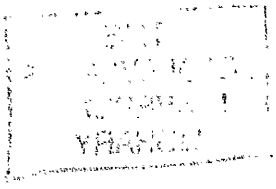
Metal catalysed cyclisations in organic synthesis

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy (PhD) in the Faculty of Science and Engineering.

James Faulkner

School of Chemistry
University of Manchester

September
2007



ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Contents

Results and Discussion

Abstract

This thesis describes processes to cyclise substrates, with certain structural motifs present, in the presence of a metal catalyst. γ-Butyrolactones are generated in the atom transfer radical cyclisation (**ATRC**) of trichloroacetates catalysed by the copper(I)/ diheptylbipyridyl complex **51**. With some certain substrates, such as (±)-2,2,2-trichloro-*N*-(hepta-1,6-dien-3-yl)acetamide **290**, can be cyclised with Grubbs catalyst **84** in toluene forming the ring closing metathesis (**RCM**) product at 40 °C and then heated to reflux to cyclise further *via* **ATRC** to form a bicyclic lactam **297**. The Grubbs catalyst, **83** and **84**, possess dual functionality depending on the reaction conditions. The catalysts can be used in a tandem process to catalyse two separate reactions sequentially or just facilitate one of the two processes.

Metal catalysed cyclisations, using Cu(I)Cl, can be integrated into synthesis towards natural products. Cyclisation of (2*E*)-3,7-dimethyl-1-(3-trimethylsilanyl-prop-2-ynyl)-octa-2,6-dienyl trichloroacetate **333,** initiated by Cu(I)Cl/ *N*,*N*,*N*',*N*'',*N*''-penta-ethyldiethylenetriamine, afforded (3*R**,3a*S**,4*R**,7*R**,7a*S**)-3-(3-trimethylsilylprop-2-ynyl)-4,7a-dichloro-7-isopropenyl-4-methylhexahydroisobenzo-furan-1-one **339a**, and (3**R*,3a*S**,4*S**,7*R**,7a*S**)-3-(3-trimethylsilylprop-2-ynyl)-4,7a-dichloro-7-isopropenyl-4-methylhexahydroisobenzofuran-1-one **339b**, as diastereomeric lactones in 28% and 10% yield respectively.

The major diastereoisomer **339a** was converted to acetate **375** in 4 steps where exposure to $BF_3.Et_2O$ and 2-(trimethylsilyloxy)furan in DCM facilitated a vinylogous Mukaiyama aldol (VMA) reaction affording (*R**)-5'-((1*R**,3*R**,3a*R**,7*S**,7a*R**)-3-(3-trimethylsilyl-prop-2-ynyl)-7-isopropenyl-4-methyl-1,3,3a,6,7,7a-hexahydro-isobenzofuran-1-yl)-5H-furan-2-one **385a** and (*S**)-5'-((1*R**,3*R**,3a*R**,7*S**,7a*R**)-3-(3-trimethylsilyl-prop-2-ynyl)-7-isopropenyl-4-methyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl)-5H-furan-2-one **385b**, in 48% and 28% yield respectively.

Both diastereoisomers, **385a** and **385b**, contain the correct stereochemistry and suitable functionality to complete the synthesis of 6-acetoxycladiella-7,11-diene-3-ol **142**. Both diastereoisomers have the potential to be contain all the carbon atoms, oxygen atoms, and contiguous stereocentres found in **142**, with the exception of $C1^{(cladielin\ numbering)}$ and are synthesised from geranial (*E*/*Z* 2:1 ratio) in 15 linear steps with a global yield of 4.5%.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or any other institute of learning.

Copyright and Ownership of Intellectual Property Rights

Author

James Thomas Faulkner was born in Northampton on the 21st January 1981. He graduated from University of Manchester in 2003 with degree of BSc in chemistry being awarded Class Two Division One Honours. In 2003, he joined the Quayle group and the work accomplished is embodied within this thesis. The author left university in 2006 to continue chemistry with the skills and knowledge learnt during his time at Manchester.

Acknowledgements

This is my last piece of work to finally be handed in to the University of Manchester. This thesis is the pinnacle of my seven years spent here and by far the most accomplished piece of work I have produced. However without the continual presence and support of a few important people, none of this would have been possible.

I'd like to thank Dr. Peter Quayle for his advice and support. As my supervisor, he has taught me the ability of independent thought and never stopped me from following my own ideas. Peter's passion for chemistry and his vast array of ideas certainly made work enjoyable throughout the various projects we worked on.

I would also like to thank the people I have "worked" with over the last three years. Chris Knight deserves special thanks. Without his training in the first six months of my PhD, I would certainly not have achieved as much as I have. James Bull deserves a huge mention. Working in the lab would have been a much more boring affair and many thanks for keeping me sane when the chemistry decided not to play fair. I would also like to thank Al, Somhairle, Sam, Tom, Anna, Alan, Chris, Mark, and James. Thanks for your invaluable advice, knowledge, and friendship over the years.

On a personal level, I'd like to thank the people who have made Manchester my home and distracted me away from the chemistry. In no particular order, as you all mean the same to me, Mick, Lorna, Adie, Nina, Chris, Tim, Yin and Dave. Let's just say you've made life a tad more interesting. For the lads I left back home, Danny, Jon, Neil, Steve, and Chris, thank you so much your constant visits and continual friendship that I will never forget. Most importantly, I'd like to thank Rachel. You've been the best distraction of all!

Saving the best for last, I'd like to thank my Mum and Dad. Thanks for the support and the belief that I could succeed to the highest level. This is for you!

Terms and abbreviations

4Å	4-angstrom
Ac	Acetyl
AD	Asymmetric dihydroxylation
AIBN	2,2'-azo*bis*(2-propionitrile)
All	Allyloxycarbonyl
Aq	Aqueous
Ar	Aryl
ATRC	Atom transfer radical cyclisation
Aux	Chiral auxiliary
B^-	Generic base
9-BBN	9-Borabicyclo[3.3.1]nonane
bipy	2,2-Bipyridyl
Bn	Benzyl
bp	Boiling point
b	Broad
Bu	Butyl
n-BuLi	*normal*-Butyl lithium
t-Bu	*tert*-Butyl
t-BuLi	*tert*-Butyllithium
^{13}C-NMR	Carbon nuclear magnetic resonance
Cat.	Catalytic
CI	Chemical ionisation
CM	Cross metathesis
conc.	Concentrated
COSY	^{1}H-^{1}H correlation spectrum
m-CPBA	3-Chloroperbenzoic acid
CSA	Camphor sulfonic acid
Cy	Cyclohexyl
d	Doublet
δ	Chemical shift
DCM	Dichloromethane
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DHQ	Dihydroquinine
DIAD	Di-*iso*-propylazodicarboxylate
DIBAL-H	Di-*iso*-butylaluminium hydride
DIP	Di-*iso*-pinocampheyl
DIPEA	See Hunig's base
DMAP	4-Dimethylaminopyridine
DMCBCy	4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane
DMF	*N,N*-Dimethylformamide
2,2-DMP	2,2-Dimethoxypropane
DMP	Dess-Martin periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
ds	Diastereoselection
ee	Enantiomeric excess
EI	Electron impact ionisation
ES+/-	Electrospray (positive or negative mode)
Et	Ethyl
Ether	Diethyl ether
eq.	Equivalents
^{19}F- NMR	Fluorine nuclear magnetic resonance
FT	Fourier transform
g	Grams
GC	Gas chromatography
gem	geminal
hr	Hour (s)
^{1}H-NMR	Proton nuclear magnetic resonance
^{2}H-NMR	Deuterium nuclear magnetic resonance
HMPA	Hexamethylphosphoramide
HMQC	^{1}H-^{13}C correlation spectrum
HPLC	High performance liquid chromatography
Hunig's base	Di-*iso*-propylethylamine
Hz	Hertz
IPC	*iso*-Pinocampheyl
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide

L	General ligand
LA	Lewis acid
LHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium di-*iso*-propylamide
m	Multiplet
M_6-tren	*N*,*N*,*N*',*N*',*N*'',*N*''-Hexamethyltriethylenetetramine
M	Molarity
M+	Molecular ion
Me	Methyl
MeLi	Methyllithium
MEM	Methoxyethoxymethyl
MHz	Megahertz
Min	Minute(s)
mg	Milligrams
mmol	Millimoles
mol	Moles
MOM	Methoxymethyl
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieve
m/z	mass-to-charge ratio
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NE	North East
NMO (or NMMO)	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
NPMI	*N*-alkyl-2-pyridylmethanimines
NW	North West
O/n	Overnight
OTf	Trifluoromethanesulfonate
P (P', P'' etc.)	General protecting group
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Petrol	Petroleum ether (40-60°C)

Ph	Phenyl
PHN	Phenanthrene
PKC	Protein kinase C
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonic acid
Pr	Propyl
pyr.	Pyridine
q	Quartet
qn	Quintet
quant.	Quantitative
R	General alkyl group
RCM	Ring closing metathesis
R_f	Retention factor
RT	Room temperature
s	Singlet
SAD	Sharpless' asymmetric dihydroxylation
SAE	Sharpless' asymmetric epoxidation
SEM	2-(Trimethylsilyl)ethoxymethoxy
SET	Single electron transfer
sm	Starting material
Stoich.	Stoichiometric
t	Triplet
tert	Tertiary
TBAF	Tetra-*N*-butylammonium fluoride
TBAI	Tetra-*N*-butylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
THP	2-(Tetrahydropyranyl)
TIPS	Tri-*iso*-propylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine

TMS	Trimethylsilyl
TPAP	Tetra-*N*-propylammonium perruthenate
Ts	4-Toluenesulfonyl
Trityl	Triphenylmethyl
V	Volume
VMA	Vinylogous Mukaiyama aldol
wt	Weight
X	General leaving group

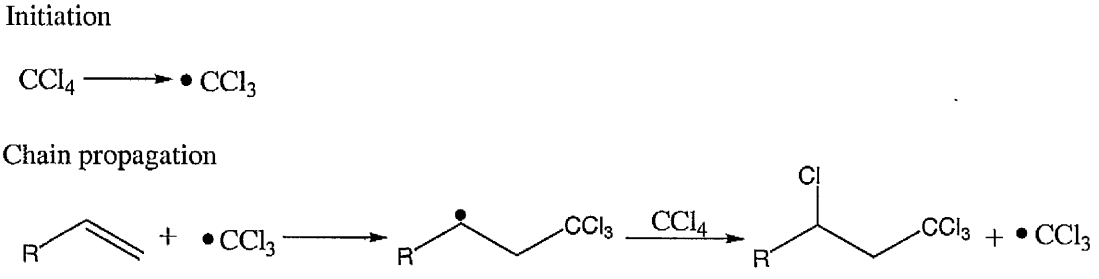
Introduction

1.0 Radical cyclisations

1.1 Introduction to metal catalysed cyclisation

Radical cyclisation reactions provide a route to the synthesis of a variety of monocyclic and polycyclic systems.[1] These reactions have the advantage that they occur in the presence of a wide range of functional groups and, in many cases, mild reaction conditions are associated with high levels of regio- and stereochemistry. Radical reactions comprise of three steps: (1) initiation, (2) propagation, and (3) termination. Transformations in which the chain transfer step involves a homolytic substitution of product radical with one of the precursors belong to the "atom transfer method".

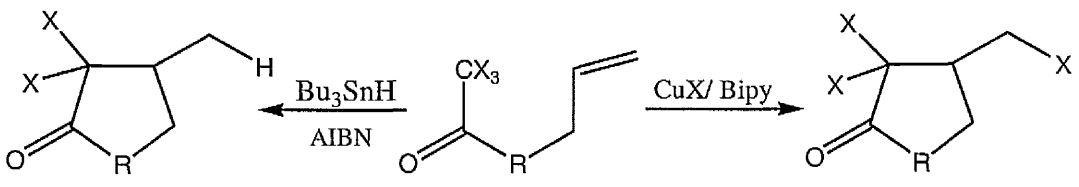
Atom transfer reactions encompass a broad range of radical additions in which C- heteroatom or heteroatom/ heteroatom bonds are added across multiple bond functionality. The first report of an atom transfer radical addition reaction was by Kharasch *et al.*[2] who showed that CCl_4 reacted with 1-octene in the presence of a radical initiator, **Scheme 1**.



Scheme 1

Copper (I) catalysed halogen atom transfer reactions offer synthetic advantages relative to the more commonly employed tin-hydride based radical reactions.[3] These include: (1) the radical-olefin addition step gives more productive radical-radical processes compared to tin-hydride mediated chemistry, where simple reduction is observed in cases where addition to the olefin is slow; (2) only a sub-stoichometric amount of copper (I) halide is required (less than 5

mol%); (3) copper (I) halide is inexpensive; (4) the metal catalyst in principle can be easily removed; and (5) they are inherently non-reductive, yielding more highly functionalised products, thus facilitating subsequent radical and non-radical transformations,[4] **Scheme 2.**

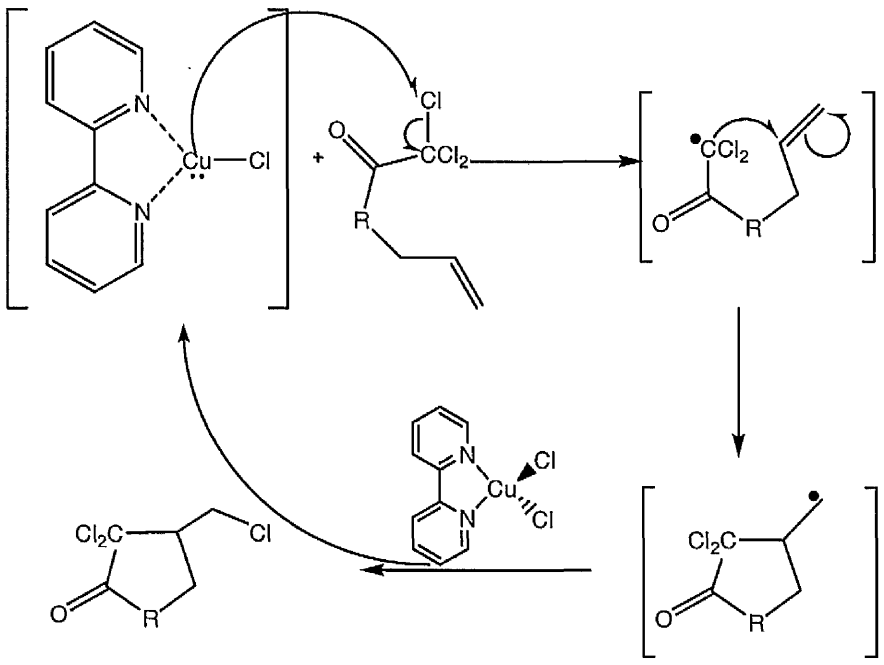


X= halogen, R= O, NR_1

Scheme 2

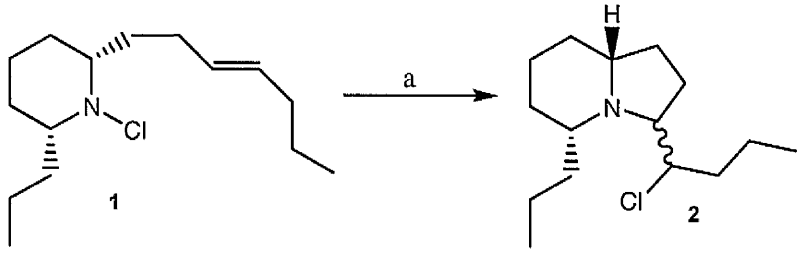
Copper mediated Atom Transfer Radical Cyclisation (**ATRC**) reactions are thought to involve a redox reaction between the Cu(I) and Cu(II) oxidation states.[5] The metal centre participates in a single electron redox cycle resulting in the desired atom transfer step depicted in **Scheme 1**. The metal should also have a high affinity for H or alkyl radicals, otherwise transfer reactions such as β-hydride elimination may take place. The reaction can be improved by the addition of 2,2'-bipyridine to Cu(I)Cl which accelerates the formation of the lactone by aiding chlorine removal. This is accomplished by the ligands ability to help solubilise the catalyst forming a homogenous solution. Without the addition of a suitable ligand, Cu(I) halide is poorly soluble in solvents effective at **ATRC**. The electron transfer step generates a carbon centred radical that can cyclise to give a more reactive carbon radical that reacts with $Cu(II)Cl_2$, **Scheme 3.**

Proposed Mechanism



Scheme 3

The atom transfer method is not restricted to the generation of carbon-centred radicals. Oxygen-halogen and nitrogen-halogen bonds are relatively weak, hence they can be used for heteroatom radical cyclisation,[1] **Scheme 4**.

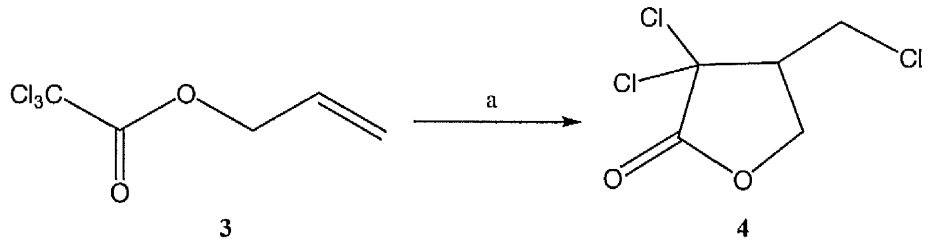


Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), THF, HOAc, H_2O, -45 °C, 67%.

Scheme 4

1.2 Formation of lactones

Atom transfer cyclisation reactions can take simple molecules such as allyl trichloroactate **3** and cyclise them to form lactones. Nagashima[6,7] demonstrated that allyl trichloroacetate **3** can be cyclised to furnish γ-lactone **4,** using Cu(I)Cl and anhydrous acetonitrile, **Scheme 5**.

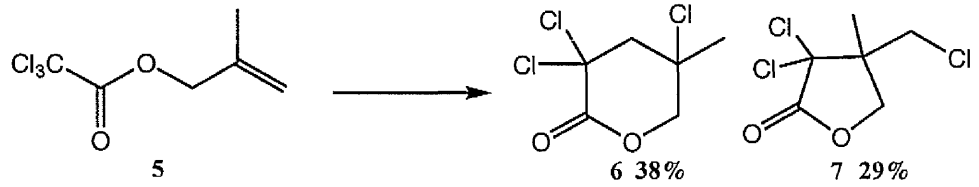


3 **4**

Reagents and conditions: a) Cu(I)Cl (5 mol%), CH_3CN, reflux, 72%

Scheme 5

Allyl trichloroacetates are volatile and can be unstable at high temperatures therefore a sub-stoichometric amount of copper(I) halide has to be used to attain the lactone in high yields. This cyclisation provides unique features in regio- and stereochemistry. Usually five-membered rings are obtained, except in the case of lactone **7**, which is the product arising from 6-*endo*-trig cyclisation. Presumably this is due to the bulky methyl substutient group present at the "5-*exo*-position", **Scheme 6**.[6]

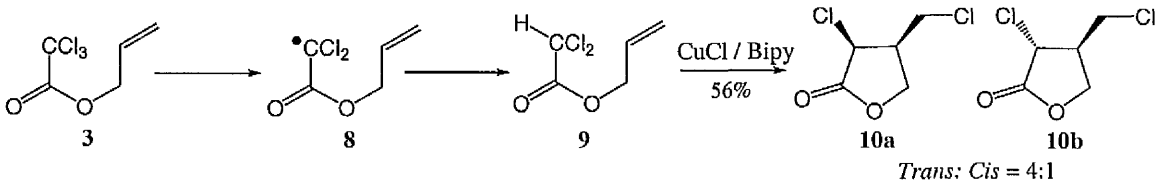


5 **6 38%** **7 29%**

Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), DCE, reflux.

Scheme 6

ATRC reactions must be carried out in suitable solvents to prevent hydrogen abstraction. Allyl trichloroacetate **3** was cyclised using Cu(I)Cl and Bipy in toluene to give lactones **10a** and **10b**.[7] Compound 9 is formed as a result of hydrogen abstraction by the dichloroacetyl radical intermediates. It is therefore important to carry out these cyclisations in suitable solvents such as acetonitrile or 1,2-dichloroethane to prevent hydrogen abstraction, **Scheme 7**.



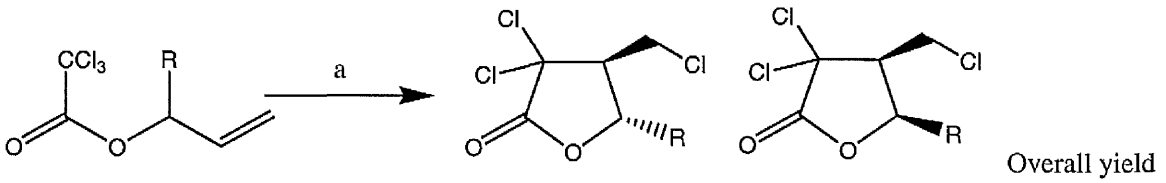
3 **8** **9** **10a** **10b**

Trans: Cis = 4:1

Scheme 7

1.3 1,2-Asymmetric induction

Secondary alcohols furnish *trans* products selectively due to the postioning of the bulky R group in an equatorial position when cyclisation takes place. Trichloroacetate **11** provided the methyl lactone as a mixture of diastereoisomers **14a,b** in which the *trans* isomer was predominantly formed over the *cis* isomer.[7] The degree of stereoselectivity is dependent on the relative steric bulk of the R group attached to the stereogenic centre, **Scheme 8**.



			Overall yield
R= Me **11**	**14a**	**14b** (89:11)	60%
R= Et **12**	**15a**	**15b** (92:8)	50%
R= *i*-Pr **13**	**16a**	**16b** (98:2)	80%

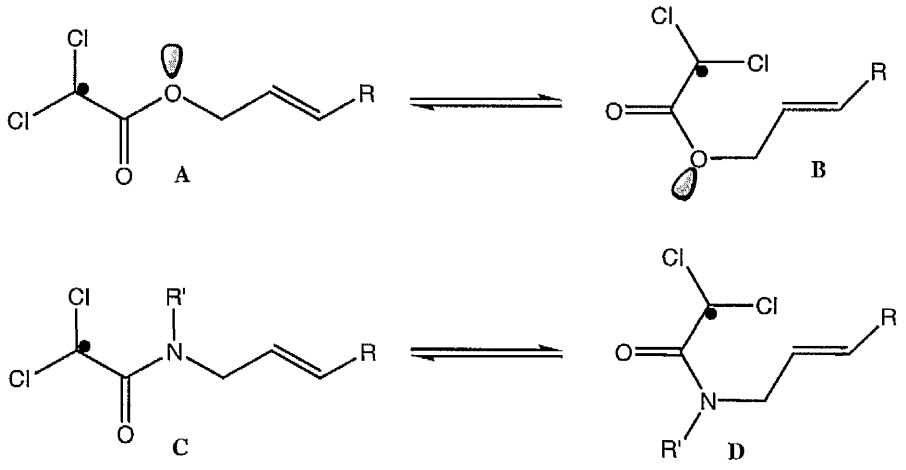
Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), DCE, reflux.

Scheme 8

1.4 Synthesis of lactams

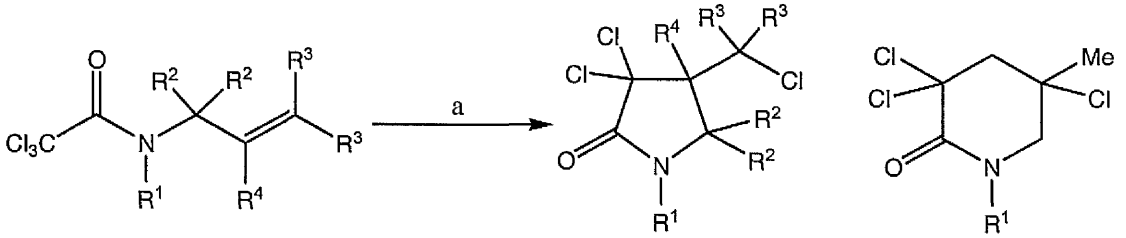
γ-Lactams are important intermediates in the synthesis of 5-membered heterocyclic compounds. Nagashima[8] synthesised trichloroacetamides by trichloroacetylation of allylic amines or by [3,3]-sigmatropic rearrangement of allyl trichloroacetoimidates. Cyclisation under **ATRC** conditions (Cu(I)Cl, 2,2'-bipyridine) led to the synthesis of γ-lactams. Cyclisation of haloacetates and haloacetamides are subject to stereoelectronic factors[9] where

the preference for the more stable, yet unreactive s-*cis* rotamer **A** of esters often results in low yields of cyclised product, **Scheme 9**. In the case of amides, the incorporation of a bulky *N*-substituent generally favours the reactive s-*trans* rotamer **D**. This is reflected in the higher yields of the cyclised products observed with these substrates.[10]



Scheme 9

N-functionalisation of the amide forces the molecule to adopt a conformation which has the alkene and haloalkyl groups *cis* to each other on the amide, **D**. Protecting groups such as benzyl are useful since they can be removed by various methods for example: hydrogenolysis, radical halogenation and oxidative cleavage, which presents the opportunity to further functionalise the molecule. Normally only 5-*exo*-trig products are formed with allyl trichloroacetamides, affording γ-lactams. δ-Lactams are obtained as a result of 6-*endo*-trig cyclisation on trichloroacetamides such as substate **19** to give a mixture of **22** and **23, Scheme 10.**

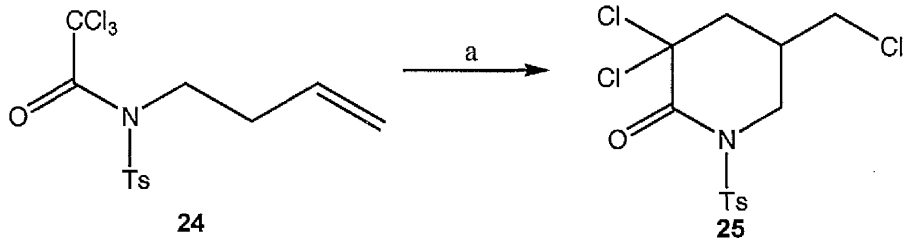


17 R^1=R^2=R^3=R^4=H	**20** 57%	0%
18 R^1=Bn, R^2=R^3=R^4=H	**21** 68%	0%
19 R^1=R^2=R^3=H, R^4=Me	**22** 23%	**23** 17%

Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), MeCN, reflux.

Scheme 10

With substrates **17** and **19**, low yields of cyclised products are obtained due to R^1 being hydrogen, hence the s-*cis* rotomer is again favoured although unreactive. δ-Lactams can also be obtained exclusively *via* 6-*exo*-trig **ATRC** cyclisation, **Scheme 11**.[97]

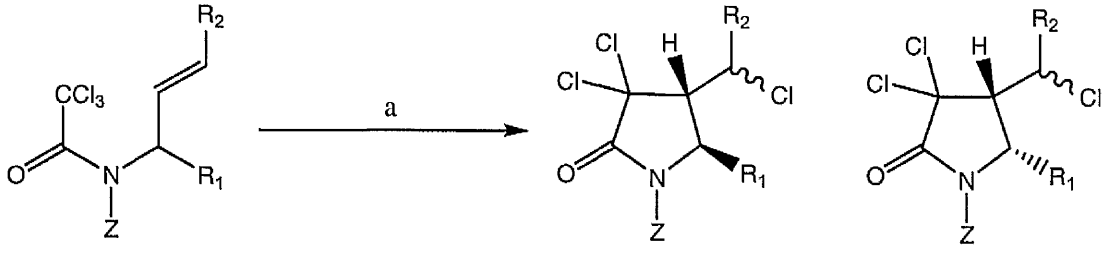


24 **25**

Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), 1,2-DCE, reflux, 64%.

Scheme 11

1,2-Asymmetric induction is also seen in the synthesis of lactams.[11,12] The stereochemistry of the lactams is governed by the protecting group on the nitrogen. *N*-Benzyl protected trichloroacetamide **27** gave the corresponding *trans* lactam **27a** predominately (*trans*: *cis* = 7:3). In sharp contract, trichloroacetamides bearing electron-withdrawing groups on the nitrogen, such as: tosyl, mesyl, Cbz and *t*-Boc, generally gave 1,2-symmetric induction, providing the corresponding *cis* isomer as the major product (*trans: cis* =1:4), **Scheme 12**.



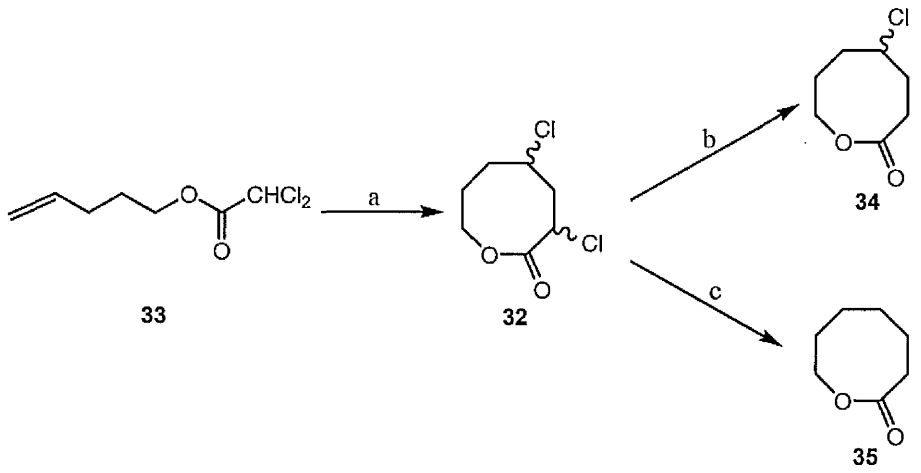
26 R_1= Me, R_2= H, Z= H	82%	**26a** (100%)	**26b** (0%)
27 R_1= Me, R_2= H, Z= Bn	78%	**27a** (70%)	**27b** (30%)
28 R_1= Me, R_2= H, Z= Ts	99%	**28a** (22%)	**28b** (78%)
29 R_1= Me, R_2= H, Z= Cbz	83%	**29a** (14%)	**29b** (86%)
30 R_1= Me, R_2= H, Z= Ms	85%	**30a** (28%)	**30b** (72%)
31 R_1= Me, R_2= *n*-Pr, Z= Cbz	98%	**31a** (20%)	**31b** (80%)

Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), MeCN, reflux.

Scheme 12

1.5 Preparation of medium sized rings by ATRC

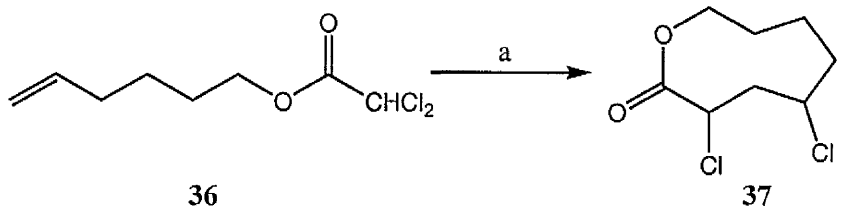
There are many natural products containing medium-sized heterocyclic rings and there is an interest to develop their synthesis using atom transfer processes. Speckamp[13] reported that upon reacting dichloroacetate **33** with Cu(I)Cl and 2,2'-bipyridine in benzene that 8-membered ring **32** are attained *via* 8- or 9-*endo*-trig cyclisations, **Scheme 13**.



Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), MeCN, reflux; b) Zn, AcOH, KI, 63%; c) Bu_3SnH, AIBN, 60%.

Scheme 13

The dichlorolactone **32** can be converted to the monochloro compound **34** by reducing with zinc and acetic acid. Exhaustive dechlorination however, was achieved using tributyltin hydride and AIBN furnishing oxocan-2-one **35**.[15] Larger rings can also be synthesised, for example 9-membered **37**, **Scheme 14**.



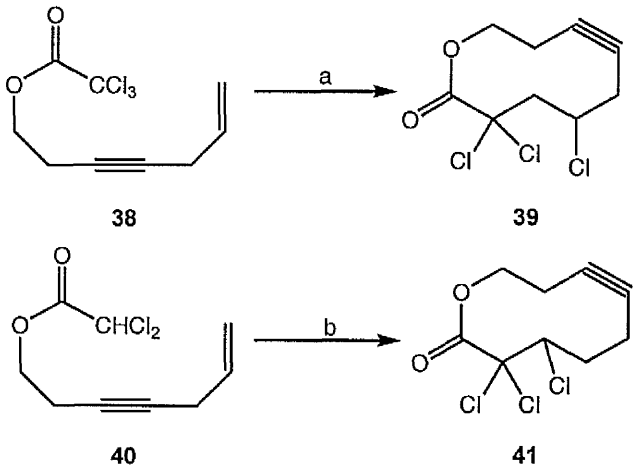
36 **37**

Reagents and conditions: a) Cu(I)Cl, Bipy, DCE, reflux, 69%.

Scheme 14

It has been reported by Speckamp[13] that cyclisation of 6-heptenyltrichloroacetate is apparently unfavourable, presumably due to the flexibility of the long chain. He suggested the

introduction of a rigid element in the carbon chain to suppress such an effect.[14] He introduced an alkyne functionality into the alkenyl chain and successfully cyclised trichloroacetates **38** and **40** by mediation of copper(I)/ bipyridine system to afford medium-sized ring lactones **39** and **41** respectively, **Scheme 15**.

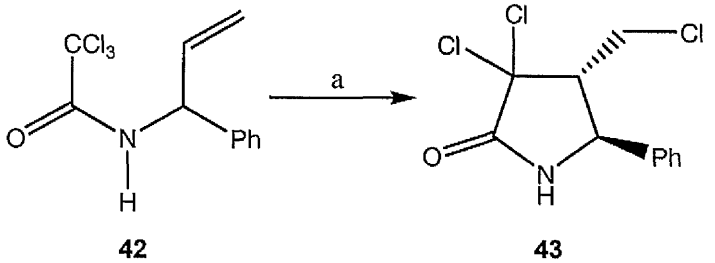


Reagents and conditions: a) Cu(I)Cl (5 mol%), Bipy (20 mol%), DCE, reflux, 36%; b) Cu(I)Cl (5 mol%), Bipy (20 mol%), DCE, reflux, 10%.

Scheme 15

1.6 Ruthenium–catalysed atom transfer cyclisations

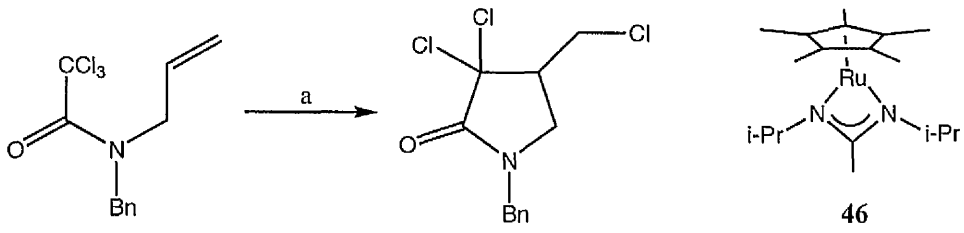
So far we have seen how Cu(I) halides and 2,2'-bipyridine can mediate **ATRC** reactions. Nagashima *et al.*[15a] reported that the simple $RuCl_2(PPh_3)_3$ catalyst can also efficiently catalyse **ATRC**. Trichloroacetamides with no bulky protecting groups on the nitrogen were successfully cyclised by $RuCl_2(PPh_3)_3$ in respectable yields, **Scheme 16**.



Reagents and conditions: a) $RuCl_2(PPh_3)_3$, toluene, reflux, 68%.

Scheme 16

Nagashima[15b] has also developed particular ruthenium catalysts, such as **46**, which can undergo **ATRC** giving high yields in mild conditions, **Scheme 17**.

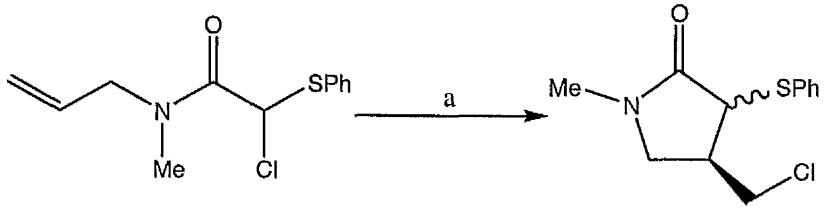


44 **45** **46**

Reagents and conditions: a) **123** (10 mol%), DCM, 25°C, >99%

Scheme 17

Nagashima[6] has also screened various metal complexes such as $RhCl(PPh_3)_3$, $Fe(CO)_5$ and $Cp_2Fe_2(CO)_4$ which have all shown an ability to promote **ATRC**. *N*-Allyl α-chloro-α-thioacetamides were used as substrates for **ATRC** reactions. Ikeda[16] found the α-chlorosulfides more reactive than the corresponding monochloroacetamides. The cyclisations of such compounds, mediated by $RuCl_2(PPh_3)_3$, was found to be highly regioselective and the lactam possesses the synthetically useful sulfur substituent, which is useful in the synthesis of alkaloids such as (-)-trachelanthamidine,[16] **Scheme 18**.



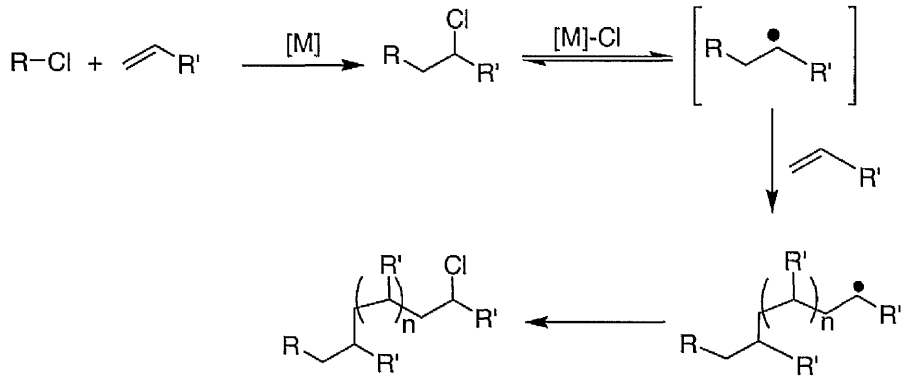
47 **48**

Reagents and conditions: a) $RuCl_2(PPh_3)_3$, toluene, reflux, 62%.

Scheme 18

1.7 Previous work on ATRC

Recent studies in the Quayle group[17] on atom transfer radical polymerisation (**ATRP**) reactions demonstrated how various copper-ligand complexes mediate **ATRP** reactions to form polymers with high conversions and narrow polydispersities, **Scheme 19**.

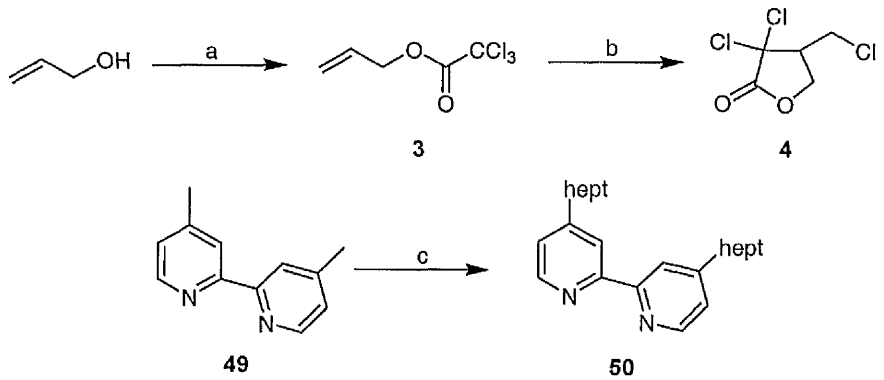


Scheme 19

Numerous multidentate amine ligands were screened in conjunction with copper halides to "fine-tune" the lipophilicity of the complex in order to maintain a completely homogeneous reaction mixture and hence good control over **ATRP** reactions. It was found that the simple bidentate amine, TMEDA, complexed with copper, polymerised methyl methacrylate (MMA) in 83% conversion with narrow polydispersity [M_w/M_n = 1.10]. Further studies showed that the tetracyclic, tertiary diamine ligand, (-)-sparteine, can also complex to copper and act as a good catalytic system in ATRP reactions. Polymerisation of MMA and styrene in the presence of Cu(I)Cl/(-)-sparteine complex resulted in the corresponding polymers being formed in 90-95% conversions and with polydispersities of 1.1-1.2. Unfortunately, no asymmetric induction was observed in these polymerisation reactions.

The synthesis of new ligands based on 2,2-bipyridine analogues and a demonstration of how they affect **ATRC** reactions has also been achieved. Previous work in the Quayle group on intramolecular **ATRC** copper(I) reactions repeated the protocol reported by Nagashima[17,18] for the cyclisation of allyl trichloroacetate **3**. Simple esterification of allyl alcohol with trichloroacetyl chloride in the presence of triethylamine afforded the desired substrate. Unfortunately, treatment of **3** with either Cu(I)Cl (0.3 eq) in acetonitrile or Cu(I)Cl (0.3 eq)/

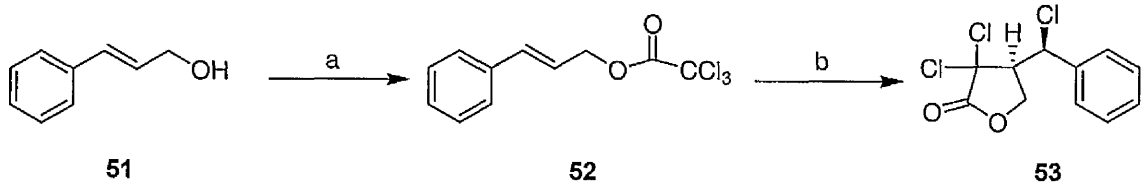
2,2'-bipyridine (0.3 eq) in acetonitrile, did not result in cyclisation and starting material was recovered in >90% yield. The solubility of the Cu(I)/ 2,2'-bipyridine complex in solvents such as DMF, toluene, acetonitrile and 1,2-DCE is poor. Matyjaszwski[19a] had reported that 4,4'-di-n-heptyl-2,2'-bipyridine **51** (dHBipy) copper complexes are soluble in organic solvents and we decided to adopt this ligand system in our **ATRC** reactions. 4,4'-di-*n*-heptyl-2,2'-bipyridine **50** (dHBipy) was readily prepared on a multi-gram scale *via* the alkylation of 4,4'-dimethyl-2,2'-bipyridine **49** with 1-bromohexane (2 eq. LDA, 2 eq. 1-bromohexane) in 84% yield. The extra carbon chain helped the copper complex be more soluble in solvents such as 1,2-dichloroethane, hence being more efficient as a catalyst for **ATRC** reactions. Cyclisation of **3** was attempted and furnished the desired lactone **4** in 85% yield, **Scheme 20**.



Reagents and conditions: a) Et_3N, CCl_3COCl, Et_2O, 91%; b) Cu(I)Cl (5 mol%), dHBipy **50** (5 mol%), 1,2-DCE, reflux, 85%; c) i) di-isopropylamine, THF, *n*-BuLi (1.6M in hexane), –78 °C, 30 mins; ii) 4,4'-dimethyl-2,2'-dipyridyl, –78 °C, 3 hrs; iii) 1-bromohexane, –78 °C to 17 °C, 16 hrs, 85%.

Scheme 20

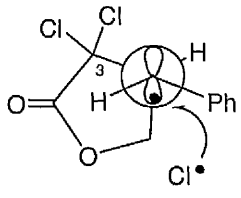
Having developed an efficient catalyst system, the cyclisation of (*E*)-cinnamyl trichloroacetate **52** afforded diastereoisomerically pure lactone **53**,[6,17] **Scheme 21**.



Reagents and conditions: a) Et_3N, CCl_3COCl, Et_2O, 93%; b) Cu(I)Cl (5 mol%), dHBipy (5 mol%), 1,2-DCE, reflux, 70%.

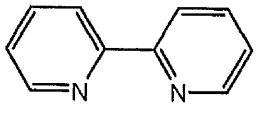
Scheme 21

In comparison to the allyltrichloroester **3**, the cinnamyl substrate **52** has increased stability. The allyl substrate forms a primary radical, while the cinnamyl system forms a stabilised benzylic radical conjugated to the aromatic ring; hence higher yields are obtained. Parsons *et al.*[20] put forward a model showing the conformation adapting during the halogen atom transfer process, **Scheme 22**. The chlorine atom approaches from the opposite face to the chlorine substituents at C-3, thus minimising electronic repulsion between the chlorine atoms. It also indicates that the phenyl ring adopts a conformation within the plane of the molecule during the cyclisation step, away from the steric bulk of the butyrolactone to enable the chlorine radical to insert without the phenyl group experiencing steric hindrance.

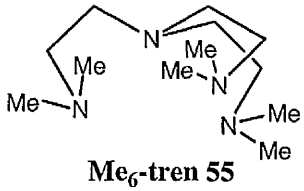


Scheme 22

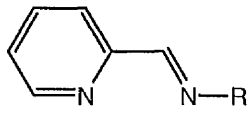
Other ligands have also been added to **ATRC** reactions to help solublise the selected copper(I) halide catalyst and modify reactivity, yield and selectivity. A large number have been synthesised, with a brief selection of some of the more successful ones shown in **Scheme 23**.[3b,19b-e]



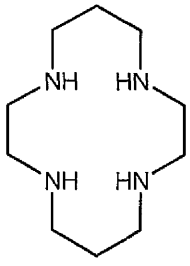
Bipy 59



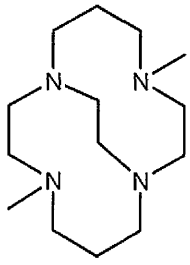
Me_6-tren 55



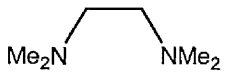
NPMI 56



Cyclam 57



DCCBCy 58

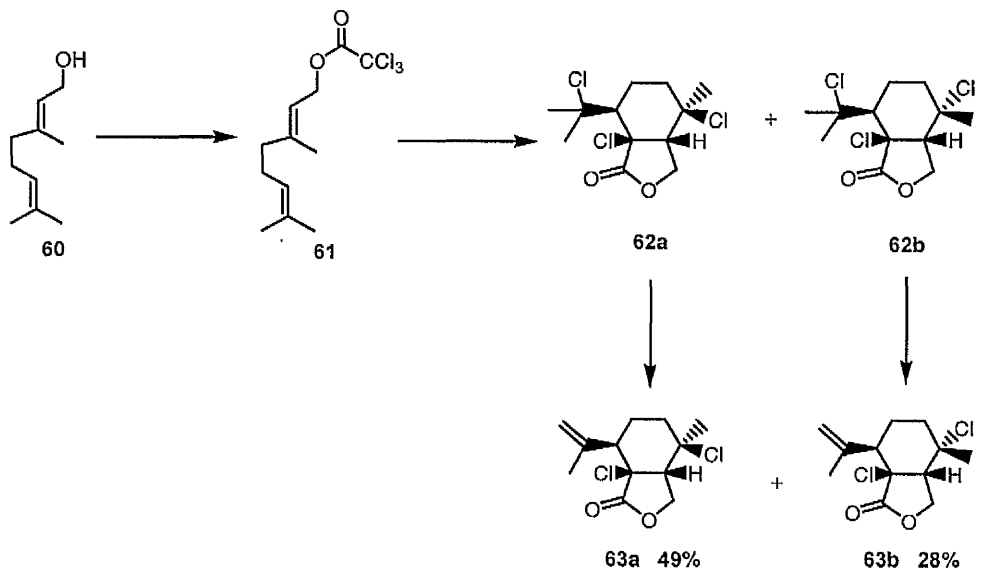


TMEDA 59

Scheme 23.

1.8 Tandem cyclisation reactions

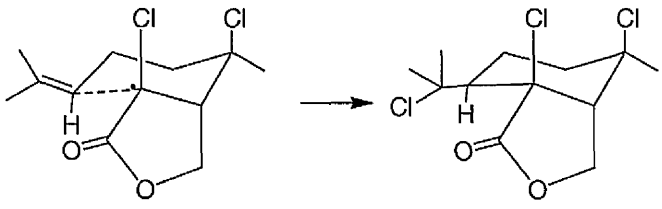
Nagashima *et al.*[18] reported that the trichloroacetamide derived from geraniol can be cyclised in the presence of the copper (I)/ bipyridine ligand system to give the bicyclic lactams as a result of a tandem **ATRC**. Previous work in the Quayle group demonstrated the cyclisation of the related ester **61** could also be achieved, and provides a facile construction of the basic core of the eunicellin skeleton. Subjecting substrate **61** to **ATRC** conditions resulted in the formation of bicyclic lactones as a mixture of diastereoisomers **62a** and **62b.**[19] As reported by Nagishima,[18] chromatography resulted in dehydrodechlorination, affording the lactones **63a** and **63b, Scheme 24**.



Reagents and conditions: a) Et_3N, CCl_3COCl, Et_2O, 93%; b) Cu(I)Cl (5 mol%), dHBipy (5 mol%), 1,2-DCE, reflux, 3.5 hrs, 70%; c) SiO_2, DCM, 1 hr, 72%, **63a: 63b** 1:1 ratio

Scheme 24

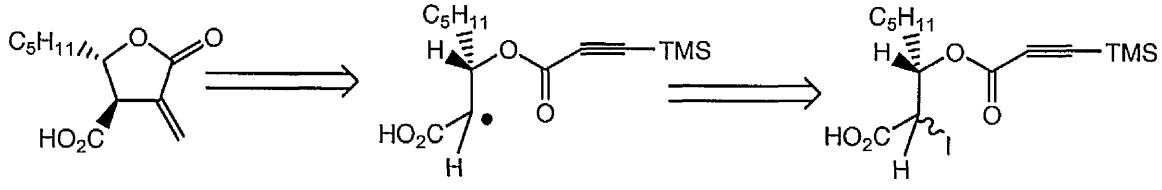
The likely conformation adopted by the radical prior to the second ring closure is illustrated in **Scheme 25**, and takes place *via* a Beckwith-Houk transition state.[20] The preferable chair conformation adopted by the cyclohexane ring is, thermodynamically, the most favoured. The chlorine and hydrogen atoms at the junction of five- and six membered rings are in a *cis*-orientation, while both chlorine atoms are pseudo-axial, whereas the isopropenyl substituent is pseudo-equatorial.



Scheme 25

1.9 Applications of ATRC in natural product synthesis.

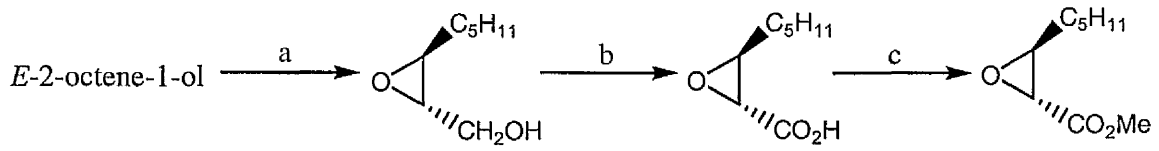
The methodology shown in previous sections has been used to its full potential by its inclusion as a key step in the formation of certain rings. Methylenolactocin **65** is an anti-tumour antibiotic. Weavers *et al.*[21] synthesised **65** using a radical cyclisation-iodine atom transfer reaction mediated by a peroxide as an initiator. Their route required the synthesis of a chiral iodoester with the *S*-configuration at C-3, followed by an atom transfer cyclisation onto an acetylene and dehalogenation, **Scheme 26.**



65

Scheme 26

The synthesis of the chiral iodoester began with Sharpless epoxidation of (*E*)-2-octen-1-ol **66** generating the chiral epoxy alcohol **67**. To improve the yield for the formation of iodoacetylinic ester, the iodohydrin route was implemented. Starting with the (2*S*, 3*S*)-epoxy alcohol **67** and converting it to the acid **68** by oxidising with ruthenium chloride and periodic acid, followed by esterification to give **69**, **Scheme 27**.

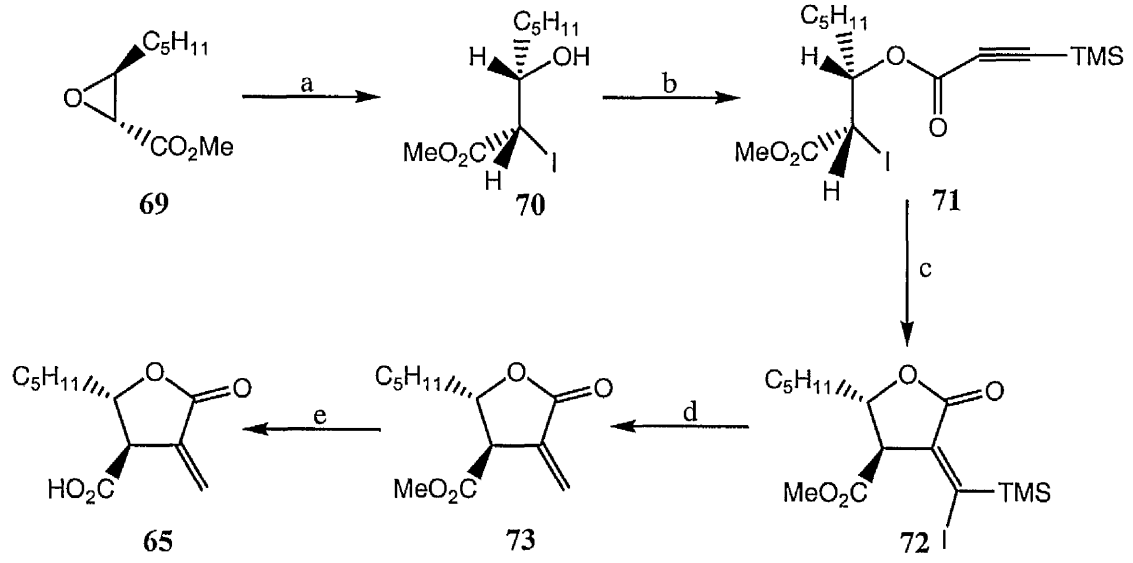


66 **67** **68** **69**

Reagents and conditions: a) Sharpless epoxidation; b) $RuCl_3$, H_5IO_6, 100%; c) esterification

Scheme 27

With **69** in hand, ring opening of the epoxide was accomplisehed using NaI and TMSCl which gave the iodide **70** *via* attack at C-2. Esterification of the alcohol **70** with TMS-propynoyl triflate gave **71** in 71% yield. Cyclisation of (2*S*,3*S*)-iodoacetylenic ester **71** gave TMS-iodo lactone **72** in good yield using hexabutylditin in conjunction with AIBN as a source for radical initiation. De-silylation of the vinylsilane was achieved by treating with KF/18-Crown-6 in THF to give **73**. Photochemical de-iodination and acid hydrolysis of the methyl ester **73** gave the natural product **65, Scheme 28.**

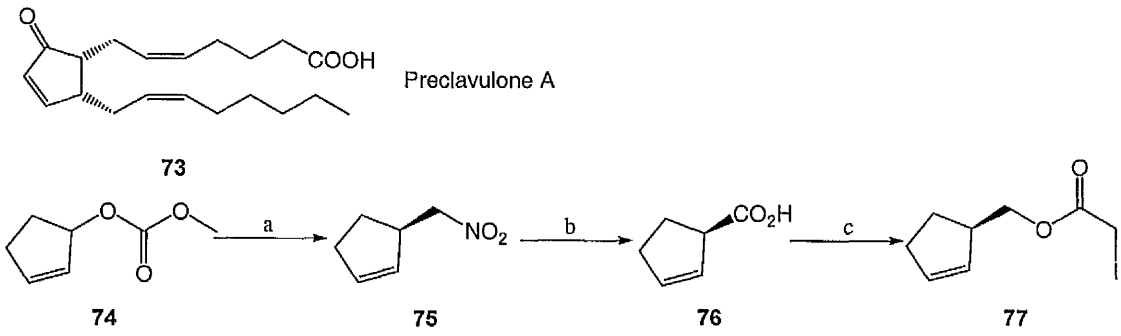


69 **70** **71** **72** **73** **65**

Reagents and conditions: a) NaI/ TMSCl, 72%; b) TMSC≡CCOOTf, DCM 71%; c) dibenzoyl peroxide, 82%; d) i) KF, 18-crown-6, ii) *hv*, THF, 67%; e) 6M $HCl_{(aq)}$, butanone, 85%.

Scheme 28

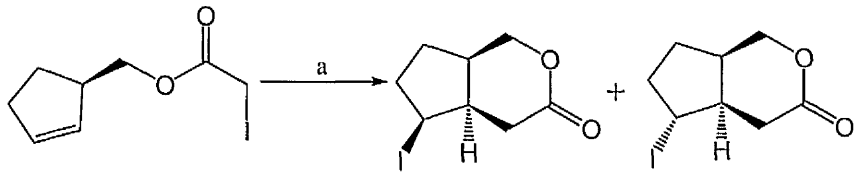
Preclavulone A **73** is a key intermediate in the biosynthesis of a group of marine prostanoids, collectively known as clavulones. These were isolated from different marine organisms such as the Okinawan coral *Clavularia viridis*. Clavulones have received recent attention due to their potent biological activity, structural features, and unique biosynthetic pathway. Zanoni *et al.* [22] synthesised Preclavulone A **73** using a radical cyclisation-iodine atom transfer reaction mediated by triethylborane as a catalyst as a key step. The iodoacetate **77,** precursor to **ATRC**, was synthesised in three steps. Cyclopentenyl carbonate **74** was subjected to nitromethane under Trost's asymmetric alkylation conditions producing the (*R*)-nitroderivate **75** in 93% yield and 98% ee. The nitromethyl functionality was converted to the corresponding carboxylic acid **76** by using $NaNO_2$, as an oxidant, in a mixture of AcOH and DMSO in 88% yield. Subsequent conversion of **76** into cyclopentenol iodoacetate **77** was produced in two steps, the first being LAH reduction followed by esterification with iodoacetic acid in the presence of DCC, giving 94% yield over the two steps, **Scheme 29**.



Reagents and conditions: a) $MeNO_2$, $Pd_2dba_3.CHCl_3$ (0.03 eq), (*S*,*S*)-L* (0.08 eq), BSA, DCM, RT, 1 hr, 93%; b) $NaNO_2$ (4 eq), AcOH (10 eq), DMSO, 38 °C, 10 hrs, 88%; c) i) LAH, Et_2O, 0 °C to RT, 3 hrs, 95%; ii) iodoacetic acid, DCC, DMAP (0.1 eq), DCM, RT, 45 mins, 92%.

Scheme 29

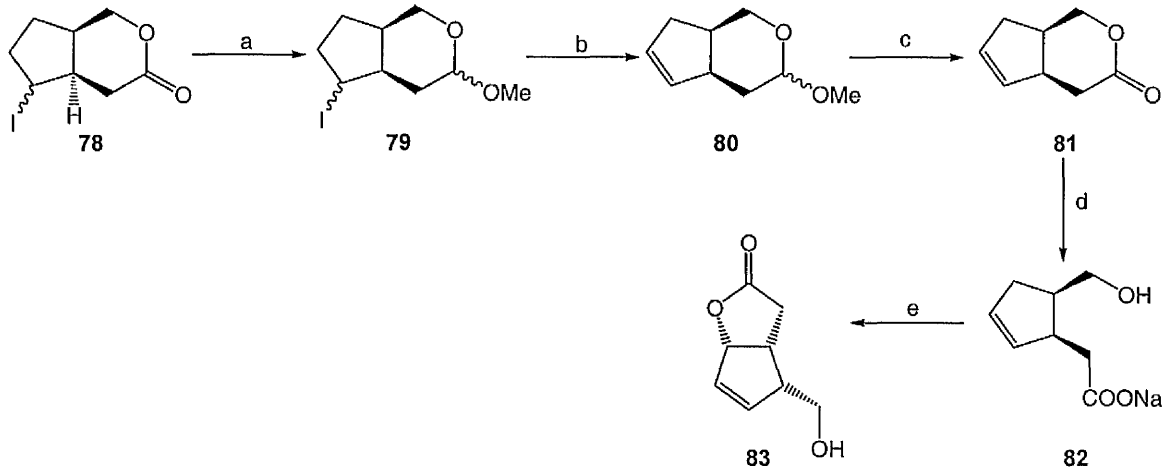
The crucial atom transfer radical cyclisation of **71** to the required bicyclic iodolactone **72** proceeded under conditions perfected by Oshima[23] (Et_3B, Ar, O_2, H_2O, RT) producing a 92:8 mixture of *syn* and *anti* C1 epimers in 92% isolated yield, **Scheme 27.**



Reagents and conditions: a) Et_3B (1M in THF, 0.1 eq), H_2O (0.01 eq), RT, 3 hrs, 92%.

Scheme 30

The main stereochemistry of **78**-*syn* indicates that the secondary C-radical intermediate resulting from the cyclisation of **77** was intercepted by a radical iodine molecule from the less hindered convex face. Continuing the synthesis, the mixture of lactones **78** was reduced to the corresponding lactols with DIBAL-H, which were immediately protected as methyl acetals in 98% yield. Hydroiodic acid is then eliminated from the acetals using KHMDS at -20 °C producing a mixture of the olefinic methyl acetals **80**. Convertion of the methyl acetal to the hemiacetal was accomplished with the addition of $HCl_{(aq)}$, followed immediately by oxidation to the regioisomerically pure olefinic lactone **81** with TPAP-NMO giving 94% over the two steps. Addition of NaOH in aqueous ethanol to **81** gave the corresponding sodium carboxylate **82** in quantitative yield, with lactonization to **83** completed *via* palladium acetate/ copper acetate addition giving 99% yield in 8 hours, **Scheme 31**.

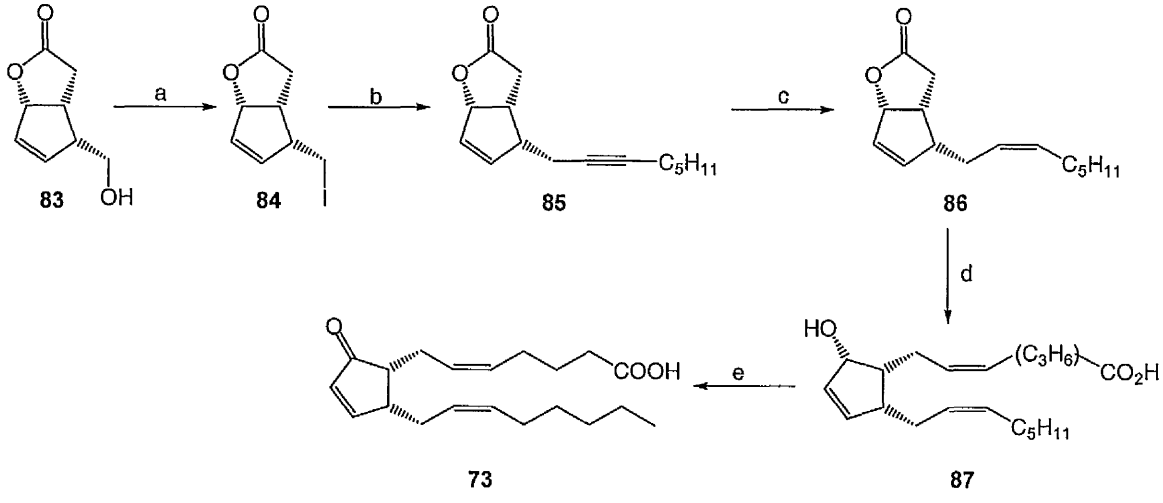


Reagents and conditions: a) i) DIBAL-H, DCM, -78 °C, 30 mins; ii) MeOH, PTSA (0.1 eq), -20 °C, 18 hrs, 98% yield over two steps; b) KHMDS, THF, -20 °C, 68 hrs, 95%; c) i) 0.3M

HCl (0.5 eq), THF-H_2O, (7:3), RT, 26 hrs, 98%: ii) TPAP (5 mol%), NMO (2 eq), DCM, RT, 2 hrs, 90%; d) NaOH, EtOH-H_2O (1:1), 80 °C, 14 hrs, 100%; e) $Pd(OAc)_2$ (0.05 eq), $Cu(OAc)_2.H_2O$, (0.05 eq), AcOH (1.05 eq), MeCN-MeOH (7:3), O_2, RT, 8 hrs, 99%.

Scheme 31

Lactone **83** was converted to the corresponding iodide **84** *via* a Mitsunobu reaction with iodine in the presence of Ph_3P. The iodide was converted to **85** *via* a one pot/ two step Knochel procedure, where the iodide **84** is initially converted to an organozinc intermediate by oxidative insertion of Zn into the C-1 bond, followed by transmetalation with CuCN.2LiCl in THF. The copper-zinc complex is then exposed to 1-bromo-1-heptyne producing the coupled product **85**. Lindlar chemoselective reduction of the alkyne functionality produced **86** exclusively in the Z-isomer in 94% yield. Compound **86** was then converted to the hemiacetal using DIBAL-H, followed by the addition of the non-stabilized Wittig reagent, $BrPh_3PCH_2(CH_2)_3CO_2H$, again giving Z-olefin **87** in 96% yield. The synthesis was completed with oxidation of the cyclopentenol moiety with Dess-Martin to give Preclavulone A **73** in 90% yield, **Scheme 32.**



Reagents and conditions: a) I_2, Ph_3P, Im (2 eq), 0 °C to RT, 85%; b) i) Et_2Zn, $Ni(acac)_2$, THF, -10 °C, 1.5 hrs; ii) CuCN (2.1 eq), LiCl (4.2 eq), THF, -40 to 0 °C, 5 mins, -78 °C; iii) 1-bromo-1-heptyne **27** (3.5 eq), -78 to 50 °C, 24 hrs, 56%; c) H_2 (1 atm), Lindlar (0.2 eq), EtOAc, RT, 5 days, 94%; d) i) DIBAL-H, DCM, -78 °C, 40 mins, quantitative; ii) $BrPh_3PCH_2(CH_2)_3CO_2H$, *t*-BuOK, THF, RT, 30 mins, 96%; e) Dess-Martin periodinane, DCM, RT, 3 hrs, 97%.

Scheme 32

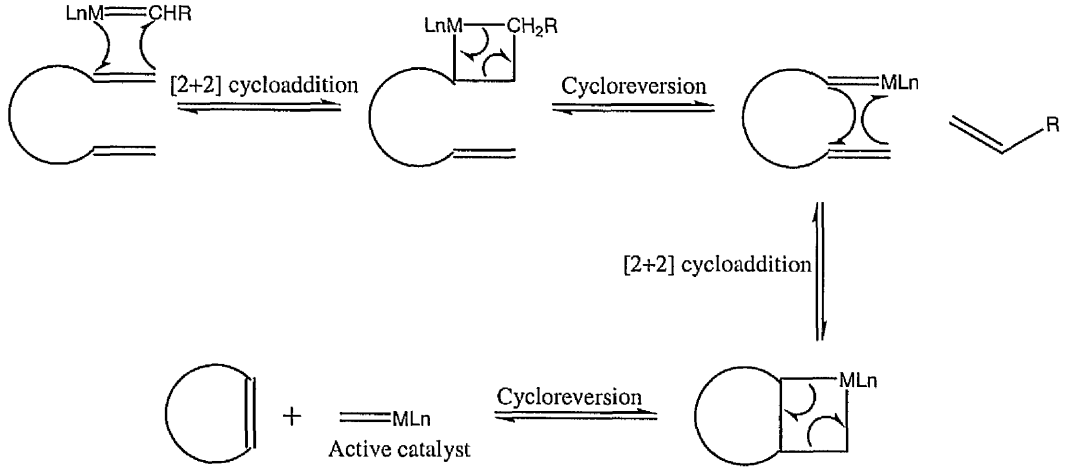
Chapter 2 Metathesis

2.1 Introduction

Metathesis has become a powerful tool in the synthesis of organic molecules. Routes to synthetic targets are now being designed with metathesis being the key step in the formation of structural motives within the molecule. As the metathesis catalysts have evolved, so too have their effectiveness. These catalysts now have the ability to react in the presence of a variety of functional groups without great loss of reactivity. High yields can also be obtained under mild conditions in relatively short reaction times. Another advantage is that stereogenic centers do not become racemised during the reaction.

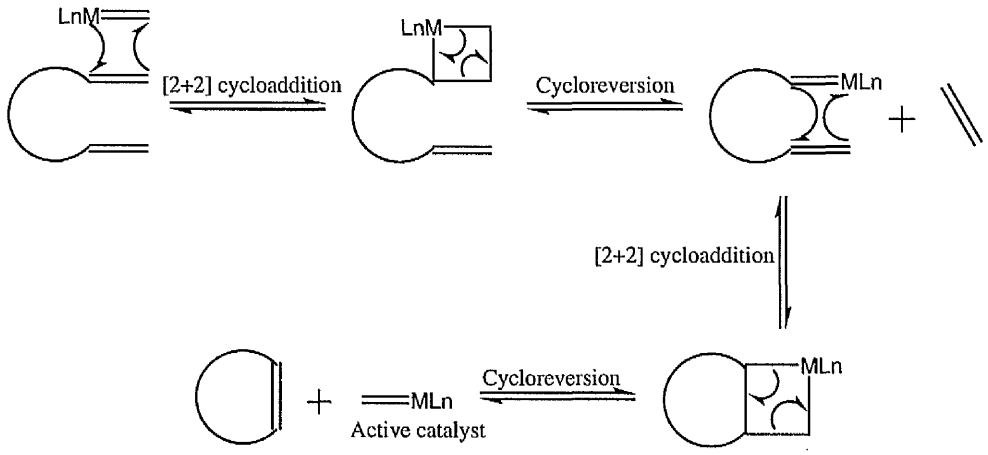
There are several types of metathesis reactions including; (a) Ring closing metathesis (**RCM**), (b) Cross metathesis (**CM**), (c) Ring opening metathesis (**ROM**), and (d) Ring opening metathesis polymerization (**ROMP**). Due to the extensive literature available for **RCM** and **CM**, these shall be discussed in more depth later.

The generally accepted mechanism for metathesis reactions consists of a formal [2+2] cycloaddition/ cycloreversion involving alkenes, metal carbenes and metallacyclobutane intermediates. Each catalyst is in fact a precatalyst and must react first to form the reactive catalyst species, **Scheme 33**.



Scheme 33

The active catalyst is a metal carbene complex, possessing a far greater turnover rate and reactivity than the pre-catalyst. The carbene-metal complex can then enter a catalytic cycle where metathesis can occur, **Scheme 34.**



Scheme 34

The above scheme shows the mechanism for ring closing metathesis. This mechanism can be used for all the other formats where a metathesis catalyst is present.

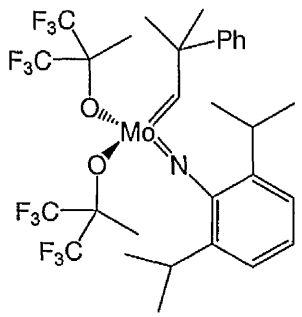
2.2 Ring closing metathesis

Ring closing metathesis (**RCM**) is a proven tool in the synthesis of cyclic structures. All sized rings, from five membered to macrocycles, both carbo- and heterocyclic, have been created *via* **RCM**. Unlike the other types of metathesis reaction, **RCM** goes with entropy with the product and ethylene being produced from the starting molecule. This factor makes **RCM** the most successful of the metathesis reactions.

2.21 Metathesis Catalysts

2.211 Molybdenum/ Tungsten Catalysts

Molybdenum catalysts, developed by Schrock *et al*,[24] are highly efficient metathesis catalysts. The tetracoordinated alkylidene species have a general formula of $[M(=CHCMe_2Ph)(=NAr)(OR)_2]$ (M=Mo, W) with bulkyl substituents Ar and R on the imide and alkoxide ligands. This produces a potent and well behaved metathesis (pre)catalyst. One commercially available molybdenum catalyst is **88**, **Scheme 35**.



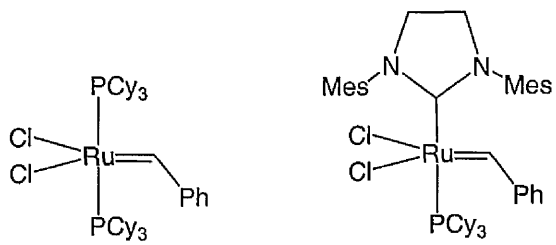
88

Scheme 35

The problem with Mo catalysts is their sensitivity towards oxygen and moisture, degrading the quantity and performance towards metathesis reactions. However, until the advent of the ruthenium based catalysts, **88** was the only metathesis catalyst allowing formation of tri- and even tetrasubstituted double bonds by **RCM**.

2.212 Ruthenium based catalysts

The Grubbs group have synthesised a collection of highly active ruthenium based precatalysts.[25] Although their activity is usually lower than that of Schrock catalyst **82**, the tolerance of these compounds towards a huge range of functional groups and their ease of handling caused by a reasonable tolerance against oxygen, water and minor impurities in the solvents make them ideal catalysts. The influence of the ligands on the catalytic activity of the 5 co-ordinate 16 electron ruthenium complexes has also been studied. The use of chloride as a ligand seems to be essential to the activity of Grubbs type catalysts. The effect of this electron withdrawing group must be stabilized by electron-donating phoshines or carbene ligands. The differences between using phosphines or carbenes to stabilise the Ru metal centre can be shown by comparing Grubbs 1st generation catalyst **89** and its successor Grubbs 2nd generation catalyst **90**, **Scheme 36.**



89 **90**

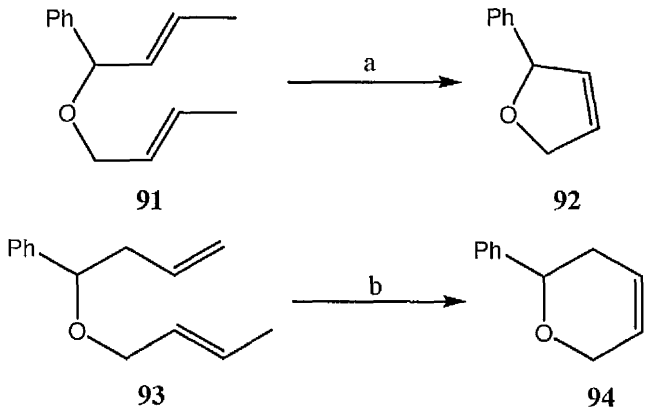
Scheme 36

The interchange of one of the phosphine ligands, in **89**, for the carbene ligand, in **90**, gives the catalyst: (1) significantly improved activity, (2) exceptional thermal stablility, (3) further tolerance towards oxygen and moisture, and (4) increased compatibility with more functional groups.

2.22 Synthesis of 5-6 membered rings

RCM is extremely effective at forming 5 and 6 membered rings. The negligible strain endured by the formation of 5 and 6 membered rings during the reaction, make these the most successful and documented rings to form. It is also an extremely prominent way into the

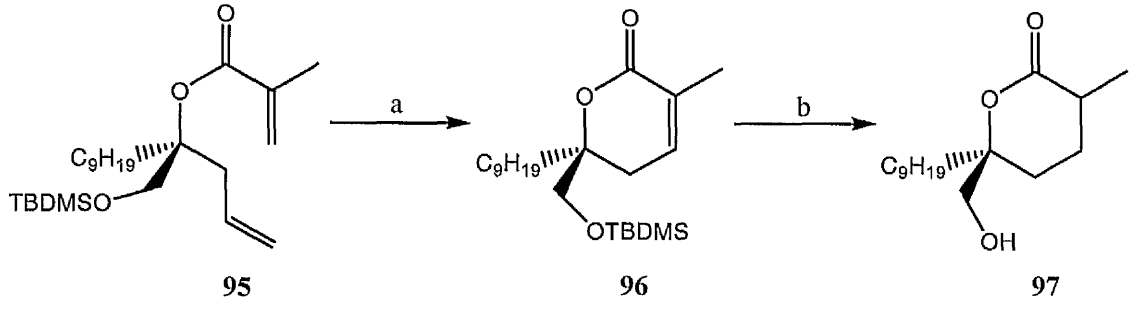
formation of heterocyclic molecules such as dihydrofurans **92** and dihydropyrans **94**,[26] **Scheme 37**.



Reagents and conditions: a) **90** (5 mol%), DCM, 2 hrs, 89%; b) **90** (5 mol%), DCM, 2 hrs, 92%.

Scheme 37

As well as the formation of highly functionalized and substituted rings, lactones can also be formed with the same relative ease. These structures feature extensively within numerous biologically active molecules. For example malyngolide **97**[27] was synthesized using **RCM**. The **RCM** substrate **95** was treated with Hoveyda Grubbs catalyst to generate lactone **96**. From the lactone **96**, malyngolide **97** was completed in two steps, **Scheme 38**.

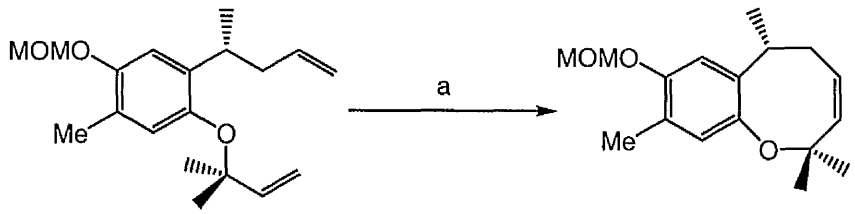


Reagents and conditions: a) Grubbs Hoveda (5 mol%), benzene, 70 °C, 88%; b) i) TsOH: ii) H_2, Pd/C, 77% over two steps.

Scheme 38

2.23 Synthesis of medium sized rings

Synthesis of medium sized rings *via* ring closing metathesis can be difficult owing to transannular repulsions and entropic factors that can develop as the ring is about to form. **RCM** works more favourably where there are other conformational constraints to aid ring formation, and this is the case for medium rings. Some of these structural features include another ring, both aromatic and cyclic, a *N*-tosyl group, or a gem dimethyl group, such as in **98**, within the acyclic chain to help link the double bonds,[28] **Scheme 39**.

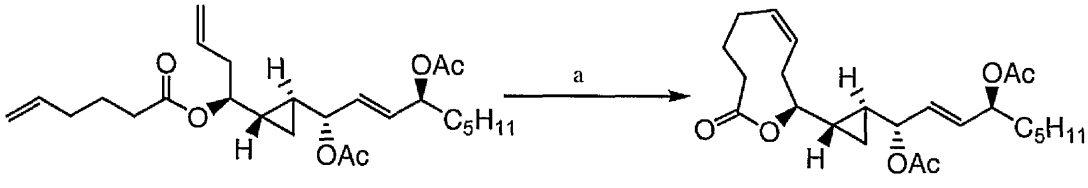


98 **99**

Reagents and conditions: a) **90** (5 mol%), DCM, RT, 88%.

Scheme 39

The above example shows that the inclusion of the benzene ring and the gem dimethyl can help the formation of the eight membered ring whilst retaining all stereochemistry. Some ring formations of medium sized rings can be challenging since the ring strain formed by the ring closure predisposes it towards subsequent **ROM** or **ROMP**. Determining whether a molecule is able of forming a medium sized ring can only be proved by attempting the reaction and changing various conditions. High dilution is one variable which can be manipulated to produce a successful ring closure. An example of this is shown by Fürstner[29] who synthesized a nine membered lactone **101** using **90** with the addition of the Lewis acid Ti(O*i*Pr)$_4$, **Scheme 40**.



