UNIVERSITY OF SOUTHAMPTON

FACULTY OF SCIENCE

SCHOOL OF CHEMISTRY

The Ring-Closing Metathesis of Vinyl Fluoro- and Bromo-Containing Dienes
Synthesis of (±)-Deoxygalanthamine

by

Vachiraporn Satcharoen

A thesis submitted for the degree of Doctor of Philosophy

January 2006

Correction Sheet

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

SCHOOL OF CHEMISTRY

Doctor of Philosophy

The Ring-Closing Metathesis of Vinyl Fluoro- and Bromo-Containing Dienes Synthesis of (±)-Deoxygalanthamine

By Vachiraporn Satcharoen

Metathesis-based methodology has been developed for the synthesis of a variety of heterocyclic and carbocyclic molecules containing fluorinated double bonds. The introduction of fluoro-olefins into acyclic and cyclic compounds is a valuable synthetic method and is relevant to the synthesis of fluorine containing biologically significant molecules. Cyclic sulfamides containing fluoro-olefins, which are novel analogues of potent HIV protease inhibitors have been synthesised, *via* the ring-closing metathesis reaction. Competition experiments were designed to compare the reactivity of fluorinated olefins with unfluorinated olefins. These metathesis reactions showed that fluoro-olefins were less reactive than their unfluorinated analogues reactions in the presence of the ruthenium alkylidene species **4**. The methodology has been used to synthesise various vinyl-fluoride carbocycles and heterocycles in good to excellent yield. RCM of vinyl bromides was also investigated, and found to proceed efficiently in a few cases. However, the RCM of vinyl bromides using Grubbs-type catalysts appears to be more limited in scope that the corresponding reactions of vinyl fluorides and vinyl chlorides. Significant limitations to the bromo-olefins metathesis included formation of 5-membered and 6-membered ring systems.

The synthesis of (±)-deoxygalanthamine has been developed successfully using Mitsunobu reaction to synthesise the precursor for the subsequent enyne ring-closing metathesis. The resulting 1,3-diene cyclised product underwent hydroboration-oxidation in order to control the selectivity of an intramolecular Heck reaction to create the quaternary carbon centre of the galanthamine ring system.

Contents

Acknowledgements

I would like to thank Dr Richard Brown who has been an excellent supervisor. Without his encouraging, supportive and useful advice, I could not have come this far.

Special thanks to Prof. Jeremy Kilburn and Asst. Prof. Roderick Bates for leading me here, University of Southampton.

I would like to thank the analytical departments at Southampton, John Langley and Julie Herniman for all the help with mass spectroscopy analysis, Joan Street and Neil Wells for NMR experiments.

I also would like to thank to all the past and present members of Lab 3003 and 3005, especially Rick, Ian, Nev and Nadeem for helping me with proof reading. Many thanks to Sofia Salim for being helpful and friendly. Nittaya, Thomas, Yulai, Sally, Louise, Fra, Linda, Carole, Rowan, Steve, Claire, Simon, Sherrif, Ian, Pete and Aim for being good friends.

Thank you very much to Emma Thomas for making the duration of my Ph. D immeasurably more enjoyable then it otherwise have been.

I would like to thank Anawat for being kind, understanding and supportive at all time and in all conditions over the last three years.

Finally, I would like to thank my parents (Chaivichit and Patchanee Satcharoen) for always their support and good honor. I thank my brother (Krisada Satcharoen) and my sister (Supawan Satcharoen) for their friendship and encouragement.

Abbreviations

δ	chemical shift
μW	microwave irradiation
ACh	acetylcholine
AcCoA	acetylcoenzyme A
AChE	acetylcholinesterase
ADMET	acyclic diene metathesis polymerization
AIBN	azobisisobutyronitrile
arom	aromatic
br	broad
9-BBN	9-borabicyclononane
Boc	*t*-butoxycarbonyl
Cbz	benzyloxycarbonyl
CM	cross metathesis
CSI	chlorosulfonyl isocyanate
Cy	cyclohexyl
d	doublet(s)
DAST	diethylaminosulfur trifluoride
dba	*trans,trans*-dibenzylideneacetone
DBAD	dibutylazodicarboxylate
DEAD	diethylazodicarboxylate
d.e.	diastereoisomeric excess
DCM	dichloromethane
DIAD	di-*iso*-propylazodicarboxylate
DIBAL-H	di-*iso*-butylaluminium hydride
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dcpe	1,2-(dicyclohexylphosphino)-ethane
dppb	1,4-bis(diphenylphosphino)butane

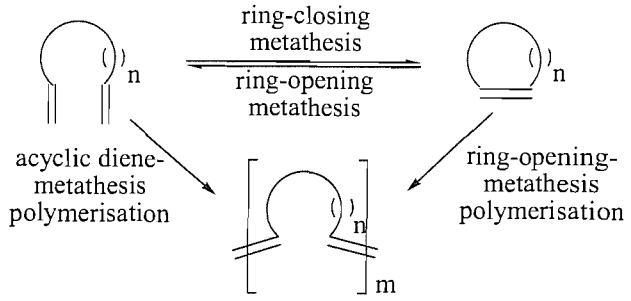
dppe	1,2-bis(diphenylphosphino)ethane
EDCI	*N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide
e.e.	enantiomeric excess
EI	electron impact ionization
equiv	equivalent
Et_2O	diethyl ether
EtOAc	ethyl acetate
FT	fourier transform
h	hour(s)
HIV	human immunodeficiency virus
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	*iso*-propyl
IR	infared
J	coupling constant
LDA	lithium di-*iso*-propylamide
m	multiplet(s)
m/z	mass to charge ratio
MeCN	acetonitrile
min	minute(s)
mmol	millimole(s)
MS	mass spectrometry
NaHMDS	sodium hexamethyldisilylamide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PCC	pyridinium chorochromate
Ph	phenyl
PhH	benzene
Piv	2,2-dimethylpropionate
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
Py	pyridine
q	quartet(s)
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride

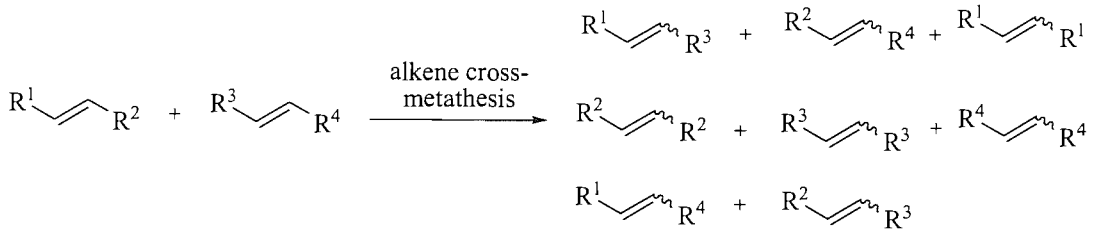
RCM	ring-closing metathesis
ROM	ring-opening metathesis
ROMP	ring opening metathesis polymerisation
s	singlet(s)
t	triplet(s)
t-Bu	*tert*-Butyl
TBAF	tetra-*n*-butylammoniumfluoride
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TlOAc	thallium acetate
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
UV	ultraviolet

Chapter 1
Introduction to metathesis

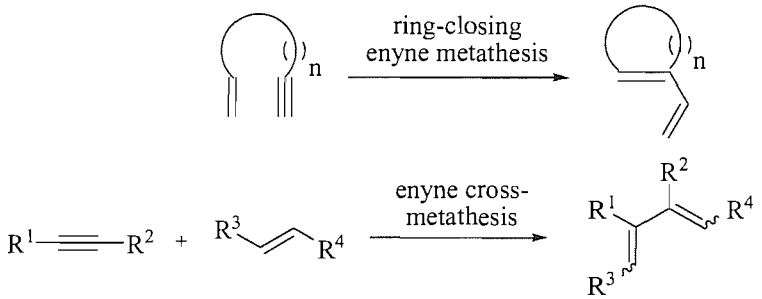
According to Nicolaou, Olefin metathesis is "marvelous in the hand of the synthetic chemist, today this powerful reaction provides solutions to many synthetic puzzles and has to do so in the future for myriad others" [1]

Olefin metathesis has been known since the 1950s involving rearrangement of unsaturated carbon-carbon bonds in the presence of metal carbene complexes.[2, 3] With the development of efficient catalysts, this reaction has become an extremely powerful tool for organic synthesis and polymer chemistry.[4] There are three important types of olefin metathesis:[5] the first type is alkene-metathesis reactions which comprise of ring-closing metathesis (RCM), ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis polymerization (ADMET) (**Scheme 1**). The second type is enyne-metathesis reactions which refer to the enyne ring-closing metathesis and enyne cross metathesis (**Scheme 2**). The last type is alkyne-metathesis reactions which involve alkyne ring-closing metathesis and alkyne cross metathesis (**Scheme 3**). Through these metathesis reactions a variety of unsaturated molecules can be obtained that would be challenging or even impossible to prepare by other means. Improved understanding of substrate and catalyst interactions has greatly contributed to the recent establishment of olefin metathesis as a synthetic method. Impressive applications of these reactions include the synthesis of heterocyclic and macrocyclic systems by RCM, the selective cross-metathesis of olefins with a functionalized partner, the use of ROMP to generate functionalized polymers and domino metathesis sequences that can greatly increase molecular complexity in a single synthetic step.[6, 7]

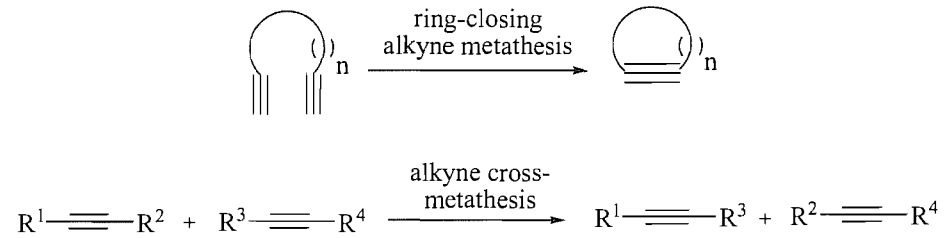




Scheme 1. Alkene-metathesis reactions.



Scheme 2. Enyne-metathesis reactions.



Scheme 3. Alkyne-metathesis reactions.

1.1 Metathesis catalysts

The widespread application of the metathesis reaction has arisen due to improvements in the functional group compatibility and the reactivity of the catalyst systems. There are two main types of catalysts in use today. The first group contains ruthenium-complexes, whereas the second group is based on a molybdenum metal centre. The Schrock-type molybdenum complex **1**[8, 9] exhibits higher reactivity

toward many diene substrates including sterically demanding and electron-deficient olefins. However, it also suffers from high sensitivity to air and moisture and certain polar or protic functional groups owing to the electrophilicity of the high-oxidation-state transition metal centre. Consequently, the ruthenium-based catalysts **2**,[10] **3**[11, 12] and **4**[13] have found more widespread use in organic synthesis due to superior stability, functional group compatibility and ease of storage and handling. The ruthenium alkylidene complex **2**[10] show high activity and stability toward functional groups and protic media. However, the multistep synthesis of the cyclopropene precursor and the low initiation rates of the resultant diphenylvinyl alkylidenes limit the utility of this catalyst. Interestingly, the "first-generation" Grubbs catalyst **3**[11, 12] displayed a remarkable tolerance to oxygen and moisture, in addition to a wide range of substrate functionality. However, it is less active than the molybdenum complex **1**. Further catalyst development by replacement of the one of the phosphine ligands with an *N*-heterocyclic carbene ligand led to the discovery of the "second-generation" Grubbs catalyst **4**[13] which exhibits extraordinary activity and stability. Recently, other advances in the development of metathesis catalysts have been the discovery of catalyst **5**[14] and the phosphine-free metathesis catalysts **6**,[15, 16] **7**,[17] **8**.[18] The first recyclable ruthenium-based catalyst **5** has been reported by Hoveyda *et al.*[14] This complex **5** demonstrated that a styrenyl ether ligand allows for the easy recovery of the ruthenium complex following metathesis, thus allowing the catalyst to be purified in high yield by flash chromatography. However, it's less reactive than the ruthenium catalyst **4**. More interestingly, Hoveyda and co-workers later developed a second-generation phosphine-free catalyst **6**.[15, 16] This complex **6** is highly reactive although it proved to undergo initialization slower than the ruthenium catalyst **4**. Blechert and Wakamatsu have shown recently that the replacement of the isopropoxybenzylidene ligand in the complex **6** by binol-based styrene **7**[17] or biphenyl-based benzylidene **8**[18] results in a dramatic improvement in catalyst activity. It was noted that increasing in steric bulk could improve the rate of ligand dissociation, thus facilitating formation of the catalytically active 14-electron species, and suppressing re-association to the metal centre, which supposedly deactivated the catalyst. To this end, a better appreciation of catalyst advancement can be attained after considering the mechanistic details of olefin metathesis.

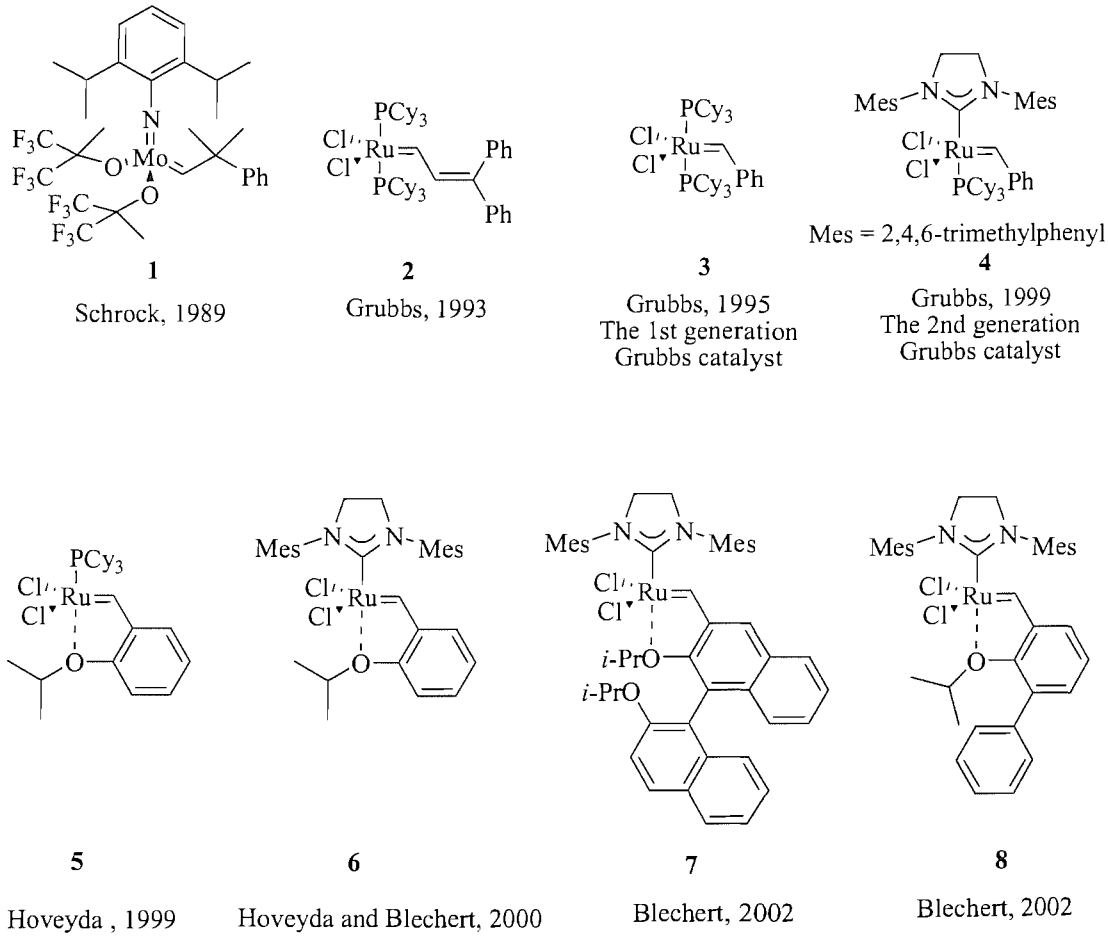
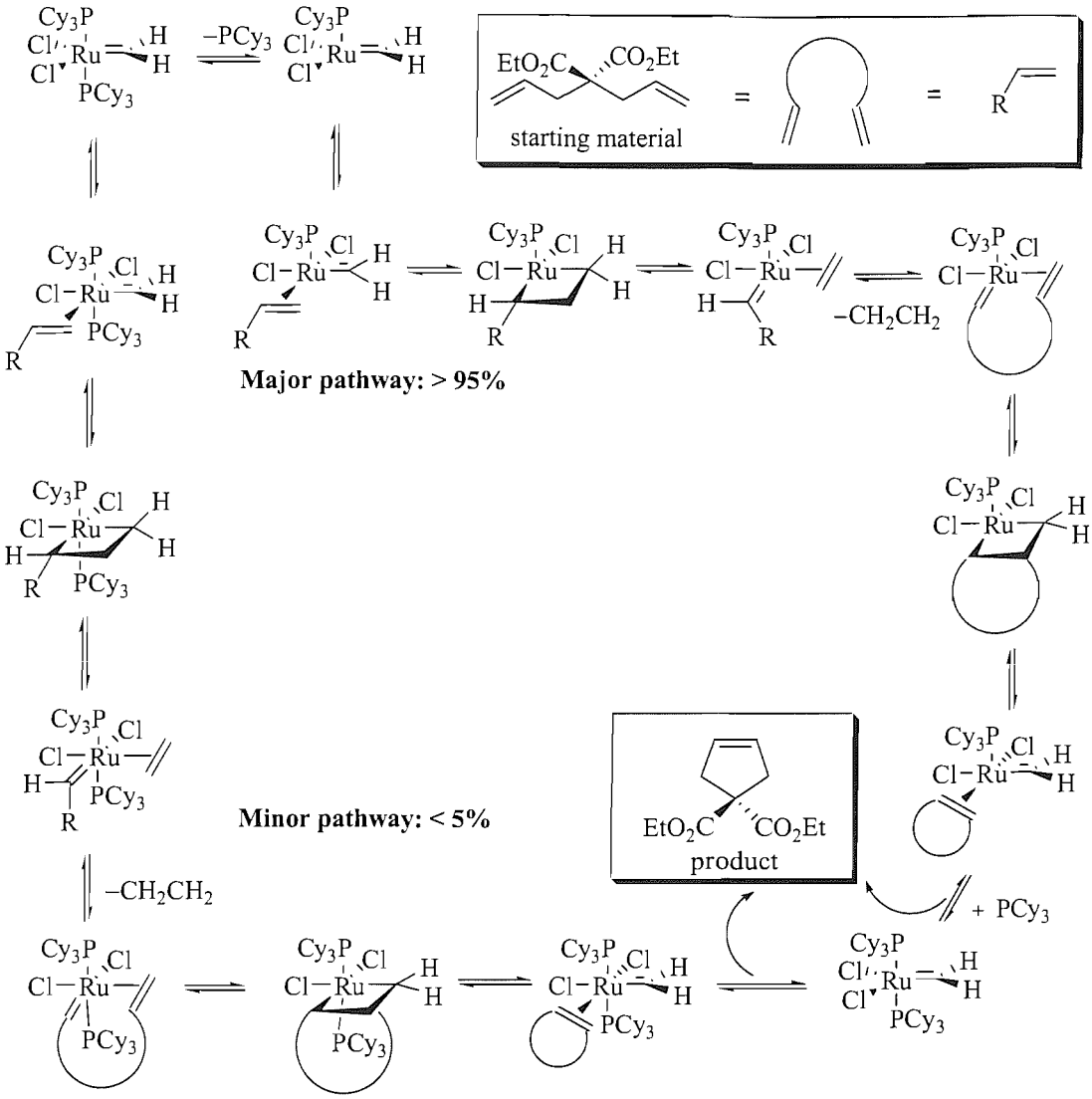


Figure 1. Commonly used metal alkylidene complexes for olefin metathesis.

1.2 Metathesis mechanism

The generally accepted mechanism for olefin metathesis involving metal alkylidene complexes proceeds by a series of formal [2+2] cycloadditions and cycloreversion reactions involving, metallocarbenes and metallacyclobutane intermediates. It has been found that the most significant operative pathway for Grubbs-type ruthenium catalysts involves dissociation of a phosphine ligand to generate a more active species (**Scheme 4**).[19] The olefin binding site is presumed to be *cis* to the carbene and *trans* to one of the chlorides. Subsequent dissociation of the phosphine paves the way for the formation of a 14-electron metallacycle which upon cycloreversion generates a productive intermediate.



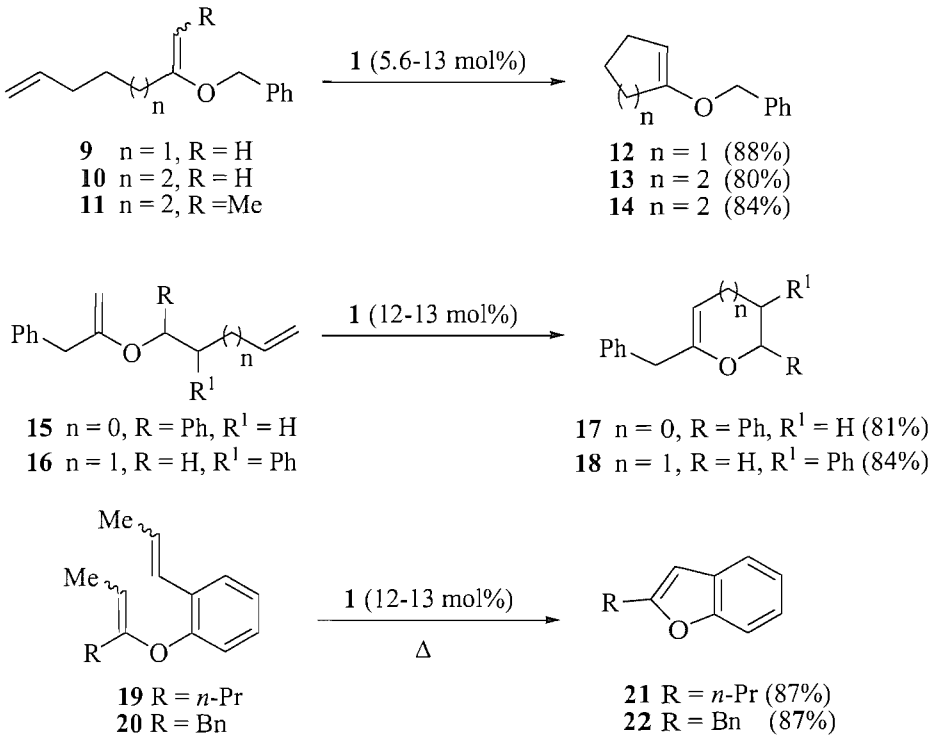
Scheme 4. Detailed mechanism for the ring-closing metathesis of diethyl diallylmalonate using $Cl_2(PCy_3)_2Ru{=}CH_2$.

1.3 Ring-closing metathesis of vinyl-substituted dienes

Ring-closing metathesis has been extensively explored as an annulation strategy. This methodology has been applied to construction of a variety of carbocyclic and heterocyclic ring systems including macrocycles. Moreover, RCM chemistry has been used as a pivotal step in total syntheses of complex natural products. However, there are some limitations of metathesis reactions involving participation of heteroatom-substituted olefins. In this section of this thesis, a summary and discussion of examples of RCM of heteroatom-substituted olefins will be presented.

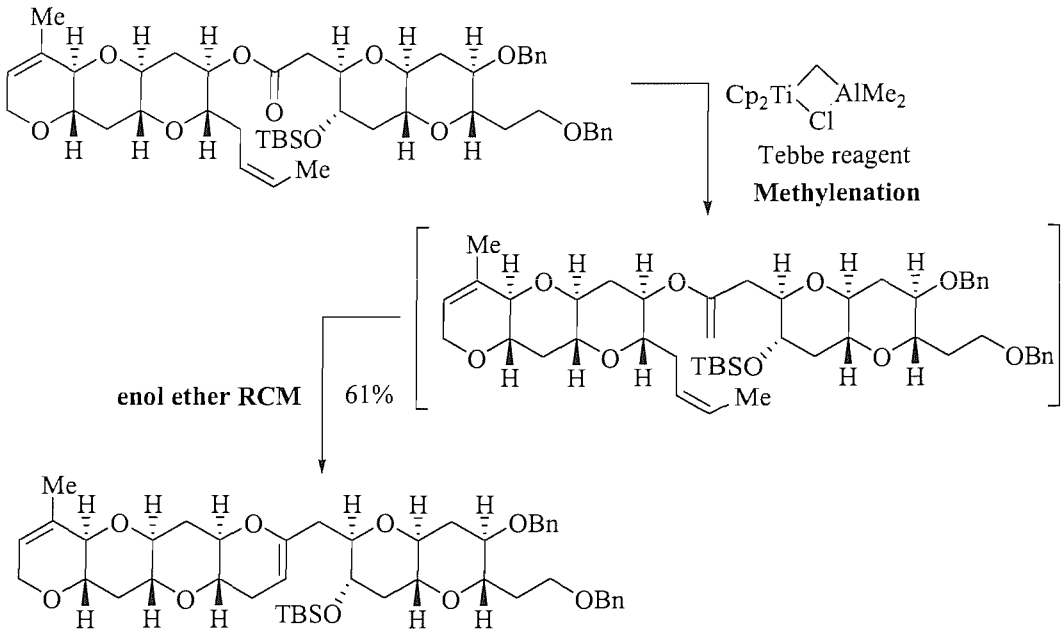
1.3.1 Ring-closing metathesis of vinyl ether-containing dienes

Since cyclic enol ethers are often found to be present in natural products and other biologically active molecules, the development of efficient methods for their construction has been an important goal in the field of organic synthesis. Indeed, it was recognized that RCM had considerable potential as synthetically useful tool in the construction of carbocycles and heterocycles.[20] The first examples of RCM of acyclic enol ethers using the Schrock molybdenum catalyst **1** were reported by Grubbs *et al.* (**Scheme 5**).[21] Interestingly, the use of ruthenium-based catalyst **3** failed to provide any of corresponding cyclic enol ether. It has been postulated that the carbene resulting from the initial metathesis of the vinyl ether and ruthenium catalyst **3** seemed to be inert to further reaction.[2, 21]



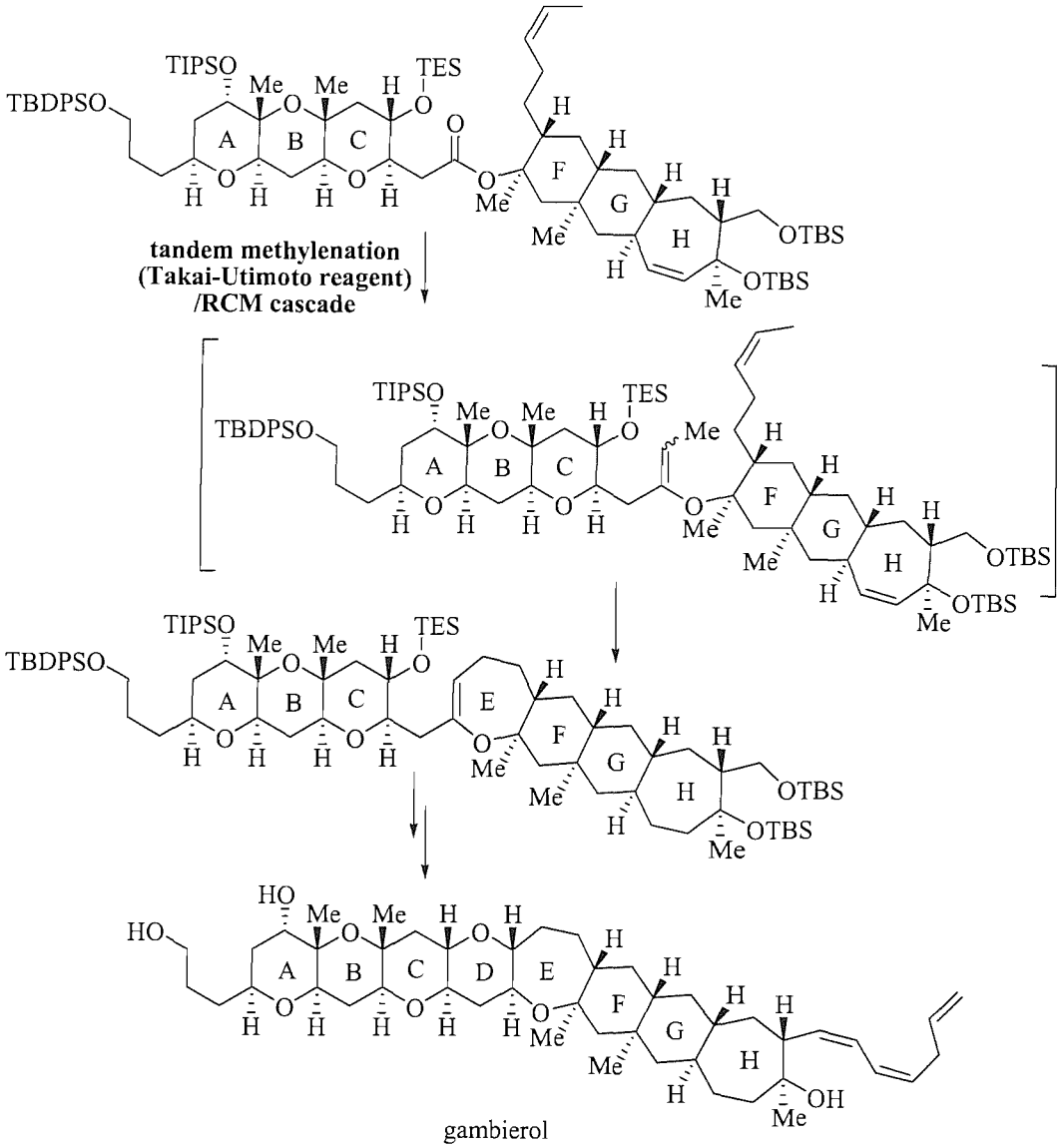
Scheme 5. RCM of acyclic enol ethers by Grubbs and co-workers.

More interestingly, another synthetic approach to synthesize the cyclic enol ethers using stoichiometric Tebbe-type reagent was demonstrated by Nicolaou and co-workers. The sequence is believed to commence with the initial methylenation of the ester carbonyl group with subsequent alkene metathesis (**Scheme 6**).[22] More specifically, this developed methodology was employed to construct the ring system in the complex marine natural product maitotoxin.[23]



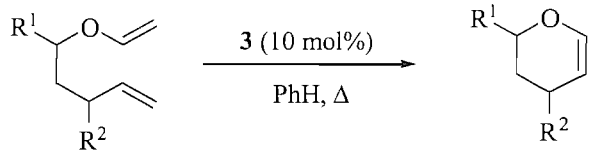
Scheme 6. Methylenation and subsequent ring-closing metathesis with Tebbe reagent by Nicolaou and co workers.

More recently, Rainier and co-workers have described an impressive example of the use of this type of tandem methylenation and subsequent ring-closing metathesis cascade sequence in their total synthesis of the polyether toxin gambierol (**Scheme 7**).[24]



Scheme 7. Total synthesis of gambierol using tandem methylenation/ RCM by Rainier and co-workers.

Despite discouraging results from the early examples of enol ether RCM when using the ruthenium-based catalyst **3**, Sturino *et al.* demonstrated that the use of ruthenium catalyst **3** under optimized conditions (reflux in benzene) allowed effective RCM of vinyl ether substrates **23a** to produce cyclic ether **24a** in excellent yields. In contrast, the alkoxy substituted diene **23b** failed to give the cyclised product **24b** (**Scheme 8**).[25] The authors suggested that the successful RCM of diene **23** was probably due to a favourable substitution pattern in the vinyl ether substrate **23a**.

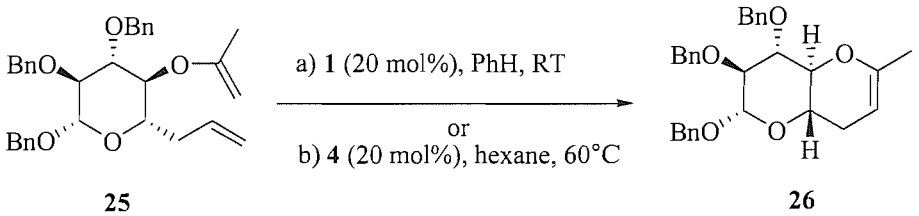


23a $R^1 = (CH_2)_2Ph$, $R^2 = H$
23b $R^1 = H$, $R^2 = OBn$

24a $R^1 = (CH_2)_2Ph$, $R^2 = H$ (95%)
24b $R^1 = H$, $R^2 = OBn$ (not observed)

Scheme 8. RCM of vinyl ethers by using the first generation Grubbs catalyst **3**.

Rainier and co-workers have reported the use of the second generation Grubbs catalyst **4** in enol ether-olefin RCM reactions (**Scheme 9**).[26] When the *β*-C-glycoside **25** was exposed to metathesis conditions utilizing the second generation Grubbs catalyst **4**, the bicyclic enol ether **26** was isolated in high yield. Similar results were obtained using the molybdenum catalyst **1** with this substrate.

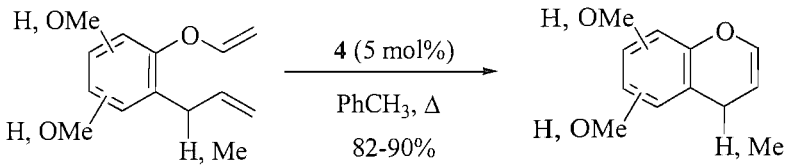


25 **26**

89% using either **1** or **4**

Scheme 9. RCM of *β*-C-glycoside **25** by Rainier and co-workers.

In order to explore the utility of enol ether-olefin RCM, van Otterlo recently reported the first examples of RCM for a series of five phenolic vinyl ethers **27** in the presence of 5 mol% of the second generation Grubbs catalyst **4** to deliver 4*H*-chromenes **28** in good to excellent yields (**Scheme 10**).[27]

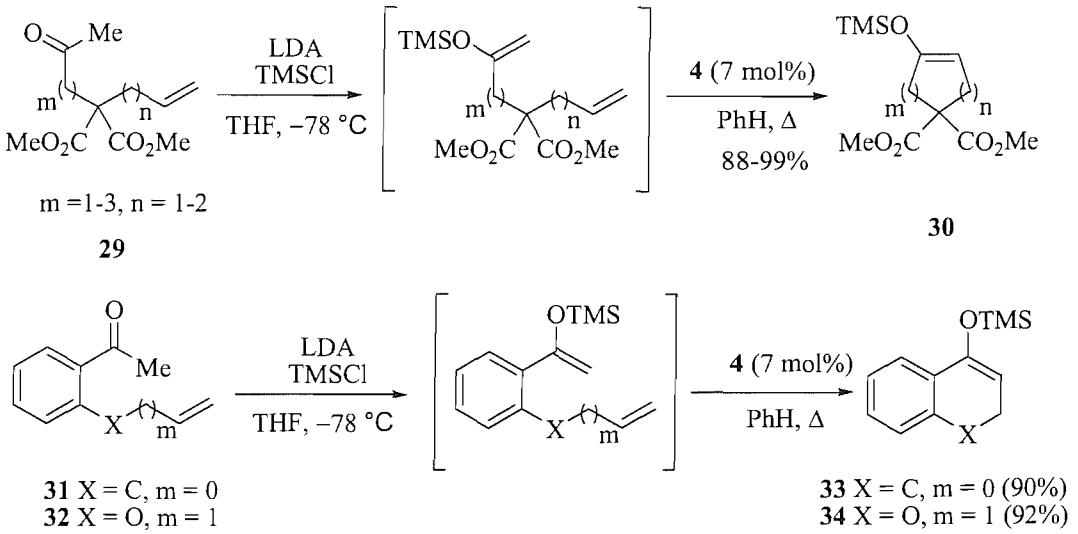


27 **28**

Scheme 10. RCM of phenolic vinyl ethers by van Otterlo.

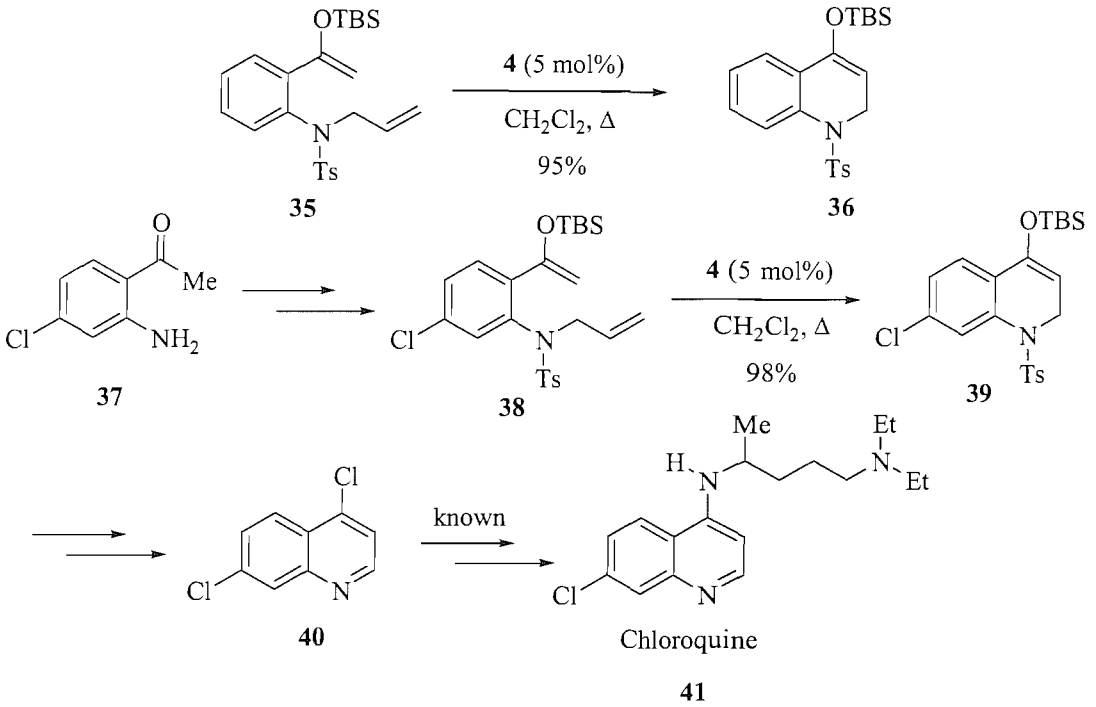
After experiencing the problem of poor regioselectivity in the formation of cyclic enol silyl ethers by using classical methods, Okada and co-workers have developed

the first highly regioselective synthesis of cyclic enol silyl ethers using intramolecular RCM reactions (**Scheme 11**).[28] The second generation Grubbs catalyst **4** promoted RCM of a variety of acyclic enol ethers to furnish five- to seven-membered rings in good to excellent yields. The products are versatile intermediates as they can be used for a variety of further transformations.



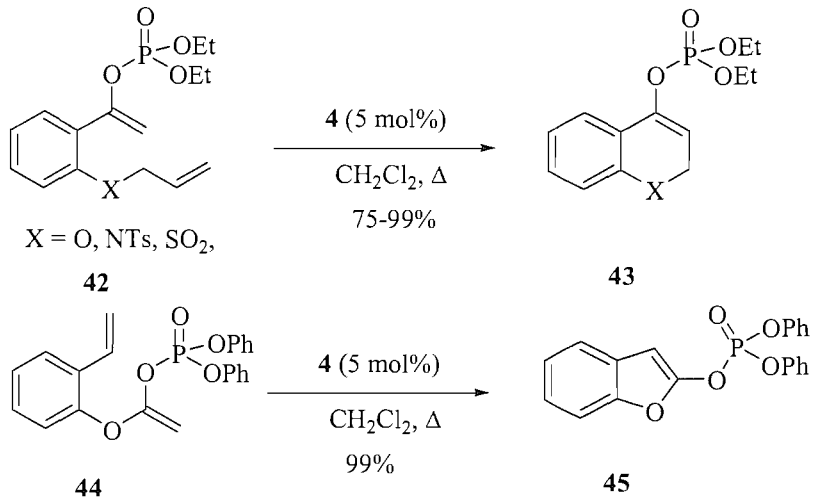
Scheme 11. RCM of a variety of acyclic enol ethers, developed by Okada.

As part of an investigation into the RCM of enol silyl ethers, Arisawa and co-workers reported examples of enol silyl ether-ene metathesis to produce the corresponding cyclic products (**Scheme 12**).[29, 30] They found that an enol TBS ether successfully underwent cyclisation to give the expected 4-siloxy-1,2-dihydroquinoline **36** in excellent yield. Having succeeded in developing an efficient synthesis of quinoline building blocks, this methodology was applied to the synthesis of anti-malarial compounds such as quinine, chloroquine **41** (**Scheme 12**) and a PPMP-quinine hybrid.[31]



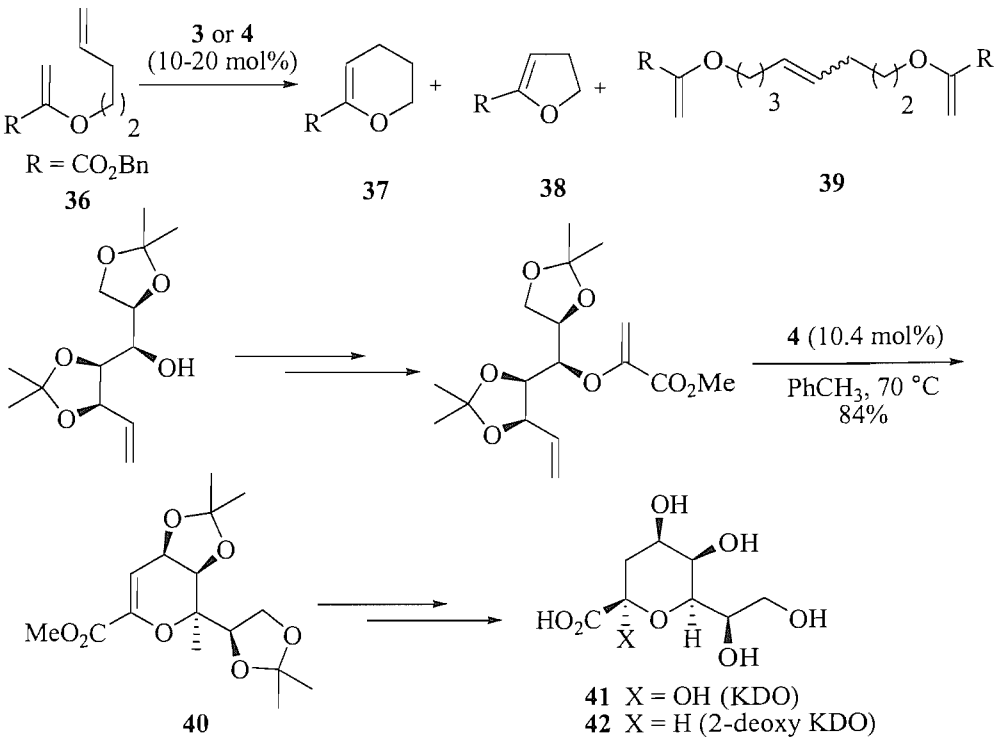
Scheme 12. Ene-enol ether metathesis and the preparation of chloroquine **41** by Arisawa and co-workers.

Following the success of the RCM of enol silanes, Whitehead and co-workers demonstrated the first examples of RCM reactions on enol phosphate templates to provide a variety of cyclic enol phosphates (**Scheme 13**).[32] The phosphate moiety has been recognized as a robust and versatile precursor in cross coupling reactions catalyzed by Pd(0) and Ni(0) to construct various substituted heterocyclic compounds.[33]



Scheme 13. RCM reactions on enol phosphate templates discovered by Whitehead and co-workers.

Interestingly, Hecking and co-workers presented examples of the RCM of olefins substituted with both electron-withdrawing (ester group) and electron-donating substituents (enol ether) (**Scheme 14**).[34] For example, RCM of compound **36** has been attempted in the presence of either catalyst **3** or **4**. It was found that RCM using the first generation Grubbs catalyst **3** failed to give any of the desired cyclisation products and instead resulted in the slow formation of homodimeric cross-metathesis product **39**. On the other hand, the use of the second generation Grubbs catalyst **4** gave cyclic products with an almost equal amount of the undesired five-membered heterocycle **38** (40%) together with the six-membered ring **37** (45%). The undesired side reaction was thought to involve isomerisation of the terminal double bond to the more stable disubstituted olefin prior to the cyclisation reaction. In fact the exact mechanism remains unknown but it is thought to be due to the reaction of the ruthenium catalyst with a vinyl ether moiety facilitating the generation of a ruthenium-hydride species which could isomerise unhindered terminal olefins.[35] In the case of a formal synthesis KDO **41** the expected RCM reactions proceeded efficiently, isomerisation may have been suppressed in this case due to the increased steric environment of the terminal olefin.



Scheme 14. RCM of precursor **36** and synthesis of KDO **41** and 2-deoxy KDO **42** reported by Hekking and co-workers.

1.3.2 Ring-closing metathesis of vinyl amine-containing dienes and alkynyl amines

Kinderman and co-workers reported the first ring–closing metathesis reactions of olefinic enamides in the presence of the ruthenium-based catalysts **3** or **4** to provide the five- and six- membered cyclic enamides in good yields (**Table 1**).[36] However, the corresponding reactions to create seven-membered rings were not successful, instead these reactions led to six-membered ring formation. It was noted that ruthenium-catalyzed isomerisation to the more stable olefin took place, prior by ring closure of the isomerised intermediates to the six-membered cyclic enamides.

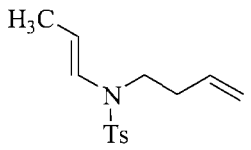
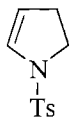
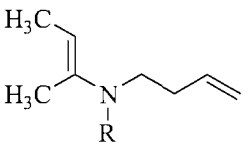
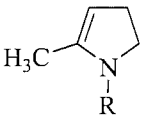
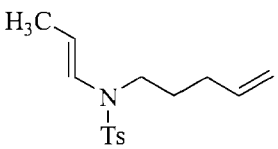
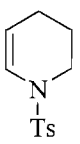
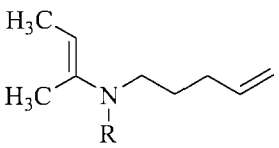
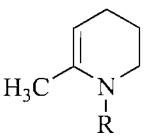
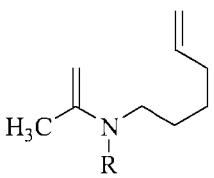
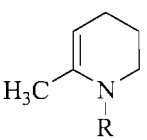
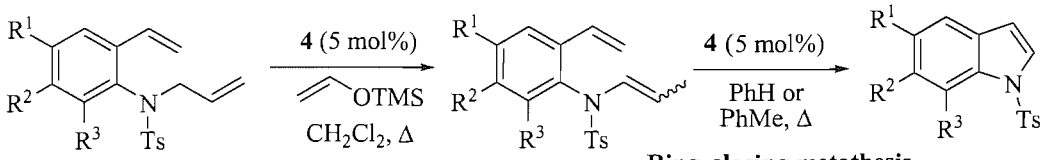
Entry	Enamides	Products	Yield
1			84%
2			R = Ts, 86% R = Bz, 63% R = CO_2Et, 62%
3			80%
4			R = Ts, 75% R = Bz, 93% R = CO_2Et, 57%
5			R = Ts, 62% R = Bz, 24% R = CO_2Et, 34%

Table 1. RCM of olefinic enamides reported by Kinderman and co-workers.

Exploiting the observed olefin isomerisation reaction, Arisawa and co-workers developed a novel synthesis of indoles (**Scheme 15**).[37] Thereby, sulfonamides **43-46** were isomerised to the enamides using Grubbs catalyst **4** and vinyloxytrimethylsilane. The resulting enamides were then isolated and heated in the presence of Grubbs catalyst **4** to provide indoles **47-50** in good to excellent yields. The mechanism of this double bond isomerisation was unknown, although the available evidence suggests that the reaction of trimethylsilylvinyl ether generated a new olefin isomerisation catalyst that isomerised the double bonds but was incapable of inducing the RCM of the enamide product.

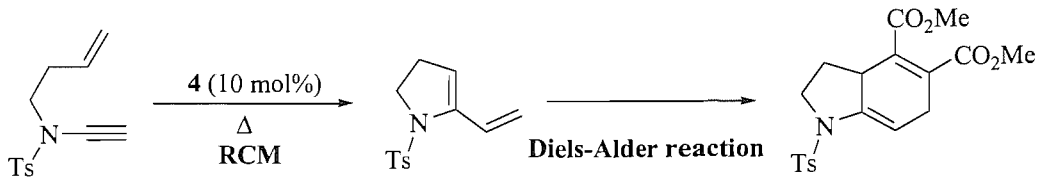


43 R^1, R^2, R^3 = H
44 R^1= OMe, R^2, R^3 = H
45 R^1, R^2, R^3 = OMe
46 R^1= H, R^2 = Cl, R^3 = H

47 R^1, R^2, R^3 = H, (94%)
48 R^1= OMe, R^2, R^3 = H, (80%)
49 R^1, R^2, R^3 = OMe, (quant.)
50 R^1= H, R^2 = Cl, R^3 = H, (79%)

Scheme 15. Novel indole synthesis *via* olefin isomerisation followed by RCM reported by Arisawa and co-workers.

Parallel to these investigations, RCM of enynes tethered by heteroatoms has been carried out by Mori and co-workers (**Scheme 16**).[38] Under the metathesis conditions using 10 mol% of the second generation Grubbs catalyst **4**, the enynamide **52** as cyclised to provide five-membered cyclic vinyl enamide **53**. The synthesised 1,3-dienes were derivatised using Diels-Alder reactions giving the bicyclic product **54**.

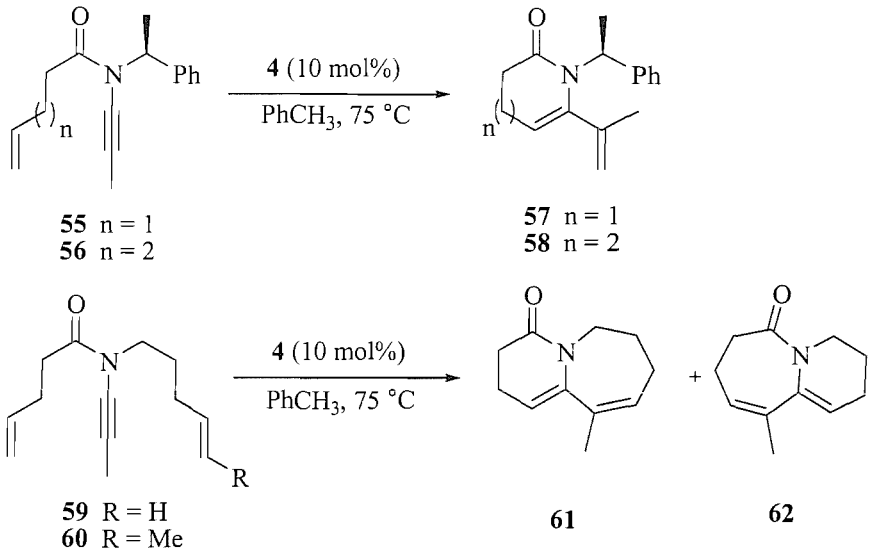


52 **53** **54**

Scheme 16. Synthesis of bicyclic compound **54** *via* an enyne metathesis and Diels-Alder sequence.

Hsung *et al.* also presented enyne metathesis reactions of enynamides **55** or **56** in the presence of the second generation Grubbs catalyst **4** to provide dienes **57** or **58** in

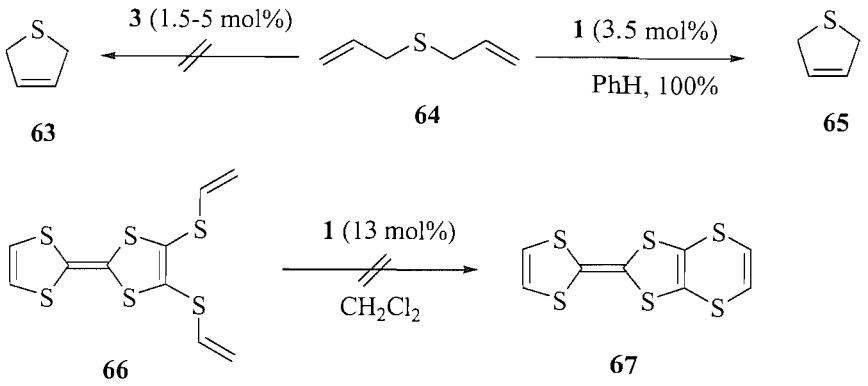
high yield.[39] This methodology was extended to the synthesis of bicyclic products using a tandem RCM reaction. Enyne metathesis of enynamide **59** gave a 1:1 mixture of bicyclic products **61** and **62**. On the other hand, the metathesis of enynamide **60** containing a methyl substituent on one side was more selective, giving cyclised products **61** and **62** in a 6:1 ratio (**Scheme 17**).



Scheme 17. Enyne metathesis of the enynamides **55-60** by Hsung and co-workers.

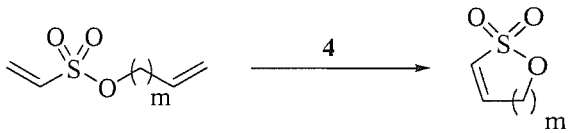
1.3.3 Ring-closing metathesis of vinyl sulfide-, sulfonate-, sulfonamide-containing dienes

In 1996, Armstrong and co-workers reported the RCM of a sulfide-containing compound using the molybdenum-based catalyst **1** (**Scheme 18**).[40] Their work demonstrated that the diallyl sulfide **64** can be converted to 2,5-dihydrothiophene **65** in quantitative yield by utilizing catalyst **1**, whereas the use of ruthenium complex **3** failed to give any cyclised products. It is likely that poisoning of the ruthenium carbene **3** by the sulfide moiety led to deactivation or decomposition of the ruthenium catalyst. Furthermore, attempted cyclisation of the *bis*-vinylsulfide **66** proved unsuccessful even using the more reactive molybdenum catalyst **1**.



Scheme 18. RCM of diallyl sulfide **64** and attempted RCM of vinyl sulfide-containing diene **66** demonstrated by Armstrong and co-workers.

The strong electron-pair donor ability of sulfur atom can adversely affect the metathesis reaction, although both Metz *et al.*[41] and Cossy *et al.*[42] have reported the RCM of the vinylic sulfonates to provide the synthetically useful cyclic sulfonates (sultones) in the presence of the ruthenium catalyst **3** or **4** (**Scheme 19**). It should be noted that sulfonyl moieties have proven to be much more compatible RCM substrates than sulfides.[43] While the potential for sulfonyl oxygen coordination to ruthenium in catalyst **4** has been reported, the sulfonyl group is less likely to induce catalyst poisoning.[44] Under the metathesis conditions in the presence of the second generation Grubbs catalyst **4**, but differing in the use of solvent and temperature (refluxing CH_2Cl_2[41] vs. C_6H_6, 70 °C[42]), the vinylsulfonates **68-70** smoothly cyclised to provide the sultones **71-73** in excellent yields.



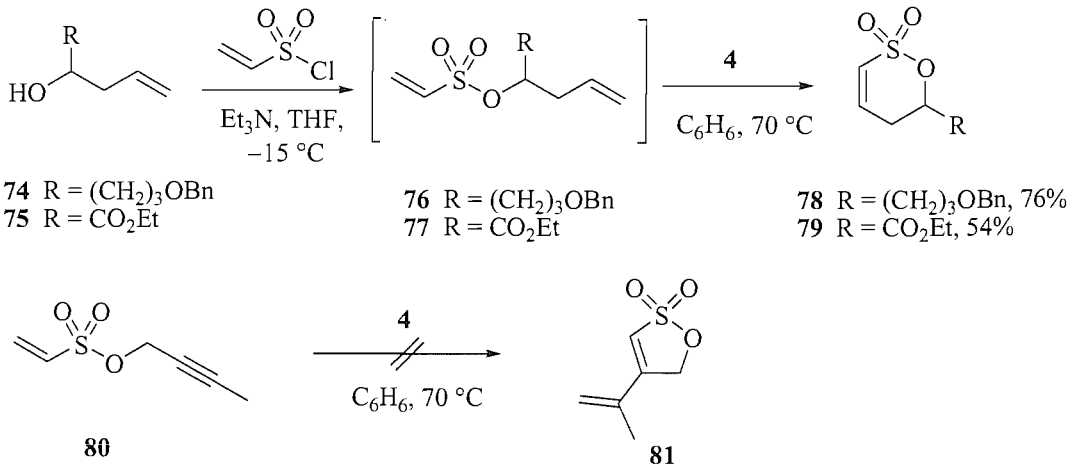
68 m = 1
69 m = 2
70 m = 3

71 m = 1, 100%[a] or 94%[b]
72 m = 2, 90%[a] or 99%[b]
73 m = 3, 94%[b]

Scheme 19. Synthesis of cyclic sulfonates by RCM reported by both Metz *et al.* and Cossy *et al.* [a] C_6H_6, 70 °C, [b] CH_2Cl_2, reflux.

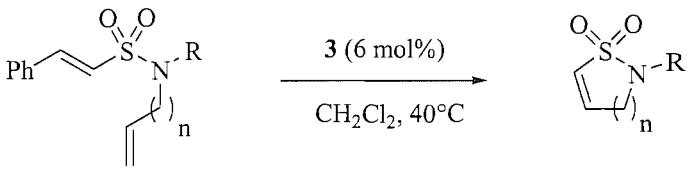
Additionally, Cossy and co-workers have further demonstrated the RCM of substituted sulfonates **76** or **77** to form the sultones **78** or **79**, respectively (**Scheme 20**).[42] In order to prepare the RCM substrates, treatment of the corresponding secondary alcohols **74** and **75** with sulfonyl chloride was accomplished. The crude

sulfonates **76** or **77** were immediately exposed to the metathesis conditions. It was found that the corresponding sultones **78** and **79** were obtained in satisfactory yields. Disappointingly, the vinylsulfonate **80** failed to undergo enyne metathesis using either catalyst **3** or **4**.



Scheme 20. RCM of vinylsulfonates **76** and **77** and attempted enyne metathesis of vinylsulfonate **80** reported by Cossy and co-workers.

It has been shown in the literature that the sulfonamide moiety is compatible with RCM using ruthenium catalysts. In 1999, the first examples of RCM of vinylsulfonamides **82-85** were reported by Hanson and co-workers to provide the five- and six-membered cyclic sulfonamides (sultams) **86-89** (**Scheme 21**).[45] The metathesis reactions using the first generation Grubbs catalyst **1** were found to be sluggish, although all reactions proceeded cleanly in good to excellent yields. It has been noted earlier that a free amino group can stop the reaction entirely, by coordinating to the metal centre, although the free sulfonamide N-H substrates did not have a significant deactivating effect on the catalyst due to the reduced Lewis-basicity of the nitrogen in sulfonamides.

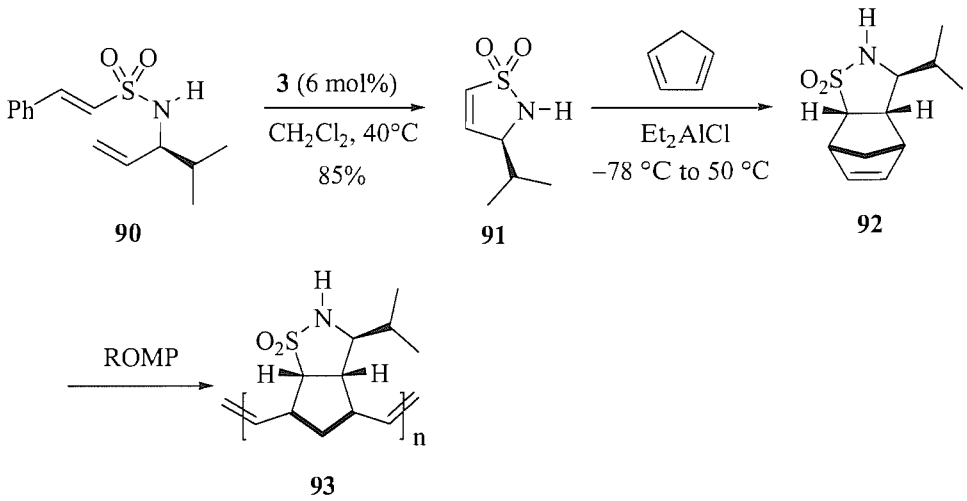


82 n = 1, R = H
83 n = 1, R = Bn
84 n = 2, R = Bn
85 n = 1, R = HC(CH$_2$*t*-Bu)(CO$_2$Me)

86 n = 1, R = H (90%)
87 n = 1, R = Bn (88%)
88 n = 2, R = Bn (65%)
89 n = 1, R = HC(CH$_2$*t*-Bu)(CO$_2$Me) (90%)

Scheme 21. RCM of vinylsulfamide **82-85** demonstrated by Hanson and co-workers.

To highlight the applications of RCM of vinylsulfonamides, Wanner and co-workers later developed a strategy employing a combination of RCM and ROMP to synthesize oligomeric sulfonamides (**Scheme 22**).[46] For example, the facile RCM of sulfonamide **90** in the presence of the first generation Grubbs catalyst **3** produced the cyclic amino acid-derived α,β-unsaturated γ-sultam **91** in good yield. Further exporation of the reactivity of this sultam revealed it underwent stereoselective Diels-Alder reaction with cyclopentadiene in the presence of a Lewis acid catalyst, providing tricyclic sulfonamide **92** with good levels of endo selectivity. It was noted that ROMP provided an attractive route to the construction of oligomeric sulfonamides. This product **92** was then subjected to ROMP conditions using Grubbs benzylidene catalyst **3** and the resulting polymer **93** was analysed by MALDI-TOF mass spectroscopy.

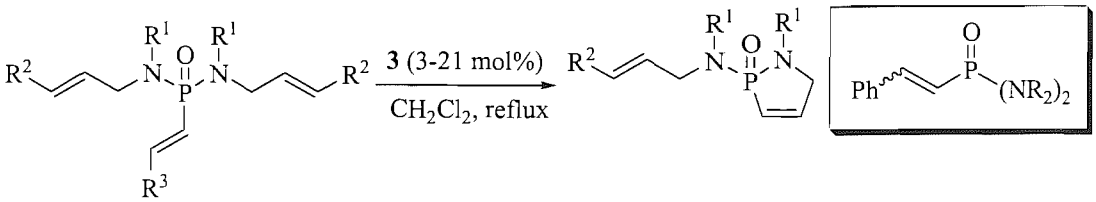


Scheme 22. Synthesis of oligomeric sulfamides using RCM/Diels-Alder sequence and ROMP developed by Wanner and co-workers.

1.3.4 Ring-closing metathesis of vinylphosphonate- and phosphonamide-containing dienes

Hanson and co-workers have discovered the first examples of RCM of vinylphosphonamides using the first generation Grubbs catalyst **3** to provide five-membered heterocycles in good yields (**Scheme 23**).[47] However, one limitation proved to be the RCM of phosphonamide **97** due to competition with cross-metathesis between styrene and the vinyl phosphonyl moiety. It was noted that substitution on the allylamino-double bond (R^2 = Ph) may force the initial metathesis

reaction to occur at the sterically-congested and electron deficient vinyl double bond, thus slowing the reaction of phosphonamide **97**.

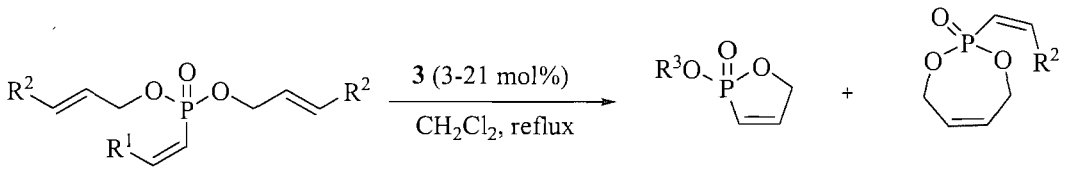


94 R^1, R^2, R^3 = H
95 R^1 = Me, R^2, R^3 = H
96 R^1, R^3 = H, R^2 = Ph
97 R^1= Me, R^2 = Ph, R^3 = H
98 R^1, R^3 = Me, R^2 = H

99 R^1, R^2, R^3 = H (74%)
100 R^1 = Me, R^2, R^3 = H (76%)
101 R^1, R^3 = H, R^2 = Ph (68%)
102 R^1= Me, R^2 = Ph, R^3 = H (13%)
103 R^1, R^3 = Me, R^2 = H (87%)

Scheme 23. RCM of vinylphosphonamides by Hanson and co-workers.

A related study led to the first synthesis of cyclic vinylphosphonates (**Table 2**).[47] The RCM of vinylphosphonates **104-107** gave a mixture of the desired products **108** and the product of metathesis between the two allyloxy groups **109**. The ratio between these two products depends on the substitution pattern at the vinyl and the allyloxy groups. It was noted that the RCM of triene **107** was particularly sluggish to afford only 30% of the desired product and 56% of recovered starting material.

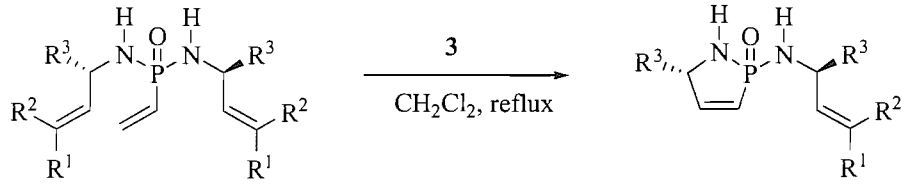


104-107 **108** **109**

Entry	Trienes	R^1	R^2	Yield (%)	
				108	**109**
1	**104**	H	H	44 (R^3 = H)	31
2	**105**	Me	H	54 (R^3 = H)	6
3	**106**	H	Me	16 (R^3 = H)	54
4	**107**	H	Ph	30 (R^3 = cinnamyl)	0

Table 2. Example RCM of vinylphosphonates by Hanson and co-workers.

As an extension of RCM of vinylphosphonamides, Stoianova and co-workers utilized RCM to desymmetrise pseudo-C_2-symmetric phosphorus templates **110-115** to produce *P*-heterocycles **116-121** containing a stereogenic phosphorus atom (**Table 3**).[48] The desymmetrisation of isopropyl terminated substrate **110-112** (R^1 or R^2 = *i*-Pr) gave the five-membered cyclic products **116-118** in good yields with low diastereoselectivity. Comparatively, these reactions gave excellent levels of selectivity (12-15:1) with vinylphosphonamides **113-115** containing an *E*-configured phenyl group at the olefin terminus.

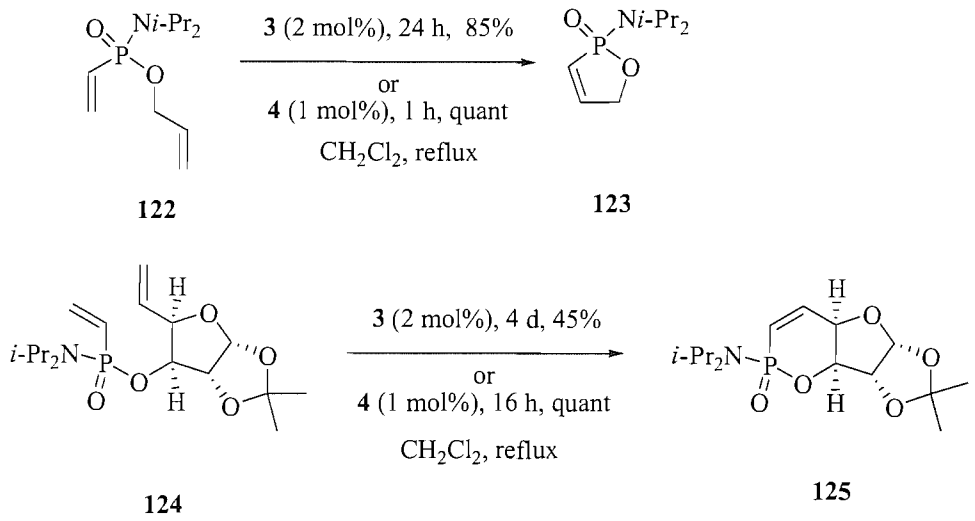


110-115 **116-121**

Entry	Trienes	R^1	R^2	R^3	Products, yield	dr
1	**110**	H	*i*-Pr	Me	**116**, 64%	2.6:1
2	**111**	H	*i*-Pr	*i*-Pr	**117**, 80%	5.0:1
3	**112**	*i*-Pr	H	Me	**118**, 61%	3.9:1
4	**113**	Ph	H	Me	**119**, 69%	12:1
5	**114**	Ph	H	*i*-Pr	**120**, 66%	15:1
6	**115**	Ph	H	*t*-Bu	**121**, 63%	15:1

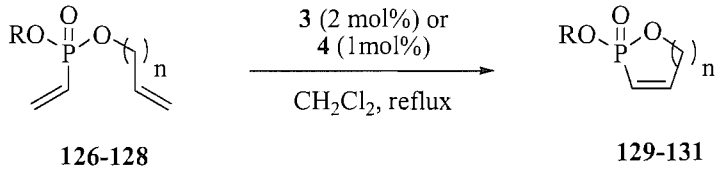
Table 3. Diastereotopic differentiation on phosphorus templates *via* RCM reactions demonstrated by Stoianova and co-workers.

Additionally, RCM approaches to phosphonamides were reported by van Boom and co-workers (**Scheme 24**).[49] Under the metathesis conditions, the phosphonamides **122** smoothly cyclised to give the five-membered *P*-heterocycles **123**. These reactions were conducted with catalysts **3** and **4**, with catalyst **4** improving yield and reducing the required reaction time. With the more sterically demanding substrate **124**, RCM proceeded to form the *cis*-fused 5,6-bicyclic derivatives **125** in quantitative yield when catalyst **4** was employed.



Scheme 24. RCM of vinylphosphonamides reported by van Boom and co-workers.

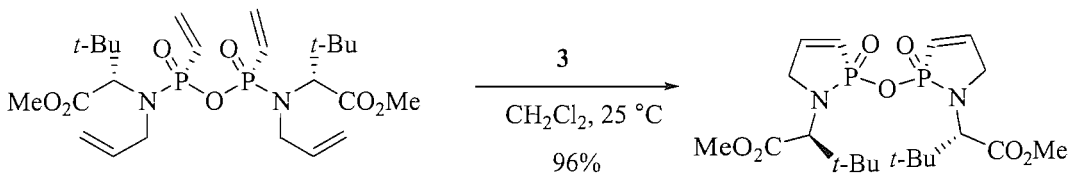
Furthermore, van Boom also demonstrated the RCM of vinylphosphonates **126-128** using the more active second generation Grubbs catalyst **4** to provide the *P*-heterocycles **129-131** (**Table 4**).[49] It was established that vinylphosphonates **126-128** were rapidly and quantitatively converted into the corresponding cyclic vinylphosphonates when catalyst **4** was used.



Entry	Substrates	R	n	Catalyst	Time	Product, yield
1	**126**	allyl	1	**3**	6 h	**129**, 44%
				4	30 min	**129**, >99%
2	**127**	Bn	1	**3**	4 d	**130**, 25%
				4	15 min	**130**, >99%
3	**128**	Bn	2	**3**	4 d	**131**, 85%
				4	20 min	**131**, >99%

Table 4. RCM of vinylphosphonates reported by van Boom and co-workers.

Sprott and Hanson have used RCM for the synthesis of a new class of *P*-chiral amino acid-derived phosphonamidic anhydride in order to facilitate the development of structurally diverse phosphorus-based compounds (**Scheme 25**).[50] Upon exposure of substrate **132** to metathesis conditions using the first generation Grubbs catalyst, the cyclic phosphonamidic anhydride **133** was afforded in excellent yield with no evidence of nine-membered ring formation.



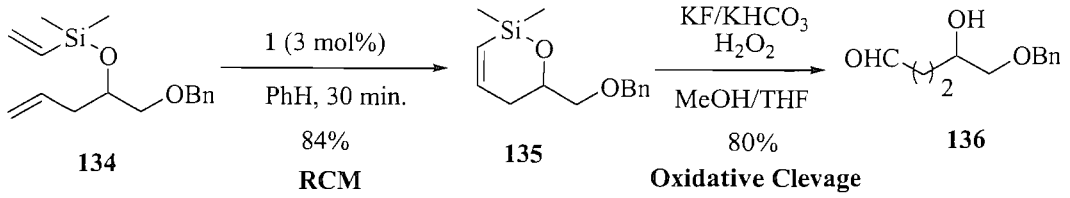
132 **133**

Scheme 25. Synthesis of phosphonamidic anhydride by Sprott and co-workers.

1.3.5 Ring-closing metathesis of vinylsilane-containing dienes

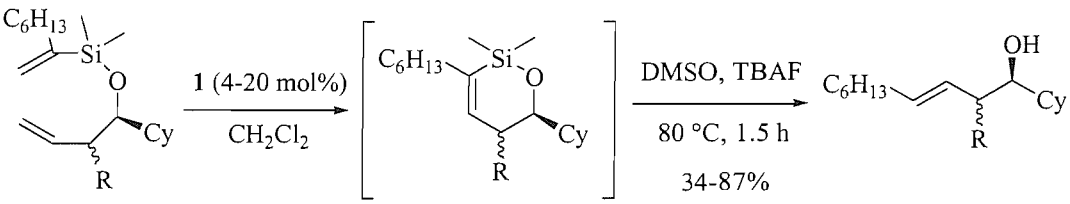
Trisubstituted vinylsilanes are widely utilized as versatile synthetic intermediates.[51] The Si-C bonds in alkenylsilanes are amenable to cleavage in the presence of fluoride, generating carbon nucleophiles that can react further with a variety of electrophiles or especially, undergo palladium cross-coupling reactions with vinyl or aryl halides.[52] The choice of the silyloxy linkage as a temporary tether for RCM reactions is attractive due to ease of formation and cleavage (Si-O bond) but also its well-known steric and stereoelectronic biasing effect in a variety of post-RCM synthetic transformations (C-Si bond).[53]

Chang and Grubbs illustrated the first examples of RCM of vinylsilyl containing olefins in the presence of the molybdenum catalyst **1** to provide the corresponding cyclic siloxanes (**Scheme 26**).[54] For example, the diene **134** underwent facile ring closure to yield the cyclic product **135** in excellent yield. The synthetic utility of these intermediates was demonstrated by the oxidative ring cleavage of **135** to provide the hydroxyaldehyde **136** in high yield.



Scheme 26. RCM of vinylsilyl containing olefins and subsequent oxidative cleavage by Chang and Grubbs.

Ahmed and co-workers reported a one pot RCM and nucleophilic ring opening sequence to furnish the corresponding homoallylic alcohols **139** (**Scheme 27**).[55] Upon exposure of dienes **137** to metathesis conditions using the molybdenum catalyst **1** and subsequent treatment with TBAF in DMSO, the desired homoallylic alcohols **139** were obtained without purification of the intermediate heterocycles.



Scheme 27. One pot synthesis of the homoallylic alcohol by Ahmed and co-workers.

As previous reports on metathesis reactions of silicon containing substrates where the silicon functionality served as a temporary tethering group, Schuman and Gouverneur have demonstrated that RCM could be applied to the preparation of a series of functionalised trimethylsilyl substituted carbocycles and heterocycles (**Table 5**).[56] RCM of diene **140** using the second generation Grubbs catalyst **4** provided the carbocycle **147** in almost quantitative yield. The *N*-Boc protected diene **141** was smoothly cyclised under the metathesis conditions to give the cyclic product **148**. To further illustrate the potential of this strategy, the RCM of some ethers **142-144** or esters **145** was investigated. Diene **143** or the more sterically demanding diene **144** underwent cyclisation to afford the five-membered ring **150** or **151** respectively, in excellent yields. Finally, the methodology allowed the preparation of the five- and six-membered α,β-unsaturated lactones **152** and **153** in good yields.

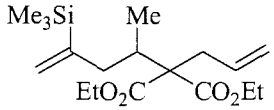
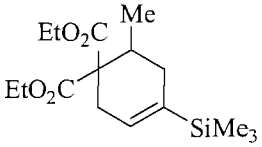
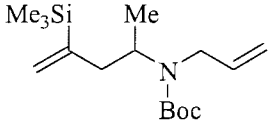
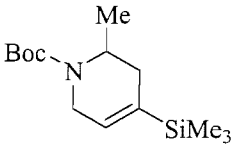
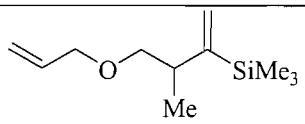
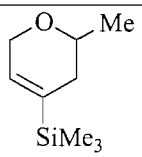
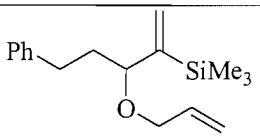
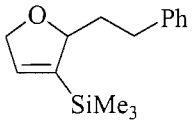
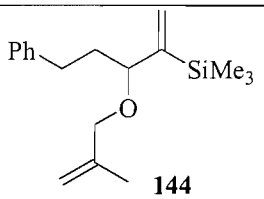
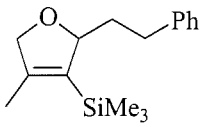
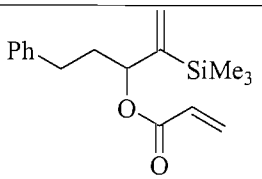
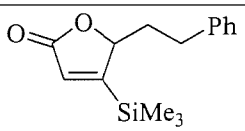
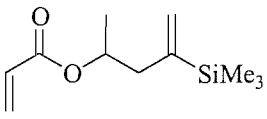
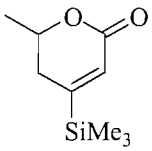
Entry	Substrates	Products	Conditions	Yield (%)
1	 **140**	 **147**	**4** (3 mol%) 8 h	98
2	 **141**	 **148**	**4** (5 mol%) 18 h	93
3	 **142**	 **149**	**4** (3 mol%) 3 h	93
4	 **143**	 **150**	**4** (2 mol%) 1 h	90
5	 **144**	 **151**	**4** (12 mol%) 29 h	83
6	 **145**	 **152**	**4** (10 mol%) 36 h	86
7	 **146**	 **153**	**4** (8 mol%) 72 h	79

Table 5. RCM of trimethylsilyl substituted dienes by Schuman and Gouverneur.

