University of Sussex

Investigation of Novel Thermal Cyclisation Reactions and Studies on their Application to the Synthesis of Selected Natural Products

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Doctor of Philosophy

School of Life Sciences

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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:……

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Acknowledgements

First and foremost I would like to thank Professor P.J. Parsons for providing the opportunity and funding to carry my DPhil research under his supervision. Other than an amazing teacher he has always been a great friend to me. I will never forget the numerous fun times we had together.

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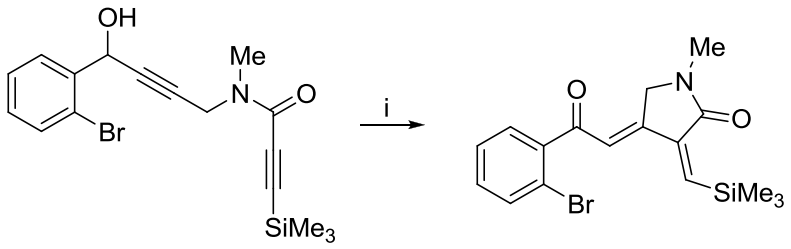
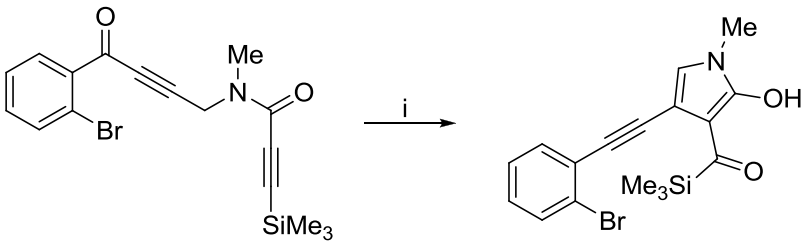
Abstract

The primary goal of this research project was to investigate the mechanism of a novel thermally activated cyclisation reaction discovered by Parsons *et al.* During these studies two novel reactions were discovered:



(2.55) **(2.56)**

Reagents and Conditions: (i) Toluene 0.1M, reflux, 4h, 32%.



(2.60) **(2.61)**

Reagents and Conditions: (i) Toluene, 0.01M, reflux, 4h, 53%

Radical and *ene* pathways for the generation of these products were proposed. However, despite extensive empirical studies, no definitive proof for either mechanism was found. The breadth of the synthetic utility of the above reactions was also investigated by synthesizing various analogues.

The general application of the Parsons' cyclisation to the synthesis of steroid cored and the complex natural product Jiadifenin was also investigated. Advanced intermediates were synthesised and invaluable information on reactivity was gained, however these investigations could not be completed due to time constraints.

Abbreviations

(-)-DIPT: (-)-diisopropyl ($_D$)-tartrate

Boc: *tert*-butoxy carbonyl

bp: boiling point

Calcd.: calculated

CIDNP: chemically induced dynamic nuclear polarization

CTAB: cetyl trimethylammonium bromide

d (NMR): doublet

DCC: *N,N'*-dicyclohexylcarbodiimide

DCM: dichloromethane

DEPT: distortionless enhancement by polarization transfer

dix: disconnection

DMAP: *N*,*N*-dimethylaminopyridine

DMF: *N*,*N*-dimethylformamide

DMSO: dimethylsulfoxide

ee: enantiomeric excess

EI: electron ionisation

eq: equivalent

ESI: electrospray ionisation

FGI: functional group interconversion

h: hour

HMBC: heteronuclear multiple bond correlation

HMPA: hexamethylphosphoramide

HoBt: hydroxybenzotriazole

HOMO: highest occupied molecular orbital

HSQC: heteronuclear single quantum correlation

IR: infrared

LDA: lithium diisopropylamide

LHMDS: lithium bis(trimethylsilyl)amide

LUMO: lowest unoccupied molecular orbital

m (IR): medium

m (NMR): multiplet

m/z: mass to charge ratio

mCPBA: *meta*-chloroperbenzoic acid

min: minute

Ms: mesylate

MW: microwave

NaHMDS: sodium bis(trimethylsilyl)amide

NGF: nerve growth factor

NMR: nuclear magnetic resonance

ORTEP: oak ridge thermal ellipsoid plot program

Ph: phenyl

ppm: parts per million

pTSA: *para*-toluenesulfonic acid

q (NMR): quartet

RF (DNA): replicative form

R_f (TLC): retention factor

rt: room temperature

s (IR): strong

s (NMR): singlet

s: seconds

S_N2: bimolecular nucleophilic substitution

t (NMR): triplet

TBAF: *tetra*-butylammonium bromide

TBS: *tert*-butyldimethylsilyl

TBS-Cl: *tert*-butyldimethylsilyl chloride

TBSOTf: *tert*-butyldimethylsilyl triflate

TEMPO: (2,2,6,6-tetramethylpiperdin-1-yl)oxyl

THF: tetrahydrofuran

TIPS: *tri-iso*propyl silyl

TIPS-OTf: *tri-iso*propyl silyl triflate

TLC: thin layer chromatography

w (IR): weak

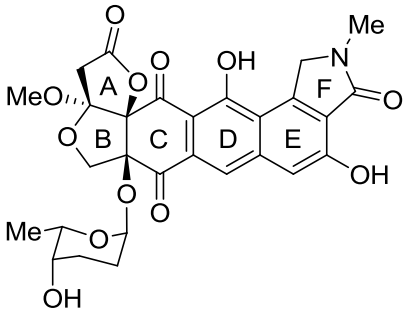
υ_{max}: absorption (IR)

1. Introduction

1.1 A Novel Cyclisation by Parsons *et al.*

1.1.1 Studies Towards the Total Synthesis of Lactonamycin

The potent antibiotic lactonamycin (**1.1**) was first reported by Matsumoto *et al.*[1] who extracted it from *Streptomyces rishiniensis* cultures found in mud samples near Yokohama City, Japan.

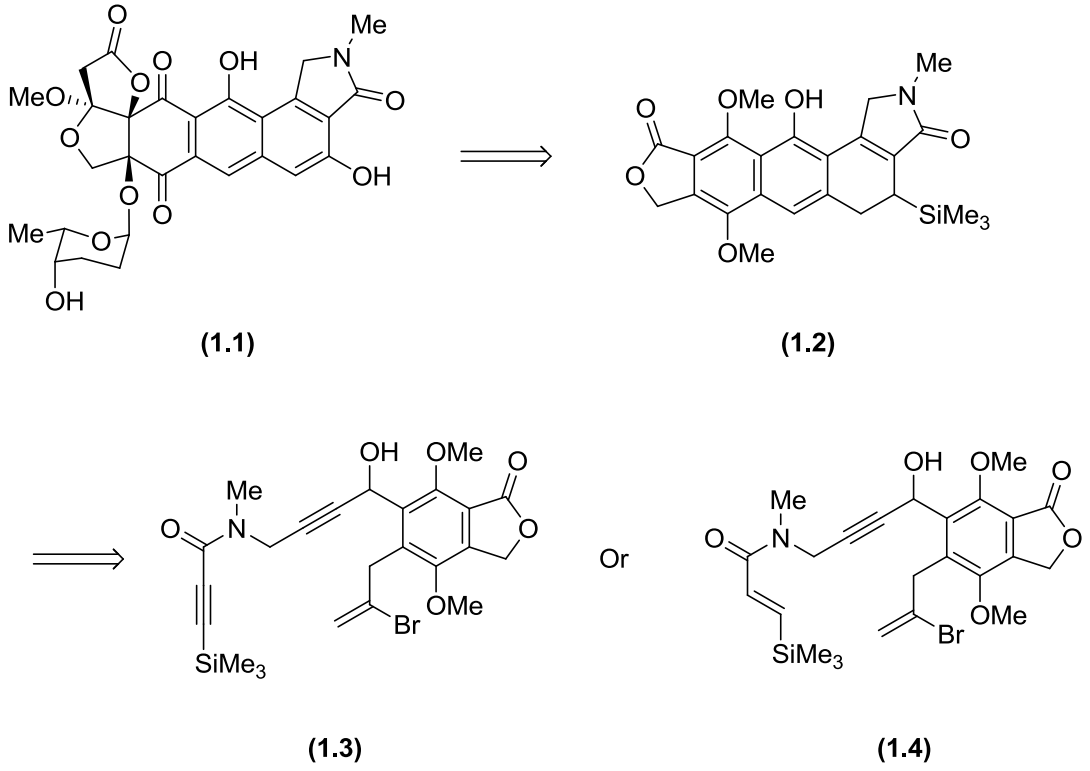


(1.1)

Figure 1.1: Lactonamycin

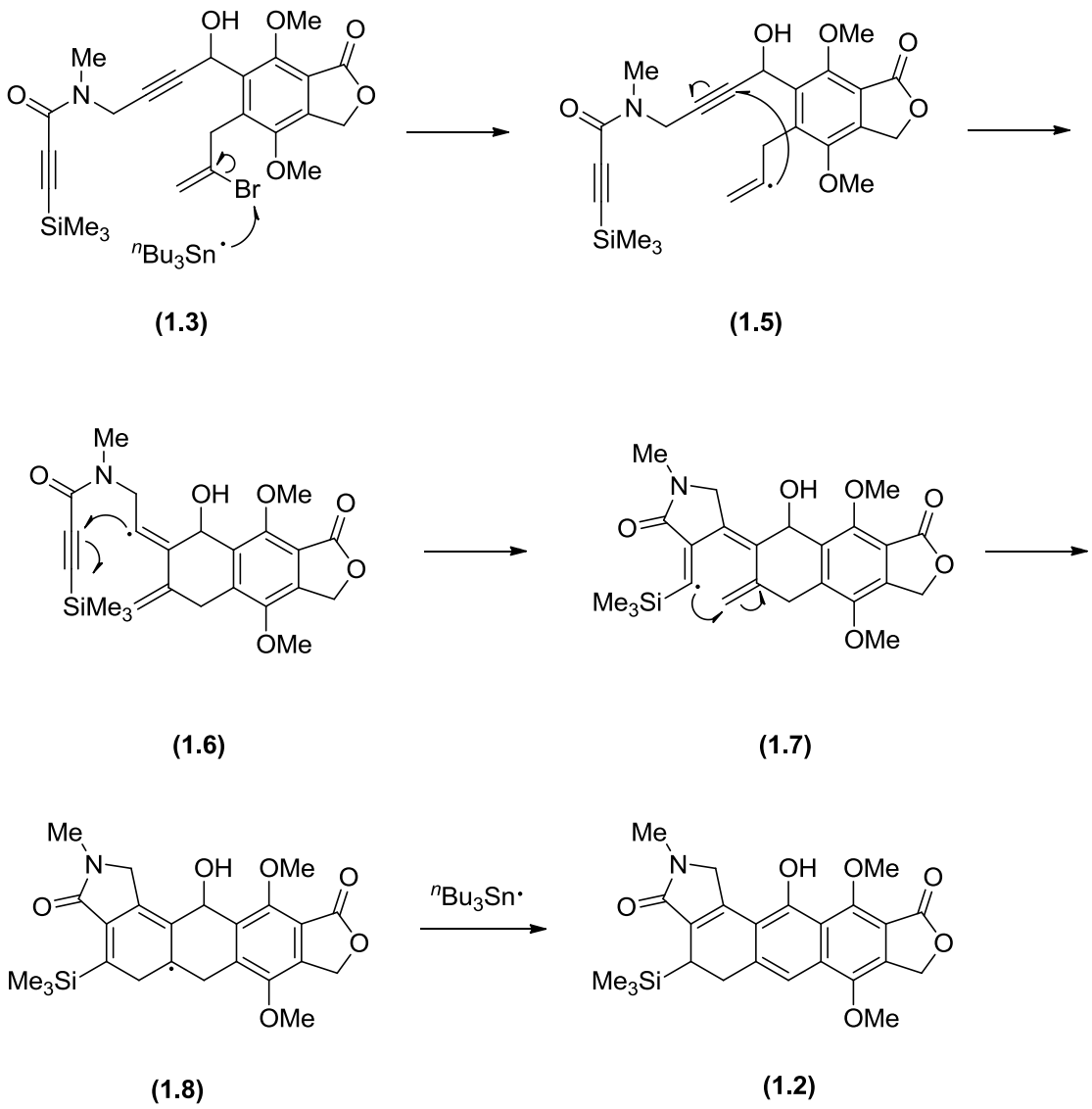
It is active against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[2] In addition, it exhibits antitumor activity against various malignant cancerous cell lines.[2] Because of the complexity of its chemical structure and obvious biological activity, many research groups have embarked in studies to synthesise lactonamycin in the laboratory.[3-7] To this date however only one total synthesis has been achieved.[8]

The Parsons group has been interested in the total synthesis of lactonamycin for some years and originally set out to achieve the construction of the core CDEF fused ring structure in **1.1** by either a palladium[9-11] or radical [12-14] cascade sequence.[15] The chosen retrosynthetic approach is depicted in **Scheme 1.1** below.



Scheme 1.1: Retrosynthetic Analysis of Lactonamycin by Parsons

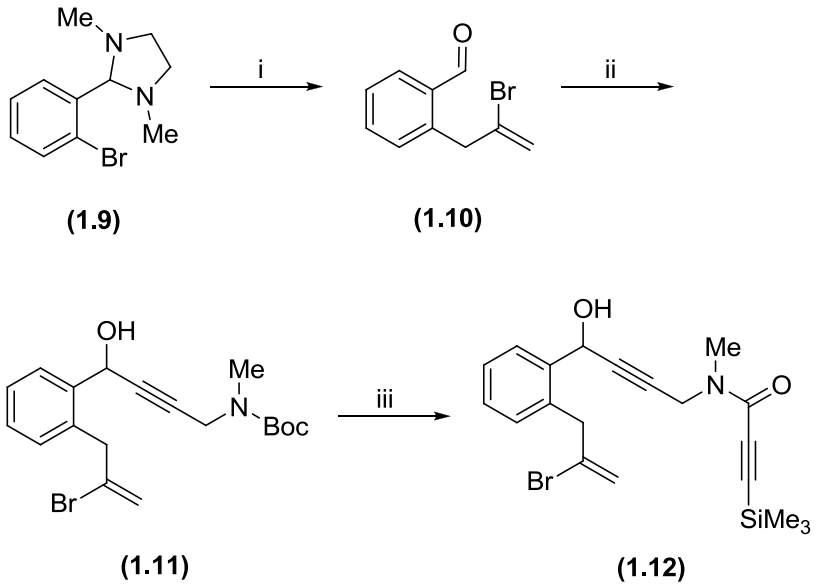
Advanced intermediate **1.2** would therefore be conveniently accessed by a single synthetic manipulation of **1.3**. The proposed tri-*n*-butyltin radical-mediated mechanism leading to **1.2** is shown below in **Scheme 1.2**.



Scheme 1.2: Mechanism of Radical Cascade with Tri-*n*-butyltin Hydride

The pre-generated tri-*n*-butyltin radical performs a halogen abstraction on **1.3** to generate alkynyl radical **1.5**. A series of favourable 6-*exo*-dig (**1.5**), 5-*exo*-dig (**1.6**) and 6-*endo*-trig (**1.7**) cyclisations yield allyl radical **1.8**; aromatisation of the scaffold is then achieved by action of tri-*n*-butyltin radicals to give **1.2**.

In order to test the feasibility of the above cascade sequence, a model system (**1.12)** was synthesised (**Scheme 1.3**).

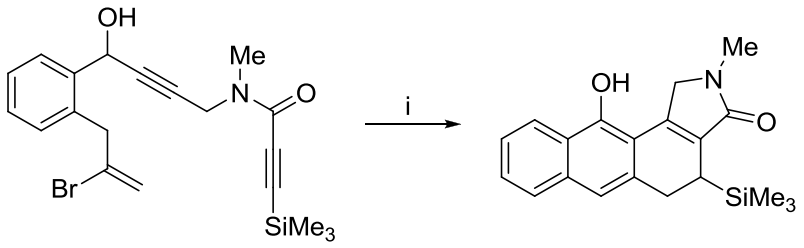


Reagents and Conditions: (i) ^{n}BuLi, CuCN, 2,3-dibromopropene, THF, -78°C to rt then 1M $HCl_{(aq)}$, rt, 73%; (ii) $LiC{\equiv}CCH_2NMeBoc$, ^{t}BuBr, -95°C to rt, 83%; (iii) 2M HCl in diethyl ether, rt, then $Me_3SiC{\equiv}CCOCl$, Et_3N, CH_2Cl_2, rt 79%.

Scheme 1.3: Synthesis of Model Cyclisation Precursor **1.12**

Imidazolidine **1.9** was subjected to lithium-halogen exchange with *n*-butyllithium and the resulting anion reacted with cuprous cyanide to generate a lower-order cyanocuprate. Addition of 2,3-dibromopropene yielded, after an acidic workup, aldehyde **1.10** which was subsequently reacted with the lithium salt of boc-protected *N*-methylpropargyl amine to give propargylic alcohol **1.11**. Hydrogen chloride-mediated BOC deprotection followed by coupling of the resulting amine with trimethylsilylpropioloyl chloride gave desired precursor **1.12**.

This material was subjected to two different radical-mediated cyclisation conditions (**Table 1.1**). [16]



(1.12) **(1.13)**

Reagents and Conditions: (i), Benzene, reflux, **radical initator**, **time**, see **Table 1.1**.

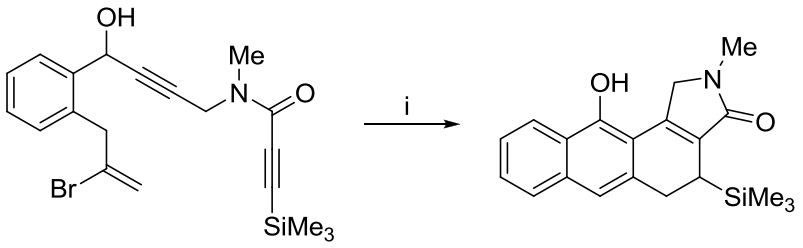
Entry	Radical initiator	Time (h)	Yield (%)
1	^{n}BuSnH / AIBN	11	14
2	$(Me_3Si)_3SiH$	72	22

Table 1.1: Radical Cyclisations of **1.12**

Tris(trimethylsilyl)silane [17] gave better results than tri-*n*-butyltin hydride. However both reactions were found to be afflicted by extensive decomposition of reagents/products. In order to identify the cause of this issue a thermal decomposition study was carried out by boiling **1.12** alone in benzene for 40 hours. Astonishingly this procedure yielded tetracycle **1.13** in 26% yield, higher than with any radical initiators previously employed.

1.1.2 The Discovery of a New Thermally Activated Cyclisation Reaction

As it appeared that the reaction is thermally activated, different solvents and temperatures were tested for the newly discovered transformation (**Table 1.2**). [16]



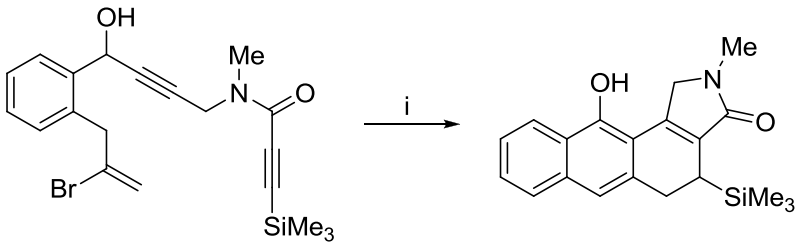
(1.12) **(1.13)**

Reagents and Conditions: (i) **Solvent**, **time**, see **Table 1.2**.

Entry	Solvent	Boiling temperature (°C)	Time	Yield (%)
1	Benzene	80	48 h	26
2	THF	66	144 h	35
3	Toluene	110	2 h	41
4	DMF	153	30 min	63
5	Diglyme	162	30 min	23
6	DMSO	189	15 min	-

Table 1.2: Different Conditions Tested for the Thermolysis of **1.12**

The best results were obtained using DMF (63% yield) and toluene (41% yield) as solvents (Entries 4 and 3 respectively); both represented a considerable improvement over the reaction with radical initiators. It then occurred to the researchers that the high yield obtained with DMF may be attributed to its tendency to decompose on boiling to small amounts of dimethylamine [18] which would scavenge reactive hydrogen bromide generated during the reaction. To test this hypothesis, **1.12** was heated in boiling toluene in the presence of methyl oxirane, an efficient acid trap first employed by Corey *et al.* during their total synthesis of gibberellic acid.[19] The higher boiling equivalents cyclohexene oxide and butyl oxirane were also tested and the results obtained are summarised in **Table 1.3** below.[16]



(1.12) **(1.13)**

Reagents and Conditions: (i) Toluene, reflux, **acid trap**, **time**, see **Table 1.3**.

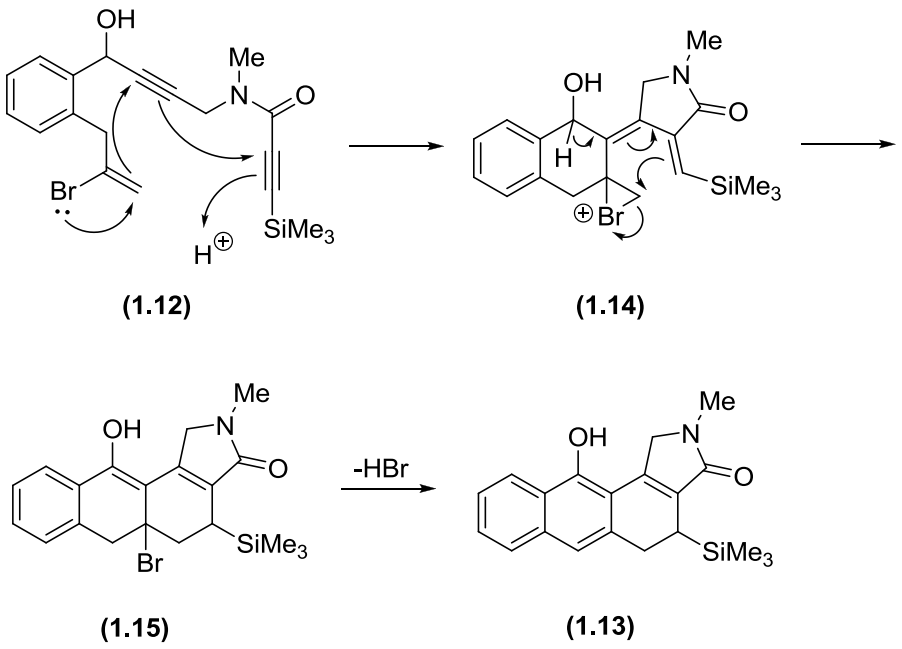
Entry	Acid Trap	Time (h)	Yield (%)
1	Methyl oxirane	3.5 h	44
2	Cyclohexene oxide	2.5 h	64
3	Butyl oxirane	3 h	76

Table 1.3: Different Acid Traps Tested for the Thermolysis of **1.12**

Methyl oxirane gave only a slightly improved yield over the corresponding reaction in toluene alone. This was attributed to its low boiling point (bp 34°C [20]) which causes its evaporation from the reaction mixture[16]. A marked improvement was seen with cyclohexene oxide (129-130°C [21]), while butyl oxirane (118-120°C [22]) gave the best yield. This was clear evidence that in the absence of acid traps, the starting material/products of the reaction are decomposed by hydrogen bromide generated in solution.

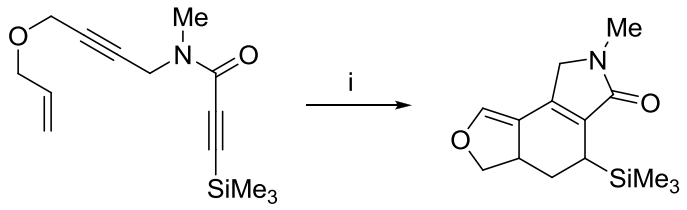
1.1.3 Mechanistic Investigations

Initially an acid-catalysed mechanism for the cyclisation of **1.12** was proposed [16] (**Scheme 1.4**).



Scheme 1.4: Proposed Acid-Catalysed Mechanism for the Formation of **1.13**

Intramolecular attack of the aryl alkenyl portion by the bromine lone pairs is followed by 6-*exo*-dig and 5-*exo*-dig cyclisations to yield **1.14** after acquisition of a proton. The construction of the tetracyclic structure is then completed by opening of the cyclic bromonium ion and aromatisation by loss of hydrogen bromide in **1.15**. This postulate however was in clear contrast with the notion that the cyclisation works better in the presence of acid scavengers. Further dismissal of the acid-catalysed mechanistic hypothesis came when precursor **1.16**, which lacks bromine atoms in its structure, was also successfully cyclised in base-washed glassware (**Scheme 1.5**). [15,23]

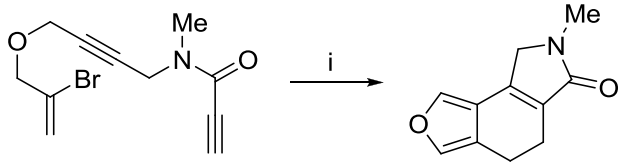


(1.16) **(1.17)**

Reagents and Conditions: (i) Toluene, reflux, 1h, 91%.

Scheme 1.5: Cyclisation in the Absence of a Bromine Atom

Another piece of information gathered by the researchers was that when **1.18** was heated in boiling toluene, tricycle **1.19** was formed in 97% yield (**Scheme 1.6**).[15] A longer reaction time of 13 hours was required to achieve cyclisation in the absence of a trimethylsilyl group.

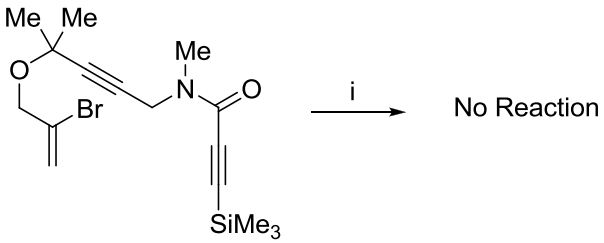


(1.18) **(1.19)**

Reagents and Conditions: (i) Toluene, reflux, 13h, 97%.

Scheme 1.6: Cyclisation with no Silicon Atom in the Molecule

Further structural manipulations of cyclisation precursors revealed that installing a *gem*-dimethyl group α to the ether functionality as in **1.20** (**Scheme 1.7**) prevents the cyclisation from taking place.[24]

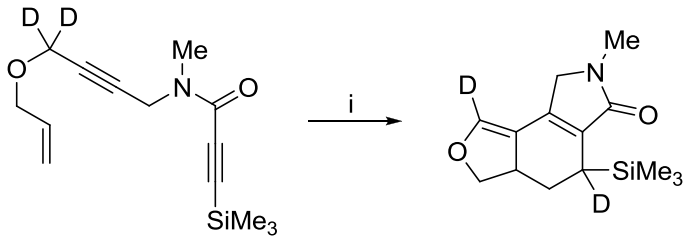


(1.20)

Reagents and Conditions: (i) Toluene, reflux, 72h.

Scheme 1.7: Failed Reaction of **1.20**

In order to investigate the vital role of the hydrogen atoms α to the ether functionality in **1.16**, deuterated compound **1.21** was subjected to heating in refluxing toluene (**Scheme 1.8**). [24,25]



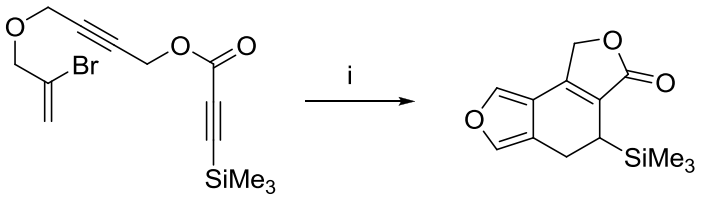
(1.21) **(1.22)**

Reagents and Conditions: (i) Toluene, reflux, 3.5h, 94%.

Scheme 1.8: Cyclisation of Deuterated Compound **1.21**

Analysis of the product revealed that a 1,5-deuterium shift had occurred.

The role of the amide linkage was also investigated. To this end ester **1.23** was constructed and then heated in refluxing toluene (**Scheme 1.9**).[23]



(**1.23**) (**1.24**)

Reagents and Conditions: (i) Toluene, epoxyhexene, reflux, 52h, 76%.

Scheme 1.9: Cyclisation of Ester Analogue

Interestingly it was noted that the ester linkage causes the rate of reaction to significantly decrease. A similar observation had previously been described by Parker *et al.*[26] during studies on the intramolecular Diels-Alder reaction of amides and esters.

The following is a summary of the notions gathered by the Parsons group on the novel cyclisation reaction:

i) The reaction works in the absence of radical initiators and is thermally activated

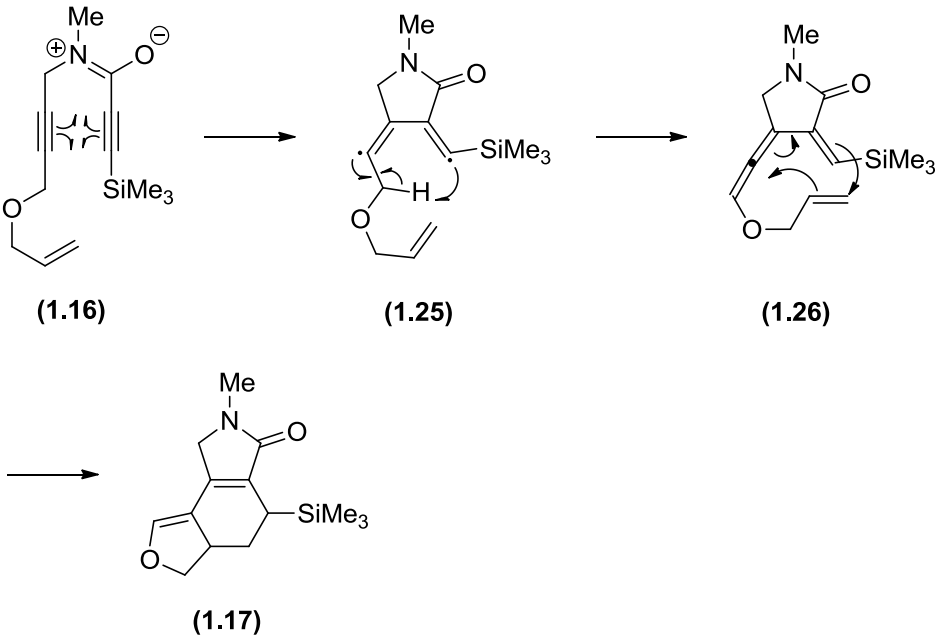
ii) The mechanism is not acid-catalysed

iii) The presence of a silicon atom at the ynone functionality accelerates the reaction

iv) The presence of one or more propargylic protons is essential

v) A 1,5-hydrogen shift occurs during the course of the reaction

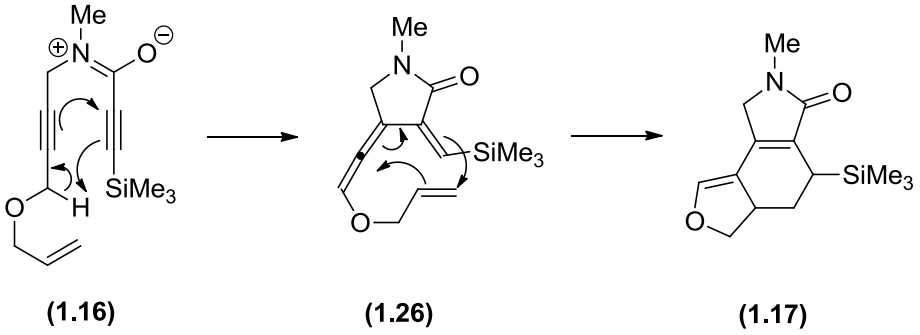
Particular weight was given to the fact that the precursor without a silicon functionality **1.18** cyclises slowly. Silicon is known to stabilise α-radicals through vicinal (d-p) π overlap [27,28] and therefore its presence would increase the rate of a reaction involving radical intermediates. Also the cyclisation precursors synthesised by Parsons *et al.* were similar to substrates involved in the Bergman, Myers-Saito and Schmittel cyclisations. These notions spurred the formulation of a radical mechanism [25], shown in **Scheme 1.10** for the cyclisation of precursor **1.16**.



Scheme 1.10: Proposed Radical Mechanism for the Formation of **1.17**

Amide resonance in **1.16** would bring the two acetylene moieties close in space and this could trigger a radical cyclisation with consequent generation of biradical **1.25**. A 1,5-hydrogen abstraction would then ensue giving allenol ether **1.26**, which would then undergo an intramolecular Diels-Alder reaction to yield observed product **1.17**.

An ene-mechanism was also formulated[25] and is depicted in **Scheme 1.11** for the cyclisation of precursor **1.16**.



Scheme 1.11: Proposed Ene-Mechanism for the Formation of **1.17**

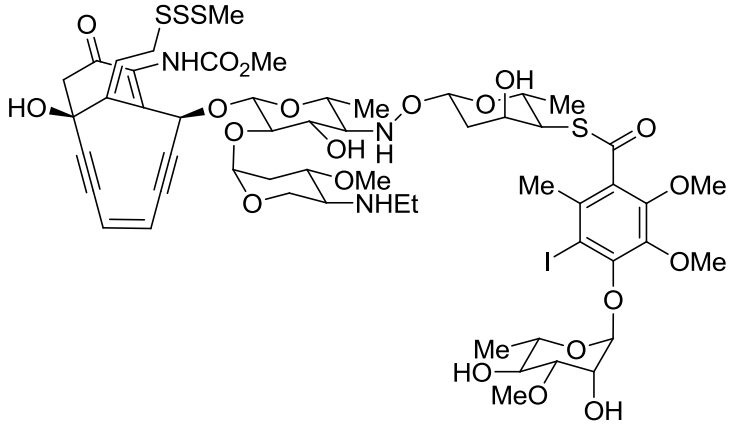
A propargylic-ene reaction could take place in **1.16** generating intermediate **1.26** in a single mechanistic step. As for the postulated radical mechanism in **Scheme 1.10** a Diels-Alder reaction in **1.26** would follow generating product **1.17**.

Previous to the commencement of the work described in the results and discussion section of this thesis (**Chapter 2**) no definitive evidence was gathered by Parsons *et al.* in favour of either mechanism.

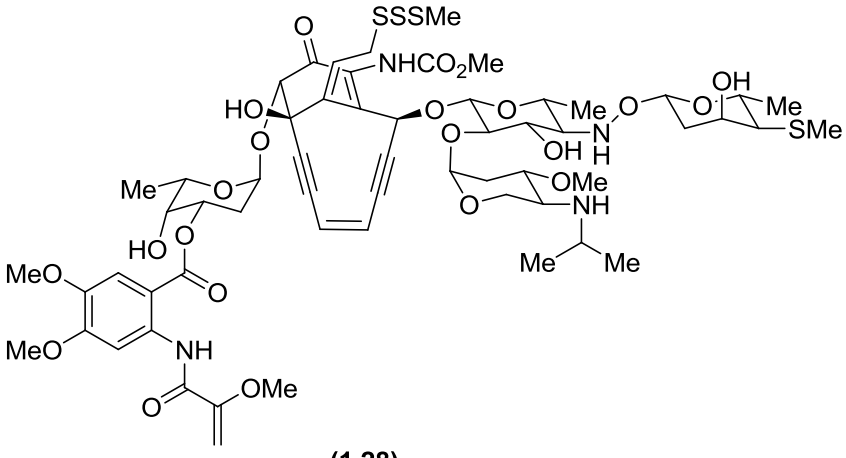
1.2 Metal-Free Radical Cyclisations

1.2.1 Enediyne Antibiotics

The term enediyne gained notoriety in 1987 with the elucidation of the chemical structure of the antibiotic and antitumor agents calicheamicins [29,30] (**1.27**: calicheamicin γ^{I}_{1}, **Figure 1.2**) and esperamicins [31-33] (**1.28**: esperamicin A_1, **Figure 1.2**).



(1.27)

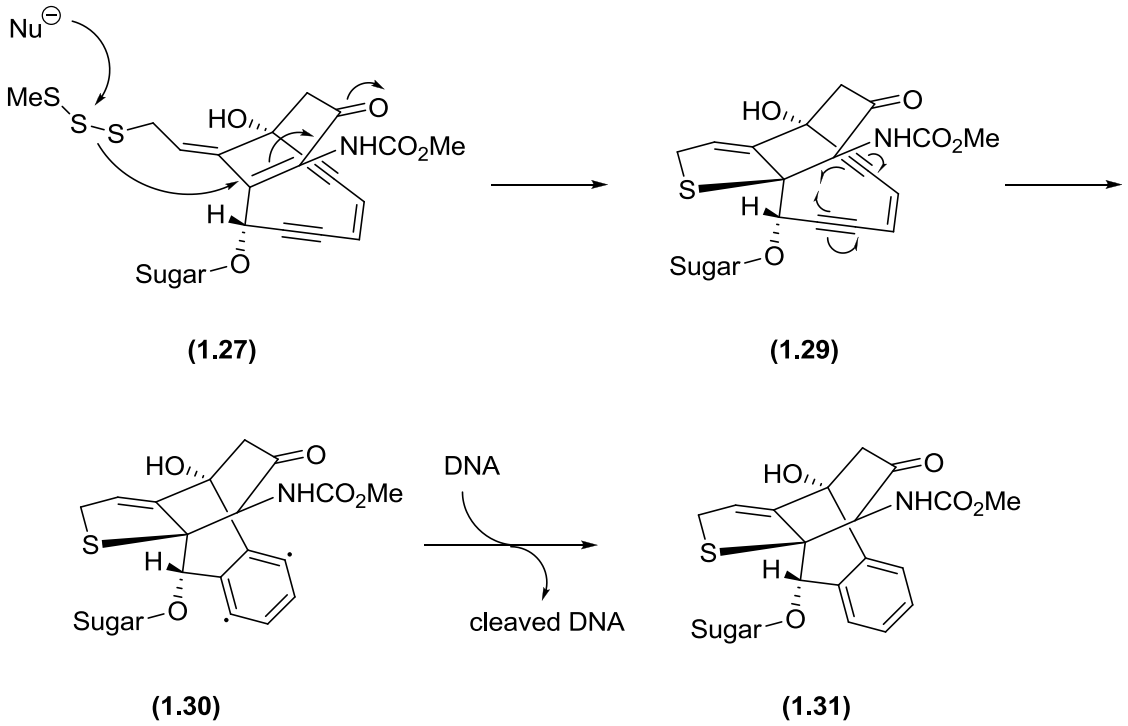


(1.28)

Figure 1.2: Calicheamicin γ^{I}_{1} (**1.27**) and Esperamicin A_1 (**1.28**)

Calicheamicin γ^{I}_{1} **1.27** is extremely active against Gram-negative bacteria, highly active against Gram-positive bacteria and shows extraordinary potency against various murine tumors such as

P338 and L1210 leukemias and solid neoplasms such as colon 26 and B-16 melanoma.[29,30] Esperamicin A_1 **1.28** has been shown to posses potent anticancer activity against the very same murine tumors.[31,32] Both **1.27** and **1.28** are thought to exert their biological activity by effectively damaging DNA strands.[34,35] Their structure is divided into an oligosaccharide fragment which is presumed to serve as a delivery system and an enediyne moiety which, upon activation in the body, exerts the biological activity observed.[34,35] The mechanism of DNA cleavage by calicheamicin γ^{I}_1 is depicted in **Scheme 1.12** below.



Scheme 1.12: Mechanism of Activation and Subsequent DNA Cleavage by Calicheamicin γ^{I}_1

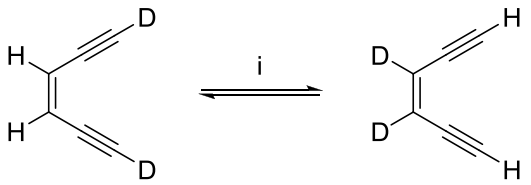
The first step in the mechanism is the selective coordination of calicheamicin γ^{I}_1 **1.27** to TCCT sites on DNA strands using its oligosaccharide tail for specific recognition.[34,35] A nucleophile such as glutathione then attacks the trisulfide group in **1.27** leading to the formation of a thiolate anion which undergoes conjugate addition with the enone moiety thus forming tricyclic structure **1.29**. The resulting conformational change causes a shortening of the distance between the two acetylene portions of the enediyne moiety which triggers a cyclization yielding biradical

intermediate **1.30**. This highly reactive intermediate is then capable of abstracting hydrogen atoms from DNA therefore causing its destruction.[34,35]

At the time of the elucidation of the structures of calicheamicin γ^{I}_{1} **1.27** and esperamicin A_1 **1.28** the ability of enediynes to undergo spontaneous cyclisation yielding biradical intermediates was not a new concept; in fact it had been discovered fifteen years earlier in the laboratories of Robert G. Bergman.

1.2.2 The Bergman Cyclisation

In 1972 Bergman and Jones described the unusual scrambling of deuterium labeling in **1.32** upon pyrolysis (**Scheme 1.13**).[36]

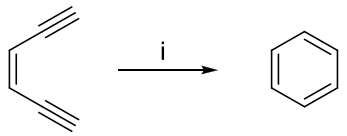


(1.32) **(1.33)**

Reagents and Conditions: (i) Neat, 300°C

Scheme 1.13: First Observation by Bergman and Jones

It was then observed that when cis-1,5-hexadiyn-3-ene **1.34** was heated in 2,6,10,14-tetramethylpentadecane at 200°C in 0.01M concentration, benzene **1.35** is generated (**Scheme 1.14**).[36,37]

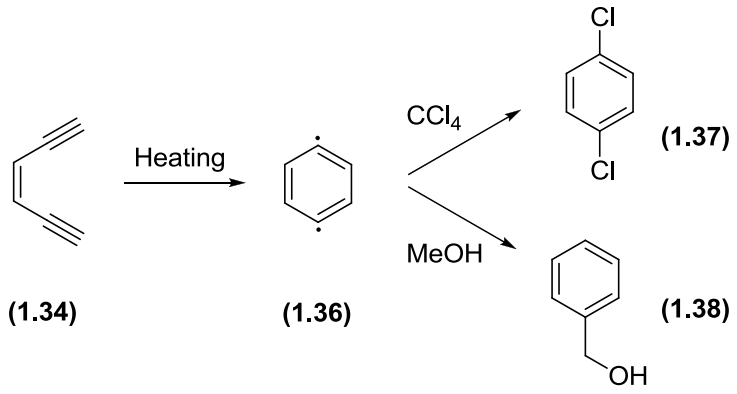


(1.34) **(1.35)**

Reagents and Conditions: (i) 2,6,10,14-tetramethylpentadecane, 200°C, 0.01M

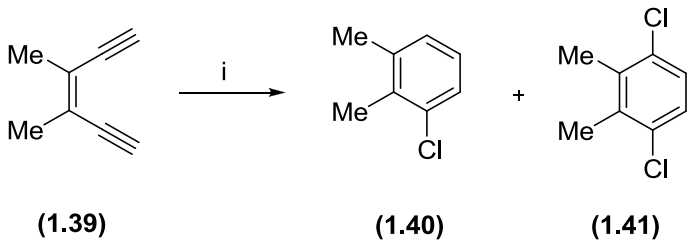
Scheme 1.14: The First Reported Bergman Cyclisation

It was deduced that during an intermediate step in the above reaction two hydrogen atoms are abstracted from the solvent and that the only species able to perform this transformation are organic radicals.[37] Biradical **1.36** (**Scheme 1.15**) was proposed as an intermediate and its presence during the course of the reaction was proved by trapping studies with carbon tetrachloride and methanol.[37]



Scheme 1.15: Trapping of 1,4- Benzendiyl **1.36** by Bergman

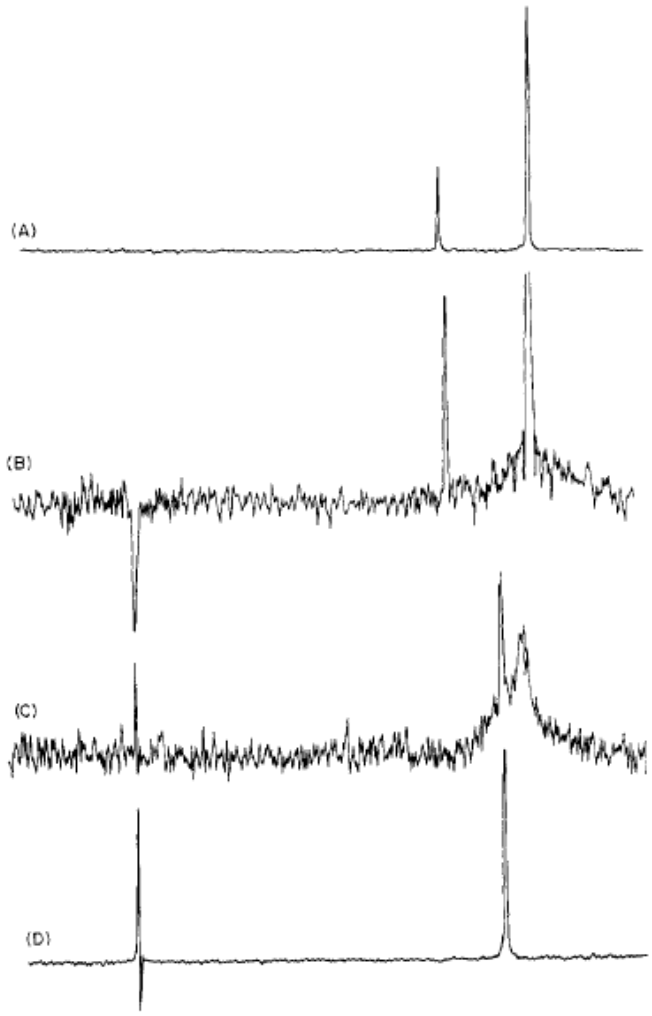
Further support for the biradical theory was then provided by the observation of a CIDNP [38,39] effect (**Figure 1.3**) during the thermolysis of **1.39** in a hexachloroacetone/cyclohexadiene-d_4 solvent mixture (**Scheme 1.16** and **Figure 1.3**). [40,41]



(1.39) **(1.40)** **(1.41)**

Reagents and Conditions: (i) Hexachloroacetone, cyclohexadiene-d_4, 160°C, relative yield **1.40:1.41**: 1:3

Scheme 1.16: Bergman Cyclisation of **1.39** in Hexachloroacetone/Cyclohexadiene-d_4

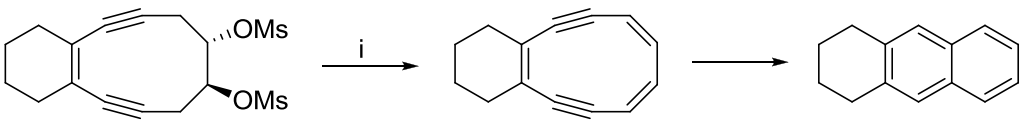


(A) NMR solution before reaction; (B) Signals observed during reaction at 160°C; (C) Room-temperature spectrum after complete reaction of **1.39**; (D) Spectrum of **1.41** in carbon tetrachloride

Figure 1.3: CIDNP Effect Observed by Bergman during Reaction of a Hexachloroacetone/ Cyclohexadiene-d_4 Solution of **1.39** [41]

The presence of an inverted emission signal in spectrum B in **Figure 1.3** was a clear indication of the intermediacy of a radical species.

Prior to the discovery of the Bergman cyclisation, Masamune *et al.* [42] described the conversion of enediyne **1.42** into a benzenoid system, but without mentioning the involvement of a biradical system (**Scheme 1.17**).



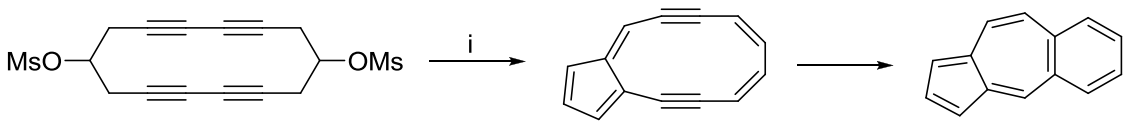
(1.42) **(1.43)** **(1.44)**

Reagents and Conditions: (i) NaOMe, solvent

Scheme 1.17: Work by Masamune *et al.*

The conversion from **1.43** to **1.44** is likely the result of a Bergman cyclisation.

In 1966 Mayer and Sondheimer [43] described the rearrangement of **1.45** to **1.47** (**Scheme 1.18**) which is also likely to involve a reaction similar to the Bergman cyclisation and a biradical intermediate.



(1.45) **(1.46)** **(1.47)**

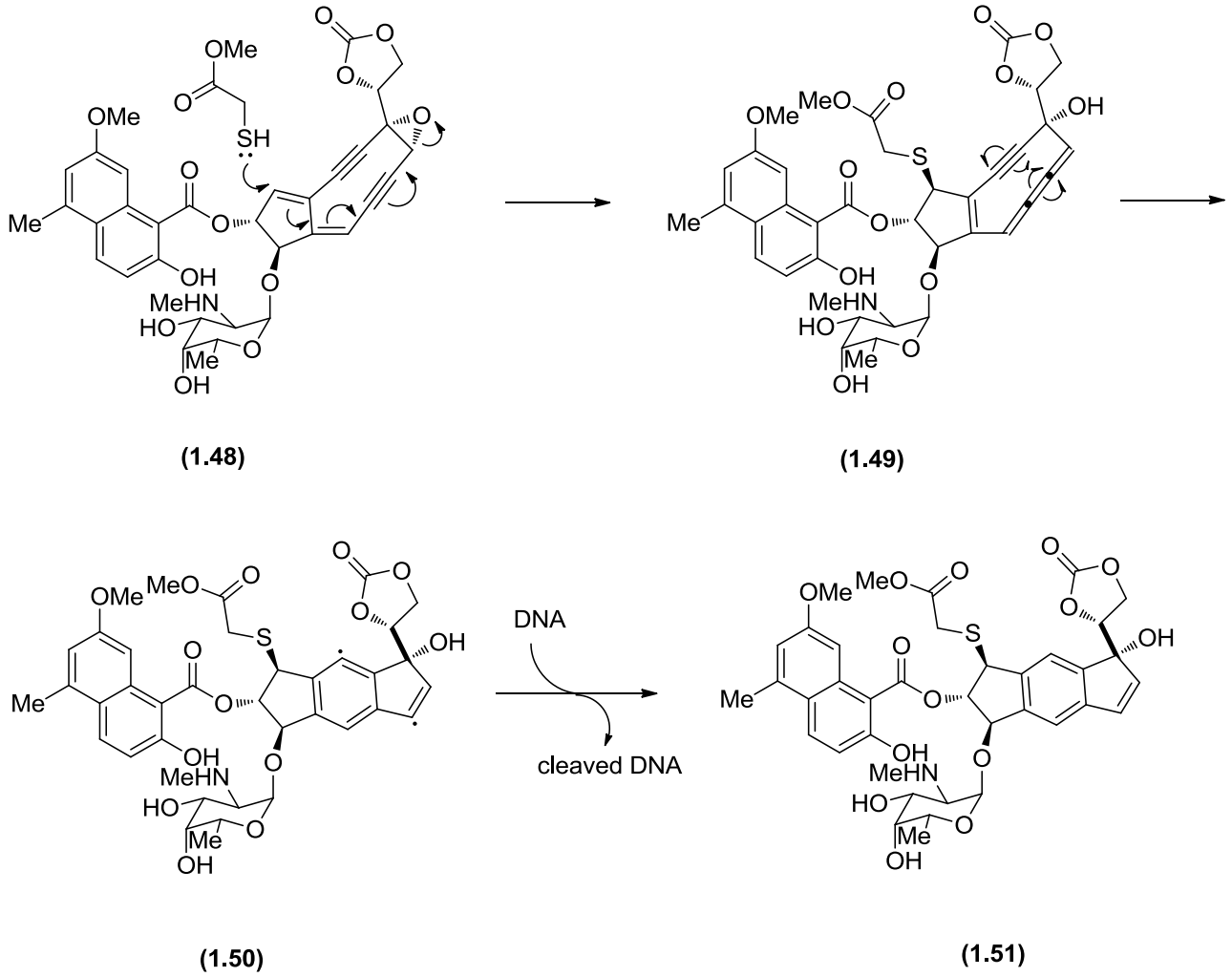
Reagents and Conditions: (i) DMSO, MeOH, 7% $KOH_{(aq.)}$, reflux, 15min, 34%.

Scheme 1.18: Work by Mayer and Sondheimer

1.2.3 The Myers-Saito Cyclisation

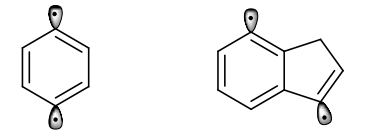
Neocarzinostatin **1.48** (**Scheme 1.19**) is another powerful antibiotic first isolated from *Streptomyces carzinostaticus* by Ishida *et al.* in 1965.[44] Its structure was elucidated in 1985 by Edo *et al.* [45]

In 1987 Myers [46] shed light on the mechanism of DNA cleavage by neocarzinostatin. He proposed that upon reaction of **1.48** with methyl thioglycolate, activation of the chromophore leads to the formation of enyne cumulene **1.49** which subsequently undergoes cyclization to yield biradical species **1.50**. Supposedly, it is this species that causes destruction of DNA strands and is therefore responsible for the biological activity of neocarzinostatin.



Scheme 1.19: Mechanism of DNA Cleavage by Neocarzinostatin

Specie **1.50** resembles the 1,4-benzenediyl biradical involved in the Bergman cyclisation. In both cases the unpaired electrons reside in two *s*-orbitals (**Figure 1.4**).

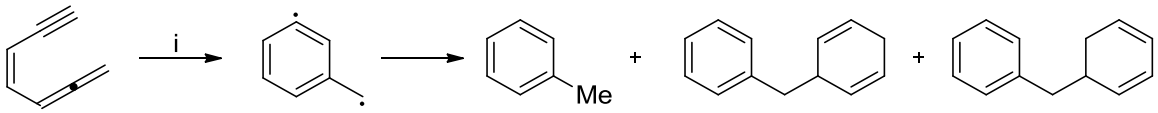


(1.36) **(1.52)**

Bergman Neocarzinostatin

Figure 1.4: Similarity Between 1,4-Benzenediyl Biradical in the Bergman Cyclisation and the Biologically Active Intermediate of Neocarzinostatin

Intrigued by this newly discovered reaction, Myers decided to test the thermal cyclisation on simple enyne-allene system **1.53**. An interesting reaction between the acetylene and allene portions was observed with formation of products **1.55**, **1.56** and **1.57.** Their isolation was attributed to the intermediacy of biradical **1.54** (**Scheme 1.20**). [47] [48]

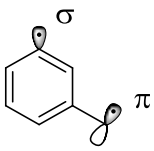


(1.53) **(1.54)** **(1.55)** **(1.56)** **(1.57)**

Reagents and Conditions: (i) 1,4-Cyclohexadiene, reflux, 0.003M, **1.55**: 60%, **1.56**: 20%, **1.57**: 20%

Scheme 1.20: First Reported Myers Cyclisation

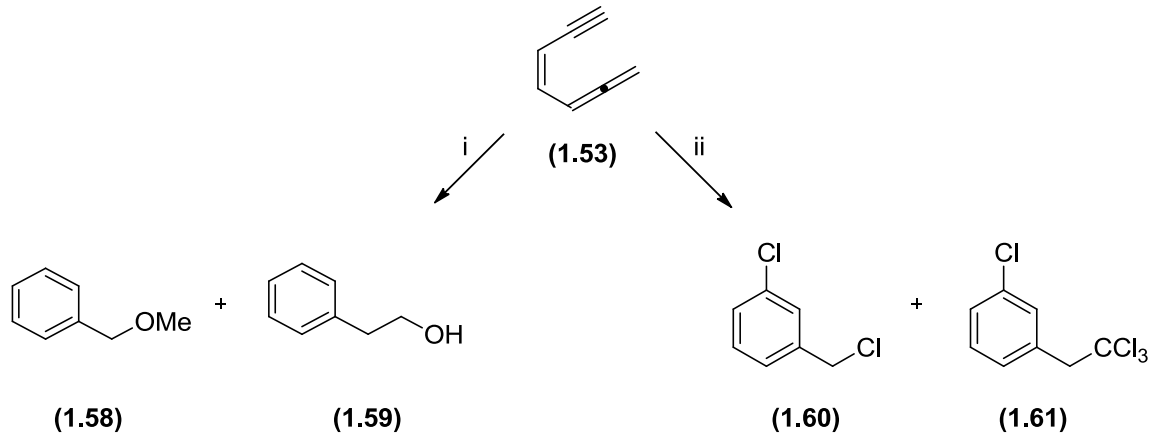
The above transformation was carried in refluxing 1,4-cyclohexadiene which has a boiling point of 88-89°C.[49] This improved reactivity over the Bergman cyclisation (which possesses a much higher thermal activation barrier) of the now commonly known as Myers-Saito cyclisation has been attributed to the generation of a stabilised benzyl π radical [48] as shown in **Figure 1.5** below.



