


Dry DMSO (9.8 mL, 138 mmol, 42 equiv.) was added to SO_3•py (4.27 g, 26.7 mmol, 8.1 equiv.) under Ar, and the suspension was stirred at RT for 15 min. Dichloromethane (70 mL) was added, then the mixture was cooled to 0 °C and stirred for a further 10 min. A solution of (2*S*,3*R*)-2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(trimethylsilyl)hex-5-yne-1,3-diol **281** (1.22 g, 3.29 mmol, 1.0 equiv.) and *N*,*N*-diisopropylethylamine (11.3 mL, 67.5 mmol, 20.5 equiv.) in dry dichloromethane (70 mL) was added, and the resulting mixture was warmed to RT and stirred for 2 h, before being quenched by addition of NH_4Cl (100 mL, sat. *aq.*). Dichloromethane was added (50 mL), the layers were separated, and the organic layer was washed with brine. The organic layer was dried ($MgSO_4$) and concentrated to the corresponding aldehyde, which was directly used in the subsequent Pinnick oxidation.

To a stirred solution of this crude aldehyde (3.29 mmol, 1.0 equiv.) in wet *t*-BuOH (120 mL) was added 2-methyl-2-butene (12.1 mL, 98.7 mmol, 30 equiv.). To the reaction mixture was added a solution of sodium chlorite (80%, 3.00 g, 32.9 mmol, 10 equiv.) and $NaH_2PO_4.2H_2O$ (4.16 g, 26.3 mmol, 8.0 equiv.) in water (43 mL). After stirring overnight, brine was added, the layers were separated, and the aqueous phase was extracted four times with EtOAc (4 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (1:1 Pet. Ether / EtOAc eluent) to give carboxylic acid **282** (1.17 g, 3.04 mmol, 92%) as a colourless highly viscous oil. **$[\alpha]_D^{25}$ –**5.7 (*c* 1.00, $CHCl_3$); **mp** 89 °C; **R_f** 0.22 (2:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3310, 2956, 2177, 1699, 1423, 125, 1190, 1130, 1074, 920, 841, 779, 760; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.30 (1H, br s, COOH), 5.79 (1H, ddt, *J* = 17.0, 10.1 and 7.0 Hz, H9), 5.11 (1H,

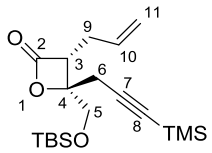
dd, *J* = 17.0 and 1.6 Hz, H10), 5.05 (1H, dd, *J* = 10.1 and 1.6 Hz, H10), 3.73 (1H, d, *J* = 10.0 Hz, H7), 3.64 (1H, d, *J* = 10.0 Hz, H7), 2.88 (1H, dd, *J* = 8.2 and 6.6 Hz, H2), 2.68 (1H, d, *J* = 17.1 Hz, H8), 2.55 (1H, d, *J* = 17.1 Hz, H8), 2.45 (2H, br t, *J* = 7.5 Hz, H4), 2.10 (1H, s, OH), 0.90 (9H, s, OSiC($C\underline{H}_3$)$_3$), 0.16 (9H, s, Si($C\underline{H}_3$)$_3$), 0.09 (3H, s, OSi($C\underline{H}_3$)$_2$), 0.09 (3H, s, OSi($C\underline{H}_3$)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 176.5, 135.4, 117.3, 101.8, 88.9, 74.2, 65.2, 50.7, 31.3, 28.4, 25.9, 18.4, 0.1, –5.4; **HRMS** (ES^+) calc. for $C_{19}H_{36}NaO_4Si_2$ $[M+Na]^+$ 407.2044; found 407.2040. Data in accordance with literature.[194]

(3*R*,4*R*)-3-allyl-4-hydroxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)dihydrofuran-2(3*H*)-one (283)



To a stirred solution of carboxylic acid **282** (200 mg, 0.577 mmol, 1.0 equiv) in wet methanol (8 mL) was added CSA (30 mg, 0.144 mmol, 0.25 equiv). The reaction mixture was stirred for 3 h before being quenched with sat. *aq.* $NaHCO_3$ solution (8 mL). The layers were separated and the aqueous layer extracted three times with ethyl acetate (3 x 15 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 Pet. Ether/ EtOAc) to yield δ-lactone **283** (112 mg, 85%) as a colourless oil. **$[\alpha]_D^{25}$** –3.8 (*c* 0.58, $CHCl_3$); **R_f** 0.31 (9:1 Pet. Ether/ EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.91 (1H, dddd, *J* = 17.0, 10.2, 7.3, 6.3 Hz, H10), 5.22 (1H, dq, *J* = 17.0, 1.4 Hz, H11), 5.16 (1H, dq, *J* = 10.2, 1.4 Hz, H11), 4.28 (1H, d, *J* = 9.5 Hz, H5), 4.08 (1H, d, *J* = 9.5 Hz, H5), 2.78 (1H, dd, *J* = 8.2, 6.3 9Hz, H9), 2.66 (1H, d, *J* = 16.7 Hz, H6), 2.56 (1H, d, *J* = 16.7 Hz, H6), 2.50 (1H, br s, OH), 2.45-2.37 (1H, m, H9), 0.18 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.9, 134.3, 118.2, 99.3, 90.6, 77.2, 75.2, 49.5, 30.1, 27.0, –0.1. Data in accordance with literature.[194]

(3*R*,4*R*)-3-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(3-(trimethylsilyl)prop-2-yn-1-yl)oxetan-2-one (284)



To a stirred solution of carboxylic acid **282** (500 mg, 1.30 mmol, 1.0 equiv.) in dry MeCN (11 mL) under argon was added dry pyridine (8.0 mL) and bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOPCl) (992 mg, 3.90 mmol, 3.0 equiv.). The reaction mixture was stirred for 3 h before being quenched with water (20 mL). The layers were separated and the aqueous phase extracted four times with ethyl acetate (4 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (19:1 Pet. Ether / Et_2O eluent) to yield β-lactone **284** (394 mg, 1.07 mmol, 83%) as a colourless oil. $\mathbf{[\alpha]_D^{25}}$ +5.8 (*c* 1.00, $CHCl_3$); $\mathbf{R_f}$ 0.58 (9:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 2958, 2929, 2857, 2360, 2180, 1833, 1462, 1251, 1111, 1009, 841, 779, 760; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.84 (1H, ddt, *J* = 17.0, 10.3 and 6.5 Hz, H10), 5.15 (1H, dq, *J* = 17.0 and 1.5 Hz, H11), 5.10 (1H, dq, *J* = 10.3 and 1.5 Hz, H11), 3.95 (2 H, *app* d, *J* = 0.7 Hz, H5), 3.66 (1H, *app* t, *J* = 8.2 Hz, H3), 2.85 (1H, d, *J* = 17.4 Hz, H6), 2.73 (1H, d, *J* = 17.4 Hz, H6), 2.64-2.57 (2H, m, H9), 0.90 (9H, s, $OSiC(CH_3)_3$), 0.16 (9H, s, $Si(CH_3)_3$), 0.09 (6H, s, $OSi(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.8, 134.5, 117.2, 99.6, 89.1, 80.4, 63.4, 55.5, 28.4, 27.3, 25.9, 18.4, 0.0, –5.4, –5.5; **HRMS** (ES^+) calc. for $C_{19}H_{34}NaO_3Si_2$ $[M+Na]^+$ 389.1939; found 389.1924. Data in accordance with literature.[194]

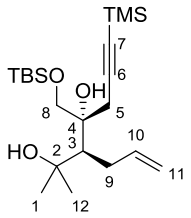
(3*S*,4*R*)-3-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-7-(trimethylsilyl)hept-6-yne-2,4-diol (262) and (3*R*,4*R*)-3-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-7-(trimethylsilyl) hept-6-yn-2-one (286)

To a stirred solution of β-lactone **284** (555 mg, 1.51 mmol, 1.0 equiv.) in THF (15 mL) under argon at –5 °C was added methylmagnesium bromide (3 M in Et_2O, 3.0 mL, 9.00 mmol, 6.0

equiv.) dropwise. The reaction mixture was warmed slowly to RT over 1.5 h before being quenched with NH_4Cl (sat. *aq.*). The layers were separated and the aqueous phase was extracted four times with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (95:5 Pet. Ether / EtOAc eluent) to afford ketone **286** (177 mg, 0.48 mmol, 31%) and tertiary alcohol **262** (383.5 mg, 0.96 mmol, 64%) as colourless oils.

Ketone **286** could be partly converted to alcohol **262** using the following representative procedure, which increased the overall yield for the formation of **262** to 75% by the following method: To a stirred solution of **286** (177 mg, 0.48 mmol, 1.0 equiv.) in THF (5 mL) under argon at –5 °C was added methylmagnesium bromide (3 M in Et_2O, 0.46 mL, 1.38 mmol, 3.0 equiv.) dropwise. The reaction mixture was warmed slowly to RT over 1.5 h before being quenched with NH_4Cl (15 mL, sat. *aq.*,). The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (95:5 Pet. Ether / EtOAc) to afford alcohol 2**62** (65 mg, 0.16 mmol, 34%) as a colourless oil.

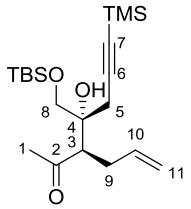
(3*S*,4*R*)-3-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-7-(trimethylsilyl)hept-6-yne-2,4-diol (262)



$[\alpha]_D^{25}$ +10.0 (*c* 1.01, $CHCl_3$); **R_f** 0.26 (4:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 3390, 2956, 2930, 2857, 2176, 1464, 1251, 1096, 841, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.84 (1H, ddt, *J* = 17.1, 10.3 and 6.6 Hz, H10), 5.01 (1H, dq, *J* = 17.1 and 1.7 Hz, H11), 4.97 (1H, dq, *J* = 10.3 and 1.7 Hz, H11), 4.22 (1H, br s, OH), 3.77 (1H, d, *J* = 10.0 Hz, H8), 3.73 (1H, d, *J* = 10.0 Hz, H8), 3.65 (1H, br s, OH), 2.66 (1H, d, *J* = 16.9 Hz, H5), 2.53 (1H, d, *J* = 16.9 Hz, H5), 2.29 (1H, dddt, *J* = 15.4, 6.6, 5.4, 1.7 Hz and H9), 2.20 (1H, t, *J* = 5.4 Hz, H3), 2.10 (1H,

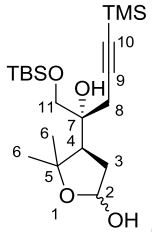
dddt, *J* = 15.4, 6.6, 5.4 and 1.7 Hz, H9), 1.29 (3H, s, H1), 1.28 (3H, s, H12), 0.92 (9H, s, OSiC(C$\underline{H}_3$)$_3$), 0.16 (9H, s, Si(C$\underline{H}_3$)$_3$), 0.10 (6H, s, OSi(C$\underline{H}_3$)$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 140.2, 114.9, 103.7, 88.3, 77.5, 74.9, 66.0, 53.3, 32.6, 32.4, 31.3, 27.0, 26.0, 18.4, 0.2, –5.3. **HRMS** (ES^+) calc. for $C_{21}H_{42}NaO_3Si_2$ $[M+Na]^+$ 421.2565; found 421.2553. Data in accordance with literature.[194]

(3*R*,4*R*)-3-Allyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-7-(trimethylsilyl) hept-6-yn-2-one (286)

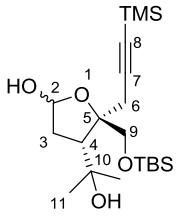


$[\alpha]_D^{25}$ +23.4 (*c* 1.00, $CHCl_3$); **R_f** 0.38 (9:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 2957, 2857, 2173, 1716, 1638, 1472, 1361, 1251, 1106, 842, 778, 669; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.70 (1H, ddt, *J* = 17.0, 10.1 and 7.1Hz, H10), 5.05 (1H, dq, *J* = 17.0, 1.5 Hz and H11), 5.01 (1H, ddt, *J* = 10.1, 1.5 and 0.7 Hz), 3.65 (1H, d, *J* = 10.0 Hz, H8), 3.57 (1H, d, *J* = 10.0 Hz, H8), 3.12 (1H, dd, *J* = 8.6 and 6.6 Hz, H3), 3.10 (1H, s, OH), 2.57 (1H, d, *J* = 17.1 Hz, H5), 2.51 (1H, d, *J* = 17.1 Hz, H5), 2.39-2.34 (2H, m, H9), 2.23 (3H, s, H1), 0.90 (9H, s, OSiC(C$\underline{H}_3$)$_3$), 0.16 (9H, s, Si(C$\underline{H}_3$)$_3$), 0.08 (6H, s, OSi(C$\underline{H}_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 213.9, 135.7, 117.2, 102.9, 88.5, 74.7, 65.6, 55.5, 34.2, 31.7, 28.8, 26.0, 18.4, 0.2, –5.3, –5.4; **HRMS** (ES^+) calc. for $C_{20}H_{38}NaO_3Si_2$ $[M+Na]^+$ 405.2252, found 405.2238. Data in accordance with literature.[194]

(4*R*)-4-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-5-(trimethylsilyl)pent-4-yn-2-yl)-5,5-dimethyltetrahydrofuran-2-ol (288) and (4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl) oxy)methyl)-4-(2-hydroxypropan-2-yl)-5-(3-(trimethylsilyl)prop-2-yn-1-yl)tetrahydrofuran -2-ol (289)



288



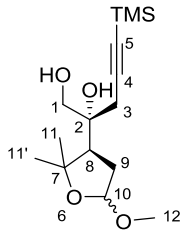
289

To a stirred solution of alkene **262** (88.4 mg, 0.222 mol, 1.0 equiv.) in 1,4-dioxane (2.3 mL) and water (0.5 mL) was sequentially added 2,6-lutidine (51 µL, 0.443 mmol, 2.0 equiv.), OsO_4 (2.5 wt% in *t*-BuOH, 58 µL, 4.4 µmol, 0.02 equiv.) and $NaIO_4$ (189 mg, 0.887 mmol, 4.0 equiv.).[153] The reaction mixture was stirred for 2 h at RT, then it was diluted with water and Et_2O. The layers were separated and the aqueous phase was extract three times with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was filtered through a short plug of silica (4:1 Pet. Ether / Et_2O eluent), then concentrated to give lactols **288** and **289** as a 40:27:22:11 inseparable mixture of isomers, as a colourless oil (78.1 mg, 0.194 mmol, 88%). $\mathbf{R_f}$ 0.15 (7:3 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 3420, 2956, 2930, 2857, 2176, 1464, 1251, 1096, 841, 779; NMR data reported for major diastereomer; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.41 (1H, d, *J* = 5.1 Hz, H2), 3.73 (1H, d, *J* = 9.3 Hz, H7), 3.45 (1H, d, *J* = 9.3 Hz, H7), 2.65 (1H, d, *J* = 16.8 Hz, H9), 2.55 (1H, dd, *J* = 13.0 and 6.7 Hz, H4), 2.50 (1H, d, *J* = 16.8 Hz, H9), 2.31 (1H, *app* td, *J* = 12.8 and 5.1 Hz, H3), 1.88 (1H, dd, *J* = 12.6, 6.7 Hz, H3), 1.53 (3H, s, H6), 1.26 (3H, s, H6), 0.92 (9H, s, $OSiC(CH_3)_3$), 0.15 (3H, s, $OSi(CH_3)_2$), 0.14 (12H, *app* br s, $OSi(CH_3)_2$ and $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 104.1, 103.4, 96.6, 96.1, 95.6, 88.1, 88.1, 86.5, 84.7, 83.4, 73.8, 73.7, 70.6, 69.2, 67.1, 66.7, 50.5, 50.1, 47.2, 37.6, 35.9, 35.1, 32.8, 32.5, 31.0, 28.3, 28.2, 27.9, 26.2, 26.0, 26.0, 25.9, 25.8, 25.5, 18.4, 18.4, 0.1, –5.3, –5.4; **HRMS** (ES^+) calc. for $C_{20}H_{40}NaO_4Si_2$ $[M+Na]^+$ 423.2357; found 423.2347.

(2*R*)-2-((3*R*)-5-Methoxy-2,2-dimethyltetrahydrofuran-3-yl)-5-(trimethylsilyl)pent-4-yne-1,2-diol (290) and 2-((2*R*,3*S*)-2-(hydroxymethyl)-5-methoxy-2-(3-(trimethylsilyl)prop-2-yn-1-yl)tetrahydrofuran-3-yl)propan-2-ol (291)

To a stirred solution of lactols **288** and **289** (73.4 mg, 0.18 mmol, 1.0 equiv.) in methanol (2.6 mL) was added CSA (10.5 mg, 0.045 mmol, 0.25 equiv.). The reaction mixture was stirred overnight, then it was quenched by addition of $NaHCO_3$ (10 mL, sat. *aq.*,). Et_2O (20 mL) was added to the solution, the layers were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (7:3 Pet. Ether / EtOAc eluent) to give a mixture of diols **290** and **291** (53 mg, 0.175 mmol, 98%) as a white solid. These diols were generally not readily separated by chromatography, and they were generally carried forward to the (separable) aldehydes **292** and **293**; the data presented below was obtained for the purpose of characterization by careful chromatography.

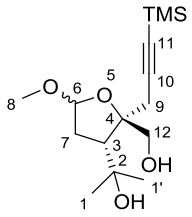
(2*R*)-2-((3*R*)-5-Methoxy-2,2-dimethyltetrahydrofuran-3-yl)-5-(trimethylsilyl)pent-4-yne-1,2-diol (290) (64:36 mixture of epimers)



IR (thin film, ν_{max} / cm^{-1}) 3436, 2958, 2928, 2175, 1467, 1250, 1105, 1051, 1033; **HRMS** (ES^+) calc. for $C_{15}H_{28}NaO_4Si$ $[M+Na]^+$ 323.1649; found 323.1641. **Major epimer: R_f** 0.23 (7:3 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.88 (1H, d, *J* = 5.0 Hz, H10), 3.68 (1H, dd, *J* = 10.9 and 5.5 Hz, H1), 3.58 (1H, dd, *J* = 10.9 and 6.5 Hz, H1), 3.33 (3H, s, H12), 2.64 (2H, *app* d, *J* = 2.8 Hz, H3), 2.48 (1H, dd, *J* = 12.6 and 6.6 Hz, H8), 2.43 (1H, s, OH), 2.21 (1H, td, *J* = 12.6 and 5.0 Hz, H9), 2.07 (1H, t, *J* = 6.3 Hz, OH), 1.90 (1H, dd, *J* = 12.6 and 6.6 Hz, H9), 1.47 (3H, s, H11), 1.30 (3H, s, H11'), 0.16 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 102.8, 102.0, 89.3, 83.9, 73.4, 67.4, 54.2, 48.8, 34.5, 32.5, 28.6, 25.7, 0.1. **Minor**

epimer: R_f 0.33 (7:3 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.95 (1H, dd, *J* = 6.0 and 3.8 Hz, H10), 3.61 (2H, *app* t, *J* = 5.8 Hz, H1), 3.36 (3H, s, H12), 2.78 (1H, s, OH), 2.64 (2H, *app* d, *J* = 0.9 Hz, H3), 2.32 (1H, td, *J* = 8.8 and 6.0 Hz, H9), 2.29 (1H, dd, *J* = 11.0 and 8.8 Hz, H8), 2.14-2.09 (1H, m, H9), 1.43 (3H, s, H11), 1.41 (3H, s, H11'), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 103.3, 103.0, 89.2, 83.4, 73.6, 67.4, 55.2, 50.9, 34.7, 31.0, 28.8, 25.6, 0.1.

2-((2*R*,3*S*)-2-(Hydroxymethyl)-5-methoxy-2-(3-(trimethylsilyl)prop-2-yn-1-yl)tetrahydrofuran-3-yl)propan-2-ol (291) (53:47 mixture of epimers)

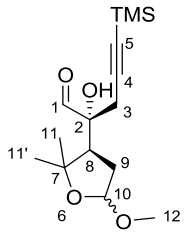


R_f 0.18 (7:3 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3414, 2957, 2923, 2179, 1463, 1250, 1104, 1046, 843; **HRMS** (ES^+) calc. for $C_{15}H_{28}NaO_4Si$ $[M+Na]^+$ 323.1649; found 323.1637. **Major epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.97 (1H, d, *J* = 5.5 Hz, H6), 3.90 (1H, d, *J* = 11.7 Hz, H12), 3.78 (1H, d, *J* = 12.4 Hz, H12), 3.38 (3H, s, H8), 2.71 (1H, d, *J* = 17.4 Hz, H9), 2.64 (1H, d, *J* = 17.4 Hz, H9), 2.63 (1H, *app* dd, *J* = 13.8 and 7.2 Hz, H3), 2.42-2.37 (1H, m, H7), 2.33 (1H, br s, OH), 2.03 (1H, ddd, *J* = 17.0, 15.4 and 4.5 Hz, H7), 1.38 (3H, s, H1), 1.26 (3H, s, H1), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 104.3, 103.6, 88.6, 85.3, 70.6, 66.6, 55.1, 49.3, 35.3, 31.0, 29.6, 25.9, 0.1. **Minor epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.98 (1H, d, *J* = 5.1 Hz, H6), 3.73 (1H, d, *J* = 11.4 Hz, H12), 3.65 (1H, d, *J* = 11.5 Hz, H12), 3.40 (3H, s, H8), 2.83 (1H, d, *J* = 17.2 Hz, H9), 2.75 (1H, d, *J* = 17.2 Hz, H9), 2.40-2.35 (1H, m, H3), 2.33 (1H, br s, OH), 2.27 (1H, ddd, *J* = 13.7, 12.5 and 5.1 Hz, H7), 1.97 (1H, dd, *J* = 12.5 and 6.7 Hz, H7), 1.39 (3H, s, H1), 1.32 (3H, s, H1), 0.14 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 104.5, 103.0, 88.0, 87.6, 70.8, 68.7, 55.9, 51.8, 35.7, 31.3, 29.9, 25.6, 0.0.

(2*R*)-2-Hydroxy-2-((3*R*)-5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)-5-(trimethylsilyl)pent-4-ynal (292) and (2*R*,3*S*)-3-(2-hydroxypropan-2-yl)-5-methoxy-2-(3-(trimethylsilyl)prop-2-yn-1-yl)tetrahydrofuran-2-carbaldehyde (293)

Dry DMSO (1.02 mL, 14.3 mmol) was added to SO_3•py (438 mg, 2.75 mmol, 8.1 equiv.) under Ar, and the suspension was stirred for 15 min at RT. Dichloromethane (5.5 mL) was added, then the mixture was cooled to 0 °C and stirred for a further 10 min. A solution of diols **290** and **291** (101 mg, 0.34 mmol, 1.0 equiv.) and *N*,*N*-diisopropylethylamine (1.00 mL, 1.85 mmol) in dichloromethane (5.5 mL) was added, and the resulting mixture stirred between 0 °C and 10 °C for 1 h before being quenched by addition of NH_4Cl (10 mL, sat. *aq.*). Et_2O was added (~30 mL), the layers were separated, and the organic layer was washed sequentially with $NaHCO_3$ (10 mL, sat. *aq.*), followed by brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography on a short plug of silica (8:2 Pet. Ether / Et_2O eluent), to yield the separable aldehydes **292** (56.2 mg, 0.19 mmol, 55%, 61:39 mixture of epimers) and **293** (29.0 mg, 0.097 mmol, 29%, 53:47 mixture of epimers), both as a colourless oils.

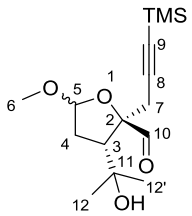
(2*R*)-2-Hydroxy-2-((3*R*)-5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)-5-(trimethylsilyl)pent-4-ynal (292) (61:39 mixture of epimers)



R_f 0.44 (4:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 3420, 2958, 2920, 2179, 1732, 1370, 1250, 1105, 1045), 977, 844, 760; **HRMS** (ES^+) calc. for $C_{15}H_{26}NaO_4Si$ $[M+Na]^+$ 321.1493; found 321.1490. **Major epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.69 (1H, d, *J* = 0.9 Hz, H1), 4.87 (1H, d, *J* = 4.8 Hz, H10), 3.48 (1H, d, *J* = 0.9 Hz, OH), 3.32 (3H, s, H12), 2.78 (1H, d, *J* = 17.0 Hz, H3), 2.77 (1H, d, *J* = 13.0, 6.6 Hz, H8), 2.74 (1H, d, *J* = 17.0 Hz, H3), 2.09 (1H, td, *J* = 12.8 and 4.8 Hz, H9), 1.73 (1H, dd, *J* = 12.6 and 6.6 Hz, H9), 1.50 (3H, s, H11), 1.43 (3H,

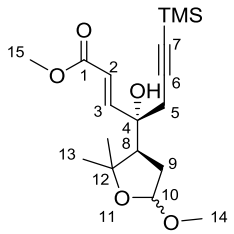
s, H11'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 202.2, 102.2, 99.5, 90.5, 83.8, 78.4, 54.2, 49.0, 34.2, 32.6, 30.8, 28.6, 0.0. **Minor epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.73 (1H, d, *J* = 0.7 Hz, H1), 4.97 (1H, dd, *J* = 6.1 and 3.8 Hz, H10), 3.71 (1H, d, *J* = 0.7 Hz, OH), 3.34 (3H, s, H12), 2.61 (1H, d, *J* = 12.0 Hz, H3), 2.57 (1H, d, *J* = 12.0 Hz, H3), 2.51 (1H, dd, *J* = 10.8 and 9.4 Hz, H8), 2.24 (1H, ddd, *J* = 13.6, 9.4 and 6.1 Hz, H9), 2.02 (1H, ddd, *J* = 13.6, 10.8 and 3.8 Hz, H9), 1.31 (3H, s, H11), 1.22 (3H, s, H11'); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 202.2, 103.4, 99.6, 90.4, 83.2, 78.4, 55.3, 51.0, 34.5, 28.7, 25.8, 25.5, 0.0.

(2*R*,3*S*)-3-(2-Hydroxypropan-2-yl)-5-methoxy-2-(3-(trimethylsilyl)prop-2-yn-1-yl)tetrahydrofuran-2-carbaldehyde (293) (53:47 mixture of epimers)



IR (thin film, ν_{max} / cm^{-1}) 3458, 2959, 2179, 1740, 1211, 1043, 842; **HRMS** (ES^+) calc. for $C_{15}H_{26}NaO_4Si$ $[M+Na]^+$ 321.1493; found 321.1496. **Major epimer: R_f** 0.26 (4:1 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.53 (1H, s, H10), 5.16 (1H, dd, *J* = 6.0 and 4.2 Hz, H5), 3.47 (3H, s, H6), 3.05 (1H, d, *J* = 17.0 Hz, H7), 2.97 (1H, d, *J* = 17.0 Hz, H7), 2.39 (1H, ddd, *J* = 12.5, 9.1 and 6.0 Hz, H4), 2.34 (1H, dd, *J* = 9.9 and 9.1 Hz, H3), 2.12 (1H, ddd, *J* = 12.5, 9.9 and 4.2 Hz, H4), 1.95 (1H, s, OH), 1.25 (3H, s, H12), 1.25 (3H, s, H12), 0.12 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 200.3, 105.1, 102.9, 87.7, 87.4, 70.3, 56.2, 54.2, 34.5, 30.7, 30.6, 24.0, 0.1. **Minor epimer: R_f** 0.34 (4:1 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.39 (1H, s, H10), 5.18 (1H, d, *J* = 5.0 Hz, H5), 3.42 (3H, s, H6), 2.86 (1H, d, *J* = 17.3 Hz, H7), 2.82 (1H, d, *J* = 17.3 Hz, H7), 2.64 (1H, dd, *J* = 13.1, 6.8 Hz, H3), 2.37 (1H, ddd, *J* = 13.1, 12.1 and 5.0 Hz, H4), 2.02 (1H, dd, *J* = 12.1 and 6.8 Hz, H4), 1.98 (1H, s, OH), 1.30 (3H, s, H12), 1.28 (3H, s, H12), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 200.6, 104.5, 103.4, 88.5, 88.1, 70.9, 55.1, 50.5, 35.2, 30.6, 30.4, 23.6, 0.0.

