

Total Synthesis of Rubriflordilactone B and *Pseudo*-rubriflordilactone B

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Abstract

Total Synthesis of Rubriflordilactone B and *Pseudo-rubriflordilactone B*

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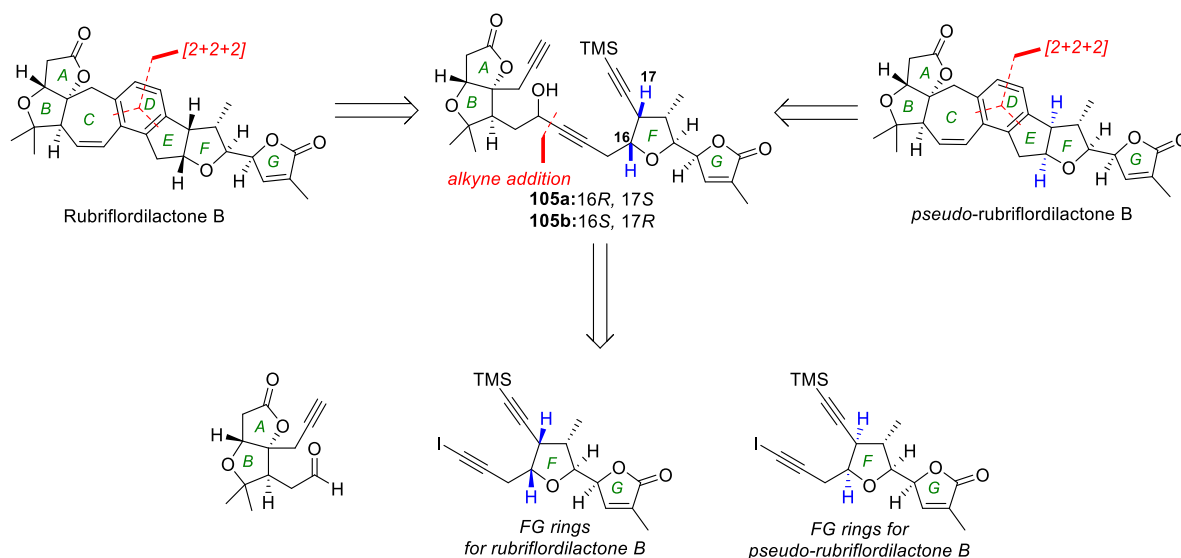
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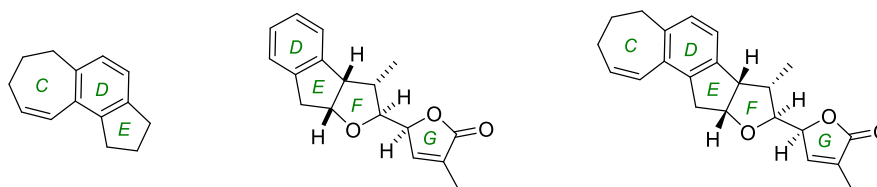
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Rubriflordilactones B is a highly oxygenated nortriterpenoid natural product first isolated from *Schisandra rubriflora* in the year 2006. This natural product is of considerable interest due to its highly oxygenated polycyclic structure and significant anti-HIV activity. However, since the spectral data of the synthetically made natural product doesn't match the isolated natural product, there is an ambiguity regarding the exact structure of the molecule. This thesis attempts to resolve the uncertainty around the structural motifs by synthesising both rubriflordilactone B and *pseudo-rubriflordilactone B*; the proposed compound responsible for the spectra in the isolation report.

A highly convergent strategy for the synthesis of the natural product rubriflordilactone B and *pseudo-rubriflordilactone B* is described hereafter. A common AB ring aldehyde is involved in the late stage coupling with the diynes containing the FG rings of the rubriflordilactone B as well as *pseudo-rubriflordilactone B*. The coupling is followed by a rhodium-catalysed [2+2+2] cyclotrimerisation reaction to form the ABCDEFG core of the natural product skeleton which is only a step away from the completion.

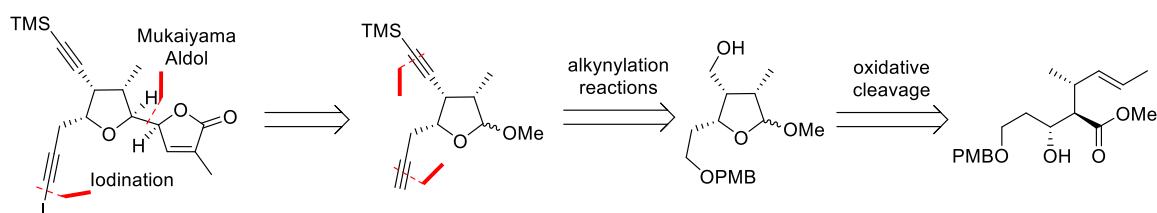


The initial attempts to optimise the reactions were performed on the CDE model, DEFG model and CDEFG model systems. The routes as well as the optimisation studies are also reported in this thesis.

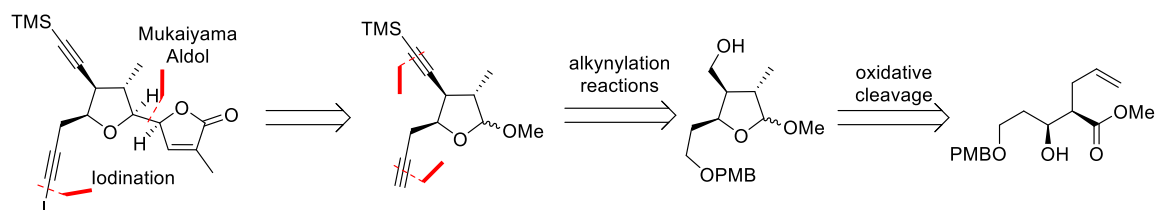


Finally, efforts towards the enantioselective synthesis of the FG ring fragments of both rubriflordilactone B and *pseudo*-rubriflordilactone B are also described in this thesis.

For rubriflordilactone B



For *pseudo*-rubriflordilactone B



Abbreviations

Å	Ångström
Ac	acetyl
AE	asymmetric epoxidation
AIBN	azobisisobutyronitrile
Ar	aryl or argon
<i>app</i>	apparent
<i>aq.</i>	aqueous
BAIB	bisacetoxyl iodobenzene
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	<i>DL</i> -10-camphorsulfonic acid
δ	chemical shift
d	doublet
DAST	(diethylamino)sulfur trifluoride
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
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
<i>dr</i>	diastereomeric ratio
EA	elemental analysis
<i>ee</i>	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
imid.	imidazole
IPA	<i>iso</i> -propanol
IR	infrared
<i>J</i>	coupling constant
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry

<i>m</i>	meta
m	multiplet
M	molar
Me	methyl
mm Hg	milimetre of mercury
MS	molecular sieves
<i>m/z</i>	mass-to-charge ratio
<i>n</i>	<i>normal</i>
n.d.	not determined
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	Nuclear Magnetic Resonance
n.r.	no reaction
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Pet. Ether	petroleum ether
PG	protecting group
Ph	phenyl
PMBTCA	<i>para</i> -methoxybenzyl trichloroacetimidate
ppm	part(s) per million
PTSA	<i>para</i> -toluenesulfonic acid
PPTS	pyridinium <i>p</i> -toluenesulfonate
<i>i</i> -Pr	isopropyl
py	pyridine
q	quartet
quant.	quantitative
quin	quintet
R	unspecified substituent
<i>R_f</i>	retention factor
rt	room temperature
s	singlet
sat.	saturated
sept	septet
sext	sextet
<i>t</i>	<i>tert</i>
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
temp.	temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TS	transition state
Ts	tosyl (<i>p</i> -toluenesulfonyl)
ν_{max}	infrared absorption maximum
v/v	volume/volume percent
wt%	weight percent

Introduction

1.1 Rubriflordilactone A and B

The *Schisandra* nortriterpenoids are a class of polycyclic compounds found in the plants of the *Schisandra* genus.¹ These plants are usually found in North America and South-East Asia. There are approximately 50 species in this genus, and since the discovery and characterisation of micrandilactone A (**1**) by Sun and coworkers in 2003 (Figure 1-1),² more than 400 of these nortriterpenoids have been isolated and characterised.^{1,3} Apart from their challenging frameworks, some of these natural products have also been found to exhibit promising biological activity, making them ideal targets for synthetic organic chemists.^{1,3}

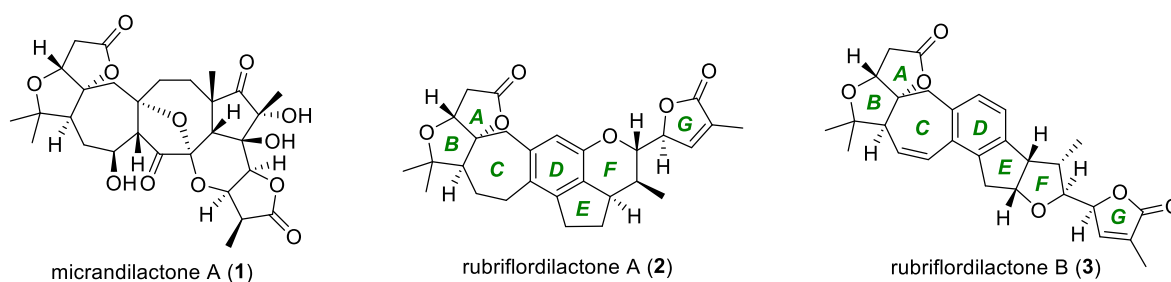


Figure 1-1 Selected examples of *Schisandra* nortriterpenoids.

Broadly, on the basis of the carbon framework, *schisandra* nortriterpenoids have been classified into 16 sub-groups.⁴ Amongst them, schiartane skeleton **I** is considered to be the most basic schinortriterpenoid framework and is thought to have evolved from cycloartane skelton **II** (Figure 1-2).

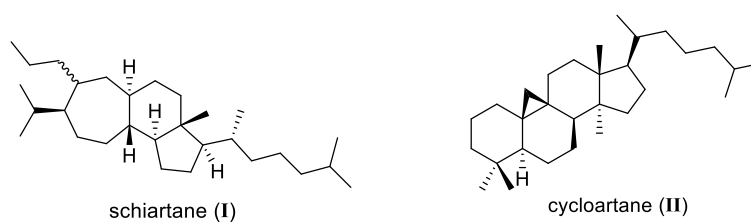
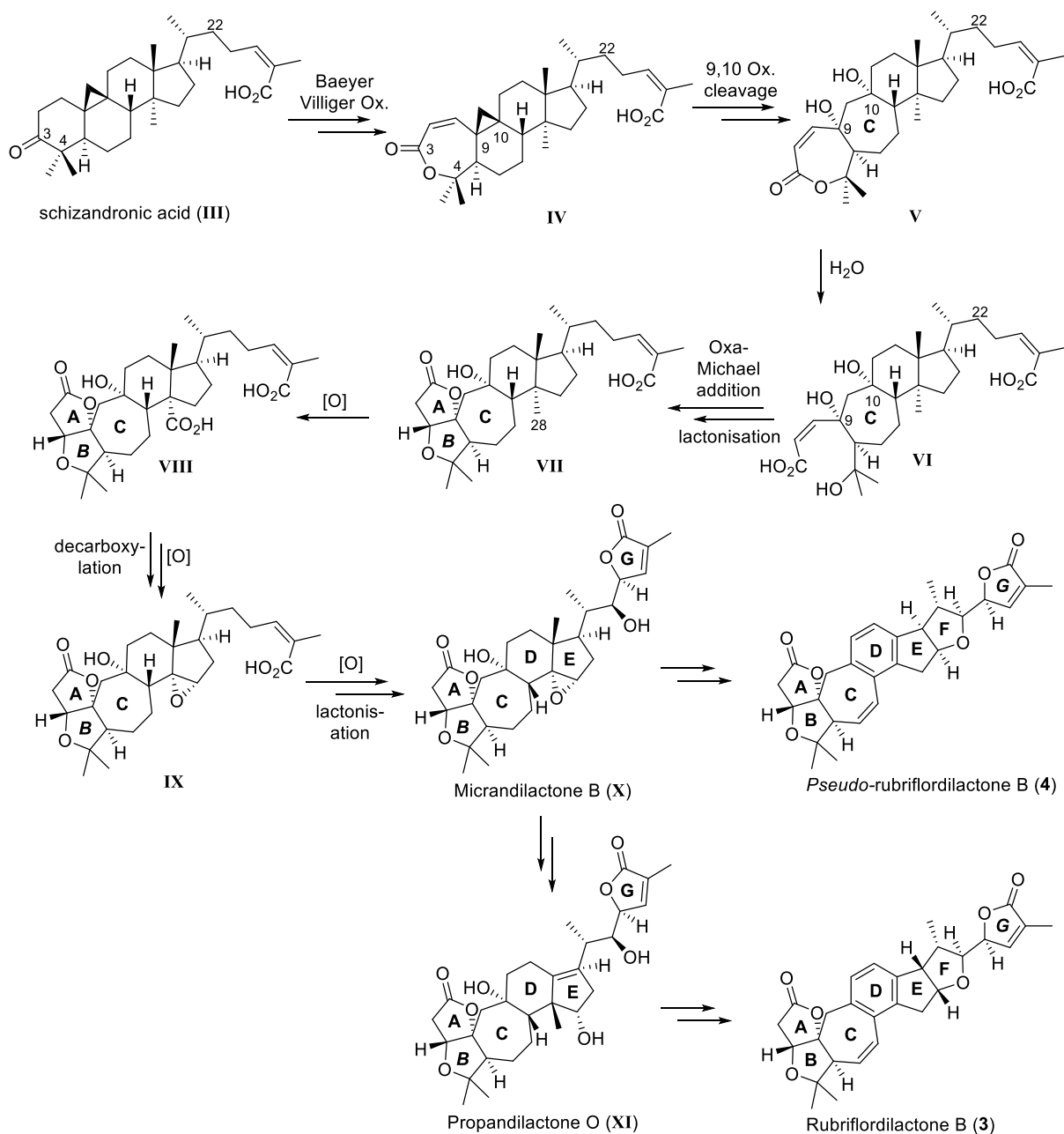


Figure 1-2 Basic schiartane and cycloartane skelton.

Sun and co-workers proposed that the *schisandra* nortriterpenoids have been biosynthetically derived from schizandronic acid (**III**).^{1,3,5} The first sequence of steps involve Baeyer- Villiger oxidation of **III** to form lactone **IV** (Scheme 1-1). Next, an oxidative cleavage at C9-C10 leads to ring expansion and

form diol **V** thereby generating schlartane core. Hydrolysis of **V** forms acid **VI** which undergoes intramolecular oxa-Michael addition followed by lactonisation to generate AB rings in **VII**. Now oxidation of the C-28 methyl group forms carboxylic acid **VIII** which is then subjected to decarboxylation/oxidation sequence to form epoxide **IX**. Subsequent oxidation and lactonisation leads to micrandilactone B (**X**) which then evolves to pseudo-rubriflordilactone B (**4**) and propindilactone O (**XI**). Finally, **XI** could finally transform to rubriflordilactone B (**3**).



Scheme 1-1 Proposed biosynthetic route to *schisandra* nortriterpenoids.

Rubriflordinilactones A (**2**) and B (**3**) (Figure 1-1) were isolated from the leaves and stems of *Schisandra rubriflora* in 2006 by Sun and coworkers.⁶ Both of these compounds contain a bisnortriterpenoid backbone derived from cycloartane and an aromatic D ring. Another point of commonality is the same polyoxygenated [3.3.0] bicyclic AB ring lactone. Additionally, these molecules possess a very similar CDE ring system differing only in the degree of unsaturation in the seven membered C ring of rubriflordinilactone B (**3**) and oxygenation in the D ring of rubriflordinilactone A (**2**). The polycyclic skeleton of rubriflordinilactone A (**2**) features seven stereogenic centres whereas rubriflordinilactone B (**3**) contains eight, stereogenic complexity which further adds to the challenge of their synthesis. However, despite being closely related, rubriflordinilactone B (**3**) shows significant biological activity ($EC_{50}=9.75$ mgmL⁻¹ for inhibition of HIV-1_{IIIB}-induced syncytium formation), while rubriflordinilactone A (**2**) has to date no reported biological properties against human diseases.⁶

The total synthesis of rubriflordinilactone A (**2**) was accomplished and reported by Li *et al*,⁷ and by our group.^{8,9} However, during the total synthesis of rubriflordinilactone B (**3**) by the Li group, a mismatch between the reported structure and its characterisation data was discovered.¹⁰ Despite having the same X-ray crystallographic structure, the NMR spectroscopic data of the molecule reported in the isolation paper was found not to match that proposed by Li group. This discrepancy seems to imply that there are two rubriflordinilactone B natural products: one corresponding to the NMR data, and the second to the X-ray diffraction structure.

To solve this conundrum, two approaches could be applied. The first would involve reisolating the natural product in reasonable quantities for X-ray analysis, and using the crystals from the same batch to acquire NMR spectroscopic data. The second would involve firstly, to narrow down the number of possible isomers by pinpointing the point of discrepancy, and then to synthesise these isomers to obtaining their NMR spectroscopic and X-ray crystallographic data. Both these methodologies, understandably, are very difficult to follow through and would require copious amounts of human resource and time. However, in 2016, the computational work of Kaufman and Sarotti, suggested that the difference between the two forms of rubriflordinilactone B lies only at the C16 and C17 positions of the EF rings (Figure 1-3), and that the *pseudo*-rubriflordinilactone B (**4**), is the most likely candidate to fit the NMR data reported in the isolation paper.¹¹

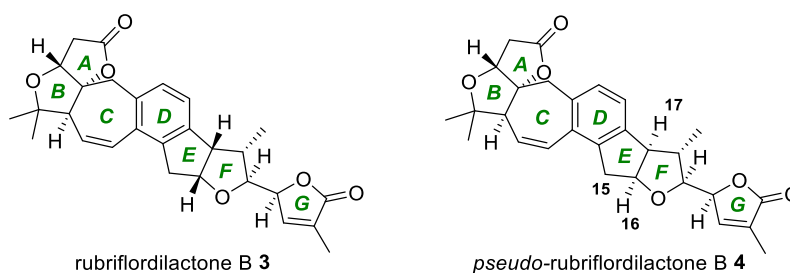


Figure 1-3 Rubriflordilactone B (**3**) and *pseudo*-rubriflordilactone B (**4**).

The computational study commenced by first narrowing down the number of possible diastereomers from 256 to 32. It was observed that there were only minor differences in the ^{13}C NMR spectra for the peaks corresponding to the ABC rings of the synthetic and isolated rubriflordilactone B. Thus, it was hypothesised that the stereochemical discrepancy didn't arise from these three rings but from the EFG rings. After calculating the NMR chemical shifts for all 32 diastereomers, it was found that the *pseudo*-rubriflordilactone B (**4**) is the most likely structure corresponding to the NMR data published in the isolation paper. Despite having a close match between the theoretical and reported NMR data for most of the carbons, a large variation was observed for C-15. The reported value placed C-15 at 30.7 ppm however, the calculated value was 41.6 ppm. Kaufman *et al.*, on closer inspection of the 2D NMR data of the isolated natural product, hypothesised that the peak at 30.7 ppm was misinterpreted by Sun *et al.* and could be attributed to the impurity present in the isolated natural product.

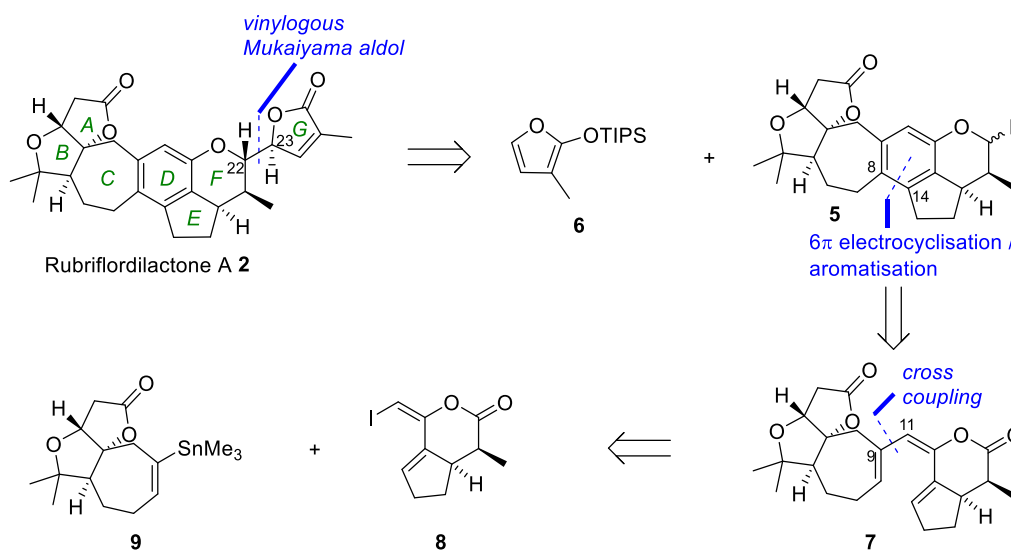
This thesis describes the second total synthesis of rubriflordilactone B (**3**) as well as the first synthesis of *pseudo*-rubriflordilactone B (**4**). Additionally, with the spectroscopic data of the synthetic **3** and **4**, we aim to clarify the uncertainty regarding the structure of these molecules.

1.2 Synthetic strategies towards rubriflordilactones A and B

Considerable attention has been devoted towards establishing routes to rubriflordilactones A and B including fragment synthesis^{12–17} and total synthesis.^{7–10} In this section, the focus is restricted to previous chemical routes that procured the natural products.

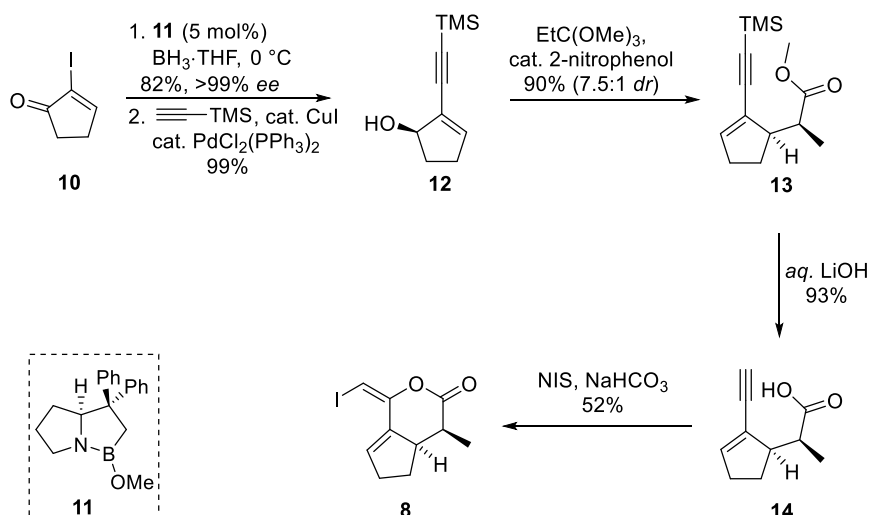
1.2.1 Total synthesis of rubriflordilactone A (Li *et al.*, 2014)⁷

The first total synthesis of rubriflordilactone A was reported by Li *et al.* in 2014.⁷ Retrosynthetically, the butenolide G ring would be installed as the final step *via* a vinylogous Mukaiyama aldol reaction between ABCDEF fragment **5** and silyloxyfuran **6** (Scheme 1-2). The polycycle **5** could be generated through a 6π -electrocyclisation/aromatisation sequence of pentacycle **7** followed by reduction and fluorination reactions. Finally, triene **7** could be traced back to the EF fragment **8** and the ABC ring fragment **9**, where the C9–C11 bond could be formed by a Stille cross-coupling reaction.



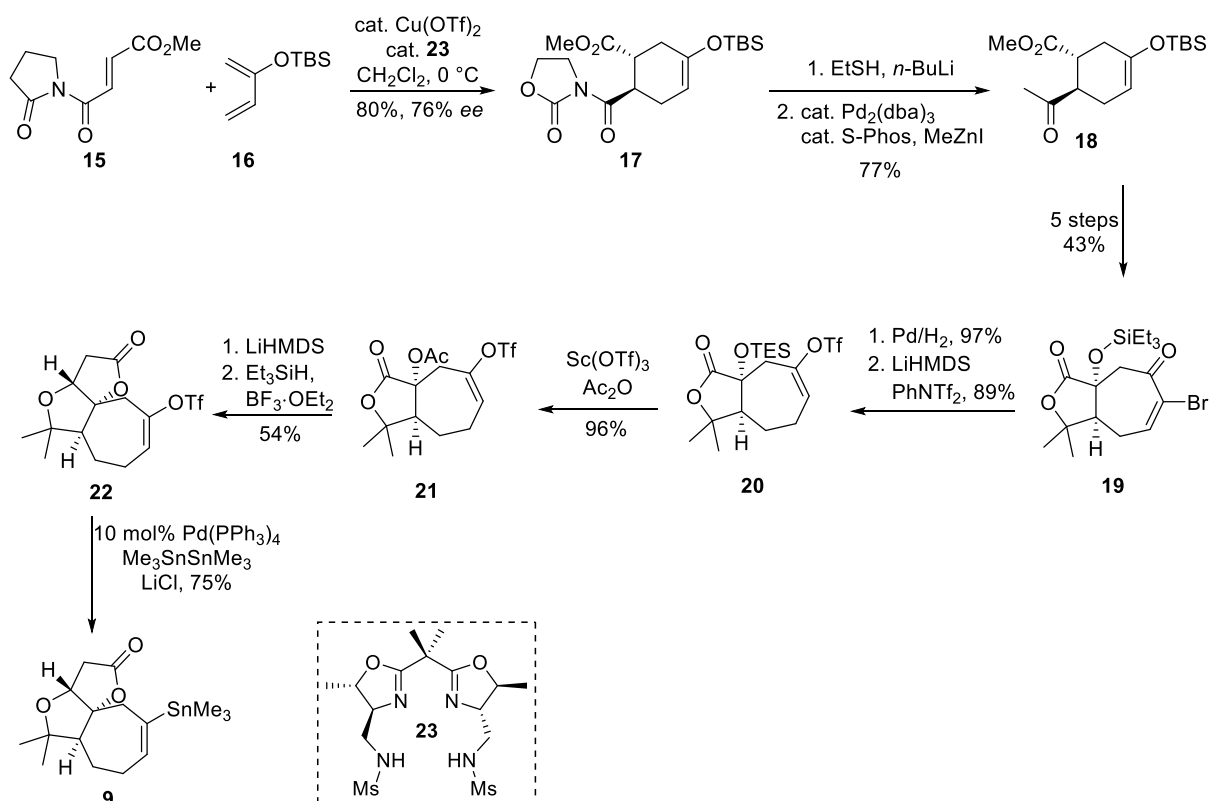
Scheme 1-2 Key disconnections to rubriflordilactone A (Li *et al.*, 2014).⁷

The forward synthesis commenced with the preparation of the EF ring fragment **8** (Scheme 1-3). 2-Iodo-2-cyclopentenone **10** was reduced stereoselectively using the Corey–Bakshi–Shibata protocol with oxazaborolidine catalyst **11**,¹⁸ the resulting alcohol underwent Sonogashira coupling with TMS-acetylene to yield alkyne **12**.¹⁹ Subsequent Johnson–Claisen rearrangement²⁰ led to the formation of the methyl ester **13**, which was followed by ester hydrolysis and deprotection of the TMS alkyne, affording acid **14** in high yields and good diastereoselectivity (82%, >99% *ee*). Finally, the EF ring iodide coupling partner **8** was generated stereospecifically through iodolactonisation of the acid **14** with NIS.²¹



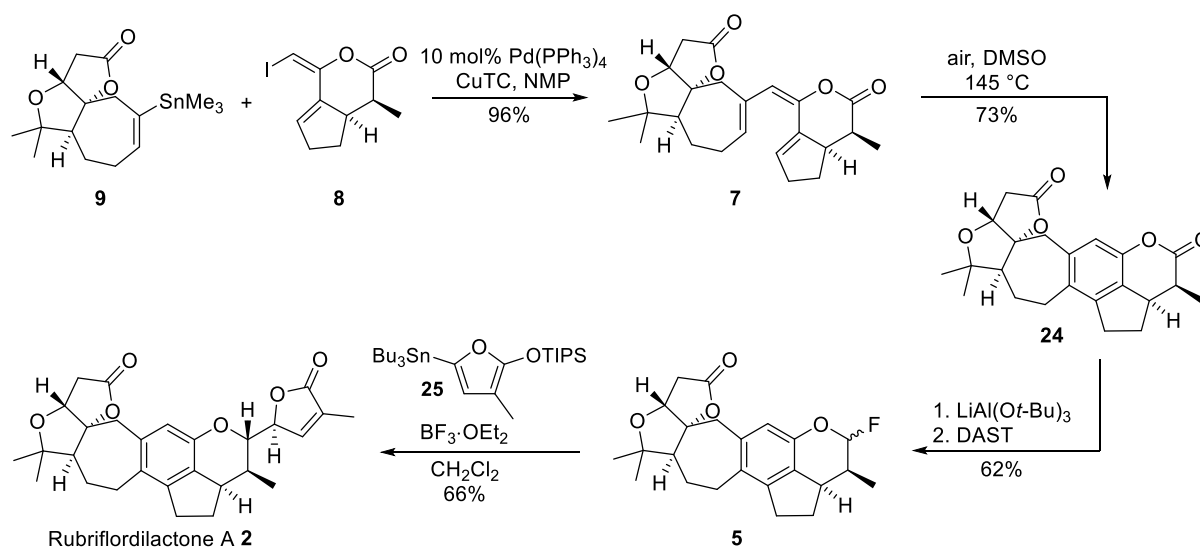
Scheme 1-3 Synthesis of the EF ring fragment **8** of rubriflordilactone A (Li *et al.*, 2014).⁷

The synthesis of the ABC fragment **9** was based upon the route developed by Yang and co-workers for the synthesis of BC ring system in their synthesis of (±)-schindilactone A.^{22–25} The first step is a copper-catalysed asymmetric Diels–Alder reaction between dienophile **15** and diene **16** that afforded cyclohexene **17** in 80% yield and 76% *ee* (Scheme 1-4). Next, the oxazolidinone moiety in **17** was transformed into ketone **18** *via* thioester synthesis, followed by a palladium catalysed coupling with methylzinc.²⁶ The resulting ketone was further subjected to a standard five-step protocol developed by Yang *et al.* to afford the BC ring bromoene **19**.^{22–25} At this point, the minor diastereomer could be removed by recrystallisation, thereby enhancing the purity of **19**. Hydrogenation of **19** and the subsequent formation of the triflate afforded **20** with good regioselectivity. The TES protected alcohol in **20** was then converted to the acetate **21**, which underwent intramolecular Dieckmann condensation^{22–25} and reduction^{27,28} to form the A ring of the ABC ring fragment **22**. Finally, AB ring stannane coupling partner **9** was generated *via* stannylation of **22** (Scheme 1-4).²⁹



Scheme 1-4 Synthesis of the ABC ring fragment **9** of rubriflordilactone A (Li *et al.*, 2014).⁷

The end game strategy for the synthesis involved a Stille–Migita reaction between iodide **8** and stannane **9**, leading to the formation of triene **7** in an excellent 96% yield (Scheme 1-5).³⁰ ABCDEF rings **24** were subsequently assembled *via* a one-pot thermal 6 π -electrocyclisation and aromatisation reaction. The F ring lactone in **24** was selectively reduced to its corresponding lactol,^{31,32} which was then treated with DAST to obtain activated fluoride donor **5**.³³ Attempts to directly attach the G ring butenolide with siloxyfuran **6** were unsuccessful, and eventually the Li group resorted to using stannane **25**³⁴ in a C-glycosylation-type reaction³⁵ to afford rubriflordilactone A **2** in 66% yield (Scheme 1-5).

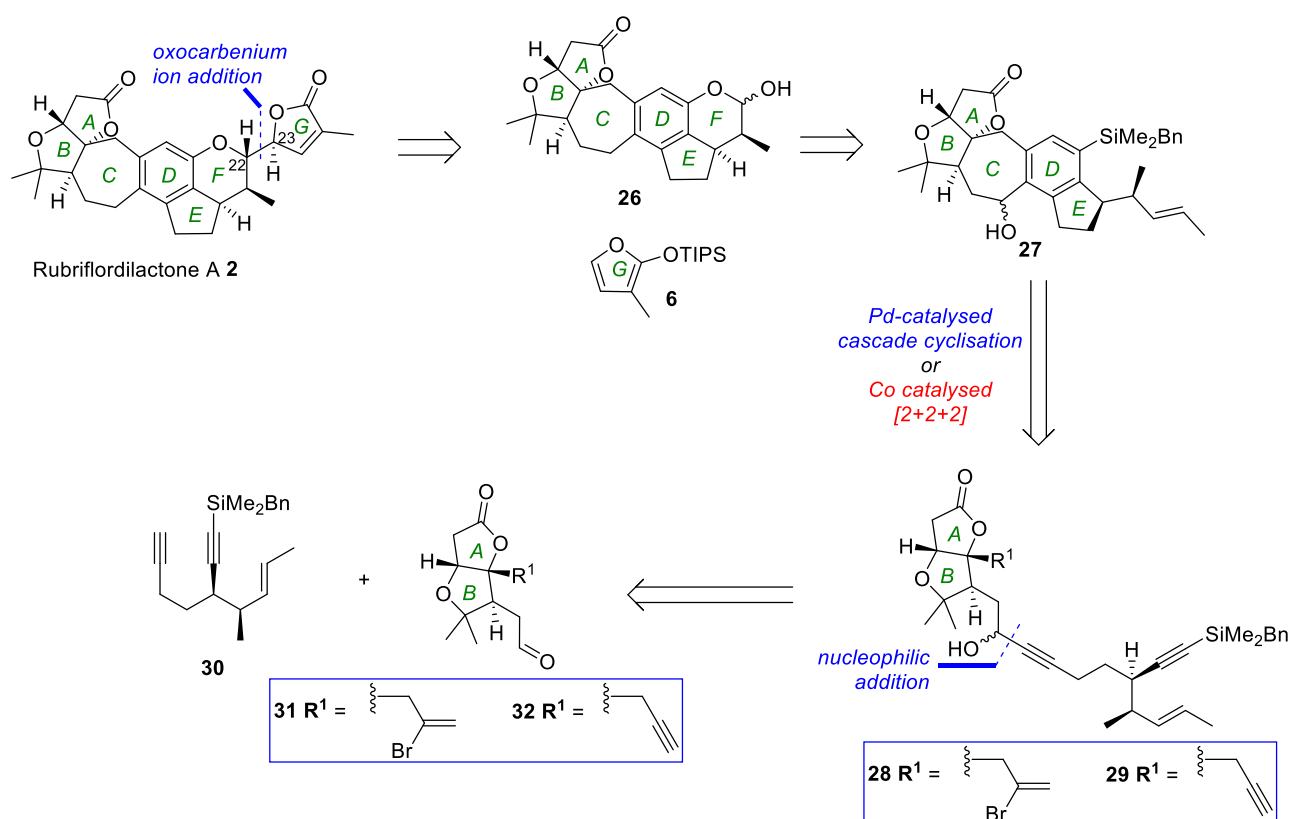


Scheme 1-5 Completion of rubriflordilactone A (Li *et al.*, 2014).⁷

In summary, the first total synthesis of rubriflordilactone A was achieved with 18 steps in its longest linear sequence from known compound **15**. The key steps of this synthesis were the one-pot 6π -electrocyclisation- aromatisation sequence and the final C-glycosylation reaction.

1.2.2 Total synthesis of rubriflordilactone A (Anderson *et al.*, 2015)⁸

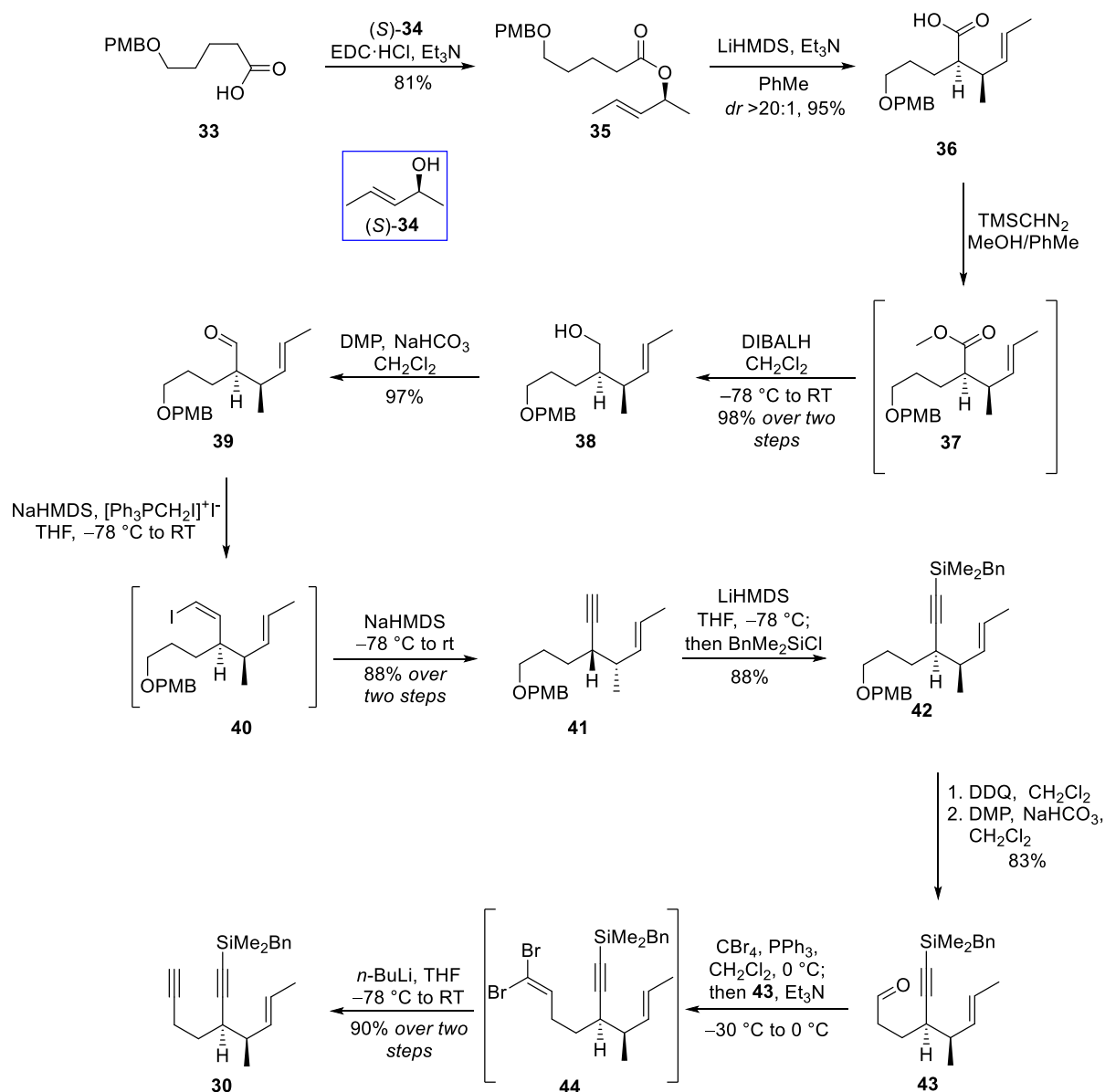
Closely following the Li group's report, our group developed two convergent total syntheses of rubriflordilactone A.⁸ The retrosynthesis began by disconnecting C22-C23 (Scheme 1-6). The G ring would be added to the ABCDEF fragment **26** *via* activation to an oxocarbenium ion followed by addition of the silyloxyfuran nucleophile **6** (Scheme 1-6). **26** would in turn be generated from pentacycle **27** through a series of transformations involving oxidative cleavage, Tamao-Fleming oxidation, and alcohol reduction. The core of pentacycle **27** could either be achieved *via* Pd-catalysed polycyclisation of vinyl bromide **28** or Co-catalysed $[2+2+2]$ cycloaddition of triyne **29**.¹²⁻¹⁴



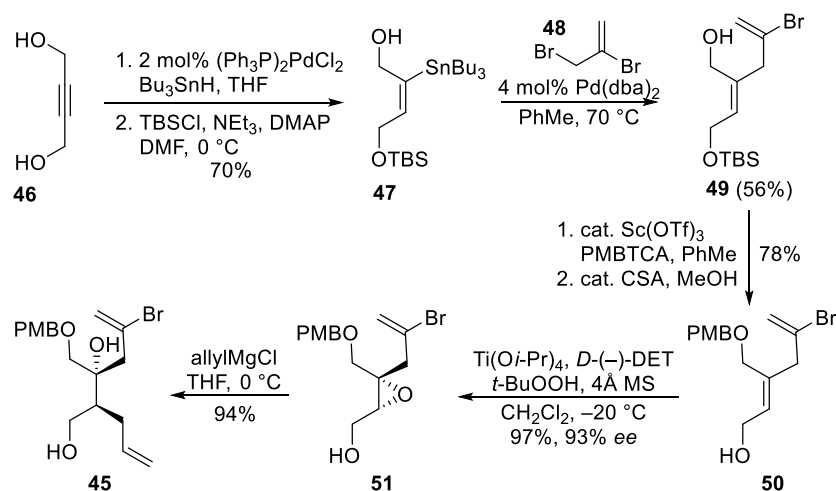
Scheme 1-6 Key disconnections to rubriflordilactone A (Anderson *et al.*, 2015).⁸

Both **28** and **29** would be accessed *via* the nucleophilic addition of diene **30** to the corresponding AB ring aldehydes **31** and **32**.

The forward synthesis began by first establishing a route to the diene **30**. Coupling acid **33** and alcohol **34**³⁶ gave ester **35** in good yield (Scheme 1-7). **35** then successfully underwent Ireland-Claisen rearrangement to give acid **36**,³⁷ which on esterification (methyl ester **37**)³⁶ and reduction generated alcohol **38** in excellent yield. DMP oxidation (aldehyde **39**) followed by Stork–Zhao olefination³⁸ and *in-situ* elimination led to the formation of alkyne **41** (Scheme 1-7).

Scheme 1-7 Synthesis of diyne **30** (Anderson *et al.*, 2015).⁸

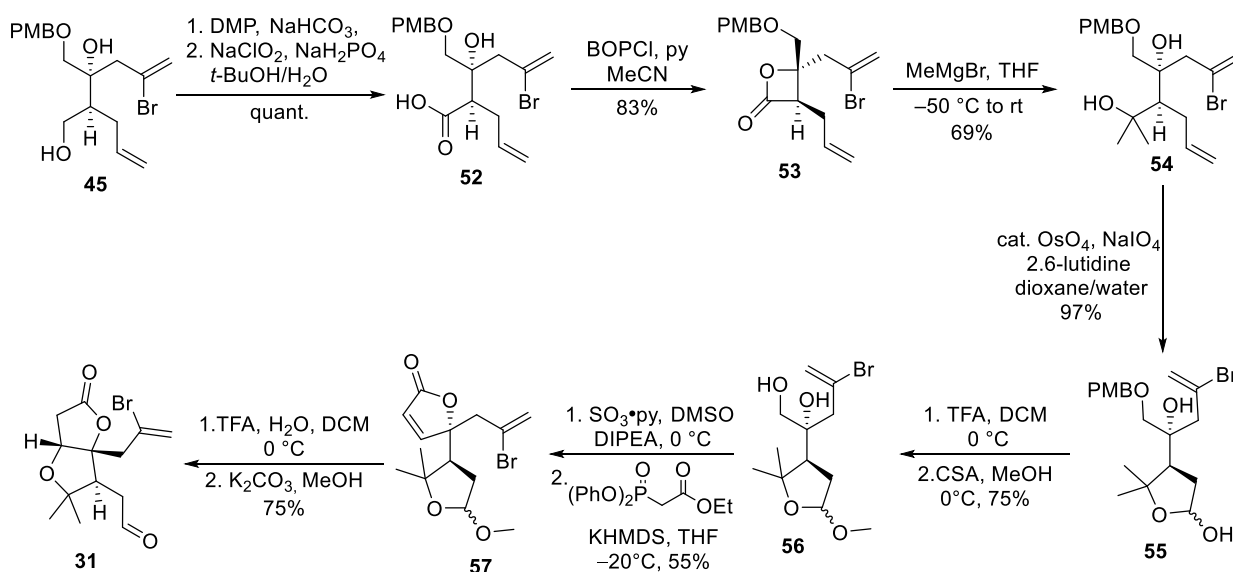
A benzyldimethylsilyl group, which would eventually become the oxygen atom of the pyran F ring, was then installed on the terminal alkyne to afford the silylated alkyne **42** (Scheme 1-7). PMB deprotection of the *p*-methoxybenzyl ether **42** and subsequent oxidation of the resulting alcohol gave aldehyde **43**, which was subjected to a Corey–Fuchs reaction forming diyne fragment **30** in an excellent 90% yield *via* dibromide **44**.



Scheme 1-8 Synthesis of alcohol **45** (Anderson *et al.*, 2015).⁸

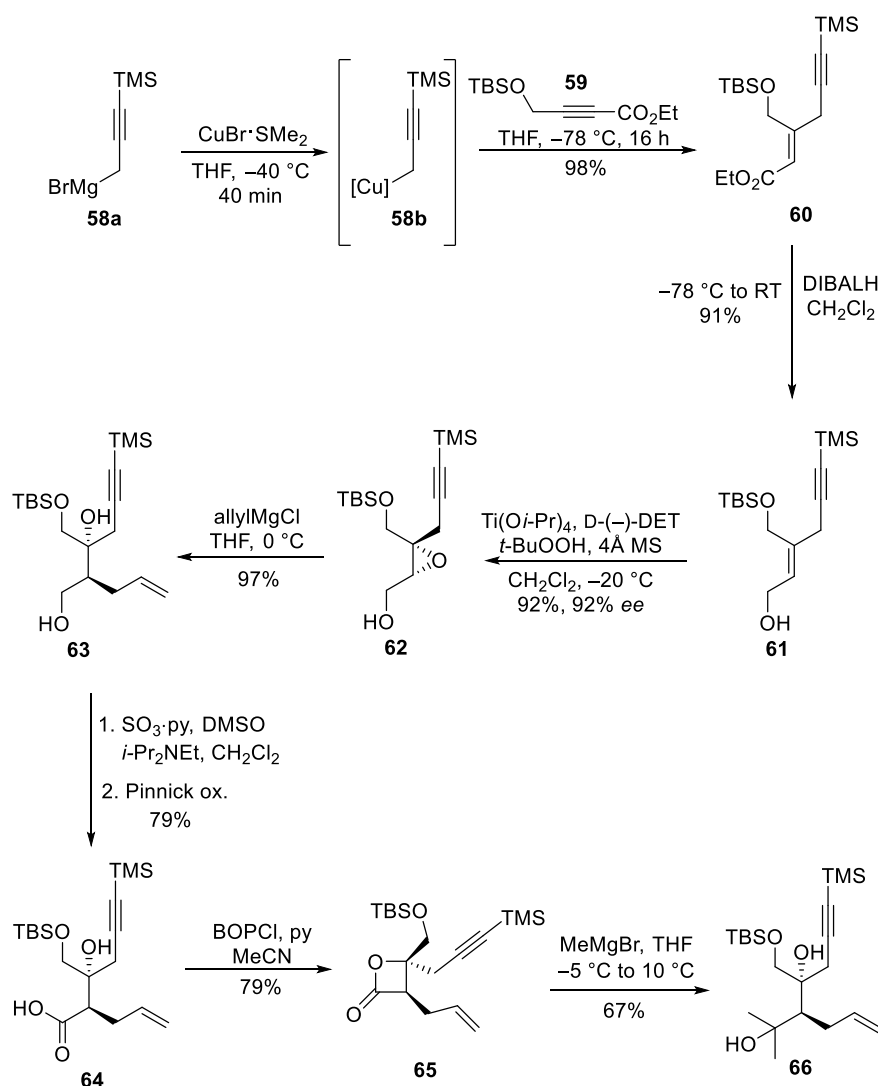
With diyne **30** in hand, the focus moved towards synthesising the AB ring-bromoene **31** and the AB ring-alkyne **32**. The synthesis of bromoene **31** commenced by first synthesising alcohol **45**. 1,4-but-2-ynediol (**46**) was subjected to a Pd-catalysed hydrostannation reaction³⁹ followed by a TBS protection to form stannane **47** (Scheme 1-8). Next, Stille coupling of **47** with 2,3-dibromopropene **48** gave bromoene **49** in 56% yield.⁴⁰ From the TBS ether **49**, a protecting group switch afforded alcohol **50**, from which a Sharpless asymmetric epoxidation delivered epoxide **51** in an excellent 97% yield with 93% *ee*.⁴¹ Regioselective ring opening of epoxide **51** with allylmagnesium chloride^{42,43} afforded diol **45** (Scheme 1-8).

Further transformation of the diol **45** involved Dess–Martin oxidation followed by a Pinnick oxidation (Scheme 1-9) to afford acid **52**, which was converted into the β -lactone **53** upon activation with BOPCl.py. Addition of methylmagnesium bromide to the β -lactone **53** led to the formation of dienol **54** in 69% yield, which then underwent oxidative cleavage to afford lactol **55**. PMB deprotection under acidic conditions and methylation of the lactol moiety led to the formation of methyl acetal **56**. Oxidation of the primary alcohol in **56** followed by a *Z*-selective Ando–HWE reaction⁴⁴ furnished methyl acetal **57**. Finally, hydrolysis of the methyl acetal set the stage for an intramolecular oxa-Michael addition to give AB ring aldehyde **31** (Scheme 1-9).¹⁴



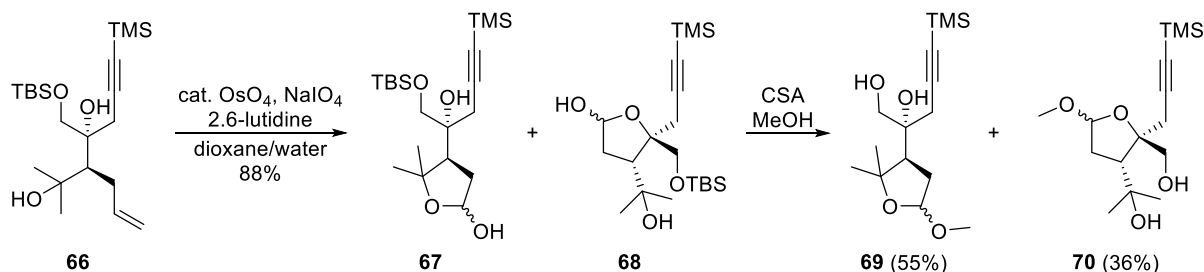
Scheme 1-9 Synthesis of AB ring **28** (Anderson *et al.*, 2015).⁸

Synthesis of the AB ring-alkyne **32** commenced with the cupration of Grignard reagent **58a** to give organocuprate **58b** which upon Normant-type carbometallation with alkyne **59** gave enyne **60** (Scheme 1-10).^{45,46} The ester functionality of **60** was then reduced to alcohol **61**, which underwent a Sharpless asymmetric epoxidation to afford epoxide **62** in excellent yield and enantioselectivity.⁴⁷ Thereafter, ring opening of epoxide **62** with allylmagnesium chloride⁴³ afforded diol **63** in 97% yield and high selectivity. Next, the primary alcohol of **63** was converted to acid **64** by a two-step procedure *via* Parikh–Doering oxidation followed by a Pinnick oxidation of the resulting aldehyde. This set the stage for an BOPCl-promoted intramolecular lactonisation to afford β -lactone **65** in good yield. Finally, nucleophilic ring opening of β -lactone **65** using methylmagnesium bromide generated diol **66** in good yield (Scheme 1-10).



Scheme 1-10 Synthesis of alcohol **66** (Anderson *et al.*, 2015).⁸

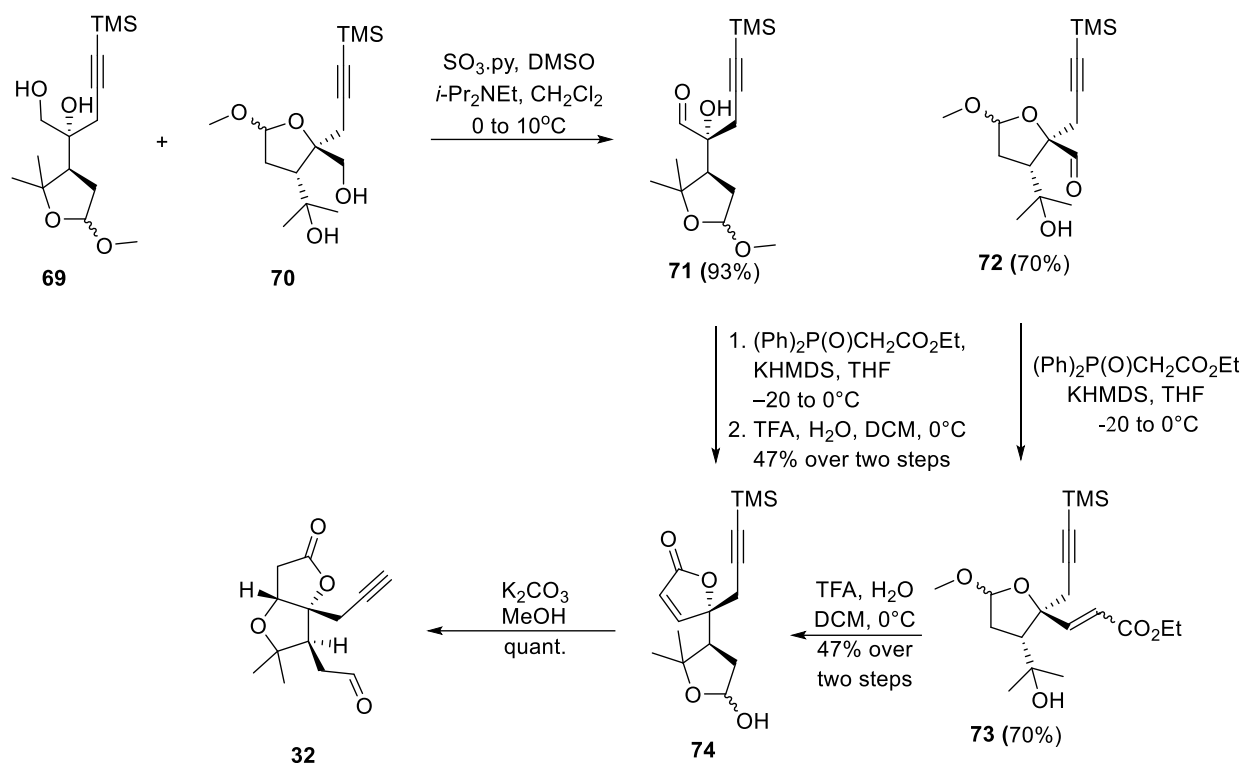
Oxidative cleavage of the **66** led to the formation of lactols **67** and **68** (Scheme 1-11), which upon treatment with CSA and MeOH led to the formation of the methyl acetals **69** and **70** respectively.



Scheme 1-11 Synthesis of methyl acetals **69** and **70** (Anderson *et al.*, 2015).⁸

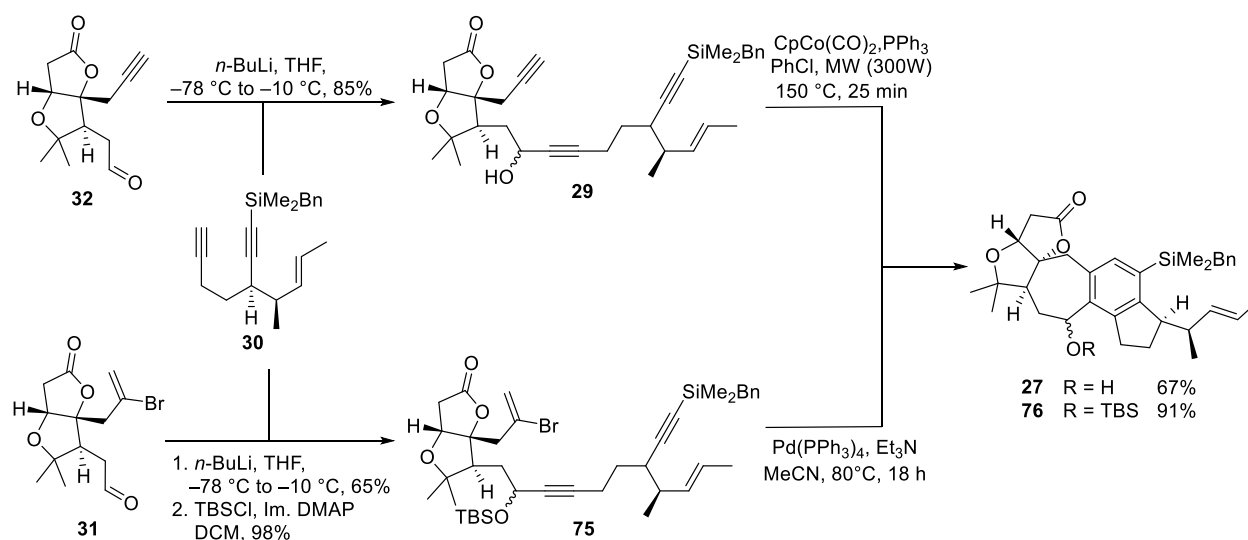
Acetals **69** and **70** were further oxidised to afford separable aldehyde **71** and **72** respectively (Scheme 1-12) in good yields. Both **71** and **72** underwent a Z-selective Ando-HWE reaction⁴⁴ followed by

hydrolysis to converge at lactol **74**. Finally, treatment with K_2CO_3 in MeOH led to the formation of the AB ring alkyne **32**.



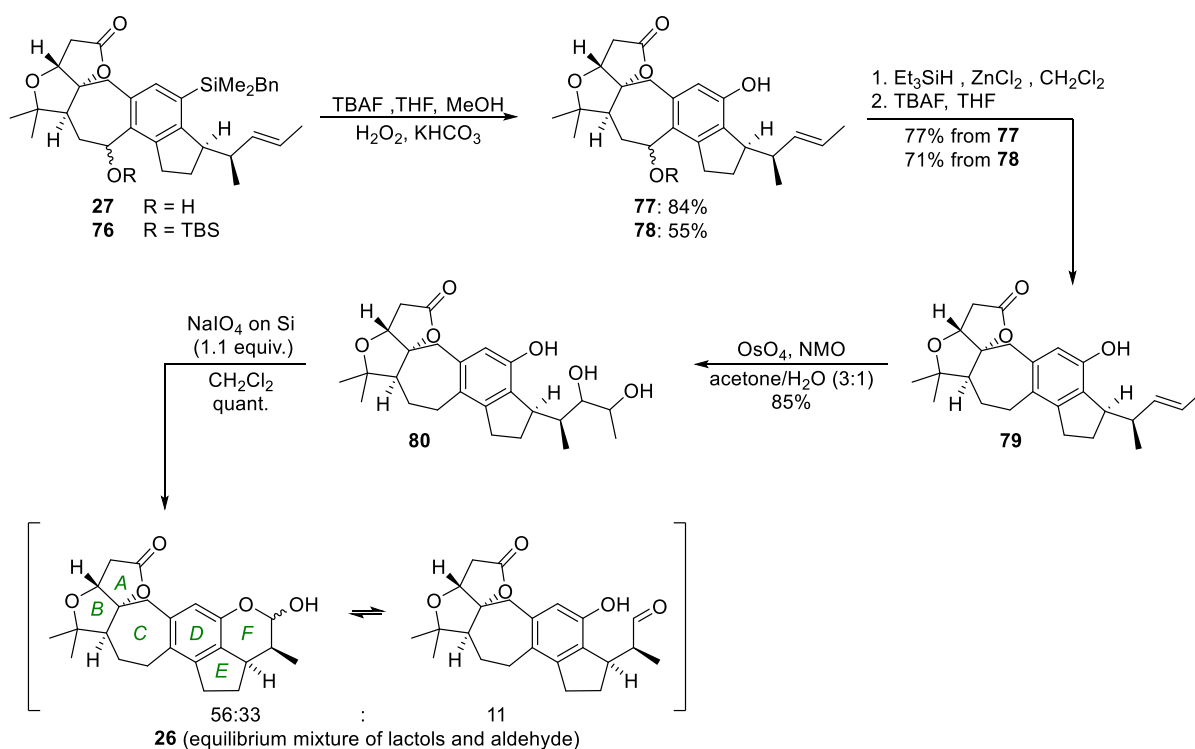
Scheme 1-12 Synthesis of AB ring alkyne **32** (Anderson *et al.*, 2015).⁸

With all the fragments **30**, **31** and **32** in hand, the synthesis moved on to the end phase. Diyne **30** was added to the aldehyde **32** to afford triyne **29** (Scheme 1-13). Next, triyne **29** underwent Co-catalysed [2+2+2] cyclotrimerisation to form pentacycle **27**. Alongside the cyclotrimerisation strategy, diyne **30** was also added to the aldehyde **31**, and the resulting alcohol was silylated to generate bromodiene **75**.⁸ It was essential to protect the free alcohol since, according to previous studies, the Pd-catalysed cascade polycyclisation is incompatible with a free propargylic hydroxyl group.¹³ Finally, **75** underwent Pd-catalysed cyclisation to generate the pentacycle **76** (Scheme 1-13).⁸

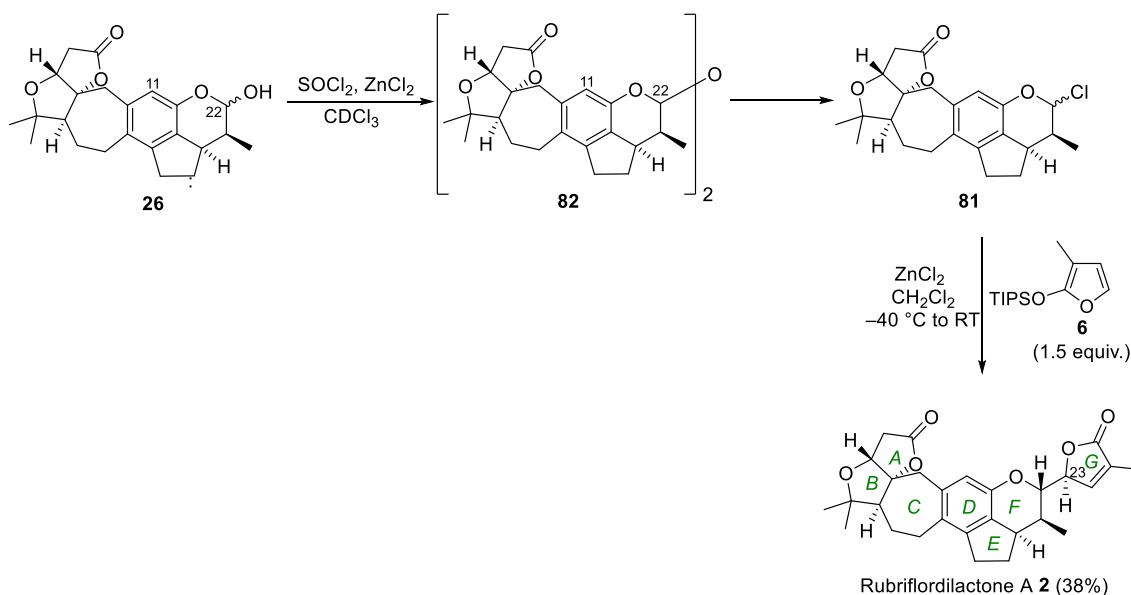


Scheme 1-13 Synthesis of pentacycle **27** and **76** (Anderson *et al.*, 2015).⁸

With the core pentacycle assembled, only a final few functional group manipulations and installation of the G ring were left. The sequence began with the Tamao-Kumada oxidation⁴⁸ of arylsilanes **27** and **76** to afford the corresponding phenols **77** and **78** (Scheme 1-14). Next, the reduction at the benzylic position was successfully carried out for both the free alcohol **77** (77%) and the TBS ether **78** (71%) leading to the ABCDE phenol **79**. Dihydroxylation of the alkene in **79** led to the formation of **80**, which underwent oxidative cleavage to give an equilibrium mixture of lactol **26** (d.r 56:33) and the corresponding aldehyde (Scheme 1-14).

Scheme 1-14 Synthesis of lactol **26** (Anderson *et al.*, 2015).⁸

Lactol **26** was then converted into the chloropyran **81**⁴⁹ via dimer **82** (Scheme 1-15), which was subjected to oxocarbenium addition of the G ring silyloxyfuran **6** (via an oxocarbenium ion intermediate) to finally afford rubriflordilactone A (**2**).

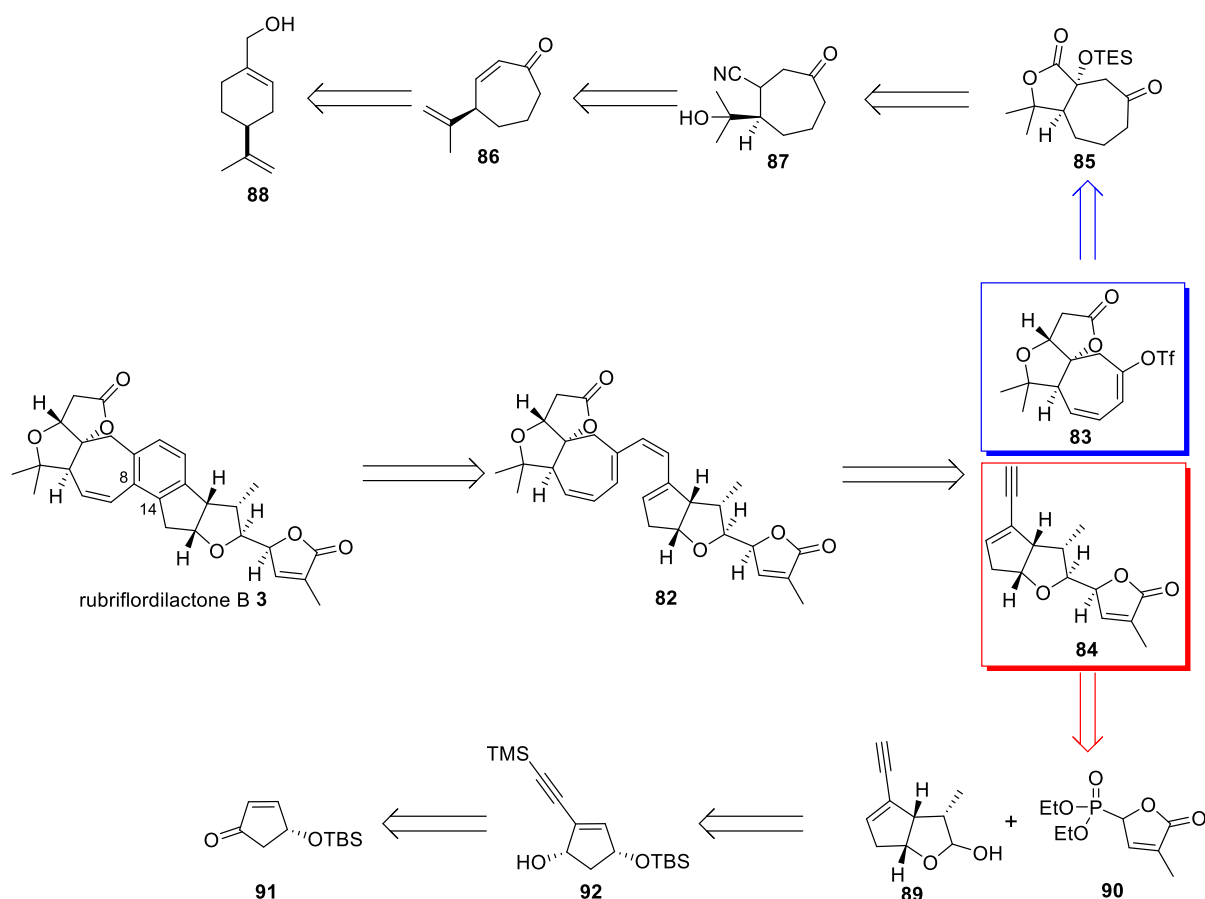


Scheme 1-15 Synthesis of rubriflordilactone A **2** (Anderson *et al.*, 2015).⁸

In summary, two strategies for the synthesis of rubriflordilactone A were reported, utilising palladium or cobalt catalysis to construct the key ABCDE ring system. The routes are strategically convergent and have a common late-stage intermediate which is just four steps from the end of the synthesis.

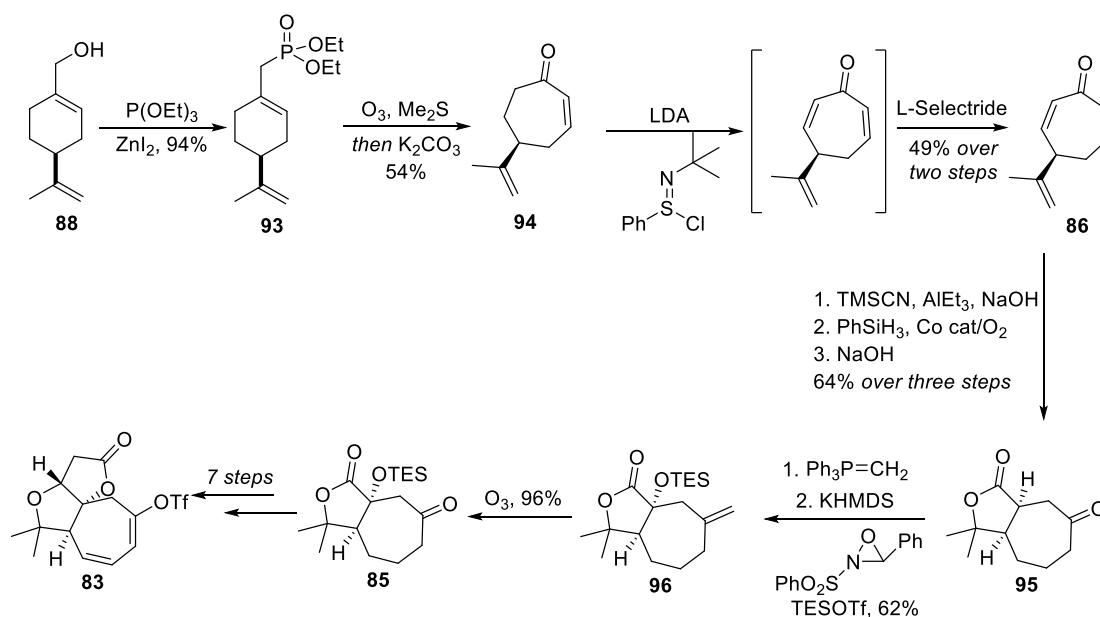
1.2.3 Total synthesis of rubriflordilactone B (Li *et al.*, 2016)¹⁰

After reporting the first total synthesis of rubriflordilactone A, the Li group focused their attention on rubriflordilactone B. Similar to their synthesis of rubriflordilactone A,⁷ this synthesis also made use of a 6π -electrocyclisation/aromatization strategy to generate the arene ring in the molecule. According to the retrosynthesis, **3** would disconnect from C8 and C14 to create triene **82** which would fragment to give ABC framework **83** and EFG framework **84** (Scheme 1-16). **83** would form from the ketoester **85** which could be traced to the cyclohexanone **86** *via* ketonitrile intermediate **87**. Compound **86** was envisaged to form from the commercially available alcohol **88**. EFG fragment **84** would disassemble to generate lactol **89** and phosphonate **90**. **89** would be synthesized from pentenone **91** *via* intermediate enyne **92**.



Scheme 1-16 Key disconnections to rubriflordinilactone B (Li *et al.*, 2016).¹⁰

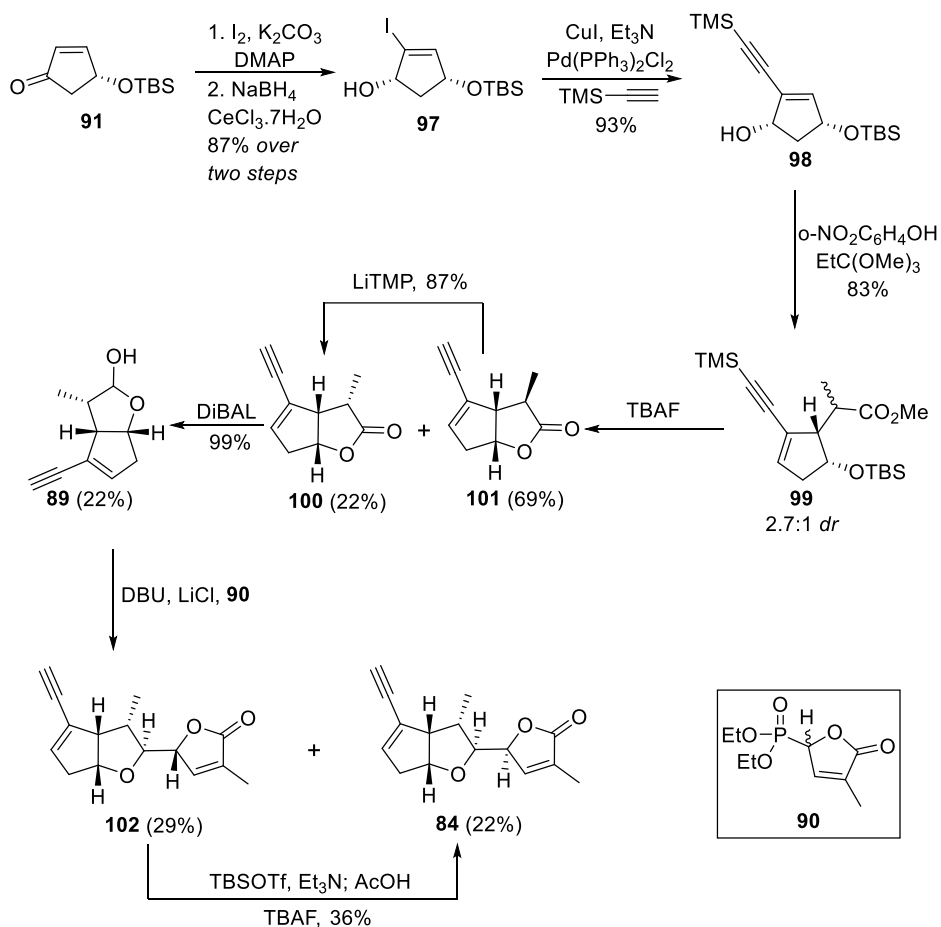
The forward synthesis began with synthesis of the ABC synthon **83**. Alcohol **88** was subjected to Arbuzov reaction with triethyl phosphite to form phosphonate **93** (Scheme 1-17), which underwent a selective ozonolysis to generate an intermediate ketoaldehyde that then underwent intramolecular HWE olefination to afford cycloheptenone **94**. Treatment of **94** with LDA followed by *N*-*tert*-butyl benzenesulfinimidoyl chloride led to the formation of a bis-enone (via a *C*-sulfinimidoylated intermediate) which was selectively reduced to form cycloheptenone **86**.⁵⁰ Conjugate addition of cyanide (from Et₂AlCN), then Mukaiyama hydration followed by hydrolysis/lactonisation led to the formation of the lactone **95**.⁵¹ The ketone functionality in **95** was methylenated, followed by α -hydroxylation and silylation leading to the formation of **96**. Subsequent ozonolysis generated the ketone **85**, which was converted to the enol triflate **83** via a standard seven-step sequence.



Scheme 1-17 Synthesis of ABC fragment **83** (Li *et al.*, 2016).¹⁰

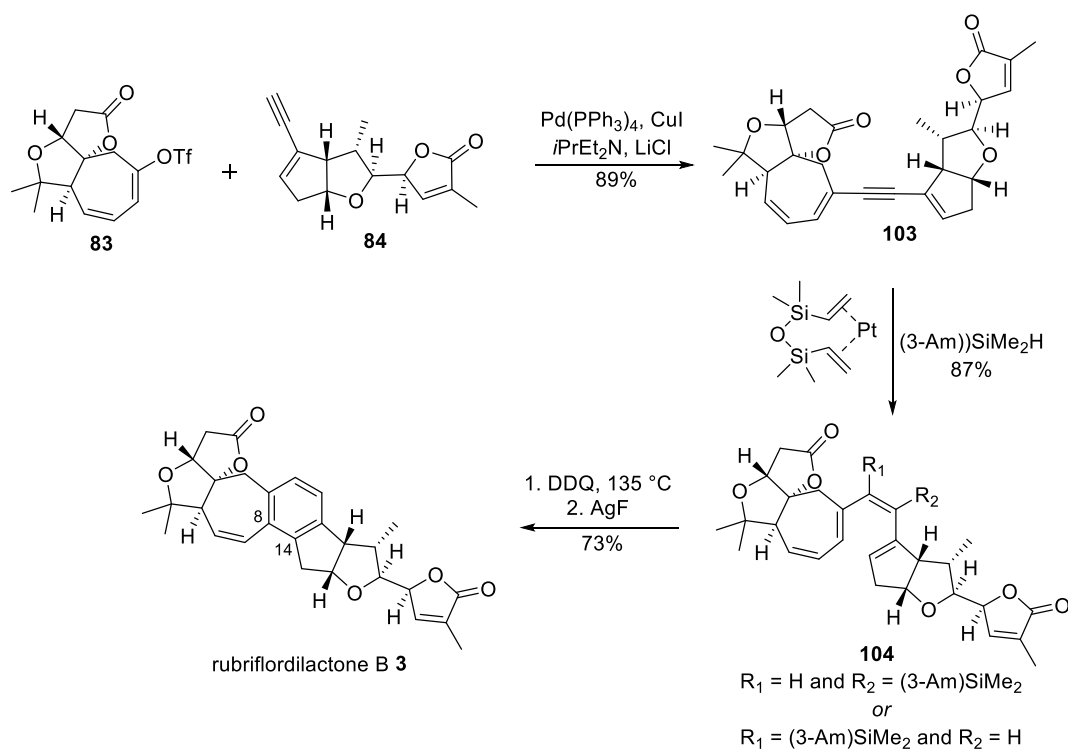
Synthesis of EFG fragment **84** commenced with the iodination of enone **91** followed by Luche reduction to afford pentenol **97** (Scheme 1-18). Sonogoshira coupling of **97** with TMS-acetylene led to enyne **98**, which underwent Johnson–Claisen rearrangement to ester **99** (2.7:1 *dr*).⁵² Desilylation of **99** followed by *in situ* lactonisation resulted in the formation of the required lactone **100** and the undesired lactone **101**. Lactone **101** was smoothly converted into the desired diastereomer by treatment with LiTMP.²² DIBAL reduction of **100** formed lactol **89**, which reacted with phosphonate **90**⁵³ (Masamune–Roush conditions) to give a pair of epimers **84** and **102** through a one-pot HWE olefination/oxa-Michael

addition process.⁵⁴ Epimer **102** was partially converted to **84** *via* silyl ether formation followed by desilylation (36% of **84** and 53% of recovered **102**).



Scheme 1-18 Synthesis of EFG fragment **84** (Li *et al.*, 2016).¹⁰

With routes to both fragments **83** and **84** established, the Li group proceeded to finish the synthesis. **83** and **84** were coupled *via* Sonogashira reaction to afford the enyne **103** (Scheme 1-19). Subsequent hydrosilylation^{55,56} of the alkyne led to the formation of tetraene **104**, which underwent the key 6 π electrocyclization/aromatization sequence followed by desilylation⁵⁷ to afford rubriflorldilactone B (**3**).

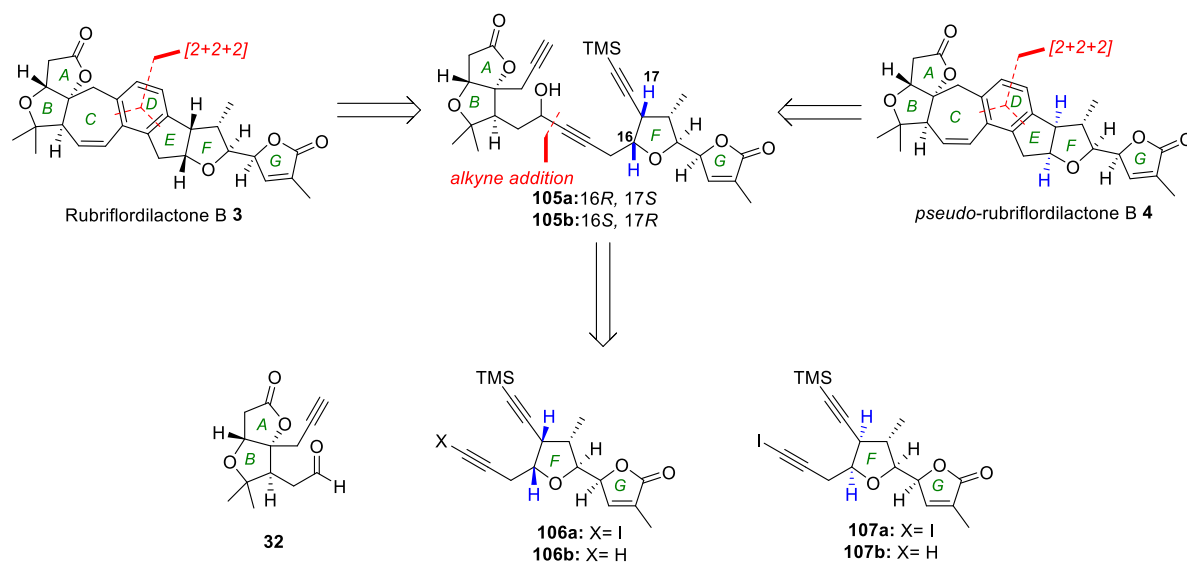


Scheme 1-19 Synthesis of rubriflordilactone B 3 (Li *et al.*, 2016).¹⁰

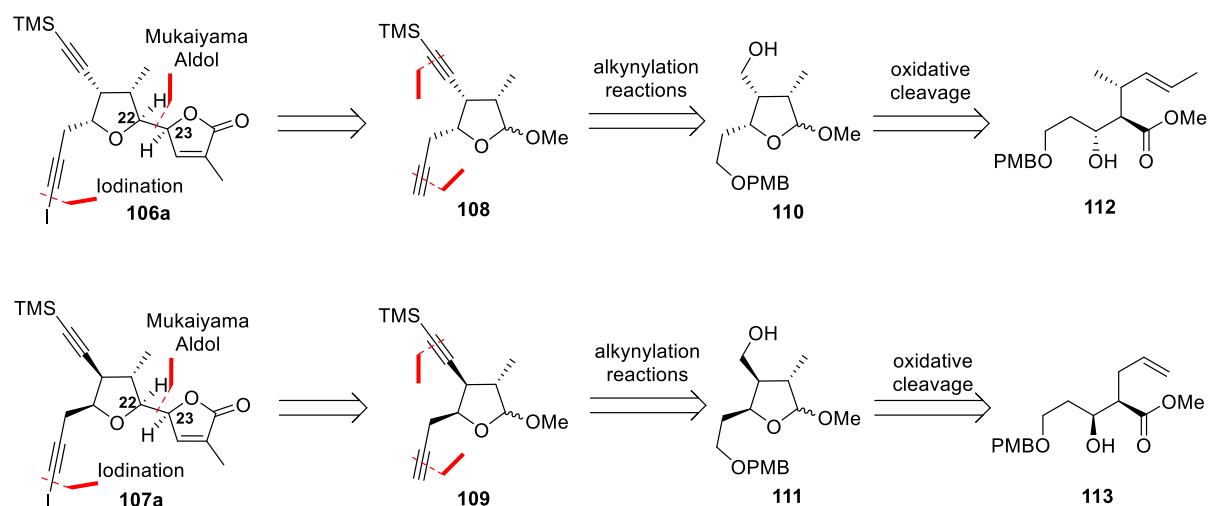
Interestingly, the Li group was able to recrystallise **3** and obtain an X-ray structure of the molecule, however, the NMR spectra didn't match the reported NMR data in the isolation paper.⁶ This observation led the Li group to hypothesise that Sun and coworkers⁶ had isolated a mixture of two inseparable compounds, one responsible for the X-ray structure and other for the NMR data.

1.3 Our approach

This project aimed to establish synthesis of both rubriflordilactone B (**3**) and *pseudo*-rubriflordilactone B (**4**). Our retrosynthesis for both targets would begin by first disconnecting the arene ring to furnish triyne **105a** and **105b** (Scheme 1-20), with arene rings formed through a [2+2+2] cyclotrimerisation reaction. **105a** and **105b** could be traced back to the AB ring aldehyde **32** and FG ring fragments **106** (for rubriflordilactone B) and **107** (for *pseudo*-rubriflordilactone B).

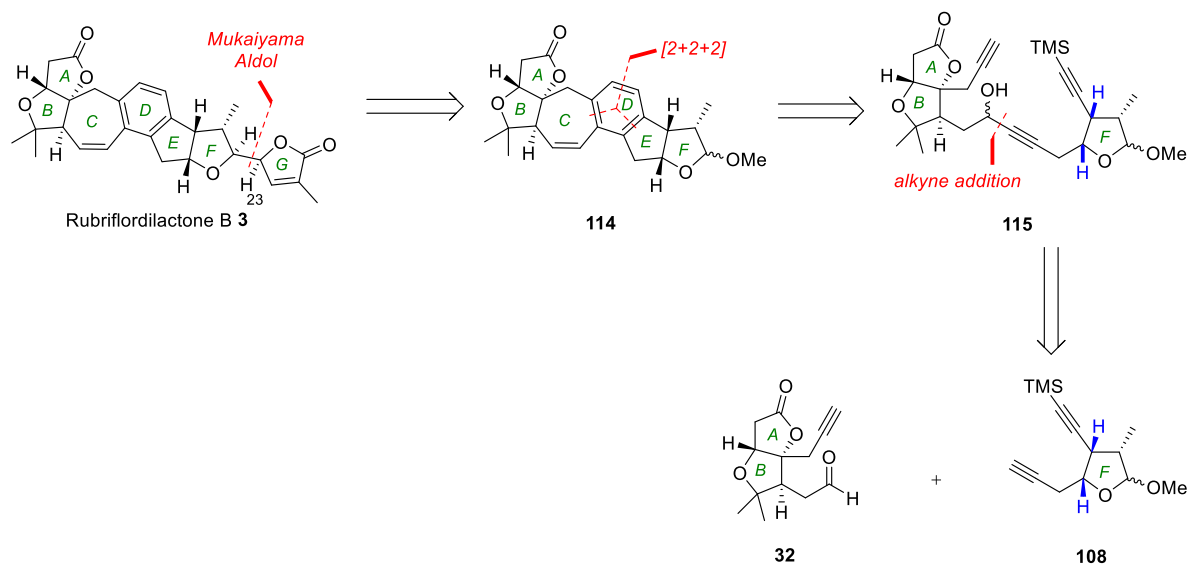


Scheme 1-20 Retrosynthesis of rubriflordilactone B (**3**) and *pseudo*-rubriflordilactone B (**4**).



Scheme 1-21 Retrosynthesis of FG fragment **106** and **107**.

FG diynes **106a** and **107a** would be disconnected from C22-C23 (Scheme 1-21) to give diynes **108** and **109** respectively. Diyne **108** and **109** would form from alcohol **110** and **111** through reaction sequences involving oxidation and alkynylation processes. **110** and **111** could be traced back to esters **112** and **113**.



