Palladium-Catalysed Cascade Cyclisation of Alkynyl Silanes and Studies Towards Rubriflordilactone A

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Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
AIBN	Azobisisobutyronitrile
app.	Apparent
BDMS	Benzyldimethylsilyl
brsm	Based on Recovered Starting Material
CAN	Ceric Ammonium Nitrate
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
dr	Diasteromeric ratio
EA	Elemental Analysis
EC_{50}	Half Maximal Effective Concentration
EDC	1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide
ee	Enantiomeric Excess

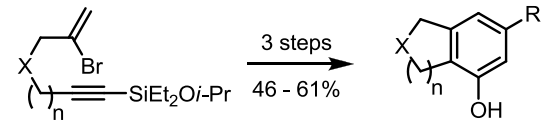
equiv.	Equivalent
ES	Electrospray
EWG	Electron Withdrawing Group
HMBC	Heteronuclear Multiple-bond Correlation Spectroscopy
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HPLC	High-performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
HSQC	Heteronuclear Single-quantum Correlation Spectroscopy
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IBX	2-Iodoxybenzoic Acid
Imid.	Imidazole
IPA	Isopropyl Alcohol
Ipc	Isopinocampheyl
IR	Infra-red
J	Coupling Constant
LAH	Lithium Aluminium Hydride
LDA	Lithium Diisopropylamide
m	Multiplet
m-CPBA	*meta*-Chloroperoxybenzoic Acid
MOM	Methoxymethyl
MS	Molecular Sieves
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect

PCC	Pyridinium Chlorochromate
PMB	*para*-Methoxybenzyl
ppm	Parts Per Million
PPTS	Pyridinium *p*-toluenesulfonate
Py.	Pyridine
q	Quartet
qu	Quintet
quant.	Quantitative
RCM	Ring Closing Metathesis
RDS	Rate Determining Step
R_f	Retention Factor
RT	Room Temperature
s	Singlet
SM	Starting Material
t	Triplet
TBA	Tetra-*n*-butylammonium
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMP	2,2,6,6-Tetramethylpiperidin-1-ide
TMS	Trimethylsilyl

TMTU	Tetramethylthiourea
Ts	Tosyl
UV	Ultra-violet

Abstract

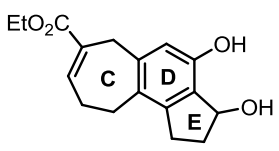
In this work, a new methodology for the synthesis of a number of silylated bicyclic dienes has been reported. These bicyclic dienes allowed access to a variety of enones and phenols in 2 further steps.



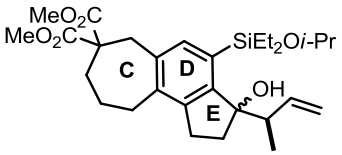
X = $(MeO_2C)_2C$, NTs, O

The stabilities and reactivities of different dialkylisopropoxy silanes have been evaluated, revealing relative instability of the dimethylisopropoxy silyl group towards chromatography. When using the analogous diethylisopropoxy silyl group instead, the products showed greater stability towards chromatography, however a higher temperature was necessary to oxidise the more sterically hindered silyl group to the desired hydroxyl moiety.

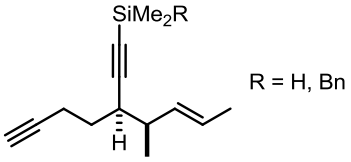
A powerful cascade cyclisation for the synthesis of the CDE-core of rubriflordilactone A was then demonstrated and was successfully used for the synthesis of two systems, **284** and **333**.



284



333



405

The phenolic oxygen has been successfully installed by oxidation of a dialkylisopropoxy silane. The synthesis of these ring systems provides a solid foundation for the completion of the total synthesis of rubriflordilactone A.

Finally the synthesis of suitable diynes **405** for the synthesis of the acyclic precursor of the cyclisation has been achieved. The stabilities of theses silanes towards a range of reaction have been demonstrated.

1. Introduction: The *Schisandra* Natural Products

1.1. Isolation

Plants from the genus Schisandra have long been employed in traditional Chinese medicine, for a wide range of purposes such as sedatives and tonic agents and for the treatment of hepatitis.[1, 2] In the past 10 years, the Sun group in China has identified over 70 highly oxygenated nortriterpenoids from the Schisandra plant family, which show various beneficial pharmacological effects, such as antihepatitis, antitumor, and anti-HIV activity (exhibiting EC_{50} values varying from 7 $\mu g.mL^{-1}$ to > 100 $\mu g.mL^{-1}$).[2-9] These varied and interesting medicinal properties make these compounds important targets from a research perspective, in addition to the synthetic challenge presented by their complex frameworks (Figure 1).

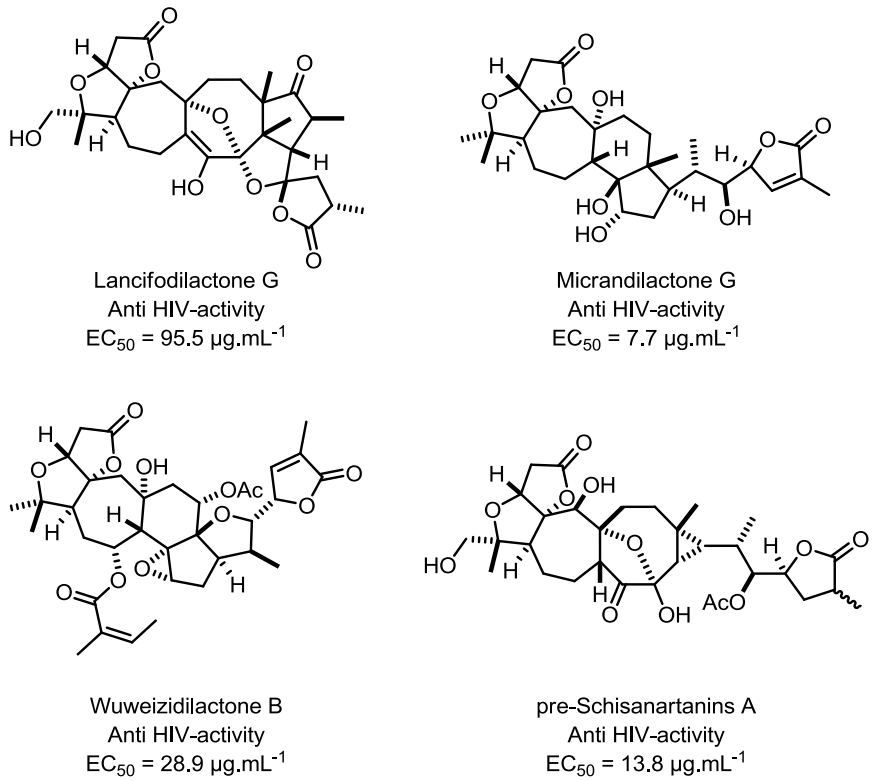


Figure 1 – Selection of natural products of the Schisandra family and anti-HIV activities

Due to the skeletal diversity of the *Schisandra* nortriterpenoids, they have been divided into six sub-groups based on patterns of oxygenation and carbon skeletons: schisanartane **1**, schiartane **2**, 18-nor-schiartane **3**, 18(13→14)-*abeo*-schiartane **4**, pre-schiasanartane **5** and wuweiziartane **6** (Figure 1).[1]

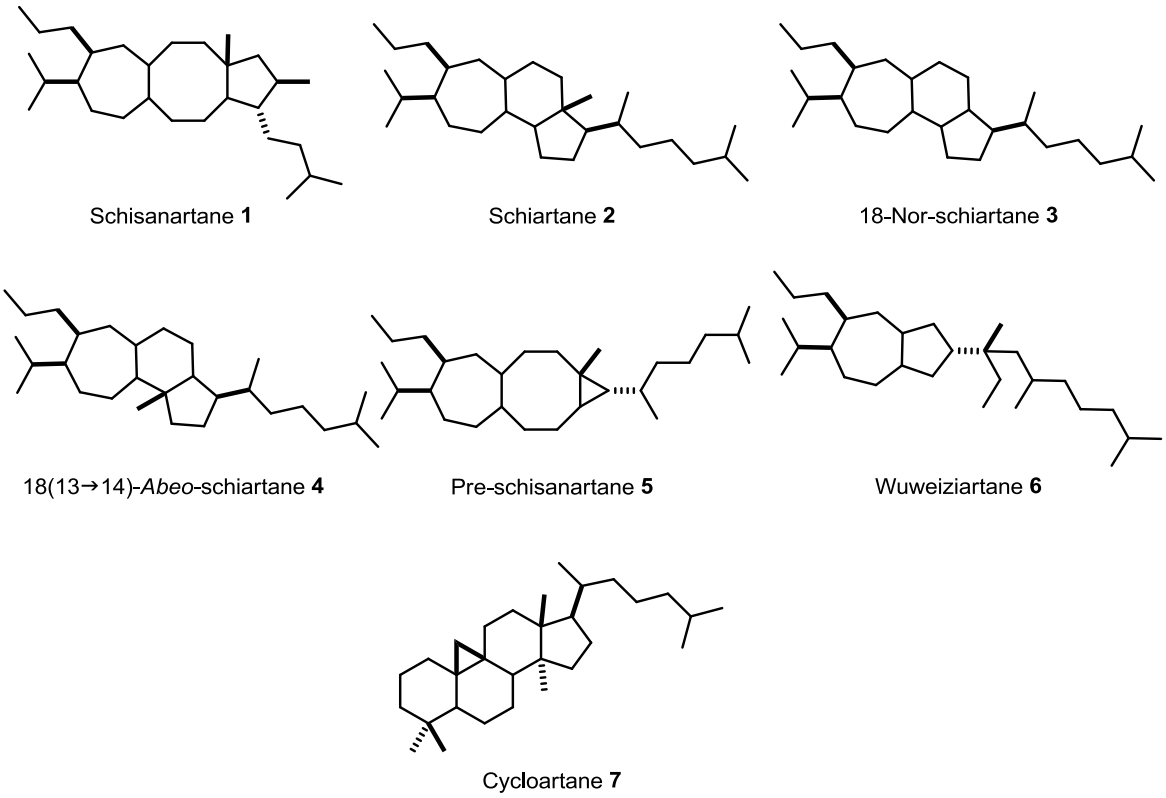
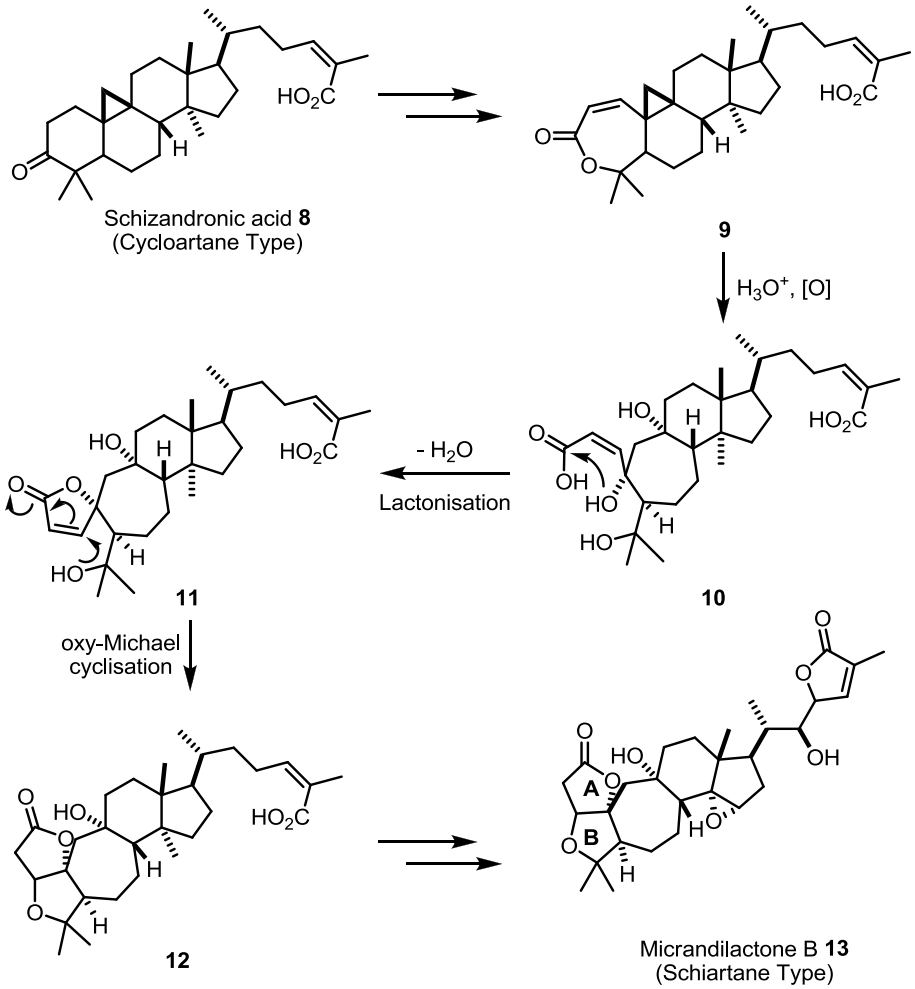


Figure 2 – Schisandra nortriterpenoid skeletons

1.2. Biosynthesis

The *Schisandra* nortriterpenoids are thought to have evolved biosynthetically from the cycloartane skeleton **7** (Figure 1).[1,10] Of the six skeletons of the *Schisandra* nortriterpenoids, the schiartane skeleton **2** featured in micrandilactone B is considered to be the first on the biosynthetic pathway (Scheme 1). Sun and co-workers reasoned that the AB-ring system should be formed early in the biosynthesis as it is common to the majority of compounds of the *Schisandra* family.[1, 10] Starting from schizandronic acid (cycloartane) **8**, the AB ring system is thought to be formed from an oxidative ring expansion of the cyclohexanone to **9**, followed by an acid-catalysed ring-opening of the cyclopropane and

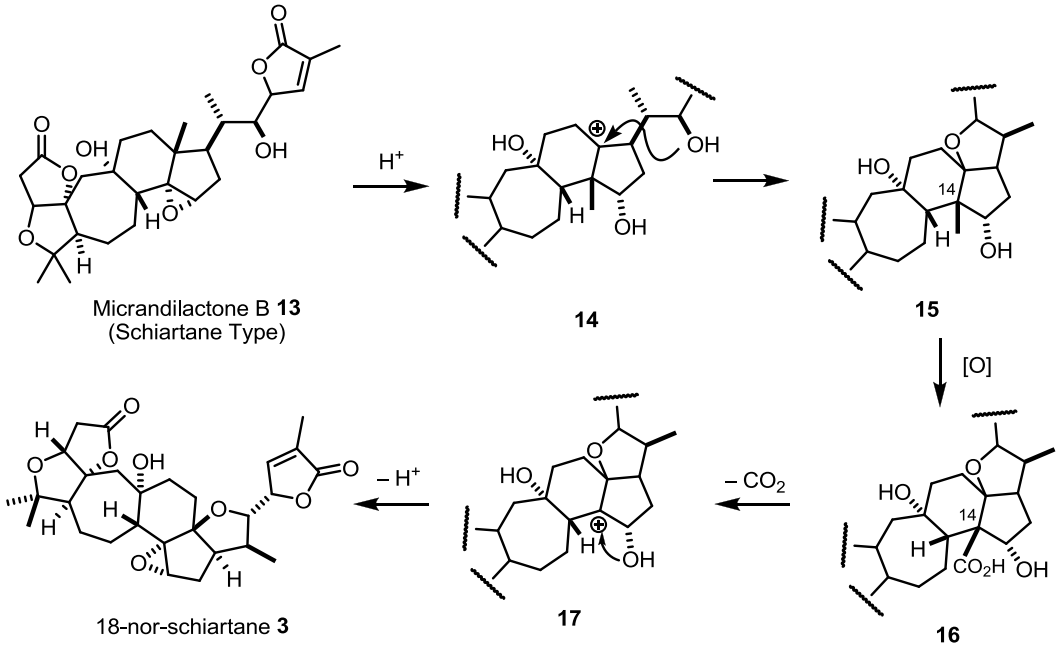
oxidation to form the seven-membered ring in product **10**. Finally, lactonisation and oxy-Michael cyclisation would form the AB ring system in **12**. Subsequent rearrangements and reactions of compound **12** would form product **13** of the Schiartane type, such as micrandilactone B, which is the starting point for the formation of many of the other skeleton types (Scheme 1).



Scheme 1 – Proposed biosynthesis of the Schiartane type

The biosynthesis of the other skeletons can be described from micrandilactone B **13**.[1] Scheme 2 suggests a mechanism for the formation of the 18-nor-schiartane type skeleton **3**. An enzymatic epoxide opening followed by a 1,2-methyl shift would afford intermediate **14**. Attack of the sidechain OH group onto the tertiary cation is followed by oxidation of the C14 methyl group affording carboxylic acid **16**, which on decarboxylation gives

intermediate **17**. Finally, epoxide formation would give the 18-nor-schiartane skeleton **3** (Scheme 2).[2, 4, 11]



Scheme 2 –Biosynthesis of the 18-nor-schiartane type skeleton

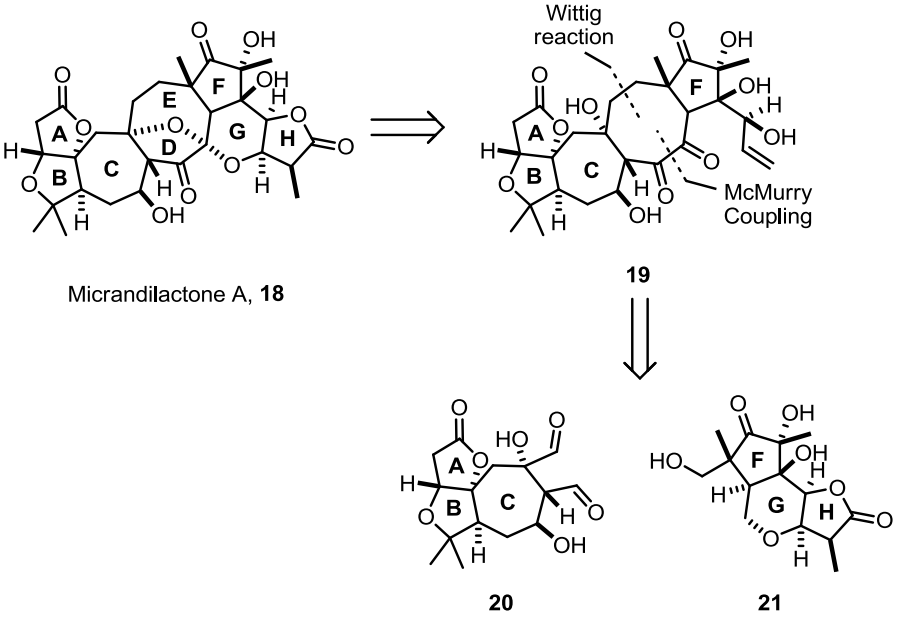
1.4. Synthetic Approaches towards Natural Products of the Schisandra Family: Retrosyntheses

1.4.1. Micrandilactone A

Micrandilactone A **18** (Scheme 3) was isolated from *Schisandra micrantha*, a medicinal plant which was traditionally used for the treatment of lumbago and traumatic injury, and was one of the first *Schisandra* natural products to be isolated.[8, 12-14] This natural product was immediately distinguished by its novel triterpene framework and highly oxygenated functionality. The molecule contains 13 stereogenic centres and 14 oxygenated carbons.

In 2005, Yang and co-workers proposed a convergent synthetic plan for the total synthesis of micrandilactone A (Scheme 3).[15-17] Their retrosynthesis led them to the disconnection of two peripheral fragments, the ABC ring system **20** and the FGH ring system **21** using

Wittig and McMurry reactions;[18] both fragments would require suitably functionalised handles to enable their coupling and the construction of the D and E rings.



Scheme 3 – Proposed retrosynthesis of micrandilactone A

In 2010, the Ghosh group proposed a synthesis of the ABC fragment common to micrandilactone A and other *Schisandra* nortriterpenoids.[19] The retrosynthesis led them to design fragment **22** (Figure 3) containing a functionalised 7-membered ring which would allow further elaboration towards the natural product. This route was designed to be tuneable in order to obtain, from a common precursor, products **22a** (from micrandilactone A) and **22b** (from lancifodilactone G, see Scheme 5).

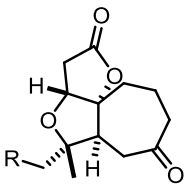
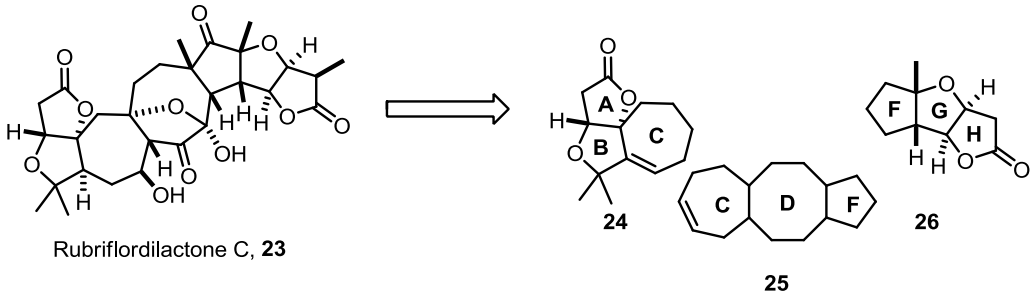


Figure 3 – ABC ring system of the Schisandra nortriterpenoids

1.4.2. Rubriflordilactone C

In 2010, Mehta and co-workers presented their approach to the ABC ring system of rubriflordilactone C (**23**, Scheme 4), a natural product featuring a unique FGH ring system.[20] The retrosynthetic analysis led them to disconnect the molecule into two peripheral fragments **24** and **26** (Scheme 4). These two fragments both possess a common furo[3,2-*b*]furanone core, which could be accessible *via* an appropriate bidirectional approach based on the Morita-Baylis-Hillman reaction.[13, 14, 20]

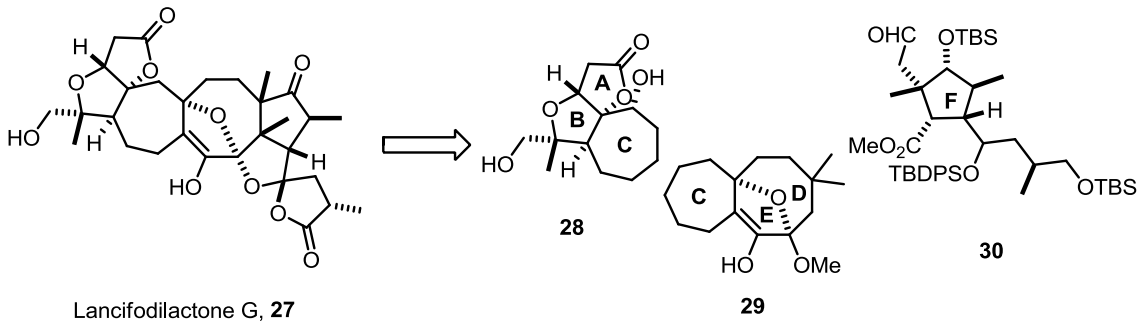


Scheme 4 – Retrosynthesis fragments

In addition, in 2011, the Mehta group reported a study towards the synthesis of the central CDEF ring system of molecules of the schisanartane group, in which rubriflordilactone C belongs.[21]

1.4.3. Lancifodilactone G

In 2008, the Paquette group proposed two disconnections for the synthesis of lancifodilactone G **27** and three fragments were designed; again this strategy relies on a division by sector of this very challenging natural product (Scheme 5).[22-24]

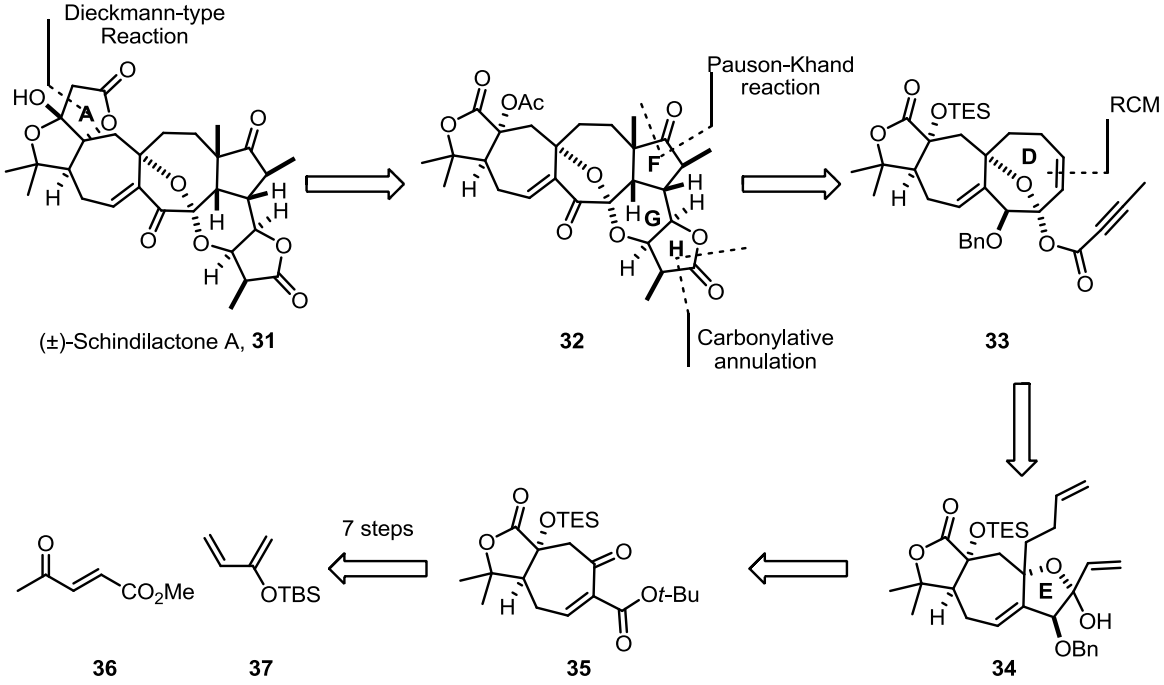


Scheme 5 – Retrosynthesis of lancifodilactone G

1.4.4. Schindilactone A

To date, only one member of the *Schisandracea* family of natural products has been prepared by total synthesis. In 2011, the Yang group achieved the total synthesis of racemic schindilactone A (**31**, Scheme 6) in 29 steps and 0.2% overall yield.[9]

For this purpose, 5 disconnections were proposed. The A ring would be formed last in the sequence via a Dieckmann-type reaction on acetate **32**.[25, 26] The FGH ring system would be formed from **33** *via* the sequence previously described by the Yang group for the synthesis of the right-hand side of micrandilactone A exhibiting the same system,[15, 27, 28] *i.e.* a carbonylative annulation to form the H ring and a Pauson-Khand reaction for the synthesis of the G ring. The D ring on compound **33** would be obtained *via* a RCM reaction on tricycle **34**.[29] The E ring hemiketal would be obtained from intermediate **35**. This intermediate would be formed in 7 steps from **36** and **37** (Scheme 6).



Scheme 6 – Proposed retrosynthesis of schindilactone A

In summary most of the retrosyntheses of *Schisandra* natural products, apart from schindilactone A, were disconnected in two or three spatial fragments. The syntheses described in the rest of this chapter are divided in three sub-groups; the left-hand, right-hand and centre ring systems of these natural products. Following this the total synthesis of schindilactone A will be discussed, and finally our own planned approach to this natural product family will be introduced.

1.5. Studies Towards the Synthesis of the Left-Hand ABC Ring Systems of the Schisandra Natural Products

The AB ring fragment (Figure 4) is a motif common to all family members,[1] and its complex architecture, incorporating four stereocentres, attracted many groups to attempt a synthesis. The AB ring system of rubriflordilactones A and B is the most abundant and appears in about 90% of the natural products of the *Schisandra* family.[7]

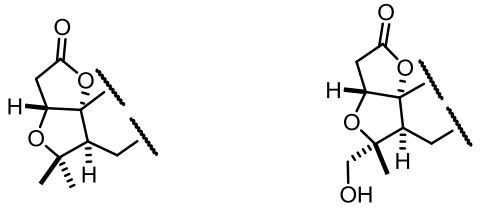
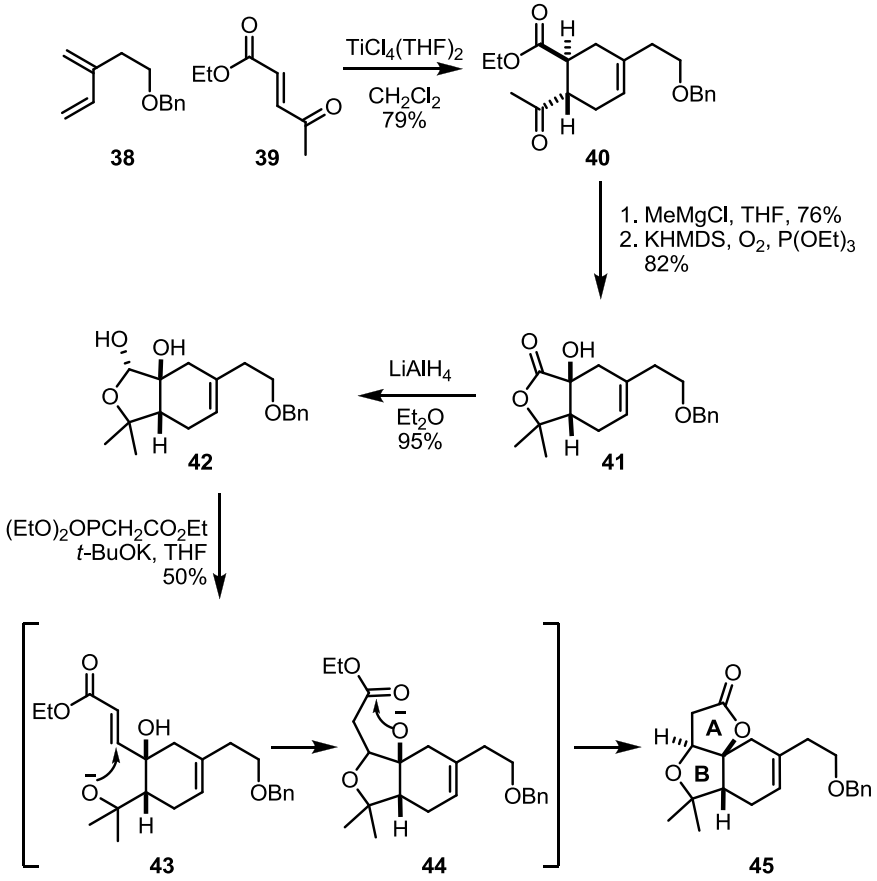


Figure 4 –AB ring systems common to many Schisandra natural products

1.5.1. Micrandilactone A (Yang)[16]

The Yang synthesis started with an intermolecular Diels-Alder reaction between diene **38** and dienophile **39** using $TiCl_4(THF)_2$ complex as a catalyst, giving product **40** in 79% yield as a single regio and diastereoisomer.[30] Lactone **41** was formed *in situ* in 76% yield after addition of MeMgCl to ketone **40** followed by treatment of the resulting ketone with KHMDS/O_2 in the presence of $P(OEt)_3$.[31-33] The lactone functionality was then reduced

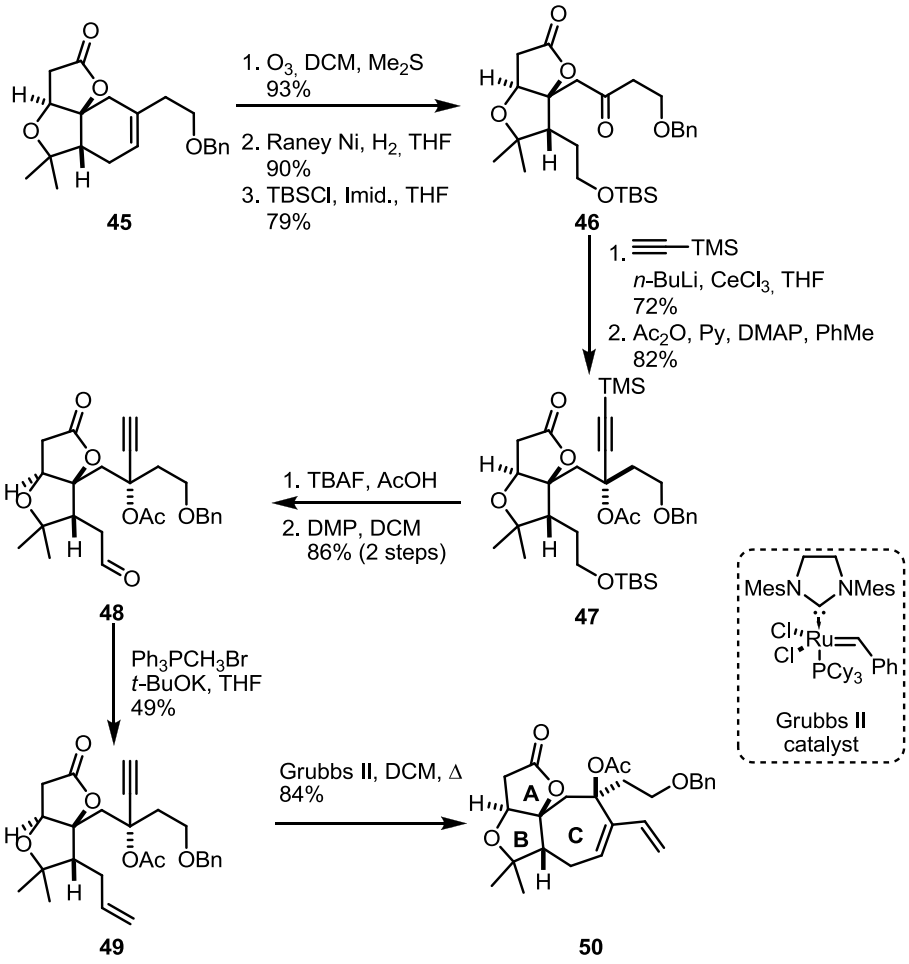
with $LiAlH_4$ in 95% yield and a Horner-Wadsworth-Emmons (HWE) reaction was performed on the lactol to give the corresponding α-β-unsaturated ester **43**, which underwent *in situ* oxy-Michael addition and lactonisation to form the AB ring system in product **45** in 50% yield (Scheme 7).



Scheme 7 – Formation of the AB ring system

With compound **45** in hand, the Yang group proceeded to form the 7-membered C ring. The cyclohexene ring was cleaved *via* ozonolysis, and reduction of the ozonide with dimethyl sulfide gave the corresponding keto-aldehyde (93% yield). Reduction of the aldehyde moiety with Raney nickel furnished the terminal alcohol in 90% yield, which was converted immediately to the corresponding TBS ether **46** (79%). Addition of TMS-acetylide, in preparation for the later enyne ring-closing metathesis, was achieved in the presence of a catalytic amount of $CeCl_3$ at –78 °C, and gave a tertiary alcohol which was

converted into the corresponding acetate **47** in 43% yield over 2 steps. The TBS ether and TMS alkyne were then cleaved with TBAF and the alcohol was re-oxidised to form aldehyde **48** using Dess-Martin periodinane (DMP) in 86% yield. Aldehyde **48** was converted into the corresponding alkene **49** *via* a Wittig olefination in a modest yield of 49% before undergoing the final key ring-closing enyne metathesis step (84% yield)[34, 35] to afford the ABC ring system **50** in a total of 14 steps with 3% overall yield (Scheme 8).[16]

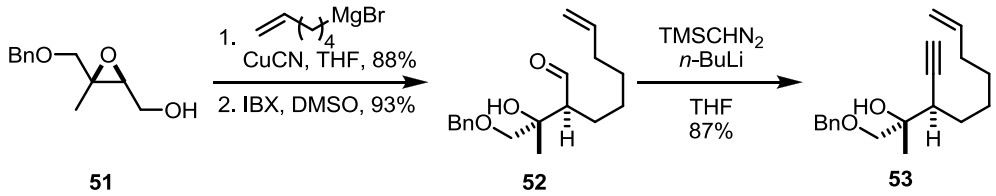


Scheme 8 – Synthesis of the ABC ring system of micrandilactone A

The main advantage of this synthesis is the very efficient synthesis of the 7-membered ring common to all of the *Schisandra* natural products, with simple modifications of the side chain in products **38** and **39** allowing further transformations for the synthesis of more elaborate systems.

1.5.2. Lancifodilactone G (Paquette)[24]

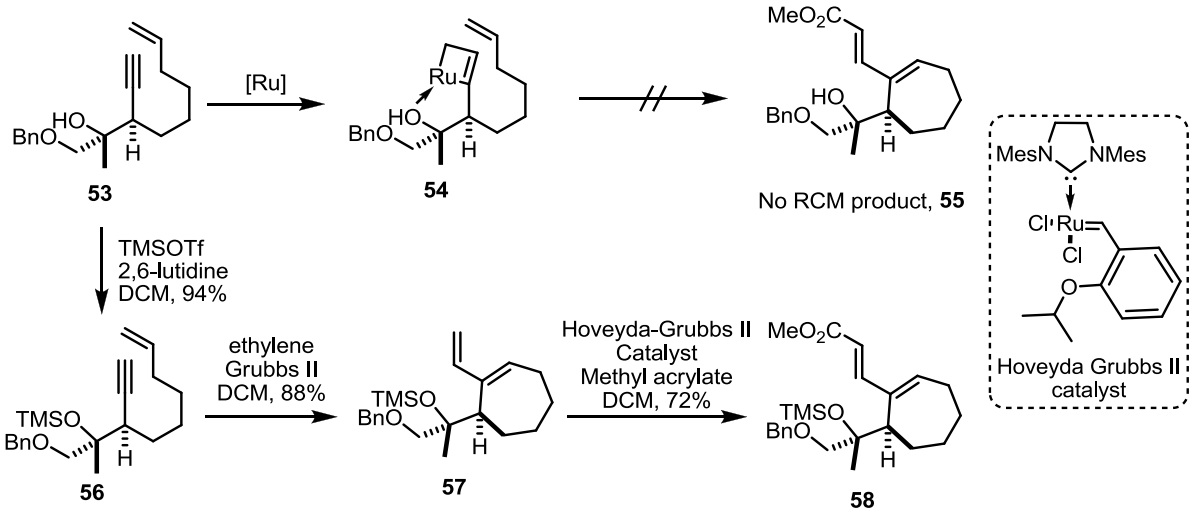
In 2008, the Paquette group turned their interest towards the asymmetric synthesis of lancifodilactone G (**27**, Figure 1), and published a short 11-step route to the ABC ring system,[24] a very challenging small molecule bearing two quaternary centres in the B ring, and a fused lactone A ring. Similar to the previously described synthesis of Yang,[16] the formation of the A ring was envisaged *via* a base-mediated *pseudo*-biomimetic oxy-Michael addition-lactonisation sequence. Similarly the C ring would be formed using an enyne RCM reaction,[34] but in comparison to the Yang group, the formation of the C ring would be attempted early in the synthesis. With these ideas, the synthesis started with known epoxy alcohol **51**,[36] exhibiting the requisite stereochemistry. The epoxide **51** was first opened with the organocuprate reagent derived from hexenylmagnesium bromide in 88% yield, and the primary alcohol was oxidised by IBX to aldehyde **52** (93%). A Colvin rearrangement on aldehyde **52** gave the desired enyne **53** in 87% yield (Scheme 9).[37]



51 **52** **53**

Scheme 9 – RCM substrate synthesis

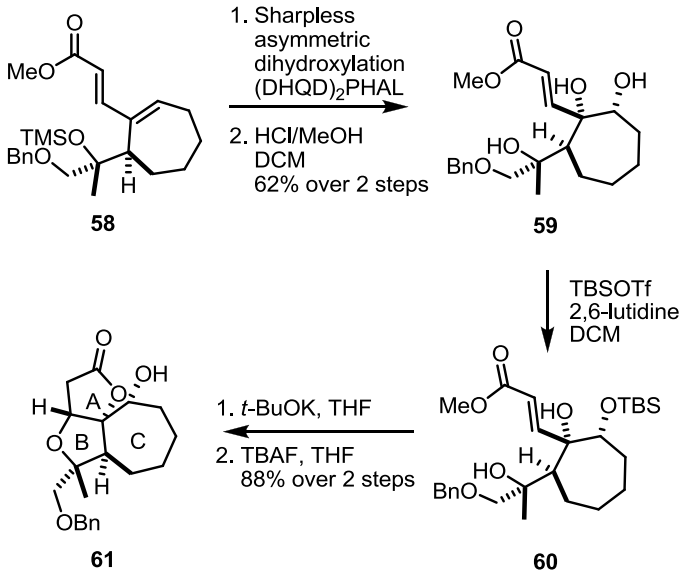
The Paquette group anticipated that the enyne RCM could be performed directly on compound **53** (Scheme 10). Unfortunately, all attempts failed and the RCM was only successful after protection of the hydroxyl functionality, giving the product **57** in 83% yield over 2 steps. This result can be explained by the formation of a stable vinyl alkylidine **54** which is presumably impeding the metathesis.[24]



Scheme 10 – RCM studies

With this 7-membered C ring product **57** in hand, the Michael acceptor required for the final cyclisation was introduced *via* a cross-metathesis reaction using the Hoveyda-Grubbs catalyst and methyl acrylate; the product **58** was formed in a good 72% yield with complete (*E*)-selectivity (Scheme 10).

The endocyclic alkene was then oxidised using a regio- and diastereoselective dihydroxylation to form the corresponding diol (Scheme 11), installing the alcohol required for subsequent lactone formation. The TMS ether was cleaved under acidic conditions to form triol **59** in 62% yield over 2 steps. The less hindered secondary alcohol was successfully protected as a TBS ether to form diol **60**. Finally, upon treatment with *t*-BuOK in THF, the cascade intramolecular oxy-Michael addition occurred to form the B ring followed by lactonisation to build the remaining A ring, affording tricycle **61**. The desired ABC tricycle was obtained in an impressive 88% yield over 2 steps after a TBAF deprotection of the TBS group (Scheme 11).

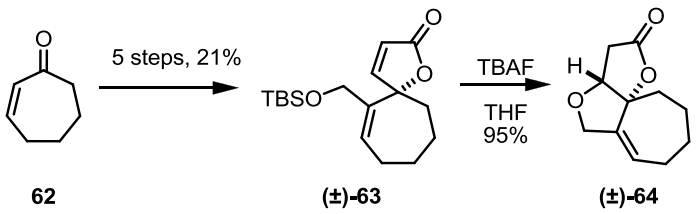


Scheme 11 – ABC ring system synthesis

The main advantage of this route lies in the relatively high yield (19% overall) and low number of steps (11). However as lancifodilactone G features a slightly modified AB ring system, this synthesis appears to be limited to this natural product. The most significant drawback with this synthesis is the limited scope for further ring formation, as the C ring bears no functionality. This synthesis would clearly require a large number of adjustments in order to be applicable to the total synthesis of lancifodilactone G.

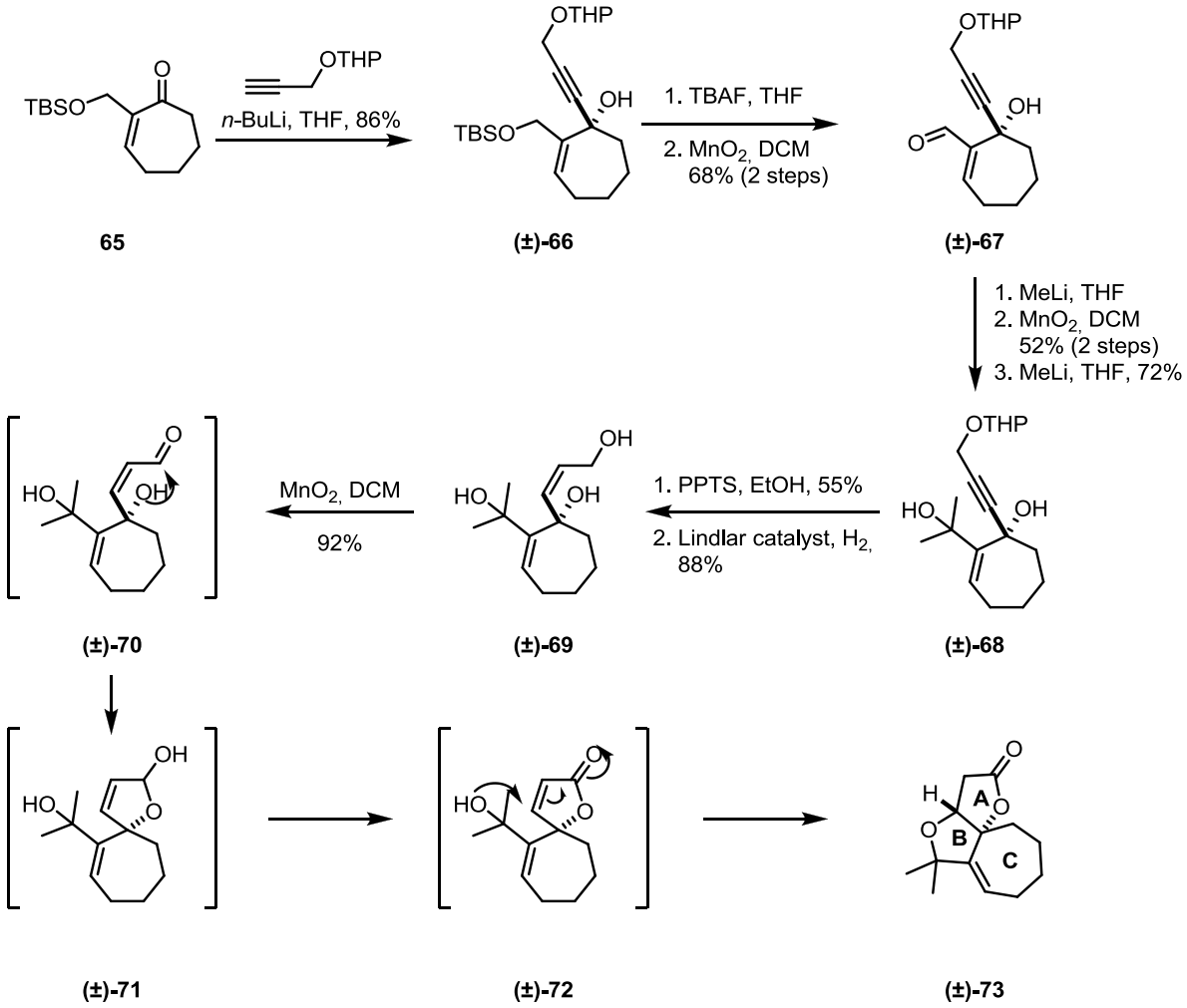
1.5.3. Rubriflordilactone C (Mehta)[38]

As a proof of principle, the synthesis was first investigated using cycloheptenone **62**. The Mehta group demonstrated a racemic synthesis of a model of the ABC ring system of the *Schisandra* natural products in 6 steps and 20% yield (Scheme 12).[38]



Scheme 12 – Model system studies

With the success of this strategy, the sequence was adapted to access the desired scaffold **24** (Scheme 13). The synthesis started from **65** which was propargylated to give THP-protected alcohol **66** (86%). TBS deprotection followed by MnO_2 oxidation gave aldehyde **67** in 68% yield over 2 steps. The tertiary alcohol **68** was introduced by sequential addition of MeLi, oxidation and second addition of MeLi in 37% yield over 3 steps. THP removal under acidic conditions followed by a regio- and stereoselective semi hydrogenation of the alkyne moiety gave **69** in 48% yield over 2 steps. The MnO_2 oxidation of **69** triggered a cascade reaction to form directly the desired tricycle ABC **24** involving an oxy-Michael addition in the intermediate butenolide **71** (Scheme 13).

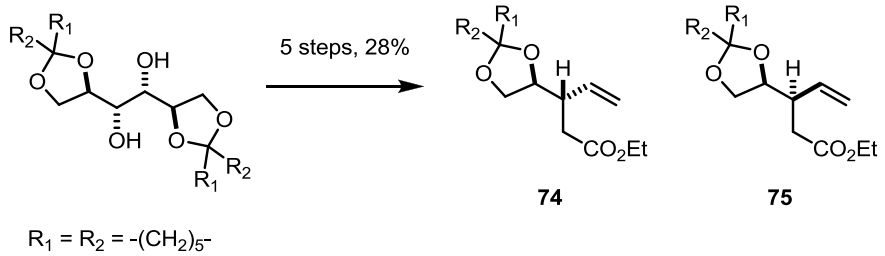


Scheme 13 – ABC ring system synthesis

Again, the main advantage of this racemic synthesis is its relatively high yield and short sequence: 9 steps from **65**, 10% overall yield. But as noted in Paquette's synthesis, its limited application has to be raised, as here again the C ring bears no functionality.

1.5.4. Micrandilactone A (Ghosh)[19]

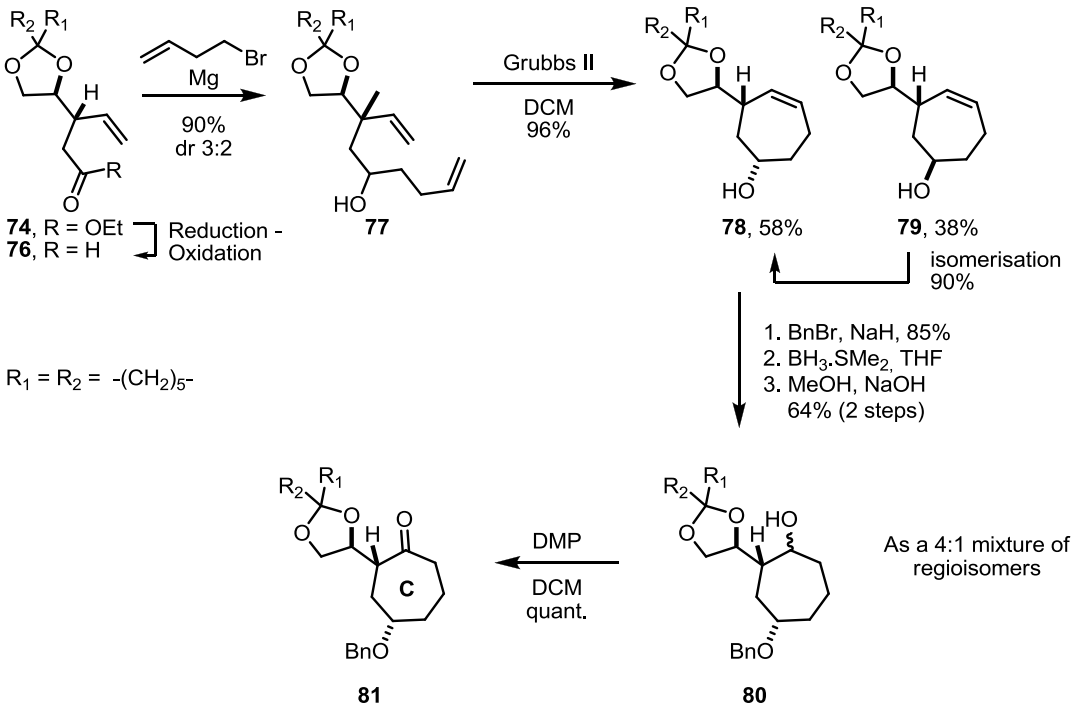
In 2010, the Ghosh group reported an asymmetric synthesis of the ABC fragment of micrandilactone A **18**.[19] The synthesis started with the enantioselective construction of the cycloheptanone ring. For this purpose, the readily available ester **74** was chosen and prepared from cheap commercially available D-mannitol in 5 steps and 28% yield as a separable 1:1 mixture of diastereomers (Scheme 14).[39]



Scheme 14 – Synthesis of esters 74 and 75

Strangely only ester **74** was carried through the sequence. This compound was expected to lead to *epi*-**22a**, but it was thought that the epimeric stereocentre could be inverted later in the synthesis. The ester was converted into aldehyde **76** *via* a two step reduction-oxidation sequence (Scheme 15),[40] and was subsequently reacted with Grignard derivative of 4-bromobut-1-ene to afford alcohol **77** as a mixture of diastereomers in 90% yield. A ring-closing metathesis with Grubbs II catalyst afforded cycloheptenols **78** and **79** which could be separated by column chromatography in 38% and 58% yield respectively, and the minor isomer could be isomerised using a Mitsunobu reaction in 90% yield. The free hydroxyl group was protected as the corresponding benzyl ether in 85% yield, and a hydroboration reaction was performed on the endocyclic alkene with moderate regioselectivity (4:1) in a

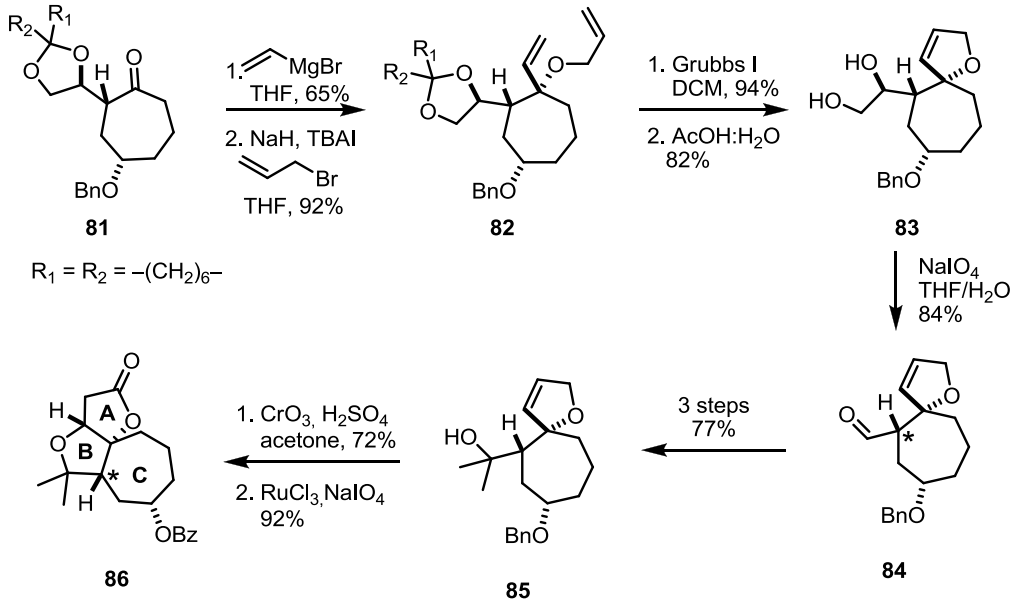
moderate yield of 64%.[41] The two regioisomers could be separated by careful column chromatography. Finally, a DMP oxidation on alcohol **80** produced the ketone **81** in quantitative yield.



Scheme 15 – Formation of the C ring

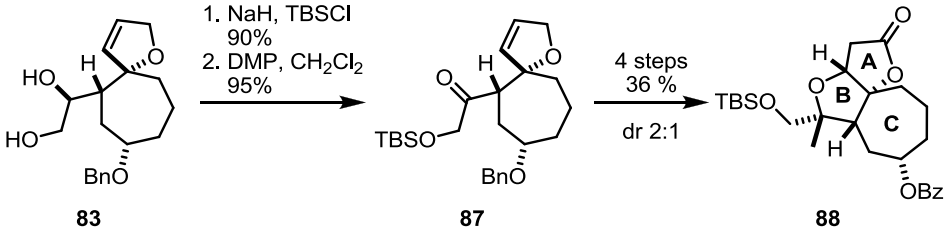
With the formation of the C ring completed, the synthesis moved on to the elaboration of the furofuranone unit (Scheme 16). Ketone **81** was treated with vinyl magnesium bromide to afford the corresponding alcohol in 65% yield as a single diastereomer which was treated with sodium hydride and allyl bromide to form the ether **82** in 92% yield. The diene was exposed to Grubbs I catalyst to form the furanone in 94% yield and the acetal was immediately removed under acidic condition in 82% yield to form diol **83**. Oxidative cleavage of the diol gave aldehyde **84** which was methylated twice in a 3 step process; the A ring butenolide was obtained by treatment of **85** with Jones reagent which underwent spontaneous intramolecular 1,4-addition to form the B ring. A final oxidation the benzyl

moiety in the presence of $RuCl_3/NaIO_4$ smoothly afforded the furofuranone derivative **86** in 92% yield (Scheme 16).



Scheme 16 – ABC ring system synthesis

In addition, from intermediate **87** a single methylation can be performed forming the *epi*-ABC ring **88** of lancifodilactone G in 4 steps (Scheme 17).



Scheme 17 – Modified route for the ABC ring system of lancifodilactone G

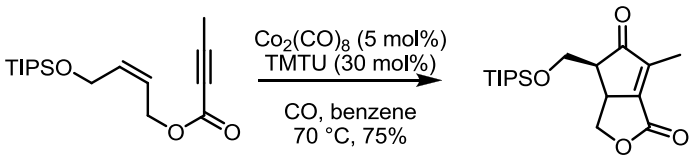
Overall, this synthesis seems to have achieved its goal, as it proves to be adaptable to the synthesis of different AB ring systems in a very convergent manner. However the synthesis requires a large number of steps: 22 to form ring system **86** in 2% overall yield, and **88** in 1% overall yield. In addition the wrong stereochemistry at C* needs to be addressed. It is worth noting that by starting the synthesis with ester **75** instead of **74**, the correct

stereochemistry could have been obtained (Scheme 14). This has not been discussed by Ghosh and may suggest **75** does not perform well in this sequence. Rather, he suggests to have the C* centre isomerised at a late stage, but this has not been shown and seems only to be possible on aldehyde **84** (Scheme 16).[19]

1.6. Studies Towards the Synthesis of the Right-Hand Ring Systems of the Schisandra Natural Products

1.6.1. Micrandilactone A (Yang)[15]

In 2005, Yang and co-workers proposed a synthesis of the FGH ring system of micrandilactone A, using a Co-thiourea-catalysed intramolecular Pauson-Khand reaction,[27, 42-44] followed by a Pd-thiourea-catalysed carbonylative annulation reaction.[15, 45] The synthesis started with the enyne **89**, prepared in 2 steps (80% yield), which was subjected to the Pauson-Khand cyclisation conditions using tetramethyl thiourea (TMTU) as a ligand which allows the use of a catalytic amount of $Co_2(CO)_8$ (Scheme 18). The desired bicyclic product **90** was obtained in 75% yield. The mechanism of this reaction can be described as a [2+2+1] cycloaddition process.

