University of Sussex

A NOVEL CYCLIZATION IN THE CONSTRUCTION OF FUSED RINGS

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Declaration

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

Signature:……

Dedication

This thesis is dedicated to **God Almighty** and to my husband Dr Sunday Olaniyi Banjoko.

Abstract

The discovery of the novel thermal cyclization of enediyne molecules within the Parsons group during studies directed towards the total synthesis of lactonamycin has stimulated an intense research into the cyclization of the enediynes.

In this research different functionalised enediynes were synthesised to investigate:-

(i) the scope and limitations of the thermal cyclization reactions,

(ii) the proposed biradical mechanism for the cyclization reactions,

(iii) the intermolecular trappings of the proposed biradical, and

(iv) the effect of sterically demanding groups on the rate of cyclization.

In the process of testing these objectives, we have been able to synthesize highly functionalised heterocyclic rings by simple thermal cyclization reactions without using any metal catalyst. We have discovered that the cyclizations may have involved free radical mechanism or an ene reaction, followed by a Diels – Alder cycloaddition reactions. Interestingly the cyclised compound **2.1** shows two stereogenic centres at C2 and C4 with an absolute configuration of R and S respectively. An in-depth exploration of the stereochemistry of these reactions may increase their application in controlling the stereochemistry of ring systems through simple metal free thermal cyclization reactions. Confirmation of the specific mechanism constitutes an ongoing research within the Parsons group. Conclusively cyclization of highly functionalised enediynes had been proved to be a versatile route to the synthesis of diverse heterocyclic compounds. The ease of cyclizations of a majority of the enediynes in this study has shown that functionalisation and diversification of the core enediyne systems could be utilized in the synthesis of pharmaceutically important antitumour drugs.

Acknowledgements

I will like to acknowledge with deep appreciation the support of my supervisor, Prof. Phillip J. Parsons. His support went far beyond the academics into other spheres of life, thus making my study and life in the United Kingdom a success. .I will also like to thank Dr. Hans Streicher, my co- supervisor for his contributions towards the success of this thesis.

I am also using this opportunity to thank my sponsor and employer, Tai Solarin University of Education, Ogun State, Nigeria for the opportunity given to me. I will like to thank in particular my former Vice Chancellor, Prof. Olukayode O. Oyesiku for his initiative, foresight and pursuit of academic excellence.

I wish to thank every member of the Parsons group, past and present, especially Dr Magalie Dale, Guillaume, Raghav, Rosa, Emma and Joe for their support and friendship. I would like to acknowledge the works of Dr Alex Waters and Dr Magalie Dale on cyclization chemistry.

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I would like to thank my family, parents, siblings and my children, Adedeji, Boluwatife Fiyinfoluwa and Ayobami for their support, encouragement and patience throughout my study, and especially my husband Dr S.O Banjoko for holding forth the home front during my absence. I cannot but mention my lovely daughter-in–law, Adeyemi and my granddaughter, Favour, for their love. I would like to re-echo my special thanks to my

‘baby’, Ayobami who did not allow me to indulge in any moment of loneliness. He was my engineer, IT consultant, personal assistant, playmate and chef. God bless you all.

Abbreviations

A^o	angstrom
Ac	acetyl
Aq	aqueous
Ar	aromatic
BC	Bergman Cyclization
Bn	benzyl
BOC, Boc	*tert*-butyloxycarbonyl
b.p	boiling point
Bu	butyl
BuLi (n-BuLi)	butyllithium
*t*Bu	tert-butyl
*n*Bu	*n*-butyl
Bz	benzoyl
^OC	degrees Celsius
Cat	catalyst
Cbz	benzyloxycarbonyl
CDI	1, 1'-carbonyldiimidazole
CHD	1-4-cyclohexadiene
DCC	1, 3-dicyclohexylcarbodiimide
DCM	dichloromethane
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMS	dimethyl sulphate
EDCl	1-[3- (Dimethylamino) propyl]-3-ehylcarbodiimide hydrochloride
ESI	electron spray ionisation
Et	ethyl
Eq	equivalents
Fw	Formula weight

g	gram(s)
GS	ground state
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared spectroscopy
K	rate constant
Kg	kilograms
M	molar
Me	methyl
MeOH	methanol
Min	minute(s)
mL	millilitre
Mol	mole
mmol	millimole
mp	melting point
MS	mass spectroscopy
Ms	mesyl
OMs	mesylate
Mw	molecular weight
MSC	Myers-Saito cyclization
NMR	nuclear magnetic resonance
Nu-	nucleophile
O/N	overnight
P	*para*
Ph	phenyl
PM3	molecular modelling
ppm	parts per million
^{i}Pr	*iso*-propyl
py	pyridine
Rf	retention factor
rt	room temperature
SM	starting material
TFA	tri-fluoroacetic acid

THF	tetrahydrofuran
TIPS	tri-isopropylsilyl
TLC	thin layer chromatography
TMS	tri-methylsilyl
Tol	toluene
d-Tol	deuterated toluene
TS	transition state

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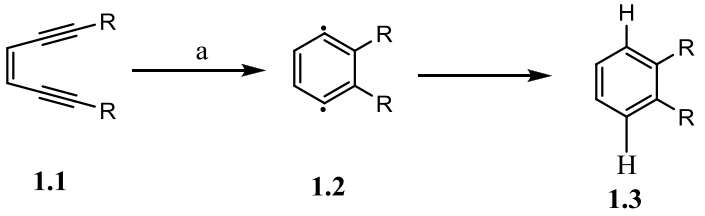
Chapter 1

Introduction

1.1 Cyclization Reactions.

The transformation of (Z)-3-ene-1,5 diynes into reactive 1,4-benzene biradical reactions (also known as Cope's rearrangement[1] or cycloaromatization reactions[2]) has found applications in areas ranging from anticancer drug design, sequence specific DNA mapping tools as well as organic and polymer synthesis[3,4.] This reaction which was first reported by Bergman *et al.,* in 1972,[5] is now known as the Bergman cyclization (BC).



1.1 **1.2** **1.3**

reagents and conditions; (a) 200°C, 1,4-CHD

Scheme 1.1: Bergman Cyclization of (Z)-3-ene-1, 5-diyne

The BC is at the heart of the chemistry of the enediynes and is primarily responsible for their biological activities[2]. However, even though the chemistry of the enediynes and some other unsaturated systems had began to be unfolded in the 1960s by Sondheimer,[6,7] Masamune[8] and Bergman,[5,9] not much attention was paid to it, largely due to the high temperature necessary to induce the rearrangement. However the discovery and isolation of naturally occurring enediynes in the 1980s sparked off remarkable and renewed interest in the thermal biradical cyclization of enediynes, enyne, cumulenes and enyne allenes over the last few years.[2, 10] This is due to the fascinating mechanism of these systems operative in the natural antitumor antibiotics as well as their potential in the synthesis of carbocyclic systems[10.] This, coupled with the pharmaceutical demand for cytotoxic antitumor drugs, has also stimulated detailed

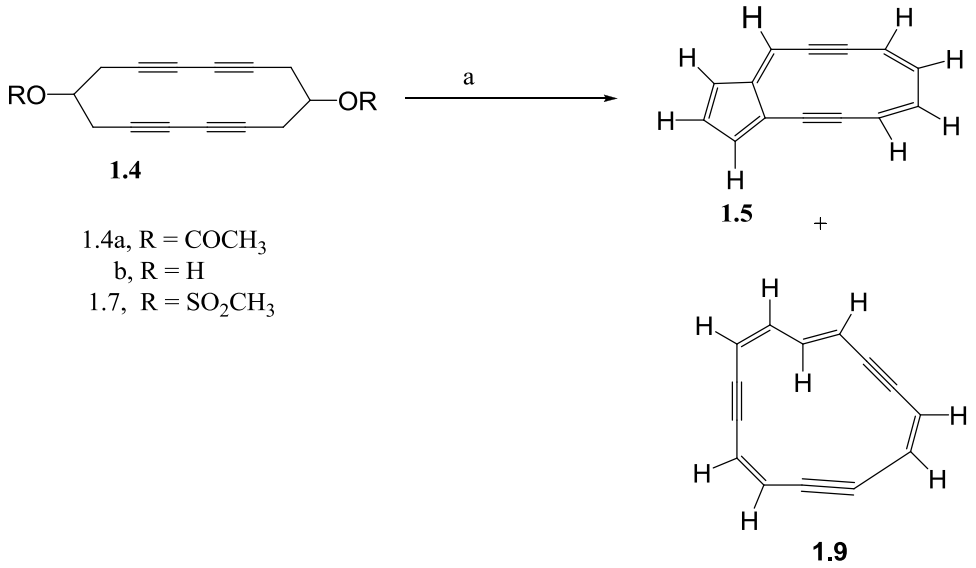
scrutiny of the cyclization reactions of polyunsaturated hydrocarbons yielding biradicaloid intermediates. Today, the BC has become a powerful tool in synthetic chemistry.

In addition to the well known Bergman ring closure, the Myers-Saito, the Schimittel, and the Schreiner cyclizations are fundamentally important[11].

This section will attempt to give a brief discussion of these different modes of cyclizations and their relevance to synthetic chemistry.

1.1.1 Pre-Bergman Cyclization

Prior to the work of Bergman *et al.,* on the biradical cyclization reactions many studies have been carried out on the annulene systems[12, 13] (a cyclic system with alternating saturated and unsaturated bonds) because of their potentially aromatic character. Sondheimer *et al.,*[6,7,13,14] carried out extensive studies on the synthesis of dehydro[14]annulenes, by base induced elimination of 3,5,10,12-cyclotetradecatetrayne-1,8-diol dimethanesulphonate **1.7**. He discovered that the reaction, in addition to the expected product 1,5,9-cyclotridehydro[14]annulene **1.9**, gave an unusual bicyclic compound **1.5**, as the major product.



1.4

1.4a, R = $COCH_3$
b, R = H
1.7, R = SO_2CH_3

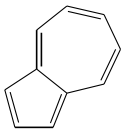
1.5 +

1.9

reagents and conditions: KOH, MeOH, Δ

Scheme 1.2: Formation of the bicycle[6]

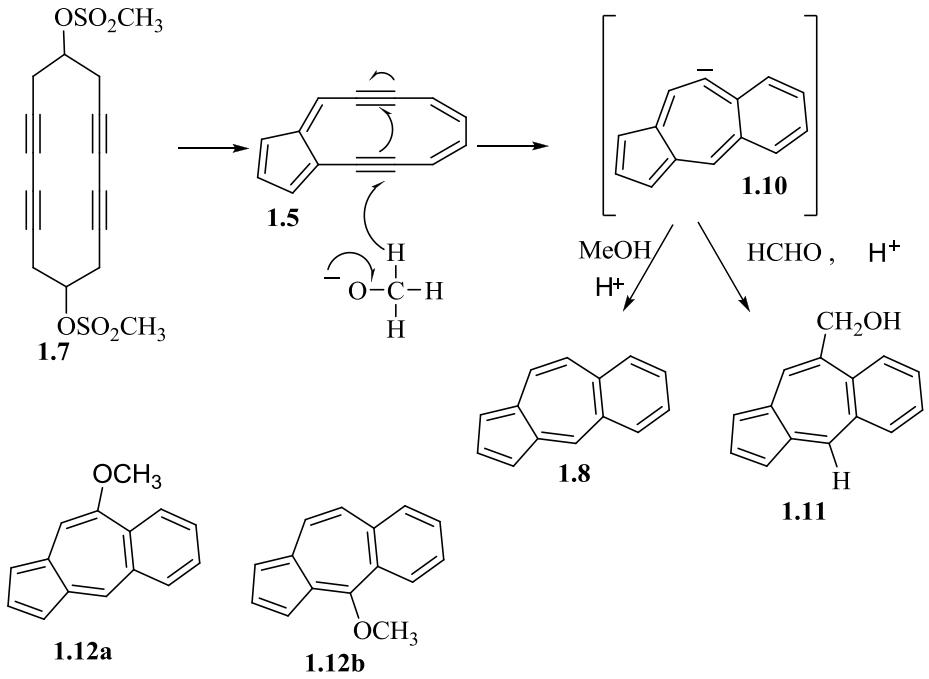
Compound **1.5** was seen as an analogue of azulene **1.6**, formally derived from this compound by insertion of two acetylenes into the seven-membered ring.



1.6

Figure 1.1 Azulene

When this reaction was carried out under more vigorous conditions (refluxing), using annulene **1.7**, a tricyclic structure **1.8** was obtained. It was then proposed that the transformation of **1.7** to the tricyclic **1.8** with base involves the addition of two atoms of hydrogen. The bicycle 1.5 produced under the milder conditions may have been the intermediate upon which there was a hydride ion transfer from the methoxide, followed by ring closure to **1.10** and protonation, forming formaldehyde. The other by-product, 1.11 is presumably formed by a similar mechanism, the anion **1.10** reacting with the formaldehyde prior to protonation.

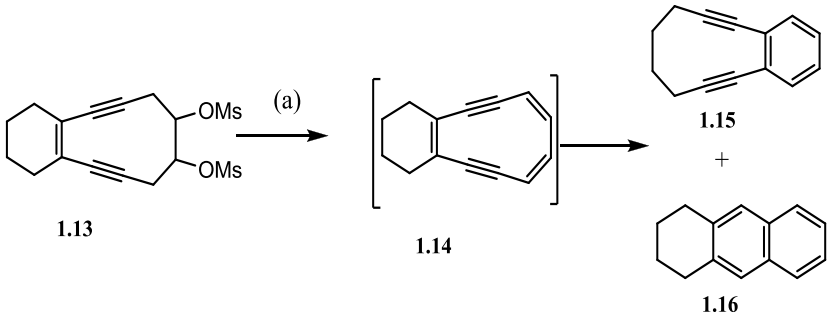


reagents and conditions: (a)7% KOH, 95% aqueous MeOH, reflux, 15 min

Scheme 1.3 Formation of tricyclic 1.8, 1.11, 1.12a and 1.12b[14]

Compound **1.12a** and **1.12b** could also be formed from **1.5** by normal nucleophilic attack by methoxide ion, again followed by ring closure and protonation.

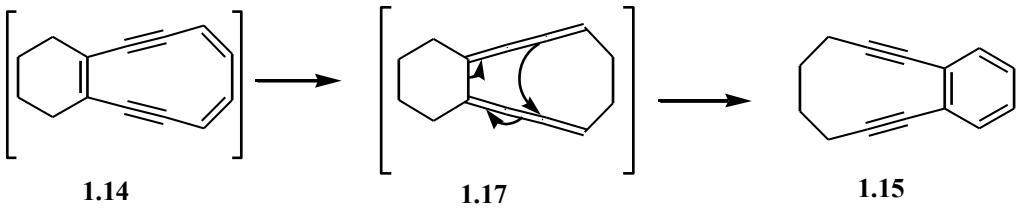
Continued studies on the annulene chemistry also carried out by Masamune[8, 15] and his co-workers, focusing on the synthesis of the [10] annulene. Their work also produced results which deviated from the expected dehydro- annulene products. Treatment of the dimesylate **1.13** with sodium methoxide produced both the bicyclic and tricyclic compounds, 3,4-benzocyclodec-3-ene **1.15** and 1,2,3,4-tetrahydroanthracene **1.16** as shown in scheme **1.4** below



reagents and conditions :(a) NaOMe, MeOH

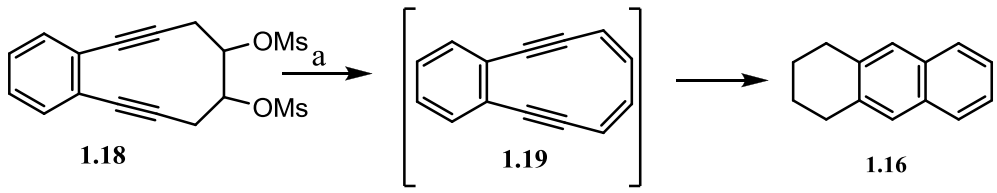
Scheme 1.4 Masamune work on [10] annulene [16]

The reaction was speculated to have proceeded through a Cope-like rearrangement involving electron pair movement, via a di-cumulene intermediate **1.17** which is a resonance form of [10] annulene **1.14.**



Scheme 1.5: Postulated mechanism[15]

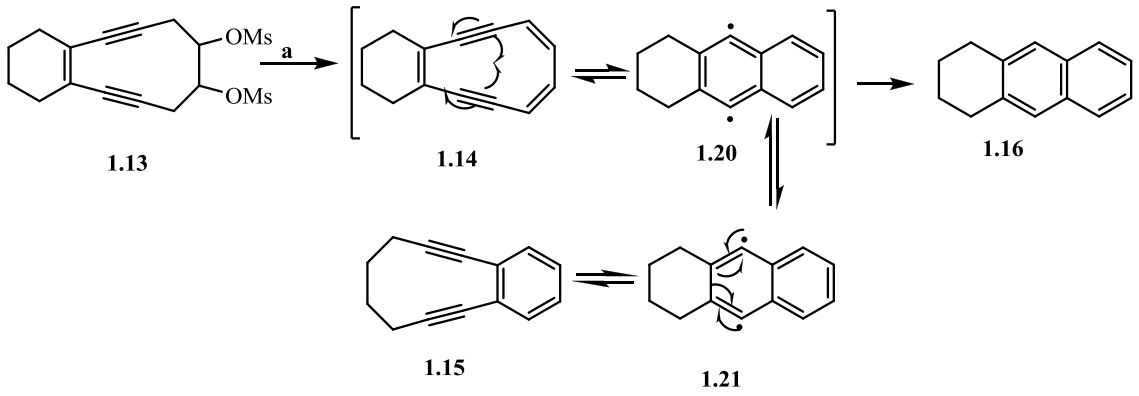
Further investigation using an aromatic dimesylate **1.18** for the formation of 1,5-didehydro-3,4-benz[10]annulene **1.19** produced only anthracene. The use of deuterated solvents showed that the additional hydrogen atoms were inserted into the 9 and 10 positions. This reaction is thought to have proceeded through an analogue mechanism to scheme **1.5** and then followed by decomposition. (scheme**1.6**)



reagents and conditions: (a) NaOMe

Scheme 1.6: Formation of anthracene

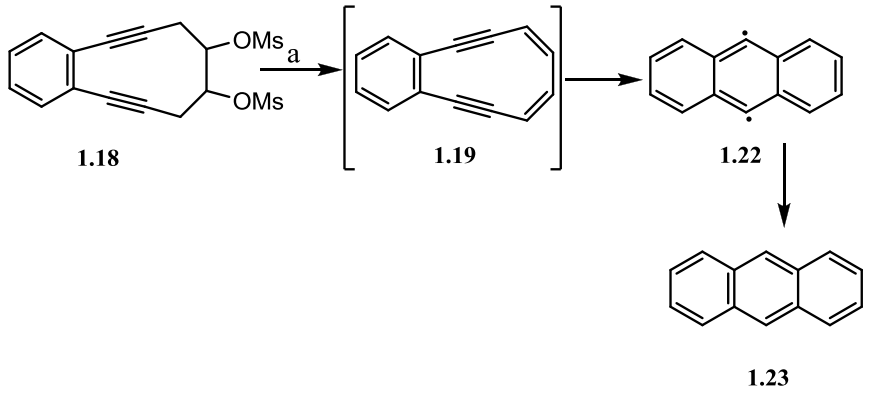
Even though Masamune[15,16] could not provide a clear and an acceptable mechanism for the formation of these unexpected results, light was later thrown upon these reactions by Bergman after his discovery of the biradical mechanism.[5, 17.] Bergman postulated that the formation of the products in scheme **1.4** must have occurred through the biradical intermediate **1.20** instead of the di-cumulene **1.17**. The biradical could then be quenched by abstraction of a hydrogen atom from the hydrogen donor to form **1.16** or collapsed to form **1.15.**



reagents and conditions: (a) NaOMe, MeOH

Scheme 1. 7: Bergman cyclization in Masamune's tetrahyroanthracene synthesis

Similar explanation was also given for the exclusive formation of anthracene in the aromatic analogue.

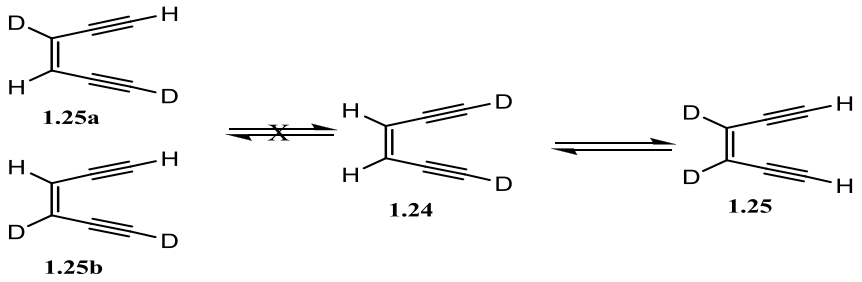


reagents and conditions: (a) NaOMe, MeOH

Scheme1:8 Bergman cyclization in Masamune's anthracene synthesis

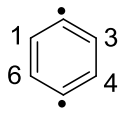
1.2 Bergman Cyclization [5, 17].

Bergman *et a*l.,[5,17] in 1972 reported that *cis*-1,5-hexadiyne undergoes a striking thermal degenerate rearrangement though the *p*-benzyne moiety. Further investigative studies confirmed the *p*-benzyne as the intermediate in the thermal isomerisation reaction of the *cis*-1,5-hexadiyne (Scheme **1:1)** and results from such studies have provided insights into the hitherto unresolved rearrangements of the annulene system, (Schemes.**1.7** and **1.8**). Reactions involving deuterium-proton transfer on the acetylenic carbons produced molecules containing only zero or two deuterium atoms, indicating that the interconversion is only between **1.24** and **1.25**, with no single exchanged product (**1.25a** and **1.25b**) formed.



Scheme 1.9: Thermal equilibrium of *cis*-1,5-hexadiyne-3-ene.

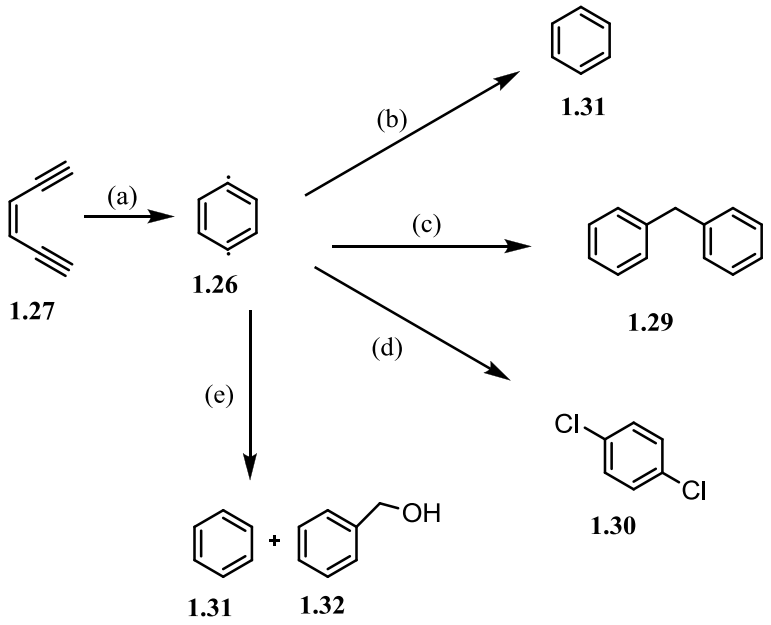
This result required that **1.24** be transformed via an intermediate or transition state **1.26** in which C1, C3, C4, and C6 are chemically equivalent, thus suggesting a *p*-benzyne as the intermediate.



1.26

Figure 1.2: *p*-benzyne or 1,4-dehydrobenzene

The *p*-benzyne was further confirmed to be the intermediate through intermolecular trappings by external reagents. When **1.26** is kept sufficiently dilute (<0.01M), it can be heated to 200^{o}C without decomposition. When heated in hydrocarbon solvent, pristane (2, 6, 10, 14-tetramethylpentadecane), benzene (**1.31**) was formed. This suggested that **1.26** is capable of abstracting hydrogen atoms from a donor solvent. The use of other solvents such as, tetrachloromethane, toluene and methanol produced 1,4-dichlorobenzene **1.30,** diphenylmethane **1.29** and benzyl alcohol **1.32** and benzene **1.31** respectively (scheme **1.10).** These results confirmed that the reaction occurred through the *p*-benzyne intermediate in a typical free radical mechanism.

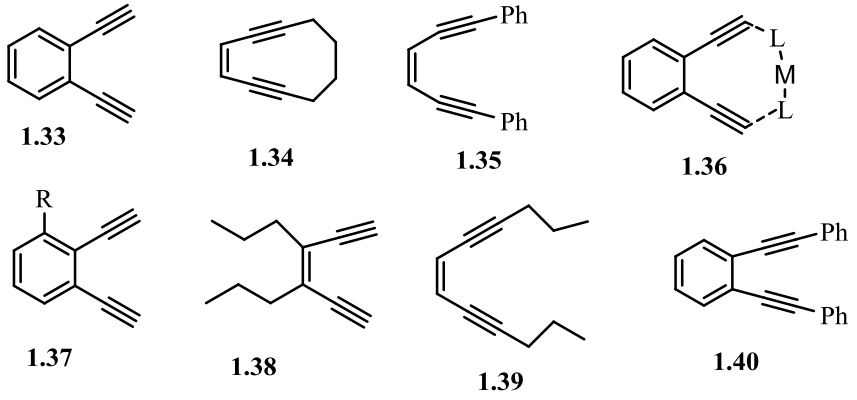


reagents and conditions: (a) Δ, (b) pristane, (c) toluene, (d) CCl_4, (e) MeOH

Scheme 1.10: Biradical trappings

Even when the intermediate is given a choice of behaving as a polar or radical species, the intermediate selected the latter, thus the reaction in methanol at 200^{o}C gives mostly benzene and some benzyl alcohol, but no anisole.

Following the acceptance of the BC, extensive studies into the application, limitation and ways of controlling the cyclization have been initiated and are still ongoing. Consequently, apart from the simple enediyne **1.27**, numerous derivatives of the enediyne systems have been developed for use in the study of the mechanism of these systems.



1.33 **1.34** **1.35** **1.36**

1.37 **1.38** **1.39** **1.40**

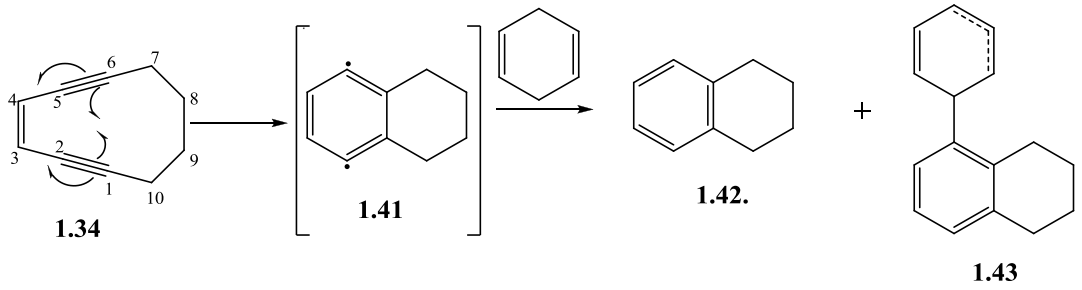
Figure 1.3: Some examples of enediynes that undergo the BC[3]

1.2.1. Nicolaou Distance Theory.

As a result of his extensive studies, Nicolaou *et al.,* [1, 18, 19] discovered that the distance of the acetylene carbons forming the new bond may be related to the activation barrier for ring closure, in other words the stability of the enediyne moiety depends largely on the distance (cd) between the terminal acetylenic carbons (C-1 and C-6) (scheme **1.11**) of the enediyne group. He concluded that the crucial turning point from stability to spontaneous cyclization must be in the cd range of 3.31-3.20 Å (now popularly known as the distance theory)**.** Recent calculations appear to have extended this range to 2.8-3.4 Å. Compounds with lower than 3.20 cd values have been claimed as transition intermediates, suffering spontaneous cyclization to benzenoid systems; while compounds with higher cd values may need higher temperatures. He has also shown that by tethering the two acetylenes into a 10-membered ring, there is a lowering of the activation energy for the Bergman cyclization[20.]

When compared with the cyclic ones, acyclic enediynes have a comparatively high cd-distance, which is much greater than the critical distance range required for spontaneous cyclization.[22] Therefore cyclic enediynes are more reactive than the acyclic ones. The

10-membered strained ring structure, cyclodeca-3-ene-1,5-diyne (1.34) (cd = 3.25) cyclised in the presence of cyclohexa-1,4-diene through BC to give tetralin(1.42) and the two adduct (**1.43**). However at 37^{o}C the cyclization proceeded with a half- life *(t / 2)* of 18h and a rate constant *(k,)* of 6.4 X 10-4/min. The structure **1.34**, may serve as a useful "warhead" in damaging molecular or cellular structures such as DNA and tumour cells without further activation[18].



Scheme 1.11: Cyclization of cyclodeca-3-ene-1,5-diyne[18]

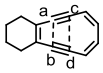
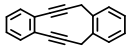
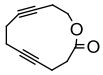
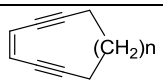
Entry	Compound	Ring Size	Strain Energy (Kcal\mole)	ab (Å)	Cd (Å)	Stability
1		10	21.20	2.51	2.99	spontaneous cyclization
2		10	19.71	2.54	3.01	spontaneous cyclization
3		10	16.50	16.50	3.03	spontaneous cyclization
4		10	15.52	2.56	3.17	should be stable at 25°C
5		10	16.42	2.65	3.36	should be stable at 25°C
6	1.184	10	22.67	2.55	3.16	cyclization
7	1.183	10	23.25	2.65	3.35	stable at 25°C
8		_	0.43	2.86	4.12	stable at 25°C
9		_	5.38	2.76	3.94	stable at 25°C
10		12	2.79	2.74	3.77	stable at 25°C
						
11	n = 1	9	14.80	2.51	2.84	should cyclise
12	n = 2	10	11.40	2.60	3.25	cyclises at 25°C
13	n = 3	11	8.96	2.72	3.61-	stable at 25°C
14	n = 4	12	7.60	2.80	3.90	stable at 25°C
15	n = 5	13	7.37	2.87	4.14	stable at 25°C
16	n = 6	14	8.21	2.87	4.15	stable at 25°C
17	n = 7	15	8.39	2.93	4.33	stable at 25°C
18	n = 8	16	11.35	2.88	4.20	stable at 25°C

Table1.1: MM2 calculations using Macromodel.
(Reported by Nicolaou *et-a.l*[18])

1.2.2 Magnus and Snyder Strain Theory[19, 23]

An alternate theory based on differential molecular strain between the GS and TS was proposed by Magnus and Snyder. Qualitative investigation led to the proposal that an

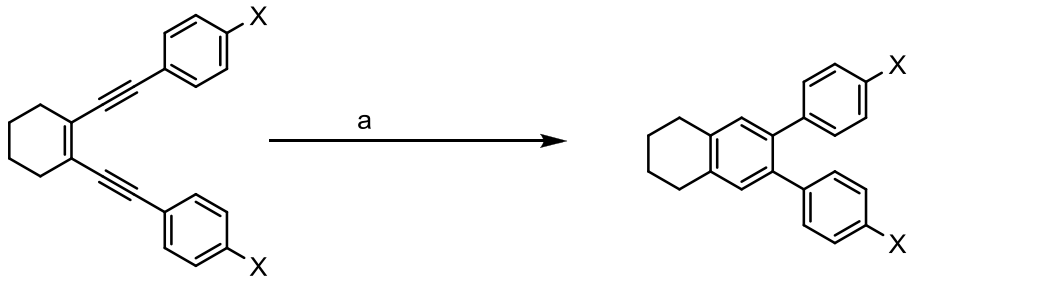
overall change in strain energy from enediyne to cycloaromatized adduct furnishes the closure driving force. Computational evidence has been given to prove that factors controlling the ease of cycloaromatization are directly related to strain energy in the transition state rather than to proximity of the acetylenic carbon atoms in the ground state. They concluded that the cyclization rates of bicyclic enediynes are best interpreted as governed by strain–energy modulation in the pseudocyclic transition state. In a broader context, it is the difference in strain energy between enediyne and the biradicaloid that determines the closure tendency. Although the strain theory appears to be more precise and is of general applicability, especially for strained cyclic systems, the distance theory has gained popularity and is more exploited because of its simplicity and user friendliness. Moreover, a recent DFT-based calculation suggests a correlation between the spontaneity of BC and the cd.

1.2.3 Controlling the rate of the Bergman cyclization.

In the design of analogues, considerable effort has been expended in determining and controlling the factors contributing to the ease of the cyclization step. Reducing the distance between terminal carbon atoms of the diyne (by the use of transition metal-ion complexation[1,2] and build- up of strain in the reactant are two strategies which have been successfully employed for improving the rate of BC. Other factors which have been indicated in the reactivity of the enediyne moiety include electronic effects[4, 24] (effects of substitution at the alkynic and vinyl positions) which have been found to play a crucial role in the BC, steric strain which can lower the activation energy and make cyclization possible at body temperature, ring size and concentration of the H atom donor[25].

1.2.4 Substitution at the Terminal Alkyne Position[1, 26]

The four-electron repulsion of two π bonds of the alkynes in the same plane necessitated large activation energy for the enediyne cyclization. It was predicted that electron-withdrawing groups in the alkynic position of an enediyne should reduce the electron- density of the alkyne π–orbitals, and lower the repulsion and activation barrier of the reaction. This prediction was confirmed by Schmittel *et al.,* in the reaction of **1.44** (Scheme **1.12**). Replacing the electron-donating methoxy substituents in **1.45** by electron-accepting nitro substituents in **1.46** led to a decrease in the activation enthalpy of the cyclization reaction. It is presumed that the cycloaromatization is accelerated by electronic stabilisation of the reaction intermediate.



T°C for t½ =71min

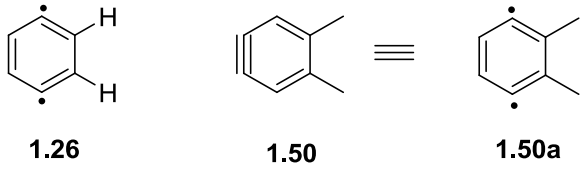
1.44	(X = H)	**1.47**	280
1.45	(X = OMe)	**1.48**	286
1.46	(X = NO_2)	**1.49**	250

reagents and conditions: (a) 240°C, 1,4-CHD, diphenylether

Scheme 1: 12: Substituent effect at the alkynic position

Schreiner *et al.*,[19] showed that the intermediate is "X-aromatic" and therefore, substituents that influence the sigma-framework of a molecule are the most effective in reducing the relative energies of the BC. Comparison of 1,4-benzyne (**1.26**) and 2,3-

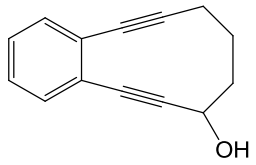
dimethyl-1,4-benzyne (**1.50**) shows that alkyl substituents at the alkynyl position have a large effect on the endothermicity of the BC (increases by about 12 kcal/mol) and stabilises the enediyne alkynes and disfavours a cyclization reaction. However ring strain in cyclic enediynes can overcome this effect[19, 22, 27]



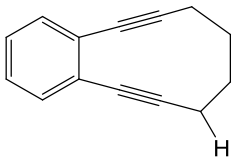
1.26 **1.50** **1.50a**

Figure 1.4: Substituted and unsubstituted *p*-benzyne

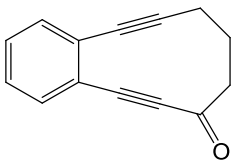
Electron-withdrawing substituents will however lower the cyclization barrier, thus if the methyl group is functionalised with a hydroxyl group in cyclic, benzo-fused systems, a small, but significant activation of the reaction is observed experimentally. The parent compound **1.52**, has a half- life of 24h at 84^{o}C while the alcohol **1.51**, decays with a $t_{1/2}$ = 4.5h, and the ketone,**1.53**, is even far reactive with a half life less than 1h at the same temperature[27]. Even though compound **1.54**, where the hydroxyl group is in the β-position to the triple bond is less reactive than **1.51**, however it is still more reactive than **1.52**



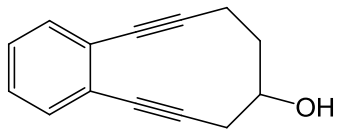
1.51



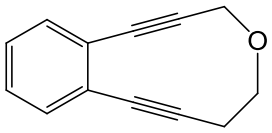
1.52



1.53



1.54

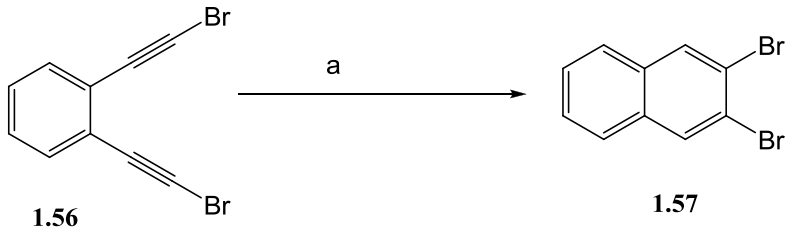


1.55

Reactivity: 1. 52 <1.51 <1.53, 1.54 < 1.51, 1.54 >1.51,

Figure 1.5: Functionalized cyclic 10-membered enediynes

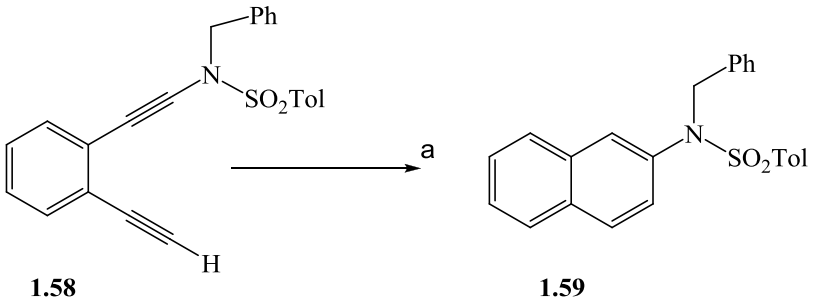
Halogenated and nitro derivatives of benzo-annulated enediynes also undergo cycloaromatization with ease when compared with the unsubstituted system. It was however noted that in addition to the electron-withdrawing effects of the halogen.



1.56 **1.57**

reagents and conditions: (a) 1,4-CHD, 180^{o}C, 70%

Scheme 1.14: BC of Halogenated benzo-annulated enediyne

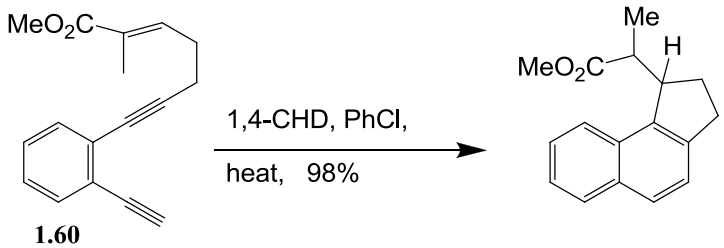


1.58 **1.59**

reagents and conditions: (a) 1,4-CHD, 141°C, 24 h

Scheme 1.15: BC of benzo-annulated enediyne sulphonamide

In another work Grissom *et al.,*[20, 21] carried out kinetic studies on the effect that substitution on the acetylene would have on the rate of cyclization. They found that the incorporation of one acetylenic substituent has a moderate effect of slowing the rate of the BC.



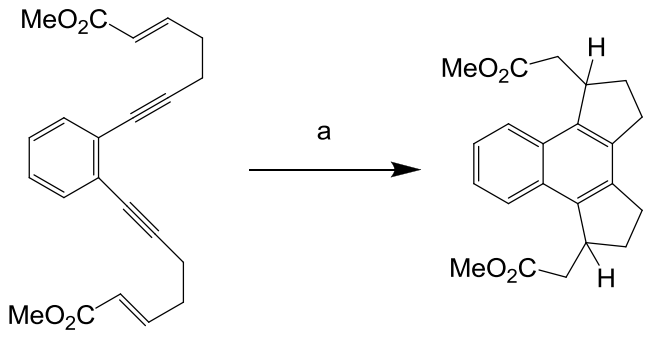
1.60 **1.61**

reagents and conditions: (a)1,4-CHD, PhCl, Δ, 98%

Scheme 1. 16; BC cyclization of substituted enediyne

The addition of a second acetylenic tether had a substantial effect on the rate of the BC. Both the 'cd-theory' and the Magnus theory may not adequately explain this observation. It is therefore assumed that steric factors would affect the rate of this cyclization. They argued that the acetylenic substituent may either push the acetylenes

apart or and distort the enediyne system from planarity; both effects will increase the energy of activation of the enediyne cyclization. This effect would be most pronounced for the substrate with two acetylenic substituents.