(1.54)

Figure 1.5: Intermediate σ,π Biradical in the Myers-Saito Cyclisation

Experimental evidence for the formation of biradical system **1.54** was subsequently gathered; thermolysis of **1.53** in methanol and carbon tetrachloride furnished trapped products **1.58**, **1.59**, **1.60** and **1.61** (**Scheme 1.21**). [47]

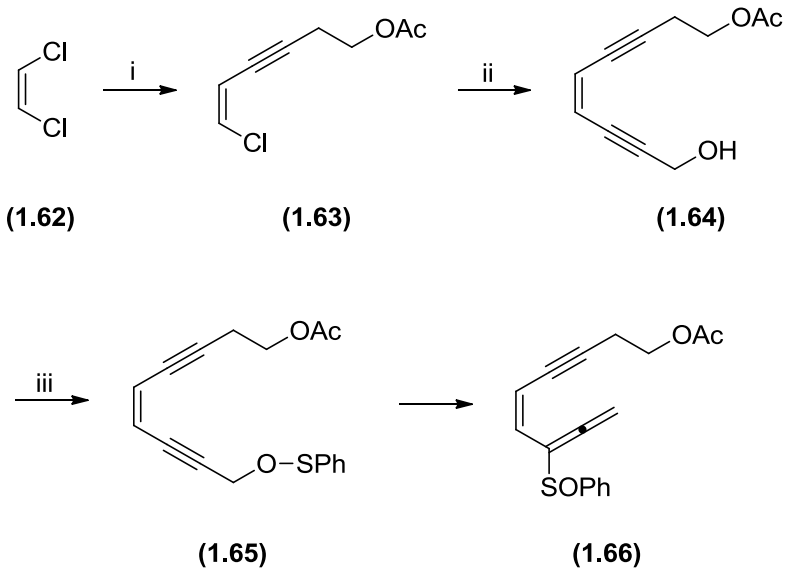


(1.58) (1.59) (1.60) (1.61)

Reagent and Conditions: (i) Methanol, 0.003M, 100°C, 30min, **1.58**: 35%, **1.59**: 10%; (ii): Carbon tetrachloride, 0.003M, 100°C, 30min, **1.60**+**1.61**= 15-25%.

Scheme 1.21: Trapping Studies by Myers *et al.*

The ease of σ,π – radical formation prompted Saito and co-workers to study these systems as potential synthetic antitumor agents.[50] Enyne-allene system **1.66** was constructed via a key [2,3]-sigmatropic rearrangement of intermediate phenyl sulfenate **1.65** [51] as shown in **Scheme 1.22** below.



Reagents and Conditions: (i) $Pd(PPh)_4$, CuI, *n*-propylamine, but-3-ynyl acetate, benzene, 71% (ii) $Pd(PPh)_4$, CuI, *n*-propylamine, propargyl alcohol, benzene, 57% (iii) Benzenesulfenyl chloride, Et_3N, CH_2Cl_2, -78°C to 0°C, 56%

Scheme 1.22: Construction of **1.66** by Saito *et al.*

Sulfoxide **1.66** was found to have a half-life of 16 minutes at 37°C. It was then incubated at different pH and temperatures in the presence of φX_{174} RF I DNA to test its ability to cause its cleavage.[51] This type of DNA is generated by the extraction of DNA from *Escherichia coli* and its treatment with alkali. Chromatographic separation of the residue yields two forms of φX_{174} RF I DNA, RF component I (double DNA strand) and RF component II (single DNA strand).[52] Testing of a DNA-cleaving candidate substance on both individual forms is accepted as providing a simple but good *in vitro* model of activity.[52] The results of the incubation of enyne-allene **1.66** with these two DNA forms are shown in **Table 1.4** below.

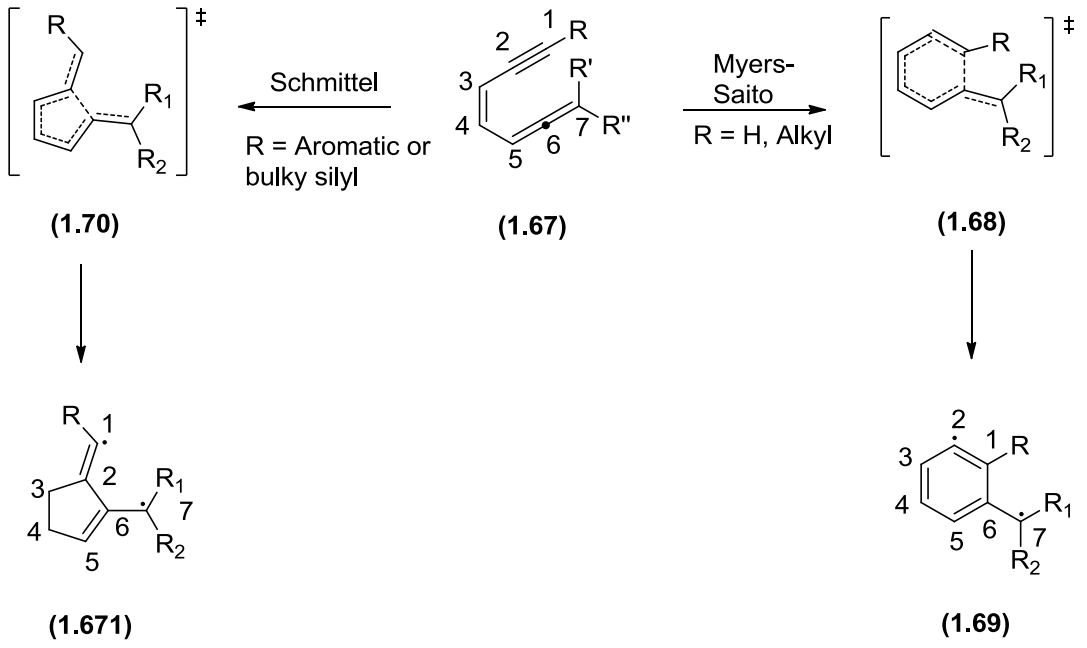
Entry	Concentration of **1.66** (μM)	Conditions	DNA RF component I (% cleavage)	DNA RF component II (% cleavage)
1	100	pH 8.0, 27°C	63	32
2	500	pH 8.0, 27°C	53	42
3	100	pH 4.6, 37°C	67	33
4	500	pH 4.6, 37°C	5	91

Table 1.4: DNA RF Component I and DNA RF Component II Cleavage by Enyne-Allene **1.66**

Saito and co-workers had therefore proved that synthetic enyne-allene **1.66** is effective at cleaving both double stranded and single stranded DNA forms at different pH and temperatures.

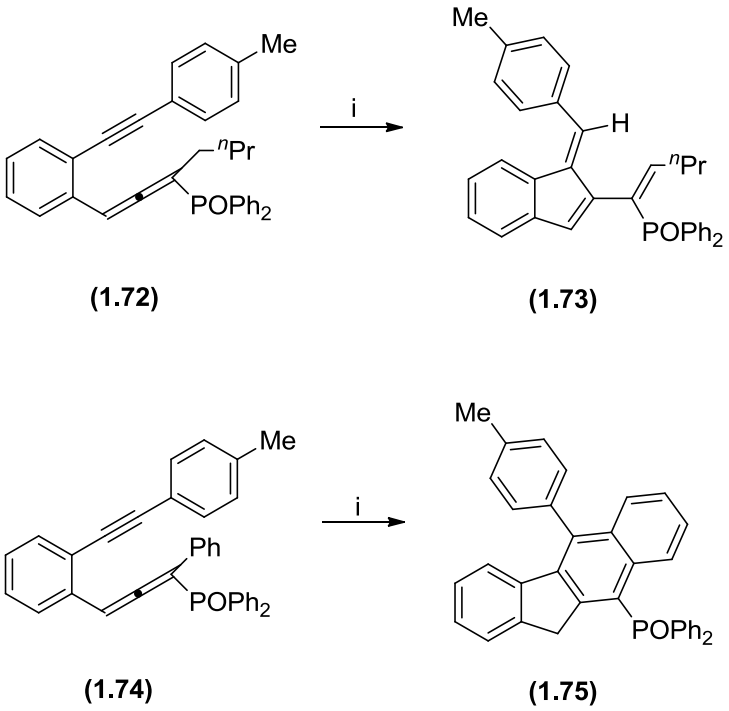
1.2.4 The Schmittel Cyclisation

During investigations of the Myers-Saito cyclization, Schmittel *et al* discovered that switching from an alkyl to an aromatic or bulky silyl substituent at the acetylene terminus of an enyne-allene causes an interesting change in reactivity.[53] Biradical **1.71** was proposed as an intermediate (**Scheme 1.23**).



Scheme 1.23: The Switch from the Myers-Saito to the Schmittel Cyclisation

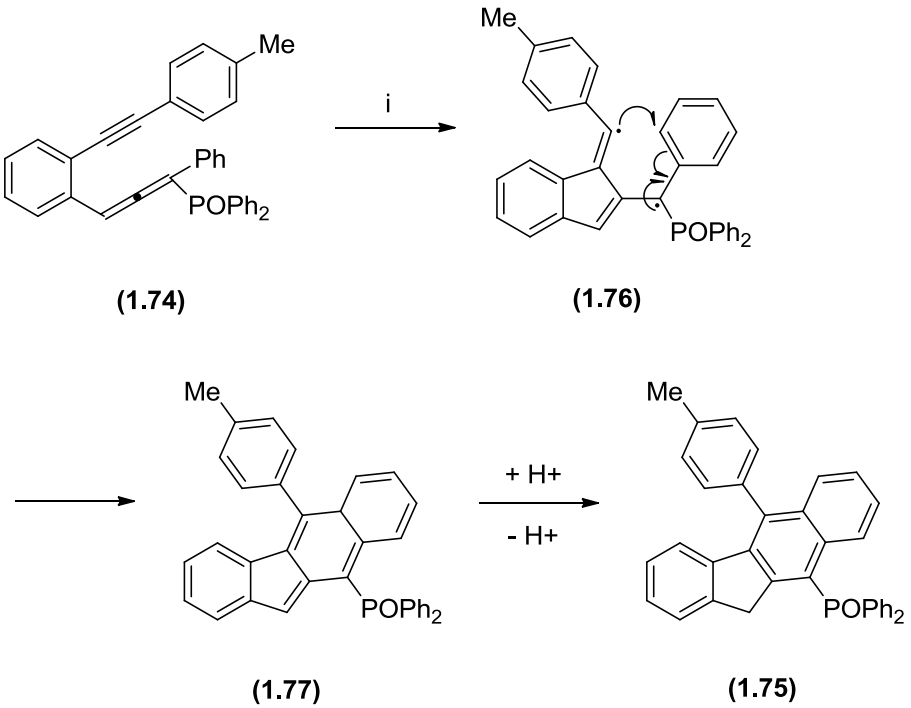
Examples of the cyclisations designed by Schmittel are shown in **Scheme 1.24.**



Reagents and Conditions: (i) 1,4-Cyclohexadiene (excess), benzene, reflux, 1h. **1.73**: 76%, **1.75**: 63%.

Scheme 1.24: Examples of the Work by Schmittel *et al.*

Addition of 1,4-cyclohexadiene was found to be essential; in its absence the yield of cyclization product **1.75** was lowered to 20%. [54] According the Schmittel the role of 1,4-cyclohexadiene is to reduce radical-mediated polymerisation during the course of the reaction.



Reagents and Conditions: (i) Benzene, reflux.

Scheme 1.25: Aromatisation Role of 1,4-Cyclohenxadiene in the Schmittel Cyclisation

Schmittel concentrated on finding a proof for the existence of the supposed intermediate biradical **1.71** (**Scheme 1.23**). He postulated the following arguments in favour of a radical mechanism: [55]

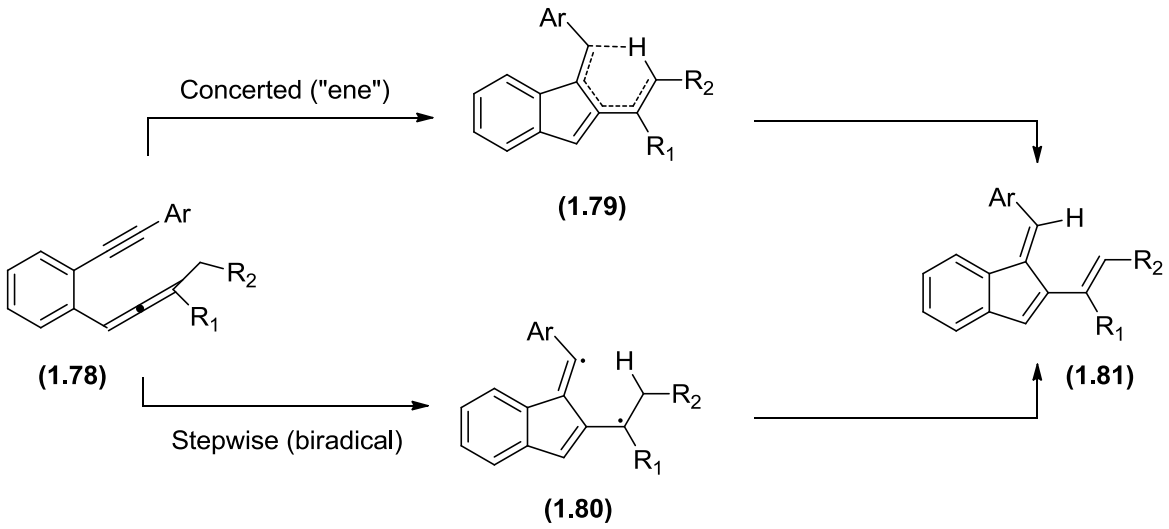
i) The switch from the Myers-Saito cyclisation when substituting the acetylene terminus with an aryl or silyl moieties could result from their ability to stabilise α-radicals

ii) The rate of cyclisation is unaffected by the introduction of large substituents at the allene terminus. This would cause a reduction in rate in pericyclic reactions but not in the case of a radical mechanism.

iii) Rates of reaction are independent of solvent polarity. This excludes the presence of any zwitterionic intermediates.

However, subsequent attempts at intermolecular radical trapping using oxygen, thiophenol, tris(trimethylsilyl)silane and TEMPO failed, giving no experimental proof for the existence of the biradical intermediate.[55]

A recent computational study of the Schmittel cyclisation by Engels *et al.* concentrated on the theoretical calculation of the activation energy for the possible biradical (stepwise) and "ene" (concerted) mechanisms (**Scheme 1.26**).[56]



Scheme 1.26: Proposed Concerted and Stepwise Mechanisms for the Schmittel Cyclisation

The study concluded that the "ene" mechanism possesses equal activation barrier height as the biradical pathway (~32 Kcal/mol).[56] It was then observed that in both proposed mechanisms, the hydrogen-abstraction is the rate determining step. Engels exploited this notion to predict kinetic isotope effects for both pathways and calculated a k_H/k_D of around 2 for the concerted reaction and a k_H/k_D close to 1 for the stepwise mechanism.[56] Schmittel then set out to experimentally measure k_H/k_D for the cyclisation of **1.82** and **1.83** in refluxing toluene (**Figure 1.6**).[57]

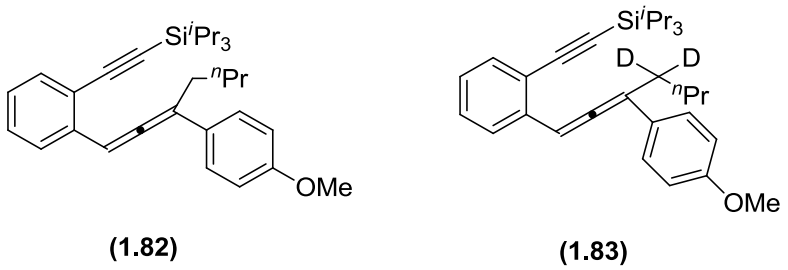
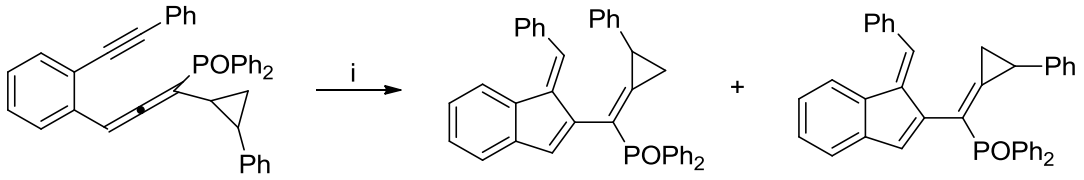


Figure 1.6: Molecules selected by Schmittel for Kinetic Isotope Effect Study

A $k_{1.78}/k_{1.79}$ value of 1.17 was calculated from the rate measurements. According to Schmittel [57] and the calculation by Engels [56] this is a clear indication that a step-wise (radical) mechanism is in operation.

Another method adopted by the Schmittel *et al.* to indirectly prove the existence of a biradical intermediate was to introduce a cyclopropane ring at the allenic terminus.[55] The rate for the radical opening of cyclopropane rings is known to be extremely fast (k (80°C) = 1.1 x 10^9 s^{-1}).[58] When enyne allene **1.84** was heated in the presence of 1,4-CHD, however, no opening of the cyclopropane was observed (**Scheme 1.27**).

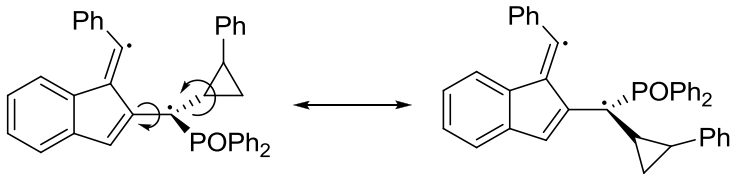


(1.84) **(1.85)** **(1.86)**

Reagents and Conditions: (i) 1,4-Cyclohexadiene (excess), benzene, reflux, 1h. Combined yield: 52%, **1.85**:**1.86** = 0.6:1.0.

Scheme 1.27: Attempted Cyclopropane Opening by Schmittel *et al.*

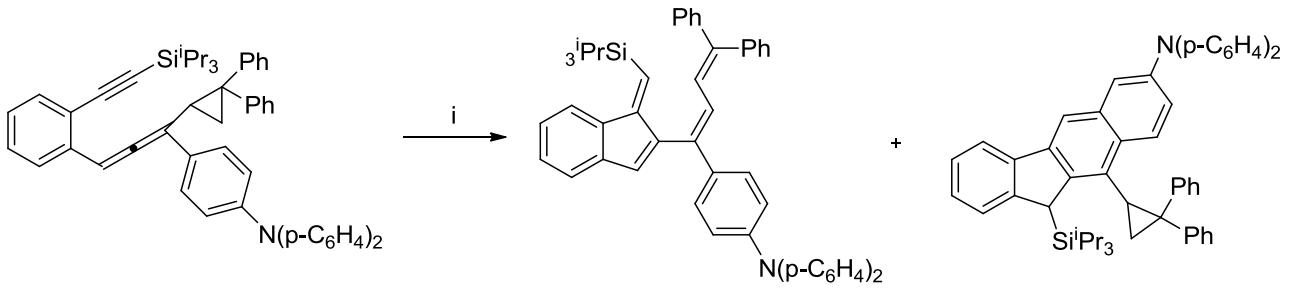
Schmittel observed that the reaction is not stereospecific giving a mixture of E/Z (**1.85**) and E/E (**1.86**) diastereomers. This meant that the mechanism cannot be concerted and rotation about bonds occurs at some stage of the reaction, as depicted in **Figure 1.7** below for the proposed radical intermediate.



(1.87) **(1.88)**

Figure 1.7: Bond Rotation in the Radical Mechanism Proposed for the Schmittel Cyclisation

The failure of isolating an open cyclopropane structure from **1.87** however did not deter Schmittel. Ten years after the initial attempt in **Scheme 1.27** he discovered that on heating new substrate **1.89**, compound **1.90** which is the result of the cyclopropyl group opening, was isolated.[59]



(1.89) **(1.90)** **(1.91)**

Reagents and Conditions: (i) 1,4-Cyclohexadiene 100eq, toluene, sealed tube, 170°C, 7h, **1.90:** 32%, **1.91:** 25%.

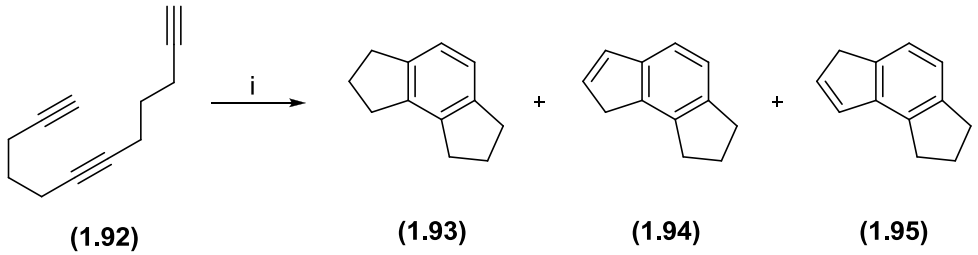
Scheme 1.28: Successful Cyclopropane Ring Opening by Schmittel

Formation of **1.91** was attributed to an intermediate silyl shift step required to aid aromatisation to the naphthalene group.[59] The difference in reactivity observed between cyclopropane analogues **1.84** and **1.89** was explained by the replacement of the phosphine oxide group in **1.84** with an aryl group in **1.89** which emphasises the radical character in intermediate biradical species.[59] The successful opening of the cyclopropane moiety in **1.89** was considered by Schmittel to be indisputable evidence that a stepwise/radical mechanism is in operation.

1.2.5 Other Radical Cyclisations

1.2.5.1 Johnson and Kociolek

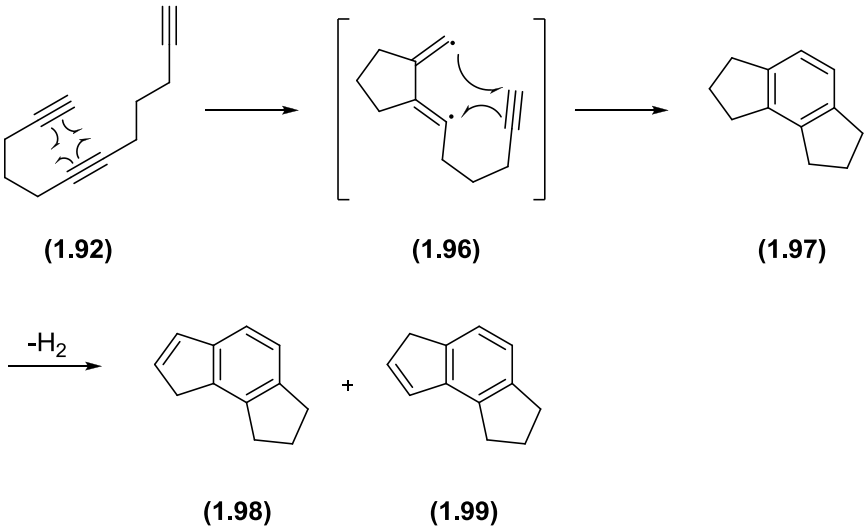
In 1999 Johnson and Kociolek reported that upon pyrolysis at 500-600°C and 0.01Torr 1,6,11-dodecatriyne **1.92** yields a mixture of products **1.93**, **1.94** and **1.95**.



Reagents and Conditions: (i) Neat, 500-600°C, 0.01Torr, total yield: 35%, **1.93:1.94+1.95= 1:5**

Scheme 1.27: Work by Johnson and Kociolek

The proposed mechanism for the above transformation involves an initial dimerisation of the 1,6-diyne system yielding a 1,4-biradical species **1.96**. Subsequent intramolecular trapping of the remaining acetylene moiety and dehydrogenation yields the observed products [60] as shown in **Scheme 1.28**.

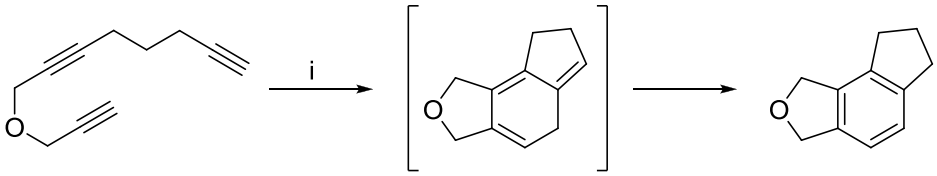


Scheme 1.28: Proposed Biradical Mechanism by Johnson and Kociolek

DFT calculations at the pBP86/DN* level predict that the conversion of **1.92** to **1.96** is exothermic by 131Kcal/mol [60] a barrier much smaller than that for the corresponding concerted cyclotrimerisation mechanism proposed for the similar Berthelot reaction [61] which involves the high temperature intermolecular condensation of three acetylene molecules to yield benzene.[62] No further work on this transformation has so far been published.

1.2.5.2 *Ley et al.*

Following Johnson and Kociolek's work, Ley *et al.* have recently reported that introducing an ether functionality in **1.92** (**Scheme 1.27**) substantially lowers the activation energy of the reaction allowing it to proceed at 200°C under microwave conditions (**Scheme 1.29**).[63]

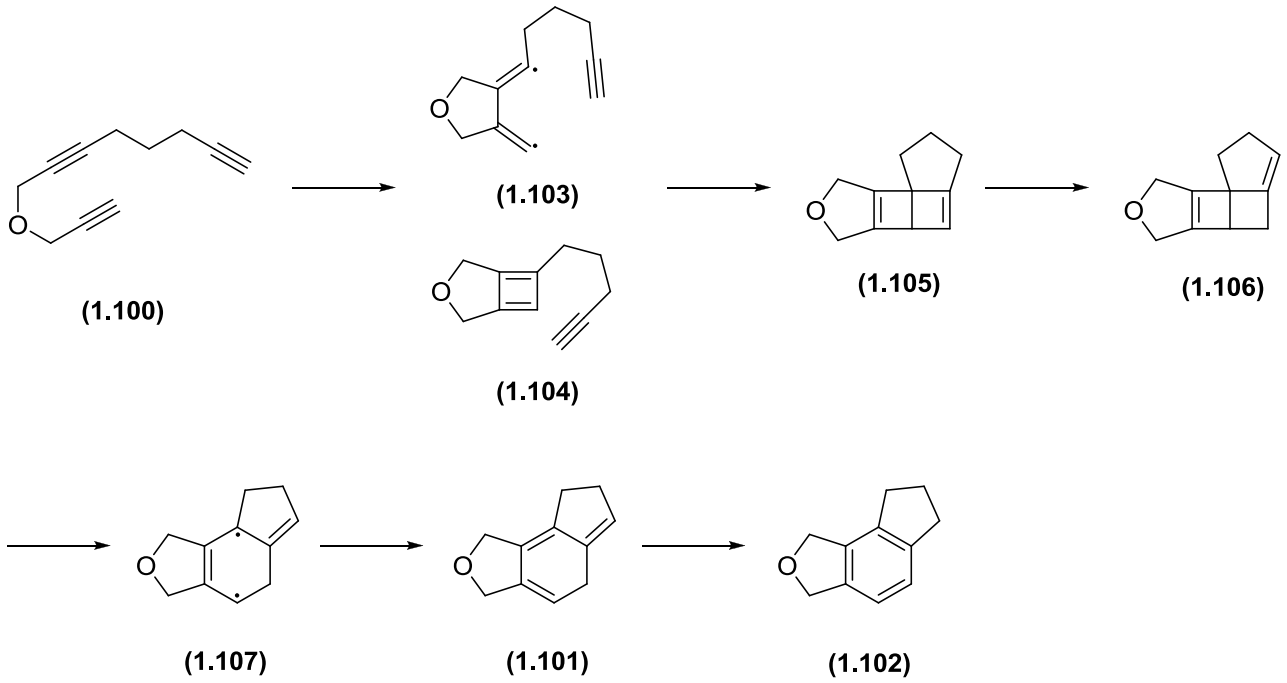


(1.100) **(1.101)** **(1.102)**

Reagents and Conditions: (i) DMF, MW, 200°C, 0.5h, **1.101**: Trace, **1.102: 94%**

Scheme 1.29: Work by Ley *et al.*

The isolation of intermediate **1.101** in trace amounts led to the formulation of a mechanistic postulate involving a 1,4-biradical (**1.103**) or a cyclobutadiene (**1.104**) species (**Scheme 1.30**).



(1.100) **(1.103)** **(1.104)** **(1.105)** **(1.106)**

(1.107) **(1.101)** **(1.102)**

Scheme 1.30: Mechanistic Postulate by Ley *et al.*

Either **1.103** or **1.104** could give access to a Dewar benzene [64,65] structure **1.105**. This could rearrange to lower energy tetracycle **1.106** which could then fragment to biradical **1.107**, which has literature precedent [66,67] and lead to the observed product **1.102** *via* detected intermediate **1.101**.

No experimental proof for the existence of any of the proposed intermediates was ever gathered and no further work on this reaction has so far been published.

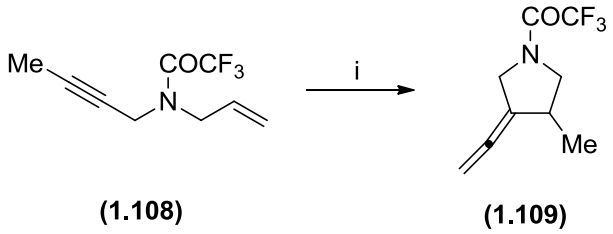
1.3 Ene Reactions Involving Triple Bonds

1.3.1 The Propargylic-Ene Reaction

Ene-reactions are very efficient methods for generating complex structures in a single synthetic step. The intramolecular variant of this type of cascade reaction is a well-established process [68] however few examples have been reported involving propargylic rather than allylic hydrogen atoms.

1.3.1.1 Oppolzer et al.

In 1973 Oppolzer *et al.* reported that thermolysis of neat propargylic amine **1.108** generates allene **1.109** in 43% yield.[69]



(1.108) **(1.109)**

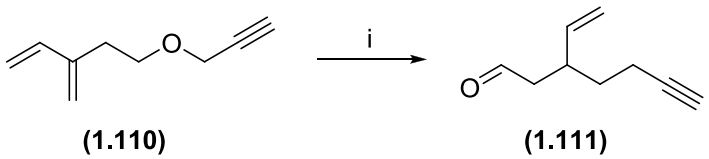
Reagents and Conditions: (i) Neat, 210°C, 2h, 43%.

Scheme 1.31: First Example of Propargylic-Ene Reaction by Oppolzer *et al.*

The above reaction was reported to occur at a significantly lower temperature than the corresponding 1,6-dialkene ene-cyclisations. A mechanistic rationale for the transformation above was not provided, however it was assumed this reaction proceeds via an ene-mechanism.

1.3.1.2 Shea et al.

While investigating the intramolecular Diels-Alder reaction of **1.110**, Shea *et al.* isolated aldehyde **1.111** as a side product (**Scheme 1.32**).[70]

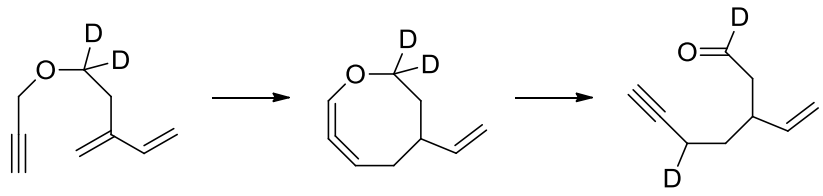


(1.110) **(1.111)**

Reagents and Conditions: (i) Neat, 402°C, 12%.

Scheme 1.32: Work by Shea *et al.*

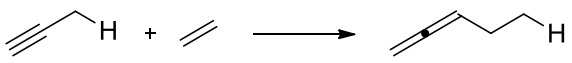
Deuterium labelling studies revealed that an intramolecular hydrogen-abstraction step takes place during the reaction. To account for this, cyclic oxallene **1.113** was proposed as an intermediate in the transformation (**Scheme 1.33**).[70]



(1.112) **(1.113)** **(1.114)**

Scheme 1.33: Proposed Mechanism by Shea *et al.*

A concerted propargylic-ene reaction with concomitant 1,6-hydrogen abstraction generates cyclic allene **1.113**. This carbocycle was calculated to posses strain energy of approximately 14Kcal/mol.[70] The feasibility of the whole process was backed up by consideration of the energetics of the parent ene-reaction shown in **Scheme 1.34**, estimated to be exothermic by 23Kcal/mol.[71]



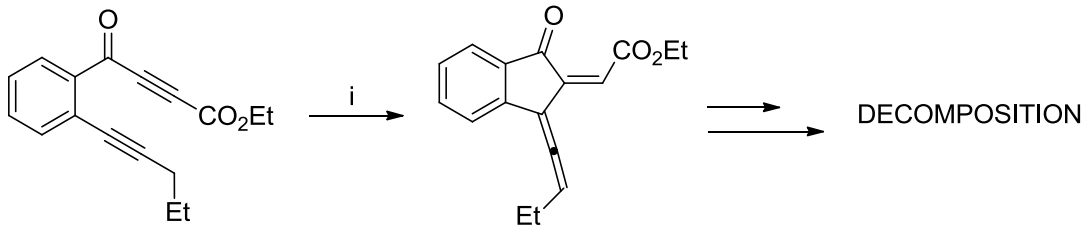
(1.115) **(1.116)** **(1.117)**

Scheme 1.34: Previous Investigation by Shea *et al.*

The second step of the rearrangement was thought to proceed via a retro-hetero ene fragmentation involving a 1,5-hydrogen abstraction step, a process well precedented at the time of this publication.[72-75]

1.3.1.3 Pérez et al.

While investigating the coclycomerisation of 1,6-enyne systems and arynes catalysed by palladium (0), Pérez *et al.* discovered that molecule **1.118** undergoes spontaneous decomposition on standing at room temperature.[76] Tentative NMR analysis of the generated mixture revealed the intermediate generation of allene **1.119**.



(1.118) **(1.119)**

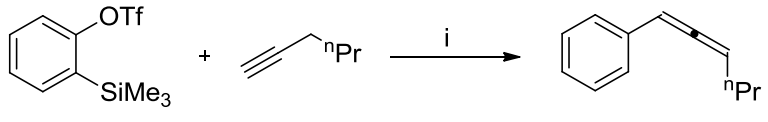
Reagents and Conditions: (i) Neat, rt

Scheme 1.35: Work by Pérez *et al.*

The proposed mechanism for this transformation involves a concerted propargylic-ene reaction.[76]

1.3.1.4 Cheng et al.

In 2005 Cheng *et al.* demonstrated a room-temperature intermolecular variant of the propargylic-ene transformation.[77] Highly reactive benzyne was found to undergo reaction with alkyne **1.121** at room temperature to generate allene **1.122** in 69% yield (**Scheme 1.36**).



(1.120) **(1.121)** **(1.122)**

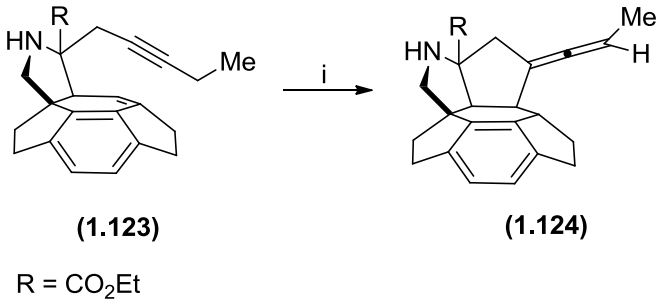
Reagents and Conditions: (i) KF, 18-crown-6, THF, rt, 6h, 69%.

Scheme 1.36: Work by Cheng *et al.*

Benzyne was generated *in situ* by reaction of 2-(trimethylsilyl)phenyl triflate **1.120** with potassium fluoride.[77]

1.3.1.5 Martin et al.

During studies on the functionalisation of fullerene C_{60} Martin *et al.* reported that upon refluxing in chlorobenzene, 1,6-fullerenynes bearing alkyl substituents on the terminal carbon of the alkyne moiety led quantitatively to new allenes (**Scheme 1.37**). [78]



(1.123) **(1.124)**

R = CO_2Et

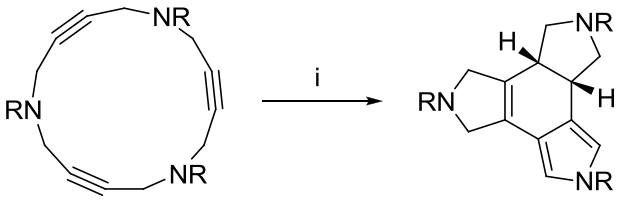
Reagents and Conditions: (i) Cl-Ph, reflux, 3h, 99%.

Scheme 1.37: Work by Martin *et al.*

A propargylic-ene mechanism was proposed for this transformation. DFT calculations revealed that this reaction is exothermic only by 9.5Kcal/mol. It was therefore concluded that the formation of allenes from 1,6-fullerenynes must be kinetically driven.[78]

1.3.1.6 Dachs et al.

While investigating the metal-catalysed cyclisation of triaza macrocylic scaffolds Dachs *et al.* discovered that tetrafused structure **1.126** can be obtained simply by refluxing molecule **1.125** in toluene under catalyst-free conditions.[79]



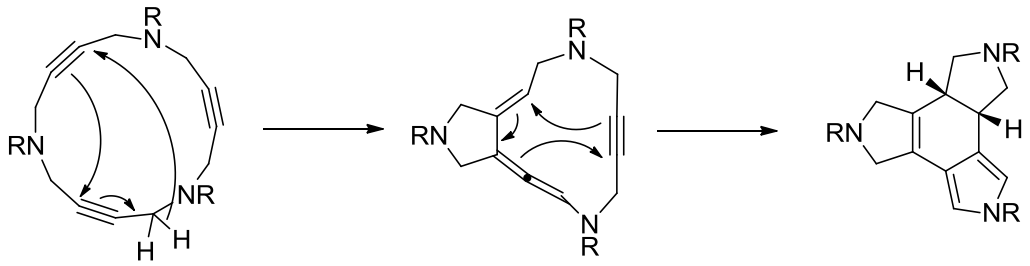
(1.125) **(1.126)**

R= $SO_2(2,4,6\text{-}^{i}PrC_6H_2)$

Reagents and Conditions: (i) Toluene, reflux, 30h, 32%.

Scheme 1.38: Work by Dachs *et al.*

It was discovered that addition of an excess of 1,4-cyclohexadiene to the reaction mixture raised the yield of the above transformation to 77% yield.[79] This finding initially led the researchers into thinking that a biradical mechanism is in operation, similar to that proposed by Parsons *et al.* [23] for their transformation. However EPR studies carried in the presence of radical traps failed to confirm the presence of radical intermediates and a propargylic-ene mechanism was instead proposed [79] as shown in **Scheme 1.39** below.



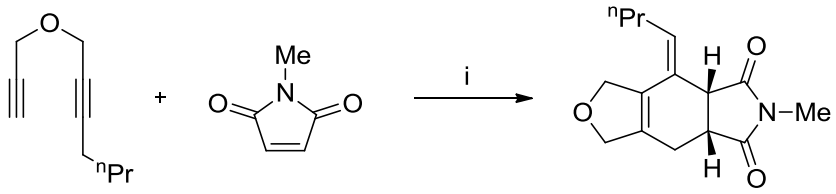
(1.125) **(1.127)** **(1.126)**

R= $SO_2(2,4,6\text{-}^{i}PrC_6H_2)$

Scheme 1.39: Proposed Mechanism Postulated by Dachs *et al.*

1.3.1.7 Danheiser et al.

Danheiser *et al.* have recently been involved in investigations of formal [2+2+2] cyclisations. The first example published involves the bimolecular cyclotrimerisation between a 1,6-diyne and alkenyl or alkynyl dienophile.[80] An example is shown in **Scheme 1.40** below.

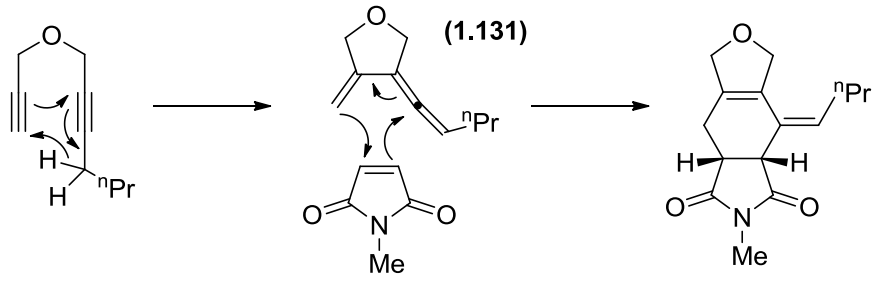


(1.128) (1.129) (1.130)

Reagents and Conditions: (i) Toluene, 0.1M, reflux, 21h, 94%, Z:E = 91:9.

Scheme 1.40: Work by Danheiser *et al.*

The proposed mechanism involves an intramolecular propargylic-ene reaction of **1.128** to genererate vinylallene **1.131**, which then undergoes an intermolecular Diels-Alder cycloaddition with dienophile **1.129** to yield product **1.130** (**Scheme 1.41**).[80]

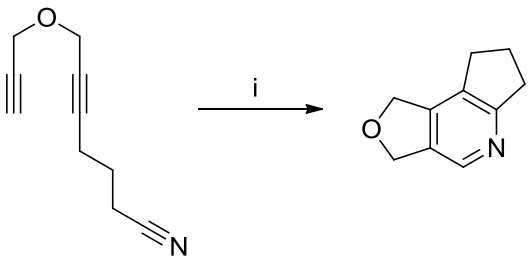


(1.128) (1.129) (1.130)

Scheme 1.41: Proposed Mechanism Postulated by Danheiser *et al.*

In this publication mention of the biradical mechanism proposed for similar transformations by Johnson *et al.*, Ley *et al.* and Parsons *et al.* was made. However it was dismissed in favour of an ene-mechanism.[80]

Another publication by Danheiser *et al.* describes the use of an intramolecular cyclotrimerisation between two alkynes and a cyano group for the synthesis of substituted pyridines.[81] An example is shown below (**Scheme 1.42**).

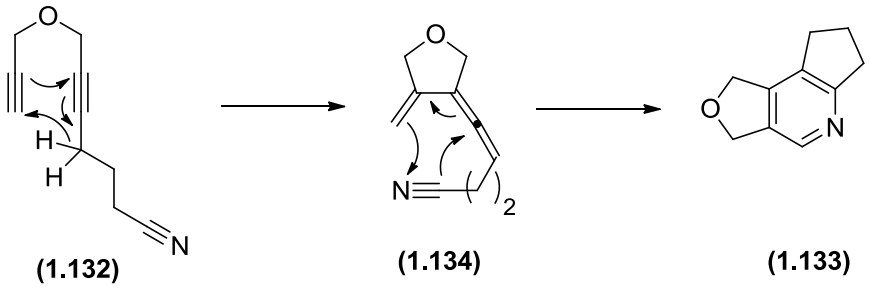


(1.132) **(1.133)**

Reagents and Conditions: (i) Toluene, 0.01M, 160°C, 21h, 71%.

Scheme 1.42: Work by Danheiser *et al.*

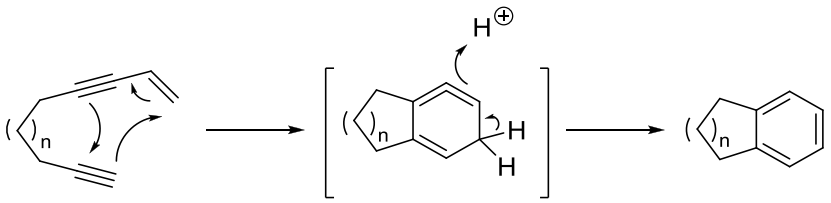
The proposed mechanism involves a propargylic-ene reaction between the 1,6-diyine with subsequent Diels-Alder cycloaddition of the resulting vinylallene with the cyano group (**Scheme 1.43**).[81]



Scheme 1.43: Proposed Mechanism Postulated by Danheiser *et al.*

1.3.2 Conjugated Ynone Cycloadditions

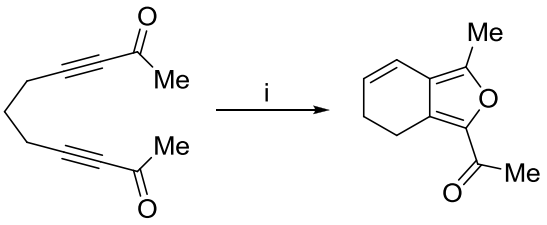
1,3-Dienes are the typical four-electron components involved in the Diels-Alder reaction. However, [4+2] cycloadditions between conjugated enynes and alkenes or alkynes have also been reported in the literature (**Scheme 1.44**). The proposed mechanisms for these transformations commonly involve the intermediacy of highly strained cyclic allene species.



(1.135) (1.136) (1.137)

Scheme 1.44: General Scheme for the Enyne Cycloaddition with Formation of a Cyclic Allene Intermediate

An insignificant amount of work has been published on the heterocyclic variant of this reaction. Danheiser *et al.* in 1998 reported the first and only examples of such transformation [82] one of which is shown below in **Scheme 1.45**.

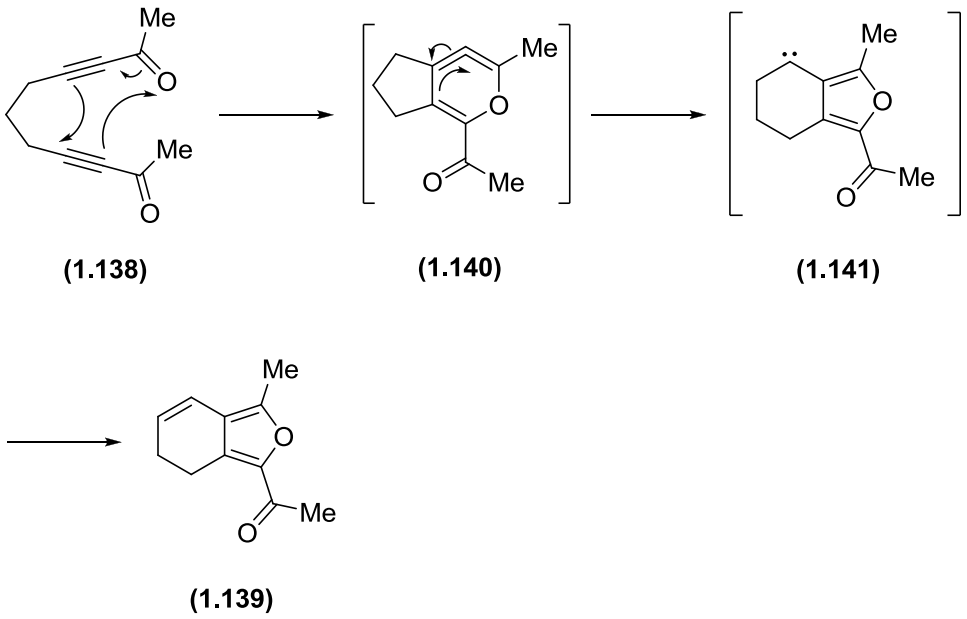


(1.138) (1.139)

Reagents and Conditions: (i) Toluene, 0.1M, 180°C, 1.1eq. γ-terpinene, 48h, 80% yield.

Scheme 1.45: First Conjugated-Ynone Cycloaddition Reported by Danheiser *et al.*

Addition of the radical inhibitor γ-terpinene was found to be essential to improve the efficiency of the transformation, which is thought to involve the generation of a carbene intermediate (**Scheme 1.46**).[82]

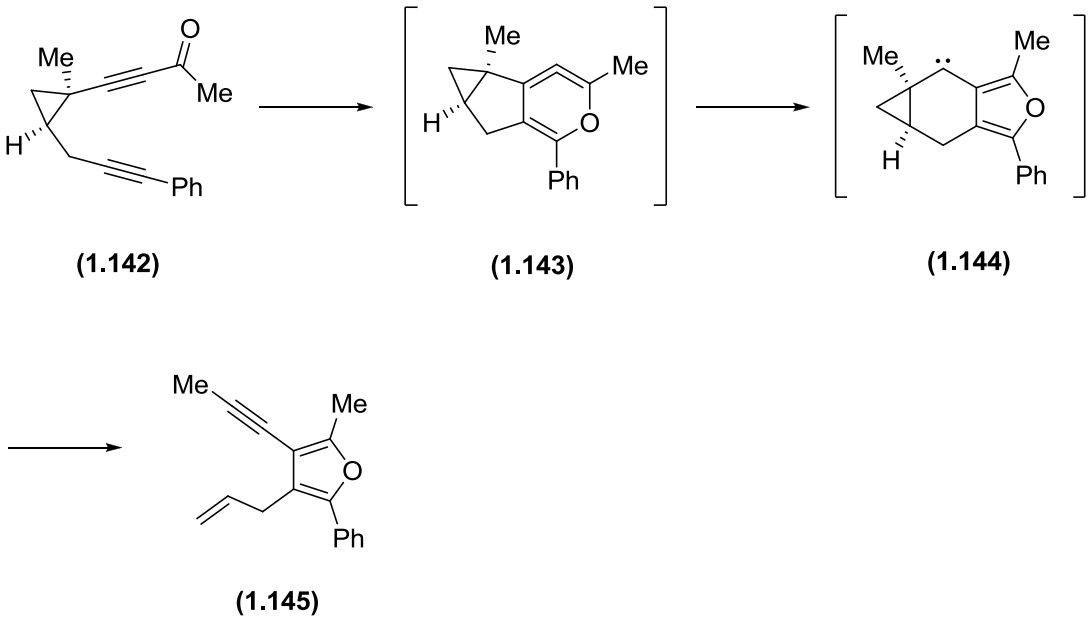


(1.138) (1.140) (1.141)

(1.139)

Scheme 1.46: Proposed Mechanism Postulated by Danheiser *et al.*

An initial intramolecular [4+2] cycloaddition between the alkyne and the conjugated ynone in **1.138** generates strained heterocyclic allene **1.140**. A subsequent 1,2-carbon shift forms the fused furan motif with concomitant generation of a carbene which then undergoes C-H bond insertion to yield observed product **1.139**.[82] Further support for the postulated formation of a carbene intermediate was provided by the result depicted in **Scheme 1.47** below.



(1.142) **(1.143)** **(1.144)**

(1.145)

Reagents and Conditions: (i) Toluene, 0.1M, 150°C, 16h, 30-35%.

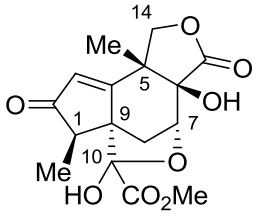
Scheme 1.47: Opening of the Cyclopropane Moiety in **1.142**

After the initial [4+2] cyclisation and generation of the carbene intermediate, a concerted fragmentation of the cyclopropane ring yields the observed product **1.145**.[82]

1.4 Jiadifenin

1.4.1 Structure and Biological Activity

Seco-prezizaane-type sesquiterpene jiadifenin **1.146** was first reported by Fukuyama *et al.* in 2002 [83] who isolated it in 0.001% yield from the methanol extract of the pericarps of *Illicium Jiadifengpi*.



(1.146)

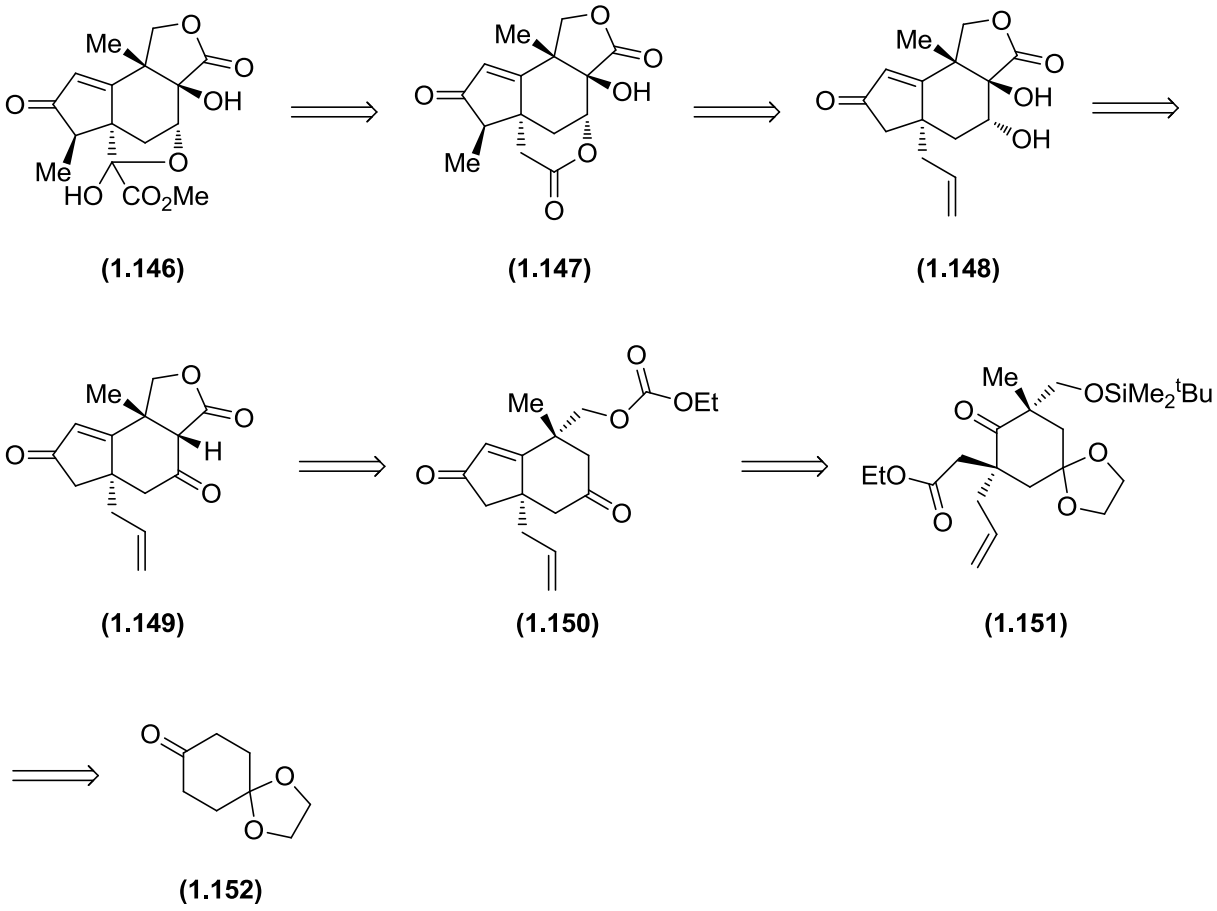
Figure 1.8: Jiadifenin

From a chemical perspective its highly oxygenated, cage-like structure makes it an appealing target for total synthesis. Added challanges to be considered are the presence of five asymmetric centers and a hemiacetal functionality which makes the C-10 centre anomeric. On the biological level, Fukuyama and co-workers [83] have shown that jiadifenin exhibits potent growth promoting activity in cultures of rat cortical neurons in concentrations ranging from 0.1 to 10 μM. Recent studies carried out by Danishefsky *et al.* demonstrated that **1.146** regulates the action of nerve growth factor protein rather than acting independently.[84] In the presence of NGF, **1.146** enhanced neurite lengths by 162% relative to a DMSO-NGF control. Jiadifenin is thus appropriately classified as a non-peptidyl neurotrophic factor [85] and could be a successful candidate for the fight against neurodegenerative diseases.

Despite the interesting characteristics described above only one total synthesis of jiadifenin has been achieved so far.

