Synthetic Approaches Towards a Total Synthesis of Colchicine

A Thesis Presented by

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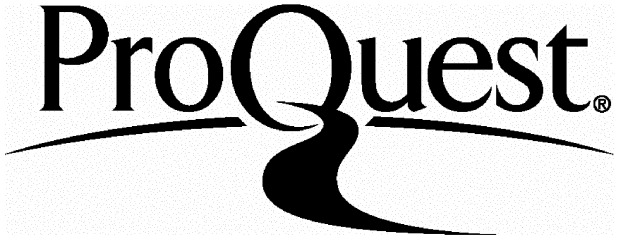

for Claire

Abstract

This thesis is divided into three chapters.

The first chapter provides a review of the fascinating chemistry of the enediynes and related compounds. The triggering systems contained within the structures of the naturally occurring enediyne antibiotics are discussed, as are general methods for the formation of the enediyne moiety itself. Moreover, since one of the key aspects of our approach to colchicine is the formation of a highly unsaturated macrocycle, significant preparative methods for the macrocyclisation of enediynes are briefly reviewed.

In the second chapter, a brief account of the occurrence, isolation, biological properties and previous syntheses of colchicine are presented, and then three synthetic approaches are described. The first approach involves the formation and subsequent Cope rearrangement of a functionalised dialkynylcyclopropane, for which preliminary studies on the formation of the cyclopropane *via* a Fischer carbene are presented. The second approach involves a novel [5+2] cycloaddition reaction for the formation of the tropolone C-ring. Although the synthesis of a suitably functionalised pentadiene model is described, attempts to construct a precursor containing all of the requisite functionality were unsuccessful. The third approach, to which most of the work was directed, involves the cycloaromatisation of a 12-membered macrocycle containing an enediyne ketone *via* a novel variant of the Bergman cyclisation. The synthesis of a 12-membered macrocycle *via* an intramolecular Noyori-type aldol reaction is described, but formation of the unsaturated macrocycle proved elusive.

The third chapter provides a formal description of experimental results and procedures.

Contents

Acknowledgements

Firstly, thanks must go to my supervisor, Willie Motherwell, for his enthusiasm, encouragement, guidance and friendship over the past three years.

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Finally, I would like to thank Claire and my parents for their love and support throughout my education.

Abbreviations

Ac	Acetyl
Ar	Aromatic
br.	Broad
Bu	Butyl
C-1027 Chrom.	C-1027 Chromophore
CAN	Ceric ammonium nitrate
cat.	Catalytic
1,4-CHD	1,4-Cyclohexadiene
CI	Chemical ionisation
cm^{-1}	Wavenumbers
COD	Cyclooct-1,5-diene
CSA	D-Camphor-10-sulfonic acid
d	Doublet
Δ	Heat
DABCO	4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dd	Double doublet
DEAD	Diethyl azodicarboxylate
dec.	Decomposes
DIBAL-H	Di-*iso*-butylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMTS	Dimethylthexylsilyl
dppp	1,3-Bis(diphenylphosphino)propane

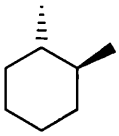
dt	Double triplet
e	Electron
EI	Electron impact
eq.	Equivalents
Et	Ethyl
ether	Diethyl ether
FAB	Fast atom bombardment
FT-IR	Fourier Transform Infra-red
GSH	Glutathione
hν	Irradiation of unspecified wavelength
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethyl phosphoramide
HRMS	High resolution mass spectrometry
^{i}Pr	*iso*-Propyl
IR	Infra red
J	Coupling constant
k	Rate constant
KHMDS	Potassium bis(trimethylsilyl)amide
L	Unspecified ligand
LDA	Lithium di*iso*propylamide
LG	Leaving group
LHMDS	Lithium bis(trimethylsilyl)amide
lit.	Literature value
LiTMP	Lithium 2,2,6,6-tetramethylpiperidine
LRMS	Low resolution mass spectrometry
M	Molar concentration
m	Multiplet
*m*CPBA	3-Chloroperbenzoic acid
Me	Methyl

mmHg	Millimetres of mercury
mol%	Molar percentage
MOM	Methoxymethyl
m.p.	Melting point
Ms	Methanesulfonyl
NADPH	Nicotinamide adenine dinucleotide phosphate
NBS	*N*-Bromosuccinamide
NCS	Neocarzinostatin
NCS-Chrom.	Neocarzinostatin chromophore
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
[O]	Unspecified oxidant
P	Unspecified protecting group
p	Para
Pd/C	Palladium on carbon
petrol	Petroleum ether (boiling range 40-60°C)
Ph	Phenyl
Piv	Pivaloyl (2,2-dimethylpropanoyl)
PMB	4-Methoxybenzyl
ppm	Parts per million
ppts	Pyridinium *p*-toluenesulfonate
Pr	Propyl
Py	Pyridine
PyBroP	Bromo-tris-pyrrolidinophosphino hexafluorophosphate
q	Quartet
R	Unspecified carbon-centred group, usually alkyl
R_f	Retention factor
r.t.	Room temperature
s	Singlet

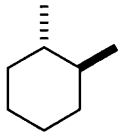
Sug	Unspecified carbohydrate group
t	Triplet
$t_{1/2}$	Half-life
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
tert	Tertiary
Tf	Trifluoromethanesulfonyl
Thexyl	1,1,2-Trimethylpropyl
THF	Tetrahydrofuran
THP	Tetrahydro-2*H*-pyranyl
TIPS	Tri-*iso*-propylsilyl
tlc	Thin layer chromatography
TMS	Trimethylsilyl
Tol	Toluene
Ts	4-Toluenesulfonyl
X, Y	Unspecified heteroatom substituent

Stereochemical Notation

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr.[1] Thus, solid and broken wedges denote absolute configuration and solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.



homochiral



racemic

CHAPTER ONE

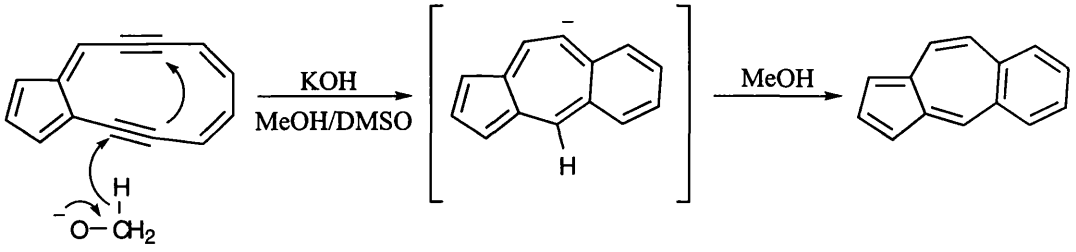
INTRODUCTION

1. The Preparation and Chemistry of Macrocyclic Enediynes and Related Compounds

At first sight this introductory review appears to be on a subject unrelated to the total synthesis of colchicine. It will become apparent, however, that the synthesis and chemistry of enediynes and their related compounds is germinal to our own synthetic approach. Of particular importance is the construction of medium-sized macrocycles containing acetylenes and their cycloaromatisation *via* diradical intermediates. Therefore, it is important to review these aspects and strategies in detail before embarking on a discussion of our own work and the results obtained.

1.1 The Bergman Reaction

Interest in the cyclisation of enediynes dates back to 1966, when Sondheimer reported the cyclisation of **1**, *via* a proposed ionic mechanism (scheme 1.1).[2]

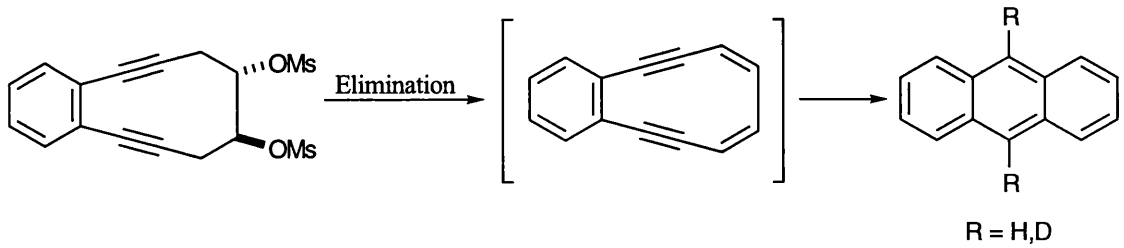


1 **2**

Scheme 1.1

This observation was followed in 1971 when Masamune found that, under elimination conditions, instead of forming an annulene (**4**), anthracene was obtained.[3] He proposed the enediyne **4** as an intermediate structure and was able to demonstrate

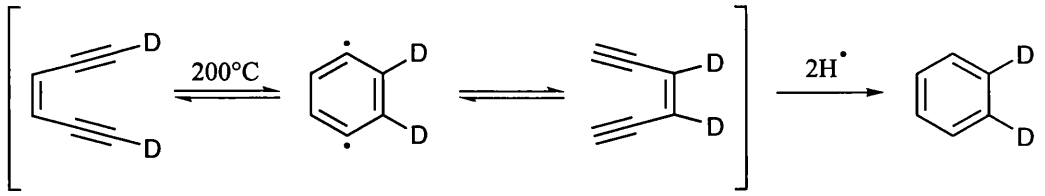
the incorporation of deuterium when the reaction was performed in deuterated solvents.



3 **4** **5**

Scheme 1.2

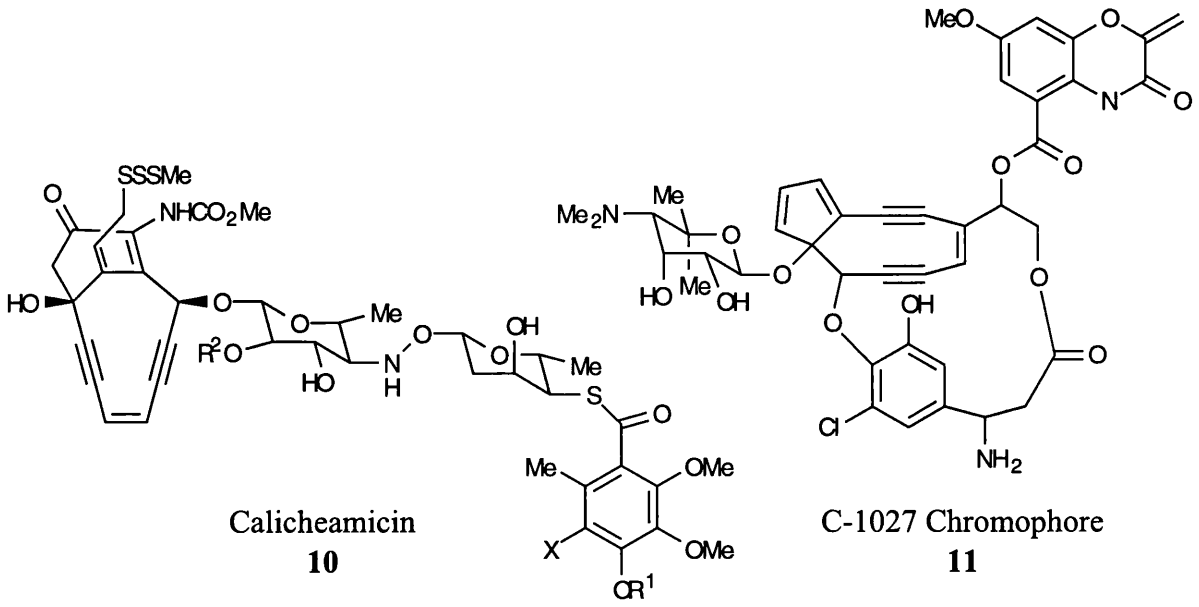
However, it was not until 1972 that the intermediacy of a 1,4-dehydrobenzene moiety was proposed by Bergman.[4] In his study, Bergman observed the cycloaromatisation of simple (*Z*)-enediynes in different solvents and noted that the benzene derivative obtained depended upon the solvent employed for the reaction. He also noted that the reaction was reversible, as supported by the apparent migration of deuterium from the acetylenic position to the vinylic position of the enediyne, as shown in scheme 1.3.



6 **7** **8** **9**

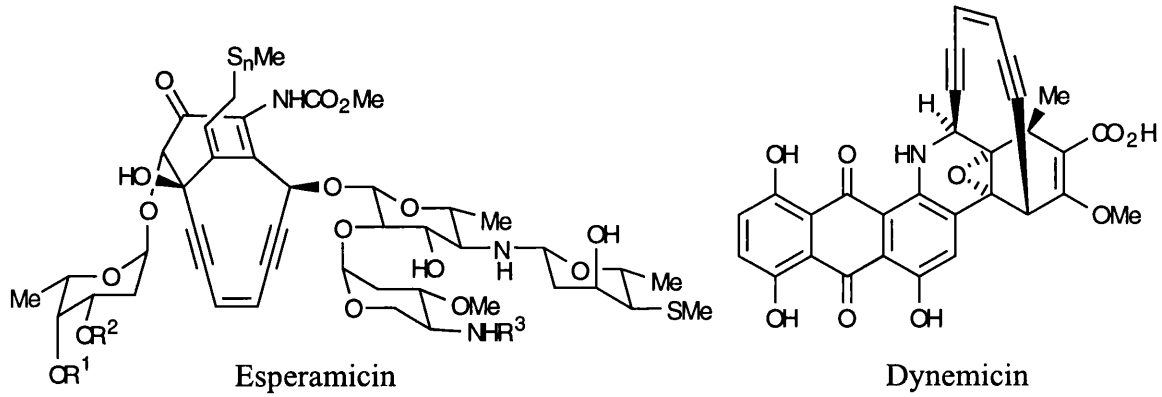
Scheme 1.3

These observations lay dormant for almost 15 years, until the isolation of a totally unexpected class of novel antibiotics revealed the existence of the enediyne unit in natural products (*vide infra*). Some representative members are shown in figure 1.1.



Calicheamicin
10

C-1027 Chromophore
11

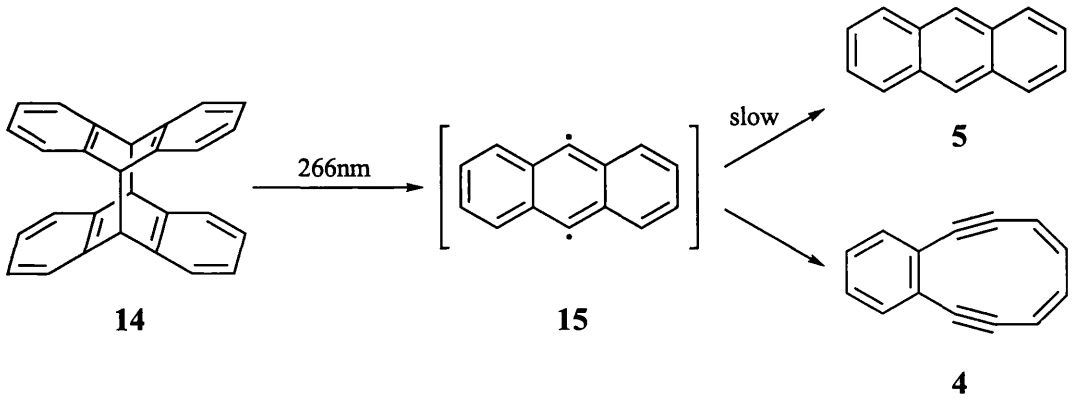


Esperamicin
12

Dynemicin
13

Figure 1.1

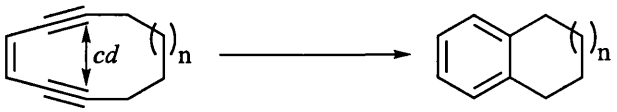
With the discovery of these novel natural products, attention once again turned to the Bergman reaction, in the hope of achieving a better understanding of the mechanism and factors which control the cycloaromatisation. Thus, further proof of the reversibility of the Bergman cyclisation has been recently provided by Schottelius *et al.*, who observed the formation of the enediyne **4** upon irradiation of **14**.[5] This observation is attributed to a slower than expected hydrogen abstraction of the intermediate diradical species **15** as a result of through-bond coupling.



Scheme 1.4

Several factors have been shown to govern the ease of cycloaromatisation of (*Z*)-enediynes. Each controlling feature has been studied in detail, but all can be seen to contribute to the overall reactivity. Most studies have been performed on 10-membered model ring systems in order to mimic the behaviour of the cyclic enediynes in the calicheamicin and antibiotics (*vide infra*).

Thus, Nicolaou and co-workers prepared a series of enediyne systems containing 10 to 16-membered rings (scheme 1.5).[6] At room temperature, the rings with n = 2 to n=7 were found to be stable, but the 10-membered ring system (n = 1) underwent spontaneous cycloaromatisation. Nicolaou theorised that the rate of cyclisation was directly linked to the distance between the two terminal acetylenic carbons in the enediyne unit (the *cd* distance). Indeed, he found that by decreasing the *cd* distance, the Bergman cyclisation occurred spontaneously at lower temperatures. In order to observe appreciable cycloaromatisation at room temperature, Nicolaou postulated an upper limit for the *cd* distance of 3.2 - 3.3Å. This distance is consistent with that found in the naturally occurring 10-membered cyclic enediyne antibiotics. In a separate study, Kraka and Cremer calculated, by *ab initio* methods, that cycloaromatisation will become spontaneous at 25°C when the *cd* distance is ≤3.0Å.[7]



(n = 1-7)

16 **17**

Scheme 1.5

Buchwald and co-workers[8] presented an enediyne-based diphosphine (figure 1.2), which undergoes a Bergman cyclisation some 30,000 times faster upon co-ordination to palladium dichloride or platinum dichloride. In contrast, by complexing to mercuric chloride (**21**) the cyclisation is inhibited. This difference in reactivity is once again related to the distance between the two terminal acetylenic carbons. A *cd* distance of less than 3.34Å was calculated[6,9,10] to be sufficient to induce spontaneous cyclisation at room temperature. Co-ordination to mercuric chloride means the *cd* distance cannot be reduced to less than 3.4Å (table 1.1), even upon heating, and so cyclisation cannot occur.

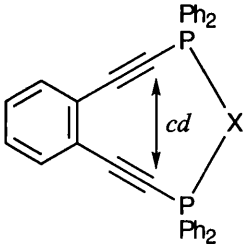
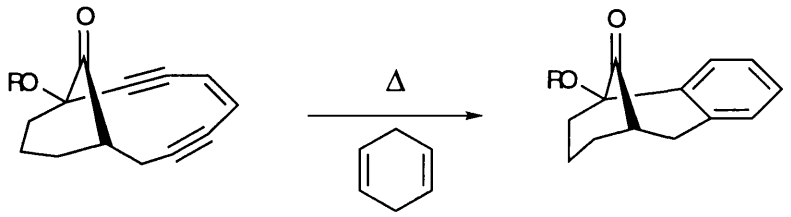


Figure 1.2

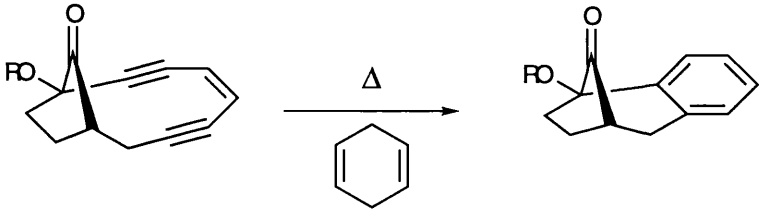
Compound	X	*cd*
18	no metal	4.1Å
19	$PdCl_2$	3.3Å
20	$PtCl_2$	3.3Å
21	$HgCl_2$	3.4Å

Table 1.1

Snyder, using *ab initio* methods, suggested that the reactivity of enediynes is governed by the difference in strain energy between the enediyne and the transition state leading to the formation of the diradical,[11,12] a suggestion which was also made independently by Magnus *et al.*,[13] who studied the reactivity of the bicyclic systems **22** and **24**. Although the *cd* distances of the two compounds are similar, the less strained ring system, **22**, undergoes cyclisation 650 times faster than **24** at 124°C. The explanation for this difference between the five- and six-membered ring analogues is that the boat cyclohexanone **22** becomes a chair upon cyclisation, which provides approximately 6kcal mol^{-1} strain release in the transition state. The five-membered ring analogue (**24**) has no comparable driving force (table 1.2).



22 **23**



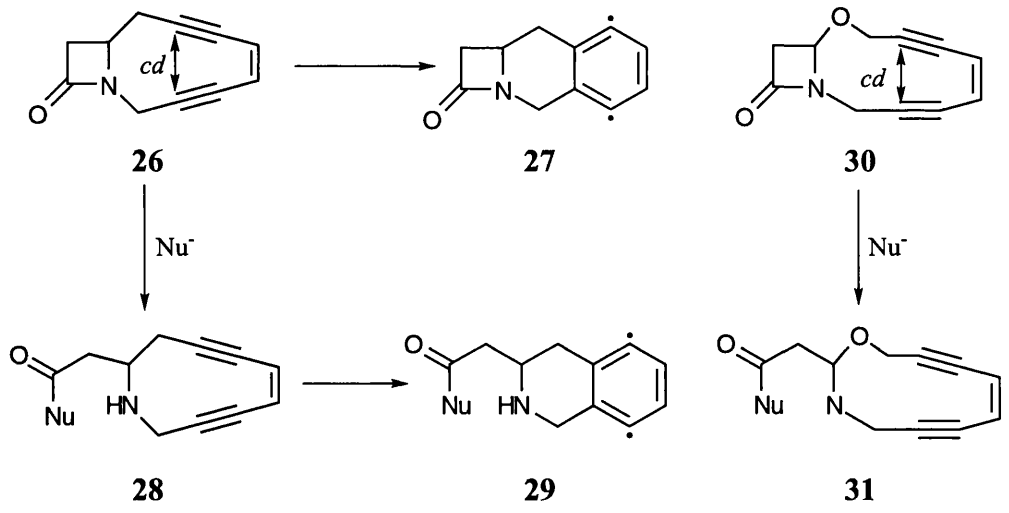
24 **25**

Scheme 1.6

Compound	T, °C	*cd*, Å	k, s^{-1}	$\Delta G^{\neq}$, kcal mol^{-1}
22	124	3.39	1.35×10^{-2}	26.9
24	124	3.37	2.08×10^{-5}	32.0

Table 1.2

A recent report by Basak *et al.* studied the cycloaromatisation of azetidinyl enediynes (scheme 1.7).[14] The presence of the β-lactam ring enhances the strain difference between the starting material and the transition state. Using PCMODEL they calculated that the *cd* distance in **26** was 3.27Å, whereas in the corresponding ring-opened system **28** it was calculated to be 3.41Å. Although a distance of 3.27Å would predict spontaneous cycloaromatisation of **26** at room temperature, the high strain energy (calculated at 33.4kcal mol^{-1}) means it is stable up to temperatures of 100°C. However, upon ring-opening by a nucleophile such as methoxide, this strain energy is released and the cyclisation becomes spontaneous. For the 11-membered enediyne **30** the *cd* distance (3.75Å) was slightly greater than for the ring-opened system **31**, and so cyclisation will not occur in either case.



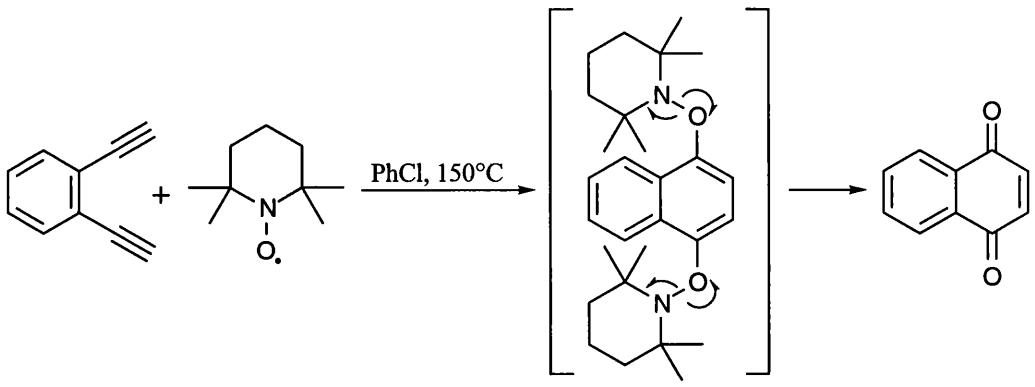
Scheme 1.7

Although most experimental evidence points towards the formation of a 1,4-dehydrobenzene diradical, theoretical calculations appear to challenge the diradical character of the intermediate structure. Kraka and Cremer have shown that the transition state has very little diradical character,[7] a contention also supported by Lindh *et al.*, who have calculated that the small change in geometry that occurs between the two terminal acetylenic carbons is not sufficient enough to energetically favour the formation of a 1,4-dehydrobenzene.[15] Lindh also suggests that joining

these two terminal carbons in a macrocycle, as found in the natural antibiotics, inhibits the reaction by this pathway and that the reaction may proceed *via* a concerted ring closure and hydrogen abstraction.[16]

The proposed 1,4-dehydrobenzene species is believed to exist in the singlet state. Intersystem crossing to the triplet state cannot be increased by either heavy atom effects or by the application of an external magnetic field.[17] This questions the presence of a diradical, although determinations of the heats of formation of such species by both experimental[18-20] and computational[7,21,22] methods agree at a figure of between 125 and 139kcal mol^{-1}.

Further evidence of the existence of a diradical intermediate in the Bergman cyclisation was recently provided by Grissom and Gunawardena.[23] Performing the cyclisation of **32** in the presence of the well known radical trapping agent TEMPO (**33**) gave the bis-aryloxyamine intermediate **34**, which underwent spontaneous homolytic cleavage of the N-O bonds, affording the naphthoquinone **35**.

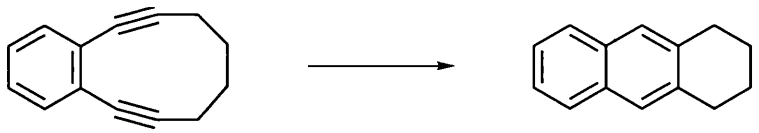


32 **33** **34** **35**

Scheme 1.8

Recently, Semmelhack and co-workers[24] found that the concentration of 1,4-cyclohexadiene (1,4-CHD) has a direct effect on the cycloaromatisation of **36** to give **37**. Changing the concentration of 1,4-CHD in the reaction mixture (table 1.3) from

zero to 10.5M (neat) caused a reduction in the half-life of the cyclisation at 84°C from 129 to 10.5 hours. This observation prompted another study of the kinetics, since until this point only first order kinetics had been observed with simple enediynes.[25,26]



36 **37**

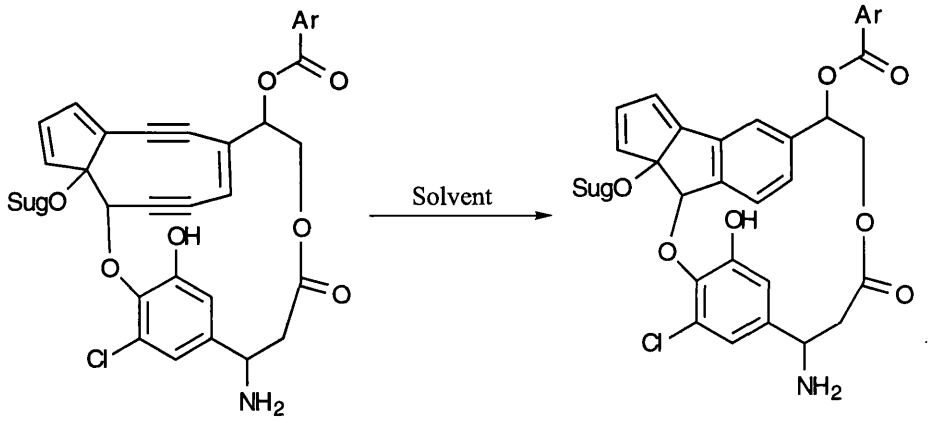
Scheme 1.9

Concentration of 1,4-CHD[a]	Half-life[b]	Temperature
0.00M	129hr	84°C
0.25M	39hr	84°C
0.50M	24hr	84°C
10.50M (neat)	10.5hr	84°C

a. in C_6D_6 solution.
b. based on disappearance of 1,4-CHD

Table 1.3

Yoshida and co-workers showed, from the observation of a kinetic isotope effect, that the rate of cyclisation of **11** (the chromophore of the natural product C-1027) is affected by the concentration of the hydrogen atom donor (table 1.4).[27] This suggests that the hydrogen abstraction step may be rate-determining.