1.62 **1.63**

reagents and conditions: (a)1,4-CHD,PhCl, Δ, 99%

Scheme 1.17: BC cyclization of highly substituted enediyne:

1.2.5 Substitution at the Vinyl position [1, 22, 24, 27-29]

Jones *et al.,* carried out studies on the effect of vinyl substitution on cycloaromatization of the enediynes, the summary of the data obtained indicated that strongly σ-electron-withdrawing groups increase the cyclization barrier, thus inhibiting BC while σ-electron-donating groups decrease the cyclization barrier, π conjugation, especially donation, has little effect.[1] In a key example the bicyclic enediyne **1.64**, a highly reactive molecule cyclises spontaneously at room temperature while the introduction of phenylmethylether, an electron donor group was shown to retard cycloaromatization, possibly by stabilizing the ground state of the enediyne.

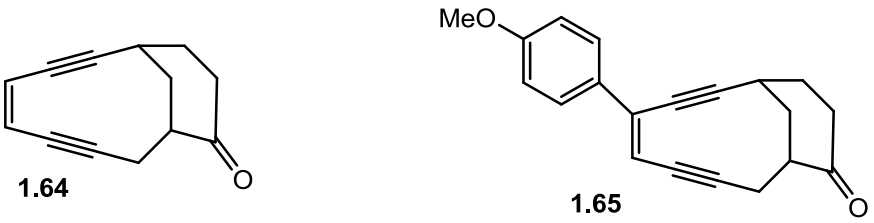
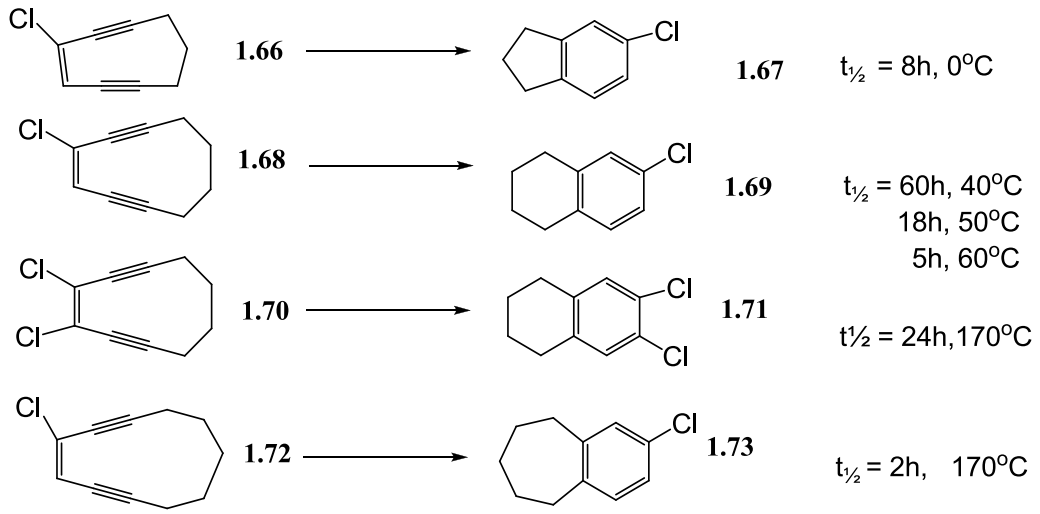


Figure 1.6: Alkene substitution in cyclic enediyne

This observation prompted further research into the effect of heteroatoms directly attached to the vinyl position[29]. It could be expected that the combination of inductive and electronegative effects may exert a unique influence on cycloaromatization, either by destabilizing the ground state or stabilizing the transition state of the process.



reagents and conditions: (a).CHD

Scheme 1.18: Thermal BC of Cyclic Haloalknyl Enediynes

As illustrated in scheme **1.18**, substitution of the vinyl bond with chlorine (halogens) (**1.68**) causes a decrease in the rate of cyclization. Cycloaromatization of the C-9 enediyne has a half-life of 8h at 0°C despite the fact that the unsubstituted parent molecule cyclised spontaneously at room temperature. The same is found for the C-10

enediyne series: the rate of cyclization is slower for the chloro-substituted than the unsubstituted molecule. Addition of a second chlorine molecule such as in **1.70** has an additive effect which significantly retards the reaction rate further.

The origins of the stabilizing effect are presumably electronic in nature, since molecular modelling (PM3) of **1.68** and **1.70** reveals essentially no difference in intermolecular cd distances. (3.298 Å and 3.297 Å, respectively and 3.293 Å for the unsubstituted enediyne.) This effect is most pronounced in C-9, **1.66**, with a cd distance of 2.864 Å, it is expected to undergo spontaneous cyclization in the absence of an electronic stabilizing effect. Jones *et al.,* gave three possible factors that could be responsible for these observations:

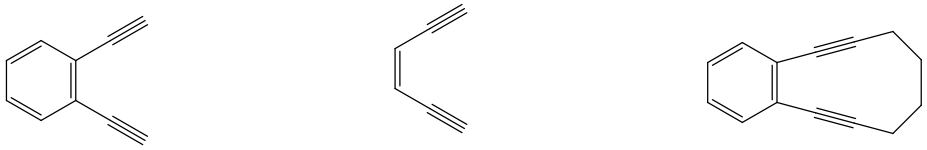
(1) the cyclization barriers are higher for the chloro-substituted compounds,

(2) the *p*-benzyne ring opening barriers are lower for the chloro- substituted cases, and

(3) the chloro- substituted *p*-benzynes are relatively more stable to H atom abstraction which extends their half-life, thus increasing the likelihood of cycloreversion. Computational work using DFT established that the observed decrease in the rate of chloro-substituted compounds is based on their higher cyclization barriers. It is important to note that apart from serving as cycloaromatization modulators, the presence of the halovinyl substituent offers potential in the synthesis of substituted arene products[27].

1.2.6 Benzo-Annulation[1, 4, 25, 26, 27]

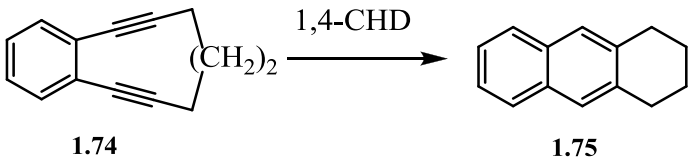
Benzo-annulation is another form of vinyl substitution which resulted in a marked increase in the cyclization barrier, that is, a lower reactivity than in the parent chain, especially for cyclic enediynes.



1.33 **1.27** **1.52**

Figure 1.7. Simple and benzannulated enediynes.

In the example above **1.27** (Ea = 28.2kcal/mol) is more reactive than **1.52** as expected, however confusion exists regarding the effects of simple benzannulation since **1.33** is found to cyclise more rapidly (Ea = 25.1kcal/mol) than **1.27**. Many factors are responsible for this observation; paramount is the fact that the hydrogen abstraction step is especially important in benzannulated enediynes where the BC is approximately 10 kcal/mol more endothermic than that of the parent enediyne and thus the barrier for the retro-Bergman ring opening of *p*-benzyne is small. This led the author to suggest that the apparent rate of cyclization for benzannulated enediynes depends on the concentration of an H-atom donor which may vary from one investigation to the other. To circumvent this problem, investigations could be carried out in large concentration of an H-atom donor or using a very reactive H- atom donor. Semmelhack *et al.,*[25, 26] in a separate study also confirmed the dependence of the cyclization on the concentration of the trapping reagent, 1, 4- CHD as shown in Scheme **1.19** and table **1.2** below;



1.74 **1.75**

reagents and conditions: (a)1,4-CHD

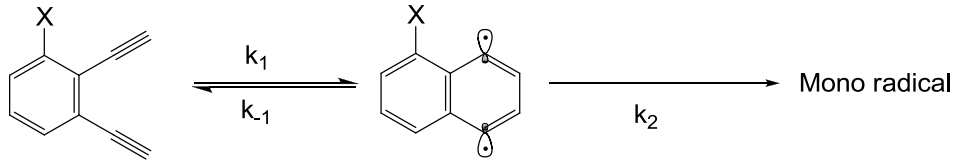
Scheme 1.19: Study of dependence of rate on H atom donor concentration

Entry	1,4-CHD conc (M)	t½
1	0.00	129
2	0.25	39
3	0.50	24
4	10.50 (neat)	10.5

Table 1.2: Dependence of rate on concentration of H atom donor.

Frank *et al*.,[4] developed a simple kinetic model (eq **1**, Scheme **1.20**), that describes the effects of the rate of H atom abstraction on the rate of disappearance for the enediyne reactant.

$$k_{eff} = k_1 \frac{k_2 [HD]}{k_2 [HD] + k_{-1}} \quad \text{Eq.1}$$

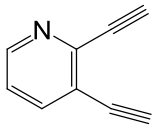


1.76 1.77

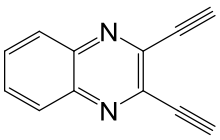
reagents and conditions: (a) 1,4-CHD

Scheme 1.20: Kinetic Model of BC of Ortho Substituted Enediyne.

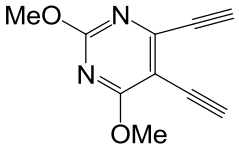
The presence of heteroatoms within the aromatic ring interestingly showed inconsistent effects on the rate of cyclization reactions, pyridine, **1.78** was more reactive, (Ea = 21.5Kcal/mol), while quinoxaline, **1.79** was less reactive, (Ea = 33.6 kcal/mol) than **1.33** and pyrimidine **1.80,** was even more reactive, (Ea = 16.1kcal/mol)



1.78



1.79



1.80

Figure 1.8: Examples of enediynes with hetero-atoms.

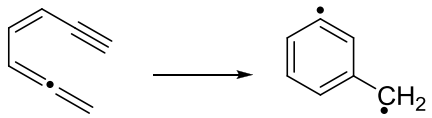
In conclusion, substitutions in the terminal alkyne position generally affect enediyne cyclization more than substitutions in the vinyl positions. The effect of benzo-fusion on the thermal reactivity of enediynes is inconsistent. While benzo-fused acyclic enediynes are activated for cyclization, in cyclic enediynes the reaction is disfavored. Substitution of the fused benzene ring has very slight effect on reactivity. Complex heterocyclic systems however showed poor correlations.

1.3 Myers-Saito Cyclization Reaction

1.3.1 Myers Reaction[31-35]

The discovery of the biradical mechanism in neocarzinostatin eventually leading to an effective DNA cleavage emphasized the importance of the enyne [3] cumulene core A in the reactive form of this natural antitumor antibiotic. This discovery prompted Myers *et al., into* further investigations into the enyne-allenes. The first order thermal

cycloaromatization of (Z)-1,2,4-heptatriene-6-yne **1.81**produced an intermediate that could be represented as α,3-dehydrotoluene biradical through a C^2-C^7 cyclization.

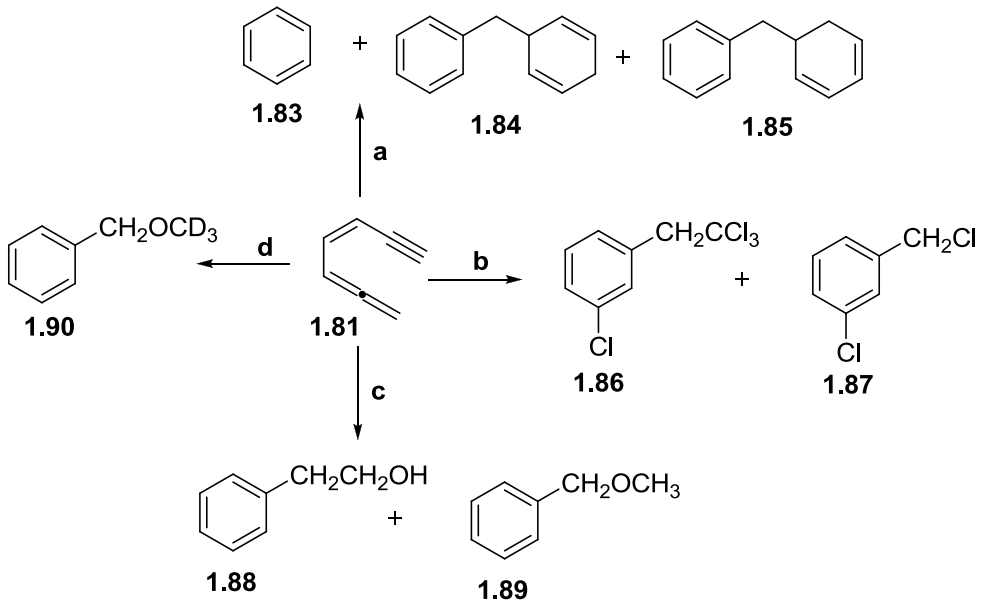


1.81 **1.82**

reagents and conditions: (a) Δ

Scheme 1. 21: Myers-Saito cyclization

Mild thermolysis of **1.81** (0.003M) in deoxygenated 1,4-cyclo-hexadiene produced toluene **1.83** and combination products **1.84** and **1.85**. Heating the compound in carbon tetrachloride solution at 100 ^oC produced the adduct 1-chloro-3-(2,2,2-trichloroethyl) benzene **1.86** and 3-chlorobenzyl chloride **1.87,** in a combined yield of 15-25%. The low yield here may be due to the poor trapping of the intermediates by carbon tetrachloride leading to competitive radical- induced polymerization of **1.81**. Pyrolysis experiment of **1.81** in methanol (0.003M, 100 ^oC, 30 min) led to the formation of products consistent with both polar (methyl benzyl ether **1.89**, 35%) and the free radical (2-phenylethanol, 10%, bi-phenyl, 2%) reaction pathways. When compound **1.81** was heated in deuterated methanol (0.003 M), methyl-*d*3 benzyl ether was formed exclusively in 70% yield.



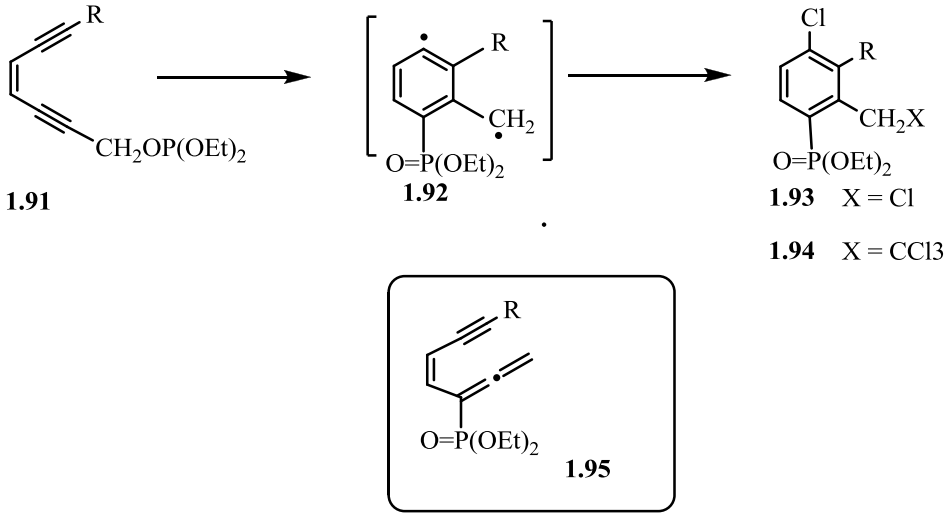
reagents and conditions: (a), 1,4-cyclohexadiene,(b) CCl_4, Δ (c) MeOH, Δ (d) CD_3OH,Δ

Scheme 1.22: Biradical trappings in the Myers reaction.[33]

1.3.2 Saito *et al.* reaction.[36-38]

Saito *et al.,* stimulated by the involvement of BC in DNA cleavage of the natural antitumor antibiotics, consequently studied the design of a simplified DNA cleaving molecule which mimics the mechanism of the action of these antibiotics. They postulated that if one of the acetylenes in acyclic enediyne system is replaced by allene (acetylene equivalent), the distance between the two acetylenes could be reduced to a range close enough for spontaneous cyclization at ambient temperature. The success of such reactions would facilitate the formation of new antibiotics by lowering the activation energy of cyclization (and therefore biradical formation and DNA scission) to physiologically relevant values. Consequently eneyne allenes activated with diphenylphosphonate group were targeted for synthesis. The allenyl part was introduced into the molecule by using [2, 3]-sigmatropic rearrangement of propargylic phosphite or

phosphinite to allenyl phosphonate or phosphine oxide. The first attempt to obtain the eneyne-allenyl phosphonate **1.95** failed and instead a mixture of cyclised compounds (**1.93 & 1.94**) was obtained (Scheme **1.23**).



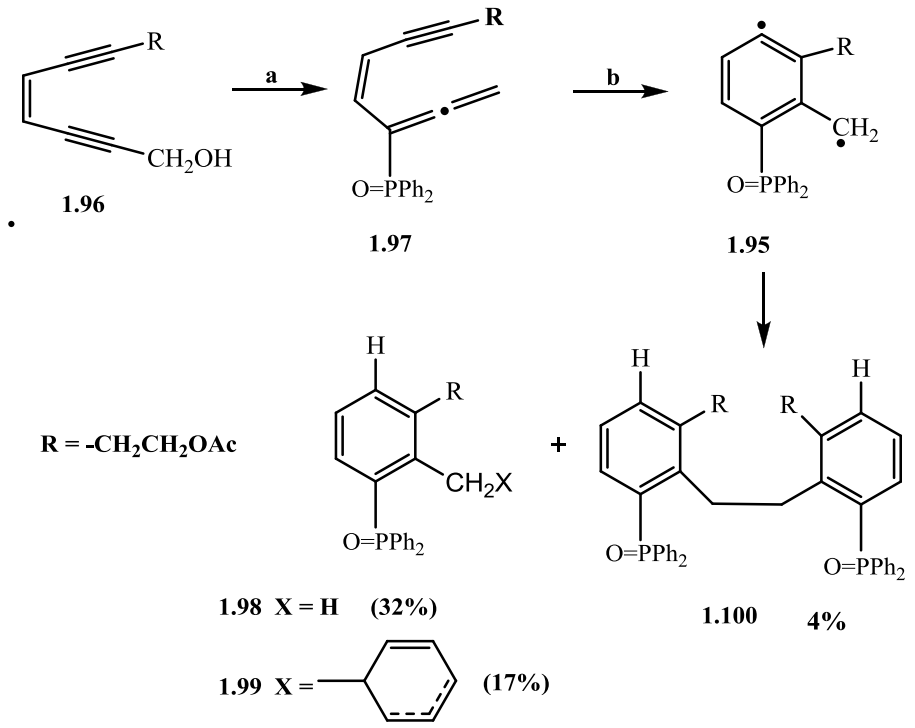
reagents and conditions: (a), CCl4, 45°C, 1.5 h

Scheme 1.23: Saito reaction.

It however appeared that both **1.93** and **1.94** were formed from biradical **1.92** which might have been formed by Bergman type cyclization of the allenyl phosphonate **1.95**. Compound **1.97** was obtained from the treatment of **1.96** with chlorodiphenylphosphine and triethylamine in hexane at -78°C to 0°C. In order to confirm whether the eneyne-allene system actually undergoes spontaneous cyclization to generate biradical **1.92**, **1.97** was heated at 37°C in benzene in the presence of 1,4-CHD. The reaction produced the expected aromatised products 1.**98, 1.99** and **1.100** after 5 h. Deuterated studies using 5:1 THF-d_8 – H_2O at 60°C confirmed that the reaction actually proceeded through the formation of the biradical intermediate, in analogy with the cases of antibiotics, neocarzinostatin, esperamicin and calicheamicin.

The importance of the Saito reaction lies in the fact that compound **1.97**;

- could readily be constructed by a simple three step operation,
- is stable enough to be handled at ambient temperature but at body temperature generates reactive biradical species in an appreciable rate,
- is structurally simple, and this might allow suitable modification of its substituents for the design of a DNA cleaving molecule.

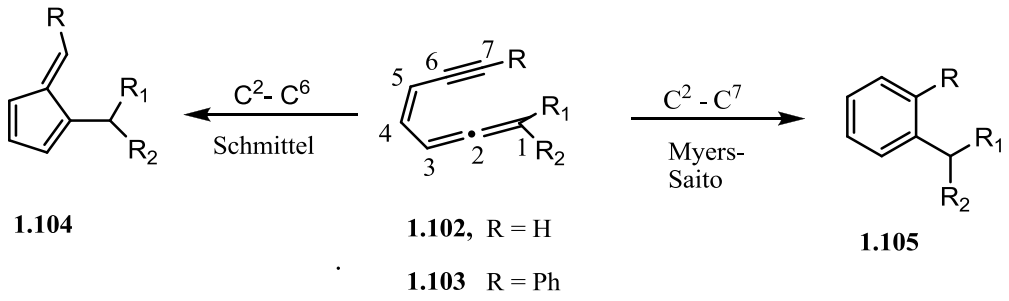


reagents and conditions: (a) chlorodiphenylphosphine, triethylamine, -78 - 0°C, (b) 1,4-CHD, 37°C, 5 h.

Scheme 1:24 Radical quenching in Saito

1.4 The Schmittel Reaction[39-65]

The synthetic potential of thermal enyne-allenes reactions was extended when Schmittel and co-workers found quite unexpectedly that the simple attachment of an aryl group or sterically bulky groups (e.g, *t*Bu, $SiMe_3$) to the terminus of the enyne allenes caused a complete switch from the Myers-Saito C2 - C7 cyclization to a C2 - C6 cyclization, giving rise to a formal ene and Diels-Alder products. Simple replacement of the H atom at the acetylene end of **1.102** with a phenyl group in **1.103** switched the reaction (Scheme **1.25**) from Myers-Saito to Schmittel cyclization.

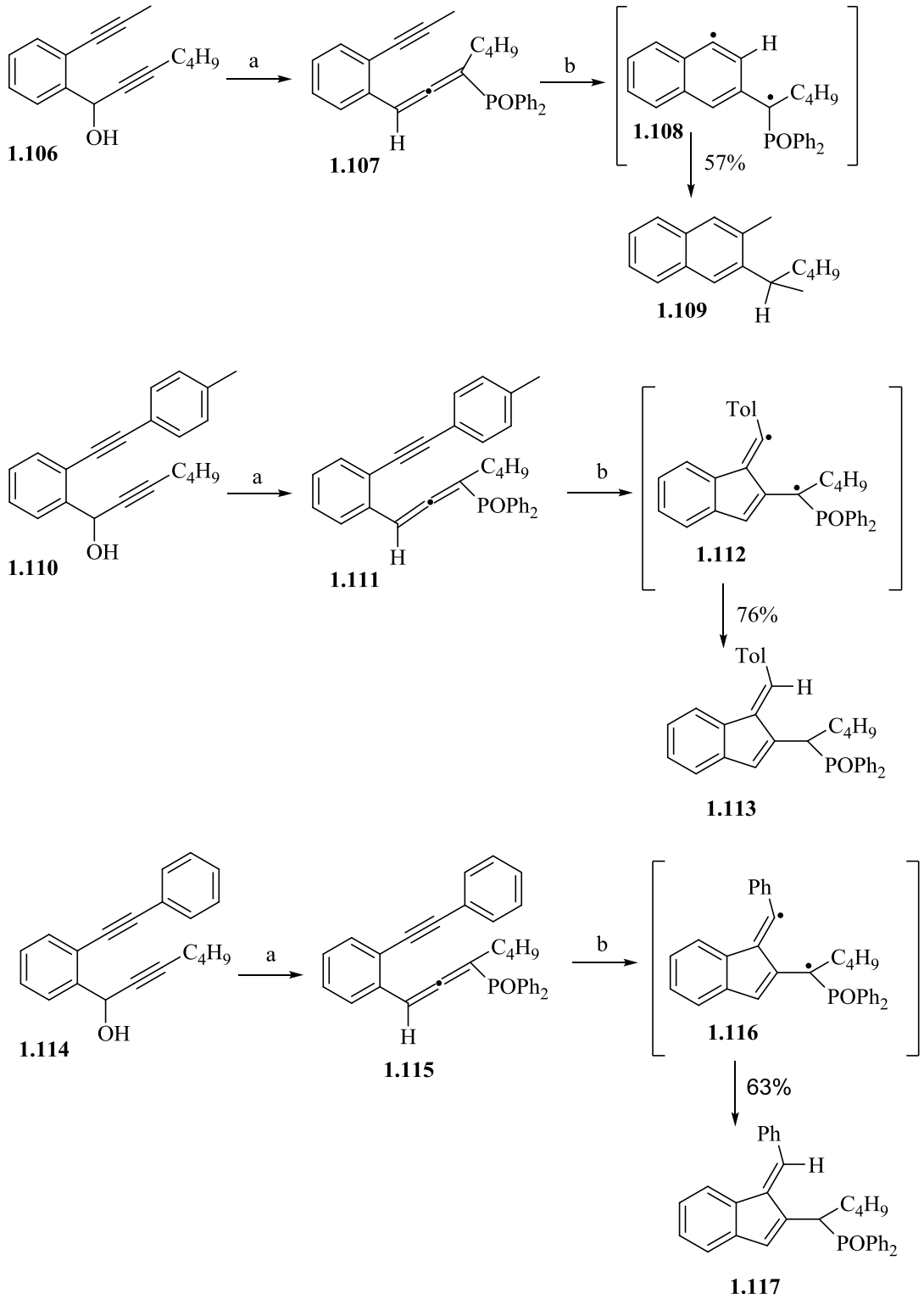


1.104 **1.102,** R = H **1.103** R = Ph **1.105**

Scheme 1.25: Switch from Myers – Saito to Schmittel cyclization.

Upon investigation of the reaction, further additional bulky groups were introduced at the allene and alkyne units, e.g. alkyl chains and or aryl groups at C1 and C7. Rearrangements of the propargyl alcohols (**1.106, 1.110,** and **1.114**) with chlorodiphenylphosphine afforded the enyne-allenes (**1.107, 1.111,** and **1.115**) with the sterically encumbering diphenylphosphinoxide units at C7 unit. These were heated with excess of 1,4-CHD in toluene for several hours. The thermal rearrangement of **1.107** produced the naphthalene derivative **1.109** in a typical Myers cyclization (C^2-C^7) at 50°C (t½ = 1 h), while **1.111** rearranges at 84°C (t½ = 1 h) in a typical Schmittel cyclization (C^2 – C^6). Even though compound **1.115** could not be isolated, the indene

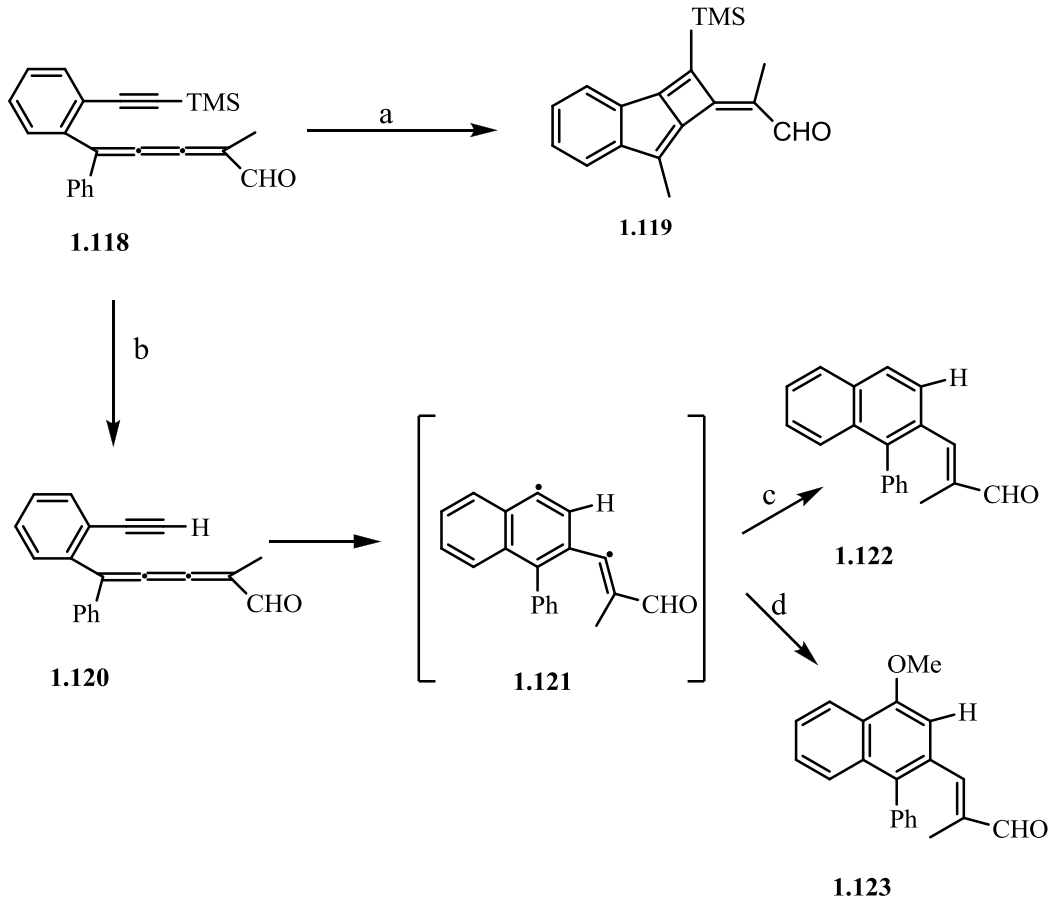
1.117 was obtained on warming up to room temperature. Initially it was thought that the switch in the mode of the reaction is as a result of the stabilising effect of the aryl group on the vinyl radicals, further investigation clearly shows that replacement of the hydrogen at the acetylene unit by a phenyl group raises the barrier of the Myers cyclization significantly, presumably by steric hindrance and ground state stabilization of the acetylene moiety.



reagents and conditions: (a) $PClPh_2/NEt_3$, -78 °C, (b) 1,4 CHD, (c) $PClPh_2$/LDA, -78 °C

Scheme 1.26: Thermal reactions of enyne-allenes (1.107, 1.111, 1.115)

A similar investigation on the effect of steric hindrance was carried out by Rodriguez *et al.* [42] .They demonstrated that the incorporation of the TMS group on the acetylene unit of an enyne [3] cumulenals selectively favoured Schmittel cyclization over the Myers–Saito cyclization.

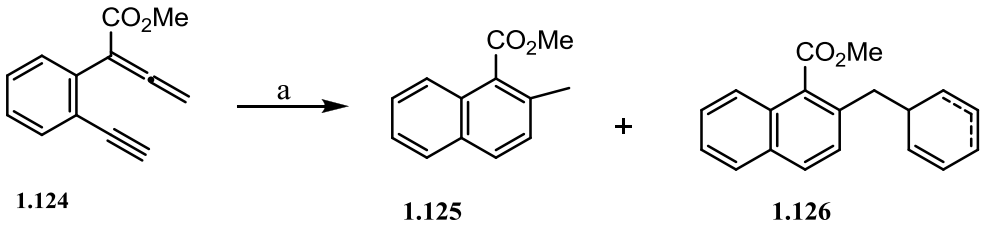


reagents and conditions: (a) toluene, 110 ^{o}C, (b) K_2CO_3, MeOH, (c) toluene, 1,4 –CHD, 60 ^{o}C, (d) toluene, MeOH, 60 ^{o}C

Scheme 1.27: Effect of steric hindrance on mode of cyclization

According to Gillmann *et al.,*[45,50,51,62] enyne allene bearing electron-withdrawing substituents seems to be able to initiate DNA cleavage not only by radical mediated steps but also by way of alkylation. An ester function may also provide the molecules with a flexible site that allows for an attachment of DNA recognition elements. This

dual mode of action prompted further investigation into the enyne allene esters and the compounds appeared to be promising substrates for the elaboration into anticancer drugs operating by either mechanism. Thermolysis of **1.124** (0.02 M) in chlorobenzene in the presence of 1,4-CHD (1.0 M) for 3h at 70°C yielded the cycloaromatization products **1.125** 8% and **1.126** (9%, mixture of regioisomers) in accordance with Myers cyclization.

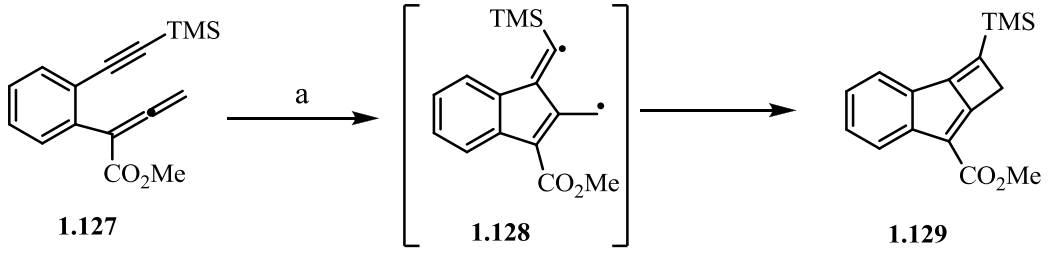


1.124 **1.125** **1.126**

reagents and conditions: (a) 1,-4 CHD, Chlorobenzene, 70°C, 3 h

Scheme 1.28: Allene ester work by Gillmann *et al.*

However heating the silyl derivative **1.127** (0.02 M) in chlorobenzene in the presence of 1,4-CHD (1.0 M) for 3 h at 70°C resulted in the formation of the tricyclic product **1.129** in 62% which is an isomer of **1.127**. Therefore hydrogen atom donor is not required for the reaction.

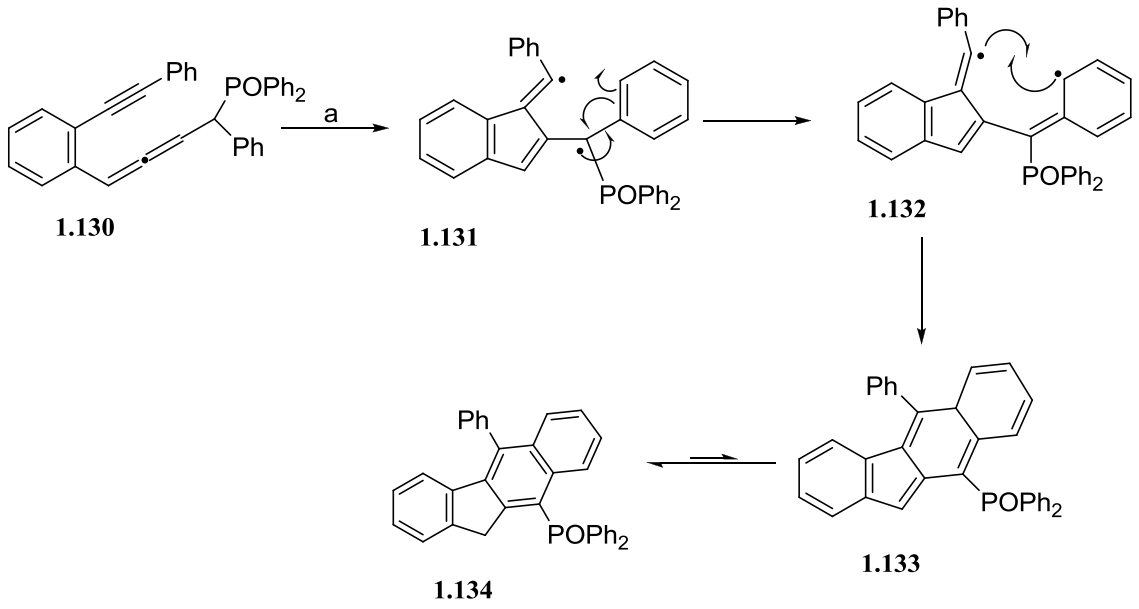


1.127 **1.128** **1.129**

reagents and conditions: (a) 1,-4 CHD, Chlorobenzene, 70°C, 3 h, 62%

Scheme 1.29: Allene ester work by Gillmann *et al.*

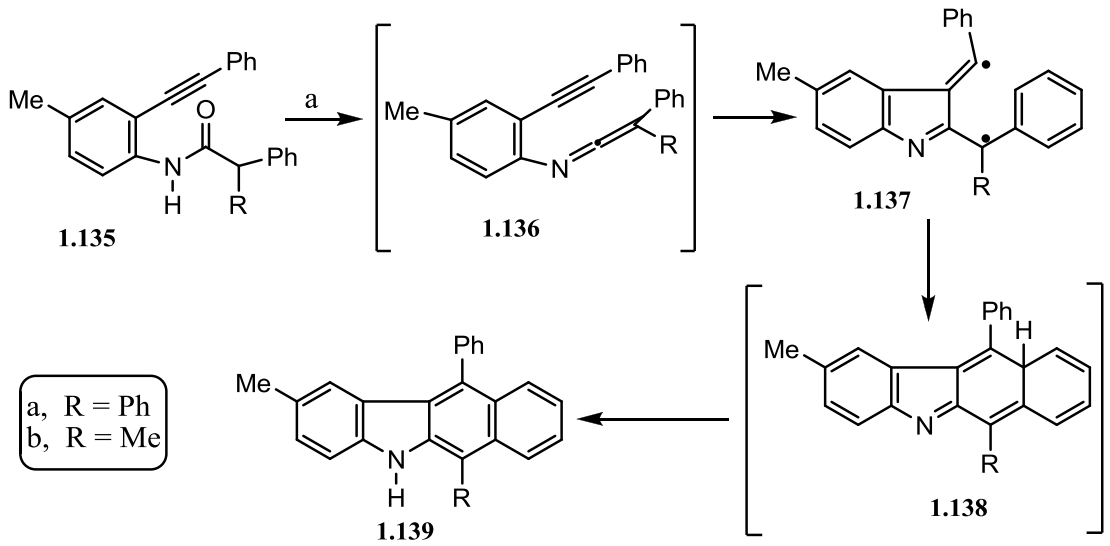
Further work by Schmittel *et al.,* also showed that the biradical intermediate could easily lead to ene- and Diels-Alder type products[43] depending on the nature of the R_2 in **1.103**, that is the biradical intermediate can react in an intramolecular way to give formal [4+2] or [2+2] cycloadducts and ene products. It is therefore a versatile intermediate for the construction of various ring systems.



reagents and conditions: (a) 1,4-CHD, Toluene,60-70 ^{o}C, 63%

Scheme 1.30: Intramolecular trapping of radicals

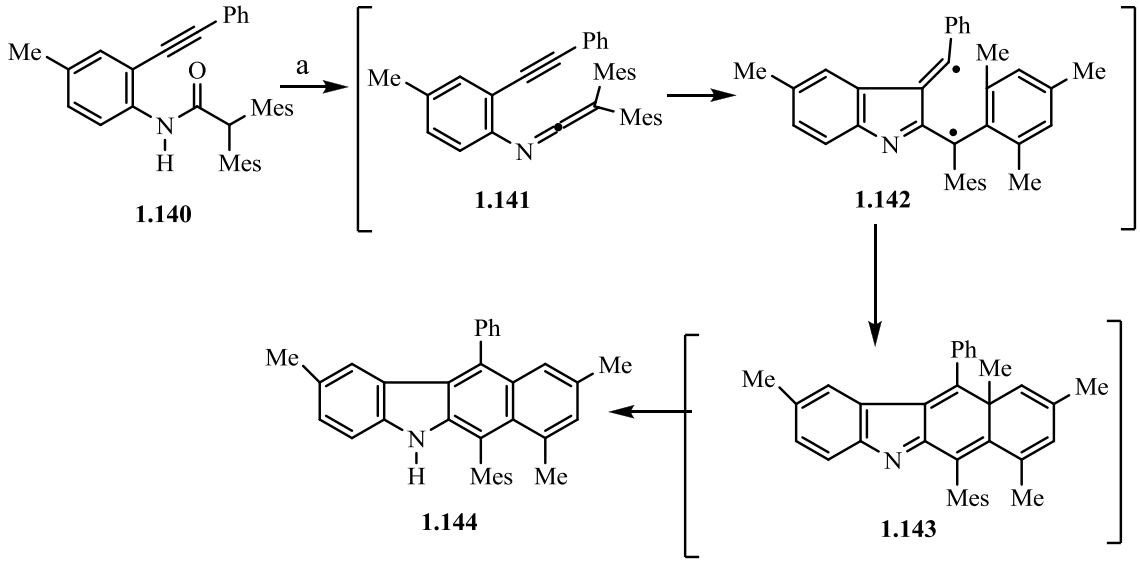
The synthetic value of the reaction was increased by replacing the CHn groups in the enyne allene by heteroatoms.[56]



reagents and conditions: (a) Ph_3P, Br_2, NEt_3, CH_2Cl_2,

Scheme 1.31: Synthesis of benzocarbazole, 1.139

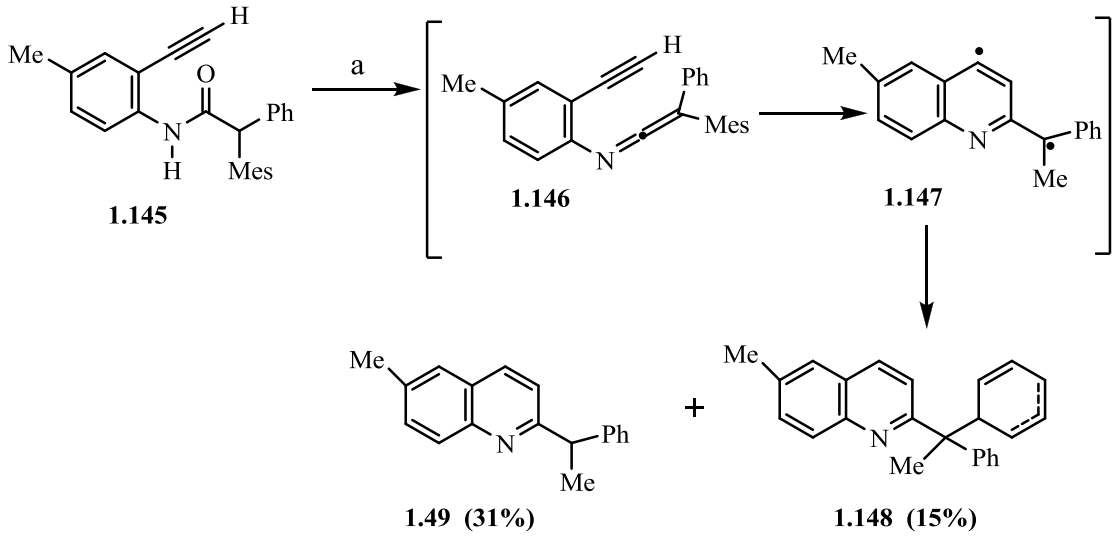
Schmittel *et al.,*[56, 57] proved theoretically through DFT calculations that the enyne-ketenimines can undergo either C2 – C7 and C2 –C6 cyclizations and suggested that a change in the regioselectivity of enyne-ketenimine cyclizations is a function of the substituents (R) attached to the alkyne terminus. To probe this prediction, many enyne-ketenimines were prepared in addition to **1.135.** Cyclization of **1.135** gave the expected product **1.139** (Scheme **1.31**). Similar cyclization was also reported by Ghosez and Differding.[58] In order to demonstrate experimentally that biradical **1.137** is an intermediate, both phenyl groups in enyne-ketenimine **1.136b** were replaced by mesityl substituents (Scheme **1.32**). It is well established that concerted Diels – Alder reactions are prevented by *ortho*-alkyl substituents because of steric hinderance,[59,60 ,61] therefore the only option is a stepwise formal Diels-Alder cycloaddition. Transformation of **1.141** to **1.144** gave strong evidence for the existence of the biradical intermediate **1.142**.



reagents and conditions: (a) Florisil, P_2O_5, 1,4-CHD, pyridine, reflux, 30 h (61% of **1.140** recovered)

Scheme 1.32: Synthesis of benzocarbazole, 1.144.