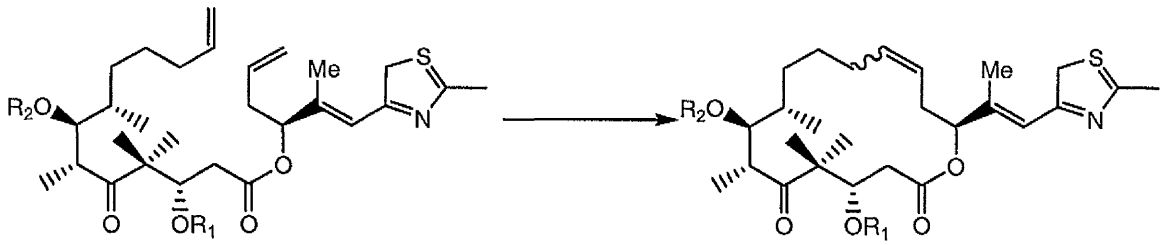
100 **101**

Reagents and conditions: a) **90** (5 mol%), Ti(O*i*Pr)$_4$, DCM, 40 °C, 72%.

Scheme 40.

2.24 Synthesis of macrocyclic systems

The synthesis of macrocyclic rings again has some of the same limitations seen with medium sized ring formation. However with macrocyclic formation, one of the major limitations is the relative proximity of the reacting olefinic bonds from each other. Conformation of the acyclic precursor can leave the olefins on either side of the molecule, making ring closure impossible. Another problem with macrocyclisation is the stereochemical outcome of the resulting cyclisation. However, modifications to reaction conditions can alter the result. A popular target for various groups[30] has been Epothione C using ring closing metathesis as the end strategy, **Scheme 41**.



102 R_1= TBS R_2= H
103 R_1= TBS R_2= TBS
104 R_1= H R_2= H

105 R_1= TBS R_2= H
106 R_1= TBS R_2= TBS
107 R_1= H R_2= H

Nicolaou et al.	Danishefsky et al.	Schinzer et al.	Danishefsky et al.
(**102** to **105**)	(**103** to **106**)	(**103** to **106**)	(**104** to **107**)
90 (10 mol%)	**88** (50 mol%)	**90** (6 mol%)	**88** (50 mol%)
DCM, 25 °C	benzene, 55 °C	DCM, 25 °C	benzene, 55 °C
(**85**%, *E*/*Z* 1:1.2)	(86%, *E*/*Z* 3:5)	(94%, *E*/*Z* 3:5)	(65%, *E*/*Z* 2:1)

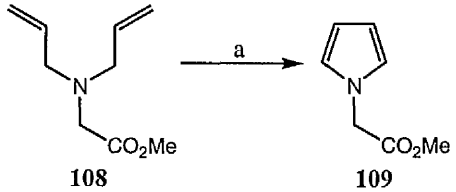
Scheme 41

The outcome from using different solvents, catalysts, loading of the particular catalyst, and the various protecting groups on certain functional groups was an affect to the stereochemistry of the eventual ring olefin formed. The yield of the reaction can also be greatly affected. Once again, the formation of macrocycles has to be investigated in a trial and error manner, to see if ring formation is possible.

2.25 Synthesis of aromatic rings *via* RCM

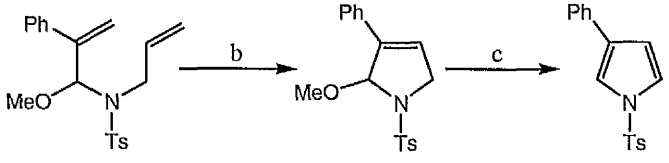
There are very few examples where there formation of aromatic rings can be accomplished *via* ring closing metathesis. There are four main strategies that have been conceived for the deliberate formation of aromatic rings. The first strategy is where **RCM** is followed by oxidation to promote aromatisation.[31] Second, **RCM** occurs to give a cyclic compound then elimination of a suitable leaving group produces the subsequent aromatic ring.[32] The third strategy is the use of a pre-existing aromatic ring as a backbone to help promote aromatisation of another.[33] Lastly, after **RCM**, tautomerism of the new ring can lead into transformation of the aromatic ring.[34] These transformations can either occur in one pot sequentially or be treated stepwise, **Scheme 42.**

1. Oxidative isomerisation



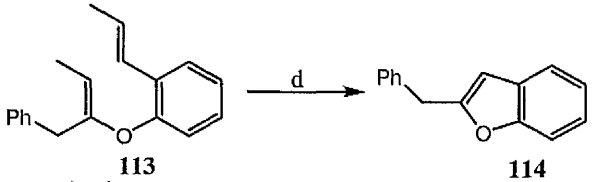
108 **109**

2. Elimination



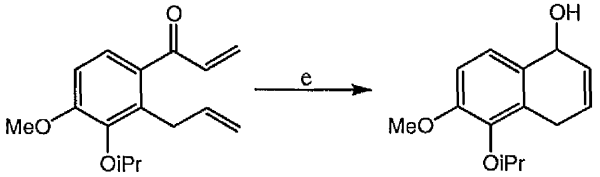
110 **111** **112**

3. Aromatic ring as backbone



113 **114**

4. Tautomerization



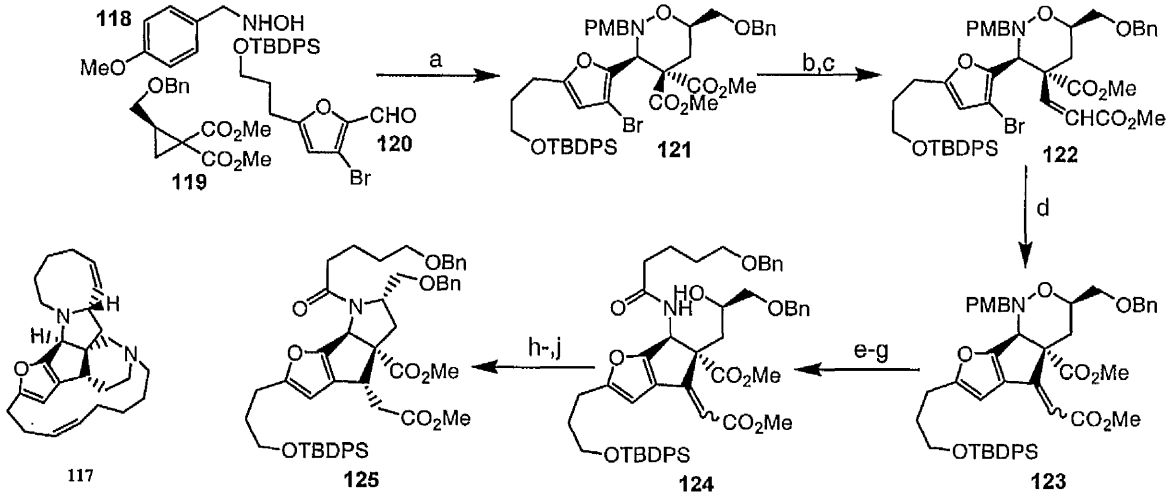
115 **116**

Reagents and conditions: a) i) **90** (5 mol%), DCM; ii) $RuCl_3.xH_2O$, 60 °C, ultrasound, 64%; b) **90** (10 mol%), DCM, reflux; c) TFA, DMF, 70% over two steps; d) **88** (13 mol%), hexane, 60 °C, 87%; e) **90** (5 mol%), DCM, 69%.

Scheme 42

2.26 Synthesis of natural products using RCM

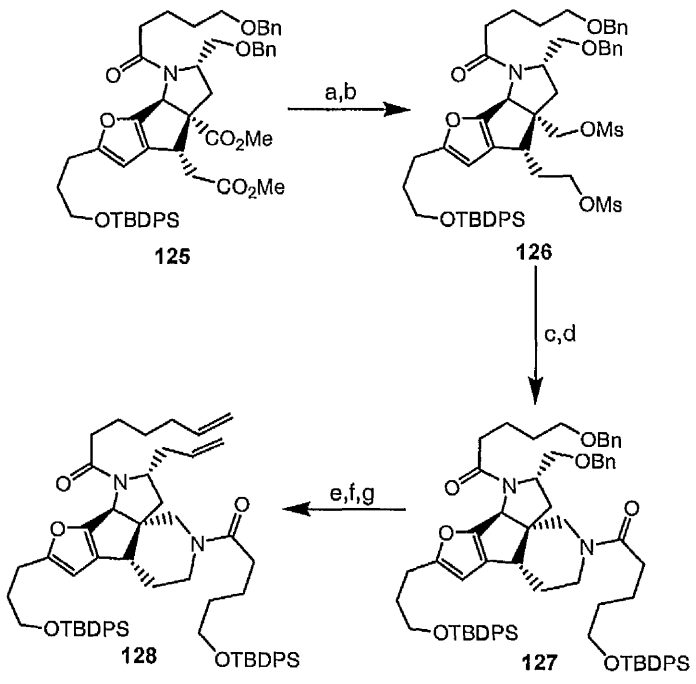
Nakadomarin A **117** contains a range of potentially useful bioactivities (anticancer, antifungal, and antibacterial). Kerr and his colleagues[35] synthesised Nakadomarin A **117** in 23 linear steps using **RCM** to overcome the molecule's unique and highly demanding structure. The total synthesis began with the cycloaddition of *p*-methyloxybenzylhydroxylamine **118**, furfural **120**, and cyclopropane **119** producing adduct **121** in 87% yield (ee >97%). Methyl ester **121** was monoreduced with DIBAL-H (87%), followed by a Horner-Emmons olefination (93%), and a Heck cyclisation producing **123** in 82% yield. Oxidative removal of the *p*-methoxybenzyl group on the oxazine nitrogen in **123** was followed by acylation with acyl chloride, $ClC(O)(CH_2)_4OBn$, and this subsequent amide was deprotected with SmI_2 to give **124**. Selective *O*-mesylation of **124** and treatment of the unstable mesylate with base gave the *trans*-2,5-pyrrolidine *via* S_N2 ring closure, giving 65% yield over the last three steps. The enolate double bond within the *trans*-2,5-pyrrolidine intermediate was reduced with nickel boride in a stereoselective fashion to yield **125** in 67% yield, **Scheme 43**.



Reagents and conditions: a) 15% $Yb(OTf)_3$, 4Å MS, 100 °C, 87%; b) DIBAL-H, DCM, -78 °C, 87%; c) $(MeO)_2P(O)CH_2CO_2Me$, *t*-BuOK, THF, RT, 93%; d) $Pd(PPh_3)_4$, Ag_2SO_4, Et_3N, DMF, reflux, 82%; e) DDQ, DCM/ H_2O (9:1 ratio), 65%; f) $ClC(O)(CH_2)_4OBn$, NEt_3, DCM, 0 °C to RT, 89%; g) SmI_2, THF, 0 °C; h) MsCl, Et_3N, DMAP, DCM, 0 °C; i) *t*-BuOK, THF, -25 °C, 65% over three steps; j) $NiCl_2.6H_2O$, $NaBH_4$, Na_2CO_3, MeOH/ THF (10:1 ratio), -40 °C, 67%.

Scheme 43

Reduction of the carbomethoxy group in **125** to the primary alcohols and exposure to methanesulfonyl chloride gave the *bis* mesylate intermediate **126** in 79% overall yield. Compound **126** was subjected to ethanolic ammonia and the resulting secondary amine acylated with 5-*tert*-butyldiphenylsilyloxy-*N*-pentanoyl chloride to produce bis-amide **127**. *Bis*-debenzylation (71%), oxidation, and Wittig olefination (30-45% yield for two steps) produced metathesis substrate **128, Scheme 44.**

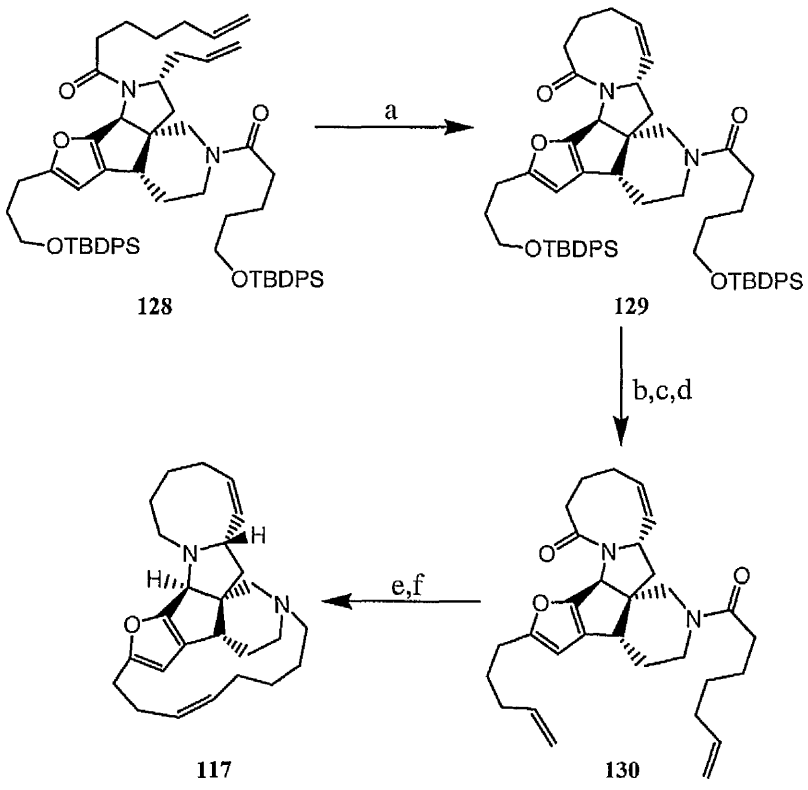


Reagents and conditions: a) $LiAlH_4$, THF, 0 °C; b) MsCl, Et_3N, DMAP, DCM, -78 °C to RT, 79% over two steps; c) NH_3, EtOH/ THF (10:1 ratio), reflux; d) $ClC(O)(CH_2)_4OTBDPS$, Et_3N, DCM, 0 °C to RT, 77% over two steps; e) BCl_3, DCM, -78 °C, 71%; f) IBX, DMSO, RT; g) *t*-BuOK, $MePPh_3Br$, THF/toluene, RT, 30-45% over two steps

Scheme 44

Azocene **129** was prepared in 84% yield by treatment of diene **128** with **90**. Removal of the silyl groups, oxidation to *bis* aldehyde (70% over two steps), and methylenation produced **130**. Treatment of **130** with **89** gave the desired *cis*-cycloalkene. All amides were globally reduced with Red-Al® to give *ent*-(+)-nakadomarin A **117** in 20% over three steps. Using **RCM** as the pivotal step twice to form two complicated rings shows the unique ability of metathesis

catalysts to help synthesis substrates which would otherwise be near-on impossible to accomplish, **Scheme 45.**

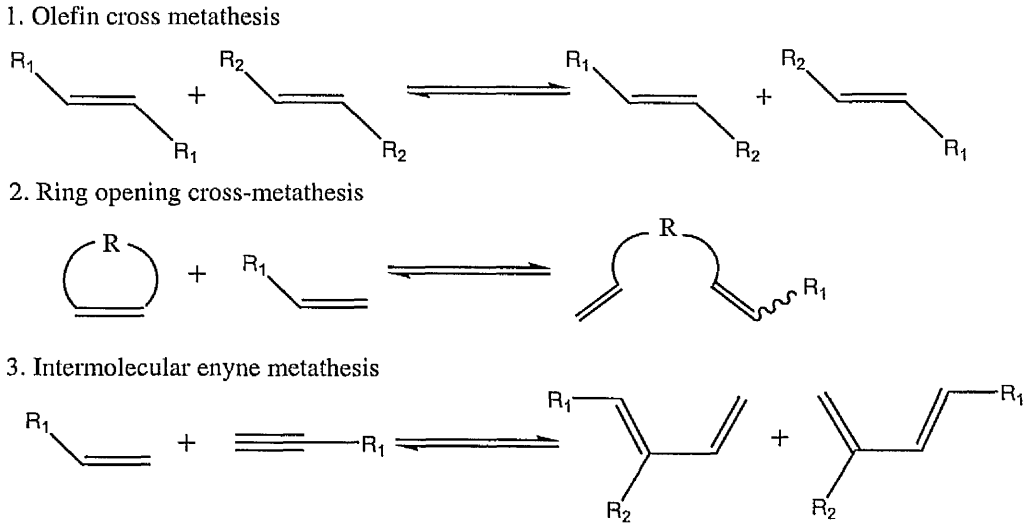


Reagents and conditions: a) **90** (20 mol%), DCM, reflux, 84%; b) MeOH, AcCl, RT; c) Dess-Martin periodinate, DCM, 0 °C to RT, 70% over two steps; d) *t*-BuOK, $MePPh_3Br$, THF/toluene, RT; e) **89** (30 mol%), DCM, reflux; f) Red-Al®, toluene, reflux, 20% over three steps.

Scheme 45

2.3 Cross metathesis

Olefin cross metathesis is the intermolecular exchange of alkylidine fragments between two olefins initiated by metal-carbene complexes. There are three variations of cross metathesis; olefin cross-metathesis, ring opening cross-metathesis and intermolecular enyne metathesis, **Scheme 46.**

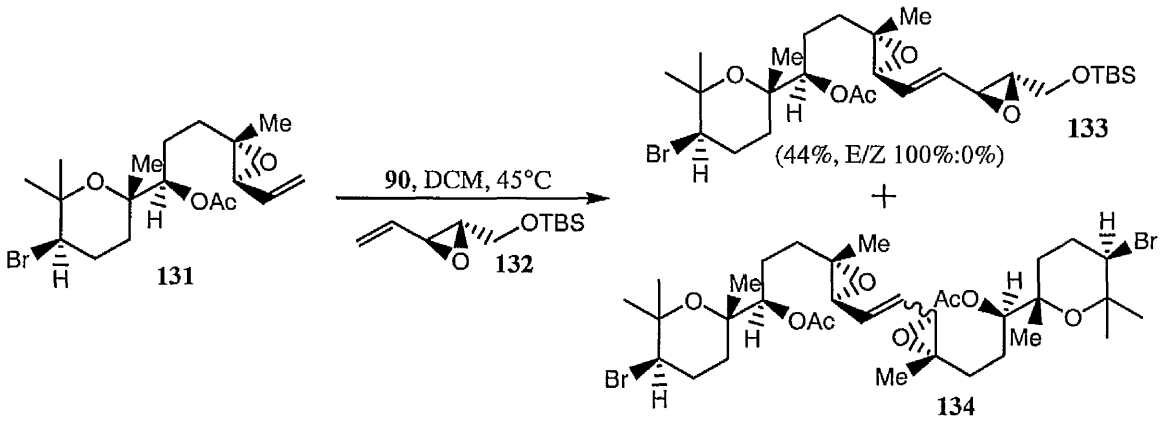


Scheme 46

Cross metathesis reactions can have the ability to further functionalise molecules in a simple and effective manner. Unfortunately, cross metathesis reactions can be highly unpredictable. Self-metathesis of substrates can be common, wasting precious starting materials and reducing yields.[36] However by placing sterically large groups and changing the electronics of the olefin by the addition of electron withdrawing substutients, there can be a significant improvement in CM selectivity and stereochemistry. Similar types of olefin have been categorised by Grubbs[37] and he has shown that certain types of olefin show different reactivity with certain metathesis catalysts. Grubbs has grouped these olefins into four types of selectivity; **Type 1** olefins participate in rapid self-metathesis with the subsequent homodimers able to reparticipate in cross-metathesis; **Type 2** shows slow self-metathesis with the homodimers being sparingly consumed in further reactions; **Type 3** olefins are not prevalent to self-metathesis formation and; **Type 4** olefins which are completely inert to cross-metathesis, however they do not deactivate the catalyst.

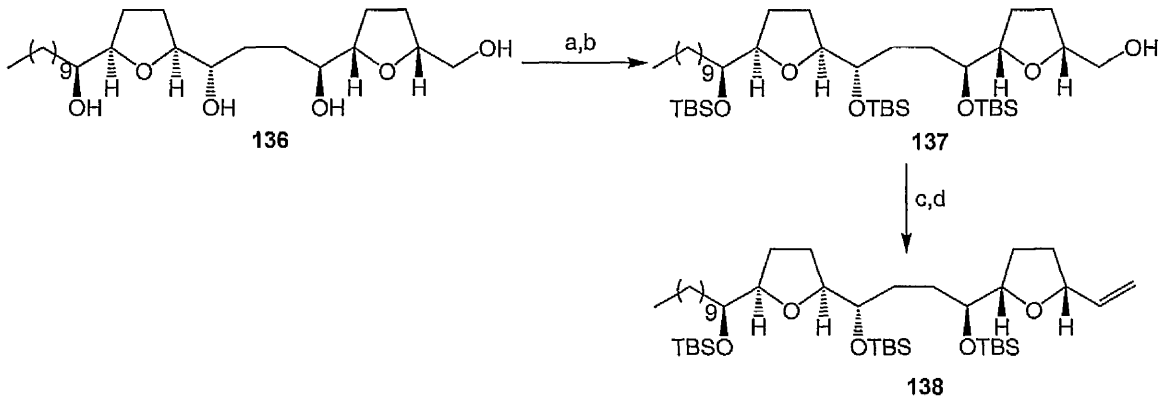
2.31 Synthesis of natural products using cross-metathesis

Recently McDonald and Wei[38] reported the synthesis of the tristetrahydropyran fragment common to the thyrsiferol natural product family using a cross-metathesis coupling. Olefin **131** was subjected to cross-metathesis using **90** with three equivalents of the chiral epoxide **132**. This gave a mixture of the coupled product **133** in 44% yield recovered along with homodimer **134** and unreacted starting material **131**. Recovered starting material was subjected to a further addition of **90** which led to an additional 20% in product, **Scheme 47**.



Scheme 47

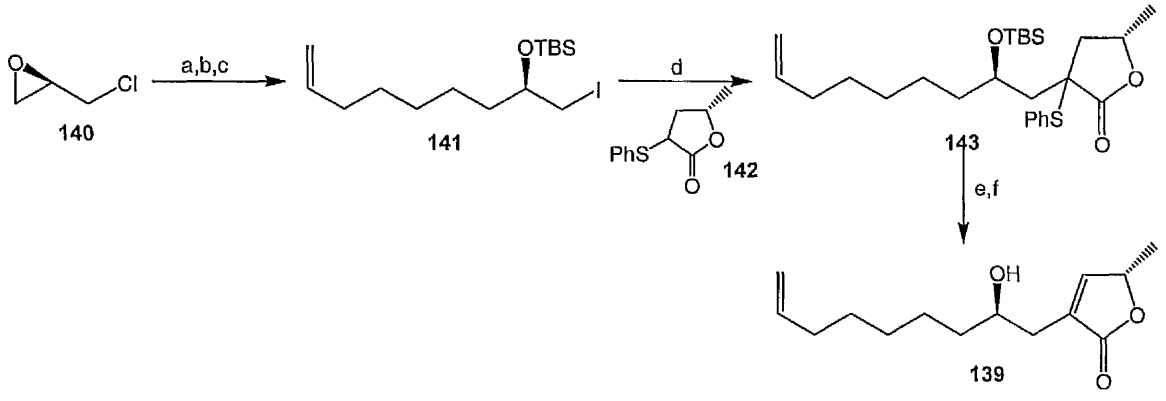
Another example of natural products being synthesised *via* cross metathesis was achieved by Donohoe *et al.*[39] and his work on (+)-*cis*-sylvaticin **135**. This target was picked due to its potent activity as an anti-tumor agent and its ability to exhibit nanomolar cytotoxicity towards human tumour cells. Compound **138** was synthesised in 4 steps from commercially available tetradecatetraene **136**, where the hydroxyl groups were globally protected with TBSOTf followed by selective deprotection of the primary alcohol with one equivalent of TBAF furnishing **137**. Oxidation of **137** with TPAP and subsequent Wittig olefination of the intermediate aldehyde gave one half of the cross metathesis coupling substrate **138, Scheme 48**.



Reagents and conditions: a) TBSOTf, lutidine, 97%; b) TBAF (1 eq), 61%; c) TPAP, NMO, 86%; d) $Ph_3P{=}CH_2$, THF, 92%

Scheme 48

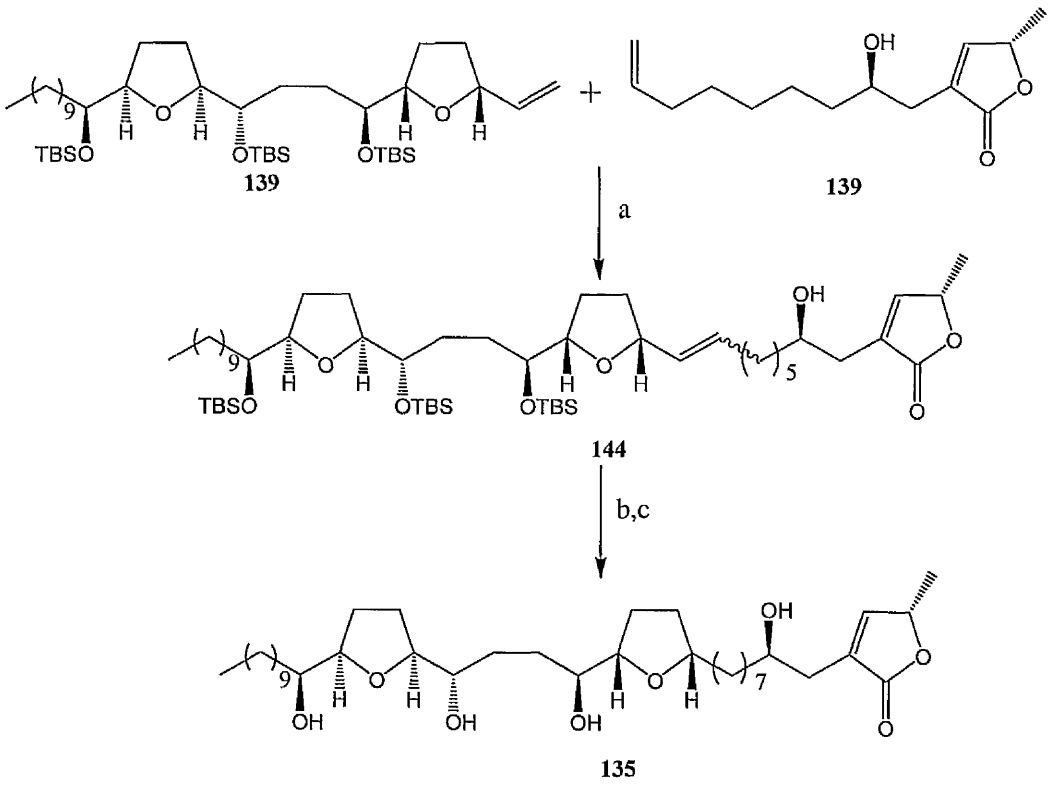
The other half of the **CM** precursor **139** was prepared initially by reacting (*R*)-epichlorohydrin **140** with Grignard reagent, $H_2C{=}CH(CH_2)_4MgBr$, followed by halogen exchange with NaI, and finally, protection of the hydroxyl group with TBSOTf to give **141** in 44% yield over three steps. Iodide **141** was coupled with **142** to produce intermediate **143**. Thermal elimination of **143** forms the butenolide, with deprotection of the TBS group producing **139** in 77% yield over two steps, **Scheme 49**.



Reagents and conditions: a) $H_2C{=}CH(CH_2)_4MgBr$, CuCN; b) NaI; c) TBSOTf, 44% over three steps; d) LDA, HMPA, **142**, 58%; e) *m*-CPBA, reflux; f) AcCl, MeOH, 77% over two steps

Scheme 49

Two components **138** and **139** were conjoined using **90**, giving **144** in 79% yield. A four fold excess of **139** was required to prevent self-metathesis of *bis*-THF **138**. This did, however, mean self-metathesis did occur with **139** with the compound being in greater excess. The isolated self-metathesised product of **139** was reused in further cross metathesis reactions with **138** producing **144** in 54% yield. The synthesis was completed by a diimide reduction of the more symmetrical alkene within **144** and acid promoted deprotection of the three TBS groups, produced *cis*-sylvaticin **135** in 69% yield over two steps, **Scheme 50**.



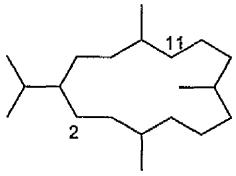
Reagents and conditions: a) **90** (10 mol%), DCM, 79%; b) $TsNHNH_2$, NaOAc, 79%; c) AcCl, MeOH, 87%.

Scheme 50

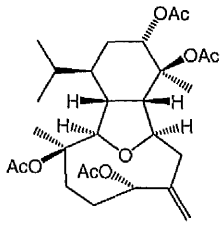
Chapter 3 The cembranoids

3.1 Introduction

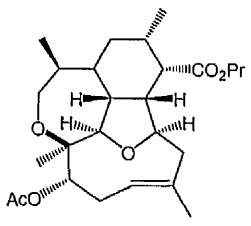
Marine invertebrates have the ability to produce an extremely extensive library of secondary metabolites, including a variety of structurally novel diterpene cyclic ethers. One family of oxa-bicyclo[6.2.1]undecane diterpenes is derived from cembrane precursors by C2-C11 bond formation and includes the cladiellins (also known as eunicellins), the briarellins, the abestinins, and the sarcodictyins,[40] **Scheme 51**. The briarellins are believed to be biosynthetically derived from the cladiellins by oxidation at C16 and oxepane formation. Conversion of the briarellins to the asbestinins is affected by a subsequent suprafacial 1,2-methyl shift from C11 to C12. Common to the asbestinins, briarellins, and cladiellins is a ring system composed of hexahydroisobenzofuran and oxacyclononane units, as well as six contiguous stereogenic centers (carbons 1, 2, 3, 9, 10, and 14). This is a rare combination and is only found in few natural products. Single-crystal X-ray diffraction,[41] CD or NMR experiments[42] indicate the six common stereogenic centers have *R* absolute configuration for cladiellin diterpenes.[43]



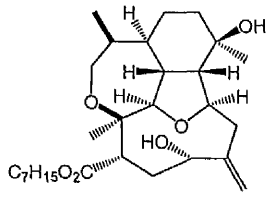
Cembrane skeleton



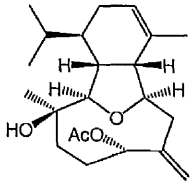
Eunicellin **145**



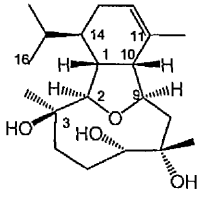
Asbestinin-1 **146**



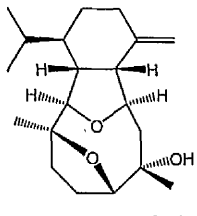
Briarellin E **147**



6-Acetoxycladiella-7,11-dien-3-ol **148**



Cladiell-11-ene-3,6,7-triol **149**



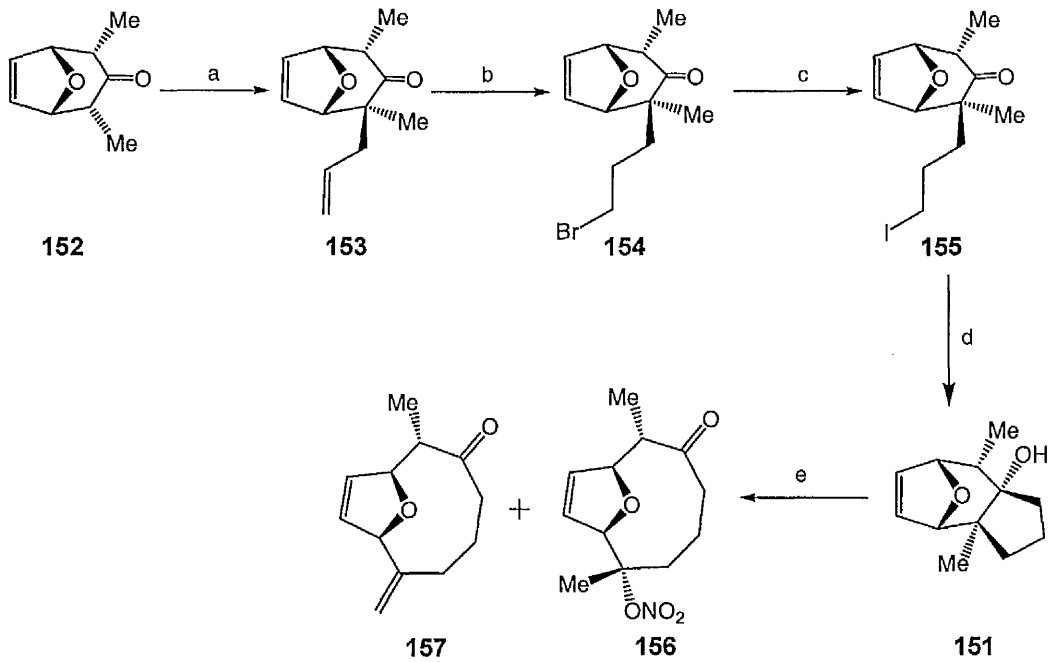
Vigulariol **150**

Scheme 51

In 1968 the first cladiellin diterpene, eunicellin **145**, was isolated from the soft coral *Eunicella stricta* off the coast of Banyuls-sur-Mer in France and structure determined by Djerassi, Kennard and co-workers.[44] Since this report, over 50 members of this subclass of diterpenes have been isolated from gorgonians and soft corals from several coelenterates found in the Mediterranean Sea and the Atlantic and Pacific Oceans. Their structural and stereochemical complexitiy along with a wide range of cytotoxic, antiproliferative and anti-inflammatory properties has prompted development of various approaches to these medium ring ethers and total syntheses of 2,11-cyclized cembranoids and sarcodictyin diterpenes.

3.2 Studies directed towards the synthesis of cladiellin diterpenes

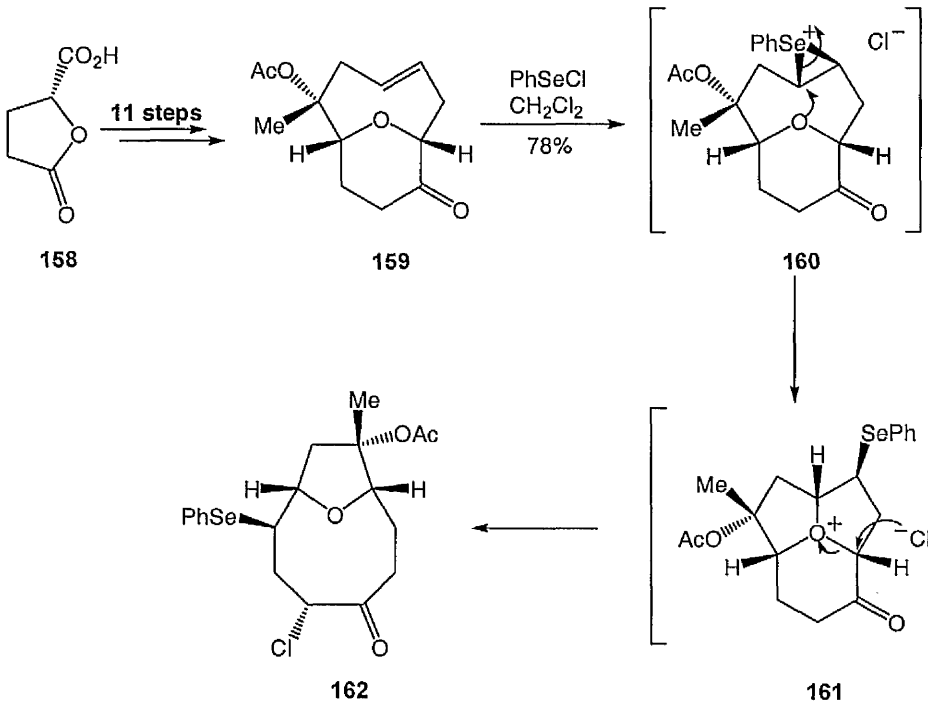
The methodology developed for the synthesis of strained medium ring ethers falls into two categories: direct cyclisation of acyclic precursors and ring enlargement achieved by fragmentation or rearrangement. An approach to the cladiellins reported in 1997 by R. Hoffmann[45] illustrates the latter of these categories and involves an oxidative scission of a tricyclic intermediate **151** using cerium(IV) ammonium nitrate (CAN) to release the bridged nine-membered ring ether skeleton. The synthesis begins with allylation of bicylic ketone **152** giving the racemic olefin **153** with complete axial diastereoselectivity. Subsequent hydrobromination of the terminal olefinic bond followed by halogen exchange *via* a Finkelstein reaction affords the iodine **155** in a straightforward manner. The tricyclic alcohol **151** is obtained in a samarium iodide induced Barbier cyclization and from this strained precursor the oxygen bridged nine-membered ring ether moiety of the eunicellin diterpenes is released in an oxidative ring fission using CAN affording the ketone **157** as the major product, **Scheme 52.**



Reagents and conditions: a) LDA, allyl bromide, THF, -20 °C, 85%; b) $HBr_{(g)}$, *hv*, hexane, 60 °C, 53%; c) NaI, $(CH_3)_2CO$, RT, 82%; d) SmI_2, THF, -78 °C to RT, 88%; e) $Ce(NH_4)_2(NO_3)_6$, CH_3CN/H_2O (1:2), 85 °C, 27% of **157**, 7% of **156** and 14% of **151**.

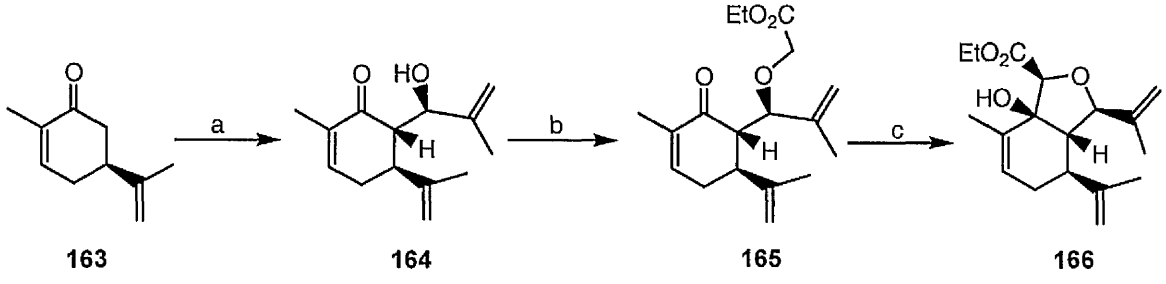
Scheme 52

A different approach to the cladiellin core has been developed by S.J. Clark during the course of a research programme directed towards the synthesis of the highly oxygenated sesquiterpene neoliacinic acid.[46] Synthesis of an oxabicyclo[5.3.1]undecane system, an olefin precursor to the acid, revealed unusual reactivity as it was found to effect a rearrangement to give the 11-oxabicyclo[6.2.1]undecane ring system **162** found in the cladiellins. The synthesis begins with the reaction of a rather unstable (*E*)-alkene **159** formed in 11 steps from the commercially available butyrolactone **158**. The instability of **159** was attributed to the transannular interaction of the bridging ether oxygen, which is forced to lie in close proximity to the alkene. Reaction of alkene **159** with phenylselenenyl chloride results in formation of a selenium ion **160**. Subsequent transannular attack of the bridging ether oxygen atom affords the tricyclic oxonium ion **161** which itself is set up for nucleophilic attack of the chloride ion α to the carbonyl group and results in the formation of the bridged bicyclic ether **162, Scheme 53**.



Scheme 53

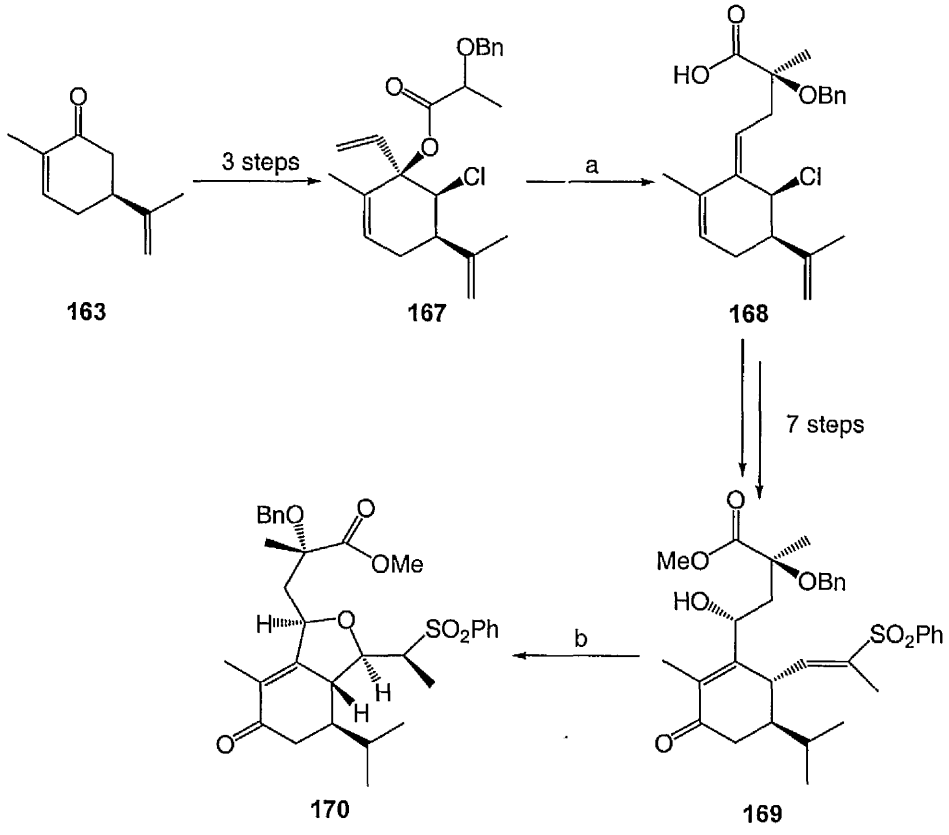
A novel cycloaldol approach to the isobenzofuran core of **145** has been developed by McIntosh,[47] arising from the chemoselective enolisation of a glycolate ester **165** yielding the aldol adduct **166** in high yield and diastereoselectivity. The cycloaldol precursor was prepared by aldol addition of (*S*)-(+)-carvone **163** and methacrolein furnishing **164** followed by etherification to the glycolate ester **165**. Subjecting **165** to KHMDS in THF causes ring formation, producing furan **166** in good yield, **Scheme 54.**



Reagents and conditions: a) LDA, THF, -78 °C, methacrolein, HOAc, 81%; b) Ag_2O, $BrCH_2CO_2Et$, 2,6-lutidine, DMF, 0 °C, 7 days, 65%; c) KHMDS, THF, -78 °C, 78%

Scheme 54

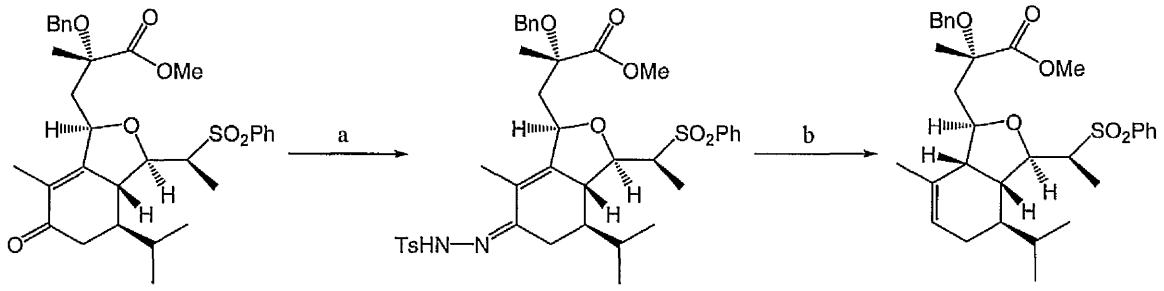
However, this elegant approach produces the isobenzofuran core without most of the required functionality to manufacture the additional 9 membered ring. A more recent publication by McIntosh[48] shows an alternative route to a more functionalized isobenzofuran core where this may be possible. The synthesis commences again from (*S*)-(+)-carvone **163** and in three steps gives an intermediate ready to participate in an Ireland- Claisen rearrangement **167**. After the eventual synthesis of **169,** this is cyclised to give the ring **170** by the addition of base, **Scheme 55**.



Reagents and conditions: a) i) KHMDS, TIPSOTf; ii) HF, MeCN, 78%; b) Potassium carbonate, MeOH, RT, 90%.

Scheme 55

The isobenzofuran core **171** is completed by selective reduction of tosylhydrazone **173** with catecholborane, followed by an *in-situ* diazene rearrangement to give **171, Scheme 56**.



172 **173** **171**

Reagents and conditions: a) NH_2NHTs, EtOH, reflux; b) i) catecholborane, $CHCl_3$, 0 °C to RT; ii) NaOAc, 0 °C to reflux, 77% over three steps.

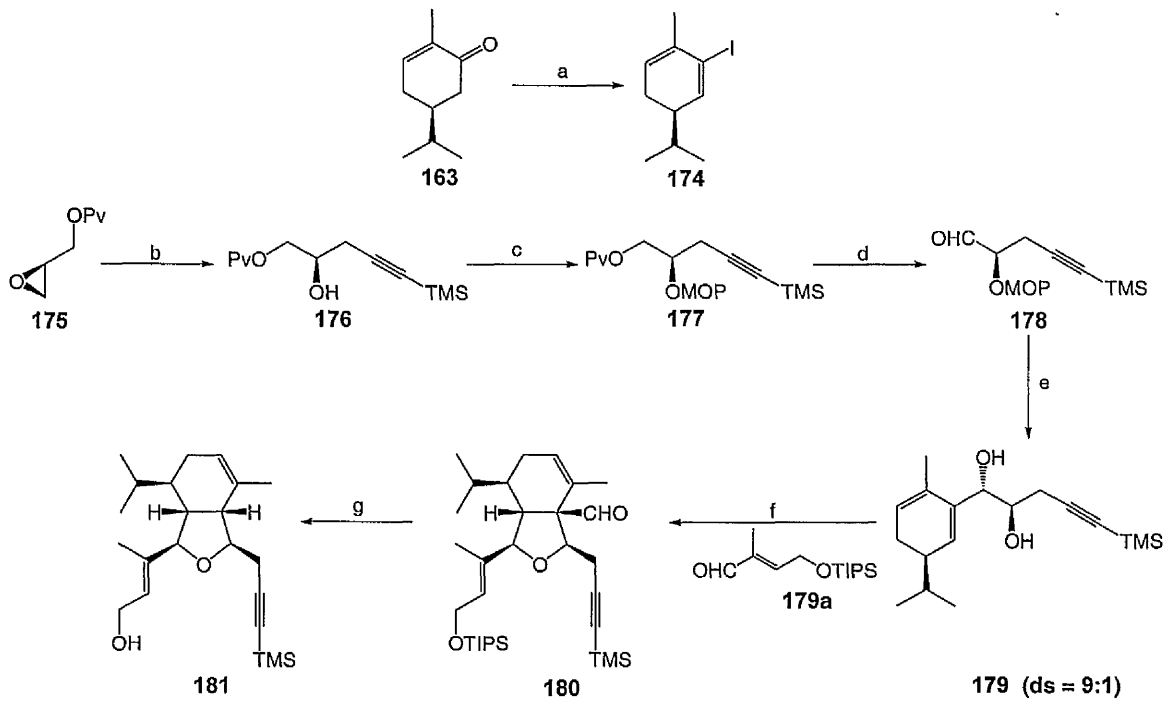
Scheme 56

3.3 Total syntheses of cladiellins

3.31 First synthesis of a cladiellin diterpene

The enantioselective synthesis of 6-acetoxycladiell-7(16),11-dien-3-ol (deacetoxyalcyonin acetate **148**), published in 1995 by MacMillan and Overman,[49] details the first total synthesis of a cladiellin diterpene. The defining reaction of this synthesis is a stereoselective Prins-pinacol condensation-rearrangement assembling the 2-oxabicyclo-[4.3.0]non-4-ene core. Synthesis of the bicyclic core of **148** is summarized in **Scheme 57**. The (*R*)-dienyl iodide **174** was first accessed from (*S*)-dihydrocarvone **163**. Regioselective opening of (*S*)-glycidal pivalate **175** gave alcohol **176**, which was protected to give the 2-methoxypropyl (MOP) ether **177** and treated with excess DIBAL-H to remove the pivalate moiety, followed by oxidation with TPAP-NMO affording the aldehyde **178**. Treatment of **178** with the dienyllithium species generated from **174** (*t*-BuLi, THF, -78 °C), followed by cleavage of the MOP group affords the substrate **179** required for a Prins-pinacol rearrangement in 64% yield as a 9:1 mixture of *anti* and *syn* stereoisomers. Exposure of diol **179** and an excess of enal **179a** to $BF_3.Et_2O$ at -55 to -20 °C in dichloromethane triggers the Prins-pinacol cyclisation and produces

hexahydroisobenzofuran **180** as a single stereoisomer in 79% yield. Cleavage of the TIPS ether under acidic conditions followed by stereoselective photolytic deformylation provided **181** in 72% yield.

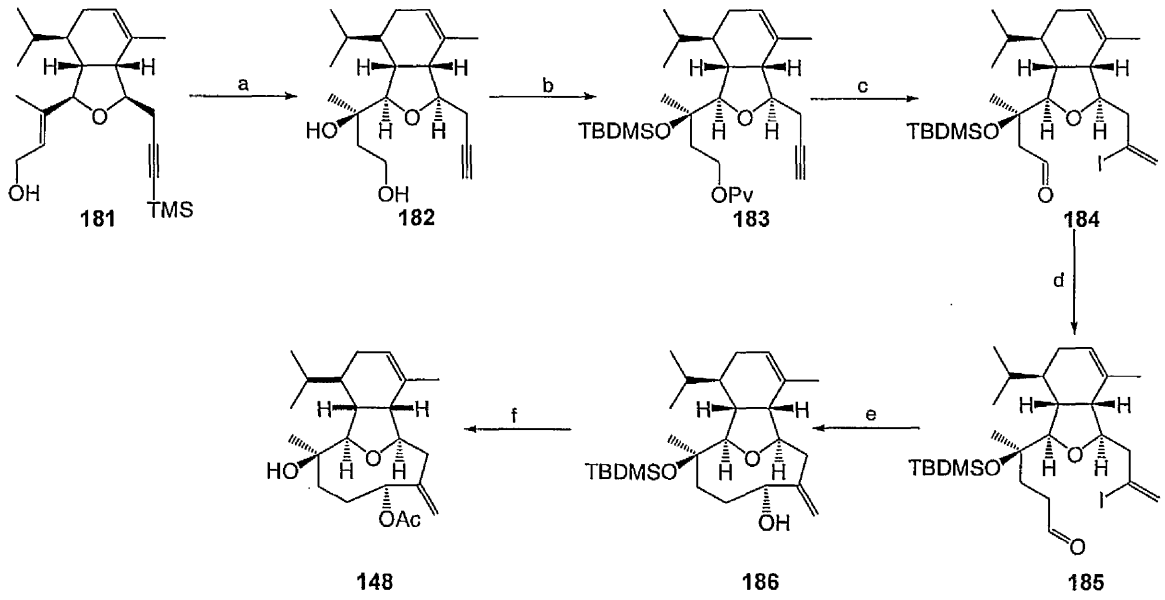


Reagents and conditions: a) i) LDA, $PhNTf_2$, -78 °C; ii) Me_6Sn_2, $Pd(PPh_3)_4$ (iii) NIS, 0 °C, 78% over three steps; b) Lithium (trimethylsilyl)acetylide, $BF_3.Et_2O$, -78 °C, 61%; c) $Me(MeO)C{=}CH_2$, PPTS, 97%; d) i) DIBAL-H, DCM; ii) TPAP, NMO, 75% yield over two steps; e) i) **174**, *t*-BuLi, THF, -78 °C; ii) PPTS, MeOH, 64% over two steps; f) **179a**, $BF_3.Et_2O$, DCM, -55 to -20 °C, 79%; f) i) AcOH, H_2O, THF; ii) *hv*, hexanes, 72% over two steps

Scheme 57

The 1,3-diol **182** is obtained in 79% yield from epoxidation followed by RedAl® reduction of the allylic alcohol **181** with cleavage of the TMS group with aqueous NaOH. Formation of the oxonane subunit proceeds with a sequential protection of **182** with pivaloyl chloride and the silyl triflate affording the *bis*-protected diol **183**. Selective iodoboration of **183** followed by removal of the pivaloyl protecting group with DIBAL-H allows oxidation of the resulting alcohol to give aldehyde **184** in 93% yield. Homologation of the aldehyde gave the required

substrate for ring closure **185.** The tricyclic ether **186** was cyclised following procedures pioneered by Nozaki and Kishi[50] using $NiCl_2$-$CrCl_2$ in DMSO. Acetylation of **186** followed by removal of the silyl protecting group by treatment with *n*-Bu_4NF giving cladiellin **148** in 88% yield, **Scheme 58.**



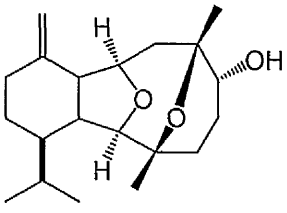
Reagents and conditions: a) Sharpless asymmetric epoxidation, 82%; b) RedAl®, H_2O, THF, 66%; c) PivCl, pyridine, 91%; d) TBDMSOTf, lutidine, 87%; e) i) I-9 BBN, AcOH; ii) *i*-Bu_2AlH; iii) TPAP, NMO, DCM, 93% over three steps; f) i) Ph_3P=CHOMe; ii) TfOH, *i*-PrOH, 77% over 2 steps; g) $NiCl_2$-$CrCl_2$, DMSO-Me_2S, 65%; h) i) Ac_2O, DMAP; ii) *n*-Bu_4NF, THF, 88% over two steps

Scheme 58

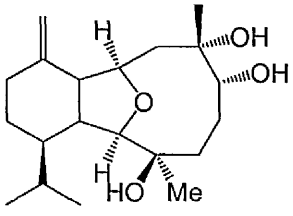
3.32 Other synthetic studies of cladiellins

Since the first synthesis of a cladiellin based structure by MacMillan and Overman in 1995, there have been several research groups who have synthesised cladiell-11-ene-3,6,7-triol,[51] the sclerophytins A and B,[52] the briarellins E and F,[53] deacetoxyalcyonin acetate,[54] 11-acetoxy-4-deoxyasbestinin D,[55] orphirin B [56] and astrogorgin [57] since. Being too many to mention in this introduction, I have decided to mention some of the more inventive and synthetically elegant total synthesis.

In 1988, Sharma and Alam[58] reported the isolation from *Sclerophytum capitalis* and charaterization of sclerophytin A (putative structure **187**). Structural ambiguities and configurational uncertainties stemming from NMR spectroscopic measurements and MM3 calculations prompted Paquette to assemble a potentially generic protocol for accessing these marine metabolites.[59] Paquette and co-workers found that the spectral properties and polarity of the synthetic product **187** exhibit substantive differences and provide convincing evidence for the revised structure cladiell-11(17)-ene-3,6,7-triol **149, Scheme 59**.



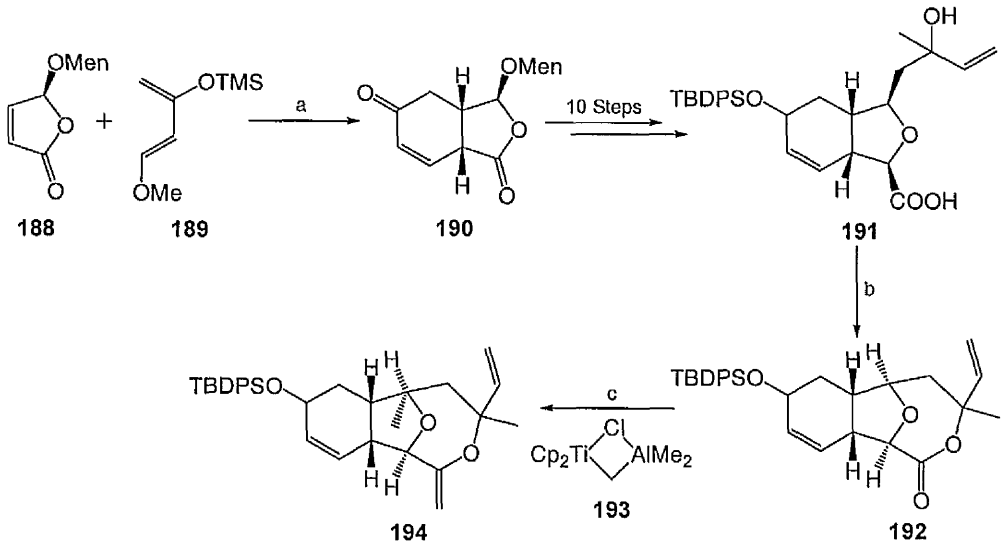
187



149

Scheme 59

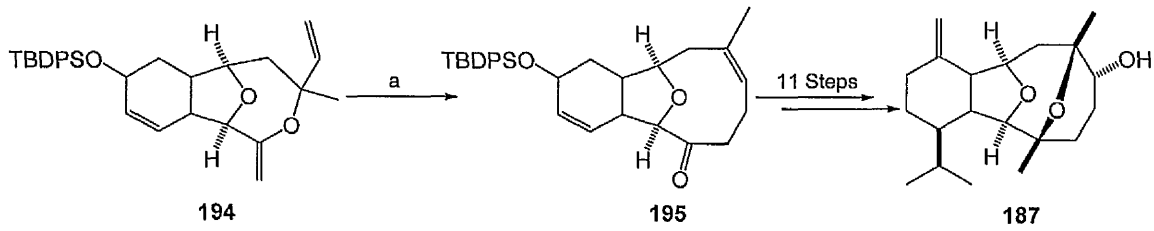
The enantioselective synthesis of **187** began with the unsaturated lactone **188** which was subjected to heating in the presence of the Danishefsky diene **189** followed by transformation into the cyclohexenone **190** by Vorndam's protocol. Exposure of **191** to the Yonemitsu modification of the Yamaguchi macrocyclisation gave rise to the lactone **192.** Tebbe methylenation of the lactone afforded **194** in 67% yield over two steps, **Scheme 60.**



Reagents and conditions: a) i) toluene, reflux; ii) TMSOTf, lutidine, 85%; b) $Cl_3C_6H_2COCl$, Et_3N, DMAP; c) **193,** 67% over two steps.

Scheme 60

Enol ether **194** was subjected to thermal activation in the presence of $NaBF_4$, to promote the sigmatropic shift, yielding **195** in 80% yield. The key step in the construction of the core found in **187** proved to be oxymercuration and subsequent oxidative demercuration with sodium borohydride and oxygen affording the secondary carbinol structure, **Scheme 61**.

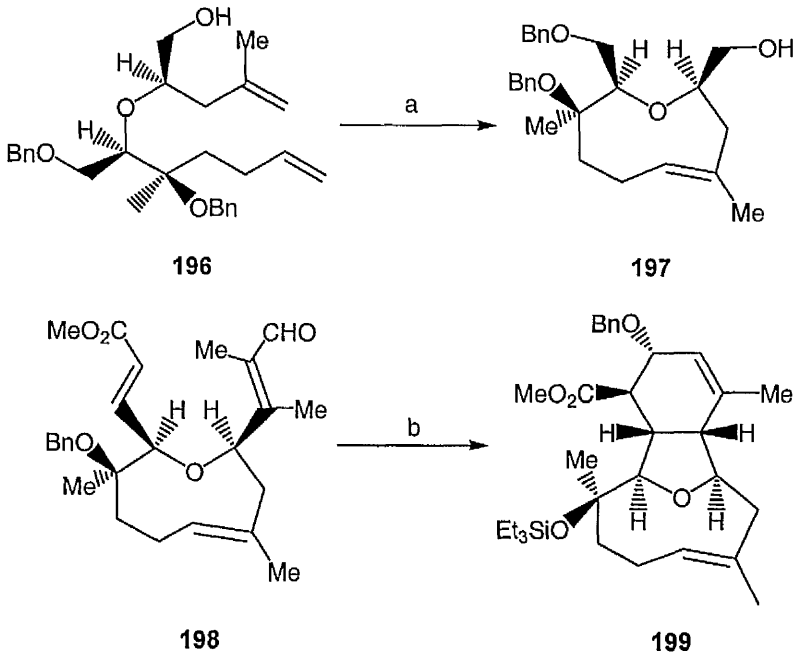


Reagents and conditions: a) $NaBF_4$, toluene, heat, 80%.

Scheme 61

An approach to **150** by Crimmins[60] and co-workers employed the Grubbs olefin metathesis catalyst to mediate the ring closure of diene **196** and an intramolecular Diels-Alder reaction as the key steps in the synthesis of the naturally occurring 6,7-*Z* isomer of ophirin. The metathesis substrate available in 10 linear steps from (*S*)-benzylglycidyl ether, was treated with **90** to afford the oxononene **197** in 80% yield. A further 10 steps from the nine-membered

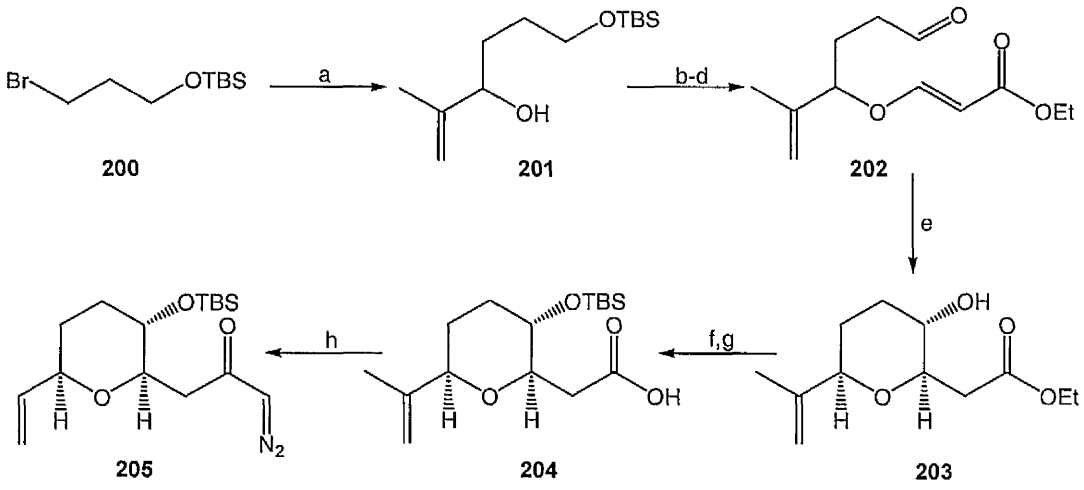
ring afforded the aldehyde **198** which, following Wittig olefination, underwent cyclisation providing a single *exo* Diels-Alder adduct **199**, as depicted in **Scheme 62.**



Reagents and conditions: a) **90**, C_6H_6, 80 °C, 80%; b) $Ph_3P^+CH_2OBn\ Cl^-$, *t*-BuOK, THF, -78 °C to RT, 80%.

Scheme 62

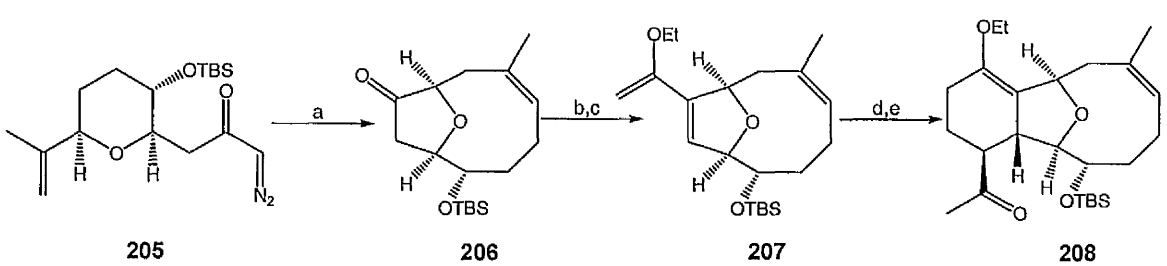
As previously mentioned in **Section 3.1**, Clark and his group had designed a novel synthetic method into producing oxabicyclo[5.3.1]undecane systems which could be used towards the synthesis of sesquiterpene neoliacinic acids.[46] However they changed strategy and successfully synthesised (±)-vigulariol **150** in twenty steps with an overall yield of 4%.[61] The synthesis commenced with a Grignard coupling of **200** with methacrolein to produce allylic alcohol **201**. Alkylation of the alcohol **201** with ethyl propiolate to give a vinylogous carbonate, followed by the removal of the TBS group with TBAF, and oxidation of the resulting alcohol produced the aldehyde **202**. Reductive cyclisation was accomplished by exposure of **202** with samarium iodide in the presence of methanol to furnish the tetrahydropyranol **203**. The secondary alcohol was protected as a TBS ether and cleavage of the ethyl ester produced carboxylic acid **204** in 82% yield. Treating acid **204** with *i*-BuO_2CCl formed the anhydride and subsequent treatment with excess diazomethane gave intermediate **205**, **Scheme 63**.



Reagents and conditions: a) i) Mg, THF, reflux; ii) methacrolein, RT, 90%; b) $HCCCO_2Et$, *N*-methylmorpholine, DCM, RT, 91%; c) *n*-Bu_4NF, THF, RT, 91%; d) i) $(COCl)_2$, Me_2SO, DCM, -78 °C; ii) Et_3N, RT, 83%; e) SmI_2, MeOH, THF, RT, 76%; f) TBSCl, imidazole, Me_2NCHO, RT, 91%; g) $LiOH_{(aq)}$, MeOH, RT, 82%; h) i) *i*-BuO_2CCl, Et_3N, RT; ii) CH_2N_2, Et_2O, 0 °C to RT, 81%.

Scheme 63

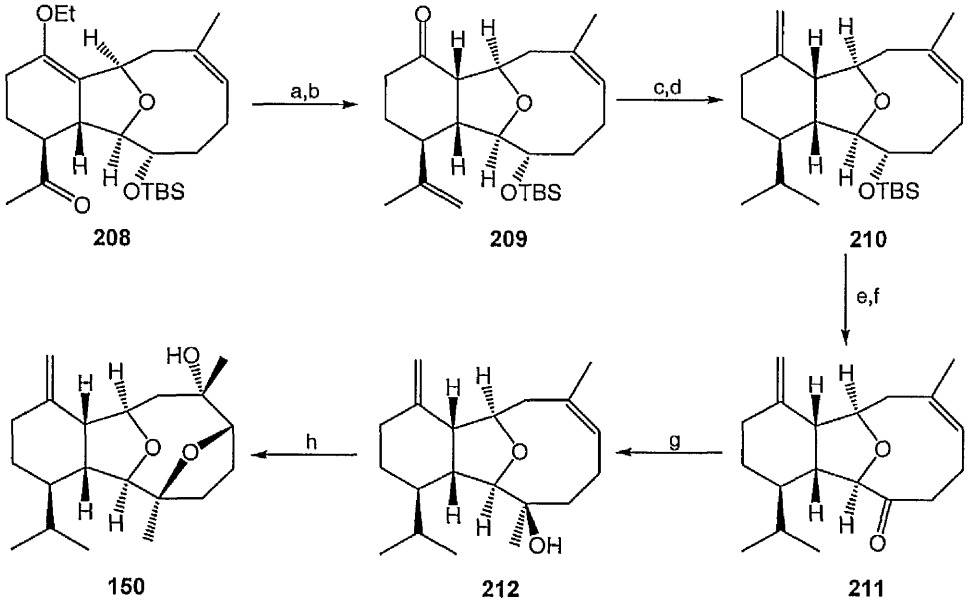
Continuing the synthesis, **205** was treated with copper (II) hexafluoroacetylacetonate producing an electrophilic copper carbenoid facilitating tandem formation and [2,3] sigmatropic rearrangement delivering **206** as a 5:1 mixture of *Z*:*E* isomers. The unwanted *E* isomer was converted to the *Z* isomer by treatment with AIBN and ethanethiol in benzene at reflux. Ketone **206** was converted to an enol triflate by regioselective deprotonation and trapping of the enolate with *N*-phenyltrifluoromethanesulfonimide, which was then subjected to Stille cross-coupling with tributyl(1-ethoxyvinyl)tin to produce **207**. Diene **207** was subjected to Diels-Alder cycloaddition with methyl vinyl ketone in toluene at reflux producing the tri-cyclic structure **208, Scheme 64.**



Reagents and conditions: a) $Cu(CF_3COCHCOCF_3)_2$ (5 mol%), DCM, reflux, 96% 5:1 *Z*/*E*; b) AIBN, EtSH, C_6H_6, reflux, 56%; c) $PhN(O_2SCF_3)_2$, $NaN(SiMe_3)_2$, THF, -78°C; d) $CH_2C(OEt)SnBu_3$, LiCl, $Pd(PPh_3)_4$, THF, reflux; e) methyl vinyl ketone, toluene, reflux, 67% over three steps; f) K_2CO_3, MeOH, RT, 87%

Scheme 64

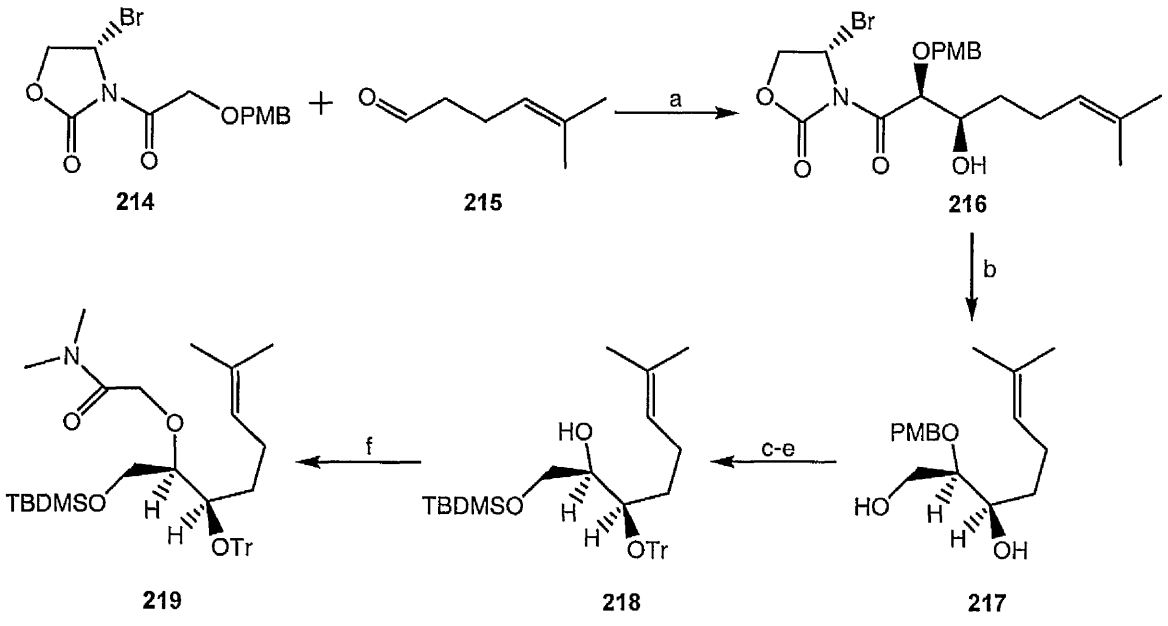
Wittig olefination of **208** followed by acid hydrolysis of the enol ether gave ketone **209**, Regioselective hydrogenation of the exocyclic alkene of the diene **209** and subsequent ketone methylation furnished the diene **210**. Deprotection and oxidation of the secondary alcohol gave ketone **211**, which was then treated with methylmagnesium chloride to produce tertiary alcohol **212**. Alkene **212** was treated with freshly purified *m*-CPBA to form the final ring system completing the synthesis of (±)-vigulariol **150**, **Scheme 65**.



Reagents and conditions: a) Ph_3PCH_2Br, *t*-BuOK, THF, RT, 85%; b) 5% $HCl_{(aq)}$, THF, RT, 86%; c) H_2, PtO_2, RT, 81%; d) Ph_3PCH_2, toluene, reflux, 98%; e) *n*-Bu_4NF, THF, RT, 84%; f) Dess-Martin periodinane, pyridine, DCM, RT; g) MeMgCl, THF, 0 °C, 89% over two steps; h) *m*-CPBA, DCM, 0 °C, 69%.

Scheme 65

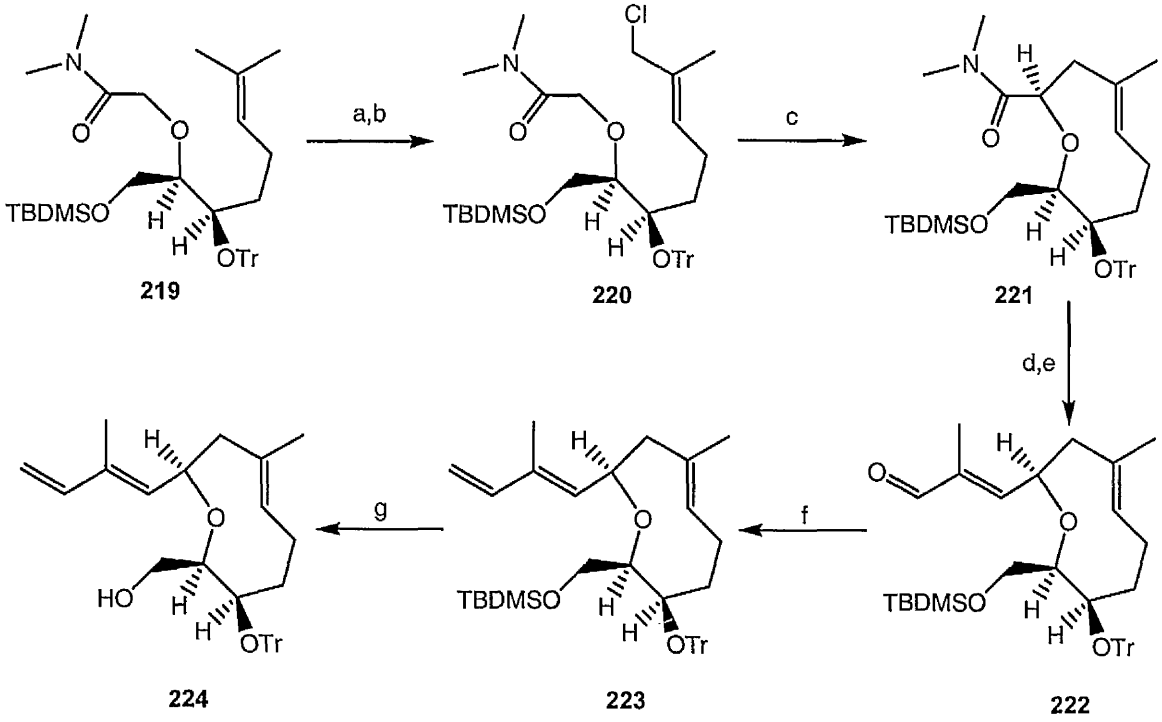
Recently Kim and his co-workers[62] have produced a general strategy for the synthesis of cladiellin diterpenes, in particular (-)-cladiella-6,11-dien-3-ol **213**. The main synthetic transformation involves an intramolecular Diels Alder cyclisation to produce the key oxatricycle motive of cladiellin diterpene. The synthesis starts with the readily available glycolate oxazolidinone **214**, forming a dibutylboron enolate with the addition of *n*-Bu_2BOTf. Reaction of this reactive intermediate with **215** gave the corresponding *syn*-aldol product adduct **216**. Reductive cleavage of the chiral auxiliary in **216** and subsequent protection of the primary and secondary alcohol functionality in the resulting diol **217** with TBDPSCl and trityl bromide produced the protected triol in 76% overall yield for the three steps. Oxidative cleavage of the PMB group using the Yonemitsu method and *O*-alkylation of the resulting alcohol **218** with *N*, *N*-dimethyl α-chloroaetamide affording α-alkoxyamide **219** giving 77% yield over two steps, **Scheme 66.**



Reagents and conditions: a) *n*-Bu_2BOTf, Et_3N, DCM, -78 to 0 °C, 2 hrs, 75% (ds 98:2); b) $NaBH_4$, THF/H_2O (3:1 ratio), RT, 2 hrs, 89%; c) TBDPSCl, imidazole, 0 °C, 30 mins, 92%; d) trityl bromide, DMAP, pyridine, 100 °C, 6 hrs, 93%; e) DDQ, DCM/ pH 8.0 buffer (9:1 ratio), 0 °C, 1 hr, 88%; f) $ClCH_2CONMe_2$, NaH, THF, 0 °C to RT, 3 hrs, 88%

Scheme 66

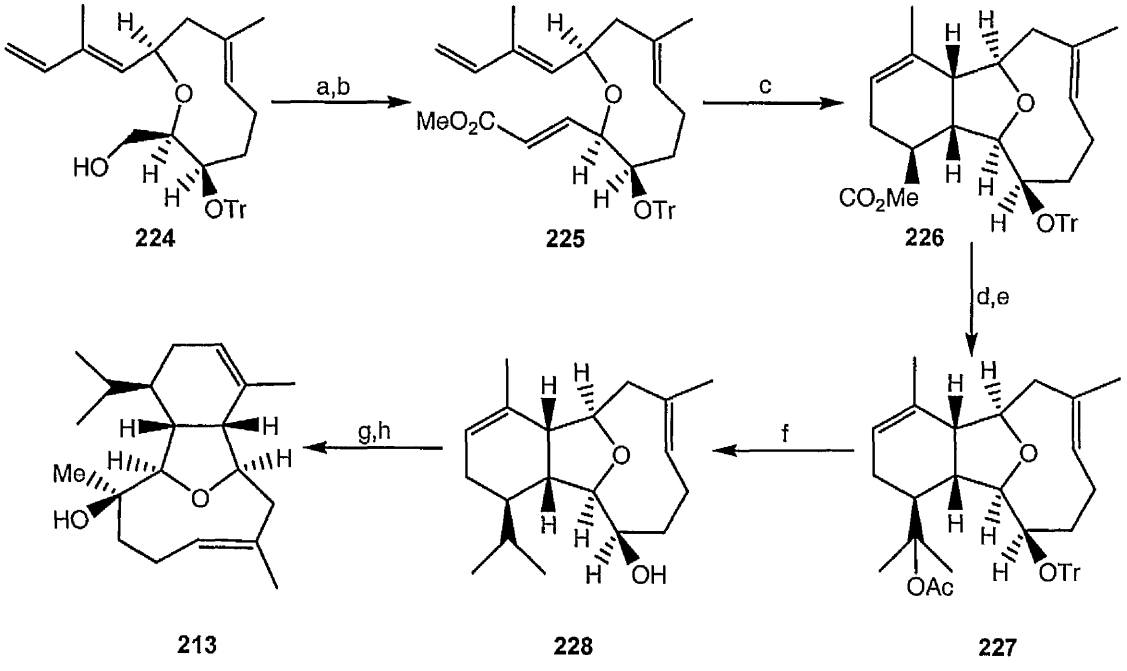
The synthesis continued with the stereoselective allylic oxidation of gem-dimethyl alkene **219** with SeO_2 and chlorination of the resulting (*E*)-allylic alcohol *via* the Hooz protocol produced (*E*)-allylic chloride **220,** yielding 80% over two steps. Treatment of **220** with LiHMDS in THF at 45 °C for 1 hour gave **221** as a single diastereoisomer in 92% yield. Partial reduction of the amide function in **221** with DIBAL-H, followed by the Corey olefination protocol on the resulting aldehyde with α-litho TMS-aldimine, produced α, β-unsaturated aldehyde **222** in 68% yield over the two steps. Compound **222** was subjected to Wittig methylenation to produce (*E*)-1,3-diene **223** in 97% yield, with the deprotection of the TBDMS group using TBAF giving adduct **224** in 93% yield, **Scheme 67**.