11 **38**

Scheme 1.10

Solvent	k_H/k_D
dioxane/dioxane-d_8	2.9
CH_3OH/CH_3OD	1.1
CH_3OH/CD_3OD	2.8
C_2H_5OH/C_2D_5OD	3.8

Table 1.4

1.2 Enediyne Natural Products

At the present time, there are five distinct classes of known enediyne-containing natural products, namely the calicheamicins (**10**), C-1027 chromophore (**11**), esperamicins (**12**), dynemicin (**13**) and kedarcidin chromophore (**39**). In addition to these, there is the closely-related neocarzinostatin chromophore (**40**), which contains a latent enyne allene moiety and thus undergoes a cycloaromatisation in a similar manner (see scheme 1.36).

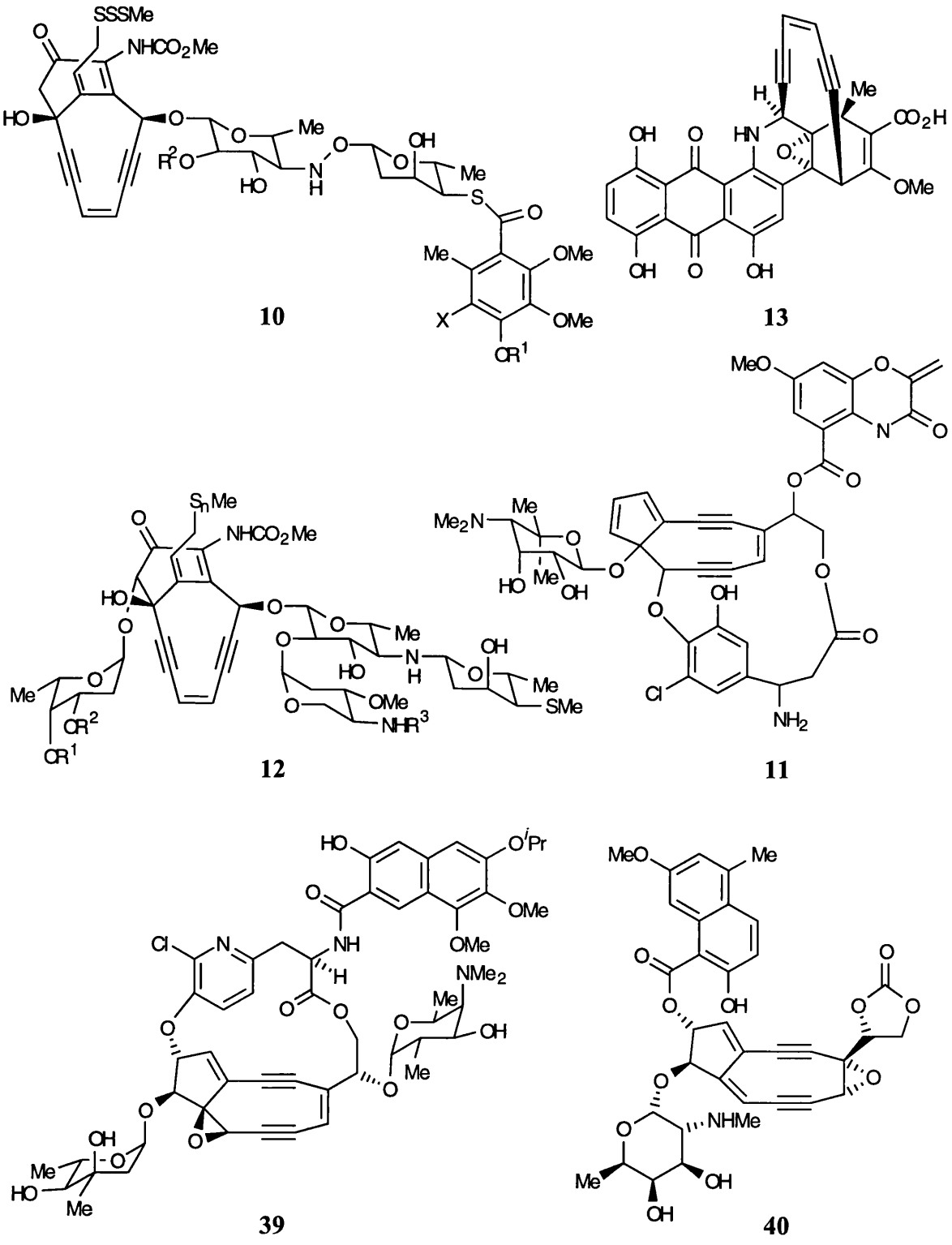


Figure 1.3

All of these antibiotics exhibit the ability to cleave DNA in an irreversible process and are amongst the most potent antitumour and antibacterial agents known.[9,10,28] The general mechanism of DNA cleavage shown by the natural compounds may be represented by a four stage process:

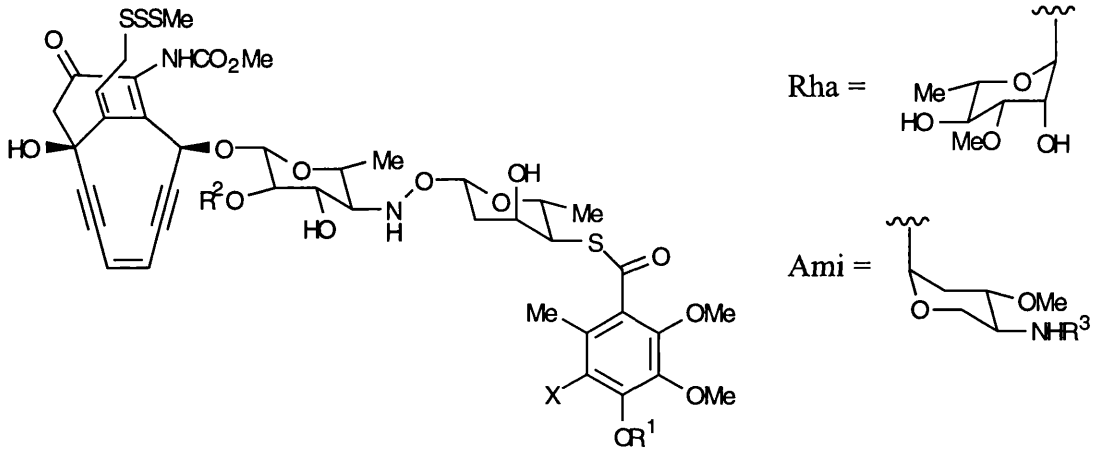
Stage one: Recognition of a particular base sequence in the DNA and binding to this by a specific structural feature attached to the enediyne.
Stage two: A process of activating the enediyne towards the Bergman cyclisation.
Stage three: Bergman cyclisation, giving rise to the highly reactive 1,4-dihydroarene radical.
Stage four: Abstraction of hydrogen atoms from the DNA, causing further structural modification and thus denaturing the genetic material.

The principal differences between the enediyne natural products lie in the structure of their enediyne-containing core and the mode of activation towards the Bergman reaction. For the purposes of this discussion we shall consider each class of natural product separately, concentrating on their structure, binding to DNA and mode of activation.

1.2.1 Calicheamicins and Esperamicins

The calicheamicins and the esperamicins share the same bicyclic enediyne-containing core and method of activation, differing only in the glycosidic structure. It was in 1987 that researchers from Lederle and Bristol-Myers simultaneously published the structural elucidation of two unique and complex glycosides. The calicheamicin family was isolated by the Lederle group from *Micromonospora echinospora ssp. clichensis* and currently contains around 20 members, the most important of which

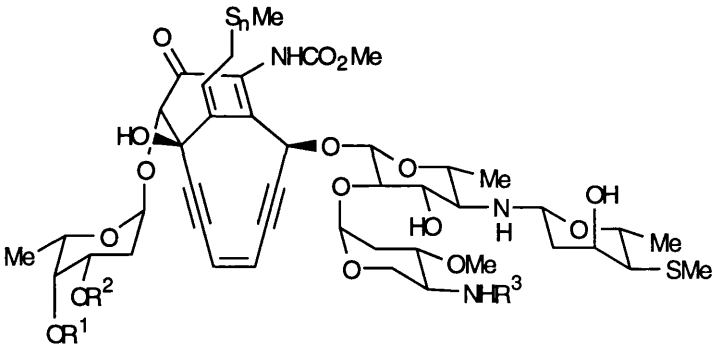
are shown in figure 1.4.[29-31] There are seven members of the esperamicin family, all produced by *Actinomadura verrucosopora* (figure 1.5).[32-36]



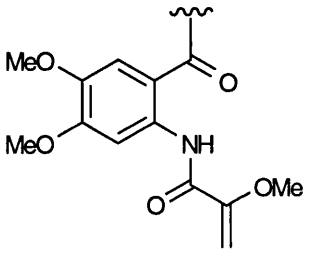
Calicheamicin	X	R^1	R^2	R^3
β_1^{Br}	Br	Rha	Ami	^{i}Pr
γ_1^{Br}	Br	Rha	Ami	Et
α_2^{I}	I	H	Ami	Et
α_3^{I}	I	Rha	H	-
β_1^{I}	I	Rha	Ami	^{i}Pr
γ_1^{I}	I	Rha	Ami	Et
δ_1^{I}	I	Rha	Ami	Me

Figure 1.4

It has been discovered that co-occurring with the esperamicins is an inactive compound, esperamicin X (**44**),[34] which is proposed to be the product formed after the metabolites undergo the Bergman cyclisation. The proposed mode of biological action of the calicheamicins and esperamicins involves nucleophilic attack on the central sulfur atom and subsequent addition of the resultant thiol to the α,β-unsaturated carbonyl group to give the intermediate **42** (scheme 1.11). The resulting change in hybridisation at C-1 from sp^2 to sp^3 essentially pulls the two ends of the enediyne towards each other to allow cyclisation of the enediyne to the 1,4-diyl **43**. The triggering thiol addition not only reduces the *cd* distance of the enediyne but also lowers the energy of the transition state by removing the bridgehead double bond.

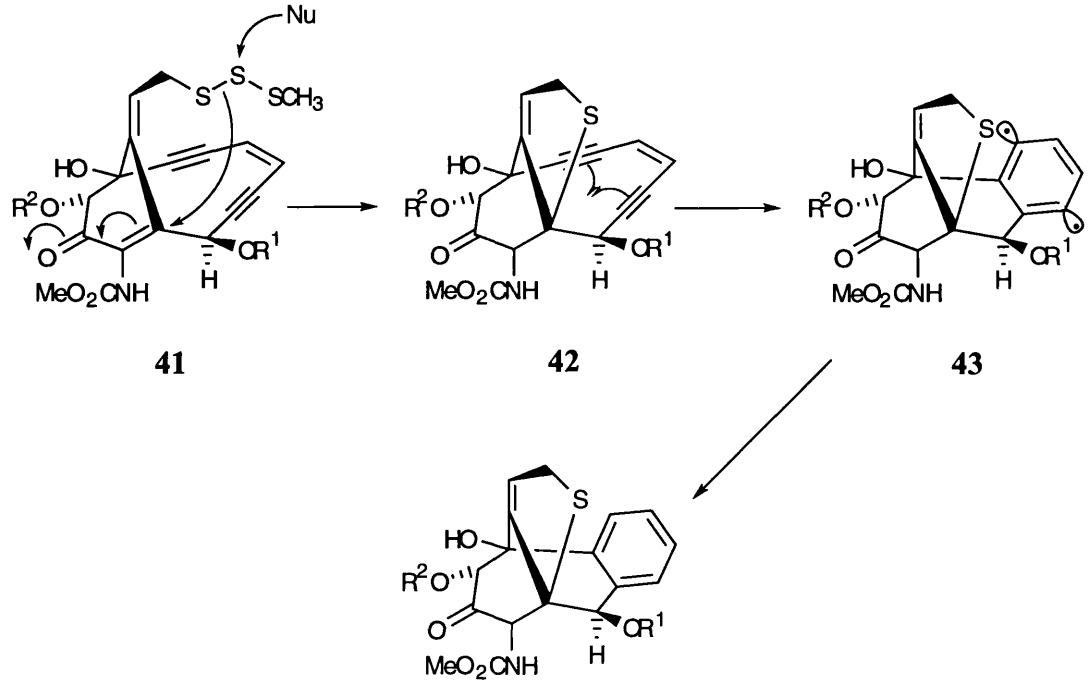


R=



Esperamicin	n	R^1	R^2	R^3
A_1	3	H	R	^{i}Pr
A_{1b}	3	H	R	Et
A_{1c}	3	H	R	Me
P	4	H	R	^{i}Pr
A_2	3	R	H	^{i}Pr
A_{2b}	3	R	H	Et
A_{2c}	3	R	H	Me

Figure 1.5

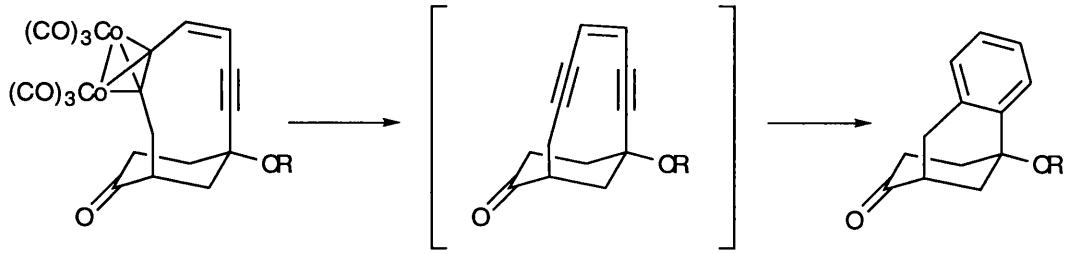


41 **42** **43**

44

Scheme 1.11

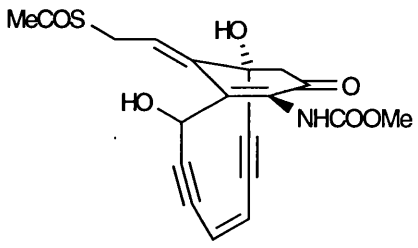
By synthesising the model compound **45**, Magnus and Carter[37] have demonstrated that conversion of the highly strained intermediate (**46**) to the aryl (**47**) is sufficiently fast at room temperature to make this a viable pathway. The difference in energy between **46** and **47** is 8.8kcal mol^{-1}. This figure compares favourably with the required 10-12kcal mol^{-1} for the cyclisation of the natural product proposed in scheme 1.11 to proceed at a reasonable rate at room temperature.



45 **46** **47**

Scheme 1.12

Townsend and co-workers have shown that the rate-determining step in the overall activation of calicheamicin γ_1^I is the formation of the allylic thiolate **42**.[38] It was suggested that the amino sugars present in calicheamicin may function as intramolecular bases in the DNA-bound forms of the drugs in order to deprotonate thiols and thus increase the rates of drug activation.[39,40] However, by comparing k_1 for the conversion of **41** to **42** with the bimolecular rate constants obtained for two analogues that lack the amino sugar functionality, Cramer and Townsend have shown that invoking the general base hypothesis is unnecessary and that the amino sugar has no chemical role in the activation process.



48

Figure 1.6

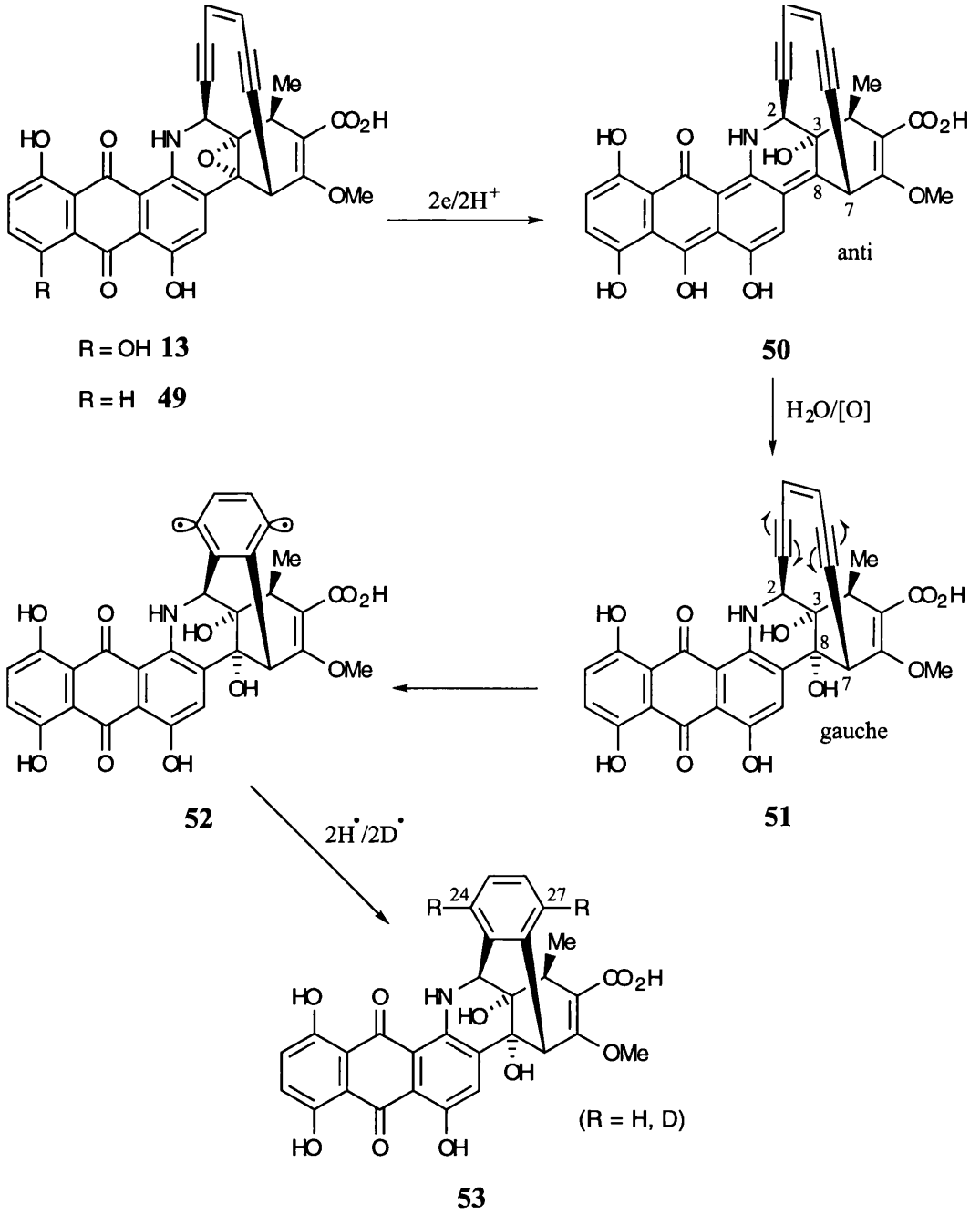
Both calicheamicin and esperamicin bind to the minor groove of the DNA double helix.[30,34] The drugs cleave double stranded DNA at homopyrimidine or homopurine tracts[40,41] *via* the 1,4-dehydrobenzene diradical produced in the aglycone sector after bioreductive activation.[42] It has been shown[43] that the free oligosaccharide of calicheamicin γ_1^I interacts with duplex DNA along specific sequences within the minor groove, although with lower specificity than the parent drug. Indeed, Nicolaou *et al.* have recently reported the striking site selectivity and affinity of head-to-head and head-to-tail dimers of the calicheamicin γ_1^I oligosaccharide.[44] In the absence of the carbohydrate, the calicheamicin γ_1^I aglycone analogue **48** (figure 1.6)[45] cleaves DNA in a non-specific manner at every base-pair.[46] This demonstrates that although the carbohydrate sector of the natural products is principally responsible for the binding of the drug to duplex DNA, it is the whole structure which provides the high specificity.

1.2.2 Dynemicins

Dynemicin A (**13**) is produced by *Micromonospora chersina* and was isolated by the Konishi and Clardy groups in 1989.[47,48] More recently, deoxydynemicin A (**49**) was isolated from the fermentation broths of *Micromonospora globosa* MG331-HF6.[49]

The molecular structure of the dynemicins combines the characteristics of both the enediyne and the anthracycline classes of antibiotics, and as such presents a two-fold challenge to organic synthesis. The anthraquinone is believed to serve both as the DNA-binding element of the drug, and as the means for triggering the proposed Bergman cyclisation. An unusual feature of the drug is that it bears a negative charge on the carboxylate group at physiological pH, as all other members of the enediyne antibiotic family are positively charged, which is normal for molecules which bind to

the DNA polyanion. Dynemicin A exhibits potent inhibitory activity against various tumour cell lines and *in vivo* activity in P388 leukaemia and B16 melanoma inoculated mice.[47] Moreover, it shows little *in vivo* toxicity.



Scheme 1.13

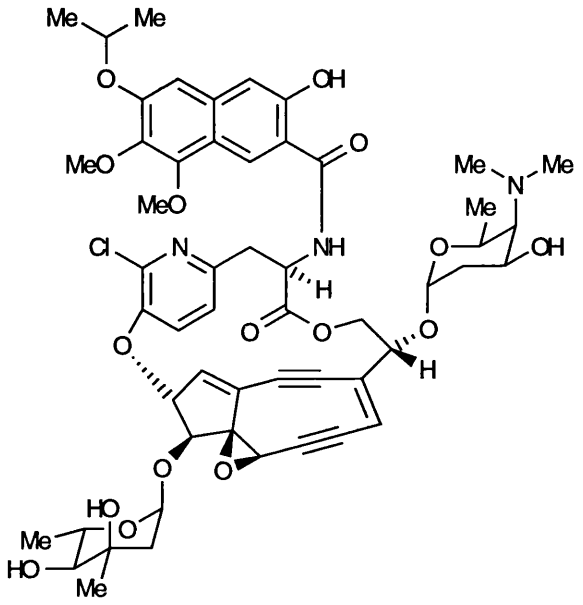
The proposed activation process for dynemicin A is a bioreductive opening of the benzylic epoxide,[47-53] promoted by the presence of a reducing cofactor such as

glutathione (GSH) or NADPH. Protonation of the resultant anthraquinone methide **50**, gives the activated enediyne **51**. This process allows carbons 2, 3, 7 and 8 to change from an anti-like conformation (**50**) and assume a gauche-like conformation (**51**), thereby permitting cycloaromatisation and furnishing the diradical. To prove the presence of a diradical species, Miyoshi *et al.*[54] have treated dynemicin A with aqueous sodium hydrosulfite in dioxane to give the rearrangement product, dynemicin H (**53**). The same reaction in d_8-dioxane gave **53** deuterated specifically at C-24 and C-27.

A detailed study of the mechanism of DNA cleavage by dynemicin A was recently performed by Myers and co-workers.[55] They showed that dynemicin A has a near-optimum balance of reaction rate, where weak binding is advantageous, and cleavage efficiency, where tight binding is advantageous.

1.2.3 Kedarcidin Chromophore

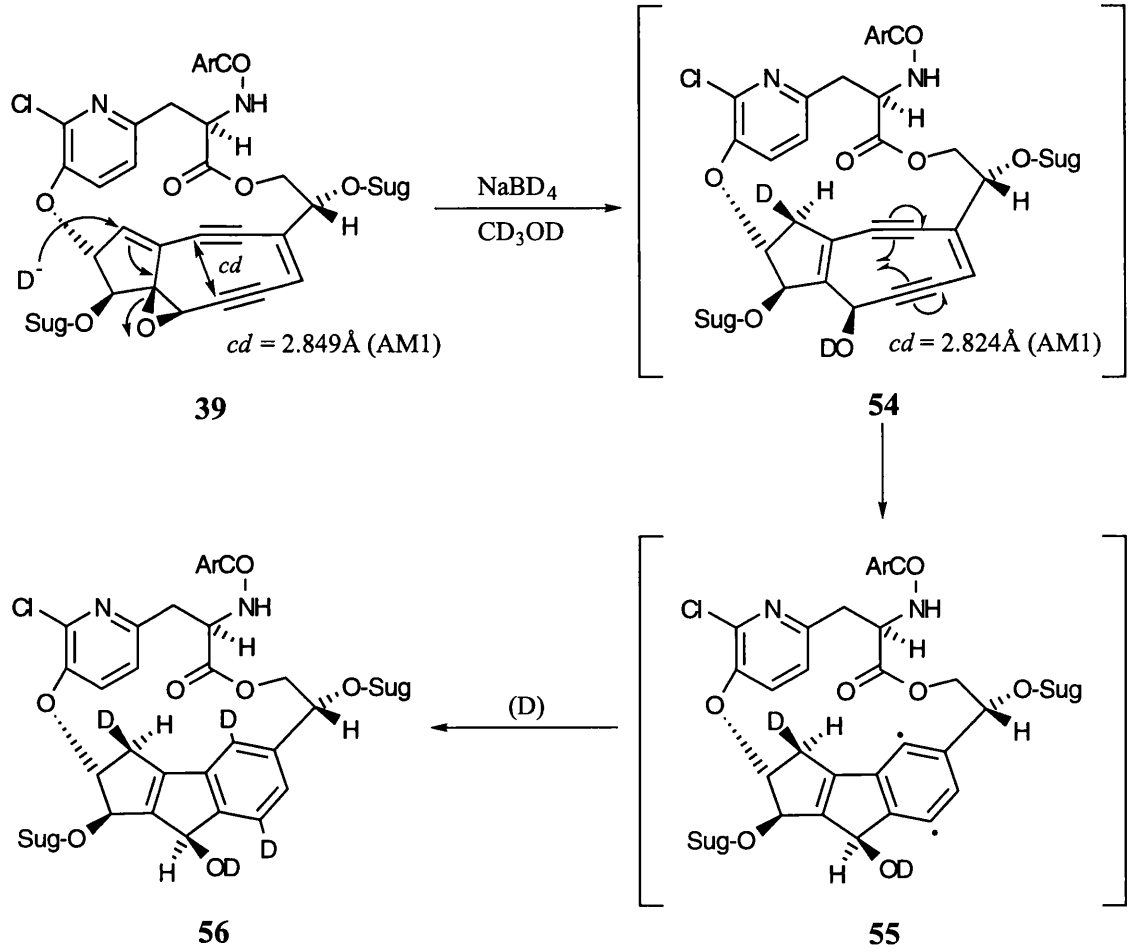
Kedarcidin was isolated in 1991 from the fermentation broth of a novel actinomycete strain.[56,57] It is a chromoprotein antitumour antibiotic, consisting of a water-soluble apoprotein and a solvent-extractable, cytotoxic and highly unstable chromophore (**39**). The major apoprotein is a single polypeptide chain consisting of 114 amino acid residues.[58] The antitumour activity of kedarcidin is due primarily to the chromophore, whereas the apoprotein is believed to play a role in the stabilisation and transport of the chromophore.[59] The kedarcidin chromophore contains two glycosidic units bound to an aglycone containing aromatic, epoxide and enediyne functionality.