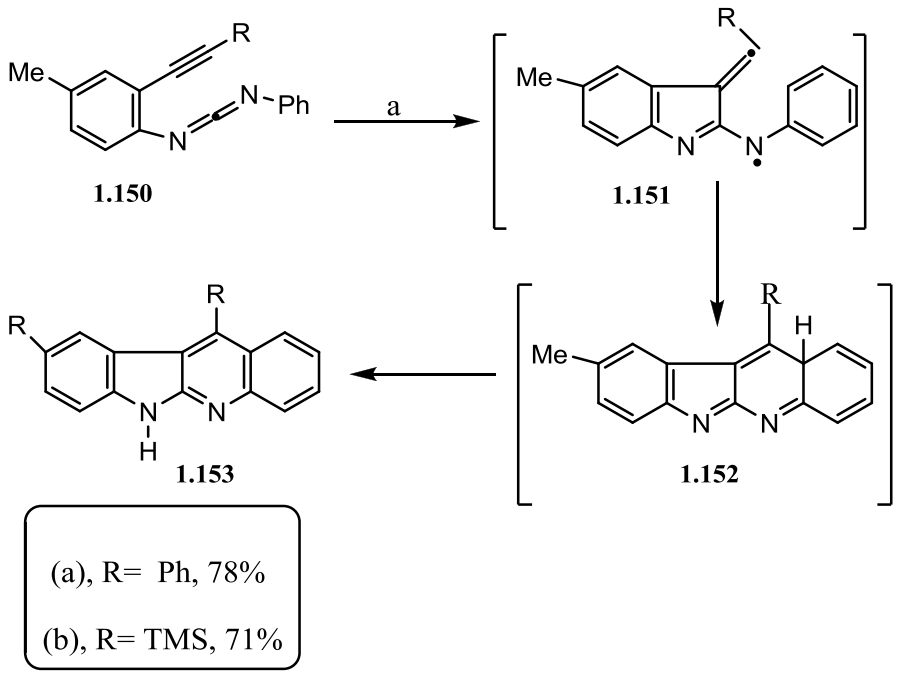
Removal of the bulky phenyl on the acetylene terminus gave the C2 – C7 type cyclization products **1.148** and **1.149.** The latter being a product of addition of biradical intermediate **1.147** to the hydrogen atom donor present (1,4-cyclohexadiene, 1,4-CHD).



reagents and conditions: (a) Florisil, P_2O_5, 1,4 CHD, pyridine, reflux, 3 h

Scheme 1.33: Effect of the removal of bulky group

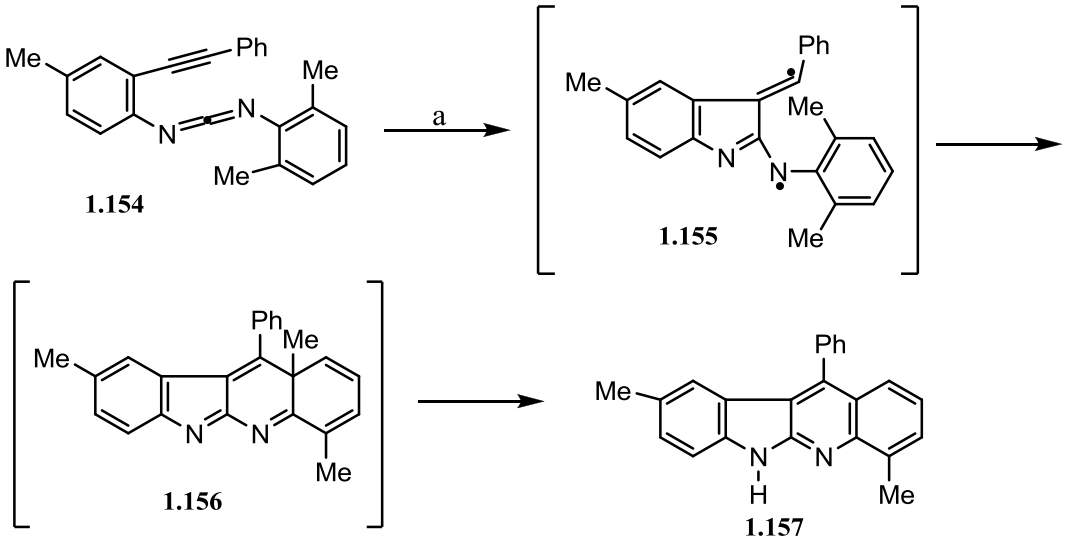
A similar switch in regioselectivity of biradical cyclization from a C2- C7 to C2 – C6 was again demonstrated with the use of enyne-carbodiimides **1.149** (Scheme **1.34**)



reagents and conditions: (a) a, R = 1,4-CHD, toluene, reflux,6 h: b, R = 1,4-CHD, mesitylene, reflux, 18h

Scheme 1.34: Cyclization of enyne carbodiimide

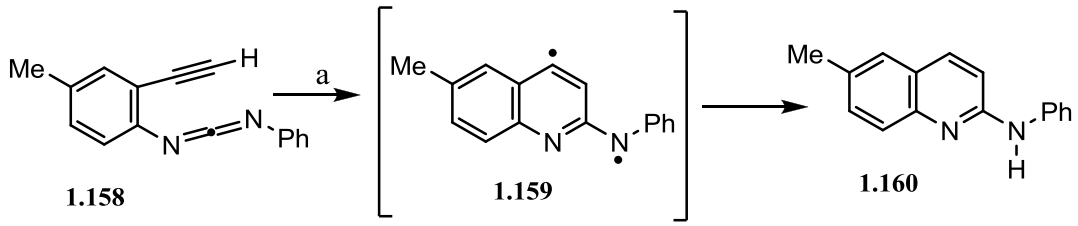
This reaction (scheme **1.34**) is not particularly good proof of the occurrence of a biradical cyclization, since the product could also have been formed in a concerted Diels-Alder reaction by skipping **1.151** To add further credence to the biradical cyclization, the phenyl group at the carbodiimide terminus was replaced by a 2,6-dimethyl phenyl group giving an *ortho*- alkyl substituted compound **1.154**. The product **1.157** is a confirmation of the C2-C6 biradical cyclization.



reagents and conditions: (a) 1,4-CHD, toluene, reflux, 2 h.

Scheme 1.35 Cyclization of *ortho*-alkyl substituted carbodiimide

The effect of substituent on the mode of cyclization was again tested, and it was also found that replacement of the bulky group at the alkyne terminal again switched the reaction mode from C2-C6 to C2-C7 (Myers- Saito cyclization).

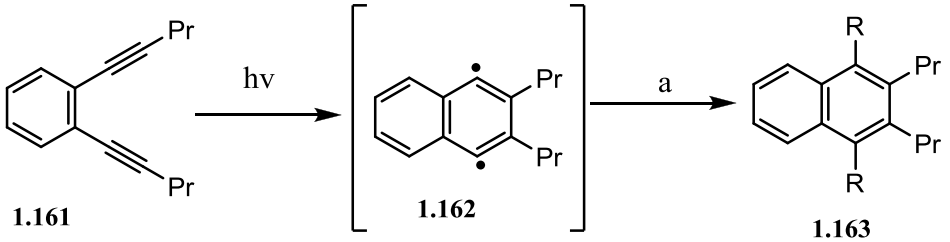


reagents and conditions: 1,4-CHD, toluene, 90-100 ^{o}C, 20h

Scheme 1.36: Switch to C^2-C^7 mode of cyclization

1.5 Photochemical Induced Cyclization Reaction[66-72,178-182.]

It has long been recognised that the emergence of photochemical reactions of the enediyne systems could offer a number of interesting features, both of mechanistic and biological significance[66, 67]. Direct irradiation of an enediyne functionality to afford a Bergman-type of product was first carried out by Turro *et al.,*[66] in 1994.



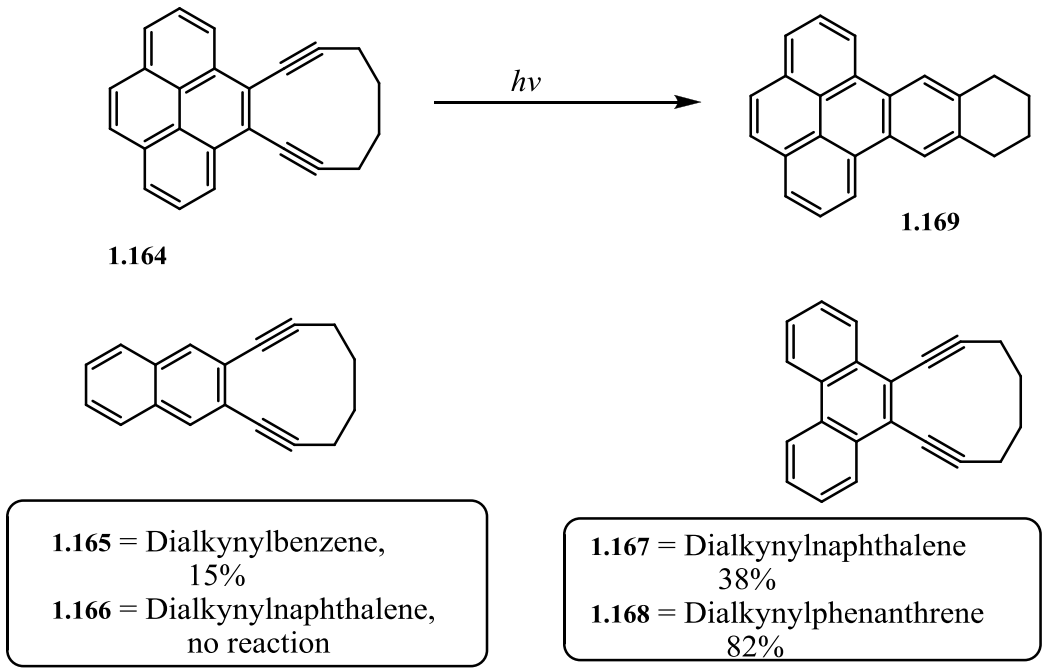
reagents and condition: (a) Solvent or other radical

Scheme 1.37: Photochemical analogue of BC.

Positive results were obtained for a good number of enediynes used and they concluded that the photochemical reactions differs from the thermal analogue mainly in that the former seems to arise as a result of excitation of an acetylenic unit rather than of a conjugate effect[67]. They determined that their result was of potential relevance to the design of photochemical analogues of the thermally active antibiotic antitumor natural products which would possess an advantage of being stable over a large temperature range, and could be structurally tailored to specific site delivery and specific spatial excitation by optical fiber techniques.

Funk and co-workers[68] prepared various dialkynylarenes (**1.164 - 1.168)** (Scheme **1.38**) to test the effectiveness of the photochemical reactions against the thermal Bergman reaction. All the compounds except **1.166** underwent photochemical cycloaromatization

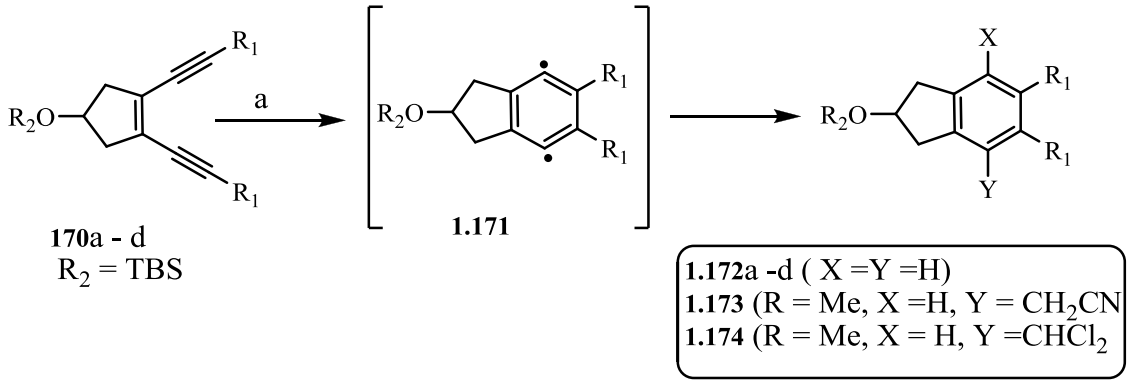
upon irradiation in the presence of 1,4-CHD. Cyclization of **1.164** is the most efficient and could actually be affected in sunlight (CH_3CN, 3 h, Pyrex) in quantitative yield. The rate of transformation is highly dependent on the concentration of the hydrogen donor. Terminal acetylenic compounds (9,10-diethynylhenanthrene and 4,5-diethynylpyrene did not undergo photochemical cycloaromatization.



reagents and conditions: 1,4-CHD, CH_3CN or Et_2O or CH_3COCH_3

Scheme 1.38: Photochemical cyclization

Hirama and co workers,[69] extended the application of photochemical cyclization to non-benzenoid enediynes. It was observed that enediynes possessing bulky substituents trimethylsilyl (TMS) and phenyl at the alkyne terminals did not undergo any cycloaromatization reaction and that the photo-cycloaromatization took place in a variety of solvents (but not in MeOH).



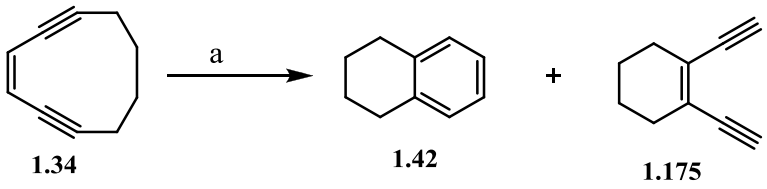
reagents and conditions: (a) *hv* (254nm), *n*-C_6H_{14}, 3.6 mM, RT

Scheme 1.39: Photoreaction of 1,2-diethynylcyclopentene

Substrate (170)	R	Yield (%)	Time (t)
a	Ph	no reaction	**18**
b	TMS	no reaction	**18**
c	H	3	**6**
d	Me	71	**18**

Table 1:3 Effects of substituent groups on cyclization.

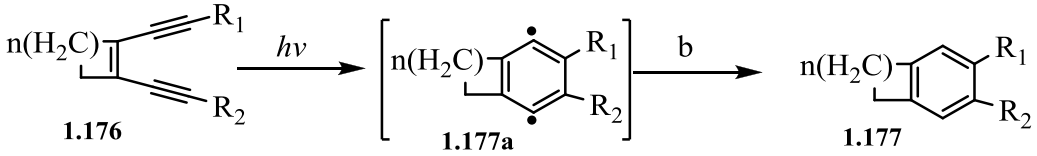
The strained ten-membered cyclic enediyne also cyclised when irradiated with a low pressure mercury lamp at room temperature for 3 h.



reagents and conditions: *hv* (254 nm), solvent, 3 h, RT.

Scheme 1.40: Photoreaction of a strain ring

Jones *et al.,*[72] also studied the photochemical activity of some enediynes, however they also deviated from using benzenoid enediynes but rather used designed alicyclic enediynes (**1.176**).

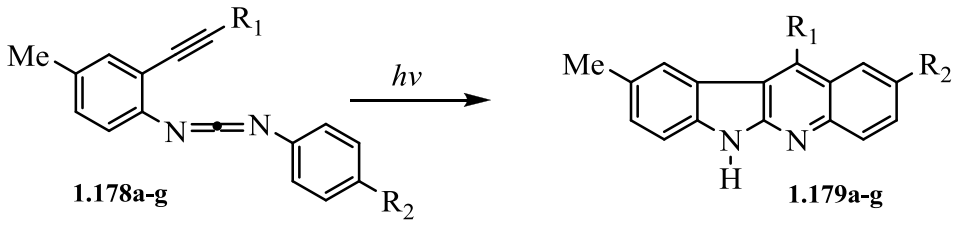


reagents and conditions: (a) *hv*, (b) 1,4 CHD or *i*-PrOH

Scheme 1.41: Photochemical cyclization of alicyclic enediynes

Consistent with other studies, **1.176** also undergoes photochemical cyclization, even though it is stable at room temperature. Optimal yields of cycloaromatization product were obtained using *iso*-propanol.

Schmittel and co workers[40] also carried out extensive studies on the photochemical reactions of enyne-carbodiimides and enyne- ketenimines. They observed that **1.178** cycloaromatized partially when exposed to sunlight for a very long period. Consequently the photochemical activity of various substituted carbodiimides was examined in different solvents and it was proposed that such cyclization provided evidence for a triplet cyclization.



Scheme 1.42 : Photocyclization of enyne-carbodiimide

1.178	**a**	**b**	**c**	**d**	**e**	**f**	**g**
R_1	Ph	H	$NO_2C_6H_4$	*p*-NCC_6H_4	*p*-$MeOC_6H_4$	TMS	Ph
R_2	H	H	H	H	H	H	NO_2

Table 1.4: R_1 and R_2 in Compound 1.178a-g

The importance of photochemical inducement in the BC - DNA cleavage cannot be over emphasized. Of recent, Tanaka *et al.,*[180] found out that the attachment of a photosensitive triggering moiety to an enediyne led to a sharp increase (100 fold) in its potency for DNA cleavage in an *in-vitro* assay compared to the enediyne without the triggering moiety. They also found out that photopromoted cycloaromatization is an effective way to control the biradical formation of enediynes. Poloukhtine *et al.,*[181] and Genovia *et al.,*[182] both concluded that photochemical BC is a common strategy employed to selectively activate enediynes and also allows a spatial selectivity of antibiotic action.

1.6 The Natural Antitumor Antibiotics[81-85, 178, 182].

In the mid to late 1980s, it became clear that an emerging series of naturally occurring antitumor antibiotics, calicheamicin, esperamicin, dynemicin, kedarcidin chromophore and C-1027 chromophore, all possess the enediyne core and mostly operated through the BC[1,2,11,24-26]. In addition to the five above, neocarzinostatin (NCS) chromophore

which does not contain the classical conjugated enediyne system also demonstrated very similar DNA cleavage mechanism once activated[31] The enediynes *per se* are biologically inactive[72] but undergo cycloaromatization reactions after being activated by a triggering reaction. For example, the strain imposed by the double bond in calicheamicin or by the epoxide in dynemicin imparts stability to the system[2]. Cycloaromatization of these natural products then give rise to cytotoxic diyl radicals which are capable of inducing DNA strand scission at low concentration. Cycloaromatization of the enediyne and hydrogen atom abstraction especially from DNA by the resultant biradical have been suggested to be responsible for the DNA cleaving capability of these compounds. The phenomenal biological profile of the calicheamicin and esperamicins includes[18]:

- subpicogram potency against Gram positive bacteria,
- activity in the biochemical induction assay at very low concentrations,
- high potency against a number of animal tumor models and,
- induction of double-stranded DNA cleavage with minimal concurrent single-stranded breakage.

These natural antitumor antibiotics could be grouped under three classes:

- The Calicheamicins and Esperamicins.
- The Dynemicins
- The Chromophore types; Kedarcidin chromophore, C-1027 and Neocarzinostatin.

Even though these natural antitumor antibiotics possess phenomenal cytotoxicity against tumor cells they are too toxic and indiscriminant for use as drugs, hence efforts have been made to synthesize various derivatives of these compounds. A notable example is gemtuzumab ozogamicin (Mylotarg), which is a derivative of calicheamicin

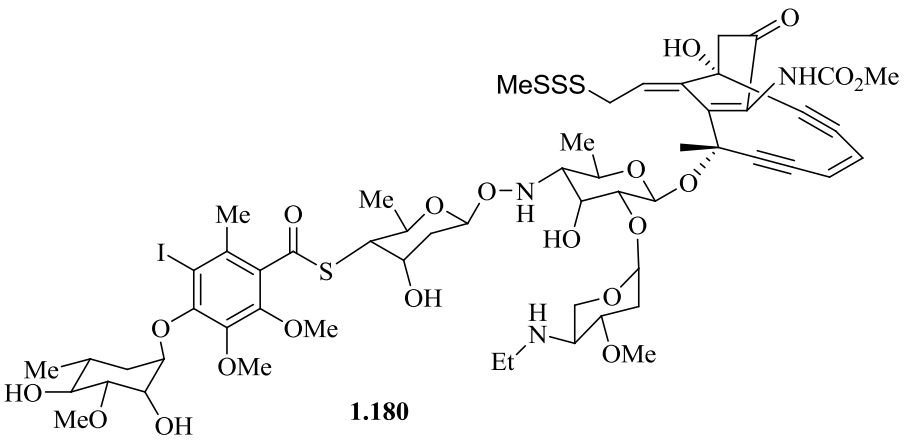
conjugated to a humanized anti-CD33 antibody; the drug is indicated for the treatment of acute myeloid leukemia (AML).[178]

1.6.1 Mechanism of DNA cleavage.

1.6.1.1 Calicheamicins & Esperamicins[86-105, 178, 179]

The Calicheamicins (also known as the LL-E 33288 antibiotics) produced from *Micromonospora echinospora* spp. *Calichensis, a* bacterium was discovered by May. D. Lee *et al.,* in 1987. [12, 81] It is the most important member of the enediyne class of natural products, and possesses phenomenal cytotoxicity against murine tumor cells.

Esperamicin A1 is also another member of the enediyne family of antibiotics exhibiting activity against marine tumor models in the 100ng/kg range. The families of Esperamicins were isolated from the bacterial *Actinomadura verrucosospora* and their structure elucidation was reported in 1987[89].



1.180

Figure 1.9: Calicheamicin

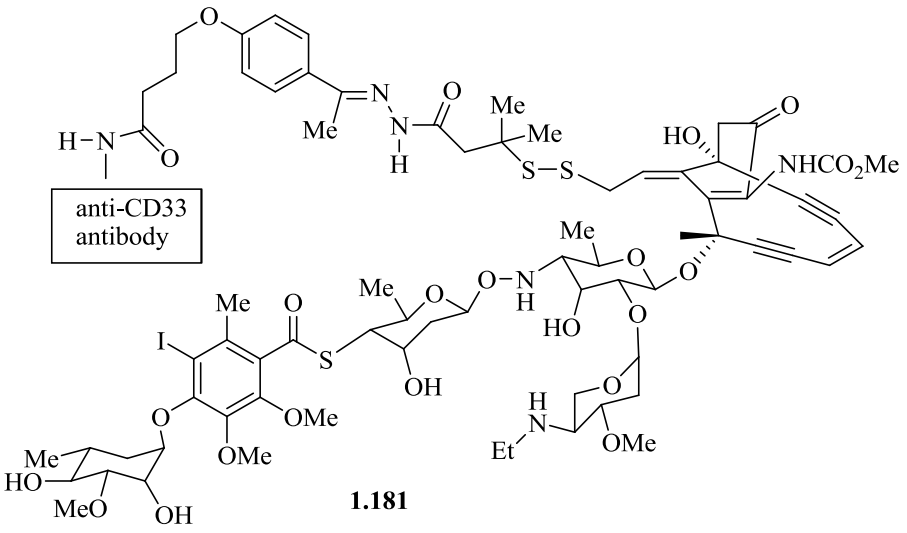


Figure 1.10: Gemtuzumab ozogamicin (Mylotarg)

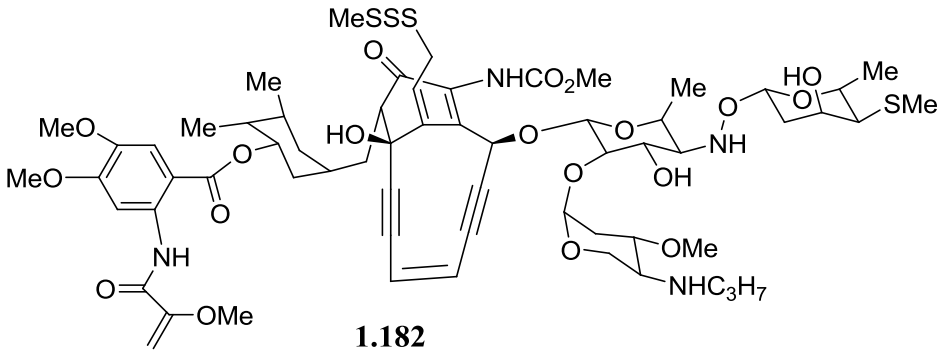


Figure 1.11: Esperamicin

The antitumor antibiotic drugs, calicheamicin, dynemicin, and esperamicin, all possessed an interesting bicyclo[7,3,1]enediyne substructure and become active *p*-benzyne biradical intermediates due to Bergman cyclizations. Precisely the reactive intermediate is proposed to be a 1, 4-dehydrobenzene derivative which is suggested to arise thermally from (Z)-enediyne in a cyclic version of the Bergman reaction.

Andrew G. Myers *et al.,* [32] reported that mechanistic studies have revealed that at a minimum, three common features are essential to the operation of these antibiotics:

(1) non-destructive high-affinity binding to DNA, and

(2) a chemical trigging mechanism leading to a high–energy intermediate capable of,

(3) rapid biradical formation at physiological temperatures.

The esperamicins and the calicheamicins both share similar structures and their structures possess three distinct domains: an oligosaccharide chain, a trisulphide moiety, and an enediyne core. Each of these domains has a specific function in DNA cleavage.[81]

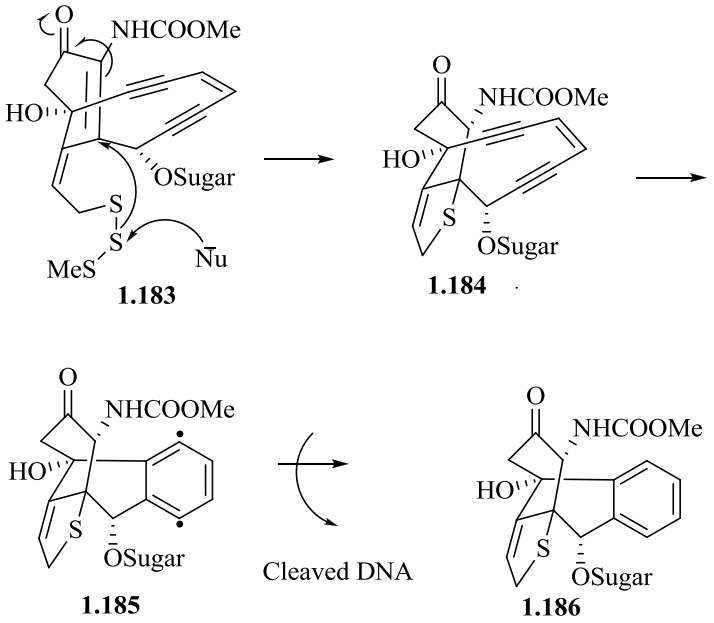
- The oligosaccharide chain recognises and targets selected base pair sequences in the minor groove of DNA, and allows the molecule to bind selectively to the minor groove of DNA through hydrophobic and electrostatic interactions (through hydrogen bonding of the sugar side chain with DNA). The natural enediynes are actually stable until they are bonded to DNA and then become activated.

- The trisulphide then serves as a molecular trigger and upon reductive activation, the resulting thiolate performs an intramolecular Michael addition onto the proximally positioned enone moiety to unlock the enediyne warhead. This brings a change in the geometry of the molecule (trigonal bridgehead to a tetragonal centre) thus reducing 'cd' distance between the two triple bonds. The decrease has been calculated to be from 3.35 to 3.16. A distance close enough for spontaneous Bergman cyclization according to Nicolau's theory[18].

- Bergman cycloaromatization of the enediyne structural motif generates a p-benzyne diradical which abstracts hydrogen radicals from DNA backbone. The reaction of

the DNA backbone radicals with molecular oxygen results in double strand cuts, leading to permanent damage of the genetic material.

The enediyne systems in both the calicheamicin and esperamicin could easily be triggered to aromatize via a free-radical intermediate by cleavage at the methyl trisulfide moiety. This aromatization process is responsible for the remarkable DNA damaging effects of the calcheamicin and the esperamicins.[12, 18]

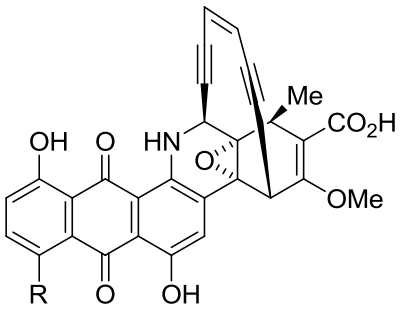


Scheme 1.43: Mechanism of DNA cleavage by calicheamicin[2].

1.6.1.2 Dynemicins [35, 81, 106-128]

Dynemicin A (DNM-A), the first known member of the family dynemicin A 1.187, was isolated from *Micromonospora chersina* M956-1[109,116] strain and the recent member deoxydynemicin A 1.187b was obtained from *Micromoonspora globosa* MG331-HF6.

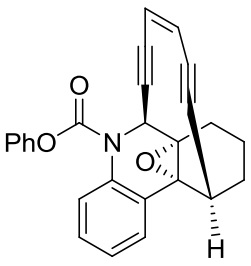
Dynemicin contain a bicyclo[7.3.1]enediyne substructure which may be related biosynthetically to the cores of calicheamicin and esperamicin. The dynemicins has a striking hybrid structure, containing not only the cyclic enediyne but an anthraquinone chromophore and unlike the other members of this class, it exhibits antibacterial and antitumor activity with low toxicity[108]. As a result of their intriguing and unique structural characteristics, various strategies have been developed to provide a synthetic route towards the natural and the non-natural dynemicin.[106]



1.187

1.187, R = OH, 1.187b R = H

FIGURE 1.12: Dynemicin A (1) and Deoxydynemicin A (2)



1.188

FIGURE 1.13: Dynemicin model

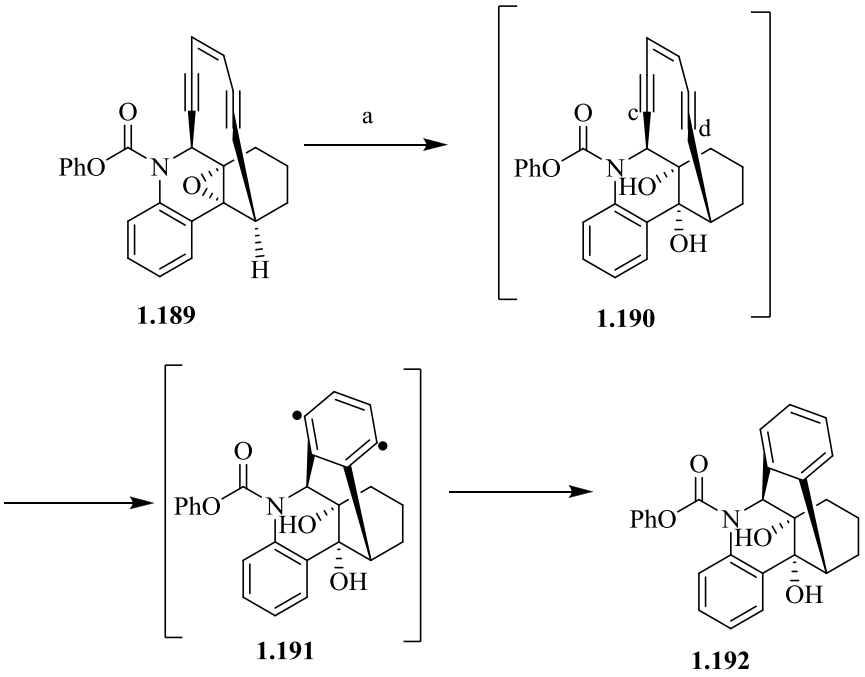
Nicolaou *et al.,*[106] reported the synthesis of the dynemicin model (figure **1.13**) to illustrate the cyclization reactions of dynemicin A. In this model the critical distance

(cd) was found to be 3.59 Å (carbon c and d), a value that agrees with the X-ray crystallographic analysis of dynemicin A (3.54 Å).

The mechanism of the cyclization reaction is outlined below:

- Protonation of the epoxide group in **1.189** initiates the formation of diol **1.190**
- Spontaneous Bergman cyclization to form benzenoid biradical **1.191.**
- Rapid trapping of the biradical by the hydrogen donor present to give the cyclized product **1.192**

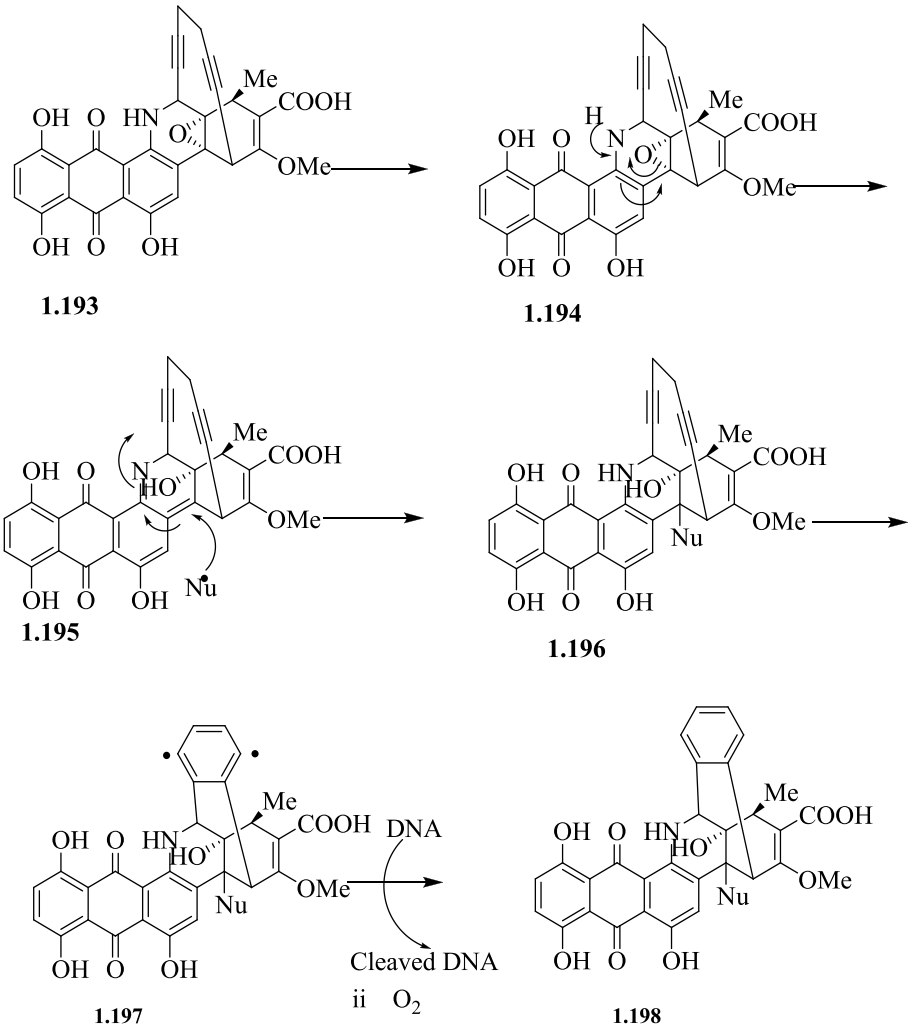
This cyclization is analogous to those observed for dynemicin A, The pharmacological activity is believed to be related to dynemicin A's ability to cleave DNA following its intercalation into DNA with its anthraquinone which in actual fact is typical of most enediyne cyclization reactions. It is the benzenoid cyclised biradical that is actually responsible for the cleavage of the DNA molecule as illustrated in the scheme below, (Scheme 1.45).



1.189 **1.190** **1.191** **1.192**

Reagents and conditions: (a) 0.05 M in benzene/1,4-cyclohexadiene (4:1), $TsOH.H_2O$ at 25°C for 24 h, 86%

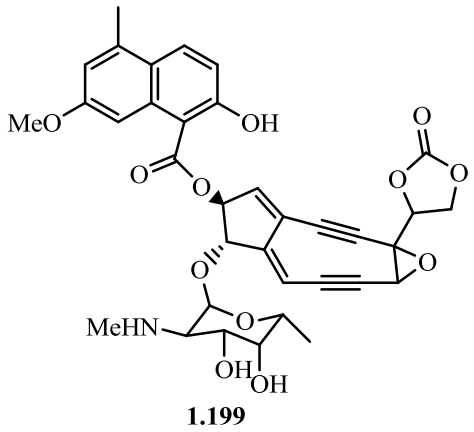
Scheme 1.44: Bergman- type cyclization of Dynemicin model



Scheme 1.45: Mechanism of biological action of dynemicin[2]

1.6.1.3 Neocarzinostatin chromophore (NCS) [32, 34,129-134,136]

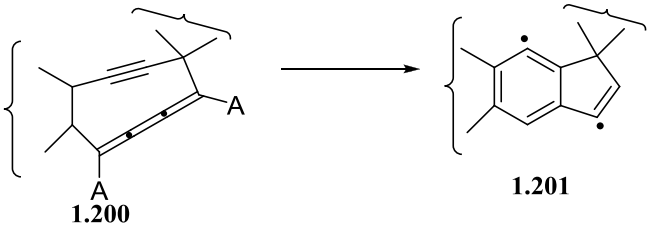
NCS the first enediyne antibiotic,[129] was first isolated from a culture of *Streptomyces carzinostaticus* var. F-41 in 1965. Its potent antibacterial and antitumor activities derive from the inhibition of DNA synthesis and DNA degradation in cells.[129] It is composed of a very unstable chromophore and a carrier apoprotein. The neocarzinostatin core is slightly different from the basic enediyne structure, it contains the bicyclo[7.3.0]dodecenediyne and shows its biological activity through the involvement of the allene eneyne system.