Scheme 1-22 Alternative retrosynthesis of rubriflordilactone B **3**.

An alternative disconnection for rubriflordilactone B (**3**) (Scheme 1-22) would be the disconnection between the F and G rings to generate ABCDEF fragment **114**. This would form from the [2+2+2] cyclotrimerisation of **115** which could be traced back to AB ring aldehyde **32** and methyl acetal **108**.

The subsequent chapters, describe work to identify the optimum route amongst the two mentioned route alternatives and the implementation of that strategy in the synthesis of both rubriflordilactone B (**3**) and *pseudo*-rubriflordilactone B (**4**).

1.4 Thesis summary

The synthesis of the FG ring fragment **106** is crucial to the synthesis of rubriflordilactone B, as it contains 5 contiguous stereocentres out of a total of 8 stereocentres present in the natural product. Preliminary investigations towards establishing a route to **112**, a key intermediate to the synthesis of **106**, were initiated by Pollyanna Sanderson (a previous Part II student in the group). These studies were further advanced and finally a route to **106a** and **106b** were established. This work is described in Chapter 2.

Following the synthesis of FG fragment **106a** and **106b**, the subsequent strategies as well as order of events were explored, by working on CDE ring, DEFG ring and CDEFG ring models. In course of these model studies, both Pd-catalysed cascade cyclisation and Co-catalysed [2+2+2] cyclotrimerisation reactions were investigated. Additionally, end game strategies were established. Details of these endeavours are given in Chapter 3.

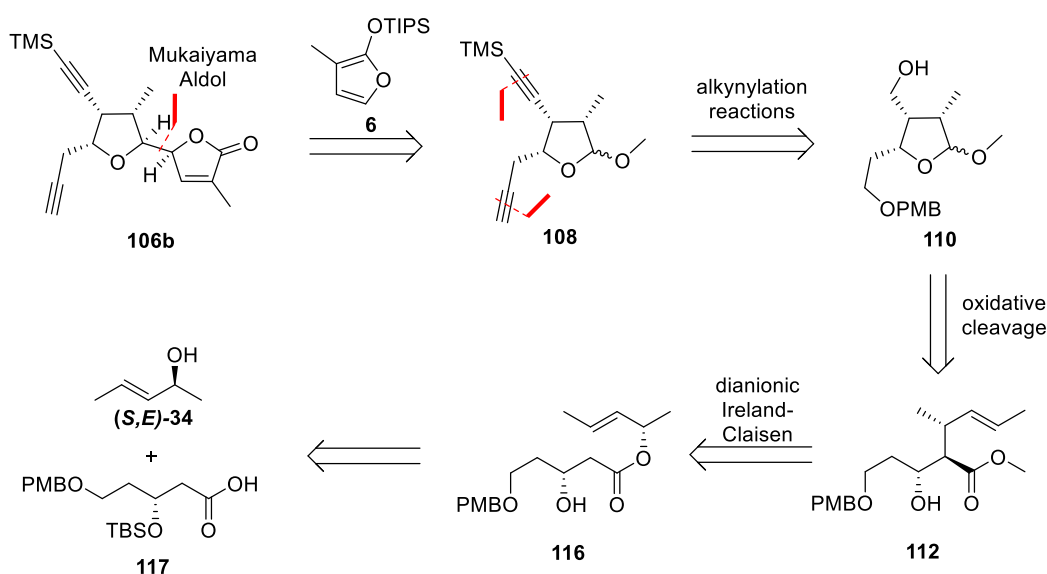
In chapter 4, the reactions optimized on model systems in Chapter 2 were extended to the synthesis rubriflordilactone B. Two separate strategies were explored; the first strategy involved installation of the G ring before assembly of the CDE core, and the second involved the installation of the G ring after the formation of the CDE core. Following this, synthesis of C-23 *epi*-rubriflordilactone B (*epi*-**3**) was also achieved.

Finally, Chapter 5 focusses on first establishing a route to FG ring fragment **107a** which was then used for the synthesis of *pseudo*-rubriflordilactone B (**4**) and C-23 *epi-pseudo*-rubriflordilactone B (*epi*-**4**). Finally, the NMR spectra of **4** were compared with the spectra from the isolation paper,⁶ to confirm the identity of the second natural product.

2. Synthesis of FG fragment 106 of rubriflordilactone B

2.1 Retrosynthetic analysis

As discussed in Section 1.3, the FG ring diyne **106b** could be procured by the addition of the silyloxyfuran **6** to the oxocarbenium ion generated from diyne **108**. This diyne could form through sequential oxidation and alkynylation reactions on the alcohol **110**, which in turn would result from a sequence of reduction, oxidative cleavage and cyclic acetal formation steps on the β -hydroxyester **112**. Finally, **112** would form through a dianionic Ireland-Claisen rearrangement of the ester **116** that could be obtained from the acid **117** and known alcohol *(S,E)*-**34**.⁵⁸



Scheme 2-1 Retrosynthesis of FG ring fragment **106b**.

2.2 Forward synthesis

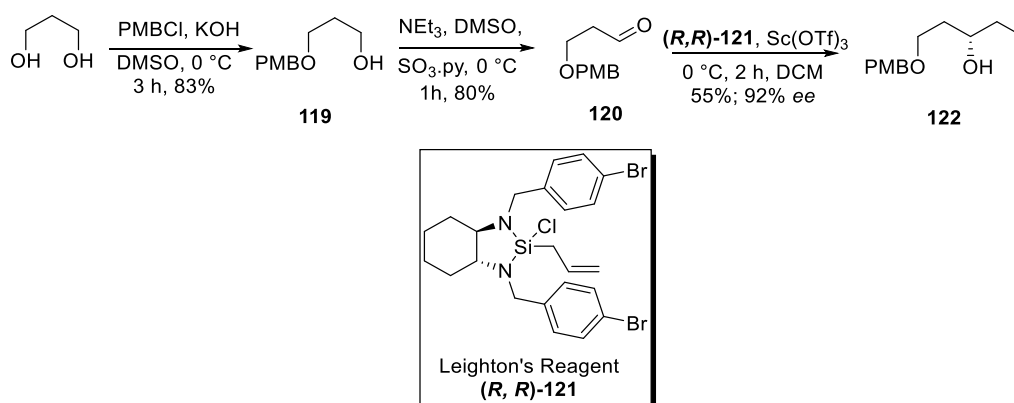
2.2.1 Synthesis of β -hydroxyester **116**ⁱ

The study towards the synthesis of rubriflordilactone B (**3**) began by first developing a route to synthesise **116**, which was envisaged to be a key intermediate for attempting the dianionic Ireland-

ⁱ This part of the work was optimised by Pollyanna Sanderson, a Part II student (2014) in the Anderson group, and was reproduced in total by the author.

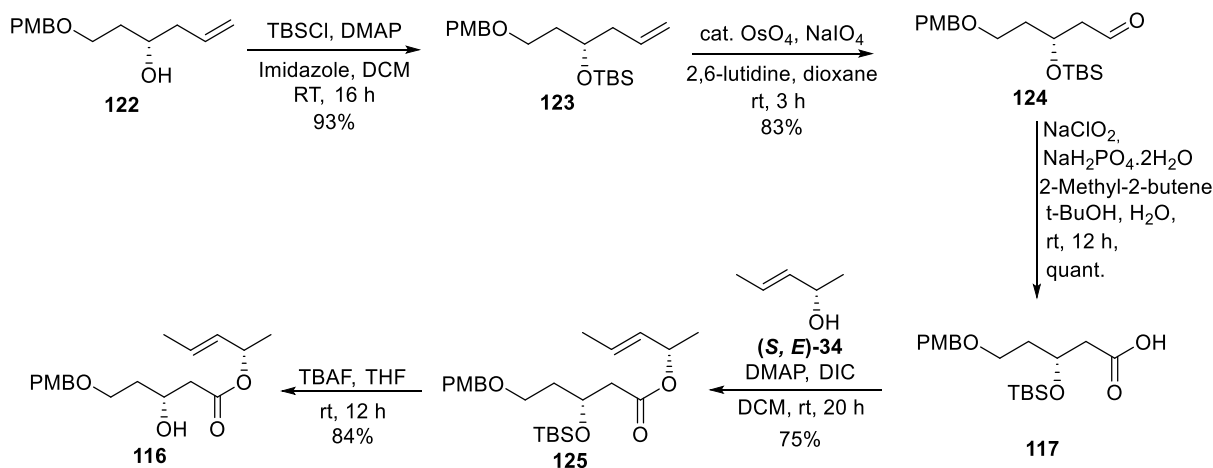
Claisen rearrangement to afford **112**. Ester **112** has three contiguous stereocentres and its successful generation would thus establish three out of the five chiral centres in **106b**.

The synthesis of **112** began with the mono-protection of 1,3-propanediol as a PMB ether **119** (83%, Scheme 2-2), followed by a Parikh-Doering oxidation to give aldehyde **120** in an excellent yield of 80% over two steps. At this stage, the enantioselective Leighton allylation⁵⁹ (using **(R,R)**-**121**) was attempted, and we were delighted to find that this reaction successfully afforded the desired allylic alcohol **122** in a reasonable yield and with high enantioselectivity (55%, 92% *ee*).



Scheme 2-2 Synthesis of alkene **122**.

The resultant alcohol was then silylated to give **123**, followed by oxidative cleavage⁵⁷ of the alkene group to give the aldehyde **124** (Scheme 2-3, 77% yield, over 2 steps). This was subjected to Pinnick oxidation to afford the carboxylic acid **117** in quantitative yield, which was then directly coupled with the alcohol **(S,E)**-**34**⁶⁰ to afford the ester **125** in 75% yield. Finally, TBS deprotection led to the formation of β -hydroxyester **116**.



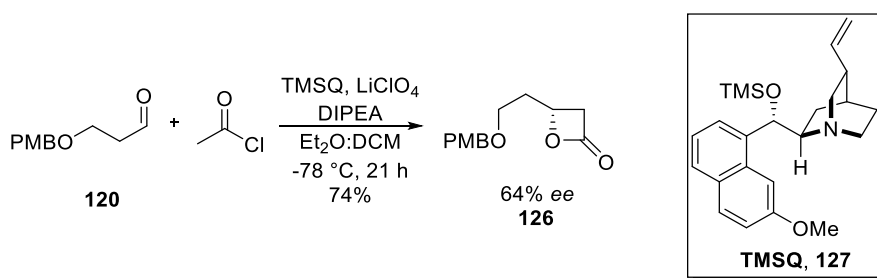
Scheme 2-3 Synthesis of β -hydroxyester **116**.

2.2.2 Revisiting the synthesis of ester 116: an alternative strategy

Despite having realised a robust stereoselective synthesis for fragment **116**, it was felt that the length of this route could be shortened (albeit it afforded the compound in an overall yield of 27% over 6 steps starting from **120**). Keeping in mind the timely advancement of the total synthesis and for having reasonable quantities of the intermediates at the later stages, it was desirable to come up with an alternative strategy to get rapid access to **116**. Furthermore, Leighton's reagent, being a moisture sensitive stoichiometric allylating agent, was somewhat cumbersome to synthesise, store and employ, thus causing issues with scalability. Finally, the synthesis involved various inelegant oxidation state manipulations and protection-deprotection strategies, rendering it inefficient. To solve these problems, we turned our attention towards an alternate route to the intermediate **116**.

In 2004, Nelson and co-workers reported an elegant cinchona alkaloid catalysed asymmetric [2+2] cycloaddition reaction between aldehydes and ketene (derived from acyl chloride). The resulting β -lactones were formed in good yields and high levels of stereoselectivity.⁶¹ We envisioned that this reaction could potentially give rapid access to **126**, a precursor of β -hydroxyester **116**.

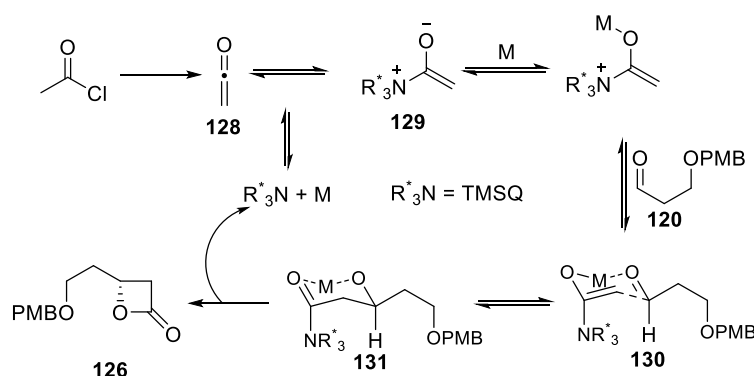
Under the literature conditions, with TMS protected quinidine (TMSQ, **127**) as catalyst, the β -lactone **126** was formed in decent yields and enantioselectivity (74%, 64% *ee*) starting from the aldehyde **120** and acyl chloride (Scheme 2-4) *via* aldehyde-acyl chloride cyclocondensation (AAC) reaction.



Scheme 2-4 Synthesis of β -lactone **126**.

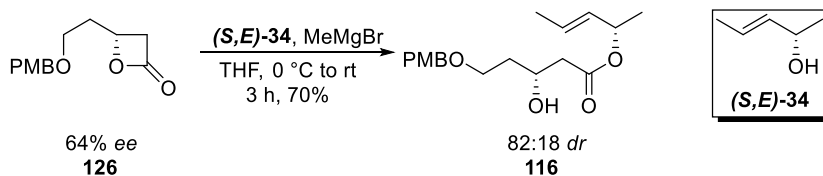
This AAC is initiated by the formation of a ketene **128** from the acyl chloride by deprotonation of the acidic α -proton, followed by elimination of the chloride ion (Scheme 2-5). Addition of the cinchona alkaloid (TMSQ) leads to the formation of the quaternary ammonium enolate **129**. Prior to the report by Nelson,⁶¹ the field of AAC had mainly focussed upon highly electrophilic aldehydes (e.g. chloral)

and more general examples of aldehydes were hard to find,^{62,63} thus indicating the ammonium enolate to have limited nucleophilicity. Moreover, without external activation, their addition on a wide range of aldehydes was seemingly unlikely. A possible solution to facilitate the reaction was to activate the aldehyde **120** using a Lewis acid (the lithium cation) that would enable the formation of the six-membered chair transition state **130** (Scheme 2-5), which eventually results in **131**.⁶⁴ Finally the alkoxide **131** then cyclises to form the β -lactone **126**, regenerating the amine catalyst.



Scheme 2-5 Proposed mechanism to the β -lactone **126**.⁶¹

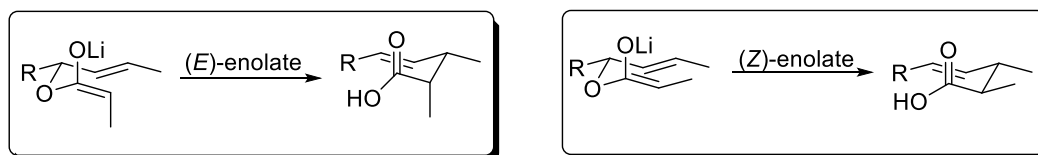
β -Lactone **126** then underwent ring-opening (Scheme 2-6) using the magnesium alkoxide derived from the alcohol (*S,E*)-**34** to give ester **116** in just two steps from aldehyde **120** with 49% overall yield (Scheme 2-4), as opposed to six steps and 27% in our first route. It should also be noted that though the *ee* of **126** in this step is not excellent, this route was still favoured over the initial strategy because, after ring opening with (*S,E*)-**34**, subsequent Ireland–Claisen rearrangement and reduction, we were able to enhance the purity of the compound. With intermediate **116** in hand, the synthesis progressed to the ambitious dianionic Ireland–Claisen rearrangement.



Scheme 2-6 Synthesis of β -hydroxyester **116**.

2.2.3 Dianionic Ireland-Claisen rearrangement; synthesis of ester 112

The Ireland-Claisen rearrangement is a [3,3]-sigmatropic rearrangement in which enolates of allylic esters convert to γ,δ -unsaturated carboxylic acids.⁶⁵ The diastereoselectivity of the reaction can be manipulated by varying the solvents and adding additives, which alter the enolate geometry ratio thus leading to different products.^{66,67} Moreover, the alkyl substituent on the allyl functionality favours the adoption of *pseudo*-equatorial position irrespective of the enolate geometry (Scheme 2-7), to minimize potential 1,3-diaxial interactions that would occur in the case of axial positioning. This enables the transfer of chirality to the β stereocentre with the α stereocentre being determined by the geometry of the enolate.



Scheme 2-7 Diastereoselectivity in the Ireland-Claisen rearrangement.

Ireland-Claisen rearrangements usually proceed through an (*E*) enolate geometry, and additives (e.g. HMPA) are required to favour (*Z*) geometry. This may seem surprising as in this chair like transition state, the enolate side chain is forced to adopt an axial position thereby increasing the 1,3-diaxial interactions. Ireland explained this seemingly paradoxical observation by proposing a model involving a cyclic six-membered transition states for enolisation.^{65–68} According to this model, the diisopropyl amine moiety of LDA remains coordinated to the Li ion (which is also coordinated to the THF solvent) in the enolization transition state thereby resulting in two potential transition states **132** and **133** (Figure 2-1). However, due to 1,3 diaxial steric clash between the diisopropyl group and the alkyl moiety in the transition state involving the (*Z*)-enolate **133**, the transition state involving (*E*) enolate **132** is preferred. On the other hand, when co-solvents and additives such as HMPA and DMPU are used, these sequester the metal cation forcing the reaction to proceed *via* acyclic transition state, thus favouring the (*Z*)-enolate. However, due to the high toxicity of these co-solvents, their use is considered undesirable.⁶⁹

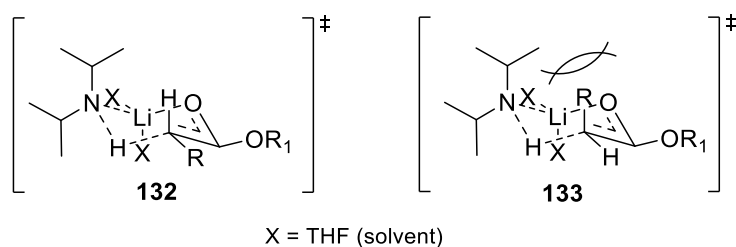


Figure 2-1 Ireland's model for enolisation transition state.⁶⁵⁻⁶⁸

More recently, another explanation was proposed by Collum *et al.*,³⁷ who reported that the addition of NEt_3 greatly enhances the yield of the product formed exclusively through the (*E*)-enolate. They proposed an 8 membered dimeric transition state **134** (which had a lower activation energy than the Ireland monomeric transition state), where NEt_3 coordinates with the Li cation in LiHMDS, thereby affording a kinetically favoured (*E*)-enolate (Figure 2-2).

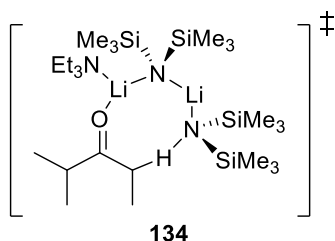
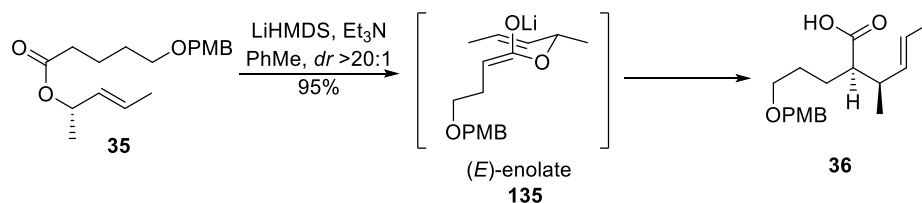


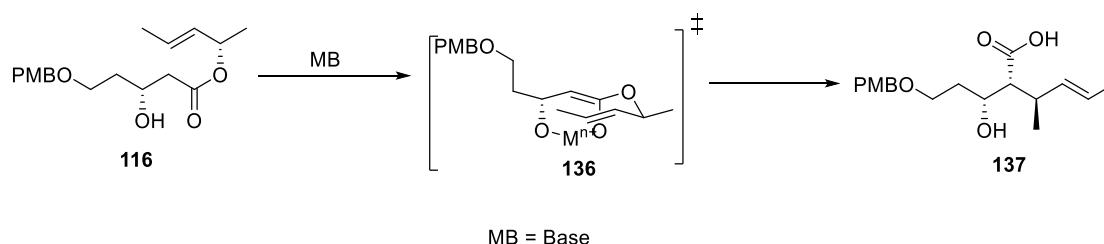
Figure 2-2 Collum's proposed 8-membered transition state for enolisation.³⁷

In our group's report of the total synthesis of rubriflorldilactone A,^{8,9} the stereochemistry around the acid functionality of **36** was established using an Ireland-Claisen rearrangement through the (*E*)-enolate **135** (Scheme 2-8). On the other hand, for synthesising ester **112**, as required in this work, the rearrangement would need to occur *via* (*Z*)-enolate.



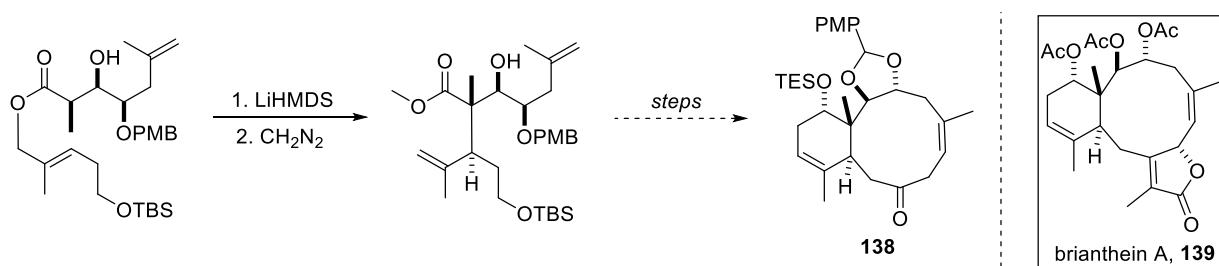
Scheme 2-8 Ireland-Claisen rearrangement in the synthesis of **36**.^{8,9}

We hypothesised that the hydroxyl group in **116**, along with the carbonyl oxygen, would chelate with the metal cation and 'lock' the ester **116** into a conformation (**136**) that would enforce formation of the *Z* enolate (Scheme 2-9). This would consequently install the requisite stereochemistry in the final product **137**.



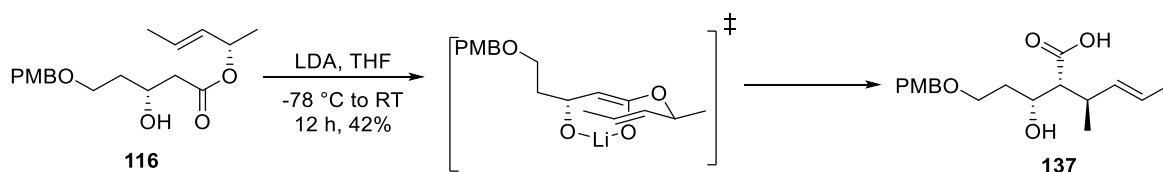
Scheme 2-9 Potential dianionic Ireland-Claisen rearrangement pathway.

In the 1980s, Fujisawa and Kurth explored the Ireland-Claisen rearrangement of β -hydroxy esters in the presence of an excess of LDA in THF.^{70,71} Similarly, they proposed that the transition state for the enolate formation would favour the (*Z*)-enolate due to chelation of the dianion to Li cation. The yields and diastereoselectivity were moderate in these reports, however, selectivity improved with more sterically-hindered substrates. More recently, in 2014, Crimmins disclosed alternative conditions for the dianionic Ireland-Claisen rearrangement using LiHMDS⁷² and again proposed a chelated transition state similar to **136**. This methodology was then applied in the synthesis of **138**, the core of brianthein A **139** (Scheme 2-10).⁷³



Scheme 2-10 Application of dianionic Ireland-Claisen in natural product synthesis.⁷³

Pollyanna Sanderson, a Part II student (2014) in the Anderson group, optimised the conditions for the dianionic Ireland-Claisen rearrangement on the ester **116** to afford the acid **137** (Scheme 2-11). She found that the modified procedure of Kurth⁷¹ gave the highest yield and diastereoselectivity (42%, >20:1 *dr*, Scheme 2-11). However, due to time constraints, she was unable to further optimise the conditions to enhance the yield of the reaction. However, she was able to confirm the stereochemistry of the product by derivatising the acid **137** to the β -lactone **140** and iodolactone **141** (Figure 2-3) and through the ¹H NMR and nOe experiments on these derivatives.



Scheme 2-11 Dianionic Ireland-Claisen rearrangement to acid **137**.

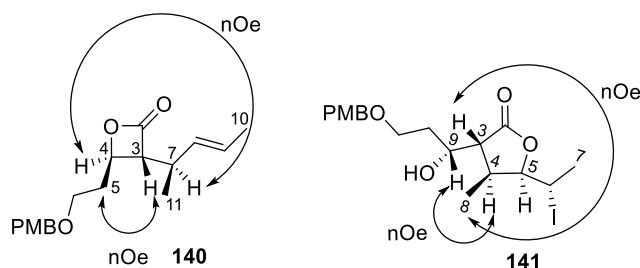
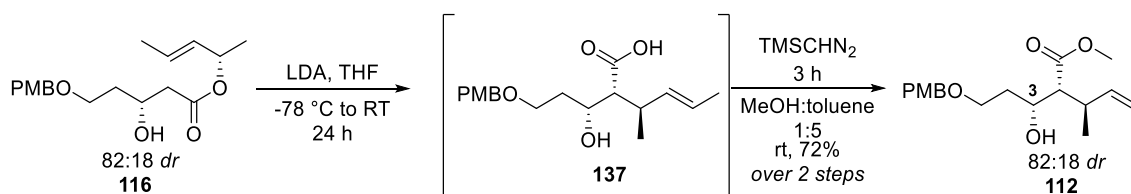


Figure 2-3 Confirmation of stereochemistry through derivatisation and nOe experiment.

While applying Pollyanna's conditions for the Ireland-Claisen rearrangement, it was discovered that even though the TLC of the reaction was very clean, the purification was quite capricious, and the yields varied from 30% to 49%. This was found to be due to the high polarity of the hydroxyacid **137**, which eluted very slowly from the column. To circumvent this problem, the hydroxyacid **137** was converted directly to the hydroxyester **112**. To our delight, this dianionic Ireland-Claisen rearrangement and esterification using TMSCHN₂ proceeded smoothly, affording the β -hydroxy ester **112** in 72% over two steps (Scheme 2-12, a 82:18 mixture of diastereomers at C3).



Scheme 2-12 Synthesis of β -hydroxyester **112**.

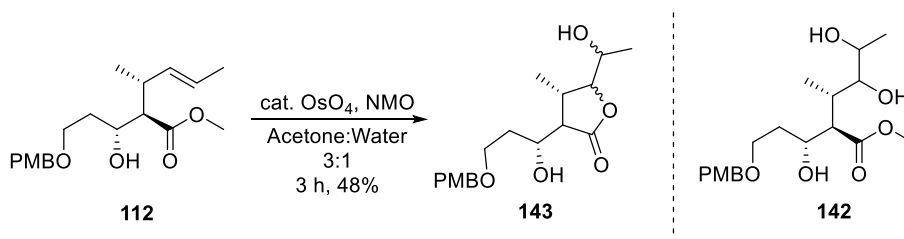
2.2.4 Synthesis of methyl acetal 110

With a reliable route to ester **112** in place, the next major intermediate in the synthesis was methyl acetal **110** (Scheme 2-13). The primary alcohol and PMB protected alcohol in **110** could then be converted into the corresponding alkynes to generate F-ring fragment **108**.



Scheme 2-13 Potential route to **110**.

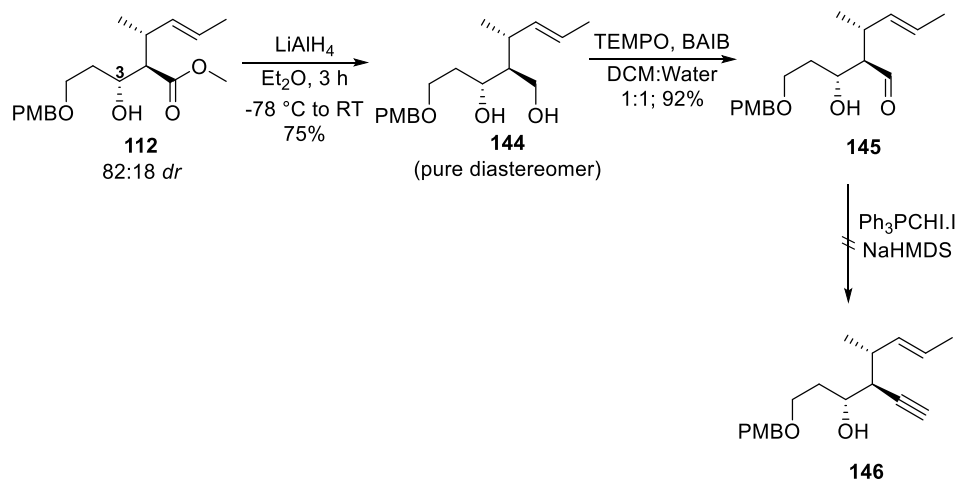
The first step in this sequence involved oxidative cleavage of the alkene in **112**. However, on subjecting **112** to the Johnson-Lemieux one-pot oxidative cleavage conditions,⁷⁴ only decomposition was observed. We decided to carry out the oxidative cleavage in a two-step sequence *i.e.* first perform the Upjohn dihydroxylation,⁷⁵ followed by the oxidative cleavage of the resulting diol. To our disappointment, instead of observing the dihydroxyl **142** (Scheme 2-14), a 5 membered lactone **143** was obtained in 48% yield.



Scheme 2-14 Upjohn dihydroxylation of **112**.

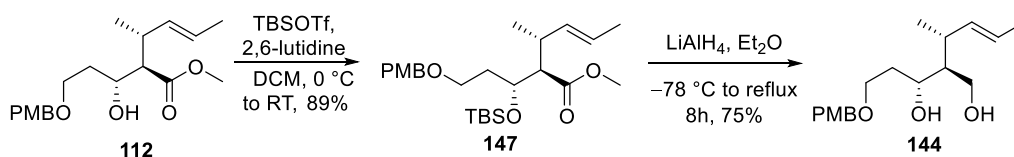
To circumvent the problem of lactonisation, a change in the order of the subsequent steps was decided. Since later in the synthesis the ester functionality was needed to be converted into the alkyne group, it was decided to carry out the alkynylation at this stage to circumvent the problem of lactonisation. The Stork–Zhao’s olefination/alkynylation³⁸ protocol was selected to generate the alkyne from the aldehyde. This began with the reduction ester **112** to the diol **144** using LiAlH_4 in 75% yield (Scheme 2-15), which enabled the isolation of the pure diastereomer **144**. The next step of the synthesis was oxidation of the diol **144** to the aldehyde **145**. Concerned with the possible epimerisation of the aldehyde **145** under the

oxidation conditions, it was decided to test pH neutral oxidation conditions of TEMPO catalyst with bisacetoxo iodobenzene as the oxidant.⁷⁶ Pleasingly, the aldehyde **145** was obtained in 92% yield. However, when the Stork-Zhao olefination was tested for the synthesis of alkyne **146**, decomposition was observed which was attributed to the free hydroxyl group in **145** (Scheme 2-15).



Scheme 2-15 Potential route to the alkyne **146**.

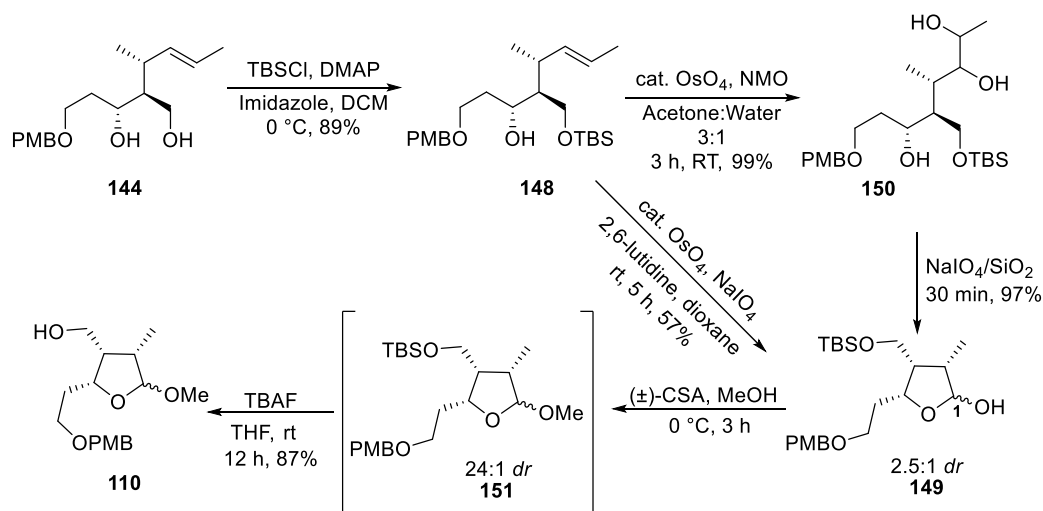
To tackle this issue, it was decided to protect the secondary alcohol as a silyl ether. Use of TBSOTf resulted in the formation of the TBS ether **147** in high yield (Scheme 2-16, diastereomerically pure **112** was used for this step). Unfortunately, attempts to reduce the ester **112** to the corresponding alcohol gave both reduction and TBS deprotection to the diol **144**. A literature search revealed precedence for TBS deprotection in diols, presumably due to intramolecular hydride transfer through oxyaluminium hydride intermediate to silicon.^{77,78}



Scheme 2-16 Route to the diol **144** through TBS ether **147**.

At this stage, a change in order of events was explored. The TBS protection of the primary alcohol in diol **144** proceeded smoothly to afford TBS ether **148** (Scheme 2-17). The one pot-oxidative cleavage reaction of **148** gave lactol **149** in 57%. The modest yield of this one-pot Johnson-Lemieux protocol could be enhanced by performing the oxidative cleavage in two steps: Upjohn dihydroxylation of **148**

thus led to the formation of the triol **150** in quantitative yield, which on treatment with NaIO₄ supported on silica gel to generated lactol **149** in 97% yield (Scheme 2-17, *ca* 2.5:1 *dr* at C1).



Scheme 2-17 Synthesis of the methyl acetal **110**.

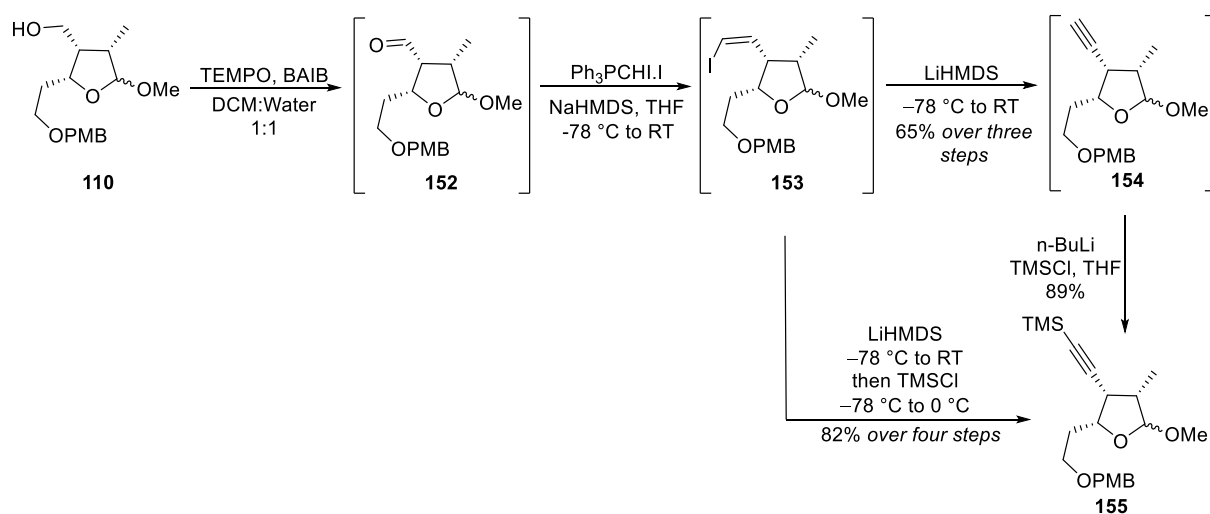
Lactol **149** was further treated with catalytic (±)-CSA in MeOH (solvent) to generate methyl acetal **151** (Scheme 2-17). The crude reaction mixture was then treated with TBAF to finally afford methyl acetal **110** in 90% yield over two steps.

In summary, synthesis of methyl acetal **110** was achieved on a multigram scale with an overall yield of 58% from the ester **112** in five steps.

2.2.5 Synthesis of diyne 108

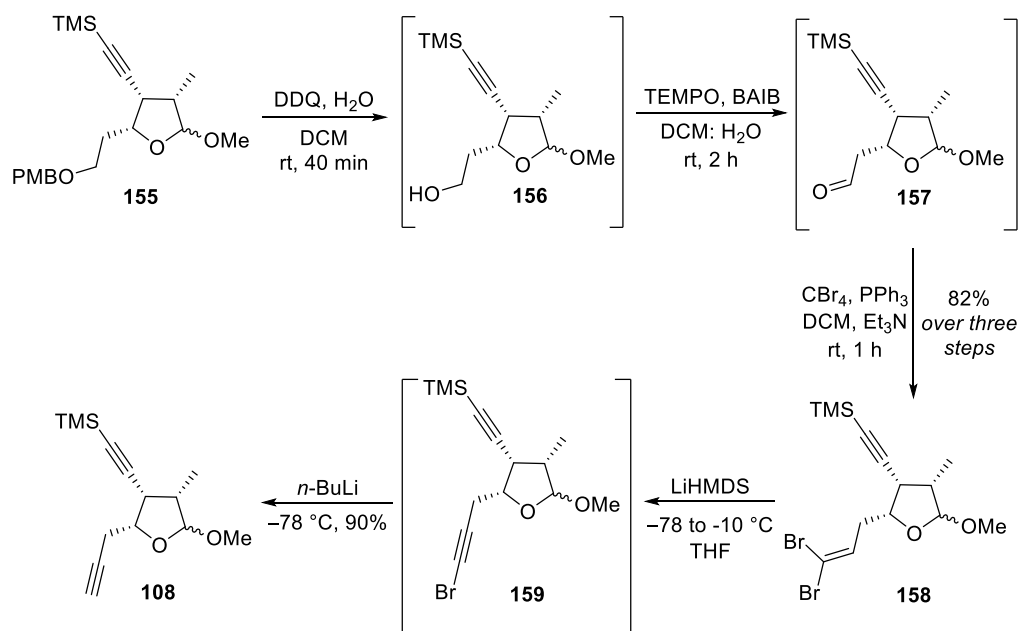
With an efficient synthesis of the methyl acetal **110** in hand, we next proceeded towards the crucial intermediate diyne **108**. This molecule would not only contain three contiguous stereocentres of the F ring but also generate the final two alkynes required for the planned [2+2+2] cyclotrimerisation reaction.

Efforts towards the synthesis of **108** began with oxidation of the alcohol **110** to the aldehyde **152**. DMP oxidation led to the formation of the aldehyde **152** in 66% yield, however, the crude reaction mixture showed epimerisation at the carbon α to the aldehyde (9:1), and further epimerisation was observed during silica gel chromatography. To tackle this problem, a neutral TEMPO-BAIB oxidation⁷⁶ was tested, with the crude reaction mixture used for the subsequent steps of the synthesis. Gratifyingly, this method proceeded with great efficiency to afford **152** (Scheme 2-18), with no epimerisation being observed in the crude ¹H NMR spectrum. The crude product **152** was then subjected to the Stork–Zhao *cis*-vinyl iodide protocol³⁸ to generate iodide **153** which was converted into the alkyne **154** in 65% yield in a one-pot/three steps sequence. Finally, a trimethylsilyl group was installed on the terminal alkyne **154**, resulting in the internal alkyne **155** in 89% yield. Alternatively, **155** was also obtained directly from **153** through **154** in 82% yield in a one-pot/four step sequence by quenching the reaction with TMSCl.



Scheme 2-18 Synthesis of alkyne **155**.

The next step in the synthesis was a PMB deprotection of **155** to afford alcohol **156** (Scheme 2-19); however, decomposition was observed during column chromatography. Alcohol **156** was then subjected to a TEMPO-BAIB oxidation to afford aldehyde **157**, however, decomposition was again observed during purification. To circumvent these problems, it was decided to proceed with the PMB deprotection and oxidation without purification; The crude aldehyde **157** was then subjected to Ramirez olefination^{79,80} to afford dibromoalkene **158** in 82% yield over three steps (Scheme 2-19).



Scheme 2-19 Synthesis of the dibromoalkene **158**.

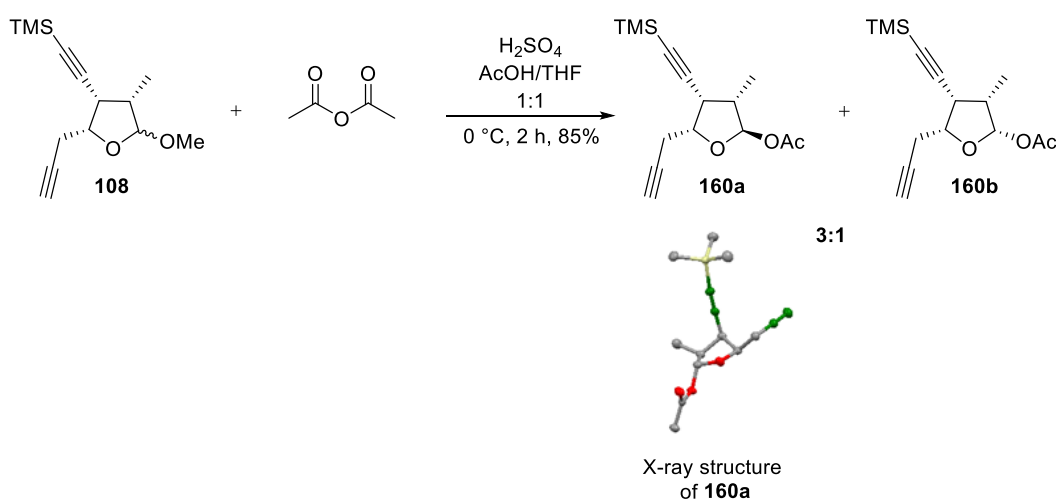
Finally, dibromoalkene **158** was treated with *n*-BuLi to generate the diyne **108**, however, the yields for this reaction varied significantly (40% to 90%). Thus, it was decided to first treat **158** with LiHMDS to generate the corresponding bromoalkyne **159** (Scheme 2-19), which underwent lithium-halogen exchange and protonation to generate the diyne **108**.

2.2.6 Synthesis of the FG ring fragment 106

Oxocarbenium ions are important intermediates in carbohydrate chemistry and are involved in *C*-glycosylation reactions.^{81,82} Typically, they are generated through Lewis acid activation of the anomeric leaving groups and are subsequently attacked by nucleophiles.^{83,84} There have also been few attempts at proposing stereoelectronic models to explain the stereoselective reactions of nucleophiles with 5 membered ring oxocarbenium ions.^{85,86} Only recently, some catalytic asymmetric approaches have been described,^{87–91} however, these are in general hard to achieve due to the absence of both; Lewis basic sites as well as large π -surfaces that are essential for the substrate–catalyst interactions.⁹¹

A good leaving group α to the tetrahydrofuran oxygen (*e.g.* acetate, halogens etc) is typically essential for the generation of an oxocarbenium ion, and no examples of methoxy leaving groups were found in the literature. However, plenty of examples with the acetate leaving group were present.

As such, the methoxy group of **108** was converted to the acetate **160** by treating with acetic anhydride in the presence of a catalytic amount of conc. H_2SO_4 (Scheme 2-20). This led to the formation of acetates **160a** and **160b** in 85% yield. The structure of **160a** was confirmed through the single crystal X-ray crystallography (Scheme 2-20).ⁱⁱ

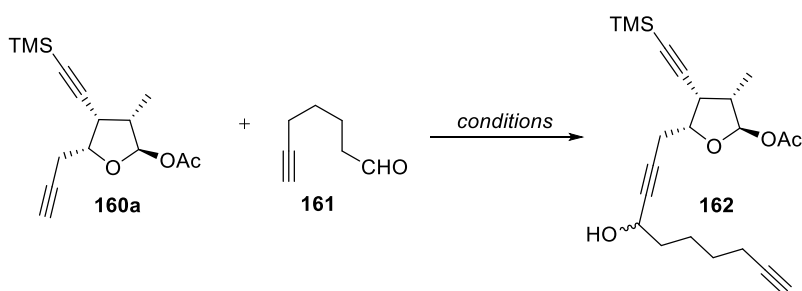


Scheme 2-20 Synthesis of the acetatea **160a** and **160b**.

ⁱⁱ The crystal was developed by the author and the X-ray analysis was done by Steven J. Mansfield, a D. Phil. student in the Anderson group.

To study the planned addition of the F or FG ring diynes to the AB ring aldehyde **32**, hept-5-yn-1-al **161** was used as a model aldehyde. Unfortunately, deprotonation of the alkyne in the presence of the acetate proved to be challenging. With *n*-BuLi as a base, only 35% of the desired product **162** formed (Table 2-1, entry 1). This yield dropped to 20% when LiHMDS was employed for this reaction (Table 2-1, entry 2).

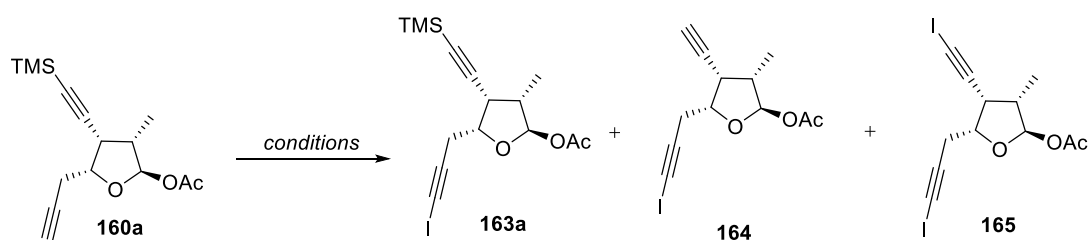
Table 2-1 Addition of **160a** to the aldehyde **161**.



S.No.	Conditions	Yield
1	<i>n</i> -BuLi, THF, -78°C to -40°C , 6 h	35%
2	LiHMDS, -78°C to -40°C , 5 h	20%

While contemplating possible solutions to facilitate this addition, the Nozaki-Hiyama-Kishi (NHK) reaction was considered which would require conversion of acetate **160a** to the iodoalkyne **163a**.

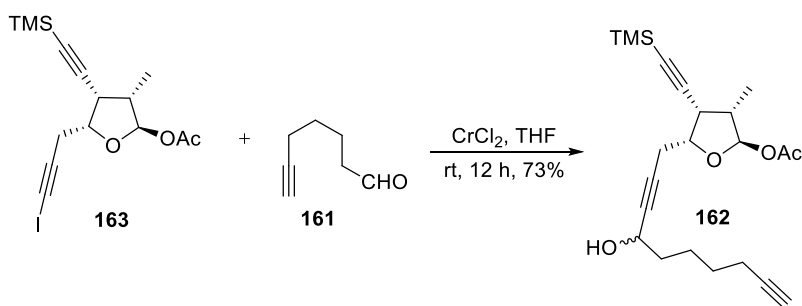
Table 2-2 Iodination of the alkyne **160a**.



S.No.	Conditions	Product
1	AgNO_3 , NIS, Acetone, rt, 30 min	163a , 164 and 165
2	DBU, NIS, MeCN, rt, 6h	No reaction
3	AgOAc , NIS, Acetone, rt, 6h	No reaction
4	AgOAc , NIS, Acetone, rt, 6h	No reaction
5	I_2 , morpholine, toluene, 45°C , 12h	90%, 163a

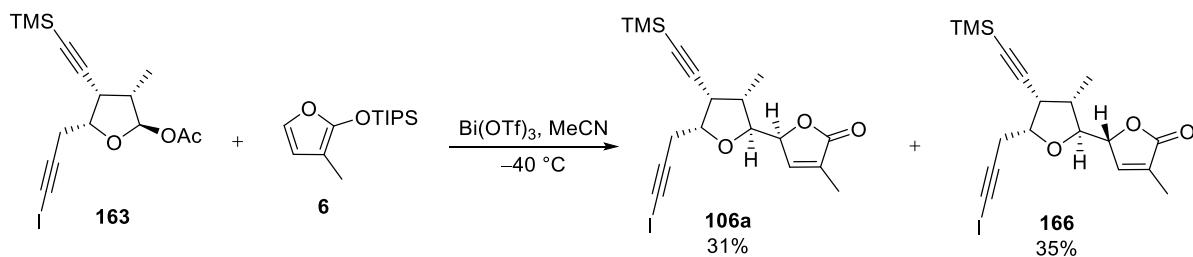
The typical conditions for synthesis of iodoalkynes from alkynes involve NIS and AgNO₃. However, on applying these conditions on to the alkyne **160a** (Table 2-2, entry 1), a complex mixture was observed, comprising iodoalkyne **163a**, desilylated alkyne **164**, and double iodination to afford **165**. Other silver salts were ineffective (Table 2-2, entries 3 and 4) as was the use of DBU (Table 2-2, entry 2). Fortunately, employing molecular iodine with morpholine afforded iodoalkyne **163a** in very high yield.⁹²

Finally, the NHK reaction was attempted with the iodoalkyne **163a** and aldehyde **161**, which pleasingly led to the smooth formation of **162** in 73% yield when CrCl₂ was used (Scheme 2-21).



Scheme 2-21 NHK reaction to form triyne **162**.

Following this successful NHK reaction, synthesis of the FG ring fragment **106a** from **163** was tested (Scheme 2-22). The Mukiyama aldol reaction was performed using Bi(OTf)₃ as promoter which gave **106a** in 31% yield and the diastereomer **166** in 35% yield.¹⁷ Further attempts were made to optimise these conditions on a model system (details of which could be found in Chapter 3).



Scheme 2-22 Synthesis of the FG ring fragment **106a**.

The stereochemistry of **106a** and **166** was established using ¹H NMR nOe correlations and X-ray crystallography.

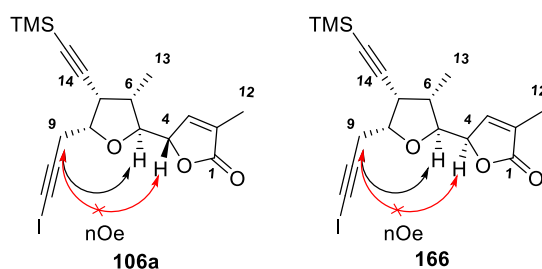


Figure 2-5 nOe correlations in **106a** and **166**.

In ^1H NMR nOe experiments for both **106a** and **166**, no through-space interactions were observed between H4 and H9 while strong enhancement was seen between H5 and H9 was prominent (Figure 2-5). This indicates that the H4 and H9 are at the opposite phases of the furan ring and **106a** and **166** are, therefore, epimeric at C4. Moreover, it proved possible to obtain a single crystal of **166** (Figure 2-6), which confirmed the absolute stereochemistry in the molecule and thus, by corollary, for the molecule **106a**.ⁱⁱⁱ

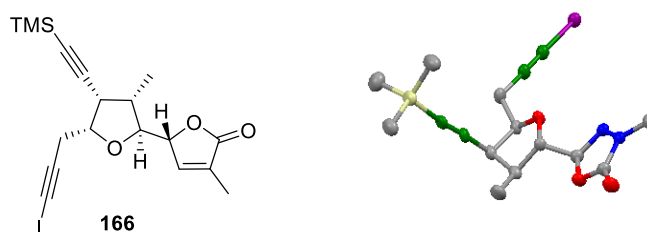


Figure 2-6 Single crystal X-ray structure of **166**.

In summary, this chapter describes the synthesis of ester **112** obtained *via* dianionic Ireland-Claisen rearrangement, and subsequent preparation of the key intermediates **160a** and **160b**. The structure of **160a** was confirmed through single crystal X-ray crystallography. Finally, FG ring fragments **106a** and **166** were obtained *via* iodination reactions and Mukaiyama aldol type addition of 2-silyloxyfuran **6** to **160a** and **160b**. The stereochemistry in **166** was confirmed through single crystal X-ray crystallography which also helped in assigning the stereochemistry of **106a** as well.

ⁱⁱⁱ The crystal was developed by the author and the X-ray analysis was done by Steven J. Mansfield, a D. Phil. student in the Anderson group.

3. Model system studies

3.1 Retrosynthetic analysis

Before continuing with the synthesis of rubriflordilactone B (**3**), subsequent reaction steps were first attempted and optimised on simpler model compounds with fewer functionalities. The three model compounds comprised the CDE model **167**, DEFG model **168** and CDEFG model **169** (Figure 3-1). The CDE model system **167** was initially studied to optimise the cyclisation conditions, as well as those to generate the alkene functionality. Reactions performed on the DEFG model system **168** were aimed towards installing the G ring on to the DEF fragment **170**. Finally, the optimised conditions of models **167** and **168** were cumulatively performed on the CDEFG model **169** to fine tune the reaction steps, as these would be employed for the synthesis of rubriflordilactone B (**3**).

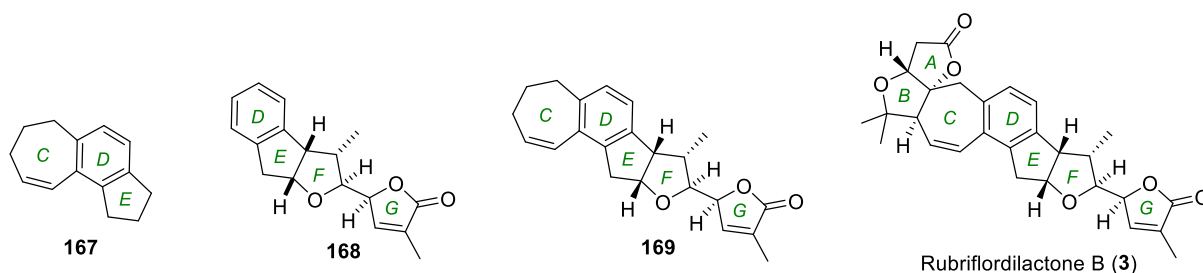
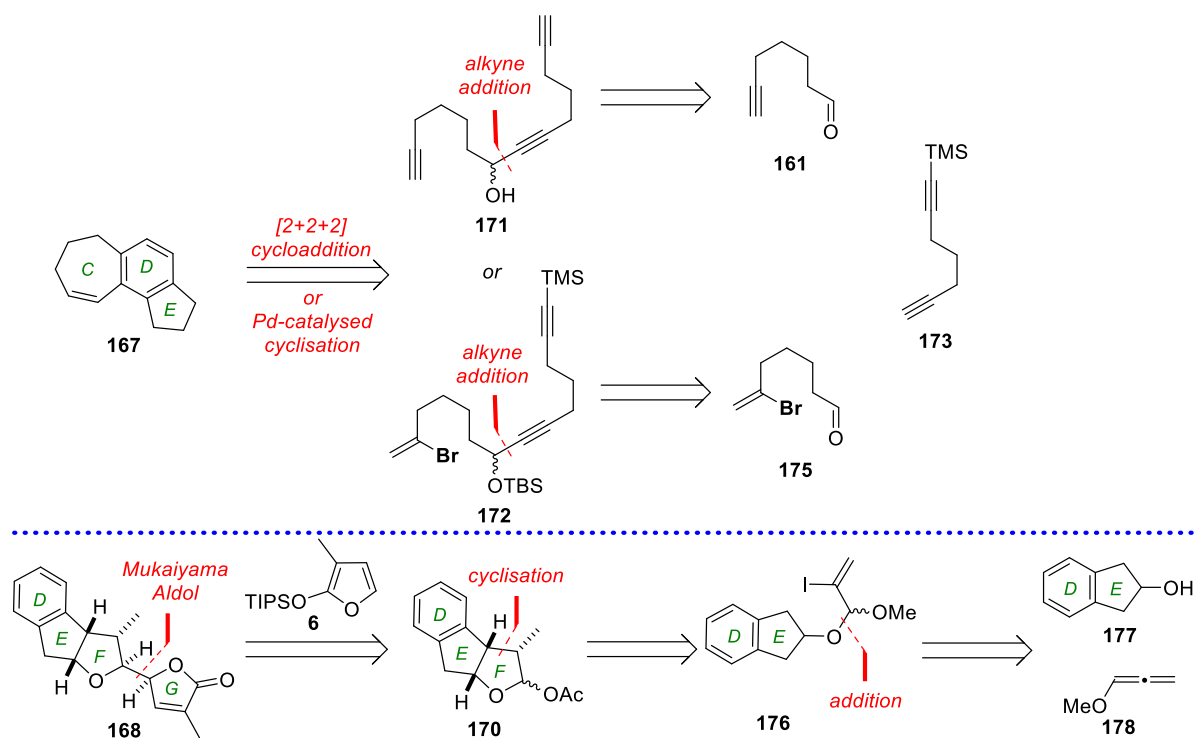


Figure 3-1 Model systems of rubriflordilactone B.

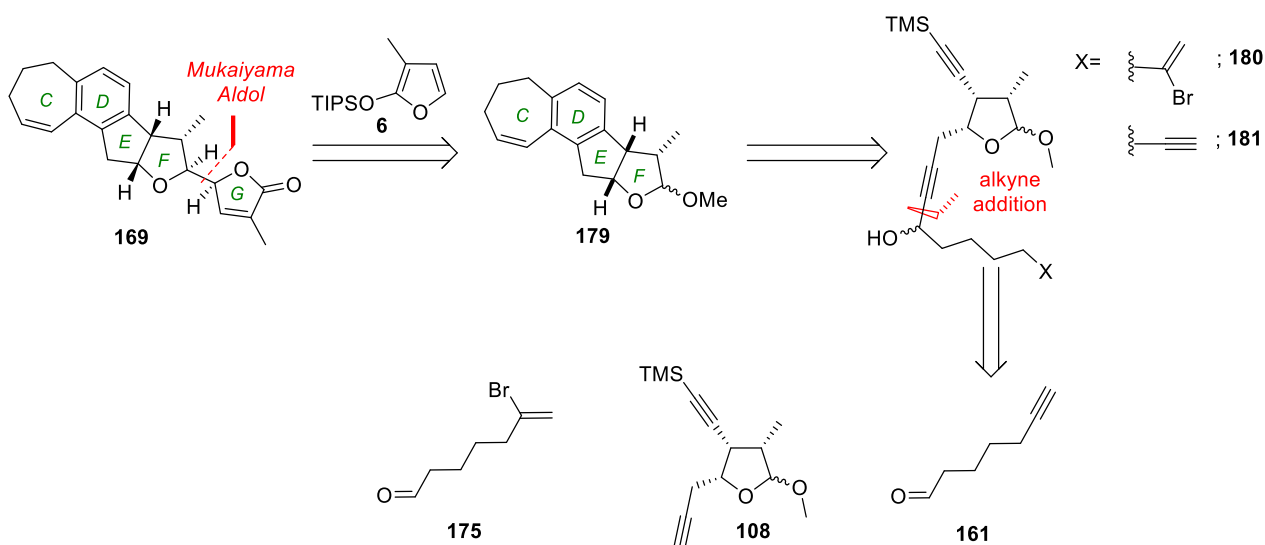
Retrosynthetically, the CDE model **167** could be assembled (Scheme 3-1; top) either by a [2+2+2] cycloaddition reaction of ynol **171** or through a Pd-catalysed polycyclisation of enynol **172**. Both **171** and **172** would in turn be formed by the addition of diyne **173** to the aldehyde **161** and **175** respectively.

The G ring in the DEFG model **168** could be added through a Mukaiyama aldol reaction of **6** with the DEF core **170** (Scheme 3-1; bottom), obtained from the intramolecular cyclisation of compound **176**. Finally, **176** could be formed by the condensation of 3-indanol (**177**) and methoxyallene (**178**).



Scheme 3-1 Disconnections for the CDE model **167** (top) and DEFG model **168** (bottom).

The first disconnection for the CDEFG system **169** would be between rings F and G (Scheme 3-2). Silyloxyfuran **6** would add onto the CDEF system **179** which would form either through a Pd-catalysed cyclisation of **180** or by a rhodium catalysed $[2+2+2]$ cyclotrimerisation reaction of **181**. Compounds **180** and **181** would form by the addition of the diyne **108** to the aldehyde **175** and **161** respectively. The sequence for synthesising **108** has been described in Chapter 2.



Scheme 3-2 Disconnections for the CDEFG model **169**.

3.2 CDE model system 167

Our efforts on optimising the reaction conditions began by first working on the CDE model **167** (Figure 3-2), which could potentially be assembled through a transition metal cyclotrimerisation or a Pd-catalysed polycyclisation. This section describes our attempts to this endeavour.

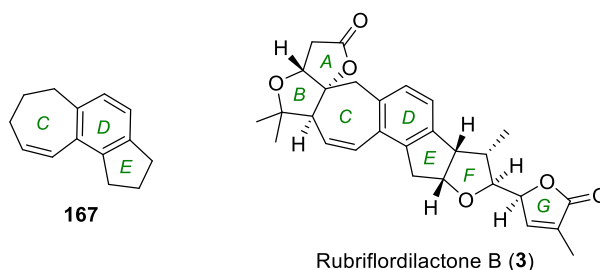


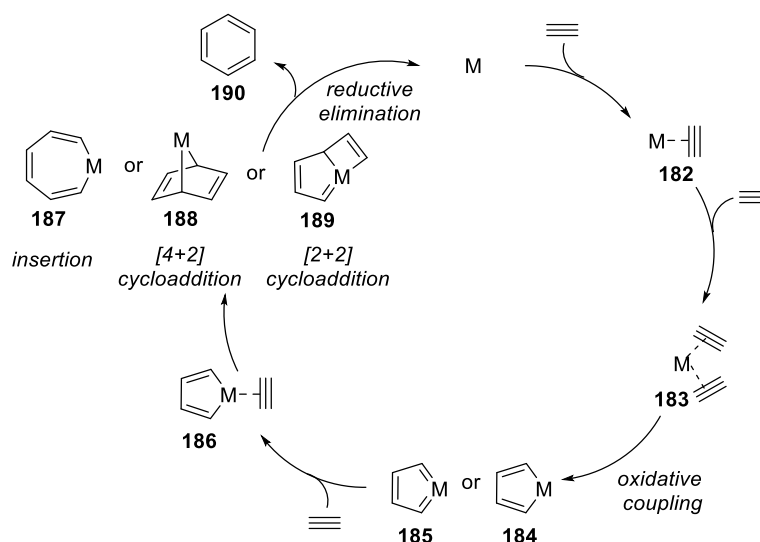
Figure 3-2 CDE model systems **167**.

3.2.1 Introduction to transition metal [2+2+2] cycloisomerisation reactions of triynes

Transition metal-catalysed [2+2+2] cycloaddition reactions are highly atom economical transformations of unsaturated substrates, where three π -bonds are consumed to generate three σ -bonds with the formation of a six-membered ring. This methodology allows assembly of different functionalities around the six-membered ring with relative ease and is an efficient route to poly-substituted benzene rings.⁹³ Monocyclic, bicyclic and tricyclic compounds can all be generated regioselectively under mild conditions.^{93,94}

The first transition-metal-catalysed [2+2+2] cycloaddition was performed by Reppe and co-workers, who used a Ni catalyst to convert acetylene to benzene.⁹⁵ Over the years, the reaction has developed to incorporate various unsaturated substrates including allenes, nitriles, olefins, carbonyls, isocyanates, imides, diimides, carbon dioxide, carbon disulfide etc. to generate six membered unsaturated cyclic and heterocyclic compounds.^{93,94,96–100} Moreover, the scope of the metal catalysts also broadened to incorporate rhodium, ruthenium, palladium, chromium, cobalt, iridium, iron, niobium, tantalum and zirconium.^{93,94,104,96–103}

Many studies have been conducted regarding the mechanism of transition-metal-catalysed [2+2+2] cycloaddition reactions. There are three generally accepted pathways; however, the applicable pathway mainly depends upon the nature of the metal catalyst, ligand, and the specific substrate employed in the reaction.^{105–107} A brief overview of these pathways is shown in Scheme 3-3.



Scheme 3-3 Mechanism of transition-metal-catalysed [2+2+2] cycloaddition reaction.

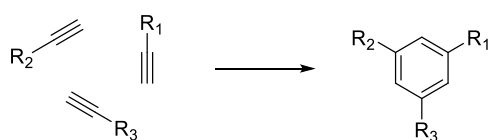
The first step of the reaction involves coordination of the first alkyne to the metal, leading to the formation of **182**. Next, the second alkyne also coordinates to **182** generating **183**. Now, the metal undergoes oxidative coupling to the alkynes, forming either the metallacyclopentadiene **184** or the metallacyclopentatriene **185**. This step is the rate determining step,^{107–110} and rhodacyclopentadienes of type **184** have also been isolated.¹¹¹ The third alkyne now coordinates to the complex **184** or **185**, both giving rise to **186**, which can then either undergo alkyne insertion leading to metallacycloheptatriene **187**,¹¹² or a [4+2] cycloaddition creating bicyclic compound **188**, or it can undergo a formal [2+2] cycloaddition reaction generating metallabicyclo[3.2.0] heptatriene **189**. Finally, reductive elimination forms the benzene ring **190**, thereby releasing the metal for the next catalytic cycle.

The whole catalytic cycle is exothermic, and the reaction is driven by the formation of the aromatic ring as well as three new σ -bonds. The energy barriers in the transition-metal-catalysed [2+2+2] cycloaddition reactions are low, thereby enabling the mild reaction conditions (compared to the uncatalysed [2+2+2] cycloaddition reaction). The metal achieves this feat by assembling the aromatic ring in a stepwise manner where the coordinated molecule orients itself appropriately to facilitate the reaction.

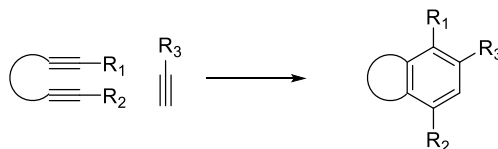
[2+2+2] cycloaddition reactions of the alkyne can be broadly divided into three categories depending on the substrate employed.

- a) **Intermolecular [2+2+2] cycloaddition reactions (Scheme 3-4a):** In these reactions, the alkyne moiety is present in three different substrates. Conventional reactions suffer from low regio- and chemoselectivity, thus leading to complex mixtures of products, and attempts to introduce heteroatoms exacerbates the problem. However, significant advances have been made to tackle this issue,^{113,114} the solution usually involves using alkynes with significant electronic differences to control the generation of the first metallacycle *e.g.* acetylene dicarboxylate, which does not form the initial metallacyclopentadiene and thus is only incorporated at the very end of the cycle.¹¹⁵ A second solution is to use alkyne surrogates like enol ethers which, at the end of the reaction, can undergo elimination reaction to generate the aromatic ring.¹¹³
- b) **Partial intramolecular [2+2+2] cycloaddition reactions (Scheme 3-4b):** In these reactions, the two alkyne moieties are present in the same molecule and an alkyne is added at the last stage of the reaction. Generally, rhodium complexes^{115–118} are very efficient for such substrates and Wilkinson's catalyst in particular has been widely used.^{116,117,119–121} This type of cycloaddition reaction overcomes some of the regio- and chemoselectivity issues faced by the fully intermolecular [2+2+2] cycloaddition reaction. However, even though these types of reactions involve readily accessible diynes, a serious disadvantage is the dimerisation of the diyne, forcing the researchers to use a large excess of monoyne, or to resort to slow addition of the diyne.
- c) **Intramolecular [2+2+2] cycloaddition reactions (Scheme 3-4c):** In totally intramolecular [2+2+2] cycloaddition reactions, all three alkyne functionalities are present in the same molecule. Similar to the partial intramolecular reactions, these reactions also widely employ rhodium or cobalt catalysts, and Wilkinson catalyst in particular. Examples of other metals like Ni can also be found.^{8,9} This type of cycloaddition is completely regio- and chemoselective and generates very high complexity around the arene ring being assembled with high efficiency. Having said that, the substrates used in this type of [2+2+2] cycloaddition reactions can be more complicated and difficult to synthesise.

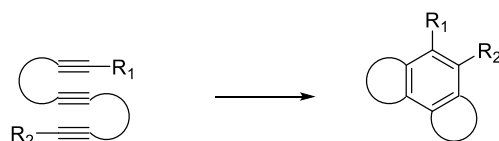
a) Intermolecular [2+2+2] cycloaddition reactions



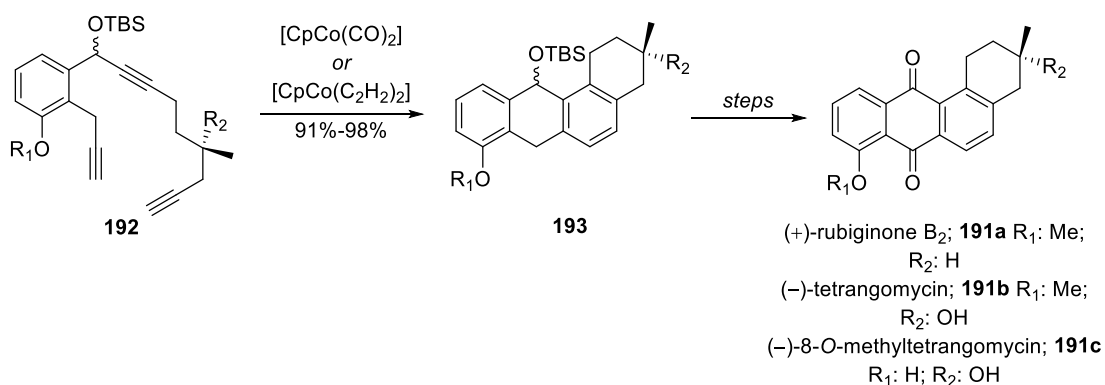
b) Partially Intramolecular [2+2+2] cycloaddition reactions



c) Intramolecular [2+2+2] cycloaddition reactions

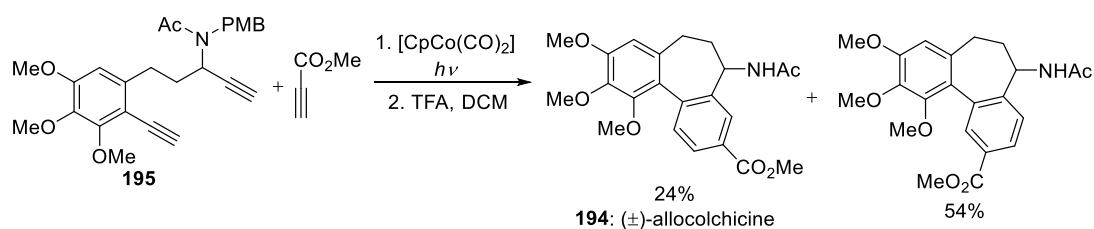
**Scheme 3-4** Types of [2+2+2] cycloaddition reactions.

Intramolecular [2+2+2] cycloaddition reactions have been extensively used in total synthesis. In 2010, Groth and co-workers reported a total synthesis of (+)-rubiginone B₂ (**191a**), (–)-tetrangomycin (**191b**) and (–)-8-*O*-methyltetrangomycin (**191c**).¹²² The key step in the synthesis was a Co-catalysed [2+2+2] cyclotrimerisation reaction of triyne **192** to generate the 6,6,6 ring framework **193** (Scheme 3-5).

**Scheme 3-5** Synthesis of (+)-rubiginone B₂ (**191a**), (–)-tetrangomycin (**191b**) and (–)-8-*O*-methyltetrangomycin (**191c**) (Groth *et al.*, 2010).¹²²

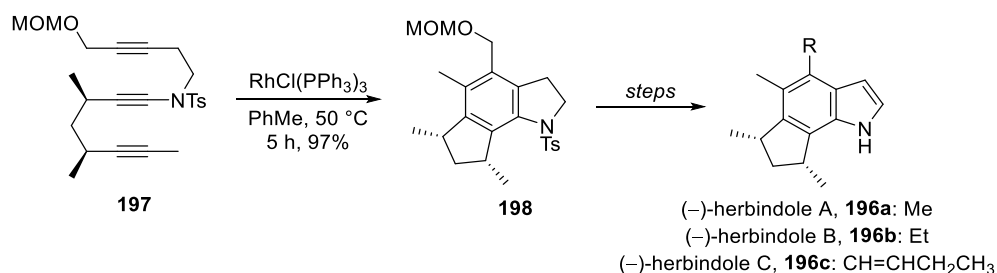
More recently, in 2017, Ramana *et al.* synthesised (±)-alcolchicine (**194**) and its analogues via a Co-catalysed [2+2+2] cyclotrimerisation reaction between diyne **195** and methyl propiolate

(Scheme 3-6).¹²³ Interestingly, a difficult to synthesise, 7,6- ring system is generated with this cyclotrimerisation reaction.



Scheme 3-6 Synthesis of (±)-alcolchicine (Groth *et al.*, 2018).¹²³

Nitrogen containing natural products have also been synthesised using [2+2+2] cyclotrimerisation reactions. Witulski *et al.*, have pioneered the cyclotrimerisation of ynamides (typically using Rh or Ru catalysts).^{124–127} With the work by Witulski as precedent, Sato and co-workers, in 2012, reported a total synthesis of (–)-herbindoles A-C (**196a-c**).¹²⁸ The key cyclotrimerisation step in this synthesis converted ynamide **197** to the (–)-herbindole framework **198** (Scheme 3-7).



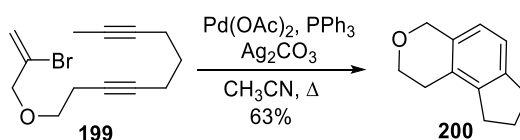
Scheme 3-7 Synthesis of (–)-herbindoles A-C (Sato *et al.*, 2012).¹²⁸

Other examples include works from the groups of Volhardt,^{129–133} Anderson,^{8,9} Sato,¹²⁸ Sorenson¹³⁴ and Govans¹³⁵ amongst many. However, 7,6,5 ring systems have rarely been generated using [2+2+2] cycloaddition reactions^{8,9,16} making it an interesting and challenging endeavour.

3.2.2 Introduction to Palladium-catalysed cascade polycyclisations

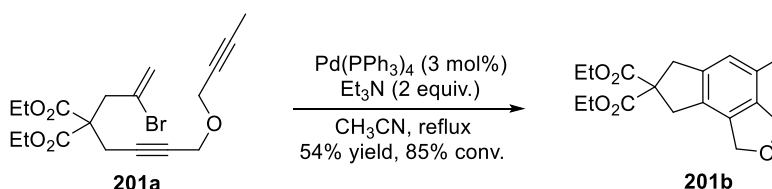
Cascade reactions are those in which multiple bonds are sequentially created through reactive intermediates formed *in situ* under the reaction conditions in a single operational step. These reactions are inherently step-efficient and can generate high levels of complexity in a single operation.^{136–138} This feat is especially impressive in the context of total synthesis.¹³⁹

In 1991, de Meijere and co-workers reported an intramolecular cascade polycyclisation sequence for converting an oxabromoendiyne precursor **199** to a 6,6,5-tricyclic framework **200** (Scheme 3-8).¹⁴⁰



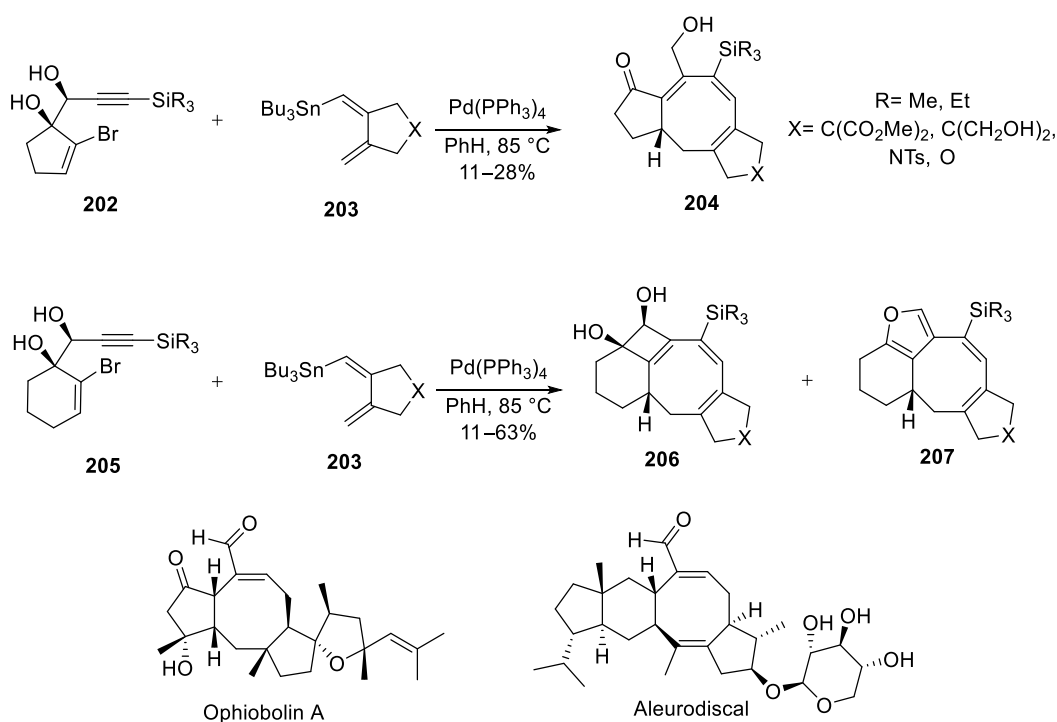
Scheme 3-8 Synthesis of tricycle **200** (de Meijere *et al.*, 1991).¹⁴⁰

Similar to de Meijere, in 1992, Negishi also proposed a Pd-catalysed polycyclisation of precursor **201a** to generate 5,6,5-ring core **201b** (Scheme 3-9).¹⁴¹



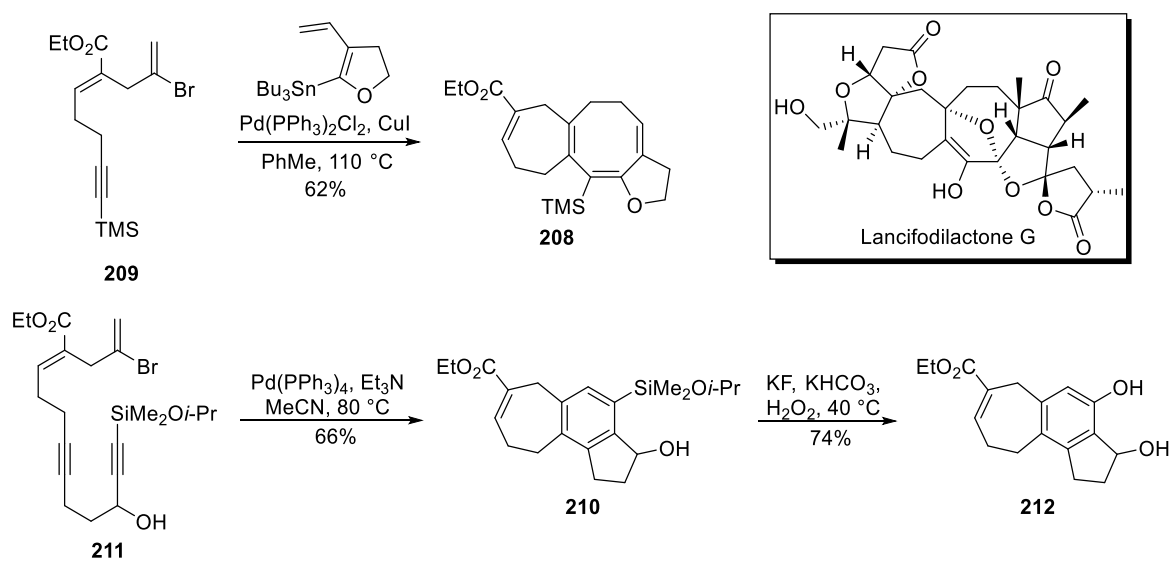
Scheme 3-9 Cyclisation of bromoenediyne **201a** (Negishi *et al.*, 1992).¹⁴¹

In 2004, Suffert and co-workers reported an elegant route to 5,8,5- tricyclic core and 6,8,5- tetracyclic core of ophiobolin A and aleurodiscal.¹⁴² The core was generated through a key 4-*exo*-dig cyclocarbopalladation/ π electrocyclization cascade.¹⁴² With palladium catalyst, bromoenyne **202** reacted with stannane **203** to form 5,8,5- tricyclic core **204** and bromoenyne **205** reacted with **203** generating 6,8,5- ring core **206** and **207** (Scheme 3-10).



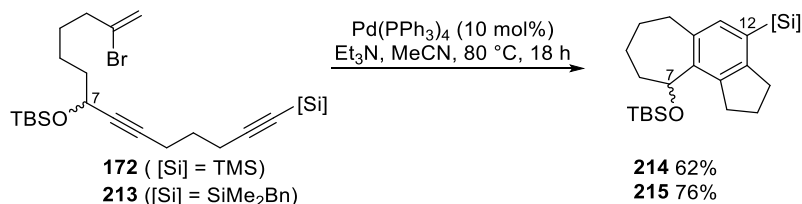
Scheme 3-10 Synthesis of 5,8,6 ring core **204** and 6,8,5 ring core **206** and **207** (Suffert *et al.*, 2004).¹⁴²

Building on the work by Suffert, in 2008, Anderson *et al.* synthesised the 7,8,5 ring CDE core **208** of lancifodilactone G from the dienyne **209** and the 7,6,5 ring framework **210** from precursor **211** using Pd-catalysed cascade cyclisation. Finally, the Tamao-Fleming oxidation of **210** led to the CDE core **212** of rubriflordilactone A (Scheme 3-11).¹²



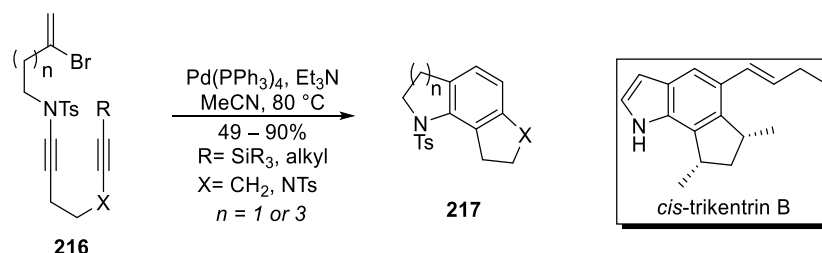
Scheme 3-11 Cyclisation to the 7,8,5 ring system and 7,6,5 ring system (Anderson *et al.*, 2008).¹²

Anderson *et al.* revisited their synthesis of the CDE core of rubriflordilactones A and B in 2012. Making use of the enediynes **172** and **213**, the group reported high yields of the 7,6,5 ring cores **214** and **215** which are common to both rubriflordilactone A and B (Scheme 3-12).¹³ This protocol was central to the Anderson group's synthesis of rubriflordilactone A.^{8,9}



Scheme 3-12 Synthesis of 7,6,5 ring systems **214** and **215** of rubriflordilactone A and B (Anderson *et al.*, 2012).¹³

The group further extended this methodology to bromoenamides, to generate trikentrin like frameworks.¹⁴³ Here, the bromoenamides **216**, on treatment with the palladium catalyst led to the formation of the class of compound **217** in moderate to high yield (Scheme 3-13).



Scheme 3-13 Bromoenamides in palladium-catalysed cascade cyclisation (Anderson *et al.*, 2014).¹⁴³

Significant work has been done in the field of palladium-catalysed cascade cyclisation,^{136,144,145} and the field has been extended to incorporate chiral biphenyls,¹⁴⁶ tricyclic aromatic azacycles,¹⁴³ chromans and isochromans,¹⁴⁷ aromatic polycycles¹⁴⁸ etc. However, the palladium-catalysed intramolecular bromoenediyne cascade cyclisation has found limited application in total synthesis.^{8,9}

3.2.3 Synthesis of the CDE model system 167

The synthesis of **167** commenced with the generation of triyne **171** for the [2+2+2] route and bromoendiyne **172** for Pd-catalysed cyclisation (Figure 3-2). Both **171** and **172** were prepared *via* modifications of our earlier report.¹³

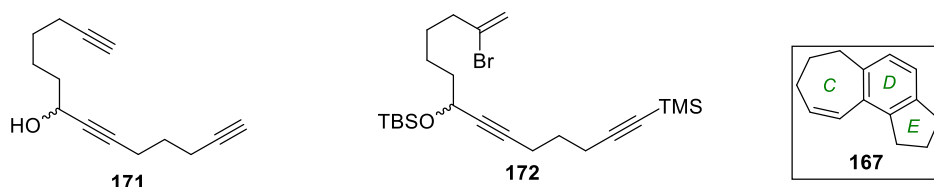
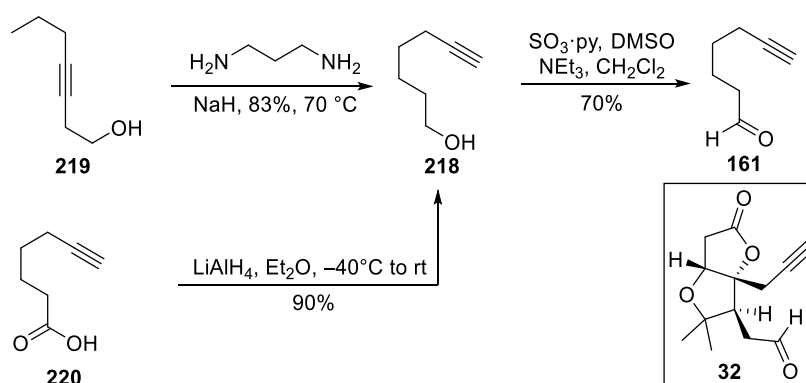


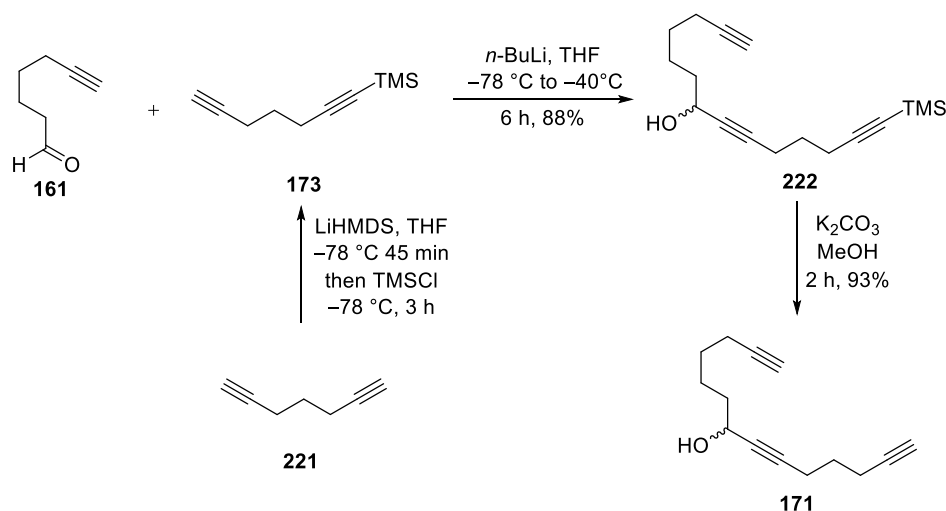
Figure 3-2 Precursors for CDE model **167**.