39

Figure 1.7

The mechanism of action of the kedarcidin chromophore was proposed by Leet *et al.*, on the basis of sodium borohydride / borodeuteride experiments.[60] Attack of the reducing agent on the less hindered side of C-12 is followed by double-bond migration and opening of the epoxide ring (scheme 1.14). Introduction of deuterium selectively at C-3 and C-6 in the reduced form of the chromophore (**56**) provides strong support for a Bergman cyclisation of the enediyne *via* a 1,4-benzenoid diradical (**55**). Calculations have shown that the epoxide ring-opening does not cause any significant change in the *cd* distance of the enediyne. This would suggest that this ring-opening reduces the strain energy developed in the transition state leading to the Bergman cyclisation.[11,61]

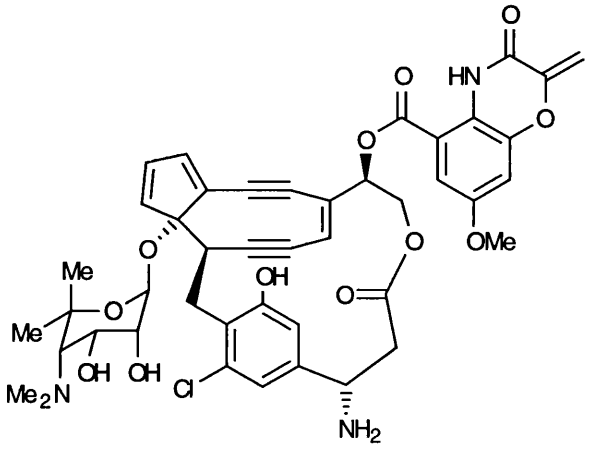


Scheme 1.14

1.2.4 C-1027 Chromophore

The most recently identified addition to the naturally occurring enediynes is C-1027 chromophore (**11**), the active principle of chromoprotein antibiotic C-1027. The antibiotic was isolated from the fermentation broth filtrate of *Streptomyces globisporus* by Hu *et al.* in 1988,[62,63] and shows cytotoxicity against KB carcinoma cells *in vitro*[64] and antitumour activity towards tumour-bearing mice *in vivo*.[65] As with kedarcidin, it is the chromophore which is responsible for this biological activity, possessing the ability to cleave double-stranded DNA.[64] It has been shown that the chromophore binds to the minor groove of DNA, assisted by the aminosugar,

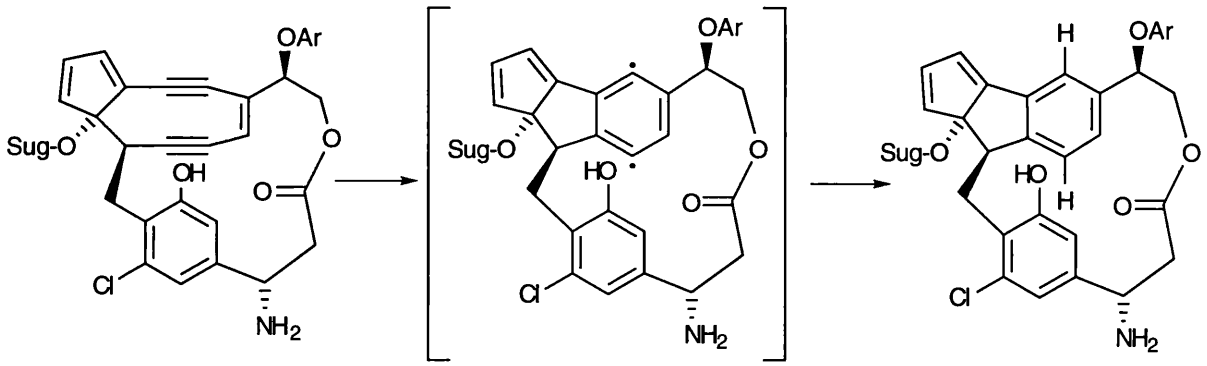
and that there are significant intramolecular nOe's in the 16-membered macrocycle, indicating a possible role in the regulation of cycloaromatisation.[66]



11

Figure 1.8

The structure of the more stable reaction product of C-1027 chromophore (**58**) was established by Minami and co-workers, by means of chemical degradation and 2D NMR studies.[67] Its benzodihydropentalene core structure suggested the presence of an enediyne in the parent compound, which led the group to discover the structure of C-1027 chromophore and propose a mechanism for the cycloaromatisation (scheme 1.15).[68] Recently, Iida *et al.* have determined the absolute configuration of the aglycone by 2D NMR and molecular modelling methods.[69]



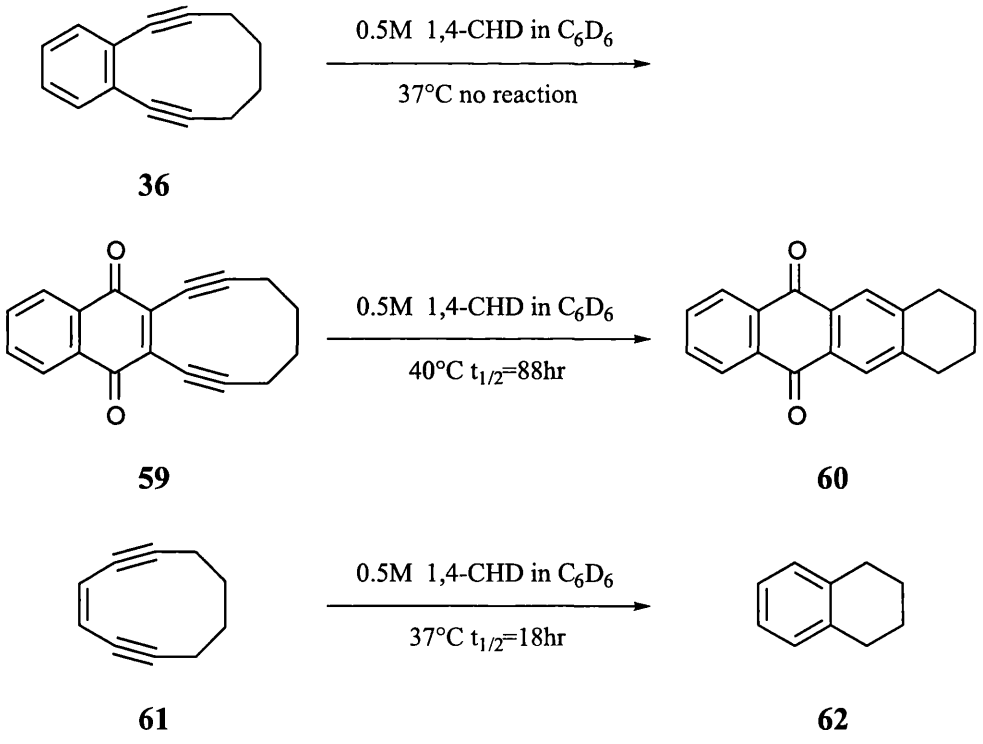
11 **57** **58**

Scheme 1.15

1.3 Triggers for Cycloaromatisation

If the Bergman reaction is to be used in a successful therapy, a degree of control is needed over the cyclisation process. To this end, a number of research groups have explored the possibility of triggering systems which could be easily incorporated into novel molecules and exhibit a large degree of control over the rate of cycloaromatisation.

Semmelhack[24] has shown that the presence of an aromatic structure in place of the ene unit within the enediyne strongly inhibits the Bergman cyclisation, but that a quinone unit, as in naphthaquinone **59**, restores the reactivity to approximately that of the parent enediyne (scheme 1.16).

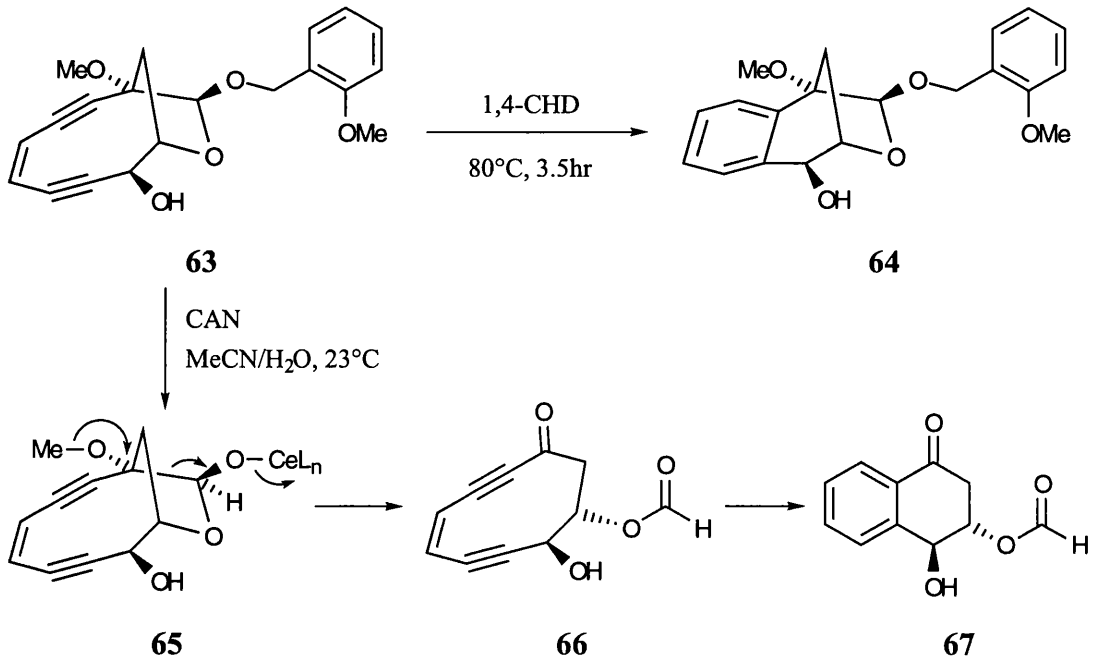


36 **59** **60** **61** **62**

Scheme 1.16

This discovery leads to the potential use of the oxidation of a hydroquinone to a quinone in order to restore the full double-bond character of the enediyne, thus triggering the cyclisation reaction.[70]

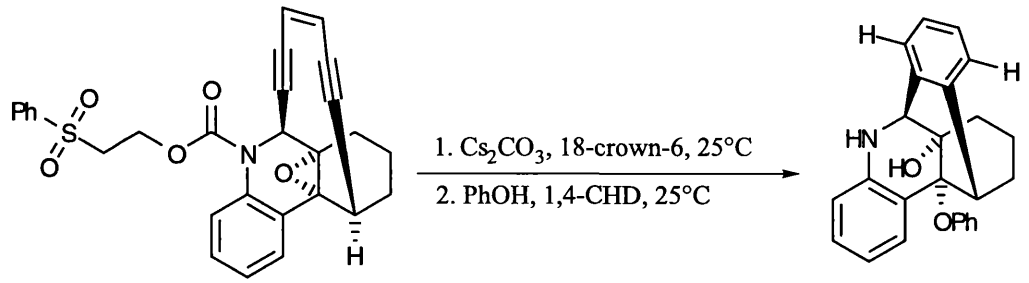
In another oxidative process, Brandstetter and Maier[71] have shown that activation of the stable enediyne **63**, by oxidation with CAN, gives the cyclised tetrahydronaphthalene derivative **67**.



63 **64** **65** **66** **67**

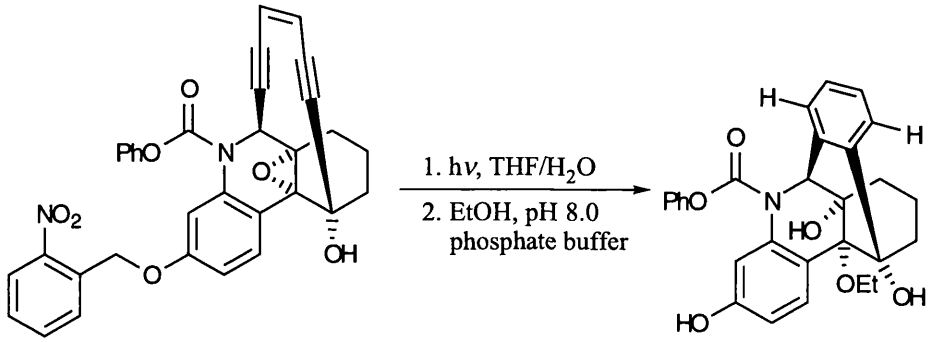
Scheme 1.17

Several analogues of dynemicin have been synthesised by Nicolaou[50,72,73] in his work designing enediynes carrying *N*-tethered and photosensitive triggering devices. The [(arylsulfonyl)ethoxy]carbonyl group, attached at nitrogen (**68**), will undergo *β*-elimination under basic conditions liberating the cycloaromatised product (**69**) upon addition of PhOH (scheme 1.18). Alternatively the photoremovable *o*-nitrobenzyl group at C-3 (**70**) (scheme 1.19) gives a phenol upon irradiation, thus promoting epoxide opening and subsequent Bergman cyclisation, to afford **71**.



68 **69**

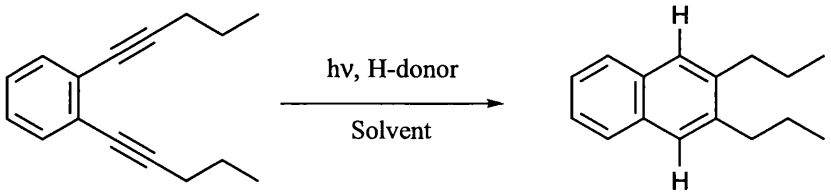
Scheme 1.18



70 **71**

Scheme 1.19

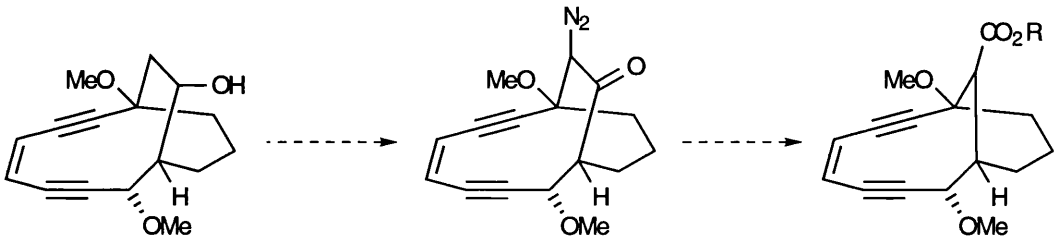
Recently, Turro *et al.*[74] presented the first mild alternative to promoting the cyclisation reaction, namely the photochemical cycloaromatisation of **72** to give the naphthalene derivative **73**. The best result was reported using benzhydrol (0.5M) as the hydrogen donor. Since that report an extensive investigation into the photo-induced Bergman cyclisation has been carried out by Funk.[75,76]



72 **73**

Scheme 1.20

Ring contraction of a stable [7.3.2]-enediyne to give a more reactive [7.3.1]-enediyne was recently proposed by Maier and Langenbacher.[77] They synthesised the [7.3.2]-enediyne **74** containing a functional group on the two-carbon bridge, and anticipated that the introduction of a diazo keto function would permit the photochemical Wolff rearrangement to give the ring contracted, and thus activated, [7.3.1]-enediyne (**76**).



74 **75** **76**

Scheme 1.21

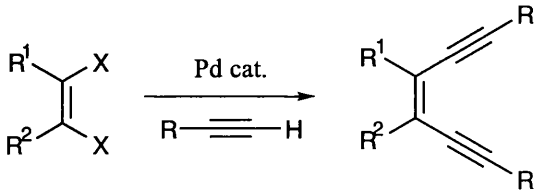
These results are of particular relevance to the design of a photochemical analogue of the chemically induced activation observed in the natural products (*vide supra*). These precursor molecules offer desirable features: they are stable over a large temperature range; may be structurally tailored to specific site delivery; and may be excited upon binding to specific sites by fibre-optic techniques already used in medicine.

1.4 The Synthesis of Enediynes

As the interest in the synthesis of the enediyne natural products has increased over the last decade, so has the need for new methodologies for the synthesis of the enediyne unit itself. These should allow more structural diversity in the enediyne unit, a greater tolerance of different functionality elsewhere in the molecule, and bring about the synthesis with greater efficiency. This section will only deal with the most

important recent approaches to the synthesis of the enediyne unit, in terms of the common routes which have been developed.

The most commonly used methodology for the synthesis of the enediyne unit is the palladium-catalysed coupling of acetylenes to a dihaloalkene or dihaloaromatic (scheme 1.22).

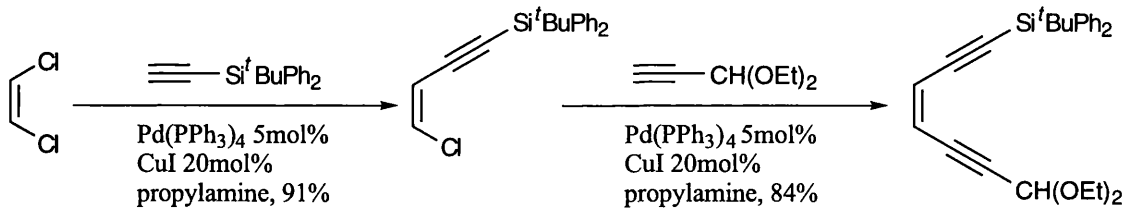


77 78

R^1 = alkyl, aryl, H
R^2 = alkyl, aryl, H
X = I, Br, Cl

Scheme 1.22

The Stephans-Castro coupling of copper(I) arylacetylenes with iodoarenes[78] or iodoalkenes,[79] first reported in the 1960's, had a limited scope due to the sometimes violent reaction conditions and difficulties in the preparation of copper(I) acetylides. In 1975, Sonogashira *et al.* reported a coupling procedure in which the acetylenic hydrogen could be substituted by iodoarenes, bromoalkenes or bromopyridines in the presence of catalytic $Pd(PPh_3)_2Cl_2$.[80]



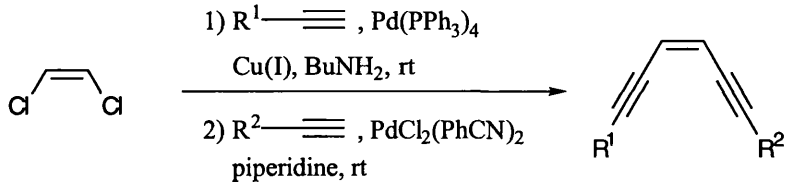
79 80 81

Scheme 1.23

A few years later, both Cassar[81] and Heck[82] independently reported similar reaction conditions. This approach was the subject of much study,[83-87] mainly by

Linstrumelle, and was used by Schreiber in his synthesis of the bicyclic core of the esperamicin/calicheamicin antibiotics (scheme 1.23). [88]

Some studies have reported the effect of base[86] and catalyst[85] on the efficiency of the reaction. Recently, Linstrumelle and co-workers[89] reported a one-pot synthesis of functionalised, unsymmetrical (*Z*)- or (*E*)-enediynes involving two sequential $Pd(PPh_3)_4$ and $PdCl_2(PhCN)_2$ catalysed coupling reactions from (*Z*) or (*E*)-dichloroethylenes and 1-alkynes (scheme 1.24, table 1.5).



79 **82**

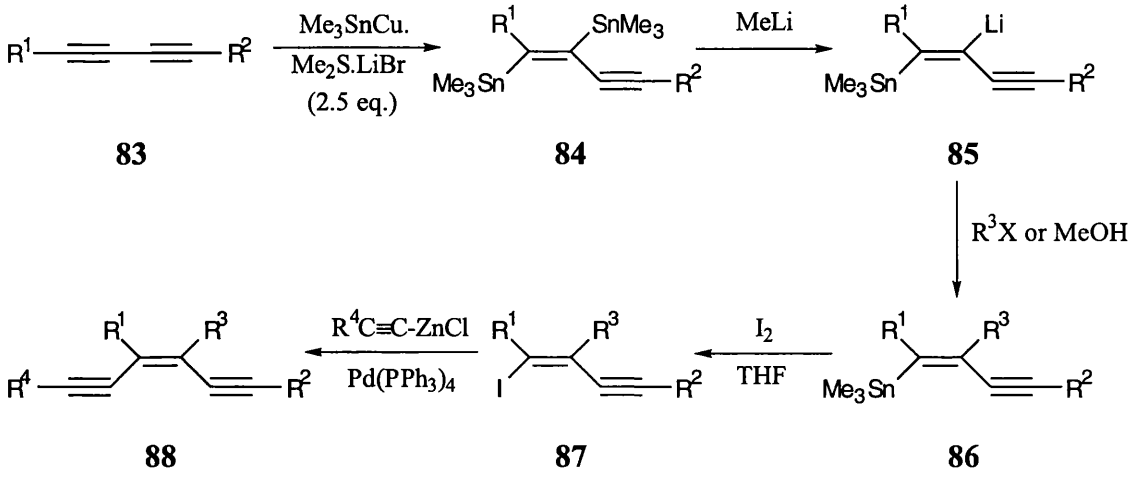
Scheme 1.24

Entry	R^1	R^2	Yield
82a	$(CH_2)_4OH$	C_5H_{11}	73%
82b	C_5H_{11}	Me_3Si	72%
82c	$C_5H_{11}CH(OH)$	CH_2OH	72%
82d	$(CH_2)_2OH$	CH_2OH	62%
82e	$C(Me)_2NH_2$	C_5H_{11}	71%
82f	$C(Me)_2NH_2$	$C_5H_{11}CH(OH)$	64%

Table 1.5

Another approach which employs palladium complexes was reported by Stracker and Zweifel.[90] The tri- or tetra-substituted enediynes (**88**) (scheme 1.25) are formed *via* the palladium catalysed cross-coupling reaction of iodoenynes (**87**), derived from mono(stannyl)enynes, with various zinc alkynylides (table 1.6). The mono(stannyl)enynes are synthesised *via* the reaction of 1-(trimethylsilyl)-1,3-diynes

(**83**) with (trimethylstannyl)copper to afford the corresponding (*E*)-bis(trimethylstannyl)enynes (**84**), which then undergo a stepwise transmetallation and alkylation (scheme 1.25).



Scheme 1.25

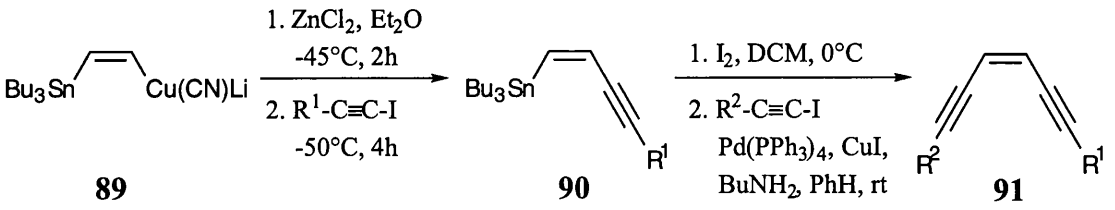
	R^1	R^2	R^3	R	Yield[a], %	
Entry					**87**	**88**
a	C_6H_{13}	$SiMe_3$	H	*n*-C_4H_9	100	85
b	C_6H_{13}	$SiMe_3$	H	C_6H_5	100	87
c	C_6H_{13}	$SiMe_2$Thexyl	H	$SiMe_3$	93	79
d	C_6H_{13}	$SiMe_3$	CH_3	*n*-C_4H_9	99	80
e	CH_3	$SiMe_2$Thexyl	H	*n*-C_4H_9	87	86
f	H	$SiMe_2$Thexyl	H	*n*-C_4H_9	85	85

a. Yields based on isolated compound.

Table 1.6

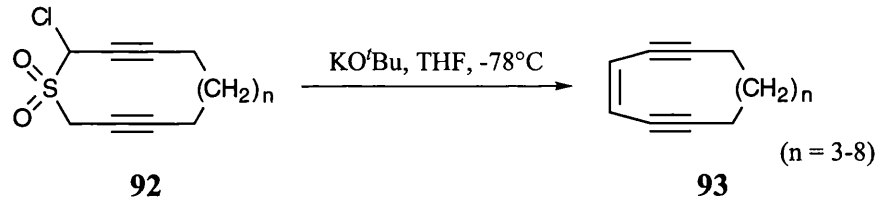
In a related approach, Magriotis *et al.*[91] reported a stannylcupration of acetylenes, followed by an *in situ* reaction of the high order cuprate intermediates (**89**) with 1-halo-1-alkynes to give rise to stannyl enynes (**90**). These in turn can readily be transformed to the desired enediynes (scheme 1.26). The yields are not as high as

those reported by Stracker and Zweifel,[90] however the methodology is more tolerant of functionality such as esters and silyl ethers.

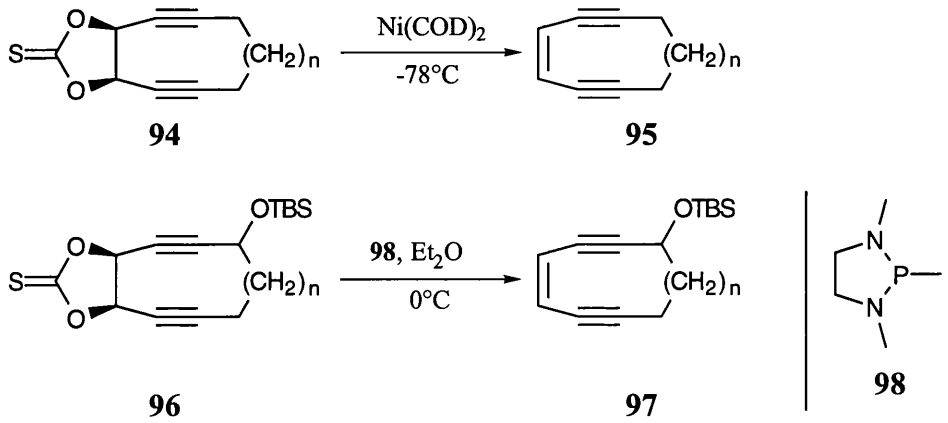


Scheme 1.26

A number of methods have been developed in which the double bond of the enediyne is inserted as the final step. Nicolaou *et al.*[92] used the Ramberg-Bäcklund reaction,[93] in which the α-chlorosulfones (**92**) were treated with potassium *tert*-butoxide to give the macrocyclic enediynes (scheme 1.27). The conversion of thionocarbonates **94** and **96** to alkenes, using either $Ni(COD)_2$ or phosphines, was first reported by Semmelack and Gallagher.[94] The best yields were obtained using the reactive Corey-Winter reagent (**98**) (scheme 1.28).

