Novel Strategies for the Construction of Cyclic Boronate Esters and Acids

&

Novel Aspects of Furan Chemistry

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DECLARATION

I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

Signature: .....

Acknowledgements

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I would last but not least like to thank my family for supporting me throughout my university career; especially my mother and father, for whom without their support none of this would have been possible. It has been a long road and they have always been there for me. I would like to thank my mum for encouraging me to go to

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Abstract

Methodology studies for cyclic boronate ester synthesis

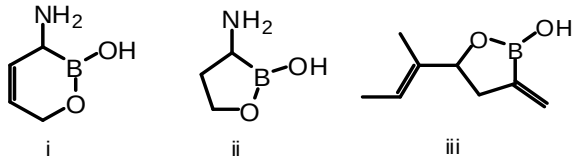


Figure i: Target molecules.

Structures **i,ii,iii** represent a general depiction of cyclic boron-containing heterocyles targeted in this methodology study. These molecules will be made using a range of new organic pathways. A 1,3 nitrogen-boron relationship in selected structures will also be investigated due to its importance in pharmaceutical chemistry.

In the pursuit of cyclic boranes a new method for the preparation of unsaturated ketones has been discovered, which utilises the boron chemistry outlined below.

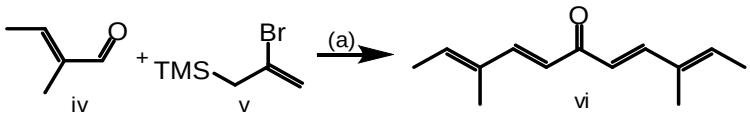


Figure ii: Reagents and Conditions: (a) ^{t}BuLi, B(O^{i}Pr)$_3$, Et$_2$O, -79 °C, 20 %.

Novel aspects of furan chemistry

It was found that the furan derivative **vii**, when treated with palladium salts, gave the bis-annulated benzene structure **viii**. This sequence gave rise to a novel method for the construction of aromatic rings. This reaction was tested on a range of substituted furans in order to examine the scope of this reaction.

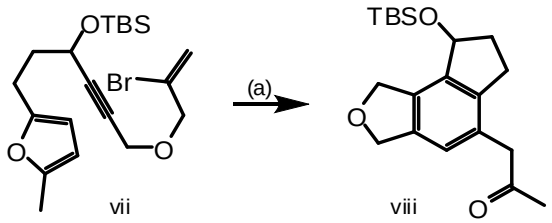


Figure iii: Reagents and Conditions: (a) Pd(OAc)$_2$, K$_2$CO$_3$, MeCN, 80 °C, 25%.

Abbreviations

Å	angstrom
Ac	acetyl
aq	aqueous
Ar	aromatic
Boc	*tert*-butoxycarbonyl
borax	sodium borate
b.p.	boiling point
Bu	butyl
^{t}Bu	*tert*-butyl
^{n}Bu	butyl
^{o}C	degrees celsius
cat.	catalytic
conc.	concentrated
CTAB	cetyltrimethylammonium bromide
Cp	cyclopentadiene
*m*CPBA	*meta*-chloroperbenzoic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DEAD	diethyl azo dicarboxylate
DIAD	diisopropyl azo dicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
DTBAD	di-*tert*-butylazodicarbonate
E^{+}	electrophile
ESI	electrospray ionisation
Et	ethyl
eq.	equivalents
g	gram(s)

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	Hertz
IR	infrared spectroscopy
LDA	lithium di-*iso*-propylamide
LHMDS	lithium hexamethyldisilazide
LRMS	low resolution mass spectrum
M	molar
Me	methyl
MeI	methyl iodide
MeOH	methanol
MHz	megahertz
MIDA	methyliminodiacetic acid
min.	minute(s)
mL	millilitre
mol	mole
mmol	millimole
m.p.	melting point
M.S.	molecular sieve
MS	mass spectrometry
MW	molecular weight
NaI	sodium iodide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu^-	nucleophile
Ph	phenyl
PINBOP	isopropyl pinacol borate
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
^{i}Pr	*iso*-propyl
Rf	retention factor
rt	room temperature
sat	saturated

SM	starting material
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
UHP	urea-hydrogen peroxide
UV	ultraviolet

Novel Strategies for the Construction of Cyclic Boronate Esters & Acids

1. Introduction

1.1 Boron

Boronate esters and borinic acids are trivalent boron containing organic compounds. Boronate esters consist of one alkyl constituent and two ester groups and generally have the molecular formula $RB(OR)_2$ but can also exist as RB(OR)(OH) whereas borinic acids consist of two alkyl groups, one hydroxyl group and have the molecular formula R_2BOH (**Figure 1.1**). Boron has three valence electrons and when in the aforementioned structures has a total of 6 valence electrons with an empty p-orbital. This gives a trigonal planar conformation and sp^2-hybridization. The empty p-orbital lies orthogonal to these three groups and it is this empty p-orbital that allows boron to act as a strong Lewis acid and gives it the ability to form an ate complex. The ate complex is boron in its tetra-bonded form which has sp^3-hybridisation.

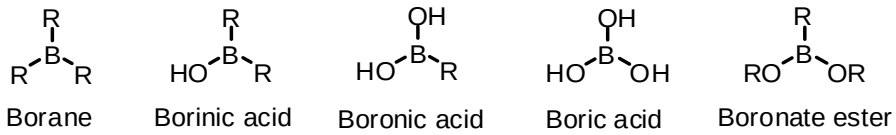


Figure 1.1

Borinic acids are the product of oxidation of boranes and boronate esters are the oxidation product of borinic acids. The toxicity of these compounds is considered low and hence makes them a useful tool for the organic chemist. These compounds are oxidised and degrade to boric acid which is of low toxicity in man.

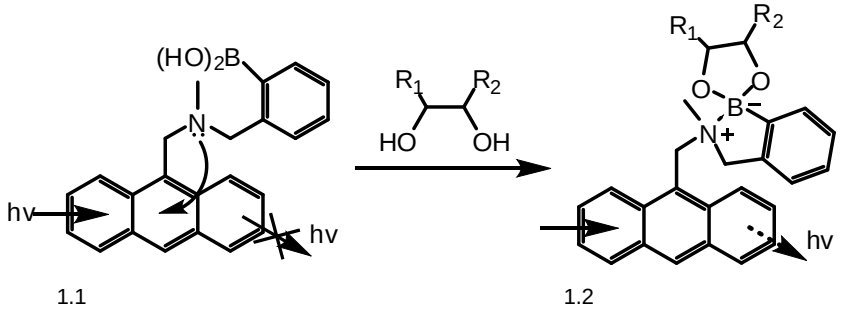
The boron oxygen bond is incredibly strong at around ~ 519 kJ mol^{-1} compared to that of C-O ~384 kJ mol^{-1}[1(1)]. This is due to the conjugation between the lone pairs on oxygen and boron's vacant p orbital, allowing partial double bonding character [(2)]. Boron's strong affinity for oxygen and its relatively strong bond with carbon, coupled with the ability to switch from sp^2 to sp^3 has meant it is of great importance in organic synthesis and is often featured in stereodirected synthesis.

1.2 Brief introduction into the use of boron derivatives in pharmaceuticals

1.2.1 Diabetes

A key area of interest and use of boronic acids is as an enzyme inhibitor. This inhibition of enzymes is mostly based on the ability of boron to convert between trigonal and tetrahedral forms by accepting lone pairs, mainly hydroxyl groups. This interaction with hydroxyl groups also extends to the diols of sugars. This effects glucose concentration variation with permeability changes[3,4,5]. These changes could therefore be used to control the release of insulin from polymer encapsulation.

Recent work with regard to boronic acid's ability to covalently bind 1,2 and 1,3 with diols concerns the monitoring of blood glucose level in real time[6]. This has been proposed utilising fluorescence which is triggered by photoelectron transmission (PET) following boron binding to the diol.



1.1 1.2

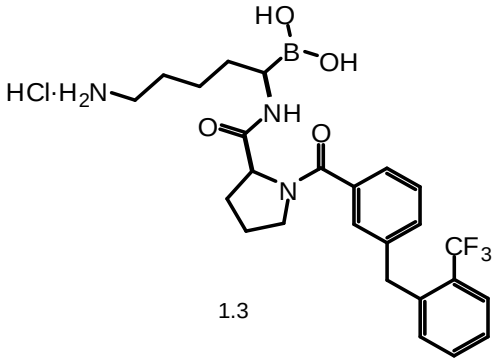
Figure 1.2

Figure **1.2** represents work done by Shinkai[7] who utilised a 1,5 relationship between boron and nitrogen due to its known ability to form B-N dative covalent bonds. This anchimeric B-N interaction was found to increase the binding affinity to glucose and fructose. The increase in binding affinity to 1,2 and 1,4-diols is thought to be favourable due to a significant release of angle strain, and rehybridization of boron from sp^2 to sp^3[8]. A difference in fluorescence intensity is observed which could be due to the nitrogen lone pair quenching the anthracene moiety through PET. The exact mechanism is not known however, and Fang *et al.* think the change in the bond strength between nitrogen and boron is not responsible and are leaning towards a

hydrolysis mechanism[9]. This system demonstrates a useful reporter and possible sensor for sugars and could help in the development of monitoring devices for diabetes sufferers.

1.2.2 Serine protease inhibitors

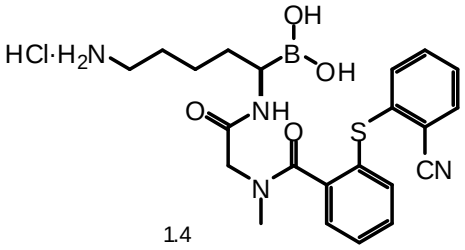
Boronic acids can also be used to inhibit serine protease, and the boronic acid **1.3** in particular was found to be a very potent thrombin inhibitor, the final serine protease in the blood coagulation cascade resulting in the transformation of fibrogen to fibrin[10]. Naturally thrombin is a good target for the development of anticoagulant agents of which boropeptides are potent inhibitors [12].



1.3

Figure 1.3

Alternatively the boropeptide **1.4** on screening for its thrombin inhibition qualities was found to inhibit factor Xa. Factor Xa like thrombin plays an important role in the coagulation cascade and has the physiological role for proteolytic cleavage of prothrombin to thrombin and is therefore considered an attractive method for thrombosis prevention[11].

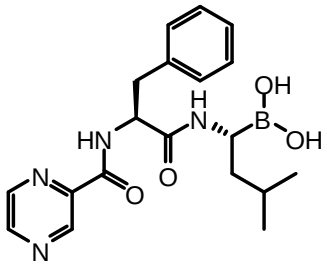


1.4

Figure 1.4

1.2.3 Proteosome inhibitors

Dipeptidyl boronic acids have been found to be potent and selective inhibitors of proteosomes[13]. Proteosomes are eukaryotic cytoplasmic proteinase complexes that play a major role in cellular pathways for the rapid breakdown and processing of proteins to peptides and amino acids[13]. Due to there function and role they have been implicated in many disease states including, muscular dystrophy, the cachexia accompanying cancer and malnutrition, emphysema, leprosy and acute leukemia as well as multiple myeloma[14]. The proteosome 26S is the multi-catalytic protease responsible for intracellular protein turnover in eukaryotic cells. This includes the degradation of damaged, oxidised or misfolded proteins and is key to cell life cycle. It should be noted however that this is also responsible for accelerated protein degradation that occurs with cancer[15]. Degradation is done by a tagging process whereby a small protein, ubiquitin; labels the cell for destruction. Adams and Behnke[16] found that tripetidyl boronic acids show a high selectivity for proteasome 26S inhibition along with leucine at p1, with generally large throphobic residues at p2 and p3.



1.5

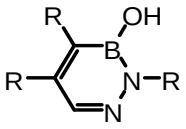
Figure 1.5

Following this on the 13th May 2003, Bortezomib[17] or Velcade **1.5** as it is marketed by millennium pharmaceuticals was cleared for public use. It is the first proteosome inhibitor to be approved by the US FDA and the first boron containing pharmaceutical. It was approved for multiple myeloma (MM), a type of blood cancer that affects 2-3 people in every 100,000. MM is a malignant B-cell tumour characterised by osteolytic bone lesions. *In vitro* it has been found that myeloma cells were 1000 times more sensitive to apoptosis than normal plasma cells when exposed to Bortezomib[18]. The dipeptidyl boronic acid forms a complex with the threonine hydroxyl group in the ‘‘chymotrypsin-like’’ active site, situated in the 20S

protesome sub-unit. Here it forms a reversible inhibitor and it is this ‘’chymotryptic-like’’ activity of the proteosome which inhibits proteolysis.

1.2.4 Enoyl Reductase

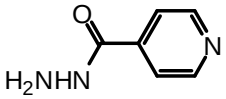
Diazaborines of general structure **1.6** contain a 1,2-diazine ring and boron as a third heteroatom and have been found to inhibit cell growth by preventing lipopolysaccharide synthesis. This is the biosynthesis of fatty acids and is carried out by enoyl reductase (ENR) and this process plays an integral role in the synthesis of the bacterial cell wall in gram-negative strains [19].



1.6

Figure 1.5

Diazaborines have been shown to bind alongside nicotinamide adenine dinucleotide (NAD^+) in order to affect ENR[20]. X-ray studies have shown that a covalent bond is formed between 2’ hydroxy of the nicotinamide ribose and boron. The inhibition is brought about *via* a tight but noncovalent binding of the bisubstrate analogue of the enzyme[21]. An already marketed drug, isoniazid **1.7** also targets ENR, and is used in the front line treatment of *tuberculosis*.



1.7

Figure 1.6

However some strains of *Mycobacterium tuberculosis* emerging are resistant[22] to isoniazid and so demonstrates the importance of developing new boron containing pharmaceuticals that could perhaps provide more effective alternatives for the future.

1.2.5 Beta Lactam inhibitors

Bacterial β-lactamases catalyse the destruction of β-lactam antibiotics *via* hydrolysis of the amide bond. This results in the resistance of some types of antibiotics and so the search for new β-lactamase inhibitors are essential in the fight against bacterial infections. It has been shown that boronic acids bind well to β-lactamases[23] and are therefore potent β-lactamase inhibitors, again due to their ability to undergo hydrolysis and form an ate complex stopping the hydrolysis of the β-lactam ring; *see* **figure 1.7**. The more the boronic acid resembles the β-lactamases natural inhibitors, the better the inhibition[24].

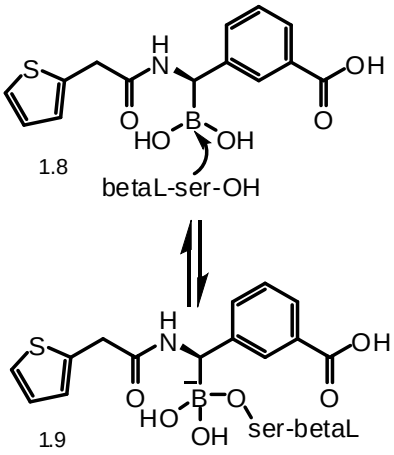


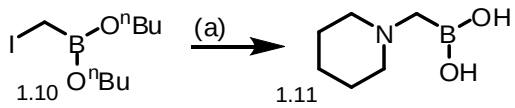
Figure 1.7

Bacterial resistance to β-lactam antibiotics continues to increase and identification of a novel class of β-lactamase inhibitors is of vital importance in the pursuit of more effective antibiotics[25]. It is therefore not surprising the vastly growing attention boronic acids are gaining within the field of pharmaceutically important molecules and it is therefore our intention to develop new methods in the construction of cyclic boronate esters with an hydroxyl moiety and nitrogen present in the α-position.

1.3 The construction of α-aminoboronic acids and their derivatives.

1.3.1 Research conducted by Matteson *et al.*

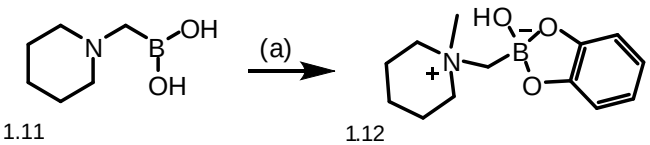
Matteson's group has been the most active in creating synthetic pathways to the construction of α-aminoboronic acids. In order to access this range of compounds Matteson employed halide displacement to introduce nitrogen.[26]



1.10 1.11

Scheme 1.1: Reagents and Conditions (a) Piperidine, 1-butanol, 0 °C.

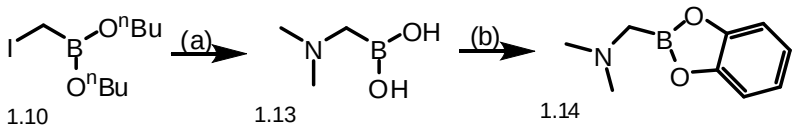
The α-haloalkaneboronic ester **1.10** was synthesised by treating iodomethylmercuric iodide with boron tribromide and sodium iodide, followed by esterification of the resulting product to give the iodomethaneboronate **1.10** in moderate yield (35-40 %). The iodide of **1.10** was then displaced on treatment with piperidine to give the the α-aminoboronic acid **1.11** which could not be purified[27].



1.11 1.12

Scheme 1.2: Reagents and Conditions (a) Catechol, MeCN, H_2O, methyl iodide, DMSO.

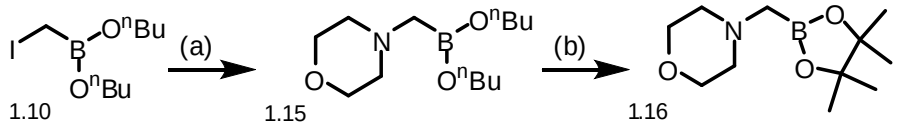
Matteson further reacted the piperdinomethaneboronic acid **1.11** esterifying with catechol and methylating nitrogen to give a stable quarternary ammonium derivative **1.12** (~50 %). Ammonia and its derivatives were also used in the displacement reaction but routes were capricious. When dimethylamine was used as the nucleophile, the product **1.13** was obtained, however, proved difficult to purify and was categorised as its catechol ester **1.14**.



1.10 1.13 1.14

Scheme 1.3: Reagents and Conditions (a) Dimethylamine, 1-butanol, 0 °C; (b) catechol, MeCN, H_2O, 0 °C.

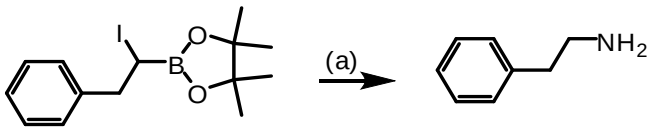
Phthalimidomethane boronic acid was also prepared but attempted hydrolyses failed to give the free amine. The iodomethaneboronic acid **1.10** reacted with morpholine to give the aminomethane boronic ester **1.15** which was esterified with pinacol to give the ester **1.16**.



1.10 1.15 1.16

Scheme 1.4: Reagents and Conditions (a) Morpholine, Et_2O, 0 °C; (b) pinacol, Et_2O, 97%.

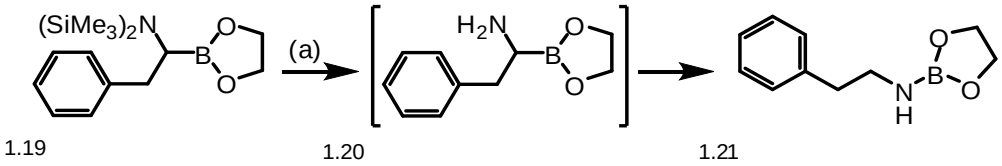
This showed that the B-C-N bond was stable to hydroxyl groups. Unfortunately the attempted deprotonation of **1.16** between boron and nitrogen failed in Matteson's hands.



1.17 1.18

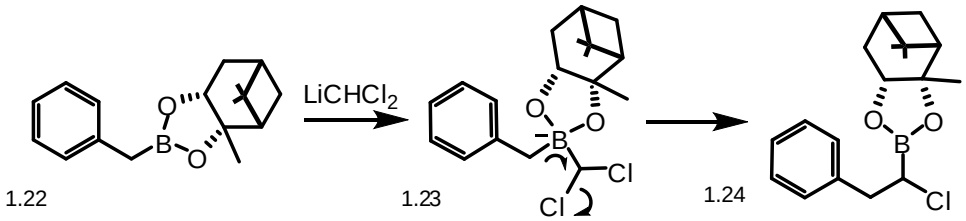
Scheme 1.5: Reagents and Conditions (a) liquid NH_3, bomb, 25 °C.

Matteson found that the α-iodoboronate **1.17** yielded the 2-phenylethylamine **1.18** on treatment with liquid ammonia under pressure. It was discovered that α-amino boronic acids are unstable if nitrogen is protonated. The boronic ester group and the proton on nitrogen are said to trade places. In another example the silylated α-aminoboronate **1.19** gave the amine derivative **1.21** when treated with methanol. The free amine **1.20** resulting in desilylation could not be purified and was found with heat or hydroxylic solvents to rearrange to the 2-phenylamine-N-boronic ester **1.21**[(28)].



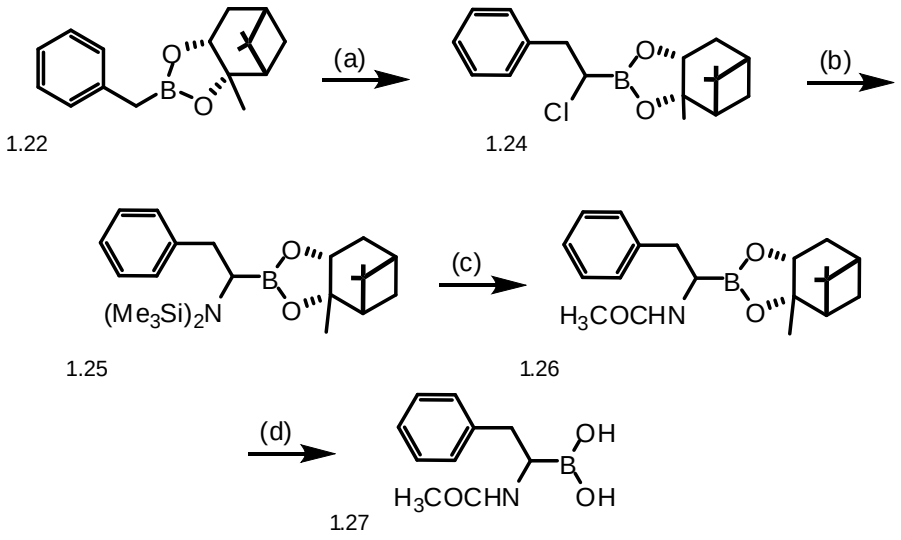
Scheme 1.6: Reagents and Conditions (a) MeOH, Et_2O, 0 °C.

The boronic acid **1.22** made in the Matteson laboratory was found to be a potent inhibitor of the serine protease, chymotrypsin[29]. Homologation of the benzylboronate **1.22** was achieved with dichloromethyllithium to give 1-chloro-2-phenylethaneboronate **1.24**. This is thought to proceed by benzyl migration from the initially formed ate complex with boron **1.23** (**scheme 1.6**).



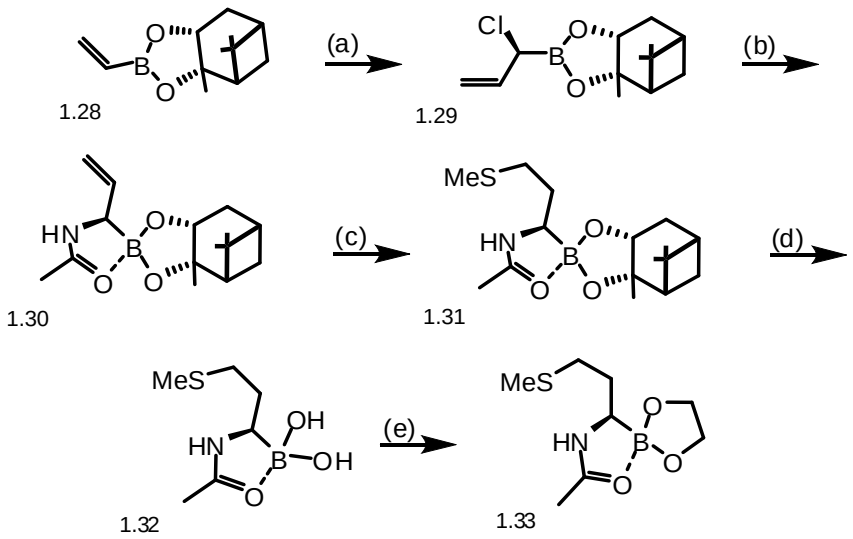
Scheme 1.7

Treatment of **1.24** with lithiohexamethyldisilazane gave the silyated amino boronic ester **1.25** in 85 % yield. The amine **1.25** was de-silylated using acetic anhydride in the presence of glacial acetic acid to give the pinanediol acetamido boronate **1.26** (56 %); then removal of pinanediol gave the acetamido boronic acid **1.27** (71 %)[30].



Scheme 1.8: Reagents and Conditions (a) $LiCH_2Cl_2$, THF, -100 °C; (b) $LiN(SiMe_3)_2$, THF, -78 °C; (c) acetic anhydride, acetic acid, THF, -78 °C; (d) BCl_3, DCM, 20 °C.

Starting with allyl borate **1.28** homologation and halide installation alpha to boron was achieved by the analogous sequence shown in **scheme 1.9**. Desilylation and acetylation to give (s)-pinanediol (r)-(1-acetamidoallyl)boronate **1.30** followed without difficulty. Radical addition of methyl mercaptan to the olefin gave the boronic ester **1.31** which was a crystalline solid. Subsequent treatment of **1.31** with boron tribromide gave the acid **1.32**. Esterification with ethylene glycol, gave again a crystalline solid **1.33**. This time an interesting X-ray structure could be deduced and was consistent with a, dative bond from the oxygen of the amide moiety[31]

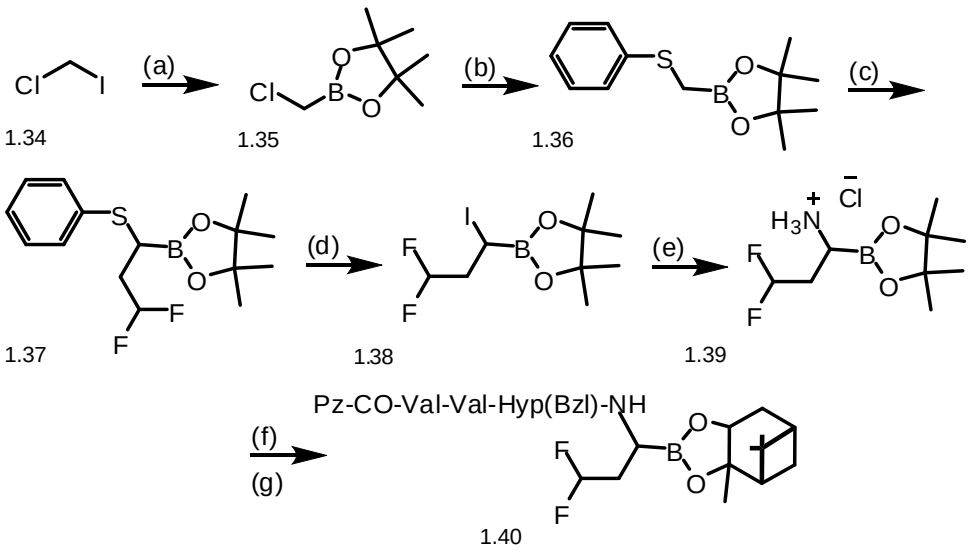


Scheme 1.9: Reagents and Conditions (a) $LiCH_2Cl_2$, THF, -100 °C; (b) $LiN(SiMe_3)_2$, acetic anhydride, acetic acid, THF, -78 °C, 71%; (c) methanethiol, irradiated (100W) mercury vapour lamp, 81%; (d) BCl_3, DCM, 20 °C; (e) ethylene glycol, methanol, (83% two steps).

Matteson has reported that many of these compounds have been extremely difficult to synthesise and are particularly capricious in nature. It appears the main route for installation of nitrogen has been through alpha halide displacement.

1.3.2 The work of Kettner in nitrogen installation.

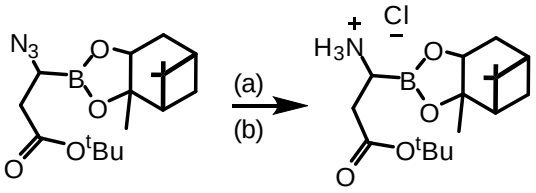
Kettner developed a range of α-aminoboronic acids in the hope of targeting hepatitis C protease inhibition[32]. Processing by this viral protease is achieved almost exclusively at the cysteine residue[33]. It was then an observation that the moiety CHF_2 is an isotere for a sulfhydryl group and so Kettner set about developing a synthesis to α-aminoboronic acids with a difluoroethyl side chain.



Scheme 1.10: Reagents and Conditions (a) ^{n}BuLi, $B(OiPr)_3$, pinacol; (b) thiophenol, diisopropylethylamine; (c) ^{n}BuLi, diisopropylamine, 2-bromo-1,1-difluoroethane, THF, 0 °C, 56%; (d) MeI, NaI, MeCN, rt, 49%; (e) $LiN(SiMe_3)_2$, THF, -78 °C, HCl, 52%; (f) Pz-CO-Val-Val-Hyp(Bzl)-OH, N-methylmorpholine, isobutyl chloroformate, THF, -20 °C; (g) (+)-pinanediol, MeOH, (67% two steps).

Kettner starts his synthesis with chloroiodomethane **1.34** which is treated with ^{n}BuLi to give chloromethyl lithium which in the presence of triisopropyl borate adds in a S_N2 fashion. Pinacol was added to the reaction mixture containing the acid which gave the transesterification product **1.35**. The α-chloride **1.35** is then reacted with thiophenol in the presence of diisopropylamine to give the thioether **1.36**. The S-CH_2-B moiety can be deprotonated and hence easily alkylated at this point. Kettner then treated the thioether **1.36** with LDA in the presence of 2-bromo-1,1-difluoroethane to give the alkylated product **1.37**. The thiophenol moiety was methylated using methyl iodide and the resulting sulfonium salt displaced with sodium iodide to give the α-iodoboronate **1.38**. By analogy to the work of Matteson shown in **scheme 1.8**, lithium bistrimethylsilylamine is used to displace iodide and

install nitrogen. This group is subsequently desilylated and turned into the amine hydrochloride salt for stability **1.39**. From here the peptide chain was incorporated onto nitrogen and the pinacol removed with the resulting boronic acid, esterified with pinanediol to give the boronate ester **1.40** which was found to demonstrate good inhibition of the hepatitis C protease.



1.41 1.42

Scheme 1.11: Reagents and Conditions (a) H_2, Pd/C; (b) HCl/dioxane.

Kettner was also able to alkylate following the same procedure as **Scheme 1.10** but with ^{t}butyl bromoacetate and methyl acrylate as electrophiles. He then followed this with iodide displacement using sodium azide **1.41** and reduction to the amine salt **1.42** by catalytic hydrogenation in the presence of anhydrous hydrochloric acid.

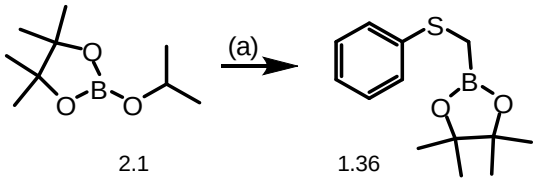
2. Results and Discussion

Aim

The aim of this project was to develop novel synthetic routes toward the construction of heterocycles containing boron as an ester or borinic acid, configuring nitrogen functionality alpha to boron as well as to synthesise novel compounds in this class. With the main focus on establishing the boron-nitrogen 1,3 proximity. Synthetic routes were then designed which utilised the 1,3-nitrogen-boron relationship and would allow a range of compounds to be effected.

2.1 Formation of methyl isocyano-pinacol borane

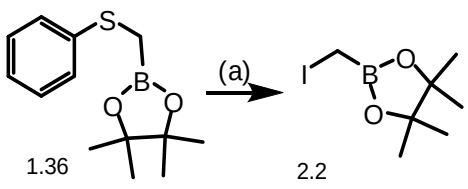
The readily available PINBOP **2.1** was treated with thioanisole which was metallated with ^{n}BuLi and TMEDA according to the procedure developed by Corey using DABCO[34] but later modified by Matteson[27]. This gave the thiophenylboronic ester **1.36** in reasonable yield (75 %).



2.1 1.36

Scheme 2.1: Reagents and Conditions (a) Thioanisole, ^{n}BuLi, TMEDA, THF, isopropyl-pinacol borate, 0 °C.

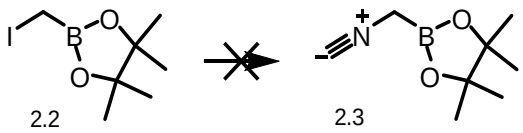
The known iodomethaneboronic ester **2.2** was then synthesised according to Matteson[27] by stirring the phenylthioboronic ester **1.36** with methyl iodide and sodium iodide at room temperature in acetonitrile for 48 hr to give the iodide **2.2** in moderate yield (57 %).



1.36 2.2

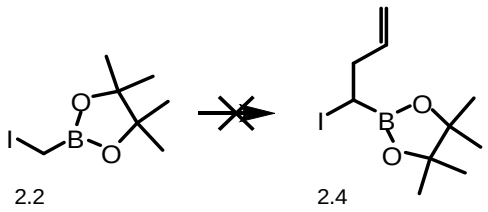
Scheme 2.2: Reagents and Conditions (a) NaI, MeI, MeCN, 48 hr.

It was thought the iodide could then be displaced using a S_N2 reaction with silver cyanide to give the isocyanide **2.3** and the required 1,3-boron-nitrogen framework.



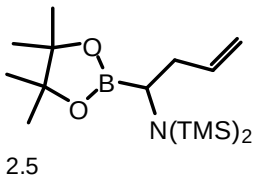
Scheme 2.3: Reagents and Conditions (a) AgCN, MeCN, heat.

However the reaction failed to proceed at room temperature and in refluxing acetonitrile for 12 hrs; starting material was recovered. Utilising the synthesised iodomethane **2.2** carbanion formation alpha to boron was investigated using LDA at -78 °C. To a solution of **2.2** and LDA was added the electrophile allyl bromide in an attempt at alkylation to give the homoallylic iodoborate **2.4**.



Scheme 2.4: Reagents and Conditions (a) ^{n}BuLi, diisopropylamine, allyl bromide, THF.

The reaction failed and decomposed. It is most likely **2.2** underwent lithium-halogen exchange before attacking itself and decomposing. Before taking a slightly different synthetic route the remaining iodide was used in attempts to displace iodide with LiHMDS followed by carbanion formation and alkylation using allyl bromide. All attempts to form the desired amine **2.5** failed.

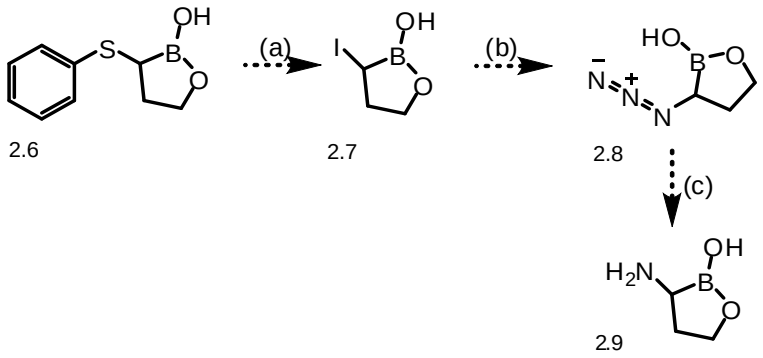


2.5

Figure 2.1

2.2 Proposed amino-oxaborolan (route 1)

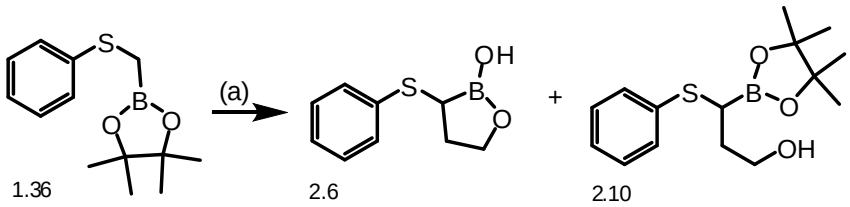
The known oxaborolan **2.6** [35,36] was a good starting point for a synthesis of the amino-oxaborolan **2.9** and it was hypothesised that **2.6** could be converted to the iodo-oxaborolan **2.7** using sodium iodide and methyl iodide. This iodide could in turn be displaced using sodium azide to give the α-azide **2.8** which could then be reduced for example with dichloroindium hydride under mild conditions[37] to give the desired amino-oxaborolan **2.9**.



Scheme 2.5: Reagents and Conditions (a) MeI, NaI, MeCN; (b) NaN_3, MeCN; (c) $InCl_3$, Et_3SiH, MeCN.

2.2.1 Synthesis of known phenylthio-oxaborolan 2.7

The borate **1.36** was added according to Matteson[38] to a solution of ^{n}BuLi and diisopropylamine in THF generating a carbanion alpha to boron.

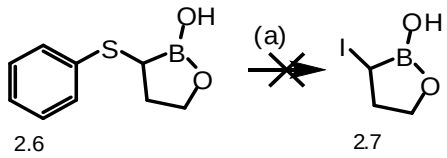


Scheme 2.6: Reagents and Conditions (a) ^{n}BuLi, diisopropylamine, ethylene oxide, -78 °C, THF.

To the *in situ* generated salt was added ethylene oxide at -78 °C which underwent nucleophilic attack to ring open and then cyclise onto boron with subsequent hydrolytic loss of pinacol to yield the cyclic boronate ester **2.6** as a white crystalline solid with the structure then confirmed by crystallography. The uncyclised product **2.10** is also formed which can be separated and further cyclised to **2.6** using borax or

BCl_3, however BCl_3 gave a slightly improved yield of 20 %. This was repeated several times due to the low original yield of **2.6** of between 5-10 %.

2.2.2 Halogenation of oxaborolan 2.6



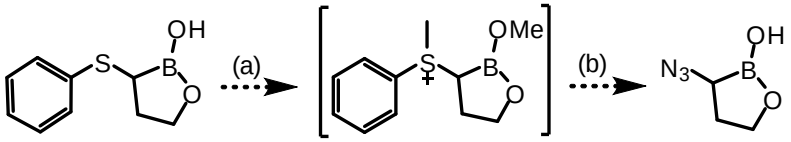
2.6 2.7

Scheme 2.7: Reagents and Conditions (a) NaI, MeI, MeCN, heat.

When **2.6** was treated with NaI and MeI in MeCN at room temperature followed by boiling in acetonitrile for six hours the desired product **2.7** was not obtained. Instead thioanisole was recovered along with decomposition products.

2.3 Proposed target amino-oxaborolan (route 2)

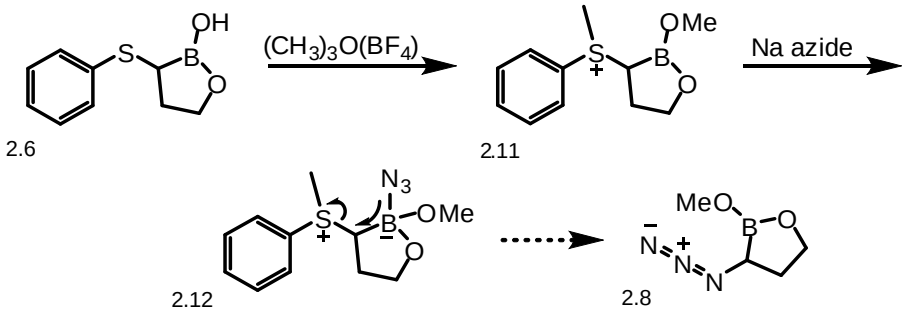
Using **2.6** as a starting material it was hypothesised that treatment with the trimethyl variant of Meerwein's salt could give the unstable compound **2.11** and on treatment of **2.6** with sodium azide, displacement of thioanisole could occur to give the boronic acid **2.7** with azide alpha to boron.



2.6 2.11 2.7

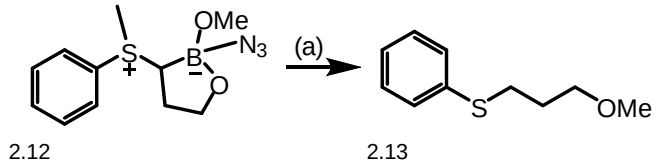
Scheme 2.8: Reagents and Conditions (a) $[(CH_3)_3O]BF_4$ 2 eq, Et_2O (b) NaN_3, MeCN.

Trimethyloxonium tetrafluoroborate was added to **2.6** in diethyl ether and stirred for two hours. After all the starting material had disappeared according to tlc, the solvent was removed and the salt taken up in acetonitrile whereupon it was heated under reflux with sodium azide for 6 hours in the hope that azide would displace thioanisole to give the desired product **2.7**. On work-up a white crystalline solid was isolated which resembled the borate salt **2.11** according to ^{1}H-NMR, after mass spectrometry it was then thought to be the ate complex **2.12**. Waiting on further mass spectrometry evidence the white crystalline solid was dissolved in DMSO and heated to 140 °C in a further attempt to obtain **2.7,** this time the idea was to induce migration of the azide into the alpha position by a 1,2-anionic shift; see **scheme 2.9**.



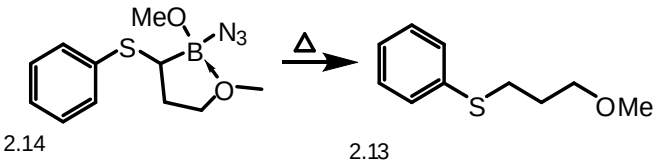
Scheme 2.9

The desired boric acid **2.7** was not formed and after flash column chromatography a decomposition product was isolated and characterised as **2.13** (87 % yield)**.**



Scheme 2.10: Reagents and Conditions (a) DMSO, 140 °C.

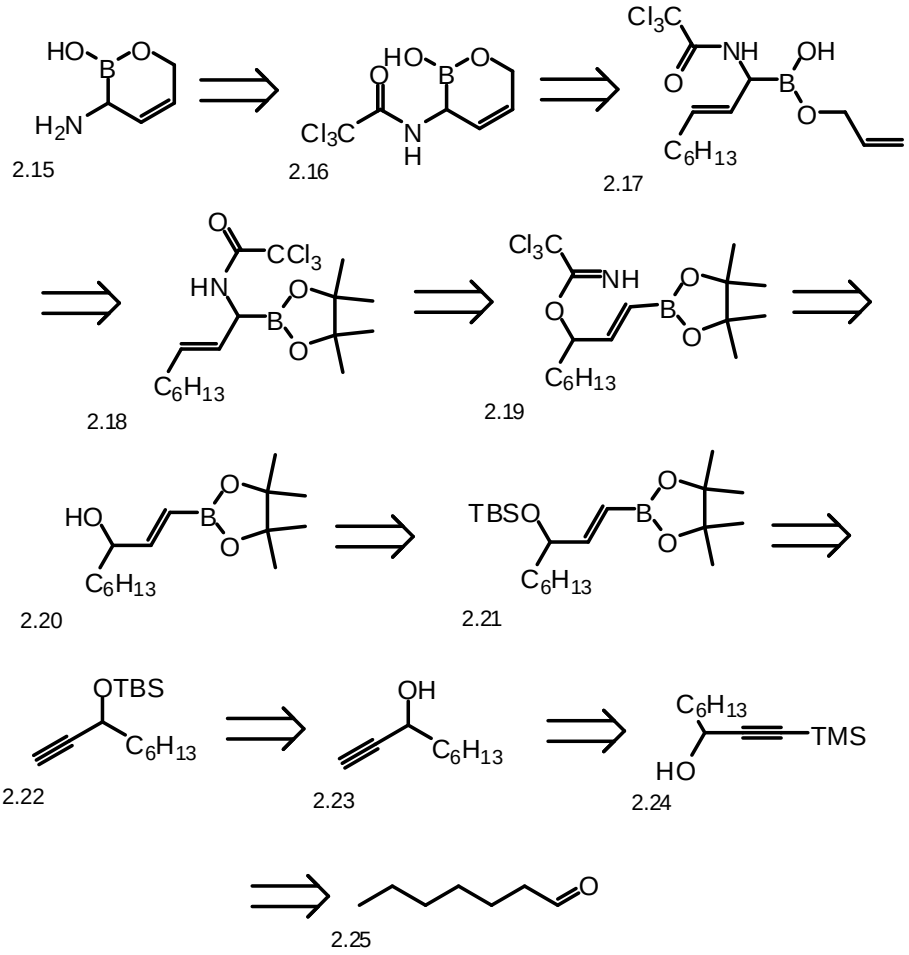
The resulting pale straw coloured oil was in fact that of the methoxy phenyl thio ether **2.13.** Extrapolating back to the starting material it is now thought that **2.12** was in fact the ring open methoxy compound **2.14** and on heating, the di-methylated species **2.14** decomposed with loss of boron to yield the ether **2.13** shown in **scheme 2.11**.



Scheme 2.11

2.4 Retrosynthetic approach to amino-oxaborolan (route 3)

By utilising alkene metathesis it was hypothesised the unsaturated oxaborolan **2.15** could be made from its metathesis precursor **2.17**. The precursor **2.17** could be generated from the pinacol protected boron-acetamide **2.18** and allyl alcohol. A key step to this synthesis will be the generation of the acetamide from its imidate precursor **2.19** which relies on a [3,3]-sigmatropic shift using Overman conditions to install nitrogen alpha to boron.