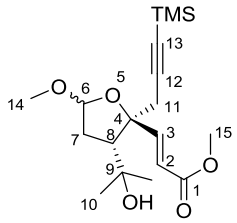
Methyl (4*S*,*E*)-4-hydroxy-4-((3*R*)-5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)-7-(trimethylsilyl)hept-2-en-6-ynoate (298)



To a solution of aldehyde **292** (25.7 mg, 0.086 mmol, 1.0 equiv) in anhydrous dichloromethane (3.1 mL) under argon was added methyl 2-(triphenyl-λ^5-phosphanylidene)acetate **297** (43.1 mg, 0.129 mmol, 1.5 equiv), obtained by pre-washing (2-methoxy-2-oxoethyl)triphenylphosphonium bromide with 1M *aq.* NaOH solution). The reaction mixture was stirred at 50 °C overnight before the solvent was carefully removed *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (6:1 Pet. Ether/ Et_2O), to yield α, β-unsaturated ester **298** (22.8 mg, 78%, 94% brsm, 62:38 mixture of epimers) as a colourless oil, and some aldehyde **292** (4.5 mg, 18%) was recovered. These epimers were generally not readily separated by chromatography, and they were generally carried forward; the data presented below was obtained for the purpose of characterization by careful chromatography. **IR** (thin film, ν_{max} / cm^{-1}) 2970 (m), 2361 (w), 1737 (s), 1370 (w), 1437 (w), 1366 (m), 1229 (m), 1217 (m), 1104 (m), 846 (w); **LRMS** (ESI$^+$, m/z (%)) 377 (100), 323 (24), 242 (25); **HRMS** (ESI$^+$) calc. for $C_{18}H_{30}NaO_5Si$ [M+Na]$^+$ 377.1755, found 377.1761. **Major epimer: R_f** 0.17 (7:3 Pet. Ether/ Et_2O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.98 (1H, d, *J* = 15.5 Hz, H3), 6.07 (1H, d, *J* = 15.5 Hz, H2), 4.86 (1H, d, *J* = 4.6 Hz, H10), 3.75 (3H, s, H15), 3.31 (3H, s, H14), 2.64 (1H, d, *J* = 16.9 Hz, H5), 2.60 (1H, dd, *J* = 13.2, 6.6 Hz, H8), 2.52 (1H, d, *J* = 16.9 Hz, H5), 2.33 (1H, s, OH), 2.08 (1H, *app* td, *J* = 12.7, 4.9 Hz, H9), 1.90 (1H, dd, *J* = 12.5, 6.6 Hz, H9), 1.45 (3H, s, H13), 1.43 (3H, s, H13), 0.14 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 166.7, 150.3 , 120.8, 102.1, 100.4, 90.1, 84.1, 74.3, 54.2 52.7, 51.8, 35.6, 34.2, 32.6, 25.8, 0.1; **Minor epimer: R_f** 0.22 (7:3 Pet. Ether/ Et_2O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.07 (1H, d, *J* = 15.4 Hz, H3), 6.12 (1H, d, *J* =

15.4 Hz, H2), 4.92 (1H, dd, *J* = 5.7, 2.6 Hz, H10), 3.75 (3H, s, H15), 3.53 (1H, s, OH), 3.34 (3H, s, H14), 2.69 (1H, d, *J* = 17.1 Hz, H5), 2.55 (1H, d, *J* = 17.1 Hz, H5), 2.45 (1H, dd, *J* = 9.5, 7.2 Hz, H8), 2.35 (1H, ddd, *J* = 13.5, 9.5, 5.7 Hz, H9), 1.95 (1H, ddd, *J* = 13.5, 7.2, 2.6 Hz, H9), 1.43 (3H, s, H13), 1.37 (3H, s H13), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 167.0, 152.0, 120.0, 103.2, 101.4, 91.1, 84.3, 74.9, 54.9, 52.4, 51.8, 36.0, 33.1, 31.4, 25.7, 0.0.

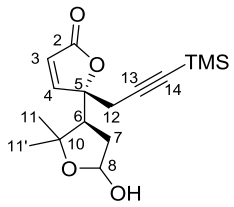
Methyl (*E*)-3-((2*S*,3*S*)-3-(2-hydroxypropan-2-yl)-5-methoxy-2-(3-(trimethylsilyl)prop-2-yn-1-yl)tetra-hydrofuran-2-yl)acrylate (299)



To a solution of aldehyde **293** (5.7 mg, 0.0191 mmol, 1.0 equiv) in anhydrous dichloromethane (0.7 mL) under argon was added methyl 2-(triphenyl-λ^5-phosphanylidene)acetate **297** (9.6 mg, 0.0286 mmol, 1.5 equiv), obtained by pre-washing (2-methoxy-2-oxoethyl)triphenylphosphonium bromide with 1M *aq.* NaOH solution). The reaction mixture was stirred at 50 °C for 4 h before the solvent was carefully removed *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (6:1 Pet. Ether/ Et_2O), to yield α,β-unsaturated ester **299** (6.0 mg, 93%, 42:38:14:6 mixture of (*E*)-epimers and (*Z*)-epimers) as a colourless oil. These epimers were generally not readily separated by chromatography, and they were generally carried forward; the data presented below was obtained for the purpose of characterization by careful chromatography. **IR** (thin film, ν_{max} / cm^{-1}) 3514 (br), 2959 (m), 2179 (w), 1726 (s), 1438 (m), 1281 (m), 1250 (m), 1036 (s), 939 (s), 843 (s); **LRMS** (ESI^+, m/z (%)) 377 (100), 304 (22), 265 (24), 242 (100); **HRMS** (ESI^+) calc. for $C_{18}H_{30}NaO_5Si$ $[M+Na]^+$ 377.1755, found 377.1755. **Major epimer: R_f** 0.28 (4:1 Pet. Ether/ EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.26 (1H, d, *J* = 15.5 Hz, H3), 6.23 (1H, d, *J* = 15.5 Hz, H2), 5.07 (1H, d, *J* = 4.1 Hz, H6), 3.76

(3H, s, H15), 3.42 (3H, s, H14), 2.98 (1H, d, *J* = 17.2 Hz, H11), 2.79 (1H, d, *J* = 17.2 Hz, H11), 2.41 (1H, *app* dt, *J* = 12.6, 6.9 Hz, H7), 2.15 (1H, ddd, *J* = 12.6, 11.7, 4.1Hz, H7), 2.13-2.08 (2H, m, H8 and OH), 1.40 (3H, s, H10), 1.24 (3H, s, H10), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 167.4, 150.6, 120.3, 104.2, 103.7, 88.7, 84.1, 70.2, 58.9, 56.0, 51.8, 34.7, 30.9, 30.7, 27.5, 0.0. **Minor epimer: R_f** 0.23 (4:1 Pet. Ether/ EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) 7.27 (1H, d, *J* = 15.5 Hz, H3), 6.19 (1H, d, *J* = 15.5 Hz, H2), 5.05 (1H, dd, *J* = 5.1 Hz, H6), 3.76 (3H, s, H15), 3.44 (3H, s, H14), 2.74 (2 H, d, *J* = 15.5 Hz, H11), 2.69 (1H, d, *J* = 15.5 Hz, H11), 2.45 (1H, dd, *J* = 13.6, 6.2 Hz, H8), 2.34 (1H, ddd, *J* = 13.6, 12.2, 5.1 Hz, H7), 2.23 (1H, s, OH), 1.99 (1H, dd, *J* = 12.2, 6.2 Hz, H7), 1.42 (3H, s, H10), 1.31 (3H, s, H10), 0.16 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 167.3, 152.3, 119.3, 104.3, 103.2, 89.0, 85.9, 70.5, 55.9, 55.2, 51.8, 35.0, 31.2, 30.9, 28.3, 0.0.

(5*S*)-5-((3*S*)-5-hydroxy-2,2-dimethyltetrahydrofuran-3-yl)-5-(3-(trimethylsilyl)prop-2-yn-1-yl)furan-2(5*H*)-one (304)

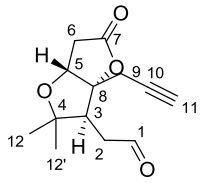


To a stirred solution of ethyl 2-(diphenoxyphosphoryl)acetate **242** (34.7 mg, 0.108 mmol, 2.0 equiv.) in THF (1 mL) under argon at 0 °C was added KHMDS (0.5 M in toluene, 0.2 mL, 0.102 mmol, 1.9 equiv.) and the resulting mixture was stirred at 0 °C for 20 min before being added dropwise to a solution of aldehyde **290** (16.1 mg, 0.054 mmol, 1.0 equiv.) in THF (0.64 mL). The reaction mixture was stirred between 0 °C and 10 °C for 2 h and was then quenched by addition of NH_4Cl (sat. *aq.*, 5 mL). Et_2O was added (10 mL), the layers were separated, and the aqueous phase was extracted two times with Et_2O (2x10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on a short plug of silica (8:2 Pet. Ether / EtOAc), to yield the

intermediate α,β-unsaturated lactone as a colourless oil, which co-eluted with residual phosphonate, and was therefore used in the next step without further purification.

To a stirred solution of the above crude lactone in dichloromethane (2.8 mL) and water (13 μL) at 0 °C was added TFA (0.26 mL) dropwise. The reaction mixture was stirred for 15 min at 0 °C before being neutralized by addition of $NaHCO_3$ (5 mL, sat. *aq.*). The layers were separated and the aqueous phase was extracted three times with dichloromethane (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography on a short plug of silica (1:1 Pet. Ether / Et_2O eluent), to give lactol **304** (7.7 mg, 0.025 mmol, 47% over 2 steps, inseparable 67:33 mixture of lactol epimers) as a colourless oil. These epimers were generally not readily separated by chromatography, and they were generally carried forward; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.18 (Pet. Ether/ EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3420, 2959, 2138, 1752, 1252, 1005, 841; **HRMS** (ES^+) calc. for $C_{16}H_{24}O_4NaSi$ $[M+Na]^+$ 331.1336; found 331.1328. **Major epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.50 (1H, d, *J* = 5.6 Hz, H4), 6.13 (1H, d, *J* = 5.6 Hz, H3), 5.38 (1H, dd, *J* = 4.6 and 1.7 Hz, H8), 2.95 (1H, dd, *J* = 13.0 and 6.5 Hz, H6), 2.94 (1H, d, *J* = 16.8 Hz, H12), 2.66 (1H, d, *J* = 16.8 Hz, H12), 2.56 (1H, br s, OH), 1.87 (1H, tdd, *J* = 12.8, 4.6 and 1.3 Hz, H7), 1.73 (1H, dd, *J* = 12.5 and 6.5 Hz, H7), 1.55 (3H, s, H11), 1.25 (3 H, s, H11'), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 172.1, 159.4 (C4), 121.2, 99.4, 95.3, 90.7, 87.9, 83.8, 48.2, 35.3, 32.4, 29.3, 25.4, –0.1. **Minor epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.49 (1H, d, *J* = 5.7 Hz, H4), 6.15 (1H, d, *J* = 5.7 Hz, H3), 5.48 (1H, ddd, *J* = 6.2, 5.0 and 3.8 Hz, H8), 2.86 (1H, d, *J* = 16.9 Hz, H12), 2.76 (1H, d, *J* = 3.8 Hz, OH), 2.66 (1H, d, *J* = 16.9 Hz, H12), 2.59 (1H, dd, *J* = 12.5 and 8.3 Hz, H6), 2.23 (1H, ddd, *J* = 13.6, 7.9 and 6.2 Hz, H7), 1.63 (1H, td, *J* = 12.9 and 5.0 Hz, H7), 1.43 (3H, m, H11), 1.35 (3H, s, H11'), 0.15 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 171.8, 158.5, 121.7, 99.3, 96.1, 90.8, 87.9, 82.7, 51.9, 36.2, 30.3, 30.1, 25.8, –0.1.

2-((3*S*,3a*R*,6a*R*)-2,2-dimethyl-5-oxo-3a-(prop-2-yn-1-yl)hexahydrofuro[3,2-*b*]furan-3-yl)acetaldehyde (261)

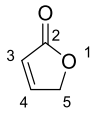


To a stirred solution of lactol **304** (134 mg, 0.436 mmol, 1.0 equiv.) in MeOH (18 mL) under argon was added K_2CO_3 (241 mg, 1.74 mmol, 4.0 equiv.). The reaction mixture was stirred at RT for 2 h, then NH_4Cl (10 mL, sat. *aq.*) was added. The mixture was extracted three times with EtOAc (3 x 10 mL), then the combined organic layers were dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography on a short plug of silica (2:1 Pet. Ether / EtOAc) to give the aldehyde **261** (103 mg, 0.436 mmol, quant.) as a white solid. $\mathbf{[\alpha]_D^{25}}$ +38.5 (*c* = 1.05, $CHCl_3$); **mp** 93-96 °C; $\mathbf{R_f}$ 0.26 (3:2 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 2977, 1775, 1722, 1475, 1246, 1199, 1058; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.81 (1H, t, *J* = 2.0 Hz, H1), 4.54 (1H, d, *J* = 6.4 Hz, H5), 3.02 (1H, dd, *J* = 18.7 and 6.7 Hz, H6), 2.80 (1H, dd, *J* = 9.0 and 6.2 Hz, H3), 2.73 (1H, dd, *J* = 18.7 and 0.5 Hz, H6), 2.70 (1H, dd, *J* = 17.0 and 2.6 Hz, H9), 2.61 (1H, ddd, *J* = 16.7, 9.0 and 2.1 Hz, H2), 2.51 (1H, dd, *J* = 17.0 and 2.6 Hz, H9), 2.43 (1H, ddd, *J* = 16.7, 6.2 and 1.9 Hz, H2), 2.13 (1H, t, *J* = 2.6 Hz, H11), 1.37 (3H, s, H12), 1.14 (3H, s, H12); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 199.3 (C1), 175.0 (C7), 94.1 (C8), 83.2 (C4), 78.7 (C5), 77.4 (C10), 72.9 (C11), 52.8 (C3), 40.7 (C2), 37.3 (C6), 28.0 (C12), 25.5 (C9), 21.2 (C12); **HRMS** (ES^+) calc. for $C_{13}H_{16}NaO_2$ $[M+Na]^+$ 259.0941; found 259.0938.

7.5. Procedures and Characterisations for Attachment of the G Ring

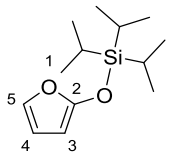
7.5.1. Investigations with a simple model system

Furan-2(5*H*)-one (306)



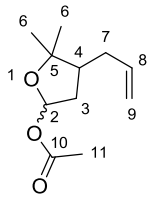
To a stirred solution of furfuraldehyde (12.9 mL, 156 mmol, 1.0 equiv.) in dichloromethane (50 mL) in a three-necked round-bottomed flask fitted with a condenser and a dropping funnel, were added sequentially sodium sulphate (7.5 g, 50 w/w%), *N*,*N*-dimethylethanolamine (5.3 mL, 53.1 mmol, 0.34 equiv.) and formic acid (11.8 mL, 312 mmol, 2.0 equiv.). Hydrogen peroxide (50% w/v in water, 17.0 mL, 250 mmol, 2.0 equiv.) was added slowly through the dropping funnel and the reaction mixture spontaneously started refluxing. After complete addition of hydrogen peroxide, the reaction mixture was stirred vigorously overnight. Upon completion of reaction, the biphasic reaction mixture was separated and the aqueous layer extracted with dichoromethane (20 mL). The combined organic layer was washed with sat. *aq.* Na_2SO_3 solution (2 × 50 mL) and then tested negative with peroxide test. The organic layer was dried with Na_2SO_4 and the solvent removed carefully *in vacuo*. The residue was purified by distillation under reduced pressure at 90-92 °C (19 mbar) to yield furanone **307** as a light yellow oil (2.16 g, 16%). **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.58 (1H, dt, *J* = 5.8, 1.7 Hz, H4), 6.18 (1H, dt, *J* = 5.8, 2.2 Hz, H3), 4.91 (2H, dd, *J* = 2.2, 1.7 Hz, H5); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.8, 152.9, 121.8, 72.3. Data in accordance with literature.[206]

(Furan-2-yloxy)triisopropylsilane (308)



To a stirred solution of furanone **307** (500 mg, 5.95 mmol, 1.0 equiv.) in dry dichloromethane (5 mL) at 0 °C was added sequentially triethylamine (1.66 mL, 11.9 mmol, 2.0 equiv.) and triisopropylsilyl trifluoromethanesulfonate (1.74 mL, 7.14 mmol, 1.2 equiv.). The reaction mixture was warmed quickly to RT and stirred vigorously for 3 h before being quenched with water (5 mL). The phases were separated, the organic phase was dried with Na_2SO_4 and the solvent removed carefully *in vacuo*. The residue was purified by distillation under reduced pressure at 110-112 °C (11 mbar) to yield the siloxyfuran **308** as a colorless oil (1.24 g, 87%). $\mathbf{R_f}$ 0.80 (Pet. Ether / EtOAc (9:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.80 (dd, 1H, *J* = 2.2, 1.1 Hz, H5), 6.20 (dd, 1H, *J* = 3.1, 2.2 Hz, H3), 5.12 (dd, 1H, *J* = 3.1, 1.1 Hz, H4), 1.36-1.18 (3H, m, Si(C<u>H</u>$Me_2)_3$), 1.11 (18H, d, J = 6.8 Hz, Si(CH<u>Me_2</u>)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.1, 132.0, 111.2, 83.6, 17.7, 12.3. Data in accordance with literature.[207]

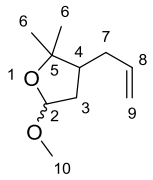
4-Allyl-5,5-dimethyltetrahydrofuran-2-yl acetate (309)



To a stirred solution of 4-allyl-5,5-dimethyltetrahydrofuran-2-ol **254** (100 mg, 0.640 mmol, 1.0 equiv.) in dry dichloromethane (6.4 mL) at 0 °C was sequentially added triethylamine (133 µL, 0.640 mmol, 1.0 equiv.), DMAP (16 mg, 0.128 mmol, 0.2 equiv.) and acetic anhydride (72 µL, 0.768 mmol, 1.2 equiv.). The reaction mixture was stirred overnight, warming to RT before being quenched with sat. *aq.* NH_4Cl solution. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude

product was purified by flash column chromatography on a short plug of silica (Pet. Ether/ Et_2O (9:1)) to yield acetate **309** (85 mg, 67%, as a 65:35 mixture of diastereomers) as a colourless oil. $\mathbf{R_f}$ 0.24 (Pet. Ether / Et_2O (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3078 (m), 2976 (m), 2934 (m), 1742 (s), 1642 (s), 1447 (m), 1373 (m), 1327 (m), 1236 (s), 1133 (m), 974 (s); **HRMS** (FI^+) calc. for $C_{11}H_{18}O_3$ $[M]^+$ 198.1256, found 198.1263. **Major diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.16 (1H, d, *J* = 4.8 Hz, H2), 5.77 (1H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H8), 5.08 (1H, dd, *J* = 17.0, 1.2 Hz, H9), 5.02 (1H, dd, *J* = 10.1, 1.2, H9), 2.23-2.15 (2H, m, H4 and H7), 2.12 (1H, dd *J* = 13.2, 6.1, H3), 2.03 (3H, s, H11), 2.01-1.93 (1H, m, H7), 1.84 (1H, ddd, *J* = 13.2, 11.9, 4.8, H3), 1.35 (3H, s, H6), 1.07 (3H, s, H6); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 170.8, 137.0, 116.3, 97.4, 85.5, 45.0, 38.5, 34.4, 29.6, 23.3, 21.6. **Minor diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.18 (1H, dd, *J* = 6.4, 4.3 Hz, H2), 5.77-5.69 (1H, m, H8), 5.06 (1H, dq, *J* = 17.1, 1.5 Hz, H9), 5.01 (1H, dd, *J* = 9.7, 1.5 Hz, H9), 2.52 (1H, ddd, *J* = 14.1, 8.1, 6.4 Hz, H3), 2.09-2.04 (2H, m, H7), 2.04 (3H, s, H11), 1.95-1.90 (1H, m, H4), 1.79 (1H, ddd, *J* = 14.1, 10.1, 4.3 Hz, H3), 1.28 (3H, s, H6), 1.19 (3H, s, H6); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 170.8, 136.9, 116.2, 97.8, 84.9, 47.6, 38.5, 34.7, 28.0, 22.9, 21.6.

3-allyl-5-methoxy-2,2-dimethyltetrahydrofuran (310)

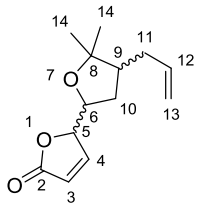


To a stirred solution of lactol **254** (50 mg, 0.320 mmol, 1.0 equiv.) in dry methanol (6.4 mL) under argon was added pyridinium *p*-toluenesulfonate (3.2 mg, 0.013 mmol, 0.04 equiv.). The reaction mixture was stirred at RT for 2 h before the solvent was removed carefully *in vacuo*. The residue was diluted with diethyl ether and filtered through a short pad of celite to yield crude methyl ether **310** (24.1 mg, 44%) as a colourless oil. The methyl ether was used without further purification in the next step.

5-(4-Allyl-5,5-dimethyltetrahydrofuran-2-yl)furan-2(5H)-one and (311) and 5-(4-allyl-5,5-dimethyltetrahydrofuran-2-yl)furan-2(3H)-one (312)

To a stirred solution of zinc(II) chloride (5.5 mg, 0.040 mmol, 0.4 equiv.) in dry dichloromethane (0.2 mL) at –40 °C was added a solution of acetate **309** (20.0 mg, 0.101 mmol, 1.0 equiv.) and siloxyfuran **308** (48.5 mg, 0.202 mmol, 2.0 equiv.) in dry dichloromethane (0.8 mL). The reaction mixture was stirred at –40 °C for 2 h before being quenched with NH_4Cl (2 mL, sat. *aq.*) and diluted with diethyl ether (3 mL). The layers were separated and the aqueous layer extracted three times with diethyl ether (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica with gradient elution (Pet. Ether/ EtOAc (19:1 to 4:1)) to yield butenolides **311** (20.2 mg, 90%, as a 1:1 mixture of diastereomers) and **312** (2.3 mg, 10%) as colourless oils.

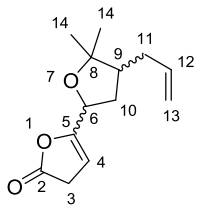
5-(4-Allyl-5,5-dimethyltetrahydrofuran-2-yl)furan-2(5*H*)-one (311)



IR (thin film, ν_{max} / cm^{-1}) 3078 (m), 2972 (m), 2932 (m), 1755 (s), 1641 (w), 1460 (w), 1382 (w), 1369 (w), 1157 (m), 1040 (m), 911 (m); **HRMS** (FI^+) calc. for $C_{13}H_{18}O_3$ $[M]^+$ 222.1256, found 222.1259. **Diastereomer a: R_f** 0.27 (Pet. Ether / EtOAc (4:1)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.57 (1H, dd, *J* = 5.8, 1.5 Hz, H4), 6.15 (1H, dd, *J* = 5.8, 1.9 Hz, H3), 5.75 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, H12), 5.05 (1H, dd, *J* = 17.0, 1.4 Hz, H13), 5.00 (1H, d, *J* = 10.2 Hz, H13), 4.80 (1H, dt, *J* = 7.1, 1.7 Hz, H5), 3.89-3.81 (1H, m , H6), 2.19-2.06 (2H, m , H11 and H10), 2.00-1.89 (2H, m, H11 and H9), 1.83 (1H, ddd, *J* = 13.2, 12.5, 8.0 Hz, H10), 1.28 (3H, s, H14), 1.02 (3H, s, H14); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.1, 155.5, 136.9, 122.3, 116.2, 85.2, 83.8, 76.6, 46.8, 34.7, 34.2, 28.0, 21.9. **Diastereomer b: R_f** 0.14 (Pet. Ether / EtOAc (4:1)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.41 (1H, dd, *J* = 5.7, 1.5 Hz, H4), 6.18 (1H, dd, *J* = 5.7,

2.0 Hz, H3), 5.80-5.67 (1H, m, H12), 5.04 (1H, dd, *J* = 17.1, 1.4 Hz, H13), 5.02-4.96 (2H, m, H13 and H5), 4.29 (1H, dt, *J* = 8.9, 3.2 Hz, H6), 2.15-2.08 (1H, m, H11), 2.08-2.02 (1H, m, H10), 1.98- 1.88 (2H, m, H9 and H11), 1.84 (1H, ddd, *J* = 12.4, 10.6, 9.1 Hz, H10), 1.22 (3H, s, H14), 1.02 (3H, s, H14); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 173.3, 153.5, 137.1, 123.0, 116.0, 85.1, 84.0, 74.1, 46.7, 34.9, 33.8, 27.4, 21.8.

5-(4-allyl-5,5-dimethyltetrahydrofuran-2-yl)furan-2(3*H*)-one (312)



R_f 0.25 (Pet. Ether / EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2971 (m), 2923 (m), 1754 (s), 1641 (w), 1458 (m), 1369 (w), 1157 (m), 1039 (m), 911 (m), 892 (m), 822 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.33 (1H, q, *J* = 1.3 Hz, H4), 5.74 (1H, ddt, *J* = 17.0, 10.1, 6.9 Hz, H12), 5.06 (1H, ddd, *J* = 17.0, 3.2, 1.5 Hz, H13), 5.03-4.97 (1H, m, H13), 4.84 – 4.75 (3H, m, H3 and H6), 2.21-2.13 (1H, m, H11), 2.13-2.06 (2H, m, H10), 2.04-1.92 (1H, m, H11), 1.92-1.83 (1H, m, H9), 1.35 (3H, s, H14), 1.10 (3H, s, H14); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 172.4, 144.6, 137.5, 136.8, 116.0, 83.2, 70.9, 70.4, 46.6, 36.6, 34.4, 28.0, 21.8; **HRMS** (ESI^+) calc. for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1148, found 245.1156.

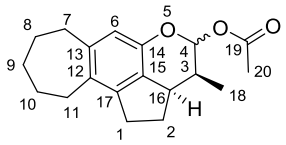
7.5.2. Investigations with the CDEF ring system

(2a*R*,3*S*)-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromen-4-yl acetate (313) and (*R*)-3-((*S*)-1-oxopropan-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl acetate (314)

To a stirred solution of lactol **181** (5.6 mg, 0.0217 mmol, 1.0 equiv.) in dry dichloromethane (0.25 mL) at 0 °C was sequentially added triethylamine (4.5 µL, 0.0325 mmol, 1.5 equiv.), DMAP (0.5 mg, 0.0043 mmol, 0.2 equiv.) and acetic anhydride (2.5 µL, 0.026 mmol, 1.2 equiv.). The reaction mixture was stirred overnight, warming to RT before being quenched

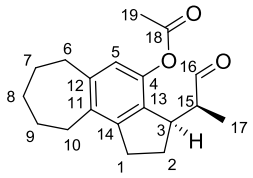
with sat. *aq.* NH_4Cl solution. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether/ Et_2O (9:1)) to yield lactol acetate **313** (2.3 mg, 35%, as a 74:26 mixture of epimers) as a colourless oil and phenol acetate **314** (3.3 mg, 51%) as a colourless oil.

(2a*R*,3*S*)-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromen-4-yl acetate (313)



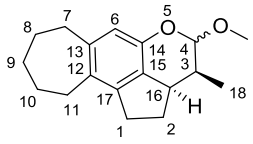
R_f 0.65 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2919 (s), 2849 (m), 2361 (m), 2342 (m), 1762 (m), 1611 (m), 1475 (m), 1222 (m), 1160 (m), 1123 (m), 1028 (m), 940 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.46 (1H, s, $H6^{maj}$), 6.41 (1H, s, $H6^{min}$), 6.29 (1 H, d, *J* = 2.2 Hz, $H4^{maj}$), 6.26 (1H, d, *J* = 2.1 Hz, $H4^{min}$), 3.48-3.38 (1H, m, H16), 2.91-2.77 (2H, m, 2 x H1), 2.77- 2.63 (4H, m, 2 x H7 and 2 x H11), 2.36-2.28 (1H, m, H3), 2.19 (3H, s, $OC(O)CH_3^{min}$), 2.19-2.14(1H, m, H2), 2.06 (3H, s, $OC(O)CH_3^{maj}$), 1.90-1.72 (3H, m, H9 and H2), 1.72-1.61 (2H, m, H8 and H10), 1.62-1.54 (2H, m, H8 and H10) 0.82 (3H, d, *J* = 7.0 Hz, $H18^{min}$), 0.79 (3H, d, *J* = 7.2 Hz, $H18^{maj}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 170.0 ($O\underline{C}(O)CH_3$), 146.4 (C14), 144.6 (C12), 143.1 (C13), 132.4 (C17), 123.8 (C15), 113.2 (C6), 95.2 (C4), 36.9 (C7), 35.8 (C16), 32.9 (C9), 31.7 (C3), 31.3 (C1), 31.1 (C11), 30.0 (C2), 28.6 (C8), 28.1 (C10), 21.4 ($O\underline{C}(O)CH_3$), 10.7 (C18); **HRMS** (ESI^+) calc. for $C_{19}H_{24}NaO_3$ $[M+Na]^+$ 323.1618, found 323.1630.

(*R*)-3-((*S*)-1-oxopropan-2-yl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-4-yl acetate (314)



[α]$_D^{25}$ +52.5 (*c* = 0.267, $CHCl_3$); **R_f** 0.15 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2921 (m), 2851 (m), 1763 (m), 1723 (m), 1476 (m), 1369 (m), 1210 (s), 1176 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.61 (1H, d, *J* = 1.0 Hz, H16), 6.68 (1H, s, H5), 3.59 (1H, dt, *J* = 8.9, 4.4 Hz, H3), 2.96-2.79 (2H, m, H1), 2.77-2.68 (5H, m, H6, H15 and H10), 2.36-2.28 (1H, , H2), 2.27 (3H, s, H19), 1.91-1.77 (3H, m, H2 and H8), 1.68-1.56 (4H, m, H7 and H9), 1.05 (3H, d, *J* = 7.0 Hz, H17); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 205.2 (C16), 169.5 (C18), 144.8 (C4) , 144.8 C14), 144.6 (C11), 137.3 (C12), 131.7 (C13), 121.1 (C5), 49.9 (C15), 44.9 (C3), 36.3 (C6), 32.8 (C8), 31.4 (C10), 31.0 (C1), 29.2 (C2), 28.3 (C7), 27.5 (C9), 21.4 (C19), 11.6 (C17); **HRMS** (FI^+) calc. for $C_{19}H_{24}O_3$ $[M]^+$ 300.1725, found 300.1731.