1.199

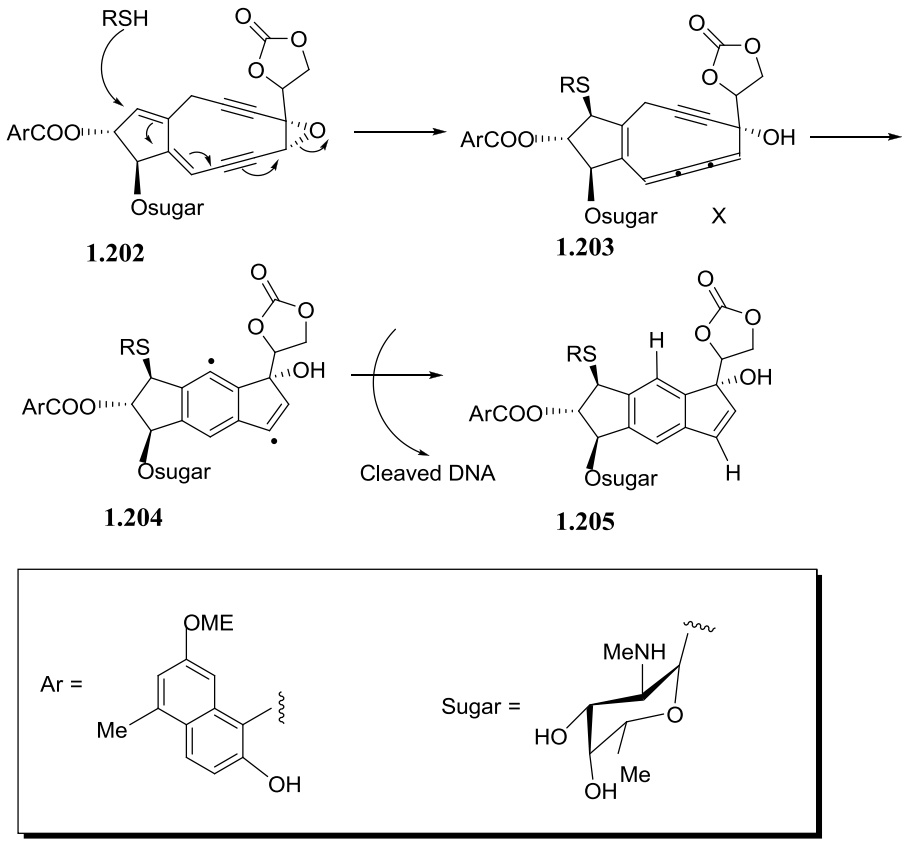
FIG 1.14: Neocarzinostatin chromophore A

Meyer-Saito cyclization (MSC) has been proposed as the key step in the mechanism of action of the antitumor agent neocarzinostatin chromophore[130] through which it produced a 3, 7-dehydroindene derivative as shown below[13, 17].



1.200 **1.201**

Scheme 1.46: Cyclization of the enediyne core of NCS

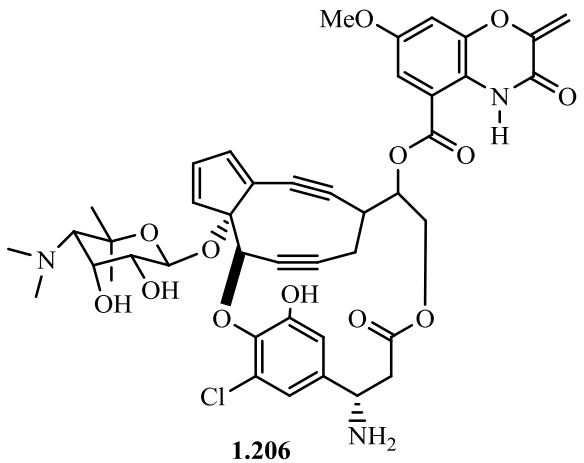


reagents and conditions: (a) RSH

Scheme 1.47: Mechanism of DNA cleavage[2,34]

1.6.1.4 C-1027 Chromophore[62, 134-142]

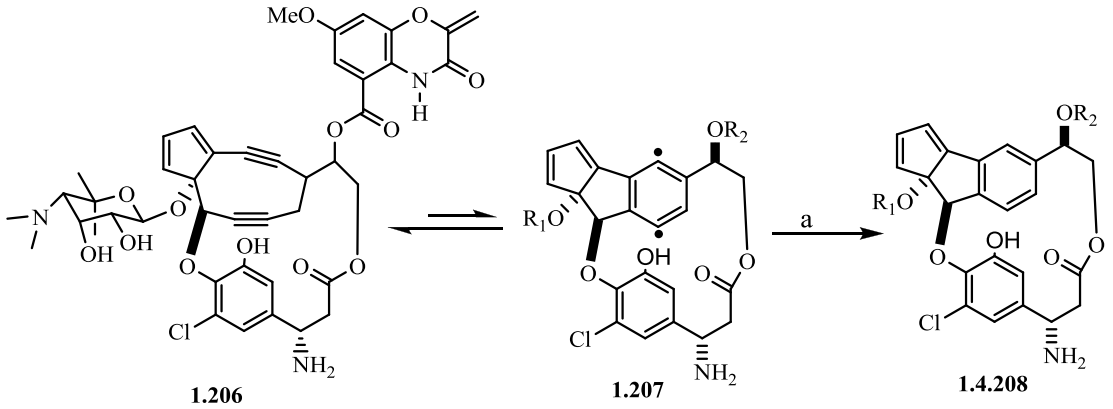
C-1027 is one of the most potent antitumor antibiotic chromoproteins, composed of an 11-kDa apoprotein and a highly reactive chromophore.



1.206

Fig 1.15: C-1027 Chromophore

The C-1027 chromophore is in equilibrium with its active biradical **1.207** form in the apoprotein and unlike NCS does not need nucleophiles or radicals for its activation. The *p*-benzyne biradical **1.207** generated exerts its potent biological activity by abstracting hydrogen atoms from the sugar portion of double stranded DNA, which ultimately leads to oxidative cleavage.

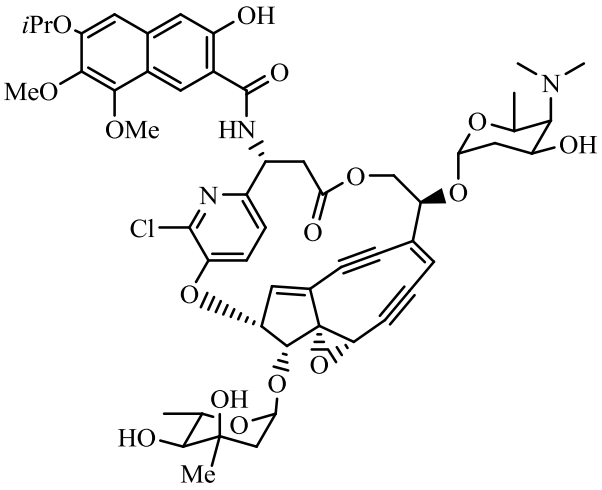


1.206 **1.207** **1.4.208**

Reagents and conditions: (a) hydrogen abstraction

Scheme 1.48: Cycloaromatization process of C-1027 chromophore.

1.6.1.5 Kedarcidin[62, 143-153]



1.209

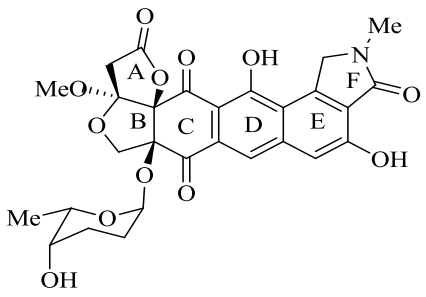
Fig 1.16: Kedarcidin chromophore

Kedarcidin is a new chromoprotein antitumor antibiotic that was isolated from the fermentation broth of a novel actinomycete strain. It consists of an apoprotein and a cytotoxic, highly labile, non protein chromophore. The apoprotein is water soluble while the chromophore is solvent-extractable, cytotoxic and highly unstable. As with NCS, the antitumor activity of kedarcidin is due primarily to the chromophore. The enediyne core is activated by chemical reduction (e.g. sodium borohydride) followed by spontaneous cyclization to a biradical intermediate and DNA cleavage.

1.7 The Parsons-Board-Walter Cyclization.[38,46,47,48]

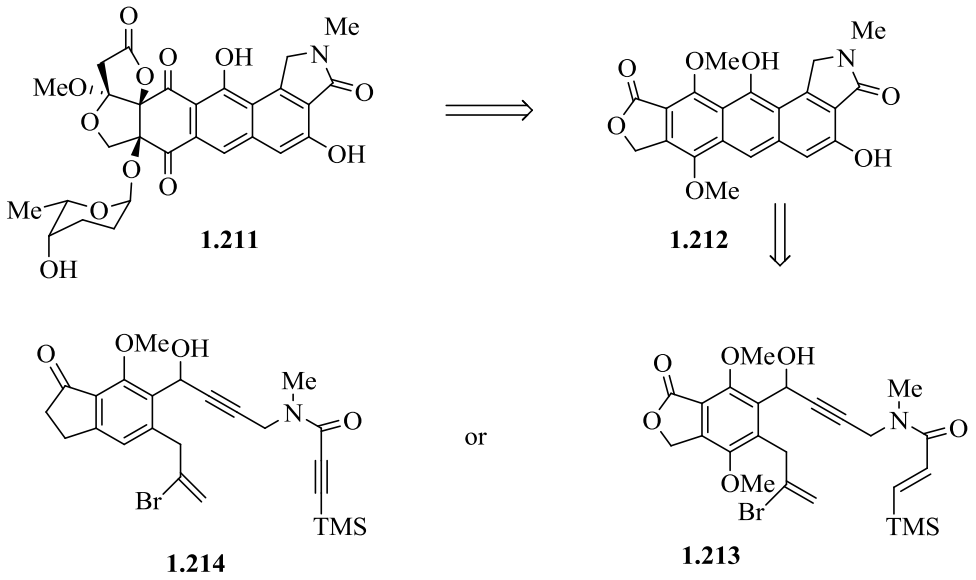
1.7.1 Retrosynthesis of Lactonamycin

Lactonymicin, **1.210** a natural product isolated from *Streptomyces rishiniensis* by Matsumoto *et al.,* in 1996,[1] has been found to possess good antimicrobial activity against bacteria including excellent efficacy against Gram- methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin- resistant *Enterococcus* (VRE), it was also found to possess antitumour activity. Many synthetic approaches have been carried out on the construction of the molecule mainly on the partial synthesis of the ABCD and the CDEF rings. Recently within the Parsons group effort was made towards the synthesis of the ABCD ring. Initial retrosynthesis of the molecule led to **1.213** which theoretically should cyclise in the presence of palladium salts or mediated in a radical cascade by trialkytin hydride.



1.210

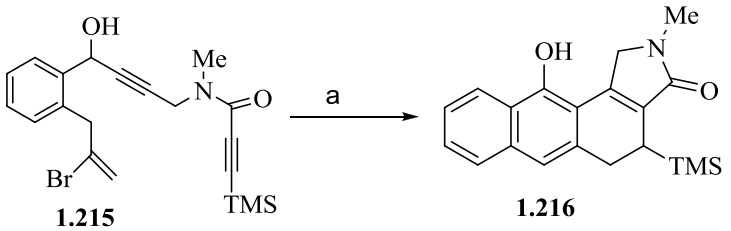
FIG 1.17: Lactonamycin



Scheme 1.49: Retrosynthesis of Lactonamycin

1.7.2 Thermal Cyclization of the Model Systems

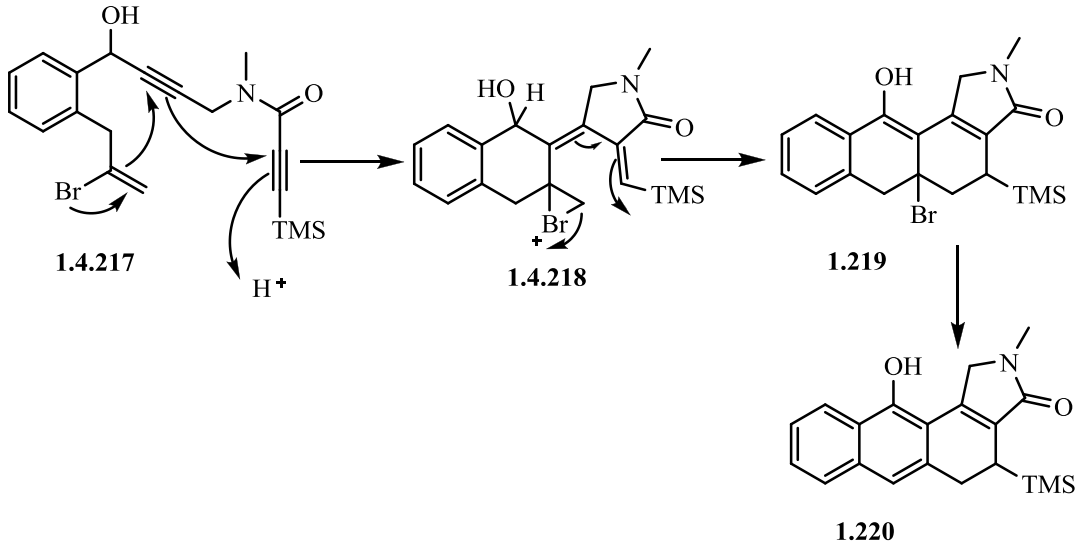
A model system (an enediyne) **1.215** was constructed to evaluate the palladium or radical –mediated (tin hydride) cyclization. However it was discovered that the model system cyclised when heated alone in toluene to afford the tetracycle **1.216** in 50% yield.



reagents and conditions: (a)PhMe, reflux, 2 h, (50%).

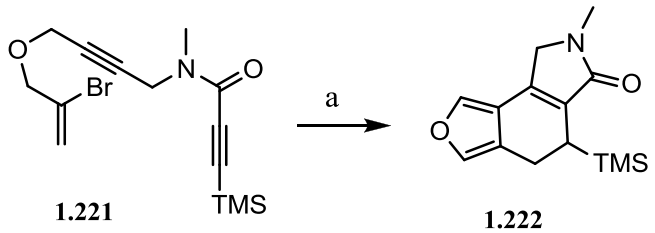
Scheme 1.50: Thermal cyclization of the model system.

The use of an acid trap 1-epoxyhexene improved the yield of **1.216** to 74%. This led to the initial proposal that the reaction may be acid catalysed.



Scheme 1.51: Postulated acid catalysed mechanism

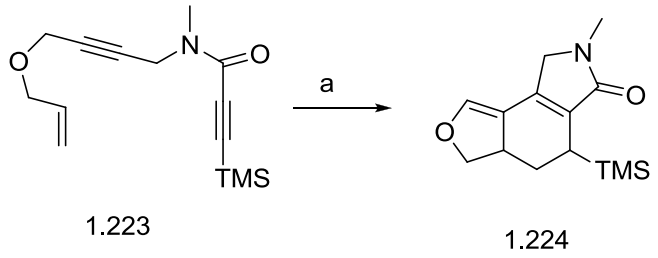
In order to investigate the mechanism of this finding and increase the versatility of the cyclization process, the aromatic portion was removed and the alcohol unit was converted to an ether bridge. The new precursor **1.221** was found to cyclise in boiling toluene containing 1-epoxyhexene as an acid scavenger, and the tricycle **1.222** was obtained in 90% yield



reagents and conditions: toluene, reflux, 1 h, 1-epoxyhexene, 90%

Scheme 1.52: Cyclization

In order to test the acid catalysed postulate the precursor **1.221** was modified to **1.223** (removal of the halogen), and neat toluene was used without the acid scavenger. Dihydrofuran **1.223** was obtained in 92% yield. The result suggested that the cyclization might have been by another mechanism other than acid catalysed and the acid catalysed pathway was discounted in favour of a radical process because the cyclization still proceeded in the absence of an alkenyl bromide[47] (Scheme **1.53**).

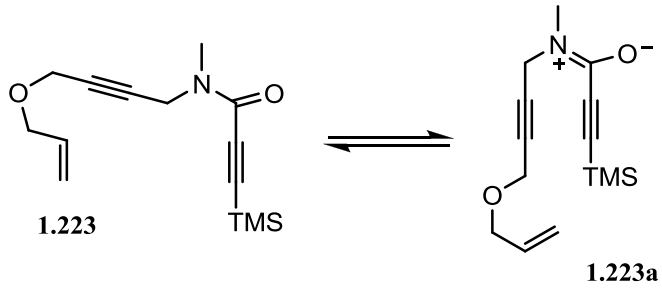


1.223 1.224

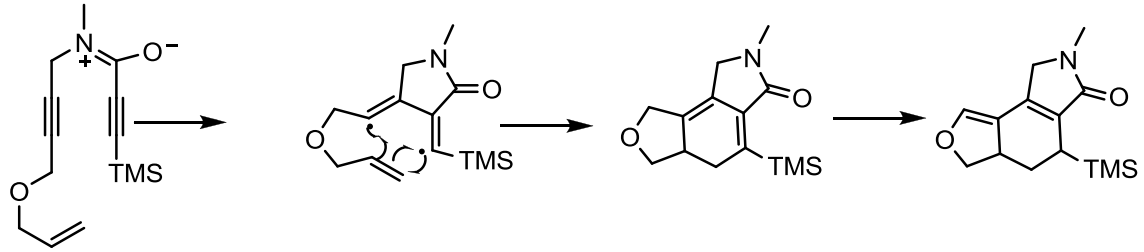
reagents and conditions: (a) toluene, reflux, 92%

Scheme 1.53: Cyclization in the absence of an alkenyl bromide[47]

In order to explain this observation it was postulated that the reaction may have been initiated by the formation of a diene biradical generated from the two triple bonds. It was assumed that the two triple bonds are held closely together in space within a cisoid geometry **1.223a** enhanced by amide resonance. This causes homolytic cleavage in each of the triple bonds to form the biradical intermediate. The radical **1.225** then cyclised onto the available terminal alkene to form the second and third rings in one operation. A double bond isomerisation occurred to minimise the strain produced in tricycle **1.226** to give **1.224**

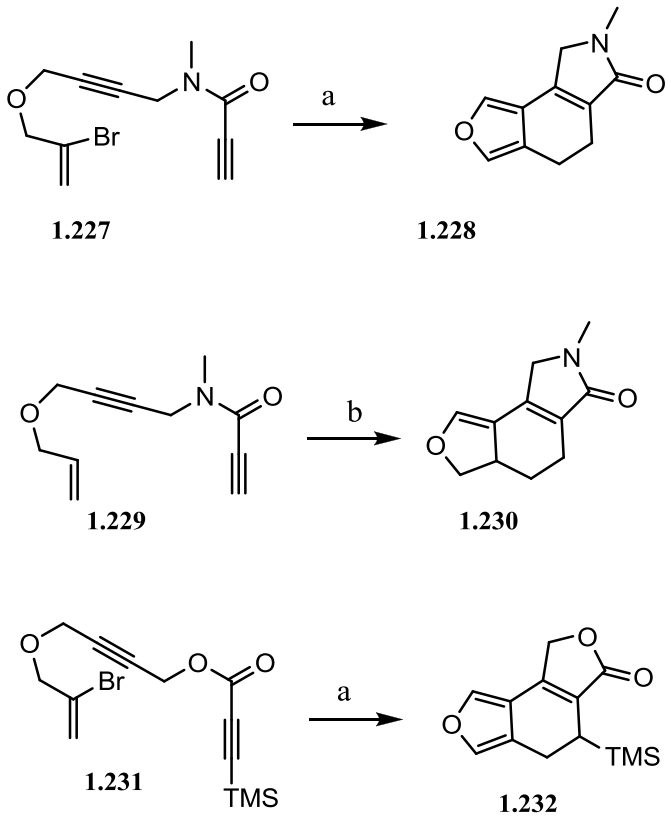


Scheme 1.54: Amide resonance



Scheme 1.55: Biradical mechanism

In view of this new biradical mechanism, a number of different substrates were also tested and found to undergo thermal induced cyclization (Scheme **1.56**).



reagents and conditions: (a) toluene, reflux, epoxyhexene, 13 h, 97%

(b) toluene, reflux, 13 h, 89%

(c) toluene, epoxyhexene, reflux, 52 h, 76%

Scheme 1.56: Different thermal cyclizations

These studies have opened up a novel cyclization reaction for the construction of fused heterocyclic ring systems, which is metal free and hence environmentally friendly.

1.8 Aim of Current Thesis.

The discovery of the novel thermal cyclization of highly functionalised enediyne molecules within the Parsons' group is thought to be a great prospect for synthetic chemistry. Interest in this type of cyclization is heightened due to the fact that they are not metal-catalysed and therefore environmentally friendly. This in essence has prompted more research into this type of cyclization.

The aim of this research work is to:

- Synthesise different precursors that would be used to investigate the thermal cyclization reaction.
- Investigate the scope and the limitations of the thermal cyclization reactions by extending the novel cyclization reaction to the synthesis of diverse functionalised heterocyclic rings.
- Investigate the intermolecular trappings of the proposed biradical formed.
- Investigate the effect of sterically demanding group on the rate of cyclization.

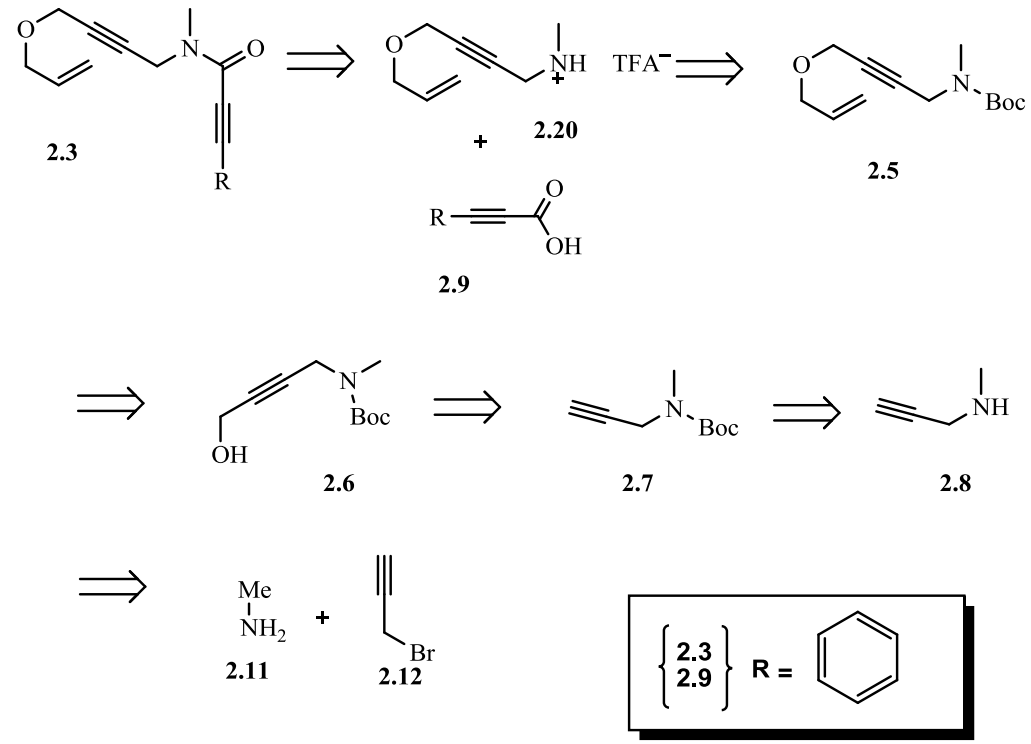
Chapter 2

Results and discussion

2.1. Retrosynthetic Analysis.

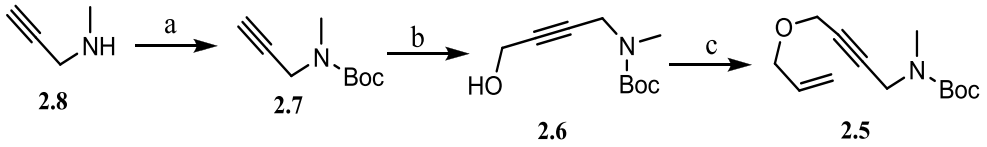
Investigation into the novel thermal cyclization reactions of the enediyne started with the synthesis of the basic precursors which would then be adapted for the synthesis of the various functionalised precursors.

Retrosynthesis of the basic precursors provided us with the disconnection to *N*-methyl propargyl amine **2.8**, which could be obtained commercially or from the propargylation of methyl amine or methyl amine hydrochloride.



Scheme 2.1: Retrosynthetic Analysis.

2.2 Synthesis of the Precursors 2.3 and 2.4.



2.8 2.7 2.6 2.5

reagents and conditions: (a) $(Boc)_2O$, DCM, (b) *n*-BuLi, THF, $(CH_2O)n$, (c) NaH, allyl bromide

Scheme 2.2: Formation of ether 2.5

2. 2.1 *N*-Boc Protection and Propargylation of amine

Initially we started the synthesis with the use of the commercially available *N*-methylpropargyl amine. The amine was protected with Boc anhydride and the desired product was obtained on distillation in 79% yield as a clean and pure liquid which solidified on cooling. (Inset in scheme **2.3**).

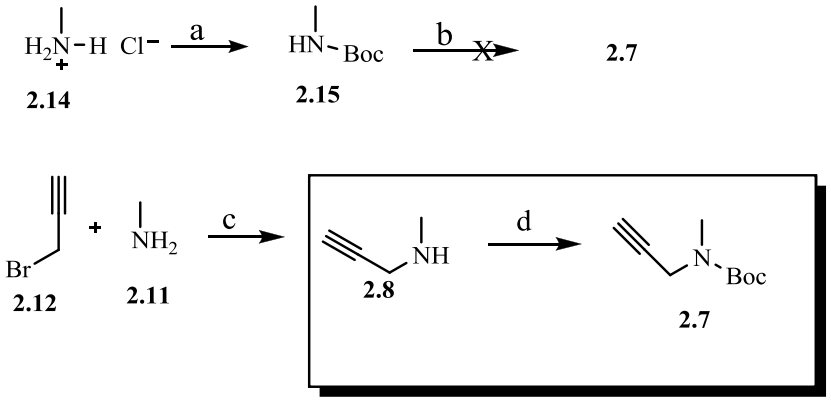
We also attempted the synthesis of the Boc protected amine from the less costly reagents, methyl amine hydrochloride and methyl amine;

The first method employed the use of methylamine hydrochloride from which the free amine was generated in-situ by its reaction with triethylamine. Subsequent reaction with Boc anhydride afforded the protected amine in 33% yield. The protected amine was deprotonated with sodium hydride and subsequently treated with propargyl bromide. Protection of the amine proved successful even though the yield was small, but the expected propargylation did not take place.

In the second method,[154] propargylation of the amine was carried out with the addition of propargyl bromide to aqueous methyl amine producing a mixture of *N*-methyl propargyl amine **2.8** and unreacted starting material **2.11** on distillation of reaction

mixture. Protection of the amine with excess Boc anhydride was successful. *N-N-D*i-methylethylenediamine was used to quench any unreacted Boc anhydride in the mixture. The reaction produced a mixture of **2.7** and **2.15** in 35% and 15% yield respectively.

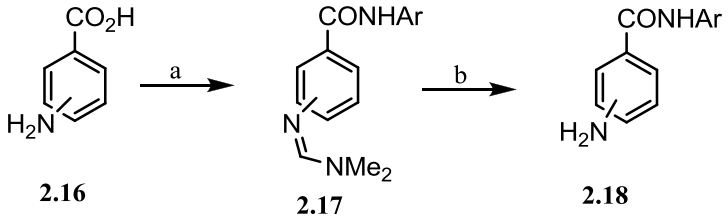
The use of the commercial *N*-methylpropargyl amine proved to be the best method.



reagents and conditions: (a) THF, Et_3N, $(Boc)_2O$, -1 ^{O}C, 33%. (b) THF, NaH, C_3H_3Br, H_2O, $NaHCO_3$ (c) H_2O, $NaHCO_3$ (d) Boc, H_2O, 0 ^{O}C

Scheme 2.3: Preparation of *N*-methylpropargyl-*N*-Boc amine.

The amine was *N*-protected as a *tert*-butyl carbamate ester (Boc group) to make it unreactive in the follow up reactions with nucleophiles and bases. From literature many different protecting groups are applicable for amines[155, 156]. For example Paul E Zhichkin *et al.,*[155] made use of *N,N* dimethylformamidines as a protecting group for amine in the one-pot synthesis of amides from amino acids.(Scheme **2.4**). We decided to use the Boc anhydride because of the ease of its removal with acids.



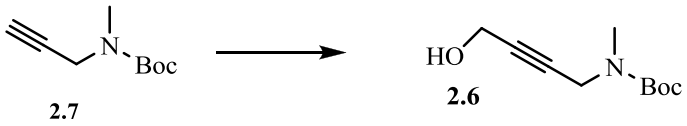
2.16 **2.17** **2.18**

reagents and conditions: (a) (i) DMF/$(COCl)_2$ (ii) pyridine, $ArNH_2$, (b) ethylenediamine

Scheme 2.4: Use of *N,N*- dimethylformamidine as a protective group.

2.2.2 Formation of the Propargyl alcohol

Deprotonation of the terminal (alkynyl) proton was carried out by treating with *n*-butylithium (2.2M in hexanes) in dry THF at -78 ^{o}C. This was followed by addition of parafomaldehyde the reaction afforded the primary alcohol **2.6** in 83% yield.



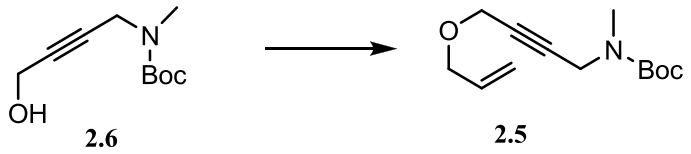
2.7 **2.6**

reagents and conditions: (i) *n*-BuLi, THF, -78 ^{O}C, (ii) $(CH_2O)n$, 83%.

Scheme 2.5: Synthesis of propargyl alcohol

2.2.3 Williamson Ether Synthesis.

Deprotonation of the primary alcohol **2.6** with sodium hydride produced the necessary alkoxide ion for the formation of the allyl ether when treated with 3-bromopropene through an SN_2 mechanism.



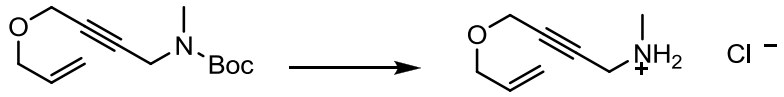
2.6 **2.5**

reagent and conditions: NaH, THF, allyl bromide, 80%.

Scheme 2.6: Williamson ether synthesis.

2.2.4 Deprotection of Amine

Deprotection of the amine compound **2.5** was attempted by treatment with 2M solution of hydrogen chloride in dichloromethane. This method was successful (84%) on a 50mg scale but unsuccessful when scaled up (3g) (Scheme **2.7**).



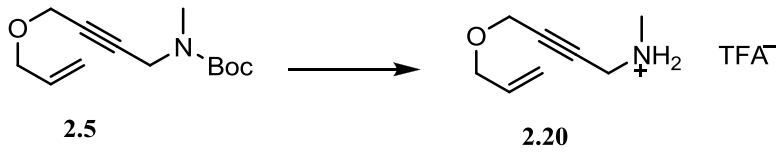
2.5 **2.19**

reagents and conditions: 2.0 M HCl in DCM, 84%

Scheme 2.7: N-Boc deprotection with HCl

Nazih *et al.,*[157]reported in their study of one-pot conversion of t-butyl carbamate to amides with acyl halide-methanol mixtures that the hydrogen chloride acid generated in situ has a low acidity which is not enough to accomplish the complete cleavage of the Boc group. In order to make the reaction medium more acidic and to improve the yield of the deprotection, the reaction was conducted in a medium that would generate hydrogen iodide *in situ* by the addition of sodium iodide. This system worked with good yields (62-100%). Trifluoroacetic acid (TFA) was also found to give very good yields [46, 47, 158].

This latter method was used in this research and the method afforded a complete removal of the Boc group in all cases. The TFA salt obtained was used without further purification (Scheme **2.8**).



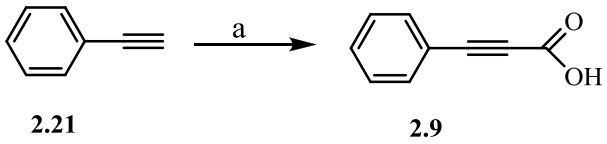
2.5 **2.20**

reagents and conditions: TFA, DCM,RT.

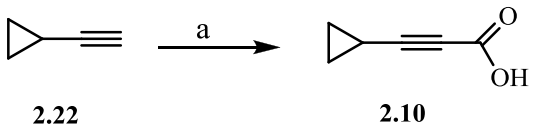
Scheme 2.8 *N*-Boc deprotection of 2.5 with TFA

2.2.5 Formation of Acetylenic Acids.

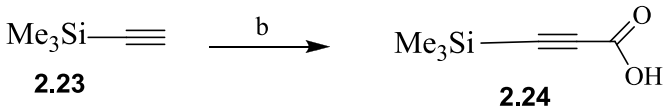
The acid **2.9**, used for the coupling reaction was prepared from acetylene **2.21** by deprotonation with butyllithium or methyllithium followed by addition of carbon dioxide gas obtained from dry ice at room temperature and passed through a cannula. This method was used for the synthesis of the other acids **2.10**, **2.24.**



2.21 **2.9**



2.22 **2.10**



2.23 **2.24**

reagents and conditions: (a) *n*-BuLi, CO_2, HCl. (b) MeLi, CO_2, HCl

Scheme 2.9: Synthesis of acetylenic acids

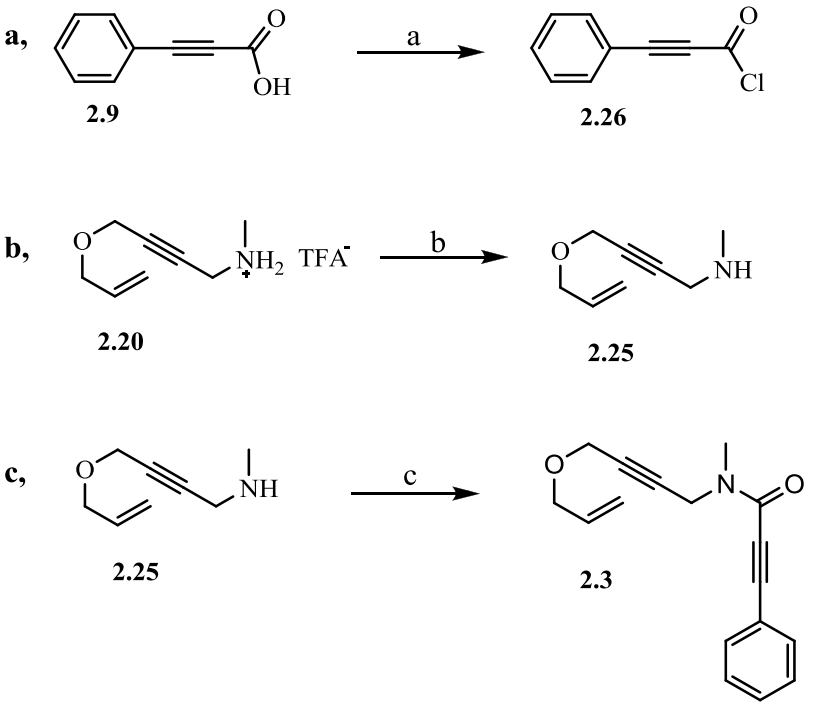
2.2.6 Formation of the amide.

The last step in the synthesis of the precursor involved the coupling of the free amine with the acid. The coupling was carried out in three steps;

Treatment of the TFA salt **2.20** with triethylamine at 0^{o}C generated the free amine **2.25**. (Scheme **2.10b**)

The acid **2.9** is not nucleophilic enough to couple with the free amine, it is therefore activated with a good leaving group by conversion into its reactive but unstable form (acyl chloride) **2.26** with the use of Vilsmeier reagent[155] (in DCM), prepared *in situ* from oxalyl chloride and DMF (cat.). (Scheme **2.10a**) *Iso*-butylchloroformate[159] is another versatile reagent that could be used to activate the carboxylic acid.

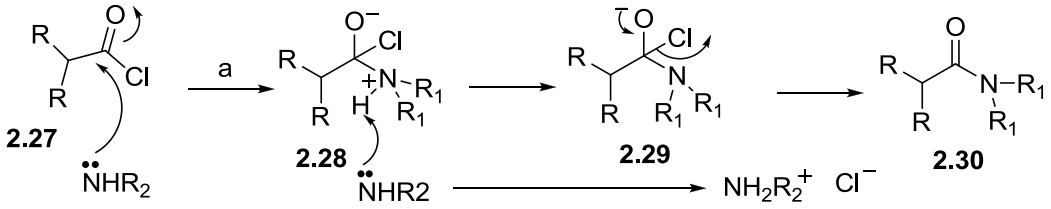
The acyl chloride formed was added to the free amine to form the amide (66%) through a nucleophilic attack on the carbonyl carbon of the acid chloride. (Scheme **2.10c**)



reagents and conditions: (a), DCM, oxalyl chloride, DMF,(b) DCM, Et_3N, (c) **2.26,** 66% (over 2 steps)

Scheme 2.10: Synthesis of Precursor 2.3

Repeating the coupling reaction to generate more of the precursor proved difficult resulting in low yields, ranging from as low as 15% to 66% (based on the amine). The mechanism of the reaction showed that two equivalents of the amine were necessary for one equivalent of the acyl chloride, which constitutes a 'waste' of the amine.



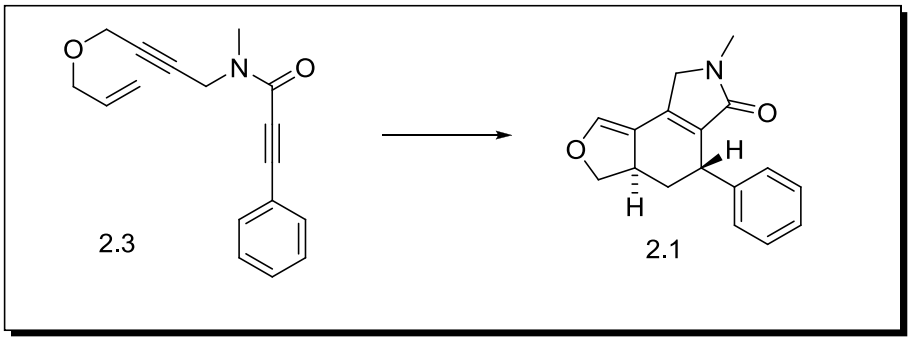
reagents and mechanism: (a) H_2O, DCM, NaOH

Scheme 2.11: Mechanism of amide formation

To circumvent this problem and conserve the amine, Schotten-Baumann[158] adopted another approach involving the use of a different base in the place of the second amine molecule. The hydroxyl ion was used, however in a biphasic mixture of water and DCM, to prevent the hydroxyl ion from attacking the acyl chloride. Even though Schotten- Baumann recorded 80% yield, the reaction did not work in this particular system. It is assumed that the reason for the failure may be the functionalised nature of our substrates.

2.2.7 Thermal Cyclization Reaction.

The enediyne **2.3** was heated under reflux in toluene and the progress of the reaction was followed by tlc analysis on hourly basis for 5 h, until the starting material was no longer visible on the tlc plate. The tetracyclic product was obtained on purification as the only product.



reagents and conditions: Toluene, Reflux, 5 h, 71 %.