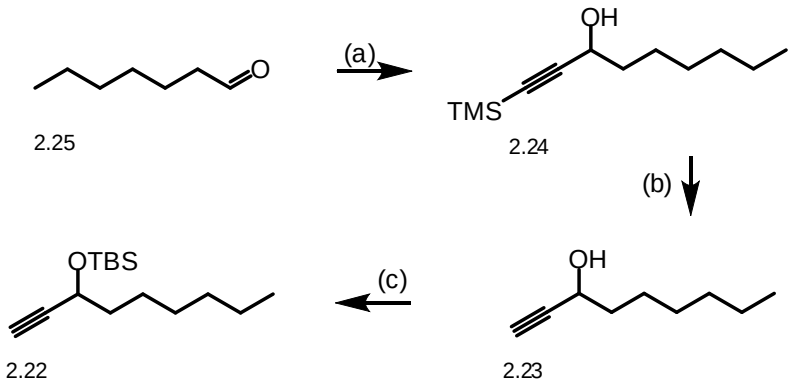
Scheme 2.11: Retrosynthesis of **2.15**.

The imidate precursor **2.19** is simply constructed from the allylic alcohol **2.20**, a base and trichloroacetonitrile. The alkenyl alcohol **2.20** is a product of hydroboration between the alkyne **2.22** and pinacol borane followed by TBDMS removal. The starting alkynyl alcohol **2.23** is formed from the aldehyde **2.25** using routine steps. The long chain aldehyde heptanal **2.25** was chosen purely for its ability to add mass and create a less volatile set of compounds.

2.5 Oxaborolan synthetic approach (route 3)

2.5.1 Generation of the hydroboration precursor

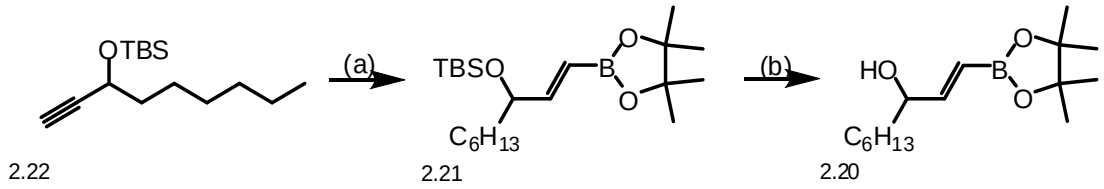
Heptaldehyde **2.25** was reacted with the anion of TMS-acetylene created with butyllithium to give the secondary alcohol **2.24** in good yield (96 %). The TMS group was removed using a catalytic amount of sodium methoxide in methanol to give the secondary alkynyl alcohol **2.23** (92 %) which was then protected with TBDMSCl in the presence of imidazole and a catalytic amount of DMAP to give **2.22** (72 %). This was carried out in preparation for the hydroboration of the acetylene moiety **2.22** with pinacol borane.



Scheme 2.12: Reagents and Conditions (a) ^{n}BuLi, TMS-acetylene, THF; (b) NaOMe, MeOH, DCM; (c) TBDMSCl, Et_3N, DMAP, DCM.

2.5.2 Hydroboration of alkyne 2.22

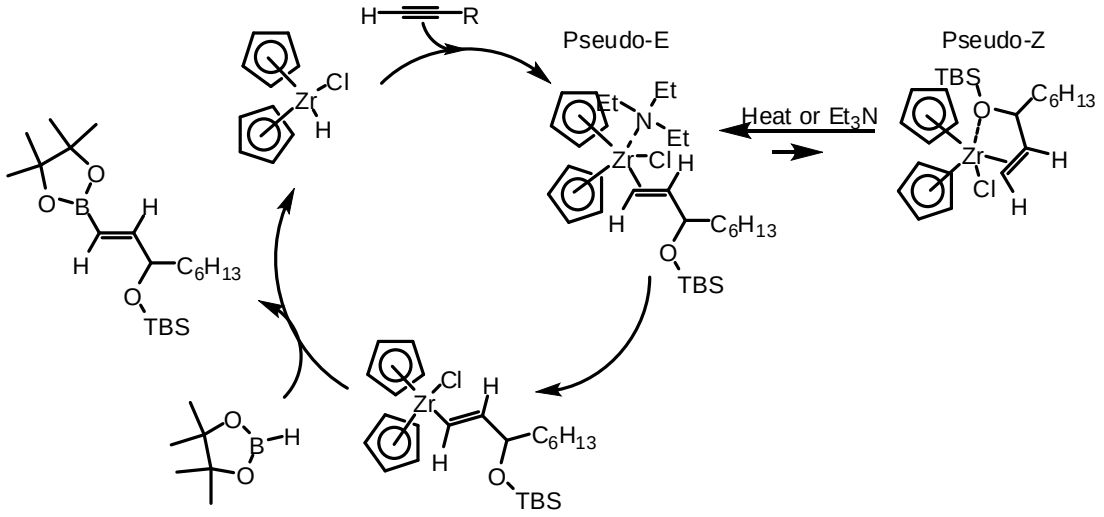
Pinacolborane was added across the acetylenic triple bond which was activated using Schwartz reagent (Cp_2ZrHCl). This transition metal complex has been reported to catalyse hydroboration with alkynes and pinacolborane at room temperature by Pereira and Srebnik[38]. Y. D. Wang & G. Kimball[39] have reported a method for the hydroboration of alkynes that give excellent yields as well as stereoselectivity and regioselectivity (E)-vinylboronic esters.



2.22 2.21 2.20

Scheme 2.13: Reagents and Conditions (a) Pinacolborane, Schwartz reagent; (b) $Ni(Cl)_2{\cdot}(H_2O)_6$, 1,2-ethanedithiol, DCM/methanol.

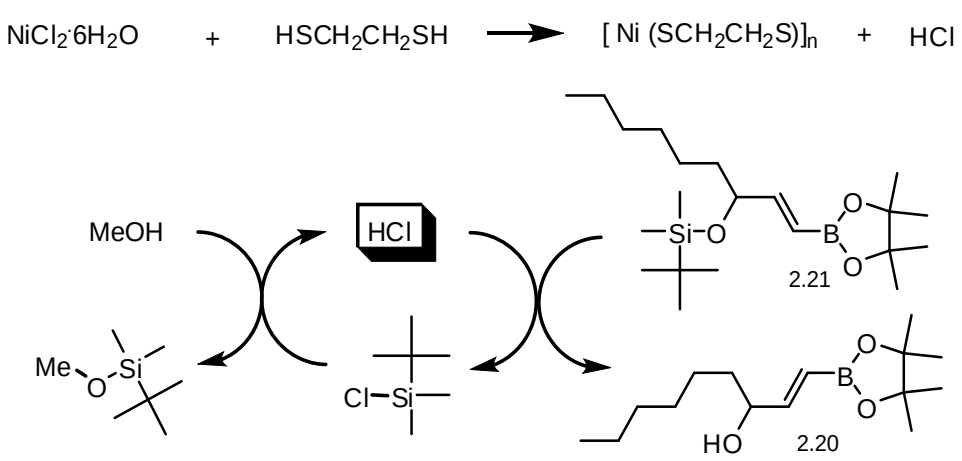
This method uses a base and slightly elevated temperatures to increase E stereochemistry. This is achieved by reducing the formation of an intermediate zirconocene complex that has pseudo-Z conformation with the oxygen on the TBDMS-ether group. Under this intermediate conformation hydroboration would achieve the Z-stereoisomer. The resulting (E)-vinylboronic ester **2.21** was achieved in good yield (92%).



Scheme 2.14: Mechanistic pathway for hydroboration with Schwartz reagent.

2.5.3 TBDMS removal

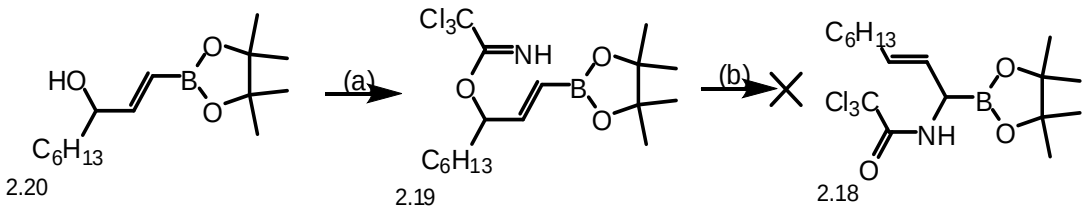
Removal of the *tert*-butyldimethylsilyl protecting group using a fluoride source was not achieved and after failure of this with TBAF and HF another non-fluoride method was sort. The failure of deprotection using a fluoride source is not known and due to the reported success of such methods was peculiar. Removal of the TBDMS ether also failed using a method developed by Khan[40], using catalytic acetyl chloride in dry methanol. In the end the (E)-alkenylboronic ester **2.21** was deprotected using a catalytic amount of nickel (II) chloride hexahydrate and 1,2-ethanedithiol[41].



Scheme 2.15: Mechanistic pathway for TBDMS deprotection of **2.21**.

These two compounds react to form a polymeric nickel complex that is black in solution and can release hydrochloric acid. It is hydrochloric acid which is thought to catalyse the deprotection of TBDMS ethers and is highlighted in **scheme 2.15**. The reaction was carried out in methanol/DCM (2:5), which is said to be the best ratio and gave the resulting allylic alcohol **2.20** in good yield (82 %). The alcohol was purified using flash column chromatography.

2.5.4 Imidate formation and 3,3-sigmatropic rearrangemnet



Scheme 2.16: Reagents and Conditions (a) DBU, trichloroacetonitrile, THF; (b) Heat, xylene.

Conversion of the secondary allylic alcohol **2.20** to an imidate was achieved using DBU to deprotonate the alcohol and then the addition of trichloroacetonitrile at 0 °C. The reaction worked well using a slight excess of trichloroacetonitrile and gave the crude imidate **2.19** in good yield (97 %). It is well known that on heating, allylic trichloroacetimidates undergo a facile [3,3]-sigmatropic rearrangement which was first reported by L. Overman[(42)]. On heating the imidate **2.19** in xylene no reaction occurred and so a number of different conditions and reagents were used in order to facilitate the desired [3,3]-shift. Overman has also looked at catalysts to assist the rearrangement of imidates and this is well documented in other [3,3]-sigmatropic reactions such as the Cope and Claisen varients. These reactions can need heat in excess of 180 °C. Palladium (II) and mercury (II) catalysts were looked at including palladium chloride, palladium bis(benzonitrile) dichloride and mercury trifluoroacetate[(43,44,45)].

Reagent	Reagents and conditions	Yield %	Temperature
2.19	toluene	0	reflux
2.19	toluene, K_2CO_3	0	reflux
2.19	xylene	0	reflux
2.19	xylene, K_2CO_3	0	reflux
2.19	1,4 dioxane	0	reflux
2.19	THF, 5% Pd bis(benzonitrile) dichloride	0	reflux
2.19	THF, 5% Pd Cl_2	0	reflux
2.19	THF, 20% Hg trifluroacetate	0	reflux
2.19	THF, microwave 125 °C, 4 bar	0	85 °C
2.19	Xylene, microwave 180 °C, 6 bar	decomp	180 °C
2.19	xylene, 10% Pd bis(benzonitrile) dichloride	0	reflux

Table 2.1: Results for attempts on the rearrangement of imidate **2.19**.

Table 2.1 lists numerous attempts to carry out this reaction. It is also reported that the Overman reaction works well and in good yield with inductively electron donating groups alpha[46] to the double bond. As boron occupies this position and has an empty p orbital it can behave as a Lewis acid accepting electron density and it could be this effect that has stopped the electron rich double bond from undergoing a [3,3]-sigmatropic shift. It has been reported by Hall[47] that the alkenyl boronates could generate mesomeric resonance forms. As the electron rich double bond donates into the empty boron p orbital it generates a degree of carbon-boron π-bonding; see **figure 2.2**.

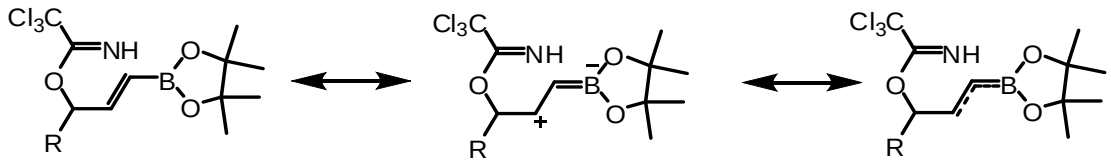


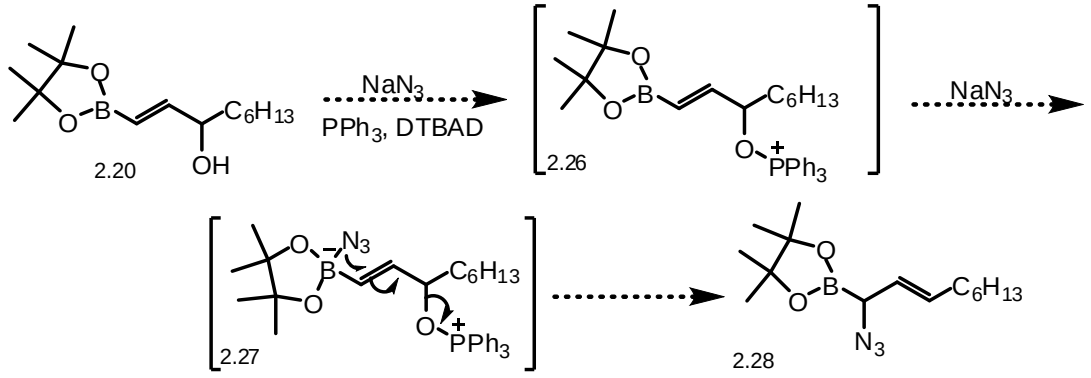
Figure 2.2: Polarising effects on alkenyl boronates.

A ^{13}C-NMR study carried out by Yamamoto and Moritani[48] concurs that there is significant evidence that points towards π-bonding in alkenylboranes.

It could be this effect that has prevented the alkenyl imidate from undergoing a [3,3]-sigmatropic shift. Another possibility is intermolecular interactions from the lone pair on nitrogen donating into the Lewis acidic boron centre forming an ate complex, although this could not be verified.

2.6 Boron mediated Mitsunobu S_N2

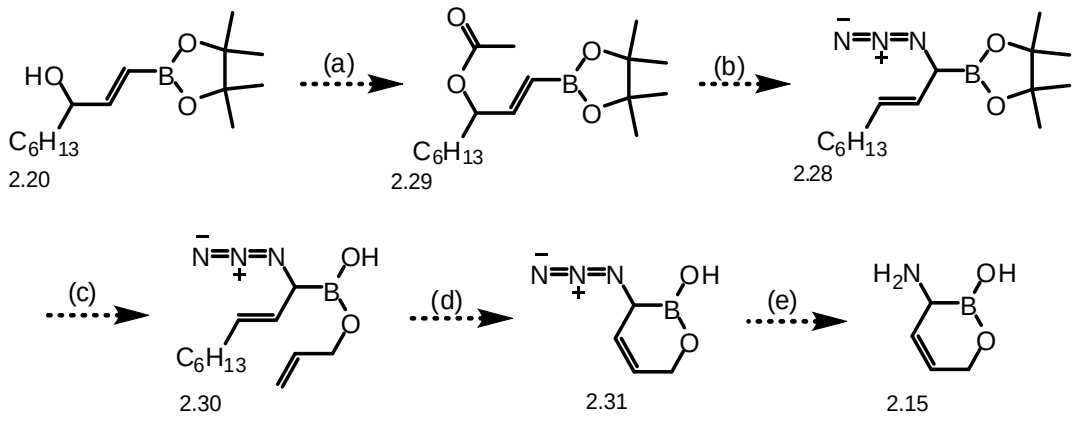
Utilising the allylic secondary alcohol **2.20**, a new scheme was then proposed.



Scheme 2.17: Reagents and Conditions (a) NaN_3, PPh_3, DTBAD, THF.

According to a new publication entitled S_N2' boron-mediated Mitsunobu reactions[49], an interesting method for installing nucleophiles alpha to boron on allylic alcohol boronate esters was discovered. In this paper it is reported that in a one pot synthesis, an alkenic boronate secondary alcohol can be converted to an α-substituted allylboronate. This is done by treating the alcohol with triphenylphosphine and DTBAD as in a Mitsunobu reaction to form the phosphonium intermediate **2.26**. It was then postulated by analogy to Berreé's reaction that benzoate forms an ate complex with boron, if an azide could be substituted for benzoate this would then undergo an anionic 1,2-shift **2.27** displacing the phosphonium as phophine oxide to afford the alkenyl azide **2.28**. However the reaction did not proceed and the allyl alcohol **2.20** was recovered. This could be due to sodium azide not being a strong enough nucleophile or the postulated ate complex **2.27** could be stable to migration.

2.7 Nitrogen installation using allylic acetate



Scheme 2.18: Reagents and Conditions (a) DBU, DCM, trichloroacetoacetate; (b) $Pd(PPh_3)_4$, NaN_3, THF, heat; (c) allyl alcohol, NH_3, THF, NH_4Cl; (d) Grubbs (II), DCM; (e) PPh_3.

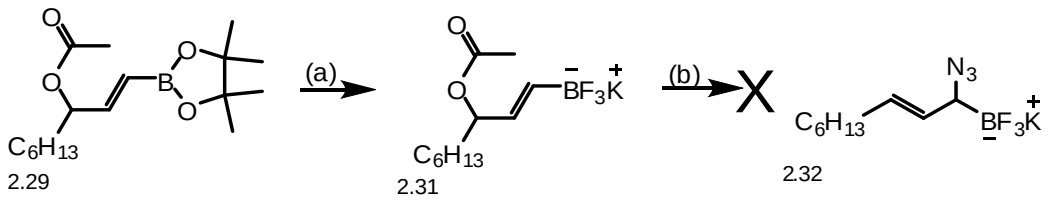
A new route was proposed; again starting from the secondary alcohol **2.20** then by conversion to an allylic acetate **2.29**. Allylic acetates interact with tetrakis triphenylphosphine palladium (0) which activates the allyl-O bond of allyl acetate to afford η3-allyl(acetate)palladium species[50,51]. It was hoped that this species could be formed on the current system and the acetate ultimately displaced by azide either by a 1,2-shift from the ate complex or by a direct S_N2 displacement of acetate. If the latter worked it would be possible to detect isomers as this would allow the azide to approach from either end of the π-allyl bond. $Pd(PPh_3)_4$ was freshly prepared according to the method of Hegedus[51] and was isolated as a bright yellow solid which was kept at -20 °C under argon.

The boronate allyl acetate **2.29** was heated in refluxing acetonitrile with catalytic $Pd(PPh_3)_4$ and sodium azide for two hours, a UV active spot was observed using thin layer chromatography however after work-up only decomposition products were isolated. The reaction was tried again this time without the palladium, resulting in recovery of starting material.

The nucleophile was changed from sodium azide to sodium cyanide and then to TMS cyanide respectively and adopting the previous palladium conditions; again the starting material remained unchanged.

Looking back to **scheme 2.16**; it seemed worth changing the properties of the boron moiety to see if this would have any bearing on the [3,3]-sigmatropic shift to give the acetamide. One possible reason for this failed reaction was due to boron's empty p orbital. It is known that if the group alpha to the electron rich double bond has a positive inductive effect this speeds up the reaction[(46)] . Looking at the work reported by Vedejs and more recently by Molander involving alkenyl-potassium trifluoroborate salts[(52,53)], it was thought that by changing the pinacolborate moiety to potassium trifluoroborate the inductive qualities could be beneficial to the [3,3]-sigmatropic shift reaction in this system. The potassium trifluoroborate protecting group is also much more stable and less sensitive to air than pinacol borate. It would hopefully allow ease of purification for further steps and could provide help in removing the difficulties in purifying compound **2.19** which was decomposed by both column chromatography and distillation.

2.8 Potassium trifluoride protection of boron

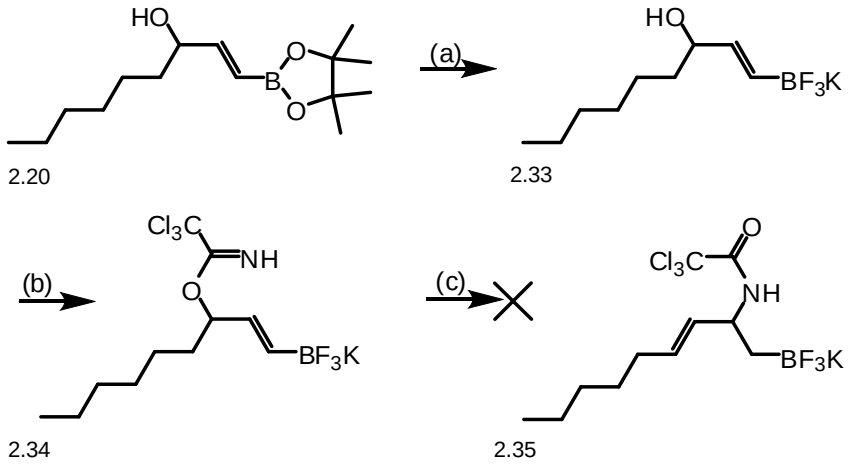


2.29 2.31 2.32

Scheme 2.19: Reagents and Conditions (a) KHF_2, DCM, H_2O; (b) $Pd(PPh_3)_4$, NaN_3, MeCN, reflux.

The alkenyl acetate **2.29** was easily converted to its alkenyl-trifluoroborate salt **2.31** using potassium hydrogen fluoride and water[(54)] in good yield (98 %). The resulting allyl acetate trifluoroborate salt **2.31** was then reacted with tetrakis(triphenylphosphine)palladium (0) and sodium azide and heated to reflux in acetonitrile and again in methanol. However only starting material was obtained after 24 hr in each medium respectively.

2.8.1 Potassium trifluoroborate imidate formation



Scheme 2.20: Reagents and Conditions (a) KHF_2, DCM, water; (b) DBU, trifluoroacetonnitrile, DCM, 0° C; (c) DMSO heat 140 0 °C.

The alkenyl alcohol **2.20** was easily converted to its boron trifluoroborate potassium salt **2.33** (98 %) using KHF_2 and water. The salt **2.33** was then dissolved in hot acetonitrile and cooled to room temperature whereupon DBU was added. The reaction mixture was then cooled further to 0 °C whereupon trichloroacetonitrile was added dropwise, left for an hour and worked up with water to afford the crude trichloroacetimidate **2.34** as an off white solid, the structure of which was tentatively confirmed at the time with proton NMR. The product from the previous reaction was heated in deuterated DMSO in a sealed NMR tube at 140 °C for 36 hours in an attempt to rearrange the little product retrieved. The trichloroacetimidate was thought to have undergone a [3,3]-sigmatropic shift to afford the trichloroacetamide **2.35** according to ^{1}H-NMR. This was only done on a small amount of the crude and hence in a sealed NMR tube. The ^{1}H-NMR spectrum depicted a loss of starting material and in favour of the imidate. The ^{1}H-NMR was taken every twelve hours and loss of the alkene peaks in the starting material was observed. The new peaks were thought to be associated with the acetamide and consisted of two doublet of doublets and a multiplet. **Figure 2.3** depicts the ^{1}H-NMR study and shows spectra taken after twelve hour intervals.

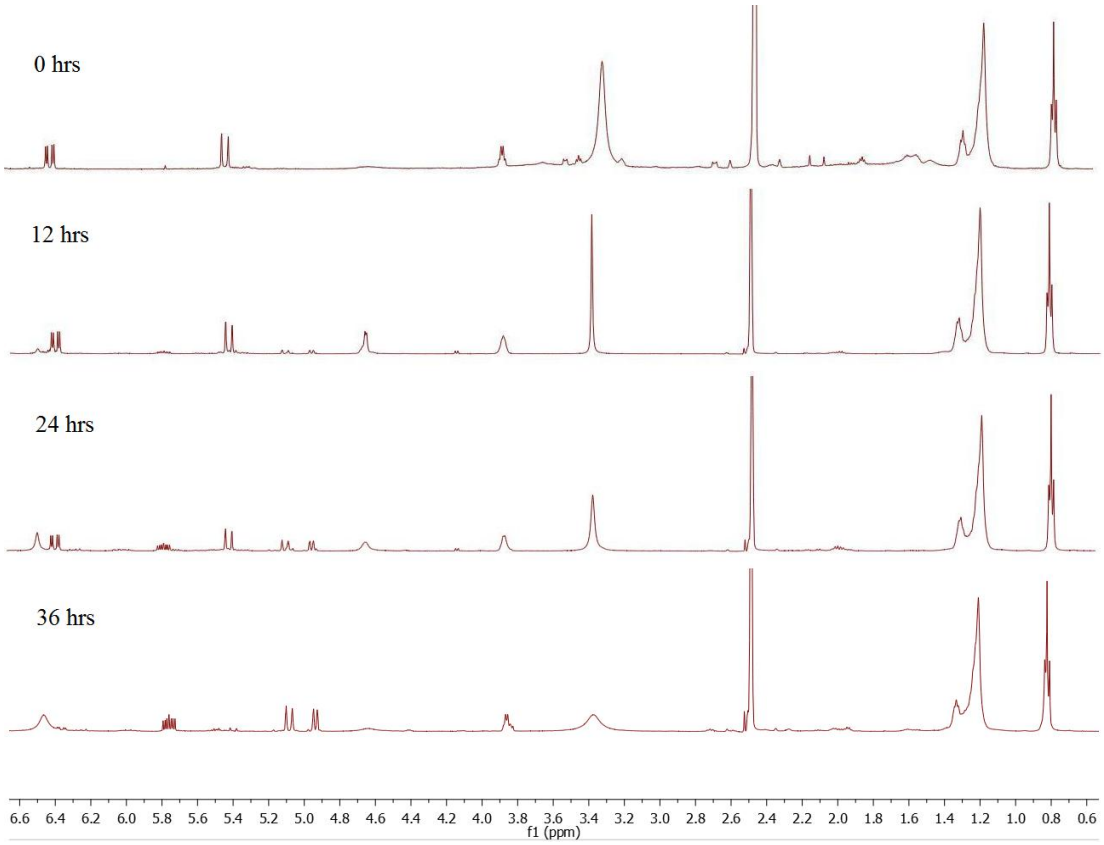


Figure 2.3: Shows ^{1}H-NMR taken every 12 hours for **2.34** heated at 140° C in DMSO.

Further characterization of **2.35** using mass spectrometry was not possible, the parent ion was not found and ^{13}C-NMR analysis gave inconclusive results partly due to the small amount of material recovered (~10 mg). Sadly resynthesis of the potassium trifluoroborate salt **2.34** and hence the Overman reaction to give **2.35** was not possible. Due to the encouraging initial findings, attempts to remake the precursor were tried repeatedly; altering many variables slightly and drastically to try and repeat the previous findings. **Table 2.2** lists the numerous attempts to remake **2.34**. The reason for the inability to remake the imidate **2.34** is still unknown and clearly represents how capricious this chemistry is. Alas no more time could be justified on this one reaction and so an alternative route was sought.

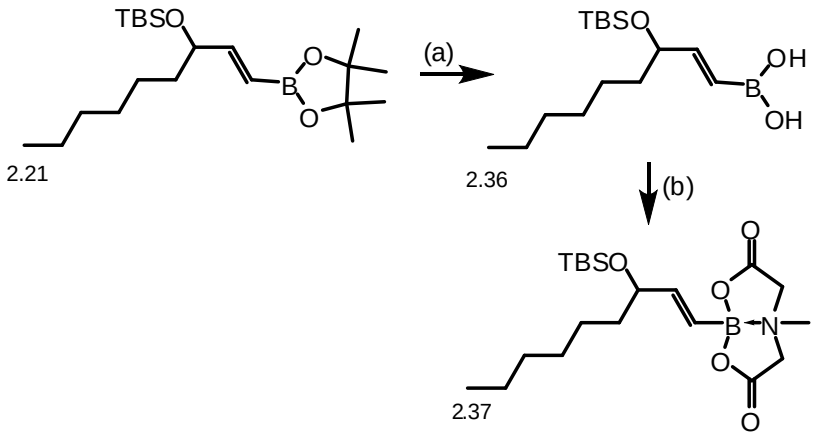
Reagent	Reagents and conditions	Yield %	Temperature
2.33	CCl_3CN (1.2 eq), DBU, MeCN	0	25 °C
2.33	CCl_3CN, DBU, MeCN, NH_4Cl	0	25 °C
2.19	KHF_2, MeCN, H_2O	decomp	0 °C
2.33	CCl_3CN, DIPEA, MeCN	0	25 °C
2.33	CCl_3CN, DBU, DCM	0	25 °C

2.33	CCl_3CN, DBU, DME	0	25 °C
2.33	CCl_3CN, DBU, MeOH	0	25 °C
2.33	CCl_3CN (1.2 eq), DBU, MeCN	0	40 °C
2.33	CCl_3CN, NaH, MeCN	0	70 °C
2.33	CCl_3CN, DBU	decomp	25 °C
2.33	CCl_3CN (5 eq), DBU, NH_4Cl	0	25 °C

Table 2.2: Results for resynthesis of 2.34.

2.9 N-Methyliminodiacetic acid boron protection

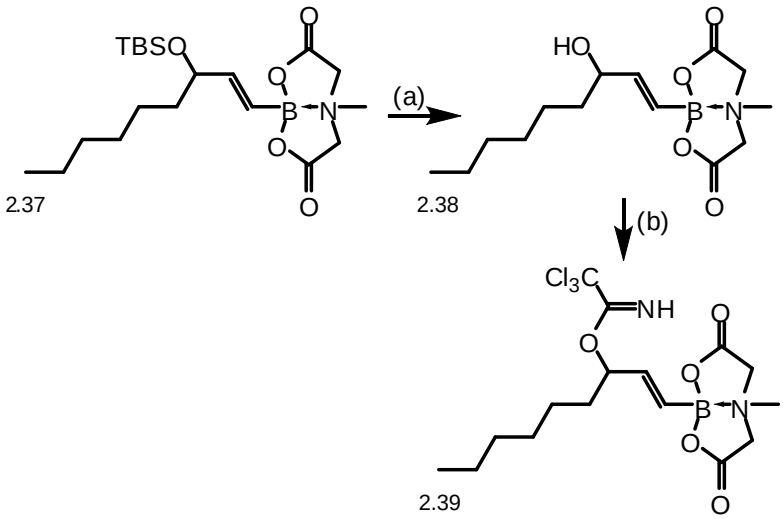
An alternative protecting group for boron was then found, one that had greater solubility but also retained the similarity to potassium trifluoroborate in that it could attenuate reactivity by rehybridization from sp^2 to sp^3. Work recently done on just this by Gillis and Burke[55] looked at prevention of transmetalation by reduced attenuation in the Suzuki Miyaura coupling of protected haloboronic acids as building blocks. They found that N-methyliminodiacetic acid (MIDA) was a good trivalent ligand capable of reduced attenuation and easy protection and removal. Protection was achieved by heating a boronic acid in a benzene/DMSO solvent mixture to reflux with water removal using a Dean-Stark apparatus. Deprotection can then easily be achieved with sodium hydroxide or sodium hydrogen carbonate. Methyliminodiacetic acid was prepared according to G. J. Berchet[56] from methylamine and chloroactic acid in a basic solution of sodium hydroxide.



Scheme 2.21: Reagents and Condition (a) $NaIO_4$, NH_4OAc, acetone, H_2O, 48hr; (b) Benzene/DMSO, N-MIDA, Dean-Stark, 16 hr.

The stable tetracoordinated MIDA-protected boronates stem initially from work carried out by Rettig and Trotter[57] who showed the stable nature of such compounds and confirmed with the use of crystallography the dative B-N bond is 1.67 Å long. Matteson found that when in these tetracoordinated states the B-O bond of boronic esters increases to somewhere in between 1.43-1.47 Å, 0.10 Å, longer than its tricoordinated analogues. This undoubtedly reduces the B-O bond strength, however due to the initial strength of such bonds even when in the tetrahedral conformation they are still comparable to that of C-O at about ~1.43 Å[1].

The TBDMS protected borate **2.21** was treated with sodium periodate and ammonium acetate in an acetone/water mixture to remove pinacol. The resulting boronic acid **2.36** (92 %) was then treated with methyliminodiacetic acid resulting in the MIDA boronate **2.37** (59.5 %) as an off white solid.

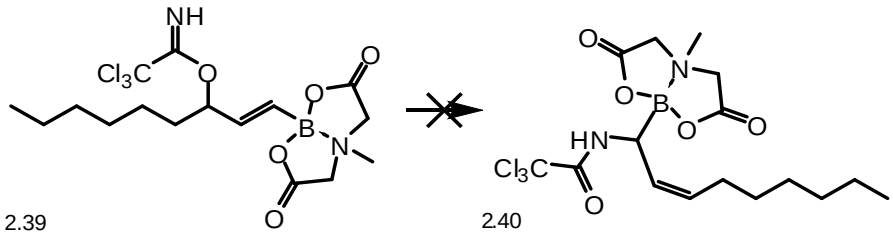


Scheme 2.22: Reagents and Conditions (a) HF (40%) Aq, MeCN, 8 hr; (b) DBU, CCl_3CN, DCM, 2 hr.

The TBDMS protected MIDA boronate **2.37** was desilylated using HF and purified using flash column chromatography to give the secondary alcohol **2.38** in good yield (98.8 %). To this alcohol was added trichloroacetonitrile and DBU dropwise at -78 °C giving the imidate **2.39** as a pale off white/green semi solid (32.4 %).

2.10 MIDA boronate Overman precursor

The newly formed Overman precursor **2.39** did not undergo the required [3,3]-sigmatropic rearrangement despite numerous attempts and given its greater solubility benefits. This was an impediment to the synthetic study which meant that a route not dependent on the [3,3]-sigmatropic rearrangement to install the alpha nitrogen moiety would be required. **Table 2.3** lists the results of the rearrangement attempts.



Scheme 2.23: Reagents and Conditions; See table below.

Reagent	Reagents and conditions	Yield %	Temperature
2.39	xylene	0	refluxing
2.39	xylene, K_2CO_3	0	refluxing
2.39	5% $Pd(OAc)_2$, toluene	0	refluxing
2.39	5% $PdCl_2$, toluene	decomp	refluxing
2.39	MeCN	0	refluxing
2.39	Toluene, 5% Pd bis(benzonitrile) dichloride	0	refluxing
2.39	K_2CO_3, MeCN	0	refluxing
2.39	NBS, $CDCl_3$	decomp	rt
2.39	K_2CO_3, MeCN	0	refluxing

Table 2.3: Results for attempts on the rearrangement of imidate **2.39**.

When **2.39** was heated in boiling toluene with a catalytic amount of palladium chloride the allylic chloride **2.41** was formed in moderate yield (68.4 %). It is thought palladium (II) chloride formed a η3-allyl complex with the olefin of **2.39** and this resulted in the loss of imidate and capture of chloride by nucleophilic attack.

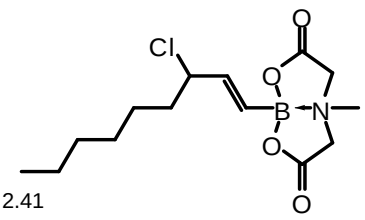
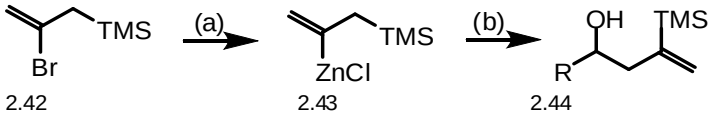


Figure 2.4

2.11 1-Trimethylsilyl-2-propenylzinc reagent

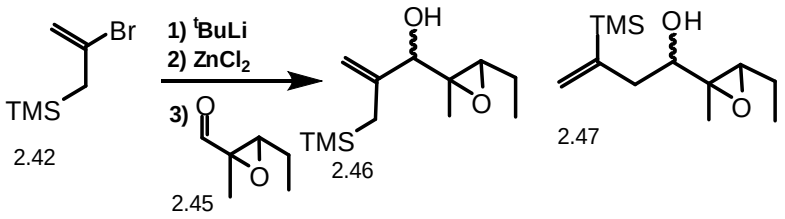
Parsons and Eshelby[58,59] found that the organozinc reagent **2.43** derived from 1-trimethylsilyl-2-bromoprop-2-ene **2.42** when treatment with ^{t}BuLi followed by the addition of zinc chloride reacts with aldehydes to give alkylated products with an apparent silicon shift **2.44**.



2.42 2.43 2.44

Figure 2.5: Reagents and Conditions (a) ^{t}BuLi, ZnCl; (b) aldehyde**.**

Parsons was able to trap the organozinc reagent **2.43** with a range of electrophiles giving at times two differently alkylated products. This seemed dependent on the temperature that the organozinc reagent **2.43** was allowed to reach after it was made *in situ*. Parsons *et al.* reacted the organozinc reagent with a range of electrophiles including the aldehyde **2.45** which was being investigated for its use in the total synthesis of galbonalide b. It was found that reagent **2.43** attacked the aldehyde **2.45** to give the alcohol **2.46** as expected; however it also formed the homo allyic alcohol **2.47**, which appeared to involve the migration of silicon.



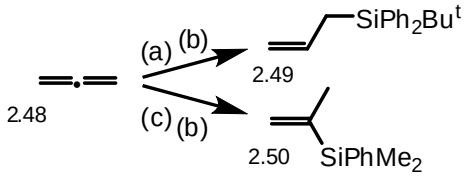
2.42 2.45 2.46 2.47

Scheme 2.24: Reagents and Conditions. *See table below*

Temp. (°C) for organozinc formation	*Yields of Isomers (%)*			
	2.46a (anti)	**2.46b** (syn)	**2.47a**	**2.47b**
-70 to 0	0	0	48	17
-70 to 20 to -70	0	0	58	19
-70 to -50	25	13	7	5
-100	10	50	10	6

Table 2.4: Reaction of organozinc reagent **2.43** with aldehyde **2.45**

The work stemmed initially from that carried out by Fleming and Pulido *et al.*[60,61,62] who were investigating the reaction of silyl-cuprate reagents with allenes giving allyl or vinylsilanes. Fleming found when treating the reagents, *tert*-butyl(diphenyl)silyl cuprate and phenyl(dimethyl)silyl cuprate with propa-1,2-diene cupration occured prop-1-en-2-yl and prop-2-enyl respectively.



Scheme 2.25: Reagents and Conditions (a) (^{t}BuPh$_2$Si)$_2$CuLi, THF, -78 °C; (b) NH_4Cl, MeOH, -78 °C; (c) (PhMe$_2$Si)$_2$CuLi, THF, -78 °C.

It was therefore hypothesised that the mechanism of synthesis for the allylic alcohol **2.47** could be from the organozinc reagent **2.43** transmetalating to that of its isomer **2.51** through possible allene formation.

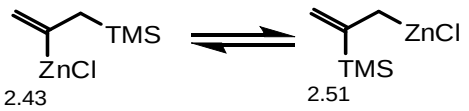
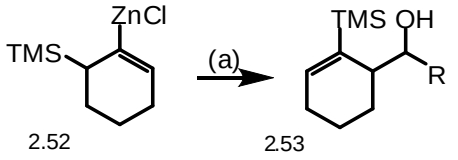


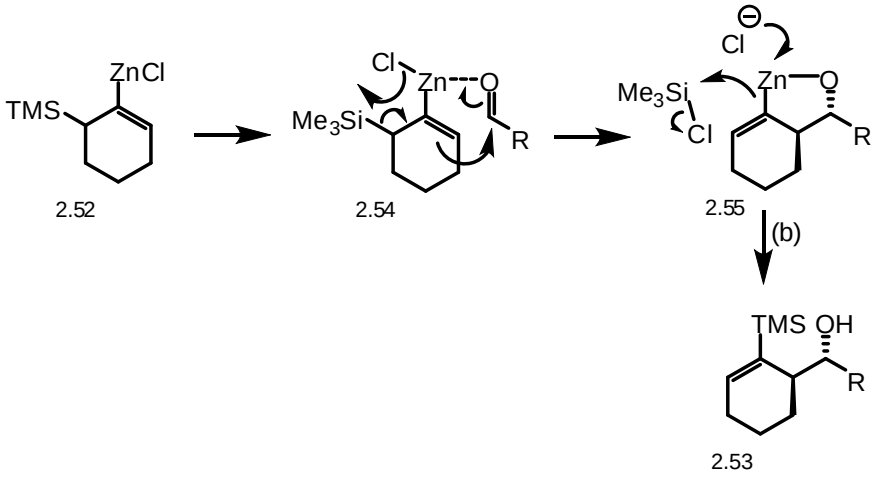
Figure 2.6: Proposed isomerisation of organozinc reagent **2.43** to its isomer **2.51**.

To test this theory the cyclic silane organozinc reagent **2.52** was treated with benzaldehyde which gave the homo allylic alcohol **2.53** solely. This example proved the migration of silicon cannot proceed through an allenyl intermediate and led to a revised mechanism being proposed.



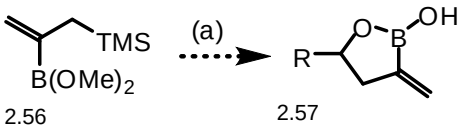
Scheme 2.26: Reagents and Conditions (a) RCHO.

Therefore Parsons and Viseux[63] proposed a new mechanism for this type of reaction whereby the organozinc reagent acts as a Lewis acid and a nucleophile. Zinc coordinates to the oxygen on the carbonyl group, chlorine then associates with the silicon atom to induce 1,2-nucleophilic attack on the aldehyde as the trimethysilyl group is lost and recaptured with the breaking of the carbon zinc bond.



Scheme 2.27: Proposed mechanistic pathway for the construction of **2.53**.

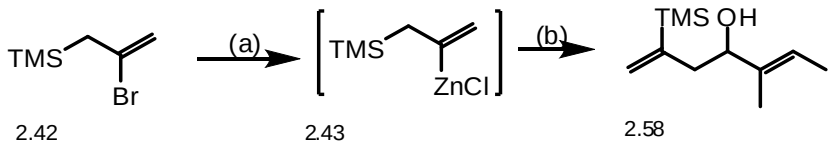
It is believed therefore that the organozinc reagent acts as both a Lewis acid in accepting the lone pair on oxygen and a nucleophile as it attacks silicon to recapture the trimethylsilyl group. The proposed mechanism of attack for the organozinc reagent **2.52** on an aldehyde is therefore thought to progress through chelation of the carbonyl group with zinc and in a concerted step forms a transitionary 5-membered ring **2.55** followed by the loss and recapture of TMS to give the alcohol **2.53** see **scheme 2.27**. If the reaction does proceed through a 5-membered heterocyclic intermediate then it may be possible to replicate this chemistry on a boron system. Replacing zinc chloride with an appropriate boron source would give the organoboron reagent **2.56**. The addition of aldehydes to **2.56** could form stable 5-membered heterocycles that could generate a new synthetic route in the construction of cyclic boronate esters like **2.57** providing an easy route into the construction of such compounds.



Scheme 2.28: Reagents and Conditions (a) RCHO.

2.12 Prop-2-enylzinc reagent and tiglic aldehyde

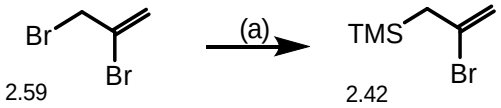
The organozinc reagent **2.43** can be used in the generation of carbon-carbon bonds utilising electrophilic capture as outlined in chapter **2.10**. Tiglic aldehyde was then used as the electrophile to generate a homoallylic alcohol when reacted with the organozinc reagent according to Eshelbys conditions[64] to test the chemistry.



2.42 2.43 2.58

Scheme 2.25: Reagents and Conditions (a) ^{t}BuLi, Et_2O, -78 °C; (b) Tiglic aldehyde, -78 °C.

The organozinc reagent **2.43** was prepared in two steps from 2,3-dibromopropene **2.59**. 2,3-Dibromopropene **2.59** was reacted with trichlorosilane in the presence of triethylamine and copper (I) chloride followed by the reaction of the resulting trichloride with three equivalents of methylmagnesium bromide according to Itoh[65] to give the allylic silane **2.42**. 2-Bromo-1-trimethylsilylprop-2-ene is then treated with ^{t}BuLi followed by the addition of zinc chloride to give the organozinc reagent **2.43** *in situ*. To this was added tiglic aldehyde and the allylic alcohol **2.58** was isolated as a colourless oil in a rather disappointing yield (12.6 %) owing to a suspected loss during purification.

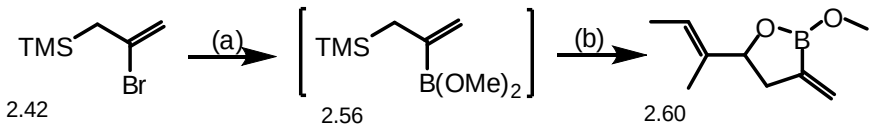


2.59 2.42

Scheme 2.26: Reagents and Conditions (a) $HSiCl_3$, Et_3N, CuCl, MeMgBr.

2.13 1-Trimethylsilyl-2-propenyl organoboron

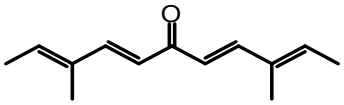
It was hypothesised that instead of zinc chloride, trimethyl borate could be used to generate the organoborate reagent **2.56**. The resulting borate should react in a similar fashion, however hopefully trapping out as the cyclic boronate ester **2.60** after forming a five membered ring. This would therefore provide a promising method for the construction of cyclic organoborates that could be extended.



2.42 2.56 2.60

Scheme 2.27: Reagents and Conditions (a) ^{n}BuLi, Et_2O, -78 °C; (b) tiglic aldehyde, -78 °C.

However after the suspected formation of the organoboron **2.56** reagent *in situ* with trimethylborate and then subsequent treatment with tiglic aldehyde the hypothesised cyclic organoborate **2.60** was not found and instead the unsaturated ketone **2.61** was isolated as a bright orange solid (7.5 %).