Chapter 2

Ring-closing metathesis of halogenated substrates

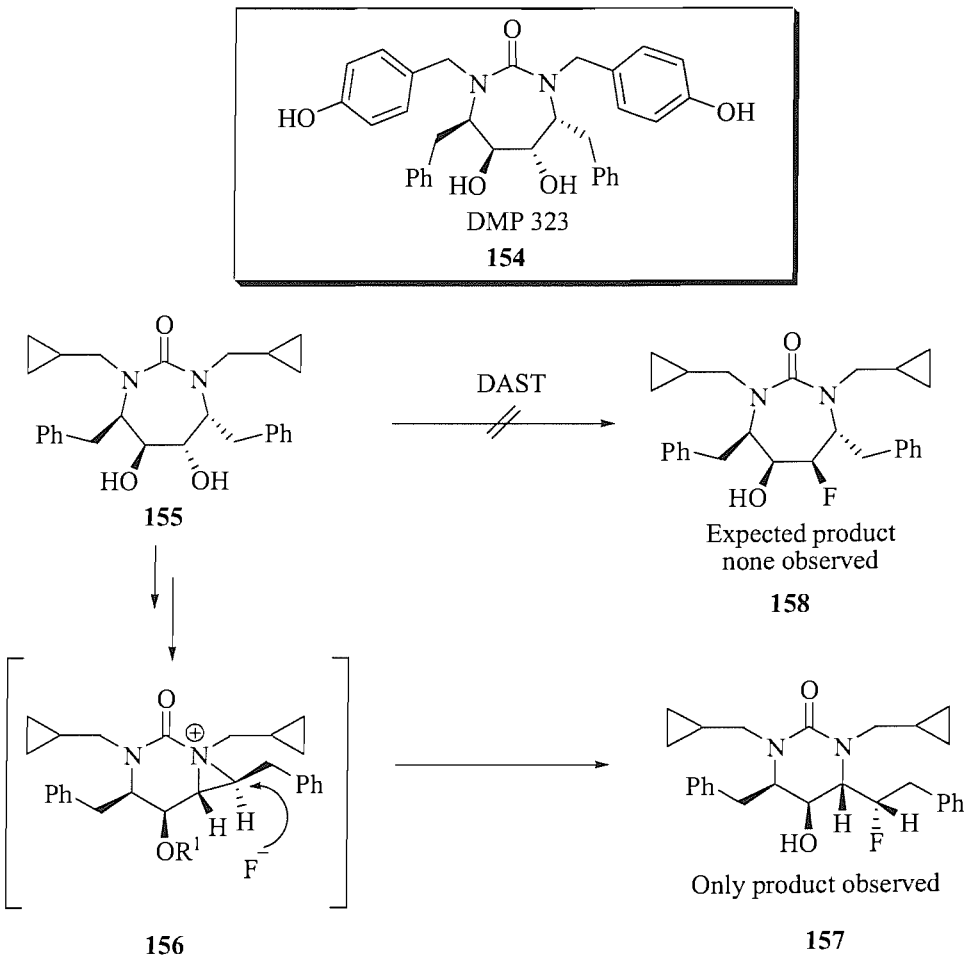
Since the advent of functional group-compatible, well-behaved pre-catalysts such as the ruthenium alkylidene complexes pioneered by Grubbs, the scope of ring-closing metathesis (RCM) has continuously increased from regular terminal olefins to include a variety of olefins ranging from electron-rich to electron-poor.[2, 20] Our research carried out on the investigation of new methodology for the incorporation of halides into molecules *via* vinyl halide metathesis is presented. We believed that RCM should provide a powerful method for the regiocontrolled synthesis of cyclic halo-olefins.

2.1 Ring-closing metathesis of vinyl fluoro dienes

Introduction of fluorinated double bonds into acyclic and cyclic compounds can have a great effect on the chemical properties, biological activity and metabolism of a molecule. Fluoro-olefins have been recognized as hydrolytically stable, nonclassical isosteric replacements for the carboxamide group.[57, 58] In contrast to simple double bonds, which are generally considered to behave as noninteracting conformationally constrained spacers, fluoro-olefins have been suggested as superior isosteric replacements for the amide group, and are therefore of considerable interest in the synthesis of peptidomimetics and other biologically active molecules.[59, 60] Consequently, mild and general methods that allow the straightforward introduction of fluorinated double bonds into acyclic and cyclic systems would constitute valuable synthetic methodology. In principle, internal fluoro-substituted double bond-containing systems should be accessible either by intermolecular cross metathesis (CM) of a 2-fluoroalkene and an α-olefin or, for cyclic systems, by intramolecular ring-closing metathesis (RCM) of monofluorinated α,ω-dienes. However, no example of the RCM of vinyl fluoro dienes substrates was known at the outset of our research. Here we described our research carried out on the ring-closing metathesis of monofluorinated dienes.

Additional inspiration for our research derived from efforts by De Lucca to improve the solubility and to determine the structure-activity relationships (SAR) of the HIV

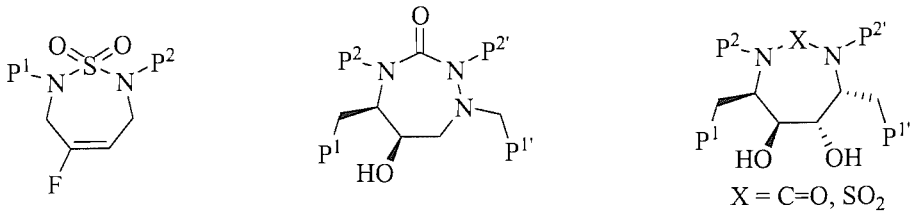
protease inhibitor DMP 323 (**154**) by attempted substitution of one of the hydroxy groups with a fluorine atom (**Scheme 28**).[61] They discovered that seven-membered ring cyclic ureas underwent stereospecific, stereoselective-ring contraction rearrangement to give the corresponding tetrahydropyrimidinone derivatives upon attempted direct nucleophilic fluorination using (diethylamino) sulfur trifluoride (DAST). For example when diol **155** was treated with 1 equiv. of fluorinating agent, DAST rather than the expected seven-membered product **158**, the undesired tetrahydropyrimidinone **157** was observed in excellent yield. It was noted that the rearrangement proceeds through the formation of the aziridinium cationic intermediate **156**. The fluoride ion then opens the aziridine intermediate at the less hindered carbon to give the observed fluoro alcohol.



Scheme 28. Research carried out by De Lucca at Dupont pharmaceuticals.

Furthermore, Hanson and co-workers had previously reported that analogues of the cyclic sulfamide protease inhibitors could be prepared efficiently by RCM strategy.[45, 62] It was therefore thought that it might be possible to access the fluoro-olefins by

RCM creating novel analogues with potentially interesting properties. Consequently, our initial investigations focused on the RCM reactions of sulfamide-linked diene substrates, as these provided the seven-membered cyclic scaffold present in a series of highly potent HIV protease inhibitors (**Figure 1**).

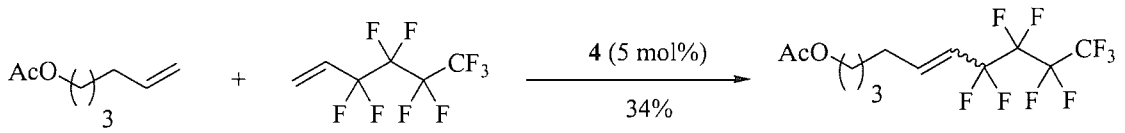


159 **160** **161**

Figure 1. Structures of sulfamide-linked fluoro-olefins RCM products and related small-molecule HIV protease inhibitors.

2.2 Previous and present metathesis reactions of fluorine-containing olefins

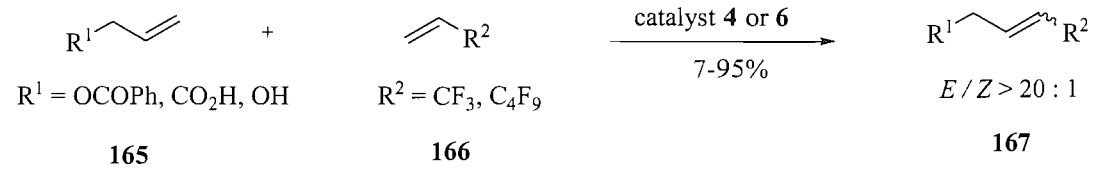
Considering the review literature concerning RCM of vinyl halides, it become apparent that very little work had been carried out on the metathesis of fluoro-containing olefins. The first examples of cross metathesis of perfluoro-alkyl substituted olefins **163** had been reported by Grubbs and co-workers. Disappointingly, the yield and the *E/Z* selectivity of the cross metathesis product **164** was modest (**Scheme 29**).[63] They noted that some homodimerisation of terminal alkene **162** occurred and the lack of reactivity may result from the sequestering of the catalyst in a stabilized Fischer-type carbene complex, which either rapidly decomposes or fails to react further.



162 **163** **164**

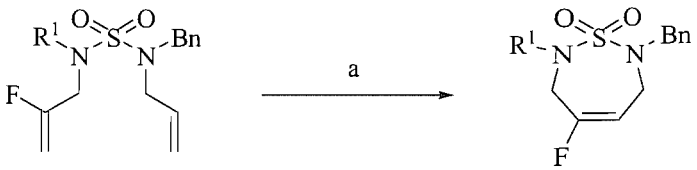
Scheme 29. Cross-metathesis reaction of an electron deficient fluorinated alkene reported by Grubbs and co-workers.

Blechert *et al.* later demonstrated that cross metathesis reactions of terminal alkenes with a range of fluorinated terminal olefin partners **166** could provide high *E*-selectivity in cross metathesis products **167** in moderate to excellent yield.[64] It should be noted that up to 10 equivalents of fluorinated terminal olefin partners **166** had to be used in order to suppress the dimerisation of the terminal alkene **165**. Either the Hoveyda-Grubbs **6** or the second generation Grubbs catalyst **4** were employed, returning products with excellent *E*-selectivity (**Scheme 3**).



Scheme 30. Cross metathesis of a variety of olefins with fluorinated partners by Blechert and co-workers.

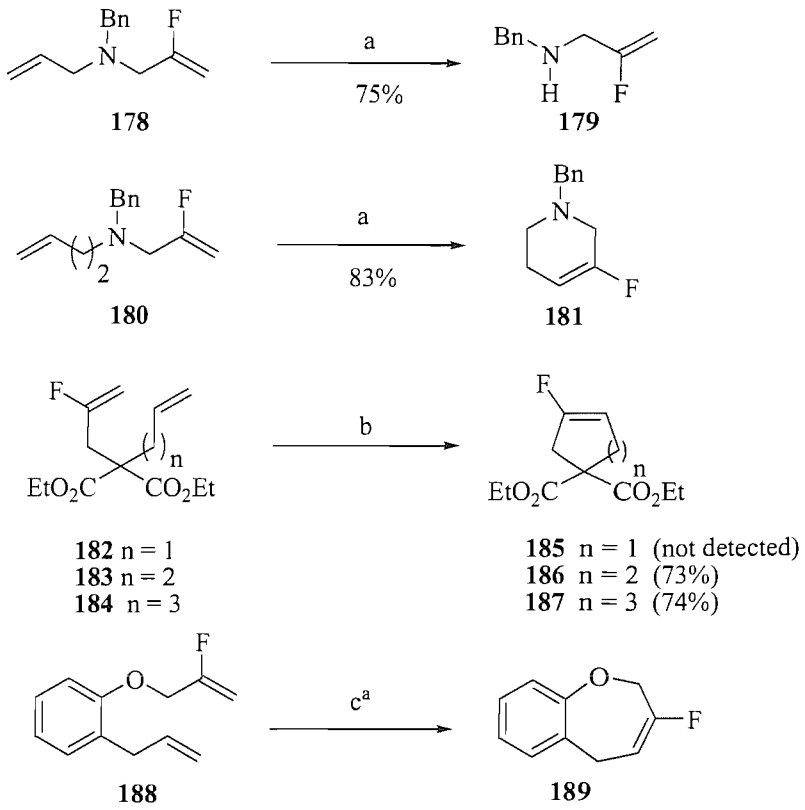
Recently, the first ever successful examples of ring-closing metathesis of vinyl fluoride-containing dienes were reported by our group.[65] We have shown that RCM of fluoro-olefins proceeded efficiently to give six- and seven-membered cyclic vinyl fluorides. The Boc-, H-, and alkyl-substituted sulfamides cyclised smoothly to give the desired cyclic sulfamides in good to excellent yields (**Scheme 31**). Moreover, the RCM reaction was used to prepare various other heterocyclic and carbocyclic systems (**Scheme 32**).



168 R^1 = Boc
169 R^1 = H
170 R^1 = Bn
171 R^1 = Me
172 R^1 = Et

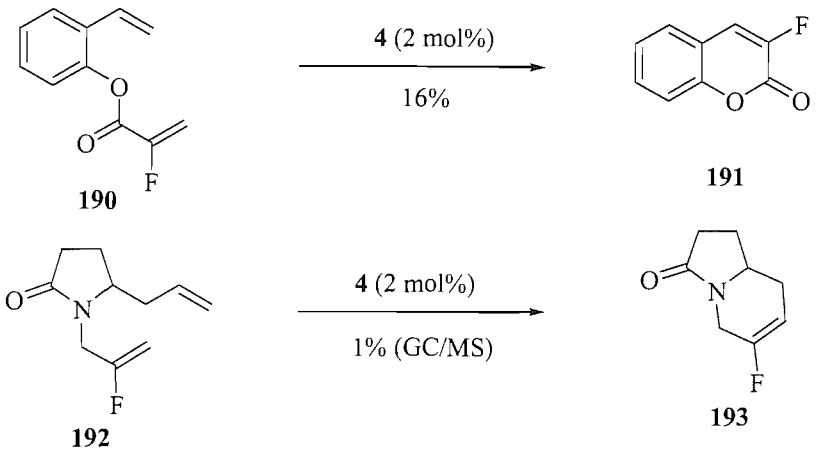
173 R^1 = Boc (90%)
174 R^1 = H (79%)
175 R^1 = Bn (78%)
176 R^1 = Me (77%)
177 R^1 = Et (85%)

Scheme 31. RCM reactions of sulfamides by Brown and co-workers. *Reagents and conditions*: a) **4** (6 mol%), CH_2Cl_2, 40-100 °C

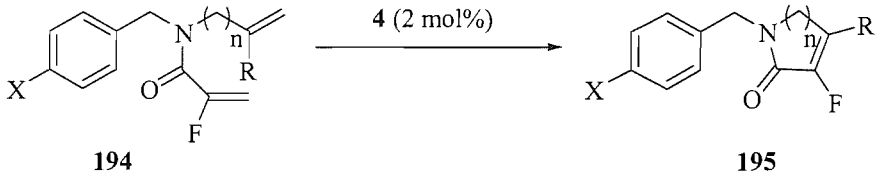


Scheme 32. Further RCM reactions of vinyl fluorides by Brown and co-workers. *Reagents and conditions*: a) **4** (6 mol%), TFA, CH_2Cl_2, 100 °C, 10 h; b) **4** (10 mol%), CH_2Cl_2, reflux, 4 h; c) **4** (20 mol%), CH_2Cl_2, μw, 140 °C, 30 min. [a] isolation of a pure sample was not possible due to its instability and volatility.

Subsequently, ring-closing olefin metatheses of alkenyl α-fluoroacrylamides or acrylates incorporating a fluorinated double bond were reported by Marhold and co-workers (**Scheme 33**, **Table 6**).[66] It was shown that RCM of the α-fluoroacrylate **190** gave 3-fluoro-coumarin **191**, however, the yield was low. Additionally, RCM of the monofluorinated 4-aza-1,7-diene **192** was attempted and only a trace of RCM product was observed. However, they demonstrated that the α-fluoroacrylamides **194a-g** could undergo RCM reactions to give the corresponding δ-lactams with moderate to high yield. Conversion was >95% in all cases. It was noted that these RCM reactions seem to profit from the combined but opposite action of fluorine and the carbonyl group on the electronic properties of the double bond.



Scheme 33. RCM of α-fluoroacrylate **190**, monofluorinated 4-aza-1,7-diene **192**.



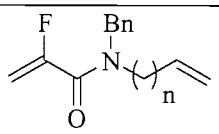
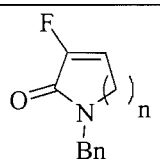
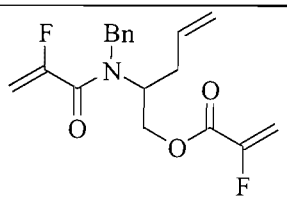
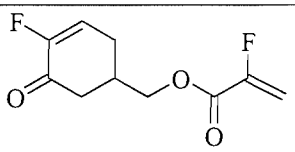
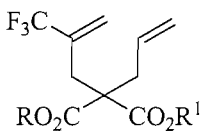
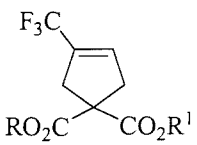
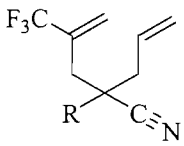
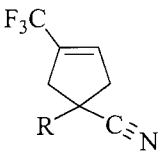
Precursors **194**	R	X	n	Time (min)	Temp. (°C)	Products **195**	Yield (%)
a	H	H	1	10	RT	a	79
b	H	H	2	120	80	b	86
c	H	H	3	240	80	c	ND [a]
d	H	H	4	240	80	d	ND [a]
e	CH_3	H	1	480	80	e	46
f	H	OMe	2	240	80	f	81
g	H	F	2	240	80	g	76

[a] ND = Not Detected, only a homodimeric product involving the nonfluorinated double bond was found.

Table 6. RCM of *N*-alkenyl-*N*-benzyl-α-fluoroacrylamides **194a-g**.

Parallel to this work Matteis and co-workers published some examples of ring-closing metathesis of fluoride- and trifluoromethyl-functionalized olefins (**Table 7**).[67] Their work demonstrated that 2-fluoroacrylamides can be cyclised to the corresponding unsaturated lactams. Upon exposure of fluoroacrylates in entry **1** and **2** to metathesis conditions, the five- and six-membered lactams were observed in

good to excellent yield, whereas the corresponding reactions to form eight-membered ring was not successful. Furthermore, RCM of trifluoromethyl-substituted olefins can be carried out on heterocyclic and carbocyclic systems to yield trifluoromethylated cyclopentenes, pyrrolines and dihydrofuran derivatives. Under the similar conditions to the previously described RCM of fluoroacrylates, RCM of malonates and malonitrile in entries **3** and **4** gave smooth cyclisation to the corresponding cyclopentenes in moderate to good yields. Unfortunately, RCM of acrylamide in entry **5** failed to give any cyclised products. The author suggested that this was probably because these olefins were too electron poor for RCM to take place. Interestingly, RCM of olefins bearing an acyl group at nitrogen in entry **6** provided the desired pyrrolidines in good yields, whereas RCM of olefins containing benzyl protected group at nitrogen in entry **7** did not give any cyclised products. It was noted that probably due to the presence of the basic amine functionality. The last precursor in entry **8** demonstrated that RCM of ether precursor gave the desired trifluoromethyl-substituted dihydrofuran in good yield.

Entry	Precursors	Products	Yield (%)
1			n = 1, 68%[a] n = 2, 80%[a] n = 3, 0%[a]
2			99%[b]
3			R = R[1] = Et, 88%[b] R = *t*-Bu, R[1] = Me, 45%[c]
4			R = CO_2Me, 52%[d] R = CN, 42%[e]

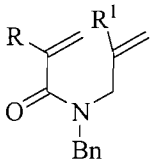
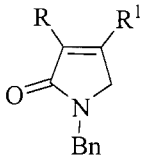
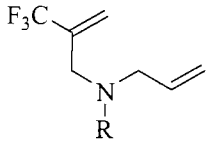
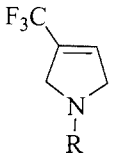
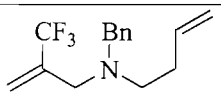
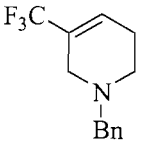
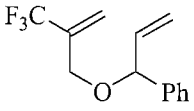
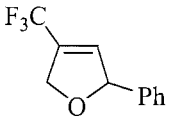
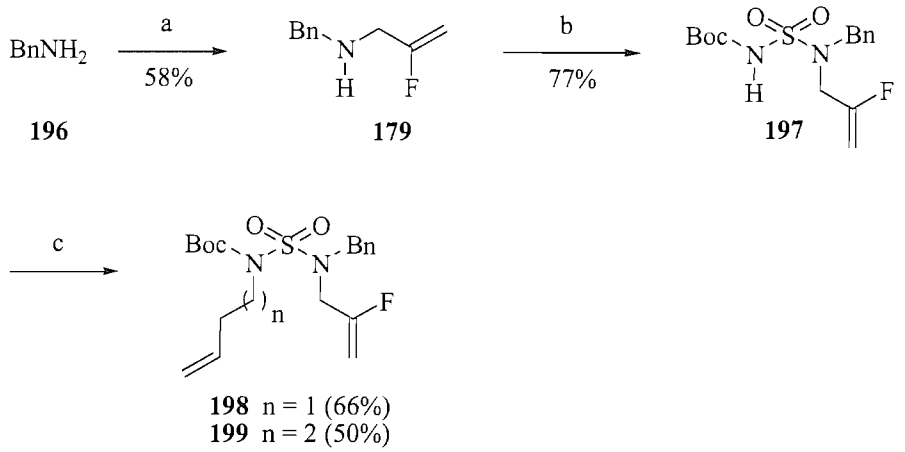
Entry	Precursors	Products	Yield (%)
5			R = CF_3, R^1 = H, 0%[f] R = H, R^1 = CF_3, 0%[a]
6			R = Bz, 68% [g] R = Boc, 97%[h]
7			0%[i]
8			78%[j]

Table 7. RCM of 2-fluoroacrylamides and trifluoromethylated olefins by Matteis and co-workers. *Reagents and conditions*: [a] **2** (7 mol%), 4 h, [b] **2** (4 mol%), 4 h, [c] **2** (7 mol%), 2 h, [d] **2** (3 mol%), 4 h, [e] **2** (15 mol%), 24 h, [f] **2** (3 mol%), 72 h, [g] **2** (10 mol%), 24 h, [h] **2** (10 mol%), 2 h, [i] **2** (7 mol%), 48 h, [j] **2** (5 mol%), 24 h. All reactions were carried out in toluene at 100 °C.

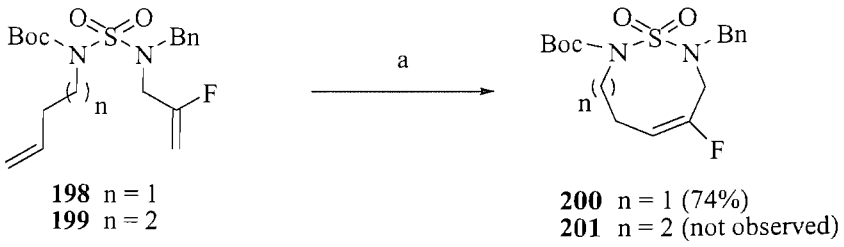
2.2.1 Synthesis and metathesis of sulfamide-linked vinyl fluorides

Having obtained successful results within our group for the ring-closing metathesis of sulfamide-linked vinyl fluorides to provide the seven-membered cyclic sulfamides,[65] we wished to investigate the construction of eight- and nine-membered cyclic sulfamides. In order to prepare the sulfamide precursors **198** and **199**, the synthesis of **196** was carried out. By treatment of benzylamine with NaH and commercially available 1-chloro-2-fluoroprop-2-ene gave the secondary amine **179** in good yield. The resulting amine **179** was reacted with chlorosulfonyl isocyanate (CSI) and *tert*-butanol to afford **197** in good yield.[62, 68] Subsequent alkylation of sulfamide **197** was carried out by treatment with NaH followed by 4-bromo-1-butene or 5-bromo-1-pentene to give the desired sulfamide-linked precursors **198** and **199** respectively (**Scheme 34**).



Scheme 34. *Reagents and conditions*: a) NaH, 1-chloro-2-fluoroprop-2-ene, DMF; b) CSI, *t*-BuOH, Et_3N, CH_2Cl_2; c) NaH, 4-bromo-1-butene (n = 1) or 5-bromo-1 pentene (n = 2), DMF.

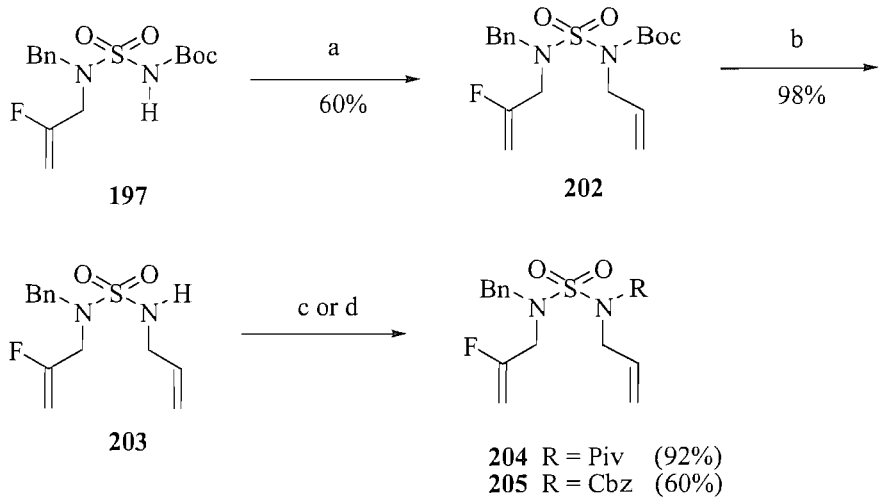
Exposure of these metathesis precursors **198** and **199** to RCM conditions was then investigated. The ring-closing metathesis of sulfamide precursor **198** proceeded smoothly to afford the desired eight-membered ring in good yield. The reaction required 10 mol% of the second generation Grubbs catalyst **4** over 10 h under reflux in CH_2Cl_2. However, none of the cyclised product was obtained with precursor **199**. Either refluxing in CH_2Cl_2 for 10 hours or under microwave conditions, none of desired product was obtained and eventually (after a prolonged reaction time) decomposition of starting material occurred. It was thought that the presumed retardation of the rate of cyclisation was consistent under both thermal reflux and microwave conditions **(Scheme 35)**.



Scheme 35. *Reagents and conditions*: a) **4** (10 mol%), CH_2Cl_2, reflux, 10 h.

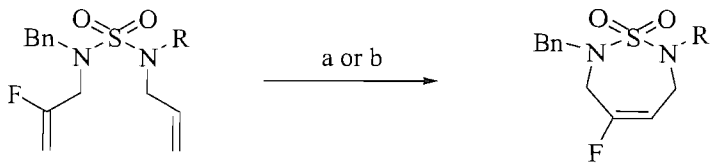
As an extension of the earlier study investigating RCM of sulfamide-linked vinyl fluorides, our group has demonstrated that RCM of Boc-, H-, and alkyl-substituted sulfamides provided the desired cyclised products in good to excellent yields (**Scheme 36**).[65] It was noted that the reason for the difference in the reaction rates

between the Boc-, H-, and alkyl-substituted sulfamide is not immediately apparent. In parallel with the previous investigations concerning RCM of alkyl-substituted sulfamides, RCM of acyl-substituted sulfamides was then investigated. In order to synthesise the precursors **204** and **205**, allylation of the key sulfamide **197** was carried out to provide sulfamide **202**, which was subsequently Boc deprotected to yield **203**. Pivaloyl (Piv) or carbobenzyloxy (Cbz) groups were used to couple with the resulting sulfamide **203** by acylation to produce sulfamide-linked precursors **204** and **205** in good yields (**Scheme 36**).



Scheme 36. *Reagents and conditions*: a) NaH, allyl bromide, DMF; b) TFA, CH_2Cl_2; c) *t*-BuOK, 18-crown-6, PivCl, THF; d) NaH, CbzCl, DMF.

The metathesis precursors **202**, **204** and **205** were then exposed to ring-closing metathesis conditions. The RCM of **202** proceeded smoothly using 10 mol% of the second generation Grubbs catalyst **4** under reflux in CH_2Cl_2 for 10 hours to afford the desired seven-membered ring product **206** in excellent yield. However, the Piv-substituted analogue **204** required an increased amount of the catalyst (12 mol%), added in sequential portions of 6 mol% to produce the desired cyclic sulfamide **207** in good yield. Under the same conditions used for the RCM of Piv-substituted sulfamide **204**, the Cbz-protected analogue **205** cyclised to give the desired cyclic sulfamide **208**. However, the yield was moderate (48%) and 35% of the recovered starting material was also obtained (**scheme 37**).

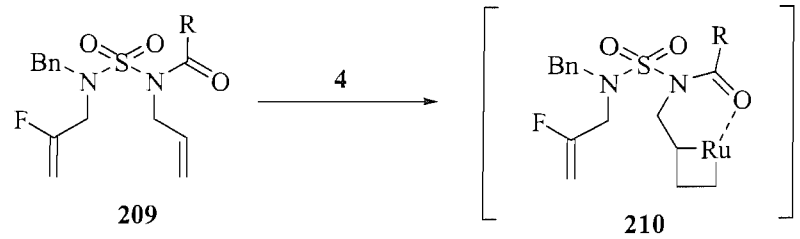


202 R = Boc
204 R = Piv
205 R = Cbz

206 R = Boc (90%, method a)
207 R = Piv (76%, method b)
208 R = Cbz (48%, method b)

Scheme 37. *Reagents and conditions*: a) **4** (10 mol%), CH_2Cl_2, reflux, 10 h; b) **4** (12 mol%), CH_2Cl_2, reflux, 10 h.

Investigation of the RCM of *N*-acyl-substituted sulfamides revealed that the reaction of *N*-Boc derivative **202** using 10 mol% of the second generation Grubbs catalyst **4** gave the desired cyclised product **206** in excellent yield. The RCM of *N*-Piv derivative **204** provided the cyclic sulfamide **207** in good yield, whereas the *N*-Cbz derivative **205** cyclised to the cyclic sulfamide **208** under similar conditions in moderate yield. It was thought that the difficulty observed in cyclising a *N*-Cbz derivative **205** was probably due to the coordination between the ruthenium complex and the acyl carbonyl group to form a chelated intermediate **210** (**Scheme 38**), which could not convert to cyclic sulfamide **208**. Indeed, the involvement of such chelates in problematic cyclisations of unsaturated amide *via* RCM had been previously proposed by Grubbs.[69]



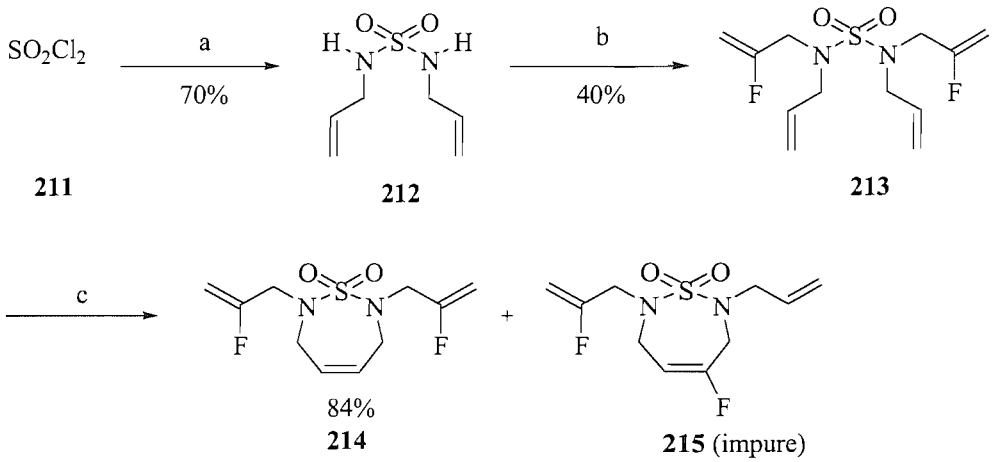
209 **210**

Scheme 38. Proposed chelation effect for RCM of sulfamide **209**.

2.2.1.1 Competition experiments

Due to previous reports from our group suggesting that RCM reactions of fluoro-olefins are typically slower than that of their nonfluorinated analogues.[65] Competition experiments were carried out with various sulfamides containing several possible reactive sites for RCM. We therefore set up the first competition experiment by investigating the RCM of the sulfamide **213**. The synthesis of sulfamide **213** was

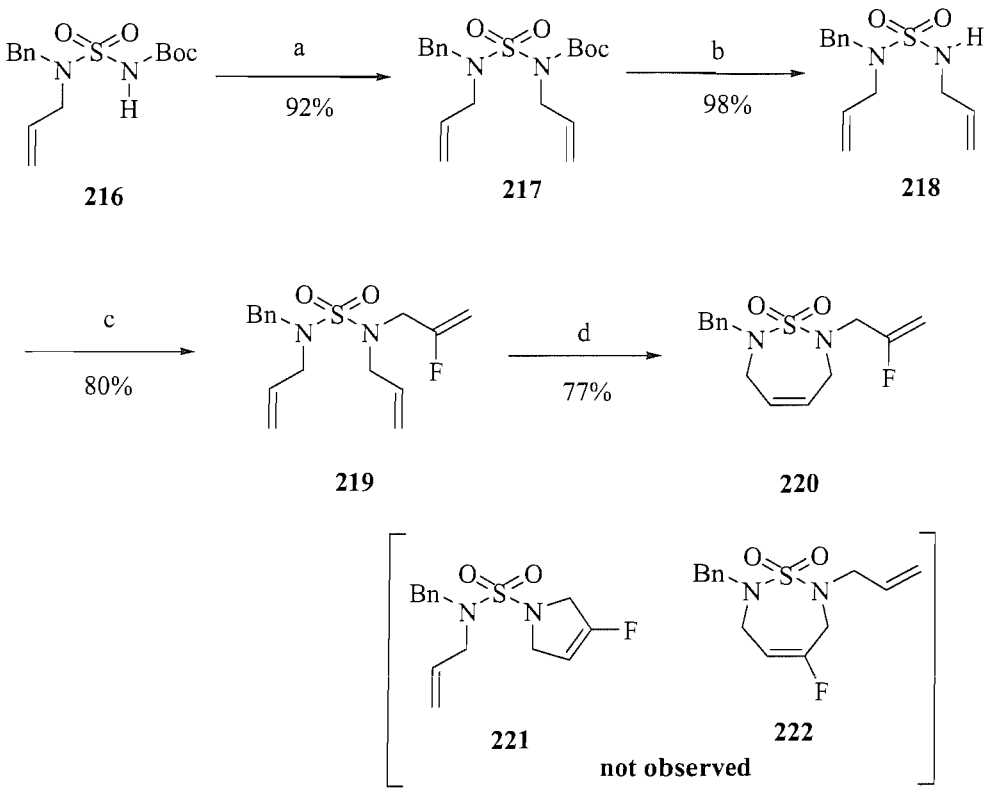
carried out by treatment of allylamine with sulfuryl chloride and subsequent diallylation of **212** with commercially available 3-chloro-2-fluoro-propene to afford **213** in moderate yield (**scheme 39**). The disappointing yield may be due to the low reactivity of the 2-fluoroallylic system. The resulting sulfamide **213** was then exposed to metathesis conditions affording the seven-membered sulfamide **214** in good yield and a trace amount of sulfamide **215**.



211 **212** **213** **214** **215** (impure)

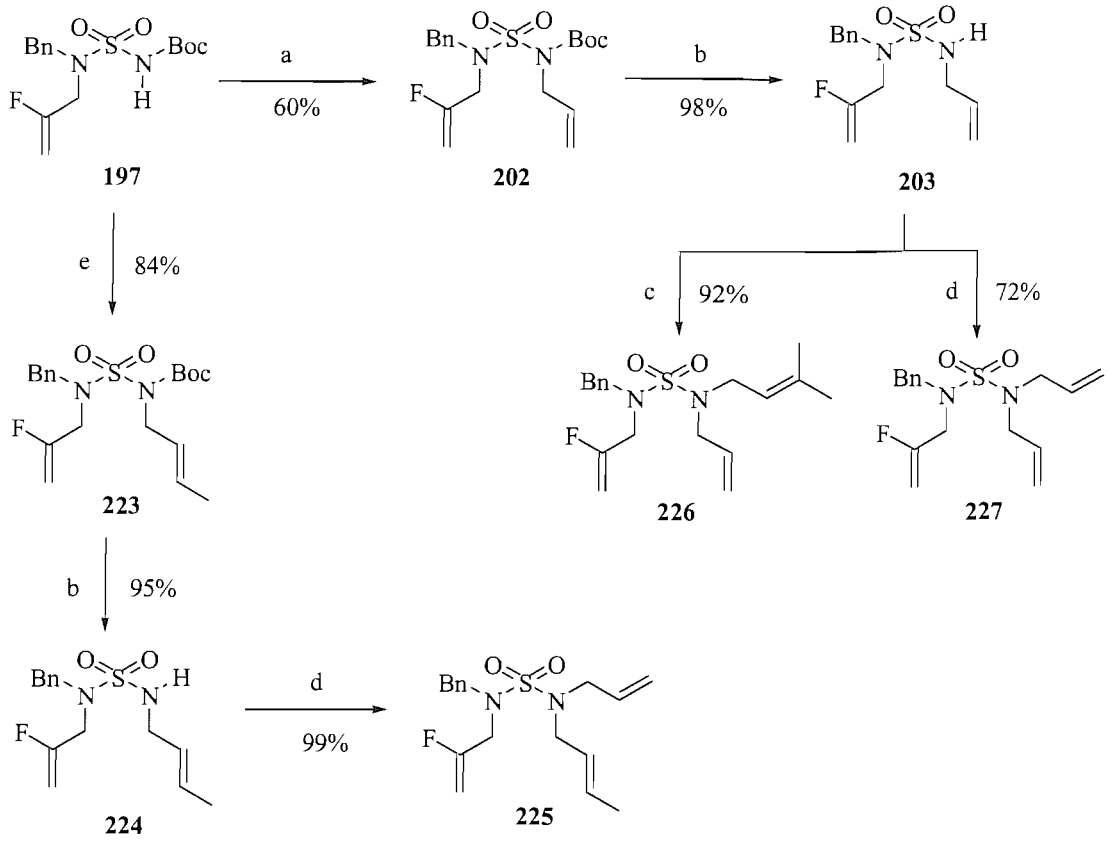
Scheme 39. *Reagents and conditions*: a) Et_3N, allylamine, CH_2Cl_2; b) NaH, NaI, 3-chloro-2-fluoro-propene, DMF; c) **4** (12 mol%), reflux, CH_2Cl_2, 10 h.

RCM of sulfamide **219** was also attempted. Substrate **216** (kindly supplied by S. Salim) was allylated to produce the intermediate **217**. The resulting sulfamide **218** was then alkylated with commercially available fluoro-olefin to yield RCM precursor **219** (**scheme 40**). Upon exposure of sulfamide **219** to RCM conditions, a good yield of cyclised product **220** was obtained. Interestingly, none of the five-membered cyclised product **221** or the cyclic sulfamide **222** was isolated.



Scheme 40. *Reagents and conditions*: a) NaH, allyl bromide, DMF; b) TFA, CH_2Cl_2; c) NaH, NaI, 3-chloro-2-fluoro-propene, DMF; d) **4** (12 mol%), CH_2Cl_2, reflux, 9 h.

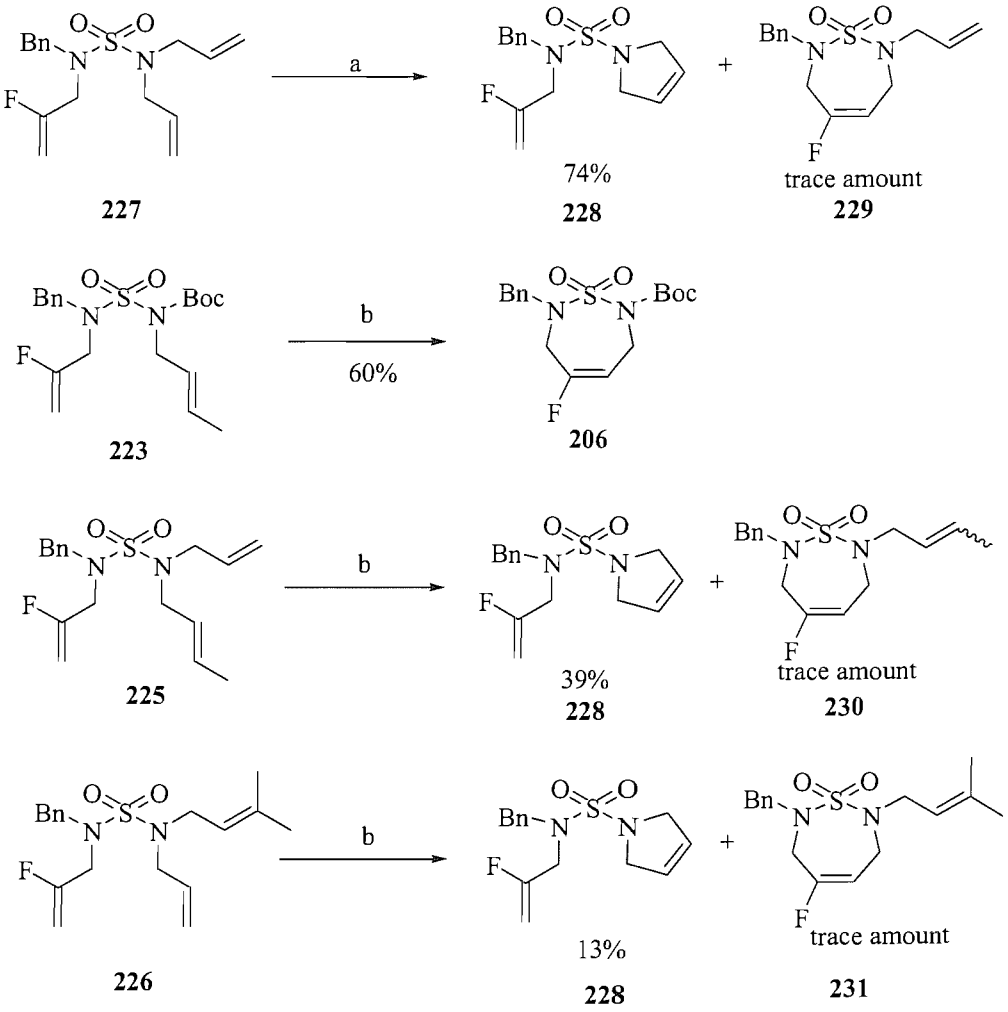
Another investigation was then undertaken to compare the reactivity of the fluorinated double bond with unfluorinated and substituted double bonds. RCM of the sulfamides **226** and **227** were attempted (**Scheme 41**). The synthesis of sulfamide **226** was carried out in a similar manner to that of sulfamide **204**, *via* the intermediate **203** which underwent alkylation with 4-bromo-2-methyl-2-butene to produce sulfamide **226** in good yield. In addition, the intermediate **203** was also allylated to produce another sulfamide-linked precursor **227** ready for subsequent RCM studies. The synthesis of sulfamide **225** was accomplished by treatment of sulfamide **197** with crotyl bromide in the presence of *t*-BuOK and 18-crown-6 to give the sulfamide **223** in good yield. Removal of the Boc group from sulfamide **223** yielded **224**, which was allylated with allyl bromide to give the desired sulfamide precursor **225** in excellent yield.



Scheme 41. *Reagents and conditions*: a) NaH, allyl bromide; b) TFA, CH_2Cl_2; c) *t*-BuOK, 18-crown-6, 4-bromo-2-methyl-2-butene; d) *t*-BuOK, 18-crown-6, allyl bromide; e) *t*-BuOK, 18-crown-6, crotyl bromide, THF.

Upon exposure of sulfamide **227** to metathesis conditions, the five-membered sulfamide **228** was obtained as the major product (74%) along with a trace amount of seven-membered sulfamide **229** (**Scheme 42**). From these results, we postulated that the formation of the minor product **229** could result from ring-opening metathesis of the five-membered ring **228**. To investigate this postulation, the five-membered sulfamide **228** was re-submitted to the metathesis conditions. It was found that none of the seven-membered sulfamide **229** was observed and only the starting material was recovered. RCM of substrate **223** which contains disubstituted and fluorinated double bonds was also attempted. This metathesis reaction gave the cyclic sulfamide **206** in moderate yield and 20% yield of recovered starting material. We therefore continued investigating RCM reaction of sulfamide **225** and **226**. The metathesis of **225** proceeded to afford five-membered sulfamide **228** as the major product (39%) and a trace amount of seven-membered cyclised product **230**. In addition, the RCM

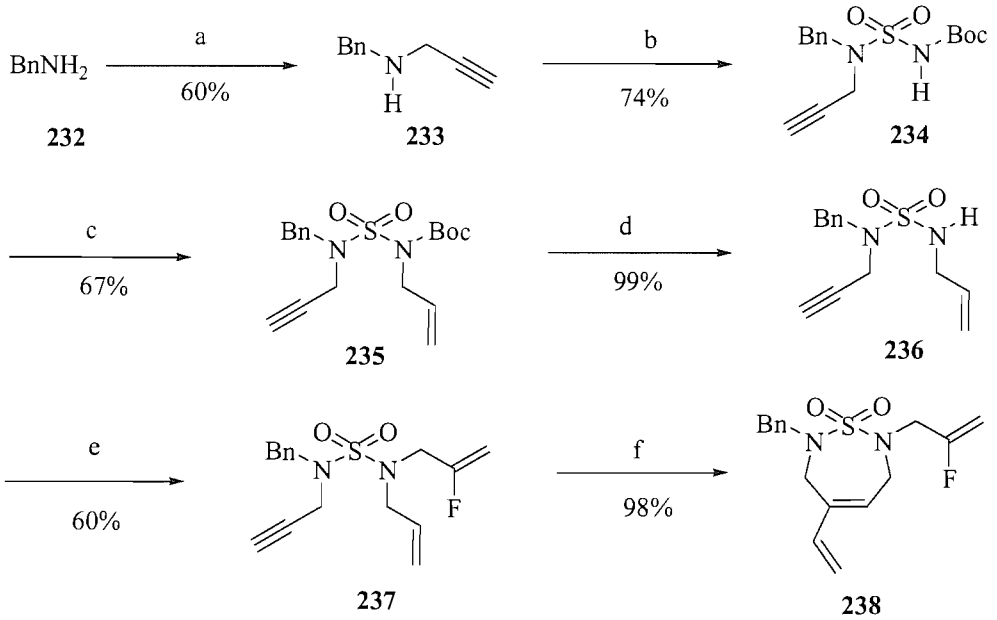
of sulfamide **227** also gave five-membered sulfamide **228** as the major product (13%), a trace amount of seven-membered cyclised product **231** and eventually decomposition of starting material. It was thought that the poor yields observed for the RCM of di- and tri-substituted sulfamides **225** and **226** were probably due to the substitution effect that may force the metathesis event to occur at the sterically-congested double bond, thus slowing the RCM reaction followed by decomposition of the ruthenium complex **4**.



Scheme 42. *Reagents and conditions*: a) **4** (5 mol%), CH_2Cl_2, reflux, 3 h; b) **4** (10 mol%), CH_2Cl_2, reflux, 10 h.

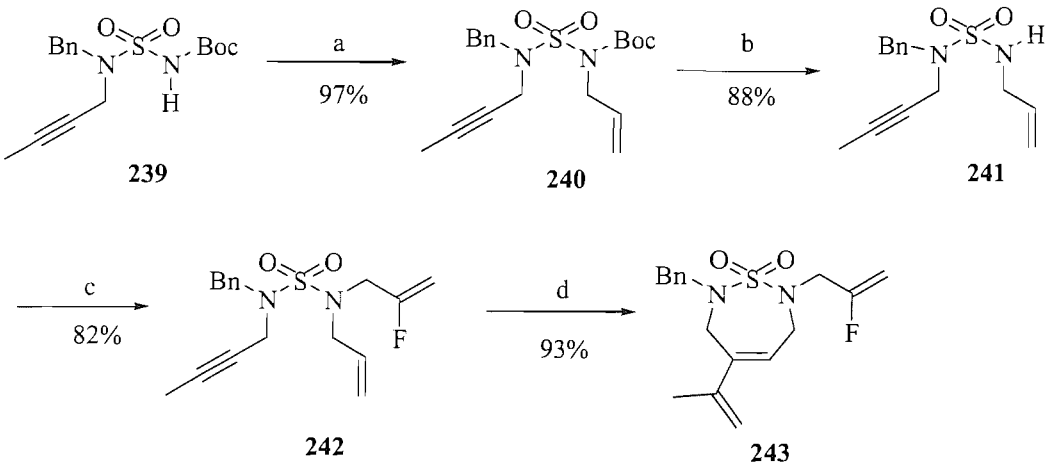
An extension of this study involved the exploration of the relative rates of the RCM between olefins, fluoro-olefins and alkynes. The sulfamide precursor **237** was synthesised starting from alkylation of benzylamine **232** with propargyl bromide to produce **233** (kindly supplied by S. Salim). The amine **233** was reacted with

chlorosulfonyl isocyanate and *t*-BuOH to afford sulfamide **234** in good yield which was subsequently alkylated to give **235**. Removal of the Boc protection from substrate **235** gave sulfamide **236**, which was alkylated with 3-chloro-2-fluoro-propene to afford sulfamide precursor **237** (**scheme 43**). The metathesis precursor **237** was then exposed to metathesis conditions. The metathesis reaction proceeded smoothly to give the enyne metathesis product **238** in excellent yield.



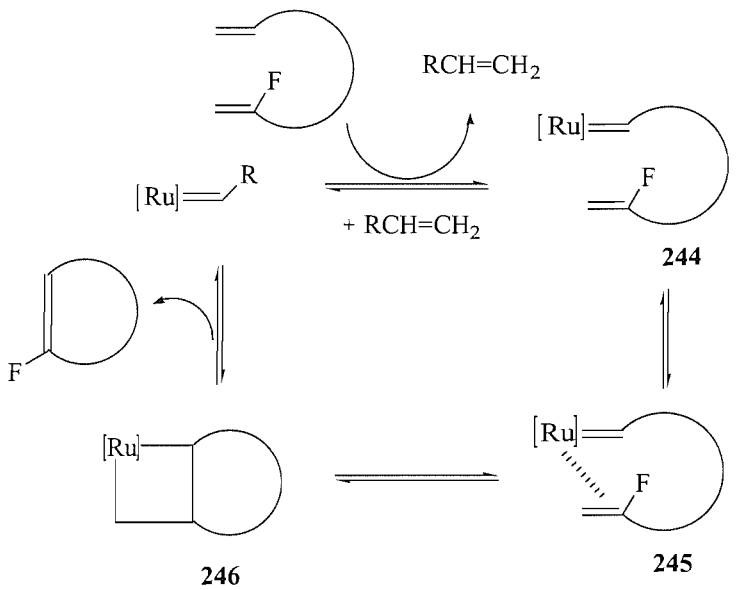
Scheme 43. *Reagents and conditions*: a) K_2CO_3, propargyl bromide, CH_3CN; b) chlorosulfonyl isocyanate, *t*-BuOH, Et_3N, CH_2Cl_2; c) NaH, allyl bromide, DMF; d) TFA, CH_2Cl_2; e) NaH, NaI, 3-chloro-2-fluoro-propene, DMF; f) **4** (10 mol%), CH_2Cl_2, reflux, 18 h.

Encouraged by these results, RCM of sulfamide precursor **242** was also attempted. The synthesis of sulfamide **242** was accomplished by alkylation of **239** (kindly supplied by S. Salim) to produce the intermediate **240**. From this point, the synthesis of sulfamide **242** was carried out in a similar manner to that of sulfamide **237** (**scheme 43**). The RCM of the sulfamide **242** was successfully carried out to afford the enyne metathesis product **243** in excellent yield (**Scheme 44**).



Scheme 44. *Reagents and conditions*: a) *t*-BuOK, 18-crown-6, allyl bromide; b) TFA, CH_2Cl_2; c) *t*-BuOK, 18-crown-6, NaI, 3-chloro-2-fluoro-propene; d) **4** (10 mol%), CH_2Cl_2, reflux, 18 h.

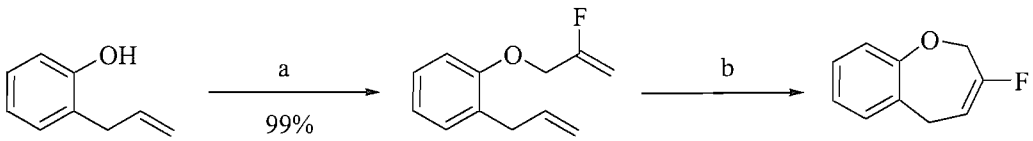
All competition experiments appeared to confirm our hypothesis that RCM reactions of fluoro-olefins are typically slower than their nonfluorinated analogues. The reaction pathway proposed below as previously reported (**Scheme 45**).[65] The first step would be reaction at the non-fluorinated olefin to form a ruthenium alkylidene complex **244**. Olefin coordination and subsequent cycloaddition can occur to provide the intermediate metallacyclobutane **246** when a suitable linking group is present. Breakdown of the metallacycle releases the alkene (**Scheme 45**).



Scheme 45. Proposed reaction pathway for RCM of fluoro-olefin containing dienes.

2.2.2 Synthesis and metathesis of ether-linked diene vinyl fluorides

Following the successful metathesis reactions of sulfamide-linked dienes, we attempted to extend this methodology to the synthesis of carbocyclic and heterocyclic compounds. The example of RCM of the ether-linked precursor **188** was commenced. The RCM substrate **188** was obtained from alkylation of 2-allyl phenol **247** with commercially available fluoro-olefins in the presence of (NaHMDS) (**Scheme 46**). The RCM precursor **188** was then exposed to metathesis conditions. Initially, the reaction was carried out by using 20 mol% of **4** and stirring at room temperature in CH_2Cl_2. However the reaction failed to go completion. The characteristic signals of the desired seven-membered product **189** were observed in the ^1H NMR spectra of the crude mixture at δ 5.61 ppm. More forcing conditions were required for the cyclisation. To this end, both microwave irradiation at 140 °C for 14 minutes and heating in sealed vial at 100 °C for 10 hours were carried out. The ^1H NMR spectra of the crude mixture of both methods indicated the improved conversion to the desired product however the reaction did not proceed cleanly. The purification of the desired product was extremely difficult. A partially purified sample (40% yield) was obtained after chromatography with base washed SiO_2. Unfortunately, isolation of a pure sample of the product was not possible due to its instability and volatility.

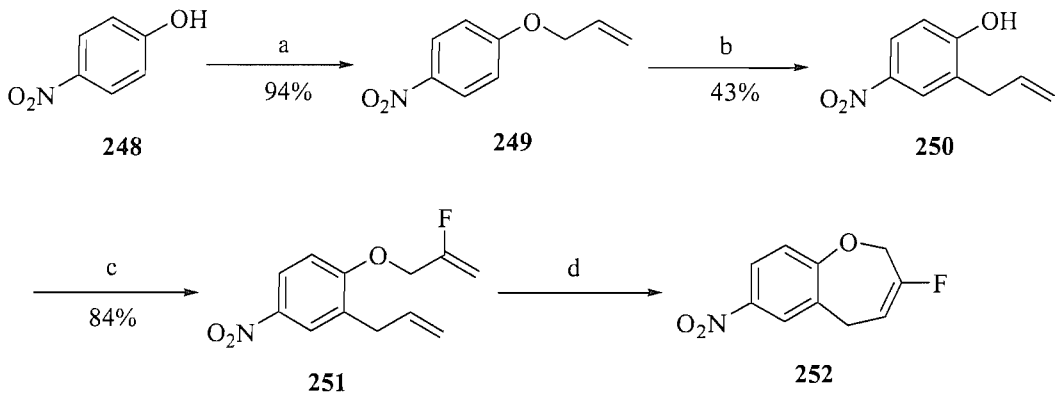


247 **188** **189**

Scheme 46. *Reagents and conditions*: a) NaHMDS, 3-chloro-2-fluoro-propene, DMF; b) **4** (20 mol%), CH_2Cl_2, μw, 140 °C, 12 min. or sealed vial, 100 °C, 10 h.

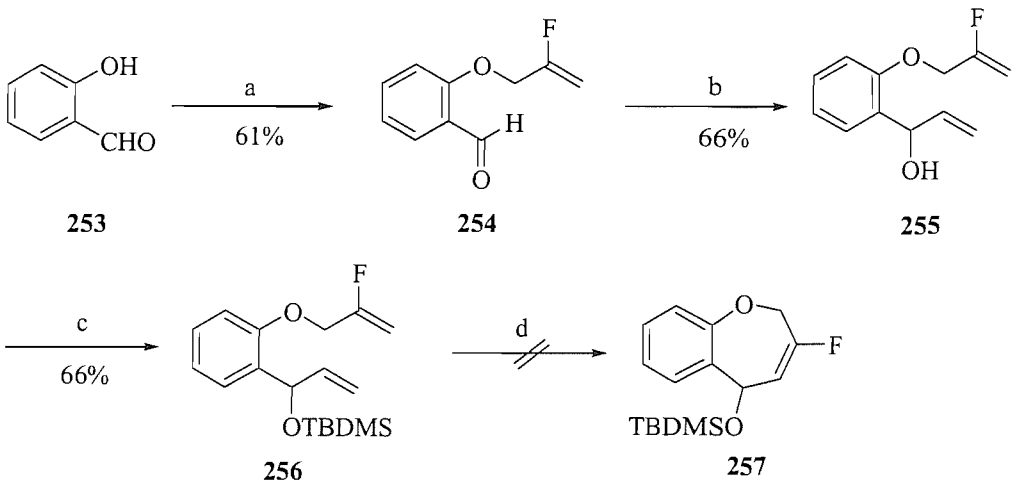
As an extension of the investigation on the RCM of ether-linked diene, the RCM substrate **251** was synthesized. It was believed that the inductive effect of *para*-nitro group could reduce any potential problems due to coordination between the ether oxygen and the ruthenium complex. Synthesis of diene precursor **251** was then carried out, starting with allylation of *p*-nitro phenol **248** to produce the phenyl ether **249** followed by *ortho*-Claisen rearrangement reaction to prepare intermediate **250**.[70]

The rearranged product **250** was then allylated to give RCM precursor **251**. Upon exposure of **251** to the metathesis conditions under microwave irradiation, the characteristic signals of the desired seven-membered product **252** were observed in the ^{1}H NMR spectra of the crude mixture. However the isolation of a pure sample of the product was again not possible (**Scheme 47**).



Scheme 47. *Reagents and conditions*: a) K_2CO_3, allyl bromide; b) *o*-dichlorobenzene, reflux; c) K_2CO_3, Bu_4NI, 3-chloro-2-fluoro-propene, DMF; d) **4** (20 mol%), CH_2Cl_2, μw, 12 min., 140°C.

In order to solve the problem of instability and volatility, the introduction of substituent group into the precursor **256** was attempted. The salicylaldehyde **253** was alkylated with commercially available fluoro-olefin in the presence of NaI to yield **254**. The transformation of the chloride to the iodide was required due to low reactivity of fluoro substrate to yield **254**. The aldehyde **254** was treated with a Grignard reagent to produce the intermediate **252**. The synthesis of the RCM substrate **256** was then completed by protection of the hydroxy group as a TBS-ether (**Scheme 48**).



Scheme 48. *Reagents and conditions*: a) NaH, NaI, 3-chloro-2-fluoro-propene, DMF; b) vinylmagnesium bromide, dry Et_2O; c) NaH, TBDMSCl, DMAP, THF; a) **4** (20 mol%), CH_2Cl_2, reflux, 10 h.

Upon exposure of the substrate **256** to metathesis conditions, the desired product was not detected and 75% of starting material **256** was recovered. The ^{1}H- and ^{19}F-NMR spectra of a minor compound showed that the characteristic signals of the fluorinated allyl group had disappeared and some decomposed catalyst. We considered that the formation of intermediate **258** or **259** might have taken place (**Figure 2**).

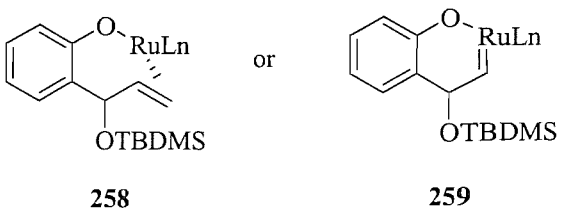
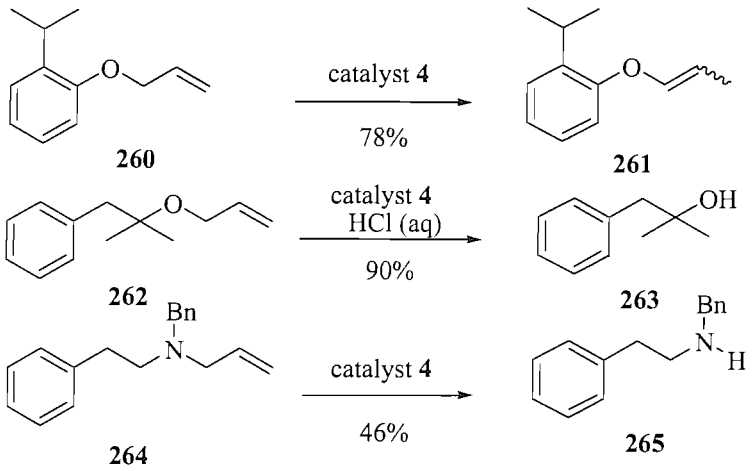


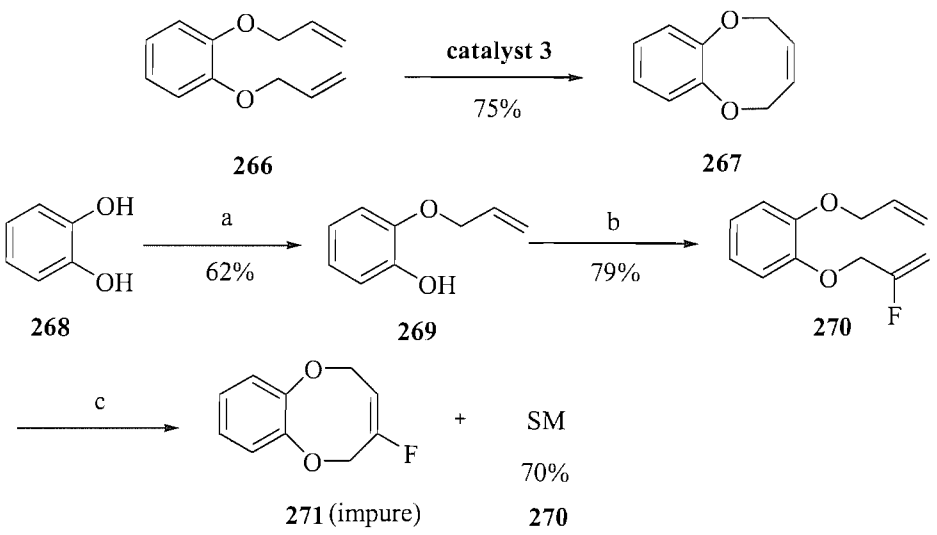
Figure 2. Proposed chelated intermediate from the RCM of precursor **253**.

Deallylation reactions in the presence of the second generation Grubbs catalyst **4** have previously been reported in the literature. Cossy *et al.* have reported that allyl and homo-allyl groups can undergo isomerisation in the presence of a ruthenium carbene complex **4** and acid (**Scheme 49**).[71]



Scheme 49. Isomerisation and deallylation of ether substrates reported by Cossy *et al.*

Despite the disappointing results from the formation of the seven-membered ether-linked fluoro-olefin *via* RCM reactions, a survey of the literature encouragingly revealed that the formation of eight-membered cyclic ether through RCM was feasible. The reaction appeared facile in systems where dienes are conformationally predisposed for ring formation, such as the catechol derivative **266** shown in **Scheme 50**.[72] We therefore set out to explore ring-closing metathesis of ether-linked vinyl fluoride substrate **270**. However, in this case RCM did not proceed cleanly. Again, the ^{1}H NMR spectra of crude mixture showed the characteristic peak of the desired cyclised product **271** at δ 5.90 ppm but the isolation of a pure sample of the product was not possible. Only 70% yield of recovered starting material was obtained (**Scheme 50**).



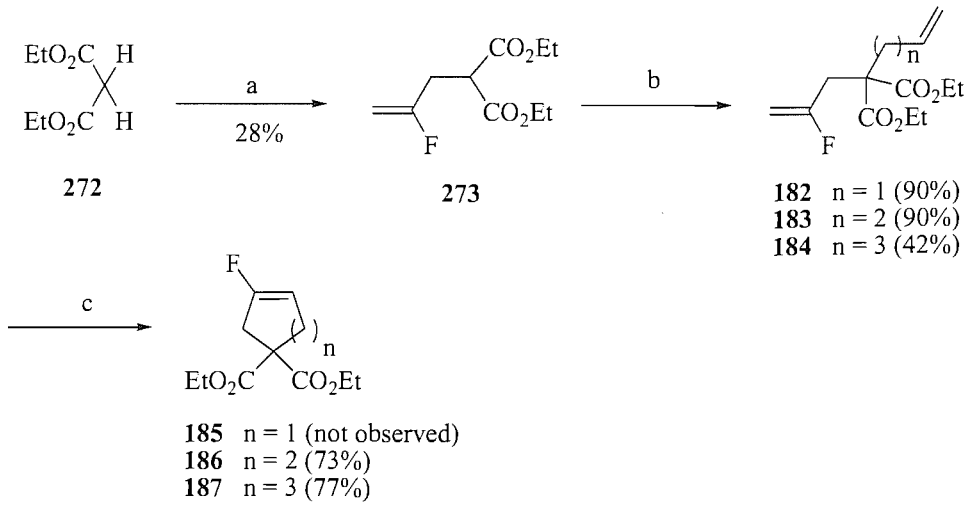
Scheme 50. *Reagents conditions*: a) K_2CO_3, Bu_4NI, allyl chloride, DMF; b) NaH, 3-chloro-2-fluoro-propene, DMF; c) **4** (20 mol%), CH_2Cl_2, μw, 12 min., 140°C.

All attempts to carry out RCM of ether-linked vinyl fluorides were unsuccessful. The RCM reactions did not proceed cleanly and only trace amounts of the desired cyclic products could only be observed from the ^1H NMR spectra of the crude mixture. It was initially thought that the RCM did not proceed to give the cyclic compound due to a combination of instability and possibly due to the volatility of the products. We therefore synthesized substrates **251**, **256**, and **270** in order to avoid any potential volatility of products. However, their cyclisation reactions were not successful.

2.2.3 Synthesis and metathesis of carbon-linked diene vinyl fluorides

In order to investigate the RCM of other classes of compounds, a variety of monofluorinated dienes with carbon in the linking chain were synthesized. The RCM substrates were obtained *via* the mono-alkylation of diethyl malonate **272** with the commercially available fluoro-olefin to produce the intermediate **273**. Subsequent alkylation of **273** with the corresponding alkylating agents was carried out to afford RCM substrates **182-184**. With these precursors in hand, RCM experiments were undertaken. The RCM of **183** and **184** proceeded smoothly to produce the expected six- and seven-membered carbocycles **186** and **187**, respectively in good yield. However the RCM of precursor **182** failed to provide the expected five-membered

carbocycle **185** and only starting material was recovered following exposure to metathesis conditions (**Scheme 51**).



272

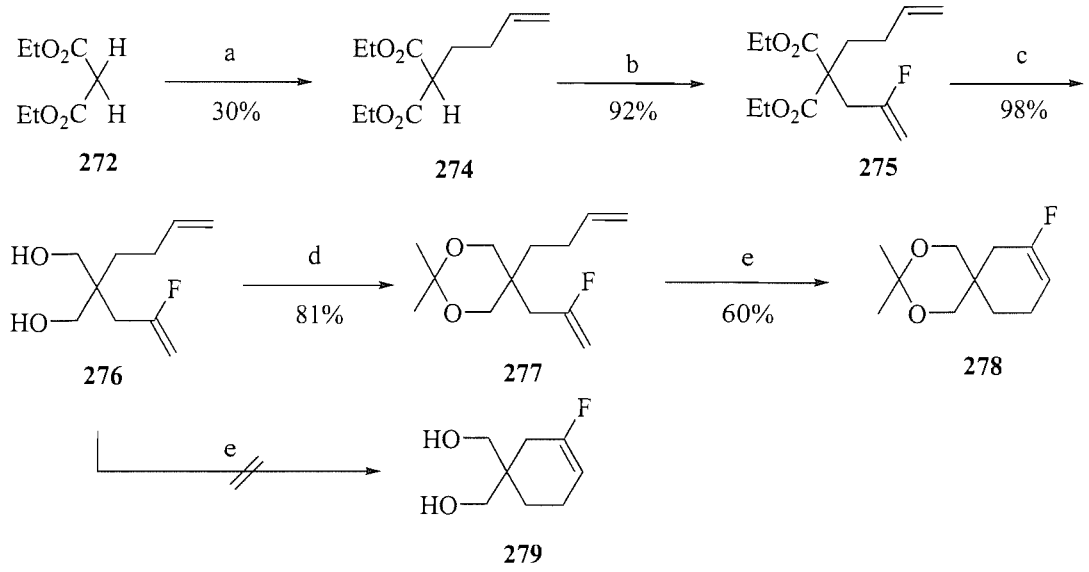
273

182 n = 1 (90%)
183 n = 2 (90%)
184 n = 3 (42%)

185 n = 1 (not observed)
186 n = 2 (73%)
187 n = 3 (77%)

Scheme 51. *Reagents and conditions*: a) NaH, 1-chloro-2-fluoroprop-2-ene, DMF; b) NaHMDS, NaI, allylbromide (n = 1) or 4-bromo-1-butene (n = 2) or 5-bromo-1-pentene (n = 3), DMF; c) **4** (12 mol%), CH_2Cl_2, reflux, 18 h.

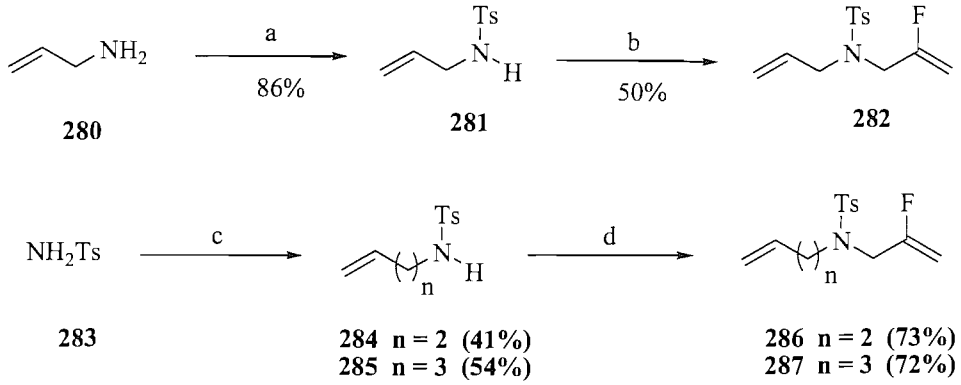
As an extension of the investigation on the RCM of carbon-chain dienes, the RCM precursors **276** and **277** were synthesized. Thereby, reduction of the ester groups gave 1,3-diol product **276** ready for subsequent RCM reaction. Furthermore, the RCM of the protected diol **277** was also attempted. The substrate **277** was obtained by the reaction of diol with dry acetone in the presence of Amberlyst® 15 and molecular sieves (**Scheme 52**). Precursors **276** and **277** were then exposed to metathesis conditions, but unfortunately none of the expected product **279** was observed in the case of diol substrate **276**. However the RCM of protected diol **277** gave the desired six-membered ring **278** in good yield.



Scheme 52. *Reagents and conditions*: a) NaHMDS, 4-bromo-1-butene, DMF; b) NaH, NaI, 3-chloro-2-fluoro-propene, DMF; c) $LiAlH_4$, THF; d) acetone, Amberlyst® 15, 4°A molecular sieve; e) **4** (10 mol%), CH_2Cl_2, reflux, 10 h.

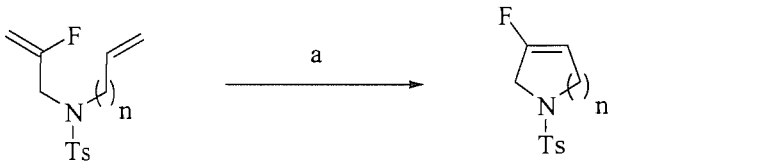
2.2.4 Synthesis and metathesis of amine-linked diene vinyl fluorides

In order to investigate the RCM of monofluorinated amine-linked dienes, a number of amine precursors were synthesized. The precursor **282** was obtained by tosylation of allylamine followed by alkylation with commercially available fluoro-olefin. Other amine precursors **286** and **287** were prepared by alkylation of *p*-toluenesulfonamide with 4-bromo-1-butene or 5-bromo-1-pentene to give alkenes **284** and respectively **285**. Products **284** or **285** were then fluoro-alkylated to produce RCM substrates **286** and **287** (**Scheme 53**).



Scheme 53. *Reagents and conditions*: a) TsCl, Et_3N, CH_2Cl_2; b) NaH, 1-chloro-2-fluorprop-2-ene, DMF; c) NaH, 4-bromo-1-butene (n =2) or 5-bromo-1-pentene (n = 3), DMF; d) NaH, 1-chloro-2-fluorprop-2-ene, DMF

We were very pleased to find that RCM of **286** or **287** occurred successfully afford the six- and seven-membered vinyl fluoride in excellent yields. However, no cyclisation was observed in the case of the five-membered ring precursor **282** and only starting material was recovered (**Scheme 54**). It was noted that deallylation did not occur in this case.



282 n = 1
286 n = 2
287 n = 3

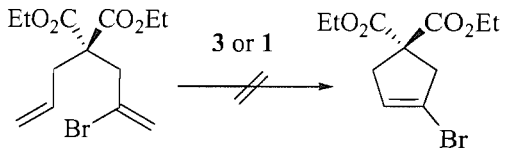
288 n = 1 (not observed)
289 n = 2 (94%)
290 n = 3 (84%)

Scheme 54. *Reagents and conditions*: a) **4** (14 mol%), CH_2Cl_2, reflux.

2.3 Ring-closing metathesis of vinyl bromo-containing dienes

Despite the tremendous advances that have been made in the development of practically useful catalysts, there still remain limitations to the RCM process. Exposure of *mono*-bromo dienes to the widely used Grubbs' metathesis catalysts have been reported not to afford the products of RCM.[73] Given the potential value of bromo-olefins as one of the most significant building blocks for transition metal catalyzed reactions, such as palladium cross-coupling,[74] and in halogen-magnesium exchange[75] reactions we decided to reinvestigate their synthesis by RCM.

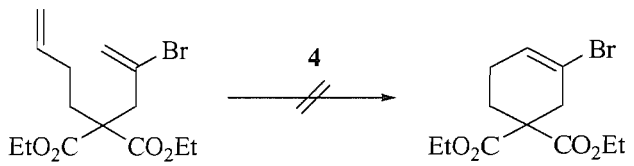
Prior to our study, the RCM of vinyl-bromo dienes had been reported not to proceed. In 1997, Grubbs and co-worker reported that the RCM reaction of bromo-substituted dienes **291** with the first generation Grubbs catalyst **3** or molybdenum alkylidine complex **1** afforded none of the cyclic products **292** and only dienes and alkylidene decomposition products were detected (**Scheme 55**).[73] Presumably, due to a combination of the steric effect of substituent and the electron-withdrawing group effect of the halide group, the rate of ring-closing metathesis becomes so slow that catalyst decomposition is competitive with ring-closing metathesis.



291 **292**

Scheme 55. Attempted ring-closing metathesis of bromo-substituted dienes as reported by Grubbs *et al.*

Since the discovery of new catalysts with high metathesis activity, for example the second generation Grubbs catalyst **4** which exhibits excellent functional group compatibility, particularly with electron deficient olefins,[13] exposure of *mono*-bromo dienes to the powerful Grubbs metathesis catalysts has been reported. Weinreb and Chao attempted RCM of a vinyl bromide under conditions developed for vinyl chlorides. But no reaction was observed (**Scheme 56**).[76] The author postulated that the vinyl bromide functionality in **293** would first react with Grubbs catalyst leading to the formation of unstable Fischer-type carbene.



293 **294**

Scheme 56. Attempted metathesis of vinyl bromide **43** as reported by Weinreb

Despite previous reports on the failure of the metathesis of vinyl-bromo diene precursors by Grubbs and Weinreb, it was decided to apply the expertise developed for fluoro-olefin metathesis to investigate the viability of the analogous metathesis of

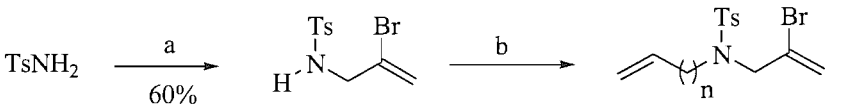
vinyl bromides. It also would be interesting to investigate some unanswered mechanistic questions regarding these RCM reactions. Moreover, if successful this methodology would provide an important new regioselective route to cyclic bromo-olefins which are difficult to prepare otherwise.

2.4 Synthesis and metathesis of vinyl bromo-containing dienes

In order to investigate the RCM of vinyl bromides, we decided to prepare a variety of *C*, *N* and *O*-linked substrates. Those efforts will be described in the following section.

2.4.1 Synthesis and metathesis of amine-linked diene vinyl bromides

In order to investigate the RCM of monobrominated dienes with a heteroatom in the linking chain, a number of amine precursors were synthesized. Beginning with alkylation of *p*-toluenesulfonamide **283** with commercially available 2,3-dibromo-1-propene. A variety of monobrominated dienes in the amine series were obtained by subsequent alkylation with the corresponding alkylating agents in the presence of *t*-BuOK and 18-crown-6 to provide the metathesis precursors **296**, **297**, **298** and **299** (**Scheme 57**). The alkylations were carried out in the presence of 18-Crown-6 which specifically solvates K^+ and enhances the reactivity of the sulfonamide anion.



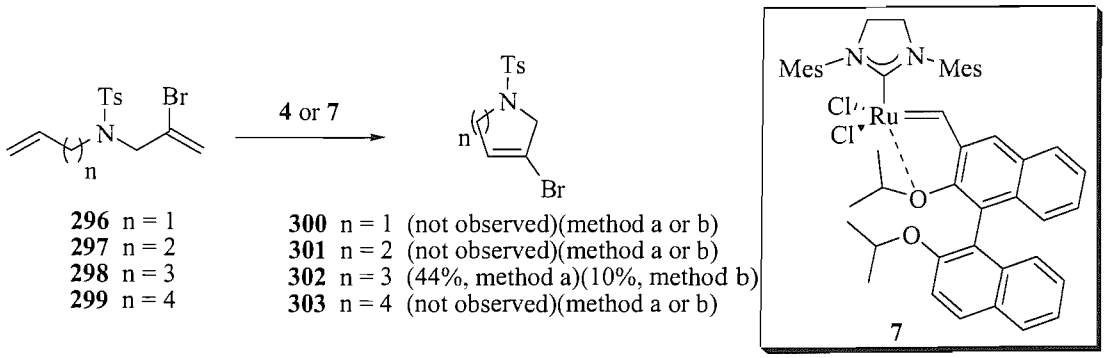
283 **295**

296 n = 1 (94%)
297 n = 2 (85%)
298 n = 3 (83%)
299 n = 4 (80%)

Scheme 57. *Reagents and conditions*: a) *t*-BuOK, 18-crown-6, 2,3-dibromo-1-propene, THF; b) *t*-BuOK, 18-crown-6, allyl bromide (n = 1) or 4-bromo-1-butene (n = 2) or 5-bromo-1-pentene (n = 3) or 6-bromo-1-hexene (n = 4), THF.