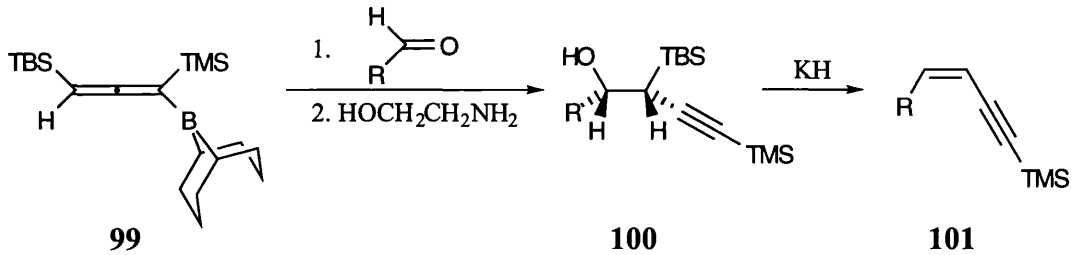


Scheme 1.27



Scheme 1.28

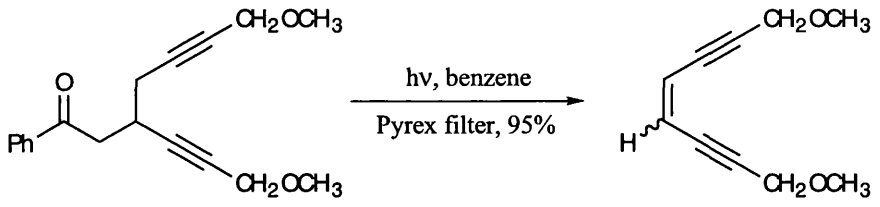
The Peterson elimination was utilised by Wang and co-workers in their synthesis of non-symmetrical enediynes.[95] The intermediate alcohols (**100**) were synthesised by treating the appropriate propargylic aldehydes with γ-(*tert*-butyldimethylsilyl) allenylboranes (**99**).



99 **100** **101**

Scheme 1.29

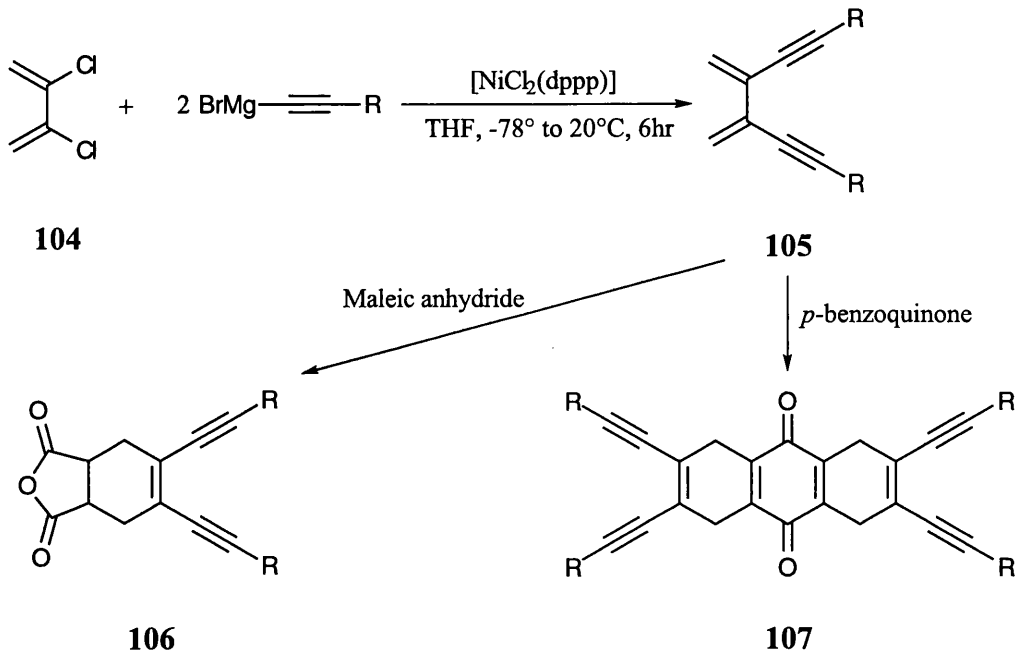
A highly efficient photochemical synthesis of the enediyne moiety *via* a Norrish type II reaction was reported by Nuss and Murphy (scheme 1.30).[96] Fragmentation of the ketone **102** led only to acetophenone and a 1:1 mixture of the enediyne stereoisomers (**103**).



102 **103**

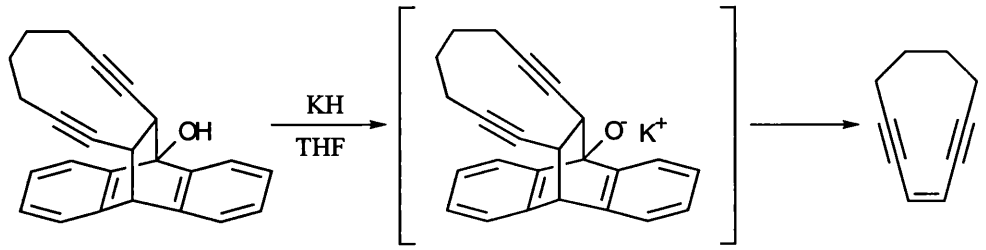
Scheme 1.30

In an unusual approach, Hopf and Theurig installed the alkene using a Diels-Alder reaction.[97] The [4+2] cycloaddition of **105** with either maleic anhydride or the double dienophile, *p*-benzoquinone, gave, respectively, the expected enediynes, **106** and **107**, in moderate yields (scheme 1.31).



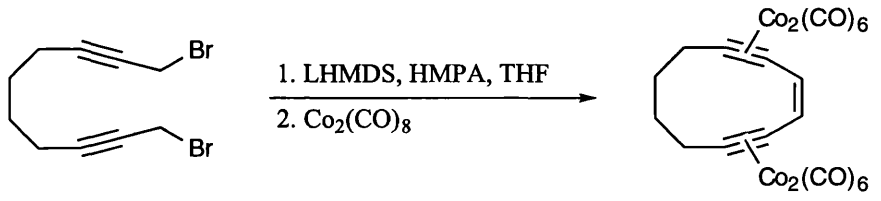
Scheme 1.31

A retro Diels-Alder approach has recently been reported by Bunnage and Nicolaou.[98] Although the alcohol (**108**) is highly stable under acidic or neutral conditions, treatment with KH at room temperature results in formation of the enediyne (**61**) in 90% yield (scheme 1.32).



Scheme 1.32

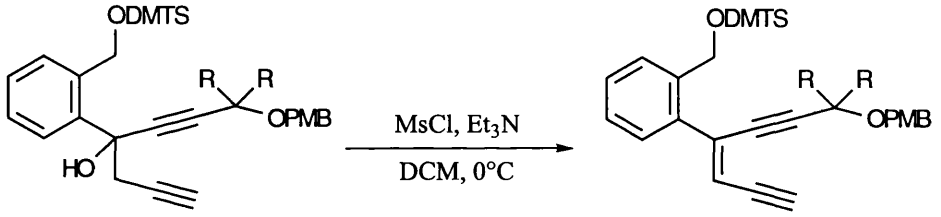
Jones and co-workers have reported the synthesis of both cyclic[99] and acyclic[100] enediynes *via* a "carbenoid" coupling reaction. For the formation of the 10-membered cyclic enediyne complex **111** from the acyclic dibromide precursor **110**, the HMPA/base ratio was found to be crucial to the efficiency of the reaction (scheme 1.33).



110 **111**

Scheme 1.33

Shibuya *et al.*[101] reported that elimination of the tertiary hydroxyl group of **112** by the action of mesyl chloride and triethylamine gave the acyclic hex-3-ene-1,5-diyne **113** with a (*Z*):(*E*) ratio of more than 96:4 (scheme 1.34, table 1.7).



112 **113**

Scheme 1.34

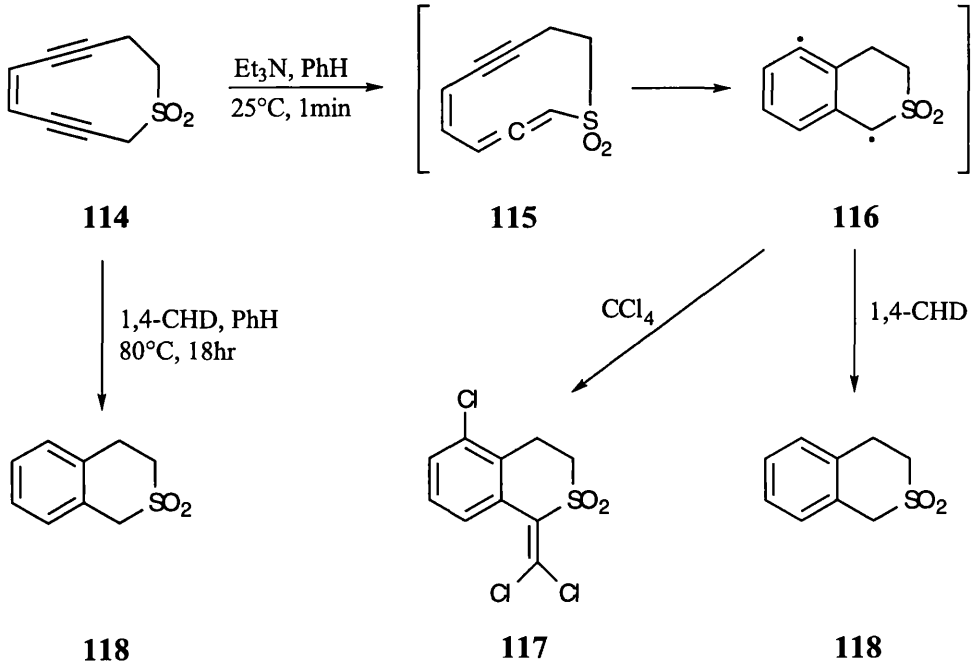
R	*cis (Z):trans (E)*	Yield
H	96:4	76%
Me	98:2	70%
Ph	>99:1	72%

Table 1.7

1.5 Enyne-Allenes, Enyne-Cumulenes and Enyne-Ketenes

Related to the enediynes, and sharing similar reactivity, are the enyne-allenes, enyne-cumulenes and enyne-ketenes. It has been elegantly shown that an enyne-allene will

form a diradical intermediate at a lower temperature than the equivalent enediyne (scheme 1.35).[102-104] Thus, heating the 10-membered enediyne **114** in the presence of 1,4-CHD at 80°C for 18 hours gave the expected Bergman cyclisation product (**118**). However, in the presence of triethylamine a very rapid cycloaromatisation reaction ($t_{1/2}$ < 1min) was observed at 25°C. This observation, and the formation of the trichloro derivative (**117**) when the reaction was performed in CCl_4, suggests the intermediacy of an enyne-allene (**115**) and a diradical (**116**). This is commonly referred to as the Myers cyclisation.



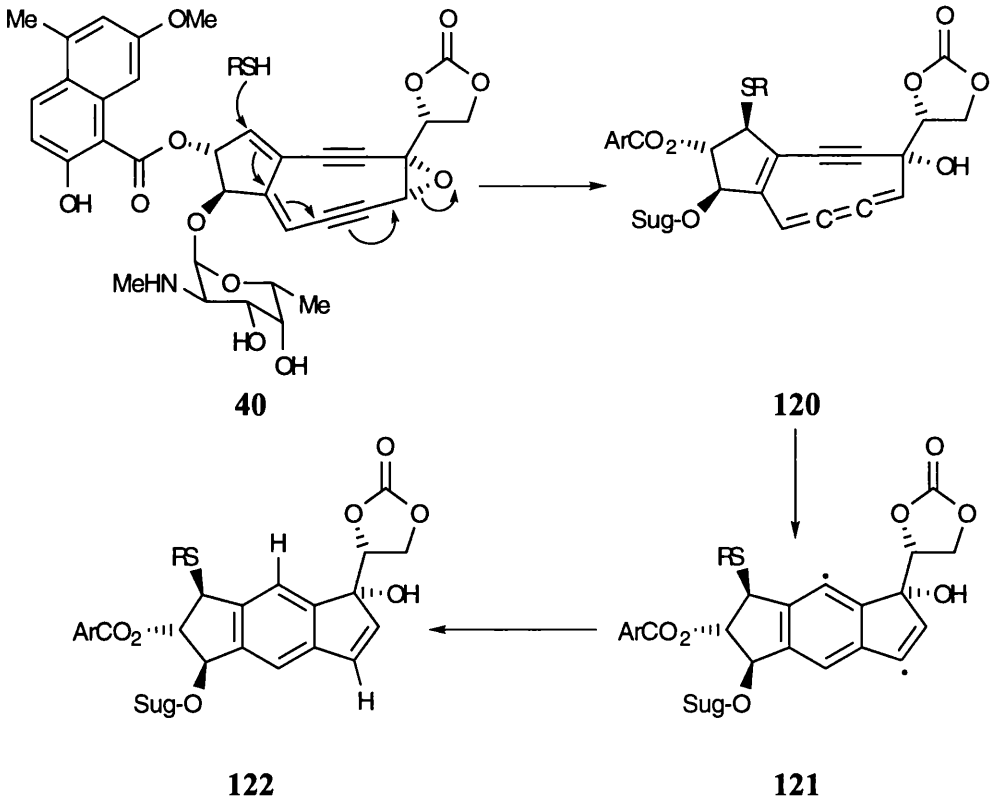
Scheme 1.35

This difference in reactivity between enediynes and enyne-allenes has been attributed to a more favourable orbital interaction in the (σ,π)-diradical of the enyne-allene cyclisation product (such as **116**, scheme 1.35), giving a more exothermic reaction with a lower activation energy.[105] Experimental and theoretical evidence suggests the existence of a singlet ground state for the diradical intermediate.[106] Also worth noting is the shorter *cd* distance between the reacting centres in the enyne-allene systems compared to the analogous enediynes.[107]

1.6 Neocarzinostatin

Neocarzinostatin (NCS) is an antitumour antibiotic isolated from *Streptomyces cartinostaticus* var. F-41 by Ishida *et al.*.[108] NCS consists of a protein subunit non-covalently complexed to a highly labile non-protein chromophore (NCS-Chrom) **40**.[109] The biological activity of NCS is retained by NCS-Chrom itself,[110,111] which is proposed to function as a thiol-activated form by intercalation into the minor groove of DNA followed by hydrogen abstraction from the deoxyribosyl residues, preferentially at thimidine rich sites.[112-114]

Nucleophilic attack by a thiol on C-12 followed by epoxide ring opening is thought to generate the enyne-cumulene (**120**) which spontaneously cyclises to form the indacene diradical **121** (scheme 1.36).[115,116]

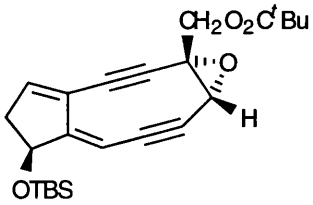


40 **120** **122** **121**

Scheme 1.36

An NMR study of NCS has shown that the hydrophobic pocket formed by the internal 4-strand β-sheet of the apoprotein binds NCS-Chrom with the conformation in which its naphthoate moiety sits on the bottom of the pocket and both the aminosugar and the carbonate group face outwards.[117,118]

Myers and co-workers have proposed the participation of the aminoglycoside functionality in the thiol activation process.[119] They found that although the addition of thiol and cyclisation will occur readily at -70°C in acetic acid-THF for NCS-Chrom, cyclisation of **123** required heating to 60°C or the addition of triethylamine to the reaction mixture at room temperature.

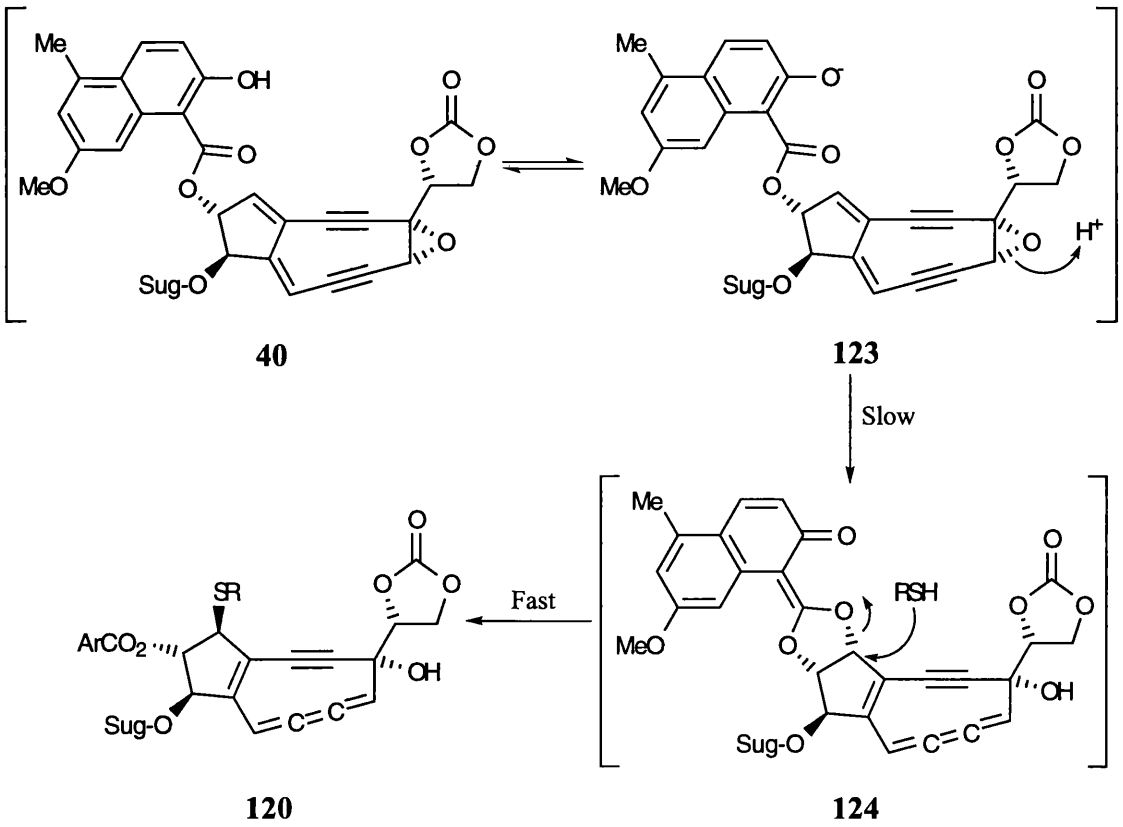


123

Figure 1.9

Lamothe and Fuchs proposed that the naphthoate moiety in NCS participates during the epoxide opening reaction *via* an intramolecular oxygen alkylation, as shown in scheme 1.37.[120] This mechanism may also explain the stereospecificity of thiol addition.

It has also been reported that when complexed with the apoprotein, NCS-Chrom was found to react with 2-mercaptoethanol to afford an unusual cyclisation product **125**.[121,122] However, when the same addition was performed in tris-HCl buffer containing 80% isopropanol, **122** was formed preferentially.



Scheme 1.37

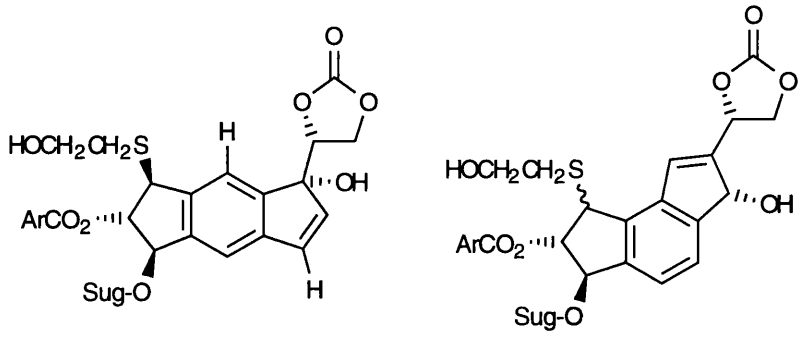
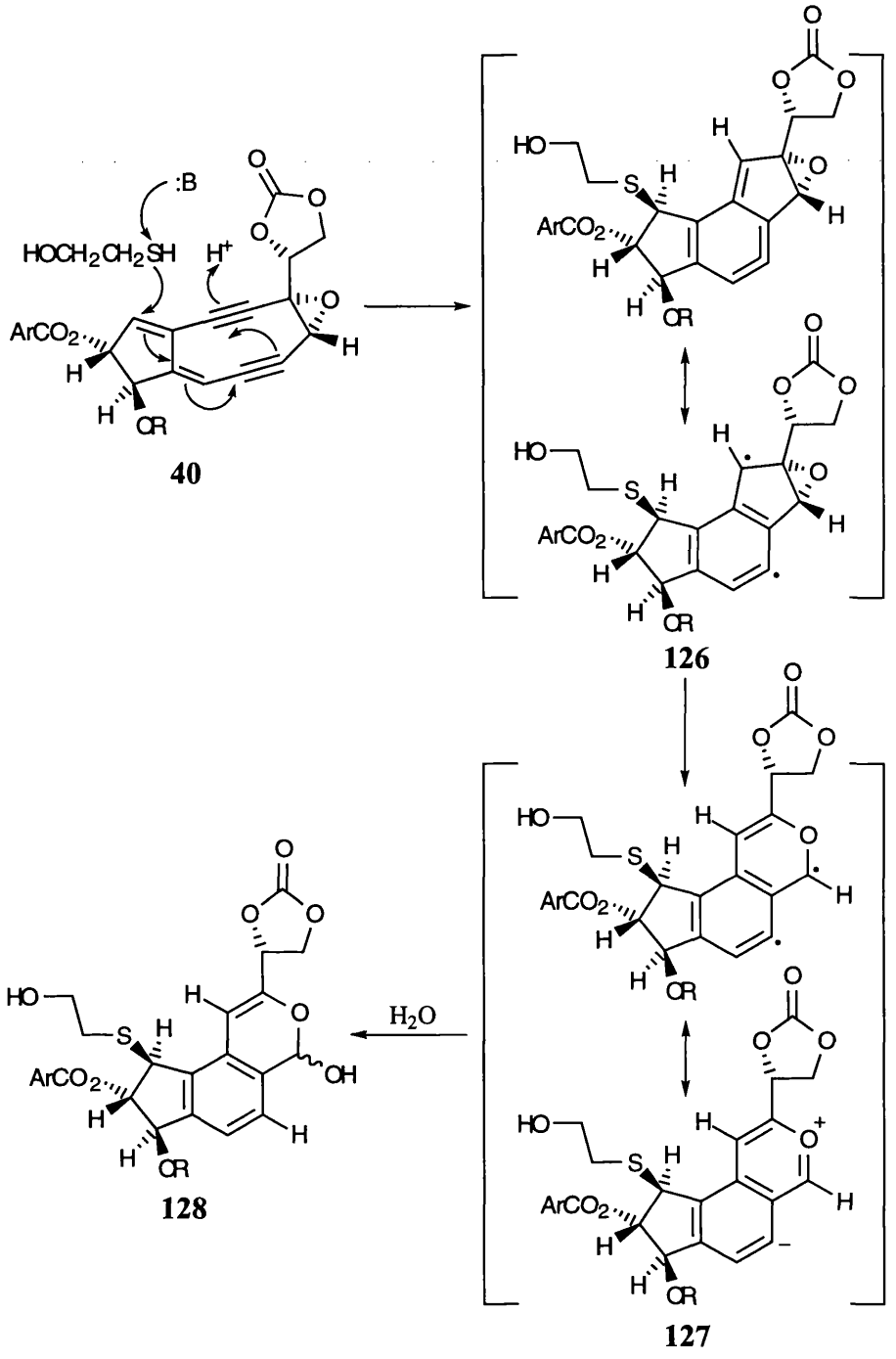


Figure 1.10

This reactivity is attributed to the fact that the binding constant of **125** toward the apoprotein is one order of magnitude higher than that of **122** and that NCS-Chrom may be extracted from the apoprotein with an organic solvent such as acidic alcohol.



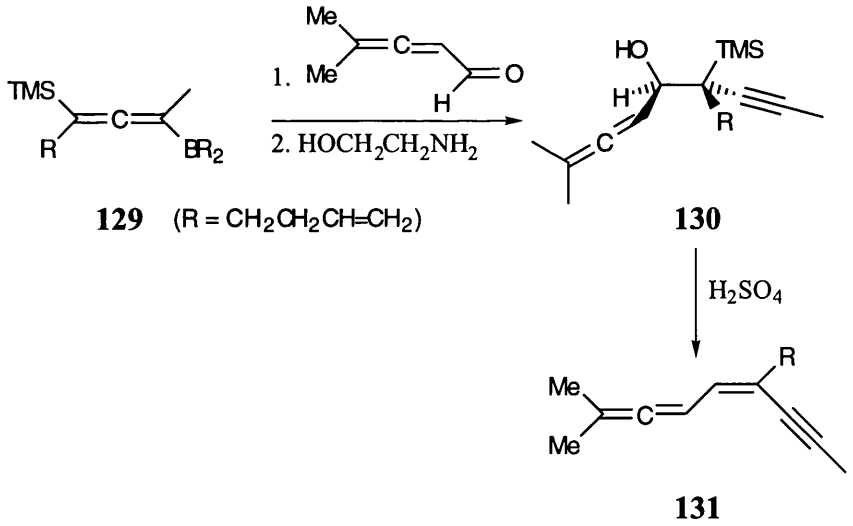
Scheme 1.38

Myers *et al.* have since proposed a revised hydroxyisochromene structure **128**.[123] This structure would account for the unexplained diastereoisomerism observed by Saito[121,122] with the presence of a hemiacetal group at C-5 (scheme 1.38).

1.7 Synthesis and Cycloaromatisation of Enyne-Allenes, Enyne-Cumulenes and Enyne-Ketenes

Given their very high propensity to cycloaromatise, most compounds in this class are generated *in situ*. However, the acyclic enyne-allenes, -cumulenes and -ketenes are stable at room temperature and the synthesis of these compounds will be discussed first.