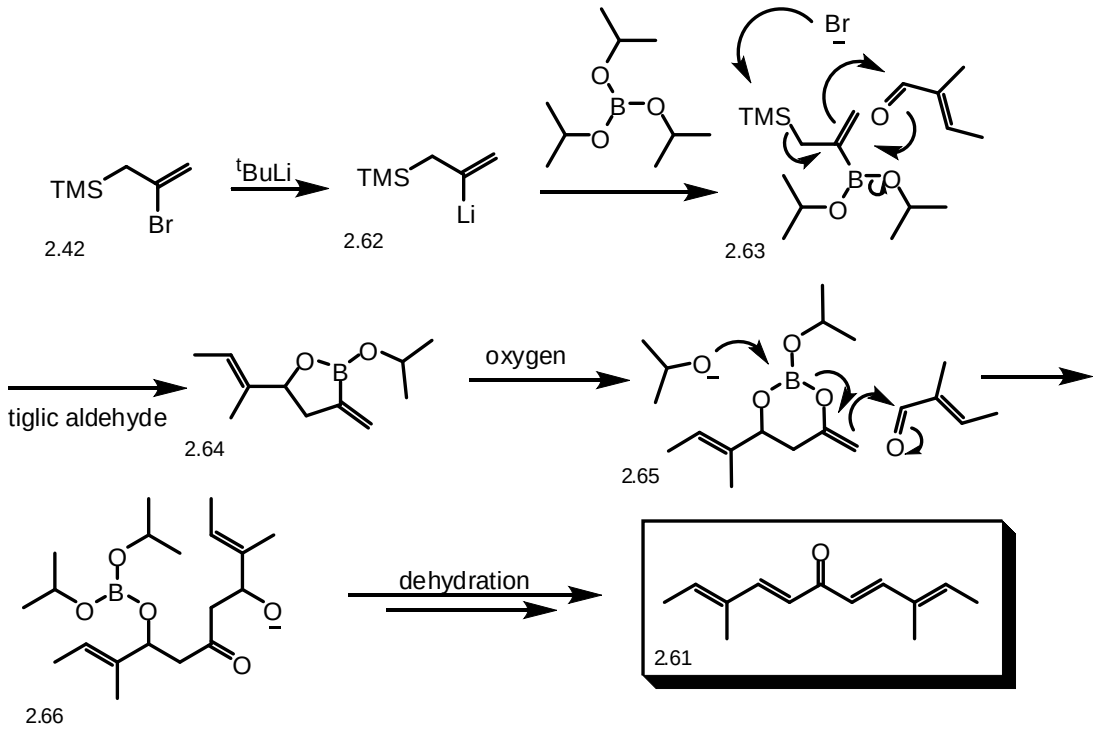
2.61

Figure 2.7

The reaction was carried out again but this time with the slightly more stable triisopropyl borate in the hope this would generate a less reactive intermediate, however the unsaturated ketone **2.61** was obtained again.

A proposed mechanism for such a reaction is set out in **scheme 2.27** below. The bromo-trimethylsilyl reagent **2.42** on addition of ^{t}BuLi undergoes lithium-halogen exchange. When treated with triisopropyl borate this lithiate forms the organo-boron reagent **2.63**. On addition of tiglic aldehyde boron is thought to behave as a Lewis acid accepting a lone pair from the oxygen of the aldehyde coupled with loss of the trimethylsilyl group by nucleophilic attack of bromide on the silicon; this can allow nucleophilic addition of the alkene in a concerted step to give an intermediate 5-membered cyclic boronate ester **2.64**. It is then thought diradical oxygen inserts into

the boron oxygen bond giving the intermediate boronate ester **2.65.** Once this ester **2.65** has formed it can add to another equivalent of tiglic aldehyde by nucleophilic attack from the terminal alkene as oxygen leaves boron to form a ketone producing the alkoxide **2.66**. With proton exchange the unstable intermediate **2.66** then undergoes dehydration to lose two molecules of water and give the unsaturated enone **2.61**.

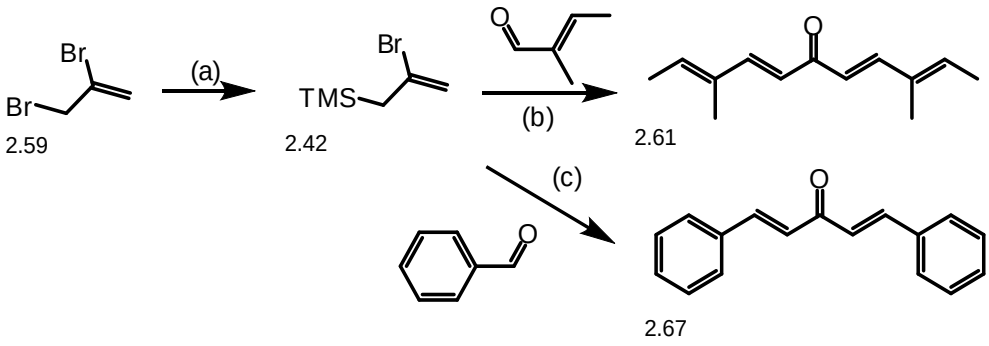


Scheme 2.28: Proposed mechanistic pathway for **2.61**.

Increasing the amount of tiglic aldehyde from 1 to 1.5 equivalents and carrying out the reaction under an atmosphere of oxygen increased the yield of enone isolated to 26.3 %.

In order to determine the true mechanism for the synthesis of enone **2.61**, it was our intention to react tiglic aldehyde in a similar manner as before but using degassed solvents in an inert atmosphere and in the dark to test the insertion of oxygen into the carbon-boron bond.

Following the discovery that tiglic aldehyde when added to 2-bromoallyl-TMS **2.42** in the presence of tri-isopropyl borate and ^{t}BuLi afforded the enone **2.61,** it was thought the same reaction could occur in the presence of other aldehydes. Benzaldehyde was chosen as it had been successfully alkylated using Parsons' organozinc method[63]. Benzaldehyde was redistilled from zinc powder and reacted in the same manner as tiglic aldehyde adding 1.5 equivalents of aldehyde to the organoboron reagent followed by switching to an atmosphere of oxygen after addition. The reaction yielded a bright yellow solid that resembled the enone **2.67** by ^{1}H-NMR in its crude state. However purification of the small quantity isolated proved difficult and the enone mixture seemed to be unstable and after purification using flash column chromatography nothing of significance could be identified.

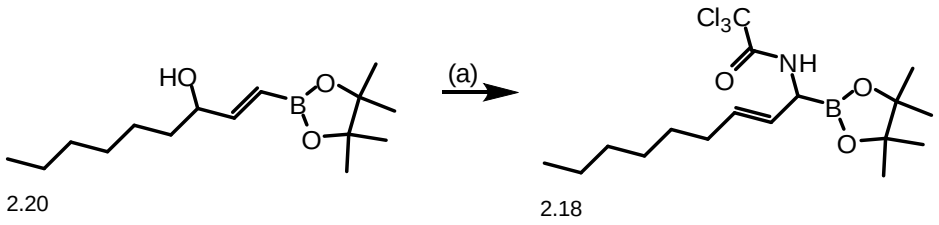


Scheme 2.29: Reagents and Conditions (a) ^{t}BuLi, TMSCl; (b) ^{t}BuLi, B(O^{i}Pr)$_3$, O_2, Et_2O, -78 °C; (c) ^{t}BuLi, B(O^{i}Pr)$_3$, O_2, Et_2O, -78 °C.

Following the promising initial proton NMR of the reaction between benzaldehyde and the TMS reagent, it would be of benefit to try the reaction again and on differing aldehydes to establish the depth and scope of this new and interesting chemistry. However it appeared this chemistry would not be beneficial to the construction of cyclic boronate esters as previously thought and the chemistry was abandoned in favour of a new palladium cyclisation project outlined in chapter **5**.

2.14 Effecting the Overman rearrangement

In a final attempt to synthesise the imidate **2.19** and to allow further attempts at the Overman rearrangement, excess base (DBU, 1.5 eq) and excess trichloroacetonitrile (12 eq) were added to the free alcohol **2.20** at 0 °C and allowed to warm to rt, stirring in DCM. This unusually gave the acetamide **2.18** in 35 % yield as a colourless oil as well as the intended imidate **2.19** in an estimated 60 % yield.



Scheme 2.30: Reagents and Conditions (a) DBU (1.5 eq), trichloroacetonitrile (12 eq), DCM, 4 hr, rt.

The acetamide **2.18** however is thought to be present in the ate complex, forming a five membered ring with oxygen **2.68**. This is hypothesised due to the diastereotopic nature of the pinacol group which is seen as four separate singlet peaks on ^{1}H-NMR indicating a change from sp^2 to sp^3 hybridisation of boron and so differing the conformation and therefore the environment of each methyl attributed to the pinacol moiety.

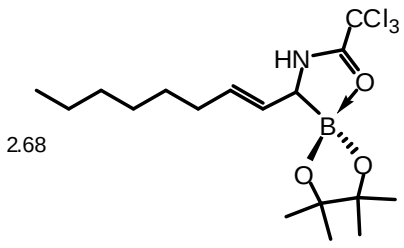
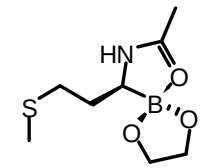


Figure 2.8

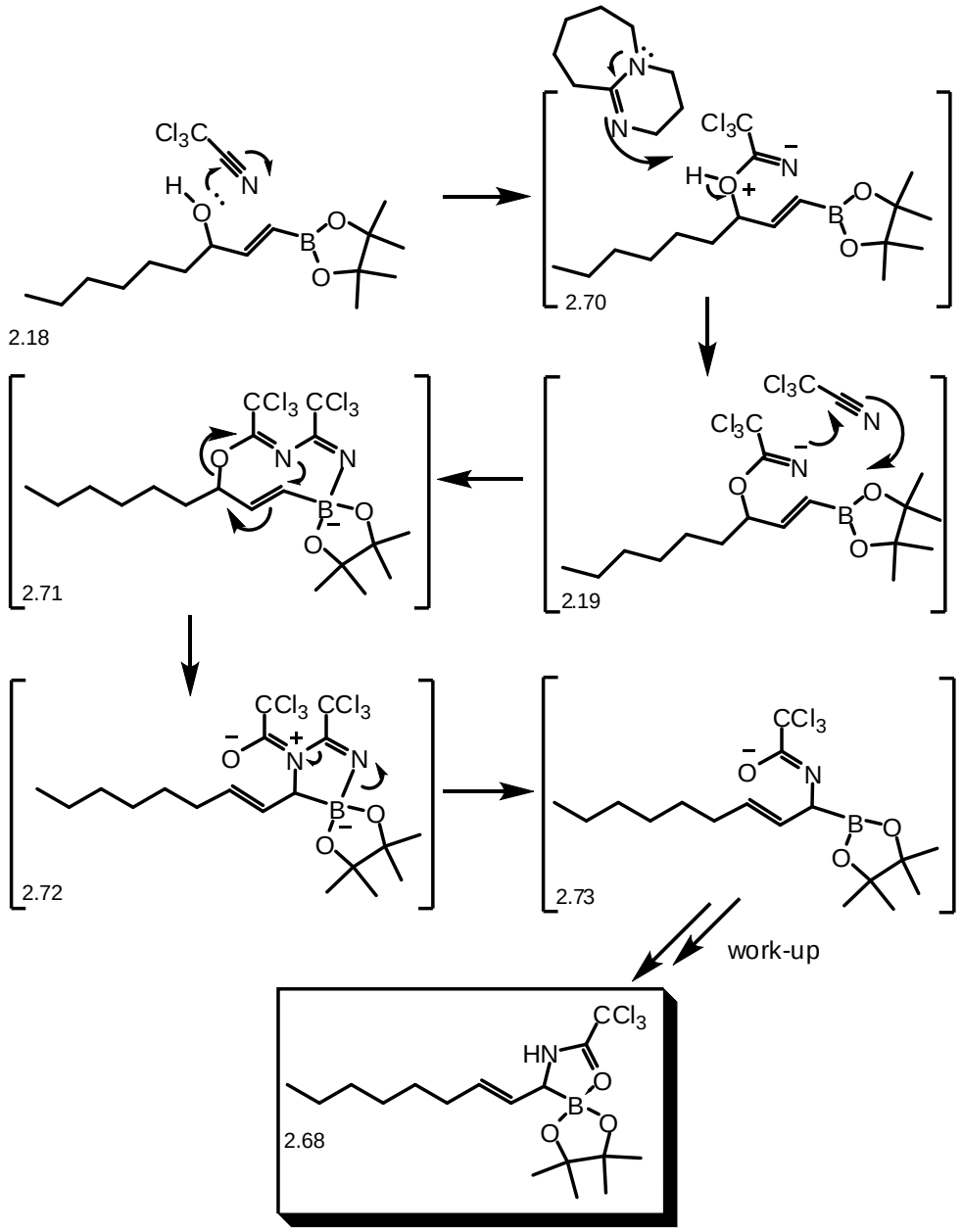
It is not the first time a structure like this has been proposed and Matteson[(31)] proved, using crystallography, that the oxygen in the acetamide **1.33** coordinated to boron proving the 5-membered 1,3,2-dioxaborolane ring was no longer planar as seen in its tricoordinated state. This resulted in longer B-O bond lengths reducing the ability of oxygen to partially π-bond with boron.



1.33

Figure 2.9

The formation of the acetamide **2.18** from its free alcohol **2.20** under excess conditions only, and at room temperature was a curious result and indicated that in these conditions the energy barrier to the [3,3]-sigmatropic rearrangement had been greatly reduced along with the perceived issue of boron polarising the double bond alpha to it. A mechanism for this reaction was then proposed.



Scheme 2.31: Possible mechanistic pathway for acetamide **2.68** formation.

DBU is used to aid the formation of the intermediate imidate **2.70,** which due to the excess base and trichloroacetonitrile in solution attacks a second equivalent of trichloroacetonitrile giving the double addition product **2.71**. The second generated imine can then form an ate complex with boron and hence the nine membered ring **2.71**. Now with the double bond alpha to boron no longer polarised and the nitrogen associated with the first equivalent of trichloroacetonitrile in close proximity and in a facile position next to the double bond the 3,3-sigmatropic rearrangement can take place and at room temperature. The intermediate ate complexed heterocycle **2.72**

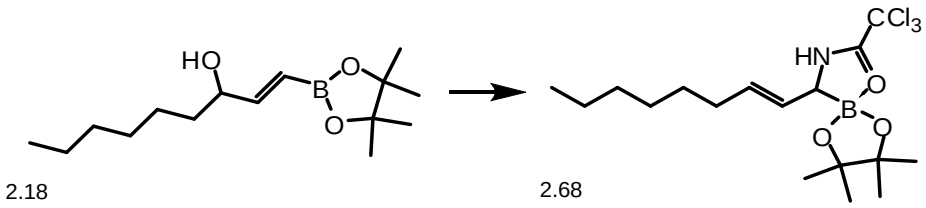
then fragments to give the alkoxide acetamide **2.73** which forms the ate complexed acetamide **2.67** on work-up.

The acetamide **2.67** is stable to purification using flash column chromatography but is however highly unstable to air and must be kept under nitrogen and in the freezer. As with all the boron imidates synthesised in this study the acetamide did not give a high resolution mass spectrum with the molecular ion. The data proved inconsistent and repeatedly gave differing mass spectra. A boron chemical test was carried out by dissolving the pure product in methanol and acidified with conc. sulphuric acid. The mixture was then heated until a gas evolved which burnt with a green flame on ignition with a lit splint indicating the presence of boron. This result is also backed up with an ^{11}B-NMR.

3. Future Work

3.1 Dioxaborolan-2-yl(non-2-enyl)acetamide

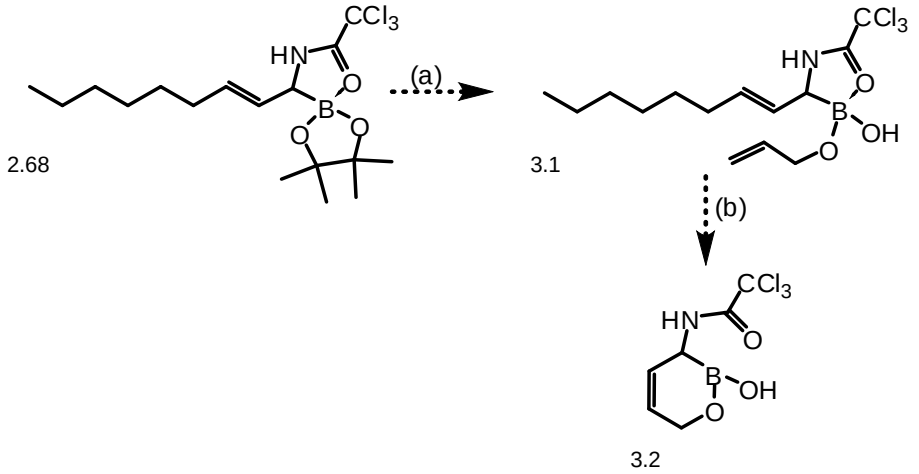
Following the discovery that the alcohol **2.18** when treated with excess DBU and trichloroacetonitrile rearranges to the acetamide **2.68**, a continuation of this route has been proposed.



2.18 2.68

Scheme 3.1: Reagents and Conditions (a) DBU (1.5 eq), trichloroacetonitrile (12 eq), DCM, 4 hr, rt.

Treatment of the acetamide **2.68** with the alkoxide of prop-2-en-1-ol would hopefully add to the boron centre displacing pinacol and on work up with water give the boronate ester **3.1**. Cross metathesis of **3.1** using Grubbs (II) catalysts could then give the cyclic boronate acetamide **3.2**.

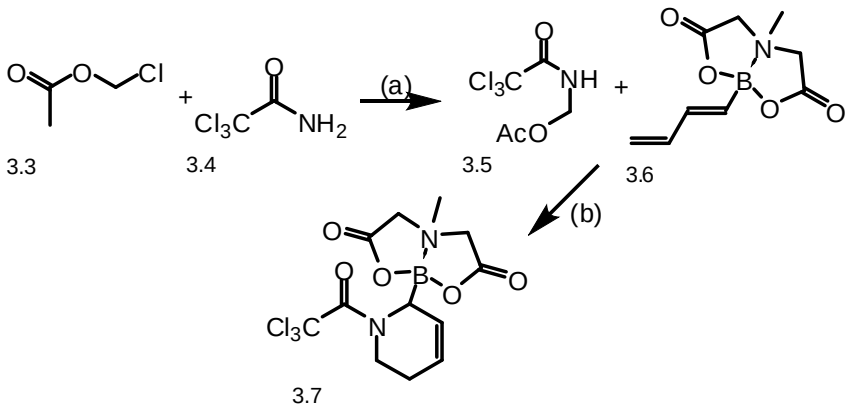


2.68 3.1 3.2

Scheme 3.2: Reagents and Conditions (a) propenyl alcohol, Et_3N; (b) Grubbs (II).

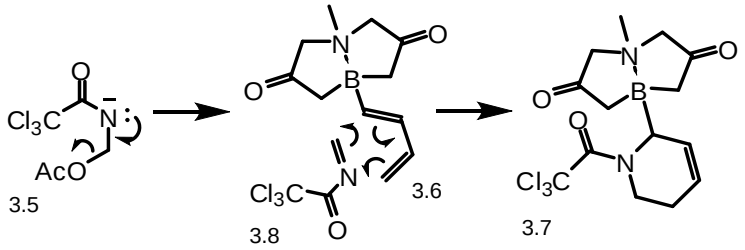
3.2 Alkenylboron-trichloroacetamide

There are so many compounds within this class that could be of interest, focus must really be about developing methods that give building blocks for further exploration. Following the work conducted with MIDA protected boronates the proposed alternative route to synthesising cyclic compounds with a 1,3-boron-nitrogen framework is shown in **scheme 3.3**.



Scheme 3.3: Reagents and Conditions (a) K_2CO_3, DCM; (b) Et_3N, Heat.

The known chloromethyl acetate **3.3** can be synthesised from heating acetyl chloride, paraformaldehyde and zinc chloride together according to Tendler[66]. When treated with trichloroacetamide **3.4** this compound would undergo S_N2 attack from the lone pair attributed to nitrogen to give the trichloroacetamide acetate **3.5**. This when treated with the known butadiene boronate **3.6** which is in turn prepared by a Stille coupling between allyl-bromide, N-MIDA boronate and alkenyl stannane[67] could give the unsaturated piperidine **3.7**. Upon heating the imine and the diene in the presence of potassium carbonate the acetamide **3.5** could collapse to the dienophile **3.8** whereupon it should undergo a [4+2] cycloaddition to give the unsaturated piperidine **3.7** with boron functionality alpha to nitrogen.

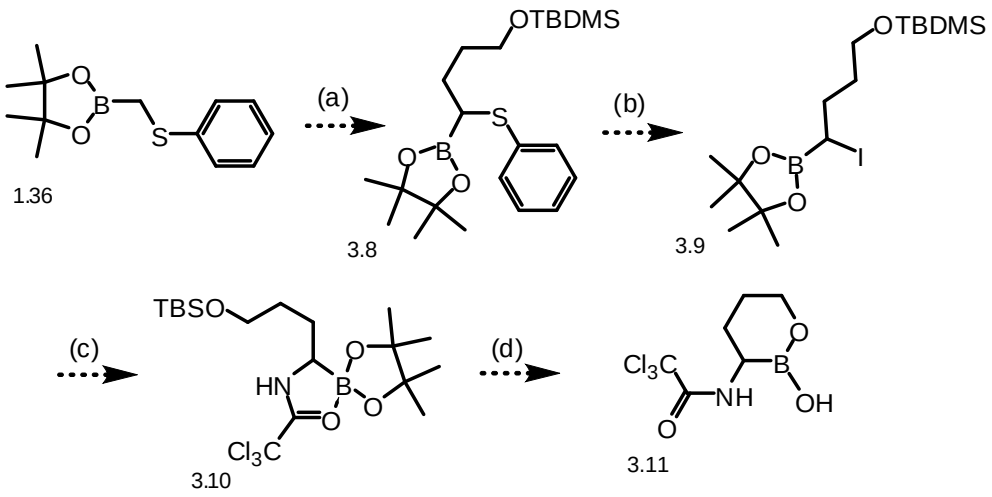


Scheme 3.4: Proposed mechanistic pathway for synthesis of **3.7**.

This would be an effective method for the construction of a series of compounds with structure flexibility introduced by changing the groups attached to the dienophile.

3.3 Five and six membered oxaborine synthesis

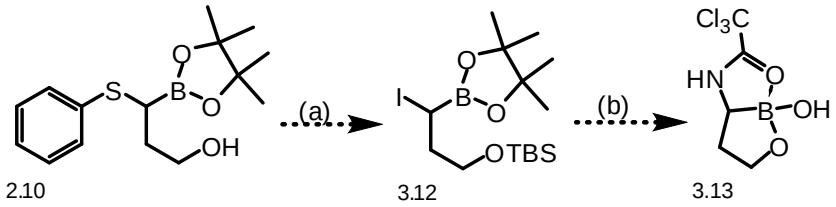
The thioanisole boronate ester **1.36** can be deprotonated alpha to boron as shown in the construction of the oxaborolan **2.6** in chapter **2.2.1**. When the carbanion of **1.36** is treated with oxetane the cyclised oxaborolane results as well as the ring open alcohol which when protected would give the boronate ester **3.8**. Nitrogen functionality could then be installed by methylating sulfur with methyl iodide and displacing phenylthiol with iodide from sodium iodide as has been proven on a similar system[32].



Scheme 3.5: Reagents and Conditions (a) ^{n}BuLi, Et_2O, oxetane, TBDMSCl, -78 °C; (b) MeI, NaI, DCM; (c) acetamide, Et_3N; (d) HF (40%), MeCN.

The hope would then be that the trichloroacetamide could displace iodide to give the boro-acetamide **3.10**. TBDMS-deprotection followed by heating in a boiling water methanol mixture with borax could then potentially bring about cyclisation to give the oxaborolane **3.11** with nitrogen functionality alpha to boron.

If successful this method could also be adapted to create the 5-membered oxaborolan **3.13** and utilise the already synthesised open chain boronate ester **2.10** from the reaction of thio-phenyl pinacol borate **1.36** and ^{t}BuLi followed by alkylation with ethylene oxide.



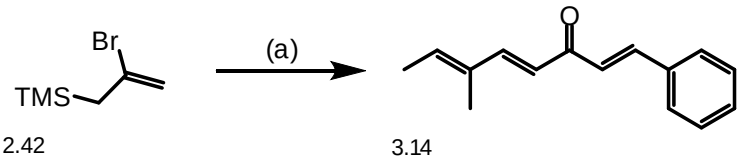
2.10 3.12 3.13

Scheme 3.6: Reagents and Conditions (a) TBDMSCL, imidazole, DMAP, Et_2O; (b) acetamide, Et_2N, DCM; (c) HF (40%), MeCN.

Simple TBDMS protection of this open chain primary alcohol followed by halogen substitution of the thio-phenyl moiety and then amidation using trichloroacetamide would give a nice synthesis of the amino oxaborolan **3.13**. If successful a range of compounds can be developed varying the alkylation substituents and to possibly include propylene oxide and 1,3-propylene oxide giving access to a 3-methyl substituted 5 membered or 6-membered variants respectively.

3.4 Modification of the synthesis of unsaturated ketones

Following the discovery of the unusual method for preparing enones from aldehydes and the TMS-bromo reagent **2.42** it is proposed that a series of different enones could be synthesised from varying aldehydes. If this were to be successful it would also be of interest to investigate the possibility of using two different aldehydes added at varying times to produce asymmetric enones. The example in **scheme 3.7** shows the formation of an unsaturated enone **3.14** using tiglic aldehyde and benzaldehyde. A possible method for the synthesis of **3.14** could be to ensure formation of the organoboron reagent **2.63** *in situ* is in excess comparatively to the addition of the first aldehyde. The reaction would then be held at -78 °C for an hour, followed by the addition of the second aldehyde.



2.42 3.14

Scheme 3.7: Reagents and Conditions (a) ^{t}BuLi, B(O^{i}Pr)$_3$, tiglic aldehyde (0.75 eq). benzaldehyde (0.75 eq), O_2, Et_2O, -78 °C.

Investigation into the possible mechanism would also be beneficial with emphasis on trapping out the proposed cycloboronate intermediate. This could be achieved by substituting triisopropyl borate with partially protected boron derivatives for example, isopropylpinacol borate and investigating the reaction on less reactive boronates. If so, this could still be a good novel method for the construction of cyclic boronate esters and is worth more attention.

4. Experimental

4.1 General Procedure

All reactions were carried out under an atmosphere of nitrogen unless otherwise stated, using oven dried glassware. Commercially available chemicals and reagents were used as supplied unless otherwise stated.

Tetrahydrofuran and diethyl ether were distilled from sodium using benzophenone as an indicator. Dichloromethane and acetonitrile were distilled from calcium hydride. Dry alcohol solvents were distilled from magnesium turnings and stored over 4 Å molecular sieves. Triethylamine and pyridine were distilled from calcium hydride and stored over potassium hydroxide. All solvents for high temperature reactions (>100 °C) were first deoxygenated by sparging for at least 1 hour with nitrogen or argon gas.

Microwave reactions were carried out using a CEM Discover-S 300W microwave system with a pressure tolerance of up to 18bar.

Reactions were monitored by crude NMR of the RM or by tlc using Merck glass backed tlc plates coated with a 0.25 mm layer of 60 F_{254} silica gel. Visualisation was achieved using 254 nm UV radiation (where applicable) and potassium permanganate, phosphomolybdic acid or vanillin stains as deemed appropriate. Column chromatography was carried out using Merck Kieselgel 60.

NMR spectroscopy was performed using either Varian NMR System-600 MHz (600 MHz for ^{1}H and 151 MHz for ^{13}C), or Varian NMR System-500 MHz (500 MHz for ^{1}H and 126 MHz for ^{13}C). The solvent used for NMR samples was either deuterated chloroform or perdeuterated dimethylsulfoxide.

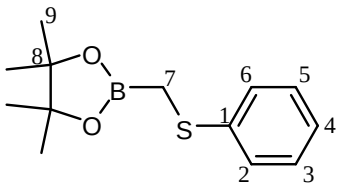
Heteronuclear Single Quantum Coherence (HSQC), Heteronuclear Multiple Bond Coherence (HMBC), Correlation Spectroscopy (COSY) and Hydrogen-Deuterium exchange (H-D) experiments were also run where necessary to allow for the full elucidation of structures.

Mass spectrometry was performed using a Fissons Instrument VG Autospec and a Bruker Daltonics Apex III.

Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier transform instrument with an ATR attachment.

Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected.

(1.36) 4,4,5,5-Tetramethyl-2-(phenylthiomethyl)-1,3,2-dioxaborolane[27]



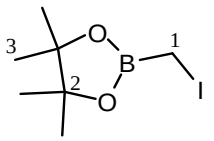
To a solution of thioanisole (2.4 g, 2.27 ml 19.35 mmol) in THF (40 ml) was added TMEDA (1.97 g, 2.4 ml, 19.35 mmol) and treated with butyllithium (8.25 ml, 20.64 mmol) at or below rt. The solution was then allowed to stir for 1 hour whereupon it was cooled to –78 °C and PINBOP (3.6 g, 3.95 ml, 19.35 mmol) was added dropwise over a period of 0.5 hr, then allowed to warm to rt overnight. The reaction mixture was quenched with saturated ammonium chloride solution (40 ml) and the organic phases separated, washed with brine (3 x 20 ml) and reduced *in vacuo* to give a crude pale yellow oil. This oil was purified using flash column chromatography and eluted with 95 % diethyl ether in hexane to give the title compound as a pale straw coloured oil (3.64 g, 75 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31 (2H, d, J=8.0, H-2 + H-4), 7.26 (2H, t, J=6.8, H-1 + H-5), 7.12 (1H, t, J=7.2, H-3), 2.42 (2H, s, H-7), 1.24 (12H, s, H-9).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.74 (1-C), 128.61 (2+6-CH), 127.09 (3+5-CH), 125.01 (4-CH), 84.18 (8-C x 2), 24.69 (9-CH_3 x 4), 13.30 (7-CH_2).

HRMS (ESI+) calcd for $C_{13}H_{19}BNaO_2^+$ *m/z* 273.1097 found 273.1111.

(2.2) 2-(Iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[35]

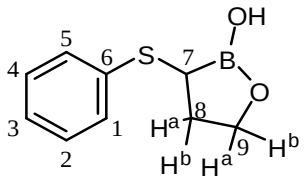


A mixture of 4,4,5,5-tetramethyl-2-(phenylthiomethyl)-1,3,2-dioxaborolane (1.25 g, 5 mmol), methyl iodide (3.55 ml, 50 mmol, 10 eq) and sodium iodide (1.125 g, 7.5 mmol, 1.5 eq) in acetonitrile (25 ml) was stirred at rt for 48 hr. After which the reaction was quenched with sat ammonium chloride solution (25 ml) and the aqueous layer extracted with diethyl ether (3 x 25 ml). The organic fractions were dried over magnesium sulfate, reduced *in vacuo* and the resulting crude oil purified using flash column chromatography eluting with 5 % diethyl ether in hexane to give the title compound as a pale straw coloured oil (741 mg, 57 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.17 (2H, s, H-1), 1.27 (12H, s, H-3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 109.99 (1-CH_2), 84.20 (2-C), 24.40 (3-CH_3).

(2.6) 3-(Phenylthio)-1,2-oxaborolan-2-ol[35]



To a solution of diisopropylamine (2.02 g, 2.80 ml, 19.98 mmol) in THF (2.6 ml) was added 1.6M ^{n}BuLi (12.5 ml, 19.98 mmol) dropwise at 0 °C over 5 mins and allowed to stir for a further 5 mins giving a pale yellow solution. To this was added at 0 °C a solution of 4,4,5,5-tetramethyl-2-(phenylthiomethyl)-1,3,2-dioxaborolane (5 g, 4.72 ml, 19.98 mmol, 1 eq) in THF (2.6 ml) as drops over 5 mins which precipitated the lithium salt as a white solid. To this solution was slowly bubbled ethylene oxide at -5 ° C. The reaction mixture was then stirred at 0 °C for a further hr and allowed to warm to rt overnight whereupon the reaction mixture was quenched with 2M HCl (20 ml). The aqueous phase was extracted with diethyl ether (2 x 20 ml) and the combined organic layers basified with 6N sodium hydroxide. The basic layer was then washed with diethyl ether and re-acidified using 2M HCL, extracted with diethyl ether, dried over magnesium sulfate and reduced *in vacuo* to give a crude mixture of the ring open and closed products. The crude reaction mixture was refluxed overnight with borax (3 g) sodium borate (3 g) in water (25 ml) and then purified using flash column chromatography which also helped to convert the ring open variant to the title compound isolated as a white solid (1.34 g, 35 %).

H-NMR (500 MHz, $CDCl_3$) δ 7.39 (2H, dd, J=8.1, 0.8, H-1 + H-5), 7.30 (2H, t, J=7.7, H-2 +H-5), 7.20 (1H, t, J=7.4, H-3), 4.85 (1H, s, OH), 4.22 (1H, ddd, J=9.2, 7.4, 6.0, H-9^a/H-9^b), 4.07 (1H, dt, J=9.3, 6.8, H-9^b/H-9^a), 3.05 (1H, dd, J=7.8, 6.7, H-7), 2.51 (1H, td, J=13.5, 7.2, H-8^a/H-8^b), 2.08 (1H, td, J=13.5, 6.4, H-8^b/H-8^a).

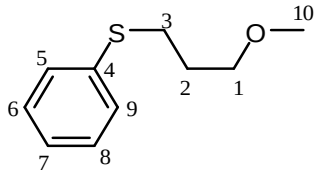
^{13}C-NMR (126 MHz, $CDCl_3$) δ 129.24, 128.93, 126.17, 67.36, 67.36, 33.85.

IR (cm^{-1}) 3337 (br), 1582, 1479, 1427, 1360, 1261, 1024, 738;

HRMS (ESI+) calcd for $C_9H_{11}BNaO_2S$ *m/z* 217.0465 found 217.0467
mp 104-106 °C.

See supporting information for crystal structure.

(2.13) (3-Methoxypropyl)(phenyl)sulfide



A crude solution of azido(methoxy)(3-methoxy-1-(phenylthio)propyl)borane (50 mg) in deuterated DMSO was sealed into an NMR tube and heated to 140 °C for 48 hours or untill the starting material no longer remained, according to ^{1}H-NMR. The reaction material was then diluted with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). Following extraction the organic solvent was dried over magnesium sulfate, reduced *in vacuo* and purified using flash column chromatography to give the title compound as a pale straw coloured oil (30 mg, 12.8 % over 2 steps).

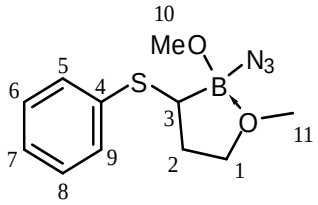
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35 (2H, d, J=7.3, H-9 + H-5), 7.31-7.25 (2H, m, H-8 + H-6), 7.17 (1H, t, J=7.3, H-7), 3.48 (2H, t, J=6.1, H-1/H-3), 3.33 (3H, s, H-10), 3.01 (2H, t, J=7.2, H-3/H-1), 1.94-1.87 (2H, m, H-2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.56, 129.07, 128.80, 70.91, 58.59, 30.32, 29.30.

HRMS (ESI+) calcd for $C_{10}H_{14}KOS^{+}$ *m/z* 221.0397 found 221.0607.

LRMS: (EI) *m/z* 182 ($C_{10}H_{14}OS$).

(2.14) Azido(methoxy)(3-methoxy-1-(phenylthio)propyl)borane



3-(Phenylthio)-1,2-oxaborolan-2-ol (340 mg, 1.75 mmol) was dissolved in diethyl ether (34 ml) whereupon trimethyloxonium tetrafluoroborate (518 mg, 3.5 mmol, 2 eq) was added in one portion and allowed to stir for two hours. The diethyl ether was then removed by rotary evaporation and replenished with acetonitrile (34 ml). To the stirring solution was added sodium azide (114 mg, 1.75 mmol, 1 eq) and heated to reflux for two hours. Saturated ammonium chloride was added (30 ml) and the organic layer separated, dried and reduced *in vacuo* to give a crude mixture which was then purified by crystallising from hexane and diethyl ether to give a crude brown/white solid (50 mg) which resembled the title compound and was hence tentatively assigned.

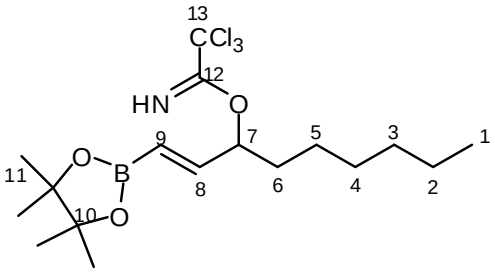
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.76 (2H, d, H-5 + H-9), 7.65 (3H, m, H-6 + H-7 + H-8), 3.62-3.51 (1H, m, H-2^{a}/H-2^{b}), 3.21 (3H, d, J=10.6, H-11), 3.05 (3H, s, H-10), 2.88 (1H, s, H-3), 1.83 (2H, s, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ 1.33.59, 130.73, 130.02, 70.54, 58.28, 48.07, 29.03, 27.85.

HRMS (ESI+) calcd for $C_{11}H_{14}BN_3NaO_2S^{2+}$ *m/z* 287.0859 found 287.0855.

HRMS (ESI+) calcd for $C_{11}H_{14}BNaO_2S^{3+}$ *m/z* 245.0997 found 245.0976.

(2.19) (*E*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-yl 2,2,2-trichloroacetimidate



To a solution of (*E*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-ol (1 g, 3.7 mmol) in dry DCM (25 ml) was added DBU (685 mg, 4.5 mmol, 0.680 ml, 1.2 eq) dropwise over 5 mins at rt. The resulting solution was then cooled to 0 °C where-on trichloroacetonitrile was added dropwise over 15 minutes to a stirring solution. The reaction mixture was left to stir for 1 hour when, saturated ammonium chloride solution (25 ml) was added. The aqueous layer was separated and extracted with diethyl ether and the organic layers where then combined, dried over magnesium sulfate and reduced *in vacuo*. This gave the title compound as a crude brown oil (1.49 g, 97 %).

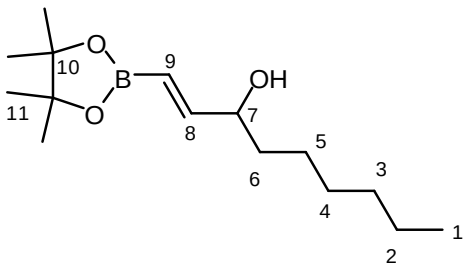
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, S, N-H), 6.20 (1H, dd, J=17.9, 5.3, H-8), 5.73 (1H, d, J=17.9, H-9), 5.34 (1H, s, H-7), 3.95-3.88 (2H, m, H-12$^{a/b}$ + H-13$^{a/b}$), 3.68 (2H, t, J=16.8, H-13$^{a/b}$ + H-13$^{a/b}$), 1.75 (2H, m, H-6), 1.49-1.38 (2H, m, H-5), 1.36-1.22 (6H, m, H-4 + H-3 + H-2), 0.92-0.85 (3H, m, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ167.36 C=O, 167.31 C=O, 143.60 (8-C), 80.27 (7-CH), 61.42 (11-CH_2/12-CH_2), 61.38 (12-CH_2/11-CH_2), 46.81 (14-CH_3), 34.09 (6-CH_2), 31.64 (CH_2), 28.94 (CH_2), 24.99 (5-CH_2), 22.52 (CH_2), 14.01 (1-CH_3), C-9 (not seen due to boron α effect).

IR (cm^{-1}) 3409.25, 1655.25, 1023.03;

HRMS: (ESI+) Ion could not be found.

(2.20) (*E*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-ol



To a solution of methanol and dichloromethane (2:5 ratio, 350ml) and 1,2-ethanethiol (100 mg, 0.089 ml, 1.06 mmol, 0.2 eq) was added nickel(II)chloride hexahydrate (251 mg, 1.06 mmol, 0.2 mmol). The reaction mixture was then cooled to 0 °C and (*E*)-*tert*-butyldimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-yloxy)silane (2.1 g, 5.3 mmol) was added and allowed to stir overnight. The reaction mixture was worked up with ammonium chloride, separated and the aqueous layer extracted with diethyl ether and the organic fractions combined, dried over magnesium sulfate and reduced *in vacuo* to give a crude oil. The crude oil was purified using flash column chromatography to give the title compound as a colourless oil (1.177 g, 82 %).

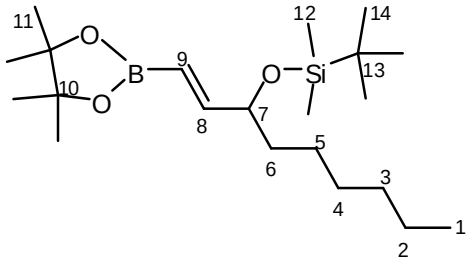
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.63 (1H, dd, J=18.1, 5.3, H-8), 5.63 (1H, dd, J=18.1, 1.4, H-9), 4.16 (1H, dd, J=11.3, 5.5, H-7), 1.51 (2H, dt, J=9.8, 5.2, H-6), 1.46-1.22 (20H, m, H-11 + H-5 + H-4 + H-3 + H-2), 0.89 (3H, t, J=6.9, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.27 (8-CH), 83.27 (10-C x 2), 73.78 (7-CH), 36.67 (6-CH_2), 31.73 (CH_2), 29.20 (CH_2), 25.25 (CH_2), 24.76 (11-CH_3 x 2), 24.74 (11-CH_3 x 2), 22.58 (CH_2), 14.03 (1-CH_3), C-9 (not seen due to boron α effect).

IR (cm^{-1}) 3309.34, 2927.87, 2858.29, 2094.00, 1683.14;

HRMS (ESI+) calcd for $C_{15}H_{29}BNaO_2^+$ *m/z* 291.2101 found 291.2098.

(2.21) (*E*)-*tert*-Butyldimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-yloxy)silane



To (*E*)-*tert*-butyldimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-yloxy)silane and pinacol borane (95.9 mmol, 12.27 g, 13.91 ml) was added zirconocene hydrochloride (0.1 eq) and triethylamine (9.59 mmol, 970 mg, 1.33 ml). This mixture was heated at 60 °C for 16 hours and then diluted with hexane. The precipitate was removed *via* a silica plug and washed with hexane. The resulting organic layer was reduced *in vacuo* to give the title compound as a colourless oil (34 g, 92 %).

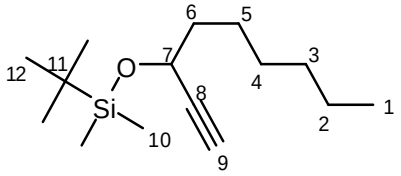
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.56 (1H, dd, J=4.9, 18.0, H-11), 5.56 (1H, dd, J=1.3, 18.0, H-10), 4.14 (1H, app.q, J=4.8, H-12), 1.52-1.42 (2H, m, H-14) 1.26 (22H, m, H-15,16,17,18,3,1,6,7) 0.96-0.81 (12H, m, H-19,24,25,26), 0.02 (6H, d, J=8.3, H-21,22).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.34, 83.13, 74.34, 37.55, 31.78, 29.35, 24.93, 24.76, 24.54, 22.56, 18.19, 14.05, 24.93, 24.70, 24.54, 13.99, -4.40, -4.91.

IR (cm^{-1}) 2929.48, 2857.32, 1641.96, 1362.99;

HRMS (ESI+) calcd for $C_{21}H_{43}BO_3SiNa^+$ *m/z* 405.2965740, found 405.2966.

(2.22) *tert*-Butyldimethyl(non-1-yn-3-yloxy)silane



Non-1-yn-3-ol (133 mmol, 18.582 g), 4-dimethylaminopyridine (catalytic), triethylamine (266 mmol, 26.92 g, 37 ml) and dichloromethane (70 ml) were added to a 250 ml round bottomed flask under nitrogen and cooled to 0 °C. The *tert*-butylchlorodimethylsilane in hexane 50 % w/w (146.3 mmol, 22 g) was then added dropwise and the reaction mixture was left overnight. The reaction mixture was worked up with ammonium chloride and the layers separated. The organic layer was washed with brine and reduced *in vacuo* to give a crude oil. This crude oil was then purified *via* flash column chromatography and eluted with hexane to give the title compound as a pale straw coloured oil (24.4 g, 72 %).

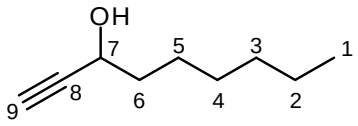
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.35 (1H, td, J=6.5, 1.8, H-7), 2.39-2.35 (1H, m, H-9), 1.71-1.65 (2H, m, H-6), 1.43 (2H, m, H-5), 1.37-1.26 (6H, m, H-4 + H-3 + H-2), 0.99-0.85 (12H, m, H-1 + H-12), 0.14 (6H, d, J=12.3, H-10).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 85.77 (2-C), 71.76 (9-CH), 62.75 (7-CH), 38.57 (6-CH_2), 31.74 (CH_2), 28.89 (CH_2), 25.74 (12-CH x 3), 25.05 (CH_2), 22.55 (CH_2), 18.17 (11-C), 14.00 (2-CH_3), -4.61 (CH_3), -5.11 (CH_3).

IR (cm^{-1}) 2928.67, 2857.44, 1463.29, 1251.27;

HRMS (ESI+) calcd for $C_{15}H_{30}NaOSi^{+}$ *m/z* 277.1958, found 277.1953.

(2.23) Non-1-yn-3-ol



1-(Trimethylsilyl)non-1-yn-3-ol (144 mmol, 30.7 g) was dissolved in methanol (225 ml), dichloromethane (225 ml) and stirred under nitrogen. To this solution sodium methoxide (7.2 mmol) was added and allowed to undergo removal of the trimethylsilyl group catalytically over 24 hours. The reaction mixture was then washed with water and the organic layers dried over magnesium sulfate and reduced *in vacuo* to give the title compound as a pale straw coloured oil (18.582 g, 92 %).