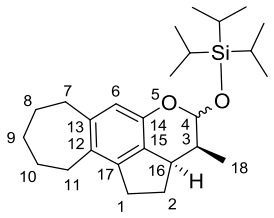
(2a*R*,3*S*)-4-methoxy-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[g]cyclopenta[*de*]chromene (315)



To a stirred solution of lactol **181** (3.5 mg, 0.0135 mmol, 1.0 equiv.) in dry methanol (0.3 mL) under argon was added pyridinium *p*-toluenesulfonate (0.1 mg, 0.00049 mmol, 0.04 equiv.). The reaction mixture was stirred at RT for 7 h before the solvent was removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (9:1 Pet. Ether/ Et_2O), to yield methyl ether **315** (3.3 mg, 89%, as a 65:35 mixture of epimers) as a white solid. These epimers were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization

by careful chromatography. **R_f** 0.56 (Pet. Ether/ Et_2O (19:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2917 (s), 2361 (s), 1967 (m), 1611 (m), 1477 (m), 1362 (m), 1262 (m), 1085 (s), 913 (m), 800 (m). **Major epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.42 (1H, s, H6), 4.87 (1H, d, *J* = 1.9 Hz, H4), 3.49 (3H, s, OCH_3), 3.37 (1H, dt, *J* = 12.0, 6.3 Hz, H16), 2.87-2.76 (2H, m, H1), 2.76-2.63 (4H, m, H7 and H11), 2.32-2.21 (1H, m, H3), 2.15-2.05 (1H, m, H2), 1.91-1.80 (1H, m, H9), 1.80-1.61 (4H, m, H9, H2, H8 and H10), 1.53-1.44 (2H, m, H8 and H10), 0.73 (3H, d, *J* = 7.3 Hz, H18); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 146.8 (C14), 144.2 (C12), 143.1 (C13), 131.7 (C17), 124.6 (C15), 113.0 (C6), 104.1 (C4), 55.9 (OCH_3), 36.9 (C7), 36.1 (C16), 33.0 (C9), 32.3 (C3), 31.3 (C1), 31.2 (C11), 29.9 (C2), 28.7 (C8), 28.2 (C10), 11.0 (C18). **Minor epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.41 (1H, s, H6), 5.01 (1H, d, *J* = 1.6 Hz, H4), 3.65 (3H, s, OCH_3), 3.38-3.35 (1H, m, H4), 2.87-2.76 (2H, m, H1), 2.76-2.63 (4H, m, H7 and H11), 2.32-2.21 (1H, m, H3), 2.15-2.05 (1H, m, H2), 1.91-1.80 (1H, m, H9), 1.80-1.61 (4H, m, H9, H2, H8 and H10), 1.53-1.44 (2H, m, H8 and H10), 0.77 (3H, d, *J* = 6.9 Hz, H18); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 148.4 (C14), 144.4 (C12), 142.8 (C13), 131.4 (C17), 124.0 (C15), 112.6 (C6), 105.5 (C4), 57.5 (OCH_3), 42.8 (C7), 36.8 (C16), 33.6 (C9), 33.0 (C3), 31.9 (C1), 30.5 (C11), 29.9 (C2), 28.7 (C8), 28.2 (C10), 6.0 (C18).

Triisopropyl(((2a*R*,3*S*)-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromen-4-yl)oxy)silane (316)

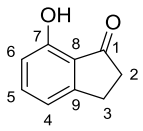


To a stirred solution of zinc(II) chloride (1.4 mg, 0.010 mmol, 0.4 equiv.) in dry dichloromethane (0.1 mL) at –40 °C was added a solution of lactol **181** (6.4 mg, 0.025 mmol, 1.0 equiv.) and siloxyfuran **308** (11.9 mg, 0.050 mmol, 2.0 equiv.) in dry dichloromethane (0.2 mL). The reaction mixture was stirred at –40 °C for 5 h, then allowed to warm to –10 °C over 2 h, before being quenched with NH_4Cl (1 mL, sat. *aq.*) and diluted with diethyl ether (1

mL). The layers were separated and the aqueous layer extracted three times with diethyl ether (3 x 1 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether/ Et_2O (99:1)) to yield **316** (3.8 mg, 37%, as a 63:37 mixture of diastereomers) as a colourless oil. These epimers were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.91 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2919 (m), 2866 (m), 2360 (s), 2342 (s), 1611 (m), 1477 (m), 1283 (m), 1260 (m), 1086 (s), 964 (m); **HRMS** (FI^+) calc. for $C_{26}H_{42}O_2Si$ $[M]^+$ 414.2951, found 414.2954. **Major epimer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.33 (1 H, s, H6), 5.35 (1 H, d, *J* = 1.9 Hz, H4), 3.46 (1 H, dt, *J* = 12.2, 6.0 Hz, H16), 2.87-2.74 (3 H, m, H1 and H11), 2.73-2.62 (3 H, m, H7 and H11), 2.24-2.16 (1H, m, H3), 2.16-2.02 (1H, m, H2), 1.89-1.82 (2H, m, C9), 1.82-1.62 (1H, m, H2), 1.66-1.57 (4H, m, H8 and H10), 1.23-1.13 (3H, m, SiC<u>H</u>$(CH_3)_2$), 1.07-1.02 (18H, *app* m, SiCH(C<u>H</u>$_3)_2$), 0.68 (3H, d, *J* = 7.3 Hz, H18); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 147.1 (C4), 143.9 (C17), 142.7 (C13), 131.0 (C12), 125.7 (C15), 112.9 (C6), 97.4 (C4), 36.9 (C7), 35.5 (C16), 34.6 (C3), 33.0 (C9), 31.3 (C1), 31.2 (C11), 29.8 (C2), 28.9 (C8), 28.3 (C10), 18.1 (C20), 18.0 (C29), 12.3 (C19), 11.0 (C18). **Minor epimer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.37 (1 H, s, H6), 5.49 (1 H, d, *J* = 1.9 Hz, H4), 3.36 (1 H, dt, *J* = 11.5, 5.9 Hz, H16), 2.87-2.74 (3 H, m, H1 and H11), 2.73-2.62 (3 H, m, H7 and H11), 2.24-2.16 (1H, m, H3), 2.16-2.02 (1H, m, H2), 1.89-1.82 (2H, m, C9), 1.82-1.62 (1H, m, H2), 1.66-1.57 (4H, m, H8 and H10), 1.23-1.13 (3H, m, H19), 1.13-1.09 (18H, m, H20), 0.77 (3H, d, *J* = 6.9 Hz, H18); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 144.2 (C4), 142.8 (C17), 131.1 (C13), 124.4 (C12), 124.0 (C15), 112.6 (C6), 98.5 (C4), 42.8 (C16), 36.8 (C7), 35.5 (C3), 34.4 (C9), 33.0 (C1), 32.0 (C11), 30.2 (C2), 28.8 (C8), 28.2 (C10), 18.1 (C20), 18.1 (C29), 12.4 (C19), 5.6 (C18).

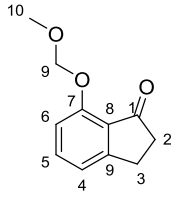
7.5.3. Investigations the DEF rings model system

7-Hydroxyindan-1-one (318)



A mixture of 4-chromanone **317** (2.00 g, 13.5 mmol, 1.0 equiv.) and anhydrous, powdered aluminum(III) chloride (5.20 g, 39 mmol, 2.9 equiv.) was heated with a heat gun for 10 min, and the mixture turned black. The reaction mixture was allowed to cool to RT before dichloromethane (40 mL) and cold HCl (10 mL) were added to the mixture. The resulting black slurry was diluted with water (40 mL) and extracted three times with dichloromethane (40 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (4:1 Pet. Ether/ EtOAc), then concentrated to yield hydroxyindanone **318** (0.88 g, 44%) as a yellow solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 9.07 (1H, s, OH), 7.47 (1H, *app* t, *J* = 7.8 Hz, H5), 6.95 (1H, dd, *J* = 7.3, 0.5 Hz, H4), 6.76 (1H, dd, *J* = 8.3, 0.5 Hz, H6), 3.12 (2H, t, *J* = 6.0 Hz, H3), 2.72 (2H, t, *J* = 6.0 Hz, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.2, 157.4, 155.4, 137.7, 117.6, 113.6, 36.1, 26.0. Data in accordance with literature.[258]

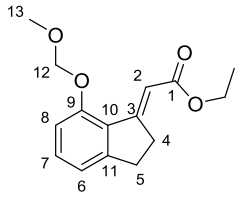
7-(Methoxymethoxy)-2,3-dihydro-1*H*-inden-1-one (319)



To a stirred solution of phenol **318** (1.16 g, 7.83 mmol, 1.0 equiv.) in anhydrous THF (14 mL) under argon at 0 °C was added sodium hydride (328 mg, 60% in mineral oil, 7.83 mmol, 1.0 equiv.). The resulting solution was stirred at 0 °C for 30 min before MOMCl (1.33 g, 15.7 mmol, 2.0 equiv.) was added dropwise. The ice bath was removed, and the reaction mixture stirred at RT for 2 h before being quenched with $NaHCO_3$ (14 mL, sat. *aq.*). The layers were

separated and the aqueous layer extracted three times with ethyl acetate (3 x 14 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (3:1 Pet. Ether/ Et_2O), to yield MOM ether **319** (1.23 g, 82%) as a yellow oil. $\mathbf{R_f}$ 0.14 (Pet. Ether/ Et_2O (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2924 (m), 2362 (m), 1708 (s), 1599 (s), 1237 (m), 1153 (s), 1008 (s), 925 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.49 (1H, *app* t, *J* = 7.9 Hz, H5), 7.07 (1H, *app* dd, *J* = 7.6, 0.7 Hz, H4), 7.04 (1H, *app* dd, *J* = 8.2, 0.5 Hz, H6), 5.34 (2H, s, H9), 3.52 (3H, s, H10), 3.13-3.05 (2H, m, H3), 2.74-2.63 (2H, m, H2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 204.7, 157.8, 155.7, 136.3, 126.1, 119.9, 113.2, 94.7, 56.6, 37.0, 25.6; **HRMS** (ESI^+) calc. for $C_{11}H_{12}O_3$ $[M+Na]^+$ 215.0679, found 215.0681.

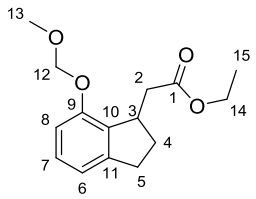
Ethyl (*E*)-2-(7-(methoxymethoxy)-2,3-dihydro-1*H*-inden-1-ylidene)acetate (320)



To a stirred suspension of sodium hydride (536 mg, 60% in mineral oil, 13.4 mmol, 2.1 equiv.) in anhydrous toluene (24 mL) under argon at 0 °C was added triethyl phosphonoacetate (2.63 mL, 13.4 mmol, 2.1 equiv.) dropwise. The resulting solution was stirred at RT, before being cooled to 0 °C. A solution of ketone **319** (1.23 g, 6.40 mmol, 1.0 equiv.) in anhydrous toluene (37 mL) was added dropwise. The ice bath was removed, and the reaction mixture was heated to reflux overnight. The deep red solution was allowed to cool to RT before being quenched with NaCl (60 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with ethyl acetate (3 x 60 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (19:1 Pet. Ether/ EtOAc), to yield α,β-unsaturated ester **320** (1.11g, 66%) as a yellow oil. $\mathbf{R_f}$ 0.42 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2926 (m), 1703 (m), 1622 (m), 1598 (m), 1478

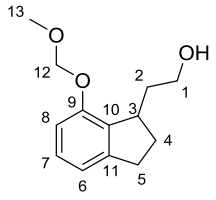
(m), 1258 (m), 1154 (s), 1037 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (1H, t, *J* = 7.8 Hz, H7), 7.00-6.96 (2H, m, H8 and H2), 6.87 (1H, t, *J* = 2.4 Hz, H6), 5.32 (2H, s, H12), 4.22 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.51 (3H, s, H13), 3.34-3.27 (2H, m, H5), 3.8-3.01 (2H, m, H4), 1.33 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 168.3, 161.5 , 155.6, 152.0, 131.5, 128.4, 118.5, 111.9, 111.6, 93.9, 59.5, 56.2, 31.5, 30.7, 14.5;; **HRMS** (ESI^+) calc. for $C_{15}H_{28}NaO_4$ $[M+Na]^+$ 285.1097, found 285.1093.

Ethyl 2-(7-(methoxymethoxy)-2,3-dihydro-1*H*-inden-1-yl)acetate (321)



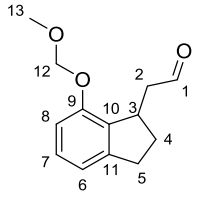
To a stirred solution of α,β-unsaturated ester **320** (1.11 g, 4.23 mmol, 1.0 equiv.) in methanol (17 mL) was added 10% Pd/C (450 mg, 0.423 mmol, 10 mol%). The hydrogen gas was bubbled through the resulting suspension for 30 min, before the reaction mixture was filtered through a pad of Celite® to yield ester **321** as a colourless oil (863 mg, 77%). The crude product was used in the following step without further purification. $\mathbf{R_f}$ 0.38 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2921 (m), 2851 (m), 2359 (m), 2335 (m), 1734 (s), 1476 (m), 1254 (m), 1154 (m), 1032 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.12 (1H, t, *J* = 7.8 Hz, H7), 6.88 (2H, *app* dd, *J* = 7.7, 3.8 Hz, H8 and H6), 5.19 (2H, s, H12), 4.16 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.80-3.72 (1H, m, H3), 3.47 (3H, s, H13), 3.04-2.93 (2H, m, H2 and H5), 2.80 - 2.89 (1H, m, H5), 2.28 - 2.38 (2H, m, H2 and H4), 1.86 (1H, ddt, *J* = 13.1, 8.7, 4.4 Hz, H4), 1.27 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.1, 153.9, 146.9, 133.5, 128.3, 118.1, 111.4, 94.0, 60.2, 56.0, 39.6, 38.4, 31.3, 31.0, 14.3; **HRMS** (ESI^+) calc. for $C_{15}H_{20}NaO_4$ $[M+Na]^+$ 287.1254, found 287.1243.

2-(7-(Methoxymethoxy)-2,3-dihydro-1*H*-inden-1-yl)ethan-1-ol (322)



To a stirred solution of ester **321** (100 mg, 0.378 mmol, 1.0 equiv.) in in anhydrous diethyl ether (47 mL) under argon at 0 °C was added lithium aluminium hydride (4 M in Et_2O, 0.95 mL, 0.38 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred warming to RT for 2 h, before being cool to 0 °C and quenched dropwise with water (0.1 mL), then NaOH (0.2 mL, 10% *aq.*), and then water (0.3 mL). The resulting suspension was stirred at RT for 1 h, then filtered through a pad of Celite® and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (3:2 Pet. Ether/ EtOAc), to yield alcohol **322** (78 mg, 93%) as a colourless oil. $\mathbf{R_f}$ 0.15 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3358 (br), 2941 (m), 1588 (m), 1475 (m), 1251 (m), 1152 (m), 1033 (s), 934 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.14-7.09 (1H, m, H7), 6.90 (2H, *app* d, *J* = 7.8 Hz, H6 and H8), 5.22 (2H, s, H12), 3.74-3.62 (2H, m, H1), 3.50 (3H, s, H13), 3.49-3.40 (1H, m, H3), 3.07-2.96 (1H, m, H5), 2.81 (1H, ddd, *J* = 16.0, 8.9, 2.6 Hz, H5), 2.31-2.19 (1H, m, H4), 2.11 (1H, br s, OH), 1.95-1.75 (3H, m, H2 and H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 154.0, 146.4, 134.9, 128.2, 118.6, 111.5, 94.6, 60.2, 56.4, 38.9, 37.0, 32.2, 31.5, 15.4; **HRMS** (ESI^+) calc. for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1148, found 245.1145.

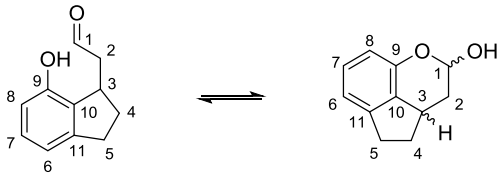
2-(7-(Methoxymethoxy)-2,3-dihydro-1*H*-inden-1-yl)acetaldehyde (323)



Dry DMSO (3.2 mL, 43.5 mmol, 42 equiv.) was added to the sulfur trioxide pyridine complex (1.45 g, 8.38 mmol, 8.1 equiv.) under argon, and the suspension was stirred at RT for 15

min. Dichloromethane (20 mL) was added, then the mixture was cooled to 0 °C and stirred for a further 10 min. A solution of alcohol **322** (230 mg, 1.03 mmol, 1.0 equiv.) in dry dichloromethane (20 mL) and *N*,*N*-diisopropylethylamine (3.85 mL, 21.2 mmol, 20.5 equiv.) were added simultaneously, and the resulting mixture stirred warming to RT for 2 h before being quenched with NH_4Cl (50 mL, sat. *aq*). The layers separated and the organic layer was washed with NaCl solution (40 mL, sat. *aq.*). The organic layer was dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (9:1 Pet. Ether/ EtOAc), to yield aldehyde **323** (217 mg, 95%) as a white solid. $\mathbf{R_f}$ 0.32 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2947 (m), 1722 (m), 1589 (m), 1475 (m), 1253 (m), 1152 (m), 1031 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.84 (1H, t, *J* = 2.2 Hz, H1), 7.19-7.06 (1 H, m, H7), 6.96-6.83 (2H, m, H6 and H8), 5.18 (2H, s, H12), 3.87-3.74 (1H, m, H3), 3.46 (3H, s, H13), 3.04-2.93 (2H, m, H2 and H5), 2.92-2.83 (1H, m, H5), 2.56 (1H, ddd, *J* = 16.6, 8.6, 2.2 Hz, H2), 2.43-2.31 (1H, m, H4), 1.79 (1H, ddt, *J* = 13.0, 8.4, 4.8 Hz, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.7, 153.7, 145.9, 133.1, 128.5, 118.1, 111.3, 93.9, 56.1, 48.1, 37.4, 31.6, 31.4; **HRMS** (ESI^+) calc. for $C_{13}H_{16}NaO_3$ $[M+Na]^+$ 243.0992, found 243.0993.

Equilibrium mixture of aldehyde 2-(7-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetaldehyde and lactols 3,3a,4,5-tetrahydro-2*H*-cyclopenta[*de*]chromen-2-ol (324)



To a stirred solution of **323** (100 mg, 0.454 mmol, 1.0 equiv.) in wet THF (1.5 mL) was added HCl (1.5 mL, 6N *aq.*). The resulting mixture was stirred at RT for 2 h, before being diluted with ethyl acetate (2 mL) and NaCl solution (2 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with ethyl acetate (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product

was purified by flash column chromatography on a short plug of silica (9:1 Pet. Ether/ EtOAc), to yield lactol **324** (68 mg, 85%, as a 53:37:10 inseparable mixture of open-chain aldehyde form and epimeric lactols) as a colourless oil. **R_f** 0.23 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2926 (s), 1731 (m), 1455 (m), 1378 (m), 1237 (m), 1125 (m); **HRMS** (ESI^+) calc. for $C_{11}H_{12}NaO_2$ $[M+Na]^+$ 199.0730, found 199.0735. **^{1}H NMR** (500 MHz, $CDCl_3$; note that shifts for the minor lactol diastereomer are not reported) δ_H 9.82 (0.53H, s, $C1^{ald}$), 7.13-7.02 (1.53H, m, $H7^j$ and OH^{ald}), 6.85 (0.37H, d, *J* = 7.3 Hz, $H6^{maj}$), 6.79 (0.53H, d, *J* = 7.3 Hz, $H6^{ald}$), 6.66 (0.53H, d, *J* = 7.9 Hz, $H8^{ald}$), 6.62 (0.37H, d, *J* = 7.9 Hz, $H8^{maj}$), 5.76 (0.37H, t, *J* = 2.0 Hz, $H1^{maj}$), 3.72-3.63 (0.53H, m, $H3^{ald}$), 3.28 (0.37H, tt, *J* = 11.7, 6.1 Hz, $H3^{maj}$), 3.04 (0.53H, dd, *J* = 19.2, 9.5 Hz, $H2^{ald}$), 3.01-2.92 (1H, m, H5), 2.87 (0.53H, dd, *J* = 19.2, 4.1 Hz, $H2^{ald}$), 2.85-2.80 (0.53H, m, $H5^{ald}$), 2.79 (0.74H, dd, *J* =16.4, 7.9 Hz, $H5^{maj}$), 2.49-2.40 (0.37H, m, $H4^{maj}$),2.40-2.31 (0.90H, m, $H2^{maj}$ and $H4^{ald}$), 1.82 (0.53H, ddt, *J* = 12.9, 7.3, 1.9 Hz, $H4^{ald}$), 1.64 (0.37H, qd, *J* = 11.3, 7.9 Hz, $H4^{maj}$), 1.45 (0.37H, td, *J* = 12.9, 2.5 Hz, $H2^{maj}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 204.9 (C^{ald}), 152.7 (C^{ald}), 150.0 (C^{maj}), 145.8 (C^{ald}), 144.8 (C^{maj}), 131.6 (C^{ald}), 129.6 (C^{maj}), 128.8 (C^{ald}), 128.3 (C^{maj}), 116.7 (C^{maj}), 116.6 (C^{ald}), 114.3 (C^{ald}), 112.0 (C^{maj}), 93.0 (C^{maj}), 50.1 (C^{ald}), 35.2 (C^{maj}), 34.9 (C^{ald}), 33.9 (C^{ald}), 33.1 (C^{maj}), 32.3 (C^{maj}),31.2 (C^{ald}), 30.9(C^{maj}).

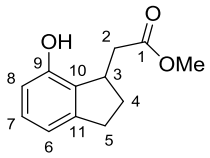
Methyl 2-(7-hydroxy-2,3-dihydro-*1H*-inden-1-yl)acetate (326) and 4,5-Dihydro-*2H*-cyclopenta[*de*]chromen-2-one

7-Hydroxy-2,3-dihydro-1*H*-inden-1-one **318** (565 mg, 3.81 mmol, 1.0 equiv.) and Wittig ylide methyl 2-(triphenyl-λ^5-phosphanylidene)acetate **297** (1.90 g, 5.72 mmol, 1.5 equiv.) in toluene (6.8 mL) was heated to reflux overnight, before the solvent was removed *in vacuo*. The residue was passed through a short pad of silica 4:1 Pet. Ether/ EtOAc) to yield a crude mixture of α,β-unsaturated ester **325** and 4,5-dihydro-*2H*-cyclopenta[*de*]chromen-2-one.

To a stirred solution of the crude mixture from the above Wttig reaction in methanol (7 mL) was added palladium on carbon (10 wt%, 406 mg, 10 mol%). Hydrogen gas was bubbled through the stirred reaction mixture for 1 h, before the resulting suspension was filtered

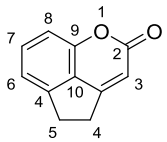
through a pad of Celite and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica (9:1 Pet. Ether/ EtOAc) to yield ester **326** (409 mg, 52%) as a colourless oil and chromenone 4,5-dihydro-*2H*-cyclopenta[*de*]chromen-2-one (103 mg, 17%) as a white foam.

Methyl 2-(7-hydroxy-2,3-dihydro-*1H*-inden-1-yl)acetate (326)



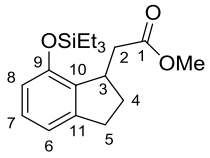
R_f 0.30 (9:1 Pet. Ether/ EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3378 (br), 2951 (m), 1708 (s), 1591 (m), 1467 (s), 1439 (m), 1262 (m), 1168 (m), 991 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.07 (1H, t, *J* = 7.7 Hz), 6.78 (1H, d, *J* = 7.3 Hz), 6.69 (1H, d, *J* = 8.0 Hz), 3.73 (3H, s, $CO_2C\underline{H}_3$), 3.64 (1H, dddd, *J* = 10.0, 8.1, 3.8, 1.8 Hz, H3), 3.00 (1H, ddd, *J* = 15.7, 10.8, 7.3 Hz, H5), 2.79 (1H, *J* = 15.7, 8.4, 1.8 Hz, H5), 2.77 (1H, dd, *J* = 17.8, 10.0 Hz, H2), 2.67 (1H, dd, *J* = 17.8, 3.8 Hz, H2), 2.33 (1H, *app* ddt, *J* = 12.6, 10.8, 8.4 Hz, H4), 1.85 (1H, ddt, *J* = 12.6, 7.3, 1.8 Hz, H4); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 177.0, 153.3, 146.0, 131.5, 128.9, 116.6, 114.8, 52.6, 39.5, 37.6, 34.4, 31.4; **HRMS** (ESI^+) calc. for $C_{12}H_{14}NaO_3$ $[M+Na]^+$ 229.0835, found 229.0835.

4,5-Dihydro-*2H*-cyclopenta[*de*]chromen-2-one



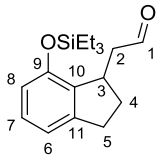
R_f 0.25 (4:1 Pet. Ether/ EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 2922 (w), 1706 (s), 1644 (m), 1603 (s), 1487 (m), 1414 (m), 1264 (m), 1141 (s), 1101 (m), 841 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.46 (1H, t, *J* = 7.8 Hz, H7), 7.14 (1H, d, *J* = 7.4 Hz, H8), 7.04 (1H, d, *J* = 8.2 Hz, H6), 6.13 (1H, d, *J* = 1.3 Hz, H3), 3.33-3.26 (2H, m, H5), 3.16-3.14 (2H, m, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 163.8, 163.0, 151.4, 146.3, 133.6, 126.0, 120.1, 112.6, 107.9, 31.2, 29.8; **HRMS** (ESI^+) calc. for $C_{11}H_9O_2$ $[M+H]^+$ 173.0597, found 173.0595.

Methyl 2-(7-((triethylsilyl)oxy)-2,3-dihydro-*1H*-inden-1-yl)acetate (327)



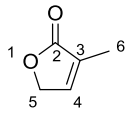
To a stirred solution of phenol **326** (1.58 g, 7.66 mmol, 1.0 equiv.) in dichloromethane (31 mL) under argon at RT was added sequentially imidazole (782 mg, 11.5 mmol, 1.5 equiv.), DMAP (cat.) and chlorotriethylsilane (1.55 mL, 9.19 mmol, 1.2 equiv.). The reaction mixture was stirred for 2 h before being quenched with sat. *aq.* NH_4Cl solution. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica (19:1 Pet. Ether/ Et_2O) to yield silyl ether **327** (2.00 g, 81%) as a colourless oil. $\mathbf{R_f}$ 0.51 (19:1 Pet. Ether/ Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 2954 (m), 2877 (m), 1739 (s), 1588 (s), 1472 (s), 1269 (s), 1169 (m), 1007 (s), 775 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.04 (1H, t, *J* = 7.7 Hz, H7), 6.81 (1H, d, *J* = 7.4 Hz, H6), 6.60 (1H , d, *J* = 8.0 Hz, H8), 3.73-3.65 (1H, m, H3), 3.70 (3H, s, OC$\underline{H}_3$), 3.04 (1H, dd, *J* = 15.4, 3.2 Hz, H2), 2.97 (1 H, dd, *J* = 16.1, 8.2 Hz, H5), 2.83 (1 H, ddd, *J* = 16.1, 9.1, 4.0 Hz, H5), 2.33-2.22 (1H, m, H4), 2.20 (1H, dd, *J* = 15.4, 11.5 Hz, H2), 1.84 (1 H, ddd, *J* = 12.7, 8.2, 4.0 Hz, H4), 1.00 (9H, t, *J* = 7.6 Hz, Si($CH_2C\underline{H}_3$)$_3$), 0.78 (4H, d, *J* = 7.6 Hz, Si($C\underline{H}_2CH_3$)$_3$), 0.75 (2H, dd, *J* = 7.6, 1.7 Hz, Si($C\underline{H}_2CH_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.8, 152.5, 146.1, 135.3, 128.3, 117.6, 116.2, 51.6, 39.9, 38.1, 31.5, 30.8, 6.8, 5.4; **HRMS** (EI^+) calc. for $C_{18}H_{28}O_3Si$ $[M]^+$ 320.1808, found 320.1801.

2-(7-((Trimethylsilyl)oxy)-2,3-dihydro-*1H*-inden-1-yl)acetaldehyde (328)



To a stirred solution of ester **327** (1.44 g, 4.46 mmol, 1.0 equiv.) in dichloromethane (15 mL) under argon at –78 °C was added a cooled solution of DIBALH (4.46 mL, 1.0 M in hexanes, 4.46 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred at –78 °C for 30 min before being quenched with sat. *aq.* Rochelle's salt solution. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica 19:1 Pet. Ether/ Et_2O) to yield aldehyde **328** (1.10 g, 84%) as a colourless oil. $\mathbf{R_f}$ 0.51 (19:1 Pet. Ether/ Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 2956 (m), 2877 (m), 1725 (s), 1588 (m), 1472 (s), 1271 (s), 1023 (s), 745 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.81 (1H, dd, *J* = 2.3, 1.4 Hz, H1), 7.05 (1H, t, *J* = 7.7 Hz, H7), 6.83 (1H, d, *J* = 7.4 Hz, H6), 6.61 (1H, d, *J* = 8.0 Hz, H8), 3.75 (1H, ddt, *J* = 9.6, 8.7, 3.9 Hz, H3), 3.00 (1H, ddd, *J* = 16.5, 3.9, 1.4 Hz, H2), 2.96 (1H, dd, *J* = 16.0, 8.3 Hz, H5), 2.86 (1H, ddd, *J* = 16.0, 8.9, 4.2 Hz, H5), 2.55 (1H, ddd, *J* = 16.5, 9.6, 2.3 Hz, H2), 2.33 (1H, dq, *J* = 12.9, 8.3 Hz, H4), 1.77 (1H, ddt, *J* = 12.9, 8.3, 4.2 Hz, H4), 0.92 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.79 (4H, t, *J* = 7.9 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.76 (2H, dd, *J* = 7.8, 1.8 Hz, $Si(C\underline{H}_2CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.8, 152.4, 146.1, 136.0, 128.4, 117.7, 116.2, 48.2, 37.6, 31.7, 31.3, 6.8, 5.4; **HRMS** (EI^+) calc. for $C_{17}H_{26}O_2Si$ $[M]^+$ 290.1702, found 290.1707.