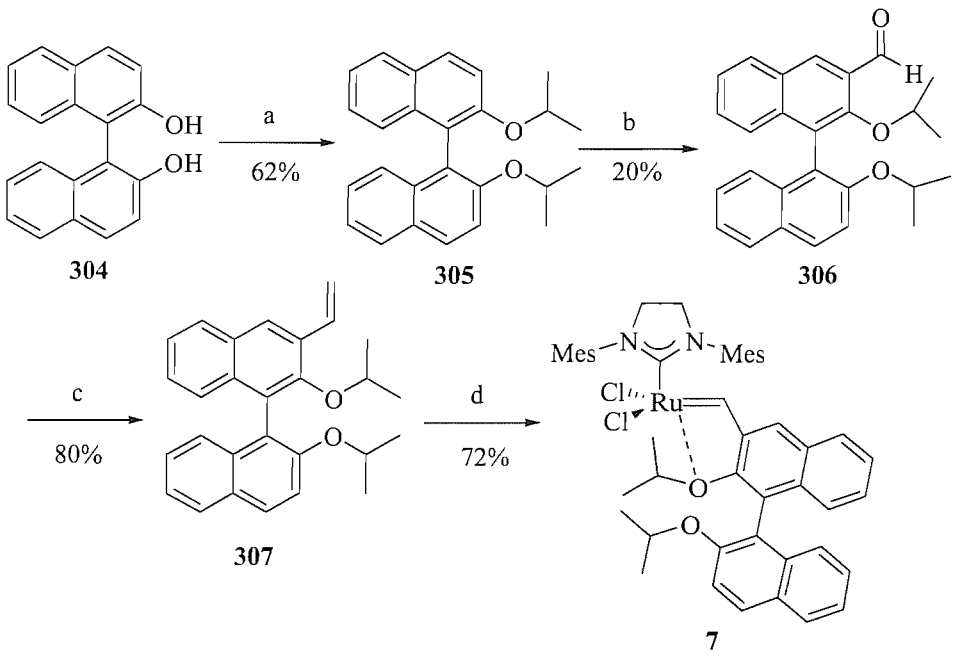
The metathesis precursors **296-299** were then exposed to ring-closing metathesis conditions developed for the fluoro-olefins RCM (**Section 2.1**). Disappointingly, the

RCM reactions of bromo-substituted precursors **296**, **297** and **299** did not give the expected five-, six- and eight-membered bromo-alkene products and only starting materials were recovered. Surprisingly, the seven-membered cyclised product **302** was observed with moderate yield from the RCM of **298** using 10 mol% of the second generation Grubbs catalyst under reflux in CH_2Cl_2 or benzene for 10 hours (**Scheme 58**).



Scheme 58. *Reagents and conditions*: a) **4** (10 mol%), CH_2Cl_2 or benzene, reflux, 10 h; b) **7** (5-10 mol%), CH_2Cl_2 or benzene, RT or reflux, 10 h.

Meanwhile, a survey of the literature revealed that the BINOL-derived ruthenium complex **7** developed by Blechert and Wakamatsu exhibits high reactivity toward electron-deficient olefins such as acrylonitrile and fluorinated olefins.[17] Therefore, we turned attention to investigation of the RCM of the above vinyl bromo dienes using BINOL-based ruthenium complex **7**. To synthesize the required catalyst **7**, ligand **307** was prepared from commercially available, 2,2'-dihydroxy-1,1-binaphthyl (racemic) **304** by treatment with *i*-PrBr in the presence of NaH to give isopropoxy protected alcohol **305** in good yield. Subsequent monoformylation was carried out by treatment with *n*-BuLi and DMF to give aldehyde product **306** in poor yield. The *ortho*-lithiation of **305** with *n*-BuLi gave many unidentifiable products resulting in the low yield of desired products **306**. Wittig olefination was utilised to produce ligand **307** in high yield. The complexation of ligand **307** with the second generation Grubbs catalyst **4** proceeded in the presence of CuCl to furnish the ruthenium complex **7** in good yield (**Scheme 59**).[17]

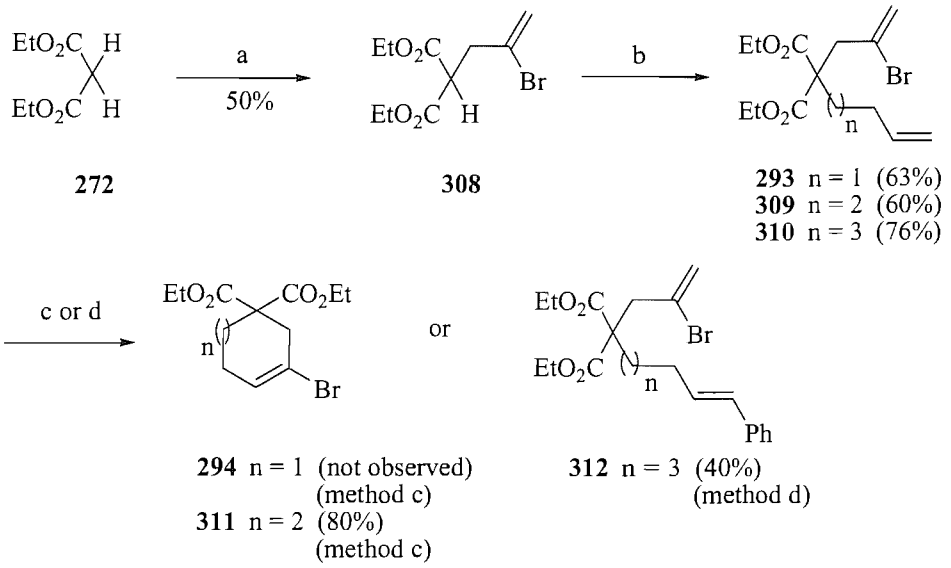


Scheme 59. *Reagents and conditions*: a) i. NaH, DMF, ii. *i*-PrBr, RT; b) i. *n*-BuLi, THF, 0 °C, ii. DMF, RT; c) $Ph_3(CH_3)P^+Br^-$, *t*-BuOH, Et_2O, 0 °C; d) **4** (2 equiv), CuCl (1 equiv), CH_2Cl_2, 40 °C.

However, having moderate success for the RCM of **298** using ruthenium complex **7**, treating diene **298** with 5-10 mol% of ruthenium complex **7** stirring in CH_2Cl_2 or benzene at room temperature for 10 hours gave some of the desired product **302**, however, in poor yield (10% yield). Either refluxing for 10 hours in CH_2Cl_2 or benzene also gave the desired product in poor yield in addition to recovered starting material.

2.4.2 Synthesis and metathesis of carbon-linked diene vinyl bromides

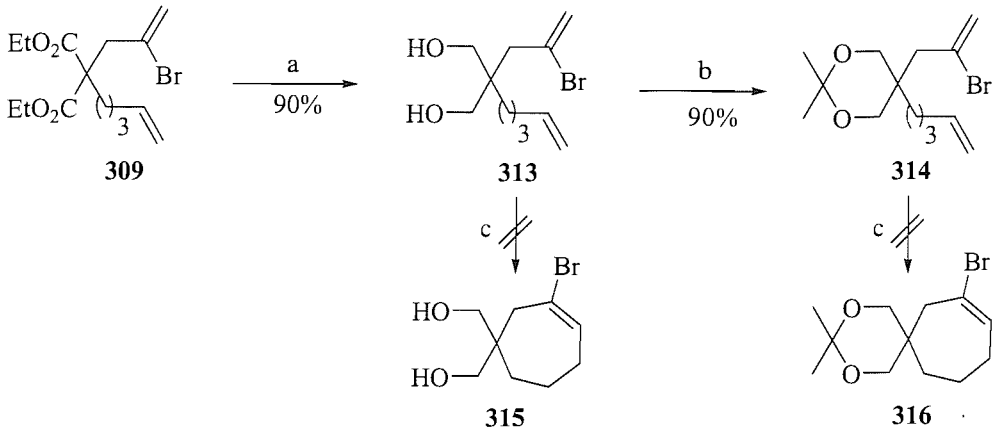
It was of interest to investigate whether this methodology could be applied to other classes of compounds. A number of carbocyclic precursors were easily obtained *via* the mono-alkylation of diethyl malonate **272** with commercially available 2,3-dibromo-1-propene, followed by alkylation with the required bromo-alkene to provide RCM substrates **293**, **309**, **310** in moderate to good yields (**Scheme 60**).



Scheme 60. *Reagents and conditions*: a) *t*-BuOK, 18-crown-6, 2,3-dibromo-1-propene, THF; b) *t*-BuOK, 18-crown-6, 4-bromo-1-butene (n = 1) or 5-bromo-1-pentene (n = 2) or 6-bromo-1-hexene (n = 3), THF; c) **4** (10 mol%), benzene, reflux, 10 h; d) **4** (20 mol%), benzene, reflux, 18 h.

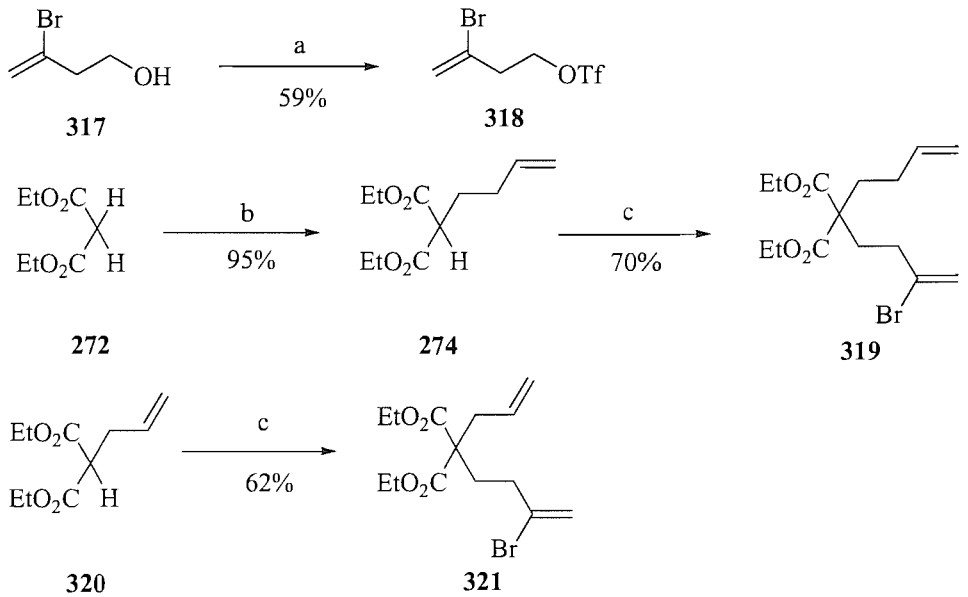
Upon exposure of **293** to metathesis conditions, the metathesis failed to provide the six-membered carbocyclic ring **294** and only starting material was recovered. As in the case of the nitrogen-linked series, attempted RCM of **297** to produce the cyclohexene derivatives **301** was not successful (**Scheme 58**). However, surprisingly, RCM of **309** carried out using 10 mol% of the second generation Grubbs catalyst under reflux in benzene for 10 hours afforded the seven-membered cyclised product **311** in high yield. In addition, the RCM of substrate **310** carried out using 20 mol% of the second generation Grubbs catalyst under reflux in benzene for 18 hours producing 20% yield of cross coupling product **312** and 50% yield of recovered starting material (**Scheme 60**).

As an extension of the investigation on the RCM of carbon-linked dienes, the RCM precursor **313** and **314** were synthesized (**Scheme 61**). Thereby, reduction of the ester group with $LiAlH_4$ gave 1,3-diol product **313** ready for the subsequent RCM reaction. Protection of 1,3-diol **313** was carried out to provide another substrate **314** for RCM reaction. RCM reaction of diol substrate **313** and protected diol **314** were investigated (**Scheme 61**). However, no cyclisation product was observed in this case and only recovered starting material was obtained.



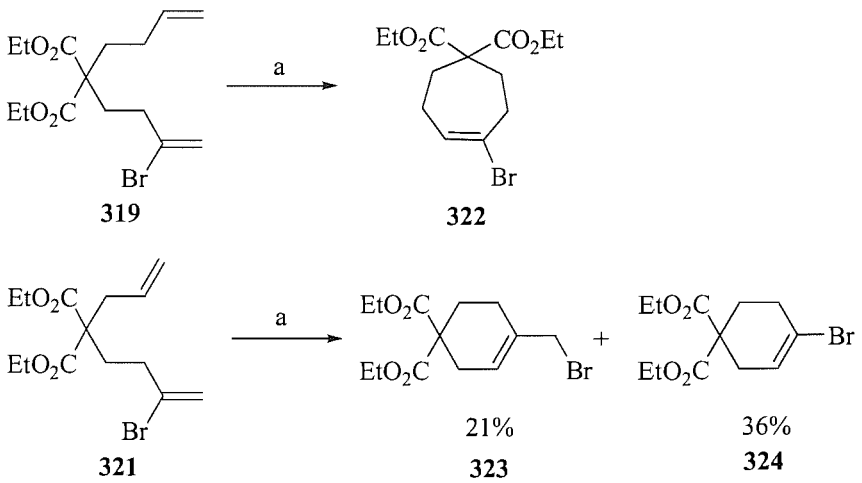
Scheme 61. *Reagents and conditions*: a) $LiAlH_4$, THF; b) Amberlyst® 15, 4 Å molecular sieves, acetone; c) **4** (10 mol%), PhH, reflux, 10 h.

Despite previous reports on the failure of RCM of vinyl bromides to provide six-membered cyclised products (**Scheme 60**), we felt that it would be interesting to investigate the RCM of carbon-linked dienes by extending the carbon length adjacent to the bromo diene moiety which would give the corresponding six-membered products (**Scheme 62**). Alkylation of diethyl malonate **272** with 4-bromo-1-butene was carried out to produce monoalkylated product **274**. Subsequent alkylation was accomplished by treatment of **274** with the corresponding triflate **318** to yield **319**. An additional RCM substrate **321** was prepared by alkylation of diethyl allylmalonate **320** and triflate **318**.



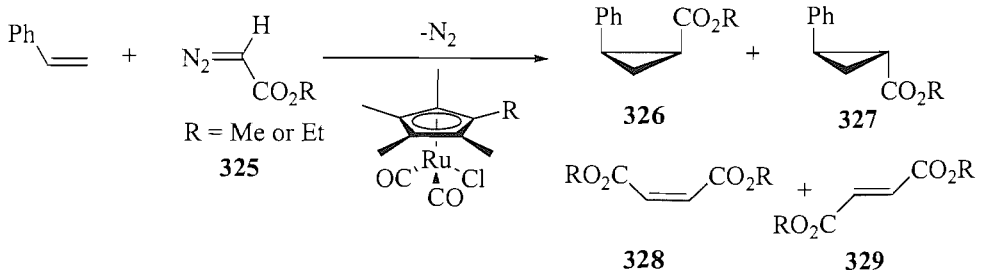
Scheme 62. *Reagents and conditions*: a) Tf_2O, pyridine, CH_2Cl_2. 0 °C; b) *t*-BuOK, 18-crown-6 and 4-bromo-1-butene; c) *t*-BuOK, 18-crown-6 and **318**.

Under metathesis conditions developed previously for vinyl-bromo olefin RCM using 10 mol% of the second generation Grubbs catalyst **4** under reflux for 10 hours, the bromo-substituted precursor **319** gave some cyclised product. The characteristic triplet at around 6.15 ppm was observed in the ^{1}H NMR spectra of the crude mixture. However, purification by normal flash column chromatography was not possible (**Scheme 63**). Surprisingly, under the identical conditions the bromo precursor **321** gave the cyclised product **323** (21%) which exhibited characteristic triplet at 5.78 ppm and desired product **324** (36%) which showed the characteristic triplet at 6.02 ppm in the ^{1}H NMR spectra. Moreover, low resolution mass spectroscopy analysis shown mass numbers (341, 342) and (327, 328) which could be attributed to the cyclised product **323** and the desired product **324** respectively.



Scheme 63. *Reagents and conditions*: a) **4** (10 mol%), PhH, 60 °C, 10 h.

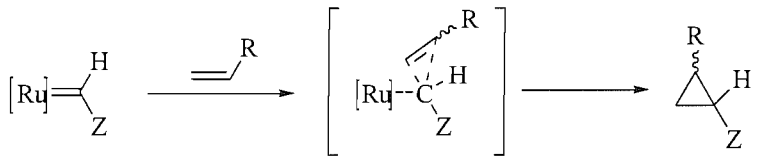
Ruthenium-based carbene complexes can function as versatile catalysts for olefin metathesis and olefin cyclopropanation. Several different ruthenium complexes are presented which have been shown to be suitable catalysts for carbenoid cyclopropanation.[77] Cyclopropanation of styrenes with methyl diazoacetate (MDA) or ethyl diazoacetate (EDA) has been reported (**Scheme 64**).[78]



Scheme 64. Ruthenium-carbene complexes structure mediated cyclopropanation reaction.

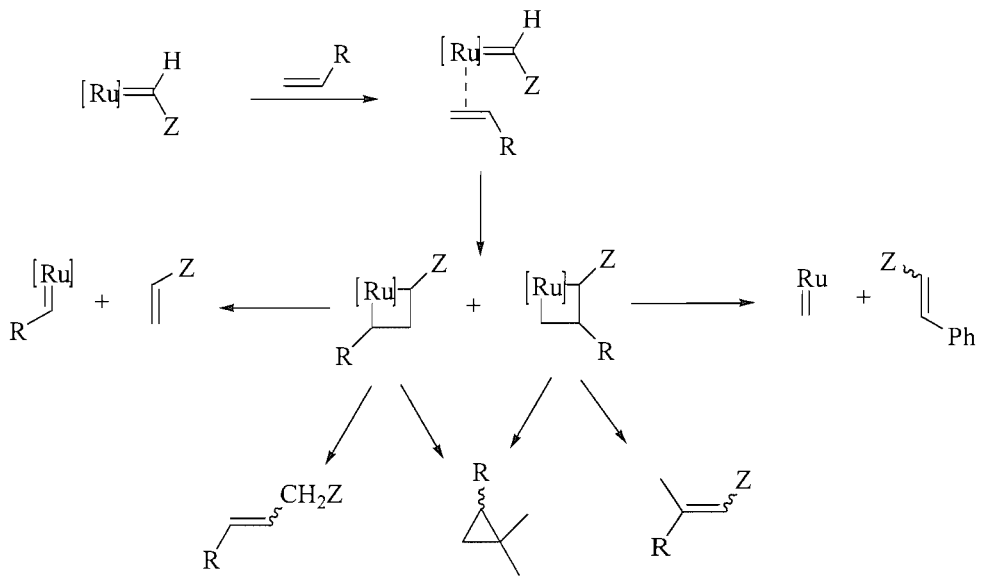
The reaction yielded a diastereomeric mixture of cyclopropanes *cis*-**326** and *trans*-**327**, accompanied by the formal carbene dimer *Z*-**328** and *E*-**329**. Two principle pathways may be discussed for the carbene transfer from a carbene complex to an alkene, *via* carbenoid (**pathway A**) (**Scheme 65**) and a coordination mechanism (**pathway B**) (**Scheme 66**).

Pathway A



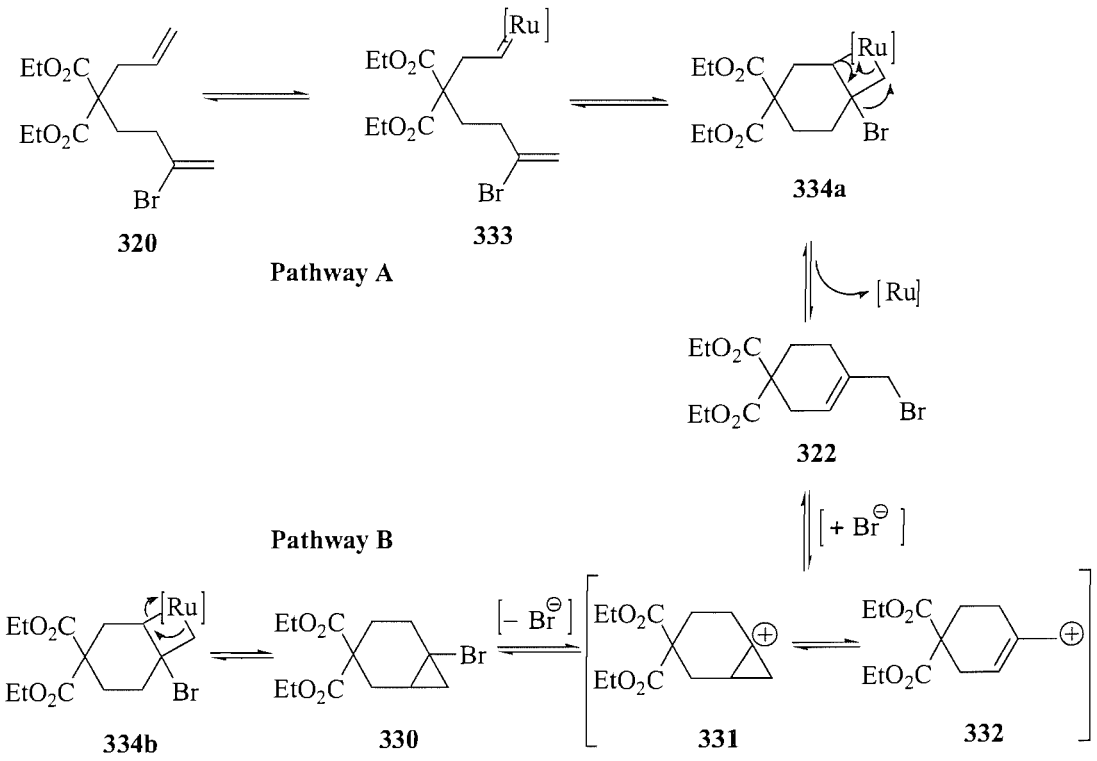
Scheme 65. Carbenoid pathway

Pathway B



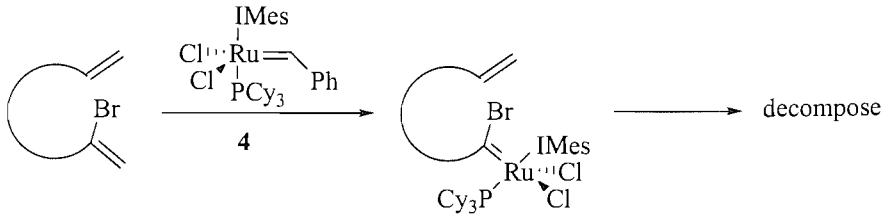
Scheme 66. Coordination mechanism

In view of the mechanistic studies of the ruthenium carbene complex-catalysed reactions described above, we therefore suggest that two possible pathways can be exhibited in the reactions of bromo-olefins (**Scheme 67**). A reaction might involve the formation of metallacycle **334a** and subsequent rearrangement of the bromine to release the cyclised product **322** with the elimination of ruthenium (**pathway A**). The second possible pathway (**pathway B**) might involve reductive elimination from metallacycle **334b** to produce bromo-cyclopropanated intermediate **330**. Subsequent rearrangement of **330** would lead to the allylic bromide **322** (**pathway A**). However, neither of the two mechanisms presented provide a clear catalytic pathway to the allylic bromide.



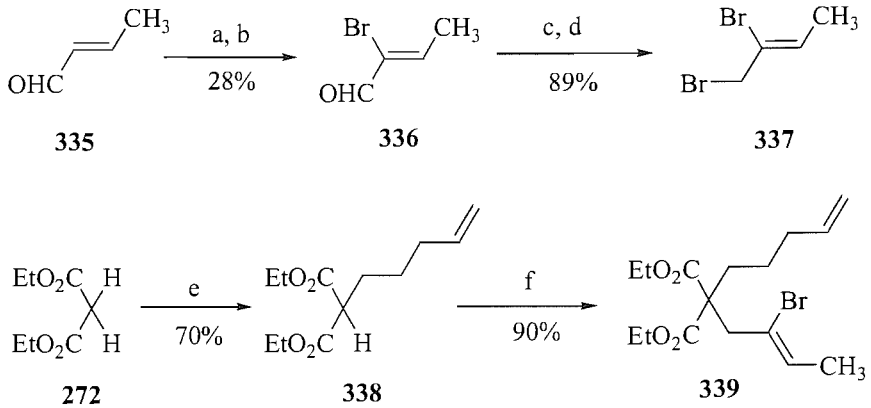
Scheme 67. Proposed pathways for the formation of the cyclised product **322**.

Initially it was thought that the reaction may not proceed due to the vinyl bromide functionality first reacting with the Grubbs catalyst forming Fischer-type carbene complex (**Scheme 68**).



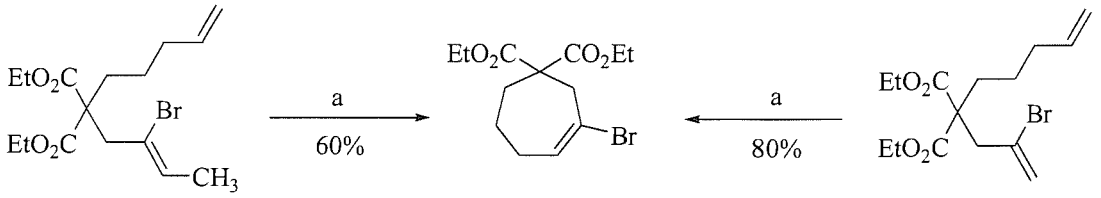
Scheme 68. Ruthenium Fischer-type carbene complex

Therefore, preventing initial reaction of the halo-olefin with the catalyst was attempted by directing the initial reaction of the catalyst to the unbrominated olefin. According to this plan, the synthesis of trisubstituted bromo-olefin precursors was carried out (**Scheme 69**). Synthesis of alkylating agents **337** were carried out following the procedure of Kowalski.[79] Treatment of *trans*-crotonaldehyde **335** with bromine solution and subsequent addition of triethylamine gave the bromo-enone **336** in a yield of 28%. Reduction of the aldehyde **336** gave the bromo-alcohol in good yield.[80] Conversion of hydroxyl group into bromide was achieved using phosphorus tribromide in diethyl ether to give bromo compound **337** in good yield (89%).[11] A trisubstituted brominated compound **339** was obtained by alkylation of **338** with alkylating agent **337** in the presence of *t*-BuOK and 18-crown-6 in good yield (90%) (**Scheme 69**).



Scheme 69. *Reagents and conditions*: a) Br_2, CH_2Cl_2, –78 °C to 0 °C; b) NEt_3, –78 °C; c) $NaBH_4$, THF/H_2O 9:1; d) PBr_3, Et_2O; e) *t*-BuOK, 18-crown-6, 5-bromo-1-pentene, THF; f) *t*-BuOK, 18-crown-6, **337**, THF.

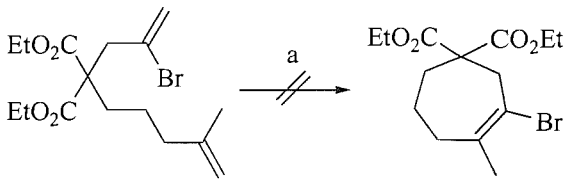
Precursor **339** was then subjected to metathesis conditions, the seven-membered product **311** was obtained in moderate yield (60%) (**Scheme 70**). The cyclised product was observed, however, a reduced yield was obtained. For comparison, the yield from the RCM of disubsituted bromo-olefin precursor **309** was 80%. These results demonstrated that presumed retardation of the rate of reaction at the bromo-olefin functionality by introduction of substitution allowed the catalyst to initiate at the less substituted alkene. However, it can also decrease the reaction rate of the subsequent cyclisation step.



339 **311** **309**

Scheme 70. *Reagents and conditions*: a) **4** (10 mol%), PhH, reflux, 10 h.

In order to investigate the relative rates of the RCM with other substituted olefins, alkyl substituted-olefins and bromo-olefins, the RCM of **340** was carried out using 10 mol% of the second generation Grubbs catalyst **4** refluxing in PhH (**Scheme 71**). Disappointingly, no cyclisation was observed and only starting material was recovered.

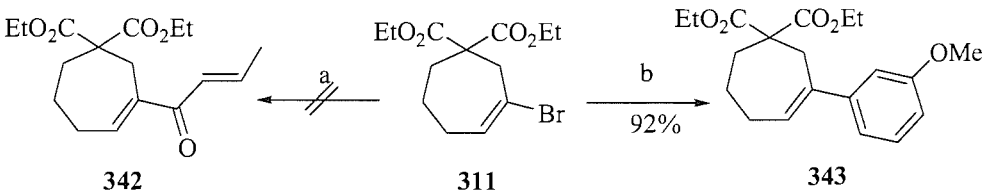


340 **341**

Scheme 71. *Reagents and conditions*: a) 10 mol% catalyst **4**, PhH, reflux, 10 h.

In order to illustrate the utility of some of the products obtained from bromo-olefin metathesis. We decided to investigate Pd-cross coupling reactions and halogen-metal-exchange. An example of a Suzuki cross coupling reaction of **311** was carried out to in order to demonstrate the utility of this type of product. Treatment of cyclised products **311** with aq. Na_2CO_3 and 3-methoxyphenyl boronic acid in the presence of catalytic amount of $Pd(PPh_3)_4$ gave the coupled product **343** in excellent yield.[74] Disappointingly, a bromine–magnesium exchange of metathesis product **311**

with *iso*-propylmagnesium bromide did not give the desired product **342** (**Scheme 72**).[75] We have not made any further efforts to develop halogen-magnesium exchange reaction.

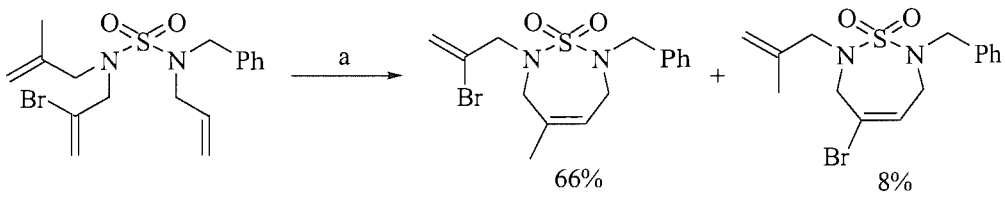


342 **311** **343**

Scheme 72. *Reagents and conditions*: a) *i*-PrMgCl, *trans*-crotonyl chloride, THF; b) 2 M Na_2CO_3, 3-methoxyphenyl boronic acid and $Pd(PPh_3)_4$ (5 mol%), THF.

2.4.3 Metathesis of sulfamide-linked diene vinyl bromides

To evaluate the feasibility of bromo-olefin metathesis a number of substrates were prepared following established methods.[76] RCM of sulfamide precursor **344** also carried out using 10 mol% of the second generation Grubbs catalyst **4** under reflux in PhH (**Scheme 73**). Ring-closing metathesis of sulfamide **344** proceeded to afford sulfamide **345** as the major product (66%) and a minor of sulfamide **346** (8%).

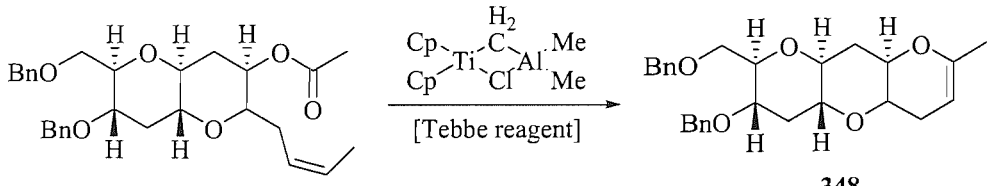


344 66% **345** 8% **346**

Scheme 73. *Reagents and conditions*: a) **4** (10 mol%), PhH, 60 °C, 10 h.

2.5 Ring-closing metathesis of thioacetal precursors using titanium-carbene complexes

Transition metal mediated ring-closing metathesis of dienes is a useful method for the synthesis of various cyclic compounds. Ruthenium,[72, 81] molybdenum,[82] tungsten[83] and rhenium[84] have been employed as catalyst for such transformation. In 1996, Nicolaou and his co-workers reported a new strategy for preparation of cyclic enol ethers **348** directly from unsaturated esters **347** based on RCM using the Tebbe reagent (**Scheme 74**).[22]

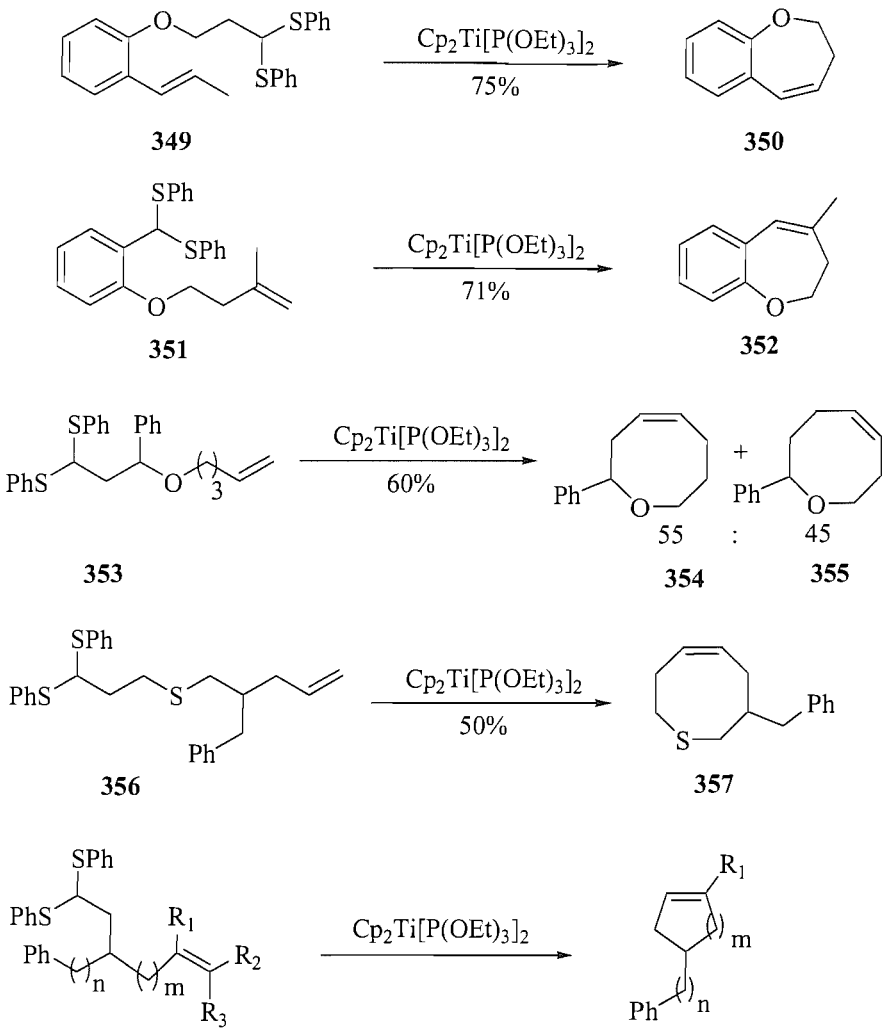


347 **348**

Scheme 74. Titanium-mediated metathesis strategy for the conversion of unsaturated esters to cyclic enol ethers

Initially, Tebbe reagent would methylenate the ester **347** forming an *exo*-methylene group. Subsequently, the methylenation product would react with a second molecule of Tebbe reagent to afford titanocyclobutane and then lead to a titanium-alkylidene complex. Intramolecular reaction *via* olefin metathesis occurred to produce the desired cyclic enol ethers **348**.

Following the development of RCM using titanium-carbene complexes, the ring-closing metathesis of diphenyl thioacetals dienes using low-valent titanium species was reported by Takeda and co-workers.[85] Titanocene (II) species underwent metathesis reaction with thioacetal dienes producing the cyclic ethers and sulfides in moderate to good yield (**Scheme 75**).



358 n = 3, m = 1, R_1, R_2, R_3 = H
359 n = 3, m = 1, R_1, R_3 = H, R_2 = Me
360 n = 3, m = 1, R_1 = H, R_2, R_3 = Me
361 n = 3, m = 1, R_1 = Me, R_2, R_3 = H
362 n = 1, m = 1, R_1, R_2, R_3 = H
363 n = 3, m = 2, R_1, R_2, R_3 = H
364 n = 3, m = 2, R_1 = Me, R_2, R_3 = H
365 n = 1, m = 3, R_1, R_2, R_3 = H
366 n = 1, m = 3, R_1 = Me, R_2, R_3 = H

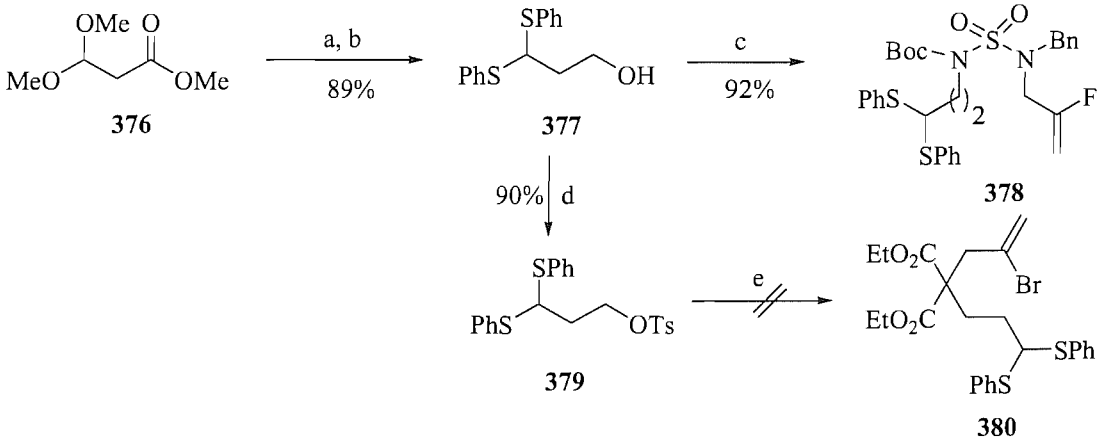
367 n = 3, m = 1, R_1 = H (71%)
368 n = 3, m = 1, R_1 = H (71%)
369 n = 3, m = 1, R_1 = H (8%)
370 n = 3, m = 1, R_1 = Me (87%)
371 n = 1, m = 1, R_1 = H (74%)
372 n = 3, m = 2, R_1 = H (50%)
373 n = 3, m = 2, R_1 = Me (87%)
374 n = 1, m = 3, R_1 = H (58%)
375 n = 1, m = 3, R_1 = Me (81%)

Scheme 75. Preparation of cycloalkanes, cyclic ethers and sulfides.

2.5.1 Synthesis and attempted metathesis of thioacetal precursors

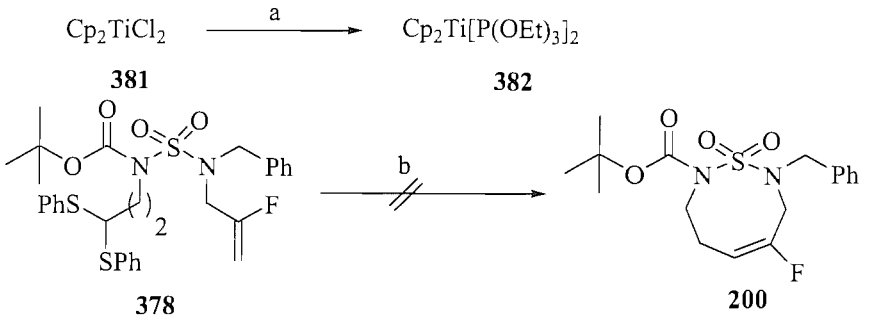
Encouraged by the results detailed above, an alternative strategy for the synthesis of cyclic vinyl bromides was envisaged, by using thioacetals as carbene precursors. According to this plan, treatment of thiophenol with commercially available methyl

3,3-dimethoxypropanoate **376** in the presence of $BF_3 \cdot OEt_2$ followed by subsequent reduction furnished the hydroxy thioacetal **377** in high yield.[86] Tosylation of **377** was carried out in order to prepare the alkylating agent **379**. Under alkylating conditions, however, the tosylate thioacetal **379** failed to afford the desired alkylated products **380**, probably due to the low reactivity of tosylate compound **379** (**Scheme 76**). Fortunately, we were able to prepare another thioacetal precursor **378** for subsequent RCM studies by coupling of the alcohol **377** with sulfamide **197** under Mitsunobu conditions in high yield.[87, 88]



Scheme 76. *Reagents and conditions*: a) PhSH, $BF_3.OEt_2$, THF; b) $LiAlH_4$, THF; c) **197**, DIAD, PPh_3, THF; d) TsCl, Pyridine, CH_2Cl_2; e) *t*-BuOK, 18-crown-6, **379**, THF.

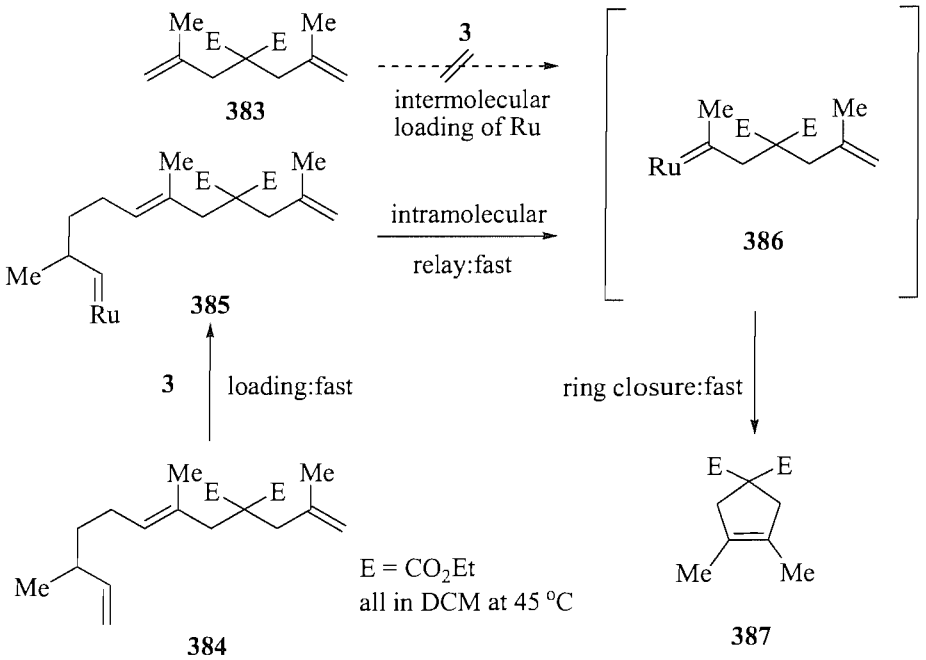
The ring-closing metathesis of sulfamide thioacetal **378** was attempted using the titanocene (II) species **382**, which was prepared by the reduction of titanocene dichloride **381** with magnesium in the presence of triethylphosphite and 4 Å molecular sieves.[85] Thermal decomposition of the intermediate was observed and none of the desired cyclised product **200** was obtained (**Scheme 77**). The cyclisation of sulfamide thioacetal precursor failed, probably due to the incompatibility of the substrate with titanocene (II) species, therefore we abandoned this strategy.



Scheme 77. *Reagents and conditions*: a) Mg, $P(OEt)_3$, 4 Å molecular sieves, THF; b) $Cp_2Ti[P(OEt)_3]_2$, THF.

2.6 Relay ring-closing metathesis (RRCM)

Recently, relay ring-closing metathesis (RRCM), which is a strategy for directing metal movement throughout olefin metathesis sequence has been described. Hoye have reported their first example of RRCM for the synthesis of cyclopentene derivatives (**Scheme 78**).[89, 90]

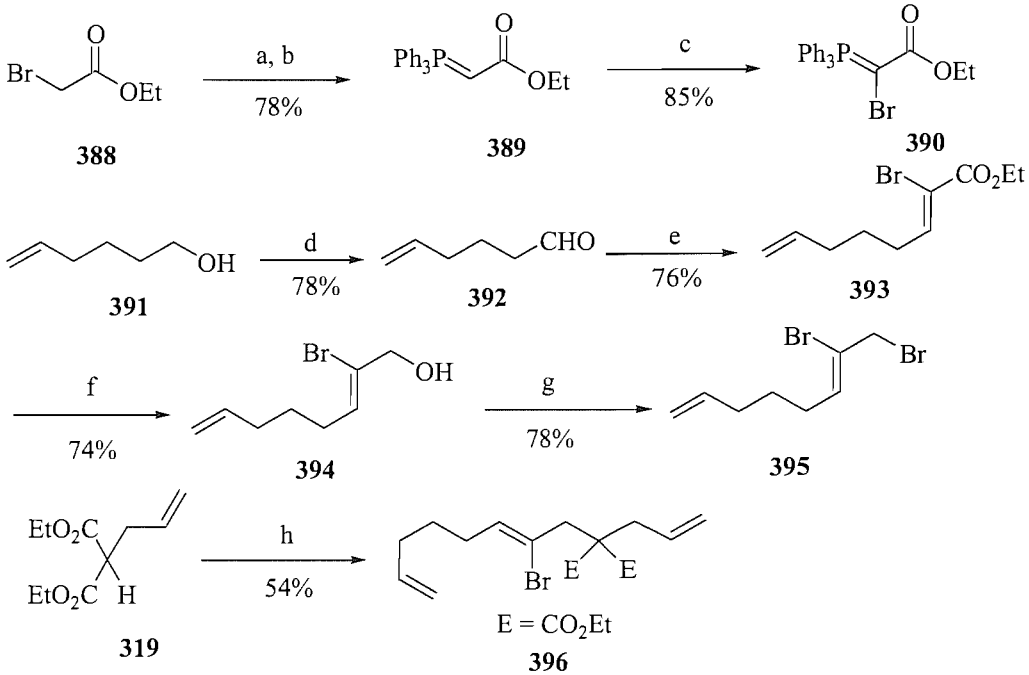


Scheme 78. Relay ring-closing metathesis (RRCM).

The RCM of dienes which contain two 1,1-disubstituted ethylene moieties does not proceed toward the first generation Grubbs catalyst. However, exposure of the relay substrate to the identical metathesis conditions resulted in smooth cyclisation to the

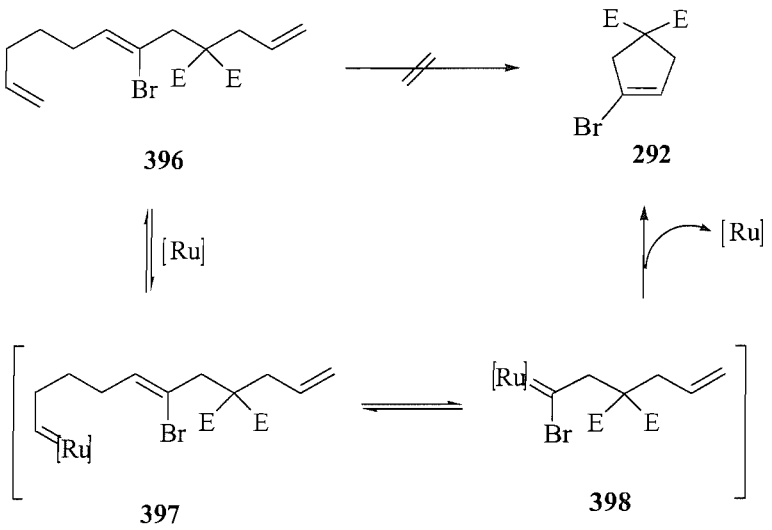
tetrasubstituted cyclopentene derivatives. The relay moieties which contain the less hindered alkene became the site for initial reaction with catalyst, leading to intramolecular derivery of the ruthenium onto the less accessible position.

In order to investigate the alternative strategy for the RCM of bromo-olefins using RRCM, the synthesis of precursors **396** was attempted (**Scheme 79**). Oxidation of 5-hexen-1-ol **391** gave the corresponding aldehyde **392** in good yield.[91] Apparently, Swern oxidation has also been reported to oxidize the alcohol **391** to aldehyde **392** in moderate yield.[92] The Wittig reagent **390** was also synthesized by treatment of ethylbromoacetate **388** with triphenylphosphine in PhH followed by addition of aq. NaOH to give **389** in high yield. Bromination of **389** was accomplished by treatment with bromine and subsequently addition of aq. KOH to produce the Wittig reagent **390** in high yield.[93] The aldehyde **392** was reacted with the Wittig reagent **390** to produce bromoacrylate **393** in good yield. Reduction of the ester **393** with DIBALH at room temperature afforded the bromo alcohol **394** in good yield.[94] Conversion of the alcohol **394** was carried out by treatment with phosphorus tribromide to furnish bromide **395** in good yield.[95] Alkylation of **319** with bromide **395** in the presence of *t*-BuOK and 18-crown-6 gave the relay precursors **396**, ready for subsequent ring-closing metathesis reaction (**Scheme 79**).



Scheme 79. *Reagents and conditions*: a) PPh_3, PhH; b) aq. NaOH; c) Br_2, follow by aq. KOH; d) PCC; e) **390**; f) DIBALH; g) PBr_3, Et_2O; h) **319**, *t*-BuOK, 18-crown-6, **395**, THF.

Upon exposure of the relay precursors **396** to ring-closing metathesis conditions using 10 mol% of second generation Grubbs catalyst refluxing in PhH for 10 hours, none of the desired product **292** was observed (**Scheme 80**). Only decomposed product and some remaining starting material were recovered.



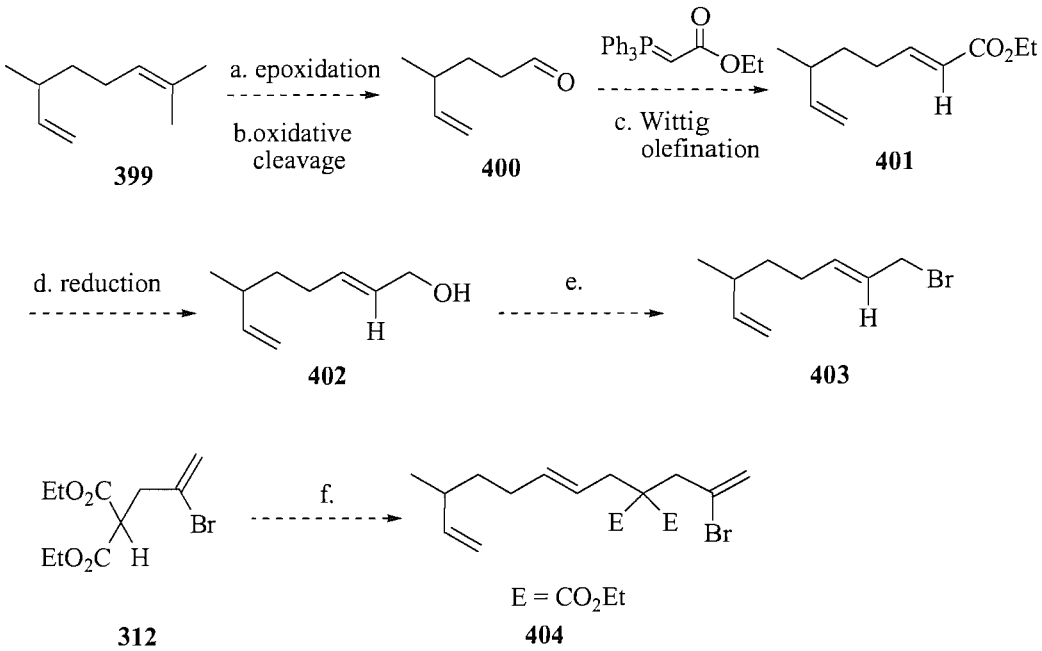
Scheme 80. Relay ring-closing metathesis of precursor **396**.

2.7 Conclusions and further work

Ring-closing metathesis of halo-olefins provides a novel approach to a variety of vinyl halides in good to excellent yield. RCM of fluoro-olefins has been shown to provide a convenient approach to a variety of carbocyclic and heterocyclic vinyl fluorides from a commercially available fluoro-olefin (1-chloro-2-fluoroprop-2-ene). Fluoro-olefins have been suggested as superior isosteric replacements for amide bonds in medicinal chemistry and are therefore of considerable interest. Hence RCM of vinyl fluorides constitutes useful methodology for the easy incorporation of fluorine into carbocycles and heterocycles.

RCM of vinyl bromides has been shown to be effective for the synthesis of certain seven-membered hetero- and carbocycles. In contrast, the corresponding reactions to form five- and six-membered rings were not generally successful. In the majority of the unsuccessful reactions starting materials were recovered, although some cross-metathesis products were obtained under more forcing conditions. Future work

should focus on establishing an improved mechanistic understanding that will be required to underpin development of the reaction. The scope of the metathesis methodology should also be studied further along with investigations into the use of different catalysts. The relay ring-closing metathesis (RRCM) strategy may help to provide some clues, for example the use of this strategy for the synthesis of cyclic vinyl bromides. An alternative RRCM precursor could be synthesized following **Scheme 81**.



Scheme 81. Attempt synthesis of alternative relay precursor.

Chapter 3

Synthesis of (±)-Deoxygalanthamine

3.1 Introduction to galanthamine

Galanthamine[96, 97] is an alkaloid found in the bulbs of snowdrops and many other plants belonging to the *Amaryllidaceae* family.[98, 99] It has recently received significant attention as a selective inhibitor of acetylcholinesterase (AchE) and consequently for its potential clinical application for Alzheimer's disease (AD) treatment. It is a marketed drug being used in Austria and most recently in the rest of Europe and in the United States.[100, 101]

3.2 Alzheimer's disease (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system (CNS), affecting approximately 10% of the population over the age of 65 years, 25% of the people over 75 and up to 45% of the people over 80. This disease is also one of the most common forms of dementia, which is characterized clinically by multiple cognitive deficits, including loss of memory, emotional disturbance, personality changes and eventually, death.

The exact causes of AD are not known, however, neurochemical and neuroanatomical studies suggest that the loss of cholinergic neurons which make acetylcholine (Ach) neurotransmitter in the neocortex and hippocampus are those predominantly affected in AD.[102] The development of neuritic plaques between neurons and neurofibrilary tangles within neurons are thought to be associated with neuronal destruction leading to a reduction in the release of neurotransmitters. This is particularly true of cholinergic neurons, where the result is a deficit in cholinergic neurotransmission. According to the cholinergic hypothesis, the decline of the levels of acetylcholine (Ach) neurotransmitter in the brain is intimately involved in memory loss in AD.[102]

3.3 Acetylcholine (ACh)

Acetylcholine (Ach) is one of several neurotransmitters which carry nerve impulses from one neuron to another in the brain's communication system. It is produced by a reversible reaction catalyzed by the enzyme cholineactyltransferase (ChAT). The biosynthesis involves transfer of an acetyl group from acetylcoenzyme A (AcCoA) to choline. The transmitter substances released from the presynaptic neuron cross the synaptic gap and interact with receptors on the postsynaptic muscarinic (mAChR) and/or nicotinic (nAChR) receptors. After each impulse it is necessary to deactivate or terminate the signal through hydrolysis of acetylcholine by the enzyme acetyl cholinesterase (AChE) to choline and acetate, or simple diffusion from the receptor site. The neurotransmitter Ach may be retaken back into the storage site or it can be synthesized in the presynaptic neuron (**Diagram 1**[a]).

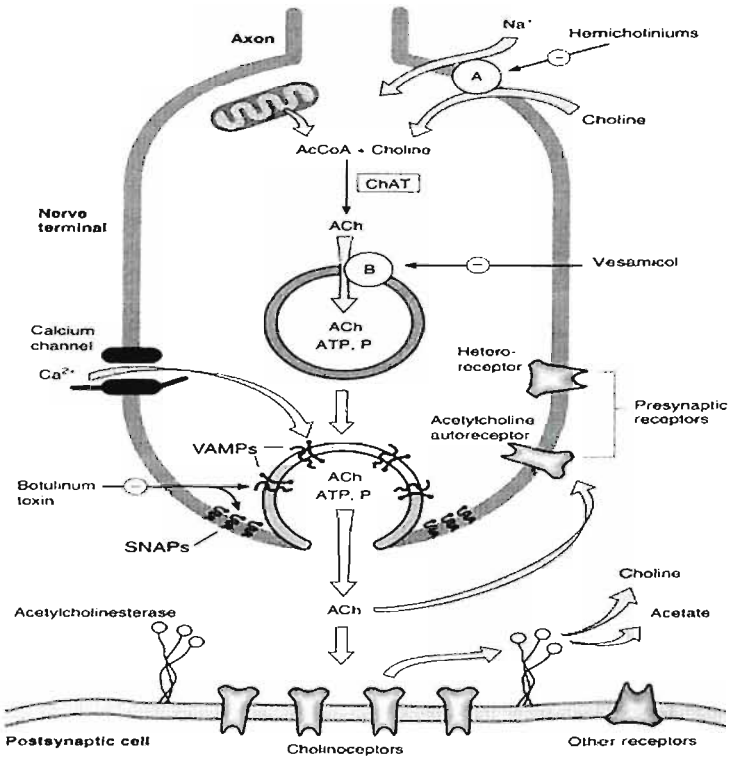
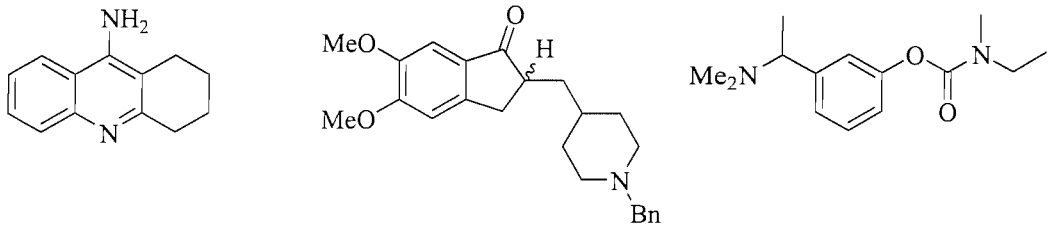


Diagram 1. Diagrammatic representation of the synthesis, release and destruction of Ach at the nerve terminal from [a] www.pharmacy.wsu.edu.

At present no drug has been discovered that provides complete protection of neurons. However, effective AD treatments are realized by blocking Ach breakdown within the synapse itself by use of AChE inhibitors and thus prolonging Ach action. An example of one of the first generation of AChE inhibitors drug is tacrine (Cognix™)[103] which is rarely used because of its potential liver toxicity. Currently, the acetylcholine inhibitors donepezil (Aircept™),[104] rivastigmine (Exelon™)[105] and galanthamine (Reminyl™)[96] have been proved effective in clinical trials (**Figure 3**).



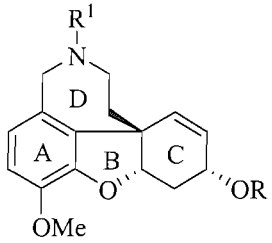
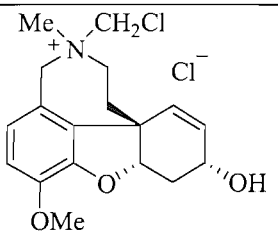
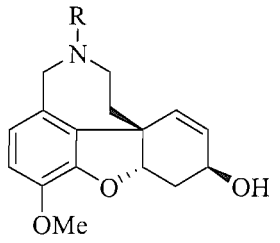
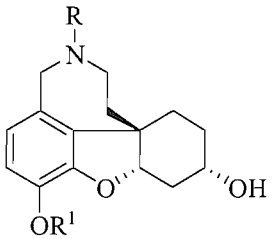
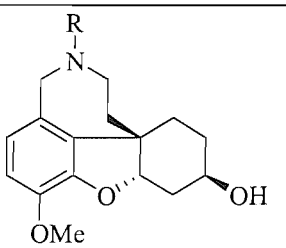
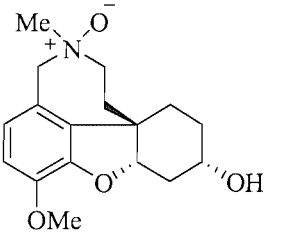
Cognix™ Aircept™ Exelon™

Figure 3. Marketed AchE inhibitors for AD treatment.

Galanthamine is the last approved drug for the treatment of AD. It is a specific, competitive and reversible AchE inhibitor. Distinct from the other drugs, it also displays an increased beneficial effect due to its agonist action on nicotinic Ach receptors at the postsynaptic site.[96]

3.4 Discovery and synthesis of galanthamine

Galanthamine was isolated from the bulbs of the Caucasian snowdrop *Galanthus woronowi* in 1952 and the common snowdrop *G. nivaltis* in 1954.[98] It has also been found in a number of other sources, for example, the extraction of the flowers of *Lycoris incarnata* led to the isolation of galanthamine, sanguinine, lycoramine, *O*-demethyllycoramine and galanthamine *N*-oxide. In addition, the extract of the bulbs and aerial parts of *Narcissus leonensis* have been found to contain two new alkaloids, *epi*-norgalanthamine and *epi*-norlycoramine. The structures of the representative alkaloids isolated are shown in **Table 8**.[98]

Structure	R	R^1	Name of alkaloids
	H	Me	Galanthamine
	Ac	Me	*O*-Acetyl galanthamine
	H	Allyl	*N*-Allyl galanthamine
	H	H	Norgalanthamine
	H	CHO	*N*-Formyl galanthamine
	-	-	*N*-Chloromethyl-galanthaminium chloride
	H	-	*Epi*-Norgalanthamine
	Ac	-	Narcisine
	Me	Me	Lycoramine
	Me	H	*O*-Dementhyl lycoramine
	H	Me	Norlycoramine
	Me	-	*Epi*-Lycoramine
	H	-	*Epi*-Norlycoramine
	-		Lycoramine *N*-oxide

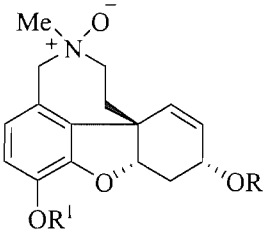
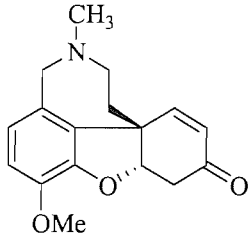
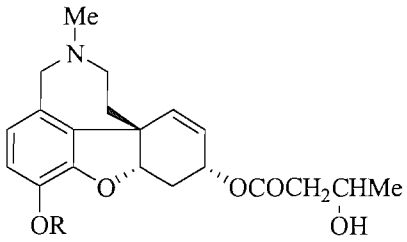
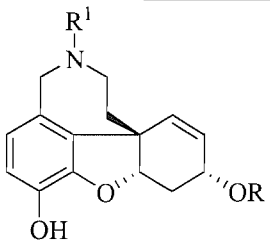
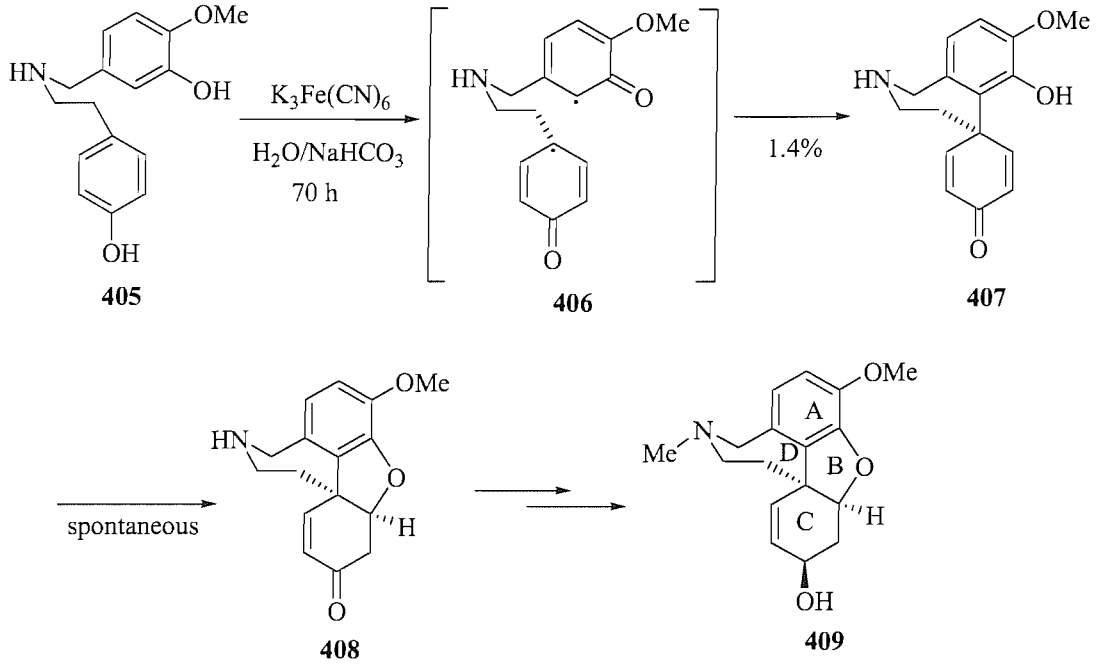
Structure	R	R^1	Name of alkaloids
	H	Me	Galanthamine *N*-oxide
	Ac	Me	*O*-Acetyl galanthamine *N*-oxide
	H	H	Sanguinine *N*-oxide
	-		Narwedine
	H	-	Leucotamine
	Me	-	*O*-Methyl leucotamine
	H	Me	Sanguinine
	Ac	Me	2-*O*-Acetyl-chlidanthine
	H	H	Norsanguinine
	$COCH_2CH(OH)Me$	H	Norbutsanguinine

Table 8. Structures of galanthamine and its derivatives.

Importantly, galanthamine and related compounds have been evaluated as potential agents for the treatment of AD. However, the botanical supply of the alkaloids has been limited and the cost of isolation from natural sources is extremely expensive. Therefore, a number of total syntheses of galanthamine have been developed. Early syntheses have utilized the classical, biomimetic phenolic oxidative coupling to establish the critical quaternary centre of the galanthamine ring system. These processes were initially addressed by Barton.[106] It has been shown that 4'-*O*-

methylnorbelladine **405** was the precursor for the production of *N*-demethylnarwedine **407**, presumably through spontaneous cyclisation of dienone **406** generated from the oxidative phenol coupling (**Scheme 82**).

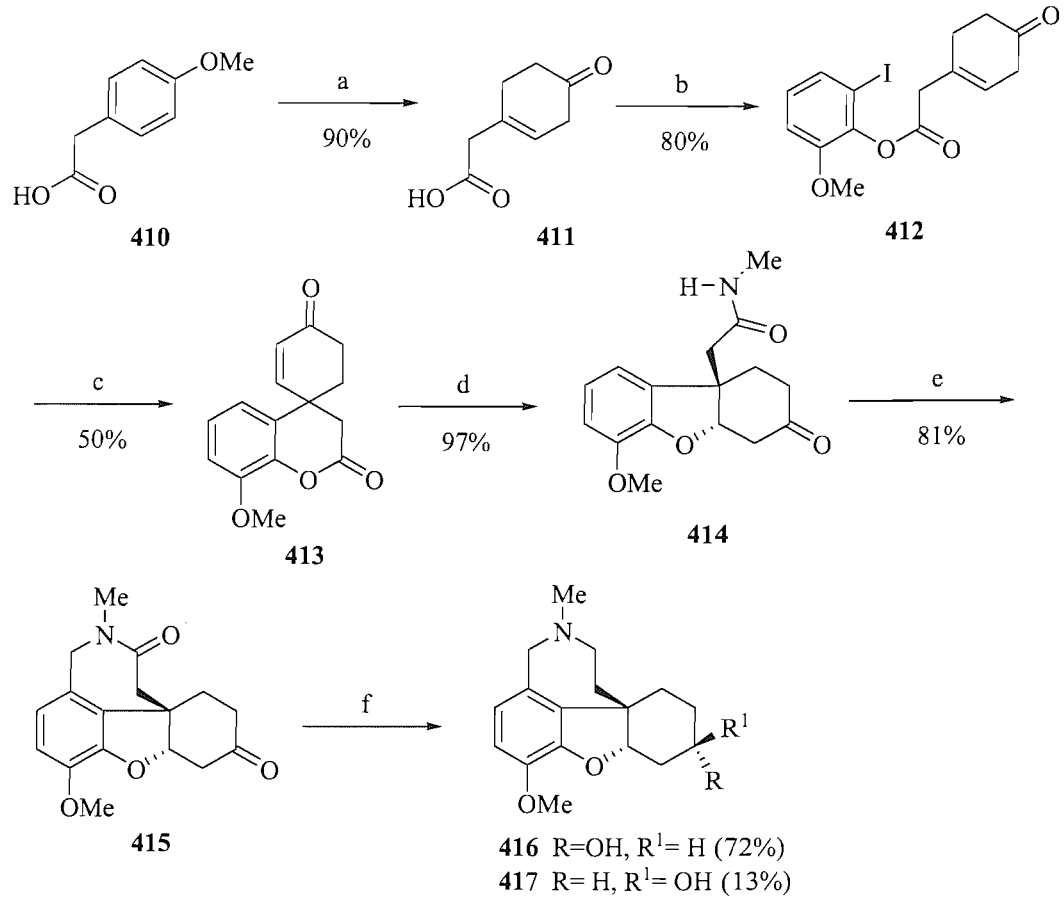


Scheme 82. First biosynthesis of galanthamine *via* oxidative bisphenol coupling by Barton *et al.*

However, these syntheses have not been applied for direct access to galanthamine derivatives which were found to be more potent (up to 70-fold) than galanthamine in inhibiting AChE. This limitation has inspired the development of alternative synthetic strategies by employing an intramolecular Heck reaction to create the spiro quaternary carbon atom.

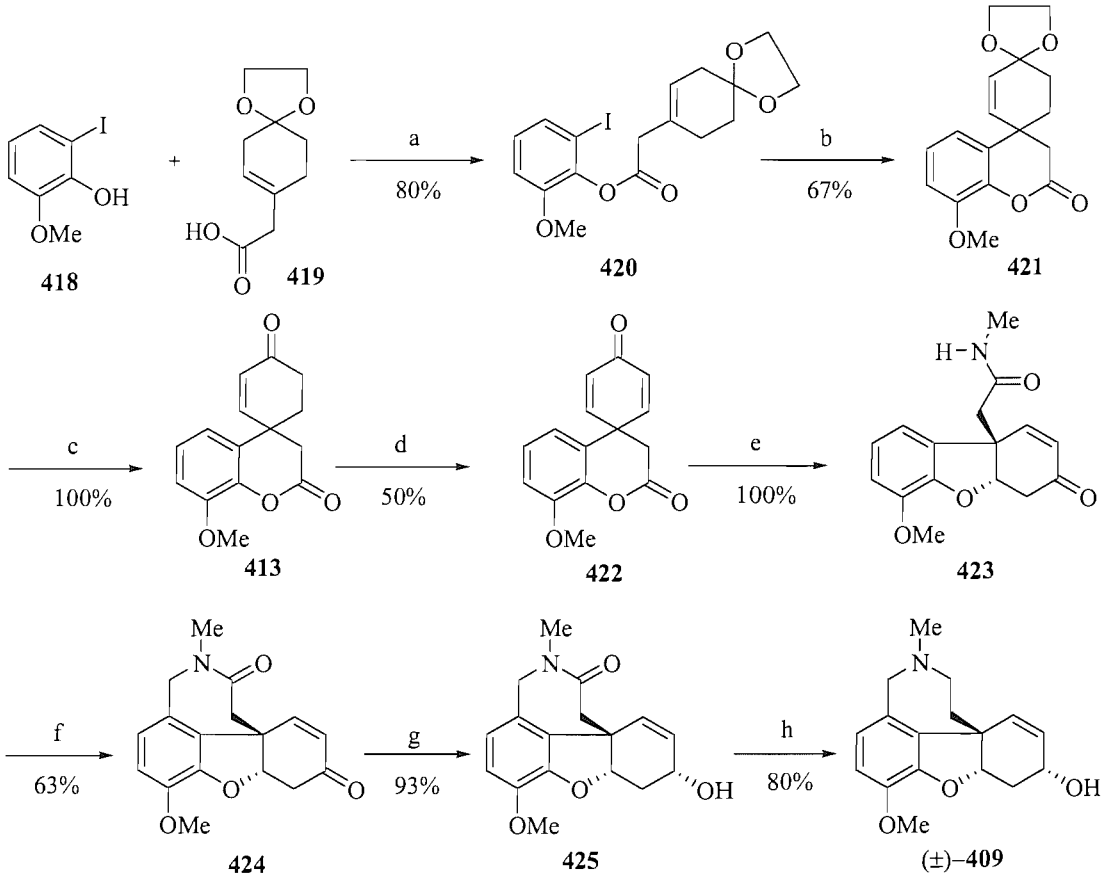
In 1999, Guillou and co-workers reported a formal synthesis of (±)-lycoramine, by the use of an intramolecular Heck reaction as the key step to build the quaternary centre (**Scheme 83**).[107, 108] The synthesis starts with the Birch reaction of 4-methoxyphenylacetic acid **410** followed by acidic work up which gave the unsaturated cyclohexenone **411** in 90% yield. Subsequent esterification of **411** with 2-iodo-6-methoxyphenol led to **412**. Heck cyclisation of **412** was accomplished using a reactive catalyst formed from $Pd(OAc)_2$ and dppe in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP) and Bu_4NOAc. However, this key step delivered the expected α,β-unsaturated ketone **413**, in only a moderate yield (50%). Reaction of **413** with 40% aq. $MeNH_2$ gave the keto amide **414** in 97% yield, which was cyclised

using a modified Pictet-Spengler reaction. Treatment of **414** with paraformaldehyde and TFA at ambient temperature produced **415** in 81% yield. Finally, reduction of **415** with $LiAlH_4$ provided (±)-**416** and (±)-**417** in 72% and 13% yield, respectively.



Scheme 83. Formal synthesis of (±)-lycoramine by Guillou and co-workers. *Reagents and conditions*: a) Li, NH_3, *t*-BuOH, –78 °C; b) 2-iodo-6-methoxyphenol, EDCI, DMAP, CH_2Cl_2, 25 °C, 10 h; c) $Pd(OAc)_2$ (10 mol%), dppe (20 mol%), PMP (2 eq.), Bu_4NOAc (1 eq.), toluene, 70 °C, 5 h; d) $MeNH_2$ (aq); e) $(CH_2O)_n$, TFA, $ClCH_2CH_2Cl$; f) $LiAlH_4$, THF.

In 2001, the same group reported their total synthesis of (±)-galanthamine **409** (**Scheme 84**).[109] Interestingly, this synthesis which was based on the synthesis of (±)-oxonarwedine **424**, could easily introduce the allylic hydroxyl group to furnish (±)-galanthamine **409**.

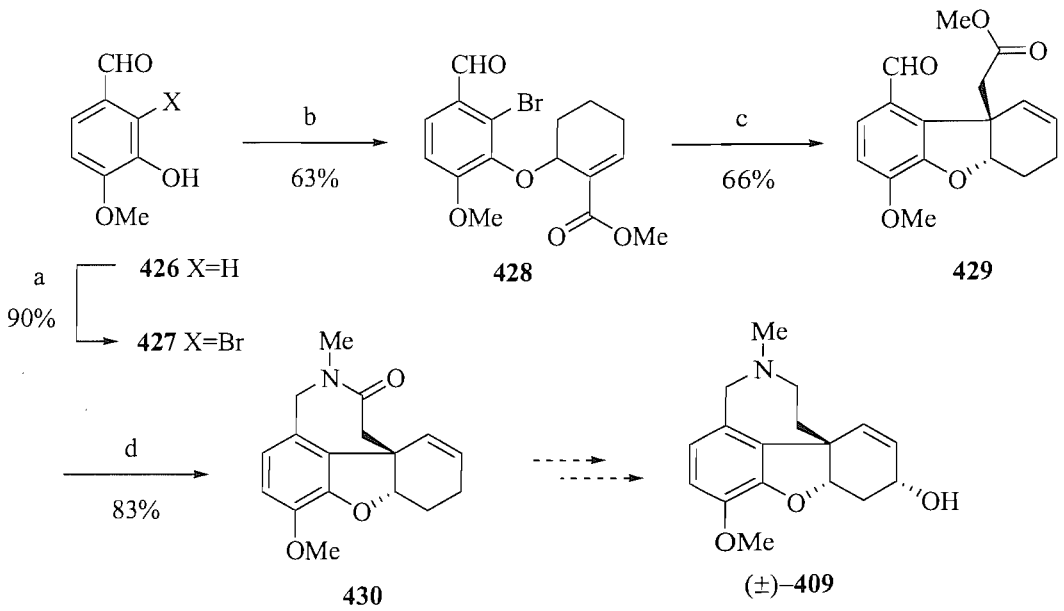


Scheme 84. Total synthesis of (±)-galanthamine by Guillou and co-workers. *Reagents and conditions*: a) EDCI, DMAP, CH_2Cl_2, 0→20 °C, 5 h; b) $[Pd_2(dba)_3]$, dppe, TlOAc, CH_3CN, reflux, 2 days; c) Ph_3CBF_4, CH_2Cl_2, 1 h; d) 4 Å MS, $(PhSeO)_2O$, CH_2Cl_2, reflux, 20 h; e) 40% $MeNH_2$, THF, 20 min.; f) $(CH_2O)_n$, TFA, $CHCl_2CH_2Cl$, 60 °C, 20 h; g) L-selectride, THF, –78 °C, 1 h; h) $LiAlH_4$, DME, 50 °C, 12 h.

Starting from the protected ketone **419**, esterification with 2-iodo-6-methoxyphenol **418** gave the ester **420** in 80% yield. Subsequent intramolecular Heck reaction was carried out in the presence of 10 mol% of $Pd_2(dba)_3$, dppe and thallium acetate. The dioxolane group was removed under mild conditions by using triphenylcarbenium tetrafluoroborate. Oxidation of the resulting unsaturated ketone **413** gave the dienone **422** in moderate yield. Treatment of **422** with 40% aq. $MeNH_2$ gave the amide **423** in quantitative yield. Cyclisation of **423** was accomplished by treatment with paraformaldehyde and TFA. The resulting enone **424** was reduced with L-selectride to give alcohol **425** in 93% yield. Finally, reduction of **425** with $LiAlH_4$ in DME

produced (±)-galanthamine **409** in 80% yield. To this end, (±)-galanthamine **409** was synthesized in 8 steps with 12% overall yield.

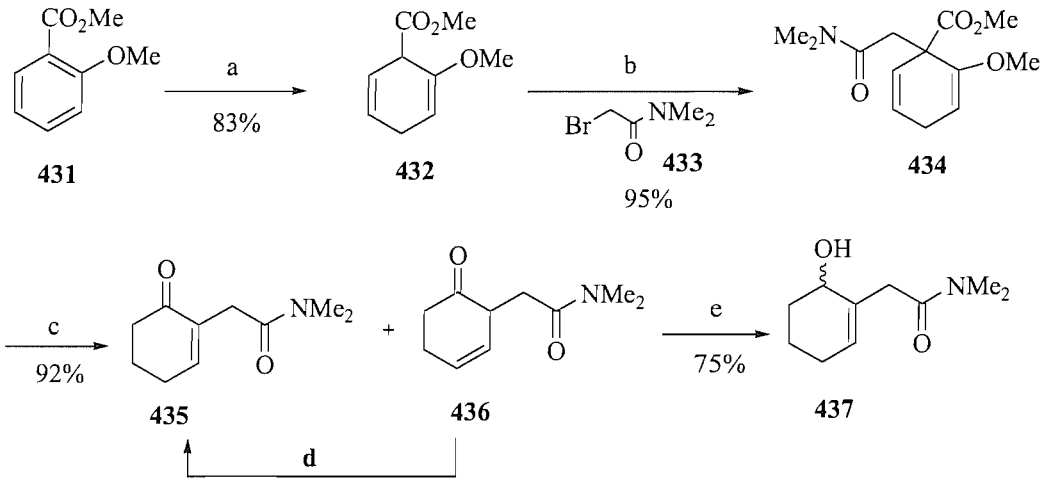
An alternative synthetic route to the tetracyclic galanthamine framework, also employing an intramolecular Heck reaction as the key step, was also developed by Fels and co-workers (**Scheme 85**).[110] Treatment of the commercially available isovaniline **426** with Br_2 and *t*-$BuNH_2$ gave 2-bromoisovaniline **427** in high yield. Coupling of the corresponding racemic alcohol with the resulting phenol **427** under Mitsunobu conditions produced ether **428** in moderate yield. Stereoselective intramolecular Heck reaction of **428** was accomplished by using $Pd(PPh_3)_4$ and anhydrous K_2CO_3 to secure the tricyclic intermediate **429** in moderate yield. Treatment of **429** with $MeNH_2$ and $NaBH_4$ followed by an acidic work-up procedure produced the tetracyclic galanthamine framework **430**. This is a formal synthesis of (±)-galanthamine **409** which can be obtained from **430** by reduction of the amide and functionalization of allylic position.