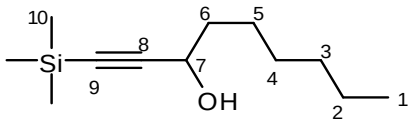
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.33 (1H, td, J=6.6, 1.6, H-7), 2.68 (1H, s, OH), 2.42 (1H, d, J=2.0, H-9) 1.74-1.62 (2H, m, H-6), 1.48-1.36 (2H, m, H-5), 1.34-1.20 (6H, m, H-4 + H-3 + H-2), 0.86 (3H, t, J=6.7, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ 85.15 (8-C), 72.63(9-CH), 62.12 (7-CH), 37.58 (6-CH_2), 31.66 (CH_2), 28.86 (CH_2), 24.95 (5-CH_2), 22.50 (CH_2), 13.96 (1-CH_3).

IR (cm^{-1}) 3403.01, 2256.91, 1658.80;

HRMS: (ESI+) Ion could not be found.

(2.24) 1-(Trimethylsilyl)non-1-yn-3-ol



To a stirred solution of TMS acetylene (150 mmol, 14.73 g, 21 ml) in tetrahydrofuran (600 ml), ^{n}BuLi (165 mmol) was added slowly at -78 °C. The resulting mixture was stirred for one hour before heptaldehyde (150 mmol, 17.1g, 20.96 ml) was added slowly. The mixture was then left to warm overnight. The reaction mixture was neutralised with 2M HCl and extracted with diethyl ether. The organic layers were then washed with saturated aqueous sodium hydrogen carbonate, brine and then dried over magnesium sulfate. The dried organic layers were then reduced *in vacuo* to give the title compound as a colourless oil (30.7 g, 96 %).

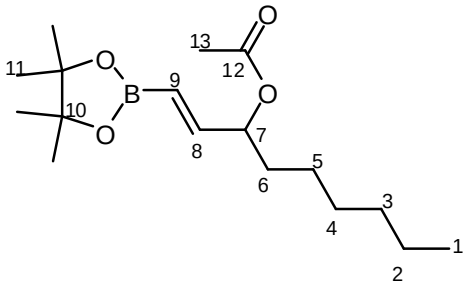
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.33 (1H, t, J=6.6, H-7), 1.67 (2H, m, H-6), 1.42 (2H, m, H-2), 1.29 (6H, m, H-5 + H-4 + H-3), 0.87 (3H, t, J=6.8, H-1), 0.15 (9H, s, H-10).

^{13}C NMR (126 MHz, $CDCl_3$) δ 107.29 (9-C), 12.13 (10-C), 37.66 (6-C), 31.61 (CH_2) 28.81 (CH_2) 22.50 (CH_2), 25.05 (2-C), 13.93 (1-C), -0.18 (10-C).

HRMS (ESI+) calcd for $C_{12}H_{24}NaOSi^{+}$ *m/z* 235.15 found 235.1489.

IR (cm^{-1}) 3329, 2957, 2929, 1249;

(2.29) (*E*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-yl acetate



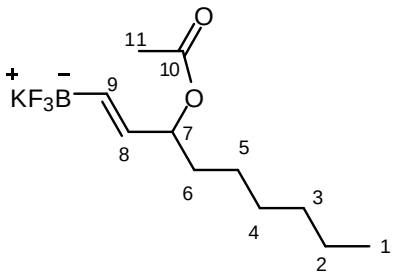
Acetyl chloride (30.44 mmol, 2.39 g, 2.15 ml, 1.5 eq) was added to a solution of (*E*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-ol (20.29 mmol, 5.444 g), triethylamine (22.32 mmol, 2.25 g, 3.1 ml), DMAP (2.02 mmol, 0.1 eq) in dichloromethane (100 ml). The reaction mixture was then allowed to warm to rt and left overnight. Water (100 ml) was then added and the organic layer separated, washed with brine (100 ml) and reduced *in vacuo*. The resulting crude yellow oil was purified by flash column chromatography eluting with 20 % Et_2O in hexane to give the title compound as a colourless oil (4.024 g, 63 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.49 (1H, dd, J=18.1, 5.0, H-8), 5.55 (1H, dd, J=18.2, 1.3, H-9), 5.28 (1H, dt, J=11.7, 3.2, H-7), 2.05 (3H, s, H-13), 1.65-1.54 (2H, m, H-6), 1.35-1.19 (20H, m, H-5 + H-4 + H-3 + H-2 + H-11), 0.86 (3H, t, H-1).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.15 C=O, 150.27 (8-CH), 83.27 (10-C), 74.97 (7-CH), 60.26 (9-CH), 33.83 (6-C), 31.59 (CH_2), 28.97 (CH_2), 24.97 (CH_2), 24.76 (CH_2), 24.68 (CH_3 x 4), 22.49 (CH_2), 21.01 (22-CH_3), 13.96 (1-CH_3).

HRMS (ESI+) calcd for $C_{17}H_{31}BO_4$ *m/z* 310.2300, found 310.2308.

(2.31) Potassium (*E*)-(3-acetoxynon-1-enyl)trifluoroborate



(*E*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolane-2-yl)non-1-en-3-yl acetate (0.64 mmol, 200 mg) was dissolved in acetonitrile (5 ml) and potassium difluoride (1.98 mmol, 192 mg, 3.1 eq) was added at room temperature followed by the addition of water (5 ml) over the period of one hour. The reaction mixture was reduced *in vacuo* and washed with hexane (10 ml) and then dried under high vacuum to give the title compound as a white solid (182 mg, 98 %).

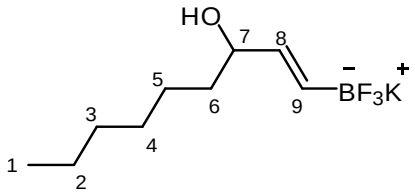
^{1}H-NMR (500 MHz, d_6-DMSO) δ 5.42 (2H, m, H-8 + H-9), 4.98 (1H, dd, J=10.6, 6.2, H-7), 1.95 (3H, s, H-13), 1.47 (2H, td, J=14.3, 6.4, H-6), 1.29-1.15 (8H, m, H-5 + H-4 +H-3 + H-2), 0.85 (3H, t, J=6.8, H-1).

^{13}C NMR (126 MHz, d_6-DMSO) δ 170.05 C=O, 132.47 (8/9-CH), 132.43 (9/8-CH), 77.20 (7-CH), 34.59 (6-CH_2), 31.64 (CH_2), 28.93 (CH_2), 25.26 (CH_2), 22.47 (13-CH_3), 14.36 (1-CH_3).

IR (cm^{-1}) 3274.69, 2933.2, 1724.3, 1238.6, 734.92;

HRMS (ESI+) calcd for $C_{11}H_{19}BF_3O_2^-$ *m/z* 251.1436 found 251.1436.

(2.33) Potassium (*E*)-trifluoro(3-hydroxynon-1-enyl)borate



(*E*)-1-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-ol (3.7 mmol, 1 g) was dissolved in acetonitrile (25 ml) and potassium difluoride (11.5 mmol, 1.12 g) added at room temperature, followed by the addition of water (25 ml) over the period of one hour. The reaction mixture was then reduced *in vacuo*, washed with hexane, dried over magnesium sulfate and reduced *in vacuo* to give the title compound as a white solid (900 mg, 98 %).

^{1}H-NMR (500 MHz, d_6-DMSO) δ 5.44 (1H, dd, J=18.0, 6.1, H-8), 5.27 (1H, d, J=17.6, H-9), 4.04 (1H, d, J=4.4, OH), 3.71-3.61 (1H, m, H-7) 1.37-1.16 (10H, m, H-2 + H-3 + H-4 + H-5 + H-6), 0.84 (3H, t, J=6.9, H-1).

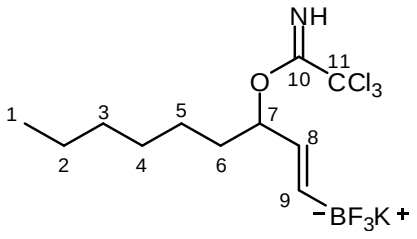
^{13}C NMR (126 MHz, d_6-DMSO) δ 138.78 (CH), 138.75 (CH), 74.38 (7-CH), 38.08 (CH_2), 31.87 (CH_2), 29.37 (CH_2), 25.68 (CH_2), 22.55 (CH_2), 14.41 (1-CH_3).

IR (cm^{-1}) 3287 (br), 2925, 1642, 995;

HRMS (ESI+) calcd for $C_9H_{17}BF_3O^-$ *m/z* 209.1330 found 209.1330.

m.p. decomposed above 270 °C.

(2.34) Potassium (*E*)-trifluoro(3-(2,2,2-trichloro-1-iminoethoxy)non-1-enyl)borate



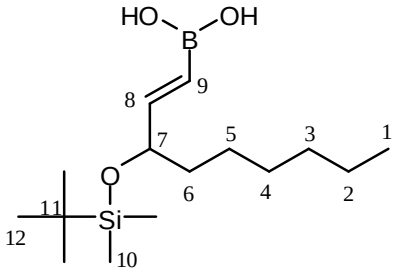
Potassium (*E*)-trifluoro(3-hydroxynon-1-enyl)borate (200 mg, 0.8 mmol) was partially dissolved in acetonitrile by gentle heating and then cooled to room temperature whereupon DBU (0.98 mmol, 146 mg, 0.145 ml, 1.2 eq) was added. The reaction mixture was then cooled further to 0 °C and trichloroacetonitrile (1.2 mmol, 173 mg, 0.120 ml, 1.5 eq) was added dropwise over 15 minutes. The reaction mixture was allowed to stir for 1 hour at room temperature and then quenched with saturated ammonium chloride (5 ml). The aqueous solution was then washed with dichloromethane (20 ml) and reduced *in vacuo* to give a white solid most of which was ammonium chloride. The crude ^{1}H-NMR for such, showed a positive correlation to that of the title compound however with numerous attempts to resynthesise unsuccessfull the ^{1}H-NMR has been tentatively assigned.

^{1}H-NMR (500 MHz, d_6-DMSO) δ 6.37 (1H, dd, J=5.3, 17.9, H-8), 5.41 (1H, dd, J=18, 1.2, H-9), 4.64 (1H, s, NH), 3.88 (1H, dd, J=11.1, 5.6, H-7), 1.39-1.13 (10H, m, H-6 +H-5 + H-4 + H-3 + H-2), 0.84 (3H, t, J=6.6, H-1).

^{13}C-NMR (126 MHz, d_6-DMSO) δ 141.47, 138.83, 108.88, 74.32, 38.06, 31.86, 29.35, 25.67, 22.54, 14.40, C-9 (not seen due to boron α-effect).

HRMS: (ESI+) Ion could not be found.

(2.36) (*E*)-3-(*tert*-Butyldimethylsilyloxy)non-1-enylboronic acid



To a solution of (*E*)-*tert*-butyldimethyl(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-yloxy)silane (5.5 g, 14.38 mmol) in acetone (90 ml) and water (135 ml) in a 2:1 ratio was added sodium metaperiodate (9.54 g, 44.58 mmol, 3.1 eq) and ammonium acetate (3.33 g, 43.15 mmol, 3 eq). The resultant cloudy solution was stirred at ambient temperatures for 48 hr. After this the recation mixture was placed under reduced pressure to remove the acetone, diluted with ethyl acetate (135 ml) and the phases separated. The aqueous phase was extracted with ethyl acetate (100 ml) and the organic layers combined, washed with brine and reduced *in vacuo* to give the title compound as pale straw coloured oil (4 g, 92 %).

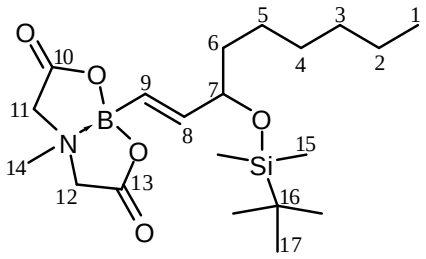
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, dd, J=17.5, 5.1, H-8), 5.69 (1H, d, J=17.4, H-9), 4.22 (1H, s, H-7), 1.67-1.42 (2H, m, H-6), 1.28 (10H, m, H-5 + H-4 + H-3 + H-2 + OH + OH), 0.99 -0.79 (12H, m, H-12 + H-1), 0.05 (6H, d, J=7.7, H-10).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 159.43 (8-CH), 119.67 (9-CH), 74.29 (7-CH), 37.52 (6-CH_2), 31.78 (CH_2), 29.31 (CH_2), 25.90 (CH_3), 24.99 (CH_2), 22.59 (CH_2), 18.27 (11-C), -4.41 (CH_3), -4.86 (CH_3).

IR (cm^{-1}) 2928.68, 2857.14, 1463.10, 1251.13, 1086.36, 833.28;

HRMS: (ESI+) Ion could not be found.

(2.37) (*E*)-2-(3-(*tert*-Butyldimethylsilyloxy)non-1-enyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione



A 100ml flask was charged with (*E*)-3-(*tert*-butyldimethylsilyloxy)non-1-enylboronic acid (3 g, 9.92 mmol, 1 eq), N-methyliminodiacetic acid (1.47 g, 9.92 mmol, 1 eq), benzene (225 ml) and DMSO (25 ml) in a 9:1 ratio respectively. The resulting solution was heated to reflux with the addition of a Dean Stark trap and water cooled condenser for 16 hr. The reaction mixture was then reduced *in vacuo* and the resulting crude mixture was absorbed onto silica from ethyl acetate and eluted from the column using 100 % ethyl acetate to give a white semi-solid (2.43 g, 59.5 %).

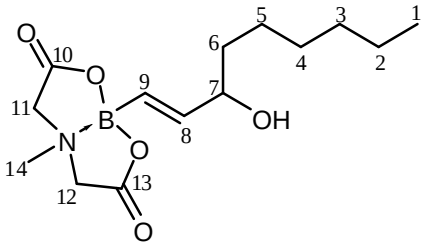
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, dd, J=17.7, 4.9, H-8), 5.56 (1H, dd, J=17.7, 0.7, H-9), 4.16 (1H, dd, J=11.4, 5.6, H-7), 3.86 (2H, d, J=16.4, H11/12), 3.65 (2H, dd, J=16.3, 9.0, H12/11), 2.82 (3H, s, H-14), 1.49-1.43 (2H, m, H-6), 1.33-1.22 (8H, m, H-5 + H-4 + H-3 + H-2), 0.89 (12H, m, H-1 + H-17), 0.03 (6H, d, J=16.2, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 167.75 C=O, 167.67 C=O, 150.26 (8-CH), 121.03 (9-CH), 74.11 (7-CH), 61.40 (2 x CH_2), 46.75 (14-CH_3), 37.90 (6-CH_2), 31.79 (CH_2), 29.29 (CH_2), 25.88 (CH_3 x 3), 25.11 (CH_2), 22.58 (CH_2), 18.24 (16-C), 14.03 (CH_3), -4.30 (CH_3), -4.75 (CH_3).

IR (cm^{-1}) 2856.53, 2954.94, 2928.74, 1766.13, 1461.52;

HRMS (ESI+) calcd for $C_{20}H_{38}BNNaO_5Si^+$ *m/z* 434.25 found 434.2505.

(2.38) (*E*)-2-(3-Hydroxynon-1-enyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione



To a solution (*E*)-2-(3-(*tert*-butyldimethylsilyloxy)non-1-enyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (2.35 g, 5.7 mmol) dissolved and stirring in acetonitrile (50 ml) was added 40 % HF (0.72 ml, 0.28 mmol, 0.05 eq). This was allowed to stir for 8 hrs or until all the starting material had vanished (monitored using tlc). Water (0.5 ml) was then added followed by sodium hydrogen carbonate (2 g) and stirred for a further 10 mins after which time sodium hydrogen sulfate (4 g) was added and the reaction mixture filtered and reduced *in vacuo*. The resulting white solid was washed twice using hexane and dried to yield the allyl alcohol as a white solid (1.675 g, 98.8 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, dd, J=17.8, 5.1, H-8), 5.60 (1H, d, J=17.7, H-9), 4.12 (1H, dd, J=11.5, 5.7, H-7), 4.01 (2H, d, J=16.7, H11/12), 3.75 (2H, dd, J=16.7, 8.4, H-12/11), 2.85 (3H, s, H-14), 2.19 (1H, s, OH), 1.55-1.45 (2H, m, H-6), 1.44-1.21 (8H, m, H-5 + H-4 + H-3 + H-2), 0.88 (3H, t, J=6.8, H-1).

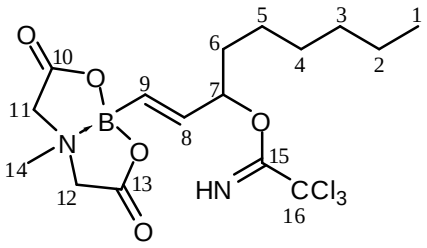
^{13}C-NMR (126 MHz, $CDCl_3$) δ 168.25 C=O, 168.23 C=O, 149.52 (8-CH), 73.47 (7-CH), 61.59 (CH_2), 61.56 (CH_2), 47.01 (14-CH_3), 37.05 (6-CH_2), 31.78 (CH_2), 29.21 (CH_2), 25.49 (CH_2), 22.59 (CH_2), 14.04 (1-CH_3).

IR (cm^{-1}) 3451.91, 2927.95, 2857.41, 1743.71, 1693.75;

HRMS (ESI+) calcd for $C_{14}H_{24}BNNaO_5^+$ 320.16 found 320.1640.

m.p. 34-36 °C.

(2.39) (*E*)-1-(6-Methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)non-1-en-3-yl 2,2,2-trichloroacetimidate



To a solution of (*E*)-2-(3-hydroxynon-1-enyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (125 mg, 0.42 mmol) and trichloroacetonitrile (173 mg, 1.2 mmol), in DCM (10 ml) was added DBU (15.2 mg, 0.1 mmol) slowly, dropwise at -78 °C. The reaction mixture was not allowed to warm higher than -60 °C. After 2 hours a further 0.25 equiv of DBU was added in the same manner followed by an additional 0.5 equiv an hour after that. Following this the reaction was worked up with sat aq ammonium chloride (10 ml) separated and the organic layer washed with water (2 x 10 ml). The organic layer was then dried over magnesium sulfate and reduced *in vacuo*. This crude mixture was then purified using flash column chromatography eluting with 20 % acetonitrile in ethyl acetate to give the title compound as a white pale green semi-solid (60 mg, 32.4 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, s, N-H), 6.20 (1H, dd, J=17.9, 5.3, H-8), 5.73 (1H, d, J=17.9, H-9), 5.34 (1H, s, H-7), 3.95-3.88 (2H, m, H-12/H-11), 3.68 (2H, t, J=16.8, H-11/H-12), 1.75 (2H, m, H-6), 1.49-1.38 (2H, m, H-5), 1.36-1.22 (6H, m, H-4 + H-3 + H-2), 0.92-0.85 (3H, m, H-1).

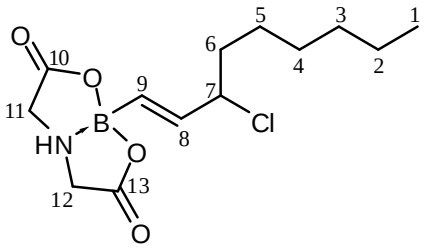
^{13}C-NMR (126 MHz, $CDCl_3$) δ 167.36 C=O, 167.31 C=O, 143.60 (8-C), 110.78 (C), 109.99 (C), 80.27 (7-CH), 61.42 (11-CH_2/12-CH_2), 61.38 (12-CH_2/11-CH_2), 46.81 (14-CH_2), 34.09 (6-CH_2), 31.64 (CH_2), 28.94 (CH_2), 24.99 (5-CH_2), 22.52 (CH_2), 14.01 (1-CH_3), C-9 (not seen due to boron α-effect).

IR (cm^{-1}) 3409.25, 1655.25, 1023.03;

LRMS *m/z* (EI) 156: $H_7C_5NO_4$.

HRMS: (ESI+) Ion could not be found.

(2.41) (*E*)-2-(3-Chloronon-1-enyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione



Palladium (II) acetate (10 mg, 0.045 mmol, 0.05 eq) was added to a stirring mixture of (*E*)-1-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)non-1-en-3-yl 2,2,2-trichloroacetimidate (200 mg, 0.45 mmol) in toluene (5 ml) and refluxed overnight. Water (5 ml) was then added and the reaction mixture extracted with diethyl ether (3 x 5 ml). The combined organic layers were dried over magnesium sulfate, filtered and reduced *in vacuo*. The crude product was then purified *via* flash column chromatography eluting with 20 % diethyl ether in hexane to give the title compound as a white solid (97 mg, 68.4 %).

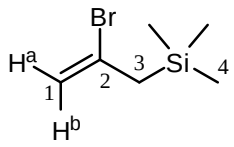
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, dd, J=17.4, 7.7, H-8), 5.66 (1H, d, J=17.4, H-9), 4.39 (1H, q, J=7.0, H-7), 4.05 (2H, dd, J=16.8, 1.7, H-12), 3.74 (2H, dd, J=16.8, 1.2, H-11), 2.86 (3H, s, H-14), 1.81 (2H, dd, J=14.8, 7.3, H-6), 1.51-1.22 (8H, m, H-5 + H-4 + H-2), 0.89 (3H, t, J=7.1, H-1).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 168.02 C=O, 167.92 C=O, 146.06 (8-CH), 126.44 (9-CH), 64.19 (7-CH), 61.64 (CH_2), 61.63 (CH_2), 47.13 (14-CH_3), 38.00 (6-C), 31.62 (CH_2), 28.68 (CH_2), 26.44 (CH_2), 22.54 (CH_2), 14.01 (1-CH_2).

IR (cm^{-1}) 2926.78, 2857.37, 1749.01, 1643.64, 1456.75;

HRMS (ESI+) calcd for $C_{14}H_{23}BClNNaO_4^+$ *m/z* 338.13 found 338.1301.

(2.42) (2-Bromo-allyl)-trimethyl-silane[65]



Trichlorosilane (56 ml, 0.556 mol) was added drop wise to a solution of 2,3-dibromopropene (101 g, 0.505 mol), triethylamine (70 ml, 0.505 mol) and cuprous chloride (5.0 g, 0.051 mol) in diethyl ether (300 ml) at -10 °C. the reaction mixture was warmed to room temperature where it was stirred for 3 hours before being filtered under an atmosphere of nitrogen. The solids were washed with dry diethyl ether (3 x 100 ml). The yellow filtrate was cooled to 0 °C where methyl magnesium bromide (555 ml, 1.668 mol, 3M in diethyl ether) was added dropwise maintaining the temperature below 0 °C. The reaction mixture was then allowed to warm to room temperature where it was stirred for 15 hr. the reaction was quenched by pouring it slowly onto a cooled solution of 2 M HCl (1 L). The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 800 ml). The combined organic layers were washed with brine (300 ml) then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was distilled (41-43 °C, 17 mbar) to afford the title compound as a colourless oil (74.0 g, 76 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.31 (1H, s, H-1^{a}/H-1^{b}), 5.22 (1H, d, J=1.3 H-1^{b}/H-1^{a}), 2.10 (2H, s, H-3), 0.11 (9H, s, H-4 x 3).

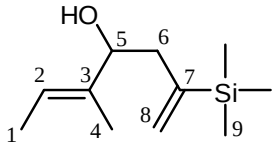
^{13}C-NMR (126 MHz, $CDCl_3$) δ 131.15 (2-C), 113.92 (1-CH_2), 33.34 (3-CH_2), 1.56 (4-CH_3 x 4).

IR (cm^{-1}) 2959, 2180, 1730, 1255, 843;

LRMS: (EI) *m/z* 192, 73.

HRMS: (ESI+) Ion could not be found.

(2.58) (*E*)-5-methyl-2-(trimethylsilyl)hepta-1,5-dien-4-ol



^{t}BuLi was added to a solution of 2-bromo-3-(trimethylsilyl)propene in diethyl ether (30 ml) at -70 °C over 20 min. The solution was then allowed to warm to 0 °C and stirred for 1.5 hr then re-cooled to -70 °C. To this, a solution of zinc chloride (2.72 g, 20 ml, 20 mmol, 1 eq) was added over 10 min and allowed to warm to 0 °C stirring for a further 2 hr and then re-cooled to -70 °C. To the resulting solution of organozinc reagent, trans-2-methyl-2-butenal was added over 5 mins dropwise and allowed to warm to rt and stirred for 48 hr. The reaction mixture was quenched with sat ammonium chloride solution (90 ml) and extracted with diethyl ether (3 x 30 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude oil was purified by distillation using a kugelrohl apparatus under vacuum (125 °C, 5.3 mbar) to give the title compound as a colourless oil (500 mg, 12.6 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.72-5.67 (1H, m, H-8^{a}/H-8^{b}), 5.56-5.47 (2H, m, H-2 + H-8^{b}/H-8^{a}), 4.07 (1H, dd, J=9.5, 3.4, H-5), 2.46 (1H, dd, J=13.9, 3.0, H-6^{a}/H-6^{b}), 2.29 (1H, dd, J=13.9, 9.5, H-6^{b}/H-6^{a}), 2.29 (1H, dd, J=13.9, 9.5, H-6^{a}/H-6^{b}), 1.67-1.61 (6H, m, H-1 + H-4), 0.13 (9H, s, H-9).

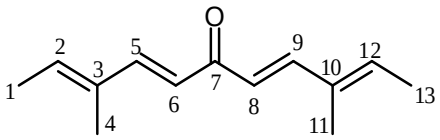
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.40 (7-C), 137.43 (3-C), 127.54 (8-CH_2), 120.37 (2-CH), 75.31 (5-CH), 42.96 (6-CH_2), 13.00 (1-CH_3), 11.44 (4-CH_3), -1.33 (9-CH_3 x 3).

IR (cm^{-1}) 3388 (br), 2955, 1379, 1249, 834;

HRMS: (ESI+) Ion could not be found.

GCMS: (EI) *m/z* 183, 99, 85.

(2.61) (2*E*,4*E*,7*E*,9*E*)-3,9-dimethylundeca-2,4,7,9-tetraen-6-one



^{t}BuLi (23.5 ml, 40 mmol) was added dropwise to a solution of 2-bromo-3-(trimethylsilyl)propene in diethyl ether (30 ml) at -70 °C over 20 mins. The solution was allowed to warm to 0 °C and stirred for a further 1.5 hr then re-cooled to -70 °C. To this a solution of triisopropyl borate (4.615 ml, 20 mmol, 1 eq) in diethyl ether (20 ml) was added over 10 minutes and again allowed to warm to 0 °C, stirred for 2 hr and re-cooled to -70 °C. To the resulting solution, trans-2-methyl-2-butenal (2.89 ml, 30 mmol, 1.5 eq) was added over 5 minutes and left to stir overnight. The reaction mixture was quenched with ammonium chloride solution (90 ml) and extracted with diethyl ether (3 x 30 ml). The orange yellow solution was dried over magnesium sulfate, filtered, reduced *in vacuo* and purified using flash column chromatography eluting with 20 % diethyl ether in hexane to yield a bright yellow/orange solid (750 mg, 19.7 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29 (2H, d, J=15.6, H-5 + H-9), 6.33 (2H, d, J=15.6, H-6 + H-8), 6.04 (2H, q, J=6.9, H-2 + H-12), 1.81 (H12, m, H-1 + H-4 + H-11 + H-13).

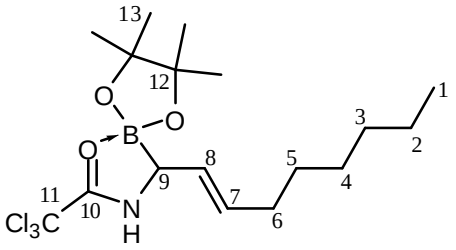
^{13}C-NMR (126 MHz, $CDCl_3$) δ 189.86 C=O, 147.50 (5+9-CH), 137.19 (2+12-CH), 134.31 (3+10-C), 123.24 (6+8-CH), 14.68 (4+11-CH_3), 11.85 (1+13-CH_3).

IR (cm^{-1}) 2922.74, 1655, 1622, 1446;

HRMS (ESI+) calcd for $C_{13}H_{18}NaO^{+}$ *m/z* 213.12 Found: 213.1250.

m.p. decomposed above 170 °C.

(2.68) (*Z*)-2,2,2-Trichloro-N-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-2-enyl)acetamide



To a solution of (*E*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-1-en-3-ol (250 mg, 0.932 mmol) in DCM (10 ml) at 0 °C was added DBU (213 mg, 1.398 mmol, 0.21 ml). To this was added trichloroacetonitrile (1.614 g, 11.184 mmol, 1.12 ml) dropwise over 15 mins and then stirred for an hour at 0 °C and a further 3 hours after that at rt. The reaction mixture was quenched with saturated ammonium chloride solution (10 ml) and extracted with DCM (3 x 10 ml). The organic layers were combined, dried over magnesium sulfate and reduced *in vacuo* to give a crude brown oil. The crude mixture was purified using flash column chromatography eluting with 20 % Et_2O in hexane to give the title compound as a colourless oil (120 mg, 31 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.71 (1H, dtd, J=7.8, 6.6, 1.2, H-7), 5.59 (1H, dd, J=15.2, 7.3, H-8), 4.08 (1H, s, NH), 4.00 (1H, d, J=7.0, H-9), 2.09-2.01 (2H, m, H-6), 1.38 (2H, dq, J=14.6, 7.2, H-5), 1.34-1.20 (18H, m, H-13 X 4 + H-4 + H-3 + H-2), 0.89 (3H, t, J=6.0, H-1).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 131.39 (7-CH), 127.57 (8-CH), 110.78 (C), 109.98 (C), 79.35 (C), 76.50 (C), 64.87 br (9-CH), 32.50 (6-CH_2), 31.69 (CH_2), 29.27 (CH_2), 28.90 (CH_2), 25.55 (CH_3), 25.24 (CH_3), 24.54 (CH_3), 22.58 (CH_2), 21.13 (CH_3), 14.03 (1-CH_3).

IR (cm^{-1}) 3200, 2931, 2858, 1726, 1459, 1392, 1150;

LRMS (EI) 251: $C_{15}H_{28}BO_2^+$.

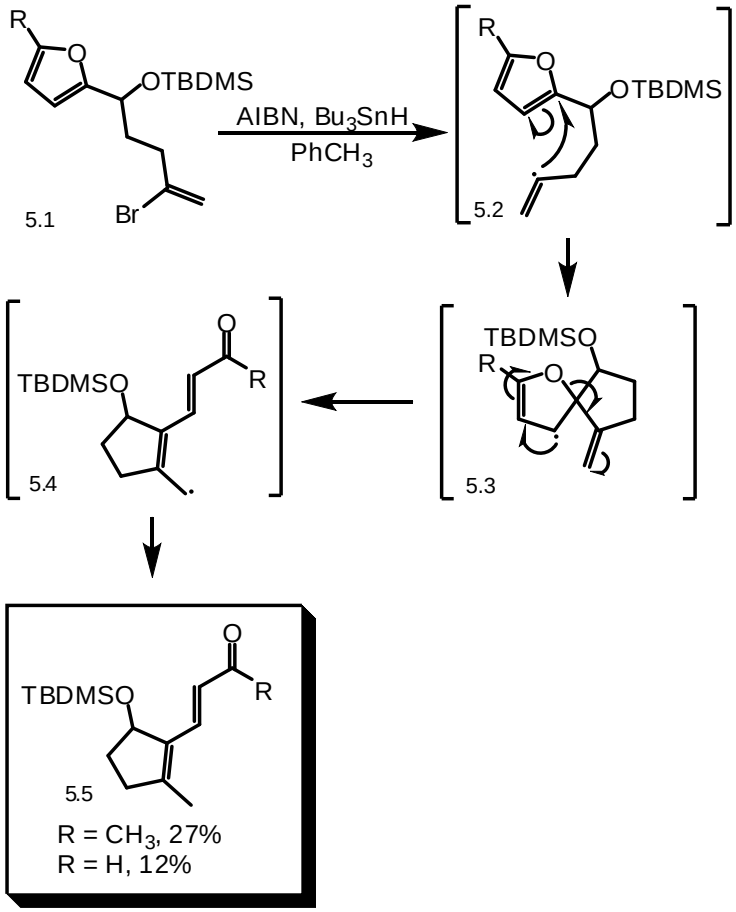
HRMS: (ESI+) Ion could not be found.

Novel Aspects of Furan Chemistry

5. Introduction

5.1 The Chemistry of Penverne *et al*.

This project aims to develop the work undertaken by Michael Annis on free radical cascade reactions involving furan rings. Annis expanded on initial work done by Penverne and Demircan. Penverne was investigating unwanted addition of radicals to furans and their subsequent fragmentation. He initially showed that cyclopentenes could be prepared from the alkenyl bromide **5.1** in a tandem radical addition/fragmentation sequence; see **scheme 5.1**[68,69].

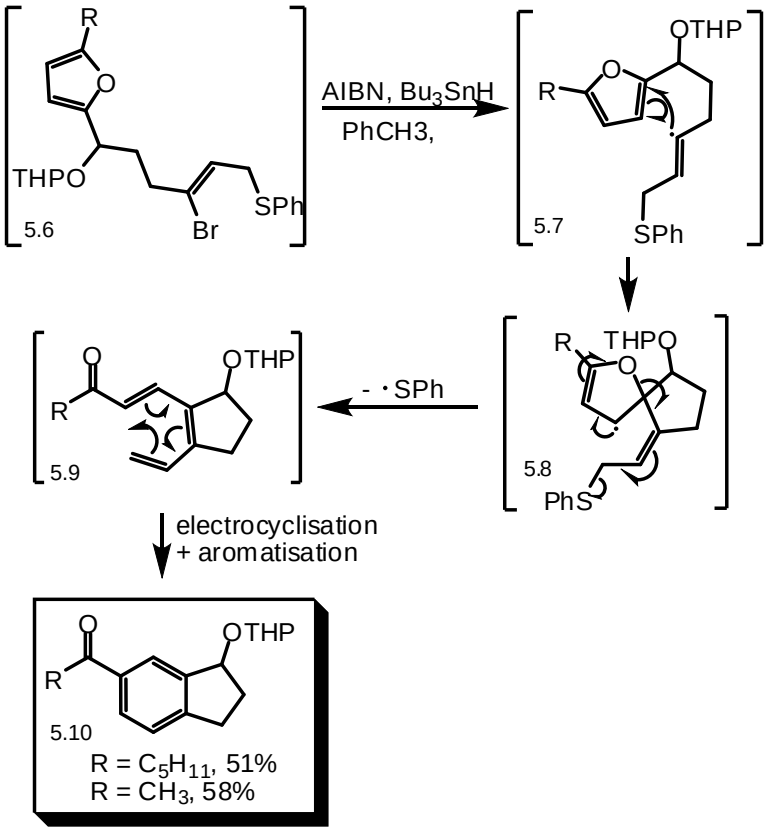


Scheme 5.1: Tandem radical addition/fragmentation sequence.

The alkenyl bromide was treated with tributyltin hydride/AIBN creating a radical that then attacked the furan ring giving an intermediary spirocycle that then fragmented to form the resulting cyclopentene **5.5**.

5.2 The chemistry of Demircan *et al.*

Following on from Penvern's work, Demircan utilised the furan fragmentation in his synthesis to construct the CD rings of the steriodal skeleton. He achieved this by replacing the TBDMSO moiety with a phenylthiol group that would subsequently eliminate to give a terminal alkene making up the last of three ready for [2+2+2] electrocyclisation creating the C ring[70,71].

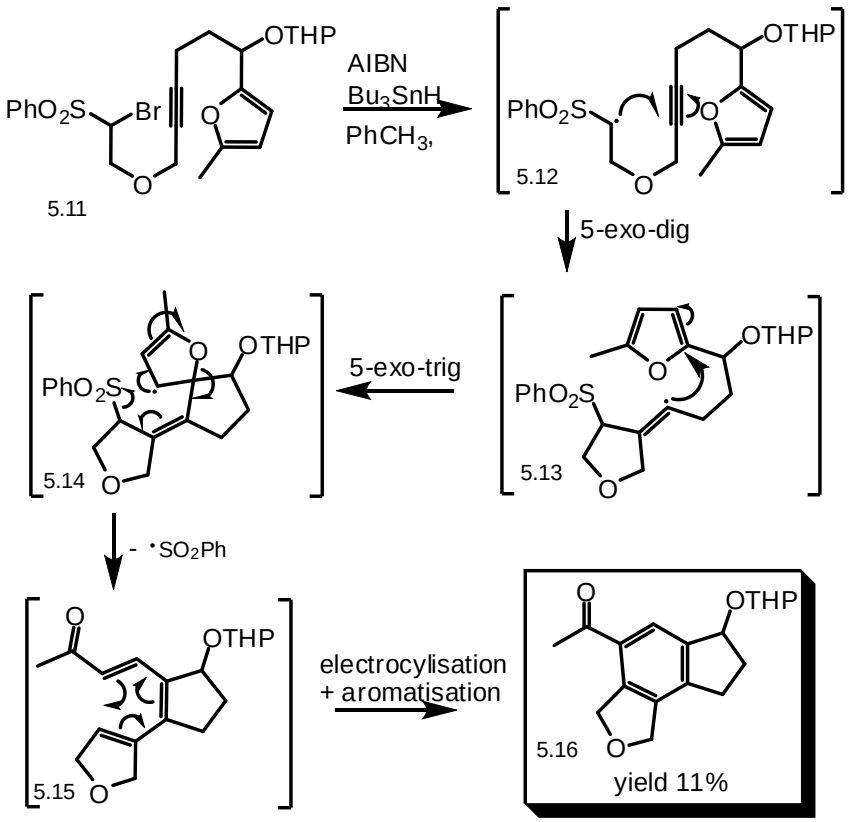


Scheme 5.2: Mechanistic pathway to **5.10** involving furan fragmentation.

The alkenyl bromide was treated with tributyl tin hydride/AIBN to form a radical that attacks the furan 5-exo-trig passing through an intermediary spirocycle **5.8** that then fragments to lose a phenylthiol radical. The resulting unsaturated compound **5.9** then undergoes [2+2+2] electrocylisation and aromatisation to give the bicycle **5.10** in good yield.

5.3 The chemistry of Annis *et al.*

Annis who was working on radical cascade reactions involving furan rings set out to create the ABCD rings of the steroidal core. Annis mediated the approach made by Demircan and Ueono and expanded it adding a further ring closing reaction to the cascade sequence[72].



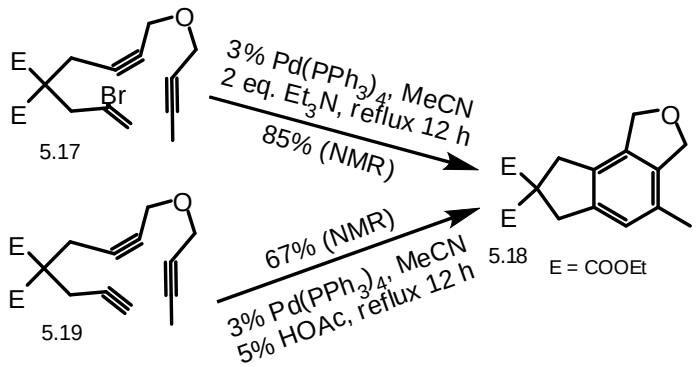
Scheme 5.3: Mechanistic pathway of **5.16** involving a cascade sequence and furan fragmentation**.**

This was achieved by extending the carbon chain by adding an ether moiety and a sulfone to act as the radical leaving group. The precursor was then treated with tributyltin hydride/AIBN creating a radical which underwent 5-exo-dig addition to create the new furan ring **5.13** followed by subsequent radical 5-exo-trig addition and fragmentation of furan with loss of the sulfonyl radical to give the intermediary compound **5.15.** This then underwent [2+2+2] electrocylisation and aromatisation to give the tricycle **5.16** in 11 % yield.

With numerous studies and developments in the field of palladium chemistry specifically those concerned with palladium-catalysed oligocyclisations by carbopalladation ring formation there are a plethora of different papers to review, however I will focus on work done by Negishi and of those within the University of Sussex and its partners. Recent work is concerned with the influence of tether lengths on oligocyclsations of 2-bromoalk-1-ene-(n+1),(m+n+1)-diynes *via* palladium catalysis and looking at the associated effects of different terminal substituents. This work is an investigative study that also looks into possible mechanistic pathways.

5.4 The chemistry of Negishi *et al.*

Negishi[73] investigated selective carbopalladation routes to benzene derivatives with varying degrees of substitution. This work was developed from his previous work into the construction of benzene derivatives from a partially intramolecular reaction that gave highly regiocontrolled benzene derivatives. Negishi chose **5.17** and **5.19** as test substrates to achieve intramolecular formation of benzene derivative **5.18**. Both substrates gave a reasonable yield with the stated reagents in **scheme 5.4**.

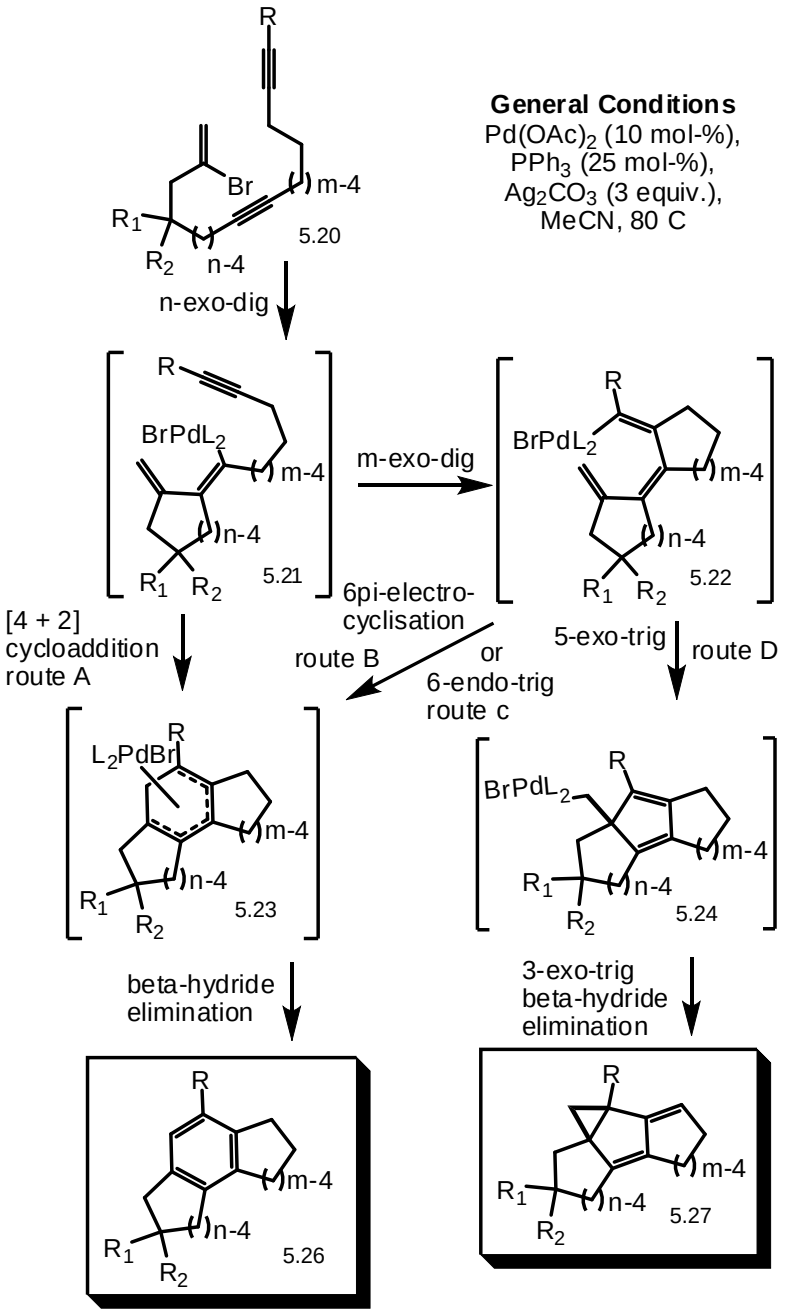


Scheme 5.4

At the time of writing his paper Negishi was not certain of the mechanism, however it was presumed highly likely that the tetrakis(triphenylphosphine)palladium (0) formed *in situ* undergoes oxidative addition and subsequent 5-exo-dig carbopalladation followed by further 5-exo-dig carbopalladation to give an intermediary compound that either undergoes further carbopalladation or electrocyclic rearrangement to give the resulting bis annulated benzene derivative **5.18**.

5.5 The chemistry of Parsons, de Mejiere *et al.*

In a summary of Parsons and de Mejieres[74] work various tricyclic rings were produced with many different combinations of tether links between multiple bond fragments giving [5-6-5], [6-5-6], [6-6-6] and [5-6-6] tricyclic ring systems all with varying substituents at terminal non-brominated vinylic locations[75]. Tricyclic rings with a bridge-annulated cyclopropane moiety between rings A and B were also reported which provided insight into an alternative mechanistic pathway.



Scheme 5.6: Possible pathways for cascade oligocyclizations of 2-bromoalk-1-ene-(*n*+1),(*m*+*n*+1)-diynes **5.20**, *n* = 5 or 6, *m* = 5 or 6.