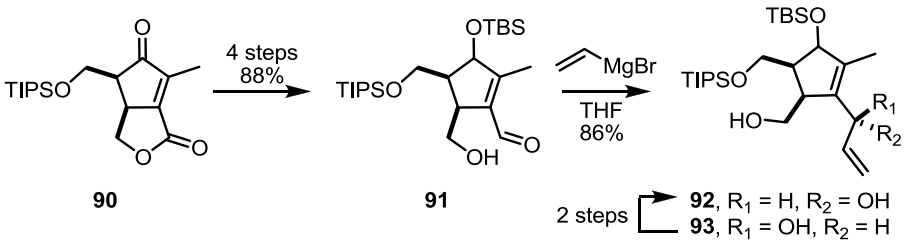


89 **90**

Scheme 18 – Synthesis of the FGH ring system

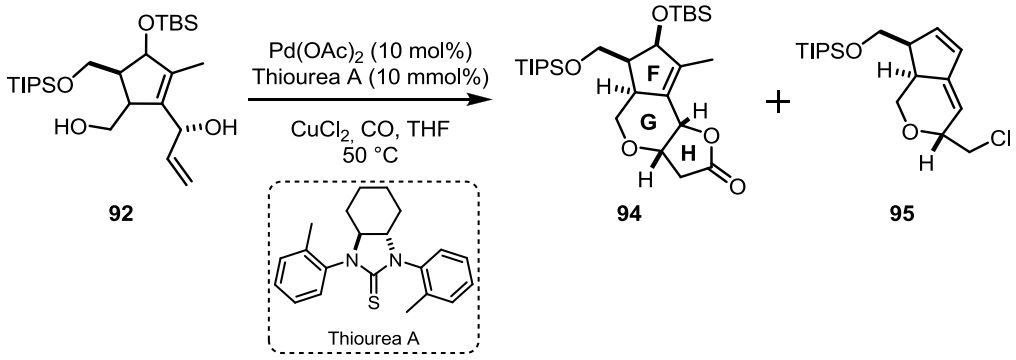
Enone **90** was reduced and selectively protected as a TBS ether in a two step process (Scheme 19), the lactone was further reduced with DIBALH and the allylic alcohol was selectively oxidised with MnO_2. Vinylmagnesium bromide was then added to the aldehyde

91 providing the alcohols **92** and **93** as a mixture of diastereomers (3:2). The undesired isomer **93** was converted into **92** by an oxidation-reduction process.



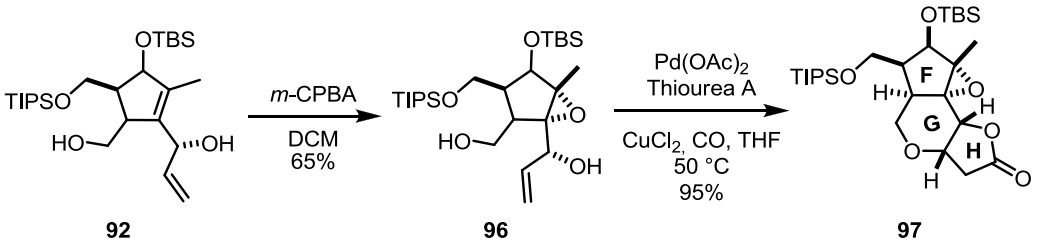
Scheme 19 – Synthesis of 92

The first attempts to form the G and H rings using a carbonylative annulation reaction (Scheme 20)[46] led to the formation of the desired product **94** in only 25% yield alongside an undesired byproduct **95** (30%).



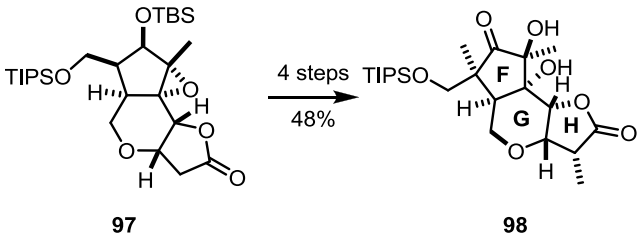
Scheme 20 – Carbonylation annulations of 92

Through screening reaction conditions, the Yang group showed that the double bond in the cyclopentene was detrimental to the desired reaction.[15] The compound **92** was converted into epoxide **96** by an interesting regioselective epoxidation with *m*-CPBA in 95% yield. Finally, when this compound **96** was subjected to the reaction conditions, the desired FGH ring system **97** was obtained in an outstanding 95% yield (Scheme 21).



Scheme 21 – Synthesis of the FGH ring system 97

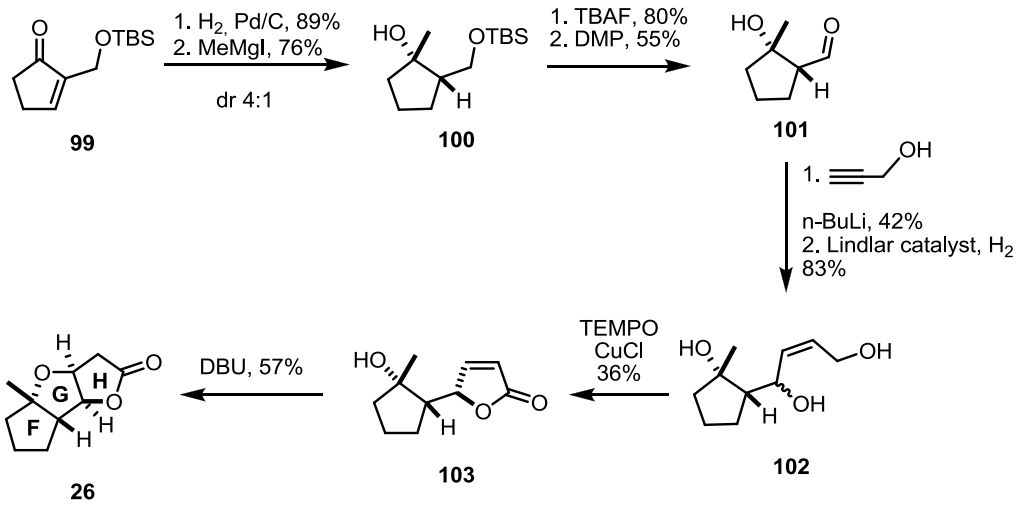
The product **97** was then elaborated to the FGH ring system **98** with the essential functionalities presented in micrandilactone A in 4 steps and 48% yield (Scheme 22).[15]



Scheme 22 – FGH ring system of micrandilactone A

1.6.2. Rubriflordilactone C (Mehta)[20]

A simple modification of the route devised for the synthesis of the ABC ring system of rubriflordilactone C was also applied by Mehta to the synthesis of the FGH ring system (Scheme 23).[20]

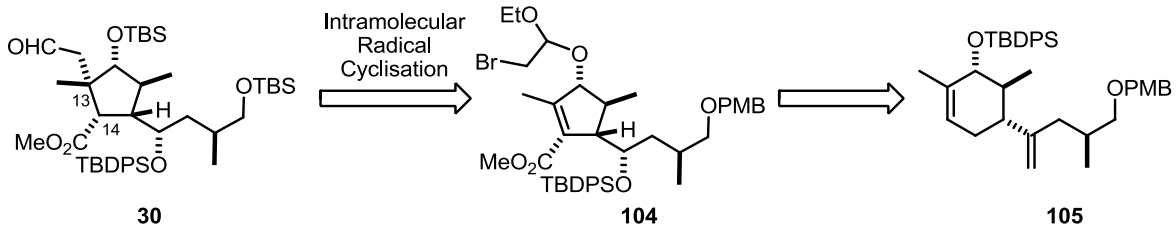


Scheme 23 – Synthesis of the FGH ring system of rubriflordilactone C

The double bond in cyclopentenone **99** was first reduced and MeMgI was added, resulting in alcohol **100** (as a 4:1 mixture of diastereomers) in 68% yield over 2 steps. The TBS group was cleaved and the corresponding alcohol was oxidised with DMP. Aldehyde **101** was then reacted with propargyl alcohol in a non-stereoselective fashion, followed by reduction of the triple bond using Lindlar catalyst to afford triol **102** (35% over 2 steps). The primary alcohol could be chemoselectively oxidised using TEMPO/CuCl,[47] and the butenolide **103** was obtained directly in 36% yield. Finally, exposure of **103** to DBU afforded tricycle **26** in 57% yield (Scheme 23).

1.6.3. Lancifodilactone G (Paquette)[22]

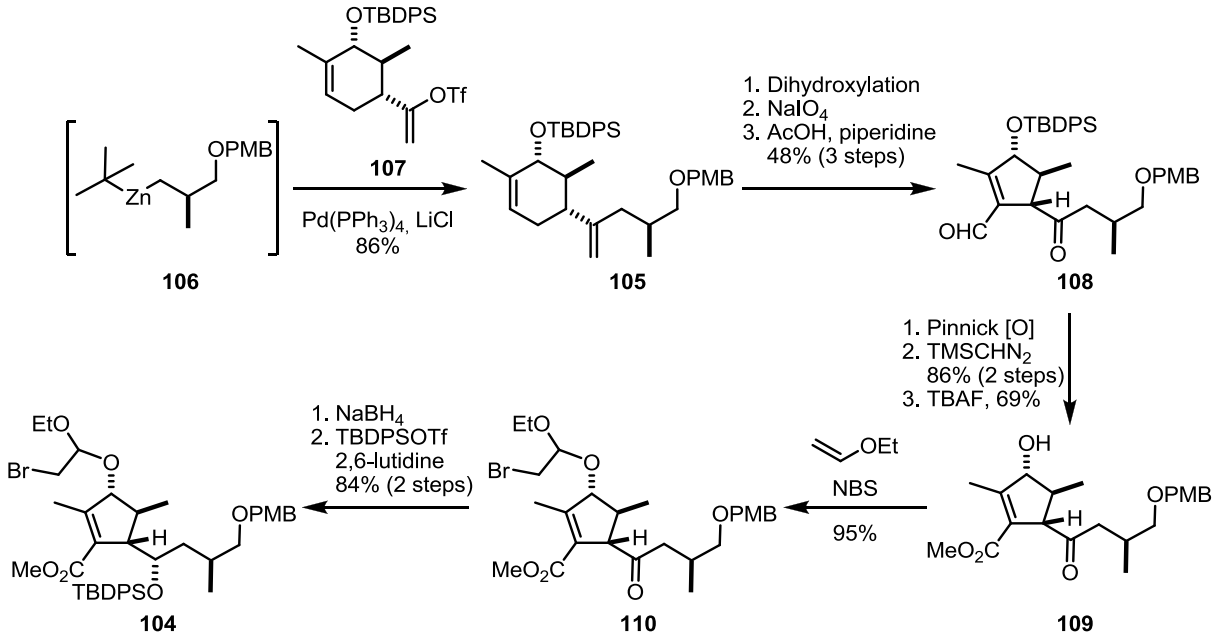
As part as their ongoing work towards the synthesis of lancifodilactone G, the Paquette group published a 19 step synthesis of the F ring **30** containing every stereocentre, and key side chains for the incorporation of this building block in the construction of the rest of the molecule.[24] Retrosynthetically, **30** would arise from **104**: the stereocentres at C13 and C14 in **30** would be introduced *via* an intramolecular free-radical cyclisation of bromide **104**,[48] which would be obtained after a ring contraction in **105** (Scheme 24).



Scheme 24 – Proposed retrosynthesis of the F ring of lancifodilactone G

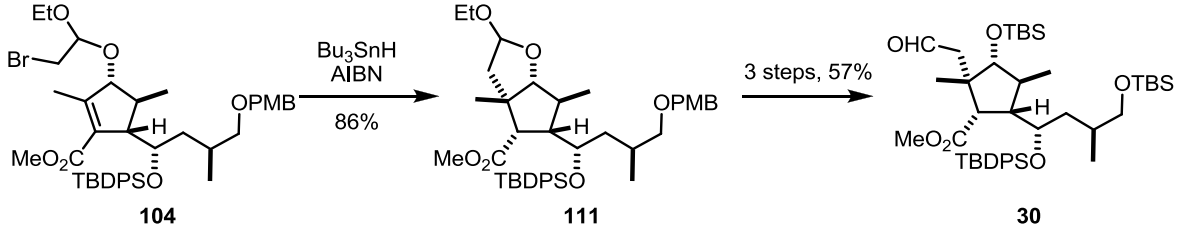
The synthesis started with the synthesis of triflate **107** in 5 steps and 68% yield.[22] The triflate was added to the freshly prepared organozinc species **106**[49] in the presence of a catalytic amount of $Pd(PPh_3)_4$, and the cross-coupling product **105** was obtained in 86% yield.[50, 51] Oxidative cleavage of the double bonds under classical conditions afforded, after

an intramolecular aldol cyclisation and elimination, the ring contracted product **108** in 48% yield over 3 steps.[52, 53] Pinnick oxidation,[54] followed by esterification of the newly formed acid with $TMSCHN_2$ afforded the corresponding ester (86%). The secondary alcohol was revealed by removal of the TBDPS group with TBAF, and immediately reacted with ethyl vinyl ether to form the bromo acetal **110**. The ketone was reduced (dr 8:1) and the corresponding alcohol was protected as a TBDPS ether in 84% yield (Scheme 25).



Scheme 25 – Synthesis of intermediate 104

Intermediate **104** was then subjected to classical radical cyclisation conditions,[48] and the bicyclic product **111** was obtained in 86% as a 6:1 mixture of diastereoisomers at the ester-bearing carbon, which was then converted into aldehyde **30** (Scheme 26).

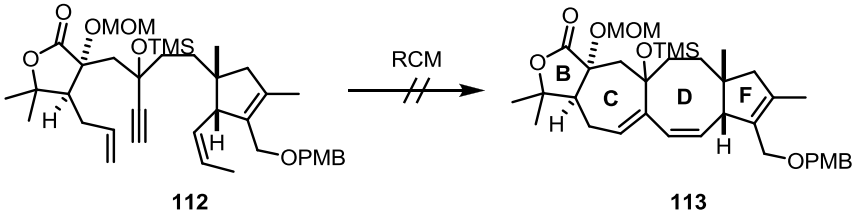


Scheme 26 – Formation of the sterically encumbered F ring of lancifodilactone G

1.7. Studies Towards the Synthesis of the Centre Ring Systems of the Schisandra Natural Products

1.7.1. Micrandilactone A (Yang)[17]

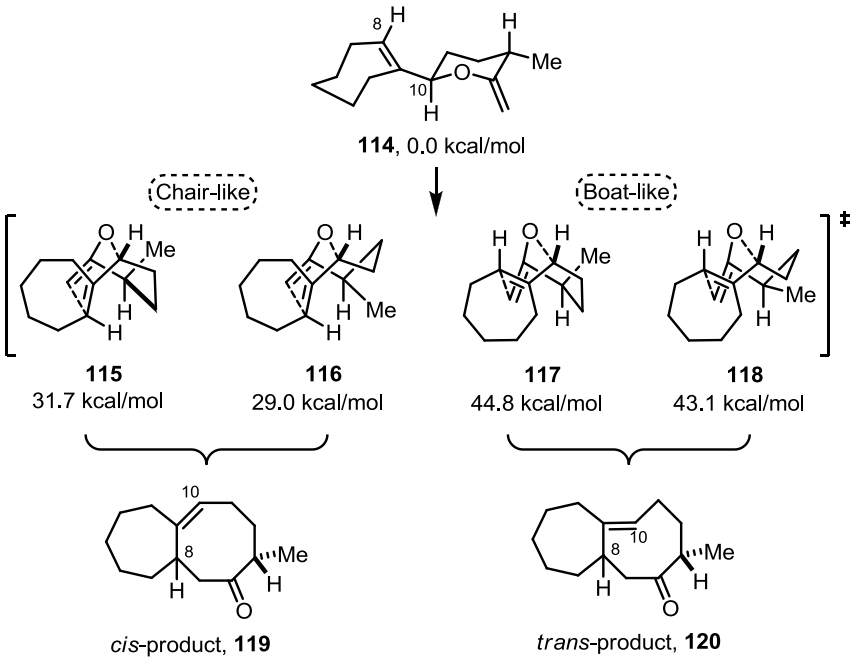
After efficiently synthesising the ABC ring system and the FGH ring system (described in part 1.7.1.),[15, 16] the Yang group turned their interest in the central ring system of micrandilactone A, which bears an unusual 7,8-trans-fused carbobicyclic ring skeleton.[12] Early attempts to construct the CD ring system using an RCM approach proved very difficult. Enyne **112** was subjected to both first- and second-generation Grubbs catalysts, but none of the desired tetracycle **113** was obtained (Scheme 27).[34, 55, 56]



112 **113**

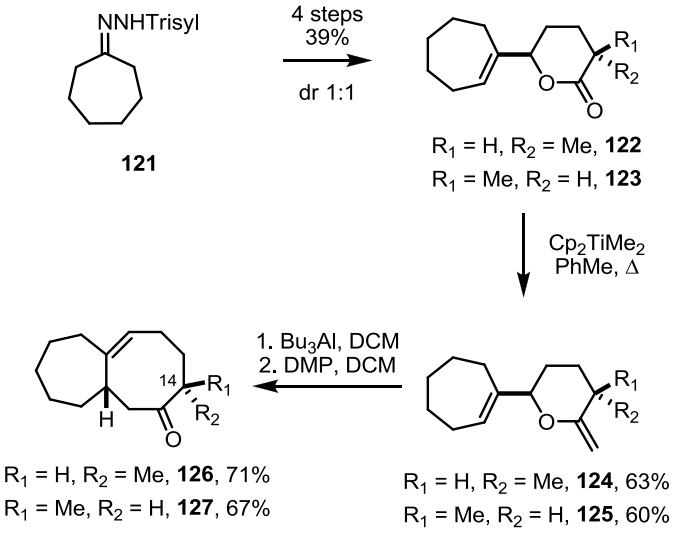
Scheme 27 – Attempts to form 113 via RCM

Because of these difficulties, the Yang group decided to consider a Claisen rearrangement[57] ring-expansion strategy for the synthesis of the 7-8 ring system. The mechanism of this [3,3]-sigmatropic rearrangement can either be described *via* a chair-like transition state or a boat-like transition state (Scheme 28). The stereochemical outcome is essential for the synthesis of the complex architecture of micrandilactone A, and as demonstrated in Scheme 28, both *cis*- and *trans*- double bonds could be formed at the 7,8-ring junction. To this end, the Yang group embarked on some computational studies, which indicated that the chair-like transition states are favoured, leading to the formation of the desired *cis*-product **119**, with complete transfer of stereochemistry from C10 to C8.



Scheme 28 – DFT calculations

These computational studies were then confirmed with the synthesis of the two diastereomers **122** and **123** (1:1) in 4 steps and 39% yield from hydrazone **121**,[58] which were separated and treated with Petasis reagent[59] to form the two compounds **124** and **125** in 63% and 60% yield respectively. Surprisingly, these enol ethers did not undergo reaction *in situ*, but required treatment with the Lewis acid Bu_3Al[60] to initiate the Claisen rearrangement. The desired products **126** and **127** were obtained after DMP oxidation in 67% and 71% yield respectively over 2 steps (Scheme 29).



Scheme 29 – Formation of the 7,8-fused ring system of micrandilactone A

In both cases, the Claisen rearrangement products were obtained with the predicted (*Z*)-double bond geometry in the newly formed 8-membered ring, and the chirality transfer was also excellent through this concerted process. Finally it is worth noting that the stereochemistry at C14 did not interfere with the outcome of the reaction, which is very useful as it means that the FGH ring could be preassembled without interfering with the stereochemical outcome of the Claisen rearrangement. However, because of the use of Bu_3Al and Cp_2TiMe_2, this methodology is unsuitable for acid-labile substrates.

1.7.2. Rubriflordilactone C (Mehta)[21]

As in the case of the Yang group, the Metha group, after completing the synthesis of the ABC and FGH ring systems,[20] turned their interest towards a general synthesis of the 7,8,5-tricarbocyclic core of the schisanartane type nortriterpenoids.[21] The F ring of this complex core was disconnected using a Diels-Alder reaction between cyclooctadiene and a pentadiene bearing the suitable functionalities. The 7-membered C ring would be installed through the addition of two "organometallic reagents" followed by an RCM reaction (Figure 5).

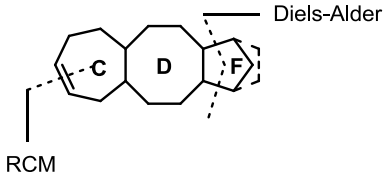
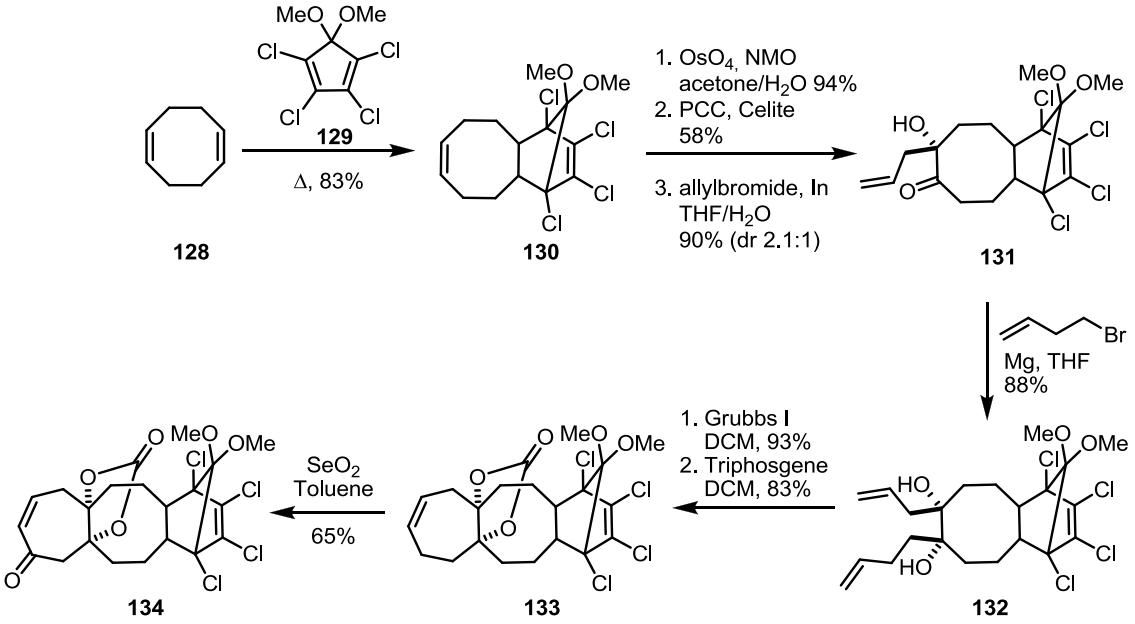


Figure 5 – Key disconnections

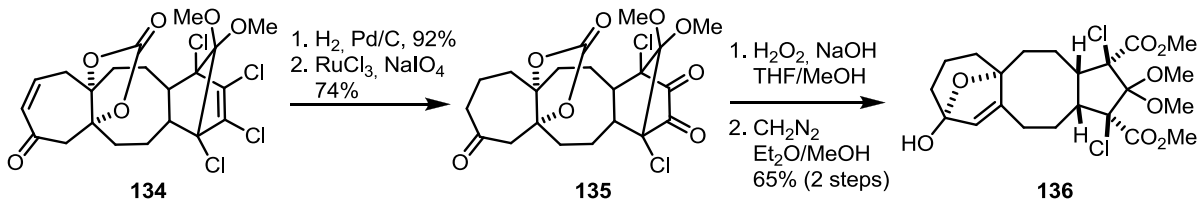
With these ideas in mind the synthesis started with the Diels-Alder reaction between cyclooctadiene **128** and pentadiene **129**,[61] from which the corresponding adduct **130** was obtained in 83% yield. The remaining cyclooctadiene double bond was dihydroxylated and oxidised to form the corresponding diketone in 55% yield. A desymmetrising Barbier reaction[62] introduced the first alkene for the RCM reaction in alcohol **131** in 90% yield; a

Grignard reaction on the remaining ketone introduced the second alkene in product **132** (88%). An RCM reaction on diene **132** produced the 7-membered C ring. The two alcohols were protected as carbonate **133**, and allylic oxidation using SeO_2 afforded **134** in 65% yield.



Scheme 30 – Synthesis of tricycle 134

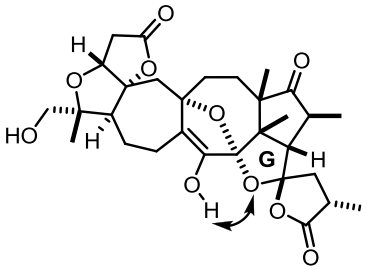
Finally in order to achieve their synthetic goal, the enone moiety in **134** was reduced in 92% yield, and an elegant catalytic oxidation of the unconjugated double bond led to dienone **135** in 74% yield.[63] Oxidation with hydrogen peroxide under basic conditions followed by treatment with CH_2N_2 with concurrent carbonate deprotection, delivered the 7,8,5-tricycle **136** in 65% yield over 2 steps (Scheme 31).



Scheme 31 – Formation of the 7,8,5-tricycle 136

1.7.3. Lancifodilactone G (Paquette)[23]

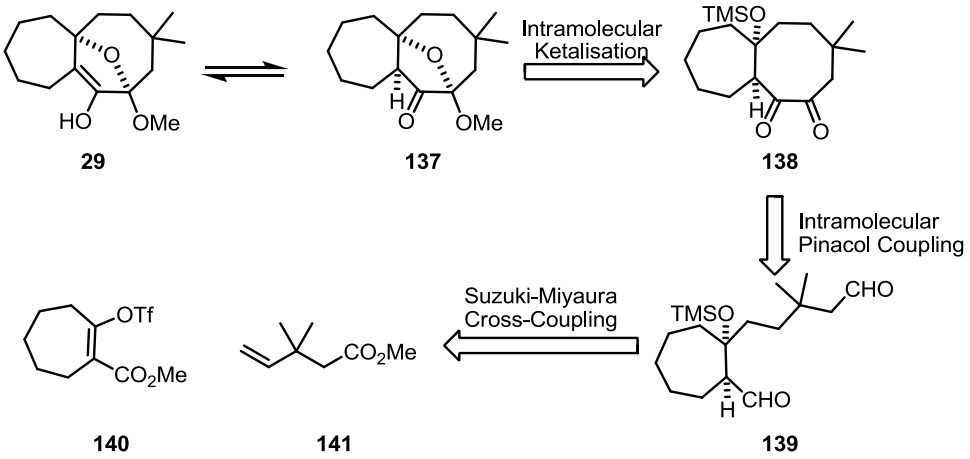
Once again, after studying the contruction of the ABC ring system[24] and F ring of lancifodilactone G,[22] the Paquette group turned their interest towards the construction of the central CDE polyfused ring system.[23] One of the interesting features of lancifodilactone G is its existence in the enol form. A speculated reason for this could be the stability induced by hydrogen bonding between the enol proton and the oxygen on the G ring (Figure 6).[64]



Lancifodilactone G, **27**

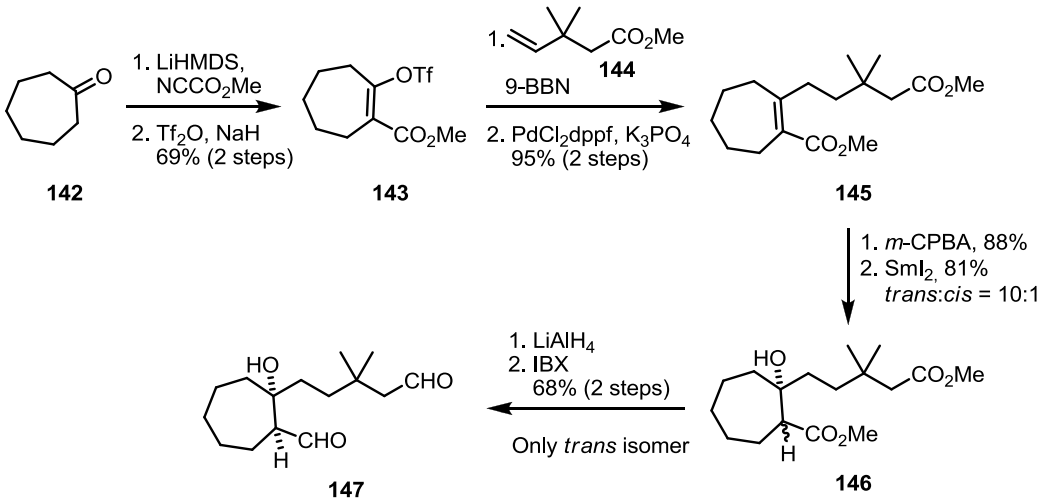
Figure 6 –Stabilisation of the enol via hydrogen bonding

Therefore the Paquette group decided to target the ketone **137**, which is in equilibrium with the desired enol form **29**. Retrosynthetically, this ketone could be formed *via* an intramolecular ketalisation of bicyclic diketone **138**, the product of an intramolecular Pinacol coupling of dialdehyde **139**.[65] This dialdehyde could be assembled from two key fragments **140** and **141** *via* a Suzuki-Miyaura cross coupling reaction (Scheme 32).[66]



Scheme 32 – Retrosynthesis of the CDE ring system of lancifodilactone G

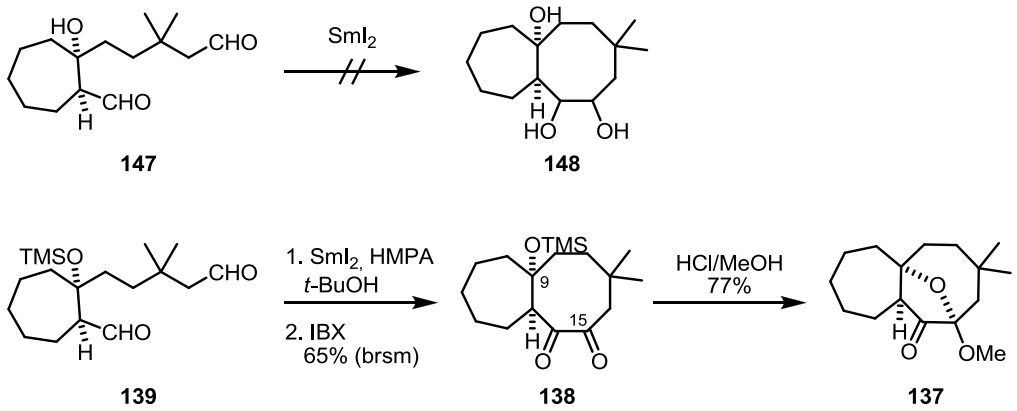
The synthesis started with the synthesis of triflate **143** in 2 steps and 69% yield (Scheme 33). The triflate was then reacted with the olefin partner **144** which was hydroborated *in situ* for the *B*-alkyl Suzuki-Miyaura cross-coupling reaction.[66] The cross coupling product **145** was obtained in very good yield. Epoxidation of the double bond followed by SmI_2-induced reductive ring-opening yielded hydroxyl-ester **146** stereoselectively (*trans*:*cis* = 10:1) in 71% yield over 2 steps.[67] Complete reduction of the diester **146** followed by oxidation to dialdehyde **147** was achieved in 68 % yield.



Scheme 33 – Formation of intermediate 147

Unfortunately all attempts at the SmI_2-mediated cyclisation[65] on dialdehyde **147** failed to form the desired the desired cyclic triol (Scheme 34), and only the corresponding reduced triol product was isolated. In order to form the desired bicycle, the free alcohol had to be protected as a TMS ether prior to the reduction-oxidation sequence. This new substrate was prepared in 3 steps from **146** in 73% yield. This intermediate **139** was then subjected to the macrocyclisation reaction conditions and the desired bicycle **138** was obtained in 65% yield (brsm) after oxidation of the newly formed hydroxyl groups using IBX. This oxidation was performed to facilitate structural characterization, as the diol was obtained as a mixture of diastereomers. Finally the oxa-bridge between C9 and C15 was introduced

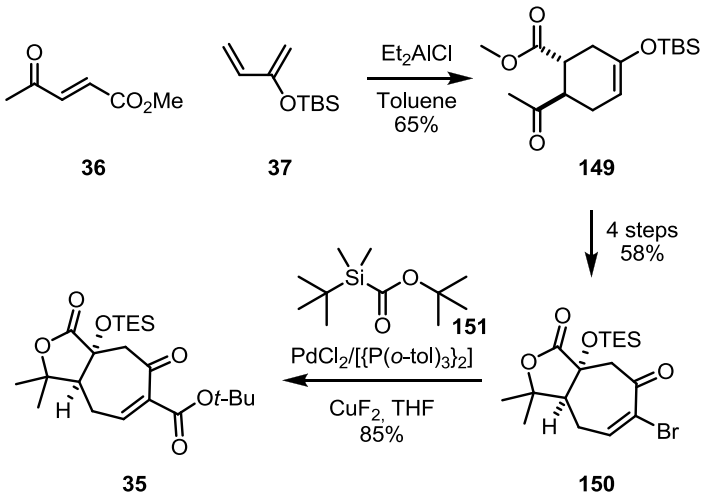
by deprotection of the TMS ether under acidic conditions, which produced the tertiary alcohol, which underwent methoxyketalisation *in situ* to deliver tricycle **137**. Interestingly, the enol form was not observed (Scheme 34).



Scheme 34 – Formation of tricycle 137

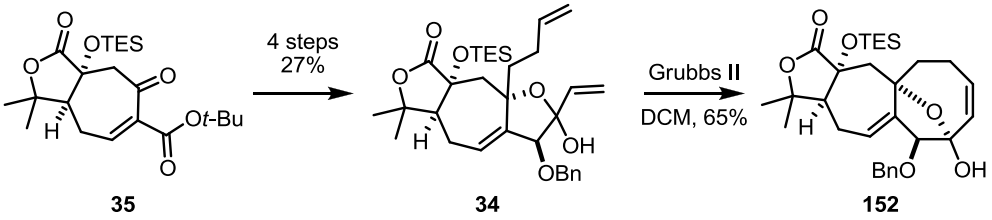
1.8. Total Synthesis of Schindilactone A (Yang)[9]

The synthesis started with **36** and **37** which underwent a Diels-Alder reaction to access ketone **149** in 65% yield (Scheme 35),[16] which upon treatment with MeMgBr cyclised to form the corresponding lactone. The 7-membered ring **150** was obtained in 4 steps in 58% yield *via* a cyclopropanation/ring expansion reaction.[68] An unusual palladium-catalysed Hiyama cross-coupling reaction of **150** with the silylformate **151**[69] afforded intermediate **35** in 85% yield.



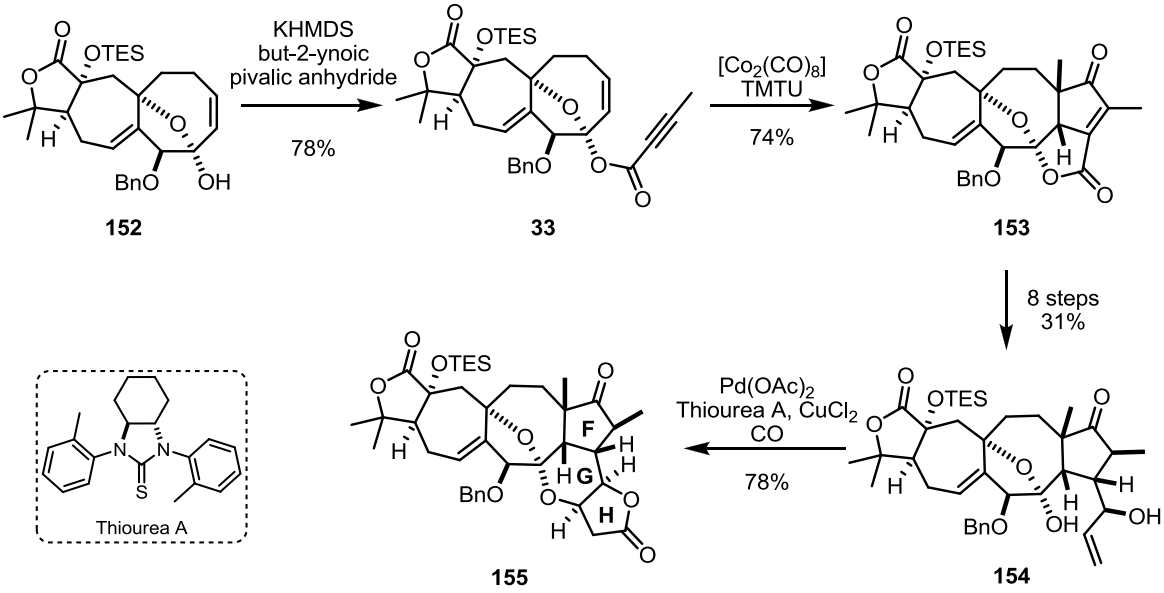
Scheme 35 – Formation of intermediate 35

With **35** in hand, the preparation of intermediate **34** for the RCM reaction was performed in 4 steps and 27% yield. The RCM reaction with Grubbs II catalyst gave **152** as a single isomer in 65% yield (Scheme 36).



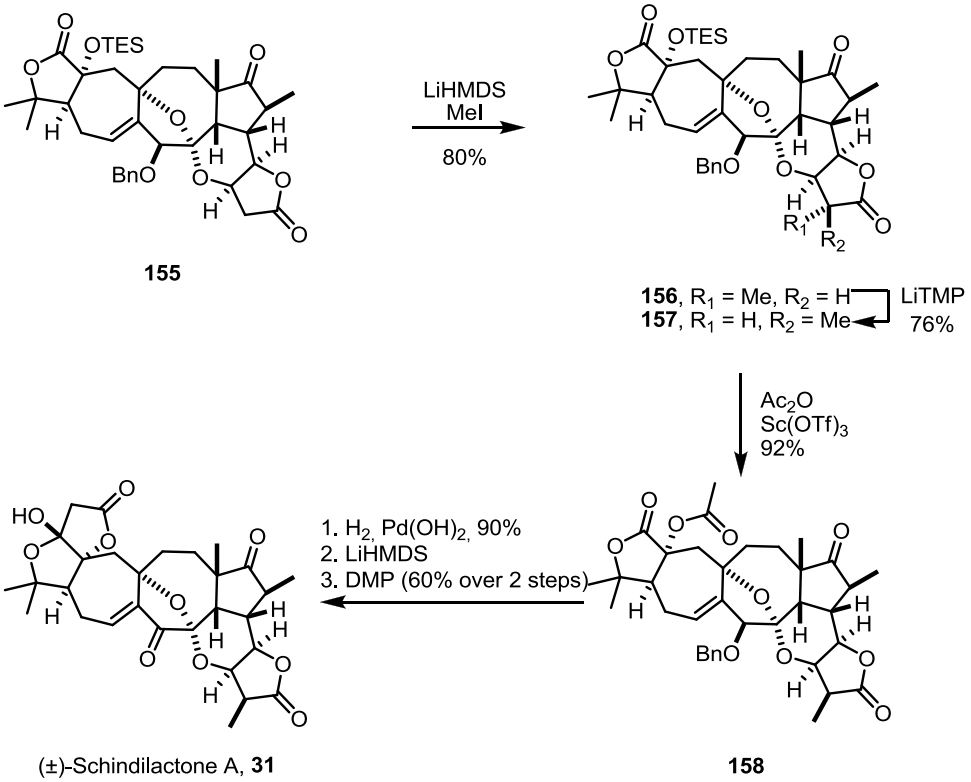
Scheme 36 – Formation of intermediate 152

From this alcohol **152**, the FGH ring system in polycycle **155** was constructed applying the methodology developed in part 1.7.1. by the Yang group (Scheme 18, Scheme 19, Scheme 20).[15] The Pauson-Khand reaction allowed access to **153** in an impressive 74% yield. After similar manipulations to those presented in earlier studies, the key intermediate **154** was subjected to the carbonylative annulation reaction conditions and afforded product **155** in 78% yield (Scheme 37).



Scheme 37 – Formation of the FGH ring system of schindilactone A

The lactone in **155** was then methylated with MeI in 80% yield and isomerised to obtain the desired β-stereochemistry using lithium 2,2,6,6-tetramethylpiperidin-1-ide in 76% yield.[70] Finally the A ring was introduced in 4 steps by switching the TES group for an acetate in a one-pot procedure using $Ac_2O/Sc(OTf)_3$ in 92% yield,[71] followed by removal of the benzyl ether by hydrogenolysis to afford the corresponding alcohol in 90% yield. The acetate group upon treatment with LiHMDS underwent smooth intramolecular Dieckmann-type condensation, and the obtained product was immediately oxidised using DMP to give schindilactone A **31** in 60% yield over 2 steps (Scheme 38).



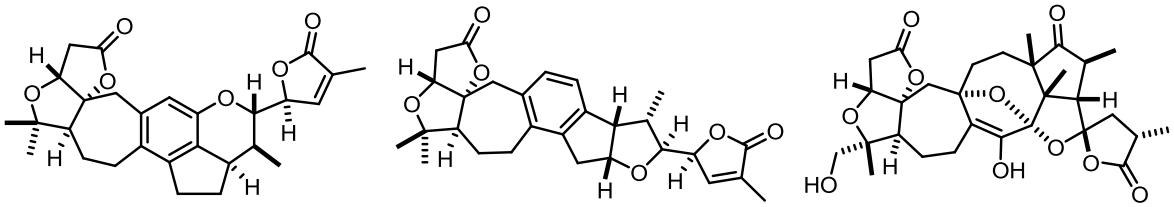
Scheme 38 – End of the synthesis of schindilactone A

1.9. A New Approach to Rubriflordilactone A and Lancifodilactone G

1.9.1. Rubriflordilactones A and B and Lancifodilactone G

Lancifodilactone G **27** (Figure 7) was isolated in 2005 by Sun and co-workers from the medicinal plant *Schisandra lancifolia*.[6] This compound showed minimal cytotoxicity against C8166 cells (CC_{50} > 200 μg/mL) and showed anti-HIV activity with an EC_{50} of 95.47 μg/mL.

Rubriflordilactones A **159** and B **160** (Figure 7) were isolated in 2006 by Sun and co-workers from the leaves and stems of *Schisandra rubriflora*.[7] They belong to the 18-nor-schiartane group of *Schisandra* nortriterpenoids, and feature a biosynthetically modified aromatic ring. They were both tested for their cytotoxicity against K562 cell lines, and for anti-HIV activity, with rubriflordilactone B exhibiting moderate activity with an EC_{50} of 9.75 μg/mL, with low cytotoxicity, whilst rubriflordilactone A showing weak anti HIV-1 activity.



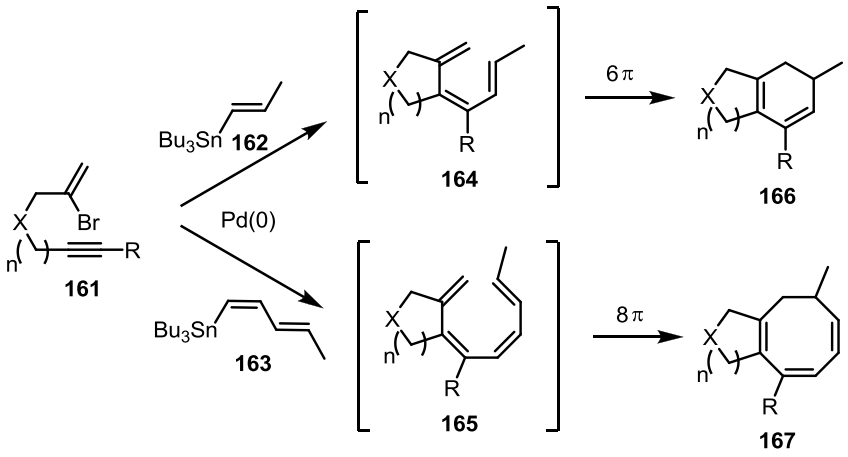
Rubriflordilactone A, **159** Rubriflordilactone B, **160** Lancifodilactone G, **27**

Figure 7 – Rubriflordilactones A and B and Lancifodilactone G

1.9.2. Proposed Retrosynthesis

As demonstrated above, most groups have been working so far on the development of a strategy towards the common fragments of the natural products of the *Schisandra* family. However, these approaches have often led to fragments which cannot always be further manipulated in order to enable the total syntheses of the natural products.

Previous work within the Anderson group revealed that the synthesis of bi- and tricyclic ring systems could be achieved from acyclic precursors *via* a palladium-mediated cascade process. This method proved to be a versatile strategy for the synthesis of a great variety of ring systems (*e.g.* 7,6- and 7,8-bicycles) (Scheme 39).[72]



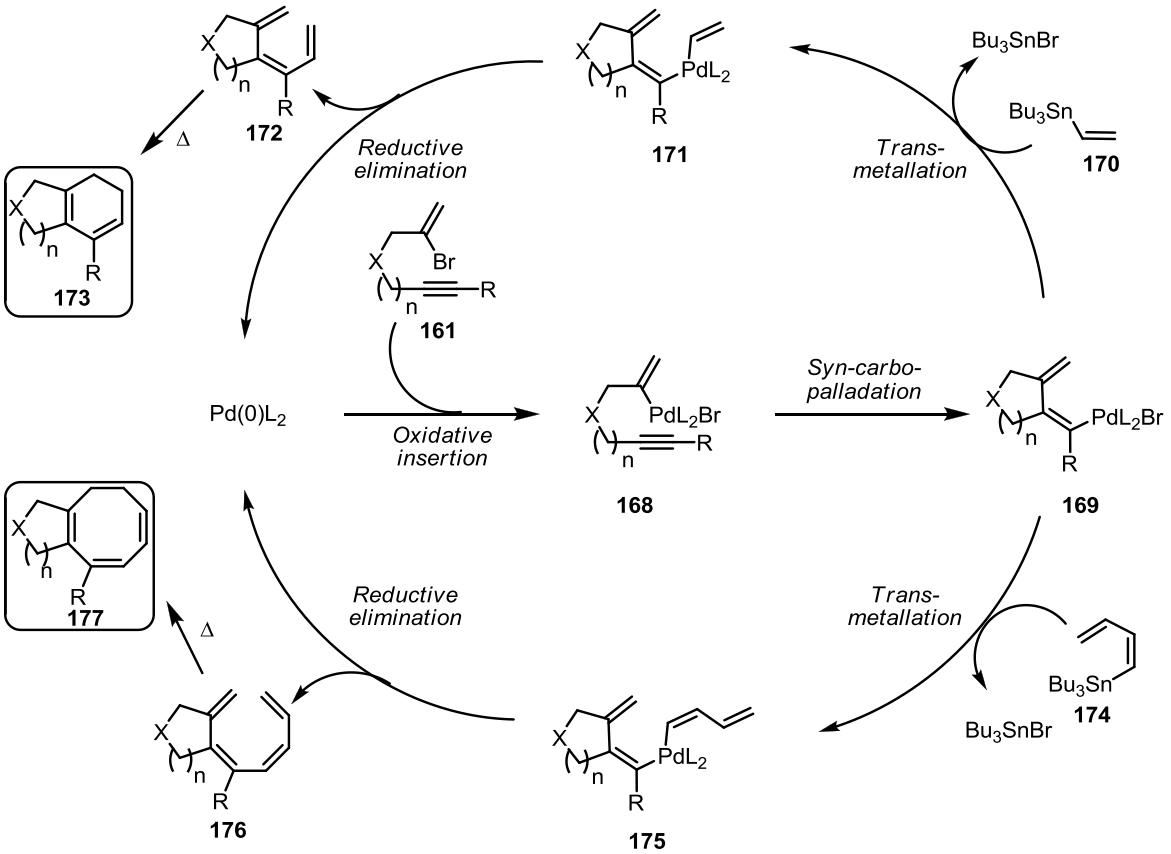
Scheme 39 – One-pot synthesis of bicyclic systems

It was anticipated that acyclic bromoenyne **161** could be subjected to a palladium(0) catalyst, which would initiate a *syn*-carbopalladation followed by an *in situ* cross-coupling reaction with stannane **162** and **163** to form triene **164** or tetraene **165**.[73-75] Finally triene **164** and tetraene **165** could undergo a 6π- or 8π- eletrocyclisation respectively (Scheme 39). This methodology was in fact inspired by the natural products rubriflordilactone A **159** and lancifodilactone G **27**, and clearly has the potential to form the 7,6- and 7,8-fused rings as found in the natural products.

2. Palladium Catalysed Cascade Cyclisation of Alkynyl Silanes

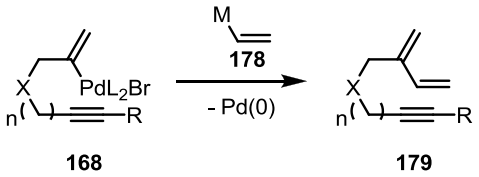
2.1. Methodology Conception and Background

In our efforts to construct n,6- or n,8- fused bicycles (**173**, **177**) from acyclic compounds suitable for use in natural product synthesis and organic synthesis in general, a strategy was developed using Pd(0)-catalysed cascade polycyclisations between a suitable bromoenyne **161** and alkenyl or dienyl stannanes **170** or **174** (Scheme 40).[72] The first step would be an oxidative addition of Pd(0) to the C–Br bond followed by a *syn*-carbopalladation forming **169**.[76] In the presence of a suitable alkenyl organometallic, this species could be intercepted to form the corresponding triene **172** or tetraene **176** after transmetallation and reductive elimination, which could then undergo *in situ* 6π- or 8π-electrocyclisation to give the desired bicyclic products **173** and **177**.[72, 77]



Scheme 40 – Cascade process

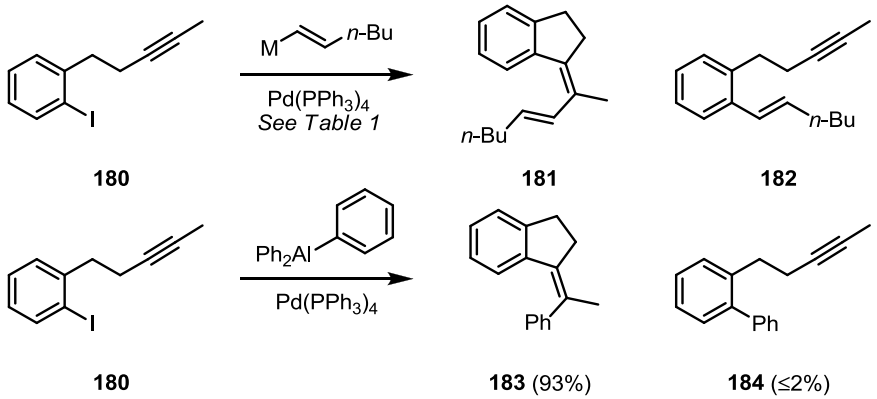
A foreseeable side reaction could be envisaged due to direct cross-coupling of the first intermediate **168** formed upon oxidative insertion; this reaction must be controlled, or even suppressed (Scheme 41).[77]



168 **179**

Scheme 41 – Undesired direct cross-coupling

Pioneering work from Negishi unveiled a clue as to which organometallic species could be used.[77] Their early experiments to trap alkenyl palladium intermediates (formed upon intramolecular carbopalladation) were carried out using organozinc reagents, but were disappointing due to direct cross coupling before carbopalladation, giving product **182** in 68% yield (Entry **1**, Table 1).



180 **181** **182**

180 **183** (93%) **184** (≤2%)

Entry	Metal	Solvent	180 (%)	181 (%)	182 (%)
1	ZnCl	THF (RT)	Trace	19	68
2	$ZrCp_2Cl$	THF (Reflux)	10	84	≤3
3	$SnMe_3$	THF - HMPA (Reflux)	18	69	≤2

Table 1 – Negishi's studies on direct coupling versus carbopalladation

On screening further metals, it was found that alkenylzirconium (Entry **2**), alkenylstannane (Entry **3**), and arylalane reagents were suitable and afforded the corresponding cyclised products in good yields (Table 1).[77]

Based on these results, stannanes were chosen for our proposed cascade cyclisation, as they have the right reactivity for the process, but are also easily accessible and stable to isolation and prolonged storage.

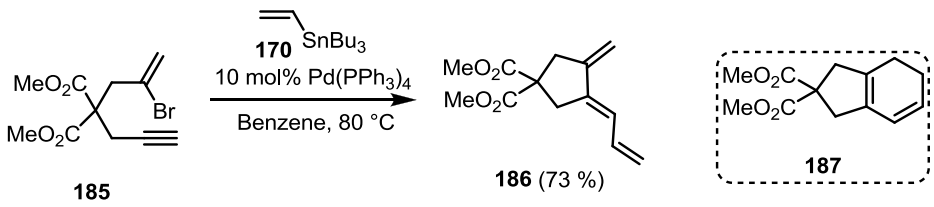
2.2. Methodology Development and Diversification

2.2.1. Cyclisation Reaction: Mechanism and Preliminary Results

Initial studies within the group on the cyclisation reactions were carried out by Kan using a simple malonate derived bromoenyne **185** which was coupled with tributylvinyltin **170** as a proof of principle of the Heck/Stille-cross-coupling/electrocyclisation cascade reaction.[72] The proposed mechanism for this transformation is shown in Scheme 40.

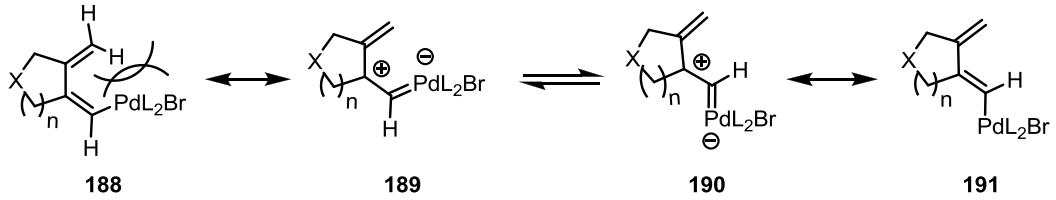
The process gives access, in a single step, to all-carbon, and heteroatom-containing bicycles.

When the first experiments were carried out (Scheme 42), the terminal alkyne **185** was used, but surprisingly only formation of the triene **186** was observed in 73% yield. **186** could not engage in the electrocyclisation process to provide the anticipated 5,6-fused bicycle **187.**



Scheme 42 – Initial studies

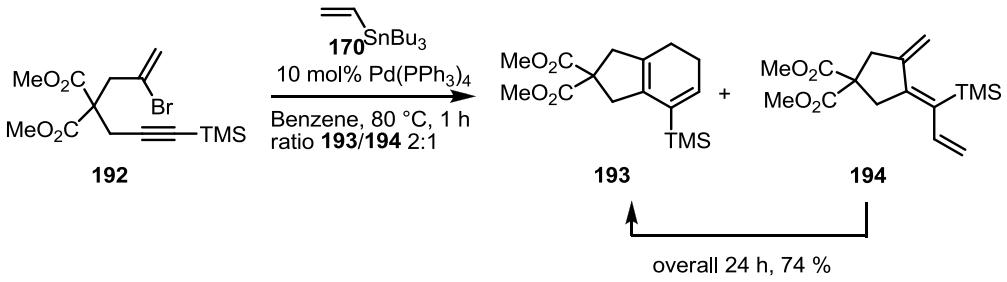
A proposed rationalisation for the isomerisation process is shown in Scheme 43:[78]



Scheme 43 – Isomerisation rationalization

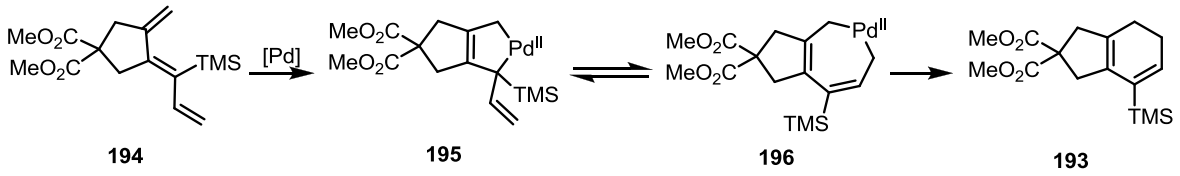
This isomerisation process would be driven by relief of 1,3-allylic strain between the palladium complex *syn*- to the exocyclic methylene in **188**. Rotation about the single bond in **189** would afford a less hindered intermediate **190** to form the isomeric alkenylpalladium species **191**,[79, 80] which would then undergo cross-coupling, which is also likely to be more rapid, to provide the *anti*-triene **186**.

It was then decided to test this reaction with bromoenyne **192**, bearing a large substituent on the end of the alkyne (Scheme 44). After 1 h, two compounds were isolated: the electrocyclisation product **193** and an undesired triene **194** in a 2:1 ratio.



Scheme 44 – Synthesis of bicyclic diene 193

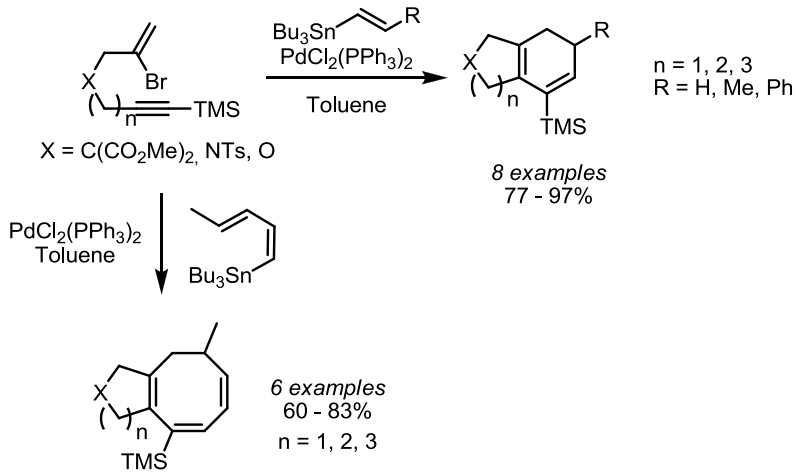
When resubmitted to the reaction conditions, or with the original reaction time prolonged to 24 h, triene **194** could be completely converted into the desired bicycle **193**.[72] However, if this triene was simply heated in benzene or toluene, in the absence of catalyst, it was not converted to the desired bicycle and only degraded over time. This suggests that the palladium catalyst must also be involved in this second isomerisation process. A possible mechanism is shown in Scheme 45.[81, 82]



Scheme 45 – Second isomerisation process

This isomerisation process might occur by oxidative addition of the palladium (0) catalyst to form palladacycle **195**. This intermediate **195** could isomerise to afford the 7-membered ring palladacycle **196** which would then undergo reductive elimination to provide the bicycle **193**.