3-methylfuran-2(5*H*)-one[209] (330)



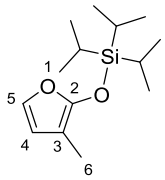
To a stirred solution of citraconic anhydride **329** (11.2 mL, 125 mmol, 1.0 equiv.) in MeOH (100 mL) at –15 °C was added dicyclohexylamine (27.3 mL, 137 mmol, 1.1 equiv.) dropwise. The reaction mixture as warmed to RT immediately and stirred for 30 min before the solvent was removed *in vacuo* in cooled water bath. Ethyl acetate (50 mL) was added to the residue, and the mixture was stirred for 1 h. The mixture was filtered to obtain (*Z*)-4-methoxy-3-

methyl-4-oxobut-2-enoic acid as its dicyclohexylamine salt (25.0 g, 61%) as colourless crystals.

To a stirred solution of the above salt (25.0 g, 76.7 mmol, 1.0 equiv.) in dichloromethane (60 mL) at –10 °C was added isobutyl chloroformate (11.5 mL, 84.6 mmol, 1.1 equiv.) dropwise. The reaction mixture was then stored in a freezer at –20 °C overnight, before being warmed to –10 °C again. THF (60 mL) was then added, and the resulting mixture was allowed to stand at –10 °C for 1 h, before being filtered to remove any solids. The residue was washed with cold THF (10 mL), and the filtrate was kept at 0 °C.

To a stirred solution of the filtrate in THF (70 mL) at 0 °C was added dropwise a 0 °C solution of $NaBH_4$ (5.44 g, 144 mmol, 2.0 equiv.) in water (11.5 mL) over 1 h. The reaction mixture was stirred at 0 °C for a further 2 h before being filtered to remove any solids. The residue was washed diethyl ether (10 mL) and the solvent was removed *in vacuo*. The resulting solid was dissolved in diisopropyl ether (10 mL) and dried over MgSO4. After filtration and removal of solvent *in vacuo*, the resulting oil was distilled (92 °C, 17 mbar) to obtain furanone **330** (2.34 g, 31% over 2 steps) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.16-7.12 (1H, d, *J* = 1.4 Hz, H4), 4.83-4.69 (2H, m, H5), 1.94 (3H, d, *J* = 1.5 Hz, H6); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.8, 144.9, 129.9, 70.0, 10.7. Data in accordance with literature.[209]

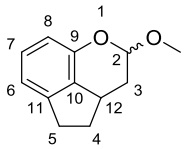
Triisopropyl((3-methylfuran-2-yl)oxy)silane[210] (55)



To a stirred solution of furanone **330** (1.23 g, 12.5 mmol, 1.0 equiv.) in Et_2O (9.6 mL) was added triethylamine (2.3 mL, 16.3 mmol, 1.3 equiv.). The reaction mixture was cooled to 0 °C before TIPSOTf (4.1 mL, 15.1 mmol, 1.2 equiv.) was added. The reaction mixture was immediately warmed to RT, then stirred for 3 h before being quenched with NH_4Cl (10 mL, sat. *aq*.). The layers were separated and the aqueous layer extracted three times with diethyl

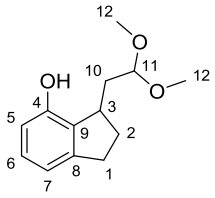
ether (3 x 10 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by vacuum distillation (113 °C, 5 mbar) to yield siloxyfuran **55** (1.93 g, 60%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.73 (d, 1H, *J* = 2.1 Hz, H5), 6.10 (dd, 1H, *J* = 2.1 Hz, H3), 1.83 (3H, s, H6), 1.34-1.16 (3H, m, $Si(C\underline{H}Me_2)_3$), 1.08 (18H, d, J = 7.2 Hz, $Si(CH\underline{Me}_2)_3$). Data in accordance with literature.[210]

2-Methoxy-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*de*]chromene (331a)



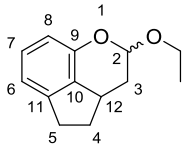
To a stirred solution of lactol **324** (20 mg, 0.113 mmol, 1.0 equiv.) in anhydrous dichloromethane (1.2 mL) under argon was added trimethyl orthoformate (15 µL, 0.136 mmol, 1.2 equiv.) and chlorotrimethylsilane (17.5 µL, 0.136 mmol, 1.2 equiv.). The reaction mixture was stirred at RT for 6 h before being quenched with distilled water (1.2 mL). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 1.2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (19:1 Pet. Ether/ Et_2O), to yield methyl acetal **331a** (12 mg, 56%) as a colourless oil, and some lactol **324** (7.0 mg, 35%) was recovered. **R_f** 0.54 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2926 (s), 2360 (m), 1736 (s), 1455 (m), 1366 (m), 1217 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.07 (1H, td, *J* = 7.7, 0.8 Hz, H7), 6.83 (1H, d, *J* = 7.3 Hz, H6), 6.65 (1H, d, *J* = 8.2 Hz, H8), 5.24 (1H, t, *J* = 2.2 Hz, H\2), 3.53 (3H, s, OCH_3), 3.22 (1H, tt, *J* = 11.7, 5.8 Hz, H12), 2.95 (1 H, dddd, *J* = 15.4, 12.3, 6.6, 0.6 Hz, H5), 2.76 (1 H, dd, *J* = 15.4, 7.9 Hz, H5), 2.40 (2 H, dt, *J* = 11.6, 6.6 Hz, H4), 2.33 (1 H, ddd, *J* = 12.9, 5.4, 1.7 Hz, H3), 1.60 (1 H, qd, *J* = 11.6, 8.0 Hz, H4), 1.47 (1 H, td, *J* = 12.9, 2.5 Hz, H3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 150.4, 145.0 , 130.1, 128.3, 116.7, 112.2, 99.8, 56.0, 35.4, 33.2, 32.5, 31.9; **HRMS** (FI^+) calc. for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.0992.

3-(2,2-Dimethoxyethyl)-2,3-dihydro-1*H*-inden-4-ol (333)



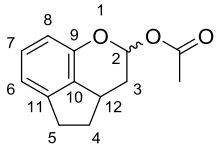
To a stirred solution of lactol **324** (10 mg, 0.057 mmol, 1.0 equiv.) in dry methanol (1.0 mL) under argon was added pyridinium *p*-toluenesulfonate (0.6 mg, 0.0023 mmol, 0.04 equiv.). The reaction mixture was stirred at RT for 3 h before being quenched with $NaHCO_3$ (3 mL, sat. *aq.*). Diethyl ether was added (3 mL), the layers separated and the aqueous layer extracted three times with diethyl ether (3 x 3 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (7:3 to 3:2 Pet. Ether/ EtOAc), to yield methyl acetal **331a** (2.7 mg, 25%) as a colourless oil, and dimethyl acetal **333** (0.5 mg, 4%) as a colourless oil. **R_f** 0.13 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3341 (br), 2926 (s), 1739 (w), 1591 (m), 1466 (s), 1366 (m), 1228 (m), 1125 (s), 1056 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.56 (1H, s, OH), 7.07 (1H, t, *J* = 7.7 Hz, H6), 6.78 (1H, d, *J* = 7.7 Hz, H7), 6.69 (1H, d, *J* = 7.7 Hz, H5), 4.46 (1H, dd, *J* = 7.9, 4.5 Hz, H11), 3.38 (6H, s, H12), 3.21 (1H, dddd, *J* = 10.4, 8.4, 5.0, 1.9 Hz, H3), 3.02 (1H, ddd, *J* = 15.6, 10.4, 7.9 Hz, H1), 2.77 (1H, ddd, *J* = 15.6, 8.4, 1.9 Hz, H1), 2.29 (1H, ddt, *J* = 12.3, 10.4, 8.4 Hz, H2), 1.99 (1H, ddd, *J* = 14.3, 7.9, 5.0 Hz, H10), 1.89 (1H, ddd, *J* = 14.3, 10.4, 4.5 Hz, H10), 1.83 (1H, ddt, *J* = 12.3, 7.3, 1.9 Hz, H2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 153.5, 146.2 , 131.2, 128.6, 116.5, 114.3, 102.8, 55.3, 49.7, 37.2, 36.6, 34.4, 31.4; **HRMS** (EI^+) calc. for $C_{13}H_{18}NaO_3$ $[M+Na]^+$ 245.1148, found 245.1147.

2-Ethoxy-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*de*]chromene (331b)



To a stirred solution of lactol **324** (10 mg, 0.057 mmol, 1.0 equiv.) in anhydrous dichloromethane (0.6 mL) under argon was added trimethyl orthoformate (7.5 µL, 0.068 mmol, 1.2 equiv.) and chlorotrimethylsilane (9.0 µL, 0.068 mmol, 1.2 equiv.). The reaction mixture was stirred at RT for 6 h before being quenched with distilled water (0.6 mL). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 0.6 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (49:1 Pet. Ether/ Et_2O), to yield lactol **331b** (2.8 mg, 24%) as a colourless oil. $\mathbf{R_f}$ 0.38 (Pet. Ether/ Et_2O (19:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2922 (m), 2360 (m), 1619 (m), 1598 (m), 1470 (s), 1242 (s), 1028 (s), 964 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.10-7.04 (1H, m, H7), 6.84 (1H, d, *J* = 7.3 Hz, H6), 6.63 (1H, d, *J* = 7.9 Hz, H8), 5.36 (1H, t, *J* = 2.0 Hz, H2), 3.96 (1H, dq, *J* = 9.6, 7.0 Hz, $OC\underline{H}_2CH_3$), 3.67 (1H, dq, *J* = 9.6, 7.0 Hz, $OC\underline{H}_2CH_3$), 3.31-3.21 (1H, m, H12), 2.96 (1H, ddd, *J* = 15.4, 11.7, 6.6 Hz, H5), 2.77 (1H, dd, *J* = 15.4, 8.0 Hz, H5), 2.41 (1H, dt, *J* = 11.7, 6.3 Hz, H4), 2.33 (1H, ddd, *J* = 13.0, 5.4, 1.9 Hz, H3), 1.61 (1H, dd, *J* = 11.7, 8.0 Hz, H4), 1.47 (1H, td, *J* = 13.0, 3.3 Hz, H3), 1.22 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 150.6, 144.9 , 130.2, 128.2, 116.6, 112.2, 98.4, 64.0, 35.4, 33.3, 32.5, 32.0, 15.3; **HRMS** (FI^+) calc. for $C_{13}H_{16}O_2$ $[M]^+$ 204.1150, found 204.1159.

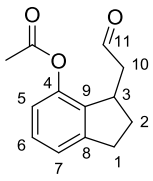
3,3a,4,5-Tetrahydro-2*H*-cyclopenta[*de*]chromen-2-yl acetate (331c)



To a stirred solution of lactol **324** (10 mg, 0.057 mmol, 1.0 equiv.) in anhydrous THF (0.1 mL) at 0 °C was added acetic anhydride (16 µL, 0.170 mmol, 3.0 equiv.) and boron trifluoride diethereate (2 µL, 0.014 mmol, 0.25 equiv.). The reaction mixture was stirred at 0 °C for 2 h before being quenched with $NaHCO_3$ (0.5 mL, sat. *aq.*) and diluted with diethyl ether (0.5 mL). The layers were separated and the aqueous layer extracted three times with diethyl

ether (3 x 0.5 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether/ EtOAc (19:1)) to yield acetate **331c** (4.7 mg, 38%) as a colourless oil and some **324** (2.5 mg, 25%) was recovered. $\mathbf{R_f}$ 0.59 (Pet. Ether/ Et_2O (9:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2970 (m), 1739 (s), 1367 (s), 1228 (m), 1217 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.15-7.04 (1H, m, H7), 6.88 (1H, d, *J* = 7.3 Hz, H6), 6.69 (1H, d, *J* = 8.2 Hz, H8), 6.60 (1H, t, *J* = 2.2 Hz, H2), 3.26 (1H, tt, *J* = 11.7, 6.0 Hz, H12), 2.99 (1H, ddd, *J* = 15.6, 11.7, 6.8 Hz, H5), 2.80 (1H, dd, *J* = 15.6, 7.9 Hz, H5), 2.46 (1H, dt, *J* = 11.9, 6.8 Hz, H4), 2.36 (1H, ddd, *J* = 13.2, 5.3, 2.2 Hz, H3), 2.09 (3H, s, $COCH_3$), 1.65 (2H, qd, *J* = 11.9, 7.9 Hz, H4), 1.60 (1H, td, *J* = 13.2, 2.2 Hz, H3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 170.0, 149.9, 145.0, 129.3, 128.6, 117.5, 112.5, 91.3, 35.5, 32.5, 32.1, 31.5, 21.4; **LRMS** (ESI^+, m/z (%)) 459 (32), 242 (100), 241 (90); **HRMS** (ESI^+) calc. for $C_{13}H_{14}NaO_3$ $[M+Na]^+$ 241.0835, found 241.0839.

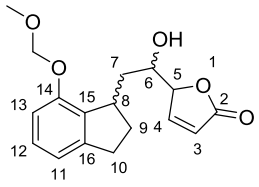
3-(2-oxoethyl)-2,3-dihydro-1*H*-inden-4-yl acetate (332)



To a stirred solution of lactol **324** (10 mg, 0.057 mmol, 1.0 equiv.) in anhydrous dichloromethane (0.7 mL) at 0 °C was added triethylamine (12 µL, 0.086 mmol, 1.5 equiv.), acetic anhydride (6.5 µL, 0.068 mmol, 1.2 equiv.) and DMAP (1.4 mg, 0.011 mmol, 0.2 equiv.). The reaction mixture was stirred at RT for 3 h before being quenched with NH_4Cl (0.7 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 0.7 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether/ EtOAc (9:1)) to yield acetate **332** (6.7 mg, 54%) as a colourless oil. $\mathbf{R_f}$ 0.21 (Pet. Ether/ EtOAc (9:1)); **IR** (thin film, ν_{max} / cm^{-1})

2924 (m), 2360 (m), 1723 (m), 1467 (m), 1207 (s); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.80 (1 H, t, *J* = 1.7 Hz, H11), 7.20 (1H, t, *J* = 7.7 Hz, H6), 7.11 (1H, d, *J* = 7.6 Hz, H7), 6.91-6.84 (1H, m, H5), 3.72 (1H, tt, *J* = 8.5, 4.5 Hz, H3), 3.01 (1H, dt, *J* = 16.2, 8.5 Hz, H1), 2.91 (1H, ddd, *J* = 16.2, 9.0, 4.5 Hz, H1), 2.81 (1H, ddd, *J* = 17.0, 4.5, 1.8 Hz, H10), 2.59 (1H, ddd, *J* = 17.0, 9.0, 1.8 Hz, H10), 2.39 (1H, dq, *J* = 13.0, 8.5 Hz, H2), 2.29 (3H, s, $COCH_3$), 1.81 (1H, ddt, *J* = 13.0, 8.5, 4.5 Hz, H2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 201.7, 169.3, 147.3 , 146.6, 137.8, 128.6, 122.6, 120.2, 48.1, 37.4, 32.0, 31.5, 21.2; **HRMS** (ESI^+) calc. for $C_{13}H_{14}NaO_3$ $[M+Na]^+$ 241.0835, found 241.0841.

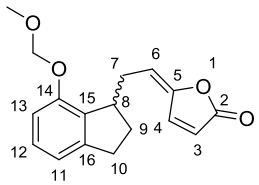
5-(1-Hydroxy-2-(7-(methoxymethoxy)-2,3-dihydro-1*H*-inden-1-yl)ethyl)furan-2(5*H*)-one (336a)



To a stirred solution of aldehyde **323** (25.7 mg, 0.117 mmol, 1.0 equiv.) and siloxyfuran **308** (56.1 mg, 0.233 mmol, 2.0 equiv.) in dry diethyl ether (1.4 mL) at –78 °C was added boron trifluoride diethyl etherate (5.8 µL, 0.047 mmol, 0.4 equiv.) dropwise. The reaction mixture was stirred at –78 °C for 2 h, then allowed to warm to 0 °C over 2 h, before being quenched with $NaHCO_3$ (2 mL, sat. *aq.*) and diluted with diethyl ether (2 mL). The layers were separated and the aqueous layer extracted three times with diethyl ether (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica with gradient elution (Pet. Ether/ EtOAc (2:1 to 1:1)) to yield aldol adduct **336a** (26.7 mg, 75%, as a 68:32 mixture of diastereomers) as a colourless oil. These alcohols were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.18 (Pet. Ether/ Et_2O (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3456 (br), 2942 (m), 1753 (s), 1588 (m), 1474 (m), 1252 (m), 1154 (m),

1031 (s); **HRMS** (ESI$^+$) calc. for $C_{17}H_{20}NaO_5$ $[M+Na]^+$ 327.1203, found 327.1203. **Major diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.47 (1H, dd, *J* = 5.8, 1.4 Hz, H4), 7.16-7.09 (1H, m, H12), 6.96-6.85 (2H, m, H11 and H13), 6.17 (1H, td, *J* = 5.8, 2.1 Hz, H3), 5.25-5.19 (2H, m, $OC\underline{H}_2OCH_3$), 5.02 (1H, dt, *J* = 4.4, 1.9 Hz, H5), 3.88 (1H, dt, *J* = 9.1, 4.4 Hz, H6), 3.50 (3H, s, $OCH_2OC\underline{H}_3$), 3.50-3.48 (1H, m, H8) 3.08-2.95 (1H, m, H10), 2.80 (1H, ddd, *J* = 16.1, 8.8, 1.6 Hz, H10), 2.34-2.22 (1H, m, H9), 1.88 (1H, ddt, *J* = 12.3, 7.6, 1.3 Hz, H9), 1.77-1.70 (2H, m, H7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 173.1, 154.1, 153.6, 146.7, 134.1, 128.6, 122.7, 119.1, 111.5, 95.0, 85.8, 70.0, 56.7, 38.5, 37.0, 33.2, 31.2. **Minor diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.47 (1H, dd, *J* = 6.0, 2.0 Hz, H4), 7.16-7.09 (1H, m, H12), 6.96-6.85 (2H, m, H11 and H13), 6.17 (1H, td, *J* = 6.0, 2.0 Hz, H3), 5.25-5.19 (2H, m, $OC\underline{H}_2OCH_3$), 5.07 (1H, dt, *J* = 4.4, 1.9 Hz, H5), 3.93 (1H, dt, *J* = 9.9, 3.9 Hz, H6), 3.56 (1H, ddt, *J* = 12.5, 8.3, 3.8 Hz, H8), 3.49 (3H, s, $OCH_2OC\underline{H}_3$), 3.08-2.95 (1H, m, H10), 2.84 (1H, ddd, *J* = 16.1, 9.1, 3.8 Hz, H10), 2.34-2.22 (1H, m, H9), 2.17 (1H, td, *J* = 9.3, 4.9 Hz, H7), 1.85-1.81 (1H, m, H9), 1.66 (1H, ddd, *J* = 13.9, 9.3, 3.5 Hz, H7); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 173.1, 154.5, 154.0, 146.0, 134.7, 128.4, 122.8, 118.5, 111.8, 94.5, 86.4, 70.8, 56.4, 39.2, 37.4, 31.4, 31.4.

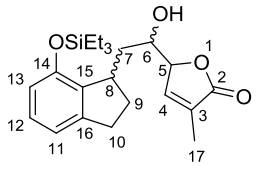
(*E*)-5-(2-(7-(Methoxymethoxy)-2,3-dihydro-*1H*-inden-1-yl)ethylidene)furan-2(*5H*)-one (338a)



To a stirred solution of alcohol **336a** (12.0 mg, 0.039 mmol, 1.0 equiv.) in anhydrous dichloromethane (0.6 mL) under argon at 0 °C was added triethylamine (13.7 µL, 0.098 mmol, 2.5 equiv.) and methanesulfonyl chloride (3.4 µL, 0.043 mmol, 1.1 equiv.). The resulting solution was stirred warming to RT over 2 h before being quenched with NaCl (0.6 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with

dichloromethane (3 x 0.6 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (4:1 Pet. Ether/ EtOAc), to yield alkene **338a** (6.7 mg, 59%, as a 59:41 mixture of E/Z diastereomers) as a colourless oil. These alkenes were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.18 (Pet. Ether/ Et_2O (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3456 (br), 2942 (m), 1753 (s), 1588 (m), 1474 (m), 1252 (m), 1154 (m), 1031 (s); **HRMS** (ESI^+) calc. for $C_{17}H_{20}NaO_5$ $[M+Na]^+$ 327.1203, found 327.1203. **Major diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.52 (1H, d, *J* = 5.7 Hz, H4), 7.13 (1H, t, *J* = 7.7 Hz, H12), 6.92-6.85 (2H, m, H11 and H13), 6.18-6.12 (1H, m, H3), 5.83 (1H, td, *J* = 8.5, 1.6 Hz, H6), 5.21 (2H, s, $OC\underline{H}_2OCH_3$), 3.59-3.50 (1H, m, H8), 3.49 (3H, s, $OCH_2OC\underline{H}_3$), 2.96 (1H, ddd, *J* = 16.1, 8.5, 3.8 Hz, H10), 2.88-2.80 (1H, m, H10), 2.76 (1H, dt, *J* = 8.5, 2.8 Hz, H7), 2.50 (1H, dt, *J* = 14.2, 8.5 Hz, H7), 2.22 (1H, td, *J* = 8.5, 4.4 Hz, H9), 1.88-1.77 (1H, m, H9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 170.2, 154.0, 150.8, 146.1, 139.5, 133.5, 128.8, 120.2, 118.4, 115.5, 111.6, 94.4, 56.3, 43.0, 31.6, 30.9, 30.4. **Minor diastereomer: ^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.30 (1H, d, *J* = 5.7 Hz, H4), 77.13 (1H, t, *J* = 7.7 Hz, H12), 6.92-6.85 (2H, m, H11 and H13), 6.18-6.12 (1H, m, H3), 5.30 (1H, t, *J* = 8.0 Hz, H6), 5.21 (2H, s, $OC\underline{H}_2OCH_3$), 3.59-3.50 (1H, m, H8), 3.49 (3H, s, $OCH_2OC\underline{H}_3$), 2.93-2.88 (1H, m, H10), 2.88-2.77 (1 H, m, H10), 2.72 (1H, dd, *J* = 15.1, 7.9 Hz), 2.50 (1H, dt, *J* = 14.2, 8.5 Hz, H7), 2.22 (1H, td, *J* = 8.5, 4.4 Hz, H9), 1.88-1.77 (1H, m, H9); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 170.3, 154.1, 150.6, 146.3, 143.7, 133.6, 128.5, 119.2, 118.3, 116.5, 111.5, 94.3, 56.2, 42.6, 31.7, 30.7, 30.6.

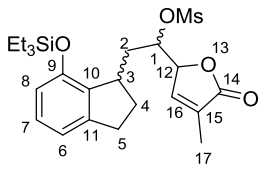
5-(1-Hydroxy-2-(7-((triethylsilyl)oxy)-2,3-dihydro-*1H*-inden-1-yl)ethyl)-3-methylfuran-2(*5H*)-one (336b)



To a stirred solution of aldehyde **328**(1.47 g, 5.06 mmol, 1.0 equiv.) and triisopropyl((3-methylfuran-2-yl)oxy)silane (1.54 g, 6.07 mmol, 1.2 equiv.) in diethyl ether (50 mL) under argon at –78 °C was added $BF_3{\cdot}OEt_2$ (0.25 mL, 2.02 mmol, 0.4 equiv.) dropwise. The reaction mixture was stirred warming to 0 °C over 3 h before being quenched with sat. *aq.* $NaHCO_3$ solution. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica 17:3 Pet. Ether/ EtOAc) to yield aldol adduct **336b** (1.97 g, quant.) as a colourless oil. These alcohols were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography. **IR** (thin film, ν_{max} / cm^{-1}) 3473 (br), 2955 (w), 1761 (s), 1587 (m), 1471 (s), 1270 (s), 1059 (m), 1019 (m), 743 (m); **HRMS** (ESI^+) calc. for $C_{22}H_{32}NaO_4Si$ $[M+Na]^+$ 411.1962, found 411.1953. **Major diastereomer: R_f** 0.15 (Pet. Ether/ EtOAc (7:3)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.94 (1H, t, *J* = 7.7 Hz, H12), 6.92 (1H, quin, *J* = 1.6 Hz, H4), 6.77 (1H, d, *J* = 7.4 GHz, H11), 6.52 (1H, d, *J* = 8.0 Hz, H13), 4.72 (1H, dquin, *J* = 5.6, 1.9, H6), 3.67 (1H, td, *J* = 9.2, 4.9 Hz, H6), 3.33 (1H, td, *J* = 8.0, 1.3 Hz, H8), 3.11 (1 H, d, *J* = 4.7 Hz, OH), 2.91 (1H, ddd, *J* = 16.0, 10.4, 5.6 Hz, H10), 2.67 (1H, ddd, *J* = 16.0, 8.6, 1.6 Hz, H10), 2.13 (1H, ddt, *J* = 12.5, 10.4, 8.6 Hz, H9), 1.82 (3 H, t, *J* = 1.8 Hz, H17), 1.78 (1H, ddt, *J* = 12.4, 7.4, 1.7 Hz, H9), 1.61-1.55 (2H, m, H7), 0.88 (9H, t, *J* = 7.9 Hz, $SiCH_2C\underline{H}_3$), 0.69 (6 H, ddd, *J* 13.8, 7.9, 5.1, $SiC\underline{H}_2CH_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 174.2, 152.1, 146.7, 146.3, 136.1, 131.2, 128.2, 118.6, 116.1, 83.7, 70.8, 39.0, 36.6, 33.1, 31.4, 10.9, 6.7, 5.2. **Minor diastereomer: R_f** 0.20 (Pet. Ether/ EtOAc (7:3)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.92 (1H, t, *J* = 7.7 Hz, H12), 6.91-6.89 (1H, m, H4), 6.72 (1H, d, *J* = 7.3 Hz, H13), 6.50 (1H, d, *J* = 8.0 Hz, H11), 4.75 (1H, dquin, *J* = 5.3, 2.0 Hz, H5), 3.74 (1H, dtd, *J* = 10.3, 5.2, 2.7 Hz, H6), 3.47-3.30 (1H, m, H8), 2.87 (1H, dt, *J* = 16.0, 8.4 Hz, H10), 2.70 (1 H, ddd, *J* = 16.0, 8.9, 3.6 Hz, H10), 2.41-2.35 (1H, m, OH), 2.11 (1H, dq, *J* = 12.7, 8.7 Hz, H9), 1.95 (1H, ddd, *J* = 13.9, 10.3, 4.6 Hz, H7), 1.81 (3H, t, *J* = 1.7 Hz, H17), 1.74-1.68 (1H, m, H9), 1.43 (1 H, ddd, *J* = 13.8, 9.2, 2.6 Hz, H7), 0.89 (9H, t, *J* = 7.9 Hz, $SiCH_2C\underline{H}_3$), 0.72- 0.64 (6H, m, $SiC\underline{H}_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.0,

152.0, 146.1, 146.1, 136.5, 131.4, 128.0, 117.9, 116.4, 84.3, 71.2, 39.4, 36.6, 31.5, 31.1, 10.9, 6.8, 5.4.