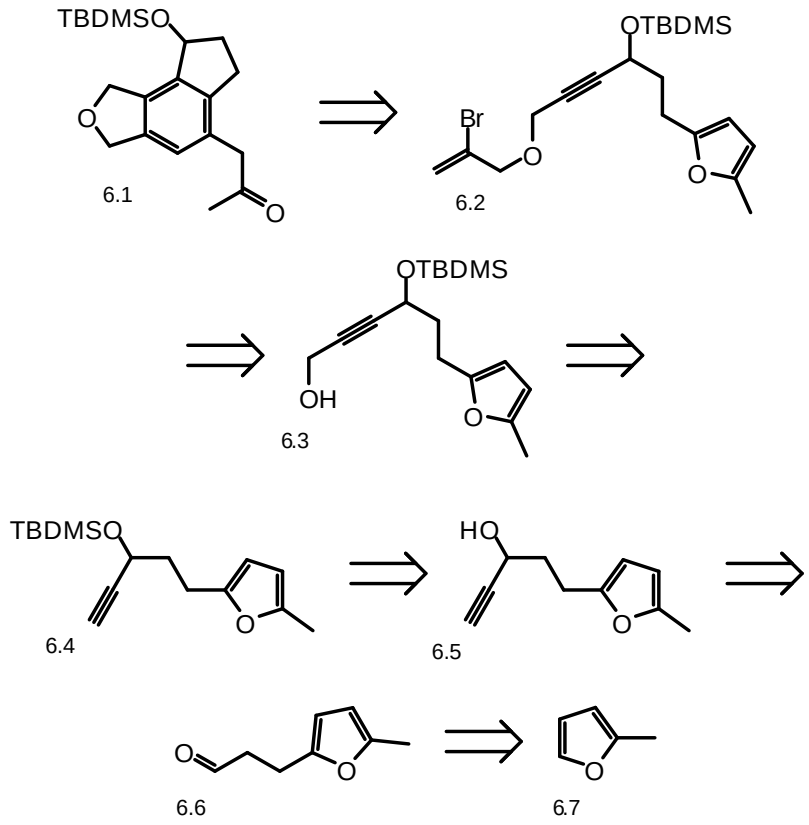
It was noted from previous work that it would be of benefit to develop access to core tricyclic ring structures of importance in organic synthesis. The ABC ring systems in steroids could be constructed from long chain 2-bromoalk-1-ene-alkyne chains with a terminal furan moiety. This could utilise the carbopalladation type reactions expanded on by Parsons and de Miejire and combining it with the attack and subsequent fragmentation of furans seen by that of Penverne, Annis and Demircan.

6. Results & Discussion

6.1 Formation of oxygen containing tricycle

6.1.1 Retrosynthesis of 6.1

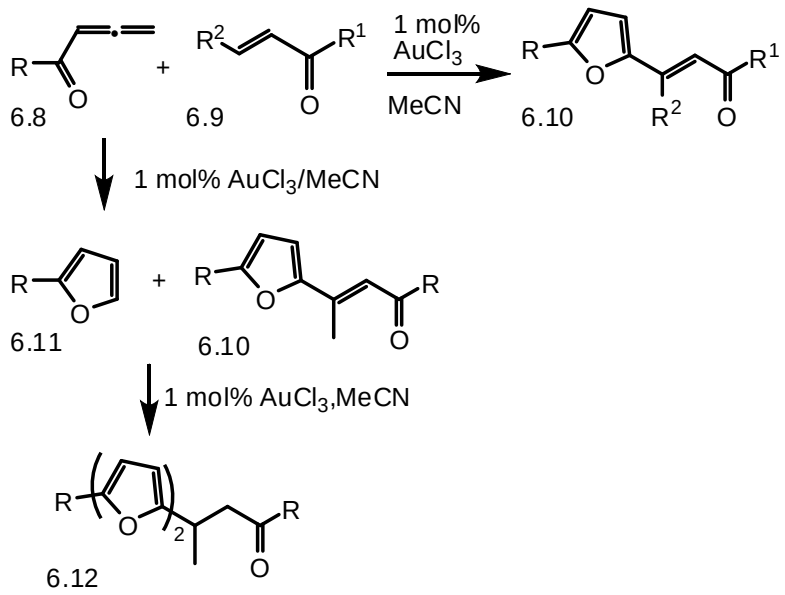
It was hypothesised the 2-bromoalkene precursor **6.2** of the bis annulated benzene derivative **6.1** could be prepared from the propargyl alcohol **6.3** which in turn could be generated from the alkyne **6.4** using ^{n}BuLi and paraformaldehyde. The alkyne **6.4** could be generated from the aldehyde **6.6** on treatment with ethynylmagnesium bromide and TBDMS protection. The furan aldehyde **6.6** would be synthesised using conditions developed by Hashmi[76] reacting methyl furan with acrolein in the presence of a catalytic amount of gold chloride.



Scheme 6.1: Retrosynthesis of 1-(8-(*tert*-butyldimethylsilyloxy)-3,6,7,8-tetrahydro-1H-indeno[5,4-c]furan-5-yl)propan-2-one **6.1**.

6.2 Synthetic approach to 6.1

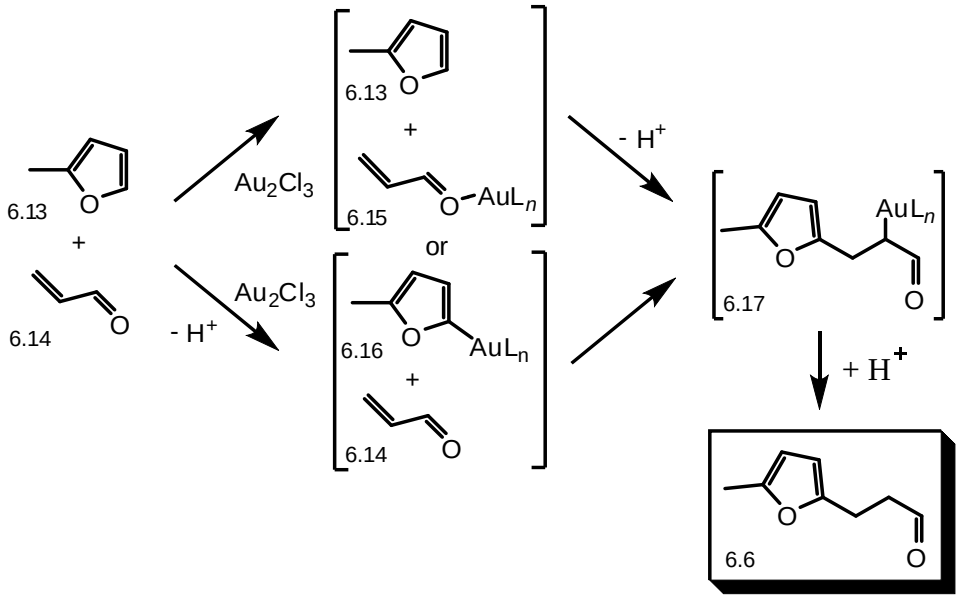
Hashmi found when treating allenyl ketones with gold (III) chloride they produced substituted furan derivatives[76,77]. Hashmi showed that although the allenyl ketone **6.8** initially formed a substituted furan **6.11** that it would react further with an α,β-unsaturated ketone to give the corresponding furan substituted at 2 and 5 positions **6.10**. Once the α,β-unsaturated ketone furan derivative **6.10** had formed it could then react further with the monosubstituted furan **6.11** to give the double addition product **6.12** and enone saturation.



Scheme 6.2: Hashmi furan synthesis and alkylation of furan with enones, catalysed by gold chloride.

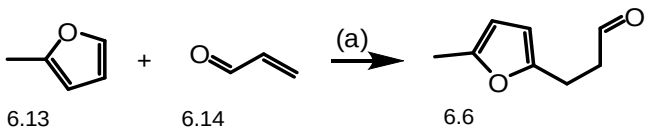
Scheme 6.2 depicts the various outcomes witnessed by Hashmi when treating the allene **6.8** and the enone **6.9** with a catalytic amount of gold chloride. The allene **6.8** forms the 2-substituted furan **6.11** which can then add to the enone **6.9** to give the 2,5-disubstitued furan **6.10**. It is then possible for the mono-substituted furan **6.11** to add again to the 2,5-disubstituted furan **6.10** to give the di-furan product **6.12**. The reaction is thought to proceed either by gold activation of the enone, which then forms the new C-C bond at the 5-position of the furan by electrophilic aromatic substitution or direct electrophilic attack of gold at the furan forming a furyl-gold species which subsequently attacks the α,β-unsaturated ketone 1,4. The gold enolate

then undergoes protonation from the freed proton during electrophilic aromatic substitution; see **scheme 6.3.**



Scheme 6.3: Possible mechanistic routes to aldehyde **6.6**.

Synthesis of the 2-methylfuran-5-propanal **6.6** was achieved by adding dropwise a solution of acrolein in MeCN to methylfuran and gold (III) chloride in MeCN at -20 °C. The reaction was monitored using thin layer chromatography.

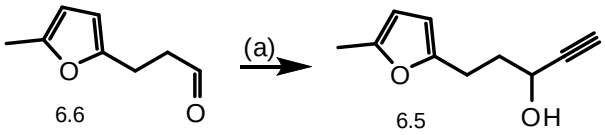


Scheme 6.4: Reagents and Conditions (a) gold (III) chloride 1 mol%, MeCN, 0 °C, 0.5 hr.

The reaction seemed to work well on a small scale with a yield in excess of 80 %, when carried out on a small quantity (1 g) of the methylfuran. On a larger scale the reaction proved capricious and the best yield that could be achieved was around 35 % when using 15 g of methylfuran. This was due to the increased formation of side products namely the di and tri-substituted furan as well as a large amount of a black, presumably polymeric substance.

6.2.1 Alkylation of 2-methylfuran-5-propanal

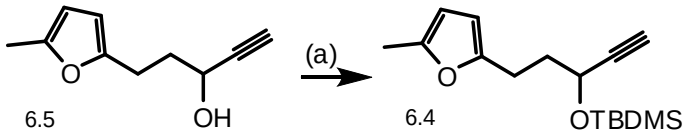
The aldehyde was simply alkylated with 2 equivalents of ethynylmagnesium bromide in THF which gave the resulting alkynyl alcohol **6.5** in good yield. This was achieved by nucleophilic attack of the lone pair of the ethynyl anion at the electrophilic centre of the carbonyl and aided by stabilisation due to magnesium bromide thought to go through a six membered transition state.



Scheme 6.5: Reagents and Conditions: (a) ethynylmagnesium bromide (2 eq), THF, 0 °C, 80 %.

6.2.2 Protection of secondary alcohol using TBDMSCl

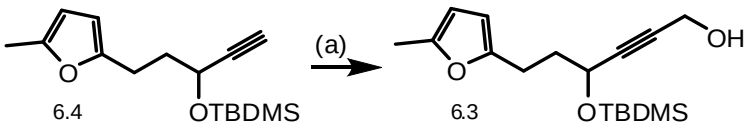
TBDMSCl offered an easy protection of the secondary alcohol **6.5** and also added significant weight on taking the resulting product forward. Imidazole was used as a base along with a catalytic amount of DMAP to assist a fast reaction. A catalytic amount of DMAP is used to activate the TBDMSCl as DMAP displaces the chloride ion making the resulting nitrogen-silicon bond more susceptible to nucleophilic attack from the hydroxyl due to the 4-dimethylaminopyridine moiety's propensity to lose its positive charge. The reaction is then worked up with ammonium chloride and generally gave the protected alcohol **6.4** in good yields in the range 70-99 %.



Scheme 6.6: Reagents and Conditions: (a) TBDMSCl (1.1eq), imidazole (1.2eq), DMAP (0.1 eq), DCM, rt.

6.2.3 Preparation of propargyl alcohol moiety

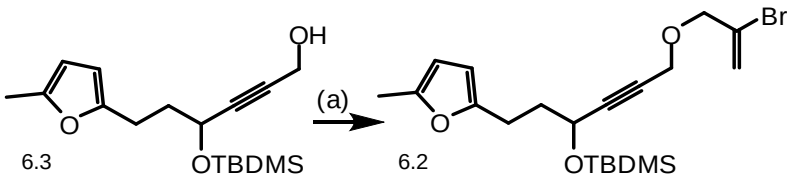
The alkyne **6.4** was deprotonated using ^{n}BuLi at -78 °C and the resulting lithium salt added to dry paraformaldehyde in THF to give the resulting primary alcohol **6.3** in good yield (69 %).



Scheme 6.7: Reagents and Conditions: (a) ^{n}BuLi (1.1 eq), -78 °C, THF. (b) paraformaldehyde (2 eq), THF, 0 °C.

6.2.4 Preparation of oxygen tricycle precursor

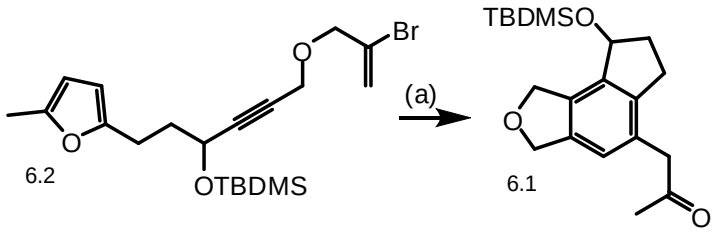
The primary alcohol **6.3** was deprotonated using NaH in THF at 0 °C and the resulting alkoxide attacked 2,3-dibromopropene to give the ether **6.2** in moderate yield (64 %).



Scheme 6.8: Reagents and Conditions: (a) NaH (1.1 eq), 2,3-dibromopropene (1 eq), THF, 0 °C.

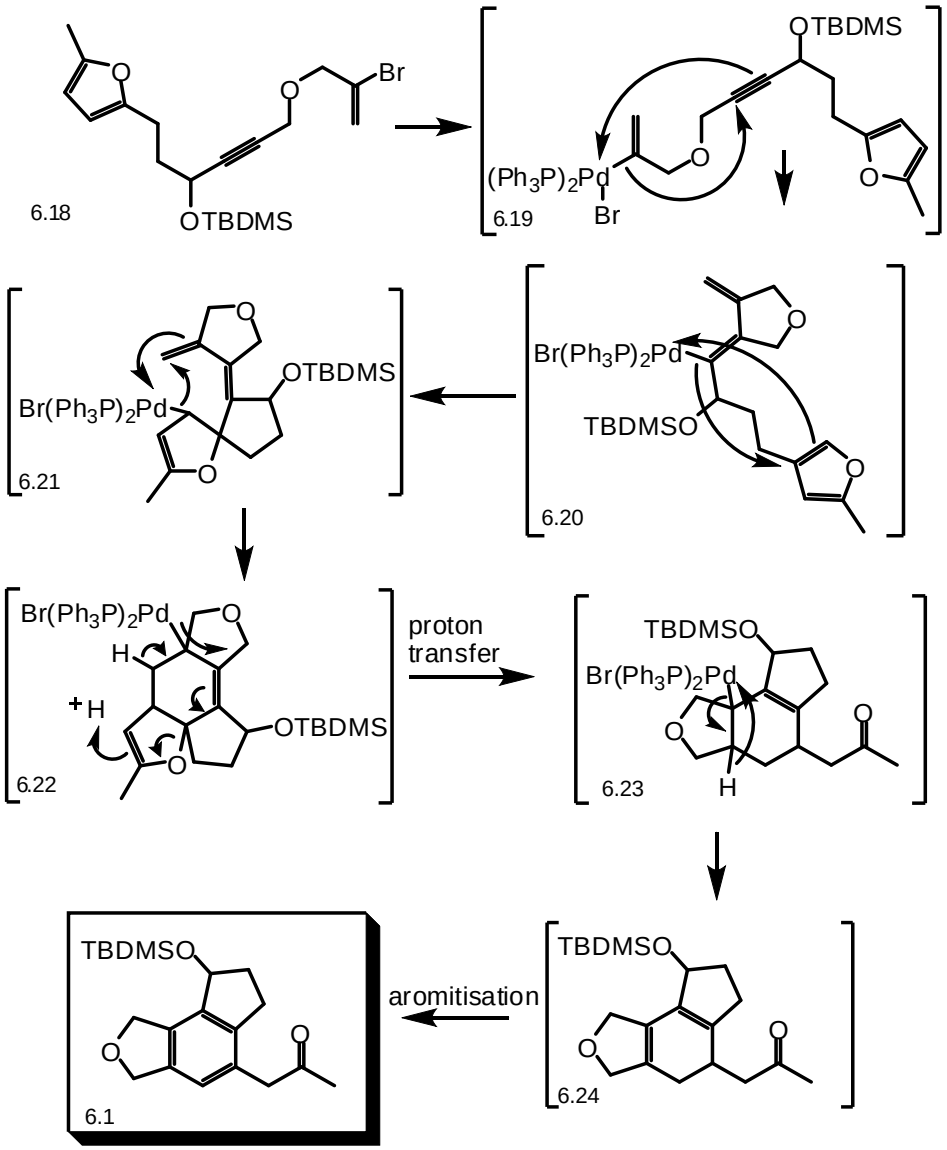
6.2.5 Cyclisation of 6.1 precursor

The open chain precursor **6.2** was treated under Heck conditions and heated at 80 °C for 5 hr in MeCN to give the resulting bis annulated benzene derivative **6.1** in 27 % yield.



Scheme 6.9: Reagents and Conditions: (a) $Pd(OAc)_2$ (0.1 eq), PPh_3 (0.3 eq), KCO_3 (2 eq), MeCN, 80 °C, 5 hr.

The mechanism for this reaction is thought to start with oxidative addition of palladium (0) into the carbon-bromine bond and is thought to be followed by 5–exo-dig carbopalladation mediated cyclisation to give the 3,4-substituted oxalone intermediate **6.20**. This cyclises further by carbopalladation, 5-exo-dig onto the furan to give the intermediate spiro-cycle **6.21**, with palladium then mediating a further cyclisation to create the tetracyclic compound **6.22** 6-endo-trig. Palladium can then migrate opening the furan ring resulting in the ketone **6.23** followed by beta hydride elimination of the palladium species and aromatisation to give the bis annulated benzene product **6.1**.

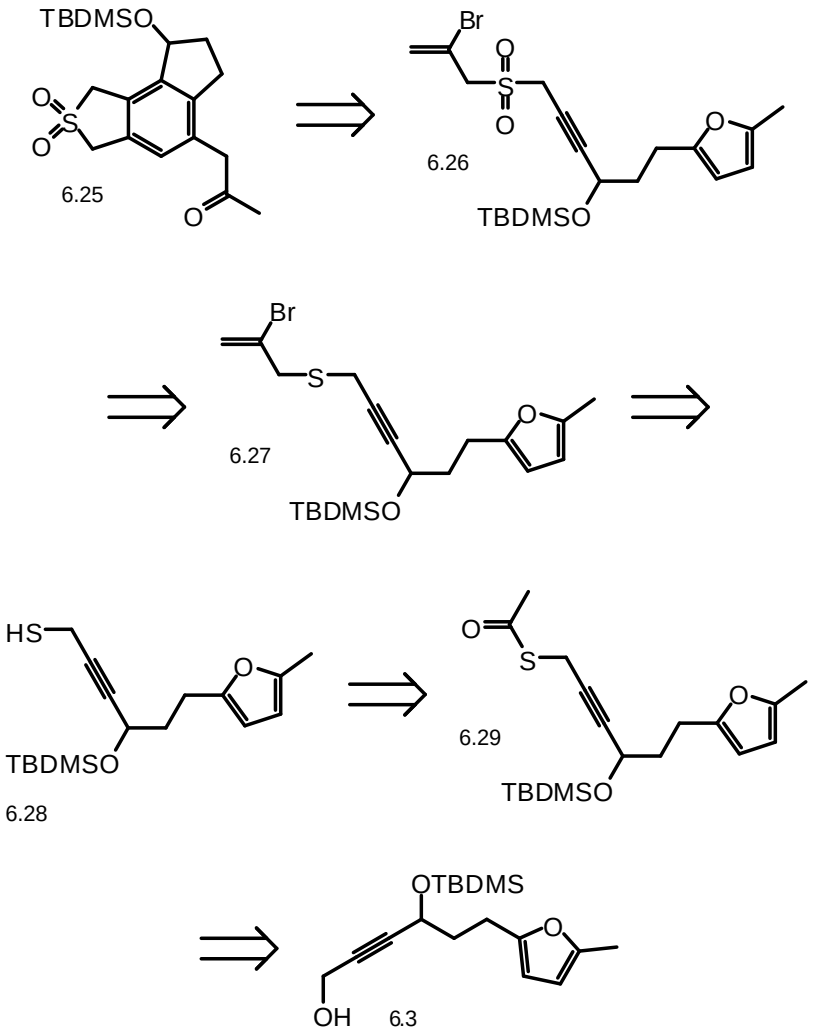


Scheme 6.10: Proposed mechanistic pathway for the construction of **6.1**.

6.3 Sulfur containing tricycle

6.3.1 Retrosynthesis of 6.25

It was hypothesised that the bis-annulated benzene sulfone derivative **6.25** could be synthesised from the previously made propargyl alcohol **6.3** by utilising Mitsunobu chemistry and displacing triphenylphosphine oxide formed on treatment with DEAD and triphenylphosphine with thioacetic acid to give the thio ester **6.29**. The resulting ester could then be reduced using lithium aluminium hydride to give the thiol **6.28.**



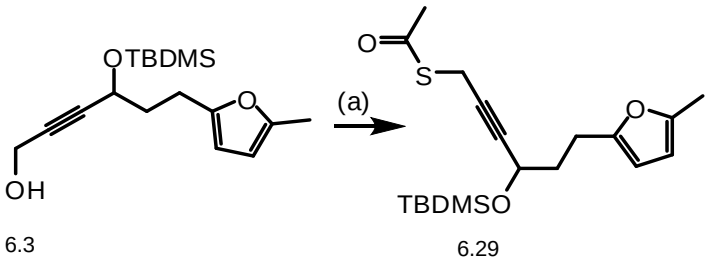
Scheme 6.11: Retrosynthesis of target molecule bis-thiophenone cyclopentane benzene derivate **6.25**.

The thiol can be alkylated using 2,3-dibromopropene and sodium hydride to give the 2-bromo-ene moiety on the thiol **6.27**. The last step before attempting cyclisation would be oxidation of the thiol to a sulfone perhaps using *m*-CPBA before cyclising using the same conditions developed in the previous cyclisation in chapter **6.2.5**.

6.4 Synthetic approach to 6.25

6.4.1 Preparation of thioacetate using Mitsunobu conditions

The propargyl alcohol **6.3** and thioacetic acid were added to a canary yellow solution of DEAD and triphenylphosphine under Mitsunobu conditions[(78)]. DEAD and triphenylphosphine form a phosphonium intermediate that then adds to the oxygen of the alcohol to give a triphenylphosphine moiety that is displaced by thioacetic acid to give the thioacetate compound **6.29** in a 74 % yield.

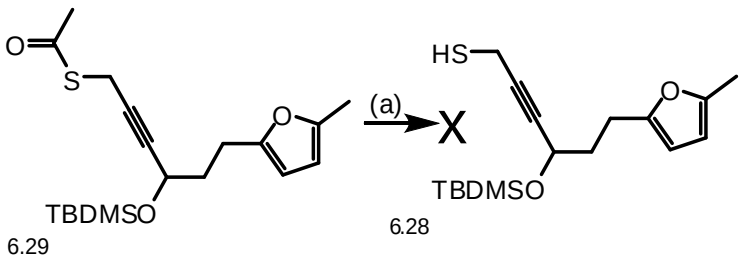


6.3 6.29

Scheme 6.12 Reagents and Conditions: (a) Thioacetic acid, DEAD, PPh_3, THF, -20 °C.

6.4.2 Reduction of the thioacetic moiety in 6.29

The thioacetate **6.29** was treated with 4 eq of lithium aluminium hydride in an attempt to reduce the thioester moiety and monitored *via* thin layer chromatography. The reaction gave a major product that was not that of the thiol but an allene. It seemed the hydride had added 1,4 through the alkynyl triple bond to give an allene and turn the thioacetate moiety into a leaving group.



Scheme 6.13: Reagents and Conditions: (a) $LiAlH_4$, THF, 0 °C.

Figure 6.1 demonstrates the possible mechanism of allene formation. Lithium aluminium hydride can add to the alkyne triple bond to form an allene displacing thioacetic acid stabilised by lithium.

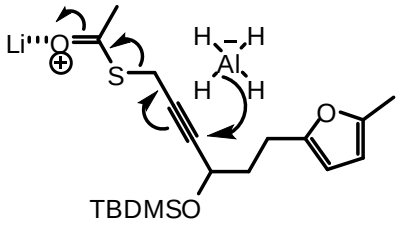
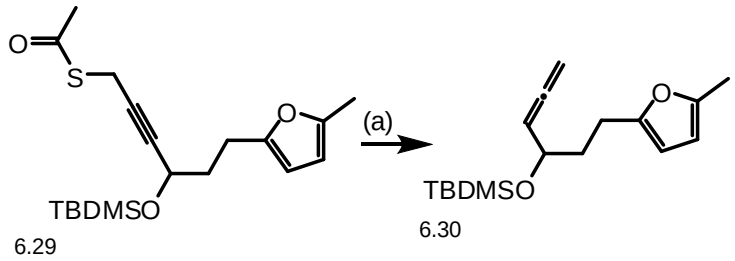


Figure 6.1: Shows the proposed mechanism of allene **6.30** formation**.**

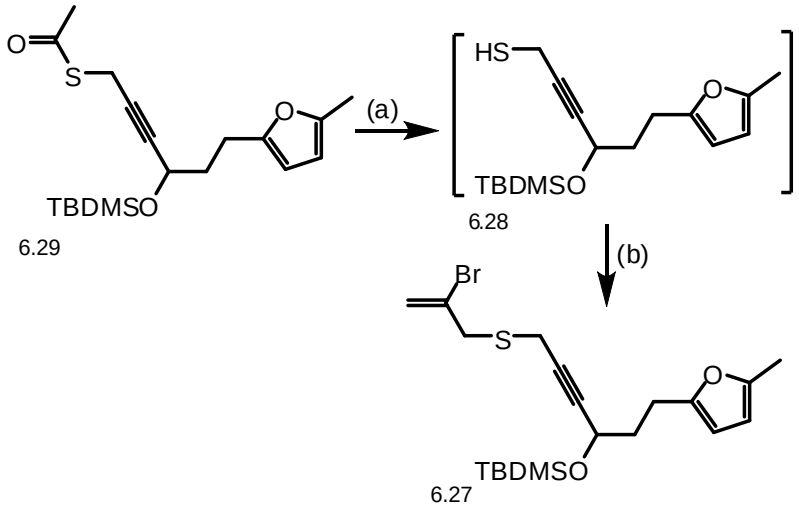
Although the thiol was relatively easy to synthesise from **6.29** using sodium methoxide, isolation and hence purification proved difficult due to its propensity to decompose in air and during purification using flash column chromatography.



Scheme 6.15: Reagents and Conditions: (a) $LiAlH_4$ (4 eq), THF, 0 °C.

To bypass the need for purification a one pot synthesis of the sulfur bis-annulated benzene precursor was proposed. In actual fact this proved to be by far a better solution giving an almost quantitative yield (99 %). So after treatment with sodium

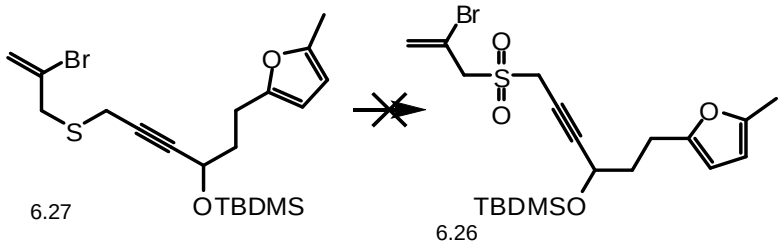
methoxide in methanol, 2,3-dibromopropene was simply added dropwise at 0 °C and left to stir for an hour. The reaction mixture worked up with ammonium chloride and extracted with no need of further purification to give **6.27**.



Scheme 6.16: Reagents and Conditions: (a) NaOMe, MeOH; (b) 2,3-dibromopropene, MeOH.

6.4.3 Oxidation of thioether 6.27 to a sulfone

Attempts to oxidise the thioether all failed, either the substrate decomposed or remained unchanged. **Table 6.1** lists attempts including a mild solid-state oxidation using urea-hydrogen peroxide complex developed by Varma *et al.*[79] to oxidise **6.27.**



Scheme 6.16: Reagents and Conditions; *See table on next page*.

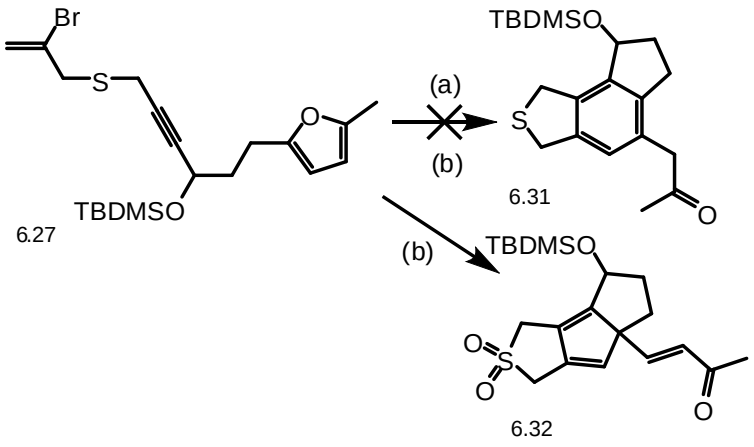
Reagent	Reagents and conditions	Yield %	Temperature
5.2.4	UHP, neat, 24 hr	0	85 °C
5.2.4	*m*-CPBA, DCM	decomp	rt
5.2.4	H_2O_2, DCM	decomp	rt

Table 6.1: Results for attempts at oxidation of thioether **6.27** to a sulfone.

Only a small number of attempts were tried as it was thought more important to achieve the tricycle and then to see if subsequent oxidation could be achieved following cyclisation.

6.4.4 Formation of spirocycle following Heck type conditions

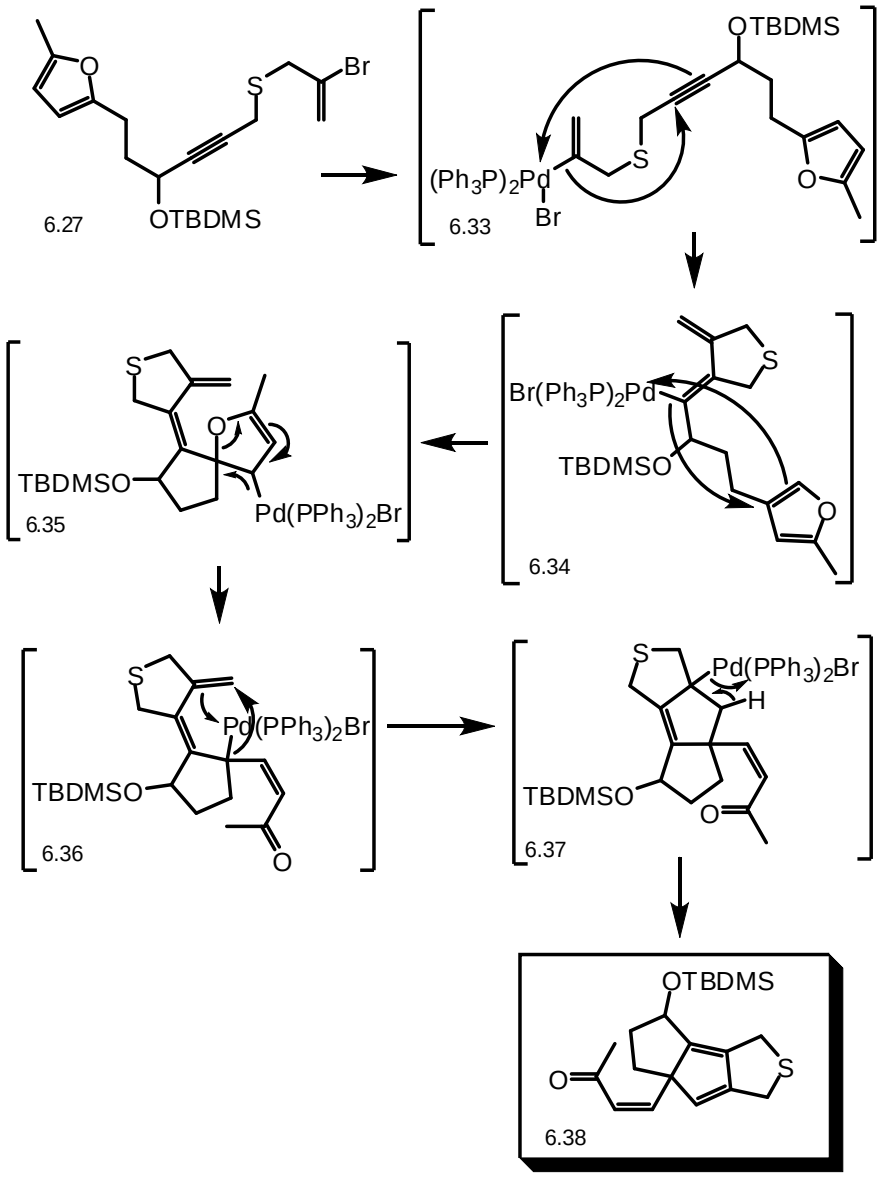
The thioether tricyclic precursor **6.27** was treated as before with triphenylphosphine, potassium carbonate and palladium acetate in acetonitrile at 80 °C for 12 hours this didn't give the expected bis-annulated benzene-thiophane derivative **6.31** but gave instead the cyclopentadiene sulfone **6.32**.



Scheme 6.17: Reagents and Conditions: (a) $Pd(AcO)_2$ (0.1 eq), $P(Ph)_3$ (0.3 eq), K_2CO_3 (2 eq), MeCN; (b) $Pd(AcO)_2$ (0.1 eq), dppe (0.3 eq), K_2CO_3 (2 eq), DMF.

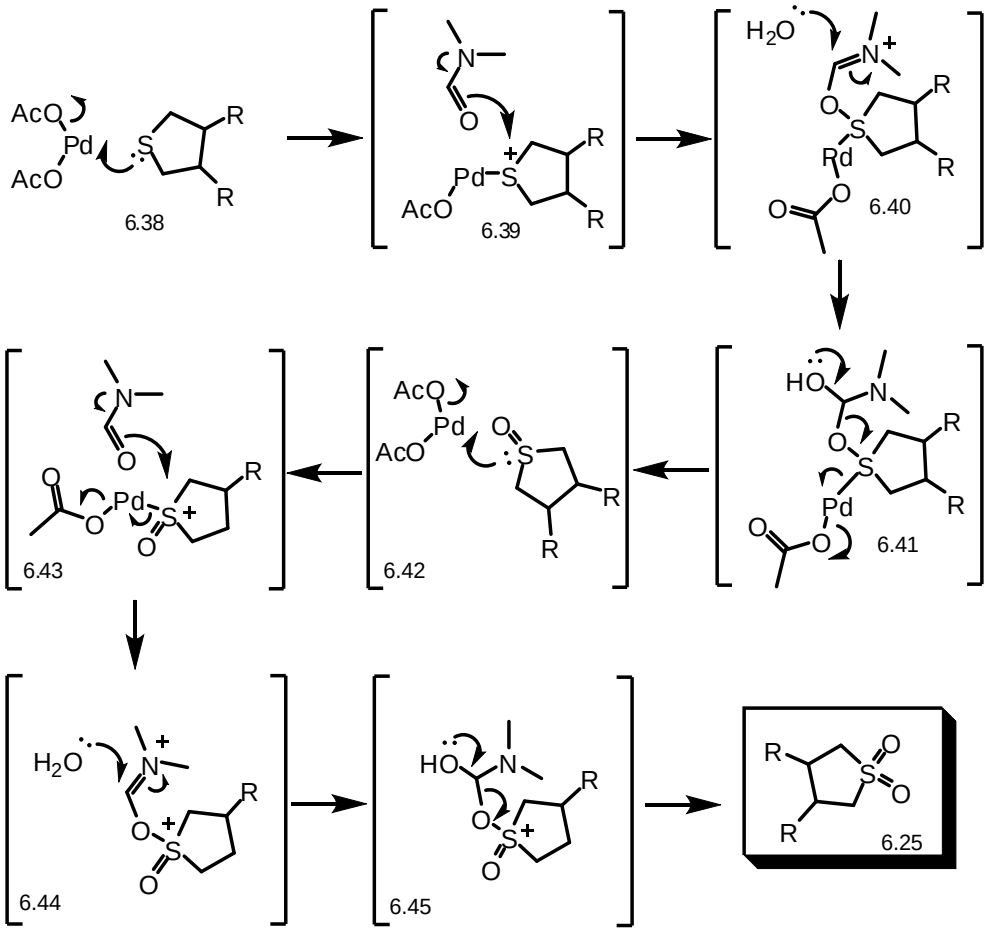
The reaction was then repeated substituting MeCN for DMF and triphenylphosphine for a more stable ligand at high temperatures 1,2-bis(diphenylphosphino)ethane and heated to a higher temperature of 120 °C for approximately 0.5 hr giving a more respectable 40 % yield in a much quicker period. It was hoped using an elevated temperature, cyclopentadiene **6.32** would ring expand by one carbon to give the

desired [5,6,5] tricycle **6.31**. However, the observed tricycle was again that of the cyclopentadiene **6.32,** easily identifiable by its alpha beta unsaturated enone in the ^{1}H-NMR signature. Subsequently a new proposed mechanism was formulated for its construction. As before the palladium inserts *via* oxidative addition into the carbon-bromine bond which then inserts *via* carbopalladation undergoing cyclisation 5-exo-dig, giving a thiolane intermediate **6.34.** This intermediate undergoes further carbopalladation mediated cyclisation to create a spirocycle with the furan ring 5-exo-trig **6.35.** Palladium then instead of cyclising to the ethane 2 substituted thiolane moiety, migrates opening the furan ring to give **6.36.** From here palladium adds onto the 2-methylene thiolane moiety in a further carbopalladation reaction 5-endo-trig, to give the resulting tricycle **6.37** that then undergoes beta hydride elimination to yield the bis annulated cylopentadiene **6.38**.



Scheme 6.18: Proposed mechanistic pathway for the construction of cyclopentadiene **6.38**.

Another surprising but welcome result was the oxidation of the sulfide to a sulfone reducing the need to oxidise before or even after cyclisation. This was thought to occur *via* palladium mediated oxidation utilising acetate and DMF as an oxygen source. For the mechanism in **Scheme 6.19** to work the assumption is made that the DMF used in this reaction is slightly wet.



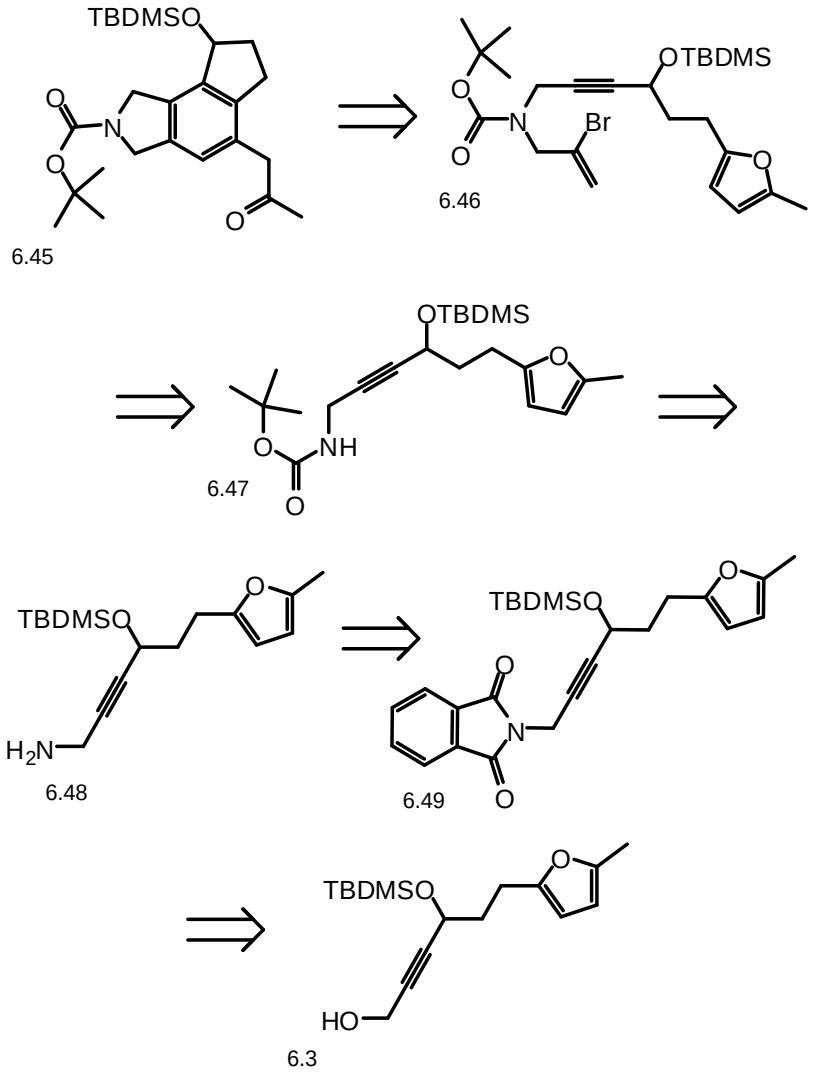
Scheme 6.19: Proposed mechanistic pathway for the oxidation of thiol to sulfone **6.25**.

Sulfur is thought to attack palladium in an S_N2 fashion displacing acetate to give the intermediary pallado-sulfur compound **6.39**. DMF can then attack sulfur to form the more stable tetravalent sulfur intermediary **6.40**, which can then undergo loss of palladium and oxidative addition to give the sulfoxide **6.41** as DMF reforms with the addition of water. Sulfur is then thought to attack palladium acetate again in an S_N2 fashion giving the pentavalent pallado-sulfur intermediary **6.43** which can then undergo a similar loss of palladium triggered by oxidative addition from DMF followed by loss of DMF through the addition of water **6.44**.

6.5 Formation of nitrogen containing tricycle

6.5.1 Retrosynthetic analysis of 6.45

It was proposed that the nitrogen variant bis-annulated benzene pyrrolidine derivative **6.45** could also be synthesised much like the thiophane derivative **6.32**, starting from the proparlgyl alcohol **6.3** and employing Mitsunobu chemistry to install the nitrogen *via* a phthalimide moiety **6.49**.



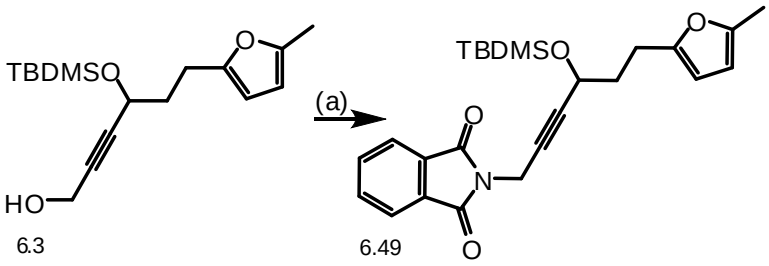
Scheme 6.20: Retrosynthesis for target molecule pyrole cyclopentane-bis-annulated benzene derivative **6.45**.

The phthalimide **6.49** could be reduced to the free amine **6.48** and protected using Boc anhydride before alkylation to give the nitrogen tricycle precursor **6.47**.

6.6 Synthetic approach of 6.45

6.6.1 Mitsunobu coupling

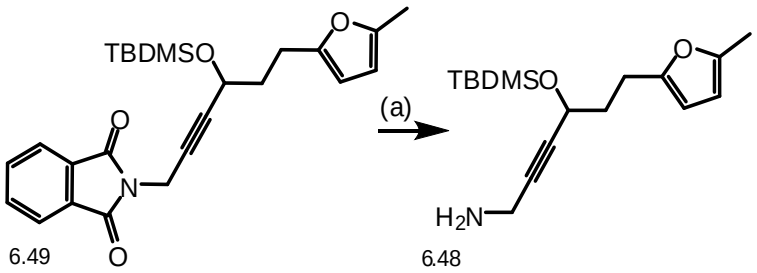
Treating the propargyl alcohol **6.3** with an intermediary phosphonium complex formed from DEAD and triphenylphosphine as described previously in chapter **6.4.1** and forms a phosphonium-oxide moiety which is then displaced by phthalimide to give the propargyl phthalimide compound **6.49** in good yield (73 %).



Scheme 6.21: Reagents and Conditions (a) DEAD (1.2 eq), PPh_3 (1.2 eq), phthalimide (1.2 eq), THF, - 20°C.

6.6.2 Phthalimide deprotection

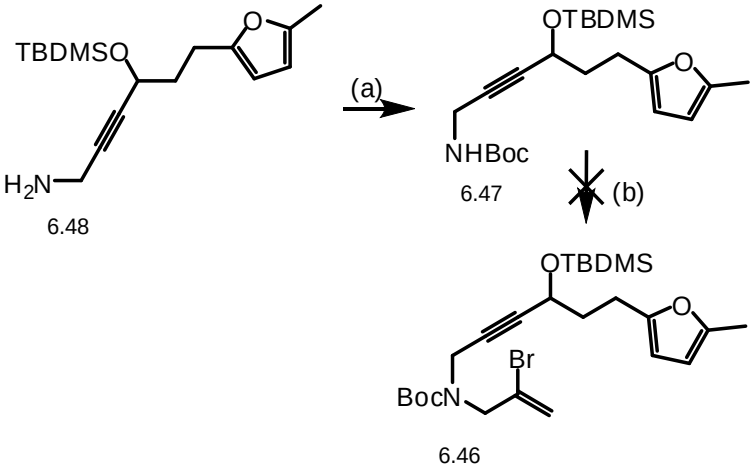
The phthalimide was successfully cleaved to the free amine with hydrazine in refluxing methanol in excellent yield (98 %). It follows a modification of the Gabriel synthesis[80] first achieved by Ing and Manske[81] and a procedure for this has been reported by Sen[82].



Scheme 6.22: Reagents and Conditions (a) hydrazine hydrate, HCl, MeOH.

6.6.3 Free amine protection and alkylation

The free amine **6.48** was quickly protected using Boc-anhydride in ethanol. Excess di-*tert*-butyl dicarbonate was found in the reaction mixture and after purification failed using flash column chromatography a method described by Hassner[83] was employed. Any excess $(BOC)_2O$ was destroyed using one equivalent of TFE and a catalytic amount of DMAP.