Under the optimised reaction conditions, a range of n,6-, n-8-bicycles were prepared proving the power of this strategy (Scheme 46).[72]

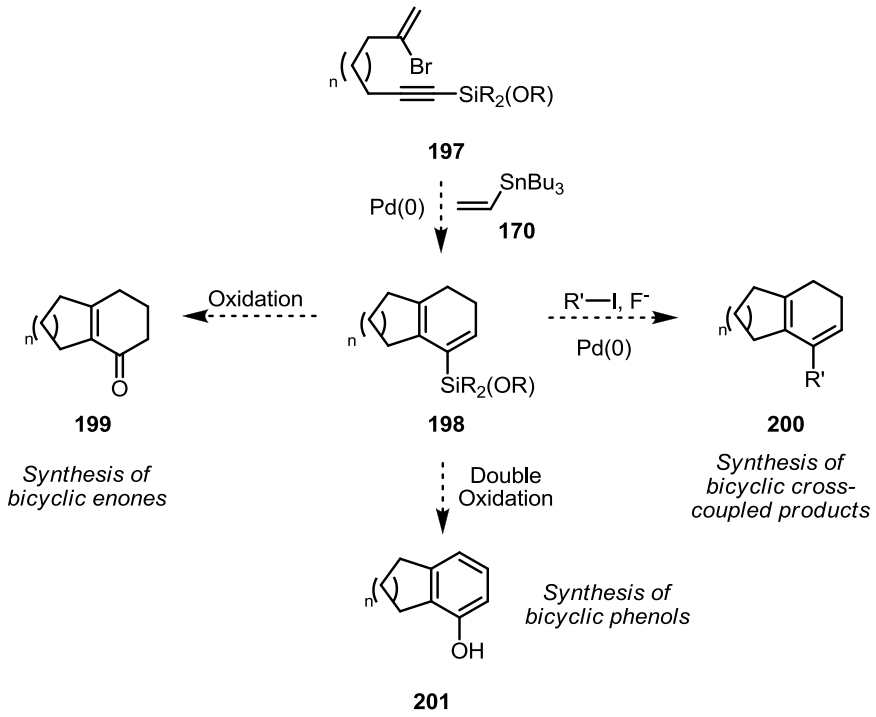


Scheme 46 – Range of products prepared with the cascade cyclisation reaction

2.2.2. Proposed Diversification

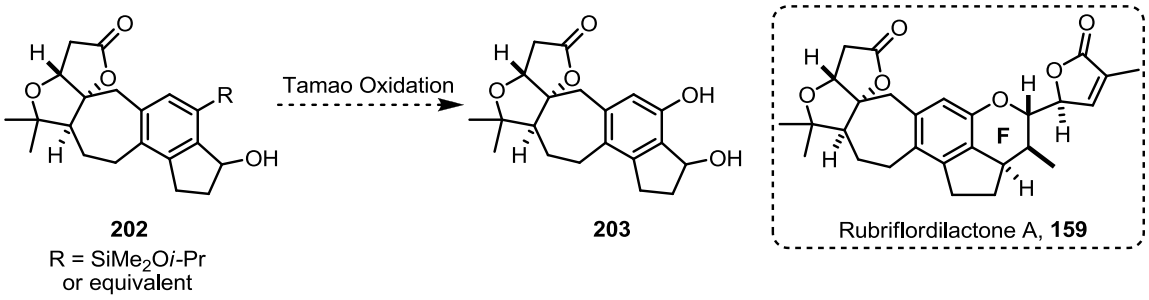
This preliminary work successfully realised our ambitious strategy to prepare bicyclic ring systems from acyclic starting materials.[72] It was demonstrated that terminal alkynes gave rise to undesired products and in order to prevent side reactions silyl-protected alkynes were used extensively in this early work. However, these silyl groups (TMS, TBS) have limited value and cannot be used in further chemistry, and we recognised that the use of a more functional silane (*e. g.* an alkoxy silane) would enhance the value of the reaction. In

this chapter the product diversity that could be realised *via* simple substrate modifications is described, including (Scheme 47): variation of carbopalladation tether size, substitutions of the cross-coupling partners and alkyne substitution. These variations could lead to an array of functionalised silylcyclohexadienes which themselves could be employed in further transformations: for example: Tamao-Fleming oxidation[83, 84] of intermediate silyldienes **198** (arising from appropriate silylalkynes) to bi/tricyclic enones **199** or Hiyama couplings of these vinyl silanes to **200**,[85-88] or double oxidation to the phenols **201**.



Scheme 47 – Potential scope of products

The feasibility of carrying out the cascade using substrates containing these oxidisable silicon groups is of particular importance in view of their potential as a "masked hydroxyl" group in the total synthesis of rubriflordilactone A **159**. This natural product contains a benzopyran F ring system which we propose can be formed from **202** with R = $SiMe_2O$*i*-Pr or equivalent (Scheme 48).

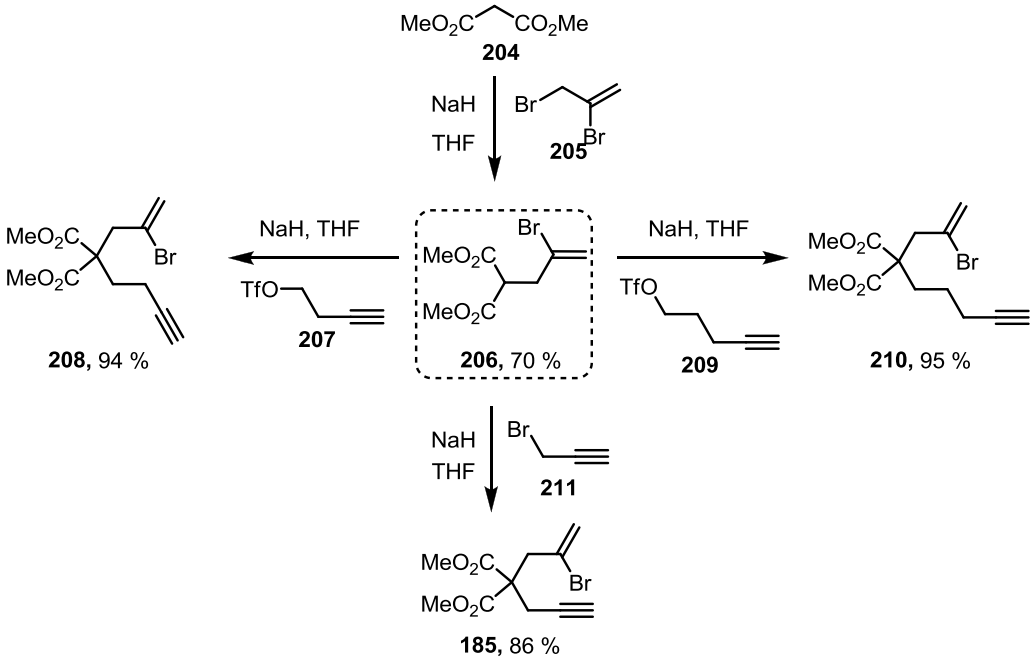


Scheme 48 – Relevance to rubriflordilactone A

2.2.4. Preparation of the Cyclisation Substrates

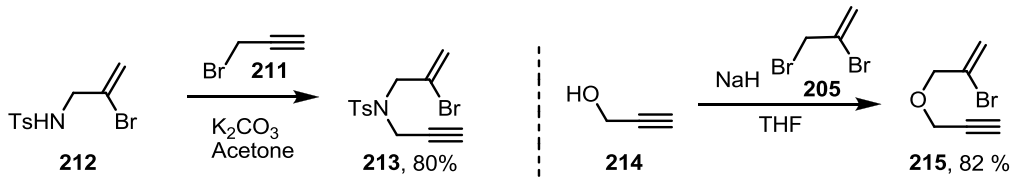
2.2.4.1. Bromoenyne Synthesis

Representative substrates **185**, **208** and **210** were prepared from cheap and commercially available dimethyl malonate **204**. Initial alkylation with 2,3-dibromopropene **205** in 70% yield[89] followed by a second alkylation step using propargyl bromide **211**, but-3-ynyl triflate **207**[90] or pent-4-ynyl triflate **209**,[90] provided **185** (86%), **208** (94%) and **210** (95%) respectively (Scheme 49).



Scheme 49 – Bromoenyne synthesis

In order to expand the scope of products obtained, nitrogen and oxygen[91] containing tethers **213** and **215** were synthesised in 80% and 82% yield respectively, allowing the eventual synthesis of isobenzofurans and isoindoles (Scheme 50).



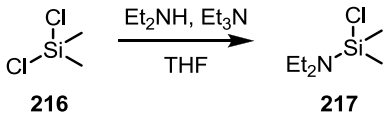
Scheme 50 – Heteroatom containing bromoenynes

2.2.4.2. Alkyne Silylation

In order to functionalise these molecules after cyclisation, a dimethylisopropoxysilyl[83] group was introduced on the alkyne, which should be stable under the cyclisation conditions but could later be transformed into a variety of products.

*Preparation of the chlorodimethyl(diethylamino)silane **217***: [83, 92]

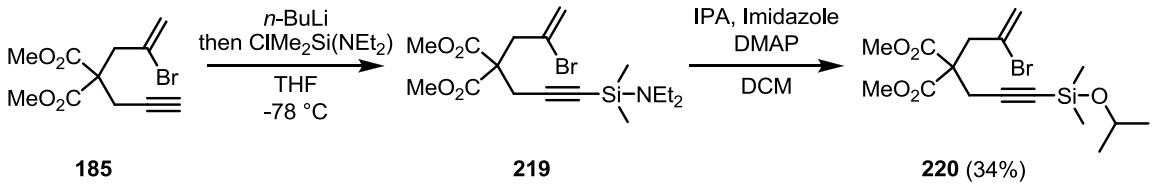
At the outset of our investigation, the chlorodimethyl(diethylamino)silane **217** was commercially available, but has since been discontinued. However, we found that the reagent could be prepared more economically and with higher purity in the laboratory on up to a 10 g scale, *via* a selective mono-substitution on dichlorodimethylsilane **216**, a cheap commodity chemical (Scheme 51).



Scheme 51 – Synthesis of 217

The preparation of the requisite alkynyl alkoxysilanes was achieved in a two step sequence (Scheme 52). Following deprotonation with *n*-BuLi, the alkyne **185** was silylated using the moisture sensitive chlorodimethyl(diethylamino)silane **217**. After concentration of the THF solution, dissolution in pentane and filtration of the resulting salt, the crude mixture

was reacted with isopropyl alcohol under standard silyl protecting conditions, which afforded the desired alkynyl alkoxysilane **220** in 34% yield.[83] An alternative one step sequence using chlorodimethyl(isopropoxy)silane **218** to afford **220** could not be employed due to the unavoidable formation of diisopropoxydimethylsilane. The cheap dimethyldichlorosilane **216** was also unsuitable as the product chlorosilane readily undergoes double addition of carbon nucleophiles (unlike the aminosilane **219**, which is selective for a single substitution of the chlorine).

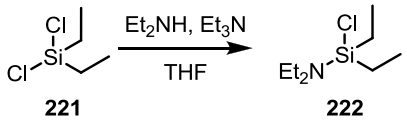


Scheme 52 – Starting material synthesis

Unfortunately, the isolated yields for this reaction were repeatedly significantly lower than the crude mass recovery would have suggested; this could possibly be due to the low stability of the product to chromatography, as the alkynyl dimethylsilyl ether may be compared to a relatively acid-sensitive TMS ether. These compounds required very rapid silica column chromatography with Et_3N added to the mobile phase to make the silica less acidic.

2.2.4.3. The Diethylisopropoxy Silane Group

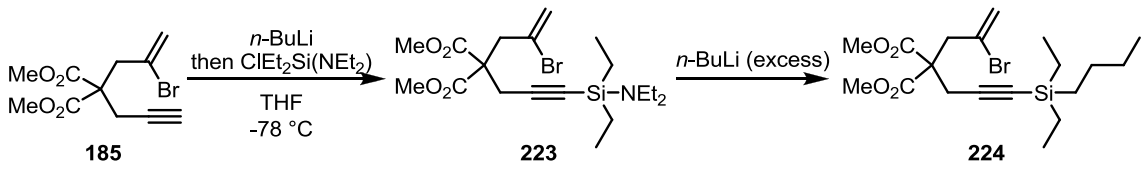
Due to the lack of stability of the dimethylisopropoxysilyl alkynes we decided to prepare the analogous chlorodiethyl(diethylamino)silane **222**.[93] Once reacted with an alkyne, the product silylalkyne should be more stable to column chromatography. The moisture sensitive chlorodiethyl(diethylamino)silane **222** was prepared, using the same reaction conditions[83] as previously described, in 70% yield (Scheme 53).



Scheme 53 – Synthesis of 222

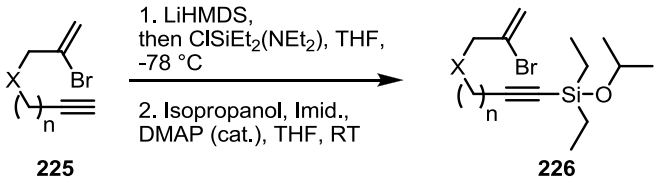
Pleasingly the diethyl derivative proved more stable than the dimethylsilane **217** but still had to be kept in the fridge under inert atmosphere and required regular distillation before use, as it decomposed on prolonged storage.

Using this new silane, a wide range of acyclic silylated bromoenynes were prepared. The conditions for the silylation were also simplified into a one-pot procedure. The alkynes were firstly deprotonated with the less nucleophilic strong base LiHMDS, rather than *n*-BuLi, as it proved to give better yields. The slight excess of *n*-BuLi was observed to react with the aminosilylated product to give a diethylbutylsilane **224**, lowering the overall yield, making the purification difficult (Scheme 54).



Scheme 54 – Byproduct of the reaction

In the optimised procedure, after deprotonation at −78 °C, the lithiated alkynes were trapped with aminochlorosilane **222**. Isopropanol, imidazole and catalytic DMAP were subsequently added to the reaction mixture without a solvent swap as previously practised, and the reactions allowed to warm up to room temperature to give, in all cases, the desired diethylisopropoxysilanes **226** (Scheme 55). The yields are reported in Table 2. Satisfyingly these products could be purified by column chromatography, without stability issues and were obtained in good to excellent yields (59-94%).



225 226

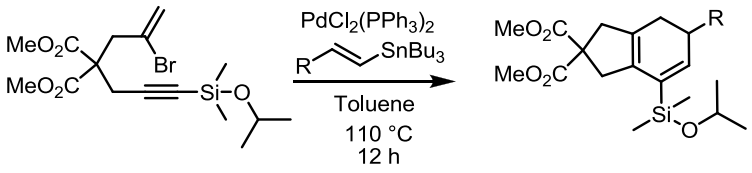
Scheme 55 – Synthesis of substrates

Entry	X	n	Product	Yield (%)
1	$C(CO_2Me)_2$	1	**226a**	94
2	$C(CO_2Me)_2$	2	**226b**	90
3	$C(CO_2Me)_2$	3	**226c**	75
4	NTs	1	**226d**	60
5	O	1	**226e**	59

Table 2 – Scope of substrates prepared

2.2.5. Cyclisation Results

Using the optimised reaction conditions developed,[72] our first attempts at cyclisation used the less stable dimethylsilane starting materials, namely substrate **220** (Scheme 56).



220 227

Scheme 56 – Initial cyclisation test

Entry	R	Product	Yield (%)
1	Me	**227a**	92
2	Ph	**227b**	97

Table 3 – Initial results

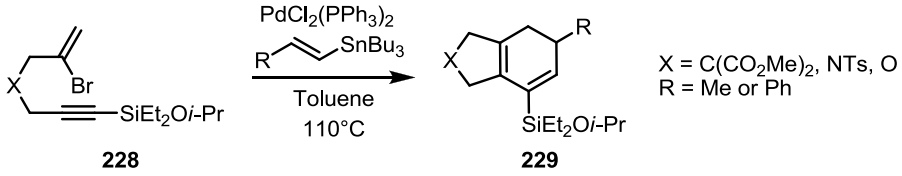
Satisfyingly these results showed that coupling with alkyl and aryl substituted vinyl stannane substrates was tolerated, and more importantly, that the dimethylisopropoxysilyl group was stable to the cascade reaction conditions. It is also worth noting that after

cyclisation the products were quite stable towards purification on silica gel (Table 3), as the alkynyl silane had now become a cyclohexenyl silane.

With these results in hand, further substrates containing the diethylisopropoxysilane moiety were subjected to the reaction conditions.

2.2.5.1. Formation of 5,6-Fused Ring Systems

The cyclisation reaction conditions were applied to the synthesis of 5,6-fused ring systems. These systems varied through an all-carbon, nitrogen or oxygen containing tether.



Scheme 57 – Synthesis of 5,6-ring systems

The cyclisation results are shown in Table 4:

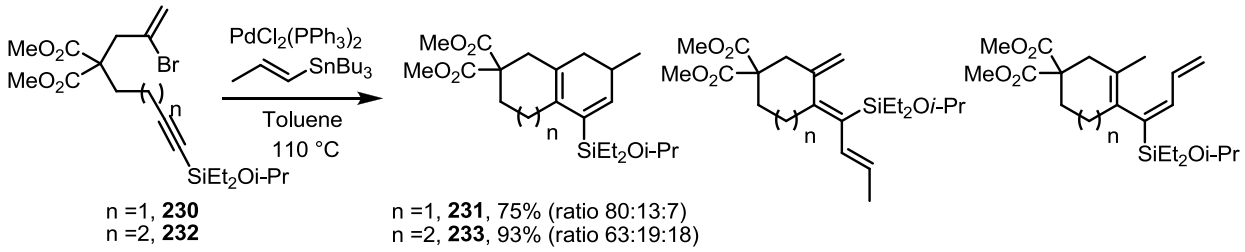
Entry	X	R	Product	Yield (%)
1	$C(CO_2Me)_2$	Ph	**229a**	75
2	NTs	Me	**229b**	60
3	O	Me	**229c**	30

Table 4 – Formation of a range of 5,6-fused rings

The bicyclic dienes were all obtained in good yield (Entries **1**-**2**), except for the oxygen containing bicycle (Entry **3**). The electron-withdrawing effect of the oxygen atom in **228** proved detrimental to the stability of both starting material and product, resulting in a lower yielding process (Table 4).

2.2.5.2. Formation of Larger Size Ring Systems

Having demonstrated 5-*exo*-dig carbopalladation, more challenging ring size carbopalladation products were investigated. Substrates **230** and **232** were subjected to the optimised reaction conditions (Scheme 58).



Scheme 58 – Formation of a larger size ring systems

Pleasingly, the products **231** and **233** were isolated in 75% and 93% yield respectively. Unfortunately in both cases, these products were contaminated with two by-products, which could not be separated. However, the structure of the two by-products could be assigned by proton NMR spectroscopic analysis (Figure 8).

The alkene peaks related to the first by-product are shown with a black square (■): an *exo*-methylene (H1) can be recognised in this data, with the proton resonances found at 5.02 ppm and 4.87 ppm, this product also contains two other alkene protons H2 and H3 at 6.02 and 5.33 ppm.

The alkene peaks related to the second by-product are shown with black dots (●): terminal alkene proton resonances (H6) can be found at 6.36 and 6.33 ppm, with the other two alkene protons H5 and H4 at 5.29 and 5.25 ppm. Analysis of the COSY spectrum showed these protons formed part of a buta-(1,3)-dienyl unit.

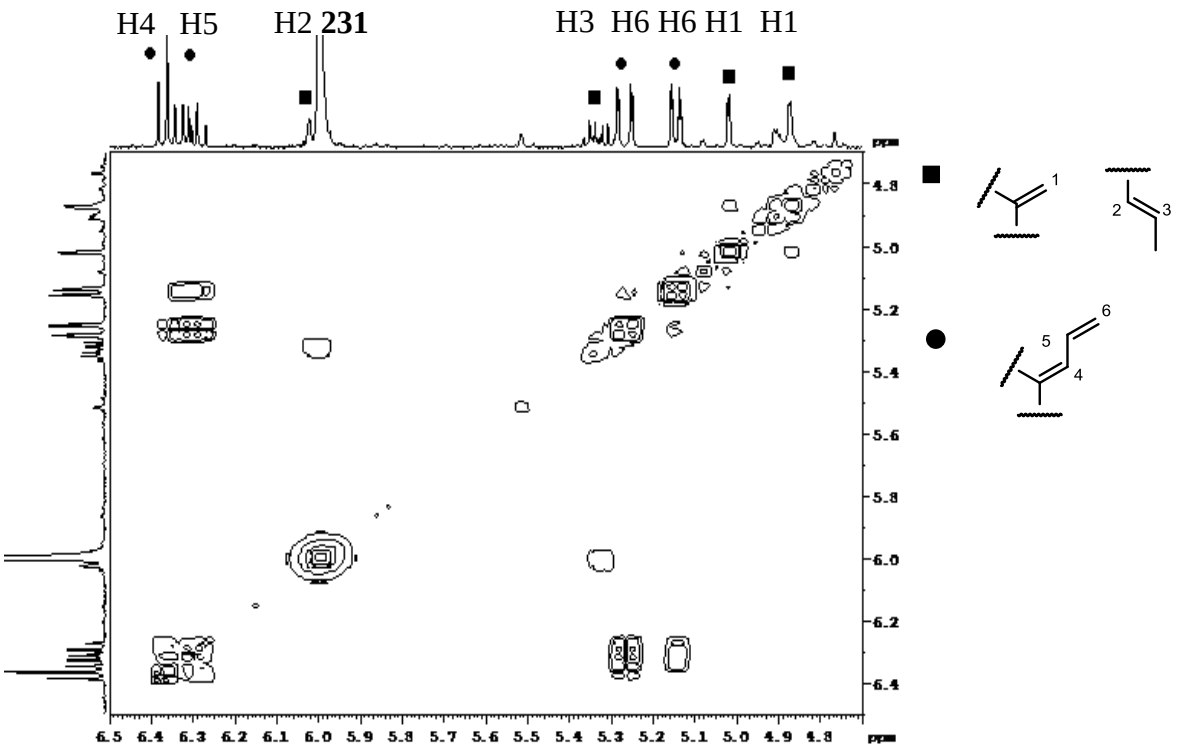
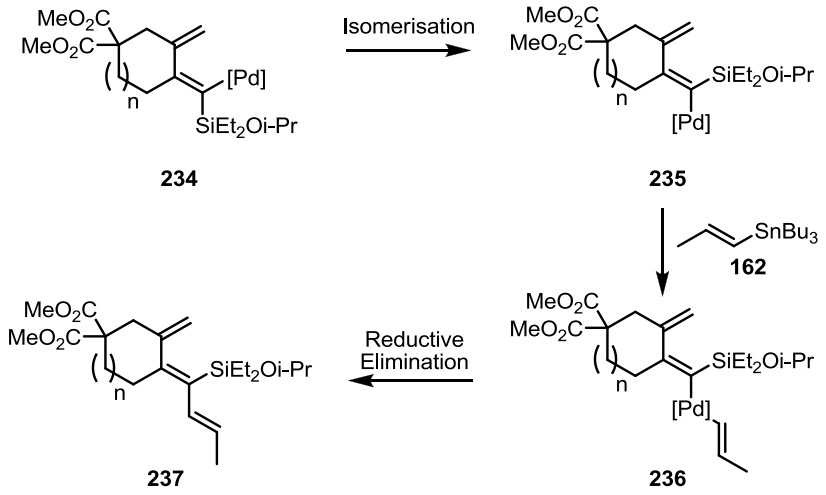


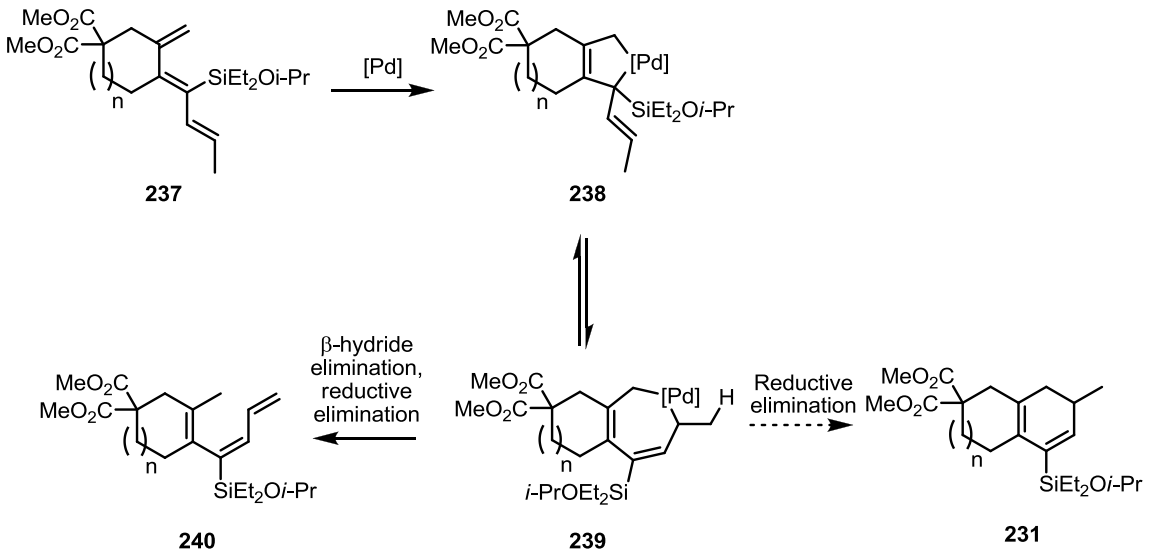
Figure 8 – COSY experiment on 231

The proposed structure for the first of these by-products (■) is the *anti*-triene **237**, produced after isomerisation of the dienylpalladium species **234** as described earlier (see Scheme 43). This isomerisation produces intermediate **235** which can undergo transmetallation followed by reductive elimination to afford product **237** (Scheme 59). The formation of this by-product is not unexpected and is consistent with our earlier observations.[78]



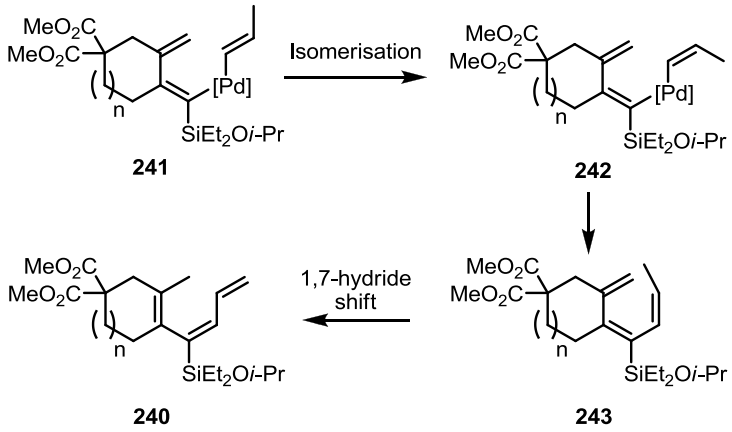
Scheme 59 – Formation of by-product 1

The other by-product **240** (●) is thought to arise from the first by-product **237**. This can undergo a similar [4+1] oxidative addition to the one described for the second isomerisation process in Scheme 45, here forming the 7-membered ring palladacycle **239**. This could form the desired bicycle **231**, but in the presence of a hydrogen in the β-position, instead undergoes β-hydride elimination, and after reductive elimination of the resultant palladium hydride species the triene **240** is obtained (Scheme 60).[81, 82]



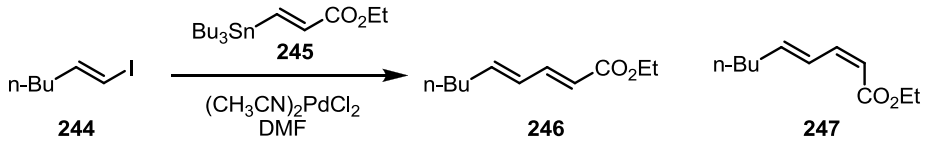
Scheme 60 – Formation of by-product 2

Another possible explanation for this isomerisation, which has precedent in the literature, is a 1,7-hydride shift of triene **243**, itself resulting from a *trans-cis* isomerisation of intermediate **241** prior to reductive elimination, in the course of the Stille coupling.



Scheme 61 – Formation of by-product 2

This isomerisation during coupling is a known issue in the literature. For example, early work by Stille showed that the coupling reaction between **244** and **245**, both *E*-isomers, led to a mixture of desired product **246** and *E*,*E*:*Z*,*E* product **247** in a 93:7 ratio (Scheme 62).[94]



Scheme 62 – Example of isomerisation in Stille cross-coupling reaction

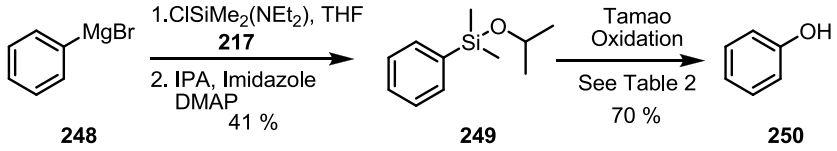
In both of the cases described here, the products were carried through as a mixture and purified at a later stage (following oxidations).

2.2.6. Oxidation of the Alkylisopropoxysilane

2.2.6.1. Aryl Silane Oxidation

The cumulative work of Tamao and Fleming introduced certain silicon groups as masked "hydroxyl groups".[83, 84, 95-97] Notably these groups are stable to a wide range of reaction

conditions and can be carried along a multistep sequence, until a chosen stage where the silicon group can simply be converted into the corresponding hydroxy group in a single oxidation step. The normal conditions for the Tamao oxidation involve the use of KF (2 equiv.), $KHCO_3$ (2 equiv.) and H_2O_2 (excess) in THF/MeOH at 40 °C.[97, 98] Although this reaction is well precedented for alkyl silane oxidations,[83] there are very few literature examples of aryl silane oxidations and relatively few examples of vinyl silane oxidations. Aware of this lack of precedent, a model substrate **248** was prepared, *via* a two step sequence in 41% yield (unoptimised), in order to test appropriate oxidation conditions. The Tamao conditions for the oxidation were tested on arylsilane **249**, which gave easily identified phenol product **250** (Scheme 63).



Scheme 63 – Aryl oxidation

The results are presented in Table 5.

Entry	Conditions (equiv.)	Yield (Time)
1	KF (2), $KHCO_3$ (2), H_2O_2 (1),THF/MeOH (1:1), RT	10:1 (**250**:**249**) (2 h)
2	KF (2), $KHCO_3$ (2), H_2O_2 (1), THF/MeOH (1:1),40 °C	70% (1 h)
3	$KHCO_3$ (2), H_2O_2 (1), THF/MeOH (1:1), RT	No reaction (2 h)
4	$KHCO_3$ (2), H_2O_2 (1), THF/MeOH (1:1), 40 °C	No reaction (12 h)

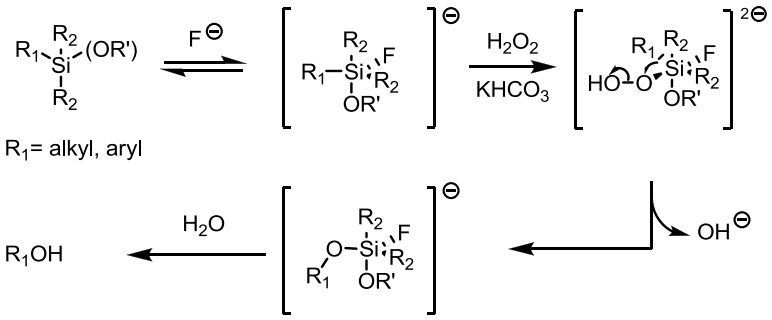
Table 5 – Screen of conditions for the Tamao oxidation of aryl silane 249

These results showed that the standard Tamao conditions for oxidising alkoxy silanes readily gave the desired phenol in good yield if heated at 40 °C (Entries **1** and **2**). Entries **3** and **4** showed that the reaction needed the use of KF to allow successful oxidation of the

intermediate to the desired product although subsequent results in the group suggest that only a catalytic amount of fluoride is required for the oxidation to take place.[99]

2.2.6.2. Mechanism of the Oxidation of the Silicon Group

One possible mechanism for the reaction is shown below (Scheme 64):[84, 97, 100, 101]



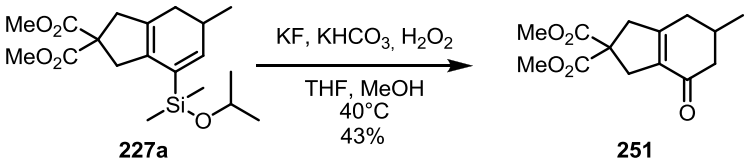
Scheme 64 – Proposed mechanism for the Tamao oxidation

The starting silane is attacked by fluoride in a fast and reversible step to produce a penta-coordinate species. The resulting penta-coordinate silicon is more electrophilic, promoting attack by the nucleophilic oxidant (HOO^-) to produce a transient hexa-coordinate species. The group *cis* to the peroxide oxygen migrates and finally the new silicon-oxygen bond of the now penta-coordinate species is hydrolysed by water to produce the expected alcohol (Scheme 64).

2.2.6.3. Enone Formation

Attention was now turned to the oxidation of cyclised products **227a** and **227b**. In the case of **227a**, the enone **251** was successfully obtained in 43% yield (Scheme 65).

^{13}C NMR spectroscopic analysis showed that enone formation had proceeded with no concomitant oxidation of the alkene. The ^{13}C NMR contained clear signals for the alkene carbons (δ 160.3 and 134.4 ppm), and a ketone signal at δ 196.7 ppm (Figure 9).



Scheme 65 – Enone formation

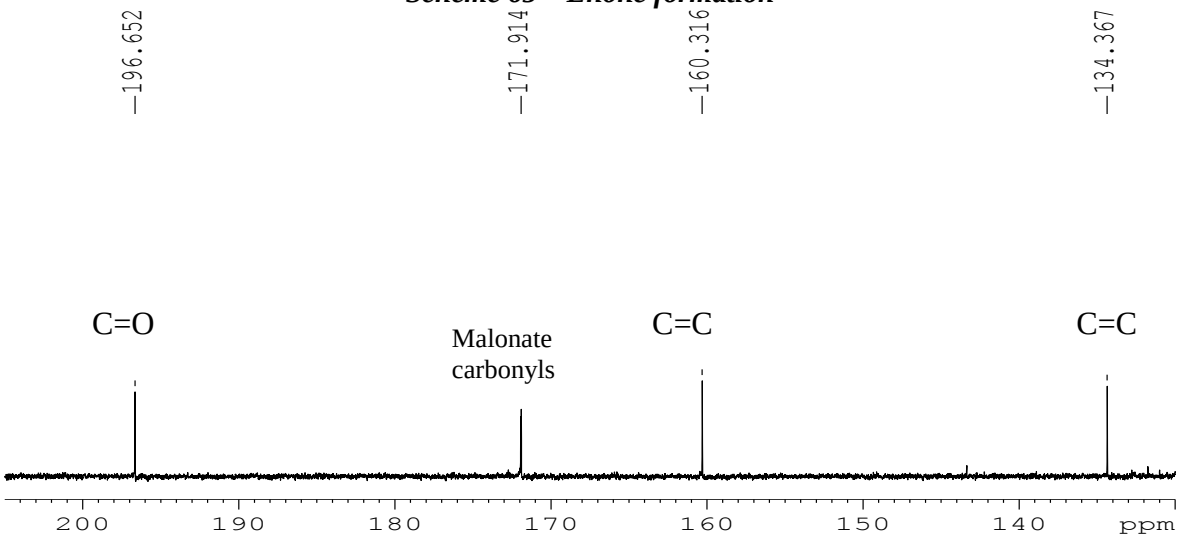
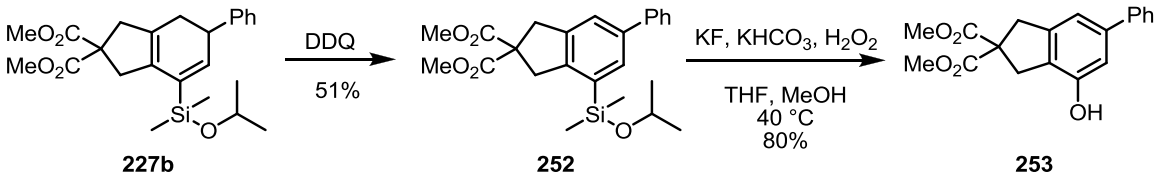


Figure 9 – ^{13}C NMR of 251 (Selected region)

2.2.6.4. Phenol Formation

In the case of **227b**, initial oxidation with DDQ was carried out to prepare the biaryl **252** in a moderate 51% yield. A Tamao oxidation was then carried out to demonstrate the use of this sequence to prepare bicyclic phenols. The phenol **253** was obtained in a very encouraging 80% yield. The overall yield for this sequence from the acyclic starting material was 17% (Scheme 66).



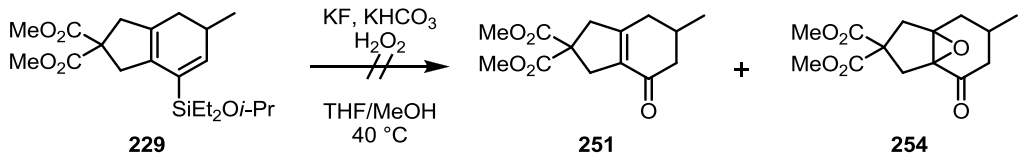
Scheme 66 – Synthesis of phenol 253

These two results were highly encouraging and validated the strategy developed with these oxidisable silicon groups. In addition, it was crucial to prove that the bicyclic molecules

containing a diethylisopropoxysilane could also be unmasked to the requisite hydroxyl group, as we would like to use this strategy in the total synthesis of rubriflordilactone A.

2.2.7. Oxidation of the Diethylisopropoxysilane

Having demonstrated a successful oxidation of the aryl dimethylsilane product **252**, we next set out to prove that the diethyl derivative could equally be used. The oxidation of diene **229** was attempted, unfortunately the enone **251** could not be formed (Scheme 67).

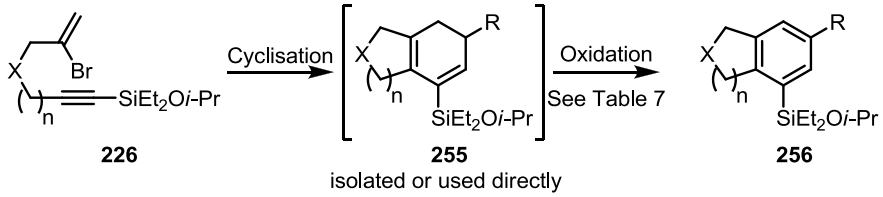


Scheme 67 – Oxidation of diene 229

As expected, this oxidation proved to be more difficult, certainly due the sterically more hindered ethyl substituted silicon centre. Performing the oxidation at an elevated temperature (60 °C) led to full consumption of the starting material, but afforded a complex mixture which may have contained the desired enone, but also a side product tentatively assigned as an epoxide **254**. Therefore we decided to proceed to the aromatisation of all substrates, in order to avoid the complications of a possible epoxidation of the enone under these more forcing reaction conditions.[102]

2.2.7.1. Aromatisation

In the previous experiment carried out on bicyclic aromatic **252**, the aromatisation reaction was performed using DDQ and gave **252** in a moderate yield of 51% (Scheme 66). Test experiments were run on the products bearing the diethylisopropoxy silane in an attempt to improve this oxidation method (Scheme 68).



Scheme 68 – Oxidation of the bicyclic aromatic

The yields are shown Table 6:

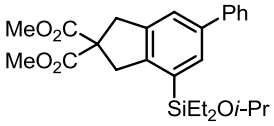
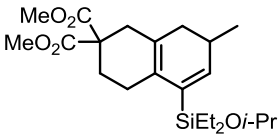
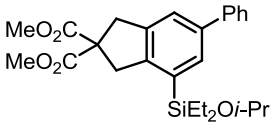
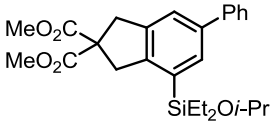
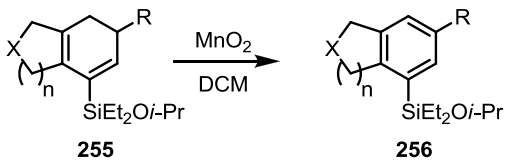
Entry	Oxidant	Product		Yield
1	DDQ		**256a**	a) 51% from the isolated diene **229a** b) 41% from **226a**
2	DDQ		**256b**	a) 42% from the isolated diene **231** b) 58% from **226b**
3	CAN		**256a**	Decomposition
4	Activated MnO_2[103]		**256a**	88% from the isolated diene **229a**

Table 6 – Aromatisation condition screen

DDQ oxidation gave the desired aromatic products but in all cases the crude reaction mixture was complex by NMR, necessitating chromatography. The yields in all cases were moderate but there was no recovered starting material (Entries **1**–**2**). However when using MnO_2 as oxidant, the reaction proved to be very selective to give the desired aromatic product **256** (Entry **4**) in significantly improved yield. Therefore, given the success when using MnO2, all subsequent oxidations were performed using these conditions (Table 7).



In all cases, apart from aromatisation of **229c** (Entry **5**), the aromatic product was obtained in very high yield. The low yield for the aromatisation of **229c** is probably again due to the latent instability of the bicyclic diene.

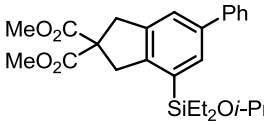
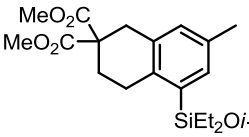
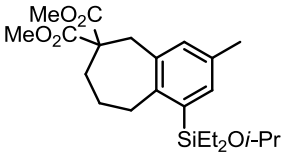
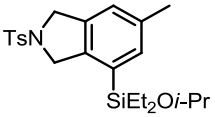
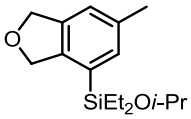
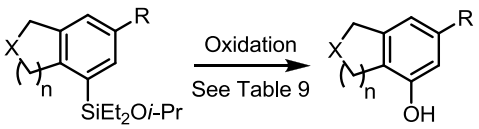
Entry	Bicyclic diene	Product		Yield
1	**229a**		**256a**	88%
2	**231**		**256b**	95%
3	**233**		**256c**	88%
4	**229b**		**256d**	93%
5	**229c**		**256e**	46%

Table 7 – Aromatisation scope

2.2.7.2. Tamao oxidation

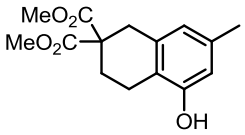
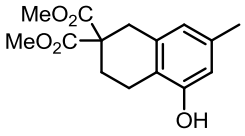
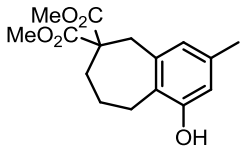
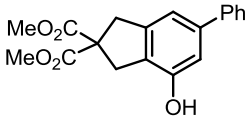
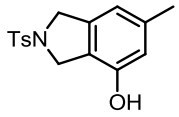
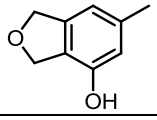
The optimised Tamao conditions were applied to the oxidation of the aromatic diethylisopropoxysilane to afford the desired phenol products (Scheme 69).



256 **257**

Scheme 69 – Oxidation of the diethylisopropoxy silane

While the reaction did not proceed at 40 °C, the desired phenols were obtained in good to excellent yield when the reactions were carried out at 60 °C; the yields were also improved by using TBAF instead of KF (Table 8).[99]

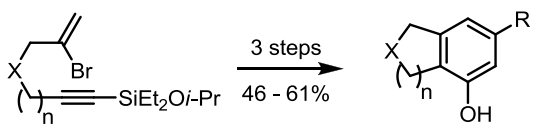
Entry	Bicyclic diene	Conditions	Product		Yield
1	**256b**	A		**257b**	58%
2	**256b**	B		**257b**	65%
3	**256c**	A		**257c**	74%
4	**256a**	B		**253**	93%
5	**256d**	B		**257d**	98%
6	**256e**	B		**257e**	99%

Conditions: A: KF (2 equiv.), $KHCO_3$ (2 equiv.), H_2O_2 (3 equiv.) in THF/MeOH
B: TBAF (1 equiv.), $KHCO_3$ (2 equiv.), H_2O_2 (3 equiv.) in THF/MeOH

Table 8 – Oxidation to the phenols

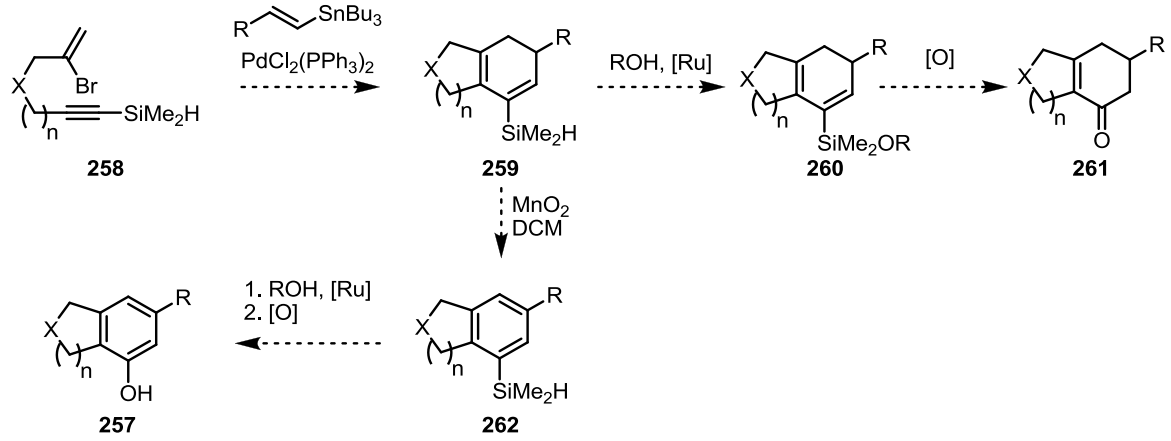
2.3. Conclusion

In conclusion, a successful three-step methodology for the synthesis of bicyclic phenols from acyclic starting materials has been demonstrated, with overall yield ranging from 46% to 61%.



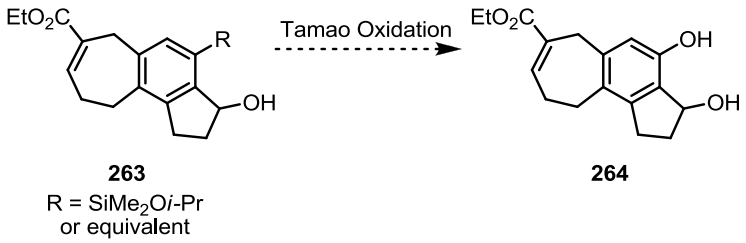
Scheme 70 – Range of products prepared

In this work, the stabilities, and reactivities of different dialkylisopropoxy silanes were evaluated (Me *vs.* Et), and showed that both of these silanes have benefits and drawbacks. In order to avoid their potential stability issues, a dimethylsilane could instead be adopted as demonstrated in Chapter 4.[104] This silane proved to be very stable to a wide range of reactions, and we suggest that this work could be carried out with this group on the alkyne (Scheme 71). This dimethyl silane **258** could potentially be compatible with the conditions of the cascade cyclisation process and transformed post-cyclisation into the alkoxysilane **260** or **262**, in preparation for the conversion to the phenol **257**. The increased stability of the silane may result in more facile purification and thus improve the yield of the process. This would be expected to yield the phenols is higher yields. This would also allow access to the enone **261**, as the oxidation of a dimethylalkoxy silane can be performed under less forcing reaction conditions.



Scheme 71 – Potential use of a dimethyl silane

With the successful demonstration of the arylsilane oxidation reaction, we now intended that this alkoxysilane would be introduced for the synthesis of a model system **263** of rubriflordilactone A. It was hoped that this silane could be oxidised to form the phenol oxygen present in **264**.[105]



263
R = $SiMe_2O$*i*-Pr
or equivalent

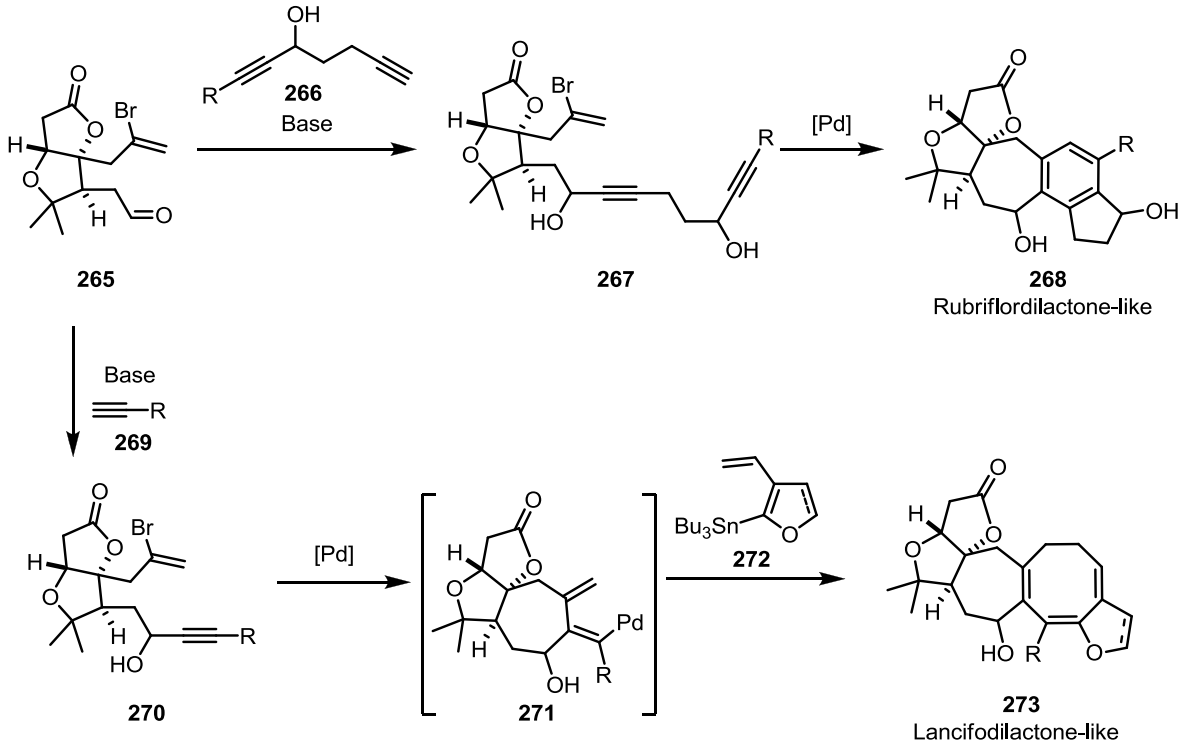
264

Scheme 72 – Planned use of Tamao-oxidation in a model system of rubriflordilactone A

3. Rubriflordilactone A, Model Studies

3.1. Proposed Retrosynthesis

We suggest that many of these natural products featuring the AB ring system (including the rubriflordilactones A and B and lancifodilactone G) could be elaborated from a common precursor **265** (Scheme 73).



Scheme 73 – Proposed general strategy towards the Schisandra natural products

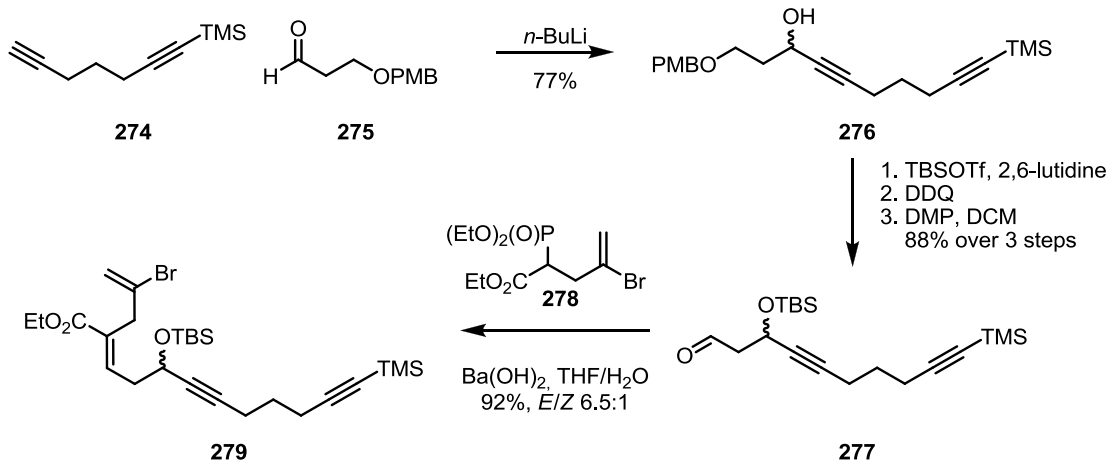
This aldehyde **265** could be reacted with a derivative of the diyne **266**, then undergo a fully intramolecular variant of the cascade cyclisation process, which will be discussed later in detail, producing the ABCDE core of rubriflordilactone A **268**.[105] Alternatively **265** could be coupled with alkyne **269** followed by cascade cyclisation with diene **272** to afford the ABCDE core of lancifodilactone G **273**.[72, 105]

3.2. Initial Studies towards the Synthesis of the CDE-Ring System of Rubriflordilactone A and Lancifodilactone G

3.2.1. Previous Work towards the Schisandra Natural Products

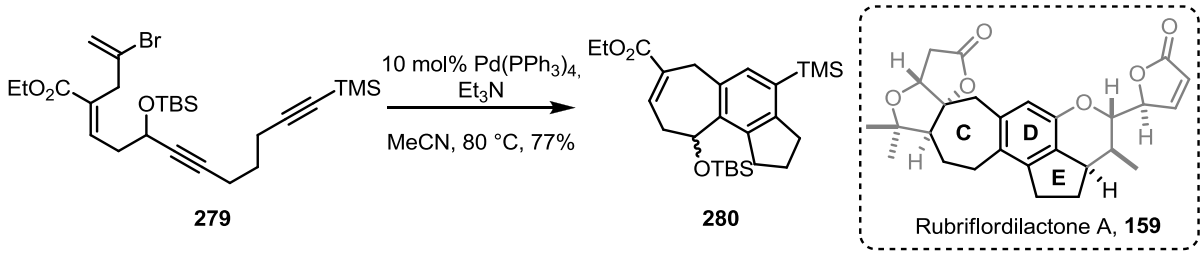
Synthesis of the 7,6,5-Tricyclic Core of Rubriflordilactone A

In previous work within the group, Kan had synthesised a trimethylsilyl-substituted CDE ring system of rubriflordilactone A.[105] The synthesis of this system started with the lithiation of mono-protected 1,6-heptadiyne **274**, which was trapped with aldehyde **275** to afford secondary alcohol **276** in good yield (77%). The alcohol **276** was protected as a TBS ether, the PMB group was removed and the corresponding alcohol was oxidised using Dess-Martin periodinane to form aldehyde **277** in 88% yield over 3 steps. Finally a Horner–Wadsworth–Emmons (HWE) reaction with phosphonate **278** afforded the desired bromoenyne **279** in 92% yield with good *E*/*Z* selectivity (6.5:1) (Scheme 74).[106]



Scheme 74 – Construction of precursor 279

With the synthesis of the bromoenyne accomplished, the intramolecular cascade cyclisation was investigated. Pleasingly, the use of $Pd(PPh_3)_4$ (10 mol%) in MeCN afforded the desired tricycle **280** in excellent yield (77%) (Scheme 75). [77, 107-113]

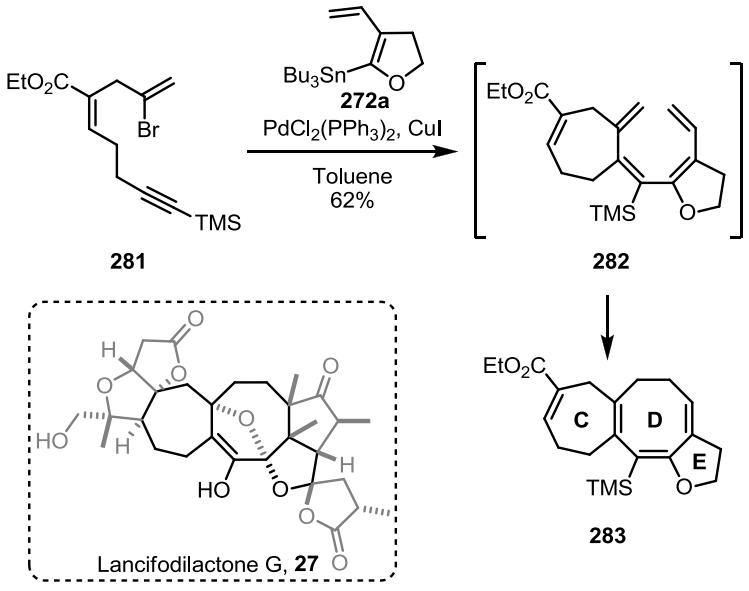


Scheme 75 – Synthesis of the 7,6,5-tricyclic core of Rubriflordilactone A

The aim of this first synthesis was successfully achieved. This result gave us confidence that the envisaged strategy could be applied efficiently towards the synthesis of such 7,6,5-tricycles. This is crucial as even though intramolecular bromoenyne cyclisations have precedent, there are very rarely applied with a 7-membered tether and there are no examples in total synthesis. The mechanism of this transformation will be discussed later in this chapter.

Synthesis of the 7,8,5-Tricyclic Core of Lancifodilactone G

In order to form the tricyclic core of lancifodilactone G, a related intermolecular cascade cyclisation was envisaged.[72, 114, 115] Alkyne **281** and stannane **272a** were prepared.[116] Under a slight modification of the original cyclisation reaction conditions, the challenging 7,8,5-CDE core of lancifodilactone G **283** was isolated in 62% yield (Scheme 76).[105, 114, 115]

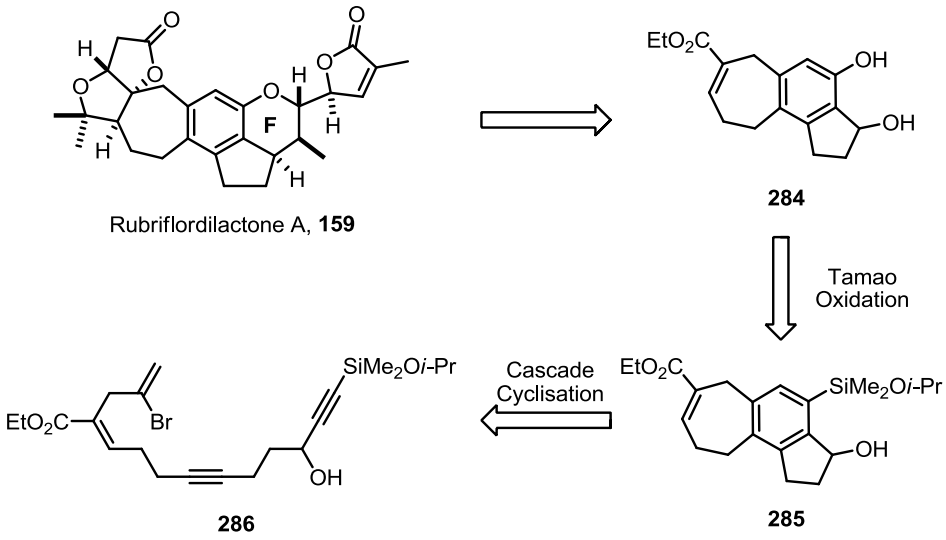


Scheme 76 – Successful synthesis of the core of lancifodilactone G

3.3. Studies Towards the Core of Rubriflordilactone A

3.3.1. Retrosynthesis

Building on the formation of the 7,6,5-fused ring system **280**, investigations were carried out towards a model system which would allow installation of the benzopyran F-ring oxygen atom of rubriflordilactone A, using the oxidation chemistry described in chapter 2 (Scheme 77).[84, 100]

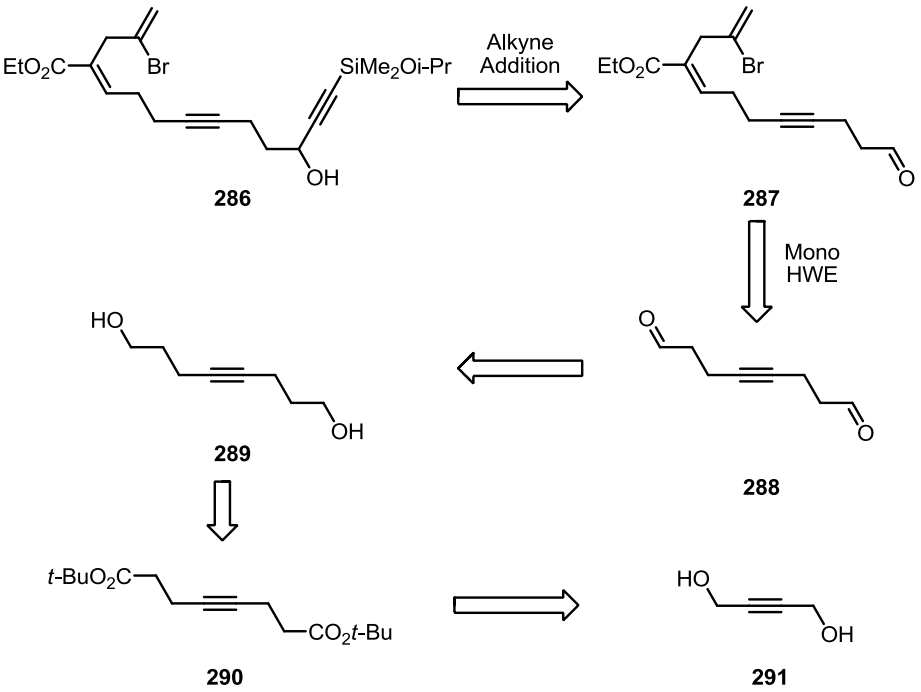


Scheme 77 – Retrosynthesis of the key step

It was envisaged that tricycle **284** could be prepared from acyclic precursor **286** *via* the previously developed intramolecular cyclisation (Scheme 77), with the key step of this model synthesis again being a fully-intramolecular application of the cascade methodology to form the 7-, 6- and 5-membered rings in a single step.[105] As a result, this preliminary work should set a solid foundation for the construction of the remaining rings of rubriflordilactone A and completion of its total synthesis.