Scheme 85. Synthesis of the tetracyclic galanthamine core by Fels and co-workers. *Reagents and conditions*: a) Br_2, *t*-$BuNH_2$, CH_2Cl_2, –78 °C, 5 h; b) **427**, DEAD, PPh_3, toluene, 4 d; c) $Pd(PPh_3)_4$, K_2CO_3, toluene, 107 °C, 12 h; d) i. $MeNH_2$, CH_3OH, 2 h, ii. $NaBH_4$, 0 °C, 2 h.

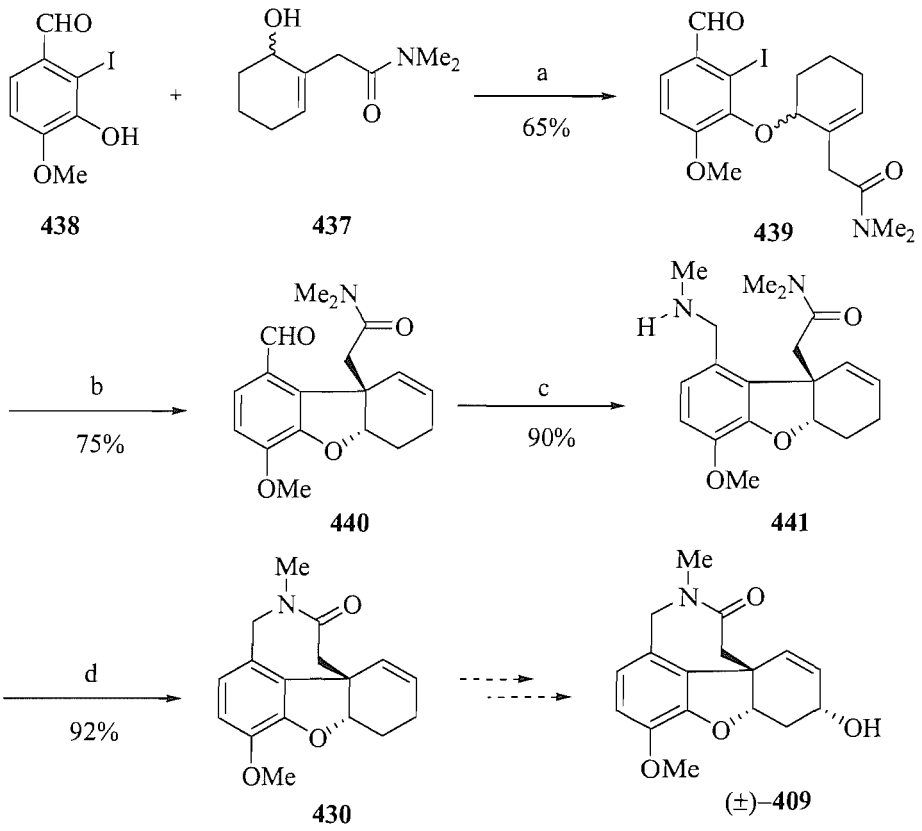
Another closely related approach to the galanthamine ring system has been reported by Parsons *et al.* (**Scheme 87**).[111] This route is similar to Fels *et al.*[110] however, the Mitsunobu and intramolecular Heck reaction were optimized leading to the

formation of the galanthamine framework in an improved overall yield. The required allylic alcohol **437** for the Mitsunobu reaction was synthesized following a 4 step sequence (**Scheme 86**). Birch reduction of methyl 2-methoxy-benzoate **431** gave the cyclohexadiene **432** in 83% yield. Deprotonation with LDA and subsequent quenching with *N,N*-dimethyl bromoacetamide **433** produced **434** in quantitative yield. Saponification of the ester **434** followed by hydrolysis with conc. HCl afforded the β-keto acid, which underwent spontaneous decarboxylation to give isomeric cyclohexenes **435** and **436**. The mixture was heated in THF and 1M HCl to give the thermodynamic 2-ene isomer **435**. Treatment of **435** with $NaBH_4$ furnished the desired allylic alcohol fragment **437**.



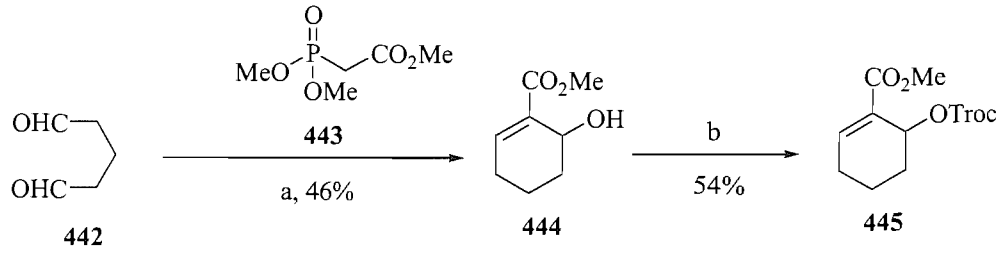
Scheme 86. Synthesis of allylic alcohol fragment. *Reagents and conditions*: a) K, liq NH_3, THF, *t*-BuOH; NH_4Cl; b) LDA, THF, **433**; c) NaOH, H_2O; conc. HCl; d) 1M HCl, THF; e) $NaBH_4$, MeOH.

In order to synthesise the galanthamine ring system, the Mitsunobu coupling of phenol **438** with alcohol **437** using tributylphosphine and the morpholine derivative of DEAD gave the easily purified product **439** in 65% yield. Subsequent intramolecular Heck reaction of **439** in the presence of $Pd(OAc)_2$ using Ag_2CO_3 as base to prevent isomerisation, produced tricyclic compound **440** in 75% yield. The aldehyde **440** was condensed with $MeNH_2$ and subsequent reduction gave the secondary amine **441**. The hydrochloride salt of this amine was heated under high vacuum to furnish the galanthamine ring system **430** in 92% yield (**Scheme 87**)

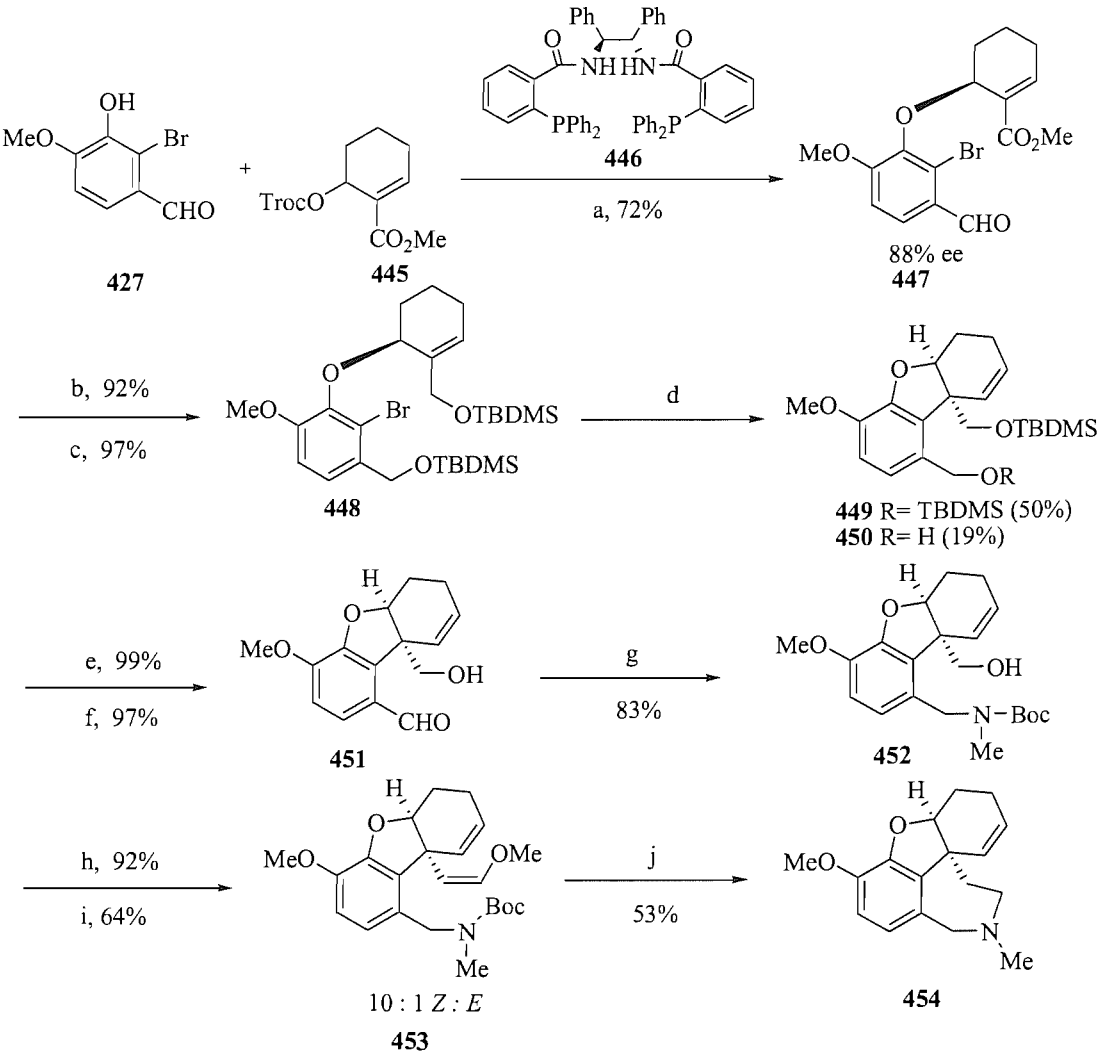


Scheme 87. Synthesis of the (±)-galanthamine framework by Parsons and co-workers. *Reagents and conditions*: a) azodicarboxylic dimorpholide, Bu_3P, THF; b) $Pd(OAc)_2$, Ag_2CO_3, dppe, DMF, reflux, 2 h; c) $MeNH_2$, EtOH; $NaBH_4$, MeOH; d) HCl, MeOH; vacuum, 120 °C.

In 2000, the first enantioselective total synthesis of (–)-galanthamine was reported by Trost and co-workers. Sequential palladium-catalyzed asymmetric allylic alkylation (AAA) and intramolecular Heck reaction have been employed (**Scheme 89**).[112] In order to prepare the carbonate precursor for asymmetric Heck reaction, a practical synthesis of ester **445** utilizing the Horner-Wadsworth-Emmons reaction of dialdehyde **442** was carried out. Treatment of glutaraldehyde **442** with trimethyl phophonoacetate **443** in aq. K_2CO_3 prepared alcohol **444** in moderate yield (46%). Direct treatment of crude alcohol **444** with trichloroethyl carbonate (Troc) gave the desired carbonate **445** with a moderate yield (54%) (**Scheme 88**).



Scheme 88. Synthesis of 2-substituted cyclohexyl carbonate. *Reagents and conditions*: a) aq. K_2CO_3, 2 d; b) Troc-Cl, DMAP, Pyr, CH_2Cl_2.

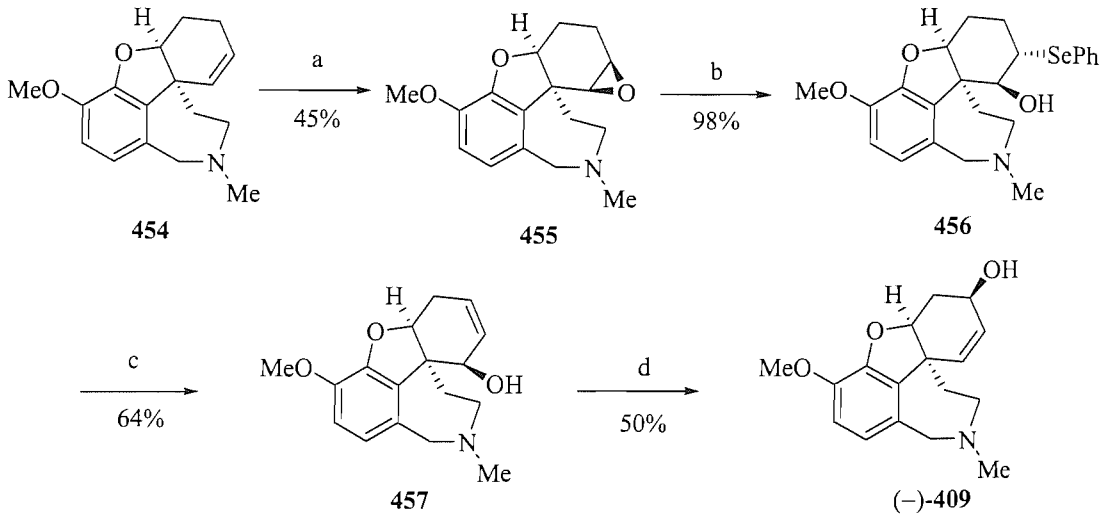


Scheme 89. Synthesis of (–)-3-deoxygalanthamine by Trost. *Reagents and conditions*: a) **446** (3 mol%), $[\eta^3\text{-}C_3H_5PdCl]_2$ (1 mol%), NEt_3, CH_2Cl_2; b) DIBAL-H, $PhCH_3$, –78 °C; c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; d) proton sponge, $Pd(OAc)_2$ (20 mol%), dcpe (18 mol%), DMA. 80 °C; e) TBAF, THF; f) MnO_2, acetone; g) i. $MeNH_3Cl$, $NaCNBH_3$, CH_3OH, ii. Boc_2O, CH_2Cl_2, NEt_3; h) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2; i) $NaN(TMS)_2$, $CH_3OCH_2P^+Ph_3Br^-$; j) i. TFA, CH_2Cl_2, ii. $NaCNBH_3$, CH_3OH, 4 Å molecular sieve, 0 °C.

Palladium-catalyzed reaction of 2-bromo isovanillin **427** and carbonate **445** in the presence of ligand **446** produced the required aryl ether **447** in good yield (72%) and enantioselectivity (88% ee). However, attempted intramolecular Heck reaction of aryl ether **447** failed, resulting in ionization of phenol. It was suggested that the presence of an electron-withdrawing group on the phenol allows for palladium-catalyzed ionization rather than the intramolecular Heck reaction. Thus, treatment of **447** with DIBAL-H followed by diol protection with TBDMS-triflate delivered *bis*-TBDMS ether **448** in 89% yield. Subsequently, the crucial step was achieved by the intramolecular Heck reaction of **448** catalyzed by $Pd(OAc)_2$ in presence of the dicyclohexylphosphine ligand, dcpe to give benzofuran **449** in 50% yield and 19% of the monodeprotected product **450** without detectable amounts of ionization.

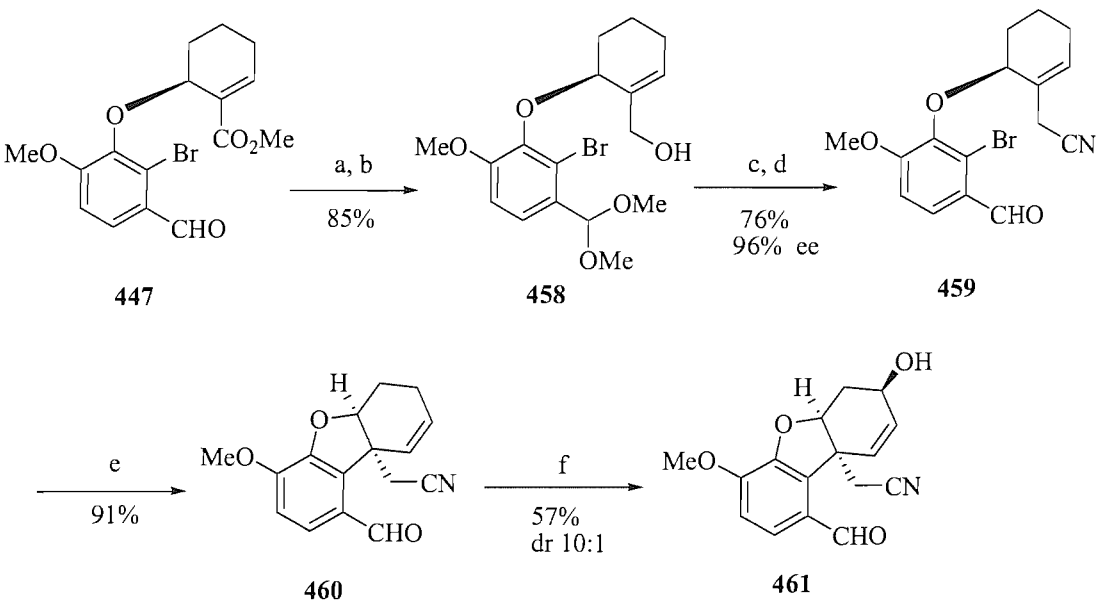
In order to prepare hydrobenzazepine ring of galanthamine, TBDMS protecting groups were removed and chemoselective MnO_2 oxidation of the diol was carried out to produce aldehyde **451**. Reductive amination of aldehydes **451** was accomplished by treatment with methylamine followed by reduction with $NaCNBH_3$ to afford the secondary amine **452**. The subsequent Boc protection was carried out to give **452** in 83% yield. Dess-Martin oxidation of **452** produced the amino aldehyde in 92% yield. The Wittig olefination of the aldehyde with the ylide derived from methoxymethyltriphenylphosphonium bromide and NaHMDS gave the adduct **453** in 64% yield. Deprotection of the amine **453** with concomitant reductive amination led to (–)-deoxygalanthamine **454** in 53% overall yield (**Scheme 89**).

Attempts to carry out direct allylic oxidation on **454** failed. Therefore, a four-step oxidation was developed to introduce the C3 hydroxy group stereoselectively (**Scheme 90**). Treatment of the tosylammonium salt of **454** with dimethyldioxirane gave the mixture the corresponding α-hydroxy tosylate and epoxide **455** which was isolated in 45% yield, after treatment of the mixture with DBU. Regioselective opening of epoxide **455** with sodium phenylselenide gave α-hydroxy selenide **456** in 98% yield. Chemoselective oxidation of selenide **456** with $NaIO_4$ followed by heating to eliminate the selenoxides furnished (–)-isogalanthamine **457** in 64% yield. Treatment of **457** with Osborn's rhenium (VII) catalyst delivered (–)-galanthamine **409** in 50% yield. In conclusion, this strategy required 14 steps starting from the synthesis of aryl ether **447** with 88% ee and 1.5% overall yield for an enantioselective synthesis of (–)-galanthamine **409**.



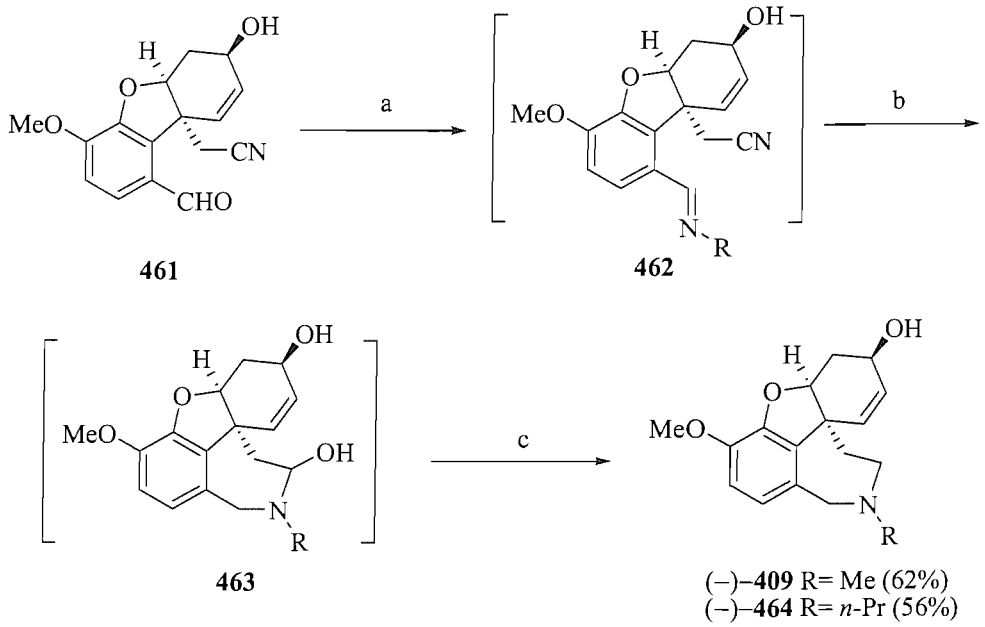
Scheme 90. Four-step sequence to achieve allylic oxidation. *Reagents and conditions*: a) i) TsOH, CH_2Cl_2, ii) DMDO, iii) DBU; b) PhSeSePh, $NaBH_4$, EtOH, 80 °C; c) $NaIO_4$, THF, H_2O then $CHCl_3$, 80 °C; d) $Ph_3SiOReO_3$, TsOH, PhH, 60 °C.

In 2002, Trost and Tang reported the second-generation strategy for an enantionselective synthesis of (–)-galanthamine **409** (Scheme **91**, **92**).[113] This strategy represented the first successful direct allylic oxidation, introducing the C3 allylic hydroxyl to the (–)-galanthamine skeleton. As in the previous synthesis, aryl ether **447** was prepared utilizing the palladium-mediated asymmetric allylic alkylation (AAA) in good yield (72%) and with high enantioselectivity (87% to 88% *ee*). Dimethylacetal protection of aldehyde **447** was carried out by treatment with trimethyl orthoformate and TsOH. Selective reduction of the unsaturated ester with DIBAL-H provided allylic alcohol **458** in good yield (85%), which underwent a modified Mitsunobu reaction followed by acid hydrolysis to return the unsaturated nitrile **459**. The Pd-catalyzed cyclisation of the acetronitrile substituted cyclohexene **459** smoothly produced the desired Heck product **460** in high yield (91%). The direct allylic oxidation was carried out by treatment of olefin **460** with SeO_2 in dioxane at 150°C in the presence of NaH_2PO_4 and quartz sand in a sealed tube. However, the yield of the allylic alcohol **461** was moderate (57%) with 7% recovered starting material (**Scheme 91**).



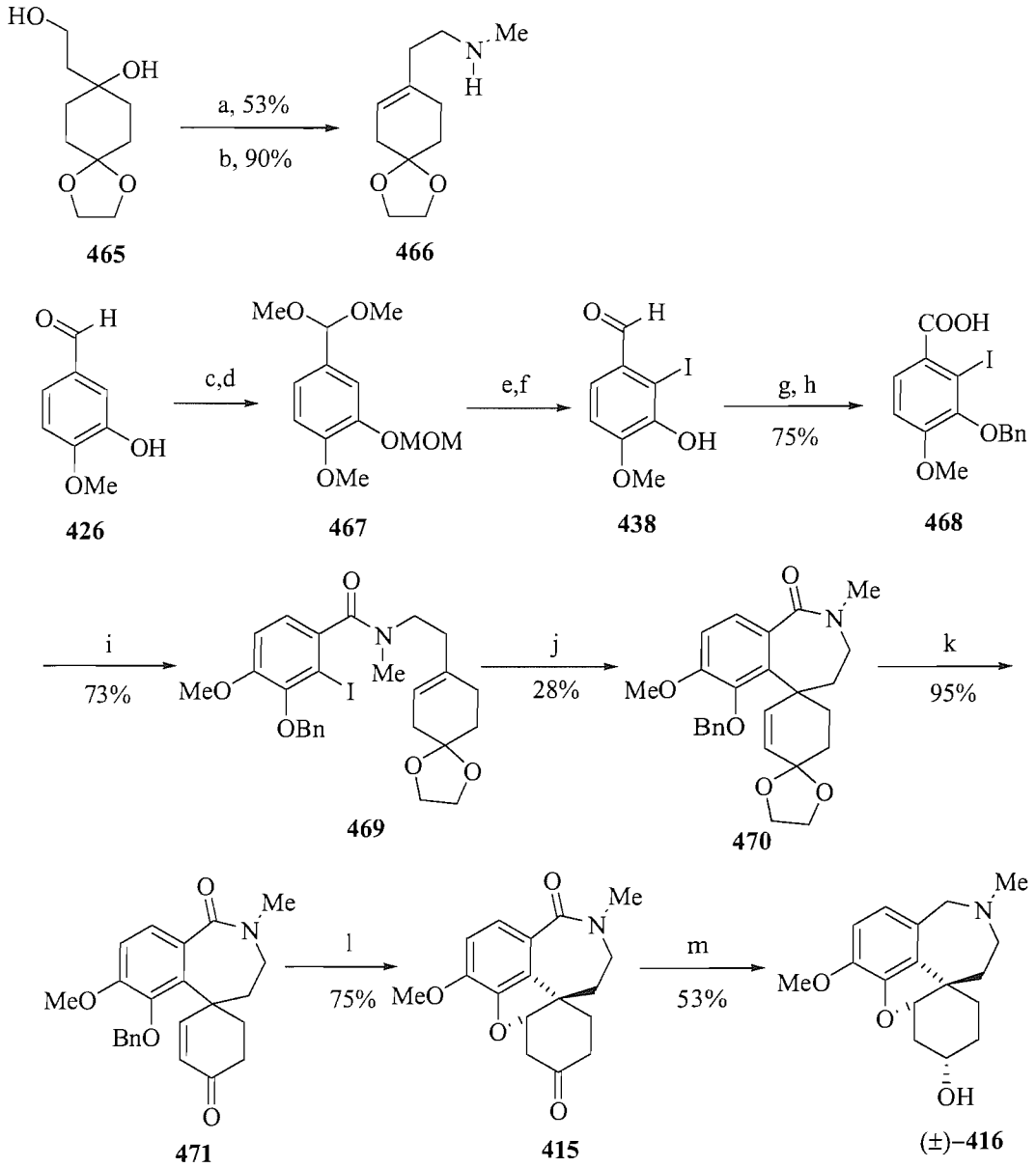
Scheme 91. Synthesis of tricyclic skeleton of galanthamine. *Reagents and conditions:* a) 5% TsOH, $CH(OMe)_3$, MeOH; b) DIBAL-H, toluene, –78 °C; c) Ph_3P, acetonecyanohydrin, DIAD, Et_2O; d) 20% TsOH, THF, H_2O; e) $Pd(OAc)_2$ (15 mol%), dppp (15 mol%), Ag_2CO_3, $PhCH_3$, 107 °C, 24 h; f) SeO_2, NaH_2PO_4, dioxane, 150 °C, 3 h.

To accomplish the synthesis of D-ring, treatment of aldehyde **461** with methylamine in methanol solution followed by reduction with DIBAL-H and acid quenching presumably gave the seven-membered ring of hemiaminal **463**. The solution was treated directly with $NaCNBH_3$ to provided (–)-galanthamine **409** in 62% yield and *epi*-**409** in 6% yield. This synthetic route provided improved overall yield (14.8% yield from **427** and **445**, 96% *ee*) in fewer steps (8 steps) in comparison to the previous synthetic strategy.



Scheme 92. Complete the synthesis by one-pot procedure. *Reagents and conditions:* a) RNH_2, MeOH; b) DIBAL-H then aq. NaH_2PO_4; c) $NaCNBH_3$.

Lastly, novel synthetic strategy for the preparation of (±)-lycoramine **416** has been reported by Hsin and his co-worker (**Scheme 93**).[114] This strategy has utilized a Pd-catalyzed Heck reaction and a spontaneous intramolecular Michael addition to construct the seven-membered azepane ring (ring D) and the five-membered furan ring (ring B) respectively.



Scheme 93. Total synthesis of (±)-lycoramine by Hsin *et al. Reagents and conditions:* a) MsCl, CH_2Cl_2; b) $MeNH_2$ (aq), reflux; c) trimethyl orthoformate, CH_2Cl_2; d) LDA, MOMCl, THF, –78 °C; e) *n*-BuLi, I_2, –78 °C; f) 3 N HCl; g) BnBr, K_2CO_3, acetone; h) $KMnO_4$, acetone-H_2O; i) $SOCl_2$, THF then **465**, Et_3N, THF; j) $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, 130 °C; k) silica gel, MeOH; l) $SnCl_4$, CH_2Cl_2; m) $LiAlH_4$, THF, reflux.

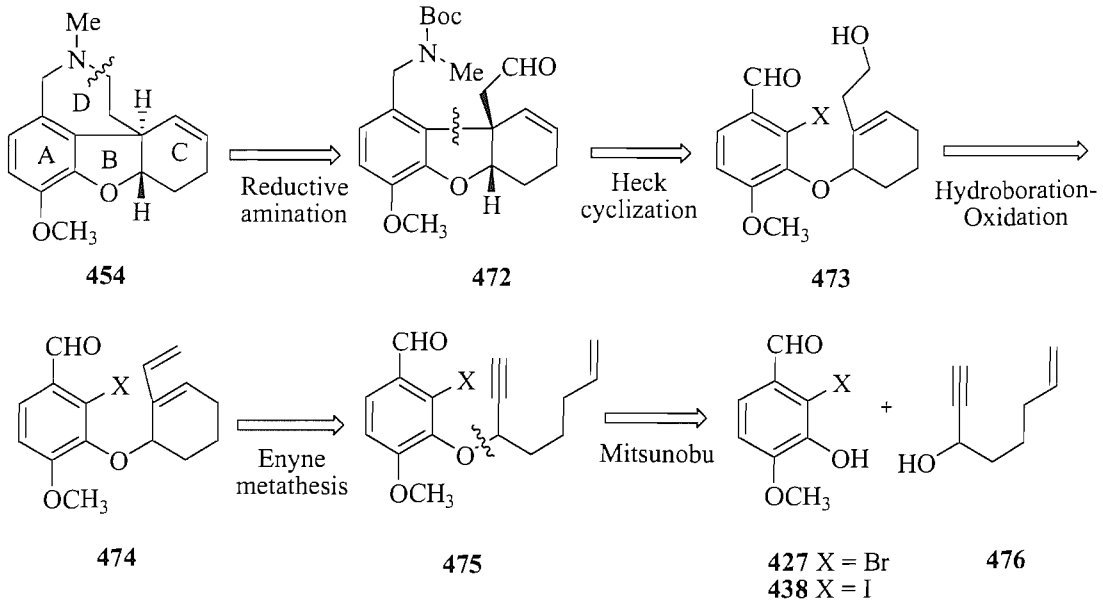
The simple mesylation of diol **465**, which was prepared from cyclohexene-1,4-dione monoethylene ketal, led to the *bis*-mesylate which was subject to a substitution reaction and also elimination with methylamine to produce the secondary amine **466**. Coupling of amine **466** with 2-iodobenzoic acid derivative **468** gave amide **469** in

good yield (73%). The acid **468** was obtained from oxidation of protected aldehyde **438**, which was prepared in five steps. Subsequent intramolecular Heck reaction was carried out using $Pd(OAc)_2$, Ph_3P and K_2CO_3 in CH_3CN leading to the formation of cyclized product **469** with 28% yield, 21% of recovered starting material and 15% of de-iodinated product. The ethylene ketal group was removed upon contact with silica gel in MeOH to afford ketone **471** in high yield (95%). Removal of benzyl group was accompanied by a spontaneous Michael addition to produce the tetracyclic oxolycoraminone **415** in 75% yield. Reduction of both ketone and amide groups with $LiAlH_4$ gave (±)-lycoramine **416** with excellent diastereoselectivity, however in moderate yield (53%). This strategy has firstly demonstrated the direct formation of seven-membered azepene ring by using an intramolecular Heck reaction.

In conclusion, several synthetic strategies for the synthesis of galanthamine and its derivatives have been developed. Particularly, the intramolecular Heck reaction has been employed as the key convergent step to construct the galanthamine framework. There is, however, considerable scope to utilize other methodologies, such as radical cyclisation and the well known metathesis reaction, to develop efficient asymmetric routes for the construction of galanthamine and related compounds.

3.5 The Southampton approach to the (±)-galanthamine framework

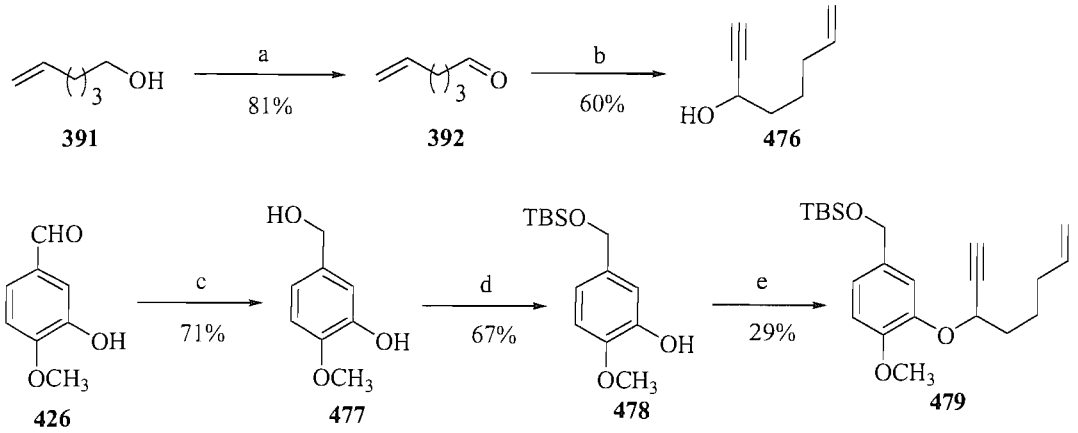
The aim of these initial studies was to discover novel strategies for the synthesis of the galanthamine framework. A new approach was formulated utilizing the Mitsunobu reaction, enyne ring-closing metathesis and a radical cyclisation as key steps. The retrosynthetic consideration led us to propose the route as shown in **Scheme 94**. It was envisaged that ring D could be constructed by a reductive amination of the corresponding amine and the aldehyde functionality in **472**. An intramolecular Heck reaction was envisioned to build the five-membered furan ring (ring B) *via* Pd-catalyzed 5-*exo-trig* cyclisation of intermediate **473**. The latter would be obtained from the synthesis of intermediate **474** by a hydroboration-oxidation sequence. Enyne metathesis was considered for the formation of ring C. Finally, the intermediate **475** could be synthesized from the coupling of a 2-haloisovanillin **427** or **438** and the propargylic alcohol **476** by utilizing the Mitsunobu reaction.



Scheme 94. Retrosynthetic analysis of (±)-deoxygalanthamine **454**.

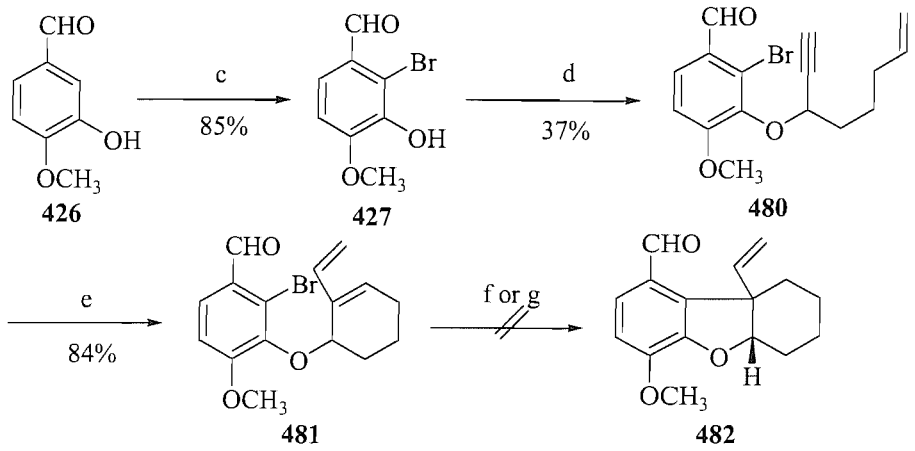
3.6 Synthesis of (±)-galanthamine framework

The synthetic work commenced by oxidation of the commercially available 5-hexen-1-ol **392** with PCC to afford aldehyde **393** in good yield.[91] The aldehyde **393** was reacted with ethynylmagnesium bromide by reverse addition to afford the secondary alcohol **476** in moderate yield (**Scheme 95**). Coupling of the resulting alcohol **476** with the phenol **478**, which was obtained from bromination of isovanillin **426** in acetic acid with Fe and NaOAc catalysis,[115] was carried out using the Mitsunobu reaction in the presence of DIAD and Ph_3P.[87] Unfortunately, the yield for this coupling reaction was moderate. Meanwhile, Mitsunobu reaction of phenol **478** with alcohol **476** was also carried out under the same conditions, giving the coupling product **479** in low yield (**Scheme 95**).



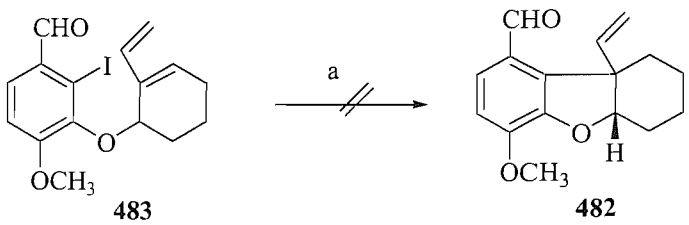
Scheme 95. *Reagents and conditions*: a) PCC, CH_2Cl_2; b) ethynylmagnesium bromide, THF; c) $NaBH_4$, MeOH; d) TBSCl, DMAP, Et_3N, CH_2Cl_2; e) DIAD, PPh_3, **476**.

Disappointing results using DIAD and PPh_3 as the Mitsunobu reagents to couple the two fragments led us to investigate the use of other reagents for the Mitsunobu reaction. It was found that the use of DBAD and *n*-Bu_3P gave better yields of the coupling product and an easier purification process.[116] Compound **480** was now in hand and ready for an investigation of the enyne ring-closing metathesis reaction.[3] Treatment of **480** with 3 mol% of the first generation Grubbs catalyst refluxing in dry CH_2Cl_2 for 10 hours produced the enyne RCM product **481** in good yield. We were then able to investigate the radical mediated closure of the ring B. Intramolecular radical cyclisation of diene **481** was investigated using Bu_3SnH in the presence of AIBN refluxing in dry benzene.[117, 118] According to Baldwin rules,[119] an intramolecular radical cyclisation of this precursor **481** could provide four possible cyclised products through 7-*endo*, 6-*exo*, 5-*exo* and 6-*endo* cyclisation modes for the trigonal system. The 5-*exo-trig* product should be kinetically favored leading to the formation of the tricyclic compound **482**. However, the intramolecular radical cyclisation of **481** failed to produce any of the expected products, and only decomposed products were observed (**Scheme 96**).



Scheme 96. *Reagents and conditions*: a) PCC, CH_2Cl_2; b) ethynylmagnesium bromide; c) NaOAc, Fe, AcOH, Br_2; d) DIAD, PPh_3, **476**, THF; e) **3** (3 mol%), CH_2Cl_2, reflux; f) Bu_3SnH, AIBN, PhH, reflux; g) Bu_3SnH, AIBN, PhH, sealed tube, 130-135 °C.

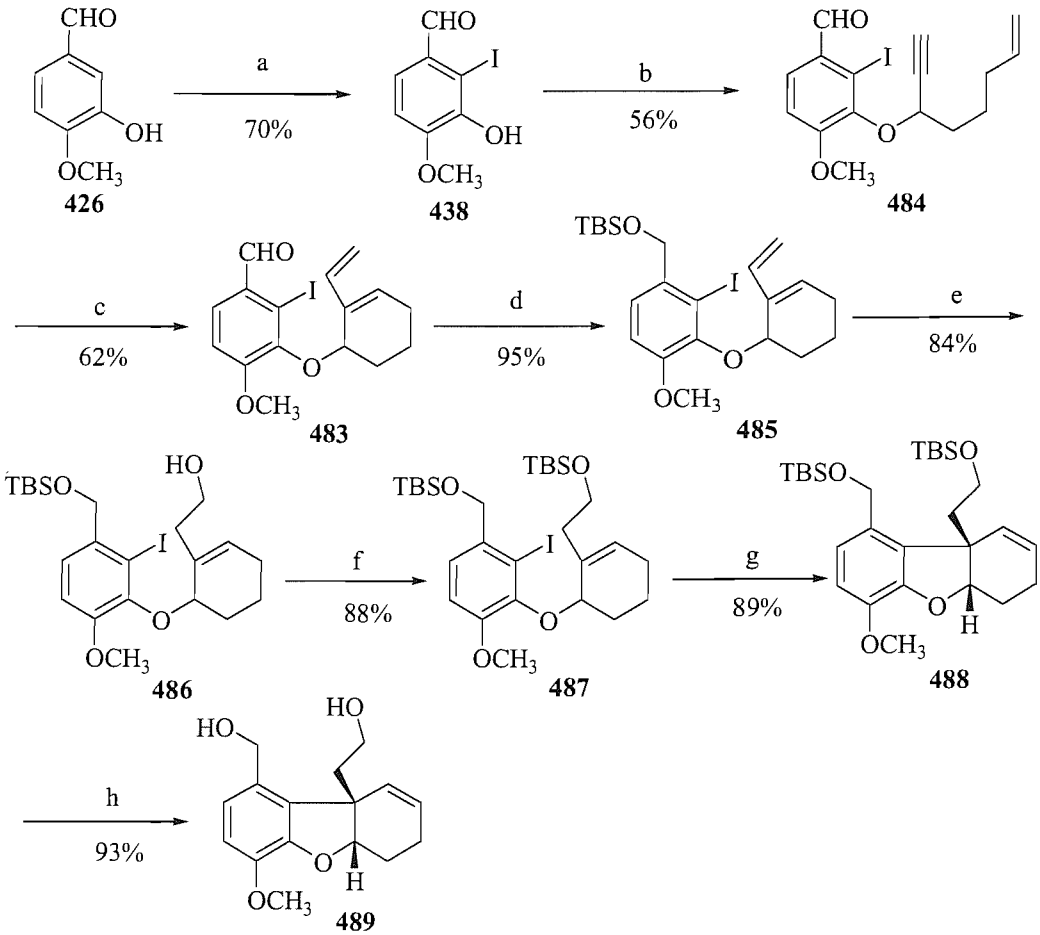
The failed cyclisation of bromide substrate **481** was thought to be due to the bromide substrate **481** acting as a poor precursor to an aryl radical. The iodo compound **483** was an alternative choice for the cyclisation. Disappointingly, the reaction did not give the expected product **482** and only decomposed products were detected again (**Scheme 97**).



Scheme 97. *Reagents and conditions*: a) Bu_3SnH, AIBN, PhH, reflux.

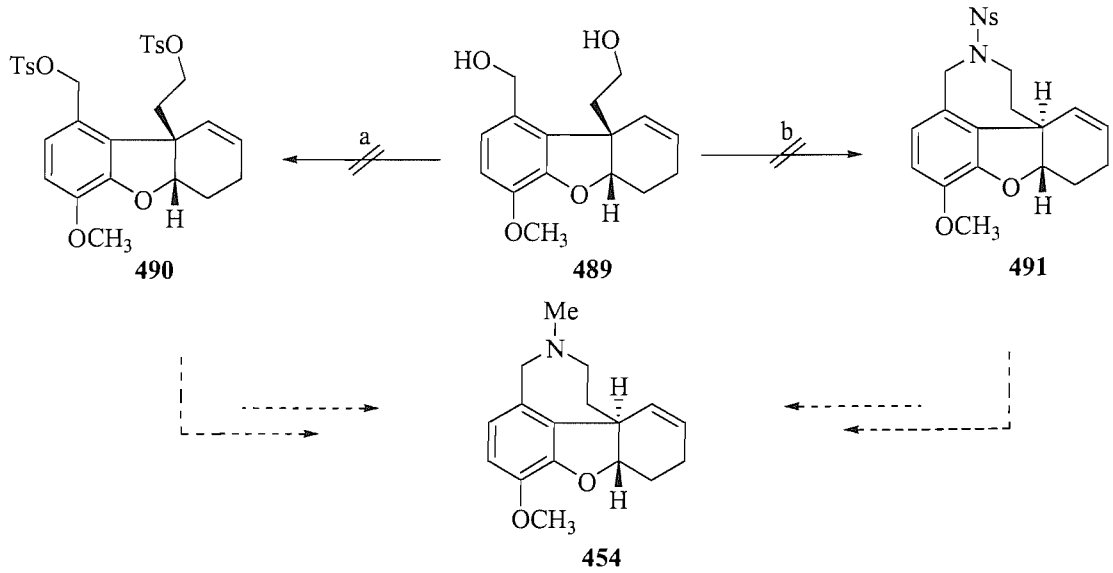
In order to prepare the tricyclic galanthamine framework, an intramolecular radical cyclisation of diene **483** using Bu_3SnH and AIBN was attempted (**Scheme 96, 97**). However, poor results were observed. Therefore, attempts to cyclise **481** or **483** by this pathway were abandoned. It was decided to investigate an intramolecular Heck reaction, which had been used previously to create the quaternary carbon centre by others in their approaches to galanthamine (**Scheme 98**).[112, 113] Synthesis of the precursor for the Heck reaction was commenced by iododination of commercially available isovanillin **426** to afford the *o*-iodophenol **438** in good yield.[120] Mitsunobu reaction of phenol **438** with **476** utilizing DBAD and *n*-Bu_3P gave the coupling

product **484** in better yield in comparison to the corresponding reaction using DIAD and Ph_3P. The enyne ring-closing metathesis was accomplished using 3 mol% of the first generation Grubbs catalyst **3** refluxing in CH_2Cl_2 for 2 hours to produce the cyclised product **483** in good yield. Purification by flash column chromatography was carried out to remove some decomposed catalyst giving a good yield of the pure product **483**. The aldehyde **483** was reduced and subsequent protection gave silyl ether **485**. Hydroboration of the protected diene **485** was accomplished by treatment with 9-BBN and subsequent oxidation with NaOH and H_2O_2 in one-pot process to give alcohol **486** in good yield.[121] After protection of the resulting alcohol **486**, a palladium catalyzed intramolecular Heck reaction gave tricyclic compound **488** in excellent yield.[121] Removal of the silyl protection then gave diol **489** in high yield.



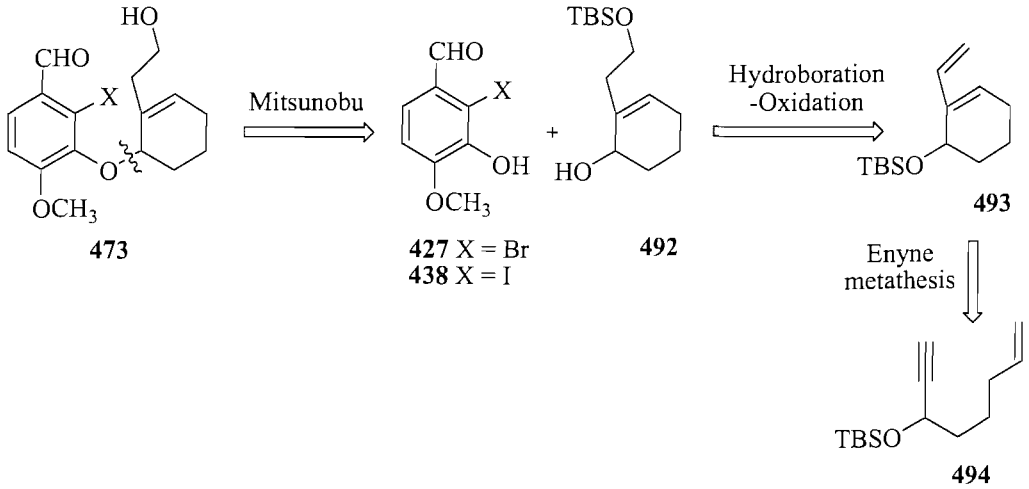
Scheme 98. *Reagents and conditions*: a) ICl, dioxane, pyridine; b) DBAD, *n*-Bu_3P, **476**, THF; c) **3** (3 mol%), CH_2Cl_2; d) i) $NaBH_4$, MeOH, ii) TBSCl, DMAP, imidazole, Et_3N, CH_2Cl_2; e) 9-BBN, THF, NaOH, H_2O_2; f) TBSCl, DMAP, imidazole, Et_3N, CH_2Cl_2; g) $Pd(OAC)_2$, Ag_2CO_3, dppp, $PhCH_3$; h) TBAF, THF.

To accomplish the synthesis of (±)-deoxygalanthamine, tosylation of the resulting diol **489** was carried out by treatment with tosyl chloride and Et_3N in the presence of DMAP (**Scheme 99**). The ^1H NMR spectrum of the crude mixture showed signals suggesting that tosylation had occurred, and it was assumed that the *bis*-tosylate product **490** had been formed. Addition of a solution of methylamine hydrochloride in CH_2Cl_2 to the presumed *bis*-tosylate **490** did not proceed to give the desired product. It was thought that the problem arose from incomplete tosylation of the diol **489** in the previous step. Due to the development of alternative approaches, this *bis*-tosylate route was not investigated further. As an alternative, a Mitsunobu reaction to generate ring D of the galanthamine framework was investigated (**Scheme 99**). Unfortunately, treatment of diol **489** with nosylamine in the presence of DBAD and *n*-Bu_3P failed to give the desired product **491** and only starting material was recovered. For the reasons described above, this approach was also abandoned.



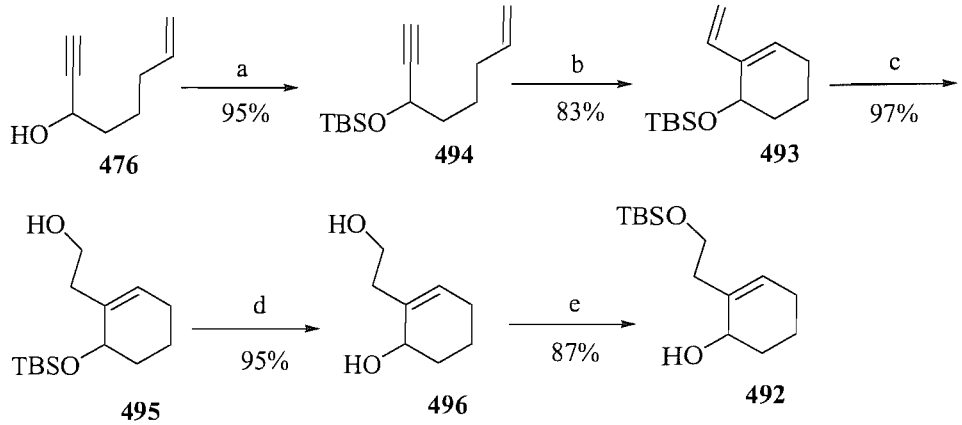
Scheme 99. *Reagents and conditions*: a) TsCl, Et_3N, DMAP, CH_2Cl_2; b) $NsNH_2$, DBAD, *n*-Bu_3P, THF.

An alternative route to the galanthamine framework starting with the synthesis of substituted cyclohexene **492** was devised. The new route would employ an enyne ring-closing metathesis and hydroboration-oxidation reaction sequence. Subsequent Mitsunobu and intramolecular Heck reactions would also be carried out to generate the galanthamine ring system.



Scheme 100. Alternative retrosynthetic analysis of (±)-deoxygalanthamine **454**.

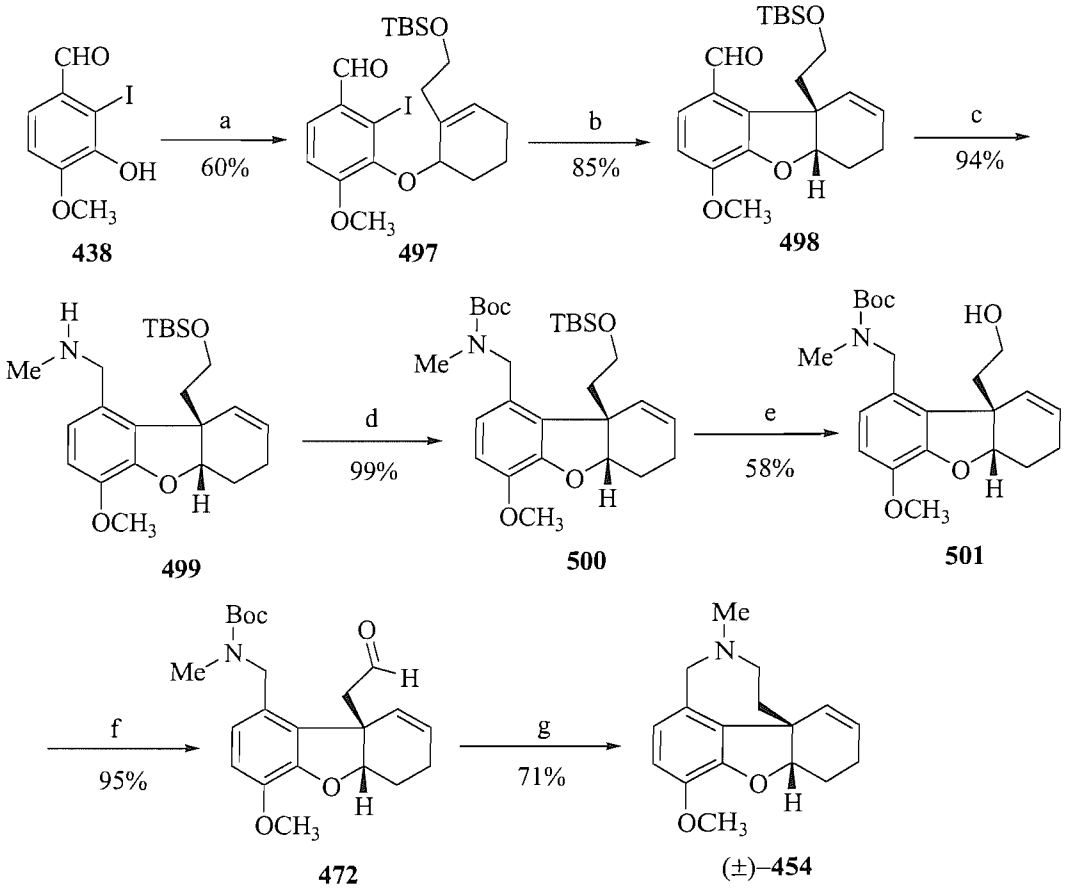
In order to synthesise the C-ring fragment, alcohol **476** was protected as its TBS ether. Subsequent enyne ring-closing metathesis was accomplished by treatment with 3 mol% of the first generation Grubbs catalyst **3** in CH_2Cl_2 at reflux for 2 hours to generate the cyclised product **493** in high yield. This diene **493** was exposed to the hydroboration-oxidation regimen by treatment with 9-BBN at room temperature followed by oxidation with $NaOH/H_2O_2$ to furnish alcohol **495** in excellent yield.[121] After deprotection of **495**, the primary hydroxy group of the resulting diol **496** was selectively protected to provide alcohol **492** (**Scheme 101**).[122]



Scheme 101. *Reagents and conditions*: a) TBSCl, DMAP, imidazole, Et_3N, DMF; b) **3** (3 mol%), CH_2Cl_2; c) 9-BBN, THF, NaOH, H_2O_2; d) TBAF, THF; e) TBSCl, DMAP, Et_3N, DMF.

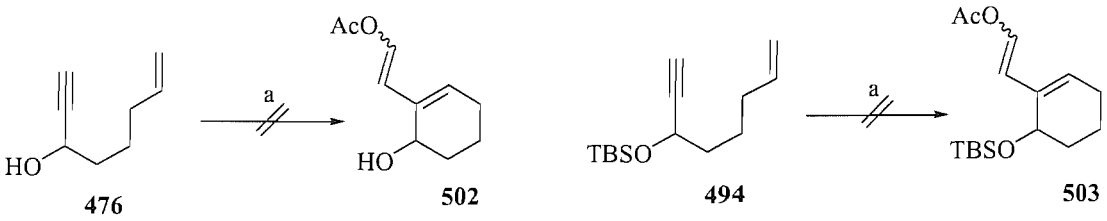
Coupling **492** with the *o*-iodophenol **438** using the pivotal Mitsunobu reaction afforded the desired aryl ether in acceptable yield. Subsequent intramolecular Heck reaction of **497** was carried out by treatment with 15 mol% of $Pd(OAc)_2$ in the

presence of 15 mol% of dppp and excess amount of Ag_2CO_3 to produce the tricyclic product **498** in high yield. In order to create the seven-menbered ring, the aldehyde functionality of the cyclised product **498** was converted to secondary amine **499** following the procedure of Bhattacharyya and co-workers.[123] The aldehyde **498** was treated with methylamine hydrochloride in the presence of Et_3N followed by reduction with $NaBH_4$ to give the crude amine **499** in high yield. Without further purification of the amine **499**, the Boc-protection was accomplished to give the crude carbamate **500.** TBS-deprotection of alcohol **500** was carried out to produce the free hydroxy group, which was subjected to oxidation by treatment with Dess-Martin periodinane giving the aldehyde product **472** in excellent yield.[124] Finally, the Boc group was removed with TFA at room temperature, followed by treatment with $NaCNBH_3$. Purification by flash column chromatography eluting with 1:9 of Et_3N:EtOAc furnished the (±)-deoxygalanthamine **454** in good yield (**Scheme 102**).



Scheme 102. *Reagents and conditions*: a) DBAD, *n*-Bu_3P, **492**, THF; b) $Pd(OAC)_2$, Ag_2CO_3, dppp, $PhCH_3$; c) i) $MeNH_2.HCl$, EtOH, $Ti(O^iPr)_4$, ii) $NaBH_4$; d) Boc_2O, NEt_3, CH_2Cl_2; e) TBAF, THF; f) Dess-Martin periodinane, CH_2Cl_2; g) TFA, 4 Å MS, CH_2Cl_2, then $NaCNBH_3$, MeOH.

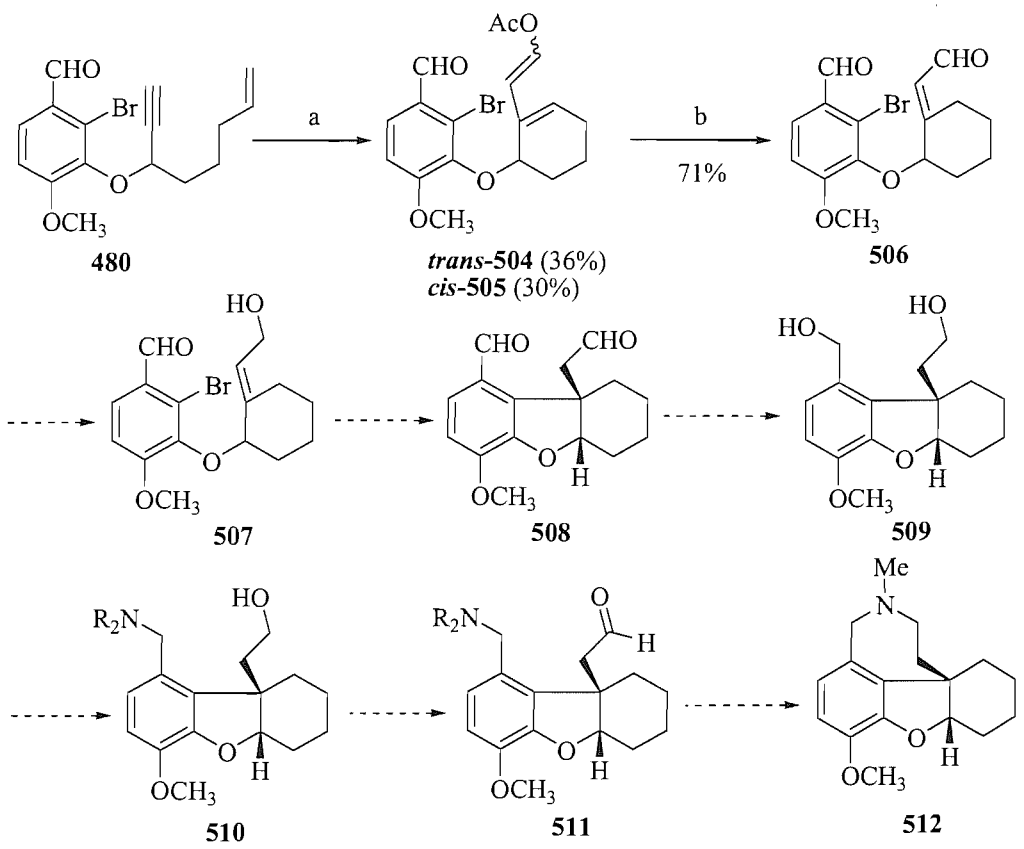
Alongside the routes described above, an alternative approach to the galanthamine alkaloids was also investigated (**Scheme 103**). Exposure of **476** or **494** to cross metathesis conditions in the presence of 10 mol% of the second generation Grubbs catalyst **4** refluxing in CH_2Cl_2 was carried out. However, the reaction failed to give the desired cyclised products, and only decomposed products were observed (**Scheme 103**).



476 **502** **494** **503**

Scheme 103. *Reagents and conditions*: a) **4** (10 mol%), CH_2Cl_2, reflux.

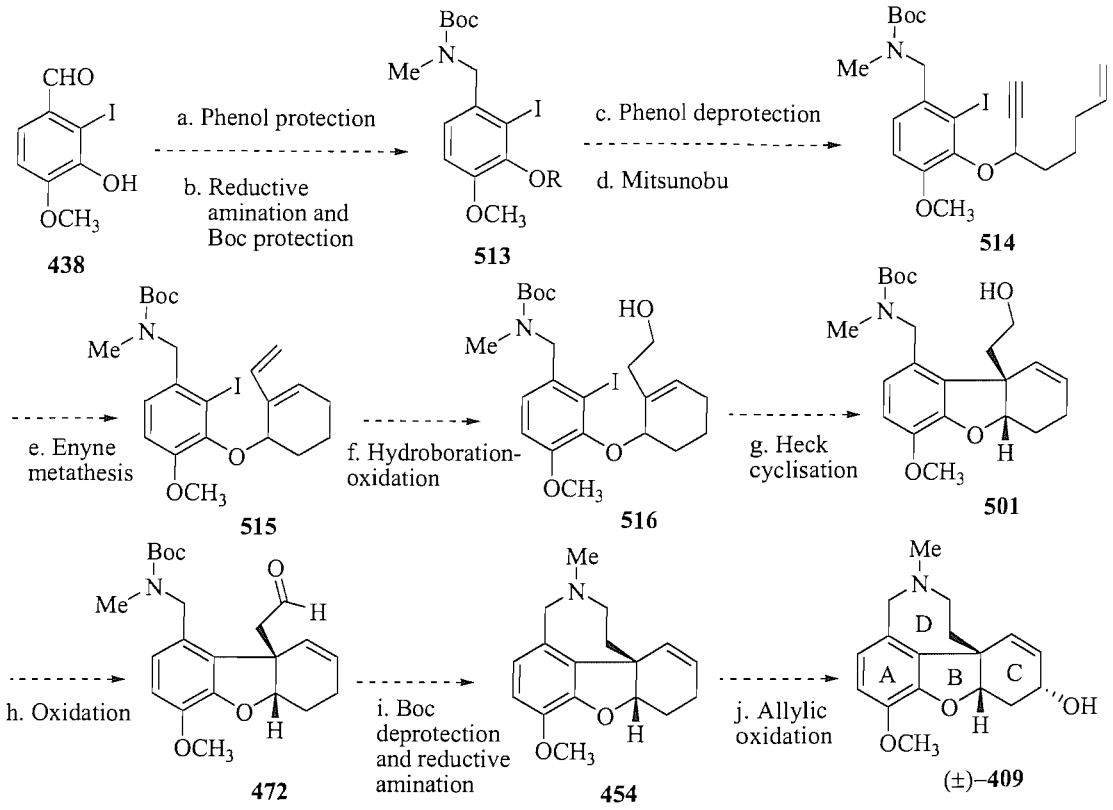
Interestingly, exposure of metathesis precursor **480** to cross metathesis conditions in the presence of the second generation Grubbs catalyst **4** and excess amount of vinyl acetate refluxing in CH_2Cl_2 gave *trans*- and *cis*-cross metathesis products (**504** and **505**) in 36% and 30% yields respectively (**Scheme 104**).[125, 126] Removal of the acetyl group by treatment with potassium carbonate in MeOH produced the conjugated aldehyde **506** in good yield. It was believed that this compound **506** would be a useful intermediate to build up the galanthamine ring system. An Intramolecular Heck reaction could be employed to construct the B-ring. The resulting aldehyde moieties could be converted to diol **509**. Attention to preparation of the ring D, the benzylic alcohol could be selectively oxidized and converted into amino alcohol by reductive amination. Oxidation and subsequent reductive amination would be accomplished to complete the (±)-galanthamine framework. The investigations along this line are currently in progress.



Scheme 104. *Reagents and conditions*: a) **3** (10 mol%), CH_2Cl_2; b) K_2CO_3, MeOH.

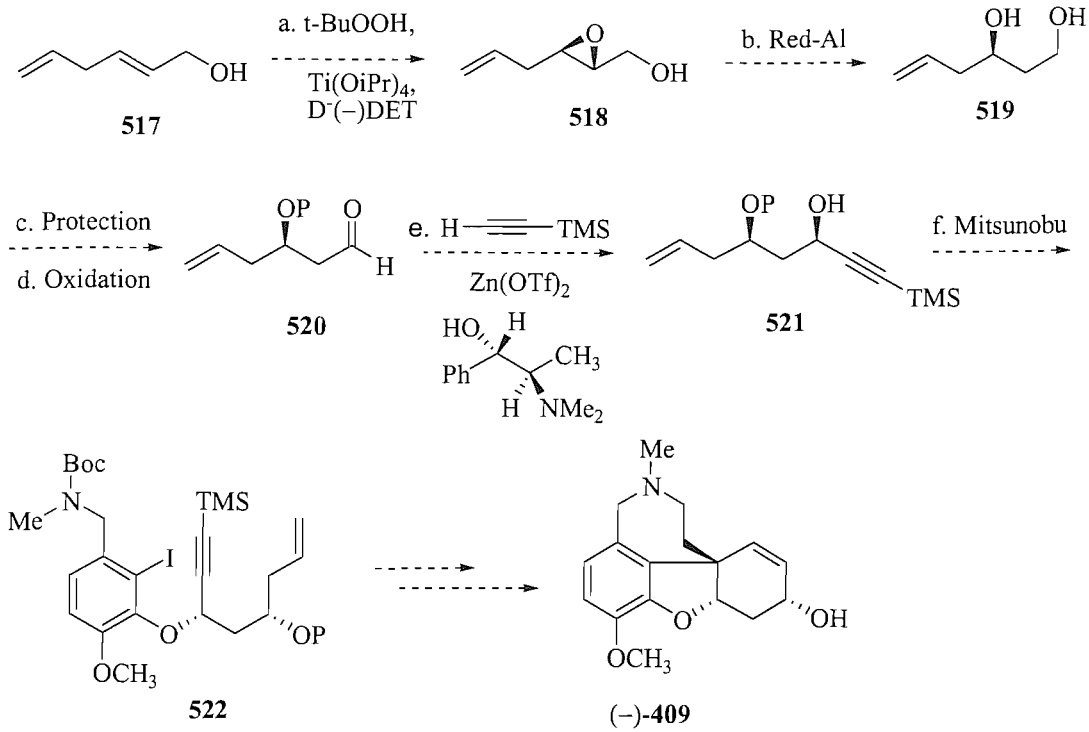
3.7 Conclusions and future work

The synthesis of (±)-deoxygalanthamine **454** has been carried out successfully using a Mitsunobu reaction to link the two major fragments. Enyne ring-closing metathesis and intramolecular Heck reaction allowed us to complete the lower three rings present in galanthamine. However, protection and deprotection steps render the current route somewhat cumbersome in terms of the longest linear sequence. Future work should concentrate on alternative routes in order to reduce the number of linear synthetic steps. One such approach could involve the introduction of tertiary amine to ring A followed by the Mitsunobu reaction, enyne ring-closing metathesis, hydroboration-oxidation sequence producing intermediate **516**. Heck cyclisation could then be used to form the ring B. Subsequent oxidation and reductive amination could be accomplished to complete ring D. It also would be interesting to investigate the directed allylic oxidation of the resulting (±)-deoxygalanthamine **454** to generate (±)-galanthamine **409** (**Scheme 105**), although this is a well-established process.[112]



Scheme 105. Proposed alternative synthetic approach to (±)-galanthamine **409**.

The asymmetric synthetic approaches for the preparation of enantiomerically pure galanthamine should also be considered. The synthesis of the enantiopure alcohol **521** could be accomplished by various methods.[127, 128] One possible approach is outlined in **Scheme 106**. The previous established method could then be used to complete an asymmetric synthesis of (–)-galanthamine **409** (**Scheme 106**).



Scheme 106. Proposed asymmetric synthesis of (–)-galanthamine **409**.

Chapter 4

Experimental

4.1 General procedures

All chemicals were used as received from standard chemical suppliers unless otherwise state. All non-aqueous experiments were performed in oven or fram-dried apparatus under argon atmosphere using distilled dry solvents. All reactions were followed by thin layer chromatography (TLC) using Merk aluminium sheets coated with silica gel F_{254} and visualized under UV light with wavelength 254 nm, iodine, potassium permanganate or molybdate solution. Flash chromatography was carried out on Fisher Matrix*Silica 60. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane was distilled from CaH_2. Acetonitrile was dried over $CaCl_2$ and distilled from CaH_2. Acetone was dried over $CaSO_4$ and distilled. Other chemicals were obtained from Fluka or Merck and used as received. Evaporation refers to rotary evaporation of solvent.

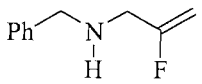
^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ solution using a Bruker AC300 (300 and 75MHz respectively), a Bruker AM300 (as for the AC300) or a Bruker DPX400 (400 and 100 MHz respectively). Chemical shift (δ) are in ppm and coupling constants (J) are in Hertz (Hz). The abbreviations s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) are used when reporting the data.

IR spectra were recorded on a Nicolet Impact 400 spectrometer fitted with a Spectra Tech Thunderdome accessory. Samples were supported on sodium chloride cells. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the data.

Mass spectra acquired using an electrospray technique (ES^+) were recorded on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode. Those obtained using an electron (EIMS) or chemical ionisation technique (CIMS) were recorded on a Thermoquest trace GC-MS with combined EI / CI source using a Macherey – Nagel Optima Delta-3 column – 0.25μm (30 m x 0.25 mm). Relative abundances are reported in brackets after the mass.

4.2 Procedures relating to research described in Chapter 2, section 2.1 Ring-closing metathesis of vinyl fluoro dienes

Benzyl-(2-fluoro-allyl)-amine (179)



$C_{10}H_{12}N$
M.w. = 165.10 g/mol
pale yellow oil

To a stirred solution of benzylamine **196** (500 mg, 4.67 mmol) in DMF (5 ml) was added NaH, 60% dispersion in mineral oil (112 mg, 4.67 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro propene (385 μl, 4.67 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 ml). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (15 g) eluting with 10% EtOAc/hexane to yield the title compound **196** as a pale yellow oil (449 mg, 2.72 mmol, 58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.29 (5H, m, Ar**H**), 4.73 (1H, dd, $J_{H\text{-}F}$ = 17.1 Hz, J = 2.8 Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.50 (1H, dd, $J_{H\text{-}F}$ = 49.6 Hz, J = 2.8 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 3.90 (2H, s, $PhC\mathbf{H_2}$), 3.36 (2H, d, $J_{H\text{-}F}$ = 14.2 Hz, $H_2C{=}CFC\mathbf{H_2}$), 1.63 (1H, s, N**H**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (d, $J_{C\text{-}F}$ = 257 Hz, $H_2C{=}\mathbf{C}FCH_2$), 139.8 ($\mathbf{C}_{Ar}$), 128.6 (2 x $\mathbf{C}H_{Ar}$), 128.4 (2 x $\mathbf{C}H_{Ar}$), 127.3 ($\mathbf{C}H_{Ar}$), 91.7 (d, $J_{C\text{-}F}$ = 18.2 Hz, $H_2\mathbf{C}{=}CFCH_2$), 52.6 ($Ph\mathbf{C}H_2$), 48.9 (d, $J_{C\text{-}F}$ = 30.2 Hz, $H_2C{=}CF\mathbf{C}H_2$).

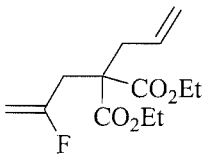
^{19}F NMR (282 MHz, $CDCl_3$) δ –5.50-(–6.00) (1F, m).

IR ν_{max} neat (cm^{-1}): 3352 (m), 3087 (m), 3050 (m), 1687 (m), 1488 (s), 1445 (m), 1195 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 166 $[M+H]^+$ (100).

HRMS (ES^+): Calcd. for $C_{10}H_{13}N$: 166.1027, found 166.1027.

2-(2-Fluoro-allyl)-2-prop-2-enyl-malonic acid diethyl ester (182)



$C_{13}H_{19}FO_4$

M.w. = 258.29 g/mol

colourless oil

To a stirring solution of **270** (100 mg, 0.45 mmol) in DMF (4 mL) was added sodium iodide (15 mg) and a 1M solution of NaHMDS in THF (450 μL, 0.45 mmol). After stirring for 10 minutes, allyl bromide (40 μL, 0.45 mmol) was added. The reaction mixture was heated at 60°C for 4 hours before being quenched with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The combined ether phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as a colourless oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 5% Et_2O/hexane to provide the title compound **182** as a colourless oil (104 mg, 0.40 mmol, 90 %).

^{1}H NMR (400MHz, $CDCl_3$) δ 5.56 (1H, ddt, J = 17.9, 10.3, 7.0 Hz, H_2C=C**H**CH_2), 5.09-5.04 (2H, m, **H_2**C=CHCH_2), 4.60 (1H, dd, $J_{H\text{-}F}$ = 17.0 Hz, J = 2.8 Hz, **H_A**H_BC=CFCH_2), 4.25 (1H, dd, J = 2.8 Hz, $J_{H\text{-}F}$ = 49.3 Hz, H_A**H_B**C=CFCH_2), 4.13 (4H, q, J = 7.1 Hz, CO_2C**H_2**CH_3), 2.78 (2H, d, $J_{H\text{-}F}$ = 21.0 Hz, H_2C=CFC**H_2**), 2.67 (2H, d, J = 7.0 Hz, H_2C=CHC**H_2**), 1.63 (6H, t, J = 7.1 Hz, CO_2CH_2C**H_3**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (**CO_2**Et), 162.4 (d, $J_{C\text{-}F}$ = 258.0 Hz, H_2C=**C**FCH_2), 132.1 (H_2C=**C**HCH_2), 119.8 (H_2**C**=CHCH_2), 94.4 (d, $J_{C\text{-}F}$ = 19.3 Hz, H_2**C**=CFCH_2), 61.7 (H_2**C**=CHCH_2, CO_2**C**H_2CH_3), 55.9 (d, J = 3.2 Hz, **C**H(CO_2Et)$_2$), 36.4 (H_2C=CH**C**H_2), 35.1 (d, $J_{C\text{-}F}$ = 26.5 Hz, H_2C=CF**C**H_2), 14.1 (CO_2CH_2**C**H_3).

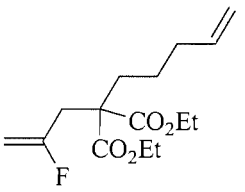
^{19}F NMR (282 MHz, $CDCl_3$) δ 4.50-3.50 (1F, m).

IR ν_{max} neat (cm^{-1}): 2983 (w), 1731 (s), 1676 (s), 1205 (m), 1182 (s), 859 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 239 (100) $[M\text{-}F]^+$

HRMS (ES$^+$): Calcd. for $C_{26}H_{38}F_2O_8Na$: 539.2432, found 539.2444.

2-(2-Fluoro-allyl)-2-pent-4-enyl-malonic acid diethyl ester (184)



$C_{15}H_{23}FO_4$
M.w. = 286.17 g/mol
colourless viscous oil

To a stirring solution of **270** (114 mg, 0.52 mmol) in DMF (5 mL) was added a 1M solution of NaHMDS (520 μL, 0.52 mmol). After stirring for 10 minutes, 5-bromo-1-pentane (56 μL, 0.48 mmol) was added. The reaction mixture was heated at 60°C for 12 hours before being quenched with H_2O (10 mL) and sat'd NH_4Cl (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a colourless oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 1% Et_2O/hexane to yield the compound **184** as a colourless viscous oil (63 mg, 0.22 mmol, 42%).

^{1}H NMR (400MHz, $CDCl_3$) δ 5.77 (1H, ddt, J = 17.1, 10.5, 6.2 Hz, H_2C=C**H**CH_2), 5.01 (1H, dd, J = 17.1, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.96 (1H, dd, J = 10.1, 1.0 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.63 (1H, dd, $J_{H\text{-}F}$ = 17.0 Hz, J = 2.5 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.31 (1H, dd, $J_{H\text{-}F}$ = 49.2 Hz, J = 2.5 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 4.19 (4H, q, J = 7.0 Hz, $CO_2C\mathbf{H_2}CH_3$), 2.88 (2H, d, $J_{H\text{-}F}$ = 21.5 Hz, H_2C=$CFC\mathbf{H_2}$), 2.07 (2H, q, J = 7.0 Hz, H_2C=$CHC\mathbf{H_2}$), 1.97-1.98 (2H, m, $C\mathbf{H_2}$), 1.33-1.20 (2H, m, $C\mathbf{H_2}$), 1.24 (6H, t, J = 7.0 Hz, $CO_2CH_2C\mathbf{H_3}$).

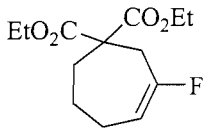
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (**C**O_2Et), 162.7 (d, $J_{C\text{-}F}$ = 257.7 Hz, H_2C=**C**FCH_2), 138.2 (H_2C=**C**HCH_2), 115.2 ($H_2\mathbf{C}$=$CHCH_2$), 94.2 (d, J = 20.3 Hz, $H_2\mathbf{C}$=$CFCH_2$), 61.7 ($H_2\mathbf{C}$=$CHCH_2$, $CO_2\mathbf{C}H_2CH_3$), 56.3 (**C**H(CO_2Et)$_2$), 35.3 (d, $J_{C\text{-}F}$ = 26.0 Hz, H_2C=$CF\mathbf{C}H_2$), 33.9 (H_2C=$CH\mathbf{C}H_2$), 31.4 ($\mathbf{C}H_2$), 23.5 ($\mathbf{C}H_2$), 14.2 ($CO_2CH_2\mathbf{C}H_3$).

^{19}F NMR (282 MHz, $CDCl_3$) δ 4.40-3.70 (1F, m).

IR ν_{max} neat (cm^{-1}): 2982 (w), 1732 (s), 1180 (s), 1043 (m), 913 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 350 $[M+Na+CH_3CN]^+$ (100).
HRMS (ES^+): Calcd. for $C_{15}H_{23}FO_4Na$: 309.1472, found 309.1472.

3-Fluoro-cyclohept-3-ene-1,1-dicarboxylic acid diethyl ester (187)



$C_{13}H_{19}FO_4$

M.w. = 258.29 g/mol

colourless oil

To a stirring solution of **270** (30 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) was added the second generation Grubbs catalyst **4** (8.5 mg, 10 μmol). The mixture was heated in a sealed vial for 4 h at 100°C, concentrated under reduced pressure to give the crude product as a black oil. Purification was accomplished by column chromatography, eluting with 20% Et_2O/hexane to furnish the title compound **187** as a colourless oil (20 mg, 0.08 mmol, 77 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (1H, dt, $J_{H\text{-}F}$ = 19.0 Hz, J = 6.5 Hz, FC=C**H**), 4.25-4.05 (4H, m, $CO_2CH_2CH_3$), 2.90 (2H, d, $J_{H\text{-}F}$ = 6.0 Hz, HC=CFC**H**$_2$), 2.25-2.21 (2H, m, C**H**$_2$), 2.10-2.02 (2H, m, C**H**$_2$), 1.69-1.62 (2H, m, C**H**$_2$), 1.25 (6H, t, J = 7.2 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (**C**O_2Et), 160.1 (d, $J_{C\text{-}F}$ = 285.9 Hz, F**C**=CH), 106.9 (d, $J_{C\text{-}F}$ = 21.5 Hz, FC=**C**H), 61.7 ($CO_2CH_2CH_3$), 54.5 (**C**$(CO_2Et)_2$), 35.5 (**C**H_2), 35.8 (d, $J_{C\text{-}F}$ = 25.0 Hz, HC=CF**C**H_2), 23.2 (d, J = 8.0 Hz, FC=CH**C**H_2), 22.9 (**C**H_2), 14.2 ($CO_2CH_2CH_3$).