Reagents and conditions: a) SeO_2, pyridine, EtOH, 80 °C, 6 hrs, then $NaBH_4$, EtOH, 0 °C, 30 mins, 76%; b) Ph_3P, CCl_4, pyridine, reflux, 2 hrs, 93%; c) LiHMDS, THF, 45 °C, 1 hr, 92%; d) DIBAL-H/ *n*-BuLi (1:1), THF, 0 °C to RT, 30 mins; e) $CH_3CH(TMS)C{=}N$-*t*-Bu, *n*-BuLi, THF, -78 °C to 0 °C, 1 hr, 68% over two steps,(*E*/*Z*= 5:1 ratio); f) $Ph_3P{=}CH_2$, THF, -78 °C to RT, 2 hrs, 97%; g) TBAF, THF/DMF (2:1), RT, 16 hrs, 93%.

Scheme 67

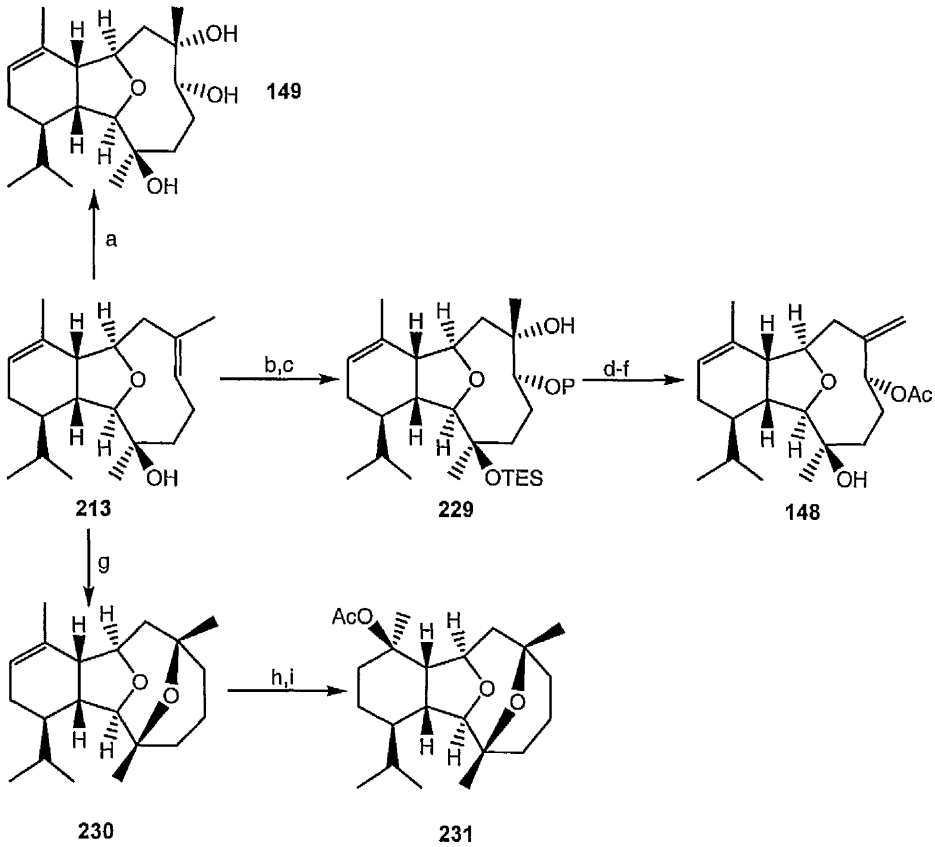
Subsequent oxidation on **224** using Dess-Martin reagent and Wittig reaction on the resulting aldehyde gave the required intramolecular Diels-Alder precursor **225** in 78% yield over the two steps. The Diels-Alder reaction on **225** was initiated with the addition of BHT and allowed to reflux in xylene, producing the key oxatricycle **226** with the correct stereochemistry. With the main oxatricycle **226** synthesised, the final stages of the production of (-)-cladiella-6,11-dien-3-ol **213** are within sight. Ester **226**, was converted to the tertiary acetate **227** by the addition of MeLi in the presence of $CeCl_3$, followed by the acetylation of the resulting tertiary alcohol. Dissolving metal reduction of tertiary acetate **227** proceeded by chemoselective deoxygenation of the 3° ester and deprotection of the trityl ether gave secondary alcohol **228** in 55% yield over three steps. Finally, Dess-Martin oxidation of alcohol **228** and its subsequent treatment of the unstable ketone with MeLi in the presence of $NaBF_4$, using the Paquette procedure, gives (-)-cladiella-6,11-dien-3-ol **213, Scheme 68**.



Reagents and conditions: a) Dess-Martin periodinane, $NaHCO_3$, DCM, RT, 30 mins; b)$Ph_3P{=}CHCO_2Me$, DCM, RT, 1 hr, 78% over two steps; c) BHT, xylene, reflux, 1 hr, 85%; d) MeLi, $CeCl_3$, THF, -78 °C, 30 mins, 89%; e) Ac_2O, DMAP, Et_3N, DCM, RT, 48 hrs; f) K, 18-crown-6, *t*-$BuNH_2$, THF, 1 hr, 62% for two steps; g) Dess-Martin periodinane, pyridine, DCM, RT, 30 mins; h) MeLi, $NaBF_4$, THF, -78 °C, 30 mins, 82% over two steps.

Scheme 68

It has also been shown by Kim and his co-workers[62] that (-)-cladiella-6,11-dien-3-ol **213** can act as a common intermediate for highly stereo-, region-, and chemoselective synthesis of other members of cladiellins such as (+)-polyanthellin A **231**, (-)-clandiell-11-ene-3,6,7-triol **149**, and (-)-deacetoxyalcyonin acetate **148**. These synthesis are possible due to a few reasons, one being that the trisubstituted (6*E*)-oxonene double bond in **213** is more susceptible to electrophilic attack than the cyclohexene C(11) double bond. This is possibly due to a transannular interaction with the ring oxygen atom and the ensuing ring strain.[62] Another significant chemoselective property of **213** is that (6*E*)-oxonene moiety of the oxytricyclic skeleton is conformationally more rigid compared to that of the corresponding (*Z*)-oxonene, which should render peripheral attack in a highly stereoselective manner, **Scheme 69**.



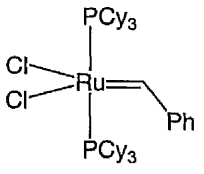
Reagents and conditions: a) OsO_4, NMO, THF/ H_2O (3:1 ratio), 0 °C, 94%; b) TESOTf, DCM, RT, 30 mins, 97%; c) OsO_4, NMO, THF/ H_2O (3:1 ratio), 0 °C, 94%; d) Ac_2O, DMAP, Et_3N, DCM, 1 hr, 97%; e) Burgess salt, toluene, 70 °C, 30 mins; f) TBAF, THF, 50 °C, 3 hrs, 92% over two steps; g) $BF_3.Et_2O$, EtOH, RT, 30 mins, 84%; h) $Hg(OAc)_2$, THF/ H_2O, 1 hr, then Et_3B, $NaBH_4$, 62%; i) Ac_2O, DMAP, Et_3N, DCM, 24 hrs, 78%

Scheme 69

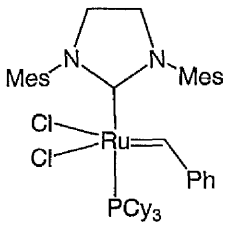
Results and Discussion

Chapter 4. Molecular Queuing

Investigation within the Quayle group into the development of **ATRC** reactions using the Grubbs catalysts, **89** and **90, Scheme 70**, have shown that they can initiate two different carbon-carbon bond forming processes, namely metathesis and **ATRC** reactions. There is a large mechanistic difference between these two transformations, as our investigations have shown, with the catalyst going through differing pathways for both cyclisations.



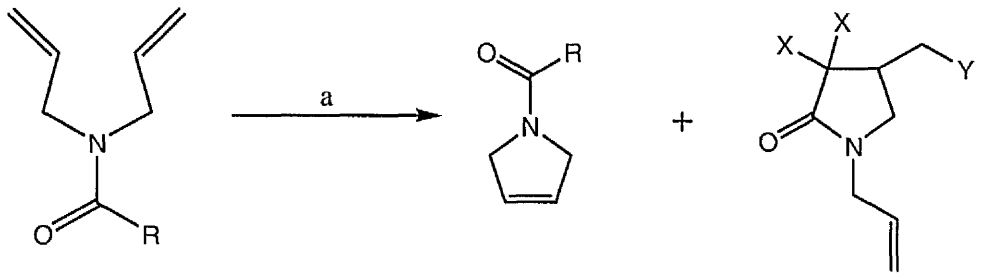
89



90

Scheme 70

This interest began by a chance observation in a publication by Snapper.[63] The Quayle group's main research at the time centred on the optimisation of copper catalysts for the use in **ATRC** and **ATRP** reactions. Snapper *et al.* had noted a side reaction with **89,** which resulted in **ATRC** rather than the obligatory metathesis. Wishing to repeat Snapper's observation however on our own substrates, **232-234** were subjected to **89** (5 mol%) in degassed toluene and refluxed for 3 hours, giving predominantly **235, 236,** and **237** in excellent yield. Interestingly there was also production of the **ATRC** product in trace amounts of **238**, **239** and **240** (<1%), **Scheme 71**.[64]



232 R=CCl_3
233 R=CF_2Br
234 R=CF_2Cl

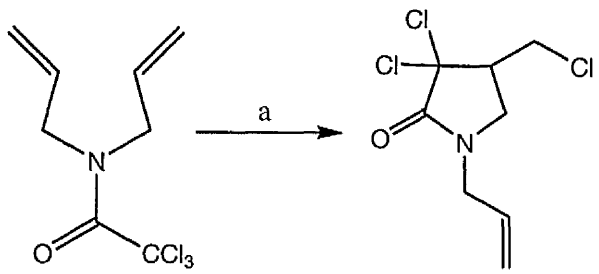
235 R=CCl_3 (98%)
236 R=CF_2Br (88%)
237 R=CF_2Cl (89%)

238 X=Y=Cl (<1%)
239 X=F; Y=Br (<1%)
240 X=F; Y=Cl (<1%)

Reagents and conditions: a) **89** (5 mol%), toluene, 3 hrs, reflux.

Scheme 71

In order to demonstrate that **232** has the capability of undergoing **ATRC** as well as metathesis,a blank reaction was carried out using the tried and tested Cu(I)Cl/ dHBipy ligand system. **ATRC** of **232** gave product **238** in 85% isolated yield after column chromatography, **Scheme 72.**



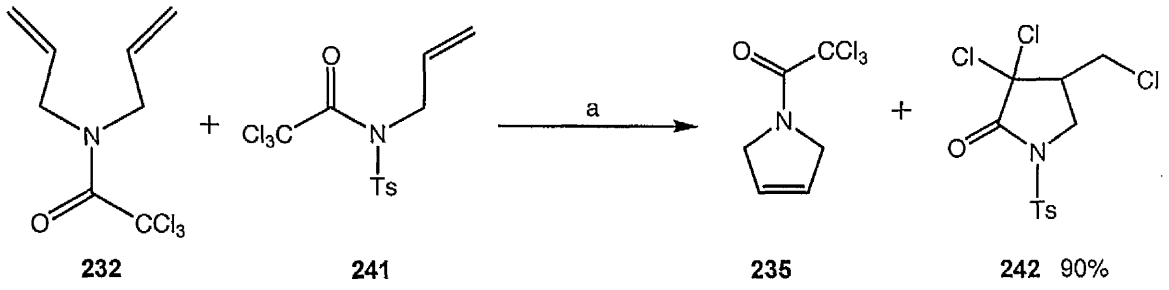
232 **238**

Reagents and conditions: a) Cu(I)Cl (5 mol%), dHBipy (20 mol%), DCE, 3 hrs, reflux, 85%.

Scheme 72

The observation described in **Scheme 71** tempted us to investigate the possibility that the Grubbs' catalysts, **89** and **90**, could promote molecular queuing reactions, where one reaction is followed by the other in the same pot. Following this, our attention turned to attempting a mixed inter/ intramolecular competition experiment in which a 1:1 mixture of amide **232** and tosylamide **241** was subjected to **89** (5 mol%) in toluene and refluxed for 3 hours, from which the pyrroline **235** and γ-lactam **242** were isolated in excellent yields after column

chromatography (93% and 90% respectively). There was no presence of **238** seen in the crude ^{1}H-NMR. These results indicate that the metathesis reaction proceeds at a much faster rate (ca. 100 times faster) than the **ATRC** reaction and that the catalyst affecting the metathesis remains active as an **ATRC** catalyst, **Scheme 73.**

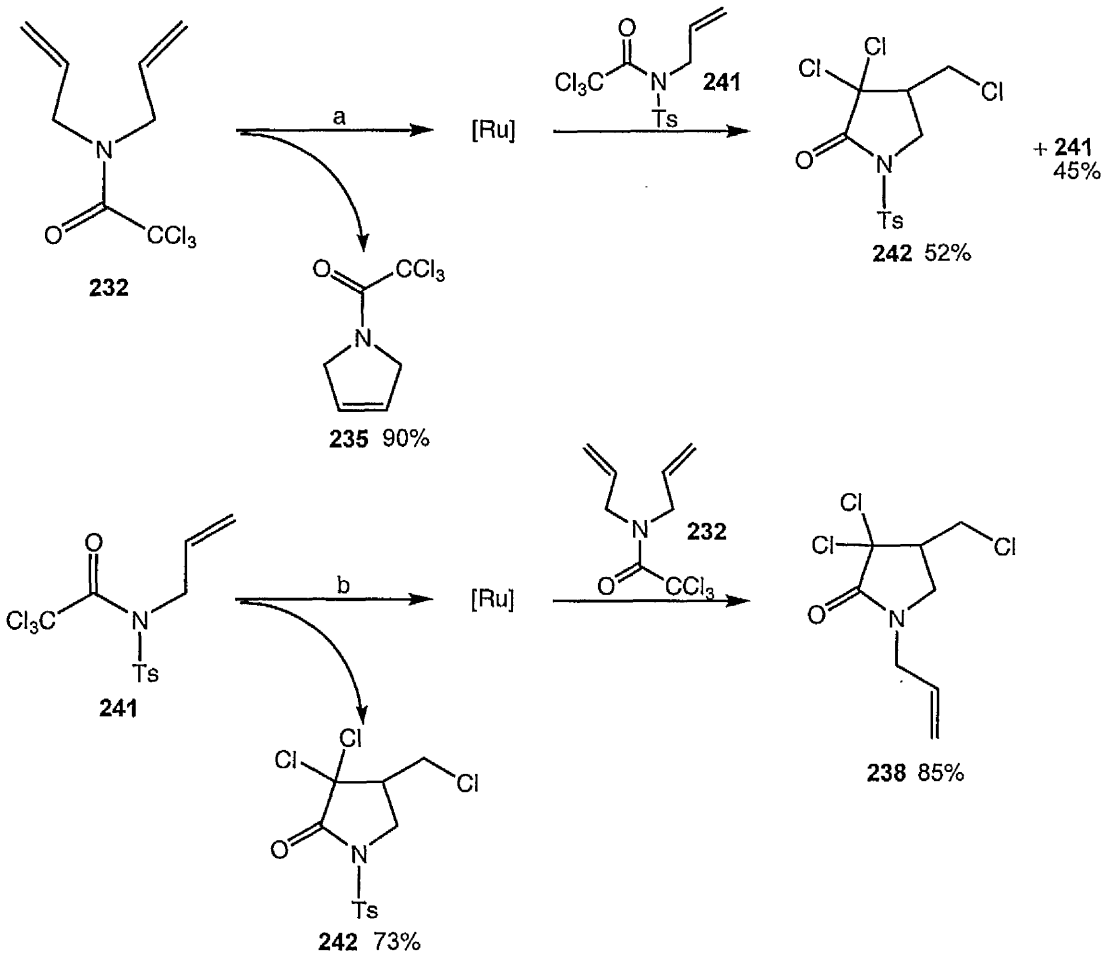


232 **241** **235** **242** 90%

Reagents and conditions: a) **89** (5 mol%), toluene, 3 hrs, reflux.

Scheme 73

Once again, a blank reaction was carried out to show the ability of **241** to undergo **ATRC** using Cu(I)Cl/ dHBipy. Repeating the reaction at 17 °C in toluene with a 1:1 mixture of amide **232** and tosylamide **241** gave the pyrroline **235** in excellent yield. However the γ-lactam **242** was only produced in trace amounts with mainly starting material **241** being recovered. These reactions show that metathesis reactions occur very rapidly at 17 °C ($t_{1/2} \approx 5$ mins) whilst **ATRC** is initiated at temperatures exceeding 70 °C. Variable temperature ^{1}H-NMR experiments conducted by a previous group member[65] showed that when **89** is refluxed in toluene-d_8 it possesses a half life of *ca.* 30 mins to perform metathesis. This is considerably shortened to approximately 10 minutes when in the presence of substrates such as **227**. Identification and isolation of catalyst **89** decomposition product has been difficult. There is the possibility of two different decomposition products; i) thermal decomposition of the **89** catalyst before it is able to form a methylidene catalyst and ii) decomposition of the methylidene complex after it has participated in metathesis. To be certain which one was participating in **ATRC** cyclisation, we varied the order in which competing substrates were added to **89, Scheme 74.**

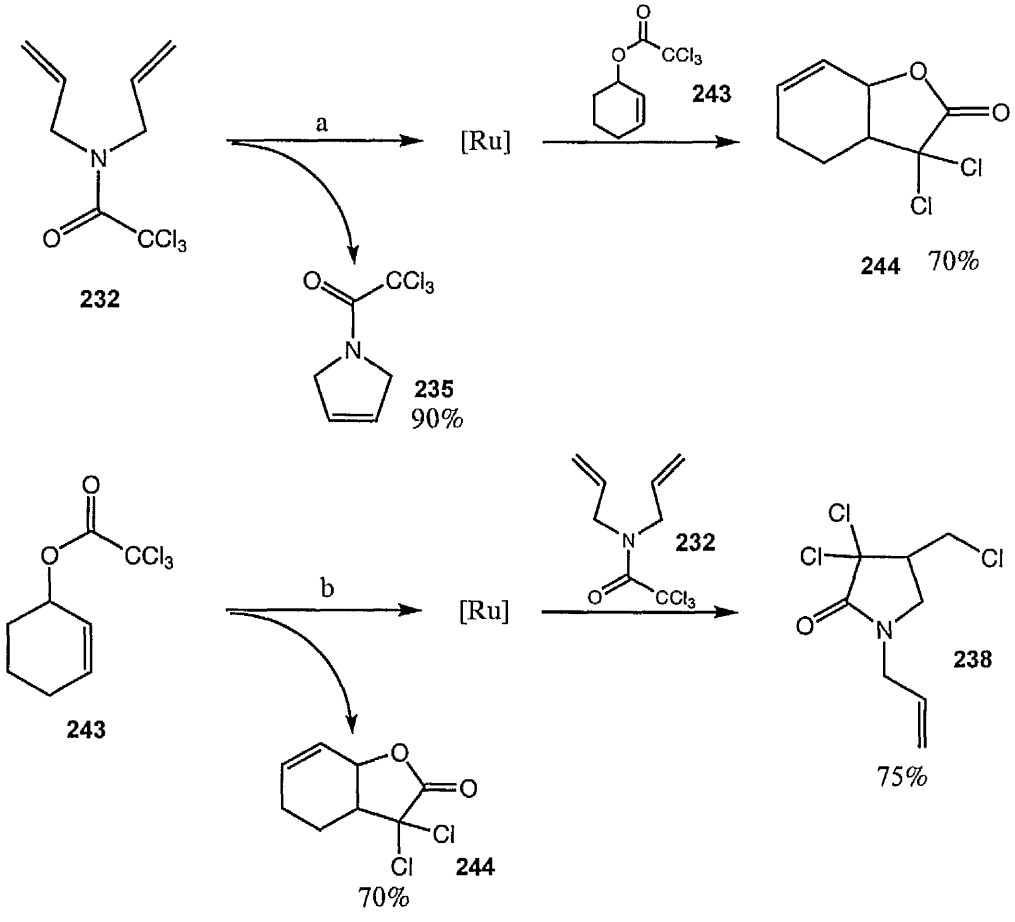


Reagents and conditions: a) i) **89** (5 mol%), toluene, 3 hrs, reflux; ii) **241**, 3 hrs, reflux; b) i) **89** (5 mol%), toluene, 3 hrs, reflux; ii) **232**, 3 hrs, reflux.

Scheme 74

Sequential addition of amide **232** followed by **236** to refluxing toluene and **89** (5 mol%) gave metathesis product **235** and the **ATRC** lactam **242** in 95% and 52% yield isolated, respectively. Reversing the addition, **241** was added first to a solution of **89** in toluene at 110 °C followed by the amide **232**, isolating **ATRC** products **242** and **238** in 73% and 85% yield respectively. Interaction of **89** with **241** in refluxing toluene alters the catalyst so it's no longer capable of performing effective metathesis reactions, however it does remain effective as a **ATRC** catalyst, successfully acting as a radical initiator. The same method of experiment was tried using another **ATRC** capable substrate **243**, this time giving a bicyclic lactone **ATRC**

product **244, Scheme 75**. The isolation of **244** from this reaction sequence poses a number of mechanistic questions, a point which will be addressed in Chapter 7.

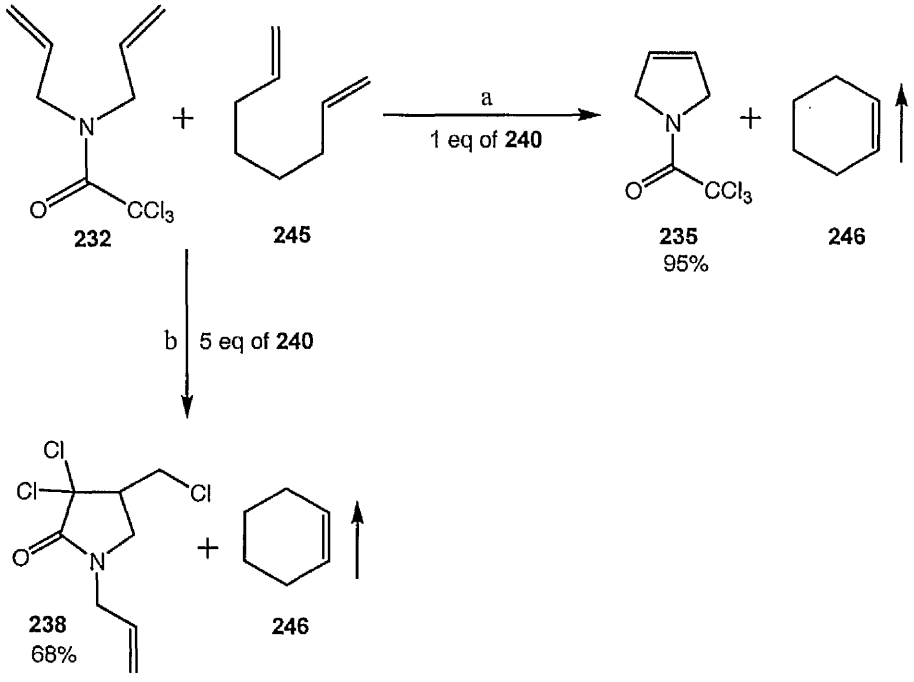


Reagents and conditions: a) i) **89** (5 mol%), toluene, 3 hrs, reflux; ii) **246**, 3 hrs, reflux; b) i) **89** (5 mol%), toluene, 3 hrs, reflux; ii) **232**, 3 hrs, reflux.

Scheme 75

Following on the theme of denaturing the **89** to form an effective **ATRC** catalyst, sacrificial ω-dienes were tried for the generation of the methylidene complex. When a 1:1 mixture of 1,7-octadiene **245** and diallylamide **232** were reacted together in toluene using **89** (5 mol%) at ambient temperature, only the metathesis product **235** was isolated (95% yield). However with the addition of a 1:1 mixture of **232** and 1,7-octadiene **245** to a solution of **89** (5 mol%) in toluene, pre-heated to 110°C, led to the isolation of the **ATRC** product **238** in 42% yield together with 21% yield of metathesis product **235**. Increasing the ratio of 1,7-octadiene to **232** from 1:1 to 5:1 gave a near complete reversal in reaction pathway, producing the **ATRC** product **238** in 68% yield after column chromatography, with only trace amounts of metathesis

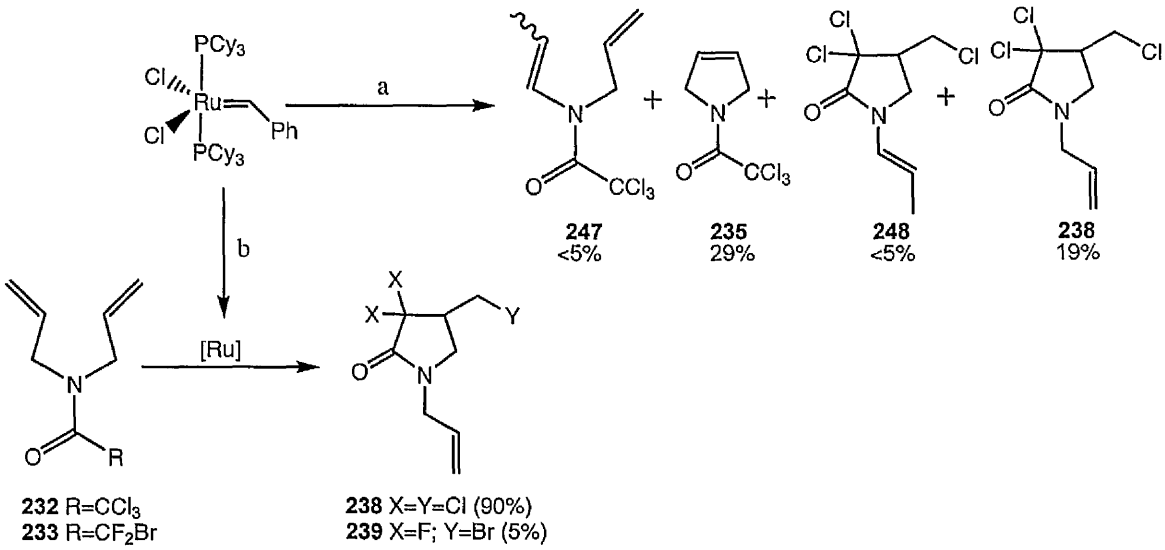
product **235** being seen in the ^{1}H NMR spectra of the crude reaction mixture. By-product cyclohexene **246,** from the metathesis of 1,7-octadiene **245**, was lost during work-up due to its volatility, **Scheme 76.**



Reagents and conditions: a) **89** (5 mol%), **240** (1 eq), toluene, 3.5 hrs, 20 °C ; b) **89** (5 mol%), **245** (5 eq), toluene, 3.5 hrs, reflux.

Scheme 76

To test out the hypothesis of whether denaturing **89** will achieve **ATRC** cyclisation, thermolysis of **89** was taken place prior to the addition of a substrate. Previous work in the Quayle group[66] has shown that **89** has the ability to promote redox isomerisation of allyl alcohols, which is linked to the catalysts thermal instability and proceeds *via* the generation of hydrido-ruthenium complexes. Interestingly we observed that warming a solution of **89** in degassed toluene from 17 °C to 110 °C for 3 minutes prior to the addition of **232**, followed by stirring for a further 3 hrs at 110 °C, produced a variety of products consisting of **235** (29%), **238** (19%), starting material **232** (34%), and isomerised starting material **247**. This result seemed to be a one off. Repeating the reaction with **232** only produced trace amounts of **ATRC** product. Refluxing **89** in toluene for 3.5 hours, followed by addition of amide **232** and further reflux for an additional 3.5 hours produced **238** in 90% yield, **Scheme 77.**

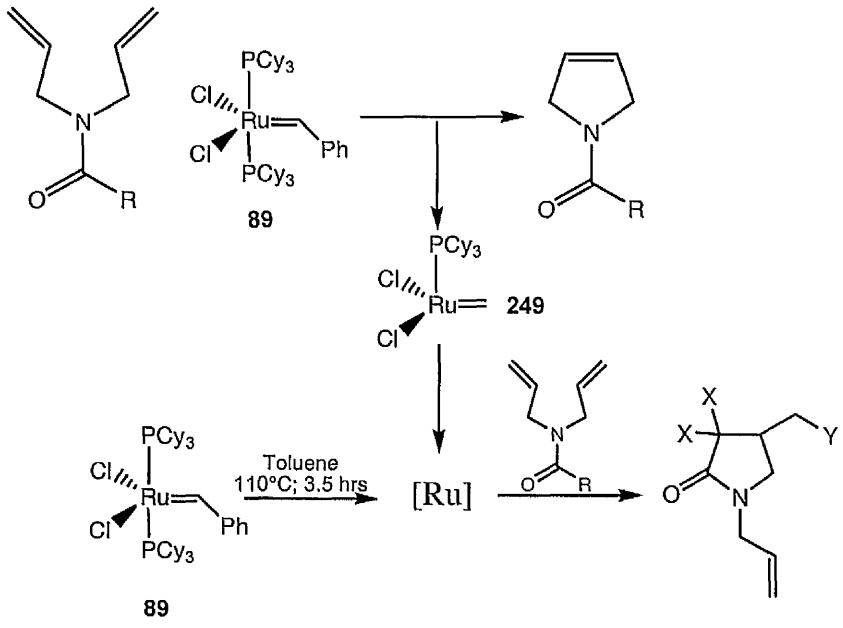


Reagents and conditions: a) i) **89** (5 mol%), toluene, 3 mins, 25 to 110 °C; ii) **232**, reflux, 3.5 hrs; b) i) **89** (5 mol%), toluene, 3.5 hrs, reflux; ii) **232** or **235**, 3.5 hrs, reflux.

Scheme 77

Comparisons have been made between **89** and Cu(I)Cl/ dHBipy catalyst as a **ATRC** catalyst. Cu(I)Cl/ dHBipy catalyst system has been found to be more efficient due to **89** having to thermally decompose as a metathesis catalyst first to then act as a **ATRC** catalyst.

The previous results indicate that catalyst **89** can act in a dual capacity, performing two different carbon-carbon forming reactions sequentially, **Scheme 78**. Catalyst **89** performs the metathesis reaction first, forming the metathesis product at an increased rate to any potential **ATRC** activity. During this reaction the catalyst **89**, either through direct decomposition of the active methylidene complex **249** or thermal decomposition of **89** itself, subsequently stops exhibiting all metathetical activity and initiates **ATRC** reactions. The catalyst then acts as a radical initiator. The ruthenium complex, or complexes, initiating **ATRC** radical cyclisation is a different moiety than the complex which begins at the start of the reaction.



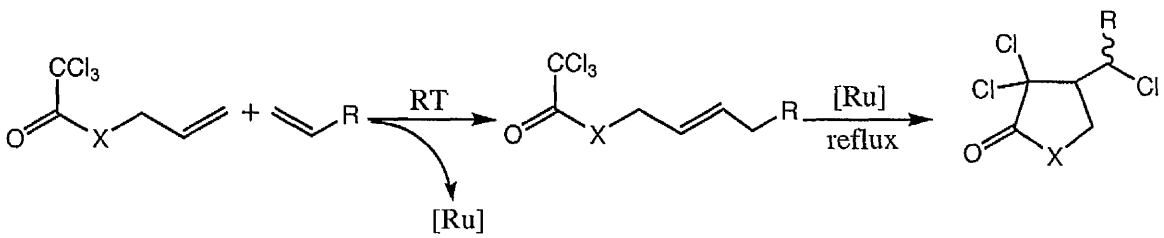
Scheme 78

We have successfully shown that the conversion of **89** from a metathesis catalyst into an **ATRC** catalyst by changing the reaction conditions. We have also showed that the idea of catalyst economy is realistic, using **89** to perform two different organic reactions on two different substrates in "one pot".

Chapter 5. Tandem Intermolecular metathesis- ATRC cyclisation

5.1 Introduction

Having demonstrated proof of concept for the notion of "molecular queuing", intramolecular variants were next sought. As Grubbs catalysts, **89** and **90**, can accomplish various types of metathesis, it was decided to attempt cross-metathesis (**CM**) as the first stage of a cascade process, **Scheme 79**.

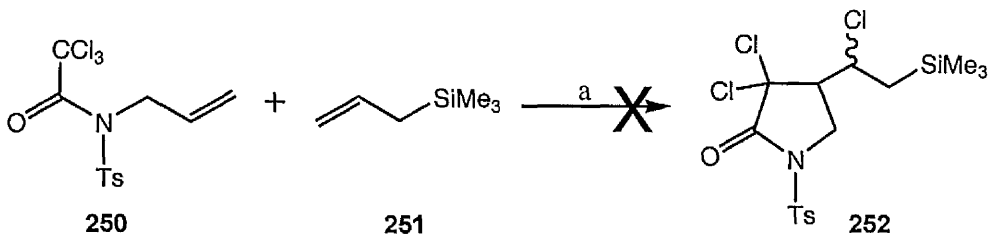


Scheme 79

Functionalised allyl trichloroacetamides were to be used as one metathesis olefin partner. This was due to our familiarity with these compounds, ease and scalability of their synthesis, and their ability to undergo successful **ATRC** reactions with Cu(I)Cl/ dHBipy and denatured Grubbs catalysts. Once again, blank reactions were carried out to show the ease at which they perform **ATRC** cyclisation. For the other half of the cross metathesis reactions, a variety of functionalised alkenes were screened. However, the success of the **CM** reaction is dependent on whether **89** or **90** are used. Precatalyst **90** has a higher success rate for more sensitive metathesis reactions due to its increased tolerance to a diverse range of functional groups and with extra stability to oxygen and temperature.[25] This inherent stability causes its downfall as an effective **ATRC** catalyst, making cross-metathesis high yielding and the subsequent **ATRC** poor yielding. This reactivity is reversed for the **89** precatalyst due to its poor ability for cross metathesis and its easier decomposition under temperature, moisture and oxygen. This leads to a metathetically inactive complex. If the catalyst cannot perform **CM** effectively then there will be no **CM** product to cyclise.

5.2 Functionalised alkenes as CM partners.

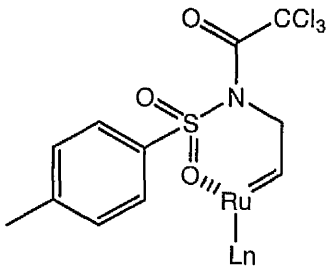
As described in section 2.2, the success of **CM** depends on the nature of the partner alkene present. In the reaction mixture, it is prudent to add an excess of the more reactive olefin which will self-metathesise the quickest. This gives the selected **CM** partner an increased chance of participating in cross metathesis with the other less reactive olefin. All selected olefins are commercially available. The first reaction that was attempted was the reaction of *N*-allyl-2,2,2-trichloroacetamide **250** with allyltrimethylsilane **251** in toluene with **90** (5 mol%). Unfortunately only starting materials was recovered. The reaction was repeated twice more, changing the conditions slightly by degassing the solution *via* the freeze-thaw method. Both attempts proved unsuccessful, **Scheme 80**.



Reagents and conditions: a) i) **90** (5 mol%), toluene, 40 °C, 3 hrs; ii) 110 °C, 18 hrs.

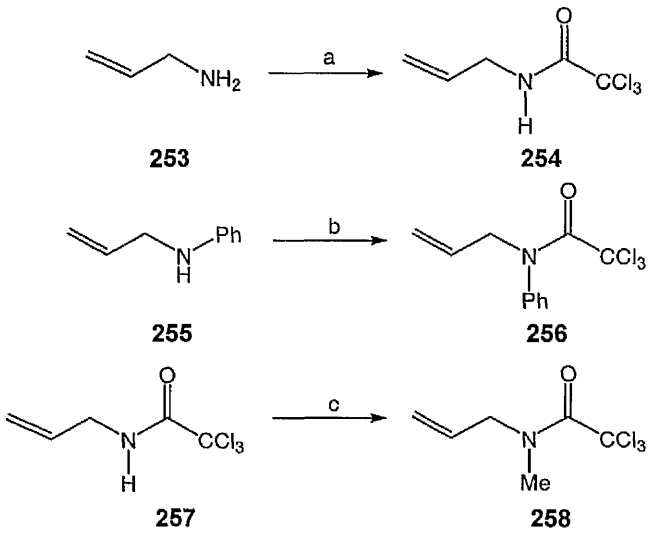
Scheme 80

The unsuccessful nature of the process led to the possibility of formation of a 6-membered metallocycle between **250** and **90**, **Scheme 81**. The formation of this chelate complex during metathesis could stall the reaction and prevent **CM** from occurring. Although this hypothesis has not been vigorously investigated, it is in keeping with recent similar literature precedents.[67]



Scheme 81

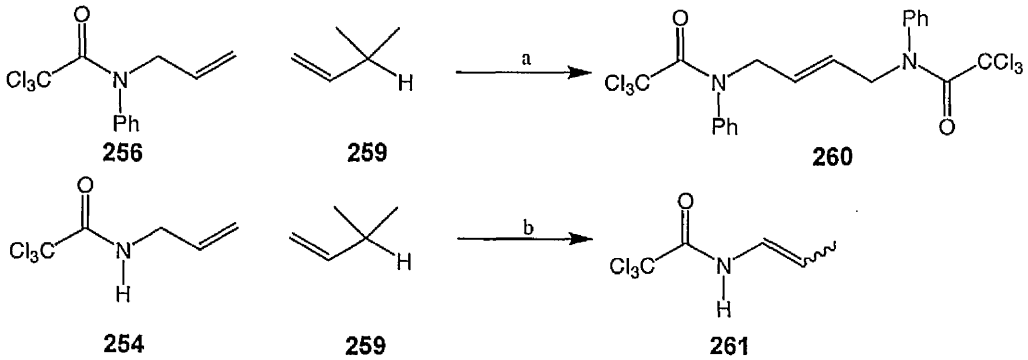
The nitrogen group on the *N*-allyl-2,2,2-trichloroacetamide was then varied to counter any possible future chelation with the ruthenium centre. Three were synthesised **254**, **256** and **258**, **Scheme 82.**



Reagents and conditions: a) trichloroacetyl chloride, Et_3N, THF, 0 °C, 3 hrs, 79%; b) trichloroacetyl chloride, *n*-BuLi (1.34M solution in hexanes), THF, 0 °C, 3 hrs, 83%; c) NaH, MeI, THF, 0 °C, 2.5 hrs, 71%.

Scheme 82

The nature of the *N*-substituent has a marked effect upon the outcome of the reaction. For example, 3-methylbut-1-ene **246**, had the ability to make **256** dimerise to **260**. Alternatively, where the *N*-substituent is simply hydrogen, as in the case of **254**, attempted cross metathesis with **246** resulted in the isomerisation of the substrate to (*E*+*Z*)-enamide **261, Scheme 83.**

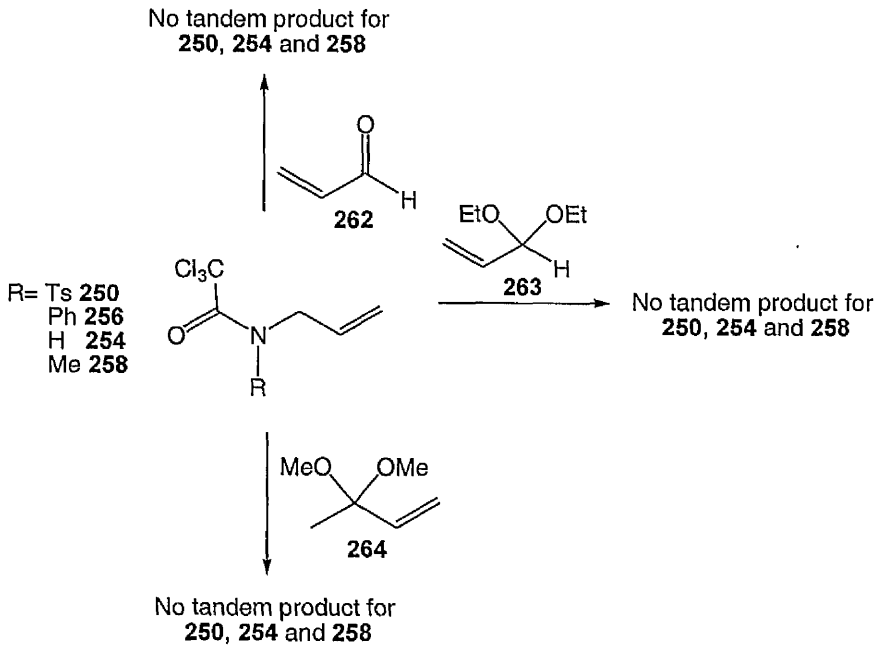


Reagents and conditions: a) **90** (5 mol%), toluene, 40 °C, 3 hrs, 68%; b) **90** (5 mol%), toluene, 40 °C, 3 hrs, 62%.

Scheme 83

In both of these examples no cross metathesis product were observed. In the above cases, the gem dimethyl group in **239** seems to add enough steric hindrance which inhibits metallocycle formation. This unwillingness to take part promotes self-metathesis of **256** and isomerisation of **254**. However there are cases within the literature where **260** has been successfully been used as a **CM** olefin.[37]

Other substrates, such as acrolein **262** and the hemi-acetals **263** and **264,** did prove reactive when **256** was used as the *N*-allyl-2,2,2-trichloroacetamide, however the results were irreproducible giving a complex mixture of products, inseparable by flash silica column chromatography. Small amounts of **CM** products were observed, when **90** was used as the catalyst, which were seen in the crude ^{1}H-NMR, however these were never successfully isolated. The minor impurities common to all reactions was the observation of **ATRC** cyclisation of the specific *N*-allyl-2,2,2-trichloroacetamide being used. Isomerisation was exclusive to **254** with trace amounts (>1%) seen with the other protected *N*-allyl-2,2,2-trichloroacetamides, **Scheme 84**.

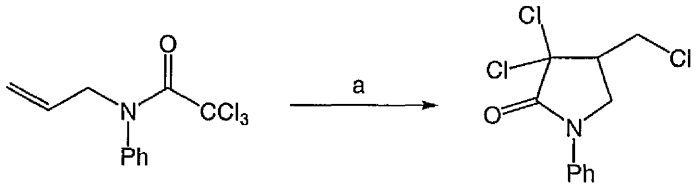


Reagents and conditions: a) **90** (5 mol%), toluene, 40°C, 3 hrs.

Scheme 84

5.3 Substituted styrenes as cross metathesis partners.

Given our success of undergoing **ATRC** reactions on substituted styrenes,[72] it seemed prudent to investigate styrenes as potential substrates for **CM-ATRC** reactions. With styrenes we have the opportunity to subtly control the electronics of the olefin by the introduction of functional groups on the aromatic ring. Strategically placed groups on the aromatic ring would be able to donate or withdraw electron density and therefore affect the olefin in a non-evasive manner. For the other half of the cross metathesis reaction, we continued using the protected *N*-allyl-2,2,2-trichloroacetamides, however for these reactions it was limited to solely the *N*-phenyl protected substrate, **256**. Compound **256** was subjected to standard blank reaction was carried out using Cu(I)Cl/ dHBipy ligand system. The **ATRC** product **265** was isolated to give 89% yield after column chromatography, **Scheme 85**.

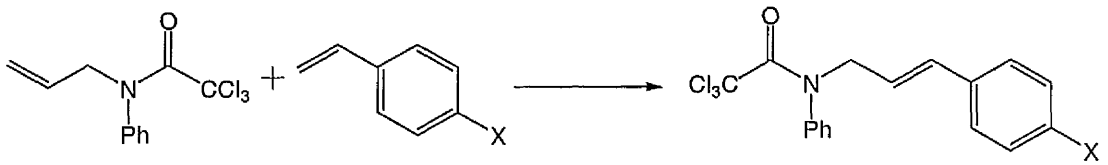


256 **265**

Reagents and conditions: a) Cu(I)Cl (5 mol%), dHBipy (20 mol%), 1,2-DCE, 80 °C, 3.5 hrs, 89%.

Scheme 85

Initial reactions centred on primarily the cross-metathesis of various styrenes to **256** to ascertain if the reaction was possible. This would also help gauge how many equivalents of styrene were needed to push the reaction to completion. Exposure of **256** to an excess of styrenes **266**, **267**, **268**, or **269** (**256**: styrene 1:5 ratio) in toluene using **90** (5 mol%, 40 °C, 2 hrs) as catalyst afforded the cross metathesis products **270**, **271**, **272** and **273** in yields ranging from 59-68% (*E:Z*> 95:5) together with corresponding stilbene side products. We were unable to detect any products arising from the self-metathesis of **256** or γ-lactam **265**, which would be the result of competing **ATRC** reactions. The reactions were also attempted with **89**; however no cross-coupled product was produced with only small amounts of self-metathesised by-product stilbene being seen, **Scheme 86**.



256

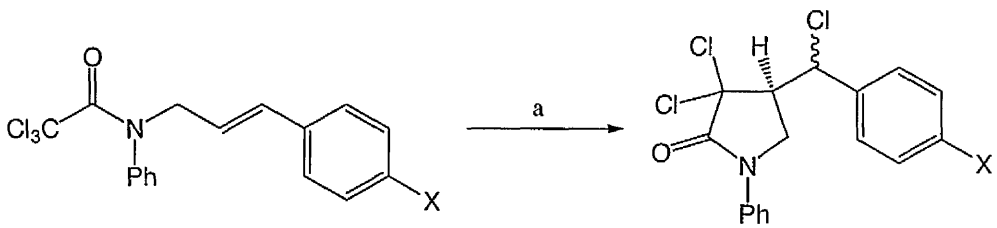
266 X= H
267 X= F
268 X= Br
269 X= OMe

270 X= H
271 X= F
272 X= Br
273 X=OMe

Reagents and conditions: i) **90** (5 mol%), toluene, 40 °C, 2 hrs, 59-68%.

Scheme 86

The next stage was to take these **CM** products and verify if they are able to under-go **ATRC** cyclisation. Exposure of **270**, **271**, **272**, and **273** to Cu(I)Cl/ dHBipy in refluxing 1,2-DCE produced the corresponding γ-lactams **274**, **275**, **276** and **277** in yields ranging from 60-71% giving a single diastereoisomer in each case (apart from **277** which gave a 1:1 mixture), **Scheme 87**.



270 X= H
271 X= F
272 X= Br
273 X=OMe

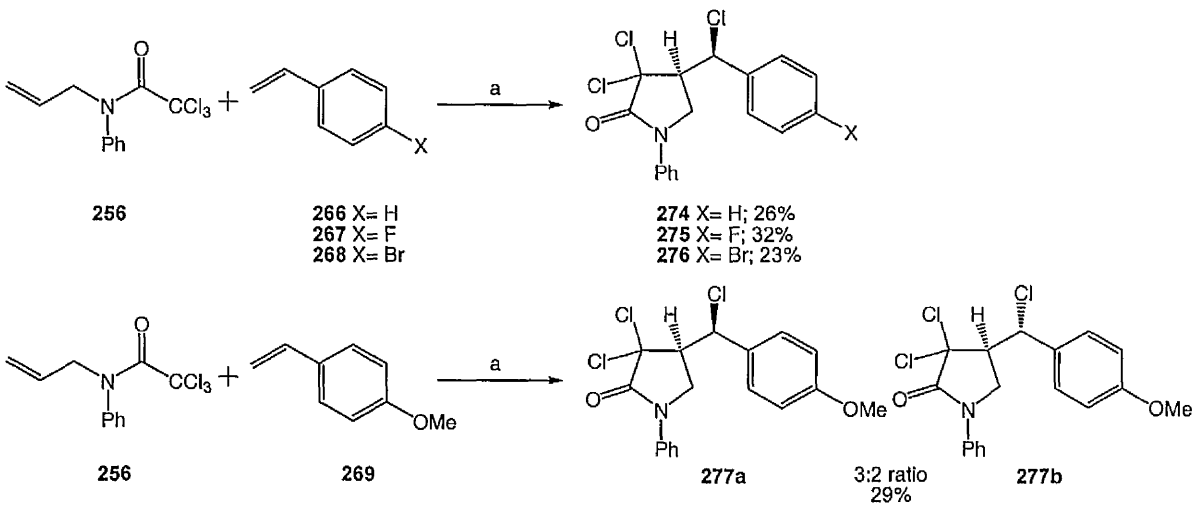
274 X= H
275 X= F
276 X= Br
277 X=OMe

Reagents and conditions: a) Cu(I)Cl (5 mol%), dHBipy (5 mol%), toluene, 110 °C, 3 days.

Scheme 87

In the knowledge that the two separate components of the **CM** -**ATRC** sequence were viable, we know decided to telescope these two sequences together. Cross-metathesis of **251** with the styrenes **266**, **267**, **268**, or **269** (5:1 ratio of styrene:**256**) with **90** in degassed toluene at 40 °C for 2 hours followed by thermolysis at 110 °C for a further 3 days, led to the isolation of γ-lactams **274**, **275**, and **276** in moderate yields ranging from 23-32%. *p*-Methoxystyrene **277a** and **277b** was isolated in 29% yield as an unseperatable mixture of diastereoisomers (3:2

ration by ^{1}H-NMR), whilst the others gave a single diastereoisomer in each respective case, **Scheme 88**.



Reagents and conditions: a) i) **90** (5 mol%), toluene, 40 °C, 2 hrs; ii) 110 °C, 3 days.

Scheme 88

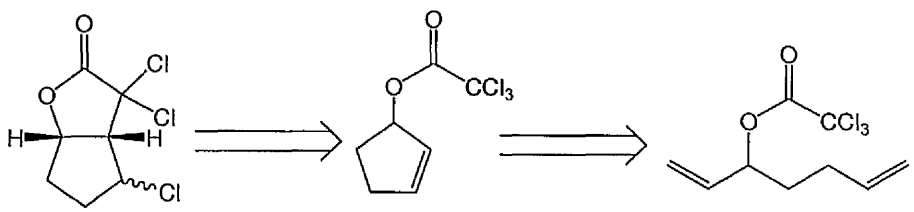
The reactions in **Scheme 90** show proof of concept that tandem reactions using **90,** for two different carbon-carbon bond forming reactions, in a "one pot" are not just possible but also highly effective. Even though the yields are moderate, they are still impressive considering the process, especially with competing homodimerisation in the cross-metathesis phase.

Chapter 6. Tandem Intramolecular metathesis- ATRC cyclisation

6.1 Synthesis of cyclopentafuran-2-ones

6.11 Introduction

From the results from the tandem **CM-ATRC** reactions, proving that one-pot tandem reactions were possible, our attentions were turned to investigating intramolecular version of this sequence. We looked to produce a substrate which would first be able to undergo ring closing metathesis successfully, followed by **ATRC** cyclisation to form a bicyclic ring system. This in turn required the synthesis of **280** in order to achieve **RCM** to produce cyclopentene **279, Scheme 89.**

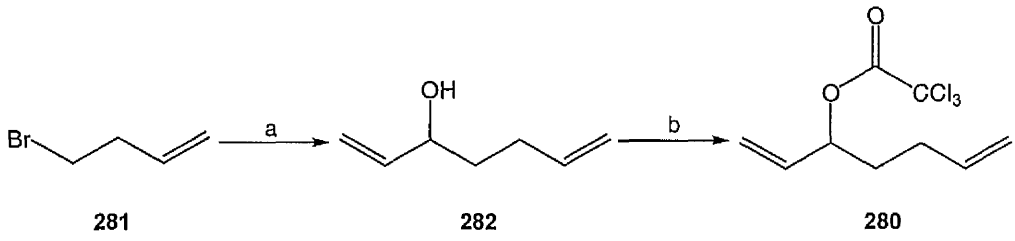


278 **279** **280**

Scheme 89

6.12 Synthesis of the tandem RCM-ATRC precursor

Our initial approach to the synthesis of the precursor **280** for the tandem **RCM-ATRC** reaction preceded through a Grignard coupling reaction of acrolein **262** with 4-bromobutene **281** to give alcohol **282** in varied yields between 35-59%. This was followed by trichloroacetylation of the secondary alcohol to give **280** in 75% yield, **Scheme 90.** However the Grignard reaction is not a consistent and unidentifiable impurities led to further problems down the reaction pathway.

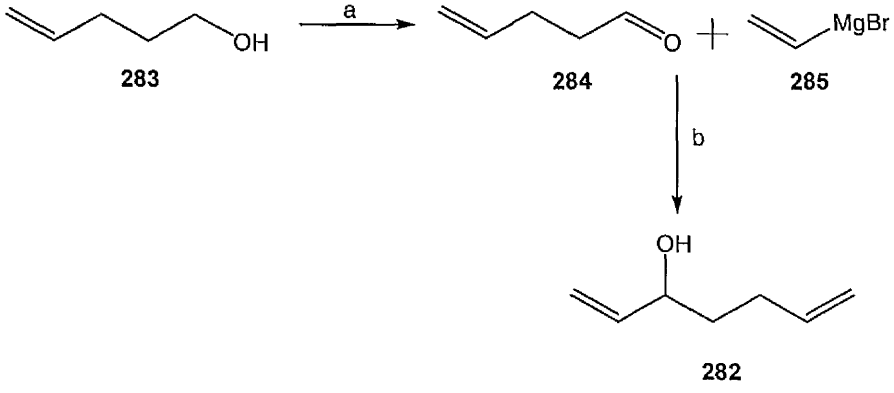


281 282 280

Reagents and conditions: a) i) Mg, Et_2O, -78 °C; ii) **262**, 17 °C, 44%; b) trichloroacetyl chloride, Et_3N, Et_2O, 0 °C, 95%.

Scheme 90

Staying with the Grignard reaction but reversing the coupling partners, oxidation of pent-4-enol **283** was accomplished using a variety of techniques (PCC, PDC, Swern) which was reacted with vinylmagnesium bromide **285** to give alcohol **282**. However purifying the crude oxidation mixtures proved difficult due to the volatile nature of **284**, leading to a range of poor yields. Attempts to proceed with the Grignard reaction using unpurified oxidation material produced small amounts of product **282.** This low yield was due to impurities from the various oxidations reducing the Grignards reactivity and efficiency, **Scheme 91**.

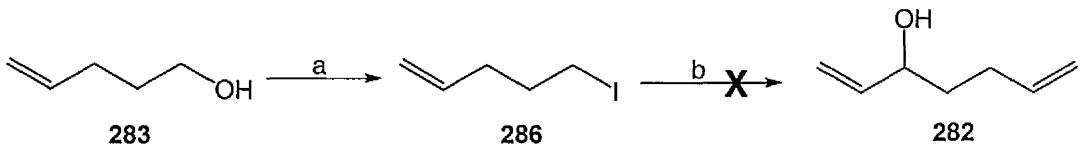


283 284 285 282

Reagents and conditions: a) oxidation, 15-45%; b) **285**, Et_2O, 0 °C, 25-68%.

Scheme 91

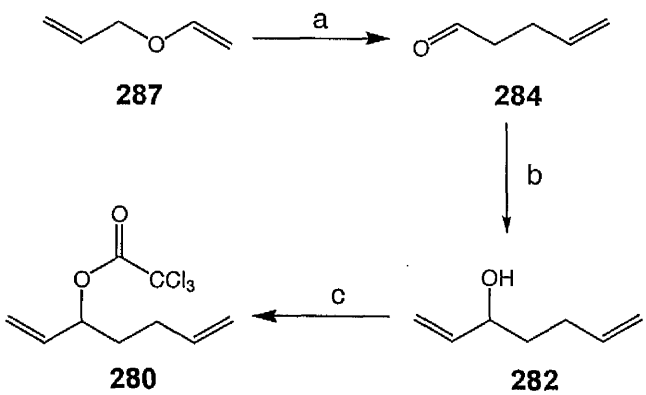
Due to low overall yields and unreliability of the process shown in **Scheme 91**, another synthesis was devised. Attempts were made on halogen-metal exchange; however on successful synthesis of iodide **286** the crucial step to give alcohol **282** proved uneventful, **Scheme 92**.



Reagents and conditions: a) i) Et_3N, TsCl, DCM; ii) NaI, acetone, 78%; b) *n*-BuLi, acrolein, THF, -78 °C, no reaction.

Scheme 92

A way was needed to produce the aldehyde in sizable quantity, fortunately we observed that microwave assisted Claisen rearrangement of allyl vinyl ether **287** gave the volatile aldehyde **284** in quantative yield. Aldehyde **284** was then reacted cleanly with vinylmagnesium bromide **285** to give the desired secondary alcohol **282** in 98% yield. Trichloroacetylation of **282** proceeded smoothly to give the tandem precursor **280** in 95% yield. This route finally gave an extremely reliable method of producing **280** on a moderate scale, being able to manufacture up to 20 g at a time, **Scheme 93**.

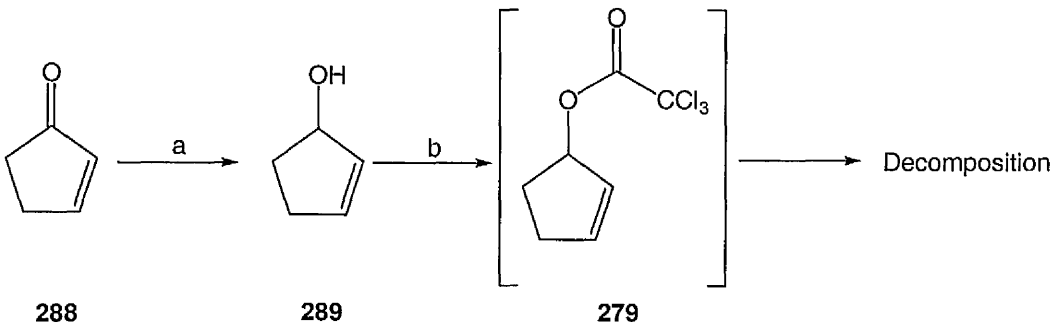


Reagents and conditions: a) microwave, neat, 1 hr, 100%; b) vinylmagnesium bromide **285**, Et_2O, -78 °C, 98%; iii) trichloroacetyl chloride, triethylamine, diethyl ether, 0 °C, 95% .

Scheme 93

Before attempting a tandem synthesis with **280**, we decided to prepare an authentic sample of cyclopentene **279** in order to verify that it could indeed participate in **ATRC** leading to **278**. Reduction of **294** using Luche conditions gave alcohol **295** in excellent yield. Trichloroacetylation of **295** proved unsuccessful as **279** was unstable under work-up

conditions, proceeding to decompose, **Scheme 94**. Due to the inability to isolate **279**, we were unable to verify if it was able to cyclise *via* **ATRC**.

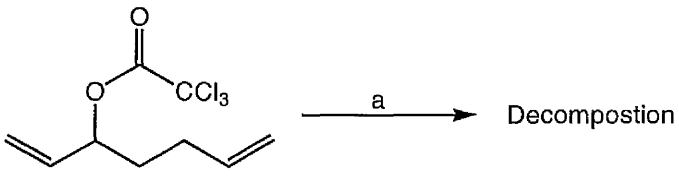


Reagents and conditions: a) $CeCl_3$, $NaBH_4$, ethanol, 78%; b) trichloroacetyl chloride, Et_3N, Et_2O, 0 °C, decomposition.

Scheme 94

6.13 Tandem synthesis of cyclopentafuran-2-ones

Without being able to independently verify the potential tandem product **278** by a different synthetic route, we decided to push on with the tandem reaction. Diene **280** was subjected to a range of conditions to achieve tandem cyclisation and produce **278.** All these conditions failed, leading to decomposition of the **RCM** product as seen previously, **Scheme 95.**



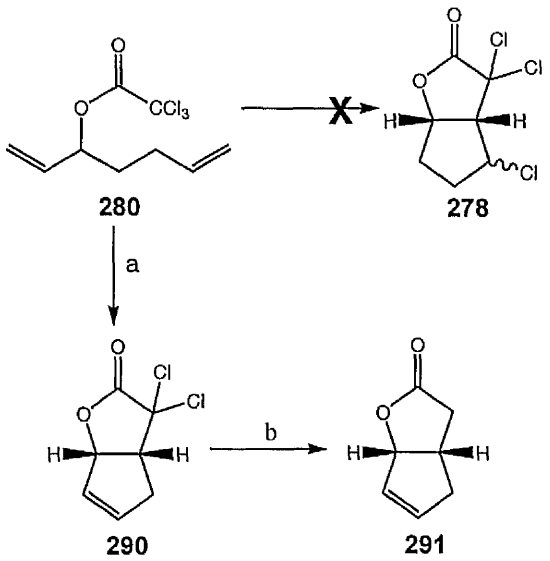
280

Catalyst	Solvent	Additives (5 mol%)
89	Toluene	None
89	DCE	None
89	Benzene	None
90	Toluene	None
90	DCE	None
90	Benzene	None
89	Toluene	Cu(I)Cl, dHBipy
89	DCE	Cu(I)Cl, dHBipy
89	Benzene	Cu(I)Cl, dHBipy

Reagents and conditions: a) i) 2 hrs, 17 °C; ii) 3 hrs reflux.

Scheme 95

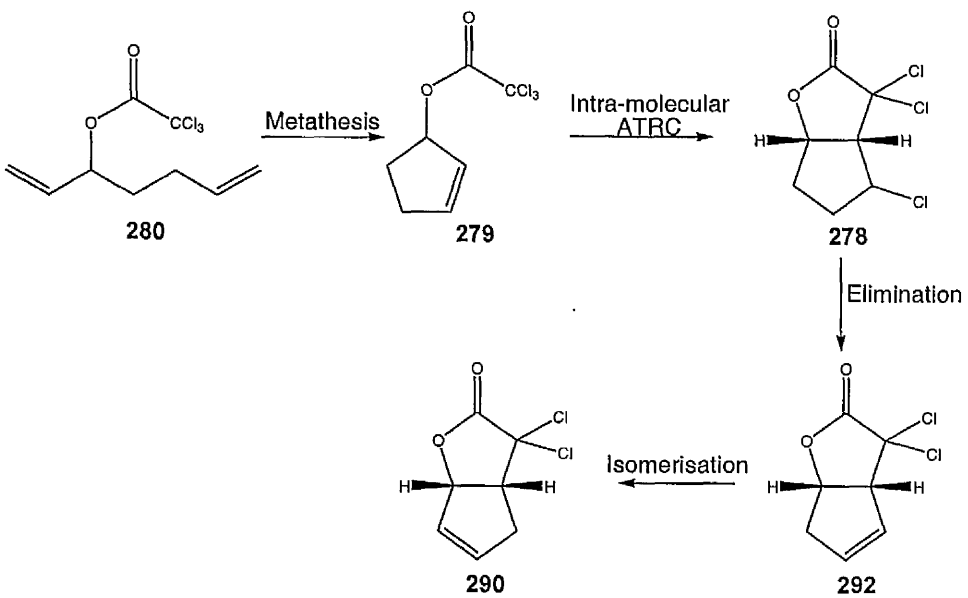
The reactions were attempted with and without the solvents and reaction mixture being degassed (*via* freeze thaw). However, when **280** was reacted with **90**, Cu(I)Cl, and dHBipy in refluxing chloroform, it gave near quantitative yield of **280** rather than **278**. Dechlorination of **290** with zinc in acetic acid gave bicyclic lactone **291**. Stereochemistry of **290** was confirmed by nOe/COSY analysis and direct comparison to the same compound being synthesised by other research groups,[91] **Scheme 96**.



Reagents and conditions: a) i) **90** (5 mol%), Cu(I)Cl (5 mol%), dHBipy (5 mol%), chloroform, 2 hrs, 17 °C; ii) 3 hrs reflux; 95%; b) $Zn_{(s)}$, 10 eq, 1:3 AcOH-H_2O, 100 °C, 69%.

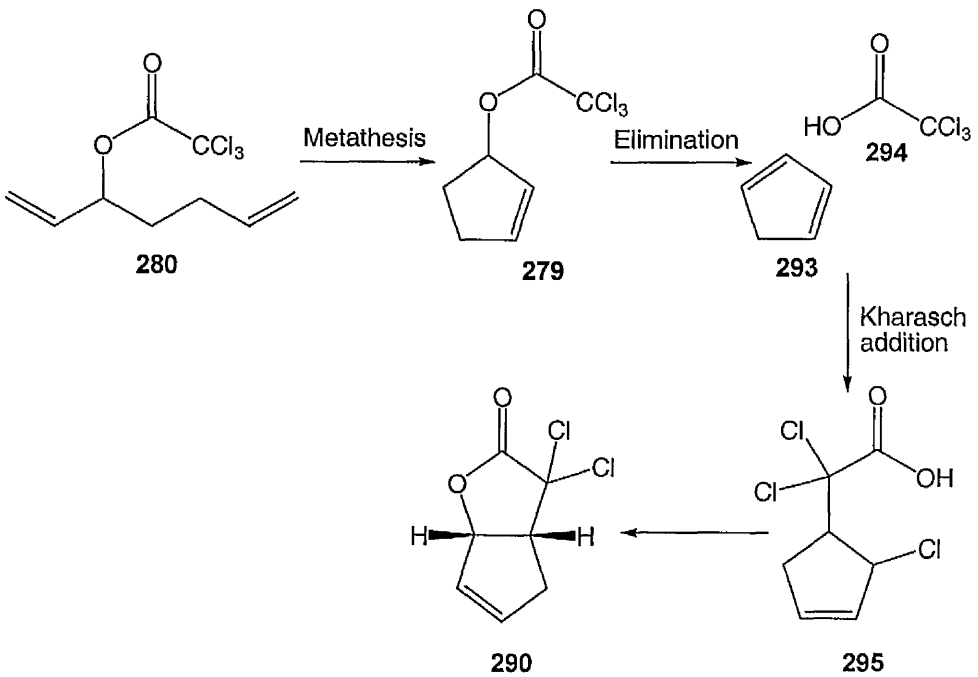
Scheme 96

This unexpected result led us to speculate that cyclisation of **RCM** intermediate **279** led initially to bicyclic **278**, which suffered elimination followed by isomerisation to the lactone **290**. Although alkene isomerisations using ruthenium catalysts are well documented, we still had concerns as to the reasons behind the total regiospecificity of the overall sequence, **Scheme 97**.



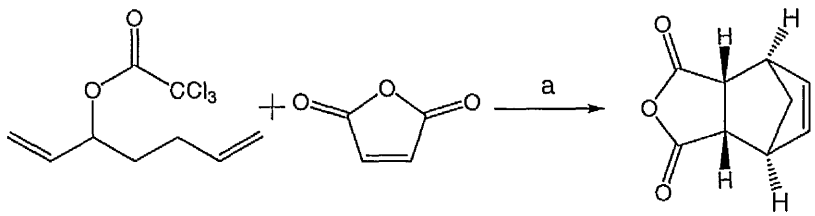
Scheme 97

Further investigation in fact led us to conclude that the pathway outlined in **Scheme 97** was incorrect. In particular the total absence of intermediates **278** and **292** from the reaction mixture was quite perplexing. By substituting chloroform to deuterated chloroform, the reaction was continuously followed by ^{1}H-NMR. From these studies we were able to conclude that trichloroacetate **280** is metathesised to **279** which is quickly converted to cyclopentadiene **293**. After a period of time, **293** is rapidly converted to lactone **290.** This set of reactions suggests that the overall pathway, **280** to **290**, can be described as a cascade of reactions involving an **RCM**-elimination-intermolecular **ATRC** addition-displacement, **Scheme 98**.



Scheme 98

To confirm that the reaction goes through the suggested pathway with cyclopentadiene **293** being produced, maleic anhydride **296** was added at the beginning of the procedure to trap the diene **293**. The Diels-Alder adduct **297** was isolated in an excellent 92% yield, **Scheme 99**.



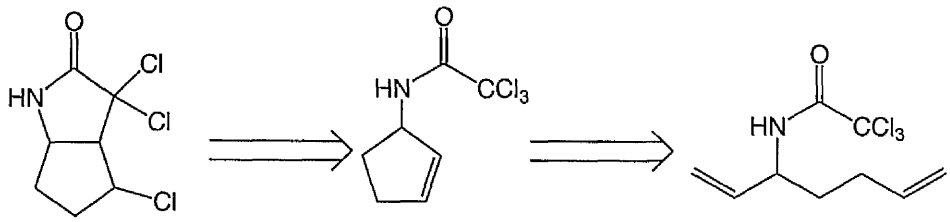
280 296 297

Reagents and conditions: a) i) **90** (5 mol%), Cu(I)Cl (5 mol%), dHBipy (5 mol%), chloroform, 2 hrs, 17 °C; ii) 3 hrs, reflux, 95%.

Scheme 99

6.2 Preparation and tandem synthesis of cyclopentapyrrol-2-ones

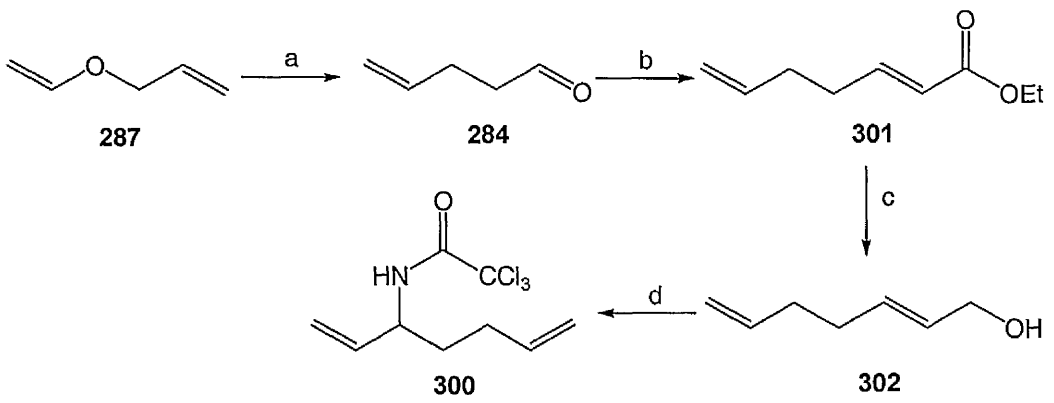
Working from the success of cyclopentafuran-2-one **290**, it was decided to replace the lactone for a lactam ring, suppressing any possible chance for elimination and promoting intramolecular **ATRC** after metathesis, **Scheme 100.**



298 299 300

Scheme 100

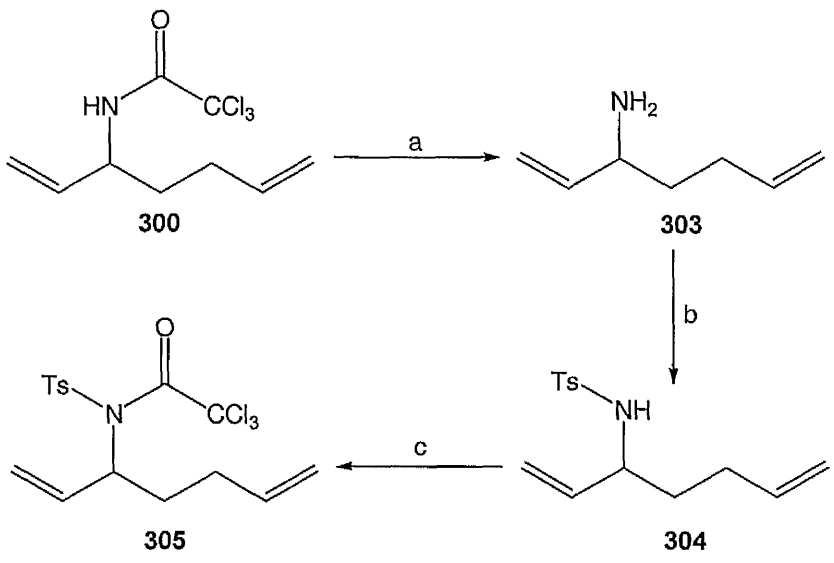
Starting from the now readily available aldehyde **284**, this was subjected to Wittig homologation producing ester **301**, followed by reduction with DIBAL-H affording **302**. Conversion of **302** to the amide **300** proceeded smoothly *via* the Overman procedure in excellent overall yield, **Scheme 101**.



Reagents and conditions: a) neat, microwave, 100%; b) $Ph_3P{=}CHCO_2Et$, DCM 94%; c) DIBAL-H, THF, -78 °C, 97%; d) i) Cl_3CCN, Et_3N, Et_2O, 0 °C; ii) xylenes, overnight, reflux,reflux, 89%.

Scheme 101

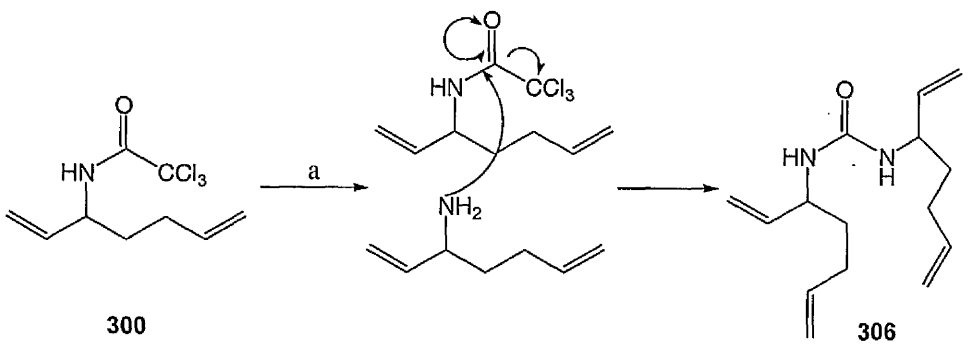
Before attempting the tandem procedure as carried out in **Scheme 92**, it was decided to protect the amide as previous work has shown that Grubbs catalysts can isomerise secondary allylic amides. Attempts to effect the alkylation with benzyl bromide and in the presence of base, failed to produce any of the required protected amide. Further attempts to form a lithium species on the nitrogen with *n*-BuLi also failed. Changing strategy, it was decided to remove the trichloroacetamide giving the primary amine. It would then be possible to protect the amine with a benzyl or tosyl group, then re-trichloroacetylate giving the required **RCM/ ATRC** precursor. Removal of the trichloroacetamide on **300** with 6M $NaOH_{(aq)}$ in refluxing methanol [69] was accomplished in poor yield, affording amine **303** where it converted into substrate **305** in two steps, **Scheme 102.**



Reagents and conditions: a) 6M $NaOH_{(aq)}$, methanol, reflux, 4 hrs; 0-18%; b) TsCl, *n*-BuLi, THF, 3 hrs, 72%; c) trichloroacetyl chloride, pyridine, Et_2O, 0 °C, 3 hrs, 94%.

Scheme 102

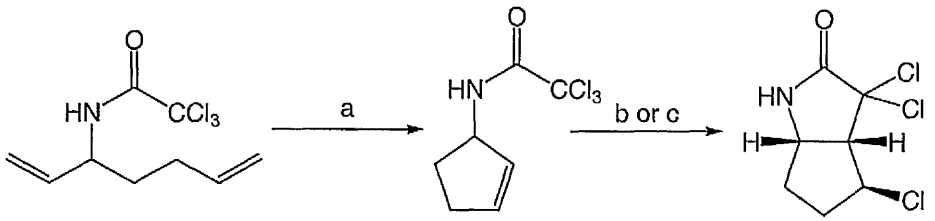
Due to the poor yields obtained from deprotection, it became impossible to bring through a substantial amount of **300** through. Enough material was needed so adequate experimentation could take place to discover the best methods for **RCM** and **RCM-ATRC**, so another method for deprotection was investigated. However, deprotection of **300** proved very problematic, for example, exposure to cesium carbonate7[0] in DMSO at 100 °C afforded the dimeric urethane **306, Scheme 1030.**



Reagents and conditions: a) Cs_2CO_3, DMSO, 100 °C, 4 hrs, 67%.

Scheme 103

Again we worked to establish that each of the constituent reactions in the cascade proceeded well, and preparation of the amide **299**, *via* **RCM**, was therefore attempted. The **RCM** of **300** was accomplished using **90** giving 95% yield in 30 mins using a microwave. Amide **299** was then subjected to **ATRC** using two different catalysts; i) Cu(I)Cl (5 mol%), dHBipy (20 mol%) and ii) $RuCl_2(PPh_3)_3$ (5 mol%). Both afforded the same compound, lactam **307,** in excellent yield, **Scheme 104**. Stereochemistry was confirmed by nOe experiments, and also comparisons of ^{1}H-NMR with examples within the literature published after the initial synthesis of **307**.[71]

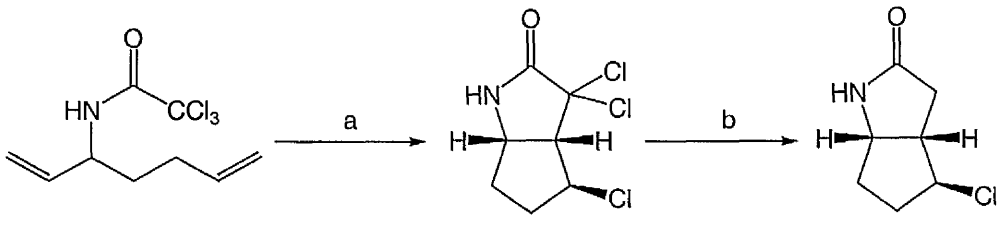


300 **299** **307**

Reagents and conditions: a) **90**, neat solution, microwave, 30 mins, 95%; b) Cu(I)Cl (5 mol%), dHBipy (20 mol%), toluene, reflux, 12 hrs, 75%; c) $RuCl_2(PPh_3)_3$ (5 mol%), toluene, reflux, 65%.

Scheme 104

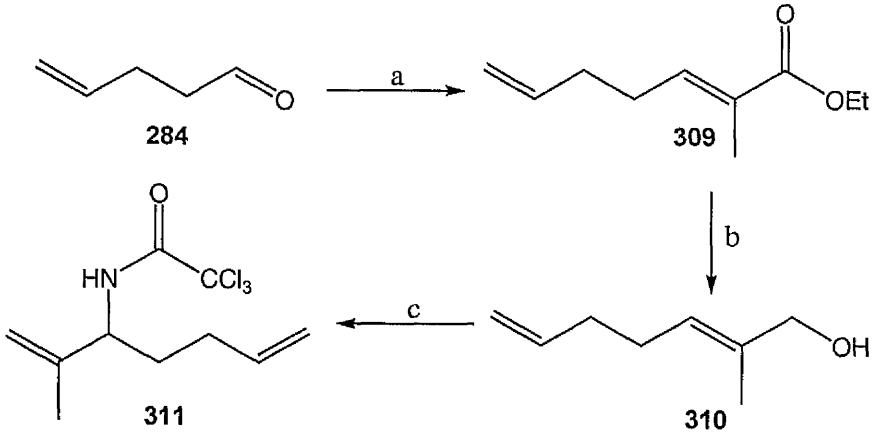
With the success of the independent cyclisations, the tandem reaction was attempted on **300**. Initial results gave 53% yield using **90** (5 mol%) in degassed toluene (2 hrs at 17 °C and 2 days at reflux) and 65% yield using **89** (5 mol%) in anhydrous xylenes (2 hours at 17 °C and 12 hours at reflux). However these results were improved by exchanging toluene with xylenes and extending the reaction time to 2 days affording a range of yields from 82-91%, with no sign of decomposition of **297** seen due to the harsh conditions. Dechlorination of **307** with zinc and acetic acid proved highly selective affording the mono-chlorolactam **308** in 73% yield, **Scheme 105**.