Retrosynthetic analysis of model substrate **286** began with alkyne addition to aldehyde **287**. To remove the previous use of protecting groups, this aldehyde would be obtained from a HWE reaction on dialdehyde **288**, prepared by double oxidation of the diol **289**.

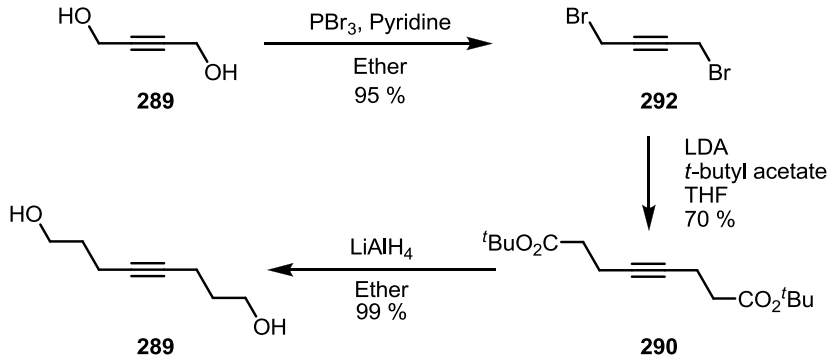
This diol would be prepared by homologation from commercially available diol **291** (Scheme 78).



Scheme 78 – Retrosynthetic analysis

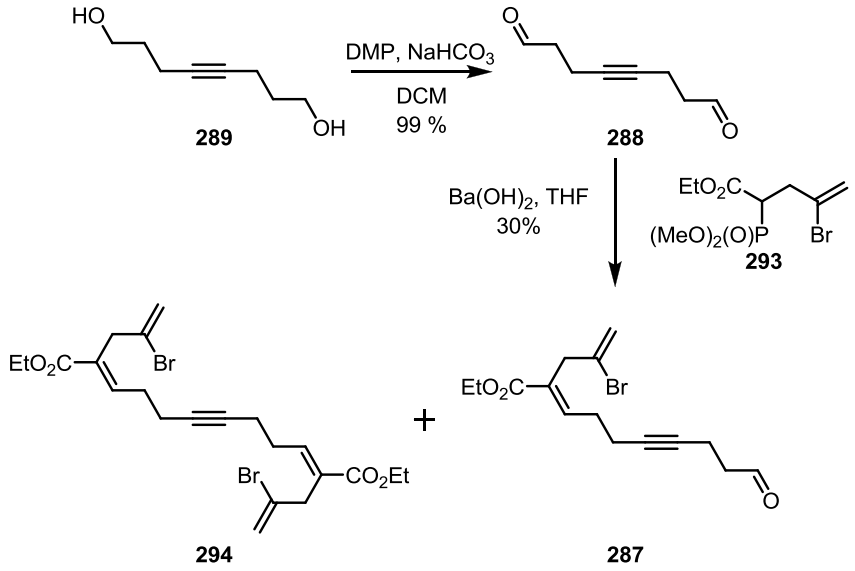
3.3.2. Synthesis of Fragment 286

The homologation sequence to diol **289** was achieved in 3 steps (Scheme 79). Initial reaction of **291** gave the dibromide **292** with PBr_3, which was used as a dielectrophile with the anion of *tert*-butyl acetate. Subsequent reduction of the ester with $LiAlH_4$ gave **289** with an overall yield of 47%.[117]



Scheme 79 – Synthesis of diol 289

The octynediol **289** was then oxidised with Dess–Martin periodinane to the dialdehyde **288** in 99% yield.[118] Several other oxidants were screened (Swern oxidation, SO_3•Py), but none of these reactions proceeded with a reproducible yield. Single HWE reaction was performed on the dialdehyde **288** using phosphonate **293**,[106] which was prepared from ethyl dimethylphosphonoacetate *via* alkylation with 2,3-dibromopropene **205.** The functionalised aldehyde **287** was obtained in moderate yield alongside the double HWE product. Whilst the HWE reaction gave only a modest yield, the overall route allowed rapid installation of the olefin moiety without the need for protecting group manipulation (Scheme 80). In an attempt to reduce the amount of double olefination product **294**, an excess of dialdehyde **288** was used. Disappointingly when 2 equivalent of dialdehyde **288** and 1 equivalent of phosphonate **293** were used, the reaction never proceeded cleanly and surprisingly no unreacted dialdehyde was recovered.



Scheme 80 – Synthesis of aldehyde 287

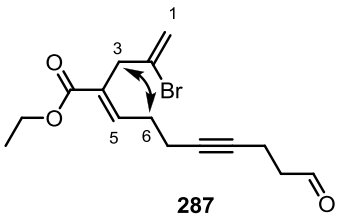
The geometry of this double bond is crucial for the synthetic strategy, as a (*Z*)-olefin would completely prevent the formation of the 7-membered C ring.

As discussed, the best yield obtained for the olefination was a disappointing 30%, although the *E*/*Z* selectivity was good (10:1, see Table 9). Different bases were examined to improve the sequence but none of these were more successful (Entries **2**, **3** and **4**).[119]

Entry	Base	Yield	*E*/*Z*
1	$Ba(OH)_2$ (0.8 equiv.)	30%	10:1
2	NaH (1 equiv.)	8%	3:1
3	LDA (1 equiv.)	9%	3:1
4	NaHMDS (1 equiv.)	12%	4:1

Table 9 – HWE reaction conditions screening

An nOe experiment unambiguously confirmed the geometry of the double bond by showing a clear through-space interaction between the protons attached to C3 and C6. On the other hand if the opposite geometry had been observed an interaction between the protons attached to C6 and the CH_2 of the ester could arise.

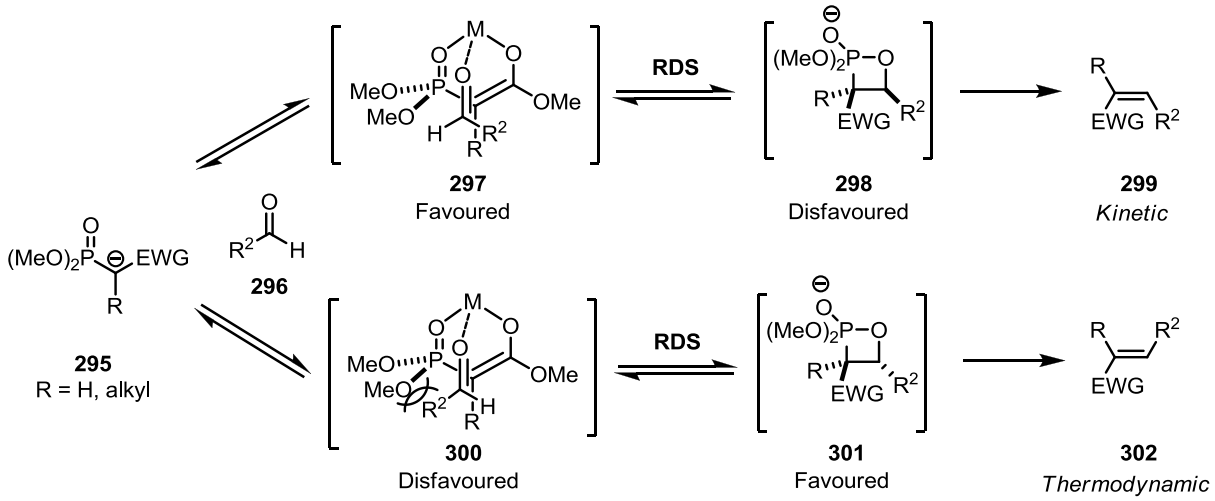


287

The chemical shifts of the protons at positions C3, C6, C5 and the CH_2 of the ester were assigned at 3.52, 2.41, 6.98 and 4.20 ppm respectively. The nOe experiment showed by irradiation of the proton attached to C3 a very clear enhancement of the protons at C6, confirming the expected (*E*)-olefin geometry.

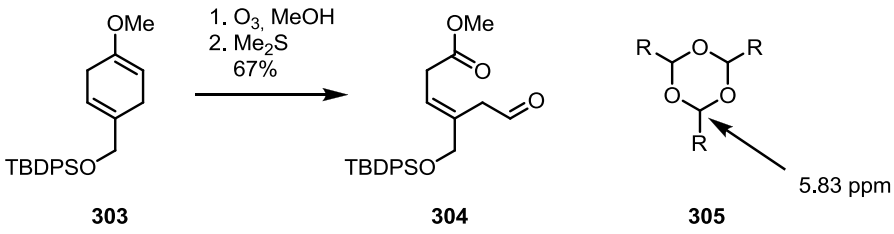
In general, the HWE reaction provides good (*E*)-olefin geometry selectivity. The phosphonate is firstly deprotonated, then reversible nuclephilic addition of this phosphonate to aldehyde **296** produces intermediates **297** and **300** in an aldol-like process, which decomposes via a 4-membered ring intermediate to yield olefin **299** and **302**

(Scheme 81). In this mechanism the addition of the aldehyde is a fast reversible process, while the rate determining step (RDS) is the formation of the 4-membered ring, due to steric effects. For this reason the reaction is selective towards the formation of **302**.



Scheme 81 – HWE reaction mechanism

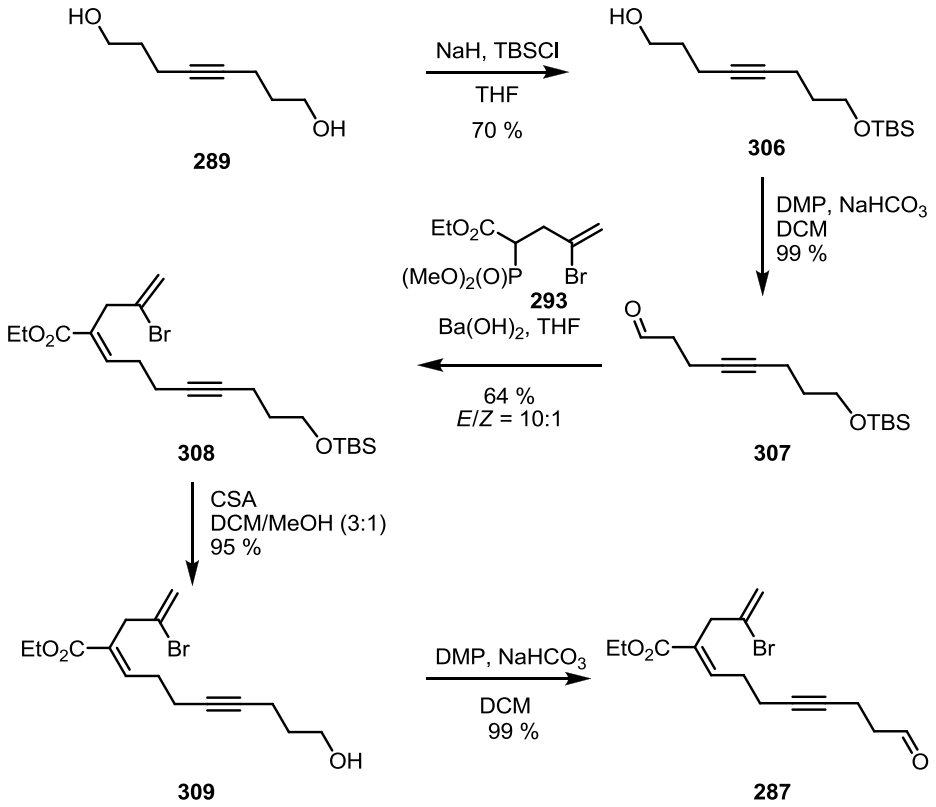
In addition, an unidentified product was observed by ^{1}H NMR spectroscopic analysis of the HWE reaction mixture which was tentatively attributed to trioxane **305** (Scheme 82). This trimerisation was supported by the presence of a peak by ^{1}H NMR at 5.31 ppm. This hypothesis has some literature precedent: Hallberg *et al.* had observed such trimerisation upon prolonged storage of their aldehyde **304**. The characteristic ^{1}H resonance of the trimer is found at 5.83 ppm, which suggests that our impurity could have a similar structure.[120]



Scheme 82 – Literature precedent for the synthesis of the trimer by-product

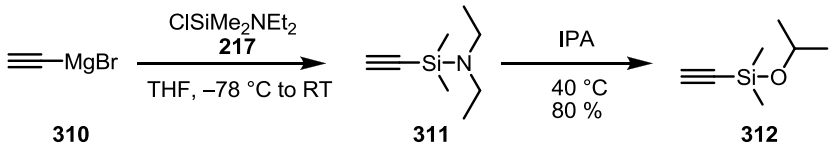
3.3.4. Route Improvement Towards Acyclic Precursor 287

A new, but longer route, was therefore developed to avoid the use of the dialdehyde **288** which could hopefully increase the yield of the HWE reaction. Monoprotection of oct-4-yne-1,8-diol with a TBS group followed by oxidation of the resulting free alcohol gave aldehyde **307** in 70% yield. To our delight, the HWE reaction using the previously optimised conditions on **307** proceeded cleanly in a much improved 64% yield with no degradation in the *E*/*Z* selectivity (*E*/*Z* = 10:1). The resulting product **308** was deprotected using a catalytic amount of CSA in DCM/MeOH to afford the free alcohol **309** which was then oxidised to aldehyde **287** using Dess-Martin periodinane (Scheme 83).



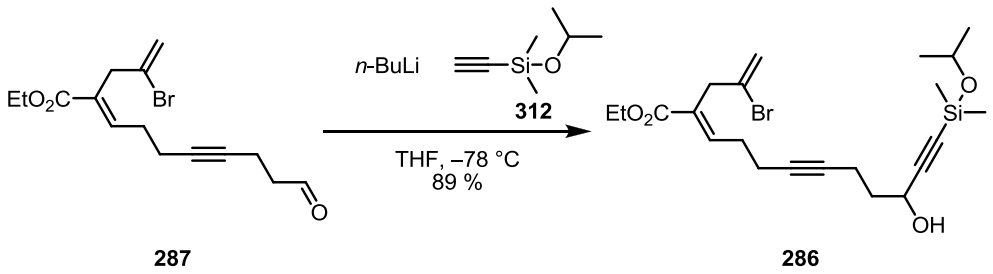
Scheme 83 – Synthesis of aldehyde 287

The next step consisted of the addition of the lithium acetylide of ethynyl(isopropoxy)dimethylsilane **312**, prepared using the procedure of Chan *et al.*, to aldehyde **287** (Scheme 84).[121]



Scheme 84 – Syntheis of alkyne 312

The key addition of this alkyne **312** with aldehyde **287** was now attempted. This reaction proved challenging, the main problem being the dryness of aldehyde **287**. As such, the reaction often did not go to completion, but could be optimised by drying the reaction mixture over CaH_2 (ca. 2 h). Once the problem of consumption of starting material was solved, the crude mass of the product **286** seemed to be very encouraging, but the yields after purification again did not reflect the success of the reaction. In some cases, two products were obtained: the desired compound **286** and a by-product identified spectroscopically as a potentially desilylated alkyne (^{1}H NMR doublet at 2.11 ppm). It was thought that the alkynyl alkoxy silane might be somewhat unstable to chromatography, which seemed reasonable as, like the silanes previously used (See Section 2.2.4.), it should possess similar stability to a TMS ether. A solution to this issue might be to use the diethyl(isopropoxy) silane. To minimise degradation, the product was purified using neutralised silica, and using this technique, the product **286** was isolated in a very pleasing 89% yield (Scheme 85). Thus, the cyclisation substrate **286** was prepared in 3 steps (or 6 steps) from diol **289**, with an overall yield of 26%.



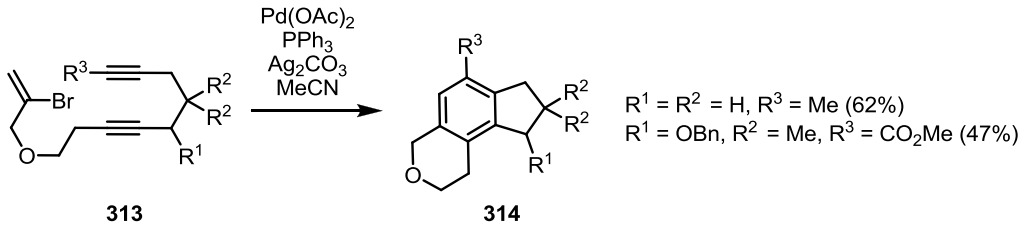
Scheme 85 – Alkyne addition to aldehyde 287

3.4. Formation of the CDE-Ring System of Rubriflordilactone A

3.4.1. Cyclisation reaction

The key acyclic precursor **286** was now ready to be used in the cyclisation step.

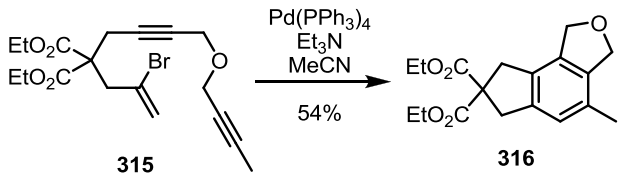
One of the earliest examples of such domino cyclisations for the construction of polycyclic molecules was published in 1991, by de Meijere *et al.*.[108] In this example, the bromoenediyne **313** formed the benzene derivative **314** under palladium catalysis in moderate yield (47-62%) (Scheme 86).



Scheme 86 – Synthesis of tricyclic benzene derivative 314

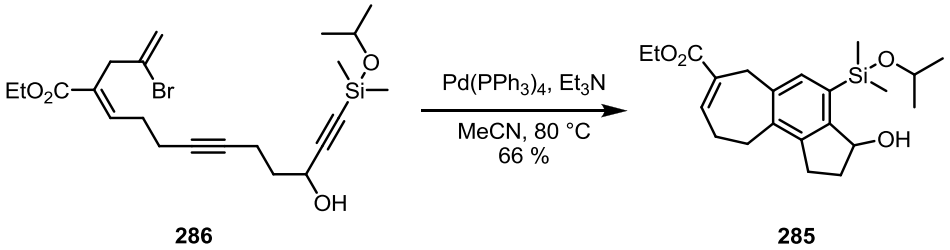
In this early work, de Meijere suggests that the last step of this reaction can either be described as a cyclisation *via* a Heck coupling or *via* a 6π-electrocyclisation with subsequent reductive elimination.

Similarly, in 1992, Negishi published the palladium-catalysed cascade cyclisation of bromoendiyne **315** which afforded **316** in 54% isolated yield (85% by NMR) (Scheme 87).[107]



Scheme 87 – Negishi's synthesis of tricycle 316

These latter conditions were tested on substrate **286**. Pleasingly, treatment of **286** with $Pd(PPh_3)_4$ in the presence of Et_3N in refluxing CH_3CN proceeded cleanly with good conversion based on analysis of the crude reaction mixture. The structure of the molecule was once again confirmed by ^1H NMR experiments. Whilst the enoate alkene peak remained relatively unchanged with a chemical shift of 6.89 ppm, the two other alkene protons had disappeared, and were replaced by a singlet at 7.13 ppm, which strongly suggested an aromatic proton. In addition the ^{13}C NMR supported assignment of the structure by the presence of six peaks for the aromatic ring. This result demonstrates the great potential of the cascade strategy, but again the purification proved quite problematic, the product being obtained in 66% yield (Scheme 88).

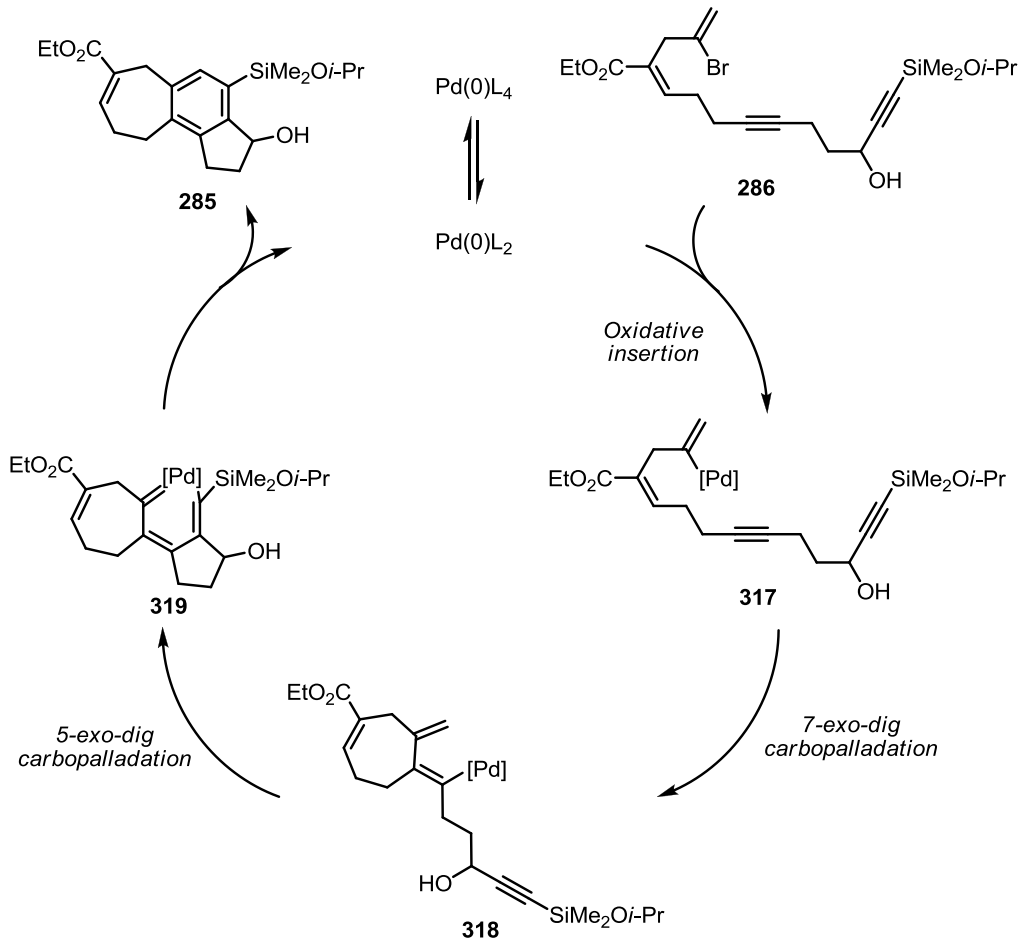


286 **285**

Scheme 88 – Key Cyclisation

3.4.2. Mechanism

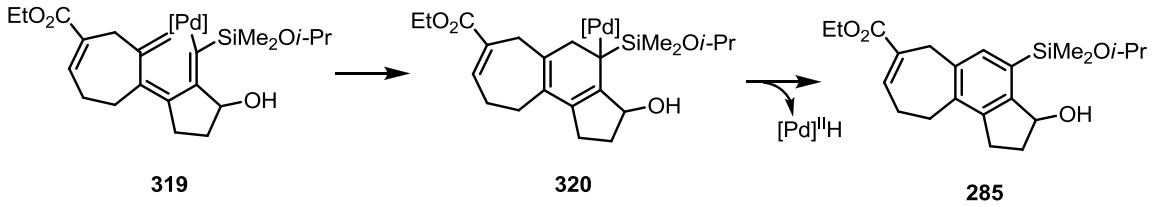
The mechanism of the reaction is depicted in Scheme 89. As previously seen, the first step is the oxidative addition of Pd(0) in the C–Br bond of **286** to form **317**, followed by a first *syn*-carbopalladation (7-*exo*-dig), building the 7-membered ring of **318**. A second carbopalladation (5-*exo*-dig) can occur in **318** to form a 5-membered ring in the triene **319**. Finally the palladium(0) is recycled and tricycle **285** is obtained.



Scheme 89 – Proposed mechanism for the cyclisation of 286

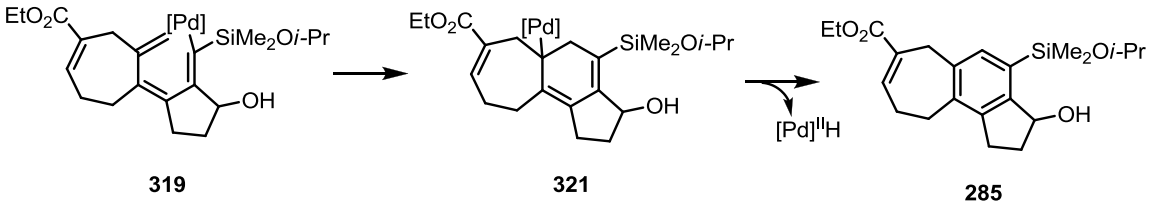
For the last step of this cycle, namely the regeneration of the Pd(0), three possible mechanisms can be proposed:

- The last step of the mechanism can be described as an electrocyclisation to give **320** followed by a β-hydride elimination, which gives the desired tricycle **285** (Scheme 90).



Scheme 90 – Possible mechanism 1

- A final carbopalladation could take place in a 6-*endo*-trig fashion to give **321**, followed by a β-hydride elimination (Scheme 91).

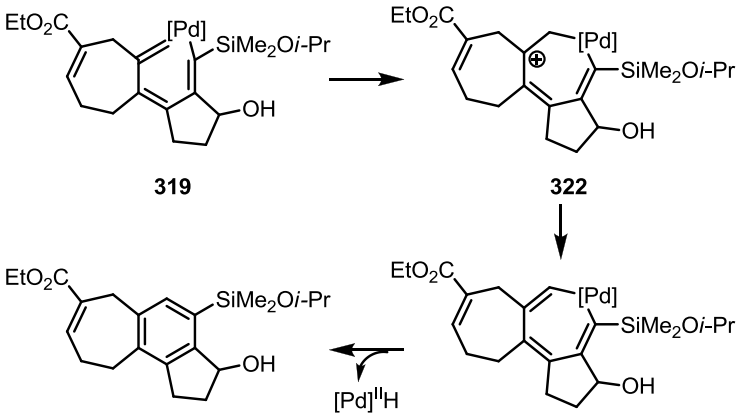


319 **321** **285**

Scheme 91 – Possible mechanism 2

In these two cases, the palladium is regenerated from the Pd(II) hydride species with Et_3N.

- Finally a 7-membered palladacycle **322** could be formed, followed by a reductive elimination of the palladium (Scheme 92).

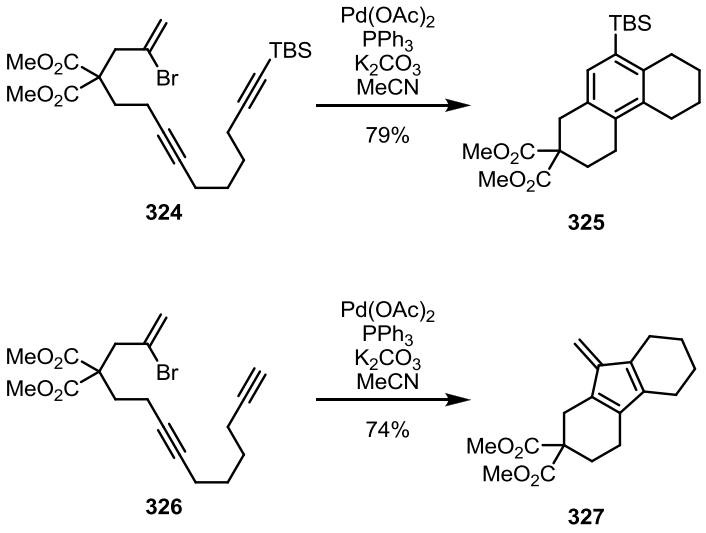


319 **322** **285** **323**

Scheme 92 – Possible mechanism 3

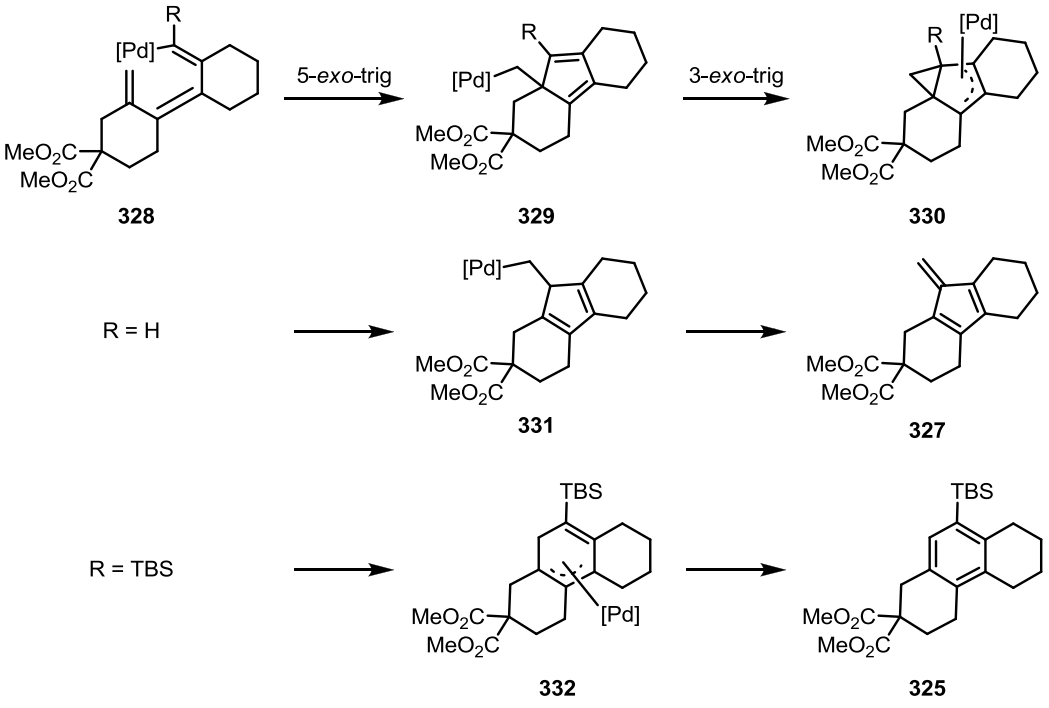
The proposed mechanism 1 cannot easily be verified.

In addition, de Meijere studied the formation of benzene and fulvene from bromoenediynes **324** and **326**.[112] While **324** cyclised under his original conditions to form the benzene derived polycycle **325**, the corresponding desilylated derivative did not form the expected product but exclusively the fulvene derivative **327**.



Scheme 93 – Studies of the different reactivities of silyl substituted bromoenediynes

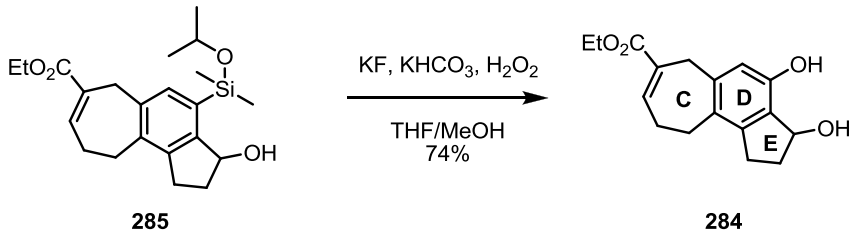
This result may suggest that mechanism 2 is unlikely and that a 5-*exo*-trig cyclisation would take place followed by a 3-*exo*-trig carbopalladation forming **330**. When R = H in **330**, a ring opening would take place followed by β-hydride elimination forming fulvene **327**. However, when R = TBS, induced by the trialkylsilyl subsituent a different ring opening of the cyclopropane in **330** followed by β-hydride elimination would afford the aromatic product **325**.



Scheme 94 – Mechanistic rationale

3.5. Oxidation of the Alkoxy Silyl Group

The last step of the planned sequence was the oxidation of alkoxy silane **285** to form the corresponding phenol. The conditions developed in Chapter 2 were applied and the reaction proceeded smoothly to afford the desired phenol product **284** in 74% yield (Scheme 95).[84, 100, 101] The formation of the phenol was again confirmed by ^{1}H NMR spectroscopic analysis with a notable upfield shift of the chemical shift for the aromatic proton, from 7.13 to 6.60 ppm, which is indicative of the increased electron density on the phenol ring.



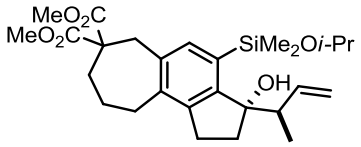
285 **284**

Scheme 95 – Oxidation of aryl silane 284

With the success of the strategy developed for the construction of the CDE-ring core of rubriflordilactone A, and introduction of the phenolic oxygen on the D ring,[105] the next challenge is to build a more elaborate system in order to form the F ring.

3.6. Retrosynthesis

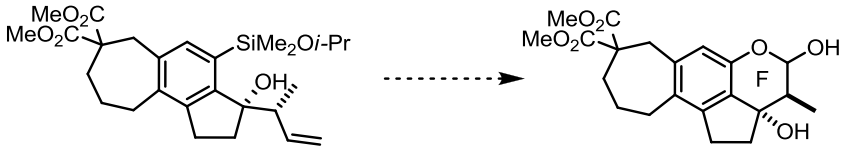
The first model system led to the construction of the CDE ring core of rubriflordilactone A (Figure 10), proving the possibility of using a palladium mediated cascade cyclisation for the total synthesis. A more advanced new model system **333** bearing a crotyl side chain has been designed.



333

Figure 10 – New model system 333

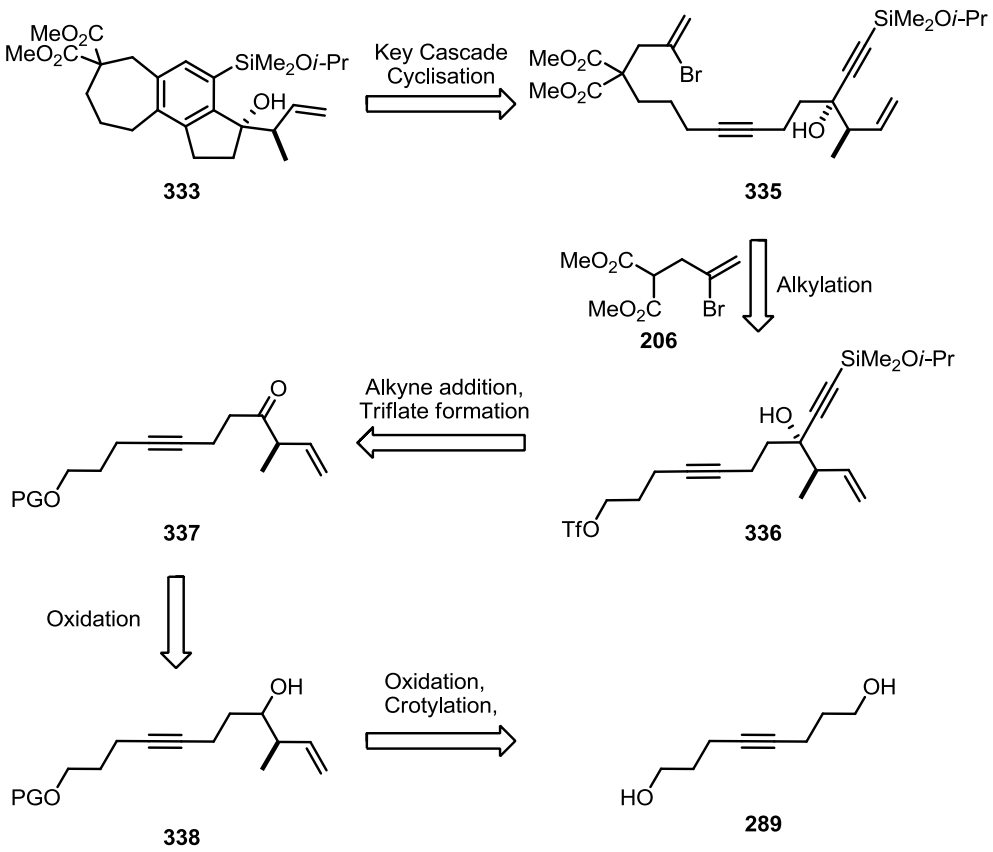
The installation of the crotyl group allows for derivatisation to form an aldehyde following ozonolytic cleavage,[122] which could form the lactone F ring in **334** following Tamao oxidation of the silyl group (Scheme 96).



333 **334**

Scheme 96 – Possible derivatisation

A proposed retrosynthesis of this model system **333** is shown in Scheme 97:



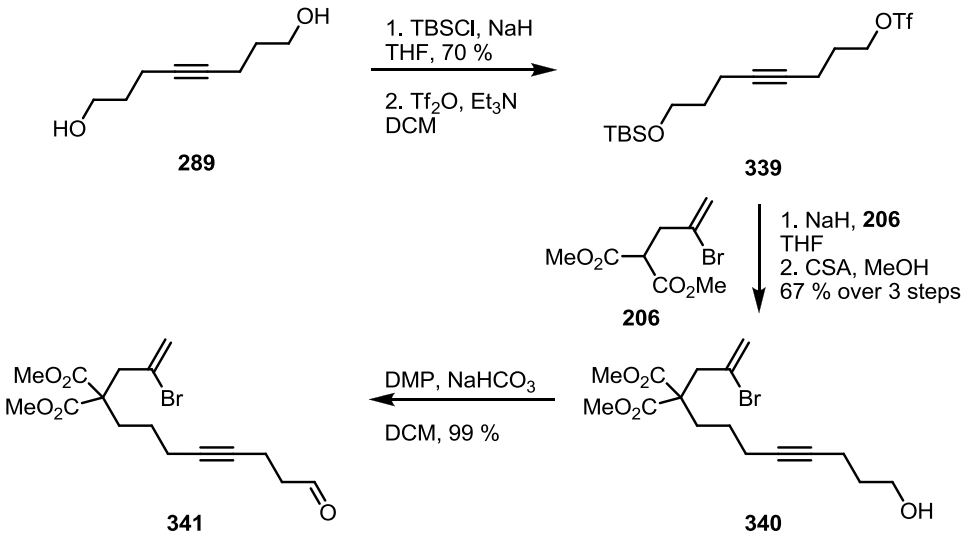
333 **335** **206** **337** **336** **338** **289**

Scheme 97 – Proposed retrosynthesis of 333

Tricycle **333** would be formed after the palladium mediated cascade cyclisation of **335**. This fragment for the cyclisation would be the result of an alkylation of malonate **206** with triflate **336**. This compound **336** would be obtained after a diastereoselective crotylation[123] performed on a mono-aldehyde derivative of **289**; following oxidation of the corresponding alcohol **338** to the ketone, a second alkylation could take place introducing the second alkyne and the oxidisable silicon (Scheme 97).

3.7. Synthesis of 333

The synthesis started with **289**, which was prepared in Section 3.3 in 3 steps and 66% yield (Scheme 79). The diol **289** was mono-protected in 70% yield and the remaining alcohol was sulfonylated with triflic anhydride and Et_3N, then used immediately to alkylate malonate derivative **206**. After cleavage of the TBS ether, with camphorsulfonic acid, alcohol **340** was obtained in 67% yield over 3 steps. Finally the alcohol was oxidised with DMP to aldehyde **341** in quantitative yield (Scheme 98).



Scheme 98 – Synthesis of aldehyde 341

3.7.1. Crotylation Reaction

Brown crotylation reaction proceeds *via* a chair-like transition state where the aldehyde approaches to minimise the steric interaction between the crotyl group and the axial Ipc ligand. The R group of the aldehyde occupies a pseudo-equatorial position. This transition state controls the outcome of the reaction which is highly enantioselective (> 90% ee) and diastereoselective (~ 95:5) (Figure 11).[123-125]

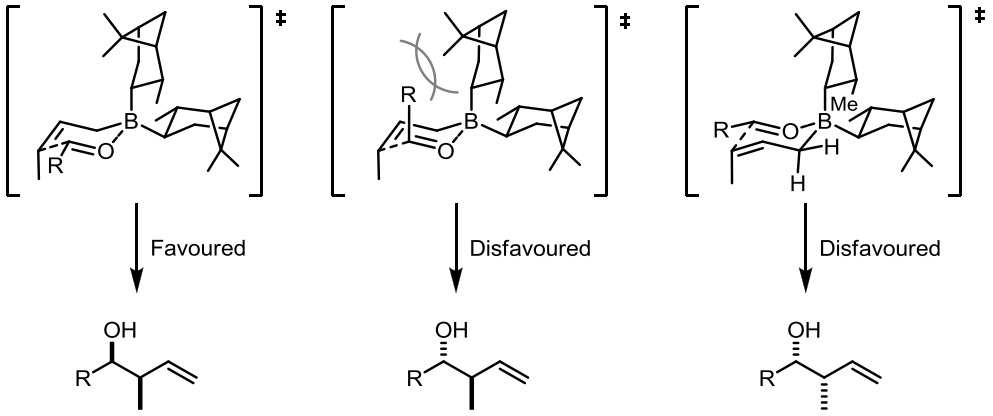
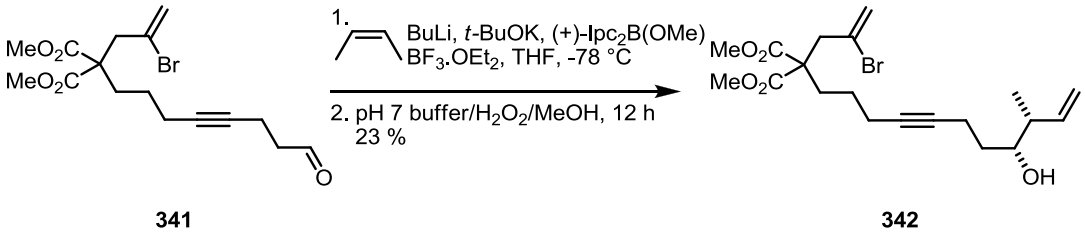


Figure 11 – Brown crotylation

Because of this very high level of stereochemical control, the reaction conditions were applied for the crotylation of **341** (Scheme 99).



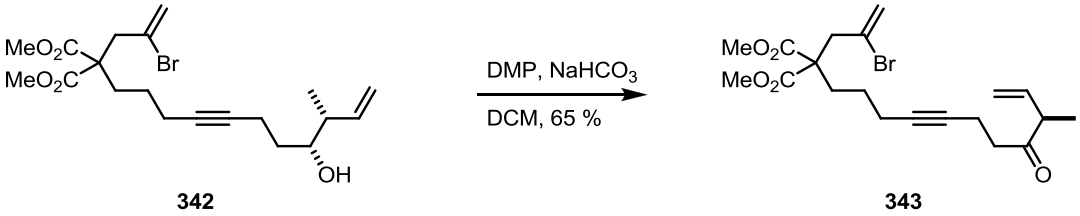
341 **342**

Scheme 99 – Brown crotylation on model system 341

The product **342** was obtained in a very poor 23% yield. In addition the product was obtained as a mixture with IpcOH. Simple manipulation (protection of the mixture as TBS ethers) allowed the separation of the protected product. The desired alcohol **342** was obtained after cleavage of the TBS ether under acidic conditions.

3.7.2. Cyclisation

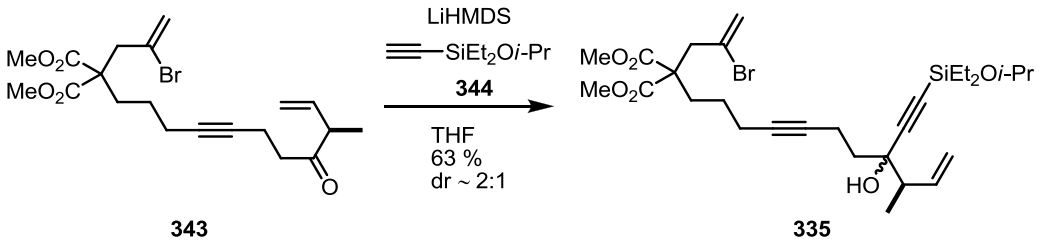
Following the crotylation reaction, alcohol **342** was oxidised with DMP to yield ketone **343** in 65% yield (Scheme 100). This compound was used directly after isolation to avoid possible isomerisation of the double bond.



342 **343**

Scheme 100 – Formation of ketone 343

Knowing from previous experience that the dimethyl(isopropoxy) silane protected alkyne was quite unstable to silica purification unless extra precautions were taken, and also that diethyl(isopropoxy) silanes are also readily oxidised, therefore alkyne **344** was used rather than alkyne **312**. The product **335** was isolated in 63% yield, with no precaution required during the work-up or purification on silica gel (Scheme 101).

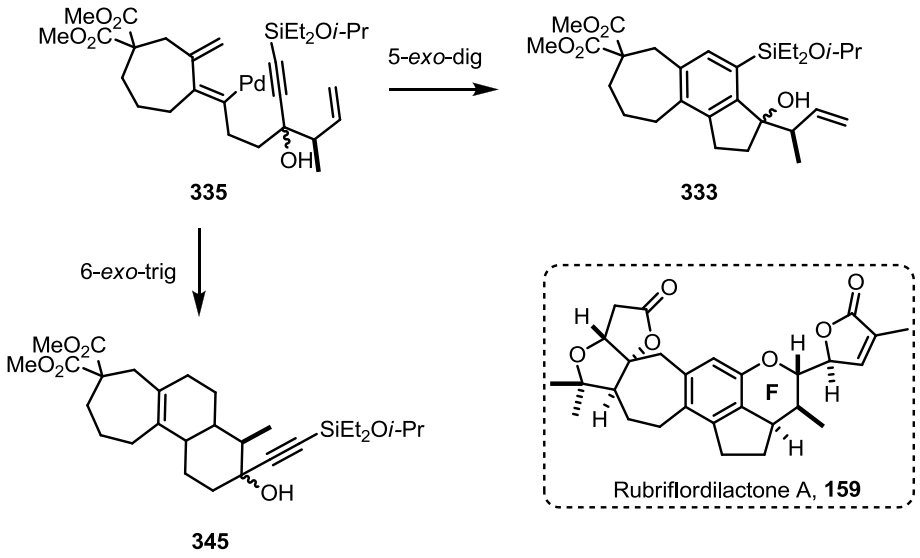


343 **335**

Scheme 101 – Addition of alkyne 344

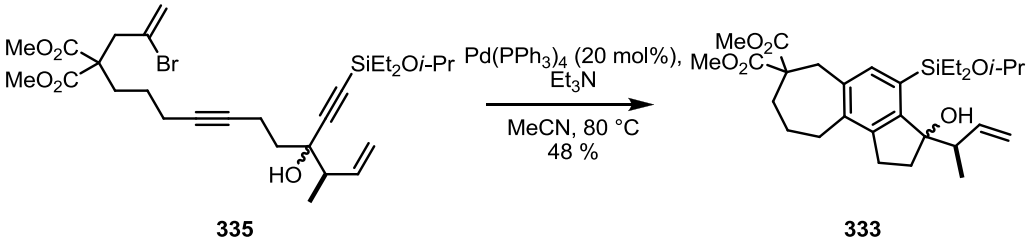
Finally, **335** was subjected to the cyclisation reaction conditions; this test was very important for the pursuit of this research, as for the first time, a competitive second carbopalladation could occur during the cyclisation process. Indeed in this fragment **335**, a competition between a 5-*exo*-dig and a 6-*endo*-trig cyclisation can take place as depicted in

the scheme below, leading to the formation of either the desired 7,6,5-tricycle **333**, or an undesired 7,6,6-tricycle **345** (Scheme 102).[126]



Scheme 102 – Possible cyclisation pathways

Pleasingly, when **335** was subjected to the reaction conditions only product **333** was detected by ^{1}H NMR. The reaction proceeded cleanly to give exclusively the desired tricycle **333** which was isolated in a moderate 48% yield likely due to scale issues (Scheme 103).



Scheme 103 – Key Cyclisation

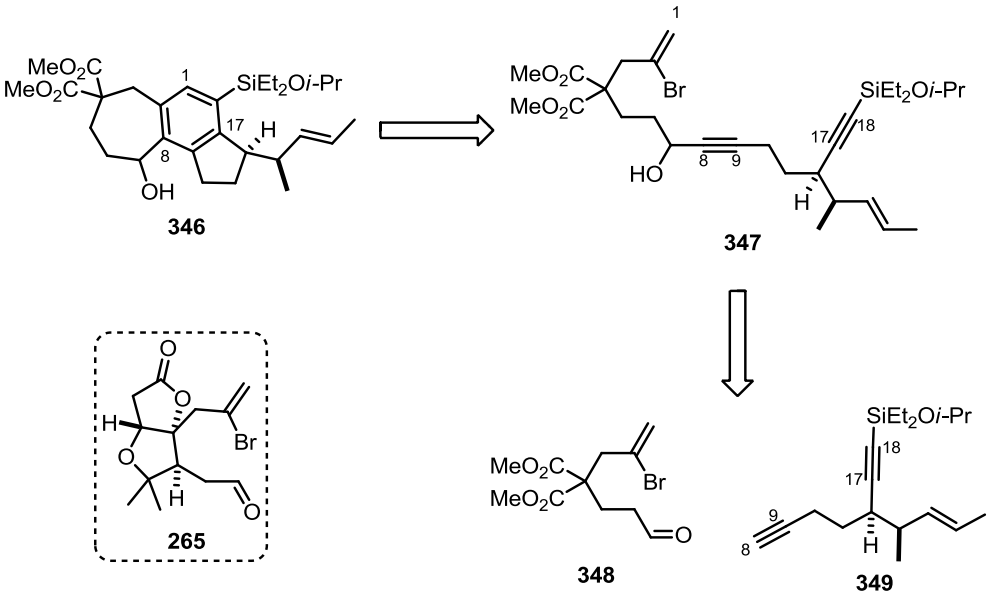
Unfortunately, due to a lack of material, the sequence could not be carried further. In addition the crotylation proved to be very difficult, and could not be reliably repeated. Therefore, it was decided that a different approach to the synthesis of fragment **335** was needed, which forms the focus of the next chapter.

4. Studies Towards Rubriflordilactone A

4.1. A New Approach for the Introduction of the Side Chain

4.1.1. Retrosynthesis

Keeping model system **346** as a target, a new disconnection was envisaged and the key intermediate **347** was the new aim, as described below (Scheme 104):

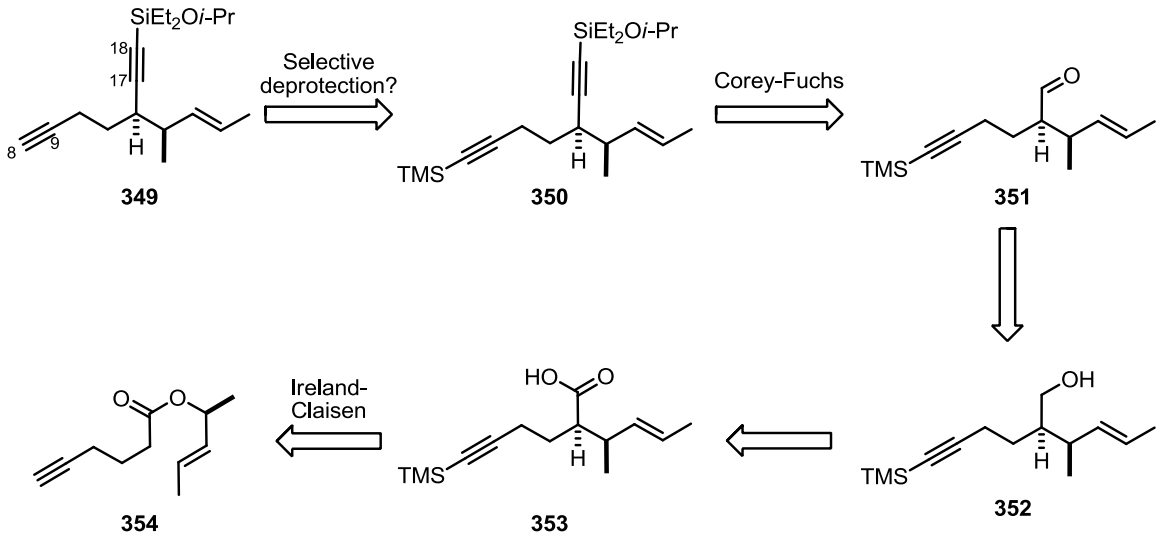


Scheme 104 – New approach

This new retrosynthesis led to the design of two fragments **348** and **349**. Diyne **349** would prove to be a considerably more appealing target as this alkyne could be transposed directly to application in the real natural product synthesis using aldehyde **265**, which is currently under study within the Anderson group.[127] The secondary alcohol obtained from the alkyne addition reaction to the aldehyde should to be easily removed, as it is at a labile benzylic position, *e.g.* by hydrogenation.[128]

4.2. First Retrosynthesis of Fragment 349

The first approach to fragment **349** relies on a possible late stage selective deprotection of a TMS-protected alkyne **350**. The alkyne bearing the oxidisable silicon group could be formed *via* a Corey-Fuchs reaction on aldehyde **351**,[129, 130] followed by protection of the newly formed alkyne. An Ohira-Bestmann homologation[131-133] could not be envisaged due to the presence of the TMS alkyne, as this utilises conditions which readily deprotect TMS alkynes (K_2CO_3, MeOH). This aldehyde **351** would arise from a reduction of acid **353**, which would be obtained after an Ireland-Claisen rearrangement of ester **354** (Scheme 105).[134-137]

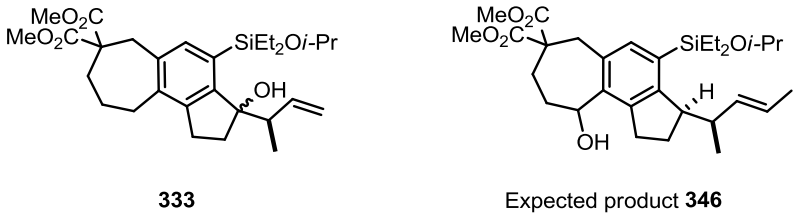


Scheme 105 – First retrosynthesis of fragment 349

This planned synthesis has one potential problem: the completely unprecedented selective deprotection of the TMS alkyne over the diethyl(isopropoxy) silane, which could have a very similar stability.

This route has a significant advantage over the previous route, where the side chain was introduced *via* a Brown crotylation, which afforded tricycle **333** after cyclisation (See Section 3.7.2.). This tricycle **346** bears a hydroxyl group where rubriflordilactone A has a

hydrogen substituent (Figure 12). This hydroxyl was thought to be removed selectively by hydrogenation later in the synthesis.[128] In this synthesis, the required oxidation state is obtained directly.



333 Expected product **346**

Figure 12 – Tricycle targets

The formation of the two stereogenic centres is controlled *via* the Ireland-Claisen reaction, as the reaction has a very high selectivity for the formation of the *E*-enolate (Figure 13).[138]

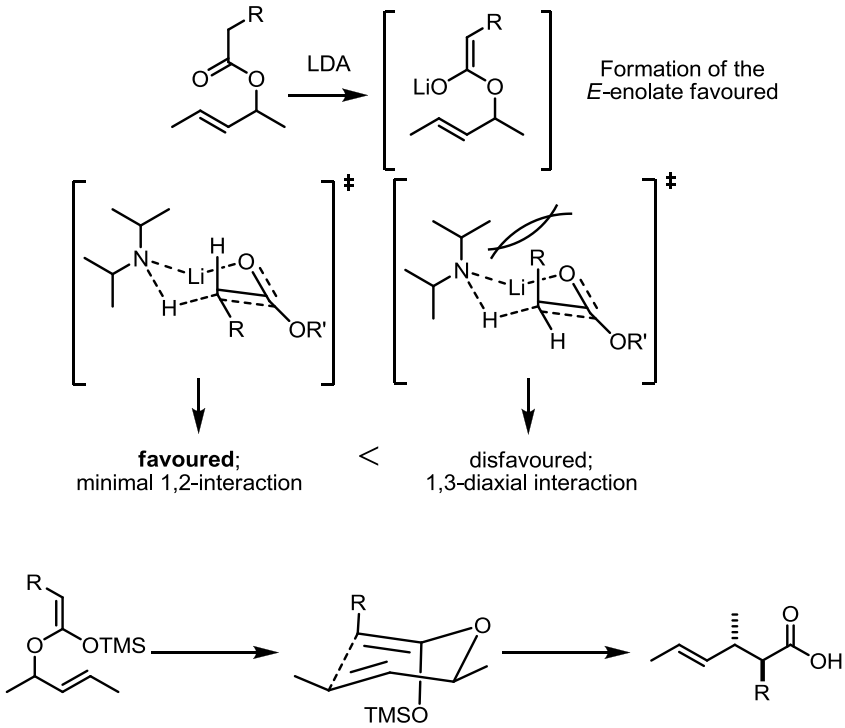
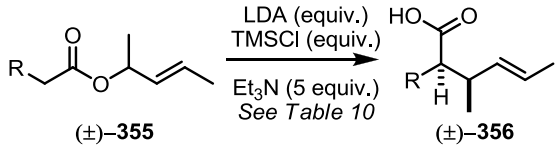


Figure 13 – Ireland –Claisen reaction: Stereochemical control

In order to understand how to perform the Ireland-Claisen reaction, a model substrate (±)-**355** was synthesised in two steps, and examined under various reaction conditions (Scheme 106, Table 10):



Scheme 106 – Ireland-Claisen reaction studies

Entry	R	LDA (equiv.)	TMSCl (equiv.)	Temperature	Yield
1[b]	CH_3	1.6	5	–78 °C to 60 °C	40%
2[a]	C_4H_9	1.6	5	–78 °C to RT	No reaction
3[b]	C_4H_9	1.7	5	–78 °C to RT	52%
4[b]	C_4H_9	1.7	5	–78 °C to RT	55%
5[b]	C_4H_5	3.4	7	–78 °C to RT	80% conversion 35% yield
6[b]	C_4H_5	3	5	–78 °C to RT	40%

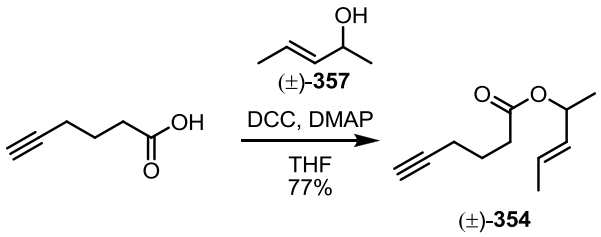
[a] LDA was added to a solution of ester (1 equiv.) and the reaction mixture was stirred for10 min at −78 °C, TMSCl and Et_3N were then added.
[b] LDA was added to a premixed solution of ester (1 equiv.), Et_3N and TMSCl.