1.4.2 Total synthesis by Danishefsky *et al.*

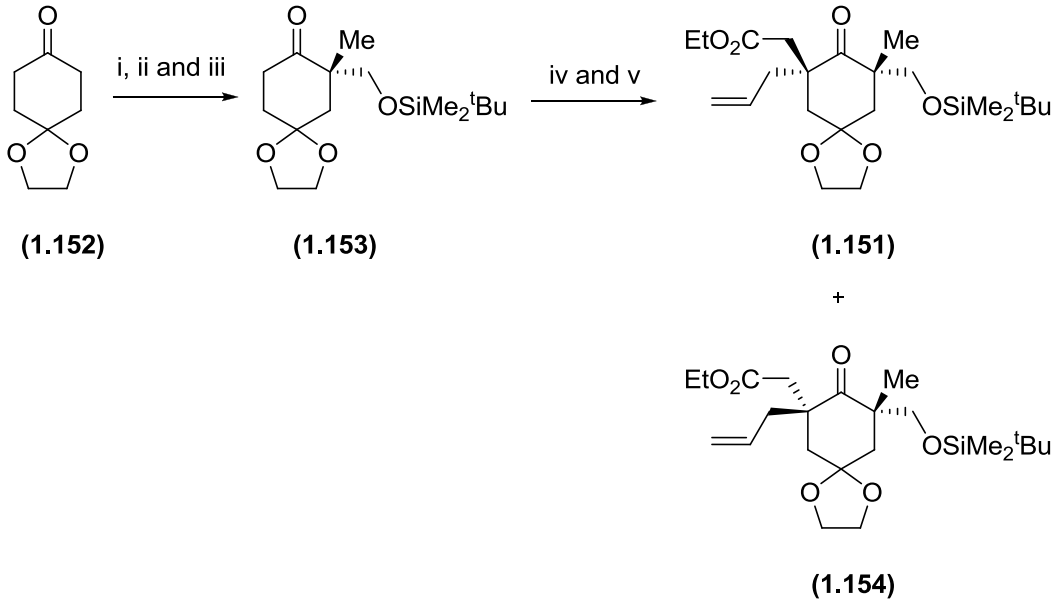
The retrosynthetic rationale chosen by Danishefsky and co-workers for the synthesis of jiadifenin is shown in **Scheme 1.48** below.[84]



Scheme 1.48: Retrosynthetic Rationale of Jiadifenin by Danishefsky *et al.*

As previously reported by Fukuyama *et al.*[83] **1.146** can be obtained by the oxidative ring-contraction of an α-hydroxy lactone which would in turn be obtained by oxidative-cleavage of the allyl group in **1.148**. The tertiary hydroxyl group was expected to be introduced by α-hydroxylation of the lactone functionality in **1.149**. Intramolecular Claisen condensation followed by intramolecular Horner-Wadsworth-Emmons reaction would deliver the tricyclic skeleton of **1.149** from **1.151** through **1.150**. The construction of the two quaternary centers in **1.151** would then be achieved by a series of stereoselective alkylations of symmetrical cyclohexanone **1.152**.

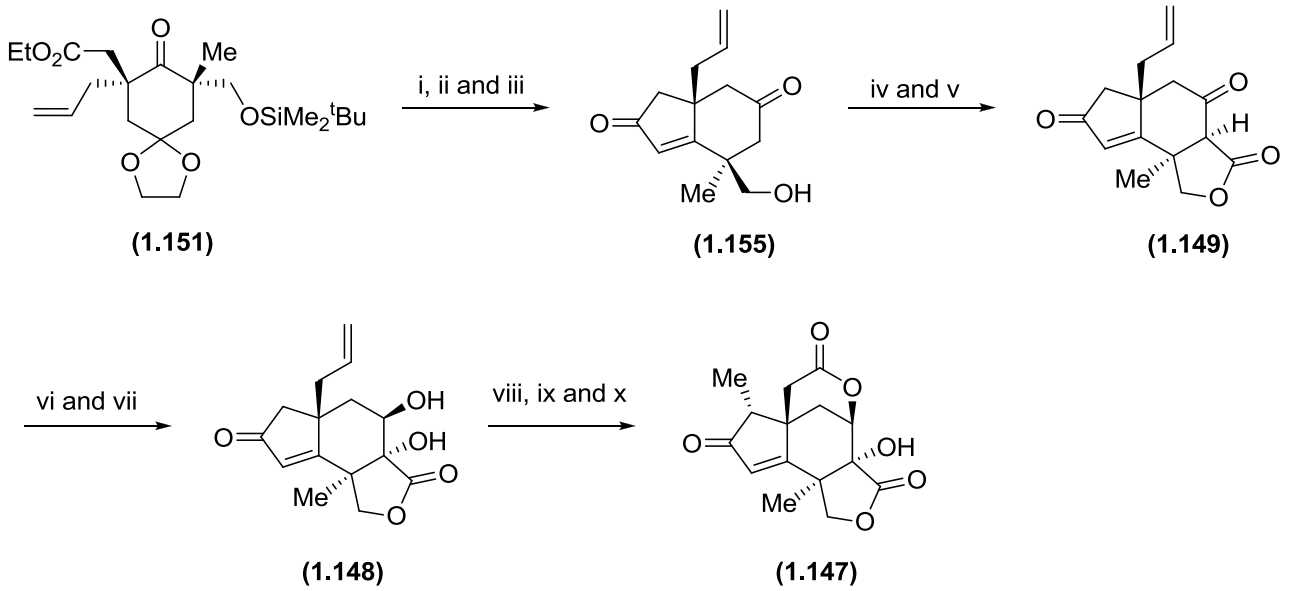
Therefore the first challenge in the synthetic plan devised by Danishefsky *et al.* involved the de-symmetrisation of ketone **1.152** (Scheme **1.49**).



Reagents and Conditions: (i) LHMDS, THF, -78°C then MeI, -78°C to rt; (ii) 10% aq.KOH, MeOH, aq. HCHO, 0°C; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 64% over three steps; (iv) LHMDS, THF, -78°C, to rt, 73%; (v) LDA, THF, -78°C to -20°C, $BrCH_2CO_2Et$, HMPA, -78°C, **1.151**: 73%, **1.154**: 24%

Scheme 1.49: Synthesis of **1.151**

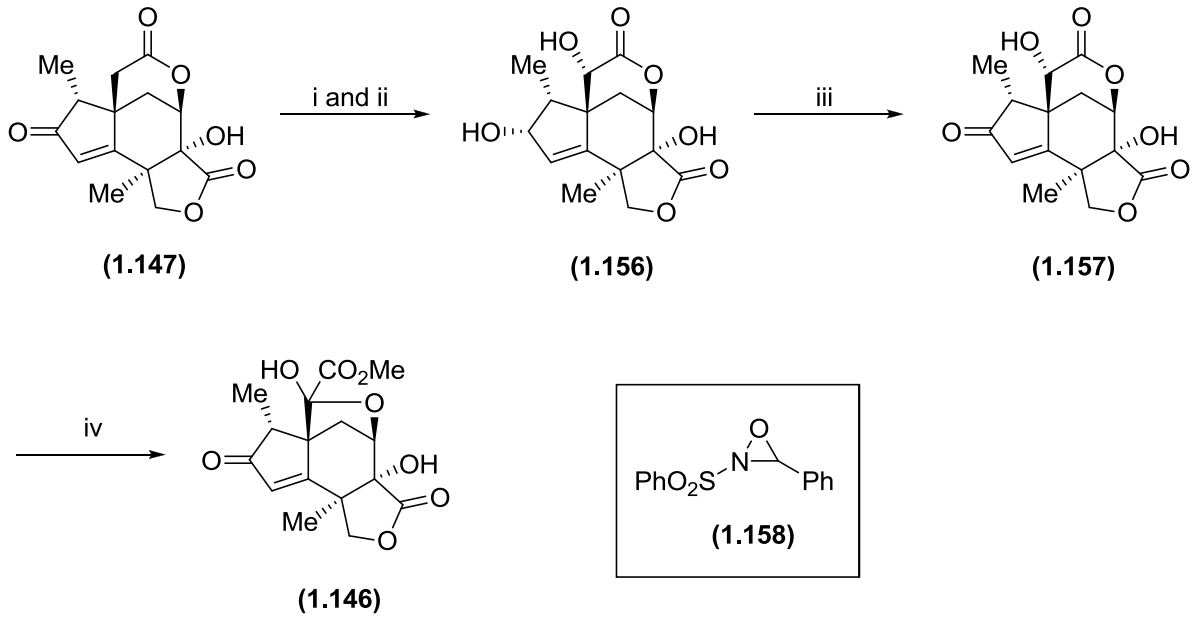
Methylation followed by hydroxymethylation under thermodynamic conditions gave **1.153**. This material was then subjected to two further alkylations with allyl bromide and ethyl bromoacetate respectively to yield a diastereomeric mixture of **1.151** and **1.154**.



Reagents and Conditions: (i) $LiCH_2P(O)(OMe)_2$, THF, -78°C, 81%; (ii) NaH, THF, reflux, 91%; 2N aq. HCl, THF, 94%; (iv) $ClCO_2Et$, pyridine, DMAP, CH_2Cl_2, 0°C to rt, 93%; (v) NaH, THF, reflux, 94%; (vi) mCPBA, CH_2Cl_2, 90%; (vii) $NaBH_4$, THF/MeOH (1:1), -78°C, 93%; (viii) LDA, THF, -40°C to -15°C then MeI, HMPA, -35°C, 64%; (ix) O_3, Sudan 7B Red, CH_2Cl_2/EtOH (1:1), -78°C; (x) Jones reagent, acetone, 90% over two steps.

Scheme 1.50: Synthesis of **1.147**

Conversion of the ester moiety in **1.151** into a β-keto phosphonate followed by intramolecular Horner-Wadsworth-Emmons reaction and global deprotection gave **1.155** in 70% combined yield. Reaction of **1.155** with ethyl chloroformate and Claisen condensation gave tricyclic **1.149** in 94% as a single diastereomer. Hydroxylation of the 1,3-dicarbonyl system in **1.149** with mCPBA and sodium borohydride-mediated reduction of the ketone moiety at C7 gave **1.148** This material was then methylated using LDA and methyl iodide and the construction of the second lactone ring was then achieved by ozonolysis of the allylic group and oxidation of the resulting hemiacetal.



Reagents and Conditions: (i) $NaBH_4$, $CeCl_3.7H_2O$, THF/MeOH (3:1), -65°C, 88%; (ii) NaHMDS, THF, -78°C, then **1.158**, THF, -78°C, 48% after one recycle; (iii) Jones' reagent, acetone, MeOH, 0°C, 29%; Jones' reagent, acetone, MeOH, 0°C, 40%.

Scheme 1.51: Synthesis of Jiadifenin by Danishefsky *et al*.

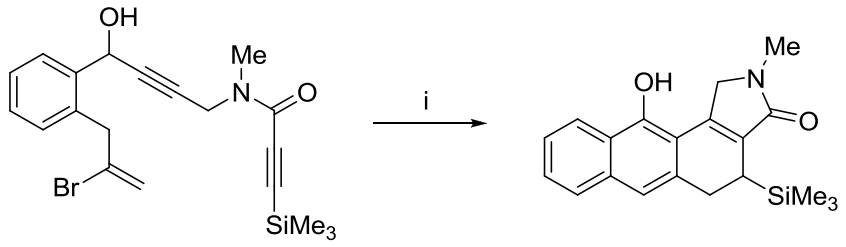
Luche reduction of the enone moiety followed by α-hydroxylation of the lactone moiety using oxaziridine **1.158** gave **1.157**. Finally, **1.157** was oxidised in two steps to racemic Jiadifenin using excess Jones' reagent in a mixture of acetone and methanol. Racemic Jiadifenin was therefore obtained over 19 steps in a total 0.5% yield.

2. Results and Discussion

2.1 Novel Cyclodimerisation of 1,6-Diynes for the Generation of (Z,Z) Exo-Cyclic Conjugated Dienes Fused to Lactams

2.1.1 Outline of Investigation

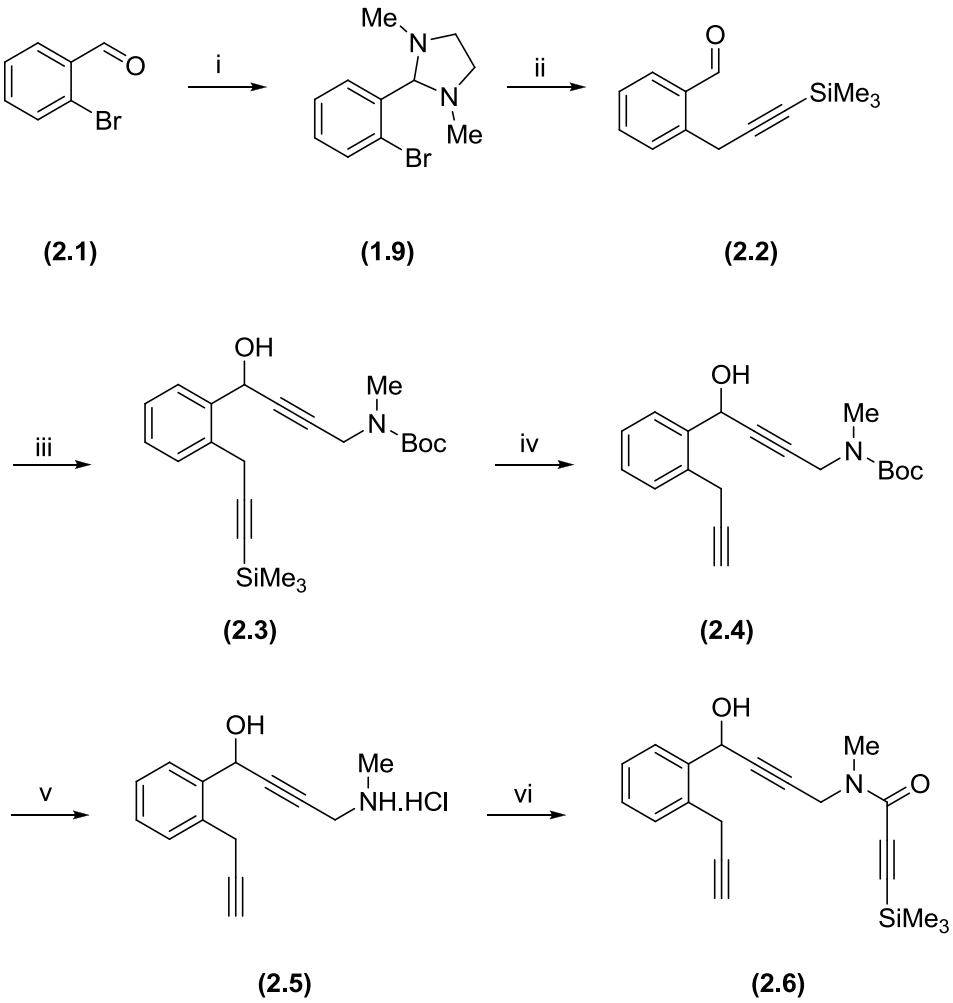
The aim of the following DPhil research project was to devise and execute a series of experiments with the intention of gaining a better mechanistic understanding of the novel thermal cyclisation discovered by Parsons *et al.* (**Scheme 2.1**).[15,23]



(1.12) **(1.13)**

Scheme 2.1: Original Cyclisation Discovered by Parsons *et al.*

As explained in **Section 1.1.3** the possibility of an acid-catalysed mechanism had been previously discarded.[15] To further extend this notion to cyclisation precursors containing an aromatic group the alkenyl bromide portion of precursor **1.12** was replaced by a terminal alkyne.[25] The construction of desired material **2.6** is detailed below in **Scheme 2.2**.



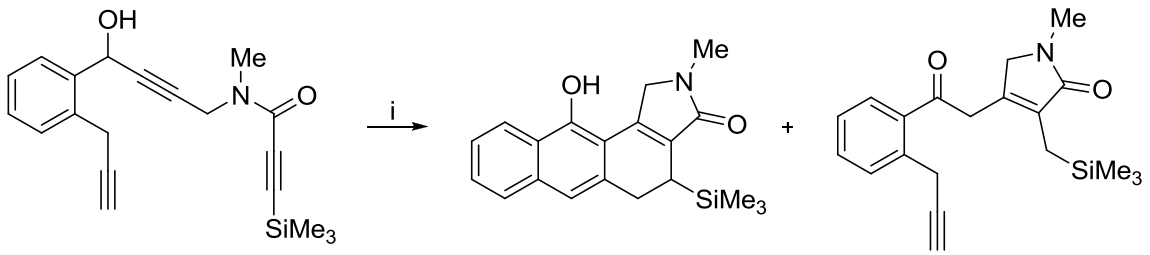
Reagents and Conditions: (i) N,N-Dimethylethylene diamine, *cat.* pTSA, toluene, reflux, 92%; (ii) ^{n}BuLi, CuCN, (3-bromo-1-propynyl)(trimethyl)silane, THF, -60°C then 1M $HCl_{(aq)}$, rt, 69%; (iii) $LiC{\equiv}CCH_2NMeBoc$, ^{t}BuBr, -95°C, then 1M $HCl_{(aq)}$, rt, 90%; (iv) *cat* NaOMe, CH_2Cl_2:MeOH 1:1, 97%; (v) 2M HCl in diethyl ether, 60%; (vi) $Me_3SiC{\equiv}CCOCl$, Et_3N, CH_2Cl_2, 28%.

Scheme 2.1: Synthesis of cyclisation precursor **2.6**

2-Bromobenzaldehyde **2.1** was protected to give imidazolidine **1.9** with N,N-dimethylethylene diamine in the presence of *p*ara-toluene sulfonic acid under Dean-Stark conditions.[86,87] This protecting group has the advantage of facilitating *ortho*-lithiation and is also easily removed by addition of a weak, aqueous acid solution.[88] Aryl bromide **1.9** was subjected to lithium-halogen exchange with *n*-butyllithium and reaction of the resulting anion with one equivalent of cuprous cyanide afforded the corresponding lower-order cyanocuprate. As previously reported by Eberbach

et al [89], the obtained cuprate was then reacted with (3-bromo-1-propynyl)(trimethyl)silane to yield desired 2-substituted benzaldehyde **2.2**. Carbamate **2.3** was subsequently formed by alkylation of the aldehyde by the lithium salt of *tert*-butyl methyl(prop-2-ynyl)carbamate. Desilylation of **2.3** was achieved in excellent yield by the action of catalytic sodium methoxide in methanol to give terminal alkyne **2.4**, which was then converted into amine salt **2.5** by addition of hydrogen chloride in diethyl ether. Reaction of amine salt **2.5** with the acyl chloride derived from 3-(trimethylsilyl)-2-propynoic acid in the presence of triethylamine as a base yielded desired cyclization precursor **2.6**.

Thermolysis of **2.6** in toluene in the absence of acid scavengers furnished two new products (**Scheme 2.2**)

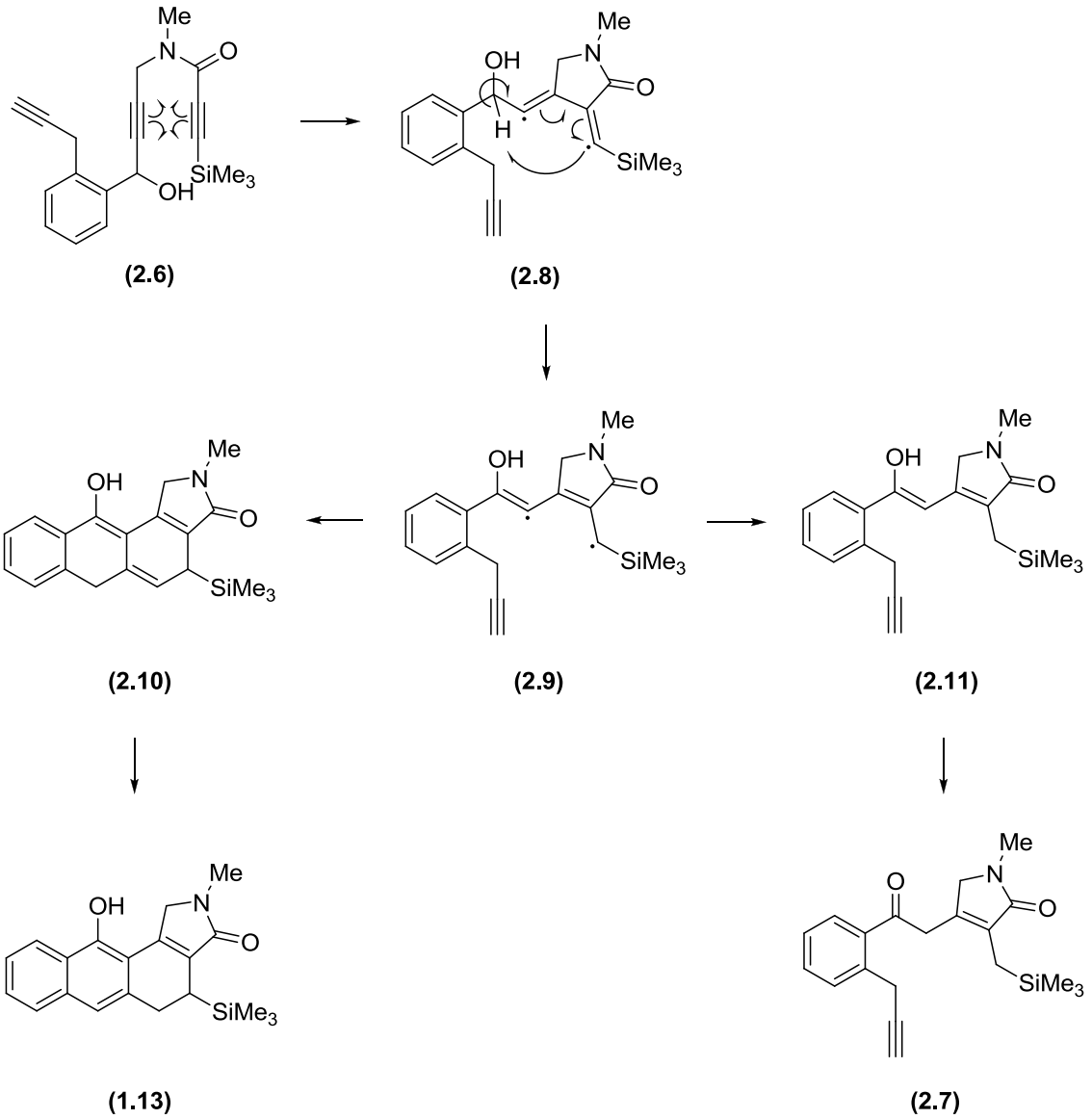


(2.6) **(1.13)** **(2.7)**

Reagents and Conditions: (i) Toluene, reflux, 0.1M, 4h, **1.13**: 76%, **2.7**: 9%.

Scheme 2.2: Thermal cyclisation of precursor **2.6**

As in the example shown in **Section 1.1.3**, the isolation of **1.13** ruled out the previously proposed acid-catalysed mechanism as no bromine is present in the molecule to generate catalytic amounts of hydrogen bromide in solution.[23] The formation of unexpected product **2.7** was the most interesting factor; its structure revealed that the lower alkynyl portion in **2.6** failed to participate in the cyclisation and that two extra hydrogen atoms are incorporated during the course of the reaction. Following these observations the mechanism in **Scheme 2.3** was proposed.



Scheme 2.3: Postulated Mechanism for the Formation of **1.13** and **2.7**

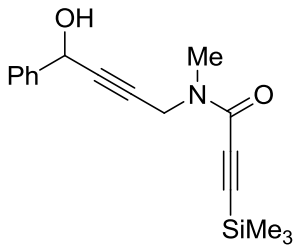
In the postulated mechanism alkyne **2.6** cyclises to give a concentration of biradical **2.8** which in turn could give biradical **2.9** by intramolecular 1,5-hydrogen atom abstraction and tautomerism. This reacts intramolecularly to give tetracycle **2.10** followed by isomerisation to phenol **1.13**. Alternatively it could hydrogen-abstract from the solvent to generate enol **2.11** which is in equilibrium with the observed product **2.7**.

Since it was now obvious that the terminal alkyne was not necessary for the cyclisation to occur, the chosen course of action was to synthesise a novel cyclisation precursor consisting solely of a 1,6-diyne system.

2.1.2 Synthesis of a new cyclisation precursor

2.1.2.1 Retrosynthetic Analysis

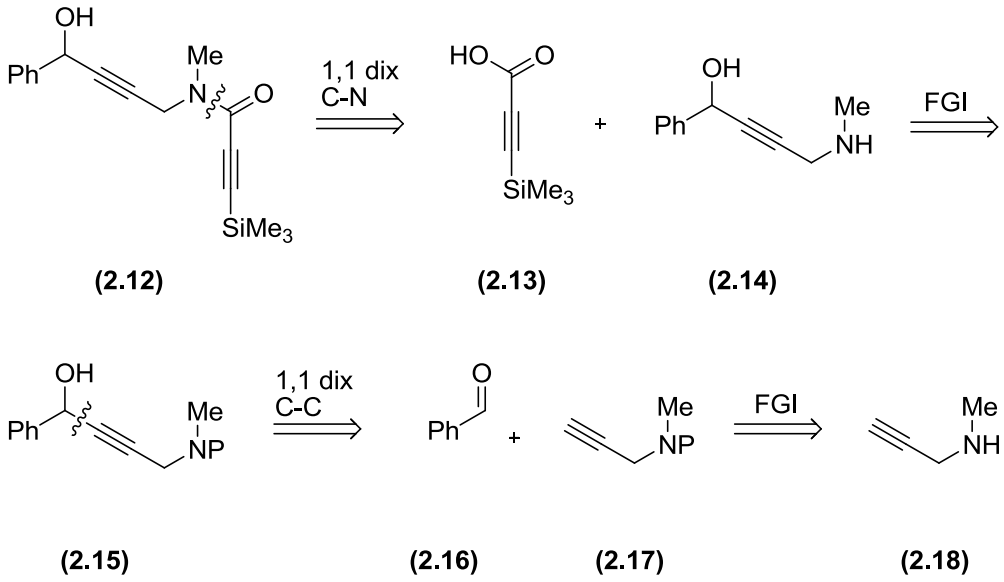
Due to the immediate availability of benzaldehyde in the laboratory, amide **2.12** (**Figure 2.1**) was selected as a new synthetic target.



(2.12)

Figure 2.1: Novel Cyclisation Precursor

The retrosynthetic approach for **2.12** is depicted in **Scheme 2.4** below.

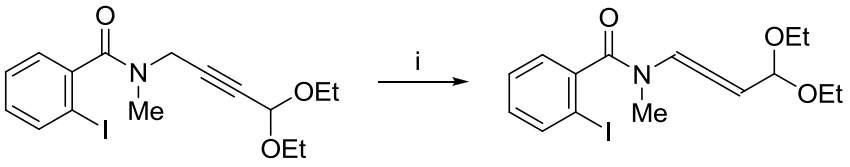


Scheme 2.4: Retrosynthetic Analysis of Amide **2.12**

A disconnection at the amide moiety leads to the commercially available (3-(trimethylsilyl)-2-propynoic acid) **2.13** and secondary amine **2.14**. The latter could be generated from protected amine **2.15** which could be obtained from the alkylation of benzaldehyde by the lithium salt of protected *N*-methylpropargyl amine **2.17**.

2.1.2.2 Investigation of Nitrogen Protection/Deprotection Sequence

In order to be selectively deprotonated at the terminal alkyne position (pKa ~ 29 in DMSO [90,91]) *N*-methylpropargyl amine needed primarily to be protected at the nitrogen atom. Another factor to take into account was that deprotonation by strong bases of the propargylic protons α to the nitrogen atom can be a competing possibility, as shown in **Scheme 2.5** below for a selected example.[92]



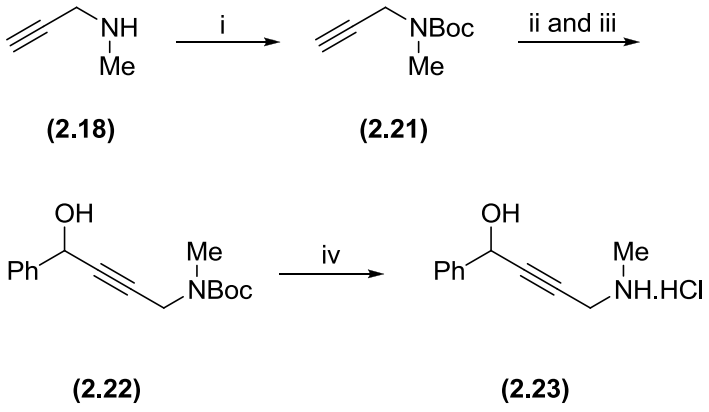
(2.19) **(2.20)**

Reagents and Conditions: (i) ^{t}BuOK, THF, 0°C, 10min, 88%.

Scheme 2.5: Work by Maddaluno *et al.*

On this basis the ideal protecting group for *N*-methylpropargyl amine should replace the proton on the nitrogen atom while sterically hindering the propargylic position. One of the most commonly employed groups for amine protection in organic synthesis is *tert*-butyl carbamate.[93] It is stable to strong, nucleophilic bases and is moderately bulky.

The adaptation of the Boc protecting group for the synthesis of amine **2.23** is shown in **Scheme 2.6** below.



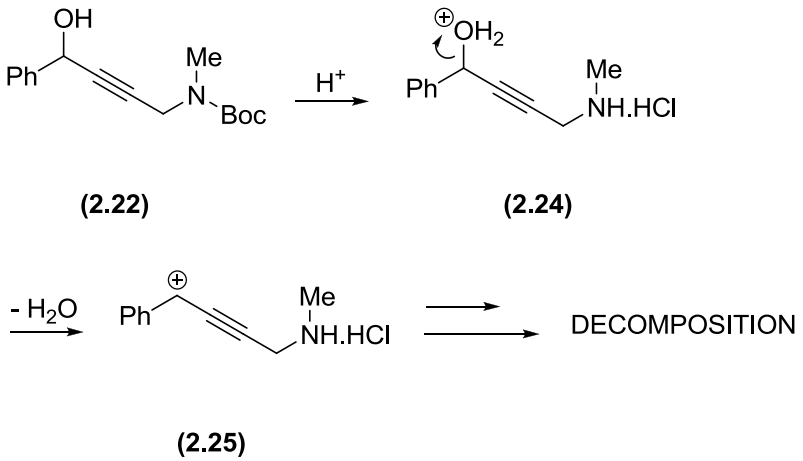
Reagents and Conditions: (i) Di(tert-butyl)dicarbonate, CH_2Cl_2, 0°C to rt, 99%; (ii) ^{n}BuLi, THF, -70°C; (iii) Benzaldehyde, -70°C to RT, then sat. $NH_4Cl_{(aq)}$, rt, 81%; (iv) 2M HCl in Et_2O, rt, 44%.

Scheme 2.6: The Use of Boc for the Synthesis of Amine **2.23**

Boc protection of commercially available *N*-methylpropargylamine **2.18** was easily achieved by reaction with di(tert-butyl) dicarbonate in CH_2Cl_2 at 0°C to room temperature. Deprotonation of the terminal alkyne in **2.21** was then performed by addition of *n*-butyllithium at -70°C and the newly generated anion underwent smooth alkylation with benzaldehyde to furnish alcohol **2.22** in 81% yield**.**

The next step in the synthetic sequence was the removal of the Boc protecting group. Typical methods employ protic acids such as HCl in ethyl acetate [94], diethyl ether and dioxane [95], trifluoroacetic acid in dichloromethane [96,97] or Lewis-acids such as zinc(II) bromide in dichloromethane [97,98]. An initial attempt at Boc deprotection was carried using trifluoroacetic acid in dichloromethane. Unfortunately addition at 0°C followed by stirring at room temperature for one hour led to complete decomposition of the reaction mixture. More encouraging results were obtained when a solution of hydrogen chloride in diethyl ether was employed. On a small scale (~1mmol), this process gave a mediocre yield (44%) of the hydrochloride salt **2.23**. However, on scaling up (~10mmol) little or no product was isolated. Closer inspection of the structure of the starting material revealed that the use of the required strong protic acids might cause a negative interaction with the benzylic hydroxyl group in **2.22**. Acid-catalysed alcohol dehydration is a well

known process [99,100], and is especially efficient even at room temperature for the generation of tertiary, benzylic or allylic carbocations. This possible effect on alcohol **2.22** is depicted below (**Scheme 2.7**).

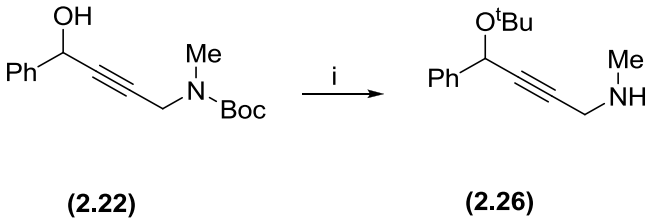


(2.22) **(2.24)** **(2.25)**

Scheme 2.7: Possible Acid-Catalysed Decomposition Pathway of **2.22**

Protonation of the secondary alcohol in **2.22** and consequent loss of a water molecule in **2.24** could generate stabilised benzylic carbocation **2.25** which would then undergo a series of reactions/rearrangements leading to the formation of unwanted products.

Zinc(II) bromide in dichloromethane was also tested as the Boc-deprotecting agent. After a basic workup the residue was purified on column chromatography in the presence of 1% triethylamine to yield unexpected amine **2.26** (**Scheme 2.7**).

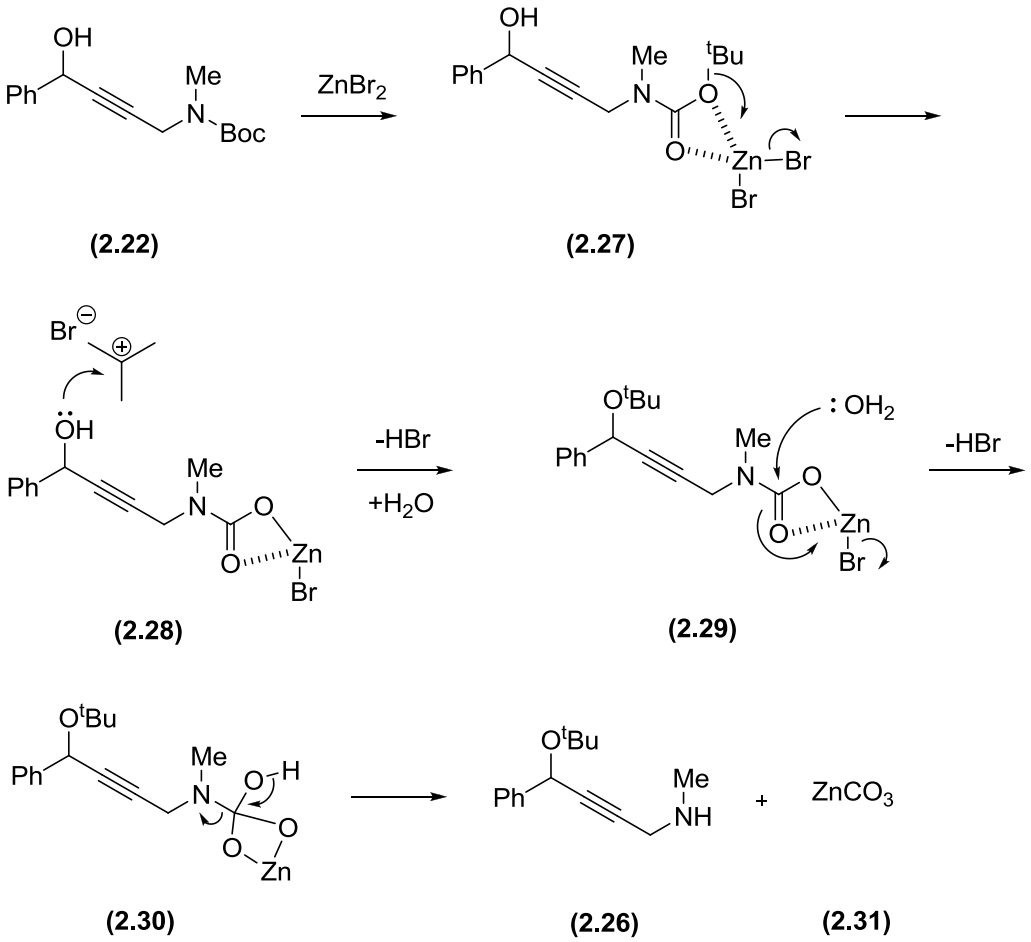


(2.22) **(2.26)**

Reagents and Conditions: (i) Anhydrous $ZnBr_2$, CH_2Cl_2, rt then 10% $K_2CO_{3\,(aq)}$, 62%

Scheme 2.7: Attempted Boc-deprotection employing zinc(II) bromide

The net outcome of this reaction is a Boc-deprotection of the secondary amine with concomitant protection of the benzylic alcohol with a *tert*-butyl group. A postulated mechanism is shown below in **Scheme 2.8**.



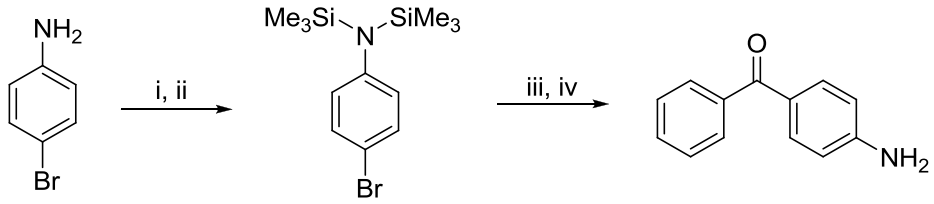
Reagents and Conditions: (i) anhydrous $ZnBr_2$, CH_2Cl_2 then H_2O.

Scheme 2.8: Possible mechanism for the formation of **2.26**

The first step involves the coordination of zinc(II) bromide to the oxygen atoms' lone pairs. A stable tert-butyl cation is then eliminated in favour of the generation of a covalent oxygen-zinc bond. Resulting 2-bromo-2-methylpropane then reacts in a S_N1 fashion with the benzylic alcohol. On addition of water the complex collapses, releasing the free amine and generating zinc(II) carbonate. Support for the intermediate generation of 2-bromo-2-methylpropane is provided by studies carried by Marcantoni *et al* [101] on the deprotection of *tert*-butyl esters with cerium(III) chloride and sodium iodide. After aqueous work-up the presence of 2-iodo-2-methylpropane in solution was detected by gas chromatography.

Having failed to find suitable conditions for the Boc-deprotection in **2.22** the focus was directed towards finding a different protecting group for the secondary amino group. Silyl amines are not frequently encountered in organic synthesis mainly because high reactivity to moisture [93] which

makes their handling a delicate task. However they have been successfully employed in the synthesis of complex molecules. For example Pratt and co-workers have exploited trimethylsilyl protection of anilines for the synthesis of substituted benzophenones (**Scheme 2.9**).[102]



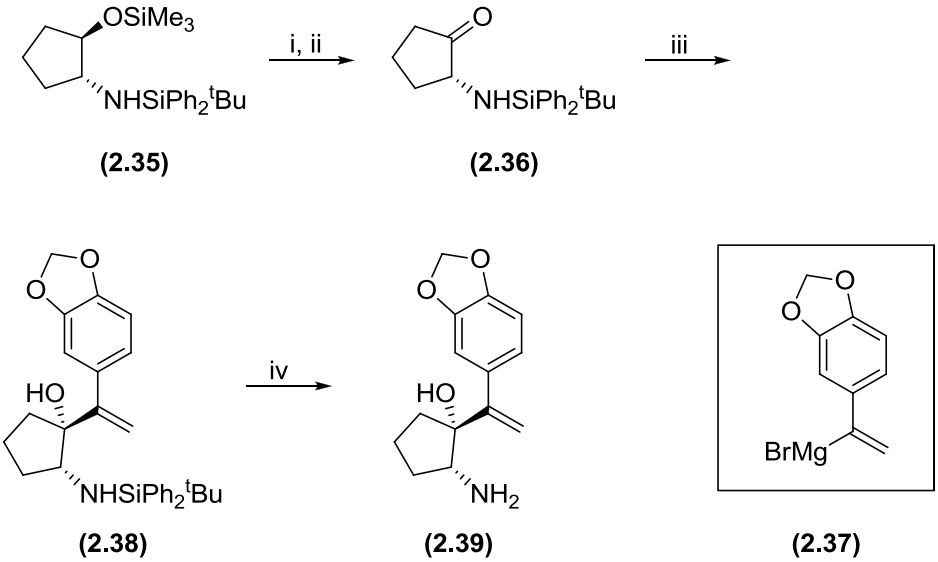
(2.32) **(2.33)** **(2.34)**

Reagents and Conditions: (i) ^{n}BuLi, THF, 0°C; (ii) Me_eSiCl, rt, 61%; (iii) ^{n}BuLi, Et_2O, 0°C; (iv) Benzonitrile, rt, then H_2O, 85%.

Scheme 2.9: Work by Pratt *et al.*

The bis-trimethylsilyl group not only substitutes the potentially reactive hydrogen atoms on the amine but also prevents *ortho* lithiation of the aromatic ring in the presence of excess n-butyllithium.

Overman and co-workers have employed *tert*-butyldiphenylsilyl protection of a primary amine for the synthesis of compound **2.39** in **Scheme 2.10**. [103]



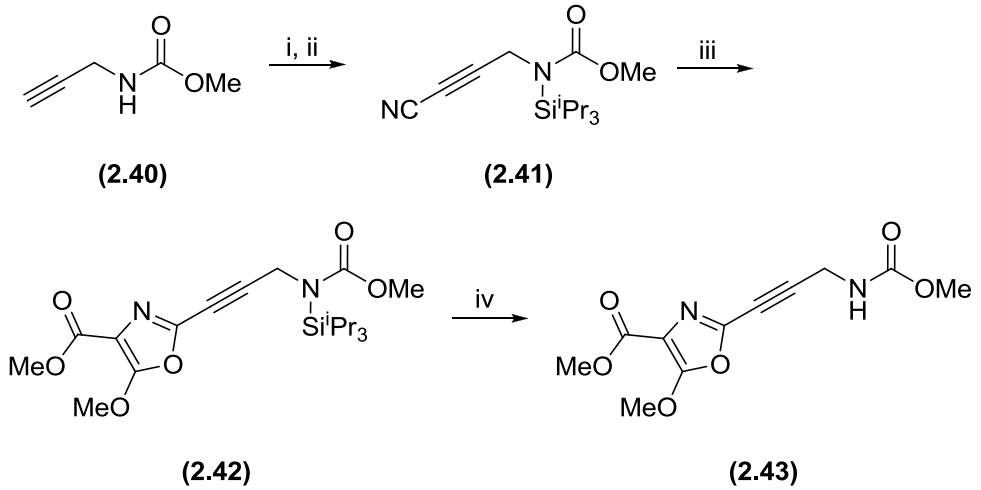
(2.35) **(2.36)** **(2.38)** **(2.39)** **(2.37)**

Reagents and Conditions: (i) cat. K_2CO_3, MeOH, rt, 97%; (ii) DMSO, oxalyl chloride, Et_3N, -78°C, 97%; (iii) **2.37**, Et_2O, -78°C to 0°C, 47%; (iv) 4:1 THF:1M $HCl_{(aq)}$, rt, 88%.

Scheme 2.10: Work by Overman *et al.*

The bulky *tert*-butyldiphenylsilyl protection was shown to be stable to organometallic reagents and oxidative conditions. In this instance amine **2.38** was deprotected using aqueous hydrochloric acid in tetrahydrofuran, however in the same publication pyridine-hydrofluoric acid is also mentioned as a possible deprotecting agent. Although very toxic, diluted aqueous solutions of hydrofluoric acid have a pKa of 3.45 [104], considerably less acidic than corresponding solutions of aqueous hydrogen chloride.

Wang *et al.*[105] have more recently reported the use of the tri-*iso*propylsilyl protection in the synthesis of **2.43** (**Scheme 2.11**).



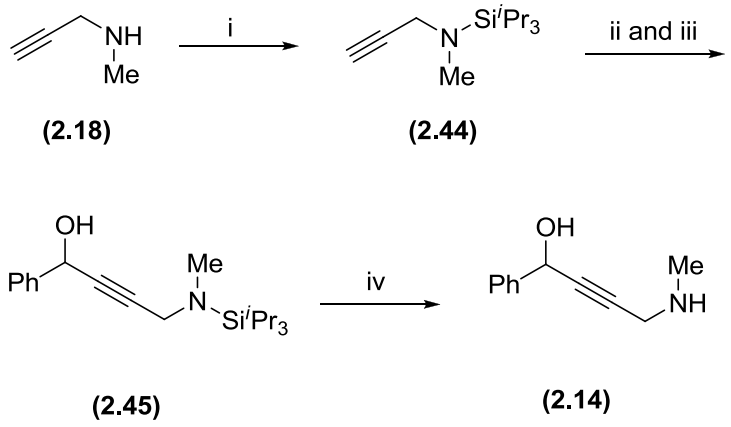
Reagents and Conditions: (i) ^{n}BuLi, THF, -78°C then TIPS-OTf, -78°C to rt; ii) ^{n}BuLi, -78°C then TsCN, -78°C to rt 72%; (iii) 5 mol% $Rh(OAc)_2$, diazomalonate, 1,2-DCE, reflux; (iv) 5M HF in MeCN, rt, 60%.

Scheme 2.11: Work by Wang *et al.*

The silyl amine is stable to *n*-butyllithium and remarkably it is also resilient to a metal carbenoid generated from diazomalonate and rhodium acetate. Silyl removal in this study was performed by action of a solution of hydrofluoric acid in acetonitrile.

All the positive points described above prompted the study of silyl protection for the synthesis of cyclisation precursor **2.12** and due to its availability in the laboratory the tri-*iso*propylsilyl group

was chosen for the investigation. Protection of *N*-methylpropargylamine **2.18** was achieved in quantitative yield with tri-*iso*propylsilyl trifluoromethanesulfonate in the presence of triethylamine as an acid scavenger (**Scheme 2.12**).



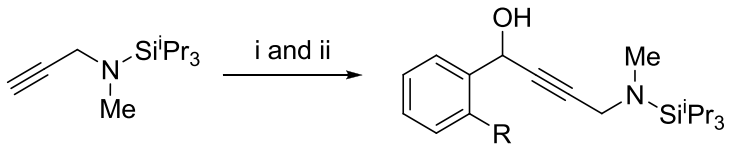
Reagents and Conditions: (i) TIPS-OTf, Et_3N, CH_2Cl_2, 0°C to rt, 99%; (ii) ^{n}BuLi, THF, -70°C; (iii) Benzaldehyde, -70°C to rt, then sat. aq. NH_4Cl, 95%; (iv) 40% aq HF, MeCN, rt, then 10% aq K_2CO_3, 87%.

Scheme 2.12: Silyl-Protection of *N*-Methylpropargylamine, Alkylation and Silyl-deprotection

Deprotonation at the terminal acetylene of silyl-protected amine **2.44** and alkylation with a slight excess of benzaldehyde proceeded in 95% yield. After quenching with saturated aqueous ammonium chloride and washing with saturated aqueous sodium bisulfate to remove excess aldehyde *via* its bisulfate adduct [106] the product **2.45** was found to be adequately pure so further purification was not performed. This reduces the required time for the synthesis and also avoids the potentially problematic column chromatography of the silyl amine.

Silyl deprotection of **2.45** was achieved using 40% aqueous hydrofluoric acid in acetonitrile inside a plastic container. A basic work up furnished desired amine **2.14** as a white, pure solid in 87% yield. This material required no further purification.

With an optimised route in hand, a small series of aryl substituted precursors was created in order to test the replicability of the devised synthesis. The results are presented below in **Table 2.1**.



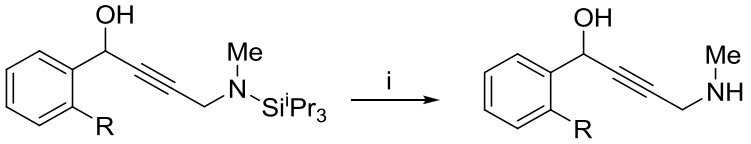
(2.44)

Reagents and Conditions: (i) ^{n}BuLi, THF, -70°C; (ii) 2-R-benzaldehyde see **Table 2.1**, -70°C to rt then sat. aq. NH_4Cl.

Scheme 2.13: Alkylation of Different Benzaldehydes with **2.44**

Entry	R	Compound reference	Yield (%)
1	H	**2.45**	92
2	F	**2.46**	86
3	Cl	**2.47**	91
4	Br	**2.48**	95

Table 2.1: Alkylation of Different Benzaldehydes with **2.44**



Reagents and Conditions: (i) 40% aq HF, MeCN, rt then 10% aq K_2CO_3.

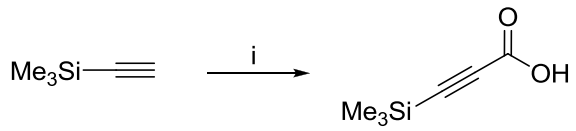
Scheme 2.14: TIPS-Deprotection of Different Analogues

Entry	R	Compound reference	Yield
1	H	**2.14**	94
2	F	**2.49**	96
3	Cl	**2.50**	92
4	Br	**2.51**	87

Table 2.2: TIPS-Deprotection of Different Analogues

2.1.2.3 Investigation of Amide Coupling

The required acid for the coupling (3-(trimethylsilyl)-2-propynoic acid) **2.13** was synthesised using a slightly modified version of Fleming's and co-workers procedure.[107]



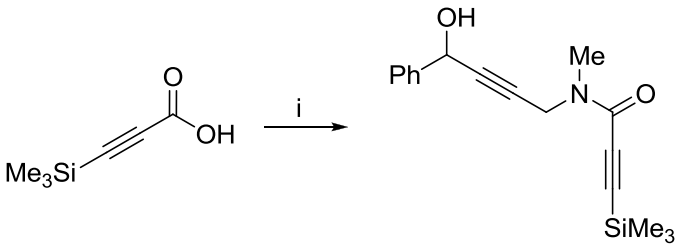
(2.52) **(2.13)**

Reagents and Conditions: (i) MeLi, THF, -70°C to -50°C then $CO_{2(s)}$ then 1M $HCl_{(aq)}$, 78%.

Scheme 2.15: Synthesis of (3-(trimethylsilyl)-2-propynoic acid)

The terminal acetylene proton in ethynyl(trimethyl)silane was removed by action of methyllithium. This step was found to require gentle warming form -78°C to -50°C in order for complete deprotonation to occur. The resulting solution was then carefully transferred *via* cannula into a flask containing crushed, solid carbon dioxide and the resultant slurry was stirred overnight. Quenching of the resulting lithium carboxylate with aqueous hydrochloric acid solution gave acid **2.13** in 78% yield.

The formation of amide **2.12** was subsequently investigated and to this end various coupling reagents and additives [108] were tested as shown in **Table 2.3** below.



(2.13) **(2.12)**

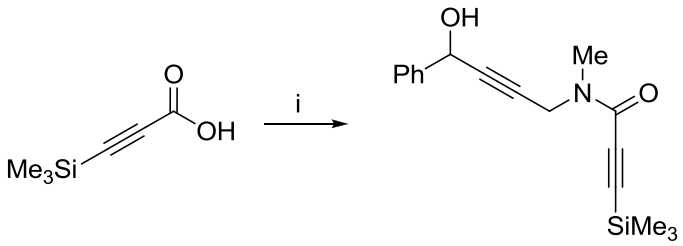
Reagents and Conditions: (i) Activating agent, see **Table 2.3** then **2.14**, Et_3N, CH_2Cl_2

Scheme 2.16: Generalised Amide Coupling

Entry	Activating agents	Yield (%)
1	Oxalyl Chloride / DMF	55
2	Oxalyl Chloride / DMAP	0
3	DCC	35
4	CDI	12
5	HBtU	46
6	DCC / HOBt	41

Table 2.3 Different Activating Agents Tested for Amide Coupling

The best results were obtained with oxalyl chloride [109] in the presence of a catalytic amount of DMF which gave amide **2.12** in 55% yield. This result however was deemed not satisfactory due to the high cost of *N*-methylpropargylamine **2.18** which is needed at the start of the synthesis of precursor **2.12**. Therefore attention was shifted to other reagents involved in the reaction, and different bases were screened for the amide coupling (**Table 2.4**).



(2.13) **(2.12)**

Reagents and Conditions: (i) Oxalyl chloride, $DMF_{(cat)}$, CH_2Cl_2 then **2.14**, Base, see **Table 2.2**, CH_2Cl_2

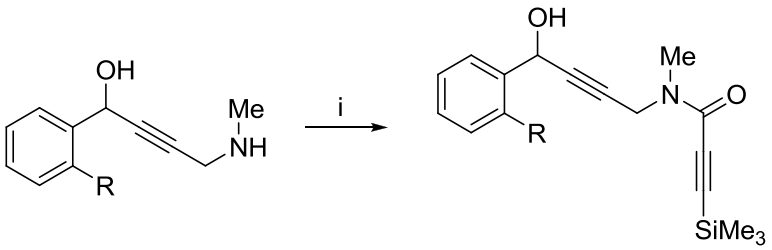
Scheme 2.17: Generalised Amide Coupling

Entry	Base	Yield (%)
1	Et_3N	55%
2	Pyridine	Trace
3	Imidazole	Trace
4	DIPEA	61%
5	2,6-Lutidine	82%

Table 2.4 Different Bases Tested for Amide Coupling

Pyridine and imidazole gave traces of product as detected by ^{1}H NMR analysis, while *N*,*N*-diisopropylethylamine provided a slight improvement over triethylamine. The best result however was obtained with the sterically hindered base 2,6-lutidine (Entry 5) which gave the desired amide **2.12** in 82% yield. A trend is visible in **Table 2.4** indicating that more sterically hindered bases give higher yields of desired amide **2.12**. At the start of this section during the synthesis of precursor **2.6** the terminal trimethylsilyl group in **2.3** was removed by action of a catalytic amount of sodium methoxide in methanol; a similar effect could be induced by unhindered nitrogen bases during the formation of amide **2.12**.

The optimised route to amide **2.13** was then applied to the synthesis of other cyclisation precursor analogues (**Table 2.5**).



Reagents and Conditions: (i) $Me_3SiC{\equiv}CCOCl$, CH_2Cl_2, 2,6-Lutidine, 0°C to rt.

Scheme 2.18: Amide Coupling of Different Analogues

Entry	R	Compound reference	Yield
1	H	**2.12**	84
2	F	**2.53**	81
3	Cl	**2.54**	80
4	Br	**2.55**	82

Table 2.5: Amide Coupling of Different Analogues

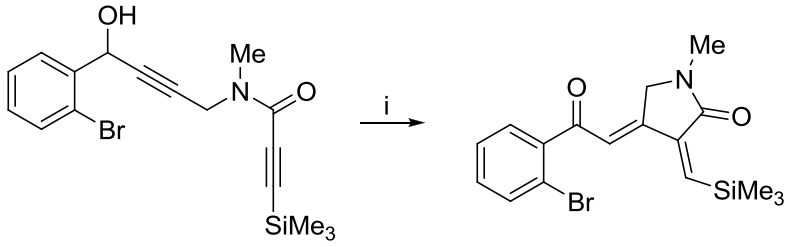
Yields for all three steps and for all the analogues were very satisfactory. However it must be noted that the products of the amide couplings always contained small quantities of solvent after purification (max 5% by ^{1}H NMR). This was caused by their high viscosity which makes the evaporation of residual volatiles a difficult task, made even harder by the fact that these molecules are not stable for prolonged periods of time (hours) even at room temperature. They were also found to be extremely sensitive to even mild acidic conditions, so much in fact that for ^{1}H and ^{13}C NMR analyses the deuterated chloroform employed had to be purified prior use by addition of 5Å molecular sieves and solid potassium carbonate.[110]

The problems associated with the amine protection/deprotection and amide coupling for the synthesis of the cyclisation precursors had been successfully solved. The newly developed method has proven very popular in research in the Parsons group and it will be employed for studies towards the total synthesis of the antibiotic Lactonamycin and other natural products.

2.1.3 Cyclisations

2.1.3.1 Cyclisation Reactions of Analogues

Compound **2.55** was chosen to test the thermolysis and a concentration of 0.1M was set in order to ensure replicability of future cyclisations. After refluxing in anhydrous, degassed toluene for four hours column chromatography afforded a bright-yellow, amorphous solid while attempts at isolating another minor product were unsuccessful. NMR, IR and mass analysis of the solid obtained revealed its structure to be diene **2.56** below.



(2.55) **(2.56)**

Reagents and Conditions: (i) Toluene 0.1M, reflux, 4h, 32%.

Scheme 2.19: Thermal Cyclisation of **2.13**

Interestingly, NMR data revealed that **2.56** had been formed as a single diastereomer, most likely the Z,Z diene. Numerous attempts were made at finding suitable recrystallisation conditions for X-ray analysis; this task however was made rather difficult by the instability of **2.56** in different hot solvents. Eventually it was discovered that relatively thick needle-like crystals could be obtained by the slow evaporation of a 1:5 v/v diethyl ether: hexane solution of **2.56**. The result of crystallographic analysis confirmed that the diene was indeed the Z,Z diastereomer (**Figure 2.2**). The crystal system was found to be orthorhombic and belonging to the Pbca (No.61) space group.