Reagents and conditions: a) i) **90** (5 mol%), xylenes, 17 °C, 2 hrs; ii) reflux, 2 days, 82-91%; b) Zn (10 eq), 1:3 AcOH-H_2O, reflux, 73%.

Scheme 105

As a change of direction, we decided to investigate a tandem cyclisation where a larger substituent other than hydrogen was positioned where **ATRC** would occurs to form the second ring. This would add further functionality to the final tandem product. Changing the Wittig reagent from $Ph_3P{=}CHCO_2Et$ to $Ph_3P{=}C(Me)CO_2Et$, gave **309** in 89% yield. Ester **309** was reduced to 1° alcohol **310** with DIBAL-H, and then converted to trichloroacetamide **311** again *via* Overman chemistry, **Scheme 106**.

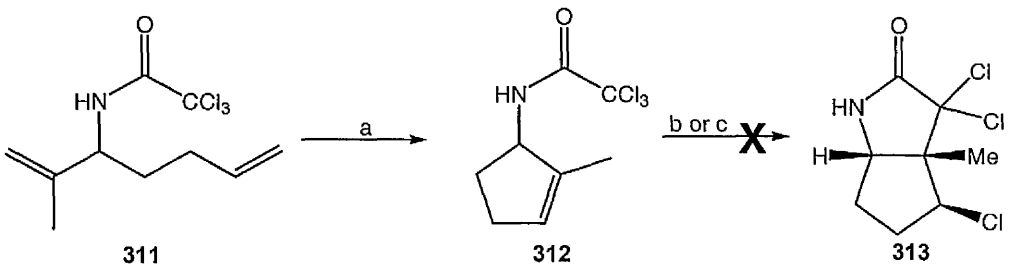


Reagents and conditions: a) $Ph_3P{=}C(Me)CO_2Et$, DCM 89%; c) DIBAL-H, THF, -78 °C, 91%; d) i) Cl_3CCN, Et_3N, Et_2O, 0 °C; ii) xylenes, overnight, reflux, 82%.

Scheme 106

Again we worked to ensure that each of the constituent reactions in the cascade process proceeded well, and preparation of the amide **312**, *via* **RCM**, was therefore attempted. The **RCM** of **311** was accomplished using **90** giving **313** in 91% yield after 60 mins *via*

microwave irradiation. Amide **312** was then subjected to **ATRC** using two different catalysts; i) Cu(I)Cl (5 mol%), dHBipy (20 mol%) and ii) thermolysed **89**. Both failed to initiate **ATRC** with amide **312** being recovered in quantative yield, **Scheme 107**.



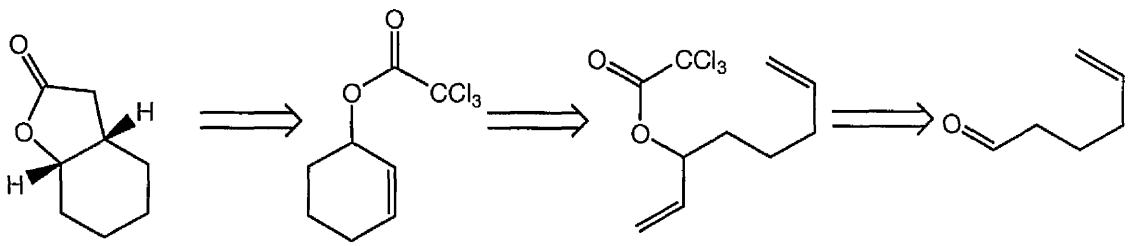
Reagents and conditions: a) **90**, neat solution, microwave, 30 mins, 91%; b) Cu(I)Cl (5 mol%), dHBipy (20 mol%), toluene, reflux, 12 hrs, no reaction; c) **89** (5 mol%), toluene, reflux, 2 days, no reaction.

Scheme 107

Due to the inability of **89** or Cu(I)Cl/ dHBipy to cyclise **312**, no attempt of tandem cyclisation on **311** was made. Presumably the methyl substituent offers enough steric hindrance to prevent **ATRC** from occurring in this case.

6.3 Synthesis of the hexahydrobenzofuran-2(3*H*)-one system

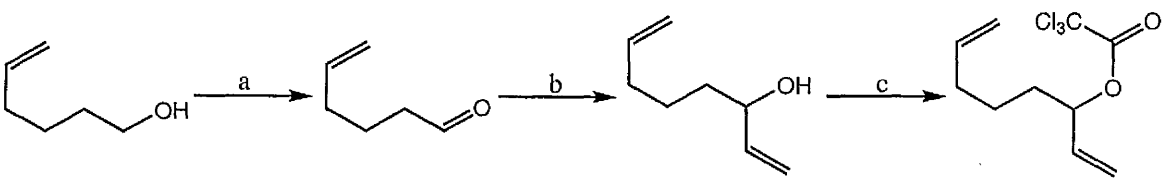
Following the same lines of investigation as the previous **RCM-ATRC** tandem cyclisation reaction, it was decided to attempt a tandem synthesis to give the familiar hexahydrobenzofuran-2(3*H*)-one system **314, Scheme 108.**



314 **243** **315** **316**

Scheme 108

The tandem precursor **315** was acquired *via* Swern oxidation of hex-5-enol **317** followed by a Grignard reaction with vinylmagnesium bromide. Trichloroacetylation of alcohol **318** gave the required trichloroacetamide **315** in excellent yield. The increased molecular weight of hex-5-enal **317** compared to pent-4-enal **283** insures the molecule is less volatile. This gives the opportunity to obtain higher yields after purification, **Scheme 109.**

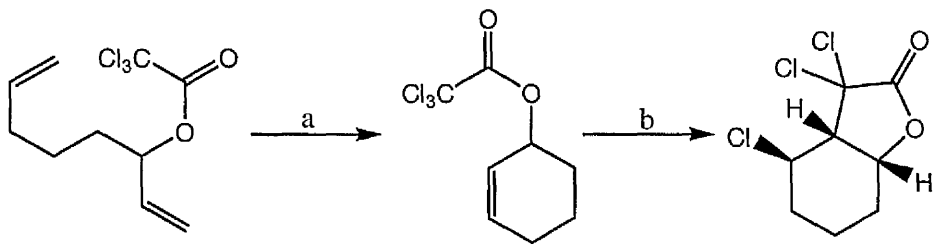


317 **316** **318** **315**

Reagents and conditions: a) i) $(COCl)_2$, DMSO, DCM, -78 °C; ii) Et_3N, -78 to 17 °C, 65%; b) vinylmagnesium bromide, Et_2O, 0 °C, 67%; c) trichloroacetyl chloride, Et_3N, Et_2O, 0 °C, 83%.

Scheme 109

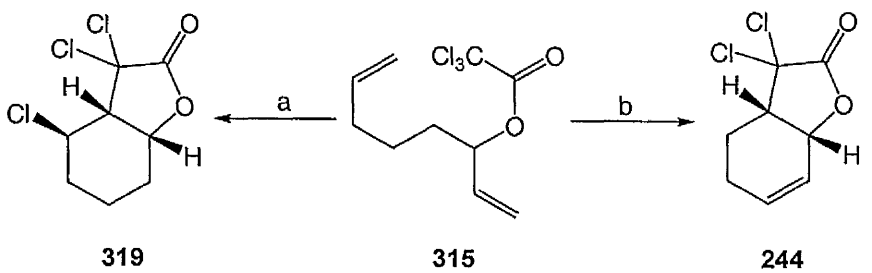
Trichloroacetamide **315** was reacted with **90** in DCM at 40 °C in order to confirm that it would facilitate ring closing metathesis. Under these conditions **243** could be isolated in 95% yield. Subjecting **243** to **ATRC** using Cu(I)Cl and dHBipy gave the bicyclic lactone **319** in excellent yield, **Scheme 106.**



Reagents and conditions: a) **90**, DCM, 40 °C, 95%; b) Cu(I)Cl (5 mol%), dHBipy (20 mol%), DCE, reflux, 80%.

Scheme 110

Exposing **315** to **89** (5 mol% at 17 °C for three hours followed by reflux for a further 16 hrs) afforded unsaturated lactone **244** in 64% yield together with trace quantities (<5%) of the trichlorolactone **319**. However when repeating the reaction, this time with **90**, this resulted in the isolation of trichlorolactone **319** as the major product in 62% yield together with a minor amount of **244** (approx 5% by ^{1}H-NMR of crude reaction), **Scheme 111**.



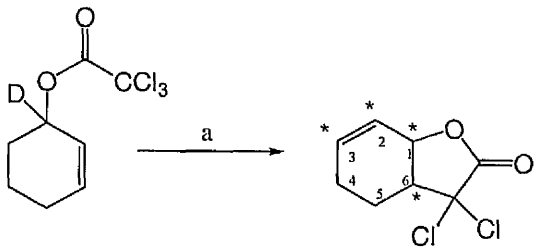
Reagents and conditions: a) i) **90** (5 mol%), toluene, 3 hrs, 17 °C; ii) reflux, 16 hrs, 64%; b) i) **89** (5 mol%), toluene, 3 hrs, 17 °C; ii) reflux, 16 hrs, 62%.

Scheme 111

The different catalysts seem to enter different reaction pathways for cyclisation; **89** initiating elimination of trichloroacetic acid **294** from intermediate **243** then promoting intermolecular **ATRC** addition to give **244** with catalyst **90** initiating sigmatropic rearrangement and **ATRC** mainly forming the trichlorolactone **319**.

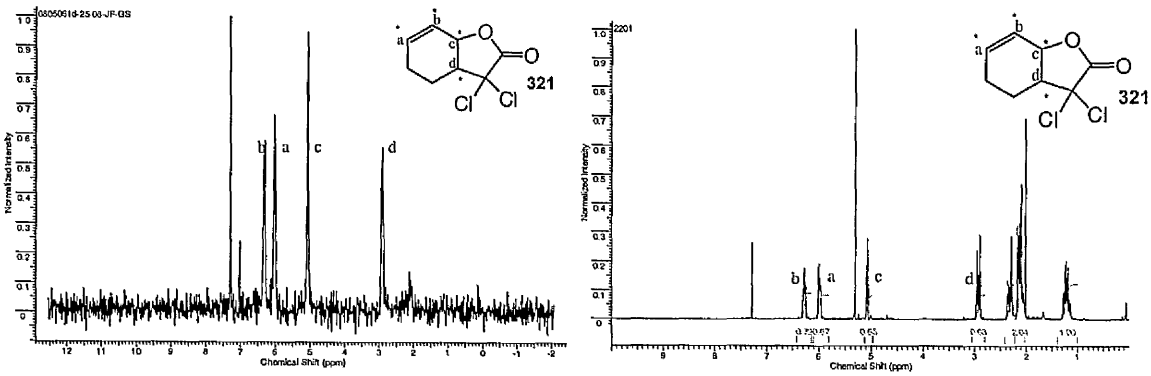
Chapter 7. Deuterium scrabbling from ATRC

From initial results reported in chapter 6, it would appear that intermediates such as **315** suffer from sequential **RCM**-elimination-isomerisation reactions ultimately leading to unsaturated lactones such as **244.** However further investigations into this reaction cascade provided a mechanistic conundrum: why did the deuterated substrate **320** afford the lactone **321** in which the D-label had undergone regiospecific scrabbling as shown in **Scheme 112**[66] Such a scrabbling pattern is inconsistent with our initially proposed isomerisation mechanism as deuterium incorporation at C4 and C5 would also be expected. This observation implies the intervention of a different mechanism, namely elimation of trichloroacetic acid after the initial **RCM** reaction. NMR data for **321** can be seen in **Scheme 113.**



Reagents and conditions: a) **89**, toluene, reflux, 3 hrs, 81%.

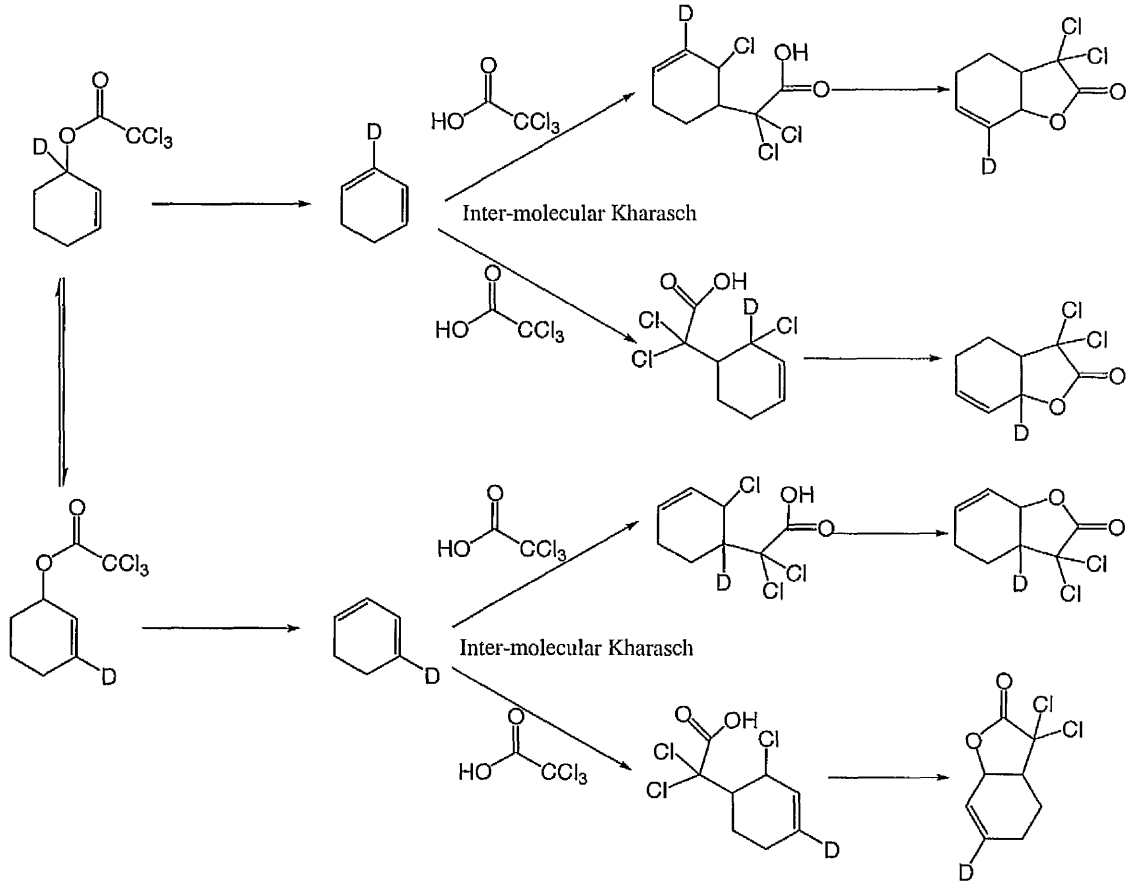
Scheme 112



^{2}H-NMR spectra of **321** ^{1}H-NMR spectra of **321**

Scheme 113

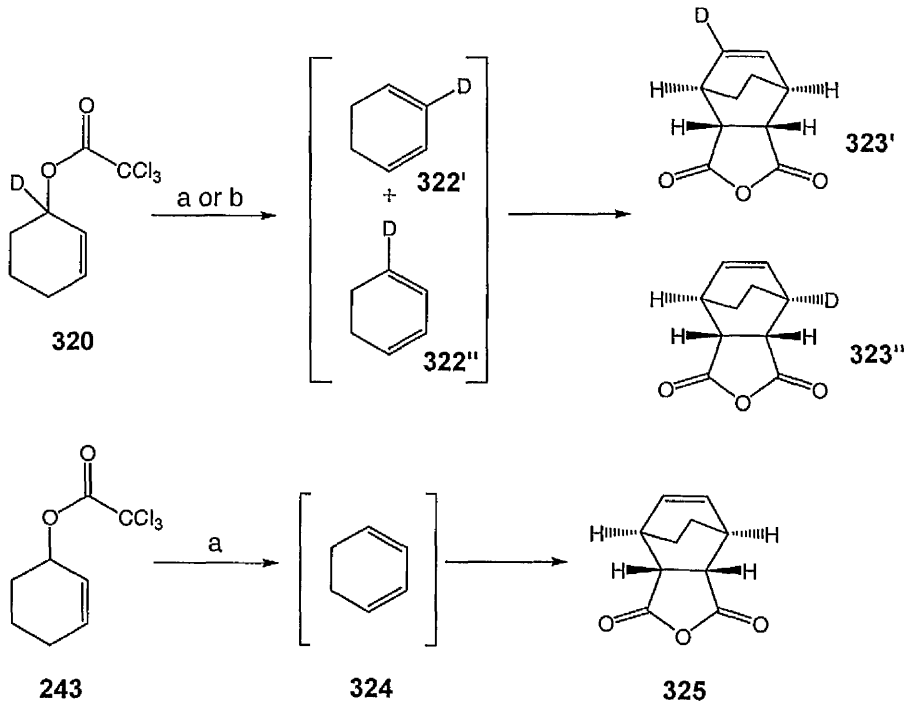
Previously it was suggested that the transformation proceeded *via* a domino **ATRC**/ elimination/ isomerisation reaction. However, we can now conclude that a more likely series of events is similar to the one seen in the synthesis of **290**, **Scheme 114**.



Scheme 114

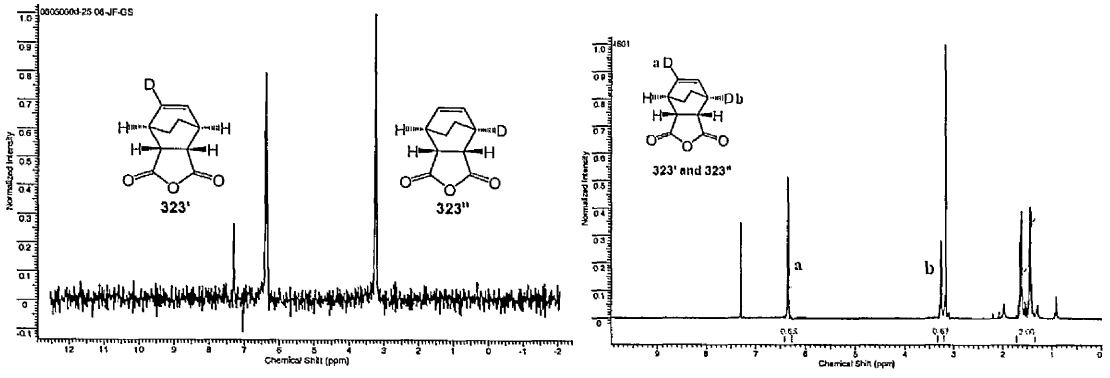
This gives an excellent explanation why there are only certain positions where the deuterium label is seen. Catalyst **89** initiates elimination of the trichloroacetic acid. In the case of the cyclopent-2-enyl 2,2,2-trichloroacetate **279**, Cu(I)Cl and HBipy are needed to help stabilize and increase the rate of the intermolecular **ATRC** reaction before the onset of decomposition and **ADMET** occurs. This is not seen with the six membered systems as it is much more stable. Evidence of the cyclohexa-1,3-diene intermediate has been further proven by its trapping with maleic anhydride *via* a Diels-Alder reaction, both using a labelled and unlabelled molecules. This suggests that the [4+2]-cycloaddition reaction of cyclohexa-1,3-diene competes favourably with the intermolecular **ATRC** reaction. Exposure of the deuterated substrate **320** to the same set of reaction conditions, with or without the Grubbs

catalyst, but in the presence of one equivalent of maleic anhydride leads to the isolation of the Diels-Alder products **323'** and **323''** in excellent yield (74-94%), **Scheme 115**. The same reaction can also be carried out with undeuterated **243**, giving the same result. The deuterium is present in a 55:45 ratio (**323'':323'**) as shown by the ^{2}H-NMR spectra, **Scheme 116.**



Reagents and conditions: a) **89** (5 mol%), maleic anhydride, toluene, reflux, 3.5 hrs, 92%; b) maleic anhydride, toluene, reflux, 3.5 hrs, 79%.

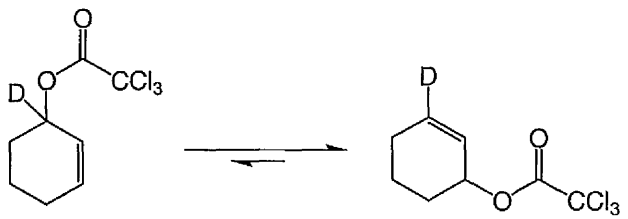
Scheme 115



^{2}H-NMR spectra of **323'** and **323''** ^{1}H-NMR spectra of **323'** and **323''**

Scheme 116

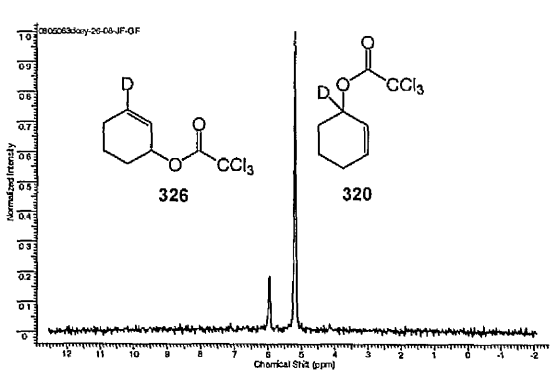
Trichloroacetate **320** tautomerises at temperatures greater than 0 °C commencing [3,3]-sigmatropic rearrangement, **Scheme 117**.



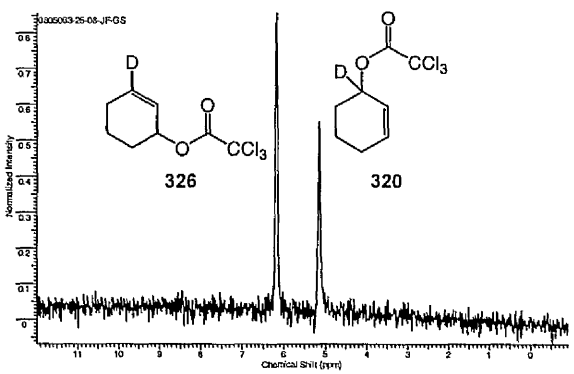
320 **326**

Scheme 117

The trichloroacetate also prefers to exist as isomer **326**. On synthesis of **320** the ^{2}H-NMR spectra shows very little of **326** present. However when the same NMR sample is allowed to sit at 17 °C for 16 hours and resubmitted, the ^{2}H-NMR spectra shows a shift from the majority of compound being **320** to **326, Scheme 118**.



^{2}H-NMR spectra of **320** after synthesis and storage at 0 °C

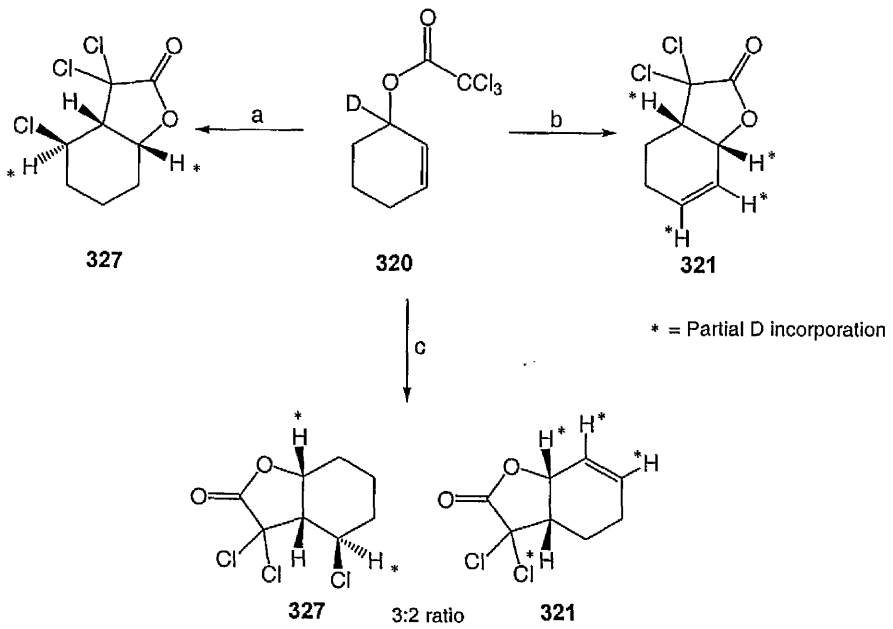


^{2}H-NMR spectra of **320** after 16 hrs storage at 17 °C

Scheme 118

Reinvestigating the events which occurred in **Scheme 111** with the help of deuterium labelling, **320** was subjected to a series of reactions to ascertain certain mechanistic details. Cyclisation of **320** with **89** resulted in the formation of unsaturated lactone **321** with the deuterium atoms approximately distributed equally between the four deuterium containing carbons. Cyclisation of **320** with **90** or Cu(I)Cl/ dHBipy resulted in the formation of trichlorolactone with the deuterium label equally distributed between the two main deuterium

containing carbons. When **320** was subjected to **90** in refluxing toluene a mixture of the unsaturated lactone **321** and the trichlorolactone **327** was seen with the deuterium label again scrambled in near equal measures over all deuterium containing carbons. Instead of using **89** on its own, exposure of **320** to a 1:1 mixture of a catalyst system comprising of Cu(I)-dHBipy and **89** in 1,2-DCE at reflux afforded trichlorolactone **327** in 79% yield and unsaturated lactone **321** in 10% yield, **Scheme 119**. These results show that cyclisation of **320** with an **ATRC** catalyst or the more robust carbene catalyst **90** proceeds *via* a **ATRC** cyclisation which is slower than the competing [3,3]-sigmatropic rearrangement and results in scrambling of the deuterium atom. Catalyst **89** initiates elimination of trichloroacetic acid and enters the pathway seen in **Scheme 114**. Unfortunately these results did not give any definitive answers to the preferential formation of **327** to **321** when **315** is treated with either **89** or **90**. An explanation could be that in these reactions **89** and **90** do not participate in metathesis therefore not forming a methylidine complex. This is more susceptible to decomposition (O_2, thermolysis) and could possibly lead to different reaction pathways for **ATRC**.



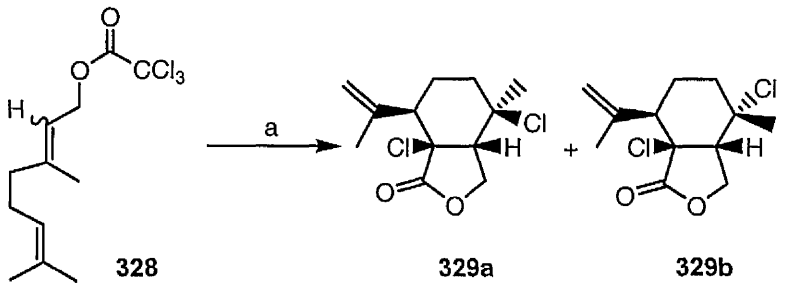
Reagents and conditions: a) Cu(I)Cl (5 mol%), dHBipy (5 mol%), **89** (5 mol%), 1,2-DCE, 12 hrs, reflux, 12 hrs or Cu(I)Cl (5 mol%), dHBipy (5 mol%), 1,2-DCE, 12 hrs, reflux, 12 hrs 79%; b) **89** (5 mol%), toluene, 3 hrs, reflux, 12 hrs, 89%; c) **90**, (5 mol%), toluene, reflux, 12 hrs, 3:2 ratio of **327**:**321**.

Scheme 119

Chapter 8. Previous work on Eunicillin

8.1 Formation of functionalised bicyclic γ-butyrolactones

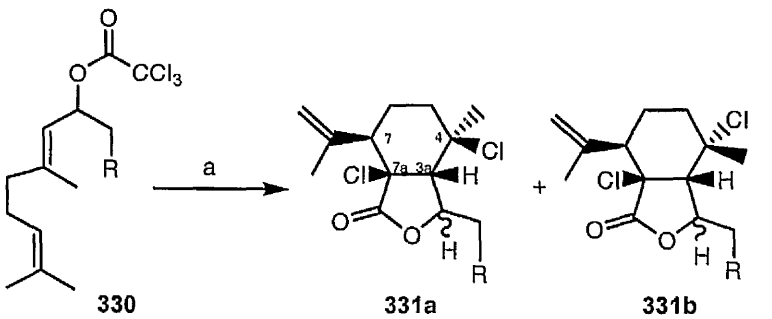
Previous work in the Quayle group[72] has revealed that the formation of bicyclic γ-butyrolactones **329a** and **329b** can be derived from the **ATRC** of (*E*+*Z*)-geranyl trichloroacetate **328, Scheme 120**.



Reagents and conditions: a) CuCl (5 mol%), dHBipy (5 mol%), 1,2-DCE, reflux 3.5 hrs, 67% global yield (dr = 2:1 **329a**:**329b**).

Scheme 120

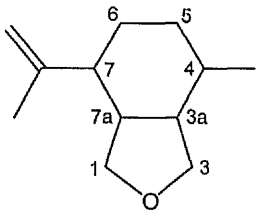
The cyclisation of secondary trichloroacetates such as **330** can yield the diastereomeric lactones **331a** and **331b** which possesses the bicyclic core found in eunicellin **144**. Lactone **331a** also possesses the correct relative stereochemistry at C-3a, C-4, C-7 and C-7a required to synthesise the diterpenoid eunicillin **144, Scheme 121.**



Reagents and conditions: a) CuCl (5 mol%), dHBipy (5 mol%), 1,2-DCE, reflux, 3.5hrs, **331a**:**331b** 2:1 ratio.

Scheme 121

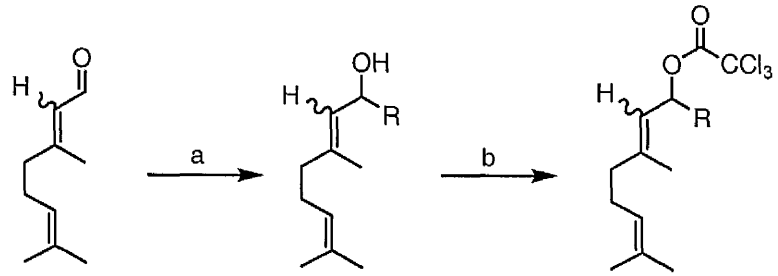
For the following sections related to the synthesis of cladiellins, the identification of individual atoms is based on the IUPAC numbering system (unless otherwise indicated), **Scheme 122**.



Scheme 122

8.2 Synthesis of C3 substituted bicyclic butyrolactones

With two rings of eunicillin **144** being formed *via* **ATRC** of the trichloroacetate derived from geranial, functionalisation of the lactone ring could give the means for the formation of the third, more synthetically demanding 9 membered ring. The construction of C3-substituted lactones required the synthesis of secondary trichloroacetates which were prepared from the addition of a suitable organometallic species to geranial **332** (2:1 ratio of *E*:*Z*), followed by trichloroacetylation of the resulting secondary alcohol. A number of alcohols were prepared by Dr. C. Knight, **Scheme 123**.



332 **333** **334**

Reagents and conditions: a) RMgBr or RLi, THF, -78 °C; b) $ClCOCCl_3$, Et_3N, Et_2O; yields and reagents for steps a) and b) are summarised in the table below.

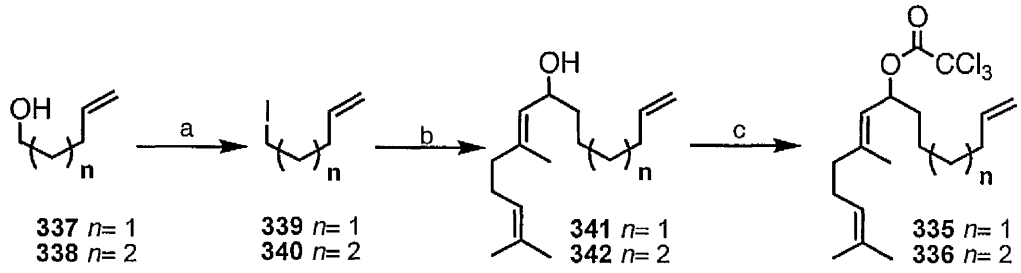
	Organometallic species	Secondary alcohol (**333**)	Trichloroacetate (**334**)[a]
a	MeLi	89%	87%
b	EtMgBr	72%	83%
c	BuLi	76%	72%
d	Propargyl magnesium bromide	93%	94%

[a] Yields refer to the crude residues as these substrates readily decompose at 17 °C (typically with a half life of 1 hour). Attempts to chromatograph all secondary acetates resulted in decomposition.

Scheme 123

The pentenyl and hexenyl acetates, **335** (*n*= 1) and **336** (*n*= 2) respectively, were prepared by Dr. C. Knight by converting alcohols **337** and **338** to iodides **339** and **340** in 92% and 94%

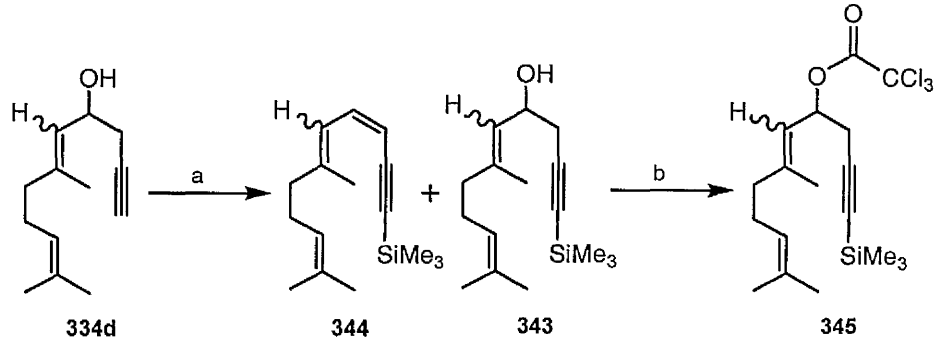
yields respectively.[73] Halogen-metal exchange[74] of **339** and **340** with *t*-BuLi at -78 °C produced the unsaturated organolithium species which reacted with geranial to afford the secondary alcohols **341** and **342** in 72 and 83% yield respectively, **Scheme 124.**



Reagents and conditions: a) PPh_3, imidazole, penten-1-ol or hexen-1-ol, I_2, 92% for **339** and 94% for **340**; b) i) *t*-BuLi (2 eq), -78 °C, Et_2O; ii) (*E*+*Z*)-geranial, 72% for **341** and 83% for **342**; c) $ClCOCCl_3$, Et_3N, Et_2O, 0 °C, 85% for **335** and 87% for **336.**

Scheme 124

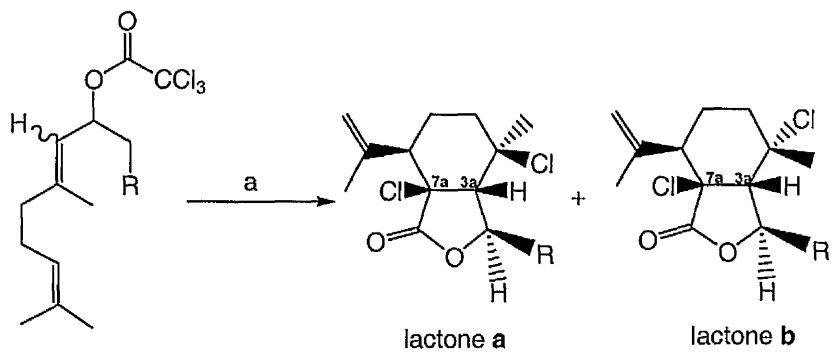
Trimethylsilylpropargyl alcohol **343** was synthesised *via* the alkyl alcohol **334d** by reaction with *n*-BuLi (2 eq) followed by trimethylsilyl chloride. The silyl ether was then hydrolysed with 1M $HCl_{(aq)}$ affording the desired alcohol **343.** A small amount of eliminated **344** was also produced *via* hydrolysis of the silyl ether. Trichloroacetylation of **343** afforded the acetate **345.** All compounds made were synthesised as a mixture of *E*/*Z* isomers (*ca.* 50:50 ratio), **Scheme 125.**



Reagents and conditions: a) *n*-BuLi (2 eq), TMSCl (2 eq), 1M $HCl_{(aq)}$, 68%; b) $ClCOCCl_3$, Et_3N, Et_2O, 0 °C, 89%.

Scheme 125

With a wide range of trichloroacetates synthesised, they were subjected to cyclisation under **ATRC** conditions. 1,2-Induction was observed with the stereochemistry of C3-H and C3a-H being *trans* with respect to each other. In some cases both C-4 diastereoisomers were observed generally in a 2:1 ratio in favour of the product with a pseudo-equatorially disposed methyl group, lactone **a**, the isolated yields and diastereomeric ratios are tabulated below, **Scheme 126.**



lactone **a** lactone **b**

Reagents and conditions: a) Cu(I)Cl (5 mol%), dHBipy (5 mol%), 1,2-DCE, reflux, 3.5 hrs.

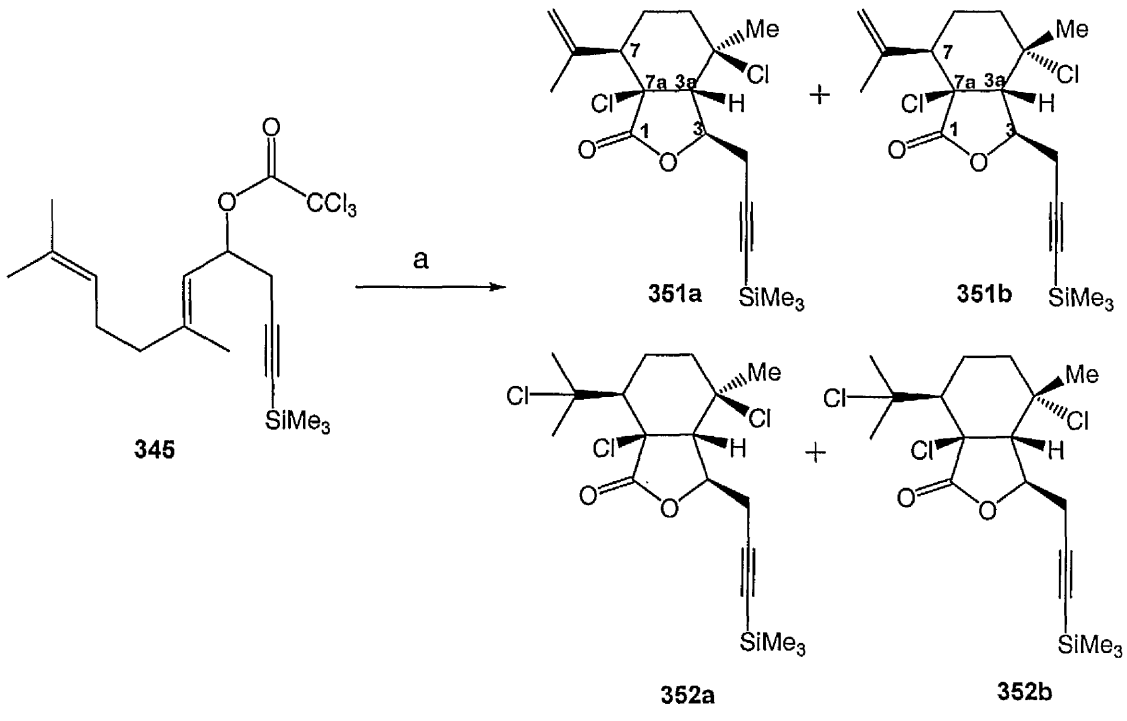
Cyclisation of **R**	Yield of lactone **a**	Yield of lactone **b**
Methyl **346**	45%	19%
Ethyl **347**	38%	20%
Butyl **348**	25%	5%
Pentenyl **349**	20%	7%
Hexenyl **350**	15%	5%
Trimethylsilyl propargyl **351**	30%	11%

Scheme 126

The relative stereochemistry of **348a** was assigned using single crystal X-ray diffraction analysis, revealing the relative *trans* stereochemistry. **Scheme 126** shows that increasing the size and complexity of the C3 substituent can decrease the yield of cyclised products. The trichloroacetates are also thermally unstable, with competition between decomposition and cyclisation. This instability is largely due to the dissociation of the acetate group. The reaction

is tolerant to alkyne and alkene functionality, however it is sensitive to oxygen and the reaction requires degassing.

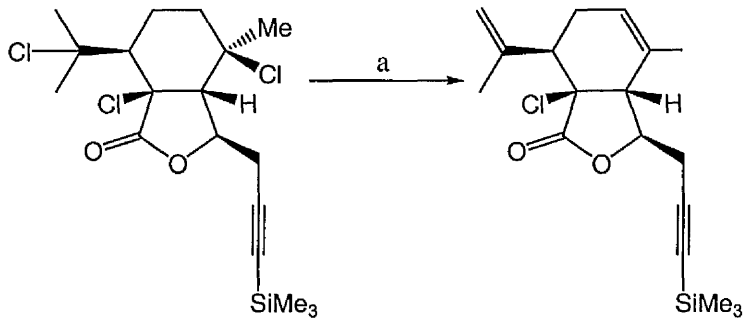
Repetition the reaction of trimethylsilylproparyl **345** with Cu(I)Cl/ dHBipy proved erratic with global yields ranging from 0 to 25%. A new catalyst system was devised using Cu(I)Cl (5 mol%), *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (5 mol%) and $Ln(OTf)_3$ (5 mol%). This gave more consistency to the yields ranging from 20 to 30%. However there was the inclusion of new intermediates within the reaction, trichlorolactones **352a** and **352b**, **Scheme 127**.



Reagents and conditions: a) Cu(I)Cl (5 mol%), *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylene-triamine (5 mol%), $Ln(OTf)_3$ (5 mol%), 1,2-DCE, reflux, 3.5 hrs.

Scheme 127

Compounds **352a** and **352b** were easily isolatable *via* flash chromatography and are intermediates previous to **351a** and **351b**. Elimination of chlorine to give the isopropenyl moiety appears to be sluggish with the new catalyst system. Trichlorolactone **352a** was converted to the lactone **353** using Li_2CO_3/ LiCl in DMF, **Scheme 128**.



352a **353**

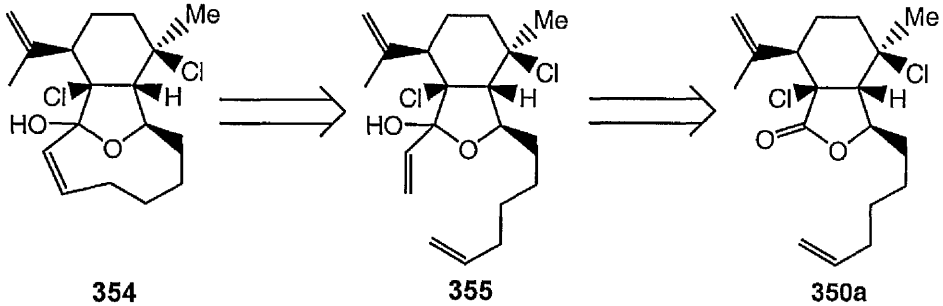
Reagents and conditions: a) LiCl, Li_2CO_3, DMF, 100 °C, 89%.

Scheme 128

8.3 First attempted formation of the bicyclo[6.2.1] undecane skeleton *via* RCM.

8.31 Introduction

The initial work into the formation of the bicyclo[6.2.1] undecane skeleton by Dr. C. Knight[72] was to produce a model system with the simple three major rings in place. The hexenyl lactone **350a** was attempted to look at functionalisation of the lactone ring. Synthesis of a diene, such as **355**, might have the ability to undergo ring closing metathesis when subjected to either **89** or **90**. The alkene **354** was to be synthesised *via* metathesis of **355**, containing the full tricyclic skeleton found in the cladiellins and briarellins, **Scheme 129**.

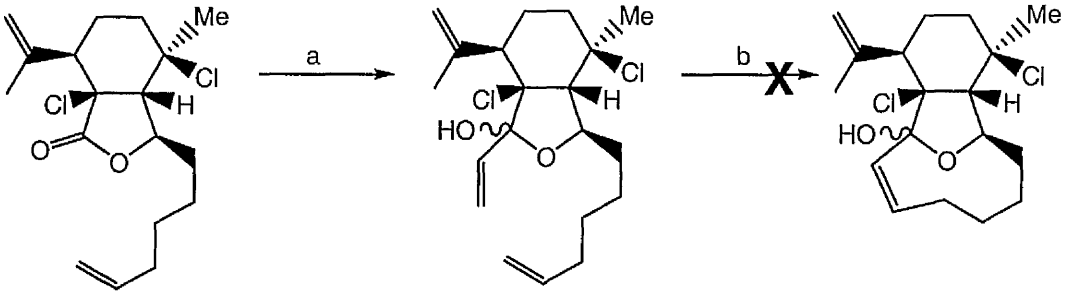


354 **355** **350a**

Scheme 129

8.32 Attempted synthesis of the oxa-bicyclo[6.2.1] undecane skeleton *via* RCM.

When lactone **350a** was treated with vinylmagnesium bromide, this afforded the vinyl lactol **356** as a 1:1 mixture of diastereoisomers in 89% global yield. Column chromatography resulted in decomposition and when the crude reacted with **89** without purification, only decomposition was detected. The lactols were deemed thermally unstable, with an approximate half life of about 1 hour, **Scheme 130**.

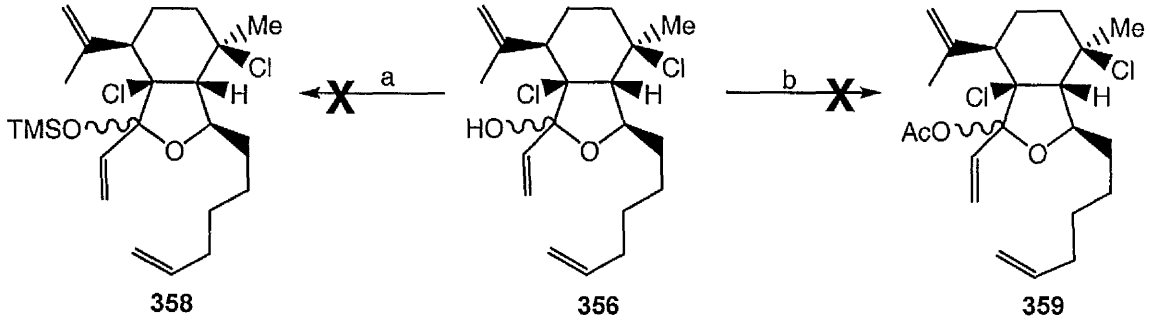


350a **356** **357**

Reagents and conditions: a) vinylmagnesium bromide, THF, -78 °C, 89%; b) **89**, DCM, reflux, no reaction.

Scheme 130

Due to instability of **356** no metathesis products were observed at 17 °C or in refluxing DCM. Another reason for the inability of the molecule to methathesis could be due to the allyl alcohol. It has been documented[68] that an adjacent hydroxyl group may inhibit the formation of the metallocyclobutane, essential for metathesis to occur. Protection of the hydroxyl group in **356** was unsuccessful either as the trimethylsilyl ether **358** or the acetate **359**, **Scheme 131**.

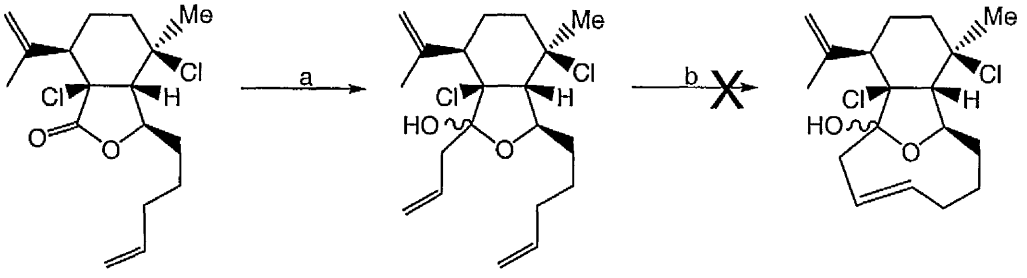


358 **356** **359**

Reagents and conditions: a) TMSCl, imidazole, DCM, no reaction; b) Ac_2O, pyridine, Et_2O, no reaction.

Scheme 131

As a consequence of allyl alcohol **356** being unable undergo metathesis, substrate **360** was prepared in an effort to move the olefin further away from the polar functionality and prevent any possible interaction with the metallocyclobutane. Addition of allylmagnesium bromide to the pentenyl derivative **349a** provided **360** as a 1:1 mixture of diastereoisomers in 83% yield. Exposure of **360** to **89** and **84** resulted in no observable metathesis products being isolated. Refluxing the reagent in dichloromethane resulted in decomposition of the starting material, **Scheme 132.**

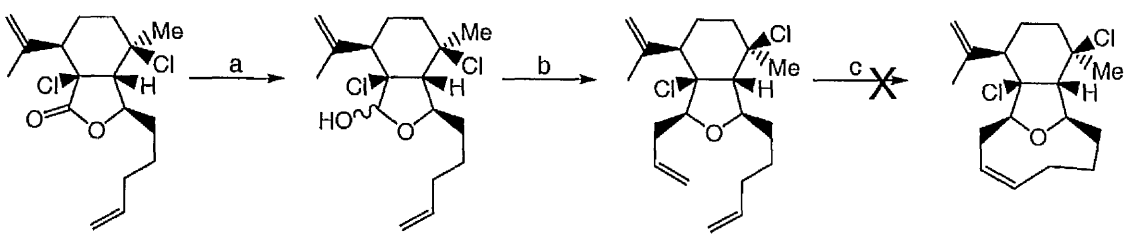


349a **360** **361**

Reagents and conditions: a) allylmagnesium bromide, THF, -78 °C, 83%; b) **89** or **90** (10 mol%), DCM, reflux, no reaction.

Scheme 132

Due to decomposition of diene **360**, an improved route was designed. Tetrahydrofuran **362,** devoid of a C-1 hydroxyl, was synthesised *via* lactol **278**, available as a single unidentifiable diastereoisomer from DIBAL-H reduction of **349a.** Treated with a Lewis acid, the oxonium ion was generated and addition of trimethylallyl silane gave the C-1,C-3 *cis* disubstituted tetrahydrofuran **362,** produced in 74% yield over 2 steps, **Scheme 133.**



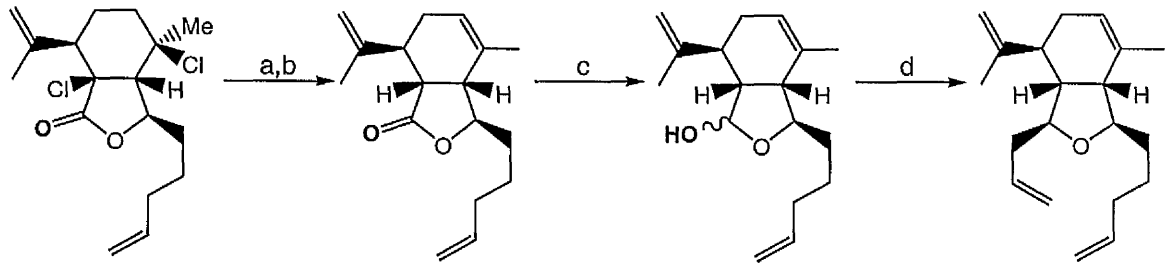
349a **363** **362** **364**

Reagents and conditions: a) DIBAL-H, DCM, -78 °C, 84%; b) $BF_3.Et_2O$, DCM, -78°C, trimethylallyl silane, 89%; c) **89** or **90**, DCM, no reaction.

Scheme 133

All attempts at coaxing the metathesis of **362** failed mainly leading to the decomposition of the starting material. A possible conclusion for decompostion was that the chlorines may have had a negative effect on **89** and **90**. Possible insertion into the carbon-halide bond may destroy the active metathesis catalyst and generate an organoruthenium species which could potentially undergo any number of isomerisations or eliminations. Evidence for this process has been previously observed within the Quayle group.[66]

Thinking that the C-X chlorine substituent maybe detrimental to the course of the metathesis reaction of **362**, we next decided to prepare the THF derivative **367**. Lactone **349a** was converted to alkene **365** *via* elimination and chlorine abstraction. Following dechlorination, the olefin was subjected to an allylation which afforded the tetrahydrofuran **367** *via* the lactol **366** in 73% yield over four steps, **Scheme 134.**

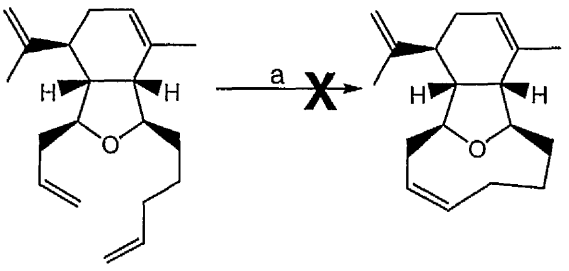


349a **365** **366** **367**

Reagents and conditions: a) LiCl, Li_2CO_3, DMF, 140 °C, 95%; b) Bu_3SnH, AIBN, benzene, reflux, 2 hrs, 89%; c) DIBAL-H, DCM, -78 °C, 95%; d) $BF_3.Et_2O$, DCM, -78 °C, trimethylallyl silane, 91%.

Scheme 134

Diene **367** reacted with **89** in DCM or refluxing toluene resulted in starting material being recovered in quantitative yield, **Scheme 135.**

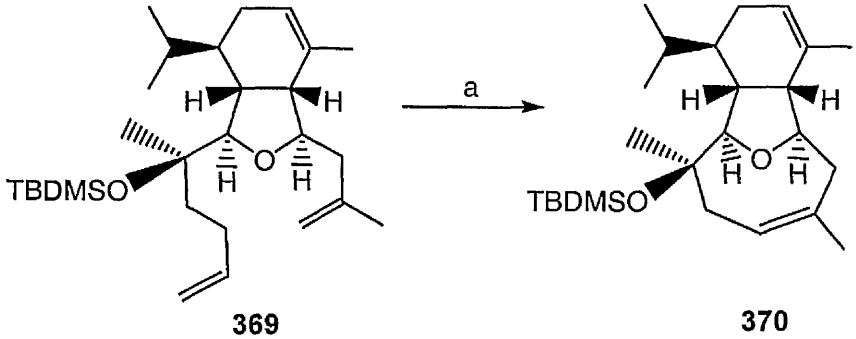


367 **368**

Reagents and conditions: a) **89**, DCM, no reaction.

Scheme 135

Resubjecting **367** to **90** in refluxing DCM for 12 hours led to a complex mixture of products. With no starting material present in the crude ^{1}H-NMR, a speculative explanation for the disappearance of the terminal olefin signals could be due to isomerisation prior to cyclisation leading to a multitude of products. This theory was confirmed by a report by Overman[75] who showed that when diene **369** was subjected to **88**, a metathesis product **370** was isolated in 40% yield. This was the result of an isomerisation of the terminal alkene prior to cyclisation and afforded the unexpected eight-membered ring, **Scheme 136**.



369 **370**

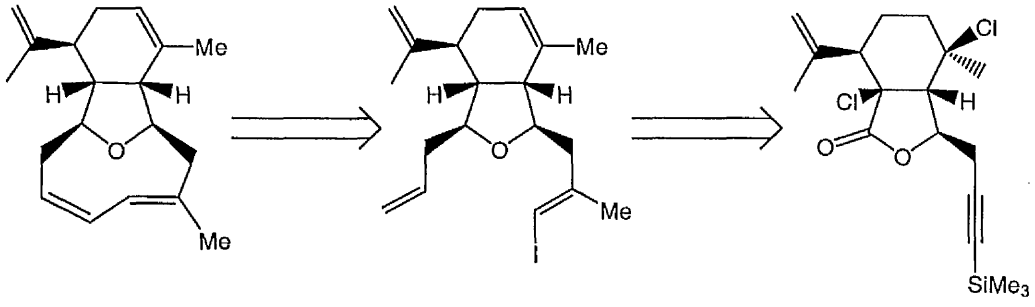
Reagents and conditions: a) **88** (10 mol%), toluene, 40%.

Scheme 136

8.4 Second attempted formation of the bicyclo[6.2.1] undecane skeleton

8.41 Introduction

After failure to cyclise the nine membered ring *via* **RCM**, Dr. C. Knight[72] moved on to the next strategy. It was envisaged that the most convergent route to eunicellin **144** involved the construction of as much of the oxanonene subunit as possible subsequent to the cyclisation of a secondary trichloroacetate. From the initial experiments, the efficiency of the **ATRC** with highly functionalised acetate would be too poor to provide enough material to complete the synthesis of **144**. The first problem to overcome was the use of the trimethylsilylpropargyl unit as a C-3 substituent. This gave moderate yield from **ATRC** and the possessed the functional density required to construct a wide range of oxanonenes from the minimum number of transformations. The next choice of strategy for construction of the nine-membered ring was using an intramolecular Heck cyclisation, **Scheme 137**.

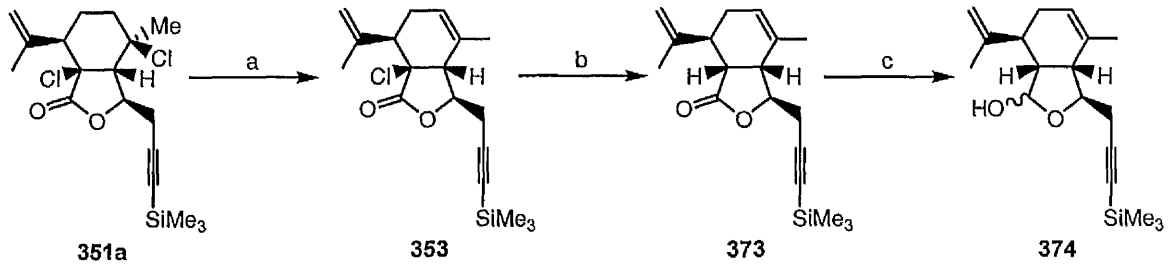


371 **372** **351a**

Scheme 137

8.42 Attempted synthesis of the oxa-bicyclo[6.2.1] undecane skeleton *via* intramolecular Heck cyclisation.

Post **ATRC** diastereoisomer **351a** was dechlorinated in two steps, first using LiCl and Li_2CO_3 to selectively eliminate the chlorine on the cyclohexane ring to produce **353**, followed by exposure to tributyltin hydride to eliminate the final chlorine to give **373**. Lactone **373** was reduced to lactol **374** using DIBAL-H, **Scheme 138**.

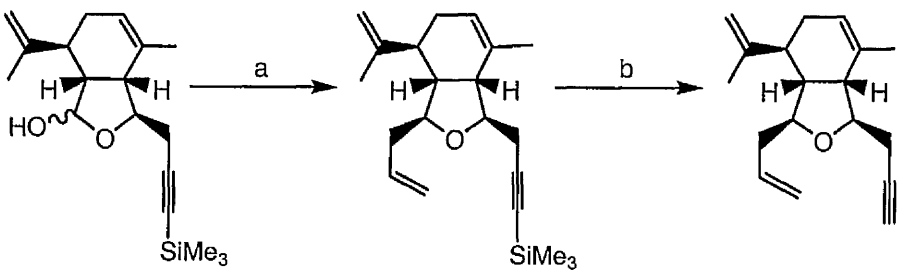


351a **353** **373** **374**

Reagents and conditions: a) LiCl, Li_2CO_3, DMF, 100 °C, 89%; b) Bu_3SnH, AIBN, benzene, reflux, 2 hrs, 95%; c) DIBAL-H, DCM, -78 °C, 97%.

Scheme 138

Allylation of **375** was accomplished *via* the Lewis acid catalysed addition of allyltrimethylsilane affording **376** as a single diastereoisomer (determined by ^{1}H-NMR) in high yield. The trimethylsilyl group was removed by reacting **376** with tetrabutylammonium fluoride producing the terminal alkyne **377** in 60% overall yield over 5 steps from the dichlorolactone **351a, Scheme 135**.

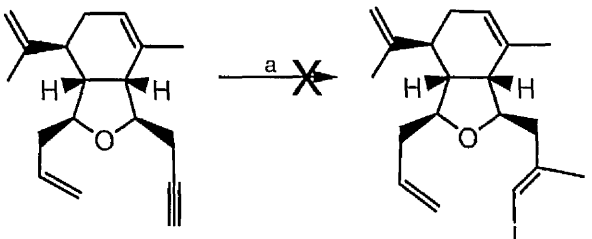


375 **376** **377**

Reagents and conditions: a) $BF_3.Et_2O$, DCM, -78 °C, allyltrimethylsilane, 89%; b) TBAF, THF, 83%.

Scheme 139

Zirconium catalysed carboalumination of **377,** followed by an iodine quench, failed to produce any of the desired trisubstituted olefin **378.** Attempted modification[76] using the Negishi[77] procedure, which involving the addition of 1 mole equivalent of water, also proved unsuccessful, **Scheme 140.**

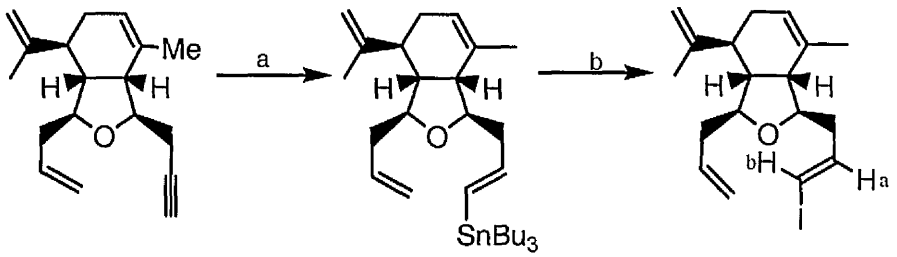


377 378

Reagents and conditions: a) Cp_2ZrCl_2, $AlMe_3$, H_2O (1eq), 1,2-DCE 60 °C, 24h then I_2 at 0°C, no reaction.

Scheme 140

Hydrostannylation of **377** using tributyltin hydride and catalytic AIBN produced the *trans* vinyl stannane **379** in excellent yield. Addition of iodine to the crude stannane **379**, in DCM at 0 °C, gave the *trans* vinyl iodide **380** in 87% yield over two steps after column chromatography, **Scheme 141**.

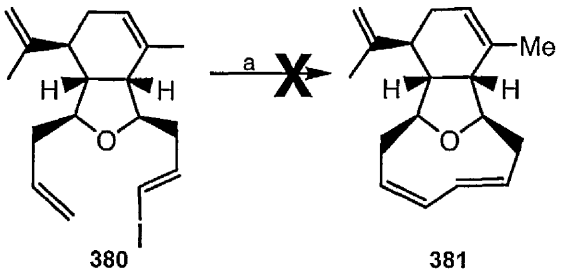


377 379 380

Reagents and conditions: a) Bu_3SnH, AIBN, benzene, reflux, 4 hrs; b) I_2, benzene, 0°C, 87% over two steps.

Scheme 141

Numerous attempts were made by Dr. C. Knight to cyclise the vinyl iodide **380** using Pd(0) catalysed intramolecular Heck chemistry using palladium tetrakistriphenylphosphine. None of the desired diene **381** was observed, even when several equivalents of the palladium catalyst was used. Iodide **380** proved to be quite unstable, undergoing decomposition at temperatures in excess of 50 °C, **Scheme 142**.



380 381

Reagents and conditions: a) $Pd(PPh_3)_4$, K_2CO_3, MeCN, 17 °C to 50°C.

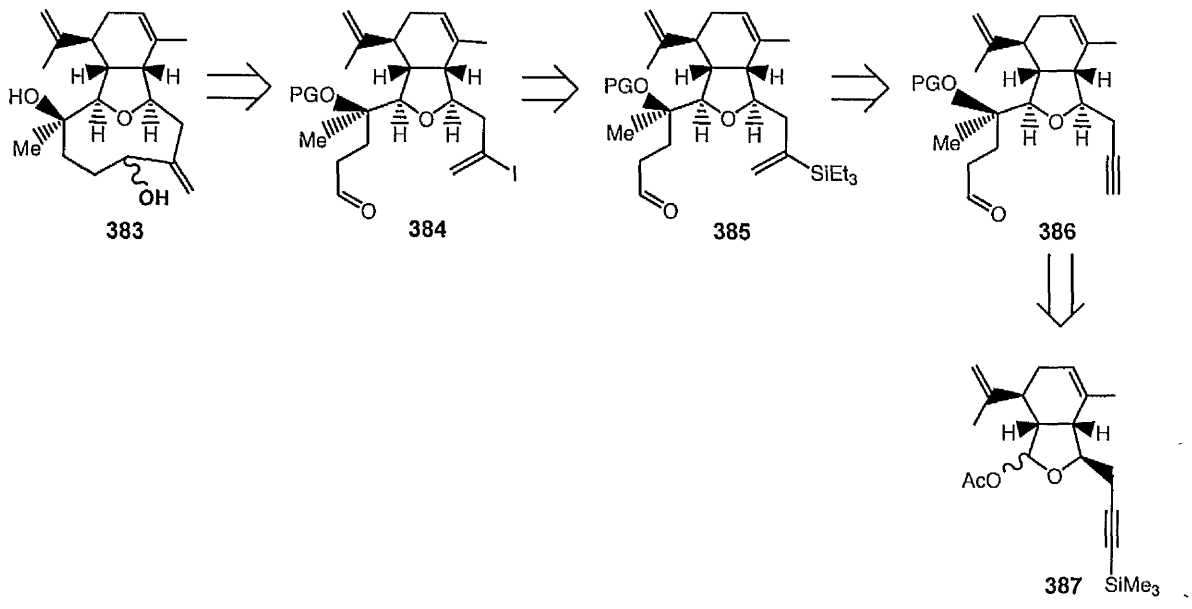
Scheme 142

The inability to form the nine-membered ring in this case may be due to the large degree of strain that may possibly exist in the cyclic *cis-trans* diene.

Section 9. Current work: Third attempted formation of the bicyclo[6.2.1] undecane skeleton. Directions towards Nozaki-Hiyama-Kishi coupling.

9.1 Introduction

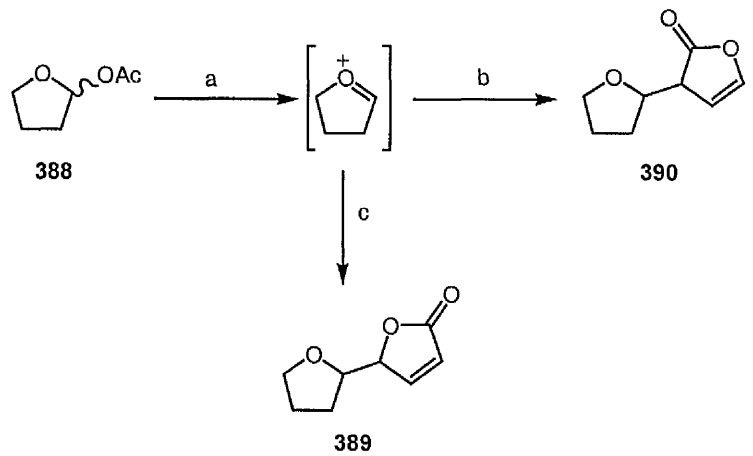
Given the limited success of the previous approaches to produce the nine membered ring, it was decided to turn to a reaction which has proven to be a reliable tool in the synthesis of oxanonenes[78]. The Nozaki-Hiyama-Kishi reaction[79] employs chromium (I) chloride and catalytic nickel chloride for the coupling of aldehydes with the vinyl iodide functionality. Intramolecular coupling of **384** would produce the nine-membered ring bridged ether **383** found in the cladiellins and briarellins. The internal vinyl iodide might be furnished from the hydrosilylation of the terminal alkyne **386**, generating the vinyl silane **385**, which upon treatment with iodine might provide the desired olefin **384**. The synthesis of the C3-C6 (cladiellin numbering) substituent, highlighted in the scheme below, with a protected C-3 tertiary alcohol and C-6 aldehyde is expected to proceed *via* the C-glycosylation of the acetate **387, Scheme 143**.



Scheme 143

9.2 The vinylogous Mukaiyama aldol reaction (VMA)

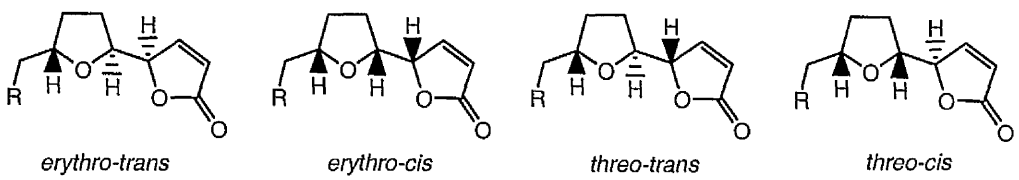
C-glycosylations of acetates such as **388** have been investigated, showing their potential towards the synthesis of the C3-C6 aldehyde moiety. The overall transformation requires the generation of an oxonium ion followed by addition of a nucleophile from the *exo* face, generating a C-1,C-3 disubstituted *cis* tetrahydrofuran. The vinylogous Mukaiyama aldol reaction (**VMA**) has been used by several groups to produce functionalised butenolides.[xx] Lewis acid-mediated addition of trimethylsilyloxy furans to anomeric acetoxytetrahydrofurans[80] producing tetrahydrofuranic butenolides is of great interest. It has been shown by Dr. C. Knight that in the case of 2-trimethylsilyloxyfuran, the addition from the γ-position of the butenolide is favoured generating the α,β-unsaturated butenolide **389.** However attack from the α-position is also possible and produces lactone **390, Scheme 144.**



Reagents and conditions: a) Lewis acid; b) α-addition of 2-(trimethylsilyloxy)furan; c) γ-addition of 2-(trimethylsilyloxy)furan.

Scheme 144

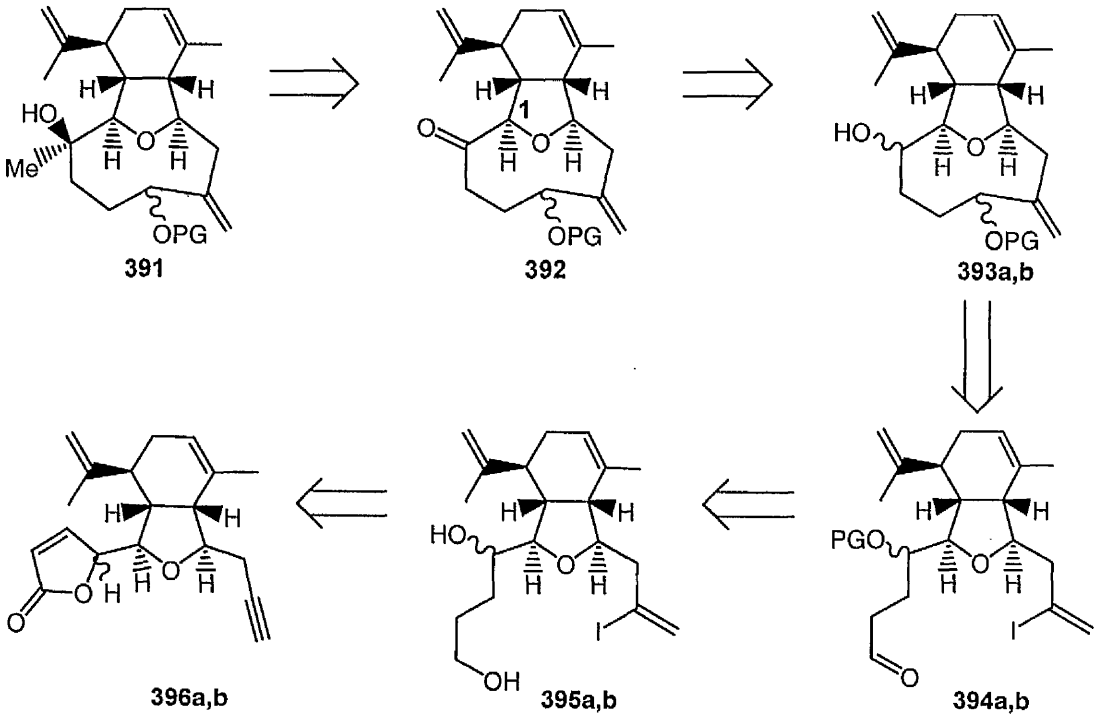
Throughout this section the VMA adducts are referred to as *threo-cis*, *threo-trans*, *erythro-cis* and *erythro-trans,* **Scheme 145.**



Scheme 145

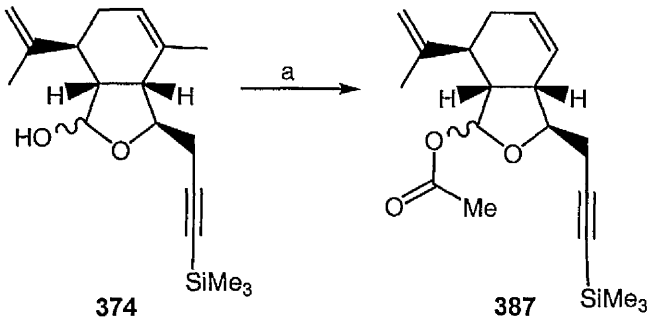
9.3 Strategy for the synthesis of the C3-C6 (cladiellin numbering) aldehyde moiety

Our strategy for the synthesis of aldehyde **394** from intermediate **396** is shown in **Scheme 146**. It is believed that the aldehyde **394** can be accessible from the diol **395**, following a protection strategy and oxidation. Treatment of the butenolide **396** with lithium aluminium hydride would give the desired diol **395**. Addition of 2-trimethylsilyloxyfuran to the acetate **387** could potentially afford 4 diastereoisomers as previously discussed. We hoped the C3 (cladielin numbering) methyl substituent would be furnished stereoselectively upon treatment of the ketone **392** with a methylating reagent, such as methyl lithium. We envisaged the ketone **392** can arise from oxidation of alcohol **393** derived from either the *threo* or *erythro* adducts **396a** and **396b**.



Scheme 146

The acetate **387** is synthesised from the lactol **374**, when exposed to acetic anhydride and pyridine, in 94% yield, **Scheme 147**.

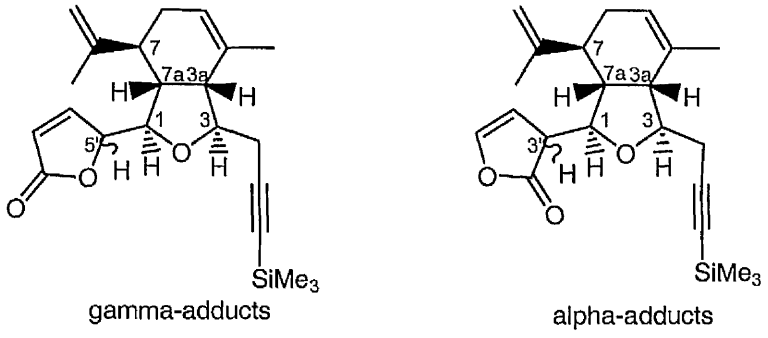


Reagents and conditions: a) Ac_2O, pyridine, DMAP, DCM, -78°C, 94%.

Scheme 147

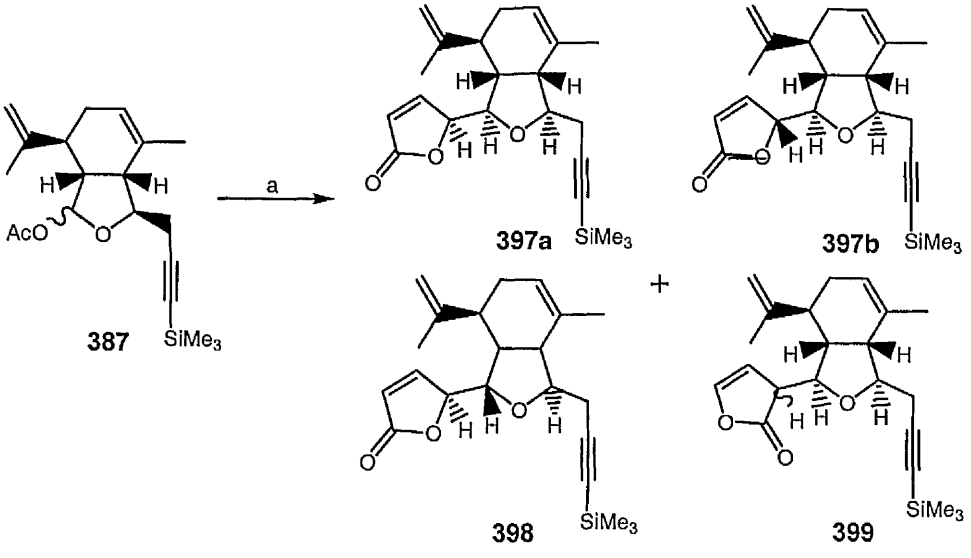
9.4 The vinylogous Mukaiyama aldol (VMA) reaction – results and discussion

Throughout this section the identification of individual atoms in the compounds resulting from the VMA reaction are based upon the standard IUPAC numbering system, **Scheme 144**.



Scheme 148

Acetate **387** was reacted with 2-trimethylsilyloxyfuran in the presence of $BF_3.Et_2O$, giving a selection of products, **Scheme 145**.



Reagents and conditions: a) 2-trimethylsilyloxyfuran, $BF_3.Et_2O$, 2 hrs, DCM, -78 °C, 40% of *erythro-cis* adduct **397a**, 28% of *threo-cis* adduct **397b**, 9% of **398**, and 5% of **399**.

Scheme 149

Compounds **398** and **399** were isolated as discrete compounds after column chromatography. All components have undergone the VMA reaction giving different products, with all containing butenolide signals in the 1H-NMR, **Scheme 150**.