Scheme 2.12: Cyclization reaction

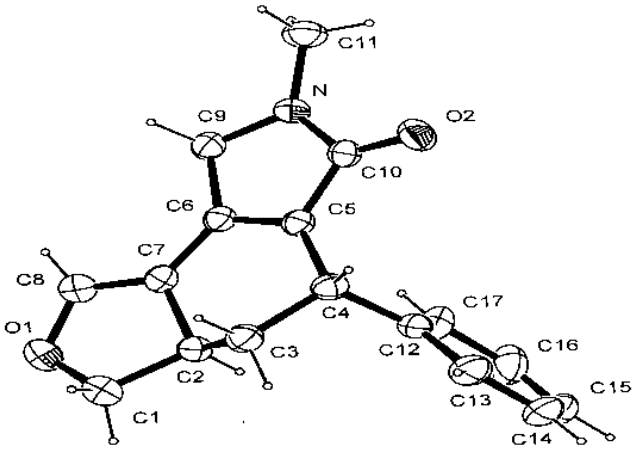


Figure 2.1: Crystal structure of tetracyclic 2.1

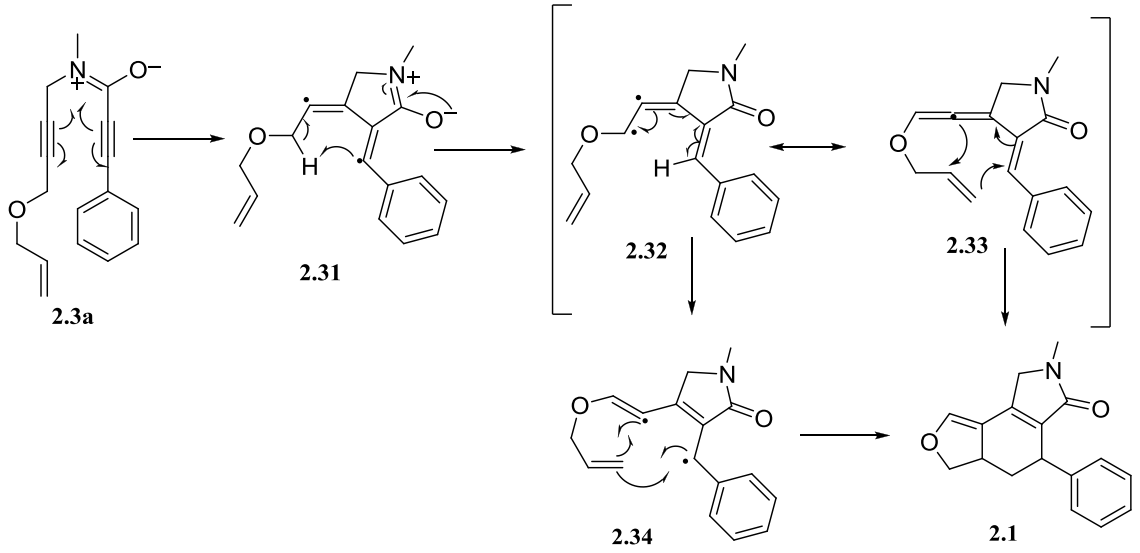
2.2.8 Mechanism of Cyclization

Based on studies carried out within the Parsons' group (section **1.7,** scheme **1.55**.) the mechanism of the thermal cyclization has been proposed to be radical based rather than acid based. In this particular study, the cyclization reaction was carried out by refluxing in toluene without any added acid trap; this confirmed that the cyclization is not acid based. Amide resonance which has been confirmed in the NMR experiments contributed to bringing the two alkynes bonds into close proximity thus satisfying the

critical distance theory proposed by Nicolaou *et al.*[18] It has been suggested that the biradical mechanism probably occurred in the following steps;

- Homolytic cleavage of the two triple bonds in **2.3a** to form a biradical intermediate **2.31** similar to the Bergman intermediate **1.2** in scheme **1**,
- followed by a 1,5- H atom abstraction and double bond formation in the lactam ring to give **2.34**, and
- finally, the addition of the remaining terminal double bond in **2.34** to give the fully cyclised product.

It is also a possibility that the intermediate **2.32** could collapse to form the allene **2.33** which could also undergo a Diels-Alder cycloaddition reaction to finally give the product **2.1**



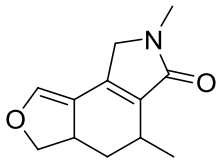
Scheme 2.13: Mechanism of thermal cyclization

Compound **2.1** has two stereogenic centres at C2 and C4. From the X-ray crystallography the absolute configuration at the two centres are 2R and 4S, it also shows that the hydrogen atoms are *trans* to one another. Diels-Alder reactions are

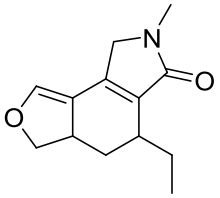
known to be stereoselective and the substituents on the dienophiles and the dienes retain their relative stereochemistry prior to the reaction. The product being obtained with a *trans* configuration may be an indication of the biradical mechanism, since Diels-Alder reactions are known to be stereoselective and the dienes react only in the *cisoid* configuration, thus producing an adduct in which the substituent are in *cis* position to one another.

2.3 Further Studies on the Intramolecular Cyclization Reactions

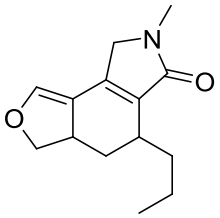
Results obtained with the silyl **1.231**, and phenyl **2.3** and the unsubstituted (R= SiMe3[47], Ph, and H[47]) moieties during the intramolecular cyclizations prompted us to investigate a series of other enediynes, with the view of increasing the versatility of the thermal cyclization reactions in synthesis. We aimed to prepare the methyl, ethyl and propyl substituted moieties for use in the synthesis of the various heterocycles.



2.35



2.36

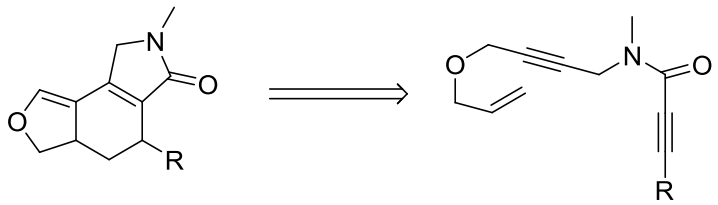


2.37

Figure **2.2**: Compounds **2.35, 2.36, 2.37**

2.3.1 Synthesis of the Precursors 2.38, 2.39, and 2.40

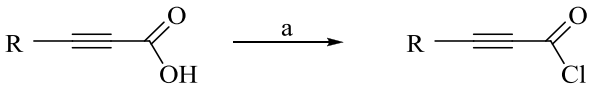
Retrosynthesis of compounds **2.35, 2.36, 2.37** gave the precursors **2.38, 2.39, 2.40** respectively.



2.35	R= CH_3, (Me),	**2.38**
2.36	R= CH_3CH_2, (Et),	**2.39**
2.37	R= $CH_3CH_2CH_2$, (*n*Pr)	**2.40**

Scheme **2.14:** Retrosynthesis of Compounds **2.35, 2.36, 2.37.**

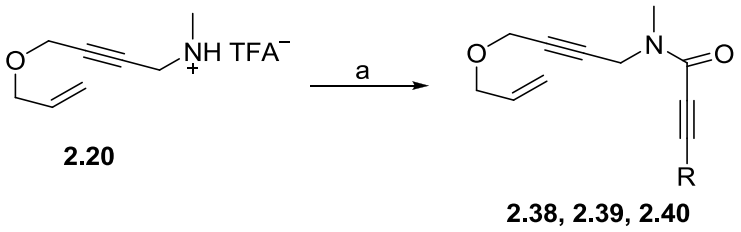
Each of these precursors was prepared by the coupling reactions of **2.20** with the corresponding acyl chlorides which were prepared (*in-situ*) (scheme **2.15**) from the corresponding commercial acids**.**



2.44	R = Me	**2.47**
2.45	R = Et	**2.48**
2.46	R = *n*-Pr	**2.49**

reagents and condition: (a) $(COCl)_2$, DMF (cat), DCM, $0^{O}C$, 1 h

Scheme 2.15; '*In situ*' preparation of the acyl chlorides.



2.20 **2.38, 2.39, 2.40**

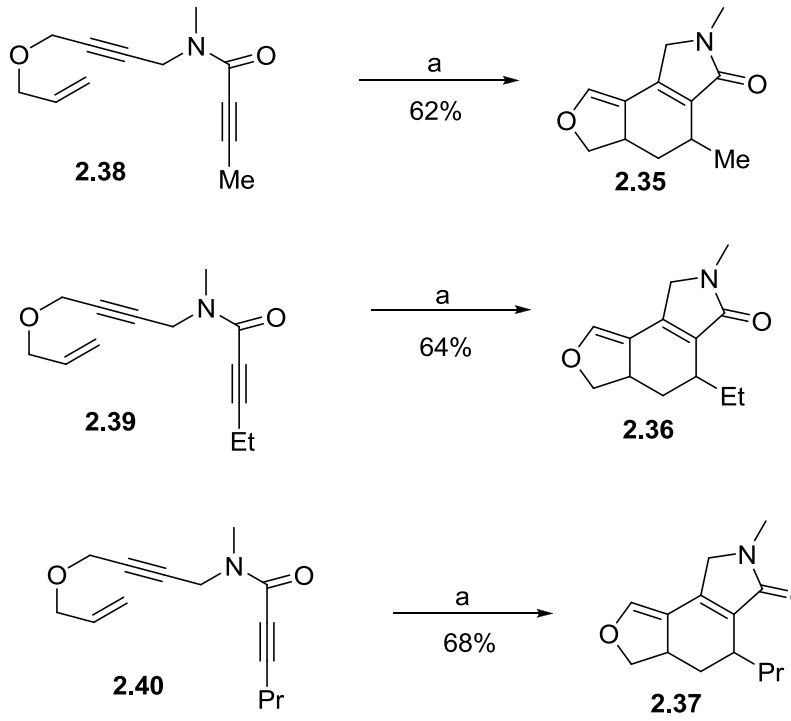
reagents and condition: (a) NEt_3, 0^oC, **2.47/2.48/2.49**

Scheme 2.16: Synthesis of acyl chlorides and coupling reactions.

2.3.2 Thermal Cyclization Reactions of 2.38, 2.39, 2.40

The precursors were heated to reflux in dry toluene for forty-eight hours, providing the tricycles in moderate yields of **49, 50** and **54%.**

A comparison of the spectra of these compounds compared well with those of similar compounds.[46,47,48]



reagents and conditions: (a) toluene, reflux, 48 h.

Scheme 2.17: Cyclization reactions for compounds 2.38, 2.39 and 2.40

When the reactions were repeated under the microwave conditions, the yields improved to 62, 64 and 68% respectively. It was also observed that the rate of reactions were slower for these enediynes than for the silyl and phenyl moieties.

Substrate	Yield (%)conventional heating (48 h)	Yield (%) m/w (2 h)
2.38	49	62
2.39	50	64
2.40	54	68

Table 2.1 Yields of thermal cyclizations.

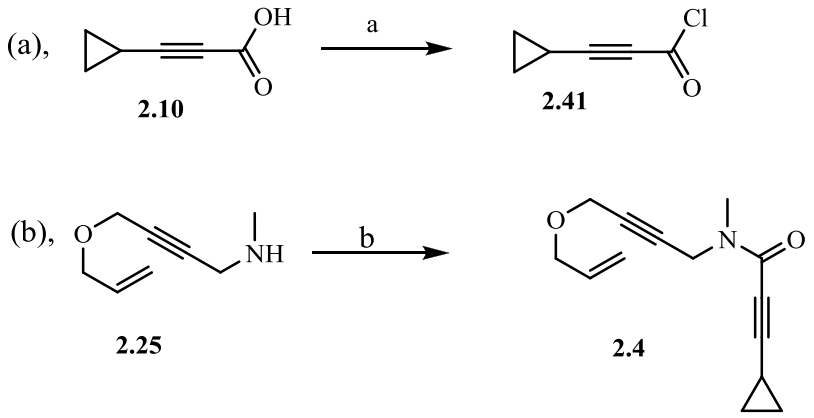
This observation agrees with the observation made by Schreiner *et al*. (section **1.2.4**) that alkyl substitution at the alkynyl positions increases the endothermicity of the BC and stabilizes the alkynes and therefore disfavour cyclization.

2.4 Investigation of the Biradical Mechanism

We proceeded to test the proposed biradical mechanism on a different substrate employing the use of the cyclopropyl group on one of the terminal alkynes instead of a TMS group or a phenyl group. Schmittel *et al.,*[10] observed that simple attachment of an aryl group to the alkyne terminus of an enyne allenes has a stabilising effect on vinyl radicals and they redirected the reaction from Meyers - Saito mode (C2 –C7) to Schimittel mode (C2 – C6).[10] (Scheme **1.26**.) Rodriguez *et al.* also observed similar redirection on the enyne cumulenal systems. (Scheme **1.27**) Summarily, earlier studies have established that cyclization reactions are highly affected by the type of substituent group on the terminal alkyne.

2.4.1 Synthesis of the Precursor

The cyclopropyl moiety was synthesised starting from the free amine **2.25**. Cyclopropyl propynoyl chloride was generated *in situ*, (Scheme **2.18a)** and coupled with the free amine to produce the expected amide **2.4** in 67% yield.

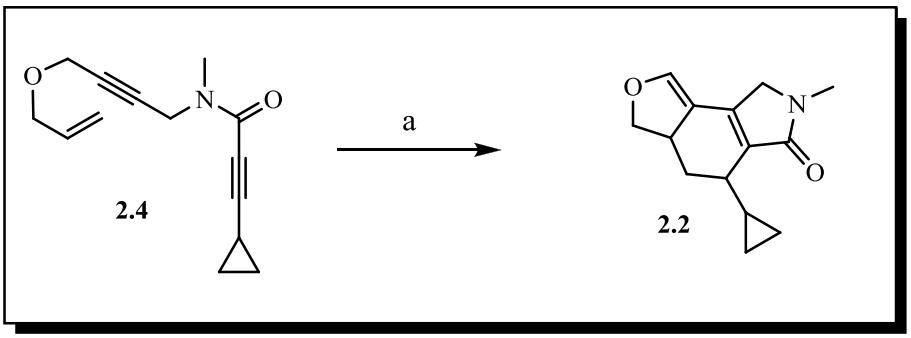


reagents and conditions: (a) DCM, DMF, oxalyl acid (b) 2.25, 67%

Scheme 2.18: Synthesis of cyclopropyl precursor

2.4.2 Thermal Cyclization reaction

Precursor **2.4** was heated under reflux in toluene, TLC monitoring showed the completion of the reaction after 25h.



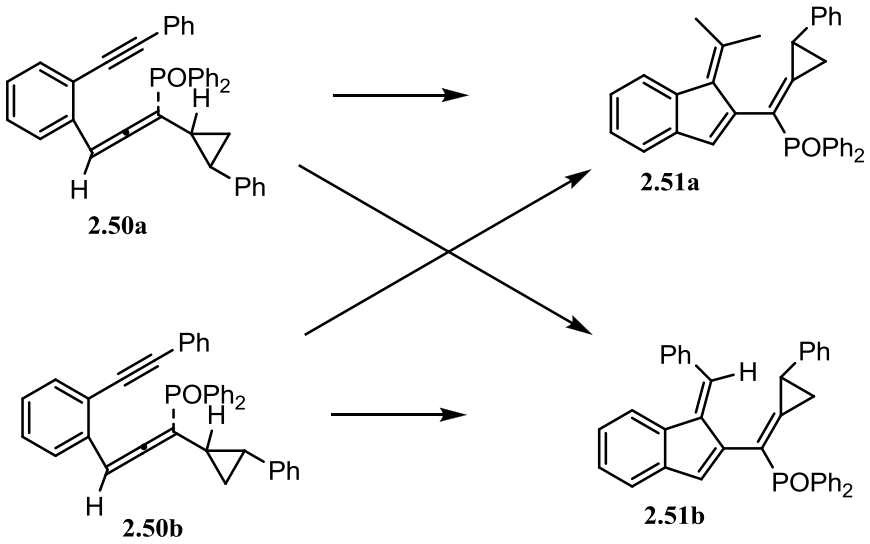
reagents and conditions: toluene, reflux, 25 h, 83%

Scheme 2.19: Thermal Cyclization reaction

Surprisingly precursor **2.4** also cyclised into a solid compound **2.2** as indicated in the ^{1}H and ^{13}C NMR experiments. ^{1}H NMR and correlation data confirmed that the cyclopropyl ring remained unopened against expectation. Signals for the protons of the cyclopropyl ring which hitherto was observed at 0.9ppm (4H for the two CH_2) and 1.4ppm (1H) in the precursor now showed different signals for which all the five protons are coupled together as indicated in the *COSY* experiment. This is an indication that the cyclopropyl ring remains unopened in the product. The coupling observed may be due to the rigid structure of the ring system of the cyclised compound. For the same reason the splitting observed for the *N*-methyl and the *N*-methylene protons in the precursors were no longer observed in the cyclised compound. Unfortunately all attempts to obtain crystals for X-ray analysis failed.

Even though compound **2.2** was formed against our expectation, a closer look showed that it did not negate the proposal that the reaction may have occurred through the biradical mechanism.

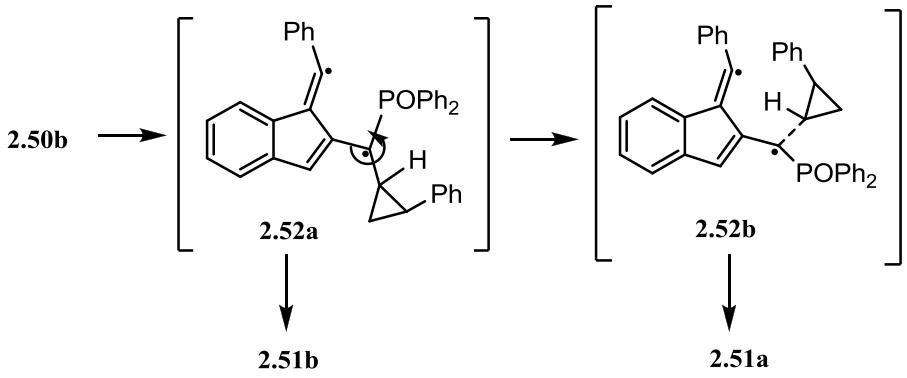
Detailed study carried out by Schimittel *et* a*l.,*[10] (Schemes **2.20** and **2.21**) on the C2-C6 cyclization using the cyclopropyl- substituted enyne allene pointed to a stepwise biradical mechanism for the cyclization reactions. Evidence for the stepwise mechanism over a concerted one was also provided by the measurement of activation barriers and the lack of solvent effect (polar and non polar) apparently precludes a zwitterion as an intermediate. The proposed mechanism is given in scheme **2.21**. Two plausible explanations were given for the conversion of the biradical into the two diastereomers, (i) a coupled bond rotation about the bonds linking the radical centre to the cyclopropyl group and to the benzofulvene moiety, and (ii) reversible opening of the cyclopropyl ring.



reagents and conditions: 1,4-CHD, 80^{o}C,

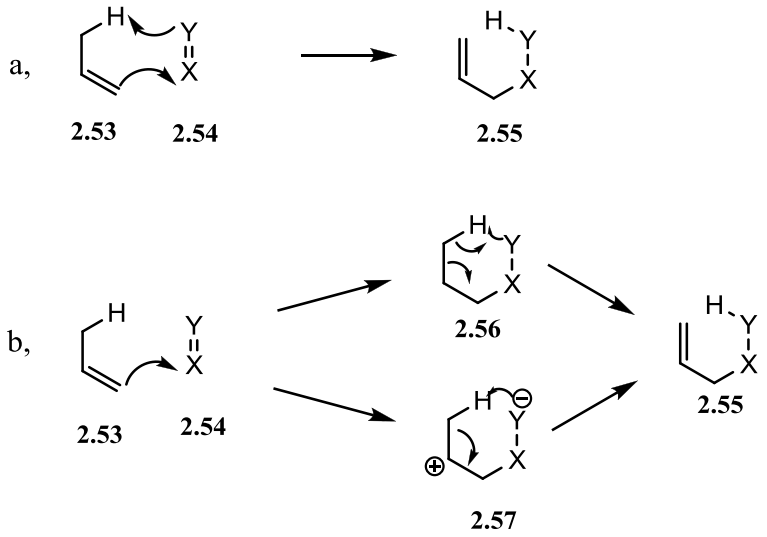
Scheme 2.20: Thermal reaction of cyclopropyl-substituted enyne allene

In scheme **2.20** above when **2.50a** and **2.50b** (1.1 mixture of the two *trans* diastereomers) was gently heated, a mixture of **2.51**a and **2.51b** was obtained. Furthermore each of the diastereomers of **2.50** still produced both **2.51a** and **b** when heated separately. This ene reaction is not stereospecific, which indicated a stepwise mechanism through a biradical intermediate **2.52.**



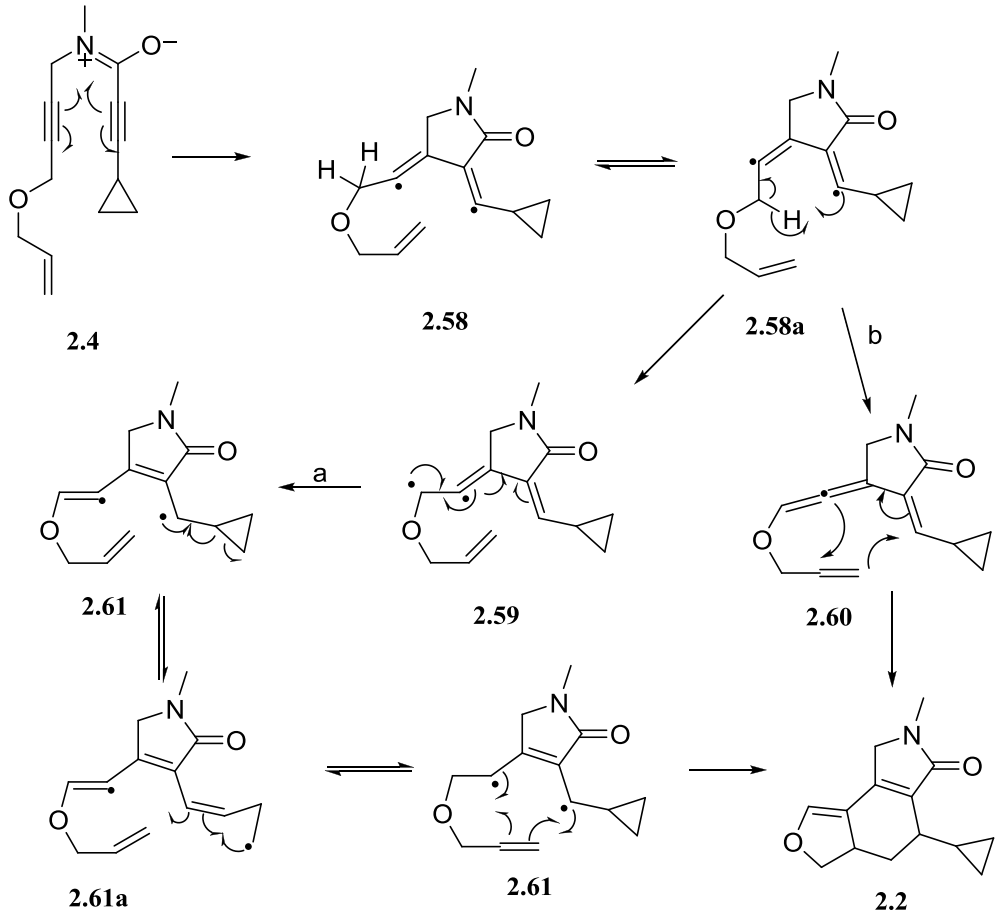
Scheme 2.21: Proposed mechanism (Coupled bond rotation)

According to Snider and Ron[160], the ene reactions are mechanically diverse and could occur through concerted pericyclic reactions (Scheme **2.22a**) or through stepwise mechanisms with a zwitterion or biradical as intermediates. The actual mechanism followed would depend on the nature of R group.



Scheme 2.22: Ene reaction, concerted and stepwise mechanism.

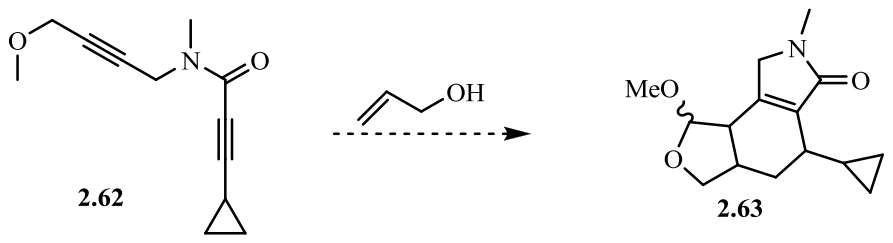
Conclusively the formation of compound **2.2** in scheme **2.19** could be explained on the basis of reversible opening of the cyclopropyl ring. This could also account for the observed slow rate of the cyclization, 25 h as against the 5 h taken for precursor **2.3** to cyclise into **2.1.** The proposed mechanism for the reversible ring opening of the cyclop ropyl group through a stepwise pathway is shown in scheme **2.23**.



Scheme 2.23: Mechanism of (a) the reversible ring opening of cyclopropyl ring and (b) Diels-Alder cycloaddition

2.5 Investigation of Intermolecular Radical Trapping.

Having proposed the biradical mechanism for the cyclization reactions, we needed to investigate the cyclization reaction through an intermolecular radical trapping.

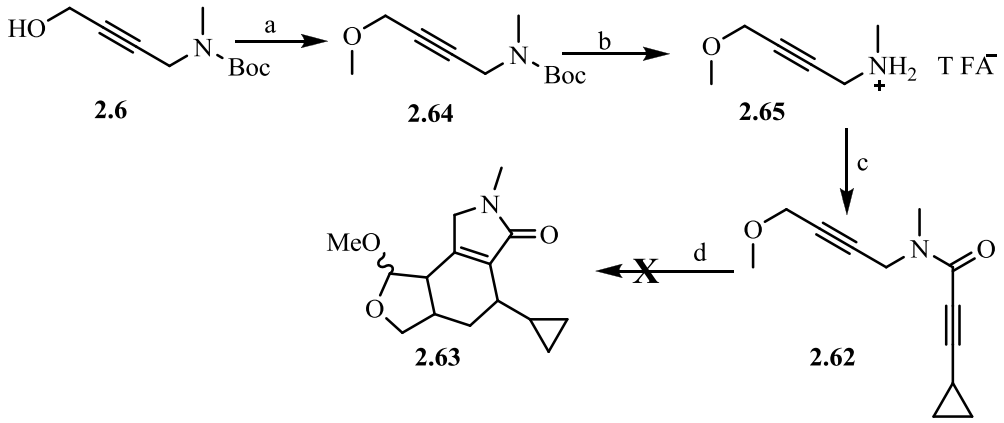


Scheme 2.24: Proposed cyclization reaction

2.5.1 Cyclization of 2.62 with Allyl Alcohol.

The investigation involved the use of a diyne and an external ene system provided by allyl alcohol.

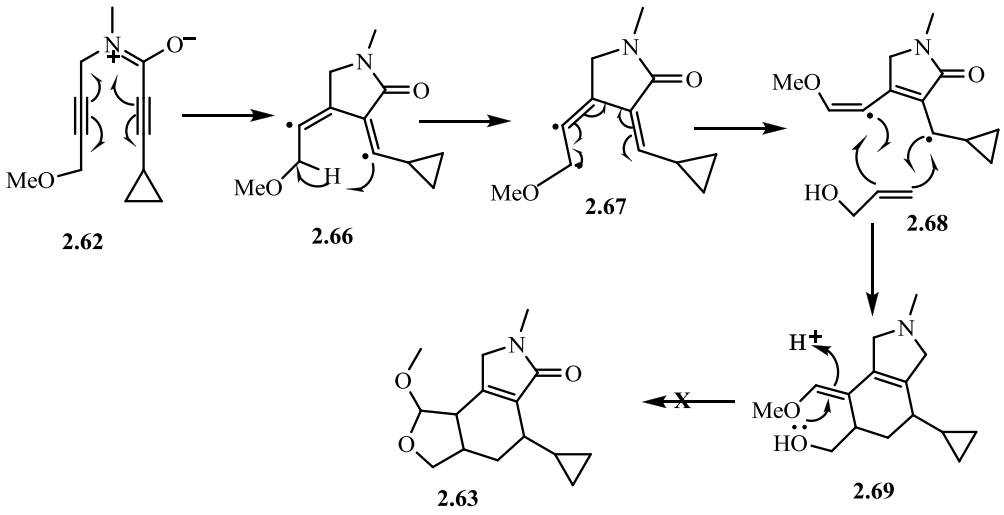
Synthesis of the precursor **2.62** followed exactly the same procedure for compound **2.6.** Thereafter compound **2.6** was deprotonated with sodium hydride and methylated using methyl iodide to produce **2.64** followed by Boc removal with TFA. Triethylamine was added to the TFA salt to generate the free amine in solution. Simultaneously the acyl chloride of the cyclopropylpropiolic acid was generated *in situ* (Scheme **2.18a**). This was coupled with the free amine to produce precursor **2.62**.



reagents conditions: (a) THF, NaH, MeI, (b) DCM, TFA, (c) NEt_3, DCM, 2.27 (d) toluene, allyl alcohol, (i) microwave, 140 ^{O}C, 5 h, (ii) reflux, 110^{O}C, 25 h.

Scheme 2.25: Investigation of intermolecular trapping.

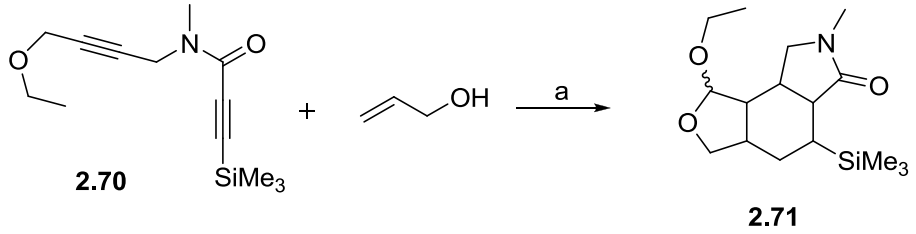
Thermal cyclization of precursor **2.62** was attempted in refluxing toluene for 25 h, ^{1}H NMR experiments on the expected product did not give any meaningful signal indicating that the starting material has probably been destroyed. The cyclization was again attempted in toluene under a microwave condition and the expected product was still not obtained after 5 h.



reagents and conditions: (a) toluene, reflux, allyl alcohol.

Scheme 2.26. Expected mechanism for the intermolecular cyclization

Initially we thought that the failure of the cyclization reaction may be due to the distance between the radical formed and the allyl alcohol which may have been too far apart for the necessary trapping that would lead to the closure of the second and third rings. However, Geering[161] found that the ethoxy analogue **2.70** cyclised in the presence of the allyl alcohol into compound **2.71.**

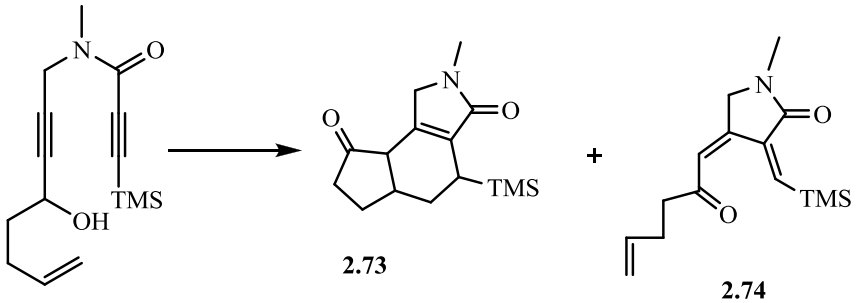


reagents and conditions: (a) Toluene, 120 ^{o}C, microwave

Scheme 2.27: Thermal cyclization of the ethoxy moiety

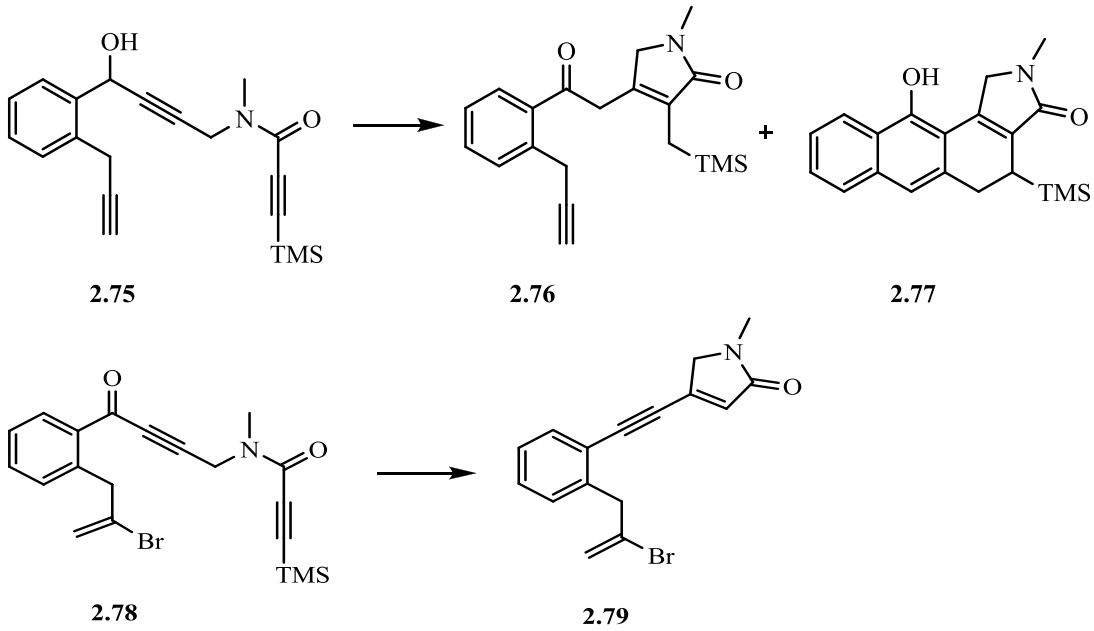
The proposed explanation is that the methoxy moiety is less stable than the ethoxy. Even though we were able to obtain the cyclised compound from the intermolecular

cyclization of the ethoxy moiety, we still cannot rule out the effect of the distance of the double bond on cyclization reactions. Findings by Board[38] (scheme **2.28**) and Woodford[163] (scheme **2.29**) showed that even when the double bond is within the molecule, but separated from the alkyne bond by more than four bonds (**2.72**) or a phenyl ring (**2.75** and **2.78**), the yield of the cyclised products were very low and partially cyclised compounds were obtained as major products.



reagents and conditions: toluene, reflux

Scheme 2.28: Complete and partial cyclization of 2.72[162].



reagents and conditions: toluene, reflux

Scheme 2.29: Complete and partial cyclization [163].

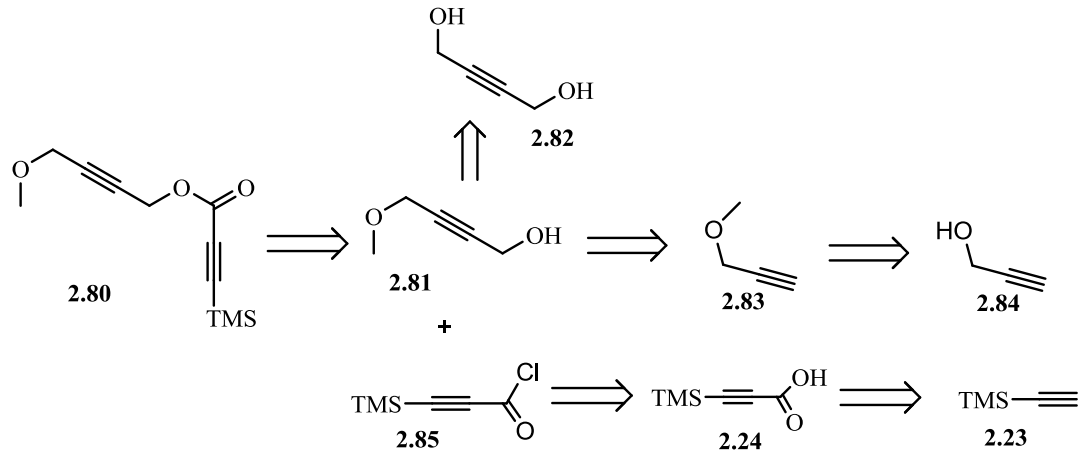
2.6 Investigations through Ether Linkage

To further extend and investigate the capability of the thermal cyclization reactions, we proceeded to make some variations to our precursors.

The amide linkage of compounds **2.62** was replaced with ether linkage and the alkyne terminal groups were also replaced to produce precursors **2.80, 2.86** and **2.89.**

Earlier work within the Parsons group has suggested that the presence of the silicon on the terminal alkyne of **1.222** has a profound effect on the stability of radicals α to the silicon [46, 47]. Hitherto we have studied cyclization reactions with substrates such as phenyl, methyl, ethyl, propyl and cyclopropyl groups, we now introduced the use of the TMS group for comparison.

2.6.1 Retrosynthesis of the precursors.

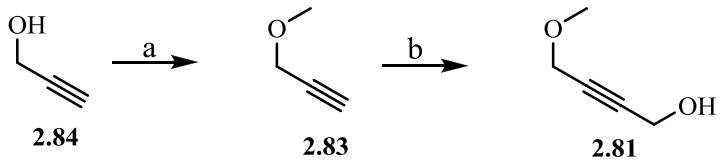


Scheme 2.30: Retrosynthesis analysis of 2. 80

2.6.2 Synthesis of Alcohols 2.81 and 2.88

Treatment of a solution of propargyl alcohol with aqueous sodium hydroxide followed by the addition of dimethyl sulphate[164-168] gave the propargyl ether **2.84**. Deprotonation

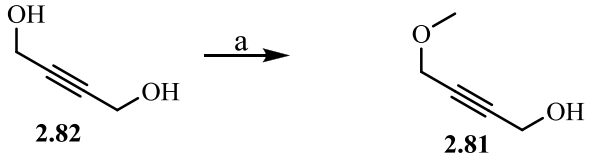
of the alkynic hydrogen of **2.83** with n-butyl lithium and subsequent addition of paraformaldehyde produced 4-methoxy propyn-2-ol, **2.81** in 65% yield.



reagents and conditions: (a) NaOH, H_2O, Me_2SO_4, (b) n-BuLi, $(CH_2O)n$, CH_3CN

Scheme 2.31: Synthesis of 2.8

Alternatively an excess (5 eq.) of recrystallised 2-butyn-1, 4-diol **2.82** was heated with aqueous sodium hydroxide in the presence of dimethyl sulphate and the mono alkylated product **2.81** was obtained in 87% yield. A very small amount of the di-alkylated product was also obtained. Another method that has been reported[48] is the treatment of the mono *t*-butyldimethylsilyl ether of butyne-1, 4 diol with sodium hydride and and the subsequent removal of the silyl protecting group with tetrabutylammonium fluoride in THF.



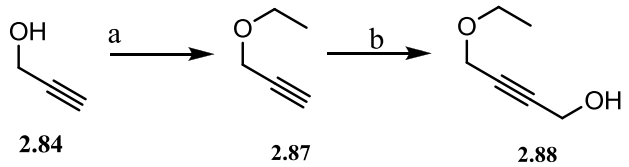
reagents and conditions: (a) NaOH, H_2O, Me_2SO_4,

Scheme 2.32: Alternate synthesis of 2.81

Even though the alternate method appeared to be more efficient, it however required the use of an excess of the starting material which made it to be less economical overall.

The reported method was not used so as to avoid the protection and deprotection steps.

The synthesis of the ethoxy alcohol was carried out in a similar manner.



2.84 **2.87** **2.88**

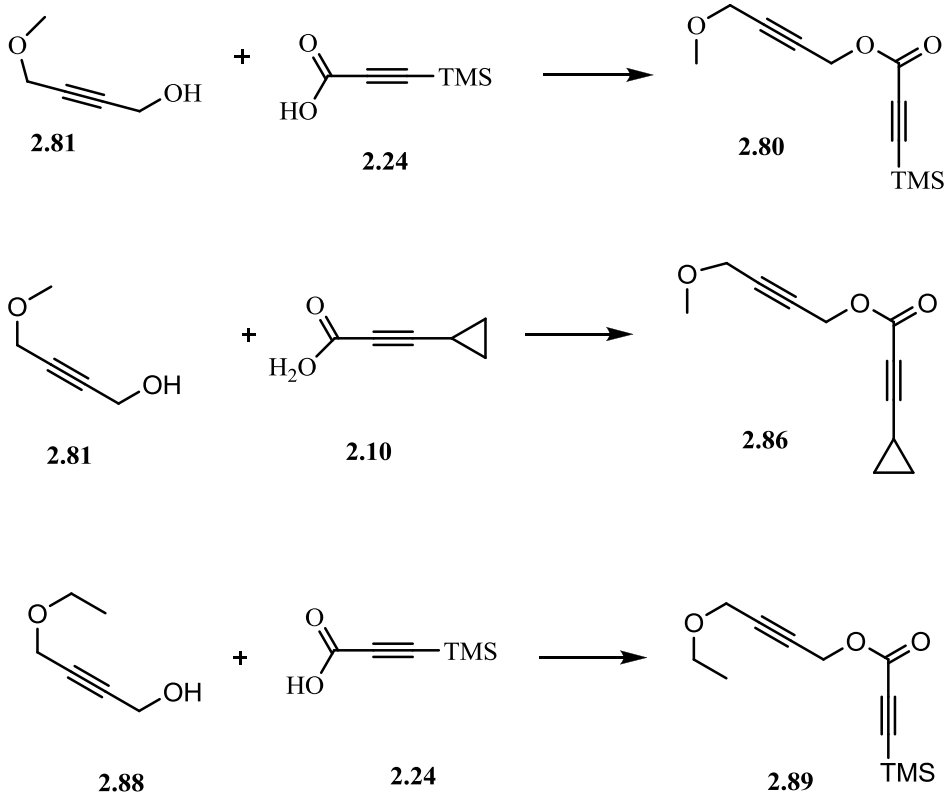
reagents and conditions: (a) NaOH, H_2O, Et_2SO_4, (b) n-BuLi, $(CH_2O)n$, CH_3CN,

Scheme 2.33: Synthesis of 4-ethoxypropyn-2,3-ol.