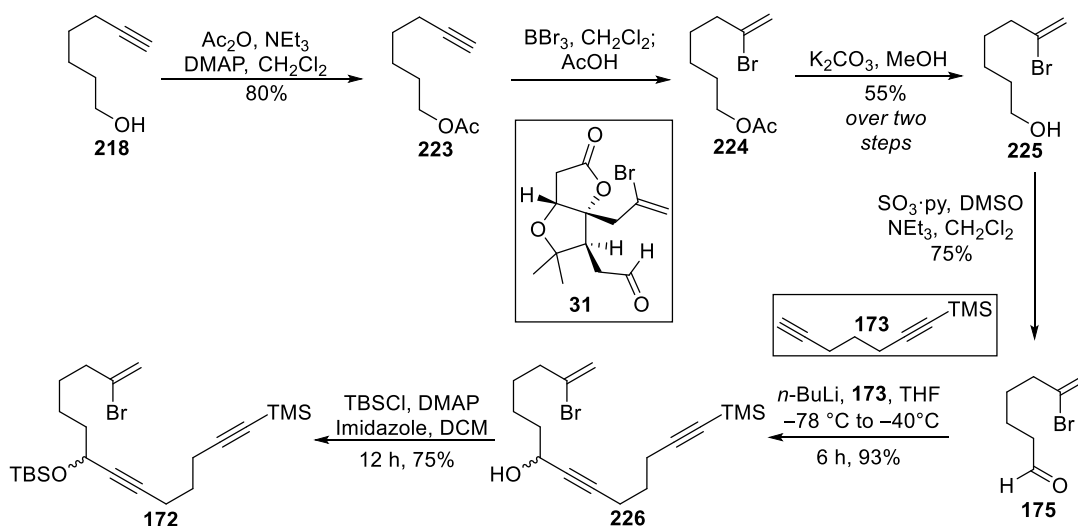
Scheme 3-14 Synthesis of aldehyde **161**.

Synthesis of **172** began by producing the terminal alkynol **218** from 3-heptyn-1-ol (**219**) in 83% yield, by employing an alkyne zipper reaction (Scheme 3-14).¹⁴⁹ Alternatively, LiAlH_4 reduction of hept-6-ynoic acid (**220**) furnished **218** in high yield. Parikh-Doering oxidation of **218** led to the formation of **161**, which would act as a simplified surrogate for the AB ring aldehyde **32** in the optimisation studies. Extra care was taken while working with **161** due to its volatile nature and tendency to decompose on prolonged storage.

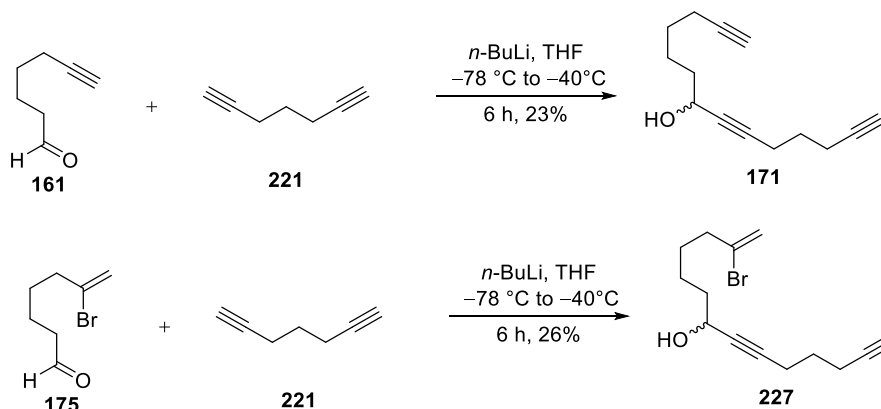
Next, the diyne **173** was synthesised by deprotonation of hepta-1,6-diyne (**221**) followed by quenching with TMSCl (Scheme 3-15). The diyne **173** was also deprotonated and aldehyde **161** was then added to it, to generate triynol **222** in 88% yield. Finally, treating **222** with K_2CO_3 in MeOH solvent led to the formation of **171** in 93% yield (Scheme 3-15).

Scheme 3-15 Synthesis of CDE precursor **171**.

The synthesis of bromoenyne **172** commenced with protection of the alcohol **218** with an acetate group (80%) (Scheme 3-16). This acetate **223** was subjected to bromoborylation/protodeborylation to afford bromoene **224** which on hydrolysis gave bromoenol **225** in 55% yield (over two steps). Finally, Parikh-Doering oxidation yielded bromoenal **175** (75%). Like compound **161**, **175** can also act as a simplified model for the AB ring aldehyde **31**. Deprotonation of the diyne **173** followed by addition to the aldehyde **175** formed the alcohol **226** in 93% yield, which on TBS protection furnished **172** in 75% yield (Scheme 3-16).

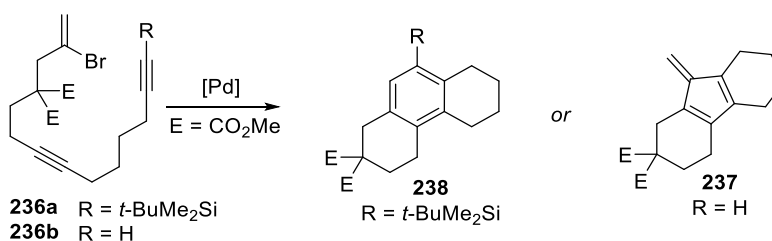
Scheme 3-16 Synthesis of bromoenediene **172**.

It should also be noted that the direct addition of hepta-1,6-diyne (**221**) to the aldehyde **161** and **175** was met with limited success with only 23% of **171** and 26% of **227** being formed along with the recovery of the remaining alkyne **221** (Scheme 3-17).



Scheme 3-17 Direct addition of diyne **221** to **161** and **175**.

With bromoenyne and triyne precursors in hand, the cyclisation studies were addressed. Initial attempts were made with the Pd-catalysed polycyclisation of **172** to **214**. Pleasingly, our previously established conditions¹³ were suitable to carry out this cyclisation to afford **214** in 55% yield (Table 3-1, entry 1). On attempting cyclisations of precursors **226** and **227** to **231** and **232**, only decomposition was observed, indicating that the protected propargyl alcohol and the presence of TMS group on the alkyne is essential for the cyclisation to proceed smoothly (Table 3-1, entries 2 and 3). Similarly, attempted cyclisation of **228** to **233** was also met with failure (Table 3-1, entry 4). This observation was in agreement with the work by de Meijere *et al.* on 2-bromo-tetradec-1-ene-7,13-diynes **236a** and **236b** where presence of terminal alkyne led to bisannulated fulvene **237** instead of 6,6,6- tricycle **238** (Scheme 3-18).^{136,144,145} Finally, switching the alcohol TBS protection group to TMS or TES reduced the efficiency of the reaction (39% and 43% respectively, Table 3-1, entries 5 and 6).



Scheme 3-18 Pd-catalysed cascade cyclisation of **236a** and **236b** (de Meijere *et al.*).^{136,144,145}

Table 3-1 Cyclisation studies to assemble the CDE core.

172 R₁= TBS; R₂=TMS; **226** R₁= H; R₂=TMS
227 R₁= H; R₂=H; **228** R₁= TBS; R₂=H
229 R₁= TMS; R₂=TMS; **230** R₁= TES; R₂=TMS

214 R₁= TBS; R₂=TMS; **231** R₁= H; R₂=TMS
232 R₁= H; R₂=H; **233** R₁= TBS; R₂=H
234 R₁= TMS; R₂=TMS; **235** R₁= TES; R₂=TMS

S.No.	Substrate	Product	Conditions	Yield
1	172	214	10 mol% Pd(PPh ₃) ₄ , Et ₃ N, MeCN, 80 °C, 20 h	55%
2	226	231	10 mol% Pd(PPh ₃) ₄ , Et ₃ N, MeCN, 80 °C, 20 h	decomp.
3	227	232	10 mol% Pd(PPh ₃) ₄ , Et ₃ N, MeCN, 80 °C, 20 h	decomp.
4	228	233	10 mol% Pd(PPh ₃) ₄ , Et ₃ N, MeCN, 80 °C, 20 h	decomp.
5	229	234	10 mol% Pd(PPh ₃) ₄ , Et ₃ N, MeCN, 80 °C, 20 h	39%
6	230	235	10 mol% Pd(PPh ₃) ₄ , Et ₃ N, MeCN, 80 °C, 20 h	42%

Following Pd-catalysed cyclisation, attention shifted to the transition-metal catalysed [2+2+2] cyclotrimerisation reaction. For the previous synthesis of rubriflordinolactone A, a Co catalyst was employed to facilitate this transformation.^{8,9} However, use of microwave heating was essential for this reaction, which could limit the scalability of the process. Since rhodium is widely used for fully-tethered [2+2+2] cyclotrimerisation reactions, it was decided to focus on this metal. Additionally, results by Xie *et al.*¹⁶ on a truncated rubriflordinolactone B model were highly encouraging.

Table 3-2 [2+2+2] cyclotrimerisation studies to assemble the CDE core.

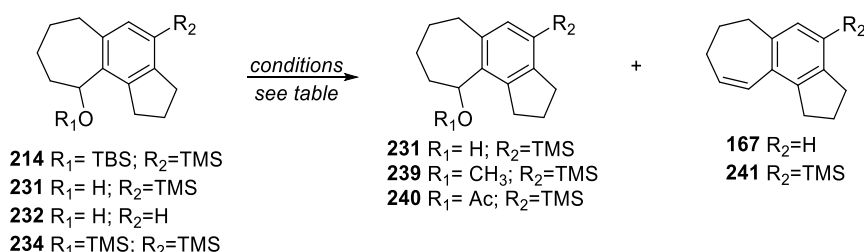
S.No.	Conditions	Yield
1	20 mol% [Rh(PPh ₃) ₃]Cl, 1,2-DCE, 50 °C, 24 h	52%
2	10 mol% [Rh(PPh ₃) ₃]Cl, 1,2-DCE, 50 °C, 30 h	30% (55% conv.)
3	20 mol% [Rh(PPh ₃) ₃]Cl, EtOH, 80 °C, 30 h	15% (35% conv.)

Initial attempts were made by employing substrate **171** and 20 mol% Wilkinson's catalyst with 1,2-DCE as the solvent. Encouragingly, the formation of the product **232** was observed in 52% yield (Table 3-2, entry 1). The moderate yield could be attributed to the high degree of freedom and a large number

of conformers possible for the triyne **171**. This imparts higher enthalpic and entropic requirements on the substrate to reorganise and adopt appropriate conformation with the catalyst, thus, facilitating the alternative decomposition pathways. Reducing the catalyst loading limited the reaction to a conversion of 55% and even after prolonged heating, the reaction did not show any progress (Table 3-2, entry 2). Moreover, changing the solvent to EtOH,¹³⁴ a well-known solvent for these transformations, was also not efficient (Table 3-2, entry 3).

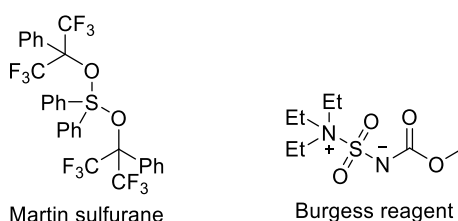
With reasonably successful cyclisation achieved, the focus shifted towards the elimination reaction to generate the CDE rings model **167**.

Table 3-3 Attempted eliminations to assemble CDE core.



S.No.	Substrate	Product	Conditions	Yield
1	214	231	TBAF (5 equiv.), THF, 9 h, 60 °C	92%
2	214	239	AcCl, MeOH/THF, 12 h, 40 °C	73%
3	234	240 and 241	AcOH, Ac ₂ O, H ₂ SO ₄ , THF, 12 h, 40 °C	80% <i>conv.</i> (3:1)
4	214	167	ZnCl ₂ , TMSCl, THF, 3 h, rt; NaI, TMSCl, H ₂ O, MeCN, 2 h, rt	72%
5	231	167	ZnCl ₂ , TMSCl, THF, 3 h, rt; NaI, TMSCl, H ₂ O, MeCN, rt, 2 h	75%
6	232	167	ZnCl ₂ , TMSCl, THF, 3 h, rt	80%
7	231	241	Burgess reagent, THF, 2 h, rt	65%
8	231	241	Martin sulfurane, DCM, 15 min, 0 °C	68%
9	241	167	AcCl, MeOH, 40 °C, 12 h	<i>quant.</i>

On attempting global deprotection of **214** using TBAF, only TBS deprotection was observed (Table 3-3, entry 1) while the TMS group remained untouched (**231**). Surprisingly, no desilylation was observed at room temperature and heating was essential for even alcohol deprotection. When **214** was subjected to the HCl in MeOH (Table 3-3, entry 2), only substitution product **239** formed with no elimination.



In summary, conditions to form CDE core of rubriflordilactone B were identified. Pd-catalysed polycyclisation of bromoenyne **172** and Rh-catalysed [2+2+2] cyclotrimerisation reaction of **171** are able to generate 7,6,5 ring core. Martin sulfurane and Burgess reagent proved to be effective in facilitating the dehydration of the benzylic alcohol **231** to alkene **241**. Finally, methanolic HCl was efficient in carrying out protodesilylation of **241** to give model **167**.

3.3 DEFG model system 168

After successfully concluding our studies on the CDE model systems, we, next decided to work on DEFG model **168** to optimise the reaction conditions for installing the G ring (Figure 3-4).

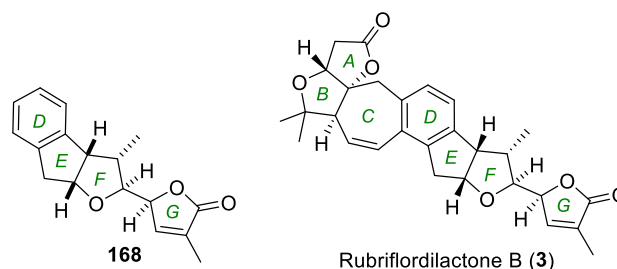
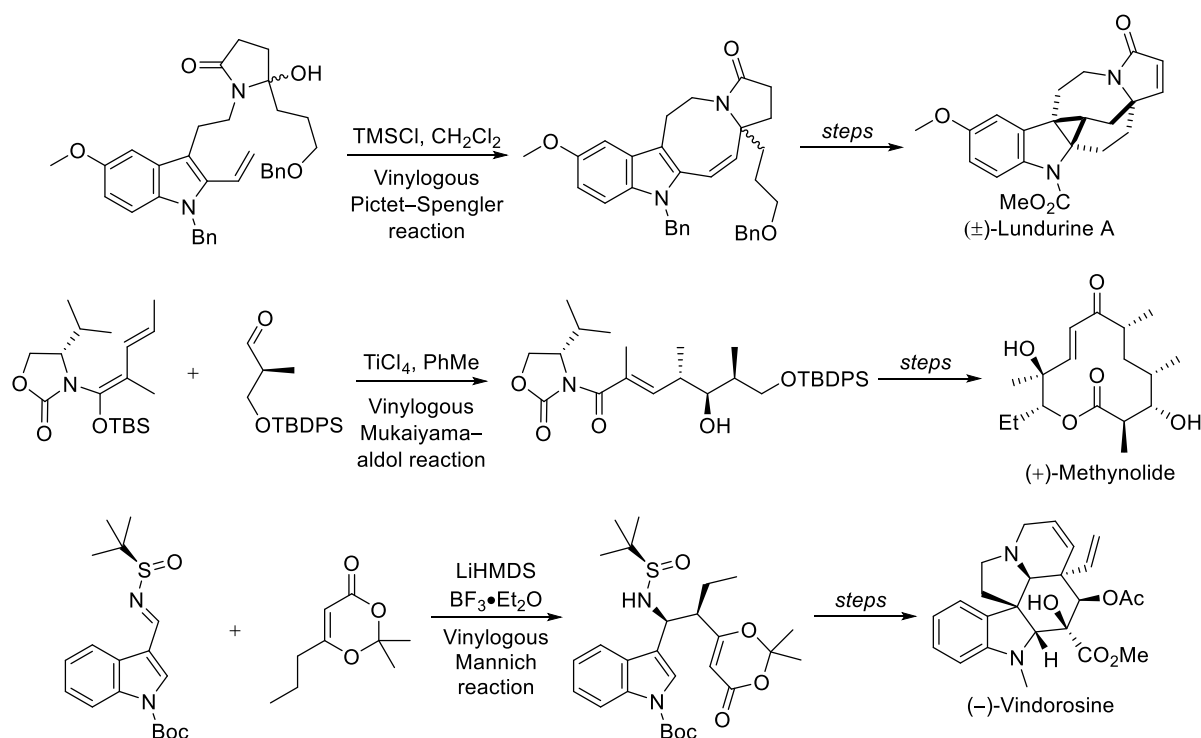


Figure 3-4 DEFG model systems **168**.

3.3.1 Vinylogous addition of 2-silyloxyfurans to heteroatom-stabilised carbenium ions.

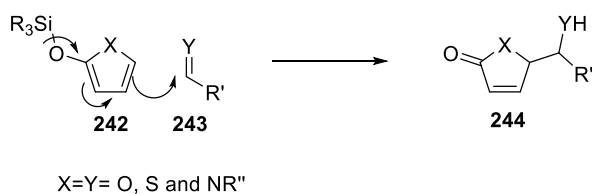
The term “vinylogy” refers to the transfer of the electronic effects of a molecule through a conjugate system due to the presence of functional groups like esters, ethers, carbonyls etc.^{150,151} The principle was first proposed by Claisen in 1926 to describe the acidity of formylacetone and related β -keto aldehydes.¹⁵² Since then, the concept has been extended to explain a myriad of observations including the overall effect of more than one functional group on additions through conjugated π systems as in S_N' reactions.

Vinylogous reactions have been used to generate high degrees of complexity in relatively sensitive molecules and have, thus, been incorporated in many total syntheses. Recent examples include the application of a vinylogous Pictet–Spengler cyclisation in the total synthesis of ($\pm$)-lundurine-A,¹⁵³ the synthesis of (+)-methynolide involving a Mukaiyama aldol reaction¹⁵⁴ and utilisation of a vinylogous Mannich reaction in the synthesis of (–)-vindorosine (Scheme 3-19).¹⁵⁵



Scheme 3-19 Recent application of vinylogous reactions in total synthesis.

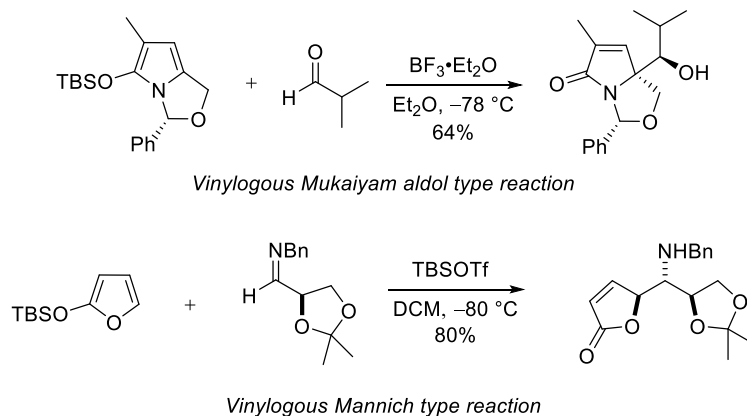
Five-membered 2-silyloxy heterocycles (**242**) originating from thiophenes, furans and pyrroles (Scheme 3-20) can act as vinylogous nucleophiles and add to suitable electrophiles (**243**) forming compounds containing butenolide rings (**244**).



Scheme 3-20 Additions of 2-silyloxy heterocycles to the electrophiles.

The first report describing the synthesis and application of 2-silyloxyfurans **242** (X=O) appeared in 1977.¹⁵⁶ The potential of this reagent was recognised by several groups, and its application as a vinylogous nucleophile could be seen in a few early total syntheses.^{157,158} These reports clearly demonstrated the utility of silyloxyfurans in target-based synthesis and opened up the field; subsequent application of 2-silyloxy 5-membered heterocycles as vinylogous nucleophiles could be seen in the application of vinylogous aldol^{159–161} and Mannich-type^{162,163} reactions (Scheme 3-21). Another application of these nucleophiles is in the field of vinylogous addition to cyclic heteroatom-stabilised carbenium ions (akin to C-glycosylation). Unlike the aldol and mannich reaction variants, it is hard to

control the stereoselectivity of these *C*-glycosylation reactions involving 5-membered ring oxocarbenium through chiral Lewis acids, presumably due to the lack of extended π -system, in the cyclic carbocation, for the substrate-catalyst coordination.^{81,82,85,86}

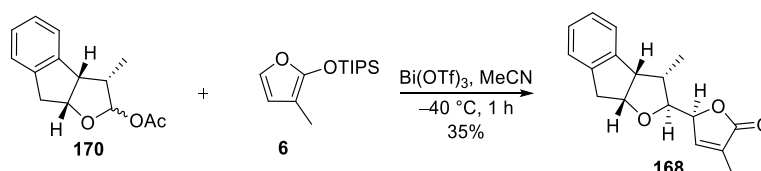


Scheme 3-21 Vinylogous Mukaiyama aldol and Mannich reaction.^{159,162}

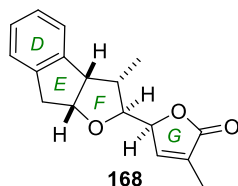
Despite challenges, such *C*-glycosylations have been successfully used in many total syntheses.^{164–166}

In the total synthesis of rubriflordilactone A by both Li¹⁶⁷ and Anderson,^{8,9} pyranosides and 2-silyloxyfurans have been involved in the *C*-glycosylation reactions to install the G-ring. Furthermore, a recent report by Peng *et al.*¹⁷ on the DEFG model of rubriflordilactone B highlighted the possibility of using a *C*-glycosylation reaction to install the G-ring in rubriflordilactone B.

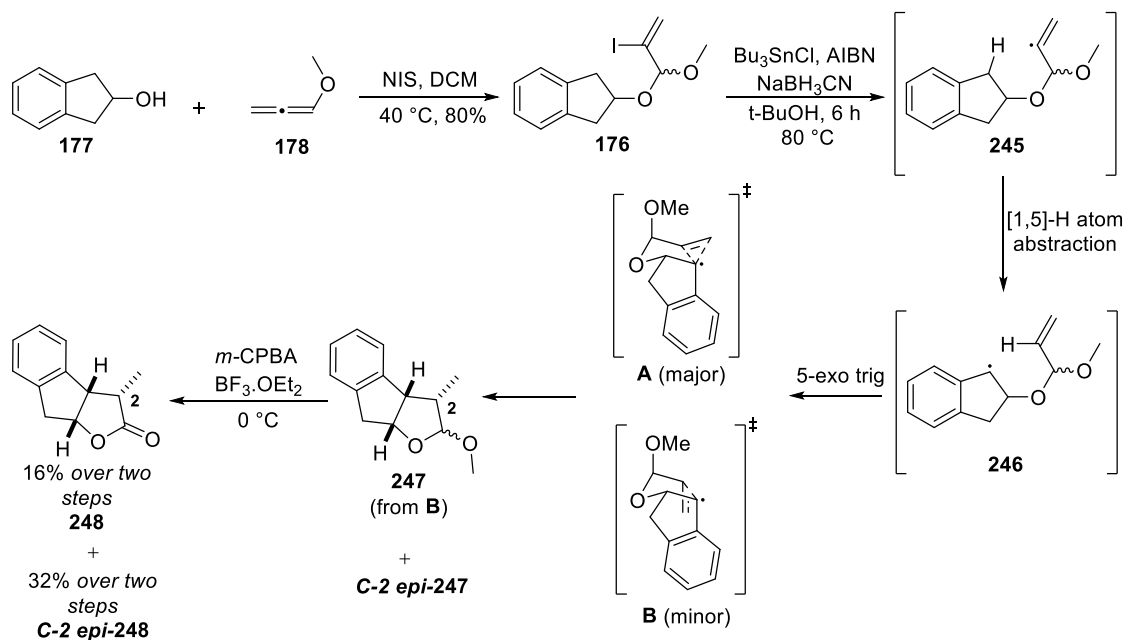
In 2016, the Peng group¹⁷ described a concise synthesis of the racemic DEFG model **168** of the rubriflordilactone B (Scheme 3-22). The synthesis made use of bismuth Lewis acid to install the G ring on the truncated DEF system **170**. To understand the reaction as well as the nature of the product formed, it was decided to follow the described protocol. Additionally, the yield for the final vinylogous Mukaiyama aldol-type reaction described by Peng *et al.* was low (35%) thus attempts to improve the yields were made.



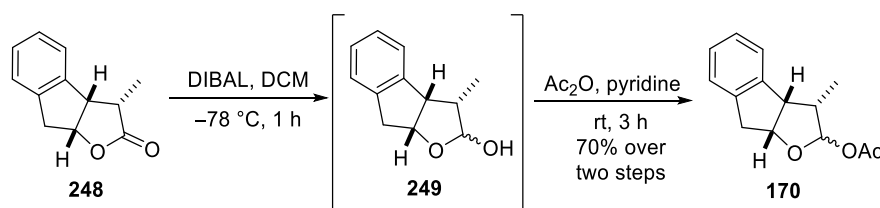
Scheme 3-22 Synthesis of DEFG model **168** (Peng *et al.*, 2016).¹⁷

3.3.2 Synthesis of the DEFG model system **168**¹⁷Figure 3-2 DEFG model **168**.

The synthesis of **168** (Figure 3-2) began by first adding 2-indanol (**177**) to 1-methoxyallene (**178**) in the presence of *N*-iodosuccinimide to yield methyl acetal **176** in 80% yield (Scheme 3-23). Substoichiometric, Bu_3SnCl generated radical **245** which underwent a 1,5-H atom abstraction to generate the more stable benzyl radical **246**. The cyclisation of **246** likely occurs through chair like transition states **A** (major) and boat like transition state **B** (minor).¹⁶⁸ The alkene functionality is attacked in a 5-*exo-trig* fashion to give a crude mixture of tricycle **247** (minor product *via* transition state **B**) and *epi-247* (major product *via* transition state **A**, 1:2 mixture at C-2). Finally, direct oxidation to the lactone proceeded smoothly, generating **248** (16% yield over two steps) and *epi-248* (32% over two steps, Scheme 3-23).

Scheme 3-23 Synthesis of lactone **248**.

Lactone **248** was then reduced to the lactol **249** which was acetylated *in situ* to form the acetate **170**, thereby providing a substrate for addition of silyloxyfuran **6** (Scheme 3-24).

Scheme 3-24 Synthesis of the acetate **170**.

The Mukaiyama aldol reaction was next performed to install the G ring using compound **170**. It was found that the literature reaction conditions with $\text{Bi}(\text{OTf})_3$ gave 45% of the desired DEFG system **168**, with 35% of diastereomer **250** and 15% of diastereomer **251** (Table 3-4, entry 1). The stereochemical assignment, for **168** was done by comparing the ^1H and ^{13}C NMR data with the literature report.¹⁷ Changing the Lewis acid only had adverse effects on to the reaction (Table 3-4, entries 2-6) with only $\text{Zn}(\text{OTf})_3$ achieving a moderate yield of **168** (Table 3-4, entry 6). Moreover, switching the solvent from acetonitrile to dichloromethane led to a fall in yield of **168** to only 15%. With these results in hand, it was decided that the reported conditions were by far the best conditions for installing the G ring on such molecules.

Table 3-4 Installation of the G ring to the DEF model **170**.

		Yield (%)		
Entry	Conditions ^{a,b}	168	250	251
1	2 eq $\text{Bi}(\text{OTf})_3$, MeCN, $-40\text{ }^\circ\text{C}$	45 ^c	35	14
2	5 eq $\text{BF}_3\cdot\text{OEt}_2$, MeCN, 3.5 eq. 6 , $-15\text{ }^\circ\text{C}$	31	21	11
3	2 eq ZnCl_2 , MeCN, $-40\text{ }^\circ\text{C}$	Decomposition		
4	2 eq TMSOTf, MeCN, $-40\text{ }^\circ\text{C}$	31	21	12
5	2 eq $\text{Sc}(\text{OTf})_3$, MeCN, $-40\text{ }^\circ\text{C}$	31	23	10
6	2 eq $\text{Zn}(\text{OTf})_2$, MeCN, $-40\text{ }^\circ\text{C}$	36	24	11
7	2 eq $\text{Bi}(\text{OTf})_3$, DCM, $-40\text{ }^\circ\text{C}$	15	unknown	8

^aAll reactions ran for 1 h and the yields were calculated using ^1H NMR spectroscopy and 2,3,5,6-tetrachloronitrobenzene. ^b 1.5 eq of **6** was used unless stated otherwise. ^c Isolated yield was 38%.

3.4 CDEFG model system 169

With the reaction conditions optimised on CDE model **167** and DEFG model **168**, we focused our attention towards applying this knowledge to our most complicated model system; CDEFG model **169** (Figure 3-5).

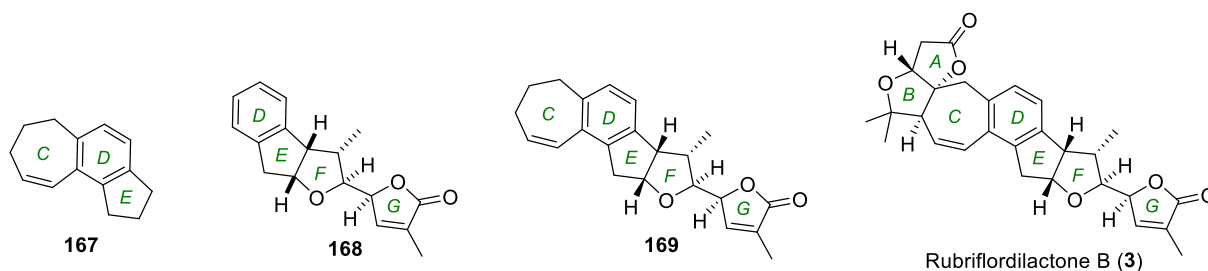
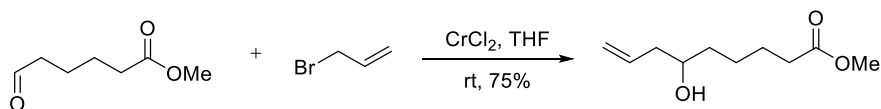


Figure 3-5 Model systems of rubriflorldilactone B.

3.4.1 The Nozaki-Hiyama-Kishi (NHK) reaction

Reactions which create new C–C bonds are central to synthetic organic chemistry. Organomagnesium, organolithium and organocopper reagents have been extensively used for creating new C–C bonds with carbonyls; however, a lack of stereo- and chemoselectivity, harsh reaction conditions or inherent basicity of these reagents limit their widespread application at the later stages of target-oriented synthesis with complex molecular architectures. In 1977, Nozaki and Hiyama *et al.* discovered a mild CrCl_2 -mediated “Barbier type” coupling of aldehydes and allyl halides (Scheme 3-25).¹⁶⁹ In subsequent years, the substrate scope has expanded to include allyl-, alkenyl-, alkynyl-, propargyl-, and aryl halides or sulfonates under aprotic conditions thereby significantly increasing the applicability of this reaction.^{169–173}

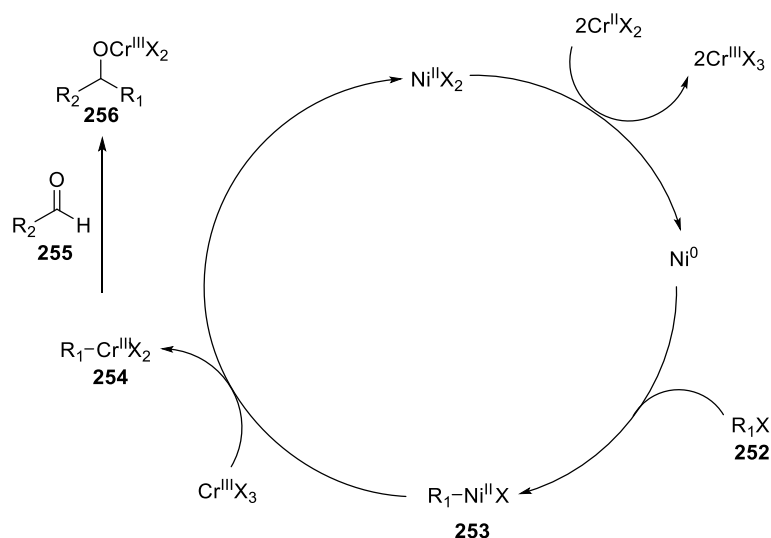


Scheme 3-25 Aldehyde allylation using allyl bromide (Nozaki and Hiyama, 1977).¹⁶⁹

The efficiency of the reaction was found to depend on the batch of chromium salt used. In 1986, Kishi *et al.*¹⁷⁴ and Nozaki *et al.*¹⁷⁵ independently discovered the catalytic effect that traces of NiCl_2 impart on the coupling. This discovery made this reaction much more versatile and robust, and it has become

common practice to add traces of Ni(II)-salts to the less reactive substrates. However, care is taken not to have too much Ni(II) as that leads to dimerisation of the halide substrate.

Mechanistically, the Ni^{II} salt is reduced to Ni⁰ by Cr^{II} salts, which *in turn* is oxidised to a Cr^{III} species (Scheme 3-26). The halide coupling partner **252** then undergoes oxidative addition with the Ni⁰ forming an organonickel intermediate **253**. Next, a transmetalation reaction between species **253** and the Cr^{III} species takes place generating organochromium compound **254**. This species acts as the nucleophile and adds to the carbonyl electrophile **255** to form compound **256** (Scheme 3-26).

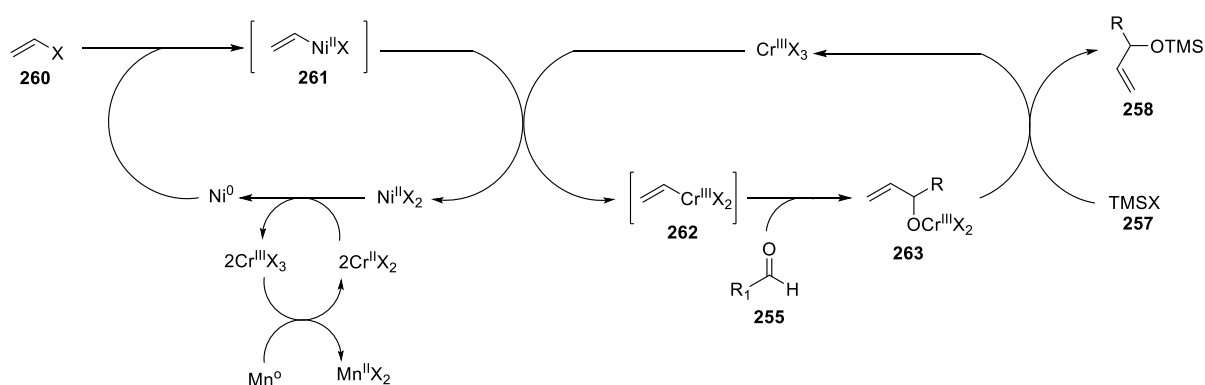


Scheme 3-26 Mechanism of Ni-catalysed Nozaki-Hiyama-Kishi reaction.

The NHK reaction has been widely used for close to four decades, and the field has been regularly reviewed.^{176–181} Asymmetric versions of the reaction are also known¹⁸¹ and both the enantioselective and non-enantioselective versions have found extensive applications in the field of natural product synthesis.¹⁸⁰ The main reasons behind the popularity of the NHK reaction are a) magnificent chemoselectivity towards the addition to the aldehydes over ketones; b) exquisite compatibility with a large variety of functional groups on both coupling partners; c) neutrality of the organochromium reagent making their application with sensitive substrates feasible; d) a high driving force for the addition reaction owing to the formation of strong O–Cr(III) bond thereby making the synthesis of strained molecules feasible; e) predictable stereochemical outcome *e.g.* allyl chromium reagents forms anti-adduct irrespective of the halide geometry, and disubstituted alkenes reacts with complete retention of the alkene geometry.

Despite these advantages, there are still a few disadvantages associated with the NHK reaction. These include a) the necessity of using super-stoichiometric amounts of chromium salts; b) adverse physiological effect associated with chromium and nickel salts and c) the relatively high cost of these salts. These above disadvantages have led to the limited applications of the NHK reaction in industrial settings.

Some advances have nonetheless been made to overcome these problems, most notably the report by Fürstner¹⁷⁹ which made the reaction catalytic with respect to the chromium salt by utilising Mn^0 as a stoichiometric co-oxidant (Scheme 3-27). In this report, trimethylsilyl halide **257** was used to release Cr^{III} from the product **263**, since silicon is more oxophilic than Cr^{III} .

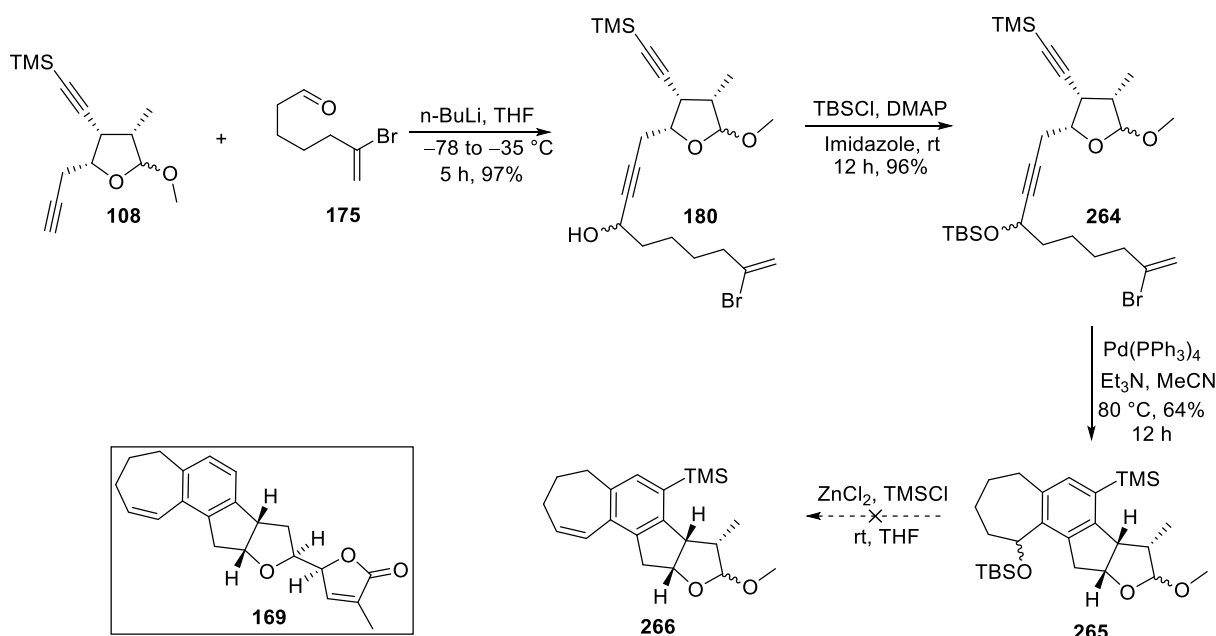


Scheme 3-27 Mechanism of the Fürstner variant of Nozaki-Hiyama-Kishi reaction (catalytic in chromium).¹⁷⁹

The reaction duplicates Scheme 3-26 upto the addition of **262** to the aldehyde **255** to form **263** (Scheme 3-27). The Cr^{III} is then released from the product **263** using TMS halide **257** forming **258** (Scheme 3-27). The released Cr^{III} is then again reduced back to Cr^{II} by making use of Mn^0 reductant.

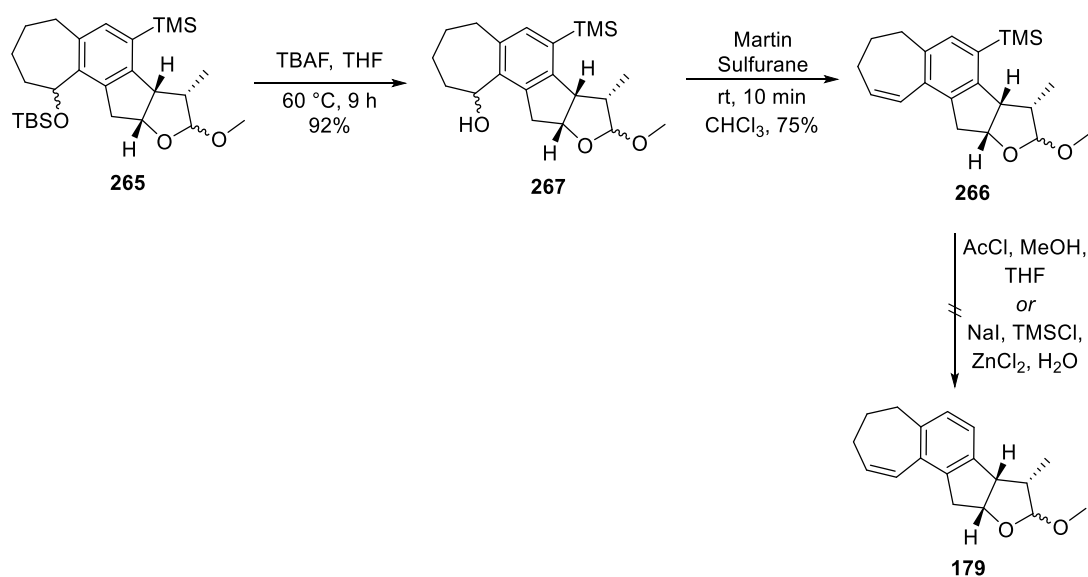
3.4.2 Synthesis of the CDEFG model system 169

Efforts towards **169** started with the synthesis of enediyne **180** (for the Pd-catalysed route) and triyne **181** (for the Rh-catalysed route). The synthesis of **180** began with deprotonation of diyne **108**, followed by addition to aldehyde **175** to give **180** (97% yield, Scheme 3-28). The alcohol was silylated using TBSCl to afford **264**, setting up the key Pd-catalysed cascade cyclisation. Pleasingly, the previously optimised conditions for the cyclisations could be directly translated to substrate **264**, assembling CDEF core **265** in 64% yield in a single transformation. However, attempts to promote elimination of **265** to obtain **266**, using the conditions optimised in the CDE model, proved futile.



Scheme 3-28 Attempted synthesis of alkene **266**.

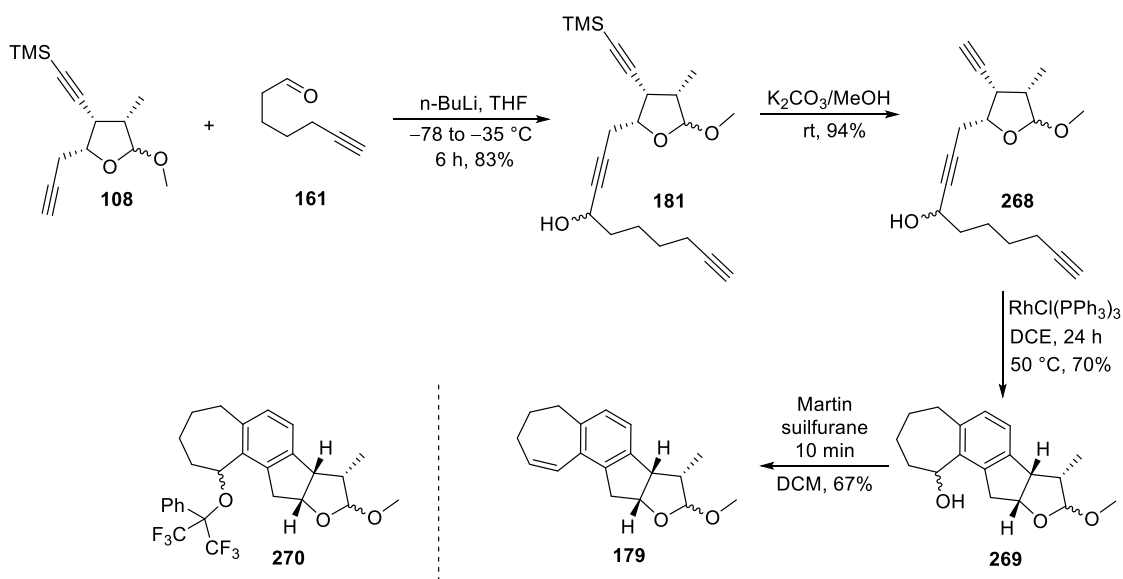
To facilitate the elimination, it was then decided to carry out TBS deprotection of **265** to the alcohol **267** (Scheme 3-29). Burgess reagent, which worked well in the CDE model, did not effect the elimination, but to our delight, Martin sulfurane was able to promote the elimination to create alkene **266**. Unfortunately, when **266** was subjected to the previously optimised protodesilylation conditions, decomposition occurred and we were unable to synthesise **179** (Scheme 3-29).



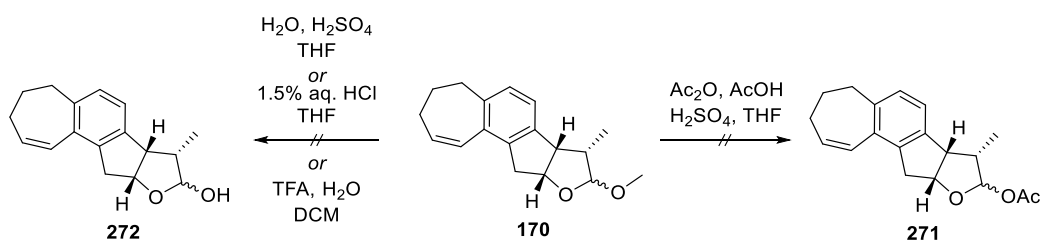
Scheme 3-29 Attempted synthesis of alkene **179**.

At this point, the attempts with the Pd-catalysed cascade cyclisation route ceased, and efforts were instead focused towards the [2+2+2] cyclotrimerisation route. At the outset, a few advantages offered by the latter route were identified; Firstly, the propargylic alcohol is tolerated in the [2+2+2] cyclotrimerisation, avoiding the need for additional silylation/desilylation steps. More crucially, as terminal alkynes are tolerated in this reaction, the alkynyl TMS group could be removed before carrying out the cycloaddition, thus circumventing the need to carry out a more difficult protodesilylation of the aromatic **D** ring.

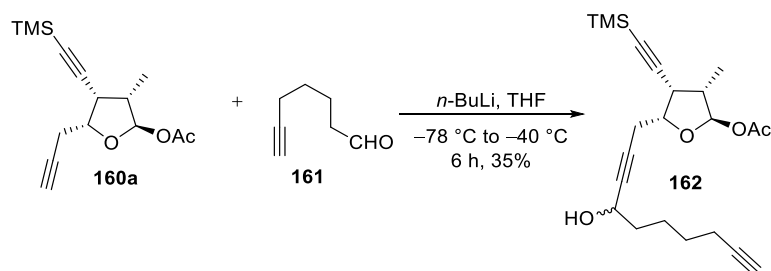
This route began with addition of diyne **108** to the aldehyde **161** to generate triyne **181**, which was then desilylated to form **268** in quantitative yield (Scheme 3-30). Triyne **268** was then subjected to the previously optimised conditions for the Rh-catalysed [2+2+2] cyclotrimerisation reaction. To our delight, CDEF core alcohol **269** was obtained successfully which, on treatment with Martin sulfurane, formed the CDEF fragment **179** in good yield along with a small amount of substitution product **270** (Scheme 3-30).

Scheme 3-30 Synthesis of the alkene **179**.

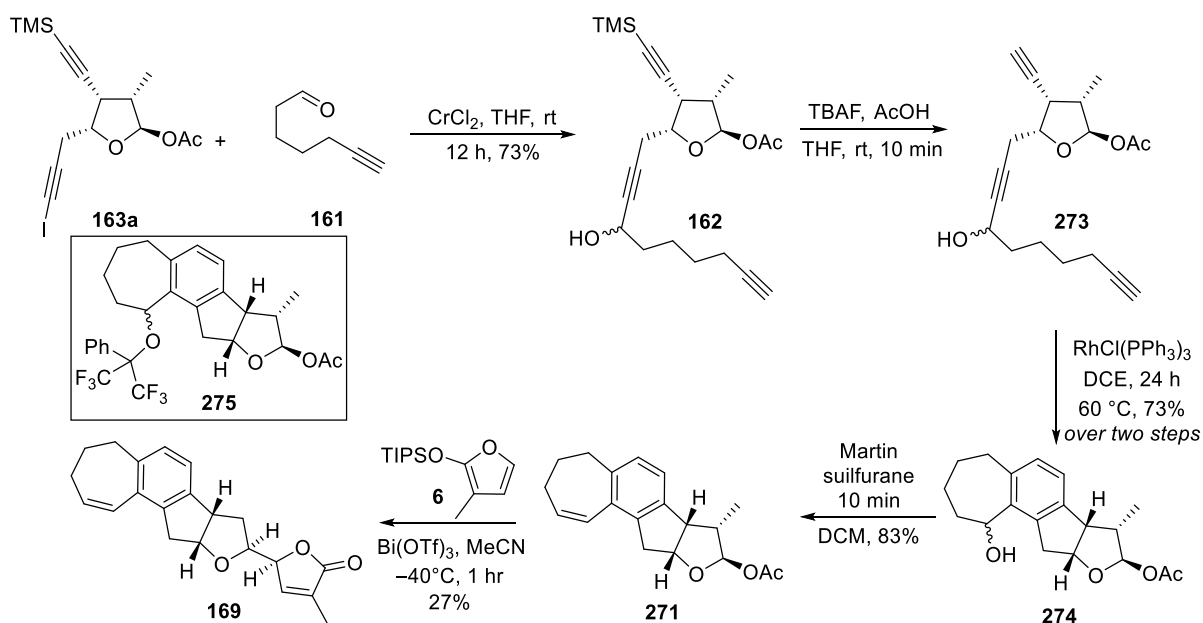
Next, attempts were made to convert the methyl acetal **179** to the acetate **271**. Unfortunately a one-pot acetylation protocol¹⁸² led, only to decomposition (Scheme 3-31), as did attempted hydrolysis of methyl acetal **170** to lactol **272** (using TFA¹⁴, H₂SO₄/H₂O and aq. HCl).

Scheme 3-31 Attempted acetylation or hydrolysis of the alkene **179**.

To overcome the late-stage functionality switch, it was first decided to use **160a** where the acetate functionality was pre-installed before performing the addition reaction to the aldehyde **161**. As mentioned in section 2.2.6, the direct deprotonation/addition of **160a** to **161** proved inefficient (Scheme 3-32), and thus it was decided to use the NHK reaction with alkynyl iodide **163a**.

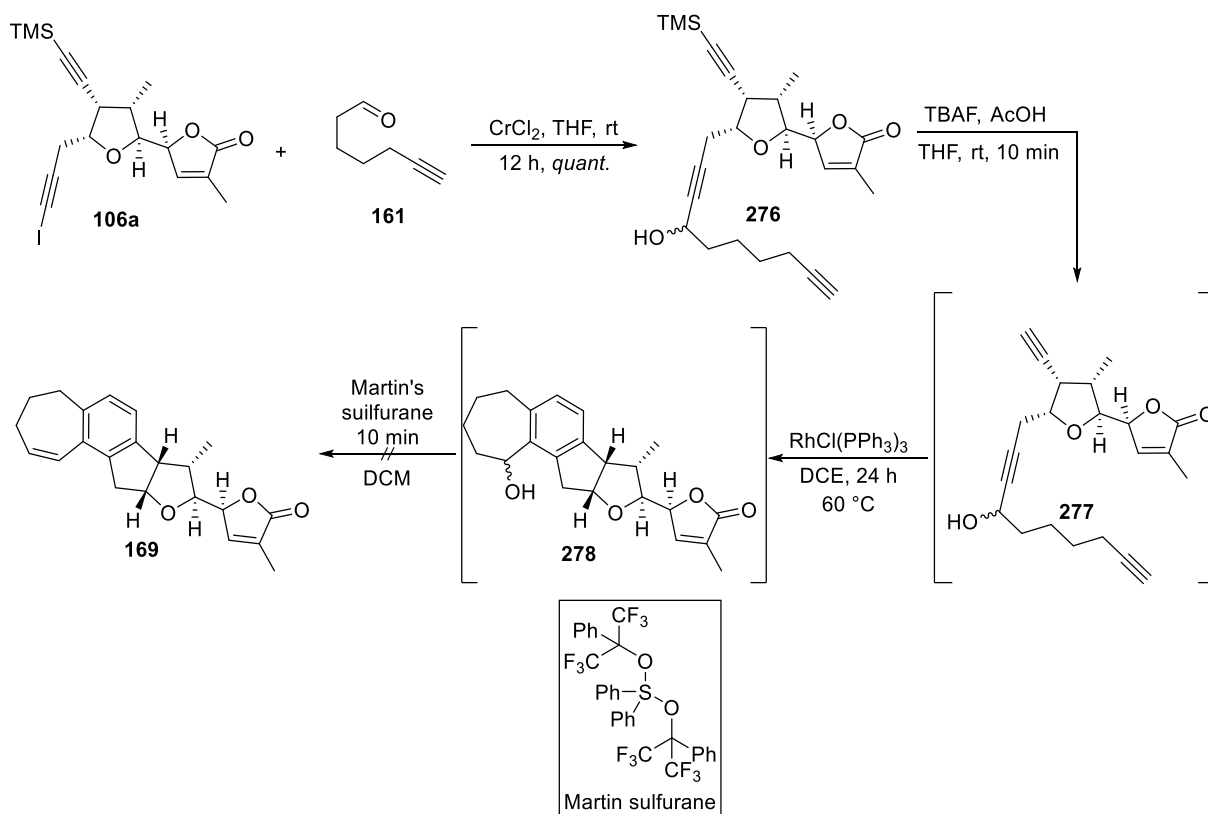
Scheme 3-32 Attempted addition of **160a** to **161**.

Gratifyingly, the NHK reaction worked very well giving us access to the triyne **162** in good yield (Scheme 3-33). Triyne **162** was then desilylated to afford the terminal alkyne **273**. It should be noted that the addition of acetic acid was crucial for moderating the basicity of the fluoride ions, and its absence resulted in significant decomposition. The optimised conditions for the [2+2+2]-cyclootrimerisation reaction were translated effectively to **273**, thus affording the CDEF alcohol **274**, which underwent elimination using Martin sulfurane to give compound **271** along with a small amount of the substitution product **275**. Finally, **169** was obtained through Bi-catalysed addition of **6** to **271** in 27% yield (Scheme 3-33).

Scheme 3-33 Synthesis of CDEFG fragment **169**.

Before progressing with synthesis to the rubriflorldilactone **B** (**3**), the possibility of installing the G ring before the NHK reaction was also explored. In pursuit to this end, the NHK reaction was performed with the iodide **106a** and aldehyde **161**, which afforded triyne **276** (Scheme 3-34). The desilylation to **277** followed by [2+2+2] cyclootrimerisation reaction, to give **278**, was monitored using ^1H NMR

spectroscopy and the presumed product was indeed observed. Unfortunately, attempted dehydration using Martin sulfurane led only to decomposition, and no CDEFG fragment **169** was seen.



Scheme 3-34 Synthesis of the CDEFG model **169** from **106a**.

With these experiments, our model studies were concluded. The key insights gained through these experiments were:

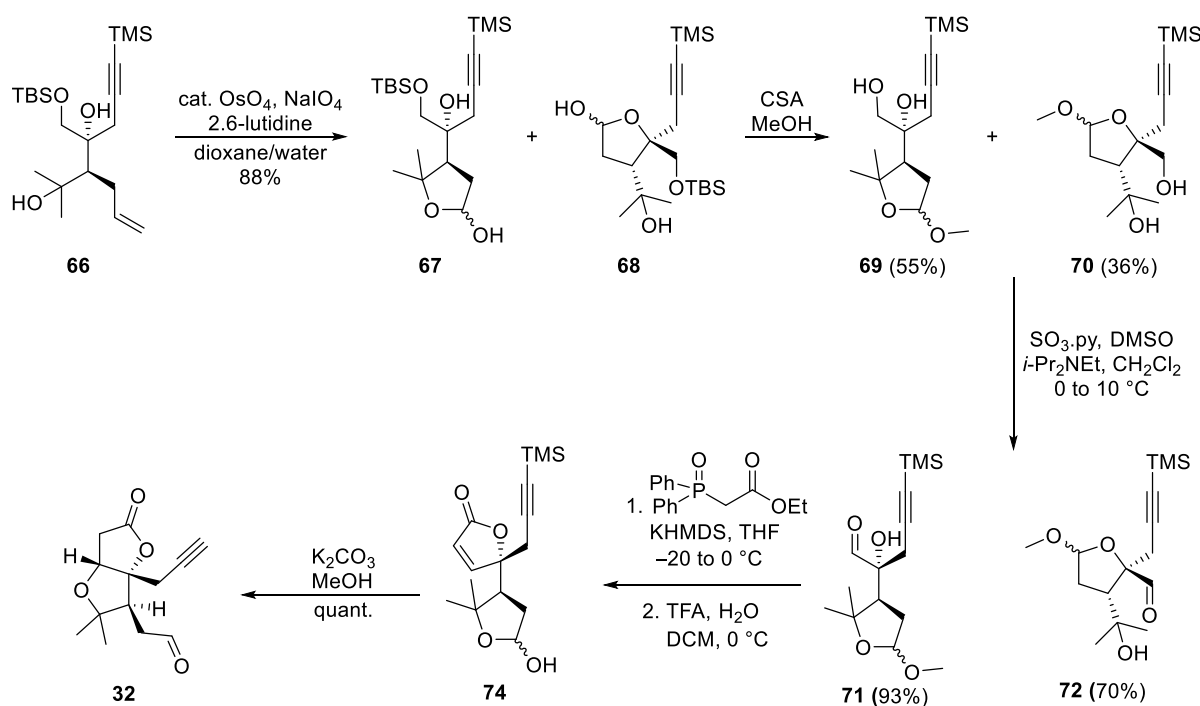
- a. Both Pd and Rh catalysis could be used to generate the central CDE core of the rubriflordilactone B. However, Rh-catalysed [2+2+2] cycloaddition reaction is preferred over the Pd-catalysed cascade cyclisation for more complex substrates due to the decrease in step count and lack of harsh reaction conditions at the late stage of the synthesis.
- b. Installation of the G ring is feasible through a Bi(OTf)₃-mediated addition of the furan **6**.
- c. G ring could potentially be installed before the NHK reaction to give **106a** making the synthesis more convergent. Moreover, this would circumvent the need to have a low yielding Mukaiyama aldol type reaction at the end of the synthesis. However, to pursue this strategy, alternative dehydration conditions would be required due to the apparent incompatibility of the optimised conditions with the G ring.
- d. NHK reactions could potentially be used to couple AB ring aldehyde **32** and iodoalkyne **163a/b** or **106a**.

These insights were incorporated in the overall strategy, and the synthesis moved towards assembling rubriflordilactone B, as described in Chapter 4.

4. Synthesis of rubriflordilactone B (3) and C-23 *epi*-rubriflordilactone B (*epi*-3)

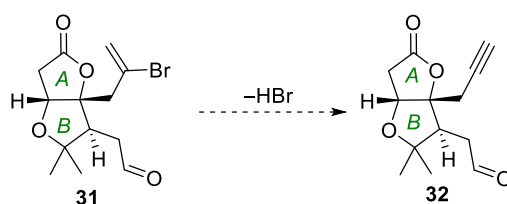
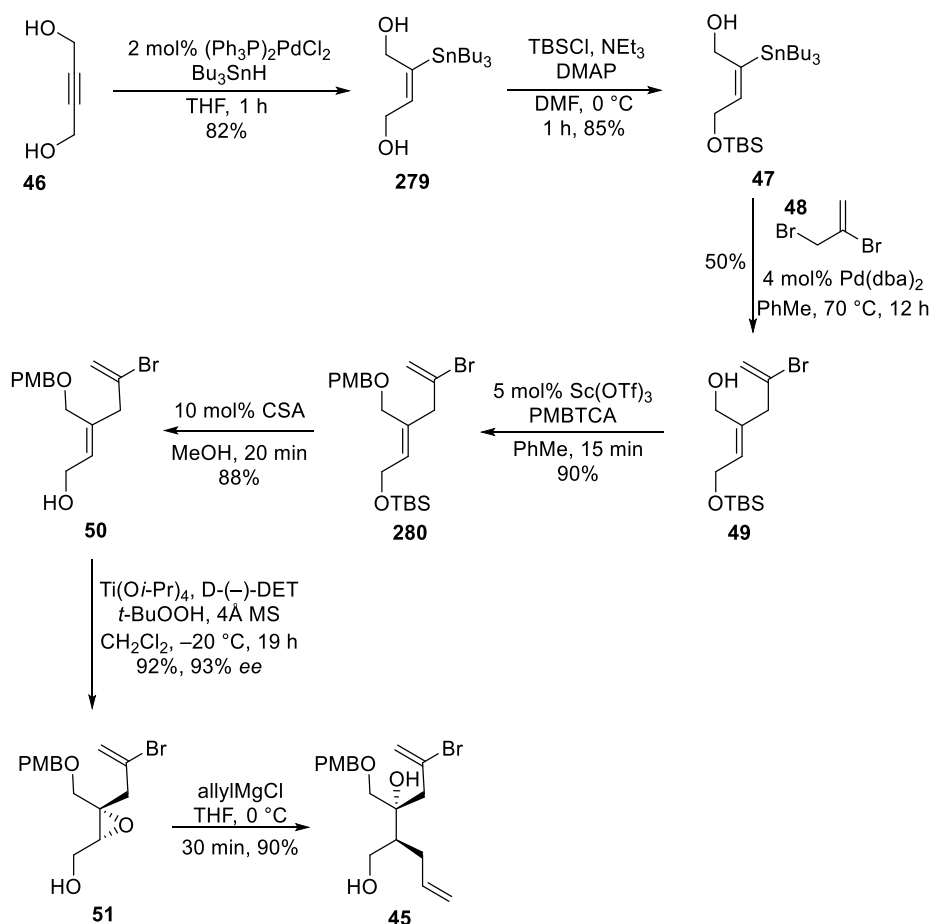
4.1 Synthesis of the AB ring aldehyde 32

Based on the model studies described in chapter 3, attention was turned towards the use of AB ring aldehyde **32**. A synthetic approach to obtain the AB ring aldehyde has previously been described by our group.⁸ However, there were still a few challenges to be addressed (Scheme 4-1). The generation of regioisomers in the oxidative cleavage of the alcohol **66** was one such problem, as despite the fact that later in the synthesis, compounds **67** and **68** afforded a common intermediate **74** (Scheme 4-1), the synthetic divergence and separation of the isomers posed a bottleneck for rapid access to aldehyde **32**.



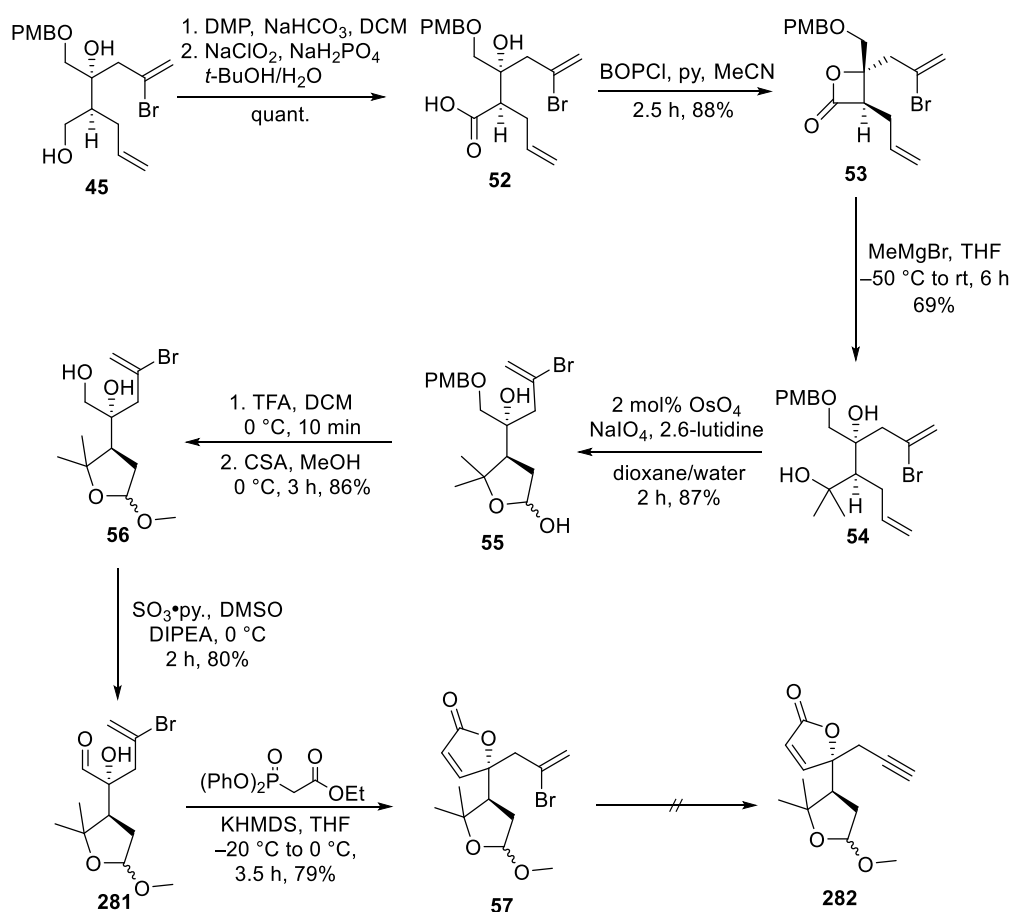
Scheme 4-1 Synthesis of methyl acetals **69** and **70** (Anderson *et al.*, 2015).⁸

In contrast, the route *via* AB ring bromoenal **31** (Scheme 4-2) had no such obstruction, and thus could provide smooth access to the aldehyde **32**.¹⁴ Since, the bromoene moiety in **31** could be converted into the alkyne through the elimination of HBr, either at the AB ring aldehyde stage (Scheme 4-2) or *en route*, thus, it was decided to modify the overall sequence to access aldehyde **32**.

Scheme 4-2 planned conversion of **31** to **32**.Scheme 4-3 Synthesis of alcohol **45**.

Synthesis of the AB ring aldehyde **32** commenced with hydrostannation of 1,4-but-2-yne-1,4-diol (**46**) to stannane **279** in 82% yield (Scheme 4-3).³⁹ Mono TBS protection led to the formation of **47** (85%). Next, Stille coupling of **47** with the dibromide **48** afforded 50% of bromoene **49**.⁴⁰ PMB protection of TBS ether **49** led to compound **280**, which was smoothly converted to the alcohol **50** (88%) by TBS deprotection. Sharpless asymmetric epoxidation⁴¹ delivered epoxide **51** in an excellent 92% yield with 93% *ee* (by HPLC), and a subsequent regioselective ring opening of epoxide **51** with allylmagnesium chloride^{42,43} afforded the diol **45**, also in high yield (90%).

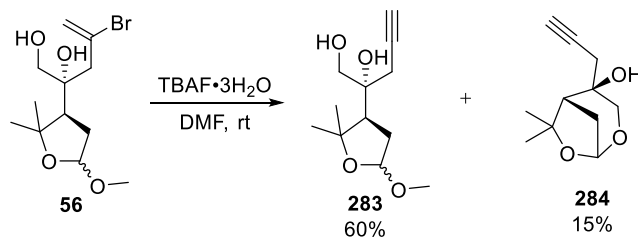
Further transformation of **45** involved Dess-Martin oxidation and Pinnick oxidation (Scheme 4-4) to afford the acid **52** which was converted into the β -lactone **53** upon activation with BOPCl.py. Addition of methylmagnesium bromide to the β -lactone **53** led to the formation of dienol **54** in 69% yield, which then underwent oxidative cleavage to afford the lactol **55**. PMB deprotection under acidic conditions and methyl acetal formation resulted in methyl acetal **56**. Oxidation of the primary alcohol in **56** furnished aldehyde **281** which was further subjected to a Z-selective HWE reaction using Ando phosphonate,⁴⁴ thereby affording the methyl acetal **57**. At this stage, attempts were made to eliminate HBr group and form alkyne **282**. Unfortunately all reactions (using TBAF,¹⁸³ KO^tBu¹⁸⁴ and LiHMDS) only led to the decomposition of starting material.



Scheme 4-4 Attempted synthesis of **282**.

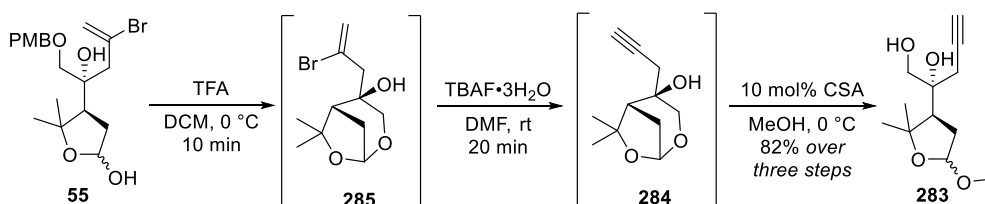
Unperturbed by this failure to convert **57** to **282**, we decided to look for an optimal substrate along the route to unmask the bromoene moiety and furnish the alkyne. To our delight, on treating **56** with TBAF, formation of the alkyne **283** was observed along with the bicycle **284** (Scheme 4-5), which could have formed from attack of the primary alcohol on to an oxacarbenium ion intermediate generated from the

methyl acetal moiety. **284** could be converted into **283** by subjecting it to the acidic methanolic conditions (Scheme 4-6).



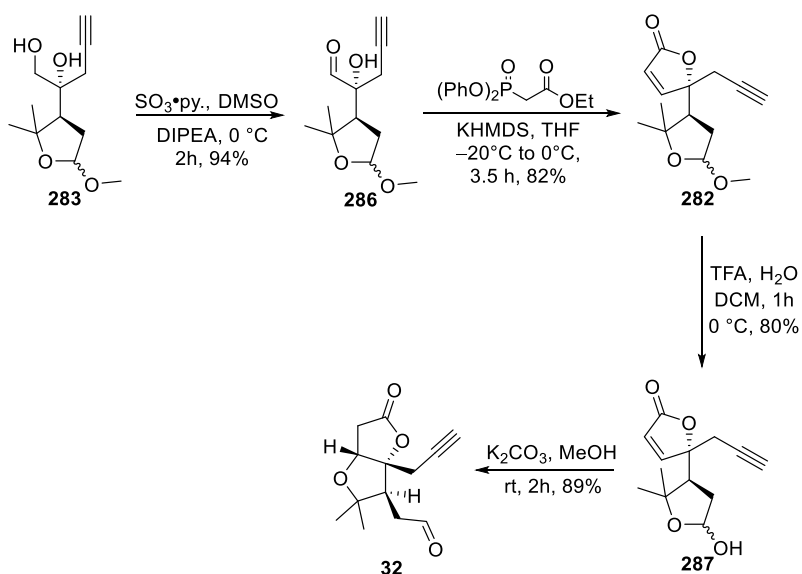
Scheme 4-5 Attempted elimination reaction on **56**.

Yield of **283** were further improved by subjecting intermediate **285** to the elimination conditions resulting in the formation of **284**, which under acidic conditions led to the formation of **283** in 82% yield over three steps (Scheme 4-6).



Scheme 4-6 Elimination reaction to synthesise **283**.

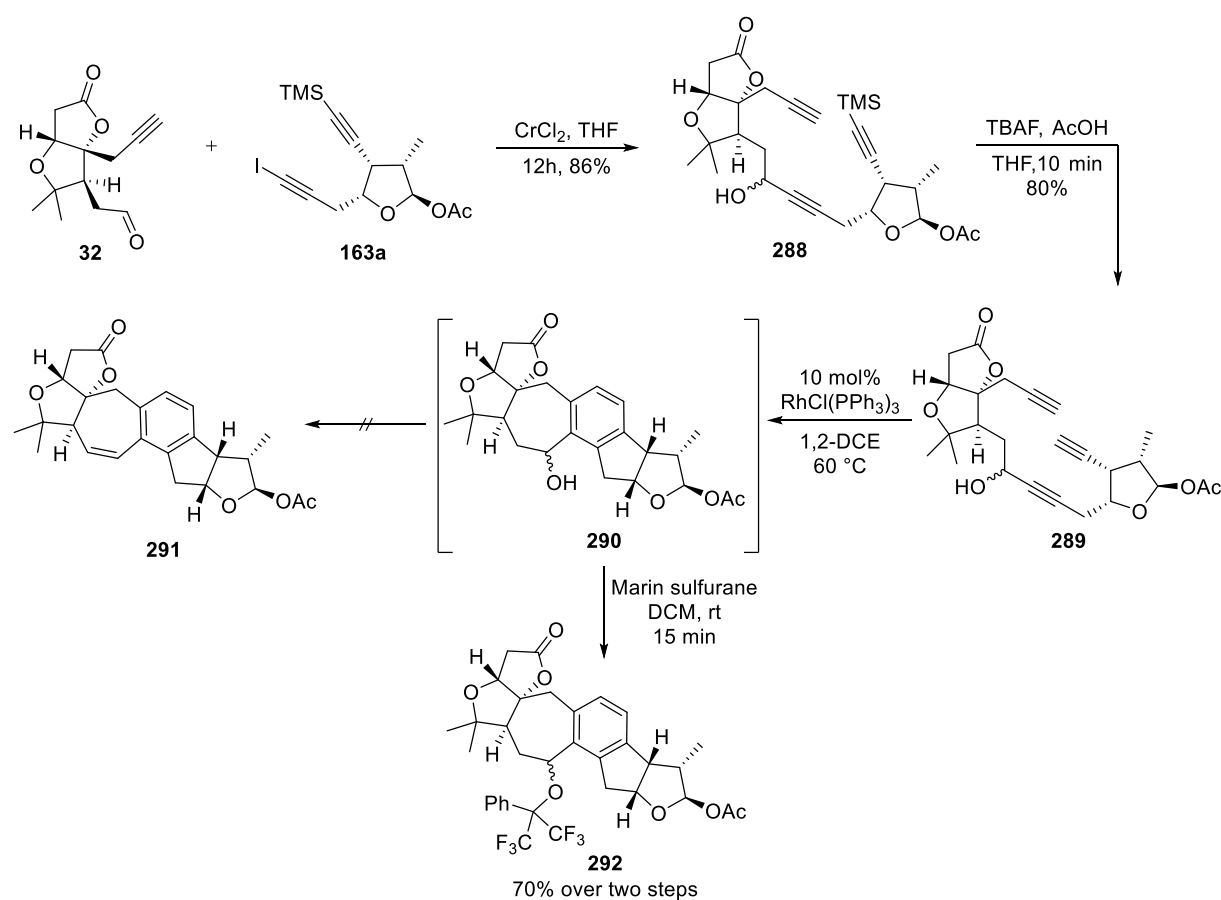
Alcohol **283** was then oxidised to the aldehyde **286** in 94% yield (Scheme 4-7). Subsequent *Z*-selective HWE reaction also led to the formation of the lactone **282** in excellent yield. Finally, hydrolysis of the methyl acetal moiety followed by an intramolecular Michael addition furnished AB ring aldehyde **32**.



Scheme 4-7 Synthesis of AB ring aldehyde **32**.

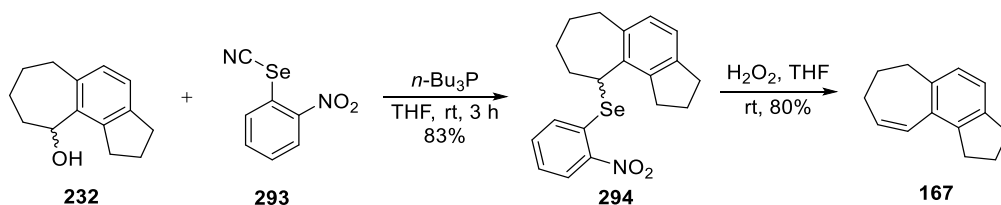
4.2 Synthesis of rubriflordilactone B (**3**) and *epi*-rubriflordilactone B (*epi*-**3**) with **163a** coupling partner

With both the AB ring aldehyde **32** and diyne fragment **163a** in hand, the stage was set for the Nozaki-Hiyama-Kishi (NHK) coupling reaction between the fragments. This coupling proceeded smoothly to give rise to **288**, which on desilylation furnished the triyne **289** (Scheme 4-8). Next, **289** was then subjected to the previously described Rh-catalysed [2+2+2] cyclotrimerisation reaction conditions (Chapter 3), with only 10 mol% catalyst loading. To our delight, the cyclotrimerisation reaction proceeded without any problem to form compound **290**. It should be noted that the residual catalyst co-eluted with the alcohol **290** and thus the reaction mixture was treated without purification with Martin sulfurane to mediate dehydration. Unfortunately, elimination product **291** was not observed, and only the rather surprising substitution product **292** was seen towards the end of the reaction (Scheme 4-8).



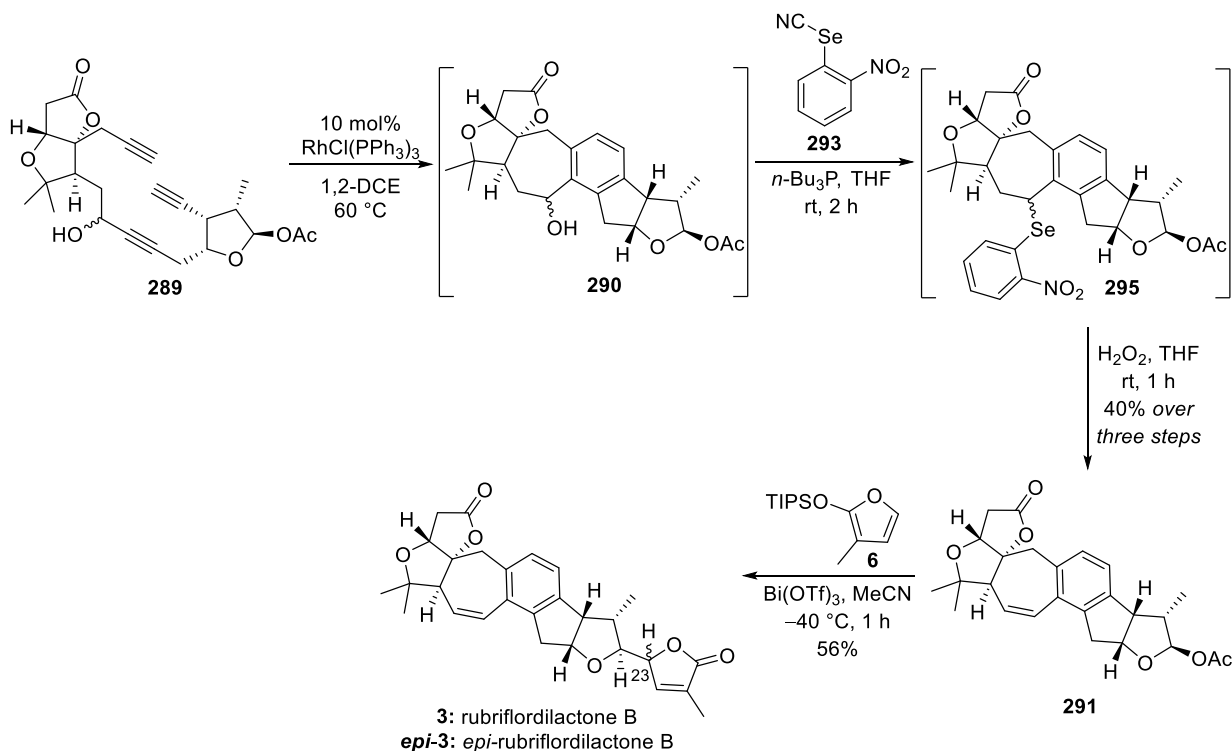
Scheme 4-8 Attempted synthesis of **291**.

The elimination reaction on the CDE model system, was therefore, revisited and a mild two-step dehydration reaction, pioneered by Grieco¹⁸⁵ and Sharpless¹⁸⁶ was attempted. Delightfully, treatment of the alcohol **232**, with *o*-nitrophenylselenocyanate (**293**) formed the selenide **294**, which on stirring with 30% w/w H₂O₂ led to the alkene **167** (Scheme 4-9).



Scheme 4-9 Grieco elimination of the CDE model **232**.

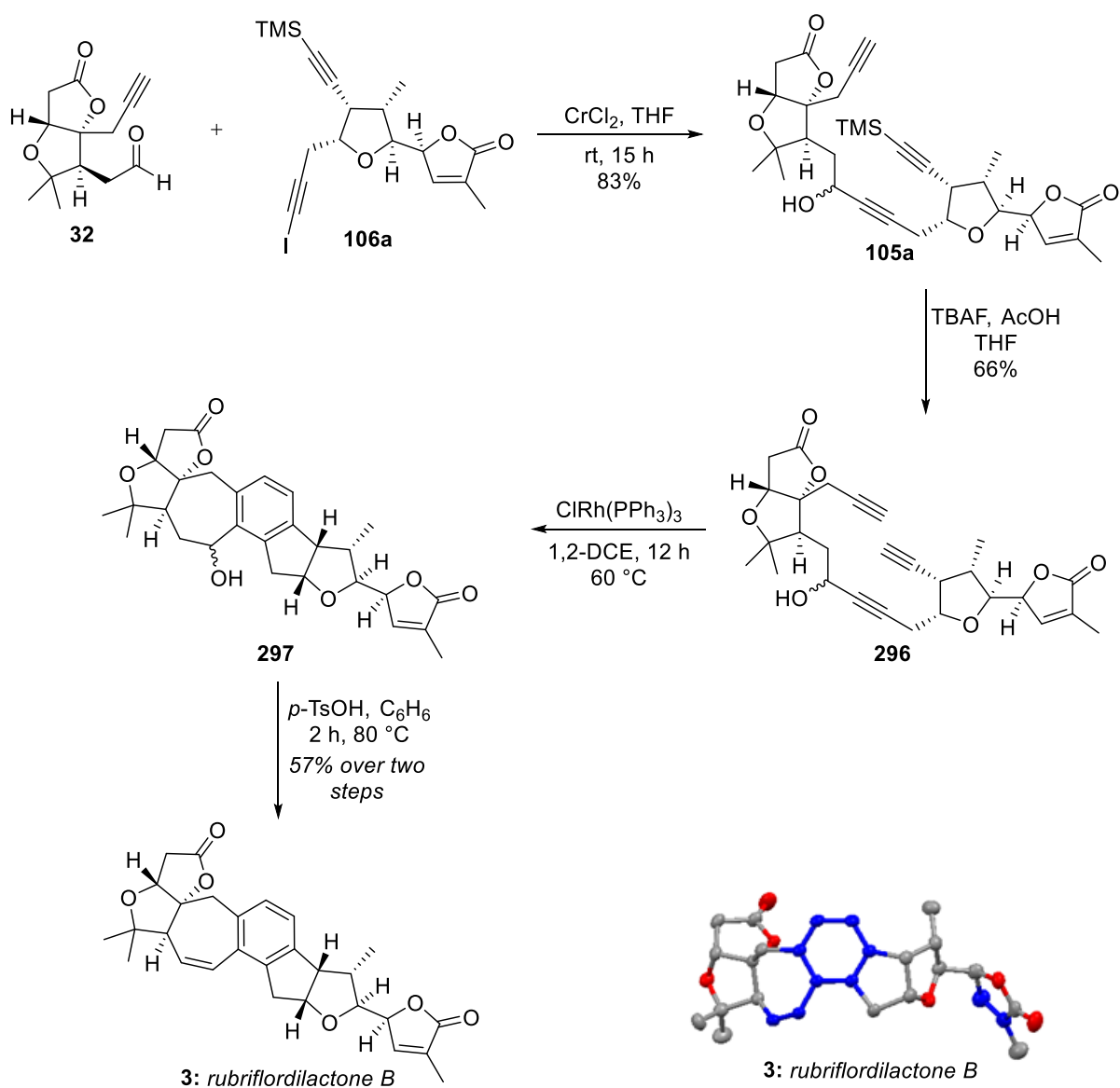
These conditions translated reasonably well to the substrate **290**, forming alkene **291** *via* selenide intermediate **295** (40% over 3 steps, Scheme 4-10). Finally, silyloxyfuran **6** was added to **291** to afford rubriflordinolactone B (**3**), as an inseparable 1:1 mixture with C-23 *epi*-rubriflordinolactone B (*epi*-**3**). Attempts to separate the diastereomers using HPLC were unsuccessful urging us to look at the alternative strategies to get diastereomerically pure **3**.



Scheme 4-10 Synthesis of rubriflordinolactone B (**3**) and *epi*-rubriflordinolactone B (*epi*-**3**).

4.3 Synthesis of diastereomerically pure rubriflordilactone B (**3**) using coupling partner **106a**

Although we were pleased to complete the synthesis of rubriflordilactone B (**3**), the in-separability of **3** and *epi*-**3** encouraged us to look at the early installation of the G ring. Iodide **106a** was regarded as an alternative partner for the NHK reaction with aldehyde **32**, and they indeed coupled to form **105a** in excellent yield (Scheme 4-11). The subsequent desilylation generated triyne **296**, thereby setting up the [2+2+2] cycloaddition reaction. It is worth mentioning that a successful [2+2+2] cycloaddition would afford the full ABCDEFG framework **297**, only a dehydration step away from **3**. Gratifyingly, the Rh-catalysed cyclotrimerisation reaction of triyne **296** proceeded smoothly to generate the ABCDEFG framework **297**, and on subsequent PTSA-catalysed dehydration (which was deemed to be superior to Greico elimination due to higher yield and lower step count) finally led to rubriflordilactone B (**3**) in 57% yield over two steps (Scheme 4-11).