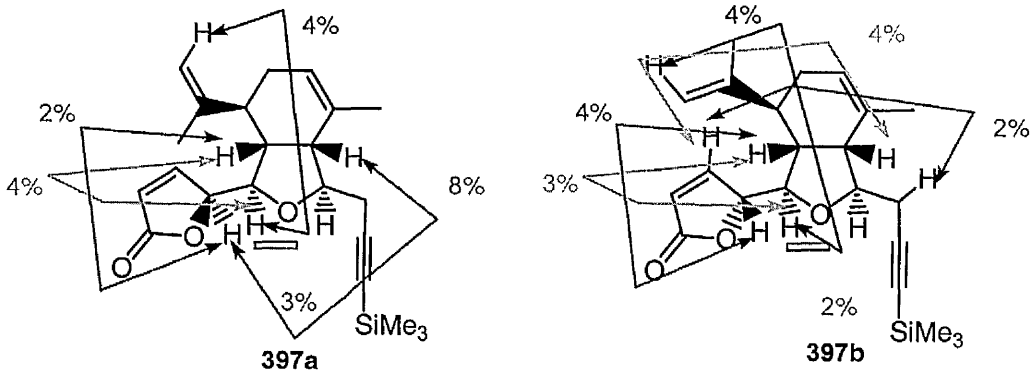
	Butenolide protons (δ)
397a	6.18 (1H, dd) and 7.75 (1H, dd)
397b	6.18 (1H, dd) and 7.82 (1H, dd)
398	6.05 (1H, dd) and 7.42 (1H, dd)
399	5.80 (1H, dd) and 6.80 (1H, dd)

Scheme 150

The major product **397a** was assigned as the *erythro-cis* adduct based on coupling constants and certain enhancements in nOe experiments. The minor component **397b** was isolated in 28% yield and assigned in the same way as the *threo-cis* adduct. In reported[81] examples, the β-olefinic proton is between 0.1 and 0.2 ppm further downfield for the *threo* adducts. ^{1}H NMR data backs up this finding further proving that **397a** is *erythro-cis*. Other reported examples of this reaction[82] have shown that a larger coupling constant is often seen between C5′-H and C1-H for the *threo* adduct rather than the *erythro* adduct. Using 3D representations for *threo* adduct **397a** and *erythro* adduct **397b,** we can show that the dihedral angles between C5′-H and C1-H are approximately 170° and 70° respectively. This observation would suggest that the coupling constant for the *threo* adduct should be larger than the *erythro*. From analysis of the ^{1}H-NMR spectrum, a coupling constant of 9 Hz and 4 Hz for **397a** and **397b** respectively is observed between C1-H and C5′-H. However this data does not coincide with the relative stereochemistry depicted in **Scheme 149**. The larger coupling for the *erythro cis* butenolide **397a** is possibly due to the presence of a rotomer effect produced from the equatorial isopropenyl substituent.

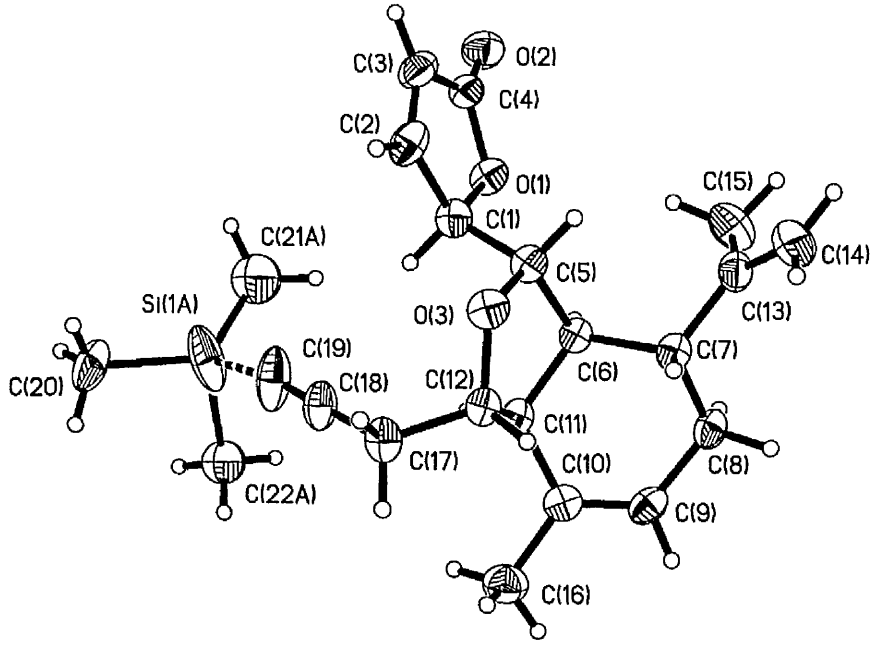
Evidence for the *cis* relative stereochemistry, with respect to C-1 and C-3, of the furan is observed in nOe experiments on both the *threo* and *erythro* adducts. Irradiating the double doublet at δ7.85, corresponding to the β-oleinic proton in the butenolide, on *threo* adduct **397b** an enhancement is observed in the characteristic AB system of the propargylic methylene

protons and also to C3a-H. This suggests *cis* relative stereochemistry with respect to C1-H and C3-H. Irradiation of the same proton on the *erythro* butenolide **397a**, an enhancement of 8% is observed between C5'-H and C3a-H. This indicates that the butenolide is orientated on the same face as C3a-H and the *cis* relative stereochemistry (with respect to C1 and C3) of the furan, **Scheme 151**.



Scheme 151

An unambiguous stereochemical assignment in the case of **397a** was proved by the way of a single crystal X-ray diffraction study on **397a,** produced by Dr. C. Knight, revealing that this butenolide was indeed the *erythro-cis,* **Scheme 152.**



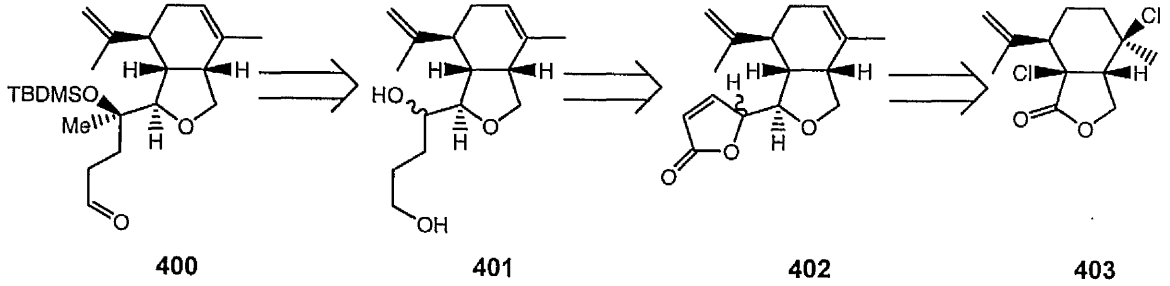
Scheme 152

From analysis of the ^{1}H-NMR spectrum *threo-cis* butenolide **397b,** a trace amount of a butenolide **398** in the ratio of 1:19 **397b:398** (estimated from analysis of the ^{1}H-NMR integrals) was also visible. It was not possible to determine the relative stereochemistry of **398** from ^{1}H-NMR coupling constants or nOe experiments. We have suggested that it may be the *threo* adduct resulting from addition to the *endo* face of the oxonium cation. Also isolated was a trace amount of regioisomer **399** in 5% yield which are a result of addition from the α-position of the furan. From analysis of the proton NMR spectrum the characteristic butenolide olefinic protons found in **397a** and **397b** are no longer present. The butenolide olefinic protons in **399** are now double doublets at δ5.80 and δ6.80 respectively, which suggests the protons are not in conjugation with the carbonyl group. The C5′-H resonance is no longer visible and has been replaced with the C3′-H signal, 2.00ppm further upfield, indicating oxygen is not attached to this carbon. We were unsure of the stereochemistry of this particular regioisomer however only one isomer was produced.

9.5 Model studies investigating viable routes on the post VMA adduct of C1 substituted furan fragments

9.51 Introduction

At this point it became prudent to test any further reactions on a model system. All material gained after the **VMA** reaction was of high value, with incorrect decisions proving costly in both time and resources. By elaborating on the C1 substituted side of the molecule after the **VMA** reaction, it would be possible to determine, test and optimise the best conditions to prepare one half of the molecule for the proposed NHK coupling, **Scheme 153**.

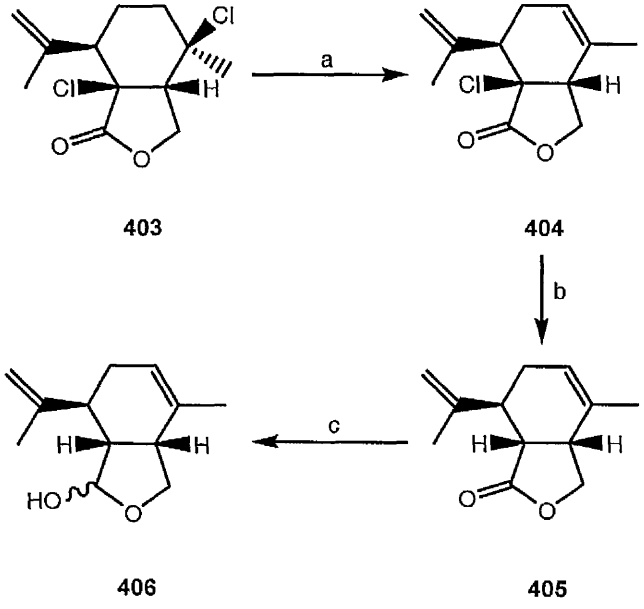


400 **401** **402** **403**

Scheme 153

9.52 Investigation of potential routes towards the formation of the C1 substituted furan fragment.

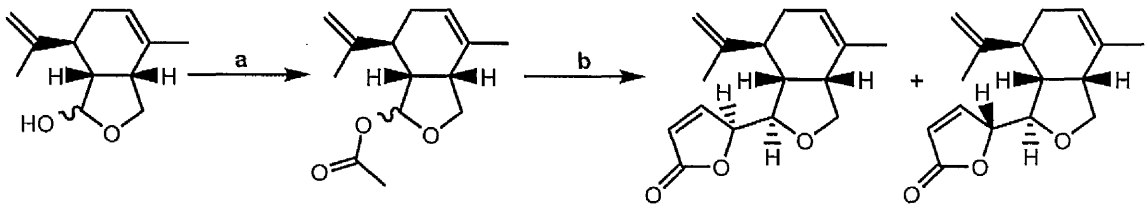
Starting from diastereoisomer **403**, synthesised by **ATRC** cyclisation of trichloroacetylated geraniol, elimination of HCl (Li_2CO_3, LiCl) gave **404**, followed by reduction of the C-Cl bond using tributyltin hydride afforded lactone **405.** Reduction of lactone **405** cleanly afforded lactol **406** as one unidentifiable stereoisomer**, Scheme 154.**



Reagents and conditions: a) Li_2CO_3, LiCl, DMF, 30 mins, DMF, 50 °C, 98%; b) Bu_3SnH, AIBN, benzene, reflux, 2 hrs, 95%; c) DIBAL-H, DCM, -78 °C, 97%.

Scheme 154

Lactol **406** was acetylated and VMA reaction carried out in the same manner as described in the previous section, producing major adducts *erythro-cis* **408a** and *threo-cis* **408b** in moderate yields, **Scheme 155**



406 407 408a 408b

Reagents and conditions: a) Ac_2O, pyridine, DMAP, DCM, -78 °C, 94%; b) 2-trimethylsilyloxyfuran, $BF_3.Et_2O$, 2 hrs, DCM, -78 °C, 44% of *erythro-cis* adduct **408a** and 35% of *threo-cis* adduct **408b**.

Scheme 155

^{1}H-NMR data undertaken on **408a** and **408b** is consistent with previous findings **397a** and **397b**, with the β-olefinic proton being 0.1 ppm further downfield for the *threo* adduct, **Scheme 156.**

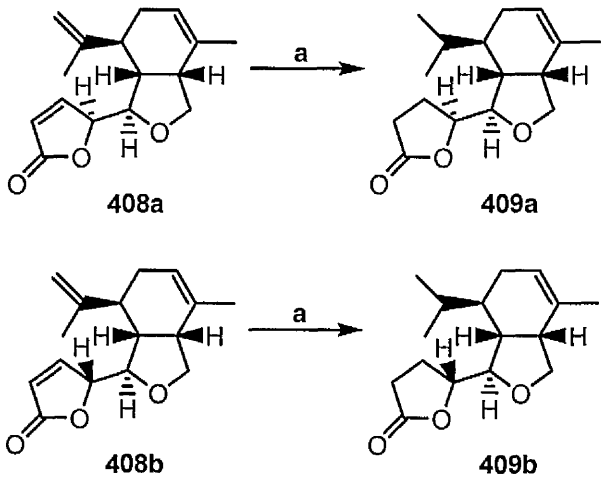
	Butenolide protons (δ)
397a *erytho*	6.18 (1H, dd) and 7.75 (1H, dd)
397b *threo*	6.18 (1H, dd) and 7.82 (1H, dd)
408a erytho	6.22 (1H, dd) and 7.47 (1H, dd)
408b *threo*	6.19 (1H, dd) and 7.53 (1H, dd)

Scheme 156

With the separated VMA products in hand, **408a** and **408b** were exposed separately to the same chemistry throughout the rest of the model synthesis with the hope of separately converting them into the same diastereoisomer.

With the synthesis carried out on both diastereoisomers, it would help prove the consistency of the reactions and increase potential material to successfully finish the synthesis. The next reaction in the sequence was to successfully reduce the butenolide without reduction of the cyclohexene fragment. Using Raney Nickel in THF/ water with an external source of H_2, **408a** and **408b** gave **409a** and **409b** in excellent yield. Instead of just selectively reducing the

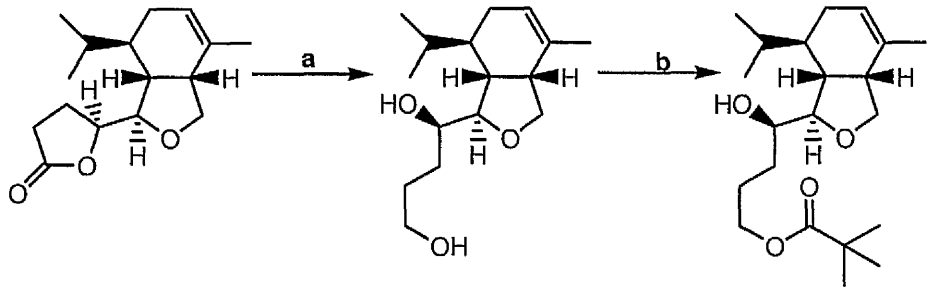
butenolide, the reaction also reduced the isopropenyl group. This was an unexpected but a welcomed result as the isopropenyl moiety would eventually have had to be reduced later under different proposed reaction conditions, **Scheme 157**.

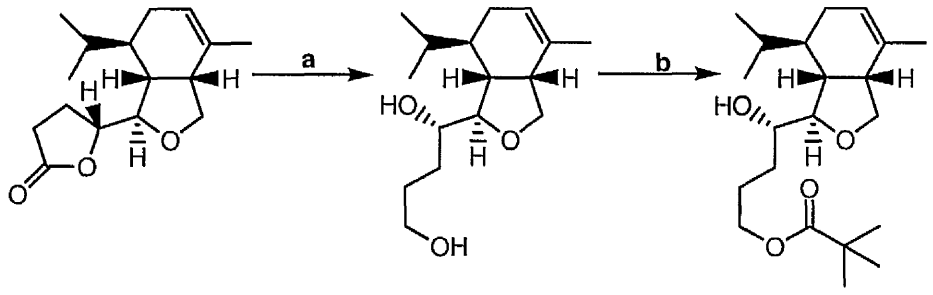


Reagents and conditions: a) Raney Nickel, THF/H_2O (3:1 ratio), H_2, 62-68%.

Scheme 157

Opening of lactone **409a** and **409b** to diol **410a** and **410b** was accomplished with excess amounts of $LiAlH_4$ in 89% yield. At this point it was decided to follow the same protecting group strategy as published by Macmillan.[49] Even though not our first initial choice for protection, the pivaloyl group chosen have proved successful.[46] Selective protection of the primary alcohol by reaction with pivaloyl chloride gave **411a** and **411b** with the secondary alcohol unaffected, **Scheme 158**.

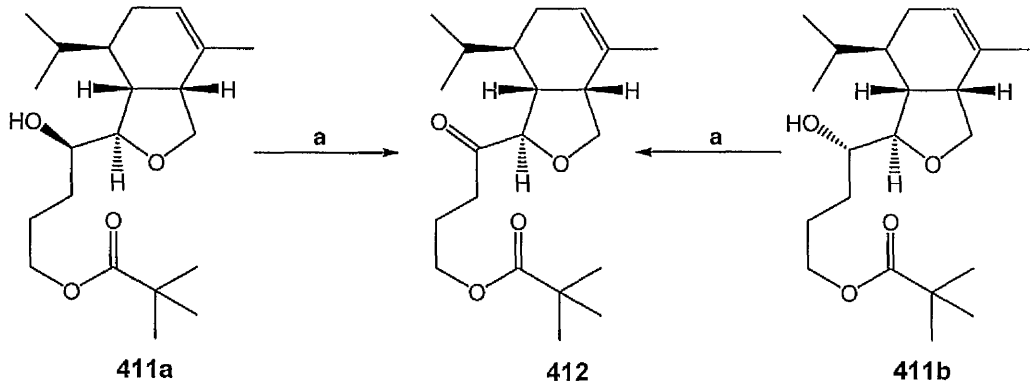




Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 85%; b) pivaloyl chloride, pyridine, Et_2O, 0 °C, 2 hrs, 82%.

Scheme 158

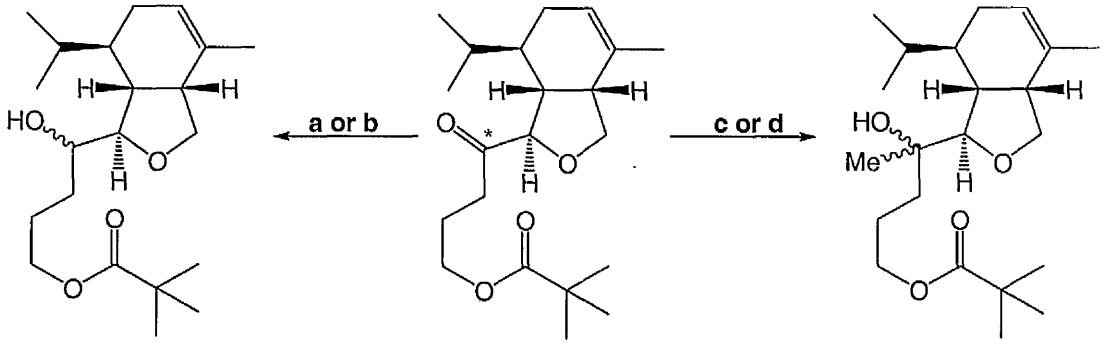
As previously described, it has always been our intention to convert alcohols **411a** and **411b**, epimeric at C-2, into a single key intermediate, ketone **412**. After protection of the primary alcohol, this became possible. Oxidation of **411a** and **411b** with TPAP and NMO afforded the same ketone **412, Scheme 159.**



Reagents and conditions: a) TPAP, NMO, DCM, 82-89%.

Scheme 159

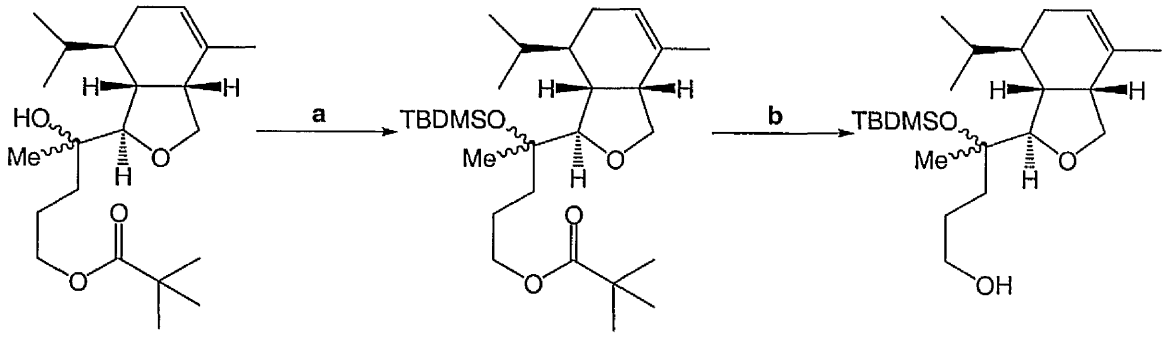
With ketone **412** in hand, we next attempted to generate the quaternary centre at *C by the reaction of a suitable "CH_3^-" equivalent. Reacting **412** with MeMgBr afforded **413** as a single diastereoisomer however we were unable at this stage to determine the relative stereochemistry at the newly converted stereogenic centre *C. Both methyl lithium and methylmagnesium bromide gave the same compound by ^{1}H-NMR, however this and subsequent nOe experiments could not conclusively prove which isomer was produced. However all was not lost as there was the possiblity to insert it further into the synthesis, when the nine membered ring had been formed. As an alternative strategy, an attempt was made to selectively reduce the ketone back to the secondary alcohol as a single diastereoisomer. Both attempts failed, giving a 50:50 mixture of **411a** and **411b**, **Scheme 160**.



Reagents and conditions: a) L-selectride, THF, 0 °C, 3 hrs, 65%; b) $LiAlH_4$, THF, 0 °C, 81%; c) trimethylaluminium, 2,6-di-tert-butyl-4-methylphenol, toluene, MeLi (1.5 M in THF), d) MeMgBr (1M in THF), THF, -78 °C, 3 hrs, 71%.

Scheme 160

Unable to ascertain the stereochemistry of the inserted methyl group into the model system, it was decided to use **413** to see how efficient protection of the tertiary alcohol was, with subsequent deprotection of the primary alcohol. TBDMS protection went smoothly to give **414** in 94% yield, with DIBAL-H reduction of the pivaloyl group giving the primary alcohol **415** in 65% yield. At this point, enough information had been gained to transfer it to the C1-C3 substituted furan fragment **385a** and **385b** and continue towards the synthesis of the clandiellins, **Scheme 161**.



413 **414** **415**

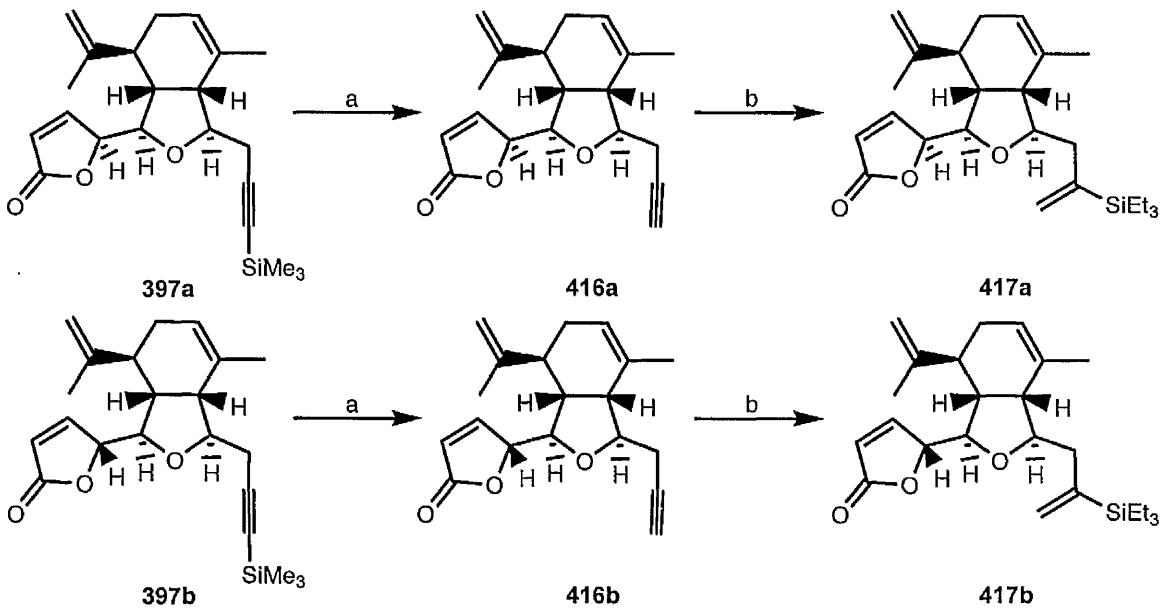
Reagents and conditions: a) TBDMS triflate, 2,6-lutidine, DCM, 0 °C, 3 hrs, 94%; b) DIBAL-H, DCM, 2 hrs, 0 °C, 65%.

Scheme 161

9.6 Manipulation of the VMA adduct

As discussed previously, it is possible to convert both butenlides into a viable intermediate for the eventual synthesis of eunicillen **144**. This strategy utilises the VMA adducts to maximum effect and justifies the retro aldol reaction as a powerful transformation in the reaction sequence.

Butenolides **397a** and **397b** could then be separated *via* flash chromatography and were desilylated (silver triflate/ water/ DCM/ methanol) affording the terminal alkyne **416a** and **416b** respectively in 84% yield. The silicon group can also be removed with silver nitrate and potassium cyanide in 92% yield. The hydrosilylation of **416a** and **416b** proceeded with Trost's catalyst (pentamethylcyclopentadienylruthenium *tris*acetonitrilehexafluoro phosphate), furnishing the internal vinyl silane **417a** and **417b** in 79-84% yield, **Scheme 162.**

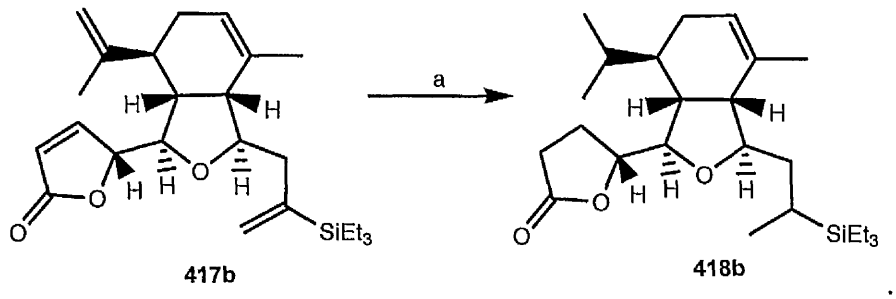


Reagents and conditions: a) AgOTf, H_2O, MeOH, DCM (1:3:5 ratio), 18 hrs, 92% yield; b) pentamethylcyclopentadienylruthenium *tris*acetonitrilehexafluoro phosphate, Et_3SiH, DCM, 0 °C, 79-84% yield

Scheme 162

9.7 Reduction of the butenolide

Previous work accomplished by Dr. Chris Knight saw him reduce the butenolide with Raney Nickel. However when this procedure was repeated, the reaction would not proceed to the γ-butyrolactone with 100% starting material being recovered. When an external source of hydrogen was added, the butenolide did reduce however along with the isopropenyl group, as seen on the C-3 model system. Unfortunately, the reduction of the molecule did not stop there with reduction of the vinyl silane also taking place, giving a 1:1 mixture of diastereoisomers, **Scheme 163.**

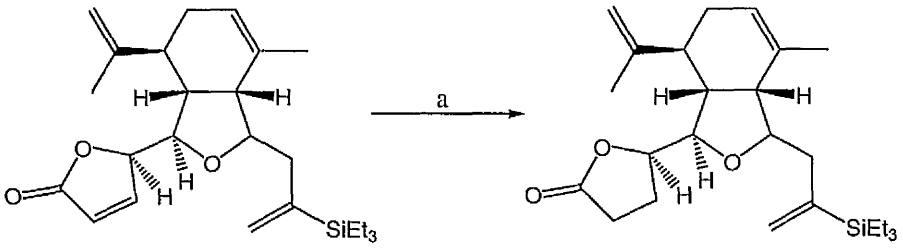


417b **418b**

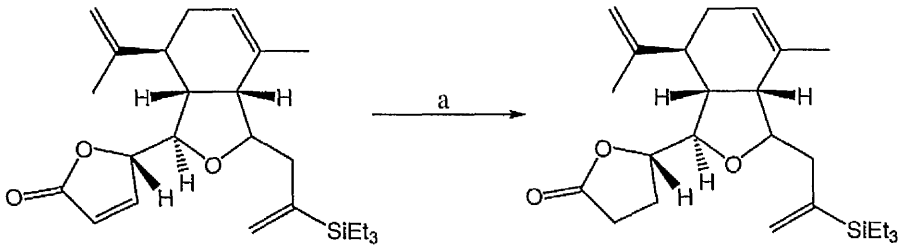
Reagents and conditions: a) Raney $Ni_{(aq)}$, 50 wet wt%, THF, H_2O, H_2, 6hrs, 70%.

Scheme 163

Fortunately the Raney Nickel reduction did leave the more sterically hindered cyclohexene olefin intact. At this point some time was spent trying to selectively reduce both the butenolide and the isopropenyl group without touching the vinyl silane. Repeating the reaction but this time reducing the reaction times (30 mins-4 hours) gave the same result. Due to the similarity in polarity of the different components it was extremely difficult to follow the reduction with NMR being the only possible option. All conditions gave either inseparable mixtures of starting material and product or gave product and reduced vinyl silane. Moving to a less reactive catalyst, Spongy Cobalt®, the reaction proceeded to reduce butenolide **417a** and **417b** to give **418a** and **418b.** The catalyst left all other olefins on the molecule intact, **Scheme 164.**



417a **418a**



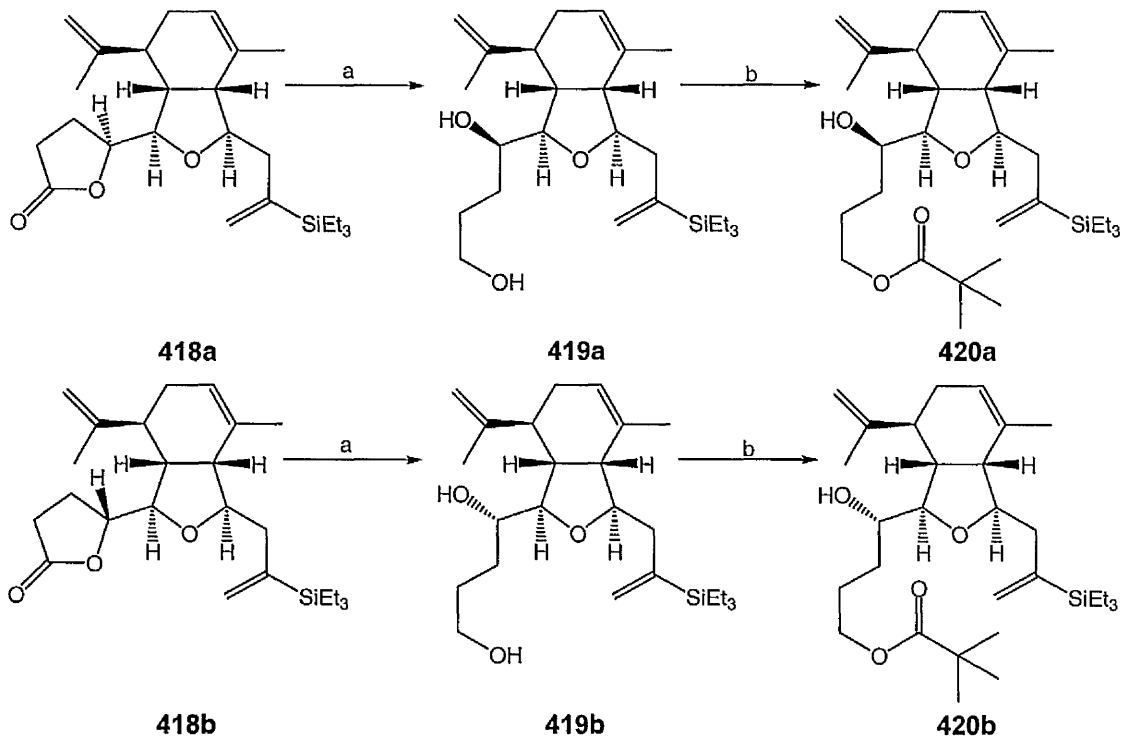
417b **418b**

Reagents and conditions: a) Spongy Cobalt $^{®}_{(aq)}$, 50 wet wt%, THF, H_2O, H_2, 6hrs 88%.

Scheme 164

9.8 Final stages: expansion of the lactone ring

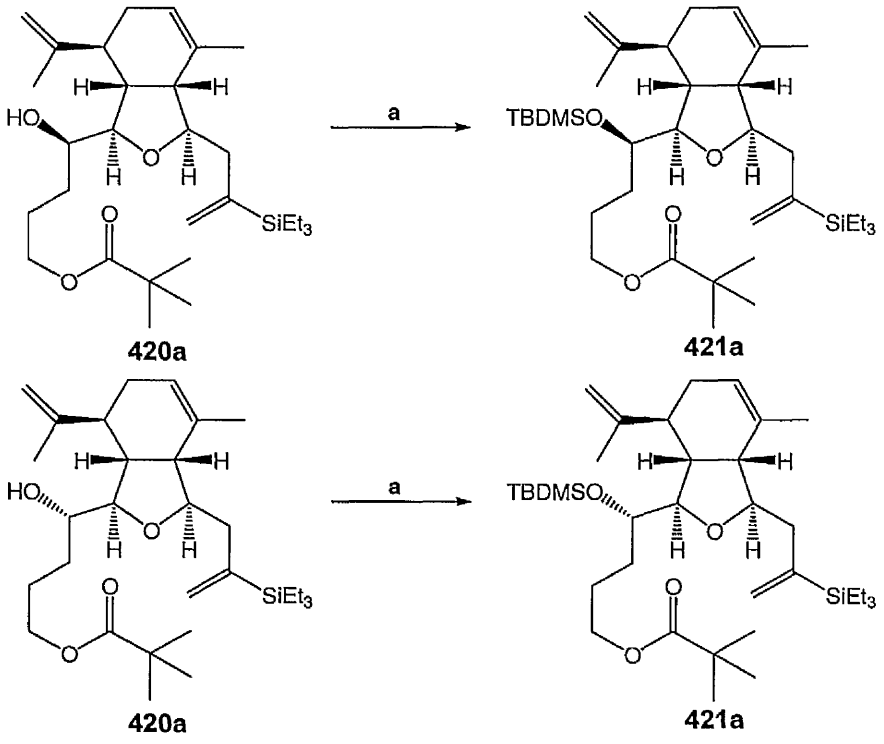
Following the previous work established in **Section 9.5** as a template, both epimeric lactones **418a** and **418b** were converted to advanced intermediates towards the synthesis of eunicellin **144**. Hence reduction of lactones **418a** and **418b** to diols **419a** and **419b** proceeded smoothly with excess amounts $LiAlH_4$ in 69-76% yield. Protection of the primary alcohol **419a** and **419b** with pivaloyl chloride gave **420a** and **420b** in 82-85% yield, **Scheme 165**.



Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 69-76%; b) pivaloyl chloride, pyridine, Et_2O, 0 °C, 2 hrs, 82-85%.

Scheme 165

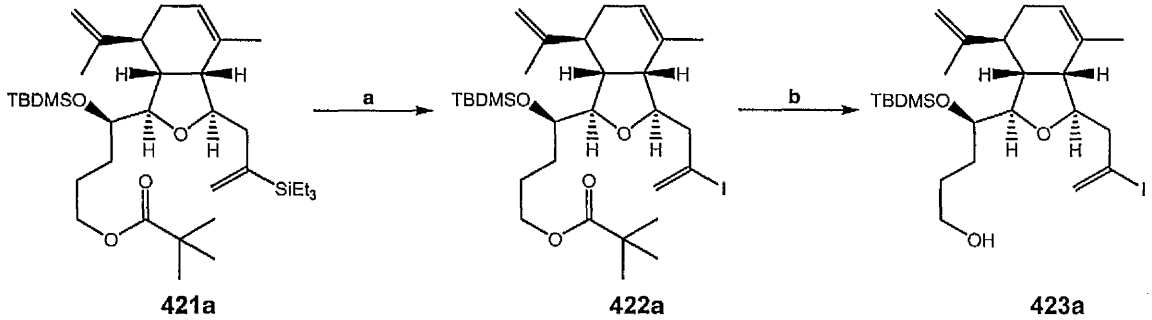
Protecting the 2° alcohol in **420a** and **420b** with TBDMS triflate gave compounds **421a** and **421b** in excellent yield, **Scheme 162.**



Reagents and conditions: a) TBDMS triflate, 2,6-lutidine, DCM, 0 °C, 3 hrs, 94%;

Scheme 166

Conversion of **421a** to the vinyl iodide **422a** proved to be capricious, for example iodine in the presence of silver triflate failed to remove the silyl group.[95] NIS in acetonitrile was also unsuccessful.[96] Vinyl iodide **422a** was successfully synthesised *via* the addition of iodine monochloride to **421a** and subsequent work up with TBAF.[97] Selective deprotection of vinyl iodide **422a** with DIBAL-H furnished 1° alcohol **423a** in 75% yield, **Scheme 163.**



Reagents and conditions: a) i) ICl (1M in DCM), DCM; ii) TBAF (1 eq), THF, 88%; b) DIBAL-H, DCM, 2 hrs, 0 °C, 75%.

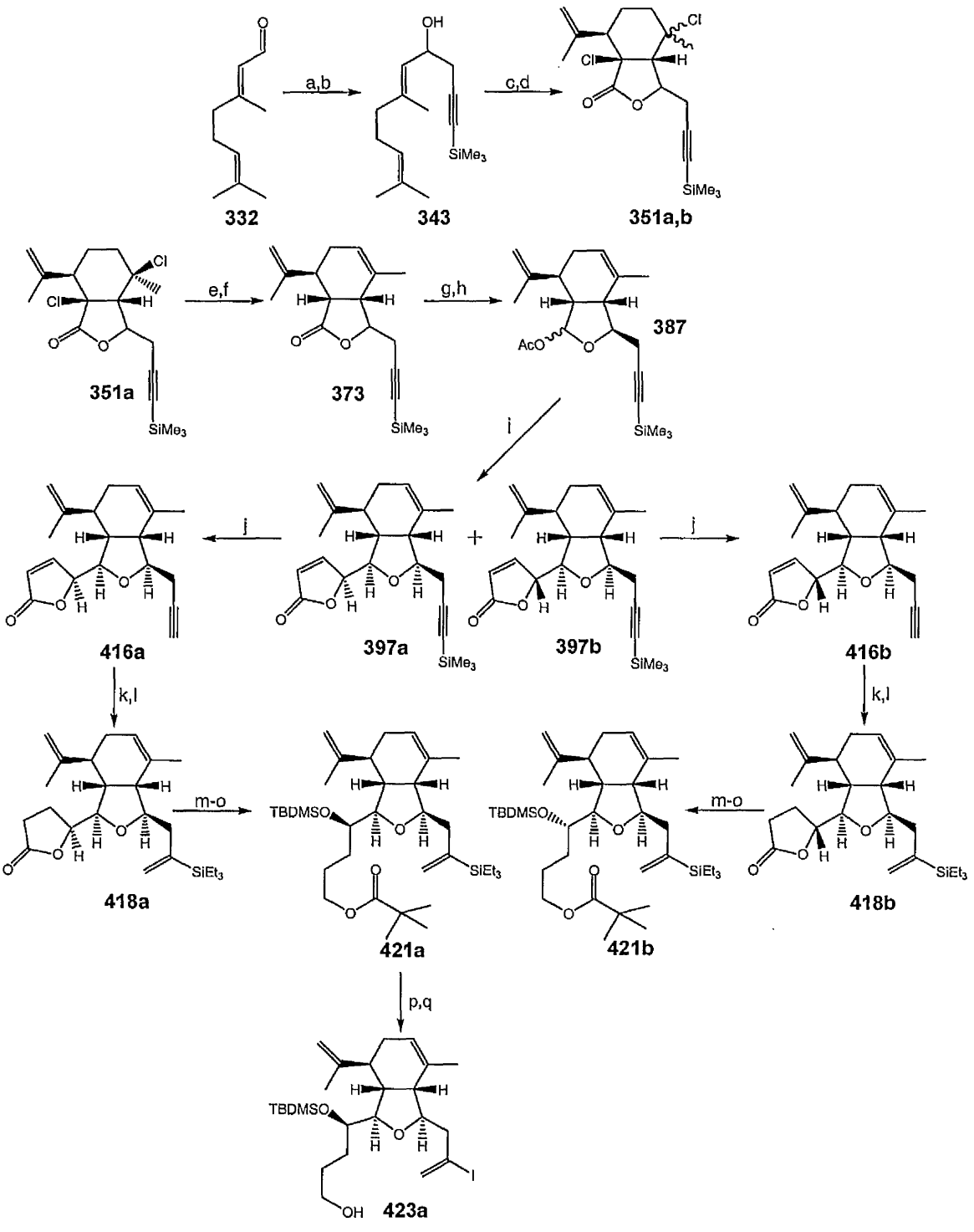
Scheme 167

Chapter 9.9 Summary and conclusions

A general approach towards a total synthesis of the cladiellins has been discussed. Previous group members have attempted the synthesis of the 9 membered ring *via* metathesis and an intramolecular Heck cyclisation with both these attempts failing. The current synthesis relies on the Nozaki-Hiyama-Kishi reaction, a strategy which has proven to be a reliable tool in the synthesis of oxanonenes.[83]

The first obstacle to be addressed in the current route was the **ATRC** of a secondary trichloroacetate generating the bicyclic hexahydroisobenzofuran core found at the heart of many cladiellins and briarellins. Increasing size and complexity of the C3 substituent affects the yield of cyclised product, however with optimisation the TMS-propargyl system afforded the bicyclic lactone **351a** and **351b** with a combined 36% yield.

To perform the Nozaki-Hiyama-Kishi reaction, this required the construction of the unaddressed C3-C6$^{(\text{cladiellin numbering})}$ functionality and the conversion of **387** to a substrate such as **424a** incorporating aldehyde and vinyl iodide functionality, **Scheme 168 and 170**. A vinylogous Mukaiyama aldol reaction of **387** and 2-(trimethylsilyloxy)furan introduced an aldehyde functionality as the butenolide **397a** and **397b.** The butenolide only required an additional methyl substituent which was to be added after the formation of the 9 membered ring. This would give the correct number of carbons and oxygens found in decetoxyalcyonin **148** with only one carbon-carbon bond formation required to construct the full tricyclic structure of the cladiellins. Both diastereoisomers after the VMA reaction can be processed towards the Nozaki-Hiyama-Kishi reaction, with the conversion to one diastereoisomer to be attempted after ring formation, **Scheme 168**.

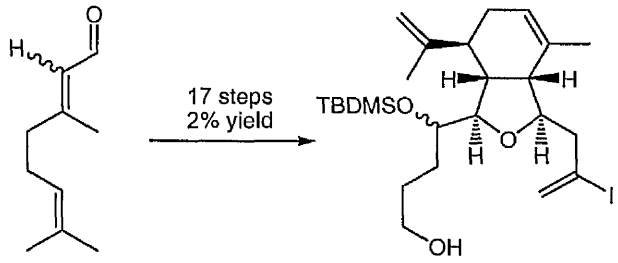


Reagents and conditions: a) Mg (2 eq), catalytic I_2, catalytic $HgCl_2$, propargyl bromide, -40 °C, Et_2O, geranial, 89%; b) *n*-BuLi (2 eq), TMSCl (2 eq), 1M $HCl_{(aq)}$, 87%; c) $ClCOCCl_3$, Et_3N, Et_2O, 0 °C, 92%. d) Cu(I)Cl (5 mol%), dHBipy (5 mol%), 1,2-DCE, reflux, 3.5 hrs, 28% of **351a** and 10% of **351b**; e) LiCl, Li_2CO_3, DMF, 110 °C, 89%; f) Bu_3SnH, AIBN, PhH,

reflux 2hrs, 97%; g) DIBAL-H, DCM, -78 °C, 92%; h) 2-(trimethylsilyloxy)furan, $BF_3.Et_2O$, 2 hrs, DCM, -78 °C, 48% of *erythro-cis* adduct **397a** and 28% of *threo-cis* adduct **397b**; j) AgOTf, H_20, CH_3OH, DCM, -20 °C, EtOH, H_2O, 81%; k) **409**, Et_3SiH, DCM, 0 °C, 88%; l) Spongy cobalt®$_{(aq)}$, 50 wet wt%, THF, H_2, 88%; m) $LiAlH_4$, THF, 0 °C, 69%; n) pivaloyl chloride, pyridine, Et_2O, 0 °C, 2 hrs, 82%; o) TBDMS triflate, 2,6-lutidine, DCM, 0 °C, 3 hrs, 94%; p) i) ICl (1M in DCM), DCM; ii) TBAF, THF, 88%; q) DIBAL-H, DCM, 2 hrs, 0 °C, 75%.

Scheme 168

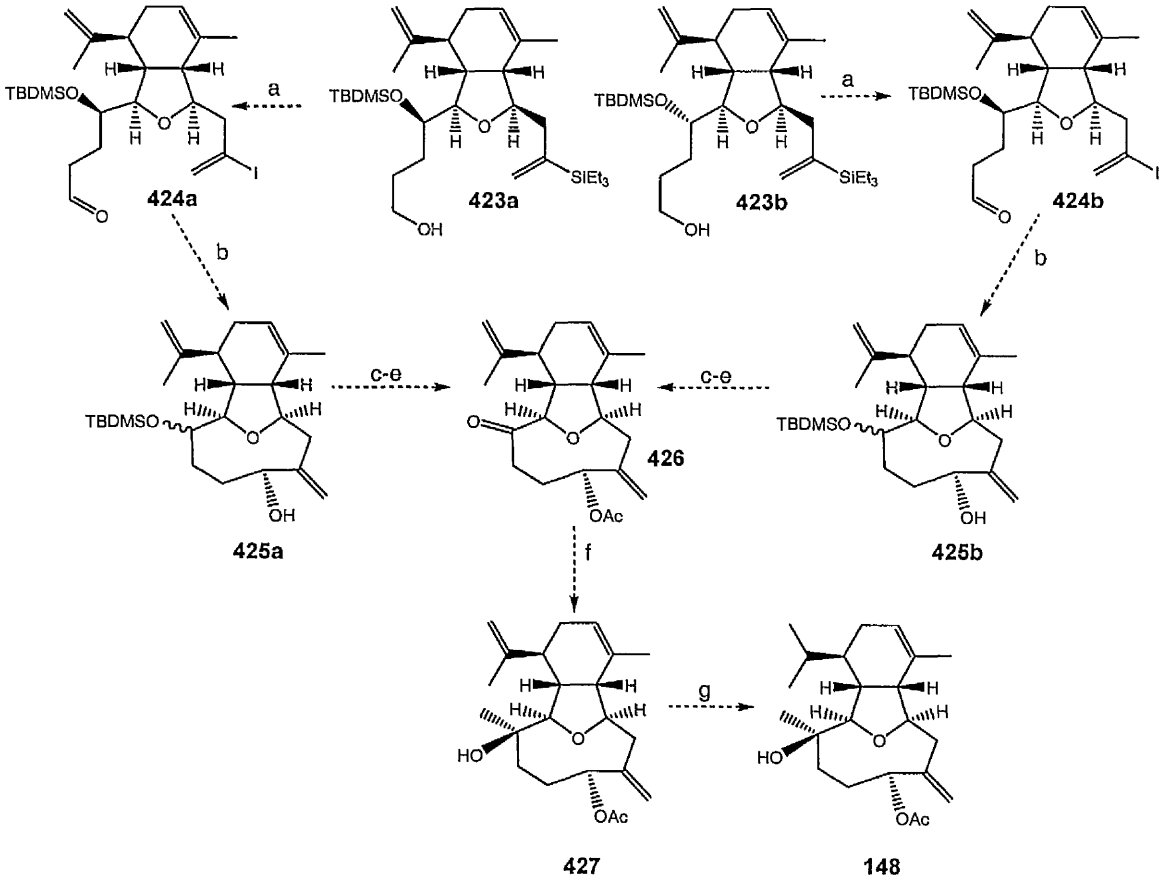
From geraniol (2:1 ratio of *E*:*Z*) to primary alcohol **423a** is 17 linear steps giving a global yield of 2%, **Scheme 165.**



Scheme 169

As our structure is now familiar to intermediates in Overman's latter half of his synthesis of 6-acetoxycladiell-7(16),11-dien-3-ol,[48] future work would revolve around similar lines. The envisaged end game strategy would see the 1° alcohol on vinyl iodide **423a** and **423b** oxidised using TPAP and NMO to aldehyde **424a** and **424b**. Both halves of the C-1 and C-3 substituted furan ring would be prepared for the Nozaki-Hiyama-Kishi reaction and with the addition of $NiCl_2$-$CrCl_2$ should furnish oxanonenes **425a** and **425b**. With the main cladiellin skeleton in place, acetylation of the remaining hydroxyl group and subsequent deprotection of the TBDMS group would hopefully reveal the 2° alcohol. Conversion of the two diastereoisomers into just one would eventually take place here with oxidation of the 2° alcohol using TPAP and NMO furnishing ketone **426**. Ketone **426** would be subjected to selective methylation to give **427**. The final step would be to selectively reduce the isopropenyl moiety in **427** without any reduction in the other olefinic centres. This, in theory, would give 6-acetoxycladiell-7(16),11-dien-3-ol **148** with all correct stereochemistry in place, **Scheme 170.** Unfortunately

any further work on eunicillin will have to be passed on to future aspiring chemists who hopefully will take as much joy in crafting its difficult structure as I did.



Reagents and conditions: a) TPAP, NMO, DCM; b) $NiCl_2$-$CrCl_2$, DMSO; c) Ac_2O, pyridine; d) TBAF; e) TPAP, NMO, DCM; f) methylation; g) selective reduction.

Scheme 170

EXPERIMENTAL

10.1 General experimental

Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Varian Gemini 200 at 200 MHz, Varian Unity Inova 300 at 300 MHz, Varian Unity Inova 400 at 400 MHz and a Varian Unity Inova 500 at 500 MHz instruments. Splitting patterns are abbreviated to singlet (s), doublet (d), triplet (t), double-doublet (dd), double-double-doublet (ddd), double triplet (dt), quartet (q) and multiplet (m). The symbol (b) in front of the splitting pattern indicates broad. All chemical shifts (δ) are quoted in parts per million (ppm) relative to an internal standard (TMS). Coupling constant (J) are quoted in hertz (Hz) and chemical shifts for multiplets are quoted as midpoints for single or equivalent protons and as ranges for more than one overlapping signal.

Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Unity Inova 300 at 75 MHz, Varian Unity Inova 400 at 100 MHz and Varian Unity Inova 500 at 125 MHz instruments.

Fluorine nuclear magnetic resonance (δ_F) spectra were recorded on a Varian Gemini 300 at 272 MHz. All chemical shifts (δ) are quoted in parts per million (ppm) relative to an internal standard (C_6F_6).

Infra red spectra were recorded on an Ati Mattson Genesis series FT spectrophotometer. Absorption maxima (νmax) are quoted in wavenumbers (cm^{-1}) and only structurally significant peaks are listed.

Mass spectra were recorded on a Fisons VG Trio 2000 instrument, using direct electron impact ionisation (EI) and chemical ionisation (CI) using ammonia as ionisation modes. Accurate mass measurements were recorded on a Kratos concept. Electrospray technique (ES) was recorded on a Micromass Platform II, to obtain low-resolution spectra.

Thin layer chromatography (TLC) was carried out on Polygram SIL G/UV254 precoated plates, and spots were visualised, where appropriate, by UV fluorescence at 254 or 297 nm or by spraying with phosphomolybdic acid in ethanol, iodine or vanillin in ethanol/sulphuric acid.

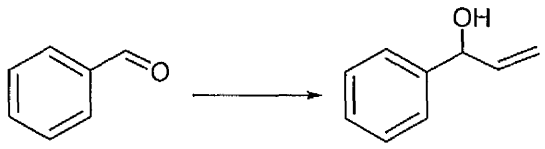
Flash column chromatography was performed using Merck Kieselgel 60 (230-400 mesh) silica.

Melting points were recorded on a Köfler heated stage microscope and are uncorrected.

Tetrahydrofuran and diethyl ether were dried by distillation from sodium-benzophenone; di-*n*-butyl ether was dried by distillation from potassium-benzophenone; toluene, dichloromethane, acetonitrile, 1,4-dioxane and 1,2-DCE were dried by distillation from calcium hydride; dimethylformamide was dried over 4Å molecular sieves. Sodium hydride (60% dispersion in oil) was washed three times with petrol under an atmosphere of nitrogen prior to using. All reactions were carried out under an atmosphere of either nitrogen or argon unless otherwise stated.

10.2 Molecular queuing and work towards tandem cyclisations

Synthesis of (±)-1-phenyl-2-propen-1-ol 428.[90]



428

To a solution of redistilled benzaldehyde (1.6 g, 15.1 mmol, 1 eq) in anhydrous THF (100 mL) was added vinylmagnesium bromide (1M in THF, 15 mL, 1 eq) at 0 °C. After 3 hours stirring at 17 °C, the reaction was quenched with water (100 mL), and extracted with ether (3x 75 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Purification of the crude material by column chromatography (flash silica, 10% EtOAc/petrol) gave the product **428** as a yellow oil (1.01 g, 50% yield).

δ_H(200MHz, $CDCl_3$) 2.81 (1H, bs, OH), 5.12-5.19 (1H, m, C*H*-OH), 5.22-5.41 (2H, m, olefin), 6.12-6.32 (1H, m, olefin), 7.26-7.56 (5H, m, Ar).

δ_C(75MHz, $CDCl_3$) 67.1, 124.1, 127.5, 128.4, 128.5, 136.9, 137.4.

ν_{max}(evaporated film) 3350 cm^{-1}.

m/z (EI) 105 (45%), 117 (100%), 134 (60%).

HRMS (EI) $C_9H_{10}O$ requires 134.0732; found 134.0729.

Synthesis of propiophenone 429

428 **429**

A dry flask was charged with **89** (50 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of alcohol **428** (200 mg, 1.33 mmol, 1 eq) in toluene (3 mL). After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen

for 3.5 hours. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford the ketone **429** as a pale yellow oil (35mg, 40% yield).

δ_H(200MHz, $CDCl_3$) 1.31 (3H, t, *J*= 7 Hz, CH_3), 3.00 (2H, q, *J*= 7, CH_2), 7.62 (3H, m, Ar), 8.00 (2H, m, Ar).

δ_C(75MHz, $CDCl_3$) 8.1, 31.7, 127.9, 128.4, 128.6, 132.8, 200.7.

ν_{max}(evaporated film) 1689, 2931 cm^{-1}.

m/z (CI) 105 (60%), 135 ($M+H^+$, 100%).

HRMS (CI) $C_9H_{10}O$ requires 134.0732; found 134.0736.

Synthesis of 3-phenylpropanal 430.

430

A dry flask was charged with **89** (60 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of the cinnamyl alcohol (200 mg, 1.5 mmol, 1 eq) in toluene (3 mL). After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for 3.5 hours. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford the aldehyde **430** as a colourless oil (65 mg, 33% yield).

δ_H(300MHz, $CDCl_3$) 2.86 (2H, dt, *J*= 3 and 7 Hz, H-a), 3.02 (2H, t, *J*= 7 Hz, H-b), 7.24 (5H, m, Ar), 9.85 (1H, t, *J*= 3 Hz, C*H*O).

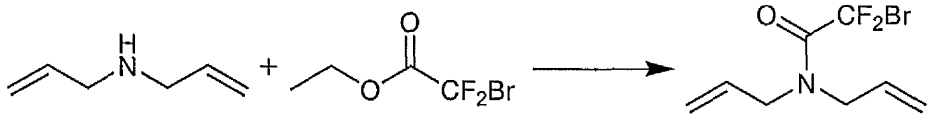
δ_C(75MHz, $CDCl_3$) 28.1, 45.2, 126.2, 128.5, 129.0, 140.2, 201.4.

ν_{max}(evaporated film) 1710 cm^{-1}.

m/z (EI) 49 (100%), 78 (50%), 91 (65%), 134 (100%).

HRMS (EI) C_9H_9O requires 134.0732; found 134.0735.

Synthesis of *N,N*-diallyl-2-bromo-2,2-difluoroacetamide 233.[92]



233

N,N-Diallylamine (2.5 g, 25.8 mmol, 2.5 eq) was dissolved in anhydrous EtOAc (10 mL) and the mixture was placed in a ice bath and allowed to stir for 10 minutes. Ethyl bromodifluoroacetate (1 g, 10.3 mmol, 1 eq) was added and the reaction mixture left to stir for 18 hrs at 17 °C. The reaction mixture was quenched with 1M $HCl_{(aq)}$ (50 mL) and extracted with ether (3x50 mL). The combined organic extracts were washed with water (50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography (flash silica, 25% EtOAc/ 75% petrol) to give product **233** as a colourless oil (1.2 g, 50% yield).

δ_H(300MHz, $CDCl_3$) 4.05 (2H, d, *J*= 6 Hz, -CH_2), 4.13 (2H, d, *J*= 6 Hz, -CH_2), 5.30 (4H, m, olefin), 5.80 (2H, m, olefin).

δ_C(75MHz, $CDCl_3$) 49.3, 51.6, 108.7, 118.5, 121.1, 130.6, 132.9, 160.1.

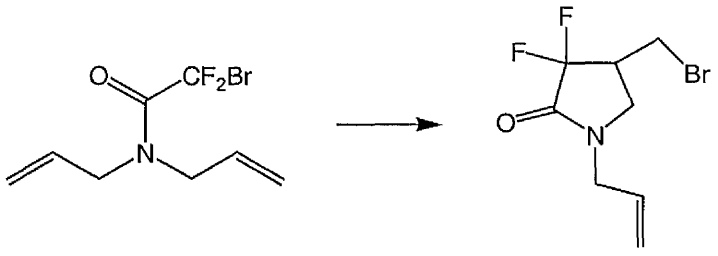
δ_F(282 MHz, $CDCl_3$) -55.5 (2F, s).

ν_{max}(evaporated film) 1689 cm^{-1}.

m/z (AP^+) 253 (100%), 311 (50%)

HRMS (AP^+) $C_8H_{11}{}^{79}Br_1F_2NO$ ($M+H^+$) requires 253.9987; found 253.9987

Synthesis of 1-allyl-4-(bromomethyl)-3,3-difluoro-2-pyrrolidinone 239.[85]



233 239

Method A

A dry flask was charged with **89** (50 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) and the reaction mixture was brought to reflux under nitrogen for 3.5 hours. After cooling to 17 °C, a solution of *N,N*-diallyl-2-bromo-2,2-difluoroacetamide **233** (200 mg, 0.79 mmol, 1 eq) in toluene (3 mL) was added *via* a syringe. After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for a further 3.5 hours. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford the lactam **239** as colourless oil (10 mg, 5% yield).

Method B

A dry vessel was charged with Cu(I)Cl (5 mg, 5 mol%), dHBipy (20 mg, 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of *N,N*-diallyl-2-bromo-2,2-difluoroacetamide **233** (200 mg, 0.79 mmol) in 1,2-DCE (3 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for a further 3.5 hours. The 1,2-DCE was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford the lactam **239** as colourless oil (35 mg, 15% yield).

δ_H**(300MHz, CDCl$_3$)** 3.0 (1H, m, C*H*CF_2), 3.24 (1H, dd, *J*= 8 and 10 Hz, C*H*Br), 3.43 (1H, dd, *J*= 7 and 10 Hz, C*H*Br), 3.66 (1H, dd, *J*= 7 and 10 Hz, C*H*N), 3.73 (1H, dd, *J*= 5 and 10 Hz, C*H*N), 4.04-4.12 (2H, d, *J*= 7 Hz, CH_2-CH=CH_2), 5.31-5.36 (2H, m, CH_2-CH=CH_2), 5.77 (1H, ddt, *J*= 7, 10 and 17 Hz, CH_2-C*H*=CH_2).

δ_C**(75MHz, CDCl$_3$)** 25.9, 45.9, 46.8, 83.6, 116.7, 120.1, 130.2, 162.4.

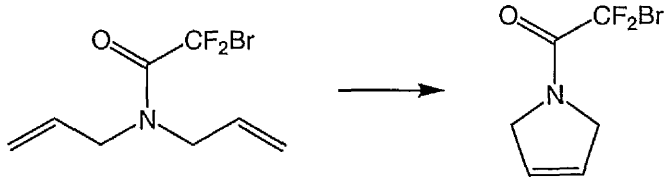
δ_F(282MHz, $CDCl_3$) -105.2 (1F, ddd, 2, 12 and 271 Hz), -113.9 (1F, dd, 15 and 271 Hz).

ν_{max}(evaporated film) 1734, 2965 cm^{-1}.

m/z (EI) 254 ($M+H^+$, 65%).

HRMS (EI) $C_8H_{10}{}^{79}BrF_2NO$ requires 252.9914; found 252.9910.

Synthesis of 2-bromo-1-(cyclopent-3-enyl)-2,2-difluoroethanone 236.



233 **236**

A dry flask was charged with **89** (33 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) and a solution of difluorobromoacetamide **233** (200 mg, 0.79 mmol, 1 eq) in toluene (3 mL) was added *via* a syringe. After again degassing (three times, freeze-thaw cycle), the reaction mixture was brought to a gentle reflux under nitrogen for 3.5 hours. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford the product as a off-white solid **236** (152 mg, 88% yield).

δ_H(300MHz, $CDCl_3$) 4.39 (2H, m, $-CH_2$), 4.52 (2H, m, $-CH_2$), 5.93 (2H, m, olefin).

δ_F(282MHz, $CDCl_3$) -58.0 (2F, s).

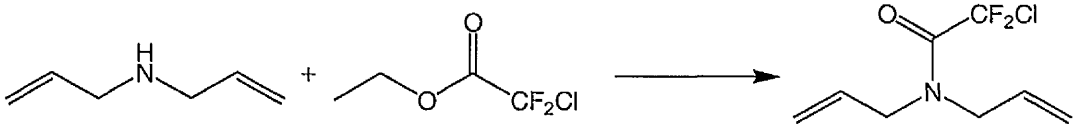
ν_{max}(evaporated film) 1665, 2945, 2970 cm^{-1}.

Mp 132-135 °C

m/z (EI) 242 ($M+NH_4^+$, 90%).

HRMS (EI) $C_6H_6{}^{79}BrF_2NO$ requires 224.9601; found 224.9609.

Synthesis of *N,N*-diallyl-2-bromo-2,2-difluoroacetamide 234.[92]



234

N,N-Diallylamine (1.5 g, 16 mmol, 2.5 eq) was dissolved in EtOAc (10 mL) and the mixture was placed in a ice bath and allowed to stir for 10 minutes. Ethyl chlorodifluoroacetate (1 g, 6.39 mmol, 1 eq) was added and the mixture stirred overnight at 17 °C. The reaction mixture was quenched with 1M $HCl_{(aq)}$ (50 mL) and extracted with ether (3x50 mL). The combined organic extracts were washed with water (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give crude gummy oil. The crude product was purified by column chromatography (flash silica, 25% EtOAc/petrol) to give compound **234** as colourless oil (1.1 g, 81% yield).

δ_H(300MHz, $CDCl_3$) 4.05 (2H, d, *J*= 6 Hz, $-CH_2$), 4.13 (2H, d, *J*= 6 Hz, $-CH_2$), 5.33 (4H, m, olefin), 5.81 (2H, m, olefin).

δ_C(75MHz, $CDCl_3$) 49.3, 50.6, 108.7, 118.5, 119.1, 130.2, 132.4, 159.5.

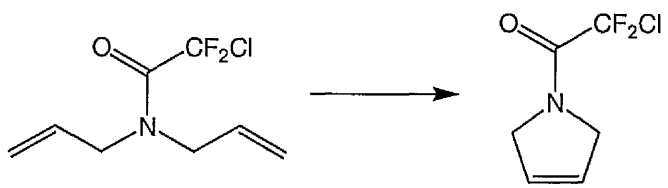
δ_F(282MHz, $CDCl_3$) -55.0 (2F, s).

ν_{max}(evaporated film) 1680 cm^{-1}.

m/z (EI) 210 ($M+H^+$, 100%).

HRMS (EI) $C_8H_{10}{}^{35}ClF_2NO$ requires 209.0419; found 209.0424.

Synthesis of 2-chloro-1-(cyclopent-3-enyl)-2,2-difluoroethanone 237



234 **237**

A dry flask was charged with **89** (33 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) and a solution of chlorodifluoroacetamide **234** (200 mg, 0.79 mmol, 1 eq) in toluene (3 mL) was added *via* a syringe. After again degassing (three times, freeze-thaw cycle), the reaction mixture was

stirred at 17 °C for 3.5 hours. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford the product **237** as an off-white solid (170 mg, 89% yield).

δ_H(300MHz, $CDCl_3$) 4.39-4.45 (2H, m, CH_2), 4.52-4.59 (2H, m, CH_2), 5.90-6.12 (2H, m, olefin).

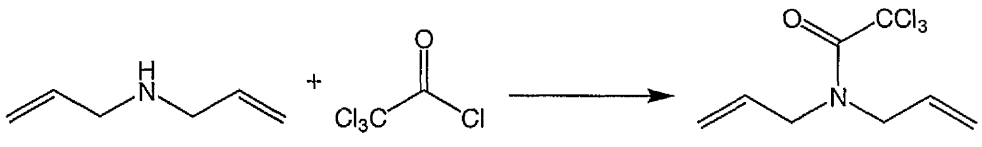
δ_F(282MHz, $CDCl_3$) -62.0 (2F, s).

ν_{max}(evaporated film) 1670, 2940, 2972 cm^{-1}.

m/z (EI) 182 ($M+H^+$, 100%).

HRMS (EI) $C_6H_6{}^{35}ClF_2NO$ requires 181.0106; found 181.0110.

Synthesis of *N,N*-diallyl-2,2,2-trichloroacetamide 232[86]



232

To a solution of *N,N*-diallylamine (1.0 g, 10.3 mmol, 1 eq) and triethylamine (1.0 g, 11.3 mmol, 1.1 eq) in anhydrous ether (30 mL) was added slowly *via* a syringe trichloroacetylchloride (1.15 mL, 11.3 mmol, 1.1 eq) at 0°C, and the reaction mixture was left to stir at 17 °C for 3 hours. The reaction mixture was then quenched with water (50 mL) and the organic phase extracted with ether (2x50 mL), washed with 1 M $HCl_{(aq)}$ (2x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (flash silica, 25% EtOAc/ 75% petrol) afforded the *title compound* as a yellow oil (2.23 g, 90% yield).

δ_H(300MHz, $CDCl_3$) 4.0 (2H, bs, CH_2), 4.4 (2H, bs, CH_2), 5.2 (4H, bs, olefin), 5.8 (2H, bs, olefin).

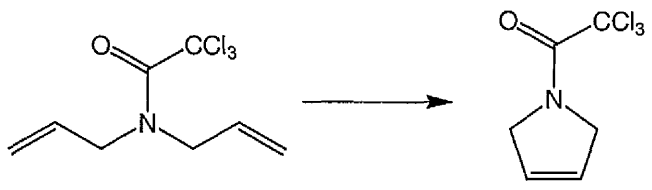
δ_C(75MHz, $CDCl_3$) 49.6, 51.5, 92.9, 117.9, 119.2, 130.9, 131.9, 160.1.

ν_{max}(evaporated film) 1679 cm^{-1}.

m/z (CI) 172 (30%), 208 (20%), 242 ($M+H^+$, 90%).

HRMS (CI) $C_8H_{11}{}^{35}Cl_3N_3O$ ($M+H^+$) requires 241.9906; found 241.9907.

Synthesis of 2,2,2-trichloro-1-(2,5-dihydro-1*H*-1-pyrrolyl)-1-ethanone 235.



232 **235**

To a mixture of **89** (30 mg, 5 mol%) in toluene (5 mL) was added trichloroacetate **232** (200 mg, 0.83 mmol, 1 eq) in toluene (2 mL) and the reaction mixture was allowed to stir at 17 °C for 1 hour. The toluene was removed *in vacuo* and the residue was washed through a pad of silica (flash silica, DCM) to give **235** as a yellow oil (170 mg, 98% yield).

δ_H(300MHz, $CDCl_3$) 4.31-4.39 (2H, m, $-CH_2$), 4.60-4.66 (2H, m, $-CH_2$), 5.82-5.86 (2H, m, olefin).

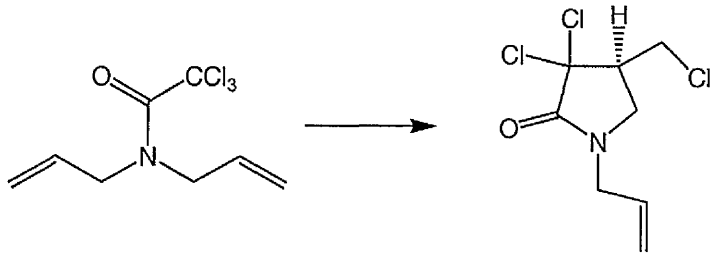
δ_C(75MHz, $CDCl_3$) 55.1, 57.1, 91.2, 124.6, 125.3, 159.0.

ν_{max}(evaporated film) 1672, 2935 cm^{-1}.

m/z (CI) 96 (60%), 180 (50%), 214 ($M+H^+$, 100%).

HRMS (CI) $C_6H_7Cl_3NO$ ($M+H^+$) requires 213.9593; found 213.9597.

Synthesis of 1-allyl-3,3-dichloro-4-(chloromethyl)-2-pyrrolidinone 238.



232 **238**

Method A

A dry flask was charged with **89** (50 mg, 5 mol%) and anhydrous toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) and the reaction mixture was brought to reflux under nitrogen for 3.5 hours. After cooling to 17 °C, a solution of trichloroacetamide **232** (200 mg, 0.83 mmol, 1 eq) in toluene (3 mL) was added *via* a syringe. After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a

gentle reflux under nitrogen for a further 3.5 hours. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford the lactam **238** as colourless oil (165 mg, 80% yield).

Method B

A dry vessel was charged with Cu(I)Cl (5 mg, 5 mol%), dHBipy (20 mg, 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of trichloroacetamide **232** (200 mg, 0.83 mmol, 1 eq) in 1,2-DCE (3 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for a further 3.5 hours. The 1,2-DCE was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford the lactam **238** as colourless oil (180 mg, 90% yield).

δ_H(300MHz, $CDCl_3$,) 3.12 (1H, m, C*H*CCl_2), 3.23 (1H, dd, *J*= 8 and 11 Hz, C*H*Cl), 3.61 (1H, dd, *J*= 7 and 11 Hz, C*H*Cl), 3.86 (1H, dd, *J*= 10, 11 Hz, C*H*N), 4.03 (1H, dd, *J*= 4 and 11 Hz), 3.91-4.20 (2H, m), 5.28-5.42 (2H, m, olefin), 5.75 (1H, ddd, *J*= 4, 11 and 15 Hz, olefin).

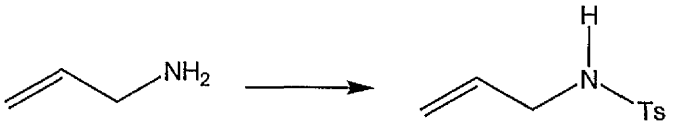
δ_C(75MHz, $CDCl_3$) 40.9, 46.2, 47.3, 51.5, 83.6, 119.5, 130.4, 165.6.

ν_{max}(evaporated film) 1644, 1728, 2922 cm^{-1}.

m/z (CI) 172 (65%), 208 (75%), 242 ($M+H^+$, 100%).

HRMS (CI) $C_8H_{11}{}^{35}Cl_3NO$ ($M+H^+$) requires 241.9906; found 241.9912.

Synthesis of 1-allyl-4-methyl-1-benzenesulfonamide 431.[87]



431

To a solution of allylamine (15 mL, 263 mmol, 1 eq) and triethylamine (26.6 mL, 263 mmol, 1 eq) in DCM (50 mL) was added a solution of tosylchloride (25 g, 263 mmol, 1eq) in DCM (50 mL). After stirring at 17 °C for 16 hours, the reaction mixture was quenched with water (200 mL) and the organic phase was extracted, washed with 1M $HCl_{(aq)}$ (200 mL), dried ($MgSO_4$)

and evaporated *in vacuo* to give product **431** (recrystallised from DCM in hexane) as a white crystalline solid (22 g, 80% yield).

δ_H(300MHz, $CDCl_3$) 2.43 (3H, s, Me), 3.61 (2H, m, CH_2-CH), 4.87 (1H, br t, *J*= 6 Hz, N-H), 5.10–5.27 (2H, m, CH_2=CH), 5.78 (1H, m, CH=CH_2), 7.37 (2H, d, *J*= 8 Hz, Ar), 7.87 (2H, d, *J*= 8Hz, Ar).

δ_C(75MHz, $CDCl_3$) 21.4, 45.7, 117.5, 127.0, 129.6, 132.9, 136.9, 143.4.

ν_{max}(Nujol) 1598, 3279 cm^{-1}.

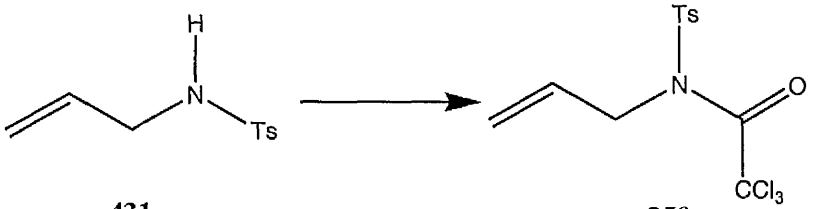
Mp 59-60 °C (lit[10] mp 59-61°C).

m/z (EI) 212 ($M+H^+$, 100%).

m/z (CI) 229 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{10}H_{14}NO_2S$ ($M+H^+$) requires 212.0745; found 212.0748.

Synthesis of *N*-allyl-*N*-(2,2,2-trichloroacetyl)-4-methyl-1-benzenesulfonamide 250.[31]



431 **250**

To a solution of *N*-allyltosylamide **431** (10 g, 47.1 mmol, 1 eq) in anhydrous THF (170 mL) was added at -78 °C, *n*-BuLi (1.34M solution in hexanes, 36 mL, 47.1 mmol, 1 eq) and the mixture was allowed to stir at -78 °C for 30 minutes. Trichloroacetyl chloride (5.8 mL, 47.1 mmol, 1 eq) was added *via* a syringe at –78 °C and the mixture was left to stir at that temperature for a further 2 hours. The reaction mixture was warmed up to 17 °C and was quenched with saturated NH_4Cl solution, which was quickly extracted with diethylether (5x 50 mL). The combined ethereal layers were washed with 1M $NaOH_{(aq)}$ (50 mL) and brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the trichloroacetamide **250** as a white solid (recrystallised from ether in hexane), (9.8 g, 60% yield).

δ_H(300MHz, $CDCl_3$) 2.45 (3H, s, Me), 4.92 (2H, dt, 1.5 and 5.5 Hz, CH_2-CH), 5.4 (2H, ddt, 5.5, 10.5 and 17 Hz, CH_2=CH), 5.96 (1H, ddt, 5.5, 10.5 and 17 Hz, CH=CH_2), 7.34 (2H, d, *J*= 8 Hz, Ar), 8.0 (2H, d, *J*= 8 Hz, Ar).

δ_C(75MHz, $CDCl_3$) 21.7, 51.0, 92.1, 119.4, 129.4, 129.7, 132.1, 134.6, 145.6, 164.0

ν_{max}(Nujol) 1711 cm^{-1}.

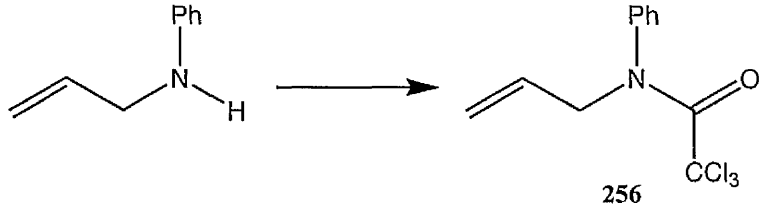
Mp 70-71°C (lit[10] mp 74-76°C).

m/z (EI) 91 (100%), 155 (80%), 257 (70%), 291 (60%), 356 ($M+H^+$, 15%).

m/z (CI) 373 ($M+NH_4^+$, 95%).

HRMS (CI) $C_{12}H_{13}{}^{35}Cl_3NO_3S$ ($M+H^+$) requires 355.9682; found 355.9682.

Synthesis of *N*-allyl-2,2,2-trichloro-N-phenylacetamide 256.[93]



256

N-Allylaniline (1 g, 7.5 mmol, 1 eq) and triethylamine (0.77 g, 8.96 mmol, 1.2 eq) was dissolved in diethyl ether (50 mL). The solution was allowed to stir at 0 °C for 30 minutes then trichloroacetyl chloride (1.63 g, 8.96 mmol, 1.2 eq) was added *via* a syringe at 0 °C and the mixture was left to stir at that temperature for a further 2 hours The reaction mixture was warmed up to 17 °C and was quenched with saturated NH_4Cl solution, which was quickly extracted with diethylether (3x 10 mL). The combined ethereal layers were washed with 1M $NaOH_{(aq)}$ (2x 25 mL), brine (2x 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product. The crude product was purified by column chromatography (flash silica, 25% EtOAc/ 75% petrol) to give the product **256** as an off-white crystalline solid (1.76 g, 84% yield).

δ_H(300MHz, $CDCl_3$) 4.39 (2H, d, *J*= 6 Hz), 5.13 (1H, dq, *J*= 1 and 17 Hz), 5.20 (1H, dq, *J*= 1 and 10 Hz), 5.94 (1H, ddt, *J*= 6, 10 and 17 Hz), 7.40 (5H, m).

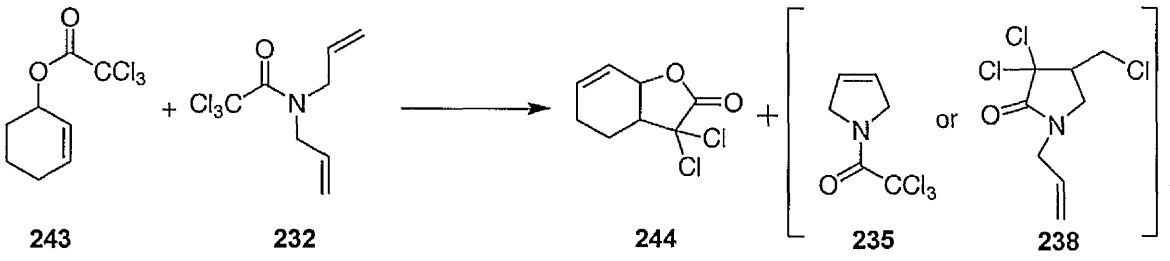
δ_C(75MHz, $CDCl_3$) 58.1, 119.9, 128.9, 129.2, 129.8, 131.4, 141.4, 160.5. (CCl_3 carbon missing due to electronegativity of Cl)

ν_{max}(evaporated film) 1766, 2874, 2934, 2961 cm^{-1}.

m/z (ES^+) 278 (40%), 301 (80%, $M+Na^+$)

HRMS (ES^+) $C_{11}H_{11}{}^{35}Cl_3NO$ ($M+H^+$) requires 277.9901; found 277.9906.

Protocols for intermolecular queuing/ competition experiments mediated by Grubbs' catalyst.



243 232 244 235 238

A: Equimolar mixture of radical substrate 243 and metathesis substrate 232.

A dry flask was charged with **89** (25 mg, 5 mol%) and 1,2-DCE (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of **243** (200 mg, 0.83 mmol, 1 eq) and **232** (200 mg, 0.83 mmol, 1 eq) in toluene (3 mL). After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen overnight. The DCE was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford **244** (75% yield) and **235** (90% yield).