Scheme 6.23: Reagents and Conditions (a) $(BOC)_2O$, MeOH, TFE, DMAP (b) *see table below.*

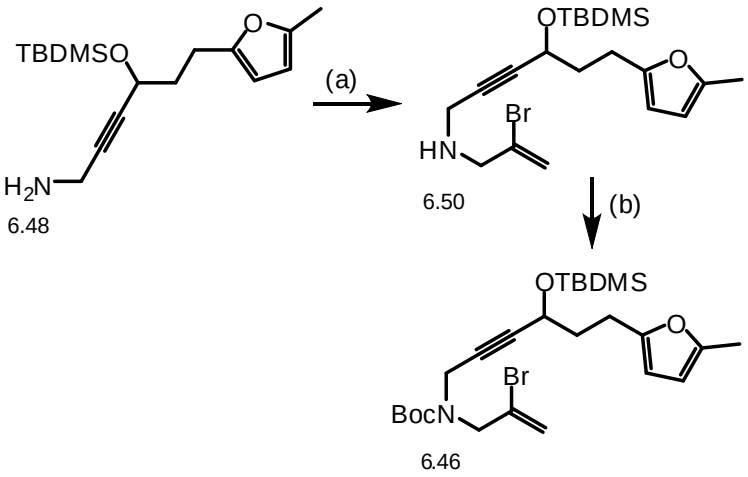
Alkylating the now partially protected amine **6.47** however failed; **table 6.2** lists various attempts. It is thought the bulky Boc protecting group sterically hindered attempts to deprotonate the amide.

Reagent	Reagents and conditions	Yield %	Temperature
6.47	NaH (60% dispersion in mineral oil), THF	0	25 °C
6.47	^{n}BuLi (1.1 eq), THF	0	0 °C
6.47	CTAB, NaOH	decomp	0 °C
6.47	TBAI, NaH, DMF	decomp	0 °C
6.47	NaH (60% dispersion in mineral oil), Et_2O	0	25 °C
6.47	NaH, THF	0	25 °C
6.47	K_2CO_3, MeCN, 48 hr	0	25 °C
6.47	NaH (60%), THF	0	reflux
6.47	K_2CO_3, MeCN	0	reflux

Table 6.2: Results for attempts at alkylating the amide **6.47**.

6.6.4 Alkylation followed by protection

To reduce the hindrance around the amine moiety it was decided alkylation should be carried out first. Alkylation didn't work as before with NaH acting as a base so potassium carbonate was used along with the alkylating agent 2,3-dibromopropene to give the 2-bromo-alkene amine **6.50** in a reasonable 60 % yield. The reaction was slow however and took 48 hours and was left for 72 hours with no extra visible effect (tlc).

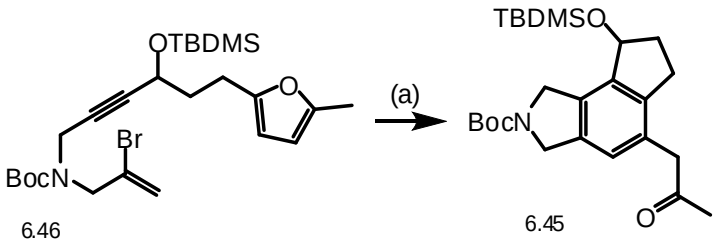


Scheme 6.24: Reagents and Conditions (a) K_2CO_3 (1 eq), 2,3-dibromopropene (1 eq), THF, rt; (b) $(BOC)_2O$ (1.1 eq), TFE (1 eq), DMAP (0.1 eq), EtOH, rt.

The alkylated amine **6.50** was then easily protected as before using Boc anhydride and subsequent TFE and DMAP to remove any excess Boc residue.

6.6.5 Formation of pyrole based bis-annulated benzene tricycle

The tricyclic precursor **6.46** was treated with palladium acetate, dppe and potassium carbonate in DMF at 80 °C for 4 hr and gave the expected bis-annulated benzene derivative **6.45** in 35 % yield.

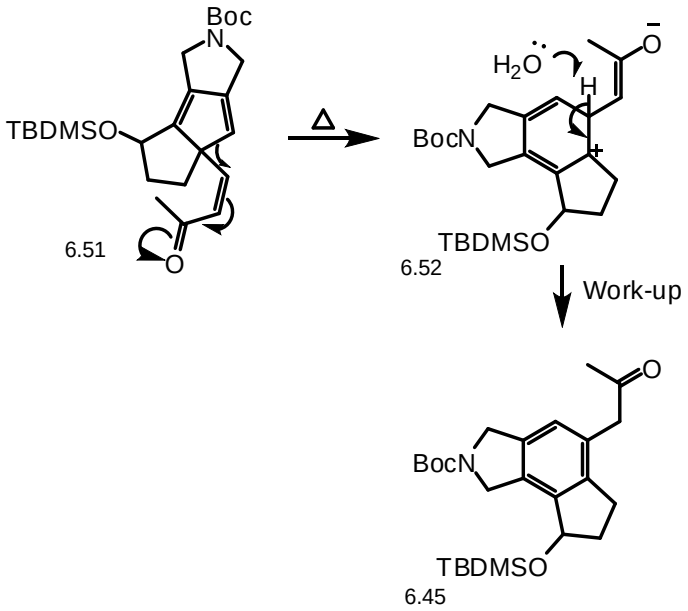


6.46 6.45

Scheme 6.25: Reagents and Conditions (a) $Pd(OAc)_2$ (0.1 eq), dppe (0.3 eq), K_2CO_3 (2 eq), DMF, 80 °C.

6.6.6 Proposed new mechanistic route to 6.45

Due to the discovery that the sulfide based precursor **6.26** when treated with palladium acetate, dppe, potassium carbonate and refluxed in DMF gave the fused cyclopentadiene **6.25** it is now thought that all the oligocycles go through the cylopentadiene **6.51** system as described in **scheme 6.26**. It is therefore hypothesised that the cyclopentadiene ring **6.51** expands to give the [5,6,5] ring system **6.52** through the help of Pd (II) which can act as a catalytic Lewis acid[84] for this process. The bis annulated cyclohexene **6.52** can then undergo proton loss and aromatization in basic conditions to give the bis-annulated benzene tricyclic structure **6.45**.

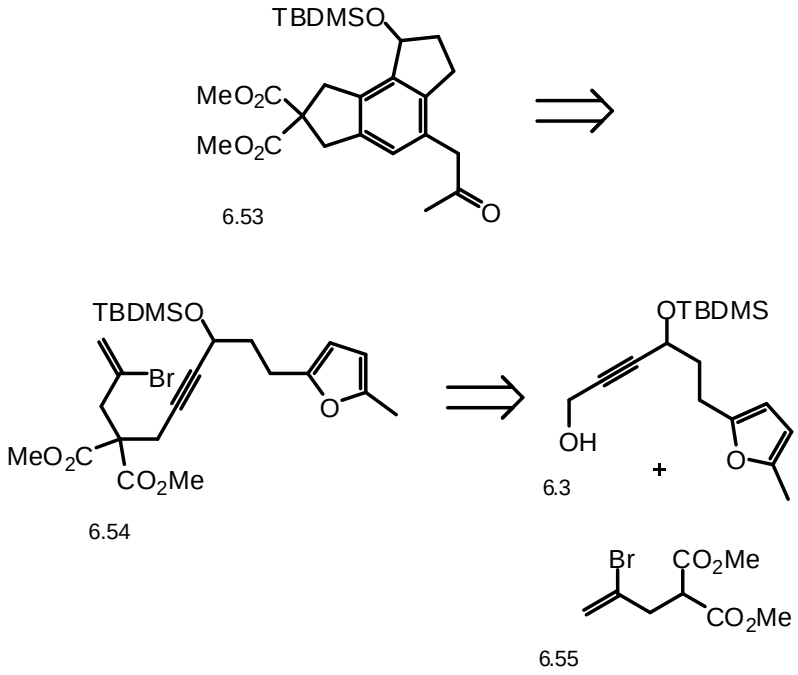


Scheme 6.26: Mechanistic pathway depicting ring expansion and continuation to mechanism shown in scheme **6.18** to give nitrogen containing tricycle **6.45**.

6.7 Formation of an all carbon tricycle

6.7.1 Retrosynthetic analysis of 6.53

The hypothesised all carbon variant **6.53** would hopefully cyclise from its precursor **6.54** using the same Heck conditions deployed in all previous cyclisations. The precursor could be made simply. Starting again with the propargyl alcohol **6.3** and using Mitsunobu chemistry to couple **6.3** with 2-bromo-alkenyl-dimethylmalonate **6.55** which can be made from dimethyl malonate and 2,3-dibromopropene.

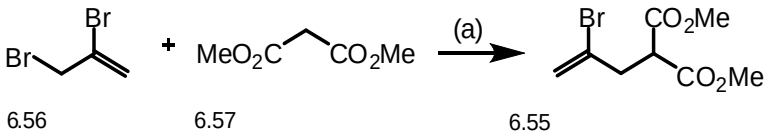


Scheme 6.27: Retrosynthesis for target molecule cyclopentane-bis-annulated benzene derivative **6.53**.

6.8 Synthetic approach to 6.53

6.8.1 Preparation of dimethyl 2-(2-bromoallyl)malonate

It has been shown that that di-methyl 2-(2-bromoallyl)malonate **6.55** can be constructed by treating di-methyl malonate **6.57**[85] in THF with sodium hydride to give the corresponding sodium salt and adding to it, dropwise a solution of 2,3-dibromopropene **6.56** in THF at 0 °C. The reaction mixture generally contained about a 3:1 ratio of the mono **6.55** (37 %) and di-substituted malonate derivative respectively.

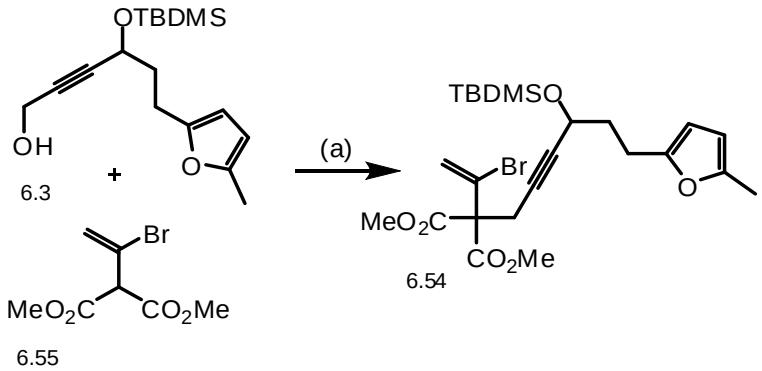


6.56 6.57 6.55

Scheme 6.28: Reagents and Conditions (a) NaOMe, MeOH, 2,3-dibromopropane, 0 °C.

6.8.2 Construction of carbon bis-annulated benzene precursor

The precursor **6.54** was constructed by using Mitsunobu conditions and turning the malonate moiety into a nucleophile, and has been shown previously by Takacs[86]. The primary propargyl alcohol was treated with a phosphino complex created by triphenylphosphine and DEAD while **6.55** was treated with ^{n}BuLi and added to the alcohol, displacing triphenyphosphine oxide to give **6.54** in good yield (57 %).

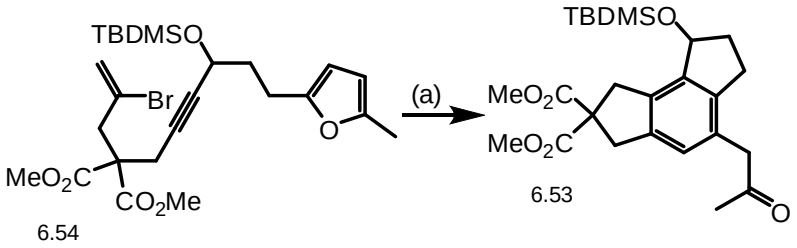


6.3 6.55 6.54

Scheme 6.29: Reagents and Conditions (a) DEAD, PPh_3, THF, -20 °C.

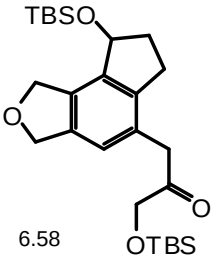
6.8.3 Cyclisation of the carbon tricyle 6.53

The cyclisation worked well under the previously established conditions and was monitored using thin layer chromatography until all notable starting material had been used up. This gave the tricycle **6.53** as a viscous, colourless oil in a reasonable yield (32 %).



Scheme 6.30: Reagents and Conditions (a) $Pd(OAc)_2$ (0.1 eq), dppe (0.3 eq), K_2CO_3 (2 eq), DMF, 120 °C, 1 hr.

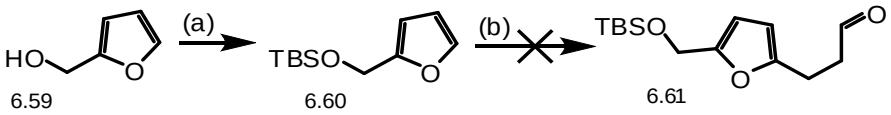
6.9 New target tricycle starting with furfuryl alcohol



6.58

Figure 6.2

It was proposed the tricyclic structure **6.58** could be achieved starting with furfuryl alcohol. The alcohol could be protected first with TBDMSCl and then treated with acrolein in the presence of gold chloride under Hashmi conditions to give the aldehyde **6.61**. This aldehyde would then be built upon following the same steps as laid out in chapter **6.1** to give the desired tricycle **6.58**.



6.59 6.60 6.61

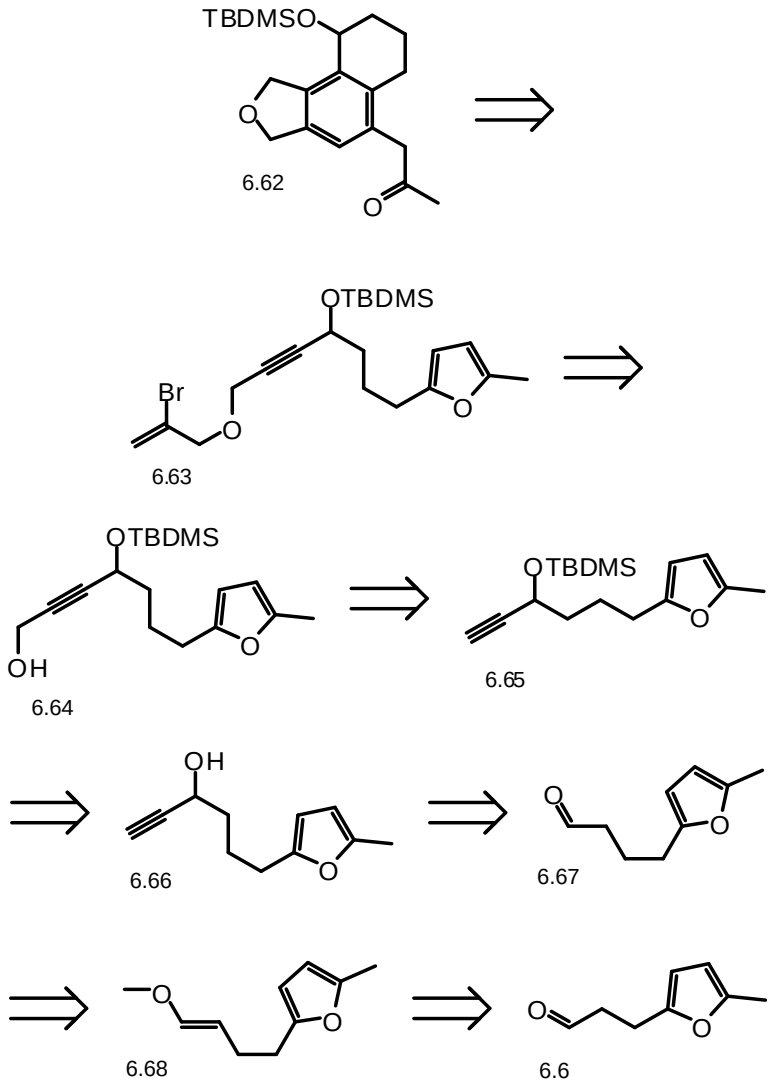
Scheme 6.31: Reagents and Conditions (a) TBDMSCl, imidazole, DMAP, rt; (b) acrolein, $AuCl_3$, MeCN.

The furfuryl alcohol was distilled and then protected with TBDMSCl using imidazole and a catalytic amount of DMAP in a good yield (90 %). However treatment with acrolein and gold chloride did not yield the aldehyde **6.61** and even under heating gave only the starting furan back. In an addition to gold catalysis a method by Borcherdt[87] was tried. Borcherdt reported that furans when heated in the presence of acrolein and glacial acetic acid give substituted furans but sadly this too failed. It was unclear why the protected furfuryl alcohol **6.60** failed and so to check the possibility of the TBDMS group interfering with the reaction the unprotected furfuryl alcohol **6.59** was treated with acrolein under the same conditions, but this also failed to undergo addition to the enone and so an alternative target molecule was sought.

6.10 Formation of a [5:6:6] bis-annulated benzene tricycle

6.10.1 Retrosynthetic analysis of 6.62

The conditions established to construct [5,6,5] and [5,5,5] tricycles work on a variety of different substrates; but could the newly developed route to these tricycles work for [5,6,6] or even [5,5,6] tricycles. Below is a proposed retrosynthetic route to creating [5,6,6] ring systems that possibly go through a [5,5,6] mechanism.



Scheme 6.32: Retrosynthesis for target molecule bis-annulated benzene derivative **6.62**.

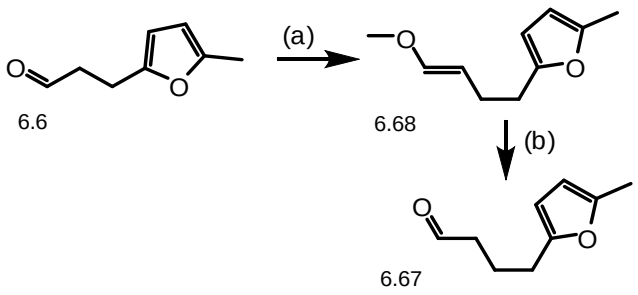
The route starts with the aldehyde **6.6** already developed using gold chemistry. Using Wittig chemistry, the aldehyde can be homologated to the extended chain aldehyde

6.67 using methoxymethyltriphenylphosphonium chloride increasing the chain length by one and going through the enol ether **6.68** which is then hydrolysed to the corresponding aldehyde **6.67**. Much like the previous synthesis it is simply building up the chain from here on. Alkylation of the aldehyde using ethynylmagnesium bromide followed by protection of the resulting alcohol **6.66** to **6.65**. Then treatment of this alkyne with ^{n}BuLi and paraformaldehyde should give the propargyl alcohol **6.64** which can then be alkylated with 2,3-dibromopropene to give the [5,6,6] precursor **6.63**.

6.11 Synthetic approach to 6.62

6.11.1 Formation of extended chain aldehyde

The Wittig reagent (methoxymethyltriphosphonium chloride) was treated with *n*-butyllithium at –20 °C and to this was added the aldehyde **6.6** to give the corresponding enol ether **6.68**.



Scheme 6.33: Reagents and Conditions (a) $MeOCH_2PPh_3Cl$, ^{n}BuLi, Et_2O; (b) PPTS, H_2O, MeCN, acetyl chloride, rt, 48 hr.

The enol ether reaction mixture was then worked up with 2M HCl in an attempt to hydrolyse **6.68** *in situ* to its corresponding aldehyde emitting methanol. However a complex molecule of relatively high mass was isolated instead that has currently not been identified. The reaction was carried out again this time isolating the enol ether **6.68** (82 %) and trying various hydrolysis methods to yield the desire aldehyde **6.67**. Table **6.3** on the next page shows the hydrolysis attempts employed, it was found that only pyridinium *para*-toluene sulfonic acid would give the desired hydrolysis product.

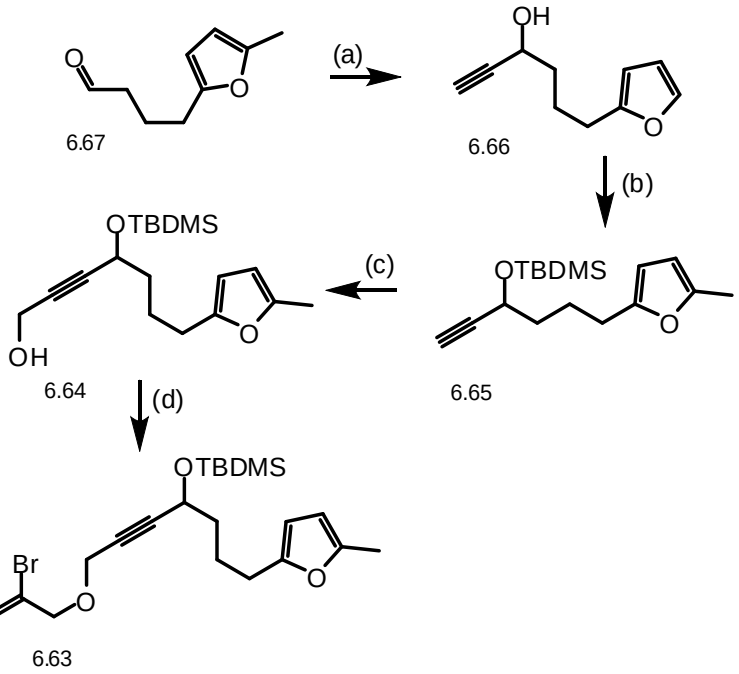
Reagent	Reagents and Conditions	Yield %	Temperature
6.68	HCl (2M), THF	0	rt
6.68	HCl (0.5 M), THF	0	0 °C
6.68	pTSA	0	rt
6.68	Amberlyst-15	0	rt
6.68	iron (III) chloride	0	rt
6.68	palladium acetate	0	rt
6.68	oxalic acid	0	rt
6.68	PPTS, THF	35	rt
6.68	PPTS, acetyl	50	rt

Table 6.3: Results for hydrolysis attempts on **6.68**.

PPTS gave a 50 % yield which was the best single reaction yield obtained. However the remaining starting material could be recovered and reacted again to give further product. This was carried out repeatedly to give a reasonable overall yield (~ 80 %).

6.11.2 Construction of extended chain precursor

The remaining synthesis was then relatively straightforward, following the previous route discussed in the beginning of this chapter and with similar associated yields. The extended aldehyde was treated with ethynylmagnesium bromide to give the secondary alkynyl alcohol **6.66** (86.8 %).

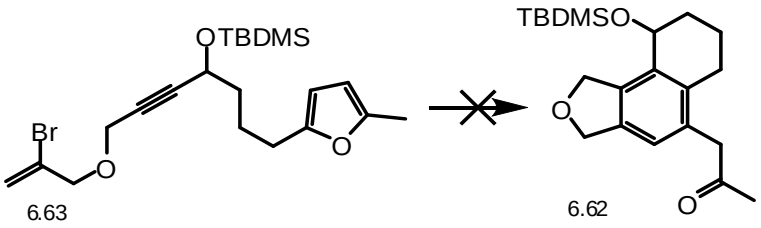


Scheme 6.34: Reagents and Conditions (a) ethynylmagnesium bromide, THF, -20 °C; (b) TBDMSCl, imidazole, DMAP, DCM, 0 °C, 8 hr; (c) ^{n}BuLi, propargyl alcohol, -78 °C, THF; (d) NaH (60 %), 2,3-dibromopropene, MeCN, rt.

This secondary alcohol **6.66** was then protected using TBDMSCl and the resulting alkynyl protected alcohol **6.65** (99 %) alkylated using ^{n}BuLi and paraformaldehyde at -78 °C to give the propargyl alcohol **6.64** (90 %). This was followed by alkylation with 2,3-dibromopropene using sodium hydride as a base to give the extended chain precursor **6.63** (62 %).

6.11.3 Extended chain cyclisation

The extended chain precursor **6.63** was initially subjected to the same Heck type conditions developed in the previous three cyclisations with palladium acetate, dppe and potassium carbonate in DMF, however no observed tricyclic product could be isolated. Numerous attempts to cyclise **6.63** were made and table **6.4** illustrates these.



Scheme 6.35: Reagents and Conditions; See table below.

Reagent	Reagents and conditions	Yield %	Temperature
6.63	$Pd(OAc)_2$, dppe, K_2CO_3, DMF, 6hr	0	140 °C
6.63	$Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 12hr	0	140 °C
6.63	$Pd(OAc)_2$, dppe, K_2CO_3, MeCN, 12hr	0	85 °C
6.63	$Pd(OAc)_2$, PPh_3, K_2CO_3, MeCN, 24hr	0	85 °C

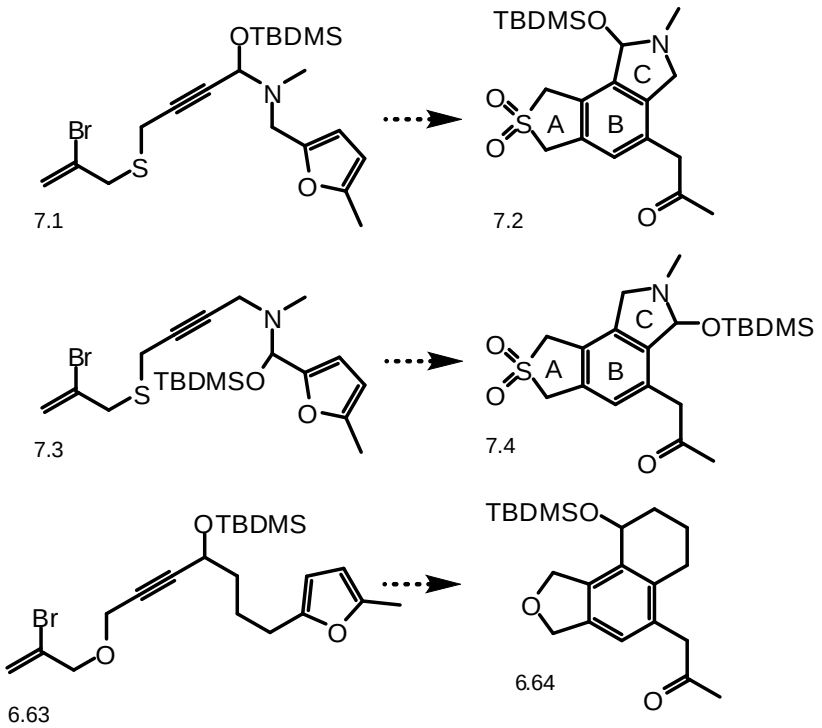
Table 6.4: Results for attempts at extended chain cyclisation **6.63**.

7. Future Work

7.1 Extending the range of examples for the new cyclisation

7.1.1 Nitrogen heterocycle formation

It would be of interest to extend the range of tricyclic compounds synthesised in this novel reaction and to test the versatility and scope of these cyclisations, probing their limitations in organic synthesis. Nitrogen functionality in the C cyclopentane ring beta to oxygen as seen in **7.2** & **7.4** could be investigated. The formation of a [5,6,6] ring system would also be worth investigating further following the failed cyclisation of **6.63** as well as optimisation of all the current cyclisations. A trial of microwave induced cyclisations on all the precursors could be of interest. The cyclisation reactions seem very dependent on temperature, with too long exposure at the required temperature they tend to decompose and it is therefore possible the differing conditions provided in a microwave with higher pressures over shorter time lengths may suit this reaction.



Scheme 7.1: Reagents and Conditions: $Pd(OAc)_2$, K_2CO_3, dppe, DMF, 140 °C, 4 Bar, 5 mins.

7.2 Synthetic application of tricyclic compounds

Formation of these new tricyclic compounds gives a good method for constructing the backbone of pharmaceutically important molecules that contain three or more rings. One possible application could be lactonamycin **7.5** and its analogues **7.6** and **7.7**.

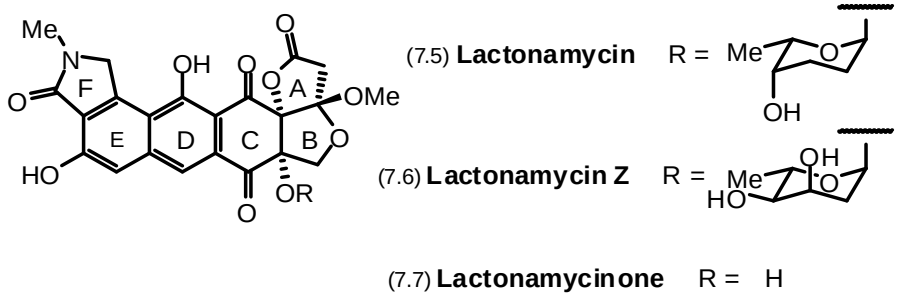
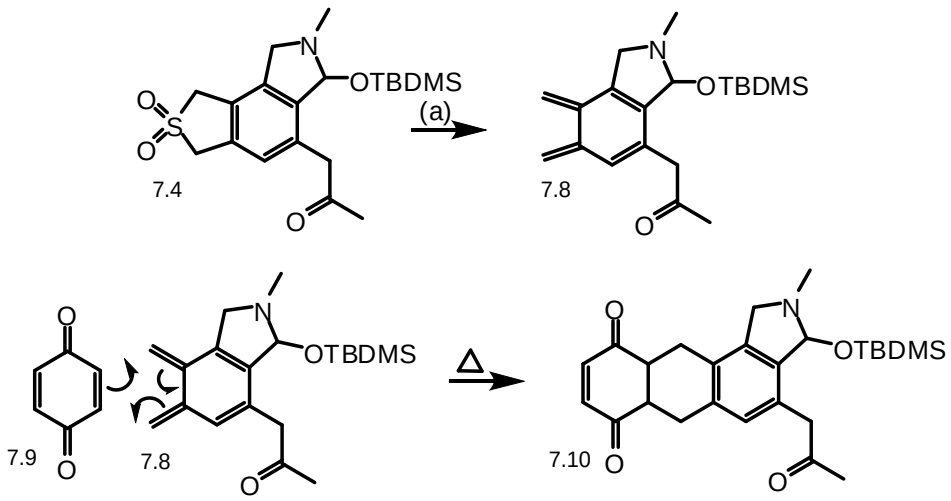


Figure 7.1

If the tricycle **7.4** could be synthesised from its precursor **7.3** using the reagents and conditions previously described in **scheme 7.1** it would also be feasible that **7.4** when heated could perform a retro Diels-Alder reaction to give the diene **7.8**. When **7.8** is heated in the presence of benzoquinone the [4+2] Diels-Alder product **7.10** could result providing an elegant synthesis into tetracycles and a possible means to construct the core of lactonamycin.



Scheme 7.1: Reagents and Conditions (a) Heat, Lewis acid.

8. Experimental

8.1 General Procedure

All reactions were carried out under an atmosphere of nitrogen unless otherwise stated, using oven dried glassware. Commercially available chemicals and reagents were used as supplied unless otherwise stated.

Tetrahydrofuran and diethyl ether were distilled from sodium using benzophenone as an indicator. Dichloromethane and acetonitrile were distilled from calcium hydride. Dry alcohol solvents were distilled from magnesium turnings and stored over 4 Å molecular sieves. Triethylamine and pyridine were distilled from calcium hydride and stored over potassium hydroxide. All solvents for high temperature reactions (>100 °C) were first deoxygenated by sparging for at least 1 hour with nitrogen or argon gas.

Microwave reactions were carried out using a CEM Discover-S 300W microwave system with a pressure tolerance of up to 18bar.

Reactions were monitored by crude NMR of the RM or by tlc using Merck glass backed tlc plates coated with a 0.25 mm layer of 60 F_{254} silica gel. Visualisation was achieved using 254 nm UV radiation (where applicable) and potassium permanganate, phosphomolybdic acid or vanillin stains as deemed appropriate. Column chromatography was carried out using Merck Kieselgel 60.

NMR spectroscopy was performed using either Varian NMR System-600 MHz (600 MHz for ^{1}H and 151 MHz for ^{13}C), or Varian NMR System-500 MHz (500 MHz for ^{1}H and 126 MHz for ^{13}C). The solvent used for NMR samples was either deuterated chloroform or perdeuterated dimethylsulfoxide.

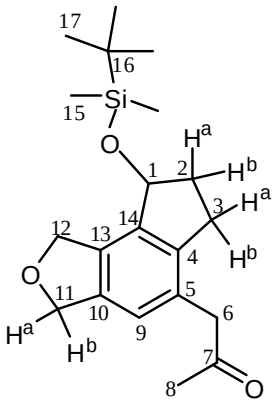
Heteronuclear Single Quantum Coherence (HSQC), Heteronuclear Multiple Bond Coherence (HMBC), Correlation Spectroscopy (COSY) and Hydrogen-Deuterium exchange (H-D) experiments were also run where necessary to allow for the full elucidation of structures.

Mass spectrometry was performed using a Fissons Instrument VG Autospec and a Bruker Daltonics Apex III.

Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier transform instrument with an ATR attachment.

Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected.

(6.1) 1-(8-(*tert*-Butyldimethylsilyloxy)-3,6,7,8-tetrahydro-1H-indeno[4,5-c]furan-5-yl)propan-2-one



To a stirred solution of triphenylphosphine (178 mg, 0.68 mmol, 0.3 eq), potassium carbonate (625 mg, 4.52 mmol, 2 eq) and (6-(2-bromoallyloxy)-1-(5-methylfuran-2-yl)hex-4-yn-3-yloxy)(*tert*-butyl)dimethylsilane (1 g, 2.26 mmol) in acetonitrile (20 ml) was added palladium (II) acetate (50 mg, 0.226 mmol, 0.1 eq). The resulting mixture was heated at 80 °C for 5 hr and quenched with water (40 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic fractions were then dried over magnesium sulfate, filtered and reduced *in vacuo*. The resulting crude brown oil was purified using flash column chromatography eluting with 10 % diethyl ether in hexane to yield the title compound as a orange/green viscous oil (226 mg, 28 %).

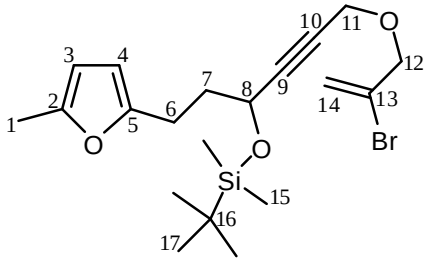
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.94 (1H, s, H-9), 5.35-5.25 (2H, m, H-1 + H-11^{a}/H-11^{b}), 5.10-5.02 (3H, m, H-12 + H-11^{b}/H-11^{a}), 3.68 (2H, m, H-6), 2.90 (1H, ddd, J=15.7, 9.0, 2.0, H-3^{a}/H-3^{b}), 2.69-2.61 (1H, m, H-3^{b}/H-3^{a}), 2.52-2.46 (1H, m, H-2^{a}/H-2^{b}), 2.16(3H, s, H-8), 1.93 (1H, dtd, J=12.6, 9.1, 7.6, H-2^{b}/H-2^{a}), 0.93 (9H, s, H-17), 0.16(6H, d, J=10.7, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.71 (C=O), 140.79 (C), 139.01 (C), 134.56 (C), 129.64 (C), 121.36 (9-CH), 76.41 (1-CH), 72.93 (11-CH_2), 72.44 (12-CH_2), 48.43 (6-CH_2), 36.39 (2-CH_2), 29.34 (8-CH_3), 28.54 (3-CH_2), 25.83 (17-CH_3 x 3), 17.96 (C), -4.18 (CH_3), -4.81 (CH_3).

IR (cm^{-1}) 3403, 2928, 2854, 1709, 1412, 1358;

HRMS (ESI+) calcd for $C_{20}H_{30}O_3SiNa^+$ *m/z* 369.1862 found 369.1860.

(6.2) (6-(2-Bromoallyloxy)-1-(5-methylfuran-2-yl)hex-4-yn-3-yloxy)(*tert*-butyl)dimethylsilane



To a stirred suspension of NaH (284 mg, 7.1 mmol, 1.1 eq) in THF (25 ml) was added dropwise 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-ol (2 g, 6.5 mmol) at 0 °C. The solution was stirred for 1 hr, after this time 2,3-dibromopropene was added dropwise over 5 min at 0 °C. The solution was allowed to warm to room temperature over 2 hr and then added to a stirring biphasic mixture of 10% aq potassium carbonate (20 ml) solution and diethyl ether (20 ml). The aq layer was separated and extracted with diethyl ether (3 x 20 ml). The combined organic fractions were dried over magnesium sulfate, filtered and reduced *in vacuo* to yield a crude pale yellow oil. This crude oil was then purified using flash column chromatography eluting with 10 % ethyl acetate in hexane to yield the title compound as a colourless oil (1.79 g, 64 %).

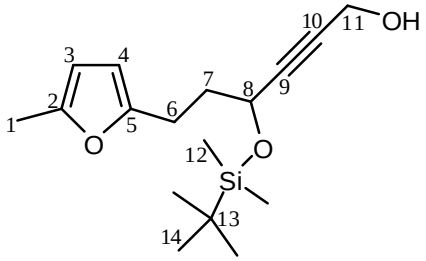
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.94 (1H, d, J=1.3, H-14^a/H-14^b), 5.87 (1H, d, J=2.9, H-4), 5.85 (1H, app s, H-3), 5.65 (1H, d, J=0.8, H-14^b/H-14^a), 4.45 (1H, t, J=6.3, H-8), 4.24 (2H, d, J=1.5, H-11), 4.19 (2H, s, H-12), 2.75-2.70 (2H, m, H-6), 2.25 (3H, s, H-1), 2.03-1.97 (2H, m, H-7), 0.92 (9H, s, H-17), 0.13 (6H, d, J=12.3, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.34 (5-C), 150.34 (2-C), 128.61 (13-C), 118.34 (14-CH_2), 105.78 (3-CH), 105.61 (4-CH), 88.47 (9-C), 79.36 (10-C), 73.15 (12-CH_2), 62.04 (8-CH), 57.40 (11-CH_2), 36.89 (7-CH_2), 25.77 (17-CH_3 x 3), 23.78 (6-CH_2), 18.19 (16-C), 13.45 (1-CH_3), -4.52 (CH_3), -5.05 (CH_3).

IR (cm^{-1}) 2928, 2856, 1639, 1360;

HRMS (ESI+) calcd for $C_{20}H_{31}BrNaO_3Si^+$ *m/z* 449.11 found 449.1118.

(6.3) 4-(*tert*-Butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-ol



To a solution of *tert*-butyldimethyl(5-(5-methylfuran-2-yl)pent-1-yn-3-yloxy)silane (12.25 g, 44 mmol) in THF (300 ml) was added 2.5M ^{n}BuLi (19.4 ml, 48.4 mmol, 1.1 eq) dropwise at -78 °C over 5 minutes. The reaction mixture was allowed to warm to -40 °C over 1 hour where-on it was re-cooled to -78 °C and para-formaldehyde (2.65 g, 88 mmol, 2 eq) was added in one lot. The mixture was left to stir overnight and quenched with saturated aqueous ammonium chloride solution (300 ml). This mixture was then extracted with diethyl ether (3 x 200 ml) and the combined organic fractions washed with brine, dried over magnesium sulfate, filtered and reduced *in vacuo*. The resulting yellow oil was then purified using flash column chromatography eluting with 20 % diethyl ether in hexane to give the title compound as a colourless oil (9.44 g, 69 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.87 (1H, d, J=3.0, H-3), 5.85 (1H, dd, J=2.9, 0.9, H-4), 4.45 (1H, tt, J=6.4, 1.6, H-8), 4.29 (2H, dd, J=6.1, 1.6, H-11), 2.73 (2H, td, J=7.2, 2.0, H-6), 2.26 (3H, s, H-1), 2.00 (2H, ddd, J=13.5, 7.1, 1.5, H-7), 1.63-1.53 (1H, m, OH), 0.92, (9H, s, H-14), 0.13 (6H, d, H-12).

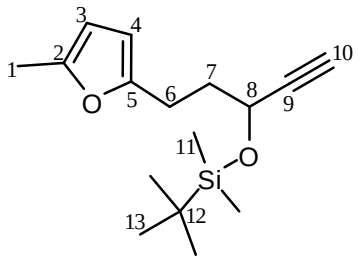
^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.41 (5-C), 150.33 (2-C), 105.77 (3-CH), 105.60 (4-CH), 87.21 (9-C), 82.43 (10-C), 62.04 (8-CH), 51.17 (11-CH_2), 36.83 (7-CH_2),

25.80 (14-CH_3 x 3), 23.74 (6-CH_2), 18.20 (13-C), 13.45 (1-CH_3), -4.48 (12-C), -5.04 (12-C).

IR (cm^{-1}) 3374.04, 2929.63, 2857.03, 1681.00, 1567.58, 1463.02, 1360.91, 1252.29;

HRMS (ESI+) calcd for $C_{17}H_{28}NaO_3Si^+$ *m/z* 331.17 found 331.17.

(6.4) *tert*-Butyldimethyl(5-(5-methylfuran-2-yl)pent-1-yn-3-yloxy)silane



To a solution of 5-(5-methylfuran-2-yl)pent-1-yn-3-ol (10 g, 60.9 mmol) in DCM (150 ml) was added TBDMSCl (10.10 g, 67 mmol, 1.1 eq), imidazole (4.97 g, 73.08 mmol, 1.2 eq), DMAP (744mg, 6.09 mmol, 0.1eq). The reaction mixture was stirred overnight and water added (150 ml) then extracted with diethyl ether (3 x 100 ml) and the combined organic fractions washed with brine, dried over magnesium sulfate and reduced *in vacuo*. The crude yellow oil was then purified using flash column chromatography eluting with 5 % diethyl ether in hexane yielding the title compound as a pale straw coloured oil (12.35 g, 73 %).

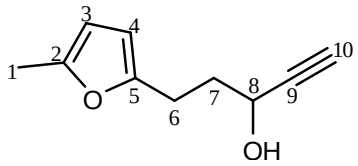
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.87 (1H, d, J=3.0, H-4), 5.84 (1H, dd, J=2.8, 0.9, H-3), 4.40 (1H, td, J=6.4, 2.1, H-8), 2.74 (2H, dd, J=8.8, 6.9, H-6), 2.40 (1H, d, J=2.1, H-10), 2.25 (3H, s, H-1), 2.04-1.98 (2H, m, H-7), 0.92 (9H, s, H-13), 0.13 (6H, d, J=13.8, H-11).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.39 (5-C), 150.33 (2-C), 105.76 (3-CH), 105.58 (4-CH), 85.20 (9-C), 72.28 (10-CH), 61.86 (8-CH), 36.89 (7-CH_2), 25.76 (13-CH x 3), 23.69 (6-CH_2), 18.18 (12-C), 13.45 (1-CH_3), -4.69 (CH_3), -5.12 (CH_3).

IR (cm^{-1}) 3309.96, 2954.28, 2929.08, 2857.47, 1570.96, 1251.87;

HRMS (ESI+) calcd for $C_8H_{10}NaO_2^+$ *m/z* 161.06 found 161.05732.

(6.5) 5-(5-Methylfuran-2-yl)pent-1-yn-3-ol



Ethynylmagnesium bromide (448 ml, 112 mmol, 2 eq) was added to a stirred solution of 3-(5-methylfuran-2-yl)propanal (15.5 g, 112 mmol) in THF (200 ml) dropwise at -60 °C over a period of 30 minutes. The resulting solution was allowed to warm to 0 °C and quenched with saturated aqueous ammonium chloride solution. The reaction mixture was then extracted with diethyl ether (3 x 50 ml) and the combined organic fractions washed with brine, dried over magnesium sulfate, filtered and reduced *in vacuo* to give a crude pale yellow oil. This oil was then purified using flash column chromatography eluting with 20 % diethyl ether in hexane to yield the title compound as a colourless oil (12.74 g, 69 %).

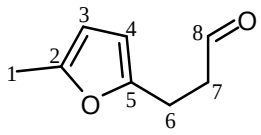
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.90 (1H, d, J=2.7, H-4), 5.85 (1H, app s, H-3), 4.43 (1H, app s, H-8), 2.79 (2H, td, J=7.5, 3.2, H-6), 2.50 (1H, s, H-10), 2.26 (3H, s, H-1), 2.05 (2H, ddd, J=9.1, 7.8, 2.1, H-7), 1.92 (1H, s, OH).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 152.89 (5-C), 150.59 (2-C), 105.93 (3/4-CH), 105.85 (4/3-CH), 84.42 (10-CH), 73.25 (9-C), 61.53 (2-CH), 35.99 (7-CH_2), 23.67 (6-CH_2), 13.46 (1-CH_3).

IR (cm^{-1}) 3400, 3287.50, 2924.11, 1712.93;

HRMS (ESI+) calcd for $C_{10}H_{12}O_2Na^+$ *m/z* 187.0735 found 187.0735.

(6.6) 3-(5-Methylfuran-2-yl)propanal[76]



To a stirred solution of 2-methylfuran (2.0 g, 2.44 mmol) and gold (III) chloride (37 mg, 0.12 mmol, 0.05 eq) in acetonitrile (20 ml) was added acrolein (2.07 g, 3.7 mmol, 1.5 eq) dropwise over 5 minutes at 0 °C. The reaction mixture was then allowed to stir for 1 hour over an ice bath at which point flash grade silica was added and the resulting crude mixture reduced *in vacuo* absorbing the crude resulting oil onto silica. It was then purified using column chromatography eluting with 5 % diethyl ether in hexane to yield the title compound as a straw coloured oil (2.35 g, 70 %).

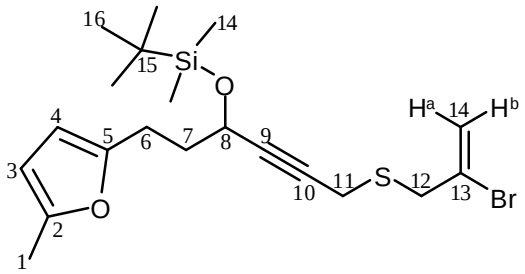
^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.81 (1H, q, J=1.3, H-8), 5.88 (1H, d, J=3.0, H-4), 5.84 (1H, dd, J=2.8, 0.7, H-3), 2.93 (2H, t, J=7.3, H-6), 2.78-2.74 (2H, m, H-7), 2.24 (3H, s, H-1).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 201.18 (8-CH), 151.93 (5-C), 150.81 (2-C), 106.09 (4-CH), 105.94 (3-CH), 41.99 (7-CH_2), 20.83 (6-CH_2), 13.40 (1-CH_3).