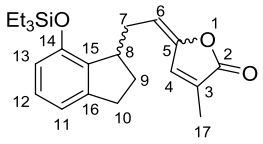
1-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-(7-((triethylsilyl)oxy)-2,3-dihydro-*1H*-inden-1-yl)ethyl methanesulfonate (337b)



To a stirred solution of alcohol **336b** (566 mg, 1.46 mmol, 1.0 equiv.) in dichloromethane (2.9 mL) under argon at 0 °C was added triethylamine (0.24 mL, 1.75 mmol, 1.2 equiv.), followed by methanesulfonyl chloride (0.13 mL, 1.60 mmol, 1.1 equiv.) dropwise. The reaction mixture was stirred warming to RT over 2 h before being quenched with NH_4Cl (3 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 3 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica (9:1 Pet. Ether/ EtOAc) to yield mesylate **337b** (609 mg, 90%) as a colourless oil. These mesylates were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography. **IR** (thin film, ν_{max} / cm^{-1}) 2955 (m), 1764 (s), 1660 (m), 1472 (s), 1352 (s), 1271 (m), 1174 (s), 1020 (m), 906 (m); **HRMS** (ESI^+) calc. for $C_{23}H_{34}NaO_6SSi$ $[M+Na]^+$ 489.1738, found 489.1724. **Major diastereomer: R_f** 0.15 (Pet. Ether/ EtOAc (7:3)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.06-7.01 (2H, m, H7 and H16), 6.82 (1H, d, *J* = 7.4 Hz, H6), 6.60 (1H, d, *J J* = 8.0 Hz, H8), 5.09 (1H, dquin, *J* = 5.4, 1.9 Hz, H12), 4.90 (1H, ddd, *J* = 10.3, 5.2, 3.2 Hz, H1), 3.48 (1H, ddt, *J* = 11.7, 7.8, 3.7 Hz, H3), 2.99 (3H, s, SO_2CH_3), 3.00-2.94 (1H, m, H5), 2.85 (1H, ddd, *J* = 16.0, 9.0, 3.8 Hz, H5), 2.41 (1H, ddd, *J* = 14.4, 5.9, 3.4 Hz, H2), 2.29 (4 H, dq, *J* = 13.0, 8.6 Hz, H4), , 1.95 (3H, d, *J* = 2.1 Hz, H17), 1.82 (1H, tdd, *J* = 15.6, 9.7, 5.6 Hz, H4), 1.57 (1H, tt, *J* = 11.0, 3.1 Hz, H2), 1.00 (9H, td, *J* = 7.9, 3.0 Hz, $SiCH_2C\underline{H}_3$), 0.80 (6H, qd, *J* = 7.9, 1.5 Hz, $SiC\underline{H}_2CH_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 173.0, 152.3, 146.0, 144.3, 135.3, 132.7, 128.4,

117.8, 116.4, 81.1, 79.6, 38.9, 38.8, 34.3, 31.5, 30.0, 11.0, 6.9, 5.4. **Minor diastereomer: R_f** 0.20 (Pet. Ether/ EtOAc (7:3)); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.06-7.01 (2H, m, H7 and H16), 6.82 (1H, d, *J* = 7.4 Hz, H6), 6.60 (1 H, d, *J* = 8.0 Hz, H8), 5.00 (1 H, dquin, *J* = 5.7, 1.8 Hz, H12), 4.93 (1H, ddd, *J* = 7.3, 5.8, 4.7 Hz, H1), 3.41 (1H, tt, *J* = 8.9, 3.4 Hz, H3), 3.08 (3H, s, SO_2CH_3), 3.07-3.01 (1H, m, H5), 2.90-2.85 (1H, m, H5), 2.41 (1H, ddd, *J* = 14.4, 5.9, 3.4 Hz, H2), 2.29 (4 H, dq, *J* = 13.0, 8.6 Hz, H4), 2.00 (1H, ddd, *J* = 13.0, 8.1, 4.2 Hz, H4), 1.94 (3H, dd, *J* = 2.1 Hz, H17), 1.89 (1H, ddd, *J* = 14.5, 9.5, 7.4 Hz, H2), 1.00 (9H, td, *J* = 7.9, 3.0 Hz, $SiCH_2C\underline{H}_3$), 0.80 (6H, qd, *J* = 7.9, 1.5 Hz, $SiC\underline{H}_2CH_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 173.1, 152.4, 146.1, 144.4, 135.4, 132.6, 128.5, 117.8, 116.2, 80.8, 80.8, 40.6, 39.0, 34.8, 31.8, 30.9, 10.9, 6.9, 5.4.

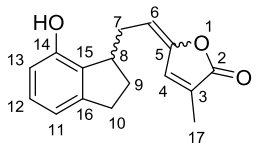
(*E*)-3-Methyl-5-(2-(7-((triethylsilyl)oxy)-2,3-dihydro-*1H*-inden-1-yl)ethylidene)furan-2(*5H*)-one (338b)



To a stirred solution of alcohol **336b** (130 mg, 0.335 mmol, 1.0 equiv.) in dichloromethane (0.7 mL) under argon at 0 °C was added triethylamine (0.12 mL, 0.836 mmol, 2.5 equiv.), followed by methanesulfonyl chloride (28.5 µL, 0.368 mmol, 1.1 equiv.) dropwise. The reaction mixture was stirred warming to RT overnight before being quenched with sat. *aq.* NH_4Cl solution. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica (19:1 Pet. Ether/ EtOAc) to yield alkene **338b** (94.5 mg, 76%, as a 65:35 mixture of diastereomers) as a colourless oil. These alkenes were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography. **R_f** 0.79 (Pet. Ether/ EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 2955 (m), 1765 (s), 1587 (w), 1472 (m), 1366 (m), 1270 (m), 1217 (m), 1017 (m), 745 (m); **HRMS**

(ESI$^+$) calc. for $C_{22}H_{30}NaO_3Si$ $[M+Na]^+$ 393.1856, found 393.1855. **Major diastereomer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.20 (1H, d, *J* = 0.7 Hz, H4), 7.03 (1H, t, *J* = 7.7 Hz, H12), 6.81 (1H, d, *J* = 7.4 Hz, H11), 6.60 (1H, d, *J* = 8.0 Hz, H13), 5.64 (1H, t, *J* = 8.6 Hz, H6), 3.44 (1H, *app* ddq, *J* = 11.8, 8.0, 3.9 Hz, H8), 3.00-2.88 (1H, m, H10), 2.83 (1H, dd, *J* = 9.1, 3.8 Hz, H10), 2.72 (1H, ddd, *J* = 14.0, 8.4, 4.5 Hz, H7), 2.43 (1H, dt, *J* = 14.0, 8.7 Hz, H7), 2.16 (1H, dq, *J* = 13.0, 8.7 Hz, H9), 1.99 (3H, s, H17), 1.79 (1H, dtd, *J* = 12.7, 8.3, 3.7 Hz, H9), 1.01 (9H, t, *J* = 7.7 Hz, $SiCH_2C\underline{H}_3$), 0.82-0.76 (6H, m, $SiC\underline{H}_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.4, 152.5, 149.5, 146.1, 135.3, 134.0, 130.2, 128.3, 117.7, 116.2, 112.5, 43.2, 31.7, 30.5, 30.0, 10.9, 6.9, 5.5. **Minor diastereomer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.03 (1H, t, *J* = 7.7 Hz, H12), 6.95 (1H, s, H4), 6.81 (1H, d, *J* = 7.4 Hz, H11), 6.60 (1H, d, *J* = 8.0 Hz, H13), 5.12 (1H, t, *J* = 8.0 Hz), 3.50-3.41 (1H, m, H8), 3.00-2.88 (1H, m, H10), 2.90-2.82 (1H, m, H7), 2.83 (1H, dd, *J* = 9.1, 3.8 Hz, H10), 2.65 (1H, dd, *J* = 14.8, 8.0 Hz, H7), 2.22-2.10 (1H, m, H9), 1.99 (3H, s, H17), 1.84-1.75 (1H, m, H9), 1.01 (9H, t, *J* = 7.7 Hz, $SiCH_2C\underline{H}_3$), 0.82-0.76 (6H, m, $SiC\underline{H}_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.2, 152.6, 149.2, 146.5, 137.9, 135.5, 129.1, 128.1, 117.6, 116.2, 113.6, 42.9, 31.8, 30.3, 30.0, 10.6, 6.9, 5.5.

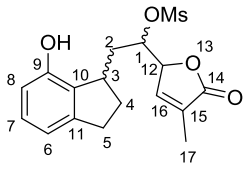
(*E*)-5-(2-(7-hydroxy-2,3-dihydro-*1H*-inden-1-yl)ethylidene)-3-methylfuran-2(*5H*)-one (339)



To a stirred solution of mesylate **337b** (555 mg, 1.50 mmol, 1.0 equiv.) in THF (21 mL) under argon was added TBAF (1.25 mL, 1.0 M in THF, 1.57 mmol, 1.05 equiv.). The reaction mixture was stirred overnight before being quenched with sat. *aq.* NH_4Cl solution. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica (4:1 Pet. Ether/ EtOAc)

to yield alkene **339** (307 mg, 80%, as a 87:13 mixture of diastereomers) as a colourless oil. **R_f** 0.41 (Pet. Ether/ EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3383 (br), 2944 (m), 1735 (s), 1591 (m), 1466 (m), 1278 (m), 1087 (m), 991 (m), 760 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 (1H, s, $H4^{min}$), 7.04 (1H, t, *J* = 7.7 Hz, H12), 6.97 (1H, d, *J* = 1.2 Hz, $H4^{maj}$), 6.79 (1H, d, *J* = 7.4 Hz, H11), 6.59 (1H, d, *J* = 7.9 Hz, H13), 5.70 (1H, t, *J* = 8.5 Hz, $H6^{min}$),5.28 (1H, br s, OH), 5.20 (1H, t, *J* = 8.0 Hz, $H6^{maj}$), 3.49 (1H, qd, *J* = 8.1, 3.7 Hz, H8), 2.95 (1H, dt, *J* = 16.1, 8.1 Hz, H10), 2.89-2.76 (2H, m, H7 and H10), 2.70 (1H, dt, *J* = 14.7, 8.1 Hz, $H7^{maj}$), 2.47 (1H, dt, *J* = 14.2, 8.5 Hz, $H7^{min}$),2.19 (1H, dq, *J* = 12.6, 8.4 Hz, H9), 1.97 (3H, s, H17), 1.83 (1H, ddd, *J* = 12.6, 7.9, 3.8 Hz, H9); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.6, 152.5, 149.4, 146.7, 138.0, 131.5, 129.2, 128.4, 117.2, 113.5, 113.3, 42.4, 31.7, 30.9, 30.3, 10.6; **HRMS** (ESI^+) calc. for $C_{16}H_{16}NaO_3$ $[M+Na]^+$ 279.0992, found 279.0989

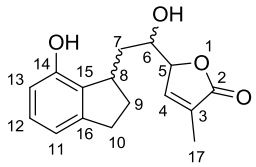
2-(7-Hydroxy-2,3-dihydro-*1H*-inden-1-yl)-1-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl methanesulfonate (343)



To a stirred solution of silyl ether **337b** (24.0 mg, 0.0514 mmol, 1.0 equiv.) in acetronitrile (2.2 mL) under argon was added TFA (5 µL, 0.0771 mmol, 1.5 equiv.). The reaction mixture was stirred at 80 °C for 1 h before being quenched with $NaHCO_3$ (2 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 2 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica (4:1 Pet. Ether/ EtOAc) to yield phenol **343** (14.9 mg, 82%, as a 90:10 mixture of diastereomers) as a white foam. **R_f** 0.37 (Pet. Ether/ EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3398 (br), 2922 (m), 1745 (s), 1591 (m), 1467 (m), 1351 (s), 1173 (s), 912 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.11-7.08 (1H, m, H16), 7.05 (1H, t, *J* = 7.7 Hz, H7), 6.82 (1H, d, *J* = 7.4 Hz, H6), 6.59 (1 H, d, *J* = 7.9

Hz, H8), 5.54 (1 H, s, OH), 5.13 (1H, dt, *J* = 8.5, 4.4 Hz, H1), 5.03 (1H, dt, *J* = 4.1, 1.9 Hz, H12), 3.44 (1H, qd, *J* = 6.7, 3.0 Hz, H3), 3.09 (3H, s, $SO_2C\underline{H}_3$), 3.00 (1H, dt, *J* = 16.3, 8.4 Hz, H5), 2.83 (1H, ddd, *J* = 16.3, 8.7, 3.3 Hz, H5), 2.31 (1H, dq, *J* = 12.8, 8.8 Hz, H4), 2.20 (1H, ddd, *J* = 14.7, 6.7, 4.5 Hz, H2), 2.01 (1 H, ddd, *J* = 14.7, 8.2, 6.5 Hz, H2), 1.95 (3H, t, *J* = 1.6 Hz, H17), 1.91 (1H, ddd, *J* = 12.8, 7.8, 3.3 Hz, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.5, 152.2, 146.4, 144.8, 132.4, 131.7, 128.7, 117.5, 113.7, 81.3, 80.4, 39.1, 38.9, 36.4, 32.9, 31.5, 10.9; **HRMS** (ESI^+) calc. for $C_{17}H_{20}NaO_6S$ $[M+Na]^+$ 375.0873, found 375.0872.

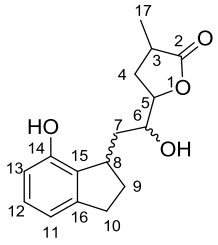
5-(1-Hydroxy-2-(7-hydroxy-2,3-dihydro-*1H*-inden-1-yl)ethyl)-3-methylfuran-2(*5H*)-one (344)



To a stirred solution of silyl ether **343** (256 mg, 0.659 mmol, 1.0 equiv.) in THF (11.5 mL) under argon was added TBAF (0.69 mL, 1.0 M in THF, 0.690 mmol, 1.05 equiv.). The reaction mixture was stirred overnight before being quenched with sat. *aq.* NH_4Cl solution. The layers were separated and the aqueous layer extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica (3:1 Pet. Ether/ EtOAc) to yield phenol **344**(143.8 mg, 80%, as a 55:45 mixture of diastereomers) as a white foam. **R_f** 0.27 (Pet. Ether/ EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3339 (br), 2919 (m), 2850 (m), 1737 (s), 1658 (m), 1466 (s) 1271 (m), 1061 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.11 (1H, m, $H4^{maj}$), 7.09 (1H, t, *J* = 7.7 Hz, H12), 7.04 (1H, *app* quin, *J* = 1.5 Hz, $H4^{min}$), 6.82 (1H, d, *J* = 7.4 Hz, H11), 6.67 (1H, d, *J* = 8.0 Hz, H13), 4.94-4.82 (1H, m, H5), 4.17 (1H, ddd, *J* = 10.7, 3.9, 2.5 Hz, $H6^{maj}$), 3.90 (1H, ddd, *J* = 10.6, 6.0, 2.9 Hz, $H6^{min}$), 3.48 (1H, *app* qd, *J* = 8.6, 4.8 Hz, H8), 3.01 (1H, *app* dtd, *J* = 12.1, 8.3, 3.9 Hz, H10), 2.91-2.78 (2H, m, H10), 2.35 (1H, *app* dquin, *J* = 12.7, 8.3 Hz, H9), 2.07 (1H, ddd, *J* = 13.4, 10.6, 4.8 Hz, $H7^{min}$), 2.03-1.97 (1H, m, $H7^{maj}$), 1.96 (3H, s, $H17^{min}$), 1.96 (3H, s, $H17^{maj}$),

1.93-1.85 (1H, m, H9), 1.85-1.78 (1H, m, H7^{maj}), 1.73 (1H, ddd, *J* = 14.4, 6.8, 2.8 Hz, H7^{min}), 1.64 (1H, br s, OH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.8, 174.7, 152.4, 146.0, 145.9, 145.8, 145.7, 132.1, 132.0, 132.0, 131.9, 128.6, 116.9, 114.2, 84.7, 84.3, 72.2, 71.3, 38.9, 38.5, 36.8, 36.8, 32.4, 32.3, 31.4, 10.9; **HRMS** (ESI$^+$) calc. for $C_{16}H_{18}NaO_4$ $[M+Na]^+$ 297.1097, found 297.1093.

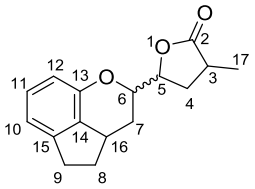
5-(1-Hydroxy-2-(7-hydroxy-2,3-dihydro-*1H*-inden-1-yl)ethyl)-3-methyldihydrofuran-2(*3H*)-one (345)



To a stirred solution of alkene **344** (25.0 mg, 0.0911 mmol, 1.0 equiv.) in methanol (0.5 mL) was added 10% Pd/C (9.7 mg, 0.0091 mmol, 10 mol%). The hydrogen gas was bubbled through the resulting suspension for 30 min, before the reaction mixture was filtered through a pad of Celite® to yield **345** as a colourless oil (25.0 mg, 99%). The crude product was used in the following step without further purification. **R_f** 0.31 (Pet. Ether/ EtOAc (1:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3375 (br), 1752 (s), 1590 (m), 1466 (s), 1201 (m); **HRMS** (ESI$^+$) calc. for $C_{22}H_{32}NaO_4Si$ $[M+Na]^+$: 411.1962; found: 411.1953. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.06 (1H, t, *J* = 7.7 Hz, H12^a), 7.06 (1H, t, *J* = 7.7 Hz, H12^b), 6.77 (2H, d, *J* = 7.3 Hz, H11), 6.70 (1H, dd, *J* = 8.0 Hz, H13^a), 6.69 (1H, dd, *J* = 8.0 Hz, H13^b), 5.52 (4H, br s, OH), 4.32 (1H, ddd, *J* = 9.9, 6.2, 3.2 Hz, H5^a), 4.30 -4.21 (2H, m, H5^b and H6^a), 3.82 (1H, ddd, *J* = 11.0, 6.8, 2.2 Hz, H6^b), 3.57-3.43 (2H, m, H8), 2.97 (2H, *app* dt, *J* = 16.4, 8.3 Hz, H10), 2.84 (1H, dd, *J* = 8.7, 3.6 Hz, H10^a), 2.80 (1H, dd, *J* = 8.8, 3.5 Hz, H10^b), 2.75-2.66 (2H, m, H3), 2.40-2.21 (4H, m, H4^b, H9 and H4^a), 1.98-1.89 (3H, m, H4^a, H9 and H6^b), 1.88-1.76 (3H, m, H9 and H7^a), 1.69 – 1.59 (1H, m, H4^a), 1.59-1.51 (2H, m, H7), 1.27 (3H, d, *J* = 7.0 Hz, H17^a), 1.26 (3H, d, *J* = 3.6 Hz, H17^b); **Diastereomer a: ^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 180.1, 152.7, 145.7, 132.2, 128.6, 116.6, 114.3, 80.8, 70.9, 39.0, 36.0, 35.6, 33.1, 31.5, 29.8, 15.1; **Diastereomer b: ^{13}C**

NMR (101 MHz, $CDCl_3$) δ_C 179.7, 152.8, 145.7, 132.3, 128.6, 116.6, 114.3, 81.9, 73.9, 38.5, 36.2, 35.9, 33.2, 32.7, 31.4, 15.1.

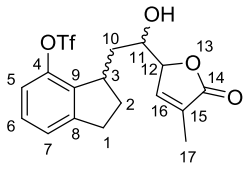
3-Methyl-5-(3,3a,4,5-tetrahydro-*2H*-cyclopenta[*de*]chromen-2-yl)dihydrofuran-2(*3H*)-one (346)



To a stirred solution of diol **345** (25.0 mg, 0.0905 mmol, 1.0 equiv.) in THF (0.9 mL) under argon at 0 °C was added sequentially triphenylphosphine (35.6 mg, 0.136 mmol, 1.5 equiv.) and DIAD (27.5 µL, 0.1346 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred warming to RT for 2 h before being filtered through a short pad of Celite®, and washed with diethyl ether. The solvent was removed *in vacuo* and the crude product was purified by to yield one diastereomer of the saturated DEFG rings **346a** (6.3 mg, 27%) as a colourless oil and a mixture of the other diastereomer **346b** with reduced DIAD, which was repurified by flash column chromatography on silica (1:99 Et_2O/ CH_2Cl_2) to yield **346b** (5.7 mg, 24%) as a colourless oil. These diastereomers were generally not readily separated by chromatography; the data presented below was obtained for the purpose of characterization by careful chromatography. **IR** (thin film, ν_{max} / cm^{-1}) 2922 (m), 1781 (s), 1597 (m), 1469 (s), 1246 (m), 1186 (m), 1169 (m), 1026 (m); **HRMS** (FI^+) calc. for $C_{16}H_{18}O_3$ $[M]^+$: 258.1256; found: 258.1251. **Diastereomer a: R_f** 0.69 (Et_2O/ CH_2Cl_2 (1:99)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H7.07 (1H, t, *J* = 7.7 Hz, H11), 6.83 (1H, d, *J* = 7.3 Hz, H10), 6.61 (1H, d, *J* = 8.1 Hz, H12), 4.44 (1H, td, *J* = 9.3, 5.1 Hz, H5), 4.36 (1H, ddd, *J* = 9.1, 4.5, 1.0 Hz, H6), 3.08 (1H, *app* tt, *J* = 11.6, 5.9 Hz, H16), 3.01-2.87 (1H, m, H9), 2.77 (1H, dd, *J* = 15.4, 7.9 Hz, H9), 2.74 -2.62 (2H, m, H8 and H3), 2.59 (1H, dd, *J* = 13.6, 5.3, 1.0 Hz, H7), 2.44 (1 H, dt, *J* = 11.8, 6.5 Hz, H8), 1.94-1.80 (1H, m, H4), 1.72-1.55 (2H, m, H4 and H7), 1.32 (3H, d, *J* = 6.6 Hz, H17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.2, 151.5, 145.6, 129.0, 128.7, 116.6, 112.2, 78.1, 75.8, 35.9,

35.9, 35.6, 32.9, 32.5 , 29.3, 15.4. **Diastereomer b: R_f** 0.51 (Et_2O/ CH_2Cl_2 (1:99)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.06 (1H, t, *J* = 7.7 Hz, H11), 6.80 (1H, d, *J* = 7.3 Hz, H10), 6.67 (1H, d, *J* = 8.1 Hz, H12), 4.51 (1H, dt, *J* = 10.6, 6.2 Hz, H5), 4.39 (1H, td, *J* = 5.7, 1.2 Hz, H6), 3.04 (1H, *app* tt, *J* = 11.7, 5.9 Hz, H16), 2.99-2.87 (1H, m, H9), 2.76 (1H, dd, *J* = 15.4, 8.0 Hz, H9), 2.67 (1H, ddt, *J* = 12.0, 8.6, 7.0 Hz, H3), 2.50 (1H, ddd, *J* = 12.3, 8.6, 5.9 Hz, H4), 2.42 (1H, dt, *J* = 11.6, 6.5 Hz, H8), 2.28 (1H, ddd, *J* = 13.7, 5.3, 1.2 Hz, H7), 1.80 (1H, td, *J* = 12.0, 10.8 Hz, H4), 1.70 (1H, *app* td, *J* = 13.1, 5.6 Hz, H7), 1.63-1.47 (1H, m, H8), 1.32 (3H, d, *J* = 7.0 Hz, H17); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 178.8, 151.6, 145.0, 128.9, 128.7, 116.4, 112.6, 79.7, 76.9, 36.2, 35.4, 33.5, 33.3, 32.4, 29.9, 15.2 .

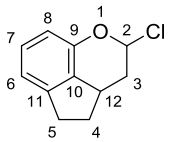
3-(2-Hydroxy-2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)ethyl)-2,3-dihydro-*1H*-inden-4-yl trifluoromethanesulfonate (356)



To a stirred solution of phenol **344** (64.3 mg, 0.235 mmol, 1.0 equiv.) in dichloromethane (2.2 mL) under argon at 0 °C was added sequentially DIPEA (86 µL, 0.493mmol, 2.1 equiv.) and trifluoromethanesulfonic anhydride (42 µL, 0.246 mmol, 1.05 equiv.). The reaction mixture was stirred for 1 h before being quenched with NH_4Cl (2 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane. (3 x 2 mL) The combined organic layers were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica (3:1 Pet. Ether/ EtOAc) to yield triflate **356** (83.5 mg, 89%, as a 1:1 mixture of diastereomers) as a yellow oil. **R_f** 0.24 (Pet. Ether/ EtOAc (4:1)); **IR** (thin film, ν_{max} / cm^{-1}) 3440 (br), 2921 (m), 1748 (s), 1463 (m), 1418 (s), 1211 (m), 1138 (m), 1061 (m), 963 (m), 853 (m); **HRMS** (ESI^+) calc. for $C_{17}H_{17}FNaO_6S$ $[M+Na]^+$ 429.0590, found 429.0583; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25-7.20 (2H, m, H7 and H5), 7.15 (1H, t, *J* = 1.6 Hz, $H16^a$), 7.07-7.01 (2.5H, m, H6 and $H16^b$), 4.88 (1H, dquin, *J* = 5.2, 1.9 Hz, $H12^b$), 4.76 (1 H, dquin, *J* = 5.2 Hz, $H12^a$), 3.90-3.81 (1H, m,

H11), 3.81-3.71 (1H, m, H3), 3.07 (1H, dtd, *J* = 16.4, 8.1, 3.8 Hz, H1), 2.93 (1H, ddt, *J* = 16.4, 8.6, 4.1 Hz, H1), 2.41-2.28 (1H, m, H2), 2.28 (1H, m, OH^b), 2.22 (1H, d, *J* = 6.5 Hz, OH^a), 2.08-1.99 (1H, m, H10), 1.99-1.89 (1H, m, H2), 1.94 (3 H, t, *J* = 1.6 Hz, $H17^a$), 1.92 (3H, t, *J* = 1.7 Hz, $H17^b$), 1.77 (1H, dd, *J* = 13.9, 11.0, 1.9 Hz, $H10^b$), 1.62 (1H, ddd, *J* = 13.9, 10.8, 2.8 Hz, $H10^a$). **Diastereomer a: ^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.0, 148.2, 146.4, 145.8, 138.8, 131.7, 129.1, 125.0, 119.0, 118.2 (q, $\underline{C}F_3$), 84.0, 70.6, 39.7, 36.8, 31.6, 30.4, 10.8. **Diastereomer b: ^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.1, 148.2 , 146.4, 145.7, 138.8, 131.7, 129.1, 124.9, 119.0, 118.2 (q, $\underline{C}F_3$), 84.1, 70.4, 39.6, 36.3, 31.6, 30.6, 10.9

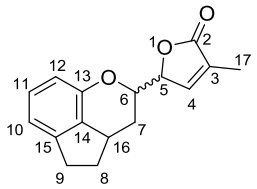
2-Chloro-3,3a,4,5-tetrahydro-*2H*-cyclopenta[*de*]chromene (363)



To an oven-dried vial charged with a stirrer bar and $ZnCl_2$ (15.3 mg, 0.113 mmol, 0.4 equiv.) under argon at 0 °C was added a cooled solution of lactol-aldehyde mixture **324** (50.0 mg, 0.284 mmol, 1.0 equiv.) in dry toluene (1.1 mL), followed by thionyl chloride (32 µL, 0.426 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred warming to RT for 6 h before being filtered through a short pad of oven-dried Celite®, and washed with dry dichloromethane. The solvent was removed *in vacuo* to yield chloropyran **363** (50.7 mg, 92%) as a pale green oil which was used in the next step without further purification. N.B. This compound is unstable to water and silica. **IR** (thin film, ν_{max} / cm^{-1}) 2957 (m), 1623 (m), 1598 (m), 1469 (s), 1232 (s), 1203 (s), 1097 (s), 753 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.10 (1H, dd, *J* = 8.1, 7.3 Hz, H7), 6.92 (1H, d, *J* = 7.3 Hz, H6), 6.68 (1H, d, *J* = 8.1 Hz, H8), 6.53 (1H, t, *J* = 2.3 Hz, H2), 3.62-3.51 (1H, m, H12), 3.08-2.95 (1H, m, H5), 2.80 (1H, dd, *J* = 15.4, 7.9 Hz, H5), 2.57 (1H, ddd, *J* = 13.5, 5.3, 2.0 Hz, H3), 2.48 (1H, dt, *J* = 11.7, 6.4 Hz, H4), 1.89 (1H, ddd, *J* = 13.5, 12.1, 2.6 Hz, H3), 1.70 (1H, qd, *J* = 11.7, 7.9 Hz, H4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 148.7 (C9), 145.3 (C11), 129.0 (C10), 128.7 (C7), 118.3 (C6), 112.7 (C8),

90.1 (C2), 37.1 (C3), 35.3 (C4), 32.4 (C5), 31.9 (C12); **HRMS** (FI^+) calc. for $C_{11}H_{11}OCl$ $[M]^+$: 194.0498; found: 194.0495.

3-Methyl-5-(3,3a,4,5-tetrahydro-*2H*-cyclopenta[*de*]chromen-2-yl)furan-2(*5H*)-one (340)

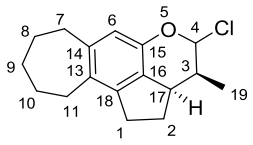


To an oven-dried vial charged with a stirrer bar and $ZnCl_2$ (14.1 mg, 0.099 mmol, 0.4 equiv.) under argon at –20 °C was added a cooled solution of chloropyran **363** (48.0 mg, 0.246 mmol, 1.0 equiv.) and siloxyfuran **55** (80.0 mg, 0.296 mmol, 1.2 equiv.) in dry dichloromethane (2.4 mL). The reaction mixture was stirred warming to RT overnight before being filtered through a short pad of oven-dried Celite®, and washed with dry dichloromethane. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica (9:1 → 5:1 Pet. Ether/ EtOAc) to yield *DEFG* rings as a 1:1 mixture of diastereomers **340a** (14.5 mg, 24%) and **340b** (14.1 mg, 23%) as a white powder. **IR** (thin film, ν_{max} / cm^{-1}) 2925 (m), 1739 (s), 1596 (m), 1470 (m), 1366 (m), 1251 (m), 1217 (m), 771 (m); **HRMS** (ESI^+) calc. for $C_{16}H_{16}NaO_3$ $[M+Na]^+$: 279.0992; found: 279.0986. **Diastereomer a: R_f** 0.42 (Pet. Ether/ EtOAc (20:3)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 (1H, quin, *J* = 1.7 Hz, H4), 7.05 (1H, dd, *J* = 8.1, 7.3 Hz, H11), 6.81 (1H, d, *J* = 7.3 Hz, H10), 6.59 (1H, d, *J* = 8.1 Hz, H12), 4.92 (1H, dq, *J* = 7.2, 1.7 Hz, H5), 4.03 (1H, ddd, *J* = 11.4, 7.2, 2.2 Hz, H6), 3.10 (1H, *app* tt, *J* = 11.3, 5.9 Hz, H16), 3.03-2.92 (1H, m, H9), 2.77 (1H, dd, *J* = 15.4, 8.0 Hz, H9), 2.50 (1H, ddd, *J* = 12.8, 5.1, 2.2 Hz, H7), 2.42 (1H, dt, *J* = 12.0, 6.4 Hz, H8), 1.98 (3H, t, *J* = 1.7 Hz, H17), 1.63 (1H, tdd, *J* = 12.0, 10.8, 8.2 Hz, H8), 1.44 (1H, dt, *J* = 12.8, 11.4 Hz, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.9 (C2), 151.8 (C13), 146.9 (C4), 145.2 (C15), 131.0 (C3), 129.5 (C14), 128.6 (C11), 116.8 (C10), 111.9 (C12), 82.0 (C5), 78.0 (C6), 37.3 (C16), 35.5 (C8), 32.7 (C9), 31.6 (C7), 10.9 (C17). **Diastereomer b: R_f** 0.32 (Pet. Ether/ EtOAc (20:3)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.15-7.12 (1H, m, H4), 7.04 (1H, t, *J* =

7.7 Hz, H11), 6.80 (1H, d, *J* = 7.2 Hz, H10), 6.58 (1H, d, *J* = 8.1 Hz, H12), 5.20-5.12 (1H, m, H5), 4.47 (1H, ddd, *J* = 11.7, 4.2, 2.2 Hz, H6), 3.12 (1H, *app* tt, *J* = 11.0, 5.2 Hz, H16), 3.03-2.88 (1H, m, H9), 2.75 (1H, dd, *J* = 15.4, 8.0 Hz, H9), 2.39 (1H, dt, *J* = 12.3, 6.5 Hz, H8), 2.17 (1H, ddd, *J* 12.7, 5.1, 2.2 Hz, H7), 1.97 (3H, s, H17), 1.59 (1H, ddt, *J* = 12.3, 11.0, 8.0 Hz, H8), 1.35 (1H, dt, *J* = 24.3, 11.7 Hz, H7); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.8 (C2), 152.0 (C13), 145.6 (C4), 145.1 (C15), 131.7 (C3), 129.5 (C14), 128.7 (+C11), 116.8 (C10), 112.0 (C12), 81.4 (C5), 76.1 (C6), 37.5 (C16), 35.5 (C8), 32.7 (C9), 29.5 (C7), 10.9 (C17).