B: Metathesis substrate 232 first then radical substrate 243

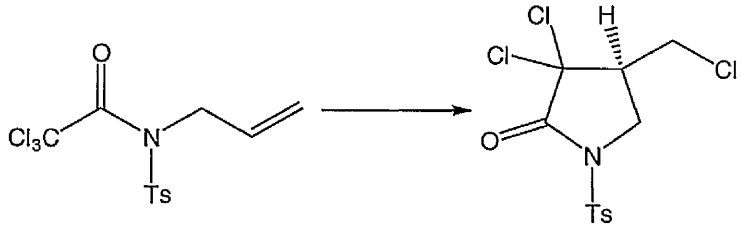
A dry flask was charged with **89** (25 mg, 5 mol%) and DCE (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of **232** (200 mg, 0.83 mmol, 1 eq) in toluene (1 mL). After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen for 3.5 hours. After 3.5 hours a second solution of **243** (200 mg, 0.83 mmol, 1 eq) in DCE (1 mL) was added and the reaction mixture was allowed to stir at refluxing temperature overnight. The toluene was then removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford **244** (70% yield) and **235** (90% yield).

C: Thermolysed Grubbs 1 catalyst with equimolar mixture of radical substrate 243 and metathesis substrate 232.

A dry flask was charged with **89** (25 mg, 5 mol%) and DCE (3 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). The solution was then heated to reflux

under a nitrogen atmosphere for two days. After the two days, a solution of **244** (200 mg, 0.83 mmol) and **232** (200 mg, 0.83 mmol) in DCE (1 mL) was added. After degassing again (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen overnight. The DCE was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford **244** (70% yield) and **238** (72% yield).

Synthesis of 3,3-dichloro-4-(chloromethyl)-1-[(4-methylphenyl)sulfonyl]-2-pyrrolidinone 242.[12]



250 **242**

Method A

A dry flask was charged with **89** (110 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of trichloroacetamide **250** (1.0 g, 2.81 mmol, 1 eq) in toluene (3 mL). The reaction mixture was brought to a gentle reflux under nitrogen for 3.5 hours. The toluene was then removed under reduced pressure and the crude product was chromatographed (flash silica, 30% EtOAc/ 70% petrol) to afford product **242** as a white solid (700 mg, 70% yield).

Method B

A dry Schlenck tube was charged with Cu(I)Cl (120 mg, 5 mol%), dHBipy (150 mg, 5 mol%) and anhydrous 1,2-DCE (4 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of allyltrichloroacetamide **250** (1.0 g, 2.81 mmol, 1 eq) in 1,2-DCE (1 mL). After degassing (three times using freeze-thaw cycle), the Schlenck tube was placed in a pre-heated oil bath (130 °C) and was allowed to stir for 3.5 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed

(flash silica, 30% EtOAc/ 70% petrol) to give a white solid that was recrystallised from ether and hexane to give compound **242** (800 mg, 80% yield).

δ_H(300MHz, $CDCl_3$) 2.50 (3H, s, Me), 3.15 (1H, m, C*H*CCl_2), 3.62 (1H, dd, *J*= 9 and 10 Hz, C*H*Cl), 3.71 (1H, dd, *J*= 10 and 11 Hz, C*H*Cl), 3.93 (1H, dd, *J*= 4 and 11 Hz, C*H*-N), 4.28 (1H, dd, *J*= 7 and 10 Hz, C*H*-N), 7.45 (2H, d, *J*= 8 Hz, Ar), 7.95 (2H, d, *J*= 8 Hz, Ar).

δ_C(75MHz, $CDCl_3$) 22.6, 40.1, 41.6, 52.8, 87.4, 128.2, 129.9, 139.4, 145.3, 167.6.

ν_{max}(Nujol) 1760 cm^{-1}.

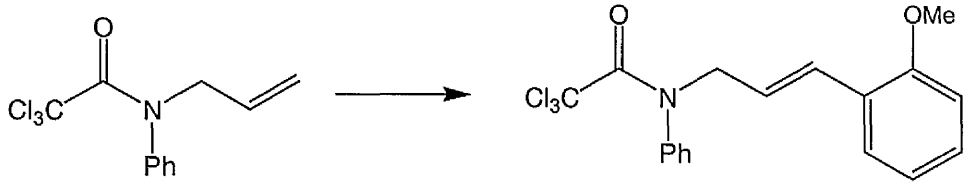
Mp 154-156°C (lit[10] mp 160°C).

m/z (EI) 91 100%), 155 (100%), 291 (55%), 356 ($M+H^+$, 20%).

m/z (CI) 339 (100%), 373 ($M+NH_4^+$, 80%).

HRMS (CI) $C_{12}H_{13}{}^{35}Cl_3NO_3S$ ($M+H^+$) requires 355.9682; found 355.9682.

Synthesis of (*E*)-*N*-(2-methoxycinnamyl)-2,2,2-trichloro-*N*-phenylacetamide 432.



256 **432**

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 2-methoxystyrene (2.9 g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After again degassing (three times, freeze-thaw cycle) the reaction mixture was allowed to stir at 40 °C for two hours. After cooling, the solvent was removed under reduced pressure, and the resulting crude product was chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give the *E* isomer **432** as a brown solid (948 mg, 67% yield).

δ_H(300MHz, $CDCl_3$) 2.2 (3H, s, OMe), 4.60 (2H, d, *J*= 6 Hz, CH_2), 6.35 (1H, dt, *J*= 6 and 16 Hz), 6.76 (1H, d, *J*= 6 Hz, olefin), 6.95 (1H, t, *J*= 8 Hz, Ar), 7.25-7.45 (7H, m, Ar).

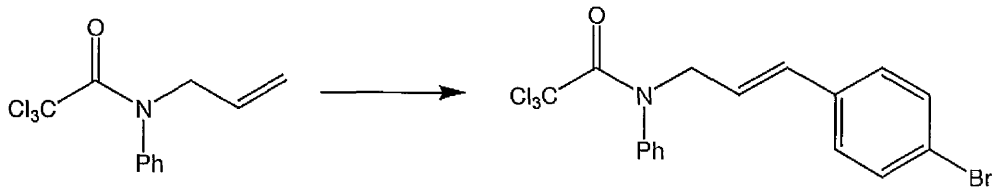
δ_C(75MHz, $CDCl_3$) 55.7, 111.2, 120.9, 122.9, 125.7, 127.3, 128.8, 129.1, 129.3, 130.1, 141.4, 157.1, 160.5.

ν_{max}(evaporated film) 1244, 1595, 1681 cm^{-1}.

m/z (CI) 147 (100%), 384 ($M+H^+$, 25%).

HRMS (CI) $C_{18}H_{17}{}^{35}Cl_3NO_2$ ($M+H^+$) requires 384.0321; found 384.0317.

Synthesis of (*E*)-*N*-(4-bromocinnamyl)-2,2,2-trichloro-*N*-phenylacetamide 272.



256 **272**

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 4-bromostyrene (3.9 g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle) the reaction mixture was allowed to stir at 40 °C for two hours. After cooling the solvent was removed under reduced pressure, and the resulting crude product was chromatographed (flash silica, 15% EtOAc/petrol) to give the *E* isomer **272** as an off white solid (1.1 g, 62% yield).

δ_H(300MHz, $CDCl_3$) 4.54 (2H, bd, *J*= 5 Hz), 6.37 (2H, s), 7.23-7.54 (9H, m, Ar).

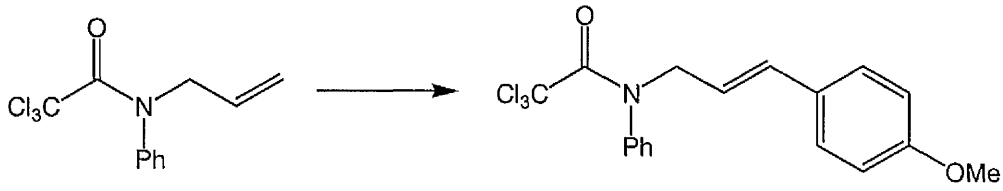
δ_C(75MHz, $CDCl_3$) 57.7, 122.2, 123.2, 128.3, 128.4, 129.0, 129.2, 130.0, 132.0, 132.2, 134.0, 135.5, 136.1, 141.3, 160.7.

ν_{max}(evaporated film) 1680, 2929, 3033 cm^{-1}.

m/z (AP^+) 194 (100%), 252 (60%), 364 (60%), 434 (80%).

HRMS (AP^+) $C_{17}H_{13}{}^{79}Br^{35}Cl_3NO$ requires 430.9226; found 430.9241.

Synthesis of (*E*)-*N*-(4-methoxycinnamyl)-2,2,2-trichloro-*N*-phenylacetamide 273.



256 **273**

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 4-methoxystyrene (2.9 g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After again degassing (three times, freeze-thaw cycle) the reaction mixture was allowed to stir at 40 °C for two hours. The reaction was then cooled to 17 °C and the solvent removed under reduced pressure, and the resulting crude product was chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give the *E* isomer **273** as an off white solid (1.03 g, 61% yield).

δ_H(300MHz, $CDCl_3$) 3.84 (3H, s, OMe), 4.53 (2H, bd, *J*= 7 Hz), 6.22 (1H, dt, *J*= 7 and 15 Hz), 6.36 (1H, d, *J*= 15 Hz), 7.31-7.43 (9H, m, Ar).

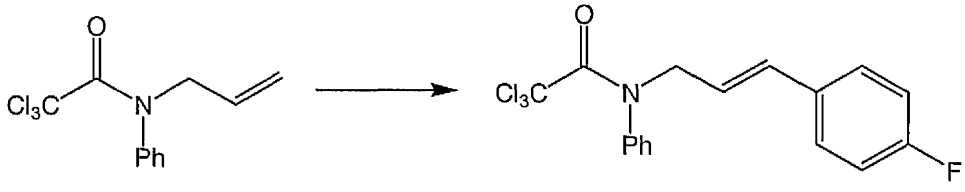
δ_C(75MHz, $CDCl_3$) 55.5, 57.9, 93.5, 114.3, 120.1, 127.7, 128.1, 128.8, 129.2, 129.4, 130.1, 134.9, 141.4, 159.8, 160.5. (CCl_3 carbon missing due to electronegativity of Cl)

ν_{max}(evaporated film) 1682, 2933, 3034 cm^{-1}.

m/z (AP^+) 147 (100%), 314 (30%), 384 (20%, $M+H^+$).

HRMS (AP^+) $C_{18}H_{17}{}^{35}Cl_3NO_2$ requires 384.0321; found 384.0319.

Synthesis of (*E*)-*N*-(4-fluorocinnamyl)-2,2,2-trichloro-*N*-phenylacetamide 271.



256 **271**

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 4-fluorostyrene (2.6

g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle), the reaction mixture was allowed to stir at 40 °C for two hours. After cooling, the solvent was removed under reduced pressure and the resulting crude product chromatographed (flash silica, 15% EtOAc/ 85% petrol). This gave the *E* isomer **271** as an off white solid (1.1 g, 67% yield).

δ_H(300MHz, $CDCl_3$) 4.54 (2H, bd, *J*= 6 Hz), 6.27 (1H, dt, *J*= 6 and 15 Hz), 6.39 (1H, d, *J*= 15 Hz), 7.03 (2H, t, *J*= 8 Hz, Ar), 7.32-7.44 (7H, m, Ar).

δ_C(75MHz, $CDCl_3$) 57.7, 93.4, 115.7, 115.9, 122.1, 128.4, 128.5, 128.9, 129.2, 130.1, 132.7, 132.8, 134.1, 141.4, 160.6, 161.2, 164.5.

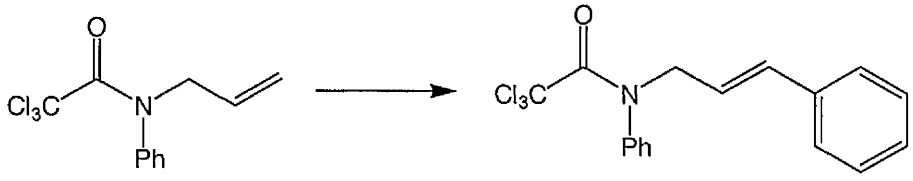
δ_F(282MHz, $CDCl_3$) -114.3.

ν_{max}(evaporated film) 1682, 3040, 3065 cm^{-1}.

m/z (ES^+) 394 (100%, $M+Na^+$).

HRMS (ES^+) $C_{17}H_{13}{}^{35}Cl_3FNO_2Na$ requires 393.9939; found 393.9947.

Synthesis of (*E*)-2,2,2-trichloro-*N*-cinnamyl-*N*-phenylacetamide 270.



256 **270**

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of styrene (2.2 g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle), the reaction mixture was allowed to stir at 40 °C for two hours. After cooling, the solvent was removed under reduced pressure and the resulting crude product chromatographed (flash silica, 15% EtOAc/ 85% petrol). This gave the *E* isomer **270** as an off white solid (890 mg, 57% yield).

δ_H(300MHz, $CDCl_3$) 4.56 (2H, bd, *J*= 6 Hz), 6.30-6.48 (2H, m), 7.30-7.44 (10H, m, Ar).

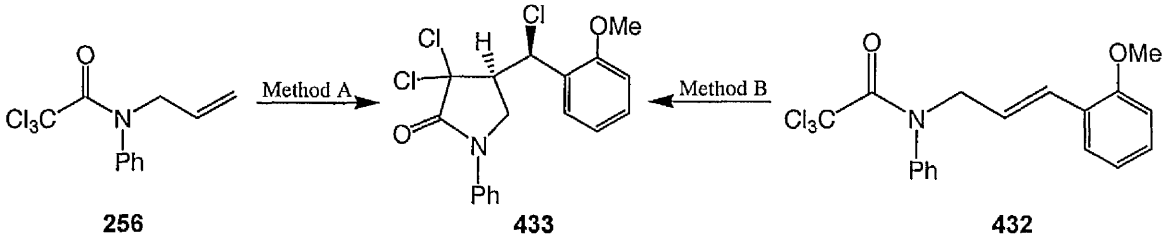
δ_C(75MHz, $CDCl_3$) 57.7, 93.4, 120.6, 122.4, 126.8, 126.8, 128.2, 128.3, 128.8, 128.9, 128.94, 129.2, 130.1, 135.3, 136.6, 141.3, 160.6.

ν_{max}(evaporated film) 1681, 2927, 3028 cm^{-1}.

m/z (AP^+) 250 (50%), 284 (40%), 354 (100%, $M+H^+$).

HRMS (AP^+) $C_{17}H_{15}{}^{35}Cl_3NO$ requires 354.0214; found 354.0214.

Synthesis of 3,3-dichloro-4-(chloro(2-methoxyphenyl)methyl)-1-phenylpyrrolidin-2-one 433.



256 **433** **432**

Method A

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 2-methoxystyrene (2.9 g, 22 mmol, 5 eq) and (*E*)-*N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After again degassing (three times, freeze-thaw cycle) the reaction mixture was allowed to stir at 40 °C for two hours. It was then immediately heated up to reflux and left to stir overnight. After cooling the solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give product **433** as an off-white solid (589 mg, 34.8% yield).

Method B

A dry vessel was charged with Cu(I)Cl (7 mg, 5 mol%), dHBipy (23 mg; 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of *N*-(2-methoxycinnamyl)-2,2,2-trichloro-*N*-phenylacetamide **432** (500 mg, 1.30 mmol, 1 eq) in 1,2-DCE (1 mL). After degassing (three times freeze-thaw cycle), the reaction was placed in a pre-heated oil bath (130 °C) and was allowed to stir for 18 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo*

and the residue chromatographed (flash silica, 10% EtOAc/ 90% hexane) to give an off white solid **433** (350 mg, 70% yield).

δ_H(300MHz, $CDCl_3$) 3.88 (1H, bt, *J*= 8 Hz), 3.97 (3H, s, OMe), 4.08 (1H, q, *J*= 8 Hz), 4.25 (1H, bt, *J*= 8 Hz), 5.72 (1H, d, *J*= 8 Hz), 7.05-7.7 (9H, m).

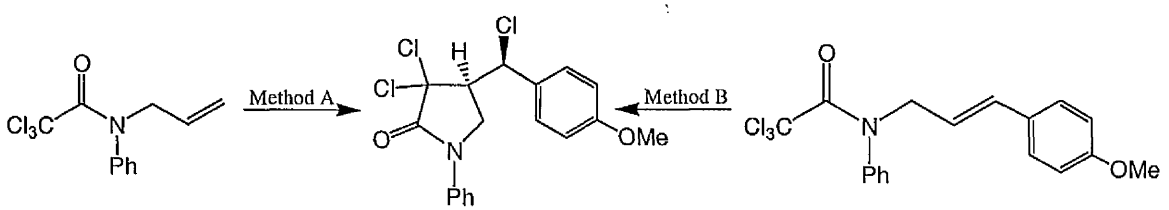
δ_C(75MHz, $CDCl_3$) 50.1, 52.4, 55.9, 58.3, 77.5, 111.8, 120.6, 120.9, 125.4, 126.4, 126.5, 129.5, 130.7, 131.2, 138.3, 157.7.

ν_{max}(evaporated film) 1728, 2831, 2998cm^{-1}.

m/z (CI) 280 (100%), 314 (60%), 384 ($M+H^+$, 20%).

HRMS (CI) $C_{18}H_{16}{}^{35}Cl_3NO_2$ requires 383.0241; found 383.0241.

Synthesis of 3,3-dichloro-4-((*R*)-chloro(4-methoxyphenyl)methyl)-1-phenylpyrrolidin-2-one 277.



256 **277** **273**

Method A

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 4-methoxystyrene (2.9 g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After again degassing (three times, freeze-thaw cycle) the reaction mixture was allowed to stir at 40 °C for two hours. It was then immediately heated up to reflux and left to stir overnight. After cooling the solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give product **277** as an off-white solid (490 mg, 29% yield).

Method B

A dry vessel was charged with Cu(I)Cl (7 mg, 5 mol%), dHBipy (23 mg; 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17

°C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of *N*-(4-methoxycinnamyl)-2,2,2-trichloro-*N*-phenylacetamide **273** (500 mg, 1.30 mmol, 1 eq) in 1,2-DCE (1 mL). After degassing (three times freeze-thaw cycle), the reaction was placed in a pre-heated oil bath (130 °C) and was allowed to stir for 18 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed (10% EtOAc/ 90% hexane) to give **277** as an off white solid (334 mg, 67% yield).

δ_H(300MHz, $CDCl_3$) 3.59 (1H, ddd, *J*= 7, 10 and 19 Hz), 3.87 (1H, t, *J*= 7 Hz), 3.89 (3H, s, OMe), 4.25 (1H, dd, *J*= 7 and 10 Hz), 5.42 (1H, d, *J*= 10 Hz), 6.99 (2H, d, *J*= 7 Hz), 7.42-7.72 (7H, m).

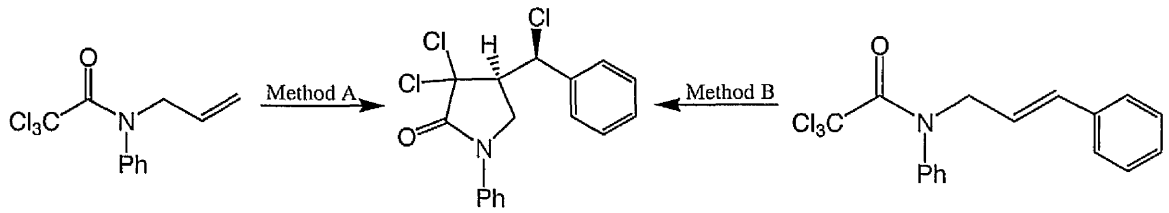
δ_C(75MHz, $CDCl_3$) 50.6, 52.3, 56.2, 59.1, 77.6, 79.2, 111.8, 120.8, 121.1, 125.6, 127.2, 127.5, 127.6, 130.7, 131.6, 139.6, 159.6.

ν_{max}(evaporated film) 1727, 2926, 2969 cm^{-1}.

m/z (AP^+), 165 (40%), 348 (50%), 384($M+H^+$, 20%).

HRMS (AP^+) $C_{18}H_{16}{}^{35}Cl_3NO_2$ requires 383.0241; found 383.0241.

Synthesis of 3,3-dichloro-4-((*R*)-chloro(phenyl)methyl)-1-phenylpyrrolidin-2-one 274.



256 **274** **270**

Method A

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of styrene (2.2 g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle), the reaction mixture was allowed to stir at 40 °C for two hours. It was then immediately heated up to reflux and left to stir overnight. After cooling the solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash

silica, 15% EtOAc/ 85% petrol) to give product **274** as an off-white solid (437 mg, 28% yield).

Method B

A dry vessel was charged with Cu(I)Cl (7 mg, 5 mol%), dHBipy (25 mg, 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of 2,2,2-trichloro-*N*-cinnamyl-*N*-phenylacetamide **270** (500 mg, 1.41 mmol, 1 eq) in 1,2-DCE (1 mL). After degassing (three times freeze-thaw cycle), the reaction was placed in a pre-heated oil bath (130 °C) and was allowed to stir for 18 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed (flash silica, 10% EtOAc/ 90% hexane) to give **274** as an off white solid (275 mg, 55% yield).

δ_H(300MHz, $CDCl_3$) 3.61 (1H, ddd, *J*= 7, 10 and 19 Hz), 3.88 (1H, t, *J*= 10 Hz), 4.27 (1H, dd, *J*= 7 and 10 Hz), 5.41 (1H, d, *J*= 10 Hz), 7.30-7.72 (10H, m, Ar).

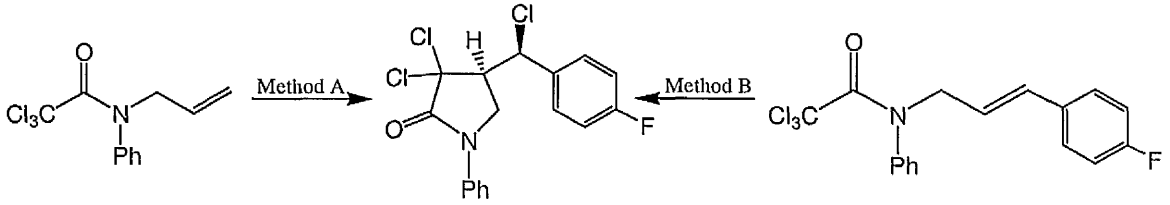
δ_C(75MHz, $CDCl_3$) 49.9, 55.5, 61.9, 84.1, 120.6, 126.5, 128.6, 129.1, 129.5, 129.8, 137.7, 138.2, 164.9.

ν_{max}(evaporated film) 1728, 2986, 3036 cm^{-1}.

m/z (AP^+) 354 ($M+H^+$, 100%).

HRMS (AP^+) $C_{17}H_{15}{}^{35}Cl_3NO$ requires 354.0214; found 354.0209.

Synthesis of 3,3-dichloro-4-((*R*)-chloro(4-fluorophenyl)methyl)-1-phenylpyrrolidin-2-one 275.



256 **275** **271**

Method A

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 4-fluorostyrene (2.6

g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle), the reaction mixture was allowed to stir at 40 °C for two hours. It was then immediately heated up to reflux and left to stir overnight. After cooling the solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give product **275** as an off-white solid (430 mg, 25% yield).

Method B

A dry vessel was charged with Cu(I)Cl (8 mg, 5 mol%), dHBipy (27 mg; 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of *N*-(4-fluorocinnamyl)-2,2,2-trichloro-*N*-phenylacetamide **271** (500 mg, 1.27 mmol, 1 eq) in 1,2-DCE (1 mL). After degassing (three times freeze-thaw cycle), the reaction was placed in a pre-heated oil bath (130 °C) and was allowed to stir for 18 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed (flash silica, 10% EtOAc/ hexane) to give **275** as an off white solid (310 mg, 62% yield).

δ_H(300MHz, $CDCl_3$) 3.56 (1H, ddd, *J*= 7, 10 and 19 Hz), 3.87 (1H, t, *J*= 10 Hz), 4.28 (1H, dd, *J*= 7 and 10 Hz), 5.44 (1H, d, *J*= 10 Hz), 7.17-7.71 (9H, m, Ar).

δ_C(75MHz, $CDCl_3$) 50.0, 55.6, 61.1, 76.8, 84.0, 115.9, 116.2, 120.6, 126.6, 129.6, 130.5, 130.6, 133.7, 138.1.

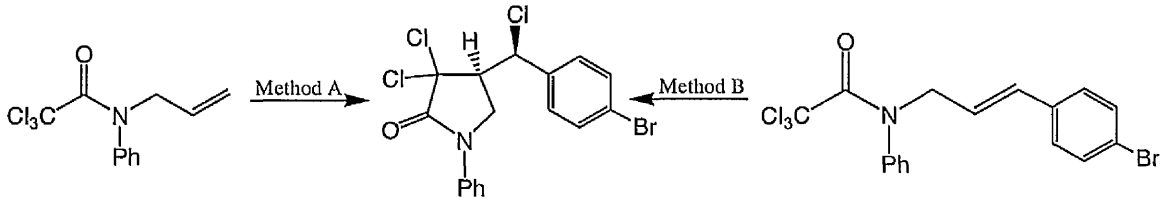
δ_F(282MHz, $CDCl_3$) -118.6.

ν_{max}(evaporated film) 1726, 2927, 3067 cm^{-1}.

m/z (AP^+) 236 (70%), 266 (60%), 394 ($M+Na^+$, 100%).

HRMS (AP^+) $C_{17}H_{13}{}^{35}Cl_3NOFNa$ ($M+Na^+$) requires 393.9939; found 393.9936.

Synthesis of 4-((*R*)-(4-bromophenyl)chloromethyl)-3,3-dichloro-1-phenylpyrrolidin-2-one 276.



256 276 272

Method A

A dry flask was charged with **90** (132 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle). A solution of 4-bromostyrene (3.9 g, 22 mmol, 5 eq) and *N*-allyl-2,2,2-trichloro-*N*-phenylacetamide **256** (1 g, 4.41 mmol, 1 eq) in toluene (10 mL) was added *via* a syringe. After further degassing (three times, freeze-thaw cycle) the reaction mixture was allowed to stir at 40 °C for two hours. It was then immediately heated up to reflux and left to stir overnight. After cooling the solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 20% EtOAc/ 80% petrol) to give product **276** as an off-white solid (398 mg, 23% yield).

Method B

A dry vessel was charged with Cu(I)Cl (5 mg, 5 mol%), dHBipy (20 mg; 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of *N*-(4-bromocinnamyl)-2,2,2-trichloro-*N*-phenylacetamide **272** (500 mg, 1.16 mmol, 1 eq) in 1,2-DCE (1 mL). After degassing (three times freeze-thaw cycle), the reaction was placed in a pre-heated oil bath (130 °C) and was allowed to stir for 18 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed (flash silica, 10% EtOAc/ 90% hexane) to give **276** as an off white solid (325 mg, 64% yield).

δ_H(300MHz, $CDCl_3$) 3.57 (1H, ddd, *J*= 7, 10 and 19 Hz), 3.90 (1H, t, *J*= 10 Hz), 4.26 (1H, dd, *J*= 7 and 10 Hz), 5.36 (1H, d, *J*= 10 Hz), 7.30 (5H, s, Ar), 7.45-7.71 (4H, m, Ar).

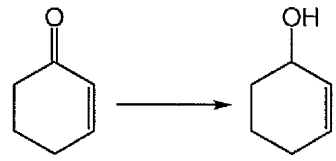
δ_C(75MHz, $CDCl_3$) 50.1, 52.4, 55.9, 58.3, 77.5, 111.8, 120.6, 120.9, 125.4, 126.4, 126.5, 129.5, 130.7, 131.2, 138.3, 157.7.

ν_{max}(evaporated film) 1726, 2927, 3067 cm^{-1}.

m/z (**AP^+**) 430 ($M+H^+$, 60%).

HRMS (AP$^+$) $C_{17}H_{14}{}^{79}Br^{35}Cl_3NO$ requires 431.9319; found 431.9306.

Synthesis of (±)-2-cyclohexen-1-ol 435.[88]



435

Cyclohexenone (7.0 g, 72.8 mmol, 1 eq) and $CeCl_3.7H_2O$ (5.43 g, 14.6 mmol, 20 mol%) were dissolved in methanol (50 mL). $NaBH_4$ (2.5 g, 72.8 mmol, 4 eq) was added slowly at 0 °C and the reaction mixture left to stir at 17 °C for 4 hours. The excess methanol was removed under reduced pressure and water (50 mL) was added to the residue along with diethylether (3x50 mL). The combined ethereal layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford alcohol **435** as a clear oil (5.1 g, 72% yield).

δ_H(300MHz, $CDCl_3$) 1.62–2.13 (6H, m), 4.25 (1H, bd, *J*= 3 Hz), 5.87-5.92 (2H, m, olefin).

δ_C(75MHz, $CDCl_3$) 18.8, 24.9, 31.9, 65.4, 129.8, 130.5.

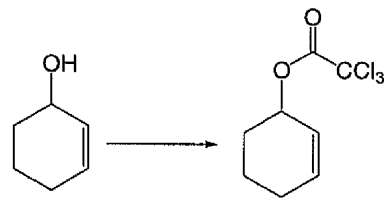
ν_{max}(liquid film) 2933, 3551 cm^{-1}.

m/z (EI) 98 (50%).

m/z (CI) 98 (100%).

HRMS (CI) $C_6H_{10}O$ requires 98.0732; found 98.0736.

Synthesis of (±)-2-cyclohexenyl 2,2,2-trichloroacetate 243[7]



435 **243**

To a solution of 2-cyclohexenol **435** (2.5 g, 25.5 mmol, 1 eq) and triethylamine (3.5 mL, 25.5 mmol, 1 eq) in anhydrous diethyl ether (50 mL) was added slowly at 0 °C,

trichloroacetylchloride (2.85 mL, 25.5 mmol, 1 eq) and the reaction mixture was left to stir at 17 °C for 3 hours. The reaction was quenched with water (100 mL) and the organic phase extracted with diethylether (3x 50 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting crude product was chromatographed (flash silica, 25% EtOAc/ 75% petrol) to furnish the *title compound* as a pale yellow oil (5.4 g, 87% yield).

δ_H(300MHz, $CDCl_3$) 1.72–2.27 (6H, m, CH_2 x3), 5.48 (1H, bd, C*H*-O), 5.72-5.79 (1H, m, olefin), 6.10-6.19 (1H, m, olefin).

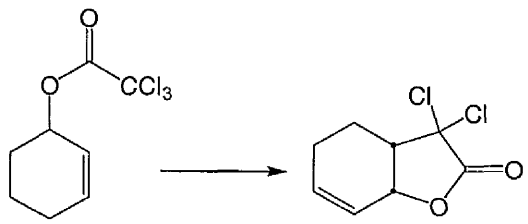
δ_C(75MHz, $CDCl_3$) 18.7, 24.7, 27.6, 68.3, 73.8, 123.1, 135.1, 161.5

ν_{max}(evaporated film) 1759, 2948 cm^{-1}.

m/z (EI) 80(100%), 161(50%), 207(50%), 241(5%).

HRMS (EI) $C_8H_{13}{}^{35}Cl_3NO_2$ ($M+NH_4^+$) requires 260.001; found 260.001.

Synthesis of (±)-(3a*S,7a*R**)-3,3-dichloro-2,3,3a,4,5,7a-hexahydrobenzo[*β*]furan-2-one 244.**



243 **244**

A dry flask was charged with **89** (80 mg, 5 mol%) and toluene (3 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of trichloroacetate **243** (1.0 g, 4.12 mmol, 1 eq) in toluene (3 mL). After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen overnight. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford lactone **244** which when recrystallised from ether/hexane gave a white crystalline solid (665 mg, 80% yield).

δ_H(300MHz, $CDCl_3$) 1.2 (1H, m), 2.2 (2H, m), 2.4 (1H, m), 2.95 (1H, dt, *J*= 4 and 13 Hz), 5.1 (1H, bt, *J*= 4 Hz), 6.0 (1H, m, olefin), 6.3 (1H, m, olefin).

δ_C(75MHz, $CDCl_3$) 21.7, 23.8, 50.4, 60.3, 82.9, 121.1, 136.2, 167.1.

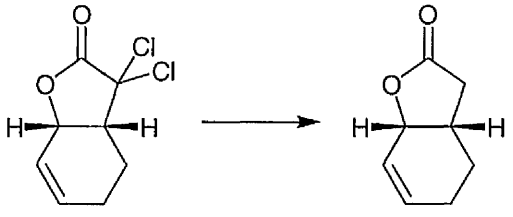
ν_{max}(Nujol) 1755, 1793 cm^{-1}.

Mp 56-58°C.

m/z (CI) 190 (45%), 224 ($M+NH_4^+$, 100%).

HRMS (CI) $C_8H_8{}^{35}Cl_2O_2$ requires 205.9901; found 205.9901.

Synthesis of (3a*S,7a*R**)-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one 436.**



244 **436**

To a solution of the dichloro lactone **244** (400 mg, 1.95 mmol, 1 eq) in acetic acid / water (1:3 ratio, 9 mL) was added zinc dust (2.2 g, 39 mmol, 20 eq) and the resulting reaction mixture was brought to reflux until all the starting material had been consumed. Upon cooling, the solvent was decanted, diluted with water (50 mL) and extracted with diethyl ether (2x50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was chromatographed (flash silica, 20% EtOAc/ 80% petrol) to give **436** as an off-white crystalline solid (240 mg, 89% yield).

δ_H(300MHz, $CDCl_3$) 1.45-1.57 (1H, m), 1.78 (1H, dq, *J*= 5 and 13 Hz), 1.99-2.25 (2H, m), 2.38 (1H, dd, *J*= 5 and 17 Hz), 2.56-2.67 (1H, m), 2.75 (1H, dd, *J*= 8 and 17 Hz), 4.80-4.85 (1H, m), 5.88-5.94 (1H, m), 6.13-6.19 (1H, m).

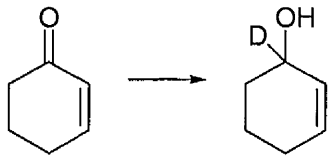
δ_C(75MHz, $CDCl_3$) 19.1, 20.7, 34.4, 35.8, 78.1, 129.7, 131.1, 176.9.

ν_{max}(Nujol) 1595, 1771, 2921 cm^{-1}.

m/z (EI) 139 ($M+H^+$, 100%).

HRMS (EI) $C_8H_{11}O_2$ ($M+H^+$) requires 139.0759; found 139.0765.

Synthesis of 1-Deuterocyclohex-2-en-1-ol 436.[94]



436

To a stirred solution of cyclohex-2-enone (1.00 g, 10 mmol, 1 eq) in methanol (10 mL) was added cerium chloride (3.88 g, 10 mmol, 1 eq), at 0 °C. After 10 minutes sodium borodeuteride (152 mg, 3.6 mmol, 1.4 eq) was added. After 15 minutes the reaction was quenched by addition of water (10 mL), diluted with EtOAc (10 mL), the phases separated, and the aqueous phase extracted repeatedly with EtOAc (3x5 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the crude residue chromatographed (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as a colourless oil (940 mg, 92% yield).

δ_H (300 MHz, $CDCl_3$) 1.61-1.68 (2H, m, CH_2), 1.70-1.91 (2H, m, CH_2), 2.02 (2H, m, CH_2), 5.78 (1H, d, *J*= 10 Hz, olefinic-H), 5.84 (1H, dt, *J*= 4 and 10 Hz, olefinic-H).

δ_C (75 MHz, $CDCl_3$) 18.9, 26.6, 33.5, 64.2, 128.3, 129.0.

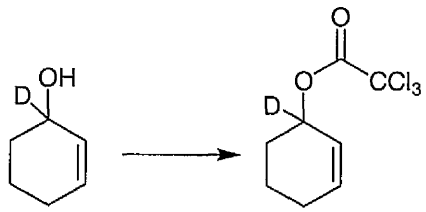
δ_D (60 MHz, $CHCl_3$) 4.88.

ν_{max} (evaporated film) 1482, 2938, 3445 cm^{-1}.

m/z (CI) 99 (100%), 117 ($M+NH_4^+$, 20%).

HRMS (CI) C_6H_9DO requires 99.0794; found 99.0791.

Synthesis of 1-Deuterocyclohex-2-enyl-1-trichloroacetate 320.



436 **320**

To a solution of 1-deuterocyclohex-2-en-1-ol **436** (940 mg, 9.49 mmol, 1 eq) and triethylamine (1.32 mL, 9.49 mmol, 1 eq) in anhydrous diethyl ether (15 mL) cooled to 0 °C was slowly added trichloroacetylchloride (1.05 mL, 9.49 mmol, 1 eq). The reaction mixture

was warmed slowly to 17 °C and left to stir for 3 hours. The reaction was quenched with water (10 mL) and the organic phase was extracted with ether (2x10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a pale yellow oil which was chromatographed (flash silica 25% EtOAc/ 75% petrol) to afford the *title compound* as a pale yellow oil (2.27 g, 98% yield).

δ_H (300 MHz, $CDCl_3$) 1.64-1.93 (2H, m, $-CH_2$), 1.98 (2H, m, $-CH_2$), 2.00-2.24 (2H, m, $-CH_2$), 5.82 (1H, d, *J*= 10 Hz, olefinic-H), 6.17 (1H, dt, *J*= 4 and 10 Hz, olefinic-H).

δ_D (60 MHz, $CHCl_3$) 5.44.

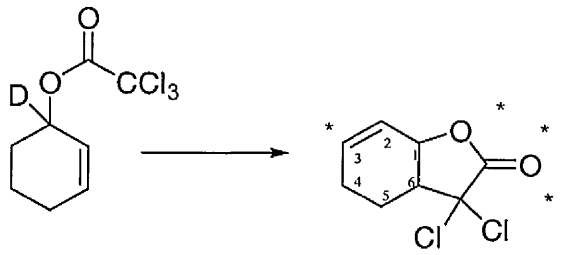
δ_C (75 MHz, $CDCl_3$) 18.4, 25.0, 27.7, 73.8 (t, 4 Hz), 90.5, 123.4, 135.5, 161.8.

ν_{max} (evaporated film) 1670, 1769, 2965 cm^{-1}.

m/z (CI) 242 (100%), 260 ($M+NH_4^+$, 20%).

HRMS (CI) $C_8H_8D^{35}Cl_3O$ requires 242.9731 found 242.9728.

Synthesis of lactone 321.



320 **321** = atoms where deutrium was found

A dry flask was charged with **89** (80 mg, 5 mol%) and toluene (3 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of trichloroacetate **320** (1.0 g, 4.12 mmol, 1 eq) in toluene (3 mL). After degassing (three times, freeze-thaw cycle) the reaction mixture was brought to a gentle reflux under nitrogen overnight. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford lactone **321** as a white crystalline solid (590 mg, 71% yield).

δ_H(300MHz, $CDCl_3$) 1.14-1.28 (1H, m), 2.04-2.17 (2H, m), 2.27-2.30 (1H, m), 2.93 (3/4H, dt, *J*= 5 and 14Hz), 5.05-5.11 (3/4H, m), 5.95-6.02 (3/4H, m, olefin), 6.24-6.31 (3/4H, m, olefin).

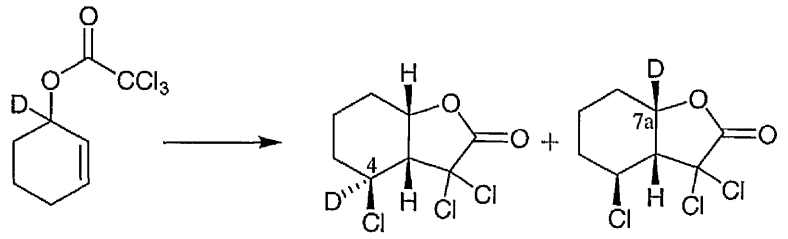
δ_C(75MHz, $CDCl_3$) 21.8, 21.9, 23.9, 24.0, 24.1, 50.6, 50.7, 53.7, 73.2, 73.3, 76.9, 77.5, 83.2, 121.1, 121.2, 121.3, 136.5, 136.6, 136.7, 167.5

ν_{max}**(Nujol)** 1767, 1790 cm^{-1}.

m/z (CI) 191 (40%), 226 (100%).

HRMS (CI) $C_8H_7D^{35}Cl_2O_2$ requires 206.9964; found 206.9987.

Synthesis of (3a*S*,4*S***,7a*S***)-3,3,4-trichloro-4-deutero-hexahydro-1-benzofuran-2(3*H*)-one 327-4D** and **(3a*S***,4*S***,7a*S***)-3,3,4-trichloro-7a-deutero-hexahydro-1-benzofuran-2(3*H*)-one 327-7aD.**



320 **327-4D** **327-7aD**

A dry flask was charged with **90** (33 mg, 5 mol%) and toluene (5 mL). The contents of the flask were degassed (three times using freeze-thaw cycle) to which was added, by syringe, a degassed (three times using freeze-thaw cycle) solution of 1-deuterocyclohex-2-enyl-1-trichloroacetate (200 mg, 0.83 mmol, 1 eq) in toluene (3 mL). The reaction mixture was brought to reflux under nitrogen for 3.5 hours. The toluene was removed under reduced pressure and the crude product chromatographed (flash silica, 20% EtOAc/ 80% petrol) to afford the trichlorinated title compounds as an 83:17 mixture of regioisomeric 7a-deutero **327-7aD**: 4-deutero lactones **327-4D** as a white crystalline solid (20 mg, 10% yield).

δ_H **(300 MHz, $CDCl_3$)** 1.64-1.93 (4H, m, CH_2), 2.20-2.42 (2H, m, CH_2), 3.22 (1H, d, *J*= 10 Hz, C*H*CCl_2), 4.01 (1H, m, C*H*Cl), 5.02 (1H, q, *J*= 5.5 Hz, C7a-H, corresponding to the 4-deuterolactone).

δ_D **(60 MHz, $CHCl_3$)** 5.04 (C7a-D, corresponding to the 7a-deuterolactone), 4.00 (C4-D, corresponding to the 4-deuterolactone).

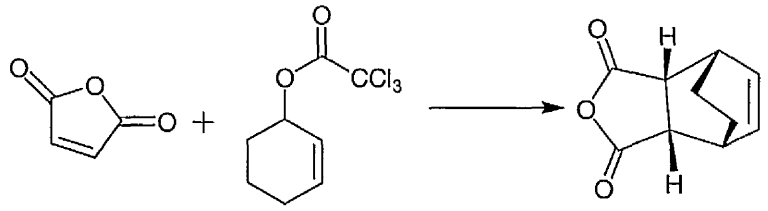
δ_C **(75 MHz, $CHCl_3$)** 17.7, 26.6, 29.3, 34.0, 58.0, 77.1, 80.3, 167.1.

ν_{max} **(evaporated film)** 1659, 1764, 2963 cm^{-1}

m/z (CI) 242 (100%), 260 ($M+NH_4^+$, 15%).

HRMS (CI) $C_8H_8\ ^{35}Cl_3DO$ requires 242.9731; found 242.9723.

Synthesis of endo-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride 325.



243 **325**

2-Cyclohexenyl 2,2,2-trichloroacetate **243** (200 mg, 0.86 mmol, 1 eq) was dissolved in deuterated chloroform (5 mL). The resulting solution was purged with nitrogen and **89** (20 mg, 5 mol%) was then added along with maleic anhydride (200 mg, 2.04 mmol, 2.3 eq). The reaction mixture was brought to reflux for 12 hours and solvent removed under reduced pressure with the resulting crude product chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give **325** as a white crystalline solid (140 mg, 92% yield).

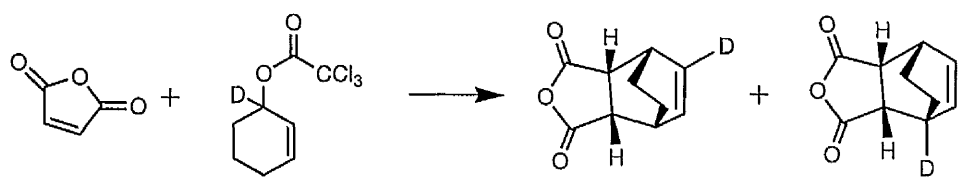
δ_H(300MHz, $CDCl_3$) 1.33-1.37 (2H, m, $-CH_2$), 1.55-1.60 (2H, m, $-CH_2$), 3.10 (2H, d, J = 2 Hz, C*H*-C=O), 3.13 (2H, m, CHCH_2), 6.23 (2H, dd, J = 2, and 4 Hz, C=C*H*).

δ_C(75MHz, $CDCl_3$) 22.7, 31.4, 44.5, 132.8, 172.8.

m/z (EI) 79 (100%), 197 ($M+NH_4^+$, 40%).

HRMS (EI) $C_{10}H_{10}O_3$ requires 178.0630; found 178.0636.

Synthesis of (3aR*,4R*,7S*,7aS*)- Tetrahydro-4-d-ethanoisobenzofuran-1,3-dione 323' and (3aR*,4R*,7S*,7aS*)-Tetrahydro-4,7-ethanoisobenzofuran-1,3-dione-5-d 323".



320 **323'** **323"**

Method A

1-Deuterocyclohex-2-enyl-1-trichloroacetate **320** (200 mg, 0.86 mmol, 1 eq) was dissolved deuterated chloroform (10 mL). The solution was degassed by passing a gentle stream of nitrogen through the reaction mixture. Catalyst **89** (50 mg, 5 mol%) was then added along

with maleic anhydride (200 mg, 2.04 mmol, 2.3 eq) and the solution heated to reflux and stirred overnight. The solvent removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 15% EtOAc/petrol) to give products **323'** and **323"** as an inseparable crystalline solid (130 mg, 84% yield).

Method B

1-Deuterocyclohex-2-enyl-1-trichloroacetate **320** (200 mg, 0.86 mmol, 1 eq) was dissolved in 5ml toluene (5 mL). To this solution was added maleic anhydride (200 mg, 2.04 mmol, 2.3 eq) and the reaction mixture heated to reflux overnight without the exclusion of oxygen. The solvent was removed under reduced pressure and the resulting crude product was recrystallised (EtOAc/ heptane) to give **323'** and **323"** as an inseparable white crystalline solid (118 mg, 77% yield).

δ_H(300MHz, $CDCl_3$) 1.40-1.45 (2H, m), 1.60-1.66 (2H, m), 3.17 (2H, bt, *J*= 2 Hz), 3.25 (2H, bs), 6.34 (2H, d, *J*= 2 Hz).

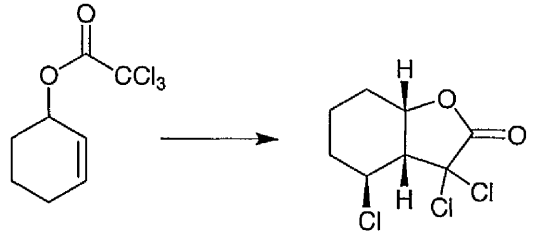
δ_C(75MHz, $CDCl_3$) 23.1, 23.2, 31.8, 44.9, 45.0, 133.3, 173.1.

δ_D(61.4MHz, $CDCl_3$) 3.11, 6.24 (55:45 ratio).

m/z (EI) 79 (100%), 197 ($M+NH_4^+$, 40%).

HRMS (EI) $C_{10}H_{13}O_3ND$ ($M+NH_4^+$) requires 197.1031; found 197.1031.

Synthesis of (3a*R,4*R**,7a*R**)-3,3,4-trichloroperhydrobenzo[*β*]furan-2-one 319.[6]**



243 **319**

A dry flask was charged with Cu(I)Cl (10 mg, 5 mol%), dHBipy (40 mg, 10 mol%) and anhydrous 1,2-DCE (5 mL) and the resultant brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of trichloroacetate **243** (500 mg, 2.07 mmol, 1 eq) in 1,2-DCE (2 mL). After further degassing (three times freeze-thaw cycle), the flask

was placed in a pre-heated oil bath (130 °C) and stirred at reflux for 3.5 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed (flash silica, 20% EtOAc/ 80% petrol) to give lactone **319** which was recrystallised (ether in hexane) to give a white solid (390 mg, 78% yield).

δ_H(300MHz, $CDCl_3$) 1.83 (4H, m, ring protons), 2.21-2.42 (2H, m, ring protons), 3.27 (1H, d, *J*= 9 Hz, H_a), 4.00 (1H, m, H_c), 5.03 (1H, q, *J*= 5, H_b).

δ_C(75MHz, $CDCl_3$) 18.2, 27.9, 34.5, 55.2, 58.5, 72.8, 80.8, 167.7.

Mp 95–97°C (lit[4] mp 97-97.5°C).

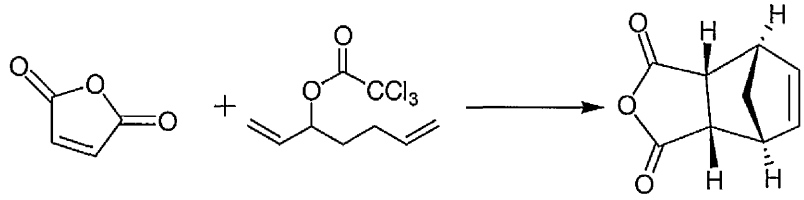
ν_{max}(Nujol) 1798 cm^{-1}.

m/z (EI) 190 (60%), 224 (100%), 260 ($M+NH_4^+$, 100%).

m/z (CI) 74 (100%), 91 (95%), 127 (70%), 156 (30%), 226 (25%), 260 ($M+NH_4^+$, 65%).

HRMS (EI) $C_8H_{13}{}^{35}Cl_3NO_2$ ($M+NH_4^+$) requires 260.00120; found 260.0020.

Synthesis of 5-norbornene-2,3-dicarboxylic anhydride 297.



280 **297**

To a solution of hepta-1,6-dien-3-yl 2,2,2-trichloroacetate **280** (100 mg, 0.18 mmol, 1 eq) in deuterated chloroform (10 mL) was added **84** (10 mg, 5 mol%), Cu(I)Cl (10 mg), and HBipy (30 mg). The solution was allowed to stir for 1 hour. Maleic anhydride (100 mg, 0.9 mmol, 5 eq) was then added and the solution was heated to reflux and left overnight. The solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give the product **297** as a gummy solid (140 mg, 92% yield).

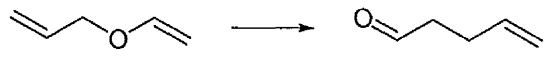
δ_H(300MHz, $CDCl_3$) 1.67 (1H, d, *J*= 9 Hz), 1.88 (1H, dt, *J*= 4 and 9 Hz), 3.55 (2H, m), 3.66 (2H, m), 6.32 (2H, t, *J*= 4 Hz).

δ_C(75MHz, $CDCl_3$) 46.3, 47.3, 53.1, 135.7, 171.6.

m/z (CI) 74 (100%), 91 (95%), 164 (60%), 182 ($M+NH_4^+$, 80%).

HRMS (CI) $C_9H_8O_3$ requires 164.0473; found 164.0478.

Synthesis of pent-4-enal 284.



284

Allyl vinyl ether (5g, 60mmol, 1 eq) was placed in a suitable vessel and microwaved for 2 hours (200 °C, medium absorbance), to produce neat pent-4-enal **284** as a viscous oil (5 g, 100% yield).

δ_H(300MHz, $CDCl_3$) 2.39-2.48 (2H, m), 2.58-2.62 (2H, m), 5.05-5.15 (2H, m), 5.85 (1H, qt, 6, 10, 16 and 27 Hz), 9.83 (1H, t, 2 Hz).

δ_C(75MHz, $CDCl_3$) 26.4, 43.0, 115.9, 136.7, 202.2.

ν_{max}(evaporated film) 1648, 2856, 2935 cm^{-1}.

m/z Unable to get MS data

Synthesis of (±)-hepta-1,6-dien-3-ol 282.

284 **282**

Method A

To a solution of anhydrous ether (50 mL) and activated magnesium turnings (2 g, 83.3 mmol, 1.2 eq) at -78 °C, 4-bromobutene (10 g, 74.5 mmol, 1 eq) was added dropwise slowly. The reaction was activated by a crystal of iodine. After half an hour acrolein (5 g, 89.4 mmol, 1.2 eq) was again slowly added dropwise at -78 °C. The milky yellow solution was allowed to stir for a further hour while letting it warm up slowly to 17 °C. The reaction was quenched with 2M $HCl_{(aq)}$ (2x 50 mL). This was then neutralised with aqueous 2M $NaOH_{(aq)}$ (2x 50 mL), extracted with diethyl ether (2x 50 mL), organic layers washed with water, dried ($MgSO_4$) and solvent was removed under reduced pressure. The crude product chromatographed (flash silica, 20% EtOAc/ 80% petrol) to afford the product **282** as a clear oil (3.6 g, 44% yield).

Method B

To a solution of pent-4-enal **284** (10 g, 120 mmol, 1 eq) in anhydrous THF (100 mL) was added vinylmagnesium bromide (1M in THF, 144 mL, 144 mmol, 1.2 eq) at -78 °C. After 3 hours stirring at 17 °C, the reaction was quenched with 1M $HCl_{(aq)}$ (2x 100 mL), and extracted with ether (3x 75 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give product **282** (13.01 g, 97% yield) as a clear oil with no further purification necessary.

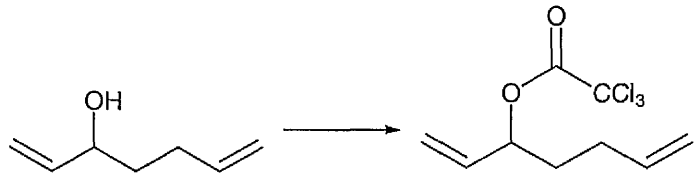
δ_H(300MHz, $CDCl_3$) 1.65-1.79 (2H, m), 2.20-2.36 (2H, m), 4.18 (1H, q, *J*= 6 Hz, tertiary H), 5.05 (2H, ddt, *J*= 1, 10 and 17 Hz, olefin), 5.2 (2H, ddt, *J*= 1, 10 and 17 Hz, olefin), 5.9 (2H, m).

δ_C(75MHz, $CDCl_3$) 29.8, 36.2, 72.9, 115.1, 115.2, 138.5, 141.2.

ν_{max}(evaporated film) 3351, 3079, 2935, 2856 cm^{-1}.

m/z Unable to get MS data

Synthesis of (±)-hepta-1,6-dien-3-yl 2,2,2-trichloroacetate 280.



282 **280**

To a solution of (±)-hepta-1,6-dien-3-ol **282** (435 mg, 3.88 mmol, 1 eq) and triethylamine (470 mg, 4.67 mmol, 1.2 eq) in anhydrous diethyl ether (50 mL) was added slowly at 0 °C, trichloroacetylchloride (846 mg, 4.67 mmol, 1.2 eq) and the reaction mixture was left to warm up to 17 °C and continue stirring for 3 hours. The reaction was quenched with water (100 mL) and the organic phase extracted with diethyl ether (3x 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to furnish the *title compound* as a clear oil (940 mg, 95% yield) with no further purification needed.

δ_H(300MHz, $CDCl_3$) 1.9-2.21 (2H, m), 5.05 (2H, ddt, *J*= 1, 10 and 17 Hz, olefin), 5.39 (1H, dt, *J*= 1 and 10 Hz, tertiary H), 5.40 (2H, ddt, *J*= 1, 10 and 17 Hz, olefin), 5.83 (2H, m, olefin).

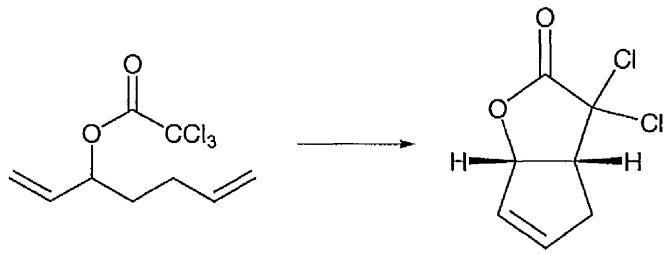
δ_C(75MHz, $CDCl_3$) 29.2, 33.2, 80.1, 90.4, 126.1, 119.1, 134.3, 137.0, 161.3.

ν_{max}(evaporated film) 1765, 2941, 2980, 3078, cm^{-1}

m/z (AP^+) 109 (40%), 279 ($M+Na^+$,100%).

HRMS (AP^+) $C_9H_{11}{}^{35}Cl_3O_2$ requires 255.9825; found 255.9813.

Synthesis of (3a*R,6a*S**)-3,3-dichloro-3a,4-dihydro-3*H*-cyclopenta[β]furan-2(6a*H*)-one 290.**



280 **290**

To a solution of (±)-hepta-1,6-dien-3-yl 2,2,2-trichloroacetate **280** (500 mg, 1.9 mmol, 1 eq) in deuterated chloroform (10 mL) was added **90** (57 mg, 5 mol%), Cu(I)Cl (10 mg, 5 mol%), and dHBipy (15 mg, 5 mol%). The solution was allowed to stir for 2 hours at 17 °C then heated to reflux for 3 hours. The solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 20% EtOAc/ 80% petrol) to give the *title compound* as an off-white solid (350 mg, 95% yield).

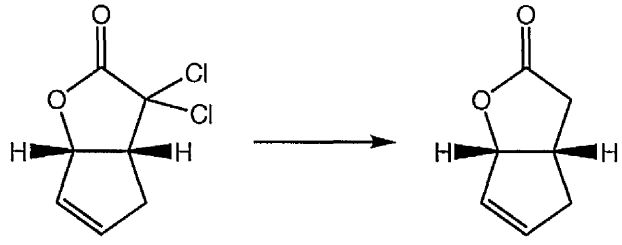
δ_H(300MHz, $CDCl_3$) 2.68-2.79 (1H, m), 2.82-2.87 (1H, m), 3.61 (1H, dt, *J*= 6 and 8 Hz), 5.42 (1H, d, *J*= 6 Hz), 5.98-6.11 (1H, m), 6.22-6.31 (1H, m).

δ_C(75MHz, $CDCl_3$) 35.6, 54.6, 86.4, 127.1, 140.6, 168.1.

ν_{max}(evaporated film) 1788 cm^{-1}.

m/z Unable to attain MS

Synthesis of (3a*S,6a*R**)-3a,4-dihydro-3*H*-cyclopenta[β]furan-2(6a*H*)-one 291.**



290 **291**

To a solution of the dichlorolactone **290** (200 mg, 1.05 mmol, 1 eq) in acetic acid / water (1:3 ratio, 6 mL) was added zinc dust (1.35 g, 21 mmol, 20 eq) and the resulting reaction mixture was brought to reflux until all the starting material had been consumed. Upon cooling, the solvent was decanted, diluted with water (25 mL) and extracted with diethylether (2x 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was chromatographed (flash silica, 20% EtOAc/ 80% petrol) to give **291** as an off-white crystalline solid (112 mg, 86% yield).

δ_H (300 MHz, $CDCl_3$) 2.32 (1H, dd, *J*= 5 and 18 Hz), 2.33 (1H, dd, *J*= 5 and 18 Hz), 2.71-2.81 (1H, m), 2.82 (1H, dd, *J*= 10 and 18 Hz), 3.09-3.20 (1H, m), 5.49-5.54 (1H, m), 5.87 (1H, dq, *J*= 1 and 5 Hz), 6.06-6.10 (1H, m).

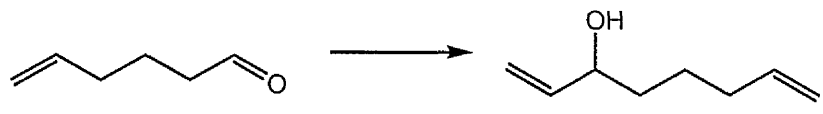
δ_C (75 MHz, $CDCl_3$) 35.3, 36.3, 39.8, 89.9, 129.2, 137.3, 177.5.

ν_{max} (evaporated film) 1770, 2857, 2930, 3063 cm^{-1}.

m/z (CI) 142 ($M+NH_4^+$, 100%).

HRMS (CI) $C_7H_8O_2$ requires 124.0519; found 124.0521.

Synthesis of octa-1,7-dien-3-ol 318.



316 **318**

To a solution of hex-5-enal **316** (5 g, 51 mmol, 1 eq) in anhydrous THF (100 mL) was added vinylmagnesium bromide (1M in THF, 61 mL, 61 mmol, 1.2 eq) at -78 °C. After 3 hours

stirring at 17 °C, the reaction was quenched with 1M $HCl_{(aq)}$ (100 mL), and extracted with ether (3x 75 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the product **318** (4.4 g, 67% yield) as a clear oil with no further purification necessary.

δ_H(300MHz, $CDCl_3$) 1.39-1.61 (4H, m), 1.96 (1H, s), 2.06-2.14 (2H, m), 4.08 (1H, bq, 6 Hz), 4.95-5.06 (2H, m), 5.11 (1H, dt, 2 and 10 Hz), 5.24 (1H, dt, 2 and 17 Hz), 5.73-5.94 (2H, m).

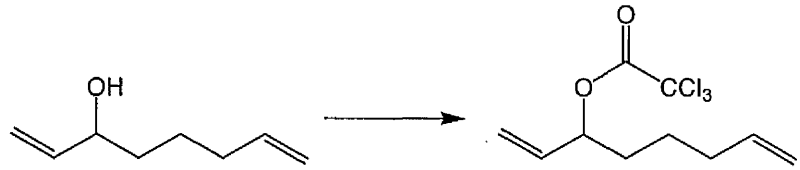
δ_C(75MHz, $CDCl_3$) 24.8, 33.8, 36.6, 73.3, 114.8, 114.9, 138.9, 141.5.

ν_{max}(evaporated film) 2856, 2935, 2979, 3351 cm^{-1}.

m/z (CI) 58 (60%), 126 (100%).

HRMS (CI) $C_8H_{14}O$ requires 126.1403; found 126.1398.

Synthesis of octa-1,7-dien-3-yl 2,2,2-trichloroacetate 315.



318 **315**

To a solution of octa-1,7-dien-3-ol **318** (1.2 g, 9.2 mmol, 1 eq) and triethylamine (1.1 g, 11.1 mmol, 1.2 eq) in anhydrous diethyl ether (50 mL) was added slowly at 0 °C, trichloroacetylchloride (2.0 g, 11.1 mmol, 1.2 eq) and the reaction mixture was left to warm up to 17 °C and continue stirring for 3 hours. The reaction was quenched with water (100 mL) and the aqueous phase extracted with diethyl ether (3x 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to furnish the *title compound* as a pale yellow oil (2.2 g, 83% yield) with no further purification needed.

δ_H(300MHz, $CDCl_3$) 1.45-1.59 (2H, m), 1.71-1.88 (2H, m), 2.09-2.18 (2H, m), 4.99-5.10 (2H, m), 5.31 (1H, dt, 1 and 10 Hz), 5.36-5.40 (1H, m), 5.40 (1H, dt, 1 and 17 Hz), 5.75-5.93 (2H, m).

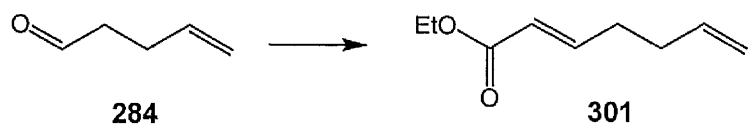
δ_C(75MHz, $CDCl_3$) 24.3, 33.4, 33.5, 80.8, 115.5, 118.9, 134.5, 138.1, 161.4. (CCl_3 carbon missing due to electronegativity of Cl)

ν_{max}(evaporated film) 1764, 2864, 2938, 2977 cm^{-1}.

m/z (AP^+) 109 (40%), 293 ($M+Na^+$,100%).

HRMS (AP^+) $C_{10}H_{17}{}^{35}Cl_3O_2N$ ($M+NH_4^+$) requires 288.319; found 288.0311.

Synthesis of (*E*)-ethyl hepta-2,6-dienoate 301.



284 **301**

To a solution of **284** (7.4 g, 88 mmol, 1 eq) dissolved in anhydrous DCM (300 mL) was (ethoxycarbonylmethylene)triphenylphosphorane (36.7 g, 105.7 mmol, 1.2 eq). The reaction mixture was allowed to stir overnight at 17 °C. The resulting mixture was filtered through celite and the solvent was removed under reduced pressure. The crude product was chromatographed (flash silica, 20% EtOAc/ 80% petrol) to afford the (*E*)-Wittig product **301** as a transparent oil (12.7 g, 94% yield).

δ_H(300MHz, $CDCl_3$) 1.30 (3H, t, *J*= 7 Hz), 2.18-2.39 (4H, m), 4.19 (2H, q, *J*= 7 Hz), 5.01-5.16 (2H, m), 5.75-5.86 (2H, m), 6.98 (1H, dt, *J*= 7 and 15 Hz).

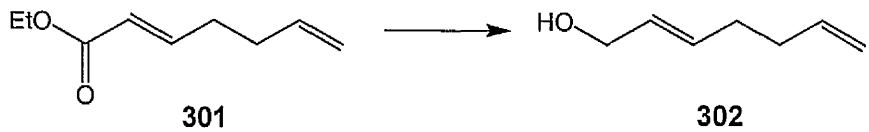
δ_C(75MHz, $CDCl_3$) 14.5, 31.7, 32.3, 60.4, 115.7, 121.9, 137.3, 148.5, 166.8.

ν_{max}(evaporated film) 1721, 2933, 2981, 3079 cm^{-1}.

m/z (CI) 154 (100%).

HRMS (CI) $C_9H_{14}O_2$ requires 154.0988; found 154.0990.

Synthesis of (*E*)-hepta-2,6-dien-1-ol 302.



301 **302**

(*E*)-Ethyl hepta-2,6-dienoate **301** (9.1 g, 59.1 mmol, 1 eq) was dissolved in anhydrous THF (400 mL) under an atmosphere of nitrogen and cooled to -78 °C. 1M solution of DIBAL-H in hexane (148 mL, 148 mmol, 2.5 eq) was added to the reaction slowly over a period of 20 minutes. Conditions were kept the same for one hour and then allowed to warm up to 17 °C. After further stirring for 90 minutes, the reaction was quenched with a saturated solution of Rochelle's salt (100 mL), vigorously stirred for 2 hours, extracted with diethyl ether (2x 150 mL), organic layers washed with water and dried ($MgSO_4$). The dried solvent was removed

under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/petrol) to afford the product **302** as a transparent oil (6.4 g, 97% yield).

δ_H(300MHz, $CDCl_3$) 1.99 (1H, s), 2.15-2.17 (4H, m), 4.10 (2H, d, *J*= 5 Hz), 4.86-5.07 (2H, m, olefinic), 5.64-5.71 (2H, m), 5.70-5.89 (1H, m).

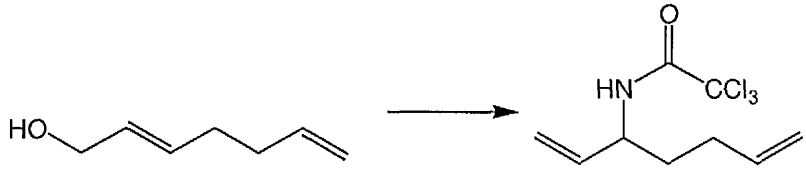
δ_C(75MHz, $CDCl_3$) 31.7, 33.5, 63.7, 115.1, 129.7, 132.4, 138.3.

ν_{max}(evaporated film) 2849, 2923, 3340 cm^{-1}.

m/z (CI) 58 (20%), 108 (80%), 112 ($M+H^+$,100%).

HRMS (CI) $C_7H_{11}O$ requires 111.0804; found 111.0807.

Synthesis of (±)-2,2,2-trichloro-*N*-(hepta-1,6-dien-3-yl)acetamide 300.



302 **300**

To a solution of (*E*)-hepta-2,6-dien-1-ol **302** (5.8 g, 51.79 mmol, 1 eq) in anhydrous THF (200 mL) was added sodium hydride (248 mg, 10.4 mmol, 0.2 eq) and trichloroacetonitrile (22.4 g, 115.4 mmol, 3 eq) at 0 °C. The reaction mixture was stirred at 0 °C for a further 3 hours where it was warmed to 17 °C and evaporated to dryness under reduced pressure. Petrol (200 mL) was added, left to stir for 15 minutes, filtered, and the filtrate evaporated under reduced pressure to reveal a sticky brown gum. The gum was dissolved in xylenes (200 mL), heated to reflux and left to stir for 18 hours. The reaction was cooled to 17 °C, quenched with the addition of water (150 mL) with the organic layer separated and the aqueous layer extracted with diethyl ether (2x 150 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and solvent was removed under reduced pressure. The crude product was passed through a silica pad (flash silica, 20% EtOAc/ 80% petrol) to afford the product **300** as light yellow oil (11.8 g, 89% yield).

δ_H(300MHz, $CDCl_3$) 1.71-1.80 (2H, m), 2.12-2.19 (2H, m), 4.41-4.51 (1H, m), 5.00-5.09 (2H, m), 5.19-5.28 (2H, m), 5.75-5.88 (2H, m), 6.71 (1H, bs).

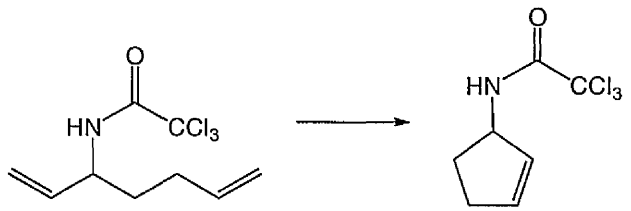
δ_C(75MHz, $CDCl_3$) 30.3, 32.1, 33.6, 53.5, 116.2, 116.6, 136.7, 137.4, 161.4.

ν_{max}(evaporated film) 1694, 2931, 3080, 3326 cm^{-1}.

m/z (CI) 203 (30%), 273 ($M+NH_4^+$, 100%).

HRMS (CI) $C_9H_{16}{}^{35}Cl_3ON_2$ ($M+NH_4^+$) requires 273.0323; found 273.0319.

Synthesis of 2,2,2-trichloro-*N*-(cyclopent-2-enyl)acetamide 299.



300 **299**

To a mixture of **90** (130 mg, 5 mol%) in anhydrous DCM (5 mL) was added trichloroacetamide **300** (1.2 g, 4.4 mmol, 1 eq) in anhydrous DCM (2 mL) and the reaction mixture was allowed to stir at 17 °C for 1 hour. The reaction mixture was filtered through a pad of silica (flash silica, DCM) and filtrate solvent removed *in vacuo* to give **299** as an off-white solid (920 mg, 93% yield).

δ_H(300MHz, $CDCl_3$) 1.65-1.78 (1H, m), 2.36-2.61 (3H, m), 4.96-5.05 (1H, m), 5.78 (1H, dq, *J*= 2 and 6 Hz), 6.11 (1H, dq, *J*= 2 and 6 Hz), 6.65 (1H, bs).

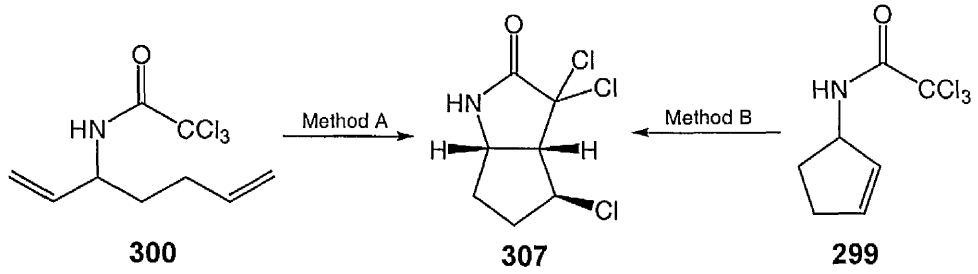
δ_C(75MHz, $CDCl_3$) 31.1, 31.5, 58.2, 129.6, 136.8, 161.4. (CCl_3 carbon missing due to electronegativity of Cl)

ν_{max}(evaporated film) 1689, 2931, 3042, 3285 cm^{-1}.

m/z (CI) 245 ($M+NH_4^+$, 100%).

HRMS (CI) $C_7H_{12}{}^{35}Cl_3ON_2$ ($M+NH_4^+$) requires 245.0010; found 245.0010.

Synthesis of (3a*S*,4*S***,6a*S***)-3,3,4-trichloro-hexahydrocyclopenta[β]pyrrol-2(1*H*)-one 307.**



300 **307** **299**

Method A

To a aerobic solution of (±)-2,2,2-trichloro-*N*-(hepta-1,6-dien-3-yl)acetamide **300** (500 mg, 2 mmol, 1 eq) in xylenes (10 mL) was added **90** (57 mg, 5 mol%). The solution was allowed to stir for 2 hour at 17 °C then heated to reflux for 48 hours. The solvent was removed under reduced pressure and the resulting crude product was chromatographed (flash silica, 20% EtOAc/petrol) to give the *title compound* as an off-white solid (413 mg, 91% yield).

Method B

A dry vessel was charged with Cu(I)Cl (7 mg, 5 mol%), dHBipy (25 mg, 5 mol%) and anhydrous 1,2-DCE (10 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of **299** (350 mg, 1.41 mmol, 1 eq) in 1,2-DCE (1 mL). After degassing (three times freeze-thaw cycle), the reaction was placed in a pre-heated oil bath (130 °C) and was allowed to stir for 18 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed (flash silica, 20% EtOAc/ 80% hexane) to give **307** as an off white solid (240 mg, 75% yield).

δ_H(300MHz, $CDCl_3$) 1.95 (1H, m), 2.1 (1H, m), 2.3 (2H, m), 3.70 (1H, dd, *J*=2 and 3 Hz), 4.46 (1H, m), 4.65 (1H, dt, *J*=3 and 5 Hz), 7.44 (1H, bs).

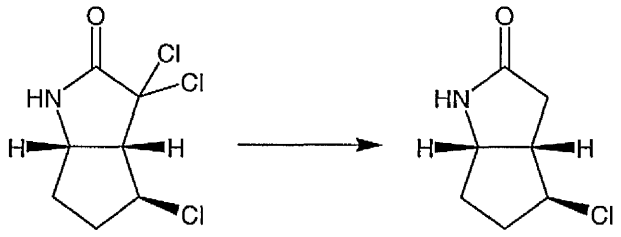
δ_C(75MHz, DMSO-d_6) 30.7, 35.6, 56.1, 61.6, 65.4, 85.1, 166.8.

ν_{max}(evaporated film) 1763, 2929, 3134, 3256 cm^{-1}.

m/z (CI) 102 (30%), 245 (100%).

HRMS (CI) $C_7H_8NO_2{}^{35}Cl$ ($M+NH_4^+$) requires 245.0010; found 245.0009.

Synthesis of (3a*S*,4*S***,6a*S***)-4-chloro-hexahydrocyclopenta[β]pyrrol-2(1H)-one 308.**



307 **308**

To a solution of the dichlorolactam **307** (95 mg, 0.42 mmol, 1 eq) in acetic acid / water (1:3 ratio, 3 mL) was added zinc dust (546 mg, 8.4 mmol, 20 eq) and the resulting reaction mixture was brought to reflux until all the starting material had been consumed. Upon cooling, the solvent was decanted, diluted with water (10 mL) and extracted with diethylether (2x15 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ solution, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was chromatographed (flash silica, 15% EtOAc/ 85% petrol) to give **308** as an off-white crystalline solid (58 mg, 86% yield).

δ_H (300 MHz, $CDCl_3$) 1.72-1.81 (1H, m), 1.96-2.31 (4H, m), 2.7 (1H, dd, *J*= 11 and 18 Hz), 3.08-3.16 (1H, m), 4.19 (1H, bs), 4.31 (1H, bt, *J*= 7 Hz), 7.00 (1H, bs).

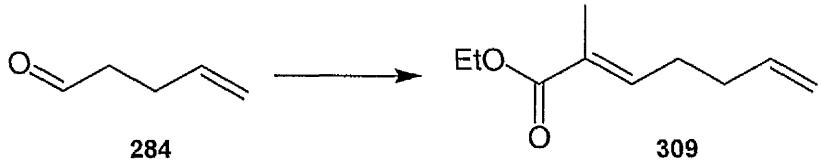
δ_C (75 MHz, $CDCl_3$) 31.7, 33.7, 36.2, 48.7, 58.3, 66.4, 177.0.

ν_{max} (evaporated film) 1686, 2933, 3188 cm^{-1}.

m/z (ES^+) 160 ($M+H^+$, 100%).

HRMS (ES^+) $C_7H_{11}ON^{35}Cl$ ($M+H^+$) requires 160.0524; found 160.0528.

Synthesis of (*E*)-ethyl 2-methylhepta-2,6-dienoate 309.



284 **309**

To a solution of **284** (1 g, 11.9 mmol, 1 eq) in anhydrous DCM (70 mL) was added $Ph_3P{=}C(Me)CO_2Et$ (6.47 g, 17.85 mmol, 1.5 eq). The reaction mixture was allowed to stir overnight at 17 °C. The resulting mixture was filtered through silica plug (flash silica, 10%

EtOAc/ 90% petrol) with the filtrate evaporated under reduced pressure to afford the (*E*)-Wittig product **309** as a transparent oil (1.8 g, 98% yield).

δ_H (300 MHz, $CDCl_3$) 0.98 (3H, t, *J*= 7 Hz), 1.81 (3H, s), 1.86-2.01 (4H, m), 4.03 (2H, q, *J*= 7 Hz), 4.89-4.97 (2H, m), 5.56-5.69 (1H, m), 6.85 (1H, dt, *J*= 3 and 7 Hz).

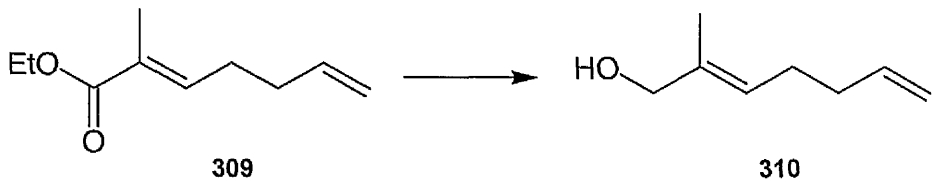
δ_C (75 MHz, $CDCl_3$) 12.6, 14.5, 28.3, 32.8, 60.6, 115.5, 128.4, 137.7, 141.4, 168.4.

ν_{max} (evaporated film) 1712, 2933, 2981 cm^{-1}.

m/z (CI) 169 ($M+H^+$, 100%), 186 ($M+NH_4^+$, 50%).

HRMS (CI) $C_{10}H_{16}O_2$ requires 168.1145; found 168.1152.

Synthesis of (*E*)-2-methylhepta-2,6-dien-1-ol 310.



309 **310**

(*E*)-Ethyl hepta-2,6-dienoate **309** (1.8 g, 10.7 mmol, 1 eq) was dissolved in anhydrous THF (50 mL) under an atmosphere of nitrogen and cooled to -78 °C. DIBAL-H (1M solution in hexane, 26.8 mL, 26.8 mmol, 2.5 eq) was added to the reaction slowly over a period of 20 minutes. Conditions were kept the same for one hour and then allowed to warm up to 17 °C. After further stirring for 90 minutes, the reaction was quenched with a saturated solution of Rochelle's salt (100 mL), vigorously stirred for 2 hours, extracted with diethyl ether (2x 150 mL), organic layers washed with water and dried ($MgSO_4$). The dried solvent was removed under reduced pressure and the crude product chromatographed (flash silica, 10% EtOAc/ 90% petrol) to afford the product **310** as a transparent oil (1.24 g, 92% yield).