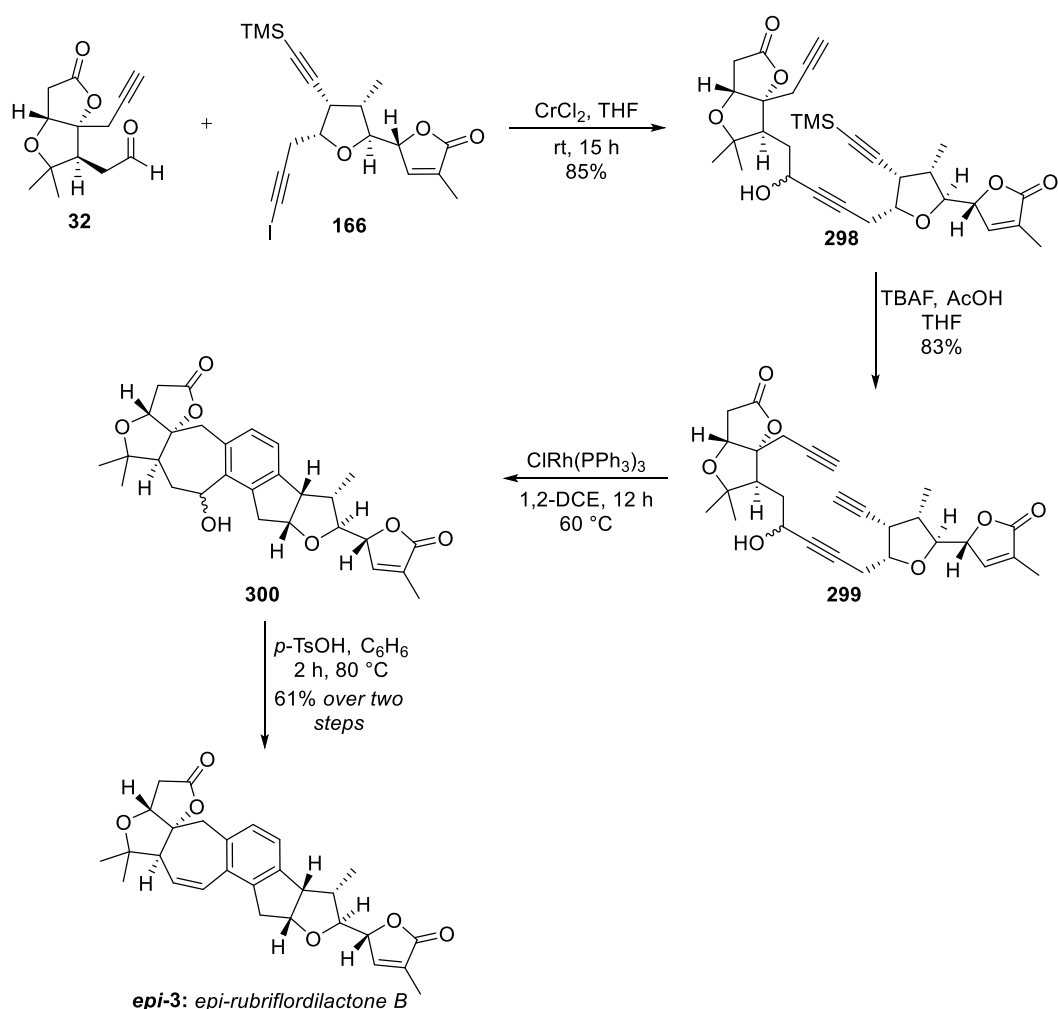
Scheme 4-11 Synthesis of rubriflordilactone B (3).

The structure of rubriflordilactone B was confirmed using single crystal X-ray diffraction (Scheme 4-11), confirming the relative and absolute stereochemistry in the molecule.ⁱ

ⁱ The crystal was developed by the author and the X-ray analysis was done by Steven J. Mansfield, a D. Phil. student in the Anderson group.

4.4 Synthesis of diastereomerically pure *epi*-rubriflordilactone B (*epi*-3) using 166 as coupling partner

Following the successful synthesis of diastereomerically pure rubriflordilactone B (**3**), we focussed attention towards the C-23 epimer (*epi*-**3**). Similar to the synthesis of **3**, the use of the FG fragment **166** as the halide partner envisioned for the NHK coupling with the aldehyde **32**. Again, the NHK reaction between iodide **166** and aldehyde **32** progressed smoothly, forming fragment **298** in 85% yield. Desilylation afforded the triyne **299** in high yield. Furthermore, the Wilkinson catalyst successfully mediated the [2+2+2] cyclotrimerisation, affording the ABCDEFG core **300** of *epi*-rubriflordilactone B. This underwent PTSA-catalysed dehydration, which concluded the synthesis of *epi*-rubriflordilactone B (*epi*-**3**).

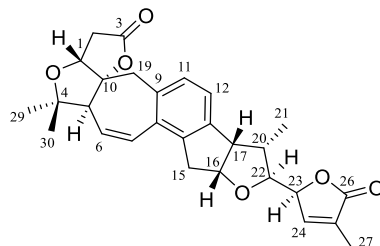


Scheme 4-12 Synthesis of C-23 *epi*-rubriflordilactone B (*epi*-3).

4.5 Comparison of the NMR data of synthetic rubriflordilactone B.

The spectroscopic comparison of the synthetic rubriflordilactone B made by us and the Li group was undertaken. Table 4-1 illustrates the comparison between ^1H NMR spectra of both the samples.

Table 4-1 Comparison of ^1H NMR chemical shifts of synthetic rubriflordilactone B in CDCl_3



3: rubriflordilactone B

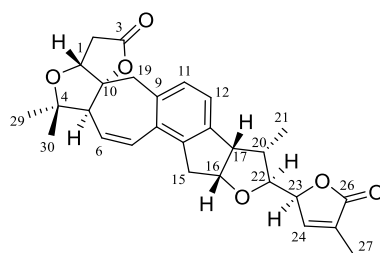
	Li <i>et al.</i> ¹⁰ δ ^1H (ppm, mult, J (Hz)) 600 MHz	Anderson <i>et al.</i> ^a δ ^1H (ppm, mult, J (Hz)) 500 MHz	$\Delta\delta$ (ppm)
1	4.32 (br s)	4.32 (br s)	0.00
2	3.13–2.63 (m, overlapped)	3.18–2.85 (m, overlapped)	-
5	3.13–2.63 (m, overlapped)	2.83–2.61 (m, overlapped)	0.00
6	5.80 (br s)	5.80 (br s)	0.00
7	6.59 (d, 11.8)	6.59 (d, 11.8)	0.00
11	7.14 (d, 7.6)	7.11 (d, 7.8)	0.03
12	6.96 (d, 7.6)	6.96 (d, 7.7 Hz)	0.00
15	3.13–2.63 (m, overlapped)	3.18–2.85 (m, overlapped)	-
16	4.91–4.86 (m)	5.01–4.74 (m)	-
17	3.82 (dd, 6.7, 6.7)	3.81 (t, 6.9 Hz)	0.01
19 α	3.13–2.63 (m, overlapped)	3.18–2.85 (m, overlapped)	-
19 β	2.73 (d, 18.4)	2.83–2.61 (m, overlapped)	-
20	3.13–2.63 (m, overlapped)	2.83–2.61 (m, overlapped)	0.00
21	1.25 (d, 6.8)	1.25 (d, 6.9)	0.00
22	3.50 (dd, 9.6, 1.5)	3.50 (dd, J = 9.6, 2.1)	0.00
23	4.91–4.86 (m)	5.01–4.74 (m)	-
24	7.00–6.97 (m)	6.98 (t, 1.7 Hz)	0.00
27	1.95 (dd, 1.6, 1.6)	1.95 (t, 1.8)	0.00
29	1.31–1.08 (m)	1.56 (s)	0.25
30	1.39 (s)	1.39 (br s)	0.00

^a Data were recorded in CDCl_3 on a Bruker AVX 500 MHz spectrometer with a cryoprobe (^1H , ^{13}C , COSY, HSQC, HMBC).

The comparison of the ^1H NMR spectra of synthetic compound **3** shows a high degree of correlation between the data sets except for on H29 where the difference is 0.25 ppm

Table 4-2 represents the comparison between the ^{13}C NMR chemical shifts of our synthetic rubriflordilactone B with the Li group's¹⁰ synthetic sample.

Table S-2 Comparison of ^{13}C NMR chemical shifts of synthetic rubriflordilactone B in CDCl_3



3: rubriflordilactone B

	Li <i>et al.</i> ¹⁰ δ ^{13}C (ppm) 600 MHz	Anderson <i>et al.</i> ^a δ ^{13}C (ppm) 500 MHz	$\Delta\delta$ (ppm)
1	Not visible	Not visible	-
2	41.6	41.6	0.0
3	174.9	174.9	0.0
4	85.3	85.3	0.0
5	59.4	59.5	-0.1
6	128.2	128.2	0.0
7	127.5	127.7	-0.2
8	Not visible	133.0	-
9	142.5	142.5	0.0
10	103.4	103.7	-0.3
11	125.6	125.6	1.0
12	129.2	129.2	0.0
13	139.6	139.6	0.0
14	Not visible	133.0 ^b	-
15	Not visible	39.5	-
16	79.7	79.7	0.0
17	53.9	53.9	0.0
19	35.8	35.8	0.0
20	39.4	39.4	0.0
21	13.2	13.2	0.0
22	82.4	82.4	0.0
23	83.4	83.4	0.0

4. Synthesis of rubriflordilactone B and *epi*-rubriflordilactone B

24	146.5	146.5	0.0
25	130.6	130.6	0.1
26	174.6	174.6	0.0
27	11.0	11.0	0.0
29	28.7	28.6	0.1
30	22.3	22.3	0.0

^a Data were recorded in CDCl₃ on a Bruker AVX 500 MHz spectrometer with a cryoprobe (¹H, ¹³C, COSY, HSQC, HMBC). ^b Identified using HSQC.

Similarly, the comparison of ¹³C NMR spectra of synthetic **3** shows a high degree of correlation between both the samples and there was a negligible variation ($\Delta\delta$) of less than 0.5 ppm between some of the signals.

The NMR spectra of **3** (both ¹H as well as ¹³C) exhibited broadening of some of the signals and some of the ¹³C signals were not visible. This is likely be due to overlapping with existing signals or due to the broadening of the signals attributed to conformational interconversion of the molecule on the NMR timescale.

In summary, this chapter, describes the crucial final steps of our synthesis of rubriflordilactone B (**3**) and C-23 *epi*-rubriflordilactone B (*epi*-**3**). The key highlights of the chapter are:

- a. Rubriflordilactone B (**3**) and *epi*-rubriflordilactone B (*epi*-**3**) were synthesised as a 1:1 mixture using iodide **163a** and aldehyde **32** as the reactants in the key Nozaki-Hiyama-Kishi reaction. The G ring was installed in the final step on to the fragment **291** (Scheme 4-10).
- b. Diastereomerically pure rubriflordilactone B (**3**) was synthesised using the FG fragment iodide **106a** and aldehyde **32** in the Nozaki-Hiyama-Kishi reaction. The highlight of this sequence is the rhodium-catalysed [2+2+2] cycloaddition reaction which formed the ABCDEFG core in a single step (Scheme 4-11). The final dehydration step was facilitated by the PTSA.
- c. Following the same chemical route as **3**, synthesis of *epi*-rubriflordilactone B (*epi*-**3**) involved the FG fragment **166** and aldehyde **32** as the synthons in the Nozaki-Hiyama-Kishi step. Akin to the synthesis of **3**, Wilkinson's catalyst was crucial for generating the ABCDEFG core, and PTSA achieved the dehydration step (Scheme 4-12).

Furthermore, early installation of G ring was deemed to be superior to the late stage installation due to the difficulties in separation of **3** and *epi*-**3** owing to their similar R_f values.

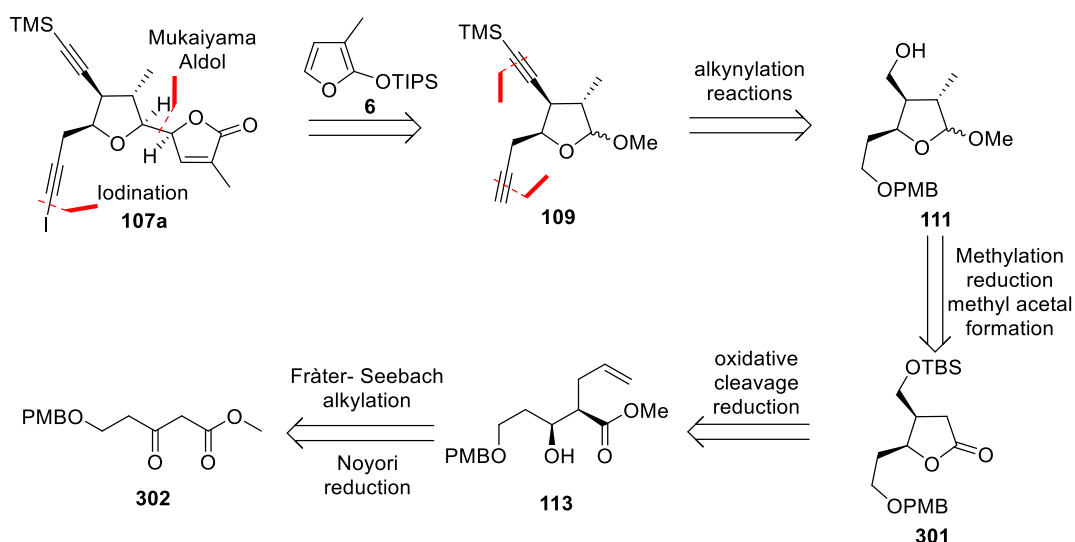
5. Synthesis of *pseudo*-rubriflordilactone B (**4**) and C-23 *epi-pseudo*-rubriflordilactone B (*epi-4*)

After synthesising rubriflordilactone B (**3**) and comparing the NMR spectra with the report by Li group's,¹⁰ we were eager to synthesise *pseudo*-rubriflordilactone B and compare the spectra to the isolated natural product. In doing so we hoped to resolve the confusion surrounding the structure of *pseudo*-rubriflordilactone B.

The synthetic route optimised for the synthesis of rubriflordilactone B (**3**) was now extended to *pseudo*-rubriflordilactone B (**4**) and C-23 *epi-pseudo*-rubriflordilactone B (*epi-4*). A similar order of reactions was envisaged for the transformations following the NHK reaction, however, since the required stereochemical arrangement of the tetrahydrofuran F ring was now not easily installed by Ireland-Claisen rearrangement, a different approach was necessary to access the FG ring fragment **107a**. Dr. Venkaiah Chintalapudi (post-doctoral fellow in the group) and Prof. Jeffrey Carney (visiting academic from Christopher Newport University) helped achieve this part of the project; their efforts are acknowledged at the relevant points in this chapter.

5.1 Retrosynthetic analysis of the FG ring synthon **107a**

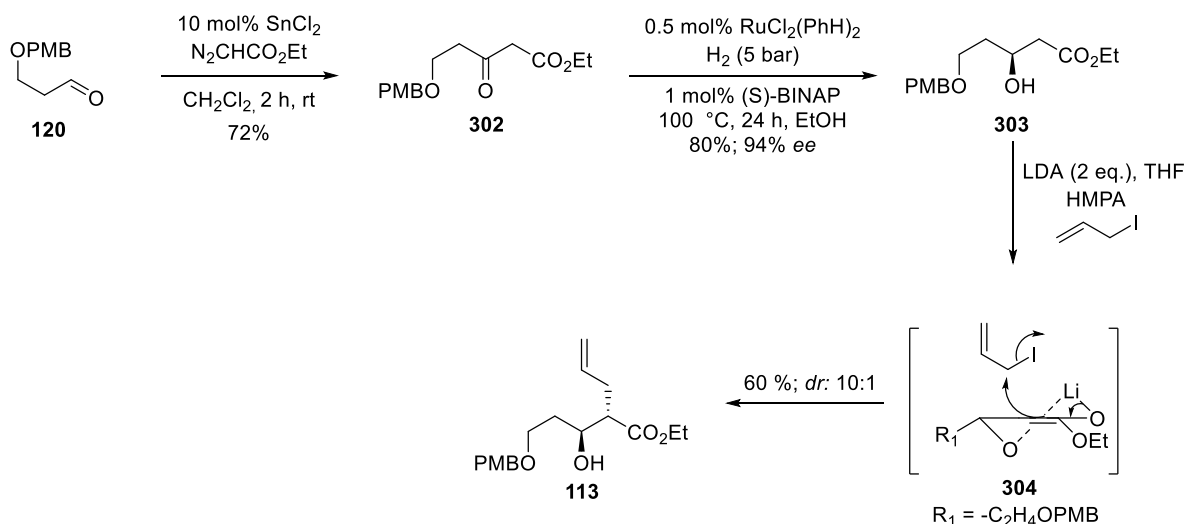
The FG ring diyne **107a** was proposed to arise by the addition of the silyloxyfuran **6** to the oxocarbenium ion generated from diyne **109** (Scheme 5-1). This diyne could be obtained through sequential oxidation and alkynylation reactions on the alcohol **111**, which in turn would arise from a sequence of methylation, reduction and methyl acetal formation on the lactone **301** (Scheme 5-1).

Scheme 5-1 Retrosynthesis of the FG ring fragment **107a**.

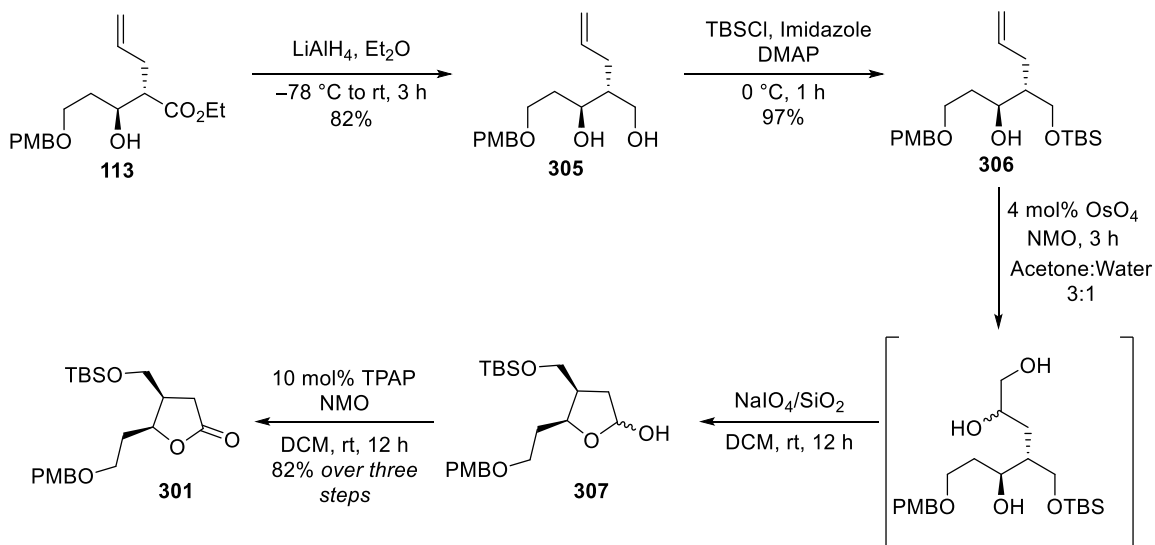
β -hydroxyester **113** could act as a precursor for compound **301** via suitable reaction sequence. Finally, **113** would form through Noyori reduction and Fräter-Seebach alkylation of β -ketoester **302** (Scheme 5-1).

5.2 Synthesis of FG fragment **107a**

The synthesis of the FG ring fragment **107a** began with the known β -hydroxyester **302**. A route to ester **303** had been described by the Maier group for their formal total synthesis of salicylihalamide.¹⁸⁷ The synthesis commenced with the Roskemp chain extension of the aldehyde **120** with ethyl diazoacetate, affording β -ketoester **302** (Scheme 5-2).¹⁸⁸ Noyori reduction of the ketone functionality in **302** afforded **303** in good yield and high *ee* (as determined by Mosher ester analysis).¹⁸⁹ The Fräter-Seebach allylation reaction of **303** gave ester **113** via transition state **304** in 60% yield and good *dr* (Scheme 5-2),^{190,191} with allylation occurring on the less-hindered face.

Scheme 5-2 Synthesis of β -hydroxyester **113**.ⁱ

Next, β -hydroxyester **113** was reduced to the diol **305** (82%), which on TBS protection of the primary alcohol afforded **306** in high yield (Scheme 5-3). The following Upjohn dihydroxylation and oxidative cleavage steps furnished lactol **307** which then underwent a TPAP-catalysed oxidation to form lactone **301** in 82% yield over three steps.

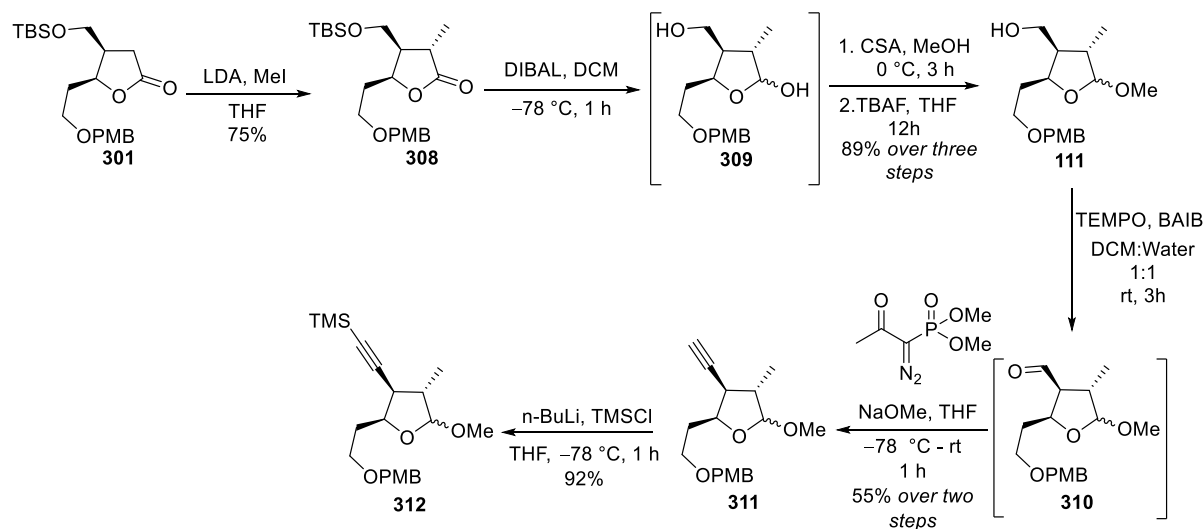
Scheme 5-3 Synthesis of intermediate **301**.ⁱⁱ

Due to the two substituents of **301** being on the same face of the ring, methylation of its enolate gave lactone **308** with good diastereoselectivity (>10:1, Scheme 5-4). Reduction of **308** to the lactol **309**,

ⁱ The work in this scheme was optimised by Dr. Venkaiah Chintalapudi, a post-doctoral fellow in the group, and was reproduced in total by the author.

ⁱⁱ The work in this scheme was optimised by Dr. Venkaiah Chintalapudi, a post-doctoral fellow in the group, and was reproduced in total by the author.

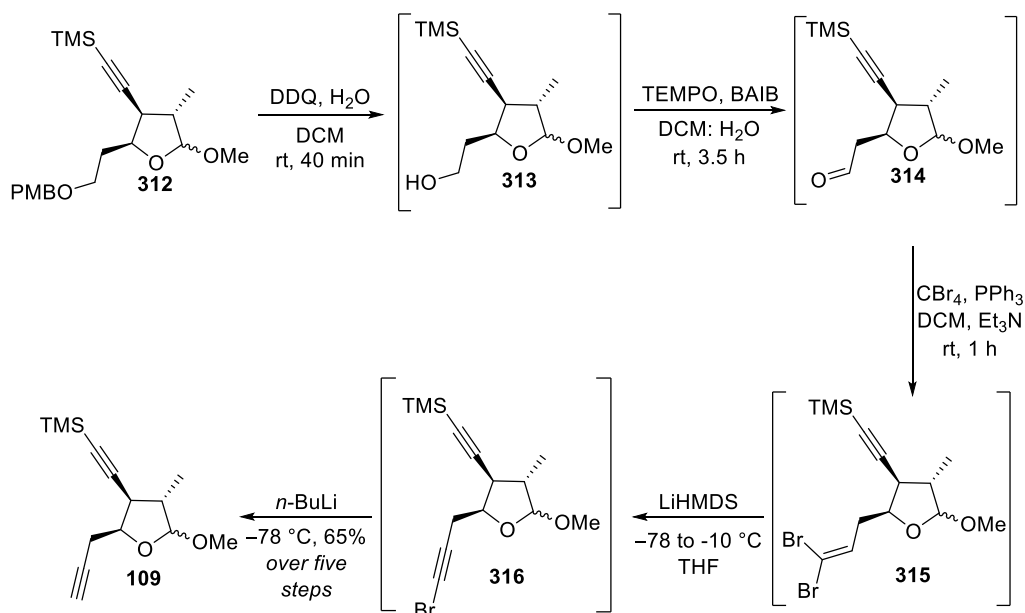
followed by acid-catalysed methyl acetal formation and desilylation, led to intermediate **111** in 89% yield over three steps. The following sequence of reactions was similar to the steps followed for the synthesis of the FG fragment **106a**: Alcohol **111** was oxidised to the aldehyde **310**, which was further transformed to the alkyne **311** by Seyferth-Gilbert homologation reaction using the Ohira–Bestmann reagent.^{192,193} Further deprotonation of the alkyne followed by quenching with TMSCl afforded alkyne **312** in 92% yield (Scheme 5-4).



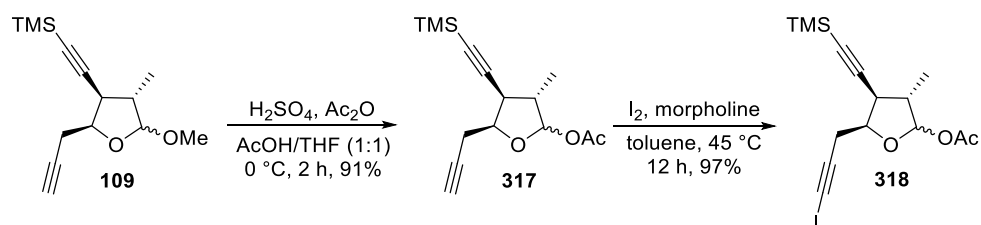
Scheme 5-4 Synthesis of the alkyne **312**.ⁱⁱⁱ

Next, PMB deprotection unmasked alcohol **313**, which was oxidised to aldehyde **314** (Scheme 5-5).⁷⁶ This was subjected to Ramirez olefination⁷⁹ conditions to generate dibromoalkene **315**; however, olefin **315** could not be purified by chromatography due to co-elution with 1-(2,2-dibromovinyl)-4-methoxybenzene. Product separation was effected by subjecting the mixture to the previously optimized elimination conditions, thus forming **109** in high overall yield through the intermediate bromoalkyne **316** (Scheme 5-5).

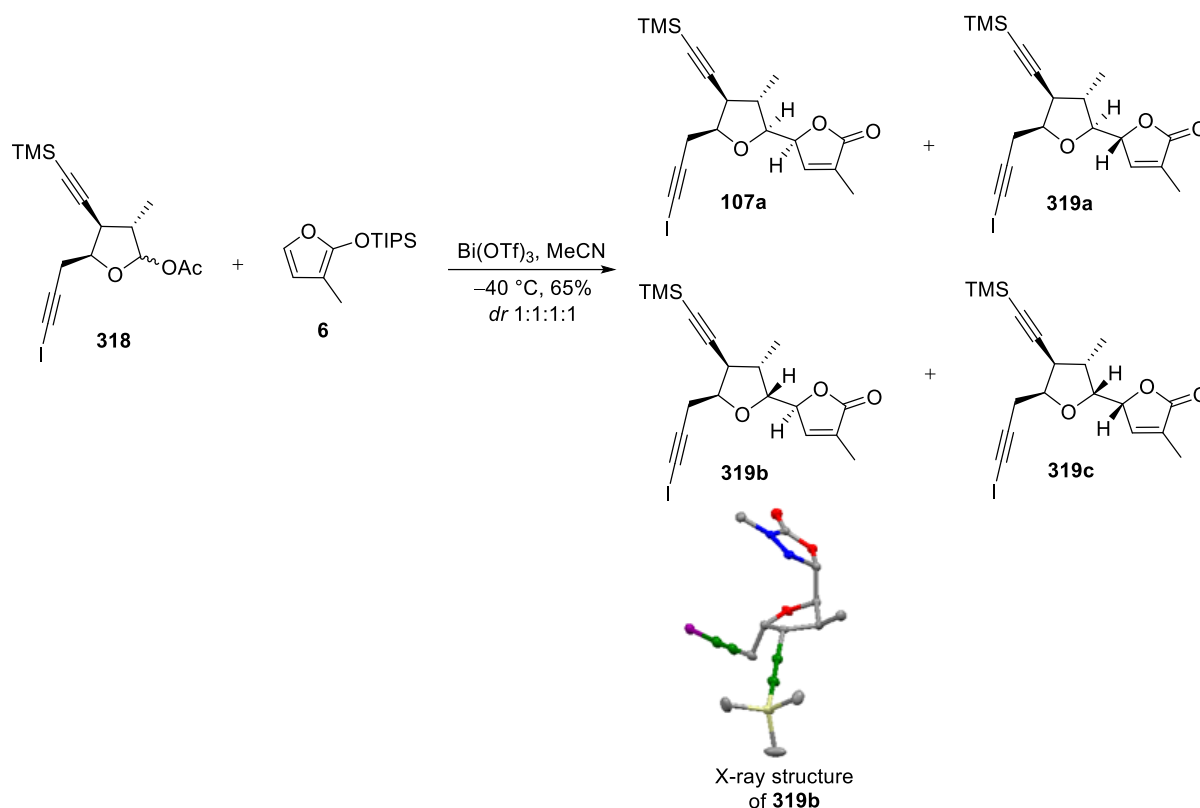
ⁱⁱⁱ The work in this scheme was optimised by Dr. Venkaiah Chintalapudi, a post-doctoral fellow in the group, and was reproduced in total by the author. Prof. Jeffrey Carney, a visiting academic from Christopher Newport University, helped with the scale-ups of the reactions.

Scheme 5-5 Synthesis of the diyne **109**.

In line with the previously described synthesis of fragment **106**, the next step was to transform the methyl acetal functionality into the acetate group. The optimised conditions were smoothly transferred to **109**, thus synthesising acetate **317** in 91% yield (Scheme 5-6). Iodination of the terminal alkyne was also successful, affording iodide **318** in 97% yield,

Scheme 5-6 Synthesis of the iodide **318**.

Finally, with iodide **318** in hand, the crucial Mukaiyama aldol type reaction to install the G ring was attempted. It was hoped that the methyl group, adjacent to the acetal, would impart the desired stereochemical bias into the system. However, all four diastereomers (**107a** and **319a-c**) were obtained in a near equimolar ratio (Scheme 5-7).

Scheme 5-7 Synthesis of the FG ring fragment **107a**.^{viii}

Fortunately, the separation of diastereomers **319a** and **319b** was possible by column chromatography, but **107a** and **319c** could not be separated, and were used as a mixture in subsequent reactions. The stereochemistry of the newly-formed stereogenic centres in the F and G rings could be assigned by ¹H NMR nOe correlations around the tetrahydrofuran ring, and by analysis of the coupling constants between these centres, in conjunction with the single crystal X-ray crystallography. The detailed assignment of stereochemistry is discussed in the next section.

^{viii} Prof. Jeffrey Carney, a visiting academic from Christopher Newport University, helped in the purification of the products.

5.3 Assignment of the stereochemistry of the FG fragments 107a and 319a-c^{ix}

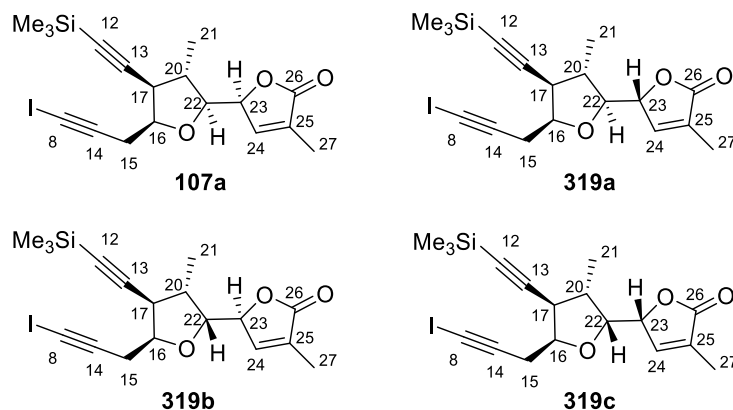


Figure 5-1 Diastereomers of the FG ring fragments from diyne **318**.

A combination of ^1H NMR nOe experiments and X-ray crystallography were used to assign the stereochemistry of the four diastereomers formed during the formation of the bond between the F and G rings.

The stereochemistry at C22 and C23 of **319b** was confirmed using X-ray crystallographic analysis (Flack parameter ~ 0 , Figure 5-2c). The C22 stereocentre was assigned to have *R* configuration and the C23 stereocentre was assigned to have *S* configuration (Figure 5-2a). The assignment was further supported by the observed nOe enhancements (Figure 5-2). The C22 stereocentre of adduct **319b** was assigned as *R* due to the lack of strong nOe enhancements between H22 and H16 and, H22 and H17 on the bottom face. However, a strong correlation was observed between H21 and H23 along with the coupling constant between H23 and H22 of 9.3 Hz. Given the crystallographic assignment of the C23 stereocentre as *S*, this suggests a major conformation with an antiperiplanar orientation of H22 and H23, as shown in Figure 5-2.

^{ix} The stereochemistry in this section was assigned concertedly by the author, Prof. Jeffrey Carney, a visiting academic from Christopher Newport University, and Prof. Edward A. Anderson.

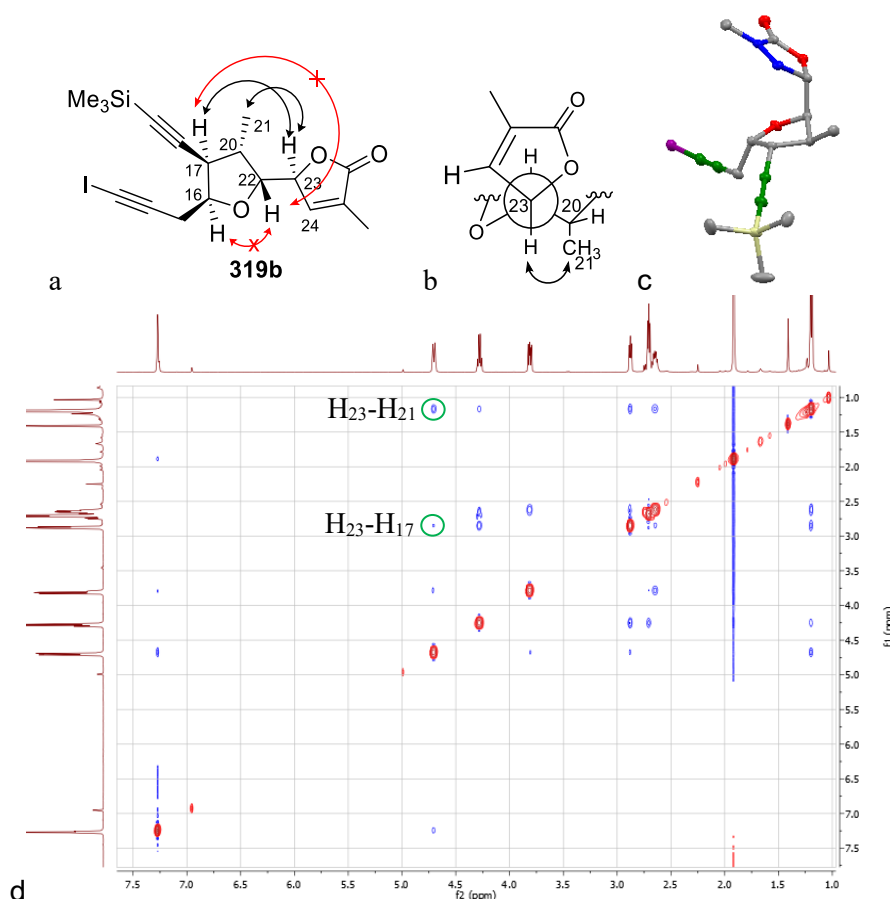


Figure 5-2 a. Strong enhancements seen in the nOe spectrum for compound **319b**; b. Conformation of butenolide ring in compound **319b**. c. X-ray structure of **319b**.^x d. ¹H-¹H-NOESY spectrum of **319b** in CDCl₃.

In adduct **319a**, a strong enhancement was observed between H₂₂ and H₁₇ as well as H₂₂ and the methyl protons H₂₁ (Figure 5-3). Thus, the C₂₂ stereocentre was assigned as *S*, with the proton on the bottom face as drawn in Figure 5-3. The C₂₃ stereocentre was assigned as *R* (proton on the top face as drawn) due to a combination of a strong enhancement of H₂₃ with H₂₀ (Figure 5-3a), an enhancement between H₂₄ and H₂₂ (Figure 5-3b), and a coupling constant of $J(\text{H}_{22}\text{-H}_{23})$ of 7.5 Hz. This observation would suggest that H₂₂ and H₂₃ are predominantly antiperiplanar which could be explained by a major conformation similar to the one shown in Figure 5-3b.

^x The crystal was developed by the author and the X-ray analysis was done by Steven J. Mansfield, a D. Phil student in the group.

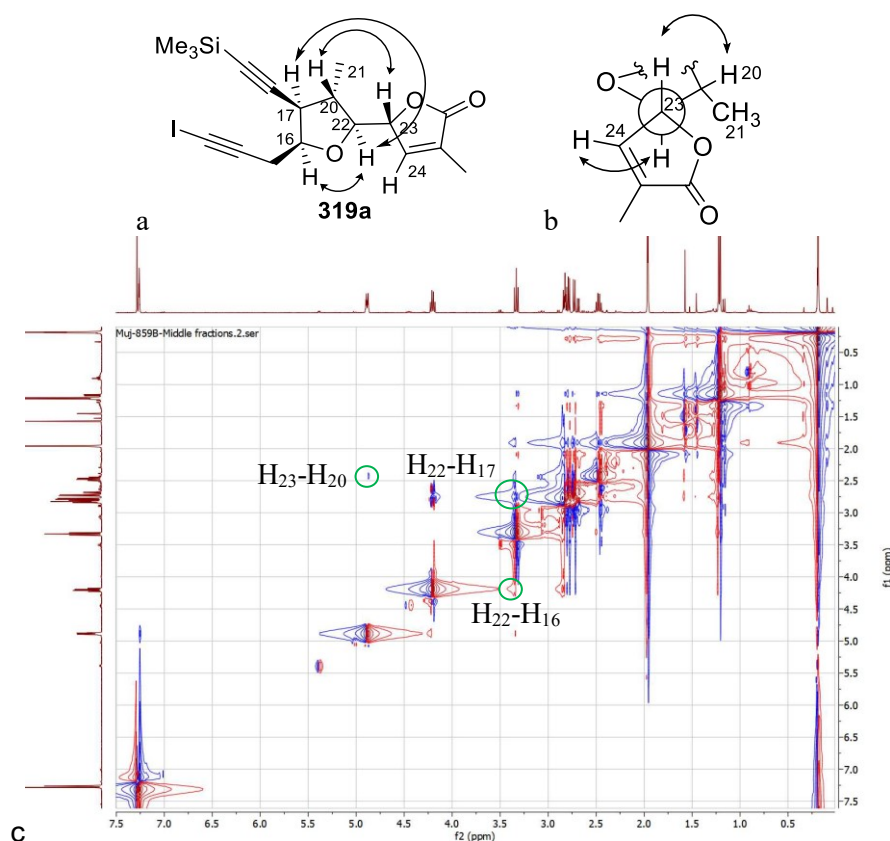


Figure 5-3 a. Strong and medium enhancements seen in the nOe spectrum for compound **319a**; b. Conformation of butenolide ring in compound **319a**. c. ^1H - ^1H -NOESY spectrum of **319a** in CDCl_3 .

Compounds **107a** and **319c** were obtained as a ~1:1 inseparable mixture. All peaks were assigned and confirmed using ^1H - ^1H COSY, following which stereochemical information for the two diastereomers was confirmed through the cross peaks in the NOESY spectrum. H22 in one diastereomer displayed strong enhancements with H17 and the methyl protons H21, indicating that it was oriented on the bottom face (Figure 5-4), which matched the *S* stereochemistry at C22 of the natural product. This diastereomer was assigned as **107a**. H23 displayed a medium strength enhancement with H20 and the methyl protons H21. The coupling constant for H22-H23, which was ~3 Hz, which together with the through space enhancement seen between H22 and H24 in the butenolide ring, would all be explained by an *S* configuration at C23, and the major conformation shown in Figure 5-4b.

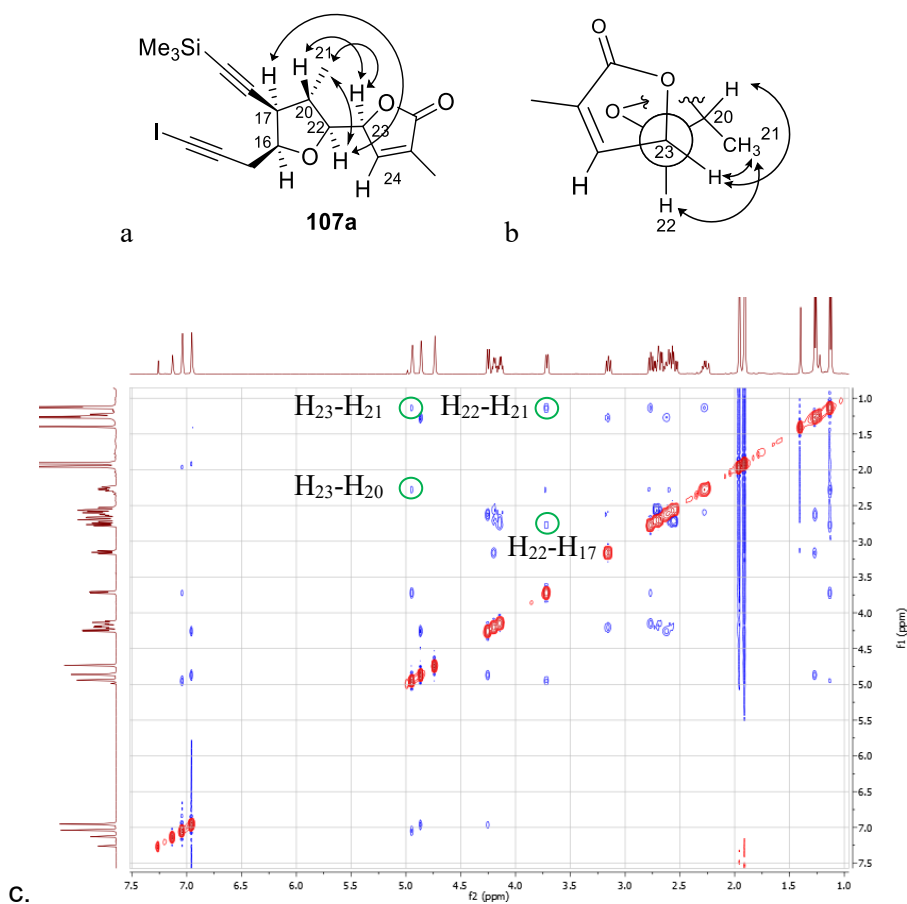


Figure 5-4. a. Enhancements seen in the nOe spectrum for compound **107**; b. Conformation of butenolide ring in compound **107a**. c. ¹H-¹H-NOESY spectrum of the mixture of **107a** and **319c** in CDCl₃

The final diastereomer **319c** did not show any strong enhancements between H₂₂ and either the H₁₆ or H₁₇ protons, indicating an *R* configuration (at C₂₂), with H₂₂ being on the top face of the F ring (Figure 5-5). Enhancement was observed between H₂₃ and H₂₁ (the methyl protons), which combined with a H₂₂-H₂₃ coupling constant of 1.9 Hz, indicated the *R* stereochemistry at C₂₃ in which the butenolide adopts a conformation with a dihedral angle between the C-H₂₂ and C-H₂₃ bonds close to 90°. This is shown by the major conformation shown in in Figure 5-5b.

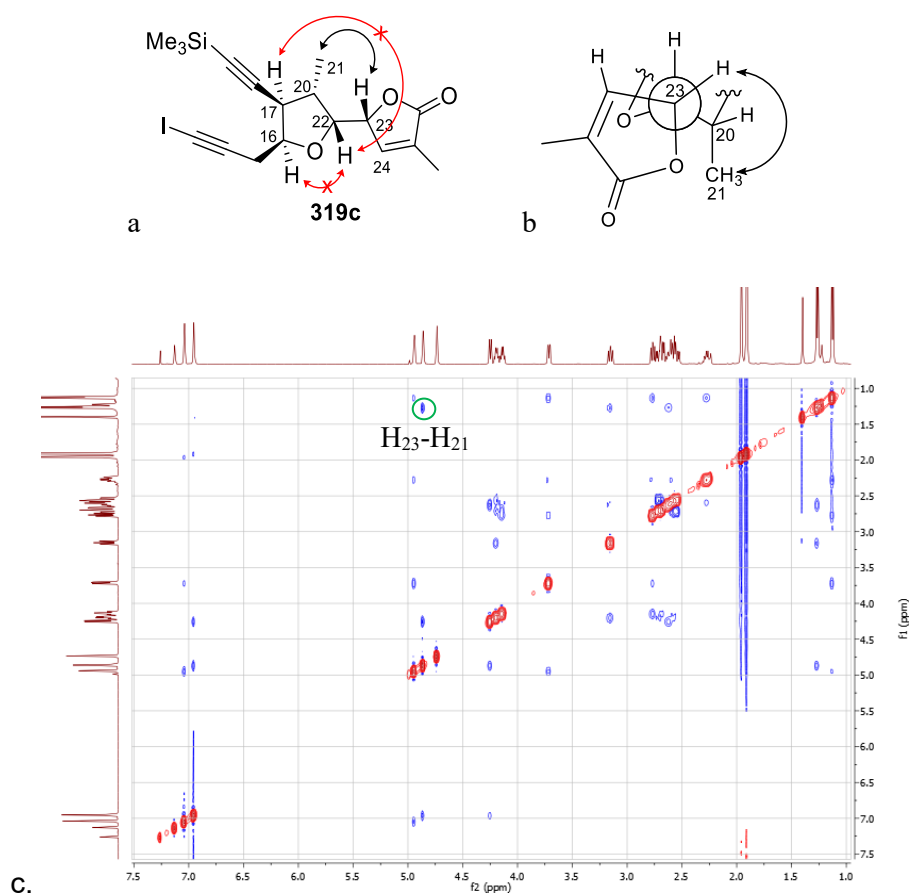
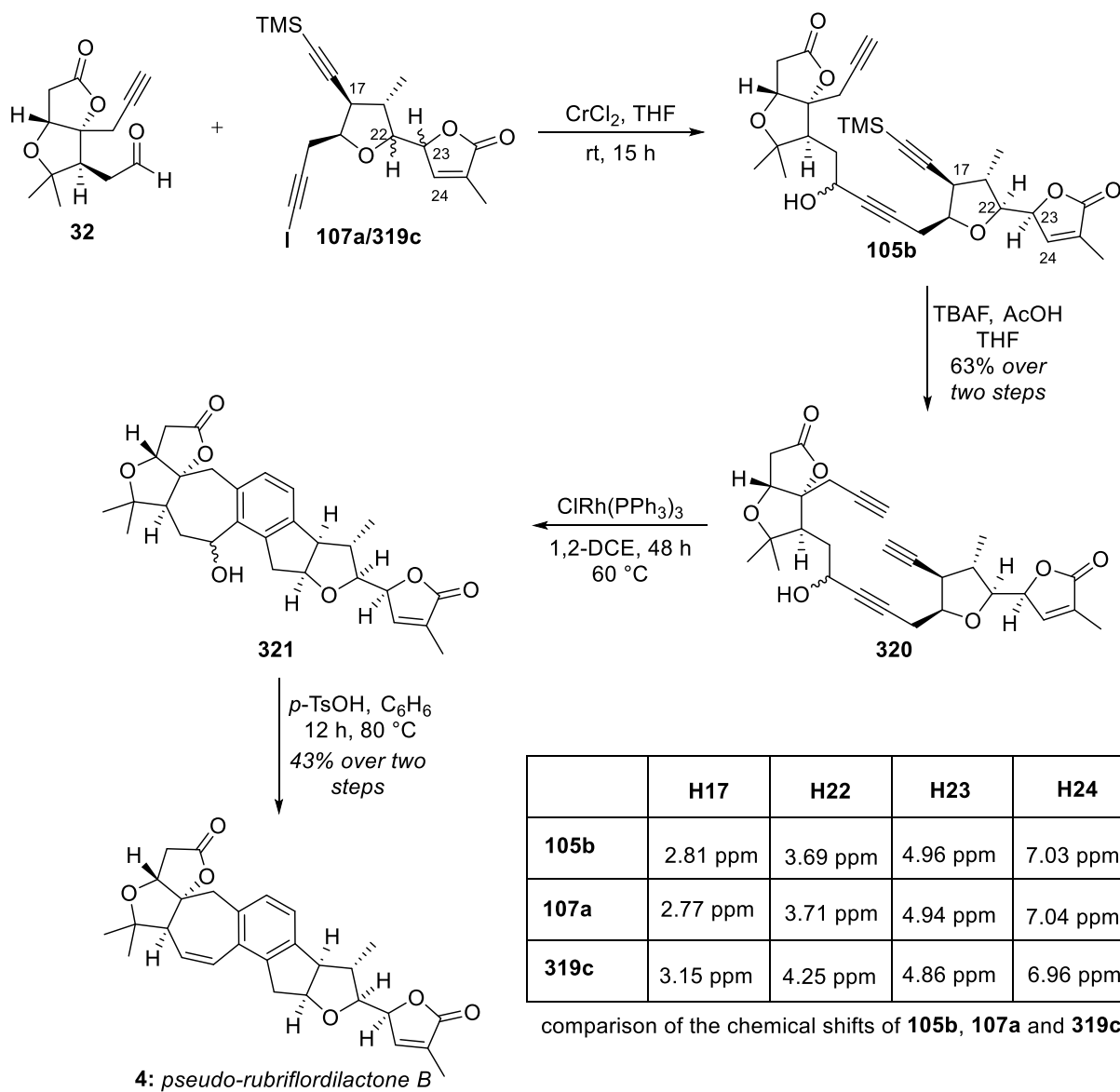


Figure 5-5. a. Enhancements seen in the nOe spectrum for compound **319c**; b. Conformation of butenolide ring in compound **319c**; c. ^1H - ^1H -NOESY spectrum of the mixture of **107a** and **319c** in CDCl_3

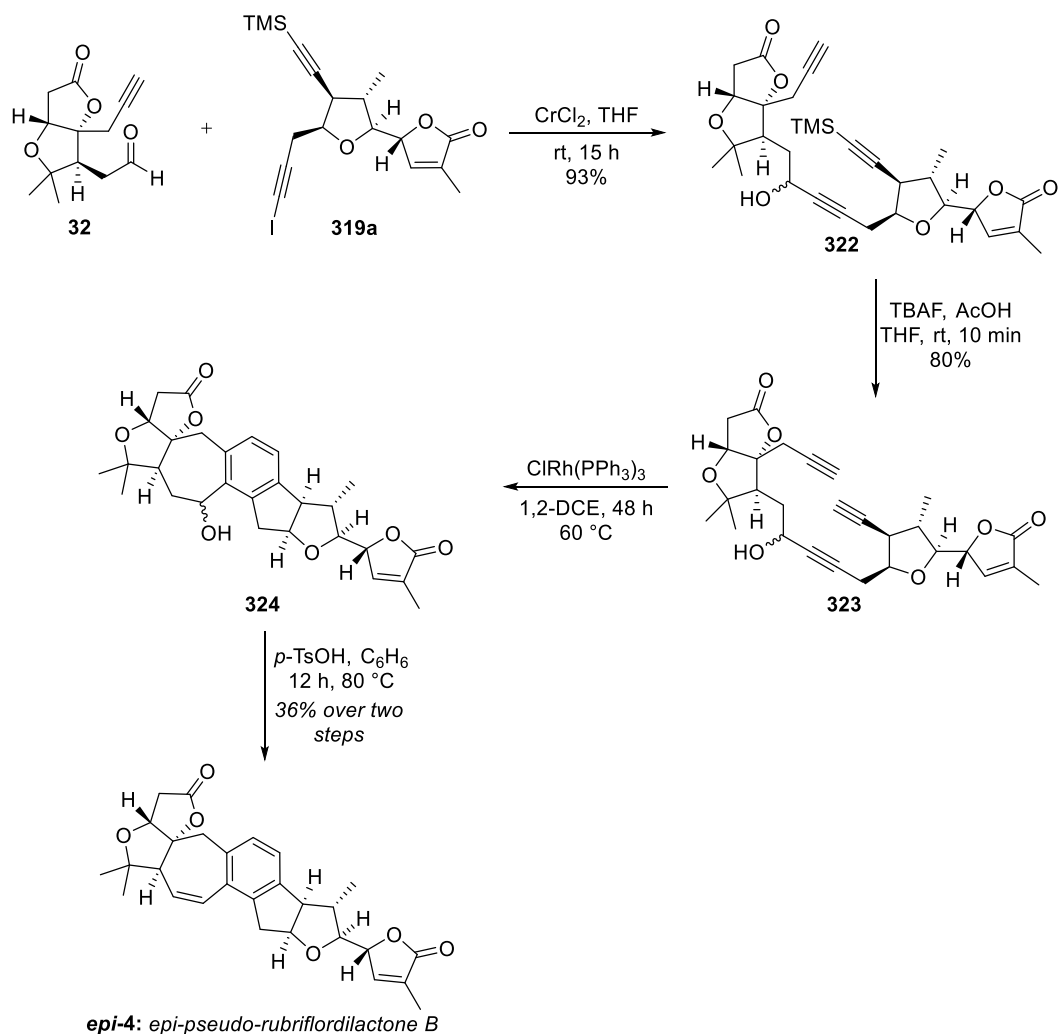
5.4 Synthesis of *pseudorubriflordilactone* B (**4**) using **107a** coupling partner

The NHK coupling between **107a/319c** and aldehyde **32** led to the formation of now separable products. Propargylic alcohol **105b** (inconsequential mixture of 1:1 diastereomers at the alcohol bearing stereocentre), the corresponding NHK product from **107b**, under desilylation conditions, then formed the triyne **320** in 63% yield over two steps (Scheme 5-8). The identity of **105b** was confirmed by comparing the chemical shifts, in the ^1H -NMR spectra, of the H17, H22, H23 and H24 of the FG rings in **107a**, **319c** and **105b** (Scheme 5-8). Close agreement between these chemical shifts was observed for **105b** and **107a**, indicating that **105b** had indeed formed from **107a**. Next, the Rh-catalysed cyclotrimerisation reaction on the triyne **320** proceeded smoothly to generate the ABCDEFG framework **321**. Finally, PTSA catalysed dehydration of **321** led to *pseudo*-rubriflordilactone B (**4**) in 43% yield over two steps (Scheme 5-8). It should be mentioned that this sequence of reactions was more challenging than the corresponding steps in the synthesis of rubriflordilactone B. Particularly, the desilylation of **105b** was sometimes capricious. Furthermore, higher catalytic loadings and extended reaction times were required for both the [2+2+2] cyclotrimerisation reaction, and for the acid catalysed dehydration step.

Scheme 5-8 Synthesis of *pseudo*-rubriflorldilactone B (4).

5.5 Synthesis of *epi-pseudo*-rubriflordilactone B (*epi*-4) using 319a coupling partner

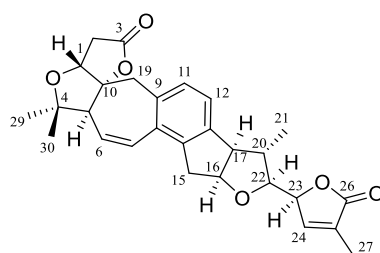
Following the successful formation of *pseudo*-rubriflordilactone B (**4**), the synthesis of C-23 *epi-pseudo*-rubriflordilactone B (*epi*-4) was attempted. The FG fragment **319a** was used in the NHK coupling with the aldehyde **32** (Scheme 5-9), affording triyne **322** in 93% yield. Desilylation then resulted in the triyne **323** in high yield. Wilkinson catalyst again promoted the [2+2+2] cycloaddition reaction, forming the ABCDEFG core **324** of *epi-pseudo*-rubriflordilactone B. This then underwent a PTSA catalysed dehydration reaction, which concluded the synthesis of *epi-pseudo*-rubriflordilactone B in 36% over two steps (*epi*-4, Scheme 5-9).



Scheme 5-9 Synthesis of C-23 *epi-pseudo*-rubriflordilactone B (*epi*-4).

Figure S-6 ^1H NMR spectra of natural⁶ (top, 600 MHz) and synthetic (bottom, 500 MHz) *pseudorubriflordinilactone B* (**4**) in pyridine- d_5

^{xi} The assignments in this section were done with the help of Prof. Jeffrey Carney, a visiting academic from Christopher Newport University.

Table 5-1 ^1H NMR chemical shifts of natural⁶ and synthetic *pseudo-rubriflordilactone B* in pyridine-*d*₅.**4:** *pseudo-rubriflordilactone B*

	Natural δ ^1H (ppm, mult, J (Hz)) 400 MHz	Synthetic ^a δ ^1H (ppm, mult, J (Hz)) 500 MHz	$\Delta\delta$ (ppm)
1	4.42 (d, 5.3)	4.42 (br s)	0.00
2 α	2.86 (d, 18.0)	2.87 (d, 18.2)	−0.01
2 β	3.23 (overlapped)	3.22 (overlapped)	0.01
5	2.87 (overlapped)	2.87 (overlapped)	0.00
6	5.72 (br d, 12.6)	5.72 (br s)	0.00
7	6.50 (d, 12.6)	6.50 (d, 12.1)	0.00
11	~7.08 (m) ^b	7.08 (m)	~0.00
12	~7.09 (m) ^b	7.09 (m)	~0.00
15 α	3.23 (overlapped)	3.22 (overlapped)	0.01
15 β	2.88 (overlapped)	2.87 (overlapped)	0.00
16	4.86 (overlapped)	4.85 (m)	0.01
17	3.29 (dd, 5.3, 5.5)	3.29 (t, 5.6)	0.00
19 α	3.00 (d, 15.2)	3.00 (overlapped)	0.00
19 β	3.22 (d, 15.2)	3.18 (overlapped)	0.04
20	2.31 (m)	2.31 (m)	0.00
21	1.17 (3H, d, 8.2)	1.17 (3H, d, 6.9)	0.00
22	3.73 (dd, 5.2, 6.7)	3.73 (t, 6.0)	0.00
23	4.86 (overlapped)	4.85 (m)	0.01
24	6.88 (br s)	6.86 (br s)	0.02
27	1.76 (s)	1.75 (s)	0.01
29	1.24 (s)	1.33 (s)	−0.06
30	1.32 (s)	1.33 (s)	−0.01

^a Data were recorded in $\text{C}_5\text{D}_5\text{N}$ on a Bruker AVX 500 MHz spectrometer with a cryoprobe (^1H , ^{13}C , COSY, HSQC, HMBC). ^b Approximate values obtained from ^1H -NMR spectrum run on a 600 MHz spectrometer

The comparison of the ^1H NMR of synthetic compound **4** with the isolated natural product shows a high degree of correlation between the data sets. There was a negligible difference ($\Delta\delta$) of less than 0.06 ppm between all signals.

Figure 5-7 and Table 5-2 represents the comparison between the ^{13}C NMR chemical shifts of the isolated natural product and the synthetic sample **4**.

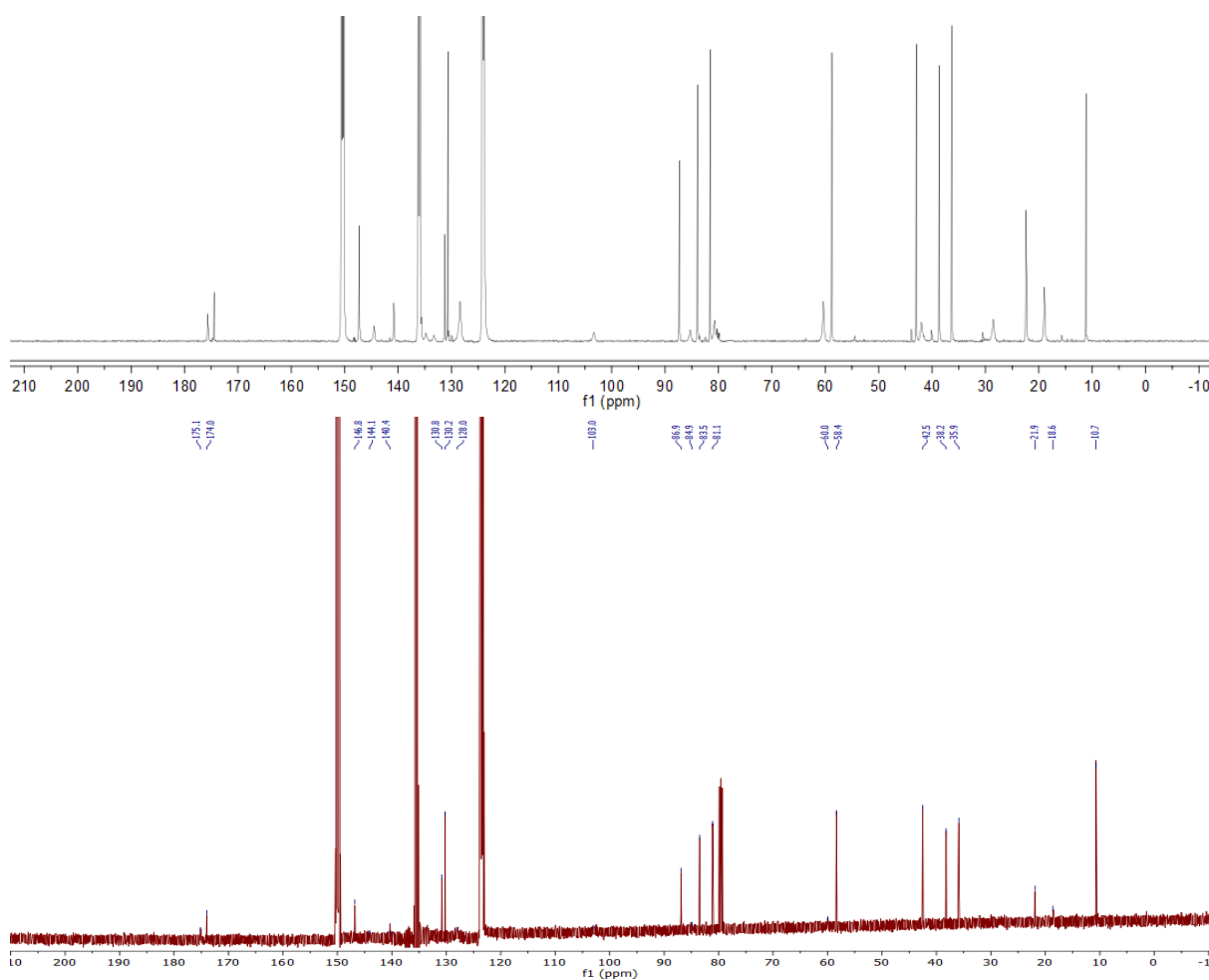
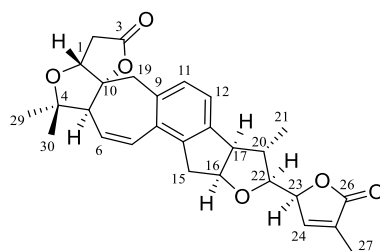


Figure 5-7 ^{13}C NMR spectra of natural⁶ (top, 600 MHz) and synthetic (bottom, 500 MHz) *pseudorubriflordilactone B* (**4**) in pyridine-*d*5

Table 5-2 ^{13}C NMR chemical shifts of natural⁶ and synthetic *pseudo*-rubriflordilactone B in pyridine-*d*5.**4:** *pseudo*-rubriflordilactone B

	Natural $\delta^{13}\text{C}$ (ppm) 400 MHz	Synthetic ^a $\delta^{13}\text{C}$ (ppm) 500 MHz	$\Delta\delta$ (ppm)
1	79.9	79.4 ^b	0.5
2	35.9	35.9	0.0
3	175.1	175.1	0.0
4	85.1	84.9	0.2
5	60.0	60.0	0.0
6	128.1	128.6 ^b	-0.5
7	127.9	128.1 ^b	-0.2
8	133.2	133.4 ^b	-0.2
9	130.2	130.2 ^b	0.0
10	103.4	103	0.4
11	130.2 (overlapped)	130.2 ^c	~0.0
12	Overlap with pyridine- <i>d</i> 5	123.5 ^c	-
13	140.3	140.3	0.0
14	144.5	144.1	0.4
15	~41.0	41.2 ^b	-0.2
16	83.5	83.5	0.0
17	58.4	58.4	0.0
19	38.2	38.2	0.0
20	42.5	42.5	0.0
21	18.6	18.5	0.1
22	86.9	86.9	0.0
23	81.1	81.1	0.0
24	146.8	146.8	0.0
25	130.8	130.9 ^b	-0.1
26	173.0	174.0	-1.0
27	10.7	10.7	0.0
29	28.3	28.2	0.1

5. Synthesis of *pseudo*-rubriflordinilactone B and *epi-pseudo*-rubriflordinilactone B

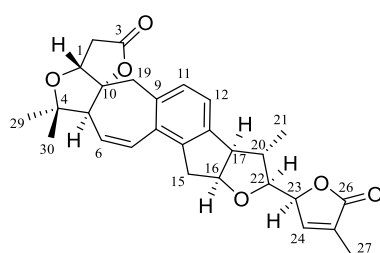
30	21.9	21.9	0.0
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^a Data were recorded in C₅D₅N on a Bruker AVX 500 MHz spectrometer with a cryoprobe (¹H, ¹³C, COSY, HSQC, HMBC). ^b Peak appear at 60 °C. ^c Identified using HSQC.

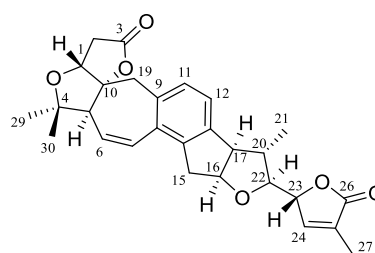
Similarly, the comparison of the ¹³C NMR spectra of synthetic **4** with the isolated natural product shows a high degree of correlation between both the samples. There was a negligible variation ($\Delta\delta$) of less than 1 ppm between the signals of both samples. For synthetic sample, peaks corresponding to C1, C6, C7, C8, C9, C15 and 25 appeared at 60 °C and C11 and C12 were assigned with the help of HSQC spectrum. Theoretical calculations by Kaufman *et al.* suggest that the peaks assigned to the proton and carbon atom at C15 in the isolation paper in fact correspond to some impurity in the sample (presumably grease), which had been wrongly assigned, and they calculated the unscaled value to be 41.6 ppm.¹¹ This value is much closer to the observed chemical shift of 41.2 ppm for C15 in the synthetic **4** and a peak could be observed at around 41 ppm in the ¹³C NMR spectrum of the isolated natural product (Figure 5-6, top).

Table 5-3 shows the comparison of the ¹H NMR chemical shifts of the isolated natural product with synthetic *epi-pseudo*-rubriflordinilactone B (*epi-4*)

Table 5-3 ¹H NMR chemical shifts of isolated natural product⁶ and synthetic C-23 *epi-pseudo*-rubriflordinilactone B (*epi-4*) in pyridine-*d*5.



4: *pseudo*-rubriflordinilactone B



epi-4: *epi-pseudo*-rubriflordinilactone B

	Natural δ ¹ H (ppm, mult, <i>J</i> (Hz)) 400 MHz	Synthetic ^a δ ¹ H (ppm, mult, <i>J</i> (Hz)) 500 MHz	$\Delta\delta$ (ppm)
1	4.42 (d, 5.3)	4.39 (br s)	0.03
2 α	2.86 (d, 18.0)	2.84 (m)	0.02
2 β	3.23 (overlapped)	3.19 (overlapped)	0.04
5	2.87 (overlapped)	2.99 (overlapped)	-0.12
6	5.72 (br d, 12.6)	5.76 (br s)	-0.04
7	6.50 (d, 12.6)	6.59 (m)	-0.09

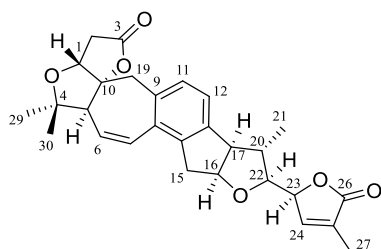
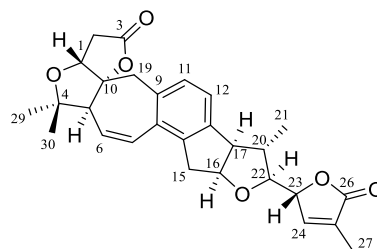
5. Synthesis of *pseudo*-rubriflordilactone B and *epi-pseudo*-rubriflordilactone B

11	7.08 (m)	7.13 (s)	0.05
12	7.09 (m)	7.13 (s)	0.06
15 α	3.23 (overlapped)	3.02 (overlapped)	0.21
15 β	2.88 (overlapped)	3.02 (overlapped)	-0.14
16	4.86 (overlapped)	4.86 (t, 6.1)	0
17	3.29 (dd, 5.3, 5.5)	3.33 (dd, 6.0, 3.5)	-0.04
19 α	3.00 (d, 15.2)	3.02 (overlapped)	-0.02
19 β	3.22 (d, 15.2)	3.16 (overlapped)	0.06
20	2.31 (m)	2.5 (s)	-0.19
21	1.17 (d, 8.2)	1.18 (d, 7)	-0.01
22	3.73 (dd, 5.2, 6.7)	3.51 (dd, 8.1, 4.3)	0.22
23	4.86 (overlapped)	4.50 (overlapped)	0.36
24	6.88 (br s)	7.03 (s)	-0.15
27	1.76 (s)	1.73 (s)	0.03
29	1.24 (s)	1.24 (overlapped)	0
30	1.32 (s)	1.24 (overlapped)	0.08

^a Data were recorded in C₅D₅N on a Bruker AVX 500 MHz spectrometer with a cryoprobe (¹H, ¹³C, COSY, HSQC, HMBC).

The comparison of the ¹H NMR of the isolated natural product with the synthetic C-23 *epi-pseudo*-rubriflordilactone B (*epi-4*) shows a high degree of variance between the data. There was a significant difference ($\Delta\delta$) of more than 0.06 ppm between many signals of two samples, indicating that it is highly unlikely for *epi-4* to be the isolated natural product.

The comparison of the ¹³C NMR chemical shifts of the isolated natural product with synthetic *epi-pseudo*-rubriflordilactone B (*epi-4*) is similarly illustrated in the Table 5-4.

Table 5-4 ^{13}C NMR chemical shifts of isolated natural product⁶ and synthetic C-23 *epi-pseudo*-rubriflordinolactone B (*epi-4*) in pyridine-*d*5.**4:** *pseudo*-rubriflordinolactone B**epi-4:** *epi-pseudo*-rubriflordinolactone B

	Natural $\delta^{13}\text{C}$ (ppm) 400 MHz	Synthetic ^a $\delta^{13}\text{C}$ (ppm) 500 MHz	$\Delta\delta$ (ppm)
1	79.9	80.4	-0.5
2	35.9	35.9	0
3	175.1	175.1	0
4	85.1	84.9	0.2
5	60.0	60	0
6	128.1	overlapped/not visible	-
7	127.9	128.2	-0.3
8	133.2	133.9 ^b	-0.7
9	130.2	130.1	0.1
10	103.4	103	0.4
11	130.2 (overlapped)	130.1	0.1
12	Overlap with pyridine- <i>d</i> 5	overlapped/not visible	-
13	140.3	140.5	-0.2
14	144.5	144.3	0.2
15	41.0	41.5	-0.5
16	83.5	83.6	-0.1
17	58.4	58.4	0
19	38.2	38.5	-0.3
20	42.5	44.3	-1.8
21	18.6	19.4	-0.8
22	86.9	87.7	-0.8
23	81.1	82.3	-1.2
24	146.8	148	-1.2
25	130.8	130.5	0.3
26	173.0	173.9	-0.9
27	10.7	10.6	0.1

5. Synthesis of *pseudo*-rubriflordilactone B and *epi-pseudo*-rubriflordilactone B

29	28.3	28.2	0.1
30	21.9	21.9	0

^a Data were recorded in C₅D₅N on a Bruker AVX 500 MHz spectrometer with a cryoprobe (¹H, ¹³C, COSY, HSQC, HMBC). ^b Identified using HMBC

Again, a high level of variance was observed on comparing the ¹³C NMR chemical shifts of the isolated natural product with synthetic *epi*-4. On comparing the data for both ¹H NMR as well as ¹³C NMR, it could be said with a high level of certainty that the structure of the isolated natural product does not correspond to *epi*-4.

The NMR spectra of **4** and *epi*-4 (both ¹H as well as ¹³C NMR spectra) exhibited broadening of some of the signals and some of the ¹³C signals were not visible. This is likely be due to the overlapping with existing signals or due to the broadening of the signals attributed to conformational interconversion of the molecule on the NMR timescale.

In conclusion, on comparing ¹H and ¹³C NMR spectra of the isolated natural product with the synthetic *pseudo*-rubriflordilactone B (**4**), a high degree of agreement was observed. Thus, with the given evidence, the structure of compound **4** very likely corresponds to the isolated natural product.

5.7 Conclusion and Future work

In summary, we have successfully established a convergent route to achieve an enantioselective total synthesis of rubriflordilactone B. The strategy was also employed to successfully synthesise C-23 *epi*-rubriflordilactone B. Furthermore, with small modifications, the approach was successfully applied to the enantioselective synthesis of *pseudo*-rubriflordilactone B and C-23 *epi-pseudo*-rubriflordilactone B.

The syntheses of *pseudo*-rubriflordilactone B and C-23 *epi-pseudo*-rubriflordilactone B enabled us to compare their NMR spectroscopic data with the isolated natural product. The comparison showed a close correlation between the spectroscopic data of *pseudo*-rubriflordilactone B (**4**) and the isolated natural product, thus attributing the structure of **4** to the isolated natural product.

Li *et al.* hypothesised that the reported biological activity of the isolated sample could be attributed to a different natural product, *pseudo*-rubriflordilactone B (the structure corresponding to *pseudo*-rubriflordilactone B was proposed by Kaufman *et al*¹¹).¹⁰ Thus, the synthesis of the other analogues as well as truncated molecules of *pseudo*-rubriflordilactone B could be of considerable importance. These molecules would not only help in establishing the structure-activity relationships within the rubriflordilactone family, which would be of interest for fine tuning of the biological properties.

While working on this synthesis, we have already synthesised rubriflordilactone B (**3**), *pseudo*-rubriflordilactone B (**4**) and their C-23 epimers (*epi*-**3** and *epi*-**4**). Moreover, synthesis of some of the truncated molecules of parent rubriflordilactone B *viz* CDE ring system **167**, DEFG ring system **168** and CDEFG ring system **169** have already been achieved, and its C-5 epimer could also be targeted (Figure 5-6). Moreover, by utilising FG ring system **107a**, CDEFG systems **325** and *epi*-**325** corresponding to **4** and *epi*-**4** could also be synthesised.

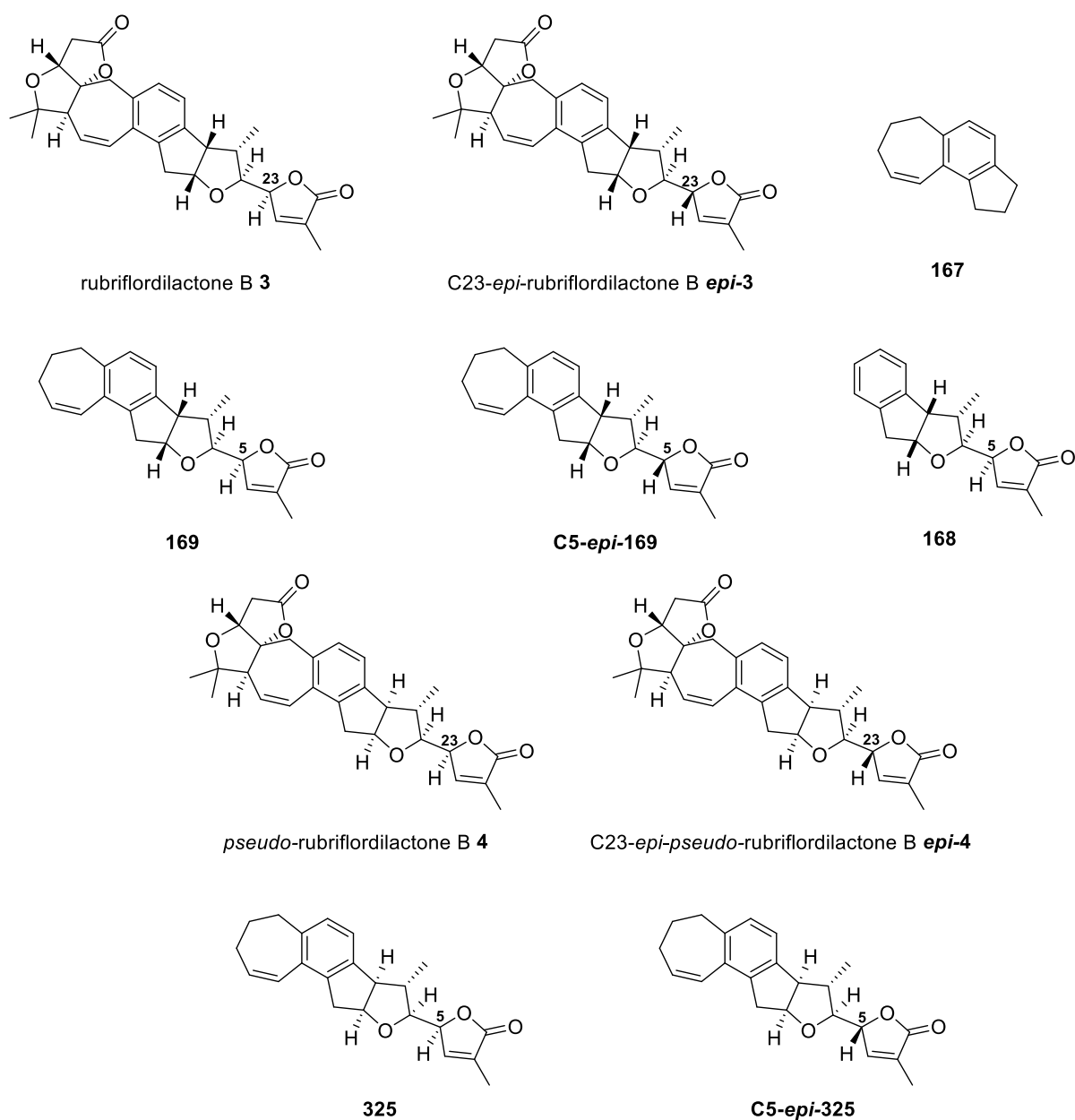


Figure 5-6 Rubriflordilactone B (**3**), *pseudo*-rubriflordilactone B (**4**) and their analogues.

Biological studies have shown that despite similar ABCD ring systems in both **3** and **4**, rubriflordilactone A (**2**) does not exhibit any anti-HIV activity (Figure 5-7). Thus, comparison of the CDEFG ring systems and DEFG ring systems of both **2** and **4** might help in unearthing the genesis of the biological activity in **4**.

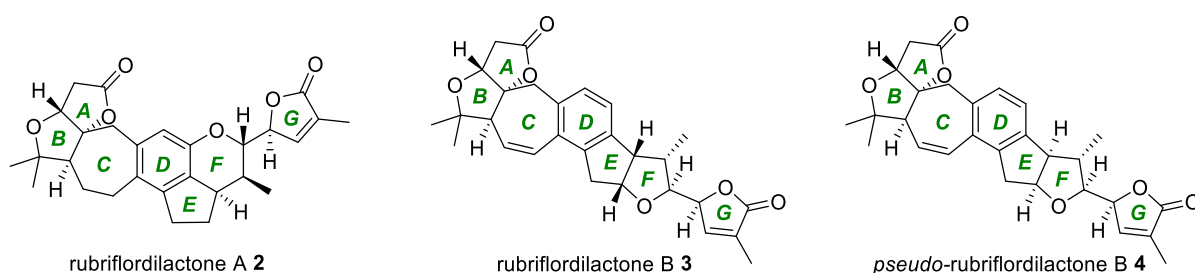


Figure 5-7 Rubriflordilactone A (**2**), rubriflordilactone B (**3**) and *pseudo*-rubriflordilactone B (**4**).

Finally, analogues of both **3** and **4** could be obtained by modifying the corresponding routes. The convergent strategy allows for easy modification pre-cyclisation, and both the AB ring aldehyde as well as the FG ring diynes can be independently altered giving access to a wide range of analogues (Figure 5-7). The D, F and G rings could be modified by varying the substituents in the FG ring systems **106** and **107**. If it is determined that the G ring is inconsequential or has adverse effects on biological activity, the F ring fragments **165** and **309** would be used which, *in turn*, would provide more opportunities to remodel the F ring. The ABC rings of the natural product could also be redesigned by modifying the AB ring aldehyde **32** (Figure 5-8).

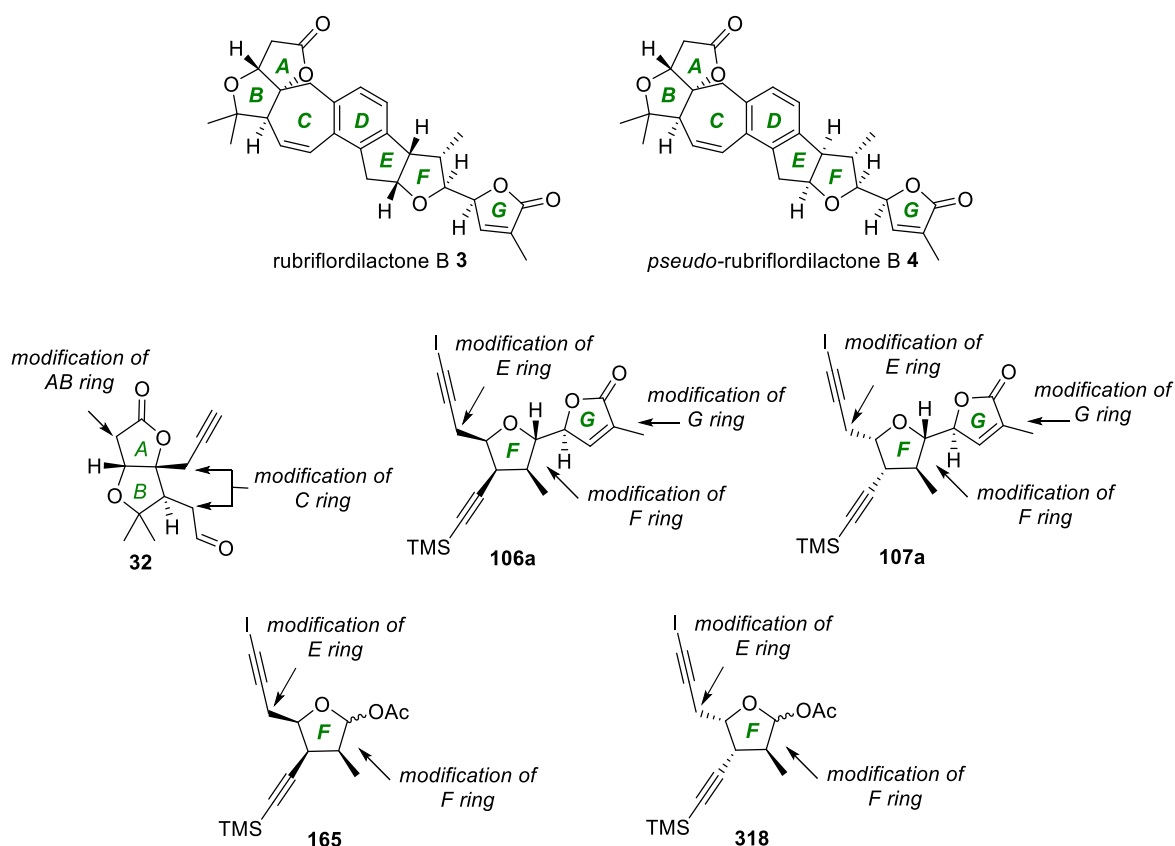


Figure 5-8 Pre-cyclisation modification to rubriflordinilactone B and *pseudo-rubriflordinilactone B* analogues.

With the synthesis of rubriflordinilactones A and B established, the focus in the group would move towards the synthesis of lancifodilactone I (**326**, Figure 5-9), another member of the *Schisandra* family.¹⁹⁴

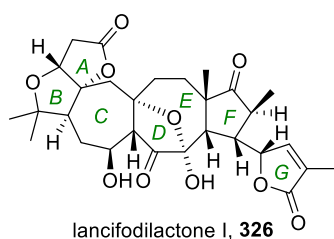
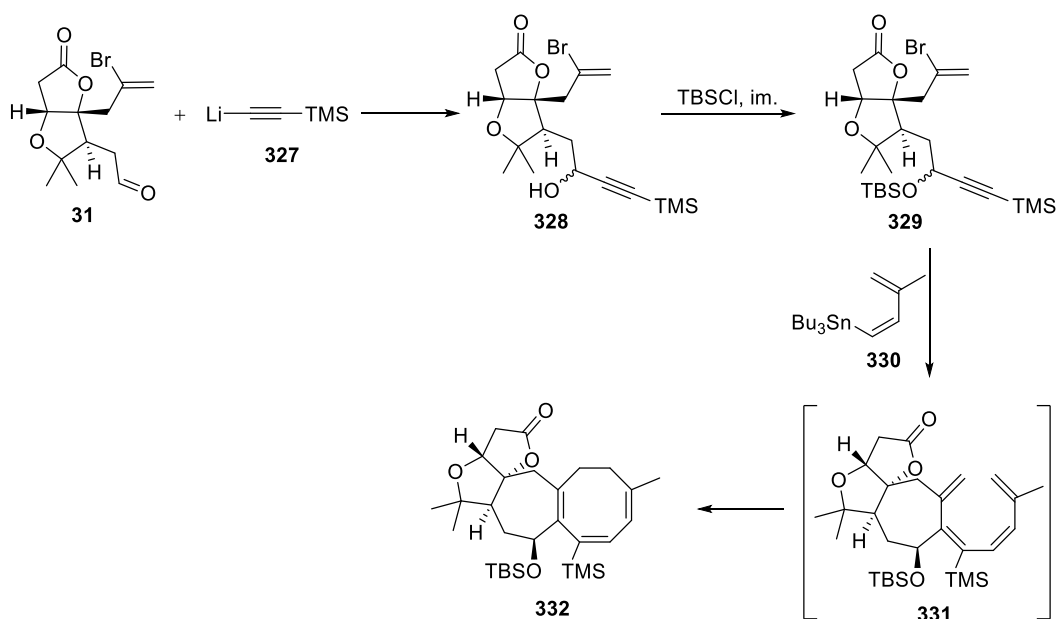


Figure 5-9 lancifodilactone I, a member of *Schisandra lancifolia* plants.