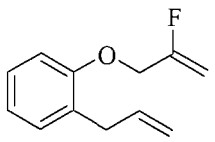
^{19}F NMR (282 MHz, $CDCl_3$) δ 6.70-6.40 (1F, m).

IR ν_{max} neat (cm^{-1}): 2979, 1733 (C=O), 1254, 1224, 1186, 1163.

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %) 281 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{13}H_{19}FO_4Na$: 281.1159, found 281.1161.

1-Allyl-2-(2-fluoro-allyloxy)-benzene (188)



$C_{12}H_{13}FO$
M.w. = 192.23 g/mol
colourless oil

To a stirring solution of 2-allylphenol **244** (389 μL, 2.98 mmol) in DMF (5 mL) was added NaHMDS (2.98 mL, 2.98 mmol, 1M solution in THF). After stirring for 30 minutes, 3-chloro-2-fluoro-propene (280 mg, 2.98 mmol) was added. The reaction mixture was stirred at RT for 15 hours before being quenched with water (10 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a colourless oil. Purification was accomplished by column chromatography on silica gel (15 g) eluting with 2% EtOAc/hexane to furnish the title compound **188** as a colourless oil (570 mg, 2.97 mmol, 99 %).

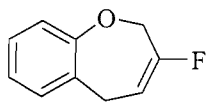
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84-7.04 (2H, m, Ar**H**), 6.98 (1H, t, J = 7.5 Hz, Ar**H**), 6.87 (1H, d, J = 8.0 Hz, Ar**H**) , 6.03 (1H, ddt, J = 16.7, 10.0, 6.7 Hz, H_2C=C**H**), 5.14-5.05 (2H, m, $\mathbf{H}_2C$=CH), 4.87 (1H, dd , $J_{H\text{-}F}$ = 16.7 Hz, J = 3.3 Hz, $\mathbf{H}_A\mathrm{H}_B$C=CF), 4.73 (1H, $ddq_{apparent}$, $J_{H\text{-}F}$ = 48.6 Hz, J = 3.3, 1.0 Hz, $\mathrm{H}_A\mathbf{H}_B$C=CF), 4.57 (2H, d , $J_{H\text{-}F}$ = 9.1 Hz, $\mathrm{H}_A\mathrm{H}_B$C=CFC$\mathbf{H}_2$), 3.46 (2H, d, J = 6.7 Hz, H_2C=CHC$\mathbf{H}_2$)

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 (d, $J_{C\text{-}F}$ = 257.7 Hz, H_2C=**C**FCH_2), 155.8 (**C**$_{Ar}$O), 136.9 (H_2C=**C**H), 130.3 (**C**H$_{Ar}$), 129.4 (**C**H$_{Ar}$), 127.5 (**C**$_{Ar}$), 121.7 (**C**H$_{Ar}$), 115.7 (H_2**C**=CH), 111.9 (**C**H$_{Ar}$), 92.9 (d, $J_{C\text{-}F}$ = 15.8 Hz, H_2C=CF**C**H_2), 47.0 (d, $J_{C\text{-}F}$ = 37.3 Hz, H_2**C**=CFCH_2), 34.5 (H_2C=CH**C**H_2).

IR ν_{max} neat (cm^{-1}): 1685 (m), 1491 (m), 1452 (m), 1238(s), 1217 (m), 854 (w).

LRMS (EI) *m/z* (relative intensity): 192 $[M]^+$ (90).

3-fluoro-2,5-dihydro-benzo-oxepine (189)

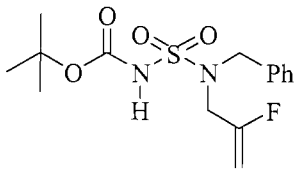


$C_{10}H_9FO$
M.w. = 160.06 g/mol
colourless oil

To a stirred solution of the second generation Grubbs catalyst **4** (39 mg, 46 μmol) in CH_2Cl_2 (1.3 ml) was added a degassed solution of **188** (44.8 mg, 0.23 mmol) in CH_2Cl_2 (1 ml). The reaction mixture was stirred for 5 minutes at RT and then reacted in the microwave at 140 °C for 12 minutes. The solvent was removed under reduced pressure. Partial purification was accomplished by flash chromatography on base-washed (Et_3N) on SiO_2 (6 g) to give the title compound **189** as a colourless oil.[a]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.05 (4H, m ArH), 5.60 (1H, dtt, J = 1.5, 4.4, 22.8 Hz, FC=CH), 4.55 (2H, s, OCH_2), 3.40-3.27 (2H, m, CH_2). [a] Partial purification of **189** was possible on base-washed (Et_3N) SiO_2, although some decomposition still occurred. An NMR sample enriched in **189** also underwent substaintial decompositionon standing in $CDCl_3$ overnight.

[(2-fluoro-allyl)(benzyl)amino][(*tert*-butoxycarbonyl)amino]dioxo-λ^6-sulfane (197)



$C_{15}H_{21}FN_2O_4S$
M.w. = 344.12 g/mol
white solid

To a stirred solution of chlorosulfonyl isocyanate (112.8 μl, 1.29 mmol) in CH_2Cl_2 (8 ml) was added *t*-BuOH (123.4 μl, 1.29 mmol). After stirring for 10 minutes, Et_3N (179.8 μl, 1.29 mmol) and **196** (214 μl, 1.29 mmol) was added. The reaction mixture was stirred for 15 hours. The solution was added CH_2Cl_2 (5 ml) and washed with 1M HCl (3x5 ml) and water (2x5 ml). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product as a white solid. Purification was accomplished by flash chromatography on silica gel (5 g) eluting with 4% EtOAc/hexane to yield the title compound **197** as a white solid (399 mg, 1.16 mmol, 90 %).

Mpt. = 69-70 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (5H, m, Ar**H**), 4.79 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.65 (2H, s, $PhC\mathbf{H_2}$), 4.50 (1H, dd, $J_{H\text{-}F}$ = 47.8 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 3.93 (2H, d, $J_{H\text{-}F}$ = 16.2 Hz, $H_2C{=}CFC\mathbf{H_2}$), 1.50 (9H, s, $C(C\mathbf{H_3})_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (d, $J_{C\text{-}F}$ = 262.2 Hz, $H_2C{=}\mathbf{C}FCH_2$), 150.1 (**C**O), 134.6 ($\mathbf{C}_{Ar}$), 128.9 (2 x $\mathbf{C}H_{Ar}$), 128.5 (2 x $\mathbf{C}H_{Ar}$), 128.2 ($\mathbf{C}H_{Ar}$), 95.1 (d, $J_{C\text{-}F}$ = 16.9 Hz, $H_2\mathbf{C}{=}CFCH_2$), 83.8($\mathbf{C}(CH_3)_3$), 52.3 ($Ph\mathbf{C}H_2$), 47.1 (d, $J_{C\text{-}F}$ = 30.5 Hz, $H_2C{=}C\mathbf{F}CH_2$), 28.1 ($C(\mathbf{C}H_3)_3$).

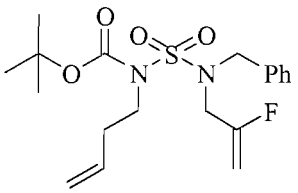
^{19}F NMR (282 MHz, $CDCl_3$) δ –4.95 (1F, dq, J = 48.0, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 3277 (w), 1741 (s), 1364 (s), 1137 (m), 906 (m), 826 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 711 $[2M+Na]^+$ (40).

HRMS (ES^+): Calcd. for $C_{15}H_{21}FN_2O_4SNa$: 367.1098, found 367.1099.

[(2-fluoro-allyl)(benzyl)amino][(*tert*-butoxycarbonyl)(1-butenyl)amino]dioxo-λ^6-sulfane (198)



$C_{19}H_{27}FN_2O_4S$

M.w. = 398.49 g/mol

white solid

To a stirred solution of **197** (129 mg, 0.37 mmol) in DMF (5 ml) was added NaH, 60% dispersion in mineral oil (8.88 mg, 0.37 mmol). After stirring for 30 minutes, 4-bromo-1-butene (38 μl, 0.37 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 ml). The organic phases was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 2% Et_2O/hexane to yield the title compound **198** as a white solid (97 mg, 0.24 mmol, 66%).

Mpt. = 92°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (5H, m, Ar**H**), 5.70 (1H, ddt, *J* = 17.1, 10.0, 7.0 Hz, H_2C=C**H**CH_2), 5.04 (1H, dq, *J* = 17.1, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.98 (1H, dd, *J* = 10.5, 1.0 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.68 (1H, dd, $J_{H\text{-}F}$ = 16.1 Hz, *J* = 3.5 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.54 (2H, s, Ph**C**H_2), 4.35 (1H, dd, $J_{H\text{-}F}$ = 48.2 Hz, *J* = 3.5 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 3.80 (2H, d, $J_{H\text{-}F}$ = 15.6 Hz, H_2C=$CFC\mathbf{H}_2$), 3.65 (2H, t, *J* = 7.5 Hz, N**C**H_2), 2.35 (2H, q, *J* = 7.0 Hz, H_2C=$CHC\mathbf{H}_2$), 1.45 (9H, s, $C(C\mathbf{H}_3)_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (d, $J_{C\text{-}F}$ = 261.1 Hz, H_2C=**C**FCH_2), 151.5 (**C**O), 135.8 (H_2C=**C**HCH_2), 134.6 (**C**$_{Ar}$), 128.9 (2 x **C**H_{Ar}), 128.5 (2 x **C**H_{Ar}), 128.2 (**C**H_{Ar}), 117.6 (H_2**C**=$CHCH_2$), 94.7 (d, $J_{C\text{-}F}$ = 18.1 Hz, H_2**C**=$CFCH_2$), 83.7 (**C**$(CH_3)_3$), 52.6 (Ph**C**H_2), 48.6 (N**C**H_2), 47.1 (d, $J_{C\text{-}F}$ = 47.1 Hz, H_2C=$CF\mathbf{C}H_2$), 34.4 (H_2C=$CH\mathbf{C}H_2$), 28.2 ($C(\mathbf{C}H_3)_3$).

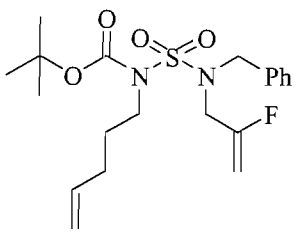
^{19}F NMR (282 MHz, $CDCl_3$) δ –4.75-(–5.15) (1F, m).

IR ν_{max} neat (cm^{-1}): 1724 (s), 1370 (s), 1142 (s), 920 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 441 $[M+CH_3CN+H]^+$(60).

HRMS (ES^+): Calcd. for $C_{19}H_{27}FN_2O_4SNa$: 421.1568, found 421.1576.

[(2-fluoro-allyl)(benzyl)amino][(*tert*-butoxycarbonyl)(4-pentenyl)amino]dioxo-λ^6-sulfane (199)



$C_{20}H_{29}FN_2O_4S$
M.w. = 412.18 g/mol
colourless oil

To a stirred solution of **197** (108 mg, 0.31 mmol) in DMF (5 ml) was added NaH, 60% dispersion in mineral oil (7.44 mg, 0.31 mmol). After stirring for 30 minutes, 5-bromo-1-pentene (37 μl, 0.31 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 2% Et_2O/hexane to yield the compound **199** as a colourless viscous oil (64 mg, 0.16 mmol, 50%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.16 (5H, m, Ar**H**), 5.73 (1H, ddt, J = 17.1, 10.5, 6.5 Hz, H_2C=C**H**CH_2), 4.97 (1H, dq, J = 17.1, 2.0 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.91 (1H, dq, J = 10.0, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.68 (1H, dd, $J_{H\text{-}F}$ = 16.5 Hz, J = 3.5 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.64 (2H, s, Ph**C**H_2), 4.35 (1H, dd, $J_{H\text{-}F}$ = 48.2 Hz, J = 3.5 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 3.80 (2H, d, $J_{H\text{-}F}$ = 15.6 Hz, H_2C=CFC**H**$_2$), 3.65 (2H, m, N**C**H_2), 2.01 (2H, m, H_2C=CHC**H**$_2$), 1.71 (2H, m, C**H**$_2$), 1.45 (9H, s, C(C**H**$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3 (d, $J_{C\text{-}F}$ = 262.2 Hz, H_2C=**C**FCH_2), 151.7 (**C**O), 137.7 (H_2C=**C**HCH_2), 135.7 (**C**$_{Ar}$), 128.9 (2 x **C**H$_{Ar}$), 128.5 (2 x **C**H$_{Ar}$), 128.2 (**C**H$_{Ar}$), 115.3 (H_2**C**=$CHCH_2$), 94.7 (d, $J_{C\text{-}F}$ = 18.1 Hz, H_2**C**=$CFCH_2$), 83.7 (**C**(CH_3)$_3$), 52.6 (Ph**C**H_2), 48.9 (N**C**H_2), 47.0 (d, $J_{C\text{-}F}$ = 30.0 Hz, H_2C=CF**C**H_2), 30.9 (H_2C=CH**C**H_2), 28.9 (**C**H_2), 28.2 (C(**C**H_3)$_3$).

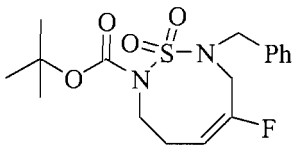
^{19}F NMR (282 MHz, $CDCl_3$) δ –4.95 (1F, tt, J = 30.5, 15.3 Hz).

IR ν_{max} neat (cm^{-1}) 1722 (s), 1366 (m), 1139 (m), 927 (m), 717 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %) 435 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{20}H_{29}FN_2O_4SNa$: 435.1724, found 435.1727.

[(2-fluoro-allyl)(benzyl)amino][(*tert*-butoxycarbonyl)amino]dioxo-λ^6-sulfane (200)



$C_{17}H_{23}FN_2O_4S$
M.w. = 370.44 g/mol
white solid

To a stirring solution of the sulfonamide **198** (50 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added a solution of the second generation Grubbs catalyst **4** (10.6 mg, 1.2 μmol) in CH_2Cl_2 (2 ml). The solution was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux at 60°C for 10 hours. The solvent was removed under reduced pressure to afford the crude product as a dark brown oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 4% Et_2O/hexane to afford the title compound **200** as a a white solid (33 mg, 89 μmol, 72%).

Mpt. = 93-94°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (5H, m, Ar**H**), 5.48 (1H, dt, J = 9.1, $J_{H\text{-}F}$ = 16.7 Hz, FC=C**H**), 4.75 (2H, s (br), PhC**H**$_2$), 3.92 (2H, t, J = 6.7 Hz, FC=CHC**H**$_2$), 3.77 (2H, d, $J_{H\text{-}F}$ = 23.4 Hz, NC**H**$_2$), 2.46 (2H, dt, $J_{H\text{-}F}$ = 9.5 Hz, J = 6.7, HC=CFC**H**$_2$), 1.57 (9H, s, C(C**H**$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0 (d, $J_{C\text{-}F}$ = 260.0 Hz, H_2C=**C**FCH$_2$), 152.4 (**C**O), 136.3 (**C**$_{Ar}$), 128.9 (2 x **C**H$_{Ar}$), 128.7 (2 x **C**H$_{Ar}$), 128.2 (**C**H$_{Ar}$), 107.0 (d, $J_{C\text{-}F}$ = 19.2 Hz, FC=**C**H), 84.4 (**C**(CH$_3$)$_3$), 55.9 (FC=CH**C**H$_2$), 46.7 (N**C**H$_2$), 42.5 (d, $J_{C\text{-}F}$ = 31.6 Hz, HC=CF**C**H$_2$), 28.3 (C(**C**H$_3$)$_3$), 24.6 (CH$_2$).

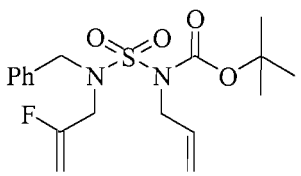
^{19}F NMR (282 MHz, $CDCl_3$) δ 2.90 (1F, dt, J = 23.9, 21.8 Hz).

IR ν_{max} neat (cm^{-1}) 1728 (s), 1382 (s), 1144 (s), 912 (m), 736 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %) 271 $[M+C_5H_9O_2+2H]^+$ (66).

HRMS (ES^+): Calcd. for $C_{34}H_{46}F_2N_4O_8S_2Na$: 763.2618, found 763.2628.

[(2-fluoro-allyl)(benzyl)amino][(*tert*-butoxycarbonyl)(allyl)amino]dioxo-λ^6-sulfane (202)



$C_{18}H_{25}FN_2O_4S$
M.w. = 384.47 g/mol
pale yellow oil

To a stirred solution of sulfamide **197** (640 mg, 1.86 mmol) in DMF (10 mL) was added NaH, 60% dispersion in mineral oil (49 mg, 2.05 mmol). After stirring for 30 minutes, allyl bromide (161 μL, 1.86 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with and water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (15 g) eluting with 4% Et_2O/hexane to afford **202** as a pale yellow oil (97 mg, 0.25 mmol, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (5H, m, Ar**H**), 5.91 (1H, ddt, J = 16.9, 10.3, 5.9 Hz, H_2C=C**H**CH$_2$), 5.31(1H, dq$_{apparent}$, J = 16.9, 1.5 Hz, **H**$_A$**H**$_B$C=CHCH$_2$),

5.31 (1H, $dq_{apparent}$, J = 10.3, 1.5 Hz, H_AH_BC=$CHCH_2$), 4.77 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, H_AH_BC=$CFCH_2$), 4.63 (2H, s, CH_2Ph), 4.44 (1H, dd, $J_{H\text{-}F}$ = 47.8 Hz, J = 3.7 Hz, H_AH_BC=$CFCH_2$), 4.27 (2H, d, J = 5.9 Hz, H_2C=$CHCH_2$), 3.88 (2H, d, $J_{H\text{-}F}$ = 15.4 Hz, H_2C=$CFCH_2$), 1.50 (9H, s, $C(CH_3)_3$).

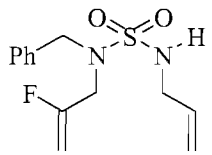
^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3 (d, $J_{C\text{-}F}$ = 262.0 Hz, H_2C=**C**FCH_2), 151.4 (**C**O), 135.7 (**C**$_{Ar}$), 133.3 (H_2C=**C**HCH_2), 128.9 (2 x **C**H_{Ar}), 128.5 (2x**C**H_{Ar}), 128.1 (**C**H_{Ar}), 118.0 (H_2C=$CHCH_2$), 94.7 (d, $J_{C\text{-}F}$ = 18.1 Hz, H_2C=**C**FCH_2), 83.9 (**C**$(CH_3)_3$), 52.4 (**C**H_2Ph), 51.2 (H_2C=$CHCH_2$), 46.9 (d, $J_{C\text{-}F}$ = 30.5 Hz, H_2C=$CFCH_2$), 28.2 ($C(CH_3)_3$).

^{19}F NMR (282 MHz, $CDCl_3$) δ –5.10 (1F, dq, J = 47.9, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 2977 (w), 1726 (s), 1368 (m), 1140 (m), 927 (m), 800 (w).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 407 $[M+Na]^+$ (100).

[(2-fluoro-allyl)(benzyl)amino][(allyl)amino]dioxo-λ^6-sulfane (203)



$C_{13}H_{17}FN_2O_4S$

M.w. = 284.35 g/mol

brown oil

Following the procedure of Sakai and Ohfune *et al.*, to a stirred solution of sulfamide **202** (404 mg, 1.05 mmol) in CH_2Cl_2 (8 mL) was added TFA (2 mL) and the solution was stirred at RT for 3 hours. The reaction mixture was diluted with Et_2O (10 mL) and concentrated under reduced pressure to yield **203** as a brown oil (292 mg, 1.03 mmol, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.30 (5H, m, Ar**H**), 5.74 (2H, ddt, J = 17.4, 10.3, 5.9 Hz, H_2C=**C**HCH_2, SO_2**N**H), 5.04 (1H, $dq_{apparent}$, J = 17.7, 1.5 Hz, H_AH_BC=$CHCH_2$), 4.68 (1H, $dq_{apparent}$, J = 10.3, 1.5 Hz, H_AH_BC=$CHCH_2$), 4.83 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, H_AH_BC=$CFCH_2$), 4.48 (1H, dd, $J_{H\text{-}F}$ = 48.5 Hz, J = 2.9 Hz, H_AH_BC=$CFCH_2$), 4.45 (2H, s, CH_2Ph), 3.85 (2H, d, J = 16.9 Hz, H_2C=$CFCH_2$), 3.69 (2H, $dt_{apparent}$, J = 5.9, 1.2 Hz, H_2C=$CHCH_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (d, $J_{C\text{-}F}$ = 261.0 Hz, H_2C=**C**FCH_2), 135.7 (**C**$_{Ar}$), 133.4 (H_2C=**C**HCH_2), 129.1 (2 x **C**H_{Ar}), 128.9 (2 x **C**H_{Ar}), 128.5 (**C**H_{Ar}), 118.3

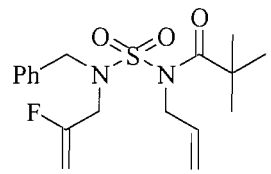
(H_2**C**=CHCH_2), 95.4 (d, $J_{C\text{-}F}$ = 17.9 Hz, H_2**C**=CFCH_2), 51.4 (**C**H_2Ph), 47.3 (d, $J_{C\text{-}F}$ = 29.5 Hz, H_2C=CF**C**H_2), 46.1 (H_2C=CH**C**H_2).

^{19}F NMR (282 MHz, CDCl$_3$) δ –5.25 (1F, dq, J = 45.8, 19.6 Hz).

IR ν_{max} neat (cm^{-1}): 3298 (w), 1425 (m), 1323 (m), 1148 (m), 1063 (m), 925 (m).

LRMS (ES$^+$, MeOH) *m/z* (relative intensity %): 307 $[M+Na]^+$ (100).

[(2-fluoro-allyl)(benzyl)amino][(trimethylacetyl)(allyl)amino]dioxo-λ^6-sulfane (204)



$C_{18}H_{25}FN_2O_4S$

M.w. = 368.47 g/mol

pale yellow oil

To a stirred solution of sulfamide **203** (156 mg, 0.55 mmol) in THF (6 mL) was added *t*-BuOK (63 mg, 0.55 mmol) and 18-crown-6 (145 mg, 0.55 mmol). After stirring for 10 minutes, pivaloyl chloride (75 μL, 0.61 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with and water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 6% Et_2O/hexane to yield **204** as a pale yellow oil (186 mg, 0.50 mmol, 92%).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35-7.27 (5H, m, Ar**H**), 5.90 (1H, ddt, J = 16.9, 10.3, 5.1 Hz, H_2C=C**H**CH_2), 5.38 (1H, dq$_{apparent}$, J = 16.9, 1.5 Hz, $\mathbf{H_A}H_B$C=CHCH_2), 5.28 (1H, dq$_{apparent}$, J = 11.0, 1.5 Hz, $H_A\mathbf{H_B}$C=CHCH_2), 4.72 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, $\mathbf{H_A}H_B$C=CFCH_2), 4.69 (2H, s, C$\mathbf{H}_2$Ph), 4.48 (2H, m, H_2C=CHC$\mathbf{H}_2$), 4.41 (1H, dd, $J_{H\text{-}F}$ = 46.3 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}$C=CFCH_2), 3.90 (2H, d, $J_{H\text{-}F}$ = 16.2 Hz, H_2C=CFC$\mathbf{H}_2$), 1.30 (9H, s, C(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (75 MHz, CDCl$_3$) δ 178.6 (**C**O), 160.3 (d, $J_{C\text{-}F}$ = 262.2 Hz, H_2C=**C**FCH_2), 136.1 (**C**$_{Ar}$), 134.0 (H_2C=**C**HCH_2), 128.8 (2 x **C**H$_{Ar}$), 128.3 (2 x **C**H$_{Ar}$), 128.0 (**C**H$_{Ar}$), 118.1 (H_2**C**=CHCH_2), 94.8 (d, $J_{C\text{-}F}$ = 17.0 Hz, H_2**C**=CFCH_2), 52.8 (**C**H_2Ph),

50.8 (H_2C=CH**C**H_2), 47.4 (d, $J_{C\text{-}F}$ = 30.5 Hz, H_2C=CF**C**H_2), 41.4 (**C**$(CH_3)_3$), 28.2 (C$(\mathbf{C}H_3)_3$).

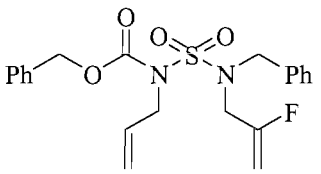
IR ν_{max} neat (cm^{-1}): 2977 (w), 1675 (s), 1365 (m), 1161 (m), 1083 (m), 927 (m).

^{19}F NMR (282 MHz, $CDCl_3$) δ –4.90 (1F, dq, J = 45.8, 19.6 Hz).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 391 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{18}H_{25}FN_2O_3SNa$: 391.1462, found 391.1457.

[(2-fluoro-2-propenyl)(phenylmethyl)amino](dioxo)[[(phenylmethyl)oxy]carbonyl](2-propenyl)amino]-λ^6-sulfane (205)



$C_{21}H_{23}FN_2O_4S$

M.w. = 418.48 g/mol

pale yellow oil

To a stirred solution of sulfamide **203** (307 mg, 1.08 mmol) in DMF (4 mL) was added NaH, 60% dispersion in mineral oil (29 mg, 1.10 mmol). After stirring for 30 minutes, benzyl chloroformate (169 μL, 1.19 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 4% Et_2O/hexane to afford **205** as a pale yellow oil (226 mg, 0.54 mmol, 50%).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.50-7.10 (10H, m, Ar**H**), 5.91 (1H, ddt, J = 16.9, 10.3, 5.9 Hz, H_2C=C**H**CH_2), 5.32 (1H, $dq_{apparent}$, J = 17.1, 1.0 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.23 (1H, $dq_{apparent}$, J = 10.0, 1.0 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 5.23 (2H, s, O**C**$\mathbf{H_2}$Ph), 4.72 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.37 (1H, dd, $J_{H\text{-}F}$ = 47.8 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 4.43 (2H, s, C$\mathbf{H_2}$Ph), 4.36 (2H, d, J = 5.9 Hz, H_2C=$CHC\mathbf{H_2}$), 3.79 (2H, d, $J_{H\text{-}F}$ = 16.9 Hz, H_2C=$CFC\mathbf{H_2}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (d, $J_{C\text{-}F}$ = 262.2 Hz, H_2C=**C**FCH_2), 152.5 (**C**O), 135.3 (**C**$_{Ar}$), 134.7 (H_2C=**C**HCH_2), 132.7 (**C**$_{Ar}$), 128.8 (2x**C**H_{Ar}), 128.7 (2x**C**H_{Ar}),

128.6 (2 x $\mathbf{C}H_{Ar}$), 128.2 (2 x $\mathbf{C}H_{Ar}$), 128.0 (2 x $\mathbf{C}H_{Ar}$), 118.5 ($H_2\mathbf{C}$=$CHCH_2$), 94.9 (d, $J_{C\text{-}F}$ = 18.1 Hz, $H_2\mathbf{C}$=$CFCH_2$), 69.1 ($O\mathbf{C}H_2Ph$), 52.3 ($\mathbf{C}H_2Ph$), 51.1 (H_2C=$CH\mathbf{C}H_2$), 46.9 (d, $J_{C\text{-}F}$ = 30.5 Hz, H_2C=$CF\mathbf{C}H_2$).

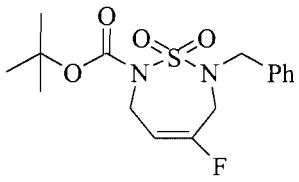
^{19}F NMR (282 MHz, $CDCl_3$) δ –5.38 (1F, dq, J = 47.9, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 3032 (w), 1725 (s), 1368 (s), 1163 (s), 1153 (m), 927 (m), 698 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 441 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{21}H_{23}FN_2O_4SNa$: 441.1255, found 441.1262.

1,1-dimethylethyl 5-fluoro-1,1-dioxo-7-(phenylmethyl)2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thaidizepine-2-carboxylate (206)



$C_{16}H_{21}FN_2O_4S$
M.w. = 356.41 g/mol
white solid

To a stirred solution of sulfamide **223** (57 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added a solution of the second generation Grubbs catalyst **4** (12 mg, 14 μmol) in CH_2Cl_2 (2 mL). The mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 10 hours then concentrated under reduced pressure to give a black oil residue. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 4% Et_2O/hexane to afford **206** as a white solid (30 mg, 0.08 mmol, 60%).

Mpt. = 106-107 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (5H, m, Ar**H**), 5.68 (1H, dt, $J_{H\text{-}F}$ = 18.6 Hz, J = 6.5 Hz, FC=C**H**), 4.40 (2H, s, C$\mathbf{H}_2$Ph), 4.24-4.20 (2H, s, FC=CHC$\mathbf{H}_2$), 3.87 (2H, d, $J_{H\text{-}F}$ = 4.5 Hz, HC=CFC$\mathbf{H}_2$), 1.47 (9H, s, C(C$\mathbf{H}_3$)$_3$).

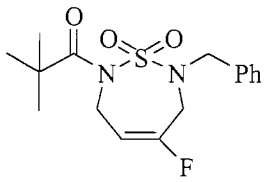
^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6 (d, $J_{C\text{-}F}$ = 265.3 Hz, F**C**=CH), 151.6 (**C**O), 134.7 ($\mathbf{C}_{Ar}$), 129.3 (2 x $\mathbf{C}H_{Ar}$), 128.9 (3 x $\mathbf{C}H_{Ar}$), 105.5 (d, $J_{C\text{-}F}$ = 19.4 Hz, FC=**C**H), 84.9 (**C**(CH$_3$)$_3$), 53.0 (**C**H$_2$Ph), 45.9 (d, $J_{C\text{-}F}$ = 38.9 Hz, HC=CF**C**H$_2$), 40.3 (FC=CH**C**H$_2$), 28.4 (**C**(CH$_3$)$_3$).

IR ν_{max} neat (cm^{-1}): 1722 (s), 1367 (s), 1325 (s), 1257 (s), 1144 (s), 1079 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 379 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{21}FN_2O_4SNa$: 379.1091, found 379.1098.

2-benzyl-7-(2,2-dimethylpropanoyl)-4-fluoro-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thaiadizepine-1,1-dione (207)



$C_{16}H_{21}FN_2O_3S$
M.w. = 340.41 g/mol
colourless oil

To a stirred solution of sulfamide **204** (144 mg, 0.39 μmol) in CH_2Cl_2 (3 mL) was added a solution of the second generation Grubbs catalyst **4** (40 mg, 47 μmol) in CH_2Cl_2 (3 mL). The mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 10 hours then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 4% Et_2O/hexane to afford the sulfamide **207** as a colourless oil (101 mg, 0.30 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.30 (5H, m, Ar**H**), 5.68 (1H, dt, $J_{H\text{-}F}$ = 17.2 Hz, J = 6.2 Hz, FC=C**H**), 4.50 (2H, s, C**H**$_2$Ph), 4.18-4.12 (2H, m, FC=CHC**H**$_2$), 3.95 (2H, d, $J_{H\text{-}F}$ = 5.7 Hz, HC=CFC**H**$_2$), 1.40 (9H, s, C(C**H**$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1 (**C**O), 157.7 (d, $J_{C\text{-}F}$ = 266.2 Hz, F**C**=CH), 134.7 (**C**$_{Ar}$), 129.3 (2 x **C**H$_{Ar}$), 128.9 (3 x **C**H$_{Ar}$), 105.4 (d, $J_{C\text{-}F}$ = 18.9 Hz, FC=**C**H), 52.9 (**C**H$_2$Ph), 45.3 (d, $J_{C\text{-}F}$ = 37.9 Hz, HC=CF**C**H$_2$), 43.4 (**C**(CH$_3$)$_3$), 28.6 (FC=CH**C**H$_2$), 28.3 (C(**C**H$_3$)$_3$).

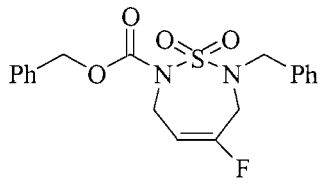
^{19}F NMR (282 MHz, $CDCl_3$) δ –2.00 (1F, d, J = 17.44 Hz).

IR ν_{max} neat (cm^{-1}): 1972 (w), 1680 (m), 1369 (s), 1156 (s), 1079 (m), 903 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 363 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{21}FN_2O_3SNaCH_3CN$: 404.1415, found 404.1414.

Phenylmethyl 5-fluoro-1,1-dioxo-7-(phenylmethyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiaadizepine-2-carboxylate (208)



$C_{19}H_{19}FN_2O_4S$
M.w. = 390.43 g/mol
colourless oil

To a stirred solution of sulfamide **205** (101 mg, 0.24 mmol) in CH_2Cl_2 (2.5 mL) was added a solution of the second generation Grubbs catalyst **4** (24.6 mg, 28 μmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 10 hours then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (5 g) eluting with 4% Et_2O/hexane to afford the sulfamide **208** as a colourless oil (45 mg, 0.12 mmol, 48%).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.55-7.30 (10H, m, Ar**H**), 5.77 (1H, dt, $J_{H\text{-}F}$ = 17.6 Hz, J = 6.6 Hz, **H**C=CF), 5.03 (2H, s, OC**H**$_2$Ph), 4.45 (2H, s, C**H**$_2$Ph), 4.37 (2H, dd, $J_{H\text{-}F}$ = 6.6 Hz, J = 2.9 Hz, HC=CFC**H**$_2$), 3.96 (2H, d, J = 5.2, FC=CHC**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2 (d, $J_{C\text{-}F}$ = 265.6 Hz, HC=**C**F), 152.6 (**C**O), 134.9 (**C**$_{Ar}$), 134.0 (**C**$_{Ar}$), 130.0 (2 x **C**H$_{Ar}$), 128.7 (2 x **C**H$_{Ar}$), 128.5 (4 x **C**H$_{Ar}$), 128.1 (2 x **C**H$_{Ar}$), 105.1 (d, $J_{C\text{-}F}$ = 20.3 Hz, H**C**=CF), 69.3 (O**C**H$_2$Ph), 52.5 (**C**H$_2$Ph), 45.6 (d, $J_{C\text{-}F}$ = 38.4 Hz, HC=CF**C**H$_2$), 40.5 (FC=CH**C**H$_2$).

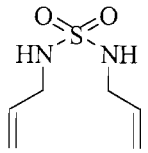
^{19}F NMR (282 MHz, $CDCl_3$) δ –0.64 (1F, d, J = 17.4 Hz).

IR ν_{max} neat (cm^{-1}): 1723 (s), 1322 (s), 1256 (s), 1156 (s), 1082 (w), 736 (s).

LRMS (ES$^+$, MeOH) *m/z* (relative intensity %): 413 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{19}H_{19}FN_2O_4SNa$: 413.0942, found 413.0954.

[(allyl)amino][(allyl)amino]dioxo-λ^6-sulfane (212)



$C_6H_{12}N_2O_2S$

M.w. = 176.24 g/mol

white powder

To a solution of allylamine (1.11 mL, 15 mmol) in CH_2Cl_2 (85 mL) was added triethylamine (3.09 mL, 22 mmol). The reaction mixture was stirred at 0 °C for 15 minutes. Sulfuryl chloride **211** (596 μL, 7.40 mmol) was added dropwise at 0 °C over a period of 45 minutes. The reaction mixture was warmed at RT and then stirred for 15 hours. The reaction mixture was concentrated to 15 mL, ethyl acetate (225 mL) was added. The reaction mixture was washed with sat'd $NaHCO_3$ (4 x 20 mL) then dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow powder. Purification was accomplished by flash chromatography on silica gel (24 g) eluting with 20% EtOAc/hexane to afford **212** as a white powder (910 mg, 5.16 mmol, 70%).

Spectroscopic characteristics are consistent with those reported in the literature.[129]

Mpt. = 64-65 °C

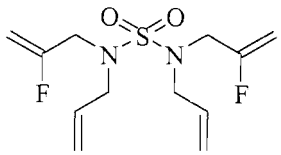
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (2H, ddt, *J* = 11.8, 10.1, 5.9 Hz, 2 x H_2C=C**H**CH_2), 5.32-5.17 (4H, m, 2 x **H**$_2$C=CHCH_2), 4.50 (2H, br, 2xN**H**), 3.69 (4H, m, 2xH_2C=CHC**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5 (2 x H_2C=**C**HCH_2), 117.9 (2 x H_2**C**=CHCH_2), 45.9 (2xH_2C=CH**C**H_2).

IR ν_{max} neat (cm^{-1}): 3278 (NH), 1423 (m), 1313 (s), 1147 (s), 907.

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 199 $[M+Na]^+$(100).

[(2-fluoro-allyl)(allyl)amino][(2-fluoro-allyl)(allyl)amino]dioxo-λ^6-sulfane (213)



$C_{12}H_{18}F_2O_2S$

M.w. = 292.11 g/mol

pale yellow oil

To a stirred solution of sulfamide **212**(315 μL, 1.79 mmol) in DMF (4 mL) was added NaI (537 mg, 3.58 mmol) and NaH, 60% dispersion in mineral oil (107 mg, 4.46 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro-propene (324 μL, 3.94 mmol) was added. The reaction mixture was heated at reflux for 4 hours then stirring was continued at RT for 15 hours before being quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 5% Et_2O/hexane to afford **213** as a pale yellow oil (186 mg, 0.64 mmol, 40%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (2H, ddd, J = 16.9, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.29 (2H, dq, J = 16.2, 3.7 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.25 (2H, dq, J = 11.8, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.80 (2H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 3.7 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.55 (2H, dd, $J_{H\text{-}F}$ = 48.5 Hz, J = 3.7 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 3.90 (4H, d, $J_{H\text{-}F}$ = 15.4 Hz, H_2C=$CFC\mathbf{H}_2$), 3.83 (4H, d, J = 6.6 Hz, H_2C=$CHC\mathbf{H}_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (d, $J_{C\text{-}F}$ = 261.0 Hz, H_2C=**C**FCH_2), 133.5 (H_2C=**C**HCH_2), 120.2 (H_2**C**=$CHCH_2$), 94.5 (d, $J_{C\text{-}F}$ = 18.1 Hz, H_2**C**=$CFCH_2$), 50.2 (H_2C=$CHC\mathbf{H}_2$), 46.9 (d, $J_{C\text{-}F}$ = 31.6 Hz, H_2C=$CFC\mathbf{H}_2$).

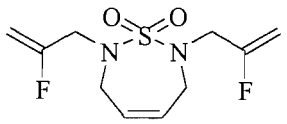
^{19}F NMR (282 MHz, $CDCl_3$) –5.85 (1F, dq, J = 47.9, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 1677 (m), 1340 (m), 1148 (s), 1062, 900, 848 (s), 795.

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 315 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{24}H_{36}F_4N_2O_4S_2Na$: 607.2006, found 607.2004.

2,7-di(2-fluoroallyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiazepine-1,1-dione (214)



$C_{10}H_{14}F_2N_2O_2S$
M.w. = 264.29 g/mol
yellow oil

To a stirred solution of sulfamide **213** (100 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) was added a solution of the second generation Grubbs catalyst **4** (34 mg, 40 μmol) in CH_2Cl_2 (3.8 mL). The reaction mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 9 hours. Another portion of a solution of the second generation Grubbs catalyst **4** (5.6 mg, 6.8 μmol) in CH_2Cl_2 (1 mL) was added. The reaction mixture was heated at reflux at 60 °C for 2 hours then concentrated under reduced pressure. The black oil residue was purified by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to afford the cyclised product **214** as a yellow oil (77 mg, 0.29 mmol, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (2H, t, J = 2.21 Hz, **H**C=C**H**), 4.80 (2H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 3.7 Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.59 (2H, dd, $J_{H\text{-}F}$ = 47.8 Hz, J = 3.7 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 3.94 (4H, d, $J_{H\text{-}F}$ = 13.2 Hz, $H_2C{=}CFC\mathbf{H}_2$), 3.85 (4H, d, J = 2.9 Hz, $\mathbf{H}_2CHC{=}CHC\mathbf{H}_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (d, $J_{C\text{-}F}$ = 260.0 Hz, $H_2C{=}\mathbf{C}FCH_2$), 128.2 (H**C**=**C**H), 93.6 (d, $J_{C\text{-}F}$ = 18.1 Hz, $H_2\mathbf{C}{=}CFCH_2$), 49.2 (d, $J_{C\text{-}F}$ = 32.8 Hz, $H_2C{=}CF\mathbf{C}H_2$), 44.4 ($H_2\mathbf{C}HC{=}CH\mathbf{C}H_2$).

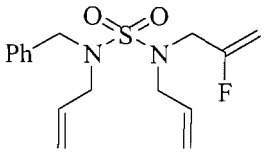
^{19}F NMR (282 MHz, $CDCl_3$) δ –5.85 (1F, dq, J = 47.9, 13.1 Hz).

IR ν_{max} neat (cm^{-1}): 1679 (m), 1359 (w), 1160 (s), 912 (m).

LRMS (ES$^+$, MeOH) *m/z* (relative intensity %): 287 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{10}H_{14}F_2N_2O_2SNa$: 287.0636, found 287.0639.

[(2-fluoro-allyl)(benzyl)amino][(2-fluoro-allyl)(allyl)amino]dioxo-λ^6-sulfane (219)



$C_{16}H_{21}FN_2O_2S$

M.w. = 324.41 g/mol

yellow oil

To a stirred solution of sulfamide **218** (151 mg, 0.58 mmol) in DMF (4 mL) was added NaI (446 mg, 0.29 mmol) and NaH, 60% dispersion in mineral oil (15 mg, 0.62 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro-propene (51.45 μL, 0.62 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 5% EtOAc/hexane to afford **219** as a yellow oil (155 mg, 0.48 mmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.30 (5H, m, Ar**H**), 5.84 (1H, ddt, J = 23.5, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.85 (1H, ddt, J = 23.9, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.30 (1H, $dq_{apparent}$, J = 3.7, 1.5 Hz, H_A**H**$_B$C=$CHCH_2$), 5.26 (1H, $dq_{apparent}$, J = 8.1, 1.5 Hz, **H**$_A$$H_B$C=$CHCH_2$), 5.23 (1H, $dq_{apparent}$, J = 6.6, 1.5 Hz, H_A**H**$_B$C=$CHCH_2$), 5.14 (1H, $dq_{apparent}$, J = 16.9, 1.5 Hz, **H**$_A$$H_B$C=$CHCH_2$), 4.80 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 3.7 Hz, **H**$_A$$H_B$C=$CFCH_2$), 4.55 (1H, dd, $J_{H\text{-}F}$ = 48.5 Hz, J = 2.9, H_A**H**$_B$C=$CFCH_2$), 4.38 (2H, s, C**H**$_2$Ph), 3.92 (2H, d, $J_{H\text{-}F}$ = 15.4 Hz, H_2C=CFC**H**$_2$), 3.86 (2H, d, J = 6.6 Hz, H_2C=CHC**H**$_2$), 3.70 (2H, d, J = 6.6 Hz, H_2C=CHC**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (d, $J_{C\text{-}F}$ = 161.1 Hz, H_2C=**C**FCH_2), 136.3 (**C**$_{Ar}$), 132.9 (H_2C=**C**HCH_2), 132.7 (H_2C=**C**HCH_2), 128.9 (2 x **C**H_{Ar}), 128.8 (2 x **C**H_{Ar}), 128.0 (**C**H_{Ar}), 120.1 (H_2**C**=$CHCH_2$), 119.8 (H_2**C**=$CHCH_2$), 94.6 (d, $J_{C\text{-}F}$ = 16.9 Hz, H_2**C**=$CFCH_2$), 50.6 (H_2C=CH**C**H_2), 50.4 (H_2C=CH**C**H_2), 49.8 (**C**H_2Ph), 47.1 (d, $J_{C\text{-}F}$ = 30.5 Hz, H_2C=CF**C**H_2).

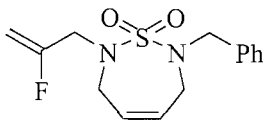
^{19}F NMR (282 MHz, $CDCl_3$) δ -5.60 (1F, dq, J = 47.9, 13.1 Hz).

IR ν_{max} neat (cm^{-1}): 1677 (m), 1341 (m), 1148 (m), 929 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 347 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{21}FN_2O_2SNa$: 671.2508, found 671.2510.

2-benzyl-7-(2-fluoroallyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiadiazepine-1,1-dione (220)



$C_{14}H_{17}FN_2O_2S$
M.w. = 296.36 g/mol
colourless oil

To a stirred solution of sulfamide **219** (99 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was added a solution of the second generation Grubbs catalyst (31 mg, 36.6 μmol) in CH_2Cl_2 (3.10 mL). The reaction mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 9 hours then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to afford the cyclised product **220** as a colourless oil (69 mg, 0.23 mmol, 77%).

^{1}H NMR (300MHz, $CDCl_3$) δ 7.32-7.20 (5H, m, Ar**H**), 5.83-5.76 (1H, m, **H**C=CH), 5.73–5.68 (1H, m, HC=C**H**), 4.71 (1H, dd, $J_{H\text{-}F}$ = 16.1 Hz, J = 3.5 Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.55 (1H, dd, $J_{H\text{-}F}$ = 47.7 Hz, J = 3.5 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 4.33 (2H, s, $C\mathbf{H_2}Ph$), 3.93 (2H, d, $J_{H\text{-}F}$ = 12.5 Hz, $H_2C{=}CFC\mathbf{H_2}$), 3.81 (2H, dd, J = 5.0, 1.5 Hz, $HC{=}CHC\mathbf{H_2}$), 3.58 (2H, dd, J = 5.0, 1.5 Hz, $HC{=}CHC\mathbf{H_2}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (d, $J_{C\text{-}F}$ = 260.5 Hz, $H_2C{=}\mathbf{C}FCH_2$), 136.5 ($\mathbf{C}_{Ar}$), 129.4 (2 x $\mathbf{C}H_{Ar}$), 129.3 (2 x $\mathbf{C}H_{Ar}$), 129.2 ($\mathbf{C}H_{Ar}$), 128.7 (**H**C=CH), 128.3 (HC=**C**H), 93.8 (d, $J_{C\text{-}F}$ = 17.5 Hz, $H_2\mathbf{C}{=}CFCH_2$), 52.7 ($\mathbf{C}H_2Ph$), 49.7 (d, $J_{C\text{-}F}$ = 34.0 Hz, $H_2C{=}CF\mathbf{C}H_2$), 44.9 ($HC{=}CH\mathbf{C}H_2$), 43.8 ($HC{=}CH\mathbf{C}H_2$).

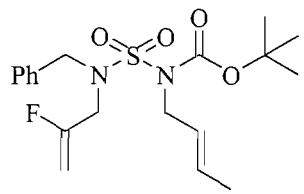
^{19}F NMR (282 MHz, $CDCl_3$) δ 58.9 (1F, ddt, J = 13.1, 15.3, 47.9 Hz).

IR ν_{max} neat (cm^{-1}): 1678 (w), 1357 (m), 1157 (m), 916 (m), 701 (w).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 319 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{28}H_{34}F_2N_4O_4S_2Na$: 615.1882, found 615.1882.

((E)-2-butenyl[[(1,1-dimethylethyl)oxy]carbonyl]amino)[2-fluoro-2-prooenyl)(phenylmethyl)amino]dioxo-λ^6-sulfane (223)



$C_{19}H_{27}FN_2O_4S$
M.w. = 398.49 g/mol
colourless oil

To a stirred solution of sulfamide **197** (317 mg, 0.92 mmol) in THF (4 mL) was added *t*-BuOK (14 mg, 0.58 mmol) and 18-crown-6 (243 mg, 0.92 mmol). After stirring for 30 minutes, crotyl bromide (95 μL, 0.92 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 4% Et_2O/hexane to afford **223** as a colourless oil (307 mg, 0.77 mmol, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (5H, m, Ar**H**), 5.83-5.69 (1H, m, H_2C**H**C=CH(CH_3)), 5.68-5.49 (1H, m, H_2CHC=C**H**(CH_3)), 4.78 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC$=CFCH_2), 4.62 (2H, s, C$\mathbf{H_2}$Ph), 4.45 (1H, dd, , $J_{H\text{-}F}$ = 45.6 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C$=CFCH_2), 4.22 (2H, d, J = 6.6 Hz, $\mathbf{H_2}$CHC=CH(CH_3)), 3.87 (2H, d, J = 14.8 Hz, H_2C=CFC$\mathbf{H_2}$), 1.75-1.65 (3H, m, H_2CHC=CH(C$\mathbf{H_3}$)), 1.54 (9H, m, C(C$\mathbf{H_3}$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (d, $J_{C\text{-}F}$ = 262.2 Hz, H_2C=**C**FCH_2), 151.3 (**C**O), 135.6 (**C**$_{Ar}$), 128.7 (2x**C**H$_{Ar}$), 127.9 (3x**C**H$_{Ar}$), 127.7 (H_2CH**C**=CH(CH_3)), 126.0 (H_2CHC=**C**H(CH_3)), 94.4 (d, $J_{C\text{-}F}$ = 18.1 Hz, H_2**C**=CFCH_2), 52.1 (H_2**C**HC=CH(CH_3)), 50.5 (**C**H_2Ph), 46.7 (d, $J_{C\text{-}F}$ = 30.5 Hz, H_2C=CF**C**H_2), 45.6 (**C**(CH_3)$_3$), 28.1 (3x**C**H_3), 17.7 (**C**H_3).

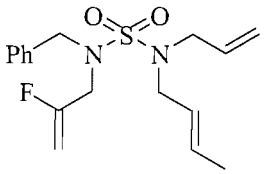
^{19}F NMR (282 MHz, $CDCl_3$) δ –5.15 (1F, ddt, J = 48.0, 30.5, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 2978 (w), 2934 (w), 1723 (s), 1367 (s), 1137 (s), 927 (m).

LRMS (ES$^+$, MeOH) *m/z* (relative intensity %): 421 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{19}H_{27}FN_2O_3SNa$: 421.1568, found 421.1568.

_N_-((E)-2-butenyl)-_N'_-(2-fluoro-2-propenyl)-_N'_-phenylmethyl-_N_-(2-propenyl)sulfamide (225)



$C_{17}H_{23}FN_2O_2S$

M.w. = 338.44 g/mol

colourless oil

To a stirred solution of sulfamide **224** (172 mg, 0.58 mmol) in THF (10 mL) was added *t*-BuOK (65 mg, 0.58 mmol) and 18-crown-6 (153 mg, 0.58 mmol). After stirring for 10 minutes, allyl bromide (60 μL, 0.69 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to **225** as a colourless oil (195 mg, 0.58 mmol, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (5H, m, Ar**H**), 5.95-5.76 (1H, m, H_2C=C**H**CH_2), 5.75-5.60 (1H, m, H_2C**H**C=CH(CH_3)), 5.55-5.42 (1H, m, H_2CHC=C**H**(CH_3)), 5.30-5.23 (2H, m, **H**$_2$C=CHCH_2), 4.78 (1H, dd, $J_{H\text{-}F}$ = 16.5 Hz, J = 3.3 Hz, **H**$_A$H$_B$C=CFCH_2), 4.46 (1H, dd, $J_{H\text{-}F}$ = 47.9 Hz, J = 2.9 Hz, H$_A$**H**$_B$C=CFCH_2), 4.45 (2H, s, C**H**$_2$Ph), 3.85-3.73 (6H, m, (H_3C)HC=CHC**H**$_2$, H_2C=CHC**H**$_2$, H_2C=CFC**H**$_2$), 1.73 (3H, dq$_{apparent}$, J = 6.2, 1.1 Hz, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (d, $J_{C\text{-}F}$ = 261.6 Hz, H_2C=**C**FCH_2), 135.7 (**C**$_{Ar}$), 133.2 (H_2C=**C**HCH_2), 128.7 (2 x **C**H$_{Ar}$), 128.5 (2 x **C**H$_{Ar}$), 127.9 (**C**H$_{Ar}$), 125.6 ((H_3C)HC=**C**HCH_2), 125.0 ((H_3C)H**C**=CHCH_2), 118.8 (H_2**C**=CHCH_2), 94.5 (d, $J_{C\text{-}F}$ = 20.8 Hz, H_2**C**=CFCH_2), 51.1 (**C**H_2Ph), 49.3 (H_2C=CH**C**H_2), 48.9 ((H_3C)HC=CH**C**H_2), 46.7 (d, $J_{C\text{-}F}$ = 29.7 Hz, H_2C=CF**C**H_2), 17.7 (**C**H_3).

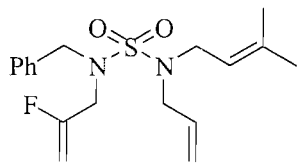
^{19}F NMR (282 MHz, $CDCl_3$) δ –102.10–(–102.6) (1F, m).

IR ν_{max} neat (cm^{-1}): 3031 (w), 2919 (w), 1329 (m), 1145 (s), 924 (m), 897(m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 339 $[M+H]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{17}H_{23}FN_2O_2SNa$: 361.1356, found 361.1344.

_N_-(2-fluoro-2-propenyl)-_N'_-(3-methyl-2-butynyl)-_N_-phenylmethyl-_N'_-(2-propenyl)sulfamide (226)



$C_{18}H_{25}FN_2O_2S$

M.w. = 352.47 g/mol

colourless oil

To a stirred solution of sulfamide **203** (200 mg, 0.70 mmol) in THF (10 mL) was added *t*-BuOK (79 mg, 0.70 mmol) and 18-crown-6 (185 mg, 0.70 mmol). After stirring for 10 minutes, 4-bromo-2-methyl-2-butene (80.6 μL, 0.70 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to afford **226** as a colourless oil (227 mg, 0.64 mmol, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.30 (5H, m, 5xAr**H**), 5.87 (1H, ddt, J = 17.6, 9.9, 6.2 Hz, H_2C=C**H**CH_2), 5.29-5.18 (3H, m, **H**$_2$C=C**H**CH_2, $(H_3C)_2$C=C**H**CH_2), 4.78 (1H, dd, $J_{H\text{-}F}$ = 16.5 Hz, J = 3.3 Hz, **H**$_A$H$_B$C=CFCH_2), 4.46 (1H, dd, $J_{H\text{-}F}$ = 48.3 Hz, J = 3.3 Hz, H$_A$**H**$_B$C=CFCH_2), 4.45 (2H, s, C**H**$_2$Ph), 3.86-3.75 (6H, m, $(H_3C)_2$C=CHC**H**$_2$, H_2C=CHC**H**$_2$, H_2C=CFC**H**$_2$), 1.76 (3H, s, C**H**$_3$), 1.66 (3H, s, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (d, $J_{C\text{-}F}$ = 261.6 Hz, H_2C=**C**FCH_2), 136.8 (**C**$_{Ar}$), 135.7 (H_2C=**C**HCH_2), 133.6 (($H_3C)_2$**C**=$CHCH_2$), 128.7 (2x**C**H$_{Ar}$), 128.6 (2x**C**H$_{Ar}$), 127.9 (**C**H$_{Ar}$), 119.3 (($H_3C)_2$C=**C**HCH_2), 118.5 (H_2**C**=$CHCH_2$), 94.5 (d, $J_{C\text{-}F}$ = 17.8 Hz, H_2**C**=$CFCH_2$), 51.1 (H_2C=CH**C**H_2), 49.6 (**C**H$_2$Ph), 46.7 (d, $J_{C\text{-}F}$ = 29.7 Hz, H_2C=CF**C**H_2), 44.8 (($H_3C)_2$C=CH**C**H_2), 25.8 (**C**H$_3$), 17.9 (**C**H$_3$).

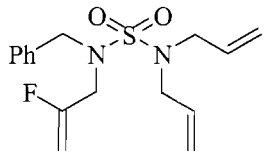
^{19}F NMR (282 MHz, $CDCl_3$, decoupled) –102.40 (1F, s).

IR ν_{max} neat (cm^{-1}): 2979 (w), 1723 (s), 1367 (s), 1147 (s), 1062 (m), 926 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 353 $[M+H]^+$ (50), 416 $[M+2MeOH]^+$ (60), 727 $[2M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{18}H_{26}FN_2O_2SNa$: 353.1694, found 353.1509.

_N_-(2-fluoro-2-propenyl)-_N_-phenylmethyl-_N'_, _N'_-di(2-propenyl)sulfamide (227)



$C_{16}H_{21}FN_2O_2S$

M.w. = 324.41 g/mol

colourless oil

To a stirred solution of sulfamide **203** (150 mg, 0.56 mmol) in DMF (2 mL) was added NaH, 60% dispersion in mineral oil (14 mg, 0.58 mmol). The solution was stirred for 30 minutes before allyl bromide (50.45 μL, 0.58 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 4% Et_2O/hexane to afford **227** as a colourless oil (124 mg, 0.38 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (5H, m, Ar**H**), 5.83 (2H, ddt, J = 17.6, 9.6, 6.6 Hz, 2 x H_2C=C**H**CH_2), 5.28-5.25 (2H, m, 2 x H_A**H**$_B$C=CHCH_2), 5.22 (2H, $dq_{apparent}$, J = 5.9, 1.5 Hz, 2 x **H**$_A$H$_B$C=CHCH_2), 4.78 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, **H**$_A$H$_B$C=CFCH_2), 4.45 (1H, dd, $J_{H\text{-}F}$ = 48.5 Hz, J = 2.9 Hz, H_A**H**$_B$C=CFCH_2), 4.44 (2H, s, C**H**$_2$Ph), 3.85-3.75 (6H, m, 2 x H_2C=CHC**H**$_2$, H_2C=CFC**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (d, $J_{C\text{-}F}$ = 261.1 Hz, H_2C=**C**FCH_2), 135.6 (**C**$_{Ar}$), 132.9 (2 x H_2C=**C**HCH_2), 128.7 (4 x **C**H$_{Ar}$), 128.0 (**C**H$_{Ar}$), 119.2 (2 x H_2**C**=CHCH_2), 94.7 (d, $J_{C\text{-}F}$ = 18.1 Hz, H_2**C**=CFCH_2), 51.1 (**C**H$_2$Ph), 49.6 (2 x H_2C=CH**C**H$_2$), 46.7 (d, $J_{C\text{-}F}$ = 29.4 Hz, H_2C=CF**C**H$_2$).

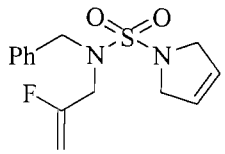
^{19}F NMR (282 MHz, $CDCl_3$) δ –5.20 (1F, ddt, J = 47.9, 17.4, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 3150 (w), 2917 (w), 1338 (s), 1146 (s), 927 (m), 795 (w).

LRMS (ES$^+$, MeOH) *m/z* (relative intensity %): 347 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{16}H_{21}FN_2O_2SNa$: 347.11999, found 347.1205.

***N*-(2-fluoro-2-propenyl)-*N*1-phenylmethyl-2,5-dihydro-1*H*-1-pyrrolesufonamide (228)**



$C_{14}H_{17}FN_2O_2S$

M.w. = 296.36 g/mol

colourless oil

To a stirred solution of sulfamide **227** (100 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was added a solution of the second generation Grubbs catalyst **4** (26 mg, 31 μmol) in CH_2Cl_2 (4 mL). The mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 5 hours then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 4% Et_2O/hexane to afford the cyclised product **228** as a colourless oil (68 mg, 0.23 mmol, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.30 (5H, m, Ar**H**), 5.76 (2H, t, J = 4.4 Hz, **H**C=C**H**), 4.77 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.49 (1H, dd, $J_{H\text{-}F}$ = 47.8 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 4.48 (2H, s, C$\mathbf{H}_2$Ph), 4.18 (4H, s, $\mathbf{H}_2$CHC=CHC$\mathbf{H}_2$), 3.83 (2H, d, J = 16.2 Hz, $H_2C{=}CFC\mathbf{H}_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (d, $J_{C\text{-}F}$ = 262.2 Hz, $H_2C{=}\mathbf{C}FCH_2$), 135.6 ($\mathbf{C}_{Ar}$), 128.7 (2x$\mathbf{C}H_{Ar}$), 128.6 (2x$\mathbf{C}H_{Ar}$), 128.0 ($\mathbf{C}H_{Ar}$), 125.4 (H**C**=**C**H), 94.5 (d, $J_{C\text{-}F}$ = 16.9 Hz, $H_2\mathbf{C}{=}CFCH_2$), 55.1 (**C**H_2Ph), 51.2 (H_2**C**HC=CH**C**H_2), 46.8 (d, $J_{C\text{-}F}$ = 29.4 Hz, $H_2C{=}CF\mathbf{C}H_2$).

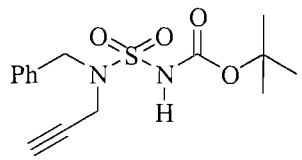
^{19}F NMR (282 MHz, $CDCl_3$) δ -5.30 (1F, ddt, J = 48.0, 32.7, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 2867 (w), 1328 (s), 1152 (s), 926 (m), 739 (w).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 319 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{14}H_{17}FN_2O_2SNa$: 319.0887, found 319.0893.

[(alkynyl)(benzyl)amino][(*tert*-butoxycarbonyl)amino]dioxo-λ^6-sulfane (234)



$C_{15}H_{20}N_2O_4S$

M.w. = 324.40 g/mol

colourless oil

Chlorosulfonyl isocyanate (153 μL, 1.76 mmol) was added to CH_2Cl_2 (5 mL) at 0 °C followed by *tert*-butyl alcohol (168 μL, 1.76 mmol) was added and the mixture stirred for 10 minutes. NEt_3 (245 μL, 1.76 mmol) was added and followed by a solution of **233** (kindly supplied by S. Salim) (256 mg, 1.76 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 15 hours at RT before being diluted with CH_2Cl_2. The organic phase was washed with 1M HCl (3 x 10 mL) and water (5 mL). The organic phases were dried with $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 8% EtOAc/hexane to yield **234** as a colourless oil (423 mg, 1.30 mmol, 74%).

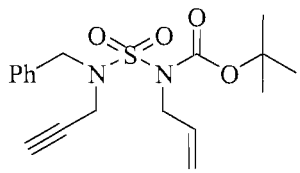
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.31 (5H, m, Ar**H**), 7.17 (1H, s (br), N**H**), 4.71 (2H, s, PhC**H**$_2$), 3.97 (2H, d, J = 2.2 Hz, C**H**$_2$C$_{Alkyne}$), 2.34 (1H, t, J = 2.2 Hz, C**H**$_{Alkyne}$), 1.50 (9H, s, C(C**H**$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1 (**C**O), 135.4 (**C**$_{Ar}$), 129.0 (2 x **C**H$_{Ar}$), 128.8 (2 x **C**H$_{Ar}$), 128.4 (**C**H$_{Ar}$), 83.9 (**C**(CH$_3$)$_3$), 74.1 (**C**$_{Alkyne}$), 60.6 (**C**H$_{Alkyne}$), 52.2 (Ph**C**H$_2$), 36.7 (**C**H$_2$C$_{Alkyne}$), 28.3 (C(**C**H$_3$)$_3$).

IR ν_{max} neat (cm^{-1}): 3279 (w), 1744 (s), 1426 (m), 1367 (m), 1142 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 347 $[M+Na]^+$ (100).

[(alkynyl)(benzyl)amino][(*tert*-butoxycarbonyl)(allyl)amino]dioxo-λ^6-sulfane (235)



$C_{18}H_{24}N_2O_2S$
M.w. = 364.46 g/mol
pale yellow oil

To a stirred solution of sulfamide **234** (405 mg, 1.25 mmol) in DMF (6 mL) was added NaH, 60% dispersion in mineral oil (30 mg, 1.25 mmol) and the reaction mixture was stirred for 30 minutes. Allyl bromide (108 μL, 1.25 mmol) was added and the reaction mixture was stirred for 18 hours before being quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3x10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 5% EtOAc/hexane to yield **235** as a pale yellow oil (307 mg, 0.84 mmol, 67%).

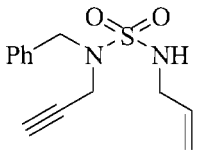
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.31 (5H, m, Ar**H**), 5.91 (1H, ddt, J = 16.9, 10.3, 5.9 Hz, H_2C=C**H**CH_2), 5.31 (1H, $dq_{apparent}$, J = 16.9, 1.5 Hz, **H**$_A$$H_B$C=CH$CH_2$), 5.31(1H, $dq_{apparent}$, J = 10.3, 1.5 Hz, H_A**H**$_B$C=CHCH_2), 4.68 (2H, s, C**H**$_2$Ph), 4.32 (2H, d, J = 5.9 Hz, H_2C=CHC**H**$_2$), 3.91 (2H, d, J = 2.2 Hz, C**H**$_2C_{Alkyne}$), 2.29 (1H, t, J = 2.9 Hz, C**H**$_{Alkyne}$), 1.50 (3H, s, C(C**H**$_3$)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4 (**C**O), 135.7 (**C**$_{Ar}$), 133.3 (H_2C=**C**HCH_2), 128.9 (2 x **C**H$_{Ar}$), 128.6 (2 x **C**H$_{Ar}$), 128.2 (**C**H$_{Ar}$), 117.9 (H_2**C**=CHCH_2), 84.0 (**C**(CH_3)$_3$), 77.0 (**C**$_{Alkyne}$), 73.7 (**C**H$_{Alkyne}$), 52.6 (**C**H_2Ph), 51.4 (H_2C=CH**C**H_2), 36.0 (**C**H_2C_{Alkyne}), 28.3 (C(**C**H_3)$_3$).

IR ν_{max} neat (cm^{-1}): 1728 (s), 1369 (m), 1248 (m), 1140 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 387 $[M+Na]^+$(100).

[(alkynyl)(benzyl)amino][(allyl)amino]dioxo-λ^6-sulfane (236)



$C_{13}H_{16}N_2O_2S$
M.w. = 264.34 g/mol
pale brown oil

Following the procedure of Sakai and Ohfune *et al.*,[130] to a stirred solution of sulfamide **235** (404 mg, 1.05 mmol) in CH_2Cl_2 (8 mL) was added TFA (2 mL) and the solution stirred at room temperature for 4 hours. The reaction mixture was diluted with Et_2O (10 mL) and concentrated under reduced pressure to yield **236** as a pale brown oil (204 mg, 0.77 mmol, 99%).

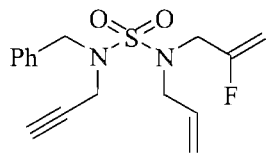
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.30 (5H, m, Ar**H**), 5.92 (1H, ddt, *J* = 16.9, 10.3, 5.9 Hz, H_2C=C**H**CH_2), 5.31 (1H, dq, *J* = 17.7, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.22 (1H, dq, *J* = 10.3, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.49 (2H, s, CH_2Ph), 3.89 (2H, d, *J* = 2.9 Hz, CH_2C_{Alkyne}), 3.78 (2H, d, *J* = 5.9 Hz, H_2C=$CHCH_2$), 2.65 (1H, br, N**H**), 2.40 (1H, t, *J* = 2.2 Hz,CH_{Alkyne}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4 (C_{Ar}), 133.6 (H_2C=**C**HCH_2), 128.9 (2xCH_{Ar}), 128.8 (2 x CH_{Ar}), 128.3 (CH_{Ar}), 117.9 (H_2C=$CHCH_2$), 77.9 (C_{Alkyne}), 74.1 (CH_{Alkyne}), 50.6 (CH_2Ph), 46.1 (H_2C=$CHCH_2$), 36.3 (CH_2C_{Alkyne}).

IR ν_{max} neat (cm^{-1}) 3285 (w), 1323 (m), 1148 (m), 1059 (m), 894 (w).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %) 287 $[M+Na]^+$(100).

[(alkynyl)(benzyl)amino][(2-fluoro-allyl)(allyl)amino]dioxo-λ^6-sulfane (237)



$C_{16}H_{19}FN_2O_4S$
M.w. = 322.40 g/mol
colourless oil

To a stirred solution of sulfamide **236** (204 mg, 0.77 mmol) in DMF (5 mL) was added NaH, 60% dispersion in mineral oil (22 mg, 0.89 mmol) and the solution was stirred for 30 minutes. 3-Chloro-2-fluoro-propene (70 μL, 0.85 mmol) was added. The reaction mixture was stirred for 18 hours and quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10

mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 5% Et_2O/hexane to yield **237** as a colourless oil (151 mg, 0.47 mmol, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (5H, m, Ar**H**), 5.70 (1H, ddt, J = 16.9, 6.6, 10.3 Hz, H_2C=C**H**CH_2), 5.35-5.25 (2H, m, **H_2**C=CHCH_2), 4.82 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, **H_A**H_BC=CFCH_2), 4.58 (1H, dd, $J_{H\text{-}F}$ = 48.5 Hz, J = 3.7 Hz, H_A**H_B**C=CFCH_2), 4.49 (2H, s, C**H_2**Ph), 3.97 (2H, d, $J_{H\text{-}F}$ = 14.7 Hz, H_2C=CFC**H_2**), 3.91 (2H, d, J = 6.6 Hz, H_2C=CHC**H_2**), 3.86 (2H, d, J = 2.2 Hz, C**H_2**C_{Alkyne}), 2.38 (1H, t, J = 2.2 Hz, C**H**$_{Alkyne}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (d, $J_{C\text{-}F}$ = 261.1 Hz, H_2C=**C**FCH_2), 135.3 (C), 132.5 (H_2C=**C**HCH_2), 129.0 (2 x **C**H_{Ar}), 128.9 (2 x **C**H_{Ar}), 128.3 (**C**H_{Ar}), 120.3 (H_2**C**=CHCH_2), 94.5 (d, $J_{C\text{-}F}$ = 16.9 Hz, H_2**C**=CFCH_2), 77.9 (**C**$_{Alkyne}$), 74.0 (**C**H$_{Alkyne}$), 50.4 (**C**H_2Ph), 50.3 (**C**H_2), 47.1 (d, $J_{C\text{-}F}$ = 31.6 Hz, H_2C=CF**C**H_2), 36.2 (**C**$H_2$$C_{Alkyne}$).

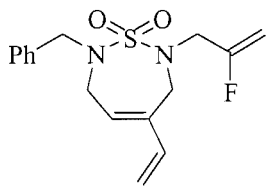
^{19}F NMR (282 MHz, $CDCl_3$) –5.50 (1F, dq, J = 47.9, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 3285 (w), 1329 (m), 1148 (m), 1060 (m), 889 (w).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 345 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{32}H_{38}F_2N_4O_8S_2Na$: 667.2195, found 667.2209.

4-(1-ethenyl)-2-(2-fluoro-2-propenyl)-7-(phenylmethyl)-2,3,6,7-tetrahydro-1*H*-1λ^6, 2,7-thiadiazepine-1,1-dione (238)



$C_{16}H_{19}FN_2O_2S$

M.w. = 322.4 g/mol

white solid

To a stirred solution of sulfamide **237** (200 mg, 0.62 mmol) in CH_2Cl_2 (6 mL) was added a solution of the first generation Grubbs catalyst (25 mg, 31 μmol) in CH_2Cl_2 (6 mL). The mixture was stirred and degassed for 10 minutes. The reaction mixture then was heated at reflux for 18 hours and concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash

chromatography on silica gel (10 g) eluting with 4% Et_2O/hexane to afford the sulfamide **238** as a white solid (63 mg, 0.20 mmol, 31%).

Mpt. = 68-69 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.20 (5H, m, Ar**H**), 6.30 (1H, dd, J = 17.6, 11.0 Hz, **H**C=CH_2), 6.68 (1H, t, J = 5.5 Hz, H_2C**H**C=C), 5.17 (1H, d, J = 17.6 Hz, HC=C$H_A$$H_B$), 5.07 (1H, d, J = 11.0 Hz, HC=CH_A**H_B**), 4.71 (1H, dd, $J_{H\text{-}F}$ = 16.1 Hz, J = 3.3 Hz, **H_A**H_BC=CFCH_2), 4.53 (1H, $ddq_{apparent}$, $J_{H\text{-}F}$ = 47.9 Hz, J = 3.3, 0.7 Hz, H_A**H_B**C=CFCH_2), 4.30 (2H, s, C**H_2**Ph), 4.05 (2H, s, HC=CC**H_2**), 3.87 (2H, d, J = 11.7 Hz, C=CHC**H_2**), 3.66 (2H, d, $J_{H\text{-}F}$ = 4.5 Hz, H_2C=CFC**H_2**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (d, $J_{C\text{-}F}$ = 260.6 Hz, H_2C=**C**FCH_2), 139.4 (HC=**C**), 138.0 (**C_{Ar}**), 135.9 (H**C**=CH_2), 128.7 (2x**CH_{Ar}**), 128.3 (2x**CH_{Ar}**), 128.0 (**CH_{Ar}**), 114.0 (H**C**=C, HC=**C**H_2), 93.4 (d, $J_{C\text{-}F}$ = 16.8 Hz, H_2**C**=CFCH_2), 52.2 (**C**H_2Ph), 48.7 (d, $J_{C\text{-}F}$ = 34.7 Hz, H_2C=CF**C**H_2), 43.3 (HC=C**C**H_2), 43.2 (C=CH**C**H_2).

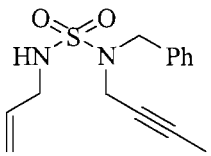
^{19}F NMR (282 MHz, $CDCl_3$, decoupled) δ –97.0 (1F, s).

IR ν_{max} neat (cm^{-1}): 1360 (s), 1158 (s), 901 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 345 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{19}FN_2O_2SNa$: 345.1043, found 345.1049.

_N_-(2-butynyl)-_N_-phenylmethyl-_N'_-(2-propenyl)sulfamide (241)



$C_{14}H_{18}N_2O_2S$

M.w. = 278.37 g/mol

brown oil

Following the procedure of Sakai and Ohfune *et al.*,[130] to a stirred solution of sulfamide **240** (147 mg, 0.39 mmol) in CH_2Cl_2 (8 mL) was added TFA (2 mL) and the solution stirred at room temperature for 2 hours. The reaction mixture was diluted with Et_2O (10 mL) and concentrated under reduced pressure to yield **241** as brown oil (96 mg, 0.34 mmol, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.29 (5H, m, Ar**H**), 5.93 (1H, ddt, J = 17.2, 10.2, 5.9 Hz, H_2C=C**H**CH_2), 5.29 (1H, $dq_{apparent}$, J = 17.2, 1.8 Hz, **H_A**H_BC=CHCH_2), 5.22 (1H, $dq_{apparent}$, J = 10.3, 1.5 Hz, H_A**H_B**C=CHCH_2), 4.48 (2H, s, C**H_2**Ph), 4.32

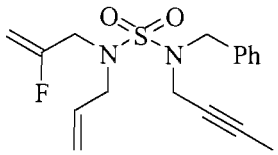
(1H, s (br), N**H**), 3.85 (2H, q, J = 2.6 Hz, H_2C=CHC**H_2**), 3.77 (2H, t (br), C**H_2**C_{alkyne}), 1.88 (3H, t, C**H_3**C_{alkyne}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 (**C_{Ar}**), 133.6 (H_2C=**C**HCH_2), 128.7 (4 x **CH_{Ar}**), 127.9 (**CH_{Ar}**), 117.5 (H_2**C**=CH), 81.7 (C**H_2**C_{alkyne}), 73.1 (**C_{alkyne}**CH_3), 50.7 (**CH_2**Ph), 46.0 (H_2C=CH**CH_2**), 36.7 (**CH_2**C_{alkyne}), 3.53 (C_{alkyne}**CH_3**).

IR ν_{max} neat (cm^{-1}) 3299 (m), 1324 (s), 1148 (s), 1057 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %) 301 $[M+Na]^+$(100).

_N_-(2-butynyl)-_N'_-(2-fluoro-2-propenyl)-_N_-phenylmethyl-_N'_-(2-propenyl)sulfamide (242)



$C_{17}H_{21}FN_2O_2S$

M.w. = 336.43 g/mol

pale yellow oil

To a stirred solution of sulfamide **241** (96 mg, 0.35 mmol) in THF (5 mL) was added *t*-BuOK (39 mg, 0.35 mmol), 18-crown-6 (93 mg, 0.35 mmol) and NaI (53 mg, 0.35 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro propene (36 μL, 0.38 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to afford **243** as a pale yellow oil (96mg, 0.28 mmol, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (5H, m, Ar**H**), 5.81 (1H, ddt, J = 16.5, 10.6, 6.6 Hz, H_2C=C**H**CH_2), 5.22 (1H, q (br), **H_A**H_BC=$CHCH_2$), 5.17 (1H, dq, J = 7.7, 1.5 Hz, H_A**H_B**C=$CHCH_2$), 4.71 (1H, dd, $J_{H\text{-}F}$ = 16.1 Hz, J = 2.9 Hz, **H_A**H_BC=$CFCH_2$), 4.49 (1H, dd, $J_{H\text{-}F}$ = 48.3 Hz, J = 3.3 Hz, H_A**H_B**C=$CFCH_2$), 4.36 (2H, s, C**H_2**Ph), 3.87 (2H, d, J = 14.6 Hz, H_2C=CFC**H_2**), 3.82 (2H, d, J = 6.6 Hz, H_2C=CHC**H_2**), 3.73 (2H, q, J = 2.6 Hz, C**H_2**C_{alkyne}), 1.78 (3H, t, J = 2.2 Hz, C**H_3**C_{alkyne}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (d, $J_{C\text{-}F}$ = 260.6 Hz, H_2C=**C**FCH_2), 136.3 (**C**$_{Ar}$), 135.6 (H_2C=**C**HCH_2), 128.7 (2x**C**H$_{Ar}$), 128.6 (2x**C**H$_{Ar}$), 127.9 (**C**H$_{Ar}$), 119.8 (H_2**C**=CHCH_2), 93.9 (d, $J_{C\text{-}F}$ = 17.8 Hz, FC=**C**H_2), 81.7 (CH_2**C**$_{alkyne}$), 73.0 (**C**$_{alkyne}CH_3$), 50.2 (**C**H_2Ph), 46.9 (d, $J_{C\text{-}F}$ = 31.7 Hz, H_2C=CF**C**H_2), 36.6 (**C**H_2C_{alkyne}), 22.6 (H_2C=CH**C**H_2), 3.5 (C_{alkyne}**C**H_3).

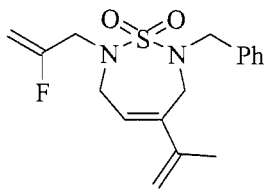
^{19}F NMR (282 MHz, $CDCl_3$, decoupled) δ –102.65 (1F, s).

IR ν_{max} neat (cm^{-1}): 1351 (s), 1150 (s), 1060 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %) 359 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{17}H_{21}FN_2O_2SNa$: 359.1199, found 359.1212.