Wang and co-workers reported the synthesis of an enyne-allene using the Peterson olefination methodology developed for the synthesis of enediynes (scheme 1.39).[95,124] Condensation of the γ-(trimethylsilyl)allenylborane **129** with the readily available conjugated allenic aldehyde afforded, after treatment with 2-aminoethanol, the hydroxypropargylsilane **130**. Sulfuric acid-induced elimination gave the (*Z*)-enyne-allene **131**, which has been shown to cycloaromatise upon heating in the presence of 1,4-CHD.[125]

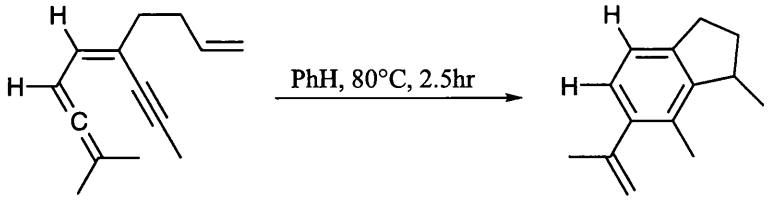


129 (R = $CH_2CH_2CH{=}CH_2$) **130** **131**

Scheme 1.39

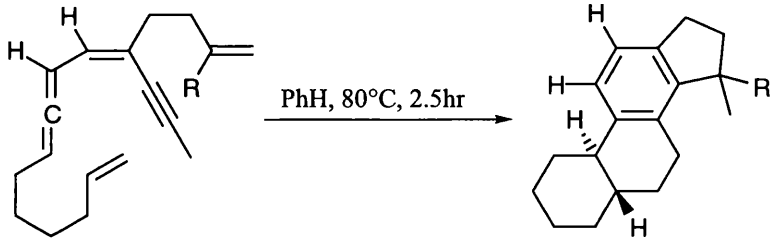
Wang has also demonstrated the diradical character of the cycloaromatisation products. Enyne-allene **132**, when heated in refluxing benzene, afforded the bicycle

133 (scheme 1.40), formed by intramolecular trapping of the benzenoid radical centre by the carbon-carbon double bond in a fashion characteristic of a free radical cyclisation reaction.[124] In a similar manner, the tetracyclic steroidal skeleton is formed upon heating enyne-allene **134** (scheme 1.41).[126]



132 **133**

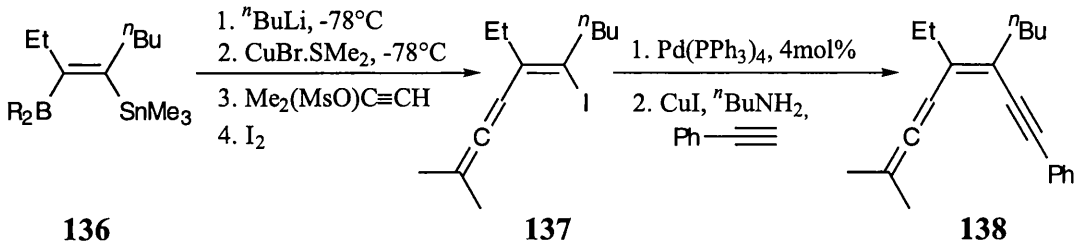
Scheme 1.40



134 **135**

Scheme 1.41

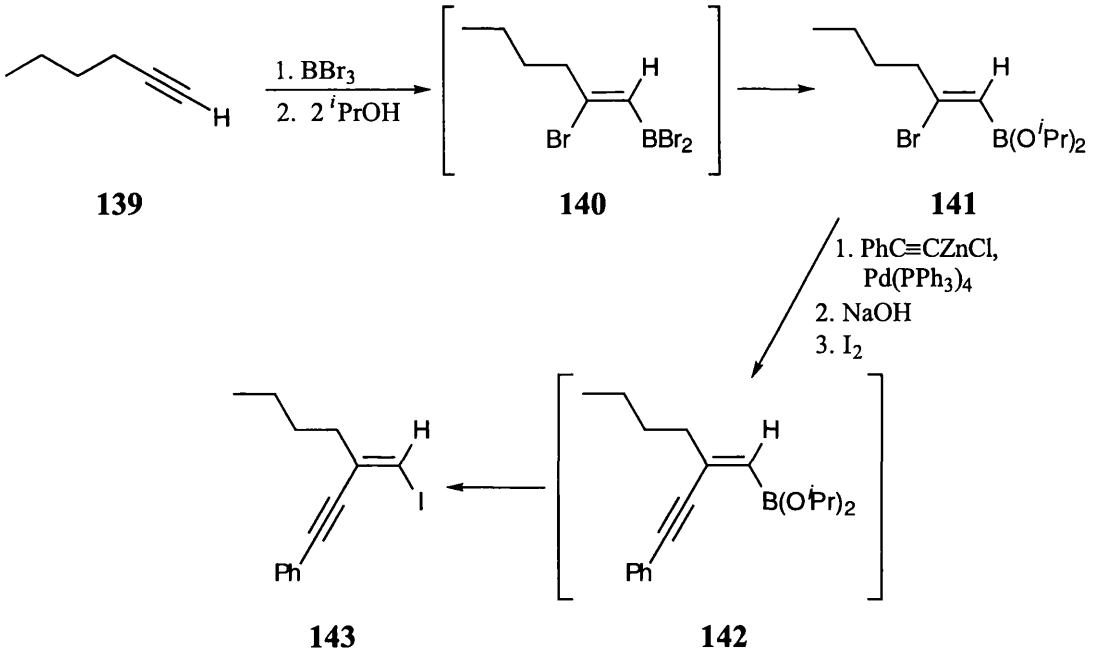
In an alternative approach, Wang and Wang have reported the use of trimethyltin substituted alkenylboranes (scheme 1.42).[127] Sequential treatment of the alkenylborane **136** with *n*-butyllithium, copper(I) bromide dimethyl sulfide complex, propargyl methanesulfonate and iodine furnished the corresponding enynyl iodide **137**. Subsequent palladium-catalysed coupling of the vinyl iodide to a terminal alkyne gave the expected enyne-allene **138**.



136 **137** **138**

Scheme 1.42

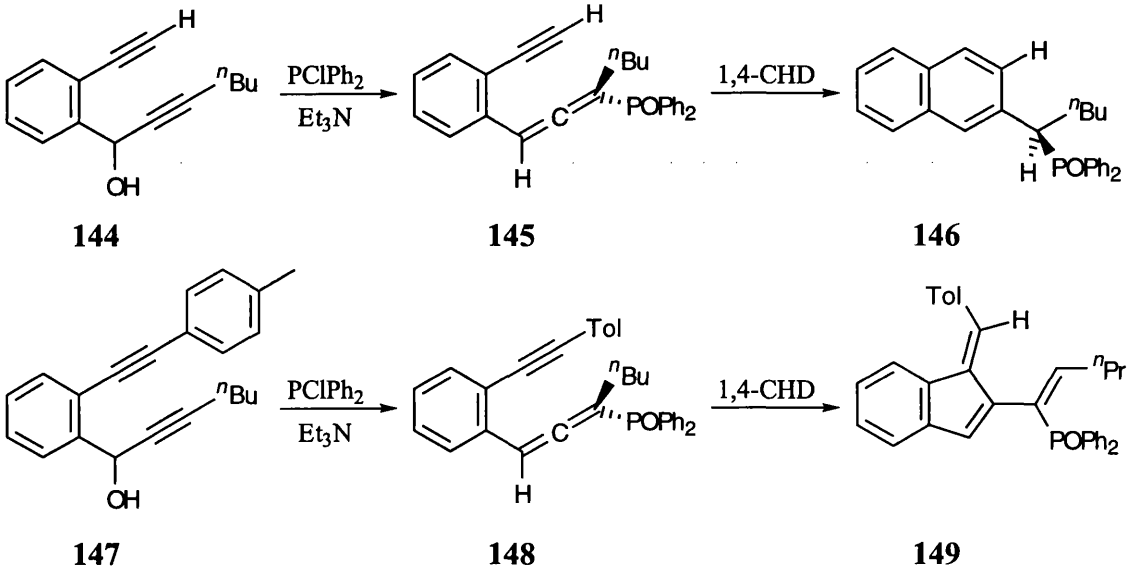
The coupling of acetylenic zinc chlorides with the alkenyl boronic ester **141** using a palladium(0) catalyst, followed by iodination has been used to synthesise the enyne iodide **143** (scheme 1.43).[128] This may also be elaborated to the enyne-allene by the palladium-catalysed coupling of allenylzinc chloride.



139 **140** **141** **143** **142**

Scheme 1.43

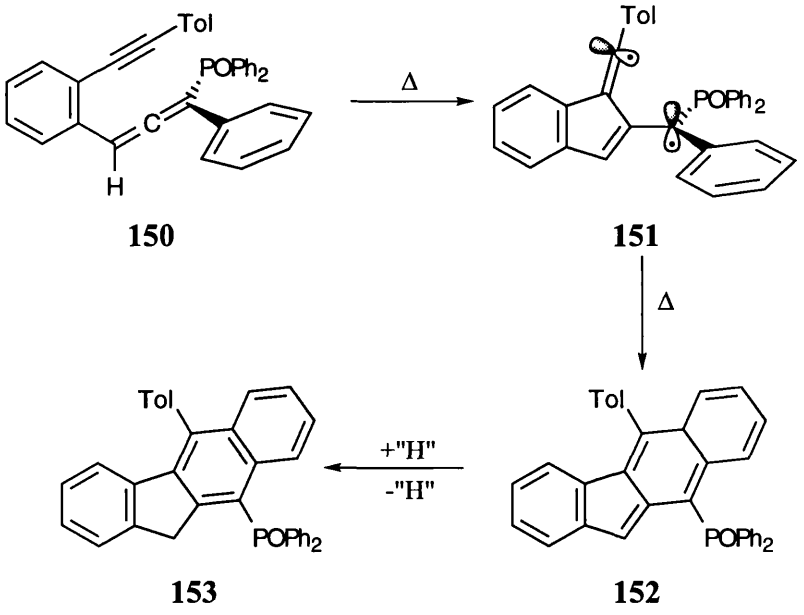
Schmittel *et al.* reported the rearrangement of propargyl alcohols **144** and **147** with chlorodiphenylphosphine to afford the stable enyne-allenes **146** and **149**, respectively (scheme 1.44).[129] Whilst the thermal rearrangement of **144** afforded the naphthalene derivative **146** in a typical Myers cyclisation, the more hindered aryl alkyne furnished the indene **149**. This unexpected outcome has recently been explained by heating **150** at 70°C in the presence of 1,4-CHD.[130] The proposed aryl-stabilised vinyl radical intermediate **151** may undergo a formal Diels-Alder reaction and an intermolecular H-addition/H-abstraction in order to provide **153** (scheme 1.45).



144 145 146

147 148 149

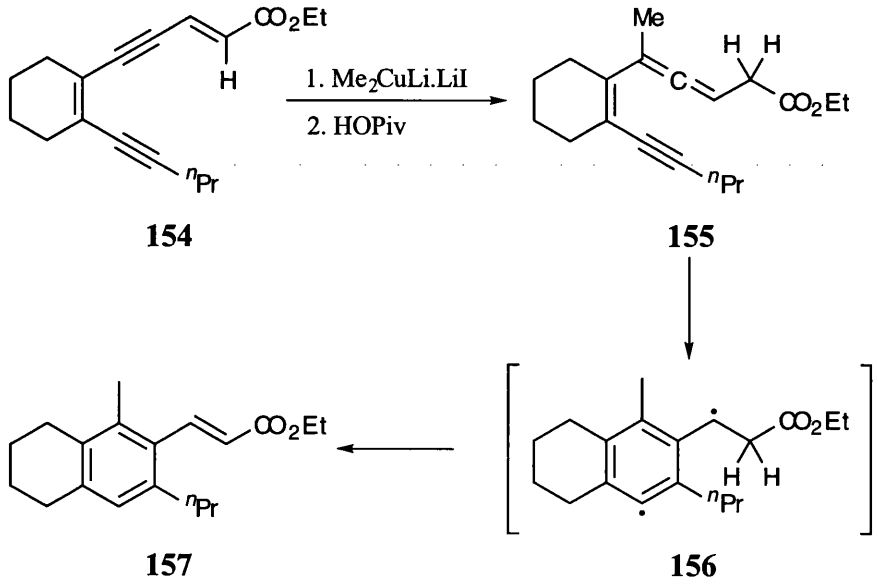
Scheme 1.44



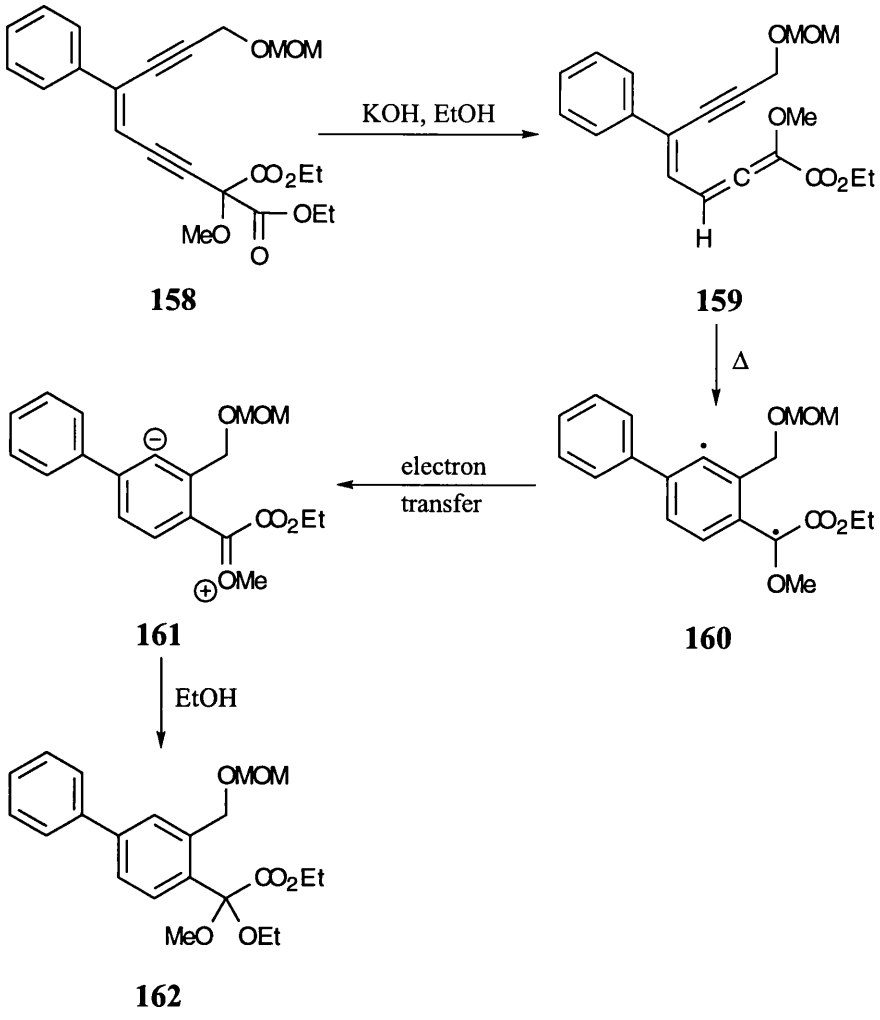
150 151 152 153

Scheme 1.45

Krause and Hohmann have recently reported the synthesis of enyne-allene **155** from dienediynoate **154** (scheme 1.46).[131] Addition of lithium dimethylcuprate to **154** and subsequent regioselective protonation of the allenyl enolate with pivalic acid at -80°C afforded **155** in >90% yield. Heating **155** at 50°C for 4 hours resulted in formation of the cyclisation product **157**.



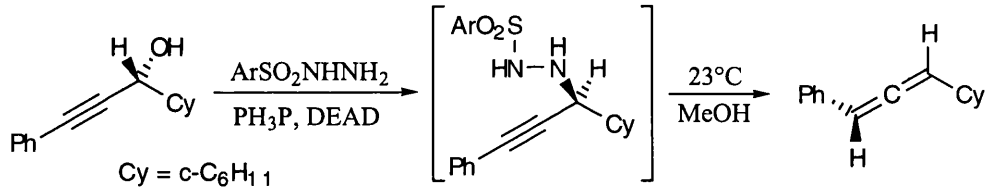
Scheme 1.46



Scheme 1.47

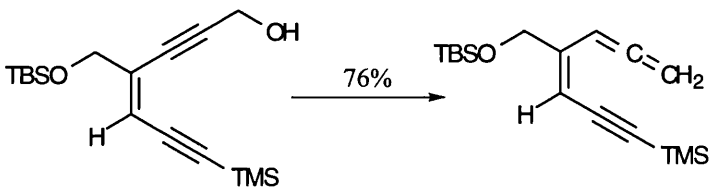
The cycloaromatisation of enyne-allenes *via* a reaction cascade triggered by the hydrolysis of α-alkynylmalonates has been reported by Shibuya and co-workers.[132] Treatment of **158** with potassium hydroxide and ethanol results in conversion to the acetal **162** in 78% yield, *via* the mechanism proposed in scheme 1.47.

Myers and Zheng have recently reported a stereospecific synthesis of allenes in a single step from propargylic alcohols,[133] based on the Mitsunobu inversion reaction.[134] Addition of a solution of DEAD to **163**, in the presence of triphenylphosphine and tosylhydrazine in methanol, resulted in the formation of 1-alkyl-1-tosylhydrazine derivative **164** (scheme 1.48). Stirring in methanol brought about spontaneous elimination of *p*-toluenesulfinic acid and nitrogen to afford **165**. This procedure has also been used for the conversion of enediynes to enyne-allenes (scheme 1.49).



163 **164** **165**

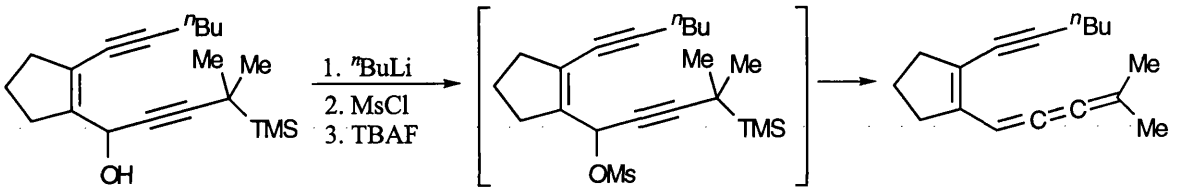
Scheme 1.48



166 **167**

Scheme 1.49

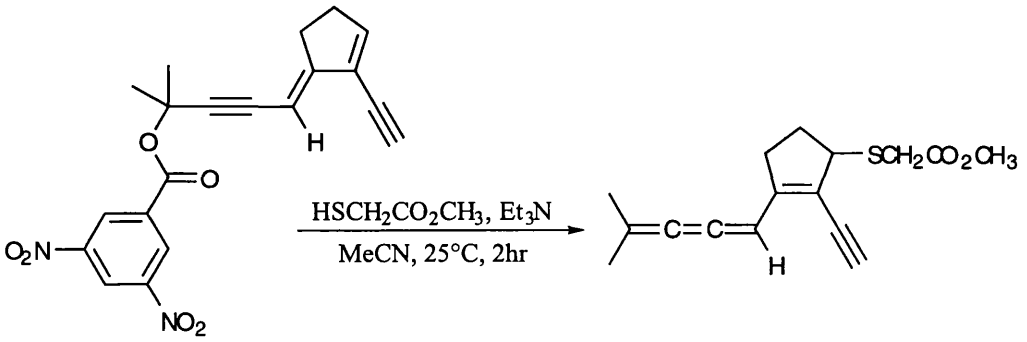
A 1,4-elimination of hydroxytrimethylsilane from 4-(trimethylsilyl)-2-butyn-1-ols, furnishing enyne-cumulenes, has recently been reported by Wang.[135] Treatment of the propargyl alcohol **168** with *n*-butyllithium, methanesulfonyl chloride and TBAF in sequence afforded the enyne[3]cumulene in 35% yield (scheme 1.50).



168 **169** **170**

Scheme 1.50

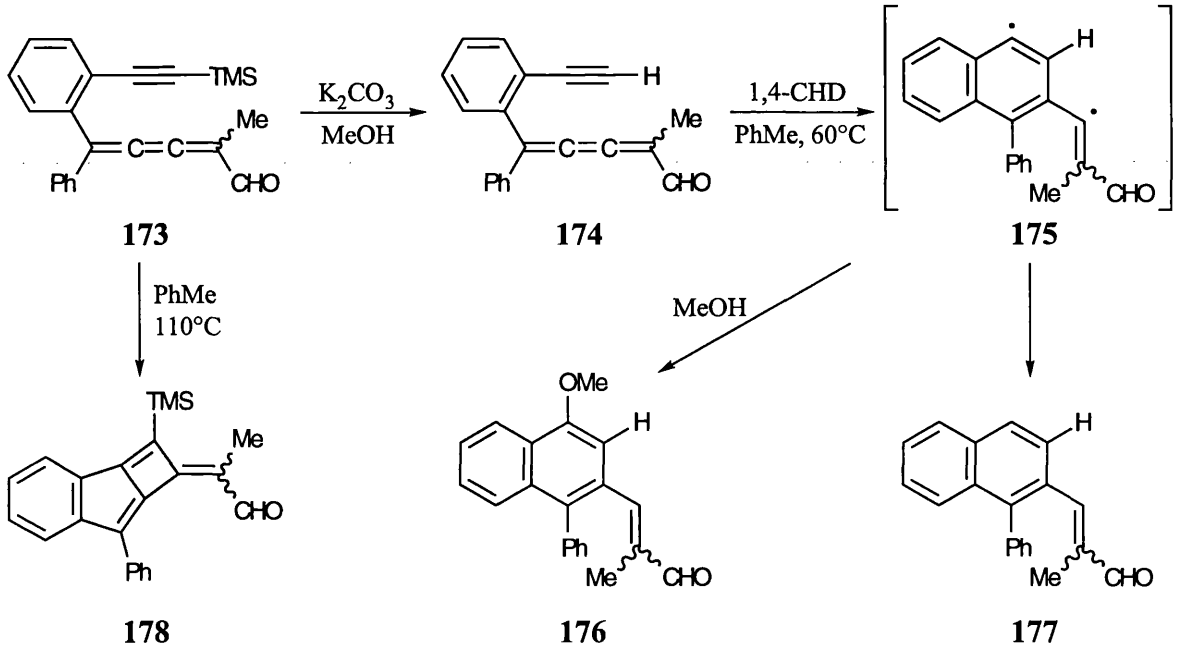
Hirama and co-workers reported a synthesis of enyne-cumulene **172** using a mimic of the thiol activation pathway for neocarzinostatin (scheme 1.51).[136] Reaction of **171** with methyl thioglycolate in acetonitrile furnished the desired enyne-cumulene **172** in 46% yield, which cycloaromatised upon heating with 1,4-CHD.



171 **172**

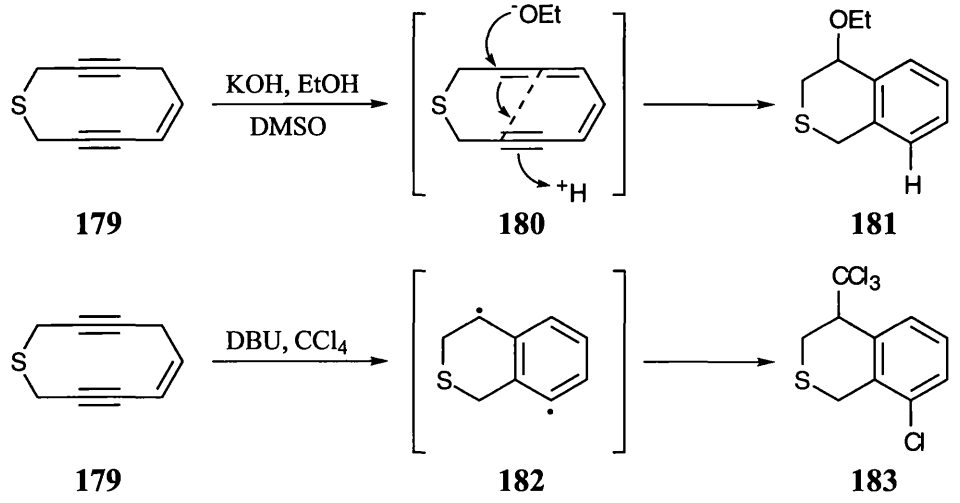
Scheme 1.51

Garcia *et al.* have demonstrated the ability of enyne-cumulenes to undergo both a [2+2] and a cycloaromatisation pathway.[137] The products formed upon heating **173** and the desilylated compound **174** in toluene indicate that cumulenals containing bulky substituents at the terminal alkynyl carbon will not undergo cycloaromatisation, but rather add in a [2+2] fashion across the central bond of the cumulenal to afford indane **178** (scheme 1.52).



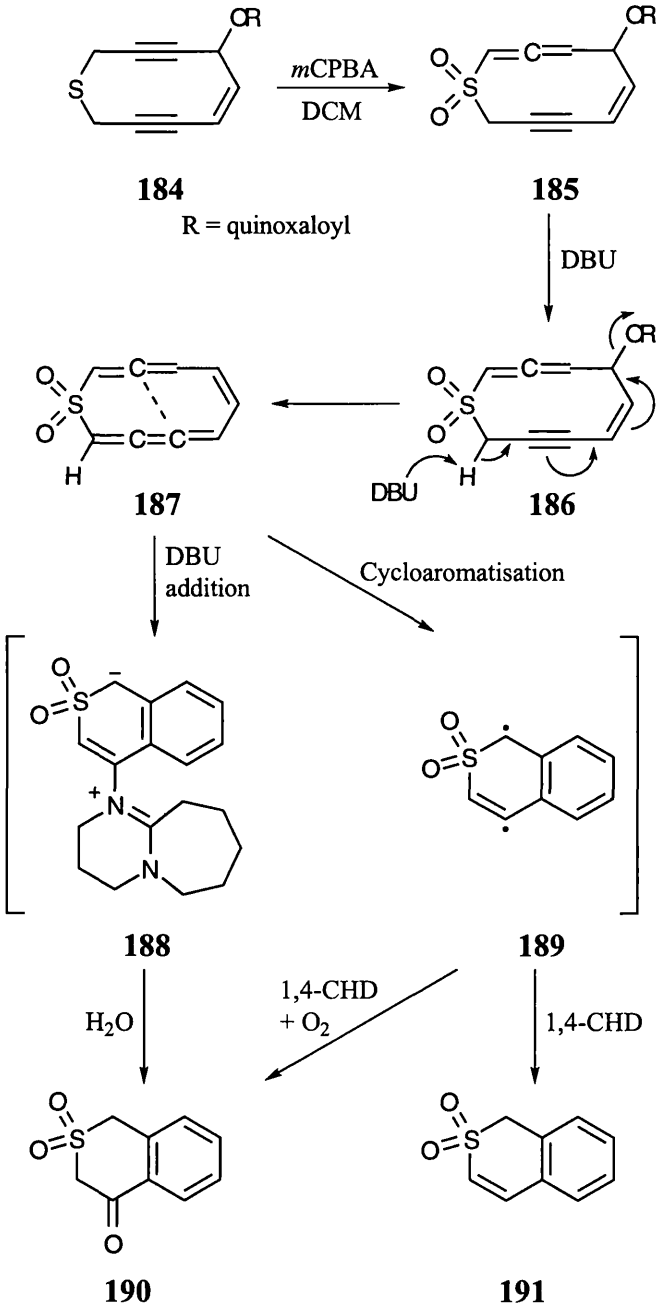
Scheme 1.52

Toshima *et al.* have reported that the cyclisation of the 1,6-diyn-3-ene system **179** under basic conditions proceeds *via* two different modes.[138-140] Treatment of **179** with alkoxide led to a polar reaction pathway, which gave the isochromanol derivative **181** (scheme 1.53). However treatment of **179** with DBU in CCl_4, under anaerobic conditions produced 8-chloroisothiochromane **183**. These results suggest that, in both cases, a deprotonation at the propargylic position occurs to afford the highly reactive enyne-allene intermediate **180**.