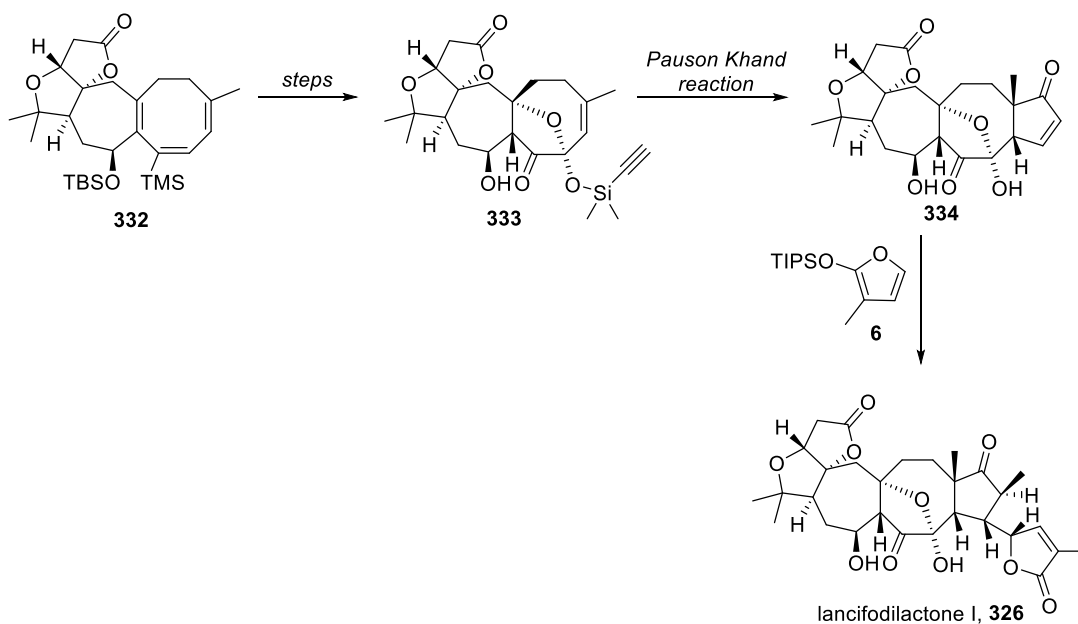
The planned synthesis would begin with the addition of trimethylsilylacetyl anion **327** to AB ring aldehyde **31** to give enyne **328** (Scheme 5-10). TBS protection would afford **329**, which with the stannane coupling partner **330**, would be subjected to a Pd-catalysed carbopalladation / Stille cross

coupling cascade to form tetraene **331**. The tetraene intermediate **331** should then undergo a facile 8π electrocyclization to give the triene core **332** of lancifodilactone I (Scheme 5-10).



Scheme 5-10 Proposed synthesis of triene **332**.

A sequence of selective oxidations and reductive cleavage using SmI_2 would lead to **333** (Scheme 5-11). Finally, a Si-tethered Pauson Khand reaction followed by installation of the butenolide would form lancifodilactone I (**326**).



Scheme 5-11 Proposed synthesis of lancifodilactone I.

6. Experimental

6.1 General Experimental Considerations

Nuclear Magnetic Resonance Spectroscopy: ^1H 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 ($\delta = 7.26$) or $\text{C}_5\text{D}_5\text{N}$ ($\delta = 8.74, 7.58, 7.22$). 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 ($\delta = 77.16$) or $\text{C}_5\text{D}_5\text{N}$ ($\delta = 150.35, 135.91, 123.87$).

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), electron ionisation (EI) or field ionisation (FI). The parent ion $[\text{M}]^+$, $[\text{M}+\text{H}]^+$, $[\text{M}+\text{Na}]^+$ or $[\text{M}-\text{H}]^-$ 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 ($[\alpha]_{\text{D}}$) are reported in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Concentrations are reported in g/100 mL. Temperatures are reported in $^{\circ}\text{C}$ (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.

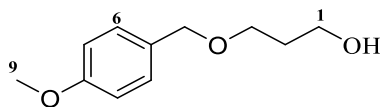
Chromatography: Flash chromatography refers to normal phase column chromatography on silica gel using a head pressure of N₂, using either Merck Geduran[®] Silicagel 60 (40 - 63 µm) or Macherey-Nagel Silica 60 M (40 - 63 µm). Thin-layer chromatography was performed on Merck Kieselgel 60 F₂₅₄ plates with visualization by ultraviolet light (254 nm) and/or heating the plate after staining with vanillin or KMnO₄ stains. 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. Et₂O, 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.

6.2 Procedures and Characterisations

6.2.1 Procedures and characterisations of the compounds in Chapter 2

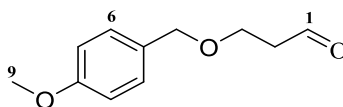
3-((4-Methoxybenzyl)oxy)propanol: **119**



To a stirring solution of 1,3-propanediol (12.07 g, 0.159 mol, 2.0 equiv.) in anhyd. DMSO (60 mL) under argon at 0 °C, KOH (8.90 g, 0.159 mol, 2.0 equiv.) was added portion wise. The stirred solution was allowed to warm to rt and was further stirred for 1h. The reaction mixture was again cooled to 0 °C and 4-methoxybenzylchloride (12.42 g, 0.079 mol, 1 eq) was added. It was allowed to reach rt and stirred for further 3 h. The reaction was cooled to 0 °C, diluted with Et₂O (50 mL) followed by slow addition of 4 N HCl (50 mL). The layers were separated, aqueous layer was extracted with Et₂O (50 mL × 3) and combined organic layer was dried over MgSO₄. The solvent was removed under *vacuo* and the crude product purified *via* column chromatography (2:1 Petroleum ether/ EtOAc) to afford alcohol **119** (12.97 g, 0.066 mol, 83%) as a light yellow oil.

R_f 0.15 (3:2 Petroleum ether / EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.18 (2H, dd, *J* = 6.7 and 4.5 Hz, H₆), 6.81 (2H, dd, *J* = 6.6 and 4.6 Hz, H₇), 4.38 (2H, s, H₄), 3.73 (3H, s, H₉), 3.70 (2H, m, H₃), 3.56 (2H, t, *J* = 14 Hz, H₁), 2.19 (1H, t, *J* = 14 Hz, O-H) and 1.78 (2H, m, H₂); **¹³C NMR** (100 MHz, CDCl₃) δ_C 159.2 (C₈), 130.2 (C₅), 129.3 (C₆), 113.9 (C₇) 72.9 (C₄), 69.1 (C₉) 62.0 (C₃), 55.3 (C₁), 32.1 (C₂).

3-((4-Methoxybenzyl)oxy)propanal: **120**

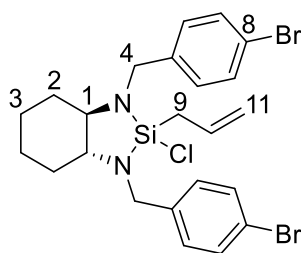


To a stirring solution of anhyd. DMSO (22.8 mL, 321 mmol, 7.0 equiv.), NEt₃ (31.8 mL, 229 mmol, 5.0 equiv.) and SO₃.py (21.9 g, 138 mmol, 3.0 equiv.) a solution of alcohol **119** (9.01 g, 45.90 mmol, 1.0 eq) in DCM (25 mL) was added at 0 °C. It was stirred for 30 min at 0 °C. The reaction was quenched

with 100 mL phosphate buffer (pH 7) and was extracted with EtOAc (50 mL $\times$ 3) and the combined organic layers were dried over anhyd. Na_2SO_4 . The solvent was removed *in vacuo* and the crude product purified *via* column chromatography (4:1 Petroleum ether / EtOAc) to afford aldehyde **120** (6.67 g, 34.40 mmol, 75%) as a light yellow oil.

R_f 0.38 (4:1 Petroleum ether / EtOAc); **¹H NMR** (400 MHz, CDCl_3) δ_{H} 9.81 (1H, t, J = 1.6 Hz, H1), 7.27 (2H, dd, J = 6.5 and 4.6 Hz, H6), 6.91 (2H, dd, J = 6.4 and 4.6 Hz, H7), 4.49 (2H, s, H4), 3.83 (3H, s, H9), 3.81 (2H, t, J = 6.1 Hz, H3), 2.70 (2H, td, J = 6.1 and 1.8 Hz, H2); **¹³C NMR** (100 MHz, CDCl_3) δ_{C} 201.3 (C=O), 159.3 (C8), 130.0 (C5), 129.4 (C6), 113.9 (C7), 72.9 (C4), 63.5 (C9), 55.3 (C3), 43.9 (C2).

(3a*R*,7a*R*)-2-Allyl-1,3-bis(4-bromobenzyl)-2-chlorooctahydro-1*H*-benzo[*d*][1,3,2]diazasilole:
(*R,R*)-121



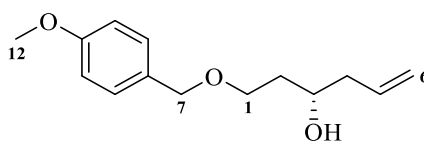
To a stirred suspension of salt (*R,R*)-1,2-diaminocyclohexane mono-($-$)-tartrate (5.00 g, 18.932 mmol, 1.0 equiv.) in water (80 mL) was added K_2CO_3 (5.22 g, 37.80 mmol, 2.0 equiv.), EtOH (48 mL) and a solution of *p*-bromo benzaldehyde (2.80 g, 15.11 mmol, 2.0 equiv.) and methanesulfonic acid (150 μL , 2.25 mmol, 0.1 equiv.) in DCM (80 mL). The biphasic solution was stirred at rt overnight followed by reflux for 1 h. The mixture was concentrated in vacuum followed by filtration. The residue was stirred in methanol (25 mL), cooled to 0 $^{\circ}\text{C}$ followed by addition of NaBH_4 (1.58 g, 42.52 mmol, 2.3 equiv.). It was allowed to warm to rt followed by reflux for 1 h. The resultant solution was concentrated followed by addition of 20 mL each of EtOAc, Petroleum ether and 1 N NaOH. The aqueous layer was extracted using (3 $\times$ 30 mL) 1:1 EtOAc / Petroleum ether, organic layers dried using MgSO_4 and purified *via* column chromatography using 1:5 EtOAc / Petroleum ether to 1:1:0.02 EtOAc / Petroleum ether / Et_3N to afford diamine (7.01 g, 15.521 mmol, 82 %) as a viscous oil.

^1H NMR (400 MHz, C_6D_6) δ_{H} 7.35–7.31 (4H, m, H7), 7.10–7.05 (4H, m, H6), 5.40–5.35 (2H, m, NH), 3.89–3.54 (2H, m, H4), 2.62–2.57 (2H, m, H1), 1.63–1.60 (2H, m, H2), 1.26–1.22 (2H, m, H3); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 140.1 (C5), 131.4 (C7), 129.8 (C6), 120.5 (C8), 60.9 (C1), 50.2 (C4), 31.5 (C2), 25.0 (C3). Data in accordance with literature.⁵⁹

To a stirring solution of allyltrichlorosilane (2.02 mL, 13.96 mmol, 1.2 eq) and DBU (4.1 mL, 28.0 mmol, 2.4 eq) in dry DCM (52 mL) at 0 °C under argon, was added the above diamine (5.2 g, 11.6 mmol, 1.0 eq) in dry DCM (22 mL) *via* syringe pump over 90 min. The reaction mixture was allowed to warm to RT and stirred overnight. The solvent was removed *via* distillation under argon and the resulting residue dried under vacuum. Dry pentane (65 mL) was added to the residue and the suspension stirred vigorously for 3 h. The mixture was filtered under argon and the filter cake rinsed with a further portion of dry pentane (6 mL). The filtrate was concentrated *in vacuo* to afford reagent as yellow oil (**(R,R)**-121 (5.7 g, 10.44 mmol, 88%).

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.36 (4H, ddd, J = 6.9, 6.4 and 4.7 Hz, H7), 7.21–7.17 (4H, m, H6), 5.55 (1H, ddt, J = 15.9, 11.1 and 6.9 Hz, H10), 4.83 (2H, dd, J = 11.1 and 6.9 Hz, H11), 3.96–3.92 (4H, m, H4), 2.68–2.64 (2H, m, H1), 1.86–0.68 (10 H, m, H2, H3 and H9); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 140.2 (C5), 131.2 (C10), 129.9 (C7), 129.0 (C6), 120.3 (C8), 116.3 (C11), 66.3 (C1), 47.9 (C4), 30.7 (C2), 24.7 (C3), 14.1 (C9). Data in accordance with literature.⁵⁹

(S)-1-((4-methoxybenzyl)oxy)hex-5-en-3-ol: 122



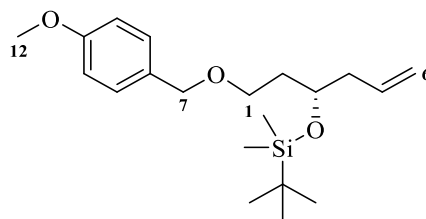
To a suspension of $\text{Sc}(\text{OTf})_3$ (191 mg, 0.388 mmol, 0.05 equiv.) in DCM (10 mL) was added aldehyde **120** (1.508 g, 7.762 mmol, 1.0 equiv.) as a solution in DCM (28 mL). To this was added reagent (**(R,R)**-121 as a solution in DCM (0.3 M, 1.2 eq) at 0 °C and the resulting solution was allowed to stir at 0 °C for 2 h. The solvents were then removed under *vacuo*, 100 mL of 1:1 Et_2O / 1N HCl was added and the biphasic solution was stirred for 2 h. The solution was filtered, layers separated, and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layer was dried (Na_2SO_4) and

concentrated *in vacuo*. The crude was purified *via* column chromatography (9:1 Petroleum ether / Et₂O) to afford **122** (1.008 g, 4.269 mmol, 55%, 92 % ee) as a colourless oil.

R_f 0.23 (3:2 Petroleum ether Ether / Et₂O); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.2 (2H, d, *J* = 8.5 Hz, H₉), 6.82 (2H, d, *J* = 8.8 Hz, H₁₀), 5.90–5.80 (1H, m, H₅), 5.15–5.10 (2H, m, H₆), 4.45 (2H, q, *J* = 12 Hz, H₇), 3.91–3.85 (1H, m, H₃), 3.82 (3H, s, H₁₂), 3.73–3.63 (2H, m, H₁), 2.89 (1H, br, OH), 2.27–2.24 (2H, t, *J* = 6.8 Hz, H₄), 1.81–1.74 (2H, m, H₂); **¹³C NMR** (100 MHz, CDCl₃) δ_C 159.1 (C₁₁), 134.9 (C₅), 130.7 (C₈), 129.3 (C₉), 117.0 (C₆), 113.8 (C₁₀), 72.6 (C₇), 70.4 (C₃), 68.6 (C₁), 55.3 (C₁₂), 41.9 (C₄), 35.9 (C₂). Data in accordance with literature.¹⁹⁵

Enantiomeric excess was determined by chiral HPLC: 95% *ee* (CHIRALPAK IB, 0.9 mL/min, 0.7% IPA/hexanes, Rt (*R*) – 23.88 min, Rt (*S*) – 25.23.

(*S*)-*t*-Butyl((1-((4-methoxybenzyl)oxy)hex-5-en-3-yl)oxy)dimethylsilane: 123

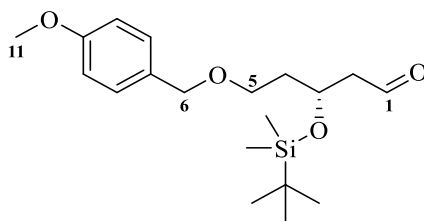


To a solution of **122** (1.110 g, 4.697 mmol, 1.0 eq) in anhydrous DCM (6.3 mL) at rt under argon was added DMAP (57 mg, 0.470 mmol, 0.1 eq), imidazole (0.640 g, 9.401 mmol, 2.0 eq) and TBSCl (1.476 g, 9.401 mmol, 2.0 eq). The reaction was stirred 8 h at rt and quenched with sat. *aq.* NaHCO₃ (15 mL), the layers were separated and the aqueous layer extracted with DCM (3×15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude was purified *via* column chromatography (9:1 Petroleum Ether / Et₂O) to afford **123** (1.482 g, 4.228 mmol, 90%) as a colourless oil.

R_f 0.63 (4:1 Petroleum ether / Et₂O); **[α]_D²⁵** +11.9 (*c* = 1.00, CHCl₃); **IR** (thin film) ν_{max}/cm⁻¹ = 2953, 2929, 2856, 1614, 1514, 1464, 1362, 1302, 1248, 1173, 1092, 1040; **¹H NMR** (400 MHz, CDCl₃) δ_H 7.2 (2H, d, *J* = 8.5 Hz, H₉), 6.82 (2H, d, *J* = 8.8 Hz, H₁₀), 5.79–5.72 (1H, m, H₅), 5.0–4.98 (1H, m, H₆), 4.96–4.95 (1H, m, H₆), 4.35 (2H, q, *J* = 12 Hz, H₇), 3.85–3.82 (1H, m, H₃), 3.75 (3H, s, H₁₂),

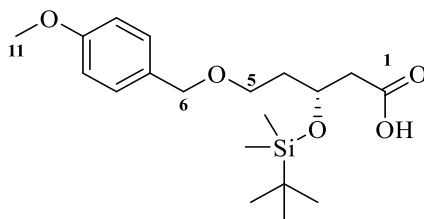
3.45 (2H, t, $J = 7.2$ Hz, H1), 2.20–2.14 (2H, m, H4), 1.70–1.64 (2H, m, H2), 0.87 (9H, s, SiC(CH₃)₃), 0.01 (3H, s, Si(CH₃)₂); 0.00 (3H, s, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_c 159.1 (C11), 134.9 (C5), 130.7 (C8), 129.3 (C9), 117.0 (C6), 113.8 (C10), 72.6 (C7), 69.0 (C3), 66.8 (C1), 55.3 (C12), 42.3 (C4), 36.7 (C2), 25.9 (SiC(CH₃)₃), 18.1 (SiC(CH₃)₃), -4.3 (Si(CH₃)₂), -4.7 (Si(CH₃)₂); HRMS (ESI⁺) calculated for C₂₀H₃₄O₃Si [M+Na]⁺ 373.2169, found 373.2164.

(*R*)-3-((*t*-Butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)pentanal: 124



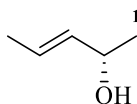
To the alkene **123** (290 mg, 0.827 mmol, 1.0 eq), stirring in 1,4-dioxane (6.4 mL) and water (1.4 mL), 2,6-lutidine (177 mg, 1.654 mmol, 2.0 equiv.), NaIO₄ (707 mg, 3.309 mmol, 4.0 equiv.) and OsO₄ (4.0 wt% in water, 0.105 mL, 0.017 mmol, 0.2 equiv.) was added. The reaction was stirred at rt for 2 h and then diluted with water (10 mL) and Et₂O (10 mL). The layers were separated and the aqueous layer extracted with Et₂O (3×15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude was purified *via* column chromatography (4:1 Petroleum ether / Et₂O) to yield aldehyde **124** (260 mg, 0.680 mmol, 81%) as colourless oil.

R_f 0.22 (9:1 Petroleum ether / EtOAc); [α]_D²⁵ +8.8 ($c = 1.00$, CHCl₃); **IR** (thin film) $\nu_{\max}/\text{cm}^{-1} = 2954$, 2930, 2857, 2361, 2341, 1725, 1613, 1514, 1464, 1362, 1302, 1249, 1173, 1094, 1034; ¹H NMR (400 MHz, CDCl₃) δ_H 9.72 (1H, t, $J = 2.8$ Hz, H1), 7.18 (2H, d, $J = 8.4$ Hz, H8), 6.80 (2H, d, $J = 8.8$ Hz, H9), 4.38–4.27 (3H, m, H3 and H6), 3.73 (3H, s, H11), 3.46–3.42 (2H, m, H5), 2.54–2.42 (2H, m, H2), 1.83–1.75 (2H, m, H4), 0.81 (9H, d, $J = 2.8$ Hz, SiC(CH₃)₃), 0.03 (3H, s, Si(CH₃)₂), 0.00 (3H, s, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_c 202.1 (C=O), 159.2 (C10), 130.4 (C7), 129.3 (C8), 113.8 (C9), 72.7 (C6), 66.0 (C5), 65.7 (C3), 55.3 (C11), 51.1 (C2), 37.6 (C4), 25.6 (SiC(CH₃)₃), 18.0 (SiC(CH₃)₃), -4.6 (Si(CH₃)₂); HRMS (ESI⁺) calculated for C₁₉H₃₂O₄Si [M+Na]⁺ 375.1962, found 375.1956.

(*R*)-3-((*t*-Butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)pentanoic acid: 117

To a stirring solution of aldehyde **124** (1.504 g, 4.269 mmol, 1.0 equiv.) in *t*-BuOH (50 mL) was added 2-methyl-2-butene (13.6 mL, 128.028 mmol, 30 equiv.). To it, a solution of NaClO₂ (3.861 g, 42.694 mmol, 10.0 equiv.) and NaPO₂(OH)₂·2H₂O (5.329 g, 34.155 mmol, 8.0 equiv.) in water (22 mL) was added using a syringe pump over 15 min. The biphasic mixture was stirred overnight at rt. Once shown to be complete by TLC, the reaction mix was concentrated, and 10 mL water was added to the resulting residue. It was then extracted with petroleum ether (50 mL × 4). The organic layers were combined, dried (Na₂SO₄) and concentrated *in vacuo* to afford acid **117** (1.573 g, 4.269 mmol g, 99%) as a colourless oil. The crude was used without further purification.

R_f 0.32 (7:3 Petroleum ether / EtOAc); [α]_D²⁵ +2.5 (*c* = 1.00, CHCl₃); **¹H NMR** (400 MHz, CDCl₃) δ _H 10.03 (1H, bs, OH), 7.3 (2H, m, H8), 6.78 (2H, d, *J* = 8 Hz, H9), 4.36–4.29 (2H, m, H6), 4.22–4.17 (1H, m, H3), 3.7 (3H, s, H11), 3.4 (2H, t, *J* = 6.0 Hz, H5), 2.53–2.39 (2H, m, H2), 1.87–1.83 (2H, m, H4), 0.85 (9H, s, SiC(CH₃)₃), 0.09 (3H, s, Si(CH₃)₂), 0.07 (3H, s, Si(CH₃)₂); **¹³C NMR** (100 MHz, CDCl₃) δ _C 175.3 (C=O), 159.2 (C10), 130.3 (C8), 129.3 (C9), 113.8 (C7), 72.7 (C6), 66.9 (C5), 66.0 (C3), 55.3 (C11), 42.0 (C2), 37.1 (C4), 25.7 (SiC(CH₃)₃), 17.9 (Si(CH₃)₂), –4.8 (Si(CH₃)₂); **HRMS** (ESI⁺) calculated for C₁₉H₃₂O₅Si [M+Na]⁺ 391.1911, found 391.1906.

(*S,E*)-Pent-3-en-2-ol: (*S, E*)-34

To a stirring solution of crotonaldehyde (5.95 mL, 72.0 mmol, 1.0 eq) in anhydrous Et₂O (25 mL) under nitrogen at 0 °C was added MeLi (1.6 M in Et₂O, 45 mL, 1.0 eq) drop-wise. The solution was allowed to warm to rt. After 1 h, the reaction was quenched with sat. *aq.* NH₄Cl dropwise (50 mL) and the

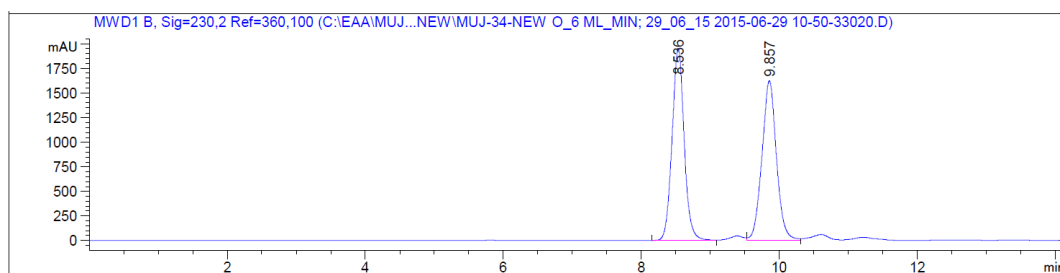
aqueous layer extracted with Et₂O (3 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified via column chromatography (1:4 DCM / Pentane) to yield a solution of achiral alcohol ***rac*-34** (17.2 g, 38.8 mmol in 9.3 g solution of DCM / Pentane).

Kinetic Resolution: To a solution of the alcohol ***rac*-34** (1.00 g, 11.61 mmol, 1.0 eq) in pentane (15 mL) under an inert atmosphere was added Novozyme 435 (0.10 g, 10 wt%), vinyl acetate (0.86 mL, 9.30 mmol, 0.8 eq) and 4 Å MS (crushed, 0.5 g, 50 wt%). The reaction was stirred at RT for 40 min. before the mixture was filtered through Celite® and concentrated *in vacuo*. The crude product was purified *via* column chromatography (4:1 Pentane / DCM → 7:3 Pentane / Et₂O) to yield a solution of (***S,E***)-**34** (0.347 g, 4.06 mmol in 1.46 g Et₂O / Pentane, 35%, 99% *ee*,) in Et₂O / Pentane.

R_f 0.45 (1:1 Petroleum ether 30-40 °C/Et₂O); **¹H NMR** (400 MHz, CDCl₃) δ_H 5.75-5.4 (2H, m, H3 and H4), 4.32-4.18 (1H, m, H2), 1.69 (3H, d, *J* = 6.0 Hz, H5), 1.5 (1H, bs, OH), peak for H1 overlapping with the solvent.

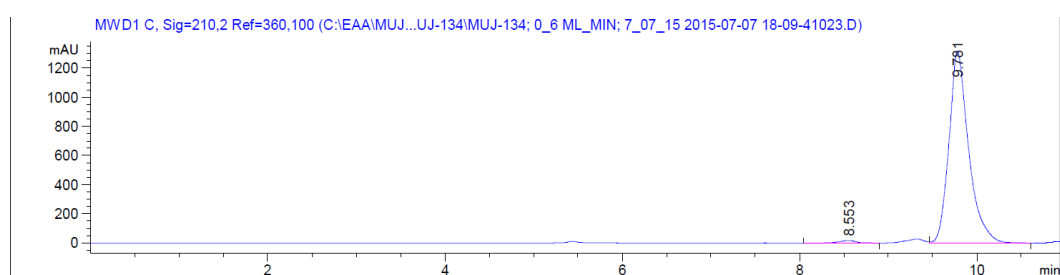
Enantiomeric excess was determined as follows: a vial under an inert atmosphere was charged with the alcohol (20 mg) in DCM (0.5 mL) and to it was added benzoyl chloride (33 mg), NEt₃ (46 µL) and DMAP (1 mg). The reaction was stirred overnight at RT and quenched with sat. *aq.* NH₄Cl. The layers separated, and the aqueous layer was extracted with DCM. The combined organic layers were dried (Na₂SO₄) and the crude purified *via* column chromatography (4:1 Petroleum ether 30-40 °C/Et₂O) to yield the ester, which was used for HPLC analysis.

Enantiomeric excess was determined by chiral HPLC: 99% *ee* (CHIRALPAK IA, 1.3 mL/min, 0.5% IPA/hexanes, Rt (*R*) – 8.55 min, Rt (*S*) – 9.86 min).



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

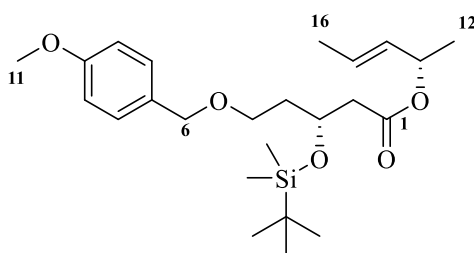
Totals : 4.76162e4 3579.78699



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

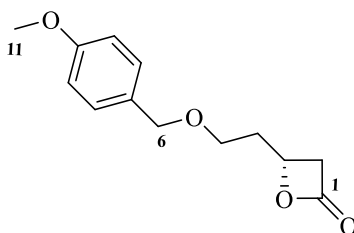
(*S,E*)-Pent-3-en-2-yl (*R*)-3-((*t*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy) pentanoate: **125**



To a stirring solution of chiral alcohol (***S,E*-34**) (66 mg, 0.697 mmol, 1.1 equiv.) and acid **117** (252 mg, 0.633 mmol, 1.0 equiv.) in THF (0.5 mL) under argon, EDC·HCl (182 mg, 0.951 mmol, 1.5 equiv.), NEt₃ (0.177 mL, 1.267 mmol, 2.0 equiv.) and DMAP (7.7 mg, 0.063 mmol, 0.1 equiv.) was added. The reaction was stirred overnight at rt and then quenched with water (10 mL). The aqueous layer was extracted with EtOAc (10 mL × 3) and the combined organic layers dried (Na₂SO₄) and evaporated *in vacuo* to afford the crude product, which was purified *via* column chromatography (9:1 Petroleum ether/Et₂O) to yield the desired ester **125** (121 mg, 0.253 mmol, 40%) as a colourless oil.

R_f 0.2 (9:1 Petroleum ether / Et₂O); $[\alpha]_D^{25}$ -25.9 (*c* = 1.00, CHCl₃); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.20 (2H, d, *J* = 8.8 Hz, H8), 6.82 (2H, d, *J* = 8.6 Hz, H9), 5.68-5.63 (1H, m, H15), 5.42-5.38 (1H, m, H14), 5.26-5.23 (1H, m, H13), 4.39-4.32 (2H, m, H6), 4.24-4.21 (1H, m, H3), 3.75 (3H, s, H11), 3.45 (2H, t, *J* = 6.4 Hz, H5), 2.42-2.38 (2H, m, H2), 1.79-1.73 (2H, m, H4), 1.64-1.61 (3H, m, H16), 1.22 (3H, d, *J* = 6.4 Hz, H12), 0.80 (9H, s, SiC(CH₃)₃), 0.00 (3H, s, Si(CH₃)₂), -0.08 (3H, s, Si(CH₃)₂); **¹³C NMR** (100 MHz, CDCl₃) δ_C 170.8 (C=O), 159.1 (C10), 130.9 (C14), 130.6 (C8), 129.2 (C7), 128.1 (C15), 113.8 (C9), 72.5 (C6), 71.1 (C13), 66.9 (C3), 66.3 (C5), 55.3 (C11), 43.2 (C2), 37.3 (C4), 25.8 (SiC(CH₃)₃), 20.4 (SiC(CH₃)₃), 18.0 (C12), 17.7 (C16), -4.7 (Si(CH₃)₂); **HRMS** (ESI⁺) calculated for C₂₄H₄₀O₅Si [M+Na]⁺ 459.25372, found 459.25234.

(*R*)-4-(2-((4-Methoxybenzyl)oxy)ethyl)oxetan-2-one, 126

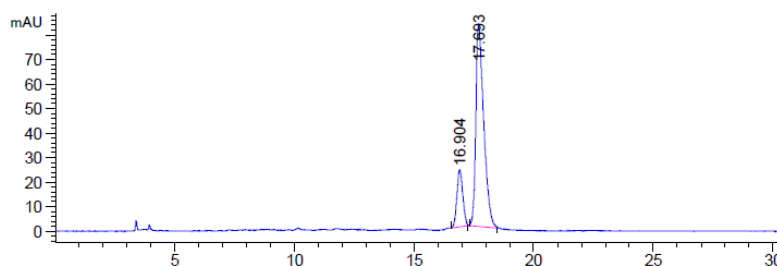


To a solution of TMSQ (1.02 g, 2.56 mmol, 0.1 equiv.)⁶¹ and LiClO₄ (819 mg, 7.70 mmol, 0.3 equiv.) in Et₂O (20 mL) was added CH₂Cl₂ (20 mL). The reaction mixture was cooled to -78 °C. To this was added DIPEA (12.0 mL, 71.8 mmol, 2.8 equiv.), followed by aldehyde **120** (4.98 g, 25.7 mmol, 1.0 equiv.). A solution of acetyl chloride (3.30 mL, 50.5 mmol, 1.8 equiv.) in CH₂Cl₂ (20 mL) was added over 3 h *via* syringe pump, and the resulting solution was stirred at -78 °C for 21 h. The reaction was quenched by addition of Et₂O (50 mL) followed by saturated aq. NH₄Cl (50 mL). It was then extracted using CH₂Cl₂ (3 x 50 mL). The combined organic layer was dried using Na₂SO₄, concentrated, and purified using column chromatography (7:3 petroleum ether / Et₂O) to yield **126** (64% *ee*, 4.36 g, 18.5 mmol, 72 %) as a light-yellow viscous oil.

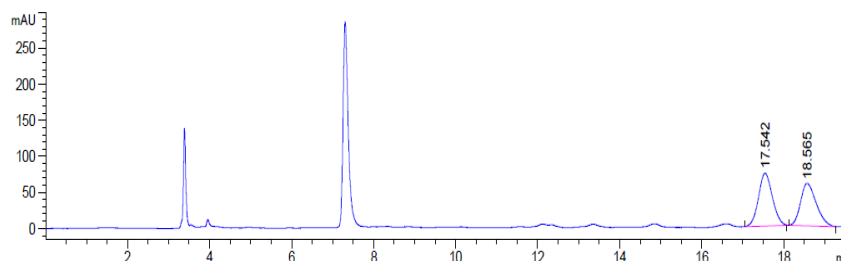
R_f 0.12 (4:1 petroleum ether/EtOAc); **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$: 2866, 1822, 1612, 1586, 1464, 1302, 1175, 938, 822, 756; **¹H NMR** (400 MHz, CDCl₃) δ_H 7.24 (2H, d, *J* = 8.4 Hz, H8), 6.88 (2H, d, *J* = 8.4, H9), 4.71-4.66 (1H, m, H3), 4.43 (2H, s, H6), 3.80 (3H, s, H11), 3.61-3.56 (2H, m, H5), 3.37 (1H, dd,

$J = 13.2$ and 5.6 Hz, H2), 3.33 (1H, dd, $J = 13.2$ and 5.6 Hz, H2) 2.16-2.02 (2H, m, H4); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 168.4 (C=O), 159.4 (C10), 130.0 (C7), 129.3 (C8), 128.5, 113.9 (C9), 73.0 (C6), 69.2 (C5), 65.5 (C3), 55.3 (C11), 43.2 (C2), 34.8 (C4); **Anal.** (%) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C 66.09; H 6.83. Found: C 66.18; H 6.72.

Enantiomeric excess was determined by chiral HPLC: *er* 82:18 (CHIRALPAK IB, 1.0 mL/min, 5% IPA/hexanes, Rt (*S*)-17.05 min, Rt (*R*)-17.97 min).

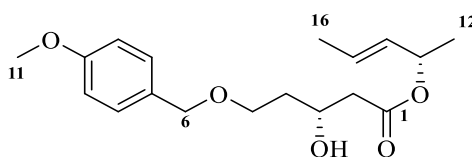


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.904	VV	0.2031	397.09665	23.27376	17.3989
2	17.693	VV	0.2896	1885.20837	82.48370	82.6011



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.542	VV	0.2775	1733.28320	73.27393	52.5029
2	18.565	VV	0.3119	1568.02527	58.93707	47.4971

(*R*)-(S,*E*)-Pent-3-en-2-yl 3-hydroxy-5-((4-methoxybenzyl)oxy)pentanoate, 116



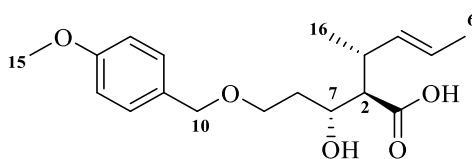
To a stirring solution of **125** (2.65 g, 6.062 mmol, 1.0 equiv.) in THF (72.0 mL) at 0 °C under argon, was added TBAF (1 M in THF, 6.67 mL, 1.1 equiv.) and the reaction was allowed to warm up to rt

overnight. This was quenched with sat. *aq.* NH₄Cl (10 mL), and the aqueous layer extracted with Et₂O (10 mL × 3). The combined organic layers were dried over Na₂SO₄, concentrated *in vacuo*. The crude was purified *via* column chromatography (3:2→1:1 Petroleum ether/Et₂O) to yield **116** (68 mg, 0.212 mmol, 84%) as a colourless oil

Alternatively, to a solution of alcohol (**S,E**)-**34** (1.55 g, 18.0 mmol, 1.8 equiv.) in THF (35 mL) at -20 °C was added MeMgBr (6 mL, 18.0 mmol, 3 M in THF, 1.8 equiv.). The solution was stirred for 20 min followed by the addition of a solution of **126** (2.49 g, 9.99 mmol, 1.0 equiv.) in THF (10 mL). The resulting solution was slowly warmed to rt over 3 h. The reaction was quenched by addition of saturated *aq.* NH₄Cl (50 mL), the layers were separated, and the aqueous layer was extracted with Et₂O (4 x 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified *via* column chromatography (3:2→1:1 petroleum ether / Et₂O) to afford **116** (2.07 g, 6.00 mmol, 60%, 82:18 mixture of diastereomers at C3) as a colourless oil.

R_f 0.22 (3:2 Petroleum Ether/Et₂O); [α]_D²⁵ -34.2 (*c* = 1.00, CHCl₃) (this value is obtained from deprotection of **125**); **IR** (thin film) ν_{max} /cm⁻¹ 2936, 2860, 1727, 1613, 1586, 1513, 1444, 1370, 1247, 1208, 1173, 1094; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.19 (2H, d, *J* = 8.4 Hz, H8), 6.75 (2H, d, *J* = 8.4, H9), 5.70-5.63 (1H, dq, *J* = 13.0 and 6.5 Hz, H15), 5.44-5.38 (1H, m, H14), 5.32-5.25 (1H, m, H13), 4.39 (2H, s, H6), 4.17-4.13 (1H, m, H3), 3.74 (3H, s, H11), 3.63-3.52 (2H, m, H5), 3.3 (1H, br, OH), 2.41 (2H, d, *J* = 6.4 Hz, H2), 1.75-1.69 (2H, m, H4), 1.64-1.62 (3H, m, H16), 1.22 (3H, d, *J* = 6.4 Hz, H12); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 171.8 (C=O), 159.3 (C10), 130.6 (C14), 130.2 (C7), 129.3 (C8), 128.5 (C15), 113.9 (C9), 72.9 (C6), 71.5 (C13), 67.6 (C5), 66.9 (C3), 55.3 (C11), 41.9 (C2), 36.0 (C4), 20.3 (C12), 17.7 (C16). **HRMS** (ESI⁺) calculated for C₁₈H₂₆O₅[M+Na]⁺ 345.1673, found 345.1665.

(2*R*,3*R*,*E*)-2-((*R*)-1-Hydroxy-3-((4-methoxybenzyl)oxy)propyl)-3-methylhex-4-enoic acid, 137

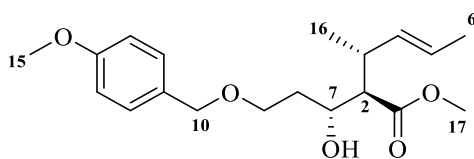


To a solution of DIPA (84 μ L, 0.605 mmol, 3.0 equiv.) in THF (0.3 mL) at 0 °C under argon, was added *n*-BuLi (2.5 M in hexanes, 0.242 mL, 0.605 mmol, 3.0 equiv.) dropwise. After 10 min, the resulting

LDA solution was added drop-wise, over 1 h, to a stirred suspension of **116** (65 mg, 0.202 mmol, 1.0 equiv., obtained from **125**) in THF (3.0 mL) at -78°C under argon. The reaction was further stirred for 90 min then allowed to warm to RT and stirred for another 24 h. It was then acidified (pH 2) with 1 N HCl. The layers were separated, and the aqueous layer extracted with EtOAc (3×15 L). The combined organic layers were dried over Na_2SO_4 , concentrated and purified *via* column chromatography (7:3:0.1 Petroleum ether/EtOAc/AcOH) to afford acid **137** as yellow solid (30.0 mg, 0.093 mmol, 46%) with dr > 40:1.

R_f 0.24 (7:3:0.01 Petroleum ether/EtOAc / AcOH); **m. pt.** $93-96^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} +30.0$ ($c = 1.00$, CHCl_3) **¹H NMR** (500 MHz, C_6D_6) $\delta_{\text{H}} \sim 7.2$ (2H, d, H12), 6.75 (2H, d, $J = 7$ Hz, H13), 5.58-5.53 (1H, m, H4), 5.43-5.39 (1H, m, H5), 4.23 (2H, s, H10), 4.09 (1H, m, H7), 3.5-3.42 (2H, m, H9), 3.3 (3H, s, H15), 2.7-2.63 (1H, m, H3), 2.35-2.32 (1H, m, H2), 1.78-1.71 (2H, m, H8), 1.56 (3H, d, $J = 6.0$ Hz, H6), 1.08 (3H, d, $J = 7.0$ Hz, H16); **¹³C NMR** (125 MHz, C_6D_6) δ_{C} 177.6 (C=O), 159.5 (C14), 133.8 (C5), 130.3 (C11), 129.2 (C12), 128.2 (C4), 113.8 (C13), 72.6 (C10), 68.6 (C7), 67.6 (C9), 57.0 (C2), 54.4 (C15), 36.6 (C3), 35.2 (C8), 18.7 (C16), 17.7 (C6); **HRMS** (ESI^+) calculated for $\text{C}_{18}\text{H}_{26}\text{O}_5$ $[\text{M}+\text{Na}]^+$ 345.1673, found 345.1665.

(2R,3R,E)-Methyl 2-((R)-1-hydroxy-3-((4-methoxybenzyl)oxy)propyl)-3-methylhex-4-enoate, 112

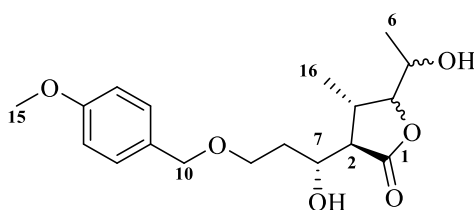


To a solution of *i*-Pr₂NH (2.10 mL, 14.9 mmol, 2.5 equiv.) in THF (10 mL) at 0°C under argon was added *n*-BuLi (2.5 M in hexanes, 5.95 mL, 14.9 mmol, 2.5 equiv.) dropwise. After 10 min, the resulting solution of LDA was added dropwise, over 1 h, to a stirred suspension of **116** (1.92 g, 5.95 mmol, 1.0 equiv., 82:18 mixture of diastereomers at C3) in THF (90 mL) at -78°C under argon. The reaction was further stirred for 90 min then allowed to warm to RT and stirred for another 24 h. It was then acidified to pH 2 with 1 N HCl. The layers were separated, and the aqueous layer extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. This residue was

dissolved in toluene (120 mL) and MeOH (30 mL) and placed under Ar. To the stirred solution at 0 °C was added 3.9 mL TMSCHN₂ (2 M in hexane, 1.35 equiv.). The mixture was stirred at 0 °C for 30 min and then at rt for 90 min before being quenched with acetic acid (3.0 mL). The resulting solution was extracted with EtOAc (3 × 25 mL), dried over Na₂SO₄, concentrated and purified *via* flash chromatography (8:2 petroleum ether / Et₂O) to afford ester **112** (1.42 g, 4.28 mmol, 72%, 82:18 mixture of diastereomers at C7).

R_f 0.33 (1:1 petroleum ether / Et₂O); [α]_D²⁵ +5.9 (c = 0.64, CHCl₃) (this value is obtained from the route involving **125**); **IR** (thin film) ν_{max} /cm⁻¹ 3504, 2954, 2858, 1732, 1613, 1586, 1514, 1362, 1248, 1035, 970; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.23 (2H, d, *J* = 8.6 Hz, H12), 6.85 (2H, *J* = 8.6 Hz, H13) 5.51-5.28 (2H, m, H4, H5), 4.42 (2H, s, H10), 3.96 (1H, m, H7), 3.78 (3H, s, H15) 3.68-3.55 (2H, m, H9), 3.65 (3H, s, H17), 2.63-2.53 (1H, m, H3), 2.46 (1H, d, *J* = 6.3 Hz, OH), 2.28-2.24 (1H, dd, *J* = 4.8 Hz, H2), 1.8-1.72 (1H, m, H8), 1.69-1.64 (1H, m, H8) 1.6 (3H, d, *J* = 5.9 Hz, H6), 1.05 (3H, d, *J* = 6.8 Hz, H16); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 175.0 (C=O), 159.2 (C14), 133.6 (C5), 130.3 (C11), 129.3 (C12), 125.2 (C4), 113.8 (C13), 72.9 (C17) 68.2 (C10), 67.5 (C7), 56.6 (C9), 55.2 (C15), 51.1 (C2), 36.7 (C3), 35.6 (C8), 18.7 (C16), 17.8 (C6); **HRMS** (ESI⁺) calculated for C₁₉H₂₉O₅ [M+H]⁺ 337.2010, found 337.2016.

(3*R*,4*S*)-3-((*R*)-1-Hydroxy-3-((4-methoxybenzyl)oxy)propyl)-5-(1-hydroxyethyl)-4-methyl-dihydrofuran-2(3H)-one: 143

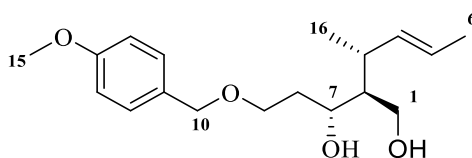


To a stirred solution of **112** (21 mg, 0.062 mmol, 1.0 equiv., single diastereomer) in acetone (0.4 mL) and water (0.13 mL), OsO₄ (4% wt in water, 15.9 μ L, 2.50 μ mol, 0.04 equiv.) was added followed by NMO (50% wt in water, 21.9 μ L, 0.094 mmol, 1.5 equiv.). The reaction mixture was stirred at rt for 2 h before being quenched with sat. *aq.* Na₂SO₃ solution. The layers were separated, and the aqueous layer extracted three times with ethyl acetate (5 mL × 3). The combined organic layers were dried with

Na₂SO₄ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (3:2 petroleum ether / EtOAc) to give a pale yellow oil **143** (10 mg 0.030 mmol, 48%, single diastereomer).

R_f 0.34 (1:4 petroleum ether / Et₂O); [α]_D²⁵: +5.05 (c = 0.925, CHCl₃); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3429, 2921, 1762, 1660, 1633, 1514, 1302, 1249, 1033, 991; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.23 (2H, d, *J* = 8.6 Hz, H12), 6.87 (2H, *J* = 8.6 Hz, H13), 4.48–4.41 (2H, q, *J* = 12.3 Hz, H10), 4.06 (1H, m, H7), 3.85–3.78 (5H, m, H15, H4, H5) 3.73–3.62 (2H, m, H9), 3.59 (1H, br, C7 OH), 2.53–2.43 (1H, m, H3), 2.38–2.35 (1H, *app* q, *J* = 4.6 Hz, H2), 2.20–2.10 (1H, m, H8), 2.10 (1H, br, C5 OH), 1.79–1.72 (1H, m, H8) 1.31–1.29 (3H, d, *J* = 5.9 Hz, H6), 1.20–1.18 (3H, d, *J* = 6.8 Hz, H16); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 176.7 (C=O), 159.3 (C14), 129.9 (C11), 129.4 (C12), 113.8 (C13), 88.5 (C4) 73.0 (C10), 70.0 (C7), 68.1 (C5), 67.6 (C9), 55.3 (C15), 53.4 (C2), 33.9 (C3), 33.7 (C8), 19.6 (C16), 17.8 (C6); **HRMS** (ESI⁺) calculated for C₁₈H₂₇O₆ [M+H]⁺ 339.1802, found 339.1805.

(2*S*,3*R*)-5-((4-Methoxybenzyl)oxy)-2-((*R,E*)-pent-3-en-2-yl)pentane-1,3-diol, 144

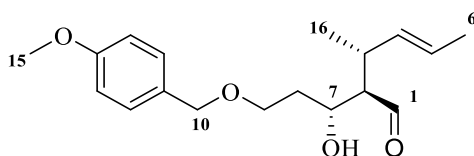


To a stirred solution of **112** (2.00 g, 5.96 mmol, 1.0 equiv., 82:18 mixture of diastereomers at C7) in Et₂O (40 mL) at –78 °C was added LiAlH₄ (3.0 mL, 4M in Et₂O, 12.0 mmol, 2.0 equiv.) dropwise. The reaction was allowed to warm to RT over 3 h, then it was quenched by addition of 1 N NaOH (50 mL) and extracted with Et₂O (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, concentrated, and purified by flash column chromatography (2:3 petroleum ether / Et₂O) to afford **144** (1.45 g, 4.71 mmol, 75%, single diastereomer) as a clear oil.

R_f 0.23 (3:7 EtOAc/ petroleum ether); [α]_D²⁵: +13.7 (c = 1.02, CHCl₃); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3429, 2959, 2916, 2855, 1613, 1586, 1439, 1351, 1248, 1175, 1094, 1035, 971, 849; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.23 (2H, d, *J* = 8.6 Hz, H12), 6.87 (2H, *J* = 8.6 Hz, H13), 5.47–5.40 (1H, m, H5), 5.30–5.24 (1H, dd, *J* = 8.9 Hz and 15.6 Hz, H4), 4.45 (2H, m, H10), 4.03 (1H, m, H7), 3.88–3.82 (1H, m, OH),

3.80 (3H, s, H15), 3.79–3.60 (4H, m, H1, H9), 3.23 (1H, t, $J = 5.4$ Hz, OH), 2.47–2.38 (1H, m, H3), 2.03–1.91 (1H, m, H8), 1.79–1.73 (1H, m, H8), 1.64 (3H, dd, $J = 1.4$ Hz and 6.1 Hz, H6), 1.23–1.28 (1H, m, H2), 1.06 (3H, d, $J = 6.8$ Hz, H16); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 159.4 (C14), 134.5 (C5), 129.8 (C11), 129.4 (C12), 125.0 (C4), 113.9 (C13), 74.2 (C7) 73.1 (C10), 69.4 (C9), 62.06 (C1), 55.8 (C15), 50.1 (C2), 35.6 (C3), 35.1 (C8), 19.2 (C6), 17.9 (C16); HRMS (ESI^+) calculated for $\text{C}_{18}\text{H}_{28}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 331.1880, found 331.1873.

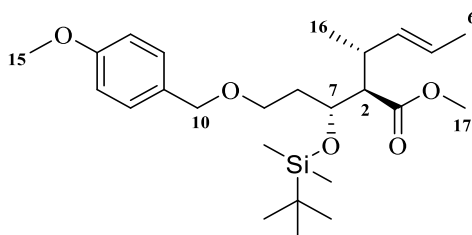
(2*R*,3*R*,*E*)-2-((*R*)-1-Hydroxy-3-((4-methoxybenzyl)oxy)propyl)-3-methylhex-4-enal, 145



To a stirring solution of **144** (25 mg, 0.081 mmol, 1.0 equiv.) in DCM (0.5 mL) and water (0.5 mL), TEMPO (14 mg, 0.089 mmol, 1.1 equiv.) and BAIB (24 mg, 0.105 mmol, 1.3 equiv.) was added. The resulting biphasic solution was stirred for 50 min. and then quenched with saturated Na_2SO_3 (2 mL) solution. It was then extracted thrice by Et_2O (5 mL $\times$ 3). The combined organic layer was dried over Na_2SO_4 and purified by flash column chromatography (4:1 Petroleum ether/ Et_2O) to yield **145** (22 mg, 0.075 mmol, 92%) as a colourless oil.

R_f 0.13 (3:7 Et_2O / petroleum ether); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3425, 2960, 2858, 1732, 1440, 1341, 1175, 1092, 1031, 970; ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.72 (1H, d, $J = 3.72$ Hz), 7.23 (2H, d, $J = 8.6$ Hz, H12), 6.87 (2H, $J = 8.6$ Hz, H13), 5.53–5.40 (1H, m, H5), 5.35–5.27 (1H, m, H4), 4.44 (2H, t, $J = 12.3$ Hz, H10), 4.17 (1H, m, H7), 3.80 (3H, s, H15), 3.73–3.60 (2H, m, H9), 3.26 (1H, br, OH), 2.79–2.69 (1H, m, H3), 2.07–2.01 (1H, m, H2), 1.88–1.70 (2H, m, H8), 1.63 (3H, d, $J = 5.86$ Hz, H6), 1.1 (3H, d, $J = 6.8$ Hz, H16); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 206.6 (C1), 159.4 (C14), 133.2 (C5), 129.8 (C11), 129.3 (C12), 126.3 (C4), 113.9 (C13), 73.1 (C10), 70.3 (C7), 68.7 (C9), 61.9 (C2), 55.8 (C15), 35.3 (C3), 34.7 (C8), 18.9 (C6), 17.8 (C16). HRMS (ESI^+) calculated for $\text{C}_{18}\text{H}_{27}\text{O}_4$ $[\text{M}+\text{H}]^+$ 307.1831, found 307.1826.

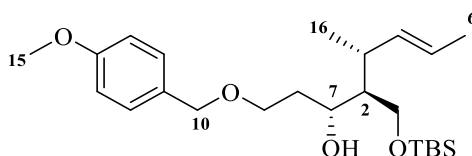
Methyl (2*R*,3*R*,*E*)-2-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)propyl)-3-methylhex-4-enoate, **147**



A stirred solution of **112** (16 mg, 0.047 mmol, 1.0 equiv.) and 2,6-lutidine (16.3 μ L, 0.141 mmol, 3.0 equiv.) was cooled to 0 $^{\circ}$ C before TBSOTf (21.5 μ L, 0.093 mmol, 2.0 eq) was added to it. This was allowed to warm to rt and further stirred for 2 h. The reaction was quenched with water, extracted with Et₂O thrice (10 mL $\times$ 3). The combined organic layers were dried over MgSO₄ and purified by flash column chromatography (9:1 petroleum ether/Et₂O) to give **147** as a colourless oil (19 mg, 0.042 mmol, 89%).

R_f: 0.29 (47:3 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2956, 2930, 2856, 1736, 1514, 1249, 1172, 1096, 1039, 1015, 974, 776; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.23 (2H, d, J = 8.6 Hz, H12), 6.86–6.84 (2H, J = 8.6 Hz, H13), 5.47–5.3 (2H, m, H4), 4.40 (2H, t, J = 12.3 Hz, H10), 4.04 (1H, m, H7), 3.78 (3H, s, H15), 3.60 (3H, s, H17) 3.55–3.50 (2H, m, H9), 2.50–2.42 (2H, m, H2 and H3), 1.96–1.85 (1H, m, H8), 1.82–1.76 (1H, m, H8) 1.60 (3H, d, J = 5.9 Hz, H6), 0.93 (3H, d, J = 6.8 Hz, H16), 0.80 (9H, s, SiC(CH₃)₃), 0.00 (3H, s, Si (CH₃)₂), -0.15 (3H, s, Si(CH₃)₂); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 173.7 (C=O), 159.1 (C14), 132.8 (C5), 130.6 (C11), 129.2 (C12), 125.4 (C4), 113.7 (C13), 72.7 (C17) 69.7 (C10), 65.4 (C7), 56.3 (C9), 55.3 (C15), 50.9 (C2), 36.0 (C3), 33.3 (C8), 25.7 (SiC(CH₃)₃), 20.0 (C6), 18.0 (C16), 17.9 (SiC(CH₃)₃), -5.0 and -4.3 (Si(CH₃)₂); **HRMS** (ESI⁺) calculated for C₂₅H₄₂O₅SiNa [M+Na]⁺ 473.2694, found 473.2694.

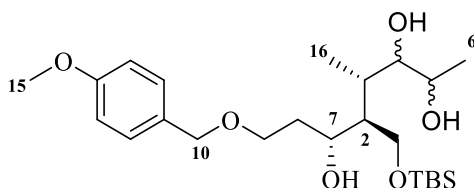
(3*R*,4*S*,5*R*,*E*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy)-5-methyloct-6-en-3-ol, **148**



To a solution of **144** (2.67 g, 8.67 mmol, 1.0 equiv.) in CH₂Cl₂ (21 mL) at 0 °C was added TBSCl (1.57 g, 10.4 mmol, 1.2 equiv.), DMAP (106 mg, 0.87 mmol, 0.1 equiv.) and imidazole (1.18 g, 17.3 mmol, 2.0 equiv.). The mixture was allowed to stir at 0 °C for 50 min before quenching with water (50 mL). It was then extracted with Et₂O (3 × 25 mL), dried (Na₂SO₄), and concentrated. Purification by flash column chromatography (4:1 petroleum ether / Et₂O) afforded **148** (3.37 g, 7.97 mmol, 92%) as a yellow oil.

R_f 0.36 (4:1 petroleum ether / Et₂O); **[α]_D²⁵** +16.85 (c = 0.99, CHCl₃); **IR** (thin film) ν_{max}/cm⁻¹: 3512, 2927, 2047, 1741, 1584, 1362, 1249, 1172, 1075, 969; **¹H NMR** (400 MHz, CDCl₃) δ_H 7.26 (2H, d, *J* = 8.6 Hz, H12), 6.87 (2H, *J* = 8.6 Hz, H13), 5.47–5.39 (1H, m, H5), 5.28–5.21 (1H, m, H4), 4.46 (2H, t, *J* = 12.3 Hz, H10), 3.98–3.87 (2H, m, H1, H7), 3.82–3.79 (1H, m, H1), 3.80 (3H, s, H15), 3.64 (2H, t, *J* = 6.6 Hz, H9), 3.53 (1H, d, *J* = 7.3 Hz, OH), 2.61–2.52 (1H, m, H3), 1.93–1.85 (1H, m, H8), 1.82–1.73 (1H, m, H8), 1.65 (3H, d, *J* = 6.0 Hz, H6), 1.15–1.10 (1H, m, H2), 1.06 (3H, d, *J* = 6.9 Hz, H16), 0.89 (9H, s, SiC(CH₃)₃), 0.05 (3H, s, Si(CH₃)₂), 0.04 (3H, s, Si(CH₃)₂); **¹³C NMR** (100 MHz, CDCl₃) δ_C 159.3 (C14), 135.9 (C5), 130.8 (C11), 129.4 (C12), 124.8 (C4), 113.9 (C13), 73.0 (C7), 70.0 (C10), 68.1 (C9), 62.5 (C1), 55.4 (C15), 48.8 (C2), 36.7 (C3), 35.4 (C8), 25.9 (SiC(CH₃)₃), 19.2 (C6), 18.0 (SiC), 17.9 (C16), -5.5 and -5.6 (SiC(CH₃)₂); **HRMS** (ESI⁺) calcd for C₁₈H₂₇O₆ [M+Na]⁺ 445.2745, found 445.2749.

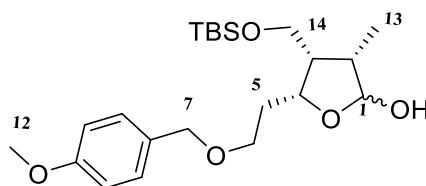
(4*S*,5*S*,6*R*)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-8-((4-methoxybenzyl)oxy)-4-methyloctane-2,3,6-triol, **150**



To a stirred solution of alkene **148** (612 mg, 1.45 mmol, 1.0 equiv.) in acetone (14 mL) and water (4.6 mL) was sequentially added OsO₄ (4% wt in water, 0.37 mL, 0.058 mmol, 0.04 equiv.) and NMO (50% wt in water, 0.61 mL, 2.61 mmol, 1.8 equiv.). The reaction mixture was stirred at RT for 3 h before being quenched with sat. *aq.* Na₂S₂O₃ solution (20 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with Na₂SO₄, and concentrated. The crude product was purified by flash column chromatography through a short plug of silica (49:1 CH₂Cl₂ / MeOH) to afford the triols **150** (686 mg, 1.45 mmol, 2.8:1 inconsequential mixture of diastereomers at C7 and C8, 99%) as a yellow oil.

R_f 0.3 (49:1 DCM/MeOH); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3373, 2959, 1514, 1464, 1362, 1259, 1088, 1038, 836, 802, 703; **¹H NMR** (400 MHz, CDCl₃, peaks corresponding to major diastereomer reported) δ_{H} 7.23 (2H, d, J = 8.6 Hz, H13), 6.87 (2H, J = 8.6 Hz, H12), 4.43 (2H, s, H10), 4.08–3.17 (12H, m, H1, H4, H5, H7, H9 and H15), 2.04 (1H, m, H2), 2.02 (1H, m, H3), 1.90 (2H, m, H8), 1.22 (3H, d, H6), 1.03 (3H, d, H16) 0.93 (9H, s, SiC(CH₃)₃), 0.02 (3H, s, Si(CH₃)₃); 0.01 (3H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃, peaks corresponding to major diastereomer reported) δ_{C} 159.3 (C14), 130.0 (C11), 129.9 (C12), 113.9 (C13), 76.9 (C10), 73.0 (C7), 69.6 (C4, C5), 69.0 (C4, C5), 67.8 (C9), 61.0 (C1), 55.3 (C15), 49.1 (C2), 37.7 (C3), 35.4 (C8), 25.9 (SiC(CH₃)₃), 20.8 (C6), 17.2 (C16), 11.3 (SiC), –5.6 (SiC(CH₃)₂); **HRMS** (ESI⁺) calculated for C₂₄H₄₅O₆Si [M+H]⁺ 457.2980, found 457.2976.

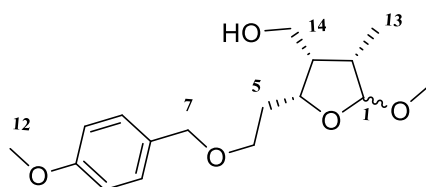
(3*S*,4*S*,5*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)-3-methyltetrahydrofuran-2-ol, **149**



To a stirred solution of triol **150** (660 mg, 1.45 mmol, 1.0 equiv.) in CH₂Cl₂ (16 mL) was added NaIO₄ on silica (10 wt%, 3.71 g, 1.73 mmol, 1.2 equiv.). The suspension was stirred for 30 min before passed through a short plug of silica, concentrated, and purified by flash column chromatography (99:1 CH₂Cl₂ / MeOH) to afford lactols **149** (578 mg, 1.41 mmol, 97%, 2.5:1 inseparable inconsequential mixture of epimers) as a yellow oil.

R_f 0.56 (49:1 DCM / MeOH); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3479, 2955, 2857, 1514, 1250, 1096, 1039, 837; **¹H NMR** (400 MHz, CDCl₃, peaks corresponding to major diastereomer reported) δ_{H} 7.26 (2H, d, J = 8.6 Hz, H10), 6.87 (2H, J = 8.6 Hz, H9), 5.10 (1H, m, H1), 4.50 (2H, m, H7), 4.26 (1H, m, H4), 3.84 (1H, d, J = 10.2 Hz, H14), 3.80 (3H, s, H12), 3.72–3.58 (3H, m, H6, H14), 2.55–2.45 (1H, m, H2) 2.14–1.82 (3H, m, H3, H5), 1.08 (3H, d, J = 7.2 Hz, H13), 0.95 (9H, s, SiC(CH₃)₃), 0.15 (6H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃, peaks corresponding to major diastereomer reported) δ_{C} 159.1 (C11), 130.7 (C8), 129.3 (C9), 113.8 (C10), 99.0 (C1), 72.8 (C7), 67.9 (C4), 59.2 (C6), 55.2 (C12 and C14), 45.6 (C5), 41.4 (C2), 30.3 (C3), 25.8 (SiC(CH₃)₃), 18.2 (C13), 12.5 (SiC), -5.5 (SiCH₃) and -5.6 (SiCH₃); **HRMS** (ESI⁺) calculated for C₂₂H₃₈O₅SiNa [M+Na]⁺ 433.2381, found 433.2379.

((2*R*,3*S*,4*S*)-5-Methoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methyltetrahydrofuran-3-yl)methanol, **110**



To a stirred solution of lactols **149** (578 mg, 1.41 mmol, 1.0 equiv.) in MeOH (55 mL) at 0 °C was added (±)-CSA (26 mg, 0.11 mmol, 0.08 equiv.). The mixture was stirred at 0 °C for 3 h before addition of 0.1 mL Et₃N, then it was concentrated to give crude **151** as a yellow oil. Small amount of crude **151** was purified for the purpose of characterisation.

R_f 0.36 (4:1 petroleum ether / Et₂O); [**α**]_D²⁵: +51.6 (c = 0.97, CHCl₃); **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$: 2962, 1260, 1026, 798, 699; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.26 (2H, d, *J* = 8.6 Hz, H9), 6.87 (2H, *J* = 8.3 Hz, H10), 4.6 (1H, d, *J* = 3.2 Hz, H1), 4.50 (2H, m, H7), 4.15 (1H, m, H4), 3.86–3.77 (4H, s, H12, H14) 3.70–3.65 (4H, m, H6, H14), 2.50 (1H, m, H2), 2.30 (1H, m, H3), 1.95–1.80 (2H, m, H5) 1.05 (3H, d, *J* = 7.2 Hz, H13), 0.88 (9H, s, SiC(CH₃)₃), 0.03 (6H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} , 159.1 (C11), 130.8 (C8), 129.2 (C9), 113.8 (C10), 110.5 (C1), 72.7 (C7), 68.0 (C4), 59.1 (C6), 55.3 (C14), 55.2 (C12), 45.4 (C5), 42.3 (C2), 32.2 (C3), 25.8 (SiC(CH₃)₃), 18.1 (C13), 12.5 (SiC), -5.5 (SiCH₃) and -5.6 (SiCH₃); **HRMS** (ESI⁺) calculated for C₂₃H₄₀O₅SiNa [M+Na]⁺ 447.2537, found 447.2534.

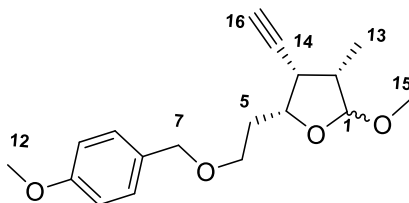
The residue was taken up in THF (24 mL), cooled to 0 °C under argon, and TBAF (1 M in THF, 1.68 mL, 1.2 equiv.) was added. The reaction was warmed to rt overnight, then quenched by addition of sat. aq. NH₄Cl (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic layers were dried over Na₂SO₄, concentrated, and the residue was purified *via* column chromatography (1:1 petroleum ether / Et₂O) to afford **110** (307 mg, 1.09 mmol, 88%) as a colourless oil.

R_f 0.17 (3:7 petroleum ether / Et₂O); [**α**]_D²⁵: +66.0 (c = 1.00, CHCl₃); **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 3444, 2932, 1613, 1586, 1513, 1461, 1364, 1247, 1174, 1094, 1031, 976; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.25 (2H, d, *J* = 8.2 Hz, H9), 6.87 (2H, *J* = 8.6 Hz, H10), 4.59 (1H, d, *J* = 3.2 Hz, H1), 4.45 (2H, s, H7), 4.29 – 4.20 (1H, m, H4), 3.80 (3H, s, H12), 3.76 (1H, dd, *J* = 11.2, 4.0 Hz, H14), 3.70 – 3.60 (2H, m, H14, H6), 3.60–3.52 (1H, m, H6), 3.36 (3H, s, C15), 2.38 – 2.22 (2H, m, H2 and H3), 2.08 – 1.99 (1H, m, H5), 1.95–1.87 (1H, m, H5), 1.10 (3H, d, *J* = 7.2 Hz, H13); **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 159.3 (C11), 130.2 (C8), 129.3 (C9), 113.8 (C10), 110.5 (C1), 78.2 (C4), 72.9 (C7), 67.8 (C6), 58.8 (C14),

55.6 (C15), 55.3 (C12), 46.1 (C3), 43.1 (C2), 31.4 (C5), 12.3 (C13); **HRMS** (ESI⁺) calc. for C₁₇H₂₆O₅Na [M+Na]⁺ 333.1673, found 333.1673.

(2*R*,3*S*,4*S*)-3-Ethynyl-5-methoxy-2-((4-methoxybenzyl)oxy)ethyl)-4-methyltetrahydrofuran:

154



To a stirring solution of **110** (30 mg, 0.097 mmol, 1.0 equiv.) in DCM (0.5 mL) and water (0.5 mL), TEMPO (23 mg, 0.145 mmol, 1.5 equiv.) and BAIB (37 mg, 0.126 mmol, 1.2 equiv.) was added. The resulting biphasic solution was stirred for 3 h at rt. This was then quenched with water and was extracted thrice by Et₂O (5 mL × 3). The combined organic layer was dried over Na₂SO₄, concentrated and dried under vacuum to give crude aldehyde **152**.

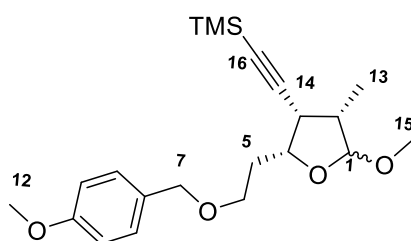
To a stirred suspension of (iodomethyl)triphenylphosphonium iodide (128 mg, 0.242 mmol, 2.5 equiv.) in dry THF (1.5 mL) under argon at rt was added NaHMDS (2 M in THF, 116 µL, 0.242 mmol, 2.4 equiv.). After 20 min, the solution was cooled to −78 °C and a solution of the crude **152** in THF (0.3 mL) 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 M in THF, 210 µL, 0.28 mmol, 3.0 equiv.) was added. The reaction mixture was warmed to rt over 30 min and stirred for a further 10 min before being quenched with 10 mL sat. *aq.* NH₄Cl solution. Diethyl ether was added, the layers were separated, and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried with MgSO₄, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (9:1 Petroleum ether/ Et₂O) to yield alkyne **154** (19.1 mg, 0.063 mmol, 65% over three steps) as a colourless oil.

R_f 0.31 (4:1 petroleum ether / Et₂O); [**α**]_D²⁵: +66.6 (c = 1.033, CHCl₃); **IR** (thin film) ν_{max} /cm^{−1}: 3287, 2930, 1613, 1586, 1456, 1364, 1302, 1248, 1174, 1099, 1016, 971; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.24 (2H, d, *J* = 7.0 Hz, H9), 6.87 (2H, *J* = 8.6 Hz, H10), 4.64 (1H, d, *J* = 3.8 Hz, H1) 4.45 (2H, s, H7),

4.26 – 4.23 (1H, m, H4) 3.8 (3H, s, H12) 3.60 (2H, t, $J = 5.6$ Hz, H6), 3.36 (3H, s, H15), 3.14 – 3.07 (1H, m, H3), 2.36 – 2.27 (1H, m, H2), 2.20 (1H, s, H16), 2.08 – 2.01 (2H, m, H5), 1.15 (3H, d, $J = 7.2$ Hz, H13); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 159.2 (C11), 130.6 (C9), 129.2 (C9), 113.8 (C10), 110.2 (C1), 80.2 (C14), 76.6 (C4), 74.3 (C14), 72.3 (C7), 67.2 (C6), 55.8 (C15), 55.3 (C12), 43.7 (C3), 39.6 (C5), 32.6 (C2) 13.3 (C13); HRMS (ESI^+) calculated for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 327.1567, found 327.1567.

(((2*R*,3*S*,4*S*)-5-Methoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methyltetrahydrofuran-3-yl)ethynyl)trimethylsilane, 155



To a stirred solution of **110** (721 mg, 2.32 mmol, 1.0 equiv.) in CH_2Cl_2 (28 mL) and water (28 mL) was added TEMPO (73 mg, 0.47 mmol, 0.2 equiv.) and BAIB (973 mg, 3.01 mmol, 1.3 equiv.). The resulting biphasic solution was stirred for 3 h. The reaction was monitored using TLC and on completion, 3 mL of MeOH was added and the solution was stirred for another 2 h. The layers were then separated, and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were dried over Na_2SO_4 , concentrated and dried under vacuum to give a crude oil.

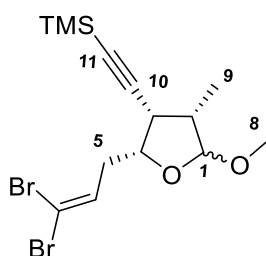
To a stirred suspension of (iodomethyl)triphenylphosphonium iodide (2.22 g, 4.18 mmol, 1.8 equiv.) in a flame dried flask in THF (35 mL) under argon at rt was added NaHMDS (1.98 mL, 3.95 mmol, 2 M in THF, 1.7 equiv.). After 20 min, the solution was cooled to -78°C and a solution of the crude product from the previous step in THF (15 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 (3.50 mL, 7.00 mmol, 2 M in THF, 3.0 equiv.) was added. The reaction mixture was warmed to rt over 30 min and stirred for a

further 10 min. The reaction was again cooled to $-78\text{ }^{\circ}\text{C}$ followed by addition of further NaHMDS (0.81 mL, 1.63 mmol, 2 M in THF, 0.7 equiv.) before adding TMSCl (0.89 mL, 7.00 mmol, 3.0 equiv.). The reaction was warmed to $-20\text{ }^{\circ}\text{C}$ before being quenched with saturated aq. NH_4Cl solution. Et_2O was added, the layers were separated, and the aqueous layer extracted three times with Et_2O ($3 \times 100\text{ mL}$). The combined organic layers were dried with Na_2SO_4 , and concentrated. The crude product was purified by flash column chromatography (19:1 petroleum ether / Et_2O) to give alkyne **155** (719 mg, 1.90 mmol, 82% over four steps) as a colourless oil.

R_f 0.14 (23:1 petroleum ether / Et_2O); $[\alpha]_D^{25} +36.0$ ($c = 0.98$, CHCl_3); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2957, 2165, 1613, 1513, 1248, 1173, 1098, 1017, 944, 913; **^1H NMR** (400 MHz, CDCl_3) δ_{H} 7.27 (2H, d, $J = 7.0\text{ Hz}$, H9), 6.87 (2H, $J = 7.7\text{ Hz}$, H10), 4.63 (1H, d, $J = 3.2\text{ Hz}$, H1) 4.45 (2H, s, H7), 4.23 (1H, q, $J = 6.1$ and 13.2 Hz , H4) 3.80 (3H, s, H12), 3.60 (2H, t, $J = 6.1\text{ Hz}$, H6), 3.36 (3H, s, H15), 3.10 (1H, t, $J = 6.0\text{ Hz}$, H3), 2.34–2.24 (1H, m, H2), 2.04 (2H, q, $J = 5.7$ and 12.5 Hz , H5), 1.18 (3H, d, $J = 7.2\text{ Hz}$, H13), 0.15 (9H, s, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100 MHz, CDCl_3) δ_{C} 159.0, 130.6, 129.1, 113.7, 110.1, 102.5, 90.9, 76.5, 72.5, 67.0, 55.6, 55.2, 43.6, 40.3, 32.6, 13.8, 0.0; **HRMS** (ESI^+) calc. for $\text{C}_{21}\text{H}_{32}\text{O}_4\text{NaSi}$ $[\text{M}+\text{Na}]^+$ 399.1962, found 399.1962.

(((2*R*,3*S*,4*S*)-2-(3,3-Dibromoallyl)-5-methoxy-4-methyltetrahydrofuran-3-yl)ethynyl)trimethylsilane, **158**



To a solution of PMB ether **155** (193 mg, 0.51 mmol, 1.0 equiv.) in CH_2Cl_2 (8.5 mL) and water (3.0 mL), was added DDQ (175 mg, 0.768 mmol, 1.5 equiv.). The solution was allowed to stir for 45 min, followed by the addition of saturated NaHCO_3 solution. This was stirred for 15 min followed by extraction using CH_2Cl_2 ($3 \times 25\text{ mL}$). The combined organic layers were dried over Na_2SO_4 , and

concentrated; the crude alcohol **156** (yellow oil) was carried forward without purification to the next step. A small amount of alcohol was purified for the purpose of characterization.

R_f 0.31 (petroleum ether / Et₂O (4:1)); [α]_D²⁵: +99.7 (c = 0.65, CHCl₃); **IR** (thin film) ν_{max} /cm⁻¹: 3402, 2960, 2929, 2170, 1455, 1380, 1251, 1082, 1018, 913, 842; **¹H NMR** (400 MHz, CDCl₃) δ : 4.67 (1H, d, *J* = 3.6 Hz, H1), 4.29 – 4.19 (1H, m, H4), 3.82 (2H, t, *J* = 6 Hz, H6), 3.36 (3H, s, H7), 3.2 (1H, t, *J* = 6.4 Hz, H3), 2.32 – 2.27 (1H, m, H2), 2.1 – 2.01 (1H, m, H5), 1.94 – 1.87 (1H, m, H5), 1.18 (3H, d, *J* = 7.2 Hz, H8), 0.16 (9H, s, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ : 110.3 (C3), 102.4 (C9), 91.3 (C10), 78.6 (C-1), 77.1 (C6), 61.6 (C7), 55.4 (C4), 43.3 (C5), 40.4 (C2), 35.1 (C2), 13.8 (C8), 0.0 (C(CH₃)₃); **HRMS** (ESI⁺) calculated for C₁₃H₂₄O₃SiNa [M+Na]⁺ 279.1387, found 279.1387.

To a solution of the crude alcohol **156** in CH₂Cl₂ (10 mL) and water (10 mL) was added TEMPO (16 mg, 0.10 mmol, 0.2 equiv.) and BAIB (248 mg, 0.77 mmol, 1.5 equiv.). The biphasic mixture was stirred at rt for 3 h. The reaction was monitored by TLC and on completion, 0.5 mL MeOH was added. The reaction was stirred for 2 h followed by separation of the layers. The aqueous layer was extracted with CH₂Cl₂ (3 × 25 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated. The crude aldehyde **157** (orange oil) was carried forward to the next step without further purification.

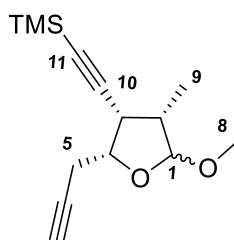
To a solution of PPh₃ (713 mg, 2.56 mmol, 5.0 equiv.) in CH₂Cl₂ (5 mL) at 0 °C was added CBr₄ (425 mg, 1.28 mmol, 2.5 equiv.). The mixture was stirred at 0 °C for 15 min before being cooled to –30 °C. To this was added dropwise a solution of the crude aldehyde **157** and Et₃N (0.71 mL, 5.13 mmol, 10 equiv.) in CH₂Cl₂ (3 mL), and the reaction mixture was warmed to 0 °C over 1 h. The reaction was quenched by addition of with saturated aq. NH₄Cl, the layers were separated and the aqueous layer extracted with DCM (3 × 15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated, and the residue was purified via flash column chromatography (99:1 petroleum ether / Et₂O) to yield dibromoalkene **158** (166 mg, 0.405 mmol, 79% over three steps) as a colourless oil.

R_f 0.49 (24:1 petroleum ether / Et₂O); [α]_D²⁵: +28.0 (c = 0.91, CHCl₃); **IR** (thin film) ν_{max} /cm⁻¹: 2961, 2170, 1625, 1455, 1249, 1197, 1100, 1081, 999, 839, 793; **¹H NMR** (400 MHz, CDCl₃) δ : 6.54 (1H, t, *J* = 7.1, H6), 4.66 (1H, d, *J* = 3.6 Hz, H1), 4.15 – 4.09 (1H, m, H4), 3.36 (3H, s, H7), 3.18 (1H, dd, *J* = 6.4 and 7.1 Hz, H3), 2.56 – 2.46 (2H, m, H5), 2.33 – 2.24 (1H, m, H2), 1.17 (3H, d, *J* = 7.2 Hz, H8),

0.17 (9H, s, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 134.9 110.3, 101.8, 91.7, 90.2, 77.1, 55.7, 43.4, 39.8, 36.6, 13.9, 0.0; HRMS (ESI⁺) calc. for C₁₄H₂₃⁷⁹Br₂O₂Si [M+H]⁺ 408.9829, found 408.9830.

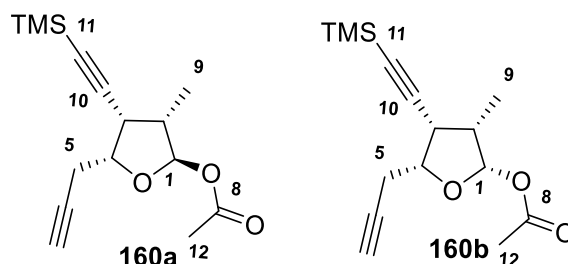
(((2*R*,3*S*,4*S*)-5-Methoxy-4-methyl-2-(prop-2-yn-1-yl)tetrahydrofuran-3-yl)ethynyl)trimethylsilane,

108



To a solution of dibromide **158** (145 mg, 0.354 mmol, 1.0 equiv.) in THF (3.2 mL) under Ar at −78 °C was added LiHMDS (0.530 mL, 0.531 mmol, 1 M in THF, 1.5 equiv.). The solution was warmed to −15 °C over 2 h, then cooled again to −78 °C. To it was added *n*-BuLi (0.220 mL, 0.531 mmol, 2.5 M in hexanes, 1.5 equiv.) dropwise along the wall of the vial, and the mixture was stirred for 5 min. On completion as judged by TLC, a solution of saturated aq. NH₄Cl was added at −78 °C. The mixture was warmed to rt and extracted with Et₂O (3 × 15 mL), and the combined organic layers were dried (Na₂SO₄), and concentrated. The crude product was purified via flash column chromatography (19:1 petroleum ether / Et₂O) to yield diyne **108** (79 mg, 0.319 mmol, 90%) as a colourless oil.

R_f 0.34 (19:1 petroleum ether / Et₂O); [α]_D²⁵ +37.0 (c = 0.97, CHCl₃); **IR** (thin film) ν_{max}/cm^{−1}: 2959, 2932, 2170, 1456, 1384, 1368, 1250, 1197, 1156, 1133, 1005, 968; **¹H NMR** (400 MHz, CDCl₃) δ_H 4.68 (1H, d, *J* = 3.6 Hz, H1), 4.27 – 4.21 (1H, m, H4), 3.38 (3H, s, H7), 3.26 (1H, t, *J* = 6.4 Hz, H3), 2.64 – 2.59 (2H, m, H5), 2.35 – 2.25 (1H, m, H2), 2.00 (1H, t, *J* = 2.7 Hz, H7), 1.18 (3H, d, *J* = 7.27 Hz, H8), 0.16 (9H, s, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 110.4, 101.5, 91.6, 80.8, 77.7, 69.6, 55.8, 43.3, 39.8, 22.7, 13.8, 0.0; HRMS (ESI⁺) calculated for C₁₄H₂₂O₂SiNa [M+Na]⁺ 273.1281, found 273.1282.

(3*S*,4*S*,5*R*)-3-Methyl-5-(prop-2-yn-1-yl)-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl acetate:**160**

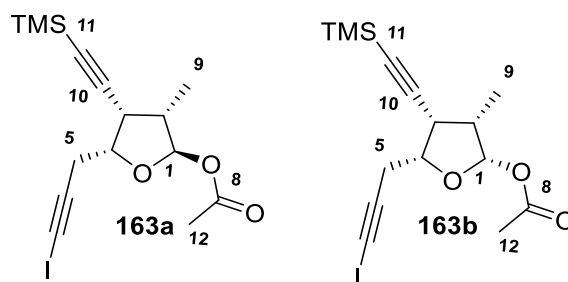
To a solution of methyl acetal **108** (140 mg, 0.561 mmol, 1.0 equiv.) in glacial AcOH (3.5 mL) at 0 °C was added acetic anhydride (0.300 mL, 3.14 mmol, 6.0 equiv.). Along the walls of the vial, conc. H₂SO₄ (15 µL, 0.28 mmol, 0.5 equiv.) was added, and the wall was rinsed with THF (3.5 mL). The solution was stirred at 0 °C for 2 h. On completion as judged by TLC, the reaction was quenched with saturated aq. NaHCO₃, and the extracted with Et₂O (4 × 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated, and the residue was purified via flash column chromatography (19:1 petroleum ether / Et₂O) to give acetate **160** (131 mg, 0.471 mmol, 84%, 3:1 mixture) as a colourless solid. The mixture was used for the subsequent reactions unless stated otherwise. From a small amount of **16**, diastereomers **160a** and **160b** were separated for the purpose of characterisation. The structure of **160a** was confirmed using single crystal X-ray diffraction.

160a: *R_f* 0.47 (4:1 petroleum ether / Et₂O); [*α*]_D²⁵ +23.0 (*c* = 1.1, CHCl₃); IR (thin film) *v*_{max}/cm⁻¹: 2980, 2961, 2924, 2169, 1743, 1376, 1248, 1236, 1060, 1009, 843; ¹H NMR (400 MHz, CDCl₃) δ_H 5.94 (1H, d, *J* = 3.9 Hz, H1), 4.38 – 4.31 (1H, m, *J* = 6.1 Hz and 13.1 Hz, H4), 3.34 (1H, dd, *J* = 1.0 Hz and 6.3 Hz, H3), 2.72 – 2.61 (2H, m, H5), 2.52 – 2.41 (1H, m, H2), 2.06 (3H, s, H12), 2.00 (1H, t, *J* = 2.7 Hz, H7), 1.21 (3H, d, *J* = 7.2 Hz, H9), 0.16 (s, Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ_C 170.4, 103.0, 100.4, 92.4, 80.3, 79.6, 69.9, 43.1, 39.7, 22.5, 21.3, 13.6, -0.00; *m. pt.*: 82-86 °C; HRMS (ESI⁺) calculated for C₁₅H₂₂O₃NaSi [M+Na]⁺ 301.1230 found 301.1230.

160b: *R_f* 0.34 (4:1 petroleum ether / Et₂O); [*α*]_D²⁵ -49.0 (*c* = 0.55, CHCl₃); IR (thin film) *v*_{max}/cm⁻¹: 2960, 2926, 2855, 2171, 1744, 1375, 1250, 1230, 1064, 1011, 990.2, 843; ¹H NMR (400 MHz, CDCl₃) δ_H 6.16 (1H, d, *J* = 4.8 Hz, H1), 4.25 (1H, *app* q, *J* = 6.7 Hz, H4), 3.22 (1H, t, *J* = 6.8 Hz, H3), 2.73 –

2.67 (2H, m, H5), 2.55 – 2.47 (1H, m, H2), 2.05 (3H, s, H12), 1.18 (3H, d, $J = 7.0$ Hz, H9), 0.18 (9H, s, Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ_C 170.2, 100.9, 98.7, 91.6, 80.7, 69.7, 41.4, 38.4, 23.5, 21.2, 10.2, -0.00; **m. pt.**: 58-64 °C; **HRMS** (ESI⁺) calculated for C₁₅H₂₂O₃NaSi [M+Na]⁺ 301.1230 found 301.1230.

(3*S*,4*S*,5*R*)-5-(3-Iodoprop-2-yn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl acetate, **163**



To a solution of I₂ (962 mg, 3.78 mmol, 10 equiv.) in toluene (8 mL) was added morpholine (0.66 mL, 7.59 mmol, 20 equiv.) was added dropwise and the resulting mixture was sonicated for 10 min before being warmed to 45 °C. The stirring was continued for 30 min before adding a solution of acetate **160** (106 mg, 0.38 mmol, 1.0 equiv.) in toluene (2 mL). The resulting mixture was stirred at 45 °C overnight before being cooled to rt and quenched with saturated aq. Na₂SO₃ (50 mL). The resulting biphasic mixture was vigorously stirred for 30 min before being extracted with Et₂O (4 × 20 mL). The combined organic layers were dried using Na₂SO₄, concentrated, and the residue purified by flash column chromatography (19:1 petroleum ether / Et₂O) to give iodoalkyne **163** (140 mg, 0.346 mmol, 91%, 3:1 mixture of diastereomers) as white solids. The mixture was used for the subsequent reactions unless stated otherwise. From a small amount of **163**, diastereomers **163a** and **163b** were separated for the purpose of characterisation.