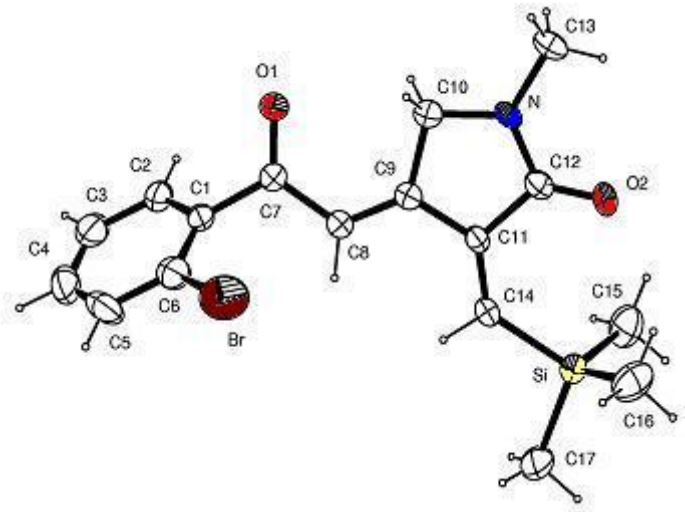
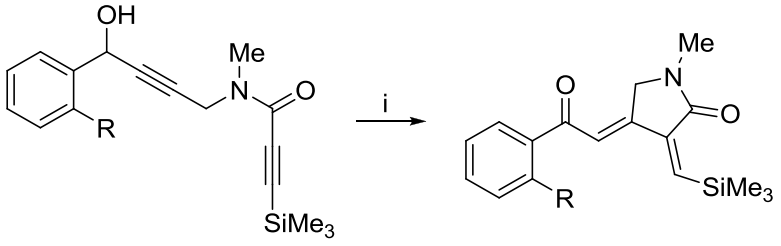


Figure 2.2: ORTEP Representation of Diene **2.56**

The other three cyclisation precursor analogues were also subjected to cyclisation conditions and the results are shown below (**Table 2.6**).



Reagents and Conditions: (i) Toluene 0.1M, reflux, 4h.

Scheme 2.20: Thermal cyclisations of Various Analogues

Entry	R	Compound reference	Yield
1	H	**2.57**	61
2	F	**2.58**	29
3	Cl	**2.59**	36
4	Br	**2.56**	32

Table 2.6: Thermal cyclisations of Various Analogues

Interestingly, amide **2.57** gave a relatively higher yield of its correspondent diene product **2.56**. The only obvious structural difference of this precursor compared to the rest is the absence of a halogen atom at the 2-position on the aromatic ring.

It was also possible to obtain X-ray crystal structures for compounds **2.57** (rhombohedral crystal structure, $R\bar{3}$ (No.148) space group) and **2.59** (monoclinic crystal structure, $P\ 2_1/c$ (No.14) space group) (**Figures 2.3** and **2.4**), however attempts at obtaining thick-enough crystals of fluoro-analogue **2.58** were always unsuccessful possibly due to increased lipophilicity imparted to the whole molecule by the fluorine atom.

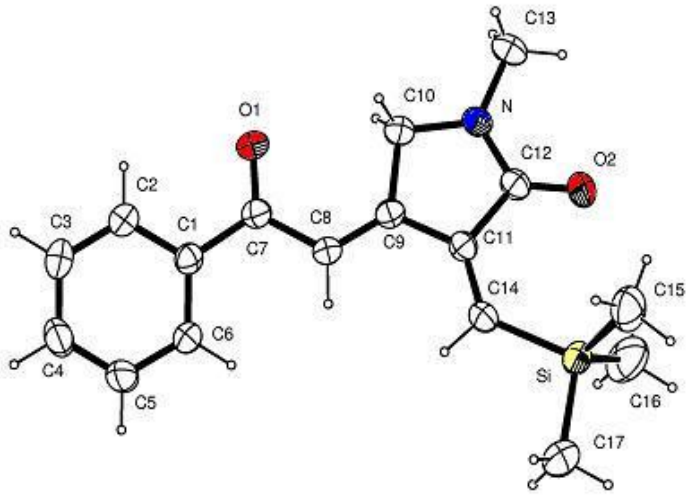


Figure 2.3: ORTEP Representation of Diene **2.57**

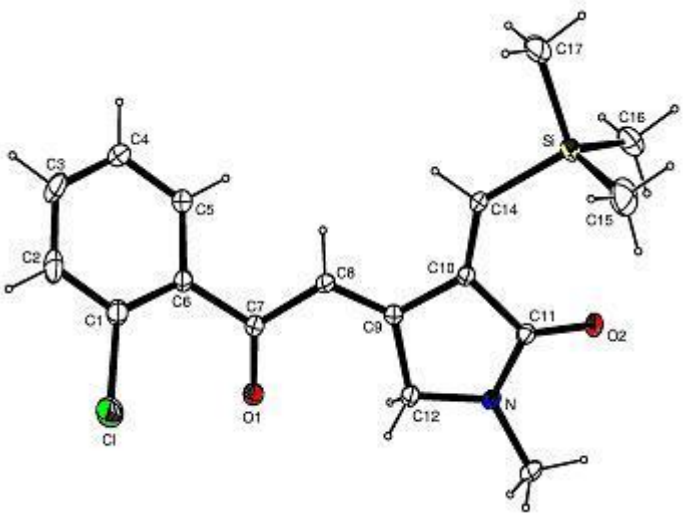
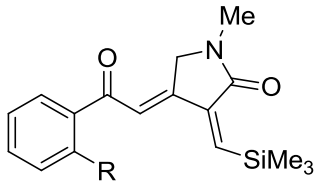


Figure 2.4: ORTEP Representation of Diene **2.59**

The above ORTEP drawings show that in all cases a single diastereomer was formed.

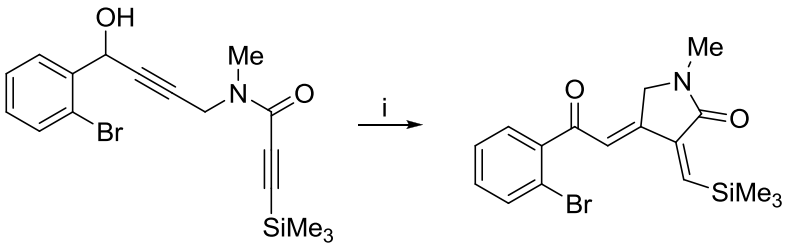
This reaction is the first example of a metal-free generation of Z,Z *exo*-cyclic conjugated dienes fused to lactams. Although the desired product was always formed under these conditions, the yields were considerably affected by decomposition during the course of the reaction. A possible cause for this was identified while recording the melting points of dienes **2.56**, **2.57**, **2.58** and **2.59**. These compounds were found to decompose at temperature only slightly higher than the boiling point of toluene (110.58°C) [111] as reported in **Table 2.7** below. Worthy of note is that the product derived from higher-yielding amide **2.57** has a higher decomposition temperature than the rest of the precursors.



Entry	Compound reference	R	Decomposition temperature (°C)
1	**2.57**	H	149-151
2	**2.58**	F	127-130
3	**2.59**	Cl	123-125
4	**2.56**	Br	122.124

Table 2.7: Decomposition temperatures of diene products

This effect could be the result of the absence of a halogen substituent in **2.57** which would hamper rotation of the aromatic ring during heating and therefore lead to a lower decomposition temperature. Decomposition could also arise from unwanted intermolecular reactions taking place at 0.1M concentration. In order to test these theories, the cyclisation of precursor **2.56** was repeated at 80°C, 0.01M concentration and a reaction time of 24 hours (**Scheme 2.20** below).

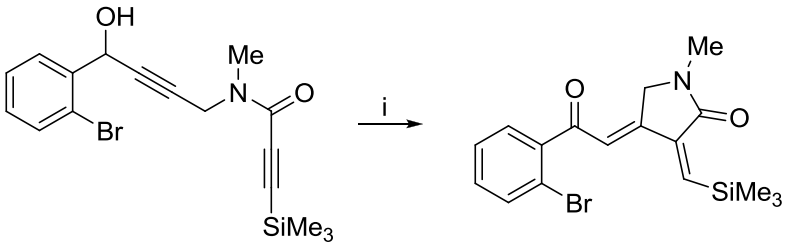


(2.55) **(2.56)**

Reagents and Conditions: (i) Toluene 0.01M, 80°C, 24h, 35%.

Scheme 2.20: Cyclisation at Reduced Temperature, Reduced Concentration and Longer Reaction Time

Although the reaction took a longer time to reach completion the yield of cyclisation product only slightly increased. Therefore decomposition in the above cyclisations is completely independent of solvent concentration and temperature. It could then be assumed that decomposition is caused by transient, very reactive species which can undergo various side reactions. During their studies into the *intra*molecular [4+2] addition of conjugated ynones, Danheiser ad co-workers [82] employed γ-terpinene to suppress polymerisation of the ynone starting material. Reflux of cyclisation precursor **2.55** in toluene in the presence of γ-terpinene however gave no improvement on the yield (**Scheme 2.21** below).



(2.55) **(2.56)**

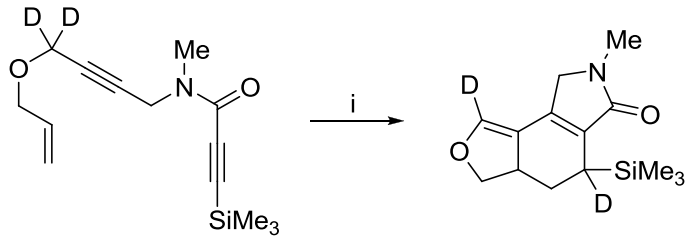
Reagents and conditions: (i) Toluene 0.1M, γ-terpinene, reflux, 4h, 30%

Scheme 2.21: Cyclisation in the presence of γ-terpinene

2.2 Ketone Modification - Novel Synthesis of 2-Hydroxypyrroles

2.2.1 Outline of Investigation

As pointed out in **Section 1.1.3**, deuterium-labeling studies have previously confirmed that during the cyclisation discovered by Parsons *et al.* a hydrogen atom is abstracted intramolecularly (**Scheme 1.8** below).

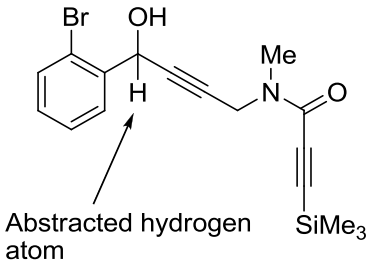


(1.21) **(1.22)**

Reagents and Conditions: (i) Toluene, reflux, 3.5h, 94%.

Scheme 1.8: Cyclisation of Deuterated Compound **1.21**

A way to drastically alter the reactivity of compound **2.55** is to completely remove this hydrogen atom by oxidising the secondary alcohol moiety to a ketone (**Figure 2.5** below).



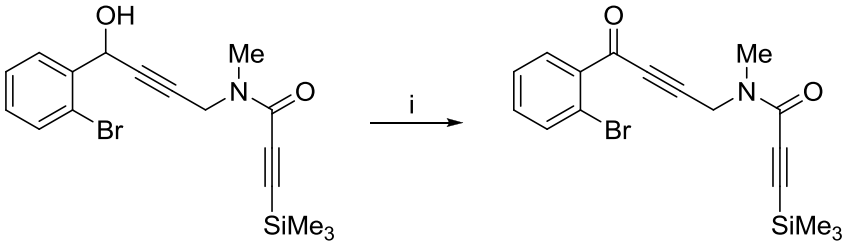
(2.55)

Figure 2.5: Position of the abstracted hydrogen atom in **2.55**

2.2.2 Oxidation of Secondary Alcohol to Ketone

There are countless procedures available in the literature to oxidise secondary alcohols to ketones.[112] One of the cheapest and most synthetically robust is the oxidation with manganese(IV) oxide (MnO_2). Pyrolusite (natural source of MnO_2) and pure synthetic MnO_2 are poor oxidants.[113] Oxidation of organic compounds requires active and specially prepared MnO_2; several procedures for the generation of this reactive oxidant have been published.[114-116] Further appeal for the use of this reagent comes from the fact that reactions are heterogeneous, they are generally fast (in the order of hours) and do not require the use of anhydrous solvents.

Oxidation of alcohol **2.55** with excess MnO_2 was carried in CH_2Cl_2 at room temperature for 24h (**Scheme 2.22**).



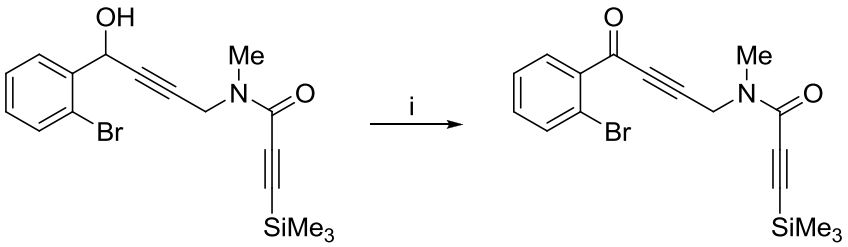
(2.55) **(2.60)**

Reagents and Conditions: (i) 20 eq MnO_2, CH_2Cl_2, rt, 24h, 54%

Scheme 2.22: Oxidation of Alcohol **2.55** with MnO_2

The yield was deemed unsatisfactory and another disadvantage included the need of a 20 fold excess of reagent which could cause problems during scale-up.

A better oxidation protocol had to be sought. Inspiration came from the work of Jones *et al.*[117-119] on the oxidation of acetylenic alcohols employing chromic acid, generated from chromium(VI) trioxide and concentrated sulfuric acid. Preparation of Jones' reagent was achieved using a published procedure.[120]



(2.55) **(2.60)**

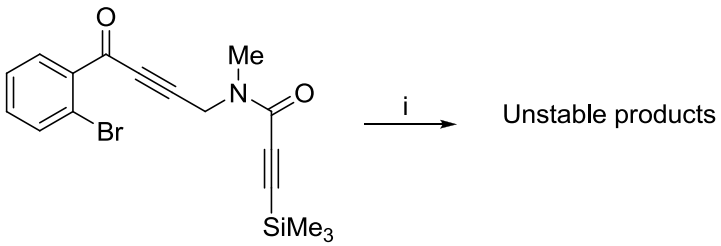
Reagents and Conditions: (i) 3.0M Jones' reagent, acetone, rt, 96%.

Scheme 2.23: Jones Oxidation of **2.55**

Oxidation of alcohol **2.55** with this solution proceeded in very high yield (**Scheme 2.23**). Added advantages to the use of this procedure are short reaction times and easy work-up conditions. Often it was found that only a simple filtration through a short column of silica gel was all that was required to obtain pure **2.60**.

2.2.3 Cyclisation

The next step was to test the thermolysis of **2.60** in refluxing anhydrous, degassed toluene. Identical to previous cyclisations a 0.1M concentration of the reaction mixture was initially chosen (**Scheme 2.24**).

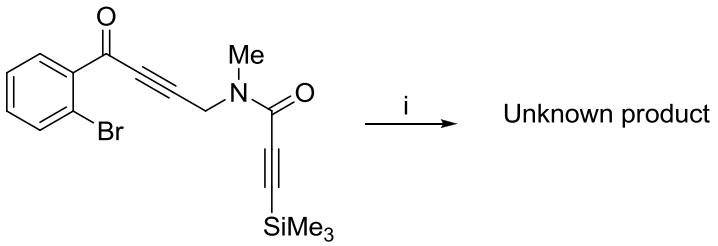


(2.60)

Reagents and conditions: (i) Toluene, 0.1M, reflux, 4h

Scheme 2.24: Thermolysis of **2.60** at 0.1M Concentration

Unfortunately the above thermolysis failed to give any isolable products. In order to test if the concentration of the starting material was an issue, heating of **2.60** in toluene was repeated at 0.01M (**Scheme 2.25**). A single product was isolated which was found to be unstable to moisture, light, prolonged heating in various solvents and mild acidic conditions.



(2.60)

Reagents and conditions: (i) Toluene, 0.01M, reflux, 4h

Scheme 2.25: Thermolysis of **2.60** at 0.01M Concentration

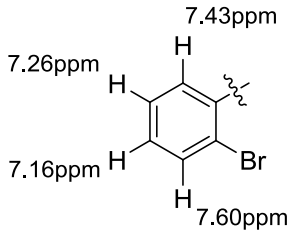
Despite this it was possible to obtain clean spectroscopic data, and the ^{1}H, ^{13}C, HSQC and HMBC data analysis is discussed below.

2.2.4 Structure Elucidation of Cyclisation Product

The ^{1}H NMR spectrum of the novel cyclisation reaction product is shown below (**Figure 2.6**).

Figure 2.6: ^{1}H NMR Spectrum of Novel Product

The spectrum displays a total of seven peaks, five in the low field region (6.68-7.60ppm) and two in the high field region (0.45, 3.24ppm). A tentative assignment of a number of these peaks can be made by comparison with the ^{1}H NMR spectrum of precursor **2.60**. The peak at 0.45ppm (singlet, integration: 9H) could correspond to a trimethylsilyl functionality and the peak at 3.24ppm (singlet, integration: 3H) could be attributed to an amide's N-methyl group. The same reasoning would lead to the assignment of the four peaks in aromatic region (7.60ppm (doublet, integration: 1H), 7.43ppm (doublet, integration: 1H), 7.27ppm (triplet, integration: 1H) and 7.16ppm (triplet, integration: 1H)) to the four proton of a substituted 2-bromoaryl group, as shown in **Figure 2.7** below.



Scheme 2.7: Assignment of Peaks in the 7.16-7.60ppm Region

At this point the peak at 6.68ppm (singlet, integration: 1H) cannot be tentatively assigned to any specific functional groups.

Analysis of the ^{13}C and DEPT spectra reveals that the cyclisation product contains a total of fifteen carbon environments, six of which are CH/CH_3 carbons and the remaining nine are quaternary centres.

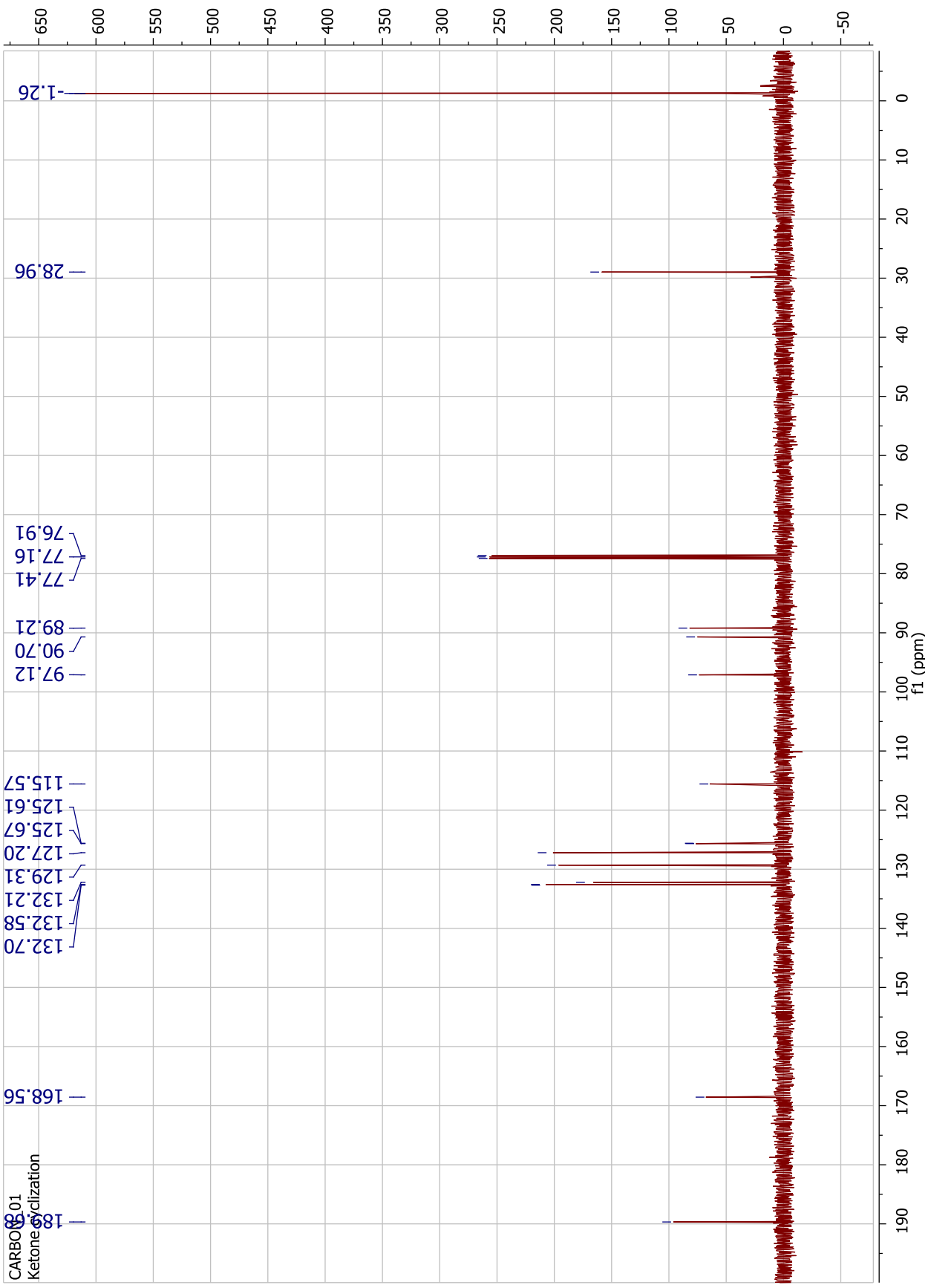


Figure 2.8: ^{13}C NMR Spectrum of Novel Product

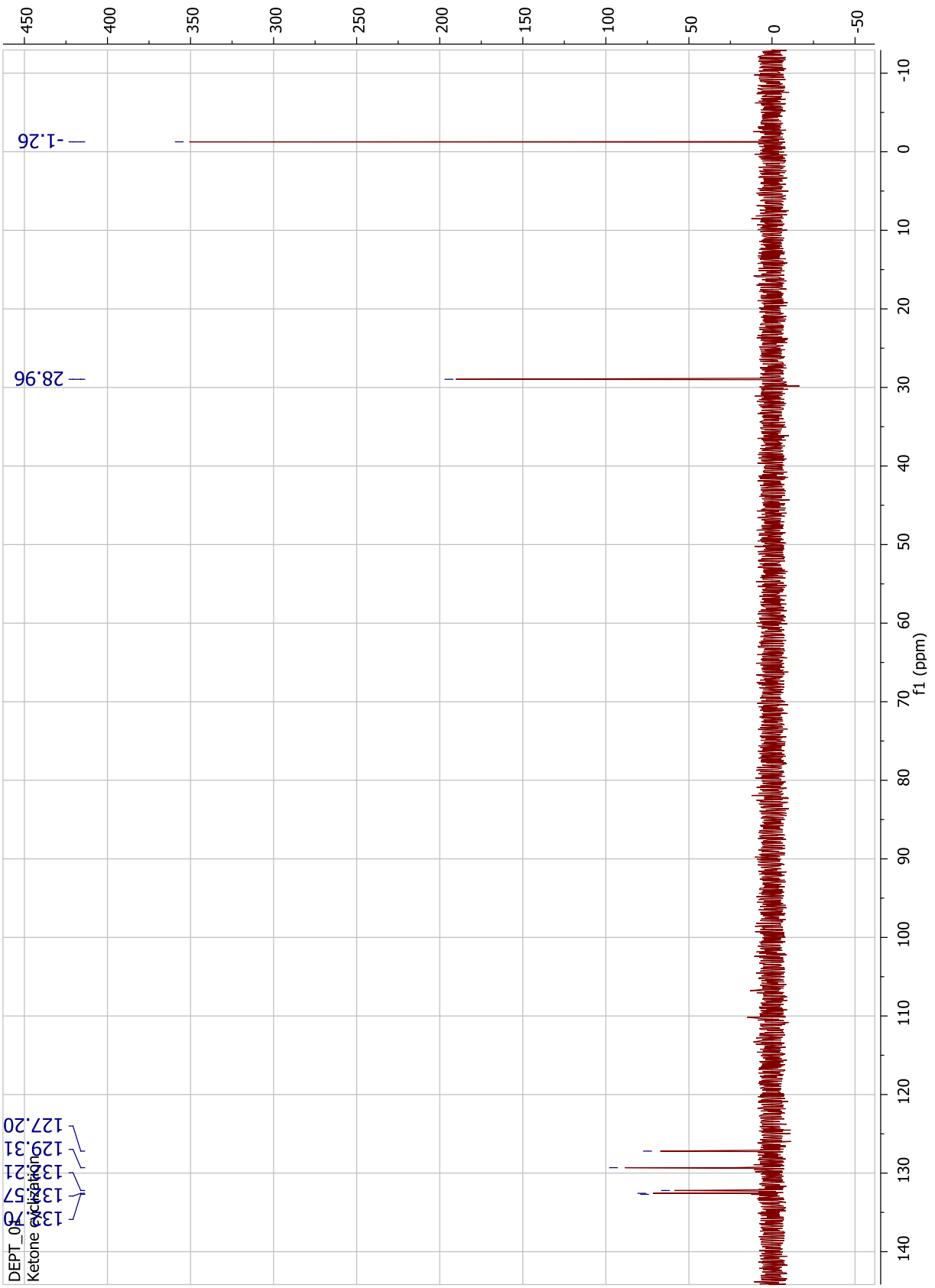


Figure 2.9: DEPT NMR Spectrum of Novel Cyclisation Product

Using the HSQC spectrum, one-bond carbon-hydrogen correlations can be made (**Table 2.8**). From this data it is revealed that ^{1}H NMR peak at 6.67ppm is related to ^{13}C NMR peak at 132.21ppm; these regions are characteristic of π-electron rich heteroaromatic fragments.

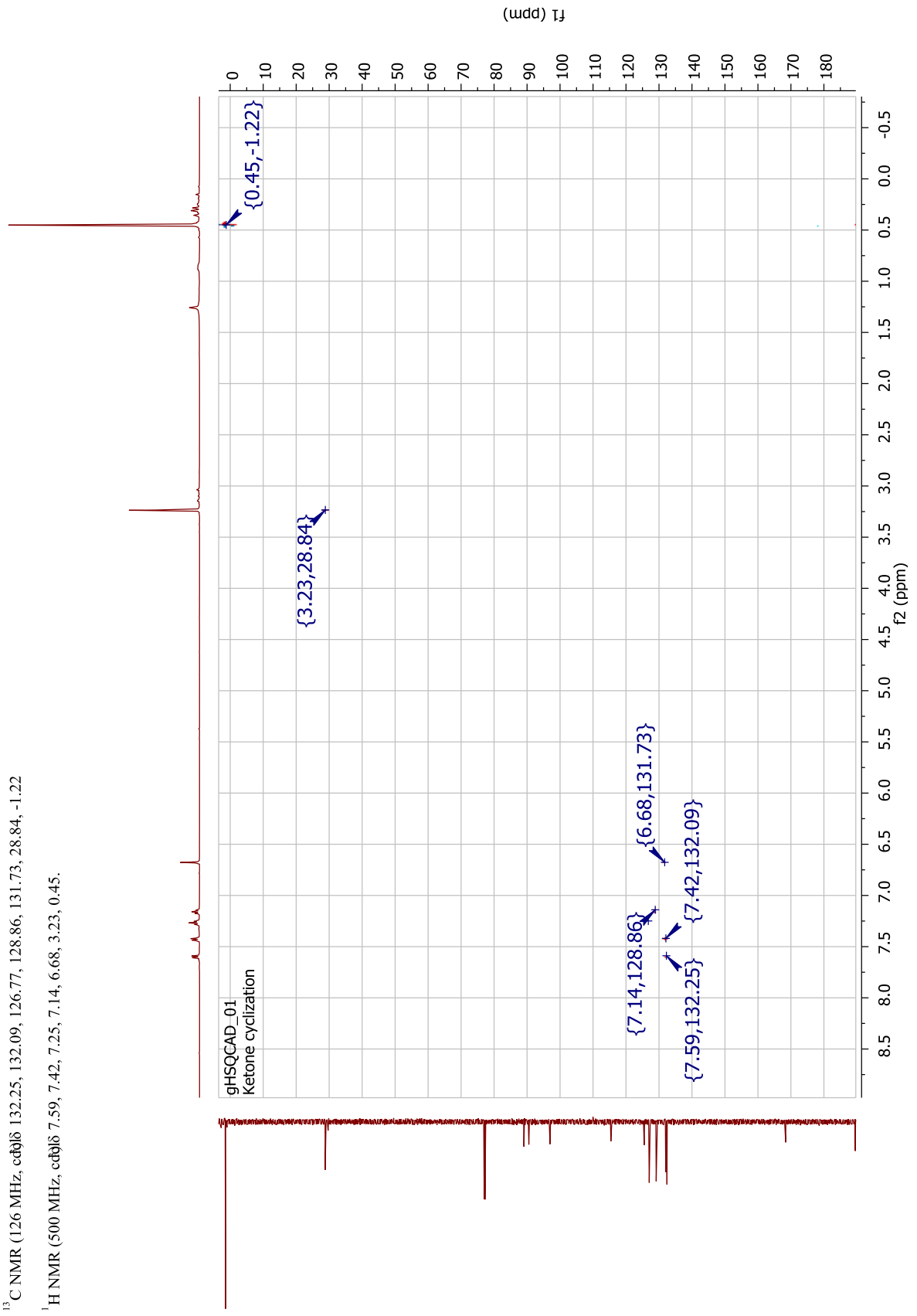


Figure 2.10: HSQC NMR Spectrum of Novel Cycliation Product. (Note: ^{13}C Signal Values are Shifted by a Fraction of ppm)

The single quantum coherence correlations are listed in **Table 2.8** below.

^{1}H Shift (ppm)	^{13}C Shift (Corrected to ^{13}C NMR spectrum) (ppm)	Fragment
0.45	-1.26	$RSiMe_3$
3.23	28.96	RCONMe
6.67	132.21	π-Electron rich heteroaromatic
7.16	129.31	Aromatic
7.27	127.20	Aromatic
7.43	132.58	Aromatic
7.60	132.70	Aromatic

Table 2.8: HSQC Derived C-H Correlations

Therefore eight ^{13}C signals remain unaccounted for. From ^{13}C functional group tables, the tentative assignments shown in **Table 2.9** below can be made.

^{13}C Shift (ppm)	Functional group
89.21	Alkyne
90.70	Alkyne
97.12	π-Electron rich heteroaromatic
115.57	π-Electron rich heteroaromatic
125.61	Aromatic
125.67	Aromatic
168.56	Conjugated carboxylic acid derivative
189.68	Conjugated ketone

Table 2.9: Tentative Assignment of Remaining ^{13}C Signals by Comparison with ^{13}C Functional Group Shifts Table

The HMBC spectrum of the novel compound is shown below (**Figure 2.11**).

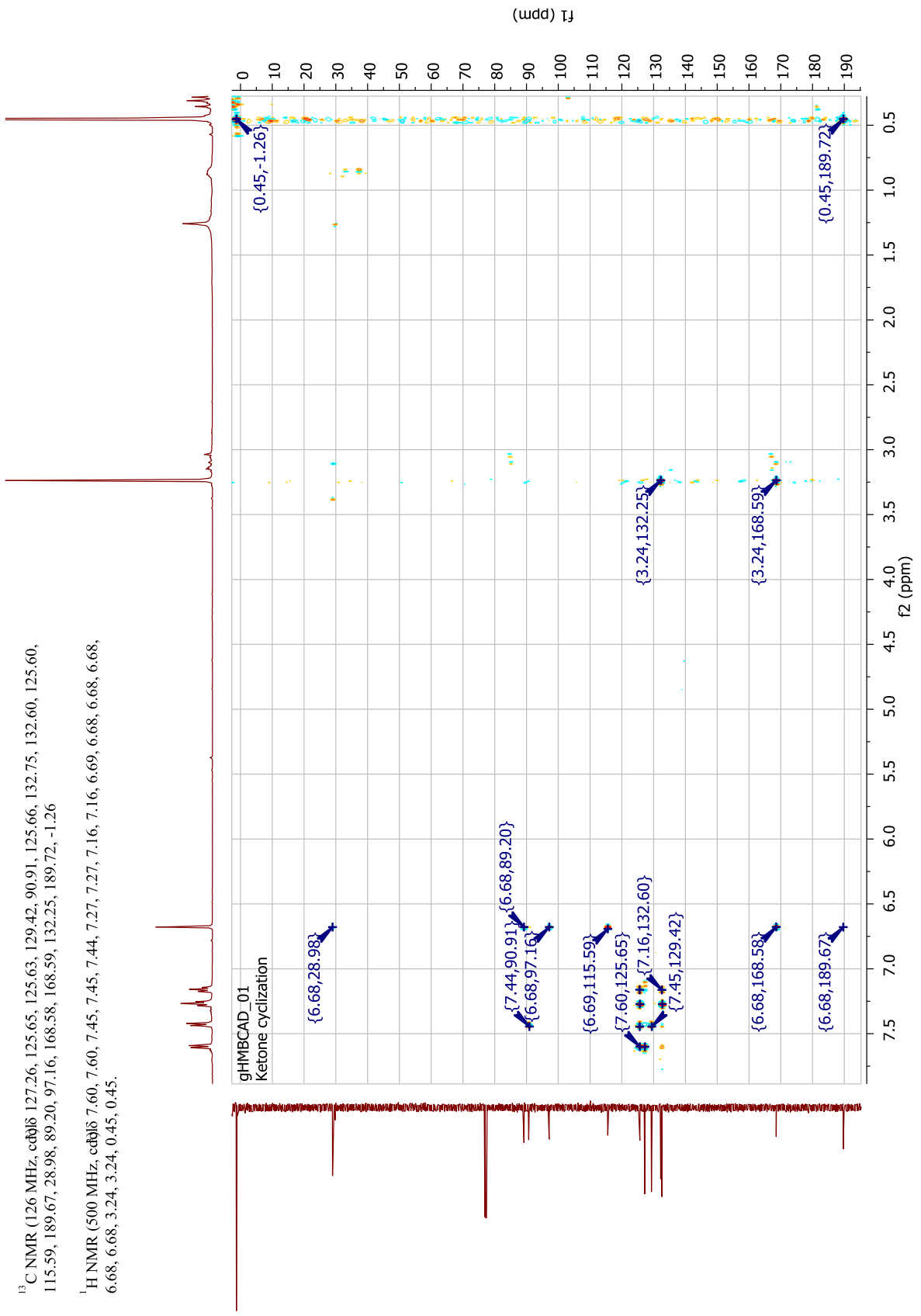


Figure 2.11: HMBC NMR Spectrum of Novel Cycliation Product. (Note: ^{13}C Signal Values are Shifted by a Fraction of ppm)

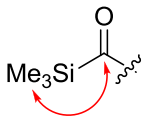
The multiple bond coherence correlations are shown in **Table 2.10** below.

^{1}H Shift (ppm)	^{13}C Shift (ppm) (Corrected to ^{13}C NMR spectrum)
0.45	-1.26, 189.68
3.24	132.21, 168.56
6.68	168.56, 97.12, 89.21, 28.96, 189.68, 115.57
7.16	125.61, 132.58
7.27	132.70, 125.67
7.43	90.70, 129.31, 125.61
7.60	125.67, 127.20

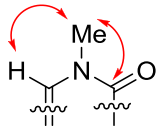
Table 2.10: HMBC Derived C-H Correlations

The following conclusions can be drawn from the above HMBC correlations:

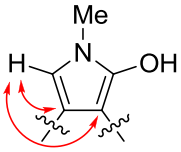
1) The trimethylsilyl group (0.45ppm, ^{1}H shift) correlates to a conjugated ketone (189.68ppm, ^{13}C shift). An acyl silane moiety is therefore present in the molecule:



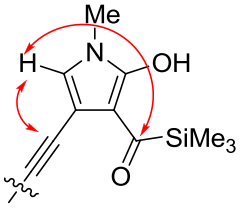
2) The N-methyl group (3.24ppm, ^{1}H shift) correlates to a conjugated carboxylic acid derivative (168.56ppm, ^{13}C shift). An amide function is therefore present in the molecule. The N-methyl group also correlates to a single proton belonging to π-electron rich heteroaromatic group (6.68ppm, ^{1}H shift, 132.21ppm, ^{13}C shift). These notions lead to the identification of an unsaturated, nitrogen-based heterocycle in the molecule:



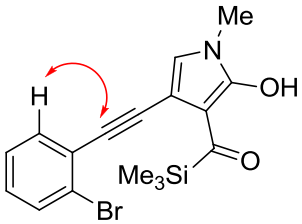
3) The single proton belonging to the heteroaromatic group (6.68ppm, ^{1}H shift) correlates to two π-electron rich heteroaromatic group signals (97.12ppm, 115.57ppm, ^{13}C shifts). Therefore the aforementioned heterocyclic group is a hydroxy-pyrrole:



4) The hydrogen atom of the hydroxy-pyrrole moiety also correlates to an alkyne carbon (89.21ppm, ^{13}C shift) and more weakly to the acyl silane carbon (189.68ppm, ^{13}C shift). Therefore, an acetylene and acyl silane substituents are present at the 4- and 3-positions of the pyrrole ring:



5) Finally, the aromatic proton at 7.43ppm in the ^{1}H spectrum correlates to an acetylene carbon atom (90.70ppm, ^{13}C shift). This last piece of information gives the complete structure of novel product **2.61**:

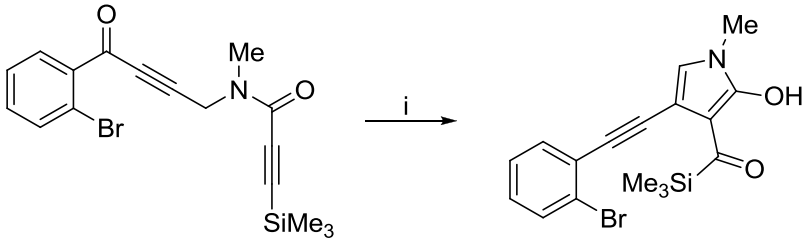


(2.61)

Chemical Formula: $C_{17}H_{18}BrNO_2Si$
Molecular Weight: 376,32

The above structure is consistent with high resolution mass spectrum values (calcd. for $C_{17}H_{18}BrNO_2NaSi$ $[M+Na]^+$: 398.02011; found: 398.0182). The IR of product **2.61** displays a weak but broad peak at around 3300cm^{-1}, consistent with a hydroxyl group. A stretch for an alkynyl moiety is also present (2204.82cm^{-1}) together with a typical conjugated acyl silane stretch [121] (1573.30cm^{-1}). All the data in hand is highly consistent with proposed structure **2.61**.

2.2.5 Synthesis and Cylisations of Ketone Analogues



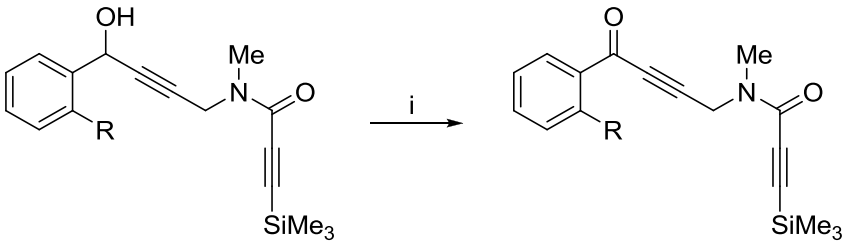
(2.60) **(2.61)**

Reagents and Conditions: (i) Toluene, 0.01M, reflux, 4h, 53%

Scheme 2.26: Thermolysis of **2.60** at 0.01M Concentration

This reaction is unprecedented in the chemical literature. The outcome of the thermolysis is the generation of a tri-substituted pyrrole containing a conjugated acetylene and acyl silane moieties. The acyl silane could be responsible for the observed light sensitivity of **2.61**; it is known that n-π^* excitations in acyl silanes occur at unusual long wavelength (380-420 nm) [122,123], well into the visible light spectrum (390-750 nm).[104]

In order to test the breadth of the synthetic utility of this cyclisation reaction three new ketone cyclisation analogues were synthesised (**Table 2.11**).



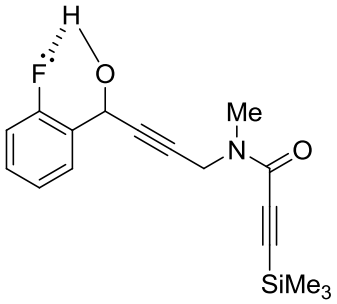
Reagents and Conditions: (i) 3.0M Jones' reagent, acetone, rt

Scheme 2.27: Alcohol Oxidation of Different Analogues

Entry	R	Product Reference	Yield (%)
1	H	**2.62**	91
2	F	**2.63**	74
3	Cl	**2.64**	88
4	Br	**2.60**	96

Table 2.11: Alcohol Oxidation of Different Analogues

Oxidation of fluorine analogue **2.53** proved to be difficult, possibly due to hydrogen bonding between the fluorine atom and the benzylic hydroxyl group (**Figure 2.11**).

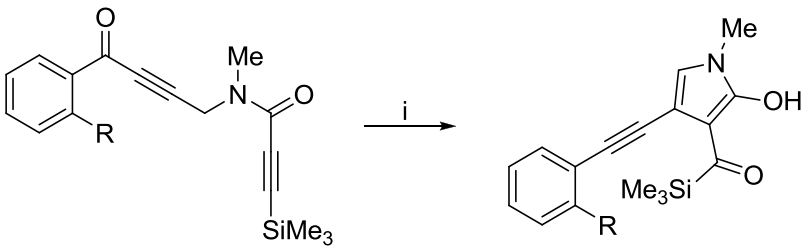


(2.53)

Figure 2.11: Hydrogen Bonding Between Fluorine Atom and Hydroxyl Group

The transformation however proceeded in fair yield with longer reaction times and addition of extra equivalents of Jones' reagent.

The results of the cyclisation of ketones **2.62**, **2.63** and **2.64** are shown in **Table 2.12** below.



Reagents and conditions: (i) Toluene, 0.01M, reflux, 4h

Scheme 2.28: Cyclisation of Ketone Analogues

Entry	R	Product reference	Yield (%)
1	H	-	Decomposition
2	F	-	Decomposition
3	Cl	**2.65**	46
4	Br	**2.61**	53

Table 2.12: Cyclisation of Ketone Analogues

Unfortunately ketones **2.62** and **2.63** decomposed completely during the course of the reaction leaving no isolable products. Chloro-analogue **2.64** instead successfully cyclised giving expected product **2.65** in 46% yield.

2.3 Investigation of Mechanisms

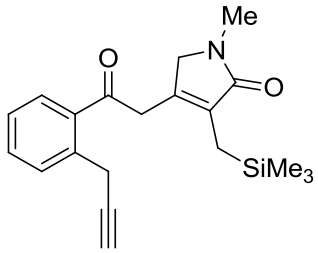
2.3.1 Cyclisation of Alcohol Analogues

The key steps in the proposed mechanism for the generation of ketone **2.7** (**Scheme 2.2**) in **Section 2.1.1** were:

i) Generation of a biradical

ii) 1,5-Hydrogen abstraction and radical tautomerism

iii) Quenching of resulting biradical by intermolecular abstraction of hydrogen (either from solvent or other species)

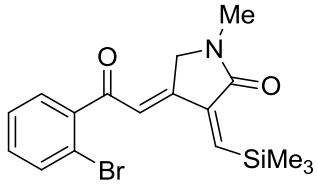


(2.7)

Figure 2.11: Previously Isolated Product

The net result is a cyclisation reaction with gain of two new hydrogen atoms which could either originate from toluene or from other organic fragments present in solution. The latter could explain the extensive decomposition observed during the course of the reaction.

Novel cyclisation product **2.56** (**Figure 2.12**) structurally resembles ketone **2.7**. However in **2.56** it is obvious that the *inter*molecular hydrogen-abstraction step does not occur.

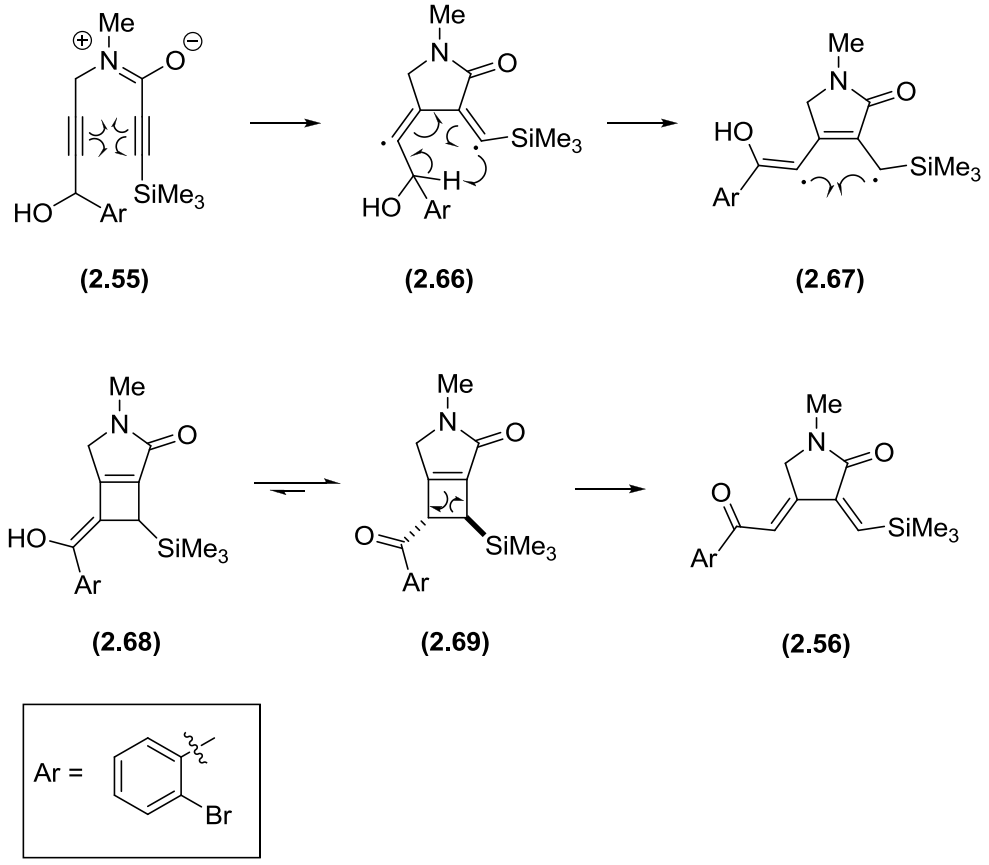


(2.56)

Figure 2.12: Novel product **2.56**

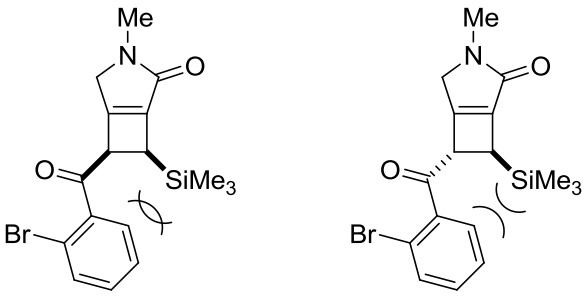
2.3.1.1 First Proposed mechanism

Following the mechanistic proposal for the formation of **2.7**, the generation of diene **2.56** could be accounted for by the mechanism depicted below in **Scheme 2.29**.



Scheme 2.29: First Proposed Mechanism for the Formation of **2.56**

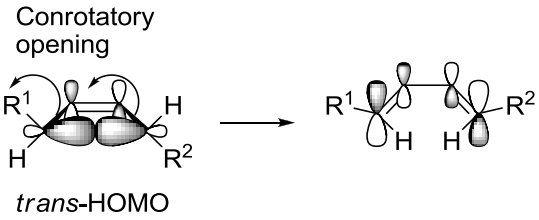
Amide resonance aids the approach of the two acetylene moieties close causing a cyclisation to pyrrole **2.66** with generation of a 1,4-biradical system. 1,5-Hydrogen abstraction and radical tautomerism would then yield biradical **2.67**. At this stage the intermolecular abstraction of hydrogen atoms does not occur; radical combination instead could yield strained fused cyclobutene **2.68.** Tautomerism of enol **2.68** yields ketone **2.69** which adopts the thermodynamically more stable *trans*-configuration in order to minimise steric interactions between the aryl and the silicon groups (**Figure 2.13**).



cis **(2.69)** *trans* **(2.69)**

Figure 2.13: Steric Interactions in the *Cis* and *Trans* Configurations of **2.69**

Cyclobutenes are known to undergo thermal isomerisation to yield open-chain butadienes.[124,125] As predicted by Woodward-Hoffmann rules [126] this electrocyclisation is stereospecific and proceeds cleanly in a conrotatory manner as shown in **Scheme 2.30** below.

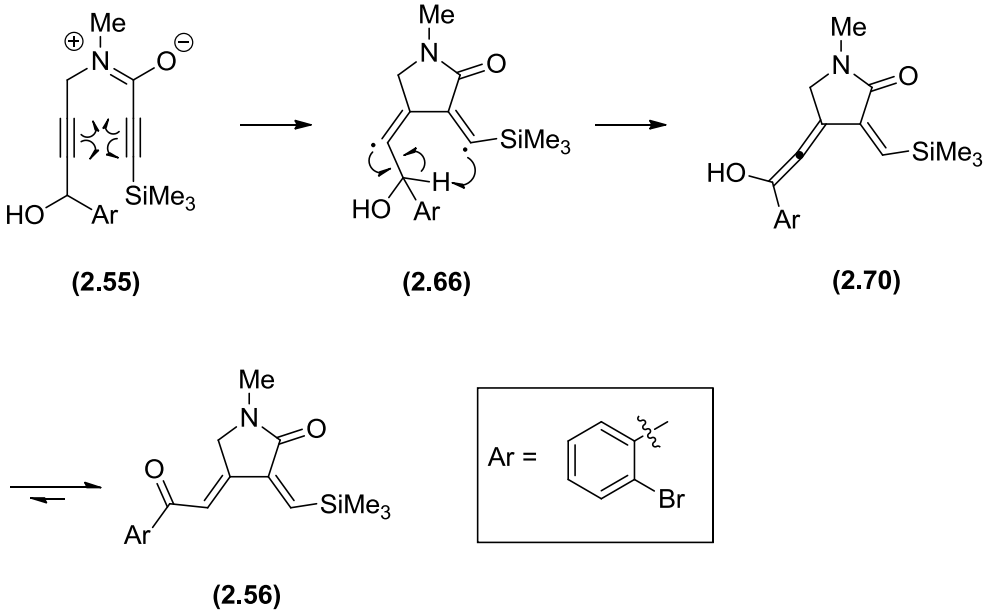


Scheme 2.30: Conrotatory Opening of Cyclobutenes

Therefore, thermal opening of *trans* **2.69** would yield exclusively the observed (Z,Z)-diene **2.56**.

2.3.1.2 Second Proposed Mechanism

A second possible mechanism for the formation of diene **2.56** is shown in **Scheme 2.31** below.

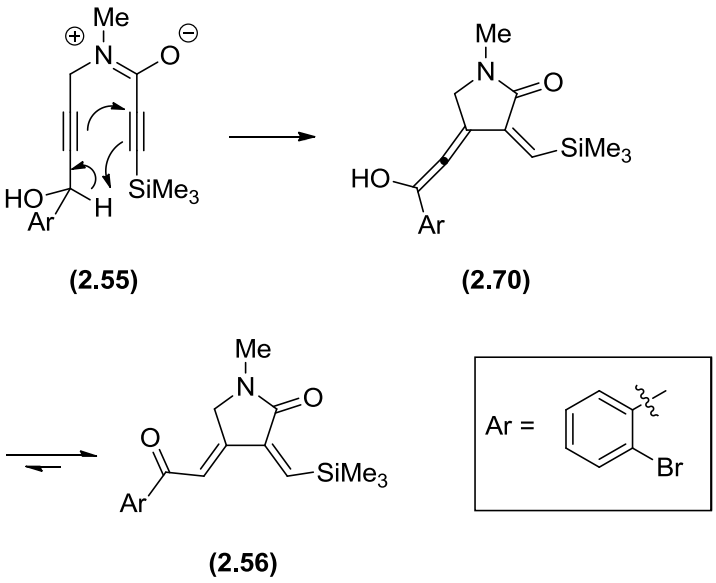


Scheme 2.31: Second Proposed Mechanism for the Formation of **2.56**

The first two steps are the same as for the previously proposed mechanisms. However, after 1,5-hydrogen abstraction in **2.66**, radical tautomerism does not take place and instead radical termination gives allenol **2.70**, which is in equilibrium with observed diene **2.56**. However the absence of radical tautomerism in structure **2.66** contradicts the previously proposed mechanism for the formation of **2.7**.

2.3.1.3 Third Proposed Mechanism

Lastly a third mechanism could be in operation (**Scheme 2.32**).



Scheme 2.32: Proposed Propargylic-*Ene* Mechanism for the Formation of **2.62**

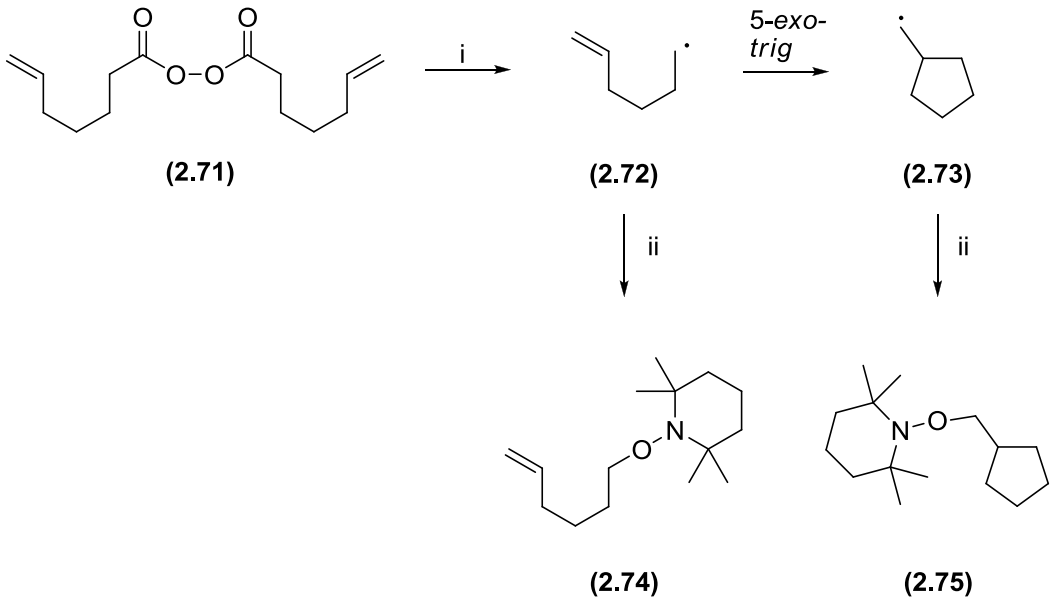
Amide resonance in **2.55** could bring the alkynes in proximity and allow a concerted propargylic-*ene* reaction to take place, yielding allenol **2.70** in a single mechanistic step. As the second mechanism proposed above however it fails to account for the isolation of product **2.7**.

Therefore the first and second proposed mechanisms are stepwise-radical whereas the third is concerted-*ene*. The first step into the investigation of which mechanism is in operation then was to test if the supposed initial generation of a biradical is actually taking place.

2.3.2 Attempted Radical Trappings by Chemical Means

A convenient method employed for the study of reaction involving carbon-centered radicals is their chemical trapping by stable nitroxyl radical species such as TEMPO.[127]

For example, Beckwith *et al.*[128] have shown that TEMPO can efficiently trap the carbon-based radical products generated from the thermolysis of bis(6-heptenoyl) peroxide **2.71** in cyclohexane to give isolable adducts **2.74** and **2.75** (**Scheme 2.33**).

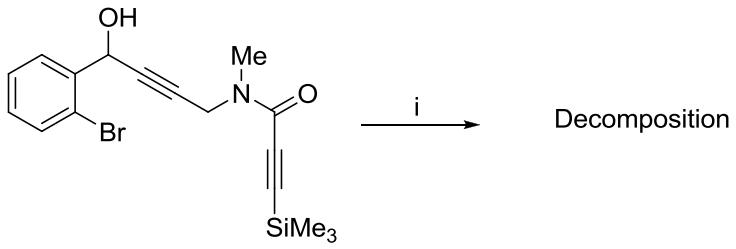


Reagents and Conditions: (i) Cyclohexane, 123.5°C, 1.53M, **2.71**; (ii) 10eq. TEMPO, **2.74**: 6.74%, **2.75**: 11.84%.

Scheme 2.33: Trapping of Carbon-Based Radicals with TEMPO by Beckwith *et al.*

The success of these trapping reactions is reported to be highly dependent on steric bulk present around the radical centre [129], the polarity of solvent employed and the bimolecular rate at which radicals in solution might terminate each other.[130]

Encouraged by the possibility of trapping potential radical intermediates the above methodology was applied for the cyclisation of amide **2.56** (**Scheme 2.34**).



(2.56)

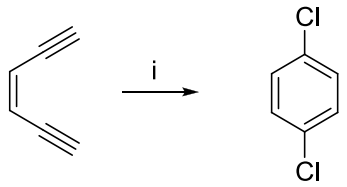
Reagents and Conditions: (i) Toluene, reflux, 0.1M, 10 eq. TEMPO, 4h.