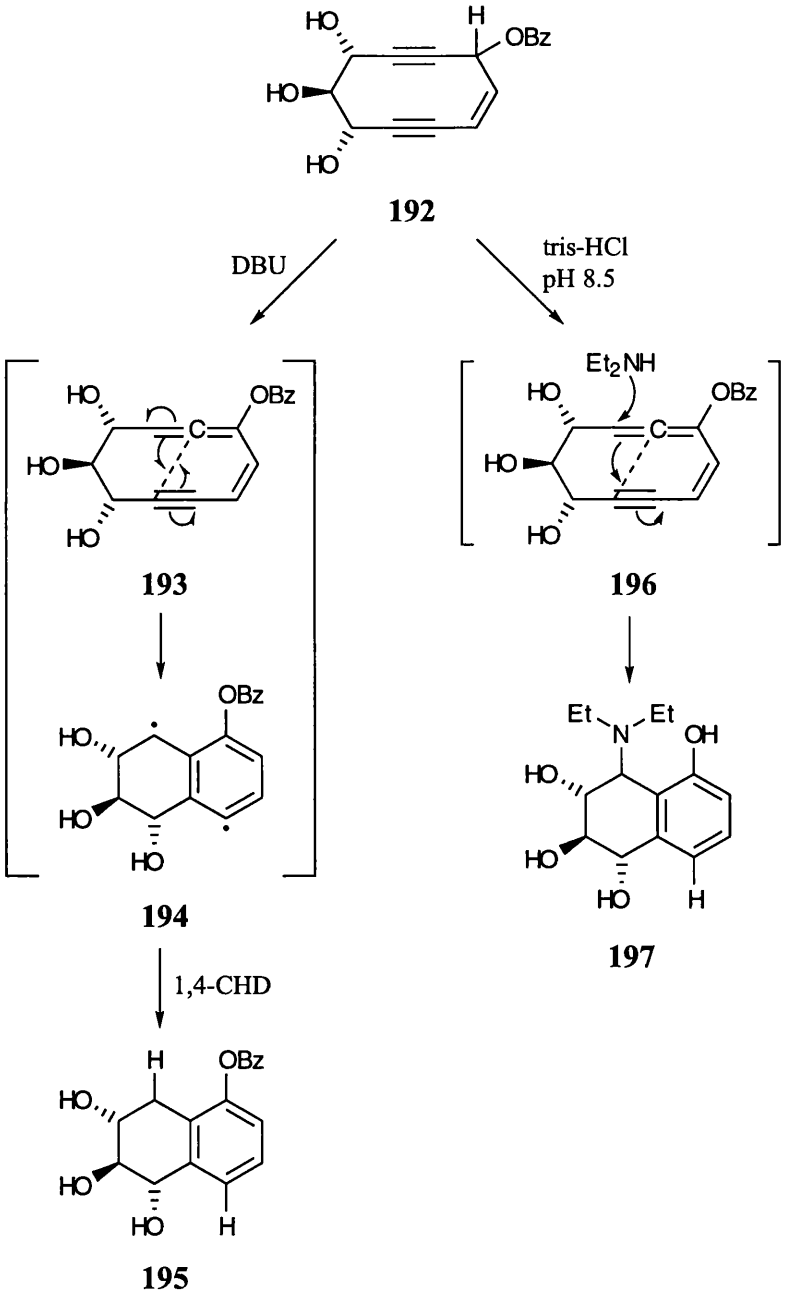
Scheme 1.53

Toshima has also performed the *m*CPBA oxidation of sulfide **184**, which gave the unexpected enyne-allene sulfone **185** in 76% yield (scheme 1.54).[141] DBU deprotonation at the propargylic position, along with elimination of the leaving group generated the allene-ene-cumulene intermediate **187**, which underwent spontaneous cyclisation to afford the benzenoid diradical **189**, and nucleophilic addition of DBU to give the ionic product **190**.



Scheme 1.54

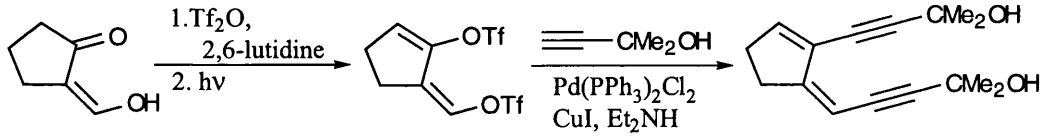
Treatment of the enediyne **192** possessing a benzoyl group at the allylic position with DBU at 25°C gave the cycloaromatisation product **195** (scheme 1.55).[142] Aromatisation *via* a polar pathway is achieved by the addition of diethylamine in Me_2SO-tris-HCl, pH 8.5 buffer, affording **197**. It is worth noting that the DNA-cleaving activity of **192** is highly Guanine-selective, but this is almost certainly a result of the ionic, and not the radical mechanism.



Scheme 1.55

Simple dienediynes, as found in neocarzinostatin, are known to undergo a rearrangement to an enyne-allene or enyne-cumulene upon treatment with a thiol, such as methyl thioglycolate (*vide supra*).[143-145] For this reason, many groups have used the addition of a thiol as the activation process for cycloaromatisation *via* the enyne-allene.

A simple method for the construction of dienediyne systems was simultaneously reported by Nakatani *et al.*[146] and Brückner *et al.*[147] (scheme 1.56). Treatment of 2-formylcyclopentanone with triflic anhydride and 2,6-lutidine afforded an (*E*)-dienolditriflate, which was isomerised to the (*Z*)-dienolditriflate **199** upon irradiation. Double palladium-catalysed coupling of the triflates with propargyl alcohol gave the expected dienediyne **200**

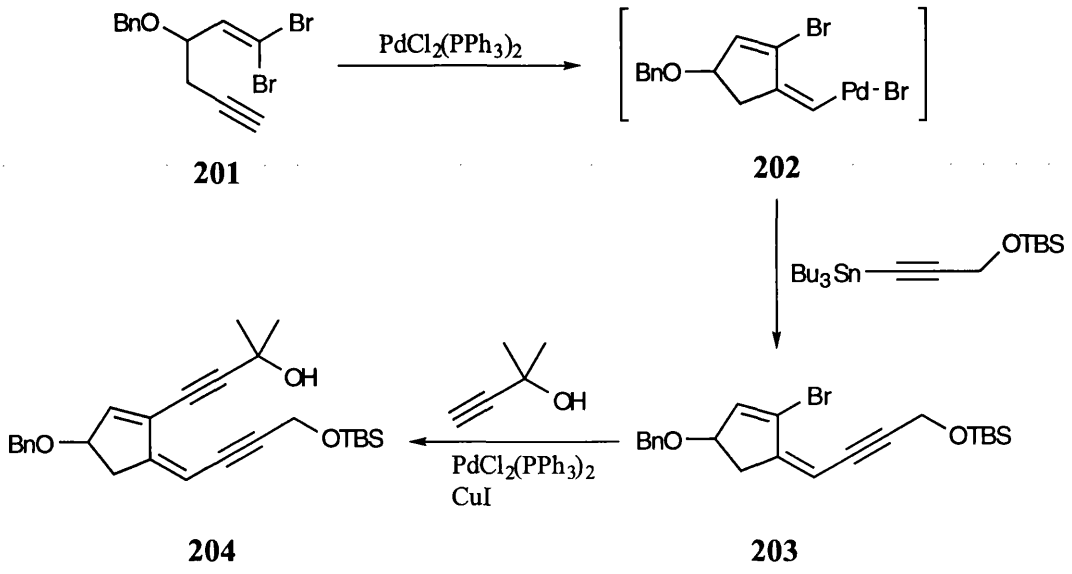


198 **199** **200**

Scheme 1.56

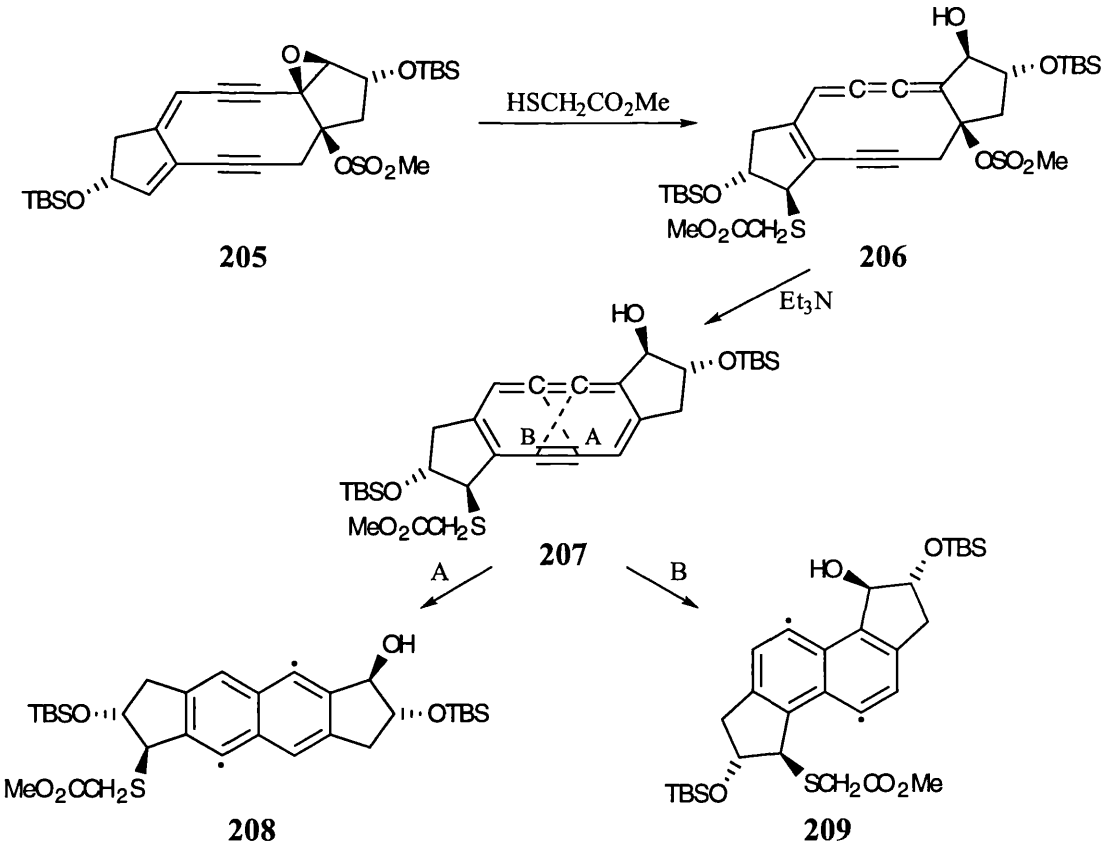
Suffert[148,149] and Terashima[150] have since demonstrated the higher reactivity of the semicyclic C=C bond, by sequential coupling to two different alkynes. Several open-chain analogues of the core dienediyne have been reported by Terashima and co-workers using this methodology.[150-153]

An alternative palladium-catalysed coupling procedure has been reported by Torii *et al.*[154] and Nuss *et al.*.[155,156] Treatment of **201** with palladium(0) resulted in an intramolecular insertion followed by cross-coupling with a stannyl acetylene affording the enyne (**203**). A further palladium-catalysed cross-coupling with another acetylene gave the desired dienediyne (scheme 1.57).



201 202 204 203

Scheme 1.57

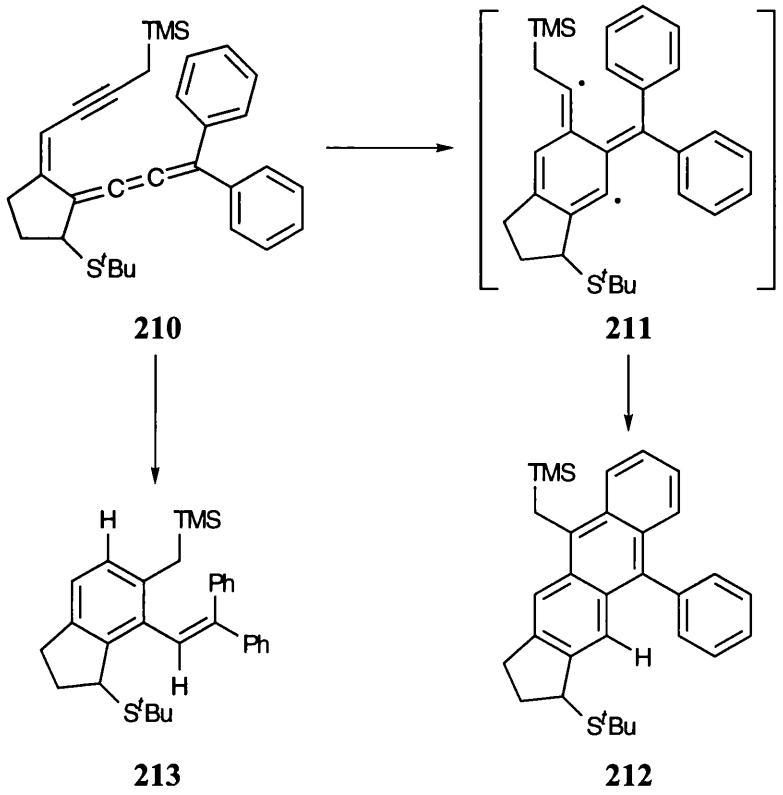


205 206 207 208 209

Scheme 1.58

A comparison of the two modes of 1,5-dehydronaphthalene formation from the asymmetrical 1,6-didehydro[10]annulene intermediate **207** was performed by Myers and Dragovich.[157] Dienediyne **205** underwent thiol addition to form the cumulene

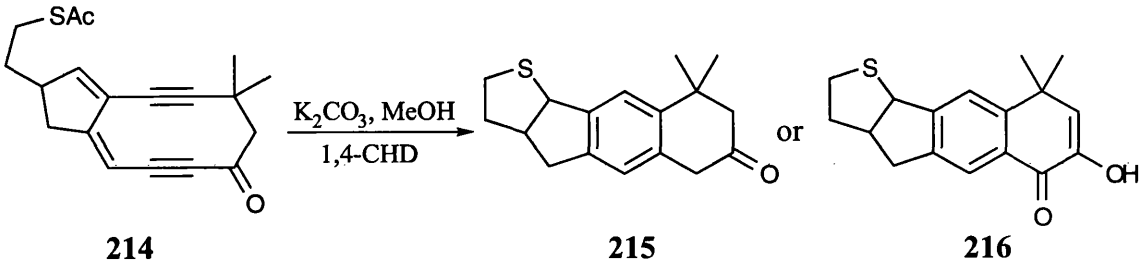
206 and, after elimination of methanesulfonic acid, the 1,6-didehydro[10]annulene intermediate **207** (scheme 1.58). The isomeric naphthalene derivatives **208** and **209** were formed in 67% and 20% yield, respectively. Whilst the formation of **208** could proceed directly from the cumulene **206** the other isomer is indicative of an annulene intermediate.



Scheme 1.59

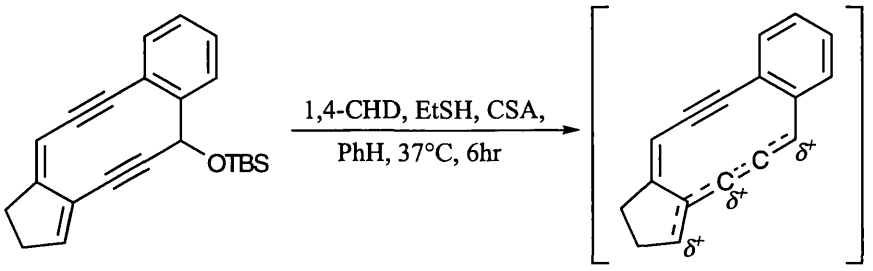
In a similar reaction, Scheuplein *et al.* reported the formation of styrene **213** and anthracene **212** from the enyne-cumulene **210**.[158]

A dienediyne containing an intramolecular nucleophile was synthesised by Hirama *et al.*.[159] Methanolysis of the thioacetate **214** by using K_2CO_3 as base, in the presence of 1,4-CHD under an argon atmosphere, gave the reductive cycloaromatisation product **215** in 28% yield. In air the corresponding α-hydroxycyclohexenone (**216**) was formed.[160]

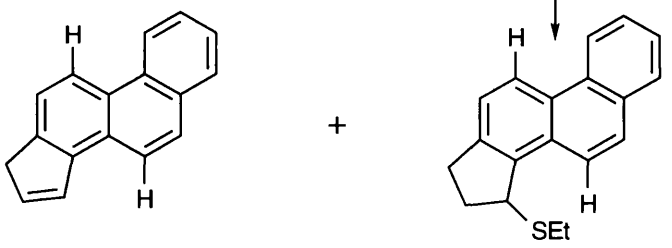


214 **215** **216**

Scheme 1.60



217 **218**



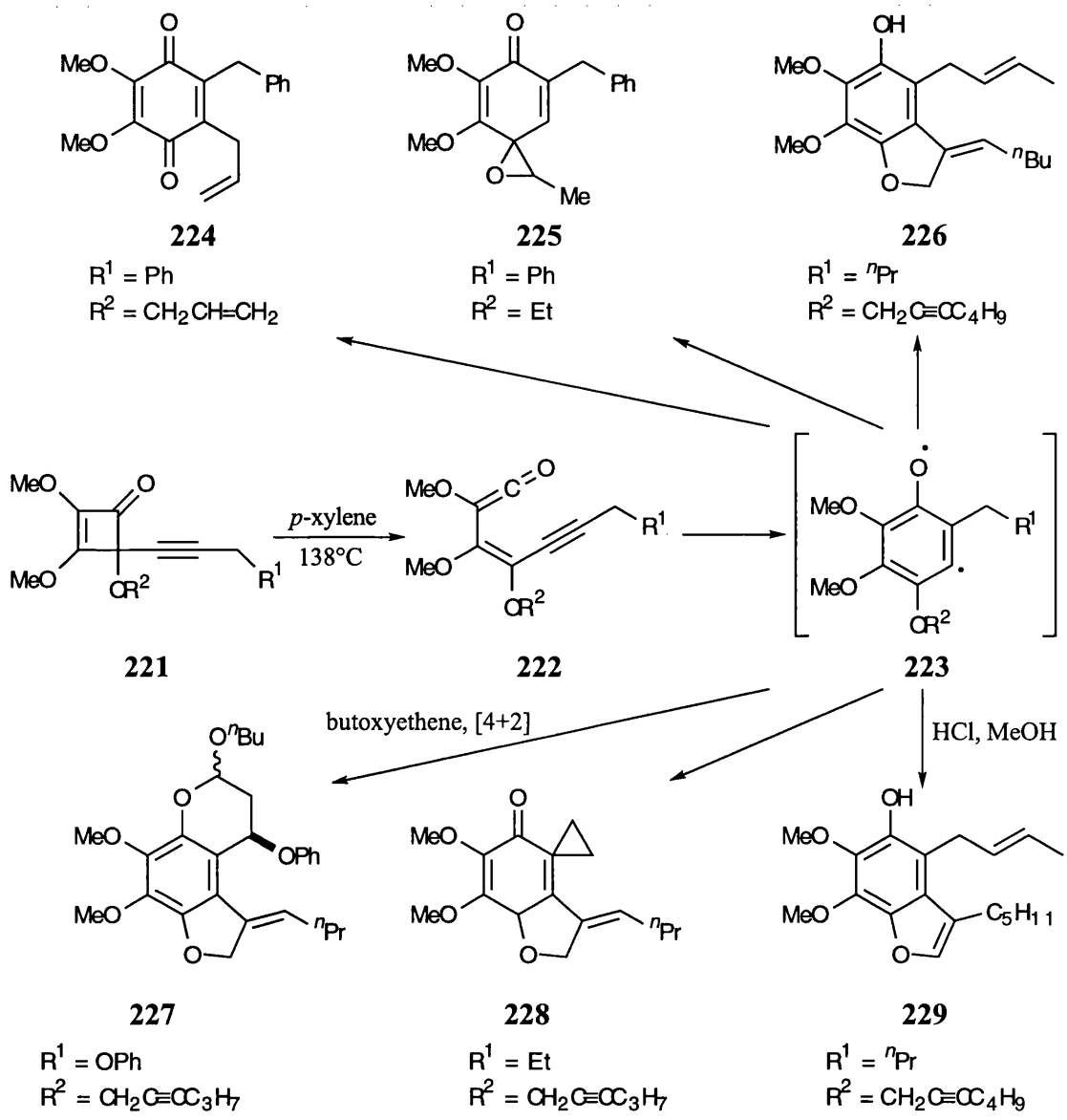
219 **220**

Scheme 1.61

The acid-induced formation of phenanthrenes **219** and **220** from dienediyne **217** was reported by Suffert and Brückner.[161] Protonation of the silyl group by camphor sulfonic acid initiates an E_1 elimination which gives an the extensively delocalised carbenium ion **218**. Uptake of EtSH followed by loss of the S-bound proton and spontaneous cycloaromatisation affords **219** and **220**.

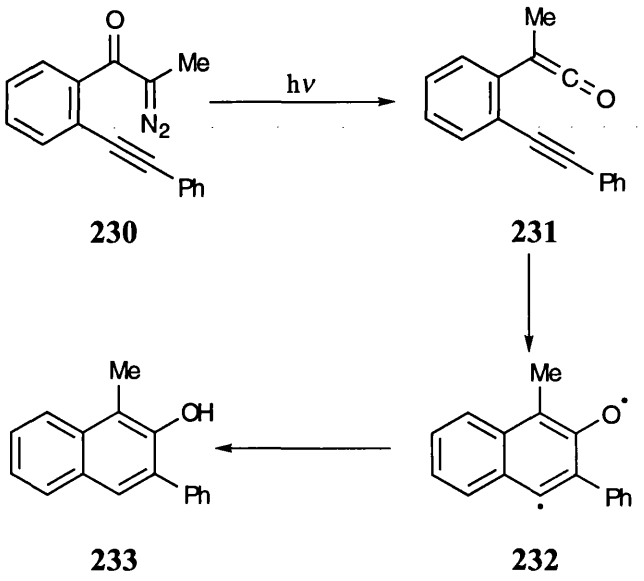
Moore and co-workers have reported the rearrangement of 4-alkynylcyclobutenes to enyne-ketene intermediates upon heating in xylene (scheme 1.62).[162-165] By variation of the substituents on the cyclobutene, the intermediate diradical species **223**

may undergo a variety of different radical cyclisation and trapping reactions affording a range of products.



Scheme 1.62

The irradiation of *o*-alkynyl substituted α-diazoacetophenones has been reported by Padwa *et al.* to proceed *via* enyne-ketene intermediates (scheme 1.63).[166,167] Formation of the naphthol ring can be explained in terms of a photochemical Wolff rearrangement which affords an *o*-alkynyl substituted arylketene intermediate **231**. Subsequent cycloaromatisation of the enyne-ketene *via* the diradical furnishes the naphthol product **233**.



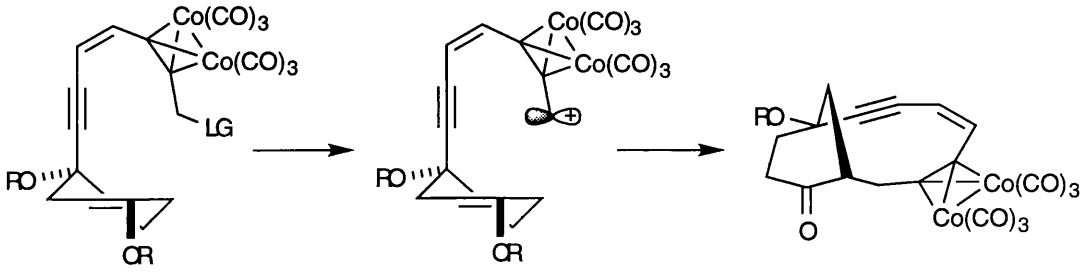
Scheme 1.63

1.8 Methods for the Ring-Closure of Enediyne-Containing Macrocycles

With the increasing interest in the synthesis of the enediyne antibiotics and their model compounds, there is a need for new methodology for the formation of medium-ring macrocycles containing the enediyne moiety. These new methodologies should allow regio- and stereospecific ring formation and be tolerant of the wide functionality present in the parent molecules. This section will only deal with the most important recent approaches, in terms of the common routes employed.

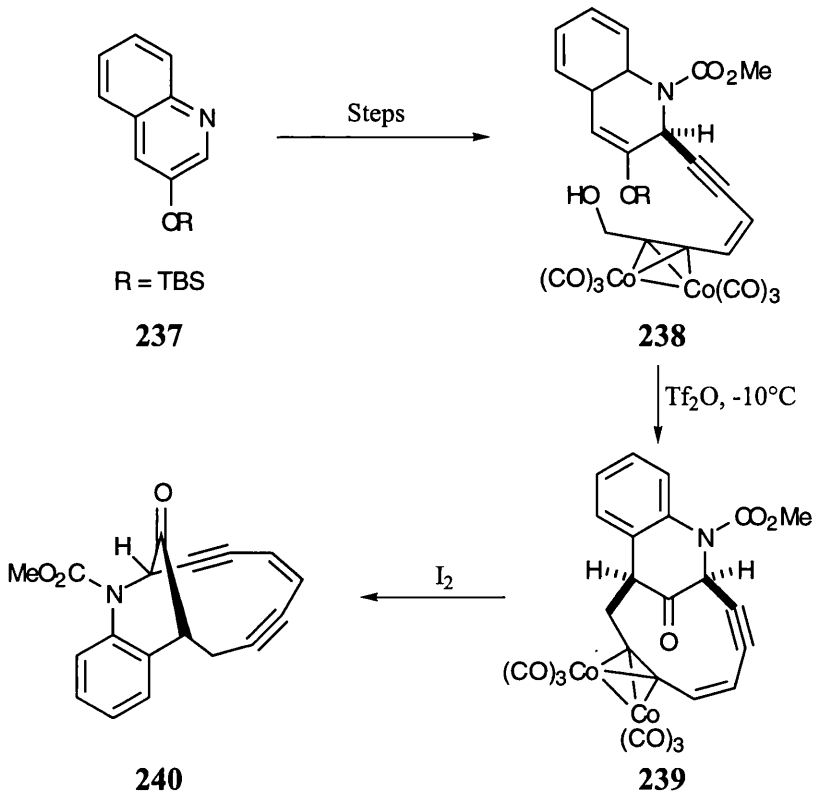
A general approach to the common core of the esperamicins and calicheamicins was introduced by Magnus *et al.*,[168-170] using a cobalt-mediated variation of the aldol reaction (scheme 1.64). Complexing one acetylene of the enediyne as the η^2-dicobalthexacarbonyl complex allows the formation of a stabilised cation **235**, when treated with Brönsted or Lewis acids.[171] In addition, complexation bends the

normally linear acetylene triple bond to approximately 145°, thus facilitating the cyclisation. The presence of the cobalt complex also has the advantage of preventing the cycloaromatisation of the enediyne until its oxidative removal, providing a trigger system for the drug.