2.6.3 Coupling Reactions.

The method used for the formation of the amides, that is, coupling of the acyl chloride derivative of the acid with the alcohol did not give the expected product for the ester moieties. Viseux [169, 170] had earlier noted that in the coupling of complex acids and alcohols, the use of coupling agents resulting in the formation of acyl chloride and isobutyl chloroformate derivatives are quite unsatisfactory, their yields are inconsistent and reactions are not clean. Most of the other reagents used also did not give the expected products. In most cases there was formation of tar, and generally the results were quite unsatisfactory.

Finally, we resorted to the use of *1,1'*-carbonyldiimidazole (CDI)[171], a coupling reagent that acts as an activating agent for acids. Its reactivity is similar to but better than those of acyl chlorides. 1-[3-(Dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (EDCl) also proved to be a suitable coupling agent, but less suitable than CDI.



reagents and conditions: DCM, CDI.

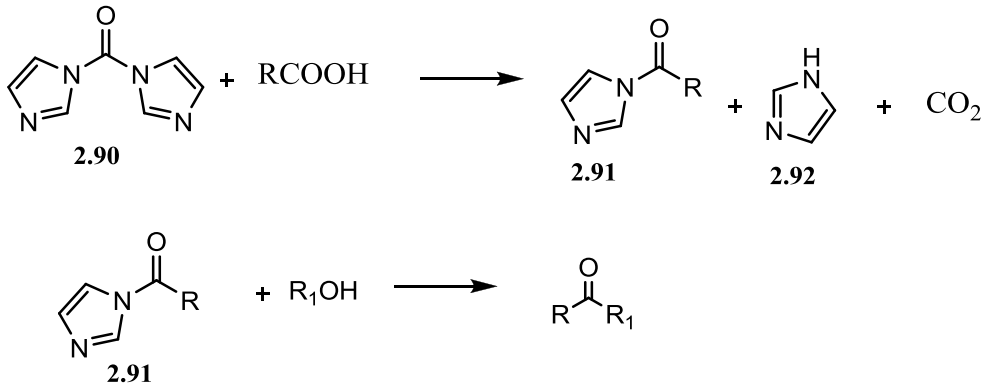
Scheme 2.34: Coupling reactions

Alcohol	Conditions	Yield
2.81	DCM, oxalyl chloride	Decomposition, SM
2.81	DCM, *Iso*-butylchloroformate	Decomposition, SM
2.81	DCM, Thionyl chloride	Decomposition
2.81	DCM, CDI	20% Product, 20% SM
2.81	DCM, EDCl	25%
2.81	DCM, EDCl, DMAP	Formation of tar
2.88	DCM, CDI, DMAP	Formation of tar
2.88	DCM, CDI	27%

Table 2.2. Result of coupling reactions

The CDI acts as a double electrophile linking two nucleophiles together by a carbonyl group, with the imidazole acting as a leaving group in the reaction. The reaction is

driven by the increase in entropy of the system. A typical reaction of CDI is illustrated below;

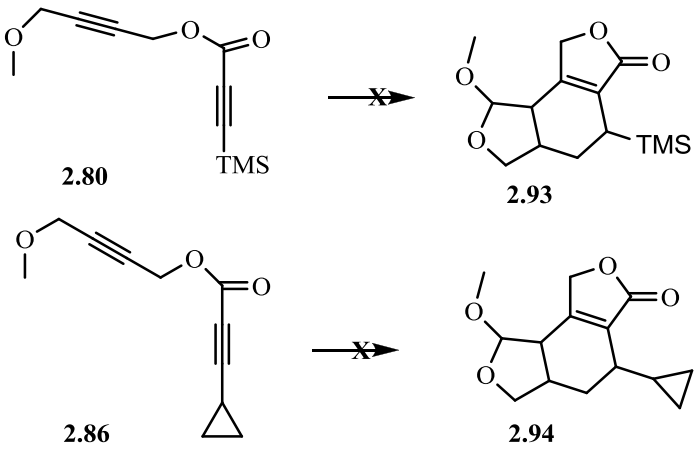


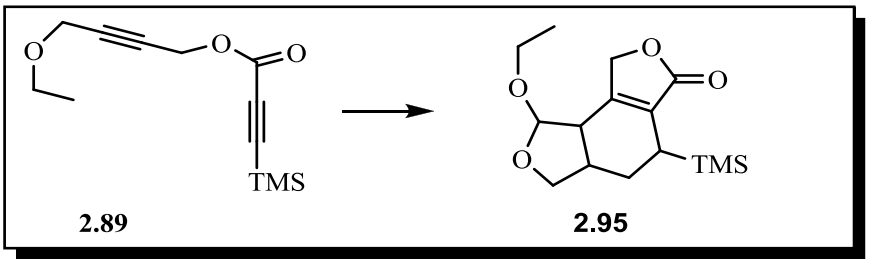
Scheme 2.35: Mechanism of CDI based coupling

2.6.4 Thermal Cyclization Reactions.

Initially precursor **2.89** was heated under reflux in toluene for 52 hours to give the tricycle in 75% yield. A repeat of the cyclization under the microwave condition showed completion after 5 h.

When the methoxy precursors, **2.80** and **2.86** were heated in the microwave for 5h each, they did not give the expected cyclization products, but rather decomposition of the starting materials was observed from the NMR analysis. Cyclization of **2.89** was also attempted in different solvent and the results are shown in table **2.2.**





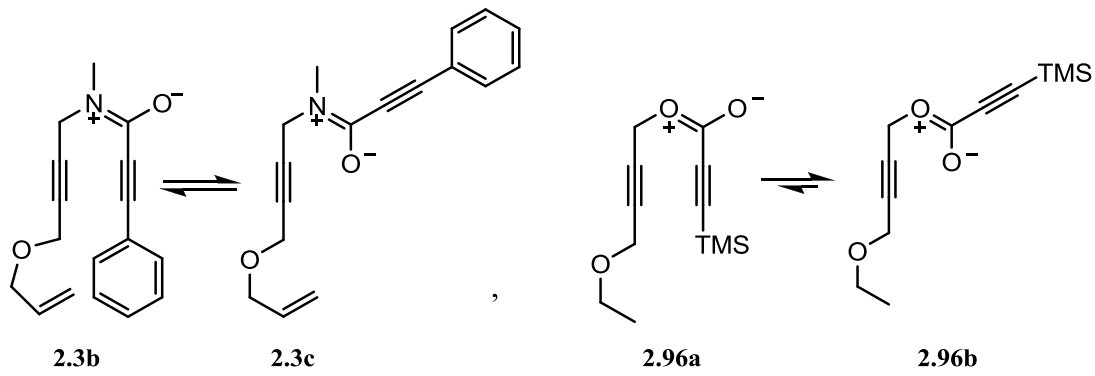
reagents and conditions: Toluene, allyl alcohol microwave, 130 ^{O}C, 75%.

Scheme 2.36; Thermal reactions of precursors 2.65, 2.71 and 2.74.

Solvent	Result (% yield)
Toluene, allyl alcohol	75
***d*8-toluene, allyl alcohol**	66
100% allyl alcohol	Failed reaction

Table 2.3: Cyclization of 2.74 in different solvents.

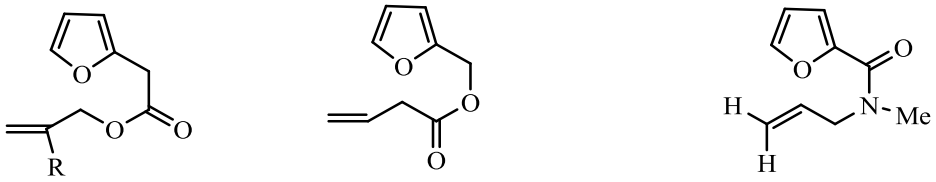
It was observed that even though precursor **2.89** cyclised to form the tricyclic compound **2.95** like the amide analogue, it took a much longer period of 52 h as against the 5 h for the amide moiety, this agreed with Waters[48] result. Accordingly Waters explained this observation by proposing that the ether moiety may have assumed the transoid (**2.96b**) geometry which is less favourable than the cisoid (**2.96a**) geometry for cyclization, while the cisoid geometry (**2.3b**) dominates in the amide moiety.



2.3b **2.3c** **2.96a** **2.96b**

Scheme 2.37: *Cis* and *Trans* resonance forms of the amide and ester.

In an earlier study Parker *et al*[173] have established the role of geometry in the cyclization reactions. They discovered that substrates, **2.97a** and **2.97b** in which the side chain contains an ester moiety are unreactive in an intramolecular Diels-Alder reaction, presumably because the molecule prefers the unreactive conformation in which the diene and dienophiles are transoid about the ester linkages, thus making it difficult for cyclization to occur. The amide moiety **2.98** was found to undergo Diels-Alder reaction when heated under reflux in benzene.



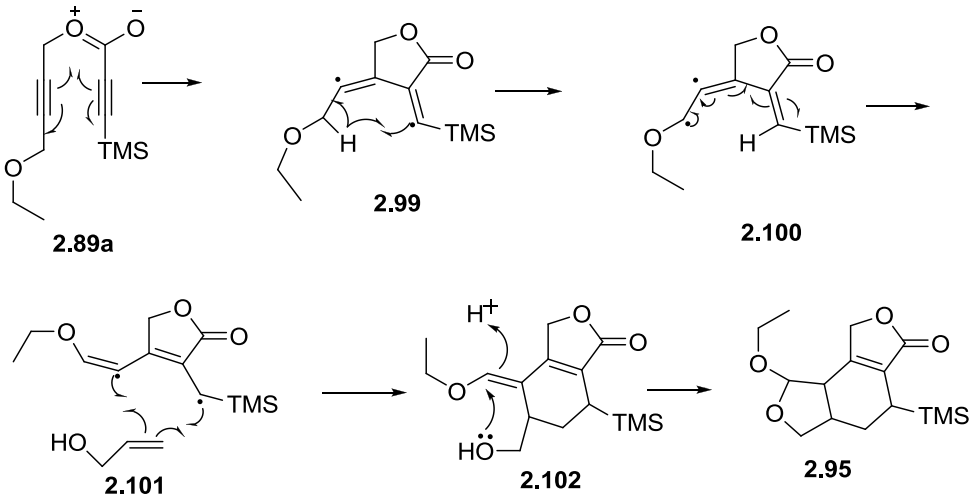
2.97a **2.97b** **2.98**

Figure 2.3: The ester and amide moieties.

2.6.5 Proposed Mechanism for Intermolecular Cyclization

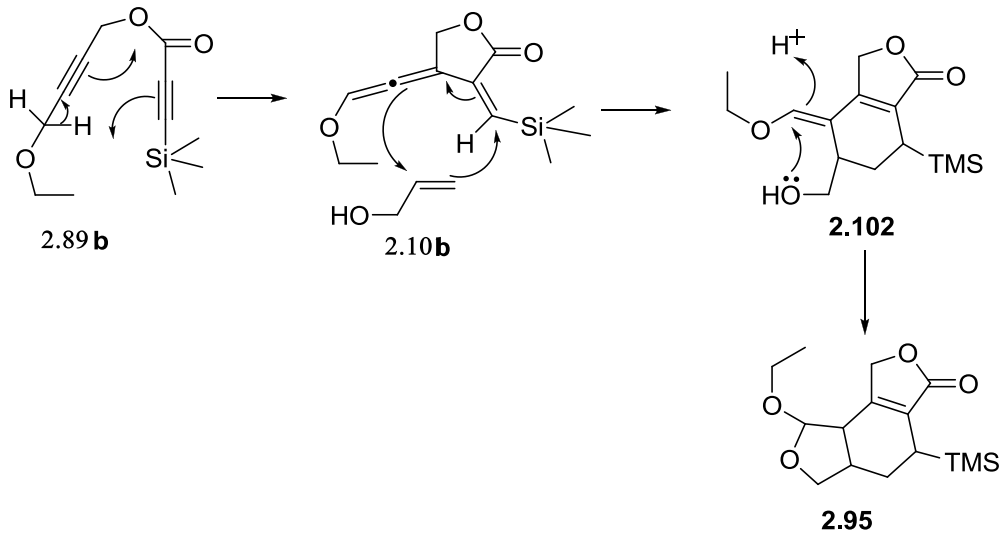
The intermolecular cyclization is assumed to have occurred through the biradical pathway as proposed for the intramolecular cyclization (scheme **2.13**). However after the double bond formation in the lactam ring in **2.86,** the required double bond for the

formation of the 6- membered ring was supplied by an external molecule (allyl alcohol). Formation of the second furan ring was accomplished with the lone pair electrons of the allyl oxygen.



Scheme 2.38: Proposed mechanism for 2.95

An alternative mechanism could involve an ene reaction followed by a Diels - Alder cycloaddition as shown in scheme **2.39b.**

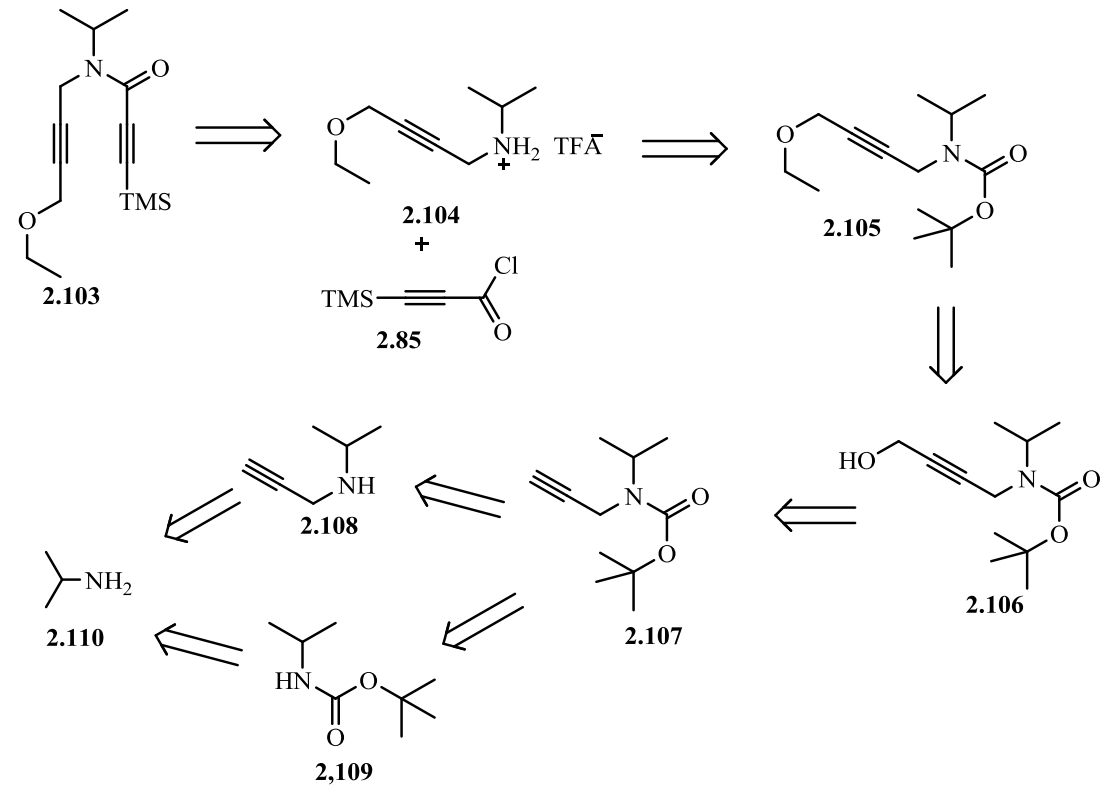


Scheme 2.39: Proposed mechanism for 2.95 via the ene reaction.

2. 7 Investigation of the Effect of a Bulky Group and the Use of Various Unsaturated Molecules.

Following the assumption that the cyclization was favoured by the cisoid geometry, it was anticipated that the attachment of a sterically demanding group on the nitrogen would enhance the cisoid geometry, displace the equilibrium to the right, decrease the distance between the two alkynic bonds and hence increase the rate of reaction. An isopropyl group was chosen for this study. The study also focused on the intermolecular trappings of the biradical formed.

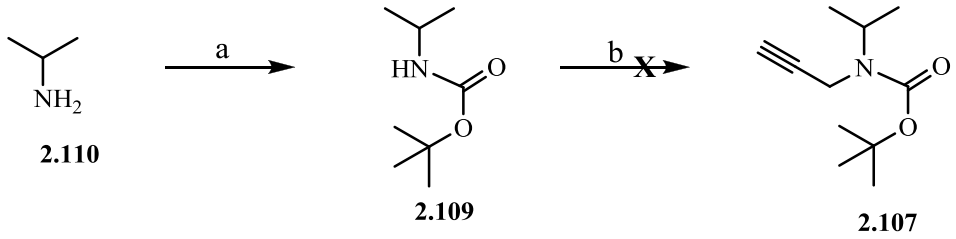
2.7.1 Retrosynthesis of the precursor.



Scheme 2.40 Retrosynthesis of Precursor 2.103.

2.7.2 Synthesis of the precursor

The starting material, *N*-isopropyl amine **2.110**, was Boc protected to give **2.109** in 51% yield. All attempts at propargylation of the protected amine proved abortive leading to the recovery of the starting material.



2.110 **2.109** **2.107**

reagents and conditions: (a) H_2O, $(Boc_2)O$, (b) table 2.3

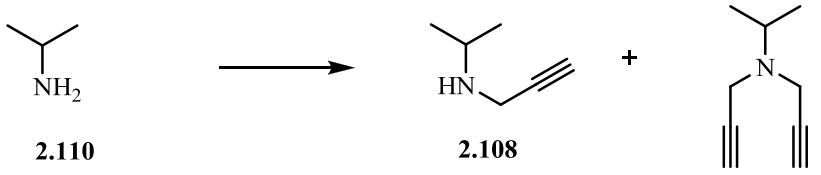
Scheme 2.41: Propargylation of Boc protected amine

Compound	reagents and conditions	results
2.94	THF, NaH, 0 ^oC, propargyl bromide, rt	SM
2.94	DMF, KH, 0 ^oC, propargyl bromide[156] rt	SM
2.94	DMF, NaH, 0 ^oC, propargyl bromide[164,165] rt	SM
2.94	THF, *n*-BuLi, -78oC, propargyl bromide	SM

Table 2.4: Reagents and conditions for propargylation of protected amine

Alternatively propargylation of the unprotected amine was carried out using propargyl bromide. The amine acts as its own base in the reaction. The mono-substituted amine becomes very reactive towards a second substitution with the propargyl bromide. Therefore an excess of the amine was used, (5: 1 equivalent) and the propargyl bromide

was added very slowly through an addition syringe over a 15 h period. Purification of the crude by flash chromatography produced only the di-substituted amine. Therefore the crude was purified by distillation to give a mixture of mono and di-substituted *N*-isopropyl-*N*- propargyl amine (b.p, 110-111 ^{o}C) and toluene (110 ^{o}C). The desired product was inseparable from the mixture.



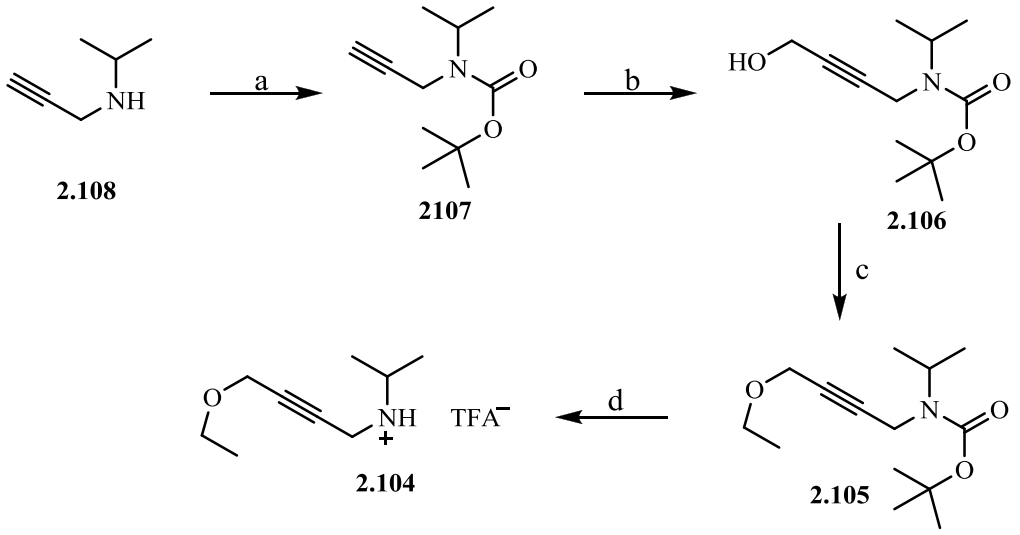
2.110 **2.108** **2.111**

reagents and conditions: H_2O, Propargyl bromide, KOH, reflux.

Scheme 2.42: Propargylation of the amine

Treatment of **2.108** with Boc anhydride in acetonitrile followed by subsequent quenching of unreacted Boc anhydride with triethylamine afforded the protected compound **2.107** in 66% yield. Compound **2.107** was deprotonated with butyllithium at -78^{o}C in THF, addition of paraformaldehyde cleanly afforded the desired alcohol **2.106** as an orange liquid in 89% yield. Deprotonation of the alcohol with sodium hydride in THF followed by alkylation with ethyl iodide produced the ester **2.106** in 80% yield. (Scheme **2.43**)

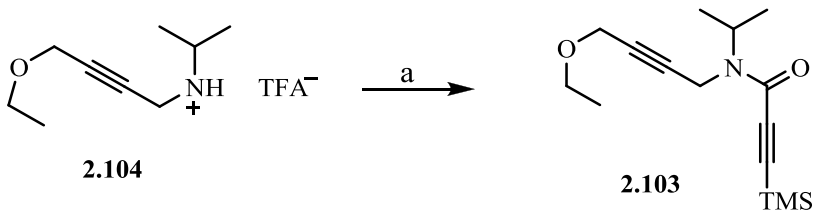
The Boc group was cleanly removed from the compound with the use of TFA in dichloromethane and the TFA salt **2.104** of the compound formed was used without purification for the subsequent coupling reaction.



Reagents and conditions **:** (a) MeCN, BOC anhydride, Et_3N, (b), *n*-BuLi, THF, Paraformaldehyde. (c) NaH, THF. CH_3CH_2I. (d) TFA, DCM.

Scheme: 2. 43: Synthesis of 2.104

The amide which is the precursor for the cyclization was obtained from **2.104** in three sequential steps as outlined in section **2.2.6** and the yield over two steps was 35%.



reagents and conditions (a) Et_3N, DCM, **2.70**

Scheme 2.44: Amide formation

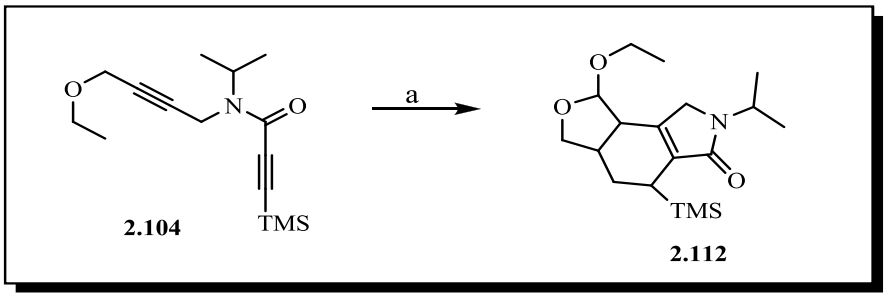
2.7.3 Thermal cyclization reaction

Allyl alcohol was added to the precursor **2.104** and refluxed in toluene. Tlc analysis and visualization under the UV light indicated the completion of the cyclization reaction

after 2 h. The cyclization reaction occurred at a faster rate than for the *N*-methyl group moiety which took 5 h, and much faster than the ester moiety which took 25 h to cyclise.

The relatively short time taken for the completion of the cyclization reaction in this case is an indication of the positive effect of the sterically demanding group on the geometry of the molecule. As envisaged a sterically demanding group like the *iso*-propyl group must have favoured the cisoid geometry (scheme **2.37**, bringing the two alkynic bonds into closer proximity thereby increasing the rate of cyclization reaction. This observation is similar to the Thorpe- Ingold effect or gem-dimethyl effect[187] which is the acceleration of cyclization by substituents in the chain and is often used in organic synthesis as a ring-closing effect.[188]The Thorpe-Ingold effect caused by the increase in the size of two substituents on a tetrahedral centre leads to enhanced reaction between the parts of the other two substituents. The effect is attributed to a kinetic effect caused by the substituents compressing the angle at the carbon bringing the end groups closer together.[189] Kathleen *et al*.,[190] also confirmed that the gem-dimethyl effect actually buttress ring formation. We can safely suggest that the introduction of the *iso*-propyl group on the central nitrogen of the precursor **2.103** may have indeed created an effect similar to the Thorpe-Ingold effect.

It is assumed that the mechanism would be identical to that of compounds **2.1** and **2.2.** (Scheme **2.13**)

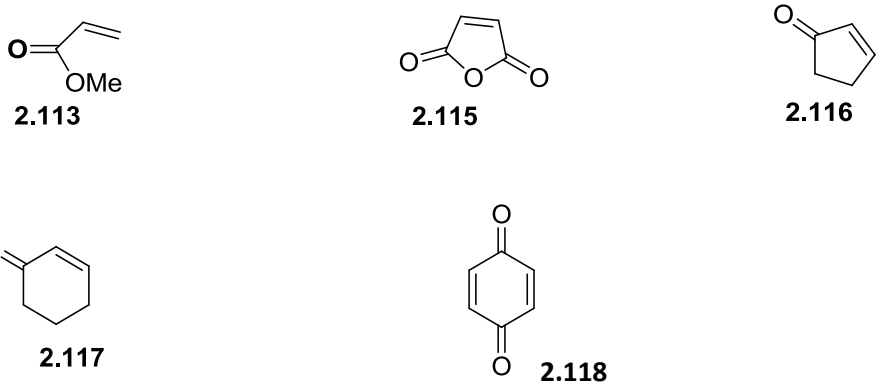


2.104 2.112

reagents and conditions: (a) toluene, allyl alcohol, reflux, 110^{o}C

Scheme 2.45: Thermal cyclization of 2.104

The success of this cyclization reaction at a faster rate motivated us to investigate the use of some other unsaturated compounds, such as methyl acrylate (**2.113),** maleic anhydride (**2.115),** cyclopent-2-enone **(2.116),** cyclohex-2-enone **(2.117),** and benzoquinone **(2.118**) for the intermolecular cyclization. It is envisaged that the success of such reactions would be of great application in the synthesis of highly functionalised heterocycles. The reactions were carried out following the established typical thermal cyclization procedure used above.

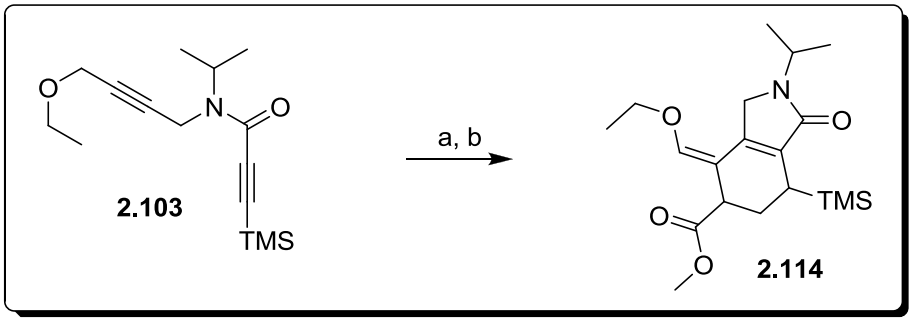


2.113 2.115 2.116

2.117 2.118

Figure 2.4: Selection of some alkenes

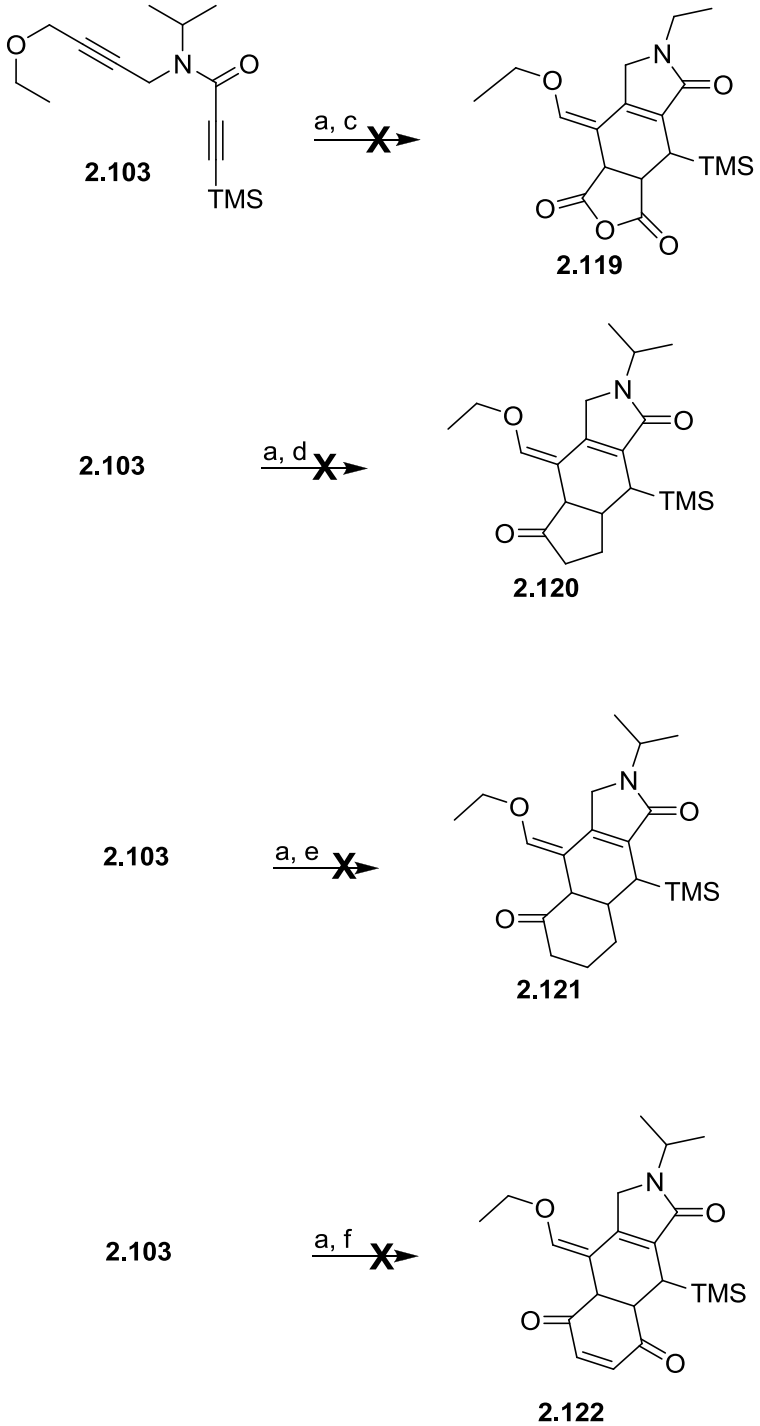
Unfortunately only the acyclic alkene, methyl acrylate **2.113**, reacted in the intermolecular cyclization with the precursor **2.103**. All the others failed to react.



reagents and conditions: (a) toluene, reflux, 110 ^{O}C, (b) methyl acrylate (**2.113**)

Scheme 2.46 Intermolecular thermal cyclization

The expected cyclization reactions are as shown below;



reagents and conditions: (a); toluene, reflux, 110 ^{O}C, 5h (c) **2.115**, (d) **2.116,** (e) **2.117** (f) **2.118.**

Scheme 2.47 Expected thermal cyclizations

We thus proposed that the failure of these reactions may be attributed to the restricted availability of the double bonds or the π-electrons necessary for the intermolecular cyclization coupled with the fact that the radical formed may be very short lived, leaving no time for the ringed alkenes to attack. On the other hand, if an allene intermediate is involved, the Diels-Alder transition state may be too sterically demanding to allow a cyclization to take place.

Chapter 3

Conclusion and Future Work

3.1 Conclusion

The cyclization reactions of enediynes; such as the Bergman cyclization and Myers-Saito cyclization found to be responsible for the DNA cleavage of the antitumour antibiotics have also been found to be versatile reactions in the synthesis of pharmaceutical products and in organic synthesis.

Within the Parsons group highly functionalised enediynes have been discovered to undergo thermal cyclization cascade reactions which allows for the formation of heterocyclic ring systems in one synthetic operation[48].

In this research, efforts were made to diversify the basic structure of the enediyne to increase the scope and applicability of these thermal cyclization reactions. Amide and ester linkers were incorporated to increase the functionality of the product, thus making them relevant to the synthesis of heterocycles. It was found that the amide moiety has a higher rate of cyclization than the ester moiety. The effects of phenyl and cyclopropyl groups on the terminal alkynes were studied, and we discovered that the rate of the cyclization reactions were dependent on the type of substituent. These results also proved that silicon though not having a stabilising effect on the biradical intermediate, has a profound positive effect[48]on the rate of cyclization. The rate of cyclization was greatly decreased with the attachment of the cyclopropyl group on the terminal alkyne than it was for the phenyl and the alkyl groups.

We also found out that the intramolecular cyclization was more highly favoured than the intermolecular cyclization (scheme **2.15** and scheme **2.19**). In the intermolecular cyclizations, only the acyclic alkenes (schemes **2.40** and **2.42)** were able to react with the biradical generated in the reaction.

Attachment of a sterically demanding group on the nitrogen was found to increase the rate of cyclization, reducing the time taken by almost 60%. This result lends credence to the fact that the amide linker assumes the cisoid geometry prior to cyclization and that this is more favoured than the transoid geometry. (Scheme **2.29**) The increase in the rate of the reaction is also assumed to be due to an effect similar to the Thorpe-Ingold effect. From the discussion so far a number of mechanistic approaches have been proposed. These include;

- the biradical mechanism,
- a simple ene reaction which would produce an allene that would undergo a Diels-Alder cycloaddition reaction.

Many natural compounds contain a six membered ring system and the control of the stereochemistry has been an important issue in synthesis.[183] If the cyclization reactions in these study are confirmed to be through the Diels-Alder cycloaddition, they would therefore be of immense value in controlling the stereochemistry of ring systems.

The discussion is far from been conclusive and the confirmation of the specific pathway is still an ongoing investigation within the Parson group.

3.2 Future Work

In future more investigations should be carried out on the coupling reactions both for the amide and the ester moieties. Even though we have successfully used oxalyl chloride and CDI respectively, the yields were far from satisfactory.

It would also be necessary to explore other ways to synthesize *N*-isopropylpropargyl amine in order to increase the yield.

The scope of this thermal cyclization should be expanded by further modifications of the substrates;

- the amide and ester linkers could be replaced by sulphur,
- changing the substituent groups on the two terminals alkynes and
- introducing highly substituted aromatic groups at both terminals.

Comparative studies on the rate of reaction should also be carried out by attaching bulkier groups to the nitrogen. Studies should be carried out using highly substituted and branched chains on the nitrogen atom in other to establish if there is an effect comparable to the Thorpe-Ingold effect. The stereochemistry of the various precursors should be noted before and after the cyclizations to be able to determine the stereo selectivity of the cyclization reactions.

Chapter 4

Experimental

General Experimental Procedure

Unless otherwise stated, commercially available reagents were used without purification and all reactions were conducted in an inert atmosphere of nitrogen gas. All glassware was oven dried and glassware for reactions requiring anhydrous conditions were flame dried.

Tetrahydrofuran and diethyl ether were distilled from sodium using benzophenone as an indicator; dichloromethane and acetonitrile were distilled from calcium hydride for immediate use. Triethylamine and toluene were distilled from calcium hydride and stored over potassium hydroxide.

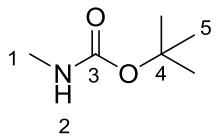
Reactions were monitored by tlc using Merck glass backed tlc plates pre-coated with a 250μm layer of 60 F_{254} silica gel. Visualization was achieved using potassium permanganate and vanillin dips and ultraviolet light at 254 nm where applicable.

Purification of products were carried out by flash chromatography using Merck Kiesel gel 60 silica gel eluting with commercially obtained eluents.

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker advance AC-300 at 300 MHz and 75 MHz respectively or a Varian-500 at 500 MHz and 125 MHz respectively. Samples were run in deuterochloroform at ambient temperature. Chemical shifts were quoted in ppm, using residual solvent peaks as internal standards (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C. Correlation experiments were run to provide clarity where necessary. Low and high resolution mass spectra were recorded on a Fison VG autospec mass spectrometer and or on a Bruker Daltonics Apex III (ESI).

Infrared spectra (IR) were recorded on a Perkin Elmer 1710 Fourier transform spectrometer with sodium chloride plates.

N-Methylamine carbamate 2.15



The synthesis of compound **2.15** was achieved following an adaptation of the method reported by Nanchen S and Pfaltz A.[156] Methylamine hydrochloride (2g, 29.63mmol) was added to THF (20mL). The flask was immersed in an ice /salt bath (-10^{o}C). Triethylamine (2.99g, 4.13mL, 29.63mmol) and Boc anhydride (6.47g, 29.63mmol) were added to the solution and the reaction was stirred for 10min after which the ice/salt bath was removed and the reaction was allowed to stir for a further 16 h. The mixture was concentrated under reduced pressure and a white solid was obtained. The solid was dissolved in diethyl ether, washed with water to dissolve the triethylamine hydrochloride. The mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over magnesium sulphate and concentrated under reduced pressure to give a yellow liquid. The crude product was purified by distillation at atmospheric pressure to give a colourless liquid at 170^{o}C. (33%)

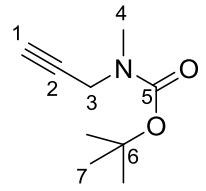
IR (NaCl, cm^{-1}); 3353, 2977, 2355, 1688, 1524, 1453, 1418, 1391, 1273, 1250,

^{1}H NMR (300 MHz, $CDCl_3$) δ; 4.8 (1H, s, H2), 2.60 (3H, d, J = 6.4. H1), 1.38 (9H, s, H5)

^{13}C NMR (75MHz, $CDCl_3$) δ; 156 (C3), 79 (C4), 28 (C5), 27 (C1).

HRMS (ESI+) Calc for $C_6H_{13}NO_2Na$, *m/z* = 154.0838, found=154.0840 (1.072 ppm error)

N-Methyl prop-2-ynylcarbamic acid *tert*- butyl ester.[46,47,48] 2.7



(a) To a solution of *N*-methylpropargylamine (20.48g, 296.70mmol) in CH_2Cl_2 (150mL) was added Boc anhydride (77.7g, 356.10mmol) in small portions at 0°C. The reaction mixture was stirred at room temperature for 20 h. *N, N'*-Dimethylethylenediamine (20ml) was added and the reaction was stirred for another 1h at room temperature. The mixture was washed with hydrochloric acid (1M, 3 x 150mL),a saturated solution of potassium carbonate, and brine (1 x 100mL each). The solution was dried over magnesium sulphate, filtered and evaporated under reduced pressure.. Purification of the residue by vacuum distillation at 50-60°C (at 0.1 mbar) gave the desired product as colourless oil. (39.33g, 79%).

(b) Sodium hydride (0.458g, 11.45mmol) was added into THF (20mL), *N*-methylamine carbamate (1.5g, 11.45mmol) was added and the reaction was left for 1h in an ice bath under continuous stirring. Propargyl bromide (1.70g, 11.45mmol) was added slowly and the reaction was left overnight to warm up to room temperature. The reaction was quenched with water (20mL) and extracted with diethyl ether (30mL). The aqueous layer was washed with diether (2 x 20mL) and the combined organic layer was dried over magnesium sulphate and concentrated under reduced pressure. Purification by column chromatography (33% of ethyl acetate in petroleum ether) gave the desired compound as colourless oil. (50%).