Scheme 2.34: Attempted Radical Trapping with TEMPO

Unfortunately, reflux of **2.56** in toluene in the presence of an excess of TEMPO gave extensive decomposition. No isolable products were detected by conventional analysis techniques and therefore purification was not attempted. This destructive effect observed in the reaction with

TEMPO however could still be an indication of interference with radicals generated during the course of the cyclisation.

Another test for the presence of radical intermediates during a reaction is to employ carbon tetrachloride as a chemical trap. As discussed in the introduction section, during their work on the enediyne thermal cyclisation Bergman and Jones trapped the *p*-benzyne intermediate by switching the solvent from benzene to carbon tetrachloride (**Scheme 2.35**).[36]

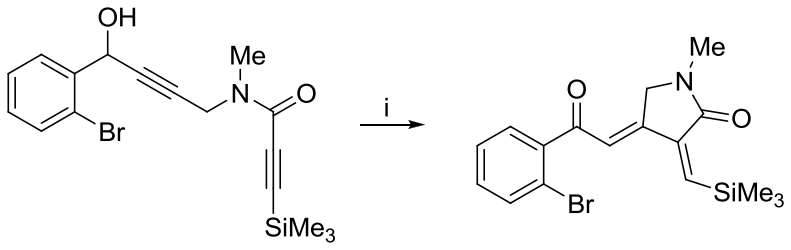


(2.74) **(2.75)**

Reagents and Conditions: (i) Carbon tetrachloride, 200°C, 0.01M.

Scheme 2.35: Trapping of Intermediate *p*-Benzyne with Carbon Tetrachloride During the Bergman Cyclisation

A solution of amide **2.55** in refluxing anhydrous, degassed carbon tetrachloride however gave the usual cyclisation product **2.56** in reduced yield compared to the reaction in toluene and no chlorinated adducts were detected (**Scheme 2.36**).



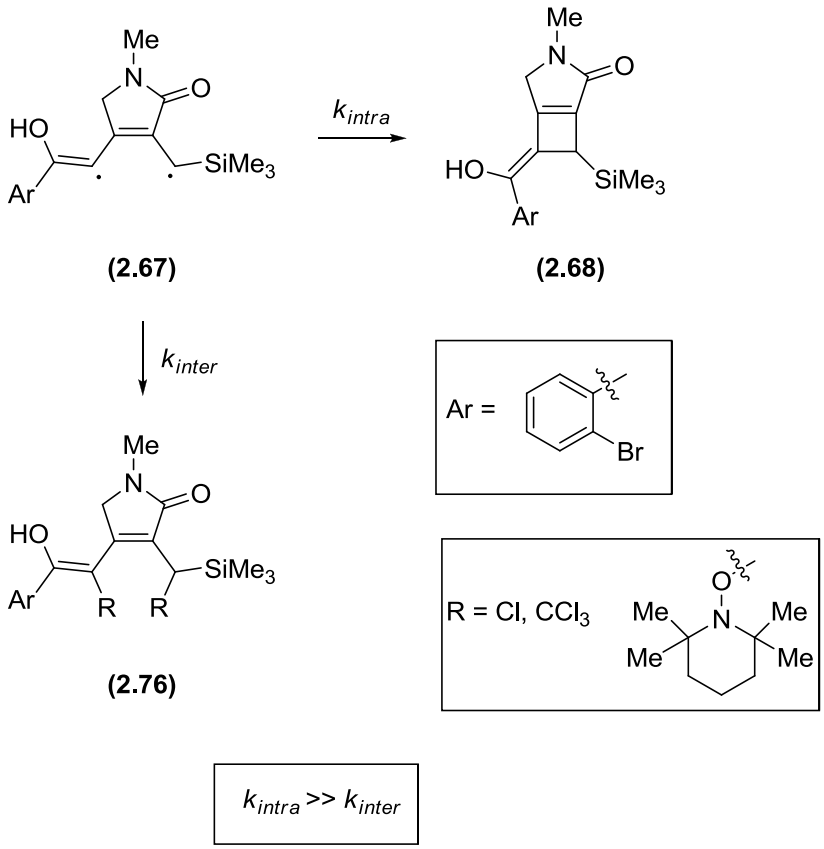
(2.55) **(2.56)**

Reagents and Conditions: (i) Carbon tetrachloride, 0.1M, reflux, 4h, 23%.

Scheme 2.36: Attempted Radical Trapping with Carbon Tetrachloride

The failure to trap the supposed intermediate radical species cannot be interpreted as definitive dismissal of a radical mechanism. As previously explained the trapping by external agents is highly dependent on the rate of bimolecular termination of radical species in solution.[130] It could be

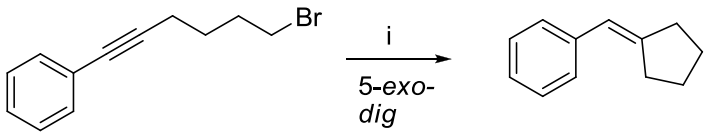
possible that in the first proposed mechanism in **Scheme 2.29** the supposed biradical intermediate **2.69** is terminated much faster than the time required for its intermolecular reaction with radical traps (**Scheme 2.37**).



Scheme 2.37: Rate of *Intra*molecular versus *Inter*molecular Quenching of Biradical **2.67**

2.3.3 Attempted Observation of Transient Radicals by Chemically Induced Dynamic Nuclear Polarisation (CIDNP)

CIDNP is a useful technique employed for the detection of free radicals using an ordinary NMR spectrometer. It was first observed by Ward in 1967 [38,39] during the lithium-halogen exchange and subsequent 5-*exo-dig* intramolecular cyclisation of 6-bomo-1-phenyl-1-hexyne **2.77** (**Scheme 2.38**).



(2.77) **(2.78)**

Reagents and Conditions: (i) Excess ^{n}BuLi, hexane/Et_2O (5:1), rt, then H_2O, 60%.

Scheme 2.38: CIDNP Experiment by Ward

The reaction was carried out in a sealed NMR tube which allowed spectra to be obtained at various points during the transformation. Ward noticed that the emission signals obtained appeared greatly enhanced or reduced and he immediately recognized this effect as being caused by CIDNP, therefore providing physical evidence for Bryce-Smith's idea [131] that organometallic reactions are radical in nature. The physical reason for such effect is that protons in a reacting molecule become dynamically coupled to an unpaired electron while proceeding from reactants to products.[99] As explained in Section 1.X observation of the CIDNP effect was effectively employed by Bergman and co-workers for the detection of radical intermediates in the Bergman cyclisation.

The Varian 600MHz NMR machine available at the Sussex University NMR facility is capable of recording variable temperature spectra. A 0.05M (13mg, 0.7ml sample) solution of amide **2.55** in anhydrous, degassed d_8-toluene was heated to 110°C in a J. Young NMR tube for four hours and a spectrum recorded every five minutes. Analysis of the total spectrum however revealed no clear enhancement or reduction in peak intensity during the course of the reaction. Although the presence of CIDNP always means that a free radical is involved, its absence does not prove that a free-radical intermediate is necessarily absent, since reactions involving free-radical intermediates can also take place without observable CIDNP.[99]

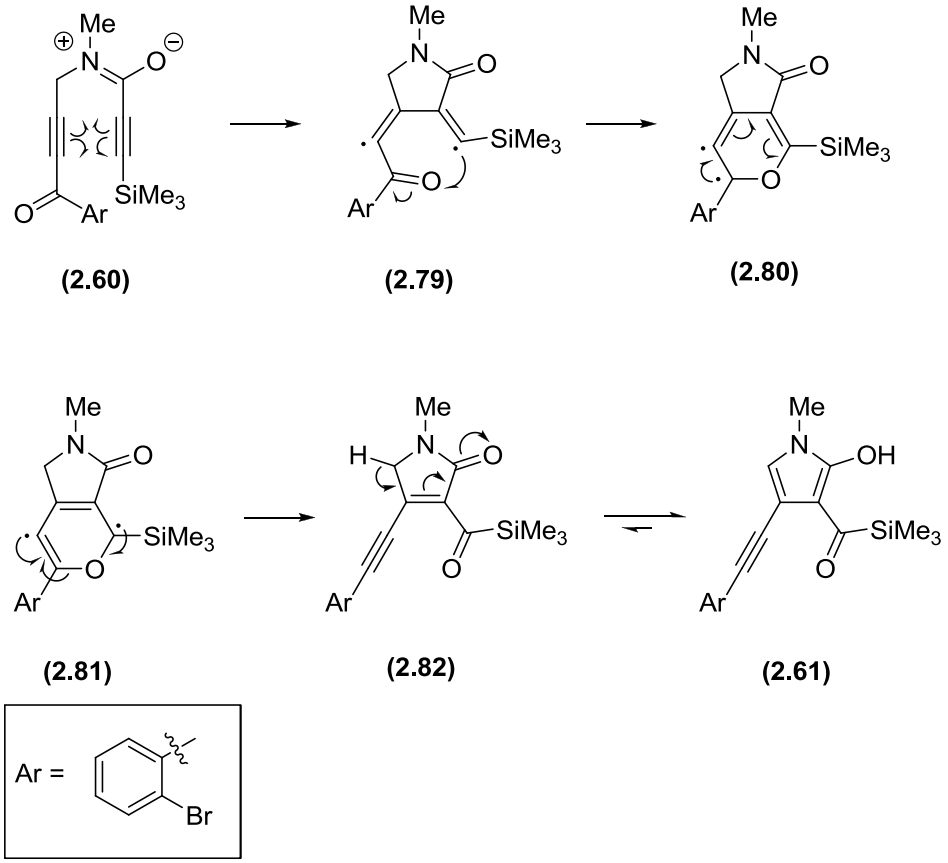
2.3.4 Future Work

The mechanism of this transformation remains undiscovered. Further studies into this field could entail the detection of supposed radicals by EPR spectroscopy and by chemical trapping with different new reagents. It would also be worthwhile investigating the application of this novel alkyne dimerisation to non-aromatic systems and possibly to natural product synthesis.

2.3.5 Proposed Mechanisms for Ketone Cyclisation

2.3.5.1 First Proposed Mechanism

The first proposed mechanism for the cyclisation of ketone **2.60** is shown below (**Scheme 2.39**).

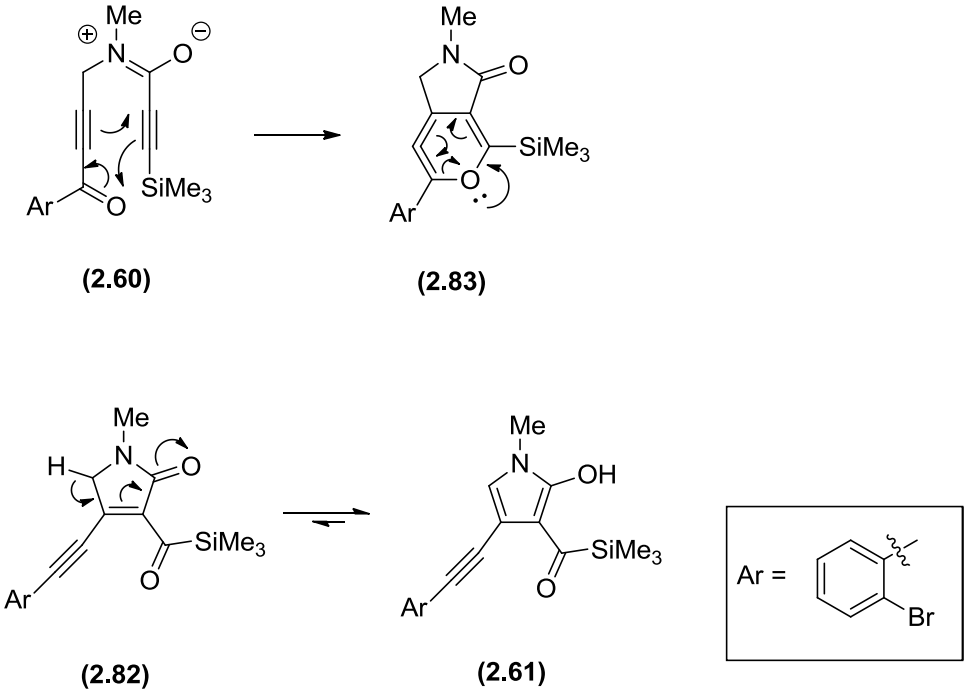


Scheme 2.39: Proposed Radical Mechanism for the Formation of **2.61**

As in the mechanism postulated for cyclisation of alcohol **2.55**, amide resonance in **2.60** aids a disproportionation of the 1,6-diyine system that causes the generation of a 1,4-biradical (**2.79**). At this stage however the benzylic hydrogen atom is absent having been removed by oxidation of the alcohol to the ketone. Therefore 1,5-hydrogen abstraction cannot occur and the radical α to silicon reacts at the oxygen at the carbonyl moiety, forming substituted pyran ring **2.80**. Radical tautomerism in **2.80** allows the biradical system in **2.81** to terminate *intra*molecularly yielding the acetylene and acyl silane observed in the product. Simple proton tautomerism in **2.82** affords substituted pyrrole **2.61**.

2.3.5.2 Second Proposed Mechanism

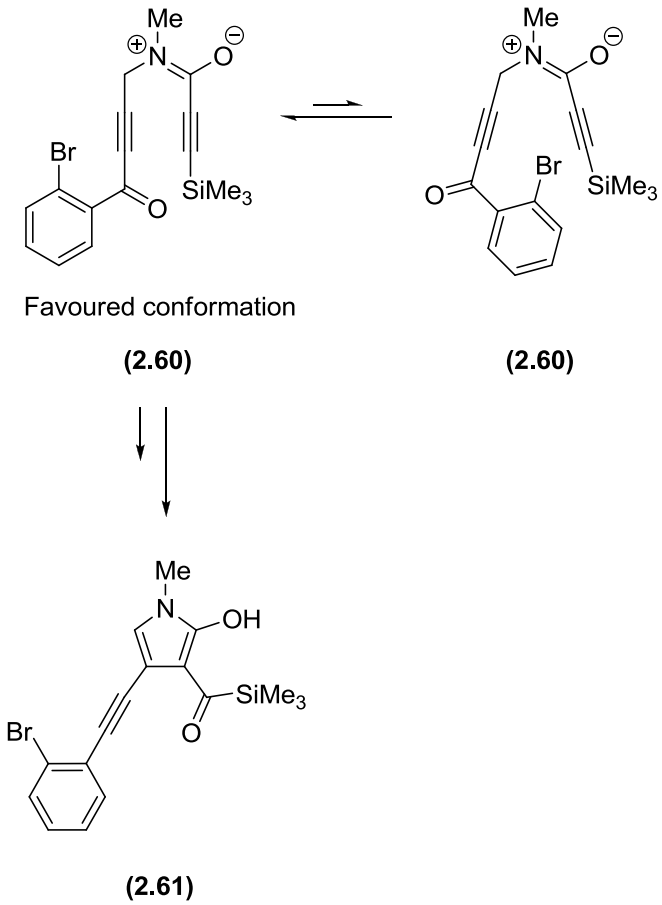
A second mechanism based on the reported *intra*molecular [4+2] cycloaddition of conjugated *ynones* [82] is shown below (**Scheme 2.40**).



Scheme 2.40: Postulate *Ynone* [4+2] Mechanism for the Formation of **2.61**

A concerted [4+2] cycloaddition between the ynone functionality and the silyl acetylene in **2.60** would yield highly strained heterocyclic allene **2.83**. Electrocyclic ring opening in **2.83** would yield the observed alkyne and acyl silane groups observed in the final product **2.61**. Unfortunately no definitive empirical evidence for either mechanism is available and the question of which of these mechanism is involved in the generation of substituted pyrrole **2.61** remains unanswered.

The failure of precursors **2.62** and **2.63** however still remains to be answered. The only obvious difference between these substrates and the successfully cyclised **2.60** and **2.64** is the size of the substituent at the 2-position of the aromatic group. It could then be postulated that there is a fundamental need for a large substituent to aid the locking of the molecule in a favourable conformation as shown in **Scheme 2.41** below.



2.41: Possible Substituent Effect During Cyclisation of **2.60**

Steric interactions in the fluoro-analogue **2.63** and precursor **2.62** would be greatly diminished therefore limiting the statistical chance of participation of the carbonyl group in the reaction.

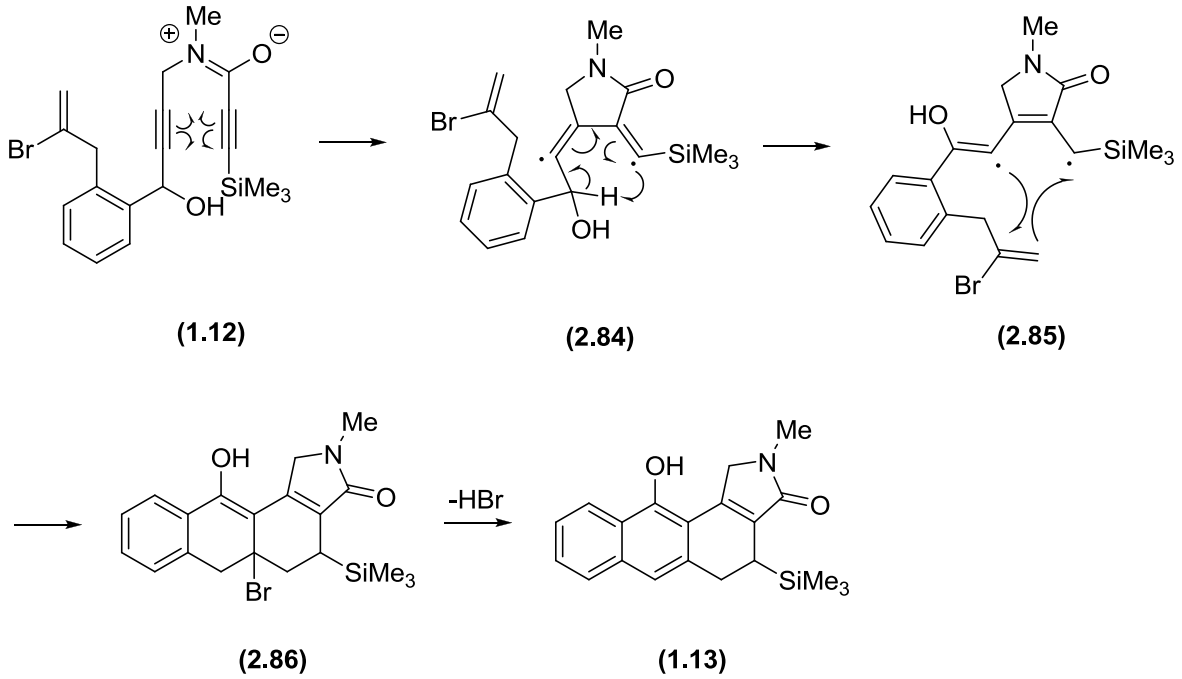
2.3.5.3 Future Work

Future work on this project would need to concentrate primarily on the confirmation of the proposed structure of the products by X-ray crystallography. Trapping of potential radical intermediates should also be pursued.

2.4 Investigating the Possibility of a [4+2] Cyclisation in the Cyclisation of Alcohol Analogues

2.4.1 Overview of the Investigation

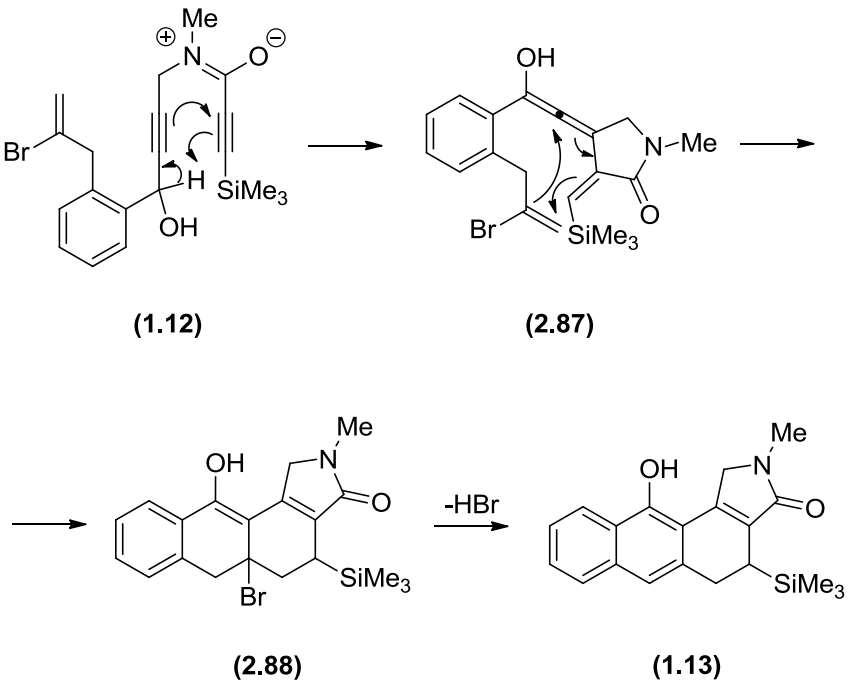
The original cyclisation discovered by Parsons *et al* for the construction of the core CDEF ring structure of Lactonamycin [15] involved the *intra*molecular reaction of a 1,6-diyine system with an alkenyl bromide. Based on the mechanistic proposals made in **Section 2.4** for the formation of diene **2.56** the following mechanisms could be in operation during the formation of **1.13**.



Scheme 2.42: Proposed Radical Mechanism for the Formation of **1.13**

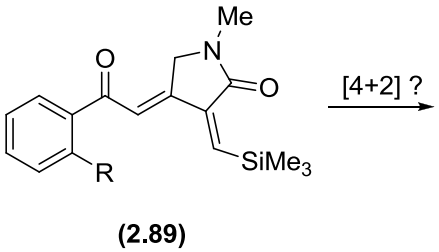
2.85 would be generated via the previously discussed mechanism. Termination of this biradical by reaction with the alkenyl bromide portion would give **2.86** which gains aromaticity by loss of hydrobromic acid to give observed product **1.13**.

A second possible mechanism would entail the generation of diene **2.89** by a propargylic-*ene* reaction and its subsequent Diels-Alder cyclisation with the alkenyl bromide portion (**Scheme 2.43**).



Scheme 2.43: Proposed Propargylic-*Ene*/[4+2] Mechanism for the Formation of **1.13**

The most fundamental difference between the two above mechanisms is the way in which the alkenyl bromide portion is attacked. The aim of this project was to test if a Diels-Alder reaction with generalised diene **2.89** (**Scheme 2.44**) is a viable option.



Scheme 2.44: Generalised Substrate for the Investigation of [4+2] Reactions

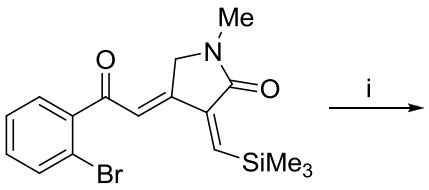
2.4.2 Attempted *Inter*molecular [4+2] Cyclisations

The diene moiety in structure **2.56** is electron-deficient as it is connected at both ends with electron-withdrawing carbonyl groups. This means that HOMO of the diene is too low in energy to react in a conventional Diels-Alder fashion. However in this case the LUMO of the diene could react with the HOMO of an electron-rich dienophile in what is referred to as an inverse electron demand Diels-Alder.

Therefore diene **2.56** was dissolved in toluene and stirred at room temperature in the presence of an excess of propargyl alcohol for ten days. No reaction took place; therefore the solution was refluxed for six hours. Slight decomposition of the starting material was observed but no reaction with the dienophile took place.

To cover every possibility diene **2.56** was also first stirred at room temperature and then refluxed in the presence of the electron-deficient dienophile maleic anhydride. In both cases no cyclisation reaction occurred.

The conditions tested for the attempted intermolecular Diels-Alder reactions with **2.56** are summarised in **Table 2.13** below.



(2.56)

Reagents and Conditions: (i) Toluene, DIENOPHILE, TEMPERATURE, TIME, see **Table 2.13** below

Entry	Dienophile (Equivalents)	Temperature (°C)	Time (h)	Products
1	Propargyl Alcohol (10)	rt	240	None
2	Propargyl Alcohol (10)	110	6	None
3	Maleic Anhydride (5)	rt	240	None
4	Maleic Anhydride (5)	110	6	None

Table 2.13: Attempted Diels-Alder Reactions with Diene **2.56**

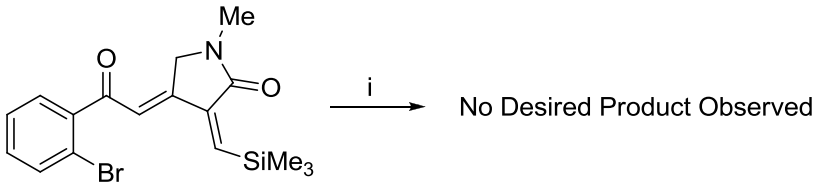
Therefore diene **2.56** was proven unable to perform an *inter*molecular Diels-Alder reaction. However in the original cyclisation by Parsons the alkenyl bromide is present in the same molecule as the diene. The next option therefore was to test if an *intra*molecular [4+2] reaction is a possibility.

2.4.3 Attempted *Intra*molecular [4+2] Cyclisation

In order to test the intramolecular [4+2] reaction it was necessary to construct the diene by the established thermal cyclisation method and then introduce a dienophile in a second distinct synthetic step.

One way to achieve this would be to perform a palladium-catalysed coupling on bromo-diene **2.56**. The 2010 Nobel prize winning Suzuki reaction [132,133] was discarded as an option as it is prone to undergo β-hydrogen elimination when using substrates with β-hydrogens [134] such as a simple allyl group. Recently a method that overcomes this problem has been reported [135], however it employs alkyltrifluoroborates which are incompatible with the trimethylsilyl moiety in **2.56** [136]. The Stille

coupling [137] does not suffer from the elimination drawback as the coupling stage of the reaction is faster than the competing β-hydrogen elimination step.[138] A typical procedure for this reaction involves heating of the substrate, a palladium(0) catalyst and a tri-*n*-butyltin derivative in a wide range of solvents. Aryl bromide **2.56** was then refluxed in anhydrous THF in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and a slight excess of allyl tri-*n*-butyltin (**Scheme 2.44**).

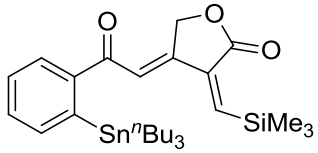


(2.56)

Reagents and Conditions: (i) 10mol% $Pd(PPh_3)_4$, allyl tri-*n*-butyltin, THF, reflux, 5h.

Scheme 2.44: Attempted Stille Coupling on **2.56**

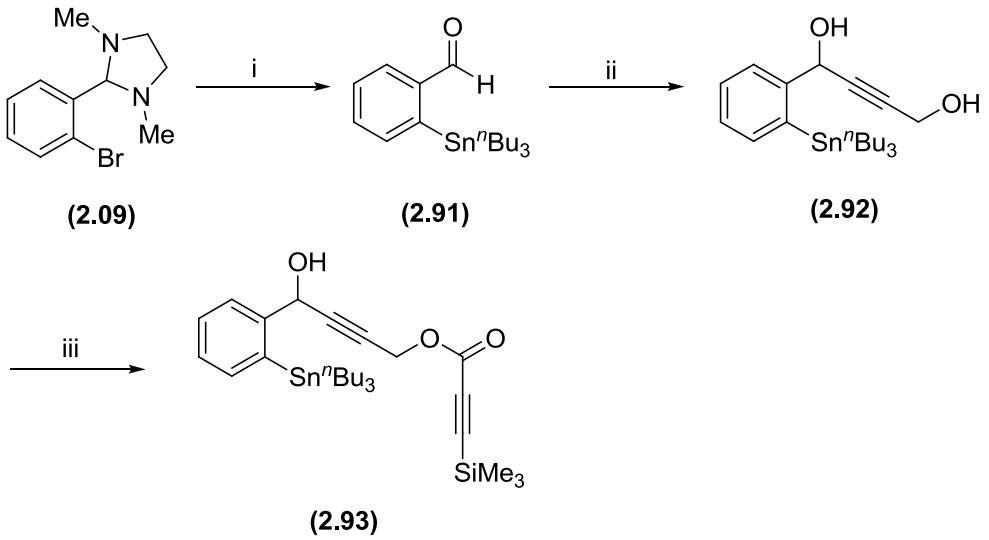
After refluxing for five hours however diene **2.56** had decomposed giving no desired product. It was then proposed that the reverse coupling between allyl bromide and aryl tin derivative **2.90** (**Figure 2.14**) could yield better results. The decision to use the ester analogue of diene **2.62** was due to the lower cost of propargyl alcohol versus *N*-methylpropargylamine and the omission of protection/deprotection steps for its synthesis.



(2.90)

Figure 2.14: New Target for Reverse Stille Coupling

Diene **2.90** would be the product of the cyclisation of precursor **2.93** which was generated by the synthetic sequence shown in **Scheme 2.45** below.



(2.09) **(2.91)** **(2.92)** **(2.93)**

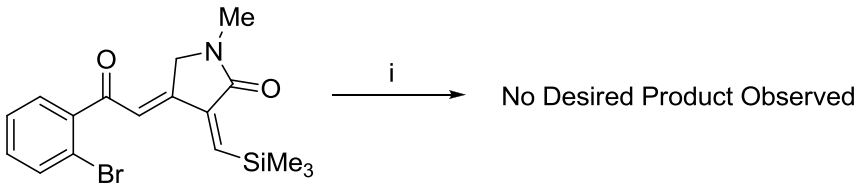
Reagents and Conditions: (i) ^{n}BuLi, THF, -20°C then ^{n}BuSnCl, -20°C to rt then 1M $HCl_{(aq.)}$, 94%; (ii) $LiC{\equiv}CCH_2OLi$, THF, -70°C to rt then sat. $NH_4Cl_{(aq.)}$, 63%; (iii) $Me_3SiC{\equiv}CCOCl$, 2,6-lutidine, CH_2Cl_2, 0°C to rt, 71%.

Scheme 2.45: Synthesis of Tin-Cyclisation Precursor **2.93**

Imidazolidine-protected 2-bromobenzaldehyde **2.09** was subjected to a lithium-halogen exchange using one equivalent of *n*-butyllithium and the resulting anion was quenched by addition of tri-*n*-butyltin chloride. The resulting aldehyde was alkylated with propargyl alcohol lithium-dianion [139] to yield, after a mildly acidic work up, diol **2.92**. The primary alcohol moiety of **2.92** was esterified by the condensation with 3-(trimethylsilyl)-2-propynyl chloride **2.14** in the presence of 2,6-lutidine to furnish desired precursor **2.93**.

Thermolysis of **2.93** in toluene at 0.1M for 4 hours unfortunately yielded a multitude of products and separation was not attempted.

As a last resort it was proposed that a mild magnesium-halogen exchange [140] on diene **2.56** followed by alkylation of allyl bromide could be a viable route to the desired material.



(2.56)

Reagents and Conditions: (i) ^{n}PrMgBr, THF, -30°C then CuCN, -30°C to -10°C then allyl bromide, -30°C to rt.

Scheme 2.46: Magnesium-Halogen Exchange and Quenching with Allyl Bromide

Addition of one equivalent of *iso*propyl magnesium bromide to diene **2.56** at -30°C effectuated the halogen exchange and the resulting Grignard reagent was added to one equivalent of copper cyanide to generate a lower-order cyanocuprate. After addition of allyl bromide and slow warming to room temperature, analysis of the crude reaction mixture revealed that a multitude of compounds had been formed and chromatographic separation was not attempted.

2.5 Studies into the Application of the Cyclisation Reactions to the Synthesis of Natural Products

2.5.1 Overview

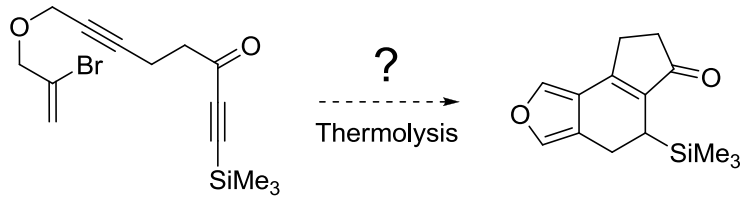
Organic synthesis is generally recognized as being divided into methods oriented and target oriented.[141] The previous entails the study of new reagents, catalysts, synthetic strategies and tactics whereas the latter is concerned with the synthesis of natural or target molecules. These two fields are inexorably connected and dependent on each other; new strategies and reagents are needed to improve the synthesis of particular targets but at the same time the quest to synthesise a specific molecule very frequently results in the discovery of a new reaction or mechanism (serendipity).

So far the novel cyclisation discovered by Parsons *et* al. has only been applied to studies towards the total synthesis of Lactonamycin.[15,25,142] However due to its ability to generate complex fused ring structures in one simple synthetic step it has the potential to be employed for the synthesis of numerous different natural products.

2.5.2 Studies towards the Synthesis of Steroidal Cores

2.5.2.1 Overview of Investigation

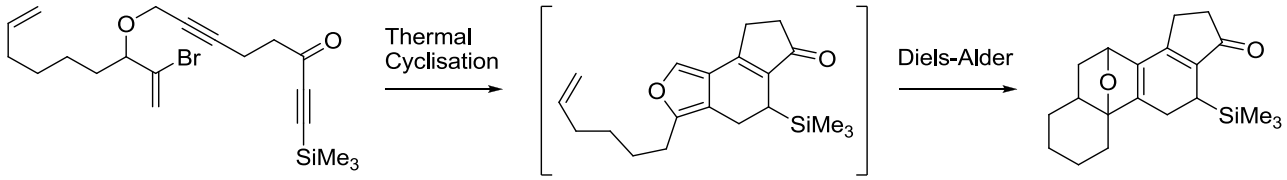
All the previously investigated cyclisation reactions in the Parsons group involved the use of a 1,6-dialkyne system separated by either an amide or an ester moiety. The first aim of this investigation was to test if molecule **2.94**, which contains a ketone spacer group, is able to perform a thermal cyclisation reaction.



(2.94) **(2.95)**

Scheme 2.47: Investigation of an All-Carbon Cyclisation

If the above hypothesis is true, manipulation of **2.95** to could furnish cyclisation precursor **2.96** which could, in theory, be able to generate simplified steroid core **2.98** by a thermal cyclisation/Diels-Alder cascade, as shown in **Scheme 2.48** below.

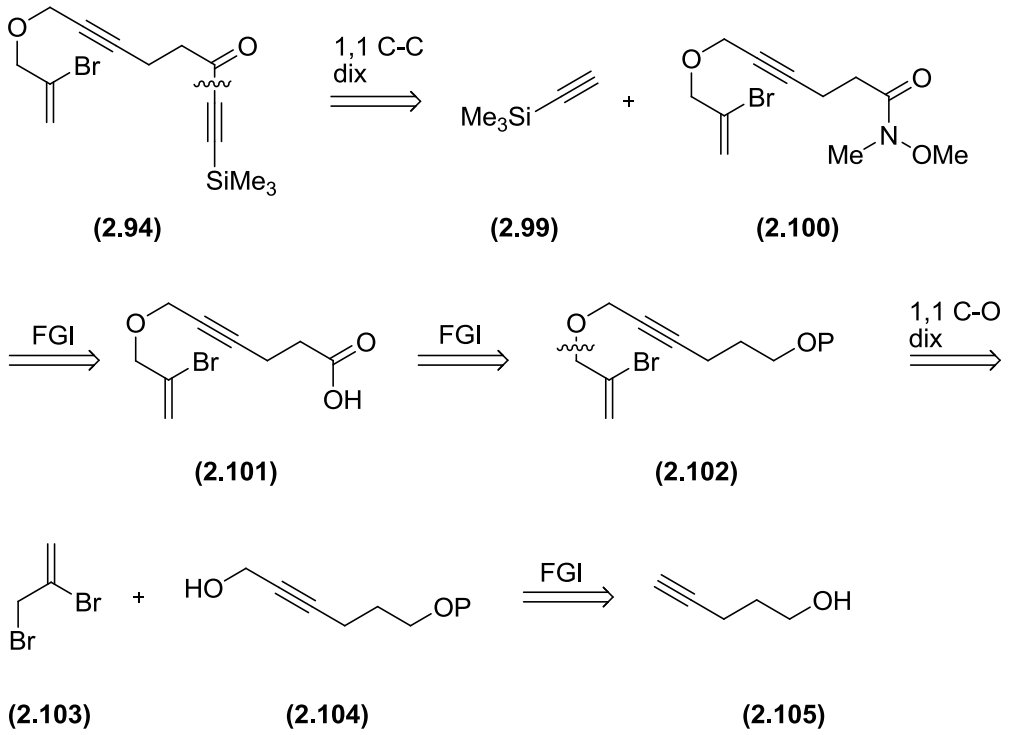


(2.96) **(2.97)** **(2.98)**

Scheme 2.48: Potential Use of a Thermal Cyclisation for the Synthesis of Steroid Cores

2.5.2.2 Synthesis of the All-Carbon Cyclisation Precursor

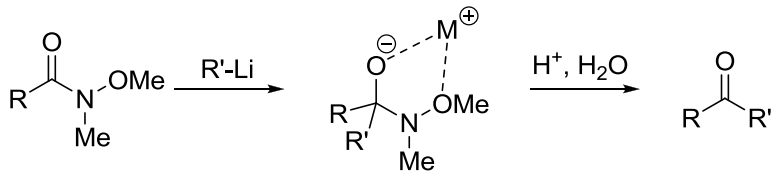
The retrosynthetic approach envisaged for **2.94** is shown in **Scheme 2.49** below.



(2.94) **(2.99)** **(2.100)** **(2.101)** **(2.102)** **(2.103)** **(2.104)** **(2.105)**

Scheme 2.49: Retrosynthetic Analysis of Compound **2.94**

Ketone **2.94** could be generated from the addition of the lithium salt of ethynyl(trimethyl)silane to Weinreb amide **2.100**, which could be obtained from the elaboration of protected alcohol **2.102**. The Weinreb ketone synthesis is a useful synthetic tool because reaction of a lithium nucleophile with an amide would yield over-alkylated products.[143] However, addition of one equivalent of lithium nucleophile to a Weinreb amide yields lithium chelate **2.107** which is impervious to a second nucleophilic attack (**Scheme 2.50**). Acid hydrolysis of this intermediate yields the desired ketone.

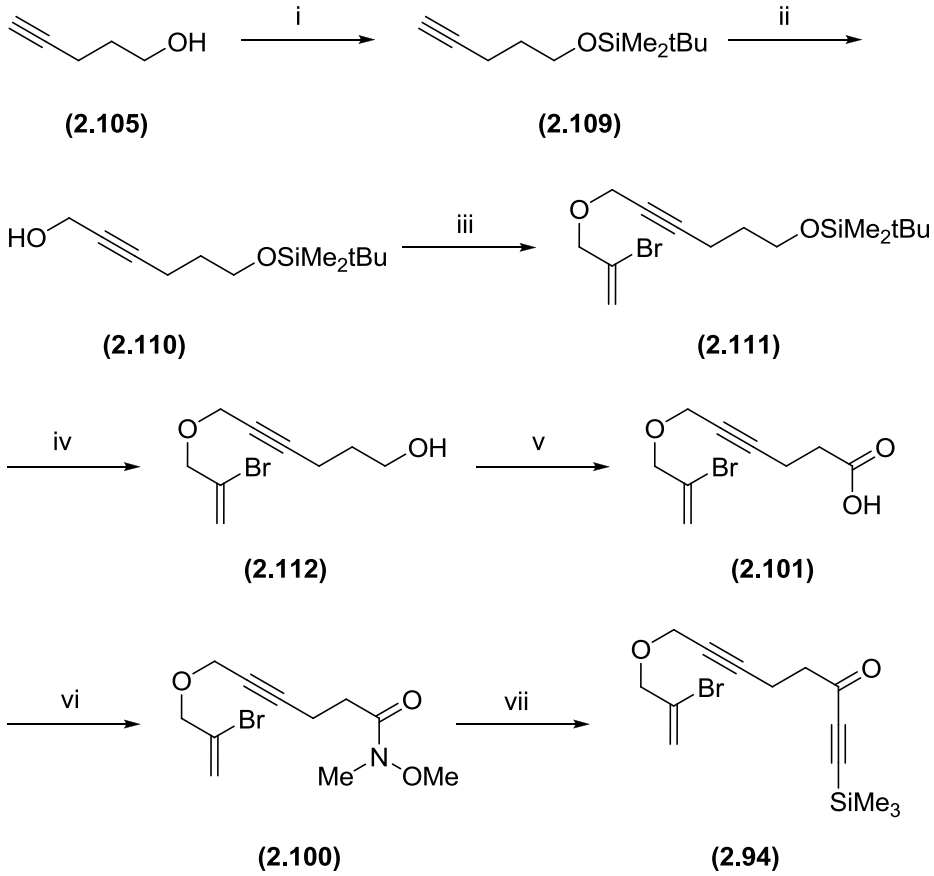


(2.106) **(2.107)** **(2.108)**

Scheme 2.50: Weinreb Ketone Synthesis

2.102 (Scheme **2.49**) could be then accessed from alcohol **2.104** and 2,3-dibromopropene **2.103** by employing Williamson's ether synthesis conditions; a straightforward disconnection at the acetylene moiety indicates to commercially available 4-pentyn-1-ol **2.105**.

Scheme 2.51 below illustrates the synthesis of desired material **2.94**.



Reagents and Conditions: (i) TBS-Cl, Et_3N, CH_2Cl_2, rt, 95%; (ii) ^nBuLi, THF, -78°C to -20°C then *para*-formaldehyde, -20°C to rt, then sat. $NH_4Cl_{(aq)}$, 77%; (iii) 2,3-Dibromopropene, CTAB, 50% aq. NaOH, CH_2Cl_2, rt, 72%; (iv) TBAF, THF, rt, 92%; (v) 3.0M Jones' reagent, acetone, rt, 79%; (vi) Oxalyl chloride, cat. DMF, CH_2Cl_2, rt then *N,O*-Dimethylhydroxylamine hydrochloride, Et_3N, CH_2Cl_2, rt, 87%; (vii) Li-C≡C-$SiMe_3$, THF, -78°C to rt then 1M $HCl_{(aq)}$, 67%.

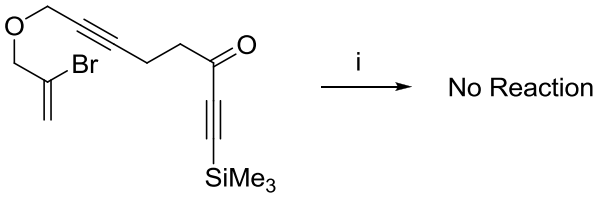
Scheme 2.51: Synthesis of Precursor **2.94**

4-Pentyn-1-ol **2.105** was protected, in near quantitative yield, as its *tert*-butyldimethylsilyl ether **2.109** using *tert*-butyldimethylsilyl chloride in the presence of triethylamine as an acid scavenger. TBS-ethers have the advantage of being relatively robust in basic conditions and are easily removed by action of a weak acid or in the case of acid-labile molecules by fluoride ions.[144] Deprotonation of **2.109** was performed by addition of one equivalent of *n*-butyllithium solution at -78°C. Warming to -20°C to ensure complete proton abstraction and reaction of the resulting lithium salt with excess *para*-formaldehyde followed by quenching with saturated aqueous NH_4Cl gave **2.110**. Formation of

ether **2.111** was accomplished using a biphasic mixture of **2.110** and 2,3-dibromopropene in DCM and 50% aqueous sodium hydroxide in the presence of phase-transfer catalyst hexadecyltrimethylammonium bromide.[145] Tetra-*n*-butylammonium fluoride mediated silyl deprotection of **2.111** and consequent Jones' oxidation of **2.112** yielded desired carboxylic acid **2.112**. Acid chloride formation was accomplished with oxalyl chloride in the presence of a catalytic amount of DMF followed by reaction with *N*,*O*-dimethylhydroxylamine hydrochloride gave Weinreb amide **2.100** in 87% yield. Deprotonation of ethynyl(trimethyl)silane was achieved by action of *n*-butyllithium and the resulting anion was reacted with amide **2.100** to furnish, after acidic work up desired ketone **2.94** in 67% yield.

2.5.2.3 Attempted Cyclisations of All-Carbon Cyclisation Precursor

Upon refluxing in anhydrous, degassed toluene at 0.1M concentration for 24 hours, no reaction took place and all of ketone **2.94** was recovered (**Scheme 2.52**).

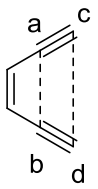


(2.94)

Reagents and Conditions: (i) Toluene, 0.1M, reflux, 24h.

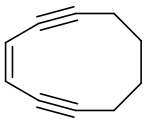
Scheme 2.52: Attempted Cyclisation of **2.94** in Refluxing Toluene

Therefore the presence of an amide or ester spacer-group in the molecule appears to be of fundamental importance for the cyclisation to proceed. During studies on rates of cyclisation of enediynes, Nicolaou *et al.*[34] have shown that reaction rates dramatically increase if the alkyne portions are close together in space (*cd* distance in **Figure 2.15** below).



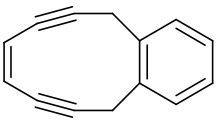
cd distance: 4.12Å
Stable at 25°C
$t_{1/2}$ = 30s at 200°C

(2.113)



cd distance: 3.25Å
$t_{1/2}$ = 18h at 37°C

(2.114)



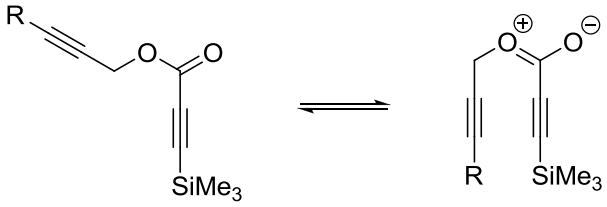
cd distance: 3.03Å
Cyclises at 25°C

(2.115)

Figure 2.15: Relationship between *cd* Distance and Rate of Cyclisation in Enediynes

It could be then postulated that in cyclisation precursors containing an amide or ester spacers the approach of the two acetylene moieties is facilitated by resonance an effect which would not be observed for the ketone analogue (**Scheme 2.53**).

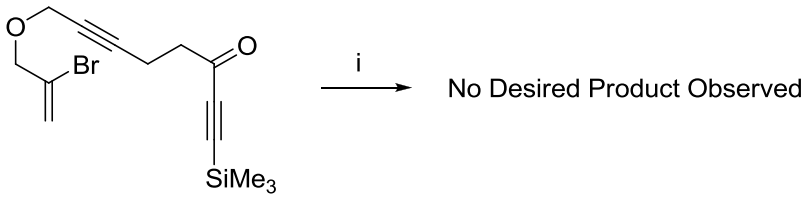
(2.116) **(2.117)**



(2.118) **(2.119)**

Scheme 2.53: Amide and Ester Resonance in Cyclisation Precursors

The rate of reaction is however proportional to the temperature as shown in the examples by Nicolaou. It should then be possible to cyclise the ketone analogue by increasing the temperature therefore increasing the statistical chance of the two acetylene moieties to encounter each other in space. In order to be able to heat toluene above its boiling point the reaction was repeated under microwave conditions at 150°C. Unfortunately no reaction took place (**Scheme 2.54**).



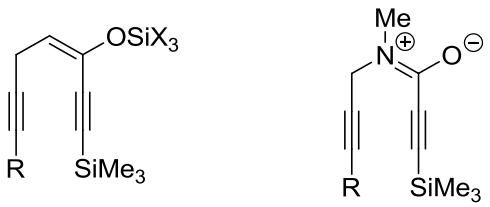
(2.94)

Reagents and Conditions: (i) Toluene, MW, 300W, 150°C, 2h.

Scheme 2.54: Attempted Cyclisation of **2.94** in Toluene under Microwave Conditions at 150°C

2.5.2.4 Future Work

Locking the ketone functionality as the *E*-silyl enol ether **2.120** could mimic the role of the amide and ester resonance in successfully cyclised precursors (**Figure 2.16**).



(2.120) **(2.116)**

Figure 2.16: Mimicking the Amide and Ester Resonance by Forming the *E*-Silyl Enol Ether

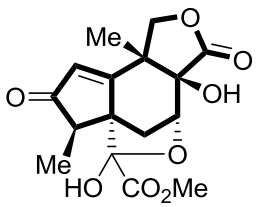
The stereoselective formation of enolates has been rationalized with the Ireland model.[146-148] Ketones with non-sterically demanding substituents can be converted selectively to the *E*-enolate by addition of a bulky, kinetic base such as lithium tetramethylpiperidide.[149]

The formation of **2.120** could be the answer to the successful cyclisation of the all carbon analogue.

2.5.3 Studies into the Application of the Thermal Cyclisation Reaction to the Synthesis of Jiadifenin

2.5.3.1 Overview of Investigation

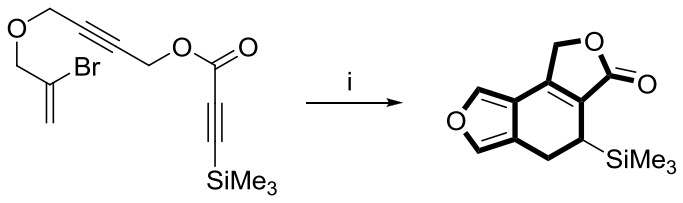
Seco-prezizaane-type sesquiterpene Jiadifenin [83] (**Figure 2.17**) is a biologically and structurally interesting molecule that provides the organic chemist with a rewarding synthetic challenge.



(1.146)

Figure 2.17: Jiadifenin

The highlighted tricyclic core of Jiadifenin in **Figure 2.17** bears resemblance to molecules previously synthesised in the Parsons' research group using the thermal cyclisation (**Scheme 2.55**).[23]



(1.23) **(1.24)**

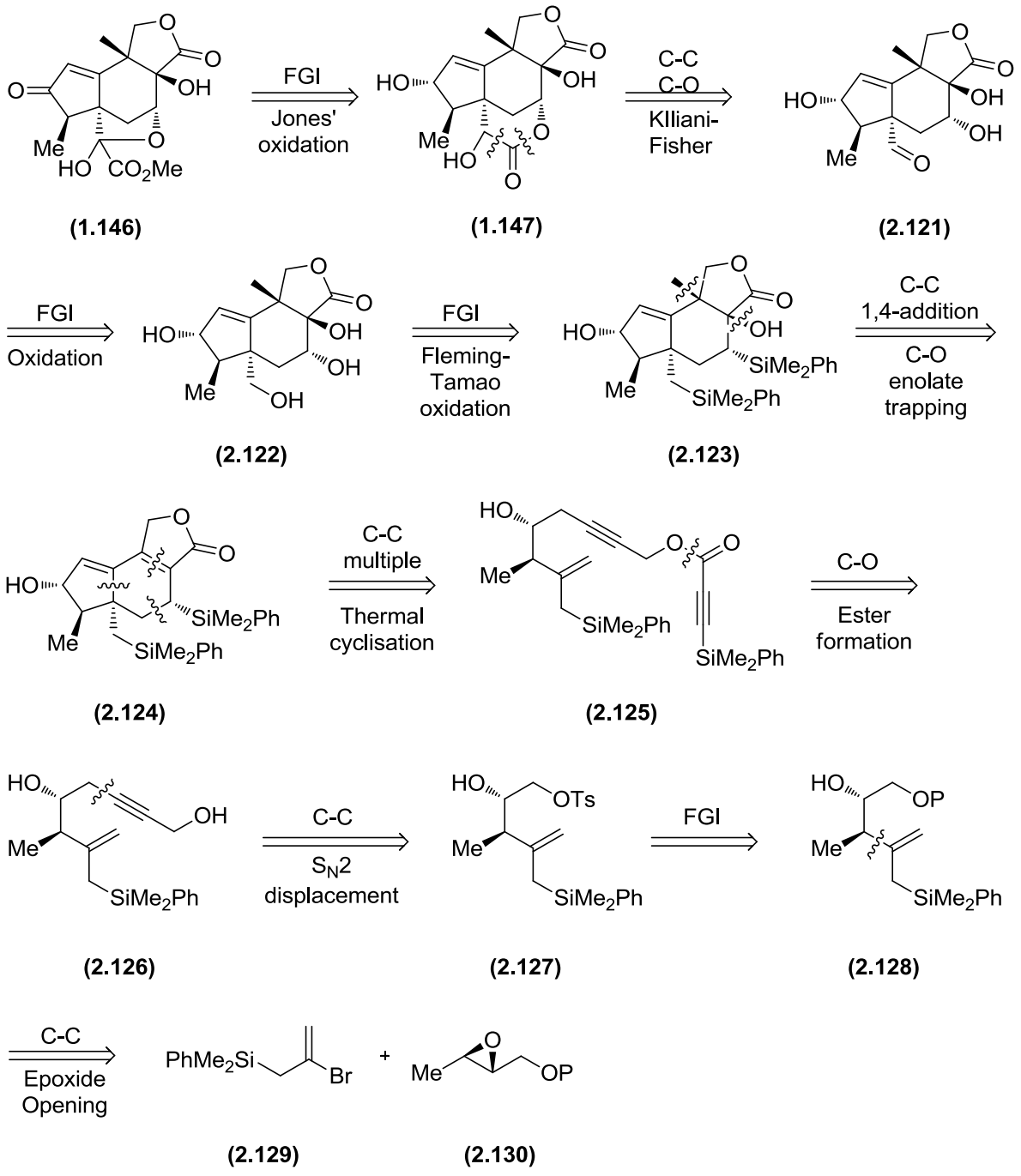
Reagents and Conditions: (i) Toluene, epoxyhexene, reflux, 52h, 76%

Scheme 2.55: Previous Work in Parsons' Group

This precedent gives support to the theory that Jiadifenin could be synthesised using the thermal cyclisation reaction.

2.5.3.2 Retrosynthetic Analysis

The chosen retrosynthetic analysis for the synthesis of Jiadifenin is shown below in **Scheme 2.56**.



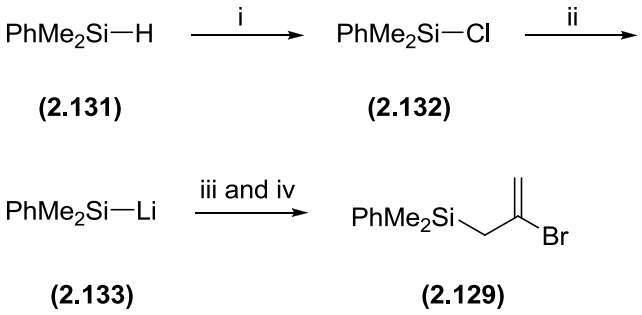
Scheme 2.56: Retrosynthetic Analysis of Jiadifenin

The ultimate transformation leading to Jiadifenin from **1.147** has been reported in the original publication by Fukuyama *et al.*[83] *α*-Hydroxylactone **1.147** could be obtained by a Kiliani-Fisher [150-152] synthesis from *γ*-hydroxyaldehyde **2.121** which would be derived from the selective oxidation of

the primary alcohol in **2.122**. The desired hydroxyl moieties of **2.122** could be generated from a Fleming-Tamao oxidation [153-156] of two dimethylphenylsilyl groups **2.123** the presence of would be coincidentally advantageous during the key thermal cyclisation step. A conjugate addition to *α,β*-unsaturated ester **2.124** followed by a lithium enolate trapping with an oxaziridine [157,158] would furnish **2.123**. **2.124** would be the product of the thermal cyclisation developed by Parsons *et al*. Precursor **2.125** could be obtained from the manipulation of **2.128** which in turn would be synthesised by a key chiral epoxide opening step.

2.5.3.3 Synthesis of Precursors

The first target in the sequence was silyl alkenyl bromide **2.129**. Initial attempts at its synthesis were based on a published procedure employing dimethylphenylsilyl lithium **2.133** and 2,3-dibromo-1-propene (**Scheme 2.57**).[159]

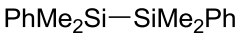


Reagents and Conditions: (i) $SOCl_2$, reflux, 84%; (ii) Li, THF, -10°C; (iii) CuCN, LiCl, -50°C; (iv) 2,3-Dibromo-1-propene, -50 to -20°C, 49%.