Table 10 – Ireland-Claisen studies results

The addition of triethylamine to the reaction mixture was crucial as no reaction was observed in its absence. It was also found that premixing of Et_3N and TMSCl was important (Entry **2**),[139] and furthermore removal of any Et_3N•HCl salt by centrifugation was required in order to achieve the desired reaction. Although quantitative conversion was observed in most cases, the isolated yield was somewhat lower than expected. This is most likely due to the highly polar nature of the carboxylic acid product. Later optimisation in more advanced systems using acetic acid in the mobile phase solved this problem (See Section 4.8.).

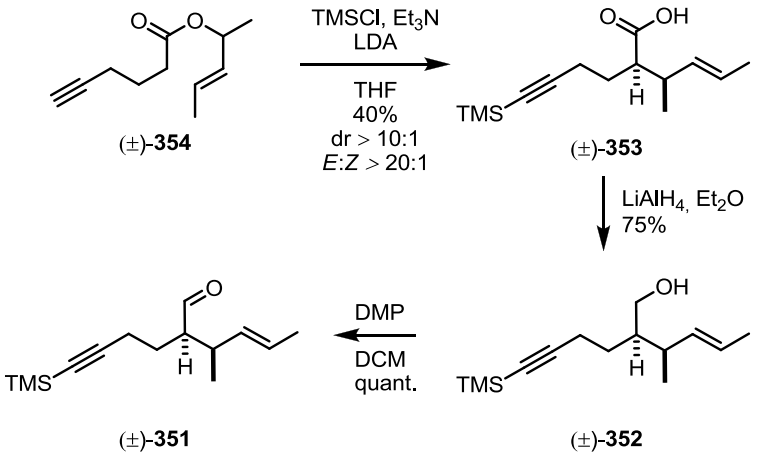
4.3. First Synthesis of Fragment 349

The preparation of enantioenriched alcohol **357** is known, and will be described in detail in Section 4.5.[140-142] However, the initial studies were carried out using the racemic alcohol (±)-**357**. Following our retrosynthetic analysis, the initial substrate to perform the Ireland-Claisen reaction was prepared. This began with esterification of hexynoic acid with alcohol (±)-**357** using DCC, which was achieved in 77% yield (Scheme 107).[143]



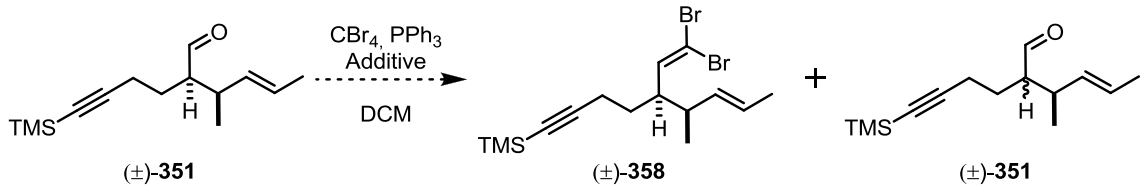
Scheme 107 – Ester (±)-354 formation

The product (±)-**354** was then subjected to the Ireland-Claisen reaction conditions (using the optimised conditions see Table 10, Entry **6**) with acid (±)-**353** being obtained with excellent stereoselectivity (dr > 10:1, *E*:*Z* > 20:1) but in a moderate yield of 40%.[139] The acid obtained was reduced to the alcohol (±)-**352** and finally oxidised to the aldehyde (±)-**351** in 75% yield over 2 steps (Scheme 108).



Scheme 108 – Synthesis of aldehyde (±)-351

The penultimate step for the synthesis of (±)-**349** was the formation of the alkyne, *via* the vinyl dibromide, using the Corey-Fuchs reaction. A variety of reaction conditions were tested (Scheme 109),[129] the results are shown in Table 11.



(±)-**351** (±)-**358** (±)-**351**

Scheme 109 – Vinyl dibromide (±)-358 synthesis

Entry	CBr_4 (equiv.)	PPh_3 (equiv.)	Additive (equiv.)	Yield (%)	Recovered aldehyde diastereomeric ratio
1	2	4	-	0	dr 1:1
2	2	4	Et_3N (2)	0	dr 1:0.9
3	1.5	3	-	0	dr 1:1
4	2.3	4.6	-	0	dr 1:0.8
5	2	4	Et_3N (10)	0	dr 1:1

Table 11 – Corey-Fuchs reaction screening

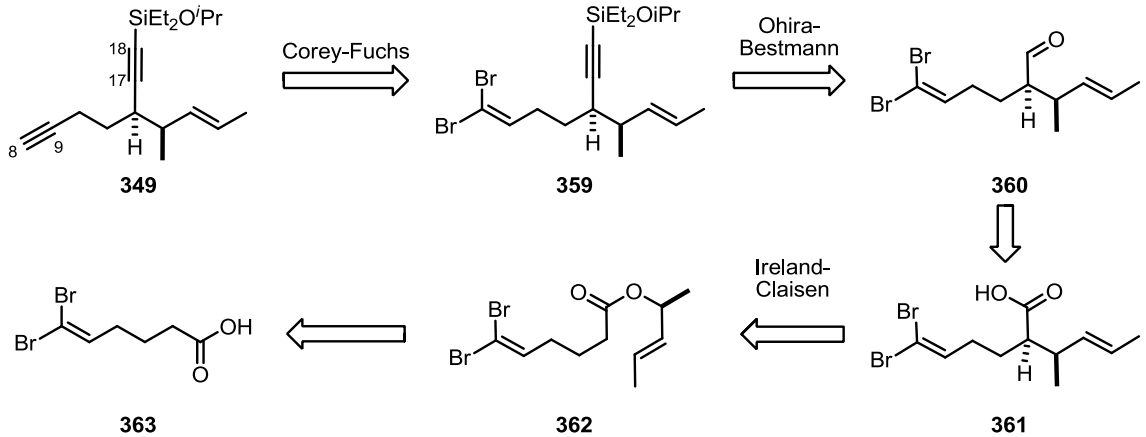
Unfortunately, all the conditions tested led to recovery of aldehyde, but as a mixture of diastereomers, as under these reaction conditions the aldehyde appeared to have epimerised. This is a surprising and disappointing result as these conditions were applied successfully for the synthesis of non-α-branched alkynes. These conditions were also used by other groups for the synthesis of alkynes from similar enolisable aldehydes.[144-147] As other methods for conversion of the aldehyde to the alkyne would be incompatible with the TMS-alkyne, a new retrosynthesis of **349** had to be drawn.

4.4. Second Retrosynthesis of Fragment 349

Considering the two issues from the previous proposed retrosynthesis:

- Epimerisation of aldehyde **351**,
- Selective deprotection of a TMS alkyne over a diethyl(isopropoxy)silane.

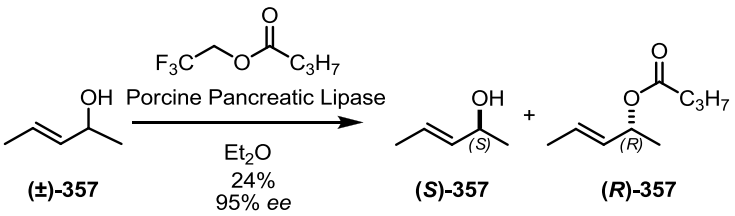
A new retrosynthesis was designed, which would avoid the possible selective deprotection issue, but would allow testing more reaction conditions for the introduction of the C17–C18 alkyne. It was decided that the unprotected C8–C9 alkyne should be introduced after silylation of the C17–C18 alkyne in **359**. For this purpose, the C8–C9 alkyne was masked as a vinyl dibromide which could be obtained from a Corey-Fuchs reaction.[129] It was hoped that this vinyl dibromide could be carried through multiple steps of the sequence and could unveil the desired C8–C9 alkyne at a late stage of the synthesis. The protected alkyne could in this case be introduced *via* a different alkyne formation method, which would prevent the epimerisation issue, for example an Ohira-Bestmann reaction on aldehyde **360**.[132] Following the earlier strategy, the aldehyde **360** would arise from a reduction of acid **361**, itself obtained from an Ireland-Claisen rearrangement of ester **362** (Scheme 110).[134-136, 138]



Scheme 110 – Second retrosynthesis of fragment 349

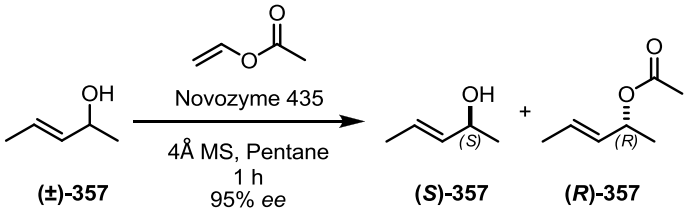
4.5. Enantioselective Synthesis of Alcohol 357

For the rest of the project, it was hoped to perform an enantioselective synthesis of fragment **349**. For this purpose, the alcohol **357** was kinetically resolved. Porcine pancreatic lipase and trifluoroethyl butyrate were used,[140, 141] giving selective esterification of the undesired (*R*)-alcohol **357**. The resolved materials could then be simply separated by silica chromatography. This resolution gave excellent results, giving the desired enantioenriched alcohol in 24% yield and 95% *ee*, The *ee* for this alcohol was determined by HPLC analysis of the derived benzoyl ester, allowing for UV detection. The major drawback was a reaction time of up to three weeks in order to obtain the desired enantiomeric excess (Scheme 111), compared to 80 h in the literature, which uses trifluoroethyl laurate instead of trifluoroethyl butyrate as the transesterification agent. The change of transesterifying agent could explain the change of reactivity.



Scheme 111 – Kinetic resolution of alcohol 357

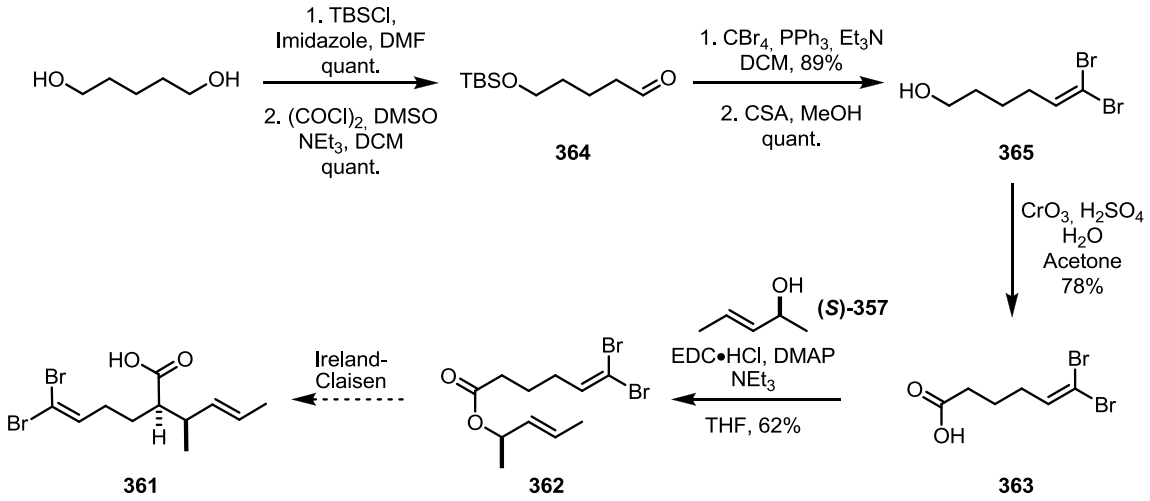
It was later found that acylation using vinyl acetate and Novozyme 435 was a more effective and rapid means of kinetic resolution,[142] giving the desired enantioenriched alcohol (*S*)-**357** in 95% *ee* in less than 1 h (Scheme 112).



Scheme 112 – Improved kinetic resolution of alcohol 357

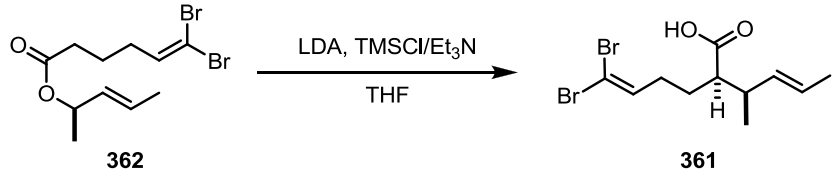
4.6. Second Synthesis of Fragment 349

The synthesis started from the cheap and commercially available 1,5-pentanediol, which was transformed into aldehyde **364** *via* a monoprotection and a Swern oxidation of the unprotected alcohol in quantitative yield.[148] The aldehyde was converted to the vinyl dibromide *via* a Corey-Fuchs reaction in 89% yield and subsequent cleavage of the TBS ether afforded **36**. To form ester **362**, the alcohol was oxidised to acid **363** *via* a Jones oxidation in 78% yield, followed by an EDC coupling with resolved alcohol (*S*)-**357** in 62% yield. EDC•HCl was used in preference to DCC in the ester formation as the dicyclohexylurea derivative could not be separated from the product, while the 1-(3-(dimethylamino)propyl)-3-ethylurea is water soluble and therefore could be removed in the work-up of the reaction (Scheme 113).



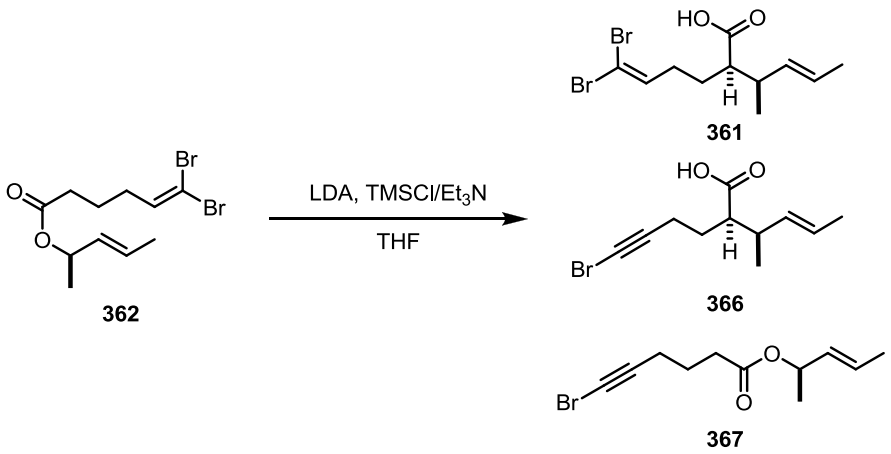
Scheme 113 – Synthesis of ester 362

With ester **362** in hand, the Ireland-Claisen rearrangement was attempted (Scheme 114).



Scheme 114 – Expected product of the Ireland-Claisen reaction

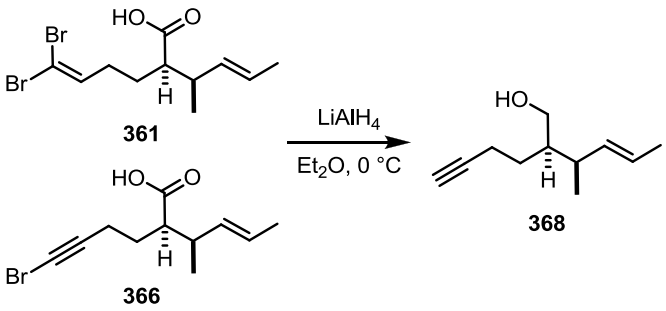
The reaction conditions described previously were utilised. Whilst the starting material was fully consumed, a mixture of three products was formed in this reaction (Scheme 115).



Scheme 115 – Products obtained from rearrangement of 362

The two acids **361** and **366** were completely inseparable by silica chromatography but could be separated from ester **367**. The alkynyl bromide is thought to arise from elimination of HBr under these conditions, which are not dissimilar to the normal conditions for the second step of the Corey-Fuchs procedure. Although the most common base used for that step in *n*-BuLi, LDA has been described as a suitable base for the formation of an alkyne from a vinyl dibromide.[149]

It was hoped that the mixture of bromoalkynyl acid **366** and dibromovinyl acid **361** could be taken directly through the subsequent steps, as both of these moieties could be converted to an alkyne anion. First the acid moiety had to be reduced to the corresponding alcohol; again the same reaction conditions were used as previously.

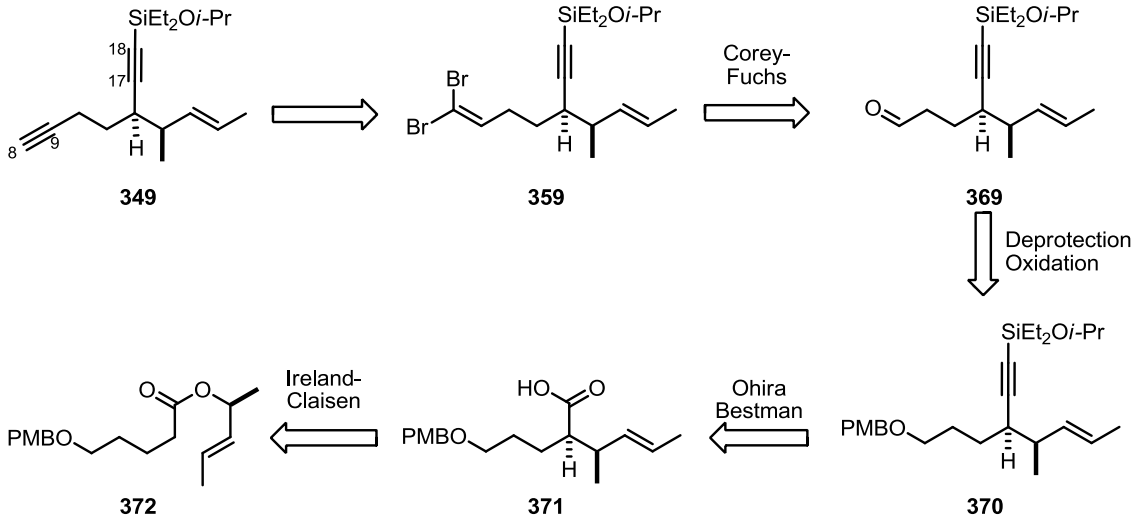


Scheme 116 – Reduction of the mixture of 361 and 366

Unfortunately, the reaction did not proceed as hoped. Although the desired alcohol functionality was obtained, the vinyl dibromide had under these reaction conditions been eliminated to form the corresponding alkyne (or alkynyl bromide) and in both cases the bromine had been displaced to form the terminal alkyne **368** (Scheme 116). This compound, disappointingly, is no longer a suitable synthetic intermediate for the desired synthesis, as the alkyne C8–C9 is now deprotected; no known protecting groups could be used that would not be deprotected by the Ohira-Bestmann reaction conditions that were intended in order to form the C18-C19 alkyne, and thus a third approach was devised.

4.7. Third Retrosynthesis of Fragment 349

As discussed in the previous section, the vinyl dibromide could not be used as a masked alkyne for the synthesis of fragment **349**. Therefore, a new route has been designed using a more traditional protecting group, which can be removed at a late stage allowing the differentiation of the two alkynes (Scheme 117).



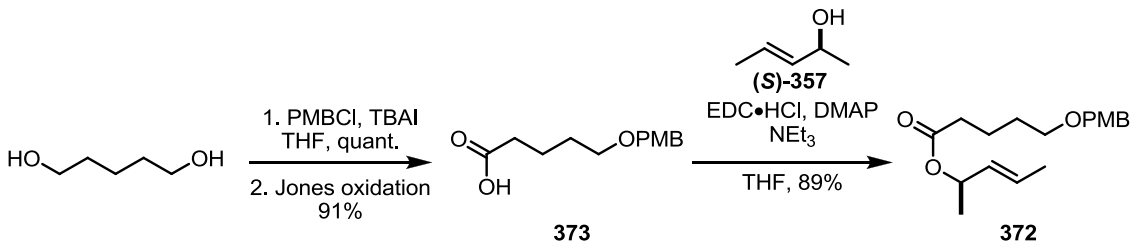
Scheme 117 – Third Retrosynthesis of fragment 349

In this strategy, the unprotected C8−C9 alkyne in **349** would be formed by a Corey-Fuchs reaction with the vinyl dibromide introduced *via* aldehyde **369**. This aldehyde would be obtained after deprotection and oxidation of **370**. The functionalised C17−C18 alkyne would be formed *via* an homologation method on the aldehyde obtained after reduction of **371**. This acid would be the result of an Ireland-Claisen rearrangement of ester **372**.

4.8. Third Synthesis of Fragment 349

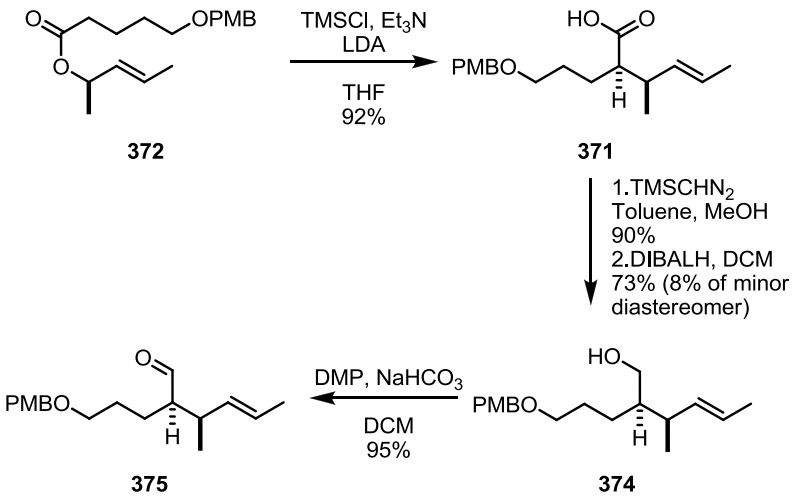
4.8.1. Synthesis of Alkyne 376

The synthesis started again with 1,5-pentanediol (Scheme 118), which was monoprotected as a PMB ether in quantitative yield. The acid was produced *via* a Jones oxidation in 91% yield and the ester was formed under the same conditions as previously to afford ester **372** in 89% yield using the procedure of Dake and co-workers.[139]



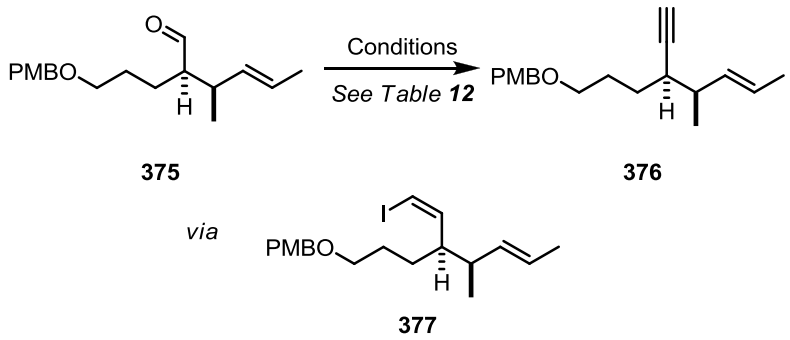
Scheme 118 – Synthesis of ester 372

Gratifyingly, when ester **372** was then subjected to the Ireland-Claisen rearrangement reaction conditions, acid **371** was formed in 92% yield, in 99% *ee* as a 10:1 mixture of diastereomers (*E*:*Z* > 20:1). Although direct reduction of the acid to the alcohol using $LiAlH_4$ was successful in the previous model system, the reduction of **371** was attempted but never gave a reliable and reproducible result. It was then decided to perform the reduction to the alcohol in a two step process, preparing the methyl ester of **371** allowing for a more facile reduction with DIBALH to the desired alcohol. A one step procedure to the aldehyde with 1 equiv. of DIBALH (at −78 °C) gave a mixture of both aldehyde **375** and alcohol **374**. The ester was prepared in 90% yield using $TMSCHN_2$,[150] and was reduced to the alcohol **374** in 73% yield. In addition, at this stage the two diastereomers could be separated by silica chromatography, and only the desired major diastereomer was carried through the rest of the sequence. The aldehyde **375** was then prepared using DMP in 95% yield (Scheme 119).



Scheme 119 – Synthesis of aldehyde 375

With aldehyde **375** in hand, methods for the transformation into the alkyne were examined in an attempt to avoid epimerisation (Scheme 120 and Table 12).



Scheme 120 – Synthesis of alkyne 376

Entry	Conditions (equiv.)	Product	Yield
1	CBr_4 (2), PPh_3 (4), Et_3N (10)	SM	-
2	Ohira-Bestman reagent (1.4), K_2CO_3 (2.0)	Complex mixture	-
3	*n*-BuLi (3.5), $TMSCHN_2$ (1.3)	**376**	71%
4	*n*-BuLi (3.5), $TMSCHN_2$ (1.3)	*n*-BuLi direct addition to aldehyde **375**	-
5	LDA (3.5), $TMSCHN_2$ (1.2)	**376** : Unknown (no alkene) (~1:1)	58%
6	*n*-BuLi (1.2), $TMSCHN_2$ (1.2)	**376**	36%
7	*n*-BuLi (3.0), $TMSCHN_2$ (3.5)	**376**	14%
8	1. NaHMDS (2), $[ICH_2PPh_3]I$ (2) 2. *t*-BuOK (2)	1. **377** 2. **376**	1. 60% 2. 82%
9	1. NaHMDS (2), $[ICH_2PPh_3]I$ (2) 2. NaHMDS (4)	1. **377** 2. **376**	1. 72% 2. 89%
10	1. NaHMDS (2), $[ICH_2PPh_3]I$ (2) 2. NaHMDS (2)	**376** without isolation of **377**	76%

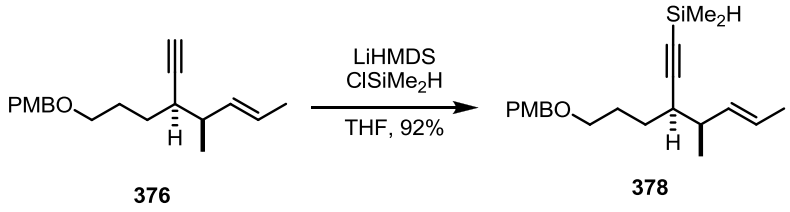
Table 12 – Condition screened for the synthesis of alkyne 376

Despite the previous epimerisation results of aldehyde **351**, the Corey-Fuchs reaction was attempted on new aldehyde **375**. Unfortunately the reaction did not form the expected vinyl dibromide and only led to a full recovery of aldehyde **375** with no degradation of the diastereomeric ratio (Entry **1**). Fortunately, this new compound had been designed in order

to test different homologation reaction conditions. The Ohira-Bestman reaction was tested but disappointingly failed for the synthesis of the alkyne **376** (Entry **2**). In a synthesis of the ABC ring system of lancifodilactone G, Paquette used a Colvin rearrangement to introduce the alkyne in **53** (See Section 1.5.2.).[23, 37, 151] These reaction conditions were directly applied to aldehyde **375** (Entry **3**). The reaction formed the desired alkyne **376** in a very good 71% yield. Unfortunately when the reaction was scaled up, direct addition of *n*-BuLi to the aldehyde was observed (Entry **4**). This is not completely unexpected considering the excess of *n*-BuLi present in the reaction mixture when the aldehyde is added. It was then decided to try the reaction with a different base which cannot add to the aldehyde (Entry **5**), with a 1:1 ratio of $TMSCHN_2$ and *n*-BuLi (Entry **6**) and with an excess of $TMSCHN_2$ (Entry **7**). Disappointingly none of these reaction conditions permitted the exclusive formation of the desired alkyne, and an unknown byproduct, showing no alkene signal by ^1H NMR spectroscopic analysis, was formed in a 1:1 to 1:2 ratio. Further review of the literature revealed that the Stork-Wittig reaction[152] followed by E2 elimination was a possible alternative. The reaction was attempted and formed the *cis*-vinyl iodide **377** in an optimised 72% yield as exclusively the *Z*-olefin, which then underwent elimination with *t*-BuOK to give the C17–C18 alkyne in 82% yield (Entry **8**). Although this reaction is a two step procedure, it was envisaged that these steps could be combined into a one step procedure; thus, attempts were made to combine both steps in one pot. Pleasingly when the elimination was attempted with NaHMDS, the alkyne **376** was obtained in 89% yield (Entry **9**). The reaction could be reproducibly performed in one-pot by adding more NaHMDS to the reaction mixture, after formation of the vinyl iodide, allowing the alkyne **376** to be obtained in 76% yield (Entry **10**).

4.8.2. Functionalisation with –$SiMe_2H$

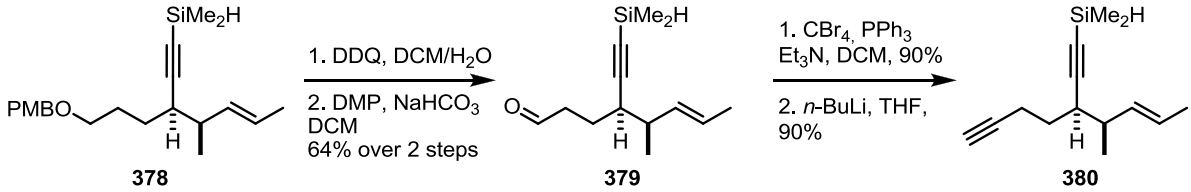
Studies from the Chang group have demonstrated an alternative method of preparing alkoxy dialkyl silanes *via* a ruthenium-catalysed oxidation of a hydrosilane.[153] This method was of great appeal to us, as the $HSiClMe_2$ reagent is inexpensive and more moisture stable following trapping. It was decided to use this method, therefore the C17–C18 alkyne **376** was functionalised with a dimethyl silane group to give **378** in 92% yield (Scheme 121).



376 **378**

Scheme 121 – C17−C18 alkyne protection

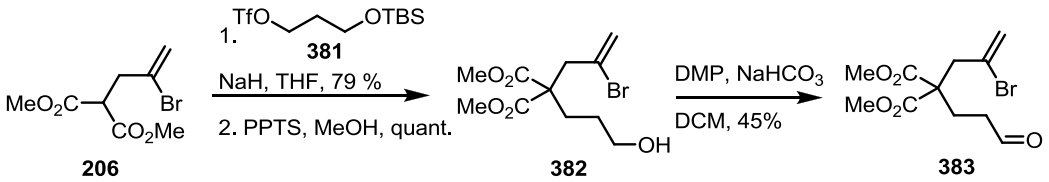
Work within the Anderson group has also proved the increased stability of this silane *versus* the dimethyl(isopropoxy) silane. This is of great interest for this work, as this dimethyl(isopropoxy) silane would have to be carried through 5 steps with silica purification, which is very likely to be problematic. Pleasingly the silane-functionalised alkyne **378** was indeed stable to various reaction conditions; **378** was first subjected to DDQ to afford the corresponding alcohol, which was immediately transformed into aldehyde **379**, as the alcohol could not be separated from *para*-methoxybenzaldehyde, but could after the oxidation. Finally aldehyde **379** was transformed into the alkyne **380**. For this reaction again, several conditions were tested, and the best yields were obtained *via* a Corey-Fuchs reaction (Scheme 122). It is noteworthy that the alkynyl silane tolerated this range of reaction conditions.



Scheme 122 – Synthesis of fragment 380

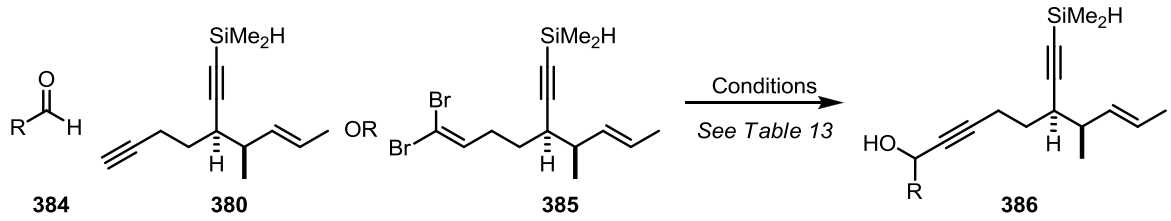
4.8.3. Coupling of Fragment 380

With the desired fragment **380** in hand, the coupling with an aldehyde was attempted. The aldehyde **383** was synthesised from malonate derivative **206** and the unstable monoprotected triflate **381** (Scheme 123).



Scheme 123 – Synthesis of aldehyde 383

The coupling reaction was then attempted, and the results are shown below (Scheme 124, Table 13).



Scheme 124 – Coupling reaction

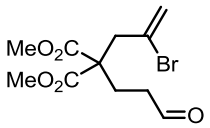
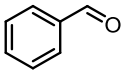
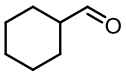
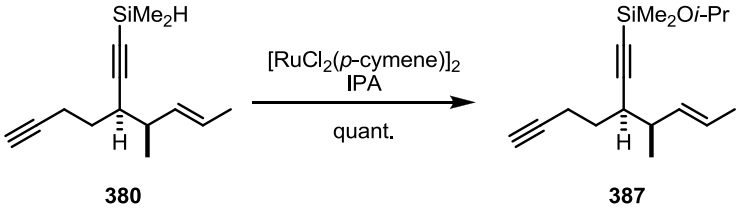
Entry	Aldehyde	Alkyne/ Surrogate	Conditions (equiv.)	Outcome
1	 **383**	**380**	LiHMDS (1.1)	**380** recovered, possible intramolecular reaction with a malonate ester of **383**
2		**385**	*n*-BuLi (2.2)	**380** recovered, possible intramolecular reaction with a malonate ester of **383**
3		**385**	*n*-BuLi (2.2)	Complex mixture
4		**380**	$Zn(OTf)_2$, *N*-methyl ephedrine, Et_3N[155]	Desilylated product

Table 13 – Conditions screen for the alkyne addition

The coupling reaction was first attempted with the desired aldehyde **383** (Entries **1**, **2**). Unfortunately in both cases, no desired alcohol was obtained; the alkyne **380** was fully recovered but the aldehyde had been fully consumed, forming an unknown product containing only one of the malonate esters. For this reason the reaction was tested on benzaldehyde (Entry **3**), but only led to a complex mixture. These results may be explained by the very close pK_a of a terminal alkyne and the silane. No experimental pK_a values of alkynyl silanes have been determined. A theoretical study has estimated the pK_a of a –C≡C$SiMe_2H$ to be around 32.2 in DMSO, while the pK_a of a terminal alkyne is approximately 29 in DMSO.[154] This suggests that competitive silane deprotonation might be occuring. Therefore the conditions developed by Carreira[155] for the enantioselective coupling of an aldehyde and an alkyne were used (Entry **4**). These conditions would be able to deprotonate the desired terminal alkyne under milder conditions and if successful would also form a single diastereomer. Although this reaction successfully allowed coupling between the C8−C9 alkyne and the carboxaldehyde, as shown by a signal at 4.19

ppm by ^{1}H NMR spectroscopic analysis, the C17−C18 alkyne had been desilylated in the course of the reaction (doublet at 2.15 ppm) (Entry **2**).

With this enlightening, but disappointing, result in hand (Entries **1**, **3**, **4**), the hydrosilane was oxidised to the alkoxysilane **387** and this product was deprotonated and reacted with aldehydes (Scheme 125).



380 **387**

Scheme 125 – Synthesis of dimethyl(isopropoxy) silane 387

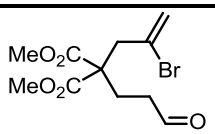
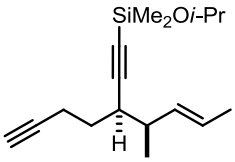
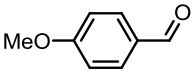
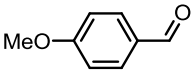
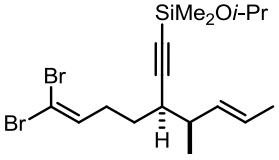
Entry	Aldehyde	Alkyne	Conditions (equiv.)	Outcome
1	 **383**	 **387**	*n*-BuLi (1.1)	No reaction
2			LiHMDS (1.1)	**387** Recovered and desilylated **387**
3		 **388**	*n*-BuLi (2.2)	No reaction, but alkyne **387** and aldehyde were recovered

Table 14 – Attempts at coupling 387 with an aldehyde

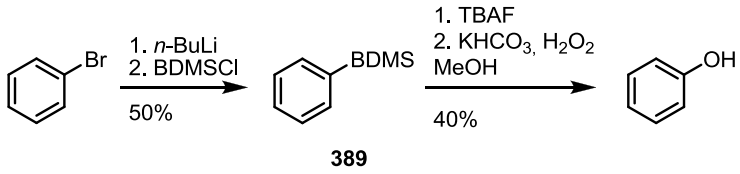
Coupling of **387** with aldehyde **383** was first attempted (Entry **1**), but surprisingly no reaction was observed, and both starting materials were recovered. Because of the issue encountered with aldehyde **383** in the previous experiments (See Table 13), it was decided to use *para*-methoxybenzaldehyde to test the reaction. Unfortunately in both cases, no desired product was formed (Entries **2**, **3**). In the case of direct deprotonation of alkyne

387, no aldehyde was recovered; instead a mixture of the starting material alkyne and the corresponding desilylated product (Entry **2**). When the vinyl dibromide **388** was used, the *in situ* formed alkyne was recovered alongside *para*-methoxybenzaldehyde but no desired alcohol (Entry **3**).

4.8.4. Functionalisation with –$SiMe_2Bn$

With this disappointing result in hand, it was decided to change functionalising group on the silane. The benzyldimethyl silane (BDMS) offered a potential solution to this issue, as it is an "oxidisable silicon" as shown by the Trost group,[156] and benefits from having a greater stability than a dimethyl(isopropoxy) silane, and thus should not be a problem towards deprotonation and desilylation.

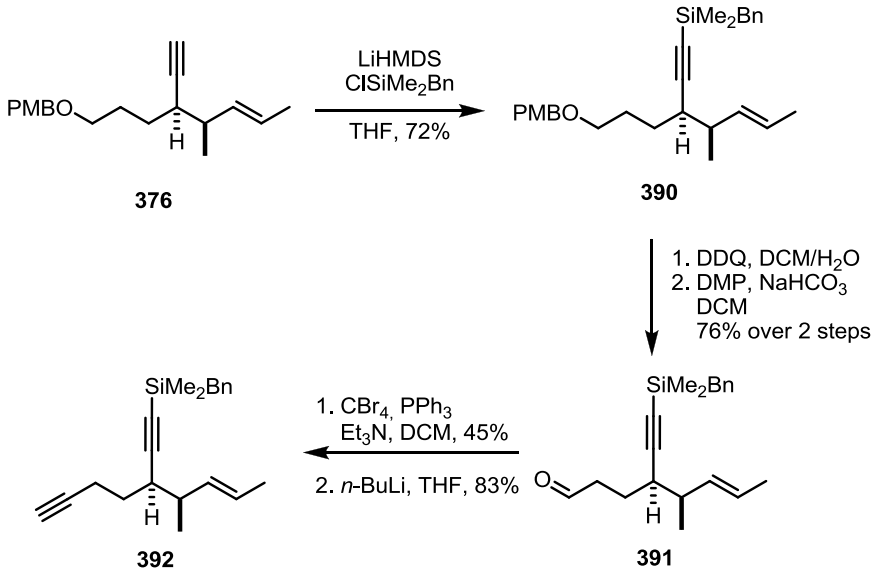
Again with this protecting group, alkyl BDMS groups have been oxidised to alcohols but there are no examples of aryl BDMS function being oxidised to the respective phenol. This was successfully shown by preparing benzyldimethyl(phenyl)silane **389** from bromobenzene, and oxidising it under standard Tamao oxidation conditions to phenol (unoptimised) (Scheme 126).



389

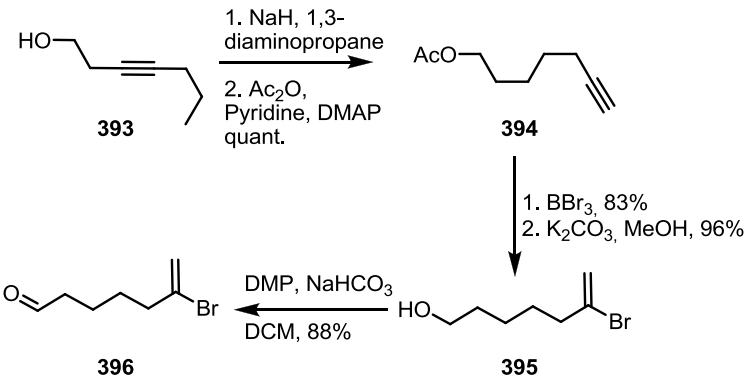
Scheme 126 – Aryl BDMS oxidation

The synthesis of the new fragment **392** started from the common precursor **376**. The terminal alkyne was protected as a BDMS derivative in 72% yield. The PMB group was removed, and the corresponding alcohol was oxidised to aldehyde **391** in 76% yield over 2 steps. Finally the Corey-Fuchs reaction led to alkyne **392** in 38% over 2 steps (unoptimised) (Scheme 127).



Scheme 127 – Synthesis of fragment 392

As the synthesis of the coupling partner aldehyde **383** proved irreproducible and sometimes very low yielding, a new aldehyde was synthesised. This aldehyde would also have the advantage of not bearing the ester groups which could be problematic for the coupling steps. Aldehyde **396** was prepared in 5 steps from hex-3-yn-1-ol **393**. An isomerisation reaction allowed access to the terminal alkyne in quantitative yield,[157] and the alcohol was protected as the corresponding acetate **394** in quantitative yield. A bromoboration step allowed access to the vinyl bromide in 83% yield,[158] then after acetate cleavage and Dess-Martin oxidation, aldehyde **396** was obtained in 88% yield (Scheme 128).



Scheme 128 – Aldehyde 396 synthesis

With aldehyde **396** and alkyne **392** in hand, the key coupling was attempted, the results are presented in Table 15.

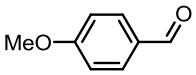
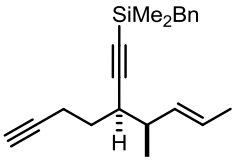
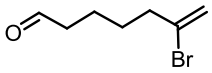
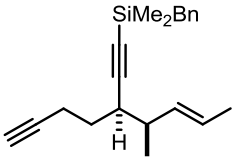
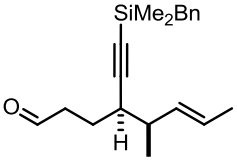
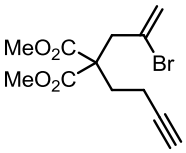
Entry	Aldehyde	Alkyne	Conditions (equiv.)	Outcome
1			*n*-Buli (2.2)	No reaction (SM recovered)
2			LiHMDS (1.4)	No reaction (SM recovered)
		392		
3			LiHMDS (1.4)	Complex Mixture
4	**396**		*n*-BuLi (2.2)	Complex Mixture
		392		
5			$Zn(OTf)_2$, *N*-methyl ephedrine, Et_3N	Alkyne **208** recovered
6	**391**	**208**	LiHMDS (1.4)	Complex mixture

Table 15 – Coupling reaction test

Unfortunately, again none of these reactions formed the desired product. In the first attempts, alkyne **392** was deprotonated with *n*-BuLi or LiHMDS and trapping was attempted trapped with *para*-methoxybenzaldehyde or aldehyde **396** (Entries **1**-**4**). Disappointingly in all cases, no expected alcohol was formed and when *para*-methoxybenzaldehyde was used, only the alkyne **392** was recovered with the aldehyde being fully consumed (Entries **1**, **2**). In the cases where the desired model aldehyde **396** was used, a complex mixture was formed and no starting or product could be identified. It was then decided to invert the coupling, using aldehyde **391**, which is an intermediate in the synthesis of diyne **392**, and alkyne **208**. Deprotonation of alkyne **208** with LiHMDS and subsequent trapping with aldehyde **391** led to a complex mixture (Entry **7**). Finally

when attempting Carreira's conditions on this system, only alkyne **208** was recovered, the aldehyde **391** has completely decomposed (Entry **6**).

As the chiral monosilylated diyne **392** is a precious intermediate, it was decided to model the reaction using achiral diyne **397** as shown in Table 16. Applying Carreira's conditions, the desired product was formed on a single occasion, but this was irreproducible (Entry **1**). Under all further attempts, alkyne **397** was fully recovered whilst some of the aldehyde was consumed. The use of traditional bases for the alkyne deprotonation (Entries **2** and **3**) gave the same mixture containing no desired product. As a last resort, it was envisaged that alkyne metallation *via* the Nozaki-Kishi-Hiyama reaction using $CrCl_2$ and the alkynyl iodide **398** for the coupling may circumvent these other issues (Entry **4**). Unfortunately this single test did not form any product, and only the deiodinated alkyne **397** was recovered. As a proof that aldehyde **396** can react with a silyl acetylene, TMS-acetylene was evaluated (Entry **5**). The expected product was formed successfully with 100% conversion, suggesting a different alkyne substrate may be effective in completing this strategy.

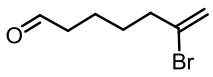
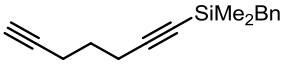
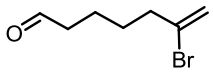
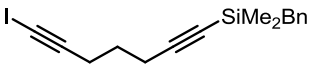
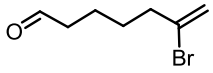
Entry	Aldehyde	Alkyne/ Surrogate	Conditions (equiv.)	Outcome
1	 **396**	 **397**	$Zn(OTf)_2$, *N*-methyl ephedrine, Et_3N	**397** recovered and 50% **396** recovered
2			LiHMDS (1.4)	**397** recovered and 50% **396** recovered
3			EtMgBr (1.1)	**397** recovered and 50% **396** recovered
4	 **396**	 **398**	$CrCl_2$ (3)	**397** recovered and 50% **396** recovered
5	 **396**		LiHMDS (1.1)	Product; 100% conversion

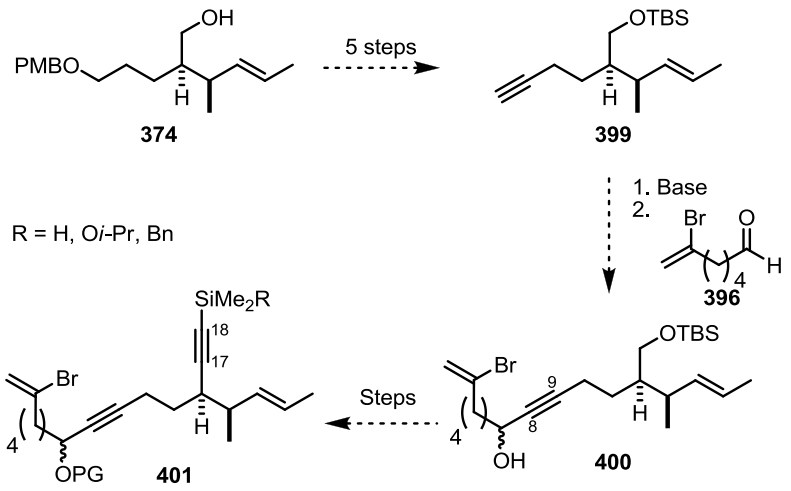
Table 16 – Coupling with model diynes

4.9. Conclusion

The difference in behaviour in these systems is intriguing, suggesting a different strategy will be required in order to achieve the desired coupling of the alkyne and aldehyde fragments. This remains a challenge for the synthesis, which will need to be addressed or circumvented in future investigations.

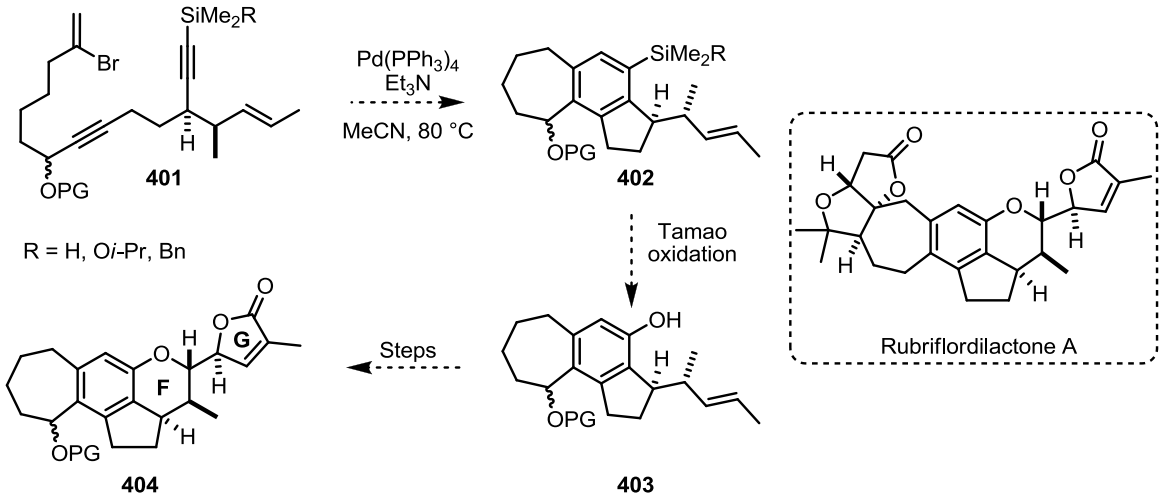
In conclusion, a number of synthetic strategies have been investigated in order to provide the key enantioenriched enediyne fragments, for coupling with the requisite aldehyde materials. To date, the coupling reactions have had limited success with only the Carreira method giving any desired coupling product. This reaction shows potential and would require further optimisation. Unfortunately limited time and material meant that this optimisation work has yet to be completed and will become the focus for further study in the group.

As suggested by Entry **5** in Table 16, a mono-alkyne can easily be reacted with aldehyde **396**. This suggests that the presence of a second alkyne might be an issue in this reaction. A possible way to circumvent this problem could be to use previously prepared alcohol **374** (6 steps, 49% yield, Scheme 119). After protection of the hydroxyl as a TBS ether, the C8−C9 alkyne could be introduced in 4 steps as described previously. It would be expected that the introduction of the final C17−C18 alkyne could then be performed by a similar sequence *via* aldehyde homologation.



Scheme 129 – Alternative synthesis of a bromoenediyne 401

This bromoenediyne could then be utilised in the desired intramolecular cyclisation to give the desired tricycle **402**. After oxidation of the silane group, studies could be performed to allow the elaboration of the F-ring, and coupling of the G-ring butenolide (Scheme 130).



Scheme 130 – Future work

5. Experimental

5.1. General Remarks

Proton (^{1}H NMR) and **Carbon** (^{13}C NMR) nuclear magnetic resonance spectra were recorded on the following instruments: Bruker-DPX200, Bruker-DPX250, Bruker-AV400 and Bruker-AVC500. The chemical shifts are given in part per million (ppm) on the delta scale. The solvent peak was used as the internal reference. For ^{1}H NMR: $CDCl_3$ = 7.26 ppm. For ^{13}C NMR: $CDCl_3$ = 77.0 ppm. Data are presented as follows; chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants (*J*/Hz) and assignments. Assignments were determined either on the basis of unambiguous chemical shifts or coupling patterns, using COSY, HSQC, HMBC, nOe experiments to fully interpreted spectra.

Infrared (IR) spectra were recorded on a Perkin-Elmer 1620 FT-IR spectrophotometer with internal calibration. Wavelengths of maximum absorbance (ν_{max}) are quoted in wavenumbers (cm^{-1}).

High resolution spectra (HRMS) were recorded by the Mass Spectroscopy Service. The parent ion $[M+H]^+$ or $[M+Na]^+$ was quoted.

EA were performed externally at the London Metropolitan University.

Analytical Thin Layer Chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualisation by ultra violet and/or potassium permanganate dip. Flash column chromatography was carried out using Merck Kieselgel 60 (40-63 μm) and the procedure includes the subsequent evaporation of solvents *in vacuo*.

Reagents and solvents were purified using standard means. Acetonitrile and pentane were distilled from CaH_2 under an argon atmosphere; THF was distilled from CaH_2 and stored under an argon atmosphere. Triethylamine (Et_3N) and pyridine were distilled from, CaH_2

and stored over, CaH_2. Ether, DCM and toluene were obtained dry and oxygen free from solvent dispenser units having been passed though an activated alumina column under argon. All other chemicals were used as received except where otherwise stated in the experimental text. All other extractive procedures were performed using non- distilled solvents and all aqueous solutions used were saturated unless otherwise specific.

Petroleum ether refers to fractions boiling at 40-60 °C. Ether refers to diethyl ether.

HPLC was carried out 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 HPLC analysis was carried out using a DAICEL CHIRALPAK-IA, IB or IC (250 mm x 4.6 mm ID), with mobile phase as stated.

5.2 General Procedures

General procedure 1:

A solution of malonate derivative (1 equiv.) in THF (2 mL/mmol) was added to NaH (60% dispersion in mineral oil, 1.2 equiv.) and alkyne derivative (1.2 equiv.) in THF (2 mL/mmol). The resulting mixture was stirred at room temperature under argon until completion of the reaction as monitored by TLC. The reaction mixture was quenched with aq. NH_4Cl. The aqueous layer was extracted with ether and the combined organic extracts washed with brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product purified by flash chromatography to afford the bromoenyne.

General procedure 2:

To a solution of bromoenyne (1 equiv.) in THF (4.5 mL/mmol) was added LiHMDS (1 M in THF, 1.5 equiv.) at −78 °C under Ar. The pale yellow solution was stirred at −78 °C for 20 min and chloro(diethylamino)diethylsilane (1.5 equiv.) was slowly added to the reaction

mixture. After stirring for 30 min and consumption of the starting material as monitored by TLC, isopropanol (4 equiv.), DMAP (cat.) and imidazole (4 equiv.) were added and the reaction mixture was allowed to warm up to room temperature. The reaction was quenched by addition of water and the aqueous layer was extracted with ether, the combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product purified by flash chromatography to afford the silylated bromoenyne.

General procedure 3:

$PdCl_2(PPh_3)_2$ (0.1 equiv.) was added to a degassed solution of bromoenyne (1 equiv.) and vinyl stannane (1.7 equiv.) in toluene under argon. The reaction mixture was refluxed at 110 °C until completion of the reaction as monitored by TLC and/or ^1H NMR spectroscopy. After evaporation of the solvent, the crude mixture was purified by flash chromatography to obtain the desired bicyclic diene.

General procedure 4:

To a solution of bicyclic diene (1 equiv.) in DCM was added MnO_2 (10 equiv.) and the reaction mixture was stirred at 30 °C for 12 h. The crude reaction mixture was filtered through a pad of Celite and the solvent was removed *in vacuo* to yield the bicyclic aromatic product.

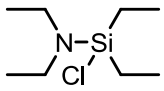
General procedure 5:

The obtained bicyclic aromatic compound (1 equiv.) was dissolved in THF/MeOH (1:1) and TBAF (2 equiv.), $KHCO_3$ (2 equiv.) and H_2O_2 (10 equiv.) were added and the reaction mixture was heated at 60 °C for 3 h and monitored by TLC. The reaction mixture was

allowed to cool down to room temperature, diluted with DCM and washed with water. The combined organic extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product purified by flash chromatography to afford the desired product.

5.3. Experimental - Chapter 2

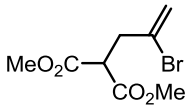
Diethyl(diethylamino)chlorosilane 222:



222

To a solution of dichlorodiethylsilane (20 mL, 133.6 mmol, 1.0 eq) and anhydrous triethylamine (20.6 mL, 146.7 mmol, 1.1 eq) in anhydrous THF at 0 °C was added a solution of anhydrous diethylamine (13.8 mL, 133.6 mmol, 1.0 eq) in anhydrous THF (6 mL) over 2 h. The resulting beige suspension was warmed to room temperature overnight with vigorous stirring maintained. The mixture was filtered through celite under N_2, the filter cake washed with anhydrous pentane and concentrated *in vacuo* as an orange oil. The mixture was purified by vacuum distillation (bp 92 − 94 °C, 36 mbar) to afford **222** as a colourless oil (17.6 g, 70%); **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 2.88 (4H, q, *J* = 7.0 Hz, $(CH_3C\underline{H}_2)_2N$), 1.07-0.99 (12H, m, $(C\underline{H}_3CH_2)_2N$ + $(C\underline{H}_3CH_2)_2Si$), 0.90 (4H, q, *J* 6.5 Hz, $(CH_3C\underline{H}_2)_2Si$). Data in accordance with literature.[92]

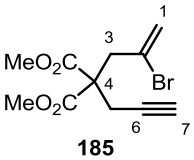
Dimethyl 2-(2-bromoallyl)malonate 206:



206

To a suspension of NaH (60% dispersion in mineral oil, 2.32 g, 58 mmol, 1.2 equiv.) in THF (50 mL) at 0 °C was added dropwise dimethyl malonate **204** (5.52 mL, 48.4 mmol, 1 equiv.) and the mixture was stirred for 1 h. 2,3–Dibromopropene **205** (80%, 5.52 mL, 48.4 mmol, 1 equiv.) was added to the milky yellow mixture and the stirring was continued for 3 h until completion of the reaction as monitored by TLC. The reaction mixture was quenched with aq. NH_4Cl. The aqueous layer was extracted with Et_2O and the combined organic extracts washed with brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product purified by distillation at 101–106 °C (1 mmHg) to afford the desired product **206** as a colorless oil (8.50 g, 33.9 mmol, 70%); $\mathbf{R_f}$ 0.22 (5:1 Pet. Ether/Ether); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.69 (1H, dt, *J* = 2.0, 1.0 Hz, H1), 5.48 (1H, d, *J* = 2.0 Hz, H1), 3.89 (2H, t, *J* = 7.5 Hz, H4), 3.76 (6H, s, CO_2Me), 3.03 (2H, dd, *J* = 7.5, 1.0 Hz, H3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 168.7, 129.2, 119.9, 52.7, 50.4, 40.5. Data in accordance with literature.[159]

Dimethyl 2-(2-bromoallyl)-2-(prop-2-ynyl)malonate 185:

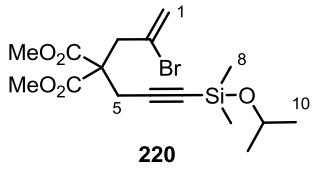


185

185 was synthesised from **206** (2.9 g, 11.7 mmol) and propargyl bromide **211** (1.6 mL, 14.0 mmol) using general procedure 1. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **185** as a colourless oil (2.91 g, 10.1 mmol, 86%); $\mathbf{R_f}$ 0.31 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3289, 2954, 1737; **^{1}H NMR**

(500 MHz, $CDCl_3$) δ_H 5.83 (1H, t, *J* = 0.6 Hz, H1), 5.63 (1H, d, *J* = 1.6 Hz, H1), 3.77 (6H, s, CO_2Me), 3.31 (2H, br s, H3), 2.93 (2H, d, *J* = 2.7 Hz, H5), 2.05 (1H, t, *J* = 2.7 Hz, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 169.5 (C=O), 126.1 (C2), 122.9 (C1), 78.6 (C6), 72.1 (C7), 56.0 (OMe), 53.0 (C4), 42.9 (C3), 22.2 (C5); **HRMS** (ES^+) calcd for $C_{11}H_{13}BrO_4$ $[M+H]^+$ 289.0074, found 289.0070.