7.5.4. Synthesis of the CDEFG Rings

(2a*R*,3*S*)-4-Chloro-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromene (369)



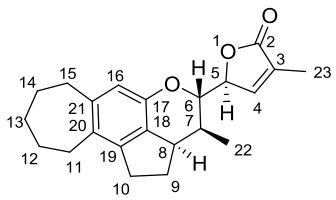
To an oven-dried vial charged with a stirrer bar and $ZnCl_2$ (132 mg, 0.965 mmol, 5.0 equiv.) under argon was added a cooled solution of CDEF rings lactol-aldehyde mixture **181** (49.9 mg, 0.193 mmol, 1.0 equiv.) in dry toluene (1.0 mL), followed by thionyl chloride (56 µL, 0.772 mmol, 4.0 equiv.) dropwise. The reaction mixture was stirred at RT for 6 h before being filtered through a short pad of oven-dried Celite®, and washed with dry dichloromethane. The solvent was removed *in vacuo* to yield crude chloropyran **369** as a white foam which was used in the next step without further purification. N.B. This compound is unstable to water and silica. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.45 (1H, s, H6), 6.19 (1H, d, *J* = 2.0 Hz, H4), 3.74 (1H, ddd, *J* = 11.7, 6.9, 5.4 Hz, H17), 2.93-2.78 (2H, m, H1), 2.78-2.64 (4H, m, H7 and H11), 2.50 (1H, qdd, *J* = 7.3, 5.4, 2.0 Hz, H3), 2.20 (1H, dddd, *J* = 11.7, 6.9, 5.6, 1.3 Hz, H2), 1.91-1.71 (3H, m, H9 and H2), 1.70-1.61 (2H, m, H8), 1.60-1.48 (2H, m, H10), 0.85 (3H, d, *J* = 7.3 Hz, H19); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.1 (C15), 144.7 (C18), 143.3 (C13), 133.4 (C14), 123.5 (C16), 113.5 (C6), 94.5 (C4), 37.0 (C3), 36.8 (C7), 35.7 (C17), 32.9 (C9), 31.4

(C11), 31.2 (C1), 30.5 (–C2), 28.6 (C8), 28.0 (C10), 12.4 (C19); **HRMS** (FI^+) calc. for $C_{17}H_{21}OCl$ $[M]^+$: 276.1281; found: 286.1271.

(*S*)- and (*R*)- 3-Methyl-5-((2a*R*,3*S*,4*S*)-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]-chromen-4-yl)furan-2(5*H*)-one (371 and 371b), and (2a*R*,2a'*R*,3*S*,3'*S*,4*R*,4'*R*)-4,4'-oxybis(3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromene) (370)

To an oven-dried vial charged with a stirrer bar and $ZnCl_2$ (10.5 mg, 0.077 mmol, 0.4 equiv.) under argon at –40 °C was added a cooled solution of the above chloropyran **369** and siloxyfuran **55** (98 mg, 0.386 mmol, 2.0 equiv.) in dry dichloromethane (1.3 mL). The reaction mixture was stirred warming to RT overnight before being filtered through a short pad of oven-dried Celite®, and washed with dry dichloromethane. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica (9:1 → 7:3 Pet. Ether/ Et_2O) to yield CDEFG rings **371a** (15.1 mg, 23%) and its C5-epimer **371b** (20.7 mg, as a 71:14:14 mixture with its C6-epimer and another unidentified compound, 22%) as white foams, and dimer **370** (5%) as a colourless oil.

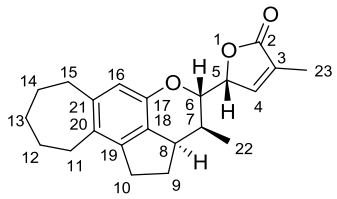
(*S*)-3-Methyl-5-((2a*R*,3*S*,4*S*)-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromen-4-yl)furan-2(5*H*)-one (371a)



$[\alpha]_D^{25}$ +49.7 (*c* = 0.527, $CHCl_3$); **R_f** 0.11 (Pet. Ether/ Et_2O (4:1)); **IR** (ν_{max} (thin film) /cm^{-1}) 2922 (s), 1760 (s), 1608 (m), 1475 (m), 1364 (w), 1287 (m), 1058 (m), 999 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.07 (1H, quin, *J* = 1.7 Hz, H4), 6.46 (1H, s, H16), 5.06 (1H, dquin, *J* = 7.2, 1.7 Hz, H5), 4.03 (1H, dd, *J* = 7.2, 1.6 Hz, H6), 3.17 (1H, *app* dt, *J* = 10.9, 6.1 Hz, H8), 2.80 (2H, dd, *J* = 9.6, 3.4 Hz, H10), 2.72 (2H, dt, *J* = 7.1, 2.8 Hz, H15), 2.70-2.67 (2H, m, H11), 2.29 (1H, qdd, *J* = 7.1, 5.4, 1.6 Hz, H7), 2.19-2.11 (1H, m, H9), 1.95 (3H, t, *J* = 1.7 Hz, H23), 1.88-1.80

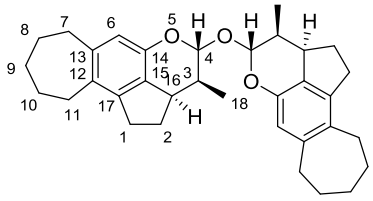
(1H, m, H13), 1.80-1.69 (2H, m, H13 and H9), 1.69-1.63 (2H, m, H14 and H12), 1.63-1.47 (2H, m, H14 and H12), 0.87 (3H, d, *J* = 7.1 Hz, H22); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 173.6 (C1), 147.7 (C17), 144.9 (C19), 144.4 (C4), 143.2 (C20), 132.3 (C3), 131.6 (C21), 122.4 (C18), 113.5 (C16), 82.5 (C6), 82.1 (C5), 37.9 (C8), 36.8 (C15), 32.9 (C13), 31.3 (C11), 31.1 (C10), 30.9 (C9), 30.2 (C7), 28.6 (C14), 28.2 (C12), 13.7 (C22), 11.1 (C23); **HRMS** (ESI^+) calc. for $C_{22}H_{26}NaO_3$ $[M+Na]^+$: 361.1774; found: 361.1771.

(*R*)-3-Methyl-5-((2a*R*,3*S*,4*S*)-3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromen-4-yl)furan-2(5*H*)-one (371b)



$[\alpha]_D^{25}$ +53.0 (*c* = 0.545, $CHCl_3$); **R_f** 0.43 (Pet. Ether/ Et_2O (4:1)); **IR** (ν_{max} (thin film) /cm^{-1}) 2925 (s), 1761 (s), 1605 (m), 1476 (m), 1364 (w), 1289 (m), 1059 (m), 999 (m); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.38 (1H, quin, *J* = 1.7 Hz, H4), 6.41 (1H, s, H16), 4.93 (1H, dquin, *J* = 10.0, 1.7 Hz, H5), 3.79 (1H, dd, *J* = 10.0, 1.6 Hz, H6), 3.37 (1H, *app* dt, *J* = 11.0, 6.0 Hz, H8), 2.85-2.79 (2H, m, H10), 2.77-2.65 (4H, m, H15 and H11), 2.63 (1H, qdd, *J* = 7.2, 5.5, 1.7 Hz, H7), 2.24-2.17 (1H, m, H9), 1.95 (3H, t, *J* = 1.7 Hz, H23), 1.99-1.82 (1H, m, H13), 1.82-1.73 (2H, m, H13 and H9), 1.73-1.63 (2H, H14 and H12), 1.62-1.45 (2H, m, H14 and H12), 0.83 (3H, d, *J* = 7.2 Hz, H22); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 174.1 (C1), 149.1 (C4), 147.8 (C17), 144.8 (C19), 143.9 (C20), 131.8 (C21), 130.0 (C3), 122.9 (C18), 112.8 (C16), 82.3 (C6), 78.5 (C5), 36.9 (C8), 36.9 (C15), 32.9 (C13), 31.3 (C11), 31.2 (C10), 30.8 (C9), 28.7 (C7), 28.6 (C14), 28.2 (C12), 13.0 (C22), 10.9 (C23); **HRMS** (ESI^+) calc. for $C_{22}H_{26}NaO_3$ $[M+Na]^+$: 361.1774; found: 361.1768.

(2a*R*,2a'*R*,3*S*,3'*S*,4*R*,4'*R*)-4,4'-oxybis(3-methyl-1,2,2a,3,4,7,8,9,10,11-decahydrocyclohepta[*g*]cyclopenta[*de*]chromene) (370)

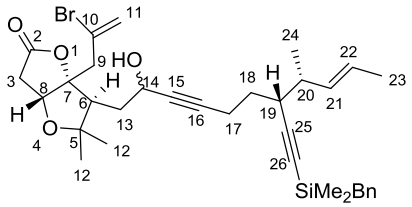


R_f 0.87 (Pet. Ether/ Et_2O (4:1)); **IR** (ν_{max} (thin film) /cm^{-1}) 2980 (m), 2880 (m), 1610 (m), 1476 (m), 1282 (m), 1126 (s), 1084 (s), 945 (s), 908 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.47 (1H, s, H6), 5.50 (1H, d, *J* = 1.7 Hz, H4), 3.38 (1H, dt, *J* = 11.4, 6.3 Hz, H16), 2.83- 2.76 (2H, m, H1), 2.76-2.72 (2H, m, H7), 2.72- 2.66 (2H, m, H11), 2.17 (1H, qdd, *J* = 7.2, 6.1, 1.7 Hz, H3), 2.13- 2.02 (1H, m, H2), 1.87-1.76 (2H, m, H9), 1.76-1.71 (1H, m, H2), 1.70-1.55 (4H, m, H8 and H10), 0.69 (3H, d, *J* = 7.2 Hz, H18); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.9 (C14), 144.1 (C17), 143.1 (C12), 131.6 (C13), 124.8 (C15), 113.2 (C6), 98.1 (C4), 36.9 (C7), 35.9 (C16), 33.0 (C9), 31.9 (C3), 31.3 (C11), 31.2 (C1), 29.8 (C2), 28.7 (C8), 28.2 (C10), 10.8 (C18); **HRMS** (FI^+) calc. for $C_{34}H_{42}O_3$ $[M]^+$: 498.3134; found: 498.2904.

7.6. Procedures and Characterisations for Synthesis of Rubriflordilactone A

7.6.1. By palladium-catalysed cyclisation of bromoenediyne

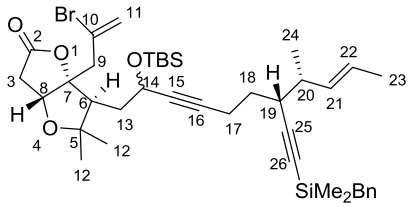
(3a*R*,6*S*,6a*R*)-6-((7*R*,8*R*,*E*)-7-((Benzyldimethylsilyl)ethynyl)-2-hydroxy-8-methylundeC9-en-3-yn-1-yl)-6a-(2-bromoallyl)-5,5-dimethyltetrahydrofuro[3,2-b]furan-2(3*H*)-one (102)



To a stirred solution of diyne **105** (16.3mg, 0.0528 mmol, 1.25 equiv.) in dry THF (1.5 mL) under argon at –78 °C was added *n*-BuLi (2.5 M in hexanes, 19.5 µL, 0.0487 mmol, 1.15 equiv.) dropwise. The reaction mixture was stirred for 30 min before a solution of AB ring aldehyde **104** (13.4 mg, 0.0422 mmol, 1.0 equiv.) in dry THF (0.5 mL) was added. The reaction mixture was stirred for 4 h from –78 °C to –10 °C before being quenched with NH_4Cl (0.2 mL, sat. *aq.*,) and warmed to RT. The mixture was filtered through a plug of Celite® and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (7:3 Pet. Ether/ Et_2O) to yield alcohol **102** (10.4 mg, as a 7:3 mixture of diastereomers, 39%) as a colourless oil. $\mathbf{R_f}$ 0.48 (7:3 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3435, 2969, 2166, 1785, 1209, 1019, 837; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.21 (2H, t, *J* = 7.4 Hz, ArH), 7.08 (3H, *app* t, *J* = 8.1 Hz, ArH), 5.77 (1H, s, H11), 5.71 (1H, s, H11), 5.44 (1H, dq, *J* = 15.2, 6.3 Hz, H22), 5.30 (1H, *app* ddd, *J* = 15.2, 8.2, 1.3 Hz, H21), 4.86 (1H, d, *J* = 6.1 Hz, $H7^{maj}$), 4.85 (1H, d, *J* = 6.1 Hz, $H7^{min}$), 4.55-4.52 (1H, m, $H14^{maj}$), 4.45-4.40 (1H, m, $H14^{min}$), 3.42 (1H, d, *J* = 14.9 Hz, $H9^{maj}$), 3.41 (1H, d, *J* = 14.9 Hz, $H9^{min}$), 2.89 (1H, dd, *J* = 18.8, 7.0 Hz, $H3^{maj}$), 2.88 (1H, dd, *J* = 18.8, 7.0 Hz, $H3^{min}$), 2.67 (1H, d, *J* = 14.9 Hz, $H9^{min}$), 2.66 (1H, dd, *J* = 18.8 and 0.7 Hz, $H3^{maj}$), 2.64 (1H, dd, *J* = 18.8 and 0.7 Hz,

H3^{min}), 2.64 (1H, d, *J* = 14.7 Hz, H9^{maj}), 2.50 (1H, dd, *J* = 9.6, 3.5 Hz, H6^{maj}), 2.41 (1H, dddd, *J* = 16.6, 9.0, 5.1, and 2.0 Hz, H17), 2.41 (1H, obscured, H6^{min}), 2.33-2.21 (2H, m, H19 and H17), 2.17 (2H, s, SiC$\underline{H}_2$Ph), 2.12 (1H, *app* sextet, *J* = 7.1 Hz, H20), 2.04 (1H, d, *J* = 4.7 Hz, OH^{min}), 2.02 (1H, d, *J* = 6.2 Hz, OH^{maj}), 1.84 (1H, ddd, *J* = 14.5, 9.6 and 5.0 Hz, H13^{maj}), 1.81 (1H, obscured, H13^{min}) 1.67 (3H, d, *J* = 6.3 Hz, H23), 1.70-1.47 (3H, m, H13, H19 and H17), 1.35 (3H, s, H12^{min}), 1.33 (3H, s, H12^{maj}), 1.09 (3H, s, H12), 1.05 (3H, d, *J* = 6.8 Hz, H24), 0.11 (6H, s, Si(CH$_3$)$_2$Bn).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.7, 175.6, 139.4 (2C), 134.9, 134.8, 128.5 (4C), 128.2 (4C), 125.2, 125.2, 124.6, 124.5, 124.4, 124.4, 124.3 (2C) 109.5, 109.5, 95.2, 95.0, 86.8, 86.4, 85.9 (2C), 83.1 (2C), 80.5, 80.3, 76.8, 76.8, 62.0, 61.2, 57.0, 55.7, 46.0, 45.9, 40.9 (2C), 38.4 (2C), 37.5, 37.4, 34.3, 33.6, 31.8 (2C), 27.5, 27.5, 26.6 (2C), 20.5, 18.1, 18.1, 18.1 (2C), 17.0 (2C), –1.6 (4C); Note: '2C' refers to overlapping peaks from a single carbon atom in both the major and minor diastereomers. '4C' refers to overlapped equivalent carbon atoms in both diastereomers on the benzyldimethylsilane group; **HRMS** (ES$^+$) calc. for $C_{34}H_{45}O_4BrNaSi$ $[M+Na]^+$ 647.21627; found 647.21582.

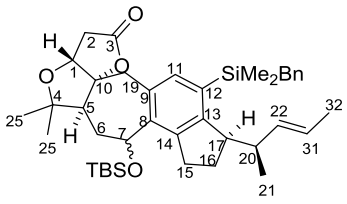
(3a*R*,6*S*,6a*R*)-6-((7*R*,8*R*,*E*)-7-((Benzyldimethylsilyl)ethynyl)-2-((*tert*-butyldimethylsilyl)oxy)-8-methylundeC9-en-3-yn-1-yl)-6a-(2-bromoallyl)-5,5-dimethyltetrahydrofuro[3,2-b]furan-2(3*H*)-one (376)



To a stirred solution of alcohol **102** (10.4 mg, 0.0167 mmol, 1.0 equiv.) in dry dichloromethane (1.0 mL) under argon at 0 °C was added sequentially imidazole (1.7 mg, 0.0249 mmol, 1.5 equiv.), 4-dimethylaminopyridine (0.2 mg, 0.002 mmol, 0.1 equiv.) and TBSCl (3.3 mg, 0.0216 mmol, 1.3 equiv.). The reaction mixture was warmed to RT and stirred for 2 h before being quenched with $NaHCO_3$ (1 mL, sat. *aq.*). The layers were separated and the aqueous layer extracted three times with dichloromethane (3 x 1 mL). The

combined organic layers were dried with Na_2SO_4 and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (9:1 Pet. Ether/ Et_2O) to yield TBS ether **376** (7.4 mg, as a 7:3 mixture of diastereomers, 60%) as a colourless oil. $\mathbf{R_f}$ 0.32 (9:1 Pet. Ether / Et_2O); **IR** (thin film, ν_{max} / cm^{-1}) 3025, 2957, 2857, 2167, 1789, 1250, 1208, 1083, 837; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.21 (2H, t, *J* = 7.7 Hz, $SiCH_2\underline{Ph}$), 7.11-7.04 (3H, m, $SiCH_2\underline{Ph}$), 5.77 (1H, s, H11), 5.71 (1H, s, H11), 5.52-5.36 (1H, m, H22), 5.36-5.24 (1H, m, H21), 4.82 (1H, d, *J* = 6.8 Hz, H8), 4.40-4.36 (1H, m, H14), 3.16 (1H, d, *J* = 14.9 Hz, $H9^{min}$), 3.14 (1H, d, *J* = 14.9 Hz, $H9^{maj}$), 2.86 (1H, dd, *J* = 18.7 and 6.5 Hz, $H3^{min}$), 2.85 (1H, dd, *J* = 18.8 and 6.8 Hz, $H3^{maj}$), 2.67 (1H, d, *J* = 15.0 Hz, H9), 2.63 (1H, dd, *J* = 18.8 and 0.7 Hz, H3), 2.45 (1H, dd, *J* = 9.8 and 3.3 Hz, H6), 2.42-2.20 (3H, m, 2 x H17 and H19), 2.17 (2H, s, $SiC\underline{H_2}Ph$), 2.15-2.07 (1H, m, H20), 1.80-1.70 (1H, m, H13), 1.70-1.63 (1H, m, H18), 1.66 (3H, d, *J* = 6.2 Hz, H23), 1.34 (3H, s, $H12^{min}$), 1.31 (3H, s, $H12^{maj}$), 1.08 (3H, s, $H12^{min}$), 1.07 (3H, s, $H12^{maj}$), 1.05 (3H, d, *J* = 6.8 Hz, $H24^{maj}$), 1.05 (3H, d, *J* = 6.8 Hz, $H24^{min}$), 0.93 (9H, s, $OSiC(C\underline{H_3})_3{}^{min}$), 0.91 (9H, s, $OSiC(C\underline{H_3})_3{}^{maj}$), 0.18-0.14 (6H, m, $Si(C\underline{H_3})_2Bn$), 0.11 (6H, s, $OSi(C\underline{H_3})_2{}^tBu^{maj}$), 0.11 (3H, s, $OSi(C\underline{H_3})_2{}^tBu^{min}$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.7 ($C2^{maj}$), 175.5 ($C2^{min}$), 139.4 (2C, $SiCH_2\underline{Ph}$), 134.9 (2C, C21), 128.5 (2C, $SiCH_2\underline{Ph}$), 128.2 (2C, $SiCH_2\underline{Ph}$), 125.2 (2C, C22), 124.5 (2C, C11), 124.4 (2C, $SiCH_2\underline{Ph}$), 124.4 (2C, C10), 109.6 (2C, C≡C), 95.2 ($C10^{min}$), 95.1 ($C10^{maj}$), 85.8 ($C{\equiv}C^{maj}$), 85.8 ($C{\equiv}C^{min}$), 85.6 (2C, C≡C), 83.3 ($C4^{min}$), 83.1 ($C4^{maj}$), 81.4 ($C{\equiv}C^{maj}$), 81.2 ($C{\equiv}C^{min}$), 77.3 ($C8^{min}$), 76.8 ($C8^{maj}$), 62.4 ($C14^{min}$), 61.2 ($C14^{maj}$), 56.2 ($C6^{min}$), 55.3 ($C6^{maj}$), 46.0 ($C9^{maj}$), 46.0 ($C9^{min}$), 40.9 ($C20^{min}$), 40.9 ($C20^{maj}$), 38.3 (2C, C19), 37.5 ($C3^{maj}$), 37.4 ($C3^{min}$), 35.5 ($C13^{min}$), 35.4 ($C13^{maj}$), 31.9 (2C, C18), 27.6 (2C, C12), 26.7 (2C, $Si\underline{C}H_2Ph$), 26.0 ($OSiC(\underline{C}H_3)_3{}^{min}$), 26.0 ($OSiC(\underline{C}H_3)_3{}^{maj}$), 20.7 ($C12^{min}$), 20.6 ($C12^{maj}$), 18.4 ($C24^{min}$), 18.3 ($C24^{maj}$), 18.2 ($C23^{min}$), 18.1 ($C23^{maj}$), 18.1 (2C, $OSi\underline{C}(CH_3)_3$), 17.0 (2C, C17), –1.6 (2C, $Si(\underline{C}H_3)_2Bn$), –4.1 ($OSi(\underline{C}H_3)_2{}^tBu^{maj}$), –4.2 ($OSi(\underline{C}H_3)_2{}^tBu^{min}$), –4.6 ($OSi(\underline{C}H_3)_2{}^tBu^{min}$), –4.6 ($OSi(\underline{C}H_3)_2{}^tBu^{maj}$); **HRMS** ($ES^+$) calc. for $C_{40}H_{59}O_4{}^{79}Br^{23}Na^{28}Si_2$ $[M+Na]^+$ 761.30275; found 761.30231.

(3a*R*,5a*S*,10*R*,13a*R*)-11-(Benzyldimethylsilyl)-7-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one (377)

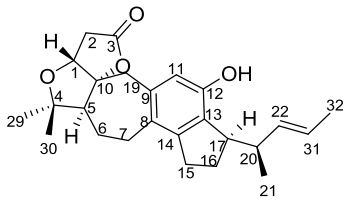


(rubriflordilactone A numbering)

Bromoenediyne **102** (7.1 mg, 0.00959 mmol, 1.0 equiv.) was dissolved in dry acetonitrile (0.4 mL), and the solution degassed with argon bubbling for 15 min. Triethylamine was separately degassed with argon bubbling for 15 min. A vial equipped with a stirrer bar was charged with tetrakis(triphenylphosphine)palladium(0) (0.6 mg, 0.0005 mmol, 5 mol%) in the glovebox, and subsequently degassed with argon bubbling for 15 min. The degassed solution of starting material was added to the catalyst by syringe, followed by the degassed triethylamine (11 µL, 0.0767 mmol, 8.0 equiv.). The reaction mixture was stirred at 80 °C overnight, then cooled to RT and the solvent carefully removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 Pet. Ether/ Et_2O) to yield pentacycle **377** (4.6 mg, as a 7:3 mixture of diasteromers, 73%) as a colourless oil. **IR** (thin film, ν_{max} / cm^{-1}) 2927, 2855, 1780, 1458, 1386, 1251, 1193, 1067, 935, 835; **HRMS** (ES^+) calc. for $C_{40}H_{58}NaO_4Si_2$ $[M+Na]^+$ 681.3766; found 681.3761. **Major diastereomer: R_f** 0.20 (3:1 Pet. Ether / Et_2O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.17 (2H, t, *J* = 7.6 Hz, $SiCH_2\underline{Ph}$), 7.04 (1H, t, *J* = 7.4 Hz, $SiCH_2\underline{Ph}$), 6.94 (2H, d, *J* = 7.3 Hz, $SiCH_2\underline{Ph}$), 6.86 (1H, s, H11), 5.25 (1H, dqd, *J* = 15.8, 6.2 and 0.9 Hz, H23), 5.15 (1H, ddd, *J* = 15.8, 5.7 and 0.9 Hz, H22), 5.03 (1H, dd, *J* = 9.2 and 6.1 Hz, H7), 4.40 (1H, d, *J* = 5.1 Hz, H1), 3.67 (1H, d, *J* = 14.4 Hz, H19), 3.17 (1H, m, H17), 2.91-2.83 (1H, m, H15), 2.84 (1H, dd, *J* = 18.2 and 5.1 Hz, H2), 2.74-2.68 (1H, m, H15), 2.69 (1H, d, *J* = 18.2 Hz, H2), 2.52-2.46 (1H, m, H20), 2.49 (1H, d, *J* = 14.4 Hz, H19), 2.33 (1H, *app* d, *J* = 4.0 Hz, $SiC\underline{H_2}Ph$), 2.21-2.12 (1H, m, H6), 2.08 (1H, dd, *J* = 12.6 and 2.8 Hz, H5), 2.01 (1H, dd, *J* = 13.4 and 8.5 Hz, H6), 1.98-1.87 (2H, m, H16), 1.51 (3H, d, *J* = 6.2 Hz, H24), 1.29 (3H, s, H25), 1.21 (3H, s, H25), 1.11 (3H, d, *J* = 6.8 Hz, H21), 0.89

(9H, s, OSiC(C<u>H</u>$_3$)$_3$), 0.28 (3H, s, Si(C<u>H</u>$_3$)$_2$Bn), 0.23 (3H, s, Si(C<u>H</u>$_3$)$_2$Bn), 0.09 (3H, s, OSi(C<u>H</u>$_3$)$_2$^{t}Bu), 0.04 (3H, s, OSi(C<u>H</u>$_3$)$_2$^{t}Bu); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 174.8 (C3), 152.7 (C13), 144.4 (C14), 140.0 (SiCH$_2$<u>Ph</u>), 137.5 (C11), 135.9 (C8), 133.2 (C12), 131.9 (C23), 130.6 (C9), 128.6 (SiCH$_2$<u>Ph</u>), 128.2 (SiCH$_2$<u>Ph</u>), 124.5 (SiCH$_2$<u>Ph</u>), 124.2 (C22), 98.9 (C10), 85.0 (C4), 79.6 (C1), 71.8 (C7), 51.6 (C5), 50.7 (C17), 41.7 (C20), 39.3 (C19), 36.9 (C2), 35.6 (C6), 31.3 (C15), 29.9 (C25), 27.3 (Si<u>C</u>H$_2$Ph), 26.3 (OSiC(<u>C</u>H$_3$)$_3$), 25.1 (C16), 23.8 (C25), 19.2 (C21), 18.6 (C24), 18.5 (OSi<u>C</u>(CH$_3$)$_3$), –1.4 (Si(<u>C</u>H$_3$)$_2$Bn), –1.5 (Si(<u>C</u>H$_3$)$_2$Bn), –3.5 (OSi(<u>C</u>H$_3$)$_2$^{t}Bu), –3.6 (OSi(<u>C</u>H$_3$)$_2$^{t}Bu). **Minor diastereomer: R_f** 0.24 (3:1 Pet. Ether / Et_2O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.15 (2H, t, *J* = 7.6 Hz, SiCH$_2$<u>Ph</u>), 7.05 (1H, t, *J* = 7.3 Hz, SiCH$_2$<u>Ph</u>), 6.88 (2H, d, *J* = 7.0 Hz, SiCH$_2$<u>Ph</u>), 6.73 (1H, s, H11), 5.12-4.97 (3H, m, H22, H31 and H7), 4.13 (1H, d, *J* = 5.3 Hz, H1), 3.70 (1H, d, *J* = 14.9 Hz, H19), 3.17-3.08 (1H, m, H17), 2.90-2.80 (2H, m, H15 and H5), 2.77 (1H, dd, *J* = 18.4 and 5.3 Hz, H2), 2.75 (1H, d, *J* = 18.4 Hz, H19), 2.67 (1H, d, *J* = 18.4 Hz, H19), 2.57 (1H, dt, *J* = 15.9 and 9.4 Hz, H15), 2.41-2.33 (1H, m, H20), 2.30 (2H, s, SiC<u>H</u>$_2$Ph), 2.14 (1H, ddd, *J* = 14.7, 6.8 and 5.5 Hz, H6), 1.97-1.88 (2H, m, 2×H16), 1.69 (1 H, ddd, *J* = 14.7, 11.7 and 1.0 Hz, H6), 1.46 (3H, d, *J* = 4.8 Hz, H32), 1.36 (3H, s, H29), 1.11 (3H, d, *J* = 6.9 Hz, H21), 1.05 (3H, s, H30), 0.89 (9H, s, OSiC(C<u>H</u>$_3$)$_3$), 0.33 (3H, s, Si(C<u>H</u>$_3$)$_2$Bn), 0.26 (3H, s, Si(C<u>H</u>$_3$)$_2$Bn), 0.12 (3H, s, OSi(C<u>H</u>$_3$)$_2$^{t}Bu), 0.02 (3H, s, OSi(C<u>H</u>$_3$)$_2$^{t}Bu); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.5 (C3), 152.9 (C13), 142.2 (C14), 139.9 (SiCH$_2$<u>C</u>$_6$H$_5$), 138.6 (C8), 137.3 (C11), 132.4 (C12), 131.8 (C31), 129.7 (C9), 128.5 (SiCH$_2$<u>C</u>$_6$H$_5$), 128.2 (SiCH$_2$<u>C</u>$_6$H$_5$), 124.3 (SiCH$_2$<u>C</u>$_6$H$_5$), 124.3 (C22), 97.5 (C10), 85.0 (C4), 78.7 (C1), 69.3 (C7), 51.0 (C17), 50.9 (C5), 42.3 (C20), 40.9 (C19), 37.1 (C2), 33.1 (C6), 30.8 (C15), 29.8 (C29), 27.5 (Si<u>C</u>H$_2$C$_6$H$_5$), 26.0 (OSiC(<u>C</u>H$_3$)$_3$), 25.0 (C16), 23.9 (C30), 19.2 (C32), 18.4 (C21), 18.3 (OSi<u>C</u>(CH$_3$)$_3$), –1.2 (Si(<u>C</u>H$_3$)$_2$Bn), –1.5 (Si(<u>C</u>H$_3$)$_2$Bn), –3.5 (OSi(<u>C</u>H$_3$)$_2$^{t}Bu), –4.8 (OSi(<u>C</u>H$_3$)$_2$^{t}Bu).