Scheme 2.57: First Synthesis of **2.129**

Dimethylphenysilyl chloride was obtained in 84% yield from the relatively less expensive dimethylphenylsilylane by a published route.[160] The corresponding lithium reagent **2.133** was generated by a lithium-halogen exchange as described by Fleming.[161] Addition of an equivalent of copper(I) cyanide furnished a lower-order cyanocuprate intermediate which upon reaction with 2,3-dibromo-1-propene gave desired product **2.129** in 49% yield. Problems afflicting this synthesis are the use of expensive starting materials, the unreliable generation of the silyl lithium reagent and the

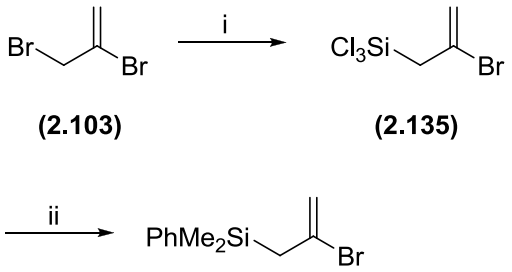
use of toxic copper(I) cyanide. Also the product obtained by this procedure was found to be contaminated with a substantial amount of disilane impurity **2.134** (**Figure 2.18**) most likely generated from the unwanted coupling of the silyl lithium reagent with unreacted silyl chloride.



(2.134)

Figure 2.18: Disilane Impurity

A published route for the generation of **2.129** [162] makes use of a copper(I) chloride-catalysed silane insertion in the carbon-bromine bond of 2,3-dibromo-1-propene **2.103** followed by alkylation of the resulting silyl chloride **2.135** by Grignard reagents. Using this relatively cheap and easy procedure furnished the desired alkenyl bromide **2.129** in very high yield and purity (**Scheme 2.58**).



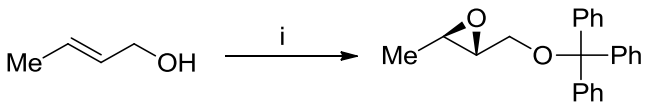
(2.103) **(2.135)** **(2.129)**

Reagents and Conditions: (i) $HSiCl_3$, $CuCl_{(cat)}$, Et_3N, Et_2O, rt, 88%; (ii) 1 eq. PhMgBr, Et_2O, reflux then 2 eq. MeMgBr, Et_2O, rt, 91%.

Scheme 2.58: Second, Improved Synthesis of **2.129**

With alkenyl bromide **2.129** in hand it was time to construct the chiral epoxide. Firstly a suitable protecting group had to be found for the primary hydroxyl group of **2.130**. Due to its resistance to strongly basic conditions, low cost and sheer size which could improve selectivity of the epoxide opening step, the triphenylmethyl (trityl) group was chosen for the investigation.

A published one-pot Sharpless epoxidation[163] /protection sequence [164] was therefore adopted starting from commercially available *E*-but-2-ene-1-ol (crotyl alcohol) (**Scheme 2.59**).



(2.136) **(2.137)**

Reagents and Conditions: (i) $Ti(O^iPr)_4$ (10mol%), (-)-DIPT (12mol%), ^{t}BuOOH, DCM, 3Å ms, -20°C then $P(OMe)_3$, -20°C then Ph_3C-Cl, $DMAP_{(cat)}$, Et_3N, CH_2Cl_2, -20°C, 62%, 95%+ *ee*

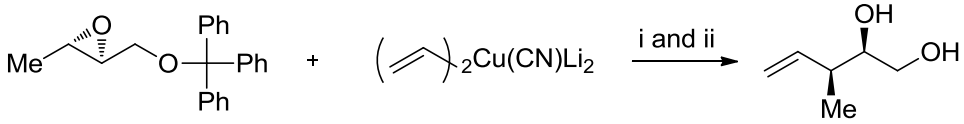
Scheme 2.59: Synthesis of Chiral Epoxide **2.137**

After evaporative recrystallisation from chloroform/hexane (1:4 v/v) **2.137** was isolated in 95%+ enantiomeric excess as determined by the ^{1}H NMR analysis of the Mosher ester of the corresponding iodohydrin.[165]

Next the epoxide opening step was investigated.

2.5.3.4 Epoxide Opening

While hetereoatom-based nucleophiles have been successfully employed for the opening of chiral 1,2-substituted epoxides, the use of carbon-based nucleophiles is much less developed.[166] Organocopper reagents are known to be some of the most efficient at carrying this transformation in a highly chemo- and stereo-selective manner.[167] The opening of epoxide **2.137** by vinyl higher-order cyanocuprate **2.138** has been previously reported (**Scheme 2.60**).[168]



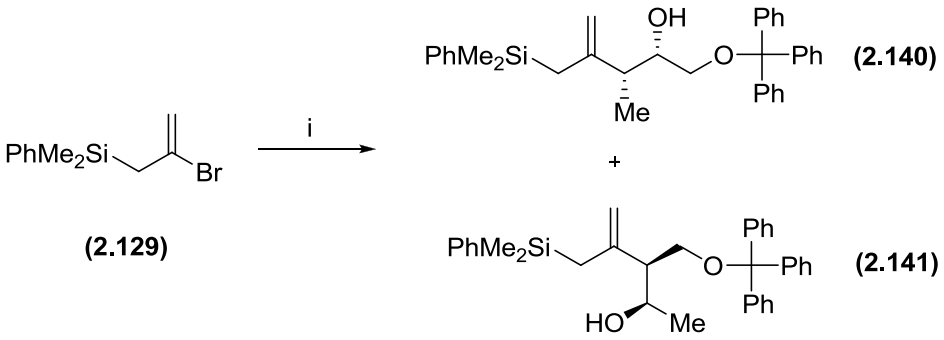
(2.137) **(2.138)** **(2.139)**

Reagents and Conditions: (i) $BF_3.OEt_2$, THF, -78°C; (ii) 60% CHCl2CO_2H, 78%.

Scheme 2.60: Work by Casalnuovo *et al.*

The additive boron trifluoride-diethyl etherate increases the reactivity of the cyanocuprate reagent by situating itself to a significant degree on the nitrile ligand of the reagent therefore increasing the Lewis acidity of the whole complex.[169] This allows many epoxide openings to occur at low temperatures and at greater rates relative to reactions in the absence of this additive. However care must be taken when employing this procedure as temperature above -50°C start to seriously decompose the cuprate-lewis acid complex.[170]

In order to generate the required higher-order cyanocuprate silyl alkenyl bromide **2.129** was subjected to a lithium-halogen exchange with two equivalents of *tert*-butyllithium and then added to a suspension of 0.5eq of copper(I) cyanide. The resulting reagent was then used in various attempts to open epoxide **2.137** (**Table 2.14**).



Reagents and Conditions: (i) 2eq. ^{t}BuLi, SOLVENT (see **Table 2.14**), -70°C then 0.5eq CuCN, -70°C to -20°C then ADDITIVE (see **Table 2.14**) , -70°C then **2.137**, TEMPERATURE (see **Table 2.14**), TIME (see **Table 2.14**) then sat. $NH_4Cl_{(aq.)}$/5M $NH_4OH_{(aq.)}$ (8:2, v/v)

Scheme 2.61: Higher-order Cyanocuprate-Mediated Opening of Epoxide **2.137**

Entry	Solvent	Temperature	Time[b]	Additive	Yield of **2.140**[c]	**2.140:2.141**[d]
1	THF	-70°C	4h	None	0	-
2	Et_2O	-70°C	4h	None	0	-
3	THF	-60°C[a]	4h	$BF_3.OEt_2$	0	-
4	Et_2O	-60°C[a]	4h	$BF_3.OEt_2$	Trace[c]	-
5	THF	18°C	24h	None	11%	3:1
6	Et_2O	18°C	24h	None	62%	2:1

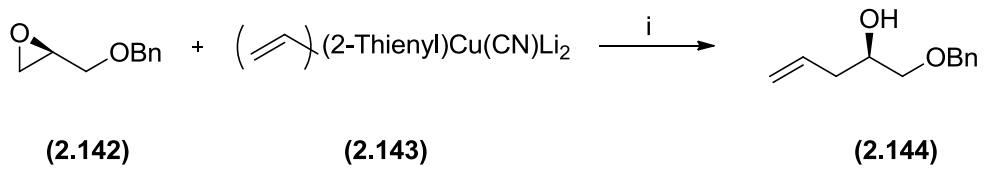
a) Heating above -50°C causes rapid decomposition of the organocuprate reagent identified by appearance of brown/black colour. b) Reaction time after addition of epoxide c) Isolated yield d) Determined by ^{1}H NMR of crude mixture.

Table 2.14: Conditions Tested for Opening of Epoxide **2.137**

In order to achieve the opening of the epoxide at the desired 2-position of **2.137** the reaction was first tested at low temperatures. The generated organocuprate alone however was found unable to perform the reaction in either tetrahydrofuran or diethyl ether at -70°C (entries 1 and 2 **Table 2.14**). Addition of $BF_3.OEt_2$ and stirring at a slightly higher temperature (entries 3 and 4 **Table 2.14**) did not significantly improve reactivity yielding only trace amounts of product. Finally it was

discovered that carrying the reaction in diethyl ether at room temperature (entry 6 **Table 2.14**) in the absence of additives effectuated the transformation neatly giving desired material **2.140** in 62% isolated yield. Undesired product **2.141**, which results from the epoxide opening at the 3-position was also obtained in 27% yield. The difference in yield observed between entries 5 and 6 in **Table 2.14** is a clear demonstration of the greater lewis-acidity of diethyl ether compared to tetrahydrofuran which results in a better stabilisation of lithium cations in solution.[171]

A clear disadvantage encountered in the use of higher-order cyanocuprates is the requirement for two equivalents of lithium reagent, one of which does not take part in the reaction and it is therefore lost at the end of the procedure. To avoid such a loss, higher-order mixed cyanocuprates can be formed where a non-transferrable ligand is included in the cluster. Examples of such "dummy" ligands are 2-thienyl, dimsyl, methyl, imdazoyl and trimethylsilylmethyl.[167] A practical example by Lipshutz [172] using higher-order mixed cyanocuprates for the opening of epoxides is shown below in **Scheme 2.62**.



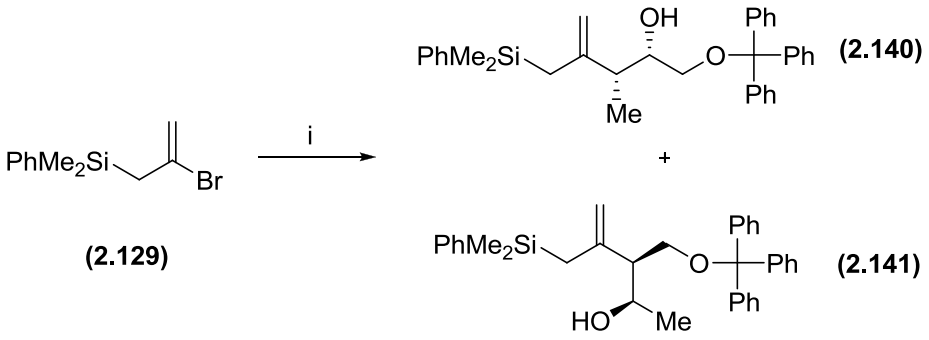
(2.142) **(2.143)** **(2.144)**

Reagents and Conditions: (i) THF, 0°C, 4h, 92%.

Scheme 2.62: Lipshutz's Work on Higher-Order Mixed Cyanocuprate-Mediated Opening of a Terminal Epoxide

The vinyl ligand was transferred selectively yielding desired product **2.144** in an excellent 92% yield.

The use of a 2-thienyl ligand for the opening of epoxide **2.137** was therefore investigated (**Scheme 2.63**).



(2.129)

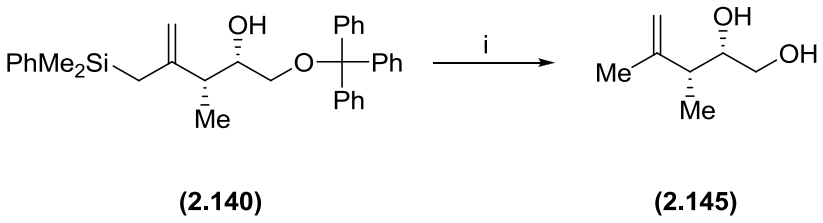
Reagents and Conditions: (i) 2eq. ^{t}BuLi, -70°C then (2-Thienyl)Cu(CN)Li, -70°C to -20°C then **2.137**, -70°C to rt, **2.140**: 59%, **2.141**: 21%.

Scheme 2.63: Higher-Order Mixed Cyanocuprate-Mediated Opening of Epoxide **2.137**

As expected the allyl silane group was transferred exclusively giving desired product **2.140** in 59% isolated yield.

2.5.3.5 Attempted Trityl-Deprotections

Due to their propensity to generate the very stable triphenylmethyl cation trityl ethers are commonly cleaved by action of acidic reagents. The first attempted deprotection on **2.140** was performed using Amberlyst-15H [173] a highly acidic ($pK_a < 1$[174]) sulphonic acid macroreticular resin. The unfortunate, yet still interesting outcome was a highly efficient deprotection of the primary alcohol with concomitant cleavage of the dimethylphenylsilyl group (**Scheme 2.64**).



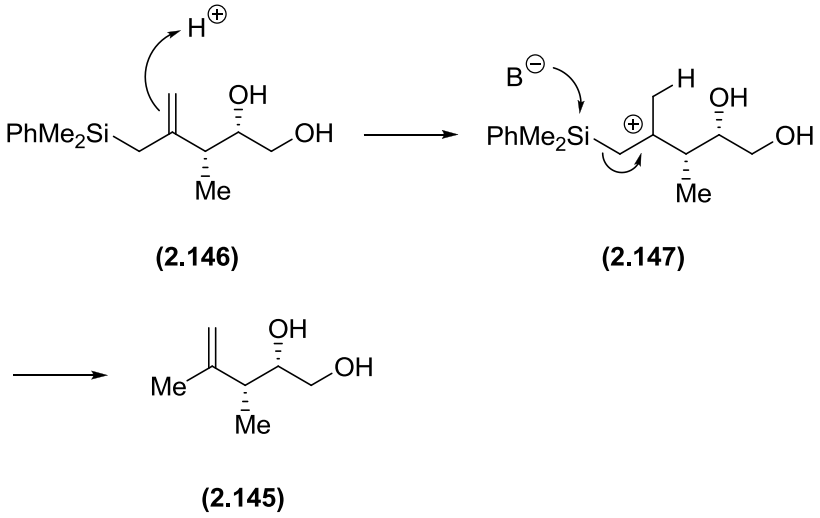
(2.140) **(2.145)**

Reagents and Conditions: (i) Amberlyst-15H, DCM, rt, 93%

Scheme 2.64: Attempted Trityl Deprotection of **2.140**

A possible cause for the cleavage of the silyl group could be its ability to stabilise a β-cation (β-effect) [27,28] which would be generated from the protonation of the terminal alkene in **2.146** as

depicted in **Scheme 2.65**. A subsequent attack by the conjugate base on the silicon group would then furnish **2.145**.



(2.146) **(2.147)** **(2.145)**

Scheme 2.65: Possible Mechanism of Elimination of the Silyl Group

Deprotection with a less acidic reagent was then pursued. Stirring **2.140** in CH_2Cl_2 in the presence of formic acid (pK_a = 3.75 [104]) however furnished the same product in 89% yield. The same result was also obtained when employing lewis acidic zinc(II) bromide [175,176] in CH_2Cl_2 (74% yield of **2.145**).

2.5.3.6 Future Work

Due to time constraints the trityl deprotection was not investigated any further. However a method employing tri-*iso*propylsilane, methanesulfonic acid and di-*iso*propylethylamine for the deprotection of highly acid-sensitive aziridine derivatives was recently published.[177] This procedure could be the answer to the successful deprotection of trityl ether **2.140**.

3. Experimental Section

3.1 General Procedure

Reactions were conducted at room temperature under an atmosphere of nitrogen unless otherwise stated. Reactions were monitored using analytical thin-layer chromatography with visualisation by UV light and alkaline potassium permanganate ($KMnO_4$).

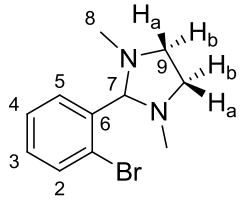
Reaction solvents were purified and dried according to literature methods. THF and diethyl ether were distilled from sodium with benzophenone as an indicator, CH_2Cl_2 and acetonitrile were distilled from CaH_2. All other solvents and reagents were used as supplied. Flash chromatography was performed using silica gel 60, 230-400 mesh.

^1H NMR spectra were recorded on a Varian 500MHz machine (operating at ambient probe temperature using an internal deuterium lock). Chemical shifts were reported in parts per million (ppm), using residual solvent as an internal standard. Standard abbreviations were used throughout (s singlet; bs broad singlet; d doublet; dd doublet of doublets; dt doublet of triplets; dq doublet of quartets; t triplet; q quartet; m multiplet). Coupling constants were measured in Hertz (Hz). ^{13}C NMR spectra were recorded at 126 MHz. Chemical shifts are reported in parts per million (ppm).

ESI Mass spectra were recorded on a Bruker Daltonics Apex III spectrometer with methanol as solvent. EI mass spectra were recorded on a Fisons VG Autospec spectrometer. Infra red spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Alpha-D were recorded on a AUTOPOL IV Polarimeter.

3.2 Compounds

2-(2-Bromophenyl)-1,3-dimethylimidazolidine (1.9)



A mixture of 2-bromobenzaldehyde (18.50g, 11.7ml, 0.1mol), N,N'-dimethylethylenediamine (9.70g, 12.0ml, 0.11mol), *para*-toluenesulfonic acid (1.90g, 0.01mol) in toluene (100ml) was refluxed for 6h while removing generated water by means of a Dean-Stark apparatus . After cooling volatiles were removed under low vacuum and the residue distilled to give the title product (bp 128-130°C at 6.8Torr) as a clear, yellow oil, 23.22g (92%).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.80 – 7.67 (m, 1H, 2C*H*), 7.57 – 7.47 (m, 1H, 4C*H*), 7.33 (dd, *J* = 7.5, 3.7 Hz, 1H, 5C*H*), 7.16 (ddd, *J* = 8.0, 6.2, 4.7 Hz, 1H, 3C*H*), 4.08 (d, *J* = 3.9 Hz, 1H, 7C*H*), 3.48 – 3.23 (m, 2H, 2x9C*H*$_a$), 2.74 – 2.53 (m, 2H, 2x9C*H*$_b$), 2.34 (s, 6H, 2x8C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 138.87, 132.36, 131.18, 129.75, 128.04, 125.65, 88.54, 53.69, 39.59

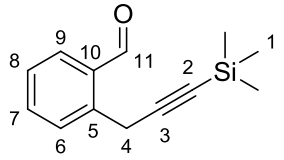
m/z (ESI+): 255, 256, 257, 258, 277, 279

HRMS (ESI+): Calcd. for $C_{11}H_{16}BrN_2$ $[M]^+$: 255.0496; found: 255.0491

υ_{max} (film/ cm^{-1}): 2943 w, 2839 w, 2778 w, 1445 w, 1240 w, 1031 m

Data consistent with those previously reported. [86]

2-[3-(Trimethylsilyl)prop-2-yn-1-yl]benzaldehyde (2.2)



2-(2-Bromophenyl)-1,3-dimethylimidazolidine **(1.9)** (5.00g, 19.60mmol) was dissolved in THF (50ml) and the resulting solution was cooled to -25°C (H_2O/acetone 40:60v/v /liq. N_2). ^{n}BuLi (1.6M, 12.3ml, 19.60mmol) was added dropwise after which the solution was warmed slowly to 0°C. Cooling was re-applied (-25°C, H_2O/Acetone 40:60v/v/liq. N_2) and copper(I) cyanide (1.84g, 20.58mmol) was added in one portion. After stirring for 45min 3-(trimethylsilyl)propargyl bromide (3.4mL, 21.56mmol) was added dropwise. The solution was allowed to warm to rt and stirring was continued for 18 h after which the reaction was quenched with 1M aq. HCl solution (30ml). After addition of Et_2O (100ml) the resulting phases were separated. The organic layer was then washed with sat. aq. NaCl solution (100ml) and dried over $MgSO_4$. Removal of volatiles under low vacuum gave a red oil which was purified by kugelröhr distillation (140ºC-150ºC at 0.07Torr) to give the title compound as a clear, colourless oil, 2.93g (69% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 10.21 (s, 1H, 11C*H*), 7.82 (d, 1H, *J* = 7.6Hz, 9C*H*), 7.74 (d, 1H, *J* = 7.6Hz, 7C*H*), 7.62-7.57 (m, 1H, 8C*H*), 7.48 (t, 1H, *J* = 7.4Hz, 6C*H*), 4.11(s, 2H, 4C*H$_2$*), 0.19 (s, 9H, 3x1C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 192.72, 138.36, 134.08, 133.44, 133.11, 129.3, 127.28, 103.34, 88.55, 23.98, 0.02

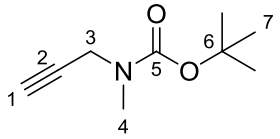
m/z (ESI+) 239, 217, 102, 79

HRMS (ESI+): Calcd. for $C_{13}H_{16}OSiNa$ $[M+Na]^+$: 239.0863; found: 239.0861

υ_{max} (film/ cm^{-1}): 3377 s, 2961 w, 2899 w, 2834 w, 2737 w, 1695 s, 1576 w, 1487 w, 1030 m

Data consistent with those previously reported.[178]

tert-Butyl methyl(prop-2-yn-1-yl)carbamate (2.21)



N-methylpropargylamine (10.00g, 12.2ml, 144.7mmol) was dissolved in CH_2Cl_2 (100ml) and the solution cooled (ice/water). *tert*-Butyldicarbonate (31.60g, 144.7mmol), previously dissolved in CH_2Cl_2 (100ml) was then added dropwise to the amine solution, and the reaction allowed to stir at rt for 2h. Volatiles were then removed *in vacuo* to yield a brown oil which was purified by column chromatography (100% CH_2Cl_2) to afford the title compound as a clear, light yellow liquid which crystallized amorphously on cooling in the freezer, 24.30g (99% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 4.06-3.89 (bs, 2H, 3-C*H*$_2$), 2.85 (s, 3H, 4-C*H*$_3$), 2.16 (t, *J* = 2.39 Hz, 1H, 1-C*H*), 1.40 (s, 9H, 7-3C*H*$_3$)

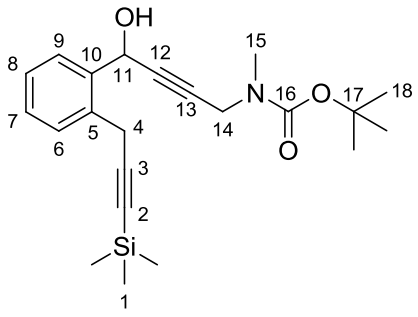
^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 155.07, 79.95, 79.07, 71.48, 37.87, 33.29, 28.23

m/z (EI+): 176, 169, 154, 147, 114, 113, 96, 73

υ_{max} (film/ cm^{-1}): 3308 s, 2979 w, 2931 w, 1693 s, 1481 w, 1249 w, 1050 m

R_f: 0.30 in 1:9 Et_2O/40-60 petroleum ether ($KMnO_4$)

***tert*-Butyl(4-hydroxy-4-{2-[3-(trimethylsilyl)prop-2-yn-1-yl]phenyl}but-2-yn-1-yl)methylcarbamate (2.3)**



^{n}BuLi (2.5M, 5.1ml, 12.71mmol) was added to a cooled (-90°C, methanol/liq. N_2) solution of *tert*-butyl methyl(prop-2-yn-1-yl)carbamate **(2.21** (2.15g, 12.71mmol) in THF (200 ml) and the reaction mixture stirred for 30min. A solution of 2-[3-(trimethylsilyl)prop-2-yn-1-yl]benzaldehyde **(2.2)** (2.50g, 11.56mmol) in THF (5ml) was then added dropwise and the reaction mixture allowed to stir for 1h. The reaction was quenched with 2-bromo-2-methylpropane (2.0ml, 17.33mmol) and was then allowed to warm slowly to rt. The resulting solution was diluted with Et_2O (200ml), washed with water (50ml) and the aqueous fraction extracted with diethyl ether (2x50ml). The combined organic fractions were washed with sat. aq. NaCl solution and dried over $MgSO_4$. Removal of volatiles *in vacuo* gave a dark orange oil which was purified by flash column chromatography (3:2 hexane/Et_2O) to give the title compound as a clear, yellow oil, 4.01g (90% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.66-7.62 (m, 1H, 9C*H*), 7.49-7.46 (m, 1H, 6C*H*), 7.34-7.28 (m, 2H, 8C*H*, 7C*H*), 5.71 (s, 1H, 11C*H*), 4.11 (s, 2H, 14C*H$_2$*), 3.82 (s, 2H, 4C*H$_2$*), 2.90 (s, 3H, 5C*H$_3$*), 1.44 (s, 9H, 3x18C*H$_3$*), 0.17 (s, 9H, 3x1C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 155.29, 137.2, 134.21, 129.38, 128.84, 127.38, 104.23, 87.78, 82.53, 82.25, 80.22, 62.11, 38.68, 37.94, 33.65, 28.31, 23.56, -0.03

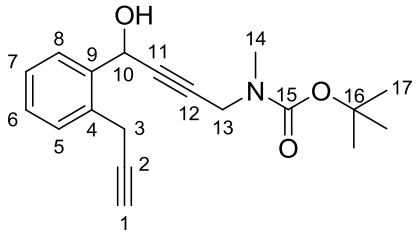
m/z (EI+) 410, 409, 408, 354, 353, 352, 136

HRMS (ESI+): Calcd. for $C_{22}H_{31}NO_3SiNa$ $[M+Na]^+$: 408.1965; found: 408.1958

υ_{max} (film/ cm^{-1}): 3396 s, 2963 br, 2248 w, 2177 w, 1678 s, 1483 w, 1368 w, 1251 m

R_f: 0.22 in 2:3 Et_2O/hexane ($KMnO_4$)

***tert*-Butyl[4-hydroxy-4-(2-prop-2-yn-1-ylphenyl)but-2-yn-1-yl]methylcarbamate (2.4)**



A solution of *tert*-butyl(4-hydroxy-4-{2-[3-(trimethylsilyl)prop-2-yn-1-yl]phenyl}but-2-yn-1-yl)methylcarbamate **(2.3)** (2.53g, 6.70mmol) and sodium methoxide (0.11g, 1.97mmol) in CH_2Cl_2 (10ml) and methanol (10ml) was stirred at room temperature for 18h. It was then diluted with CH_2Cl_2 (20ml), washed with water (50ml) and the aqueous fraction extracted with CH_2Cl_2 (2x20ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the title compound as a thick, yellow oil which was used in the next step without further purification 2.04g (97% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.66 (d, *J* = 6.9Hz, 1H, 8C*H*), 7.53 (d *J* = 6.8Hz, 1H, 5C*H*), 7.36-7.29 (m, 2H, 6C*H*, 7C*H*), 5.73 (d, *J* = 4.3Hz, 1H, 10C*H*), 4.12 (s, 2H, 13C*H$_2$*), 3.80 (s, 2H, 3C*H$_2$*), 2.91 (s, 3H, 14C*H$_3$*), 2.46 (s, 1H, O*H*), 2.21 (t, *J* = 1.4Hz, 1H, 1C*H*), 1.45 (s, 9H, 3x17C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 155.24, 137.78, 134.02, 129.21, 128.73, 127.29, 127.13, 82.62, 82.26, 81.77, 80.21, 71.15, 62.13, 38.60, 37.94, 28.36, 21.92

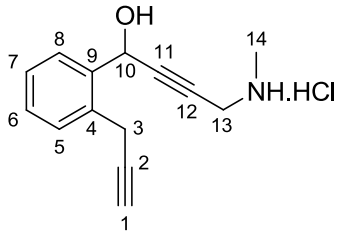
m/z (ESI+) 336, 330, 280, 112, 101, 58

HRMS (ESI+): Calcd. for $C_{19}H_{23}NO_3Na$ $[M+Na]^+$: 336.1570; found: 336.1552

υ_{max} (film/ cm^{-1}): 3396 s, 2977 br, 2248 w, 2120 w, 1677 s, 1483 w, 1368 w, 1251 m

R_f: 0.31 in 1:1 Et_2O/40-60 petroleum ether ($KMnO_4$)

4-(Methylamino)-1-(2-prop-2-yn-1-ylphenyl)but-2-yn-1-ol hydrochloride salt (2.5)



A solution of *tert*-butyl [4-hydroxy-4-(2-prop-2-yn-1-ylphenyl)but-2-yn-1-yl]methylcarbamate (**2.4)** (781mg, 2.52mmol) and hydrogen chloride in Et_2O (2M, 2.5ml, 5.00mmol) was stirred at rt for 3h. Pentane (7ml) was added and the precipitate removed by filtration. The filter cake was washed with Et_2O (2x20ml) and pentane (1x20ml) and dried under a nitrogen gas flow to give the title compound as an off white solid, 378mg (60% yield).

^{1}H NMR (500 MHz, *DMSO-d_6)* δ ppm 9.48 (bs, 2H, N*H*$_2$), 7.62 (d, *J* = 6.3Hz, 1H, 8C*H*), 7.48 (d, *J* = 6.5Hz, 1H, 5C*H*), 7.34-7.28 (m, 2H, 6C*H*, 7C*H*), 6.28 (s, 1H, 10C*H*), 3.91 (s, 2H, 13C*H*), 3.80 (s, 2H, 3C*H*), 3.15 (s, 1H, 1C*H*), 2.52 (s, 3H, 14C*H*$_3$)

^{13}C NMR (126 MHz, *DMSO-d_6*) δ ppm 138.59, 133.72, 128.40, 128.05, 126.77, 126.12, 88.22, 81.87, 78.03, 73.98, 59.91, 36.83, 31.37, 21.05

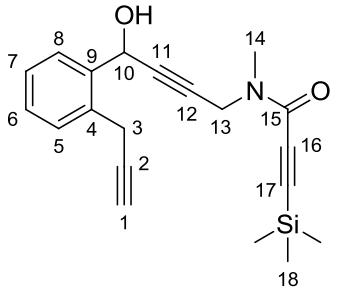
m/z (EI+) 213, 194, 181, 165, 153, 141, 128, 115, 103

HRMS (ESI+): Calcd. for $C_{14}H_{16}NO$ $[M]^+$: 214.1226; found: 214.1217

υ_{max} (neat/ cm^{-1}): 3584 s, 3246 s, 2925 s, 2855 w, 2727 w, 2397 w, 1602 w, 1461 w, 1377 w, 1205 m

Mp: 96ºC-100ºC

***N*-[4-Hydroxy-4-(2-prop-2-yn-1-ylphenyl)but-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.6)**



DMF (4 drops) was added to a solution of 3-(trimethylsilyl)prop-2-ynoic acid **(2.13)** (196mg, 1.38mmol) and oxalyl chloride (0.13ml, 1.38mmol) in CH_2Cl_2 (20ml) and the resulting solution was stirred at rt for 40min. This solution was then added dropwise *via* syringe to a mixture of 4-(methylamino)-1-(2-prop-2-yn-1-ylphenyl)but-2-yn-1-ol hydrochloride **(2.5)** (327mg, 1.31mmol) and triethylamine (334mg, 0.46ml, 3.27mmol) in CH_2Cl_2 (10ml). The resulting cloudy solution was stirred at rt for 20min and then quenched with water (20ml). The phases were separated, the organic layer washed with aq. HCl (2M, 2x10ml), sat. aq. $NaHCO_3$ solution (50ml), dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to give a red oil. This was purified by flash column chromatography (3:2 Et_2O/hexane) to give the title compound as a viscous, yellow oil, 174mg (28% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.63-7.60 (m, 1H, 8C*H*), 7.53-7.50 (m, 1H, 5C*H*), 7.34-7.29 (m, 2H, 6C*H*, 7C*H*), 5.74 (d, *J* = 12.9Hz, 1H, 10C*H*), 4.48 (s, 1H, 13C*H$_2$*), 4.30 (s, 1H, 13C*H$_2$*), 3.79 (d, *J* = 2.7Hz, 2H, 3C*H$_2$*), 3.25 (s, 1.5H, 14C*H$_3$*), 3.00 (s, 1.5H, 14C*H$_3$*), 2.73 (bs, 1H, O*H*), 2.23-2.20 (m, 1H, 1C*H*), 0.24 (d, *J* = 2.8Hz, 9H, 3x18C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 153.63, 153.49, 137.14, 136.36, 134.04, 129.59, 129.41, 129.03, 128.98, 127.41, 127.35, 127.22, 127.17, 98.35, 95.49, 84.04, 83.30, 81.76, 81.62, 80.79, 80.51, 71.12, 62.16, 41.03, 35.59, 35.78, 31.75, 22.05, -0.77

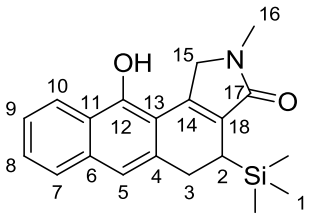
m/z (EI+) 725, 697, 530, 461, 360, 330, 242, 120

HRMS (ESI+): Calcd. for $C_{20}H_{23}NO_2SiNa$ $[M+Na]^+$: 360.1390; found: 360.1373

υ_{max} (neat/ cm^{-1}): 3378 s, 3306 s, 2961 s, 2853 w, 2247 w, 1716 s, 1485 w, 1348 w, 1253 w

R_f: 0.15 in 1:1 Et_2O/hexane ($KMnO_4$)

11-Hydroxy-2-methyl-4-(trimethylsilyl)-1,2,4,5-tetrahydro-3*H*-naphtho[2,3-*e*]isoindol-3-one (1.13)



A solution of *N*-{4-[2-(2-bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}-*N*methyl-3-(trimethylsilyl)prop-2-ynamide **(2.6)** (0.50g, 1.23mmol) and butyl oxirane (2.9mL, 23.92mmol) in de-gassed toluene (20ml) was heated at reflux for 4h. After cooling to rt, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:1 Et_2O/hexane) to give the title compound as a yellow, amorphous solid, 316mg (76% yield).

^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 9.79 (bs, 1H, O*H*), 8.22 (d, *J*=8.6Hz, 1H, 10C*H*), 7.74-7.71(m, 1H, 5-C*H*), 7.45-7.41 (m, 1H, 7C*H*), 7.26-7.22 (m, 2H, 8C*H*, 9C*H*), 4.82(dd, *J*1 = 20.1Hz *J*2 = 122.3Hz, 2H, 15CH_2) 3.29-3.22 (m, 2H, 3CH_2), 3.09-2.96 (m, 3H, 16CH_3), 2.21 (t, *J*=7.3Hz, 1H, 2C*H*), -0.19 (s, 9H, 3x1CH_3)

^{13}C (126MHz, *DMSO-d_6*) δ ppm 169.7, 148.3, 141.6, 135.6, 134.2, 133.9, 127.3, 126.5, 124.8, 124.7, 122.2, 118.3, 114.9, 54.7, 31.1, 28.8, 21.2, -2.1

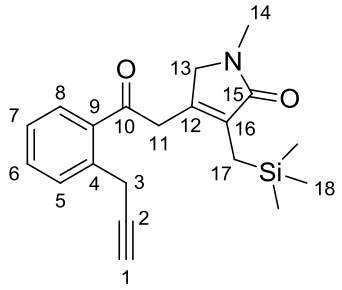
m/z (ESI+) 360, 338, 322, 232

HRMS (ESI+): Calcd. for $C_{20}H_{23}NO_2SiNa$ $[M+Na]^+$: 360.1390; found: 360.1388

υ_{max} (neat/ cm^{-1}): 3043 s, 2955 s, 2855 w, 1943 w, 1647 s, 1570 w, 1487 w, 1371w, 1247 m

Melting point: decomposes at 278ºC-281ºC (CH_2Cl_2/hexane)

1-Methyl-4-[2-oxo-2-(2-prop-2-yn-1-ylphenyl)ethyl]-3-[(trimethylsilyl)methyl]-1,5-dihydro-2*H*-pyrrol-2-one (2.7)



A solution of *N*-{4-[2-(2-bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}-*N*methyl-3-(trimethylsilyl)prop-2-ynamide **(2.6)** (0.50g, 1.23mmol) and butyl oxirane (2.9mL, 23.92mmol) in toluene (20ml) was heated at reflux for 4h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (24:1 Et_2O/hexane) to give the title compound as a yellow, amorphous solid, 38mg (9% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.73-7.69 (m, 2H, 8C*H*, 6C*H*), 7.55-7.50 (m, 1H, 7C*H*), 7.41-7.36 (m, 1H, 5C*H*), 3.95 (s, 2H, 13CH_2), 3.91 (s, 2H, 11CH_2), 3.89 (d, *J* = 2.6Hz, 2H, 3CH_2), 3.02 (s, 3H, 14CH_3), 2.18 (t, *J* = 2.7Hz, 1H, 1C*H*), 1.77 (s, 2H, 17CH_2), 0.02 (s, 9H, 3x18CH_3)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 199.38, 171.74, 137.12, 136.68, 136.03, 134.61, 132.57, 130.68, 128.84, 127.12, 81.88, 71.06, 54.92, 40.57, 29.34, 23.66, 14.73, -1.10

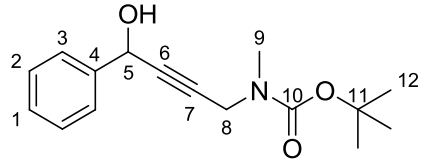
m/z (ESI+) 413, 362, 274, 234, 218, 121, 101

HRMS (ESI+): Calcd. for $C_{20}H_{25}NO_2SiNa$ $[M+Na]^+$: 362.1547; found: 362.1533

υ_{max} (neat/ cm^{-1}): 2954 w, 2926 w, 2856 w, 1681 s, 1450 w, 1249 w

R_f: 0.28 in 100% Et_2O ($KMnO_4$)

tert-Butyl (4-hydroxy-4-phenylbut-2-yn-1-yl)methylcarbamate (2.22)



tert-Butyl methyl(prop-2-ynyl)carbamate **(2.21)** (15.00g, 88.64mmol) was dissolved in THF (100ml) and the temperature of the solution was lowered to -70°C (EtOAc/liq. N_2). ^{n}BuLi (2.2M, 40.0ml, 88.64mmol) was then added dropwise at moderate rate to yield a dark orange solution. Stirring was continued at –70°C for 1 hour. A solution of benzaldehyde (9.41g, 88.64mmol) in THF (50ml) was then added dropwise *via* cannula . The temperature was then allowed to rise slowly to rt and the reaction was stirred at this temperature for 18h. After quenching with sat. aq. NH_4Cl solution (100ml) the solution was diluted with ethyl acetate (200ml) and then washed with water (1x200ml). Drying of the organic phase on $MgSO_4$, filtration and evaporation of volatiles yielded a brown, viscous oil which was purified by column chromatography (1:9 to 3:7 EtOAc/40-60 petroleum ether with a 5% gradient) to give the title compound as a light yellow, viscous oil, 19.72g (81%).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.52 (d, *J* = 7.56 Hz, 2H, 2x3C*H*), 7.36 (t, *J* = 7.36, 7.36 Hz, 2H, 2x2C*H*), 7.31 (d, *J* = 7.24 Hz, 1H, 1C*H*), 5.47 (s, 1H, 5C*H*), 4.11 (bs, 2H, 8C*H*$_2$), 2.90 (s, 3H, 9C*H*$_3$), 1.45 (s, 9H, 3x12C*H*$_3$).

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 140.75, 128.51, 128.24, 126.58, 83.51, 81.92, 80.20, 64.46, 38.31, 33.57, 28.35.

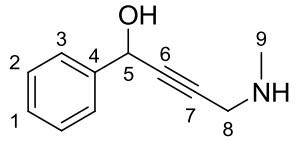
m/z (ESI+): 298, 242, 202, 100

HRMS (ESI+): Calcd. for $C_{16}H_{21}NO_3Na$ $[M+Na]^+$: 298.1412; found: 298.1414

υ_{max} (neat/ cm^{-1}): 3404 br, 2976 w, 2930 w, 1696 s, 1677 s, 1481w, 1392 w, 1249 m, 1151 m

R_f: 0.46 in 1:1 EtOAc/40-60 petroleum ether ($KMnO_4$)

4-(Methylamino)-1-phenylbut-2-yn-1-ol (2.26)



From *tert*-Butyl (4-hydroxy-4-phenylbut-2-yn-1-yl)methylcarbamate **(2.22)**:

To a solution of *tert*-butyl 4-(2-bromophenyl)-4-hydroxybut-2-ynyl(methyl)carbamate **(2.22)** (3.97g, 11.97mmol) in Et_2O (30 ml) was added hydrogen chloride in Et_2O (4M, 9ml, 35.91mmol) and the reaction allowed to stir at rt for 18 hours. The resulting suspension was cooled to 0°C in a freezer, filtered and washed with cold Et_2O (1x50ml). Air drying afforded a white, amorphous solid, which was then suspended in fresh EtOAc (50ml). The resulting mixture was carefully treated with 10% aq. K_2CO_3 solution (100ml), the aqueous phase was saturated with NaCl and was then extracted with EtOAc (3x50ml). The combined organic fractions were dried on Na_2SO_4, filtered and the volatiles removed *in vacuo* to afford the title compound as an amorphous, off-white solid, 4.35g (44%).

From 4-[methyl(triisopropylsilyl)amino]-1-phenylbut-2-yn-1-ol **(2.14)**:

To a solution of 4-[methyl(triisopropylsilyl)amino]-1-phenylbut-2-yn-1-ol **(2.14)** (3.97g, 11.97mmol) in MeCN (50ml) in a PTFE container was added 40% aq. HF (10ml) in one portion *via* PTFE pipette. After stirring for 10min the reaction was quenched by careful addition of 10% aq. K_2CO_3 (200ml). The aqueous phase was saturated with NaCl and extracted with EtOAc (3x100ml). The combined organic fractions were dried on Na_2SO_4, filtered and the solvent removed *in vacuo* to yield an off-white solid, 1.97g (94% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.51 (d, *J* = 7.4 Hz, 2H, 2x3C*H*), 7.34 (t, *J* = 7.4 Hz, 2H, 2x2C*H*), 7.31 – 7.26 (m, 1H, 1C*H*), 5.43 (s, 1H, 5C*H*), 3.37 (d, *J* = 1.8 Hz, 2H, 8C*H*), 3.08 (bs, 1H, O*H*), 2.38 (s, 3H, 9C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 141.51, 128.56, 128.12, 126.60, 84.42, 83.64, 64.11, 40.10, 35.08

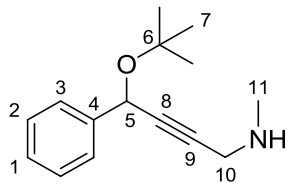
m/z (EI+): 199, 198, 177, 176

HRMS (ESI+): Calcd. for $C_{11}H_{14}NO$ $[M]^+$: 176.1069; found: 176.1068

υ_{max} (neat/ cm^{-1}): 3269 s, 2871 br, 1601 w,1492 m, 1451 s, 1336 m, 1120 s, 1017 s

Mp: 91-93°C (CH_2Cl_2/hexane)

[4-(2-Bromophenyl)-4-*tert*-butoxybut-2-yn-1-yl]methylamine (2.26)



To a suspension of anhydrous zinc(II) bromide (16.57g, 73.60mmol) in CH_2Cl_2 (150ml) at rt was added a solution of *tert*-butyl (4-hydroxy-4-phenylbut-2-yn-1-yl)methylcarbamate **(2.22)** (4.05g, 14.72mmol) in CH_2Cl_2 (20ml). The resulting mixture was stirred at rt for 24h and then quenched by addition of 10% aq.K_2CO_3 solution (100ml). The phases were separated and the aqueous layer was washed with CH_2Cl_2 (2x50ml). The combined organic layers were dried on Na_2SO_4, filtered and the volatiles removed *in vacuo*. Flash column chromatography of the crude (1:19 MeOH/CH_2Cl_2 with 1% Et_3N) gave the title compound as a light yellow oil, 1.52g (62%).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.51 (d, *J* = 7.5 Hz, 2H, 5C*H*, 2x3C*H*), 7.33 (t, *J* = 7.5 Hz, 2H, 2x2C*H*), 7.26 (t, *J* = 7.3 Hz, 1H, 1C*H*), 5.29 (s, 1H, 5C*H*), 3.44 (d, *J* = 1.6 Hz, 2H, 10C*H$_2$*), 2.45 (s, 3H, 11C*H$_3$*), 1.33 (s, 9H, 3x7C*H$_3$*)

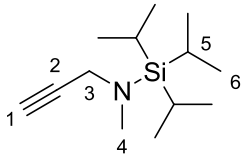
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 141.44, 128.34, 127.63, 126.76, 84.77, 83.94, 75.55, 64.26, 40.54, 35.43, 28.50

m/z (ESI+): 205, 174, 158, 157, 144, 143, 128, 115

HRMS (ESI+): Ion not found

υ_{max} (neat/ cm^{-1}): 2974 w, 2932 w, 1449 w, 1366 w, 1190m, 1010 m

1,1,1-Triisopropyl-*N*-methyl-*N*-prop-2-yn-1-ylsilanamine (2.44)



N-Methylpropargylamine (5g, 72.35mmol) and triethylamine (10.97g, 15.1ml, 108.53mmol) were dissolved in CH_2Cl_2 and the resulting solution cooled using an ice/water bath. Neat triisopropylsilyl trifluoromethanesulfonate (23.28g, 75.97mmol) was then added dropwise *via* syringe. The resulting solution was stirred at rt for 18h. The organic phase was washed with 10% aq. K_2CO_3 solution (2x100 ml) and then dried on Na_2SO_4. Distillation under reduced pressure (84-87°C at 1.6Torr) gave a colourless, clear oil, 16.14g (99% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 3.57 (d, *J* = 2.1Hz, 2H, 3C*H$_2$*), 2.61 (s, 3H, 4C*H$_3$*), 2.14 (t, *J* = 2.3Hz, 1H, 1C*H*), 1.22 – 1.10 (m, 3H, 3x5C*H*), 1.06 (d, *J* = 7.5Hz, 18H, 6x6C*H$_3$*)

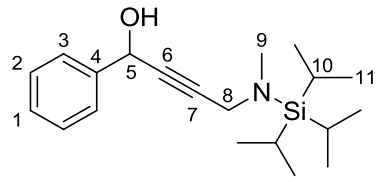
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 83.39, 70.20, 40.82, 36.34, 18.47, 12.26

m/z (ESI+): 226, 175, 155

HRMS (ESI+): Calcd. for $C_{13}H_{28}NSi$ $[M]^+$: 226.1991; found: 226.1986

υ_{max} (neat/ cm^{-1}): 2944 w, 2866 w, 1463 w, 1142 w

4-[Methyl(triisopropylsilyl)amino]-1-phenylbut-2-yn-1-ol (2.14)



A solution of 1,1,1-triisopropyl-*N*-methyl-*N*-prop-2-yn-1-ylsilanamine **(2.44)** (5.51g, 24.47mmol) in THF (50ml) was cooled to -70°C (EtOAc/liq. N_2). ^{n}Buli (2.5M, 9.8ml, 24.47mmol) was then added dropwise. After stirring for 10 min, the temperature was allowed to raise to -20°C and then lowered again to -70°C at which point it was allowed to stir for 30min. Benzaldehyde (2.86g, 2.7ml 26.92mmol) was then added neat *via* syringe, and the solution stirred at -70°C for 20min. The cooling bath was removed and the temperature allowed to slowly rise to rt. The reaction was quenched with sat. aq. NH_4Cl solution (20ml). EtOAc (100ml) was added and the organic phase separated and washed with 10% aq. K_2CO_3 solution (100ml), 10% aq. $NaSO_3H$ solution (2x100ml) and water (100ml). Drying on Na_2SO_4, filtering and evaporation of volatiles gave a light yellow, clear oil which was used in the next step without further purification, 7.46g (95% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.56 (d, *J* = 7.3 Hz, 2H, 3C*H*), 7.37 (t, *J* = 7.3 Hz, 2H, 2C*H*), 7.32 (d, *J* = 7.2 Hz, 1H, 1C*H*), 5.49 (d, *J* = 5.9 Hz, 1H, 5C*H*), 3.67 (d, *J* = 1.3 Hz, 2H, 8C*H*$_2$), 2.63 (s, 3H, 9C*H*$_3$), 2.17 (d, *J* = 6.2 Hz, 1H, O*H*), 1.22 – 1.10 (m, 3H, 3x10C*H*), 1.10 – 1.02 (m, 18H, 6x11C*H*$_3$)

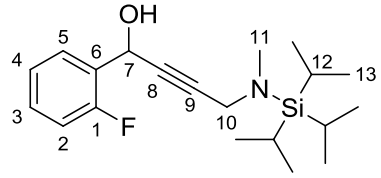
^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 128.45, 128.15, 126.64, 86.50, 81.96, 64.78, 40.98, 36.42, 18.32, 17.68, 12.07

m/z (ESI+): 354, 351, 332, 313, 176

HRMS (ESI+): Calcd. for $C_{20}H_{34}NOSiNa$ $[M+Na]^+$: 332.2391; found: 332.2404

υ_{max} (neat/ cm^{-1}): 3348 br, 2943 m, 2864 m, 1462 w, 1141 w, 1006 m

1-(2-Fluorophenyl)-4-[methyl(triisopropylsilyl)amino]but-2-yn-1-ol (2.46)



A solution of 1,1,1-triisopropyl-*N*-methyl-*N*-prop-2-yn-1-ylsilanamine **(2.44)** (2.61g, 11.59mmol) in THF (50ml) was cooled to -70°C (EtOAc/liq. N_2). ^{n}Buli (2.5M, 4.6ml, 11.92mmol) was then added dropwise . After stirring for 10 min, the temperature was allowed to raise to -20°C and then lowered again to -70°C at which point it was allowed to stir for 30min. 2-Fluorobenzaldehyde (1.58g, 1.4ml, 12.75mmol) was then added neat *via* syringe, and the solution stirred at -70°C for 20min. The cooling bath was removed and the temperature allowed to slowly rise to rt. The reaction was quenched with sat. aq. NH_4Cl solution (10ml). EtOAc (100ml) was added and the organic phase separated and washed with 10% aq. K_2CO_3 solution (100ml), 10% aq. $NaSO_3H$ solution (2x100ml) and water (100ml). Drying on Na_2SO_4, filtering and evaporation of solvents gave a light yellow, clear oil which was used in the next step without further purification, 3.48g (86% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.66 (td, *J* = 7.6, 1.6 Hz, 1H, 2C*H*), 7.30 (tdd, *J* = 7.3, 5.3, 1.7 Hz, 1H, 5C*H*), 7.15 (td, *J* = 7.6, 0.9 Hz, 1H, 3C*H*), 7.10 – 6.98 (m, 1H, 4C*H*), 5.76 (s, 1H, 7C*H*), 3.65 (d, *J* = 1.4 Hz, 2H, 10C*H*$_2$), 2.60 (s, 3H, 11C*H*$_3$), 1.19 – 1.09 (m, 3H, 3x12C*H*), 1.08 – 1.04 (m, 18H, 6x13C*H*$_3$)

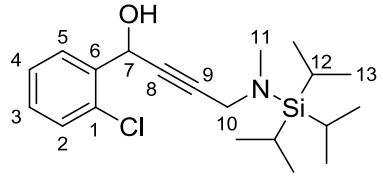
^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 129.96, 128.34, 128.31, 124.19, 115.57, 86.51, 80.85, 59.25, 40.95, 36.39, 18.27, 17.67, 12.29

m/z (ESI+): 372, 350, 216, 194, 176, 124

HRMS (ESI+): Calcd. for $C_{20}H_{32}NOFSiNa$ $[M+Na]^+$: 372.2121; found: 372.2129

υ_{max} (neat/ cm^{-1}): 3311 br, 2944 m, 2865 m, 1616 w, 1589 w, 1488 m, 1458 m, 1008 m

1-(2-Chlorophenyl)-4-[methyl(triisopropylsilyl)amino]but-2-yn-1-ol (2.47)



A solution of 1,1,1-triisopropyl-*N*-methyl-*N*-prop-2-yn-1-ylsilanamine **(2.44)** (3.12g, 13.86mmol) in THF (50ml) was cooled to -70°C (EtOAc/liq. N_2). ^{n}Buli (2.5M, 5.5ml, 13.86mmol) was then added dropwise . After stirring for 10 min, the temperature was allowed to raise to -20°C and then lowered again to -70°C at which point it was allowed to stir for 30min. 2-Chlorobenzaldehyde (1.95g, 13.86mmol) was then added neat *via* syringe, and the solution stirred at -70°C for 20min. The cooling bath was removed and the temperature allowed to slowly rise to rt. The reaction was quenched with sat. aq. NH_4Cl solution (10ml). EtOAc (100ml) was added and the organic phase separated and washed with 10% aq. K_2CO_3 solution (100ml), 10% aq. $NaSO_3H$ solution (2x100ml) and water (100ml). Drying on Na_2SO_4, filtering and evaporation of solvents gave a light yellow, clear oil which was used in the next step without further purification, 4.61g (91% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.77 (dd, *J* = 7.6, 1.8 Hz, 1H, 2C*H*), 7.37 (dd, *J* = 7.7, 1.3 Hz, 1H, 5C*H*), 7.30 (dd, *J* = 7.4, 1.3 Hz, 1H, 3C*H*), 7.29 – 7.23 (m, 1H, 4C*H*), 5.84 (d, *J* = 5.4 Hz, 1H, 7C*H*), 3.65 (d, *J* = 1.4 Hz, 2H, 10C*H*$_2$), 2.61 (s, 3H, 11C*H*$_3$), 2.38 (d, *J* = 5.5 Hz, 1H, O*H*), 1.19 – 1.08 (m, 3H, 3x12C*H*), 1.04 (d, *J* = 7.1 Hz, 18H, 6x13C*H*$_3$)

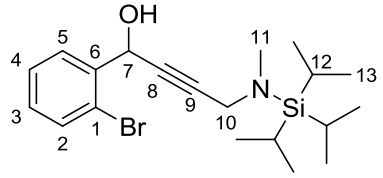
^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 138.36, 132.69, 129.61, 129.40, 128.28, 127.05, 86.64, 80.82, 62.08, 40.97, 36.42, 18.29, 12.04

m/z (ESI+): 388, 385, 366, 313, 210

HRMS (ESI+): Calcd. for $C_{20}H_{32}NOClSiNa$ $[M+Na]^+$: 388.1831; found: 388.1833

υ_{max} (neat/ cm^{-1}): 3330 br, 2943 m, 2864 m, 1597 w, 1467 m, 1443 m, 1007 m

1-(2-Bromophenyl)-4-[methyl(triisopropylsilyl)amino]but-2-yn-1-ol (2.48)



A solution of 1,1,1-triisopropyl-*N*-methyl-*N*-prop-2-yn-1-ylsilanamine **(2.44)** (2.96g, 13.14mmol) in THF (50ml) was cooled to -70°C (EtOAc/liq. N_2). ^{n}Buli (2.5M, 5.3ml, 13.14mmol) was then added dropwise . After stirring for 10 min, the temperature was allowed to raise to -20°C and then lowered again to -70°C at which point it was allowed to stir for 30min. 2-Bromobenzaldehyde (2.43g, 13.14mmol) was then added neat *via* syringe, and the solution stirred at -70°C for 20min. The cooling bath was removed and the temperature allowed to slowly rise to rt. The reaction was quenched with sat. aq. NH_4Cl solution (10ml). EtOAc (100ml) was added and the organic phase separated and washed with 10% aq. K_2CO_3 solution (100ml), 10% aq. $NaSO_3H$ solution (2x100ml) and water (100ml). Drying on Na_2SO_4, filtering and evaporation of solvents gave a light yellow, clear oil which was used in the next step without further purification, 5.11g (95% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.83 (dd, *J* = 7.8, 2.0 Hz, 1H, 2C*H*), 7.67 (d, *J* = 8.3 Hz, 1H, 4C*H*), 7.35 (t, *J* = 7.6 Hz, 1H, 5C*H*), 7.22 (m, 1 H, 3C*H*), 5.81(m, 1H, 7C*H*), 3.60 (s, 2H, 10C*H*$_2$), 2.66 (s, 3H, 11C*H*$_3$), 2.42 (d, *J* = 4.9 Hz, 1H, O*H*), 1.15 (m, 3 H, 3x12C*H*), 1.16 (m, 18 H, 6x13C*H*$_3$)

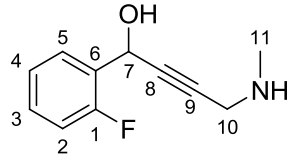
^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 140.01, 132.95, 129.71, 128.56, 127.70, 122.77, 86.89, 80.93, 64.37, 41.00, 36.54, 18.37, 12.11

m/z (ESI+): 434, 410, 277, 144.