Dimethyl 2-(2-bromoallyl)-2-(3-(isopropoxydimethylsilyl)prop-2-ynyl)malonate 220:

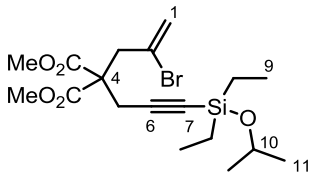


220

To a solution of **185** (dried over CaH_2, 110 mg, 0.44 mmol, 1 equiv.) in THF (2 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 210 µL, 0.53 mmol, 1.2 equiv.) at –78 °C and the reaction mixture was stirred at –78 °C for 30 min. Chloro(diethylamino)dimethylsilane **217** (105 µL, 0.53 mmol, 1.2 equiv.) was added at –78 °C and the reaction mixture was allowed to warm up to room temperature. The reaction was monitored by TLC and after 2 h additional *n*-BuLi (210 µL, 0.53 mmol, 1.2 equiv.) and chloro(diethylamino)dimethylsilane **217** (105 µL, 0.53 mmol, 1.2 equiv.) were added to the reaction mixture at –78 °C. The reaction mixture was again allowed to warm up slowly to room temperature. After 2 h, the reaction mixture was concentrated, diluted in dry pentane, stirred for 15 min, filtrated through oven–dried celite and the clear filtrate was evaporated to give dimethyl 2-(2-bromoallyl)-2-(3-((diethylamino)dimethylsilyl) prop-2-ynyl)malonate **219**. The crude intermediate was dissolved in DCM (2 mL) at 0 °C and imidazole (60 mg, 0.88 mmol, 2 equiv.), isopropanol (68 µL, 0.88 mmol, 2 equiv.) and DMAP (cat.) were added to the mixture and stirred at room temperature for 3 h until completion of the reaction as monitored by TLC. The reaction mixture was quenched with

H_2O, and the aqueous layer was extracted with DCM and the combined organic extracts washed with brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product was purified by flash chromatography (5:1 Pet. Ether/Ether with 1% Et_3N) to afford the title compound **220** as a colorless oil (143 mg, 0.39 mmol, 89%); $\mathbf{R_f}$ 0.38 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2360, 1658, 1568, 1382, 1369, 1290, 1030; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.83 – 5.81 (1H, m, H1), 5.63 (1H, d, *J* = 1.5 Hz, H1), 4.09 (1H, septet, *J* = 6.1 Hz, H9), 3.76 (6H, s, $CO_2\underline{Me}$), 3.30 (2H, s, H3), 2.97 (2H, s, H5), 1.18 (6H, d, *J* = 6.1 Hz, H10), 0.22 (6H, s, H8); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 169.4 (C=O), 126.2 (C2), 122.7 (C1), 100.8 (C6), 87.4 (C7), 65.9 (C9), 56.0 (O<u>Me</u>), 53.0 (C4), 43.0 (C3), 25.4 (C10), 23.4 (C5), 0.6 (C8); **HRMS** (ES^+) calcd for $C_{16}H_{25}BrNaO_5Si$ $[M+Na]^+$ 427.0533, found 427.0547.

Dimethyl 2-(2-bromoallyl)-2-(3-(diethyl(isopropoxy)silyl)prop-2-ynyl)malonate 226a:

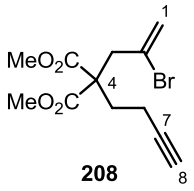


226a

226a was synthesised from **185** (500 mg, 1.7 mmol), LiHMDS (2.6 mL, 2.6 mmol), $ClSiEt_2(NEt_2)$ **222** (606 µL, 2.6 mmol), IPA (530 µL, 6.9 mmol) and imidazole (471 mg, 6.9 mmol) using general procedure 2. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **226a** as a colourless oil (701 mg, 1.0 mmol, 94%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2956, 2178, 1742, 1626, 1025, 733; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.84 – 5.82 (1H, m, H1), 5.63 (1H, d, *J* = 1.7 Hz, H1), 4.10 (1H, septet, *J* = 6.1 Hz, H10), 3.76 (6H, s, $CO_2\underline{Me}$), 3.32 (2H, s, H3), 3.00 (2H, s, H5), 1.18 (6H, d, *J* = 6.1 Hz, H11), 0.98 (6H, t, *J* = 7.9 Hz, H9), 0.62 (4H, qd, *J* = 7.9 Hz, 2.2 Hz, H8); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 169.3 (C=O), 126.2 (C2), 122.7

(C1), 101.6 (C6), 85.5 (C7), 66.0 (C10), 56.1 (OMe), 53.0 (C4), 42.9 (C3), 25.4 (C11), 23.5 (C5), 6.8 (C8), 6.6 (C9); **HRMS** (ES^+) calcd for $C_{18}H_{29}NaBrO_5Si$ $[M+Na]^+$ 455.0860, found 455.0862; **EA** calcd for $C_{18}H_{29}BrO_5Si$: C, 49.88; H, 6.74, found: C, 49.96; H, 6.72.

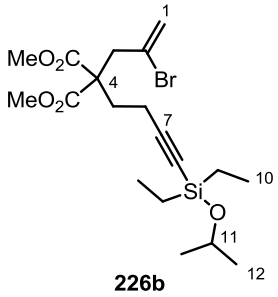
Dimethyl 2-(2-bromoallyl)-2-(but-3-ynyl)malonate 208:



208

208 was synthesised from **206** (876 mg, 3.5 mmol) and but-3-ynyl trifluoromethanesulfonate **207** (847 mg, 4.2 mmol) using general procedure 1. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **108** as a colourless oil (730 mg, 3.3 mmol, 94%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3285, 2954, 1730, 1624, 1433, 1201, 1150, 959, 649; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.70 – 5.68 (1H, m, H1), 5.61 (1H, d, *J* = 1.8 Hz, H1), 3.75 (6H, s, CO_2Me), 3.19 (2H, d, *J* = 0.5 Hz, H3), 2.30 – 2.28 (2H, m, H6), 2.21 – 2.19 (2H, m, H5), 1.97 (1H, t, *J* = 2.8 Hz, H8); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.4 (C=O), 126.7 (C2), 122.2 (C1), 82.8 (C7), 68.9 (C8), 56.4 (C4), 52.8 (OMe), 43.3 (C3), 30.7 (C5), 14.0 (C6); **HRMS** (ES^+) calcd for $C_{12}H_{15}BrNaO_4$ $[M+Na]^+$ 325.0070, found 325.0062.

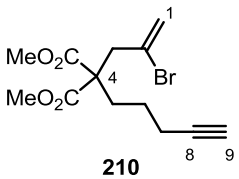
Dimethyl 2-(2-bromoallyl)-2-(4-(diethyl(isopropoxy)silyl)but-3-ynyl)malonate 226b:



226b

226b was synthesised from **208** (545 mg, 1.8 mmol), LiHMDS (2.7 mL, 2.7 mmol), $ClSiEt_2(NEt_2)$ **222** (634 µL, 2.7 mmol), IPA (550 µL, 7.2 mmol) and imidazole (490 mg, 7.2 mmol) using general procedure 2. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **226b** as a colourless oil (723 mg, 1.6 mmol, 90%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2956, 2173, 1735, 1625, 1435, 1088, 1027, 732; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.84 – 5.82 (1H, m, H1), 5.63 (1H, d, *J* = 1.7 Hz, H1), 4.10 (1H, septet, *J* = 6.1 Hz, H11), 3.76 (6H, s, $CO_2\underline{Me}$), 3.18 (2H, s, H3), 2.31 – 2.29 (2H, m, H6), 2.23 – 2.24 (2H, m, H5), 1.18 (6H, d, *J* = 6.1 Hz, H12), 0.98 (6H, t, *J* = 7.9 Hz, H10), 0.62 (4H, qd, *J* = 7.9 Hz, 2.2 Hz, H9); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.4 (C=O), 126.6 (C2), 122.2 (C1), 106.0 (C7), 81.9 (C8), 65.9 (C11), 56.5 (C4), 52.8 (O<u>Me</u>), 43.4 (C3), 30.9 (C5), 25.5 (C12), 15.3 (C6), 6.8 (C9), 6.5 (C10); **HRMS** (ES^+) calcd for $C_{19}H_{31}BrNaO_5Si$ $[M+Na]^+$ 469.1016, found 469.1015; **EA** calcd for $C_{19}H_{31}BrO_5Si$: C, 51.00; H, 6.98, found: C, 50.92, H; 7.02.

Dimethyl 2-(2-bromoallyl)-2-(pent-4-ynyl)malonate 210:

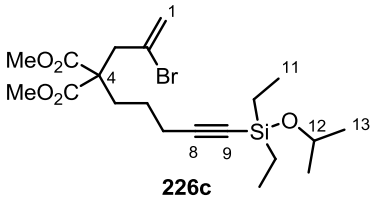


210

210 was synthesised from **206** (200 mg, 0.4 mmol) and pent-4-ynyl trifluoromethanesulfonate **209** (207 mg, 0.5 mmol) using general procedure 1. The crude

product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **210** as a colourless oil (227 mg, 0.3 mmol, 95%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3291, 2952, 1731, 1625, 1434, 1278, 1150, 901, 640; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.69 – 5.67 (1H, m, H1), 5.59 (1H, d, *J* = 1.7 Hz, H1), 3.75 (6H, s, CO_2Me), 3.17 (2H, s, H3), 2.21 (2H, dt, *J* = 7.0, 2.6 Hz, H7), 2.12 – 2.10 (2H, m, H5), 1.96 (1H, t, *J* = 2.6 Hz, H9), 1.44 – 1.42 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.8 (C=O), 126.9 (C2), 121.9 (C1), 83.5 (C8), 68.8 (C9), 56.8 (C4), 52.7 (OMe), 43.1 (C3), 30.8 (C5), 23.4 (C6), 18.5 (C7); **HRMS** (ES^+) calcd for $C_{13}H_{17}BrNaO_4$ $[M+Na]^+$ 339.0202, found 339.0200.

Dimethyl 2-(2-bromoallyl) -2-(5- (diethyl(isopropoxy)silyl)pent-4-ynyl)malonate 226c:

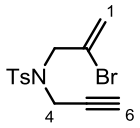


226c

226c was synthesised from **210** (320 mg, 1.0 mmol), LiHMDS (1.5 mL, 1.5 mmol), $ClSiEt_2(NEt_2)$ **222** (355 µL, 1.5 mmol), IPA (306 µL, 4.0 mmol) and imidazole (272 mg, 4.0 mmol) using general procedure 2. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **226c** as a colourless oil (337 mg, 0.8 mmol, 75%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2955, 2172, 1735, 1625, 1434, 1278, 1026, 732; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.68 – 5.66 (1H, m, H1), 5.59 (1H, d, *J* = 1.5 Hz, H1), 4.14 (1H, septet, *J* = 6.4 Hz, H12), 3.75 (6H, s, CO_2Me), 3.18 (2H, s, H3), 2.29 (2H, t, *J* = 7.3 Hz, H7), 2.14 – 2.12 (2H, m, H5), 1.49 – 1.47 (2H, m, H6), 1.20 (6H, d, *J* = 3.4 Hz, H11), 1.00 (6H, app. t, *J* = 6.4 Hz, H13), 0.65 – 0.62 (4H, m, H10); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.8 (C=O), 127.0 (C2), 121.9 (C1), 106.8 (C8), 81.8 (C9), 65.9 (C12), 56.9 (C4), 52.9 (OMe), 43.2 (C3), 30.9 (C5), 25.5 (C13), 23.4 (C6), 19.9 (C7),

6.9 (C10), 6.6 (C11); **HRMS** (ES^+) calcd for $C_{20}H_{33}BrNaO_5Si$ $[M+Na]^+$ 483.1173, found 483.1179; **EA** calcd for $C_{20}H_{33}BrO_5Si$: C, 52.05; H, 7.21, found: C, 51.94; H, 7.30.

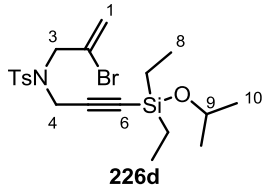
***N*-(2-Bromoallyl)-4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide 213:**



213

To a mixture of *N*–(2–bromoallyl)–4–methylbenzenesulfonamide **212** (1 g, 3.44 mmol, 1 equiv.) and K_2CO_3 (953 mg, 6.89 mmol, 2 equiv.) in acetone (10 mL) was added propargyl bromide (80% in toluene, 460 µL, 4.14 mmol, 1.2 equiv.). The reaction mixture was stirred at 60 °C for 12 h and was quenched with water. The aqueous layer was extracted with Et_2O, the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (2:1 Pet. Ether/Ether) to afford the title compound **213** as a colourless oil (903 mg, 2.75 mmol, 80%); $\mathbf{R_f}$ 0.35 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3280, 1629, 1344, 1181, 1150, 892, 679; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, *J* = 8.1 Hz, HAr), 7.31 (2H, d, *J* = 8.1 Hz, HAr), 5.97 – 5.95 (1H, m, H1), 5.69 – 5.67 (1H, m, H1), 4.13 (2H, d, *J* = 2.3 Hz, H4), 4.08 (2H, s, H3), 2.44 (3H, s, Ts–C$\underline{H}_3$), 2.05 (1H, t, *J* = 2.3 Hz, H6) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.9 (CAr), 135.8 (CAr), 129.6 (CAr), 127.7 (CAr), 126.9 (C1), 120.5 (C2), 76.0 (C5), 74.2 (C6), 53.8 (C3), 36.1 (C4), 21.6 (Ts–$\underline{C}H_3$); **HRMS** (ES^+) calcd for $C_{13}H_{14}BrNO_2S$ CH_3OHNa $[M+MeOH+Na]^+$ 382.0083, found 382.0077.

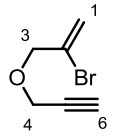
***N*-(2-Bromoallyl)-*N*-(3-(diethyl(isopropoxy)silyl)prop-2-ynyl)-4-methylbenzene sulfonamide 226d:**



226d

226d was synthesised from **213** (150 mg, 0.5 mmol), LiHMDS (686 µL, 0.7 mmol), $ClSiEt_2(NEt_2)$ **222** (160 µL, 0.7 mmol), IPA (140 µL, 1.8 mmol) and imidazole (125 mg, 1.8 mmol) using general procedure 2. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **226d** as a colourless oil (107 mg, 0.3 mmol, 60%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2960, 1353, 1163, 1119, 1092, 1002, 899, 734, 661; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.1 Hz, HAr), 7.33 (2H, d, *J* = 8.1 Hz, HAr), 5.98 (1H, d, *J* = 1.8 Hz, H1), 5.72 (1H, d, *J* = 1.8 Hz, H1), 4.23 (2H, s, H3), 4.11 (2H, s, H4), 3.95 (1H, septet, *J* = 6.0 Hz, H9), 2.45 (3H, s, Ts–C$\underline{H}_3$), 1.14 (6H, d, *J* = 6.0 Hz, H10), 0.89 (6H, t, *J* = 7.8 Hz, H8), 0.51 (4H, q, *J* = 7.8 Hz, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.0 (CAr), 136.3 (CAr), 130.4 (CAr), 130.1 (CAr), 128.1 (C1), 119.7 (C2), 98.9 (C5), 66.5 (C6), 45.4 (C9), 41.0 (C3), 38.6 (C4), 26.2 (C10), 25.8 (Ts–$\underline{C}H_3$), 7.8 (C7), 7.0 (C8); **HRMS** (ES^+) calcd for $C_{20}H_{30}BrNNaO_3SSi$ $[M+Na]^+$ 494.0791, found 494.0789; **EA** calcd for $C_{20}H_{30}BrNO_3SSi$: C, 50.84; H, 6.40; N, 2.96, found: C, 50.90; H, 6.32; N, 2.95.

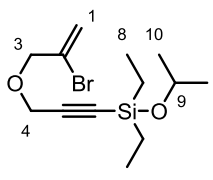
2-Bromo-3-(prop-2-ynyloxy)prop-1-ene 215:



215

To a solution of NaH (60% in mineral oil, 1.5 g, 35.8 mmol, 2.5 equiv.) in THF (10 mL) at 0 °C was added propargyl alcohol (1 mL, 17 mmol, 1.2 equiv.) and the reaction mixture was stirred for 30 min. 2,3–Dibromopropene **205** (1.5 mL, 14.3 mmol, 1 equiv.) was slowly added, the reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The reaction was quenched by addition of water and the aqueous layer was extracted with Et_2O; the combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was then evaporated *in vacuo* and the crude product purified by flash chromatography (5:1 Pet. Ether/Ether) to afford the title compound **215** as a colourless oil (2.15 g, 11.7 mmol, 82%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3300, 2923, 2130, 1639, 1443, 1l62, 1086, 899, 668; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 5.97 – 5.95 (1H, m, H1), 5.67 – 5.65 (1H, m, H1), 4.23 – 4.19 (4H, m, H3, H4), 2.47 (1H, t, *J* = 2.4 Hz, H6); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 128.4 (C2), 118.7 (C1), 78.8 (C3), 75.1 (C5), 73.3 (C6), 57.0 (C4); **HRMS** (ES^+) calcd for C_6H_7BrO $[M+H]^+$ 173.9681, found 173.9679.

(3-(2-Bromoallyloxy)prop-1-ynyl)diethyl(isopropoxy)silane 226e:

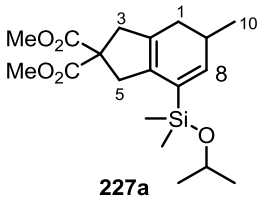


226e

226e was synthesised from **215** (500 mg, 2.9 mmol), LiHMDS (4.3 mL, 4.3 mmol), $ClSiEt_2(NEt_2)$ (1.0 mL, 4.3 mmol), IPA (875 µL, 11.4 mmol) and imidazole (778 mg, 11.4

mmol) using general procedure 2. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **226e** as a colourless oil (537 mg, 1.7 mmol, 59%); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2969, 1461, 1380, 1240, 1122, 1088, 878, 734; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.93 (1H, d, *J* = 1.7 Hz, H1), 5.64 – 5.62 (1H, m, H1), 4.23 (2H, s, H3), 4.21 (2H, s, H4), 4.12 (1H, septet, *J* = 6.1 Hz, H9), 1.17 (6H, d, *J* = 6.1 Hz, H10), 0.96 (6H, t, *J* = 7.8 Hz, H8), 0.58 (4H, q, *J* = 7.9 Hz, H7); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 128.5 (C2), 118.6 (C1), 101.1 (C5), 89.9 (C6), 73.1 (C3), 66.2 (C9), 64.5 (C4), 25.7 (C10), 6.6 (C8), 4.5 (C7); **HRMS** (ES^+) calcd for $C_{13}H_{23}BrNaO_2Si$ $[M+Na]^+$ 341.0543, found 341.0531.

Dimethyl 7-(isopropoxydimethylsilyl)-5-methyl-4,5-dihydro-1*H*-indene-2,2(3*H*)-dicarboxylate 227a:

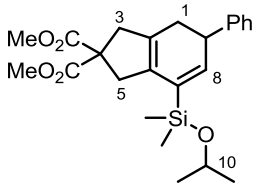


227a

227a was synthesised from **220** (23.9 mg, 0.06 mmol) and (*E*)-tributyl(prop-1-enyl)stannane (29.3 mg, 0.09 mmol) using general procedure 3. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **227a** as a colourless oil (20 mg, 0.05 mmol, 92%); $\mathbf{R_f}$ 0.33 (5:1 Pet.Ether/Ether); **IR** (thin film) ν_{max} = 2358, 1737, 1252, 1024, 890, 822, 781; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.95 (1H, d, *J* = 3.3 Hz, H8), 3.95 (1H, septet, *J* = 6.3 Hz, H11), 3.74 (3H, s, $CO_2\underline{Me}$), 3.74 (3H, s, $CO_2\underline{Me}$), 3.67 – 3.65 (1H, m, H9), 3.20 (2H, br s, H5), 3.03 – 3.01 (1H, m, H1), 2.96 – 2.94 (1H, m, H1), 2.46 – 2.44 (1H, m, H3), 2.20 – 2.18 (1H, m, H3) , 1.13 (3H, d, *J* = 6.3 Hz, H12), 1.12 (3H, d, *J* = 6.3 Hz, H12), 1.04 (3H, d, *J* = 7.1 Hz, H10), 0.23 (6H, s, H13); **^{13}C NMR** (125 MHz,

$CDCl_3$) δ_C 172.8, 143.9, 132.1, 131.1, 65.1, 58.5, 52.7, 52.7, 43.0, 41.7, 31.1, 30.0, 25.6, 20.1, -0.90; **HRMS** (ES^+) calcd for $C_{19}H_{30}NaO_5Si$ $[M+ Na]^+$ 389.1743, found 389.1755.

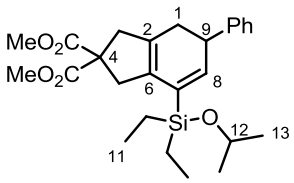
Dimethyl 7-(isopropoxydimethylsilyl)-5-phenyl-4,5-dihydro-1*H*-indene-2,2(3*H*)-dicarboxylate 227b:



227b

227b was synthesised from **220** (26.6 mg, 70 µmol) and (*E*)-tributyl(styryl)stannane (38.8 mg, 0.10 mmol) using general procedure 3. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **227b** as a colourless oil (27.4 mg, 60 µmol, 97%); $\mathbf{R_f}$ 0.30 (5:1 Pet.Ether/Ether); **IR** (thin film) ν_{max} = 2391, 1737, 1434, 1367, 1252, 1023, 782; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.30 (2H, m, HAr), 7.24 (3H, m, HAr), 6.10 (1H, d, *J* = 3.1 Hz, H8), 3.99 (1H, septet, *J* = 6.2 Hz, H10), 3.76 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 3.65 – 3.63 (1H, m, H9), 3.28 – 3.26 (2H, m, H5), 3.10 (1H, d, *J* = 17.4 Hz, H1), 2.94 (1H, d, *J* = 17.4 Hz, H1), 2.45 (1H, s, H3), 2.29 (1H, s, H5), 1.16 (3H, d, *J* = 6.2 Hz, H11), 1.14 (3H, d, *J* = 6.2 Hz, H11), 0.25 (6H, s, H12); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.7, 145.4, 140.7, 133.4, 131.7, 131.1, 128.5, 127.6, 126.3, 65.2, 58.5, 52.7, 42.9, 41.2, 41.7, 32.0, 25.6, -0.90; **HRMS** (ES^+) calcd for $C_{24}H_{32}NaO_5Si$ $[M+ Na]^+$ 451.1892, found 451.1911.

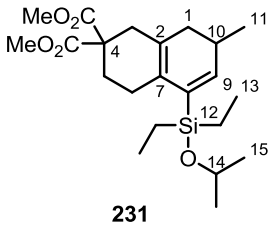
Dimethyl 7-(diethyl(isopropoxy)silyl)-5-phenyl-4,5-dihydro-1*H*-indene-2,2(3*H*)-dicarboxylate 229a:



229a

229a was synthesised from **226a** (300 mg, 0.69 mmol) and (*E*)-tributyl(styryl)stannane (435 mg, 1.10 mmol) using general procedure 3. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **226a** as a colourless oil (237 mg, 0.52 mmol, 75%); $\mathbf{R_f}$ 0.42 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2955, 1736, 1434, 1381, 1243, 1005, 874, 730, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32 – 7.30 (2H, m, HAr), 7.27 – 7.23 (3H, m, HAr), 6.12 – 6.10 (1H, m, H8), 4.01 (1H, septet, *J* = 6.2 Hz, H12), 3.76 (3H, s, CO_2Me), 3.73 (3H, s, CO_2Me), 3.64 – 3.62 (1H, m, H9), 3.25 (2H, br s, H3), 3.10 (1H, d, *J* = 17.5 Hz, H5), 2.94 (1H, d, *J* = 17.5 Hz, H5), 2.45 – 2.43 (1H, m, H1), 2.27 – 2.25 (1H, m, H1), 1.16 (3H, d, *J* = 6.2 Hz, H13), 1.15 (3H, d, *J* = 6.2 Hz, H13), 1.00 – 0.95 (6H, m, H11), 0.77 – 0.74 (4H, m, H10); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.8 (C=O), 172.7 (C=O), 145.5 (C6), 141.3 (C8), 131.8 (CAr), 131.5 (C7), 130.9 (C2), 128.5 (CAr), 127.6 (CAr), 126.3 (CAr), 65.2 (C12), 58.5 (C4), 52.7 (OMe), 52.7 (OMe), 42.9 (C5), 42.2 (C9), 41.8 (C3), 32.1 (C1), 25.7 (C13), 25.6 (C13), 6.8 (C11), 5.0 (C10), 4.9 (C10); **HRMS** (ES^+) calcd for $C_{27}H_{40}NaO_6Si$ $[M+MeOH+Na]^+$ 511.2486, found 511.2432.

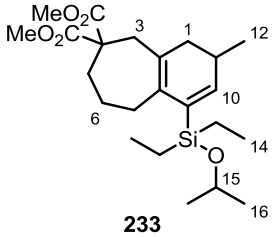
Dimethyl 5-(diethyl(isopropoxy)silyl)-7-methyl-3,4,7,8-tetrahydronaphthalene-2,2(1*H*)-dicarboxylate 231:



231

231 was synthesised from **226b** (100 mg, 0.22 mmol) and (*E*)-tributyl(prop-1-enyl)stannane (126 mg, 0.38 mmol) using general procedure 3. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **231** as a colourless oil (68 mg, 0.17 mmol, 75%); $\mathbf{R_f}$ 0.52 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2956, 1735, 1435, 1250, 1170, 1121, 1083, 1018, 872, 731; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.99 (1H, d, *J* = 3.4 Hz, H9), 3.94 (1H, septet, *J* = 6.1 Hz, H14), 3.72 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 2.60 (2H, br s, H3), 2.31 – 2.29 (2H, m, H6), 2.22 – 2.20 (2H, m, H5), 2.13 – 2.11 (2H, m, H1), 1.98 (1H, m, H10), 1.12 (6H, t, *J* = 6.1 Hz, H15), 1.01 (3H, d, *J* = 6.8 Hz, H11), 0.95 – 0.90 (6H, m, H13), 0.75 – 0.72 (4H, m, H12); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.2 (C=O), 171.8 (C=O), 144.7 (C9), 133.9 (C7), 127.6 (C8), 125.5 (C2), 65.0 (C14), 53.3 (C4), 52.5 (OMe), 52.5 (OMe), 36.3 (C3), 36.0 (C1), 29.3 (C10), 28.4 (C5), 25.7 (C15), 25.0 (C6), 19.5 (C11), 6.9 (C13), 5.5 (C12); **HRMS** (ES^+) calcd for $C_{22}H_{36}NaO_5Si$ $[M+Na]^+$ 431.2224, found 431.2236.

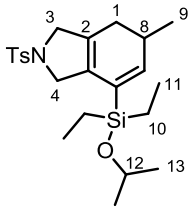
Dimethyl 4-(diethyl(isopropoxy)silyl)-2-methyl-5,6,7,9-tetrahydro-1*H*-benzo[*7*] annulene-8,8(*2H*)-dicarboxylate 233:



233

233 was synthesised from **226c** (51.4 mg, 0.11 mmol) and (*E*)-tributyl(prop-1-enyl)stannane (55 mg, 0.17 mmol) using general procedure 3. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **233** as a colourless oil (27.5 mg, 0.06 mmol, 58%); $\mathbf{R_f}$ 0.52 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2954, 1736, 1455, 1228, 1172, 1007, 873, 729; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.98 (1H, d, *J* = 3.2 Hz, H10), 3.95 (1H, septet, *J* = 5.9 Hz, H15), 3.71 (3H, s, CO_2Me), 3.70 (3H, s, CO_2Me), 2.46 (2H, br s, H3), 2.29 – 2.20 (2H, m, H1), 2,17 – 2.04 (4H, m, H5, H7), 2.00 – 1.95 (1H, m, H6), 1.74 (1H, t, *J* = 3.2 Hz, H11), 1.67 – 1.65 (1H, m, H6), 1.18 (3H, d, *J* = 6.1 Hz, H12), 1.13 (6H, t, *J* = 5.9, H16), 1.02 – 0.87 (10H, m, H13, H14); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.3 (C=O), 172.0 (C=O), 145.3 (C10), 137.8 (C8), 135.6 (C9), 129.2 (C2), 65.1 (C15), 55.0 (C4), 52.3 (OMe), 52.1 (OMe), 39.7 (C5), 37.2 (C1), 31.4 (C3), 29.8(C7), 28.6 (C6), 25.6 (C16), 25.4 (C12), 6.8 (C14), 5.3 (C13); **HRMS** (ES^+) calcd for $C_{23}H_{38}NaO_5Si$ $[M+Na]^+$ 445.2381, found 445.2386.

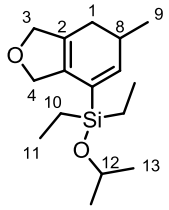
7-(Diethyl(isopropoxy)silyl)-5-methyl-2-tosyl-2,3,4,5-tetrahydro-1*H*-isoindole 229b:



229b

229b was synthesised from **226d** (50 mg, 0.11 mmol) and (*E*)-tributyl(prop-1-enyl)stannane (60 mg, 0.18 mmol) using general procedure 3. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **229b** as a colourless oil (29 mg, 0.06 mmol, 60%); $\mathbf{R_f}$ 0.29 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2958, 1436, 1378, 1230, 1015, 874, 730, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.0 Hz, HAr), 7.31 (2H, d, *J* = 8.0 Hz, HAr), 5.93 (1H, d, *J* = 3.5 Hz, H7), 4.22 – 4.20 (2H, m, H4), 4.11 – 4.09 (2H, m, H3), 3.95 (1H, septet, *J* = 5.9 Hz, H12), 2.42 (4H, s, H8, Ts–C$\underline{H}_3$), 2.16 – 2.14 (1H, m, H1), 1.79 – 1.77 (1H, m, H1), 1.11 (6H, t, *J* = 5.9 Hz, H13), 1.02 (6H, d, *J* = 7.1 Hz, H11), 0.89 (4H, app. td, *J* = 8.0, 1.7 Hz, H10), 0.68 – 0.65 (3H, m, H9); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 145.1 (C7), 143.2 (CAr), 134.4 (CAr), 129.9 (C5), 129.6 (CAr), 128.1 (C2), 127.8 (C6), 127.5 (CAr), 65.3 (C12), 56.3 (C3), 55.4 (C4), 29.8 (Ts–$\underline{C}H_3$), 28.7 (C1), 25.7 (C13), 25.7 (C13), 21.5 (C8), 19.9 (C9), 6.8 (C11), 5.0 (C10); **HRMS** (ES^+) calcd for $C_{23}H_{35}NNaO_3SSi$ $[M+Na]^+$ 456.1999, found 456.2000.

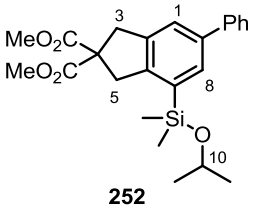
Diethyl(isopropoxy)(6-methyl-1,3,6,7-tetrahydroisobenzofuran-4-yl)silane 229c:



229c

229c was synthesised from **226e** (50 mg, 0.16 mmol) and (*E*)-tributyl(prop-1-enyl)stannane (88.1 mg, 0.27 mmol) using general procedure 3. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **229c** as a colourless oil (10 mg, 0.05 mmol, 30%); $\mathbf{R_f}$ 0.29 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2955, 1732, 1463, 1210, 866; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.99 (1H, d, *J* = 3.3 Hz, H7), 4.75 – 4.73 (2H, m, H4), 4.60 – 4.58 (2H, m, H3), 3.99 (1H, septet, *J* = 6.0 Hz, H12), 2.53 – 2.51 (1H, m, H8), 2.27 – 2.25 (1H, m, H1), 1.89 – 1.87 (1H, m, H1), 1.15 (6H, app. dd, *J* = 6.0, 3.0 Hz, H13), 1.09 (3H, d, *J* = 7.0 Hz, H9), 0.94 (6H, t, *J* = 7.9 Hz, H11), 0.70 – 0.67 (4H, m, H10); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 144.6 (C7), 131.3 (C2), 129.7 (C6), 127.4 (C5), 76.3 (C4), 75.7 (C3), 65.2 (C12), 29.9 (C1), 27.7 (C8), 25.7 (C13), 20.1 (C10), 6.7 (C11), 4.9 (C10); **HRMS** (ES^+) calcd for $C_{16}H_{28}NaO_2Si$ $[M+Na]^+$ 303.1751, found 303.1749.

Dimethyl 4-(isopropoxydimethylsilyl)-6-phenyl-1*H*-indene-2,2(3*H*)-dicarboxylate 252:

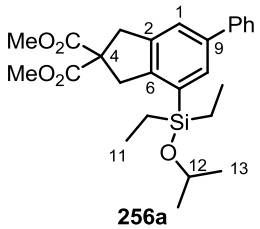


252

227b (13.9 mg, 0.03 mmol, 1 equiv.) was dissolved in toluene (0.6 mL) and DDQ (8.8 mg, 0.04 mmol, 1.2 equiv.) was added at 0 °C. The reaction turned red and was stirred for 1 h at room temperature. The reaction mixture was diluted in DCM and quenched with $NaHCO_3$, extracted with DCM and the combined organic extracts washed with brine and

dried ($MgSO_4$). The solvent was then evaporated *in vacuo* and the crude product purified by flash chromatography (5:1 Pet.Ether/Ether) to afford **252** as a colourless oil (7 mg, 0.02 mmol, 51%); $\mathbf{R_f}$ 0.31 (5:1 Pet.Ether/Ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.59 – 7.57 (3H, m, HAr), 7.45 – 7.24 (3H, m, HAr), 7.34 – 7.32 (1H, m, HAr), 4.04 (1H, septet, J = 5.9 Hz, H10), 3.77 (6H, s, CO_2Me), 3.76 (2H, s, H3), 3.64 (2H, s, H5), 1.17 (6H, d, *J* = 5.9 Hz, H11), 0.45 (6H, s, H12); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.1 (C=O), 144.4 (C6), 141.5 (C9), 140.0 (CAr), 139.5 (C7), 134.3 (CAr), 132.0 (C1), 128.7 (CAr), 127.1 (CAr), 127.0 (CAr), 124.5 (C9), 65.5 (C12), 60.4 (C4), 53.0 (OMe), 41.2 (C3), 40.1 (C5), 25.7 (C13), -0.6 (SiMe); **HRMS** (ES^+) calcd for $C_{24}H_{30}NaO_2Si$ $[M+Na]^+$ 449.1755, found 449.1754.

Dimethyl 4-(diethyl(isopropoxy)silyl)-6-phenyl-1*H*-indene-2,2(3*H*)-dicarboxylate 256a:

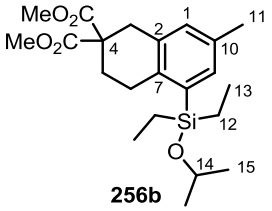


256a

256a was synthesised from **229a** (20 mg, 0.04 mmol) and MnO_2 (19 mg, 0.22 mmol), using general procedure 4. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **256a** as a colourless oil (17 mg, 0.03 mmol, 88%); $\mathbf{R_f}$ 0.31 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2923, 2853, 1740, 1460, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.60 – 7.58 (3H, m, H1, HAr), 7.48 – 7.44 (3H, m, H8, HAr), 7.33 (1H, t, *J* = 7.3 Hz, HAr), 4.08 (1H, septet, *J* = 6.1 Hz, H12), 3.76 (6H, s, CO_2Me), 3.74 (2H, s, H5), 3.63 (2H, s, H3), 1.19 (6H, d, *J* = 6.1 Hz, H13), 1.03 – 0.93 (10H, m, H10, H11); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.2 (C=O), 144.6 (C6), 141.5 (C9), 139.9 (CAr), 139.4 (C7), 132.7 (C2), 132.5 (C1), 128.7 (CAr), 127.1 (CAr), 127.0 (CAr), 124.3 (C8), 65.5

(C12), 60.4 (C4), 52.9 (O<u>Me</u>), 41.4 (C3), 40.1 (C5), 25.8 (C13), 6.8 (C11), 5.5 (C10); **HRMS** (ES^+) calcd for $C_{26}H_{34}NaO_5Si$ $[M+Na]^+$ 477.2068, found 477.2053.

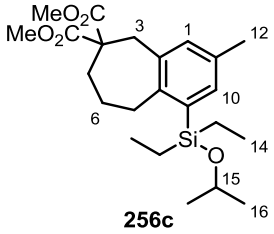
Dimethyl 5-(diethyl(isopropoxy)silyl)-7-methyl-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate 256b:



256b

256b was synthesised from **231** (40 mg, 0.10 mmol) and MnO_2 (85 mg, 0.98 mmol) using general procedure 4. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **256b** as a colourless oil (38 mg, 0.07 mmol, 95%); $\mathbf{R_f}$ 0.34 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2957, 2923, 1739, 1460, 1251, 1082, 1004, 743, 697; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.16 (1H, s, H9), 6.96 (1H, s, H1), 3.95 (1H, septet, *J* = 6.1 Hz, H14), 3.72 (6H, s, CO_2<u>Me</u>), 3.24 (2H, s, H3), 2.94 (2H, t, *J* = 6.5 Hz, H6), 2.31 (2H, t, *J* = 6.5 Hz, H5), 2.29 (3H, s, H11), 1.12 (6H, d, *J* = 6.1 Hz, H15), 0.99 – 0.93 (10H, m, H12, H13); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.0 (C=O), 137.8 (C7), 134.6 (C9), 134.4 (C2), 134.3 (C10), 132.9 (C8), 131.2 (C1), 65.3 (C14), 53.4 (C4), 52.6 (O<u>Me</u>), 35.3 (C3), 30.9 (C6), 28.7 (C5), 25.6 (C15), 21.1 (C11), 6.9 (C12), 5.6 (C13); **HRMS** (ES^+) calcd for $C_{22}H_{34}NaO_5Si$ $[M+Na]^+$ 429.2068, found 429.2053.

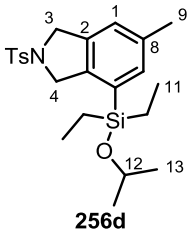
Dimethyl 1-(diethyl(isopropoxy)silyl)-3-methyl-8,9-dihydro-5*H*-benzo[*7*]annulene-6,6(7*H*)-dicarboxylate 256c:



256c

256c was synthesised from **233** (27.5 mg, 0.07 mmol), and MnO_2 (57 mg, 0.65 mmol) using general procedure 4. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **256c** as a colourless oil (24.0 g, 0.06 mmol, 88%); $\mathbf{R_f}$ 0.42 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2955, 1734, 1435, 1255, 1204, 1013, 801, 730; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.17 (1H, s, H10), 6.97 (1H, s, H1), 3.99 (1H, septet, *J* = 6.1 Hz, H15), 3.65 (6H, s, $CO_2\underline{Me}$), 3.31 (2H, s, H3), 3.01 – 2.95 (2H, m, H7), 2.27 (3H, s, H12), 2.17 – 2.10 (2H, m, H5), 1.86 – 1.78 (2H, m, H6), 1.14 (6H, d, *J* = 6.1 Hz, H16), 1.00 – 0.85 (10H, m, H13, H14); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 171.9 (C=O), 145.8 (C8), 135.7 (C2), 134.8 (C10), 134.0 (C9), 133.5 (C1), 65.1 (C15), 55.5 (C4), 52.4 (O$\underline{Me}$), 39.5 (C3), 35.8 (C5), 32.4 (C7), 26.0 (C16), 23.5 (C6), 21.1 (C12), 7.3 (C14), 6.1 (C13); **HRMS** (ES^+) calcd for $C_{23}H_{36}NaO_5Si$ $[M+Na]^+$ 443.2224, found 443.2221.

4-(Diethyl(isopropoxy)silyl)-6-methyl-2-tosylisoindoline 256d:

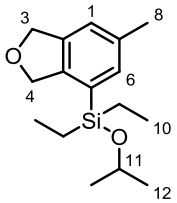


256d

256d was synthesised from **229b** (29 mg, 0.05 mmol) and MnO_2 (50 mg, 0.46 mmol) using general procedure 4. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **256d** as a colourless oil (27 mg, 0.04 mmol, 93%); $\mathbf{R_f}$ 0.30 (5:1 Pet.

Ether/Ether); **IR** (thin film) ν_{max} = 2958, 1733, 1596, 1433, 1259, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.3 Hz, HAr), 7.29 (2H, d, *J* = 8.3 Hz, HAr), 7.14 (1H, s, H7), 6.99 (1H, s, H1), 4.67 (2H, s, H4), 4.56 (2H, s, H3), 4.05 (1H, septet, *J* = 6.3 Hz, H12), 2.40 (3H, s, Ts–C$\underline{H}_3$), 2.31 (3H, s, H9), 1.18 (6H, d, *J* = 6.3 Hz, H13), 0.92 (6H, t, *J* = 6.8 Hz, H11), 0.88 – 0.82 (4H, m, H10); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 143.4 (CAr), 138.8 (C8), 136.3 (C2), 135.6 (C5), 134.4 (C7), 133.7 (CAr), 131.1 (C6), 129.7 (CAr), 127.6 (CAr), 124.2 (C1), 65.4 (C12), 54.6 (C4), 53.3 (C3), 25.7 (C13), 21.4 (Ts–$\underline{C}H_3$), 21.2 (C9), 6.8 (C11), 5.5 (C10); **HRMS** (ES^+) calcd for $C_{23}H_{33}NNaO_3SSi$ $[M+Na]^+$ 454.1843, found 454.1845.

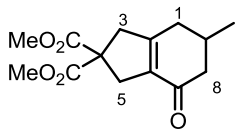
Diethyl(isopropoxy)(6-methyl-1,3-dihydroisobenzofuran-4-yl)silane 256e:



256e

256e was synthesised from **229c** (10 mg, 0.04 mmol) and MnO_2 (32 mg, 0.37 mmol) using general procedure 4. The crude product was purified by flash chromatography (5:1 Pet. Ether/Ether) to afford **256e** as a colourless oil (5 mg, 0.02 mmol, 46%) which was used immediately in the next step; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.20 (1H, s, H1), 7.07 (1H, s, H6), 5.17 (2H, s, H3), 5.06 (2H, H4), 4.05 (1H, septet, *J* = 6.1 Hz), 2.37 (3H, s, H8), 1.18 (6H, d, H12, *J* = 6.1 Hz), 0.99 – 0.95 (6H, m, H9), 0.88 – 0.84 (4H, m, H10).

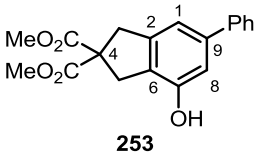
Dimethyl 6-methyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indene-2,2(3*H*)-dicarboxylate 251:



251

227a (16.8 mg, 0.05 mmol, 1 equiv.) was dissolved in THF/MeOH (1:1, 400 µL) and KF (5.3 mg, 0.09 mmol, 2 equiv.), $KHCO_3$ (9.2 mg, 0.09 mmol, 2 equiv.), H_2O_2 (5.2 µL, 0.05 mmol, 1 equiv) were added and the reaction mixture was heated at 40°C for 3 h and monitored by TLC. The reaction mixture was then allowed to cool to room temperature, diluted with DCM and washed with water. The combined organic extracts were washed with water and dried ($MgSO_4$). The solvent was then removed *in vacuo* and the crude product purified by flash chromatography (2:1 Pet.Ether/Ether) to afford the title compound **251** as a colourless oil (5.3 mg, 0.02 mmol, 43%); $\mathbf{R_f}$ 0.21 (2:1 Pet.Ether/Ether); **IR** (thin film) ν_{max} = 2349, 1734, 1667, 1434, 1262, 913, 745; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.75 (6H, s, $CO_2\underline{Me}$), 3.23 – 3.21 (4H, m, H3, H5), 2.42 – 2.40 (2H, m, H1), 2.27 – 2.25 (1H, m, H9), 2.11 – 2.09 (2H, m, H8), 1.07 (3H, d, *J* = 6.5 Hz, H10); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 194.9, 172.0, 158.7, 134.8, 57.8, 52.5, 45.8, 45.2, 38.6, 33.8, 31.0, 21.0; **HRMS** (ES^+) calcd for $C_{14}H_{19}O_5$ $[M+H]^+$ 267.1227, found 267.1225.

Dimethyl 4-hydroxy-6-phenyl-1*H*-indene-2,2(3*H*)-dicarboxylate 253:



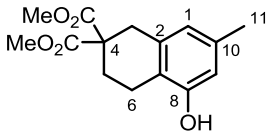
253

Method A: **252** (8 mg, 0.019 mmol, 1 equiv.) was dissolved in THF/MeOH (1:1, 400 µL) and KF (2.2 mg, 0.038 mmol, 2 equiv), $KHCO_3$ (3.8 mg, 0.038 mmol, 2 equiv.), H_2O_2 (2.1 µL, 0.019 mmol, 1 equiv) were added and the reaction mixture was heated at 40°C for 3 h and monitored by TLC. The reaction mixture was then allowed to cool to room

temperature, diluted with DCM and washed with water. The combined organic extracts were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product purified by flash chromatography (2:1 Pet.Ether/Ether) to afford the title compound **253** as a colourless oil (3 mg, 0.015 mmol, 80%).

Method B: 253 was synthesised from **256a** (17.0 mg, 0.04 mmol), TBAF (13 µL, 0.04 mmol), $KHCO_3$ (7.5 mg, 0.08 mmol) and H_2O_2 (4.2 µL, 0.04 mmol) using general procedure 5. The crude product was purified by flash chromatography (2:1 Pet. Ether/Ether) to afford **253** as a colourless oil (11.4 mg, 0.03 mmol, 93%, 61% over 3 steps); $\mathbf{R_f}$ 0.15 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2954, 1733, 1596, 1434, 1260, 1165, 864, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.52 (2H, d, *J* = 7.5 Hz, HAr), 7.41 (2H, t, *J* = 7.5 Hz, HAr), 7.32 (1H, t, *J* = 7.5 Hz, HAr), 7.01 (1H, s, H1), 6.85 (1H, s, H8), 3.78 (6H, s, CO_2Me), 3.66 (2H, s, H3), 3.60 (2H, s, H5); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.0 (C=O), 151.8 (C7), 142.8 (C2), 142.5 (C9), 140.9 (CAr), 128.7 (C6), 127.2 (CAr), 127.1 (CAr), 124.7 (CAr), 115.6 (C1), 112.6 (C8), 60.3 (C4), 53.0 (OMe), 40.9 (C3), 36.8 (C5); **HRMS** (ES^+) calcd for $C_{19}H_{17}O_5$ $[M+H]^+$ 325.1081, found 325.1081.

Dimethyl 5-hydroxy-7-methyl-3,4-dihydronaphthalene-2,2(1*H*) -dicarboxylate 257b:

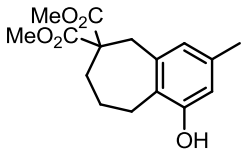


257b

257b was synthesised from **256b** (25 mg, 0.08 mmol), TBAF (30 µL, 0.08 mmol), $KHCO_3$ (16 mg, 0.16 mmol) and H_2O_2 (10 µL, 0.08 mmol) using general procedure 5. The crude product was purified by flash chromatography (2:1 Pet. Ether/Ether) to afford **257b** as a colourless oil (11.2 mg, 0.05 mmol, 65%, 46% over 3 steps); $\mathbf{R_f}$ 0.23 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2954, 1733, 1596, 1433, 1259, 1200, 765; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.54 (1H, s, H1), 6.42 (1H, s, H9), 3.72 (6H, s, CO_2Me), 3.22 (2H,

s, H3), 2.68 (2H, t, *J* = 6.7 Hz, H6), 2.33 (2H, t, *J* = 6.7 Hz, H5), 2.23 (3H, s, H11); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 171.7 (C=O), 153.0 (C8), 136.5 (C2), 134.7 (C10), 121.8 (C7), 118.1 (C1), 113.3 (C9), 53.4 (C4), 52.7 (OMe), 34.7 (C3), 27.8 (C5), 21.0 (C6), 19.8 (C11); **HRMS** (ES^+) calcd for $C_{15}H_{18}NaO_5$ $[M+Na]^+$ 301.1046, found 301.1040.

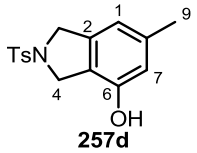
Dimethyl 1-hydroxy-3-methyl-8,9-dihydro-5*H*-benzo[7]annulene-6,6(7*H*)-dicarboxylate 257c:



257c

257c was synthesised from **256c** (29.1 mg, 0.07 mmol), TBAF (30 µL, 0.07 mmol), $KHCO_3$ (15 mg, 0.14 mmol) and H_2O_2 (10 µL, 0.07 mmol) using general procedure 5. The crude product was purified by flash chromatography (2:1 Pet. Ether/Ether) to afford **257c** as a colourless oil (15 mg, 0.05 mmol, 74%, 49% over 3 steps); **R_f** 0.24 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3468, 2925, 2854, 1733, 1590, 1250, 1213, 1040, 731; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.53 (1H, s, H1), 6.45 (1H, s, H10), 3.65 (6H, s, CO_2Me), 3.29 (2H, s, H3), 2.83 – 2.77 (2H, m, H5), 2.21 (3H, s, H12), 2.20 – 2.14 (2H, m, H7), 1.88 – 1.80 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.0 (C=O), 151.7 (C9), 137.9 (C11), 135.8 (C2), 125.6 (C8), 124.5 (C1), 115.1 (C10), 55.3 (C4), 52.4 (OMe), 39.6 (C7), 36.1 (C5), 23.0 (C6), 21.0 (C12); **HRMS** (ES^+) calcd for $C_{16}H_{20}NaO_5$ $[M+Na]^+$ 315.1203, found 315.1203.

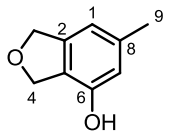
6-Phenyl-2-tosylisoindolin-4-ol 257d:



257d

257d was synthesised from **256d** (20 mg, 0.05 mmol), TBAF (16 µL, 0.05 mmol), $KHCO_3$ (9 mg, 0.10 mmol) and H_2O_2 (15 µL, 0.15 mmol) using general procedure 5. The crude product was purified by flash chromatography (2:1 Pet. Ether/Ether) to afford **257d** as a colourless oil (14 mg, 0.05 mmol, 98%, 47% over 3 steps); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2954, 1733, 1596, 1434, 1260, 1165, 864, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 7.7 Hz, HAr), 7.31 (2H, d, *J* = 7.7 Hz, HAr), 6.54 (1H, s, H1), 6.47 (1H, s, H7), 4.57 (4H, s, H3, H4), 2.40 (3H, s, Ts-C$\underline{H}_3$), 2.24 (3H, s, H9); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 150.6 (C6), 143.6 (CAr), 139.8 (C2), 138.2 (C8), 133.6 (CAr), 129.8 (CAr), 127.6 (CAr), 119.7 (C5), 115.2 (C1), 114.8 (C7), 54.0 (C4), 51.4 (C3), 21.5 (Ts-$\underline{C}H_3$), 21.2 (C9); **HRMS** (ES^+) calcd for $C_{16}H_{17}NNaO_3S$ $[M+Na]^+$ 326.0821, found 326.0824.

6-Methyl-1,3-dihydroisobenzofuran-4-ol 257e:



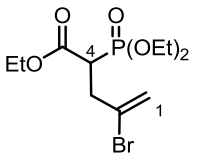
257e

257e was synthesised from **256e** (5 mg, 0.02 mmol), TBAF (6 µL, 0.02 mmol), $KHCO_3$ (1 mg, 0.04 mmol) and H_2O_2 (6 µL, 0.06 mmol) using general procedure 5. The crude product was purified by flash chromatography (2:1 Pet. Ether/Ether) to afford **257e** as a colourless oil (2 mg, 0.02 mmol, 99%, 29% over 3 steps); $\mathbf{R_f}$ 0.26 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2954, 1733, 1596, 1434, 1260, 1165, 864, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.62 (1H, s, H1), 6.46 (1H, s, H7), 5.09 (2H, s, H4), 5.06 (2H, s, H3), 2.30 (3H,

s, H9); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 150.1 (C6), 142.2 (C2), 139.4 (C8), 122.4 (C5), 114.7 (C1), 113.8 (C7), 73.9 (C3), 71.5 (C4), 21.1 (C9); **HRMS** (ES^+) calcd for $C_9H_{10}NaO_2$ $[M+Na]^+$173.0573, found 173.0575.

5.4. Experimental - Chapter 3

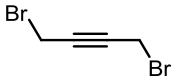
4-Bromo-2-(diethoxy-phosphoryl)-pent-4-enoic-acid-ethylester 278:



278

278 was synthesised from ethyl 2-(diethoxyphosphoryl)acetate (98%, 8.20 mL, 40.5 mmol, 1.4 equiv.), NaH (60% dispersion in mineral oil, 1.78 g, 44.5 mmol, 1.5 equiv.) and 2,3-dibromopropene **205** (80%, 3.80 mL, 29.4 mmol, 1 equiv.) using general procedure 1. The crude product was purified by flash chromatography (2:1 EtOAc/Pet. Ether) to afford **278** (5.65 g, 16.5 mmol, 56%) as a colourless oil; $\mathbf{R_f}$ 0.24 (ether); **IR** (thin film) ν_{max} = 2983, 1733, 1252, 1017, 968; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.69 (1H, br s, H1), 5.47 (1H, d, *J* = 1.8 Hz, H1), 4.22 (2H, q, *J* = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.17 – 4.15 (4H, m, $P(O)(OC\underline{H}_2CH_3)_2$), 3.38 (1H, dt, *J* = 23.2, 11.4 Hz, H4), 3.12 (1 H, ddd, *J* = 11.4, 7.0, 0.6, H3), 2.85 (1H, ddd, *J* = 11.4, 7.0, 1.8, H3), 1.35 (3H, t, *J* = 6.9 Hz, $P(O)(OCH_2C\underline{H}_3)_2$), 1.34 (3H, t, *J* = 6.9 Hz, $P(O)(OCH_2C\underline{H}_3)_2$), 1.28 (3H, t, *J* = 7.2 Hz, $CO_2CH_2C\underline{H}_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 167.8 (C=O), 130.1 (C=C), 119.2 (C=C), 62.9 ($CO_2\underline{C}H_2CH_3$), 61.6 (C4), 43.9 (C3), 38.7 (d, $J_{P\text{-}C}$ = 2.7 Hz, $P(O)(O\underline{C}H_2CH_3)_2$), 16.3 (d, $J_{P\text{-}C}$ = 6.4 Hz, $P(O)(OCH_2\underline{C}H_3)_2$), 14.1 ($CO_2CH_2\underline{C}H_3$); **HRMS** ($ES^+$) calcd for $C_{11}H_{20}BrO_5P$ $[M+Na]^+$ 365.0127, found 365.0124.

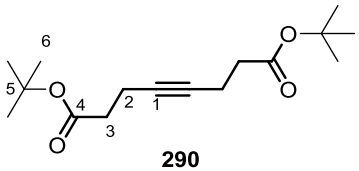
1,4-Dibromobut-2-yne 292:



292

To a solution of but-2-yne-1,4-diol **291** (10.0 g, 110 mmol, 1 equiv.) and pyridine (0.9 mL, 11 mmol, 0.1 equiv.) in Et_2O (100 mL) at −30 °C under Ar, was added PBr_3 (7.5 mL, 77 mmol, 0.7 equiv.) dropwise. After warming to room temperature over 1 h, the reaction mixture was refluxed until completion of the reaction as monitored by TLC. The reaction mixture was poured into brine, extracted with Et_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by distillation (bp 91 – 92 °C) provided the title compound **292** as a yellow oil (23.3 g, 95%); $\mathbf{R_f}$ 0.60 (Pet. Ether/Ether 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.96 (4H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 81.5 (C≡C), 13.8 ($\underline{C}H_2$). Data in accordance with literature.[117]

Di-*tert*-butyl oct-4-ynedioate 290:

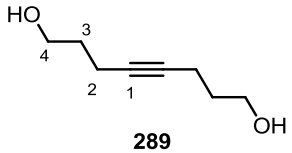


290

LDA was formed by the addition of *n*–BuLi (200 mL, 0.5 mol, 4 equiv.) to a solution of diisopropylamine (70 mL, 0.5 mol, 4 equiv.) in dry THF (200 mL) at 0 °C. After cooling at −78 °C, *tert*–butyl acetate (67 mL, 0.5 mol, 4 equiv.) was added slowly keeping the temperature at −78 °C, and the reaction mixture was stirred for 30 min. **292** (26.5 g, 0.2 mol, 1 equiv.) was added dropwise to the mixture at −78 °C and stirred for 2 h at −78 °C. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with aq. NH_4Cl and allowed to warm up, extracted with Et_2O, washed with water, brine,

dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (Pet. Ether/Ether 10:1) to afford the title compound **290** as a colorless oil (31.8 g, 0.11 mol, 90%); $\mathbf{R_f}$ 0.55 (Pet. Ether/Ether 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.40 – 2.38 (8H, m, H2, H3), 1.45 (18H, s, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 171.4 (C=O), 80.5 (C5), 78.9 (C1), 35.0 (C3), 28.0 (C6), 14.8 (C2). Data in accordance with literature.[117]

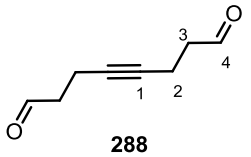
Oct-4-yne-1,8-diol 289:



289

A solution of **290** (1.0 g, 3.6 mmol, 1 equiv.) in dry ether (5 mL) was added to a stirred solution of LAH (1 M in THF, 4.0 mL, 4.0 mmol, 1.1 equiv.) in dry Et_2O as such rate as to maintain gentle reflux. The mixture was refluxed for 2 h. LAH (1 M in THF, 2.0 mL, 2.0 mmol, 0.6 equiv.) was added to the reaction mixture and refluxed for a further 2 h. After completion of the reaction, the reaction mixture was quenched by dropwise sequential addition of H_2O (2 mL), 15% NaOH (2 mL) and H_2O (6 mL) and the resulting mixture was further stirred. The colourless precipitate was filtered. The resulting solution was concentrated *in vacuo*. Purification by flash chromatography afforded the desired compound **289** as a colorless oil (500 mg, 3.5 mmol, 99%); $\mathbf{R_f}$ 0.10 (Ether); **IR** (thin film) ν_{max} = 3332, 2944, 2877, 1436; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.75 (4H, t, *J* = 6.1 Hz, H4), 2.28 (4H, t, *J* = 6.1 Hz, H2), 1.73 (4H, q, *J* = 6.1 Hz, H3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 80.1 (C1), 61.9 (C4), 31.4 (C3), 15.3 (C2). Data in accordance with literature.[117]

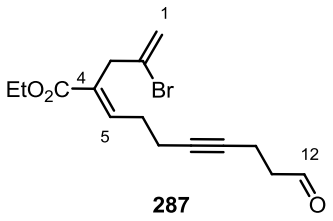
Oct-4-ynedial 288:



288

To a solution of oct-4-yne-1,8-diol **289** (831 mg, 5.0 mmol, 1.0 equiv.) in DCM (15 mL) at 0 °C was added $NaHCO_3$ (982 mg, 1.1 mmol, 2.0 equiv.) and Dess-Martin periodinane (6.0 g, 1.4 mmol, 2.4 equiv.). The reaction was stirred for 1 h until completion as monitored by TLC. The reaction was quenched with a solution of $NaHCO_3$ (15 mL) and $Na_2S_2O_3$ (15 mL) and stirred for 1 h until the solution became clear. The aqueous layer was extracted with DCM (2 × 15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resultant aldehyde **288** (777 mg, 4.8 mmol, 96%) was used crude in the subsequent reaction, or could be purified for the purposes of characterisation by flash chromatography (Ether); $\mathbf{R_f}$ 0.6 (Ether); **IR** (thin film) ν_{max} = 2913, 2836, 2733, 1725, 1410, 1390, 1058, 850; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.78 (2H, t, *J* = 1.3 Hz, H4), 2.62 (4H, br t, *J* = 7.3 Hz, H2), 2.47 (4H, td, *J* = 7.3, 1.3 Hz, H3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 200.6 (C4), 79.0 (C1), 42.7 (C3), 11.9 (C2); **HRMS** (CI^+) calcd for $C_8H_{14}NO_2$ $[M+NH_4]^+$ 156.1025, found 156.1020.