δ_H (300 MHz, $CDCl_3$) 1.65 (3H, s), 1.90-2.30 (4H, m), 4.01 (2H, s), 4.96-5.07 (2H, m), 5.40-5.44 (2H, m), 5.79-5.90 (1H, m).

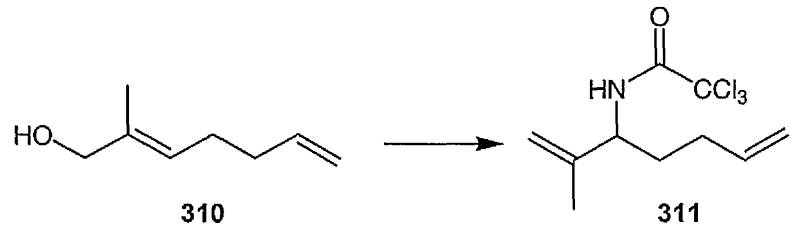
δ_C (75 MHz, $CDCl_3$) 13.9, 27.3, 33.8, 68.9, 114.9, 125.6, 135.4, 138.6.

ν_{max} (evaporated film) 2860, 2921, 3338 cm^{-1}.

m/z (CI) 109 (50%), 126 (100%).

HRMS (CI) $C_8H_{14}O$ requires 126.1039; found 126.1041.

Synthesis of 2,2,2-trichloro-*N*-(2-methylhepta-1,6-dien-3-yl)acetamide 311.



310 **311**

To a solution of (*E*)-hepta-2,6-dien-1-ol **310** (1.24 g, 9.8 mmol, 1 eq) in anhydrous THF (20 mL) was added sodium hydride (47 mg, 1.96 mmol, 0.2 eq) and trichloroacetonitrile (4.2 g, 29.4 mmol, 3 eq) at 0 °C. The reaction mixture was stirred at 0 °C for a further 3 hours where it was warmed to 17 °C and evaporated to dryness under reduced pressure. Petrol (50 mL) was added, left to stir for 15 minutes, filtered, and the filtrate evaporated under reduced pressure to reveal a sticky brown gum. The gum was dissolved in xylenes (20 mL), heated to reflux and left to stir for 18 hours. The reaction was cooled to 17 °C, quenched with the addition of water (30 mL) with the organic layer separated and the aqueous layer extracted with diethyl ether (2x 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and solvent was removed under reduced pressure. The crude product was passed through a silica pad (flash silica, 20% EtOAc/ 80% petrol) to afford the product **311** as a light yellow oil (2.14 g, 81% yield).

δ_H (300 MHz, $CDCl_3$) 1.67-1.90 (2H, m), 1.79 (3H, s), 2.11-2.18 (3H, m), 4.38-4.40 (1H, m), 4.97 (2H, s), 5.01-5.12 (1H, m), 5.76-5.90 (1H, m), 6.71 (1H, bs).

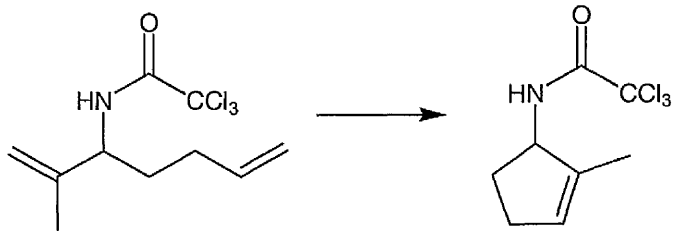
δ_C (75 MHz, $CDCl_3$) 19.6, 30.3, 32.1, 56.4, 93.1, 112.9, 116.2, 137.4, 143.2, 161.4.

ν_{max} (evaporated film) 1697, 2859, 2939, 2977, 3335 cm^{-1}.

m/z (ES^+) 59 (40%), 269 (20%), 292 ($M+Na^+$, 100%).

HRMS (ES^+) $C_{10}H_{18}ON_2{}^{35}Cl_3$ ($M+NH_4^+$) requires 287.0479; found 287.0482.

Synthesis of 2,2,2-trichloro-*N*-(2-methylcyclopent-2-enyl)acetamide 312.



311 **312**

To a mixture of **90** (110 mg, 5 mol%) in anhydrous DCM (5 mL) was added trichloroacetamide **311** (1 g, 3.7 mmol, 1 eq) in anhydrous DCM (2 mL) and the reaction mixture was allowed to stir at 17 °C for 1 hour. The reaction mixture was filtered through a pad of silica (flash silica, DCM) and filtrate solvent removed *in vacuo* to give **312** as an off-white solid (800 mg, 90% yield).

δ_H (300 MHz, $CDCl_3$) 1.76 (3H, s), 2.26-2.54 (4H, m), 4.81-4.90 (1H, m), 5.62-5.65 (1H, m), 6.54 (1H, bs).

δ_C (75 MHz, $CDCl_3$) 14.0, 30.4, 31.6, 60.5, 129.9, 138.7, 161.8. (CCl_3 carbon missing due to electronegativity of Cl)

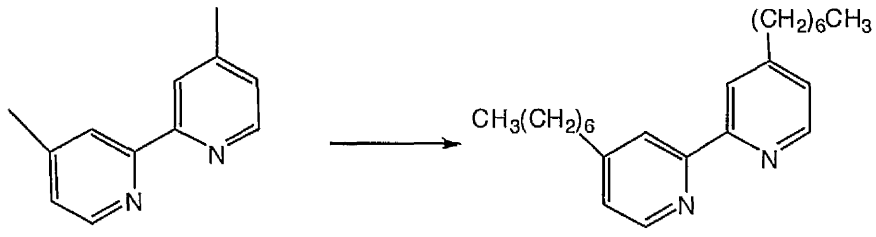
ν_{max} (evaporated film) 1685, 2848, 3267 cm^{-1}.

m/z (CI) 259 ($M+NH_4^+$, 100%).

HRMS (CI) $C_8H_{14}ON_2{}^{35}Cl_3$ ($M+NH_4^+$) requires 259.0166; found 259.0164.

Section 10.3 Towards the synthesis of Eunicillin

4,4'-di-n-heptyl-2,2'-dipyridyl 50.[89]



50

To a solution of di-isopropylamine (7.36 mL, 75 mmol, 3 eq) in anhydrous THF (70 mL) was added, under argon at –78 °C, *n*-BuLi (1.6 M in hexane, 31.05 mL, 50 mmol, 2 eq). After 15 minutes, the solution was warmed to 0 °C and allowed to stir at 0 °C for 15 minutes. The mixture was then re-cooled to –78 °C and a solution of 4,4'-dimethyl-2,2'-dipyridyl (4.0 g, 25 mmol, 1 eq) in dry THF (120 mL) was added slowly *via* a syringe. After 3 hours, 1-bromohexane (9.2 mL, 55.75 mmol, 2.2 eq) was added and the mixture was allowed to warm up to 17 °C and stirred for 16 hours. The reaction mixture was then poured onto chilled brine (250 mL) with the aqueous layer extracted with diethyl ether (2x 50 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. The yellow solid was recrystallised from acetonitrile to yield the *title compound* as a white solid (7.48 g, 85% yield).

δ_H (300 MHz, $CDCl_3$) 0.8 (6H, t, *J*= 6 Hz), 1.2-1.4 (20H, m), 1.6-1.8 (4H, m), 2.7 (4H, t, *J*= 6 Hz), 7.1 (2H, d, *J*= 6 Hz), 8.2 (2H, s), 8.5 (2H, d, *J*= 6 Hz).

δ_C (75 MHz, $CDCl_3$) 13.9, 22.5, 29.2, 30.4, 31.6, 35.5, 121.2, 123.8, 148.6, 152.6, 156.1.

ν_{max} (Nujol) 1466, 1595, 2852, 2921, 2953 cm^{-1}.

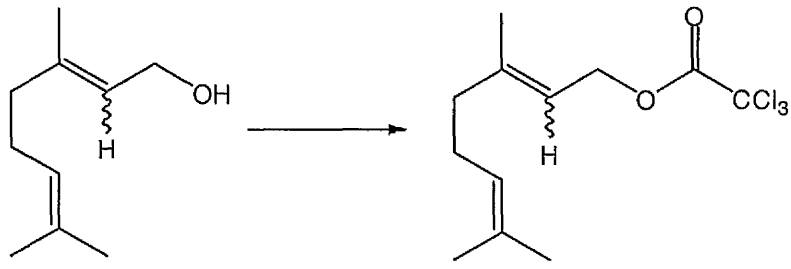
Mp 52-53°C (lit mp 50-51°C).

m/z (EI) 281 (100%), 353 ($M+H^+$, 20%).

m/z (CI) 353 ($M+H^+$, 95%).

HRMS (CI) $C_{24}H_{36}N_2$ requires 352.2878; found 352.2869.

(*E*+*Z*)-3,7-dimethyl-2,6-octadienyl-2,2,2-trichloroacetate 328.[17]



328

To a solution of (*E*+*Z*)-geraniol (3:2 ratio) (3.37 mL, 26 mmol, 1 eq) and triethylamine (3.61 mL, 26 mmol, 1 eq) in anhydrous diethyl ether (90 mL) was slowly added at 0 °C, trichloroacetylchloride (3.45 mL, 31 mmol, 1.2 eq) and the mixture was allowed to stir at 17 °C for 3 hours. After stirring for 3 hours, the reaction was quenched with water (100 mL) and the organic phase was extracted with diethyl ether (2x100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil which was chromatographed (flash silica, 20% EtOAc/ 80% petrol) to afford the *title compound* as a pale yellow oil (7.40 g, 96% yield) as a mixture of *E*/*Z* isomers (50:50 ratio).

δ_H (300 MHz, $CDCl_3$) 1.6 (3H, s, Me), 1.7 (3H, s, Me), 1.8 (3H, s, Me), 2.2 (4H, m, $(CH_2)_2$), 4.9 (2H, d, *J*= 7 Hz), 5.1 (1H, m), 5.4 (1H, t, *J*= 7 Hz).

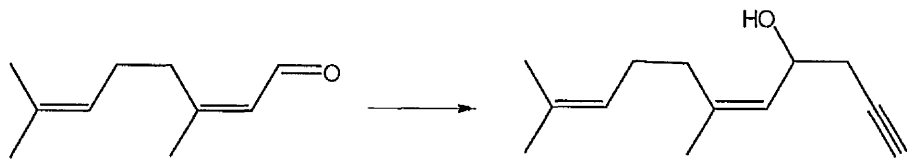
δ_C (75 MHz, $CDCl_3$) 17.2, 23.1, 25.6, 26.5, 34.5, 60.6, 89.6, 118.1, 123.3, 131.6, 135.8, 159.5.

ν_{max} (evaporated film) 1666, 1763, 2960 cm^{-1}.

m/z (CI) 81(25%), 137(100%), 154(35%), 316 ($M+NH_4^+$, 20%).

HRMS (CI) $C_{12}H_{17}{}^{35}Cl_3O_2$ requires 298.0284; found 298.0291.

Synthesis of (*E*+*Z*)-6,10-dimethylundeca-5,9-dien-1-yn-4-ol 334d.



334d

To a mechanically stirred suspension of magnesium turnings (24.0 g, 991 mmol, 2 eq), iodine (620 mg, 2.47 mmol, 0.5 mol%), and mercuric chloride (1.34 g, 4.94 mmol, 1 mol%) in

diethyl ether (900 mL), was added, propargyl bromide (approximately 5 mL), with careful monitoring of the internal temperature, until reflux is obtained. The suspension was immediately cooled to -50 °C to which was added, by dropping funnel, a solution of propargyl bromide (125 g, 841 mmol, 1.7 eq) and (*E*+*Z*)-geranial (75.2 g, 495 mmol, 1 eq, 3:2 ratio of *E*/*Z*) in diethyl ether (400 mL), dropwise over 2 hours. The suspension was allowed to warm to -20 °C (care must be taken to ensure the temperature does not rise above -20 °C) and after stirring for 1 hour the mixture was allowed to warm to 17 °C and was quenched with careful addition of saturated $NH_4Cl_{(aq)}$ solution (500 mL). The phases were separated, the aqueous phase extracted repeatedly with EtOAc (3x 500 mL), the combined organic phases washed with brine (300 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material was filtered through a pad of silica (flash silica, 50% EtOAc/ 50% petrol) and evaporated under reduced pressure to give the *title compound* as light yellow oil (84.5 g, 89% yield) as a mixture of *E*/*Z* isomers (50:50 ratio).

δ_H(300MHz, $CDCl_3$) 1.62 (3H, d, *J*= 2 Hz), 1.70 (1H, s), 1.72 (1H, s), 1.77 (2H, d, *J*= 2 Hz), 2.01-2.15 (5H, m), 2.42 (2H, dd, *J*= 2 and 7 Hz), 4.55 (1H, m), 5.11 (1H, m), 5.29 (1H, dt, *J*= 2 and 7 Hz).

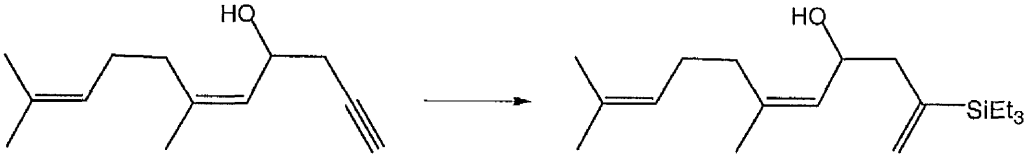
δ_C(75MHz, $CDCl_3$) 17.0, 17.9, 23.6, 25.9, 25.9, 26.5, 26.7, 27.8, 27.9, 29.5, 32.7, 39.7, 66.6, 67.0, 70.6, 81.1, 81.2, 124.1, 125.9, 126.9, 131.9, 132.8, 140.3, 140.5.

ν_{max}(evaporated film) 2857, 2917, 2967, 3309, 3340 cm^{-1}.

m/z (CI) 175 (100%).

HRMS (CI) $C_{13}H_{20}O$ requires 192.1509; found 192.1505.

Synthesis of (*E*+*Z*)-2-(triethylsilyl)-6,10-dimethylundeca-1,5,9-trien-4-ol 437.



334d **437**

To a stirred solution of **334d** (2 g, 10 mmol, 1 eq) in anhydrous DCM (40 mL) was added triethylsilane (1.6 g, 15 mmol, 1.5 eq). After 5 minutes the flask was cooled to 0 °C and pentamethylcyclopentadienylruthenium trisacetonitrilehexafluorophosphate (252 mg, 0.5

mmol, 5 mol%) was added. The flask was immediately allowed to warm to 17 °C. After 30 minutes the mixture was filtered through a silica pad, eluting with 30% EtOAc/ 70 % petrol (3x20 mL) and the solvent removed *in vacuo*. The residue was chromatographed (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as colourless oil (2.1 g, 68% yield).

δ_H(300MHz, $CDCl_3$) 0.66 (6H, q, *J*= 7.5 Hz), 0.96 (9H, t, *J*= 7.5 Hz), 1.64 (3H, s), 1.73 (6H, s), 2.06-2.15 (4H, m), 2.34 (2H, m), 4.45 (1H, m), 5.15 (1H, m), 5.51 (1H, d, *J*= 3 Hz), 5.81 (1H, d, *J*= 3 Hz).

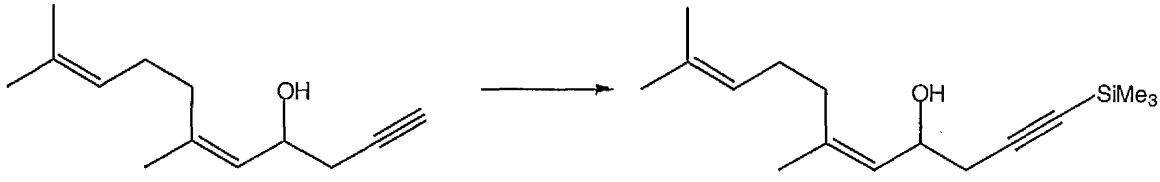
δ_C(75MHz, $CDCl_3$) 3.2, 7.5, 16.9, 17.9, 23.6, 25.9, 26.6, 26.8, 32.8, 39.8, 45.1, 45.2, 66.3, 66.7, 124.2, 124.3, 127.6, 128.7, 129.3, 129.4, 131.9, 132.5, 138.7, 138.9, 146.0, 146.1.

ν_{max}(evaporated film) 2340, 2360, 2875, 2912, 3367 cm^{-1}.

m/z (CI) 132 (100%), 175 (30%), 291 (50%), 308 (10%).

HRMS (CI) $C_{19}H_{36}SiO$ requires 308.2530; found 308.2523.

Synthesis of (*E*+*Z*)-3,7-dimethyl-1-(3-silanyl-prop-2-ynyl)-octa-2,6-dienylester 343.



334d **343**

To a stirred solution of the crude alkyne **334d** (95 g, 495 mmol, 1 eq) in anhydrous tetrahydrofuran (400 mL), at -78 °C, was added *n*-BuLi (1.6 M in hexanes, 626 mL, 1.99 mol, 4 eq). After 1 hour, trimethylsilyl chloride (217 ml, 2.0 mol, 4 eq) was added and after a further hour the reaction was quenched by the addition of a saturated solution of ammonium chloride (300 mL). The phases were separated, the aqueous phase extracted repeatedly with EtOAc (3x 100 mL), the combined organic phases were washed with 10% $HCl_{(aq)}$ (2x 100 mL), brine (100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude oil was purified by distillation (168 °C, 5 mm) affording the *title compound* as a pale yellow (88.8 g, 68% yield) as a mixture of *E*/*Z* isomers (50:50 ratio).

δ_H (300 MHz, $CDCl_3$) 0.20 (9H, s, $SiMe_3$), 1.64 (3H, s, Me), 1.78 (3H, s, Me), 2.0-2.20 (4H, m, $-CH_2$), 2.44 (2H, dd, *J*= 2 and 4 Hz, $-CH_2$), 4.58-4.62 (1H, m, C*H*OH), 5.18-5.21 (1H, m, olefinic H), 5.24-5.31 (1H, m, olefinic H).

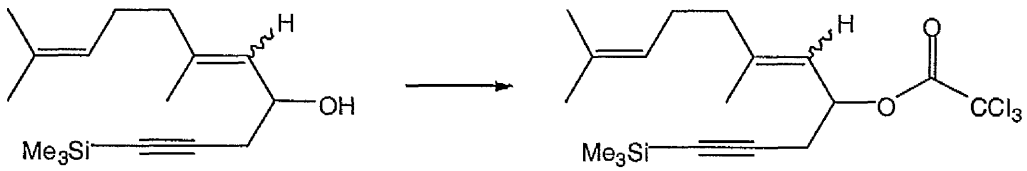
δ_C (75 MHz, $CDCl_3$) 0.3, 17.1, 17.9, 23.6, 25.9, 26.6, 26.8, 29.5, 32.7, 39.7, 66.7, 67.1, 87.4, 103.5, 124.1, 125.9, 126.9, 131.9, 132.6, 140.1, 140.3.

ν_{max} (evaporated film) 1372, 1655, 2943, 3449 cm^{-1}.

m/z (CI) 81 (20%), 137 (20%), 154 (40%), 282 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{16}H_{28}OSi$ requires 264.1909; found 264.1915.

Synthesis of (*E*+*Z*)-3,7-dimethyl-1-(3-trimethylsilanyl-prop-2-ynyl)-octa-2,6-dienyl 345.



343 **345**

To a solution of the secondary alcohol **343** (6.86 g, 26 mmol, 1 eq) and triethylamine (3.61 mL, 26 mmol, 1 eq) in anhydrous ether (90 mL) was slowly added at 0 °C, trichloroacetylchloride (2.89 mL, 26 mmol, 1 eq) and the mixture was allowed to stir at 0 °C for 3 hours. After stirring for 3 hours, the reaction was quenched with water (100 mL) and the organic phase was extracted with ether (2x100 mL). The combined organic phases were washed with saturated sodium bicarbonate solution (50 mL), brine (200 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the *title compound* as a pale yellow oil (9.5g, 92%) as a 50:50 mixture of *E*+*Z* diastereoisomers. Compound **345** was used in the next step without further purification.

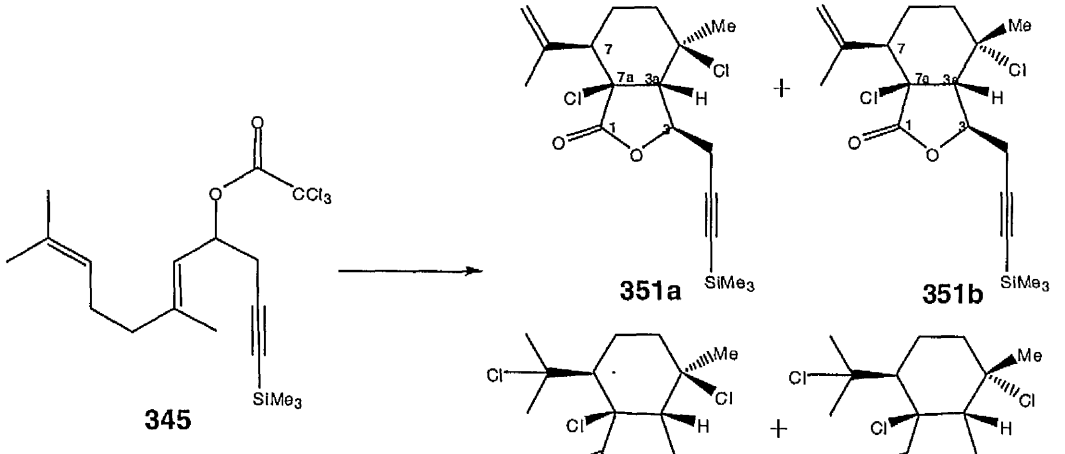
δ_H (300 MHz, $CDCl_3$) 0.16 (9H, s, $SiMe_3$), 1.63 (1.5H, s, Me), 1.65 (1.5H, s, Me), 1.70 (1.5H, s, Me), 1.73 (1.5H, s, Me) 1.82 (1.5H, s, Me), 1.83 (1.5H, s, Me), 2.03-2.22 (4H, m), 2.55-2.77 (2H, m, $-CH_2$), 5.07-5.17 (1H, m), 5.23-5.30 (1H, m, olefinic H), 5.71-5.79 (1H, m, olefinic H).

δ_C (75 MHz, $CDCl_3$) 0.3, 17.3, 17.3, 17.9, 23.5, 23.6, 25.9, 26.3, 39.9, 75.1, 75.4, 101.0, 101.1, 120.2, 120.8, 123.6, 123.7, 132.3, 132.8, 144.8, 145.0, 161.2, 161.3.

ν_{max} (evaporated film) 1760, 2959 cm^{-1}.

m/z Unable to attain MS

Synthesis of (3*R,3a*S**,4*R**,7*R**,7a*S**)-3-(3-trimethylsilylprop-2-ynyl)-4,7a-dichloro-7-isopro penyl-4-methyl-hexahydro-isobenzofuran-1-one 351a** and **(3*R**,3a*S**,4*S**,7*R**, 7a*S**)-3-(3-trimethylsilylprop-2-ynyl)-4,7a-dichloro-7-isopropenyl-4-methyl-hexa hydro-isobenzofuran-1-one 351b.**



A dry Schlenck tube was charged with Cu(I)Cl (42 mg, 0.426 mmol, 5 mol%), *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (139 mg, 0.426 mmol, 5 mol%) and anhydrous 1,2-DCE (15 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a solution of trichloroacetate **345** (3.5 g, 8.52 mmol, 1 eq) in degassed (three times freeze thaw cycle) 1,2-DCE (10 mL) and the Schlenck tube was placed in a pre-heated oil bath (90 °C) and was allowed to stir for 3.5 hours under argon. Upon cooling, the solvent was removed *in vacuo* and the residue chromatographed (flash silica, 5% EtOAc/ 95% petrol) to give isopropenyl diastereoisomeric lactones **351a** and **351b**, trichlorolactones **352a** and **352b**.

Major diastereoisomer 351a (R_f=0.10 in 5% EtOAc/petrol), white solid [recrystallised from DCM in hexane] (830 mg, 28% yield).

δ_H (300 MHz, $CDCl_3$) 0.20 (9H, s, $Si(CH_3)_3$), 1.70 (3H, s, CH_3), 1.90 (3H, s, CH_3), 2.20-2.42 (4H, m, CH_2CH_2), 2.68 (1H, dd, *J*= 4 and 18 Hz, $CH_2CCSi(CH_3)_3$), 3.01 (1H , dd, *J*=4 and 18

Hz, CH_2CCSi(CH_3)$_3$), 3.51 (1H, dd, *J*=1 and 10 Hz, C3a-H), 4.43 (1H, ddd, *J*=1, 4 and 10 Hz, C3-H), 4.82 (1H, s, olefinic H), 5.10 (1H, m, olefinic H).

δ_C (75 MHz, $CDCl_3$) 0.1, 22.3, 23.1, 27.0, 32.7, 39.7, 48.7, 58.2, 65.8, 69.0, 75.8, 91.5, 99.1, 117.7, 142.0, 171.1.

ν_{max} (Nujol) 1369, 1442, 1639, 1792, 2940 cm^{-1}.

m/z (EI) 73 (100%), 93 (80%), 105 (40%), 189 (20%) .

m/z (CI) 90 (100%), 320 (25%), 354 (20%), 390 ($M+NH_4^+$, 40%).

HRMS (CI) $C_{18}H_{30}{}^{35}Cl_2NO_2Si$ ($M+NH_4^+$) requires 390.1417 found 390.1419.

Minor diastereoisomer 351b (Rf = 0.45 in 1:19 EtOAc/ petrol), white solid [recrystallised from EtOAc in petrol] (276 mg, 10% yield)

δ_H (300 MHz, $CDCl_3$) 0.18 (9H, s, Si(CH_3)$_3$), 1.60-2.01 (2H, m, CH_2CH_2), 1.85 (3H, s, CH_3), 1.94 (3H, s, CH_3), 2.18-2.30 (2H, m, CH_2CH_2), 2.64 (1H, dd, *J*= 4 and 10 Hz, C7-H), 3.07 (2H, m, CH_2CCSi(CH_3)$_3$), 3.25 (1H, d, *J*= 8 Hz, C3a-H), 4.72 (1H, td, *J*= 4 and 8 Hz, C3-H), 4.82 (1H, s, olefinic H), 5.10 (1H, t, *J*=1 Hz, olefinic H).

δ_C (75 MHz, $CDCl_3$) 0.1, 22.6, 24.6, 27.3, 33.1, 39.7, 47.8, 57.6, 68.1, 70.3, 77.1, 90.3, 100.2, 117.6, 141.8, 170.8.

ν_{max} (Nujol) 1369, 1442, 1639, 1792, 2940 cm^{-1}.

m/z (EI) 189 (10%), 105 (30%), 93 (60%), 73 (100%).

m/z (CI) 90 (100%), 320 (35%), 354 (20%), 390 ($M+NH_4^+$, 50%).

HRMS (CI) $C_{18}H_{30}C_{12}NO_2Si$ requires 390.1417; found 390.1415.

Major trichloro-bicyclic lactone impurity 352a (250 mg, 9% yield)

δ_H (300 MHz, $CDCl_3$) 0.21 (9H, s, Si(CH_3)$_3$), 1.71 (3H, s), 1.83 (3H, s, CH_3), 1.87 (3H, s, CH_3), 2.22-2.39 (2H, m), 2.67 (1H, dd, *J*= 3 and 18 Hz), 2.99 (1H, dd, *J*= 3 and 18 Hz), 3.41 (1H, dd, *J*= 2 and 10 Hz), 4.44 (1H, ddt, *J*= 2, 3 and 14 Hz)

δ_C (75 MHz, $CDCl_3$) 0.07, 21.6, 27.2, 29.8, 32.8, 33.6, 39.7, 52.5, 59.9, 65.9, 68.8, 75.4, 76.6, 91.9, 98.9, 171.6

ν_{max} (Nujol) 1794, 2956 cm^{-1}.

m/z Unable to attain MS

Minor trichloro-bicyclic lactone impurity 352b (125 mg, 5% yield)

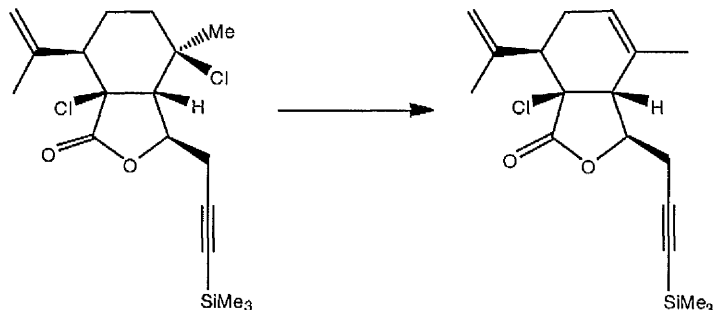
δ_H (300 MHz, $CDCl_3$) 0.18 (9H, s, $Si(CH_3)_3$), 1.75 (3H, s), 1.85 (3H, s, CH_3), 1.86 (3H, s, CH_3), 2.22-2.41 (2H, m), 2.82 (1H, dd, *J*= 4 and 11 Hz), 2.93 (1H, dd, *J*= 4 and 17 Hz), 3.06 (1H, dd, *J*= 4 and 17 Hz), 3.11 (1H, d, *J*= 8 Hz), 4.78 (1H, dt, *J*= 4 and 8 Hz)

δ_C (75 MHz, $CDCl_3$) 0.15, 22.4, 26.2, 31.5, 31.6, 34.2, 38.5, 49.6, 60.2, 67.9, 70.3, 73.9, 76.9, 90.6, 99.8, 171.4

ν_{max} (Nujol) 1797, 2958 cm^{-1}

m/z Unable to attain MS

Synthesis of (3*R,3a*R**,7*R**,7a*S**)-7a-Chloro-7-isopropenyl-4-methyl-3-(3'-trimethylsilanyl-prop-2-ynyl)-3a,6,7,7a-tetrahydro-3*H*-isobenzofuran-1-one 353.**



351a **353**

To a solution of the lactone **351a** (500 mg, 1.33 mmol, 1 eq) in anhydrous dimethylformamide (35 mL) was added lithium carbonate (196 mg, 2.67 mmol, 2.0 eq) and lithium chloride (83 mg, 2.00 mmol, 1.5 eq). The resulting mixture was placed in an oil bath at 125 °C and heated for 30 minutes. The reaction mixture was partitioned between water (100 mL) and EtOAc (200 mL), and the aqueous layer extracted with EtOAc (3x 100 mL). The combined organic extracts were washed with brine (4x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was chromatographed (flash silica, 5% EtOAc/ 95% petrol) to afford the *title compound* as a colourless oil (400 mg, 89% yield). R_f = 0.80 (1:4 EtOAc/ petrol).

δ_H (300 MHz, $CDCl_3$) 0.10 (9H, m, $SiMe_3$), 1.81 (3H, s, Me), 1.83 (3H, s, Me), 2.21 1H, m, CH_2), 2.39 (1H, m, CH_2), 2.90 (1H, m), 2.85 (1H, dd, *J*= 4 and 12 Hz), 3.06 (1H, dd, *J*= 7 and 14 Hz,), 3.24 (1H, d, *J*= 4 Hz), 4.41 (1H, ddd, *J*= 4, 7 and 14 Hz), 4.92 (1H, s, olefinic-H), 5.01 (1H, m, olefinic-H), 5.64 (1H, m, olefinic-H).

δ_C (75 MHz, $CDCl_3$) 0.1, 22.6, 26.6, 27.9, 45.1, 53.1, 60.6, 67.7, 80.4, 89.7, 100.2, 116.1, 123.9, 129.3, 142.9, 172.7.

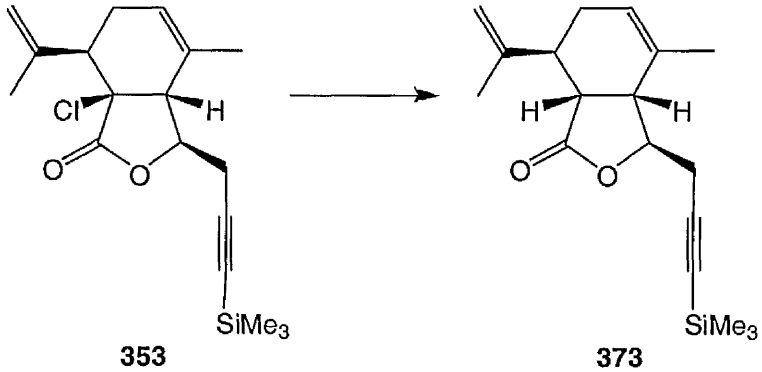
ν_{max} (evaporated film) 1549, 1632, 1786, 2942 cm^{-1}.

m/z (EI) 73 (100%), 119 (50%),189 (80%).

m/z (CI) 189 (30%), 301 (10%), 337 (5%), 354 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{18}H_{25}O_2{}^{35}ClSi$ requires 336.1312; found 336.1307.

Synthesis of (3*R,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-(3-trimethylsilanyl-prop-2-ynyl)-3a,6,7,7a-tetrahydro-3*H*-isobenzofuran-1-one 373.**



353 **373**

To a stirred solution of **353** (150 mg, 0.45 mmol, 1 eq) in benzene (10 mL) at 80 °C was added, dropwise by syringe over 10 minutes, a solution of aza-*bis*isobutyronitrile (4 mg, 0.022 mmol, 0.05 eq) and tributyltin hydride (515 mg, 0.223 mmol, 0.5 eq) in benzene (2 mL). After 1 hour this addition was repeated and the mixture was stirred for a further hour. The solvent was removed *in vacuo* and the crude residue was chromatographed (flash silica, 10% EtOAc/ 90% petrol) affording **373** as a colourless oil (127 mg, 95% yield). R_f = 0.8 (1:4 EtOAc/ petrol).

δ_H (300 MHz, $CDCl_3$) 0.18 (9H, s, $Si(CH_3)_3$), 1.82 (3H, s, Me), 1.85 (3H, s, Me), 2.18 (2H, m, CH_2), 2.74 (2H, m, $CH_2CCSi(CH_3)_3$), 2.78 (1H, m), 2.92 (1H, m), 3.18 (1H, dd, J= 6 and 10 Hz), 4.42 (1H, dt, J=6 and 10 Hz), 4.80 (1H, s), 4.88 (1H, s), 5.60 (1H, m).

δ_C (75 MHz, $CDCl_3$) 0.1, 21.5, 26.0, 26.9, 38.3, 41.7, 42.2, 80.4, 89.0, 100.9, 111.6, 123.5, 128.6, 130.4, 145.9, 178.0.

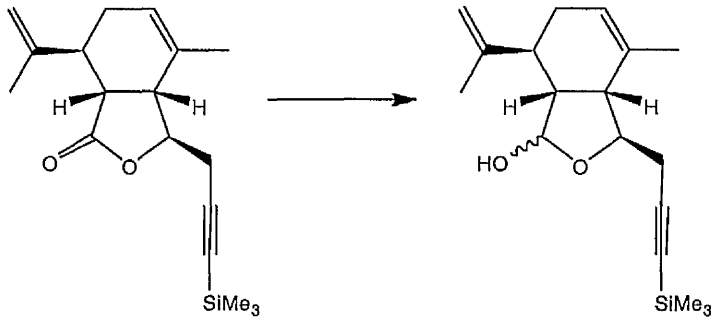
ν_{max} (evaporated film) 1642, 1779, 2950 cm^{-1}.

m/z (EI) 73 (100%), 119 (40%), 145 (65%), 190 (30%), 302 (5%).

m/z (CI) 90 (40%). 185 (20%), 258 (10%), 303 ($M+H^+$, 25%), 320 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{18}H_{26}O_2Si$ requires 302.1697; found 302.1699.

Synthesis of (1*S,3*R**,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-(3-trimethylsilanyl-prop-2-ynyl)-1,3,3a,6,7,7a-hexahydro-isobenzofuran-1-ol 374.**



373 **374**

To a solution **373** (1.0 g, 3.33 mmol, 1 eq) in DCM (50 mL) was added DIBAL-H (1M in hexanes, 4.01 mL, 4.01 mmol, 1.2 eq), at –78 °C, and the resulting solution was stirred for 1 hour. The reaction was quenched by addition of a saturated solution of sodium potassium tartrate$_{(aq)}$ (10 mL) and the aqueous phase extracted repeatedly with dichloromethane (3x25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (flash silica, 5% EtOAc/ 95% petrol) affording lactol **374** as transparent oil (980 mg, 97% yield).

δ_H **(300 MHz, $CDCl_3$)** 0.20 (9H, $Si(CH_3)_3$), 1.78 (3H, s, CH_3), 1.79 (3H, s, CH_3), 2.02 (2H, m), 2.10 (1H, m), 2.28 (1H, dd, *J*= 8 and 12 Hz), 2.64 (1H, dd, *J*= 5 and 17, $CH_2CCSi(CH_3)_3$), 2.86 (1H, dd, *J*= 5 and 17 Hz, $CH_2CCSi(CH_3)_3$), 2.84 (1H, m), 3.02 (1H, d, *J*= 8 Hz, O*H*), 4.04 (1H, ddd, *J*= 5, 5 and 8 Hz), 4.85-4.90 (2H, m, olefinic H), 5.20 (1H, d, *J*= 5 Hz), 5.52 (1H, m, olefinic H).

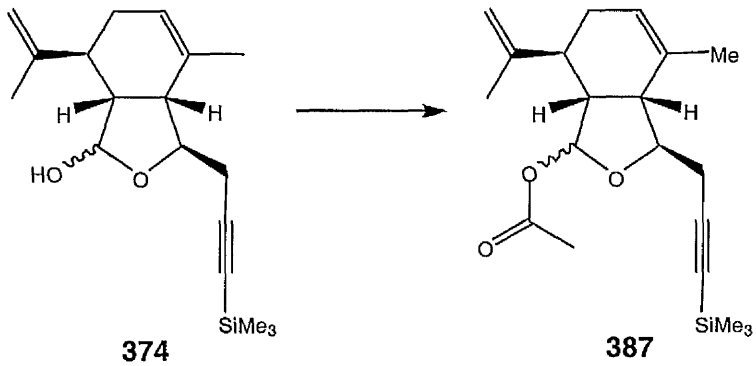
δ_C **(75 MHz, $CDCl_3$)** 0.3, 19.5, 23.3, 29.0, 30.6, 40.9, 44.1, 49.2, 83.2, 88.0, 101.2, 104.5, 112.7, 123.0, 131.2, 147.0.

ν_{max} **(evaporated film)** 1532, 2940, 3071, 3439 cm^{-1}.

m/z (CI) 90 (60%), 193 (50%), 259 (20%), 287 (100%), 304 (80%), 322 ($M+NH_4^+$, 10%).

HRMS (CI) $C_{18}H_{28}O_2Si$ requires 304.1859; found 304.2011.

Synthesis of (1*R,3*R**,3a*R**,7*S**,7a*R**)-1-Acetoxy-7-isopropenyl-4-methyl-3-prop-2-ynyl-1,3,3a,6,-7,7a-hexahydro-isobenzofuran 387.**



374 **387**

To a solution of **374** (1.77 g, 5.9 mmol, 1 eq) in dichloromethane (40 mL) was added pyridine (463 mg, 5.9 mmol, 1 eq), acetic anhydride (717 mg, 7.03 mmol, 1.2 eq), and *N*-dimethylamino pyridine (143 mg, 1.172 mmol, 0.2 eq) at -78 °C. After stirring for 1 hour the solution was allowed to warm to 17 °C and after 3 hours was quenched by addition of methanol (2 mL). The solution was diluted with DCM (100 mL) and the resulting organic phase was washed with aqueous 10% potassium hydrogen sulfate solution (20 mL), aqueous saturated sodium bicarbonate solution (25 mL), and brine prior to drying ($MgSO_4$) and removal of solvent under reduced pressure. The crude residue was chromatographed (flash silica, 15% EtOAc/ 85% petrol) affording the *title compound* as a viscous oil (1.86 g, 92% yield).

δ_H (300 MHz, $CDCl_3$) 0.20 (9H, s, $Si(CH_3)_3$), 1.76 (3H, s, CH_3), 1.81 (3H, s, CH_3), 2.02 (2H, m), 2.04 (3H, s, CH_3), 2.18 (1H, m), 2.40 (1H, dd, *J*= 9 and 13 Hz), 2.68 (1H, dd, *J*=9 and 16 Hz, $CH_2CCSi(CH_3)_3$) and 2.80 (1H, dd, *J*= 9 and 16 Hz, $CH_2CCSi(CH_3)_3$), 2.79 (1H, m), 4.08 (1H, ddd, *J*= 4, 9 and 10 Hz), 4.84 (1H, s, olefinic-H), 4.90 (1H, m, olefinic-H), 5.58 (1H, m, olefinic-H), 6.13 (1H, s).

δ_C (75 MHz, $CDCl_3$) 0.3, 19.3, 21.8, 23.4, 28.9, 30.4, 40.8, 45.3, 47.3, 84.3, 87.1, 101.3, 123.2, 123.1, 128.6, 130.8, 146.3, 170.4.

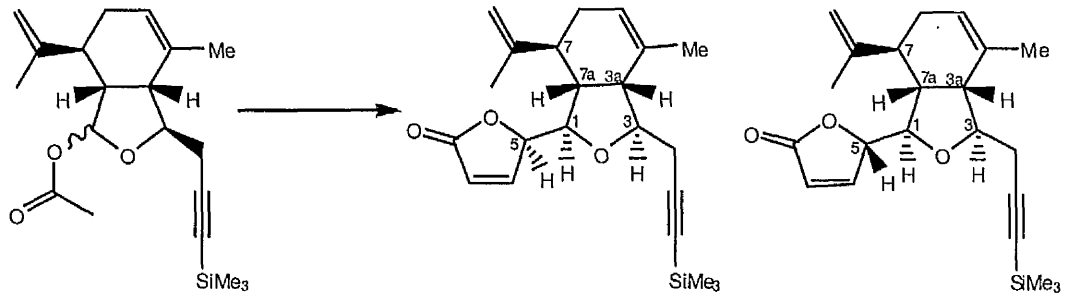
ν_{max} (evaporated film) 1392, 1447, 1543, 1769, 2940 cm^{-1}.

m/z (EI) 346 (5%).

m/z (CI) 346 (70%), 364 ($M+NH_4^+$, 80%).

HRMS (CI) $C_{20}H_{30}O_3Si$ requires 346.1964; found 346.2001.

Synthesis of (*S)-5′-((1*R**,3*R**,3a*R**,7*S**,7a*R**)-3-(3′-trimethylsilyl-prop-2′-ynyl)-7-isopropenyl-4-methyl-1,3,3a,6,7,7a-hexahydro-isobenzofuran-1-yl)-5*H*-furan-2-one 385a** and **(*R**)-5′-((1*R**,3*R**,3a*R**,7*S**,7a*R**)-3-(3′-trimethylsilyl-prop-2′-ynyl)-7-isopropenyl-4-methyl-1,3,3a,6,7,7a-hexahydro-isobenzofuran-1-yl)-5*H*-furan-2-one 385b.**



387 **397a** **397b**

To a stirred solution of **387**(100 mg, 0.29 mmol, 1 eq) in dichloromethane (4 mL) was added 2-trimethylsilyloxyfuran (90 mg, 0.58 mmol, 2 eq) at 17 °C. After 10 minutes borontrifluoride diethyletherate (82 mg, 0.58 mmol, 2 eq) was added by syringe pump, over 2 hours, at -78 °C. After 2 hours the resulting bright yellow coloured solution was quenched with saturated sodium bicarbonate solution (10 mL), diluted with DCM (50 mL), the phases separated, the aqueous layer extracted with DCM (3x30 mL), the organics washed with brine (30 mL), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed (flash silica, 5% EtOAc/ 95% petrol) affording the *title compounds*.

The major diastereoisomer, *erythro* adduct 397a, was obtained as a white solid (50 mg, 48% yield) R_f = 0.56 (20% EtOAc/ 80% petrol):

δ_H **(300 MHz, $CDCl_3$)** 0.16 (9H, s, $SiCH_3$), 1.75 (3H, s, CH_3) 1.78 (3H, s, CH_3), 2.12 (2H, m, C6-H), 2.28 (1H, m, C7-H), 2.54 (1H, dd, *J*= 9 and 12 Hz, C7a-H), 2.64 (1H, dd, *J*= 3 and 18 Hz), 2.92 (1H, dd, *J*= 3 and 18 Hz, $CH_2CCSi(CH_3)_3$), 2.90 (1H, m, C3a-H), 3.68 (1H, d, *J*= 9 Hz, C1-H), 3.96 (1H, dt, *J*= 4 and 9 Hz, C3-H), 4.84 (2H, m, olefinic), 5.08 (1H, dt, *J*= 2 and 9 Hz, C5′-H), 5.60 (1H, m, olefinic H), 6.18 (1H, dd, *J*= 2 and 6 Hz, α-olefinic), 7.75 (1H, dd, *J*= 2 and 6 Hz, β-olefinic-H).

δ_C **(75 MHz, $CDCl_3$)** 0.2, 18.6, 23.0, 26.9, 30.8, 42.6, 44.3, 44.6, 82.2, 82.4, 84.2, 88.3, 103.5, 113.7, 121.9, 124.0, 130.2, 146.6, 156.9, 173.2.

ν_{max}**(evaporated film)** 1787, 2898, 2950 cm^{-1}.

Mp 146-148 °C.

M/z (EI) 73 (100%), 175 (40%), 258 (60%).

M/z (CI) 147 (70%), 175 (100%), 259 (80%), 371 ($M+H^+$, 10%), 388 ($M+NH_4^+$, 70%).

HRMS (CI) $C_{22}H_{30}O_3Si$ requires 370.1959; found 370.1962.

The minor diastereisomer, *threo* adduct 397b was obtained as a white solid (30 mg, 28% yield) R_f=0.38 (20% EtOAc/ 80% petrol);

δ_H **(300 MHz, $CDCl_3$)** 0.98 (9H, s, $SiCH_3$), 1.68 (3H, s, CH_3) 1.74 (3H, s, CH_3), 2.05 (2H, m, C6-CH_2), 2.12 (1H, ddd, *J*= 2, 8 and 12 Hz, C7a-H), 2.24 (1H, ddd, *J*= 8, 8 and 12 Hz, C7-H), 2.52 (1H, m, C3a-H), 2.56 (1H, dd, *J*=2 and 18 Hz), 2.84 (1H, dd, *J*=2 and 18 Hz $CH_2CCSi(CH_3)_3$), 3.82 (1H, ddd, *J*= 2, 5 and 8 Hz, C3-H), 4.26 (1H, dd, *J*= 2 and 4 Hz, C1-H), 4.83 (1H, m, olefinic), 4.89 (1H, m, olefinic-H), 5.11 (1H, dt, *J*= 2 and 5 Hz, C5'-H), 5.55 (1H, m, olefinic), 6.18 (1H, dd, *J*= 2 and 6 Hz, α-olefinic), 7.82 (1H, dd, *J*= 2 and 6 Hz, β-olefinic-H).

δ_C **(75 MHz, $CDCl_3$)** 0.3, 19.0, 22.8, 26.2, 30.5, 41.3, 43.3, 46.3, 79.9, 81.6, 84.2, 87.8, 103.7, 113.7, 122.7, 124.1, 130.1, 146.5, 154.4, 173.0.

ν_{max}**(evaporated film)** 1787, 2890, 2956 cm^{-1}.

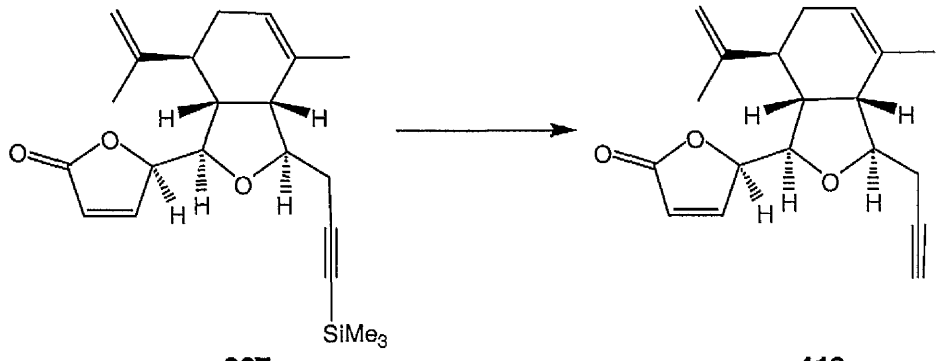
Mp 130-132 °C.

m/z (EI) 73 (100%), 147 (50%), 175 (50%), 258 (40%).

m/z (CI) 147 (50%), 175 (100%), 259 (60%), 371 ($M+H^+$, 15%), 388 ($M+NH_4^+$, 80%).

HRMS (CI) $C_{22}H_{30}O_3Si$ requires 370.1959; found 370.1949.

Synthesis of (*R)-5'-((1*R**,3*R**,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-prop-2-ynyl-1,3,3a,6,7,7a- hexahydro-isobenzofuran-1-yl)-5'*H*-furan-2-one 407a.**



397a **416a**

Method A

To a vigorously stirred, -20 °C, solution of the alkyne **397a** (69 mg, 0.186 mmol, 1 eq) in ethanol (3 mL) was added silver nitrate, 10 wt% on silica (692 mg, 0.41 mmol, 2.2 eq) portionwise over 10 minutes and deionised water (0.5 mL). After 2 hours, the suspension was allowed to warm to 0 °C over a period of 30 minutes and potassium cyanide (121 mg, 1.86 mmol, 10 eq) was added. After 30 minutes the suspension was diluted with EtOAc (20 mL), filtered through celite, eluting with EtOAc (3x20 mL). The filtrate was transferred to a separating funnel to which was added water (20 mL) and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the residue was chromatographed (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as a colourless oil (51 mg, 92% yield). Rf = 0.42 (25% EtOAc/ 75% petrol).

Method B

To a vigorously stirred solution of the alkyne **397a** (175 mg, 0.46 mmol, 1 eq) in methanol (2 mL), DCM (4 mL) and deionised water (0.7 mL) was added silver triflate (12.4 mg, 0.046 mmol, 10 mol%). The reaction mixture was stirred at 18 °C for 18 hours where after the suspension was diluted with EtOAc (20 mL), filtered through celite, eluting with EtOAc (3x 20 mL). The filtrate was transferred to a separating funnel to which was added water (10 mL) and the aqueous layer was extracted with EtOAc (3x 5 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), the solvent removed under reduced pressure

and the residue was chromatographed (flash silica, 25% EtOAc/ 75% petrol) affording the *title compound* as a colourless oil (111 mg, 81% yield).

δ_H (300 MHz, $CDCl_3$) 1.67 (3H, s, CH_3) 1.76 (3H, s, CH_3), 2.04 (2H, m), 2.11 (1H, t, *J*= 3 Hz, CH_2CCH), 2.28 (1H, dd, *J*= 6 and 9 Hz), 2.37 (1H, ddd, *J*=3, 6 and 11 Hz), 2.43 (1H, dd, *J*= 3 and 6 Hz, C*H*HCCH), 2.49 (1H, dd, *J*= 3 and 6 Hz, C*H*HCCH), 2.63 (1H, m), 2.78 (1H, t, *J*= 3 Hz, CH*H*CCH), 3.86 (1H, ddd, *J*= 3, 6 and 9 Hz), 4.25 (1H, dd, *J*= 2 and 3 Hz), 4.86 (1H, m, olefinic), 4.92 (1H, m, olefinic-H), 5.05 (1H, m), 5.58 (1H, m, olefinic), 6.23 (1H, dd, *J*=2 and 6 Hz, α-olefinic), 7.61 (1H, dd, *J*= 2 and 6 Hz).

δ_C (75 MHz, $CDCl_3$) 19.5, 22.9, 25.0, 29.5, 30.7, 42.7, 43.4, 46.4, 70.9, 80.0, 81.9, 85.1, 113.5, 122.8, 124.1, 130.1, 146.7, 154.0, 173.4.

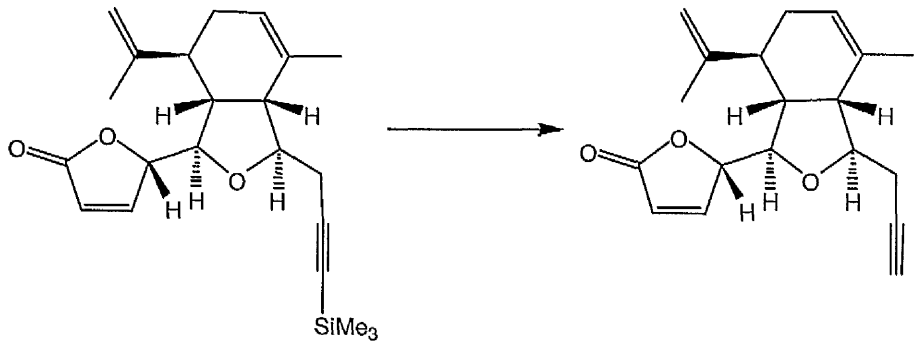
ν_{max} (evaporated film) 1760, 1780, 2890, 2943 cm^{-1}.

M/z (EI) 91 (70%), 147 (40%), 259 (20%), 298 (10%).

m/z (CI) 259 (5%), 299 ($M+H^+$, 30%), 316 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{19}H_{22}O_3$ requires 298.1569; found 298.1567.

Synthesis of (*S)-5'-((1*R**,3*R**,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-prop-2-ynyl-1,3,3a,6,7,7a- hexahydro-isobenzofuran-1-yl)-5'*H*-furan-2-one 416b.**



397b **416b**

Method A

To a vigorously stirred solution of the alkyne **397b** (69 mg, 0.19 mmol, 1 eq) in ethanol (3 mL) at -20 °C was added silver nitrate, 10 wt% on silica (692 mg, 0.41 mmol, 2.2 eq) portion wise over 10 minutes and deionised water (0.5 mL). After 2 hours, the suspension was allowed to warm to 0 °C over 30 minutes and potassium cyanide (121 mg, 1.86 mmol, 10.0 eq) was added. After 30 minutes the suspension was diluted with EtOAc (20 mL) and filtered through

celite, eluting with EtOAc (3x20 mL). The filtrate was transferred to a separating funnel to which was added water (20 mL) and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the residue was chromatographed (flash silica, 25% EtOAc/ 75% petrol) affording the *title compound* as a colourless oil (51 mg, 92% yield). R_F = 0.62 (25% EtOAc/ 75% petrol).

Method B

To a vigorously stirred solution of the alkyne **397b** (150 mg, 0.4 mmol, 1 eq) in methanol (2 mL), DCM (3.5 mL) and deionised water (0.5 mL) was added silver triflate (10 mg, 0.04 mmol, 10 mol%). The reaction mixture was stirred at 18 °C for 18 hours where after the suspension was diluted with EtOAc (20 mL), filtered through celite, eluting with EtOAc (3x20 mL). The filtrate was transferred to a separating funnel to which was added water (10 mL) and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the residue was chromatographed (flash silica, 25% EtOAc/ 75% petrol) affording the *title compound* as a colourless oil (103 mg, 87% yield). R_F= 0.62 (25% EtOAc/ 75% petrol).

δ_H (300 MHz, $CDCl_3$) 1.69 (3H, s), 1.77 (3H, s), 2.02-2.14 (3H, m), 2.21-2.32 (1H, m), 2.41 (1H, dd, *J*= 6 and 12 Hz), 2.58-2.69 (1H, m), 2.78-2.93 (2H, m), 3.72 (1H, d, *J*= 9 Hz), 3.92-3.99 (1H, m), 4.81 (2H, dt, *J*= 2 and 9 Hz), 5.03 (1H, dt, *J*= 2 and 9 Hz), 5.59 (1H, bs), 6.17 (1H, dd, *J*= 2 and 6 Hz), 7.70 (1H, dd, *J*= 2 and 6 Hz).

δ_C (75 MHz, $CDCl_3$) 18.7, 21.3, 23.1, 25.7, 30.8, 42.7, 43.8, 45.4, 71.3, 81.1, 82.3, 82.3, 84.4, 113.8, 122.1, 124.1, 130.1, 146.5, 156.4, 173.2.

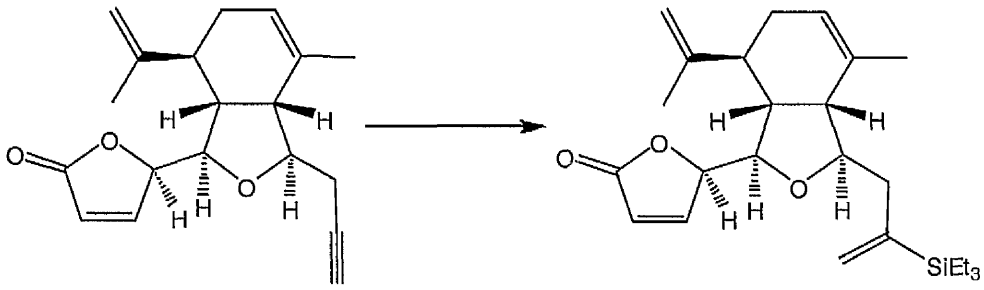
ν_{max} (evaporated film) 1759, 1786, 2854, 2923 cm^{-1}.

M/z (EI) 215 (40%), 299 ($M+H^+$, 40%), 316 ($M+NH_4^+$, 100%).

m/z (CI) 299 ($M+H^+$, 10%), 316 ($M+NH_4^+$, 100%).

HRMS (EI) $C_{19}H_{22}O_3$ requires 298.1562; found 298.1557.

Synthesis of (*R)-5′-[(1*R**,3*R**,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-(2-triethylsilanyl-allyl)-1,3,3a- 6,7,7a-hexahydro-isobenzofuran-1-yl]-5′*H*-furan-2-one 417a.**



416a **417a**

To a stirred solution of **416a** (160 mg, 0.53 mmol, 1 eq) in DCM (5 mL) was added triethylsilane (92 mg, 0.79 mmol, 1.5 eq). After 5 minutes the flask was cooled to 0 °C and pentamethylcyclopentadienylruthenium trisacetonitrilehexafluorophosphate (10 mg, 0.026 mmol, 5 mol%) was added. The flask was immediately allowed to warm to 17 °C. After 30 minutes the mixture was filtered through a silica pad, eluting with 30% EtOAc/ 70% petrol (3x20 mL) and the solvent removed *in vacuo*. The residue was purified by chromatography eluting with 20% EtOAc/ 80% petrol affording the *title compound* as colourless oil (184 mg, 84% yield).

δ_H (300 MHz, $CDCl_3$); 0.62 (6H, q, *J*= 7 Hz), 0.94 (9H, t, *J*= 7 Hz), 1.74 (3H, s, Me), 1.77 (1H, s, Me), 2.09 (2H, m), 2.14-2.31 (2H, m), 2.38-2.50 (2H, m), 2.65 (1H, d, *J*= 15 Hz), 3.88 (1H, dt, *J*= 2 and 10 Hz), 4.19 (1H, dd, *J*= 2 and 2 Hz), 4.86 (1H, bs), 4.92 (1H, m, olefinic-H), 4.98 (1H, dt, *J*= 1 and 3 Hz), 5.40 (1H, d, *J*= 3 Hz), 5.58 (1H, m, olefinic-H), 5.72 (1H, dd, *J*= 1 and 3 Hz), 6.17 (1H, dd, *J*= 2 and 6 Hz, α-olefinic-H), 7.46 (1H, dd, *J*= 2 and 6 Hz, β-olefinic-H).

δ_C (75 MHz, $CDCl_3$) 3.0, 7.6, 19.7, 23.8, 30.8, 42.6, 43.3, 43.4, 48.4, 80.1, 83.6, 85.6, 113.2, 122.4, 123.7, 127.5, 131.1, 146.2, 147.2, 154.3, 173.6.

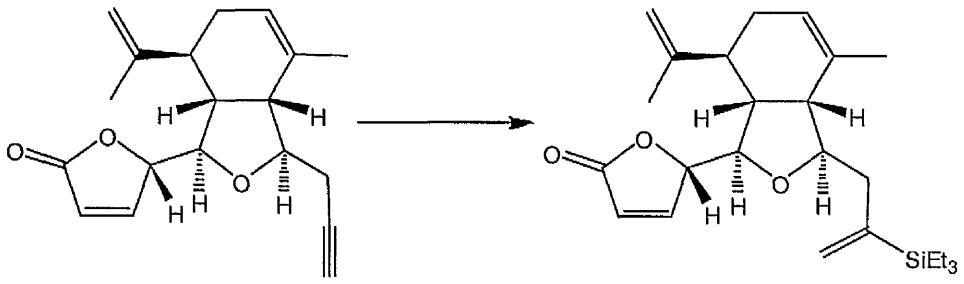
ν_{max} (evaporated film) 1761, 1787, 2875, 2912, 2952 cm^{-1}.

M/z (EI) 59 (100%), 115 (70%), 259 (20%), 385 (10%).

M/z (CI) 132 (40%), 259 (20%), 432 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{25}H_{42}O_3SiN$ ($M+NH_4^+$) requires 432.2928; found 432.2926.

Synthesis of (*S)-5′-[(1*R**,3*R**,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-(2-triethylsilanyl-allyl)-1,3,3a- 6,7,7a-hexahydro-isobenzofuran-1-yl]-5′*H*-furan-2-one 417b.**



416b **417b**

To a stirred solution of **416b** (400 mg, 1.32 mmol, 1 eq) in DCM (14 mL) was added triethylsilane (230 mg, 2.0 mmol, 1.5 eq). After 5 minutes the flask was cooled to 0 °C and pentamethylcyclopentadienylruthenium trisacetonitrilehexafluorophosphate (25 mg, 0.065 mmol, 5 mol%) was added. The flask was immediately allowed to warm to 17 °C. After 30 minutes the mixture was filtered through a silica pad, eluting with 35% EtOAc/ 65% petrol (3x 20 mL), and the solvent removed *in vacuo*. The residue was chromatographed (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as colourless oil (442 mg, 79% yield).

δ_H **(300 MHz, $CDCl_3$)**; 0.67 (6H, q, *J*= 7 Hz), 0.98 (9H, t, *J*= 8 Hz), 1.68 (3H, s), 1.79 (3H, s), 2.09 (2H, bs), 2.20-2.45 (4H, m), 2.71 (1H, d, *J*= 15 Hz), 3.86 (1H, d, *J*= 7 Hz), 4.0 (1H, bt, *J*= 7 Hz), 4.81 (2H, d, *J*= 12 Hz), 4.97 (1H, dt, *J*= 2 and 7 Hz), 5.48 (1H, d, *J*= 3 Hz), 5.59 (1H, bs), 5.86 (1H, t, *J*= 2 Hz), 6.18 (1H, dd, *J*= 2 and 6 Hz), 7.54 (1H, dd, *J*= 2 and 6 Hz)

δ_C **(75 MHz, $CDCl_3$)** 3.1, 7.6, 19.1, 23.7, 30.6, 42.6, 42.8, 44.1, 48.8, 82.1, 83.7, 85.2, 113.6, 122.3, 123.8, 127.5, 130.9, 146.4, 146.8, 155.6, 173.2.

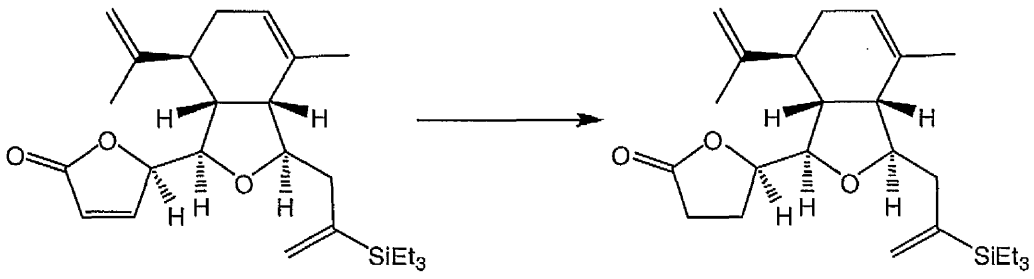
ν_{max} **(evaporated film)** 1763, 1790, 2885, 2923, 2960 cm^{-1}.

M/z (EI) 59 (100%), 259 (40%), 385 (20%).

M/z (CI) 259 (20%), 432 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{25}H_{42}O_3SiN$ ($M+NH_4^+$) requires 432.2928; found 432.2926 .

Synthesis of (*R)-5'-[(1*R**,3*R**,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-(2-triethylsilanyl-allyl)-1,3, 3a,6,7,7a-hexahydro-isobenzofuran-1-yl]-dihydro-furan-2-one 418a.**



417a **418a**

To a vigorously stirred solution of **417a** (580 mg, 1.4 mmol, 1 eq) in ethanol (5 mL) was added fresh spongy cobalt (1g, wet wt), at 17 °C, and the vessel sealed to produce a closed system. After 2 hours the suspension was filtered through a pad of celite (10 g), with the filtrate being concentrated under reduced pressure to give an oily solid. The crude residue was subjected to chromatography (flash silica, 10% EtOAc/ 90% petrol) affording the *title compound* as a colourless oil (500 mg, 88% yield).

δ_H**(300MHz, CDCl$_3$)** 0.62 (6H, q, *J*= 7 Hz), 0.96 (9H, t, *J*= 7 Hz), 1.74 (3H, s, Me), 1.76 (1H, s, Me), 2.06-2.14 (2H, m), 2.24-2.28 (3H, m), 2.40-2.47 (4H, m), 2.71-2.79 (2H, m), 3.81-3.84 (1H, m), 3.89 (1H, td, *J*= 2 and 8 Hz), 4.45 (1H, ddd, *J*= 2, 5 and 8 Hz), 4.83 (1H, bs), 4.87 (1H, t, *J*= 2 Hz), 5.40 (1H, d, *J*= 3 Hz), 5.56 (1H, m, olefinic-H), 5.80 (1H, t, *J*= 2 Hz).

δ_C**(75MHz, CDCl$_3$)** 3.1, 7.5, 19.9, 23.7, 24.6, 24.6, 28.6, 30.7, 43.0, 43.4, 43.7, 49.2, 82.0, 82.6, 83.4, 112.8, 123.6, 127.2, 131.3, 146.5, 147.4, 178.4.

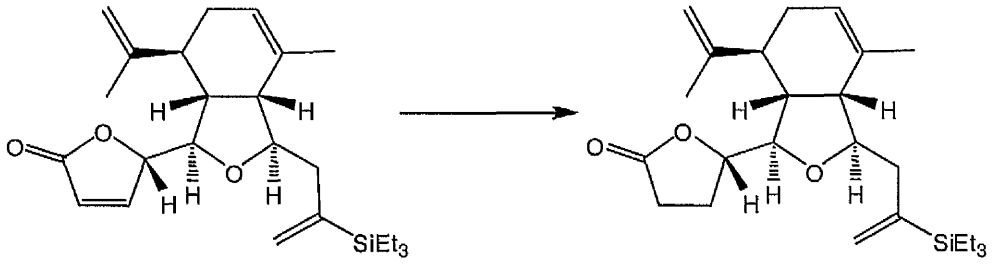
ν_{max}**(evaporated film)** 1780, 2871, 2927, 2958 cm^{-1}.

M/z (EI) 59 (100%),115 (75%), 261 (20%), 387 (20%).

M/z (CI) 102 (100%), 387 (5%), 434 ($M+NH_4^+$, 80%).

HRMS (CI) $C_{25}H_{40}O_3Si$ requires 416.2747; found 416.2752.

Synthesis of (S*)-5'-[(1*R,3*R**,3a*R**,7*S**,7a*R**)-7-Isopropenyl-4-methyl-3-(2-triethylsilanyl-allyl)-1,3, 3a,6,7,7a-hexahydro-isobenzofuran-1-yl]-dihydro-furan-2-one 418b.**



417b **418b**

To a vigorously stirred solution of **417b** (386 mg, 1.4 mmol, 1 eq) in ethanol (3 mL) was added fresh spongy cobalt (700 mg, wet wt), at 17 °C, and the vessel sealed to produce a closed system. After 2 hours the suspension was filtered through a pad of celite (10 g), with the filtrate being concentrated under reduced pressure to give an oily solid. The crude residue was subjected to chromatography (flash silica, 10% EtOAc/ 90% petrol) affording the *title compound* as a colourless oil (287 mg, 76% yield).

δ_H**(300MHz, $CDCl_3$)** 0.66 (6H, q, *J*= 8 Hz), 0.95 (9H, t, *J*= 8 Hz), 1.73 (3H, s, Me), 1.79 (1H, s, Me), 2.09-2.46 (9H, m), 2.50-2.58 (1H, m), 2.67-2.73 (1H, m), 3.86 (1H, bd, *J*= 7 Hz), 3.94 (1H, t, *J*= 4 Hz), 4.40 (1H, t, *J*= 4 Hz), 4.84 (1H, bs), 4.88 (1H, bs), 5.44 (1H, d, *J*= 4 Hz), 5.56-5.59 (1H, m, olefinic-H), 5.80-5.84 (1H, m).

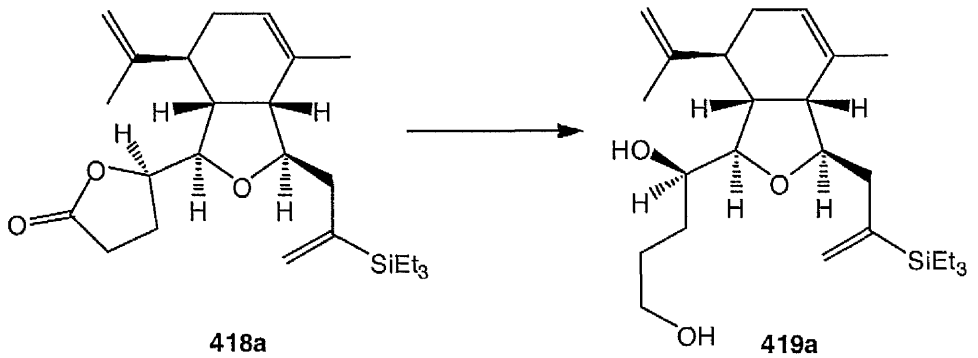
δ_C**(75MHz, $CDCl_3$)** 3.1, 7.6, 19.1, 23.7, 24.5, 28.2, 30.4, 42.9, 43.0, 44.2, 48.8, 81.4, 82.4, 83.2, 113.4, 123.8, 127.7, 131.0, 146.2, 147.0, 177.3

ν_{max}**(evaporated film)** 1775, 2935, 2962 cm^{-1}.

M/z (CI) 387 (5%), 416 (90%).

HRMS (CI) $C_{25}H_{40}O_3Si$ requires 416.2747; found 416.2752.

Synthesis of (*R)-1-((1*R**,3*R**,3a*R**,4*S**,7a*R**)-1-(2-(triethylsilyl)allyl)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)butane-1,4-diol 419a.**



418a **419a**

Lactone **418a** (500 mg, 1.2 mmol, 1eq) was dissolved in THF (20 mL) and allowed to stir for 5 minutes. To this reaction mixture was added $LiAlH_4$ (137 mg, 3.61 mmol, 3 eq) and allowed to stir at 17 °C for 30 minutes. The reaction was quenched with a saturated solution of Rochelle's salt (5 mL) and allowed to stir vigorously for a further 30 minutes. The resulting mixture was partitioned between EtOAc (10 mL) and water (10 mL), with the organic layer being removed and the aqueous layer being washed with a further 10 mL of EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a gummy crude solid. This was subjected to column chromatography, (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as a white crystalline solid (360 mg, 72% yield).

δ_H(500MHz, $CDCl_3$) 0.46 (6H, q, *J*= 8 Hz), 0.77 (9H, t, *J*= 8 Hz), 1.51 (3H, s), 1.56 (3H, d, *J*= 2 Hz), 1.88 (2H, m), 1.95-2.05 (1H, m), 2.06-2.11 (2H, m), 2.14 (1H, t, *J*= 8 Hz), 2.53 (1H, dd, *J*= 2 and 15 Hz), 3.2 (1H, ddd, *J*= 2, 5 and 7 Hz), 3.49 (3H, m), 3.75 (1H, dt, *J*= 2 and 9 Hz), 4.63 (1H, s), 4.68 (1H, t, *J*= 2 Hz), 5.25 (1H, d, *J*= 2 Hz), 5.37 (1H, m), 5.65 (1H, t, *J*= 2 Hz).

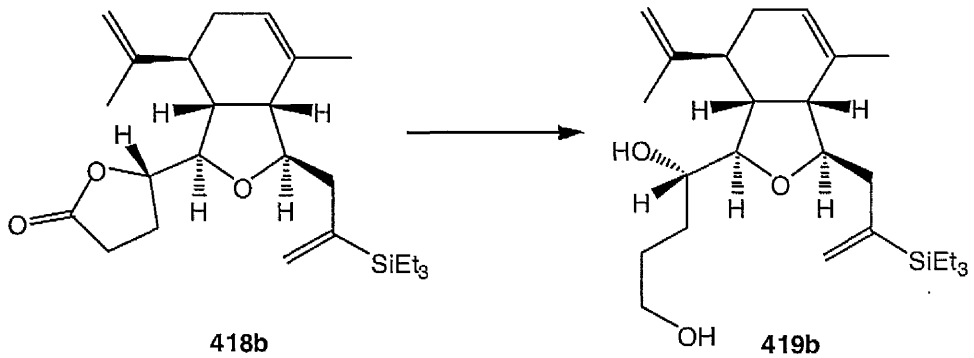
δ_C(75MHz, $CDCl_3$) 2.7, 7.3, 19.4, 23.4, 29.5, 30.1, 31.0, 42.7, 42.8, 45.2, 49.4, 62.9, 73.1, 82.3, 84.4, 113.0, 123.2, 127.5, 131.1, 146.2, 146.8.

ν_{max}(evaporated film) 2874, 2913, 2951, 3400 cm^{-1}.

m/z (ES^+) 421 ($M+H^+$, 50%), 443 ($M+Na^+$, 90%).

HRMS (ES^+) $C_{25}H_{44}O_3SiNa$ ($M+Na^+$) requires 443.2952; found 443.2948.

Synthesis of (*S)-1-((1*R**,3*R**,3a*R**,4*S**,7a*R**)-1-(2-(triethylsilyl)allyl)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)butane-1,4-diol 419b.**



418b **419b**

Lactone **418b** (400 mg, 0.96 mmol, 1eq) was dissolved in THF (20 mL) and allowed to stir for 5 minutes. To this reaction mixture was added $LiAlH_4$ (110 mg, 2.9 mmol, 3 eq) and allowed to stir at 17 °C for 30 minutes. The reaction was quenched with a saturated solution of Rochelle's salt (5 mL) and allowed to stir vigorously for a further 30 minutes. The resulting mixture was partitioned between EtOAc (10 mL) and water (10 mL), with the organic layer being removed and the aqueous layer being washed with a further 10 mL of EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a gummy crude solid. This was subjected to column chromatography, eluting with 20% EtOAc/ 80% petrol affording the *title compound* as a white crystalline solid (260 mg, 69% yield).

δ_H(500MHz, $CDCl_3$) 0.51 (6H, q, *J*= 8 Hz), 0.82 (9H, t, *J*= 8 Hz), 1.23-1.30 (1H, m), 1.59-1.69 (3H, m), 2.06-2.19 (5H, m), 2.5 (1H, dd, *J*= 2 and 15 Hz), 3.4 (1H, ddd, *J*= 2, 6 and 15 Hz), 3.57 (2H, t, *J*= 6 Hz), 3.61 (2H, dd, *J*= 2 and 6 Hz), 3.75-3.79 (1H, m), 4.69-4.72 (2H, m), 5.31 (1H, d, *J*= 3 Hz), 5.42 (1H, bs), 5.70 (1H, t, *J*= 2 Hz).

δ_C(75MHz, $CDCl_3$) 0.93, 5.57, 12.2, 17.2, 21.1, 27.6, 28.2, 39.6, 42.6, 47.3, 58.5, 60.9, 71.7, 80.2, 82.6, 111.0, 121.5, 125.3, 129.1, 144.2, 145.3, 169.3.

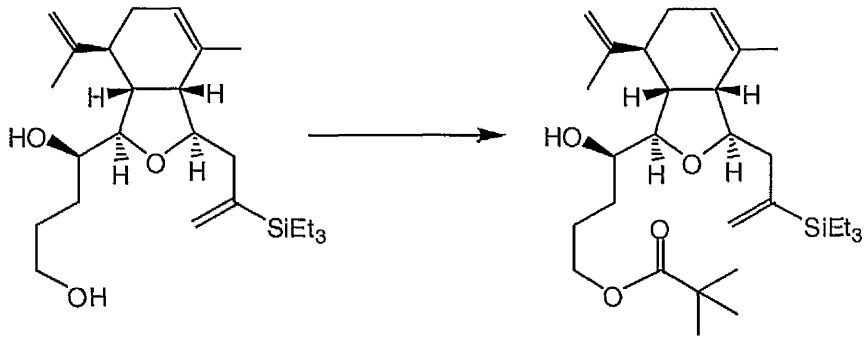
ν_{max}(evaporated film) 2875, 2952, 3365 cm^{-1}.

m/z (ES$^-$) 361 (100%), 419 ($M-H^+$, 70%).

m/z (ES$^+$) 421 ($M+H^+$, 40%), 443 ($M+Na^+$, 100%).

HRMS (ES$^+$) $C_{25}H_{44}O_3SiNa$ ($M+Na^+$) requires 443.2952; found 443.2948.

Synthesis of (*R)-4-((1*R**,3*R**,3a*R**,4*S**,7a*R**)-1-(2-(triethylsilyl)allyl)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)-4-hydroxybutyl pivalate 420a.**



419a **420a**

Diol **419a** (450 mg, 1.1mmol, 1 eq) was dissolved in diethyl ether (25 mL), cooled to 0 °C and allowed to stir for 5 minutes. To this reaction mixture was added pyridine (255 mg, 3.25 mmol, 3 eq) and immediately after trimethylacetyl chloride (384 mg, 3.25 mmol, 3 eq) was added, with the reaction mixture allowed to stir at 0 °C for 1.5 hours. The reaction was quenched with the addition of water (15 mL). The resulting mixture was partitioned between EtOAc (10 mL) and water (5 mL), with the organic layer being removed and the aqueous layer being washed with a further portion of EtOAc (10 mL). The organic layers were combined, washed with $CuSO_{4(aq)}$ solution (2x 20 mL), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a gummy crude solid. This was subjected to column chromatography (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as a clear viscous oil (470 mg, 85% yield).

δ_H(300MHz, $CDCl_3$) 0.64 (6H, q, *J*= 8 Hz), 0.97 (9H, t, *J*= 8 Hz), 1.22 (9H, s), 1.27-1.58 (3H, m), 1.7 (3H, s), 1.77 (3H, s), 1.81-1.94 (1H, m), 2.05-2.35 (7H, m), 2.70 (1H, d, *J*= 6 Hz), 3.36-3.43 (1H, m), 3.65 (1H, dd, *J*= 2 and 6 Hz), 3.94 (1H, dt, *J*= 2 and 10 Hz), 4.03-4.16 (2H, m), 4.87 (2H, bd, *J*= 14 Hz), 5.44 (1H, d, *J*= 2 Hz), 5.57 (1H, bs), 5.84 (1H, t, *J*= 2 Hz).