(3a*R*,5a*S*,10*R*,13a*R*)-11-hydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one (387)



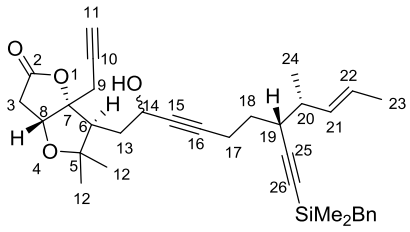
To a stirred solution of benzyldimethylarylsilane **377** (30.9 mg, 47.0 µmol, 1.0 equiv.) in THF (1.1 mL) was added TBAF (1 M in THF, 0.19 mL, 0.19 mmol, 4.0 equiv.). The reaction mixture was stirred for 30 min, then H_2O_2 (30% w/v in water, 0.11 mL, 0.94 mmol, 20.0 equiv.) in MeOH (1.1 mL) and $KHCO_3$ (9.4 mg, 94 µmol, 2.0 equiv.) were added.[151] The reaction mixture was stirred overnight at RT, then diluted with Et_2O (8.0 mL), quenched by addition of $Na_2S_2O_3$ (4.0 mL, sat. *aq.*) and NH_4Cl (4.0 mL, sat. *aq.*). The layers separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were dried ($MgSO_4$), concentrated, and quickly filtered through a short pad of silica gel to remove the remaining TBAF (1:1 Pet. Ether / EtOAc eluent). The resulting mixture of phenols **386** was used without further purification in the next step.

To a stirred solution of these phenols in dichloromethane (0.9 mL) was added anhydrous zinc(II) chloride (9.7 mg, 71 µmol, 1.5 equiv.) and triethysilane (30.3 µL, 0.19 mmol, 4.0 equiv.).[140] The reaction mixture was stirred for 3 h at RT before being quenched by addition of NH_4Cl (2 mL, sat. *aq.*) and diluted with Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting crude was dissolved in THF (2.0 mL) and TBAF (47 µL, 47 µmol, 1.0 equiv.) was added. The reaction mixture was stirred 30 min at RT before being quenched by addition of NH_4Cl (2.0 mL, sat. *aq.*) and diluted with Et_2O (5.0 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 x 5.0 mL). The combined organic phases were dried ($MgSO_4$), concentrated, and the resulting crude was

was purified by flash chromatography on a short plug of silica (6:4 Pet. Ether / EtOAc) to yield phenol **387** (9.5 mg, 24 µmol, 51% over three steps) as a colourless. $[\alpha]_D^{25}$ +20.0 (*c* = 0.20, $CHCl_3$); R_f 0.21 (3:2 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 3397, 2925, 1774, 1601, 1458, 1318, 1202, 1172, 935, 848; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.25 (1H, s, H11), 5.56-5.47 (2H, m, H22 and H31), 4.83 (1H, br s, ArOH), 4.26 (1H, d, *J* = 6.0 Hz, H1), 3.53 (1H, d, *J* = 15.4 Hz, H19), 3.28 (1H, dt, *J* = 9.0 and 3.8 Hz, H17), 2.97 (1H, br dd, *J* = 17.2 and 4.4 Hz, H7), 2.85 (1H, dd, *J* = 18.6 and 6.0 Hz, H2), 2.77-2.66 (2H, m, H7 and H15), 2.70 (1H, d, *J* = 18.6 Hz, H2), 2.62 (1H, d, *J* = 15.4 Hz, H19), 2.62-2.53 (2H, m, H15 and H20), 2.28 (1H, dd, *J* = 12.7 and 3.4 Hz, H5), 2.15 (1H, ddd, *J* = 17.3, 13.0 and 9.0 Hz, H16), 2.05-1.96 (1H, m, H6), 1.93 (1H, m, H16), 1.76 (1H, ddt, *J* = 14.3, 5.4 and 3.4 Hz, H6), 1.66 (3 H, br d, *J* = 3.2 Hz, H32), 1.36 (3H, s, H29), 1.15 (3H, s, H30), 0.97 (3H, d, *J* = 6.9 Hz, H21); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.4 (C3), 150.4 (C12), 147.1 (C14), 135.9 (C22), 132.5 (C9), 129.0 (C13), 126.0 (C8), 125.8 (C31), 117.5 (C11), 99.2 (C10), 84.5 (C4), 79.7 (C1), 59.5 (C5), 48.9 (C17), 40.8 (C19), 39.9 (C20), 36.0 (C2), 31.5 (C15), 31.0 (C7), 29.1 (C16), 28.5 (C32), 24.1 (C6), 21.3 (C29), 18.2 (C30), 16.6 (C21); **HRMS** (ES^+) calc. for $C_{25}H_{31}NaO_4$ $[M+Na]^+$ 395.2228; found 395.2224.

7.6.2. By cobalt-catalysed cyclotrimerisation

(3a*R*,6*S*,6a*R*)-6-((7*R*,8*R*,*E*)-7-((benzyldimethylsilyl)ethynyl)-2-hydroxy-8-methylundec-9-en-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (378)



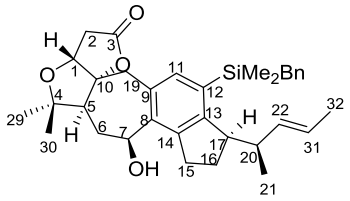
To a stirred solution of diyne **105** (137 mg, 0.444 mmol, 1.4 equiv.) in THF (3.7 mL) under argon at –78 °C was added *n*-BuLi (2.5 M in hexanes, 0.165 mL, 0.412 mmol, 1.3 equiv.) dropwise. The reaction mixture was stirred for 30 min, then a solution of AB ring aldehyde

261 (75 mg, 0.317 mmol, 1.0 equiv.) in THF (2 mL) was added. The reaction mixture was stirred for 4 h, with warming from –78 °C to –50 °C, then quenched by addition of NH_4Cl (0.2 mL, sat. *aq.*) and warmed to RT. The mixture was filtered through a plug of Celite®, eluted with EtOAc, and concentrated. The product was purified by flash chromatography on silica gel (7:3 Pet. Ether / EtOAc) to afford alcohol **378** (147 mg, inseparable 64:36 mixture of C14 diastereomers, 0.270 mmol, 85%) as a colourless oil. $\mathbf{R_f}$ 0.34 (7:3 Pet. Ether / EtOAc); **IR** (thin film, v_{max} / cm^{-1}) 3291, 2969, 2924, 2165, 1787, 1600, 1495, 1624, 1375, 1319, 1250, 1197, 1021, 837; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.21 (2H, t, *J* = 7.6 Hz, ArH), 7.14-6.99 (3H, m, ArH), 5.44 (1H, dq, *J* = 15.3 and 6.2 Hz, H22), 5.30 (1H, ddd, *J* = 15.3, 8.1 and 1.2 Hz, H21), 4.55-4.49 (1.64H, m, H8 and H14^{maj}), 4.45-4.39 (0.36H, m, H14^{min}), 3.10-2.97 (2H, m, H9 and H3), 2.68 (1H, ddd, *J* = 18.7, 8.0 and 0.9 Hz, H3), 2.54-2.45 (2H, m, H6 and H9), 2.45-2.36 (1H, m, H17), 2.34-2.20 (2H, m, H19 and H17), 2.16 (1H, s, SiC$\underline{H}_2$Ph), 2.12 (1H, *app* quin, *J* = 7.1 Hz, H20), 2.09-2.05 (1H, m, H11), 1.98 (0.64H, d, *J* = 4.3 Hz, OH^{maj}), 1.96 (0.36H, *J* = 6.3 Hz, OH^{min}) ,1.86-1.75 (1H, m, H13), 1.71-1.62 (1H, m, H18), 1.66 (3H, dd, *J* = 6.3 and 1.4 Hz, H23), 1.58 (0.36H, dd, *J* = 7.2 and 3.2 Hz, H13^{min}), 1.55-1.47 (1.64H, m, H13^{maj} and H18), 1.34 (1.08H, s, H12^{min}), 1.33 (1.92H, s, H12^{maj}), 1.07 (3H, s, H12), 1.05 (3H, *app* d, *J* = 6.8 Hz, H24), 0.11 (6H, s, Si(C$\underline{H}_3$)$_2$Bn); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.6 (C2), 139.4 (C_{Ar}), 134.9 (C21^{min}), 134.8 (C21^{maj}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 125.2 (C22), 124.4 (C_{Ar}), 109.5 (C25), 94.9 (C7^{maj}), 94.7 (C7^{min}), 86.8 (C16^{maj}), 86.4 (C16^{min}), 85.9 (C26), 83.5 (C5), 80.5 (C15^{min}), 80.3 (C15^{maj}), 78.9 (C8^{min}), 78.8 (C8^{maj}), 78.1 (C10^{maj}), 78.0 (C10^{min}), 72.4 (C11), 62.0 (C14^{min}), 61.3 (C14^{maj}), 56.1 (C6^{min}), 54.7 (C6^{maj}), 40.9 (C20), 38.4 (C19), 37.7 (C3^{maj}), 37.6 (C3^{min}), 34.3 (C13^{min}), 33.6 (C13^{maj}), 31.8 (C18), 27.7 (C12), 26.7 (Si$\underline{C}H_2$Ph), 26.1 (C9^{maj}), 25.9 (C9^{min}), 20.6 (C12), 18.2 (C24), 18.1 (C23), 17.1 (C17^{min}), 17.0 (C17^{maj}), –1.6 (Si(CH$_3$)$_2$Bn); **HRMS** (ES$^+$) calc. for $C_{34}H_{44}NaO_4Si$ $[M+Na]^+$ 567.2901; found 567.2895.

(3a*R*,5a*S*,10*R*,13a*R*)-11-(Benzyldimethylsilyl)-7-hydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one ((7*S*)-100 and (7*R*)-100)

To a solution of triyne **378** (63.0 mg, 0.116 mmol, 1.0 equiv.) in chlorobenzene (2.9 mL, 0.04 M) in a microwave tube was added PPh_3 (12.1 mg, 0.046 mmol, 40 mol%), and the mixture was degassed with argon bubbling for 30 min. $CpCo(CO)_2$ (4.2 mg, 0.023 mmol, 20 mol%) was added and the reaction mixture was heated in a microwave (300 W) at 150 °C for 25 min. Upon cooling, the reaction was concentrated. The product was purified by flash chromatography (4:1 Pet. Ether / EtOAc eluent) to afford **(7*R*)-100** (16.1 mg, 0.0296 mmol, 22%), which co-eluted as a 85:15 inseparable mixture with a C31–C32 terminal alkene isomer (4%), as a colourless oil, and **(7*S*)-100** (28.3 mg, 0.0519 mmol, 45%) as a white foam. **IR** (thin film, ν_{max} / cm^{-1}) 3476, 2957, 2930, 1776, 1600, 1493, 1373, 1248, 1201, 1059, 1107, 937, 817; **HRMS** (ES^+) calc. for $C_{34}H_{44}NaO_4Si$ $[M+Na]^+$ 567.2901; found 567.2882.

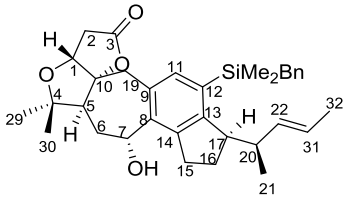
(3a*R*,5a*S*,7*S*,10*R*,13a*R*)-11-(benzyldimethylsilyl)-7-hydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one ((7*S*)-100)



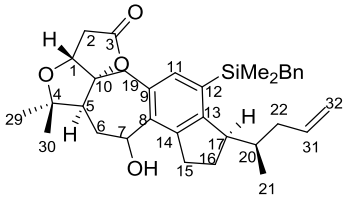
R_f 0.23 (3:2 Pet. Ether / EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.18 (2H, t, *J* = 7.5 Hz, $SiCH_2\underline{Ph}$), 7.06 (1H, t, *J* = 7.4 Hz, $SiCH_2\underline{Ph}$), 6.95 (2H, d, *J* = 7.4 Hz, $Si\underline{Ph}$), 6.84 (1H, s, H11), 5.16 (1H, ddd, *J* = 15.4, 6.7 and 0.8 Hz, H22), 5.02 (1H, dq, *J* = 15.4 and 6.1 Hz, H31), 4.92 (1H, dt, *J* = 9.9 and 6.1 Hz, H7), 4.32 (1H, d, *J* = 5.5 Hz, H1), 3.62 (1H, d, *J* = 15.0 Hz, H19), 3.12 (1H, dd, *J* = 8.1 and 2.1 Hz, H17), 2.93-2.83 (1H, m, H15), 2.84 (1H, dd, *J* = 18.2 and 5.5 Hz, H2), 2.80-2.72 (1H, m, H5), 2.69 (1H, d, *J* = 18.2 Hz, H2), 2.56 (1 H, d, *J* = 15.0 Hz, H19), 2.41-2.34 (1H, m, H20), 2.33 (2H, s, $SiC\underline{H_2}Ph$), 2.24 (1H, dd, *J* = 12.2, 3.5 Hz, H5),

2.21-2.04 (2H, m, H6), 2.03-1.83 (2H, m, H16), 1.65 (1H, d, *J* = 5.8 Hz, OH), 1.48 (3H, d, *J* = 6.1 Hz, H32), 1.38 (3H, s, H29), 1.22 (3H, s, H30), 1.12 (3H, d, *J* = 6.9 Hz, H21), 0.29 (3H, s, Si(C$\underline{H}_3$)$_2$Bn), 0.25 (3H, s, Si(C$\underline{H}_3$)$_2$Bn); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.7 (C3), 153.6 (C13), 145.3 (C14), 139.9 (SiCH$_2$$\underline{Ph}$), 137.8 (C8), 136.0 (C11), 133.7 (C12), 132.1 (C22), 129.5 (C9), 128.6 (SiCH$_2$$\underline{Ph}$), 128.3 (SiCH$_2$$\underline{Ph}$), 124.3 (C31), 124.2 (SiCH$_2$$\underline{Ph}$), 98.7 (C10), 84.7 (C4), 79.5 (C1), 72.0 (C7), 52.8 (C5), 51.0 (C17), 42.2 (C20), 40.0 (C19), 36.1 (C2), 34.3 (C6), 31.7 (C15), 29.0 (C29), 27.2 (Si$\underline{C}$H$_2$Ph), 25.4 (C16), 22.2 (C30), 19.3 (C21), 18.3 (C32), –1.3 (Si($\underline{C}$H$_3$)$_2$Bn), –1.4 (Si($\underline{C}$H$_3$)$_2$Bn). The stereochemistry at C7 was assigned using a NOESY experiment, in which an enhancement was seen between H7 and H5. This enhancement was not observed in the equivalent NOESY experiment for **(7*R*)-100**.

(3a*R*,5a*S*,7*R*,10*R*,13a*R*)-11-(benzyldimethylsilyl)-7-hydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one ((7*R*)-100)



Co-eluted as a 85:15 mixture with C31-C32 terminal alkene (on right).



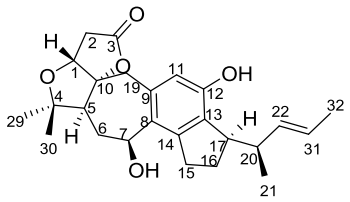
This product contains a small amount (15%) of the C31–C32 terminal alkene regioisomer; signals from this compound are indicated as H^{ter} in the ^{1}H NMR data. **R_f** 0.51 (3:2 Pet. Ether / EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.19 (2H, t, *J* = 7.6 Hz, SiCH$_2$C$_6$$\underline{H}_5$), 7.06 (1H, t, *J* = 7.4 Hz, SiCH$_2$$\underline{Ph}$), 6.94 (2H, d, *J* = 7.2 Hz, SiCH$_2$$\underline{Ph}$), 6.82 (0.85H, s, H11), 6.79 (0.15H, s, H11^{ter}), 5.58-5.49 (0.15H, m, H31^{ter}), 5.10-5.06 (1.7H, m, H22 and H31), 5.04 (1H, dd, *J* = 8.8, 6.5 Hz, H7), 4.91-4.86 (0.3H, m, 2 × H32^{ter}), 4.30 (1H, d, *J* = 6.6 Hz, H1), 3.40 (1H, d, *J* = 15.8 Hz, H19), 3.19 (1H, dt, *J* = 8.0 and 2.6, H17), 3.11 (1H, dd, *J* = 16.0, 8.6 and 1.9 Hz, H15), 2.93 (1H, dd, *J* = 19.0 and 6.6, H2), 2.83-2.75 (1H, m, H5), 2.80 (1H, d, *J* = 15.8 Hz, H19), 2.75 (1H, d, *J* = 19.0 Hz, H2), 2.74-2.67 (1H, m, H15), 2.43-2.35 (1 H, m, H20), 2.32 (2H, s, SiC$\underline{H}_2$Ph), 2.13 (1H, ddd, *J* = 14.2, 6.5 and 3.8 Hz, H6), 2.06-1.93 (3H, m, H6 and 2 × H16), 1.80 (1H, d, *J* = 9.0 Hz, OH), 1.73-1.64 (0.3H, m, 2 × H22^{ter}), 1.49 (2.55H, d, *J* = 3.6

Hz, H32), 1.40 (3H, s, H29), 1.20 (3H, s, H30), 1.12 (2.55H, d, *J* = 6.9 Hz, H21), 1.04 (0.45H, d, *J* = 6.8 Hz, H21^{ter}), 0.29 (3H, s, Si(C$\underline{H}_3$)$_2$Bn), 0.25 (3H, s, Si(C$\underline{H}_3$)$_2$Bn); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.0 (C3), 153.0 (C13), 145.8 (C14), 139.9 (SiCH$_2$$\underline{Ph}$), 137.8 (C11), 136.3 (C8), 133.7 (C12), 131.8 (C22), 129.3 (C9), 128.6 (SiCH$_2$$\underline{Ph}$), 128.3 (+, SiCH$_2$$\underline{Ph}$), 124.3 (+, SiCH$_2$$\underline{Ph}$), 124.3 (C31), 98.4 (C10), 84.1 (C4), 79.8 (C1), 68.8 (C7), 52.5 (C5), 50.9 (C17), 42.1 (C20), 42.0 (C19), 36.1 (C2), 30.7 (C15), 30.6 (C6), 28.2 (C29), 27.2 (Si$\underline{C}$H$_2$Ph), 25.0 (C16), 21.4 (C30), 19.1 (C21), 18.3 (C32), –1.3 (Si($\underline{C}$H$_3$)$_2$Bn), –1.6 (Si($\underline{C}$H$_3$)$_2$Bn).

(3a*R*,5a*S*,10*R*,13a*R*)-7,11-Dihydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one ((7*S*)-385 and (7*R*)-385)

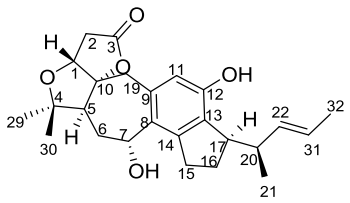
Representative procedure for the oxidation of **(7*S*)-100**, separated in the previous step: To a stirred solution of **(7*S*)-100** (39.5 mg, 0.0725 mmol, 1.0 equiv.) in THF (1.3 mL) was added TBAF (1 M in THF, 290 µL, 0.290 mmol, 4.0 equiv.). The reaction mixture was stirred for 30 min, then H_2O_2 (30% w/v in water, 184 µL, 1.45 mmol, 20 equiv.) in methanol (1.3 mL), and $KHCO_3$ (14.5 mg, 0.145 mmol, 2.0 equiv.) were added.[151] The reaction mixture was stirred at RT overnight, then quenched with $Na_2S_2O_3$ (1 mL, sat. *aq.*) and NH_4Cl (1 mL, sat. *aq.*). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography (99:1 CH_2Cl_2 / MeOH eluent) to afford the phenol **(7*S*)-385** (25.2 mg, 84%) as a white foam. **IR** (thin film, ν_{max} / cm^{-1}) 3376 (br s), 2961 (s), 2925 (s), 1774 (s), 1597 (m), 1461 (m), 1389 (m), 1319 (m), 1437 (m), 1246 (m), 1195 (m), 1171 (s), 1071 (m), 970 (m); **HRMS** (ESI$^+$) calc. for $C_{25}H_{32}NaO_5$ [M+Na]$^+$ 435.2142, found 435.2142.

(3a*R*,5a*S*,7*S*,10*R*,13a*R*)-7,11-Dihydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one ((7*S*)-385)

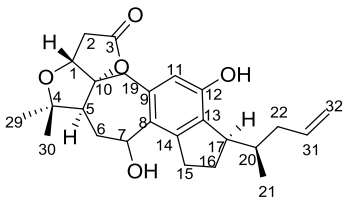


R_f 0.35 (19:1 CH_2Cl_2 / MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.23 (1H, s, H11), 5.53-5.46 (2H, m, H22 and H31), 5.16 (1H, br s, OH), 4.94-4.84 (1H, m, H7), 4.31 (1H, d, *J* = 5.3 Hz, H1), 3.58 (1H, d, *J* = 14.9 Hz, H19), 3.22 (1H, ddd, *J* = 8.8, 4.7 and 2.5 Hz, H17), 3.08 (1H, dt, *J* = 16.6 and 8.5 Hz, H15), 2.81 (1H, dd, *J* = 18.4 and 5.3 Hz, H2), 2.77 (1H, ddd, *J* = 16.6, 9.1 and 2.7 Hz, H15), 2.69 (1H, d, *J* = 18.4 Hz, H2), 2.59-2.53 (1H, m, H20), 2.50 (1H, d, *J* = 14.9 Hz, H19), 2.26-2.20 (1H, m, H5), 2.16-2.07 (3H, m, H16 and H6), 2.00 (1H, ddt, *J* = 12.9, 8.5 and 2.5 Hz, H16), 1.66 (3H, d, *J* = 4.5 Hz, H32), 1.36 (3H, s, H29), 1.21 (3H, s, H30), 0.99 (3H, d, *J* = 6.9 Hz, H21); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 174.9 (C3), 152.1 (C12), 149.4 (C14), 135.8 (C22), 132.7 (C9), 130.9 (C13), 127.6 (C8), 126.0 (C23), 117.5 (C11), 98.7 (C10), 84.8 (C4), 79.4 (C1), 71.7 (C7), 52.7 (C5), 48.6 (C17), 40.3 (C20), 39.7 (C19), 36.1 (C2), 34.6 (C6), 32.1 (C15), 29.5 (C16), 29.0 (C29), 22.3 (C30), 18.3 (C32), 17.0 (C21).

(3a*R*,5a*S*,7*R*,10*R*,13a*R*)-7,11-Dihydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one ((7*S*)-385)



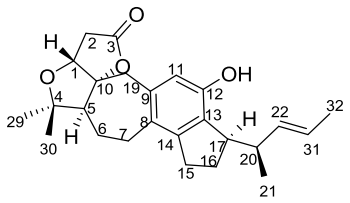
Co-eluted as a 85:15 mixture with terminal alkene (on right).



An equivalent procedure was carried out for **(7*R*)-100**, to give **(7*R*)-S100:** This product contains a small amount (15%) of the C31–C32 terminal alkene regioisomer (contained in the starting material, see above); signals from this impurity are indicated as H^{ter} in the ^{1}H

NMR data. **R_f** 0.31 (19:1 CH_2Cl_2 / MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.27 (0.85H, s, H11), 6.23 (0.15H, s, H11^{ter}), 5.76-5.64 (0.15H, m, H31^{ter}), 5.58-5.41 (1.7H, m H22 and H31), 5.22 (1H, br s, ArOH), 5.04 (1H, d, *J* = 5.9 Hz, H7), 4.99-4.90 (0.3H, m, 2 × H32^{ter}), 4.29 (1H, d, *J* = 6.4 Hz, H1), 3.37 (1H, d, *J* = 15.7 Hz, H19), 3.30 (1H, dt, *J* = 8.2 and 4.0 Hz, H17), 3.10 (1H, ddd, *J* = 16.1, 9.3 and 4.4 Hz, H15), 2.96-2.84 (1H, m, H15), 2.90 (1H, dd, *J* = 19.2 and 6.4 Hz, H2), 2.80 (1H, dd, *J* = 13.1 and 3.6 Hz, H5), 2.77-2.68 (2H, m, H2 and H19), 2.68-2.58 (1H, m, H20), 2.23-2.14 (1H, m, H16), 2.10 (1H, ddd, *J* = 14.2, 6.1 and 4.0 Hz, H6), 2.06-1.88 (3H, m, H6, H16 and OH), 1.84-1.68 (0.3H, m, 2 × H22^{ter}), 1.66 (2.55H, d, *J* = 4.5 Hz, H32), 1.39 (3H, s, H29), 1.18 (3H, s, H30), 0.98 (2.55H, d, *J* = 6.9 Hz, H21), 0.95 (0.45H, d, *J* = 6.9 Hz, H21^{ter}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.1 (C3), 152.1 (C12), 149.6 (C14), 135.6 (C22), 132.5 (C9), 130.0 (C13), 128.3 (C8), 126.0 (C23), 117.4 (C11), 98.5 (C10), 84.3 (C4), 79.7 (C1), 68.5 (C7), 52.3 (C5), 49.0 (C17), 41.8 (C19), 39.3 (C20), 36.0 (C2), 31.2 (C15), 30.9 (C6), 29.1 (C16), 28.2 (C29), 21.4 (C30), 18.3 (C21), 16.5 (C32).

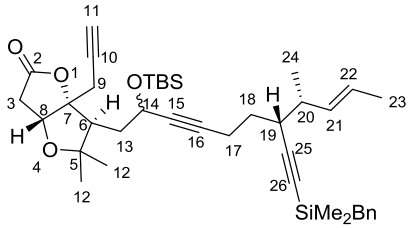
(3a*R*,5a*S*,10*R*,13a*R*)-11-hydroxy-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one (387)



To a stirred solution of the benzylic alcohols **385** (16.9 mg, 41.0 µmol, 1.0 equiv.) in dichloromethane (0.8 mL) was added $ZnCl_2$ (8.4 mg, 0.061 mmol, 1.5 equiv.) and triethylsilane (26 µL, 0.164 mmol, 4.0 equiv.).[140] The reaction mixture was stirred at RT for 3 h, then NH_4Cl (1.5 mL, sat. *aq.*) was added, and the mixture was diluted with EtOAc (3 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (3:2 Pet. Ether / EtOAc eluent) to give phenol **23** (12.5 mg,

31.5 µmol, 77%) as a colourless oil. The data for this compound was identical to that recorded for **387** derived from the Pd-catalyzed route (see above).