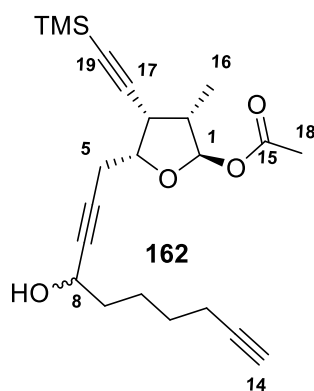
163a: **R_f** 0.47 (4:1 petroleum ether / Et₂O); [α]_D²⁵ -16.0 ($c = 1.00$, CHCl₃); **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2970, 2171, 1738, 1457, 1376, 1249, 1130, 1009, 915, 843; ¹H NMR (400 MHz, CDCl₃) δ_H 5.93 (1H, d, $J = 3.7$ Hz, H1), 4.37 – 4.28 (1H, m, H4), 3.34 (1H, d, $J = 13.3$ Hz, H3), 2.85 – 2.77 (2H, m, H5), 2.48 – 2.36 (1H, m, H2), 2.06 (3H, s, H12), 1.20 (3H, d, $J = 7.2$ Hz, H9), 0.16 (9H, s, Si(CH₃)₃); ¹³C NMR

(101 MHz, CDCl₃) δ_C 170.4, 102.9, 100.4, 92.5, 90.2, 79.4, 43.0, 39.5, 24.8, 21.2, 13.6, -0.0, -4.5;

HRMS (ESI⁺) calculated for C₁₅H₂₁IO₃NaSi [M+Na]⁺ 427.0197 found 427.0198.

163b: **R_f** 0.34 (4:1 petroleum ether / Et₂O); [α]_D²⁵ -77.0 (c = 0.99, CHCl₃); **IR** (thin film) $\nu_{\max}$ /cm⁻¹ 2980, 2173, 1739, 1458, 1374, 1248, 1164, 1133, 1058, 907, 843; ¹H NMR (400 MHz, CDCl₃) δ_H 6.11 (1H, d, *J* = 4.8 Hz, H1), 4.21 (1H, q, *J* = 6.7 Hz, H4), 3.19 (1H, dd, *J* = 4.6 Hz and 5.6 Hz, H3), 2.84 (2H, q, *J* = 3.1 Hz and 6.6 Hz, H5), 2.51 – 2.40 (1H, m, H2), 2.01 (3H, s, H12), 1.15 (3H, d, *J* = 7.0 Hz, H9), 0.16 (s, 9H, Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ_C 170.1, 100.9, 98.7, 91.6, 90.5, 80.5, 41.3, 38.3, 25.8, 21.1, 10.2, -0.0, -4.8; **HRMS** (ESI⁺) calculated for C₁₅H₂₁IO₃NaSi [M+Na]⁺ 427.0197 found 427.0197.

(2*R*,3*S*,4*S*,5*R*)-5-(4-Hydroxydeca-2,9-diyn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl acetate, 162



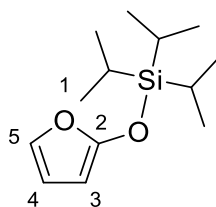
To a solution of iodoalkyne **160a** (20 mg, 0.070 mmol, 1.5 equiv.) in THF (0.3 mL) at -78 °C was added *n*-BuLi (24 μ L, 2.5 M in hexanes, 0.061 mmol, 1.3 equiv.) dropwise. The solution was stirred for 45 min, then a solution of hept-6-ynal (5.0 mg, 0.047 mmol, 1.0 equiv.) in THF (0.2 mL) was added. The solution was slowly warmed to -40 °C and was stirred for 4 h. The reaction was quenched with saturated aq. NH₄Cl (5 mL). The aqueous layer was extracted using EtOAc (4 $\times$ 5 mL). The combined organic layers were dried using Na₂SO₄ and concentrated, and the residue was purified via flash chromatography (5:1 petroleum ether / EtOAc to yield **162** (6.0 mg, 0.025 mmol, 35%) as a viscous oil.

Alternatively, to a solution of hept-6-ynal (10.0 mg, 0.053 mmol, 1.3 equiv.) and iodoalkyne **163a** (17 mg, 0.041 mmol, 1.0 equiv.) in THF (2 mL) was added CrCl₂ (97%, 30.0 mg, 0.245 mmol, 6.0 equiv., addition in the glovebox), and the solution was stirred at rt for 15 h. The reaction was quenched with 1

M serine solution (15 mL). The aqueous layer was extracted using EtOAc (4×10 mL), the combined organic layers were dried using Na_2SO_4 , and concentrated. The residue was purified via flash column chromatography (10:3 petroleum ether / EtOAc) to yield **162** (12 mg, 0.039 mmol, 73%) as a viscous oil.

R_f 0.51 (1:1 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3459, 3311, 2930, 2171, 1740, 1461, 1374 1187, 1162, 1087, 966; **¹H NMR** (400 MHz, CDCl_3) δ_{H} 5.92 (1H, d, $J = 4.1$ Hz, H1), 4.38 – 4.30 (1H, m, H8), 4.31 (1H, tdd, $J = 7.1, 5.7, 1.1$ Hz, H4), 3.31 (1H, dd, $J = 7.3, 5.7$ Hz, H3), 2.70 – 2.60 (2H, m, H5), 2.50 – 2.40 (1H, m, H2), 2.25 – 2.03 (2H, m, H12), 2.06 (3H, s, H15), 1.94 (1H, t, $J = 2.7$ Hz, H14), 1.81 (1H, br s, OH), 1.72-1.63 (2H, m, H9), 1.56 (4H, m, H10, H11), 1.21 (3H, d, $J = 7.1$ Hz, H16), 0.16 (9H, s, (SiMe₃)); **¹³C NMR** (101 MHz, CDCl_3) δ 170.2, 125.5, 101.0, 98.7, 91.4, 8.3, 82.5, 81.6, 80.8, 68.3, 62.4, 41.3, 4.4, 37.3, 30.3, 28.1, 25.9, 25.8, 24.3, 24.3, 21.1, 18.3, 15.2, 14.0, 10.2, - 0.00; **HRMS** (ESI⁺) calc. for $\text{C}_{22}\text{H}_{32}\text{O}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 411.1962; found 411.1961.

(Furan-2-yloxy)triisopropylsilane, **6**



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 dichloromethane (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 *in vacuo*. The residue was purified by

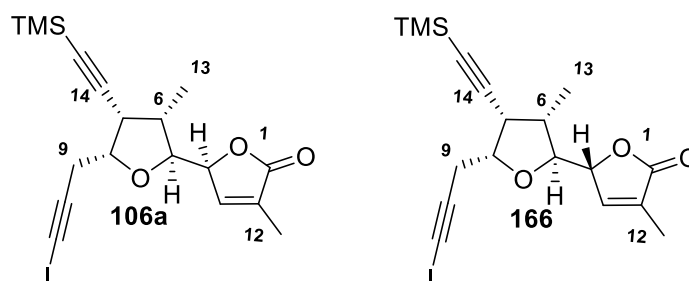
distillation under reduced pressure at 90-92 °C (19 mbar) to yield furan-2(5*H*)-one as a light yellow oil (2.16 g, 16%).

¹H NMR (200 MHz, CDCl₃) 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); **¹³C NMR** (101 MHz, CDCl₃) δ_C 173.8, 152.9, 121.8, 72.3. Data in accordance with literature.¹⁹⁶

To a stirred solution of furan-2(5*H*)-one (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 Na₂SO₄ and the solvent removed *in vacuo*. The residue was purified by distillation under reduced pressure at 110-112 °C (0.5 mbar) to yield the siloxyfuran **6** as a colorless oil (1.24 g, 87%).

R_f 0.80 (9:1 petroleum ether / EtOAc); **¹H NMR** (400 MHz, CDCl₃) 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(CHMe₂)₃), 1.11 (18H, d, *J* = 6.8 Hz, Si(CHMe₂)₃); **¹³C NMR** (101 MHz, CDCl₃) δ_C 157.1, 132.0, 111.2, 83.6, 17.7, 12.3. Data in accordance with literature.¹⁹⁷

(*S*)-5-((2*S*,3*S*,4*S*,5*R*)-5-(3-Iodoprop-2-yn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)-3-methylfuran-2(5*H*)-one, 106a, and (*R*)-5-((2*S*,3*S*,4*S*,5*R*)-5-(3-Iodoprop-2-yn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)-3-methylfuran-2(5*H*)-one, 166



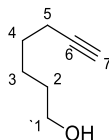
To a solution of acetates **163a** and **163b** (140 mg, 0.346 mmol, 1.0 equiv.) and silyloxyfuran **6** (0.148 mL, 0.519 mmol, 1.5 equiv.) in anhydrous MeCN (4.5 mL) at -40 °C, was added dropwise a solution of Bi(OTf)₃ (454 mg, 0.693 mmol, 2.0 equiv.) in anhydrous MeCN (2.0 mL). The mixture was stirred

at $-40\text{ }^{\circ}\text{C}$ for 1 h before being quenched with saturated aq. NH_4Cl (20 mL). The solution was warmed to rt, then extracted with Et_2O ($4 \times 20\text{ mL}$). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified via flash column chromatography (19:1 to 4:1 petroleum ether / Et_2O) to give **106a** (46 mg, 0.107 mmol, 31%, viscous oil) and **166** (52 mg, 0.121 mmol, 35%, white solid).

106a *R_f* 0.46 (3:2 petroleum ether / Et_2O); $[\alpha]_{\text{D}}^{25} -89.0$ ($c = 1.01$, CHCl_3); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2959, 2926, 2167, 1760, 1456, 1250, 1085, 1050, 986, 944, 843, 760; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.00 (1H, t, $J = 1.7\text{ Hz}$, H3), 4.90 (1H, q, $J = 2.0\text{ Hz}$, H4), 4.03 (1H, ddd, $J = 7.5, 6.5, 4.4\text{ Hz}$, H8), 3.89 (1H, dd, $J = 9.5, 2.1\text{ Hz}$, H5), 3.14 (1H, dd, $J = 6.4, 4.4\text{ Hz}$, H7), 2.73 (2H, dd, $J = 7.1, 2.8\text{ Hz}$, H9), 2.60 (1H, dt, $J = 9.5, 6.6\text{ Hz}$, H6), 1.94 (3H, t, $J = 1.8\text{ Hz}$, H12), 1.21 (3H, d, $J = 6.7\text{ Hz}$, H13), 0.16 (9H, s, $\text{Si}(\text{CH}_3)_3$); **¹³C NMR** (126 MHz, CDCl_3) δ_{C} 174.1, 145.9, 131.1, 100.6, 92.7, 90.2, 82.3, 80.1, 79.8, 42.0, 38.9, 24.4, 13.4, 10.8, 0.1, -5.0; **HRMS** (ESI^+) calc. for $\text{C}_{18}\text{H}_{23}\text{IO}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 465.0353; found 465.0352.

166 *R_f* 0.51 (3:2 petroleum ether / Et_2O); $[\alpha]_{\text{D}}^{25} +18.0$ ($c = 0.91$, CHCl_3); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 2926, 2167, 1758, 1457, 1250, 1104, 1043, 993, 843; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.15 (1H, t, $J = 1.7\text{ Hz}$, H3), 4.84 (1H, dt, $J = 6.4, 1.9\text{ Hz}$, H4), 4.13 (1H, td, $J = 6.9, 4.6\text{ Hz}$, H8), 3.61 (1H, dd, $J = 8.8, 6.4\text{ Hz}$, H5), 3.16 (1H, dd, $J = 6.5, 4.6\text{ Hz}$, H7), 2.78 (2H, dd, $J = 6.9, 3.4\text{ Hz}$, H9), 2.33 (1H, dt, $J = 8.9, 6.7\text{ Hz}$, H6), 1.93 (3H, t, $J = 1.8\text{ Hz}$, H12), 1.20 (3H, d, $J = 6.7\text{ Hz}$, H13), 0.15 (9H, s, $\text{Si}(\text{CH}_3)_3$); **¹³C NMR** (126 MHz, CDCl_3) δ_{C} 174.0, 146.9, 130.8, 100.5, 92.8, 90.5, 84.11, 82.5, 79.5, 42.4, 40.6, 24.6, 14.2, 10.7, 0.0, -4.9; **mp** 108-113 $^{\circ}\text{C}$; **HRMS** (ESI^+) calculated for $\text{C}_{18}\text{H}_{23}\text{IO}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 465.0353 found 465.0353.

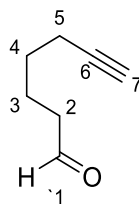
6.2.2 Procedures and characterisations of the compounds in Chapter 3

Hept-6-yn-1-ol, **218**

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 **219** (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 Na₂SO₄. The solvent was removed *in vacuo* to yield hept-6-yn-1-ol (2.08 g, 18.3 mmol, 83%) as a colourless oil.

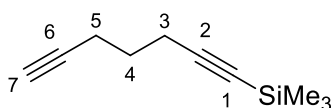
Alternatively, to hept-6-ynoic acid **220** (2.2 g, 17.4 mmol, 1.0 equiv.) in Et₂O (20 mL) under Ar at –40 °C, LiAlH₄ solution (4M in Et₂O, 8.7 mL, 34.8 mmol, 2.0 equiv.) was added dropwise. It was then slowly warmed to rt and was stirred for 3 h. After completion of reaction, the reaction mixture was cooled to 0 °C before quenching slowly with 20 mL *sat.* NH₄Cl solution. The layers were separated, and the aqueous layer extracted three times with diethyl ether (20 mL). The combined organic layers were dried with Na₂SO₄. The solvent was removed *in vacuo* to yield hept-6-yn-1-ol (1.75 g, 15.6 mmol, 90%) as a colourless oil.

R_f 0.4 (1:1 Petroleum Ether / Et₂O); **¹H NMR** (400 MHz, CDCl₃) δ_H 3.65 (2H, t, *J* = 6.4 Hz, H1), 2.20 (2H, dt, *J* = 6.9 Hz, *J* = 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), 1.36 (1H, bs, OH); **¹³C NMR** (101 MHz, CDCl₃) δ_C 84.5, 68.4, 62.9, 32.3, 28.3, 25.0, 18.5. Data in accordance with literature.¹⁹⁸

Hept-6-yn-1-al, 161

To a stirring solution of anhyd. DMSO (4.5 mL, 64.2 mmol, 7.0 equiv.), NEt₃ (6.3 mL, 46 mmol, 5.0 equiv.) and SO₃.py (4.38 g, 27.6 mmol, 3.0 equiv.) a solution of alcohol **218** (1.00 g, 9.07 mmol, 1.0 eq) in DCM (5 mL) was added at 0 °C. It was stirred for 30 min at 0 °C. The reaction was quenched with 20 mL phosphate buffer (pH 7) and was extracted with Et₂O (20 mL × 3) and the combined organic layers were dried over anhyd. Na₂SO₄. The solvent was removed *in vacuo* and the crude product purified *via* column chromatography (4:1 Petroleum ether / EtOAc) to afford aldehyde **161** (0.696 g, 6.35 mmol, 70%) as a colourless oil.

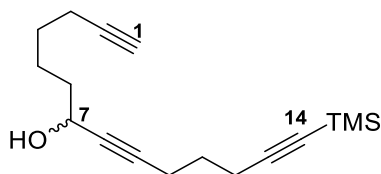
R_f 0.42 (2:1 Petroleum Ether / Et₂O); ¹H NMR (400 MHz, CDCl₃): δ_H 9.69 (1H, *app s*, H1), 2.40 (2H, t, *J* = 7.1 Hz, H2), 2.14 (2H, dt, *J* = 6.8, 2.6 Hz, H5), 1.91 (1H, t, *J* = 2.6 Hz, H7), 1.42–1.77 (3H, m, H3 and H4); ¹³C NMR (101 MHz, CDCl₃) δ_C 202.0, 83.7, 68.7, 43.2, 27.7, 21.0, 18.1; Data in accordance with literature.¹⁹⁹

Hepta-1,6-diynyl)trimethylsilane, 173

To a stirred solution of 1,6-heptadiyne (0.82 mL, 7.16 mmol, 1.0 equiv.) in dry THF (3 mL) under argon at –78 °C was added LiHMDS (1 M in THF, 7.2 mL, 7.2 mmol, 1.0 equiv.). After stirring for 45 min, a solution of chlorosilane (1.10 mL, 8.60 mmol, 1.2 equiv.) in dry THF (0.5 mL) was added. The reaction mixture was stirred for 3 h at –78 °C before it was quenched with 10 mL sat. *aq.* NH₄Cl solution. After warming to rt the layers were separated and the aqueous layer extracted three times with 10 mL diethyl ether. The combined organic layers were dried with Na₂SO₄ and the solvent removed *in vacuo*. The crude was purified using Kugelrohr distillation (80-100 °C at 11 mbar) afforded trimethylsilane **173** (0.699 g, 4.30, 60%) as a colourless oil.

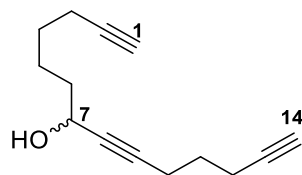
R_f 0.69 (Pet. Ether/ Et₂O (19:1)); **¹H NMR** (400 MHz, CDCl₃) δ_H 2.39-2.32 (2H, m, H3), 2.34-2.27 (2H, td, *J* = 2.6 Hz, H5), 1.96 (1H, t, *J* = 2.6 Hz, H7), 1.76-1.69 (2H, m, H4), 0.15 (9H, s, Si(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ_C 106.2, 85.4, 83.7, 68.9, , 19.1, 17.7, −0.3. Data in accordance with literature.²⁰⁰

14-(Trimethylsilyl)tetradeca-1,8,13-triyn-7-ol, **222**



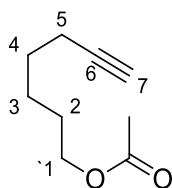
To a solution of diyne **173** (240 mg, 1.46 mmol, 1.5 equiv.) in THF (6 mL) at −78 °C was added *n*-BuLi (0.50 mL, 2.5 M in hexanes, 1.27 mmol, 1.3 equiv.) dropwise. The solution was stirred for 45 min, then a solution of hept-6-ynal (107.0 mg, 0.97 mmol, 1.0 equiv.) in THF (1.0 mL) was added. The solution was slowly warmed to −40 °C and was stirred for 4 h. The reaction was quenched with saturated aq. NH₄Cl (25 mL). The aqueous layer was extracted using EtOAc (4 × 15 mL). The combined organic layers were dried using Na₂SO₄ and concentrated, and the residue was purified via flash chromatography (9:1 petroleum ether / EtOAc) to yield **222** (234 mg, 0.85 mmol, 88%) as a viscous oil.

R_f 0.22 (4:1 petroleum ether / EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ_H 4.40–4.33 (1H, m, H7), 2.36–2.29 (4H m, H10 and H12), 2.25–2.18 (2H, m, H3), 1.96 (1H, t, *J* = 2.6 Hz, H1), 1.76–1.65 (5H, m, H6, H11 and OH), 1.60–1.52 (4H, m, H4 and H5), 0.14 (9H, s, Si(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ_C 106.2 (C14), 85.2 (C8), 84.6 (C13), 84.3 (C2), 81.7 (C9), 68.4 (C1), 62.5 (C7), 37.5 (C6), 28.1 (C11), 27.1 (C4), 24.3 (C5), 19.0 (C10), 18.3 (C3), 17.8 (C12), 0.1 (Si(CH₃)₃). Data in accordance with literature.¹³

Tetradeca-1,8,13-triyn-7-ol, 171

To a solution of diyne **222** (100 mg, 0.494 mmol, 1.0 equiv.) in MeOH (5 mL) at rt, K_2CO_3 (136 mg, 0.988 mmol, 2.0 equiv.) was added. The suspension was stirred for 2 h before quenching the reaction with 1 N HCl solution. The reaction mixture was extracted with EtOAc (4×15 mL). The combined organic layers were dried using Na_2SO_4 and concentrated, and the residue was purified via flash chromatography (4:1 petroleum ether / EtOAc) to yield **171** (234 mg, 0.459 mmol, 93%) as a viscous oil.

R_f 0.3 (7:3 petroleum ether / Et_2O); IR: 1H NMR (500 MHz, $CDCl_3$) δ_H 4.40–4.32 (1H, m, H-7), 2.35 (2H, td, $J = 7.0$ Hz, 2.0 Hz, H10), 2.31 (2H, td, $J = 7.0$ Hz, 2.6 Hz, H12), 2.25–2.19 (2H, m, H-3), 1.97 (1H, t, $J = 2.7$ Hz, H14), 1.96 (1H, t, $J = 2.7$ Hz, H1), 1.78–1.66 (5H, m, H6, H11 and OH), 1.61–1.53 (4H, m, H4 and H5); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 84.3 (C-2), 84.3 (C-8), 83.4 (C-13), 81.8 (C-9), 68.9 (C14), 68.4 (C-1), 62.5 (C-7), 37.5 (C-6), 28.1 (C-11), 27.4 (C-4), 24.3 (C-5), 18.3 (C-3), 17.7 (C-10), 17.5 (C-12). Data in accordance with literature.¹³

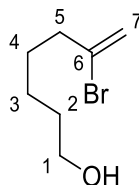
Hept-6-ynyl acetate, 223

To a stirred solution of crude hept-6-yn-1-ol **218** (2.50 g, 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 *in vacuo*. The crude product was

purified by flash column chromatography on silica gel (4:1 to 1:1 Petroleum Ether / Et₂O) to yield acetate **223** (2.74 g, 17.84 mmol, 80%) as a colourless oil.

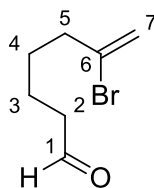
R_f 0.47 (4:1 petroleum ether / EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ_H 4.06 (2H, t, *J* = 6.7 Hz, H1), 2.20 (2H, dt, *J* = 6.7 Hz, *J* = 2.6 Hz, H5), 2.04 (3H, s, OCH₃), 1.94 (1H, t, *J* = 2.6 Hz, H7), 1.68–1.60 (2H, m, H2), 1.59–1.51 (2H, m, H4), 1.51–1.43 (2H, m, H3); **¹³C NMR** (101 MHz, CDCl₃) δ_C 171.3 (C=O), 84.3 (C6), 68.5 (C7), 64.4 (C1), 28.2 (C2), 28.1 (C4), 25.2 (C3), 21.1 (OCH₃), 18.4 (C5). Data in accordance with literature.²⁰¹

6-Bromohept-6-en-1-ol, **225**



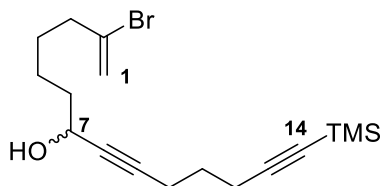
Boron tribromide (1 M in dichloromethane, 11.0 mL, 11.0 mmol, 0.5 equiv.) was cooled under argon to –78 °C before hept-6-ynyl acetate **223** (3.44 g, 22.0 mmol, 1.0 equiv.) was added dropwise. The reaction was warmed to rt quickly and stirred for 5 h before it was quenched with acetic acid (22 mL). 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 Na₂SO₄ and the solvent removed *in vacuo*. The crude 6-bromohept-6-enyl acetate **224** was used in the next step without further purification. To a solution of the crude acetate **224** 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 *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 Na₂SO₄ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (4:1 to 2:1 petroleum ether/ Et₂O) to yield bromoalkene **225** (2.34 g, 12.1 mmol, 55% over 2 steps) as a pale yellow oil.

R_f 0.30 (4:1 petroleum ether/ EtOAc); **¹H NMR** (400 MHz, CDCl₃) 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), 1.31 (1H, bs, OH); **¹³C NMR** (101 MHz, CDCl₃) δ_C 134.7 (C6), 116.7 (C7), 62.9 (C1), 41.5 (C5), 32.5 (C2), 27.7 (C4), 24.6 (C3). Data in accordance with literature.²⁰⁰

6-Bromohept-6-enal, 175

To a stirred solution of 6-bromohept-6-en-1-ol (1.07 g, 5.05 mmol, 1.0 equiv.) in dichloromethane (28 mL) under argon was added triethylamine (5.4 mL, 38.8 mmol, 7.0 equiv.) and DMSO (3.8 mL, 53 mmol, 9.5 equiv.). The reaction mixture was cooled to 0 °C and sulfur trioxide pyridine complex (2.65 g, 16.6 mmol, 3.0 equiv.) was added portionwise. The reaction mixture was stirred for 1.5 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 Na₂SO₄ and the solvent removed *in vacuo*. Flash column chromatography on silica gel (4:1 Petroleum Ether/ Et₂O) afforded aldehyde **175** (802 mg, 3.79 mmol, 75%) as a pale yellow oil.

R_f 0.46 (9:1 petroleum ether/ EtOAc); **¹H NMR** (400 MHz, CDCl₃) 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); **¹³C NMR** (101 MHz, CDCl₃) δ_C 202.3 (C1), 134.0 (C6), 117.0 (C7), 43.6 (C2), 41.2 (C5), 27.4 (C4), 20.9 (C3). Data in accordance with literature.²⁰⁰

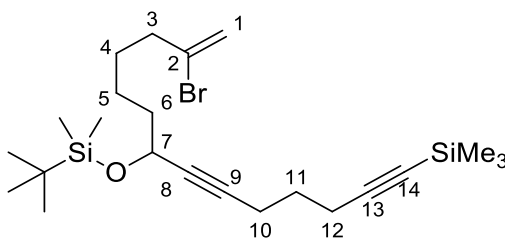
14-(Trimethylsilyl)tetradeca-1,8,13-triyn-7-ol, 226

To a solution of diyne **173** (129 mg, 0.785 mmol, 1.5 equiv.) in THF (4 mL) at –78 °C was added *n*-BuLi (109 μL, 2.5 M in hexanes, 0.109 mmol, 1.3 equiv.) dropwise. The solution was stirred for 45 min, then a solution of bromoenal **175** (100 mg, 0.523 mmol, 1.0 equiv.) in THF (1.0 mL) was added. The solution was slowly warmed to –40 °C and was stirred for 6 h. The reaction was quenched with

saturated aq. NH_4Cl (15 mL). The aqueous layer was extracted using EtOAc (4 x 15 mL). The combined organic layers were dried using Na_2SO_4 and concentrated, and the residue was purified via flash chromatography (9:1 petroleum ether / EtOAc) to yield **226** (173 mg, 0.486 mmol, 93%) as a viscous oil.

^1H 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, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 134.6 (C2), 116.7 (C1), 106.3 (C14), 85.4 (C8), 84.7 (C13), 81.9 (C9), 62.7 (C7), 41.4 (C3), 37.9 (C6), 27.9 (C11), 27.6 (C4), 24.1 (C5), 19.2 (C10), 18.0 (C12), 0.28 ($\text{Si}(\text{CH}_3)_3$). Data in accordance with literature.¹³

((2-Bromo-14-(trimethylsilyl)tetradeca-1-en-8,13-diyn-7-yl)oxy)(tert-butyl)dimethylsilane, 172

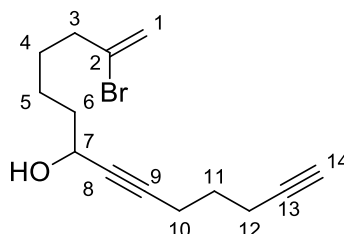


To a solution of **226** (75 mg, 0.211 mmol, 1.0 equiv.) in anhydrous DCM (1 mL) at rt under argon was added DMAP (2.5 mg, 21.1 μmol , 0.1 eq), imidazole (28.7 mg, 0.422 mmol, 2.0 eq) and TBSCl (64 mg, 0.422 mmol, 2.0 eq). The reaction was stirred for 16 h at rt and quenched with sat. aq. NaHCO_3 (15 mL), the layers were separated, and the aqueous layer extracted with DCM (3x10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude was purified *via* column chromatography (9:1 Petroleum Ether / Et_2O) to afford **172** (1.482 g, 4.228 mmol, 90%) as a colourless oil.

R_f 0.65 (19:1 petroleum ether/ Et_2O); ^1H 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, $\text{Si}(\text{CH}_3)_3$), 0.15 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.11 (6H, d, $J = 7.8$ Hz, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (101

MHz, CDCl₃) 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(CH₃)₃), 24.3 (C5), 19.2 (C10), 18.4 (SiC(CH₃)₃), 18.0 (C12), 0.3 (Si(CH₃)₃), -4.3 (Si(CH₃)₂), -4.8 (Si(CH₃)₂). Data in accordance with literature.¹³

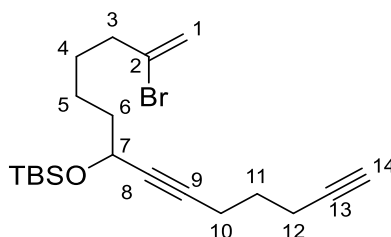
2-Bromotetradeca-1-en-8,13-diyn-7-ol, **227**



To a solution of diyne **221** (197 μ L, 1.72 mmol, 1.5 equiv.) in THF (5 mL) at -78 °C was added *n*-BuLi (0.6 mL, 2.5 M in hexanes, 1.50 mmol, 1.3 equiv.) dropwise. The solution was stirred for 45 min, then a solution of bromoenal **175** (219 mg, 1.15 mmol, 1.0 equiv.) in THF (1.0 mL) was added. The solution was slowly warmed to -40 °C and was stirred for 6 h before quenching with saturated aq. NH₄Cl (15 mL). The aqueous layer was extracted using EtOAc (4 x 15 mL). The combined organic layers were dried using Na₂SO₄ and concentrated, and the residue was purified via flash chromatography (9:1 petroleum ether / EtOAc) to yield **227** (85 mg, 0.299 mmol, 26%) as a viscous oil.

R_f 0.40 (9:1 petroleum ether/ EtOAc); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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). Data in accordance with literature.¹³

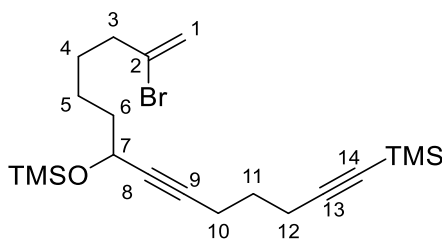
((2-Bromotetradeca-1-en-8,13-diyn-7-yl)oxy)(tert-butyl)dimethylsilane, **228**



To a solution of **227** (42 mg, 0.150 mmol, 1.0 equiv.) in anhydrous DCM (1 mL) at rt under argon was added DMAP (1.8 mg, 15.1 μ mol, 0.1 eq), imidazole (20.4 mg, 0.300 mmol, 2.0 eq) and TBSCl (45 mg, 0.300 mmol, 2.0 eq). The reaction was stirred for 16 h at rt and quenched with sat. *aq.* NaHCO₃ (15 mL), the layers were separated, and the aqueous layer extracted with DCM (3 $\times$ 10 mL). The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude was purified *via* column chromatography (19:1 petroleum ether / Et₂O) to afford **228** (48 mg, 0.120 mmol, 80%) as a colourless oil.

R_f 0.80 (9:1 petroleum ether/ Et₂O); **¹H NMR** (400 MHz, CDCl₃) 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(CH₃)₃), 0.11 (6H, d, J = 7.8 Hz, Si(CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 134.8 (C2), 116.6 (C1), 83.7 (C8), 83.4 (C13), 82.7 (C9), 68.9 (C14), 63.1 (C7), 41.5 (C3), 38.7 (C6), 27.7 (C4 and C11), 26.0 (SiC(CH₃)₃), 24.3 (C5), 18.4 (SiC(CH₃)₃), 17.9 (C-10), 17.7 (C-12), -4.3 (Si(CH₃)₂), -4.8 (Si(CH₃)₂). Data in accordance with literature.¹³

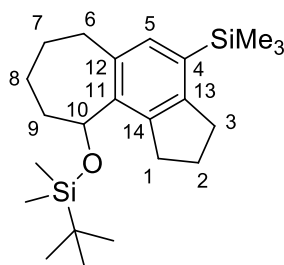
((2-Bromo-14-(trimethylsilyl)tetradeca-1-en-8,13-diyn-7-yl)oxy)trimethylsilane, 229



To a solution of **226** (45 mg, 0.128 mmol, 1.0 equiv.) in anhydrous DCM (0.5 mL) at rt under argon was added pyridine (0.31 mL, 3.843 mmol, 30.0 eq). The above solution was cooled to 0 °C and to it, TMSCl (162 μ L, 1.280 mmol, 10.0 eq) was added. The reaction was stirred at rt for 10 h and then was quenched with sat. *aq.* NH₄Cl solution (15 mL), the layers were separated, and the aqueous layer extracted with DCM (3 $\times$ 10 mL). The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude was purified *via* column chromatography (19:1 petroleum ether / Et₂O) to afford **229** (35 mg, 0.099 mmol, 77%) as a colourless oil.

R_f 0.27 (99:1 petroleum ether/ Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3209, 2912, 1629, 1343, 1250, 1091, 867, 814, 766; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 5.56 (1H, d, J = 1.4 Hz, H1), 5.38 (1H, d, J = 1.4 Hz, H1), 4.31 (1H, tt, J = 6.6, 2.1 Hz, H7), 2.42 (2H, t, J = 7.0 Hz, H3), 2.36 – 2.25 (5H, m, H10, H12 and H14), 1.75 – 1.63 (6H, m, H4, H6 and H11), 1.62 – 1.52 (2H, m, H5) 0.14 (9H, s, TMS). **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 134.5 (C2), 116.3 (C1), 106.2 (C8), 85.0 (C13), 83.6 (C9), 82.0 (C14), 62.5 (C7), 41.2 (C3), 38.4 (C6), 27.5 (C4), 27.4 (C11), 24.0 (C5), 18.9 (C10), 17.7 (C12), -0.00 (TMS); **HRMS** (ESI⁺) calculated for C₁₇H₂₇⁷⁹BrOSiNa [M+Na]⁺ 377.0912 found 377.0914.

tert*-Butyldimethyl((4-(trimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-10-yl)oxy)silane, **214*

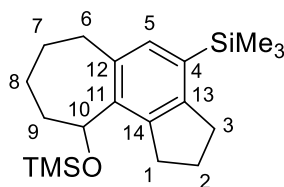


Bromoendiyne **172** (59.0 mg, 0.145 mmol, 1.0 equiv) dissolved in dry acetonitrile (3.7 mL) was degassed with Ar bubbling for 30 min. Triethylamine was separately degassed with Ar bubbling for 30 min. A vial equipped with a stirrer bar was charged with tetrakis(triphenylphosphine)palladium(0) (17 mg, 14.5 μmol , 0.1 equiv.) in the glovebox. The degassed solution of starting material was added to the catalyst by syringe, followed by the degassed triethylamine (123 μL , 0.871 mmol, 6.0 equiv). The reaction mixture was stirred at 80 °C overnight, then cooled to rt and the solvent removed in vacuo. The crude product was then loaded onto a silica gel column and was purified (99:1 petroleum ether/ Et₂O) to afford **214** (31 mg, 0.080 mmol, 55%) as an oil.

R_f 0.57 (Petroleum Ether); **¹H NMR** (400 MHz, CDCl₃) 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, Si(CH₃)₃), 0.27 (9H, s, Si(CH₃)₃), 0.07 (3H, s, Si(CH₃)), -0.18 (3H, s, Si(CH₃)); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 147.2

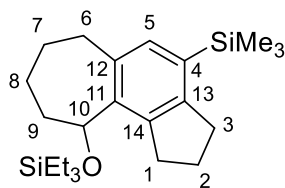
(C14), 140.5 (C12), 140.4 (C11), 140.3 (C13), 134.2 (C5), 133.3 (C4), 71.6 (C10), 35.5 (C6), 34.6 (C9), 34.0 (C3), 31.3 (C1), 29.3 (SiC(CH₃)₃), 26.1 (C7), 25.3 (C2), 25.2 (C8), 18.4 (SiC(CH₃)₃), -0.4 (Si(CH₃)₃) -4.6 (Si(CH₃)₂), -4.8 (Si(CH₃)₂). Data in accordance with literature.¹³

Trimethyl((4-(trimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[e]inden-10-yl)oxy)silane, 234



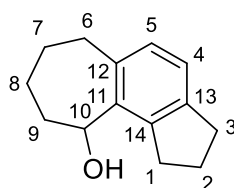
Bromoendiyne **229** (38.0 mg, 90.0 μ mol, 1.0 equiv) dissolved in dry acetonitrile (2.2 mL) was degassed with Ar bubbling for 30 min. Triethylamine was separately degassed with Ar bubbling for 30 min. A vial equipped with a stirrer bar was charged with tetrakis(triphenylphosphine)palladium(0) (10.5 mg, 9.00 μ mol, 0.1 equiv.) in the glovebox. The degassed solution of starting material was added to the catalyst by syringe, followed by the degassed triethylamine (76 μ L, 0.540 mmol, 6.0 equiv). The reaction mixture was stirred at 80 °C overnight, then cooled to rt and the solvent removed in vacuo. The crude product was then loaded onto a silica gel column and was purified (49:1 petroleum ether/ Et₂O) to afford **214** (13 mg, 37.8 μ mol, 42%).

R_f 0.4 (Petroleum Ether); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2923, 2851, 1439, 1248, 1109, 1087, 1054, 879, 839, 689; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 6.99 (1H, s, H5), 5.11 (1H, d, J = 6.3 Hz, H10), 3.31 (1H, t, J = 12.9 Hz, H6), 3.06 – 2.76 (4H, m, H1 and H3), 2.56 (1H, dd, J = 13.7, 6.9 Hz, H6), 2.25 – 2.11 (1H, m, H8), 2.12 – 1.92 (3H, m, H2 and H9), 1.97 – 1.82 (1H, m, H7), 1.77 – 1.63 (1H, m, H8), 1.64 – 1.55 (1H, m, H9), 1.42 – 1.31 (1H, m, H7), 0.27 (9H, s, TMS), 0.05 (9H, s, TMS); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 147.1 (C14), 140.2 (C12), 140.0 (C11), 139.9 (C13), 133.9 (C5), 133.2 (C4), 71.3 (C10), 35.1 (C6), 34.3 (C9), 33.7 (C3), 31.0 (C1), 28.8 (C7), 25.0 (C2), 24.8 (C8), -0.00 (Si(CH₃)₃), -0.77 (Si(CH₃)₃). **HRMS** (ESI⁺) calculated for C₂₁H₃₄ONaSi₂ [M+Na]⁺ 369.2046 found 369.2050.

Trimethyl((4-(trimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[e]inden-10-yl)oxy)silane, 235

Bromoendiyne **230** (52.0 mg, 0.110 mmol, 1.0 equiv) dissolved in dry acetonitrile (3.0 mL) was degassed with Ar bubbling for 30 min. Triethylamine was separately degassed with Ar bubbling for 30 min. A vial equipped with a stirrer bar was charged with tetrakis(triphenylphosphine)palladium(0) (13 mg, 10.98 μmol , 0.1 equiv.) in the glovebox. The degassed solution of starting material was added to the catalyst by syringe, followed by the degassed triethylamine (94 μL , 0.659 mmol, 6.0 equiv). The reaction mixture was stirred at 80 °C overnight, then cooled to rt and the solvent removed in vacuo. The crude product was then loaded onto a silica gel column and was purified (49:1 petroleum ether/ Et₂O) to afford **235** (17 mg, 42.9 μmol , 39%).

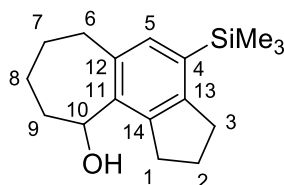
R_f 0.45 (petroleum ether); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2951, 2851, 1438, 1247, 1109, 1087, 1053, 877, 836, 689; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 6.81 (1H, s, H5), 4.93 (1H, d, J = 6.7 Hz, H10), 3.20 (1H, t, J = 12.9 Hz, H6), 3.02 – 2.58 (4H, m, H1 and H3), 2.38 (1H, dd, J = 13.8, 6.8 Hz, H6), 2.16 – 1.98 (1H, m, H8), 1.96 – 1.80 (3H, m, H2 and H9), 1.80 – 1.66 (1H, m, H7), 1.53 (1H, dt, J = 13.5, 3.8 Hz, H8), 1.48 – 1.35 (1H, m, H7), 1.27 – 1.13 (1H, m, H9), 0.71 (9H, t, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.36 (6H, qd, J = 7.9, 2.3 Hz, Si(CH₂CH₃)₃), 0.10 (9H, s, TMS); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 147.7 (C14), 141.0 (C12), 140.9 (C11), 140.8 (C13), 134.6 (C5), 133.8 (C4), 71.8 (C10), 35.9 (C6), 35.1 (C9), 34.4 (C3), 31.8 (C1), 30.90 (Si(CH₂CH₃)₃), 30.30 (C7), 25.8 (C2), 25.7 (C8), 7.42 (Si(CH₂CH₃)₃), 5.55 (Si(CH₂CH₃)₃), 0.00 (Si(CH₃)₃); **HRMS** (ESI⁺) calculated for C₂₃H₄₀ONaSi₂ [M+Na]⁺ 411.2515 found 411.2518.

1,2,3,6,7,8,9,10-Octahydrocyclohepta[e]inden-10-ol, 232

To a stirred solution of $\text{RhCl}(\text{PPh}_3)_3$ (14.4 mg, 15.6 μmol , 0.2 equiv.) in DCE (5 mL) was added a solution of the triyne **171** (16.0 mg, 79.0 μmol , 1.0 equiv.) in DCE (6 mL). The reaction was stirred at 50 °C for 24 h, then cooled to rt and concentrated. The residue was purified via flash chromatography (3:1 petroleum ether / Et_2O) to yield **232** (8.3 mg, 41.1 μmol , 52%) as a white solid.

R_f 0.45 (4:1 petroleum ether / Et_2O); **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.03 (1H, d, $J = 7.4$, H4 or H5), 6.92 (1H, d, $J = 7.4$ Hz, H4 or H5), 5.23–5.18 (1H, m, H10), 3.24 (1H, app t, $J = 13.1$ Hz, H6), 3.07–2.91 (2H, m, H3), 2.90 (2H, t, $J = 7.4$ Hz, H1), 2.67 (1H, dd, $J = 14.2$, 6.9 Hz, H6), 2.24–2.13 (2H, m, H8 and H9), 2.11–2.01 (2H, m, H2), 2.00–1.92 (1H, m, H7), 1.82–1.74 (1H, m, H8), 1.73–1.57 (2H, m, H9 and OH), 1.49–1.38 (1H, m, H7); **¹³C NMR** (126 MHz, CDCl_3) δ_{C} 142.6 (C14), 142.2 (C13), 140.8 (C11), 138.5 (C12), 128.8 (C5), 123.5 (C4), 71.4 (C10), 35.5 (C6), 33.1 (C9), 32.8 (C3), 31.7 (C1), 28.7 (C7), 25.0 (C8), 24.9 (C2). Data in accordance with literature.¹³

4-(Trimethylsilyl)-1,2,3,6,7,8,9,10-octahydrocyclohepta[*e*]inden-10-ol, **231**

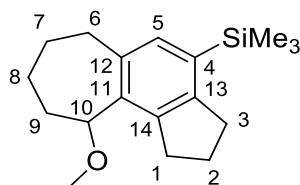


To a stirred solution of TBS ether **214** (40.0 mg, 0.102 mmol, 1.0 equiv.) in THF (1.0 mL) was added TBAF (1 M in THF, 0.52 mL, 0.520 mmol, 5.0 equiv.). The reaction mixture was stirred at 60 °C for 9 h, then cooled to rt. The reaction was quenched with 5 mL sat. *aq.* NH_4Cl solution, the layers separated, and the aqueous layer extracted three times with diethyl ether (10 mL). The combined organic layers were dried with Na_2SO_4 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 alcohol **231** (25 mg, 0.094 mmol, 92%) as a white solid.

R_f 0.31 (9:1 petroleum ether/ EtOAc); **¹H 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

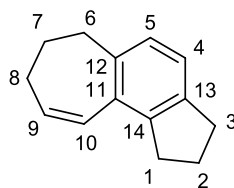
(1H, m, H8), 1.74–1.67 (1H, m, H9), 1.64 (1H, d, $J = 3.0$ Hz, OH), 1.52–1.37 (1H, m, H7), 0.28 (9H, s, Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ_c 147.9 (C14), 141.9 (C12), 140.0 (C11), 139.4 (C13), 134.7 (C5), 134.6 (C4), 71.5 (C10), 35.8 (C6), 34.0 (C9), 33.1 (C3), 31.3 (C1), 28.9 (C7), 25.1 (C2), 25.0 (C8), -0.5 (Si(CH₃)₃). Data in accordance with literature.¹³

(10-Methoxy-1,2,3,6,7,8,9,10-octahydrocyclohepta[e]inden-4-yl)trimethylsilane, 239



To a stirred solution of TBS ether **214** (20.0 mg, 51.5 μ mol, 1.0 equiv.) in methanol (1.5 mL) was added AcCl (8 μ L, 0.103 mmol, 2.0 equiv.). The reaction mixture was stirred at 40 °C overnight, then cooled to rt. The reaction mixture was quenched with triethylamine (50 μ L) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (99:1 petroleum ether/Et₂O) to yield methyl ether **239** (10.8 mg, 37.6 μ mol, 73%) as a colourless oil.

R_f 0.55 (9:1 petroleum ether/ Et₂O); **IR** (thin film, $\nu_{\max}$ / cm⁻¹) 2922 (s), 1737 (m), 1440 (m), 1247 (m), 1091 (s), 835 (s), 732 (m); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.01 (1H, s, H5), 4.63 (1H, d, $J = 6.3$ Hz, H10), 3.24–3.17 (4H, m, OCH₃ 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(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ_c 147.3 (C13), 142.6 (C14), 140.4 (C12), 137.2 (C11), 134.3 (C5), 134.2 (C4), 79.7 (C10), 56.2 (OCH₃), 35.4 (C6), 34.0 (C3), 31.6 (C9), 31.5 (C1), 28.9 (C7), 25.3 (C8), 25.1 (C2), -0.5 (Si(CH₃)₃); **HRMS** (ESI⁺) calc. for C₁₈H₂₈OSiNa [M+Na]⁺ 311.1802, found 311.1794.

1,2,3,6,7,8-Hexahydrocyclohepta[e]indene, 167

To a stirred solution of TBS ether **241** (24.0 mg, 62 μmol , 1.0 equiv.) in dry THF (1.5 mL) was added zinc(II) chloride (12.0 mg, 92 μmol , 1.5 equiv.) and chlorotrimethylsilane (15.0 μL , 0.124 mmol, 2.0 equiv.).²⁰² The reaction mixture was stirred for 3 h before it was cooled to 0 °C, diluted with 3 mL diethyl ether and quenched with 2 mL sat. *aq.* NH_4Cl solution and warmed to rt. The layers were separated and the aqueous layer extracted three times with diethyl ether (5 mL). The combined organic layers were dried with Na_2SO_4 , and the solvent removed *in vacuo*. The residue was filtered through a short plug of silica using 9:1 petroleum ether / Et_2O , then concentrated. To a solution of this crude mixture, in acetonitrile (1.0 mL) was added sodium iodide (9.3 mg, 62 μmol , 1.0 equiv.), distilled water (1 μL , 62 μmol , 1.0 equiv.) and chlorotrimethylsilane (6.6 μL , 62 μmol , 1.0 equiv.).²⁰³ The reaction mixture was stirred at rt for 2 h, then quenched with sat. *aq.* NaHCO_3 solution. The layers were separated and the aqueous layer extracted three times with diethyl ether (5 mL). The combined organic layers were dried with Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether), to yield **167** (8.2 mg, 44.6 μmol 72%) as a colourless oil.

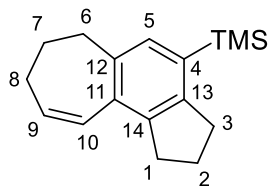
Alternatively, To a solution of **231** (10 mg, 36.4 μmol , 1.0 equiv.) in dry THF (0.8 mL), zinc(II) chloride (7.4 mg, 54.6 μmol , 1.5 equiv.) and chlorotrimethylsilane (9.5 μL , 72.8 μmol , 2.0 equiv.) were added.²⁰² The reaction mixture was stirred for 3 h before it was cooled to 0 °C, diluted with 3 mL diethyl ether and quenched with 2 mL sat. *aq.* NH_4Cl solution and warmed to rt. The layers were separated and the aqueous layer extracted three times with diethyl ether (5 mL). The combined organic layers were dried with Na_2SO_4 , and the solvent removed *in vacuo*. The residue was filtered through a short plug of silica using 9:1 petroleum ether / Et_2O , then concentrated. To a solution of this crude mixture, in acetonitrile (0.5 mL) was added sodium iodide (5.4 mg, 36.4 μmol , 1.0 equiv.), distilled water (0.6 μL , 36.4 μmol , 1.0 equiv.) and chlorotrimethylsilane (4.7 μL , 36.4 μmol , 1.0 equiv.).²⁰³ The reaction mixture was

stirred at rt for 2 h, then quenched with sat. *aq.* NaHCO₃ solution. The layers were separated and the aqueous layer extracted three times with diethyl ether (5 mL). The combined organic layers were dried with Na₂SO₄ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether), to yield **167** (5.0 mg, 27.3 μmol 75%) as a colourless oil.

Alternatively, To a solution of **232** (10 mg, 49.4 μmol, 1.0 equiv.) in dry THF (1.2 mL), zinc(II) chloride (10.0 mg, 74.1 μmol, 1.5 equiv.) and chlorotrimethylsilane (12.5 μL, 98.8 μmol, 2.0 equiv.) were added.²⁰² The reaction mixture was stirred for 3 h before it was cooled to 0 °C, diluted with 3 mL diethyl ether and quenched with 2 mL sat. *aq.* NH₄Cl solution and warmed to rt. The layers were separated and the aqueous layer extracted three times with diethyl ether (5 mL). The combined organic layers were dried with Na₂SO₄, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether), to yield **167** (7.3 mg, 39.5 μmol, 80%) as a colourless oil.

Alternatively, to a solution of **241** (5 mg, 19.5 μmol, 1.0 equiv.) in MeOH (1.0 mL), was added Acetyl chloride (2.8 μL, 39.0 μmol, 2.0 equiv.) The reaction mixture was stirred at 40 °C overnight, then cooled to rt. The reaction mixture was quenched with triethylamine (50 μL) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on a short plug of silica (Pet. Ether), to yield **167** (3.5 mg, 19.1 μmol, 98%) as a colourless oil.

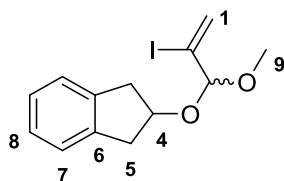
R_f 0.54 (petroleum ether); **¹H NMR** (500 MHz, CDCl₃) δ_H 6.99 (1H, d, *J* = 7.6 Hz, H5), 6.91 (1H, d, *J* = 7.6 Hz, H4), 6.48 (1H, dt, *J* = 12.1, 2.2 Hz, H10), 5.97 (1H, dt, *J* = 12.1, 4.7 Hz, H9), 2.90 (4H, *app* q, *J* = 6.7 Hz, H1 and H3), 2.81-2.74 (2H, m, H6), 2.38 (2H, tdd, *J* = 6.8, 4.7, 2.2 Hz, H8), 2.07 (2H, *app* quin, *J* = 7.5 Hz, H2), 2.02-1.91 (2H, m, H7); **¹³C NMR** (126 MHz, CDCl₃) δ_C 143.6 (C14), 141.9 (C13), 139.9 (C11), 132.7 (C9), 132.5 (C12), 127.2 (C4), 127.1 (C10), 122.6 (C5), 35.4 (C6), 33.0 (C3), 32.0 (C8 and C1), 28.8 (C7), 25.1 (C2). Data in accordance with literature.¹³

(1,2,3,6,7,8-Hexahydrocyclohepta[e]inden-4-yl)trimethylsilane, 241

To a solution of alcohol **231** (6.2 mg, 22.6 μmol , 1.0 equiv.) in dry THF (0.5 mL), Burgess reagent (16.1 mg, 67.8 μmol , 3.0 equiv.) was added. The solution was stirred at rt for 2 h before diluting with 5 mL Et₂O and quenching with 5 mL *sat.* NH₄Cl solution. The layers were separated, and the aqueous layer extracted three times with diethyl ether (5 mL). The combined organic layers were dried with Na₂SO₄, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (Pet. Ether), to yield **241** (3.6 mg, 14.7 μmol , 65%) as an oil.

Alternatively, To a solution of alcohol **231** (5.1 mg, 18.6 μmol , 1.0 equiv.) in dry DCM (0.4 mL), Martin reagent (15.0 mg, 22.3 μmol , 1.2 equiv.) was added. The solution was stirred at rt for 15 min before diluting with 5 mL Et₂O and quenching with 5 mL *sat.* NaHCO₃ solution. The layers were separated, and the aqueous layer extracted three times with diethyl ether (5 mL). The combined organic layers were dried with Na₂SO₄, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether), to yield **241** (3.2 mg, 12.6 μmol , 68%) as an oil.

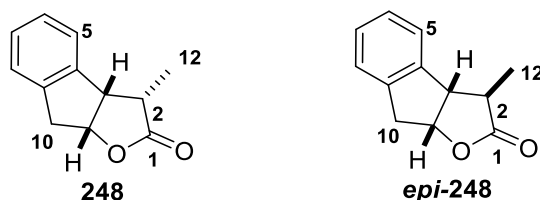
R_f 0.61 (petroleum ether); **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.05 (1H, s, H5), 6.48 (1H, dt, $J = 12.2$, 2.0 Hz, H10), 5.98 (1H, dt, $J = 12.2$, 4.7 Hz, H9), 2.96 (2H, t, $J = 7.5$ Hz, H1), 2.90 (2H, t, $J = 7.5$ Hz, H3), 2.84 – 2.73 (2H, m, H6), 2.40 (2H, tdd, $J = 6.7$, 4.6, 2.0 Hz, H8), 2.07 (2H, *app* quint., $J = 7.5$ Hz, H2), 2.02 – 1.94 (2H, m, H7) 0.28 (9H, s, TMS); **¹³C NMR** (126 MHz, CDCl₃) δ_{C} 147.8 (C14), 143.1 (C13), 139.5 (C11), 133.9 (C9), 133.8 (C12), 133.7 (C4), 133.4 (C10), 127.5 (C5), 36.0 (C6), 34.5 (C3), 32.7 (C8), 32.0 (C1), 29.1 (C7), 25.5 (C2), -0.00 (Si(CH₃)₃).

2-((2-Iodo-1-methoxyallyl)oxy)-2,3-dihydro-1H-indene, 176

To a stirred solution of 2-indanol (4.0 g, 14.75 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL), in a two necked flask, was added 1-methoxyallene (1.05 g, 15.0 mmol, 1.05 equiv) followed by N-iodosuccinimide (5.2 g, 22.6 mmol, 1.5 equiv.) portionwise at $-20\text{ }^\circ\text{C}$. The flask was wrapped with aluminum foil and was slowly warmed to $40\text{ }^\circ\text{C}$ and stirred for 6 h then cooled down to rt, and poured into a separatory funnel. The organic layer was washed with 5% aqueous KOH (10 mL), water ($3 \times 10\text{ mL}$) and brine (10 mL) and was dried over Na_2SO_4 . The solvent was removed *in vacuo* and crude product was purified by flash column chromatography (10:1 Petroleum Ether / EtOAc) on silica gel to afford **176** (3.9 g, 11.80 mmol, 80%) as a colorless oil.

$R_f = 0.5$ (9:1 petroleum ether / EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_{H} 7.24 – 7.09 (4H, m, H7 and H8), 6.59 (1H, t, $J = 1.3\text{ Hz}$, H1), 6.07 (1H, dd, $J = 1.6, 0.7\text{ Hz}$, H1), 4.64 (1H, d, $J = 0.9\text{ Hz}$, H4), 4.63 – 4.55 (1H, m, H4), 3.35 (3H, s, H9), 3.21 (2H, ddd, $J = 17.8, 16.1, 6.8\text{ Hz}$, H5), 3.07 (2H, ddd, $J = 18.4, 16.1, 5.3\text{ Hz}$, H5); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ_{C} 140.3, 140.2, 128.4, 126.4 (2C), 124.4, 124.3, 108.3, 103.4, 77.3, 52.8, 39.6, 39.2. Data in accordance with literature.¹⁶⁸

3-Methyl-3,3a,8,8a-tetrahydro-2H-indeno[2,1-b]furan-2-one, **248**



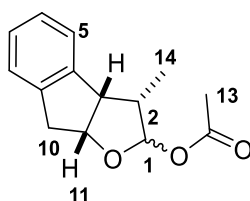
To a solution of **176** (990 mg, 3.00 mmol, 1.0 equiv.) in degassed *t*-BuOH (150 mL) under argon, at rt, was added NaBH_3CN (95%, 397 mg, 6.0 mmol, 2.0 equiv) and AIBN (99%, 50 mg, 0.3 mmol, 10 mol %). Bu_3SnCl (99%, 41 μL , 0.15 mmol, 0.05 equiv.) was then added dropwise, and the resulting mixture was heated to $80\text{ }^\circ\text{C}$ and stirred for 6 h. The reaction solution was cooled down to room temperature and *t*-BuOH was evaporated under reduced pressure. The residue was filtered with a short plug of silica gel (9:1 petroleum ether / EtOAc) to afford the crude acetals **247** and *epi*-**247** (1:2), which were used directly without further purification. To a stirred solution of the mixture of these acetals in CH_2Cl_2 (30 mL) was added *m*CPBA (70–75%, 2.2 g, 9.0 mmol, 3.0 equiv) portionwise at $0\text{ }^\circ\text{C}$ followed by the addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.75 mL, 6.0 mmol, 2.0 equiv) dropwise. After 2 h, the reaction mixture was

quenched by saturated aqueous Na_2SO_3 (15 mL) and extracted with CH_2Cl_2 (30 mL). The resulting water layer was extracted with CH_2Cl_2 (30 mL) again. The combined organic layers were washed with saturated aqueous NaHCO_3 (5×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (9:1 Petroleum Ether/EtOAc) to afford **epi-248** (185 mg, 0.960 mmol, 32% yield) as a white solid and **248** (89 mg, 0.430 mmol, 16% yield) as a white solid as well.

epi-248: $R_f = 0.50$ (2:1 petroleum ether / EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 7.26 – 7.22 (4H, m, H5, H6, H7, H8), 5.33 (1H, ddd, $J = 7.2, 4.8, 2.4$ Hz, H11), 3.65 (1H, dd, $J = 6.0, 2.0$ Hz, H3), 3.32 – 3.38 (2H, m, H10), 2.83 (1H, dq, $J = 7.6, 2.0$ Hz, H2), 1.50 (3H, d, $J = 7.6$ Hz, H12); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_C 179.7, 141.8, 139.9, 128.3, 127.7, 125.4, 124.7, 82.6, 53.5, 42.3, 38.8, 17.3. Data in accordance with literature.¹⁷

248: $R_f = 0.30$ (2:1 petroleum ether / EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ_H 7.30 – 7.20 (4H, m, H5, H6, H7 and H8), 5.23 (1H, td, $J = 5.6, 1.6$ Hz, H11), 4.08 (1H, dd, $J = 9.2, 5.6$ Hz, H), 3.33 (d, $J = 16.8$ Hz, 1H), 3.27 (dd, $J = 17.6, 5.2$ Hz, 1H) 3.12 (dq, $J = 9.2, 7.2$ Hz, 1H), 1.41 (d, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ_C 178.6, 141.2, 138.3, 128.2, 126.9, 126.7, 125.6, 81.7, 49.6, 38.9, 38.5, 12.2. Data in accordance with literature.¹⁷

3-Methyl-3,3a,8,8a-tetrahydro-2H-indeno[2,1-b]furan-2-yl acetate, **170**

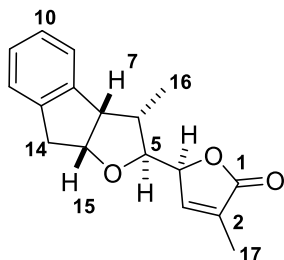


To a stirred solution of lactone **248** (150 mg, 0.799 mmol, 1.0 equiv.) in CH_2Cl_2 (9.5 mL) was added DIBAL-H (1.0 M in hexane, 0.96 mL, 0.96 mmol, 1.2 equiv) dropwise at -78°C . The mixture was stirred for 1 h followed by the addition of pyridine (0.26 mL, 3.194 mmol, 4.0 equiv), DMAP (99%, 117 mg, 0.958 mmol, 1.2 equiv) followed by Ac_2O (0.38 mL, 3.993 mmol, 5.0 equiv). This one-pot reaction mixture was allowed to warm to room temperature slowly and further stirred for 1 h followed by the addition of equal amounts of pyridine and Ac_2O again. After 30 min, the reaction mixture was

quenched by saturated aqueous NH_4Cl (10 mL), then diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL) again. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (10:1 petroleum ether / EtOAc) acetate **170** (dr = 2.5:1, 244 mg, 81% yield) as a white solid. The major diastereomer from a small amount of **170** was purified for the purpose of characterisation.

R_f 0.35 (4:1 petroleum ether / EtOAc); ^1H NMR (400 MHz, CDCl_3) 7.23 – 7.10 (4H, m, H5, H6, H7 and H8), 5.95 (1H, d, $J = 1.6$ Hz, H1), 5.18 (1H, td, $J = 7.4, 2.9$ Hz, H11), 4.06 (1H, *app t*, $J = 8.0$ Hz, H3), 3.24 (1H, dd, $J = 17.4, 7.4$ Hz, H10), 3.10 (1H, dd, $J = 17.5, 2.9$ Hz, H10), 2.76 – 2.63 (1H, m, H2), 2.09 (3H, s, H13), 0.86 (3H, d, $J = 7.5$ Hz, H14); ^{13}C NMR (101 MHz, CDCl_3) δ 170.7, 142.6, 140.2, 127.4, 126.5, 126.3, 125.2, 105.9, 85.0, 51.7, 42.3, 39.4, 21.4, 14.5. Data in accordance with literature.¹⁷

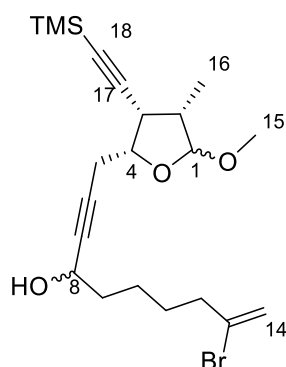
(S)-3-Methyl-5-((2S,3S,3aS,8aR)-3-methyl-3,3a,8,8a-tetrahydro-2H-indeno[2,1-b]furan-2-yl)furan-2(5H)-one, 168



To a solution of acetates **170** (20.3 mg, 0.093 mmol, 1.0 equiv.) and silyloxyfuran **6** (40 μL , 0.140 mmol, 1.5 equiv.) in anhydrous MeCN (1.0 mL) at -40 $^\circ\text{C}$, was added dropwise a solution of $\text{Bi}(\text{OTf})_3$ (122 mg, 0.186 mmol, 2.0 equiv.) in anhydrous MeCN (1.0 mL). The mixture was stirred at -40 $^\circ\text{C}$ for 1 h before being quenched with saturated aq. NH_4Cl (10 mL). The solution was warmed to rt, then extracted with Et_2O (4 $\times$ 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified via flash column chromatography (19:1 $\rightarrow$ 6:1 petroleum ether / Et_2O) to give **168** (46 mg, 0.107 mmol, 35%, colourless solid).

R_f 0.44 (2:1 petroleum ether / EtOAc); **¹H NMR** (400 MHz, CDCl₃): δ_H 7.29 (1H, d, *J* = 6.7 Hz, H_{Ar}), 7.24–7.14 (3H, m, H_{Ar}), 6.97 (1H, t, *J* = 1.6 Hz, H₃), 4.88 (1H, td, *J* = 2.0, 1.6 Hz, H₄), 4.86 (1H, dd, *J* = 5.6, 1.6 Hz, H₁₅), 3.82 (1H dd, *J* = 7.6, 6.0 Hz, H₅), 3.49 (1H, dd, *J* = 9.2, 2.0, Hz, H₇), 3.10 (1H, dd, *J* = 17.2, 5.6 Hz, H₁₄), 3.02 (1H, d, *J* = 17.2 Hz, 1H), 2.78 (1H, dq, *J* = 16.8, 7.6 Hz, H₆), 1.94 (3H, t, *J* = 1.6 Hz, H₁₇), 1.24 (3H, d, *J* = 7.2 Hz, H₁₆); **¹³C NMR** (101 MHz, CDCl₃) δ_C 174.5, 146.4, 143.6, 140.2, 130.7, 127.4, 126.6, 126.3, 125.3, 83.7, 82.7, 80.0, 54.0, 40.6, 39.4, 13.5, 11.0. Data in accordance with literature.¹⁷

9-Bromo-1-((2*R*,3*S*,4*S*)-5-methoxy-4-methyl-3-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)dec-9-en-2-yn-4-ol, **180**

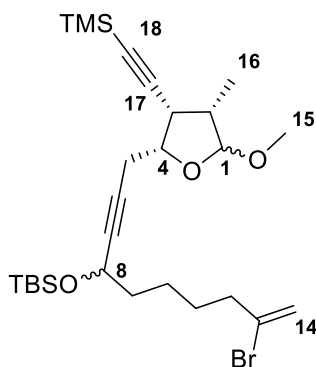


To a solution of diyne **108** (137 mg, 0.546 mmol, 1.5 equiv.) in *anhyd.* THF (0.4 mL) at -78°C , *n*-BuLi (2.5 M in hexanes, 0.195 mL, 0.49 mmol, 1.3 eq) was added. It was allowed to warm to -40°C over 30 min and was stirred at the same temperature for additional 90 min. The solution was again cooled to -78°C and to it a solution of aldehyde (72 mg, 0.377 mmol, 1.0 eq) in THF (0.2 mL) was added. The reaction was again warmed to -40°C and was stirred for 6 hr. On completion, the reaction was quenched with 10 mL *sat.* NH₄Cl (aq) and was warmed to rt. The aqueous layer was extracted using Et₂O (10 mL $\times$ 4). The combined organic layer was dried using Na₂SO₄, the solvent removed *in vacuo* and the crude purified via flash column chromatography (19:1 to 3:1 Petroleum ether/ Et₂O) to yield **180** (161 mg, 0.366 mmol, 97%) as a colourless oil and recovered alkyne (41 mg, 0.48 eq).

R_f 0.3 (1:1 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3442, 2934, 2860, 2169, 1629, 1456, 1250, 1101, 1025, 1002, 843, 760; **¹H NMR** (400 MHz, CDCl₃) δ 5.56 (1H, s, H₁₄), 5.39 (1H, s, H₁₄), 4.64

(1H, d, $J = 3.6$ Hz, H1), 4.36 (1H, br t, H8), 4.2 (1H, d, $J = 6.5$ Hz, H4), 3.38 (3H, s, H15), 3.21 (1H, dd, $J = 6.3$ and 7.0 Hz, H3), 2.64 (2H, d, $J = 6.4$ Hz, H5), 2.43 (2H, t, $J = 7.5$ Hz, H12), 2.34 – 2.24 (1H, m, H2), 1.7 – 1.43 (6H, m, H9, H10 and H11), 1.17 (3H, d, $J = 7.7$ Hz, H8), 0.15 (9H, s, Si(CH₃)₃). ¹³C NMR (101 MHz, CDCl₃) δ 134.4, 116.5, 110.5, 101.5, 91.6, 82.3, 81.8, 77.8, 62.4, 55.8, 43.3, 41.2, 40.0, 37.5, 27.4, 23.9, 22.7, 13.7, -0.0, -0.01. HRMS (ESI⁺) calculated for C₂₁H₃₄O₃⁷⁹BrSi [M+H]⁺ 441.1461 found 441.1456.

((9-Bromo-1-((2R,3S,4S)-5-methoxy-4-methyl-3-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)dec-9-en-2-yn-4-yl)oxy)(tert-butyl)dimethylsilane, 264

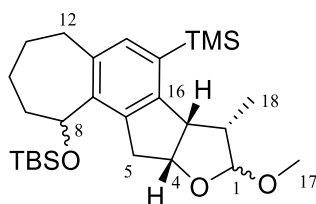


To a solution of alcohol **180** (159 mg, 0.361 mmol, 1.0 equiv.) in *anhyd.* DCM (1.5 mL) at rt was added DMAP (5 mg, 0.042 mmol, 0.1 eq), imidazole (52 mg, 0.903 mmol, 2.5 eq) and TBSCl (82 mg, 0.540 mmol, 1.5 eq). It was stirred overnight at rt. On completion, the reaction was quenched with 10 mL *sat.* NH₄Cl (aq) and was warmed to rt. The aqueous layer was extracted using Et₂O (10 mL $\times$ 4). The combined organic layer was dried using Na₂SO₄, the solvent removed *in vacuo* and the crude purified via flash column chromatography (99:1 petroleum ether/ Et₂O) to yield **264** (192 mg, 0.346 mmol, 96%) as a colourless oil.

R_f 0.35 (97:3 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2931, 2858, 2171, 1629, 1461, 1361, 1250, 1099, 1026, 1004, 840, 777; ¹H NMR (400 MHz, CDCl₃) δ 5.55 (1H, s, H14), 5.38 (1H, s, H14), 4.66 (1H, d, $J = 3.6$ Hz, H1), 4.33 (1H, m, H8), 4.18 (1H, *app* q, $J = 6.5$ Hz, H4), 3.37 (3H, s, H15), 3.19 (1H, dd, $J = 6.3$ and 7.0 Hz, H3), 2.66 – 2.60 (2H, m, H5), 2.42 (2H, t, $J = 7.5$ Hz, H12), 2.33 – 2.26 (1H, m, H2), 1.7 – 1.43 (6H, m, H9, H10 and H11), 1.18 (3H, d, $J = 7.7$ Hz, H8), 0.89 (9H, s, Si

(*t*-Bu)), 0.16 (9H, s, Si(CH₃)₃), 0.13 (3H, s, Si(CH₃)) 0.10 (3H, s, Si(CH₃)). ¹³C NMR (101 MHz, CDCl₃) δ 134.6, 116.5, 110.5, 101.6, 91.5, 82.9, 80.6, 78.1, 62.9, 55.8, 43.4, 41.3, 40.2, 38.4, 27.5, 24.0, 22.5, 18.1, 13.7, -0.0, -4.4, -5.1. **HRMS** (ESI⁺) calculated for C₂₇H₄₈O₃⁷⁹BrSi₂ [M+H]⁺ 555.2320 found 555.2321.

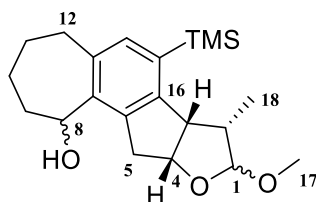
(7b*S*,8*S*,10a*R*)-9-Methoxy-8-methyl-1,2,3,4,5,7b,8,9,10a,11-decahydrocyclohepta[4,5]indeno[2,1-b]furan-1-ol, **265**



Bromoendiyne **264** (50 mg, 0.09 mmol, 1.0 equiv) was dissolved in *anhyd.* MeCN (3 mL), and the solution was degassed with Ar bubbling for 30 min. Et₃N was separately degassed for 30 min. To a flame dried vial with a stirrer bar was added Pd(PPh₃)₄ (10.3 mg, 9.2 μmol, 0.1 eq) in a glovebox. The degassed solution of starting material was added to the catalyst by syringe followed by Et₃N (76 μL, 0.54 mmol, 6.0 eq). The reaction was stirred at 80 °C for 15 h. On completion, the reaction was cooled to rt and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (49:1 petroleum ether/ Et₂O) to yield **265** (27 mg, 0.058 mmol, 64%, inseparable 1:0.7 mixture of diastereomers) as a colourless oil.

R_f 0.36 (97:3 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2972, 2923, 1457, 1382, 1245, 1101, 1085, 1060, 940, 833; **¹H NMR** (400 MHz, CDCl₃) δ 7.0 (1H, s, H14), 5.10 – 5.00 (1H, m, H4), 4.95 (1H, d, *J* = 6.9 Hz, H8) 4.79 (1H, d, *J* = 3.6 Hz, H1), 4.16 (1H, t, *J* = 8.4 Hz, H3), 3.37 (3H, s, H17), 3.36 – 3.24 (2H, m, H5 and H12), 2.90 (1H, dd, *J* = 4.8 and 17.1 Hz, H5), 2.57 – 2.42 (2H, m, H2 and H12), 2.25 – 2.12 (1H, m, H11), 2.05 – 1.82 (2H, m, H9) 1.72 – 1.61 (1H, m, H11), 1.50 – 1.25 (2H, m, H10), 0.89 (9H, s, Si(*t*Bu)), 0.52 (3H, d, *J* = 7.5 Hz, H18), 0.2 (9H, s, Si(CH₃)₃), 0.06 (3H, s, Si(*t*Bu)(CH₃)), -0.14 (3H, s, Si(*t*Bu)(CH₃)). **¹³C NMR** (101 MHz, CDCl₃) δ 143.6, 141.0, 140.2, 138.2, 134.5, 112.8, 82.8, 71.2, 54.2, 51.8, 43.0, 39.2, 35.1, 34.6, 28.7, 25.8, 25.0, 14.1, 0.0, -4.9, -4.9; **HRMS** (ESI⁺) calculated for C₂₇H₄₆O₃NaSi₂ [M+Na]⁺ 497.2883 found 497.2882.

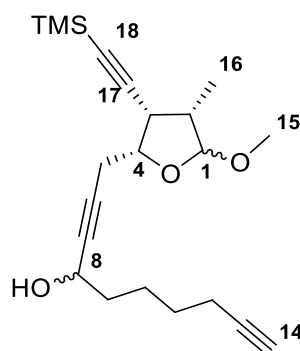
((7b*S*,8*S*,10a*R*)-9-Methoxy-8-methyl-7-(trimethylsilyl)-1,2,3,4,5,7b,8,9,10a,11-decahydrocyclohepta[4,5]indeno[2,1-b]furan-1-ol, **267**



To a solution of **265** (19 mg, 0.041 mmol, 1.0 eq) in *anhyd.* THF (0.75 mL) at rt, 0.2 mL TBAF solution (1M in THF, 0.202 mmol, 5.0 eq) was added. The reaction was heated at 50 °C for 15 h and the reaction was monitored using TLC. After disappearance of starting material, the reaction was quenched by adding 10 mL *sat.* NH₄Cl (aq) and cooled to rt. The aqueous layer was extracted using Et₂O (5 mL × 4). The combined organic layer was dried using Na₂SO₄, the solvent removed *in vacuo* and the crude purified via flash column chromatography (49:1 to 9:1 Petroleum ether / Et₂O) to yield **267** (13 mg, 0.037 mmol, 92%, viscous oil).

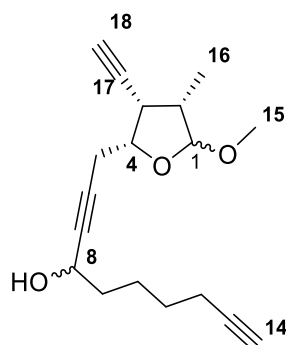
R_f 0.28 (9:1 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3442, 2970, 2927, 1456, 1380, 1248, 1100, 1085, 1060, 939, 834; **¹H NMR** (400 MHz, CDCl₃) δ 7.08 (1H, s, H14), 5.09 – 4.99 (2H, m, H4 and H8), 4.79 (1H, d, J = 3.6 Hz, H1), 4.26 – 4.15 (1H, m, H3), 3.50 – 3.10 (7H, m, H5, H12, H17 and OH), 2.98 (1H, dd, J = 4.8 and 17.1 Hz, H5), 2.55 – 2.45 (1H, m, H2), 2.22 – 2.12 (2H, m, H9 and H11), 2.01 – 1.88 (1H, m, H9) 1.71 – 1.58 (1H, m, H11), 1.23 – 1.18 (2H, m, H10), 0.52 (3H, d, J = 7.5 Hz, H18), 0.29 (9H, s, Si(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 143.3, 140.7, 140.0, 139.2, 135.8, 112.8, 110.5, 82.7, 71.0, 62.2, 54.3, 52.0, 43.0, 39.2, 35.6, 33.1, 28.4, 24.7, 24.6, 14.3, 0.0. **HRMS** (ESI⁺) calculated for C₂₁H₃₂O₃SiNa [M+Na]⁺ 383.2018 found 383.2020.

1-((2*R*,3*S*,4*S*)-5-Methoxy-4-methyl-3-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)deca-2,9-diyne-4-ol; **181**



To a solution of alkyne **108** (118 mg, 0.472 mmol, 1.4 equiv.) in *anhyd.* THF (0.4 mL) at $-78\text{ }^{\circ}\text{C}$, *n*-BuLi (2.5 M in hexanes, 0.175 mL, 0.437 mmol, 1.3 equiv.). It was allowed to warm to $-40\text{ }^{\circ}\text{C}$ over 30 min and was stirred at the same temperature for additional 90 min. The solution was again cooled to $-78\text{ }^{\circ}\text{C}$ and to it a solution of aldehyde **161** (37 mg, 0.337 mmol, 1.0 equiv.) in THF (0.4 mL) was added. The reaction was again warmed to $-40\text{ }^{\circ}\text{C}$ and was stirred for 5.5 hr. On completion, the reaction was quenched with 10 mL *sat.* NH_4Cl (aq) and was warmed to rt. The aqueous layer was extracted using Et_2O (10 mL $\times$ 4). The combined organic layer was dried using Na_2SO_4 , the solvent removed *in vacuo* and the crude purified via flash column chromatography (4:1 to 2:1 petroleum ether / Et_2O) to yield **181** (98 mg, 0.392 mmol, 83%) as a colourless oil.

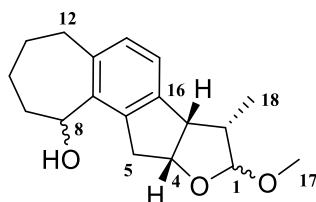
R_f 0.33 (1:1 petroleum ether / Et_2O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3311, 2927, 2856, 2169, 1541, 1456, 1300, 1250, 1199, 1102, 1025, 1003, 921, 843, 761; **¹H NMR** (400 MHz, CDCl_3) δ 4.67 (1H, d, $J = 4.0$ Hz, H1), 4.37 (1H, br s, H8), 4.20 (1H, *app.* quint., $J = 6.1$ Hz, H4), 3.38 (3H, s, H15), 3.22 (1H, dd, $J = 7.2, 5.6$ Hz, H3), 2.64 (2H, dt, $J = 7.1, 2.0$ Hz, H5), 2.30 (1H, m, H2), 2.30 – 2.18 (2H, m, H12), 1.94 (1H, t, $J = 2.6$ Hz, H14), 1.71– 1.58 (7H, m, OH, H9, H10 and H11), 1.17 (3H, d, $J = 7.2$ Hz, H16), 0.16 (9H, s, $\text{Si}(\text{CH}_3)_3$); **¹³C NMR** (101 MHz, CDCl_3) δ 110.5, 101.6, 91.6, 84.3, 82.3, 81.9, 77.9, 77.1, 68.3, 62.4, 55.8, 43.4, 40.0, 37.3, 28.1, 24.3, 22.8, 18.3, 13.8, -0.0; **HRMS** (ESI⁺) calculated for $\text{C}_{21}\text{H}_{32}\text{O}_3\text{NaSi}$ $[\text{M}+\text{Na}]^+$ 383.2013 found 383.2012.

1-((2*R*,3*S*,4*S*)-3-Ethynyl-5-methoxy-4-methyltetrahydrofuran-2-yl)deca-2,9-diyn-4-ol, **268**

To a solution of TMS-alkyne **181** (82 mg, 0.229 mmol, 1.0 equiv.) in MeOH (2 mL), K₂CO₃ (51 mg, 0.367 mmol, 1.6 equiv.) was added. The reaction was stirred for 3 h at rt before quenching with 10 mL *sat.* NH₄Cl (aq). The aqueous layer was extracted using Et₂O (10 mL × 4). The combined organic layer was dried using Na₂SO₄, the solvent removed *in vacuo* and the crude purified via flash column chromatography (4:1 to 2:1 Petroleum ether/ Et₂O) to yield **268** (62 mg, 0.215 mmol, 94%) as a colourless oil.

R_f 0.31 (1:1 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3301, 2911, 2848, 2159, 1542, 1452, 1309, 1255, 1200, 1026, 1003, 843, 760; **¹H NMR** (400 MHz, CDCl₃) δ 4.67 (1H, d, J = 4.4 Hz, H1), 4.40 – 4.30 (1H, m, H8), 4.22 (1H td, J = 7.0, 5.2 Hz, H1), 3.38 (3H, s, H15), 3.20 (1H, ddd, J = 7.6, 5.2, 2.6 Hz, H3), 2.67 (2H, dd, J = 7.1, 2.0 Hz, H5), 2.37 – 2.28 (1H, m, H2), 2.25 (1H, d, J = 2.6 Hz, H18), 2.26 – 2.19 (2H, m, H12), 1.94 (1H, t, J = 2.7 Hz, H14), 1.89 (1H, s, OH), 1.76 – 1.63 (2H, m, H9), 1.63 – 1.50 (4H, m, H10 and H11), 1.20 (3H, d, J = 7.2 Hz, H16); **¹³C NMR** (101 MHz, CDCl₃) δ 110.6, 84.4, 82.6, 81.5, 79.4, 77.9, 74.8, 68.4, 62.5, 56.0, 43.5, 39.3, 37.4, 28.1, 24.3, 22.5, 18.4, 13.7; **HRMS** (ESI⁺) calculated for C₁₈H₂₄O₃Na [M+Na]⁺ 311.1618 found 311.1617.

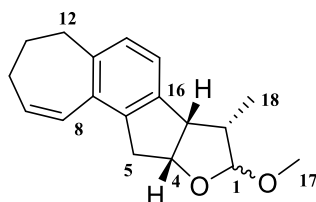
(7b*S*,8*S*,10a*R*)-9-Methoxy-8-methyl-1,2,3,4,5,7b,8,9,10a,11-decahydrocyclohepta[4,5]indeno[2,1-b]furan-1-ol, 269



To a stirred solution of $\text{RhCl}(\text{PPh}_3)_3$ (27.0 mg, 0.03 mmol, 0.2 eq) in *anhyd.* DCE (10 mL), a solution of **268** (42 mg, 0.145 mmol, 1.0 eq) in DCE (11 mL) was added. The reaction was stirred at 50 °C. After 18 h, on completion of the reaction, the reaction vessel was cooled to rt and DCE was evaporated. The crude was purified via flash column chromatography (4:1 to 1:1 Petroleum ether/ Et_2O) to yield **269** (30 mg, 70%) as a colourless oil.

R_f 0.24 (1:1 petroleum ether / Et_2O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3447, 2923, 2853, 1456, 1378, 1196, 1160, 1101, 1084, 1059, 1023, 940, 809.3; ^1H NMR (400 MHz, CHCl_3 -*d*) δ 7.12 – 6.59 (2H, m, H14 and H15), 5.09 (1H, dd, J = 6.4, 1.5 Hz, H8), 5.02 – 4.92 (1H, m, H4), 4.62 (0.5H, d, J = 1.9 Hz, H1), 4.56 (0.5H, d, J = 2.2 Hz, H*1), 3.97 – 3.85 (1H, m, H3), 3.36 (1.55H, s, H17), 3.34 (1.45H, s, H*17), 3.32 – 2.97 (3H, m, H5 and H12), 2.67 – 2.57 (1H, m, H5), 2.58 – 2.43 (1H, m, H2), 2.24 – 1.83 (4H, m, H9, H11 and OH), 1.75 – 1.44 (3H, m, H10 and H11), 0.85 (1.5H, d, J = 8.9 Hz, H18), 0.80 (1.5H, d, J = 8.7 Hz, H*18); ^{13}C NMR (101 MHz, CDCl_3) δ 142.2, 141.7, 141.2, 141.1, 139.1, 138.9, 138.9, 129.2, 129.2, 125.6, 125.5, 112.3, 112.3, 82.5, 82.4, 71.3, 70.9, 65.9, 55.0, 54.9, 52.0, 51.9, 42.7, 42.7, 38.6, 38.4, 35.5, 35.5, 33.2, 32.9, 28.7, 28.4, 24.9, 24.8, 15.3, 14.8; **HRMS** (ESI^+) calculated for $\text{C}_{18}\text{H}_{24}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 311.1618 found 311.1617.

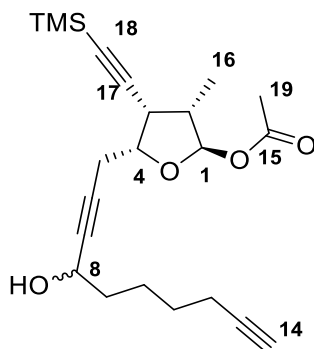
((7b*S*,8*S*,10a*R*)-9-Methoxy-8-methyl-3,4,5,7b,8,9,10a,11-octahydrocyclohepta[4,5]indeno[2,1-b]furan-7-yl)trimethylsilane, **179**



To a solution of alcohol **269** (32 mg, 0.111 mmol, 1.0 equiv.) in dry CHCl_3 (5 mL), Martin sulfurane (112 mg, 0.166 mmol, 1.5 equiv.) was added in the glovebox. The solution was stirred at rt for 10 min before diluting with 15 mL Et_2O and quenching with 15 mL *sat.* NaHCO_3 solution. The layers were separated, and the aqueous layer extracted three times with diethyl ether (15 mL). The combined organic layers were dried with Na_2SO_4 , and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (19:1 petroleum Ether / Et_2O), to yield **179** (20.3 mg, 0.074 mmol, 67%) and **270** (~15%) as an inseparable yellow solid.

R_f 0.33 (9:1 petroleum ether / Et_2O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2958, 2855, 1737, 1581, 1456, 1379, 1216, 1193, 1101, 1013, 968, 834; **¹H NMR** (400 MHz, CDCl_3) δ 6.99 – 6.83 (2H, m, H14 and H15), 6.39 (1H, dt, J = 12.2, 2.0 Hz, H8), 5.98 (1H, dt, J = 12.1, 4.7 Hz, H7), 5.03 (1H, td, J = 7.3, 2.6 Hz, H4), 4.64 (1H, d, J = 1.9 Hz, H1), 3.96 (1H, app. t, J = 8.0 Hz, H3), 3.38 (3H, s, H17), 3.19 (1H, dd, J = 17.5, 7.3 Hz, H5), 3.03 (1H, dd, J = 17.5, 2.6 Hz, H5), 2.77 (2H, app. t, J = 5.5 Hz, H12), 2.60 – 2.45 (1H, m, H2), 2.43 – 2.26 (2H, m, H10), 2.07 – 1.85 (2H, m, H11), 0.83 (3H, d, J = 7.4 Hz, H18); **¹³C NMR** (101 MHz, CDCl_3) δ 142.0, 140.8, 138.5, 133.0, 132.8, 127.5, 126.5, 124.4, 112.4, 82.6, 54.9, 52.0, 42.6, 38.9, 35.3, 31.9, 28.5, 14.7. **HRMS** (ESI^+) calculated for $\text{C}_{18}\text{H}_{22}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 293.1512 found 293.1512.

(2*R*,3*S*,4*S*,5*R*)-5-(4-Hydroxydeca-2,9-diyn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl acetate, **162**



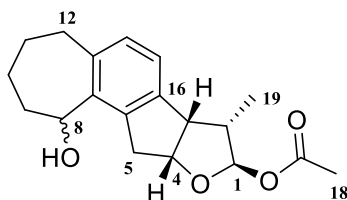
To a solution of iodoalkyne **160a** (20 mg, 0.070 mmol, 1.5 equiv.) in THF (0.3 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (24 μL , 2.5 M in hexanes, 0.061 mmol, 1.3 equiv.) dropwise. The solution was stirred for 45 min, then a solution of hept-6-ynal (5.0 mg, 0.047 mmol, 1.0 equiv.) in THF (0.2 mL) was added. The solution was slowly warmed to $-40\text{ }^{\circ}\text{C}$ and was stirred for 4 h. The reaction was quenched with saturated aq. NH_4Cl (5 mL). The aqueous layer was extracted using EtOAc (4 x 5 mL). The combined organic layers were dried using Na_2SO_4 and concentrated, and the residue was purified via flash chromatography (5:1 petroleum ether / EtOAc to yield **162** (6.0 mg, 0.025 mmol, 35%) as a viscous oil.