7-(2-fluoro-2-propenyl)-4(10methyl-1-ethenyl)-2-(phenylmethyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiadiazepine-1,1-dione (243)



$C_{17}H_{21}FN_2O_2S$
M.w. = 336.43 g/mol
brown oil

To a stirred solution of sulfamide **242** (99 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was added a solution of the second generation Grubbs catalyst **4** (24 mg, 30 μmol) in CH_2Cl_2 (3 mL). The mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 14 hours then concentrated under reduced pressure to give the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to afford the cyclised product **243** as a brown oil (92 mg, 0.27 mmol, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (5H, m, Ar**H**), 5.82 (1H, t, J = 5.1 Hz, H_2C=C**H**CH_2), 4.85 (1H, s, **H**$_A$H$_B$C=CCH_3), 4.70 (1H, dd, $J_{H\text{-}F}$ = 16.1 Hz, J = 3.3 Hz, **H**$_A$H$_B$C=$CFCH_2$), 4.66 (1H, s (br), H$_A$**H**$_B$C=CCH_3), 4.54 (1H, dd, $J_{H\text{-}F}$ = 47.9 Hz, J = 3.3 Hz, H$_A$**H**$_B$C=$CFCH_2$), 4.30 (2H, s, C**H**$_2$Ph), 3.88 (2H, d, J = 20.1 Hz, H_2C=CFC**H**$_2$), 3.89 (4H, s (br), HC=C**H**$_2$, H_2C=CHC**H**$_2$), 1.79 (3H, s (br), H_2C=CC**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (d, $J_{C\text{-}F}$ = 260.6 Hz, H_2C=**C**FCH_2), 142.2 (H_2C=**C**CH_3), 141.0 (HC=**C**CH_2), 136.3 (**C**$_{Ar}$), 128.6 (2x**C**H$_{Ar}$), 128.2 (2x**C**H$_{Ar}$),

127.9 (**C**H_{Ar}), 123.4 (**C**=CH), 113.8 (H_2**C**=CCH_3), 93.5 (d, $J_{C\text{-}F}$ = 16.9 Hz, FC=**C**H_2), 52.0 (**C**H_2Ph), 48.9 (d, $J_{C\text{-}F}$ = 33.7 Hz, H_2C=CF**C**H_2), 44.6 (HC=C**C**H_2), 44.2 (C=**C**CH_2), 21.3 (H_2C=C**C**H_3).

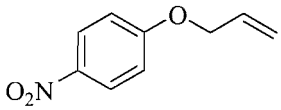
^{19}F NMR (282 MHz, $CDCl_3$, decoupled) –102.80 (1F, s).

IR ν_{max} neat (cm^{-1}) 1363 (m), 1332 (m), 1160 (s), 1109 (m), 907 (s), 726 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %) 359 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{17}H_{21}FN_2O_2SNa$: 359.1200, found 359.1210.

2-Allyloxy-4-nitro-benzene (249)



$C_9H_9NO_3$

M.w. = 179.17 g/mol

yellow oil

To a stirred solution of 4-nitrophenol **248** (1.00 g, 7.19 mmol) in dry acetone (10 ml) was added K_2CO_3 (1.14 g, 8.27 mmol). After stirring for 10 minutes, allyl bromide (622 µl, 7.19 mmol) was added and the reaction mixture was heated at reflux for 8 hours. The mixture was allowed to cool to RT and quenched with water (10 ml). The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over K_2CO_3 and concentrated under reduced pressure to yield crude yellow oil **249** (1.27 mg, 7.19 mmol, 99%). The crude mixture was used without further purification.

Spectroscopic characteristics are consistent with those reported in the literature.[70]

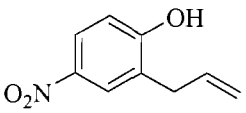
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.98 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.06 (1H, ddt, *J* = 17.6, 10.3, 5.2 Hz, H_2C=C**H**CH_2), 5.45 (1H, dq, *J* = 16.9, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.35 (1H, dq, *J* = 10.3, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.65 (2H, dt, *J* = 5.1, 1.5 Hz, O**C**H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (**C**$_{Ar}$O), 141.7 (**C**$_{Ar}$$NO_2$), 132.0 ($H_2C$=**C**$HCH_2$), 126.0 (2 x **C**$H_{Ar}$), 118.8 (2 x **C**$H_{Ar}$), 114.9 ($H_2$**C**=$CHCH_2$), 69.5 (O**C**$H_2$).

IR ν_{max} neat (cm^{-1}): 3085 (w), 1590 (s, NO_2), 1508 (s), 1336 (s), 1255 (s), 991 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 180 (68) $[M+H]^+$.

2-Allyl-4-nitro phenol (250)



$C_9H_9NO_3$
M.w. = 179.17 g/mol
orange viscous oil

The 2-allyloxy-4-nitro benzene **249** (300 mg, 1.67 mmol) was heated at reflux in *o*-dichlorobenzene (0.5 ml) for 6 hours. The resulting dark brown solution was cooled to RT before dissolved in diethyl ether (10 ml) and then extracted with 20% NaOH (3 x 5 ml). The combined basic solutions were acidified with conc. HCl (20 ml). The resulting organic phases were dried over $CaCl_2$ and concentrated under reduced pressure to give the title compound **250** as a orange viscous oil (130 mg, 0.73 mmol, 43%).

Spectroscopic characteristics are consistent with those reported in the literature.[70]

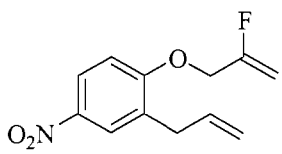
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (2H, s, Ar**H**), 6.92 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.67 (1H, s(br), O**H**), 6.01 (1H, ddt, *J* = 17.2, 10.5, 6.2 Hz, H_2C=C**H**CH_2), 5.42 (1H, dq, J = 5.2, 1.4 Hz, H_A**H**$_B$C=CHCH_2), 5.19 (1H, dq, *J* = 11.4, 1.4 Hz, **H**$_A$H$_B$C=CHCH_2), 2.28 (2H, d, *J* = 6.2 Hz, H_2C=CH**C**H_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (**C**$_{Ar}$OH), 140.9 (**C**$_{Ar}$NO$_2$), 134.8 (H_2C=**C**HCH_2), 126.6 (**C**$_{Ar}$, **C**H$_{Ar}$), 124.4 (**C**H$_{Ar}$), 118.2 (**C**H$_{Ar}$), 115.96 (H_2**C**=CHCH_2), 34.8 (O**C**H_2).

IR ν_{max} neat (cm^{-1}): 3357 (s,br), 1588 (s), 1494 (s), 1332 (s), 1281 (m), 1210 (w).

LRMS (EI, CH_3CN) *m/z* (relative intensity %): 179 (32) $[M]^+$.

2- Allyl-1-(2-fluoro-alloxy)-4-nitro-benzene (251)



$C_{12}H_{12}FNO_3$
M.w. = 237.23 g/mol
yellow oil

To a stirred solution of 2-allyl-4-nitro phenol **250** (108 mg, 0.60 mmol) in DMF (3 ml) was added K_2CO_3 (92 mg, 0.66 mmol) and *n*-Bu_4NI (244 mg, 0.66 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro propene (56 mg, 0.60 mmol) was added. The reaction mixture was stirred at RT for 12 hours before being quenched with

water (10 ml), diluted with Et_2O (10 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml), the combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a yellow oil. Purification was accomplished by column chromatography on silica gel (4 g) eluting with 2% EtOAc/hexane to yield the title compound **251** as a yellow oil (119 mg, 0.50 mmol, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19-8.06 (2H, m, Ar**H**), 6.91 (1H, d, J = 9.6 Hz, Ar**H**), 5.99 (1H, ddt, J = 17.6, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.19-5.14 (1H, m, H $\mathbf{H_A}H_BC$=$CHCH_2$), 5.13 (1H, dq, J = 8.8, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.93 (1H, dd, $J_{H\text{-}F}$ = 16.9 Hz, J = 3.7 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.75 (1H, dd, $J_{H\text{-}F}$ = 47.8 Hz, J = 3.7 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 4.67 (2H, d, J = 10.3 Hz, O**C**$\mathbf{H_2}$), 3.45 (2H, d, J = 6.7 Hz, H_2C=CHC$\mathbf{H_2}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0 (**C**$_{Ar}$O), 159.8 (d, $J_{C\text{-}F}$ = 257.7 Hz, H_2C=**C**FCH_2), 143.0 (**C**$_{Ar}NO_2$), 134.9 (H_2C=**C**HCH_2), 130.3 (**C**$_{Ar}$), 125.7 (**C**H_{Ar}), 124.0 (**C**H_{Ar}), 117.5 (**C**H_{Ar}), 110.9 (H_2**C**=$CHCH_2$), 94.4 (d, $J_{C\text{-}F}$ = 15.8 Hz, H_2**C**=$CFCH_2$), 65.8 (d, $J_{C\text{-}F}$ = 36.2 Hz, H_2C=CF**C**H_2), 34.2 (H_2C=CH**C**H_2).

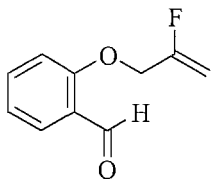
^{19}F NMR (282 MHz, $CDCl_3$) δ –8.90-(–9.25) (1F, m)

IR ν_{max} neat (cm^{-1}): 1589 (m), 1516 (s), 1343 (s), 1256 (m), 1222 (w).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 238 (90) $[M+H]^+$.

HRMS (EI): Calcd. for $C_{12}H_{12}FNO_3$: 237.08057, found 237.08012.

2-(2-fluoro-allyloxy)-benzaldehyde (254)



$C_{10}H_9FO_2$

M.w. = 180.18 g/mol

pale yellow oil

To a stirred solution of salicylaldehyde **253** (436 μL, 4.09 mmol) in DMF (6 mL) was added NaI (306 mg, 2.05 mmol) and NaH, 60% dispersion in mineral oil (108 mg, 4.50 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro-propene (340 μL, 4.09 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic layer was separated and the aqueous was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10

mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (15 g) eluting with 4% Et_2O/hexane to yield **254** as a pale yellow oil (449 mg, 2.42 mmol, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (1H, s, C**H**O), 7.85 (1H, d, J = 1.5, 8.1 Hz, Ar**H**), 7.55 (1H, dt, J = 8.8, 1.5 Hz, Ar**H**), 7.08 (1H, t, J = 7.4 Hz, Ar**H**), 6.99 (1H, t, J = 8.8 Hz, Ar**H**), 4.90 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.74 (1H, dd, $J_{H\text{-}F}$ = 47.8 Hz, J = 3.7 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 4.65 (2H, d, J = 10.3 Hz, $H_2C{=}CFC\mathbf{H}_2$).

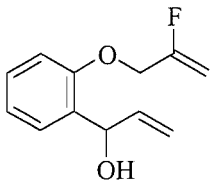
^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4 (**C**HO), 160.1 (d, $J_{C\text{-}F}$ = 258.8 Hz, $H_2C{=}\mathbf{C}FCH_2$), 160.2 ($\mathbf{C}_{Ar}O$), 135.9 ($\mathbf{C}H_{Ar}$), 128.6 ($\mathbf{C}H_{Ar}$), 125.3 ($\mathbf{C}_{Ar}CHO$), 121.7 ($\mathbf{C}H_{Ar}$), 112.9 ($\mathbf{C}H_{Ar}$), 94.1 (d, $J_{C\text{-}F}$ = 15.8 Hz, $H_2\mathbf{C}{=}CFCH_2$), 65.9 (d, $J_{C\text{-}F}$ = 36.2 Hz, $H_2C{=}CF\mathbf{C}H_2$).

^{19}F NMR (282 MHz, $CDCl_3$) δ –8.70 – (–9.30) (1F, m)

IR ν_{max} neat (cm^{-1}): 1681 (s), 1597 (m), 1482 (m), 1455 (m), 1392 (m), 1162 (m).

LRMS (EI, CH_2Cl_2) *m/z* (relative intensity %): 180 $[M]^+$(100).

1-[2-(2-fluoro-allyloxy)-phenyl]-prop-2-en-1-ol (255)



$C_{12}H_{13}FO_2$
M.w. = 208.23 g/mol
yellow oil

To a stirred solution of **254** (351.6 mg, 1.95 mmol) in dry Et_2O (4 mL) was added vinylmagnesium bromide (1.95 mL, 1M in THF, 1.95 mmol) then the solution was stirred for 4 hours at RT. The reaction mixture was quenched with water (5 mL) and 1M HCl (5 mL). The solution was extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 10 % EtOAc/hexane to afford **255** as a yellow oil (288 mg, 1.38 mmol, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, d, J = 7.4, 1.5 Hz, Ar**H**), 7.27 (1H, dt, J = 8.1, 1.5 Hz, Ar**H**), 7.03 (1H, t, J = 6.6 Hz, Ar**H**), 6.89 (1H, d, J = 8.1 Hz, Ar**H**), 6.14

(1H, ddd, J = 16.9, 10.3, 5.2 Hz, H_2C=C**H**C(H)(OH)), 5.49 (1H, t, J = 5.1 Hz, OC**H**), 5.35 (1H, dt, J = 16.9, 2.2 Hz, $\mathbf{H_A}H_BC$=CHC(H)(OH)), 5.19 (1H, dt, J = 10.3, 1.5 Hz, $H_A\mathbf{H_B}C$=CHC(H)(OH)), 4.88 (1H, dd, $J_{H\text{-}F}$ = 16.9 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.72 (1H, dd, $J_{H\text{-}F}$ = 48.9 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 4.59 (2H, d, J = 10.3 Hz, H_2C=CFC$\mathbf{H_2}$), 2.67 (1H, d, J = 5.9 Hz, O**H**).

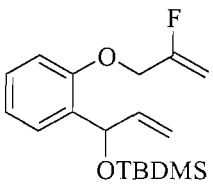
^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (d, $J_{C\text{-}F}$ = 257.7 Hz, H_2C=**C**FCH_2), 155.0 (**C**$_{Ar}$O), 139.3 (H_2C=**C**HC(H)(OH)), 131.4 (**C**H$_{Ar}$), 128.7 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$), 121.9 (**C**$_{Ar}$C(H)(OH)), 114.7 (**C**H$_{Ar}$), 111.9 (H_2**C**=CHC(H)(OH)), 93.7 (d, $J_{C\text{-}F}$ = 15.8 Hz, H_2C=CF**C**H_2), 71.2 (**C**OH), 65.6 (d, $J_{C\text{-}F}$ = 36.2 Hz, H_2**C**=$CFCH_2$).

^{19}F NMR (282 MHz, $CDCl_3$) δ –8.91 (1F, J = 48.0, 17.4, 10.9 Hz)

IR ν_{max} neat (cm^{-1}): 1488 (m), 1452 (s), 1375 (m), 1218 (m), 1035 (s), 919 (w).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 231 $[M+Na]^+$(100).

***tert*-Butyl-[1-[2-(fluoro-allyloxy)-pheny]-allyloxy]-dimethyl silane (256)**



$C_{18}H_{27}FO_2Si$

M.w. = 322.49 g/mol

colourless oil

To a stirred solution of **255** (138.4 mg, 0.66 mmol) in THF (4 mL) was added DMAP (80.5 mg, 0.66 mmol) and NaH, 60% dispersion in mineral oil (18 mg, 0.73 mmol). After stirring for 30 minutes, TBDMSCl (110 mg, 0.73 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 10% Et_2O/hexane to yield **256** as a colourless oil (141 mg, 0.44 mmol, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, dd, J = 7.4, 1.5 Hz, Ar**H**), 7.22 (1H, td, J = 7.4, 1.5 Hz, Ar**H**), 7.03 (1H, t, J = 6.6 Hz, Ar**H**), 6.84 (1H, d, J = 8.1 Hz, Ar**H**), 5.98 (1H, ddd, J = 16.9, 10.3, 5.2 Hz, H_2C=C**H**CHOTBS), 5.63 (1H, d, J = 5.2 Hz, C**H**OTBDMS), 5.32 (1H, dt, J = 16.9, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.02 (1H, dt, J =

10.3, 1.5 Hz, $H_AH_BC=CHCH_2$), 4.86 (1H, dd, J_{H-F} = 16.9 Hz, J = 2.9 Hz, $H_AH_BC=CFCH_2$), 4.69 (1H, dd, J_{H-F} = 47.8 Hz, J = 2.9 Hz, $H_AH_BC=CFCH_2$), 4.57 (2H, d, J = 10.3 Hz, $H_2C=CFCH_2$), 0.95 (9H, s, $C(CH_3)_3$), 0.08 (3H, s, CH_3), 0.00 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (d, J_{C-F} = 257.8 Hz, $H_2C=CFCH_2$), 154.1 ($C_{Ar}O$), 140.9 ($H_2C=CHCH$), 133.3 (C_{Ar}), 128.2 (CH_{Ar}), 127.4 (CH_{Ar}), 122.1 (CH_{Ar}), 112.4 ($H_2C=CHCH$), 111.7 (CH_{Ar}), 93.4 (d, J_{C-F} = 16.8 Hz, $H_2C=CFCH_2$), 69.5 (CHOTBS), 65.8 (d, J_{C-F} = 36.8 Hz, $H_2C=CFCH_2$), 30.1 ($C(CH_3)_3$), 26.2 (CH_3), -4.5 (CH_3).

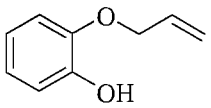
^{19}F NMR (282 MHz, $CDCl_3$) δ –8.75–(–9.10) (1F, m)

IR ν_{max} neat (cm^{-1}): 2928 (m), 2857 (m), 1487 (m), 1253 (s), 1067 (s), 1031, 834.

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 150.9 $[M\text{-}SiC_9H_{19}O]^+$ (100).

HRMS (ES^+): Calcd. for $C_{18}H_{27}FO_2SiNa$: 345.1656, found 345.1656.

2-Allyloxy-phenol (269)



$C_9H_{10}O_2$

M.w. = 150.17 g/mol

colourless oil

To a stirred solution of catechol **268** (300 mg, 2.72 mmol) in DMF (4 ml) was added K_2CO_3 (414 mg, 2.99 mmol) and *n*-Bu_4NI (1.10 g, 2.99 mmol). After stirring for 30 minutes, allyl chloride (222 µl, 2.72 mmol) was added. The reaction mixture was stirred for 18 hours before being quenched with water (10 ml), diluted with EtOAc (10 ml). The organic layer was separated and the aqueous was extracted with EtOAc (3 x 10 ml). The combined organic extracts were washed with brine (2 x 5 ml), dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with hexane to give the title compound **269** as a colourless oil (252 mg, 1.68 mmol, 62 %).

Spectroscopic characteristics are consistent with those reported in the literature.[131]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05-6.78 (4H, m, Ar**H**), 6.01 (1H, ddt, J = 16.9, 10.3, 5.2 Hz, $H_2C=CHCH_2$), 5.70 (1H, s(br), O**H**), 5.43 (1H, dq, J = 17.7, 1.5 Hz,

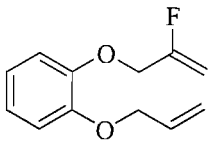
$\mathbf{H_A}H_BC{=}CHCH_2$), 5.34 (1H, dq, J = 10.3, 1.5 Hz, $H_A\mathbf{H_B}C{=}CHCH_2$), 4.62 (2H, dt, J = 5.1, 1.5 Hz, $H_2C{=}CH\mathbf{CH_2}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0 (c), 145.7 ($\mathbf{C}_{Ar}OH$), 133.0 ($H_2C{=}\mathbf{C}HCH_2$), 121.9 ($\mathbf{C}H_{Ar}$), 120.2 ($\mathbf{C}H_{Ar}$), 118.5 ($\mathbf{C}H_{Ar}$), 114.9 ($\mathbf{C}H_{Ar}$), 112.3 ($H_2\mathbf{C}{=}CHCH_2$), 70.0 ($H_2C{=}CH\mathbf{C}H_2$).

IR ν_{max} neat (cm^{-1}): 3528 (s, br), 1498 (s), 1256 (s,), 1216 (s), 994 (m).

LRMS (EI, CH_2Cl_2) *m/z* (relative intensity %): 150 (100) $[M+H]^+$.

2-Allyloxy-2-(2-fluoro-allyloxy)-benzene (270)



$C_{12}H_{13}FO_2$
M.w. = 208.23 g/mol
colourless viscous oil

To a solution of 2-allyloxy-phenol **269** (150 mg, 1 mmol) in DMF (1 ml) at 0 °C was added NaH, 60% dispersion in mineral oil (24 mg, 1 mmol). After stirring for 30 minutes, 3-Chloro-2-fluoro-propene (94 mg, 1 mmol) was added. The reaction mixture was stirred for 18 hours before being quenched with sat'd NH_4Cl (5 mL), water (5 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a colourless oil. The residue was purified by flash chromatography on silica gel (5 g) eluting with 2% EtOAc/hexane to afford the title compound **270** as a colourless viscous oil (163 mg, 0.78 mmol, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03-6.87 (4H, m, Ar**H**), 6.22-6.01 (1H, m, $H_2C{=}C\mathbf{H}CH_2$), 5.44 (1H, dq, J = 16.9, 2.2 Hz, $\mathbf{H_A}H_BC{=}CHCH_2$), 5.29 (1H, dq, J = 9.6, 2.2 Hz, $H_A\mathbf{H_B}C{=}CHCH_2$), 4.89-4.77 (1H, m, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.66-4.60 (1H, m, $H_A\mathbf{H_B}C{=}CFCH_2$), 4.62-4.56 (4H, m, $OC\mathbf{H}_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (d, $J_{C\text{-}F}$ = 257.2 Hz, $H_2C{=}\mathbf{C}FCH_2$), 149.2 ($\mathbf{C}_{Ar}O$), 148.7 ($\mathbf{C}_{Ar}O$), 133.7 ($H_2C{=}\mathbf{C}HCH_2$), 122.72 ($\mathbf{C}H_{Ar}$), 121.4 ($\mathbf{C}H_{Ar}$), 117.7 ($\mathbf{C}H_{Ar}$), 116.1 ($\mathbf{C}H_{Ar}$), 114.4 ($H_2\mathbf{C}{=}CHCH_2$), 93.3 (d, $J_{C\text{-}F}$ = 19.2 Hz, $H_2C{=}C\mathbf{F}CH_2$), 70.1 ($O\mathbf{C}H_2$), 67.1 (d, $J_{C\text{-}F}$ = 36.2 Hz, $H_2\mathbf{C}{=}CFCH_2$).

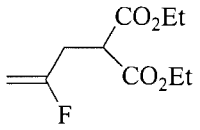
^{19}F NMR (282 MHz, $CDCl_3$) δ –8.90-(–9.27) (1F, m)

IR ν_{max} neat (cm^{-1}): 1499 (s), 1453 (m), 1249 (s), 1205 (s), 1124 (s), 994 (s).

LRMS (EI, CH_3CN) *m/z* (relative intensity %): 208 (100) $[M]^+$.

HRMS (ES^+): Calcd. for $C_{12}H_{13}FO_2$: 208.08963, found 208.08862.

Diethyl 2-(2-fluoroallyl)malonate (273)



$C_{10}H_{15}FO_4$

M.w. = 218.22 g/mol

colourless oil

To a stirred solution of diethylmalonate **272** (500 mg, 3.12 mmol) in DMF (4 ml) was added NaH, 60% dispersion in mineral oil (82 mg, 3.43 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro propene (337 mg, 3.59 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 ml) and sat'd NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (15 g) eluting with 5% EtOAc/hexane to yield the title compound **273** as a colourless oil (190 mg, 0.87 mmol, 28%).

^{1}H NMR (400MHz, $CDCl_3$) δ 4.61 (1H, dd, $J_{H\text{-}F}$ =16.9 Hz, J = 2.9, Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.36 (1H, dd, $J_{H\text{-}F}$ = 49.3 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 4.23 (4H, q, J = 6.6 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.63 (1H, t, J = 7.4 Hz, $C\mathbf{H}(CO_2Et)_2$), 2.83 (2H, dd, J = 7.4 Hz, $J_{H\text{-}F}$ = 16.2 Hz, $H_2C{=}CFC\mathbf{H_2}$), 1.29 (6H, t, J = 6.6 Hz, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 ($\mathbf{C}O_2Et$), 164.0 (d, $J_{C\text{-}F}$ = 50.9 Hz, $H_2C{=}\mathbf{C}FCH_2$), 92.3 (d, J = 120.34 Hz, $H_2\mathbf{C}{=}CFCH_2$), 61.9 ($CO_2\mathbf{C}H_2CH_3$), 49.6 ($\mathbf{C}H(CO_2Et)_2$), 31.5 (d, $J_{C\text{-}F}$ = 28.3 Hz, $H_2C{=}CF\mathbf{C}H_2$), 14.2 ($CO_2CH_2\mathbf{C}H_3$).

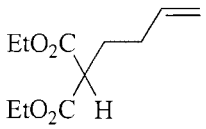
^{19}F NMR (282 MHz, $CDCl_3$) δ 0.10 (1F, dq, J = 50.1, 17.4 Hz).

IR ν_{max} neat (cm^{-1}): 2984 (w), 1734 (s), 1260 (m), 1219 (m), 1152 (s), 1034 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 257 (63) $[M+K]^+$

HRMS (ES^+): Calcd. for $C_{10}H_{15}FO_4Na$: 241.0846, found 241.0846.

2-But-3-enyl-malonic acid diethyl ester (274)



$C_{11}H_{18}O_4$

M.w. = 214.26 g/mol

colourless oil

To a stirred solution of diethyl malonate **266** (2.9 mL, 18.5 mmol) in THF (40 mL) was added *t*-BuOK (830 mg, 7.4 mmol) and 18-crown-6 (1.9 g, 7.4 mmol) at 0 °C. After stirring for 30 minutes, a solution of 4-bromo-1-butene (752 μL, 7.4 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 15 hours before being quenched with water (15 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 4% Et_2O/hexane to afford **274** as a colourless oil (1.5 g, 7 mmol, 95%).

Spectroscopic characteristics are consistent with those reported in the literature.[73]

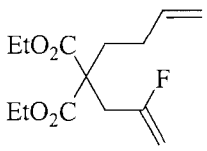
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J* = 17.2, 10.3, 6.2 Hz, H_2C=C**H**CH_2), 5.05-4.99 (1H, m, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.98-4.94 (1H, m, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.17 (4H, q, *J* = 7.2 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.32 (1H, t, *J* = 7.2 Hz, C**H**), 2.11-2.04 (2H, m, H_2C=$CHC\mathbf{H_2}$), 2.02-1.94 (2H, m, $C\mathbf{H_2}CH(CO_2Et)_2$), 1.24 (6H, t, *J* = 7.2 Hz, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (2 x $\mathbf{C}O_2Et$), 136.8 (H_2C=**C**HCH_2), 115.8 ($H_2\mathbf{C}$=$CHCH_2$), 61.2 (2 x $CO_2\mathbf{C}H_2CH_3$), 51.1 (**C**H), 31.2 (H_2C=$CH\mathbf{C}H_2$), 27.8 ($\mathbf{C}H_2CH(CO_2Et)_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2981 (w), 1730 (s), 1226 (m), 1152 (m), 1030 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 237 $[M+Na]^+$ (100).

2-But-3-enyl-2-(2-fluoro-allyl)-malonic acid diethyl ester (275)



$C_{14}H_{21}FO_4$
M.w. = 272.31 g/mol
colourless oil

To a stirred solution of **274** (330 μL, 1.54 mmol) in DMF (4 mL) was addded 1M solution of NaHMDS in THF (1.54 mL, 1.54 mmol) at 0 °C and stirred for 30 minutes. Next, NaI (231 mg, 1.54 mmol) and 2-fluoro-3-chloro propene (140 μL, 1.69 mmol) were added. The reaction mixture was stirred for 18 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 4% Et_2O/hexane to afford **275** as a colourless oil (387 mg, 1.42 mmol, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, J = 16.9, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.04 (1H, $dq_{apparent}$, J = 16.9, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.97 (1H, $dq_{apparent}$, J = 10.3, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.65 (1H, dd, $J_{H\text{-}F}$ = 16.9 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.33 (1H, dd, $J_{H\text{-}F}$ = 49.3 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 4.20 (4H, q, J = 6.6 Hz, $CO_2C\mathbf{H_2}CH_3$), 2.89 (2H, d, $J_{H\text{-}F}$ = 21.3 Hz, H_2C=$CFC\mathbf{H_2}$), 2.10-2.02 (2H, m, $C\mathbf{H_2}$), 2.00-1.91 (2H, m, H_2C=$CHC\mathbf{H_2}$), 1.26 (3H, t, J = 7.46 Hz, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (**C**O), 162.3 (d, $J_{C\text{-}F}$ = 257.7 Hz, H_2C=**C**FCH_2), 137.3 (H_2C=**C**HCH_2), 115.2 ($H_2\mathbf{C}$=$CHCH_2$), 94.0 (d, $J_{C\text{-}F}$ = 19.2 Hz, $H_2\mathbf{C}$=$CFCH_2$), 61.5 ($CO_2\mathbf{C}H_2CH_3$), 55.8 (**C**), 35.1 (d, $J_{C\text{-}F}$ = 26.0 Hz, H_2C=$CF\mathbf{C}H_2$), 31.0 ($\mathbf{C}H_2$), 28.4 (H_2C=$CH\mathbf{C}H_2$), 14.0 ($CO_2CH_2\mathbf{C}H_3$).

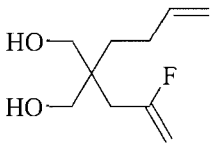
^{19}F NMR (282 MHz, $CDCl_3$) δ 68.3 (dq, J = 19.6, 50.1 Hz).

IR ν_{max} neat (cm^{-1}): 2981 (w), 1734 (s), 1201 (m), 1182 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 295 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{14}H_{21}FO_4Na$: 295.1316, found 295.1316.

2-But-3-enyl-2-(2-fluoro-allyl)-propene-1,3-diol (276)



$C_{10}H_{17}FO_2$
M.w. = 188.24 g/mol
colourless oil

To a 1M solution of $LiAlH_4$ in THF (299 μL, 2.99 mmol) was added dropwise a solution of **275** (371 mg, 1.36 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 2 hours and quenched with by dropwise addition of ether (10mL) followed by water (10 mL). The reaction mixture was poured into 2M HCl solution (10 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield a crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 1:1 EtOAc/hexane to afford **276** as a colourless oil (251 mg, 1.35 mmol, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, ddt, J = 16.9, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.04 (1H, $dq_{apparent}$, J = 16.9, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.69 (1H, $dq_{apparent}$, J = 10.3, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.67 (1H, dd, $J_{H\text{-}F}$ = 17.6 Hz, J = 2.9 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.34 (1H, dd, $J_{H\text{-}F}$ = 54.4 Hz, J = 2.9 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 3.60 (4H, s, 2 x C**H**$_2$OH), 2.46 (2H, s, 2 x CH_2O**H**), 2.35 (2H, d, $J_{H\text{-}F}$ = 24.3 Hz, H_2C=CFC**H**$_2$), 2.15-2.00 (2H, m, C**H**$_2$), 1.48-1.39 (2H, m, H_2C=CHC**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (d, $J_{C\text{-}F}$ = 257.7 Hz, H_2C=**C**FCH_2), 138.8 (H_2C=**C**HCH_2), 114.8 (H_2**C**=$CHCH_2$), 93.5 (d, $J_{C\text{-}F}$ = 21.5 Hz, H_2**C**=$CFCH_2$), 68.2 (CH_2O**H**), 68.1 (CH_2O**H**), 41.7 (**C**), 33.9 (d, $J_{C\text{-}F}$ = 30.0 Hz, H_2C=CF**C**H_2), 31.0 (**C**H_2), 27.6 (H_2C=CH**C**H_2).

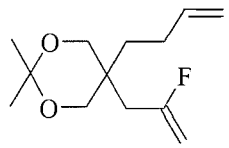
^{19}F NMR (282 MHz, $CDCl_3$) δ 7.82 (1F, ddt, J = 50.7, 17.4, 24.0 Hz).

IR ν_{max} neat (cm^{-1}): 3367 (br), 2928 (m), 1669 (m), 1201 (m), 1031 (s), 852 (m).

LRMS (ES$^+$, MeOH) *m/z* (relative intensity %): 211 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{10}H_{17}FO_2Na$: 211.1105, found 211.1104

5-But-3-enyl-5-(2-fluoro-allyl)-2,2-dimethyl-[1,3]dioxane (277)



$C_{13}H_{21}FO_2$

M.w. = 228.30 g/mol

yellow oil

To a stirred solution of **276** (85 mg, 0.45 mmol) in acetone (5 mL) was added amberlyst®15 (100 mg) and 4 Å molecular sieves. The reaction mixture was stirred for 18 hours, filtered and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (2 g) eluting with 1:1 EtOAc/hexane to afford **277** as a yellow oil (84 mg, 0.37 mmol, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (1H, ddt, J = 17.1, 10.0, 6.5Hz, H_2C=C**H**CH_2), 5.04 (1H, $dq_{apparent}$, J = 17.1, 1.5 Hz, **H**$_A$H$_B$C=CHCH_2), 4.88 (1H, $dq_{apparent}$, J = 10.0, 1.5 Hz, H$_A$**H**$_B$C=CHCH_2), 4.58 (1H, dd, $J_{H\text{-}F}$ = 17.1 Hz, J = 2.5 Hz, **H**$_A$H$_B$C=CFCH_2), 4.25 (1H, dd, $J_{H\text{-}F}$ = 47.7 Hz, J = 3.0 Hz, H$_A$**H**$_B$C=CFCH_2), 3.60 (4H, s, 2xOC**H**$_2$), 2.34 (2H, d, $J_{H\text{-}F}$ = 23.6 Hz, H_2C=CFC**H**$_2$), 2.00-1.90 (2H, m, C**H**$_2$), 1.41-1.36 (2H, m, H_2C=CHC**H**$_2$), 1.35 (6H, s, C(C**H**$_3$)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, $J_{C\text{-}F}$ = 258.5 Hz, H_2C=**C**FCH_2), 137.5 (H_2C=**C**HCH_2), 113.6 (H_2**C**=CHCH_2), 97.1 (**C**), 92.4 (d, $J_{C\text{-}F}$ = 20.4 Hz, H_2**C**=CFCH_2), 66.4 (2 x O**C**H$_2$), 33.5 (d, $J_{C\text{-}F}$ = 26.2 Hz, H_2C=CF**C**H$_2$), 30.9 (**C**H$_2$), 26.0 (H_2C=CH**C**H$_2$), 24.5 (2 x **C**H$_3$), 21.1 (**C**(CH$_3$)$_2$).

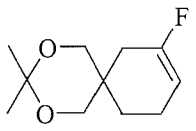
^{19}F NMR (282 MHz, $CDCl_3$) δ 7.80 (1F, ddt, J = 50.1, 23.9, 17.4 Hz).

IR ν_{max} neat (cm^{-1}): 2992 (w), 2939 (w), 2863 (w), 1671 (m), 1371 (m), 1259 (m), 1195 (s), 1113 (m), 832 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 251 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{13}H_{21}FO_2Na$: 251.1418, found 251.1417

9-Fluoro-3,3-dimethyl-2,4-dioxa-spiro[5.5]undec-8-ene (278)



$C_{11}H_{17}FO_2$

M.w. = 200.25 g/mol

brown oil

To a stirred solution of acetal **277** (52 mg, 0.23 mmol) in CH_2Cl_2 (2.5 mL) was added a solution of the second generation Grubbs catalyst (19.5 mg, 23 μmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred and degassed for 10 minutes. The reaction mixture was heated at reflux for 10 hours then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (5 g) eluting with 5% Et_2O/hexane to afford the cyclised product **278** as a brown oil (27.6 mg, 0.23 mmol, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13-5.05 (1H, m, FC=C**H**), 3.55 (4H, d, J = 3.5 Hz, 2 x O**CH$_2$**), 2.13-2.08 (2H, m, **CH$_2$**), 2.03-1.96 (2H, m, FC=CHC**H$_2$**), 1.42 (2H, dt, $J_{H\text{-}F}$ = 6.5 Hz, J = 1.5 Hz, HC=CFC**H$_2$**), 1.40 (6H, s, C(**CH$_3$**)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 (d, $J_{C\text{-}F}$ = 253.7 Hz, F**C**=CH), 99.2 (d, $J_{C\text{-}F}$ = 15.6 Hz, FC=**C**H), 96.7 (**C**(CH$_3$)$_2$), 66.4 (2 x O**CH$_2$**), 31.4 (**C**), 30.1 (d, $J_{C\text{-}F}$ = 23.3 Hz, HC=CF**CH$_2$**), 25.1 (**CH$_2$**), 25.1 (**CH$_3$**), 21.0 (**CH$_3$**), 17.3 (FC=CH**CH$_2$**).

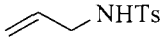
^{19}F NMR (282 MHz, $CDCl_3$, decoupled) δ 7.26 (1F, s).

IR ν_{max} neat (cm^{-1}): 2992 (w), 2922 (w), 2856 (w), 1371 (m), 1261 (m), 1202 (s), 1112 (s), 1069 (s), 828 (m), 732 (m).

LRMS (ES$^+$, MeOH) *m/z* (relative intensity %): 251 $[M\text{-}CH_3]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{10}H_{14}FO_2$: 185.09778, found 185.09710

***N*-Allyl-4-methyl-benzenesulfonamide (281)**



$C_{10}H_{13}NO_2S$

M.w. = 211.28 g/mol

white crystal solid

To a stirred solution of allylamine **280** (675 μl, 8.76 mmol) in CH_2Cl_2 (10 ml) was added Et_3N (1.46 ml, 10.51 mmol). After stirring for 30 minutes, *p*-toluenesulfonyl chloride (1.67 g, 8.76 mmol) was added. The reaction mixture was stirred for 15

hours before being quenched with water (10 ml) and sat'd NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 ml). The combined organic solutions were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the title compound **281** as a white crystal solid (1.58 g, 7.48 mmol, 86%).

Spectroscopic characteristics are consistent with those reported in the literature.[132]

Mpt. = 61-62 °C

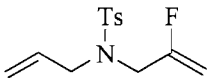
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.83-5.64 (1H, ddt, *J* = 16.9, 10.3, 5.9 Hz, H_2C=C**H**CH_2), 5.17 (1H, dq, J = 17.4, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.10 (1H, dq, J = 10.3, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.62 (1H, t(br), N**H**), 3.59 (2H, tt, *J* = 1.5, 5.9 Hz, $\mathbf{CH_2}NHTs$), 2.44 (3H, s, Ar$\mathbf{CH_3}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7 ($\mathbf{C}_{Ar}CH_3$), 137.0 ($\mathbf{C}_{Ar}SO_2$), 133.1 (H_2C=**C**HCH_2), 129.9 (2 x $\mathbf{CH}_{Ar}$), 127.3 (2 x $\mathbf{CH}_{Ar}$), 117.9 ($H_2\mathbf{C}$=$CHCH_2$), 45.9 (H_2C=CH**C**H_2), 21.7 (Ar**C**H_3).

IR ν_{max} neat (cm^{-1}): 3248 (m), 1320 (m), 1160 (s), 667 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 234 $[M+Na]^+$(100).

_N_-Allyl-_N_-(2-fluoro-allyl)-4-methyl-benzenesulfonamide (282)



$C_{13}H_{16}FNO_2S$

M.w. = 269.34 g/mol

colourless oil

To a stirred solution of **281** (600 mg, 2.84 mmol) in DMF (4 ml) was added NaH, 60% dispersion in mineral oil (74.98 mg, 3.12 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro-propene (307 mg, 3.27 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 ml) and sat'd NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 5% EtOAc/hexane to yield the title compound **282** as a colourless oil (388 mg, 1.44 mmol, 50%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, d, J = 6.6 Hz, Ar**H**), 7.31 (2H, d, J = 8.1 Hz, Ar**H**), 5.65 (1H, dd, J = 16.2, 10.3, 5.9 Hz, H_2C=C**H**CH_2), 5.26-5.14 (1H, m, **H**$_2$C=CHCH_2), 4.71 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, J = 3.7 Hz, **H**$_A$H$_B$C=CFCH_2), 4.48 (1H, dd, $J_{H\text{-}F}$ =47.8 Hz, J = 2.9 Hz, H$_A$**H**$_B$C=CFCH_2), 3.95 (2H, d, $J_{H\text{-}F}$ = 13.9 Hz, NC**H**$_2$), 3.85 (2H, d, J = 6.6 Hz, NC**H**$_2$), 2.44 (3H, s, ArC**H**$_3$);

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (d, $J_{C\text{-}F}$ = 261.1 Hz, H_2C=**C**FCH_2), 143.6 (**C**$_{Ar}$CH$_3$), 137.2 (**C**$_{Ar}$SO$_2$), 132.3 (H_2C=**C**HCH_2), 129.8 (2 x **C**H$_{Ar}$), 127.4 (2 x **C**H$_{Ar}$), 119.9 (H_2**C**=CHCH_2), 94.2 (d, $J_{C\text{-}F}$ = 18.1 Hz, H_2**C**=CFCH_2), 49.9 (H_2C=CH**C**H$_2$), 46.3 (d, $J_{C\text{-}F}$ = 31.7 Hz, H_2C=CF**C**H$_2$), 21.7 (Ar**C**H$_3$).

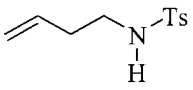
^{19}F NMR (282 MHz, $CDCl_3$) δ –5.00-(–5.40) (1F, m).

IR ν_{max} neat (cm^{-1}): 1677 (m), 1343 (s), 1158 (m), 1092 (s), 934 (m), 908, 769.

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 333 (100) $[M+Na+CH_3CN]^+$, 561 (30) $[2M+Na]^+$.

HRMS (ES^+): Calcd. for $[C_{13}H_{16}FNO_2S+ Na+CH_3CN]$: 333.1043, found 333.1044.

N-Allyl-*N*-(2-fluoro-allyl)-4-methyl-benzenesulfonamide (284)



$C_{11}H_{15}NO_2S$

M.w. = 225.31 g/mol

colourless viscous oil

To a stirred solution of *p*-toluenesulfonamide **283** (1 g, 5.84 mmol) in DMF (10 ml) was added NaH, 60% dispersion in mineral oil (1.54 g, 5.42 mmol). After stirring for 30 minutes, 4-bromo-1-butene (593 µl, 5.84 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 ml) and sat'd NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a colourless viscous oil. Purification was accomplished by flash chromatography on silica gel (25 g) eluting with 20% EtOAc/hexane to yield the title compound **284** as a colourless viscous oil (373 mg, 1.66 mmol, 50%).

Spectroscopic characteristics are consistent with those reported in the literature.[133]

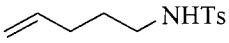
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 5.15 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.63 (1H, ddt, *J* = 16.9, 10.3, 6.6, Hz, H_2C=C**H**CH_2), 5.13-5.04 (1H, m, **H**$_2$C=CHCH_2), 4.69 (1H, s(br), N**H**), 3.01 (2H, q, *J* = 6.6 Hz, C**H**$_2$N), 2.39 (3H, s, ArC**H**$_3$), 3.01 (2H, q, *J* = 6.6 Hz, H_2C=CHC**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7 (**C**$_{Ar}$CH$_3$), 137.0 (H_2C=**C**HCH_2), 134.0 (**C**$_{Ar}$SO$_2$), 129.9 (2 x CH$_{Ar}$), 127.3 (2 x CH$_{Ar}$), 118.3 (H_2**C**=CHCH_2), 42.2 (N**C**H$_2$), 33.7 (H_2C=CH**C**H$_2$), 21.70 (Ar**C**H$_3$).

IR ν_{max} neat (cm^{-1}): 3290 (m), 2982 (m), 1372 (s), 1237 (m), 1158 (s), 1044 (m), 916 (s), 732 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 473 (65) $[2M+Na]^+$, 698 (100) $[3M+Na]^+$, 699 (45) $[3M+Na]^+$, 923 (75) $[4M+Na]^+$.

4-Methyl-*N*-pent-4-enyl-benzenesulfonamide (285)



$C_{12}H_{17}N_2O_2S$
M.w. = 239.33 g/mol
pale yellow oil

Following the procedure of Hubert *et al.*, to a stirred solution of $TsNH_2$ **283** (1 g, 5.84 mmol) in DMF (5 mL) was added NaH, 60% dispersion in mineral oil (154 mg, 6.42 mmol). After stirring for 30 minutes, 5-bromo-1-pentene (692 μL, 5.84 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with and water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield a crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (15 g) eluting with 5% EtOAc/hexane to yield **285** as a pale yellow oil (759 mg, 3.17 mmol, 55%).

Spectroscopic characteristics are consistent with those reported in the literature.[133]

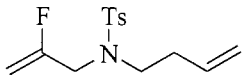
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.33 (2H, d, *J* = 8.6 Hz, Ar**H**), 5.73 (1H, ddt, *J* = 16.9, 10.3, 5.9 Hz, H_2C=C**H**CH_2), 5.02 (1H, q, *J* = 1.5 Hz, **H**$_2$C=CHCH_2), 5.22 (1H, m, **H**$_2$C=CHCH_2), 4.43 (1H, s (br), *J* = 5.3 Hz, N**H**), 2.97 (2H, q, *J* = 6.7 Hz, NC**H**$_2$), 2.45 (3H, s, C**H**$_3$), 2.07 (2H, qt, *J* = 1.0, 7.2 Hz, H_2C=CHC**H**$_2$), 1.58 (2H, quintet, *J* = 7.2, H_2C=CHCH$_2$C**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0 ($\mathbf{C}_{Ar}CH_3$), 137.2 (H_2C=$\mathbf{C}HCH_2$), 136.9 ($\mathbf{C}_{Ar}$), 129.7 (2 x $\mathbf{C}H_{Ar}$), 127.1 (2 x $\mathbf{C}H_{Ar}$), 115.6 ($H_2\mathbf{C}$=$CHCH_2$), 42.6 ($N\mathbf{C}H_2$), 30.7 (H_2C=$CH\mathbf{C}H_2$), 28.7 (H_2C=$CHCH_2\mathbf{C}H_2$), 21.5 ($\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 3280 (w), 1322 (m), 1156 (m), 1092 (m), 813 (w).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 262 $[M+Na]^+$ (100).

_N_-But-3-enyl-_N_-(2-fluoro-allyl)-4-methyl-benzenesulfonamide (286)



$C_{14}H_{18}FNO_2S$
M.w. = 283.36 g/mol
colourless oil

To a stirred solution of *N*-Allyl-4-methyl-benzenesulfonamide **284** (306 mg, 1.36 mmol) in DMF (5 ml) was added NaH, 60% dispersion in mineral oil (35.85 mg, 1.49 mmol). After stirring for 30 minutes, 3-chlro-2-fluoro-propene (307 mg, 3.27 mmol) was added. The reaction mixture was stirred for 3 hours before being quenched with water (10 ml) and sat'd NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 2% EtOAc/hexane to yield the title compound **286** as a colourless oil (280 mg, 0.99 mmol, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, d, J = 8.1 Hz, Ar**H**), 7.31 (2H, d, J = 8.1 Hz, Ar**H**), 5.72 (1H, ddt, J = 16.7, 10.0, 6.7 Hz, H_2C=$\mathbf{C}HCH_2$), 5.12-5.02 (1H, m, $\mathbf{H}_2C$=$CHCH_2$), 4.76 (1H, dd, $J_{H\text{-}F}$ =16.2 Hz, J = 3.8 Hz, $\mathbf{H}_A\mathbf{H}_BC$=$CFCH_2$), 4.48 (1H, dd, $J_{H\text{-}F}$ = 44.6 Hz, J = 2.4 Hz, $H_A\mathbf{H}_BC$=$CFCH_2$), 3.95 (2H, d, J = 13.8 Hz, H_2C=$CFC\mathbf{H}_2$), 3.26 (2H, t, J = 7.6 Hz, $N\mathbf{C}H_2$), 2.44 (3H, s, Ar$\mathbf{C}H_3$) 2.33 (2H, q, J = 7.2 Hz, H_2C=$CHC\mathbf{H}_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (d, $J_{C\text{-}F}$ = 267.2 Hz, H_2C=$\mathbf{C}FCH_2$), 143.6 ($\mathbf{C}_{Ar}CH_3$), 137.0 ($\mathbf{C}_{Ar}SO_2$), 134.6 (H_2C=$\mathbf{C}HCH_2$), 129.9 (2 x $\mathbf{C}H_{Ar}$), 127.5 (2 x $\mathbf{C}H_{Ar}$), 117.5 ($H_2\mathbf{C}$=$CHCH_2$), 94.3 (d, $J_{C\text{-}F}$ = 18.1 Hz, $H_2\mathbf{C}$=$CFCH_2$), 47.9 (d, $J_{C\text{-}F}$ = 31.7 Hz, H_2C=$CF\mathbf{C}H_2$), 47.3 ($N\mathbf{C}H_2$), 32.9 (H_2C=$CH\mathbf{C}H_2$), 21.8 (Ar$\mathbf{C}H_3$).

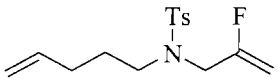
^{19}F NMR (282 MHz, $CDCl_3$) δ –4.75 (1F, dq, *J* = 47.9, 13.1 Hz).

IR ν_{max} neat (cm^{-1}): 1340 (m), 1156(s), 1090 (m), 919 (w), 814 (w).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 589 (100) $[2M+Na]^+$

HRMS (ES^+): Calcd. for $C_{28}H_{36}F_2N_2O_4S_2Na$: 589.1976, found 589.1976.

_N_-(2-Fluoro-allyl)-4-methyl-_N_-pent-4-enyl-benzenesulfonamide (287)



$C_{15}H_{20}FNO_2S$

M.w. = 297.39 g/mol

colourless oil

To a stirred solution of sulfonamide **285** (250 mg, 1.04 mmol) in DMF (3 mL) was added NaI (80 mg, 0.52 mmol) and NaH, 60% dispersion in mineral oil (27.6 mg, 1.14 mmol). After stirring for 30 minutes, 3-chloro-2-fluoro-propene (950 μL, 1.14 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as yellow oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 7% EtOAc/hexane to yield **287** as colourless oil (220 mg, 0.74 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.30 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.76 (1H, ddt, *J* = 16.9, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.04 (1H, q, *J* = 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.97 (1H, m, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.71 (1H, dd, $J_{H\text{-}F}$ = 16.2 Hz, *J* = 3.7 Hz, $\mathbf{H_A}H_BC$=$CFCH_2$), 4.51 (1H, dd, $J_{H\text{-}F}$ = 47.8 Hz, *J* = 2.9 Hz, $H_A\mathbf{H_B}C$=$CFCH_2$), 3.93 (2H, d, *J* = 14.0 Hz, H_2C=CFC**H**$_2$), 3.18 (2H, t, *J* = 8.1 Hz, NC**H**$_2$), 2.45 (3H, s, C**H**$_3$), 2.04 (2H, q, *J* = 7.4 Hz, H_2C=CHC**H**$_2$), 1.66 (2H, quintet, *J* = 7.4 Hz, H_2C=$CHCH_2$C**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (d, $J_{C\text{-}F}$ = 261.1 Hz, H_2C=**C**FCH_2), 143.4(**C**$_{Ar}CH_3$), 137.3 (H_2C=**C**HCH_2), 136.7 (**C**$_{Ar}SO_2$), 129.6 (2 x **C**H_{Ar}), 127.3 (2 x **C**H_{Ar}), 115.3 (H_2**C**=$CHCH_2$), 94.0 (d, $J_{C\text{-}F}$ = 16.9 Hz, H_2**C**=$CFCH_2$), 47.6 (d, $J_{C\text{-}F}$ = 36.2 Hz, H_2C=CF**C**H_2), 47.4 (N**C**H_2), 30.6 (H_2C=CH**C**H_2), 27.2 (H_2C=$CHCH_2$**C**H_2), 21.5 (**C**H_3).

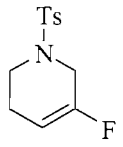
^{19}F NMR (282 MHz, $CDCl_3$) δ –4.70 (1F, dq, J = 48.0, 15.3 Hz).

IR ν_{max} neat (cm^{-1}): 1339 (m), 1157 (m), 1091 (m), 913 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 298 $[M+H]^+$ (100).

HRMS (ES^+): Calcd. for $C_{15}H_{21}FNO_2SNa$: 298.1272, found 298.1270.

5-Fluoro-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine (289)



$C_{12}H_{14}FNO_2S$

M.w. = 255.31 g/mol

white solid

To a stirring solution of **286** (50 mg, 0.18 mmol) in CH_2Cl_2 (1.6 mL) was added the second generation Grubbs catalyst **4** (19 mg, 22.5 μmol). The reaction mixture was heated in a sealed vial for 5 h at 60°C and concentrated under reduced pressure to give the crude product as a black oil. Purification was accomplished by flash column chromatography on silica gel (5g), eluting with 2% EtOAc/hexane to furnish compound **289** as a white solid (43 mg, 0.17 mmol, 94 %).

Mpt. = 86-87 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (2H, d, J = 8.1 Hz, Ar**H**), 7.35 (2H, d, J = 8.1 Hz, Ar**H**), 5.34-5.24 (1H, m, FC=C**H**), 3.65 (2H, q, J = 2.2 Hz, NC**H**$_2$), 3.14 (2H, d, $J_{H\text{-}F}$ = 5.2 Hz, HC=CFC**H**$_2$), 2.45 (3H, s, ArC**H**$_3$), 2.27-2.17 (2H, m, FC=CHC**H**$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3 (d, $J_{C\text{-}F}$ = 253.2 Hz, H_2C=**C**FCH_2), 144.2 (**C**$_{Ar}$CH$_3$), 133.2 (**C**$_{Ar}$SO$_2$), 129.9 (2 x **C**H$_{Ar}$), 127.8 (2 x **C**H$_{Ar}$), 100.8 (d, $J_{C\text{-}F}$ = 13.6 Hz, HC=CF**C**H$_2$), 43.9 (d, $J_{C\text{-}F}$ = 40.7 Hz, FC=**C**H), 42.7 (N**C**H$_2$), 22.6 (FC=CH**C**H$_2$), 21.7 (Ar**C**H$_3$).

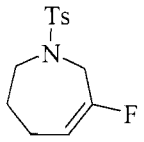
^{19}F NMR (282 MHz, $CDCl_3$) δ –15.30-(–15.43) (1F, m).

IR ν_{max} neat (cm^{-1}): 1714 (m), 1341 (m), 1160 (s), 1094 (s), 817 (m), 747 (w).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 297 $[M+CH_3CN+H]^+$ (100).

HRMS (ES^+): Calcd. for $C_{24}H_{28}F_2N_2O_4S_2Na$: 533.1350, found 533.1363.

6-Fluoro-1-(toluene-4-sulfonyl)-2,3,4,7-tetrahydro-1*H*-azepine (290)



$C_{13}H_{16}FNO_2S$

M.w. = 269.34 g/mol

white powder

To a stirred solution of sulfonamide **287** (100 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) was added a solution of the second generation Grubbs catalyst **4** (34.26 mg, 40 μmol) in CH_2Cl_2 (3.8 mL). The mixture was stirred and degassed for 10 minutes, before being heated at reflux for 9 hours. Another portion of a solution of the second generation Grubbs catalyst **4** (5.6 mg, 6.8 μmol) in CH_2Cl_2 (1 mL) was added. The mixture was heated at reflux at 60 °C for 2 hours then concentrated under reduced pressure to give the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to afford the cyclised product **290** as a white powder (77 mg, 0.29 mmol, 84%).

Mpt. = 62 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, d *J* = 8.1 Hz, Ar**H**), 7.30 (2H, d *J* = 8.1 Hz, Ar**H**), 5.31 (1H, dt, $J_{H\text{-}F}$ = 19.9 Hz, *J* = 5.9 Hz, FC=C**H**CH_2), 4.02 (2H, d, *J* = 6.6 Hz, HC=CFC**H**$_2$), 3.40 (2H, t, *J* = 5.9 Hz, NC**H**$_2$), 2.43 (3H, s, ArC**H**$_3$), 2.07-1.97 (2H, m, FC=CHC**H**$_2$), 1.38 (2H, quint, *J* = 5.9 Hz, $NCH_2C\mathbf{H}_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8 (d, $J_{C\text{-}F}$ = 153.7 Hz, HC=**C**FCH_2), 143.7 (**C**$_{Ar}CH_3$), 136.5 (**C**$_{Ar}SO_2$), 130.1 (2 x **C**H$_{Ar}$), 127.6 (2 x **C**H$_{Ar}$), 107.4 (d, $J_{C\text{-}F}$ = 19.4 Hz, FC=**C**H), 49.2 (N**C**H_2), 47.4 (d, $J_{C\text{-}F}$ = 43.7 Hz, HC=CF**C**H_2), 27.4 ($NCH_2\mathbf{C}H_2$), 21.9 (FC=CH**C**H_2), 21.4 (Ar**C**H_3).

^{19}F NMR (282 MHz, $CDCl_3$) δ –6.05 (1F, dq, *J* = 4.4, 26.2 Hz).

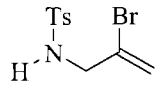
IR ν_{max} neat (cm^{-1}): 1337 (m), 1156 (m), 1093 (m), 910 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 292 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{26}H_{32}F_2N_2O_4S_2Na$: 561.1841, found 561.1827.

4.3 Procedures relating to research described in Chapter 2, section 2.3 Ring-closing metathesis of vinyl bromo dienes

N-(2-Bromo-allyl)-4-methyl-benzenesulfonamide (295)



$C_{10}H_{12}BrNO_2S$

M.w. = 290.18 g/mol

brown oil

To a stirred solution of *p*-toluenesulfonamide **283** (3.43 g, 20 mmol) in THF (80 mL) was added *t*-BuOK (561 mg, 5 mmol) and 18-crown-6 (1.32 g, 5 mmol). After stirring for 10 minutes, 2,3-dibromo propene (517 μL, 5 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 10% EtOAc/hexane to afford **295** as a brown oil (725 mg, 2.5 mmol, 50%).

Spectroscopic characteristics are consistent with those reported in the literature.[134]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.28 (2H, d, *J* = 7.9 Hz, Ar**H**), 5.80 (1H, dt, *J* = 2.3, 1.5 Hz, $\mathbf{H_A}H_BC{=}CBrCH_2$), 5.65 (1H, t, *J* = 6.4 Hz, N**H**), 5.44 (1H, dt, *J* = 2.3, 1.1 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 3.80 (2H, d, *J* = 6.4 Hz, $H_2C{=}CBrC\mathbf{H_2}$), 2.40 (3H, s, $ArC\mathbf{H_3}$).

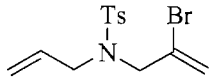
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 ($\mathbf{C}_{Ar}CH_3$), 137.0 ($\mathbf{C}_{Ar}SO_2$), 129.6 (2 x $\mathbf{C}H_{Ar}$), 127.5 (2 x $\mathbf{C}H_{Ar}$), 127.0 ($H_2C{=}\mathbf{C}BrCH_2$), 120.2 ($H_2\mathbf{C}{=}CBrCH_2$), 54.6 ($H_2C{=}CBr\mathbf{C}H_2$), 21.6 ($C_{Ar}\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 3278 (w, br), 1427 (w), 1325 (m), 1156 (s), 1091 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 312, 314 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{10}H_{12}{}^{79}BrNO_2SNa$: 311.9664, found 311.9664.

N-Allyl-N-(2-bromo-allyl)-4-methyl-benzenesulfonamide (296)



$C_{13}H_{16}BrNO_2S$
M.w. = 330.24 g/mol
pale brown oil

To a stirred solution of sulfonamide **295** (191 mg, 0.90 mmol) in THF (5 mL) was added *t*-BuOK (101 mg, 0.90 mmol) and 18-crown-6 (238 mg, 0.90 mmol). After stirring for 10 minutes, 2,3-dibromo propene (139.5 μL, 1.35 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 10% Et_2O/hexane to afford **296** as a pale brown oil (278 mg, 0.84 mmol, 94%).

Spectroscopic characteristics are consistent with those reported in the literature.[135]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.86 (1H, q, *J* = 1.5 Hz, H_2C=C**H**CH_2), 5.68-5.52 (2H, m, **H**$_2$C=CHCH_2), 5.21-5.11 (2H, m, **H**$_2$C=CBrCH_2), 4.04 (2H, s, H_2C=CH**C**H_2), 5.86 (2H, d, *J* = 6.6 Hz, H_2C=CBr**C**H_2), 2.45 (3H, s, Ar**C**H_3).

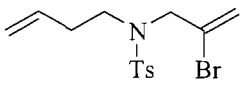
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6 (**C**$_{Ar}$$CH_3$), 137.2 (**C**$_{Ar}$$SO_2$), 132.4 ($H_2C$=**C**$HCH_2$), 129.8 (2 x **C**$H_{Ar}$), 127.3 (2 x **C**$H_{Ar}$), 127.9 ($H_2C$=**C**Br$CH_2$), 119.9 ($H_2$**C**=$CHCH_2$), 119.3 ($H_2$**C**=$CBrCH_2$), 53.8 ($H_2C$=CH**C**$H_2$), 50.0 ($H_2C$=CBr**C**$H_2$), 21.5 ($C_{Ar}$**C**$H_3$).

IR ν_{max} neat (cm^{-1}): 1341 (m), 1156 (s), 1090 (m), 900 (m), 814 (w), 764 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 353, 354 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{13}H_{16}{}^{79}BrNO_2SNa$: 351.9977, found 351.9975.

_N_-(2-bromo-allyl)-_N_-but-3-enyl-4-methyl-benzenesulfonamide (297)



$C_{14}H_{18}BrNO_2S$
M.w. = 344.27 g/mol
colourless oil

To a stirred solution of sulfonamide **295** (150 mg, 0.52 mmol) in THF (8 mL) was added *t*-BuOK (58 mg, 0.52 mmol) and 18-crown-6 (137 mg, 0.52 mmol). After stirring for 10 minutes, 4-bromo-1-butene (79 μL, 0.78 mmol) was added. The reaction mixture was stirred for 4 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 5% Et_2O/hexane to afford **297** as a colourless oil (152 mg, 0.44 mmol, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, d, J = 8.3 Hz, Ar**H**), 7.22 (2H, d, J = 7.9 Hz, Ar**H**), 5.80 (1H, dt, J = 2.3, 1.5 Hz, $\mathbf{H_A}H_BC{=}CBrCH_2$), 5.59 (1H, ddt, J = 17.0, 10.2, 6.8 Hz, $H_2C{=}C\mathbf{H}CH_2$), 5.53 (1H, dt, J = 2.3, 1.1 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 5.00-4.90 (2H, m, $\mathbf{H}_2C{=}CHCH_2$), 3.97 (2H, s(br), $H_2C{=}CBrC\mathbf{H}_2$), 3.20-3.13 (2H, m, $NC\mathbf{H}_2CH_2$), 2.35 (3H, s, $ArC\mathbf{H}_3$), 2.25-2.15 (2H, m, $H_2C{=}CHC\mathbf{H}_2$).

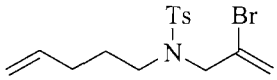
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5 ($\mathbf{C}_{Ar}CH_3$), 136.9 ($H_2C{=}\mathbf{C}HCH_2$), 134.4 ($\mathbf{C}_{Ar}SO_2$), 129.7 (2 x $\mathbf{C}H_{Ar}$), 128.2 ($H_2C{=}\mathbf{C}BrCH_2$), 127.3 (2 x $\mathbf{C}H_{Ar}$), 119.3 ($H_2\mathbf{C}{=}CHCH_2$), 117.3 ($H_2\mathbf{C}{=}CBrCH_2$), 55.5 ($H_2C{=}CBr\mathbf{C}H_2$), 47.6 ($N\mathbf{C}H_2CH_2$), 32.7 ($H_2C{=}CH\mathbf{C}H_2$), 21.5 ($C_{Ar}\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 3069 (w), 2923 (w), 1341 (m), 1157 (s), 1090 (m), 912 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 366, 368 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{14}H_{18}{}^{79}BrNO_2SNa$: 366.0134 found 366.0135.

_N_-(2-bromo-allyl)- 4-methyl-_N_-pent-4-enyl-benzenesulfonamide (298)



$C_{15}H_{20}BrNO_2S$
M.w. = 358.29 g/mol
colourless oil

To a stirred solution of sulfonamide **295** (99 mg, 0.34 mmol) in THF (5 mL) was added *t*-BuOK (38 mg, 0.34 mmol) and 18-crown-6 (90 mg, 0.34 mmol). After stirring for 10 minutes, 5-bromo-1-pentene (61 μL, 0.51 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 4% Et_2O/hexane to afford **298** as a colourless oil (68 mg, 0.19 mmol, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 6.6 Hz, Ar**H**), 7.23 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.80 (1H, dt, *J* = 2.2, 1.5 Hz, $\mathbf{H_A}H_BC{=}CBrCH_2$), 5.65 (1H, ddt, *J* = 17.2, 10.6, 6.6 Hz, $H_2C{=}C\mathbf{H}CH_2$), 5.53 (1H, dt, *J* = 2.2, 1.1 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 4.49-4.85 (2H, m, $\mathbf{H}_2C{=}CHCH_2$), 3.94 (2H, s(br), $H_2C{=}CBrC\mathbf{H}_2$), 3.12-3.05 (2H, m, $NC\mathbf{H}_2CH_2$), 2.35 (3H, s, $ArC\mathbf{H}_3$), 1.94 (2H, q, *J* = 7.3 Hz, $H_2C{=}CHC\mathbf{H}_2CH_2$), 1.64-1.49 (2H, m, $H_2C{=}CHCH_2C\mathbf{H}_2$).

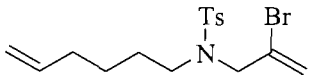
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5 ($\mathbf{C}_{Ar}CH_3$), 134.4 ($\mathbf{C}_{Ar}SO_2$), 136.8 ($H_2C{=}\mathbf{C}HCH_2$), 129.7 (2 x $\mathbf{C}H_{Ar}$), 128.4 ($H_2C{=}\mathbf{C}BrCH_2$), 127.3 (2 x $\mathbf{C}H_{Ar}$), 119.2 ($H_2\mathbf{C}{=}CHCH_2$), 115.4 ($H_2\mathbf{C}{=}CBrCH_2$), 55.6 ($H_2C{=}CBr\mathbf{C}H_2$), 48.0 ($N\mathbf{C}H_2CH_2CH_2$), 30.8 ($H_2C{=}CH\mathbf{C}H_2$), 27.3 ($H_2C{=}CHCH_2\mathbf{C}H_2$), 21.5 ($C_{Ar}\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 3069 (w), 2977 (w), 1340 (m), 1156 (s), 1090 (m), 907 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 381, 382 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{15}H_{21}{}^{79}BrNO_2S$: 358.0471 found 358.0473.

_N_-(2-bromo-allyl)- _N_-hex-5-enyl 4-methyl-benzenesulfonamide (299)



$C_{16}H_{22}BrNO_2S$
M.w. = 371.32 g/mol
colourless oil

To a stirred solution of sulfonamide **295** (256 mg, 0.54 mmol) in THF (10 mL) was added *t*-BuOK (61 mg, 0.54 mmol) and 18-crown-6 (143 mg, 0.54 mmol). After stirring for 10 minutes, 6-bromo-1-pentene (79 μL, 0.59 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to afford **299** as colourless oil (160 mg, 0.43 mmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.23 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.80 (1H, dt, *J* = 2.2, 1.5 Hz, $\mathbf{H_A}H_BC{=}CBrCH_2$), 5.66 (1H, ddt, *J* = 17.2, 10.3, 6.9 Hz, $H_2C{=}C\mathbf{H}CH_2$), 5.53 (1H, dt, *J* = 2.2, 1.1 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 4.94-4.83 (2H, m, $\mathbf{H_2}C{=}CHCH_2$), 3.94 (2H, s(br), $H_2C{=}CBrC\mathbf{H_2}$), 3.13-3.05 (2H, m, $NC\mathbf{H_2}CH_2$), 2.35 (3H, s, $ArC\mathbf{H_3}$), 1.99 (2H, q, *J* = 7.3 Hz, $H_2C{=}CHC\mathbf{H_2}CH_2$), 1.50-1.39 (2H, m, $NCH_2C\mathbf{H_2}CH_2$), 1.31-1.20 (2H, m, $H_2C{=}CHCH_2C\mathbf{H_2}$).

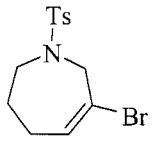
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4 ($\mathbf{C}_{Ar}CH_3$), 138.1 ($H_2C{=}\mathbf{C}HCH_2$), 136.9 ($\mathbf{C}_{Ar}SO_2$), 129.7 (2 x $\mathbf{C}H_{Ar}$), 128.4 ($H_2C{=}\mathbf{C}BrCH_2$), 127.3 (2 x $\mathbf{C}H_{Ar}$), 119.1 ($H_2\mathbf{C}{=}CHCH_2$), 114.9 ($H_2\mathbf{C}{=}CBrCH_2$), 55.4 ($H_2C{=}CBr\mathbf{C}H_2$), 48.2 ($N\mathbf{C}H_2CH_2$), 33.2 ($H_2C{=}CH\mathbf{C}H_2CH_2$), 27.4 ($NCH_2\mathbf{C}H_2$), 25.9 ($H_2C{=}CHCH_2\mathbf{C}H_2$), 21.5 ($C_{Ar}\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2930 (w), 1339 (m), 1156 (s), 1091 (m), 905 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %) 395, 396 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{23}{}^{79}BrNSO_2$: 372.0628, found 372.0631.

6-Bromo-1-(toluene-4-sulfonyl)-2,3,4,7-tetrahydro-*H*-azepine (302)



$C_{13}H_{16}BrNO_2S$
M.w. = 330.24 g/mol
colourless oil

To a stirred solution of sulfonamide **298** (20 mg, 56 μmol) in CH_2Cl_2 (3 mL) was added a solution of the second generation Grubbs catalyst **4** (4.7 mg, 5.6 μmol) in CH_2Cl_2 (3 mL). The mixture was stirred and degassed for 2 minutes. The reaction mixture was heated at reflux for 10 hours then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 4% Et_2O/hexane to afford the cyclised product **302** as a colourless oil (8 mg, 0.024 mmol, 44%).

Mpt. =103-104 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.23 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.01 (1H, tt, *J* = 5.9, 1.1 Hz, H_2C**H**C=CBrCH_2), 4.11 (2H, s(br), H_2C=CBrCH_2), 3.44 (2H, m, NCH_2CH_2), 2.38 (3H, s, ArCH_3), 2.06-1.96 (2H, m, H_2C=CHCH_2CH_2), 1.82-1.72 (2H, m, H_2C=$CHCH_2CH_2$).

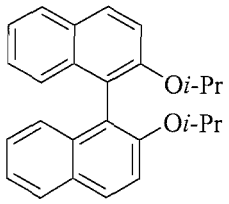
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1 ($C_{Ar}CH_3$), 136.2 ($C_{Ar}SO_2$), 133.1 (H_2CHC=CBrCH_2), 129.3 (2 x CH_{Ar}), 126.8 (2 x CH_{Ar}), 119.0 (H_2CHC=CBrCH_2), 53.9 (H_2CHC=CBrCH_2), 48.1 (NCH_2CH_2), 26.5 (NCH_2CH_2), 26.2 (H_2CHC=CBrCH_2), 21.2 ($C_{Ar}CH_3$).

IR ν_{max} neat (cm^{-1}): 2935 (w), 2879 (w), 1334 (m), 1155 (s), 1101 (m), 814 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 353, 354 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{13}H_{16}{}^{79}BrNO_2SNa$: 351.9977 found 351.9977.

2,2'-Diisopropoxy-1[1,1']binaphthalenyl (305)



$C_{26}H_{26}O_2$
M.w. = 370.48 g/mol
pale yellow oil

To a stirred solution of binaphthol **304** (1 g, 3.49 mmol) in DMF (10mL) was added NaH, 60% dispersion in mineral oil (209 mg, 8.73 mmol) and isopropyl bromide (721 μL, 7.68 mmol). The reaction mixture was stirred for 15 hours before being quenched with water (20 mL). The organic phase was separated and the organic phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil (1.2 g). Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 5% Et_2O/hexane to afford **305** as a pale yellow oil (1.11 g, 3.0 mmol, 87%).

Spectroscopic characteristics are consistent with those reported in the literature.[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 9.2 Hz, Ar**H**), 7.86 (2H, d, J = 8.4 Hz, Ar**H**), 7.41 (2H, d, J = 9.1 Hz, Ar**H**), 7.32 (2H, ddt, J = 8.1, 6.6, 1.5 Hz, Ar**H**), 7.20 (2H, m, Ar**H**), 7.15 (2H, m, Ar**H**), 4.41 (2H, septet, J = 6.2 Hz, C**H**$(CH_3)_2$), 1.05 (6H, d, J = 6.2 Hz, CH(C**H**$_3)_2$), 0.98 (6H, d, J = 6.2 Hz, CH(C**H**$_3)_2$).

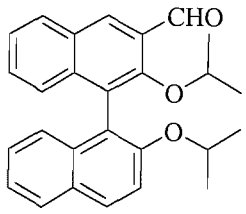
^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7 (2 x **C**H_{Ar}), 134.3 (2 x **C**$_{Ar}$), 129.3 (2 x **C**$_{Ar}$), 128.8 (2 x **C**H_{Ar}), 127.6 (2 x **C**H_{Ar}), 125.8 (2 x **C**H_{Ar}), 125.7 (2 x **C**H_{Ar}), 123.4 (2 x **C**H_{Ar}), 122.2 (2 x **C**H_{Ar}), 117.8 (2 x **C**$_{Ar}$), 71.9 (2 x **C**H$(CH_3)_2$), 22.4 (4 x CH(**C**$H_3)_2$).

IR ν_{max} neat (cm^{-1}): 3057 (w), 2974 (m), 1591 (m), 1505 (m), 1238 (s), 1109 (s), 1002 (s), 805 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 393 $[M+Na]^+$(100).

HRMS (ES^+): Calcd. for $C_{26}H_{26}O_2Na$: 393.1825, found 393.1832.

2,2'-Diisopropox-[1,1']binaphthalenyl-3-carbaldehyde (306)



$C_{27}H_{26}O_3$

M.w. = 398.49 g/mol

pale yellow oil

To a stirred solution of **305** (5 g, 13.8 mmol) in THF (40 mL) was added *n*-BuLi (5.96 mL, 13.8 mmol) dropwise at 0°C. The reaction mixture was stirred for 2 hours before being added DMF (1 mL, 13.8 mmol) and left it stirring for 15 hours. The reaction mixture was quenched with sat'd NH_4Cl (10 mL) and water (10 mL). The organic phase was separated and the organic phase was extracted with Et_2O (3 x 35 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (40 g) eluting with 5% Et_2O/hexane to afford **306** as a pale yellow oil (1.37 g, 3.4 mmol, 25%).

Spectroscopic characteristics are consistent with those reported in the literature.[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.6 (1H, s, CHO), 8.46 (1H, s, Ar**H**), 7.95-7.88 (2H, m, Ar**H**), 7.81-7.76 (1H, m, Ar**H**), 7.36-7.05 (7H, m, Ar**H**), 4.51 (1H, septet, J = 6.2 Hz, C**H**$(CH_3)_2$), 3.80 (1H, septet, J = 6.2 Hz, C**H**$(CH_3)_2$), 1.06 (3H, d, J = 5.9 Hz, C**H**$_3$), 0.93 (3H, d, J = 6.2 Hz, C**H**$_3$), 0.85 (3H, d, J = 6.2 Hz, C**H**$_3$), 0.66 (3H, d, J = 6.2 Hz, C**H**$_3$).

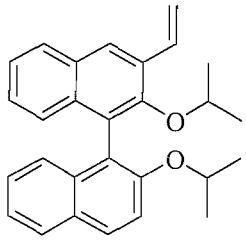
^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0 (**C**HO), 155.1 (**C**$_{Ar}$), 153.5 (**C**$_{Ar}$), 137.4 (**C**$_{Ar}$), 133.9 (**C**$_{Ar}$), 130.1 (**C**$_{Ar}$), 129.9 (**C**$_{Ar}$), 129.6 (**CH**$_{Ar}$), 128.8 (**CH**$_{Ar}$), 128.5 (**CH**$_{Ar}$), 127.9 (**CH**$_{Ar}$), 126.9 (**CH**$_{Ar}$), 126.8 (**CH**$_{Ar}$), 126.0 (**CH**$_{Ar}$), 125.3 (**CH**$_{Ar}$), 125.0 (**CH**$_{Ar}$), 123.6 (**CH**$_{Ar}$), 119.3 (**CH**$_{Ar}$), 115.2 (2 x **C**$_{Ar}$), 76.0 (2 x **C**H$(CH_3)_2$), 22.1 (4 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 3061 (w), 2975 (m), 1686 (s), 1585 (s), 1262 (s), 1099 (s), 905 (s), 728 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 421 $[M+Na]^+$(100).

HRMS (ES^+): Calcd. for $C_{27}H_{27}O_3$: 399.1955, found 399.1952.

2,2'-Diisopropoxy-3-vinyl-[1,1']binaphthalenyl (307)



$C_{28}H_{28}O_2$
M.w. = 396.52 g/mol
pale yellow oil

Following the procedure of Blechert *et al*,[7] to a stirred solution of H_3PPCH_3Br **306** (1 g, 3 mmol) in Et_2O (15 mL) was added *t*-BuOK (281 mg, 2.5 mmol). The reaction mixture was stirred and cooled to 0 °C. A solution of **25** (995 mg, 2.5 mmol) in Et_2O (10 mL) was added. The reaction mixture was stirred for 15 hours and diluted with Et_2O (5 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 5% Et_2O/hexane to afford **307** as a pale yellow oil (941 mg, 2.4 mmol, 95%).

Spectroscopic characteristics are consistent with those reported in the literature.[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (1H, s, Ar**H**), 7.86 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.76 (2H, t, *J* = 8.1 Hz, Ar**H**), 7.34-7.06 (8H, m, Ar**H**, H_2C=C**H**Ar), 5.87 (1H, dd, *J* = 17.6, 1.5 Hz, $\mathbf{H_A}H_BC$=CHAr), 5.29 (1H, dd, *J* = 11.0, 1.5 Hz, $H_A\mathbf{H_B}C$=CHAr), 4.45 (1H, septet, *J* = 5.9 Hz, C**H**$(CH_3)_2$), 3.76 (1H, septet, *J* = 6.2 Hz, C**H**$(CH_3)_2$), 1.06 (3H, d, *J* = 5.9 Hz, C**H**$_3$), 0.92 (3H, d, *J* = 5.9 Hz, C**H**$_3$), 0.80 (3H, d, *J* = 6.2 Hz, C**H**$_3$), 0.63 (3H, d, *J* = 6.2 Hz, C**H**$_3$).

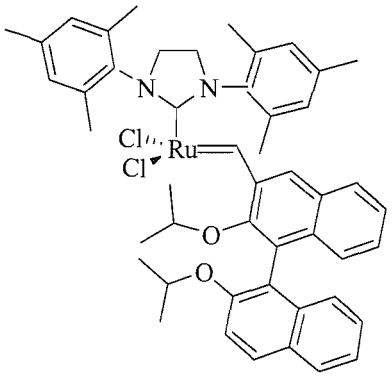
^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6 (**C**$_{Ar}$), 152.7 (**C**$_{Ar}$), 134.1 (H_2C=**C**H), 133.7 (**C**H$_{Ar}$), 132.5 (**C**H$_{Ar}$), 130.4 (**C**H$_{Ar}$), 129.3 (**C**H$_{Ar}$), 128.9 (**C**H$_{Ar}$), 127.9 (**C**H$_{Ar}$), 127.7 (2 x **C**H$_{Ar}$), 126.4 (2 x **C**H$_{Ar}$), 125.8 (**C**H$_{Ar}$), 125.5 (**C**H$_{Ar}$), 124.8 (**C**H$_{Ar}$), 124.5 (**C**H$_{Ar}$), 115.6 (2 x **C**H$_{Ar}$), 114.5 (H_2**C**=CHAr), 76.0 (**C**H$(CH_3)_2$), 70.7 (**C**H$(CH_3)_2$), 22.4 (4 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 3061 (w), 2974 (m), 1262 (s), 1235 (s), 1108 (s), 999 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 419 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{28}H_{29}O_2$: 397.2162, found 397.2162.