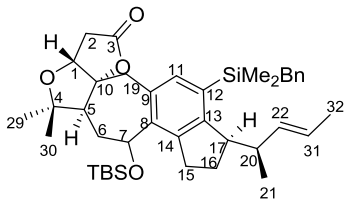
(3a*R*,6*S*,6a*R*)-6-((7*R*,8*R*,*E*)-7-((benzyldimethylsilyl)ethynyl)-2-((*tert*-butyldimethylsilyl)oxy)-8-methylundec-9-en-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (379)



To a stirred solution of alcohol **378** (20.0 mg, 0.0367 mmol, 1.0 equiv.) in dichloromethane (0.4 mL) under argon was added sequentially imidazole (3.7 mg, 0.0551 mmol, 1.5 equiv.), DMAP (0.4 mg, 0.004 mmol, 0.1 equiv.) and TBSCl (6.6 mg, 0.0441 mmol, 1.2 equiv.). The reaction mixture was stirred at RT for 6 h before being quenched with $NaHCO_3$ (0.4 mL, sat. *aq.*). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 0.4 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography (9:1 Pet. Ether / EtOAc) to afford TBS ether **379** (23.7 mg, 2:1 mixture of diastereomers, 0.0360 mmol, 98%) as a colourless oil. $\mathbf{R_f}$ 0.19 (9:1 Pet. Ether / EtOAc); **IR** (thin film, v_{max} / cm^{-1}) 2957, 2929, 2166, 1790, 1494, 1250, 1195, 1083, 930, 836, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.21 (2H, t, *J* = 7.6 Hz, ArH), 7.10-7.05 (3H, t, *J* = 6.4 Hz, ArH), 5.44 (1H, dq, *J* = 15.0 and 6.1 Hz, H22), 5.30 (1H, ddd, *J* = 15.0, 8.3 and 1.2 Hz, H21), 4.48 (1H, d, *J* = 6.7 Hz, H8), 4.43-4.35 (1H, m, H14), 2.99 (1 H, dd, *J* = 18.6 and 7.0 Hz, H3), 2.90 (1H, dd, *J* = 16.9 and 2.6 Hz, H9), 2.66 (1H, d, *J* = 18.6, H3),), 2.48 (1H, d, *J* = 16.9, H9), 2.45 (1H, dd, *J* = 7.5 and 3.2 Hz, H6), 2.43-2.29 (2H, m, H19 and H17), 2.24 (1H, ddd, *J* = 16.6, 7.9 and 1.2 Hz, H17), 2.17 (1.33H, s, $SiC\underline{H}_2Ph^{maj}$), 2.12 (1H, qd, *J* = 7.2 and 2.8 Hz, H20), 2.07 (0.67H, s, $SiC\underline{H}_2Ph^{min}$), 1.73 (1H, ddd, *J* = 14.1, 9.8 and 3.7 Hz, H13), 1.69-1.62 (1H, m, H18), 1.66 (3 H, d, *J* = 6.1 Hz, H23), 1.64-1.45 (2H, m, H13 and H18), 1.34 (1H, s, $H12^{min}$), 1.31 (2 H, s, $H12^{maj}$), 1.07-1.04 (6H, m, H12 and H24), 0.92

(3H, s, $SiC(CH_3)_3^{min}$), 0.92 (6H, s, $SiC(CH_3)_3^{maj}$), 0.21-0.13 (6H, m, $OSi(C\underline{H}_3)_2{}^tBu$), 0.11 (6H, *app* d, *J* = 1.8 Hz, $Si(CH_3)_2Bn$); **^{13}C NMR** (101MHz, $CDCl_3$) δ_C 175.6 ($C2^{min}$), 175.4 ($C2^{maj}$), 139.4 (C_{Ar}), 135.0 (C21), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 125.1 (C22), 124.4 (C_{Ar}), 109.7 (C25), 94.7 ($C7^{min}$), 94.6 ($C7^{maj}$), 85.8 (C26), 85.5 (C16), 83.7 ($C5^{min}$), 83.5 ($C5^{maj}$), 81.4 ($C15^{maj}$), 81.2 ($C15^{min}$), 78.9 (C8), 78.1 (C10), 72.4 (C11), 62.6 ($C14^{min}$), 61.2 ($C14^{maj}$), 55.5 ($C6^{min}$), 54.5 ($C6^{maj}$), 40.9 (C20), 38.3 (C19), 37.7 (C3), 35.6 ($C13^{min}$), 35.4 ($C13^{maj}$), 31.9 (C18), 27.8 ($C12^{min}$), 27.7 ($C12^{maj}$) 26.7 ($Si\underline{C}H_2Ph$), 26.1 (C9), 26.0 ($SiC(\underline{C}H_3)_3$, 20.7 (C12), 18.3 ($OSi\underline{C}(CH_3)_3$), 18.1 (C24), 18.1 (C23), 17.0 (C17), –1.6 ($Si(CH_3)_2Bn$), –4.1 ($OSi(\underline{C}H_3)_2{}^tBu^{maj}$), –4.2 ($OSi(\underline{C}H_3)_2{}^tBu^{min}$), –4.6 ($OSi(\underline{C}H_3)_2{}^tBu^{min}$), –4.9 ($OSi(\underline{C}H_3)_2{}^tBu^{maj}$); **HRMS** ($ES^+$) calc. for $C_{40}H_{58}NaO_4Si_2$ $[M+Na]^+$ 681.3766; found 681.3764.

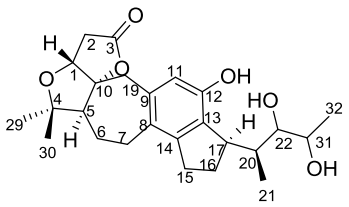
(3a*R*,5a*S*,10*R*,13a*R*)-11-(Benzyldimethylsilyl)-7-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-10-((*R*,*E*)-pent-3-en-2-yl)-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one (377)



To a solution of triyne **379** (23.7 mg, 0.036 mmol, 1.0 equiv.) in chlorobenzene (0.9 mL, 0.04 M) in a microwave tube was added triphenylphosphine (9.4 mg, 0.036 mmol, 1 equiv.) and the mixture was degassed withargonbubbling for 30 min. $CpCo(CO)_2$ (3.2 mg, 0.018 mmol, 0.5 equiv.) was added and the reaction mixture was heated in a microwave (300 W) at 150 °C for 25 min. Upon cooling, the reaction mixture was concentrated, and the product was purified by flash chromatography (9:1 Pet. Ether / EtOAc) to give pentacycle **377** (17.9 mg, as a 31:40:29 inseparable mixture of diastereomers along with terminal alkene side product, 54% of desired product by ^{1}H NMR) as a colourless oil. The data for **377** were identical to that recorded from the Pd-catalyzed route.

7.6.3. Synthesis of rubriflordilactone A from ABCDE ring system 387

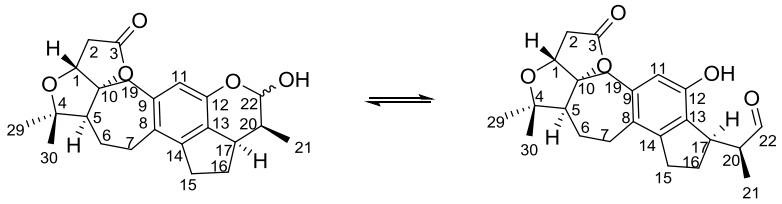
(3a*R*,5a*S*,10*R*,13a*R*)-10-((2*S*)-3,4-Dihydroxypentan-2-yl)-11-hydroxy-5,5-dimethyl-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-2-one (388)



To a stirred solution of alkene **387** (8.8 mg, 0.022 mmol, 1.0 equiv.) in acetone (0.17 mL) and water (55 µL) was sequentially added OsO_4 (4% wt in water, 5.6 µL, 0.009 mmol, 0.04 equiv.) and NMO (50% wt in water, 7.8 µL, 0.033 mmol, 1.5 equiv.). The reaction mixture was stirred at RT for 2 h before being quenched with sat. *aq.* $Na_2S_2O_3$ solution (0.3 mL). The layers were separated and the aqueous layer extracted three times with ethyl acetate (3 x 0.3 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed carefully *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (49:1 CH_2Cl_2/ MeOH), then concentrated to yield triols **388** (8.1 mg, as a 1:1 mixture of diastereomers, 85%) as a white foam. These compounds were generally carried forward as a mixture to the next step, but could be separated by careful chromatography for the purposes of characterization. **IR** (thin film, ν_{max} / cm^{-1}) 3341 (br), 2923 (s), 1773 (s), 1586 (m), 1458 (m), 1373 (m), 1227 (m), 1202 (s), 1107 (m), 1032 (m), 934 (m); **HRMS** (ESI^+) calc. for $C_{25}H_{34}NaO_6$ $[M+Na]^+$ 453.2248, found 453.2248. **Diastereomer 1:** **R_f** 0.34 (19:1 CH_2Cl_2 / MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.33 (1H, br s, ArO<u>H</u>), 6.31 (1H, s, H11), 4.26 (1H, d, *J* = 6.1 Hz, H1), 3.98 (1H, qd, *J* = 5.9 and 2.5 Hz, H31), 3.64 (1H, dt, *J* = 9.8 and 2.5 Hz, H17), 3.51 (1H, d, *J* = 15.5 Hz, H19), 3.13 (1H, dd, *J* = 8.2 and 2.5 Hz, H22), 2.95 (1H, ddd, J = 17.0, 5.4 and 1.9 Hz, H7), 2.86 (1H, dd, *J* = 18.6 and 6.3 Hz, H2), 2.79 (1H, dd, *J* = 16.0 and 8.3 Hz, H15), 2.75-2.71 (1H, m, H7), 2.70 (1H, d, *J* = 18.6 Hz, H2), 2.66 (1H, d, *J* = 15.5 Hz, H19), 2.60 (1H, ddd, *J* = 16.0, 9.7 and 1.8 Hz, H15), 2.37 (1H,

app dq, *J* = 13.0 and 9.7 Hz, H16), 2.28 (1H, dd, *J* = 12.7 and 3.5 Hz, H5), 2.11-2.04 (1H, m, H20), 1.99 (1H, *app* qd, *J* = 13.1 and 2.4 Hz, H6), 1.84 (1H, ddt, *J* = 13.0, 8.2 and 2.2 Hz, H16), 1.75 (1H, ddt, *J* = 14.3, 5.8 and 2.8 Hz, H6), 1.60 (1H, br s, OH), 1.55 (1H, s, OH), 1.36 (3H, s, H29), 1.29 (3H, d, *J* = 6.3 Hz, H32), 1.15 (3H, s, H30), 0.76 (3H, d, *J* = 6.9 Hz, H21); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.4 (C3), 151.9 (C12), 147.5 (C14), 132.9 (C8), 126.4 (C13), 124.9 (C9), 117.8 (C11), 99.1 (C10), 84.4 (C4), 79.7 (C1), 78.7 (C22), 67.5 (C31), 59.6 (C5), 42.1 (C20), 41.3 (C17), 40.8 (C19), 36.0 (C2), 32.7 (C16), 32.2 (C15), 31.1 (C7), 28.4 (C29), 24.1 (C6), 21.2 (C30), 21.0 (C32), 12.6 (C21). **Diastereomer 2: R_f** 0.32 (19:1 CH_2Cl_2 / MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.37 (1H, br s, ArOH), 6.31 (1H, s, H11), 4.26 (1H, d, *J* = 6.1 Hz, H1), 3.73 (1H, dq, *J* = 8.2 and 6.2 Hz, H31), 3.57 (1H, dd, *J* = 8.2 and 2.2 Hz, H22), 3.52 (1H, d, *J* = 15.4 Hz, H19), 3.34-3.29 (1H, m, H17), 2.98 (1H, ddd, *J* = 17.0, 5.7 and 2.5 Hz, H7), 2.86 (1H, dd, *J* = 18.6 and 6.2 Hz, H2), 2.81-2.73 (1H, m, H15), 2.73-2.70 (1H, m, H15), 2.69 (1H, d, *J* = 18.6 Hz, H2), 2.64 (1H, d, *J* = 15.4 Hz, H19), 2.57 (1H, ddd, *J* = 13.4, 9.0 and 3.8 Hz, H15), 2.38 (1H, dq, *J* = 12.5 and 8.8 Hz, H16), 2.27 (1H, dd, *J* = 12.7 and 3.3 Hz, H5), 2.06-1.92 (2H, m, H6 and H20), 1.86 (1H, ddd, *J* = 12.5, 8.0 and 3.8 Hz, H16), 1.75 (1 H, ddt, *J* = 11.4, 5.2 and 2.6 Hz, H6), 1.36 (3H, s, H29), 1.22 (3H, d, *J* = 6.2 Hz, H32), 1.15 (3H, s, H30), 0.72 (3H, d, *J* = 7.3 Hz, H21); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.5 (C3), 151.6 (C12), 147.1 (C14), 132.8 (C8), 128.4 (C13), 125.3 (C9), 118.4 (C11), 99.2 (C10), 84.4 (C4), 81.3 (C22), 79.7 (C1), 69.5 (C31), 59.5 (C5), 47.1 (C17), 40.7 (C19), 40.3 (C20), 36.0 (C2), 35.6 (C16), 31.3 (C7), 31.1 (C15), 28.5 (C29), 24.1 (C6), 21.2 (C30), 19.7 (C32), 9.6 (C21).

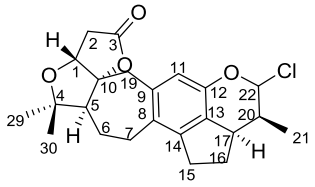
Equilibrium mixture of lactols (3a*R*,5a*S*,9a*R*,10*S*,14a*R*)-11-Hydroxy-5,5,10-trimethyl-3,3a,5,5a,6,7,8,9,9a,10,11,14-dodecahydro-2*H*-cyclopenta[de]furo[3'',2'':2',3']furo-[3',4':4,5]cyclohepta[1,2-g]chromen-2-one and aldehyde (*S*)-2-((3a*R*,5a*S*,10*R*,13a*R*)-11-hydroxy-5,5-dimethyl-2-oxo-3,3a,5,5a,6,7,8,9,10,13-decahydro-2*H*-furo[3,2-b]indeno[4',5':5,6]cyclohepta[1,2-c]furan-10-yl)propanal (389)



To a stirred solution of diol **388** (22.9 mg, 0.053 mmol, 1.0 equiv.) in dichloromethane (0.6 mL) was added $NaIO_4$ supported on silica gel (10 wt% , 137 mg, 0.0638 mmol, 1.2 equiv.).[167] The suspension was stirred for 15 min before being loaded onto a short plug of silica and purified by flash column chromatography (99:1 CH_2Cl_2/MeOH), then concentrated to yield lactol **389** (20.5 mg, 0.053 mmol, quant., as a 56:33:11 inseparable equilibrium mixture of the major lactol epimer, the open-chain aldehyde form, and the minor lactol epimer, respectively) as a colourless oil. $\mathbf{R_f}$ 0.44 (19:1 CH_2Cl_2 / MeOH); **IR** (thin film, ν_{max} / cm^{-1}) 3380, 2925, 1774, 1611, 1460, 1374, 1320, 1229, 1201, 1059, 1023, 934; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.64 (0.33H, s, H22^{ald}), 6.24 (0.56H, s, H11^{maj}), 6.24 (0.56H, s, H11^{ald}), 6.22 (0.11H, s, H11^{min}), 5.42 (0.11 H, d, *J* = 4.6 Hz, H22^{min}), 5.37 (0.56H, s, H22^{maj}), 6.06 (0.33H, s, ArOH^{ald}), 4.26 (0.67H, d, *J* = 6.1 Hz, H1$^{maj\&min}$), 4.25 (0.33H, d, *J* = 6.1 Hz, H1^{ald}), 3.73 (0.33H, dt, *J* = 7.1, 3.3 Hz, H17^{ald}), 3.54 (0.56H, d, *J* = 15.7 Hz, H19^{maj}), 3.52 (0.11H, d, *J* = 15.8 Hz, H19^{min}),3.50 (0.33H, d, *J* = 15.8 Hz, H19^{ald}), 3.42 (0.33H, dt, *J* = 11.7 and 6.1 Hz, H17^{ald}), 3.35 (0.11H, dt, *J* = 11.3 and 5.9 Hz, H17^{min}), 3.11 (0.56H, ddd, *J* = 17.2, 5.6 and 2.3 Hz, H7^{maj}), 3.11-3.05 (0.11H, m, H7^{min}), 3.05 (0.56H, br s, OH^{maj}), 2.96 (0.33H, ddd, *J* = 17.1, 5.4 and 1.9 Hz, H7^{ald}), 2.89 (0.33H, qd, *J* = 7.3 and 3.3 Hz, H20^{ald}), 2.85 (1H, dd, *J* = 18.6 and 6.1 Hz, H2), 2.80-2.68 (3H, m, H7 and 2 × H6), 2.69 (1H, d, *J* = 18.6 Hz, H2), 2.67 (0.67H, *J* = 15.7 Hz, H19 $^{maj\&min}$), 2.61 (1H, *J* = 15.8 Hz, H19^{ald}), 2.35 (0.33H, dt, *J* = 13.0 and 9.1 Hz, H15^{ald}), 2.32-2.23 (1.67H, m, H20 and H5), 2.17 (0.56H, ddd, *J* = 14.4, 7.1 and 3.8 Hz, H15

^{maj}), 2.12 (0.11H, ddd, *J* = 7.0, 4.4 and 2.8 Hz, H15^{min}), 2.04-1.93 (1H, m, H16), 1.84 (0.33H, ddd, *J* = 13.0, 8.4 and 3.9 Hz, H15^{ald}), 1.80-1.70 (1.67H, m, H15$^{maj\&min}$ and H16), 1.36 (3H, s, H29), 1.15 (3H, s, H30), 1.04 (0.99H, d, *J* = 7.3 Hz, H21^{ald}), 0.76 (0.33H, d, *J* = 7.0 Hz, H21^{min}), 0.71 (1.68H, d, *J* = 7.2 Hz, H21^{maj}); **^{13}C NMR** (126 MHz, $CDCl_3$; note that ^{13}C shifts for the minor lactol diastereomer are not reported) δ_C 207.2 (C22^{ald}), 175.4 (C3), 150.5 (C12^{ald}), 146.9 (C12^{maj}), 144.6 (C14), 133.3 (C9^{ald}), 132.8 (C9^{maj}), 127.0 (C8^{ald}), 126.5 (C8^{maj}), 126.2 (C13^{maj}), 125.9 (C13^{ald}), 117.6 (C11^{ald}), 115.4 (C11^{maj}), 99.1 (C10), 97.5 (C22^{maj}), 84.5 (C4), 79.6 (C1), 59.4 (C5^{ald}), 59.2 (C5^{maj}), 51.4 (C20^{ald}), 42.2 (C17^{ald}), 41.0 (C19^{maj}), 40.6 (C19^{ald}), 36.0 (C2), 35.1 (C17^{maj}), 32.2 (C20^{maj}), 31.5 (C6^{ald}), 31.3 (C6^{maj}), 31.0 (C7^{ald}), 30.4 (C15^{ald}), 30.4 (C7^{maj}), 29.7 (C15^{maj}), 28.5 (C29^{maj}), 28.4 (C29^{ald}), 24.4 (C16^{maj}), 24.0 (C16^{ald}), 21.3 (C30^{maj}), 21.2 (C30^{ald}), 10.9 (C21^{maj}), 10.4 (C21^{ald}); **HRMS** (ES$^-$) calc. for $C_{23}H_{27}O_5$ $[M–H^+]^-$ 383.1853; found 383.1879.

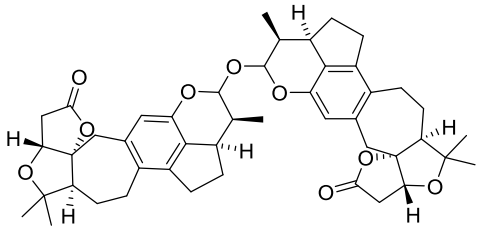
(3a*R*,5a*S*,9a*R*,10*S*,14a*R*)-11-Chloro-5,5,10-trimethyl-3,3a,5,5a,6,7,8,9,9a,10,11,14-dodecahydro-2*H*-cyclopenta[de]furo[3'',2'':2',3']furo[3',4':4,5]cyclohepta[1,2-g]chromen-2-one (390)



To an NMR tube charged with anhydrous $ZnCl_2$ (36.3 mg, 0.266 mmol, 5.0 equiv.) underargonwas added a solution of lactol-aldehyde mixture **389** (20.5 mg, 0.0532 mmol, 1.0 equiv.) in dry $CDCl_3$ (0.5 mL), followed by a solution of thionyl chloride in dry $CDCl_3$ (4.2 mM, 0.05 mL, 0.210 mmol, 4.0 equiv.). The reaction was monitored by ^{1}H NMR spectroscopy until complete conversion to the chloropyran (3 h). The mixture was then filtered through a short pad of oven-dried Celite®, and washed with dry toluene. The filtrate was concentrated to give chloropyran **390** as a colourless foam, which was used in the next step without further purification; N.B. This compound is unstable to water (in the presence of $ZnCl_2$) and silica. **^{1}H**

NMR (500 MHz, $CDCl_3$) δ_H 6.32 (1H, s, H11), 6.15 (1H, d, *J* = 1.8 Hz, H22), 4.26 (1H, d, *J* = 6.1 Hz, H1), 3.72 (1H, dt, *J* = 11.7, 6.1 Hz, H17), 3.53 (1H, d, *J* = 15.5 Hz, H19), 3.12 (1H, m, *J* = 17.4, 5.8, 2.7 Hz, H7), 2.85 (1H, dd, *J* = 18.6, 6.3 Hz, H2), 2.79-2.71 (3H, m, H7 and 2×H15), 2.72-2.68 (2H, m, H2 and H19), 2.50 (1H, qdd, *J* = 7.2, 5.4, 1.8 Hz, H20), 2.29 (1H, dd, *J* = 12.6, 3.6 Hz, H5), 2.26- 2.20 (1H, m, H16), 1.98 (1H, dtd, *J* = 14.8, 12.6, 2.5 Hz, H6), 1.82-1.71 (2H, m, H6 and H16), 1.36 (3H, s, H29), 1.15 (3H, s, H30), 0.82 (3H, d, *J* = 7.2 Hz, H21); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.4 (C3), 145.5 (C12), 144.9 (C14), 133.3 (C9), 128.2 (C8), 125.4 (C13), 116.0 (C11), 98.9 (C10), 94.0 (C22), 84.5 (C4), 79.6 (C1), 59.4 (C5), 41.0 (C19), 36.9 (C20), 36.0 (C2), 35.5 (C17), 31.3 (C15), 30.5 (C7), 30.3 (C16), 28.5 (C29), 24.0 (C6), 21.2 (C30), 12.3 (C21).

(3a*R*,3a'*R*,5a*S*,5a'*S*,9a*R*,9a'*R*,10*S*,10'*S*,14a*R*,14a'*R*)-11,11'-oxybis(5,5,10-trimethyl-3,3a,5,5a,6,7,8, 9,9a,10,11,14-dodecahydro-2*H*-cyclopenta[*de*]furo[3'',2'':2',3']furo[3',4':4,5]cyclohepta[1,2-*g*] chromen-2-one) (391)

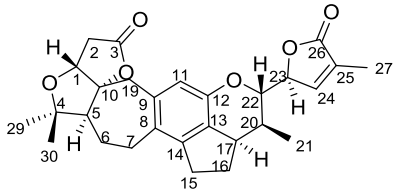


The formation and decay of dimer **391** was observed by ^{1}H NMR spectroscopy; it was not isolated. HRMS on an aliquot indicated a match to the structure: **HRMS** (ES^+) calc. for $C_{46}H_{54}O_9{}^{23}Na$ $[M+Na]^+$ 773.3660; found 773.3656.

Rubriflordilactone A (31) and C23-*epi*-rubriflordilactone A (392)

An oven-dried flask equipped with a stirrer bar and charged with anhydrous $ZnCl_2$ (2.9 mg, 0.021 mmol, 0.4 equiv.) was heated to 150 °C under vacuum overnight to remove any traces of water, cooled to RT and refilled with argon, then cooled to –30 °C. In a separate flask, to a solution of crude chloropyran **390** in dichloromethane (0.8 mL) under argon at –30 °C was added triisopropyl((3-methylfuran-2-yl)oxy)silane **55** (27.1 mg, 0.107 mmol, 2.0 equiv.). The resulting solution was transferred to the flask containing $ZnCl_2$, and the reaction mixture was stirred, warming to RT, overnight. The reaction mixture was then filtered through a short pad of Celite®, and washed with dichloromethane. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (9:1 → 4:1 → 1:1 Pet. Ether / EtOAc) to yield rubriflordilactone A 3**1** (9.3 mg, 0.020 mmol, 38%) as a white solid and its C-23 epimer **393** (8.2 mg, 0.018 mmol, 33%) as a white solid.

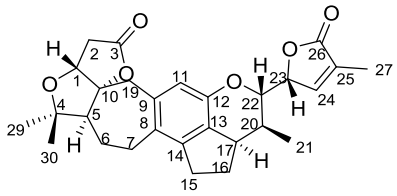
Rubriflordilactone A (31)



$[\alpha]_D^{25}$ +58.3 (*c* = 0.114, MeOH); **R_f** 0.28 (1:1 Pet. Ether / EtOAc); **IR** (thin film, ν_{max} / cm^{-1}) 2970, 2341, 2327, 1760, 1610, 1479, 1199, 1025, 934, 654; **^{1}H NMR** (500 MHz, C_5H_5N) δ_H 7.30 (1H, s, H24), 6.52 (1H, s, H11), 5.07 (1H, d, *J* = 7.9 Hz, H23), 4.33 (1H, d, *J* = 6.1 Hz, H1), 4.08 (1H, dd, *J* = 7.8, 1.3 Hz, H22), 3.56 (1H, d, *J* = 15.6 Hz, H19), 3.26-3.17 (1H, m, H17), 3.20 (1H, dd, *J* = 18.3, 6.1 Hz, H2), 3.04 (1H, dd, *J* = 17.3 and 3.9 Hz, H7), 2.87 (1H, d, *J* = 15.6 Hz, H19), 2.85 (1H, d, *J* = 18.3 Hz, H2), 2.71 (1H, dd, *J* = 15.3, 8.0 Hz, H15), 2.67-2.56 (2H, m, H7 and H15), 2.38-2.31 (2H, m, H5 and H20), 2.09 (1H, dt, *J* = 11.5, 6.6 Hz, H16), 1.95-1.83 (1H, m, H6), 1.92 (3H, s, H27), 1.81-1.68 (1H, m, H16), 1.66-1.57 (1H, m, H6), 1.35 (3H, s, H30), 1.13 (3H, s, H29), 0.85 (3H, d, *J* = 7.0 Hz, H21); **^{13}C NMR** (126 MHz, C_5H_5N) δ_c 176.0 (C3), 174.2 (C26), 148.6 (C12), 145.5 (C14), 145.5 (C24), 134.5 (C8),

132.4 (C25), 127.1 (C9), 125.2 (C13), 116.5 (C11), 99.6 (C10), 84.5 (C4), 83.9 C22), 82.6 (C23), 80.3 (C1), 60.6 (C5), 41.0 (C19), 38.2 (C17), 36.5 (C2), 31.7 (C15), 31.2 (C7), 31.2 (C16), 30.5 (C20), 28.8 (C29), 24.5 (C6), 21.4 (C30), 13.6 (C21), 11.3 (C27); **HRMS** (ES^+) calc. for $C_{28}H_{32}NaO_6$ $[M+Na]^+$ 487.2091; found 487.2092. Data in accordance with literature.[12,29]

C23-*epi*-rubriflordilactone A (392)



$[\alpha]_D^{25}$ +64.3 (*c* = 0.114, MeOH); **R_f** 0.45 (1:1 Pet. Ether/ EtOAc); **IR** (thin film, v_{max} / cm^{-1}) 2954, 2361, 1756, 1613, 1485, 1198, 1062, 931, 813, 670; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.32 (1H, *app* quint, *J* = 1.6 Hz, H24), 6.59 (1H, s, H11), 4.90 (1H, *app* dquint, *J* = 9.5 and 1.7 Hz, H23), 4.36 (1H, d, *J* = 5.9 Hz, H1), 3.92 (1H, dd, *J* = 9.5 and 1.6 Hz, H22), 3.62 (1H, d, *J* = 15.6 Hz, H19), 3.34 (1H, dt, *J* = 11.5 and 6.0 Hz, H17), 3.18 (1H, dd, *J* = 18.4 and 6.1 Hz, H2), 3.03 (1H, m, H7), 2.93 (1H, d, *J* = 15.6 Hz, H19), 2.87 (1H, d, *J* = 18.4 Hz, H2), 2.68 (1H, dd, *J* = 15.4 and 8.3 Hz, H15), 2.65-2.57 (2H, m, H15 and H7), 2.55 (1H, qdd, *J* = 7.1, 5.6 and 1.5 Hz, H20), 2.37 (1H, dd, *J* = 12.6 and 3.3 Hz, H5), 2.05 (1H, dt, *J* = 6.4 and 11.9 Hz, H16), 1.93 (1H, m, H6), 1.87 (3H, *app* t, *J* = 1.7 Hz, H27), 1.70 (1H, ddd, *J* = 19.6, 11.3 and 8.5 Hz, H16), 1.62 (1H, ddt, *J* = 14.1, 6.1 and 3.3 Hz, H6), 1.36 (3H, s, H30), 1.14 (3H, s, H29), 0.80 (3H, d, *J* = 7.1 Hz, H21); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 176.1 (C3), 174.3 (C26), 149.7 (C24), 149.0 (C12), 145.8(C14), 134.9 (C8), 130.2 (C25), 127.2 (C8), 125.4 (C13), 115.9 (C11), 99.8 (C10), 84.7 (C4), 82.7 (C22), 80.4 (C1), 79.5 (C23), 60.3 (C5), 41.0 (C19), 37.4 (C17), 36.5 (C2), 31.8 (C15), 31.3 (C7), 31.2 (C16), 29.5 (C20), 28.9 (C30), 24.5 (C6), 21.5 (C29), 13.4 (C21), 11.1 (C27); **HRMS** (ES^+) calc. for $C_{28}H_{32}NaO_6$ $[M+Na]^+$ 487.2091; found 487.2092.

8. References

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