Alternatively, to a solution of hept-6-ynal **161** (10.0 mg, 0.053 mmol, 1.3 equiv.) and iodoalkyne **163a** (17 mg, 0.041 mmol, 1.0 equiv.) in THF (2 mL) was added CrCl_2 (97%, 30.0 mg, 0.245 mmol, 6.0 equiv., addition in the glovebox), and the solution was stirred at rt for 15 h. The reaction was quenched with 1 M serine solution (15 mL). The aqueous layer was extracted using EtOAc (4 x 10 mL), the combined organic layers were dried using Na_2SO_4 , and concentrated. The residue was purified via flash column chromatography (10:3 petroleum ether / EtOAc) to yield **162** (12 mg, 0.039 mmol, 73%) as a viscous oil.

R_f 0.29 (1:1 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3459, 3311, 2930, 2171, 1740, 1461, 1374 1187, 1162, 1087, 966; **^1H NMR** (400 MHz, CDCl_3) δ_{H} 5.92 (1H, d, $J = 4.1$ Hz, H1), 4.35 (1H, m, H8), 4.31 (1H, tdd, $J = 7.1, 5.7, 1.1$ Hz, H4), 3.31 (1H, dd, $J = 7.3, 5.7$ Hz, H3), 2.72 – 2.62 (2H, m, H5), 2.52 – 2.42 (1H, m, H2), 2.23 – 2.17 (2H, m, H12), 2.06 (3H, s, H19), 1.94 (1H, t, $J = 2.7$ Hz, H14), 1.81 (1H, br s, OH), 1.72 – 1.63 (2H, m, H9), 1.61 – 1.51 (4H, m, H10, H11), 1.21 (3H, d, $J = 7.1$ Hz, H16), 0.16 (9H, s, (SiMe₃)); **^{13}C NMR** (101 MHz, CDCl_3) δ_{C} 170.2, 125.5, 101.0, 98.7, 91.4,

8.3, 82.5, 81.6, 80.8, 68.3, 62.4, 41.3, 4.4, 37.3, 30.3, 28.1, 25.9, 25.8, 24.3, 24.3, 21.1, 18.3, 15.2, 14.0, 10.2, -0.00; **HRMS** (ESI⁺) calc. for C₂₂H₃₂O₄SiNa [M+Na]⁺ 411.1962; found 411.1961.

(7b*S*,8*S*,9*R*,10a*R*)-1-Hydroxy-8-methyl-1,2,3,4,5,7b,8,9,10a,11-decahydrocyclohepta[4,5]indeno-[2,1-b]furan-9-yl acetate, 274

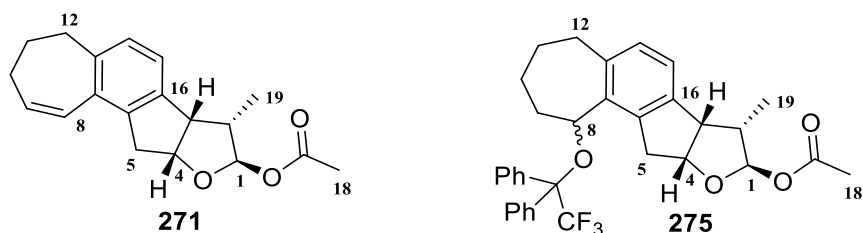


To a solution of **162** (15.0 mg, 0.039 mmol, 1.0 equiv.) in THF (1.0 mL) at rt was added AcOH (2.3 μ L, 0.039 mmol, 1.0 equiv.), and then TBAF (78 μ L, 0.078 mmol, 1 M in THF, 2.0 equiv.). The reaction was stirred for 15 min, after which time starting material had been consumed. The reaction was then quenched by addition of saturated aq. NH₄Cl (10 mL). The aqueous layer was extracted using EtOAc (4 x 10 mL). The combined organic layers were dried using Na₂SO₄ and concentrated to obtain crude **273**. The crude product was used directly in the next step without further purification.

To a stirred solution of RhCl(PPh₃)₃ (7.2 mg, 7.8 μ mol, 0.2 equiv.) in DCE (5 mL) was added a solution of the above crude triyne **273** in DCE (6 mL). The reaction was stirred at 50 °C for 12 h, then cooled to rt and concentrated. The residue was purified via flash chromatography (2:1 petroleum ether / Et₂O) to yield **274** (9.0 mg, 0.028 mmol, 73% over two steps) as a white solid (inconsequential mixture of C8 diastereomers).

R_f 0.29 and 0.36 (2:3 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3471, 2926, 1740, 1456, 1378, 1121, 1084, 1009, 972, 808; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 6.96 (2H, dd, J = 5.9, 2.3 Hz, H14 and H15), 5.91 (1H, dd, J = 10.8, 1.9 Hz, H1), 5.18 – 5.06 (2H, m, H4 and H8), 3.98 (1H, ddd, J = 10.0, 7.7, 2.7 Hz, H3), 3.56 – 3.21 (1H, m, H5), 3.22 – 3.09 (2H, m, H12), 2.78 – 2.59 (2H, m, H2 and H5), 2.33 – 2.10 (2H, m, H9, H10 or H11), 2.09 (3H, s, H18), 2.01 – 1.87 (1H, m, H9, H10 or H11), 1.83 – 1.54 (4H, m, OH and H9, H10 or H11), 0.90 (3H, 2 x s, H18); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 170.7, 142.5, 142.0, 140.9, 139.2, 139.0, 138.2, 138.1, 129.4, 129.4, 125.5, 125.4, 105.7, 105.6, 84.8, 84.7, 71.4, 71.0, 51.5, 51.4, 42.6, 42.6, 38.6, 38.4, 35.5, 35.5, 33.2, 33.0, 30.3, 29.7, 28.7, 28.3, 24.9, 24.8, 21.4, 14.5, 14.5; **HRMS** (ESI⁺) calc. for C₁₉H₂₄O₄Na [M+Na]⁺ 339.1567; found 339.1567.

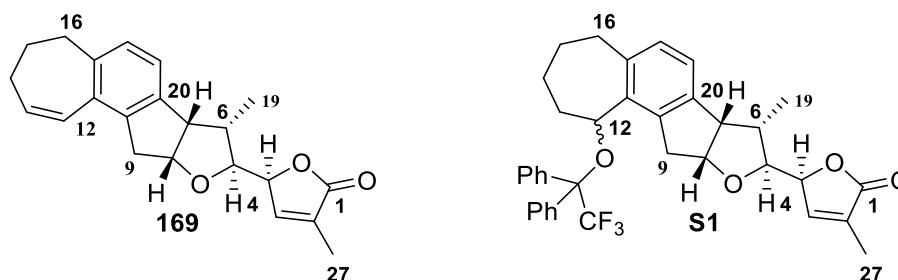
(7b*S*,8*S*,9*R*,10a*R*)-8-Methyl-3,4,5,7b,8,9,10a,11-octahydrocyclohepta[4,5]indeno[2,1-b]furan-9-yl acetate, 271



To a flame dried vial in the glovebox was added Martin sulfurane (33 mg, 0.049 mmol, 1.5 equiv.). To it was added a solution of alcohol **274** (10 mg, 0.033 mmol, 1.0 equiv.) in CH₂Cl₂ (2 mL). The reaction was stirred at rt for 10 min, then quenched by addition of saturated aq. NaHCO₃ (5 mL). After stirring for 10 min, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL). The combined organic layers were dried using Na₂SO₄, and concentrated. The residue was purified via flash chromatography (9:1 petroleum ether / Et₂O to afford an inseparable 7:1 mixture of **271** and **275** (8.3 mg, 0.041 mmol, 83%) as a viscous oil.

R_f 0.40 (4:1 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2981, 2927, 1745, 1461, 1382, 1260, 1151, 1185, 1033, 955; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 6.95 (1H, d, J = 8.0 Hz, H14), 6.94 (1H, d, J = 8.0 Hz, H15), 6.36 (1H, td, H8), 5.99 (1H, dt, J = 12.2, 4.7 Hz, H9), 5.94 (1H, d, J = 1.6 Hz, H1), 5.17 (1H, td, J = 7.4, 2.8 Hz, H4), 4.02 (1H, t, J = 8.1 Hz, H3), 3.20 (1H, dd, J = 17.6, 7.4 Hz, H5), 3.06 (1H, dd, J = 17.6, 2.8 Hz, H5), 2.77 (2H, t, J = 5.5 Hz, H12), 2.66 (1H, m, H2), 2.48-2.29 (2H, m, H10), 2.09 (3H, s, H18), 2.02-1.90 (2H, m, H11), 0.86 (3H, d, J = 7.5 Hz, H19); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 170.6, 141.8, 141.1, 137.7, 133.2, 132.9, 127.7, 126.3, 124.3, 105.9, 84.9, 51.5, 42.4, 38.7, 35.3, 31.9, 28.5, 21.4, 14.5; **HRMS** (ESI⁺) calc. for C₁₉H₂₂O₃Na [M+Na]⁺ 321.1461; found 321.1461.

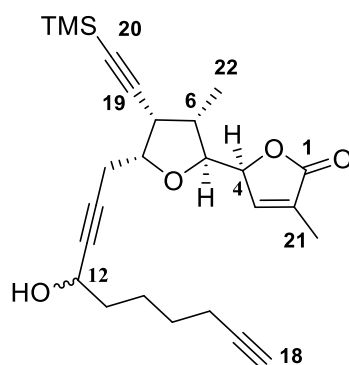
(*S*)-3-Methyl-5-((7*bS*,8*S*,9*S*,10*aR*)-8-methyl-3,4,5,7*b*,8,9,10*a*,11-octahydrocyclohepta[4,5]indeno [2,1-*b*]furan-9-yl)furan-2(5*H*)-one, **169**



To a solution of $\text{Bi}(\text{OTf})_3$ (62 mg, 0.094 mmol, 2.0 equiv.) in acetonitrile (0.2 mL) under an Ar atmosphere at -40°C was added dropwise a solution of acetate **271** (14 mg, 0.047 mmol, 1.0 equiv.) and triisopropyl((3-methylfuran-2-yl)oxy)silane (18 mg, 0.071 mmol, 1.5 equiv.) in acetonitrile (1 mL). The reaction was stirred at -40°C for 1 h until complete as judged by TLC. The reaction was quenched by addition of saturated aq. NH_4Cl (5 mL), and allowed to warm to rt. The mixture was poured into CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the organic layers were combined, washed with water, brine, and then dried over Na_2SO_4 and concentrated. Purification by flash chromatography (1:6 Et_2O / pentanes) gave an inseparable 7:1 mixture of **169** and **S1** (4.5 mg, 0.013 mmol, 27%) as a colourless oil.

R_f 0.40 (3:2 petroleum ether / Et_2O); $[\alpha]_{\text{D}}^{25} -59$ ($c = 0.49$, CHCl_3); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2925, 1759, 1660, 1451, 1283, 1261, 1213, 1191, 1143, 1107, 1082, 942, 881.4; **¹H NMR** (400 MHz, CDCl_3 , peaks assigned for only **169**) δ_{H} 7.04 (1H, d, $J = 7.7$ Hz, H18), 6.99-6.96 (1H, m, H3), 6.95 (1H, d, $J = 7.8$ Hz, H19), 6.39 (1H, dt, $J = 12.1, 2.1$ Hz, H12), 5.98 (1H, dt, $J = 12.2, 4.7$ Hz, H13), 4.89 (2H, m, H4 and H8), 3.80 (1H, dd, $J = 8.0, 5.9$ Hz, H5), 3.51 (1H, dd, $J = 9.6, 2.4$ Hz, H7), 3.05 (2H, d, $J = 3.8$ Hz, H9), 2.82-2.68 (3H, m, H6 and H16), 2.41-2.32 (2H, m, H14), 2.07-1.93 (5H, m, H15 and H21), 1.23 (3H, d, $J = 7.1$ Hz, H22); **¹³C NMR** (101 MHz, CDCl_3 , peaks assigned for only **169**) δ_{C} 174.4, 146.3, 142.7, 141.1, 137.7, 133.0, 132.9, 130.6, 127.4, 126.4, 124.5, 83.3, 82.3, 79.8, 53.7, 39.8, 39.3, 35.2, 31.9, 28.5, 13.3, 10.9; **HRMS** (ESI^+) calc. for $\text{C}_{22}\text{H}_{24}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 359.1618; found 359.1619.

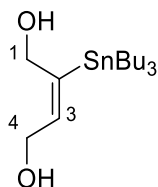
(5*S*)-5-((2*S*,3*S*,4*S*,5*R*)-5-(4-Hydroxydeca-2,9-diyn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)-tetrahydrofuran-2-yl)-3-methylfuran-2(5*H*)-one, 276



To a solution of hept-6-ynal **161** (4.4 mg, 0.041 mmol, 2.0 equiv.) and iodoalkyne **106a** (9 mg, 0.020 mmol, 1.0 equiv.) in THF (0.6 mL) was added CrCl₂ (97%, 15.0 mg, 0.122 mmol, 6.0 equiv., addition in the glovebox), and the solution was stirred at rt for 15 h. The reaction was quenched with 1 M serine solution (10 mL). The aqueous layer was extracted using EtOAc (4 x 10 mL), the combined organic layers were dried using Na₂SO₄, and concentrated. The residue was purified via flash column chromatography (10:3 petroleum ether / EtOAc) to yield **276** (5.2 mg, 0.121 mmol, *quant*) as a viscous oil.

R_f 0.25 (2:3 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3291, 2930, 2169, 1760, 1456, 1342, 1250, 1085, 1045, 987, 844, 761; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.11 – 6.83 (1H, m, H3), 4.90 (1H, dd, J = 2.1, 1.3 Hz, H4), 4.35 – 4.30 (1H, m, H12), 4.02 (1H, td, J = 6.9, 4.1 Hz, H8), 3.88 (1H, dd, J = 9.4, 1.9 Hz, H5), 3.15 – 3.06 (1H, m, H7), 2.66 – 2.60 (1H, m, H9), 2.58 (2H, dd, J = 7.2, 1.9 Hz, H7 and H9), 2.27 – 2.14 (2H, m, H16), 1.96 – 1.93 (4H, m, H16 and H21), 1.74 – 1.62 (2H, m, H13), 1.60 – 1.48 (5H, m, H14, H15 and OH), 1.22 (3H, d, J = 6.8 Hz, H22), 0.16 (9H, s, TMS); **¹³C NMR** (126 MHz, CDCl₃) δ_{C} 174.2, 174.0, 146.0, 145.9, 131.1, 100.7, 92.4, 84.4, 84.1, 82.5, 82.5, 82.2, 82.2, 81.4, 81.4, 80.6, 80.6, 79.9, 79.9, 68.4, 62.4, 42.1, 39.1, 39.0, 37.4, 37.4, 28.1, 24.3, 22.3, 22.3, 18.4, 13.4, 13.4, 10.8, 10.8, 0.1, 0.1; **HRMS** (ESI⁺) calc. for C₂₅H₂₄O₄NaSi [M+Na]⁺ 449.2119; found 449.2115.

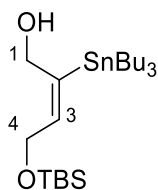
6.2.3 Procedures and characterisations of the compounds in Chapter 4

(*E*)-2-(Tributylstannyl)but-2-ene-1,4-diol, 279

To a stirred solution of but-2-yne-1,4-diol **46** (7.1 g, 82.4 mmol, 1.03 equiv.) in dry THF (150 mL) under argon was added $\text{PdCl}_2(\text{PPh}_3)_2$ (1.45 g, 1.98 mmol, 0.02 equiv.). Tributyltin hydride (21 mL, 80 mmol, 1.0 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 petroleum ether / EtOAc) to afford (*E*)-2-(tributylstannyl)but-2-ene-1,4-diol **279** (25.4 g, 67.6 mmol, 77%) as light brown oil.

R_f 0.43 (1:1 petroleum ether / EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 5.79 (1H, tt, $J_{\text{HH}} = 5.9$ and 2.1 Hz; $J_{\text{SnH}} = 66.7$ Hz, H3), 4.38 (2H, m; $J_{\text{SnH}} = 36.3$ Hz, H1), 4.20 (2H, *app* t, $J_{\text{HH}} = 5.4$ Hz, H4), 1.74 (1H, t, $J_{\text{HH}} = 4.9$ Hz, OH), 1.73-1.27 (13H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, OH), 0.96-0.85 (15H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 149.4, 138.2, 63.6, 59.8, 29.3, 27.5, 13.8, 10.1

Data in accordance with literature.^{8,9,14}

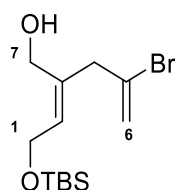
(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-(tributylstannyl)but-2-en-1-ol, 47

To a stirred solution of (*E*)-2-(tributylstannyl)but-2-ene-1,4-diol **279** (23.3 g, 61.8 mmol, 1.0 equiv.) in dry DMF (60 mL) under argon at 0 °C was added imidazole (4.21 g, 61.8 mmol, 1.0 equiv.) and TBSCl (9.31 g, 61.8 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 (150 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 (10:1 petroleum ether / EtOAc) to yield **47**

(25.82 g, 52.5 mmol, 85%) as a light brown oil.

R_f 0.57 (4:1 petroleum ether / EtOAc); **¹H NMR (400 MHz, CDCl₃)** δ_{H} 5.70 (1H, tt, $J_{\text{HH}} = 5.4$ and 2.1 Hz; $J_{\text{SnH}} = 68.2$ Hz, H3) 4.34 (2H, br d with unresolved fine coupling, $J_{\text{HH}} = 5.5$; $J_{\text{SnH}} = 37.0$ Hz, H1), 4.25–4.16 (2H, m, H4) 1.81 (1H, t, $J = 5.4$ Hz, OH), 1.55–1.46 (6H, m, SnCH₂CH₂CH₂CH₃), 1.37–1.27 (6H, m, SnCH₂CH₂CH₂CH₃), 0.94–0.85 (15H, m, SnCH₂CH₂CH₂CH₃ and Si*t*-Bu), 0.09 (6H, s, SiMe₂); **¹³C NMR (100 MHz, CDCl₃)** δ_{C} 156.1, 139.0, 63.9, 60.9, 29.3, 27.5, 26.0, 13.8, 10.1, –5.0. Data in accordance with literature.^{8,9,14}

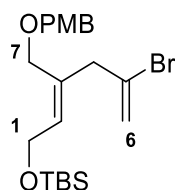
(Z)-4-Bromo-2-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)pent-4-en-1-ol, 49



To a stirred solution of **47** (18.29 g, 37.2 mmol, 1.0 equiv.) in dry degassed toluene (275 mL) under argon was added Pd(dba)₂ (856 mg, 1.49 mmol, 4 mol%). The solution was degassed (Ar purge) for a further 30 min, then 2,3-dibromopropene **48** (10.9 mL, 111.6 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 petroleum ether / EtOAc) to afford **49** (5.98 g, 18.6 mmol, 50%) as yellow oil.

R_f 0.30 (4:1 petroleum ether / EtOAc); **¹H NMR (500 MHz, CDCl₃)** 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, SiMe₂); **¹³C NMR (125 MHz, CDCl₃)** δ_{C} 137.5, 131.8, 131.0, 118.9, 60.1, 59.6, 47.7, 26.0, 18.4, –5.1. Data in accordance with literature.^{8,9,14}

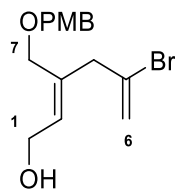
(Z)-((5-Bromo-3-(((4-methoxybenzyl)oxy)methyl)hexa-2,5-dien-1-yl)oxy)(tert-butyl)dimethylsilane, **280**



To a stirred solution of **17** (6.7 g, 20.8 mmol, 1 equiv.) in toluene (250 mL) under argon was added PMBTCA (6.6 mL, 31.0 mmol, 1.5 equiv.) and $\text{Sc}(\text{OTf})_3$ (358 mg, 0.71 mmol, 0.035 equiv.). After stirring for 5 min, sat. NaHCO_3 solution (180 mL) was added and the layers were separated. The aqueous layer was extracted three times with diethyl ether (150 mL $\times$ 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 petroleum ether / EtOAc) to yield (Z)-((5-bromo-3-(((4-methoxybenzyl)oxy)methyl)hexa-2,5-dien-1-yl)oxy)(tert-butyl)dimethylsilane **280** (8.3 g, 18.7 mmol, 90%) as light yellow oil.

R_f 0.52 (4:1 petroleum ether / EtOAc); ^1H 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, CH_2Ar), 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, SiMe₂); ^{13}C NMR (125 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. Data in accordance with literature.^{8,9,14}

(Z)-5-Bromo-3-(((4-methoxybenzyl)oxy)methyl)hexa-2,5-dien-1-ol, **50**

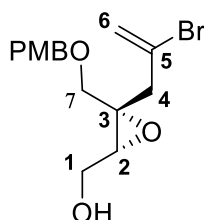


To a stirred solution of **280** (6.9 g, 15.6 mmol, 1.0 equiv.) in methanol (300 mL) was added camphorsulfonic acid (371 mg, 1.6 mmol, 0.1 equiv.). The reaction mixture was stirred for 20 min, then Et_3N (230 μL , 1.6 mmol, 0.1 equiv.) was added and the solvent was removed *in vacuo*. The crude

product was purified by flash chromatography (1:1 petroleum ether / EtOAc) to afford **50** (4.49 g, 13.7 mmol, 88%) as a light yellow oil.

R_f 0.43 (1:1 petroleum ether / EtOAc); $^1\text{H NMR}$ (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, CH_2Ar), 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); $^{13}\text{C NMR}$ (125 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. Data in accordance with literature.^{8,9,14}

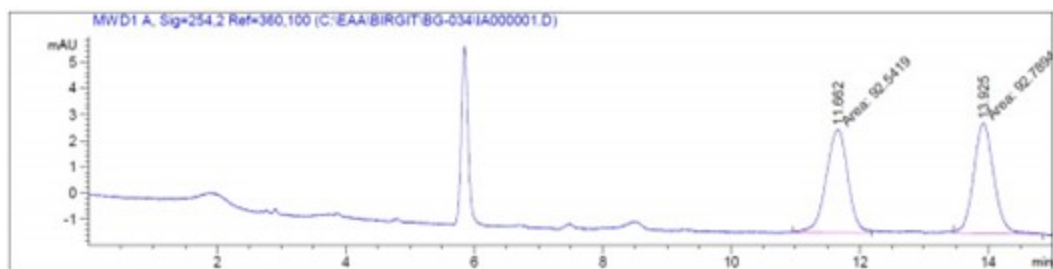
((2*R*,3*S*)-3-(2-Bromoallyl)-3-((4-methoxybenzyloxy)methyl)oxiran-2-yl)methanol, **51**



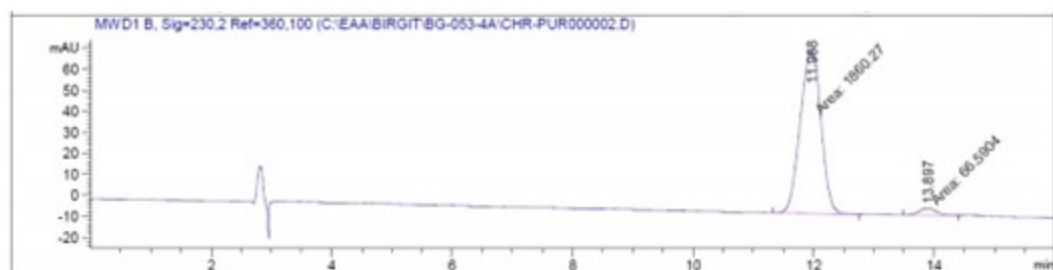
Activated 4 Å molecular sieves (1.85 g, 30 w/w%) were taken in a flame dried flask. To it, 60 mL DCM and $\text{Ti}(\text{O}i\text{-Pr})_4$ (5.80 mL, 18.93 mmol, 1.0 equiv.) was added and the solution was cooled to -30°C , then D-(–)-diethyl tartrate (4.00 mL, 22.71 mmol, 1.2 equiv.) was added dropwise.⁴⁷ After stirring the reaction mixture for 30 min at -30°C , a solution of **50** (6.17 g, 18.93 mmol, 1.0 equiv.) in dichloromethane (20 mL) was added dropwise, followed again by stirring for 30 min at -30°C . *Tert*-butyl hydroperoxide (5.5 M in hexanes, 10.30 mL, 56.779 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 (8.88 g, 59.1 mmol, 3 equiv.) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (49.2 g, 177.3 mmol, 9.0 equiv.) in water (60 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 $\times$ 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, 100 mL) was added dropwise. After stirring for 1.5 h at 0°C , water (30 mL) was added, the layers were separated and the aqueous layer was extracted three times with Et_2O (100 mL $\times$ 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 petroleum ether / EtOAc) to afford epoxide **51** (5.98 g, 17.41 mmol, 92%) as highly viscous yellow oil.

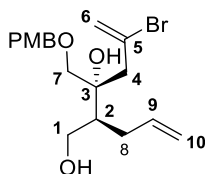
R_f 0.38 (1:1 Pet. Ether / EtOAc) **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.24 (2H, d, J = 8.5 Hz, Ar), 6.87 (2H, d, J = 8.5 Hz, Ar), 5.68 (1H, s, H₆), 5.53 (1H, d, J = 1.3 Hz, H₆), 4.50 (1H, d, J = 11.4 Hz, CH₂Ar), 4.40 (1H, d, J = 11.4 Hz, CH₂Ar), 3.79 (3H, s, OMe), 3.72-3.66 (2H, m, H₁), 3.61 (1H, d, J = 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); **¹³C NMR** (101 MHz, CDCl₃) 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; **ee**: 93% as determined by chiral HPLC: CHIRALPAK IA, 5 mL/min, 5% IPA/hexane 5 mL/min, t_{R} (2*R*,3*S*) = 12.14 min, t_{R} (2*S*,3*R*) = 13.53 min.. Data in accordance with literature.^{8,9,14}



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	

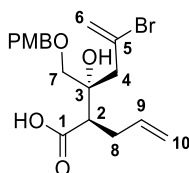


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.968	NM	0.3974	1860.26794	78.02112	96.5441
2	13.897	NM	0.3303	66.59045	3.36038	3.4559
Totals :				1926.85839	81.38150	

(2*S*,3*R*)-2-Allyl-5-bromo-3-((4-methoxybenzyloxy)methyl)hex-5-ene-1,3-diol, 45

To a stirred solution of epoxide **51** (4.04 g, 11.79 mmol, 1.0 equiv.) in dry THF (100 mL) at 0 °C was added allylmagnesium chloride (1.7 M in THF, 27.70 mL, 47.16 mmol, 4.0 equiv.) dropwise. The reaction mixture was stirred for 30 min, then it was quenched with NH₄Cl (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 petroleum ether / EtOAc) to afford diol **45** (4.09 g, 10.61 mmol, 90%) as a slightly yellow, highly viscous oil.

R_f 0.47 (1:1 Pet. Ether / EtOAc); **¹H NMR** (500 MHz, CDCl₃) 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 (1H, 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, CH₂Ar), 4.48 (1H, d, *J* = 11.6 Hz, CH₂Ar), 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); **¹³C NMR** (126 MHz, CDCl₃) 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; Data in accordance with literature.^{8,9,14}

(2*R*,3*R*)-2-Allyl-5-bromo-3-hydroxy-3-(((4-methoxybenzyl)oxy)methyl)hex-5-enoic acid, 52

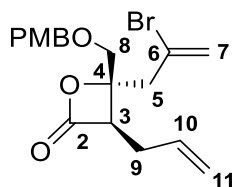
To a stirred solution of alcohol **45** (2.71 g, 7.057 mmol, 1.0 equiv.) in dichloromethane (160 mL) was added NaHCO₃ (563 mg, 6.704 mmol, 0.95 equiv.), followed by Dess-Martin periodinane (4.80 g, 11.292 mmol, 1.5 equiv.) and 2 mL water. The reaction mixture was stirred for 1.5 h, then it was quenched with NaHCO₃ (100 mL, sat. *aq.*) and Na₂S₂O₃ (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 $\times$ 3). The combined organic layers were dried (Na₂SO₄) and the solvent was removed *in vacuo*. The crude product was used without purification in the following Pinnick oxidation. The crude aldehyde was dissolved in *t*-BuOH (100 mL) and 2-methyl-2-butene (22.3 mL, 211 mmol, 30 equiv.) was added. Into the reaction mixture was poured a solution of sodium chlorite (80%, 7.9 g, 70.57 mmol, 10 equiv.) and NaH₂PO₄ (9.0 g, 56.45 mmol, 8 equiv.) in water (40 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 (Na₂SO₄) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 Pet. Ether / EtOAc) to yield acid **52** (2.81 g, 7.05 mmol, 99%) as a colourless highly viscous oil.

R_f 0.35 (1:1 Pet. Ether / EtOAc); **¹H NMR** (500 MHz, CDCl₃) 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, CH₂Ar), 4.42 (1H, d, J = 11.7 Hz, CH₂Ar), 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); **¹³C NMR** (126 MHz, CDCl₃) 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; Data in accordance with literature.

8,9,14

(3*R*,4*R*)-3-Allyl-4-(2-bromoallyl)-4-((4-methoxybenzyloxy)methyl)oxetan-2-one, 53

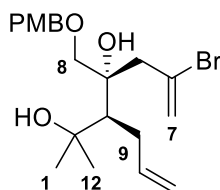


To a stirred solution of acid **52** (3.23 g, 8.116 mmol, 1.0 equiv.) in dry acetonitrile (75 mL) was added dry pyridine (54 mL) and *bis*-(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP-Cl) (6.199 g, 24.347 mmol, 3.0 equiv.). The reaction mixture was stirred for 2.5 h before it was quenched with water. The

layers were separated, and the aqueous layer was extracted four times with EtOAc. The combined organic layers were dried with (Na₂SO₄) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 Pet. Ether / EtOAc) to yield lactone **53** (2.723 g, 7.14 mmol, 88%) as light yellow oil.

R_f 0.66 (1:1 Pet. Ether / EtOAc); **¹H NMR** (500 MHz, CDCl₃) 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, CH₂Ar), 4.49 (1H, d, *J* = 11.6 Hz, CH₂Ar), 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); **¹³C NMR** (126 MHz, CDCl₃) 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. Data in accordance with literature.^{8,9,14}

(3*S*,4*R*)-3-Allyl-6-bromo-4-((4-methoxybenzyloxy)methyl)-2-methylhept-6-ene-2,4-diol, **54**

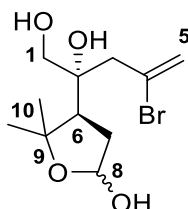


To a stirred solution of **53** (1.9 g, 5.08 mmol, 1 equiv.) in THF (50 mL) at –50°C was added dropwise MeMgBr (3 M in Et₂O, 10.2 mL, 30.48 mmol, 6.0 equiv.). The reaction mixture was warmed slowly to rt (6 h) and was then quenched with NH₄Cl (10 mL, sat. *aq.*). The resulting suspension was filtered 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 **54** (1.449 g, 3.505 mmol, 69%) as colourless oil.

R_f 0.58 (1:1 Pet. Ether/ EtOAc); **¹H NMR** (500 MHz, CDCl₃) 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, CH₂Ar), 4.46 (1H, d, *J* = 11.3 Hz, CH₂Ar), 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. Data in accordance with literature.^{8,9,14}

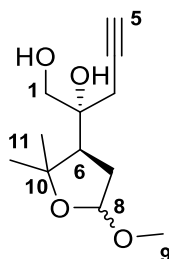
(4*R*)-4-((*R*)-4-bromo-2-hydroxy-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)-5,5-dimethyl tetrahydrofuran-2-ol, **55**



To a stirred solution of alkene **54** (87 mg, 0.210 mmol, 1.0 equiv.) in 1,4-dioxane (2.0 mL) and water (0.5 mL) was sequentially added 2,6-lutidine (49 μL , 0.421 mmol, 2.0 equiv.), osmium(VII) tetroxide (2.5% wt in *tert*-butanol, 26.7 μL , 4.2 μmol , 0.02 equiv.) and sodium periodate (180 mg, 0.842 mmol, 4.0 equiv.).⁷⁴ The reaction mixture was stirred at rt for 3 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 EtOAc (10 mL $\times$ 3). The combined organic layers were dried with MgSO_4 and the solvent removed *in vacuo*. The crude product was filtered through a short plug of silica (7:3 petroleum ether/ EtOAc), then concentrated to yield lactol **55** (71 mg, 0.164 mmol, 82%, inseparable mixture of epimers and some regional isomers) as a colourless oil, which was used in the next step without further purification.

R_f 0.36 (1:1 petroleum ether/ EtOAc)

(2*R*)-2-((3*R*)-5-Methoxy-2,2-dimethyltetrahydrofuran-3-yl)pent-4-yn-1,2-diol, **283**



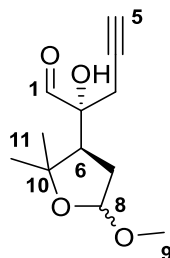
To a stirred solution of PMB ether **55** (59 mg, 0.142 mmol, 1.0 equiv.) in dichloromethane (8 mL) at 0 °C was added TFA (0.8 mL) dropwise. The reaction mixture was stirred for 15 min at 0 °C before being quenched with NaHCO_3 solution (10 mL, sat. *aq.*). The layers were separated and the aqueous layer

extracted three times with EtOAc (15 mL $\times$ 3). The combined organic layers were dried with Na₂SO₄ and the solvent removed *in vacuo* to give crude **285**. The crude product was used for the next step without further purification.

To the above crude **285** in dry DMF (10 mL), TBAF.H₂O (135 mg, 0.427 mmol, 3.0 equiv.) was added in the glovebox. The resulting solution was allowed to stir for 10 min. On completion of the reaction, 30 mL *sat.* NH₄Cl solution was added followed by 10 mL EtOAc. The layers were separated and the aqueous layer extracted three times with EtOAc (15 mL $\times$ 4). The combined organic layers were dried with Na₂SO₄ and the solvent removed *in vacuo*. The residual DMF was removed by azeotroping the residue with heptane (10 mL $\times$ 4) to afford crude **284**. The crude was used in the next reaction without further purification.

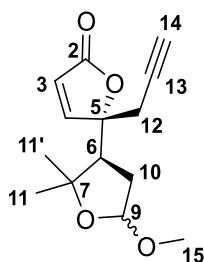
To a stirred solution of the above crude **284** in methanol (20.0 mL) at 0 °C, ($\pm$)-CSA (7.0 mg, 28.4 μ mol, 0.2 equiv.) was added. The reaction was stirred for 3 h before quenching with 1 mL Et₃N. The solvent was removed *in vacuo* and the resulting residue was purified using flash column chromatography (2:1 Petroleum ether / EtOAc) to afford **283** (26.4 mg, 0.116 mmol, 82%, 2:1 mixture of epimers) as an oil

R_f 0.21 (1:1 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3428, 3294, 2932, 1454, 1372, 1336, 1277, 1103, 1047, 978; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 4.95 (1H, d, J = 9.2 Hz, H*8), 4.88 (1H, d, J = 4.9 Hz, H8), 3.72 (1H, d, J = 10.8 Hz, H1), 3.65 (1H, d, J = 11.0 Hz, H*1), 3.60 (1H, d, J = 10.9 Hz, H*1), 3.59 (1H, d, J = 10.8 Hz, H1), 3.36 (3H, s, H*9), 3.32 (3H, s, H9), 2.70 – 2.58 (2H, m, H3), 2.70 – 2.58 (3H, m, H*3), 2.52 (1H, dd, J = 13.0, 6.5 Hz, H6), 2.35 – 2.28 (1H, m, OH), 2.35 – 2.28 (1H, m, OH*), 2.21 (1H, td, J = 12.8, 5.0 Hz, H7), 2.21 (1H, td, J = 12.8, 5.0 Hz, H*7), 2.16 – 2.13 (1H, m, H*5), 2.12 – 2.06 (1H, m, H5), 1.90 (1H, dd, J = 12.4, 6.5 Hz, H7), 1.49 (3H, s, H11), 1.44 (3H, s, H*11), 1.41 (3H, s, H*11), 1.30 (3H, s, H11); **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 103.1, 101.9, 83.8, 83.4, 80.5, 80.2, 73.6, 73.5, 72.1, 71.9, 67.0, 66.9, 55.0, 54.1, 50.5, 48.2, 34.5, 34.3, 32.4, 30.9, 26.9, 26.6, 25.6, 25.5. **HRMS** (ESI⁺) calc. for C₁₂H₂₀O₄Na [M+Na]⁺ 251.1454 found 251.1454. *= peaks corresponding to second diastereomer

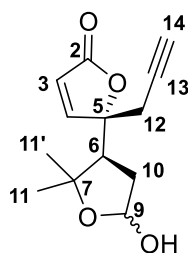
(2R)-2-Hydroxy-2-((3R)-5-methoxy-2,2-dimethyltetrahydrofuran-3-yl)pent-4-ynal, 286

Dry DMSO (1.45 mL, 18.58 mmol, 42 equiv.) was added to $\text{SO}_3 \cdot \text{py}$ (571 mg, 3.583 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 diol **283** (100.0 mg, 0.442 mmol, 1.0 equiv.) in dry dichloromethane (10 mL), and *i*-PrEt₂N (1.2 mL, 8.46 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 10 mL NH_4Cl (sat. *aq.*). Et₂O (10 mL) and water (10 mL) was then added, the phases were separated, and the aqueous layer extracted three times with Et₂O (15 mL $\times$ 3). The combined organic layers were washed sequentially with NaHCO_3 (sat. *aq.*), followed by brine. The organic layer was dried using Na_2SO_4 and concentrated. The crude product was purified by flash chromatography through a short plug of silica (4:1 Pet. Ether / EtOAc), to afford aldehyde **286** (93 mg, 0.415 mmol, 94%, 2:1 mixture of C8-epimers) as an oil.

R_f 0.35 (4:1 Petroleum Ether / Et₂O); **IR** (thin film, ν_{max} / cm^{-1}) 3481, 3291, 2919, 2850, 1731, 1456, 1368, 1279, 1101, 1045, 978; **¹H NMR** (400 MHz, CDCl_3) δ 9.74 (1H, s, H*1), 9.69 (1H, s, H1), 4.95 (1H, dd, $J = 6.2, 3.8$ Hz, H*8), 4.85 (1H, d, $J = 4.7$ Hz, H8), 3.80 (1H, s, OH*), 3.53 (1H, s, OH), 3.32 (3H, s, H*9), 3.30 (3H, s, H9), 2.84 – 2.70 (2H, m, H3 and H6), 2.70 – 2.44 (1H, m, H3), 2.70 – 2.44 (1H, m, H*3 and H*6), 2.26 (1H, ddd, $J = 14.0, 9.4, 6.2$ Hz, H*7), 2.18 – 1.96 (2H, m, H5 and H7), 2.18 – 1.96 (2H, m, H*5 and H*7) 1.72 (dd, $J = 12.5, 6.5$ Hz, H7), 1.50 (3H, s, H11), 1.41 (3H, s, H*11), 1.29 (3H, s, H*11), 1.20 (3H, s, H11); **¹³C NMR** (101 MHz, CDCl_3 , peaks for both diastereomers are listed and not assigned) δ 202.0, 201.9, 103.2, 102.1, 83.6, 83.1, 78.4, 78.2, 77.5, 73.2, 73.0, 55.2, 54.1, 51.0, 48.7, 34.4, 34.1, 32.4, 30.6, 27.2, 27.0, 25.7, 25.4; **HRMS** (ESI⁺) calc. for $\text{C}_{12}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 249.1097 found 249.1099. *= peaks corresponding to second diastereomer

(5S)-5-((3S)-5-Methoxy-2,2-dimethyltetrahydrofuran-3-yl)-5-(prop-2-yn-1-yl)furan-2(5H)-one,**282**

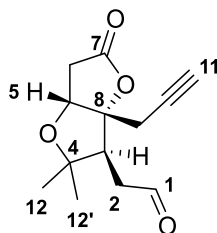
To a stirred solution of ethyl 2-(diphenoxyphosphoryl)acetate (139 mg, 0.435 mmol, 3.5 equiv.) in THF (2.0 mL) under argon at 0 °C was added KHMDS (0.7 M in THF, 845 μ L, 0.422 mmol, 3.4 equiv.) and the resulting mixture was stirred at 0 °C for 20 min. This solution was then added dropwise to a solution of aldehyde **286** (28 mg, 0.124 mmol, 1.0 equiv.) in THF (3.0 mL) under argon at –20 °C, and the reaction mixture was stirred for 3.5 h between –20 and 0 °C, before adding 5 mL MeOH followed by K₂CO₃ (34 mg, 0.248 mmol, 2.0 equiv.). The mixture was stirred for 30 min before adding NH₄Cl (20 mL, sat. *aq.*). Et₂O (20 mL) was added, the layers were separated, and the aqueous layer was extracted three times with EtOAc (10 mL $\times$ 4). The combined organic layers were dried with Na₂SO₄ and concentrated. The product was purified by flash chromatography through a short plug of silica gel (6:1 $\rightarrow$ 4:1 petroleum ether / EtOAc), to afford lactone **282** (25.5 mg, 0.102 mmol, 82%) as a white solid. **R_f** 0.56 (2:3 petroleum ether / EtOAc); **IR** (thin film, ν_{max} / cm^{–1}) 2936, 1757, 1449, 1372, 1268, 1228, 1101, 1073, 1041, 961, 821; **¹H NMR** (400 MHz, CDCl₃) δ 7.52 (1H, d, J = 5.7 Hz, H*4), 7.51 (1H, d, J = 5.7 Hz, H4), 6.13 (1H, d, J = 1.0 Hz, H*3), 6.12 (1H, d, J = 1.0 Hz, H3), 4.96 – 4.90 (1H, m, H*9), 4.82 (1H, d, J = 4.7 Hz, H9), 3.31 (3H, s, H*15), 3.30 (3H, s, H15), 2.97 – 2.84 (2H, m, H12), 2.81 (1H, ddd, J = 16.8, 2.7, 1.1 Hz, H*12), 2.66 – 2.60 (2H, m, H*6 and H*12), 2.60 – 2.55 (1H, m, H6), 2.26 – 2.17 (1H, m, H*10), 2.18 – 2.09 (1H, m, H14), 1.80 (1H, tdd, J = 13.1, 11.7, 4.8 Hz, H10), 1.68 (1H, dd, J = 12.4, 6.5 Hz, H10), 1.52 (3H, s, H11), 1.42 (3H, s, H*11), 1.27 (3H, s, H11'), 1.27 (3H, s, H*11'); **¹³C NMR** (101 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ 172.0, 171.7, 159.3, 158.1, 121.8, 121.1, 102.7, 101.5, 87.7, 87.7, 83.1, 82.3, 77.2, 77.2, 73.5, 73.4, 55.4, 54.2, 51.2, 48.2, 35.0, 34.6, 32.2, 30.0, 28.7, 27.7, 25.5, 25.1; **HRMS** (ESI⁺) calc. for C₁₄H₁₈O₄Na [M+Na]⁺ 273.1097 found 273.1095. * = peaks corresponding to second diastereomer

(5S)-5-((3S)-5-Hydroxy-2,2-dimethyltetrahydrofuran-3-yl)-5-(prop-2-yn-1-yl)furan-2(5H)-one,**287**

To a stirred solution of **282** (25.5 mg, 0.102 mmol, 1.0 equiv.) in dichloromethane (4.7 mL) and water (24 μ L) at 0 °C was added TFA (0.47 mL) dropwise. The reaction mixture was stirred for 2 h at 0 °C before being neutralized by addition of NaHCO₃ (5 mL, sat. *aq.*). The layers were separated, and the aqueous phase was extracted with EtOAc (4 $\times$ 15 mL). The combined organic layers were dried using Na₂SO₄ and concentrated. The product was purified by flash chromatography (2:1 petroleum ether / EtOAc) on a short plug of silica to give lactol **287** (19.1 mg, 0.082 mmol, 80%) as a colourless oil.

R_f 0.23 (2:3 petroleum ether/ EtOAc); **IR** (thin film, ν_{max} / cm⁻¹) 3422, 2958, 2137, 1750, 1252, 1005, 841; **¹H NMR** (400 MHz, CDCl₃) δ 7.53 (1H, d, J = 5.6 Hz, H4), 7.53 (1H, d, J = 5.6 Hz, H*4), 6.16 (1H, d, J = 5.7 Hz, H*3), 6.14 (1H, d, J = 5.6 Hz, H3), 5.51 – 5.42 (1H, m, H*8), 5.36 (1H, d, J = 4.8 Hz, H8), 2.97 (1H, dd, J = 13.1, 6.5 Hz, H6), 2.92 (1H, dd, J = 16.8, 2.7 Hz, H12), 2.82 (1H, dd, J = 16.8, 2.7 Hz, H*12), 2.61 (1H, dd, J = 16.9, 2.7 Hz, H12), 2.27 – 2.19 (1H, m, H*7), 2.18 – 2.12 (1H, m, H14), 1.84 (1H, td, J = 12.7, 4.8 Hz, 7H), 1.70 (1H, dd, J = 12.5, 6.5 Hz, H7), 1.55 (3H, s, H11), 1.41 (3H, s, H*11), 1.33 (3H, s, H*11'), 1.24 (3H, s, H11'); **¹³C NMR** (101 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ 171.99, 171.7, 159.2, 158.2, 121.7, 121.2, 95.9, 95.0, 87.6, 87.6, 83.6, 82.5, 77.2, 77.1, 73.5, 51.6, 48.0, 35.9, 35.1, 32.2, 30.1, 28.6, 27.8, 25.7, 25.3; **HRMS** (ES⁺) calc. for C₁₃H₁₆O₄Na [M+Na]⁺ 259.0942 found 259.0942. *= peaks corresponding to second diastereomer

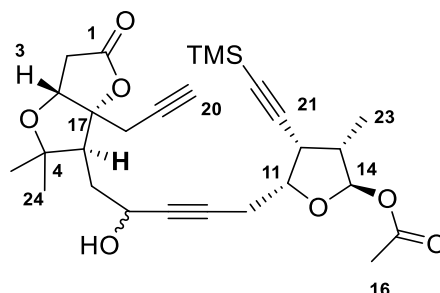
2-((3*S*,3*aR*,6*aR*)-2,2-Dimethyl-5-oxo-3a-(prop-2-yn-1-yl)hexahydrofuro[3,2-*b*]furan-3-yl)acetaldehyde, **32**



To a stirred solution of lactol **287** (19.1 mg, 0.081 mmol, 1.0 equiv.) in MeOH (3.5 mL) under argon was added K₂CO₃ (22.3 mg, 0.162 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 2 h, then NH₄Cl (10 mL, sat. *aq.*) was added. The mixture was extracted three times with EtOAc (3 × 10 mL), then the combined organic layers were dried (Na₂SO₄) and concentrated. The product was purified by flash chromatography on a short plug of silica (2:1 Pet. Ether / EtOAc) to give the aldehyde **32** (16.9 mg, 0.072 mmol, 89%) as a white solid.

R_f 0.26 (3:2 Pet. Ether / EtOAc); **¹H NMR** (400 MHz, CDCl₃) 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'); **¹³C NMR** (101 MHz, CDCl₃) 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). Data in accordance with literature.^{8,9}

(2*R*,3*S*,4*S*,5*R*)-5-((3*S*,3*aR*,6*aR*)-2,2-Dimethyl-5-oxo-3*a*-(prop-2-yn-1-yl)hexahydrofuro[3,2-*b*]furan-3-yl)-4-hydroxypent-2-yn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl acetate, **288**

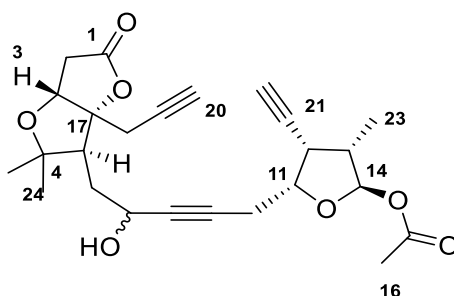


A mixture of AB ring aldehyde **32** (16.5 mg, 0.070 mmol, 1.0 equiv.) and iodoalkyne **163a** (34.0 mg, 0.084 mmol, 1.2 equiv.) in a vial was azeotroped thrice with toluene then placed under an N₂ atmosphere. To this vial, anhydrous THF (3 mL) was added and the vial was taken into glovebox. To the solution, CrCl₂ (97%, 51 mg, 0.42 mmol, 6.0 equiv.) was added, the vial was sealed and removed from the glovebox, and the solution was stirred at rt for 15 h. The reaction was quenched with 1 M serine (15 mL). The aqueous layer was extracted using EtOAc (4 × 10 mL). The combined organic layers were dried (Na₂SO₄), concentrated, and the residue purified via flash chromatography (7:3 petroleum ether / EtOAc) to yield **288** (31 mg, 0.060 mmol, 86%, 1:1 mixture of diastereomers) as a white solid.

R_f 0.39 (1:1 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3448, 3286, 2971, 2171, 1785, 1375, 1250, 1197, 1018, 930, 844, 761; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 5.91 (1H, d, *J* = 4.1 Hz, H14), 4.53-4.46 (1H, m, H3), 4.47-4.36 (1H, m, H7), 4.35-4.26 (1H, m, H11), 3.44-3.21 (1H, m, H12), 3.07-2.94 (2H, m, H2 and H18), 2.75-2.60 (3H, m, H2 and H10), 2.56-2.41 (2H, m, H13 and H18), 2.30 (1H, dd, *J* = 10.4, 3.2 Hz, H5), 2.20 (0.6H, d, *J* = 4.2 Hz, OH), 2.13 (0.35H, d, *J* = 6.0 Hz, OH*), 2.06 (4H, s, H16 and H20), 1.88-1.71 (1H, m, H6), 1.63-1.48 (1H, m, H6), 1.34 (1.71H, s, H24), 1.33 (1.36H, s, H*24), 1.20 (3H, d, *J* = 7.2 Hz, H23), 1.20 (3H, d, *J* = 7.2 Hz, H*23), 1.06 (3H, s, H24), 0.15 (9H, s, (Si(CH₃)₃), *=observable diastereomer peak; **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.4, 170.6, 102.9, 102.9, 100.6, 100.5, 94.7, 94.5, 92.4, 92.3, 83.4, 83.4, 83.1, 82.6, 81.6, 81.4, 79.5, 79.5, 78.7, 78.7, 78.7, 77.9, 77.9, 72.3, 72.3, 61.6, 61.1, 55.7,

54.7, 43.1, 43.0, 39.9, 39.9, 37.5, 37.5, 33.8, 33.4, 27.7, 27.6, 25.9, 25.7, 22.7, 22.6, 21.3, 20.5, 13.5, 0.1, 0.0.; HRMS (ESI⁺) calc. for C₂₈H₃₇O₇Si [M-H]⁻ 513.2314; found 513.2308.

(2*R*,3*S*,4*S*,5*R*)-5-((3*S*,3*aR*,6*aR*)-2,2-Dimethyl-5-oxo-3*a*-(prop-2-yn-1-yl)hexahydrofuro[3,2-*b*]-furan-3-yl)-4-hydroxypent-2-yn-1-yl)-4-ethynyl-3-methyltetrahydrofuran-2-yl acetate, 289

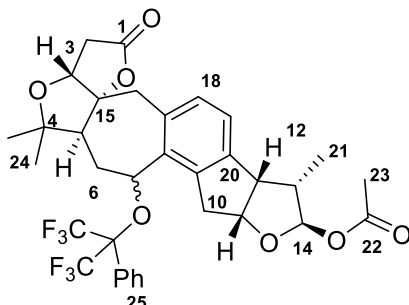


To a solution of **288** (31 mg, 0.060 mmol, 1.0 equiv.) in THF (2.0 mL) at rt was added AcOH (3.4 μ L, 0.060 mmol, 1.0 equiv.). To it was added TBAF (120 μ L, 1M in THF, 0.120 mmol, 2.0 equiv.). The reaction was stirred for 15 min, monitored by TLC. After disappearance of starting material, the reaction was quenched by addition of saturated aq. NH₄Cl (10 mL). The aqueous layer was extracted with EtOAc (4 $\times$ 10 mL), and the combined organic extracts were dried (Na₂SO₄) and concentrated. The crude product was purified via flash chromatography (1:1 petroleum ether / EtOAc) to give **289** (21 mg, 0.048 mmol, 80%, 1:1 mixture of diastereomers) as a white solid.

R_f 0.26 (1:1 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3451, 3287, 2981, 2886, 1775, 1473, 1378, 1237, 1197, 1131, 1061, 934; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 5.91 (1H, d, J = 4.5 Hz, H14), 5.91 (1H, d, J = 4.5 Hz, H*14), 4.53-4.42 (2H, m, H3 and H7), 4.33 (1H, m, H11), 3.33 (1H, ddt, J = 8.9, 6.2, 3.1 Hz, H12), 3.14-2.91 (2H, m, H2 and H18), 2.77-2.62 (3H, m, H2 and H10), 2.56-2.41 (3H, m, H13, H18 and H22), 2.38-2.32 (1H, m, H5), 2.30 (0.34H, d, J = 2.5 Hz, OH*), 2.28 (0.53H, d, J = 2.5 Hz, OH) 2.06 (4H, s, H16 and H20), 1.85-1.72 (1H, m, H6), 1.59-1.48 (1H, m, H6) 1.34 (3H, s, H24), 1.32 (3H, s, H*24), 1.23 (3H, d, J = 7.2 Hz, H23), 1.23 (3H, d, J = 7.2 Hz, H*23), 1.06 (3H, s, H24), * = observable diastereomer peak; **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.4, 170.6, 170.6, 102.9, 102.9, 94.7, 94.5, 83.4, 83.4, 82.9, 82.4, 81.8, 81.5, 79.3, 79.3, 78.7, 78.6, 78.5, 78.0, 77.8, 75.5, 75.4, 72.4, 72.2, 61.5, 61.3, 55.4, 54.7, 43.0, 43.0,

39.1, 39.0, 37.6, 37.5, 33.7, 33.2, 27.6, 27.4, 25.9, 25.7, 22.4, 22.3, 21.3, 20.5, 20.5, 13.3, 13.2; **HRMS** (ESI⁺) calculated for C₂₅H₃₀O₇Na [M+H]⁺ 465.18837 found 465.18806.

Acetate **292**



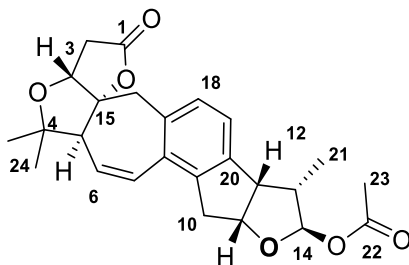
To a stirred solution of RhCl(PPh₃)₃ (2.0 mg, 0.003 mmol, 0.1 equiv.) in *anhyd.* DCE (2 mL), a solution of **289** (10 mg, 0.021 mmol, 1.0 equiv.) in DCE (3 mL) was added. The reaction was stirred at 50 °C. After 12 h, on completion of the reaction, the reaction vessel was cooled to rt and DCE was evaporated. The residue was dried under vacuum.

To a flame dried vial, in the glovebox, Martin's sulfurane was added (25 mg, 0.031 mmol, 1.5 equiv.). To it, 1 mL dry DCM was added followed by a solution of the crude residue (in 1 mL DCM) from the previous step. The reaction was stirred for 10 min before quenching with 5 mL NaHCO₃ solution. The aqueous layer was extracted with EtOAc (4 × 10 mL) and the organic layers were combined, washed with water, and then dried over Na₂SO₄. The solvent was removed to give a residue which was purified using column chromatography to afford acetate **292** (10 mg, 0.015 mmol, 70% over two steps).

R_f 0.56 (1:1 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2951, 2862, 1770 1445, 1378, 1058; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.35 (1H, tt, J = 6.8, 1.7 Hz, H25), 7.21-7.11 (4H, m, H25), 7.09 (1H, d, J = 7.6 Hz, H18), 7.04 (1H, d, J = 7.6 Hz, H19), 5.78 (1H, d, J = 2.1 Hz, H14), 5.10 (1H, dd, J = 8.8, 3.8 Hz, H11), 4.64 (1H, td, J = 7.1, 2.3 Hz, H7), 4.59 (1H, d, J = 4.9 Hz, H3), 3.83 (1H, d, J = 14.2 Hz, H10), 3.76 (1H, t, J = 7.8 Hz, H12), 2.85 (1H, dd, J = 18.3, 5.0 Hz, H2), 2.72 (1H, d, J = 18.3 Hz, H2), 2.67-2.59 (2H, m, H10 and H13), 2.58-2.44 (2H, m, H5 and H16), 2.15-2.02 (1H, m, H16), 2.06 (3H, s, H23), 1.75-1.57 (2H, m, H6), 1.23 (3H, s, H24), 1.22 (3H, s, H24), 0.88 (3H, d, J = 7.5 Hz, H21); **¹³C NMR** (101 MHz, CDCl₃) δ 175.2, 170.6, 142.1, 139.5, 134.7, 133.2, 130.1, 129.8, 129.1, 128.1, 127.9, 126.6, 105.4 98.4, 85.1, 84.4, 79.4, 74.3, 51.4, 50.5, 42.5, 38.5, 37.6, 36.8, 32.4, 31.9, 30.3, 24.9,

22.7, 21.3, 14.3, 14.1; **HRMS** (ESI⁺) calc. for C₂₅H₃₀O₇Na [M+H–C₉H₆F₆O]⁺ 447.1778; found 447.1779.

Acetate **291**



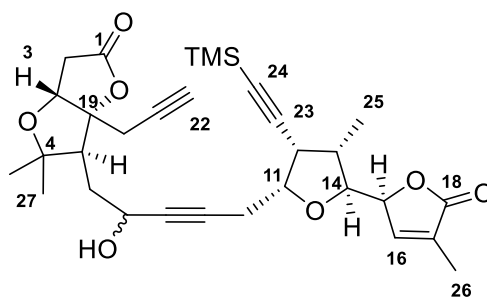
To a stirred solution of RhCl(PPh₃)₃ (2.0 mg, 3.00 μmol, 0.1 equiv.) in DCE (2 mL) was added a solution of **289** (10 mg, 0.021 mmol, 1.0 equiv.) in DCE (3 mL). The reaction was stirred at 50 °C for 12 h, then it was cooled to rt and concentrated. The residue was dried under vacuum.

To a solution of 2-nitrophenyl selenocyanate **293** (15 mg, 0.063 mmol, 3.0 equiv.) in THF (0.2 mL) under inert atmosphere at rt was added *n*-Bu₃P (13 mg, 0.063, 3.0 equiv.). The solution was stirred for 15 min following which a solution of the crude in THF (0.5 mL) from the previous step was added. The reaction was stirred for 2 h at rt before quenching with the NH₄Cl (sat. sol.). The mixture was poured into EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc and the organic layers were combined, washed with water, brine, and then dried over Na₂SO₄. The solvent was removed to give a residue which was passed through a short plug of silica to remove excess of 2-nitrophenyl selenocyanate and *n*-Bu₃P. The resulting mixture was used for the next step without further purification.

To the above crude, 1 mL THF was added followed by H₂O₂ (50 wt% solution in water, 15 μL, 0.21 mmol, 10.0 equiv.) at rt. The resulting solution was stirred for 15 min before being quenched with Na₂SO₃ (sat. sol.). After stirring for 15 min, the mixture was poured into EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 10 mL) and the organic layers were combined, washed with water, and then dried over Na₂SO₄. The solvent was removed to give a residue which was purified using column chromatography to afford alkene **291** (3.9 mg, 0.008 mmol, 40% over all yield) as a viscous oil.

R_f 0.56 (3:2 petroleum ether / EtOAc); [α]_D²⁵: +34.9 (*c* = 0.68, CHCl₃) **IR** (thin film) ν_{max} /cm⁻¹: 2923, 2851, 1776, 1743, 1557, 1513, 1458, 1382, 1260, 1151, 1039, 954; **¹H NMR** (500 MHz, CDCl₃) δ 7.04 (1H, d, *J* = 7.7 Hz, H18), 6.97 (1H, d, *J* = 7.6 Hz, H19), 6.59 (1H, d, *J* = 12.0 Hz, H7), 5.93 (1H, d, *J* = 1.6 Hz, H14), 5.80 (1H, br s, H6), 5.23-5.12 (1H, m, H11), 4.29 (1H, m, H3), 4.04 (1H, t, *J* = 8.1 Hz, H12), 3.20-2.80 (5H, m, H5, H10 and H16), 2.77-2.61 (2H, m, H2 and H13), 2.39-2.21 (1H, m, H2), 2.09 (3H, s, H23), 1.38 (3H, s, H24), 1.25 (3H, s, H25), 0.87 (3H, d, *J* = 7.4 Hz, H21); **¹³C NMR** (126 MHz, CDCl₃) δ 174.64, 170.57, 141.31, 135.22, 129.36, 127.72, 125.36, 125.04, 105.73, 84.78, 68.23, 59.92, 51.59, 42.31, 38.20, 35.71, 31.94, 29.72, 26.41, 23.85, 22.71, 22.28, 21.37, 14.63, 14.14. **HRMS** (ESI⁺) calculated for C₂₅H₃₀O₇Na [M+H]⁺ 447.17781 found 447.17791.

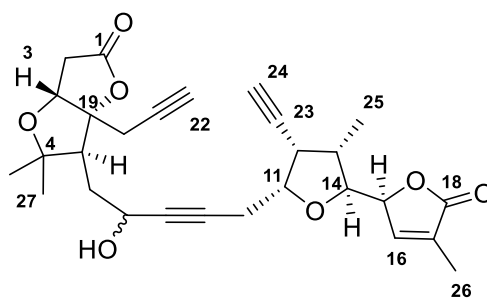
(3*aR*,6*S*,6*aR*)-6-(2-Hydroxy-5-((2*R*,3*S*,4*S*,5*S*)-4-methyl-5-((*S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)pent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, 105a



A mixture of AB ring aldehyde **32** (11.2 mg, 0.048 mmol, 1.0 equiv.) and FG ring diyne **106a** (24.2 mg, 0.055 mmol, 1.15 equiv.) was azeotroped with thrice with toluene then placed under an N₂ atmosphere. To this vial, anhydrous THF (2 mL) was added and the vial was taken into glovebox. CrCl₂ (97%, 35.0 mg, 0.29 mmol, 6.0 equiv.) was added, the vial was sealed and removed from the glovebox, and the solution was stirred at rt for 15 h. The reaction was quenched by addition of 1 M serine solution (15 mL). The aqueous layer was extracted with EtOAc (4 × 10 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via flash chromatography (10:3 petroleum ether / EtOAc) to give **105a** (22 mg, 0.040 mmol, 83%) as a white solid (inconsequential 1:1 mix of diastereomers).

R_f 0.20 (3:2 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3453, 3280, 2960, 2852, 2169, 1761, 1457, 1375, 1196, 1045, 988; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.07-6.95 (1H, m, H16), 4.91 (1H, dd, J = 2.0, 2.0 Hz, H15), 4.49 (1H, m, H3), 4.47-4.37 (1H, m, H7), 4.07-3.98 (1H, m, H11), 3.86 (1H, dd, J = 9.5, 2.2 Hz, H14), 3.15 (1H, dd, J = 6.3, 4.2 Hz, H12), 3.09-2.89 (2H, m, H2 and H20), 2.75-2.54 (4H, m, H2, H10, H13), 2.54-2.39 (1H, m, H20), 2.35-2.23 (1H, m, H5), 2.09 (1H, q, J = 2.7 Hz, H22), 1.93 (3H, d, J = 1.6 Hz, H26), 1.82-1.73 (1H, m, H6), 1.61-1.47 (1H, m, H6), 1.34 (3H, s, H27), 1.32 (3H, s, H*27), 1.21 (3H, d, J = 7.1 Hz, H25), 1.06 (3H, s, H27), 0.15 (9H, s, (SiCH₃)₃), *=observable diastereomer peak; **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.5, 175.4, 174.3, 146.0, 146.0, 131.2, 131.1, 130.9, 128.8, 100.8, 100.8, 100.8, 94.7, 94.7, 94.6, 94.6, 92.5, 92.4, 92.4, 83.4, 83.4, 82.3, 80.3, 80.3, 80.1, 80.0, 78.7, 78.7, 77.9, 72.4, 68.2, 61.5, 61.4, 61.0, 60.9, 55.7, 55.7, 54.7, 42.0, 39.1, 38.7, 37.5, 37.5, 33.7, 33.6, 30.4, 28.9, 27.7, 27.7, 25.8, 25.7, 25.7, 23.7, 23.0, 22.2, 20.5, 14.1, 13.4, 11.0, 10.8, 0.1, 0.1; **HRMS** (ESI⁺) calc. for C₃₁H₄₀O₃SiNa [M+Na]⁺ 575.2436; found 575.24340.

(3a*R*,6*S*,6a*R*)-6-(5-((2*R*,3*S*,4*S*,5*S*)-3-Ethynyl-4-methyl-5-((*S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)tetrahydrofuran-2-yl)-2-hydroxypent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, 296

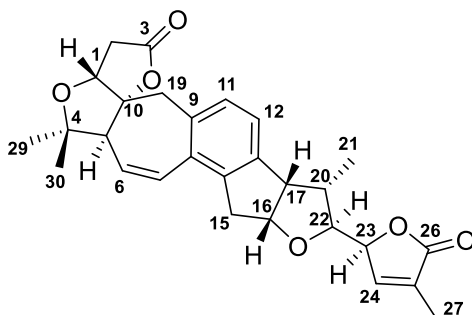


To a solution of **105a** (21 mg, 0.038 mmol, 1.0 equiv.) in THF (1.5 mL) at rt was added AcOH (2.2 μ L, 0.038 mmol, 1.0 equiv.) and then TBAF (77 μ L, 1M in THF, 0.077 mmol, 2.0 equiv.). The reaction was stirred for 15 min, after which time starting material had been consumed (TLC). The reaction was quenched by addition of saturated aq. NH₄Cl (10 mL). The aqueous layer was extracted using EtOAc (4 $\times$ 10 mL), and the combined organic layers were dried (Na₂SO₄) and concentrated. The residue was

purified via flash chromatography (1:1 petroleum ether / EtOAc) to yield triyne **296** (12 mg, 0.025 mmol, 66%) as a white solid (inconsequential 1:1 mix of diastereomers).

R_f 0.28 (2:3 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3464, 3281, 2924, 1759, 1453, 1280, 1198, 1084, 1022, 929, 654; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 6.99 (1H, t, J = 1.8 Hz, H16), 4.91 (1H, dd, J = 2.2, 2.1 Hz, H15), 4.51 (1H, dd, J = 7.1, 4.4 Hz, H3), 4.47-4.42 (1H, m, H7), 4.06 (1H, td, J = 7.2, 4.2 Hz, H11), 3.88 (1H, dd, J = 9.8, 2.3 Hz, H14), 3.21 (1H, ddt, J = 8.5, 6.5, 3.3 Hz, H12), 3.12-2.94 (2H, m, H2 and H20), 2.78-2.58 (4H, m, H2, H10 and H13), 2.55-2.42 (1H, m, H20), 2.32 (2H, ddd, J = 28.7, 10.3, 2.9 Hz, H5 and H24), 2.20-2.05 (2H, m, H22 and OH), 1.94 (3H, s, 3H), 1.84-1.72 (1H, m, H6), 1.62-1.50 (1H, m, H6), 1.34 (1.81H, s, H27), 1.33 (1.36H, s, H*27), 1.24 (3H, m, H25), 1.07 (3H, s, H27), *=observable diastereomer peak; **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.4, 174.2, 145.9, 131.2, 128.8, 94.7, 94.5, 83.4, 83.4, 83.0, 82.5, 82.4, 82.3, 81.6, 81.4, 80.1, 80.1, 79.9, 79.9, 78.8, 78.8, 78.7, 77.9, 77.8, 75.6, 75.5, 72.4, 72.3, 61.4, 61.2, 55.4, 54.7, 40.9, 39.0, 39.0, 37.6, 37.5, 33.6, 33.4, 29.7, 27.6, 27.5, 25.9, 25.7, 22.1, 20.5, 20.5, 13.3, 10.8. **HRMS** (ESI⁺) calc. for C₂₈H₃₁O₇ [M-H]⁺ 479.2075; found 479.2081.

Rubriflordilactone B, **3**



rubriflordilactone B, **3**

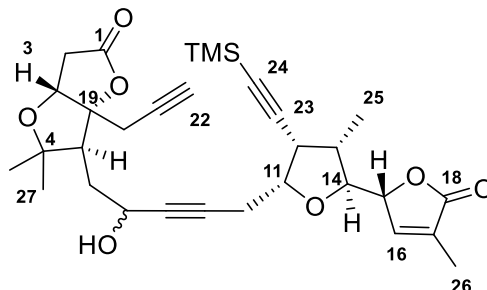
To a solution of Bi(OTf)₃ (25 mg, 0.038 mmol, 2.0 equiv.) in acetonitrile (0.2 mL) under Ar at −40 °C was added dropwise a solution of acetate **291** (8.0 mg, 0.019 mmol, 1.0 equiv.) and triisopropyl((3-methylfuran-2-yl)oxy) silane (9.0 mg, 0.025 mmol, 1.5 equiv.) in acetonitrile (0.5 mL). The reaction mixture was stirred at −40 °C for 1 h until TLC showed the reaction to be complete. The reaction was quenched with saturated aq. NH₄Cl (1 mL) and allowed to warm to rt. The mixture was poured into CH₂Cl₂ (10 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 5

mL), and the combined organic layers were washed with water, brine, dried over Na₂SO₄, and then concentrated. Purification of the residue by flash chromatography (1:6 Et₂O / pentanes) afforded rubriflordinolactone B (**3**) and C23-*epi*-rubriflordinolactone B (*epi*-**3**) as an inseparable mixture (6.0 mg, 0.021 mmol, 56%).

Alternatively, to a stirred solution of RhCl(PPh₃)₃ (2.0 mg, 3.00 μmol, 0.1 equiv.) in anhydrous DCE (2 mL) was added a solution of **296** (10 mg, 0.021 mmol, 1.0 equiv.) in DCE (3 mL). The reaction was stirred at 50 °C for 12 h, then it was cooled to rt and concentrated. The residue was dried under vacuum before addition of benzene (4 mL), followed by PTSA.H₂O (~1.0 mg, ~4.00 μmol, 0.3 equiv.). The reaction was heated to 80 °C for 2 h, and then cooled to rt and quenched by addition of H₂O (5 mL). The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via flash chromatography (10:3 petroleum ether / EtOAc) to yield **3** (5.5 mg, 2.00 μmol, 57% over two steps) as a white crystalline solid.

R_f 0.40 (2:3 petroleum ether / EtOAc); [**α**]_D²⁵ -12.1 (c = 0.47, CHCl₃); **IR** (thin film) ν_{max} /cm⁻¹ 2972, 2926, 1758, 1638, 1460, 1440, 1383, 1373, 1215, 1169, 1007, 934; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.14 (1H, d, *J* = 7.8 Hz, H11), 6.98 (1H, t, *J* = 1.7 Hz, H24), 6.96 (1H, d, *J* = 7.7 Hz, H12), 6.59 (1H, d, *J* = 11.8 Hz, H7), 5.80 (1H, br s, H6), 5.01-4.74 (2H, m, H16 and H23), 4.32 (1H, br s, H1), 3.81 (1H, t, *J* = 6.9 Hz, H17), 3.50 (1H, dd, *J* = 9.6, 2.1 Hz, H22), 3.18-2.85 (5H, m, H2, H15 and H19), 2.83-2.61 (3H, m, H5, H19 and H20), 1.95 (3H, t, *J* = 1.8 Hz, H27), 1.56 (3H, s, H29), 1.39 (3H, br s, H30), 1.25 (3H, d, *J* = 6.9 Hz, H21); **¹³C NMR** (126 MHz, CDCl₃) δ_{C} 174.9, 174.6, 146.5, 142.5, 139.6, 133.0, 130.6, 129.2, 128.2, 127.7, 125.6, 103.7, 85.3, 83.4, 82.4, 79.7, 59.5, 53.9, 41.6, 39.5, 39.4, 35.8, 28.6, 22.3, 13.2, 11.00; **mp** 310-314 °C; **HRMS** (ESI⁺) calc. for C₂₈H₃₀O₆Na [M+Na]⁺ 485.1935; found 485.1932.

(3a*R*,6*S*,6a*R*)-6-(2-Hydroxy-5-((2*R*,3*S*,4*S*,5*S*)-4-methyl-5-((*R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)pent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, 298

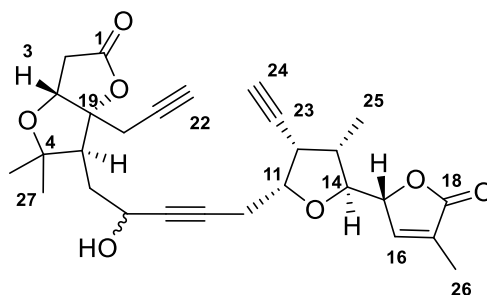


A mixture of AB ring aldehyde **32** (13.8 mg, 0.058 mmol, 1.0 equiv.) and FG ring diyne **166** (31 mg, 0.07 mmol, 1.2 equiv.) was azeotroped with thrice with toluene then placed under an N₂ atmosphere. Anhydrous THF (2.5 mL) was added, and the vial was taken into glovebox. To the solution, CrCl₂ (97%, 43 mg, 0.35 mmol, 6.0 equiv.) was added, the vial was sealed and removed from the glovebox, and the solution was stirred at rt for 15 h. The reaction was quenched with 1 M serine solution (20 mL), and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via flash chromatography (10:3 petroleum ether / EtOAc) to yield **298** (28 mg, 0.049 mmol, 85%) as a white solid (inconsequential 1:1 mix of diastereomers).

R_f 0.43 (2:3 petroleum ether / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3449, 3279, 2980, 2169, 1760, 1459, 1385, 1195, 1155, 1083, 941; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.14 (1H, t, *J* = 1.6 Hz, H16), 5.06-4.67 (1H, m, H15), 4.70-4.36 (2H, m, H3 and H7), 4.12 (1H, td, *J* = 7.0, 3.5 Hz, H11), 3.65 (1H, dd, *J* = 9.0, 6.1 Hz, H14), 3.16 (1H, dt, *J* = 6.7, 4.3 Hz, H12), 3.09-2.96 (2H, m, H2 and H20), 2.75-2.59 (3H, m, H2 and H10), 2.56-2.42 (1H, m, H20), 2.41-2.26 (2H, m, H5 and H13), 2.09 (1H, t, *J* = 2.6 Hz, H22), 1.92 (3H, s, H26), 1.86-1.73 (1H, m, H6), 1.62-1.51 (1H, m, H6), 1.34 (3H, s, H27), 1.33 (3H, s, H*27), 1.19 (3H, d, *J* = 6.7 Hz, H25), 1.07 (3H, s, H27), 0.14 (9H, s, (SiCH₃)₃), *=observable diastereomer peak; **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.4, 174.1, 146.7, 130.9, 100.7, 100.7, 94.7, 94.5, 92.6, 84.0, 83.4, 83.4, 83.4, 82.9, 82.4, 81.5, 81.2, 79.5, 79.5, 78.7, 78.7, 77.9, 77.8, 72.4, 72.3, 61.5, 61.2, 55.6, 54.8, 42.4, 40.3, 40.3, 37.5, 37.5, 33.7,

33.4, 27.7, 27.6, 25.9, 25.7, 22.4, 20.5, 14.2, 10.7, 0.1; **HRMS** (ESI⁺) calc. for C₃₁H₄₀O₃SiNa [M+Na]⁺ 575.2436; found 575.2433.

(3a*R*,6*S*,6a*R*)-6-(5-((2*R*,3*S*,4*S*,5*S*)-3-Ethynyl-4-methyl-5-((*R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)tetrahydrofuran-2-yl)-2-hydroxypent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, 299

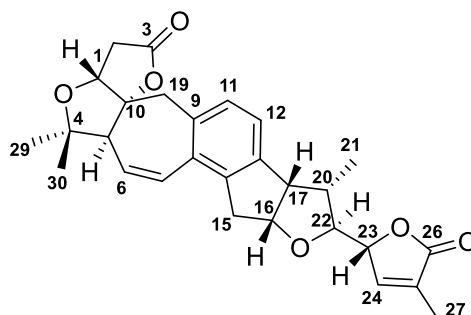


To a solution of **298** (28 mg, 0.058 mmol, 1.0 equiv.) in THF (2.0 mL) at rt was added AcOH (6.3 μ L, 0.116 mmol, 1.0 equiv.) and then TBAF (116 μ L, 1M in THF, 0.116 mmol, 2.0 equiv.). The reaction was stirred for 15 min, after which time starting material had been consumed (TLC). The reaction was quenched by addition of saturated aq. NH₄Cl (10 mL). The aqueous layer was extracted with EtOAc (4 $\times$ 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated, and the residue was purified via flash chromatography (1:3 petroleum ether / Et₂O) to yield **299** (19.7 mg, 0.047 mmol, 81%) as a white solid (inconsequential 1:1 mix of diastereomers).

R_f 0.31 (2:3 petroleum ether / EtOAc); **IR** (thin film) ν_{max} /cm⁻¹ 3464, 3281, 2924, 1759, 1453, 1280, 1198, 1084, 1022, 929; **¹H NMR** (500 MHz, CDCl₃) δ_{H} 7.13 (1H, t, *J* = 1.7 Hz, H16), 4.97-4.81 (1H, m, H15), 4.62-4.37 (2H, m, H3 and H7), 4.19-4.05 (1H, m, H11), 3.68 (1H, ddd, *J* = 8.8, 6.0, 1.8 Hz, H14), 3.32-3.15 (1H, m, H12), 3.15-2.89 (2H, m, H2 and H20), 2.83-2.59 (3H, m, H2 and H10), 2.57-2.43 (1H, m, H20), 2.41-2.33 (2H, m, H5 and H13), 2.30 (1H, d, *J* = 7.9 Hz, H*24) 2.29 (1H, d, *J* = 7.9, 2.5 Hz, 1H), 2.09 (1H, dd, *J* = 4.71, 2.4 Hz, 1H), 1.93 (3H, s, H26), 1.87-1.69 (1H, m, H6), 1.62-1.49 (1H, m, H6), 1.34 (3H, s, H27), 1.33 (3H, s, H*27), 1.21 (3H, d, *J* = 6.8 Hz, H25), 1.07 (3H, s, H27). * = observable diastereomer peak; **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.4, 174.0, 146.5, 130.9, 94.7, 94.5, 84.0, 83.5, 83.4, 82.7, 82.4, 81.6, 79.4, 79.4, 78.8, 78.74, 78.69, 78.65, 78.0, 77.8, 75.7, 75.6, 72.4, 72.3, 68.2, 61.4, 61.3, 55.4, 54.7, 41.3,

40.0, 39.9, 38.7, 37.6, 37.5, 33.6, 33.2, 30.4, 28.9, 27.6, 27.4, 25.9, 25.7, 23.7, 23.0, 22.2, 22.2, 20.5, 20.5, 14.2, 14.1, 14.1, 11.0, 10.7; **HRMS** (ESI⁺) calc. for C₂₈H₃₆O₇N [M+NH₄]⁺ 498.2486; found 498.2483.

***epi*-rubriflordilactone B, *epi*-3**



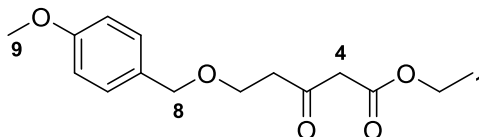
epi-rubriflordilactone B, ***epi*-3**

To a stirred solution of RhCl(PPh₃)₃ (1.9 mg, 2.05 μmol, 0.1 equiv.) in anhydrous DCE (1.5 mL) was added a solution of **299** (9.0 mg, 18.73 μmol, 1.0 equiv.) in DCE (2 mL). The reaction was stirred at 50 °C for 15 h, then it was cooled to rt and concentrated to give crude **300**. The residue was dried under vacuum, then benzene (4 mL) was added followed by PTSA.H₂O (1.2 mg, 6.30 μmol, 0.3 equiv.). The reaction was heated to 80 °C for 2 h, then cooled to rt and quenched by addition of H₂O (5 mL). The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via flash chromatography (10:3 petroleum ether / EtOAc) to give ***epi*-3** (5.4 mg, 11.68 μmol, 61% over two steps) as a thick colourless oil.

R_f 0.46 (petroleum ether / EtOAc (2:3)); [**α**]_D²⁵ +92.0 (c = 0.50, CHCl₃); **IR** (thin film) ν_{max}/cm⁻¹ 2980, 1761, 1655, 1460, 1383, 1322, 1215, 1168, 1067, 954; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.19-7.04 (2H, m, H16 and H22), 6.96 (1H, d, *J* = 7.7 Hz, H23), 6.60 (1H, d, *J* = 12.0 Hz, H7), 5.85 (1H, br s, H6), 5.10-4.94 (1H, m, H15), 4.91-4.81 (1H, m, H11), 4.31 (1H, br s, H3), 3.97-3.74 (1H, m, H14), 3.30 (1H, br s, H12), 3.14-2.65 (6H, m, H2, H5, H10 and H20), 2.71 (1H, d, *J* = 18.5 Hz, H20), 2.53 (1H, m, *J* = 7.5 Hz, H13), 1.92 (3H, app t, *J* = 1.8 Hz, H27), 1.46-0.98 (6H, m, H25), 1.20 (3H, d, *J* = 7.0 Hz, H26); **¹³C NMR** (126 MHz, CDCl₃) δ_C 174.7, 174.0, 147.0, 142.0, 139.6, 133.1, 130.5, 129.1, 127.7, 125.6, 103.7, 85.3, 84.2, 83.1, 82.5, 59.4, 54.3, 41.0, 39.2, 35.7, 28.9, 22.2, 14.0, 10.7; **HRMS** (ESI⁺) calc. for C₂₈H₃₀O₆Na [M+Na]⁺ 485.1935 found 485.1932.

6.2.4 Procedures and characterisations of the compounds in Chapter 5

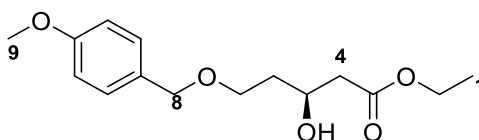
Ethyl 5-((4-methoxybenzyl)oxy)-3-oxopentanoate, **302**



Known β -ketoester **302** was prepared according to a literature procedure.¹⁸⁷ Ethyl diazoacetate (2.82 g, 24.7 mmol, 1.2 equiv.) was added with stirring at room temperature to a solution of anhydrous SnCl_2 (390 mg, 2.06 mmol, 0.1 equiv.) in CH_2Cl_2 (40 mL). A few drops of aldehyde **120** (4.00 g, 20.6 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) were added to the suspension. After nitrogen evolution had begun, the remaining aldehyde solution was added dropwise over 10 min. The solution was stirred until the evolution of nitrogen had stopped (5 h), and then the mixture was transferred to a separating funnel containing saturated brine (80 mL) and diethyl ether (240 mL). After separation of the layers, the aqueous phase was extracted with diethyl ether (3×200 mL). The organic layers were combined, dried (MgSO_4), filtered, and concentrated. Flash chromatography of the residue provided the β -ketoester **302** (4.30 g, 18.54 mmol, 75%) as a slightly yellow oil (keto-enol mixture).

R_f 0.42 (2:1 petroleum ether / EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.24 (2H, d, $J = 8.0$ Hz, ArH), 6.87 (2H, d, $J = 8.8$ Hz, ArH), 4.43 (2H, s, H8), 4.28-4.06 (2H, m, H2), 3.79 (3H, s, H9), 3.71 (2H, t, $J = 6.2$ Hz, H7), 3.47 (2H, s, H4), 2.81 (2H, t, $J = 6.2$ Hz, H6), 1.26 (3H, t, $J = 7.2$ Hz, H1); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} 201.6, 167.2, 159.3, 130.0, 129.4, 113.9, 73.0, 64.7, 61.4, 55.4, 49.8, 43.2, 14.2. Data in accordance with the literature.¹⁸⁷

Ethyl (*S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)pentanoate: **303**



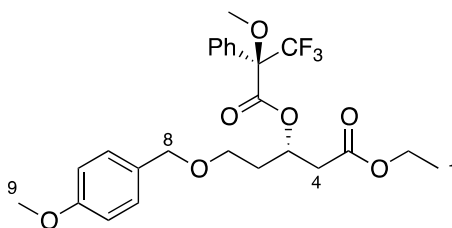
Dry, degassed DMF (3 mL) was added to a flask containing benzene ruthenium(II) chloride dimer (45 mg, 0.090 mmol, 0.03 equiv.) and (*S*)-(-)-BINAP (112 mg, 0.18 mmol, 0.006 equiv.). The slurry was heated to 90 °C with stirring for 20 min. The resulting reddish brown solution was then cooled to rt,

and was added via syringe to a Parr flask containing a degassed solution of β -ketoester **302** (8.00 g, 28.6 mmol, 1.0 equiv.) in dry ethanol (15 mL). The hydrogenation flask was flushed a few times with hydrogen, and then pressurized with 5.0 bar hydrogen, and heated to 100 °C with vigorous stirring for 20 h. The solution was then cooled to rt, concentrated, and purified by flash chromatography (4:1 petroleum ether / Et₂O) to provide the β -hydroxyester **303** (6.45 g, 22.9 mmol, 80%, 94% *ee*^{*}) as a pale-yellow liquid.

R_f 0.36 (4:1 petroleum ether / Et₂O); **[α]_D²⁵** +7.2 (c = 0.5, CHCl₃); **IR** (thin film) ν_{max} /cm⁻¹ 3485, 2936, 1730, 1613, 1514, 1173.9, 1092, 1031, 820; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.24 (2H, d, *J* = 8.5 Hz, ArH), 6.86 (2H, d, *J* = 8.5 Hz, ArH), 4.43 (2H, s, H8), 4.25-4.19 (1H, br s, H5), 4.14 (2H, q, *J* = 7.2 Hz, H2), 3.79 (3H, s, H9), 3.71-3.56 (2H, m, H7), 3.43 (1H, s, OH), 2.47 (2H, d, *J* = 6.3 Hz, H4), 1.81-1.70 (2H, m, H6), 1.25 (3H, t, *J* = 7.1 Hz, H1); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 172.5, 159.3, 130.2, 129.4, 113.9, 73.0, 67.7, 67.1, 60.6, 55.3, 41.7, 36.1, 14.3; **HRMS** (ESI⁺) calc. for C₁₅H₂₂O₅Na [M+Na]⁺ 305.1359; found 305.1361.