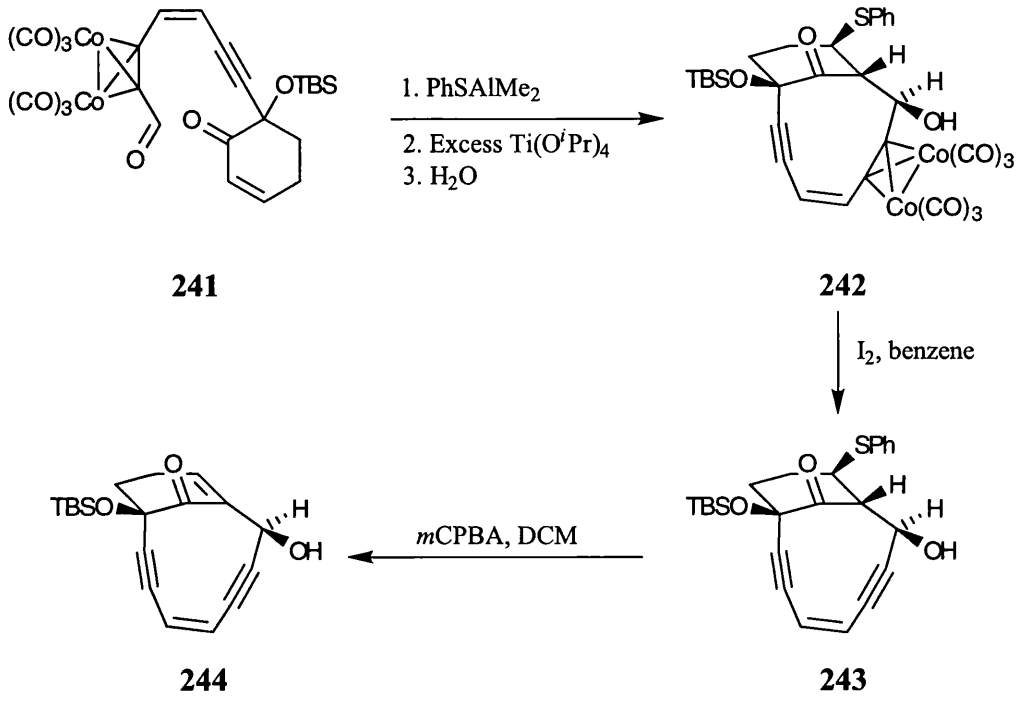
Scheme 1.64

This η^2-dicobalthexacarbonyl propargylic cation cyclisation has been used by Magnus to synthesise the dynemicin core structure **240** in five steps from the quinoline **237**.[172,173]



Scheme 1.65

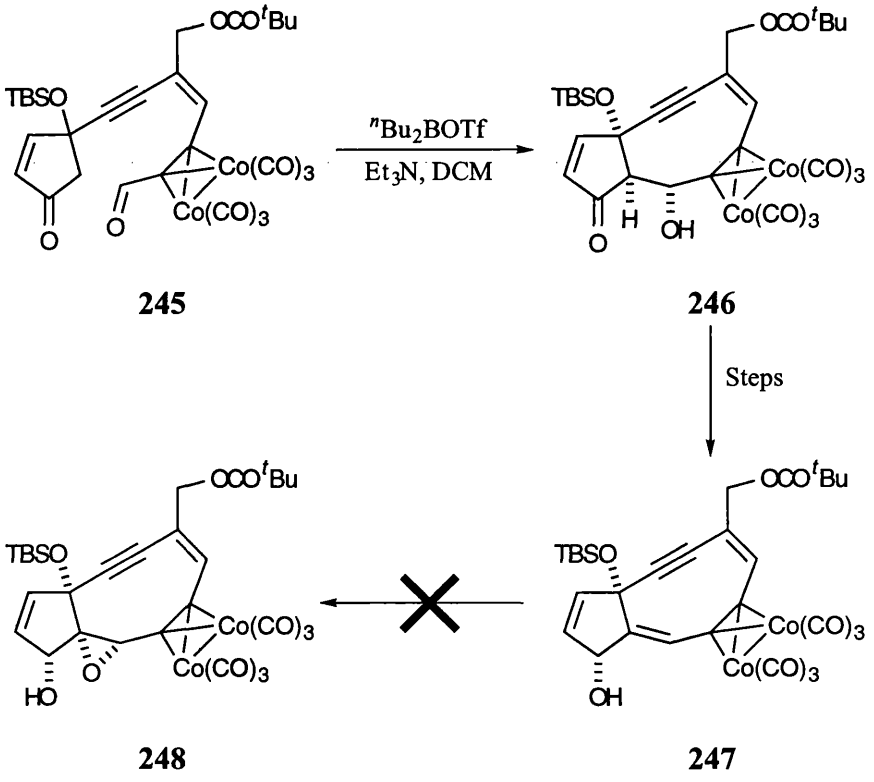
The stabilising effect of the η^2-dicobalthexacarbonyl complex has also been used extensively for aldol-type macrocyclisations. Kadow *et al.* used a conjugate addition of dimethylaluminium benzene thiolate to the η^2-dicobalthexacarbonyl complex **241** followed by an *in situ* aldol cyclisation to give the complexed bicyclic enediyne **242**.[174] The product was then oxidised and treated with *m*CPBA to give the simplified enediyne core structure (scheme 1.66).



241 **242** **243** **244**

Scheme 1.66

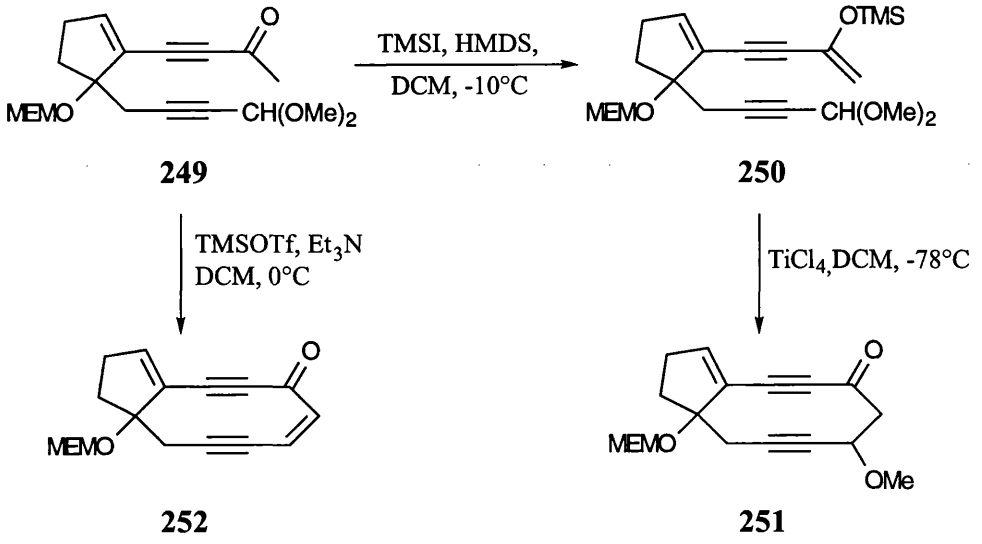
A recent study by Magnus *et al.* reported the synthesis of the nine-membered core ring structures of kedarcidin, and C-1027 chromophore (*vide supra*).[175] Using the established cobalt-mediated aldol cyclisation methodology they were able to demonstrate the formation of **246** in 74% yield. Unfortunately, after elaboration to **247** all attempts to epoxidise the 8,9-double bond were unsuccessful.



Scheme 1.67

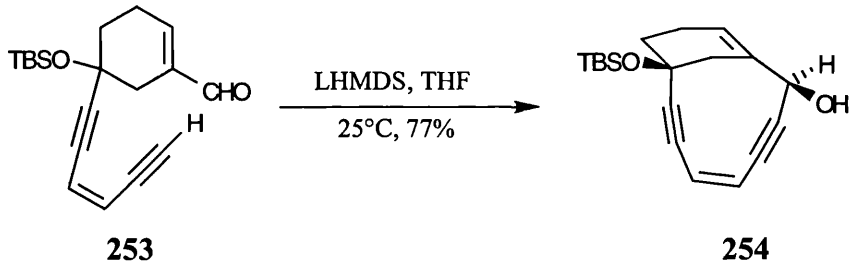
By employing their η^2-dicobalthexacarbonyl alkyne strategy, Magnus and co-workers have also reported the formation of the bicyclic skeleton of neocarzinostatin.[176,177]

The simple aldol condensation may also be performed with the aldehyde in the form of its acetal. Krebs *et al.*[178] have constructed the 10-membered macrocycle **251** *via* the Mukaiyama type intramolecular aldol reaction[179-181] between the acetal and silyl enol ether moieties in **250** (scheme 1.68). The reaction was promoted by catalytic titanium(IV) chloride. A similar cyclisation of ketone **249** took place by reaction with an excess (1.5 equivalents) of trimethylsilyl triflate (TMSOTf) to afford the bisacetylene **251** (7%) and the dienediyne ketone **252** in 39% yield. This one pot reaction was achieved by an intramolecular Noyori type aldol reaction.[182]



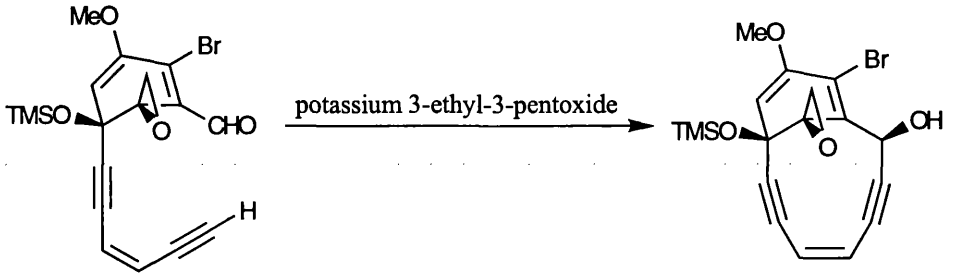
Scheme 1.68

In an alternative approach Kadow has used the intramolecular cyclisation of an enediyne acetylide onto an enolisable aldehyde, using LHMDS (scheme 1.69).[183] It is interesting to note that by using a shorter reaction time and performing the reaction at 0°C, the epimer at the C-12 propargylic alcohol could be obtained in 67% yield.



Scheme 1.69

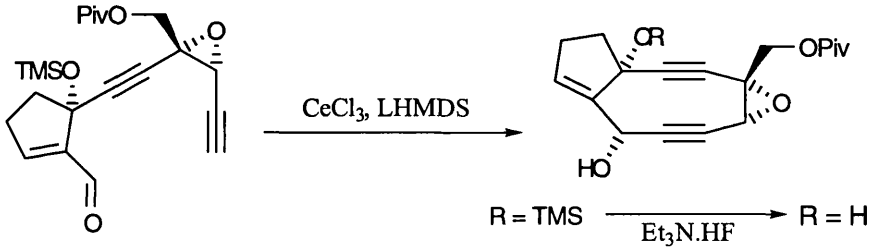
This approach was also used by Danishefsky in the first synthesis of calicheamicinone, the core aglycone of calicheamicin (scheme 1.70).[45,184,185]



255 **256**

Scheme 1.70

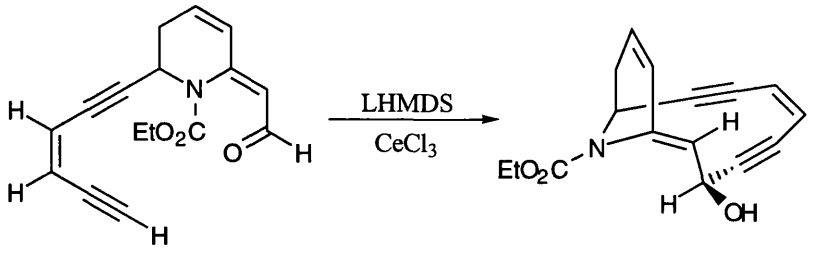
An elegant approach towards construction of NCS-Chrom in enantiomerically pure form using this methodology has been reported by Myers *et al.* (scheme 1.71).[119,186] Cyclisation of aldehyde **257**, by treating with LHMDS in the presence of $CeCl_3$, afforded the cyclic epoxy diyne **258** as a single diastereomer in 87% yield.



257 **258** **259**

Scheme 1.71

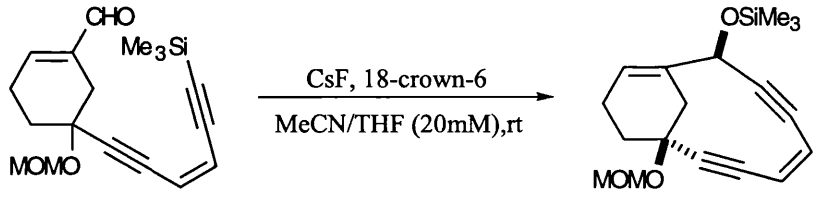
Braña *et al.* have recently reported the synthesis of the tetrahydropyridine derivative of the calicheamicin/esperamicin core (**261**).[187] Treatment of **260** with LHMDS in the presence of cerium trichloride led to the stable alcohol **261** in 35% yield.



260 **261**

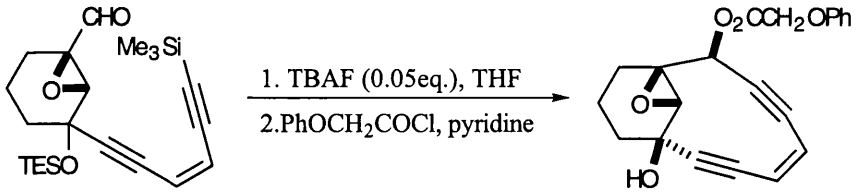
Scheme 1.72

Isobe and co-workers have employed caesium fluoride promoted conditions for the cyclisation of a trimethylsilyl acetylene onto an aldehyde to give the enediyne core macrocycle (scheme 1.73).[188] The reaction is performed in the presence of 18-crown-6 and a small amount of acetonitrile, which improved the yield and reproducibility. A similar approach has been reported by Mastalerz *et al.* for the synthesis of core analogues of esperamicin, in which the cyclisation is promoted by a catalytic quantity of TBAF (scheme 1.74).[189]



262 **263**

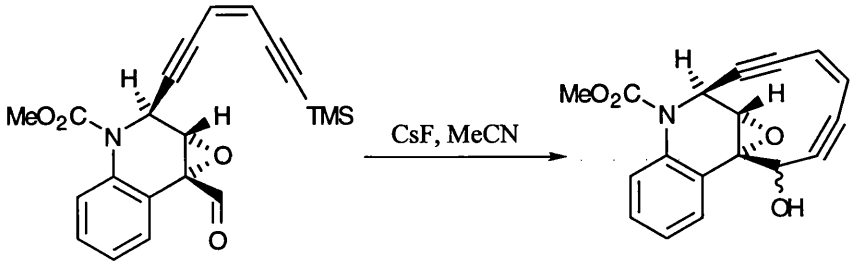
Scheme 1.73



264 **265**

Scheme 1.74

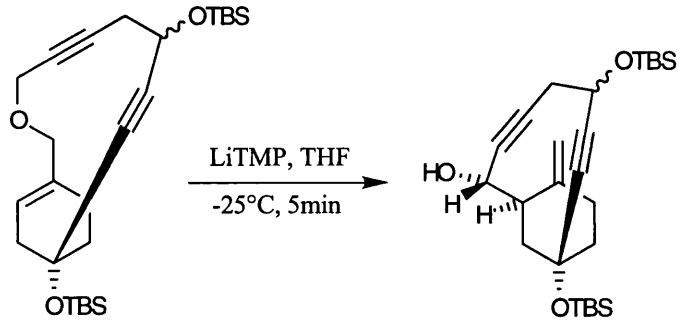
A caesium fluoride-mediated cyclisation procedure was also utilised by Wender and Zercher[190] to give a dynemicin analogue (**267**). This was shown to undergo cycloaromatisation upon treatment with 0.6N HCl in a manner similar to that of the natural product.



266 **267**

Scheme 1.75

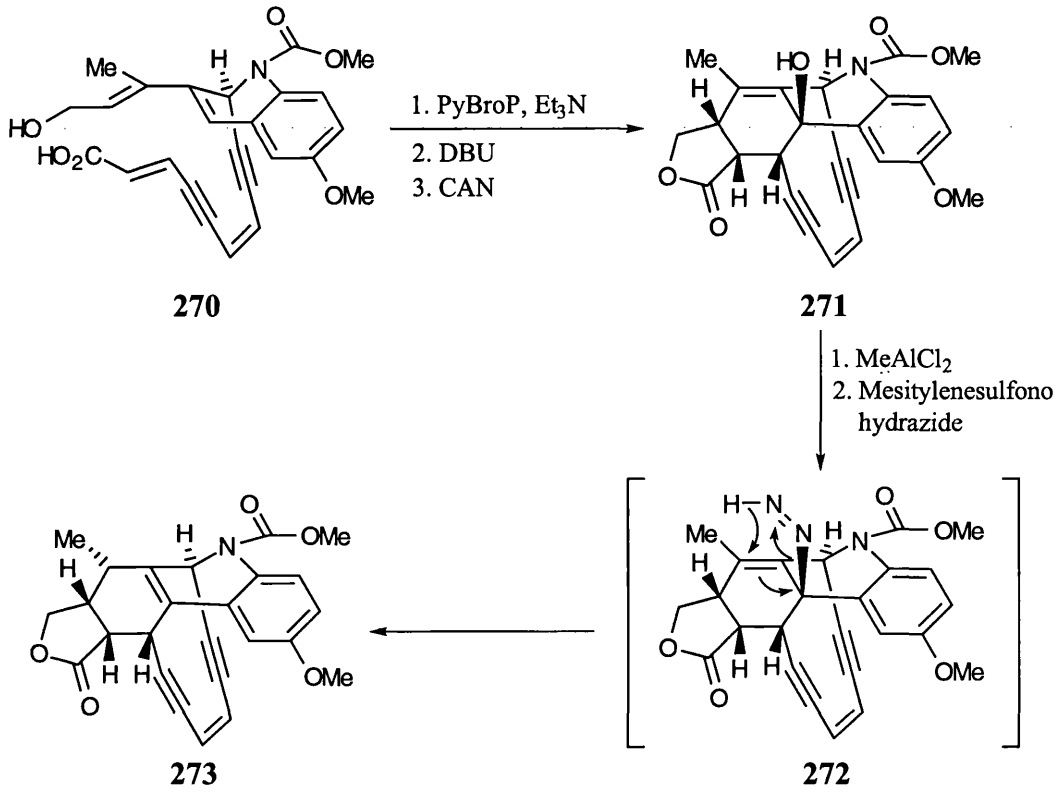
An alternative method reported by Grierson is the [2,3]-Wittig rearrangement of **268**.[191,192] Treatment of the cyclic ether **268** with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) at -25°C resulted in the diyne **269**, which can be easily elaborated to an enediyne *via* conversion of the silyl ether to the mesylate and elimination.



268 **269**

Scheme 1.76

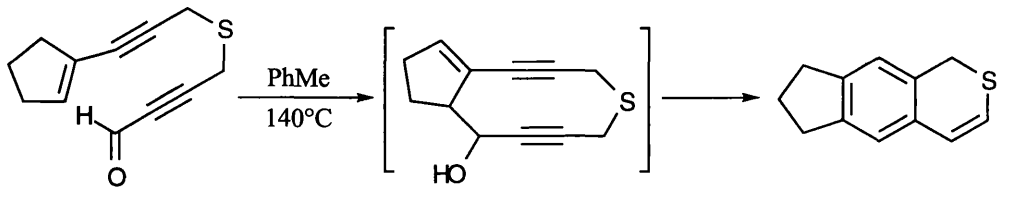
In order to resolve the stereochemical issues of the synthesis of dynemicin, Schreiber has used a Diels-Alder macrocyclisation approach (scheme 1.77).[51,193] The macrolactonisation of the seco acid **270** with bromo-tris-pyrrolidinophosphino hexafluorophosphate leads to efficient formation of the polycycle **271**. Ionisation of **271** and trapping of the presumed intermediate carbonium ion with mesitylenesulfonohydrazide provides the desired isomer of **273** in 92% yield *via* an allylic diazene rearrangement.



270 **271** **272** **273**

Scheme 1.77

Mikami and co-workers reported the [4+2] ene cyclisation of the conjugated ynal **274** in their approach to NCS-Chrom analogues.[194] Unfortunately the thermal conditions employed for the cyclisation caused spontaneous dehydration and cycloaromatisation to afford the tricycle **276**.

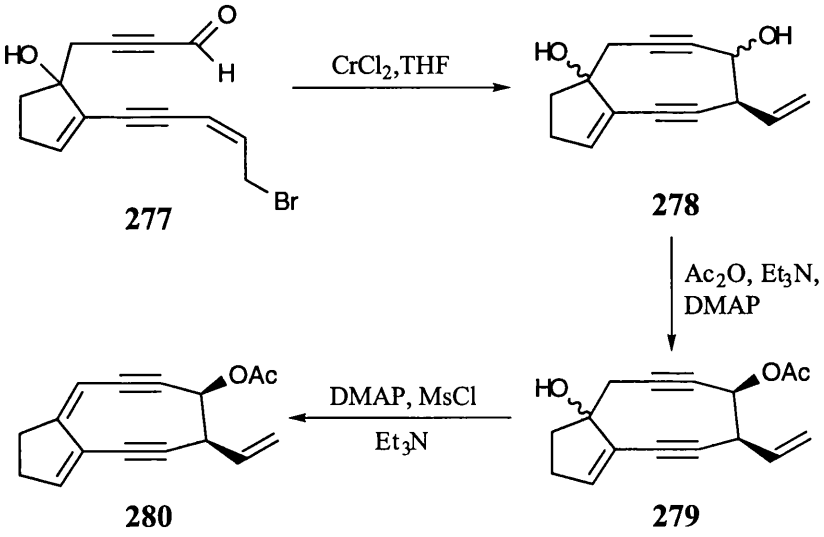


274 **275** **276**

Scheme 1.78

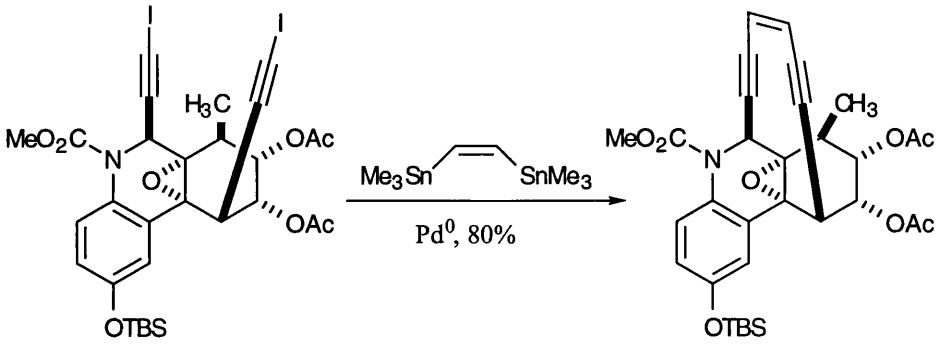
Wender has reported a chromium-mediated ring closure for formation of the NCS-Chrom analogue **280**.[195] Addition of aldehyde **277** to a suspension of chromium(II) chloride in THF gave the intramolecular ring closure product **278** in 77% yield. It is

suggested that the chromium first inserts into the carbon-bromine bond, and then co-ordinative activation of the aldehyde would generate a 13-membered macrometallocyclic chelate.[196] Ring contraction *via* a six-membered transition state affords the nine-membered carbocycle.



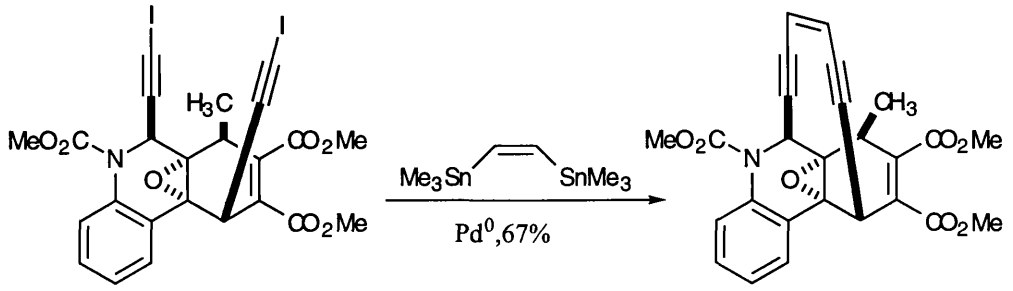
Scheme 1.79

A new innovation brought to the synthesis of Dynemicin analogues by Danishefsky is the installation of an enediyne bridge by palladium(0) coupling of (*Z*)-bis(trimethylstannyl)ethylene to the bis-iodoalkyne **281**.[197]



Scheme 1.80

This approach was also adopted by Takahashi, constructing the Dynemicin analogue **284** in 67% yield.[198]



283 **284**

Scheme 1.81

Hopefully this review has demonstrated the importance of the cycloaromatisation of the enediyne antibiotics and their triggering mechanisms. As we have seen, there are now many methods for the construction of the enediyne unit and the ring-closure of macrocyclic enediynes, and we can only expect our understanding of the Bergman cyclisation to increase as further developments are made in this dynamic field.

CHAPTER TWO

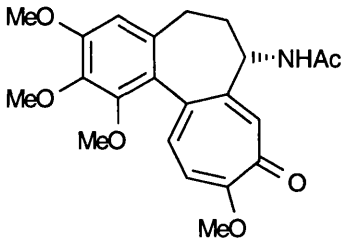
RESULTS AND DISCUSSION

2. Approaches Towards the Total Synthesis of Colchicine

2.1 Introduction

2.1.1 Isolation and Biological Activity of Colchicine

Colchicine (**285**), and related alkaloids are found in parts of several plants of the *liliacaea* family, particularly *Colchicum autumnale.*[199] *Colchicum autumnale* is the common meadow saffron, which occurs naturally in many areas of the northern hemisphere, including England and northern Africa. Colchicine itself can be found in all parts of the plant, the highest concentration occurring within the flowers.[200,201]



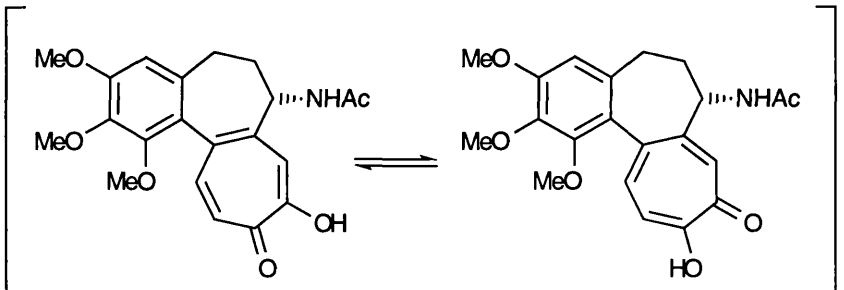
285

Figure 2.1

Colchicine was isolated in 1820 by Pelletier and Caventou[202] and for the next 100 years it was believed to be the only active alkaloid of *Colchicum autumnale.* Detailed studies have since revealed that there are many more active tropolonic alkaloids present. Most of these structures are now known and characterised, but a few still remain unknown. A tropolonic alkaloid may be detected by its UV spectrum, giving a characteristic signal at around 350nm. Many of the congeners were separated by

standard chromatographic techniques on silica gel or alumina,[203,204] leading to the characterisation of over 30 naturally occurring *Colchicum* alkaloids.