(*E*)-Ethyl 2-(2-bromoallyl)-10-oxodec-2-en-6-ynoate 287:



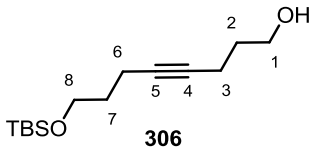
287

To a solution of ethyl 4-bromo-2-(dimethoxyphosphoryl)pent-4-enoate **293** (322 mg, 0.93 mmol, 1.0 equiv.) in dry THF (4 mL) was added $Ba(OH)_2$ (127 mg, 0.74 mmol, 0.8 equiv.), and the reaction was stirred vigourously at room temperature for 30 min. A solution of aldehyde **288** (257 mg, 1.86 mmol, 2.0 equiv.) in THF (2 mL) and H_2O (0.15

mL) was then added. After completion of the reaction as monitored by TLC, the reaction mixture was poured in DCM, washed with aq. NH_4Cl, brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (1:1 Pet. Ether/Ether) afforded the desired aldehyde **287** as a colourless oil (91 mg, 0.28 mmol, 30%); $\mathbf{R_f}$ 0.57 (1:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2981, 2916, 2727, 1712, 1650, 1628, 1278, 1211, 1110, 1058, 892; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.78 (1H, t, *J* = 1.2 Hz, H12), 6.98 (1H, t, *J* = 7.3 Hz, H5), 5.57 (1H, d, *J* = 1.6 Hz, H1), 5.43 (1H, d, *J* = 1.6 Hz, H1), 4.20 (2H, q, *J* = 7.2 Hz, $CO_2C\underline{H}_2CH_3$), 3.50 (2H, s, H3), 2.63 (2H, td, *J* = 6.9, 1.2 Hz, H11), 2.50 – 2.48 (2H, m, H10), 2.41 (2H, q, *J* = 6.9 Hz, H6), 2.32 – 2.30 (2H, m, H7), 1.19 (3H, t, *J* = 7.2 Hz, $CO_2CH_2C\underline{H}_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 200.7 (C12), 166.6 (C=O), 143.7 (C5), 130.3 (C2), 129.2 (C1), 117.2 (C4), 79.7 (C9), 79.1 (C8), 60.8 ($CO_2\underline{C}H_2CH_3$), 42.8 (C11), 38.4 (C3), 28.2 (C6), 17.9 (C7), 14.1 ($CO_2CH_2\underline{C}H_3$), 12.0 (C10); **HRMS** (ES^+) calcd for $C_{15}H_{20}BrO_3$ $[M+H]^+$ 327.0590, found 327.0589.[106]

Alternative route for the synthesis of **287**:

8-(*tert*-Butyldimethylsilyloxy)oct-4-yn-1-ol 306:

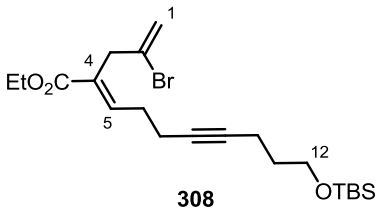


306

To a solution of NaH (60% dispersion in mineral oil, 248.0 mg, 6.19 mmol, 1 equiv.) in dry THF (20 mL) at room temperature under Ar was added a solution of diol **289** (879 mg, 6.19 mmol, 1 equiv.) in THF (5 mL). The mixture was stirred for 45 min, after which time an opaque white precipitate had formed. TBSCl (933 mg, 6.19 mmol, 1 equiv.) was added and vigorous stirring was continued for 45 min. The mixture was poured into Et_2O (40 mL), washed with K_2CO_3 (20 mL) and brine (20 mL), and the organic extracts were dried

($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (5:1 Pet. Ether/Ether) afforded the desired compound **306** as a colourless oil (1.1 g, 4.29 mmol, 70%); $\mathbf{R_f}$ 0.12 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2930, 1471, 1255, 1105, 836, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.77 – 3.75 (2H, m, H1), 3.68 (2H, t, *J* = 6.1 Hz, H8), 2.29 – 2.27 (2H, m, H6), 2.24 – 2.22 (2H, m, H3), 1.74 (2H, q, *J* = 6.5 Hz, H7), 1.68 (2H, q, *J* = 6.5 Hz, H2), 0.90 (9H, s, Si*t*-Bu), 0.06 (6H, s, $SiMe_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 80.5 (C5), 79.3 (C4), 62.0 (C8), 61.6 (C1), 32.0 (C7), 31.5 (C2), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 15.3 (C6), 15.1 (C3), -5.3 ($SiMe_2$); **HRMS** (ES^+) calcd for $C_{14}H_{28}NaO_2Si$ $[M+Na]^+$ 279.1751, found 279.1747.[160]

(*E*)-Ethyl 2-(2-bromoallyl)-10-(*tert*-butyldimethylsilyloxy)dec-2-en-6-ynoate 308:

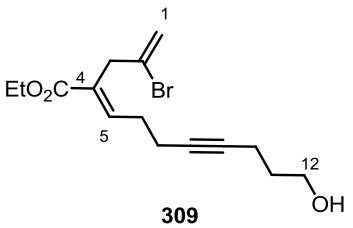


308

To a solution of **306** (175 mg, 0.68 mmol, 1 equiv.) in DCM (5 mL) was added $NaHCO_3$ (57.6 mg, 0.68 mmol, 1 equiv.) and Dess-Martin periodinane (319.6 mg, 0.74 mmol, 1.1 equiv.) at 0 °C. The reaction was warmed to room temperature and stirred for 30 min until completion of the reaction as monitored by TLC. The reaction was quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1, 10 mL) and stirred until the solution became clear (1 h). The aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography afforded aldehyde **307** as a colourless oil (170 mg, 0.68 mmol, 99%) which was used without further purification. To a stirred solution of ethyl 4-bromo-2-(dimethoxyphosphoryl)pent-4-enoate **293** (650 mg, 1.89 mmol, 1.2 equiv.) in dry THF (6 mL) was added $Ba(OH)_2$ (216 mg, 1.26 mmol, 0.8 equiv.), and the mixture was stirred at

room temperature for 30 min. A solution of the freshly prepared aldehyde (401 mg, 1.58 mmol, 1 equiv.) in THF/H_2O (40:1, 4.25 mL) was added. After completion of the reaction as monitored by TLC, the reaction mixture was poured into DCM (20 mL), washed with NH_4Cl (10 mL), brine (10 mL), and the organic extract was dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (10:1 Pet. Ether/Ether) afforded the desired compound **308** as a colourless oil (443 mg, 0.10 mmol, 64%); $\mathbf{R_f}$ 0.40 (10:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2929, 2856, 1716, 1471, 1256, 1209, 1106, 836; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.01 (1H, t, *J* = 7.4 Hz, H5), 5.59 (1H, d, *J* = 0.7 Hz, H1), 5.44 (1H, s, H1), 4.21 (2H, q, *J* = 7.0 Hz, $CO_2C\underline{H_2}CH_3$), 3.68 (2H, t, *J* = 6.1 Hz, H12), 3.50 (2H, s, H3), 2.42 (2H, q, *J* = 7.4 Hz, H10), 2.32 – 2.30 (2H, m, H6), 2.23 – 2.21 (2H, m, H7), 1.68 (2H, q, *J* = 6.2 Hz, H11), 1.30 (3H, t, *J* = 7.4 Hz, $CO_2CH_2C\underline{H_3}$), 0.89 (9H, s, Si*t*-Bu), 0.05 (6H, s, $Si\underline{Me_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.6 (C=O), 144.0 (C5), 130.3 (C4), 129.1 (C2), 117.2 (C1), 80.9 (C8), 78.5 (C9), 61.6 (C12), 60.7 ($CO_2\underline{C}H_2CH_3$), 38.4 (C3), 34.0 (C11), 31.9 ($Si\underline{C}(CH_3)_3$), 29.6 ($SiC(\underline{C}H_3)_3$), 25.9 (C6), 22.3 (C7), 18.0 (C10), 14.0 ($CO_2CH_2\underline{C}H_3$), -5.3 ($Si\underline{Me_2}$); **HRMS** (ES^+) calcd for $C_{21}H_{36}BrNaO_3Si$ $[M+Na]^+$ 443.1612, found 443.1610.

(*E*)-Ethyl 2-(2-bromoallyl)-10-hydroxydec-2-en-6-ynoate 309:

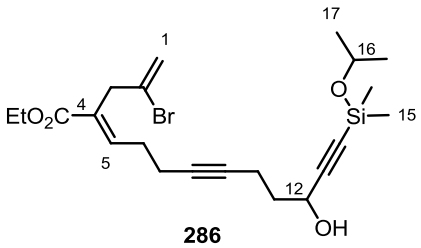


309

308 (100.0 mg, 0.22 mmol, 1 equiv.) was dissolved in a mixture of DCM/MeOH (3:1, 5 mL), and CSA (5.3 mg, 0.02 mmol, 0.1 equiv.) was added and the solution was stirred for 1 h until completion of the reaction as monitored by TLC. The reaction mixture was poured into DCM (10 mL), washed with water (10 mL), dried ($MgSO_4$), and concentrated

in vacuo. Purification by flash chromatography (1:1 Pet. Ether/Ether) afforded the desired compound **309** as a colourless oil (70.3 mg, 0.21 mmol, 95%); $\mathbf{R_f}$ 0.08 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3417, 2936, 1714, 1434, 1279, 1211, 1058, 891; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.02 (1H, t, *J* = 7.3 Hz, H5), 5.59 (1H, d, *J* = 1.6 Hz, H1), 5.45 – 5.43 (1H, m, H1), 4.21 (2H, q, *J* = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 3.75 (2H, t, *J* = 5.8 Hz, H12), 3.50 (2H, s, H3), 2.42 – 2.40 (2H, m, H10), 2.34 – 2.32 (2H, m, H6), 2.28 – 2.26 (2H, m, H7), 1.75 – 1.73 (2H, m, H11), 1.30 (3H, t, *J* = 7.0 Hz, $CO_2CH_2C\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.7 (C=O), 144.0 (C5), 130.3 (C4), 129.1 (C2), 117.3 (C1), 80.6 (C8), 79.0 (C9), 65.8 (C12), 61.7 ($CO_2\underline{C}H_2CH_3$), 60.8 (C11), 38.4 (C3), 31.3 (C6), 28.4 (C7), 15.2 (C10), 14.1 ($CO_2CH_2\underline{C}H_3$); **HRMS** (ES^+) calcd for $C_{15}H_{36}BrNaO_3$ $[M+Na]^+$ 351.0566, found 351.0566.

(*E*)-Ethyl 2-(2-bromoallyl)-10-hydroxy-12-(isopropoxydimethylsilyl)dodeca-2-en-6,11-diynoate 286:

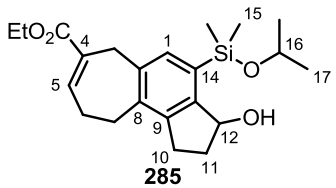


286

Ethynyl(isopropoxy)dimethylsilane **312** (94.0 mg, 0.66 mmol, 3 equiv.) was dissolved in THF, and *n*–BuLi (2.5 M in hexanes, 263 μL, 0.66 mmol, 3 equiv.) was added dropwise at –78 °C. The mixture was stirred for 20 min, and a solution of aldehyde **287** (72 mg, 0.22 mmol, 1 equiv.) in THF (1 mL) dried over CaH_2 was added to the reaction mixture *via* cannula, and the resulting solution was stirred at –78 °C until completion of the reaction as monitored by TLC. The reaction was quenched with pH 7 buffer at –78 °C, extracted with DCM, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography

(2:1 Pet. Ether/Ether) afforded the alcohol **286** as a colourless oil (98.8 mg, 0.21 mmol, 89%); $\mathbf{R_f}$ 0.37 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3437, 2971, 2172, 1711, 1279, 1255, 1028, 792; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.01 (1H, t, *J* = 7.3 Hz, H5), 5.59 (1H, d, *J* = 1.6 Hz, H1), 5.45 (1H, s, H1), 4.52 (1H, q, *J* = 6.2 Hz, H12), 4.22 (2H, q, *J* = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.13 (1H, septet, *J* = 6.1 Hz, H16), 3.50 (2H, s, H3), 2.46 – 2.35 (4H, m, H6, H7), 2.35 – 2.28 (2H, m, H10), 2.08 (1H, d, *J* = 5.6 Hz, OH), 1.91 – 1.86 (2H, m, H11), 1.30 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.19 (6H, d, *J* = 6.1 Hz, H17), 0.25 (6H, s, H15); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 166.7 (C=O), 143.9 (C5), 130.4 (C4), 129.3 (C2), 117.3 (C1), 105.7 (C13), 90.1 (C14), 88.1 (C8), 79.5 (C9), 66.0 (C16), 61.6 (C12), 60.9 ($CO_2\underline{C}H_2CH_3$), 60.8 (C11), 38.5 (C3), 36.4 (C17), 28.4 (C6), 25.4 (C7), 18.1 ($CO_2CH_2\underline{C}H_3$), 14.8 (C10), 0.6 (C15); **HRMS** (ES^+) calcd for $C_{22}H_{33}O_4BrSiNa$ $[M+Na]^+$ 491.1224, found 491.1223.

Ethyl 3-hydroxy-4-(isopropoxydimethylsilyl)-1,2,3,6,9,10-hexahydrocyclohepta[*e*] indene-7-carboxylate 285:

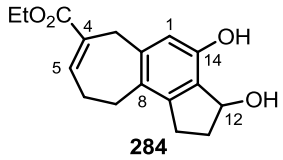


285

To a degassed solution of **286** (10 mg, 21.3 µmol, 1 equiv.) and Et_3N (12 µL, 45.2 µmol, 4 equiv.) in dry MeCN (1 mL) at room temperature under Ar was added $Pd(PPh_3)_4$ (2.5 mg, 2.13 µmol, 0.1 equiv.). The mixture was stirred for 6 h at 80 °C, after which the solution was concentrated and purified by flash chromatography (6:1 Pet. Ether/EtOAc) to afford the tricycle **285** as a colourless oil (5.5 mg, 14.2 µmol, 66%); $\mathbf{R_f}$ 0.19 (3:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3475, 2970, 1704, 1255, 965, 732; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.13 (1H, s, H1), 6.89 (1H, t, *J* = 4.3 Hz, H5), 5.36 (1H, td, *J* = 6.8, 2.1 Hz,

H12), 4.43 (1H, septet, *J* = 6.1 Hz, H16), 4.21 – 4.19 (2H, m, $CO_2C\underline{H}_2CH_3$), 3.84 (2H, s, H3), 3.11 (1H, td, *J* = 16.0, 8.0 Hz, H10), 3.00 (2H, t, *J* = 6.3 Hz, H7), 2.82 (1H, ddd, *J* = 16.0, 9.1, 3.6 Hz, H10), 2.54 – 2.52 (2H, m, H6), 2.36 – 2.34 (1H, m, H11), 2.14 – 2.12 (1H, m, H11), 1.30 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.21 (3H, d, *J* = 6.1 Hz, H17), 1.20 (3H, d, *J* = 6.1 Hz, H17), 0.49 (3H, s, H15), 0.39 (3H, s, H15); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 167.9 (C=O), 150.1 (C13), 141.3 (C9), 140.6 (C5), 139.9 (C8), 138.9 (C1), 132.5 (C2), 131.2 (C14), 129.5 (C4), 75.5 (C12), 66.2 (C16), 60.7 ($CO_2\underline{C}H_2CH_3$), 32.7 (C11), 31.1 (C7), 28.6 (C6), 28.5 (C3), 26.7 (C17), 25.7 (C17), 25.5 (C10), 14.2 ($CO_2CH_2\underline{C}H_3$), 0.3 (C15), -1.3 (C15); **HRMS** (ES^+) calcd for $C_{22}H_{32}NaO_4Si$ $[M+Na]^+$ 411.1962, found 411.1961.[105]

(*E*)-Ethyl 3,4-dihydroxy-1,2,3,6,9,10-hexahydrocyclohepta[*e*]indene-7-carboxylate 284:

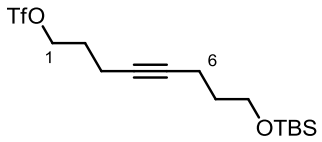


284

A solution of **285** (4.4 mg, 11.3 µmol, 1 equiv.) in THF/MeOH (1:1, 0.5 mL) was added to $KHCO_3$ (2.8 mg, 28.4 µmol, 2.5 equiv.) and KF (1.6 mg, 28.4 µmol, 2.5 equiv.). H_2O_2 (10 µL, 30% vol) was added, and the mixture was heated for 2 h at 40 °C. The reaction was allowed to cool down to room temperature, and was quenched by dilution with DCM (1 mL) and adding brine (1 mL). After further dilution with water (1 mL), the product was extracted with DCM (10 mL), the combined organic phases dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (Pet. Ether/Ether 1:1→1:3→ether) afforded phenol **284** as a colourless oil (2.4 mg, 8.32 µmol, 74%); $\mathbf{R_f}$ 0.24 (1:2 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3411, 2941, 1701, 1605, 1451, 1259, 1215, 1180 ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.87 (1H, t, *J* = 4.2 Hz, H5), 6.60 (1H, s,

H1), 5.49 (1H, t, *J* = 6.6 Hz, H12), 4.20 (2H, q, *J* = 7.3 Hz, $CO_2C\underline{H}_2CH_3$), 3.77 (2H, s, H14), 2.98 (1H, ddd, *J* = 15.9, 9.5, 2.3 Hz, H10), 2.90 (2H, t, *J* = 6.4 Hz, H7), 2.72 (1H, dt, *J* = 15.9, 8.5 Hz, H10), 2.64 – 2.62 (1H, m, H11), 2.50 – 2.48 (2H, m, H3), 1.92 – 1.90 (1H, m, H11), 1.28 (3H, t, *J* = 7.3 Hz, $CO_2CH_2C\underline{H}_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 167.9 (C=O), 151.6 (C14), 143.4 (C9), 141.6 (C5), 140.8 (C2), 129.6 (C8), 128.7 (C4), 126.9 (C13), 114.4 (C1), 76.4 (C12), 60.8 ($CO_2\underline{C}H_2CH_3$), 36.2(C11), 31.1 (C7), 29.3 (C6), 28.6 (C3), 25.5 (C10), 14.3 ($CO_2CH_2\underline{C}H_3$); **HRMS** (ES^+) calcd for $C_{17}H_{20}NaO_4$ $[M+Na]^+$ 311.1254, found 311.1250.[105]

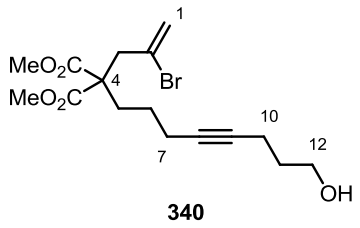
8-(*tert*-Butyldimethylsilyloxy)oct-4-ynyl trifluoromethanesulfonate 339:



339

To a solution of **306** (2 g, 7.8 mmol, 1 equiv.) and Et_3N (1.4 mL, 10.1 mmol, 1.3 equiv.) in CH_2Cl_2 under Ar at −78 °C was slowly added Tf_2O (1.5 mL, 8.6 mmol, 1.1 equiv.). The reaction was stirred at −78 °C for 30 min until completion of the reaction as monitored by TLC. The reaction was quenched at −78 °C with 1 M HCl, washed with $NaHCO_3$ and brine and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (ether) afforded the desired compound **339** as a colourless oil (2.4 g, 6.1 mmol, 78%) which is used immediately in the next step; **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 4.72 (2H, t, *J* = 6.1 Hz, H1), 3.73 (2H, t, *J* = 6.1 Hz, H8), 2.41 – 2.39 (2H, m, H2), 2.29 – 2.27 (2H, m, H7), 2.04 (2H, t , *J* = 6.1 Hz, H3), 1.73 (2H, t, *J* = 6.1 Hz, H6), 0.95 (9H, s, Si*t*-Bu), 0.11 (6H, s, $Si\underline{Me}_2$).

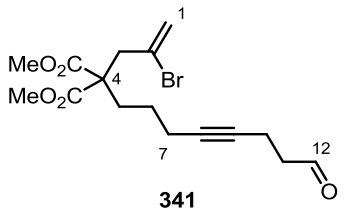
Dimethyl 2-(2-bromoallyl)-2-(8-hydroxyoct-4-ynyl)malonate 340:



340

To a solution of NaH (60% dispersion in mineral oil, 244.1 mg, 6.1 mmol, 1.2 equiv.) in THF (60 mL) at 0 °C was added **206** (1.3 g, 5.1 mmol, 1 equiv.) in THF (30 mL). The milky solution was stirred for 30 min at room temperature under Ar. A solution of **339** (2.4 g, 6.1 mmol, 1.2 equiv.) in THF (20 mL) was added at 0 °C. After completion of the reaction as monitored by TLC, the mixture was quenched with aq. NH_4Cl, washed with brine and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in MeOH, and CSA (cat.) was added. After completion of the deprotection reaction as monitored by TLC, the solvent was removed *in vacuo*. Purification by flash chromatography (1:1 Pet. Ether/Ether) afforded the desired alcohol **340** as a colourless oil (1.1 g, 2.9 mmol, 56%); $\mathbf{R_f}$ 0.16 (1:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3435, 2951, 1734, 1435, 1210, 966; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 5.67 (1H, s, H1), 5.59 (1H, d, *J* = 1.4 Hz, H1), 3.77 – 3.75 (2H, m, H12), 3.75 (6H, s, CO_2Me), 3.17 (2H, s, H3), 2.28 – 2.26 (2H, m, H10), 2.18 – 2.16 (2H, m, H7), 2.11 – 2.09 (2H, m, H6), 1.75 – 1.73 (2H, m, H11), 1.38 – 1.36 (2H, m, H5); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 170.9 (C=O), 127.0 (C2), 121.8 (C1), 80.1 (C9), 79.8 (C8), 61.8 (C12), 56.9 (C4), 52.7 (OMe), 43.1 (C3), 31.5 (C11), 30.9 (C6), 23.9 (C5), 18.9 (C7), 15.3 (C10); **HRMS** (ES^+) calcd for $C_{16}H_{23}BrNaO_5$ $[M+Na]^+$ 397.0621, found 397.0622.

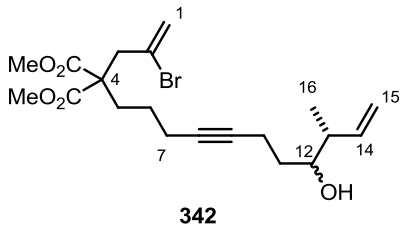
Dimethyl 2-(2-bromoallyl)-2-(8-oxooct-4-ynyl)malonate 341:



341

To a solution of alcohol **340** (500 mg, 1.33 mmol, 1 equiv.) in DCM (5 mL) was added $NaHCO_3$ (112 mg, 1.33 mmol, 1 equiv.) and DMP (678 mg, 1.60 mmol, 1.2 equiv.) at 0 °C. After addition, the reaction mixture was allowed to warm up to room temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with $NaHCO_3/Na_2S_2O_3$ (1:1) and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (1:1 Pet. Ether/Ether) afforded the desired aldehyde **341** as a colourless oil (422 mg, 1.13 mmol, 85%); $\mathbf{R_f}$ 0.25 (1:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2952, 1733, 1435, 1176, 915; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.79 (1H, t, *J* = 1.2 Hz, H12), 5.67 – 5.65 (1H, m, H1), 5.58 (1H, d, *J* = 1.7 Hz, H1), 3.74 (6H, s, CO_2Me), 3.16 (2H, s, H3), 2.62 (2H, t, *J* = 6.8 Hz, H10), 2.48 – 2.46 (2H, m, H11), 2.16 – 2.14 (2H, m, H7), 2.08 – 2.06 (2H, m, H6), 1.36 – 1.34 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 200.9 (C12), 170.9 (C=O), 127.0 (C2), 121.8 (C1), 80.3 (C9), 78.5 (C8), 56.8 (C4), 52.7 (OMe), 43.2 (C3), 42.9 (C10), 30.9 (C6), 23.7 (C5), 18.8 (C7), 12.0 (C11); **HRMS** (ES^+) calcd for $C_{17}H_{25}BrNaO_6$ $[M+Na+MeOH]^+$ 427.0727, found 427.0727.

(*R*)-Dimethyl 2-(2-bromoallyl)-2-(8-hydroxy-9-methylundec-10-en-4-ynyl) malonate 342:



342

To a stirred solution of *t*-BuOK (177 mg, 1.6 mmol, 1.2 equiv.) and *cis*-butene (excess) in THF (7 mL) at −78 °C under Ar was added dropwise *n*-BuLi (630 µL, 1.6 mmol, 1.2 equiv.). The bright yellow solution was then stirred for 15 min at −78 °C and then warmed up to −45 °C for 10 min. The reaction mixture was cooled again to −78 °C and (+)-$Ipc_2B(OMe)$ (498 mg, 1.6 mmol, 1.2 equiv.) in solution in THF (3 mL) was slowly added *via* cannula and the mixture was stirred for 30 min at this temperature. BF_3•OEt_2 (266 µL, 2.1 mmol, 1.6 equiv.) was added followed by aldehyde **341** (490 mg, 1.3 mmol, 1 equiv.) and the reaction mixture was stirred for 3 h at −78 °C. The reaction was quenched by subsequent addition of MeOH/pH7 buffer/H_2O_2 (1:2:1) and stirred for 12 h at room temperature. After evaporation of the solvents, the reaction mixture was dissolved in Et_2O and washed with H_2O and brine. The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (1:1 Pet. Ether/Ether) afforded the desired compound **342** (106 mg, 0.30 mmol, 23%) as a colourless oil in a mixture with IpcOH, which could be separated by chromatography (10:1 Pet. Ether/Ether) after TBS-protection of the alcohols; $\mathbf{R_f}$ 0.27 (1:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2952, 1735, 1625, 1435, 1209, 910 416; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.80 – 5.78 (1H, m, H14), 5.67 – 5.65 (1H, m, H1), 5.59 – 5.57 (1H, m, H1), 5.09 (1H, d, *J* = 7.8 Hz, H15), 5.07 (1H, s, H15), 3.74 (6H, s, CO_2Me), 3.62 – 3.60 (1H, m, H12), 3.16 (2H, s, H3), 2.30 – 2.28 (1H, m, H13), 2.29 – 2.27 (2H, m, H7), 2.17 – 2.15 (2H, m, H6), 2.09 – 2.07 (2H, m,

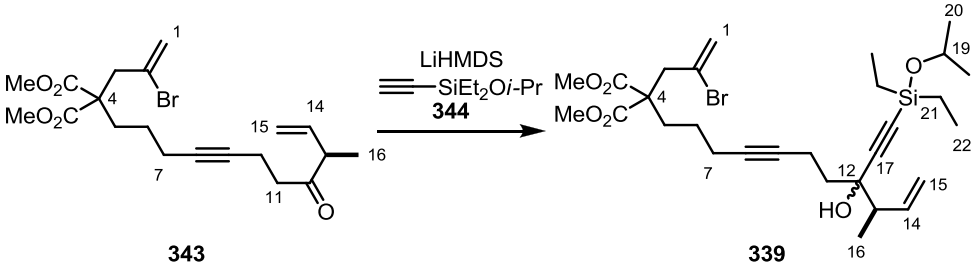
H10), 1.68 – 1.66 (1H, m, H11), 1.52 – 1.50 (1H, m, H11), 1.37 – 1.35 (2H, m, H5), 1.05 (3H, d, *J* = 6.9 Hz, H16); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.9 (C=O), 140.7 (C14), 127.0 (C2), 121.8 (C1), 115.4 (C15), 80.4 (C9), 79.8 (C8), 73.8 (C12), 56.8 (C4), 52.7 (OMe), 43.6 (C13), 43.1 (C3), 33.0 (C11), 30.9 (C10), 23.9 (C5), 18.9 (C6), 15.6 (C7), 14.5 (C16); **HRMS** (ES^+) calcd for $C_{20}H_{29}BrNaO_5$ $[M+Na]^+$ 451.1091, found 451.1090.[123]

Diethyl(ethynyl)(isopropoxy)silane 344:



To **222** (3.2 mL, 14.7 mmol, 1.0 eq) at –78 °C was added ethynylmagnesium bromide (33 mL [0.5 M in THF], 16.2 mmol, 1.1 eq). The solution was warmed to room temperature over 30 min then stirred under reflux for 3 h. After cooling to room temperature, isopropanol (2.3 mL, 29.4 mmol, 2.0 eq) and DMAP were added and the mixture stirred at room temperature overnight. The reaction mixture was concentrated, redissolved in petrol and filtered through celite. The filtrate was concentrated *in vacuo* as a yellow oil and purified by vacuum distillation to afford a 6.3:1 mixture of **344** and diethyldiisopropoxysilane as a colourless oil (1.79 g, 84% purity by weight, 60%); bp 54-56 °C, 20 mbar; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.18 (1H, sept, *J* = 6.0 Hz, OCH), 2.43 (1H, s, C≡CH), 1.21 (6H, d, *J* = 6.0 Hz, $CH(CH_3)_2$), 1.02 (6H, t, *J* = 8.0 Hz, CH_2CH_3), 0.68 (4H, q, *J* = 8.0 Hz, CH_2CH_3). Data in accordance with literature.[121]

(*R*)-Dimethyl 2-(2-bromoallyl)-2-(8-((diethyl(isopropoxy)silyl)ethynyl)-8-hydroxy-9-methylundec-10-en-4-ynyl)malonate 335:

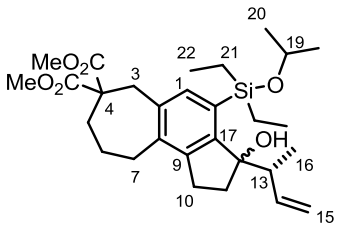


To a solution of alcohol **342** (106 mg, 0.25 mmol, 1 equiv.) in DCM (5 mL) was added $NaHCO_3$ (21 mg, 0.25 mmol, 1 equiv.) and DMP (137 mg, 0.32 mmol, 1.3 equiv.) at 0 °C. After addition the reaction mixture was allowed to warm up to room temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with $NaHCO_3/Na_2S_2O_3$ (1:1) and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (1:1 Pet. Ether/Ether) afforded the desired ketone **343** as a colourless oil (69 mg, 0.16 mmol, 65%); **^{1}H NMR** (250 MHz, $CDCl_3$) δ_H 5.77 – 5.75 (1H, m, H14), 5.65 – 5.63 (1H, m, H1), 5.55 (1H, d, *J* = 1.9 Hz, H1), 5.16 – 5.14 (2H, m, H15), 3.71 (6H, s, $CO_2\underline{Me}$), 3.19 (1H, t, *J* = 7.3 Hz, H13), 3.12 (2H, s, H3), 2.62 – 2.60 (2H, m, H11), 2.34 – 2.32 (2H, m, H7), 2.11 – 2.09 (2H, m, H10), 1.98 – 1.96 (2H, m, H5), 1.29 – 1.27 (2H, m, H6), 1.16 (3H, d, *J* = 7.3 Hz, H16).

To a solution of alkyne **344** (35 mg, 0.21 mmol, 1.3 equiv.) at −78 °C in THF (2 mL) was slowly added LiHMDS (1 M in THF, 210 µL, 0.21 mmol, 1.3 equiv.) and the reaction mixture was stirred 30 min at −78 °C, after which time a solution of ketone **343** (68 mg, 0.16 mmol, 1 equiv.) in THF (2 mL) was added. The reaction mixture was stirred at −78 °C until completion of the reaction as monitored by TLC. The reaction was quenched with aq. NH_4Cl, the organic layer was extracted with Et_2O and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (2:1 Pet. Ether/Ether) afforded the desired alcohol **335** as a colourless oil (60 mg, 0.10 mmol, 63%);

R_f 0.49 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2952, 1735, 1625, 1435, 1209, 910, 416; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.89 – 5.87 (1H, m, H14), 5.69 – 5.67 (1H, m, H1), 5.60 – 5.58 (1H, m, H1), 5.16 – 5.14 (2H, m, H15), 4.15 – 4.13 (1H, m, H19), 3.75 (6H, s, CO_2Me), 3.17 (2H, s, H3), 2.49 – 2.47 (1H, m, H13), 2.41 – 2.39 (2H, m, H7), 2.18 – 2.16 (2H, m, H5), 2.10 – 2.08 (2H, m, H10), 1.94 – 1.92 (2H, m, H11), 1.38 – 1.36 (2H, m, H6), 1.20 (6H, d, *J* = 6.0 Hz, H20), 1.17 (3H, t, *J* = 6.7 Hz, H16), 1.02 – 1.00 (6H, m, H22), 0.67 – 0.65 (4H, m, H21); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.9 (C=O), 139.2 (C14), 127.0 (C2), 121.9 (C1), 117.8 (C15), 106.9 (C17), 88.8 (C18), 80.5 (C9), 79.6 (C8), 72.9 (C12), 66.2 (C19), 56.9 (C4), 52.8 (OMe), 48.6 (C5), 48.3 (C13), 43.0 (C3), 38.5 (C11), 25.4 (C20), 23.9 (C6), 18.9 (C10), 15.8 (C16), 14.0 (C7), 6.8 (C21), 6.6 (C22); **HRMS** (ES^+) calcd for $C_{29}H_{45}NaBrO_6Si$ $[M+Na]^+$ 619.2066, found 619.2065.

(*R*)-Dimethyl 3-(but-3-en-2-yl)-4-(diethyl(isopropoxy)silyl)-3-hydroxy-2,3,6,8,9,10-hexahydrocyclohepta[*e*]indene-7,7(1*H*)-dicarboxylate 333:



333

To a degassed solution of **335** (30 mg, 0.05 mmol, 1 equiv.) and Et_3N (28 μL, 0.2 mmol, 4 equiv.) in dry MeCN (3 mL) at room temperature under Ar was added $Pd(PPh_3)_4$ (6 mg, 0.01 mmol, 0.2 equiv.). The mixture was stirred for 12 h at 80 °C, after which the solution was concentrated *in vacuo* and purified by flash chromatography (2:1 Pet. Ether/Ether) to afford the tricycle **333** as a colourless oil (12 mg, 0.02 mmol, 48%, **dr** 65:35); **R_f** 0.36 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3475, 2970, 1704, 1255, 965, 732; **94% *ee***

(CHIRALPAK IA, 1.25 mL/min, 2% IPA/hexanes, R_t (*minor*) – 9.09 min, R_t (*Major*) – 9.80 min); **HRMS** (ES^+) calcd for $C_{29}H_{44}NaO_6Si$ $[M+Na]^+$ 539.2799, found 539.2799.

Major diastereomer:

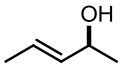
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.04 (1H, s, H1), 5.67 (1H, s, OH), 5.30 – 5.28 (1H, m, H14), 5.16 – 5.14 (1H, m, H15), 4.77 – 4.75 (1H, m, H15), 4.24 (1H, septet, *J* = 6.0 Hz, H19), 3.63 (6H, s, CO_2Me), 3.34 (2H, s, H3), 2.93 – 2.91 (1H, m, H13), 2.90 – 2.88 (1H, m, H10), 2.72 – 2.70 (2H, m, H7), 2.52 – 2.50 (1H, m, H10), 2.30 – 2.28 (1H, m, H11), 2.24 – 2.22 (1H, m, H5), 2.18 – 2.16 (1H, m, H5), 1.84 – 1.82 (1H, m, H11), 1.83 – 1.81 (2H, m, H6), 1.33 – 1.31 (6H, m, H20), 1.25 (3H, d, *J* = 6.7 Hz, H16), 0.98 – 0.81 (10H, m, H21, H22); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.0 (C=O), 154.2 (C17), 140.8 (C2), 140.2 (C14), 139.5 (C8), 136.2 (C1), 133.8 (C9), 126.2 (C18), 114.0 (C15), 86.8 (C12), 66.7 (C19), 55.8 (C4), 52.3 (OMe), 47.0 (C13), 39.0 (C3), 36.6 (C5), 32.4 (C11), 29.6 (C7), 29.7 (C10), 25.5 (C20), 22.9 (C6), 12.8 (C16), 7.3 (C22), 6.6 (C21);

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.06 (1H, s, H1), 5.69 (1H, s, OH), 6.41 – 6.39 (1H, m, H14), 5.16 – 5.14 (1H, m, H15), 4.77 – 4.75 (1H, m, H15), 4.24 (1H, septet, *J* = 6.0 Hz, H19), 3.63 (6H, s, CO_2Me), 3.35 (2H, s, H3), 2.94 – 2.92 (1H, m, H13), 2.90 – 2.88 (1H, m, H10), 2.72 – 2.70 (2H, m, H7), 2.52 – 2.50 (1H, m, H10), 2.35 – 2.33 (1H, m, H11), 2.24 – 2.22 (1H, m, H5), 2.18 – 2.16 (1H, m, H5), 1.91 – 1.89 (1H, m, H11), 1.83 – 1.81 (2H, m, H6), 1.33 – 1.31 (6H, m, H20), 0.98 – 0.81 (10H, m, H21, H22), 0.58 (3H, d, *J* = 6.7 Hz, H16); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 171.6 (C=O), 153.6 (C17), 141.0 (C2), 140.4 (C14), 139.5 (C8), 136.5 (C1), 134.0 (C9), 126.5 (C18), 114.3 (C15), 87.3 (C12), 66.8 (C19), 55.7 (C4), 52.4 (OMe), 46.7 (C13), 39.0 (C3), 36.5 (C5), 32.8 (C11), 29.6 (C7), 29.6 (C10), 25.6 (C20), 22.9 (C6), 13.8 (C16), 7.9 (C21), 7.3 (C22).

5.5. Experimental – Chapter 4

(*S*,*E*)-Pent-3-en-2-ol (*S*)-357:



(*S*)-357

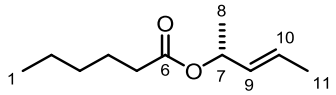
To a solution of crotonaldehyde (20 mL, 0.24 mmol, 1 equiv.) in THF (100 mL) at −78 °C under argon was added MeMgBr (3 M in Et_2O, 97 mL, 0.30 mmol, 1.2 equiv.). The reaction mixture was stirred at −78 °C for 2 h, and gradually warmed up to 0 °C. After completion of the reaction as monitored by TLC, the reaction was quenched by addition of NH_4Cl. The THF was removed *in vacuo*, and the residue was dissolved in DCM and washed with H_2O. The combined organic layers were then dried ($MgSO_4$). Purification by flash chromatography (2:1 Pet. Ether 30 – 40 °C/Ether) afforded the desired alcohol as a colourless oil (14.0 g, 0.16 mmol, 67%).

Kinetic Resolution 1:[140, 141] To a mixture of pent-3-en-2-ol (±)-**357** (5 g, 58 mmol, 1 equiv.), were added trifluoroethyl butyrate (20 mL, 132.4 mmol, 2.3 mmol) and porcine pancreatic lipase (10 g) and the mixture was stirred in Et_2O (100 mL) for 3 weeks. The PPL was filtered off and washed with Et_2O. Evaporation of the solvent gave a yellow oil which was purified by flash chromatography (1:1 Pet. Ether 30 – 40 °C/Et_2O) and the solvent was fractionally distilled to yield (*S*)-**357** as a yellow oil (1.3 g, 14 mmol, 24%). **95% *ee*** (CHIRALPAK IA, 1.3 mL/min, 0.5% IPA/hexanes, R_t (*S*) – 6.32 min, R_t (*R*) – 7.22 min).

Kinetic Resolution 2:[142] To a mixture of pent-3-en-2-ol (±)-**357** (10 mL, 97 mmol, 1 equiv.) and vinyl acetate (45 mL, 486 mmol, 5 equiv.) in pentane (50 mL) was added activated 4 Å molecular sieves (crushed, 4.2 g, 50 wt%) and Novozyme 435 (837 mg, 10 wt%). The reaction mixture was stirred at room temperature for 2 h. After filtration

through Celite, the solution was concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired alcohol (1:1 Pet. Ether 30 – 40 °C/Ether) and the solvent was fractionally distilled to yield (*S*)-**357** as a yellow oil (3.3 g, 38 mmol, 39%); $\mathbf{[a]_D^{25}}$ −14.4° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.39 (2:1 Pet. Ether/Et_2O); **96% *ee*** (CHIRALPAK IA, 1.3 mL/min, 0.5% IPA/hexanes, R_t (*S*) – 6.32 min, R_t (*R*) – 7.22 min); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 5.74 – 5.43 (2H, m), 4.24 (1H, t, *J* = 6.6 Hz), 1.68 (3H, d, *J* = 5.8 Hz), 1.24 (3H, d, *J* = 6.4 Hz); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 135.5, 125.5, 68.7, 23.3, 17.5. Data in accordance with literature.[142]

(±)-(*E*)-Pent-3-en-2-yl hexanoate (±)-**355a:**

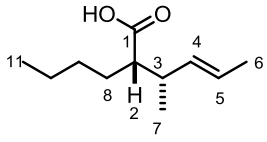


(±)-355a

To a solution of alcohol (±)-**357** (510 mg, 5.92 mmol, 1 equiv.) in THF (50 mL) were added hexanoic acid (1.5 mL, 11.8 mmol, 2 equiv.), DCC (2.4 g, 11.8 mmol, 2 equiv.) and DMAP (72 mg, 0.59 mmol, 0.1 equiv.). The reaction mixture was stirred 2 h at room temperature. After completion of the reaction as monitored by TLC, the reaction was quenched by addition of Na_2CO_3 and extracted with Et_2O. The organic fractions were combined, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (10:1 Pet. Ether/Ether) to afford the desired compound as a colourless oil (1.0 g, 5.75 mmol, 99%); $\mathbf{R_f}$ 0.45 (10:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2931, 2856, 2120, 1734, 1450, 1174, 1041, 964, 891; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 5.71 – 5.69 (1H, m, H9), 5.47 (1H, dd, *J* = 15.3, 6.8 Hz, H10), 5.31 (1H, q, *J* = 6.9 Hz, H7), 2.26 (2H, t, *J* = 7.2 Hz, H5), 1.93 – 1.91 (2H, m, H4), 1.73 – 1.71 (2H, m, H3), 1.62 – 1.60 (2H, m, H2), 1.68 (3H, d, *J* = 6.9 Hz, H8), 1.28 (3H, d, *J* = 6.8 Hz, H11), 0.88 (3H, t, *J* = 7.2 Hz, H1); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 173.1 (C=O), 130.9 (C9), 127.9 (C10),

70.8 (C7), 34.9 (C5), 31.3 (C4), 24.7 (C3), 22.3 (C2), 20.3 (C8), 17.6 (C11), 13.9 (C1); **HRMS** (FI^+) calcd for $C_{11}H_{20}O_2$ 183.9814, found 184.1463.

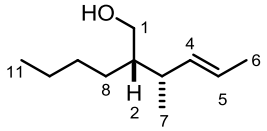
(±)-(2*S*,3*S*,*E*)-2-Butyl-3-methylhex-4-enoic acid (±)-**356a**:



(±)-356a

To a cooled solution of ester (±)-**355a** (500 mg, 2.72 mmol, 1 equiv.) in THF at −78 °C were added NEt_3 (1.9 mL, 13.6 mmol, 5 equiv.) and TMSCl (1.7 mL, 13.6 mmol, 5 equiv.). The mixture was stirred for 10 min at −78 °C, and LDA (1 M in THF, 4.6 mL, 4.62 mmol, 1.7 equiv.) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and slowly allowed to warm up to room temperature and further stirred at this temperature for 2 h. After completion of the reaction as monitored by TLC, the reaction was quenched with addition of 1 M HCl, and stirred for 30 min. The reaction mixture was extracted with EtOAc. The organic fractions were combined, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (5:1 Pet. Ether/EtOAc) to afford the desired acid (±)-**356a** as a colourless oil (276 mg, 1.49 mmol, 55%); $\mathbf{R_f}$ 0.25 (5:1 Pet. Ether/EtOAc); **IR** (thin film) ν_{max} = 2960, 1705, 1452, 1239, 966; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 5.47 – 5.45 (1H, m, H5), 5.24 – 5.22 (1H, m, H4), 2.35 – 2.33 (1H, m, H3), 2.15 – 2.13 (1H, m, H2), 1.67 (3H, dd, *J* = 6.4, 1.4 Hz, H6), 1.52 – 1.50 (2H, m, H8), 1.31 – 1.29 (4H, m, H9, H10), 1.02 (3H, d, *J* = 6.7 Hz, H7), 0.88 (3H, t, *J* = 7.0 Hz, H11); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 181.6 (C=O), 134.0 (C4), 125.7 (C5), 51.6 (C2), 39.7 (C3), 30.0 (C8), 29.8 (C9), 22.6 (C10), 19.1 (C7), 17.9 (C6), 13.9 (C11); **HRMS** (ES^+) calcd for $C_{11}H_{20}NaO_2$ $[M+Na]^+$ 207.1350, found 207.1356; **EA** calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94, found: C, 71.82; H, 10.83.

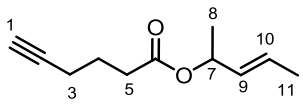
(±)-(2*S*,3*S*,*E*)-2-Butyl-3-methylhex-4-en-1-ol (±)-**356b**:



(±)-356b

To a solution of LAH (21 mg, 0.54 mmol, 2 equiv.) in Et_2O (5 mL) was added a solution of acid (±)-**356a** (50 mg, 0.27 mmol, 1 equiv.) in Et_2O (1 mL) at 0 °C under argon. After completion of the reaction after 2 h of stirring, the reaction was quenched at 0 °C by slow addtition of H_2O (21 µL), NaOH (15%, 21 µL) and H_2O (63 µL). After formation of a white precipitate, the mixture was dried ($MgSO_4$), and after filtration, the solvent was removed *in vacuo* to yield the crude alcohol (±)-**356b** as a colourless oil (35 mg, 20 mmol, 75%); $\mathbf{R_f}$ 0.38 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3330, 2959, 2929, 2872, 1453, 1377, 1037, 969; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.47 – 5.33 (2H, m, H4, H5), 3.55 (2H, d, *J* = 5.6 Hz, H1), 2.33 – 2.31 (1H, m, H3), 1.64 (3H, d, *J* = 5.5 Hz, H6), 1.43-1.17 (7H, m, H2, H8, H9, H10), 0.96 (3H, d, *J* = 7.0 Hz, H7), 0.87 (3H, t, *J* = 7.0 Hz, H11); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 135.4 (C5), 124.4 (C4), 64.1 (C1), 45.9 (C2), 37.4 (C3), 30.1 (C8), 27.2 (C9), 23.0 (C10), 18.0 (C6), 17.3 (C7), 14.0 (C11); **HRMS** (ES^+) calcd for $C_{11}H_{22}NaO$ $[M+Na]^+$ 193.1568, found 193.1570.

(*R*,*E*)-Pent-3-en-2-yl hex-5-ynoate (±)-354:

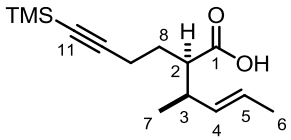


354

To a solution of alcohol (±)-**357** (1.0 g, 11.6 mmol, 1 equiv.) in THF (70 mL) were added 5-hexynoic acid (1.7 mL, 15.1 mmol, 1.3 equiv.), DCC (3.1 g, 15.1 mmol, 1.3 equiv.) and DMAP (141 mg, 1.2 mmol, 0.1 equiv.). The reaction mixture was stirred for 12 h at room temperature. After completion of the reaction as monitored by TLC, the reaction was

quenched by addition of Na_2CO_3 and extracted with Et_2O. The organic fractions were combined, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (20:1 Pet. Ether/Ether) to afford the desired ester (±)-**354** as a colourless oil (1.6 g, 8.90 mmol, 77%); $\mathbf{R_f}$ 0.37 (10:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3300, 2933, 2119, 1731, 1450, 1163, 1038, 965; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.73 – 5.71 (1H, m, H10), 5.47 (1H, dq, *J* = 14.9, 1.7 Hz, H9), 5.32 (1H, q, *J* = 7.0 Hz, H7), 2.42 (2H, t, *J* = 7.6 Hz, H4), 2.26 (2H, td, *J* = 6.9, 2.8 Hz, H3), 1.96 (1H, t, *J* = 2.8 Hz, H1), 1.84 (2H, q, *J* = 7.1 Hz, H5), 1.69 (3H, dd, *J* = 6.6, 1.7 Hz, H11), 1.28 (3H, d, *J* = 6.5 Hz, H8); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.3 (C=O), 130.7 (C9), 128.1 (C10), 83.3 (C2), 71.1 (C1), 68.9 (C7), 34.9 (C5), 33.3 (C4), 23.6 (C3), 20.3 (C11), 17.8 (C8); **HRMS** (EI/FI) calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1148.

(*2R,3R,E*)-3-Methyl-2-(4-(trimethylsilyl)but-3-ynyl)hex-4-enoic acid (±)-353:

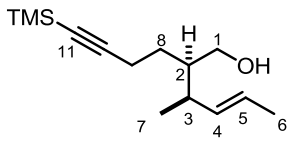


(±)-353

To a cooled solution of ester (±)-**354** (250 mg, 1.34 mmol, 1 equiv.) in THF at −78 °C were added NEt_3 (1.1 mL, 6.94 mmol, 5 equiv.) and TMSCl (900 µL, 6.94 mmol, 5 equiv.). The mixture was stirred for 10 min at −78 °C, and LDA (1 M in THF, 4.2 mL, 4.2 mmol, 3 equiv.) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h, and slowly allowed to warm up to room temperature and stirred at this temperature for 2 h. After completion of the reaction as monitored by TLC, the reaction was quenched with addition of 1N HCl, and stirred for 30 min. The reaction mixture was extracted with EtOAc. The organic fractions were combined, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (10:1 Pet. Ether/ Et_2OAc

then flushed with EtOAc) to afford the desired acid (±)-**353** as a colourless oil (139 mg, 0.55 mmol, 40%); **R_f** 0.07 (10:1 Pet. Ether/EtOAc); **IR** (thin film) ν_{max} = 2961, 2176, 1705, 1249, 1037, 842, 760; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.92 (1H, br s, OH), 5.48 (1H, dq, *J* = 15.2, 6.5 Hz, H5), 5.26 (1H, ddd, *J* = 15.2, 8.2, 1.5 Hz, H4), 2.43 – 2.41 (1H, m, H3), 2.35 – 2.33 (1H, m, H2), 2.31 – 2.29 (1H, m, H8), 2.20 – 2.18 (1H, m, H8), 1.79 – 1.77 (2H, m, H9), 1.67 (3H, dd, *J* = 6.5, 1.5 Hz, H6), 1.05 (3H, d, *J* = 6.7 Hz, H7), 0.15 (9H, s, Si<u>Me</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 180.3 (C=O), 133.4 (C4), 126.1 (C5), 106.2 (C11), 85.2 (C10), 50.3 (C2), 39.3 (C3), 28.6 (C8), 19.0 (C9), 18.3 (C6), 17.9 (C7), 0.1 (Si<u>Me</u>$_3$); **HRMS** (ES^+) calcd for $C_{14}H_{24}NaO_2Si$ $[M+Na]^+$ 275.1439, found 275.1438; **EA** calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58, found: C, 66.76; H, 9.50.

(*2R,3R,E*)-3-Methyl-2-(4-(trimethylsilyl)but-3-ynyl)hex-4-en-1-ol (±)-352:

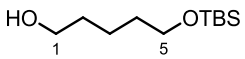


(±)-352

To a solution of LAH (21 mg, 0.55 mmol, 2 equiv.) in Et_2O (2 mL) was added a solution of acid (±)-**353** (60 mg, 0.24 mmol, 1 equiv.) in Et_2O (3 mL) at 0 °C under Ar. After completion of the reaction after 2 h of stirring, the reaction was quenched at 0 °C by slow addtition of H_2O (21 µL), NaOH (15%, 21 µL) and H_2O (63 µL). After formation of a colourless precipitate, the mixture was dried by adding $MgSO_4$, and after filtration, the solvent was removed *in vacuo* to yield the crude alcohol (±)-**352** as a colourless oil (47 mg, 0.20 mmol, 83%); **R_f** 0.63 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3344, 2959, 2174, 1249, 1034, 971, 841, 759; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.48 (1H, dq, *J* = 15.3, 6.1 Hz, H5), 5.36 (1H, ddd, *J* = 15.3, 7.8, 1.2 Hz, H4), 3.60 (2H, t, *J* = 5.6 Hz, H1), 2.33 – 2.31 (1H, m, H3), 2.26 (2H, q, *J* = 6.3 Hz, H9), 1.67 (3H, d, *J* = 6.1 Hz, H6), 1.62 – 1.60 (1H,

m, H2), 1.54 – 1.52 (1H, m, OH), 1.48 – 1.46 (2H, m, H8), 0.99 (3H, d, *J* = 7.0 Hz, H7), 0.14 (9H, s, Si<u>Me</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 135.0 (C5), 124.8 (C4), 107.6 (C11), 84.7 (C10), 63.6 (C1), 45.1 (C2), 37.5 (C3), 26.8 (C8), 18.3 (C9), 18.0 (C6), 17.7 (C7), -0.1 (Si<u>Me</u>$_3$); **HRMS** (ES+) calcd for $C_{14}H_{26}NaOSi$ $[M+Na]^+$ 261.1645, found 261.1645; **EA** calcd for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99, found: C, 70.55; H, 10.87.

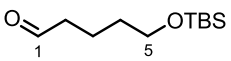
5-(*tert*-Butyldimethylsilyloxy)pentan-1-ol 364a:



364a

To a solution of 1,5-pentanediol (5 mL, 47.7 mmol, 4 equiv.) and imidazole (1.6 g, 23.7 mmol, 2 equiv.) in DMF (5 mL) was added dropwise a solution of TBSCl (1.8 g, 11.9 mmol, 1 equiv.) in DMF (10 mL). The reaction was stirred at room temperature overnight, diluted with water and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was then purified by flash chromatography (2:1 Pet. Ether/Et_2O) to afford the desired alcohol **346a** as a colourless oil (2.80 g, quant.); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.64 (2H, t, *J* = 6.5 Hz, H5), 3.61 (2H, t, *J* = 6.5 Hz, H4), 1.57 – 1.55 (4H, m, H2, H4), 1.42 – 1.40 (2H, m, H3), 0.89 (9H, s, Si*t*-<u>Bu</u>), 0.04 (6H, s, Si<u>Me</u>$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 63.1 (C5), 62.9 (C1), 32.5 (C4), 25.9 (C2), 22.0 (Si(<u>C</u>$(CH_3)_3$), 18.3 (Si(C(<u>C</u>$H_3)_3$), 14.1 (C3), -5.3 (Si<u>Me</u>$_2$). Data in accordance with literature.[161]

5-(*tert*-Butyldimethylsilyloxy)pentanal 364:

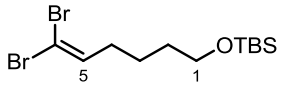


364

Oxalyl chloride (17.5 mL, 206 mmol, 3 equiv.) was dissolved in DCM (500 mL) at –78 °C. DMSO (29.3 mL, 412 mmol, 6 equiv.) was added dropwise at –78 °C and the reaction

mixture was stirred for 15 min. The monoprotected alcohol **364a** (15 g, 68 mmol, 1 equiv.) was added at −78 °C and the reaction was stirred for another 30 min, after which time Et_3N (115.0 mL, 825 mmol, 12 equiv.) was added and the reaction mixture was allowed to warm to 0 °C. After completion of the reaction, the reaction was quenched by addition of H_2O, and the organic fraction was washed with 1 N HCl, $NaHCO_3$ and brine. The organic fractions were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* and the crude product was purified by flash chromatography (2:1 Pet. Ether/ Et_2O) to afford the desired aldehyde **364** as a colourless oil (14.44 g, quant); $\mathbf{R_f}$ 0.71 (2:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 2929, 2858, 1728, 1256, 1102, 836, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.77 (1H, t, *J* = 1.7 Hz, H1), 3.63 (2H, t, *J* = 6.5 Hz, H5), 2.46 (2H, td, *J* = 7.5, 1.7 Hz, H2), 1.72 – 1.70 (2H, m, H3), 1.57 – 1.55 (2H, m, H4), 0.89 (9H, s, Si*t*-Bu), 0.05 (6H, s, $SiMe_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.7 (C=O), 62.6 (C5), 43.6 (C2), 32.1 (C4), 25.9 ($Si(\underline{C}(CH_3)_3)$), 18.6 ($Si(C(\underline{C}H_3)_3)$), 18.2 (C3), -5.4 ($Si\underline{Me}_2$). Data in accordance with literature.[161]

***tert*-Butyl(6,6-dibromohex-5-enyloxy)dimethylsilane 365a**:

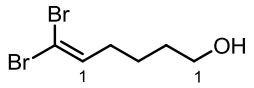


365a

To a solution of CBr_4 (11.0 g, 33.2 mmol, 2 equiv.) in DCM (60 mL) was added PPh_3 (17.4 g, 66.4 mmol, 4 equiv.) in DCM (60 mL) *via* dropping funnel over 15 min at 0 °C under argon, and the mixture was stirred for 10 min. The solution was cooled to –40 °C and NEt_3 (23.1 mL, 166 mmol, 10 equiv.) was added followed by a solution of aldehyde **364** (3.6 g, 16.6 mmol, 1 equiv.) in DCM (38 mL). The reaction mixture was allowed to warm to 0 °C. After completion of the reaction as monitored by TLC, the reaction was quenched with addition of H_2O. The reaction mixture was extracted with DCM. The

organic fractions were combined, dried ($MgSO_4$) and the volume reduced *in vacuo* and a 1:1 mixture of Pet. Ether/Ether was added and the precipitate of triphenylphosphine oxide was filtered off and the solvent was removed *in vacuo*. This operation was repeated until no triphenylphosphine oxide precipitated and the crude mixture was purified by flash chromatography (2:1 Pet. Ether/Ether) to yield the vinyl dibromide **365a** as a colourless oil (5.52 g, 14.8 mmol, 89%); $\mathbf{R_f}$ 0.90 (5:1 Pet. Ether/Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.38 (1H, t, *J* = 6.7 Hz, H5), 3.60 (2H, t, *J* = 6.1 Hz, H1), 2.11 – 2.09 (2H, m, H4), 1.50 – 1.48 (4H, m, H2, H3), 0.88 (9H, s, Si*t*-Bu), 0.03 (6H, s, $SiMe_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 138.7 (C5), 88.7 (C6), 62.7 (C1), 32.7 (C2), 32.1 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 24.2 (C4), 18.3 (C3), -5.3 ($SiMe_2$); **HRMS** (EI/FI) calcd for $C_{12}H_{24}Br_2OSi$ 371.9943, found 371.9940; **EA** calcd for $C_{12}H_{24}Br_2OSi$: C, 38.72; H, 6.50, found: C, 38.69; H, 6.39.