(c) Propargyl bromide (21.24g, 26.55mL, 0.18mmol) was added to a solution of methylamine (104.625, 1.35mol) in water. The solution was stirred for 1h and sodium hydrogen carbonate (30.24g, 0.36mol) was added and the mixture was filtered. The filtrate was distilled to give a colourless distillate at 70-80 ^{o}C at atmospheric pressure. The distillate was a mixture of methylamine and methylpropargyl amine. The mixture was added to a solution of Boc anhydride (30.5g, mmol) in water (100mL) and stirred for 1 h. The product was extracted with ethyl acetate (3 x 100mL) dried over magnesium sulphate and concentrated under reduced pressure to give a light yellow liquid. Purification was by column chromatography (25% of diethyl ether in hexanes). Two products were obtained; (i) *tert*-butyl methyl (prop-2-ynyl) carbamate (11.5g 35%), and (ii) *tert*-butyl *N*-methyl carbamate **2.15** (6.3g, 15%). The two compounds are colourless solutions.

Analysis conformed to the literature report.[48]

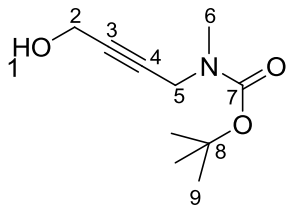
IR (NaCl, cm^{-1}); 3309, 2981, 2933, 2252, 1798, 1690

^{1}H NMR (300 MHz, $CDCl_3$) δ; 4.01 (2H, s, br, H3), 2.89 (3H, s, H4), 2.21 (1H, t, *J* = 2.4, H1), 1.40 (9H, s, H7).

^{13}C NMR (75MHz, $CDCl_3$) δ; 155.3 (C5), 80.12 (C6), 79.321 (C1), 72. (C2), 38, (C3), 34.54 (C4), 28.48 (C7).

HRMS (ESI+) Calc for $C_9H_{15}NO_2Na$, *m/z* 192.0994, found 192.0996(2.5ppm error)

tert-Butyl 4-hydroxybut-2-ynyl (_N_-methyl) carbamate [46, 47] 2.6.



To a solution of Boc propargylamine **2.7** (20g, 118.5 mmol) in dry THF (120ml) was added n-BuLi (2.5M in hexane) (141.6mmol, 61.56mL) at -78 ^{o}C under an atmosphere of nitrogen and stirred for 1h. Parafomaldehyde (7.18g, 237mmol) was added in one portion and the reaction was stirred for 20h to warm up to room temperature .Water (200mL) was added and the product was extracted with diethyl ether (300mL). The aqueous layer was extracted with diethyl ether (3 x 40mL). The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and were concentrated under reduced pressure. Purification by column chromatography (50% of petroleum ether in ethyl acetate) gave the desired product **2.6** as a light yellow oil. (19.55g, 83%)

Analysis conformed to the reported literature value. [46 , 47]

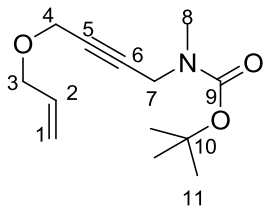
IR (NaCl, cm^{-1}) 3419, 2976, 2932, 2251, 1692, 1367.

^{1}HNMR δ (300 MHz, $CDCl_3$) δ; 4.25 (2H, s, H2), 4.00 (2H, s, H5), 3.62 (1H, s, br, H1 (OH)), 2.80 (3H, s, H6), 1.40 (9H, s, H9)

^{13}C NMR δ: (75 MHz, $CDCl_3$) δ 155.7 (C7), 82.4 (C4), 80.0 (C3), 73.0 (C8), 50.2 (C2), 38.5 (C5), 33.9 (C6), 28.7 (C9).

HRMS (+ESI): Calcd for $C_{10}H_{17}O_3N$ Na, m/z= 222.1098, found, 222.1100 (1.146 ppm error)

(4-Allyloxy-but-2-ynyl)-*N*-methyl carbamic acid *tert*-butyl ester 2.5



Sodium hydride (4.82g, 120.60mmol) was put in a flame dried flask and covered with dry THF (100mL) under nitrogen and stirring. Compound **2.6** (16.00g, 80.4mmol) was added and the reaction left for 1h in an ice bath. Allyl bromide (14.58g, 10.42mL, 120.60mmol) was added slowly and the reaction left overnight at room temperature. The product was extracted with water (100mL) and diethyl ether (200mL) .The aqueous layer was washed with diethyl ether (2 x 40mL) and the organic layer was washed with brine, dried over magnesium sulphate and concentrated under reduced pressure. Purification by column chromatography (10% ethyl acetate in petroleum ether) gave compound **2.5** as a pale yellow liquid. (14.5g, 80%).

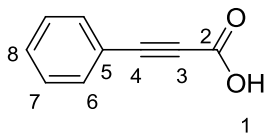
IR (NaCl, cm^{-1}) 3583, 3518, 3382, 3252, 2978, 2931, 2856, 2545, 2285, 2087, 1995, 1739, 1691, 1480, 1367, 1245,

^{1}H NMR δ (300MHz, $CDCl_3$) δ; 5.80 (1H, m, H2), 5.1-5.2(2H, m, H1) 4.05(2H, s, H3) 4.0-3.9 (4H, H4 and H7), 2.85 (3H, s, H8), 1.39 (9H, s, H11).

^{13}C NMR δ (75MHz, $CDCl_3$) δ; 155(C9), 134. (C1), 118. 7(C2), 82 (C5), 79.2 (C6), 70.2 (C3), 57. (C4), 38.3 (C7), 33. 5(C8), 28. 2(C11).

HRMS (ESI+); calcd for $C_{13}H_{21}O_3NNa$. m/z = 262.1414, found=262.1413, Error = 4.82 ppm

3-Phenylpropiolic acid [46, 47, 48] **2.9**



Compound **2.9** was prepared by a modification of the procedure reported by Parsons *et al.,*[46,47] . To a solution of phenylacetylene (11.16g, 109.3mmol) in dry THF (70mL) was added n-BuLi (2.5M in hexane, 52.46mL, 131.16mmol) at -78^{o}C. The reaction was left for 1h. Dry carbon dioxide gas was bubbled into the reaction for 2h at room temperature and hydrochloric acid (1M, 60ml) was added. The mixture was extracted with diethyl ether (2×50mL).

Sodium hydroxide solution (1M, 20mL) was added to the organic layer until alkaline. It was again extracted with diethyl ether (50ml). The aqueous layer was acidified with hydrochloric acid (1M, 50mL), and extracted with diethyl ether (50mL). The aqueous layer was washed with diethyl ether (2×30mL). The combined organic layer was dried with $MgSO_4$, filtered and concentrated under reduce pressure to give an off white solid which was purified by crystallization (PE/EA) and the product was obtained as colourless crystals.

Melting point, 138^{o}C conform to the literature value of 136-138^{o}C.[191]

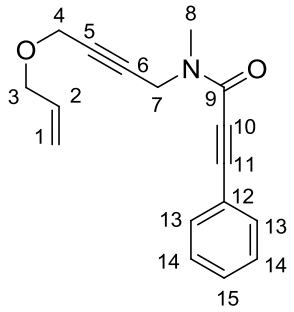
IR (NaCl, cm^{-1}); 2700, 2198, 1668, 1488, 1416, 1302, 1206.

^{1}HNMR δ (300 MHz, $CDCl_3$) δ; 7.4, 7.2, 7.1 (Phenyl hydrogens)

^{13}C NMR δ (75 MHz, $CDCl_3$) δ; 154 (C2), 133.5 (6), 131 (C8), 128.9 (C7), 119.5 (C5), 89.1 (C4), 80.4 (C3)

m/z (EI+) 146, 129, 102, 76.

N-(4-(Allyloxy)-but-2-ynyl)-*N*-methyl-3-phenylpropiolamide 2.3.



Formation of the amide **2.3** was carried out in stages, as follows;

a) Removal of the Boc protecting group.

To a solution of the ether **2.5** (164mg, 0.69mmol) in DCM (2mL) was added concentrated hydrochloric acid (32%, 1.35mL,13.43mmol) The reaction was left under nitrogen with stirring for 47h. Solid K_2CO_3 was added to neutralise any unreacted hydrochloric acid until there was no more effervescence. The mixture was washed with DCM (2 x20mL). All the organic extracts were combined and concentrated under reduced pressure. The amine salt **2.19** was obtained as a yellow oily liquid and used without any purification.

Alternatively, to a solution of **2.5** (4g, 16.7mmol) in DCM (100mL) was added TFA (6.35ml, 83.65mmol) dropwise (over10mins). The solution was left at room temperature for 20 h. The solvent was thereafter removed by evaporation under reduced pressure. [48] The amine salt **2.20** was obtained as a dark brown oily liquid. This was used without any purification.

b) *In situ* preparation of phenylpropynoyl chloride **2.26**

To a solution of the phenylpropynoic acid **2.9** (3.09g, 21.23mmol) in DCM (30mL), was added oxalyl chloride (1.85ml, 21.23mmol) and 2 drops of DMF(cat) at 0^{o}C in an

ice bath. The ice bath was removed after 5min and the reaction was left for 1h at room temperature after which it was presumed that the acid has been completely converted into the acid chloride **2.26**. The acid chloride was used immediately.

c) Formation of the amide.

To a solution of the unpurified amine salt **2.20** [(4-allyloxy-but-2-ynyl)*N*-methylamine trifluoroacetate] in DCM (30mL) was added triethylamine (Et_3N) (1.01g, 13.96mL, 10.02 mmol) dropwise over 15min at 0 ^oC under a flow of nitrogen. The freshly prepared phenylpropynoyl chloride **2.26** (3.09g, 21.23mmol) in DCM was added into the mixture dropwise and stirred for 1h.

The solution was washed with hydrochloric acid (1M, 50ml), saturated aqueous sodium hydrogencarbonate (50mL), H_2O (50mL), and brine (50mL), dried over magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (20% ethyl acetate in petroleum ether) to give the expected product, **2.3**. (1.60g, 66%, over 2 steps)

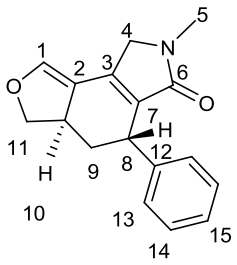
IR (NaCl, cm^{-1}); 3583, 2854, 2214, 1634, 1491, 1443, 1398, 1345, 1272, 1210,

^1H NMR (300MHz, $CDCl_3$) δ; 7.5 (2H, m, H13), 7.3 (3H, m, H14 & 15), 5.9(1H, m, H2) 5.2 (2H, m, H1), 4.46 (1H, s, H7), 4.3 (1H,s, H7), 4.2 (2H, m, H3), 4.0 (2H, m, H4, 3.3 (1.5H, s, H8), 3.0 (1.5H, s ,H8).

^{13}C NMR (75MHz, $CDCl_3$) δ; 154.65, (C9), 134.25, (C2), 132.70, 130.579, 128.94, 120.70, (phenyl ring), 118.4, (C1), 91 29, (C10), 81.55,(C11), 81 (C6), 80.55, (C5), 71.17, (C3), 57.7, (C4), 41.36/35.994, (C7), 32.21(C8).

HRMS (ESI^+); calcd for $C_{17}H_{17}NO_2Na$, m/z 290.1151 found 290.1143 (2.8ppm error).

(3aR,5S)-7-Methyl-5-phenyl-4,5,7,8-tetrahydro-3H-furo[3,4-e]isoindol-6-(3-aH)-eno 2.1



A solution of 3-phenylpropynoic acid (4-allyloxy-but-2-ynyl)-methyl-amide 2.3 (0.660g, 2.472mmol) in dry toluene (10mL) was stirred and heated under reflux at 110 ^{o}C for 5 h. Completion of the reaction was determined by tlc monitoring. There was no work-up and the solvent was removed under reduced pressure. The reddish brown solid obtained was re-dissolved in DCM and purified by column chromatography (33% ethyl acetate in petroleum ether). Recrystallisation of the brown solid gave colourless crystals **2.1** in 71% yield.

Melting point 173 ^{o}C.

See Appendix 1 for the X-ray

IR (NaCl, cm^{-1}); 2920, 1672 (s), 1639, 1490, 1451, 1418, 1391, 1277, 1235, 1211.

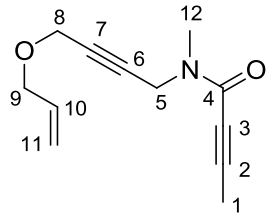
^{1}H NMR (300MHz, $CDCl_3$) δ ; 7.2 (2H, m, H13), 7.0, (3H, m, H14 & 15), 6.4, (1H, s, H1), 4.5(1H, dd, *J*=12.57Hz, H11), 4.1-4.2 (2H, dd, *J*= 12.6Hz, H4), 4.05, (IH, d, *J*= 8.9Hz, H8), 3.7, (1H, m, H11), 3.2(1H, m, H10), 2.99, (3H, s, H5), 1.8 and 2.2 (2H, dd, *J*=7.5Hz, H9),

^{13}C NMR (75MHz, $CDCl_3$) δ; 171.2 (C6), 143 (C12), 142 (C3), 141 (C1), 130

(C7), 128 (C13 and 14), 126 (C 15), 113 (C2), 76 (C11), 52 (C4), 36 (C9), 37 (C10), 38 (C8), 30 (C5).

HRMS (ESI^+); calcd for $C_{17}H_{17}NO_2Na$, m/z 290.1151 found 290.1143 (2.8ppm error).

N-(4-(Allyloxy)-but-2-ynyl)-*N*-methylbut-2-ynamide 2.38



To a stirred solution of (4-allyloxy-but-2ynyl)-methyl-carbamic acid *tert*-butyl ester **2.5** (1.0g, 4.17mmol) in DCM (40mL) was added TFA (1.23mL, 8.34mmol) dropwise (over 5min) at 0 ^{o}C. The solution was stirred for a further 15h, after this time the resulting solution was concentrated under reduced pressure to yield amine TFA salt **2.20** (1.07g, quant.) as a dark oil which was used without further purification.

To a solution of the unpurified amine salt **2.20** in DCM (7mL) was added triethylamine (1.86mL, 13.3mmol) via dropwise addition (over 10min) at 0 ^{o}C. To the reaction mixture was added freshly prepared but-2-ynoyl chloride **2.44** (427mg, 4.17mmol) in DCM (7mL) dropwise and was stirred for a further 30min. The solution was washed with hydrochloric acid solution (1M, 15mL), saturated aqueous sodium hydrogen carbonate solution (15mL), and water (15mL), dried over magnesium sulphate and concentrated under reduced pressure. The yellow oil was then purified by flash column chromatography, eluting with 50% diethyl ether in hexanes to afford the title compound **2.38** (694 mg, 81%(over 2 steps)) as a colourless oil.

IR (NaCl, cm^{-1}), 2922, 2236, 1627, 1045.

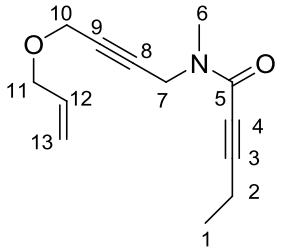
^{1}H NMR (500MHz, $CDCl_3$) δ; 5.98-5.81 (1H, m, H10), 5.35-5.17 (2H, m H11),

4.46-4.20 (4H, m, H8 & H9), 4.19-3.98 (2H, m, H5), 3.26/3.01 (3H, s, H12), 1.96 (3H, s, H1).

^{13}C NMR (125MHz, $CDCl_3$) δ; 154.2 (C4), 133.7 (C10), 118.0 (C11), 98.0 (C2), 95.5 (C6), 80.8 (C7), 80.2/80.1 (C3), 70.6 (C9), 57.3 (C8), 40.8 (C5), 35.3/31.6 (12), 1.8 (C1).

HRMS (ESI^+); calcd for $C_{12}H_{15}O_2NNa$, m/z = 228.0995, found 228.1004.

N-(4-(Allyloxy)-but-2-ynyl)-*N*-methylpent-2-ynamide 2.39



To a stirred solution of (4-allyloxy-but-2ynyl)-methyl-carbamic acid *tert*-butyl ester **2.5** (1.0g, 4.17mmol) in DCM (10mL) was added TFA (1.23mL, 8.34mmol) dropwise (over 5min) at 0 ^{o}C. The solution was stirred for a further 15h, after this time the solution was concentrated under reduced pressure to yield amine TFA salt **2.20** (1.07g, quant.) as a dark oil which was used without further purification.

To a solution of the unpurified amine salt **2.20** (1.07g, 4.17mmol) in DCM (7mL) was added triethylamine (1.62mL, 12.6mmol) via dropwise addition (over 10min) at 0 ^{o}C. To the reaction mixture was added freshly prepared pent-2-ynoyl chloride **2.45** (487mg, 4.17mmol) in DCM (3mL) dropwise and was stirred for a further 30 min. The solution was washed with hydrochloric acid solution (1M, 15mL), saturated aqueous sodium hydrogen carbonate solution (15mL), and water (15mL), dried over magnesium sulphate and concentrated under reduced pressure. The yellow oil was then purified by column chromatography, eluting with 50% diethyl ether in hexanes to afford the title compound **2.39** (733 mg, 80% (over 2 steps)) as a colourless oil.

IR (NaCl, cm^{-1}), 2234, 1712, 1630, 1442, 1423, 1397, 1265, 1245, 1124, 1069, 932.

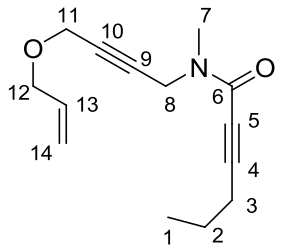
^{1}H NMR (500MHz, $CDCl_3$) δ;5.98-5.81 (1H, m, H12), 5.35-5.17 (2H, m, H13), 4.44-4.22 (4H, m, H10 & H11), 4.20- 3.98 (2H, m, H7), 3.26 (1.5H, s, H6), 3.01

(1.5H, s, H6), 2.29 (2H, q, J = 3.6, 7.5Hz, H2), 1.13 (3H, t, J = 6.3Hz, H1)

^{13}C NMR (125MHz, $CDCl_3$) δ; 154.2/154.1 (C5), 133.9/133.8 (C12), 117.7/117.6 (C13), 94.8/94.7 (C3), 80.3/80.2 (C8), 77.0/76.9 (C9), 73.0/72.8 (C4), 70.6/70.5 (C11), 57.27/57.21 (C10), 40.74 (C7), 35.4/35.3 (C6),31.42 (C2), 12.8/12.7 (C1).

HRMS (ESI^+); calcd for $C_{13}H_{17}NO_2Na$, m/z = 242.1157, found 242.1153.

N-(4-(Allyloxy)-but-2-ynyl)-*N*-methylhex-2-ynamide 2.40



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To a stirred solution of (4-allyloxy-but-2ynyl)-methyl-carbamic acid *tert*-butyl ester **2.5** (1.0g, 4.17mmol) in DCM (40mL) was added TFA (1.23mL, 8.34mmol) dropwise (over 5min) at 0 ^{o}C. The solution was stirred for a further 15h, after this time the solution was concentrated under reduced pressure to yield amine TFA salt **2.20** (1.07g, quant.) as a dark oil which was used without further purification.

To a solution of the unpurified amine salt **2.20** in DCM (7mL) was added triethylamine (1.62mL, 12.6mmol) via dropwise addition (over 10min) at 0 ^{o}C. To the reaction mixture was added freshly prepared hex-2-ynoyl chloride **2.46** (548mg, 4.2mmol) in DCM (3mL) dropwise and was stirred for a further 30 min. The solution was washed with hydrochloric acid solution (1M, 15mL), saturated aqueous sodium hydrogen carbonate solution (15mL), and water (15mL), dried over magnesium sulphate and concentrated under reduced pressure. The yellow oil was then purified by column chromatography, eluting with 50% diethyl ether in hexanes to afford the title compound **2.40** (877 mg, 90% (over 2 steps)) as a colourless oil.

IR (NaCl, cm^{-1}), 2965, 2233, 1627, 1442, 1396, 1245, 1123, 1073, 916.

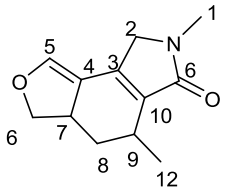
^{1}H NMR (500MHz, $CDCl_3$) δ; 5.98-5.81 (1H, m, H13), 5.35-5.17 (2H, m, H14), 4.46-4.22 (4H, m, H11 & H12), 4.19- 3.99 (2H, m, H8), 3.26 (1.5H, s, H7), 3.01

(1.5H, s, H7), 2.30-2.22 (2H, m, H3), 1.96 (2H, m, H3) 1.54 (2H, apt. ddd, *J* = 1.6, 6.2, 7.0 Hz, H2), 0.94 (3H, t, *J* = 7.2Hz, H1).

^{13}C NMR (125MHz, $CDCl_3$) δ; 154.1 (C6), 133.9/133.8 (C13), 117.7/117.6 (C14), 93.6/93.5 (C4), 80.3/80.2 (C9), 73.8/73.6 (C10), 70.6/70.5 (C5), 57.3/57.2 (C11), 40.8 (C8), 35.4/35.3 (C7), 31.5 (C2), 21.2/20.8 (C3), 13.4 (C1).

HRMS (ESI^+); calcd for $C_{14}H_{19}NO_2Na$, m/z = 256.1013, found 256.0993.

5,7-Dimethyl-4,5,7,8-tetrahydro-3*H*-furo[3,4-e]isoindol-6(3aH)-one 2.35



A solution of *N*-(4-(allyloxy)-but-2-ynyl)-*N*-methylbut-2-ynamide **2.38** (500mg, 2.44mmol) in dry toluene was prepared in a microwave tube. The reaction mixture was heated at 120 ^{o}C, and 1 atm for 2 h. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography using neat diethyl ether to afford the title compound **2.35** as a yellow oil. (310mg, 62%).

IR (NaCl, cm^{-1}), 3697, 2973, 2865, 1672, 1644, 1598, 1032.

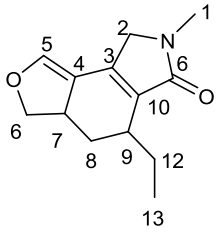
^{1}H NMR (500MHz, $CDCl_3$) δ; 6.52 (1H, s, H5), 4.68 (2H, t, *J* = 9.0 Hz, H6), 4.02-3.82 (2H, m, H2), 3.36 (1H, q, *J* = 10.6Hz H7), 3.01 (3H, s, H1), 2.87-2.80 (1H, m, H9), 1.53 (2H, apt, dt, J = 5.6, 12.6Hz, H8), 1.18 (3H, d, *J* = 6.8Hz, H12)

^{13}C NMR (125MHz, $CDCl_3$) δ; 172.9 (C11), 141.9 (C5) 138.8 (C3), 133.8 (C10), 114.5 (C4), 77.8 (C6), 52.6 (C2), 41.7 (C7), 33.4 (C8), 30.3 (C1), 30.0 (C9), 20.2 (C12).

HRMS (ESI^{+}); calcd for $C_{12}H_{15}O_2NNa$, m/z, 228.0995, found 228.1002.

5-Ethyl-7-methyl-4,5,7,8-tetrahydro-3*H*-furo[3,4-e]isoindol-6(3a*H*)-one

2.36



A solution of *N*-(4-(allyloxy)-but-2-ynyl)-*N*-methylpent-2-ynamide **2.39** (500mg, 2.28mmol) in dry toluene (10ml) was prepared in a microwave tube. The reaction mixture was heated at 120 ^{o}C and 1 atm for 2 h. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography using neat diethyl ether to afford the title compound **2.36** as a yellow oil. (321mg, 64%).

IR (NaCl, cm^{-1}), 2930, 1673, 1646, 1449, 1421, 1394, 1265, 1092, 1063, 908.

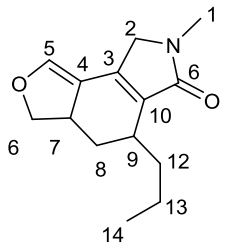
^{1}H NMR (500MHz, $CDCl_3$) δ; 6.43 (1H, s, H5), 4.67 (1H, t, *J* = 8.9Hz, H2a), 4.02-3.84 (2H, m, H6), 3.78-3.69 (1H, dd, *J* = 8.7, 12.8 Hz, H2b), 3.38-3.20 (1H, m, H7), 2.98 (3H, s, H1), 2.21-2.09 (1H, m, H9) 1.65-1.53 (2H, apt, dt, *J* = 5.8, 12.4Hz, H8), 1.42-1.31(1H, m, H12), 1.31-1.19(1H, apt, ddd, *J* = 4.9, 9.7, 18.1,Hz H12), 0.98 (3H, t, *J* = 7.3Hz, H13).

^{13}C NMR (125MHz, $CDCl_3$) δ; 171.7 (11), 140.9 (C3), 139.2 (5) 133.5 (10), 113.0 (C4), 77.3 (C6), 51.4 (C7), 37.3 (C8), 33.5 (C2), 30.3 (C9), 29.75 (C1), 26.7 (C12), 12.2 (C13).

HRMS (ESI^{+}); calcd for $C_{13}H_{17}O_2NNa$, m/z = 242.1157, found 242.1153

7-Methyl-5-propyl-4,5,7,8-tetrahydro-3H-furo[3,4-e]isoindol-6(3aH)-one

2.37



A solution of *N*-(4-(allyloxy)-but-2-ynyl)-*N*-methylhex-2-ynamide **2.40** (500mg, 2.14mmol) in dry toluene (10ml) was prepared in a microwave tube. The reaction mixture was heated at 120 ^{o}C, and 1 atm for 2 h. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography using neat diethyl ether to afford the title compound **2.37** as a yellow oil. (340mg, 64%).

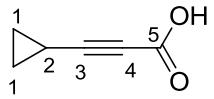
IR (NaCl, cm^{-1}), 3054, 2979, 2305, 1682, 1446, 1421, 1265, 1113

^{1}H NMR (500MHz, $CDCl_3$) δ; 6.43 (1H, s, H5), 4.67 (1H, t, *J* = 8.9Hz, H2a), 4.02-3.84 (1H, m, H2b), 3.78-3.69 (2H, dd, *J* = 8.7, 12.8 Hz H6), 3.38-3.20 (1H, m, H7), 2.98 (3H, s, H1), 2.21-2.08 (1H, m, H9), 1.65-1.53 (2H, apt, dt, J = 5.8,12.4 Hz, H8), 1.42-1.31 (2H, m, H13), 1.23 (2H, apt, dt, J = 4.91, 9.7, 18.1 Hz, H12), 0.90 (3H, t, J = 7.3 Hz, H14).

^{13}C NMR (125MHz, $CDCl_3$) δ; 171.3 (C11), 140.8 (C3), 139.1 (C5), 133.7 (C10), 113.0 (C4), 76.7 (6), 51.4 (C7), 37.3 (C12), 36.29 (C8), 31.69 (C1), 30.36 (C8), 27.5 (C9), 20.8 (C13), 14.1 (C14).

HRMS (ESI^{+}); calcd for $C_{14}H_{19}O_2NNa$, m/z = 256.1013, found 256.0985.

3-Cyclopropylpropiolic acid 2.10



Compound **2.10** was prepared by a modification of the procedure reported by Parsons *et al.,*[46,47] . n-BuLi (2.5M in hexane) (158.08mL, 363.6mmol) was added to a solution of cyclopropylacetylene (20g, 303.03mmol) in dry diethyl ether (200mL) at -78 ^{o}C. The reaction was left for 1h before dry carbon dioxide gas was bubbled into the reaction for 2h at room temperature. Hydrochloric acid (1M, 200mL) was added and the mixture was extracted with diethyl ether (2×100mL). Aqueous sodium hydroxide (200mL) was added to the organic layer (until alkaline). And it was again extracted with diethyl ether (100ml).

The aqueous layer was again acidified with hydrochloric acid (1M, 200mL), the mixture was extracted with diethyl ether (150mL). The aqueous layer was washed with diethyl ether (2 x 75mL). The combined organic layers were dried with magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by recrystallization to give the title compound **2.10** as white crystals in 82% yield.

Melting point 52 ^{o}C (literature m.pt = 55^{o}C)[191]

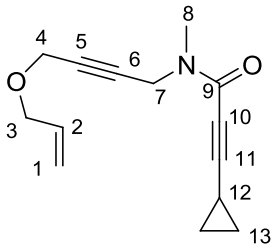
IR (NaCl, cm^{-1}); 2938, 2218, 1167, 1411, 1281.

^{1}H NMR (300MHz, $CDCl_3$) δ; 0.95(4H, m, H1), 1.4 (1H, m, H4)

^{13}C NMR (75MHz, $CDCl_3$) δ; 158,(C5), 96, (C3), 68, (C4), 1.4, (C2), 0.9, (C1).

EI+; 110, 93, 77, 66, 44

N-(4-(Allyloxy)but-2-ynyl)-*N*-methyl-3-cyclopropylpropiolamide 2.4



The first step involved the *in-situ* preparation of 3-cyclopropylpropioloyl chloride **2.10a**. To a solution of the cyclopropylpropiolic acid (0.247g, 2.25mmol) in DCM (10mL) was added oxalylchloride (0.201ml, 2.25mmol) and 2 drops of DMF at 0 ^{o}C (ice bath). The ice bath was removed after 5min and the reaction was left for 1h at room temperature. Compound 2.10a was obtained and used *in situ*.

In the second step, DCM (10mL) was added into a solution of the unpurified amine salt **2.20**, followed by the dropwise addition of triethylamine (1.366g, 1.88mL, 13.5mmol) over 15min under a flow of nitrogen at 0 ^{o}C. The freshly prepared phenylpropioloyl chloride in DCM was added dropwise into the mixture above and stirred for 1h.

The mixture was washed with hydrochloric acid (1M), saturated sodium hydrogen carbonate, water, and brine, (10mL each). It was dried over magnesium sulphate, filtered and concentrated under reduced pressure. The dark yellow oily liquid obtained was purified by column chromatography (20% ethyl acetate in petroleum ether) to give the compound **2.4** as a light yellow liquid in 67% yield. (over 2 steps)
IR (NaCl cm^{-}1); 2931, 2224, 1627, 149, 1443, 1375, 1341, 1270, 1210.

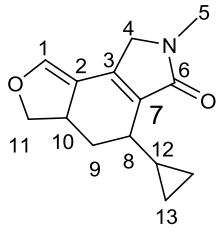
1H NMR (500MHz, $CDCl_3$) δ ; 5.82-5.95 (1H, m H2), 5.4 (1H, m, H1), 5.2 (1H, m, H1) 4.38 (1H, s, H7), 4.25 (1H,s, H7), 4.15 (2H,d, m, H3), 4.0(2H, *J* = 8.0 Hz, H4),

3.17 (1.5H, s, H8), 2.9 (1.5, s, H8), 1.39 (1H, dd, *J* = 7.0, 7.01Hz, H12), 0.9 (4H, m, H13).

^{13}C NMR (125MHz, $CDCl_3$) δ; 154 (C9), 134 (C2), 118 (C1), 95.8 (C10), 81 (C11), 80 (C6), 79 (C5), 71 (C3), 57.9 (C4), 41.2 (35.9) (C7), 35 (30) (C8), 10 (C13), 0.8 (C12).

HRMS (ESI+), Calc for $C_{14}H_{17}NO_2Na$, m/z = 254.1151, found= 254.1159. (3.12ppm error).

5-Cyclopropyl-7methyl-4,5,6,7,8-tetrahydro-3H-furo[3,4-e]isoindol-6(3aH)- one. 2.2



To the amide **2.4**, (3-cyclopropylpropynoic acid (4-allyloxy-but-2-ynyl)-methyl amide) (0.220g, 1.07mmol) was added toluene (10mL) followed with the addition of allyl alcohol (0.75g, 1.28mmol). The mixture was heated under reflux at 110 ^{o}C for 25 h under nitrogen with continuous stirring. The solvent was evaporated leaving a black reddish solid. The solid was re-dissolved in DCM and purification by column chromatography (33% ethyl acetate in petroleum ether) gave the product as a yellow tinted solid in 80% yield. However all efforts at recrystallisation failed to produce crystals required for X-ray crystallography.

Melting point 118 ^{o}C.

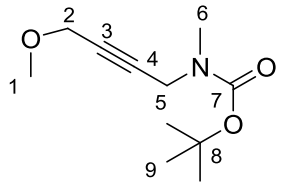
IR (NaCl cm^{-1}); 2921, 1668, 1445, 1169, 1017.

^{1}H NMR (500 MHz, $CDCl_3$)δ; 6.56 (1H, s, H1), 4.8 (1H, t, *J* = 8.9Hz, H11), 4.0 (2H, d, H4), 3.84 (1H, dd, *J* = 11.1, 23.5 Hz, H11), 3.55 (1H, d, *J* = 11.5Hz, H10), 3.0 (3H, s, H5), 2.20 (1H, d, *J* = 7.0 Hz, H9), 2.07 (1H, d, *J* = 7.0Hz, H8), 1.5 (1H, td, *J* = 5.0 ,12.4, Hz, H9), 0.75 (2H, m, H13), 0.50 (1H, d, *J* = 7.1Hz, H12), 0.40 (1H, d, *J* = 7.1Hz, H12), 0.20 (1H, d, *J* = 4.4Hz, H12).

^{13}C NMR (125 MHz, $CDCl_3$) δ; 160 (C6), 142 (C3), 140 (C1), 134 (C7), 110 (C2), 63 (C11), 54 (C10), 50 (C4), 43.8 (C8), 36 (C5), 33 (C), 29(C9), 13 (C2), 3.0 (C1).

HRMS (ESI+) Calcd for $C_{14}H_{17}NO_2Na$, m/z 254.1151, found, 254.1157 (2.2ppm error.

tert-Butyl- 4-methoxybut-2-ynyl-*N*-methylcarbamate 2.64



To sodium hydride (2.1g, 52.46mmol) covered with dry THF, was added *tert*-butyl- 4- hydroxy but-2-ynyl *N*-methylcarbamate **2.6** (8.70g, 43.71mmol) under a flow of nitrogen gas and stirring. The reaction was left for 1h in an ice bath after which methyl iodide (7.40g, 3.24mL, and 52.46mmol) was added slowly and the reaction was left overnight at room temperature. The reaction was quenched with water (100mL) and the product extracted with diethyl ether (150mL). The aqueous layer was washed with diethyl ether (2 x 40mL).The organic layer was washed with brine (40mL), dried over magnesium sulphate and concentrated. The crude product was purified by column chromatography (20% of ethyl acetate in petroleum ether) to give a pale yellow liquid. (7.9g, 85%)

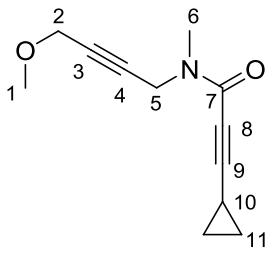
IR (NaCl cm^{-1}), 2979, 2932, 2898, 2252, 1289, 1482, 1455, 1421, 1368, 1251, 1152, 1123.

^{1}HNMR: (500 MHz, $CDCl_3$) δ; 4.05 (4H, s, H2 and H5), 3.35 (3H, s, H1), 2.85 (3H, s, H6), 1.4 (9H, s, H9)

^{13}C NMR: (125 MHz, $CDCl_3$) δ; 155.6 (C7), 82 (C4), 80 (C3), 79 (C8), 60 (C2), 58 (C1), 38 (C5), 33.8 (C6), 28 (C9).

HRMS (ESI+) Calcd for $C_{11}H_{19}NO_3Na$, m/z 236.1257, found 236.1255 (7.6 ppm error).

3-Cyclopropyl-*N*-(4-methoxybut-2-ynyl)- *N*-methylpropiolamide 2.62



To a solution of **2.64** in DCM (150mL) was added TFA (11.64ml, 152.6mmol) dropwise (over10mins). The solution was left at room temperature for 16 h. The solvent was thereafter removed by evaporation under reduced pressure, and a dark brown oily liquid was obtained, **2.65**. This was used without any purification.

A solution of the unpurified amine salt **2.65** was made in DCM (50mL) followed by a dropwise addition of triethylamine (18.52g, 25.51mL, 183mmol) over 20 min under a flow of nitrogen at 0^{o}C. A freshly prepared cyclopropylpropioloyl chloride, **2.10a** in DCM was added dropwise into the mixture above and stirred for 1h. The mixture was washed with hydrochloric acid (1M), saturated sodium hydrogen carbonate, water, and brine, (50mL each). It was dried over magnesium sulphate, filtered and concentrated under reduced pressure. The dark yellow oily liquid obtained was purified by column chromatography (10% of methanol in dichloromethane) to give the compound **2.62** as a light yellow liquid in 11% yield (over 2 steps).

IR (NaCl cm^{-1}); 3584, 3446, 2933, 2222, 1627, 1449, 1400, 1341, 1278, 1990, 1124, 1094.

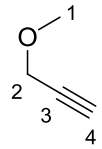
1H NMR (500MHz, $CDCl_3$) δ; 4.3 (1H, s, H5), 4.18 (1H, s, H5), 4.0 (2H, d, *J* = 2.5Hz, H2), 3.25 (3H, d, *J* = 7.5, H1), 3.1 (1.5H, d, *J* = 3.5Hz, H6), 2.85 (1.5H, d, *J*

= 3.8Hz, H6), 1.3 (1H, m, H10), 0.75 and 0.85 (4H, m, H11).

^{13}C NMR (125MHz, $CDCl_3$) δ; 154 (C7), 97 (C9), 80(C3), 79 (C4), 71 (C8), 60 (C2), 57.5 (C1), 41 (C5), 35 /31) (C6), 9 (C11), (C 10 not shown)

HRMS (ESI+), Calc for $C_{12}H_{15}NO_2Na$, m/z = 228.0993 found= 228.0994 (0.5297ppm error).

3-Methoxypropyne 2.83[168]



Compound **2.83** was prepared by the method reported by Perez *et al* [168] . To a mixture of propargyl alcohol (54g, 0,963mmol, and 56.2mL) and water was added sodium hydroxide solution (52g, 13M, 100mL) and the mixture was heated under reflux for 2 h. The mixture was allowed to cool down from 70 ^{o}C to 40^{o}C and kept at 40 ^{o}C during the dropwise addition of dimethyl sulphate. The mixture was left to reflux for 2h at 60 ^{o}C. Distillation of the mixture gave the crude at 63-65 ^{o}C. The crude product was purified by fractional distillation at atmospheric pressure to give the pure product at 59-61 ^{o}C (same as in literature) in 65% yield.

Analysis conformed to the literature.[168]

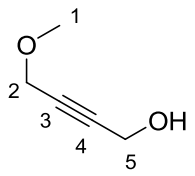
IR (NaCl cm^{-1}); 3284, 2945, 2843, 2129, 2012, 1718, 1453, 1338, 1306.

^{1}HNMR: (500 MHz, $CDCl_3$) δ; 4.07 (2H, d, J = 2.4Hz, H2), 3.38 (3H, s, H1), 2.47 (1H, t, J = 2Hz, H4).

^{13}C NMR: (125 MHz, $CDCl_3$) δ; 80 (C3), 74.2, (C4) 60 (C2), 58.8(C1).

m/z (EI+) 31, 39, 69, 71

4-Methoxybutyn-2-ol[164-168]. 2.81



a) To 3-methoxypropyne **2.83** (15g, 214mmol) in THF (10mL) was added n-BuLi (102.8mL, 257mmol) at -78 ^{o}C under nitrogen and continuous stirring. The reaction was left for 1 h, after which paraformaldehyde (12.9g, 428.6 mmol) was added and the reaction was left overnight (16 h) to warm to room temperature. The reaction was quenched with water (50mL) and extracted with diethyl ether (100mL). The aqueous layer was washed with diethyl ether (2 x 40mL). The organic layer was dried over magnesium sulphate, filtered and evaporated. Purification by flash chromatography (50% ethyl acetate) gave the desired product as a yellow oily liquid. 18.6g, 41% based on one equivalent of the propargyl alcohol).

b) Recrystallised 2-butyne-1, 4-diol **2.82** (10g, 0.116mmol) was heated with sodium hydroxide (50mL, 13M) at 70 ^{o}C for 30min, this was followed by dropwise addition of a solution of dimethyl sulphate (2.93g,2.2mL, 0.023mol) in water (3mL). The reaction was left for 2 h at 60-65 ^{o}C. The mixture was distilled at 59-61 ^{o}C to obtain the crude which was purified by fractional distillation at 60 ^{o}C to produce a colourless liquid, 2g, 87% (based on one equivalent of the propargyl alcohol).

IR (NaCl cm^{-1}); 3389, 2936, 2825, 2170, 2024, 1735, 1450, 1376, 1356, 1280, 1241

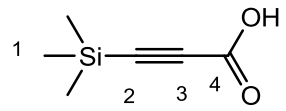
^{1}H NMR: (500 MHz, $CDCl_3$) δ; 4.22 (2H, s, H5), 4.05 (2H, s, H2), 3.38 (3H, s,

H1), 3.0 (OH)

^{13}C NMR: (125 MHz, $CDCl_3$) δ; 85 (C3&4), 60 (C2), 57.2 (C1), 50.5 (C5)

EI+; 31, 69, 99.