HRMS (ESI+): Calcd. for $C_{20}H_{33}BrNOSi$ $[M]^+$: 410.1515; found: 410.1509

υ_{max} (neat/ cm^{-1}): 3357 br, 2942 w, 2864 w, 1464 w, 1191 w

1-(2-Fluorophenyl)-4-(methylamino)but-2-yn-1-ol (2.49)



To a solution of 1-(2-fluorophenyl)-4-[methyl(triisopropylsilyl)amino]but-2-yn-1-ol **(2.46)** (1.54g, 4.41mmol) in MeCN (10ml) in a PTFE container was added 40% aq. HF (5ml) in one portion *via* PTFE pipette . After stirring for 10min the reaction was quenched by careful addition of 10% aq. K_2CO_3 (100ml). The aqueous phase was saturated with NaCl and extracted with EtOAc (3x50ml). The combined organic fractions were dried on Na_2SO_4, filtered and the solvent removed *in vacuo* to yield an off-white solid, 817mg (96% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.65 (td, *J* = 7.6, 1.7 Hz, 1H, 2C*H*), 7.30 (tdd, *J* = 7.3, 5.3, 1.8 Hz, 1H, 5C*H*), 7.16 (td, *J* = 7.6, 1.0 Hz, 1H), 4C*H*, 7.05 (ddd, *J* = 10.1, 8.3, 1.0 Hz, 1H, 3C*H*), 5.75 (t, *J* = 1.6 Hz, 1H, 7C*H*), 3.44 (d, *J* = 1.8 Hz, 2H, 10C*H$_2$*), 2.44 (s, 3H, 11C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 161.05, 129.96, 128.42, 124.29, 115.59, 109.99, 84.04, 82.78, 58.62, 40.16, 35.17

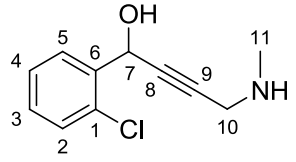
m/z (ESI+): 217, 216, 194, 176

HRMS (ESI+): Calcd. for $C_{11}H_{13}FNO$ $[M]^+$: 194.0975; found: 194.0957

υ_{max} (neat/ cm^{-1}): 3266 s, 2800 s, 1614 w, 1587 w, 1487 m, 1456 m, 1226 w, 1029 m

Mp: 99-101°C (CH_2Cl_2/hexane)

1-(2-Chlorophenyl)-4-(methylamino)but-2-yn-1-ol (2.50)



To a solution of 1-(2-chlorophenyl)-4-[methyl(triisopropylsilyl)amino]but-2-yn-1-ol **(2.47)** (2.11g, 5.77mmol) in MeCN (10ml) in a PTFE container was added 40% aq. HF (10ml) in one portion *via* PTFE pipette . After stirring for 10min the reaction was quenched by careful addition of 10% aq. K_2CO_3 (100ml). The aqueous phase was saturated with NaCl and extracted with EtOAc (3x50ml). The combined organic fractions were dried on Na_2SO_4, filtered and the solvent removed *in vacuo* to yield an off-white solid, 817mg (92% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.75 (dd, *J* = 7.6, 1.6 Hz, 1H, 2C*H*), 7.34 (dd, *J* = 7.8, 1.1 Hz, 1H, 5C*H*), 7.28 (td, *J* = 7.6, 1.2 Hz, 1H, 4C*H*), 7.23 (td, *J* = 7.6, 1.7 Hz, 1H, 3C*H*), 5.80 (s, 1H, 7C*H*), 3.40 (d, *J* = 1.7 Hz, 2H, 10C*H$_2$*), 2.41 (s, 3H, 11C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 138.73, 132.47, 129.55, 129.26, 128.11, 127.12, 83.46, 83.28, 61.13, 40.07, 35.05

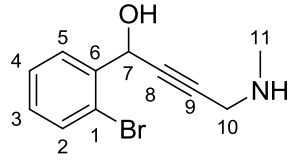
m/z (ESI+): 296, 232, 210

HRMS (ESI+): Calcd. for $C_{11}H_{12}ClNONa$ $[M+Na]^+$:232.0505; found: 232.0500

υ_{max} (neat/ cm^{-1}): 3268 s, 2903 s, 2667 br, 1592 w, 1574 w, 1484m, 1334 m, 1295 m, 1119 m, 1025 m

Mp: 111-113°C (CH_2Cl_2/hexane)

1-(2-Bromophenyl)-4-(methylamino)but-2-yn-1-ol (2.51)



To a solution of 2-(bromophenyl)-4-[methyl(triisopropylsilyl)amino]but-2-yn-1-ol **(2.48)** (3.26g, 7.97mmol) in MeCN (50ml) in a PTFE container was added 40% aq. HF (10ml) in one portion *via* PTFE pipette . After stirring for 10min the reaction was quenched by addition of 10% aq. K_2CO_3 solution (200ml). The aqueous phase was saturated with NaCl and extracted with EtOAc (3x100ml). The combined organic fractions were dried on Na_2SO_4, filtered and evaporation of the solvent gave an off-white solid, 1.76g (87%).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.76 (dd, *J* = 7.7, 1.2 Hz, 1H, 2C*H*), 7.54 (d, *J* = 7.9 Hz, 1H, 4C*H*), 7.34 (t, *J* = 7.5 Hz, 1H, 5C*H*), 7.16 (td, *J* = 7.9, 1.4 Hz, 1H, 3C*H*), 5.78 (s, 1H, 7C*H*), 3.42 (d, *J* = 1.5 Hz, 2H, 10C*H$_2$*), 2.43 (s, 3H, 11C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 140.35, 133.01, 129.76, 128.50, 127.93, 122.68, 84.07, 83.24, 63.78, 40.31, 35.31

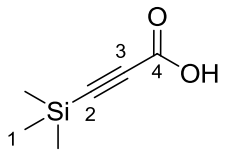
m/z (ESI+): 277, 275, 256, 254, 238, 236

HRMS (ESI+): Calcd. for $C_{11}H_{13}BrNO$ $[M]^+$: 254.0173; found: 254.0175

υ_{max} (neat/ cm^{-1}): 3268 s, 3057 br, 2978 w, 2903 w, 1485 w, 1292 w

Mp: 118-120°C (CH_2Cl_2/hexane)

3-(Trimethylsilyl)prop-2-ynoic acid (2.13)



MeLi (1.6M in Et_2O, 80.0ml, 128.00mmol) was added to a cooled (-75°C solid CO_2/acetone) solution of (trimethylsilyl)acetylene (18.1ml, 128.00mmol) in Et_2O (150ml). The temperature of the resulting solution was allowed to rise to -20°C and then was cooled again to -75°C. Previously crushed solid CO_2 pellets (50g) were then added in 3 portions *via* side-arm solid addition funnel. The reaction was allowed to warm to rt over 18hr and was then quenched with aq. HCl (1M, 300ml). The phases were separated and the aqueous fraction extracted with Et_2O (2x75ml). The combined organic fractions were washed with sat. aq. NaCl solution, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified *via* short-path distillation (bp 72-74°C at 0.08Torr) to give the title compound as a clear, colourless oil, 12.38g (78% yield).

^{1}H (500 MHz, *CDCl$_3$*) δ ppm 11.36 (1H, bs, O*H*), 0.24 (9H, s, 3x1C*H*3)

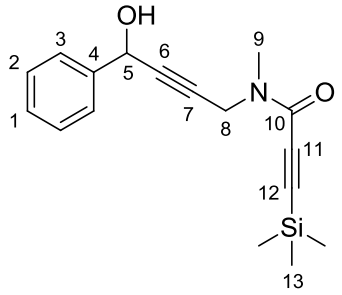
^{13}C (126 MHz, *CDCl$_3$*) δ ppm 157.82, 97.45, 93.73, -1.18

m/z (EI+) 127, 99, 83

υ_{max} (neat/ cm^{-1}): 2965 s, 2904 s, 2626 s, 2178 w, 1694 s, 1517 m, 1404 m, 1254 w

Data consistent with those previously reported. [179]

***N*-(4-Hydroxy-4-phenylbut-2-yn-1-yl)-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.12)**



To a cooled (ice/water bath) solution of 3-(trimethylsilyl)prop-2-ynoic acid **(2.13)** (426mg, 2.99mmol) and 4 drops of DMF in CH_2Cl_2 (20ml) was added oxalyl chloride (0.27ml, 399mg, 3.14mmol) dropwise *via* syringe. The solution was allowed to warm to rt and was stirred for 2h. It was then cooled again (ice/water bath) and 2,6-lutidine (0.69, 641mg, 5.98mmol) was added dropwise followed by 4-(methylamino)-1-phenylbut-2-yn-1-ol **(2.23)** (500mg, 2.85mmol) previously dissolved in CH_2Cl_2 (10ml). The resulting cloudy solution was then allowed to stir at rt for 18h. The reaction was then quenched with water (20ml), and the organic layer washed with 10% aq. citric acid solution (20ml) and 10% aqueous K_2CO_3 solution (20ml). Drying on Na_2SO_4, filtering and evaporation of volatiles *in vacuo* gave a deep yellow oil which was purified by flash column chromatography (1:1 to 3:2 Et_2O/hexane with a 10% gradient) to give the title compound as a yellow, viscous oil, 713mg, (82% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.54 – 7.48 (m, 2H, 3C*H*), 7.42 – 7.29 (m, 3H, 1C*H*, 2C*H*), 5.49 (d, *J* = 16.9 Hz, 1H, 5C*H*), 4.48 (d, *J* = 1.6 Hz, 0.8H, 8C*H$_2$*), 4.32 (d, *J* = 1.7 Hz, 1.2H, 8C*H$_2$*), 3.26 (s, 1.4H, 9C*H$_3$*), 3.01 (s, 1.6H, 9C*H$_3$*), 0.24 (d, *J* = 3.5 Hz, 9H, 3x13C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 153.60, 140.35, 128.69, 128.62, 128.54, 128.41, 126.53, 126.50, 98.24, 95.54, 84.06, 80.41, 80.26, 64.55, 40.95, 35.58, 35.52, 31.63, -0.72

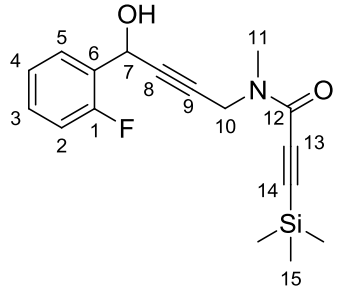
m/z (ESI+): 338, 322, 300, 282

HRMS (ESI+): Calcd. for $C_{17}H_{21}NO_2SiNa$ $[M+Na]^+$: 322.1239; found: 322.1234

υ_{max} (neat/ cm^{-1}): 3387 br, 2960 w, 2164 w, 1623 s, 1400 m, 1252 m, 1123 m

R_f: 0.18 in 3:2 Et_2O/hexane ($KMnO_4$)

***N*-[4-(2-Fluorophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.53)**



To a cooled (ice/water bath) solution of 3-(trimethylsilyl)prop-2-ynoic acid **(2.13)** (387mg, 2.72mmol) and 4 drops of DMF in CH_2Cl_2 (20ml) was added oxalyl chloride (0.25ml, 363mg, 2.86mmol) dropwise *via* syringe. The solution was allowed to warm to rt and was stirred for 2h. It was then cooled again (ice/water bath) and 2,6-lutidine (0.63ml, 583mg, 5.44mmol) was added dropwise followed by 1-(2-fluorophenyl)-4-(methylamino)but-2-yn-1-ol **(2.49)** (500mg, 2.59mmol) previously dissolved in CH_2Cl_2 (10ml). The resulting cloudy solution was then allowed to stir at rt for 18h. The reaction was then quenched with water (20ml), and the organic layer washed with 10% aq. citric acid solution (20ml) and 10% aqueous K_2CO_3 solution (20ml). Drying on Na_2SO_4, filtering and evaporation of volatiles *in vacuo* gave a deep yellow oil which was purified by flash column chromatography (1:1 Et_2O/hexane) to give the title compound as a yellow, viscous oil, 620mg, (81% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.60 (t, *J* = 7.6 Hz, 1H, 2C*H*), 7.35 – 7.27 (m, 1H, 5C*H*), 7.16 (t, *J* = 7.5 Hz, 1H, 4C*H*), 7.06 (dd, *J* = 15.9, 8.6 Hz, 1H, 3C*H*), 5.75 (d, *J* = 17.0 Hz, 1H, 7C*H*), 4.46 (s, 0.9H, 10C*H$_2$*), 4.30 (s, 1.1H, 10C*H$_2$*), 3.24 (d, *J* = 2.2 Hz, 1.6H, 11C*H$_3$*), 2.99 (d, *J* = 2.5 Hz, 1.4H, 11C*H$_3$*), 0.23 (dd, *J* = 5.9, 1.6 Hz, 9H, 3x15C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 128.22, 128.10, 124.38, 115.55, 98.30, 95.50, 95.26, 59.95, 58.90, 40.91, 35.54, 35.48, 32.71, 31.59, 28.47, -0.74

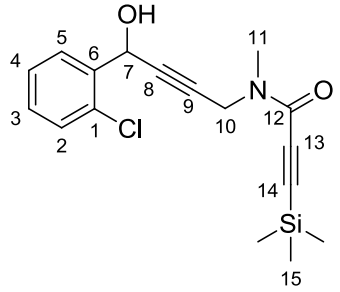
m/z (ESI+): 340, 318, 229, 194

HRMS (ESI+): Calcd. for $C_{17}H_{20}FNO_2SiNa$ $[M+Na]^+$: 340.1145; found: 340.1140

υ_{max} (neat/ cm^{-1}): 3371 br, 2961 m, 2247 w, 2165 w, 1621 s, 1488 s, 1456 s, 1252 s, 1124 s

R_f: 0.22 in 1:1 Et_2O/hexane ($KMnO_4$)

***N*-[4-(2-Chlorophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.54)**



To a cooled (ice/water bath) solution of 3-(trimethylsilyl)prop-2-ynoic acid **(2.13)** (356mg, 2.50mmol) and 4 drops of DMF in CH_2Cl_2 (20ml) was added oxalyl chloride (0.23ml, 333mg, 2.63mmol) dropwise *via* syringe. The solution was allowed to warm to rt and was stirred for 2h. It was then cooled again (ice/water bath) and 2,6-lutidine (0.58ml, 540mg, 5.00mmol) was added dropwise followed by 1-(2-chlorophenyl)-4-(methylamino)but-2-yn-1-ol **(2.50)** (500mg, 2.39mmol) previously dissolved in CH_2Cl_2 (10ml). The resulting cloudy solution was then allowed to stir at rt for 18h. The reaction was then quenched with water (20ml), and the organic layer washed with 10% aq. citric acid solution (20ml) and 10% aqueous K_2CO_3 solution (20ml). Drying on Na_2SO_4, filtering and evaporation of volatiles *in vacuo* gave a deep yellow oil which was purified by flash column chromatography (1:1 to 3:2 Et_2O/hexane with a 10% gradient) to give the title compound as a yellow, viscous oil, 615mg, (80% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.69 (d, *J* = 7.7 Hz, 1H, 2C*H*), 7.35 – 7.27 (m, 2H, 5C*H*, 4C*H*), 7.26 – 7.20 (m, 1H, 3C*H*), 5.78 (d, *J* = 4.9 Hz, 1H, 7C*H*), 4.41 (s, 1H, 10C*H$_2$*), 4.28 (s, 1H, 10C*H$_2$*), 3.22 (s, 1.5H, 11C*H$_3$*), 3.12 (d, *J* = 5.9 Hz, 1H, O*H*), 2.98 (s, 1.5H, 11C*H$_3$*), 0.18 (d, *J* = 3.6 Hz, 9H)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 152.94, 152.84, 138.73, 138.61, 131.80, 129.42, 129.37, 129.22, 129.16, 128.15, 128.02, 127.11, 84.95, 84.22, 79.41, 78.90, 78.76, 75.41, 75.17, 61.58, 61.53, 40.89, 35.50, 35.30, 31.67, 0.09

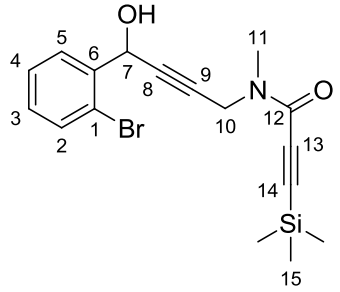
m/z (ESI+): 358, 357, 356, 230

HRMS (ESI+): Calcd. for $C_{17}H_{20}ClNO_2SiNa$ $[M+Na]^+$: 356.0838; found: 356.0844

υ_{max} (neat/ cm^{-1}): 3378 br, 2961 w, 2869 w, 1620 s, 1445 m, 1398 m, 1250 s, 1124 m

R_f: 0.17 in 1:1 Et_2O/hexane ($KMnO_4$)

***N*-[4-(2-Bromophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.55)**



To a cooled (ice/water bath) solution of 3-(trimethylsilyl)prop-2-ynoic acid **(2.13)** (400mg, 2.81mmol) and 4 drops of DMF in CH_2Cl_2 (20ml) was added oxalyl chloride (0.29ml, 428mg, 3.37mmol) dropwise *via* syringe. The solution was allowed to warm to rt and was stirred for 2h. It was then cooled again (ice/water bath) and 2,6-lutidine (0.65ml, 602mg, 5.62mmol) was added dropwise followed by 1-(2-bromophenyl)-4-(methylamino)but-2-yn-1-ol **(2.51)** (649mg, 2.55mmol) previously dissolved in CH_2Cl_2 (10ml). The resulting cloudy solution was then allowed to stir at rt for 18h. The reaction was then quenched with water (20ml), and the organic layer washed with 10% aq. citric acid solution (20ml) and 10% aqueous K_2CO_3 solution (20ml). Drying on Na_2SO_4, filtering and evaporation of volatiles *in vacuo* gave a deep yellow oil which was purified by flash column chromatography (1:1 to 3:2 Et_2O/hexane with a 10% gradient) to give the title compound as a yellow, viscous oil, 672mg, (82% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.71 (d, *J* = 7.7 Hz, 1H, 2C*H*), 7.57 – 7.47 (m, 1H, 5C*H*), 7.34 (t, *J* = 7.2 Hz, 1H, 4C*H*), 7.17 (dd, *J* = 13.8, 7.3 Hz, 1H, 3C*H*), 5.78 (d, *J* = 16.8 Hz, 1H), 4.44 (s, 0.8H, 10C*H$_2$*), 4.28 (d, *J* = 6.8 Hz, 1.2H, 10C*H$_2$*), 3.23 (s, 1.8H, 11C*H$_3$*), 3.15 (d, *J* = 4.4 Hz, 1H, O*H*), 2.98 (s, 1.2H, 11C*H$_3$*), 0.22 (d, *J* = 6.4 Hz, 9H, 3x15C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 153.62, 153.49, 139.45, 139.40, 132.98, 132.90, 129.89, 129.81, 128.37, 128.23, 127.88, 127.86, 122.44, 122.41, 98.36, 95.50, 95.27, 83.96, 83.27, 80.19, 80.02, 63.90, 40.97, 35.61, 35.55, 31.65, -0.71

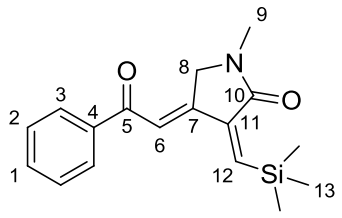
m/z (ESI+): 403, 402, 400, 201, 133

HRMS (ESI+): Calcd. for $C_{17}H_{20}BrNO_2SiNa$ $[M+Na]^+$: 400.0368; found: 400.0339

υ_{max} (neat/ cm^{-1}): 3368 br, 2961 m, 2247 w, 1622 s, 1440 m, 1401 m, 1252 s, 1127 m

R_f: 0.19 in 1:1 Et_2O/hexane ($KMnO_4$)

(3*Z*,4*Z*)-1-Methyl-4-(2-oxo-2-phenylethylidene)-3-[(trimethylsilyl)methylene]pyrrolidin-2-one (2.57)



A solution of *N*-(4-hydroxy-4-phenylbut-2-yn-1-yl)-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (436mg, 1.46mmol) **(2.12)** in de-gassed toluene (15ml) was heated at reflux for 4h. After cooling to rt the solvent was removed *in vacuo* and the crude was purified by flash column chromatography (1:4 EtOAc/hexane) to yield the title compound as a yellow, amorphous solid, 267mg (61% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.99 (d, *J* = 7.4 Hz, 2H, 3C*H*), 7.57 (t, *J* = 7.3 Hz, 1H, 1C*H*), 7.49 (t, *J* = 7.6 Hz, 2H, 2C*H*), 7.37 (s, 1H, 6C*H*), 7.04 (s, 1H, 12C*H*), 4.60 (d, *J* = 2.1 Hz, 2H, 8C*H$_2$*), 3.02 (s, 3H, 9C*H$_3$*), 0.30 (s, 9H, 3x13C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 189.94, 166.48, 148.30, 143.85, 140.70, 138.67, 133.04, 128.84, 128.19, 112.68, 54.38, 29.63, 0.05

m/z (ESI+): 338, 322, 300, 284

HRMS (ESI+): Calcd. for $C_{17}H_{21}NO_2SiNa$ $[M+Na]^+$: 322.1239; found: 322.1234

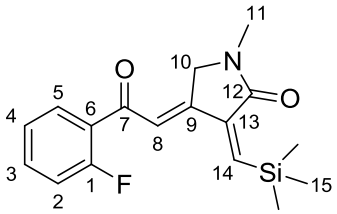
υ_{max} (neat/ cm^{-1}): 2953 m, 2251 m, 1696 s, 1655 s, 1367 m, 1245 s

$R_{f:}$ 0.31 in 3:7 EtOAc/hexane ($KMnO_4$)

Mp: decomposes at 149-151°C (hexane)

See **Appendix** for crystallographic data

(3*Z*,4*Z*)-4-[2-(2-Fluorophenyl)-2-oxoethylidene]-1-methyl-3-[(trimethylsilyl)methylene]pyrrolidin-2-one (2.58)



A solution of *N*-[4-(2-fluorophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (452mg, 1.42mmol) (**2.53)** in de-gassed toluene (14ml) was heated at reflux for 4h. After cooling to rt the solvent was removed *in vacuo* and the crude was purified by flash column chromatography (1:4 EtOAc/hexane) to yield the title compound as a yellow, amorphous solid, 131mg (29% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.64 (d, *J* = 7.2 Hz, 1H, 2C*H*), 7.48 – 7.42 (m, 2H, 4C*H*, 5C*H*), 7.31 (t, *J* = 7.1 Hz, 1H, 3C*H*), 7.15 (s, 1H, 8C*H*), 7.08 (s, 1H, 14C*H*), 4.58 (s, 2H, 10C*H$_2$*), 3.01 (s, 3H, 11C*H$_3$*), 0.22 (s, 9H, 3x15C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 194.23, 168.60, 147.65, 142.38, 139.30, 136.93, 132.12, 129.34, 128.05, 113.72, 54.27, 30.23, 0.06

m/z (ESI+): 317, 301 245

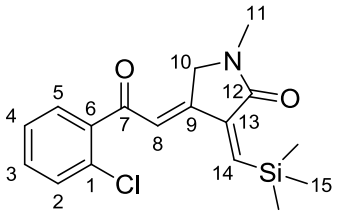
HRMS (ESI+): Calcd. for $C_{17}H_{20}FNO_2SiNa$ $[M+Na]^+$: 340.1145; found: 340.1189

υ_{max} (neat/ cm^{-1}): 2983 w, 2745 w, 1688 s, 1659 m, 1521 m, 1288 m, 1232 s

R_f: 0.30 in 2:3 EtOAc/hexane ($KMnO_4$)

Mp: decomposes at 127-130°C (hexane)

(3*Z*,4*Z*)-4-[2-(2-Chlorophenyl)-2-oxoethylidene]-1-methyl-3-[(trimethylsilyl)methylene]pyrrolidin-2-one (2.59)



A solution of *N*-[4-(2-chlorophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (410mg, 1.23mmol) **(2.54)** in de-gassed toluene (14ml) was heated at reflux for 4h. After cooling to rt the solvent was removed *in vacuo* and the crude was purified by flash column chromatography (1:4 EtOAc/hexane) to yield the title compound as a yellow, amorphous solid, 148mg (36% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.51 (d, *J* = 7.5 Hz, 1H, 2C*H*), 7.48 – 7.38 (m, 2H, 4C*H*, 5C*H*), 7.35 (t, *J* = 7.3 Hz, 1H, 3C*H*), 7.06 (s, 1H, 8C*H*), 7.00 (s, 1H, 14C*H*), 4.60 (s, 2H, 10C*H$_2$*), 3.04 (s, 3H, 11C*H$_3$*), 0.28 (s, 9H, 3x15C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 191.81, 166.26, 147.65, 143.48, 141.68, 139.92, 131.88, 131.25, 130.42, 129.40, 127.04, 116.25, 54.17, 29.50, -0.17

m/z (ESI+): 372, 356, 334, 318

HRMS (ESI+): Calcd. for $C_{17}H_{20}ClNO_2SiNa$ $[M+Na]^+$: 356.0849; found: 356.0844

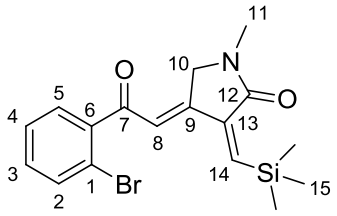
υ_{max} (neat/ cm^{-1}): 2952 w, 2896 w, 1698 s, 1666 m, 1611 s, 1589 m, 1361 m, 1242 s

R_f: 0.32 in 1:4 EtOAc/hexane ($KMnO_4$)

Mp: decomposes at 123-125°C (hexane)

See **Appendix** for crystallographic data

(3*Z*,4*Z*)-4-[2-(2-Bromophenyl)-2-oxoethylidene]-1-methyl-3-[(trimethylsilyl)methylene]pyrrolidin-2-one (2.56)



A solution of *N*-[4-(2-bromophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (497mg, 1.31mmol) **(2.55)** in de-gassed toluene (14ml) was heated at reflux for 4h. After cooling to rt the solvent was removed *in vacuo* and the crude was purified by flash column chromatography (1:4 EtOAc/hexane) to yield the title compound as a yellow, amorphous solid, 157mg (32% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.66 – 7.60 (m, 1H, 2C*H*), 7.47 (dd, *J* = 7.6, 1.6 Hz, 1H, 5C*H*), 7.40 (td, *J* = 7.5, 0.8 Hz, 1H, 4C*H*), 7.32 (td, *J* = 7.8, 1.7 Hz, 1H, 3C*H*), 7.02 (t, *J* = 2.4 Hz, 1H, 8C*H*), 6.99 (s, 1H, 14C*H*), 4.60 (d, *J* = 2.3 Hz, 2H, 10C*H$_2$*), 3.04 (s, 3H, 11C*H$_3$*), 0.27 (s, 9H, 3x15C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 192.55, 166.25, 147.67, 143.48, 141.95, 141.78, 133.57, 131.84, 129.19, 127.57, 119.33, 116.08, 54.13, 29.51, -0.17

m/z (ESI+): 418, 416, 402, 400, 380, 378

HRMS (ESI+): Calcd. for $C_{17}H_{20}BrNO_2SiNa$ $[M+Na]^+$: 400.0344; found: 400.0339

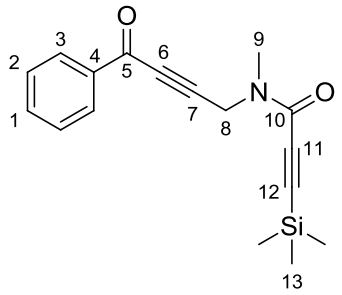
υ_{max} (neat/ cm^{-1}): 2948 w, 2900 w, 1695 s, 1663 s, 1610 s, 1588 s, 1359 s, 1240 s, 1024 m

R_f: 0.35 in 1:4 EtOAc/hexane ($KMnO_4$)

Mp: decomposes at 122-124°C (hexane)

See **Appendix** for crystallographic data

***N*-Methyl-*N*-(4-oxo-4-phenylbut-2-yn-1-yl)-3-(trimethylsilyl)prop-2-ynamide (2.62)**



Preparation of Jones' reagent:

To a cooled (ice/water bath) solution of chromium(VI) trioxide (67g, 670mmol) in water (125ml) was carefully added fuming H_2SO_4 (58ml, 110.20g, 1.124mol). Residual salts at the bottom of the flask were then dissolved using the minimum quantity of water necessary. The approximate molarity of the resulting solution is 3M.

Oxidation procedure:

To a cooled (ice/water bath) solution of *N*-(4-hydroxy-4-phenylbut-2-yn-1-yl)-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **(2.12)** (600mg, 1.80mmol) in acetone (20ml) was added Jones' reagent (3M, 1.8ml, 5.40mmol). The reaction mixture was then allowed to stir at rt for 30min, after which enough ^{i}PrOH was added to cause the solution to acquire a persistent green colour. The mixture was then filtered through a pad of Celite and the resulting cake was washed with Et_2O (50ml). The resulting filtrate phases were separated and the combine organic layers were washed with water (2x20ml) and sat. aq. NaCl solution (50ml). Drying on $MgSO_4$, filtering and evaporation of volatiles *in vacuo* afforded a brown oil which was purified by flash column chromatography (7:13 to 1:1 Et_2O/hexane with a 5% gradient) to give the title compound as a light yellow oil, 487mg (91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.08 (dd, *J* = 8.2, 1.1 Hz, 2H, 3C*H*), 7.66 – 7.56 (m, 1H, 1C*H*), 7.48 (dt, *J* = 13.9, 6.9 Hz, 2H, 2C*H*), 4.68 (s, 0.8H, 8CH_2), 4.52 (s, 1.2H, 8CH_2), 3.33 (s, 2H, 9CH_3), 3.10 (s, 1H, 9CH_3), 0.24 (d, *J* = 5.0 Hz, 9H, 3x13CH_3)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 177.30, 177.12, 153.71, 153.48, 136.31, 136.23, 134.48, 134.33, 129.58, 129.52, 128.72, 128.64, 99.03, 98.97, 95.15, 95.02, 87.80, 87.37, 82.38, 81.79, 41.01, 35.90, 35.63, 32.09, -0.76

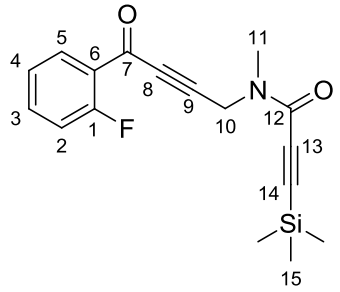
m/z (ESI+): 320, 298, 205

HRMS (ESI+): Calcd. for $C_{17}H_{20}NO_2Si$ $[M]^+$: 298.1263; found: 298.1265

υ_{max} (neat/ cm^{-1}): 2962 w, 2917 w, 2232 w, 1711 w, 1639 s, 1396 m, 1259 s

R_f: 0.26 in 1:1 Et_2O/hexane ($KMnO_4$)

***N*-[4-(2-Fluorophenyl)-4-oxobut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.63)**



To a cooled (ice/water bath) solution of *N*-[4-(2-fluorophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **(2.53)** (954mg, 3.01mmol) in acetone (20ml) was added Jones' reagent (3M, 3.1ml, 9.33mmol). The reaction mixture was then allowed to stir at rt for 30min, after which enough ^{i}PrOH was added to cause the solution to acquire a persistent green colour. The mixture was then filtered through a pad of Celite and the resulting cake was washed with Et_2O (50ml). The resulting filtrate phases were separated and the combine organic layers were washed with water (2x20ml) and sat. aq. NaCl solution (50ml). Drying on $MgSO_4$, filtering and evaporation of volatiles *in vacuo* afforded a brown oil which was purified by flash column chromatography (3:7 Et_2O/hexane) to give the title compound as a light yellow oil, 703mg (74%).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 8.10 (dt, *J* = 4.7, 2.1 Hz, 2H, 3C*H*, 5C*H*), 7.67 – 7.56 (m, 1H, 1C*H*), 7.49 (ddd, *J* = 15.2, 10.5, 6.8 Hz, 1H, 2C*H*), 4.70 (s, 0.8H, 10C*H*$_2$), 4.54 (s, 1.2H, 10C*H*$_2$), 3.35 (s, 1.8H, 11C*H*$_3$), 3.12 (s, 1.2H, 11C*H*$_3$), 0.26 (d, *J* = 4.9 Hz, 9H, 3x15C*H*$_3$).

^{13}C NMR (126 MHz, *CDCl*$_3$) δ 177.33, 153.74, 136.32, 134.49, 134.33, 130.08, 129.60, 129.54, 128.72, 128.64, 128.39, 99.03, 95.13, 95.00, 87.76, 81.82, 77.24, 76.99, 76.74, 76.64, 65.80, 54.25, 41.02, 35.90, 35.64, 32.10, 15.21, -0.76.

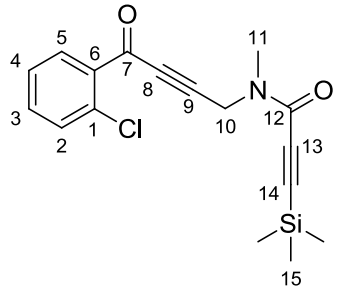
m/z (ESI+): 315, 243, 191

HRMS (ESI+): Calcd. for C17H18FNO2Si $[M]^+$: 315.1090; found: 315.1082

υ_{max} (neat/ cm^{-1}): 2958 w, 2219 w, 1621 s, 1567 w, 1232 m

R_f: 0.21 in EtOAc/hexane ($KMnO_4$)

***N*-[4-(2-Chlorophenyl)-4-oxobut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.64)**



To a cooled (ice/water bath) solution of *N*-[4-(2-chlorophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **(2.54)** (600mg, 1.80mmol) in acetone (20ml) was added Jones' reagent (3M, 1.9ml, 5.76mmol). The reaction mixture was then allowed to stir at rt for 30min, after which enough ^{i}PrOH was added to cause the solution to acquire a persistent green colour. The mixture was then filtered through a pad of Celite and the resulting cake was washed with Et_2O (50ml). The resulting filtrate phases were separated and the combine organic layers were washed with water (2x20ml) and sat. aq. NaCl solution (50ml). Drying on $MgSO_4$, filtering and evaporation of volatiles *in vacuo* afforded a brown oil which was purified by flash column chromatography (3:7 Et_2O/hexane) to give the title compound as a light yellow oil, 526mg (88%).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 8.02 – 7.92 (m, 1H, 5C*H*), 7.51 – 7.43 (m, 2H, 3C*H*, 2C*H*), 7.39 (ddd, *J* = 8.5, 5.2, 2.5 Hz, 1H, 4C*H*), 4.67 (s, 0.7H, 10C*H*$_2$), 4.51 (s, 1.3H, 10C*H*$_2$), 3.33 (s, 1.8H, 11C*H*$_3$), 3.08 (s, 1.2H, 11C*H*$_3$), 0.25 (d, *J* = 4.6 Hz, 9H, 3x15C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 175.95, 175.85, 153.70, 153.45, 135.07, 135.04, 133.76, 133.67, 133.60, 133.55, 132.80, 132.55, 131.64, 131.55, 126.86, 126.82, 99.03, 98.99, 95.10, 94.98, 88.71, 88.34, 83.58, 82.97, 41.07, 35.90, 35.67, 32.09, -0.76

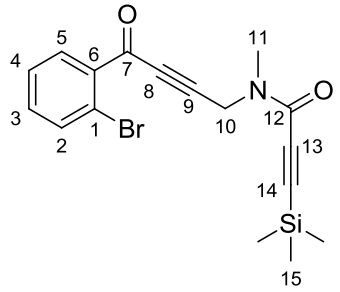
m/z (ESI+): 372, 371, 370, 355, 254, 179

HRMS (ESI+): Calcd. for $C_{17}H_{18}ClNO_2NaSi$ $[M+Na]^+$: 354.0691; found: 354.0688

υ_{max} (neat/ cm^{-1}): 2963 w, 2206 w, 1632 s, 1587 w, 1395 w, 1238 m

R_f: 0.26 in 1:1 Et_2O/hexane ($KMnO_4$)

***N*-[4-(2-Bromophenyl)-4-oxobut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (2.60)**



To a cooled (ice/water bath) solution of *N*-[4-(2-chlorophenyl)-4-hydroxybut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **(2.55)** (823mg, 2.18mmol) in acetone (20ml) was added Jones' reagent (3M, 2.3ml, 6.76mmol). The reaction mixture was then allowed to stir at rt for 30min, after which enough ^{i}PrOH was added to cause the solution to acquire a persistent green colour. The mixture was then filtered through a pad of Celite and the resulting cake was washed with Et_2O (50ml). The resulting filtrate phases were separated and the combine organic layers were washed with water (2x20ml) and sat. aq. NaCl solution (50ml). Drying on $MgSO_4$, filtering and evaporation of volatiles *in vacuo* afforded a brown oil which was purified by flash column chromatography (3:7 Et_2O/hexane) to give the title compound as a light yellow oil, 788mg (96%).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.95 (ddd, *J* = 11.1, 7.7, 1.7 Hz, 1H, 5C*H*), 7.67 (td, *J* = 8.3, 1.1 Hz, 1H, 3C*H*), 7.48 – 7.30 (m, 2H, 2C*H*, 4C*H*), 4.66 (s, 0.6H, 10C*H*$_2$), 4.49 (s, 1.4H, 10C*H*$_2$), 3.31 (s, 2.1H, 11C*H*$_3$), 3.06 (s, 0.9H, 11C*H*$_3$), 0.23 (d, *J* = 4.7 Hz, 9H, 3x15C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 176.58, 153.69, 153.44, 136.65, 135.06, 134.97, 133.71, 133.57, 133.05, 132.82, 127.42, 127.39, 121.29, 121.17, 99.03, 99.00, 95.10, 94.99, 88.95, 88.57, 83.18, 82.58, 41.06, 35.93, 35.68, 32.12, -0.75

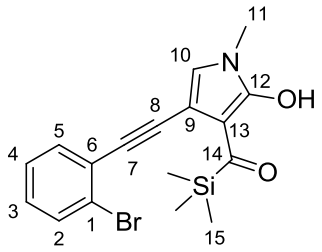
m/z (ESI+): 401, 400, 398

HRMS (ESI+): Calcd. for $C_{17}H_{18}BrNO_2NaSi$ $[M+Na]^+$: 398.0188; found: 398.0182

υ_{max} (neat/ cm^{-1}): 2961 w, 2245 w, 1634 s, 1395 m, 1240 s

R_f: 0.29 in 2:3 Et_2O/hexane ($KMnO_4$)

4-[(2-Bromophenyl)ethynyl]-1-methyl-3-[(trimethylsilyl)carbonyl]-1*H*-pyrrol-2-ol (2.61)



A de-gassed solution of *N*-[4-(2-bromophenyl)-4-oxobut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **(2.60)** (290mg, 0.77mmol) in toluene (77ml) was heated at reflux for 4h. After cooling the solvent was removed *in vacuo* and the residue purified by flash column chromatography (1:9 Et_2O/hexane) to yield the title compound as a brown oil, 154mg (53% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.60 (d, *J* = 8.1 Hz, 1H, 2C*H*), 7.43 (d, *J* = 7.7 Hz, 1H, 5C*H*), 7.27 (t, *J* = 7.5 Hz, 1H, 4C*H*), 7.16 (t, *J* = 7.7 Hz, 1H, 3C*H*), 6.68 (s, 1H, 10C*H*), 3.24 (s, 3H, 11C*H$_3$*), 0.45 (s, 9H, 3x15C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 189.52, 168.40, 132.54, 132.42, 132.05, 129.15, 127.04, 125.51, 125.45, 115.41, 96.96, 90.54, 89.05, 28.81, -1.42

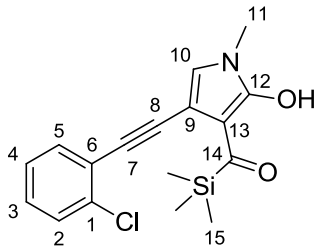
m/z (ESI+): 474, 418, 416, 414, 400, 398

HRMS (ESI+): Calcd. for $C_{17}H_{18}BrNO_2NaSi$ $[M+Na]^+$: 398.02011; found: 398.0182

υ_{max} (neat/ cm^{-1}): 2925 w, 2204 w, 1705 w, 1631 s, 1573 s, 1472 m, 1300 m, 1217 m, 1099 s

R_f: 0.29 in 1:4 Et_2O/hexane ($KMnO_4$)

4-[(2-Chlorophenyl)ethynyl]-1-methyl-3-[(trimethylsilyl)carbonyl]-1*H*-pyrrol-2-ol (2.65)



A de-gassed solution of *N*-[4-(2-chlorophenyl)-4-oxobut-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **(2.64)** (230mg, 0.69mmol) in toluene (70ml) was heated at reflux for 4h. After cooling the solvent was removed *in vacuo* and the residue purified by flash column chromatography (1:4 Et_2O/hexane) to yield the title compound as a brown oil, 105mg (46% yield).

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm 7.47 – 7.34 (m, 2H, 2C*H*, 5C*H*), 7.29 – 7.16 (m, 2H, 3C*H*, 4C*H*), 6.66 (s, 1H, 10C*H*), 3.23 (s, 3H, 11C*H_3*), 0.45 (s, 9H, 3x15C*H_3*)

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm 189.58, 168.40, 135.68, 132.49, 132.09, 129.39, 129.02, 126.47, 123.32, 115.43, 96.97, 89.57, 88.73, 28.79, -1.43

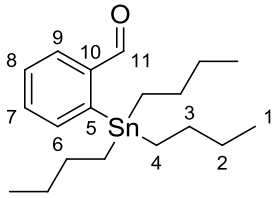
m/z (ESI+): 370, 366, 354, 348

HRMS (ESI+): Calcd. for $C_{17}H_{19}ClNO_2Si$ $[M]^+$: 332.0873; found: 332.0868

υ_{max} (neat/ cm^{-1}): 2944 w, 2208 w, 1704 w, 1629 s, 1574 s, 1475 m, 1296 m, 1214 s, 1029 m

R_f: 0.51 in 2:3 Et_2O/hexane ($KMnO_4$)

2-(Tri-*n*-butylstannyl)benzaldehyde (2.91)



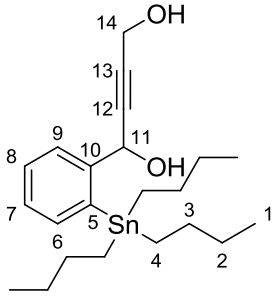
2-(2-Bromophenyl)-1,3-dimethylimidazolidine **(1.9)** (5.00g, 19.60mmol) was dissolved in Et_2O (50ml) and the resulting solution cooled to -25°C (water/acetone 40:60 v/v/liq. N_2). ^{n}BuLi (1.6M, 12.3ml, 19.60mmol) was added dropwise after which the solution left to slowly warm to 0°C and stirred for a total of 2h. It was subsequently cooled to -70°C (acetone/liq. N_2) and tri-*n*-butyltin chloride (7.02g, 5.8ml, 21.56mmol) was introduced dropwise *via* syringe. Cooling was then removed and the solution allowed to warm to rt. Stirring was continued for 18h and the reaction was quenched by addition of aq. HCl solution (1M, 100ml). The resulting phases were separated and the aqueous layer washed wit Et_2O (50ml). The combined organic phases were washed with sat. aq. NaCl solution (100ml) and then dried on $MgSO_4$. After filtration and evaporation of volatiles *in vacuo*, the residue was purified by flash column chromatography (1:9 to 1:4 Et_2O/hexane with a 10% gradient) to give the product as a colourless oil, 6.82g (94% yield).

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm 9.96 (s, 1H, 11C*H*), 7.79 (d, *J* = 7.2 Hz, 1H, 9C*H*), 7.69 (d, *J* = 7.6 Hz, 1H, 7C*H*), 7.54-7.49 (m, 2H, 8C*H*, 6C*H*), 1.58-0.86 (m, 27H, 3x(1C*H_3*, 2C*H_2*, 3C*H_2*, 4C*H_2*)

R_f: 0.58 in 1:4 Et_2O/hexane ($KMnO_4$)

Data consistent with those previously reported. [180]

1-[2-(Tri-*n*-butylstannyl)phenyl]but-2-yne-1,4-diol (2.92)



A 1l 3-neck flask was charged with THF (300ml) and freshly distilled propargyl alcohol (2.89g, 3.00ml, 51.6mmol). The solution was cooled to -70°C (EtOAc/liq. N_2) and ^{n}BuLi (2.5M, 4.13ml, 103.2mmol) was added dropwise *via* syringe. After stirring at -70°C for 2h 2-(tri-*n*-butylstannyl)benzaldehyde **(2.91)** was introduced dropwise and the reaction was then allowed to warm to rt and was stirred at this temperature for 18h. Quenching with sat. aq. NH_4Cl solution (20ml) was followed by removal of volatiles under low vacuum. Et_2O (50ml) was added to the residue and the phases separated. The organic layer was then washed with water (50ml), dried on $MgSO_4$, filtered and the solvent removed *in vacuo* to give an oil, which was purified by flash column chromatography (1:1 Et_2O/hexane) to give the title compound as a colourless oil, 5.50g (63% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.72 (app. d, *J* = 6.9 Hz, 1H, 8C*H*), 7.49 (app. dd, *J* = 7.2, 1.3 Hz, 1H, 9C*H*), 7.36 (app. td, *J* = 7.5, 1.4 Hz, 1H, 7C*H*), 7.29 (app. td, *J* = 7.3, 1.3 Hz, 1H, 6C*H*), 5.41 (dt, *J* = 5.7, 1.6 Hz, 1H, 11C*H*), 4.37 (dd, *J* = 6.2, 1.7 Hz, 2H, 14C*H*$_2$), 2.09 (d, *J* = 5.8 Hz, 1H, 1xO*H*), 1.59 – 1.49 (m, 6H, 3x4C*H*$_2$), 1.35 (app. dq, *J* = 14.6, 7.3 Hz, 6H, 3x3C*H*$_2$), 1.14 – 1.08 (m, 6H, 3x2C*H*$_3$), 0.90 (app. t, *J* = 7.3 Hz, 9H, 3x1C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm δ 146.76, 141.48, 137.05, 128.57, 127.81, 126.36, 85.92, 85.35, 66.75, 51.25, 29.13, 27.38, 13.63, 10.84

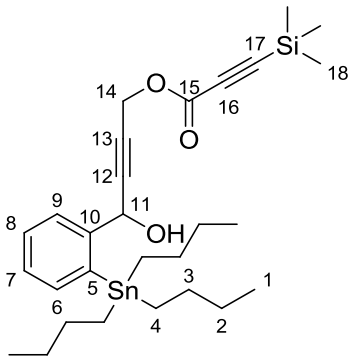
m/z (ESI+): 452, 450, 422, 132

HRMS (ESI+): Calcd. for $C_{22}H_{36}O_2SnNa$ $[M+Na]^+$: 471.1630 ; found: 471.1674

υ_{max} (neat/ cm^{-1}): 3258 br, 2907 s, 1592 w, 1574 w, 1484m, 1334 m, 1295 m, 1119 m, 1025 m

R_f: 0.18 in 1:1 Et_2O/hexane ($KMnO_4$)

4-Hydroxy-4-[2-(tri-*n*-butylstannyl)phenyl]but-2-yn-1-yl 3-(trimethylsilyl)prop-2-ynoate (2.93)



To a cooled (ice/water bath) solution of 3-(trimethylsilyl)prop-2-ynoic acid **(2.13)** (1.04g, 7.32mmol) and 4 drops of DMF in CH_2Cl_2 (20ml) was added oxalyl chloride (0.81ml, 1.21g, 9.51mmol) dropwise *via* syringe. The solution was allowed to warm to rt and was stirred for 2h. It was then cooled again (ice/water bath) and 2,6-lutidine (1.55ml, 1.43g, 13.3mmol) was added dropwise followed by 1-[2-(tri-*n*-butylstannyl)phenyl]but-2-yne-1,4-diol **(2.92)** (3g, 6.65mmol) previously dissolved in CH_2Cl_2 (20ml). The resulting cloudy solution was then allowed to stir at rt for 18h. The reaction was then quenched with water (20ml), and the organic layer washed with 10% aq. citric acid solution (20ml) and 10% aqueous K_2CO_3 solution (20ml). Drying on Na_2SO_4, filtering and evaporation of volatiles *in vacuo* gave a deep yellow oil which was purified by flash column chromatography (1:19 to 1:9 Et_2O/hexane, 5% gradient) to give the title compound as a colourless, viscous oil, 1.24g (71% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.70 (d, *J* = 7.0 Hz, 1H, 8C*H*), 7.46 (dd, *J* = 7.2, 1.1 Hz, 1H, 9C*H*), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H, 7C*H*), 7.32 (td, *J* = 7.3, 1.2 Hz, 1H, 6C*H*), 6.27 (t, *J* = 1.6 Hz, 1H, 11C*H*), 4.81 (d, *J* = 1.6 Hz, 2H, 14C*H$_2$*), 1.67 – 1.44 (m, 6H, 3x4C*H$_2$*), 1.42 – 1.26 (m, 6H, 3x3C*H$_2$*), 1.21 – 1.05 (m, 6H, 3x2C*H$_2$*), 0.90 (t, *J* = 7.3 Hz, 9H, 3x1C*H$_3$*), 0.35 – 0.16 (s, 9H, 3x18CH_3)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 151.96, 151.55, 142.41, 137.02, 128.77, 128.50, 128.32, 95.62, 95.53, 94.00, 93.64, 81.18, 69.55, 53.27, 29.02, 13.63, 10.68, -0.96

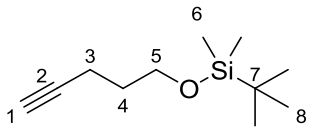
m/z (ESI+): 576, 572, 453, 163

HRMS (ESI+): Calcd. for $C_{28}H_{44}SnO_3SiNa$ $[M+Na]^+$: 595.1975; found: 595.1938

υ_{max} (neat/ cm^{-1}): 3011 br, 2108 w, 1758 w, 1635 s, 1544 s, 1467 m, 1236 m, 1211 s, 1022 m

R_f: 0.23 in 1:9 Et_2O/hexane ($KMnO_4$)

tert-Butyl(dimethyl)(pent-4-yn-1-yloxy)silane (2.109)



A 500ml 3-neck flask was charged with imidazole (19.36g, 284.05mmol), CH_2Cl_2 (500ml) and 4-pentyne-1-ol (20g, 237.36mmol). The solution was cooled in an ice/water bath and *tert*-butyldimethylsilyl chloride (37.5g, 248.84mmol) dissolved in CH_2Cl_2 (100ml) was added dropwise *via* addition funnel. The temperature was allowed to rise to rt and the reaction was stirred for 18h. Quenching was achieved with 10% aq. K_2CO_3 solution (200ml). Isolation of the organic layer, drying on $MgSO_4$, filtering and removal of solvent *in vacuo* gave the crude product which was purified by short-path distillation to give the title compound (bp 72-74ºC at 12Torr) as a colourless oil, 44.71g (95% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 3.86 (2H, dd, J = 12.2, 0.6, 5C*H*$_2$), 2.46–2.40 (2H, m, 3C*H*$_2$), 2.08 (1H, td, J = 2.6, 1.0, 1C*H*), 1.92–1.85 (2H, m, 4C*H*$_2$), 1.16–0.97 (9H, m, 3x8C*H*$_3$), 0.30–0.15 (6H, m, 2x6C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 84.31, 68.45, 61.59, 31.75, 26.11, 18.48, 15.02, -5.18

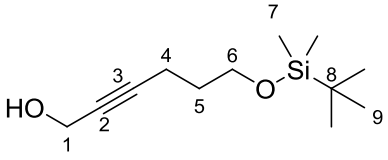
m/z (ESI+): Ion not found

υ_{max} (neat/ cm^{-1}): 2929.81 w, 2858.07 w, 1736 w, 1254 m, 1102.93 m

R_f: 0.31 in 1:4 EtOAc/hexane ($KMnO_4$)

Data consistent with those previously reported. [181]

6-{[*tert*-Butyl(dimethyl)silyl]oxy}hex-2-yn-1-ol (2.110)



To *tert*-butyl(dimethyl)(pent-4-yn-1-yloxy)silane **(2.109)** (20.0g, 101.34mmol) in THF (100ml) at -70°C (EtOAc/liq. N_2) was added ^{n}BuLi (2.5M, 40.04ml, 101mmol) dropwise *via* addition funnel. The reaction mixture was stirred for 10min and then allowed to warm to -20 ºC and stirred at this temperature for 10min. Paraformaldehyde (7.63g, 253.98mmol) was then added in one portion and the reaction was allowed to warm to rt and stirred for 1h. Quenching was achieved with sat. aq. NH_4Cl solution (100ml) and the resulting biphasic mixture diluted with EtOAc (100ml). The organic phase was separated, dried on $MgSO_4$, filtered and solvents were removed *in vacuo*. The crude was purified by flash column chromatography (1:4 EtOAc/hexane) to give the title compound as a colourless oil, 17.60g (77% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 4.24–4.16 (2H, m, 1C*H*$_2$), 3.65 (2H, t, J = 6.1, 6C*H*$_2$), 2.27 (2H, tt, J = 7.1, 2.0, 4C*H*$_2$), 1.76–1.63 (2H, m, 5C*H*$_2$), 0.91–0.80 (9H, m, 9C*H*$_3$), 0.05–-0.01 (6H, m, 7C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 86.27, 78.68, 61.80, 51.54, 31.84, 26.13, 18.52, 15.39, -5.14

m/z (ESI+): 228, 212, 178

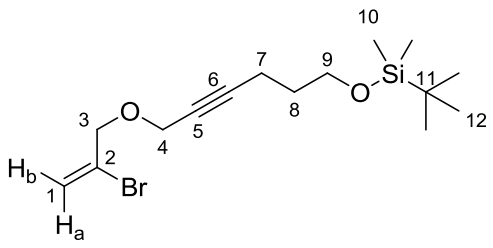
HRMS (ESI+): Calcd. for $C_{12}H_{24}O_2Si$ $[M]^+$: 228.4033; found: 228.1540

υ_{max} (neat/ cm^{-1}): 3673 br, 3339 m, 2929 w, 2858 w, 1253 m, 1102 m

R_f: 0.24 in 1:4 EtOAc/hexane ($KMnO_4$)

Data consistent with those previously reported. [182]

({6-[(2-Bromoprop-2-en-1-yl)oxy]hex-4-yn-1-yl}oxy)(*tert*-butyl)dimethylsilane (2.111)



To a solution of hexadecyltrimethylammonium bromide (1.20 g, 3.29 mmol) in CH_2Cl_2 (20ml) was added 50% aq. NaOH solution (20ml). The resulting biphasic mixture was stirred vigorously at rt for 10min. 6-{[*tert*-Butyl(dimethyl)silyl]oxy}hex-2-yn-1-ol **(2.110)** (5 g, 21.87 mmol) was then added followed by 2,3-dibromopropene (5.25 g, 26.26 mmol). The reaction was left to stir for 16h at rt. Water (50ml) and CH_2Cl_2 (50ml) were added and the organic phase separated, dried over $MgSO_4$ and filtered. Removal of solvent *in vacuo* gave an orange oil which was purified by flash column chromatography (1:19 EtOAc/hexane) to give the title compound as a colourless, viscous oil, 5.52g (72% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 5.94–5.85 (1H, m, 1C*H*$_a$), 5.61 – 5.55 (1H, m, 1C*H*$_b$), 4.21-4.03 (4H, m, 3C*H*$_2$, 4C*H*$_2$), 3.65 (2H, t, J = 6.0, 9C*H*$_2$), 2.34–2.20 (2H, m, 7C*H*$_2$), 1.75–1.60 (2H, m, 8C*H*$_2$), 0.90–0.79 (9H, m, 3x12C*H*$_3$), 0.02 (6H, s, 2x10C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 128.98, 118.15, 87.51, 75.43, 73.20, 61.68, 57.94, 31.80, 26.10, 18.49, 15.29, -5.25

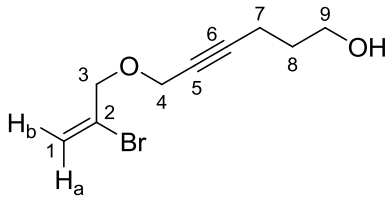
m/z (ESI+): 398, 370, 226

HRMS (ESI+): Calcd. for $C_{15}H_{27}BrO_2SiNa$ $[M+Na]^+$: 370.08563; found: 370.0853

υ_{max} (neat/ cm^{-1}): 2929 w, 2856 w, 1640 w, 1251 m, 1081 m

R_f: 0.21 in 1:19 EtOAc/hexane ($KMnO_4$)

6-[(2-Bromoprop-2-en-1-yl)oxy]hex-4-yn-1-ol (2.112)



To ({6-[(2-Bromoprop-2-en-1-yl)oxy]hex-4-yn-1-yl}oxy)(*tert*-butyl)dimethylsilane **(2.111)** (5.0g, 14.48mmol) in THF (100ml) at rt was added tetrabutylammonium fluoride solution (1M in THF, 30.4ml, 30.41mmol) dropwise. The reaction was stirred at rt for 3h and it was then diluted with

water (100ml) and EtOAc (100ml). The isolated organic layer was then washed with sat. aq. NaCl solution (50ml), dried on $MgSO_4$ and filtered. Evaporation of solvents *in vacuo* and purification of the crude material by flash column chromatography (2:3 EtOAc/hexane) gave the title compound as a colourless, viscous oil, 3.08g (92% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 5.92 (1H, dd, J = 2.9, 1.4, 1C*H*$_a$), 5.64 – 5.60 (1H, m, 1C*H*$_b$), 4.19–4.14 (4H, m, 3C*H*$_2$, 4C*H*$_2$), 3.74 (2H, m, 9C*H*$_2$), 2.35 (2H, tt, J = 7.0, 2.1, 7C*H*$_2$), 1.77 (2H, m, 8C*H*$_2$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 124.79, 118.46, 76.00, 73.49, 73.08, 61.94, 57.98, 31.45, 15.57

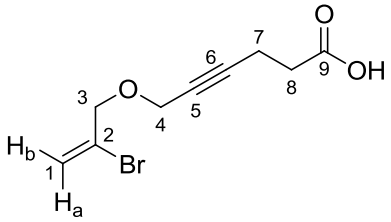
m/z (ESI+): 254, 176

HRMS (ESI+): Calcd. for $C_9H_{13}BrO_2Na$ $[M+Na]^+$: 254.9991; found: 254.9974

υ_{max} (neat/ cm^{-1}): 3380 br, 2945 w, 2851 w, 2223 w, 1639 m, 1134 m, 1070 m

R_f: 0.25 in 2:3 EtOAc/hexane ($KMnO_4$)

6-[(2-Bromoprop-2-en-1-yl)oxy]hex-4-ynoic acid (2.101)



Preparation of Jones' reagent:

To a cooled (ice/water bath) solution of chromium(VI) trioxide (67g, 670mmol) in water (125ml) was carefully added fuming H_2SO_4 (58ml, 110.20g, 1.124mol). Residual salts at the bottom of the flask were then dissolved using the minimum quantity of water necessary. The approximate molarity of the resulting solution is 3M.