Ruthenium complex (7)



$C_{48}H_{52}O_2N_2Cl_2Ru$

M.w. = 860.24 g/mol

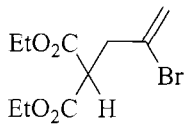
light green solid

Following the procedure of Blechert *et al*,[7] CuCl (25 mg, 0.25 mmol) was added to a solution ligand **307** (200 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) then under argon, a solution of Grubbs second generation catalyst (212 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred at 40 °C for an hour and then concentrated under reduce pressure. The residue was dissolved in a minimal volume of CH_2Cl_2 and passed through a Pasteur pipette containing a plug of cotton wool. After concentration *in vacuo*, the residue was purified by flash chromatography on SiO_2 (15 g) eluting with hexane/ MTBE (4.5:0.5) to get a green solid catalyst **7** (150 mg, 0.17 mmol, 70%).

Spectroscopic characteristics are consistent with those reported in the literature.[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 16.67 (1H, s, C**H**=Ru), 7.90 (1H, d, *J* = 8.8 Hz, C**H**), 7.85 (1H, d, *J* = 8.8 Hz, C**H**), 7.71 (1H, d, *J* = 7.7 Hz, C**H**), 7.46 (1H, s, ArH), 7.37 (1H, d, *J* = 8.8 Hz C**H**), 7.30-7.08 (9H, m, C**H**), 6.78 (1H, d, *J* = 7.7 Hz, C**H**), 4.53 (1H, septet, *J* = 6.6 Hz, C**H**$(CH_3)_2$), 4.10-4.05 (5H, m, 2 x C**H**$_2$, C**H**Me_2), 3.07 (3H, s, CH_3Ar), 2.42 (9H, s(br), 3 x CH_3Ar), 1.32 (3H, s(br), CH_3Ar), 1.08 (3H, s(br), CH_3Ar), 1.04 (d, *J* = 5.5 Hz), 0.90 (d, *J* = 5.5 Hz), 0.84 (d, *J* = 5.5 Hz), 0.52 (d, *J* = 5.5 Hz).

2-(2-Bromo-allyl)-malonic acid diethyl ester (308)



$C_{10}H_{15}BrO_4$
M.w. = 279.136 g/mol
colourless oil

To a stirred solution of diethylmalonate **272** (4 mL, 25 mmol) in THF (40 mL) was added *t*-BuOK (1.1 g, 10 mmol) and 18-crown-6 (2.64 g, 10 mmol). After stirring for 10 minutes, 2,3-dibromo propene (1 mL, 10 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 2% EtOAc/hexane to afford **308** as a colourless oil (2 g, 7.2 mmol, 50%). Spectroscopic characteristics are consistent with those reported in the literature.[136]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70-5.65 (1H, m, $\mathbf{H_A}H_BC{=}CBrCH_2$), 5.47 (1H, d, J = 1.5 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 4.21 (4H, q, J = 6.9 Hz, $CO_2C\mathbf{H}_2CH_3$), 3.76 (1H, dt, J = 1.1, 7.7 Hz, $C\mathbf{H}(CO_2Et)_2$), 3.01 (2H, dd, J = 7.7, 1.1 Hz, $H_2C{=}CBrC\mathbf{H}_2$), 1.27 (6H, dt, J = 1.1, 7.3 Hz, $CO_2CH_2C\mathbf{H}_3$).

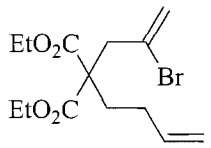
^{13}C NMR (75 MHz, $CDCl_3$) δ 168 ($\mathbf{C}O_2Et$), 129.4 ($H_2C{=}\mathbf{C}BrCH_2$), 119.6 ($H_2\mathbf{C}{=}CBrCH_2$), 61.7 ($CO_2\mathbf{C}H_2CH_3$), 51.0 ($\mathbf{C}H(CO_2Et)_2$), 40.4 ($H_2C{=}CBrC\mathbf{H}_2$), 14.0 ($CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2983 (w), 1731 (s), 1236 (m), 1152 (m), 1032 (m), 896 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 300, 301 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{10}H_{15}{}^{79}BrO_4SNa$: 301.0046 found 301.0047.

2-(2-Bromo-allyl)-2-but-3-enyl-malonic acid diethyl ester (293)



$C_{14}H_{21}BrO_4$
M.w. = 333.06 g/mol
colourless oil

To a stirred solution of **308** (400 mg, 1.43 mmol) in THF (10 mL) was added *t*-BuOK (160.5 g, 1.43 mmol) and 18-crown-6 (378 g, 1.43 mmol). After stirring for 10 minutes, 4-bromo-1-butene (145 μL, 1.43 mmol) was added. The reaction mixture was stirred 3 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 1% EtOAc/hexane to afford **293** as a colourless oil (300 mg, 0.90 mmol, 63%). Spectroscopic characteristics are consistent with those reported in the literature.[137]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (1H, ddt, *J* = 16.8, 10.2, 6.2 Hz, H_2C=C**H**CH_2), 5.58 (1H, d, *J* = 1.5 Hz, H_A**H**$_B$C=$CBrCH_2$), 5.51 (1H, d, *J* = 1.5 Hz, **H**$_A$$H_B$C=$CBrCH_2$), 5.01-4.86 (2H, m, **H**$_2$C=$CHCH_2$), 4.16-4.09 (4H, m, $CO_2CH_2CH_3$), 3.10 (2H, s, H_2C=$CBrCH_2$), 2.10-2.00 (2H, m, CCH_2CH_2), 1.95-1.84 (2H, m, H_2C=$CHCH_2$), 1.20 (6H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$).

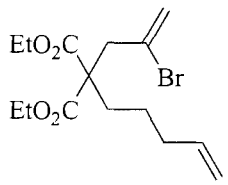
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (2 x **C**O_2Et), 137.2 (H_2C=**C**HCH_2), 132.2 (H_2C=**C**$BrCH_2$), 122.6 (H_2**C**=$CHCH_2$), 115.1 (H_2**C**=$CBrCH_2$), 61.5 (2 x CO_2**C**H_2CH_3), 56.8 (**C**), 42.9 (H_2C=CBr**C**H_2), 30.6 (CCH_2CH_2), 28.3 (H_2C=CH**C**H_2), 14.0 (2 x CO_2CH_2**C**H_3).

IR ν_{max} neat (cm^{-1}): 2980 (w), 1729 (s), 1189 (m), 1146 (m), 908 (w).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 354, 355 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{14}H_{21}{}^{79}BrO_4Na$: 355.0515 found 355.0513.

2-(2-Bromo-allyl)-2-pent-4-enyl-malonic acid diethyl ester (309)



$C_{15}H_{23}BrO_4$
M.w. = 347 g/mol
colourless oil

To a stirred solution of **308** (300 mg, 1.08 mmol) in THF (10 mL) was added *t*-BuOK (120.6 g, 1.08 mmol) and 18-crown-6 (285 g, 1.08 mmol). After stirring for 10 minutes, 5-bromo-1-pentene (128 μL, 1.08 mmol) was added. The reaction mixture was stirred 3 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 1% EtOAc/hexane to afford **309** as a colourless oil (180 mg, 0.51 mmol, 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, ddt, J = 17.2, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.58-5.55 (1H, m, $\mathbf{H_A}H_BC$=$CBrCH_2$), 5.49 (1H, d, J = 1.8 Hz, $H_A\mathbf{H_B}C$=$CBrCH_2$), 5.00-4.80 (2H, m, $\mathbf{H_2}C$=$CHCH_2$), 4.19-4.04 (4H, m, $CO_2C\mathbf{H_2}CH_3$), 3.09 (2H, d, J = 0.7 Hz, H_2C=$CBrC\mathbf{H_2}$), 2.05-1.90 (4H, m, H_2C=$CHC\mathbf{H_2}C\mathbf{H_2}$), 1.27-1.20 (2H, m $CC\mathbf{H_2}$), 1.85 (6H, t, J = 6.9 Hz, $CO_2CH_2C\mathbf{H_3}$).

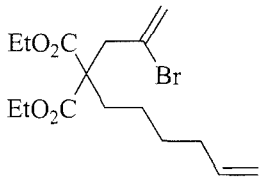
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (2 x $\mathbf{C}O_2Et$), 137.9 (H_2C=**C**HCH_2), 127.5 (H_2C=**C**$BrCH_2$), 121.5 ($H_2\mathbf{C}$=$CHCH_2$), 115.0 ($H_2\mathbf{C}$=$CBrCH_2$), 61.5 (2 x $CO_2\mathbf{C}H_2CH_3$), 57.2 (**C**), 42.9 (H_2C=$CBr\mathbf{C}H_2$), 33.7 (H_2C=**C**HCH_2), 30.9 ($C\mathbf{C}H_2CH_2$), 23.4 ($CCH_2\mathbf{C}H_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2980 (w), 1729 (s), 1187 (m), 1146 (m), 1023 (w), 907 (w).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 370, 371 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{15}H_{23}{}^{79}BrO_4Na$: 369.0672 found 369.0672.

2-(2-Bromo-allyl)-2-hex-5-enyl-malonic acid diethyl ester (310)



$C_{16}H_{25}BrO_4$
M.w. = 361.27 g/mol
colourless oil

To a stirred solution of **308** (200 mg, 0.72 mmol) in THF (10 mL) was added *t*-BuOK (81 g, 0.72 mmol) and 18-crown-6 (190 g, 0.72 mmol). After stirring for 10 minutes, 6-bromo-1-pentene (106 μL, 0.79 mmol) was added. The reaction mixture was stirred for 3 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 1% Et_2O/hexane to afford **310** as a colourless oil (196 mg, 0.54 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, ddt, *J* = 17.2, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.58-5.55 (1H, m, $\mathbf{H_A}H_BC$=$CBrCH_2$), 5.49 (1H, d, *J* = 1.8 Hz, $H_A\mathbf{H_B}C$=$CBrCH_2$), 4.96-4.84 (2H, m, $\mathbf{H_2}C$=$CHCH_2$), 4.12 (4H, dq, *J* = 2.2, 6.9 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.08 (2H, d, *J* = 0.7 Hz, H_2C=$CBrC\mathbf{H_2}$), 2.03-1.89 (4H, m, H_2C=$CHC\mathbf{H_2}$, $CC\mathbf{H_2}CH_2$), 1.40-1.29 (2H, m, H_2C=$CHCH_2C\mathbf{H_2}$), 1.20-1.08 (2H, m $CCH_2C\mathbf{H_2}$), 1.19 (6H, t, *J* = 7.3 Hz, $CO_2CH_2C\mathbf{H_3}$).

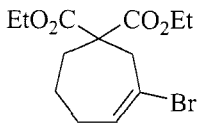
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (2 x $\mathbf{C}O_2Et$), 138.5 (H_2C=**C**HCH_2), 127.5 (H_2C=**C**$BrCH_2$), 121.5 ($H_2\mathbf{C}$=$CHCH_2$), 115.0 ($H_2\mathbf{C}$=$CBrCH_2$), 61.5 (2 x $CO_2\mathbf{C}H_2CH_3$), 57.1 (**C**), 42.8 (H_2C=$CBr\mathbf{C}H_2$), 33.3 (H_2C=$CH\mathbf{C}H_2$), 31.1 (H_2C=$CHCH_2\mathbf{C}H_2$), 28.4 ($C\mathbf{C}H_2CH_2$), 23.4 ($CCH_2\mathbf{C}H_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2979 (w), 2933 (w), 1730 (s), 1226 (m), 1226 (m), 1181 (m), 1028 (w), 906 (w).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 382, 383 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{25}{}^{79}BrO_4Na$: 383.0828, found 383.0834.

3-Bromo-cyclohept-3-ene-1,1-dicarboxylic acid diethyl ester (311)



$C_{13}H_{19}BrO_4$
M.w. = 319.19 g/mol
colourless oil

To a stirred solution of **309** (30 mg, 0.09 mmol) in benzene (3 mL) was added a solution of the second generation Grubbs catalyst (7.6 mg, 5.6 μmol) in benzene (6 mL) in portion. The mixture was stirred and degassed for an hour. The reaction mixture was heated at reflux for 18 hours then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 2% Et_2O/hexane to afford the cyclised product **311** as a colourless oil (23 mg, 72 μmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (1H, t, J = 6.2 Hz, **H**C=CBr), 4.14 (4H, q, J = 7.3 Hz, $CO_2CH_2CH_3$), 3.15 (2H, s(br), HC=CBrC**H**$_2$), 2.17-2.12 (2H, m, CC**H**$_2$CH$_2$), 2.08-2.01 (2H, m, BrC=CHC**H**$_2$), 1.69-1.60 (2H, m CCH$_2$C**H**$_2$), 1.20 (6H, t, J = 7.3 Hz, $CO_2CH_2CH_3$).

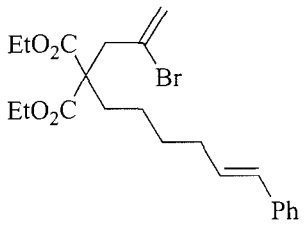
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (2 x **C**O$_2$Et), 135.5 (H**C**=CBrCH$_2$), 120.2 (HC=**C**BrCH$_2$), 62.0 (2 x $CO_2CH_2CH_3$), 56.1 (**C**), 43.2 (HC=CBr**C**H$_2$), 36.0 (C**C**H$_2$CH$_2$), 29.6 (BrC=CH**C**H$_2$), 22.2 (CCH$_2$**C**H$_2$), 14.0 (2 x $CO_2CH_2CH_3$).

IR ν_{max} neat (cm^{-1}): 2980 (w), 1729 (s), 1251 (m), 1217 (m), 1092 (w), 1030 (w).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 342, 343 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{13}H_{20}{}^{79}BrO_4$: 319.0540, found 319.0536.

2-(2-Bromo-allyl)-2-(6-phenyl-hex-5-enyl) malonic acid diethyl ester (312)



$C_{22}H_{29}BrO_4$
M.w. = 437.37 g/mol
colourless oil

To a stirred solution of **310** (50 mg, 0.14 mmol) in benzene (7 mL) was added a solution of the second generation Grubbs catalyst **4** (23.5 mg, 28 μmol) in benzene (7

mL). The reaction mixture was stirred and degassed for an hour. The reaction mixture was heated at reflux for 18 hours then concentrated under reduced pressure to yield the crude product as black oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 2% Et_2O/hexane to afford the cyclised product **312** as a colourless oil (12.5 mg, 34 μmol, 20%) and starting material **xx** as a colourless oil (20 mg, 55 μmol, 40%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.18 (5H, m, Ar**H**), 6.30 (1H, dt, *J* = 16.1, 1.6 Hz, (Ph)(**H**)C=C(H)(CH_2)), 6.10 (1H, dt, *J* = 15.7, 7.0 Hz, (Ph)(H)C=C(**H**)(CH_2)), 5.55 (1H, d, *J* = 1.5 Hz, $\mathbf{H_A}H_BC$=CBrCH_2), 5.48 (1H, d, *J* = 1.8 Hz, $H_A\mathbf{H_B}C$=CBrCH_2), 4.11 (4H, q, *J* = 7.3 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.09 (2H, s(br), H_2C=CBr$C\mathbf{H_2}$), 2.21-2.10 (2H, m, $CC\mathbf{H_2}CH_2$), 2.00-1.93 (2H, m, (Ph)(H)C=C(H)($C\mathbf{H_2}$)), 1.52 (2H, s, $CCH_2C\mathbf{H_2}$), 1.43 (2H, quint, *J* = 7.7 Hz, (Ph)(**H**)C=C(H)(CH_2)$C\mathbf{H_2}$), 1.17 (6H, t, *J* = 7.0 Hz, $CO_2CH_2C\mathbf{H_3}$).

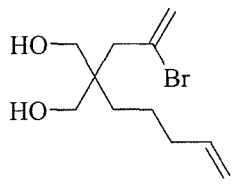
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (2 x $\mathbf{C}O_2$Et), 137.5 ($\mathbf{C}_{Ar}$), 130.5 ((Ph)(H)**C**=C(H)(CH_2)), 130.1 ((Ph)(H)C=**C**(H)(CH_2)), 128.5 (2 x $\mathbf{C}H_{Ar}$), 127.0 (H_2C=**C**BrCH_2), 126.8 ($\mathbf{C}H_{Ar}$), 125.9 (2 x $\mathbf{C}H_{Ar}$), 121.6 ($H_2\mathbf{C}$=CBrCH_2), 61.5 (2 x $CO_2\mathbf{C}H_2CH_3$), 57.1 (C), 42.8 (H_2C=CBr**C**H_2), 32.6 ((Ph)(H)C=C(H)($\mathbf{C}H_2$)), 31.1 ((Ph)(**H**)C=C(H)(CH_2)$\mathbf{C}H_2$), 29.3 ($C\mathbf{C}H_2CH_2$), 23.4 ($CCH_2\mathbf{C}H_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2932 (w), 1731 (s), 1233 (m), 1197 (m), 1152 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 460, 461 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{22}H_{30}{}^{79}BrO_4Na$: 437.1322, found 437.1324.

2-(2-Bromo-allyl)-2-pent-4-enyl-propane-1,3-diol (313)



$C_{11}H_{19}BrO_2$

M.w. = 263.17 g/mol

colourless oil

To a 1M solution of $LiAlH_4$ in THF (299 μL, 2.99 mmol) was added dropwise a solution of **309** (416 mg, 1.20 mmol) in THF (10 mL) at 0 °C .The reaction mixture was left to stir for 2 hours warming to RT. The mixture was quenched with by dropwise addition of ether (10mL) followed by water (10 mL). The mixture was

poured into 2M HCl solution (10 mL) and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil (246 mg). Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 1:1 EtOAc/hexane to afford **313** as a colourless oil (283 mg, 1.07 mmol, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, ddt, J = 17.2, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.68 (1H, d, J = 1.5 Hz, $\mathbf{H_A}H_BC$=$CBrCH_2$), 5.62 (1H, d, J = 1.8 Hz, $H_A\mathbf{H_B}C$=$CBrCH_2$), 5.03 (1H, dq, J = 17.2, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.98 (1H, ddt, J = 9.9, 1.8, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 3.66 (4H, q, J = 11 Hz, C**H**$_2$OH), 2.65 (1H, s, O**H**), 2.25 (3H, s (br), H_2C=CHC**H**$_2$, O**H**), 2.10-2.00 (2H, m, H_2C=CBrC**H**$_2$), 1.45-1.35 (4H, m, CC**H**$_2$, CCH_2C**H**$_2$).

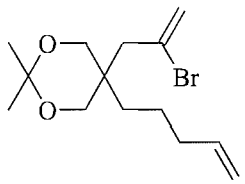
^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4 (H_2C=**C**HCH_2), 128.8 (H_2C=**C**$BrCH_2$), 121.3 (H_2**C**=$CHCH_2$), 114.8 (H_2**C**=$CBrCH_2$), 67.8 (2 x **C**H_2OH), 42.7 (**C**), 42.0 (H_2C=CBr**C**H_2), 34.3 (H_2C=CH**C**H_2), 30.8 (**C**CH_2), 22.3 (CCH_2**C**H_2).

IR ν_{max} neat (cm^{-1}): 3377 (br, OH), 2937 (s), 1435 (m), 1029 (s), 909 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 285, 287 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{11}H_{19}{}^{79}BrO_2Na$: 285.0460, found 285.0461.

5-(2-Bromo-allyl)-2,2-dimethyl-5-pent-4-enyl-[1,3]dioxane (314)



$C_{14}H_{23}BrO_2$
M.w. = 303.16 g/mol
colourless oil

Following the procedure of Dumortier *et al*,[12] to a stirred solution of **313** (270 mL, 1.02 mmol) in acetone (10 mL) was added Amberlyst®15 (100 mg) and 4°A molecular sieve. The reaction mixture was stirred for 15 hours at RT before being filtered and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 5% EtOAc/hexane to afford **314** as a colourless oil (278 mg, 0.92 mmol, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (1H, ddt, *J* = 16.8, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.58 (1H, d, *J* = 1.5 Hz, $\mathbf{H_A}H_BC$=$CBrCH_2$), 5.54 (1H, d, *J* = 1.5 Hz, $H_A\mathbf{H_B}C$=$CBrCH_2$), 4.94 (1H, dq, *J* = 17.2, 1.8 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.98 (1H, ddt, *J* = 9.9, 1.8, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 3.58 (4H, d, *J* = 7 Hz, 2x$C\mathbf{H_2}O$), 2.60 (2H, s, H_2C=$CBrC\mathbf{H_2}$), 1.98 (2H, q, *J* = 6.6 Hz, H_2C=$CHC\mathbf{H_2}$), 1.36-1.32 (10H, m, $C(CH_3)_2$, CCH_2, CCH_2CH_2).

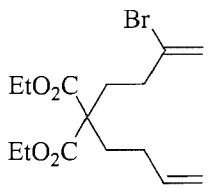
^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4 (H_2C=**C**HCH_2), 128.7 (H_2C=**C**$BrCH_2$), 121.3 (H_2**C**=$CHCH_2$), 114.8 (H_2**C**=$CBrCH_2$), 98.1 (**C**$(CH_3)_2$), 67.4 (2x$OC\mathbf{H_2}$), 42.5 (H_2C=$CBrCH_2$), 36.1 (**C**), 34.3 (H_2C=$CHCH_2$), 31.9 (CCH_2), 25.9 (CCH_2CH_2), 22.0 (CH_3), 21.9 (CH_3).

IR ν_{max} neat (cm^{-1}): 2991 (m), 2938 (m), 2862 (m), 1370 (s), 1195 (s), 1104 (s), 910 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 325, 326 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{14}H_{23}{}^{79}BrO_2Na$: 325.0774, found 325.0772.

2-(3-Bromo-but-3-enyl)-2-but-3-enyl-malonic acid diethyl ester (319)



$C_{15}H_{23}BrO_4$

M.w. = 347.22 g/mol

colourless oil

To a stirred solution of **274** (150 mg, 0.70 mmol) in THF (10 mL) was added *t*-BuOK (79 mg, 0.70 mmol) and 18-crown-6 (185 mg, 0.70 mmol). After stirring for 20 minutes, a solution of **318** (198 μL, 0.70 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 3 hours and quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 3% Et_2O/hexane to afford **319** as a colourless oil (150 mg, 0.43 mmol, 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89-5.72 (1H, m, H_2C=C**H**CH_2), 5.61 (1H, dt, *J* = 1.8, 1.1 Hz, $\mathbf{H_A}H_BC$=$CBrCH_2$), 5.42 (1H, d, *J* = 1.8 Hz, $H_A\mathbf{H_B}C$=$CBrCH_2$), 5.11-4.96

(2H, m, $\mathbf{H}_2C$=CHCH$_2$), 4.21 (4H, q, J = 7.0 Hz, $CO_2C\mathbf{H}_2CH_3$), 2.41-2.34 (2H, m, H_2C=CBrC$\mathbf{H}_2$), 2.22-2.14 (2H, m, H_2C=CHC$\mathbf{H}_2$), 2.02-1.98 (4H, m, (C$\mathbf{H}_2$)(C$\mathbf{H}_2$)C(CO_2Et)$_2$), 1.28 (6H, t, J = 7.3 Hz, $CO_2CH_2C\mathbf{H}_3$).

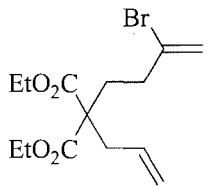
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (2 x $\mathbf{C}O_2$Et), 137.4 (H_2C=$\mathbf{C}$HCH$_2$), 133.3 (H_2C=$\mathbf{C}$BrCH$_2$), 117.0 ($H_2\mathbf{C}$=CHCH$_2$), 115.2 ($H_2\mathbf{C}$=CBrCH$_2$), 61.3 (2 x $CO_2\mathbf{C}H_2CH_3$), 56.6 (C), 36.5 (H_2C=CBr$\mathbf{C}H_2$), 31.9 (H_2C=CBrCH$_2\mathbf{C}H_2$), 31.2 (H_2C=CH$\mathbf{C}H_2$), 28.3 (H_2C=CHCH$_2\mathbf{C}H_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2979 (w), 1727 (s), 1188 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 370, 371 [M+Na]$^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{15}H_{23}O_4{}^{79}$BrNa: 369.0672, found 369.0669.

2-Allyl-2-(3-Bromo-but-3-enyl)-malonic acid diethyl ester (321)



$C_{14}H_{21}BrO_4$

M.w. = 333.22 g/mol

colourless oil

To a stirred solution of diethyl malonate **320** (101 mg, 0.51 mmol) in THF (10 mL) was added *t*-BuOK (58 mg, 0.51 mmol) and 18-crown-6 (135 mg, 0.51 mmol). After stirring for 20 minutes, a solution of **318** (145 μL, 0.51 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 3 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 2% Et_2O/hexane to afford **321** as a colourless oil (120 mg, 0.36 mmol, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, ddt, J = 16.8, 9.2, 7.7 Hz, H_2C=C$\mathbf{H}$CH$_2$), 5.62-5.58 (1H, m, $H_A\mathbf{H}_B$C=CBrCH$_2$), 5.41 (1H, d, J = 1.8 Hz, $\mathbf{H}_AH_B$C=CBrCH$_2$), 5.20-5.10 (2H, m, $\mathbf{H}_2C$=CHCH$_2$), 4.22 (4H, dq, J = 7.3, 0.7 Hz, $CO_2C\mathbf{H}_2CH_3$), 2.68 (2H, d, J = 7.3, 1.1 Hz, H_2C=CHC$\mathbf{H}_2$), 2.43-2.34 (2H, m, C$\mathbf{H}_2$C(CO_2Et)$_2$), 2.20-2.10 (2H, m, H_2C=CBrC$\mathbf{H}_2$), 1.28 (6H, dt, J = 7.3, 0.7 Hz, $CO_2CH_2C\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2 x $\mathbf{C}O_2Et$), 133.2 (H_2C=$\mathbf{C}HCH_2$), 132.1 (H_2C=$\mathbf{C}BrCH_2$), 119.3 ($H_2\mathbf{C}$=$CHCH_2$), 117.0 ($H_2\mathbf{C}$=$CBrCH_2$), 61.3 (2 x $CO_2\mathbf{C}H_2CH_3$), 56.7 (**C**), 37.3 (H_2C=$CBr\mathbf{C}H_2$), 36.4 (H_2C=$CH\mathbf{C}H_2$), 31.1 ($\mathbf{C}H_2C(CO_2Et)_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

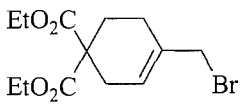
IR ν_{max} neat (cm^{-1}): 2981 (w), 1729 (s), 1192 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 356, 357 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{14}H_{21}O_4{}^{79}BrNa$: 355.0515, found 355.0514.

4-Bromomethyl-cyclohex-3-ene-1,1-dicarboxylic acid diethyl ester (323)

4-Bromo-cyclohex-3-ene-1,1-dicarboxylic acid diethyl ester (324)



$C_{13}H_{19}BrO_4$

M.w. = 319.19 g/mol

colourless oil

To a stirred solution of **321** (80 mg, 0.24 mmol) in benzene (20 mL) was added a solution of the second generation Grubbs catalyst (25 mg, 29 μmol) in benzene (4 mL). The mixture was stirred and degassed for an hour. The reaction mixture was heated at reflux for 12 hours then concentrated under reduced pressure to afford the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 4% Et_2O/hexane to afford the cyclised product **323** as a colourless oil (16 mg, 0.05 mmol, 21%) and compound **324** as a colourless oil (26 mg, 0.09 mmol, 36%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, t, J = 4.0 Hz, **H**C=CBr), 4.12 (4H, q, J = 7.0 Hz, $CO_2\mathbf{C}H_2CH_3$), 3.83 (2H, s, $\mathbf{C}H_2Br$), 2.56-2.51 (2H, m, ($\mathbf{H}_2C$)(H)C=C(CH_2Br)(CH_2)), 2.18-2.10 (4H, m, $(EtO_2C)_2C\mathbf{C}H_2\mathbf{C}H_2$), 1.18 (6H, t, J = 7.3 Hz, $CO_2CH_2\mathbf{C}H_3$).

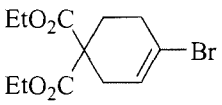
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (2 x $\mathbf{C}O_2Et$), 133.8 ((H_2C)(H)C=$\mathbf{C}$(CH_2Br)(CH_2), 124.8 ((H_2C)(H)$\mathbf{C}$=C(CH_2Br)(CH_2), 61.4 (2 x $CO_2\mathbf{C}H_2CH_3$), 52.7 (**C**), 37.9 ($\mathbf{C}H_2Br$), 30.8 (($H_2\mathbf{C}$)(H)C=C(CH_2Br)(CH_2)), 27.4 ($(EtO_2C)_2C\mathbf{C}H_2CH_2$), 23.5 ($(EtO_2C)_2CCH_2\mathbf{C}H_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2979 (w), 1727 (s), 1240 (s), 1176 (s), 1083 (m), 1034 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 341, 342 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{13}H_{19}{}^{79}BrO_4Na$: 341.0359, found 341.0365.

Data for the RCM product **324**:



$C_{12}H_{17}BrO_4$

M.w. = 305.16 g/mol

colourless oil

^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (1H, ddt, *J* = 5.9, 4.0, 1.8 Hz, **H**C=CBr), 4.22 (4H, q, *J* = 6.9 Hz, $CO_2CH_2CH_3$), 2.65 (2H, dt, *J* = 4.0, 2.2 Hz, $(H_2C)(H)C{=}CBrCH_2$), 2.56-2.49 (2H, m, CCH_2CH_2), 2.26 (2H, t, *J* = 6.6 Hz, CCH_2CH_2), 1.27 (6H, t, *J* = 7.3 Hz, $CO_2CH_2CH_3$).

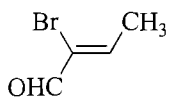
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2 x CO_2Et), 125.6 ($HC{=}CBrCH_2$), 120.6 ($HC{=}CBrCH_2$), 61.6 (2 x $CO_2CH_2CH_3$), 52.0 (**C**), 32.5 ($(H_2C)(H)C{=}CBrCH_2$), 32.1 (CCH_2CH_2), 29.2 (CCH_2CH_2), 14.0 (2 x $CO_2CH_2CH_3$).

IR ν_{max} neat (cm^{-1}): 2978 (w), 1726 (s), 1246 (s), 1174 (s), 1084 (m), 1042 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 327, 328 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{12}H_{17}{}^{79}BrO_4Na$: 327.0202, found 327.0199.

2-Bromo-but-2-enal (336)



C_4H_5BrO

M.w. = 148.99 g/mol

yellow oil

Following the procedure of Kowalski *et. al.*,[79] to a stirred solution of *trans*-crotonaldehyde **335** (1.2 mL, 14.3 mmol) in CH_2Cl_2 (6 mL) was added a solution of Br_2 (731 μL, 14.27 mmol) in CH_2Cl_2 (6 mL) dropwise at –78 °C over 10 minutes. Et_3N (4 mL, 28.54 mmol) was added. The reaction mixture was stirred at 0 °C for an hour and then at RT for 15 hours. The reaction mixture was diluted in CH_2Cl_2 (100 mL), washed with 10% HCl (40 mL) and brine (40 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to yield the

crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (25 g) eluting with 7% Et_2O/hexane to afford **336** as a yellow oil (601 mg, 4 mmol, 28%).

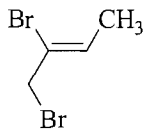
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (1H, s, **CH**O), 7.25 (1H, q, J = 6.6 Hz, (Br)(CHO)C=C(**H**)(CH_3)), 2.13 (3H, d, J = 6.6 Hz, (Br)(CHO)C=C(H)(C**H**$_3$)).

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0 ((Br)(**C**HO)C=C(H)(CH_3)), 154.0 ((Br)(CHO)**C**=C(H)(CH_3)), 130.1 ((Br)(CHO)C=**C**(H)(CH_3)), 19.0 ((Br)(CHO)C=C(H)(**C**H_3)).

IR ν_{max} neat (cm^{-1}): 1694 (s), 1621 (s), 1163 (s), 1069 (m), 958 (m), 817 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 203, 204 $[M+MeOH+Na]^+$ (100).

2-Bromo-but-2-en-1-ol (337)



$C_4H_6Br_2$

M.w. = 213.90 g/mol

yellow oil

Following the procedure of Loh *et al.*,[80] to a stirred solution of **336** (590 mg, 3.90 mmol) in Et_2O (10 mL) was added PBr_3 (817 μL, 8.60 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was continued stirring for another 10 minutes and then added brine dropwise. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with sat'd $NaHCO_3$ (10 mL) and until neutral. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product **337** as yellow oil (400 mg, 1.87 mmol, 48%) used directly for next step without further purification.

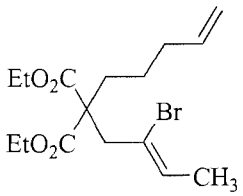
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (1H, qt, J = 6.6, 0.7 Hz, (Br)(BrH_2C)C=C(**H**)(CH_3), 4.18 (2H, dt, J = 6.6, 0.7 Hz, C**H**$_2$Br), 1.72 (3H, dt, J = 6.6, 1.1 Hz, C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6 ((Br)(BrH_2C)C=**C**(H)(CH_3)), 123.6 ((Br)(BrH_2C)**C**=C(H)(CH_3), 38.8 ((Br)(BrH_2**C**)C=C(H)(CH_3)), 17.2 ((Br)(BrH_2C)C=C(H)(**C**H_3)).

IR ν_{max} neat (cm^{-1}): 2968 (w), 1212 (s), 944 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 371, 372 $[M+Na]^+$ (100).

2-(2-Bromo-but-2-enyl)-2-pent-4-enyl-malonic acid diethyl ester (339)



$C_{16}H_{25}BrO_4$
M.w. = 361.67 g/mol
colourless oil

To a stirred solution of **338** (319 mg, 1.40 mmol) in THF (10 mL) was added *t*-BuOK (157 mg, 1.40 mmol) and 18-crown-6 (370 mg, 1.40 mmol). The reaction mixture was stirred for 30 minutes. A solution of bromo compound **337** (300 mg, 1.40 mmol) was added. The reaction mixture was stirred for 15 hours before being quenched with water (15 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 4% Et_2O/hexane to afford **339** as a colourless oil (455 mg, 1.26 mmol, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 19.4, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.80 (1H, q, *J* = 6.6 Hz, (Br)(H_2C)C=C(**H**)(CH_3)), 5.02 (1H, dq, *J* = 17.2, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.97 (1H, dq, *J* = 10.2, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.21 (4H, qd, *J* = 7.0, 1.8 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.18 (2H, s(br), (Br)($\mathbf{H_2}C$)C=C(H)(CH_3)), 2.12-2.03 (2H, m, $CC\mathbf{H_2}$), 2.02-1.94 (2H, m, H_2C=$CHC\mathbf{H_2}$), 1.73 (2H, d, *J* = 6.6 Hz, H_2C=$CHCH_2C\mathbf{H_2}$), 1.27 (6H, t, *J* = 7.3 Hz, $CO_2CH_2C\mathbf{H_3}$).

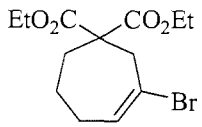
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (2 x $\mathbf{C}O_2$Et), 138.0 (H_2C=**C**HCH_2), 128.4 ((Br)(H_2C)**C**=C(H)(CH_3)), 122.1 ((Br)(H_2C)C=**C**(H)(CH_3)), 114.9 ($H_2\mathbf{C}$=$CHCH_2$), 61.3 (2 x $CO_2\mathbf{C}H_2CH_3$), 57.3 (**C**), 43.0 ((Br)($H_2\mathbf{C}$)C=C(H)(CH_3)), 33.7 (H_2C=$CH\mathbf{C}H_2$), 30.8 ($C\mathbf{C}H_2CH_2$), 23.4 ($CCH_2\mathbf{C}H_2$), 17.1 ((Br)(H_2C)C=C(H)(**C**H_3)), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2979 (w), 1730 (s), 1181 (m), 1130 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 384, 385 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{25}{}^{79}BrO_4Na$: 383.0828, found 383.0825.

3-Bromo-cyclohept-3-ene-1,1-dicarboxylic acid diethyl ester (311)



$C_{13}H_{19}BrO_4$
M.w. = 319.19 g/mol
colourless oil

To a stirred solution of **339** (71 mg, 0.19 mmol) in benzene (15 mL) was added a solution of the second generation Grubbs catalyst **4** (20 mg, 23 μmol) in benzene (5 mL). The mixture was stirred and degassed for an hour. The reaction mixture was heated at reflux for 10 hours then concentrated under reduced pressure to afford the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 2% Et_2O/hexane to afford the cyclised product **311** (37 mg, 0.11 mmol, 60%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (1H, t, J = 6.2 Hz, **H**C=CBr), 4.14 (4H, q, J = 7.3 Hz, $CO_2C\mathbf{H}_2CH_3$), 3.15 (2H, s(br), H_2C=CBr$C\mathbf{H}_2$), 2.17-2.12 (2H, m, $CC\mathbf{H}_2CH_2$), 2.08-2.01 (2H, m, H_2C=CH$C\mathbf{H}_2CH_2$), 1.69-1.60 (2H, m $CCH_2C\mathbf{H}_2CH_2$), 1.20 (6H, t, J = 7.3 Hz, $CO_2CH_2C\mathbf{H}_3$).

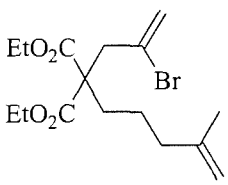
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (2 x $\mathbf{C}O_2$Et), 135.5 (H**C**=CBrCH_2), 120.2 (HC=**C**BrCH_2), 62.0 (2 x $CO_2\mathbf{C}H_2CH_3$), 56.1 (C), 43.2 (HC=CBr$\mathbf{C}H_2$), 36.0 ($C\mathbf{C}H_2CH_2$), 29.6 (BrC=CH$\mathbf{C}H_2$), 22.2 ($CCH_2\mathbf{C}H_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2980 (w), 1729 (s), 1230 (m), 1187 (m), 1146 (m), 907 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 342, 343 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{13}H_{19}{}^{79}BrO_4$: 319.0540, found 319.0536.

2-(2-Bromo-allyl)-2-(4-methyl-pent-4-enyl)-malonic acid diethyl ester (340)



$C_{16}H_{25}O_4Br$
M.w. = 361.27 g/mol
colourless oil

To a stirred solution of **308** (150 mg, 0.70 mmol) in THF (10 mL) was added *t*-BuOK (79 mg, 0.70 mmol) and 18-crown-6 (185 mg, 0.70 mmol). The reaction mixture was stirred for 20 minutes and a solution of bromo compound (198 μL, 0.70

mmol) in THF (5 mL) was added. The reaction mixture was stirred for 3 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (8 g) eluting with 3% Et_2O/hexane to afford **340** as a colourless oil (150 mg, 0.43 mmol, 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (1H, m, $\mathbf{H_AH_B}C{=}CBrCH_2$), 5.56 (1H, d, J = 1.5 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 4.72-4.69 (1H, m, $\mathbf{H_A}H_BC{=}C(CH_3)CH_2$), 4.68-4.64 (1H, m, $H_A\mathbf{H_B}C{=}C(CH_3)CH_2$), 4.19 (4H, dq, J = 2.2, 7.0 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.16 (2H, d, J = 1.1 Hz, $H_2C{=}CBrC\mathbf{H_2}$), 2.05-1.95 (4H, m, $H_2C{=}C(CH_3)(CH_2)_2C\mathbf{H_2}$, $H_2C{=}C(CH_3)C\mathbf{H_2}$), 1.35-1.29 (2H, m, $H_2C{=}C(CH_3)CH_2C\mathbf{H_2}$), 1.25 (6H, t, J = 7.3 Hz, $CO_2CH_2C\mathbf{H_3}$).

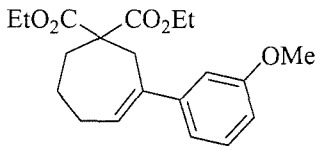
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (2 x $\mathbf{C}O_2Et$), 145.0 ($H_2C{=}\mathbf{C}(CH_3)CH_2$), 127.5 ($H_2C{=}\mathbf{C}BrCH_2$), 121.4 ($H_2\mathbf{C}{=}CBrCH_2$), 110.4 ($H_2\mathbf{C}{=}C(CH_3)CH_2$), 61.5 (2 x $CO_2\mathbf{C}H_2CH_3$), 56.6 (**C**), 43.0 ($H_2C{=}CBr\mathbf{C}H_2$), 37.7 ($H_2C{=}C(CH_3)\mathbf{C}H_2$), 31.0 ($H_2C{=}C(CH_3)(CH_2)_2\mathbf{C}H_2$), 22.0 ($H_2C{=}C(CH_3)CH_2\mathbf{C}H_2$), 14.0 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2980 (w), 2938 (w), 1730 (s), 1174 (m), 1150 (m), 891 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 383, 384 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{26}{}^{79}BrO_4$: 361.1009, found 361.1009.

3-(3-methoxy-phenyl)-cyclohept-3-ene-1,1-dicarboxylic acid diethyl ester (343)



$C_{20}H_{26}O_5$

M.w. = 346.42 g/mol

pale yellow oil

Following the procedure of Banwell *et al.*,[74] to a stirred solution of **311** (20 mg, 63 μmol) in THF (2 mL) was added a solution of Na_2CO_3 (200 mg) in H_2O (1 mL) and 3-methoxy phenyl boronic acid (14 mg, 94 μmol). $Pd(PPh_3)_4$ (3.5 mg, 3 μmol) was added. The reaction mixture was heated at reflux for 2 hours before being quenched with water (5 mL). The aqueous phase was separated and extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine and concentrated under

reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 10% Et_2O/hexane to afford the title compound **343** as a pale yellow oil (20 mg, 57 μmol, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (1H, t, *J* = 8.1 Hz, Ar**H**), 6.87-6.82 (1H, m, Ar**H**), 6.81-6.78 (1H, m, Ar**H**), 6.68 (1H, ddd, *J* = 8.4, 2.6, 1.1 Hz, Ar**H**), 6.07 (1H, t, *J* = 6.6 Hz, **H**C=C(CH_2)(Ph)), 4.06-3.80 (4H, m, $CO_2C\mathbf{H}_2CH_3$), 3.73 (3H, s, $ArOC\mathbf{H}_3$), 3.14 (2H, s(br), HC=C(Ph)($C\mathbf{H}_2$)), 2.29-2.15 (4H, m, $CC\mathbf{H}_2CH_2$, ((Ph)(H_2C)C=CH$C\mathbf{H}_2$), 1.77-1.68 (2H, m, $CCH_2C\mathbf{H}_2$), 0.97 (6H, t, *J* = 7.0 Hz, $CO_2CH_2C\mathbf{H}_3$).

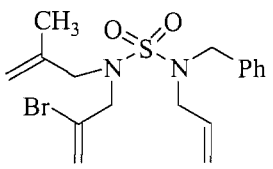
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (2 x $\mathbf{C}O_2Et$), 160.0 ($\mathbf{C}_{Ar}OCH_3$), 146.1 (HC=$\mathbf{C}$(CH_2)(Ph)), 139.0 ($\mathbf{C}_{Ar}$), 131.9 (H$\mathbf{C}$=C(CH_2)(Ph)), 129.0 ($\mathbf{C}H_{Ar}$), 118.7 ($\mathbf{C}H_{Ar}$), 111.8 (2 x $\mathbf{C}H_{Ar}$), 61.1 (2 x $CO_2\mathbf{C}H_2CH_3$), 55.3 ($ArO\mathbf{C}H_3$), 55.0 (**C**), 36.7 ($C\mathbf{C}H_2$), 36.1 (HC=C(Ph)($\mathbf{C}H_2$)), 28.2 (($H_2\mathbf{C}$)(H)C=$\mathbf{C}$(CH_2)(Ph)), 22.1 ($CCH_2\mathbf{C}H_2$), 13.7 (2 x $CO_2CH_2\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 2956 (w), 1730 (s), 1218 (m), 1185 (m), 1051 (w).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 369 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{20}H_{26}O_5Na$: 369.1672, found 369.1666.

_N_-(2-bromo-2-propenyl)-_N_-(2-methyl-2-propenyl)-_N'_-phenylmethyl-_N'_-(2-propenyl)sulfamide (344)



$C_{17}H_{23}BrN_2O_2S$

M.w. = 399.35 g/mol

Pale yellow oil

To a stirred solution of the corresponding sulfamide (kindly supplied by S. Salim) (160 mg, 0.46 mmol) in THF (10 mL) was added *t*-BuOK (52 mg, 0.46 mmol) and 18-crown-6 (122 mg, 0.46 mmol). The reaction mixture was stirred for 30 minutes. 3-Bromo-2-methyl propene (60 μL, 0.59 mmol) was added before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield

the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 5% Et_2O/hexane to afford **344** as a pale yellow oil (178 mg, 0.45 mmol, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m, Ar**H**), 5.94 (1H, dt, *J* = 2.2, 1.1 Hz, $\mathbf{H_A}H_BC{=}CBrCH_2$), 5.86 (1H, ddt, *J* = 17.2, 10.3, 6.6 Hz, $H_2C{=}C\mathbf{H}CH_2$), 5.66 (1H, dt, *J* = 2.2, 0.7 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 5.23 (1H, dq, *J* = 9.9, 1.1 Hz, $\mathbf{H_A}H_BC{=}CHCH_2$), 5.14 (1H, dq, *J* = 17.2, 1.5 Hz, $H_A\mathbf{H_B}C{=}CHCH_2$), 5.04-5.01 (1H, m, $\mathbf{H_A}H_BC{=}C(CH_3)CH_2$), 5.00-4.97 (1H, m, $H_A\mathbf{H_B}C{=}C(CH_3)CH_2$), 4.41 (2H, s, $PhC\mathbf{H}_2$), 4.07 (2H, s, $H_2C{=}C(CH_3)C\mathbf{H}_2$), 3.87 (2H, s, $H_2C{=}CBrC\mathbf{H}_2$), 3.75 (2H, d, *J* = 6.6 Hz, $H_2C{=}CHC\mathbf{H}_2$), 1.78 (3H, s, $H_2C{=}C(C\mathbf{H}_3)CH_2$).

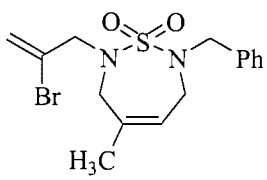
^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6 ($H_2C{=}\mathbf{C}(CH_3)CH_2$), 136.2 ($\mathbf{C}_{Ar}$), 133.0 ($H_2C{=}\mathbf{C}HCH_2$), 128.9 (2 x $\mathbf{C}H_{Ar}$), 128.6 (2 x $\mathbf{C}H_{Ar}$), 127.6 ($\mathbf{C}H_{Ar}$), 127.8 ($H_2C{=}\mathbf{C}BrCH_2$), 120.1 ($H_2\mathbf{C}{=}CHCH_2$), 119.6 ($H_2\mathbf{C}{=}CBrCH_2$), 115.3 ($H_2\mathbf{C}{=}C(CH_3)CH_2$), 54.5 ($H_2C{=}CBr\mathbf{C}H_2$), 53.7 ($H_2C{=}C(CH_3)\mathbf{C}H_2$), 50.8 ($\mathbf{C}H_2Ph$), 50.0 ($H_2C{=}CH\mathbf{C}H_2$), 20.3 ($H_2C{=}C(\mathbf{C}H_3)CH_2$).

IR ν_{max} neat (cm^{-1}): 3079 (w), 2980 (w), 2917 (w), 1329 (m), 1146 (s), 891 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 422, 423 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{17}H_{23}{}^{79}BrN_2O_2S$: 399.0737, found 399.0742.

2-(2-bromo-2-propenyl)-4-methyl-7-(phenylmethyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiadizepine-1,1-dione (345)



$C_{15}H_{19}BrN_2O_2S$
M.w. = 371.29 g/mol
white solid

To a stirred solution of sulfamide **344** (85 mg, 0.21 mmol) in benzene (10 mL) was added a solution of Grubbs second generation catalyst **4** (17.8 mg, 21 μmol) in benzene (10 mL). The mixture was stirred and degassed for an hour. The reaction mixture was heated at reflux for 10 hours before being concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 4% Et_2O/hexane to afford the cyclised product **345** as a white solid (50.4 mg, 0.14 mmol, 66%).

Mpt. = 115-116 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.20 (5H, m, Ar**H**), 5.90 (1H, $dt_{apparent}$, J = 2.2, 1.5 Hz, $\mathbf{H_A}H_BC{=}CBrCH_2$), 5.60 (1H, dt, J = 2.2, 1.1 Hz, $H_A\mathbf{H_B}C{=}CBrCH_2$), 5.38 (1H, dt, J = 1.8, 5.1 Hz, $(H_3C)C{=}C\mathbf{H}CH_2$), 4.33 (2H, s, $PhC\mathbf{H_2}$), 4.04 (2H, s (br), $H_2C{=}C(CH_3)C\mathbf{H_2}$), 3.71 (2H, s, $H_2C{=}CBrC\mathbf{H_2}$), 3.52 (2H, dd, J = 4.8, 1.5 Hz, $(H_3C)C{=}CHC\mathbf{H_2}$), 1.72 (3H, d, J = 2.5 Hz, $(\mathbf{H}_3C)C{=}CHCH_2$).

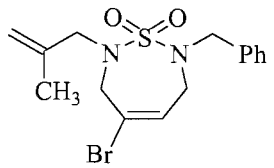
^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3 ($(H_3C)\mathbf{C}{=}CHCH_2$), 136.2 ($\mathbf{C}_{Ar}$), 128.6 (2 x $\mathbf{C}H_{Ar}$), 128.3 ($H_2C{=}\mathbf{C}BrCH_2$), 128.2 (2 x $\mathbf{C}H_{Ar}$), 127.9 ($\mathbf{C}H_{Ar}$), 121.9 ($(H_3C)C{=}\mathbf{C}HCH_2$), 118.8 ($H_2\mathbf{C}{=}CBrCH_2$), 56.7 ($H_2C{=}CBr\mathbf{C}H_2$), 52.1 ($\mathbf{C}H_2Ph$), 48.7 ($HC{=}C(CH_3)\mathbf{C}H_2$), 43.2 ($(H_3C)C{=}CH\mathbf{C}H_2$), 24.0 ($H_2C{=}C(\mathbf{C}H_3)CH_2$).

IR ν_{max} neat (cm^{-1}): 3051 (w), 2934 (w), 1360 (m), 1330 (m), 1156 (s), 898 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 393, 395 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{15}H_{19}{}^{79}BrN_2O_2S$: 371.0423, found 371.0427.

4-bromo-2-(2-bromo-2-propenyl)-7-(phenylmethyl)-2,3,6,7-tetrahydro-1*H*-1λ^6,2,7-thiadizepine-1,1-dione (346)



$C_{15}H_{19}BrN_2O_2S$

M.w. = 371.29 g/mol

white solid

To a stirred solution of sulfamide **344** (85 mg, 0.21 mmol) in benzene (10 mL) was added a solution of the second generation Grubbs catalyst **4** (17.8 mg, 21 μmol) in benzene (10 mL). The mixture was stirred and degassed for an hour. The reaction mixture was heated at reflux for 10 hours before being concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 4% Et_2O/hexane to afford the cyclised product **346** as a white solid (6 mg, 16 μmol, 8%).

Mpt. = 116 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.23 (5H, m, Ar**H**), 6.15 (1H, t, J = 5.9 Hz, HC=CBr), 4.99-4.96 (2H, m, $\mathbf{H_2}C{=}C(CH_3)CH_2$), 4.35 (2H, s, $PhC\mathbf{H_2}$), 4.07 (2H, s,

$H_2C=C(CH_3)CH_2$), 3.84 (2H, s, $H_2C=CBrCH_2$), 3.52 (2H, $d_{apparent}$, J = 5.9 Hz, $BrC=CHCH_2$), 1.73 (3H, d, J = 1.1 Hz, $(H_3C)C=CHCH_2$).

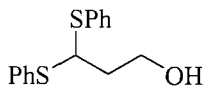
^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4 ($H_2C=C(CH_3)CH_2$), 135.6 (C_{Ar}), 130.2 (HC=CBr), 128.7 (2 x CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.0 (CH_{Ar}), 122.6 (BrC=CH), 115.6 ($H_2C=C(CH_3)CH_2$), 54.8 ($HC=C(CH_3)CH_2$), 52.3 (CH_2Ph), 51.7 ($HC=CBrCH_2$), 44.0 ($BrC=CHCH_2$), 19.5 ($H_2C=C(CH_3)CH_2$).

IR ν_{max} neat (cm^{-1}): 3079 (w), 2975 (w), 1363 (m), 1160 (s), 726 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 393, 395 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{15}H_{19}{}^{79}BrN_2O_2S$: 371.0424, found 371.0424.

3,3-Bis-phenylsulfanyl-propan-1-ol (377)



$C_{15}H_{16}OS_2$
M.w. = 276.42 g/mol
pale yellow oil

To a $CHCl_3$ (15 mL) solution of 3,3-dimethoxypropanoate **376** (957 µL, 6.75 mmol) and thiophenol (693 µL, 6.75 mmol) was added boron trifluoride diethyl etherate (1.5mL, 13.5mmol) at 0 °C. The reaction mixture was stirred for 15 hours and quenched by addition of water. The organic phase was separated and the aqueous phases were extracted with $CHCl_3$. The combined organic solutions were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude thioacetal (1.2 g) as a yellow oil. To a suspension of $LiAlH_4$ (256 mg, 6.75 mmol) in THF (10 mL) was added the solution of crude thioacetal in THF (10 mL) at 0 °C. After being stirred overnight, the reaction was quenched by dropwise addition of 1M NaOH and the insoluble materials were filtered through Celite and washed with ether. The filtrate was concentrated under reduced pressure. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 5% EtOAc/hexane to yield **377** as a pale yellow oil (1.65 g, 5.97 mmol, 89%).

Spectroscopic characteristics are consistent with those reported in the literature.[85, 86]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.47 (5H, m, Ar**H**), 7.38-7.26 (5H, m, Ar**H**), 4.66 (1H, t, J = 7.0 Hz, $HC(SPh)_2$), 3.92 (2H, t, J = 5.9 Hz, CH_2OH), 2.13 (2H, dt, J = 7.0, 5.9 Hz, $CH_2CH(SPh)_2$), 1.65 (1H, s(br), O**H**).

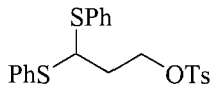
^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9 (2xC_{Ar}), 132.8 (4 x CH_{Ar}), 129.0 (4 x CH_{Ar}), 128.0 (CH_{Ar}), 60.1 (CH_2OH), 55.1 ($CH(SPh)_2$), 38.4 ($CH_2CH(SPh)_2$).

IR ν_{max} neat (cm^{-1}): 3374 (br), 1581 (m), 1478 (s), 1438 (s), 1024 (s), 907 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 299 $[M+Na]^+$ (90).

HRMS (ES^+): Calcd. for $C_{15}H_{16}OS_2Na$: 299.0535, found 299.0532.

Toluene-4-sulfonic acid 3,3-Bis-phenylsulfanyl-propyl ester (379)



$C_{22}H_{22}O_3S_3$
M.w. = 430.61 g/mol
pale brown oil

To a solution of **377** (500 mg, 1.81 mmol) in CH_2Cl_2 (10 mL) was added pyridine (1.43 mL, 18.1 mmol) and *p*-toluenesulfonyl chloride (345 mg, 1.81 mmol) at 0 °C. The reaction mixture was stirred for 15 hours and diluted with water (15 mL). The organic phases were extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with 1M HCl (3 x 15 mL), water (10 mL) and brine (10 mL). The solutions were dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude tosylate **379** as a pale brown oil (700 mg, 1.6 mmol, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.33-7.28 (5H, m, Ar**H**), 7.24-7.20 (7H, m, Ar**H**), 4.36 (1H, t, *J* = 7.3 Hz, **H**C(SPh)$_2$), 4.20 (2H, t, *J* = 5.9 Hz, CH_2OTs), 2.35 (3H, s, ArCH_3), 2.05 (2H, dt, *J* = 7.3, 5.9 Hz, CH_2CH(SPh)$_2$).

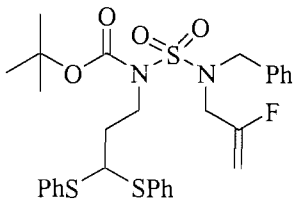
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9 ($C_{Ar}CH_3$), 133.0 (2 x C_{Ar}), 132.9 (C_{Ar}), 129.9 (2 x CH_{Ar}), 129.0 (6 x CH_{Ar}), 128.1 (4 x CH_{Ar}), 127.9 (2 x CH_{Ar}), 67.4 (CH_2OTs), 54.0 ($CH(SPh)_2$), 35.0 ($CH_2CH(SPh)_2$), 21.7 (ArCH_3).

IR ν_{max} neat (cm^{-1}): 3056 (w), 1359 (s), 1175 (s), 1095 (m), 979 (m), 746 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 453 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{22}H_{22}O_3S_3Na$: 453.0623, found 453.0629.

[[[(1.1-dimethylethyl)oxy]carbonyl][3,3-di(phenylsulfanyl)propyl)]amino][(2-fluoro-2-propenyl)(phenylmethyl)amino]dioxo-λ^6-sulfane (378)



$C_{30}H_{35}FN_2O_4S_3$

M.w. = 602.80 g/mol

yellow oil

To a stirred solution of sulfamide **197** (174 mg, 0.51 mmol) in THF (10 mL) was added PPh_3 (174 mg, 0.66 mmol) and a solution of alcohol **377** (140 mg, 0.51 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 20 minutes and DIAD (120 μL, 0.51 mmol) was added at 0 °C. The reaction mixture was stirred for 15 hours and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 5% Et_2O/hexane to afford **378** as a yellow oil (282 mg, 0.47 mmol, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.36 (5H, m, Ar**H**), 7.25-7.15 (10H, m, Ar**H**), 4.64 (1H, dd, $J_{H\text{-}F}$ = 16.1 Hz, J = 3.3 Hz, $\mathbf{H_A}H_BC{=}CFCH_2$), 4.49 (2H, s, $C\mathbf{H_2}Ph$), 4.30 (1H, dd, $J_{H\text{-}F}$ = 47.9 Hz, J = 3.3 Hz, $H_A\mathbf{H_B}C{=}CFCH_2$), 4.33 (1H, t, J = 6.6 Hz, $C\mathbf{H}(SPh)_2$), 3.86 (2H, m, $(PhS)_2(H)CCH_2C\mathbf{H_2}$), 3.75 (2H, d, J = 15.4 Hz, $H_2C{=}CFC\mathbf{H_2}$), 2.17-2.08 (2H, m, $((PhS)_2(H)CC\mathbf{H_2}$), 1.35 (9H, s, $C(C\mathbf{H_3})_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (d, $J_{C\text{-}F}$ = 261.6 Hz, $H_2C{=}\mathbf{C}FCH_2$), 151.2 (**C**O), 135.6 (2x$\mathbf{C}_{Ar}$), 133.7 ($\mathbf{C}_{Ar}$), 133.0 (4 x $\mathbf{C}H_{Ar}$), 129.0 (2 x $\mathbf{C}H_{Ar}$), 128.8 (2x$\mathbf{C}H_{Ar}$), 128.3 (2x$\mathbf{C}H_{Ar}$), 128.1 ($\mathbf{C}H_{Ar}$), 127.9 (2x$\mathbf{C}H_{Ar}$), 94.6 (d, $J_{C\text{-}F}$ = 17.8 Hz, $H_2\mathbf{C}{=}CFCH_2$), 83.8 ($\mathbf{C}(CH_3)_3$), 55.5 ($(PhS)_2(H)C\mathbf{C}H_2$), 52.6 ($\mathbf{C}H_2Ph$), 47.1 (d, $J_{C\text{-}F}$ = 47.0 Hz, $H_2C{=}CF\mathbf{C}H_2$), 35.7 ($(PhS)_2(H)CCH_2\mathbf{C}H_2$), 28.1 ($C(\mathbf{C}H_3)_3$).

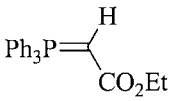
^{19}F NMR (282 MHz, $CDCl_3$) –102.5 (dq, J = 47.3, 17.9 Hz).

IR ν_{max} neat (cm^{-1}): 2975 (w), 1726 (s), 1368 (s), 1142 (s), 928 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 625 $[M+Na]^+$(100).

HRMS (ES^+): Calcd. for $C_{30}H_{35}FN_2O_4S_3Na$: 625.1635, found 625.1633.

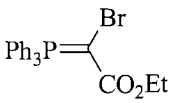
(Triphenyl-λ^5-phosphanylidene)-acetic acid ethyl ether (389)



$C_{22}H_{21}O_2P$
M.w. = 348.37 g/mol
white solid

A solution of ethyl bromoacetate **388** (6.6 mL, 58.86 mmol) in benzene (30 mL) was added dropwise to a solution of PPh_3 (15.7 g, 58.86 mmol) in benzene (30 mL).The reaction mixture was stirred vigorously. The phosphonate salt began precipitating immediately and temperature reached ca. 70 °C within a few minutes. The reaction mixture was allowed to stand for 15 hours. The solid was filtered, washed with benzene and pentane and then dried. The salt was dissolved in water (150 mL) and benzene (100 mL) was added. The stirred mixture was added aqueous NaOH. The benzene layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure to yield **390** as white solid (16 g, 45.9 mmol, 78%).
Spectroscopic characteristics are consistent with those reported in the literatures.[93]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.40 (15H, m, Ar**H**), 4.0 (2H, s(br), $CO_2C\mathbf{H}_2CH_3$), 2.90 (1H, s(br), $Ph_3P{=}C\mathbf{H}(CO_2Et)$), 1.25 (3H, s(br), $CO_2CH_2C\mathbf{H}_3$).

Bromo-(Triphenyl-λ^5-phosphanylidene)-acetic acid ethyl ether (390)



$C_{22}H_{21}O_2P$
M.w. = 348.37 g/mol
white solid

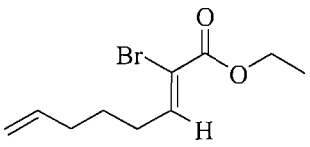
Phosphorane **389** (5 g, 14.35 mmol) was dissolved in CH_2Cl_2 (25 mL) and then added concurrently with a solution of Br_2 (760 μL, 14.78 mmol) in CCl_4 (25 mL) at –70 °C to CH_2Cl_2 (100 mL).The reaction mixture was stirred vigorously before being concentrated under reduced pressure to give a yellow solid. The solid was dissolved in MeOH (50 mL) and treated with aqueous (2N) KOH. The white solid began precipitating immediately. The solid was filtered, washed with hexane and pentane and then dried to yield a white solid **390** (5.2 g, 12.17 mmol, 85%).
Spectroscopic characteristics are consistent with those reported in the literatures.[93]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.40 (15H, m, Ar**H**), 3.90 (2H, s(br), $CO_2CH_2CH_3$), 0.90 (3H, s(br), $CO_2CH_2CH_3$).

IR ν_{max} neat (cm^{-1}): 3058 (w), 2975 (w), 1644 (s), 1437 (m), 1290 (s), 1102 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 427, 428 $[M+Na]^+$ (100).

2-Bromo-octa-2,7-dienoic acid ethyl ester (393)



$C_{10}H_{15}BrO_2$

M.w. = 247.13 g/mol

pale yellow oil

Following the procedure of Boeckman *et al.*,[94] to a stirred solution of **390** (1.5 g, 3.49 mmol) in benzene (10 mL) was added a solution of aldehyde **392** (342 mg, 3.49 mmol) in benzene (10 mL). The reaction mixture was heated at reflux for 15 hours before being quenched with water (15 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 4% Et_2O/hexane to produce **393** as a pale yellow oil (659 mg, 2.67 mmol, 76%).

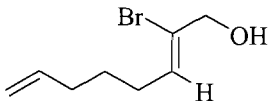
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, t, J = 7.0 Hz, (Br)(CO_2Et)C=C(**H**)(CH_2)), 5.73 (1H, ddt, J = 16.8, 10.2, 6.6 Hz, H_2C=C**H**CH_2), 5.02-4.88 (2H, m, **H**$_2$C=CHCH_2), 4.20 (2H, q, J = 7.3 Hz, $CO_2CH_2CH_3$), 2.29 (2H, q, J = 7.7 Hz, H_2C=CHCH_2), 2.09-2.19 (2H, m, (Br)(CO_2Et)C=C(H)(CH_2)), 1.54 (2H, quintet, J = 7.3 Hz, H_2C=$CHCH_2CH_2$), 1.26 (3H, t, J = 7.3 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (**C**O), 145.7 ((Br)(CO_2Et)C=**C**(H)(CH_2)), 137.8 (H_2C=**C**HCH_2), 116.6 ((Br)(CO_2Et)**C**=C(H)(CH_2)), 115.3 (H_2**C**=CHCH_2), 62.3 (CO_2**C**H_2CH_3), 33.2 (H_2C=CH**C**H_2), 31.5 (H_2C=$CHCH_2$**C**H_2), 27.9 ((Br)(CO_2Et)C=C(H)(**C**H_2)), 14.2 (CO_2CH_2**C**H_3).

IR ν_{max} neat (cm^{-1}): 2980 (w), 1726 (s), 1249 (s), 1038 (m), 911 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 268, 269 $[M+Na]^+$ (100).

2-Bromo-octa-2,7-dien-1-ol (394)



$C_8H_{13}BrO$

M.w. = 205.09 g/mol

pale yellow oil

Following the procedure of Boeckman *et al.*,[94] to a stirred solution of **393** (504 mg, 2.04 mmol) in benzene (10 mL) was a solution of DIBALH in hexane (5.11 mL, 5.11 mmol). The reaction mixture was stirred for 2 hours before being quenched with water (15 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 4% Et_2O/hexane to yield **394** as a pale yellow oil (311 mg, 1.52 mmol, 74%).

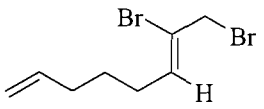
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (1H, t, J = 7.0 Hz, (Br)(HOH_2C)C=C(**H**)(CH_2)), 5.83 (1H, ddt, J = 17.2, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.05 (1H, dq, J = 17.2, 1.8 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.00 (1H, dq, J = 10.2, 1.1 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.27 (2H, dd, J = 6.6, 0.7 Hz, C**H**$_2$OH), 2.24 (2H, q, J = 7.7 Hz, H_2C=CHC**H**$_2$), 2.12 (2H, quintet, J = 7.3 Hz, (Br)(HOH_2C)C=C(H)(C**H**$_2$)), 1.90 (1H, t, J = 6.6 Hz, CH_2O**H**), 1.61-1.50 (2H, m, H_2C=$CHCH_2$C**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (H_2C=**C**HCH_2), 130.1 ((Br)(HOH_2C)C=**C**(H)(CH_2)), 126.9 ((Br)(HOH_2C)**C**=C(H)(CH_2)), 114.9 (H_2**C**=$CHCH_2$), 68.5 (**C**H_2OH), 33.2 (H_2C=CH**C**H_2), 30.3 (H_2C=$CHCH_2$**C**H_2), 27.5 ((Br)(HOH_2C)C=C(H)(**C**H_2)).

IR ν_{max} neat (cm^{-1}): 3309 (br), 2925 (m), 2858 (w), 1091 (m), 992 (s), 910 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 228, 229 $[M+Na]^+$ (100).

7,8-Dibromo-octa-1,6-diene (395)



$C_8H_{12}Br_2$
M.w. = 267.99 g/mol
pale yellow oil

To a cooled stirred solution of **394** (256 mg, 1.25 mmol) in Et_2O (10 mL) was added a solution of PBr_3 (733 μL, 2.75 mmol) in Et_2O (10 mL) dropwise. After stirring for 10 minutes at 0°C, the reaction mixture was continued stirring for 20 minutes and added brine (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3x15 mL). The combined organic phases were washed with sat'd $NaHCO_3$ (15 mL) and brine until neutral. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to yield a crude product as a pale yellow oil **395** (100 mg, 0.37 mmol, 30%) used directly for next step without further purification.

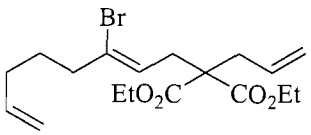
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12-5.94 (1H, m, (Br)(BrH_2C)C=C(**H**)(CH_2)), 5.73 (1H, ddt, *J* = 16.8, 10.3, 6.6 Hz, H_2C=C**H**CH_2), 5.01-4.88 (2H, m, **H_2**C=$CHCH_2$), 4.17 (2H, s, C**H_2**Br), 2.24 (2H, q, *J* = 7.7 Hz, H_2C=CHC**H_2**), 2.15 (2H, q, *J* = 7.3 Hz, (Br)(BrH_2C)C=C(H)(C**H_2**)), 1.54-1.40 (2H, m, H_2C=$CHCH_2$C**H_2**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0 (H_2C=**C**HCH_2), 134.5 ((Br)(BrH_2C)C=**C**(H)(CH_2)), 115.3 (H_2**C**=$CHCH_2$), 115.1 ((Br)(BrH_2C)**C**=C(H)(CH_2)), 38.9 (**C**H_2Br), 33.2 (H_2C=CH**C**H_2), 31.0 (H_2C=$CHCH_2$**C**H_2), 27.2 ((Br)(Br H_2C)C=C(H)(**C**H_2)).

IR ν_{max} neat (cm^{-1}): 2926 (m), 1263 (m), 1211 (m), 955 (s), 911 (s).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 290, 291 $[M+Na]^+$(100).

2-Allyl-2-(3-bromo-octa-2,7-dienyl)-malonic acid diethyl ester (396)



$C_{18}H_{27}BrO_4$

M.w. = 387.31 g/mol

pale yellow oil

To a stirred solution of diethylallyl malonate **319** (69 μL, 0.35 mmol) in THF (5 mL) was added *t*-BuOK (43 mg, 0.39 mmol) and 18-crown-6 (103 mg, 0.39 mmol). After stirring for 30 minutes, a solution of bromo compound **395** (94 mg, 0.35 mmol) was added. The reaction mixture was stirred for 4 hours before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product as yellow oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% Et_2O/hexane to yield **396** as a pale yellow oil (72 mg, 0.19 mmol, 54%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81-5.53 (2H, m, H_2C=C**H**CH_2), 5.09-4.86 (4H, m H_2C=CHC**H**$_2$), 4.21-4.02 (4H, m, CO_2C**H**$_2$$CH_3$), 3.15-3.06 (2H, m, ($CH_2$)(Br)C=CHC**H**$_2$), 2.71-2.64 (2H, m, H_2C=CHC**H**$_2$C(CO_2Et)$_2$), 2.09 (2H, q, J = 7.3 Hz, H_2C=CHC**H**$_2$), 2.04-1.94 (2H, m, H_2C=CH(CH_2)$_2$C**H**$_2$), 1.42 (2H, quintet, J = 7.3 Hz, H_2C=CHCH$_2$C**H**$_2$), 1.19 (6H, q, J = 7.3 Hz, CO_2CH_2C**H**$_3$) .

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (2 x **C**O_2Et), 138.2 ((CH_2)(Br)**C**=$CHCH_2$) 134.1 (H_2C=**C**HCH_2), 132.4 (H_2C=**C**$HCH_2C(CO_2Et)_2$), 120.9 (H_2**C**=$CHCH_2$), 114.9 ((H_2**C**=$CHCH_2C(CO_2Et)_2$), 61.4 (2 x CO_2**C**H_2CH_3), 57.2 (**C**($CO_2CH_2CH_3$)$_2$), 43.2 (H_2C=CH(CH_2)$_2$**C**H_2), 36.1 (H_2C=CH**C**$H_2C(CO_2Et)_2$), 33.2 (H_2C=CH**C**H_2), 31.0 (H_2C=$CHCH_2$**C**H_2), 27.5 ((CH_2)(Br)C=CH**C**H_2), 14.0 (2 x CO_2CH_2**C**H_3).

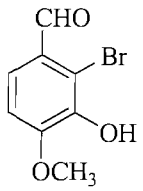
IR ν_{max} neat (cm^{-1}): 2980 (m), 1731 (s), 1211 (s), 915 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 409, 410 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{18}H_{27}{}^{79}BrO_4Na$: 409.0985, found 409.0976.

4.4 Procedures relating to research described in Chapter 3

1-(2-Bromo-3-hydroxy-4-methoxyphenyl)-1-ethanone (427)



$C_8H_7BrO_3$
M.w. = 231.04 g/mol
white solid

To a stirred solution of isovanillin **426** (3.00 g, 19.72 mmol), NaOAc (3.2 g, 39.43 mmol) and Fe (powder) (110 mg, 1.97 mmol) in AcOH (100 mL) was added a solution of Br_2 (1.10 mL, 21.49 mmol) in AcOH (20 mL). After stirring for an hour, the reaction mixture was poured onto ice-cold water (200 mL). The resulting solid was collected by filtration, washed with ice-cold water and dried at reduced pressure over P_2O_5 to give the title compound **427** (3.89 g, 16.84 mmol, 85%) as a powdery white solid.

Spectroscopic characteristics are consistent with those reported in the literature.[115]

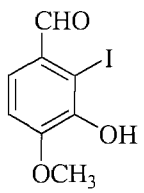
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (1H, s, ArC**H**O), 7.51 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.86 (1H, d, *J* = 8.4 Hz, Ar**H**), 5.90 (1H, s, ArO**H**), 3.95 (3H, s, ArOC**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0 (**C**HO), 151.7 (**C**$_{Ar}$OCH$_3$), 143.2 (**C**$_{Ar}$OH), 127.3 (**C**$_{Ar}$CHO), 122.8 (**C**H$_{Ar}$), 112.9 (**C**$_{Ar}$Br), 109.3 (**C**H$_{Ar}$), 56.6 (O**C**H$_3$).

IR ν_{max} neat (cm^{-1}): 3196 (br), 1666 (s), 1276 (m), 1016 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 253, 254 $[M+Na]^+$ (100).

1-(3-hydroxy-2-iodo-4-methoxyphenyl)-1-ethanone (438)



$C_8H_7IO_3$
M.w. = 278.04 g/mol
yellow solid

To a stirred solution of isovanillin **426** (2.00 g, 13.14 mmol) in pyridine (8 mL) at 0 °C was added a solution of ICl (2.13 g, 13.14 mmol) in dioxane (13 mL). The reaction mixture was stirred at RT for 6 days. The solvents were removed under

reduced pressure to give a brown oil which was added to water (50 mL) and acidified with 6N HCl. The mixture was extracted with EtOAc (2 x 15 mL) and organic extracts were washed successively with 5% sodium bisulfite solution (2 x 20 mL), water (2 x 20 mL) and brine (50 mL). The EtOAc solutions were dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound **438** as a powdery yellow solid (7.60 g, 27.60 mmol, 70%).

Spectroscopic characteristics are consistent with those reported in the literature.[120]

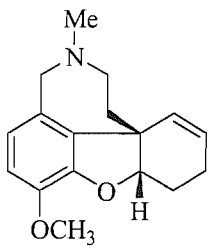
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (1H, s, ArC**H**O), 7.56 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.93 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.30 (1H, s, Ar**OH**), 3.95 (3H, s, ArOC**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7 (**C**HO), 150.7 (**C**$_{Ar}$OCH$_3$), 145.7 (**C**$_{Ar}$OH), 128.8 (**C**$_{Ar}$CHO), 123.8 (**C**H$_{Ar}$), 109.3 (**C**H$_{Ar}$), 88.0 (**C**$_{Ar}$I), 56.6 (O**C**H$_3$).

IR ν_{max} neat (cm^{-1}): 3267 (br), 1668 (s), 1583 (m), 1487 (m), 1281 (s), 1012 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 301 $[M+Na]^+$ (100).

3-methoxy-11-methyl-5,6,9,10,11,12-hexahydro-4a*H*-4-oxa-11-azacyclohepta[*de*]fluorine (454)



$C_{17}H_{21}NO_2$

M.w. = 271.35 g/mol

colourless oil

Following the procedure of Trost *et al.*,[112] to a stirred solution of **472** (73 mg, 0.19 mmol) in CH_2Cl_2 (2.5 mL) was added TFA (0.5 mL) at RT. After stirring for 30 minutes, MeOH (5 mL) was added and the mixture was cooled to 0 °C. Molecular sieves (4 Å) and $NaCNBH_3$ (12 mg, 0.19 mmol) were added. The reaction mixture was stirred for an hour before being quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 1% Et_3N/EtOAc to yield the title compound **454** as a colourless oil (37 mg, 0.13 mmol, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (1H, d, J = 8.0 Hz, Ar**H**), 6.54 (1H, d, J = 8.5 Hz, Ar**H**), 6.00 (1H, d(br), J = 10.1 Hz, **H**C=CH), 5.81 (1H, dd, J = 10.0, 5.5 Hz, HC=C**H**), 4.59 (1H, s(br), **H**C(O)), 4.11 (1H, d, J = 15.1 Hz, ArC**H**$_A$H$_B$N(CH$_3$)), 3.83 (3H, s, ArOC**H**$_3$), 3.64 (1H, d, J = 15.1 Hz, ArCH$_A$**H**$_B$N(CH$_3$)), 3.33 (1H, td, J = 15.6, 1.5 Hz, C**H**$_A$H$_B$N(CH$_3$)), 3.06 (1H, dt, J = 14.6, 3.5 Hz, CH$_A$**H**$_B$N(CH$_3$)), 2.42-2.32 (5H, m, N(C**H**$_3$), HC=CHCH$_2$C**H**$_2$), 2.14 (1H, td, J = 15.6, 3.0 Hz, HC=CHC**H**$_A$H$_B$CH$_2$), 1.99 ((1H, dt, J = 16.6, 6.0 Hz, HC=CHCH$_A$**H**$_B$CH$_2$), 1.82-1.72 (1H, m, N(CH$_3$)CH$_2$C**H**$_A$H$_B$), 1.63 (1H, ddd, J = 14.5, 4.0, 1.5 Hz, N(CH$_3$)CH$_2$CH$_A$**H**$_B$).

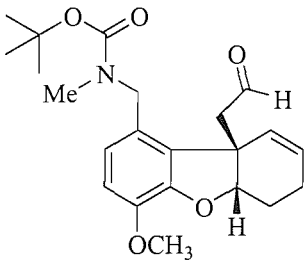
^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1 (**C**$_{Ar}$OCH$_3$), 144.2 (**C**$_{Ar}$(O)), 133.9 (H**C**=**C**H), 127.4 (**C**$_{Ar}$CH$_2$N(**C**H$_3$)), 126.0 (**C**$_{Ar}$), 121.5 (**C**H$_{Ar}$) 111.0 (**C**H$_{Ar}$), 89.0 ((O)**C**(CH$_2$)), 60.5 (Ar**C**H$_2$N(CH$_3$)), 56.0 (ArO**C**H$_3$), 53.9 (N(CH$_3$)**C**H$_2$), 48.1 (N(**C**H$_3$)), 41.8 (**C**), 35.0 (N(CH$_3$)$_3$CH$_2$**C**H$_2$), 22.6 (**C**H$_2$), 19.9 (**C**H$_2$).

IR ν_{max} neat (cm^{-1}): 2914 (m), 1505 (s), 1435 (s), 1278 (m), 1040 (s), 714 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 294 $[M+Na]^+$(30), 271 $[M+H]^+$ (100).

HRMS (ES^+): Calcd. for $C_{17}H_{22}NO_2$: 272.1645, found 272.1640.