Trimethylsilanyl-propynoic acid 2.24 [46, 47, 48]



Trimethylsilylacetylene (12.5g, 18.1mL, 128mmol) was put in diethyl ether (150mL) under nitrogen and continuous stirring at -50^{o}C. Methyllithium was added and the reaction was left for 15 min. The reaction was further cooled down to -65^{o}C, excess crushed dry ice pellets were added and it was left overnight to warm up to room temperature. The mixture was acidified with hydrochloric acid (1M, 300mL) to pH 1.The phases were separated and the aqueous fraction was extracted with diethyl ether The combined organic layer was washed with brine and dried over magnesium sulphate and evaporated under reduced pressure. The crude yellow tinted solution obtained was purified by short path distillation (bp. 72-74 ^{o}C, 0.1mmHg) to give the product as a colourless liquid (17g, 97%).

All data conformed to the literature[46, 47, 48].

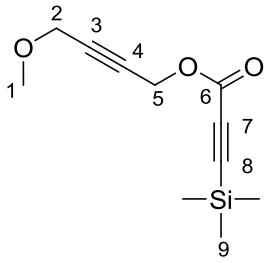
IR (NaCl, cm-1), 2965, 2904, 2626, 2178, 1694, 1517, 1404, 1254,

^{1}H NMR (500 MHz, $CDCl_3$) δ; 0.25 (9H, s H1);

^{13}C NMR (125 MHz, $CDCl_3$) δ; 157.8 (C4), 97.5 (C3), 93.7 (C2), -1.1 (C1),

HRMS (ESI+) calcd for $C_6H_{10}O_2Na$, m/z 165.0342, found 165.0346 (- 90 ppm)

4-Methoxybut-2-ynyl-3-(trimethylsilyl) propionate 2.80



4-Methoxybutyn-2-ol (1g, 10mmol) and trimethylsilylpropynoic acid, **2.24** (1.42g, 10mmol) were dissolved in DCM (10mL). A catalytic amount of 4-(dimethylamino) pyridine (DMAP) (0.025g) was added followed by 1-[3-(dimethylamino) propyl]-3- ethyl carbodiimide hydrochloride (EDCI) (1.91g, 10.00 mmol) in DCM (5mL). The reaction was left to stir for 20 h after which it was quenched with saturated sodium hydrogen carbonate (30mL). The crude product was extracted with DCM (2 x 15mL). The aqueous layer was washed with water and brine (20mL each) and dried over magnesium sulphate and concentrated under reduced pressure The desired compound **2.80** was obtained by purification through column chromatography (10% diethyl ether in hexanes) as a yellow liquid in 25% yield.

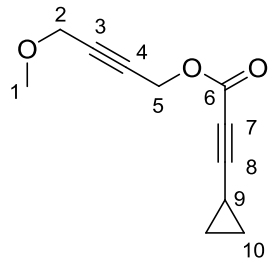
IR (NaCl cm^{-1}) 2931, 1739, 1638, 1455, 1345, 1248,

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.8 (2H, s, H5), 4.1 (2H, s, H2), 3.38 (3H, H1), 0.2 (9H, s, H9).

^{13}C NMR (125 MHz, $CDCl_3$) δ; 153 (C6), 96 (C7), 94 (C8), 83.8 (C4), 79 (C3), 60 (C2), 57.8 (C5), 53 (C1), (C9, not shown but predicted to be -1.3).

HRMS (ESI+) calcd for $C_{11}H_{16}SiO_3Na$, m/z 247.0761.found 247.0757, (error 1.43ppm)

4-Methoxybut-2-ynyl-3-cyclopropylpropionate 2.86



Cyclopropylpropiolic acid (1.21g, 11.0 mmol) was added into DCM (10mL) under a flow of nitrogen followed by a slow addition of carbonyl diimidazole (CDI) (1.78g, 11.0mmol). The reaction was left for 1h, the alcohol **2.81** (1.00g, 10.0mmol) was added and the reaction was left for another 2 h. The reaction was quenched with hydrochloric acid (1mL, 10mL), extracted with DCM (2 x 20mL), washed with saturated potassium carbonate, and water (10mL each). The solution was dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (50% of ethyl acetate in petroleum ether) and the desired product was obtained as a brownish yellow liquid in 20% yield.

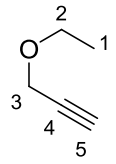
IR (NaCl cm^{-1}); 3680, 3300, 2937, 2224, 1990, 1710, 1434, 1372, 1353, 1247.

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.70(2H, m, H5), 4.12(2H, d, *J* = 2.5 Hz H2), 3.36 (3H, s, H1), 1.37(1H, d, *J* = 7.0 Hz, C9), 0.93 (4H, tdd, *J* = 4.05, 7.10, 13.86 Hz, C10)

^{13}C NMR (125 MHz, $CDCl_3$) δ; 152.8 (C6), 94.69 (C7& 8), 83.3 (C4), 79.7 (C3), 68 (C), 59 (C), 57.65 (C), 53.10 (C), 9.30 (C). 0.61 (C).

HRMS (ESI+) calcd for $C_{11}H_{12}O_3Na$, m/z, 215.0679, found 215.0669.

3-Ethoxyprop-1-yne[168]. 2.87



Sodium hydroxide pellets (52g, 13M) was dissolved in water (100mL) and transferred into a 3-necked flask. It was put under nitrogen with continuous stirring. Propargyl alcohol **2.84** was added (54g, 56.075 mL, 0. 96mmol,) dropwise from a dropping funnel and the reaction was heated under reflux at 70 ^{o}C for 1 h. The reaction was cooled to 55-60^{o}C, and diethyl sulphate was added dropwise. The reaction was left for 2 h. The crude product was distilled off the mixture at 80^{o}C, and purified by fractional distillation at 79^{o}C. The product was obtained as a colourless liquid in 70% yield (based on one equivalent of the propargyl alcohol).

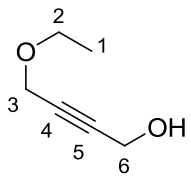
IR (NaCl cm^{-1}); 3278, 2986, 2936, 2898, 2128, 1725, 1617, 1445, 1372, 1306.

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.10(2H, d, *J* = 2.4 Hz, H3), 3.52 (2H, dq, *J* = 6.96, 13.93Hz, H2), 2.4 (1H, s, H5), 1.2 (2H, t, *J* = 7.1, H1)

^{13}C NMR (125 MHz, $CDCl_3$) δ; 80 (C4), 74 (C5), 65 (C2), 58 (C3), 15 (C1)

EI+; 45, 55, 85,

4-Ethoxybutyn-2-ol 2.88 [164-168]



3-Ethoxyprop-1-yne (15g, 178.57mmol) was dissolved in THF (150ML). The solution was cooled down to -78^{o}C and the reaction was put under nitrogen and continuous stirring followed by dropwise addition of n-BuLi (2.5M in hexanes, 78.57mL). The reaction was left for 1h at -78^{o}C and thereafter warmed up to -20^{o}C followed by the addition of parafomaldehyde. The reaction was left overnight, quenched with water (200mL) and extracted with ether (300mL). The aqueous layer was washed with ether (2 x 80mL). The combined organic layer was dried over magnesium sulphate, evaporated under reduced pressure and purified by column chromatography (50% ethyl acetate in petroleum ether). The desired product **2.88** was obtained as a light yellow liquid in 60% yield.

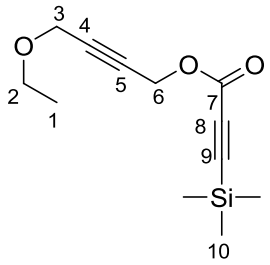
IR (NaCl cm^{-1}); 3389, 2977, 2867, 2012, 1736, 1443, 1372, 1349, 1242.

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.25 (2H, d, *J* =5.9 Hz, H6), 4.06 (2H, d, *J* = 2.5 Hz, H3), 3.55 (2H, q, *J* = 8.0Hz, H2), 1.15 (3H, m, H1)

^{13}C NMR (125 MHz, $CDCl_3$) δ; 84.9 (C5), 82 (C4), 61.8 (C2), 57.4 (C3), 50.5 (C6), 15 (C1)

EI+; 45, 86, 113.

4-Ethoxybut-2-ynyl-3-(trimethylsilyl) propionate 2.89



To a solution of trimethylsilylpropynoic acid, **2.24** (1.42g, 10.00mmol) in DCM was added carbonyl diimidazole (1.62g, 10.00mmol) slowly. There was effervescence and the reaction was left under a flow of nitrogen and stirring for 45mins, after which the alcohol **2.88** (1.14g, 10mmol) was added and the reaction left overnight. The reaction was quenched with hydrochloric acid (1M, 10mL) and extracted with DCM; the organic extract was washed with saturated potassium carbonate and water (10mL each). It was dried over magnesium carbonate, filtered and evaporated, producing a pinkish yellow liquid, which was purified by flash chromatography (50% of ethyl acetate in petroleum ether) to give the desired product **2.89** as a light yellow liquid in 33% yield.

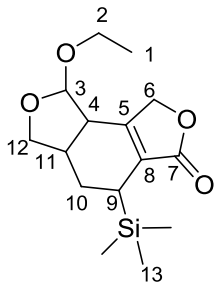
IR (NaCl cm^{-1}); 2967, 2869, 2172, 1872, 1716, 1439, 1368, 1252, 1202, 1157.

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.85 (2H, s, H6), 4.06 (2H, s, H3), 3.45 (2H, q, J = 5.0, 6.25Hz, H2), 1.2 (3H, t, J = 5.0, 8.75Hz, H1), 0.20 (9H, s, H10).

^{13}C NMR: (125 MHz, $CDCl_3$) δ; 152 (C7), 94.9 (C5), 94 (C4), 84 (C8), 79 (C9), 65.9 (C2), 58(C3), 53.5(C6), 15 (C1). (C10 not shown).

HRMS (ESI+): calcd for $C_{12}H_{18}SiO_3Na$, m/z 261.0917, found 261.0916. (0.39 ppm error).

8-Ethoxy-4-(trimethylsilyl)-4,5,5a,6,8,8a-hexahydroisobenzofuro [5,4-c]furan-3(1H)-one 2.95



The precursor 4-ethoxybut-2-ynyl-3-(trimethylsilyl) propionate **2.89** (200mg, 0.84mmol) was added in dry toluene (5mL). Allyl alcohol (224mg, 0.285mL, 4.20mmol) was added to provide the double bond necessary for intermolecular cyclization. The reaction was refluxed at 110 ^{o}C for 25 h. Completion of the reaction was indicated by tlc analysis. The solvent was evaporated off under reduced pressure to produce the crude compound as a brown liquid. Purification by column chromatography (25% of ethyl acetate in petroleum ether) produced the product as a yellow coloured liquid in 75% yield.

The reaction was repeated under microwave conditions at 130 ^{o}C and tlc analysis revealed the completion of the reaction after 4 h.

IR (NaCl cm^{-1}); 2952, 1748, 1344, 1248, 1932.

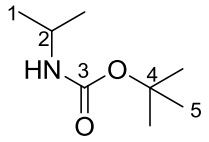
^{1}H NMR (500 MHz, $CDCl_3$)δ; 5.15 (1H, s, H3), 4.82/4.75 (2H, s, H6), 3.78 (1H, m, H12a), 3.55 (1H, m, H12b), 3.39 (2H, m, H2), 2.5 (1H, s, H4) 2.18 (1H, s, H9), 1.9 (1H, m, H11), 1.6-1.75 (2H, m, H10) 1.15 (3Ht, *J* = 5.0, 12.4Hz, H1), 0.20 (9H, d, *J* = 4.4Hz, H13).

^{13}C NMR (125 MHz, $CDCl_3$) δ; 173.5 (C7), 156.5/155.5 (C5), 130.0 (C8), 105.5

(C3), 91.9/72.5 (C6), 69.5/70.5 (C12), 64 (C2), 50 (C4), 45 (C11), 37.5 (C10), 28 (C9), 15 (C1). 0.0 (C13).

HRMS (ESI+): calcd for $C_{15}H_{24}O_4SiNa$, m/z 319.1336, found 319.1333 (0.92ppm error).

tert-Butyl-*N*-*iso*-propylcarbamate 2.109



Iso-propylamine was slowly added to a solution of Boc anhydride in THF 0^{o}C. A catalytic amount of DMAP was added, the reaction was left to stir at room temperature for 19 h. The solvent was evaporated off under reduced pressure to give a yellow tinted solid which was redissolved in diethyl ether. The solution was washed with water, saturated sodium hydrogen carbonate (100mL each), then dried over magnesium sulphate and concentrated under reduced pressure. The solid obtained was again redissolved in diethyl ether and purified by column chromatography (10% ethyl acetate in hexanes). The product **2.109** was obtained as a white solid in 51% yield.

Melting point 75 ^{o}C (literature melting point = 69-71^{o}C) [156]

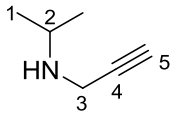
IR (NaCl cm^{-1}); 3680, 2972, 2844, 2169, 1345.

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.4 (1H, s, br, NH), 3.85 (1H, s, br, H2), 1.4 (9H, s, H5), 1.05 (6H, d, *J* = 6.53 Hz, H1)

^{13}C NMR (125 MHz, $CDCl_3$) δ; 158 (C3), 80 (C4), 45 (C2), 28 (C5), 23 (C1).

HRMS (ESI+): calcd for $C_8H_{17}O_2NNa$, m/z =182.1151, found 182.1152 (-0.40 ppm error).

N- iso-Propyl propargylamine 2.108



To a refluxing (65^{o}C) solution of *iso*propylamine (59g, 1.00mol) in water (50mL) was added propargyl bromide (47.56g, 0.40mol) through an addition syringe over 15 h. The reaction was allowed to reflux for a further 4 h. The reaction mixture was cooled down to 10^{o}C and 50% aqueous solution of potasium hydroxide was added and the mixture was allowed to reflux for another 1 h. The white precipitate of halide formed was filtered off and the top organic layer was extracted from the mixture. The organic layer was washed with brine and dried over magnesium sulphate, a brownish yellow liquid was obtained. This was purified by vacuum distillation using kugelrohr distillation unit. The product **2.108** was obtained as a colourless mixture with toluene and the disubstituted amine (**2.111**). (b.p of the product is 110-115^{o}C, b.p for toluene is 110.6^{o}C). Combined yield was 50% .

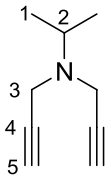
IR (NaCl cm^{-1}) ; 2968, 1601,

^{1}H NMR (500 MHz, $CDCl_3$) δ; 3.40 (2H, s, H3), 3.05-2.97 (1H, sept, J = 6.2, H2), 2.20 (1H, t, J = 2.1, H5), 1.05 (6H, d, J = 6.2 Hz, H1),

^{13}C NMR (500 MHz, $CDCl_3$) δ; 82.7 (C4). 71.4 (C5), 47.2 (C2), 36.0 (C3), 22.8 (C1),

HRMS (ESI+): calcd for $C_6H_{11}NNa$, m/z =120.1151, found 120.1148 (-0.40 ppm error).

N-iso-Propyl-*N*-(prop-2-ynyl)prop-2-yn-1-amine 2.111



Compound **2.111** was obtained as a co-product with compound **2.108**. However the pure compound was obtained by column chromatography of the mixture (33% of ethyl acetate in petroleum ether) as a brownish yellow solution.

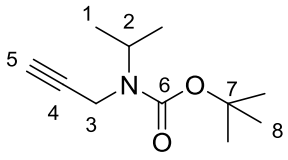
IR (NaCl cm^{-1}); 3296, 2970, 2817.

H NMR (500 MHz, $CDCl_3$) δ; 3.5 (4H, s, H3), 2.89 (1H, sept, J = 6.2 Hz, H2), 2.2 (2H, s, H5), 1.1(6H, d, J = 6.2 Hz, H1)

^{13}C NMR(125 MHz, $CDCl_3$) δ; 80 (C4), 73 (C5), 51(C2), 39 (C3), 20 (C1)

HRMS (ESI+): calcd for $C_9H_{14}N$, m/z = 136.1121, found, 136.1123, (-1.6ppm error).

tert- iso-Propyl (prop-2-ynyl)carbamate 2.107



The amine **2.108** (6.4g, 65.98mmol) was dissolved in acetonitrile and put in a flask under nitrogen and stirring at 0^{o}C. Boc anhydride (17.27g, 79.17mmol) was also dissolved in acetonitrile and added slowly into the amine solution, the reaction was left for 15 h at room temperature. Dimethylethylenediamine (3.94mL, 0.5mmol) was added to quench any unreacted Boc anhydride and the reaction was left for a further 30min. The solvent was evaporated under reduced pressure to give a bright yellow liquid.

Alternatively, the excess Boc anhydride was removed by adding five equivalents of imidazole into the reaction mixture at the end of the reaction and the mixture was allowed to stir for further 15 min. Chloroform was then added, and the mixture was washed with one percent hydrochloric acid (0 - 5^{O}C). The mixture was extracted and the organic phase was washed with sodium hydrogen carbonate, water and brine, (40ml each).The mixture was dried over magnesium sulphate and concentrated.[176]

The pure compound was obtained by column chromatography (20% of diethyl ether in hexanes) as a light colourless liquid in 66% yield.

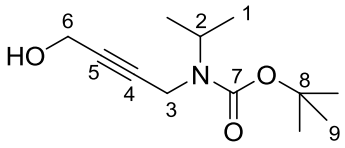
IR (NaCl cm^{-1}); 3305, 2976, 1688, 1440, 1402, 1365, 1328.

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.20 (1H, s, br, H2), 3.80 (2H, s, H3), 2.08 (1H, s, H5), 1.42 (9H, s, H8), 1.18 (6H, d, J = 6.7 Hz, H1).

^{13}C NMR (125 MHz, $CDCl_3$) δ; 155 (6), 82 (C7), 80 (C4), 70 (C5), 48 (C2), 32 (br, C3), 28 (C8) 20 (C1)

HRMS (ESI+): calcd for $C_8H_{17}O_2NNa$, m/z = 182.1151, found, 182.1152, (-0.72ppm error).

tert-Butyl-(4-hydroxy-but-2-yn-1-yl)*iso*-propylcarbamate 2.106



tert-Butyl-(4-hydroxy-but-2-yn-1-yl)isopropylcarbamate **2.107** (5g, 25.38mmol) was dissolved in THF, put under nitrogen at -78 ^{o}C. N-BuLi (11.168ml, 27.92mmol) was added slowly into the reaction mixture and stirred for 30min. Parafomaldehyde (1.52g, 50.76mmol) was added in one portion and the reaction was allowed to warm up to room temperature overnight.

The reaction was quenched with water (100mL) and extracted with diethyl ether (100mL). The aqueous portion was again extracted with diethyl ether (40mL x 2). The combined organic layers was washed with brine (100mL), dried over magnesium sulphate filtered and concentrated under reduced pressure. The crude compound was purified by column chromatography (10% methanol in DCM) to give the desired product **2.106** as an orange coloured liquid. (3.9g, 89%).

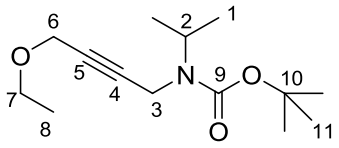
IR (NaCl cm^{-1}); 3374, 2975, 1675, 1403,

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.20 (2H, s, H6), 3.80 (2H, s, H3), 2.60 (1H, s, br, OH), 1.40 (9H, s, H9), 1.18 (6H, d, J = 6.7 Hz, H1).

^{13}C NMR (125 MHz, $CDCl_3$) δ; 155 (7), 82 (C8), 80 (C5), 80 (C4), 51 (C6), 47.5 (C3), 32 (br, C2), 28 (C9), 20 (C1)

HRMS (ESI+): calcd for $C_{12}H_{21}O_2NNa$, m/z = 250.1414, found 250.1415, (0.35ppm error).

tert-Butyl-(4-ethoxy-but-2-yn-1-yl)*iso*-propylcarbamate 2.105



A solution of NaH (60% in mineral oil, 0.77g, 19.16mmol) was prepared in THF (60mL), the reaction was put under nitrogen with stirring at 0°C. *tert*-Butyl-(4-hydroxy-but-2-yn-1-yl) isopropylcarbamate **2.106** (2.9g,12.77mmol) was added and the reaction was left to stir for 1h. Ethyl iodide (2.39, 15.33mmol) was added slowly into the solution and left overnight (15h) to warm up to room temperature. The reaction was quenched with water, and extracted with diethyl ether (10mL). The aqueous layer was washed with diethyl ether (50mL x2). The organic layers were washed with brine, and dried over magnesium sulphate, filtered and concentrated under reduced pressure. Purification of the crude by column chromatography afforded the pure compound **2.105** as a bright yellow liquid (80%).

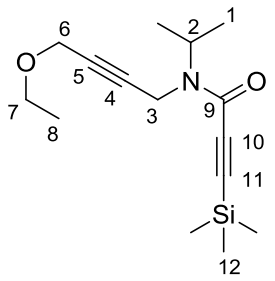
IR (NaCl cm^{-1}); 2975, 1691,

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.18 (1H, s, br, H2). 4.02 (2H, s, H6), 3.84 (2H, s br, H3), 3.41- 3.47, (2H, q, J = 12.5, 10.0, 2.5 Hz H7), 1.38 (9H, s, H11), 1.13 (3H, m, H8), 1.09 (6H, d, J = 6.9 Hz, H1).

^{13}C NMR (125 MHz, $CDCl_3$) δ; 155.1 (C9), 84 (C10), 80 (C5), 79 (C4), 65 (C6), 58 (C7), 47 (C3), 32 (C2), 28 (C11), 20.5 (C1), 15 (C8).

HRMS (ESI+): calcd for $C_{14}H_{25}NO_3Na$, m/z 278.1727, found 278.1732.

N-(4-Ethoxybut-2-ynyl)-*N-iso*-propyl-3-(trimethylsilyl)propiolamide **2.103**



Trifluoroacetic acid (1.944mL 25.49mmol) was added dropwise into a solution of *tert*-buty-(4-ethoxy-but-2-yn-l-yl)isopropylcarbamate **2.105** (1.3g, 5.09mmol) over 5min. The reaction was left to stir overnight at room temperature and the solvent was evaporated to give the crude trifluoroacetate **2.104** as a dark oily product. ^{1}H NMR of the crude showed complete removal of the Boc group. This product was used without any purification.

To a solution of the trimethylsilanyl propynoic acid (1.04g, 7.35mmol) in DCM (10mL) was added oxalylchloride (0.93g, 7.35mmol) and 2 drops of DMF at 0 ^{o}C. The ice bath was removed after 5min and the reaction was left for 1h at room temperature. Compound **2.26** was obtained and used *in situ*.

To a solution of the crude amine trifluoroacetate salt **2.104** in DCM (10mL) was added triethylamine (2.98g) slowly at 0^{o}C under nitrogen with continuous stirring. The reaction was left to stir for 30min. Freshly prepared 3-(trimethylsilyl) propioloyl chloride **2.10a** was added in drops to the solution over 10min and the reaction was stirred overnight. The reaction was quenched with hydrochloric acid (1M), washed with saturated sodium carbonate solution, water and brine (20 mL each). The mixture was dried over magnesium sulphate and concentrated under

reduce pressure to give a brownish black liquid. Purification by column chromatography (33% of diethyl ether in hexanes) gave the product as an orange oil in 38% yield (over 2 steps).

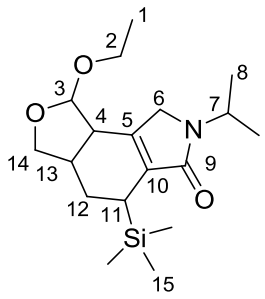
IR (NaCl cm^{-1}); 2975, 2200, 1628. 1431, 1408, 1332, 1291.

^{1}H NMR (500 MHz, $CDCl_3$) δ; 4.64 (1H, m, H2), 4.28 (1H, s, H3), 4.05 (3H, m, H3 and H6), 3.5 (2H, q, *J* = 14.1 Hz, H7), 1.3 (3H, d, *J* = 6.8 Hz, H8), 1.18 (6H, d, *J* = 13.5Hz, H1), 0.2 (9H, m, H12)

^{13}C NMR (125 MHz, $CDCl_3$) δ; 153.9/153.5 (C9), 97.8/97.4 (C11), 96.2/95.7 (C4), 82.0/81.9 (C10), 78.5 (C5), 65 (C7), 57.9 (C6), 50.6/45.8 (C2), 34/29 (C3), 20/21 (C1), 14.5 (C8), (C12 not shown).

HRMS (ESI+): calcd for $C_{15}H_{25}NO_2SiH$, m/z 280.1727, found- 280.1729, (-2.09ppm error).

Ethoxy-7-*iso*-propyl-5-(trimethylsilyl)-3,3a,4,5,7,8-hexahydro-1*H*-furo[3,4-e]isoindol-6(8b*H*)-one. 2.112



The precursor *N*-(4-ethoxybut-2-ynyl)-*N*-isopropyl-3-(trimethylsilyl)propiolamide **2.103** (200mg, 0.717mmol) was put in dry toluene (5mL). Allyl alcohol (208mg, 0.244mL, 3.584mmol) was added to provide the double bond necessary for intermolecular cyclization. The reaction was heated under reflux at 110 ^{o}C for 2 h. Completion of the reaction was indicated by tlc analysis. The solvent was evaporated under reduced pressure to produce the crude compound as a dark coloured liquid. Purification by column chromatography (33% of diethyl ether in hexanes) produced the product **2.112** as a yellow liquid in 65% yield.

IR (NaCl cm^{-1}); 2966, 2169, 1991, 1671, 1454, 1400,

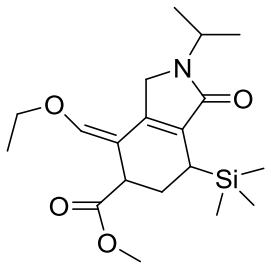
^{1}HNMR (500 MHz, $CDCl_3$) δ; 5.94 (1H, m, H7), 5.3 (1H, d, *J* =7.0Hz H3), 5.2 (1H, d, *J* = 7.0Hz H3), 4.9 (1H, s, H3), 4.4 (1H, m, H2), 4.25 / 4.18 (2H, m, H2), 4.0 (1H, dd, *J* = 12.7,5.9Hz, H14a) 3.7-3.85 (3H, m, 6 & H14b), 2.82(1H, s H4), 2.3 (1H,dd, *J* = 10.9,5.6Hz, H13), 1.85(1H, d, *J* = 8.6Hz H11) 1.7 (2H, s, H12), 1.4 (1H, m, H12), 1.15 (6H, d, *J* = 6.1Hz, H8), 1.2 (3H, m, H1) , 0.8 (9H, s, H15)

^{13}CNMR (125 MHz, $CDCl_3$) δ; 171 (C9), 145(C5), 136/135 (C10), 107.5/107.2 (C3), 72/69 (C14), 63.99 (C2), 48 (C6), 45.9 (C4), 42.6/42 (C13), 38 (C7), 27.5

(C12), 22.5/23.5 (C11), 21 (C8), 15.8 (C1), 0.1 (C15).

HRMS (ESI+): calcd for $C_{18}H_{32}O_3Si$, m/z 338.2146, found 338.2153 (-2.14ppm error).

(Z)-Methyl 4-(ethoxymethylene)-2-*iso*-propyl-1-oxo-7-(trimethylsilyl)-2, 3,4,5,6,7-hexahydro-1H-isoindole-5-carboxylate, 2.114.



N-(4-Ethoxybut-2-ynyl)-*N*-isopropyl-3-(trimethylsilyl)propiolamide, **2.103** (100mg, 0.358mmol) was put in dry toluene (5mL). Methyl acrylate (154mg, 1.792mmol) was added to provide the double bond necessary for intermolecular cyclization. The reaction was heated under reflux at 110 ^{o}C for 1 h. The solvent was evaporated under reduced pressure to produce the crude compound as a dark orange liquid. Purification by column chromatography (25% of diethyl ether in hexanes) gave the product **2.114** as an orange yellow liquid in 25% yield.

IR (NaCl cm^{-1}); 3412, 2919, 2099, 1643, 1412, 1368, 1245, 1080, 843.

^{1}HNMR (500 MHz, $CDCl_3$) δ; 6.4 (1H, d, *J* = 10Hz, H14), 6.10 (1H, d, *J* = 8Hz, H14), 4.49 (2H, m, H15), 3.95 (1H, m, H2), 3.79 (3H, s, H10),3.65 (2H, s, H11), 3.1 (1H, d, *J* = 7.0Hz, H8), 2.6 (1H, d, *J* = 7.0Hz, H5), 1.65 (1H, m, H7), 1.05 – 1.20(9H, m, H1 & H16), 0.9 (1H, d, *J* = 7.0,H7), 0.2, (9H, d, *J* = 12.4Hz, H6).

^{13}CNMR (125 MHz, $CDCl_3$) δ; 172 (C9), 168 (C3), 143.5 (C12), 138 (C14), 133.8 (C4), 119.5 (C13), 72.5 (C15), 65 (C15), 52 (C10), 44 (C8), 42 (C11), 41.8(C2), 30/28 (C7), 22 (C1), 19.5 (C5), 15 5 (C16)

HRMS(ESI+): calcd for $C_{19}H_{32}NO_4Si$, 366.2095 found 366.2103, (-2.22ppm error)

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Appendix

7-Methyl-5-phenyl-4,5,7,8-tetrahydro-3H-furo[3,4-e]isoindol-6-(3-aH)-eno 2.1

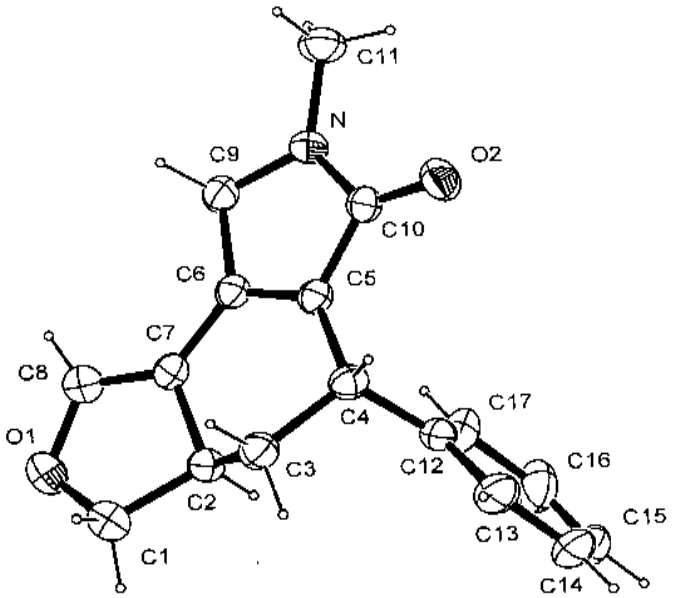

Table 1. Crystal data and structure refinement.

Identification code	aug 1407	
Empirical formula	$C_{17}H_{17}NO_2$	
Formula weight	267.32	
Temperature	173(2) K	
Wavelength	0.71073Å	
Crystal system	Triclinic	
Space group	P1 (No.2)	
Unit cell dimensions	a = 11.0444(3) Å	∞ = 109.032(2) ^{o}
	b = 11.5733(4)Å	β = 105.344(2) ^{o}
	c = 11.9077(2) Å	γ = 90.272(2) ^{o}
Volume	1380.62(6) Å ^{3}	
Z	4	

Density	1.29Mg/m^3
Absorption coefficient	0.08mm^{-1}
F(000)	568
Crystal size	0.35 x 0.30 x 0.20mm^3
Theta range for data collection	3.57 to 26.19^o
Index ranges	-13<=h<=13, -14<=k<=14, -14<=1<=14
Reflections collected	21825
Independent reflections	5441 [R (int) = 0.060]
Reflections with 1>2signals	3992
Completeness to theta = 26.19^o	98.4%
Refinement method	Full-matrix least-squares on F^2
Data/ restraints/ parameters	5441 / 0 / 363
Goodness-of-fit on F^2	1.005
Final R indices [I>2sigma(I)]	R1 = 0.047, wR2 = 0.107
R indices (all data)	R1 = 0.073, wR2 = 0.121
Largest diff. peak and hole	0.26 and -0.22 e. $Å^{-3}$

Data collection Kappa CCD, 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 isotopic displacement parameters ($Å^2x10^3$) for aug 1407. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6644(1)	1094(1)	2219(1)	46(1)
O(2)	2969(1)	1825(1)	6375(1)	36(1)
N	2313(1)	1184(1)	4242(1)	30(1)
C(1)	7428(2)	1435(2)	3497(2)	42(1)
C(2)	6552(2)	1974(2)	4297(2)	30(1)
C(3)	6739(2)	1685(2)	5492(2)	31(1)
C(4)	5669(2)	2141(2)	6099(2)	27(1)
C(5)	4416(2)	1739(1)	5128(1)	25(1)
C(6)	4252(2)	1357(2)	3897(1)	24(1)
C(7)	5286(2)	1386(2)	3394(2)	27(1)
C(8)	5429(2)	955(2)	2260(2)	36(1)
C(9)	2884(2)	929(2)	3229(2)	29(1)
C(10)	3193(2)	1611(2)	5371(2)	26(1)
C(11)	1024(2)	741(2)	4068(2)	37(1)
C(12)	5907(2)	3514(2)	6804(2)	28(1)
C(13)	6795(2)	3933(2)	7960(2)	42(1)
C(14)	7125(2)	5175(2)	8601(2)	54(1)
C(15)	6580(2)	6023(2)	8097(2)	55(1)
C(16)	5684(2)	5627(2)	6969(2)	49(1)
C(17)	5340(2)	4375(2)	6321(2)	36(1)
O(1B)	10039(1)	6414(1)	4172(1)	40(1)
O(2B)	6957(1)	991(1)	-628(1)	40(1)
N(1B)	6115(1)	2797(2)	157(1)	35(1)
C(1B)	10889(2)	5457(2)	3946(2)	35(1)
C(2B)	10220(2)	4494(2)	2693(2)	27(1)
C(3B)	10325(2)	3154(2)	2575(1)	27(1)

C(4B)	9472(2)	2290(2)	1312(1)	24(1)
C(5B)	8201(2)	2762(2)	1048(1)	25(1)
C(6B)	7918(2)	3893(2)	1625(2)	27(1)
C(7B)	8872(2)	4801(2)	2561(2)	27(1)
C(8B)	8863(2)	5894(2)	3397(2)	35(1)
C(9B)	6543(2)	3998(2)	1105(2)	36(1)
C(10B)	7060(2)	2048(2)	98(2)	30(1)
C(11B)	4839(2)	2462(2)	-646(2)	53(1)
C(12B)	10091(1)	2118(2)	272(1)	24(1)
C(13B)	10959(2)	1257(2)	92(2)	28(1)
C(14B)	11570(2)	1115(2)	-818(2)	36(1)
C(15B)	11313(2)	1823(2)	-1574(2)	39(1)
C(16B)	10438(2)	2670(2)	-1415(2)	39(1)
C(17B)	9837(2)	2821(2)	-496(2)	31(1)

Table 3.Bond lengths Å and angles for aug 1407

O(1)-C(8)	1.366(2)
O(1)-C(1)	1.460(2)
O(2)-C(10)	1.231(2)
N-C(10)	1.366(2)
N-C(11)	1.449(2)
N-C(9)	1.454(2)
C(1)-C(2)	1.530(2)
C(2)-C(7)	1.514(2)
C(2)-C(3)	1.528(2)
C(3)-C(4)	1.552(2)
C(4)-C(12)	1.519(2)
C(5)-C(6)	1.346(2)
C(5)-C(10)	1.471(2)
C(6)-C(7)	1.428(2)
C(6)-C(9)	1.503(2)
C(7)-C(8)	1.331(2)
C(12)-C(17)	1.381(3)
C(12)-C(13)	1.392(2)
C(13)-C(14)	1.383(3)
C(14)-C(15)	1.373(3)
C(15)-C(16)	1.373(3)
C(16)-C(17)	1.397(3)
O(1B)-C(8B)	1.377(2)
O(1B)-C(1B)	1.459(2)
O(2B)-C(10B)	1.231(2)
N(1B)-C(10B)	1.360(2)
N(1B)-C(11B)	1.446(2)
C(1B)-C(2B)	1.529(2)
C(2B)-C(7B)	1.511(2)
C(2B)-C(3B)	1.519(2)
C(3B)-C(4B)	1.553(2)

C(4B)-C(5B)	1.501(2)
C(4B)-C(12B)	1.526(2)
C(5B)-C(6B)	1.347(2)
C(5B)-C(10B)	1.475(2)
C(6B)-C(7B)	1.436(2)
C(6B)-C(9B)	1.503(2)
C(7B)-C(8B)	1.333(2)
C(12B)-C(17B)	1.389(2)
C(12B)-C(13B)	1.392(2)
C(13B)-C(14B)	1.389(2)
C(14B)-C(15B)	1.382(3)
C(15B)-C(16B)	1.384(3)
C(16B)-C(17B)	1.389(2)

C(8)-O(1)-C(1)	105.85(14)
C(10)-N-C(11)	123.47(15)
C(10)-N-C(9)	112.04(13)
C(11)-N-C(9)	122.74(14)
O(1)-C(1)-C(2)	105.49(14)
C(7)-C(2)-C(3)	110.46(14)
C(7)-C(2)-C(1)	100.25(13)
C(3)-C(2)-C(1)	117.27(15)
C(2)-C(3)-C(4)	110.88(14)
C(5)-C(4)-C(12)	114.56(14)
C(5)-C(4)-C(3)	109.17(13)
C(12)-C(4)-C(3)	110.78(14)
C(6)-C(5)-C(10)	109.34(14)
C(6)-C(5)-C(4)	125.19(15)
C(10)-C(5)-C(4)	125.32(14)
C(5)-C(6)-C(7)	121.38(15)
C(5)-C(6)-C(9)	109.67(14)
C(7)-C(6)-C(9)	128.95(14)
C(8)-C(7)-C(6)	134.22(16)

C(8)-C(7)-C(2)	108.47(15)
C(6)-C(7)-C(2)	117.26(14)
C(7)-C(8)-O(1)	114.20(16)
N-C(9)-C(6)	102.37(13)
O(2)-C(10)-N	125.13(15)
O(2)-C(10)-C(5)	128.45(15)
N-C(10)-C(5)	106.41(13)
C(17)-C(12)-C(13)	118.009(17)
C(17)-C(12)-C(4)	123.00(15)
C(13)-C(12)-C(4)	118.79(17)
C(14)-C(13)-C(12)	121.4(2)
C(15)-C(14)-C(13)	120.1(2)
C(16)-C(15)-C(14)	119.43(19)
C(15)-C(16)-C(17)	120.8(2)
C(12)-C(17)-C(16)	120.27(18)
C(8B)-O(1B)-C(1B)	106.12(13)
C(10B)-N(1B)-C(11B)	124.42(16)
C(10B)-N(1B)-C(9B)	112.21(14)
C(11B)-N(1B)-C(9B)	123.35(15)
O(1B)-C(1B)-C(2B)	106.23(14)
C(7B)-C(2B)-C(3B)	111.07(14)
C(7B)-C(2B)-C(1B)	100.75(13)
C(3B)-C(2B)-C(1B)	117.13(14)
C(2B)-C(3B)-C(4B)	111.16(13)
C(5B)-C(4B)-C(12B)	112.72(13)
C(5B)-C(4B)-C(3B)	109.37(13)
C(12B)-C(4B)-C(3B)	111.87(13)
C(6B)-C(5B)-C(10B)	109.25(15)
C(6B)-C(5B)-C(4B)	125.97(15)
C(10B)-C(5B)-C(4B)	124.78(14)
C(5B)-C(6B)-C(7B)	121.01(15)
C(5B)-C(6B)-C(9B)	109.60(15)
C(7B)-C(6B)-C(9B)	129.35(15)

C(8B)-C(7B)-C(6B)	134.71(17)
C(8B)-C(7B)-C(2B)	109.06(15)
C(6B)-C(7B)-C(2B)	116.22(14)
C(7B)-C(8B)-O(1B)	113.89(16)
N(1B)-C(9B)-C(6B)	102.43(14)
O(2B)-C(10B)-N(1B)	125.52(16)
O(2B)-C(10B)-C(5B)	127.98(16)
N(1B)-C(10B)-C(5B)	106.49(14)
C(17B)-C(12B)-C(13B)	118.13(15)
C(17B)-C(12B)-C(4B)	121.87(15)
C(13B)-C(12B)-C(4B)	119.98(14)
C(14B)-C(13B)-C(12B)	121.09(17)
C(15B)-C(14B)-C(13B)	120.23(17)
C(14B)-C(15B)-C(16B)	119.22(16)
C(15B)-C(16B)-C(17B)	120.51(18)
C(16B)-C(17B)-C(12B)	120.80(17)