Oxidation procedure:

To a cooled (ice/water bath) solution of 6-[(2-bromoprop-2-en-1-yl)oxy]hex-4-yn-1-ol **(2.112)** (2.50g, 10.67mmol) in acetone (20ml) was added Jones' reagent (3M, 17.8ml, 53.35mmol). The reaction mixture was then allowed to stir at rt for 30min, after which enough ^{i}PrOH was added to cause the solution to acquire a persistent green colour. The mixture was then filtered through a pad of Celite and the resulting cake was washed with Et_2O (50ml). The organic phase was separated, dried on $MgSO_4$ and filtered. Evaporation of volatiles *in vacuo* afforded the title compound as a light yellow oil, 2.10g (79%). This compound was used in the next step without further purification.

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 5.91 (1H, d, J = 1.5, 1C*H*$_a$), 5.62 (1H, d, J = 0.7, 1C*H*$_b$), 4.16 (4H, m, 3CH_2, 4C*H*$_2$), 2.62–2.57 (2H, m, 8C*H*$_2$), 2.57–2.52 (2H, m, 7C*H*$_2$)

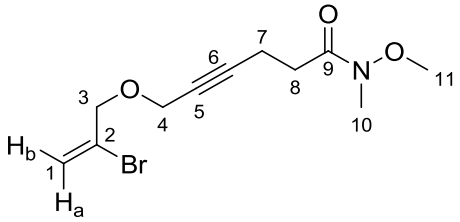
^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 176.95, 128.93, 118.61, 85.45, 76.44, 73.41, 57.72, 33.15, 14.71

m/z (ESI+): 268, 252, 175

HRMS (ESI+): Calcd. for $C_9H_{11}BrO_3Na$ $[M+Na]^+$: 268.9784; found: 268.9765

υ_{max} (neat/ cm^{-1}): 2922 br, 1708 s, 1640 w, 1248 w, 1136 m, 1075 m

6-[(2-Bromoprop-2-en-1-yl)oxy]-*N*-methoxy-*N*-methylhex-4-ynamide (2.100)



To a cooled (ice/water bath) solution of 6-[(2-Bromoprop-2-en-1-yl)oxy]hex-4-ynoic acid **(2.101)** (1.78g, 7.19mmol) and 4 drops of DMF in CH_2Cl_2 (20ml) was added oxalyl chloride (0.61ml, 910mg, 7.19mmol) dropwise *via* syringe. The solution was allowed to warm to rt and was stirred for 2h. It was then cooled again (ice/water bath) and triethylamine (1.7ml, 1.21g, 11.95mmol) was added dropwise followed by N,O-dimethylhydroxylamine hydrochloride (880mg, 8.98mmol) previously dissolved in CH_2Cl_2 (10ml). The resulting cloudy solution was then allowed to stir at rt for 18h. The reaction was then quenched with water (20ml), and the organic layer washed with 10% aq. citric acid solution (20ml) and 10% aqueous K_2CO_3 solution (20ml). Drying on Na_2SO_4, filtering and evaporation of volatiles *in vacuo* gave a deep yellow oil which was purified by flash column chromatography (2:3 EtOAc/hexane) to give the title compound as a yellow, viscous oil, 1.80g (87%).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 5.92 (1H, dd, J = 2.9, 1.4, 1C*H*$_a$), 5.63 – 5.60 (1H, m, 1C*H*$_b$), 4.16 (4H, m, 3C*H*$_2$, 4C*H*$_2$), 3.68 (3H, s, 11C*H*$_3$), 3.17 (3H, s, 10C*H*$_3$), 2.66 (2H, t, J = 7.4, 8C*H*$_2$), 2.59 – 2.51 (2H, m, 7C*H*$_2$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 128.91, 118.50, 88.53, 86.70, 71.42, 61.53, 57.95, 31.42, 28.60, 14.44

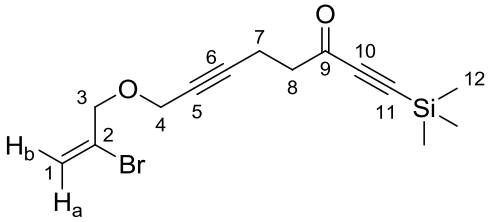
m/z (ESI+): 292, 172, 86

HRMS (ESI+): Calcd. for $C_{11}H_{16}BrNO_3Na$ $[M+Na]^+$: 314.0206; found: 314.0162

υ_{max} (neat/ cm^{-1}): 2938 w, 2857 w, 1659 s, 1385 w, 1135 m, 1075 m

R_f: 0.28 in 2:3 EtOAc/hexane ($KMnO_4$)

8-[(2-Bromoprop-2-en-1-yl)oxy]-1-(trimethylsilyl)octa-1,6-diyn-3-one (2.94)



(Trimethylsilyl)acetylene (0.51 g, 5.17 mmol) was dissolved in THF (50ml). The solution was cooled to -70 ºC (EtOAc/liq. N_2) and then ^{n}BuLi (2.5M, 2.1ml, 5.18mmol) was added dropwise. The reaction mixture was allowed to warm to -30 ºC and was then cooled back down to -70 ºC. 6-[(2-bromoprop-2-en-1-yl)oxy]-*N*-methoxy-*N*-methylhex-4-ynamide **(2.100)** (1.5 g, 5.17 mmol) was added and the resulting solution allowed to stir for 15 minutes after which it was warmed to rt and stirred for a further 3h. Quenching was achieved with sat. aq. NH_4Cl solution (50ml), EtOAc (100ml) was added and the layers separated. The organic phase was washed with water (50ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* giving a yellow/brown oil which was purified by flash column chromatography (2:23 EtOAc/hexane) to give the title compound as a colourless oil 1.13g (67% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 5.92 (1H, dd, J = 2.9, 1.3, 1CH_a), 5.63 – 5.60 (1H, m, 1CH_b), 4.17 – 4.12 (4H, m, 3CH_2, 4CH_2), 2.81 – 2.75 (2H, m, 8CH_2), 2.58 – 2.51 (2H, m, 7CH_2), 0.29 – 0.15 (9H, m, 12CH_3)

^{13}C NMR (500 MHz, *CDCl*$_3$) δ ppm 185.21, 128.92, 118.73, 110.35, 101.59, 85.66, 76.35, 73.56, 57.80, 27.76, 13.59, -0.58

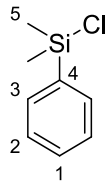
m/z (ESI+): 328, 209, 175.

HRMS (ESI+): Calcd. for $C_{14}H_{19}BrO_2Na$ $[M+Na]^+$: 351.0230; found: 351.0187

υ_{max} (neat/ cm^{-1}): 2959 w, 2857 w, 2150 w, 1640 s, 1108 w, 1078 m

R_f: 0.24 in 1:9 EtOAc/hexane ($KMnO_4$)

Chloro(dimethyl)phenylsilane (2.132)



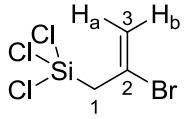
To neat dimethyl(phenyl)silane (85.5g, 627.43mmol) was added thionyl chloride (78.38g, 48.1ml, 658.80mmol) and the resulting solution was heated at reflux for 4h. After cooling, fractional distillation of the crude mixture yielded the title compound (bp 76-81°C at 15Torr) as a clear, colourless liquid, 86.2g (84% yield).

^{1}H NMR (500MHz, *CDCl$_3$*) δ ppm: 7.65-7.61 (m, 2H, 2C*H*), 7.46-7.37 (m, 3H, 5-CH, 3C*H*, 1C*H*), 0.70 (s, 6H, 2x5C*H$_3$*)

^{13}C NMR (126MHz, *CDCl$_3$*) δ ppm: 133.64, 130 95, 129.03, 128.47, 2.01

Physical properties and spectra comparable to those reported in the literature[162]

(2-Bromoprop-2-en-1-yl)(trichloro)silane (2.135)



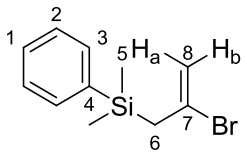
A solution of 2,3-dibromopropene (53.14g, 265.87mmol), copper(I) chloride (1.32g, 13.29mmol) and triethylamine (37.0ml, 26.9g, 265.87mmol) in Et_2O (130ml) was cooled by means of an ice/water bath. Trichlorosilane (29.5ml, 39.61g, 292.46mmol) was then added dropwise *via* dropping funnel and the reaction was allowed to warm to rt and was stirred for a total of 18h. The resulting suspension was filtered through a pad of Celite and the cake washed with Et_2O (3x100ml). Volatiles in the filtrate solution were removed *in vacuo* and the residue purified by fractional distillation to give the title compound (bp 35-37°C at 1Torr) as a colourless, clear oil, 59.52g (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.71 (dt, J = 2.0, 0.9 Hz, 1H, 3CH_a), 5.60 (d, J = 2.2 Hz, 1H, 3CH_b), 2.90 (d, J = 0.9 Hz, 2H, 1CH_2)

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 121.64, 120.56, 38.83

Physical properties and spectra comparable to those reported in the literature[162]

(2-Bromoprop-2-en-1-yl)(dimethyl)phenylsilane (2.129)



From chloro(dimethyl)phenylsilane **(2.132)**:

To lithium wire (1.78g, 256.58mmol) cut into 2-3mm segments in THF (100ml) under argon at rt was added chlorodimethyl(phenyl)silane **(2.132)** (21.9g, 128.29mmol) dropwise *via* syringe . The reaction flask was then sealed and placed in a -20°C freezer for 120h. The resulting thick, red solution was then added via cannula to a precooled (-70°C, EtOAc/liq. N_2) suspension of copper(I) cyanide (9.57g, 106.91mmol) in THF (50ml). The mixture was allowed to warm up to -50°C and stirred at this temperature for 30min. 2,3-Dibromopropene (85% purity, 25.14g, 12.3ml, 106.91mmol) was then added dropwise and the solution stirred at -70°C for 30min and at -20°C for a further 20min. After slowly warming up to 0°C the reaction was quenched by addition of water (100ml) and the biphasic mixture filtered through a pad of celite washing with copious amounts of Et_2O (3x100ml). The phases were separated and the aqueous layer was washed with a further portion of Et_2O (100ml) and the combined organic phases washed with sat. aq. NH_4Cl solution (200ml) and sat. aq. NaCl solution (200ml). Drying on $MgSO_4$, filtration and removal of volatiles *in vacuo* gave a yellow oil which was purified by flash column chromatography (100% hexane) to give the title compound a light yellow, clear oil, 1.65g (49% yield). Purity by ^1H NMR: 75%.

From (2-bromoprop-2-en-1-yl)(trichloro)silane **(2.135)**:

To a solution of (2-bromoprop-2-en-1-yl)(trichloro)silane **(2.135)** (46.45g, 182.58mmol) in Et_2O (100ml) was added phenylmagnesium bromide solution (3M in Et_2O, 60.3ml, 180.75mmol) dropwise and the resulting solution was heated at reflux (flask fitted with Et_2O condenser) for 20h. It was then cooled by means of an ice/water bath and methylmagnesium bromide (3M in Et_2O,

124.7ml, 374.29mmol) was introduced dropwise *via* dropping funnel. The reaction was stirred at rt for 4h and was then quenched by addition of sat. aq. NH_4Cl solution (200ml). The isolated organic layer was dried on $MgSO_4$, filtered and the volatiles removed *in vacuo*. The residue was purified by flash column chromatography (1:99 Et_2O/hexane) to give the title product as a colourless oil, 42.43g (91% yield). Purity by ^1H NMR: 95+%.

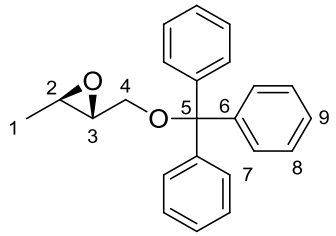
^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.68-7.59 (m, 5H, 1C*H*, 2C*H*, 3C*H*), 5.24 (m, 1H, 8CH_a), 5.17 (m, 1H, 8CH_b), 2.26 (d, J = 0.9 Hz, 2H, 6CH_2), 0.29 (s, 6H, 2x5CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 135.78, 128.49, 127.36, 126.98, 126.55, 114.65, 33.87, -1.04

m/z: 263, 261, 216, 214, 136,135, 105

Physical properties and spectra comparable to those reported in the literature[162]

(2*R*,3*R*)-2-Methyl-3-[(trityloxy)methyl]oxirane (2.137)



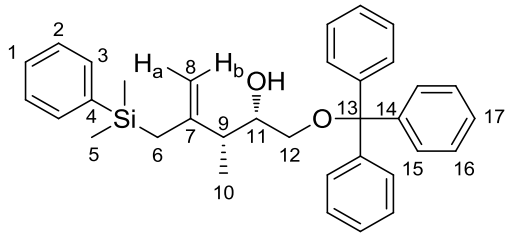
A 1l 3-neck flask was charged with CH_2Cl_2 (400ml), 3Å crushed molecular sieves (10g), freshly distilled (-) diisopropyl D-tartrate (7.0ml, 7.80g, 33.29mmol) and freshly distilled crotyl alcohol (24.0ml, 20.00g, 277.35mmol). The resulting solution was cooled to -20°C (water/acetone 40:60 v/v/liq. N_2) and stirred at this temperature for 30min. Freshly distilled titanium(IV) isopropoxide (8.2ml, 7.88g, 27.74mmol) was then added in one portion. After stirring for 20min *tert*-butylhydroperoxide solution (3.5M in toluene, 158.5ml, 554.70mmol) was introduced dropwise *via* dropping funnel making sure the reaction temperature did not rise above -20°C. After the addition the reaction flask was sealed and placed in a -25°C freezer for 7days. The reaction flask was placed under nitrogen gas flow and in a -20°C bath (water/acetone 40:60 v/v/liq. N_2) and trimethylphosphite (32.7ml, 34.4g, 277.35mmol) was added dropwise *via* syringe making sure the reaction temperature did not rise above -20°C. After stirring at -20°C for 30min, triethylamine (39.0ml, 28.06g, 277.35mmol) was added dropwise followed by a solution of trityl chloride (81.20g, 291.22mmol) and dimethylamino pyridine (1.70g, 13.87mmol) dissolved in CH_2Cl_2 (150ml). The reaction temperature was allowed to rise to rt and the resulting cloudy solution was stirred for 18h. It was then filtered through a pad of Celite and the cake washed with CH_2Cl_2 (3x100ml). The filtrate was washed with water (2x500ml), sat. aq. $CuSO_4$ solution (500ml). The isolated organic layer was dried on Na_2SO_4, filtered and volatiles were removed *in vacuo* to yield a brown oil which was purified by flash column chromatography (1:9 to 1:7 Et_2O/hexane with a 0.5% gradient) to yield a white, amorphous solid. This was then dissolved in a mixture of CH_2Cl_2/hexane (1:3, 600ml) and the solvents left to evaporate over 4 days giving the title compound as rhombohedral, white crystals, 56.77g (62% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 7.50 – 7.45 (m, 6H, 3x7C*H*), 7.31 (ddd, *J* = 6.4, 5.7, 2.2 Hz, 6H, 3x8C*H*), 7.27 – 7.22 (m, 3H, 3x9C*H*), 3.29 (dd, *J* = 10.7, 3.2 Hz, 1H, 4C*H$_a$*), 3.17 (dd, *J* = 10.8, 5.0 Hz, 1H, 4C*H$_b$*), 2.95 – 2.85 (m, 2H, 3C*H*, 2C*H*), 1.32 (d, *J* = 4.9 Hz, 3H, 1C*H$_3$*)

$[\alpha]_D^{25}$: -5.3 (c = 0.05, CH_2Cl_2)

Data consistent with those previously reported. [183]

(2*S*,3*R*)-4-{[Dimethyl(phenyl)silyl]methyl}-3-methyl-1-(trityloxy)pent-4-en-2-ol (2.140)



Homogeneous cyanocuprate method:

To a cooled (-70°C, EtOAc/liq. N_2 bath) solution of (2-bromoprop-2-en--yl)(dimethyl)phenylsilane **(2.129)** (845mg, 3.31mmol) in Et_2O (20ml) was added *tert*-butyllithium (1.7M in pentane, 4.0ml, 6.79mmol) dropwise *via* syringe. The cooling bath was removed and the reaction allowed to slowly warm to 0°C. The solution was then cooled once again to -70°C and was then transferred *via* cannula to a suspension of copper(I) cyanide (149mg, 1.66mmol) in Et_2O (30ml). The resulting mixture was allowed to slowly warm to 0°C to obtain a bright yellow, homogeneous solution. (2*R*,3*R*)-2-Methyl-3-[(trityloxy)methyl]oxirane **(2.137)** (456mg, 1.38mmol) was then introduced neat *via* syringe and the reaction allowed to stir at rt overnight. Quenching was achieved by addition of sat. aq. NH_4Cl solution (50 ml) and stirring until neat separation of phases was observed. The organic layer was separated and the aqueous washed with Et_2O (20 ml). The combined organic layers were dried over Na_2SO_4, filtered and volatiles removed *in vacuo* to give a yellow oil. Column chromatography (10% Et_2O/hexane) gave the title compound as a light yellow oil, 432mg (62% yield).

Mixed cyanocuprate method:

To a cooled (-70°C, EtOAc/liq. N_2 bath) solution of thiophene (5.7ml, 6.01g, 71.50mmol) in Et_2O (100 ml) was added *n*-butyllithium (2.5M in hexanes, 28.6ml, 71.50mmol) dropwise *via* syringe. The resulting solution was allowed to warm to -20°C and stirred at this temperature for 20 min.

In a separate flask, (2-bromoprop-2-en--yl)(dimethyl)phenylsilane **(2.129)** (16.59g, 65.00mmol) was dissolved in Et_2O (100ml) and the resulting solution cooled to -70°C (EtOAc/liq. N_2 bath).

Tert-Butyllithium (1.7M in pentane, 76.5ml,130.00 mmol) was then introduced dropwise *via* dropping funnel and the reaction allowed to slowly warm to 0°C.

The above solutions were sequentially transferred *via* cannula to a suspension of copper(I) cyanide (5.82g, 65.00mmol) in Et_2O (150ml) at -70°C (EtOAc/liq. N_2 bath). The obtained suspension was allowed to slowly warm to 0°C and stirred at this temperature for 30min, giving a homogeneous, bright yellow solution. A solution of (2*R*,3*R*)-2-Methyl-3-[(trityloxy)methyl]oxirane **(2.137)** (21.48g, 65.00mmol) in Et_2O (100ml) was the introduced dropwise *via* dropping funnel and the resulting solution was allowed to stir at rt overnight. Quenching was achieved by addition of sat. aq. NH_4Cl solution (200ml) and stirring until neat separation of phases was observed. The organic layer was separated and the aqueous washed with Et_2O (200ml). The combined organic layers were dried over Na_2SO_4, filtered and volatiles removed *in vacuo* to give a yellow oil. Column chromatography (10% Et_2O/hexane) gave the title compound as a light yellow oil, 19.36g (59% yield)**.**

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm 7.52-7.41 (m, 8H, 1C*H*, 3x15C*H*), 7.33-7.29 (m, 8H, 2C*H*, 3x16C*H*), 7.26-7.19 (m, 4H, 1C*H*, 3x17C*H*), 4.65 (s, 1H, 8CH_b), 4.63 (s, 1H, 8CH_a), 3.71 (d, *J* = 5.0 Hz, 1H, 11C*H*), 3.20 (dd, *J* = 9.3, 6.7 Hz, 1H, 12CH_b), 3.12 (dd, *J* = 9.3, 5.1 Hz, 1H, 12CH_b), 2.16 – 2.06 (m, 1H, 9C*H*), 2.04 (d, *J* = 1.8 Hz, 1H, O*H*), 1.75 (d, *J* = 13.8 Hz, 1H, 6CH_b), 1.64 (d, *J* = 13.7 Hz, 1H, 6CH_b), 0.87 (d, *J* = 6.9 Hz, 3H, 10CH_3), 0.31 (app. d, *J* = 4.0 Hz, 6H, 5CH_3)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 149.14, 143.99, 133.56, 129.01, 128.76, 128.71, 127.86, 127.80, 127.72, 127.04, 108.64, 77.28, 77.02, 76.77, 71.84, 65.64, 43.15, 25.90, 13.25, -2.86.

m/z (ESI+): 529, 443, 403, 345, 324, 243

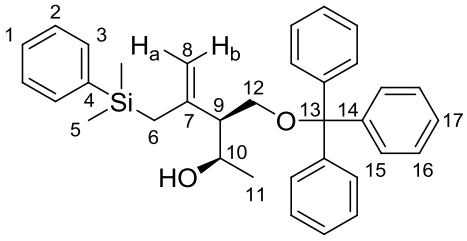
HRMS (ESI+): Calcd. for $C_{34}H_{38}O_2SiNa$ $[M+Na]^+$: 529.2538; found: 529.2533

υ_{max} (neat/ cm^{-1}): 3449 br, 3065 w, 2960 w, 2926 w, 2878 w, 1629 w, 1448 s, 1248 w, 1115 w, 836 w

R_f: 0.31 in 10% Et_2O/hexane

$[\alpha]_D^{26}$: +34.5 (c = 0.05, CH_2Cl_2)

(2*R*,3*S*)-4-{[Dimethyl(phenyl)silyl]methyl}-3-[(trityloxy)methyl]pent-4-en-2-ol (2.141)



Homogeneous cyanocuprate method:

To a cooled (-70°C, EtOAc/liq. N_2 bath) solution of (2-bromoprop-2-en--yl)(dimethyl)phenylsilane **(2.129)** (845mg, 3.31mmol) in Et_2O (20ml) was added *tert*-butyllithium (1.7M in pentane, 4.0ml, 6.79mmol) dropwise *via* syringe. The cooling bath was removed and the reaction allowed to slowly warm to 0°C. The solution was then cooled once again to -70°C and was then transferred *via* cannula to a suspension of copper(I) cyanide (149mg, 1.66mmol) in Et_2O (30ml). The resulting mixture was allowed to slowly warm to 0°C to obtain a bright yellow, homogeneous solution. (2*R*,3*R*)-2-Methyl-3-[(trityloxy)methyl]oxirane **(2.137)** (456mg, 1.38mmol) was then introduced neat *via* syringe and the reaction allowed to stir at rt overnight. Quenching was achieved by addition of sat. aq. NH_4Cl solution (50 ml) and stirring until neat separation of phases was observed. The organic layer was separated and the aqueous washed with Et_2O (20 ml). The combined organic layers were dried over Na_2SO_4, filtered and volatiles removed *in vacuo* to give a yellow oil. Column chromatography (10% Et_2O/hexane) gave the title compound as a light yellow oil, 451mg (27% yield).

Mixed cyanocuprate method:

To a cooled (-70°C, EtOAc/liq. N_2 bath) solution of thiophene (5.7ml, 6.01g, 71.50mmol) in Et_2O (100 ml) was added *n*-butyllithium (2.5M in hexanes, 28.6ml, 71.50mmol) dropwise *via* syringe. The resulting solution was allowed to warm to -20°C and stirred at this temperature for 20 min.

In a separate flask, (2-bromoprop-2-en--yl)(dimethyl)phenylsilane **(2.129)** (16.59g, 65.00mmol) was dissolved in Et_2O (100ml) and the resulting solution cooled to -70°C (EtOAc/liq. N_2 bath).

Tert-Butyllithium (1.7M in pentane, 76.5ml,130.00 mmol) was then introduced dropwise *via* dropping funnel and the reaction allowed to slowly warm to 0°C.

The above solutions were sequentially transferred *via* cannula to a suspension of copper(I) cyanide (5.82g, 65.00mmol) in Et_2O (150ml) at -70°C (EtOAc/liq. N_2 bath). The obtained suspension was allowed to slowly warm to 0°C and stirred at this temperature for 30min, giving a homogeneous, bright yellow solution. A solution of (2*R*,3*R*)-2-Methyl-3-[(trityloxy)methyl]oxirane **(2.137)** (21.48g, 65.00mmol) in Et_2O (100ml) was the introduced dropwise *via* dropping funnel and the resulting solution was allowed to stir at rt overnight. Quenching was achieved by addition of sat. aq. NH_4Cl solution (200ml) and stirring until neat separation of phases was observed. The organic layer was separated and the aqueous washed with Et_2O (200ml). The combined organic layers were dried over Na_2SO_4, filtered and volatiles removed *in vacuo* to give a yellow oil. Column chromatography (10% Et_2O/hexane) gave the title compound as a light yellow oil, 6.89g (21% yield).

^{1}H NMR (500 MHz, *CDCl*$_3$) δ ppm: 7.47 – 7.39 (m, 8H, 2C*H*, 3x16C*H*), 7.36 – 7.29 (m, 8H, 3C*H*, 3x15C*H*), 7.26 (m, *J* = 8.8, 5.6 Hz, 4H, 1C*H*, 3x17C*H*), 4.63 (m, 1H, 8H$_b$), 4.52 (m, 1H, 8H$_a$), 3.93 – 3.82 (m, 1H, 10C*H*), 3.55 (s, 1H, O*H*), 3.34 (dd, *J* = 9.6, 4.1 Hz, 1H, 12C*H*$_a$), 3.31 – 3.22 (m, 1H, 12C*H*$_b$), 2.11 (td, *J* = 8.0, 4.1 Hz, 1H, 9C*H*), 1.72 (d, *J* = 14.0 Hz, 1H, 6C*H*$_a$), 1.67 (d, *J* = 14.0 Hz, 1H, 6C*H*$_b$), 1.12 (d, *J* = 6.2 Hz, 3H, 11C*H*$_3$), 0.28 (s, 3H, 5C*H*$_3$), 0.25 (s, 3H, 5C*H*$_3$)

^{13}C NMR (126 MHz, *CDCl*$_3$) δ ppm 143.54, 133.52, 129.02, 128.63, 127.92, 127.76, 127.15, 110.30, 87.68, 77.26, 77.01, 76.75, 71.31, 66.17, 53.39, 27.48, 21.20, -2.69, -2.80

m/z (ESI+): 529, 469, 407, 324, 215. 135

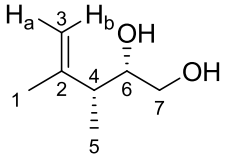
HRMS (ESI+): Calcd. for $C_{34}H_{38}O_2SiNa$ $[M+Na]^+$: 529.2538; found: 529.2535

υ_{max} (neat/ cm^{-1}): 3455 br, 3068 w, 2957 w, 1692 w, 1451 s, 1248 w, 1115 w, 834 w.

R_f: 0.29 in 10% Et_2O/hexane

$[\alpha]_D^{25}$: +67.3 (c = 0.05, CH_2Cl_2)

(2*S*,3*R*)-3,4-dimethylpent-4-ene-1,2-diol (2.145)



Amberlyst 15-H resin method:

To a solution of (2*S*,3*R*)-4-{[dimethyl(phenyl)silyl]methyl}-3-methyl-1-(trityloxy)pent-4-en-2-ol **(2.140)** (490mg, 0.97mmol) in methanol (10ml) was added Amberlyst 15-H resin (1.45g). The resulting suspension was stirred at rt for 2h. Filtration and evaporation of volatiles *in vacuo* gave a yellow oil. Column chromatography (20%, 70% Et_2O/hexane, no gradient) gave the title product as a colourless oil, 117mg (93% yield).

Formic acid method:

To a solution of (2*S*,3*R*)-4-{[dimethyl(phenyl)silyl]methyl}-3-methyl-1-(trityloxy)pent-4-en-2-ol **(2.140)** (620mg, 1.22mmol) in methanol (10ml) was added formic acid (0.23ml, 282mg, 6.12mmol). The resulting clear solution was stirred at rt for 2h. Evaporation of volatiles *in vacuo* gave a colourless oil which was purified by column chromatography (20%, 70% Et_2O/hexane, no gradient) giving the title product as a colourless oil, 141mg (89% yield).

Zinc(II) bromide method:

To a solution of (2*S*,3*R*)-4-{[dimethyl(phenyl)silyl]methyl}-3-methyl-1-(trityloxy)pent-4-en-2-ol **(2.140)** (347mg, 0.68mmol) in DCM (10ml) was added zinc(II) bromide (463mg, 2.05mmol). The resulting solution was stirred at rt for 2h and was then quenched by addition of water (10 ml). The organic layer was washed with sat. aq. NaHCO3 solution (20ml) and was then dried over Na_2SO_4. Filtration and evaporation of volatiles *in vacuo* gave a yellow oil which was purified by column chromatography (20%, 70% Et_2O/hexane, no gradient) giving the title product as a colourless oil, 66mg (74% yield).

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm 4.81 – 4.67 (m, 2H, 3C*H$_a$*, 3C*H$_b$*), 3.60 (dt, *J* = 7.1, 3.0 Hz, 2H, 7C*H$_2$*), 3.43 (dd, *J* = 11.9, 8.6 Hz, 1H, 6C*H*), 3.14 (bs, 2H, 2xO*H*), 2.32 – 2.08 (m, 1H, 4C*H*), 1.69 (d, *J* = 0.8 Hz, 3H, 1C*H$_3$*), 1.09 (d, *J* = 6.9 Hz, 3H, 5C*H$_3$*)

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm 147.12, 111.72, 73.98, 65.40, 44.13, 20.01, 15.28

m/z (ESI+): 153, 151

HRMS (ESI+): Calcd. for $C_7H_{14}O_2Na$ $[M+Na]^+$: 153.0891; found: 153.0886

υ_{max} (neat/ cm^{-1}): 3350 br, 2965 w, 2921 w, 1646 w, 1446 w, 1046 s

R_f: 0.12 in 3:2 Et_2O/hexane ($KMnO_4$)

$[\alpha]_D^{25}$: +22.1 (c = 0.05, CH_2Cl_2)

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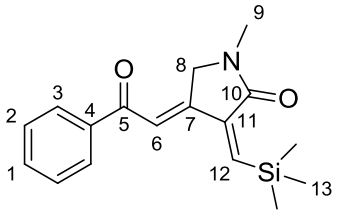
5. Appendix

5.1 X-ray data

(3*Z*,4*Z*)-1-Methyl-4-(2-oxo-2-phenylethylidene)-3-[(trimethylsilyl)methylene]pyrrolidin-2-one (2.57)



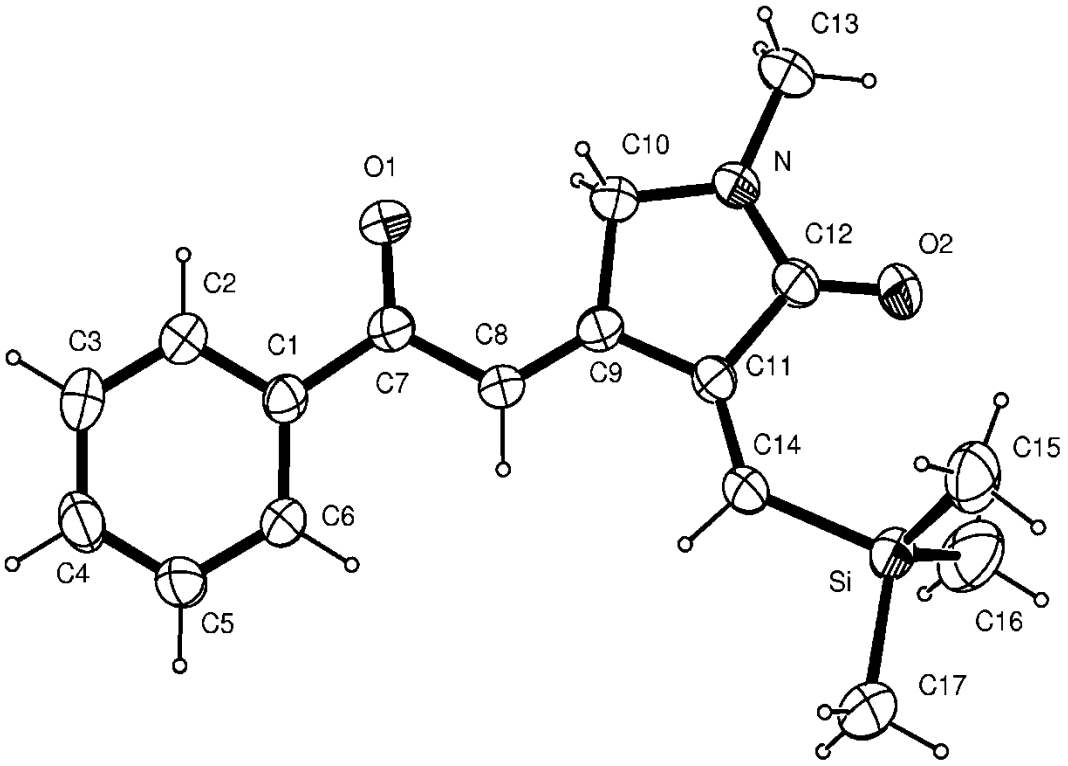


Table 1. Crystal data and structure refinement .

Identification code	apr1108
Empirical formula	C17 H21 N O2 Si
Formula weight	299.44
Temperature	173(2) K
Wavelength	0.71073 Å

Crystal system	Rhombohedral	
Space group	$R\bar{3}$ (No.148)	
Unit cell dimensions	a = 30.9588(9) Å	a= 90°.
	b = 30.9588(9) Å	b= 90°.
	c = 9.3101(3) Å	g = 120°.
Volume	7727.7(4) $Å^3$	
Z	18	
Density (calculated)	1.16 Mg/m^3	
Absorption coefficient	0.14 mm^{-1}	
F(000)	2880	
Crystal size	0.25 x 0.25 x 0.20 mm^3	
Theta range for data collection	3.48 to 25.86°.	
Index ranges	-33<=h<=38, -38<=k<=29, -11<=l<=11	
Reflections collected	12947	
Independent reflections	3319 [R(int) = 0.063]	
Reflections with I>2sigma(I)	2261	
Completeness to theta = 25.86°	99.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3319 / 0 / 194	
Goodness-of-fit on F^2	1.008	
Final R indices [I>2sigma(I)]	R1 = 0.047, wR2 = 0.097	
R indices (all data)	R1 = 0.083, wR2 = 0.109	
Largest diff. peak and hole	0.18 and -0.22 $e.Å^{-3}$	

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 apr1108. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si	1495(1)	779(1)	2645(1)	39(1)
O(1)	3074(1)	1931(1)	8694(2)	47(1)
O(2)	1854(1)	1879(1)	3425(2)	41(1)
N	2382(1)	2250(1)	5328(2)	37(1)
C(1)	2978(1)	1142(1)	9214(2)	29(1)
C(2)	3388(1)	1349(1)	10132(2)	37(1)
C(3)	3499(1)	1048(1)	10955(2)	49(1)
C(4)	3198(1)	534(1)	10887(2)	49(1)
C(5)	2789(1)	325(1)	10009(2)	44(1)
C(6)	2676(1)	623(1)	9158(2)	35(1)
C(7)	2874(1)	1487(1)	8355(2)	32(1)
C(8)	2541(1)	1294(1)	7104(2)	30(1)
C(9)	2440(1)	1584(1)	6260(2)	28(1)
C(10)	2631(1)	2134(1)	6463(2)	35(1)
C(11)	2120(1)	1424(1)	4975(2)	28(1)
C(12)	2096(1)	1866(1)	4455(2)	31(1)
C(13)	2461(1)	2750(1)	5142(3)	56(1)
C(14)	1885(1)	977(1)	4322(2)	33(1)

C(15)	1862(1)	1142(1)	1063(2)	56(1)
C(16)	907(1)	794(1)	2876(3)	68(1)
C(17)	1333(1)	119(1)	2370(3)	67(1)

Table 3. Bond lengths [Å] and angles [°] for apr1108.

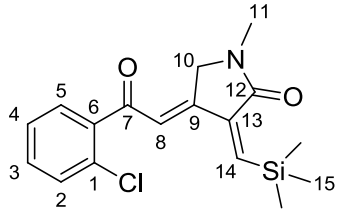
Si-C(16)	1.856(3)
Si-C(15)	1.858(2)
Si-C(17)	1.863(2)
Si-C(14)	1.880(2)
O(1)-C(7)	1.233(2)
O(2)-C(12)	1.230(2)
N-C(12)	1.344(2)
N-C(13)	1.451(3)
N-C(10)	1.456(2)
C(1)-C(2)	1.393(3)
C(1)-C(6)	1.399(3)
C(1)-C(7)	1.491(3)
C(2)-C(3)	1.375(3)
C(3)-C(4)	1.385(3)
C(4)-C(5)	1.369(3)
C(5)-C(6)	1.386(3)
C(7)-C(8)	1.471(3)
C(8)-C(9)	1.341(3)
C(9)-C(11)	1.472(3)
C(9)-C(10)	1.510(3)

C(11)-C(14)	1.343(3)
C(11)-C(12)	1.489(3)

C(16)-Si-C(15)	112.87(13)
C(16)-Si-C(17)	108.37(13)
C(15)-Si-C(17)	107.55(13)
C(16)-Si-C(14)	112.00(11)
C(15)-Si-C(14)	111.21(10)
C(17)-Si-C(14)	104.34(10)
C(12)-N-C(13)	123.92(17)
C(12)-N-C(10)	114.50(16)
C(13)-N-C(10)	121.53(17)
C(2)-C(1)-C(6)	118.80(18)
C(2)-C(1)-C(7)	118.26(17)
C(6)-C(1)-C(7)	122.93(17)
C(3)-C(2)-C(1)	120.6(2)
C(2)-C(3)-C(4)	120.0(2)
C(5)-C(4)-C(3)	120.1(2)
C(4)-C(5)-C(6)	120.5(2)
C(5)-C(6)-C(1)	119.89(19)
O(1)-C(7)-C(8)	120.92(18)
O(1)-C(7)-C(1)	119.54(18)
C(8)-C(7)-C(1)	119.53(17)
C(9)-C(8)-C(7)	122.94(17)
C(8)-C(9)-C(11)	126.40(17)

C(8)-C(9)-C(10)	126.17(17)
C(11)-C(9)-C(10)	107.44(16)
N-C(10)-C(9)	103.39(15)
C(14)-C(11)-C(9)	129.88(18)
C(14)-C(11)-C(12)	123.32(18)
C(9)-C(11)-C(12)	106.79(16)
O(2)-C(12)-N	125.67(18)
O(2)-C(12)-C(11)	126.56(18)
N-C(12)-C(11)	107.76(16)
C(11)-C(14)-Si	129.79(16)

(3*Z*,4*Z*)-4-[2-(2-Chlorophenyl)-2-oxoethylidene]-1-methyl-3-[(trimethylsilyl)methylene]pyrrolidin-2-one (2.59)



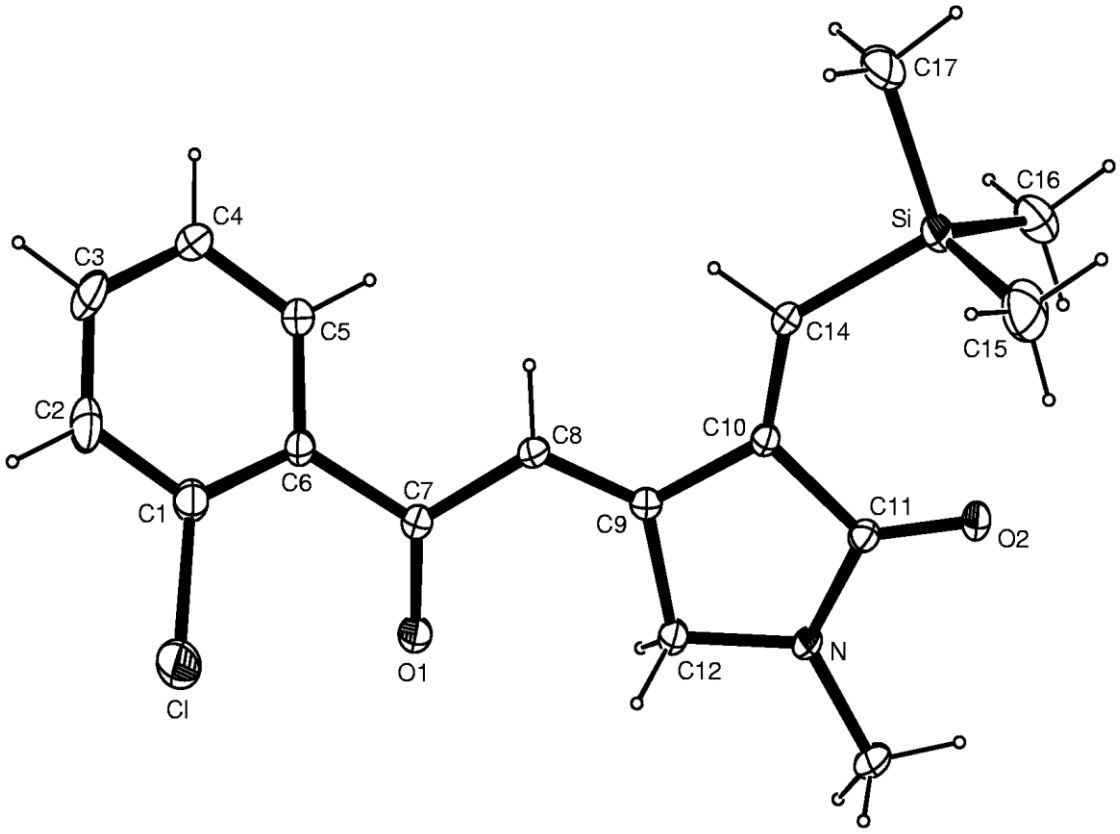


Table 1. Crystal data and structure refinement for $C_{17}H_{20}ClNO_2Si$.

Identification code	oct109b	
Empirical formula	C17 H20 Cl N O2 Si	
Formula weight	333.88	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P* $2_1/c$ (No.14)	
Unit cell dimensions	a = 13.1246(4) Å	a= 90°.
	b = 11.2116(4) Å	b= 110.280(2)°.
	c = 12.7330(3) Å	g = 90°.
Volume	1757.49(9) Å^3	

Z	4
Density (calculated)	1.26 Mg/m^3
Absorption coefficient	0.29 mm^{-1}
F(000)	704
Crystal size	0.30 x 0.14 x 0.11 mm^3
Theta range for data collection	3.41 to 26.73°.
Index ranges	-16<=h<=16, -14<=k<=14, -14<=l<=16
Reflections collected	22079
Independent reflections	3725 [R(int) = 0.062]
Reflections with I>2sigma(I)	2841
Completeness to theta = 26.73°	99.8 %
Tmax. and Tmin.	1.0088 and 0.8855
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3725 / 0 / 203
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.046, wR2 = 0.101
R indices (all data)	R1 = 0.069, wR2 = 0.110
Largest diff. peak and hole	0.33 and -0.49 $e.Å^{-3}$

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN

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 oct109b. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl	5798(1)	-2762(1)	3189(1)	56(1)
Si	10037(1)	3468(1)	2242(1)	34(1)
O(1)	5749(1)	-676(1)	1722(1)	34(1)
O(2)	8622(1)	2460(1)	-152(1)	29(1)
N	7189(1)	1212(2)	-311(1)	24(1)
C(1)	6078(2)	-1521(2)	4057(2)	30(1)
C(2)	6094(2)	-1699(2)	5143(2)	43(1)
C(3)	6294(2)	-744(3)	5867(2)	55(1)
C(4)	6473(2)	375(3)	5527(2)	52(1)
C(5)	6488(2)	532(2)	4457(2)	37(1)
C(6)	6303(2)	-410(2)	3698(2)	24(1)
C(7)	6352(2)	-167(2)	2557(2)	22(1)
C(8)	7169(2)	708(2)	2504(2)	22(1)
C(9)	7306(2)	1042(2)	1547(2)	18(1)
C(10)	8150(2)	1861(2)	1464(1)	18(1)
C(11)	8050(2)	1902(2)	260(2)	21(1)
C(12)	6665(2)	619(2)	384(2)	24(1)
C(13)	6908(2)	938(2)	-1492(2)	37(1)
C(14)	8902(2)	2460(2)	2284(2)	22(1)
C(15)	11038(2)	2655(3)	1776(3)	58(1)
C(16)	9527(2)	4814(2)	1372(2)	52(1)
C(17)	10695(3)	3896(3)	3742(2)	68(1)

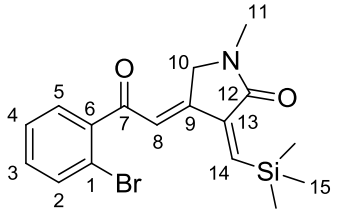
Table 3. Bond lengths [Å] and angles [°] for oct109b.

Cl-C(1)	1.735(2)
Si-C(16)	1.854(3)
Si-C(15)	1.857(3)
Si-C(17)	1.866(3)
Si-C(14)	1.885(2)
O(1)-C(7)	1.224(2)
O(2)-C(11)	1.226(2)
N-C(11)	1.354(2)
N-C(13)	1.451(2)
N-C(12)	1.456(2)
C(1)-C(2)	1.391(3)
C(1)-C(6)	1.393(3)
C(2)-C(3)	1.378(4)
C(3)-C(4)	1.373(4)
C(4)-C(5)	1.381(3)
C(5)-C(6)	1.394(3)
C(6)-C(7)	1.501(3)
C(7)-C(8)	1.472(3)
C(8)-C(9)	1.346(3)
C(9)-C(10)	1.471(3)
C(9)-C(12)	1.505(3)
C(10)-C(14)	1.342(3)
C(10)-C(11)	1.492(2)

C(16)-Si-C(15)	110.93(14)
C(16)-Si-C(17)	110.19(14)
C(15)-Si-C(17)	108.97(16)
C(16)-Si-C(14)	112.34(11)
C(15)-Si-C(14)	111.63(11)
C(17)-Si-C(14)	102.43(10)
C(11)-N-C(13)	122.90(16)
C(11)-N-C(12)	114.58(15)
C(13)-N-C(12)	121.90(16)
C(2)-C(1)-C(6)	121.5(2)
C(2)-C(1)-Cl	116.44(17)
C(6)-C(1)-Cl	122.06(16)
C(3)-C(2)-C(1)	119.2(2)
C(4)-C(3)-C(2)	120.9(2)
C(3)-C(4)-C(5)	119.3(2)
C(4)-C(5)-C(6)	121.9(2)
C(1)-C(6)-C(5)	117.15(18)
C(1)-C(6)-C(7)	124.33(18)
C(5)-C(6)-C(7)	118.52(18)
O(1)-C(7)-C(8)	122.18(17)
O(1)-C(7)-C(6)	121.65(17)
C(8)-C(7)-C(6)	116.18(16)
C(9)-C(8)-C(7)	123.74(17)
C(8)-C(9)-C(10)	125.47(17)
C(8)-C(9)-C(12)	126.81(17)

C(10)-C(9)-C(12)	107.69(15)
C(14)-C(10)-C(9)	128.67(17)
C(14)-C(10)-C(11)	124.31(17)
C(9)-C(10)-C(11)	107.01(15)
O(2)-C(11)-N	125.59(17)
O(2)-C(11)-C(10)	127.24(17)
N-C(11)-C(10)	107.16(16)
N-C(12)-C(9)	103.50(15)
C(10)-C(14)-Si	130.73(15)

(3*Z*,4*Z*)-4-[2-(2-Bromophenyl)-2-oxoethylidene]-1-methyl-3-[(trimethylsilyl)methylene]pyrrolidin-2-one (2.56)



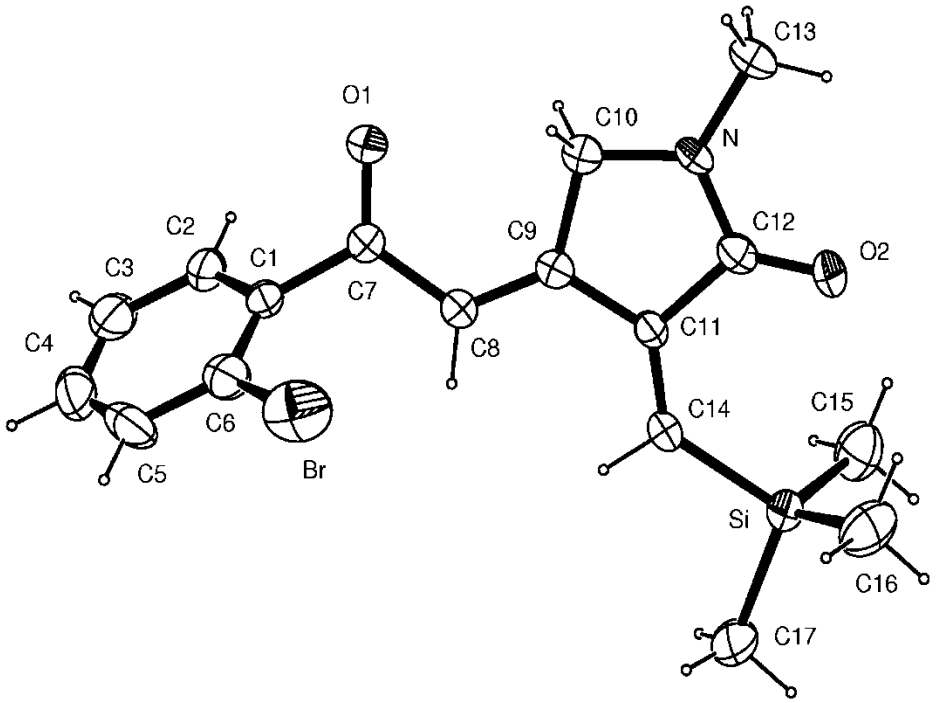


Table 1. Crystal data and structure refinement .

Identification code	dec1307	
Empirical formula	C17 H20 Br N O2 Si	
Formula weight	378.34	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca (No.61)	
Unit cell dimensions	a = 11.5307(3) Å	a= 90°.
	b = 12.4900(3) Å	b= 90°.
	c = 25.4454(7) Å	g = 90°.
Volume	3664.61(16) Å^3	

Z	8
Density (calculated)	1.37 Mg/m^3
Absorption coefficient	2.32 mm^{-1}
F(000)	1552
Crystal size	0.3 x 0.3 x 0.1 mm^3
Theta range for data collection	3.40 to 26.02°.
Index ranges	-14<=h<=14, -14<=k<=15, -27<=l<=31
Reflections collected	23989
Independent reflections	3584 [R(int) = 0.079]
Reflections with I>2sigma(I)	2529
Completeness to theta = 26.02°	99.5 %
Tmax. and Tmin.	0.6743 and 0.4910
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3584 / 0 / 203
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.055, wR2 = 0.115
R indices (all data)	R1 = 0.091, wR2 = 0.130
Largest diff. peak and hole	0.84 and -0.91 e.$Å^{-3}$

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN

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 dec1307. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br	6699(1)	4639(1)	2275(1)	62(1)
Si	8604(1)	7694(1)	109(1)	31(1)
O(1)	4016(2)	6588(2)	1920(1)	39(1)
O(2)	7494(2)	9579(2)	766(1)	36(1)
N	6010(3)	9213(2)	1340(1)	32(1)
C(1)	4510(3)	4781(3)	1764(1)	30(1)
C(2)	3447(3)	4359(3)	1597(2)	42(1)
C(3)	3218(4)	3281(4)	1645(2)	59(1)
C(4)	4032(5)	2612(4)	1860(2)	63(2)
C(5)	5088(5)	2997(4)	2030(2)	56(1)
C(6)	5318(4)	4095(3)	1979(1)	39(1)
C(7)	4704(3)	5968(3)	1711(1)	27(1)
C(8)	5665(3)	6320(3)	1377(1)	27(1)
C(9)	5944(3)	7357(3)	1298(1)	25(1)
C(10)	5381(3)	8307(3)	1557(2)	35(1)
C(11)	6839(3)	7760(3)	943(1)	22(1)
C(12)	6856(3)	8951(3)	996(1)	27(1)
C(13)	5707(4)	10301(3)	1477(2)	50(1)
C(14)	7504(3)	7222(3)	602(1)	27(1)
C(15)	7912(4)	8550(4)	-400(2)	50(1)
C(16)	9863(3)	8385(4)	411(2)	52(1)
C(17)	9100(5)	6421(4)	-202(2)	63(2)

Table 3. Bond lengths [Å] and angles [°] for dec1307.

Br-C(6)	1.888(4)
Si-C(16)	1.856(4)
Si-C(15)	1.859(4)
Si-C(17)	1.865(4)
Si-C(14)	1.880(4)
O(1)-C(7)	1.230(4)
O(2)-C(12)	1.224(4)
N-C(12)	1.351(5)
N-C(13)	1.447(5)
N-C(10)	1.453(5)
C(1)-C(6)	1.379(5)
C(1)-C(2)	1.400(6)
C(1)-C(7)	1.506(5)
C(2)-C(3)	1.377(6)
C(3)-C(4)	1.370(7)
C(4)-C(5)	1.379(7)
C(5)-C(6)	1.403(6)
C(7)-C(8)	1.464(5)
C(8)-C(9)	1.350(5)
C(9)-C(11)	1.461(5)
C(9)-C(10)	1.505(5)
C(11)-C(14)	1.338(5)
C(11)-C(12)	1.495(5)

C(16)-Si-C(15)	110.9(2)
C(16)-Si-C(17)	109.4(2)
C(15)-Si-C(17)	109.1(2)
C(16)-Si-C(14)	113.43(19)
C(15)-Si-C(14)	110.83(18)
C(17)-Si-C(14)	102.84(18)
C(12)-N-C(13)	123.9(3)
C(12)-N-C(10)	114.7(3)
C(13)-N-C(10)	121.3(3)
C(6)-C(1)-C(2)	118.6(4)
C(6)-C(1)-C(7)	123.1(4)
C(2)-C(1)-C(7)	118.3(3)
C(3)-C(2)-C(1)	120.6(5)
C(4)-C(3)-C(2)	120.0(5)
C(3)-C(4)-C(5)	121.2(4)
C(4)-C(5)-C(6)	118.5(4)
C(1)-C(6)-C(5)	121.1(4)
C(1)-C(6)-Br	120.3(3)
C(5)-C(6)-Br	118.2(4)
O(1)-C(7)-C(8)	123.5(3)
O(1)-C(7)-C(1)	119.0(3)
C(8)-C(7)-C(1)	117.4(3)
C(9)-C(8)-C(7)	123.7(3)
C(8)-C(9)-C(11)	126.2(3)
C(8)-C(9)-C(10)	126.1(3)

C(11)-C(9)-C(10)	107.8(3)
N-C(10)-C(9)	103.4(3)
C(14)-C(11)-C(9)	129.2(3)
C(14)-C(11)-C(12)	123.5(3)
C(9)-C(11)-C(12)	107.2(3)
O(2)-C(12)-N	126.1(3)
O(2)-C(12)-C(11)	127.0(3)
N-C(12)-C(11)	106.9(3)
C(11)-C(14)-Si	131.4(3)