***tert*-Butyl *N*-[[4-methoxy-9a-(2-oxoethyl)-5a, 6, 7, 9a-tetrahydrodibenzo[*b*,*d*]furan-1-yl]methyl]-*N*-methylcarbamate (472)**



$C_{22}H_{29}NO_5$
M.w. = 387.47 g/mol
colourless oil

Following the procedure of Ireland *et al.*,[124] to a stirred solution of **501** (237 mg, 0.61 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (337 mg, 0.79 mmol). The reaction mixture was stirred for 3 hours and concentrated under reduced pressure to yield the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 30% EtOAc/hexane to yield the title compound **472** as a colourless oil (224 mg, 0.58 mmol, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (1H, s(br), C**H**O), 6.75 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.63 (1H, d, *J* = 8.4 Hz, Ar**H**), 5.95-5.84 (2H, m, **H**C=C**H**), 4.89-4.80 (1H, m, **H**C(O)), 4.50 (2H, dt, *J* = 16.1, 15.4 Hz, $CH_2N(CH_3)(Boc)$), 3.89 (3H, s, $ArOCH_3$), 3.10-2.90 (1H, m, CH_AH_BCHO), 2.88-2.70 (4H, m, $CH_A\mathbf{H_B}CHO$ $CH_2N(CH_3)(Boc)$), 2.30-1.80 (4H, m, $HC{=}CHCH_2CH_2$), 1.48 (9H, s, $NCO_2C(CH_3)_3$).

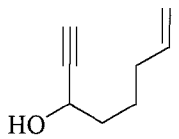
^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2 (**C**HO), 156.2 ($CO_2C(CH_3)_3$), 148.0 ($C_{Ar}OCH_3$), 145.0 (C_{Ar}(O)), 131.0 ($C_{Ar}CH_2N(CH_3)(Boc)$), 129.4 (H**C**=**C**H), 127.9 (CH_{Ar}) 125.9 (C_{Ar}), 111.9 (CH_{Ar}), 87.0 ((O)**C**(CH_2)), 80.5 ($CO_2C(CH_3)_3$), 60.8 ($CH_2N(CH_3)(Boc)$), 56.3 ($ArOCH_3$), 48.4 (CH_2CHO), 33.8 (**C**), 28.8 ($CO_2C(CH_3)_3$), 24.1 (CH_2), 21.4 ($CH_2N(CH_3)(Boc)$), 20.1 (CH_2).

IR ν_{max} neat (cm^{-1}): 2931 (m), 1688 (s), 1505 (m), 1390 (m), 1366 (m), 1239 (m), 1140 (s), 1044 (s), 872 (m).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 442 $[M+Na+MeOH]^+$ (100).

HRMS (ES^+): Calcd. for $C_{22}H_{30}O_5N$: 388.2118, found 388.2117.

Oct-7-en-1-yn-3-ol (476)



$C_8H_{12}O$

M.w. = 124.18 g/mol

pale yellow oil

A solution of 5-hexenal **393** (790 mg, 8.07 mmol) in THF (10 mL) was added dropwise to a solution of ethynylmagnesium bromide (0.5 M in THF, 19.36 mL, 9.68 mmol) at –60 °C. After stirring for an hour at –60 °C, the reaction mixture was allowed to warm to RT, sat'd NH_4Cl (10mL) and water (10 mL) were then added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (15 g) eluting with 5% Et_2O/hexane to yield the title compound **476** as a pale yellow oil (450 g, 3.62 mmol, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, ddt, *J* = 16.8, 10.2, 6.6 Hz, $H_2C{=}C\mathbf{H}CH_2$), 5.05 (1H, ddt, *J* = 17.2, 2.2, 1.5 Hz, $\mathbf{H_A}H_BC{=}CHCH_2$), 4.99 (1H, ddt, *J* = 9.9, 1.8, 1.5

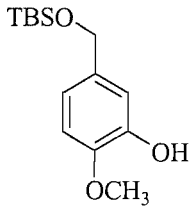
Hz, H_AH_BC=$CHCH_2$), 4.41 (1H, qd, J = 6.6, 2.2 Hz, C**H**(OH)), 2.48 (1H, q, J = 2.2 Hz, **H**C_{alkyne}), 2.12 (2H, qt, J = 7.3, 1.1 Hz, H_2C=$CHCH_2$), 1.83-1.71 (3H, m, CH(O**H**), H_2C=$CH(CH_2)_2CH_2$), 1.66-1.56 (2H, m, H_2C=$CHCH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (H_2C=**C**HCH_2), 114.9 (H_2**C**=$CHCH_2$), 72.9 (**C**$_{alkyne}$), 62.2 (**C**$_{alkyne}$H), 60.4 (**C**H(OH)), 37.0 (H_2C=$CH(CH_2)_2$**C**H_2), 33.2 (H_2C=CH**C**H_2), 21.0 (H_2C=$CHCH_2$**C**H_2).

IR ν_{max} neat (cm^{-1}): 3300 (br), 3297 (s), 2925 (s), 2861 (m), 1028(m), 995 (s), 909 (s), 628 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 271 $[2M+Na]^+$ (100).

5-([(1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy]methyl)-2-methoxyphenol (478)



$C_{14}H_{24}O_3Si$

M.w. = 268.42 g/mol

white solid

To a stirred solution of **477** (340 mg, 2.20 mmol in CH_2Cl_2 (10 mL) was added DMAP (11 mg, 0.09 mmol) and Et_3N (307 μL, 2.20 mmol). After stirring for 10 minutes, TBDMSCl (332 mg, 2.20 mmol) was added. The reaction mixture was stirred for 15 hours and then quenched with sat'd NH_4Cl (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (15g) eluting with 5% Et_2O/hexane to yield the title compound **478** as a white solid (393 mg, 1.46 mmol, 67%).

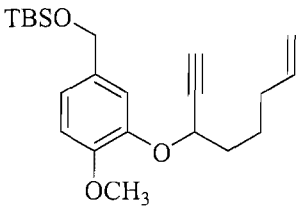
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (1H, m Ar**H**), 6.85 (2H, m, Ar**H**), 5.83 (1H, s, ArO**H**), 4.69 (2H, s, C**H**$_2$OTBS), 3.86 (3H, s, ArOC**H**$_3$), 0.99 (C(C**H**$_3$)$_3$), 0.15 (2 x C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7 (**C**$_{Ar}$$OCH_3$), 145.6 (**C**$_{Ar}$OH), 134.8 (**C**$_{Ar}$$CH_2$OTBS), 118.1 (**C**H$_{Ar}$), 112.9 (**C**H$_{Ar}$), 110.5 (**C**H$_{Ar}$), 64.8 (**C**H$_2$OTBS), 56.0 (O**C**H$_3$), 26.0 (C(**C**H$_3$)$_3$), 18.5 (**C**(CH$_3$)$_3$), –4.8 (2 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 3547 (br), 2951 (m), 2927 (m), 2853 (m), 1509 (m), 1272 (m), 1253 (m), 1076 (m), 1028 (m), 832 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 291 $[M+Na]^+$ (100).

***tert*-Butyl-[(3-[[1-(1-ethynyl)-5-hexenyl]oxy]-4-methoxybenzyl)oxy]dimethylsilane (479)**



$C_{22}H_{34}O_3Si$

M.w. = 374.59 g/mol

yellow oil

Following the procedure of Hughes *et al.*,[88] to a stirred solution of **478** (381 mg, 1.42 mmol) in THF (10 mL) was added PPh_3 (459 mg, 1.70 mmol) and a solution of **476** (176 mg, 1.42 mmol) in THF (10 mL). After stirring for 5 minutes, DIAD (559 μL, 2.84 mmol) was added. The reaction mixture was heated at reflux for 8 hours and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (15 g) eluting with 8% Et_2O/hexane to yield the title compound **479** as a yellow oil (13.3 mg, 0.04 mmol, 3%) and recovered starting material **478** as a yellow oil (110 mg, 0.41 mmol, 29%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (1H, d, J = 1.8 Hz, Ar**H**), 6.94-6.80 (2H, m, Ar**H**), 5.83 (1H, ddt, J = 17.2, 10.1, 6.6 Hz, H_2C=C**H**CH_2), 5.05 (1H, ddt, J = 17.2, 1.8, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.00-4.95 (1H, m, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.76 (1H, td, J = 6.6, 1.8 Hz, **H**C(O)), 4.67 (2H, s, C$\mathbf{H_2}$OTBS), 3.84 (3H, s, ArOC$\mathbf{H_3}$), 2.43 (1H, d, J = 2.3 Hz, **H**C_{alkyne}), 2.20-2.10 (2H, m, H_2C=CHC$\mathbf{H_2}$), 2.07-1.95 (2H, m, H_2C=$CH(CH_2)_2C\mathbf{H_2}$), 1.76-1.64 (2H, m, H_2C=$CHCH_2C\mathbf{H_2}$), 0.94 (C(C$\mathbf{H_3}$)$_3$), 0.09 (2 x C$\mathbf{H_3}$).

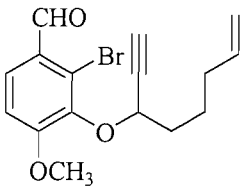
^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3 (**C**$_{Ar}$$OCH_3$), 146.8 (**C**$_{Ar}$(O)), 138.4 ($H_2C$=**C**$HCH_2$), 134.0 (**C**$_{Ar}$$CH_2$OTBS), 119.9 (**CH**$_{Ar}$), 115.2 (**CH**$_{Ar}$), 114.8 ($H_2$**C**=$CHCH_2$), 112.0 (**CH**$_{Ar}$), 74.6 (**C**$_{alkyne}$), 69.0 (**C**H(O)), 64.7 (**CH**$_{alkyne}$), 56.1 (O**C**H_3), 35.1 (H_2C=$CH(CH_2)_2\mathbf{C}H_2$), 33.3 (H_2C=$CH\mathbf{C}H_2$), 26.0 (C(**C**H_3)$_3$), 24.4 (H_2C=$CHCH_2\mathbf{C}H_2$), 18.4 (**C**$(CH_3)_3$), –1.7 (2 x **C**H_3).

IR ν_{max} neat (cm^{-1}): 3305 (br), 2927 (m), 2854 (m), 1461 (w), 1249, 1081 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 397 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{22}H_{34}O_3SiNa$: 397.2169, found 397.2173.

1-(2-Bromo-3-[[1-ethynyl-5-hexenyl]oxy]-4-methoxyphenyl)-1-ethanone (480)



$C_{16}H_{17}BrO_3$

M.w. = 337.21 g/mol

pale yellow oil

Following the procedure of Hughes *et al.*,[88] to a stirred solution of **427** (372 mg, 1.61 mmol) in THF (10 mL) was added PPh_3 (465 mg, 1.77 mmol) and a solution of **476** (200 mg, 1.61 mmol) in THF (10 mL). After stirring for 5 minutes, DIAD (349 μL, 1.77 mmol) was added. The reaction mixture was heated at reflux for 8 hours and then concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 4% EtOAc/hexane to yield the title compound **480** as a pale yellow oil (221 mg, 0.66 mmol, 37%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (1H, s, ArC**H**O), 7.73 (1H, d, *J* = 8.7 Hz, Ar**H**), 6.95 (1H, d, *J* = 8.7 Hz, Ar**H**), 5.85 (1H, ddt, *J* = 17.4, 10.6, 6.4 Hz, H_2C=C**H**CH_2), 5.16 (1H, td, *J* = 6.4, 2.3 Hz, **H**C(O)), 5.06 (1H, ddt, *J* = 17.2, 1.9, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.99 (1H, ddt, *J* = 10.2, 2.3, 1.1 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 3.95 (3H, s, ArOC$\mathbf{H_3}$), 2.37 (1H, d, *J* = 2.3 Hz, $\mathbf{H}C_{alkyne}$), 2.17 (2H, qt, *J* = 7.2, 1.5 Hz, H_2C=$CHC\mathbf{H_2}$), 2.08-1.97 (2H, m, H_2C=$CH(CH_2)_2C\mathbf{H_2}$), 1.87-1.65 (2H, m, H_2C=$CHCH_2C\mathbf{H_2}$) .

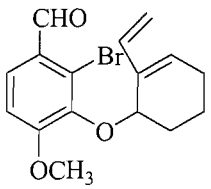
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2 (**C**HO), 158.6 ($\mathbf{C}_{Ar}OCH_3$), 143.6 ($\mathbf{C}_{Ar}$(O)), 138.3 (H_2C=**C**HCH_2), 127.5 ($\mathbf{C}_{Ar}$CHO), 126.5 ($\mathbf{C}H_{Ar}$), 124.1 ($\mathbf{C}_{Ar}$Br), 114.9 ($H_2\mathbf{C}$=$CHCH_2$), 110.8 ($\mathbf{C}H_{Ar}$), 81.2 ($\mathbf{C}_{alkyne}$), 75.4 (**C**H(O)), 71.6 ($\mathbf{C}H_{alkyne}$), 56.2 (O**C**H_3), 35.2 (H_2C=$CH(CH_2)_2\mathbf{C}H_2$), 33.3 (H_2C=$CH\mathbf{C}H_2$), 24.2 (H_2C=$CHCH_2\mathbf{C}H_2$).

IR ν_{max} neat (cm^{-1}): 3297 (m), 2938 (m), 2863 (m), 1680 (s), 1577 (s), 1274 (s), 1249 (s), 1025 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 360, 361 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{17}{}^{79}BrO_3Na$: 359.0253, found 359.0256.

1-[2-Bromo-4-methoxy-3-[2-vinyl-2-cyclohexenyl)oxy]phenyl]-1-ethanone (481)



$C_{16}H_{17}BrO_3$
M.w. = 337.21 g/mol
white solid

To a stirred solution of **480** (190 mg, 0.56 mmol) in CH_2Cl_2 (7 mL) was added a solution of the first generation Grubbs catalyst **3** (46 mg, 56 μmol) in CH_2Cl_2 (5 mL). The reaction mixture was heated at reflux for 10 hours and then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% EtOAc/hexane to afford the cyclised product **481** as a white solid (159 mg, 0.47 mmol, 84%).

Mpt. = 85 °C (EtOAc:Hexane)

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (1H, s, ArC**H**O), 7.69 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.94 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.34 (1H, dd, *J* = 17.9, 11.0 Hz, H_2C=C**H**), 6.08 (1H, dd, *J* = 4.8, 2.2 Hz, **H**C=C(HC=CH_2), 5.38 (1H, t, *J* = 3.3 Hz, **H**C(O)), 5.34 (1H, d, *J* = 18.3 Hz, $\mathbf{H_A}H_BC$=CH), 4.89 (1H, d, *J* = 11.0 Hz, $H_A\mathbf{H_B}C$=CH), 3.96 (3H, s, ArOC$\mathbf{H_3}$), 2.40-2.20 (2H, m, C=CH(CH_2)$_2$C$\mathbf{H_2}$), 2.19-1.97 (2H, m, C=CHC$\mathbf{H_2}$), 1.68-1.46 (2H, m, C=CHCH$_2$C$\mathbf{H_2}$).

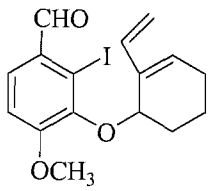
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8 (**C**HO), 158.6 (**C**$_{Ar}$OCH$_3$), 144.7 (**C**$_{Ar}$(O)), 138.4 (HC=**C**(HC=CH_2), 135.8 (H_2C=**C**H), 133.4 (**C**$_{Ar}$CHO), 128.0 (H**C**=C(HC=CH_2), 125.7 (**C**H$_{Ar}$), 124.2 (H_2**C**=CH), 112.1 (**C**H$_{Ar}$), 111.0 (**C**$_{Ar}$Br), 73.4 (**C**H(O)), 56.3 (O**C**H$_3$), 28.3 (**C**H$_2$), 26.2 (**C**H$_2$), 17.8 (**C**H$_2$).

IR ν_{max} neat (cm^{-1}): 2936 (w), 2862 (w), 1679 (s), 1574 (s), 1477 (m), 1271 (s), 1246 (s), 1023 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 360, 361 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{16}H_{17}{}^{79}BrO_3Na$: 359.0253, found 359.0253.

2-Iodo-4-methoxy-3-[(2-vinyl-2-cyclohexenyl)oxy]benzaldehyde (483)



$C_{16}H_{17}IO_3$

M.w. = 384.21 g/mol

white solid

To a stirred solution of **484** (65 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added a solution of the first generation Grubbs catalyst **3** (14 mg, 17 μmol) in CH_2Cl_2 (2 mL). The reaction mixture was heated at reflux for 12 hours and concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 5% Et_2O/hexane to afford the cyclised product **483** as a white solid (40 mg, 0.10 mmol, 62%).

Mpt. = 114 °C (Et_2O:Hexane)

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (1H, s, ArC**H**O), 7.64 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.95 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.30 (1H, dd, *J* = 17.6, 11.0 Hz, H_2C=C**H**), 6.04 (1H, dd, *J* = 4.8, 2.6 Hz, **H**C=C(HC=CH_2), 5.42 (1H, t, *J* = 3.3 Hz, **H**C(O)), 5.16 (1H, d, *J* = 17.6 Hz, $\mathbf{H_A}H_BC$=CH), 4.83 (1H, d, *J* = 11.0 Hz, $H_A\mathbf{H_B}C$=CH), 3.96 (3H, s, ArOC$\mathbf{H_3}$), 2.42-2.03 (4H, m, C=CH(CH_2)$_2$C$\mathbf{H_2}$, C=CHC$\mathbf{H_2}$), 1.69-1.48 (2H, m, C=CHCH_2C$\mathbf{H_2}$).

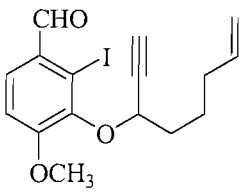
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8 (**C**HO), 158.6 ($\mathbf{C}_{Ar}OCH_3$), 144.7 ($\mathbf{C}_{Ar}$(O)), 138.4 (HC=**C**(HC=CH_2), 135.8 (H_2C=**C**H), 133.4 ($\mathbf{C}_{Ar}$CHO), 128.0 (HC=C(H**C**=CH_2), 125.7 (**C**H_{Ar}), 124.2 (H_2**C**=CH), 112.1 (**C**H_{Ar}), 111.0 ($\mathbf{C}_{Ar}$I), 73.4 (**C**H(O)), 56.3 (O**C**H_3), 28.3 (**C**H_2), 26.2 (**C**H_2), 17.8 (**C**H_2).

IR ν_{max} neat (cm^{-1}): 2936 (m), 2840 (w), 1681 (s), 1571 (s), 1473 (m), 1271 (s), 1246 (s), 1021 (m).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 791 $[2M+Na]^+$(100).

HRMS (ES$^+$): Calcd. for $C_{16}H_{17}IO_3Na$: 407.01145, found 407.01179.

3-[1-(1-ethynyl)-5-hexenyl)-2-iodo]-4-methoxybenzaldehyde (484)



$C_{16}H_{17}IO_3$
M.w. = 384.21 g/mol
yellow oil

Method A:

Following the procedure of Hughes *et al.*,[88] to a stirred solution of **438** (225 mg, 0.81 mmol) in THF (15 mL) was added PPh_3 (218 mg, 1.62 mmol) and a solution of **476** (100 mg, 0.81 mmol) in THF (8 mL). After stirring for 5 minutes, DIAD (319 μL, 1.62 mmol) was added. The reaction mixture was heated at reflux for 8 hours and concentrated under reduced pressure to yield the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 4% EtOAc/hexane to yield the title compound **484** as a yellow oil (150 mg, 0.39 mmol, 48%).

Method B:

Following the procedure of Kiankarimi *et al.*,[116] to a stirred solution of **438** (1.12 g, 4.03 mmol) in THF (30 mL) was added *n*-Bu_3P (1.2 mL, 4.84 mmol) and a solution of **476** (500 mg, 4.03 mmol) in THF (10 mL). After stirring for 5 minutes, a solution of DBAD (1.85 g, 8.05 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 15 hours and then quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 15% Et_2O/hexane to yield the title compound **484** as a yellow oil (865 mg, 2.25 mmol, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (1H, s, ArC**H**O), 7.72 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.98 (1H, d, *J* = 8.4 Hz, Ar**H**), 5.87 (1H, ddt, *J* = 17.2, 10.2, 6.6 Hz, H_2C=C**H**CH_2), 5.24 (1H, td, *J* = 6.2, 2.2 Hz, **H**C(O)), 5.07 (1H, ddt, *J* = 16.8, 1.8, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 5.03-4.97 (1H, m, $H_A\mathbf{H_B}C$=$CHCH_2$), 3.90 (3H, s, ArOC**H**$_3$), 2.36 (1H, d, *J* = 2.2 Hz, **H**C_{alkyne}), 2.19 (2H, qt, *J* = 7.0, 1.5 Hz,

H_2C=CHC**H_2**), 2.11-2.02 (2H, m, H_2C=CH(CH_2)$_2$C**H_2**), 1.89-1.69 (2H, m, H_2C=CHCH_2C**H_2**) .

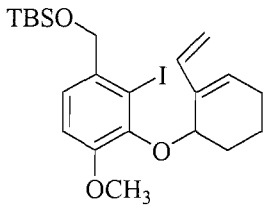
^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5 (**C**HO), 157.5 (**C**$_{Ar}$OCH$_3$), 145.9 (**C**$_{Ar}$(O)), 138.4 (H_2C=**C**HCH_2), 128.0 (**C**$_{Ar}$CHO), 127.2 (**C**H$_{Ar}$), 114.9 (H_2**C**=CHCH_2), 111.9 (**C**H$_{Ar}$), 102.0 (**C**$_{Ar}$I), 81.3 (**C**$_{alkyne}$), 75.9 (**C**H(O)), 71.4 (**C**H$_{alkyne}$), 56.2 (O**C**H$_3$), 35.3 (H_2C=CH(CH_2)$_2$**C**H_2), 35.3 (H_2C=CH**C**H_2), 24.4 (H_2C=CHCH_2**C**H_2).

IR ν_{max} neat (cm^{-1}): 3288 (m), 2936 (m), 2842 (m), 1677 (s), 1572 (s), 1270 (s), 1243 (s), 1049 (w).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 407 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{17}IO_3Na$: 407.01145, found 407.01180.

***tert*-Butyl-([2-iodo-4-methoxy-3-[(2-vinyl-2-cyclohexenyl)oxy]benzyl]dimethylsilane (485)**



$C_{22}H_{33}IO_3Si$

M.w. = 500.49 g/mol

white solid

To a solution of the corresponding alcohol (463 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) was added DMAP (15 mg, 0.12 mmol), imidazole (82 mg, 1.20 mmol) and Et_3N (167 μL, 1.20 mmol). After stirring for 10 minutes, TBDMSCl (181 mg, 1.20 mmol) was added. The reaction mixture was stirred for 12 hours and quenched with sat'd NH_4Cl (15mL) and water (15 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 10% Et_2O/hexane to yield the title compound **485** as a white solid (570 mg, 1.14 mmol, 95%).

Mpt. = 95 °C (Et_2O:Hexane)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.91 (1H, d, *J* = 8.4 Hz, Ar**H**), 6.34 (1H, dd, *J* = 17.6, 11.0 Hz, H_2C=C**H**), 6.03 (1H, dd, *J* = 4.0, 3.3 Hz, **H**C=C(HC=CH_2), 5.46 (1H, t, *J* = 3.3 Hz, **H**C(O)), 5.16 (1H, d, *J* = 17.6 Hz, $\mathbf{H_A}H_B$C=CH), 4.87 (1H, d, *J* = 11.3 Hz, $H_A\mathbf{H_B}$C=CH), 4.63 (1H, d, *J* = 15.1 Hz,

ArC**H**$_A$H$_B$OTBS), 4.57 (1H, d, *J* = 15.1 Hz, ArCH$_A$**H**$_B$OTBS), 3.90 (3H, s, ArOC**H**$_3$), 2.39-2.00 (4H, m, C=CH(CH$_2$)$_2$C**H**$_2$, C=CHC**H**$_2$), 1.63-1.43 (2H, m, C=CHCH$_2$C**H**$_2$), 0.98 (9H, s, C(C**H**$_3$)$_3$), 0.13 (6H, s, 2 x C**H**$_3$).

^{13}C NMR (75 MHz, CDCl$_3$) δ 151.4 (**C**$_{Ar}$(O)), 146.2 (**C**$_{Ar}$OCH$_3$), 138.2 (HC=**C**(HC=CH$_2$), 136.2 (**C**$_{Ar}$CH$_2$OTBS), 132.4 (H$_2$C=**C**H), 121.4 (H**C**=C(HC=CH$_2$), (**C**H$_{Ar}$), 112.2 (H$_2$**C**=CH), 111.9 (**C**H$_{Ar}$), 111.0 (**C**$_{Ar}$I), 72.6 (**C**H(O)), 69.7 (**C**H$_2$OTBS), 55.9 (O**C**H$_3$), 28.1 (**C**H$_2$), 26.0 (C(**C**H$_3$)$_3$), 25.9 (**C**H$_2$), 18.4 (**C**(CH$_3$)$_3$), 17.8 (**C**H$_2$), –5.0 (2 x **C**H$_3$).

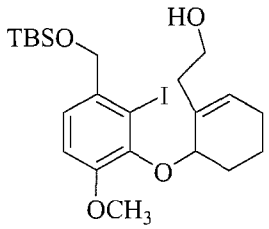
IR ν_{max} neat (cm^{-1}): 2953 (m), 2929 (m), 1475 (s), 1252 (s), 1209 (s), 1029 (s), 836 (s), 775 (s).

LRMS (ES$^+$, CH$_3$CN) *m/z* (relative intensity %): 523 [M+Na]$^+$ (100).

HRMS (ES$^+$): Calcd. for C$_{22}$H$_{33}$IO$_3$SiNa: 523.1136, found 523.1133.

Elemental analysis: % theory for C: 52.80, H: 6.65, % found for C: 52.35, H: 6.71

2-[6-[3-([[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy]methyl)-2-iodo-6-methoxyphenoxy]-1-cyclohexenyl]-1-ethanol (486)



C$_{22}$H$_{35}$IO$_4$Si

M.w. = 518.50 g/mol

yellow oil

Following the procedure of Holm *et al.*,[121] to a stirred solution of **485** (514 mg, 1.03 mmol) in THF (7 mL) was added a solution of 9-BBN (3 mL, 1.54 mmol, 0.5M in THF). The reaction mixture was stirred for 15 hours. NaOH (3M, 6 mL) was added dropwise and chilled H$_2$O$_2$ (30%, 6 mL) was added slowly. The solution was stirred at RT for 3 hours before being quenched with water (15 mL). The organic phase was separated and the aqueous phase was extracted with Et$_2$O (3 x 15 mL). The combined organic phases were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 25% Et$_2$O/hexane to afford the title compound **486** as a yellow oil (450 mg, 0.87 mmol, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, d, J = 8.4 Hz, Ar**H**), 6.91 (1H, d, J = 8.4 Hz, Ar**H**), 5.85-5.80 (1H, m, **H**C=C(CH_2)), 5.05 (1H, t, J = 4.0 Hz, **H**C(O)), 4.63 (1H, d, J = 13.9 Hz, ArC**H$_A$**H$_B$OTBS), 4.51 (1H, d, J = 13.9 Hz, ArCH$_A$**H$_B$**OTBS), 3.83 (3H, s, ArOC**H$_3$**), 3.81-3.72 (2H, m, C**H$_2$**OH), 2.66 (1H, dt, J = 13.9, 6.2 Hz, C**H$_A$**H$_B$CH$_2$OH), 2.45 (1H, dt, J = 13.9, 7.3 Hz, CH$_A$**H$_B$**CH$_2$OH), 1.58-1.39 (5H, m, C=CH(CH$_2$)$_2$C**H$_2$**, C=CHC**H$_2$**, CH$_2$O**H**), 2.24-1.83 (2H, m, C=CHCH$_2$C**H$_2$**), 0.96 (9H, s, C(C**H$_3$**)$_3$), 0.12 (6H, s, 2 x C**H$_3$**).

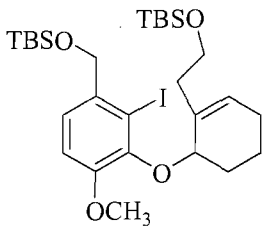
^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8 (**C**$_{Ar}$(O)), 145.7 (**C**$_{Ar}$OCH$_3$), 136.2 (HC=**C**(HC=CH$_2$), 134.3 (**C**$_{Ar}$CH$_2$OTBS), 130.1 (H**C**=C(CH$_2$)), 122.0 (**C**H$_{Ar}$), 112.2 (**C**H$_{Ar}$), 95.8 (**C**$_{Ar}$I), 76.6 (**C**H(O)), 69.6 (C$_{Ar}$**C**H$_2$OTBS), 61.8 (**C**H$_2$OH), 55.8 (O**C**H$_3$), 38.0 (**C**H$_2$), 28.1 (**C**H$_2$CH$_2$OH), 26.0 (C(**C**H$_3$)$_3$), 25.6 (**C**H$_2$), 18.7 (**C**H$_2$), 15.3 (**C**(CH$_3$)$_3$), –4.5 (2 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 3391 (br), 2925 (m), 2852 (m), 1467 (m), 1250 (m), 1025 (m), 833 (s), 731 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 541 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{22}H_{35}IO_4SiNa$: 541.1241, found 541.1232.

***tert*-Butyl[(3-[[2-[[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy]enyl)-2-cyclohexenyl]oxy]-2-iodo-4-methoxybenzyl)oxy]dimethylsilane (487)**



$C_{28}H_{49}IO_4Si_2$

M.w. = 632.22 g/mol

colourless oil

To a stirred solution of **486** (95 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was added DMAP (3 mg, 0.18 mmol), imidazole (12 mg, 0.18 mmol) and Et_3N (26 μL, 0.18 mmol). After stirring for 10 minutes, TBDMSCl (27 mg, 0.18 mmol) was added. The reaction mixture was stirred for 12 hours and then quenched with sat'd NH_4Cl (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on

silica gel (10 g) eluting with 10% Et_2O/hexane to yield the title compound **487** as a colourless oil (100 mg, 0.16 mmol, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, d, J = 8.4 Hz, Ar**H**), 6.92 (1H, d, J = 8.4 Hz, Ar**H**), 5.78-5.70 (1H, m, **H**C=C(CH_2)), 4.95 (1H, t, J = 4.0 Hz, **H**C(O)), 4.63 (1H, d, J = 13.9 Hz, ArC**H$_A$**H$_B$OTBS), 4.57 (1H, d, J = 13.9 Hz, ArCH$_A$**H$_B$**OTBS), 3.84 (3H, s, ArOC**H$_3$**), 3.82-3.73 (2H, m, C**H$_2$**OTBS), 2.60 (1H, dt, J = 13.9, 6.2 Hz, C**H$_A$**H$_B$CH$_2$OTBS), 2.39 (1H, dt, J = 13.9, 7.3 Hz, CH$_A$**H$_B$**CH$_2$OTBS), 2.23-1.87 (4H, m, C=CH(CH$_2$)$_2$C**H$_2$**, C=CHC**H$_2$**), 1.59-1.39 (2H, m, C=CHCH$_2$C**H$_2$**), 0.98 (9H, s, C(C**H$_3$**)$_3$), 0.89 (9H, s, C(C**H$_3$**)$_3$), 0.14 (6H, s, 2 x C**H$_3$**), 0.04 (6H, s, 2 x C**H$_3$**).

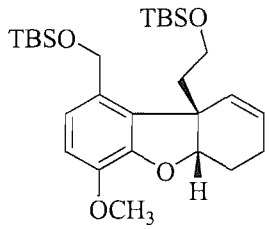
^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9 (**C**$_{Ar}$(O)), 146.6 (**C**$_{Ar}$OCH$_3$), 136.1 (HC=**C**(HC=CH$_2$), 134.5 (**C**$_{Ar}$CH$_2$OTBS), 128.9 (H**C**=C(CH$_2$)), 121.7 (**C**H$_{Ar}$), 112.2 (**C**H$_{Ar}$), 95.8 (**C**$_{Ar}$I), 76.7 (**C**H(O)), 69.7 (Ar**C**H$_2$OTBS), 63.0 (**C**H$_2$OTBS), 55.7 (O**C**H$_3$), 37.7 (**C**H$_2$), 28.5 (**C**H$_2$CH$_2$OTBS), 26.0 (2 x C(**C**H$_3$)$_3$), 25.6 (**C**H$_2$), 18.8 (**C**H$_2$), 18.3 (**C**(CH$_3$)$_3$), –4.5 (4 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 2928 (m), 2855 (m), 1472 (m), 1251(m), 1101 (m), 833 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 655 [M+Na]$^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{28}H_{49}IO_4Si_2Na$: 655.2106, found 655.2090.

[[9a-(2-[[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy]ethyl)-4-methoxy-5a, 6, 7, 9a-tetrahydrodibenzo[*b*,*d*]furan-1-yl]methoxy](*tert*-butyl)dimethylsilane (488)



$C_{28}H_{48}O_4Si_2$
M.w. = 504.85 g/mol
yellow oil

Following the procedure of Trost *et al.*,[112] to a stirred solution of **487** (300 mg, 0.47 mmol) in toluene (15 mL) was added Ag_2CO_3 (389 mg, 1.41 μmol), dppp (29 mg, 0.07 mmol) and $Pd(OAc)_2$ (16 mg, 0.07 mmol). The reaction mixture was evacuated and flushed with argon 3 times. The mixture was heated at reflux for 15 hours and allowed to cool to RT. The reaction mixture was concentrated under reduced pressure to give the crude product as a black oil. Purification was accomplished by

flash chromatography on silica gel (12 g) eluting with 10% Et_2O/hexane to afford the title compound **488** as a yellow oil (210 mg, 0.42 mmol, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.71 (1H, d, *J* = 8.0 Hz, Ar**H**), 5.82 (2H, s, **H**C=C**H**), 4.95 (1H, t, *J* = 5.0 Hz, **H**C(O)), 4.51 (1H, d, *J* = 14.1 Hz, ArC**H$_A$**H$_B$OTBS), 4.44 (1H, d, *J* = 14.1 Hz, ArCH$_A$**H$_B$**OTBS), 3.85 (3H, s, ArOC**H$_3$**), 3.68 (1H, dt, *J* = 10.0, 7.5 Hz, C**H$_A$**H$_B$OTBS), 3.62 (1H, dt, *J* = 10.6, 7.0 Hz, CH$_A$**H$_B$**OTBS), 2.30-2.03 (4H, m, C**H$_2$**CH$_2$OTBS, HC=CHCH$_2$C**H$_2$**), 1.99-1.80 (2H, m, HC=CHC**H$_2$**CH$_2$), 0.94 (9H, s, C(C**H$_3$**)$_3$), 0.86 (9H, s, C(C**H$_3$**)$_3$), 0.10 (6H, s, 2 x C**H$_3$**), -0.09 (6H, s, 2 x C**H$_3$**).

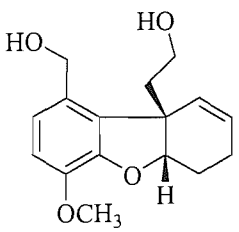
^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4 (**C**$_{Ar}$OCH$_3$), 145.3 (**C**$_{Ar}$(O)), 132.4 (**C**$_{Ar}$CH$_2$OTBS), 130.8 (H**C**=**C**H), 128.6 (**C**$_{Ar}$), 121.6 (**C**H$_{Ar}$), 111.8 (**C**H$_{Ar}$), 86.4 ((O)**C**(CH$_2$)), 63.4 (Ar**C**H$_2$OTBS), 61.1 (**C**H$_2$OTBS), 56.9 (O**C**H$_3$), 50.5 (**C**), 41.2 (**C**H$_2$CH$_2$OTBS), 27.0 (2 x C(**C**H$_3$)$_3$), 25.3 (**C**H$_2$), 20.7 (**C**H$_2$), 19.5 (**C**(CH$_3$)$_3$), 19.3 (**C**(CH$_3$)$_3$), –4.0 (2 x **C**H$_3$), –4.3 (2 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 2928 (m), 2856 (m), 1505 (m), 1278 (m), 1253 (m), 1085 (s), 833 (s), 774 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 527 [M+Na]$^+$(100).

HRMS (ES$^+$): Calcd. for $C_{28}H_{48}O_4Si_2Na$: 527.2983, found 527.2989.

2-(1-hydroxymethyl-4-methoxy-6,7-dihydro-5a*H*-dibenzofuran-9a-yl)-ethanol (489)



$C_{16}H_{20}O_4$

M.w. = 276.33 g/mol

colourless oil

To a stirred solution of **488** (200 mg, 0.40 mmol) in THF (5 mL) was added a solution of TBAF (830 μL, 0.27 μmol, 1M in THF) at 0°C. After stirring for 2 hours at RT, the reaction mixture was concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 5% MeOH/CH_2Cl_2 to afford the title compound **489** as a colourless oil (103 mg, 0.37 mmol, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (1H, d, J = 8.5 Hz, Ar**H**), 6.72 (1H, d, J = 8.5 Hz, Ar**H**), 5.85-5.80 (2H, m, **H**C=C**H**), 4.81 (1H, dd, J = 5.0, 3.5 Hz, **H**C(O)), 4.70 (1H, d, J = 12.0 Hz, ArC**H$_A$**H$_B$OH), 4.58 (1H, d, J = 12.0 Hz, ArCH$_A$**H$_B$**OH), 3.85 (3H, s, ArOC**H$_3$**), 3.68 (2H, t, J = 6.5 Hz, C**H$_2$**OH), 2.29-2.13 (3H, m, C**H$_2$**CH$_2$OH, HC=CHCH$_2$C**H$_A$**H$_B$), 2.05 (1H, dt, J = 14.6, 6.5 Hz, HC=CHCH$_2$CH$_A$**H$_B$**), 2.00-1.92 (1H, m, HC=CHC**H$_A$**H$_B$CH$_2$), 1.86-1.77 (1H, m, HC=CHCH$_A$**H$_B$**CH$_2$).

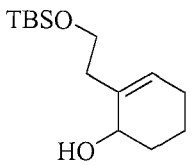
^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3 (**C**$_{Ar}$OCH$_3$), 144.8 (**C**$_{Ar}$(O)), 131.8 (**C**$_{Ar}$CH$_2$OH), 130.1 (H**C**=CH), , 129.3 (**C**$_{Ar}$), 127.6 (HC=**C**H), 122.6 (**C**H$_{Ar}$), 111.1 (**C**H$_{Ar}$), 85.1 (**C**H(O)), 62.0 (Ar**C**H$_2$OH), 59.4 (**C**H$_2$OH), 55.8 (ArO**C**H$_3$), 49.1 (**C**), 40.6 (**C**H$_2$CH$_2$OH), 24.1 (**C**H$_2$), 19.6 (**C**H$_2$).

IR ν_{max} neat (cm^{-1}): 3342 (br), 2930 (m), 1505 (s), 1429 (s), 1276 (s), 1035 (s), 923 (m), 731 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 299 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{20}O_4Na$: 299.1254, found 299.1258.

2-(2-[[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy]ethyl)-2-cyclohexen-1-ol (492)



$C_{14}H_{28}O_2Si$
M.w. = 256.46 g/mol
pale yellow oil

Following the procedure of Hernandez *et al.*,[122] to a solution of **496** (112 mg, 0.79 mmol) in DMF (3 mL) was added DMAP (10 mg, 0.08 mmol) and Et_3N (110 μL, 0.79 mmol). After stirring for 10 minutes, TBDMSCl (1.10 g, 6.79 mmol) was added. The reaction mixture was stirred for 12 hours and then quenched with sat'd NH_4Cl (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a pale brown oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 10% Et_2O/hexane to yield the title compound **492** as a pale yellow oil (176 mg, 0.69 mmol, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (1H, t, J = 3.5 Hz, **H**C=C(CH$_2$)), 4.05-3.98 (1H, m, C(**H**)(OH)), 3.80 (1H, ddd, J = 10.5, 5.5, 4.5 Hz, CH$_2$C**H$_A$**H$_B$OTBS), 3.72 (1H, d,

J = 3.5 Hz, C(H)(O**H**)), 3.65 (1H, ddd, J = 13.6, 9.0, 4.0 Hz, $CH_2CH_A\mathbf{H_B}$OTBS), 2.40 (1H, dtt, J = 14.1, 4.0, 1.5 Hz, $\mathbf{CH_A}H_BCH_2$OTBS), 2.19 (1H, ddd, J = 13.6, 9.0, 5.0 Hz, $CH_A\mathbf{H_B}CH_2$OTBS), 2.10-1.90 (2H, m, $\mathbf{CH_2}$), 1.81-1.65 (4H, m, $\mathbf{CH_2}$), 0.90 (3H, s, $C(\mathbf{CH_3})_3$), 0.07 (6H, s, 2 x $\mathbf{CH_3}$).

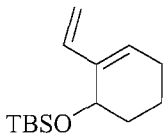
^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7 (HC=**C**(CH_2)), 125.4 (H**C**=C(CH_2)), 65.3 (**C**(H)(OH)), 62.8 (**C**H_2OTBS), 37.1 (**C**H_2CH_2OTBS), 29.6 (**C**H_2), 24.3 ($C(\mathbf{C}H_3)_3$), 24.1 (**C**H_2), 16.7 (**C**$(CH_3)_3$), 16.4 (**C**H_2), –4.1 (**C**H_3), –4.6 (**C**H_3).

IR ν_{max} neat (cm^{-1}): 3318 (br), 2928 (m), 2856 (m), 1252(m), 1064 (m), 832 (s).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 174 $[M\text{-TBS+MeOH}]^+$ (100), 279 $[M+Na]^+$ (40).

HRMS (ES^+): Calcd. for $C_{14}H_{28}O_2SiNa$: 279.1751, found 279.1751.

tert-Butyl(dimethyl)[(2-vinyl-2-cyclohexenyl)oxy]silane (493)



$C_{14}H_{26}OSi$
M.w. = 238.44 g/mol
yellow oil

To a stirred solution of **494** (500 mg, 2.09 mmol) in CH_2Cl_2 (21 mL) was added a solution of the first generation Grubbs catalyst (52 mg, 0.06 mmol) in CH_2Cl_2 (21 mL). The reaction mixture was heated at reflux for 2 hours and then concentrated under reduced pressure to give the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 5% Et_2O/hexane to afford the cyclised product **493** as a yellow oil (412 mg, 1.73 mmol, 83%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (1H, dd, J = 17.6, 11.0 Hz, H_2C=C**H**), 5.85 (1H, t, J = 3.7 Hz, **H**C=C(HC=CH_2)), 5.25 (1H, d, J = 17.6 Hz, $\mathbf{H_A}H_BC$=CH), 4.97 (1H, d, J = 10.6 Hz, $H_A\mathbf{H_B}C$=CH), 4.45 (1H, t, J = 2.9 Hz, C(**H**)(OTBS)), 2.29-2.00 (2H, m, C=CHC$\mathbf{H_2}$), 1.43-1.76 (2H, m, C=CH$(CH_2)_2C\mathbf{H_2}$), 1.68-1.48 (2H, m, C=C$HCH_2C\mathbf{H_2}$), 0.89 (9H, s, $C(\mathbf{CH_3})_3$), 0.13 (3H, s, $\mathbf{CH_3}$), 0.10 (3H, s, $\mathbf{CH_3}$).

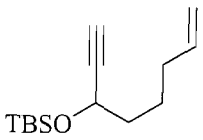
^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (HC=**C**(HC=CH_2), 138.1 (H_2C=**C**H), 130.4 (H**C**=C(HC=CH_2), 111.2 (H_2**C**=CH), 64.4 (**C**(H)(OTBS)), 32.1 (**C**H_2), 26.0 (**C**$(CH_3)_3$), 18.2 (**C**H_2), 17.0 (**C**H_2), –4.1 (**C**H_3), –4.4 (**C**H_3).

IR ν_{max} neat (cm^{-1}): 2927 (m), 2854 (m), 1249 (m), 1082 (m), 1062(m), 1014 (m), 831 (s), 769 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 261 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{13}H_{23}OSi$: 223.15167, found 223.15182.

***tert*-Butyl-[[1-(1-ethynyl)-5-hexenyl]oxy]dimethylsilane (494)**



$C_{14}H_{26}OSi$
M.w. = 238.44 g/mol
pale yellow oil

To a solution of **476** (703 mg, 5.66 mmol) in DMF (10 mL) was added DMAP (28 mg, 0.23 mmol), imidazole (585 mg, 5.66 mmol) and Et_3N (789 μL, 5.66 mmol). After stirring for 20 minutes, TBDMSCl (1.10 g, 6.79 mmol) was added. The reaction mixture was stirred for 12 hours before being quenched with sat'd NH_4Cl (10mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (20 g) eluting with 5% Et_2O/hexane to yield the title compound **494** as pale a yellow oil (1.29 g, 5.40 mmol, 95%).

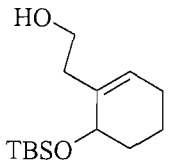
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, ddt, J = 17.2, 10.6, 6.6 Hz, H_2C=C**H**CH_2), 5.02 (1H, ddt, J = 17.2, 2.2, 1.5 Hz, $\mathbf{H_A}H_BC$=$CHCH_2$), 4.96 (1H, ddt, J = 10.3, 1.8, 1.5 Hz, $H_A\mathbf{H_B}C$=$CHCH_2$), 4.35 (1H, td, J = 6.6, 2.2 Hz, TBSOC(**H**)(CH_2)),), 2.37 (1H, d, J = 1.8 Hz, **H**C_{alkyne}), 2.09 (2H, qt, J = 7.4, 1.5 Hz, H_2C=$CHC\mathbf{H_2}$), 1.75-1.65 (2H, m, H_2C=$CH(CH_2)_2C\mathbf{H_2}$), 1.60-1.50 (2H, m, H_2C=$CHCH_2C\mathbf{H_2}$), 0.91 (9H, s, $C(C\mathbf{H_3})_3$), 0.14 (3H, s, $C\mathbf{H_3}$), 0.11 (3H, s, $C\mathbf{H_3}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6 (H_2C=**C**HCH_2), 114.6 ($H_2\mathbf{C}$=$CHCH_2$), 85.6 (**C**$_{alkyne}$), 72.0 (**C**$_{alkyne}$H), 62.6 (TBSO**C**(H)(CH_2)), 38.0 (H_2C=$CH(CH_2)_2\mathbf{C}H_2$), 33.3 (H_2C=$CH\mathbf{C}H_2$), 25.8 ($C(\mathbf{C}H_3)_3$), 24.4 (H_2C=$CHCH_2\mathbf{C}H_2$), 24.4 (H_2C=$CHCH_2\mathbf{C}H_2$), 18.2 ($\mathbf{C}(CH_3)_3$), -4.6 ($\mathbf{C}H_3$), –4.5 ($\mathbf{C}H_3$).

IR ν_{max} neat (cm^{-1}): 3308 (w), 2928 (m), 2856 (m), 1251 (m), 1091(m), 884 (s), 774 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 261 $[M+Na]^+$ (100).

2-(6-[[1-(*tert*-Butyl)-1,1-dimethylsilyl]-1-cyclohexyl)-1-ethanol (495)



$C_{14}H_{28}O_2Si$
M.w. = 256.46 g/mol
pale yellow oil

Following the procedure of Holm *et al.*,[121] to a stirred solution of **494** (205 mg, 0.86 mmol) in THF (5 mL) was added a solution of 9-BBN (2.6 mL, 1.28 mmol, 0.5M in THF). The reaction mixture was stirred for 15 hours. NaOH (3M, 6 mL) was added dropwise and chilled H_2O_2 (30%, 6 mL) was added slowly. The solution was stirred at RT for 4 hours before the reaction was quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (10 g) eluting with 9% Et_2O/hexane to afford the title compound **495** as a pale yellow oil (213 mg, 0.83 mmol, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (1H, t, *J* = 4.0 Hz, **H**C=C(CH_2)), 4.12 (1H, t, *J* = 4.4 Hz, C(**H**)(OTBS)), 3.72 (1H, dt, *J* = 10.6, 5.5 Hz, $CH_2CH_AH_BOH$), 3.63 (1H, dt, *J* = 8.4, 5.1 Hz, CH_2CH_A**H$_B$**OH), 2.46-2.34 (1H, m, C**H$_A$**H$_B$$CH_2OH$), 2.27-2.14 (1H, m, CH_A**H$_B$**CH_2OH), 2.12-1.90 (3H, m, C**H$_2$**, CH_2O**H**), 1.82-1.44 (4H, m, 2 x CH_2), 0.90 (3H, s, C(C**H$_3$**)$_3$), 0.10 (6H, s, 2 x C**H$_3$**).

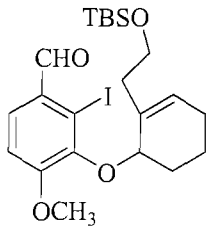
^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7 (HC=**C**(CH_2)), 127.3 (H**C**=C(CH_2)), 68.5 (**C**(H)(OTBS)), 61.5 (**C**H_2OH), 37.1 (**C**H_2), 32.8 (C**H$_2$**CH_2OH), 25.9 (**C**(CH_3)$_3$), 25.5 (**C**H_2), 18.8 (**C**H_2), 18.1 (**C**), –4.1 (**C**H_3), –4.6 (**C**H_3).

IR ν_{max} neat (cm^{-1}): 3318 (br), 2928 (m), 2856 (m), 1252 (m), 1064 (m), 832 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 279 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{14}H_{28}O_2SiNa$: 279.1751, found 279.1754.

3-[[2-(2-[[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy]ethyl)-2-cyclohexenyl]oxy]-2-iodo-4-methoxybenzaldehyde (497)



$C_{22}H_{33}IO_4Si$
M.w. = 516.48 g/mol
yellow oil

Following the procedure of Kaiankarimi *et al.*,[116] to a stirred solution of **438** (193 mg, 0.69 mmol) in THF (5 mL) was added *n*-Bu_3P (198 μL, 0.79 mmol) and a solution of **476** (170 mg, 0.66 mmol) in THF (5 mL). After stirring for 5 minutes, a solution of DBAD (304 mg, 1.32 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 15 hours and then quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 15% Et_2O/hexane to yield the title compound **497** as a yellow oil (206 mg, 0.40 mmol, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (1H, d, J = 0.7 Hz, (ArC**H**O), 7.65 (1H, d, J = 8.4 Hz, Ar**H**), 6.85 (1H, d, J = 8.4 Hz, Ar**H**), 5.79-5.73 (1H, m, **H**C=C(CH_2)), 4.94 (1H, t, J = 4.4 Hz, **H**C(O)), 3.93 (3H, s, ArOC**H**$_3$), 3.80-3.70 (2H, m, C**H**$_2$OTBS), 2.56 (1H, dt, J = 13.9, 6.2 Hz, C**H**$_A$H$_B$CH$_2$OTBS), 2.36 (1H, dt, J = 13.9, 7.3 Hz, CH$_A$**H**$_B$CH$_2$OTBS), 2.23-1.87 (4H, m, C=CH(CH$_2$)$_2$C**H**$_2$, C=CHC**H**$_2$), 1.60-1.40 (2H, m, C=CHCH$_2$C**H**$_2$), 0.90 (9H, s, C(C**H**$_3$)$_3$), 0.00 (6H, s, 2 x C**H**$_3$).

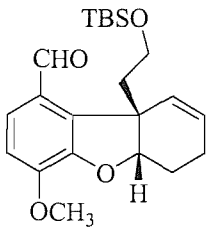
^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7 (**C**HO), 157.2 (**C**$_{Ar}$OCH$_3$), 146.6 (**C**$_{Ar}$(O)), 134.1 (HC=**C**(CH$_2$)), 129.4 (**C**$_{Ar}$CHO), 126.3 (H**C**=C(CH$_2$), **C**H$_{Ar}$), 111.7 (**C**H$_{Ar}$), 101.6 (**C**$_{Ar}$I), 77.3 (**C**H(O)), 62.9 (**C**H$_2$OTBS), 55.9 (O**C**H$_3$), 37.6 (**C**H$_2$CH$_2$OTBS), 28.6 (**C**H$_2$), 25.9 (C(**C**H$_3$)$_3$), 25.5 (**C**H$_2$), 18.6 (**C**H$_2$), 18.3 (**C**(CH$_3$)$_3$), –5.0 (2 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 2929 (m), 2855 (m), 1684 (s), 1573 (s), 1471 (s), 1247 (s), 1023 (m), 835 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 539 [M+Na]$^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{22}H_{33}IO_4SiNa$: 539.1085, found 539.1083.

9a-(2-[[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy]ethyl)-4-methoxy-5a, 6, 7, 9a-tetrahydrodibenzo[*b*,*d*]furan-1-carbaldehyde (498)



$C_{22}H_{32}O_4Si$

M.w. = 388.57 g/mol

white solid

To a stirred solution of **497** (189 mg, 0.37 mmol) in toluene (7 mL) was added Ag_2CO_3 (152 mg, 0.55 mmol), dppp (23 mg, 0.06 mmol) and $Pd(OAc)_2$ (13 mg, 0.06 mmol). The reaction mixture was evacuated and flushed with argon 3 times. The mixture was heated at reflux for 15 hours and allowed to cool to RT. The reaction mixture was concentrated under reduced pressure to give the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (12 g) eluting with 13% Et_2O/hexane to afford the title compound **498** as a white solid (123 mg, 0.32 mmol, 85%).

Mpt. = 105-106 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (1H, s, ArC**H**O), 7.33 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.85 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.04 (1H, ddd, *J* = 10.0, 1.5, 1.0 Hz, **H**C=CH), 5.84 (1H, ddd, *J* = 10.0, 5.5, 3.0 Hz, HC=C**H**), 5.16 (1H, t, *J* = 5.0 Hz, **H**C(O)), 3.93 (3H, s, ArOC**H**$_3$), 3.61 (2H, m, C**H**$_2$OTBS), 2.43 (1H, dt, *J* = 14.1, 6.5 Hz, C**H**$_A$H$_B$CH$_2$OTBS), 2.25-2.12 (3H, m, CH$_A$**H**$_B$CH$_2$OTBS, HC=CHCH$_2$C**H**$_2$), 1.99-1.86 (2H, m, HC=CHC**H**$_2$CH$_2$), 0.81 (9H, s, C(C**H**$_3$)$_3$), –0.05 (3H, s, C**H**$_3$), –0.10 (3H, s, C**H**$_3$).

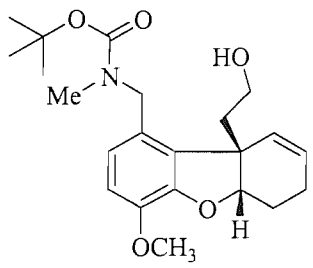
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0 (Ar**C**HO), 150.2 (**C**$_{Ar}$OCH$_3$), 149.1 (**C**$_{Ar}$(O)), 134.5 (**C**$_{Ar}$CHO), 130.2 (H**C**=**C**H), 129.4 (**C**H$_{Ar}$) 128.4 (**C**$_{Ar}$), 110.5 (**C**H$_{Ar}$), 87.2 ((O)**C**(CH$_2$)), 60.7 (**C**H$_2$OTBS), 56.4 (O**C**H$_3$), 50.0 (**C**), 40.0 (**C**H$_2$CH$_2$OTBS), 26.2 (C(**C**H$_3$)$_3$), 24.5 (**C**H$_2$), 19.4 (**C**H$_2$), 18.5 (**C**(CH$_3$)$_3$), –4.0 (2 x **C**H$_3$).

IR ν_{max} neat (cm^{-1}): 2952 (w), 2854 (w), 1681 (m), 1438 (m), 1285 (s), 1077 (m), 835 (s).

LRMS (ES$^+$, CH_3CN) *m/z* (relative intensity %): 411 $[M+Na]^+$ (100).

HRMS (ES$^+$): Calcd. for $C_{22}H_{32}O_4SiNa$: 411.1926, found 411.1959.

***tert*-Butyl *N*-[[9a-(2-hydroxyethyl)-4-methoxy-5a, 6, 7, 9a-tetrahydrodibenzo[*b*,*d*]furan-1-yl]methyl]-*N*-methylcarbamate (501)**



$C_{22}H_{31}NO_5$

M.w. = 389.49 g/mol

colourless oil

Step A: Reductive amination step

Following the procedure of Bhattacharyya *et al.*,[123] a solution of Et_3N (314 μL, 2.26 mmol) in EtOH (15 mL) was treated with $MeNH_2.HCl$ (153 mg, 2.26 mmol), $Ti(O^iPr)_4$ (622 μL, 2.26 mmol) and the aldehyde **498** (380 mg, 1.12 mmol). The reaction mixture was stirred for 6 hours before addition of $NaBH_4$ (56 mg, 1.68 mmol). After stirring for 2 hours, the reaction mixture was poured onto 2N NaOH (30 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude amine compound **499** as a pale yellow oil (423 mg, 1.05 mmol, 94%). The resulting product was used without further purification.

Step B: Protection step

To a stirred solution of the amine compound **499** (423 mg, 1.05 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (161 μL, 1.15 mmol). After stirring for 10 minutes, Boc_2O (246 μL, 1.15 mmol) was added. The reaction mixture was stirred for 15 hours and quenched with sat'd NH_4Cl (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product **500** as a pale yellow oil (523 mg, 1.04 mmol, 99%). The resulting product was used without further purification.

Step C: Deprotection step

To a stirred solution of **500** (779 mg, 1.55 mmol) in THF (10 mL) was added a solution of TBAF (1.70 mL, 1.70 mmol, 1M in THF) at 0°C. After stirring for 2 hours at RT, the reaction mixture was concentrated under reduced pressure to give

the crude product as a brown oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 40% EtOAc/ Hexane to afford the title compound **501** as a colourless oil (348 mg, 0.89 mmol, 58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (1H, d, J = 8.4 Hz, Ar**H**), 6.59 (1H, d, J = 8.4 Hz, Ar**H**), 5.91-5.79 (2H, m, **H**C=C**H**), 4.85 (1H, dd, J = 5.5, 3.7 Hz, **H**C(O)), 4.62-4.38 (2H, m, C**H**$_2$N(CH$_3$)(Boc)), 3.86 (3H, s, ArOC**H**$_3$), 3.72-3.61 (2H, m, C**H**$_2$OH), 2.82 (3H, s(br), CH$_2$N(C**H**$_3$)(Boc)), 2.22-2.00 (6H, m, C**H**$_2$C**H**$_2$OTBS, HC=CHC**H**$_2$C**H**$_2$), 1.70 (1H, s(br), O**H**), 1.48 (9H, s, NCO$_2$C(C**H**$_3$)$_3$).

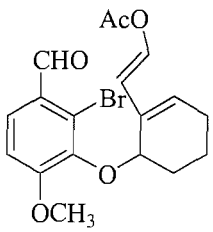
^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 (**C**O$_2$C(CH$_3$)$_3$), 147.6 (**C**$_{Ar}$OCH$_3$), 144.4 (**C**$_{Ar}$(O)), 131.5 (**C**$_{Ar}$CH$_2$N(CH$_3$)(Boc)), 129.3 (H**C**=**C**H), 128.5 (**C**H$_{Ar}$) 126.4 (**C**$_{Ar}$), 111.4 (**C**H$_{Ar}$), 85.7 ((O)**C**(CH$_2$)), 80.1 (CO$_2$**C**(CH$_3$)$_3$), 59.9 (**C**H$_2$OH), 56.0 (ArO**C**H$_3$), 49.4 (**C**H$_2$N(CH$_3$)(Boc)), 42.2 (**C**), 34.2 (**C**H$_2$CH$_2$OH), 28.7 (CO$_2$C(**C**H$_3$)$_3$), 24.8 (**C**H$_2$), 21.3 (CH$_2$N(**C**H$_3$)(Boc), **C**H$_2$).

IR ν_{max} neat (cm^{-1}): 3445, (br), 2931 (m), 1673 (s), 1504 (s), 1427 (m), 1391 (m), 1142 (s), 1040 (m), 872 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 412 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{22}H_{31}NO_5Na$: 412.2094, found 412.2084.

(*E*)-2-[6-(3-acetyl-2-bromo-6-methoxyphenoxy)-1-cyclohexenyl]-1-ethenyl acetate (504)



$C_{18}H_{19}BrO_5$
M.w. = 395.24 g/mol
white solid

To a stirred solution of **480** (142 mg, 0.42 mmol) in CH_2Cl_2 (2.2 mL) was added a solution of the second generation Grubbs catalyst (54 mg, 63 μmol) in CH_2Cl_2 (2 mL) and followed immediately by vinyl acetate (581 μL, 6.3 mmol). The reaction mixture was heated at reflux for 18 hours and then concentrated under reduced pressure to yield the crude product as a black oil. Purification was accomplished by flash chromatography on silica gel (6 g) eluting with 4% EtOAc/hexane to afford the cross product **504** as white solid (60 mg, 0.15 mmol, 36%) and the cross product **505** as white solid (50 mg, 0.13 mmol, 30%).

Mpt. = 103-104 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.26 (1H, s, ArC**H**O), 7.85 (1H, d, *J* = 12.8 Hz, HC=C(**H**)(OAc)), 7.69 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.96 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.04 (1H, d, *J* = 12.8 Hz, **H**C=C(H)(OAc)), 6.01 (1H, dd, *J* = 5.0, 3.0 Hz, C=C(**H**)(CH_2)), 5.36 (1H, t, *J* = 3.7 Hz, **H**C(O)), 4.00 (3H, s, ArOC**H**$_3$), 2.37-2.13 (4H, m, C=C(H)(C**H**$_2$), C=C(H)(CH_2)$_2$C**H**$_2$), 2.10 (3H, s, COC**H**$_3$), 1.64-1.42 (2H, m, C=C(H)(CH_2)C**H**$_2$).

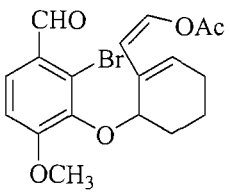
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4 (**C**HO), 168.0 (**C**OCH$_3$), 158.3 (**C**$_{Ar}$OCH$_3$), 145.7 (**C**$_{Ar}$(O)), 136.0 (**C**=C(H)(CH_2)), 133.2 (HC=**C**(H)(OAc)), 131.5 (**C**$_{Ar}$CHO), 127.6 (C=**C**(H)(CH_2)), 125.7 (**C**H$_{Ar}$), 124.0 (**C**$_{Ar}$Br), 116.7 (**C**H$_{Ar}$), 110.9 (H**C**=C(H)(OAc)), 73.2 (**C**H(O)), 56.2 (O**C**H$_3$), 27.7 (**C**H$_2$), 26.0 (**C**H$_2$), 20.7 (**C**H$_2$), 17.8 (**C**H$_3$).

IR ν_{max} neat (cm^{-1}): 2936 (m), 1752 (s), 1679 (s), 1575 (s), 1271 (s), 1211 (s), 1021 (s).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 418, 419 $[M+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{18}H_{19}{}^{79}BrO_5Na$: 417.0308, found 417.0311.

(*Z*)-2-[6-(3-acetyl-2-bromo-6-methoxyphenoxy)-1-cyclohexenyl]-1-ethenyl acetate (505)



$C_{18}H_{18}BrO_5$
M.w. = 395.24 g/mol
white solid

Mpt. = 114-115 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.26 (1H, s, ArC**H**O), 7.69 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.05 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.85 (1H, d, *J* = 14.6 Hz, HC=C(**H**)(OAc)), 6.53 (1H, dd, *J* = 4.8, 2.6 Hz, C=C(**H**)(CH_2)), 5.47 (1H, d, *J* = 7.3 Hz, **H**C=C(H)(OAc)), 5.36 (1H, t, *J* = 4.0 Hz, **H**C(O)), 3.82 (3H, s, ArOC**H**$_3$), 250-2.00 (4H, m, C=C(H)(C**H**$_2$), C=C(H)(CH_2)$_2$C**H**$_2$), 2.10 (3H, s, COC**H**$_3$), 1.68-1.50 (2H, m, C=C(H)(CH_2)C**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3 (**C**HO), 167.7 (**C**OCH$_3$), 158.5 (**C**$_{Ar}$OCH$_3$), 144.5 (**C**$_{Ar}$(O)), 134.5 (**C**=C(H)(CH_2)), 133.1 (HC=**C**(H)(OAc)), 130.3 (**C**$_{Ar}$CHO),

127.6 (C=**C**(H)(CH_2)), 125.8 (**C**H_{Ar}), 123.8 (**C**$_{Ar}$Br), 111.2 (**C**H_{Ar}), 110.8 (H**C**=C(H)(OAc)), 77.1 (**C**H(O)), 56.0 (O**C**H_3), 28.3 (**C**H_2), 26.0 (**C**H_2), 20.7 (**C**H_2), 17.4 (**C**H_3).

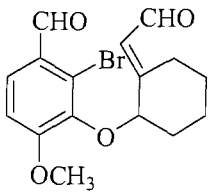
IR ν_{max} neat (cm^{-1}): 2937 (m), 1752 (s), 1679 (s), 1574 (m), 1272 (s), 1248 (s), 1199 (s), 1023 (m).

LRMS (ES^+, CH_3CN) *m/z* (relative intensity %): 418, 419 $[M+Na]^+$(100).

HRMS (ES^+): Calcd. for $C_{18}H_{19}{}^{79}BrO_5Na$: 417.0308, found 417.0311.

Elemental analysis: % theory for C: 54.70, H: 4.85, % found for C: 54.70, H: 4.89.

2-Bromo-4-methoxy-3-[[2-oxoethylidene]cyclohexyl]oxy)benzaldehyde (506)



$C_{16}H_{17}BrO_4$

M.w. = 353.21 g/mol

colourless oil

To a stirred solution of **504** (40 mg, 0.10 mmol) in MeOH (5 mL) was added K_2CO_3 (15 mg, 0.11 μmol). The reaction mixture was stirred at RT for an hour and then quenched with water (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a yellow oil. Purification was accomplished by flash chromatography on silica gel (4 g) eluting with 10% Et_2O/hexane to yield the title compound **506** as a colourless oil (25 mg, 0.07 mmol, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (1H, s, ArC**H**O), 9.76 (1H, s, C=CHC**H**O), 7.72 (1H, d, J = 8.8 Hz, Ar**H**), 6.95 (1H, d, J = 8.8 Hz, Ar**H**), 5.94 (1H, t, J = 2.9 Hz, C=C**H**CHO), 4.80 (1H, t, J = 3.7 Hz, **H**C(O)), 3.91 (3H, s, ArOC**H**$_3$), 3.52 (1H, d, J = 16.5 Hz, HC=CC**H**$_A$H$_B$), 3.25 (1H, d, J = 16.5 Hz, HC=CC**H**$_A$H$_B$), 2.32-2.17 (2H, m, C**H**$_2$), 2.15-1.89 (2H, m, C**H**$_2$), 1.68-1.50 (2H, m, C**H**$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3 (Ar**C**HO), 191.2 (C=CH**C**HO), 158.3 (**C**=CHCHO), 144.2 (**C**$_{Ar}$OCH$_3$), 133.5 (**C**$_{Ar}$(O)), 129.3 (**C**$_{Ar}$CHO), 127.6 (C=**C**HCHO), 126.1 (**C**H_{Ar}), 123.7 (**C**$_{Ar}$Br), 110.9 (**C**H_{Ar}), 77.5 (**C**H(O)), 56.0 (O**C**H_3), 49.2(**C**H_2), 28.2 (**C**H_2), 25.7 (**C**H_2), 18.1 (**C**H_2).

IR ν_{max} neat (cm^{-1}): 2934 (w), 2863 (w), 1679 (s), 1574 (s), 1479 (m), 1271 (s), 1247 (s), 1022 (s).

LRMS (ES^+, MeOH) *m/z* (relative intensity %): 407, 408 $[M+MeOH+Na]^+$ (100).

HRMS (ES^+): Calcd. for $C_{16}H_{17}{}^{79}BrO_4$+MeOH+Na: 407.0465, found 407.0468.

References

1. Rouhi, A. M. Olefin metathesis: Big-Deal Reactions. *Chemical & Engineering News* 2002; Vol. 80, p 29-33.
2. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998,** *54*, 4413-4450.
3. Fürstner, A. *Angew. Chem. Int. Ed.* **2000,** *39*, 3012-3043.
4. Grubbs, R. H. *Tetrahedron* **2004,** *60*, 7117-7140.
5. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005,** *44*, 4490-4527.
6. Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003,** *42*, 1900-1923.
7. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001,** *34*, 18-29.
8. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990,** *112*, 3875-3886.
9. Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organomettallics* **1989,** *8*, 2260-2265.
10. Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995,** *117*, 5503-5511.
11. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995,** *34*, 2039-2041.
12. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996,** *118*, 100-110.
13. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999,** *1*, 953-956.
14. Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999,** *121*, 791-799.
15. Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000,** *41*, 9973-9976.
16. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2000,** *122*, 8168-8179.
17. Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002,** *41*, 794-796.
18. Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002,** *41*, 2403-2405.
19. Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388.
20. Dieters, A.; Martin, S. F., *Chem. Rev.* **2004,** *104*, 2199-2238.
21. Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994,** *59*, 4029-4031.

22. Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996,** *118*, 1565-1566.

23. Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996,** *118*, 10335-10336.

24. Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005,** *127*, 848-849.

25. Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998,** *39*, 9623-9626.

26. Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001,** *42*, 179-181.

27. van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003,** *44*, 311-313.

28. Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2001,** *42*, 8023-8027.

29. Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M., *Tetrahedron Lett.* **2001,** *42*, 8029-8033.

30. Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. T. *Tetrahedron* **2004,** *60*, 3017-3015.

31. Arisawa, M.; Terada, Y.; Theeraladanon, C.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Organomet. Chem.* **2005,** *690*, 5398-5406.

32. Whitehead, A.; Moore, J. D.; Hanson, P. R. *Tetrahedron Lett.* **2003,** *44*, 4275-4255.

33. Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001,** *57*, 6969-6975.

34. Hekking, K. F. W.; van Deft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003,** *59*, 6751-6758.

35. Louie, J.; Grubbs, R. H. *Organomettallics* **2002,** *21*, 2153-2164.

36. Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001,** 3, 2045-2048.

37. Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2002,** *41*, 4732-4734.

38. Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002,** *4*, 803-805.

39. Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A. *Org. Lett.* **2002,** *4*, 2417-2420.

40. Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett.* **1996,** *37*, 9373-9376.

41. Karsch, S.; Schwab, P.; Metz, P., *Synlett* **2002**, 2019-2022.

42. Le Flohic, A.; Meyer, C.; Cossy, J.; Desmurs, J. R.; Galland, J. C. *Synlett* **2003**, 667-670.

43. McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004,** *104*, 2239-2258.

44. Paquette, L. A.; Fabris, F.; Tae, J.; Gallucci, J. C.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000,** *122*, 3391-3398.

45. Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999,** *40*, 4761-4764.

46. Wanner, J.; Harned, A. M.; Probst, D. A.; Poon, K. W. C.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron Lett.* **2002,** *43*, 917-921.

47. Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999,** *40*, 3297-3300.

48. Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000,** *2*, 1769-1772.

49. Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000,** *41*, 8635-8638.

50. Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000,** *65*, 4721-4728.

51. Patai, S., In *The Chemistry of Organosilicon Compounds*, ed.; Rappoport, Z., Ed. Wiley: Chichester, 1998.

52. Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001,** *11*, 1749-1752.

53. Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995,** *95*, 1253-1277.

54. Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997,** *38*, 4757-4760.

55. Ahmed, M.; Barret, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Porcopiou, P. A.; Salter, M. M. *Tetrahedron* **1999,** *55*, 3219-3232.

56. Schuman, M.; Gouverneur, V. *Tetrahedron Lett.* **2002,** *43*, 3513-3516.

57. Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem.* **2003,** *11*, 207-215.

58. Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995,** *60*, 3107-3111.

59. Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997,** *53*, 12789-12854.

60. Wipf, P.; Henningger, T. C.; Geib, S. J. *J. Org. Chem.* **1998,** *63*, 6088-6089.

61. De Lucca, G. V. *J. Org. Chem.* **1998,** *63*, 4755-4766.

62. Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000,** *56*, 9781-9790.

63. Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000,** *122*, 3783-3784.

64. Imhof, S.; Randl, S.; Blechert, S. *J. Chem. Soc., Chem. Commun.* **2001**, 1692-1693.

65. Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. *Org. Lett.* **2003,** *5*, 3403-3406.

66. Marhold, M.; Buer, A.; Hiemstra, H.; van Maarseveen, J. H.; Haufe, G. *Tetrahedron Lett.* **2004,** *45*, 57-60.

67. De Matteis, V.; van Delft, F. L.; de Gelder, R.; Tiebes, J.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2004,** *45*, 959-963.

68. Jun, J. H.; Dougherty, J. M.; Jimenez, M. d. S.; Hanson, P. R. *Tetrahedron* **2003,** *59*, 8901-8912.

69. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992,** *114*, 7324-7325.

70. White, W. N.; Gwynn, D.; Schlitt, R.; Griard, C.; Fife, W. *J. Am. Chem. Soc.* **1958,** *80*, 3271-3277.

71. Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002,** *43*, 1839-1841.

72. Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995,** *117*, 2108-2109.

73. Kirkland, T.; Grubbs, R. H. *J. Org. Chem.* **1997,** *62*, 7310-7318.

74. Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671-2672.

75. Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000,** *41*, 3319-3322.

76. Chao, W.; Weinreb, S. M. *Org. Lett.* **2003,** *5*, 2505-2507.

77. Simal, F.; Demonceau, A.; Noels, A. F.; Knowles, D. R. T.; O'Leary, S.; Maitlis, P. M.; Gusev, O. *J. Organomet. Chem.* **1998,** *558*, 163-170.

78. Mass, G. *Chem. Soc. Rev.* **2004**, *33*, 183-190.

79. Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982,** *47*, 5088-5093.

80. Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998,** *39*, 1453-1456.

81. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995,** *28*, 446-452.

82. Grubbs, R. H.; Fu, G. C. *J. Am. Chem. Soc.* **1993,** *115*, 3800-3801.

83. Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980,** *21*, 2955-2958.

84. Junga, H.; Blechert, S. *Tetrahedron Lett.* **1993,** *34*, 3731-3732.

85. Fujiwara, T.; Kato, Y.; Takeda, T. *Tetrahedron* **2000,** *56*, 4859-4869.

86. Rahim, M. A.; Fujiwara, T.; Takeda, T. *Tetrahedron* **2000,** *56*, 763-770.

87. Grice, I. D.; Harvey, P. J.; Jenkins, I. D. *Tetrahedron Lett.* **1996,** *37*, 1087-1090.

88. Hughes, D. L. *Organic Reactions* **1992,** *42*, 335-656.

89. Hoye, T. R.; Jeffery, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004,** *126*, 10210-10211.

90. Wallace, D. J. *Angew. Chem. Int. Ed.* **2005,** *44*, 1912-1915.

91. Parker, K. A.; Iqbal, T. *Tetrahedron Lett.* **1986,** *27*, 6291-6294.

92. Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002,** *58*, 4459-4479.

93. Denny, D. B.; Ross, S. T. *J. Org. Chem.* **1962,** *27*, 998-1000.

94. Boeckman, R. K.; Ko, S. S. *J. Am. Chem. Soc.* **1980,** *102*, 7149-7151.

95. Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996,** *61*, 7873-7881.

96. Marco–Contells, J.; do Carmo Carreiras, M.; Rodríguez, C.; Villarroya, M.; García, A. G. *Chem. Rev.* **2006,** *106*, 116-133.

97. Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005,** *127*, 14785-14803.

98. Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, p 323-424.

99. Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251-376.

100. Mucke, H. M. A. *Drugs Today* **1997,** *33*, 251-257.

101. Meinstock, M. *CNS Drugs* **1999,** *12*, 307-323.

102. Delagarza, V. W. Pharmacologic Treatment of Alzheimer's Disease: An Update. *American Family Physician* 2003, p 1364-1372.

103. Racchi, M.; Mazzucchelli, M.; Porrello, E.; Lanni, C.; Govoni, S. *Pharmacological Research* **2004,** *50*, 441-451.

104. Kawagami, Y.; Inoue, A.; Kawai, T.; Wakita, M.; Sugimoto, H.; Hopfinger, A. J. *Bioorg. Med. Chem. Lett.* **1996,** *4*, 1429-1449.

105. Weinstock, M.; Rasin, M.; Chorev, M.; Enz, A. *J. Neural Transm. Suppl.* **1994,** *43*, 219-225.

106. Barton, D. H. R.; Kirby, G. W. *J. Am. Chem. Soc.* **1962**, *84*, 806-817.

107. Gras, E.; Guillou, C.; Thal, C. *Tetrahedron Lett.* **1999,** *40*, 9243-9244.

108. Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993,** *58*, 3877-3885.

109. Guillou, C.; Beunard, J. L.; Gras, E.; Thal, C. *Angew. Chem. Int. Ed.* **2001,** *40*, 4745-4746.

110. Pilger, C.; Westerman, B.; Flörke, U.; Fels, G. *Synlett* **2000,** *8*, 1163-1165.

111. Parsons, P.; Charles, M. D.; Harvey, D. M.; Gill, A. L.; Smith, S. *Tetrahedron Lett.* **2001,** *42*, 2209-2211.

112. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000,** *122*, 11262-11263.

113. Trost, B. M.; Tang, W. *Angew. Chem. Int. Ed.* **2002,** *41*, 2795-2797.

114. Liang, P. H.; Liu, J. P.; Hsin, L. W.; Cheng, C. Y. *Tetrahedron* **2004,** *60*, 11655-11660.

115. Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988,** *53*, 4694-4708.

116. Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999,** *40*, 4497-4500.

117. Shankaran, K.; Sloan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985,** *26*, 6001-6002.

118. Tsai, Y. C.; Liou, J. P.; Liao, R.; Cheng, C. Y.; Tao, P. L. *Bioorg. Med. Chem. Lett.* **1998,** *8*, 1813-1818.

119. Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734-739.

120. Markovich, K. M.; Tantishaiyakul, V.; Hamada, A.; Miller, D. D.; Romstedt, K. J.; Shin, Y.; Fraundorfer, P. F.; Doyle, K.; Feller, D. R. *J. Med. Chem.* **1992,** *35*, 466-479.

121. Holm, K. H.; Skatteøl, L. *Acta Chem. Scand. B* **1984,** *38*, 783-794.

122. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979,** 99-102.

123. Bhattacharyya, S. *J. Org. Chem.* **1995,** *60*, 4928-4929.

124. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993,** *58*, 2899.

125. Salim, S. S.; Bellingham, R.; Brown, R. C. D. *Eur. J. Org. Chem.* **2004**, 800-806.

126. Royer, F.; Vilian, L.; Elkaïm, L.; Grimaud, L. *Org. Lett.* **2003,** *5*, 2007-2009.

127. Ginesta, X.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **2002,** *43*, 779-782.

128. Raifeld, Y. E.; Nikitendo, A. A.; Arshava, B. M.; Mikerin, I. E.; Zilberg, L. L. *Tetrahedron* **1994,** *50*, 8603-8616.

129. Cerezo, S.; Cortés, J.; Moreno-Manñas, M.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998,** *54*, 14869-14884.

130. Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1992,** *114*, 998-1010.

131. Foulard, G.; Brigaud, T.; Portella, C. *Tetrahedron* **1996,** *52*, 6187-6200.

132. Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004,** *6*, 2161-2163.

133. Hegadus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982,** *104*, 2444-2451.

134. Ince, J.; Ross, T. M.; Shipman, M.; Slawin, A. M. Z.; Ennis, D. S. *Tetrahedron* **1996,** *52*, 7037-7044.

135. Lee, C. W.; Oh, K. S.; Kim, K. S.; Ahn, K. H. *Org. Lett.* **2000,** *2*, 1213-1216.

136. Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983,** *48*, 4058-4067.

137. Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988,** *44*, 2033-2048.