δ_C(75MHz, $CDCl_3$) 2.9, 7.3, 15.3, 19.4, 22.6, 23.4, 24.8, 26.5, 27.2, 29.1, 29.9, 30.4, 38.7, 40.2, 42.7, 44.9, 49.4, 64.4, 65.9, 72.5, 82.3, 84.4, 112.9, 123.2, 127.5, 131.1, 146.1, 146.7, 174.1, 178.6.

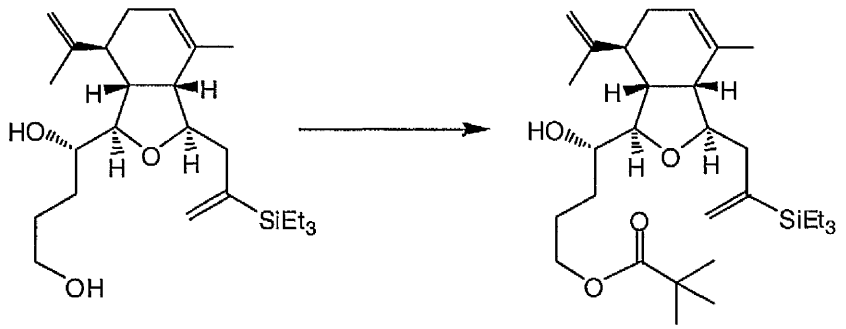
ν_{max}(evaporated film) 1729, 2955 cm^{-1}.

m/z (ES^-) 351 (30%), 503 ($M\text{-}H^+$, 100%).

m/z (ES^+) 527 ($M+Na^+$, 100%).

HRMS (ES^+) $C_{30}H_{52}O_4SiNa$ ($M+Na^+$) requires 527.3527; found 527.3531.

Synthesis of (S)-4-((1R,3R,3aR,4S,7aR)-1-(2-(triethylsilyl)allyl)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)-4-hydroxybutyl pivalate 420b



419b **420b**

Diol **419b** (540 mg, 1.29 mmol, 1 eq) was dissolved in diethyl ether (30 mL), cooled to 0 °C and allowed to stir for 5 minutes. To this reaction mixture was added pyridine (306.1 mg, 3.9 mmol, 3 eq) and immediately after trimethylacetyl chloride (464 mg, 3.9 mmol, 3 eq) was added, with the reaction mixture allowed to stir at 0 °C for 1.5 hours. The reaction was quenched with the addition of water (15 mL). The resulting mixture was partitioned between EtOAc (10 mL) and water (5 mL), with the organic layer being removed and the aqueous layer being washed with a further portion of EtOAc (10 mL). The organic layers were combined, washed with $CuSO_{4(aq)}$ solution (2x20 mL), washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a gummy crude solid. This was subjected to column chromatography (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as clear viscous oil (530 mg, 82% yield).

δ_H(500MHz, $CDCl_3$) 0.45 (6H, q, *J*= 8 Hz), 0.77 (9H, t, *J*= 8 Hz), 1.03 (9H, s), 1.10 (1H, s), 1.20-1.26 (1H, m), 1.43-1.46 (1H, m), 1.51 (3H, s), 1.58 (3H, d, *J*= 1 Hz), 1.71 (2H, m), 1.89-1.99 (2H, m), 2.06-2.20 (3H, m), 2.51 (1H, dd, *J*= 1 and 15 Hz), 3.39-3.46 (1H, m), 3.57 (1H, d, *J*= 6 Hz), 3.70 (1H, dt, *J*= 1 and 9 Hz), 3.92 (2H, dt, *J*= 1 and 6 Hz), 4.64 (1H, s), 4.66 (1H, t, *J*= 2 Hz), 5.25 (1H, d, *J*= 2 Hz), 5.38 (1H, bs), 5.65 (1H, t, *J*= 2 Hz).

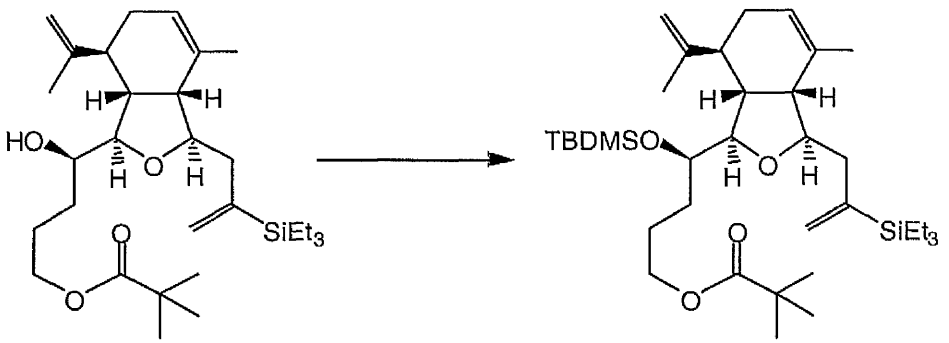
δ_C(75MHz, $CDCl_3$) 2.90, 7.37, 7.5, 7.7, 19.3, 23.1, 23.6, 25.4, 26.5, 27.2, 29.3, 30.1, 38.7, 41.3, 43.1, 43.3, 49.6, 64.4, 73.6, 82.1, 84.6, 113.1, 123.5, 127.3, 130.9, 146.1, 147.1, 178.6.

ν_{max}(evaporated film) 1735, 2960, 2982 cm^{-1}.

m/z (ES^+) 523 (30%), 527 ($M+Na^+$,100%).

HRMS (ES^+) $C_{30}H_{52}O_4SiNa$ ($M+Na^+$) requires 527.3527; found 527.3533.

Synthesis of (*R)-4-((1*R**,3*R**,3a*R**,4*S**,7a*R**)-1-(2-(triethylsilyl)allyl)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)-4-(tertbutyldimethyl silyl)butyl pivalate 421a.**



420a **421a**

Secondary alcohol **420a** (238 mg, 0.46 mmol, 1 eq) was dissolved in anhydrous DCM (10 mL) and cooled to -10 °C. To the chilled solution was added 2,6-lutidine (197.5 mg, 1.84 mmol, 4 eq) and TBDMS triflate (243 mg, 0.92 mmol, 2 eq) and the reaction mixture was stirred for a further hour before slowly warming to 17 °C. Additional stirring for another hour was followed by quenching with saturated $NH_4Cl_{(aq)}$ solution (2x 10 mL) with the organic layer being washed with brine (2x 10 mL), dried ($MgSO_4$), and solvent evaporated to dryness under reduced pressure. The resulting crude material was subjected to column chromatography (flash silica, 15% EtOAc/ 85% petrol) affording the *title compound* as a clear viscous oil (200 mg, 70% yield).

δ_H(300MHz, $CDCl_3$) 0.08 (3H, s), 0.10 (3H, s), 0.62 (6H, q, *J*= 8 Hz), 0.93 (9H, s), 0.95 (9H, t, *J*= 8 Hz), 1.22 (9H, s), 1.42-1.49 (1H, m), 1.69 (3H, s), 1.73 (3H, s), 2.14-2.31 (2H, m), 2.44-2.57 (2H, m), 3.51-3.56 (1H, m), 3.84 (1H, t, *J*= 3 Hz), 3.88 (1H, dt, *J*= 2 and 6 Hz), 4.04 (2H, dt, *J*= 2 and 6 Hz), 4.78 (1H, bs), 4.82 (1H, bs), 5.41(1H, d, *J*= 2 Hz), 5.5 (1H, bs), 5.86 (1H, t, *J*= 2 Hz).

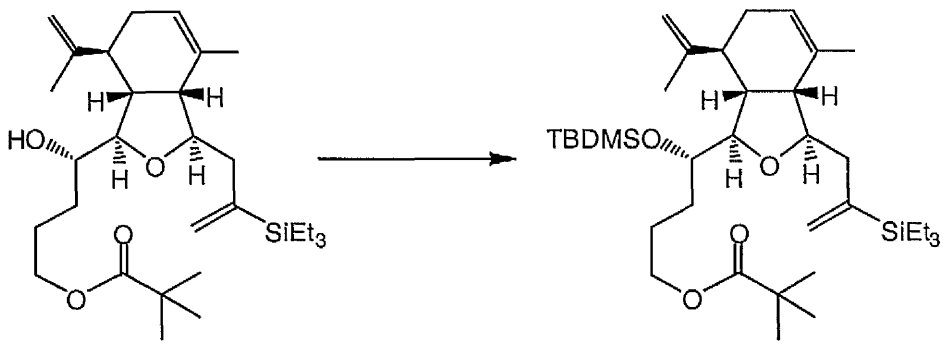
δ_C(75MHz, $CDCl_3$) -4.089, -4.028, -2.7, 3.1, 7.6, 18.3, 20.0, 23.8, 25.2, 25.9, 26.3, 27.5, 30.5, 30.7, 38.9, 42.7, 42.9, 43.0, 49.2, 64.9, 75.1, 83.0, 83.4, 112.4, 122.7, 127.1, 132.2, 146.8, 147.8, 178.8.

ν_{max}(evaporated film) 1729, 2970 cm^{-1}

m/z (ES^+) 641 ($M+Na^+$, 100%).

HRMS (ES^+) $C_{36}H_{70}O_4Si_2N$ ($M+NH_4^+$) requires 636.4838; found 636.4848.

Synthesis of (*S)-4-((1*R**,3*R**,3a*R**,4*S**,7a*R**)-1-(2-(triethylsilyl)allyl)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)-4-(tertbutyldimethyl silyl)butyl pivalate 421b.**



420b **421b**

Secondary alcohol **420b** (136 mg, 0.26 mmol, 1 eq) was dissolved in anhydrous DCM (6 mL) and cooled to -10 °C. To the chilled solution was added 2,6-lutidine (113 mg, 1.05 mmol, 4 eq) and TBDMS triflate (138 mg, 0.53 mmol, 2 eq) and the reaction mixture was stirred for a further hour before slowly warming to 17 °C. Additional stirring for another hour was followed by quenching with saturated $NH_4Cl_{(aq)}$ solution (2x 10 mL) with the organic layer being washed with brine (10 mL), dried ($MgSO_4$), and solvent evaporated to dryness under reduced pressure. The resulting crude material was subjected to column chromatography (flash silica, 15% EtOAc/ 85% petrol) affording the *title compound* as a clear viscous oil (125 mg, 74% yield).

δ_H(500MHz, $CDCl_3$) 0.01 (3H, s), 0.06 (3H, s), 0.59 (6H, q, 8 Hz), 0.87 (9H, s), 0.91 (9H, t, *J*= 8 Hz), 1.17 (9H, s), 1.44-1.49 (1H, m), 1.69 (3H, s), 1.67-1.70 (4H, m), 1.72 (3H, s), 2.07 (2H, bs), 2.17-2.27 (3H, m), 2.57 (1H, d, *J*= 15 Hz), 3.57-3.60 (1H, m), 3.76 (1H, dd, *J*= 1 and 7 Hz), 3.81 (1H, dt, *J*= 1 and 7 Hz), 3.94-4.12 (2H, m), 4.79 (2H, d, *J*= 1 Hz), 5.38 (1H, d, *J*= 2 Hz), 5.49 (1H, bs), 5.81 (1H, t, *J*= 2 Hz)

δ_C(75MHz, $CDCl_3$) -4.4, -3.9, -2.9, 2.8, 4.6, 7.4, 7.5, 18.1, 18.2, 19.4, 23.2, 23.6, 25.6, 26.0, 27.2, 29.7, 30.2, 30.4, 38.7, 41.9, 42.7, 43.8, 48.7, 64.8, 82.4, 82.9, 112.8, 123.2, 127.3, 131.5, 146.0, 147.1, 178.6

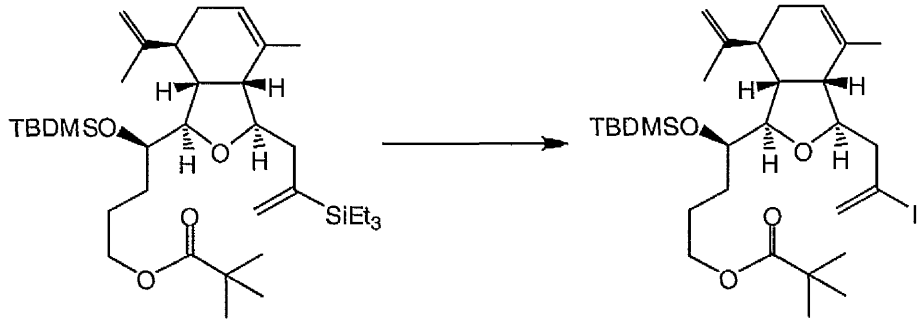
ν_{max}(evaporated film) 1730, 2955 cm^{-1}

m/z (ES^-) 397 (100%), 539 (20%)

m/z (ES^+) 641 ($M+Na^+$, 100%)

HRMS (ES^+) $C_{36}H_{70}O_4Si_2N$ ($M+NH_4^+$) requires 636.4838; found 636.4850

Synthesis of (*R)-4-((1*R**,3*R**,3a*R**,4*S**,7a*R**)-1,3,3a,4,5,7a-hexahydro-1-(2-iodoallyl)-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)-4-(*tert*-butyldimethylsilyl)butyl pivalate 422a.[84]**



421a **422a**

Iodine monochloride (0.32 mL, 1M solution in DCM, 0.32 mmol, 2 eq) was added dropwise to **421a** (100 mg, 0.16 mmol, 1 eq) dissolved in anhydrous DCM (1 mL). The reaction mixture was allowed to stir for 2.5 hours at 17 °C, where it was quenched with saturated sodium thiosulphate solution (1 mL), with the organic layer separated and washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to reveal a crude oil. The crude material was redissolved in anhydrous THF (2 mL) and TBAF (0.3 mL, 0.32 mmol, 2 eq) added. This was stirred for an hour where it was evaporated *in vacuo*, with the residue purified by column chromatography (10% EtOAc/ 90% petrol) to afford product **422a** as an oil (100 mg, 88% yield)

δ_H(500MHz, $CDCl_3$) 0.02 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 1.11 (9H, s), 1.38-1.44 (1H, m), 1.59 (3H, s), 1.57-1.64 (2H, m), 1.63 (3H, s), 1.69-1.76 (1H, m), 1.86-2.00 (2H, m), 2.06-2.19 (2H, m), 2.50 (1H, t, *J*= 8 Hz), 2.70 (1H, dt, *J*= 5 and 14 Hz), 2.76 (1H, dd, *J*= 8 and 14 Hz), 3.40 (1H, ddd, *J*= 2, 5 and 13 Hz), 3.81 (1H, t, *J*= 2 Hz), 3.89-4.01 (3H, m), 4.86 (1H, s), 4.74 (1H, t, *J*= 2 Hz), 5.41 (1H, bs), 5.69 (1H, d, *J*= 2 Hz), 6.07 (1H, d, *J*= 2 Hz).

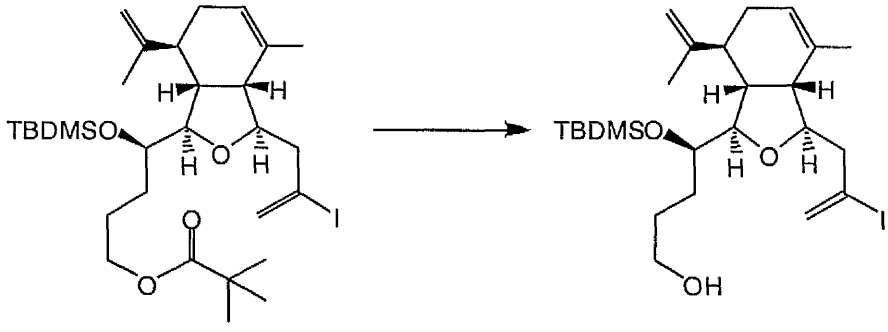
δ_C(75MHz, $CDCl_3$) -4.4, -4.3, 18.1, 19.7, 23.3, 14.8, 26.1, 27.2, 30.2, 30.8, 38.7, 42.6, 43.2, 47.7, 52.6, 64.5, 82.3, 83.6, 108.9, 112.33, 122.54, 127.1, 131.7, 147.5, 178.6.

ν_{max}(evaporated film) 1730, 2858, 2930, 2956 cm^{-1}.

m/z (ES^+) 648 ($M+NH_4^+$, 90%), 653 ($M+Na^+$, 100%).

HRMS (ES^+) $C_{30}H_{55}O_4SiN^{126}I$ ($M+NH_4^+$) requires 648.2940; found 648.2955.

Synthesis of (*R)-4-((1*R**,3*R**,3a*R**,4*S**,7a*R**)-1,3,3a,4,5,7a-hexahydro-1-(2-iodoallyl)-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)-4-(*tert*-butyldimethylsilyl)butan-1-ol 423a.**



422a **423a**

To a solution **422a** (50 mg, 0.08 mmol, 1 eq) in DCM (1 mL) was added diisobutylaluminium hydride (0.12 mL, 0.12 mmol, 1.0 M in cyclohexane, 1.5 eq), at –78 °C, and the resulting solution was stirred for 1 hour. The reaction was quenched by addition of a saturated solution of sodium potassium tartrate (1 mL) and the aqueous phase extracted repeatedly with dichloromethane (3x2 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (flash silica, 5% EtOAc/ 95% petrol) affording lactol **423a** as viscous oil (32 mg, 75% yield).

δ_H(300MHz, $CDCl_3$) 0.097 (3H, s), 0.12 (3H, s), 0.95 (9H, s), 1.46-1.66 (3H, m), 1.70 (3H, s), 1.73 (3H, s), 1.81-1.90 (1H, m), 1.81-1.90 (1H, m), 2.06 (1H, bs), 2.18-2.33 (2H, m), 2.58-2.94 (1H, m), 3.51-3.57 (1H, m), 3.98-4.13 (2H, m), 4.75 (1H, bs), 4.78 (1H, bs), 5.53 (1H, bs), 5.83 (1H, bs), 6.19 (1H, s).

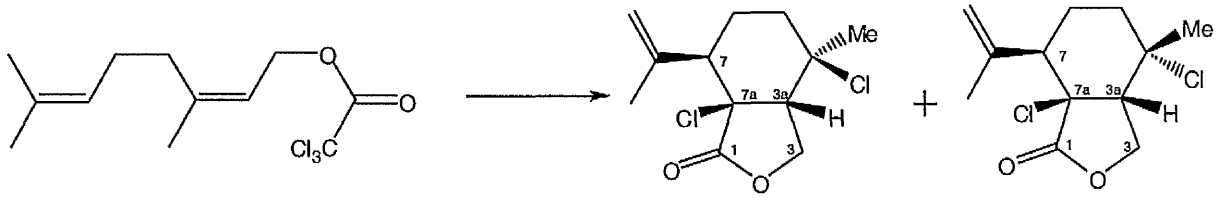
δ_C(75MHz, $CDCl_3$) -4.1, -4.0, 13.9, 18.4, 20.1, 23.6, 24.4, 26.3, 28.9, 29.9, 30.4, 30.6, 42.9, 43.4, 47.0, 48.0, 52.8, 63.2, 75.6, 81.1, 82.5, 83.9, 109.2, 112.5, 122.8, 127.3, 131.9, 147.8.

ν_{max}(evaporated film) 2857, 2929, 2953, 3398 cm^{-1}.

m/z (ES^+) 242 (100%), 545 (30%) 569 ($M+Na^+$, 70%).

HRMS (ES^+) $C_{25}H_{44}O_3Si^{126}I$ requires 547.2099; found 547.2097.

Synthesis of (3a*S,4*R**,7*R**,7a*S**)-4,7a-dichloro-7-isopropenyl-4-methylperhydro-1-isobenzo- furanone 329a** and **(3a*S**,4*S**,7*R**,7a*S**)-4,7a-dichloro-7-isopropenyl-4-methylperhydro-1-isobenzofuranone 329b**[19]



328 **329a** **329b**

A dry Schlenck tube was charged with Cu(I)Cl (31 mg, 5 mol%), dHBipy (120 mg, 5 mol%) and anhydrous 1,2-DCE (5 mL) and the brown solution was allowed to stir for 10 minutes at 17 °C under a nitrogen atmosphere. The contents of the flask were then degassed (three times using freeze-thaw cycle) to which was added, by syringe, a degassed (three times using freeze thaw cycle) solution of trichloroacetate **328** (2.0 g, 6.67 mmol, 1 eq) in 1,2-DCE (2 mL) and the Schlenck tube was placed in a pre-heated oil bath (90 °C) and was allowed to stir for 3.5 hours under nitrogen. Upon cooling, the solvent was removed *in vacuo*, the residue was dissolved in dichloromethane (10 mL) to which was added silica (10 mL). After stirring for 1 hour and removal of the solvent *in vacuo*, the residue was purified by column chromatography (5% EtOAc/ 90% petrol) to afford the *title compounds*.

Major diastereoisomer 329a (R_f=0.1 in 10% EtOAc/ 90% petrol), white solid [recrystallised from DCE in hexane] (850 mg, 49% yield)

δ_H (300 MHz, $CDCl_3$) 1.62 (3H, s, Me), 1.98 (3H, s Me), 1.63 – 2.45 (4H, m), 2.56 (1H, dd, *J*= 3 and 11 Hz, C7a-H), 3.31 (1H, t, *J*= 9 Hz, C3a-H), 4.10 (1H, t, *J*= 11 Hz, CH*H*), 4.40 (1H, bt, *J*= 9 Hz, C*H*H), 4.86 (1H, s, olefinic H), 5.10 (1H, s, olefinic H).

δ_C (75 MHz, $CDCl_3$) 22.3, 22.9, 30.3, 37.9, 45.9, 56.0, 62.3, 66.1, 67.3, 117.2, 141.6, 172.2.

ν_{max} (Nujol) 1378, 1451, 1644, 1789, 2932 cm^{-1}.

Mp 129-130°C.

m/z (EI) 91 (90%), 105 (53%), 147 (36%), 191 (60%), 227 (100%), 263 (35%).

m/z (CI) 280 ($M+NH_4^+$,100%).

HRMS (CI) $C_{12}H_{19}{}^{35}Cl_2NO_2$ ($M+NH_4^+$) requires 280.0792; found 280.0870.

Minor diastereoisomer 329b (R_f=0.6 in 10% EtOAc/ 90% petrol), white solid [recrystallized from DCE in hexane] (480 mg, 28% yield)

δ_H (300 MHz, $CDCl_3$) 1.90 (3H, s, Me), 1.95 (3H, s, Me), 1.81-2.26 (4H, m), 2.69 (1H, dd, *J*= 4 and 11 Hz, C7a-H), 3.20 (1H, dd, *J*= 8 and 11 Hz, C3a-H), 4.48 (1H, bt, *J*= 11 Hz, C*H*H), 4.67 (1H, dd, *J*= 8 and 11 Hz, CH*H*), 4.86 (1H, s olefinic H), 5.21 (1H, s, olefinic H).

δ_C (75 MHz, $CDCl_3$) 22.5, 24.7, 31.9, 38.4, 45.6, 55.6, 67.3, 67.5, 69.0, 117.0, 141.3, 171.9

ν_{max} (evaporated film) 1601, 1794, 2925 cm^{-1}.

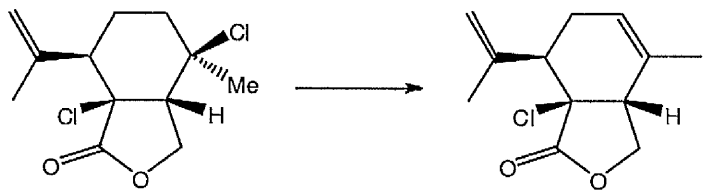
Mp 112-114°C

m/z (EI) 41 (70%), 77 (75%), 91 (100%), 105 (53%), 227 (35%), 263 (5%).

m/z (CI) 280 ($M+NH_4^+$, 100%).

HRMS (CI) $C_{12}H_{19}{}^{35}Cl_3NO_2$ ($M+NH_4^+$) requires 280.0793; found 280.0870.

Synthesis of (3a*R,7*R**,7a*S**)-7a-chloro-7-isopropenyl-4-methyl-3a,6,7,7a-tetrahydro-2-benzofuran-1(3H)-one 404.**



329a **404**

To a vigorously stirred solution of the lactone **329a** (5.06g, 18.81mmol, 1 eq) in anhydrous dimethylformamide (240 mL) was added lithium carbonate (2.73g, 47.1mmol, 2.5 eq) and lithium chloride (1.17 g, 28.21mmol, 1.5 eq). The resulting mixture was placed in an oil bath at 125 °C and heated for 30 minutes. The reaction mixture was partitioned between water (100 mL) and EtOAc (200 mL), and the aqueous layer extracted with EtOAc (3x 100 mL). The combined organic extracts were washed with brine (4x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc/ 95% petrol) to afford the *title compound* as colourless oil (4.31 g, 98% yield).

δ_H (300 MHz, $CDCl_3$) 1.78 (3H, s, CH_3), 1.85 (3H, s, CH_3), 2.34 (2H, m, CH_2), 2.98 (1H, m), 3.05 (1H, bs), 4.30 (1H, dd, *J*= 4 and 9 Hz), 4.65 (1H, dd, *J*= 4 and 9 Hz), 4.95 (1H, s, olefinic H), 5.0 (1H, s, olefinic H), 5.68 (1H, m, olefinic H).

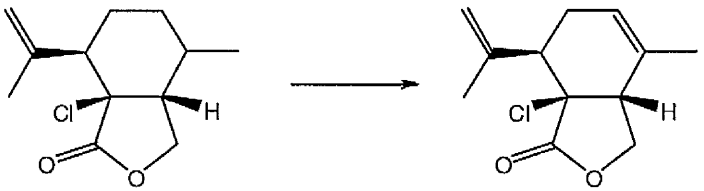
δ_C (75 MHz, $CDCl_3$) 27.6, 36.8, 39.1, 43.5, 70.6, 124.1, 118.2 130.0, 140.1, 140.9, 142.1, 178.5

ν_{max} (Nujol) 2943, 1782, 1650, 1440 cm^{-1}.

m/z (EI) 86 (100%), 191 (20%), 226 (10%)

m/z(CI) 244 ($M+NH_4^+$,100%).

Synthesis of (3a*R,7S*,7a*R**)-3,3a,7,7a-tetrahydro-4-methyl-7-(prop-1-en-2-yl)isobenzofuran-1(6*H*)-one 405.**



404 **405**

To a stirred solution of **404** (150 mg, 0.66 mmol, 1 eq) in benzene (10 mL) at 80 °C was added, dropwise by syringe over 10 minutes, a solution of aza-*bis*isobutyronitrile (8 mg, 0.033 mmol, 0.05 eq) and tributyltin hydride (515 mg, 0.33 mmol, 0.5 eq) in benzene (2 mL). After 1 hour this addition was repeated and the mixture was stirred for a further hour. The solvent was removed *in vacuo* and the crude residue was chromatographed (10% EtOAc/ 90% petrol) affording the *title compound* as a colourless oil (126 mg, 91% yield). R_f = 0.8 (25% EtOAc/ 75% petrol).

δ_H(300MHz, $CDCl_3$) 1.72 (3H, s), 1.81 (3H, s), 2.14-2.20 (2H, m), 2.64 (1H, bq, *J*= 8 Hz), 2.84 (1H, t, *J*= 8 Hz), 2.96 (1H, bq, *J*= 6 Hz), 4.15 (1H, dd, *J*= 6 and 8 Hz), 4.46 (1H, dd, *J*= 8 and 8 Hz), 4.83 (1H, bs), 4.89 (1H, bs), 5.63 (1H, bs).

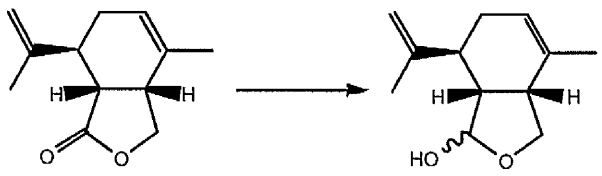
δ_C(75MHz, $CDCl_3$) 20.6, 21.3, 27.9, 38.7, 39.5, 41.9, 70.9, 112.4, 123.9, 130.1, 145.7, 178.1.

ν_{max}(evaporated film) 1774, 2931, 2968 cm^{-1}.

m/z (CI) 193 (40%), 210 (100%).

HRMS (CI) $C_{12}H_{20}NO_2$ ($M+NH_4^+$) requires 210.1489; found 210.1493.

Synthesis of (1*S,3a*R**,7*S**,7a*R**)-1,3,3a,6,7,7a-hexahydro-4-methyl-7-(prop-1-en-2-yl) isobenzofuran-1-ol 406.**



405 **406**

To a solution **405** (700 mg, 3.54 mmol, 1 eq) in DCM (40 mL) was added diisobutylaluminium hydride (4.28 mL, 4.28 mmol, 1.0 M in cyclohexane, 1.2 eq), at –78 °C, and the resulting solution was stirred for 1.5 hours. The reaction was quenched by addition of sodium potassium tartrate (10 mL) and the aqueous phase extracted repeatedly with dichloromethane (3x25 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (5% EtOAc/ 95% petrol) affording lactol **406** as viscous oil (640 mg, 91% yield).

δ_H(300MHz, $CDCl_3$) 1.67 (3H, s), 1.75 (3H, s), 1.99-2.10 (3H, m), 2.25 (1H, dd, *J*= 8 and 12 Hz), 2.98-3.07 (1H, m), 3.67 (1H, dd, *J*= 8 and 8 Hz), 4.00 (1H, s), 4.38 (1H, dd, *J*= 8 and 8 Hz), 4.83-4.87 (2H, m), 5.32 (1H, s), 5.48 (1H, bs)

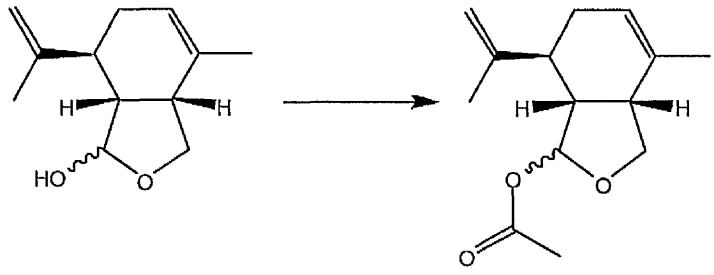
δ_C(75MHz, $CDCl_3$) 19.7, 23.0, 30.6, 40.7, 40.8, 46.9, 72.9, 101.8, 112.4, 121.5, 132.7, 147.3

ν_{max}(evaporated film) 2939, 2964, 3400 cm^{-1}

m/z (CI) 177 (100%), 194 (90%)

HRMS (CI) $C_{12}H_{22}NO_2$ ($M+NH_4^+$) requires 212.1645; found 212.1642

Synthesis of (3*R,3a*R**,4*S**,7a*R**)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl acetate 407.**



406 **407**

To a solution of **406** (2.5 g, 12.9 mmol, 1 eq) in dichloromethane (50 mL) was added pyridine (1.52g, 15.5 mmol, 1.2 eq), acetic anhydride (1.58 g, 15.5 mmol, 1.2 eq), and *N*-dimethylamino pyridine (143 mg, 2.58 mmol, 0.2 eq) at -78 °C. After stirring for 1 hour the solution was allowed to warm to 17 °C and after 3 hours was quenched by addition of methanol (2 mL). The solution was diluted with DCM (150 mL) and the resulting organic phase was washed with aqueous 10% potassium hydrogen sulfate solution (50 mL), aqueous saturated sodium bicarbonate solution (50 mL), and brine prior to drying ($MgSO_4$) and removal of solvent under reduced pressure. The crude residue was chromatographed (10% EtOAc/ 90% petrol) affording the *title compound* as a viscous oil (2.6 g, 86% yield).

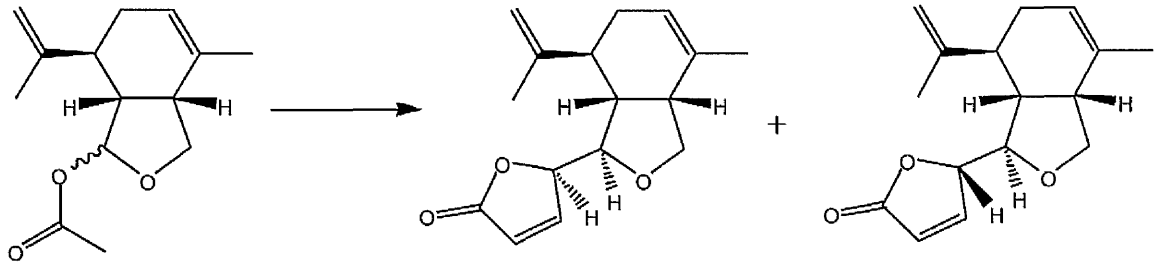
δ_H(300MHz, $CDCl_3$) 1.68 (3H, s), 1.73 (3H, s), 2.05-2.15 (3H, m), 2.05 (3H, s), 2.30 (1H, dd, *J*= 7 and 10 Hz), 2.91-2.99 (1H, m), 3.69 (1H, dd, *J*= 7 and 10 Hz), 4.36 (1H, dd, *J*= 7 and 10 Hz), 4.83 (1H, bs), 4.87 (1H, t, *J*= 2 Hz), 5.49 (1H, bs), 6.1 (1H, s)

δ_C(75MHz, $CDCl_3$) 19.4, 21.6, 23.0, 30.5, 40.5, 40.6, 45.9, 74.0, 102.0, 113.1, 121.7, 132.1, 146.5, 170.6.

ν_{max}(evaporated film) 1743, 2894, 2946, 2966 cm^{-1}.

m/z Unable to attain MS

Synthesis of (*S)-5-((3*R**,3a*R**,4*S**,7a*R**)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)furan-2(5H)-one 408a** and **(*R**)-5-((3*R**,3a*R**,4*S**,7a*R**)-1,3,3a,4,5,7a-hexahydro-7-methyl-4-(prop-1-en-2-yl)isobenzofuran-3-yl)furan-2(5H)-one 408b.**



407 **408a** **408b**

To a stirred solution of **407** (550 mg, 2.33 mmol, 1 eq) in dichloromethane (2 mL) was added 2-trimethylsilyloxyfuran (436 mg, 2.8 mmol, 1.2 eq) at 17 °C. After 10 minutes borontrifluoride diethyletherate (430 mg, 2.8 mmol, 1.2 eq) was added by syringe pump, over 2 hours, at -78 °C. After 2 hours the resulting bright yellow coloured solution was quenched with saturated sodium bicarbonate solution (20 mL), diluted with DCM (100 mL), the phases separated, the aqueous layer extracted with DCM (3x 40 mL), the organics washed with brine (40 mL), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed (10% EtOAc/ 90% petrol) affording the title compounds.

The major diastereoisomer, *erythro* adduct **408a** was obtained as a white solid (261 mg, 44% yield), R_f = 0.56 (25% EtOAc/ 75% petrol)

δ_H(300MHz, $CDCl_3$) 1.61 (3H, s), 1.75 (3H, s), 2.04-2.10 (2H, m), 2.13-2.24 (1H, m), 2.40 (1H, ddd, *J*= 2, 7 and 20 Hz), 2.81 (1H, bq, *J*= 10 Hz), 3.5 (1H, dd, *J*= 8 and 10 Hz), 4.17 (1H, t, *J*= 3 Hz), 4.22 (1H, t, *J*= 8 Hz), 4.87 (1H, bs), 4.92 (1H, t, *J*= 2 Hz), 5.03 (1H, q, *J*=2 Hz), 5.52-5.57 (1H, m), 6.22 (1H, dd, *J*= 2 and 6 Hz), 7.47 (1H, dd, *J*= 2 and 6 Hz).

δ_C(75MHz, $CDCl_3$) 19.6, 22.8, 30.7, 41.6, 43.6, 43.7, 73.6, 81.5, 85.3, 113.3, 122.3, 122.7, 131.8, 146.9, 153.7, 173.5.

ν_{max}(evaporated film) 1786, 2892, 2948 cm^{-1}.

Mp 132°C.

m/z (CI) 178 (70%), 260 (100%).

HRMS (CI) $C_{16}H_{24}NO_4$ ($M+NH_4^+$) requires 278.1751; found 278.1756.

The minor diastereisomer, *threo* adduct **408b** was obtained as a white solid (190 mg, 32% yield); R_f=0.38 (25% EtOAc/ 75% petrol);

δ_H(300MHz, $CDCl_3$) 1.69 (6H, s), 2.01-2.11 (2H, m), 2.15-2.25 (2H, m), 2.82 (1H, bs), 3.56 (1H, dd, *J*= 8 and 10 Hz), 3.91 (1H, d, *J*= 8 Hz), 4.32 (1H, t, *J*= 8 Hz), 4.81 (1H, bs), 4.85 (1H, t, *J*= 2 Hz), 4.97 (1H, dt, *J*= 2 and 6 Hz), 5.52-5.56 (1H, m), 6.19 (1H, dd, *J*= 2 and 6 Hz), 7.53 (1H, dd, *J*= 2 and 6 Hz).

δ_C(75MHz, $CDCl_3$) 19.0, 23.0, 30.5, 41.1, 42.9, 43.7, 73.5, 83.2, 84.7, 113.7, 122.4, 122.5, 131.5, 146.6, 155.1, 173.1.

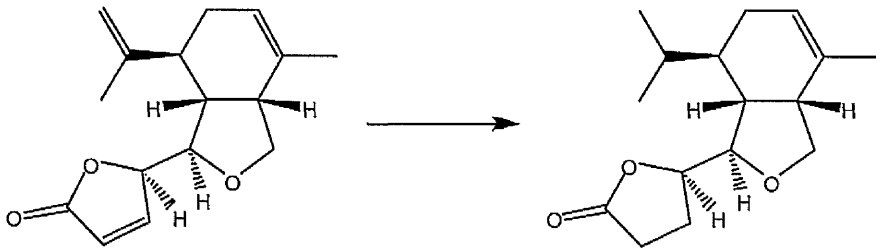
ν_{max}(evaporated film) 1787, 2892, 2948 cm^{-1}.

Mp 148°C.

m/z (CI) 177 (70%), 261 (100%), 278 (40%).

HRMS (CI) $C_{16}H_{24}NO_4$ ($M+NH_4^+$) requires 278.1751; found 278.1755.

Synthesis of (*R)-dihydro-5-((3*R**,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)furan-2(3*H*)-one 409a.**



408a **409a**

To a vigorously stirred solution of **408a** (680 mg, 2.6 mmol, 1 eq) in ethanol (9 mL) was added Raney Nickel (1.7 g, wet wt), at 17 °C, and the vessel sealed to produce a closed system. After 2 hours, the suspension was filtered through a pad of celite (10 g), with the filtrate being concentrated under reduced pressure to give an oily solid. The crude residue was chromatographed eluting with 10% EtOAc/ 90% petrol affording the *title compound* as colourless oil (520 mg, 75% yield).

δ_H(300MHz, $CDCl_3$) 0.83 (3H, d, *J*= 8 Hz), 0.97 (3H, d, *J*= 8 Hz), 1.37 (1H, m), 1.63 (3H, s), 1.69-1.99 (3H, m), 2.30 (3H, m), 2.44 (1H, dt, *J*= 8 and 17 Hz), 2.68 (1H, dd, *J*= 8 and 10 Hz), 2.73 (1H, t, *J*= 8 Hz), 3.44 (1H, t, *J*= 8 Hz), 3.91 (1H, dd, *J*= 2 and 4 Hz), 4.09 (1H, t, *J*= 8 Hz), 4.53 (1H, dt, *J*= 2 and 8 Hz), 5.48 (1H, t, *J*= 2 Hz).

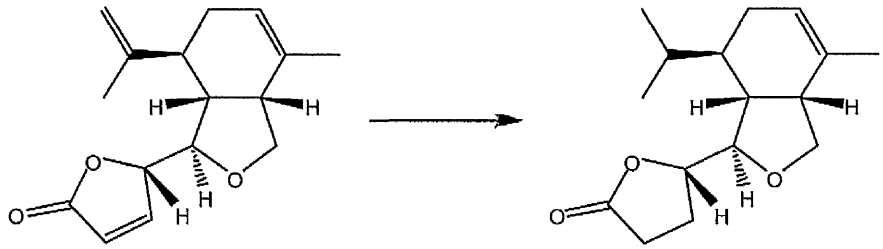
δ_C(75MHz, $CDCl_3$) 16.8, 21.9, 22.5, 23.4, 24.8, 28.1, 28.5, 39.0, 41.5, 42.9, 72.5, 81.5, 84.4, 122.2, 131.8, 178.1.

ν_{max}(evaporated film) 1775, 2872, 2930, 2959 cm^{-1}.

m/z (CI) 179 (90%), 265 (50%), 282 (100%).

HRMS (CI) $C_{16}H_{28}NO_3$ ($M+NH_4^+$) requires 282.2064; found 282.2063.

Synthesis of (*S)-dihydro-5-((3*R**,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)furan-2(3H)-one 409b.**



408b **409b**

To a vigorously stirred solution of **408b** (400 mg, 1.53 mmol, 1 eq) in ethanol (5 mL) was added Raney Nickel (1 g, wet wt), at 17 °C, and the vessel sealed to produce a closed system. After 2 hours, the suspension was filtered through a pad of celite (10 g), with the filtrate being concentrated under reduced pressure to give an oily solid. The crude residue was chromatographed eluting with 10% EtOAc/ 90% petrol affording the *title compound* as colourless oil (277 mg, 68% yield).

δ_H(300MHz, $CDCl_3$) 0.84 (3H, d, *J*= 7 Hz), 0.99 (3H, d, *J*= 7 Hz), 1.45 (1H, m), 1.68 (3H, s), 1.83 (3H, s), 1.95-2.35 (4H, m), 2.59 (3H, m), 3.49 (1H, dd, *J*= 7 and 10 Hz), 4.03 (1H, dd, *J*= 4 and 7 Hz), 4.17 (1H, t, *J*= 7 Hz), 4.46 (1H, dt, *J*= 4 and 7 Hz), 5.55 (1H, t, *J*= 2 Hz).

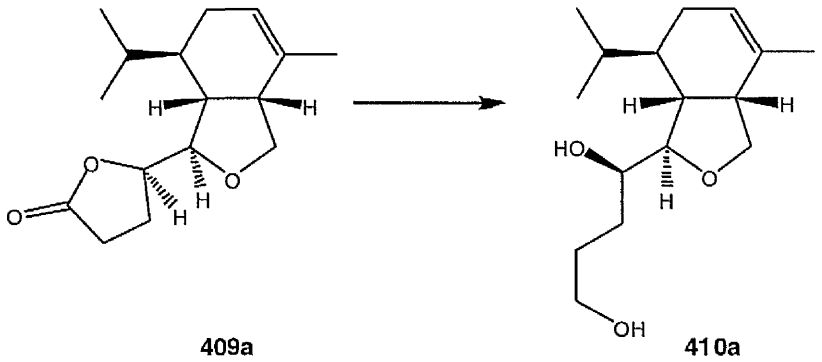
δ_C(75MHz, $CDCl_3$) 16.3, 21.9, 22.7, 22.9, 23.9, 27.8, 28.5, 38.9, 42.1, 44.1, 72.6, 81.7, 83.5, 122.8, 131.4, 177.3.

ν_{max}(evaporated film) 1780, 2871, 2927, 2958 cm^{-1}.

m/z (CI) 179 (80%), 265 (25%), 282 (100%).

HRMS (CI) $C_{16}H_{25}O_3$ requires 265.1798; found 265.1788.

Synthesis of (*R)-1-((3*R**,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)butane-1,4-diol 410a.**



409a **410a**

Lactone **409a** (466 mg, 1.76 mmol, 1 eq) was dissolved in anhydrous THF (9 mL) at 17 °C then immediately cooled to 0 °C by placing the vessel in an ice bath. The reaction mixture was allowed to stir for 10 minutes which after $LiAlH_4$ (352 mg, 8.8 mmol, 5 eq) was added in several portions. This was allowed to stir for 1 hour where immediately after a saturated solution of Rochelle's salt (35 mL) was added. This was allowed to stir vigorously for 60 minutes, then after the aqueous layer was separated and washed with EtOAc (2x 20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and the solvent concentrated under reduced pressure to revel a crude product. The crude residue was chromatographed (flash silica, 20% EtOAc/ 80% petrol) affording the *title compound* as a white crystalline solid (450 mg, 89% yield).

δ_H(300MHz, $CDCl_3$) 0.82 (3H, d, *J*= 7 Hz), 0.98 (3H, d, *J*= 7 Hz), 1.40-1.60 (2H, m), 1.66 (3H, s), 1.71-2.02 (5H, m), 2.16 (1H, ddd, *J*= 1, 3 and 7 Hz), 2.67 (1H, bq, *J*= 7 Hz), 2.95 (2H, bs, -OH), 3.45 (1H, dd, *J*= 7 and 10 Hz), 3.69 (3H, m), 3.89 (1H, t, *J*= 3 Hz), 4.16 (1H, t, *J*= 7 Hz), 5.53 (1H, bs).

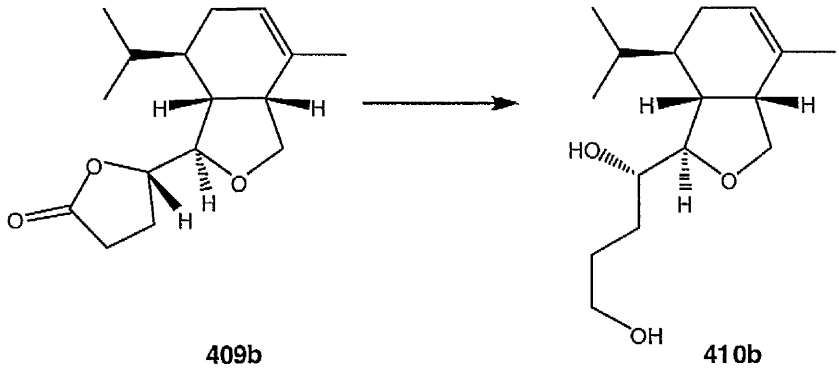
δ_C(75MHz, $CDCl_3$) 16.5, 22.1, 22.8, 23.5, 27.7, 29.9, 30.0, 39.2, 40.6, 44.9, 63.2, 72.4, 74.2, 86.2, 122.5, 131.7.

ν_{max}(evaporated film) 2871, 2921, 2953, 3230 cm^{-1}.

m/z (CI) 251 (30%), 269 (100%), 286 ($M+NH_4^+$).

HRMS (CI) $C_{16}H_{32}NO_3$ ($M+NH_4^+$) requires 286.2377; found 286.2376.

Synthesis of (*S)-1-((3*R**,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)butane-1,4-diol 410b.**



409b **410b**

Lactone **409b** (200 mg, 0.76 mmol, 1 eq) was dissolved in anhydrous THF (4 mL) at 17 °C then immediately cooled to 0 °C by placing the vessel in an ice bath. The reaction mixture was allowed to stir for 10 minutes which after $LiAlH_4$ (152 mg, 3.8 mmol, 5 eq) was added in several portions. This was allowed to stir for 1 hour where immediately after a saturated solution of Rochelle's salt (15 mL) was added. This was allowed to stir vigorously for 60 minutes, then after the aqueous layer was separated and washed with EtOAc (2x 20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and the solvent concentrated under reduced pressure to revel a crude product. The crude residue was chromatographed eluting with 20% EtOAc/ 80% petrol affording the *title compound* as a white crystalline solid (173 mg, 85% yield).

δ_H(300MHz, $CDCl_3$) 0.82 (3H, d, 7 Hz), 0.97 (3H, d, 7 Hz), 1.41 (1H, m), 1.65 (3H, s), 1.73-2.01 (4H, m), 2.15 (1H, ddd, *J*= 1, 3 and 7 Hz), 2.62 (1H, q, *J*= 7 Hz), 3.01 (1H, s), 3.50 (1H, t, *J*= 7 Hz), 3.61 (1H, m), 3.78 (1H, t, *J*= 3 Hz), 4.14 (1H, t, *J*= 7 Hz), 5.51 (1H, t, *J*= 3 Hz).

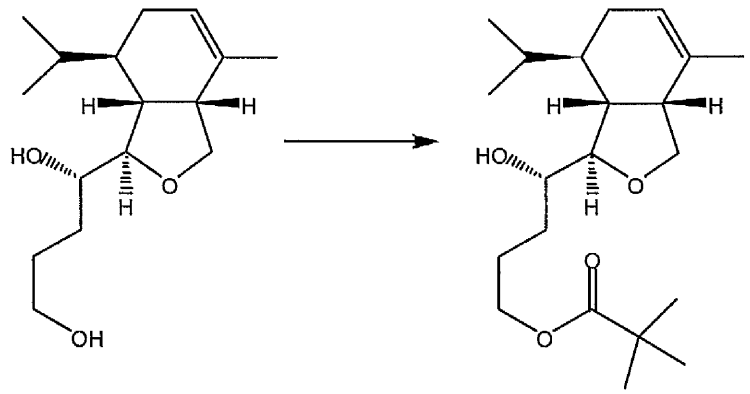
δ_C(75MHz, $CDCl_3$) 16.8, 21.9, 22.6, 23.5, 27.9, 29.5, 31.5, 39.1, 41.8, 44.4, 63.0, 72.2, 73.5, 85.8, 122.5, 131.8.

ν_{max}(evaporated film) 2871, 2928, 2957, 3391 cm^{-1}.

m/z (CI) 251 (30%), 269 (100%), 286 ($M+NH_4^+$).

HRMS (CI) $C_{16}H_{32}NO_3$ ($M+NH_4^+$) requires 286.2377; found 286.2376.

Synthesis of (*S)-4-((3*R**,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)-4-hydroxybutyl pivalate 411b.**



410b **411b**

Diol **410b** (150 mg, 0.43 mmol, 1eq) was dissolved in diethyl ether (10 mL), cooled to 0 °C and allowed to stir for 5 minutes. To this reaction mixture was added pyridine (101 mg, 1.3 mmol, 3 eq) and immediately after trimethylacetyl chloride (156 mg, 1.3 mmol, 3 eq) was added, with the reaction mixture allowed to stir at 0 °C for 1.5 hours. The reaction was quenched with the addition of water (10 mL). The resulting mixture was partitioned between EtOAc (5 mL) and water (5 mL), with the organic layer being removed and the aqueous layer being washed with a further portion of EtOAc (10 mL). The organic layers were combined, washed with copper sulphate solution, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a gummy crude solid. This was subjected to column chromatography (flash silica, 25% EtOAc/ 75% petrol) affording the *title compou*nd as a clear viscous oil (117 mg, 82% yield).

δ_H(300MHz, $CDCl_3$) 0.85 (3H, d, *J*= 7 Hz), 0.98 (3H, d, *J*= 7 Hz), 1.22 (9H, s), 1.25-1.62 (4H, m), 1.67 (3H, s), 1.73-2.04 (5H, m), 2.08-2.14 (1H, m), 2.62 (1H, bq, *J*= 7 Hz), 3.49-3.55 (2H, m), 3.75 (1H, t, *J*= 4 Hz), 4.04-4.13 (3H, m), 5.52 (1H, bs).

δ_C(75MHz, $CDCl_3$) 16.8, 21.9, 22.6, 23.5, 25.4, 27.4, 27.9, 29.9, 30.9, 39.1, 41.8, 44.5, 64.6, 72.2, 72.9, 85.8, 122.5, 131.8, 178.9.

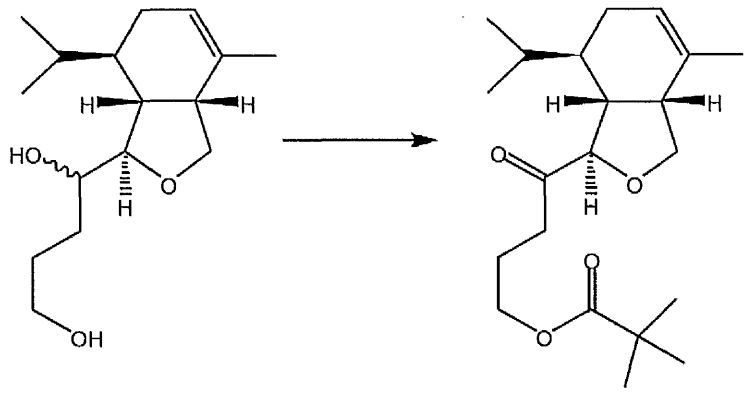
ν_{max}(evaporated film) 1728, 2930, 2960, 3450 cm^{-1}.

m/z (CI) 179 (40%), 251 (30%), 353 (100%).

m/z (EI) 71 (100%), 179 (70%), 251 (50%), 353 (70%, $M+H^+$).

HRMS (EI) $C_{21}H_{36}O_4$ requires 352.2614; found 352.2610.

Synthesis of 4-((3*R,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)-4-oxobutyl pivalate 412**



411a,b **412**

Diastereomixture of secondary alcohol **411a,b** (67 mg, 0.19 mmol, 1 eq) was added to a chilled solution (0 °C) of anhydrous DCM containing TPAP (9 mg, 0.019 mmol, 10 mol%), NMO (31 mg, 0.26 mmol, 1.5 eq) and activated 4Å molecular sieves (88 mg). The reaction mixture was stirred at 0 °C for 4.5 hours where it was filtered through a pad of celite (eluting with DCM) and evaporated to dryness under reduced pressure to give product **412** as colourless oil (55 mg, 82% yield). No further purification was needed.

δ_H(300MHz, $CDCl_3$) 0.85 (3H, d, 7 Hz), 0.98 (3H, d, *J*= 7 Hz), 1.23 (9H, s), 1.48 (1H, m), 1.67 (3H, s), 1.95 (4H, m), 2.30 (1H, ddd, *J*= 1, 3 and 7 Hz), 2.59 (1H, t, *J*= 7 Hz), 2.65 (1H, t, *J*= 7 Hz), 2.72 (1H, t, *J*= 7 Hz), 2.78 (1H, t, *J*= 7 Hz), 3.62 (1H, t, *J*= 7 Hz), 4.10 (2H, dt, *J*= 2 and 7 Hz), 4.27 (1H, t, *J*= 7 Hz), 4.32 (1H, d, *J*= 4 Hz), 5.55 (1H, m).

δ_C(75MHz, $CDCl_3$) 16.6, 21.7, 22.6, 23.5, 27.4, 28.0, 34.9, 38.5, 38.9, 43.6, 44.2, 63.7, 73.1, 87.1, 122.7, 131.3, 178.7.

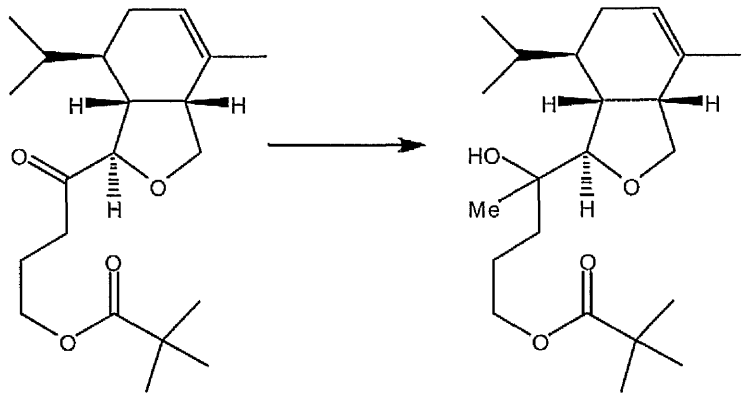
ν_{max}(evaporated film) 1727, 2872, 2930, 2960 cm^{-1}.

M/z (EI) 179 (100%), 249 (30%),

M/z (CI) 179 (30%), 249 (75%), 368 (100%, $M+NH_4^+$),

HRMS (CI) $C_{21}H_{34}O_4$ ($M+NH_4^+$) required 350.2457; found 350.2521.

Synthesis of (±)-4-((3*R,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)-4-hydroxypentyl pivalate 413.**



412 **413**

To a solution of ketone **412** (100 mg, 0.286 mmol, 1 eq) in anhydrous THF (2 mL) was added methylmagnesium bromide (2M in THF, 0.286 mL, 0.57 mmol, 2 eq) at -78°C. After 3 hours stirring at 17 °C, the reaction was quenched with 1M $HCl_{(aq)}$ (100 mL), and extracted with ether (3x5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the product **413** (70 mg, 71% yield) as a clear oil with no further purification necessary.

δ_H(300MHz, $CDCl_3$) 0.82 (3H, d, *J*= 7 Hz), 0.99 (3H, d, *J*= 7 Hz), 1.20 (3H, s), 1.24 (9H, s), 1.42 (2H, m), 1.57 (1H, dd, *J*= 4 and 12 Hz), 1.67 (3H, s), 1.71-2.05 (6H, m), 2.16 (1H, ddd, *J*= 1, 4 and 7 Hz), 2.61 (1H, m), 3.51 (1H, dd, *J*= 1 and 8 Hz), 3.82 (1H, d, *J*= 4 Hz), 4.05 (3H, m), 5.53 (1H, bs).

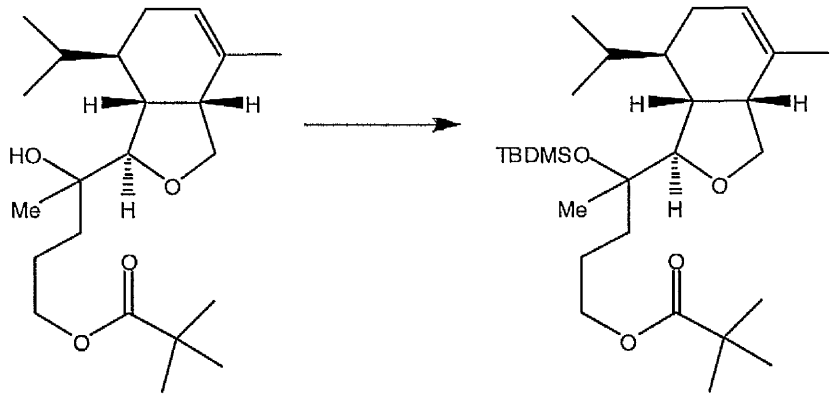
δ_C(75MHz, $CDCl_3$) 17.0, 22.2, 22.7, 22.9, 23.0, 23.5, 27.5, 27.7, 33.9, 39.0, 39.4, 40.4, 45.1, 65.2, 72.5, 74.5, 89.3, 122.3, 131.7, 178.9.

ν_{max}(evaporated film) 1728, 2872, 2931, 2960, 3499 cm^{-1}.

M/z (CI) 179 (20%), 349 (90%), 367 (10%, $M+H^+$).

HRMS (CI) $C_{22}H_{38}O_4$ required 366.2770; found 366.2795.

Synthesis of (±)-4-((3*R,3a*R**,4*R**,7a*S**)-1,3,3a,4,5,7a-hexahydro-4-isopropyliso-benzofuran-3-yl)-4-(*tert*-butyldimethylsilyl)pentyl pivalate 414.**



413 414

Secondary alcohol **4134** (70 mg, 0.19 mmol, 1 eq) was dissolved in anhydrous DCM (5 mL) and cooled to -10 °C. To the chilled solution was added 2,6-lutidine (81.5 mg, 0.76 mmol, 4 eq) and TBDMS triflate (100 mg, 0.38 mmol, 2 eq) and the reaction mixture was stirred for a further hour before slowly warming to 17 °C. Additional stirring for another hour was followed by quenching with saturated ammonium chloride solution (5 mL) with the organic layer being washed with brine (5 mL), dried ($MgSO_4$), and solvent evaporated to dryness under reduced pressure. The resulting crude material was subjected to column chromatography (20% EtOAc/ 80% petrol) affording the *title compound* as a clear viscous oil (86 mg, 94% yield).

δ_H(300MHz, $CDCl_3$) 0.16 (6H, d, *J*= 3 Hz), 0.86 (3H, d, *J*= 7 Hz), 0.92 (9H, s), 1.00 (3H, d, *J*= 7 Hz), 1.24 (9H, s), 1.32 (3H, s), 1.45 (2H, m), 1.67 (3H, m), 1.74 (2H, m), 2.02 (2H, m), 2.41 (1H, ddd, *J*= 2, 5 and 7 Hz), 2.65 (1H, q, *J*= 7 Hz), 3.60 (1H, t, *J*= 7 Hz), 3.73 (1H, d, *J*= 5 Hz), 4.04 (3H, m), 5.49 (1H, bs).

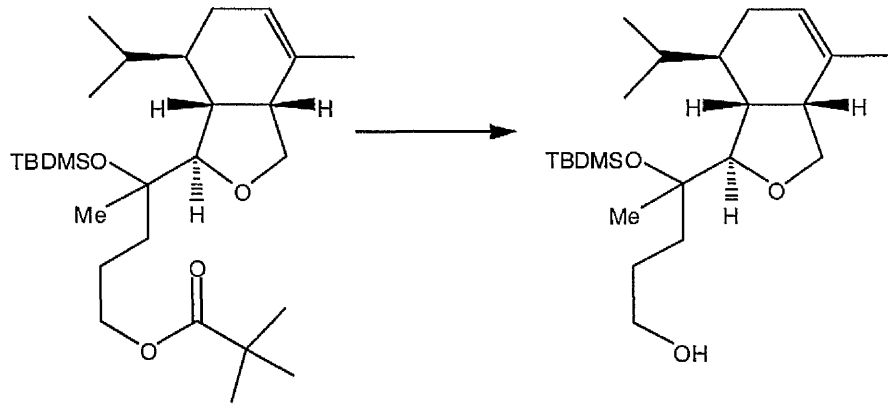
δ_C(75MHz, $CDCl_3$) -2.6, -1.6, -1.3, 19.2, 22.1, 22.5, 23.5, 23.7, 24.1, 26.0, 26.5, 27.5, 28.3, 36.9, 39.0, 39.2, 40.4, 43.8, 65.2, 71.6, 78.2, 86.8, 121.8, 132.7, 178.9.

ν_{max}(evaporated film) 1730, 2857, 2930 cm^{-1}.

M/z (CI) 179 (20%), 349 (30%), 467 (60%, $M+H^+$).

HRMS (CI) $C_{28}H_{52}O_4Si$ required 480.3635; found 480.3698.

Synthesis of (±)-4-((3*R,3a*R**,4*R**,7a*R**)-1,3,3a,4,5,7a-hexahydro-4-isopropyl-7-methylisobenzofuran-3-yl)-4-(*tert*-butyldimethylsilyl)pentan-1-ol 415.**



414 **415**

To a solution of **414** (80 mg, 0.17 mmol, 1 eq) in DCM (2 mL) was added diisobutylaluminium hydride (0.25 mL, 0.25 mmol, 1.0 M in cyclohexane, 1.5 eq), at -78°C, and the resulting solution was stirred for 1 hour. The reaction was quenched by addition of a saturated solution of sodium potassium tartrate (1 mL) and the aqueous phase extracted repeatedly with dichloromethane (3x 2 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOAc/ 95% petrol) affording the primary alcohol **415** as an off-white solid (42 mg, 65% yield).

δ_H(400MHz, $CDCl_3$) 0.00 (3H, s), 0.02 (3H, s), 0.72 (3H, d, *J*= 7 Hz), 0.76 (9H, s), 0.84 (3H, d, *J*= 7 Hz), 1.16 (3H, s), 1.28-1.35 (2H, m), 1.51 (3H, s), 1.52-1.63 (4H, m), 1.78-1.90 (2H, m), 2.25-2.29 (1H, m), 2.52 (1H, bq, *J*= 7 Hz), 3.42 (1H, t, *J*= 7 Hz), 3.47-3.52 (2H, m), 3.61 (1H, d, *J*= 5 Hz), 3.88 (1H, t, *J*= 7 Hz), 5.33 (1H, bs).

δ_C(75MHz, $CDCl_3$) -1.6, -1.3, 18.6, 19.2, 22.0, 22.4, 23.6, 24.2, 26.4, 27.4, 28.3, 36.6, 39.1, 40.3, 43.6, 63.7, 71.5, 78.2, 86.4, 121.7, 132.6.

ν_{max}(evaporated film) 1740, 2840, 2920 cm^{-1}.

M/z (CI) 120 (30%), 180 (75%), 396 (100%).

HRMS (CI) $C_{23}H_{44}O_4Si$ required 396.3060; found 396.3092.

Chapter 11. References

1. B. Giese, B. Kopping, T. Gobel, J. Dickhaut, G. Thoma, K. J. Kulicke and F. Trach, *Org. React.*, 1996, **48**, chapter 2, 301.
2. M. S. Kharasch, E. V. Jenson and W. H. Urry, *Science,* 1945, **102**, 128.
3. a) D. P. Curran, *Synthesis*, 1988, 417-439; b) A. J. Clarke, *Chem. Soc. Rev.*, 2002, **31**, 1-11..
4. D. T. Davies, N. Kapur and A. F. Parsons, *Tetrahedron. Lett.*, 1999, **40**, 8615.
5. K. Matyjaszewski and J. Xia, *Chem. Rev.*, 2001, **101**, 2921.
6. H. Nagashima, H. Wakamatsu, K. Itoh, Y. Tomo and J. Tsuji, *Tetrahedron Lett.*, 1983, **24**, 2395.
7. H. Nagashima, K. Seki, N. Ozaki, H. Wakamatsu, K. Itoh, Y. Tomo and J. Tsuji, *J. Org. Chem.*, 1990, **55**, 985.
8. H. Nagashima, H. Wakamatsu and K. Itoh, *J. Chem. Soc. Chem. Commun.*, 1984, 652.
9. D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of radical reactions*, VCH, 1995.
10. D. P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746.
11. H. Nagashima, N. Ozaki, M. Ishii, K, Seki and K. Itoh, *J. Org. Chem.*, 1989, **54**, 4497.
12. H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama, and K. Itoh, *J. Org. Chem.*, 1993, **58**, 464.
13. F. O. H. Pirrung, W. J. M. Steeman, H. Hiemstra and W. N. Speckamp, *Tetrahedron Lett.*, 1992, **33**, 5141.
14. F. O. H. Pirrung, H. Hiemstra and W. N. Speckamp, *Tetrahedron*, 1994, **50**, 12415.
15. a) H. Nagashima, H. Wakamatsu, N. Ozaki, T. Ishii, M. Watanabe, T. Tajima and K. Itoh, *J. Org. Chem.*, 1992, **57**, 1682; b) Y. Motoyama, S. Hanada, S. Niibayashi, K. Shimamoto, N. Takaoka, and H. Nagashima, *Tetrahedron*, 2005, **61**, 10216-10226.
16. H. Ishibashi, N. Uemura, H. Nakatami, M. Okazaki, T. Sato, N. Nakamura and M. Ikeda, *J. Org. Chem.*, 1993, **58**, 2360.
17. a) D. Fengas, *PhD Thesis*, 2001; b) S. Clarke and P. Quayle, *Unpublished results*; c) D. Fengas, P. Quayle and S. Richards, *Synlett*, 2003, **12**, 1797.
18. H. Nagashima, K. Matsubara, H. Kondo and S. I. Iwamatsu, *Tetrahedron*, 1999, **55**, 1687.

19. a) K. Matyjaszewski, T. Pattern and J. Xia, *J. Am. Chem. Soc.*, 1997, **119**, 674; b) N. V. Tsarevsky, W. A. Braunecker, W. Tang, S. J. Brooks, K. Matyjaszewski, G. R. Weisman and E. H. Wong, *J. Mol. Cat. A: Chem*, 2006, **257**, 132-140; c) A. J. Clarke, G. M. Battle, A. M. Heming, D. M. Haddleton and A. Bridge, *Tetrahedron Lett.*, 2001, **42**, 2003. d) F. Ghelfi and A. F. Parsons, *J. Org. Chem.*, 2000, **65**, 6249; e) A. J. Clarke, R. P. Filik and G. H. Thomas, *Tetrahedron Lett.*, 1999, **40**, 4885.

20. D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of radical reactions*, VCH, 1995.

21. R. T. Weavers and S. D. Mawson, *Tetrahedron*, 1995, **51**, 11257.

22. A. Porta, S. Re, G. Zanoni, G. Vidari, *Tetrahedron*, 2007, **63**, 3989-3994.

23. H. Yorimitsu, T. Nakamura, H. Shinokubo, K. Oshima, K. Omoto, and H. Fujimoto, *J. Am. Chem. Soc.*, 2000, **122,** 11041

24. R. R. Schrock, J. S. Murdzek, G. C. Bazan, M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875.

25. a) P. Schwab, M. B. France, J. W. Ziller, and R. H. Grubbs, *Angew Chem., Int. Ed. Engl.* 1995, **34**, 2039; b) P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.* 1996, **118**, 100-110; c) T. R. Belderrain and R. H. Grubbs, *Organometallics* 1997, **16,** 4001.

26. R. H. Grubbs and G. C. Fu, *J. Am. Chem. Soc.*, 1992, **114**, 5426.

27. a) H. Mitutain, M. Watanabe, and T. Honda, *Tetrahedron*, 2002, **58**, 8929. b) J. S. Kingsbury, J. P. Harrity, P. J. Bonitatebus, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1999, **121**, 791.

28. M. E. Jung, *Synlett*, 1999, 843.

29. A. Fürstner and T. Müller, *Synlett.*, 1997, 1010.

30. a) Z. Yang, Y. He, D. Vourloumis, H. Vallberg, and K. C. Nicolaou, *Angew. Chem.*, 1997, **109**, 170; b) K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, and J. I. Trujillo, *J. Am. Chem. Soc.*, 1997, **119**, 7960; c) D. Meng, P. Bertinato, A. Balog, D.S. Su, T. Kamenecka, E. J. Sorensen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1997, **119**, 10073; d) D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, and M. Cordes, *Angew. Chem.* 1997, **109**, 543; e) D. Schinzer, A. Bauer, O. M. Böhm, A. Limberg, and M. Cordes, *Eur. J. Chem.*, 1999, **5**, 2483.

31. N. Diethiens, C. V. Stevens, D. De Vos, B. A. Haert, R. Drozdzak, and F. Verpoort, *Tet. Lett.*, 2004, **45**, 8995.

32. V. Declerck, P. Ribiere, J. Martinez, and F. Lamaty, *J. Org. Chem.*, 2004, **69**, 8372.

33. O. Fujimura, R. H. Grubbs and G. C. Fu, *J. Org. Chem.*, 1994, **59**, 4029.

34. W. A. L. van Otterio, E. L. Ngidi, E. M. Coyanis and C. B. de Koning, *Tetrahedron Lett.*, 2003, **44**, 311.

35. I. S. Young and M. A. Kerr, *J. Am. Chem. Soc.*, 2007, **129**, 1465-1469.

36. S. Blechart and J. J. Connan, *Angew. Chem. Int. Ed.*, 2003, **42**, 1900.

37. A. K. Chatterjee, T. L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.,* 2003, **125**, 11360.

38. F. E. McDonald and X. Wei, *Org. Lett.*, 2002, **4**, 593.

39. T. J. Donohoe, R. M. Harris, J. Burrows, J. Parker, *J. Am. Chem. Soc.,* 2006, **128**, 13704.

40. a) L. A. Paqette and P. Bernardelli, *Hetrocycles*, 1998, **49**, 531; b) D.J. Faulkner, *Nat. Prod. Rep.* 2001, **18**, 1-49; c) A. Rodriguez, *Tetrahedron* 1995, **51**, 4571.

41. M. Alam, P. Sharma, A. S. Zektzer, *J. Org. Chem.* 1989, **54**, 1896-1900.

42. K. Yamada and N. Ogata, *J. Nat. Prod.* 1997, **60**, 393-396.

43. The opposite absolute configuration has been suggested for one cladiellin diterpene as a result of Horeau analysis.

44. O. Kennard, D.G. Watson, and R. Djerassi, *Tetrahedron Lett.* 1968, 2879-2884.

45. H. M. R. Hoffmann and M. Nowakowski, *Tetrahedron*, 1997, **53**, 4331.

46. J. S. Clark and Y. S. Wang, *J. Chem. Soc. Chem. Commun.*, 2000, 1079.

47. Y. Chai, D. Vicic and M. C. McIntosh, *Org. Lett., 2003,* **7**, 1039.

48. J. M. Hutchison, H. A. Lindsay, S. S. Dormi, G. D. Jones, D. A. Vicic, M. C. McIntosh, *Org. Lett.*, 2006, **17**, 3663-3665.

49. L. E. Overman and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 1995, **117**, 10391.

50. (a) A. Furstner, N. Shi, *J. Am. Chem. Soc.* 1996, **118**, 12349. (b) H. W. Choi, K. Nakajima, D. Demeke, F. A. Kang, H. S. Jun, Z. K. Wan, Y. Kishi, *Org. Lett.* 2002, **4**, 4435.

51. a) L. D. Pennington, L. E. Overman and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 9033; b) L. D. Pennington, L. E. Overman, D. W. C. MacMillan, F. Gallou, L. A. Paquette, and J. Yang, *Org. Lett.*, 2001, **3**, 135.

52. a) L. D. Pennington and L. E. Overman, *Org. Lett.*, 2000, **2**, 2683; b) P. Bernardelli, O. M. Moradei, D. Friedrich, J. Yang, F. Gallou, B. P. Dyck, R. W. Doskotch, T. Lange, and L. A. Paquette, *J. Am. Chem. Soc.*, 2001, **123**, 9021.

53. L. D. Pennington, L. E. Overman and O. Corminboeuf, *J. Am. Chem. Soc.*, 2003, **125**, 6650.

54. G. A. Molander, D. J. St. Jean, Jr., and J. Haas, *J. Am. Chem. Soc.*, 2004, **126**, 1642.

55. M. T. Crimmins and J. M. Ellis, *J. Am. Chem. Soc.*, 2005, **127**, 17200.

56. M. T. Crimmins and B. H. Brown, *J. Am. Chem. Soc.*, 2004, **126**, 10264.

57. M. T. Crimmins, B. H. Brown, and H. R. Plake, *J. Am. Chem. Soc.*, 2006, **128**, 1371.

58. M. Alam, P. Sharma and A. S. Zektzer, *J. Org. Chem.* 1989, **54**, 1896-1900

59. L. A. Paquette, O. M. Moradei, and P. Bernardelli, *Org. Lett.*, 2000, **13**, 1875-1878

60. M. T. Crimmins and B. H. Brown, *J. Am. Chem. Soc.* 2004, **126**, 10264

61. J. S. Clark, S. T. Hayes, C. Wilson and L. Gobbi, *Angew. Chem. Int. Ed.*, 2007, **46**, 437-440.

62. H. Kim, H. Lee, J. Kim, S. Kim, and D. Kim, *J. Am. Chem. Soc.*, 2006, **128**, 15851.

63. J.A. Tallarico, L.M. Malnick and M.L. Snapper, *J. Org. Chem.,* 1999, **64,** 344.

64. J. Faulkner, C. D. Edlin, D. Fengas, I. Preece, P. Quayle and S. N. Richards, *Tetrahedron Lett.*, 2005, **46**, 2381-2385.

65. D. Fengas, *PhD Thesis*, 2001.

66. C. D. Edlin, J. Faulkner, D. Fengas, C. K. Knight, J. Parker, I. Preece, P. Quayle and S. N. Richards, *Synlett* 2005, **4**, 572-576.

67. Q. Yang, W. J. Xiao and Z. Yu, *Org. Lett.*, 2005, **7**, 871-874 .

68. J. L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226.

69. D. Urabe, K. Sugino, T. Nishikawa and M. Isobe, *Tetrahedron Lett.*, 2004, **45**, 9405.

70. S. Kim, T. Lee, E. Lee, J. Lee, G. J. Fan, S. K. Lee and D. Kim, *J. Org. Chem.* 2004, **69**, 3144-3149.

71. B. A. Seigal, C. Fajardo and M. L. Snapper, *J. Am. Chem. Soc.*, 2005, **127**, 16329.

72. C. K. Knight, *PhD Thesis*, 2003.

73. L. Ackermann and D. E. Furstner, *Tetrahedron*, 2000, **56**, 2195, b) J. C. Y. Wong, *Tetrahedron Lett.*, 1998, 9623.

74. J. E. Baldwin and R. C. Whitehead, *Tetrahedron*, 1997, **53**, 2271.

75. J. Daisy and L. Overman, *Tetrahedron Lett.*, 1997, **38**, 8635.

76. P. Wipf and S. Lim, *Angew. Chem.*, 1993, **105**, 1095.

77. O. Nobuhisa and E. Negishi, *Tetrahedron Lett.*, 1978, **27**, 2357.

78. O. Corminboeuf, L. E. Overman and L. D. Pennington, *J. Am. Chem. Soc.*, 2003, **125**, 6650.

79. K. Takai, K. Kimura, T. Hiyama and H. Nozaki, *Tetrahedron Lett.*, 1983, **47**, 5281.

80. a) H. Takei, *Bull. Chem. Soc. Jap*, 1979, **52**, 1953; b) M. Szlosek, X. Franck, B. Frigadere and A. Cave, *J. Org. Chem.*, 1998, **63**, 5169 .

81. S. Hanessian and T. A. Grillo, *J. Org. Chem.*, 1998, **63**, 1049.

82. C. Jefford, D. Jaggi and J. Boukouvalas, *Tetrahedron Lett.*, 1987, **35**, 4037.

83. P. Quayle, *Unpublished results.*

84. R. B. Miller, G. McGarvey, *Syn. Comm.*, 1978, **8**, 291-9.

85. H. Nagashima, Y. Isomo and S-I. Iwamatsu, *J. Org. Chem.*, 2001, **66**, 315.

86. M.A. Rachita and G.A. Slough, *Tetrahedron Lett.*, 1993, **43**, 6821.

87. A.J. Clark, D.J. Duncalf, R.P. Filik, D.M. Haddleton, G.H. Thomas and H. Wangtap, *Tetrahedron Lett.*, 1999, **40**, 3807.

88. J.R. Henry, L.R. Marcin, M.C. McIntosh, P.M. Scola, G. Harris and S.M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 5709.

89. K. Matyjaszwski, T.Pattern and J. Xia, *J. Am. Chem. Soc.*, 1997, **119**, 674.

90. K. Yasui, Y. Goto, T. Yajima, Y. Taniseki and K. Fugami, *Tetrahedron Lett.*,1993, **34**, 7619.

91. B.-W. Au-Yeung and I. Fleming, *J. Chem. Soc., Chem. Commun.*, 1977, 79-80.

92. H. Nagashima, Y. Isono and S. Iwamatsu, *J. Org. Chem.*, 2001, **66**, 315 - 319.

93. Y. Motoyama, M. Gondo, S. Masuda, Y. Iwashita and H. Nagashima, *Chem. Lett.*, 2004, **33**, 442 - 443.

94. T. Hayashi, K. Yamasaki, M. Mimura and Y. Uozumi, *J. Am. Chem. Soc.*, 2004, **126**, 3036 - 3037.

95. R. Nakajima, Y. Takayama and F. Sato, *Angew. Chem. Int. Ed.*, 2002, **41**, 3023.

96. A. Avetolor and J. S. Panek, *J. Am. Chem. Soc.*, 2005, **127**, 5234.

97. M. Rowley and Y. Kishi, *Tetrahedron Lett.*, 1998, **39**, 4909-12.