6,6-Dibromohex-5-en-1-ol 365:

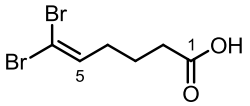


365

Vinyl dibromide **365a** (770 mg, 2.1 mmol, 1 equiv.) was dissolved in MeOH (20 mL) and CSA (cat) was added. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by adding $NaHCO_3$, the solvent removed *in vacuo*, and the reaction was extracted three times with DCM, the organic fractions were combined, dried ($MgSO_4$) and the solvent was removed *in vacuo*, the crude mixture was purified by flash chromatography (2:1 Pet. Ether/Ether) to yield alcohol **365** as a colourless oil (334 mg, 1.30 mmol, 63%); $\mathbf{R_f}$ 0.1 (5:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 3330, 2936, 1065, 780; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.40 (1H, t, *J* = 7.2 Hz, H5), 3.66 (2H, t, *J* = 6.3 Hz, H1), 2.17 (1H, s, OH), 2.14 (2H, q, *J* = 7.2 Hz, H4), 1.65-1.48 (4H, m, H2, H3); **^{13}C NMR**

(100 MHz, $CDCl_3$) δ_C 138.4 (C5), 89.0 (C6), 62.5 (C1), 31.9 (C2), 30.9 (C3), 24.0 (C3); **HRMS** (EI/FI) calcd for $C_6H_{10}Br_2O$ 257.9078, found 257.9065; **EA** calcd for $C_6H_{10}Br_2O$: C, 27.94; H, 3.91, found: C, 28.02; H, 3.88.

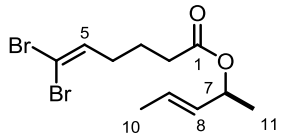
6,6-Dibromohex-5-enoic acid 363:



363

To a solution of alcohol **365** (2.2 g, 8.53 mmol, 1 equiv.) in solution in acetone (100 mL) at 0 °C was added dropwise a solution of Jones reagent (2.5 M, 8.5 mL, 21.32 mmol, 2.1 equiv.). After completion of the reaction as monitored by TLC, isopropanol was added to quench the excess Jones reagent. The mixture was filtered through a pad of Celite and rinsed with EtOAc. The solvent removed *in vacuo*, the crude mixture was purified by flash chromatography (5:1 Pet. Ether/EtOAc, 1% AcOH) to yield the desired acid **363** as a colourless oil (1.8 g, 6.65 mmol, 78%); $\mathbf{R_f}$ 0.12 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3325, 2940, 1720, 1310, 1065, 784; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.41 (1H, t, *J* = 7.3 Hz, H5), 2.43 (2H, t, *J* = 7.3 Hz, H2), 2.21 (2H, q, *J* = 7.3 Hz, H4), 1.81 (2H, q, *J* = 7.3 Hz, H3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 179.0 (C=O), 137.3 (C5), 90.0 (C6), 33.0 (C2), 32.2 (C4), 22.7 (C3); **HRMS** (EI/FI) calcd for $C_6H_7Br_2O_2$ 270.8798, found 270.8799; **EA** calcd for $C_6H_8Br_2O_2$: C, 26.50; H, 2.97, found: C, 26.57; H, 3.03.

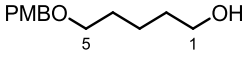
(*E*)-Pent-3-en-2-yl 6,6-dibromohex-5-enoate 362:



362

To a solution of alcohol (*S*)-**357** (317.0 mg, 3.6 mmol, 1 equiv.) and acid **363** (1.0 g, 3.6 mmol, 1 equiv.) were added EDC•HCl (1.1 g, 5.5 mmol, 1.5 equiv.), NEt_3 (1 mL, 7.3 mmol, 2 equiv.) and DMAP (45 mg, 0.36 mmol, 0.1 equiv.) in THF (2 mL). The reaction mixture was stirred for 12 h at room temperature and quenched with H_2O, extracted with EtOAc and washed with HCl. The solvent removed *in vacuo*, the crude mixture was purified by flash chromatography (5:1 Pet. Ether/Ether) to yield the desired ester **362** as a colourless oil (770 mg, 2.2 mmol, 62%); $\mathbf{R_f}$ 0.22 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3300, 2933, 2119, 1731, 1450, 1163, 1038, 965; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.38 (1H, t, *J* = 7.3 Hz, H5), 5.73 – 5.71 (1H, m, H9), 5.48 (1H, ddd, *J* = 15.5, 7.0, 1.7 Hz, H8), 5.32 (1H, q, *J* = 6.4 Hz, H7), 2.31 (2H, t, *J* = 7.5 Hz, H2), 2.15 (2H, q, *J* = 7.5 Hz, H4), 1.76 (2H, q, *J* = 7.5 Hz, H3), 1.69 (3H, dd, *J* = 6.5, 1.0 Hz, H10), 1.29 (3H, t, *J* = 6.4 Hz, H11); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.3 (C=O), 137.6 (C5), 130.7 (C8), 128.3 (C9), 89.6 (C6), 71.5 (C7), 33.7 (C2), 32.4 (C4), 23.2 (C3), 20.5 (C11), 17.8 (C10); **HRMS** (EI/FI) calcd for $C_{11}H_{16}Br_2O_2$ 339.9497, found 339.9472; **EA** calcd for $C_{11}H_{16}Br_2O_2$: C, 38.85; H, 4.74, found: C, 38.74; H, 4.59.

5-(4-Methoxybenzyloxy)pentan-1-ol 373a:

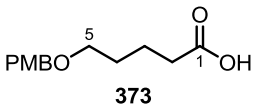


373a

A suspension of NaH (60% dispersion in mineral oil, 5.2 g, 130 mmol, 2.2 equiv.) in THF (150 mL) at 0 °C was charged with a solution of 1,5-pentanediol (43.6 mL, 395 mmol, 6.7 equiv.) in THF (60 mL) over 15 min. The suspension was stirred, heated to reflux and after

3 h was charged with TBAI (1.1 g, 2.9 mmol, 0.05 equiv.) and PMBCl (8 mL, 59.0 mmol, 1.0 equiv.). After 15 h, the reaction was quenched with H_2O, and concentrated *in vacuo*. The residue was diluted in DCM and water. The aqueous phase was extracted with DCM, and the combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (2:1 Pet. Ether/EtOAc) afforded the desired alcohol **373a** as a colourless oil (13.2 g, 59 mmol, quant.); $\mathbf{R_f}$ 0.17 (2:1 Pet. Ether/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.6 Hz, HAr), 6.87 (2H, d, *J* = 8.6 Hz, HAr), 4.43 (2H, s, –C<u>H</u>$_2$–Ar), 3.80 (3H, s, O<u>Me</u>), 3.62 (2H, t, *J* = 6.3 Hz, H1), 3.45 (2H, t, *J* = 6.6 Hz, H5), 1.61 – 1.59 (4H, m, H2, H4), 1.46 – 1.44 (2H, m, H3) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.9 (CAr), 130.4 (CAr), 129.0 (CAr), 113.6 (CAr), 72.3 (–<u>C</u>H$_2$–Ar), 69.8 (C5), 62.3 (C1), 55.0 (O<u>Me</u>), 32.2 (C2), 29.2 (C4), 22.2 (C3). Data in accordance with literature.[162]

5-(4-Methoxybenzyloxy)pentanoic acid 373:

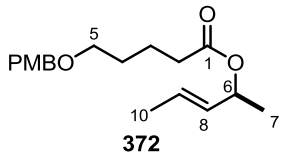


373

To a cooled solution of alcohol **373a** (14 g, 62.1 mmol, 1 equiv.) in acetone (120 mL) was added Jones reagent (2.5 M, 37.4 mL, 93.6 mmol, 1.5 equiv.). The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with isopropanol, and neutralised with $NaHCO_3$, diluted with EtOAc and washed with 3 N NaOH, the aqueous layer was neutralised with HCl, and extracted back with EtOAc and the combined organic extracts were dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the desired acid **373** as a white solid which was used without further purification (14 g, 56.8 mmol, 91%); $\mathbf{R_f}$ 0.15 (2:1 Pet. Ether/Ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.8 Hz, HAr), 6.89 (2H, d, *J* = 8.8 Hz, HAr), 4,44 (2H, s, –C<u>H</u>$_2$–Ar), 3.81 (3H, s, O<u>Me</u>), 3.47 (2H, t, *J* = 6.0

Hz, H2), 2.38 (2H, t, *J* = 7.1 Hz, H5), 1.70 – 1.68 (4H, m, H3, H4); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.8 (C=O), 159.1 (CAr), 130.4 (CAr), 129.2 (CAr), 113.8 (CAr), 72.6 (–$\underline{C}H_2$–Ar), 69.4 (C5), 55.3 (O$\underline{Me}$), 33.6 (C2), 29.0 (C4), 21.5 (C3). Data in accordance with literature.[139]

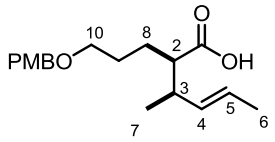
(*S*,*E*)-Pent-3-en-2-yl 5-(4-methoxybenzyloxy)pentanoate 372:



372

To a solution of alcohol (*S*)-**357** (440 µL, 5.9 mmol, 1 equiv.) and acid **373** (2.0 g, 6.5 mmol, 1.1 equiv.) were added EDC•HCl (1.7 g, 8.9 mmol, 1.5 equiv.), NEt_3 (1.7 mL, 11.9 mmol, 2 equiv.) and DMAP (362 mg, 2.9 mmol, 0.1 equiv.) in THF (5 mL). The reaction mixture was stirred for 12 h at room temperature and quenched with H_2O, extracted with EtOAc and washed with HCl. The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*, the crude mixture was purified by flash chromatography (5:1 Pet. Ether/Ether) to yield the desired ester **372** as a colourless oil (1.2 g, 5.3 mmol, 89%); **$[a]_D^{25}$** +26.8° (*c* = 1, $CHCl_3$); **R_f** 0.27 (2:1 Pet. Ether/Et_2O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.7 Hz, HAr), 6.87 (2H, d, *J* = 8.7 Hz, HAr), 5.72 – 5.70 (1H, m, H9), 5.47 – 5.45 (1H, m, H8), 5.30 (1H, q, *J* = 6.4 Hz, H6), 4.42 (2H, s, –C$\underline{H_2}$–Ar), 3.80 (3H, s, O$\underline{Me}$), 3.44 (2H, t, *J* = 6.0 Hz, H5), 2.30 (2H, t, *J* = 7.2 Hz, H2), 1.70 – 1.65 (7H, m, H3, H4, H10), 1.30 (3H, d, *J* = 6.4 Hz, H7); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 172.7 (C=O), 159.0 (CAr), 130.8 (C8), 130.5 (CAr), 129.1 (C9), 113.6 (CAr), 72.4 (–$\underline{C}H_2$–Ar), 70.8 (C6), 69.4 (C5), 55.1 (O$\underline{Me}$), 34.2 (C2), 29.0 (C4), 21.7 (C3), 20.2 (C7), 17.5 (C10). Data in accordance to literature values.[139]

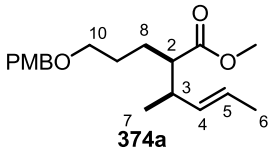
(*2S,3S,E*)-2-(3-(4-Methoxybenzyloxy)propyl)-3-methylhex-4-enoic acid 371:



371

To a solution of ester **372** (722 mg, 2.4 mmol, 1 equiv.) in THF (40 mL) at −78 °C was added a premixed solution of 1:1 NEt_3/TMSCl (3.2 mL, 24 mmol, 10 equiv.). A freshly prepared solution of LDA (1 M in THF, 7.5 mL, 7.5 mmol, 3 equiv.) was added dropwise and the resulting solution was stirred for 3 h at −78 °C and warmed up to 0 °C. After completion of the reaction as monitored by TLC, the reaction was quenched with 1 N HCl, and the solvent was removed *in vacuo*. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (2:1 Pet Ether/ Ether and 1% AcOH) to yield the desired acid **371** as a colourless oil (665 mg, 2.2 mmol, 92%); $\mathbf{[a]_D^{25}}$ −29.2° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.63 (1:1 Pet. Ether/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.4 Hz, HAr), 6.87 (2H, d, *J* = 8.4 Hz, HAr), 5.47 – 5.45 (1H, m, H5), 5.22 (1H, ddd, *J* = 15.0, 8.4, 1.4 Hz, H4), 4.42 (2H, s, –C$\underline{H_2}$–Ar), 3.81 (3H, s, O$\underline{Me}$), 3.48 – 3.46 (2H, m, H10), 2.36 – 2.34 (1H, m, H3), 2.20 – 2.18 (1H, m, H2), 1.66 (3H, dd, *J* = 6.4, 1.2 Hz, H7), 1.65-1.50 (4H, m, H8, H9), 1.02 (3H, d, *J* = 6.8 Hz, H6); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 181.5 (C=O), 159.1 (CAr), 133.8 (C4), 130.5 (CAr), 129.2 (CAr), 125.8 (C5), 113.7 (CAr), 72.4 (–$\underline{C}H_2$–Ar), 69.6 (C10), 55.3 (O$\underline{Me}$), 51.3 (C2), 39.7 (C3), 27.6 (C9), 27.0 (C8), 19.1 (C7), 17.9 (C6). Data in accordance with literature.[139]

(*2S*,*3S*,*E*)-Methyl 2-(3-(4-methoxybenzyloxy)propyl)-3-methylhex-4-enoate 374a:



374a

To a solution of acid **372** (500 mg, 1.63 mmol, 1 equiv.) in toluene and MeOH (5:1, 48 mL) at 0 °C under Ar was slowly added $TMSCHN_2$ (900 µL, 1.80 mmol, 1.1 equiv.). The reaction mixture was stirred for 30 min at room temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with AcOH, washed with Na_2CO_3 and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (2:1 Pet Ether/Ether) to yield the desired methyl ester **374a** as a colourless oil (470 mg, 1.47 mmol, 90%); $\mathbf{R_f}$ 0.5 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2951, 1733, 1513, 1248, 1036, 821; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.3 Hz, HAr), 6.87 (2H, d, *J* = 8.3 Hz, HAr), 5.46 – 5.44 (1H, m, H5), 5.21 – 5.19 (1H, m, H4), 4.41 (2H, s, –C$\underline{H_2}$–Ar), 3.81 (3H, s, $CO_2\underline{Me}$), 3.67 (3H, s, O$\underline{Me}$), 3.42 – 3.40 (2H, m, H10), 2.30 (1H, q, *J* = 7.0 Hz, H3), 2.16 (1H, td, *J* = 10.0, 3.5 Hz, H2), 1.66 (3H, dd, *J* = 6.2, 1.4 Hz, H7), 1.54 – 1.52 (4H, m, H8, H9) 0.96 (3H, d, *J* = 6.8 Hz, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 176.1 (C=O), 159.1 (CAr), 134.2 (C4), 130.6 (CAr), 129.2 (C5), 125.5 (CAr), 113.7 (CAr), 72.4 (–$\underline{C}H_2$–Ar), 69.7 (C10), 55.3 (O$\underline{Me}$), 51.5 ($CO_2\underline{Me}$), 51.2 (C2), 39.9 (C3), 27.8 (C9), 27.2 (C8), 19.2 (C7), 17.9 (C6); **HRMS** (ES^+) calcd for $C_{19}H_{28}NaO_4$ $[M+Na]^+$ 343.1880, found 343.1873.

(*2S,3S,E*)-2-(3-(4-Methoxybenzyloxy)propyl)-3-methylhex-4-en-1-ol 374:



374

To a solution of methyl ester **374a** (268 mg, 0.84 mmol, 1 equiv.) in DCM (2 mL) at −78 °C under argon was added a solution of DIBALH (2.1 mL, 2.09 mmol, 2.5 equiv.) and the solution wass warmed up to 0 °C. After completion of the reaction as monitored by TLC, the reaction wass quenched by addition of sodium potassium tartrate, stirred for 1h, and extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (2:1 Pet Ether/Ether) to yield the desired alcohol **374** as a colourless oil (178 mg, 0.61 mmol, 73%) and its diastereomer (20 mg, 0.07 mmol, 8%); $\mathbf{[a]_D^{25}}$ +17.4° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.1 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3647, 3385, 2933, 2359, 1513, 1248;

Major diastereomer:

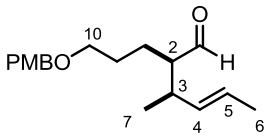
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.9 Hz, HAr), 6.89 (2H, d, *J* = 8.9 Hz, HAr), 5.42 – 5.40 (2H, m, H4, H5), 4.43 (2H, s, –C<u>H</u>$_2$–Ar), 3.81 (3H, s, O<u>Me</u>), 3.58 (2H, t, *J* = 5.5 Hz, H1), 3.44 (2H, t, *J* = 6.7 Hz, H10), 2.32 – 2.30 (1H, m, H3), 1.66 (3H, d, *J* = 5.5 Hz, H7), 1.56 – 1.54 (2H, m, H8), 1.44 – 1.42 (2H, m, H9), 1.28 – 1.26 (2H, m, H2), 0.97 (3H, d, *J* = 7.2 Hz, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.1 (CAr), 135.3 (C4), 130.6 (CAr), 129.3 (CAr), 124.5 (C5), 113.7 (CAr), 72.6 (–<u>C</u>H$_2$–Ar), 70.3 (C10), 63.9 (C1), 55.3 (O<u>Me</u>), 45.6 (C2), 37.6 (C3), 27.8 (C9), 24.2 (C8), 18.0 (C7), 17.5 (C6); **HRMS** (ES^+) calcd for $C_{18}H_{28}NaO_3$ $[M+Na]^+$ 315.1931, found 315.1925.

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.5 Hz, HAr), 6.89 (2H, d, *J* = 8.5 Hz, HAr), 5.51 – 5.49 (2H, m, H4, H5), 4.44 (2H, s, –C<u>H</u>$_2$–Ar), 3.81 (3H, s, O<u>Me</u>), 3.68 – 3.66 (2H, m, H1), 3.41 – 3.39 (2H, m, H10), 2.43 – 2.41 (1H, m, H3), 1.67 – 1.65 (3H, m, H7),

1.55-1.50 (5H, m, H2, H8, H9), 1.04 – 1.02 (3H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.1 (CAr), 135.4 (C4), 130.6 (CAr), 129.1 (CAr), 124.7 (C5), 113.7 (CAr), 72.5 (–<u>C</u>H_2–Ar), 71.0 (C10), 67.3 (C1), 55.2 (O<u>Me</u>), 39.9 (C2), 34.4 (C3), 28.3 (C9), 24.5 (C8), 18.0 (C7), 17.1 (C6).

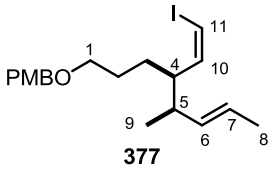
(*2S,3S,E*)-2-(3-(4-Methoxybenzyloxy)propyl)-3-methylhex-4-enal 375:



375

To a solution of alcohol **374** (120 mg, 0.41 mmol, 1 equiv.) in DCM at 0 °C under argon were added DMP (226 mg, 0.53 mmol, 1.3 equiv.) and $NaHCO_3$ (35 mg, 0.41 mmol, 1 equiv.) and the solution was stirred at room temperature until completion of the reaction as monitored by TLC, the reaction was quenched by addition of $NaHCO_3$/$Na_2S_2O_3$ (1:1), stirred for 30 min, and extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (2:1 Pet Ether/Ether) to yield the desired aldehyde **375** as a colourless oil (114 mg, 0.39 mmol, 95%); **$[a]_D^{25}$** +8.3° (*c* = 1, $CHCl_3$); **R_f** 0.45 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2933, 1722, 1513, 1247, 1098, 411; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.56 (1H, d, *J* = 3.5 Hz, H1), 7.25 (2H, d, *J* = 8.7 Hz, HAr), 6.88 (2H, d, *J* = 8.7 Hz, HAr), 5.48 – 5.46 (1H, m, H4), 5.30 – 5.28 (1H, m, H5), 4.44 (2H, s, –C<u>H</u>$_2$–Ar), 3.81 (3H, s, O<u>Me</u>), 3.42 (2H, t, *J* = 6.0 Hz, H10), 2.47 – 2.45 (1H, m, H2), 2.13 – 2.11 (1H, m, H3), 1.67 (3H, dd, *J* = 6.4, 1.1 Hz, H7), 1.61 – 1.58 (4H, m, H8, H9), 1.01 (3H, d, *J* = 6.9 Hz, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 205.6 (C=O), 159.1 (CAr), 133.3 (C4), 130.7 (CAr), 129.2 (CAr), 125.8 (C5), 113.7 (CAr), 72.5 (–<u>C</u>H_2–Ar), 69.6 (C10), 57.1 (C2), 55.3 (O<u>Me</u>), 37.2 (C3), 27.6 (C9), 23.3 (C8), 18.4 (C7), 17.9 (C6); **HRMS** (ES^+) calcd for $C_{18}H_{26}NaO_3$ $[M+Na]^+$ 313.1774, found 313.1774.

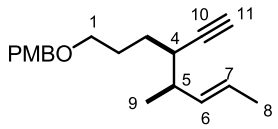
1-(((*4S,5S,E*)-4-((*Z*)-2-Iodovinyl)-5-methyloct-6-enyloxy)methyl)-4-methoxy benzene 377:



377

To a stirred suspension of (iodomethyl)triphenylphosphonium iodide (2.7 g, 5.16 mmol, 2 equiv.) in THF (22.5 mL) at room temperature under Ar was added NaHMDS (2 M in hexanes, 2.6 mL, 5.16 mmol, 2 equiv.). After 20 min, the solution was cooled to −78 °C and a solution of aldehyde **375** (750 mg, 2.58 mmol, 1 equiv.) in THF (4.5 mL) was added. After 15 min, the reaction was allowed to warm up to room temperature and was quenched after a further 30 min with aq. NH_4Cl. The reaction mixture was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (5:1 Pet Ether/Ether) to yield the desired vinyl iodide **377** as a colourless oil (775 mg, 1.86 mmol, 72%); $\mathbf{[a]_D^{25}}$ −15.4° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.51 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3011, 2980, 1705, 1512, 1360, 1172, 844; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.5 Hz, HAr), 6.88 (2H, d, *J* = 8.5 Hz, HAr), 6.28 (1H, d, *J* = 7.5 Hz, H11), 5.88 (1H, dd, *J* = 9.6, 7.5 Hz, H10), 5.32 – 5.30 (1H, m, H6), 5.30 – 5.28 (1H, m, H7), 4.43 (2H, s, –C$\underline{H_2}$–Ar), 3.81 (3H, s, O$\underline{Me}$), 3.43 – 3.41 (2H, m, H1), 2.30 – 2.28 (1H, m, H4), 2.11 (1H, sextet, *J* = 7.4 Hz, H5), 1.66 (3H, dd, *J* = 6.2, 1.4 Hz, H9), 1.61 – 1.58 (4H, m, H2, H3), 0.96 (3H, d, *J* = 6.8 Hz, H8); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.1 (CAr), 144.2 (C10), 135.0 (CAr), 130.8 (C6), 129.2 (CAr), 124.6 (C7), 113.7 (CAr), 83.0 (C11), 72.4 (–$\underline{C}H_2$–Ar), 70.1 (C1), 55.3 (O$\underline{Me}$), 49.5 (C4), 40.9 (C5), 28.1 (C2), 27.3 (C3), 18.3 (C9), 17.9 (C8); **HRMS** (ES^+) calcd for $C_{19}H_{27}INaO_2$ $[M+Na]^+$ 437.0948, found 437.0951.

1-(((*4S,5S,E*)-4-Ethynyl-5-methyloct-6-enyloxy)methyl)-4-methoxybenzene 376:



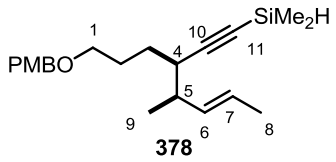
376

Method A: To a solution $TMSCHN_2$ (155 µL, 0.31 mmol, 1.3 equiv.) in THF (200 µL) at −78 °C under Ar was added *n*-BuLi (2.5 M in hexanes, 334 µL, 0.84 mmol, 3.5 equiv.). The reaction was stirred for 30 min at −78 °C, followed by addition of aldehyde **375** (134 mg, 0.47 mmol, 1 equiv.) in solution in THF (200 µL). After completion of the reaction, the reaction was quenched with MeOH, extracted with Et_2O, and washed with aq. NH_4Cl, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (2:1 Pet Ether/Ether) to yield the desired alkyne **376** as a colourless oil (79 mg, 0.27 mmol, 58%).

Method B: To a solution of iodo derivative **377** (775.0 mg, 1.87 mmol, 1 equiv.) in THF at −78 °C was added NaHMDS (2 M in hexanes, 3.7 mL, 7.48 mmol, 4 equiv.). The mixture was allowed to warm to room temperature over a 30 min period and stirred for a further 10 min. After completion of the reaction, the reaction was quenched with aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (5:1 Pet Ether/Ether) to yield the desired alkyne **376** as a colourless oil (476 mg, 1.66 mmol, 89%); $\mathbf{[a]_D^{25}}$ −22.8° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.5 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3260, 2987, 2876, 1613, 1580, 1215, 1090, 694; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.5 Hz, HAr), 6.88 (2H, d, *J* = 8.5 Hz, HAr), 5.45 – 5.43 (1H, m, H6), 5.36 – 5.34 (1H, m, H7), 4.43 (2H, d, *J* = 1.9 Hz, –C<u>H</u>$_2$–Ar), 3.81 (3H, s, O<u>Me</u>), 3.47 – 3.45 (2H, m, H1), 2.22 – 2.20 (1H, m, H4), 2.17 – 2.15 (1H, m, H5), 2.06 (1H, d, *J* = 2.6 Hz, H11), 1.87 – 1.85 (1H, m, H3), 1.66 (3H, dd, *J* = 6.2, 1.0 Hz, H9), 1.61 – 1.59 (2H, m, H2), 1.43 – 1.41 (1H, m, H3), 1.06 (3H, d, *J* = 7.2 Hz, H6); **^{13}C NMR**

(125 MHz, $CDCl_3$) δ_C 159.1 (CAr), 135.0 (CAr), 130.7 (C6), 129.2 (CAr), 124.7 (C7), 113.7 (CAr), 86.2 (C10), 72.4 (–C$\underline{H_2}$–Ar), 70.4 (C1), 69.7 (C11), 55.3 (O$\underline{Me}$), 40.5 (C4), 37.5 (C5), 29.3 (C2), 27.6 (C3), 17.9 (C7), 17.5 (C6); **HRMS** (ES^+) calcd for $C_{19}H_{28}NaO_2$ $[M+Na]^+$ 309.1825, found 309.1823.

((*3S,4S,E*)-3-(3-(4-Methoxybenzyloxy)propyl)-4-methylhept-5-en-1-ynyl) dimethylsilane 378:

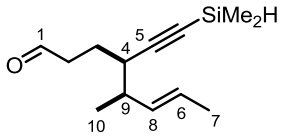


378

To a solution of alkyne **376** (746 mg, 2.6 mmol, 1 equiv.) was slowly added LiHMDS (1 M in THF, 4.2 mL, 4.2 mmol, 1.6 equiv.) and the mixture was stirred for 30 min at –78 °C, followed by addition of chlorodimethylsilane (490 µL, 4.5 mmol, 1.7 equiv.). The mixture was stirred for 30 min at –78 °C and allowed to warm up and stirred for 3 h. After completion of the reaction, the reaction was quenched with aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (20:1 to 10:1 Pet Ether/ Et_2O) to yield the desired product **378** as a colourless oil (828 mg, 2.4 mmol, 92%); $\mathbf{[a]_D^{25}}$ +5.3° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.41 (10:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 2967, 2021, 1641, 1565, 967, 838, 666; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.27 (2H, d, *J* = 8.8 Hz, HAr), 6.88 (2H, d, *J* = 8.8 Hz, HAr), 5.44 – 5.42 (1H, m, H6), 5.34 – 5.32 (1H, m, H7), 4.44 (2H, s, –C$\underline{H_2}$–Ar), 4.12 (1H, septet, *J* = 3.7 Hz, Si-H), 3.81 (3H, s, O$\underline{Me}$), 3.47 – 3.45 (2H, m, H1), 2.25 – 2.23 (1H, m, H4), 2.14 (1H, sextet, *J* = 7.3 Hz, H5), 1.87 – 1.85 (1H, m, H2), 1.66 (3H, dd, *J* = 6.3, 1.8 Hz, H8), 1.59 – 1.57 (1H, m, H2), 1.39 – 1.37 (2H, m, H3), 1.07 (3H, d, *J* = 7.01, H9), 0.22 (3H, s, Si$\underline{Me}$), 0.21 (3H, s, Si$\underline{Me}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.1 (CAr), 135.0 (CAr), 130.7

(C6), 129.2 (CAr), 124.7 (C7), 113.7 (CAr), 110.8 (C11), 83.6 (C10), 72.4 (–<u>C</u>H_2–Ar), 69.8 (C1), 55.3 (O<u>Me</u>), 40.7 (C4), 38.8 (C5), 29.1 (C2), 27.6 (C3), 17.9 (C9), 17.8 (C8), -2.6 (Si<u>Me</u>$_2$); **HRMS** (ES^+) calcd for $C_{21}H_{32}NaO_2Si$ $[M+Na]^+$ 367.2064, found 367.2047.

(*4S,5S,E*)-4-((Dimethylsilyl)ethynyl)-5-methyloct-6-enal 379:



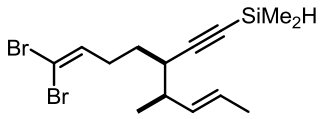
379

To a solution of **378** (150.0 mg, 0.44 mmol, 1 equiv.) in DCM/H_2O (5:1, 7.2 mL) was added DDQ (148.3 mg, 0.65 mmol, 1.5 equiv.) at room temperature under Ar. The reaction mixture was stirred for a 30 min and quenched with $NaHCO_3$ and extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The alcohol obtained was used in the next step without further purification.

To a solution of freshly prepared alcohol (0.44 mmol, 1 equiv.) in DCM (10 mL) at 0 °C was added DMP (222 mg, 0.52 mmol, 1.2 equiv.) and $NaHCO_3$ (37 mg, 0.44 mmol, 1 equiv.) and the mixture was allowed to warm up to room temperature. After completion of the reaction, the reaction was quenched with $NaHCO_3$/$Na_2S_2O_3$ (1:1), extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (10:1 Pet Ether/Ether) to yield the desired aldehyde **379** as a colourless oil (62.0 mg, 0.26 mmol, 64% over 2 steps); $\mathbf{[a]_D^{25}}$ +25.3° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.66 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2262, 2137, 2002, 1728, 841, 603; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.80 (1H, t, *J* = 1.4 Hz, H1), 5.44 – 5.42 (1H, m, H6), 5.30 – 5.28 (1H, m, H7), 4.10 (dsept, 1H, *J* = 3.6, 0.9 Hz, Si-H), 2.66 – 2.64 (1H, m, H3), 2.56 – 2.54 (1H, m, H3), 2.26 – 2.24 (1H, m, H2), 2.15 – 2.13 (1H, m, H2), 1.85 – 1.83 (1H, m, H4), 1.65 (3H, dd, *J* = 6.4, 1.4 Hz, H9), 1.61 – 1.59 (1H, m, H5), 1.08 (3H, d, *J* = 6.7 Hz, H8), 0.21 (3H, s,

Si<u>Me</u>), 0.20 (3H, s, Si<u>Me</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 202.2 (C=O), 134.4 (C6), 125.4 (C7), 109.6 (C11), 84.7 (C10), 63.2 (C1), 42.0 (C4), 40.8 (C5), 38.3 (C2), 24.9 (C3), 18.3 (C9), 17.9 (C8), -2.8 (Si<u>Me</u>$_2$); **HRMS** (ES^+) calcd for $C_{13}H_{22}NaOSi$ $[M+Na]^+$ 245.1332, found 245.1336.

((*3R,4R,E*)-3-(4,4-dibromobut-3-enyl)-4-methylhept-5-en-1-ynyl)dimethylsilane 380a:

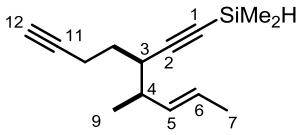


380a

To a solution of CBr_4 (447 mg, 1.35 mmol, 2 equiv.) in DCM (1.5 mL) was added PPh_3 (708 mg, 2.69 mmol, 4 equiv.) in DCM (1.50 mL) *via* dropping funnel over 15 min at 0 °C under argon, and the mixture was stirred for 10 min. The solution was cooled to –40 °C and NEt_3 (940 µL, 6.74 mmol, 10 equiv.) was added followed by a solution of aldehyde **379** (150 mg, 0.67 mmol, 1 equiv.) in DCM (1 mL). The reaction mixture was allowed to warm to 0 °C. After completion of the reaction as monitored by TLC, the reaction was quenched by addition of H_2O. The reaction mixture was extracted with DCM. The organic fractions were combined, dried ($MgSO_4$) and the volume reduced *in vacuo* and a 1:1 mixture of Pet. Ether/Ether was added and the precipitate of triphenylphosphine oxide was filtered off and the solvent was removed *in vacuo*. This operation was repeated until no triphenylphosphine oxide precipitated, then the crude mixture was purified by flash chromatography (10:1 Pet. Ether/Et_2O) to yield vinyl dibromide **380a** as a colourless oil (230 mg, 0.61 mmol, 90%); **$[a]_D^{25}$** +25.5° (*c* = 1, $CHCl_3$); **R_f** 0.9 (10:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 3025, 2960, 2167, 1601, 1493, 1250, 837; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.42 (1H, t, *J* = 7.3 Hz, H2), 5.51 – 5.40 (1H, m, H7), 5.37 – 5.27 (1H, m, H8), 4.13 (1H, dsept, *J* = 3.7, 0.9 Hz, Si-H), 2.39 – 2.28 (1H, m, H3), 2.27 – 2.10 (3H, m, H3, H5,

H6), 1.67 (3H, dd, *J* = 6.3, 1.4 Hz, H10), 1.64 – 1.56 (1H, m, H4), 1.52 – 1.42 (1H, m, H4), 1.09 (3H, d, *J* = 6.8 Hz, H9), 0.23 (1H, s, SiMe), 0.22 (1H, s, SiMe); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 138.2 (C2), 134.6 (C8), 125.2 (C7), 109.9 (C12), 89.9 (C1), 84.4 (C11), 40.8 (C5), 38.4 (C6), 31.1 (C3), 30.6 (C4), 18.2 (C9), 17.9 (C10), -2.7 ($SiMe_2$); **HRMS** (EI/FI) calcd for $C_{14}H_{22}Br_2Si$ 377.9837 found 377.9840.

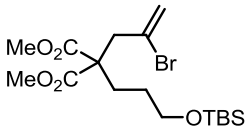
((*3S,4S,E*)-3-(But-3-ynyl)-4-methylhept-5-en-1-ynyl)dimethylsilane 380:



380

To a solution of **380a** (200 mg, 0.39 mmol, 1 equiv.) in THF (6 mL) at −78 °C was added *n*-BuLi (447 µL, 0.87 mmol, 2.2 equiv.). The reaction was stirred for 1 h at −78 °C. After completion of the reaction, the reaction was quenched with aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (20:1 Pet Ether/Et_2O) to yield the desired alkyne **380** as a colourless oil (77 mg, 90%); **$[a]_D^{25}$** +22.4° (*c* = 1, $CHCl_3$); **R_f** 0.90 (10:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 2961, 2927, 2169, 1731, 1251, 1085, 967, 883, 841; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.46 – 5.44 (1H, m, H6), 5.34 – 5.32 (1H, m, H5), 4.12 (dsept, 1H, *J* = 3.6, 0.9 Hz, Si-H), 2.41 – 2.39 (1H, m, H9), 2.30 – 2.28 (1H, m, H9), 2.16 (1H, sextet, *J* = 6.9 Hz, H4), 1.96 (1H, t, *J* = 2.5 Hz, H12), 1.73 – 1.71 (1H, m, H3), 1.67 (3H, dd, *J* = 6.4, 1.4 Hz, H7), 1.59 – 1.57 (2H, m, H10), 1.09 (3H, d, *J* = 6.5 Hz, H8), 0.23 (3H, s, SiMe), 0.22 (3H, s, SiMe); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 134.6 (C5), 125.1 (C6), 109.6 (C2), 84.3 (C1), 84.1 (C11), 68.4 (C12), 40.7 (C4), 38.1 (C3), 31.6 (C9), 18.0 (C8), 17.9 (C10), 16.6 (C7), -2.7 ($SiMe_2$); **HRMS** (ES^+) calcd for $C_{14}H_{22}NaSi$ $[M+Na]^+$ 241.1383, found 241.1376.

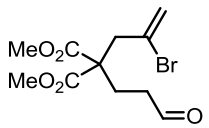
Dimethyl 2-(2-bromoallyl)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)malonate 382a:



382a

To a solution of NaH (60% dispersion in mineral oil, 90.5 mg, 2.3 mmol, 1.2 equiv.) in THF (7.5 mL) at 0 °C was added **206** (473 mg, 1.9 mmol, 1 equiv.) in THF (5 mL). The milky suspension was stirred for 30 min at room temperature under Ar. A solution of triflate **381** (790.0 g, 2.5 mmol, 1.3 equiv.) in THF (5 mL) was added at 0 °C. After completion of the reaction as monitored by TLC, the mixture was quenched with aq. NH_4Cl, washed with brine and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (5:1 Pet. Ether/Ether) afforded the desired protected alcohol **382a** as a colourless oil (632.0 mg, 1.5 mmol, 79%); $\mathbf{R_f}$ 0.43 (5:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 3291, 2952, 1731, 1625, 1434, 1278, 1150, 901, 640; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.69 – 5.67 (1H, m, H1), 5.58 (1H, d, *J* = 1.7 Hz, H1), 3.74 (6H, s, CO_2Me), 3.61 (2H, t, *J* = 6.4 Hz, H7), 3.17 (2H, s, H3), 2.08 – 2.00 (2H, m, H5), 1.44 – 1.35 (2H, m, H6), 0.89 (9H, s, Si*t*-Bu), 0.04 (6H, s, SiMe_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 171.0 (C=O), 127.1 (C2), 121.8 (C1), 62.7 (C7), 56.8 (OMe), 52.6 (C4), 43.1 (C3), 28.0 (Si$\underline{C}(CH_3)_3$), 27.6 (C6), 25.8 (C5), 18.3 (SiC($\underline{C}H_3)_3$), -5.4 (SiMe_2); **HRMS** (ES^+) calcd for $C_{17}H_{31}BrNaO_5Si$ $[M+Na]^+$ 445.1022, found 445.1026.

Dimethyl 2-(2-bromoallyl)-2-(3-oxopropyl)malonate 383:



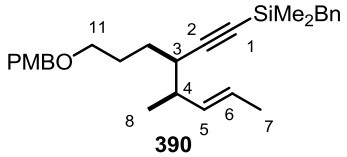
383

382a (430 mg, 1.01 mmol, 1 equiv.) was dissolved in a mixture of DCM/MeOH (3:1, 10 mL), and PPTS (26 mg, 0.10 mmol, 0.1 equiv.) was added and the solution was stirred for

1 h until completion of the reaction as monitored by TLC. The reaction mixture was poured into DCM (10 mL), washed with water (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The alcohol obtained was used in the next step without further purification.

To a solution of alcohol (1.01 mmol, 1 equiv.) in DCM (10 mL) at 0 °C were added DMP (517 mg, 1.22 mmol, 1.2 equiv.) and $NaHCO_3$ (85.0 mg, 1.01 mmol, 1 equiv.) and the mixture was allowed to warm up to room temperature. After completion of the reaction, the reaction was quenched with $NaHCO_3/Na_2S_2O_3$ (1:1), extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (1:1 Pet Ether/Ether) to yield the desired aldehyde **383** as a colourless oil (206 mg, 0.67 mmol, 66% over 2 steps); $\mathbf{R_f}$ 0.24 (1:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 2955, 2172, 1735, 1625, 1434, 1278, 1026, 732; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.74 (1H, t, *J* = 1.3 Hz, H7), 5.75 – 5.70 (1H, m, H1), 5.66 (1H, d, *J* = 1.6 Hz, H1), 3.80 (6H, s, CO_2Me), 3.24 (2H, s, H3), 2.63 – 2.47 (2H, m, H5), 2.46 – 2.29 (2H, m, H6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 200.6 (C7), 170.5 (C=O), 126.5 (C2), 122.2 (C1), 56.3 (OMe), 52.9 (C4), 44.0 (C3), 39.1 (C6), 24.3 (C5); **HRMS** (ES^+) calcd for $C_{11}H_{15}NaBrO_5$ $[M+Na]^+$ 329.0001, found 329.0010.

Benzyl((*3R,4R,E*)-3-(3-(4-methoxybenzyloxy)propyl)-4-methylhept-5-en-1-ynyl) dimethylsilane 390:

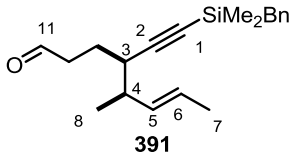


390

To a solution of alkyne **376** (490 mg, 1.7 mmol, 1 equiv.) was slowly added LiHMDS (1 M in THF, 2.4 mL, 2.4 mmol, 1.4 equiv.) and the mixture was stirred for 30 min at –78 °C, followed by addition of chlorodimethylbenzylsilane (420 µL, 2.4 mmol, 1.4 equiv.). The

mixture was stirred for 30 min at −78 °C and allowed to warm up and stirred for 3 h. After completion of the reaction, the reaction was quenched with aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (10:1 Pet Ether/ Et_2O) to yield the desired product **390** as a colourless oil (532 mg, 1.2 mmol, 72%); **$[a]_D^{25}$** +17.8° (*c* = 1, $CHCl_3$); **R_f** 0.24 (10:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 2929, 2165, 1728, 1612, 1247, 1097, 828; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.27 (2H, d, *J* = 7.3 Hz, HAr), 7.21 (3H, t, *J* = 7.4 Hz, HAr), 7.10 (2H, d, *J* = 7.3 Hz, HAr), 6.88 (2H, d, *J* = 8.5 Hz, HAr), 5.43 – 5.41 (1H, m, H6), 5.34 – 5.32 (1H, m, H5), 4.44 (2H, s, O-C$\underline{H_2}$-Ar), 3.81 (3H, s, O$\underline{Me}$), 3.48 – 3.46 (2H, m, H11), 2.23 – 2.21 (1H, m, H3), 2.18 (2H, s, Si-C$\underline{H_2}$-Ar), 2.14 (1H, m, H4), 1.83 (1H, m, H10), 1.67 (3H, d, *J* = 6.1 Hz, H7), 1.61 (2H, m, H9), 1.39 – 1.37 (1H, m, H10), 1.05 (3H, d, *J* = 6.5 Hz, H8), 0.11 (6H, s, Si$\underline{Me_2}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.1 (CAr), 139.3 (CAr), 135.1 (C5), 130.7 (CAr), 129.2 (CAr), 128.4 (CAr), 128.0 (CAr), 124.6 (C6), 124.2 (CAr), 113.7 (CAr), 100.6 (C1), 85.0 (C2), 72.4 (O-$\underline{C}H_2$-Ar), 69.8 (C11), 55.3 (O$\underline{Me}$), 40.8 (C4), 38.7 (C3), 29.2 (C9), 27.6 (C10), 26.6 (Si-$\underline{C}H_2$-Ar), 17.9 (C7), 17.8 (C8), -1.8 (Si$\underline{Me_2}$); **HRMS** (ES^+) calcd for $C_{28}H_{38}NaO_2Si$ $[M+Na]^+$ 457.2533, found 457.2532.

(*4R*,*5R*,*E*)-4-((Benzyldimethylsilyl)ethynyl)-5-methyloct-6-enal 391:



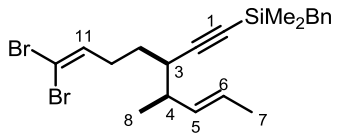
391

To a solution of **390** (531.9 mg, 1.22 mmol, 1 equiv.) in DCM/H_2O (5:1, 12 mL) was added DDQ (417 mg, 1.84 mmol, 1.5 equiv.) at room temperature under Ar. The reaction mixture was stirred for 30 min, quenched with $NaHCO_3$ and extracted with DCM, dried

($MgSO_4$) and the solvent removed *in vacuo*. The alcohol obtained was used in the next step without further purification.

To a solution of alcohol (1.22 mmol, 1 equiv.) in DCM (10 mL) at 0 °C were added DMP (727 mg, 1.71 mmol, 1.4 equiv.) and $NaHCO_3$ (102.8 mg, 1.22 mmol, 1 equiv.) and the mixture was allowed to warm up to room temperature. After completion of the reaction, the reaction was quenched with $NaHCO_3/Na_2S_2O_3$ (1:1), extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (5:1 Pet Ether/Ether) to yield the desired aldehyde **391** as a colourless oil (290 mg, 0.93 mmol, 76% over 2 steps); $\mathbf{[a]_D^{25}}$ +16.5° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.66 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2960, 2165, 1726, 1493, 1250, 836, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.77 (1H, t, *J* = 1.3 Hz, H11), 7.21 – 7.18 (2H, m, HAr), 7.11 – 7.08 (3H, m, HAr), 5.48 – 5.46 (1H, m, H5), 5.30 – 5.28 (1H, m, H6), 2.61 – 2.59 (1H, m, H10), 2.51 – 2.49 (1H, m, H10), 2.25 – 2.23 (1H, m, H3), 2.18 (2H, s, Si-C$\underline{H_2}$-Ar), 2.15 – 2.13 (1H, m, H4), 1.83 – 1.81 (1H, m, H9), 1.67 (3H, dd, *J* = 6.3, 1.4 Hz, H8), 1.60 – 1.58 (1H, m, H9), 1.08 (3H, d, *J* = 6.8 Hz, H7), 0.13 (6H, s, Si$\underline{Me_2}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 202.3 (C=O), 139.2 (CAr), 134.5 (C6), 128.3 (CAr), 128.1 (CAr), 125.3 (C5), 124.2 (CAr), 109.5 (C1), 86.0 (C2), 42.0 (C10), 41.0 (C4), 38.3 (C3), 26.4 (Si-$\underline{C}H_2$-Ar), 24.9 (C9), 18.3 (C8), 17.9 (C7), -1.8 (Si$\underline{Me_2}$); **HRMS** (ES^+) calcd for $C_{20}H_{28}NaOSi$ $[M+Na]^+$ 335.1802, 335.1795.

Benzyl((*3R*,*4R*,*E*)-3-(4,4-dibromobut-3-enyl)-4-methylhept-5-en-1-ynyl) dimethylsilane 392a:

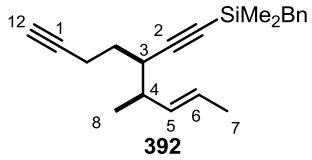


392a

To a solution of CBr_4 (488 mg, 1.47 mmol, 2 equiv.) in DCM (20 mL) was added PPh_3 (772 mg, 2.94 mmol, 4 equiv.) in DCM (20 mL) *via* dropping funnel over 15 min at 0 °C under Ar, and the mixture was stirred for 10 min. The solution was cooled to –40 °C and NEt_3 (1 mL, 7.36 mmol, 10 equiv.) was added followed by a solution of aldehyde **391** (230 mg, 0.74 mmol, 1 equiv.) in DCM (5 mL). The reaction mixture was allowed to warm to 0 °C. After completion of the reaction as monitored by TLC, the reaction was quenched by addition of H_2O. The reaction mixture was extracted with DCM. The organic fractions were combined, dried ($MgSO_4$) and the volume reduced *in vacuo* and a 1:1 mixture of Pet. Ether/Ether was added and the precipitate of triphenylphosphine oxide was filtered off and the solvent was removed *in vacuo*. This operation was repeated until no triphenylphosphine oxide precipitated, then the crude mixture was purified by flash chromatography (10:1 Pet. Ether/Ether) to yield vinyl dibromide **392a** as a colourless oil (153 mg, 0.33 mmol, 45%); $\mathbf{[a]_D^{25}}$ +22.3° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.9 (5:1 Pet. Ether/Et_2O); **IR** (thin film) ν_{max} = 3025, 2960, 2167, 1601, 1493, 1250, 837; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.22 – 7.19 (3H, m, HAr), 7.11 – 7.09 (2H, m, HAr), 6.40 (1H, t, *J* = 7.5 Hz, H11), 5.45 – 5.43 (1H, m, H5), 5.31 – 5.29 (1H, m, H6), 2.31 – 2.29 (1H, m, H10), 2.23 – 2.21 (1H, m, H4), 2.19 (2H, s, Si-C$\underline{H_2}$-Ar), 2.14 – 2.12 (2H, m, H3, H10), 1.67 (3H, dd, *J* = 6.3, 1.5 Hz, H8), 1.58 – 1.56 (1H, m, H9), 1.44 – 1.42 (1H, m, H9), 1.05 (3H, d, *J* = 6.7 Hz, H7), 0.12 (6H, s, Si$\underline{Me_2}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 138.3 (C11), 134.7 (C6), 128.3 (CAr), 128.1 (CAr), 125.1 (C5), 124.2 (CAr), 124.0 (CAr), 109.7 (C1), 88.9 (C12), 85.8

(C2), 40.8 (C3), 38.4 (C4), 31.1 (C10), 30.6 (C9), 26.5 (Si-$\underline{C}H_2$-Ar), 18.1 (C8), 17.9 (C7), -1.8 (Si$\underline{Me}_2$); **HRMS** (EI/FI) calcd for $C_{21}H_{28}Br_2Si$ 468.0307 found 468.0810.

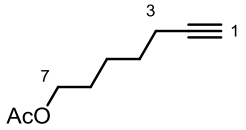
Benzyl((*3R,4R,E*)-3-(but-3-ynyl)-4-methylhept-5-en-1-ynyl)dimethylsilane 392:



392

To a solution of vinyl dibromide **392a** (153 mg, 0.33 mmol, 1 equiv.) in THF at −78 °C was added *n*-BuLi (2.5 M in hexanes, 290 µL, 0.71 mmol, 2.2 equiv.). The mixture was allowed to warm to room temperature over a 30 min period and stirred for a further 10 min. After completion of the reaction, the reaction was quenched with aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (Pet. Ether) to yield the desired alkyne **392** as a colourless oil (84 mg, 0.27 mmol, 83%); $\mathbf{[a]_D^{25}}$ +18.5° (*c* = 1, $CHCl_3$); $\mathbf{R_f}$ 0.43 (Pet. Ether); **IR** (thin film) ν_{max} = 2929, 2165, 1728, 1612, 1247, 1097, 828; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.24 – 7.21 (3H, m, HAr), 7.11 – 7.09 (2H, m, HAr), 5.46 – 5.44 (1H, m, H5), 5.33 – 5.31 (1H, m, H6), 2.38 – 2.36 (2H, m, H4, H10), 2.26 – 2.24 (1H, m, H10), 2.20 (2H, s, Si-C$\underline{H}_2$-Ar), 2.14 – 2.12 (1H, m, H3), 1.97 (1H, t, *J* = 2.6 Hz, H12), 1.72 – 1.69 (1H, m, H9), 1.54 – 1.52 (1H, m, H9), 1.67 (3H, dd, *J* = 6.4, 1.4 Hz, H8), 1.07 (3H, d, *J* = 6.8 Hz, H7), 0.12 (6H, s, Si$\underline{Me}_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 134.7 (C6), 128.3 (CAr), 128.1 (CAr), 125.0 (C5), 124.2 (CAr), 124.0 (CAr), 109.4 (C1), 85.6 (C2), 84.2 (C11), 68.4 (C12), 40.7 (C3), 38.1 (C4), 31.6 (C10), 28.5 (C9), 26.5 (Si-$\underline{C}H_2$-Ar), 18.0 (C8), 17.9 (C7), -1.8 (Si$\underline{Me}_2$); **HRMS** (ES^+) calcd for $C_{19}H_{28}NaSi$ $[M+Na]^+$ 331.1858 found 331.1860.

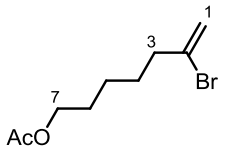
Hept-6-ynyl acetate 394:



394

To a solution of hept-6-yn-1-ol (2 g, 17.8 mmol, 1 equiv.) in DCM at −78 °C was added pyridine (1.9 mL, 23.2 mmol, 1.3 equiv.), acetic anhydride (2.2 mL, 23.2 mmol, 1.3 equiv.) and DMAP (cat.). The mixture was stirred for 2 h at room temperature. After completion of the reaction, the reaction was quenched with $NaHCO_3$, washed with HCl, extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (2:1 Pet. Ether/Ether) to yield the desired alkyne **394** as a colourless oil (2.7 g, 17.8 mmol, quant.); $\mathbf{R_f}$ 0.43 (2:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2929, 1737, 1461, 1366, 1234, 1046, 632; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ_H 4.06 (2H, t, *J* = 7.0 Hz, H7), 2.20 (2H, td, *J* = 7.0, 2.6 Hz, H3), 2.04 (3H, s, C(O)C$\underline{H}_3$), 1.94 (1H, t, *J* = 2.6 Hz, H1), 1.64 (2H, q, *J* = 7.0 Hz, H6), 1.57 – 1.54 (2H, m, H4), 1.49 – 1.46 (2H, m, H5); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ_C 171.2 (C=O), 84.2 (C2), 68.4 (C1), 64.4 (C7), 28.1 (C4), 28.0 (C6), 25.1 (C5), 21.0 (C(O)$\underline{C}H_3$), 18.3 (C3); **HRMS** (ES^+) calcd for $C_{18}H_{28}NaO_4$ $[2M+Na]^+$ 331.1880, found 331.1875.

6-Bromohept-6-enyl acetate 395a:

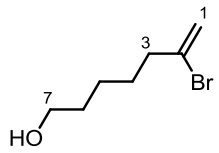


395a

To a solution of BBr_3 (1 M in DCM, 8.9 mL, 8.9 mmol, 0.5 equiv.) in DCM at −78 °C was added alkyne **394** (2.8 g, 17.9 mmol, 1 equiv.). The mixture was stirred for 4 h at room temperature. After completion of the reaction, the reaction was quenched with glacial AcOH, and the reaction was stirred for 1 h. The mixture was washed with H_2O and the

aqueous layer was extracted with DCM, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (10:1 Pet. Ether/Ether) to yield the desired vinyl bromide **395a** as a colourless oil (3.5 g, 14.9 mmol, 83%); $\mathbf{R_f}$ 0.39 (10:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2925, 2857, 1740, 1236, 1044, 886; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.56 (1H, s, H1), 5.39 (1H, s, H1), 4.06 (2H, t, *J* = 6.8 Hz, H7), 2.43 (2H, t, *J* = 7.1 Hz, H3), 2.05 (3H, s, C(O)C$\underline{H}_3$), 1.66 – 1.64 (2H, m, H6), 1.60 – 1.58 (2H, m, H4), 1.39 – 1.37 (2H, m, H5); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 171.2 (C=O), 134.4 (C2), 116.6 (C1), 64.4 (C7), 41.2 (C3), 28.3 (C4), 27.5 (C6), 24.8 (C5), 21.0 (C(O)$\underline{C}H_3$); **HRMS** (EI/FI) calcd for $C_9H_{15}BrO_2$ 234.0255, found 234.0263.

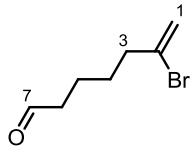
6-Bromohept-6-en-1-ol 395:



395

To a solution of vinyl bromide **395a** (223 mg, 0.95 mmol, 1 equiv.) in MeOH was added K_2CO_3 (395 mg, 2.86 mmol, 3 equiv.) and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (5:1 Pet. Ether/Ether) to yield the desired alcohol **395** as a colourless oil (176 mg, 0.91 mmol, 96%); $\mathbf{R_f}$ 0.15 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 3331, 2936, 2861, 1629, 1429, 1173, 1121, 1053, 884, 641; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.57 (1H, s, H1), 5.40 (1H, s, H1), 3.66 (2H, t, *J* = 6.6 Hz, H7), 2.44 (2H, t, *J* = 7.4 Hz, H3), 1.61 – 1.58 (4H, m, H5, H6), 1.41 – 1.39 (2H, m, H4); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 134.6 (C2), 116.6 (C1), 62.8 (C7), 41.3 (C3), 32.4 (C4), 27.7 (C6), 24.6 (C5); **HRMS** (EI/FI) calcd for $C_7H_{13}BrO$ 192.0150, found 192.0146.

6-Bromohept-6-enal 396:



396

To a solution of alcohol **395** (176 mg, 0.91 mmol, 1 equiv.) in DCM (5 mL) were added $NaHCO_3$ (77 mg, 0.91 mmol, 1 equiv.) and DMP (503 mg, 1.19 mmol, 1.3 equiv.) at 0 °C. After addition, the reaction mixture was allowed to warm up to room temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with $NaHCO_3/Na_2S_2O_3$ (1:1) and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (5:1 Pet. Ether/Ether) afforded the desired aldehyde **396** as a colourless oil (154 mg, 0.80 mmol, 88%); $\mathbf{R_f}$ 0.40 (5:1 Pet. Ether/Ether); **IR** (thin film) ν_{max} = 2940, 1722, 1629, 1429, 1119, 888, 730; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.78 (1H, t, *J* = 1.6 Hz, H7), 5.59 (1H, d, *J* = 1.4 Hz, H1), 5.42 (1H, d, *J* = 1.4 Hz, H1), 2.50 – 2.38 (4H, m, H3, H6), 1.69 – 1.57 (4H, m, H4, H5); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 202.2 (C7), 133.9 (C2), 116.9 (C1), 43.5 (C3), 41.0 (C6), 27.2 (C4), 20.7 (C5); **HRMS** (EI/FI) calcd for $C_7H_{11}BrO$ 189.9993, found 189.9990.

6. References

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