IR (cm^{-1}) 2923.11, 1723.09, 1617.13, 1570, 1217.96;

HRMS (ESI+) calcd for $C_8H_{10}O_2Na^+$ *m/z* 161.06 found 161.0573.

(6.27) (6-(2-Bromoallylthio)-1-(5-methylfuran-2-yl)hex-4-yn-3-yloxy)(*tert*-butyl)dimethylsilane



To a solution of S-4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl ethanethioate (3.3 g, 9 mmol) in methanol (75 ml) was added sodium methoxide (9.9 mmol, 1.1 eq) at rt. The reaction mixture was allowed to stir for 30 minutes whereupon 2,3-dibromopropene (879 mg, 1.8 ml, 9 mmol 1 eq) was added and allowed to stir for a further hour. The reaction mixture was then quenched with water (75 ml) and extracted with diethyl ether (3 x 75 ml). The combined organic fractions were washed with brine, dried over magnesium sulfate, filtered and reduced *in vacuo* to yield the title compound as a colourless oil (3.939 g, 99 %).

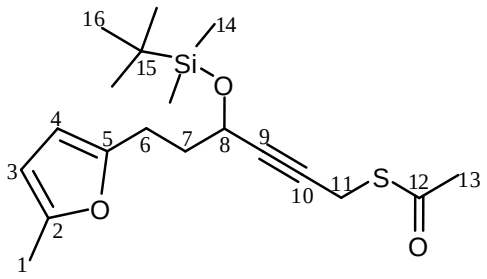
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.88-5.82 (3H, m, H-3 + H-4 + H-14^{b}), 5.57 (1H, d, J=1.6, H-14^{a}), 4.43 (1H, tt, J=6.7, 1.7, H-8), 3.62 (2H, s, H-12), 3.28 (2H, d, J=1.8, H-11), 2.74-2.70 (2H, m, H-6), 2.25 (3H, s, H-1), 2.02-1.96 (2H, m, H-6), 2.25 (3H, s, H-1), 2.02-1.96 (2H, m, H-7), 0.92 (9H, s, H-17), 0.12 (6H, d, J=12.7, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.38 (5-C), 150.32 (2-C), 128.61 (13-C), 119.34 (14-CH_2), 105.78 (3-CH), 105.58 (4-CH), 84.92 (9-C), 79.28 (10-C), 62.17 (8-CH), 41.20 (12-CH_2), 37.14 (7-CH_2), 25.78 (17-CH_3 x 3), 23.81 (6-CH_2), 18.85 (11-CH_2), 18.18 (16-C), 13.45 (1-CH_3), -4.49 (CH_3), -5.05 (CH_3).

IR (cm^{-1}) 2927, 2855, 1713, 1620, 1570, 1251, 1087;

HRMS (ESI+) calcd for $C_{20}H_{31}BrNaO_2SSi^{+}$ *m/z* 465.09 found 465.089.

(6.29) S-4-(*tert*-Butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl ethanethioate



A solution of DEAD (2.26 g, 2.05 ml, 13 mmol, 1 eq) in THF (30 ml) was added dropwise to a stirred solution of triphenylphosphine (3.4 g, 13 mmol, 1 eq) in THF (30 ml) at 0 °C. The resulting canary yellow solution was kept at 0 °C for 15 minutes and then a pre-cooled mixture of 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-ol (4 g, 13 mmol) and thioacetic acid (989 mg, 0.924 ml, 13 mmol, 1 eq) in THF (30 ml) was added in one portion. The mixture was stirred at room temperature for 4 hr and the solvent removed *in vacuo*. Purification was achieved using flash column chromatography eluting with 2-4 % diethyl ether in hexane to yield the title compound as a pale straw coloured oil (3.538 g, 74 %).

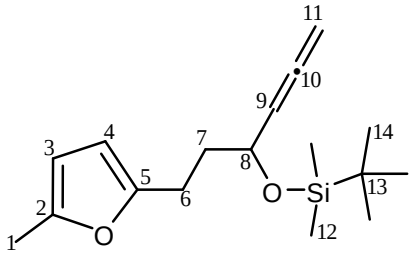
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, d, J-2.9, H-3), 5.83 (1H, d, J=2.8, H-4), 4.38 (1H, t, J=6.4, H-8), 3.68 (2H, d, J=1.8, H-11), 2.71-2.66 (2H, m, H-6), 2.35 (3H, d, J=1.0, H-13), 2.25 (3H, s, H-1), 1.98-1.92 (2H, m, H-7), 0.90 (9H, s, H-16), 0.11 (6H, d, J=12.4, H-14).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 193.93 (12-C), 153.47 (5-C), 150.27 (2-C), 105.76 (3-CH), 105.55 (4-CH), 84.21 (9-C), 78.85 (10-C), 62.09 (8-C), 36.85 (7-CH_2), 30.07 (13-CH_3), 25.80 (16-CH_3 x 3), 23.75 (6-CH_2), 18.18 (15-C), 17.96 (11-CH_2), 13.45 (1-CH_3), -4.49 (CH_3), -5.06 (CH_3).

IR (cm^{-1}) 2928, 2856, 1697, 1570, 1437, 1354;

HRMS (ESI+) calcd for $C_{19}H_{30}NaO_3SSi^+$ *m/z* 389.16 found 389.1577.

(6.30) *tert*-Butyldimethyl(1-(5-methylfuran-2-yl)hexa-4,5-dien-3-yloxy)silane



S-4-(*tert*-Butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynylethanethioate (3.3 g, 9 mmol) in THF (100 ml) was added dropwise to a stirring suspension of $LiAlH_4$ (1.36 g, 36 mmol, 4 eq) at 0 °C in THF (80 ml). The resulting reaction mixture was allowed to stir at rt for 2 hr where-on it was re-cooled to 0 °C, quenched with ice (100 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic layers were dried over magnesium sulfate, reduced *in vacuo* and purified using flash column chromatography eluting with diethyl ether in hexane to yield the title compound as an orange coloured oil (961 mg, 36.5 %).

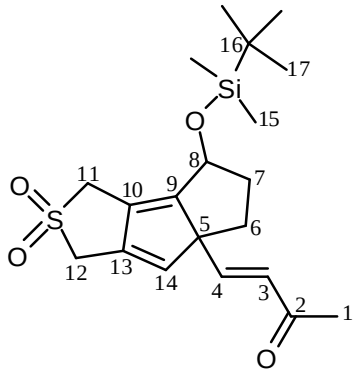
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.86-5.83 (2H, m, H-3 + H-4), 5.14 (1H, dd, J=13.8, 6.8, H-9), 4.81-4.73 (2H, m, H-11), 4.23 (1H, dt, J=7.1, 5.8, H-8), 2.74-2.58 (2H, m, H-6), 2.26 (3H, s, H-1), 1.96-1.82 (2H, m, H-7), 0.92 (9H, s, H-14), 0.08 (6H, d, J=1.6, H-12).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 207.44 (10-C), 154.05 (5-C), 150.14 (2-C), 105.72 (3-CH), 105.24 (4-CH), 94.58 (9-CH), 76.01 (11-CH_2), 70.71 (8-CH), 36.83 (7-CH_2), 25.86 (14-CH_3 X 3), 24.06 (6-CH_2), 18.16 (13-C), 13.44 (1-CH_3), -4.30 (CH_3), -4.95 (CH_3).

IR (cm^{-1}) 2928, 2856, 1956, 1571;

HRMS (ESI+) calcd for $C_{17}H_{28}NaO_2Si^+$ *m/z* 315.1751 found 315.1747.

(6.32) (E)-4-(4-(*tert*-Butyldimethylsilyloxy)-1,3,4,5,6,6a-hexahydropentaleno[1,2-c]thiophen-6a-yl-1,1-dioxide)but-3-en-2-one



To a solution of (6-(2-bromoallylthio)-1-(5-methylfuran-2-yl)hex-4-yn-3-yloxy)(*tert*-butyl)dimethylsilane (1 g, 2.26 mmol), dppe (180 mg, 0.452 mmol, 0.2 eq), potassium carbonate (624 mg, 4.52 mmol, 2 eq) in DMF (40 ml) was added palladium (II) acetate (50 mg, 0.226 mmol, 0.1 eq). The reaction mixture was heated to 120 °C for 30 minutes and then diluted down with water (400 ml). The mixture was then extracted with diethyl ether (3 x 200 ml), dried over magnesium sulfate, filtered and reduced *in vacuo* to yield a crude brown oil. The oil was then purified using flash column chromatography eluting with diethyl ether in hexane to give the title compound as a bright yellow viscous oil (356 mg, 40 %).

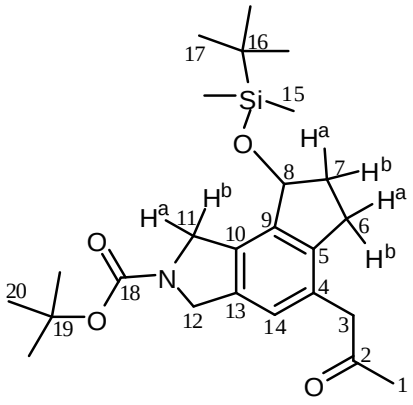
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, d, J=16.1, H-4), 6.51 (1H, s, H-14), 6.10 (1H, d, J=16.1, H-3), 4.97 (1H, dd, J=4.5, 2.7, H-12^{a}/H-12^{b}), 4.96-4.92 (1H, m, H-8), 4.76 (1H, t, J=3.0, H-12^{b}/H-12^{a}), 4.10 (2H, t, J=2.8, H-11), 2.74-2.65 (1H, m, H-6), 2.45-2.37 (1H, m, H-6), 2.37-2.29 (1H, m, H-7), 2.27 (3H, s, H-1), 1.85-177 (1H, m, H-7), 0.87 (9H, s, H-17), 0.03 (6H, d, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 198.79 (2-C), 150.80 (10-CH_2), 146.91 (5-C), 138.86 (9-C), 137.85 (4-CH), 135.51 (14-CH), 131.32 (13-C), 129.34 (3-CH), 105.66 (12-CH_2), 79.07 (8-CH), 37.19 (11-CH_3), 33.00 (7-CH_2), 29.43 (6-CH_2), 27.14 (1-CH_3), 25.77 (17-CH_3 x 3), 18.12 (16-C), -4.81 (15-CH_3), -4.84 (15-CH_3).

IR (cm^{-1}) 3405, 2927, 2855, 1666, 1590, 1462, 1252;

HRMS (ESI+) calcd for $C_{20}H_{30}NaO_4SSi^+$ *m/z* 417.15 found 417.1548.

(6.45) *tert*-Butyl 8-(*tert*-butyldimethylsilyloxy)-5-(2-oxopropyl)-3,6,7,8-tetrahydrocyclopenta[e]isoindole-2(1H)-carboxylate



To a stirring solution of *tert*-butyl 2-bromoallyl(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)carbamate (500 mg, 0.95 mmol), dppe (75 mg, 0.19 mmol, 0.2 eq), potassium carbonate (262 mg, 1.9 mmol, 2 eq) in DMF (25 ml) was added palladium (II) acetate (22 mg, 0.095 mmol, 0.1 eq) in one lot. The reaction mixture was heated to 87 °C for 4 hrs and diluted with water (250 ml) whereupon it was then extracted with diethyl ether (3 x 100 ml). The combined organic layers were dried over magnesium sulfate, filtered and reduced *in vacuo* to yield a crude brown oil. This oil was purified using flash column chromatography eluting with 20 % diethyl ether in hexane to yield the title compound as a white solid (152 mg, 35 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.95 (1H, d, J=24.3, H-14), 5.34 (1H, t, J=7.3, H-8), 4.84 (1H, dd, J=23.2, 15.1, H-11^a/H-11^b), 4.69-4.99 (3H, m, H-12 +H-11^a/H-11^b), 3.67 (2H, d, J=2.7, H-3), 2.96-2.82 (1H, m, H-6^a/H-6^b), 2.69-2.58 (1H, m, H-6^b/H-6^a), 2.55-2.43 (1H, m, H-7^a/H-7^b), 2.16 (3H, s, H-1), 1.93 (1H, ddt, J=17.4, 12.4, 8.8, H-7^b/H-7^a), 1.52 (9H, d, J=2.8, H-20), 0.95 (9H, d, J=9.4, H-17), 0.18(6H, d, J=21.6, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 205.63 (2-C=O), 154.58 (18-C=O), 140.65 (C), 139.96 (C), 136.68 (10-C), 132.90 (13-C), 129.79 (5-C), 123.18 (14-C), 79.45 (19-

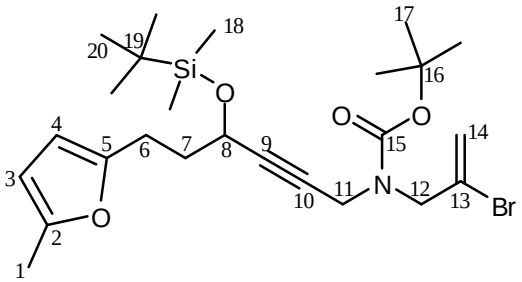
C), 76.60 (8-C), 51.31 (CH_2), 51.26 (CH_2), 48.43 (3-CH_3), 36.43 (7-CH_2), 29.34 (1-CH_3), 28.58 + 28.54 + 28.43 (20-CH_3 X 3), 25.94 + 25.89 (17-CH_3 x 3), 18.01 (16-C), -4.10 (CH_3), -4.95 (CH_3).

IR (cm^{-1}) 2929, 2857, 1697, 1472, 1399;

HRMS (ESI+) calcd for $C_{25}H_{39}NNaO_4Si^+$ *m/z* 468.25 found 468.2541.

MP 112-115 °C.

(6.46) *tert*-Butyl 2-bromoallyl(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)carbamate



To a solution of N-(2-bromoallyl)-4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-amine (460 mg, 1.08 mmol) in ethanol (15ml) was added di-*tert*-butyl dicarbonate (259 mg, 1.18 mmol, 1.1 eq). The reaction mixture was allowed to stir for 2 hr when TFE (108 mg, 0.08 ml, 1.08 mmol, 1 eq) and DMAP (13 mg, 0.108 mmol, 0.1 eq) were added in one lot. After 5 minutes the reaction mixture was quenched with water (20 ml) and extracted with diethyl ether (3 x 20 ml). The organic fractions were combined, dried over magnesium sulfate, filtered and reduced *in vacuo* to give a crude oil that was purified with flash column chromatography eluting with 20 % diethyl ether in hexane to give the title compound as a colourless oil (2.26 g, 91 %).

1H-NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, d, J=2.9, H-4), 5.84 (1H, s, H-3), 5.76 (1H, d, J=12.6, H-14^a/H-14^b), 5.58 (1H, s, H-14^b/H-14^b), 4.41 (1H, t, J=6.3, H-8), 4.17

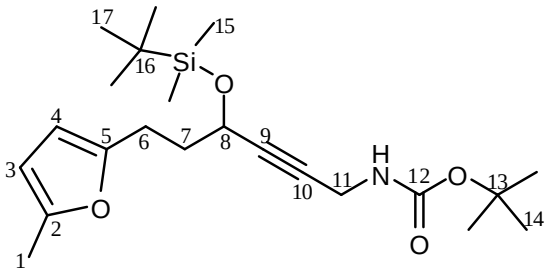
(3H, s, H-12 + H-11^a/H-11^b), 4.06 (1H, s, H-11^b/H-11^a), 2.73-2.69 (2H, m, H-6), 2.25 (3H, s, H-1), 2.00-1.95 (2H, m, H-7), 1.48 (9H, s, H-17), 0.19 (9H, s, H-20), 0.11 (6H, d, J=10.4, H-18).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.39 (5-C), 150.32 (2-C), 129.08 (15-C), 117.52 (14-CH_2), 105.77 (3-CH), 105.57 (4-CH), 85.17 (9-C), 80.87 (16-C), 53.34 (12-CH_2), 36.95 (7-CH_2), 35.5 (11-CH_2), 28.25 (17-CH_3 X 3), 25.78 (20-CH_3 X 3), 23.78 (6-CH_2), 18.19 (19-C), 13.45 (1-CH_3), -4.49 (CH_3), -5.03 (CH_3).

IR (cm^{-1}) 2930, 2856, 1701, 1402;

HRMS (ESI+) calcd for $C_{25}H_{40}BrNNaO_4Si^+$ *m/z* 548.18 found 548.1802.

(6.47) *tert*-butyl 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynylcarbamate



To a stirring solution of 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-amine (1.29 g, 4.2 mmol), in ethanol (20 ml) was added di-tert-butyl dicarbonate (1.01 g, 4.62 mmol, 1.1 eq). After one hour TFE (420 mg, 4.20 mmol, 1 eq) and DMAP (51 mg, 0.42 mmol, 0.1 eq) were added consecutively and allowed to stir for a further 5 minutes. Chloroform (50 ml) was then added and the mixture washed with 0.5 M HCl (50 ml), dried over magnesium sulfate, filtered, and purified using flash column chromatography eluting with 15 % diethyl ether in hexane to yield the title compound as a colourless oil (1.41 g, 82 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, d, J=3.0, H-4), 5.84 (1H, dd, J=2.9, 0.8, H-3), 4.63 (1H, s, NH), 4.41-4.38 (1H, m, H-8), 3.93 (2H, d, J=4.2, H-11), 2.70 (2H,

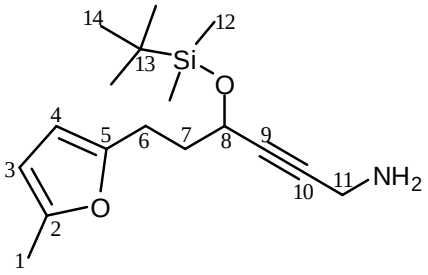
dd, J=9.2, 6.7, H-6), 2.25 (3H, s, H-1), 2.00-1.94 (2H, m, H-7), 1.46 (9H, s, H-14), 0.91 (9H, s, H-17), 0.11 (6H, d, J=12.2, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.44 (5-C), 150.29 (2-C), 105.77 (3-CH), 105.57 (4-CH), 84.45 (9-C), 80.42 (10-C), 79.85 (12-C), 62.02 (8-CH), 36.85 (7-CH_2), 30.68 (11-CH_2), 28.39 (13-C), 28.33 (14-CH_3 x 3), 25.80 (17-CH_3 X 3), 23.74 (6-CH_2), 18.19 (16-C), 13.45 (1-CH_3), -4.47 (15-CH_3), -5.05 (15-CH_3).

IR (cm^{-1}) 3356, 2930, 2856, 1698;

HRMS (ESI+) calcd for $C_{22}H_{37}NNaO_4Si^+$ *m/z* 430.24 found 430.2384.

(6.48) 4-(*tert*-Butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-amine



To 2-(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)isoindoline-1,3-dione (1.4 g, 3.2 mmol) in THF (50 ml) was added hydrazine monohydrate (0.62 ml, 12.8 mmol, 4 eq). This was then heated to reflux for 1 hr whereupon water (50 ml) was added. The organic layer was then separated and washed with brine (50 ml), dried over magnesium sulfate, filtered and reduced *in vacuo*. To give the title compound as a colourless oil (970 mg, 98 %).

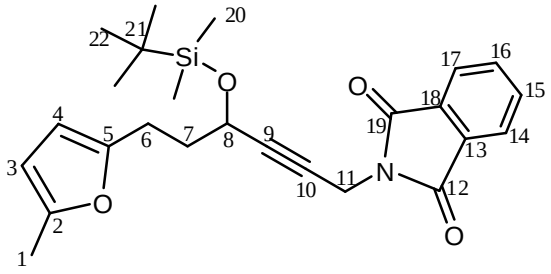
1H-NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, d, J=2.9, H-4), 5.84 (1H, dd, J=2.8, 0.9, H-3), 4.44-4.39 (1H, m, H-8), 3.44 (2H, d, H-11), 2.71 (2H, dd, J=9.0, 6.6, H-6), 2.25 (3H, s, H-1), 2.00-1.95 (2H, m, H-7), 1.36 (2H, s, NH_2), 0.92 (9h, s, H-14), 0.12 (6H, d, J=12.5, H-12).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.52 (5-C), 150.23 (2-C), 105.76 (3-CH), 105.49 (4-CH), 85.04 (10-C), 83.65 (9-C), 62.14 (8-CH), 37.01 (7-CH_2), 31.57 (11-C), 25.81 (14-CH_3 x 3), 23.80 (6-CH_2), 18.20 (13-C), 13.43 (1-CH_3), -4.45 (CH_3), -5.01 (CH_3).

IR (cm^{-1}) 2953, 2855, 1570, 1471, 1360;

HRMS (ESI+) calcd for $C_{17}H_{29}NNaO_2Si^+$ *m/z* 330.19 found 330.1860.

(6.49) 2-(4-(*tert*-Butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)isoindoline-1,3-dione



To a solution of triphenylphosphine (1.4 g, 5.3mmol, 1.2 eq) in THF (25 ml), DEAD (922 mg, 5.3 mmol, 1.2 eq) was added dropwise at 0 °C. When this solution turned canary yellow a mixture of 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-ol (1.36 g, 4.4 mmol, 1 eq) and phthalimide (780 mg, 5.3 mmol, 1.2 eq) in THF (25 ml) was added steadily and quickly. The resulting white suspension turned clear and was monitored by tlc and stirred at room temperature for 4 hr, then the solvent removed *in vacuo*. Purification was achieved using flash column chromatography eluting with diethyl ether in hexane to give the title compound as a pale straw coloured oil (1.7 g, 73 %).

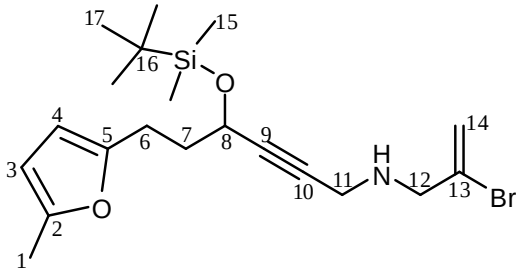
1H-NMR (500 MHz, $CDCl_3$) δ 7.9-7.85 (2H, m, H-17+14), 7.76-7.71 (2H, m, H-15+16), 5.84-5.80 (2H, m, H-3+4), 4.47 (2H, d, J=1.8, H-11), 4.39-4.35 (1H, m, H-8), 2.68 (2H, td, J=7.4, 3.5, H-6), 2.22 (3H, s, H-1), 1.98-1.92 (2H, m, H-7), 0.86 (9H, S, H-22), 0.07 (6H, d, J=8.5, H-20).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 166.92 (C), 153.38 (5-C), 150.24 (2-C), 134.07 (CH x 2), 132.07 (13+14-C), 123.43 (CH x 2), 105.75 (CH), 105.60 (CH), 84.46 (9-C), 77.82 (10-C), 61.93 (8-C), 36.71 (7-C), 27.27 (11-CH_2), 25.74 (22-CH_3 x 3), 18.13 (21-C), 13.43 (1-CH_3), -4.60 (CH_3), -5.11 (CH_3).

IR (cm^{-1}) 2928, 2856, 1773, 1717, 1570;

HRMS (ESI+) calcd for $C_{25}H_{31}NaO_4Si^+$ 460.19 found: *m/z* 460.1915.

(6.50) N-(2-Bromoallyl)-4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-amine



To a stirring solution of 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-amine (3.362 g, 11 mmol) and potassium carbonate (1.5 g, 11 mmol, 1 eq) in THF (120 ml) was added 2,3-dibromopropene (1.075 ml, 11 mmol, 1 eq) in one portion. The reaction mixture was allowed to stir at room temperature for 48 hrs. To this water (120 ml) was added and then extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and reduced *in vacuo* to give a crude pale yellow oil. This oil was then purified using flash column chromatography eluting with 20 % diethyl ether in hexane to yield the title compound as a colourless oil (2.052 g, 43 %).

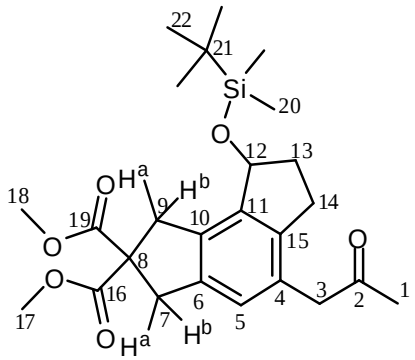
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, d, J = 3.0, H-4), 5.84 (2H, m, H-3, H-14^a), 5.58 (1H, d, J=1.7, H-14^b), 4.43 (1H, t, J=6.3, H-8), 3.55 (2H, d, J=0.4, H-12), 3.45 (2H, d, J=1.7, H-11), 2.72 (2H, dd, J=8.7, 6.7, H-6), 2.25 (3H, s, H-1), 2.01-1.96 (2H, m, H-7), 1.57 (1H, s, NH), 0.92 (9H, s, H-17), 0.12 (6H, d, J=12.2, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.49 (5-C), 150.30 (2-C), 132.11 (13-C), 118.25 (14-CH_2), 105.77 (3CH), 105.53 (4-CH), 85.12 (9-C), 81.58 (10-C), 62.15 (8-CH), 56.07 (12-CH_2), 37.09 (7-CH_2), 36.68 (11-CH_2), 25.80 (17-CH_3 x 3), 23.83 (6-CH_2), 18.21 (16-C), 13.46 (1-CH_3), -4.47 (C), -5.02 (C).

IR (cm^{-1}) 2928.53, 2856.70, 1716.84;

HRMS (ESI+) calcd for $C_{20}H_{33}BrNO_2Si^+$ *m/z* 426.15 found 426.1458.

(6.53) Dimethyl 8-(*tert*-butyldimethylsilyloxy)-5-(2-oxopropyl)-3,6,7,8-tetrahydroas-indacene-2,2(1H)-dicarboxylate



Dimethyl 2-(2-bromoallyl)-2-(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)malonate (400 mg, 0.74 mmol), DPPE (59.76 mg, 0.15 mmol, 0.2 eq), palladium (II) acetate (16.61 mg, 0.074 mmol, 0.1 eq), potassium carbonate (204 mg, 1.48 mmol, 2 eq) was heated to 120 °C in DMF (50 ml) for 25 minutes. The reaction mixture was then diluted with water (500 ml) and extracted with diethyl ether (3 x 250 ml), dried over magnesium sulfate, filtered and reduced *in vacuo*. The resulting brown oil was purified using flash column chromatography eluting with 40 % diethyl ether in hexane to yield the title compound as a colourless oil (112 mg, 32 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.92 (1H, s, H-5), 5.34 (1H, t, J=6.7, H-12), 3.76 (7H, m, H-18 + H-17 + H-9^a/H-9^b), 3.67-3.45 (5H, m, H-9^b/H-9^a + H-7^a + H-7^b + H-3), 2.88 (1H, ddd, J=15.6, 9.0, 3.2, H-14), 2.60 (1H, dt, J=15.9, 8.0, H-14), 2.48-2.39

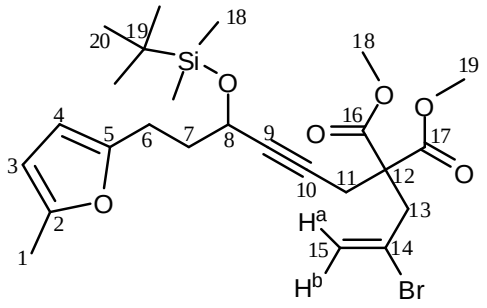
(1H, m, H-13), 2.14 (3H, s, H-1), 1.93 (1H, dtd, J=12.9, 8.5, 6.5, H-13), 0.94 (9H, s, H-22), 0.18 (6H, d, J=21.8, H-20).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 206.09 (2-C), 172.37 (19-C), 172.06 (16-C), 141.02 (C), 140.88 (4-C), 139.69 (8-C), 135.57 (10-C), 129.20 (C), 124.80 (5-CH), 76.31 (12-C), 60.53 (C), 52.91 (18-CH_3), 52.81 (17-CH_3), 48.60 (3-CH_2), 40.08 (7-CH_2), 38.82 (9-CH_2), 36.10 (15-C), 29.3 (1-CH_3), 25.86 (22-CH_3 x 3), 17.99 (21-C), -4.06 (20-CH), -4.70 (CH_3).

IR (cm^{-1}) 2954, 2856, 1734, 1472;

HRMS (ESI+) calcd for $C_{25}H_{36}NaO_6Si^+$ *m/z* 483.2173 found 483.22.

(6.54) Dimethyl 2-(2-bromoallyl)-2-(4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-ynyl)malonate



To a stirred solution of triphenylphosphine (420 mg, 1.62 mmol, 1 eq) in THF (5 ml), a solution of DEAD (280 mg, 0.25 ml, 1.62 mmol, 1 eq)) in THF (2 ml) was added dropwise at 0 °C. To this a mixture of 4-(*tert*-butyldimethylsilyloxy)-6-(5-methylfuran-2-yl)hex-2-yn-1-ol (500 mg, 1.62 mmol) and dimethyl 2-(2-bromoallyl)malonate (410 mg, 1.62 mmol, 1 eq) in THF (2 ml) was added dropwise over 1 minute. The solution was allowed to warm to room temperature overnight. The solvent was then reduced *in vacuo* and the resulting oil was purified using column chromatography eluting with 20 % diethyl ether in hexane to yield the title compound as a colourless oil (3.72 g, 57 %).

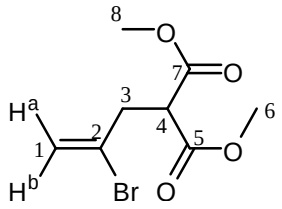
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, d, J=2.9, H-4), 5.84 (1H, app S, H-3), 5.82 (1H, S, H-15^{a}/15^{b}), 5.62 (1H, d, J=1.5, H-15^{b}/15^{a}), 4.35 (1H, t, J=6.3, H-8), 3.75 (6H, s, H-21 + H-19), 3.29 (2H, s, H-13), 2.96 (2H, d, J=1.8, H-11), 2.68 (2H, t, J=7.7, H-6), 2.25 (3H, s, H-1), 2.00-1.86 (2H, m, H-7), 0.89 (12H, S, H-17), 0.69 (6H, d, J=9.6, H-15).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 169.51 (20+18 C=O), 153.45 (5-C), 150.32 (2-C), 126.27 (14-C), 122.67 (15-CH_2), 105.77 (2-C), 105.53 (5-C), 85.41 (10-C), 78.64 (9-C), 62.07 (8-CH), 56.13 (12-C), 52.92 (21+19-CH_3), 42.99 (13-CH_2), 37.28 (7-CH_2), 25.74 (17-CH_3 x 3), 23.74 (6-CH_2), 22.52 (11-CH_2), 18.15 (16-C), 13.45 (1-CH_3), -4.60 (15-CH_3), -5.14 (15-CH_3).

IR (cm^{-1}) 2954, 1742, 1435;

HRMS (ESI+) calcd for $C_{25}H_{37}BrNaO_6Si^{+}$ *m/z* 563.14 found 563.1435.

(6.55) Dimethyl 2-(2-bromoallyl)malonate[85]



To a stirred solution of NaH (15.14 mmol, 1 eq) in THF (75 ml) dimethyl malonate was added dropwise at 0 °C and left to stir for 1 hr. To this solution was added 2,3-dibromopropene (3.03 g, 1.48 ml, 15.14 mmol, 1 eq) in THF (20 ml) dropwise and left stirring overnight. The reaction was quenched with water (100 ml) and extracted with diethyl ether (3 x 100 ml) washed with brine and dried over magnesium sulfate, the filtered solution was then reduced *in vacuo* to yield a crude oil containing the mono and di-substituted product in roughly a 3:1 ratio. This crude oil was purified using flash column chromatography eluting with 20 % EtOAc in hexane to give the title compound as a colourless oil (1.44 g, 37 %).

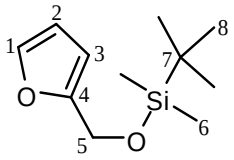
1H-NMR (500 MHz, $CDCl_3$) δ 5.70-5.68 (1H, m, H-1^a/H-1^b), 5.48 (1H, d, J=1.8, H-1^b/H-1^a), 3.82 (1H, t, J=7.5, H-4), 3.76 (6H, s, H-6 + H-8), 3.03 (2H, dd, J=7.5, 0.8, H-3).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 168.46 (5+7-C=O), 129.21 (2-C), 119.80 (1-CH_2), 52.72 (6+8-CH_3), 50.41 (4-CH), 40.47 (3-CH_2).

HRMS (ESI+) calcd for $C_8H_{11}BrNaO_4^+$ *m/z* 272.97 found 272.9733.

IR (cm^{-1}) 2924, 1736, 1435, 1151;

(6.60) *tert*-Butyl(furan-2-ylmethoxy)dimethylsilane



To a solution of TBDMSCl (8.44 g, 56 mmol, 1.1 eq), imidazole (6.95 g, 102 mmol, 2 eq), DMAP (305 mg, 2.5 mmol, 0.05 eq) in DCM (50 ml) was added furfuryl alcohol (5 g, 4.4 ml, 50.9 mmol) in one portion and stirred at rt for 2 hours. The reaction mixture was then diluted with 50ml of water extracted with diethyl ether (3 x 50 ml) washed with brine, dried over magnesium sulfate, filtered and reduced *in vacuo* to yield the title compound as a colourless oil (10.65 g , 99 %).

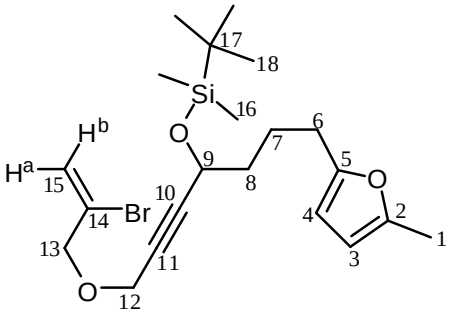
1H-NMR (500 MHz, $CDCl_3$) δ 7.38 (1H, dd, J = 1.8, 0.8 H-1), 6.33 (1H, dd, J = 3.1, 1.8, H-2), 6.34 (1H, dd, J = 3.2, 0.5, H-3), 4.65 (2H, s, H-5), 0.92 (9H, s, H-8), 0.10 (6H, s, H-6).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 154.32 (4-C), 141.97 (1-CH), 110.13 (2-CH), 107.14 (3-CH), 58.15 (5-CH_2), 25.87 (8-CH_3 x 3), 18.40 (7-C), -5.28 (6-CH_3 x 2).

IR (cm^{-1}) 2954, 2857, 1472, 1254;

HRMS (ESI+) calcd for $C_{11}H_{20}NaO_2Si^+$ 235.11 found *m/z* 235.1125.

(6.63) (1-(2-Bromoallyloxy)-7-(5-methylfuran-2-yl)hept-2-yn-4-yloxy)(*tert*-butyl)dimethylsilane



To a stirred solution of 4-(*tert*-butyldimethylsilyloxy)-7-(5-methylfuran-2-yl)hept-2-yn-1-ol (2.1 g, 6.52 mmol) in THF (25 ml) was added 60 % NaH (288 mg, 7.2 mmol, 1.1 eq) at 0 °C and left for 1 hour. 2,3-dibromopropane (1.3 g, 6.52 mmol, 1 eq) was then added dropwise at 0 °C and the reaction mixture allowed to warm to room temp. After 2 hr the reaction mixture was added to a stirring biphasic mixture of 10 % potassium carbonate (25 ml) and diethyl ether (25 ml) followed by separation and extraction of the aqueous layer using diethyl ether. The combined organic layers were then dried over magnesium sulfate, reduced *in vacuo* and purified *via* flash column chromatography eluting with 20 % diethyl ether in hexane to give the title compound as a colourless oil (1.79 g, 62 %).

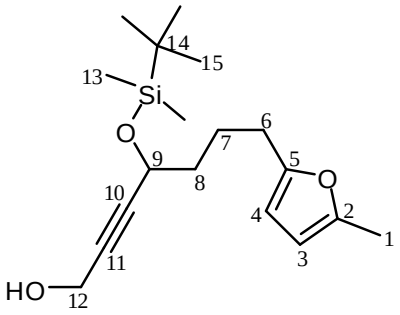
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.94 (1H, d, J=1.5, H-15^a/H-15^b), 5.86 (1H, d, J=2.9, H-4), 5.85 (1H, d, J=0.6, H-3), 5.65 (1H, s, H-15^b/H-15^a), 4.44 (1H, t, J=5.2, H-9), 4.24 (2H, d, J=1.6, H-12), 4.20 (2H, s, H-13), 2.61 (2H, t, J=6.9, H-6), 2.26 (3H, s, H-1), 1.80-1.70 (4H, m, H-7 + H-8), 0.92 (9H, s, H-18), 0.13 (6H, d, J=10.9, H-16).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 154.02 (5-C), 150.18 (2-C), 128.64 (14-C), 118.34 (15-CH_2), 105.74 (3-CH), 105.43 (4-CH), 88.74 (10-C), 79.14 (11-C), 73.12 (13-CH_2), 62.70 (9-CH), 57.41 (12-CH_2), 37.93 (CH_2), 27.62 (6-CH_2), 25.78 (18-CH_3 x 3), 23.78 (CH_2), 18.21 (17-C), 13.47 (1-CH_3), -4.52 (CH_3), -5.01 (CH_3).

IR (cm^{-1}) 2955, 2931, 2856, 1715, 1361, 1253, 1079;

HRMS (ESI+) calcd for $C_{21}H_{33}BrKO_3Si^+$ *m/z* 479.1014 found 479.1014.

(6.64) 4-(*tert*-Butyldimethylsilyloxy)-7-(5-methylfuran-2-yl)hept-2-yn-1-ol



To a stirred solution of *tert*-butyldimethyl(6-(5-methylfuran-2-yl)hex-1-yn-3-yloxy)silane (3.22 g, 11 mmol) in THF (35 ml) at -78 °C was added dropwise 2.5M ^{n}BuLi (4.85 ml, 12.12 mmol, 1.1 eq) over 5 minutes. The reaction mixture was allowed to warm to -40 °C over 1 hour before re-cooling to -78 °C whereupon para-formaldehyde (700 mg, 22 mmol, 2 eq) was added all at once. It was then stirred overnight and allowed to reach room temperature. The reaction mixture was then quenched with aqueous ammonium chloride (50 ml) and extracted with diethyl ether (3 x 50 ml). The organic fractions were combined and washed with brine, dried over magnesium sulfate, filtered and reduced *in vacuo* to give a crude pale straw coloured oil. The oil was purified using flash column chromatography eluting with 20 % diethyl ether in hexane and gave the title compound as a colourless oil (3.213 g, 90 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, d, J=3.0, H-4), 5.85 – 5.84 (1H, m, H-3), 4.44-4.40 (1H, m, H-9), 4.29 (2H, dd, J=6.1, 1.6, H-12), 2.61 (2H, t, J=7.0, H-6), 2.26 (3H, s, H-1), 1.80-1.69 (4H, m, H-7 + H-8), 0.92 (9H, s, H-15), 0.13 (6H, d, J=11.2, H-13).

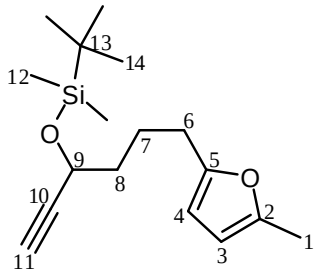
^{13}C-NMR (126 MHz, $CDCl_3$) δ 154.05 (5-C), 150.18 (2-C), 105.73 (3-CH), 105.42 (4-CH), 87.50 (10-C), 82.20 (11-C), 62.69 (9-CH), 51.18 (12-CH_2), 37.92 (8-CH_2),

27.62 (6-CH_2), 25.80 (15-CH_3), 23.76 (7-CH_2), 18.21 (14-C), -4.48 (CH_3), -5.01 (CH_3).

IR (cm^{-1}) 3344, 2928, 2857, 1576, 1466, 1388;

HRMS (ESI+) calcd for $C_{18}H_{30}NaO_3Si^+$ *m/z* 345.19 found 345.1856.

(6.65) *tert*-Butyldimethyl(6-(5-methylfuran-2-yl)hex-1-yn-3-yloxy)silane



To 6-(5-methylfuran-2-yl)hex-1-yn-3-ol (2 g, 11.22 mmol) in DCM (50 ml) was added TBDMSCl (1.86 g, 12.34 mmol, 1.1 eq), imidazole (1.53 g, 22.44 mmol, 2 eq) and DMAP (68 mg, 0.05 eq) and stirred at room temperature for two hours. To this, water (50 ml) was added and the mixture extracted with diethyl ether (3 x 50 ml). The organic layers were then combined and washed with brine (50 ml), dried over magnesium sulfate, filtered and reduced *in vacuo* to yield a pale straw coloured oil (3.253 g, 99 %).

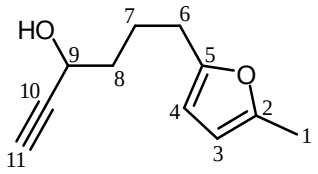
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.87 (1H, d, J=3.0, H-4), 5.85 (1H, dd, J=2.9, 0.8, H-3), 4.38 (1H, td, J=6.1, 2.0, H-9), 2.61 (2H, t, J=7.0, H-6), 2.39 (1H, d, J=2.1, H-11), 2.26 (3H, s, H-1), 1.85-1.70 (4H, m, H-7 + H-8), 0.92 (9H, s, H-14), 0.14 (6H, d, J=12.2, H-12).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 154.06 (5-C), 150.16 (2-C), 105.72 (3-CH), 105.39 (4-CH), 85.48 (10-C), 72.05 (11-CH), 62.50 (9-CH), 37.91 (CH_2), 27.61 (6-CH_2), 25.76 (14-CH_3 x 3), 23.65 (CH_2), 18.19 (13-C), 13.46 (1-CH_3), -4.59 (CH_3), -5.09 (CH_3).

IR (cm^{-1}) 3309, 2930, 2857, 1684, 1251;

HRMS (ESI+) calcd for $C_{17}H_{28}NaOSi^{+}$ *m/z* 315.18 found 315.1751.

(6.66) 6-(5-Methylfuran-2-yl)hex-1-yn-3-ol



To a stirred solution of 4-(5-methylfuran-2-yl)butanal (2.6 g, 17.08 mmol) in THF (50 ml) at -20 °C was added 0.5M ethynylmagnesium bromide (37.6 ml, 18.8 mmol) dropwise over a period of 5 minutes. The solution was then allowed to warm to room temperature over a period of 2 hours. The reaction was then quenched with aqueous ammonium chloride solution (50 ml) and extracted with diethyl ether (3 x 50 ml) the combined organic layers were dried over magnesium sulfate, filtered and reduced *in vacuo* to give a crude pale straw coloured oil. This oil was then purified using flash column chromatography eluting with diethyl ether in hexane to yield the title compound as a colourless oil (2.17 g, 86.8 %).

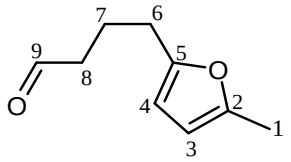
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.88 (1H, d, J=2.9, H-4), 5.85-5.84 (1H, m, H-3), 4.43-4.38 (1H, m, H-9), 2.63 (2H, t, J=6.9, H-6), 2.47 (1H, d, J=2.1, H-11), 2.26 (3H, s, H-1), 1.94 (1H, d, J=5.0, OH), 1.86-1.75 (4H, m, H-7 + H-8).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.77 (5-C), 150.28 (2-C), 105.77 (4-CH), 105.56 (3-CH), 84.77 (10-C), 73.02 (11-CH), 62.05 (9-CH), 37.00 (CH_2), 27.57 (6-CH_2), 23.66 (CH_2), 13.47 (1-C).

IR (cm^{-1}) 3287, 2945, 1711, 1375, 1032;

HRMS (ESI+) calcd for $C_{11}H_{13}O_2^{-}$ *m/z* 177.0921 found 177.0910.

(6.67) 4-(5-Methylfuran-2-yl)butanal



To a solution of (Z)-2-(4-methoxybut-3-enyl)-5-methylfuran (5 g, 30 mmol) in THF (50 ml) was added PPTS (1.885 g, 7.5 mmol, 0.25 eq.) and water (two drops). The reaction mixture was allowed to stir for 48 hours and monitored using tlc. To the reaction mixture was added acetyl chloride (0.1 eq) and allowed to stir for a further 24 hours after which water was added (50 ml) and the aqueous layer extracted with diethyl ether (3 x 50 ml), dried over magnesium sulfate, filtered and reduced *in vacuo*. The straw like oil was then purified using flash column chromatography eluting with 20 % diethyl ether in hexane to yield the title aldehyde as a colourless oil (2.61 g, 57.2 %). The unreacted starting material was recovered and the process repeated to give a similar yield.

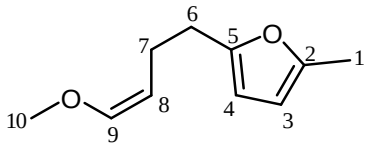
^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.75 (1H, s, H-9), 5,87 (1H, d, J=2.9, H-4), 5.84 (1H, dd, J=2.9, 0.8, H-3), 2.63 (1H, t, J=7.3, H-6), 2.48 (2H, td, J=7.3, 1.4, H-8), 2.25 (3H, s, H-1), 1.96 (2H, dq, J=14.6, 7.3, H-7).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 201.98 (9-CH), 152.94 (5-C), 150.56 (2-C), 106.11 (4-CH), 105.82 (3-CH), 43.03 (8-CH_2), 27.23 (6-CH_2), 20.76 (7-CH_2), 13.44 (1-CH_3).

IR (cm^{-1}) 2938, 1720, 1680, 1568, 1454;

HRMS (ESI+) calcd for $C_9H_{12}NaO_2^+$ *m/z* 175.07 found 175.0730.