*%*ee* was calculated through Mosher ester analysis of **303** according to the following procedure:

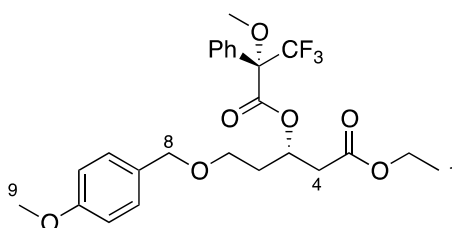
Ethyl (S)-5-((4-methoxybenzyl)oxy)-3-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)-pentanoate, S4



To solution of alcohol **303** (20.0 mg, 0.071 mmol, 1.0 equiv.) in anhydrous CH₂Cl₂ (1 mL) was added dry pyridine (0.035 mL, 0.44 mmol, 6.2 equiv.) and (S)-(-)-MTPA chloride (0.050 mL, 0.27 mmol, 3.8 equiv.) at rt. The mixture was stirred at ambient temperature for 6 h. The reaction was quenched with water, extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over MgSO₄ and purified by flash column chromatography (10:1 petroleum ether / Et₂O) to give **S4** (25.0 mg, 0.050 mmol, 71%).

R_f 0.5 (10:1 petroleum ether / Et₂O); [α]_D²⁵ +6.7 (c = 0.50, CHCl₃); **IR** (thin film) ν_{max} /cm⁻¹ 2852, 1745, 1613, 1514, 1247, 1169, 1018, 820, 717; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.55-7.48 (2H, m, ArH), 7.38 (3H, m, ArH), 7.24 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 5.63 (1H, m, H5), 4.43-4.37 (2H, m, H8), 4.04 (2H, qd, *J* = 7.1, 2.4 Hz, H2), 3.80 (3H, s, H9), 3.53-3.44 (6H, m, H10 and H7), 2.67 (2H, d, *J* = 6.4 Hz, H4), 2.03 (2H, p, *J* = 6.0 Hz, H6), 1.18 (3H, t, *J* = 7.1 Hz, H1); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 169.9, 165.9, 159.4, 132.2, 130.2, 129.7, 129.4, 128.5, 127.6, 123.4 (q, *J* = 288.7 Hz, CF₃) 114.0, 72.9, 71.6, 65.7, 60.9, 55.5, 55.4, 39.0, 33.9, 14.2; **HRMS** (ESI⁺) calc. for C₂₅H₂₉O₇F₃Na [M+Na]⁺ 521.1758; found 521.1754.

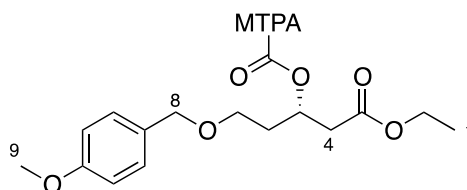
Ethyl (S)-5-((4-methoxybenzyl)oxy)-3-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)-pentanoate, S5



To solution of alcohol **303** (20.0 mg, 0.071 mmol, 1.0 equiv.) in anhydrous CH₂Cl₂ (1 mL) was added dry pyridine (0.035 mL, 0.44 mmol, 6.2 equiv.) and (*S*)-(-)-MTPA chloride (0.050 mL, 0.27 mmol, 3.8 equiv.) at rt. The mixture was stirred at ambient temperature for 6 h. The reaction was quenched with water, extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over MgSO₄ and purified by flash column chromatography (10:1 petroleum ether / Et₂O) to give **S5** (27 mg, 0.055 mmol, 77%).

R_f 0.5 (10:1 petroleum ether / Et₂O); [α]_D²⁵ -20 (c = 0.50, CHCl₃); **IR** (thin film) ν_{max} /cm⁻¹ 2855, 1745, 1613, 1514, 1247, 1169, 1019, 820, 717; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.55-7.50 (2H, m, ArH), 7.43-7.34 (3H, m, ArH), 7.22 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 5.63 (1H, m, H5), 4.38-4.27 (2H, m, H8), 4.11 (2H, qd, *J* = 7.1, 1.7 Hz, H2), 3.80 (3H, s, H9), 3.53 (3H, s, H10), 3.43-3.26 (2H, m, H7), 2.71 (2H, d, *J* = 6.3 Hz, H4), 1.96 (2H, ddt, *J* = 7.7, 5.7, 2.7 Hz, H6), 1.22 (3H, t, *J* = 7.1 Hz, H1); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 170.1, 166.0, 159.4, 132.4, 130.3, 129.7, 129.4, 128.5,

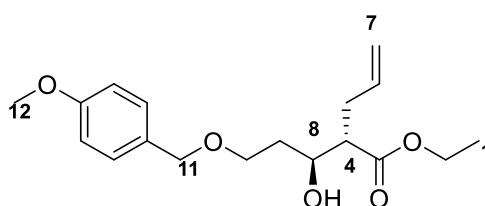
127.5, 123.4 (q, $J = 288.5$ Hz, CF_3), 114.0, 72.8, 71.4, 65.5, 61.0, 55.6, 55.4, 39.2, 33.8, 14.2; **HRMS** (ESI^+) calculated for $\text{C}_{25}\text{H}_{29}\text{O}_7\text{F}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 521.1758, found 521.1753.



Proton positions	S-Mosher's ester	R-Mosher's ester	$\Delta\delta_{\text{SR}}$
1	1.22	1.18	0.04
2	4.11	4.04	0.07
4	2.71	2.67	0.04
5	5.63	5.63	0.00
6	1.96	2.03	− 0.07
7	3.34	3.48	− 0.14
8	4.32	4.40	− 0.08

The Mosher esters were analyzed by NMR spectroscopy and the C5 hydroxyl was thus found to be of *S* configuration.

Ethyl (*S*)-2-((*S*)-1-hydroxy-3-((4-methoxybenzyl)oxy)propyl)pent-4-enoate, **113**

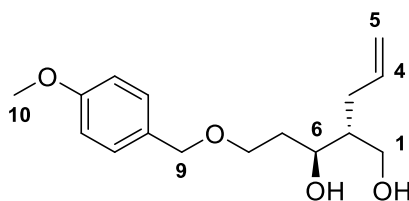


Compound **113** was prepared using a modified literature procedure.^{190,191} To a solution of hydroxyester **303** (4.00 g, 14.2 mmol, 1.0 equiv.) in THF (50 mL) at -78 °C was added LDA (17.0 mL, 34.0 mmol, 2M in THF, 2.4 equiv.) dropwise via syringe over 10 min. The mixture was stirred at -78 °C for 1 h, and then warmed to -30 °C for 30 min, then re-cooled to -78 °C. A solution of allyl iodide (2.6 mL, 28.4 mmol, 2.0 equiv.) in HMPA (5.0 mL, 17.0 mmol, 1.2 equiv.) was added, and the reaction was allowed to stir at -78 °C for 4 h before being quenched with saturated aq. NH_4Cl (20 mL) and EtOAc. The mixture was extracted with EtOAc (3×100 mL), and the combined organic extracts were washed

with brine, dried (MgSO_4) and concentrated. The residue was purified by flash chromatography (4:1 petroleum ether / Et_2O) to afford the title compound **113** as a mixture of 14:1 mixture of diastereomers (2.65 g, 7.81 mmol, 55%) as yellow oil, along with recovered starting material (600 mg, 2.13 mmol, 15%);

R_f 0.33 (1:1 petroleum ether / Et_2O); $[\alpha]_{\text{D}}^{25} +4.5$ ($c = 0.50$, CHCl_3); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3486, 2936, 2862, 1730, 1613, 1513, 1176, 1093, 1033, 821, 638; **¹H NMR** (500 MHz, CDCl_3) δ_{H} 7.24 (2H, d, $J = 8.0$ Hz, ArH), 6.88 (2H, d, $J = 8.0$ Hz, ArH), 5.82-5.68 (1H, m, H6), 5.11 (1H, d, $J = 17.0$ Hz, H7), 5.05 (1H, d, $J = 10.1$ Hz, H7), 4.45 (2H, s, H11), 4.17 (2H, q, $J = 7.0$ Hz, H2), 4.01-3.90 (1H, m, H8), 3.81 (3H, s, H12), 3.72-3.66 (1H, m, H10), 3.72-3.60 (2H, m, H10), 2.57-2.49 (1H, m, H4), 2.49-2.33 (2H, m, H5), 1.88-1.70 (2H, m, H9), 1.27 (3H, t, $J = 7.0$ Hz, H1); **¹³C NMR** (126 MHz, CDCl_3) δ_{C} 174.6, 159.4, 135.1, 130.2, 129.5, 117.2, 114.0, 73.1, 71.0, 68.1, 60.6, 55.4, 51.1, 34.8, 33.5, 14.4; **HRMS** (ESI^+) calc. for $\text{C}_{18}\text{H}_{26}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 345.16731; found 345.1676.

(2*R*,3*S*)-2-Allyl-5-((4-methoxybenzyl)oxy)pentane-1,3-diol, 305

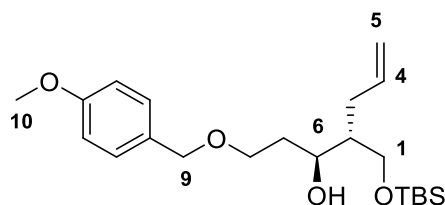


To a stirred solution of **113** (2.50 g, 7.76 mmol, 1.0 equiv.) in ether (75 mL) at -78 °C was added dropwise LiAlH_4 (3.90 mL, 15.5 mmol, 4 M in ether 2.0 equiv.). The reaction was stirred at -78 °C for 15 min, and then warmed to rt and stirred for 3 h. The reaction was then quenched by addition of 1 N NaOH (50 mL) and extracted with Et_2O (3×100 mL). The combined organic layers were dried (MgSO_4), concentrated, and purified by flash chromatography (2:3 petroleum ether / Et_2O) to yield **305** (1.75 g, 6.36 mmol, 82%) as a viscous oil.

R_f 0.23 (3:7 EtOAc / petroleum ether); $[\alpha]_{\text{D}}^{25} +9.8$ ($c = 0.50$, CHCl_3); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3387, 2864, 1613, 1513, 1246.0, 1175, 1086, 1033, 820; **¹H NMR** (400 MHz, CDCl_3) δ_{H} 7.24 (2H, d, $J = 8.6$ Hz, ArH), 6.88 (2H, d, $J = 8.6$ Hz, ArH), 5.87-5.69 (1H, m, H4), 5.09 (1H, s, H5), 5.03 (1H, d, $J = 11.1$ Hz, H5), 4.46 (2H, s, H9), 3.92-3.85 (2H, m, H1), 3.80 (3H, s, H10), 3.76-3.61 (1H, m, H6), 3.69-3.61

(2H, m, H8), 2.25-2.07 (2H, m, H3), 2.00-1.87 (1H, m, H2), 1.81-1.72 (1H, m, H7), 1.61-1.54 (1H, m, H7); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.5, 136.7, 129.8, 129.5, 116.7, 114.0, 75.9, 73.3, 69.6, 64.1, 55.4, 44.8, 34.7, 33.4; HRMS (ESI^+) calc. for $\text{C}_{16}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 303.1567; found 303.1567.

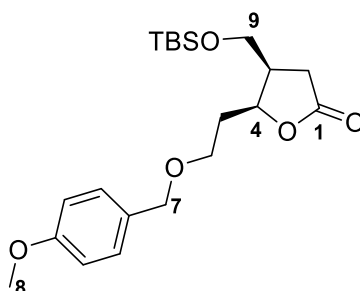
(3*S*,4*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy)hept-6-en-3-ol, 306



To a solution of diol **305** (2.48 g, 8.86 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) at 0 °C was added TBSCl (1.59 g, 10.6 mmol, 1.2 equiv.), DMAP (108 mg, 0.89 mmol, 0.1 equiv.) and imidazole (1.20 g, 17.7 mmol, 2.0 equiv.). The reaction was stirred at 0 °C for 60 min before quenching with water. It was extracted with Et_2O (3×100 mL), and the combined organic extracts were dried (MgSO_4) and concentrated. Purification by flash chromatography (4:1 petroleum ether / Et_2O) gave **306** (3.40 g, 8.59 mmol, 97%) as a colourless oil.

R_f 0.36 (4:1 petroleum ether / Et_2O); $[\alpha]_{\text{D}}^{25} -1.9$ ($c = 0.50$, CHCl_3); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3505, 2929, 2857, 1513, 1464.4, 1248, 1088, 1038, 834, 776; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.20 (2H, d, $J = 8.5$ Hz, ArH), 6.81 (2H, d, $J = 8.5$ Hz, ArH), 5.78-5.63 (1H, m, H4), 4.97 (1H, s, H5), 4.98 (1H, d, $J = 26.4$ Hz, H5), 4.39 (2H, s, H9), 3.79 (2H, ddd, $J = 11.4, 8.8, 3.4$ Hz, H1), 3.74 (3H, s, H10), 3.63-3.58 (3H, m, H6 and H8), 3.48 (1H, d, $J = 5.2$ Hz, OH), 2.21 (1H, dt, $J = 14.7, 8.0$ Hz, H3), 2.11 (1H, dt, $J = 14.7, 8.0$ Hz, H3), 1.80-1.72 (2H, m, H7), 1.50 (1H, m, H2), 0.83 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.00 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 159.3, 137.0, 130.6, 129.4, 116.5, 113.8, 73.0, 72.4, 68.4, 63.7, 55.4, 44.5, 35.4, 33.0, 26.0, 18.2, -5.5, -5.5; HRMS (ESI^+) calc. for $\text{C}_{22}\text{H}_{38}\text{O}_4\text{NaSi}$ $[\text{M}+\text{Na}]^+$ 417.2432; found 417.2435.

(4*R*,5*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)-dihydro-furan-2(3*H*)-one, 301



To a stirred solution of alkene **306** (3.20 g, 8.12 mmol, 1.0 equiv.) in acetone (75 mL) and water (25 mL), was sequentially added OsO₄ (4% wt in water, 2.0 mL, 0.325 mmol, 0.04 equiv.) and NMO (50% wt in water, 3.2 mL, 14.6 mmol, 1.8 equiv.). The reaction mixture was stirred at rt for 3 h before being quenched with saturated *aq.* Na₂S₂O₃. The mixture was stirred for 1 h, then the layers were separated, and the aqueous layer extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried (MgSO₄) and concentrated to give the crude triol as a 3:1 mixture of diastereomers, which was carried forward without purification.

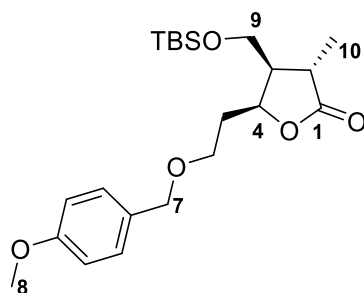
To a stirred solution of crude triol in CH₂Cl₂ (180 mL) was added NaIO₄ on silica (10 wt%, 51.9 g, 24.4 mmol, 3.0 equiv.). The suspension was stirred for 12 h before being filtered through a short plug of silica. Following concentration, the crude lactol was carried forward without further purification.

To a stirred solution of the lactol in CH₂Cl₂ (85 mL) at rt were successively added 4Å MS (5.00 g), NMO (2.40 g, 16.2 mmol, 2.0 equiv.) and TPAP (284 mg, 0.812 mmol, 0.1 equiv.). Stirring was continued for 12 h, then the mixture was filtered through a Celite pad, and concentrated. The residue was purified by flash chromatography (9:1 petroleum ether / EtOAc) to give lactone **301** (2.60 g, 6.58 mmol, 81% over 3 steps) as a colourless oil.

R_f 0.5 (4:1 petroleum ether / AcOEt); [α]_D²⁵ -37 (c = 0.50, CHCl₃); **IR** (thin film) ν_{max} /cm⁻¹ 2935, 2862, 1729, 1613, 1513, 1246, 1176, 1093, 1033, 820, 638; **¹H NMR** (400 MHz, CDCl₃) δ _H 7.21 (2H, d, *J* = 8.6 Hz, ArH), 6.83 (2H, d, *J* = 8.6 Hz, ArH), 4.69 (1H, q, *J* = 6.6 Hz, H4), 4.48-4.30 (2H, m, H7), 3.76 (3H, s, H8), 3.68-3.50 (4H, m, H6 and H9), 2.60 (1H, dd, *J* = 16.6, 8.4 Hz, H2), 2.56-2.49 (1H, m, H3), 2.39 (1H, dd, *J* = 16.6, 3.1 Hz, H2), 1.99-1.87 (2H, m, H5), 0.83 (9H, s, SiC(CH₃)₃), 0.00 (3H, s,

Si(CH₃)₂), -0.01 (3H, s, Si(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ_C 176.6, 159.3, 130.3, 129.4, 113.9, 79.4, 73.0, 66.6, 61.4, 55.4, 40.0, 33.0, 30.6, 25.8, 18.2, -5.6; HRMS (ESI⁺) calc. for C₂₁H₃₄O₅NaSi [M+Na]⁺ 417.2432; found 417.2433.

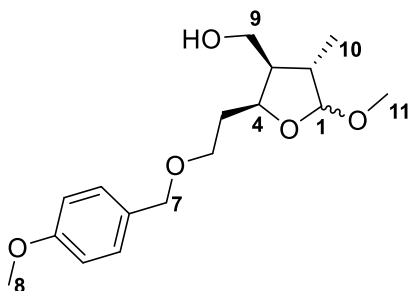
(3*S*,4*R*,5*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)-3-methyldihydrofuran-2(3*H*)-one, 308



To a stirred solution of lactone **301** (2.00 g, 5.08 mmol, 1.0 equiv.) in THF (32 mL) at -78 °C was added LDA (3.06 mL, 6.12 mmol, 2 M in THF, 1.2 equiv.) dropwise over 10 min. The mixture was stirred at -78 °C for 2 h, then methyl iodide (1.26 mL, 20.3 mmol, 4.0 equiv.) was added dropwise. The reaction was stirred at -78 °C for a further 8 h before being quenched with saturated aqueous NH₄Cl and EtOAc. The mixture was warmed to rt and extracted with EtOAc (3 × 200 mL), and the combined organic extracts were washed with brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (4:1 petroleum ether / EtOAc) to afford the title compound **308** (1.56 g, 3.81 mmol, 75%) as yellow liquid (>10:1 *dr*).

R_f 0.50 (4:1 petroleum ether / Et₂O); [α]_D²⁵ -25 (c = 0.50, CHCl₃); **IR** (thin film) ν_{max}/cm⁻¹ 2930, 2850, 1725, 1618, 1513, 1246, 1168, 1020, 824, 632; ¹H NMR (400 MHz, CDCl₃) δ_H 7.24 (2H, s, *J* = 8.2 Hz), 6.87 (2H, d, *J* = 8.2 Hz), 4.75 (1H, ddd, *J* = 10.6, 7.2, 2.7 Hz, H₄), 4.53-4.31 (2H, m, H₇), 3.80 (3H, s, H₈), 3.74-3.57 (4H, m, H₆ and H₉), 2.51 (1H, m, H₂), 2.38-2.27 (1H, m, H₃), 2.03-1.88 (1H, m, H₅), 1.85-1.77 (1H, m, H₅), 1.27 (3H, d, *J* = 7.2 Hz, H₁₀), 0.87 (9H, s, SiC(CH₃)₃), 0.04 (3H, s, Si(CH₃)₂), 0.04 (3H, s, Si(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δ 179.6, 159.3, 130.4, 129.4, 113.9, 77.3, 73.0, 66.5, 61.0, 55.4, 47.8, 36.9, 30.8, 25.9, 18.2, 14.8, -5.4, -5.5; HRMS (ESI⁺) calc. for C₂₂H₃₆O₅SiNa [M+Na]⁺ 431.2224; found 431.2223.

((2*S*,3*R*,4*S*)-5-Methoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methyltetrahydrofuran-3-yl)methanol, **111**



To a stirred solution of lactone **308** (905 mg, 2.21 mmol, 1.0 equiv.) in CH_2Cl_2 (18 mL) at -78°C was added DIBALH (4.0 mL, 3.76 mmol, 0.94 M in THF, 1.7 equiv.) dropwise. The reaction was stirred for 1 h, then it was quenched with 1 M NaOH (10 mL) at -78°C , allowed to warm to rt, and diluted with dichloromethane (20 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4 , and concentrated to give a mixture of lactols.

To a stirred solution of these lactols in MeOH (80 mL) at 0°C was added ($\pm$)-CSA (41 mg, 0.18 mmol, 0.08 equiv.). The reaction was stirred at 0°C for 3 h, then Et_3N (2 mL) was added, and the reaction was concentrated. The residue was used directly in the next step without further purification.

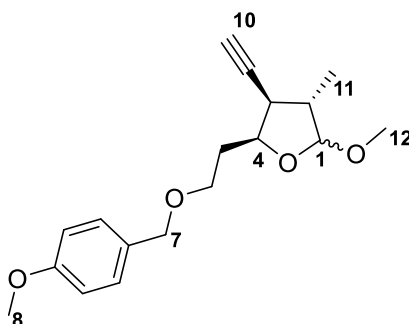
To a stirring solution of methyl acetals in THF (24 mL) at 0°C was added TBAF (1 M in THF, 2.43 mL, 2.43 mmol, 1.1 equiv.). The reaction was warmed to rt overnight, then quenched with saturated *aq.* NH_4Cl (10 mL). The layers were separated, and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified *via* column chromatography (1:1 petroleum ether / Et_2O) to give a mixture **111** as a 1:1 mixture of diastereomers (610 mg, 1.97 mmol, 89% over three steps) as a colourless oil.

R_f 0.17 (3:7 petroleum ether / Et_2O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3432, 2930, 2862, 1613, 1586, 1247, 1093, 1032, 1001, 820.6; **¹H NMR** (400 MHz, CDCl_3) δ_{H} 7.30 (2H, d, $J = 8.8$ Hz, ArH), 6.91 (2H, d, $J = 8.8$ Hz, ArH), 4.77 (0.5H, d, $J = 4.9$ Hz, H1), 4.59 (0.5H, d, $J = 2.3$ Hz, H1), 4.53–4.46 (2H, m, H7), 4.40 (0.5H, ddd, $J = 9.3, 6.3, 4.3$ Hz, H4), 4.31 (0.5H, ddd, $J = 9.1, 7.9, 4.1$ Hz, H4), 3.82 (3H, s, H8), 3.73–3.56 (4H, m, H6 and H9), 3.37 (1.5H, s, H11), 3.36 (1.5H, s, H11), 2.17 (0.5H, ddd, $J = 8.0, 6.6, 3.8$

Hz, H2), 2.12-2.00 (1.5H, m, H2 and H5), 2.00-1.86 (1.5H, m, H3 and H5), 1.80-1.71 (0.5H, m, H3), 1.14 (1.5H, d, $J = 6.7$ Hz, H10), 1.06 (1.5H, d, $J = 6.9$ Hz, H10); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 159.2, 159.2, 130.4, 130.3, 129.4, 129.4, 113.8, 113.8, 111.4, 105.1, 78.4, 76.5, 72.9, 72.8, 68.1, 67.9, 61.8, 61.6, 55.3, 55.3, 55.3, 54.7, 50.6, 48.4, 43.2, 40.6, 31.6, 31.1, 17.2, 12.6; HRMS (ESI⁺) calc. for $\text{C}_{17}\text{H}_{26}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 333.1673; found 333.1673.

(2*S*,3*R*,4*S*)-3-Ethynyl-5-methoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methyltetrahydrofuran,

311



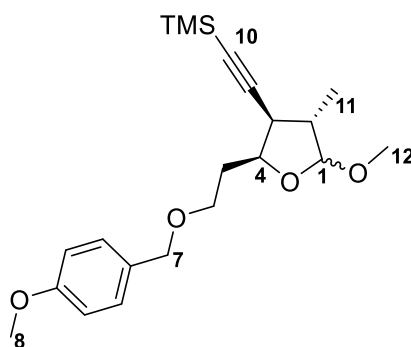
To a stirred solution of alcohol **111** (410 mg, 1.32 mmol, 1.0 equiv.) in CH_2Cl_2 (7 mL) and water (7 mL) was added TEMPO (41 mg, 0.26 mmol, 0.20 equiv.) and BAIB (638 mg, 1.98 mmol, 1.5 equiv.). The biphasic solution was stirred for 7 h at rt, and then quenched with saturated aq. Na_2SO_3 (20 mL). It was then extracted with Et_2O (3×20 mL). The combined organic layers were dried over MgSO_4 , and concentrated. The resulting crude aldehyde **310** was carried forward without further purification.

To a solution of Ohira–Bestmann reagent (760 mg, 3.96 mmol, 3.0 equiv.) in dry THF (12 mL) at -78°C was added NaOMe (25% solution in MeOH, 5.1 mL, 3.96 mmol) dropwise. The mixture was stirred for 20 min, then a solution of the above crude aldehyde in dry THF (12 mL) was added dropwise. The reaction was allowed to slowly warm to rt over 30 min, and was then quenched with saturated aq. NH_4Cl (25 mL). The mixture was diluted with H_2O (20 mL) and extracted with Et_2O (3×50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO_4 , and concentrated to afford the crude product as a yellow oil. Purification by flash chromatography (9:1 petroleum ether / EtOAc) afforded **311** as a white solid (233 mg, 0.752 mmol, 57%).

R_f 0.31 (4:1 petroleum ether / Et_2O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3291, 2932, 1613, 1513, 1246, 1174, 1099, 1075, 988, 820, 757; ^1H NMR (500 MHz, CDCl_3) δ_{H} 7.28 (2H, d, $J = 8.6$ Hz, ArH), 6.88 (2H, d, $J =$

8.6 Hz, ArH), 4.76 (0.5H, d, $J = 4.5$ Hz, H1), 4.57 (0.5H, d, $J = 4.0$ Hz, H1), 4.50-4.43 (2H, m, H7), 4.37-4.26 (1H, m, H4), 3.80 (3H, s, H8), 3.67-3.58 (2H, m, H6), 3.36 (1.5H, s, H12), 3.31 (1.5H, s, H12), 2.88 (0.5H, ddd, $J = 10.8, 8.4, 2.6$ Hz, H3), 2.73 (0.5H, ddd, $J = 8.4, 7.2, 2.5$ Hz, H3), 2.36-2.29 (0.5H, m, H2), 2.24-2.16 (0.5H, m, H2), 2.15 (0.5H, d, $J = 2.5$ Hz, H10), 2.13 (0.5H, d, $J = 2.5$ Hz, H10), 2.12-2.04 (1H, m, H5), 1.94 (0.5H, ddt, $J = 14.1, 10.6, 5.4$ Hz, H5), 1.82 (0.5H, dddd, $J = 13.9, 9.5, 6.6, 5.3$ Hz, H5), 1.17 (1.5H, d, $J = 7.0$ Hz, H11), 1.11 (1.5H, d, $J = 6.9$ Hz, H11); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 159.2, 159.2, 130.8, 130.8, 129.4, 129.4, 113.9, 113.9, 111.9, 105.0, 82.9, 82.1, 77.34, 75.3, 72.8, 72.8, 72.1, 72.0, 67.3, 67.2, 56.0, 55.4, 55.4, 54.8, 46.6, 45.2, 41.2, 39.0, 33.8, 33.4, 16.3, 11.8; HRMS (ESI^+) calc. for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 327.1567; found 327.1566.

(((2*S*,3*R*,4*S*)-5-Methoxy-2-(2-((4-methoxybenzyl)oxy)ethyl)-4-methyltetrahydrofuran-3-yl)ethynyl)trimethylsilane, **312**

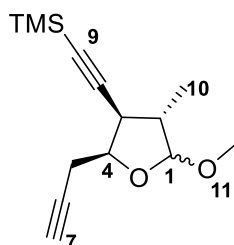


To a stirred solution of terminal alkyne **311** (170 mg, 0.559 mmol, 1.0 equiv.) in dry THF (12 mL) under argon at -78 °C was slowly added n -BuLi (2.5 M in THF, 0.67 mL, 1.68 mmol, 3.0 equiv.). The mixture was stirred for 30 min at -78 °C, then chlorotrimethylsilane (0.14 mL, 1.12 mmol, 2.0 equiv.) was added. The mixture stirred for 60 min at -78 °C, and then the reaction was quenched by addition of saturated aq. NH_4Cl (20 mL). Et_2O was added, and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried with MgSO_4 , and concentrated. The crude product was purified by flash chromatography (19:1 petroleum ether / Et_2O) to give **312** (193 mg, 0.551 mmol, 92%) as a light yellow oil.

R_f 0.36 (4:1 petroleum ether / Et_2O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2957, 2862, 2175, 1613, 1513, 1247, 1173, 1099, 1073, 998, 841, 759; ^1H NMR (500 MHz, CDCl_3) δ_{H} 7.28 (2H, d, $J = 8.6$ Hz, ArH), 6.88 (2H, d,

$J = 8.6$ Hz, ArH), 4.74 (1H, d, $J = 4.5$ Hz, H1), 4.46 (2H, s, H7), 4.29 (1H, td, $J = 8.8, 4.2$ Hz, H4), 3.80 (3H, s, H8), 3.68-3.55 (2H, m, H6), 3.33 (3H, s, H12), 2.90 (1H, dd, $J = 10.6, 8.5$ Hz, H3), 2.23-2.11 (1H, m, H5), 2.07 (1H, m, H5), 1.80 (1H, m, H2), 1.10 (3H, d, $J = 6.9$ Hz, H11), 0.14 (9H, s, TMS); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 159.2, 130.8, 129.3, 113.9, 88.4, 88.3, 77.5, 77.4, 77.2, 76.9, 75.4, 72.8, 55.4, 54.7, 45.4, 40.0, 33.7, 16.1, 11.9, 0.0; HRMS (ESI⁺) calc. for $\text{C}_{21}\text{H}_{32}\text{O}_4\text{NaSi}$ $[\text{M}+\text{Na}]^+$ 399.1962; found 399.1956.

(((2*S*,3*R*,4*S*)-5-Methoxy-4-methyl-2-(prop-2-yn-1-yl)tetrahydrofuran-3-yl)ethynyl)trimethylsilane, 109



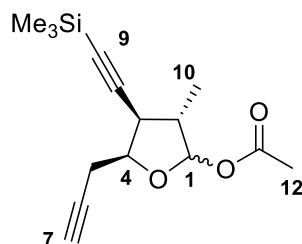
To a solution of **312** (190 mg, 0.505 mmol, 1.0 equiv.) in CH_2Cl_2 (8.5 mL) at rt was added H_2O (3 mL), followed by DDQ (172 mg, 0.758 mmol, 1.5 equiv.). The reaction mixture was stirred for 35 min (monitored by TLC). The reaction was then quenched with saturated aq. NaHCO_3 (50 mL) and was stirred for 30 min to dissolve all solids. The layers were separated, and the aqueous layer was extracted with dichloromethane (3×20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated to give crude **313**. The residue was dissolved in CH_2Cl_2 (3 mL) and water (3 mL) and stirred at rt. TEMPO (16 mg, 0.10 mmol, 0.2 equiv.) and BAIB (244 mg, 0.758 mmol, 1.5 equiv.) were added sequentially, and the reaction was stirred at rt for 3.5 h, after which time TLC indicated complete consumption of the alcohol. The reaction was quenched with MeOH (1 mL) and stirred for 30 min. Water (5 mL) and CH_2Cl_2 (5 mL) were added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford crude aldehyde **314**. The residue was azeotroped twice with 5 mL dry toluene, and then stored under Ar.

To a solution of PPh_3 (662 mg, 2.53 mmol, 5.0 equiv.) in CH_2Cl_2 (7 mL) at 0 °C was added CBr_4 (419 mg, 1.26 mmol, 2.5 equiv.). The mixture was stirred at 0 °C for 15 min, then cooled to -30 °C. To this,

a solution of the crude aldehyde **314** and Et₃N (0.70 mL, 5.05 mmol, 10 equiv.) in CH₂Cl₂ (3 mL) was added dropwise, and the reaction mixture was allowed to warm to 0 °C over 1h. The reaction was quenched with saturated aq. NH₄Cl (20 mL), the layers were separated, and the aqueous layer extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried over Na₂SO₄, concentrated, and the residue was purified via flash chromatography (49:1 petroleum ether / Et₂O) to give the crude dibromoalkene **315** (which co-eluted with 1-(2,2-dibromovinyl)-4-methoxybenzene from the PMB deprotection).

This mixture was transferred to a flame-dried flask as a solution in THF (10 mL). The solution was cooled to –78 °C, then LiHMDS (2.05 mL, 2.05 mmol, 1 M in THF, 4.0 equiv.) was added. The resulting solution was warmed slowly to –15 °C over 2 h, then cooled again to –78 °C. *n*-BuLi (0.61 mL, 1.51 mmol, 2.5 M in hexanes, 3.0 equiv.) was added dropwise along the walls of the vial, and stirred for 5 min. The reaction was monitored by the TLC and on completion, a solution of saturated aq. NH₄Cl (10 mL) was added at –78 °C. The mixture was warmed to rt, and extracted with Et₂O (3 × 25 mL). The combined organic layers were dried over Na₂SO₄, and concentrated. The residue was purified via flash chromatography (49:1 petroleum ether / Et₂O) to yield diyne **109** (82 mg, 0.33 mmol, 65%) as a colourless oil.

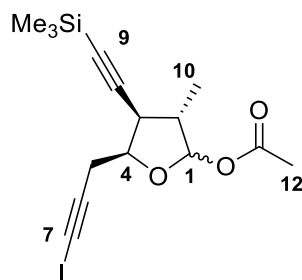
R_f 0.34 (19:1 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3313, 2956, 2175, 1613, 1513, 1249, 1104, 1099, 1016, 842, 760; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 4.65–4.56 (1H, m, H1), 4.31 (1H, q, *J* = 7.4 Hz, H4), 3.42 (3H, s, H11), 2.77 (1H, t, *J* = 8.1 Hz, H3), 2.69–2.53 (2H, m, H5), 2.33 – 2.25 (1H, m, H2), 2.02 (1H, br s, H7), 1.19 (3H, d, *J* = 7.2 Hz, H10), 0.0 (9H, s, TMS); **¹³C NMR** (101 MHz, CDCl₃) δ 111.6, 103.4, 89.0, 82.2, 79.2, 69.5, 56.0, 46.7, 42.3, 23.8, 16.4, 0.1; **HRMS** (ESI⁺) calc. for C₁₄H₂₂O₂SiNa [M+Na]⁺: 273.1281; found 273.1281.

(3*S*,4*R*,5*S*)-3-Methyl-5-(prop-2-yn-1-yl)-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl acetate:**317**

To a solution of methyl acetal **109** (147 mg, 0.588 mmol, 1.0 equiv.) in THF (4 mL) was added acetic acid (4 mL) and the mixture was cooled to 0 °C. Conc. sulfuric acid (20 µL, 0.33 mmol, 0.5 equiv.) was added slowly to the reaction, followed by Ac₂O (0.32 mL, 3.53 mmol, 6.0 equiv.), and the mixture was stirred at 0 °C for 2 h until TLC indicated the consumption of starting material. The reaction was quenched with saturated aq. NaHCO₃ (30 mL), poured into Et₂O (20 mL), and the layers were separated. The aqueous layer was extracted with Et₂O (3 × 20 mL), then the organic layers were combined and dried over Na₂SO₄. The mixture was concentrated, and the residue was purified by flash chromatography (4:1 pentane / Et₂O) to give a 3.3:1 mixture of acetates **317** (148 mg, 0.535 mmol, 91%) as an oil.

R_f 0.30 (4:1 petroleum ether / Et₂O); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2961, 2173, 1753, 1458, 1330, 1230, 1111, 1088, 1007, 958, 899, 842; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 6.29 (1H, d, J = 4.4 Hz, H1), 5.85 (1H, d, J = 2.5 Hz, H1*_{minor}), 4.45 (1H, ddd, J = 8.4, 7.0, 4.7 Hz, H4), 4.39 (1H, m, H4*_{minor}), 3.00 (1H, dd, J = 11.5, 8.6 Hz, H3), 2.87 (2H, dd, J = 7.0, 5.8 Hz, H5*_{minor}), 2.68-2.59 (1H, m, H5), 2.68-2.59 (1H, m, H5*_{minor}), 2.56-2.40 (2H, m, H2 and H5), 2.05 (3H, s, H12*_{minor}), 2.05 (3H, s, H12), 2.03-1.94 (1H, m, H7), 1.18 (3H, d, J = 7.2 Hz, H10*_{minor}), 1.09 (3H, d, J = 6.8 Hz, H10), 0.16 (9H, s, SiMe₃); **¹³C NMR** (101 MHz, CDCl₃) δ_{C} 170.4*, 170.1, 103.8, 102.9*, 102.6, 98.6, 98.6*, 89.8, 89.5*, 81.0, 80.9*, 80.2*, 78.7, 70.2, 69.9*, 46.8*, 44.2, 41.2*, 39.3, 23.5, 23.5*, 21.4*, 21.2, 16.2*, 11.5, 0.0*, -0.0; **HRMS** (ESI⁺) calc. for C₁₅H₂₂O₃SiNa [M+Na]⁺ 301.1230; found 301.1230. * = peaks corresponding to minor diastereomer.

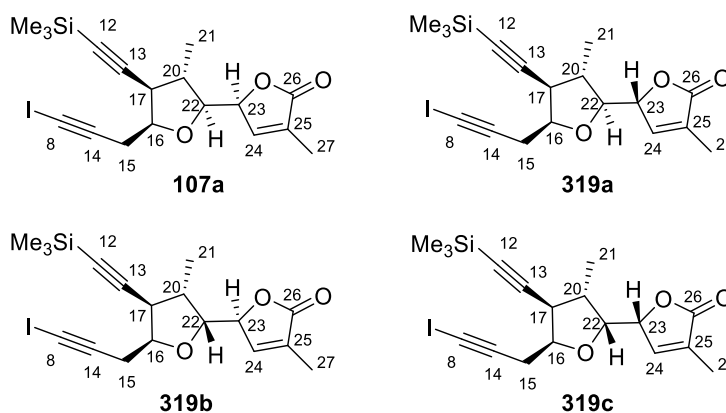
(3*S*,4*R*,5*S*)-5-(3-Iodoprop-2-yn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl acetate, **318**



To a solution of I_2 (2.73 g, 10.7 mmol, 11 equiv.) in toluene (30 mL) under an Ar atmosphere at 0 °C was added morpholine (1.9 mL, 21.5 mmol, 22 equiv.) dropwise. The mixture was sonicated to remove solids from the sides of the flask, then heated to 45 °C for 30 min. A solution of diyne **317** (270 mg, 0.970 mmol, 1.0 equiv.) in toluene (5 mL) was then added dropwise at 45 °C, and the reaction mixture was stirred at 45 °C for 16 h. The mixture was then allowed to cool to room temperature and was filtered, washing the filtered solids with toluene. The filtrate was washed with saturated aq. Na_2SO_3 , brine, and then dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (4:1 pentane / Et_2O) to give **318** (378 mg, 0.936 mmol, 97%) as an oil.

R_f 0.30 (4:1 petroleum ether / Et_2O); **IR** (thin film) ν_{max}/cm^{-1} : 2961, 2171, 1737, 1457, 1420, 1372, 1248, 1111, 1054, 977, 841; **¹H NMR** (500 MHz, $CDCl_3$) δ_H 6.26 (1H, d, J = 4.5 Hz, H1), 5.84 (1H, d, J = 2.7 Hz, H1*), 4.43 (1H, ddd, J = 8.5, 6.2, 5.0 Hz, H4), 4.38 (1H, q, J = 6.9 Hz, H4*), 3.00 (1H, dd, J = 11.5, 8.6 Hz, H3), 2.88-2.81 (3H, m, H3* and H5*), 2.80 (1H, dd, J = 17.0, 5.1 Hz, H5), 2.63 (1H, dd, J = 17.0, 6.3 Hz, H5), 2.57-2.52 (1H, m, H2*), 2.48-2.44 (1H, m, H2), 2.06 (3H, s, H12*), 2.05 (3H, s, H12), 1.17 (3H, d, J = 7.2 Hz, H10*), 1.10 (3H, d, J = 6.8 Hz, H10) 0.17 (9H, s, (SiMe₃)), 0.16 (9H, s, (SiMe₃)*); **¹³C NMR** (126 MHz, $CDCl_3$) δ_C 170.4*, 170.1, 103.7, 102.7*, 102.5, 98.6, 98.6*, 90.8*, 90.8, 89.9, 89.5*, 80.0*, 78.6, 46.6*, 44.1, 41.1*, 39.2, 25.8*, 25.7, 21.4*, 21.1, 16.1*, 11.5, 0.0, 0.0*, -4.5, -4.7*; **HRMS** (ESI⁺) calc. for $C_{15}H_{21}O_3^{127}ISiNa$ $[M+Na]^+$ 427.0197; found 427.0202. * = peaks corresponding to minor diastereomer.

5-((3*S*,4*R*,5*S*)-5-(3-Iodoprop-2-yn-1-yl)-3-methyl-4-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)-3-methylfuran-2(5*H*)-one, 107a, 319a-c



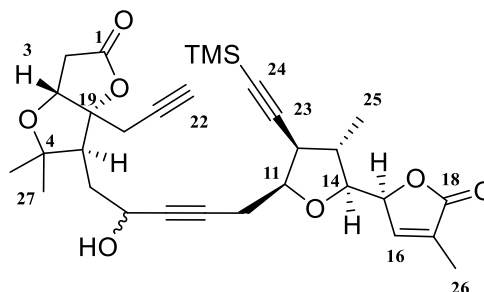
To a solution of $\text{Bi}(\text{OTf})_3$ (1.23 g, 1.87 mmol, 2.0 equiv.) in acetonitrile (16 mL) under an Ar atmosphere at $-40\text{ }^\circ\text{C}$ was added dropwise a solution of acetate **26** (378 mg, 0.936 mmol, 1.0 equiv.) and triisopropyl((3-methylfuran-2-yl)oxy)silane **6** (0.401 mL, 1.40 mmol, 1.5 equiv.) in acetonitrile (4 mL). The reaction mixture was stirred at $-40\text{ }^\circ\text{C}$ for 1 h until TLC showed the reaction to be complete. The reaction was quenched with saturated aq. NH_4Cl (10 mL) and allowed to warm to rt. The mixture was poured into CH_2Cl_2 and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 ($3 \times 100\text{ mL}$), the organic layers were combined, washed with water and then brine, and dried over Na_2SO_4 . After concentration, purification of the residue by flash chromatography (19:1 pentane / Et_2O) gave **319b** (81 mg), **319a** (65 mg), and **107a/319c** (121 mg, inseparable mixture of $\sim 1:1$ diastereomers, also contaminated with the furanone from hydrolysis of **6**).

319b: R_f 0.43 (3:1 pentane / Et_2O); $mp = 113\text{--}115\text{ }^\circ\text{C}$; $[\alpha]_D^{25} -121.0$ ($c = 1.01$, CHCl_3); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 2171, 1761, 1249, 1094, 1059, 1007, 843, 760; **^1H NMR** (500 MHz, CDCl_3) δ 7.30–7.24 (m, 1H, H24), 4.70 (1H, dt, $J = 9.3, 1.9\text{ Hz}$, H23), 4.28 (1H, q, $J = 6.5\text{ Hz}$, H16), 3.81 (1H, dd, $J = 9.3, 5.8\text{ Hz}$, H22), 2.88 (1H, dd, $J = 6.2, 4.4\text{ Hz}$, H17), 2.76–2.68 (2H, m, H15), 2.68–2.61 (1H, m, H20), 1.92 (3H, t, $J = 1.7\text{ Hz}$, H27), 1.19 (3H, d, $J = 7.2\text{ Hz}$, H21), 0.13 (9H, s, TMS); **^{13}C NMR** (126 MHz, CDCl_3) δ 174.0, 149.0, 130.2, 125.5, 102.8, 90.9, 90.5, 82.0, 78.6, 77.9, 43.1, 42.6, 25.2, 13.7, 10.7, 0.0; **HRMS** (ESI^+) calc. for $\text{C}_{18}\text{H}_{23}\text{O}_3^{127}\text{ISiNa}$ $[\text{M}+\text{Na}]^+ 465.0353$; found 465.0357.

319a R_f 0.32 (3:1 pentane / Et₂O); $[\alpha]_D^{25}$ -14.0 (c = 0.63, CHCl₃); **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2960, 2926, 2357, 2173, 1761, 1657, 1454, 1317, 1249, 1207, 1091, 1071, 1039, 951, 843, 759, 700, 668; **¹H NMR** (400 MHz, CDCl₃) δ 7.24 (1H, m, H24), 4.86 (1H, m, H23), 4.18 (1H, td, J = 6.8, 5.4 Hz, H16), 3.31 (1H, t, J = 7.2 Hz, H22), 2.84-2.63 (3H, m, H15/H17), 2.45 (1H, m, H20), 1.94 (3H, t, J = 1.8 Hz, H27), 1.19 (3H, d, J = 6.8 Hz, H21), 0.16 (9H, s, TMS); **¹³C NMR** (101 MHz, CDCl₃) δ_c 174.0, 147.6, 130.5, 103.1, 91.0, 90.1, 86.2, 82.5, 78.1, 77.2, 44.3, 43.1, 25.6, 17.2, 10.7, 0.0; **HRMS** (ESI⁺) calc. for C₁₈H₂₃O₃¹²⁷ISiNa [M+Na]⁺465.0353; found 465.0356.

107a/319c: R_f 0.19 (3:1 pentane / Et₂O); **IR** (thin film) $\nu_{\max}/\text{cm}^{-1}$ 2959, 2926, 2167, 1759, 1456, 1250, 1051, 989, 944, 843, 760, 699; **¹H NMR** (500 MHz, CDCl₃) δ_H 7.06-7.02 (1H, m, H24(**107a**)), 6.97-6.94 (1H, m, H24(**319c**)), 4.94 (1H, dt, J = 3.5, 1.9 Hz, H23(**107a**)), 4.86 (1H, q, J = 1.9 Hz, H23(**319c**)), 4.73 (1H, m, furanone impurity), 4.25 (1H, dd, J = 7.8, 1.7 Hz, H22(**319c**)), 4.19 (1H, dt, J = 7.5, 5.6 Hz, H16(**319c**)), 4.14 (1H, td, J = 7.6, 5.0 Hz, H16(**107a**)), 3.71 (1H, dd, J = 8.8, 3.1 Hz, H22(**107a**)), 3.15 (1H, dd, J = 10.6, 8.1 Hz, H17(**319c**)), 2.77 (1H, dd, J = 9.6, 7.4 Hz, H17(**107a**)), 2.74-2.51 (5H, m, H15/H20(**319c**); H15(**107a**)), 2.27 (1H, dt, J = 13.7, 6.9 Hz, H20(**107a**)), 1.96 (3H, t, J = 1.7 Hz, H27(**107a**)), 1.93-1.90 (5H, m, H27(**319c**); furanone), 1.26 (3H, d, J = 7.0 Hz, 3H, H21(**319c**)), 1.13 (3H, d, J = 6.7 Hz, 3H, H21(**107a**)), 0.13 (18H, s, TMS(**107a/319c**)); **¹³C NMR** (126 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_c 174.1, 173.7, 146.3, 145.6, 131.3, 130.9, 103.4, 102.5, 91.3, 91.1, 89.8, 89.3, 84.0, 80.7, 79.6, 79.4, 78.9, 78.0, 77.4, 77.1, 76.8, 43.0, 42.2, 41.2, 40.7, 26.0, 25.6, 15.9, 13.1, 11.0, 10.8, 0.1, 0.0 ppm; **HRMS** (ESI⁺) calc. for C₁₈H₂₃O₃¹²⁷ISiNa [M+Na]⁺465.0353; found 465.0357.

(3a*R*,6*S*,6a*R*)-6-(2-Hydroxy-5-((2*S*,3*R*,4*S*,5*S*)-4-methyl-5-((*S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)pent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, **105b**

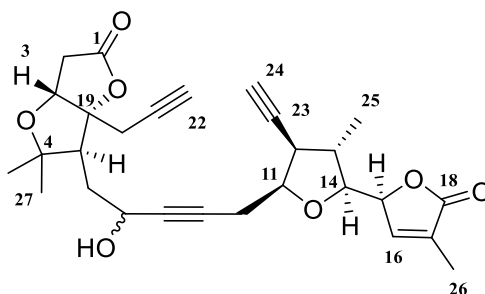


A mixture of AB ring aldehyde **32** (36 mg, 0.15 mmol, 1.0 equiv.) and FG ring diynes **107a/319c** (78 mg, 0.175 mmol, 1.15 equiv.) were azeotroped thrice with toluene then placed under an N₂ atmosphere. To this vial, anhydrous THF (6 mL) was added, and the vial was taken into the glovebox. To the solution, CrCl₂ (97%, 111 mg, 0.912 mmol, 6.0 equiv.) was added, then the vial was sealed and removed from the glovebox. The solution was stirred at rt for 15 h, then the reaction was quenched by addition of 1 M serine solution (30 mL). The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via flash chromatography (10:3 petroleum ether / EtOAc) to give the triyne products (73 mg, 0.130 mmol, 87% yield). Further careful chromatography enabled separation of the diastereomers at the C14 and C15 positions (25 % EtOAc /pentane), giving the desired (C14*S*, C15*S*) alcohols **105b** (33 mg) (inconsequential 1:1 mix of diastereomers at the C7 alcohol).

R_f 0.43 (7:3 pentane / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3427, 3280, 2960, 2925, 2177, 1762, 1661, 1457, 1387, 1301, 1277, 1178, 1021, 931; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.03 (1H, q, $J = 1.7$ Hz, H16), 4.96 (1H, m, H15), 4.49 (1H, d, $J = 7.0$ Hz, H3), 4.45-4.35 (1H, m, H7), 4.15 (1H, dtd, $J = 7.5$, 4.6, 2.4 Hz, H11), 3.69 (1H, ddd, $J = 9.4$, 7.4, 2.2 Hz, H14), 3.17 (1H, d, $J = 4.0$ Hz, OH), 3.12-2.90 (2H, m, H2 and H20), 2.81 (1H, ddd, $J = 10.6$, 7.6, 3.5 Hz, H12), 2.66 (1H, ddd, $J = 18.7$, 3.3, 1.1 Hz, H2), 2.58-2.43 (4H, m, H10, H13 and H20), 2.33 (1H, dd, $J = 9.6$, 3.9 Hz, H5), 2.09-2.02 (1H, m, H22), 1.96 (3H, dt, $J = 3.6$, 1.8 Hz, H26), 1.89-1.74 (1H, m, H6), 1.61-1.52 (1H, m, H6), 1.35 (3H, s, H27), 1.18 (3H, d, $J = 6.6$ Hz, H*25), 1.18 (3H, d, $J = 6.6$ Hz, H25), 1.08 (3H, s, 1H), 1.08 (3H, s, H*27), 0.16

(9H, s, (SiCH₃)₃); ¹³C NMR (101 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_C 175.5, 175.5, 174.9, 174.8, 146.2, 146.2, 131.2, 131.1, 102.5, 102.4, 94.9, 94.8, 89.7, 89.7, 83.7, 83.7, 83.4, 83.4, 82.4, 82.2, 79.1, 79.0, 78.7, 78.6, 78.1, 78.0, 77.5, 77.5, 72.2, 72.1, 61.3, 60.6, 55.6, 54.5, 43.1, 43.1, 40.7, 40.7, 37.5, 34.1, 34.0, 29.7, 29.4, 27.8, 27.7, 25.7, 25.7, 23.6, 20.5, 20.5, 15.3, 15.3, 10.8, 10.8, 0.03, 0.02; HRMS (ESI⁺) calc. for C₃₁H₄₀O₇SiNa [M+Na]⁺ 575.2436; found 575.2434. (* = peaks corresponding to second diastereomer)

(3a*R*,6*S*,6a*R*)-6-(5-((2*S*,3*R*,4*S*,5*S*)-3-Ethynyl-4-methyl-5-((*S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)tetrahydrofuran-2-yl)-2-hydroxypent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, 320

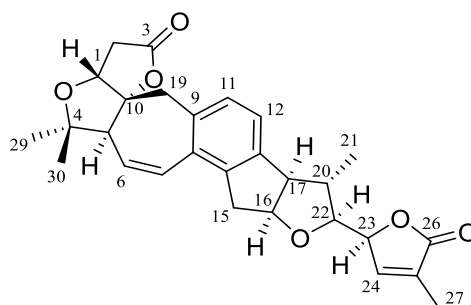


To a solution of **105b** (10.8 mg, 0.019 mmol, 1.0 equiv.) in THF (1 mL) was added AcOH (3 μL, 0.028 mmol, 2.0 equiv.) followed by TBAF (58 μL, 1 M in THF, 0.057 mmol, 3.0 equiv.). The solution was stirred for 5 min before being quenched by addition of saturated aq. NH₄Cl (5 mL). The mixture was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified via flash chromatography (10:3 petroleum ether / EtOAc) to provide triynes **320** (7.9 mg, 0.016 mmol, 85% yield) (inconsequential 1:1 mix of diastereomers).

R_f 0.33 (3:7 EtOAc / pentane); **IR** (thin film) ν_{max}/cm⁻¹ 3425, 3329, 2960, 2925, 2171, 1761, 1661, 1457, 1375, 1276, 1250, 1197, 1021, 932; ¹H NMR (400 MHz, CDCl₃) δ_H 7.04 (1H, t, *J* = 1.7 Hz, H16), 5.00 (1H, q, *J* = 2.0 Hz, H15), 4.64-4.41 (2H, m, H3 and H7), 4.26-4.11 (1H, m, H11), 3.78 (1H, d, *J* = 3.5 Hz, OH), 3.68 (1H, dd, *J* = 9.4, 2.1 Hz, H*14), 3.67 (1H, dd, *J* = 9.4, 2.1 Hz, H14), 3.09-2.93 (2H, m, H2 and H20), 2.83 (1H, ddd, *J* = 11.9, 8.1, 2.6 Hz, H12), 2.76-2.52 (4H, m, H2, H10 and H13), 2.51-2.47 (1H, m, H20), 2.47-2.37 (1H, m, H5), 2.28 (1H, d, *J* = 2.5 Hz, H*24), 2.27 (1H, d, *J* = 2.5 Hz, H24), 2.11-2.03 (1H, m, H22), 1.96 (3H, *app* q, *J* = 1.9 Hz, H26), 1.78 (1H, ddd, *J* = 13.9, 10.6, 5.6 Hz,

H6), 1.58-1.51 (1H, m, H6), 1.35 (3H, s, H*27), 1.34 (3H, s, H27), 1.23 (3H, d, $J = 6.5$ Hz, H25), 1.10 (3H, s, H*27), 1.07 (3H, s, H27); ^{13}C NMR (101 MHz, CDCl_3 , peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.1, 175.1, 146.3, 146.3, 131.1, 131.0, 95.1, 94.7, 83.7, 83.7, 83.5, 83.4, 82.9, 82.6, 82.2, 81.8, 80.6, 80.5, 79.0, 78.7, 78.5, 78.2, 78.0, 77.2, 73.3, 73.1, 72.2, 72.1, 61.2, 60.7, 55.1, 54.4, 42.0, 41.9, 40.9, 40.8, 37.6, 37.6, 34.1, 33.5, 28.0, 27.4, 25.7, 23.7, 23.7, 22.7, 20.6, 20.5, 15.1, 15.0, 14.1, 10.8; HRMS (ESI $^{+}$) calc. for $\text{C}_{28}\text{H}_{32}\text{O}_7\text{Na}$ $[\text{M}+\text{Na}]^{+}$ 503.2040 found 503.2037. (* = peaks corresponding to second diastereomer).

pseudo-rubriflordilactone B, **4**



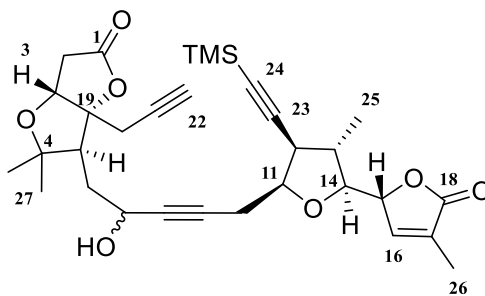
pseudo-rubriflordilactone B, **4**

To a stirred solution of $\text{RhCl}(\text{PPh}_3)_3$ (3.0 mg, 3.24 μmol , 0.2 equiv.) in anhydrous DCE (2 mL) was added a solution of **320** (7.9 mg, 16.28 μmol , 1.0 equiv.) in DCE (0.5 mL). The mixture was stirred at 50 $^{\circ}\text{C}$ for 48 h (until completion), then it was cooled to rt and concentrated to afford crude **321**. The residue was dried under vacuum, then benzene (2.5 mL) was added followed by PTSA. $\cdot\text{H}_2\text{O}$ (3.6 mg, 18.93 μmol , 1.1 equiv.). The reaction was heated to 80 $^{\circ}\text{C}$ for 12 h, then cooled to rt and quenched by addition of H_2O (5 mL). The aqueous layer was extracted using EtOAc (4×10 mL), and the combined organic phases were dried using (Na_2SO_4) and concentrated. The residue was purified via flash chromatography (2:1 petroleum ether / EtOAc) to give **4** (3.2 mg, 6.91 μmol , 43% over two steps) as a thick colourless oil.

R_f 0.27 (1:1 EtOAc / pentane); $[\alpha]_{\text{D}}^{25} -14.2$ ($c = 0.10$, CHCl_3); IR (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2980, 2889, 1758, 1656, 1460, 1383, 1260, 1217, 1166, 1071, 1008, 952; ^1H NMR (500 MHz, CDCl_3) δ_{H} δ 7.0 (2H, s, H11 and H12), 6.61 (1H, dd, $J = 12.1, 2.3$ Hz, H7), 6.56 (1H, br m, H24), 5.79 (1H, br s, H6), 4.91 (1H, dt, $J = 6.3, 3.9$ Hz, H16), 4.74 (1H, m, H23), 4.35 (1H, br s, H1), 3.80 (1H, dd, $J = 6.8, 4.8$ Hz, H22),

3.37 (1H, dd, $J = 6.3, 4.5$ Hz, H17), 3.05 (2H, s, H15 $\alpha\beta$), 2.91 – 2.85 (4H, m, H2 $\alpha\beta$, H5, and H19 β), 2.73 (1H, d, $J = 18.5$ Hz, H19 α), 2.18 (1H, m, H20), 1.82 (3H, t, $J = 1.8$ Hz, H27), 1.55 (3H, s, H29), 1.40 (3H, br s, H30), 1.29 (3H, d, $J = 6.9$ Hz, H21); $^1\text{H NMR}$ (500 MHz, Pyridine- d_5) δ 7.08 (2H, m, H11 and H12), 6.86 (1H, m, H24), 6.50 (1H, dd, $J = 12.1, 2.4$ Hz, H7), 5.72 (1H, br s, H6), 4.85 (2H, m, H16 and H23), 4.42 (1H, br s, H1), 3.73 (1H, dd, $J = 7.0, 4.9$ Hz, H22), 3.29 (1H, dd, $J = 6.40, 4.66$ Hz, H17), 3.21 (6H, m, H2 α , H2 β , H15 α , H15 β , H19 α and H19 β), 2.89-2.81 (1H, m, H5), 2.34-2.38 (1H, m, H20), 1.75 (3H, app t, $J = 1.8$ Hz, H27), 1.41-1.08 (6H, m, H29 and H30), 1.17 (3H, d, $J = 6.8$ Hz, H21). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 174.6, 173.7, 145.6, 143.5, 140.0, 131.2, 129.8, 128.0, 123.3, 104.0, 86.4, 85.3, 83.4, 80.4, 59.2, 58.1, 41.7, 37.9, 35.7, 29.7, 28.3, 22.1, 19.1, 10.8. $^{13}\text{C NMR}$ (126 MHz, Pyridine- d_5) δ 175.1, 174.0, 146.8, 144.1, 140.3, 133.4, 130.9, 130.2, 130.2, 128.6, 128.1*, 123.5*, 103.0, 86.9, 84.9, 83.5, 81.1, 79.4, 60.0, 58.4, 42.5, 41.2, 38.2, 35.9, 28.2, 21.9, 18.5, 10.7 ppm (* = identified from HSQC); **HRMS** (ESI^+) calc. for $\text{C}_{28}\text{H}_{30}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 485.1935; found 485.1932.

(3a*R*,6*S*,6a*R*)-6-(2-Hydroxy-5-((2*S*,3*R*,4*S*,5*S*)-4-methyl-5-((*R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-((trimethylsilyl)ethynyl)tetrahydrofuran-2-yl)pent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, 322

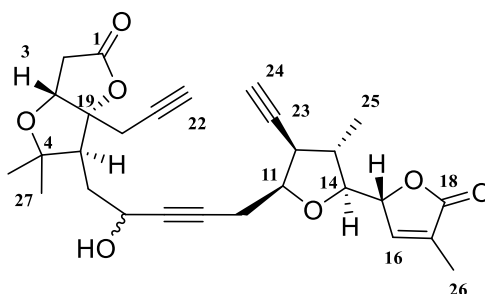


A mixture of AB ring aldehyde **32** (12 mg, 0.049 mmol, 1.0 equiv.) and FG ring diyne **319a** (25 mg, 0.057 mmol, 1.15 equiv.) were azeotroped thrice with toluene before placing under an N_2 atmosphere. To this vial, anhydrous THF (2 mL) was added, and the vial was taken into glovebox. To the solution, CrCl_2 (97%, 36 mg, 0.30 mmol, 6.0 equiv.) was added, the vial was sealed and removed from the glovebox, and then the solution was stirred at rt for 15 h. The reaction was quenched with 1 M serine solution (15 mL). The aqueous layer was extracted using EtOAc (4×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified via flash chromatography

(10:3 petroleum ether / EtOAc) to give triynes **322** (25 mg, 0.046 mmol, 93%) (inconsequential 1:1 mix of diastereomers).

R_f 0.37 (2:3 pentane / EtOAc); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3457, 3272, 2970, 2927, 2173, 1764, 1665, 1460, 1387, 1376, 1277, 1197, 1084, 931; **¹H NMR** (400 MHz, CDCl₃) δ_{H} 7.21 (1H, t, $J = 1.7$ Hz, H16), 4.99–4.80 (1H, m, H15), 4.50 (1H, dd, $J = 6.0, 4.3$ Hz, H3), 4.46–4.40 (1H, m, H7), 4.25–4.09 (1H, m, H11), 3.36 (1H, td, $J = 6.9, 3.6$ Hz, H14), 3.15–2.93 (2H, m, H2 and H20), 2.78 (1H, td, $J = 6.9, 1.5$ Hz, H12), 2.71–2.65 (1H, m, H2), 2.65–2.59 (1H, m, H10), 2.57–2.47 (2H, m, H10 and H20), 2.47–2.35 (2H, m, H13 and OH), 2.30 (1H, dd, $J = 10.2, 3.2$ Hz, H5), 2.07 (1H, t, $J = 2.6$ Hz, H22), 1.99–1.80 (3H, m, H26), 1.87–1.72 (1H, m, H6), 1.65–1.50 (1H, m, H6), 1.34 (3H, s, H27), 1.33 (3H, s, H*27), 1.15 (3H, d, $J = 6.8$ Hz, H25), 1.07 (3H, s, H27), 0.15 (9H, s, (SiMe₃)₃); **¹³C NMR** (101 MHz, CDCl₃, peaks for both diastereomers are listed and not assigned) δ_{C} 175.5, 175.4, 174.1, 174.1, 147.3, 147.3, 130.6, 130.6, 103.4, 94.8, 94.6, 90.1, 90.05, 86.1, 86.08, 83.7, 83.4, 83.4, 83.1, 82.3, 82.2, 81.7, 81.4, 78.7, 78.6, 78.2, 78.19, 77.94, 77.9, 77.3, 72.27, 72.25, 61.7, 61.1, 55.8, 54.7, 43.7, 43.6, 43.0, 43.02, 37.6, 37.5, 33.9, 33.5, 27.6, 27.57, 25.8, 25.7, 23.4, 23.3, 20.5, 17.5, 17.47, 10.7, –0.0; **HRMS** (ESI⁺) calc. for C₃₁H₄₀O₇SiNa [M+Na]⁺ 575.24355; found 575.24323. (* = peaks corresponding to second diastereomer)

(3a*R*,6*S*,6a*R*)-6-(5-((2*S*,3*R*,4*S*,5*S*)-3-ethynyl-4-methyl-5-((*S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)tetrahydrofuran-2-yl)-2-hydroxypent-3-yn-1-yl)-5,5-dimethyl-6a-(prop-2-yn-1-yl)tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one, 323

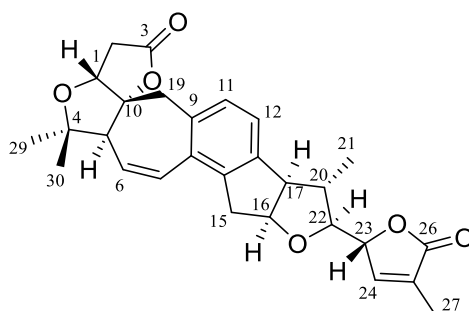


To a solution of **322** (25 mg, 0.045 mmol, 1.0 equiv.) in THF (2 mL) was added AcOH (6.0 μ L, 0.090 mmol, 2.0 equiv.) followed by TBAF (135 μ L, 1 M in THF, 0.135 mmol, 3.0 equiv.). The solution was stirred for 5 min before being quenched by addition of saturated aq. NH₄Cl (5 mL). The mixture was

extracted with EtOAc (4×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the crude purified via flash chromatography (10:3 petroleum ether / EtOAc) to provide triynes **323** (17 mg, 0.036 mmol, 80%) (inconsequential 1:1 mix of diastereomers).

R_f 0.29 (3:2 EtOAc / pentane); **IR** (thin film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3446, 3284, 2972, 1759, 1458, 1388, 1320, 1278, 1197, 1019, 930; **¹H NMR** (400 MHz, CDCl_3) δ_{H} 7.21 (1H, q, $J = 1.7$ Hz, H16), 5.03–4.91 (1H, m, H15), 4.58–4.32 (2H, m, H3 and H7), 4.28–4.10 (1H, m, H11), 3.37 (1H, dd, $J = 14.3, 7.2$ Hz, H14), 3.12–2.91 (2H, m, H2 and H20), 2.78 (1H, td, $J = 7.1, 2.4$ Hz, H12), 2.73–2.56 (3H, m, H2 and H10), 2.56–2.43 (3H, m, H13, H20 and OH), 2.36–2.22 (2H, m, H5 and H24), 2.14–2.05 (1H, m, H22), 1.93 (3H, s, H26), 1.93 (3H, s, H*26), 1.87–1.74 (1H, m, H6), 1.63–1.49 (1H, m, H6), 1.34 (3H, s, H27), 1.33 (3H, s, H27), 1.17 (3H, d, $J = 6.9$ Hz, H*25) 1.16 (3H, d, $J = 6.9$ Hz, H25), 1.08 (3H, s, H*27) 1.07 (3H, s, H27); **¹³C NMR** (101 MHz, CDCl_3 , peaks for both diastereomers are listed and not assigned) δ 175.5, 175.4, 174.1, 174.0, 147.3, 147.2, 130.7, 130.7, 94.8, 94.5, 86.0, 86.0, 83.5, 83.4, 83.4, 82.9, 82.1, 82.1, 81.9, 81.5, 81.2, 81.1, 78.7, 78.6, 78.0, 77.9, 77.8, 73.6, 72.4, 72.2, 61.5, 60.2, 55.6, 54.6, 43.6, 43.3, 41.9, 41.9, 37.5, 37.5, 33.8, 33.4, 27.7, 27.5, 25.8, 25.7, 23.3, 23.3, 20.5, 17.4, 17.4, 10.7; **HRMS** (ESI^+) calc. for $\text{C}_{28}\text{H}_{32}\text{O}_7\text{Na}$ $[\text{M}+\text{Na}]^+$ 503.2040; found 503.2037. (* = peaks corresponding to second diastereomer)

23-*epi*-pseudo-rubriflordinilactone **B**; *epi*-4



23-*epi*-pseudo-rubriflordinilactone **B, *epi*-4**

To a stirred solution of $\text{RhCl}(\text{PPh}_3)_3$ (8.4 mg, 9.08 μmol , 0.2 equiv.) in anhydrous DCE (4 mL) was added a solution of **323** (22 mg, 45.78 μmol , 1.0 equiv.) in DCE (3 mL). The reaction was stirred at 50 °C for 48 h and then cooled to rt and concentrated to afford crude **324**. The residue was dried under vacuum before adding benzene (2.5 mL), followed by PTSA. $\cdot\text{H}_2\text{O}$ (8.6 mg, 0.046 mmol, 1.0 equiv.).

The reaction was heated to 80 °C for 12 h and was then cooled to rt and quenched by addition of H₂O (5 mL). The aqueous layer was extracted using EtOAc (4 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated, and the residue was purified via flash chromatography (2:1 petroleum ether / EtOAc) to yield **epi-4** (7.5 mg, 16.48 μmol, 36% over two steps) as a thick colourless oil.

R_f 0.42 (3:2 petroleum ether / EtOAc); [α]_D²⁵ +18.0 (c = 0.25, CHCl₃); **IR** (thin film) $\nu_{\max}$ /cm⁻¹ 2979, 2926, 1760, 1659, 1459, 1383, 1260, 1216, 1168, 1065, 953, 799, 756; **¹H NMR** (500 MHz, CDCl₃) δ _H 7.12 (1H, d, *J* = 7.5 Hz, H12), 7.01 (1H, d, *J* = 7.5 Hz, H11), 6.94 (1H, br s, H24), 6.62 (1H, dd, *J* = 12.0, 1.9 Hz, H7), 5.84 (1H, br s, H6), 4.96–4.87 (1H, m, H16), 4.32 (1H, br s, H1), 4.12 (1H, br s, H23), 3.43 (1H, dd, *J* = 5.8, 2.6 Hz, H17), 3.35 (1H, dd, *J* = 8.2, 4.3 Hz, H22), 3.23–2.77 (6H, m, H2 α , H2 β , H5, H15 α , 15 β , 19 β), 2.71 (1H, d, *J* = 18.4 Hz, H19 α), 2.67–2.56 (1H, m, H20), 1.83 (3H, t, *J* = 1.8 Hz, H27), 1.38 (3H, br s, H29), 1.32 (3H, d, *J* = 7.1 Hz, H21), 1.25 (3H, br s, H29); **¹H NMR** (500 MHz, Pyridine-*d*₅) δ 7.13 (2H, s, H11 and H12), 7.03 (1H, s, H24), 6.63 – 6.54 (1H, m, H7), 5.76 (1H, br s, H6), 4.86 (1H, t, *J* = 6.1 Hz, H16), 4.50 (1H, br s, H23), 4.39 (1H, br s, H1), 3.51 (1H, dd, *J* = 8.1, 4.3 Hz, H22), 3.33 (1H, dd, *J* = 6.0, 3.5 Hz, H17), 3.28–3.13 (2H, m, H2 β and H19 β), 3.13–2.89 (4H, m, H5, H15 α , 15 β and H19 α), 2.89–2.80 (1H, m, H2 α), 2.50 (1H, br s, H20), 1.73 (3H, s, H27), 1.34 (3H, br s, H29), 1.26 (3H, br s, H30), 1.18 (3H, d, *J* = 7.0 Hz, H21); **¹³C NMR** (126 MHz, CDCl₃) δ 174.7, 174.1, 148.0, 144.0, 140.1, 130.3, 130.2, 127.8, 123.7, 103.1, 88.2, 85.2, 83.9, 82.3, 79.9, 59.5, 58.2, 44.3, 41.9, 38.6, 35.8, 29.8, 22.1, 20.2, 10.7 ppm. **¹³C NMR** (126 MHz, Pyridine-*d*₅) δ 175.1, 173.9, 148.0, 144.3, 140.5, 133.9 (HMBC), 130.5, 130.1, 128.2, 123.1, 103.0, 87.7, 84.9, 83.7, 82.4, 80.4, 60.0, 58.4, 44.3, 41.5, 38.5, 35.9, 28.2, 21.9, 19.4, 10.6; **HRMS** (ESI⁺) calc. for C₂₈H₃₀O₆Na [M+Na]⁺ 485.1935; found 485.1932.

6.3 X-ray Crystallography¹²

Low temperature single crystal X-ray diffraction data were collected for **160a**, **166** and **3** with a (Rigaku) Oxford Diffraction SuperNova A diffractometer at 150 K, and data for **319b** were collected using I19-1 at the Diamond Light Source^[1] at 100 K. All data were reduced using CrysAlisPro, solved using SuperFlip^[2] and the structures were refined using CRYSTALS.^[3]

Structure **XX** contained solvent accessible voids comprising of weak, diffuse electron density. The discrete Fourier transforms of the void regions were treated as contributions to the A and B parts of the calculated structure factors using PLATON/SQUEEZE^[4] integrated within the CRYSTALS software. This enabled a comparison of models, one of which contained the disordered solvent, the other without.

The Flack x parameter^[5] was refined in all cases. Bayesian analysis of the Bijvoet pairs was also carried out using all the data used in the refinement.^[6] This gave the Hooft y parameter, the P2 probability (the likelihood that the hand is correct given the crystal was enantiopure), and the P3 probability (the likelihood that the hand is correct given the crystal was enantiopure or racemic).

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¹² The crystal was developed by the author and the X-ray analysis was done by Steven J. Mansfield, a D. Phil. student in the group.

Table 6.1 Crystal data and structure refinement for **160a**.

Identification code	013eaa17b	
Empirical formula	C15 H22 O3 Si1	
Formula weight	278.42	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.99150(10) Å	$\alpha = 90^\circ$.
	b = 10.9371(2) Å	$\beta = 90^\circ$.
	c = 16.3586(3) Å	$\gamma = 90^\circ$.
Volume	1608.72(5) Å ³	
Z	4	
Density (calculated)	1.150 Mg/m ³	
Absorption coefficient	1.304 mm ⁻¹	
F(000)	600	
Crystal size	0.17 x 0.10 x 0.04 mm ³	
Theta range for data collection	4.864 to 76.263°.	
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13, -20 ≤ l ≤ 20	
Reflections collected	34467	
Independent reflections	3372 [R(int) = 0.0432]	
Completeness to theta = 76.263°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.95 and 0.88	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3371 / 0 / 173	
Goodness-of-fit on F ²	1.0140	
Final R indices [I > 2σ(I)]	R1 = 0.0219, wR2 = 0.0564	
R indices (all data)	R1 = 0.0234, wR2 = 0.0574	
Largest diff. peak and hole	0.17 and -0.14 e.Å ⁻³	
Absolute structure parameter (Flack)	0.003(16) for 1411 Friedel pairs	
Absolute structure parameter (Hooft)	-0.003(8) for 1218 Friedel pairs	
Hooft probability analysis	P2(correct) > 99.9999%, P3(correct) > 99.9999%	

Table 6.2 Crystal data and structure refinement for **166**.

Identification code	013eaa18	
Empirical formula	C18 H23 I1 O3 Si1	
Formula weight	442.37	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.74910(10) Å	$\alpha = 90^\circ$.
	b = 10.7705(2) Å	$\beta = 90.519(2)^\circ$.
	c = 16.6286(3) Å	$\gamma = 90^\circ$.
Volume	1029.61(3) Å ³	
Z	2	
Density (calculated)	1.427 Mg/m ³	
Absorption coefficient	12.862 mm ⁻¹	
F(000)	444.000	
Crystal size	0.09 x 0.07 x 0.01 mm ³	
Theta range for data collection	4.892 to 76.342°.	
Index ranges	-7 ≤ h ≤ 7, -13 ≤ k ≤ 13, -20 ≤ l ≤ 20	
Reflections collected	21593	
Independent reflections	4271 [R(int) = 0.0565]	
Completeness to theta = 76.342°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.88 and 0.49	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4270 / 391 / 264	
Goodness-of-fit on F ²	0.9937	
Final R indices [I > 2σ(I)]	R1 = 0.0280, wR2 = 0.0684	
R indices (all data)	R1 = 0.0306, wR2 = 0.0705	
Largest diff. peak and hole	0.71 and -0.49 e.Å ⁻³	
Absolute structure parameter (Flack)	-0.022(6) for 1951 Friedel pairs	
Absolute structure parameter (Hooft)	-0.032(6) for 1589 Friedel pairs	
Hooft probability analysis	P2(correct) > 99.9999%, P3(correct) > 99.9999%	

Table 6.3 Crystal data and structure refinement for Rubriflodilactone-B (**3**).

Identification code	020eaa18	
Empirical formula	C ₂₈ H ₃₀ O ₆	
Formula weight	462.54	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.16740(10) Å	$\alpha = 90^\circ$.
	b = 10.77070(10) Å	$\beta = 90^\circ$.
	c = 21.5191(3) Å	$\gamma = 90^\circ$.
Volume	2356.56(5) Å ³	
Z	4	
Density (calculated)	1.304 Mg/m ³	
Absorption coefficient	0.740 mm ⁻¹	
F(000)	984	
Crystal size	0.16 x 0.16 x 0.02 mm ³	
Theta range for data collection	4.109 to 75.911°.	
Index ranges	-12 ≤ h ≤ 10, -13 ≤ k ≤ 12, -27 ≤ l ≤ 26	
Reflections collected	41106	
Independent reflections	4900 [R(int) = 0.0452]	
Completeness to theta = 75.911°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.89	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4898 / 0 / 308	
Goodness-of-fit on F ²	1.0084	
Final R indices [I > 2σ(I)]	R1 = 0.0337, wR2 = 0.0874	
R indices (all data)	R1 = 0.0359, wR2 = 0.0899	
Largest diff. peak and hole	0.29 and -0.16 e.Å ⁻³	
Absolute structure parameter (Flack)	-0.087(15) for 2042 Friedel pairs	
Absolute structure parameter (Hooft)	-0.034(6) for 1689 Friedel pairs	
Hooft probability analysis	P2(correct) > 99.9999%, P3(correct) > 99.9999%	

Table 6.4 Crystal data and structure refinement for **319b**.

Identification code	DIA0360
Empirical formula	C ₁₈ H ₂₃ I O ₃ Si
Formula weight	442.37
Temperature	100 K
Wavelength	0.68890 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 5.59160(10) Å α = 90°. b = 11.18080(10) Å β = 90°. c = 31.4928(4) Å γ = 90°.
Volume	1968.88(5) Å ³
Z	4
Density (calculated)	1.492 Mg/m ³
Absorption coefficient	1.541 mm ⁻¹
F(000)	888
Crystal size	0.14 x 0.01 x 0.01 mm ³
Theta range for data collection	1.873 to 36.035°.
Index ranges	-9 ≤ h ≤ 9, -18 ≤ k ≤ 18, -52 ≤ l ≤ 51
Reflections collected	40497
Independent reflections	9616 [R(int) = 0.064]
Completeness to theta = 34.323°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.69
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9606 / 0 / 209
Goodness-of-fit on F ²	1.0130
Final R indices [I > 2σ(I)]	R1 = 0.0340, wR2 = 0.0829
R indices (all data)	R1 = 0.0378, wR2 = 0.0843
Largest diff. peak and hole	1.17 and -1.08 e.Å ⁻³
Absolute structure parameter (Flack)	-0.018(10) for 4051 Friedel pairs
Absolute structure parameter (Hooft)	-0.020(8) for 3881 Friedel pairs
Hooft probability analysis	P2(correct) > 99.9999%, P3(correct) > 99.9999%

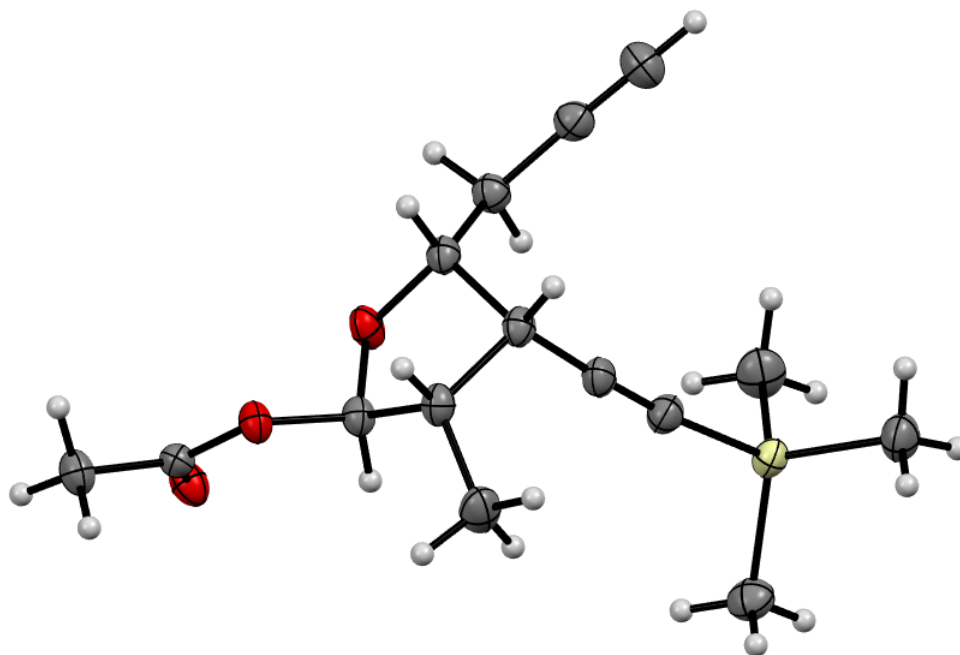


Figure 6.1: Solid state structure of **160a**. Displacement ellipsoid plots are drawn at 50% probability.

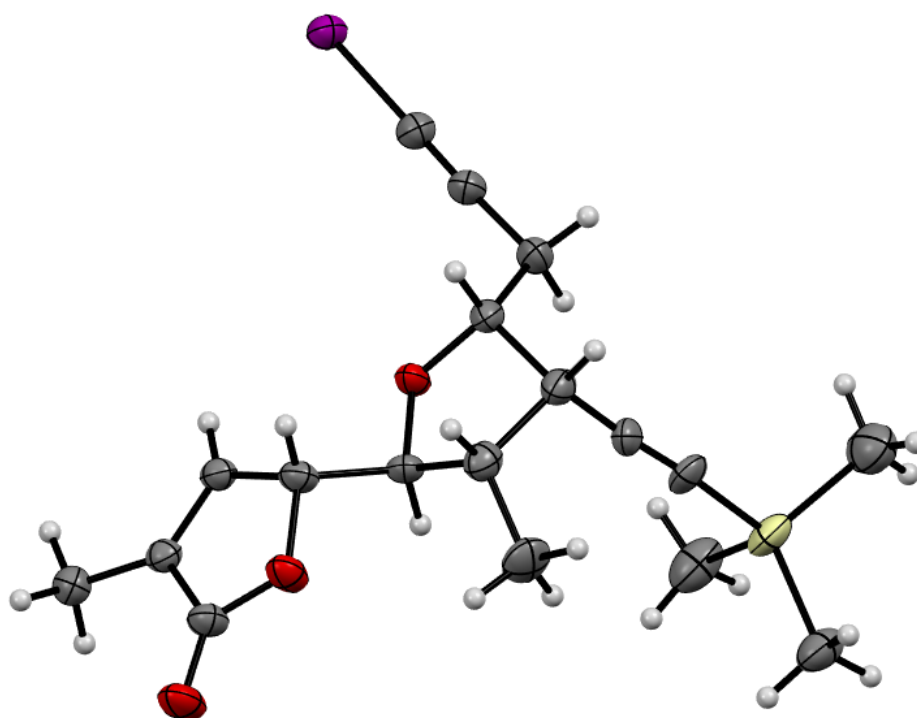


Figure 6.2: Solid state structure of **166**. Displacement ellipsoid plots are drawn at 50% probability.

Disordered components are omitted for clarity

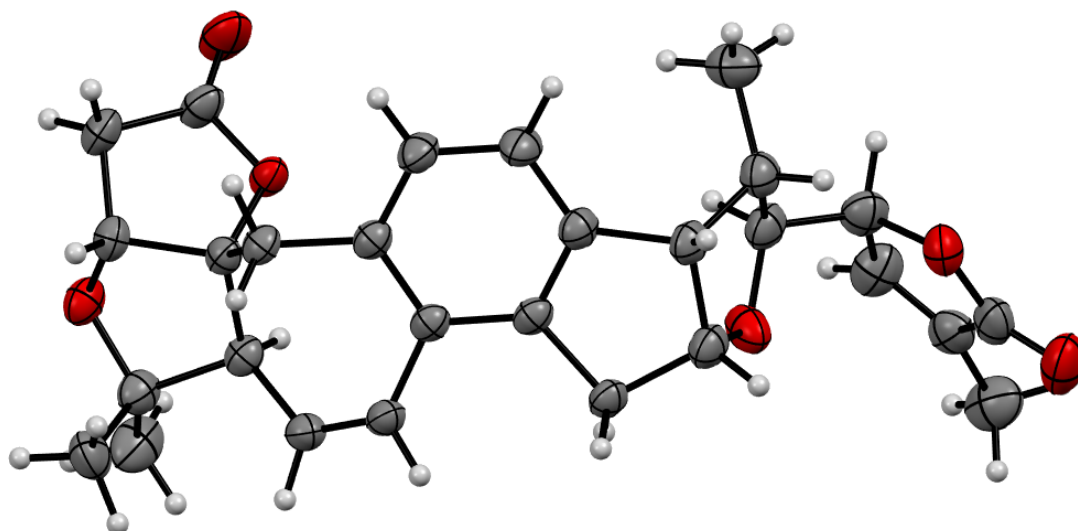


Figure 6.3: Solid state structure of Rubriflorldilactone B (**3**). Displacement ellipsoid plots are drawn at 50% probability.

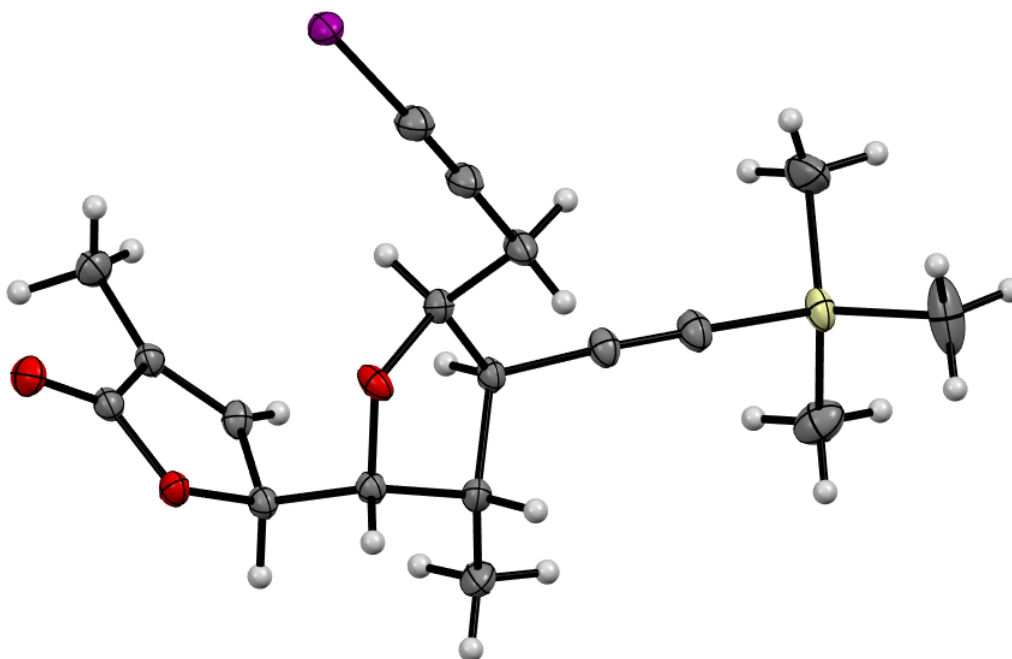


Figure 6.4: Solid state structure of **319b**. Displacement ellipsoid plots are drawn at 50% probability.

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