(6.68) (Z)-2-(4-Methoxybut-3-enyl)-5-methylfuran



To a solution of (methoxymethyl)triphenylphosphonium chloride (24.68 g, 72 mmol, 1.1 eq) in THF (350 ml) was added 2.5M ^{n}BuLi (29 ml, 72 mmol 1.1 eq) dropwise over 1 hour at -20 °C. To the resulting brick red solution was added 3-(5-methylfuran-2-yl)propanal (9 g, 65.2 mmol) over 5 mins at -20 °C. The reaction mixture was quenched with water (350 ml) and the organic layer separated and washed with brine, dried over magnesium sulfate and reduced *in vacuo* to give a crude yellow oil. This oil was then purified using flash column chromatography eluting with 5 % diethyl ether in hexane to give the title compound as a colourless oil (8.898 g, 82 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.34 (1H, d, J=12.6, H-9), 5.87 (1H, s, H-4), 5.85 (1H, s, H-3), 4.78 (1H, dt, 12.7, 7.3, H-8), 3.51 (3H, s, H-10), 2.63 (2H, t, J=7.6, H-6), 2.30 – 2.21 (5H, m, H-1 + H-7).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 153.86 (5-C), 150.15 (2-C), 147.63 (9-CH), 105.75 (3-CH), 105.48 (4-CH), 101.93 (8-CH), 55.84 (10-CH_3), 29.57 (6-CH_2), 26.60 (7-CH_2), 13.45 (1-CH_3).

IR (cm^{-1}) 2942, 1717, 1571, 1083;

HRMS (ESI+) calcd for $C_{10}H_{14}NaO_2^+$ *m/z* 189.0886 found 189.0886.

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Appendix A:
Crystallographic Data

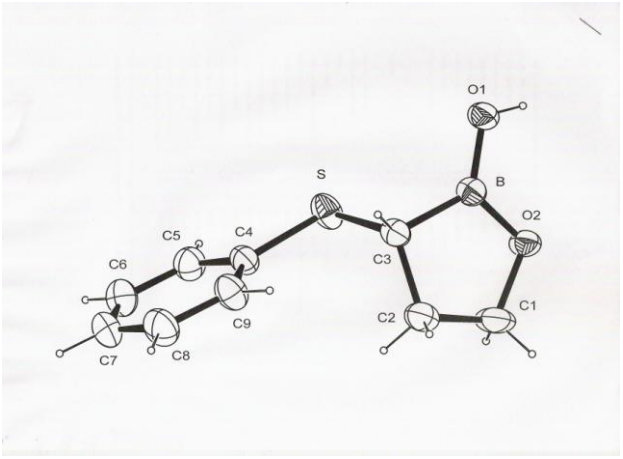


Table 1. Crystal data and structure refinement .

Identification code	may708	
Empirical formula	C9 H11 B O2 S	
Formula weight	194.05	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (No.14)	
Unit cell dimensions	a = 19.8089(9) Å	α= 90°.
	b = 7.9247(4) Å	β= 90.141(3)°.
	c = 6.1422(3) Å	γ = 90°.
Volume	964.20(8) $Å^3$	
Z	4	
Density (calculated)	1.34 Mg/m^3	
Absorption coefficient	0.30 mm^{-1}	
F(000)	408	
Crystal size	0.4 x 0.3 x 0.05 mm^3	
Theta range for data collection	4.02 to 26.72°.	
Index ranges	-25<=h<=24, -9<=k<=9, -7<=l<=6	
Reflections collected	10453	
Independent reflections	2011 [R(int) = 0.072]	
Reflections with I>2sigma(I)	1684	
Completeness to theta = 26.72°	98.8 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2011 / 0 / 122	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2sigma(I)]	R1 = 0.048, wR2 = 0.118	
R indices (all data)	R1 = 0.059, wR2 = 0.126	

Largest diff. peak and hole 0.44 and -0.38 e.Å^{-3}

The hydroxyl H atom was refined.

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for may708. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

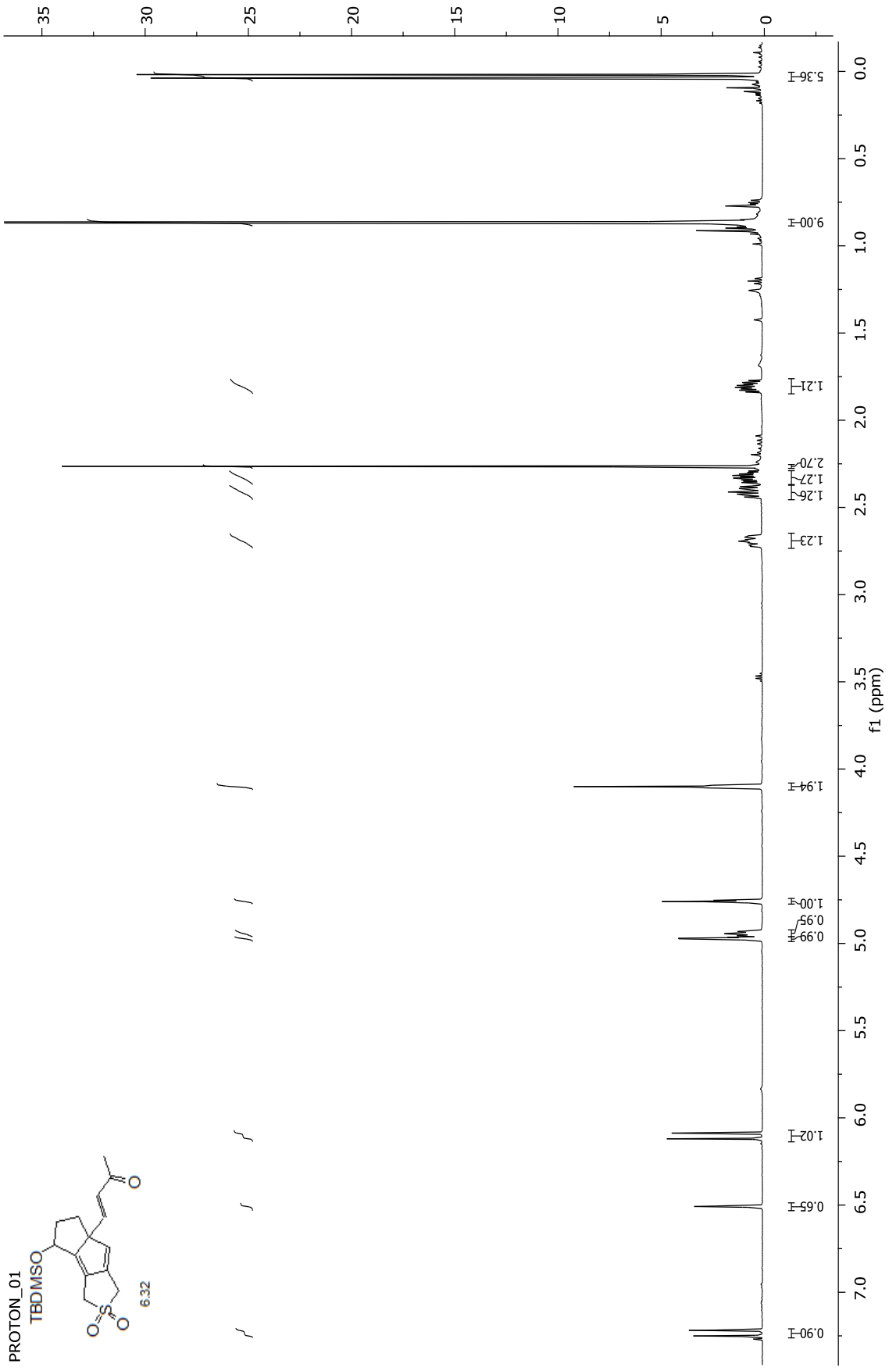
	x	y	z	U(eq)
S	2229(1)	5122(1)	5085(1)	36(1)
O(1)	706(1)	3463(2)	5844(2)	36(1)
O(2)	544(1)	5386(2)	2927(2)	31(1)
C(1)	935(1)	6164(3)	1191(4)	48(1)
C(2)	1581(1)	5201(3)	962(4)	37(1)
C(3)	1674(1)	4192(2)	3085(3)	28(1)
C(4)	3041(1)	5055(2)	3882(3)	30(1)
C(5)	3540(1)	5993(3)	4934(4)	36(1)
C(6)	4196(1)	5951(3)	4173(4)	44(1)
C(7)	4359(1)	4989(3)	2355(4)	45(1)
C(8)	3865(1)	4084(3)	1308(4)	44(1)
C(9)	3203(1)	4105(3)	2056(4)	37(1)
B	935(1)	4265(3)	4068(4)	27(1)

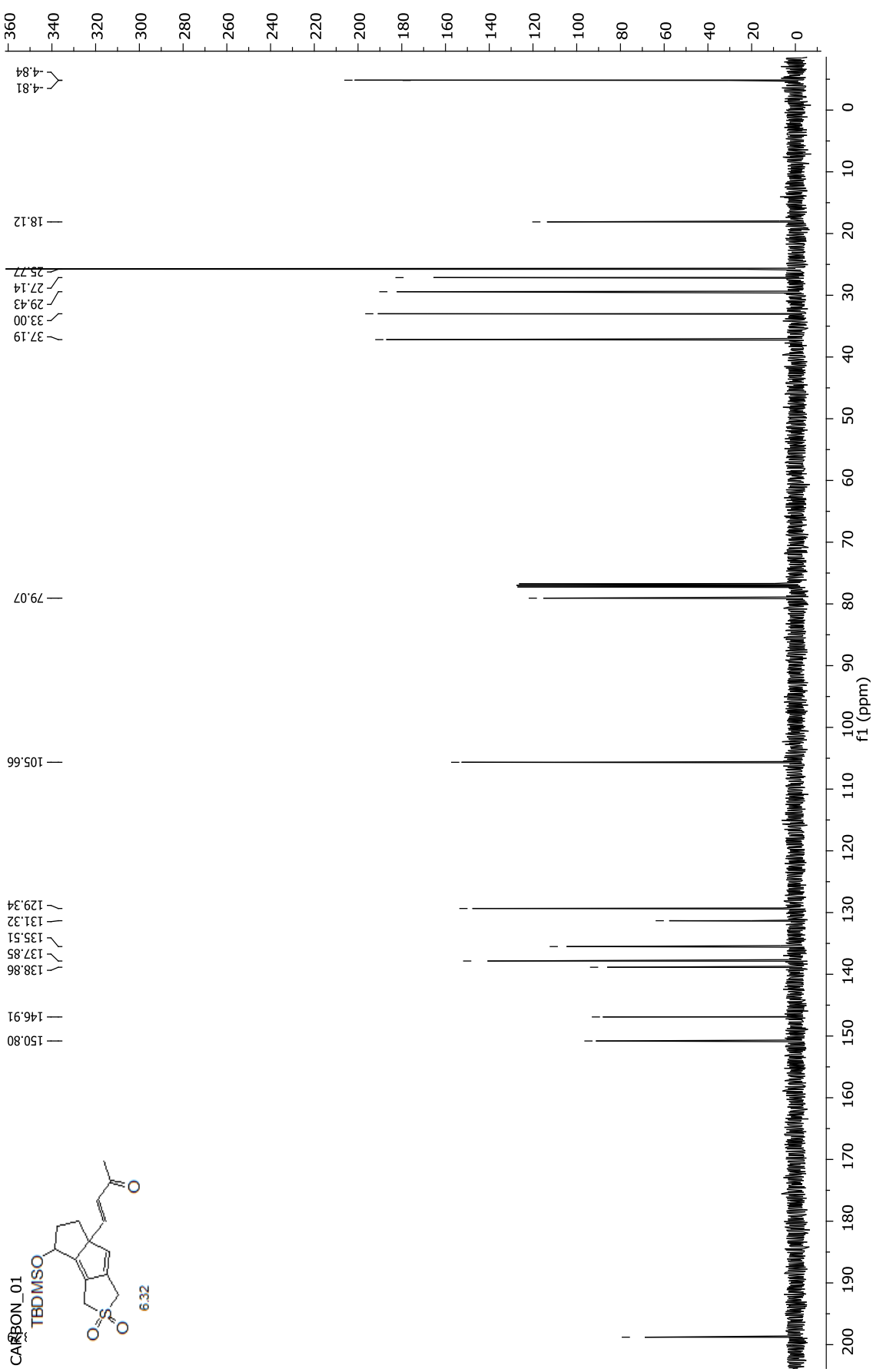
Table 3. Bond lengths [Å] and angles [°] for may708.

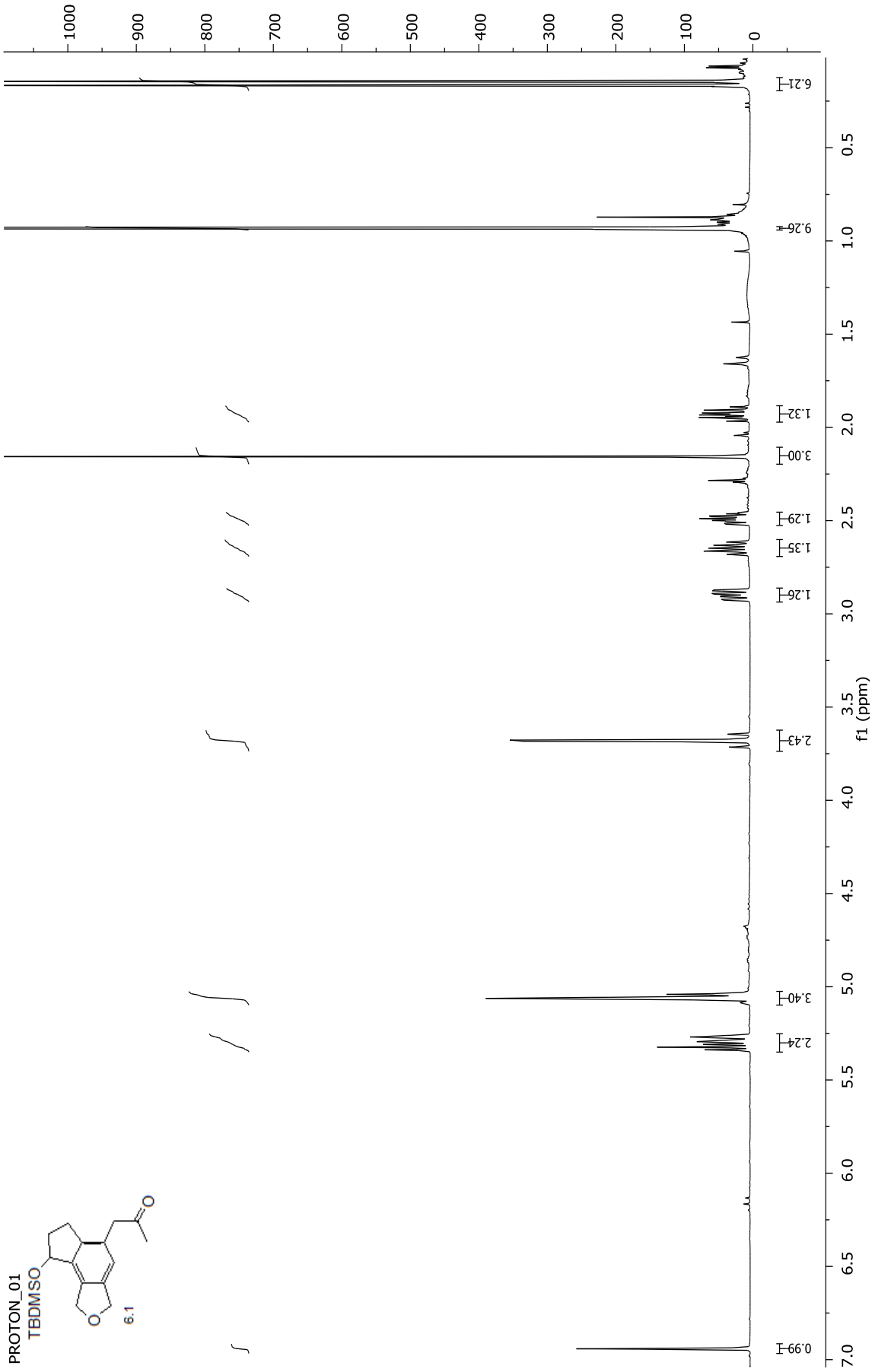
S-C(4)	1.773(2)
S-C(3)	1.804(2)
O(1)-B	1.343(3)
O(2)-B	1.371(3)
O(2)-C(1)	1.456(3)
C(1)-C(2)	1.498(3)
C(2)-C(3)	1.540(3)
C(3)-B	1.585(3)

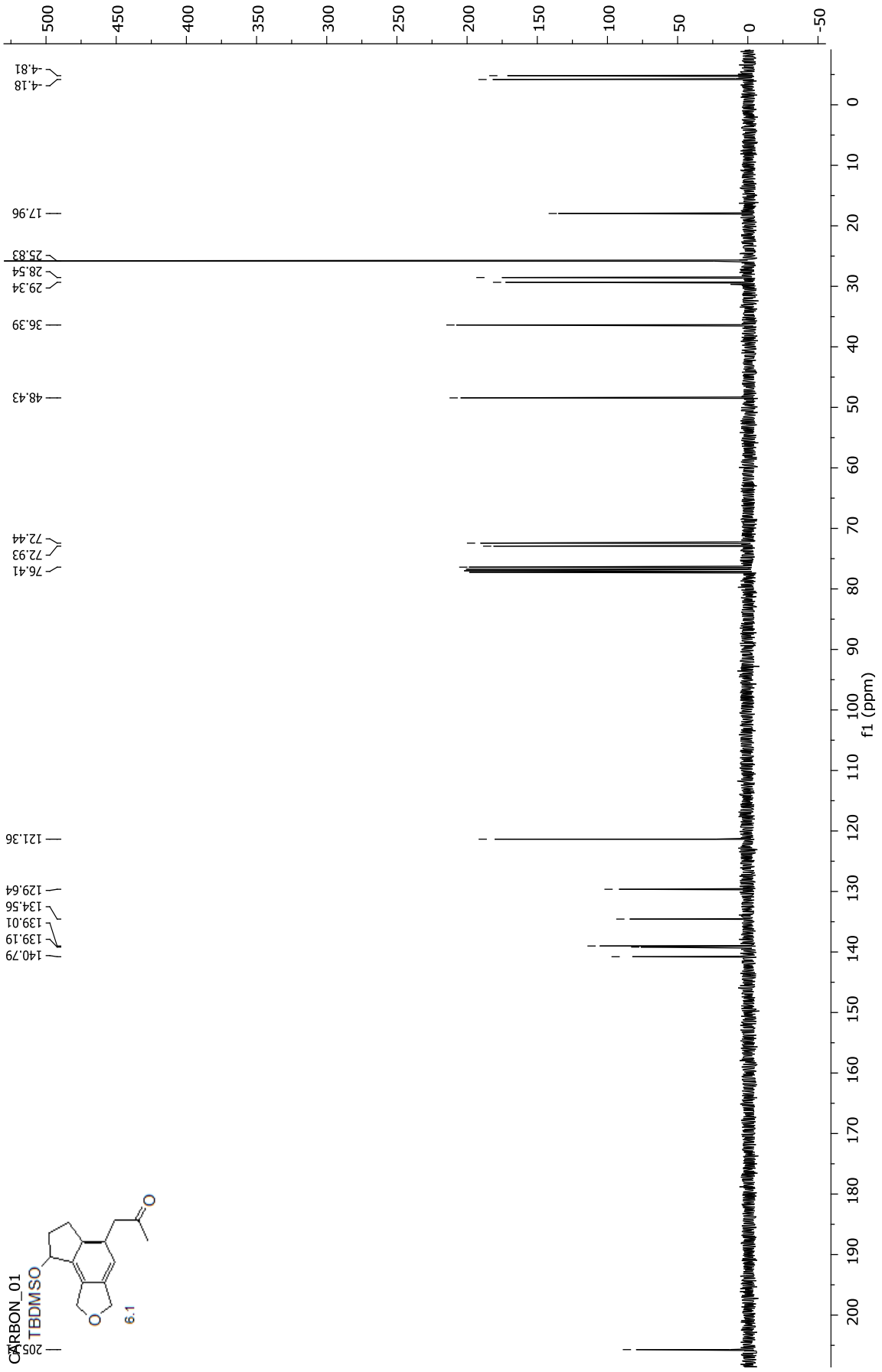
C(4)-C(9)	1.389(3)
C(4)-C(5)	1.393(3)
C(5)-C(6)	1.384(3)
C(6)-C(7)	1.391(4)
C(7)-C(8)	1.372(4)
C(8)-C(9)	1.392(3)
C(4)-S-C(3)	104.85(9)
B-O(2)-C(1)	110.30(16)
O(2)-C(1)-C(2)	108.03(18)
C(1)-C(2)-C(3)	106.58(17)
C(2)-C(3)-B	101.25(16)
C(2)-C(3)-S	115.82(15)
B-C(3)-S	106.68(13)
C(9)-C(4)-C(5)	119.95(19)
C(9)-C(4)-S	124.33(16)
C(5)-C(4)-S	115.69(16)
C(6)-C(5)-C(4)	119.7(2)
C(5)-C(6)-C(7)	120.3(2)
C(8)-C(7)-C(6)	119.8(2)
C(7)-C(8)-C(9)	120.7(2)
C(4)-C(9)-C(8)	119.5(2)
O(1)-B-O(2)	121.97(19)
O(1)-B-C(3)	127.35(19)
O(2)-B-C(3)	110.55(17)

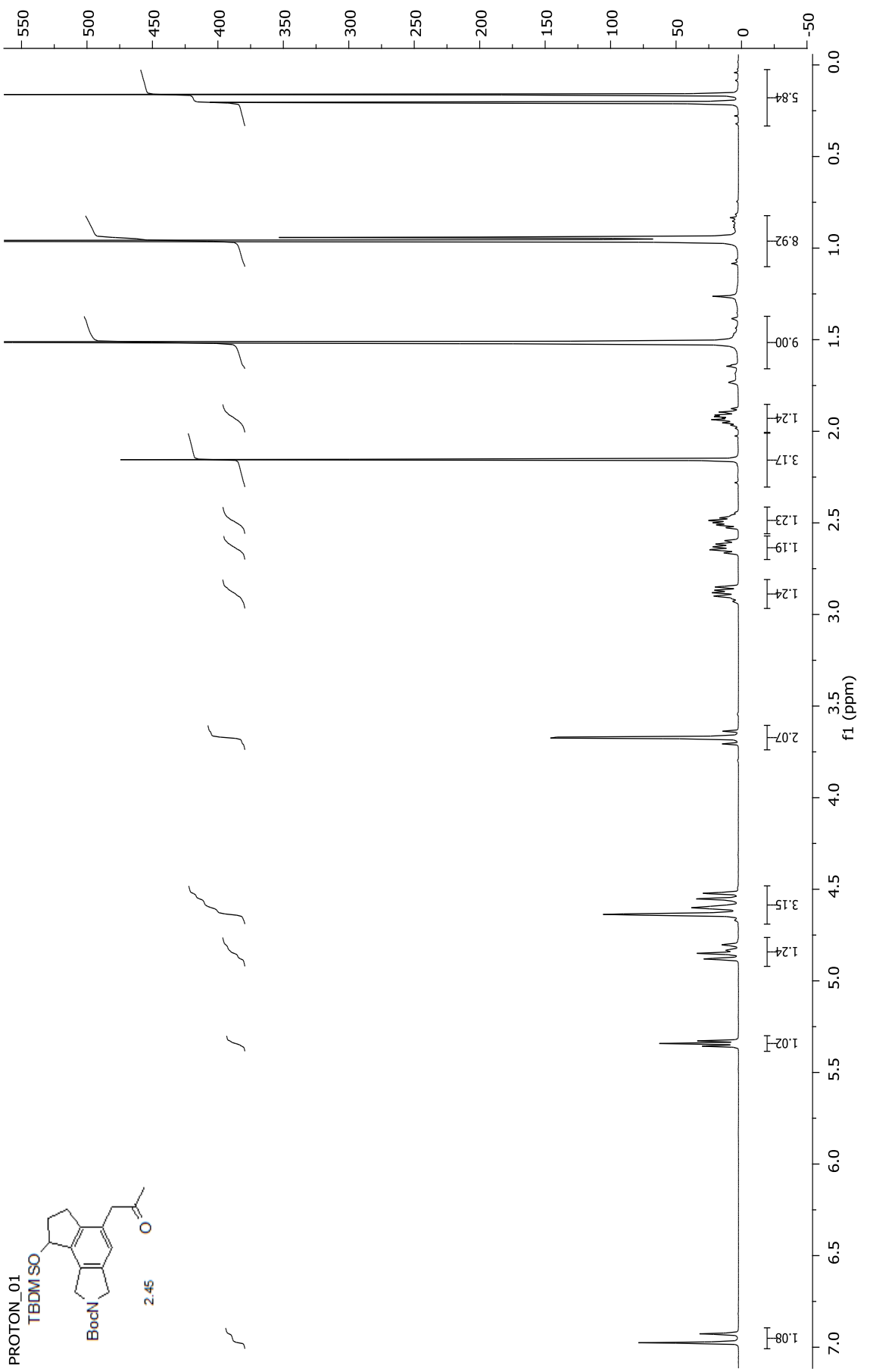
Appendix B: NMR Spectra

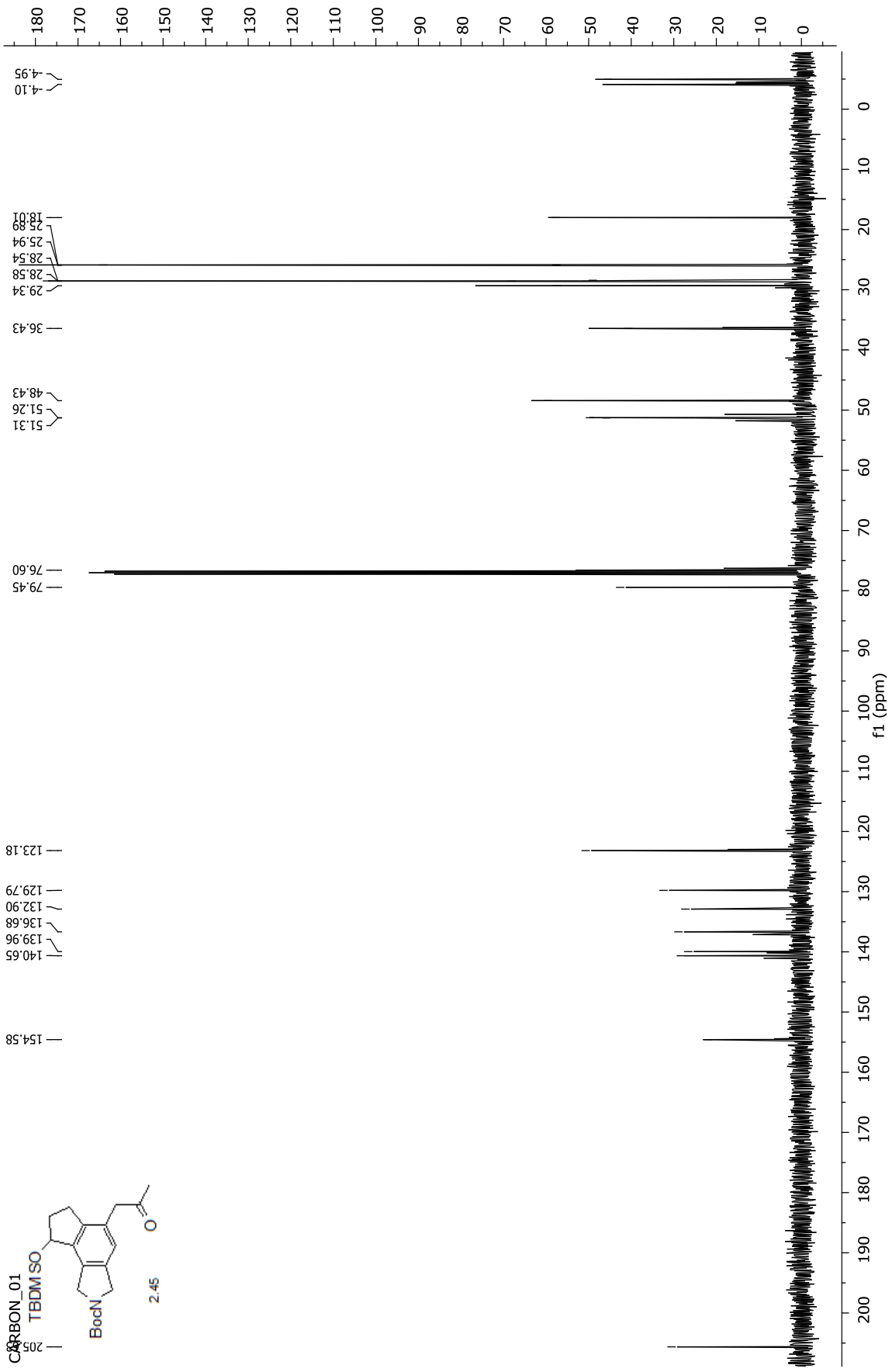

PROTON_01
TBDMSO
6.32
f1 (ppm)
5.36
9.00
1.21
2.70
1.27
1.26
1.23
1.94
1.00
0.99
0.95
1.02
0.65
0.90

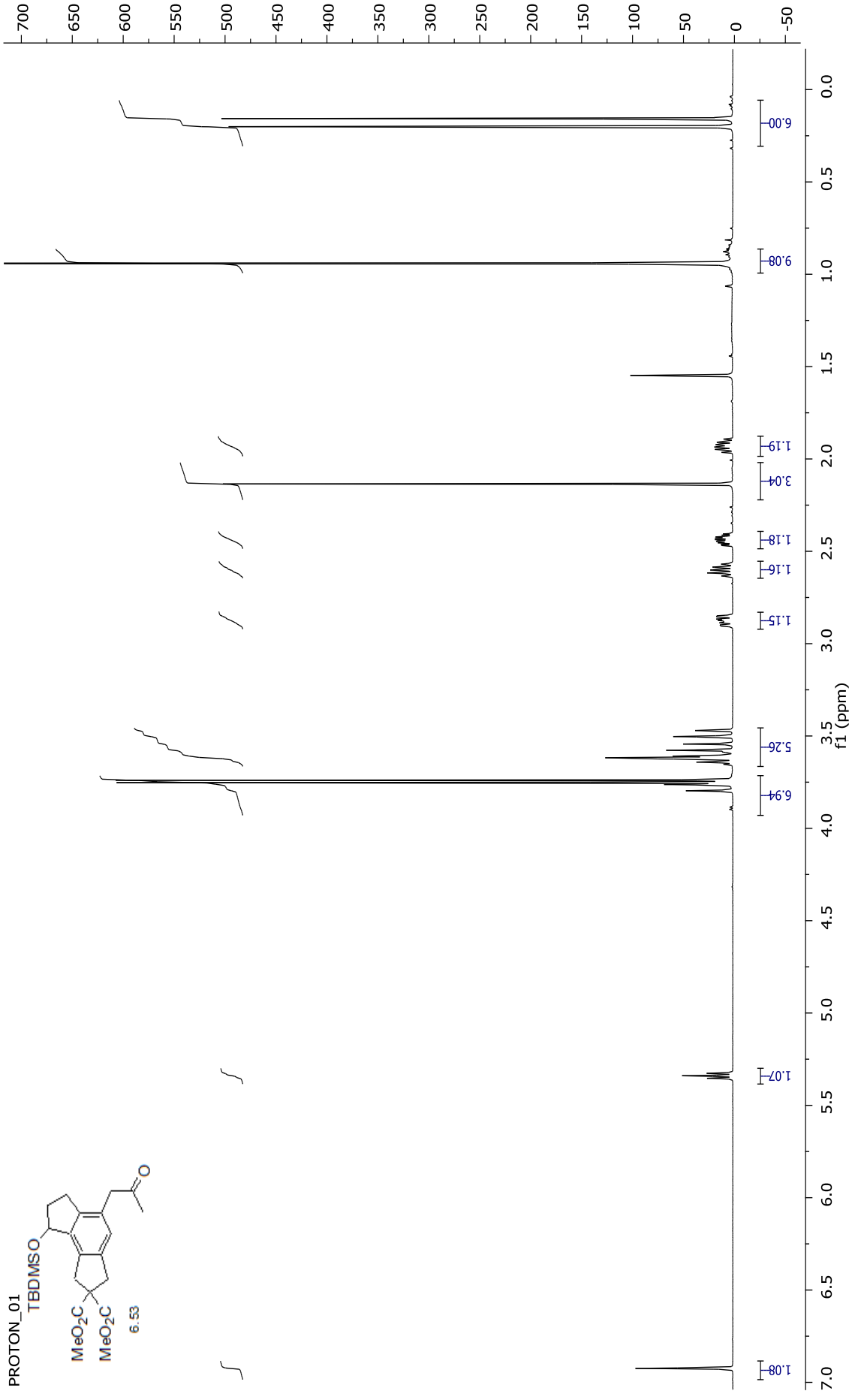

CARBON_01
TBDMSO
6.32
-4.84
-4.81
18.12
25.77
27.14
29.43
33.00
37.19
79.07
105.66
129.34
131.32
135.51
137.85
138.86
146.91
150.80
f1 (ppm)

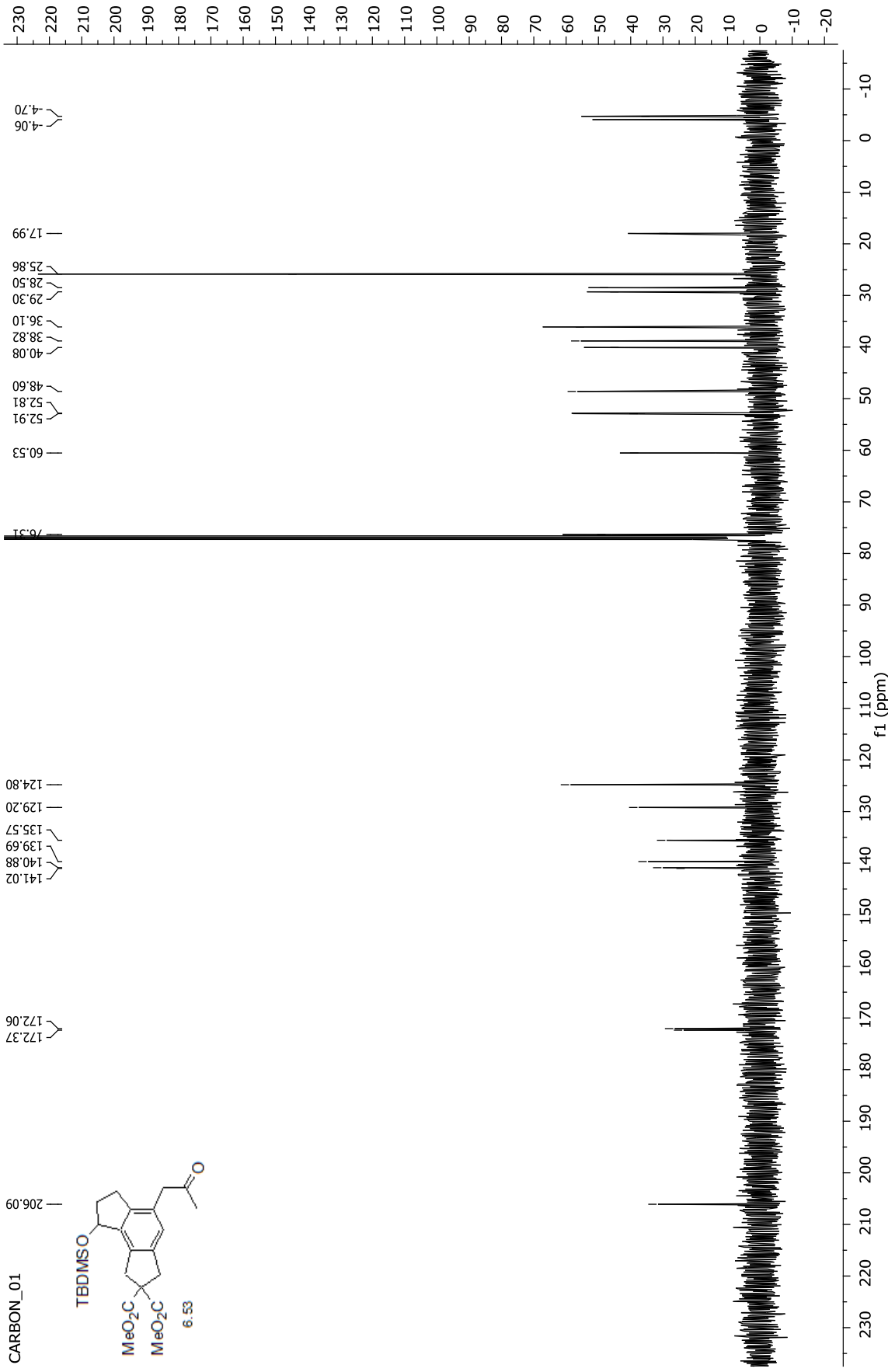

PROTON_01
TBDMSO
6.21
9.26
1.32
3.00
1.29
1.35
1.26
2.43
3.40
2.24
0.99
f1 (ppm)

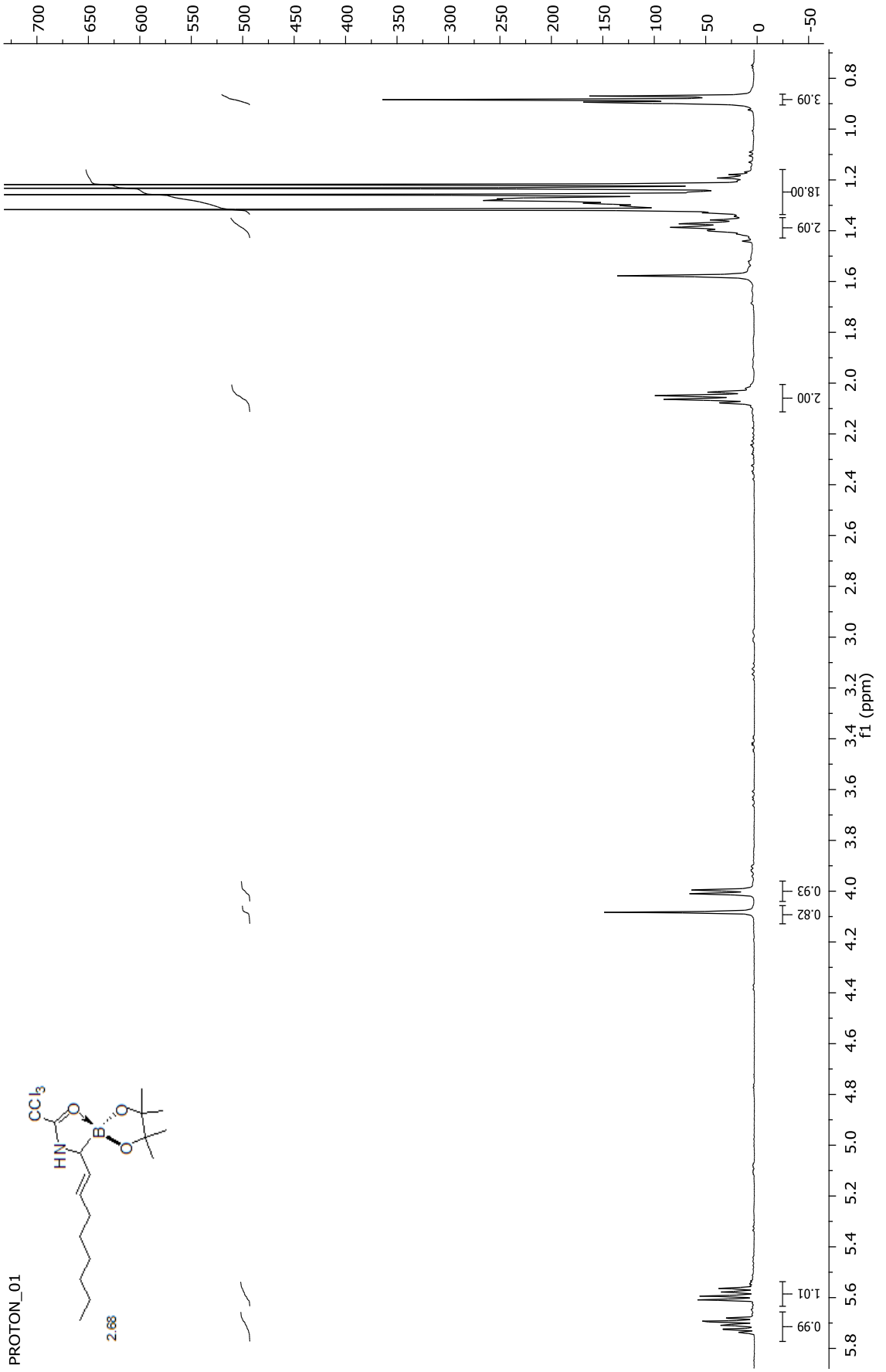

CARBON_01
TBDMSO
6.1
-4.81
-4.18
17.96
25.83
28.54
29.34
36.39
48.43
72.44
72.93
76.41
121.36
129.64
134.56
139.01
139.19
140.79
205.57
f1 (ppm)

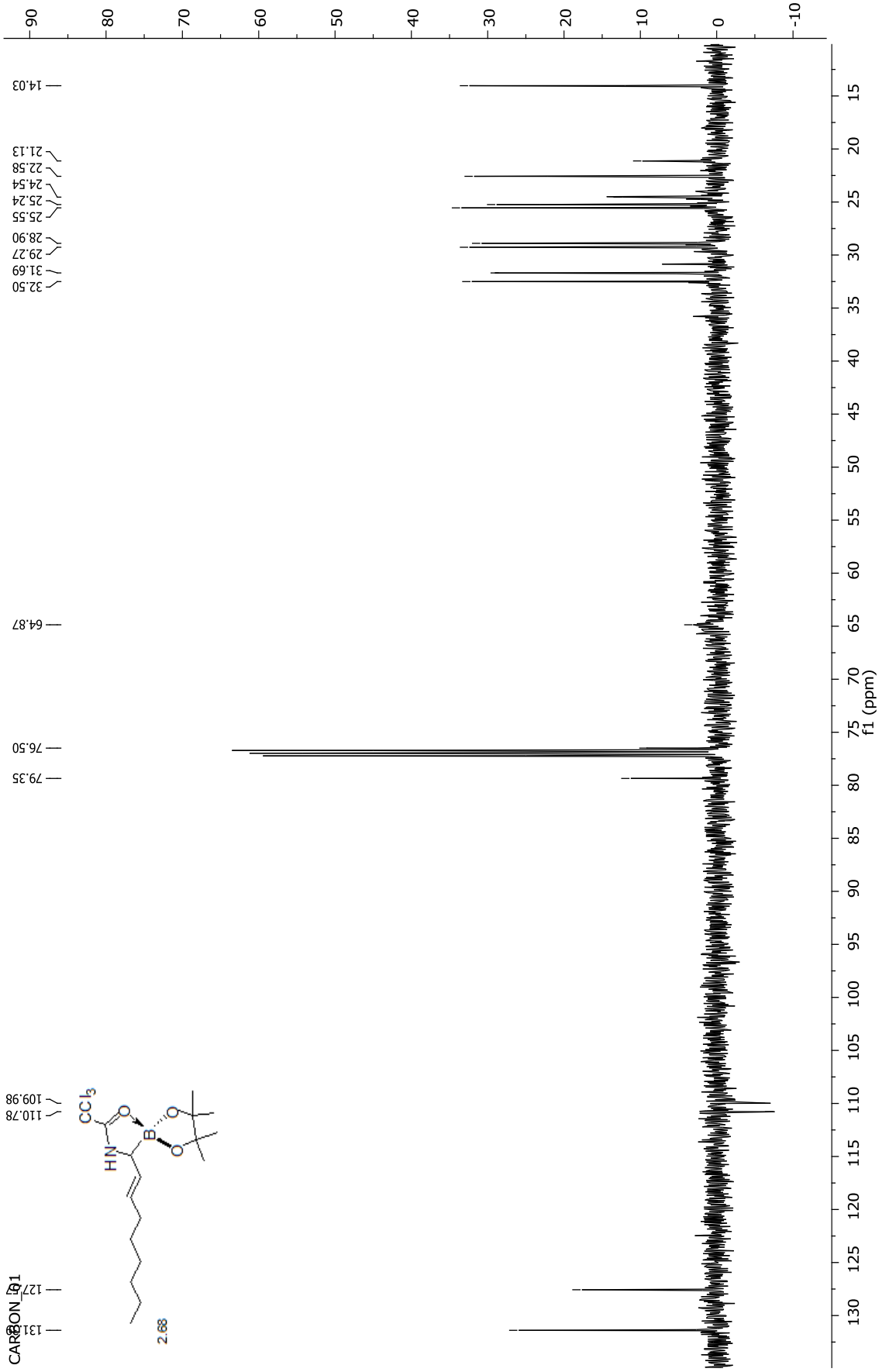

PROTON_01
TBDMSO
BocN
O
2.45
f1 (ppm)
5.84
8.92
9.00
1.24
3.17
1.23
1.19
1.24
2.07
3.15
1.24
1.02
1.08


CARBON_01
TBDMSO
BocN
O
2.45
f1 (ppm)
-4.95
-4.10
18.01
25.89
25.94
28.54
28.58
29.34
36.43
48.43
51.26
51.31
76.60
79.45
123.18
129.79
132.90
136.68
139.96
140.65
154.58
205.48


PROTON_01
TBDMSO
MeO2C
MeO2C
6.53
O
f1 (ppm)
6.00
9.08
1.19
3.04
1.18
1.16
1.15
5.26
6.94
1.07
1.08


CARBON_01
TBDMSO
MeO2C
MeO2C
6.53
206.09
172.37
172.06
141.02
140.88
139.69
135.57
129.20
124.80
76.51
60.53
52.91
52.81
48.60
40.08
38.82
36.10
29.30
28.50
25.86
17.99
-4.06
-4.70
f1 (ppm)


PROTON_01
2.68
f1 (ppm)
3.09
18.00
2.09
2.00
0.93
0.82
1.01
0.99


14.03
21.13
22.58
24.54
25.24
25.55
28.90
29.27
31.69
32.50
64.87
76.50
79.35
109.98
110.78
127.
131.
CARBON_01
2.68
f1 (ppm)