Colchiceine (**286**) was discovered in 1833, following the work of Geiger,[205] although at that time it was not appreciated that its structure was different from the toxic principle isolated by Pelletier and Caventou. In 1857, however, Oberlin[200] showed that the crystalline solid discovered by Geiger could be obtained by mild acid hydrolysis of colchicine.



286

Figure 2.2

The correct molecular composition of crystalline colchicine is $C_{22}H_{25}NO_6$ and a series of investigations showed the compound to have a tricyclic structure containing a trimethoxyphenyl A-ring and a seven-membered B-ring. In 1945 Dewar, with remarkable insight, postulated that stipitatic acid (**287**) possessed a tautomeric seven-membered ring structure,[206] which would explain its aromatic character, and applied this principle to colchicine, suggesting two isomeric structures, **288** and **289**, containing a tropolonic ring system (figure 2.4).[207]

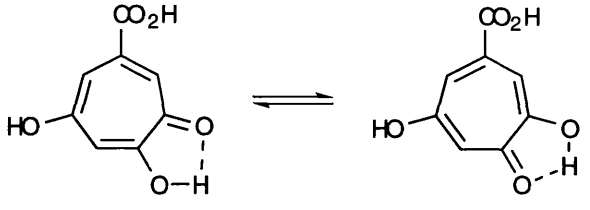


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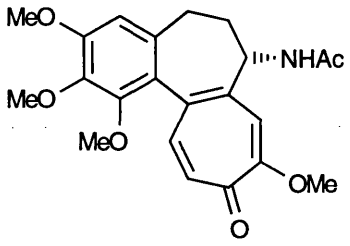
Figure 2.3



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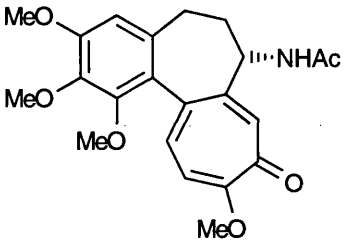

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Figure 2.4

Naturally occurring colchicine possesses only one asymmetric centre at C-7, and its absolute configuration, as shown in figure 2.1, was established by Corrodi and Hardegger[208] by ozonolysis to *N*-acetyl-L-glutamic acid. Three years earlier, the first X-ray crystallographic study of colchicine was reported by King *et al.*.[209] A more detailed study was carried out in 1978 by Lessinger and Margulis,[210] who showed that colchicine exists as two conformers, differing in the dihedral angle formed between rings A and C. Ring B is boat shaped, forcing a dihedral angle of 51° which leads to a skewed structure with *R* chirality around the biaryl axis (figure 2.5).

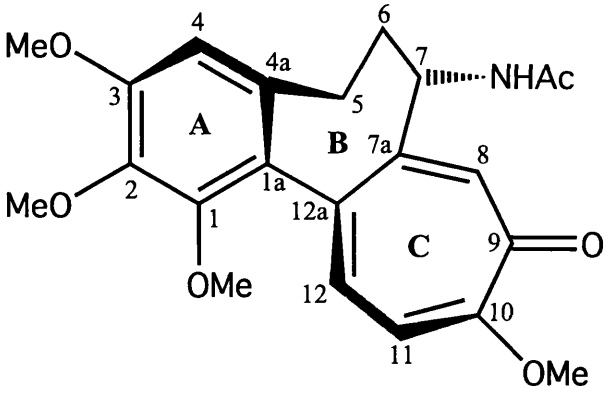


Figure 2.5

As early as Egyptian times, *Colchicum autumnale* was used as a medical remedy, as described in the work *De Materia Medica* by the Greek physician Dioscorides,[211] and its use in the treatment of gout dates from at least the sixteenth century. It was Dustin and Lits who noted the specific ability (shown also by some other substances such as

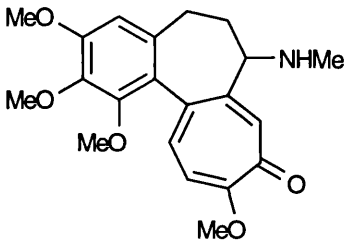
the Vinca alkaloids and podophyllotoxin) of bringing mitosis, or cell division, to halt at a particular stage.[212] This antimitotic effect is brought about by extremely small quantities of colchicine which bind stoichiometrically to β-tubulin, the dimeric subunit of microtubules, in a non-covalent manner, thus blocking microtubule formation.[213,214] Cell division is subsequently halted at the early metaphase, as the genetic material cannot pass from one half of the splitting cell to the other.[215]

Colchicine has also been shown to inhibit catecholamine secretion from the adrenal medulla,[216] iodine secretion from the thyroid gland[217] and prolactin secretion from pituitary tumour cells in culture.[218] Moreover, *in vivo* studies have shown that colchicine inhibits many of the processes which require the intercellular transport of vesicles or ameboid movements, such as the marked inhibition of glucose-induced insulin secretion in a rat.[219] Polymorphonuclear leukocytes (white blood cells) are demobilised by the action of colchicine on microtubule formation. These leukocytes are involved in the natural inflammatory process, which suggests a mechanism for the antigout effect shown by the drug.

Colchicine is an extremely intense poison.[220] Its action is slow, since it acts by absorption into the central nervous system and finally causes death by vasomotor paralysis. With larger doses the cells may recover and resume division, either normally or in a modified manner.[221] However, because of its toxicity, many analogues have been studied in order to find an active compound with a more favourable ratio of the minimum effective dose to the maximum tolerated dose. Evidence suggests, however, that in similar alkaloids where the tropolone ring has rearranged to a benzenoid system, toxicity is decreased.[222,223]

Considerable efforts have been made, particularly by Lettre in Germany[224] and Velluz in France,[225] to overcome these toxicity effects. Structural modification has

not yet afforded greatly improved compounds, although demecolcine (**290**) and the thiocolchicines (not shown) have some advantages.



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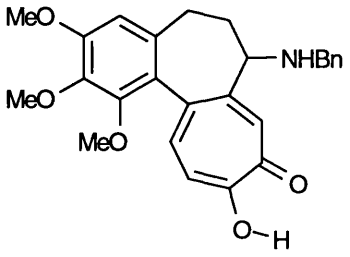

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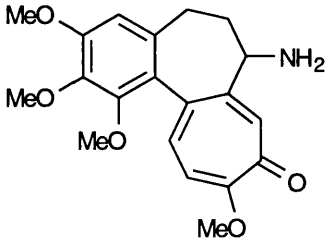


292

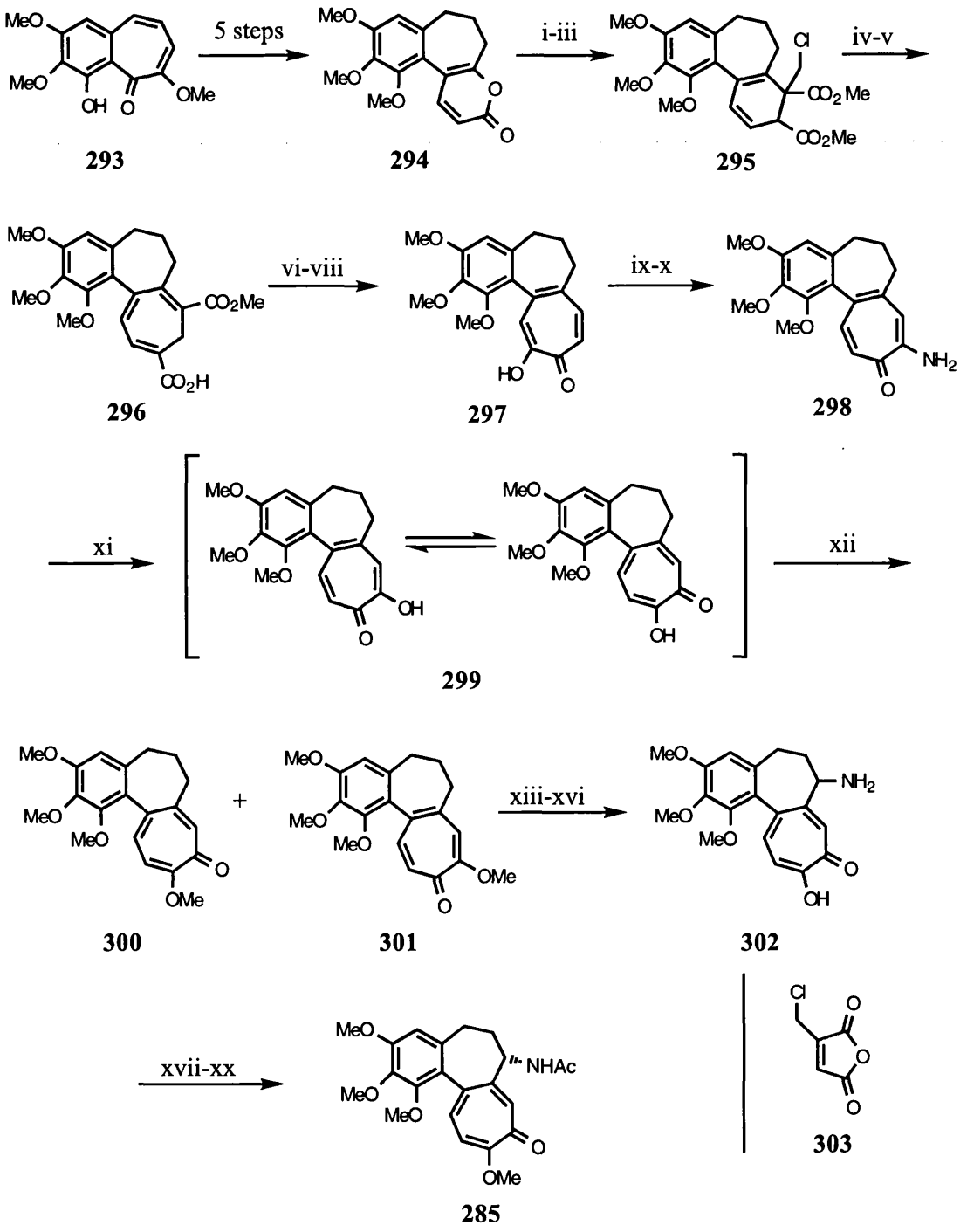
Figure 2.6

Colchiceine (**286**), *N*-benzoyldeacetylcolchicine (**291**) and deacetylcolchicine (**292**), although much less toxic, show only limited antimitotic effects.[226] Deacetylcolchicine was selected for clinical trials in the form of its tartrate salt, and showed some activity in lymphoma and chrome myelogenous leukaemia, but the results were no better than those obtained from existing antitumour agents, and the problem of toxicity was still present. Progress on the chemistry and biology of colchicine has been the subject of many reviews.[199-201,227-234]

2.1.2 Previous Syntheses of Colchicine

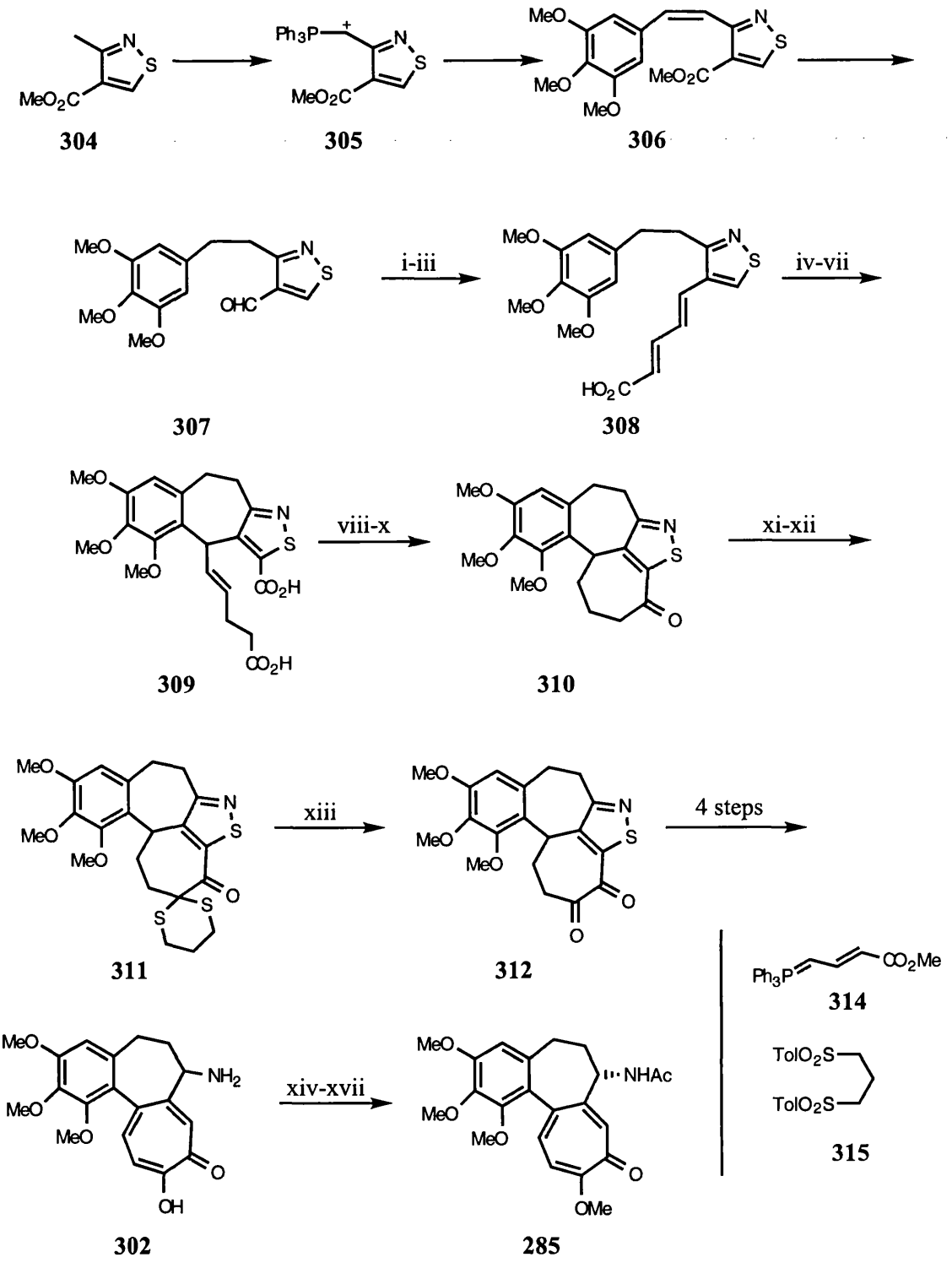
The first total synthesis of colchicine was published in 1961 by Eschenmoser (scheme 2.1).[235,236] Purpurogallin trimethyl ether (**293**) was used as the starting material, which was reduced and treated with methyl propiolate and base to furnish the pyrone **294**. Methylation of the phenol, a Diels-Alder cycloaddition to chloromethylmaleic anhydride, hydrolysis of the resulting anhydride and then esterification with diazomethane gave rise to the chlorinated tricycle **295** ready for ring expansion. The action of potassium *tert*-butoxide followed by selective hydrolysis of one of the ester groups led to **296**, which possesses the full carbocyclic framework of colchicine. Introduction of the hydroxyl and carbonyl groups was achieved by oxidation with osmic acid and the remaining ester group was eliminated by hydrolysis and subsequent decarboxylation. The produced tropolone **297** was then isomerised *via* the aminotropone **298** by treatment with *p*-toluenesulfonyl chloride, followed by ammonia and then potassium hydroxide.

Desacetamidocolchiceine (**299**), existing as a pair of tautomers was methylated with diazomethane to a regioisomeric mixture of desacetamidocolchicine (**300**) and desacetamidoisocolchicine (**301**). As the C-7 position of **301** is electronically unfavourable for allylic bromination by NBS, only **300** is converted to the bromide, which is treated with ammonia then sodium hydroxide to give *N*-desacetylcolchiceine (**302**). Resolution of **302** using D-camphor-10-sulfonic acid, followed by *O*-methylation, separation and *N*-acetylation gives (-)-colchicine (**285**).



i) **303**; ii) MeOH, H^+; iii) CH_2N_2; iv) KO^{t}Bu; v) NaOH; vi) OsO_4, $NaHCO_3$, $KClO_3$; vii) NaOH; viii) SiO_2/270°C; ix) TsCl/Py; x) NH_3; xi) KOH; xii) CH_2N_2; xiii) separation; xiv) NBS; xv) NH_3; xvi) NaOH; xvii) resolution; xviii) CH_2N_2; xix) separation; xx) Ac_2O

Scheme 2.1



i) **314**; ii) NaOH; iii) I_2; iv) $HClO_4$, H_2O; v) N_2H_4, Cu(II), H_2O_2; vi) *O*-biphenyl lithium; vii) CO_2; viii) CH_2N_2; ix) NaH; x) H^+; xi) NaH/HCO_2Et; xii) **315**; xiii) $Hg(OAc)_2$, H^+; xiv) Ac_2O/Py; xv) resolve; xvi) CH_2N_2; xvii) separation

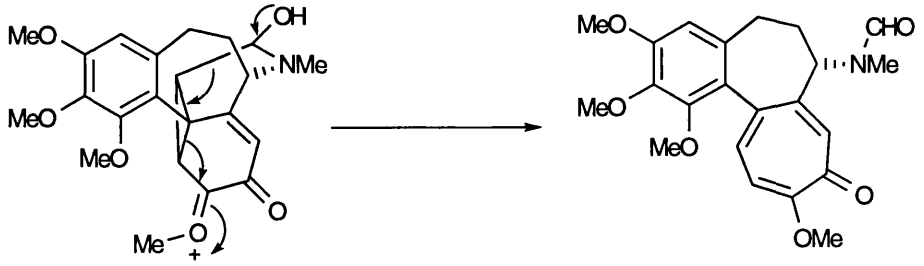
Scheme 2.2

Woodward's synthesis[237] was reported in 1963, and involves the elegant usage of an isothiazole group as a masked nitrogen moiety as well as a directing platform for the construction of rings B and C (scheme 2.2). The phosphonium salt of the isothiazole **305** was coupled with 3,4,5-trimethoxybenzaldehyde and transformed to aldehyde **307** *via* a series of reductions and re-oxidation. **307** was then converted to the conjugated acid **308** and cyclisation achieved by the action of perchloric acid. Introduction of a second carboxyl group on the isothiazole ring was achieved using *O*-biphenyl lithium and carbon dioxide, giving the diacid **309**. The second cyclisation to construct ring C was furnished by a Dieckmann reaction, by esterification of **309** and treatment with base. Generation of an α-dithiane and then treatment with mercury(II) acetate formed a second keto group. Oxidation of the diketone **312** gave a tropolone and the isothiazole was broken down and reduced to the amine **313**. This was *N*-acetylated and *O*-methylated to give (-)-colchicine (**285**), obtained after separation of the isomers.

The main drawback of this approach is that each methylation on the tropolone C-ring results in half of the material being unsuitable for further elaboration. Obviously, this problem with the tautomeric diosphenol is a considerable disadvantage and gives low overall yields. However, these syntheses enabled a number of later syntheses of colchicine to be achieved,[238-245] by establishing desacetamidocolchicine (**300**) and desacetylcolchiceine (**302**) as key intermediates.

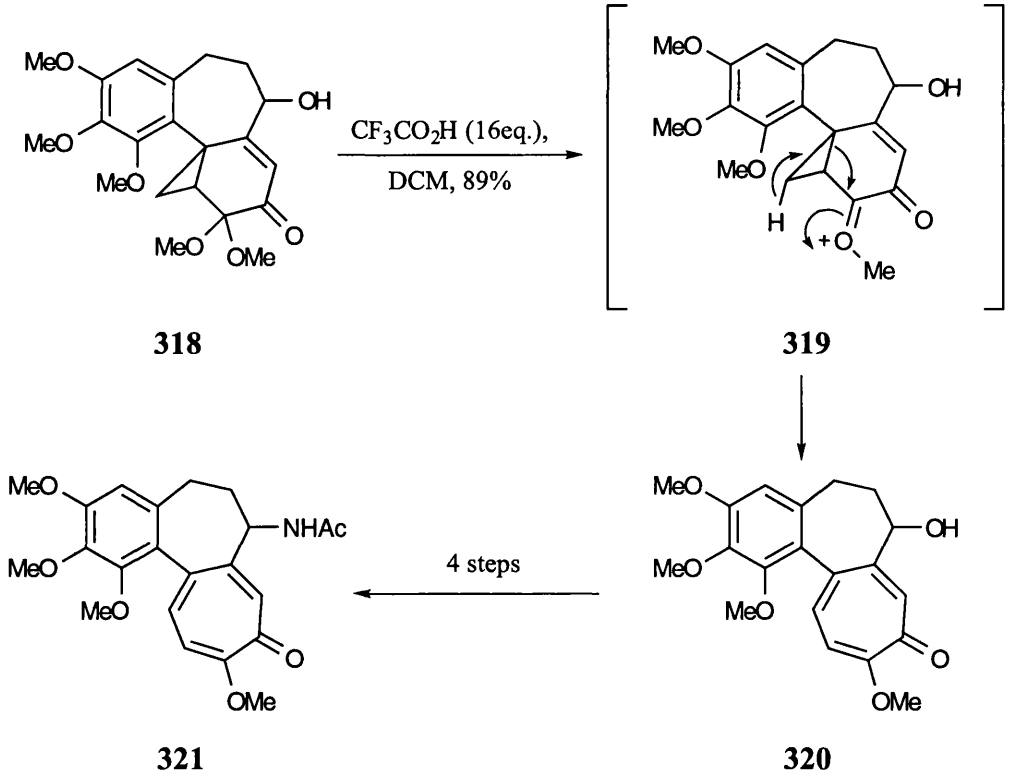
The most recent synthesis of colchicine is that reported by Banwell and co-workers.[246-250] This represents the first fully regiocontrolled synthesis, with the formation of the tropolone methyl ether controlled by a biomimetic process. In the final stages of the proposed biosynthesis of colchicine[251] the tropolone is formed by the ring opening of the cyclopropanated benzenoid precursor **316** (scheme 2.3). In his synthesis, Banwell was able to demonstrate the ring opening of the σ-homo-*o*-benzoquinone monoacetal **318** into the α-tropolone-*O*-methyl ether **320**, by treatment

with an excess of trifluoroacetic acid (scheme 2.4). The 7-hydroxydesacetamido-colchicine **320** could then be easily transformed into racemic colchicine using established methodology.[238,252]



316 **317**

Scheme 2.3



318 **319** **320** **321**

Scheme 2.4

2.2 Synthetic Approach

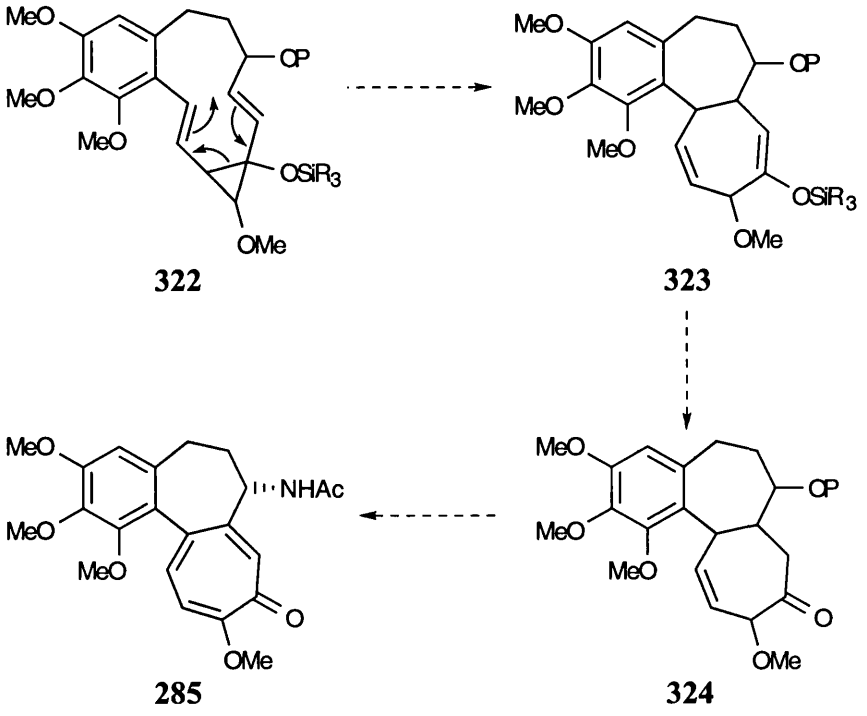
Although a large amount of effort has been focused on the synthesis of colchicine over the last 35 years, there are still problems which are left to be addressed. Apart from the elegant work carried out by Banwell in 1992, all the syntheses have suffered from the inevitable loss of yield when separating the products from methylation of a free tropolone (the "diosphenol problem"). In addition to this there have been no reported syntheses in which the acetamido function at C-7 has been produced in a chiral fashion.

There is, therefore, room for a synthesis of colchicine which will address these problems, and the regio- and stereoselective synthesis of colchicine remains a highly attractive goal. Moreover, none of the routes so far developed is sufficiently flexible to allow for the construction of a range of unnatural analogues, which may provide valuable insight into the mode of action of this intriguing compound. It was our aim, therefore, to develop novel methodology for the formation of a variety of substituted tropolone rings at a late stage in the synthesis.

We hoped to develop the first regio- and enantioselective synthesis by employing three basic strategies. Firstly, we wished to find a method for the formation of a tropolonic methyl ether in which there would be no methylation of a free tropolone. Secondly, the substituent at C-7 should be introduced in an asymmetric step. Thirdly, in order to reduce the overall number of steps and allow for the introduction of different functionality into the molecule, we wished to construct both the B and C-rings of colchicine in a single step.

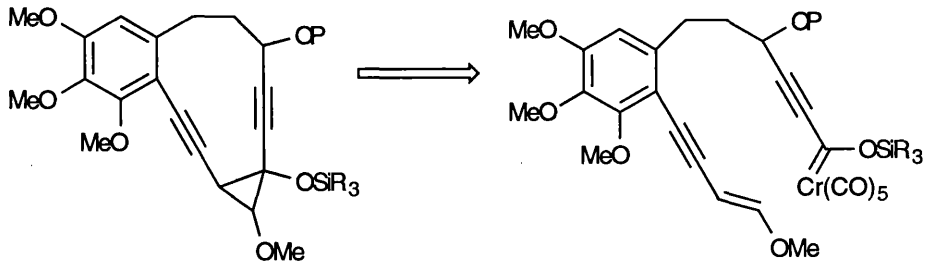
Three interrelated strategies were thus planned which meet these conditions. The first of these involves the ring-opening of a suitably substituted dialkynyl- or

divinylcyclopropane. For the construction of the colchicine B and C-rings, we envisage the cyclopropanated macrocycle **322**. This may undergo the Cope rearrangement to afford cycloheptadiene **323**. Hydrolysis of the silyl enol ether would produce **324**, which possesses the correct regiochemistry of colchicine, and which can be elaborated to the natural product by oxidation.



Scheme 2.5

It was considered that if such a ring-opening and cyclisation were feasible, the problem of regioselectivity could be solved by judicious use of functionality around the cyclopropane. Several options for the formation of the cyclopropanation present themselves, but the potential for a Fischer carbene[253,254] such as **326** to cyclopropanate an intramolecular methyl vinyl ether would permit the formation of both the functionalised cyclopropane and the macrocycle in a single step.

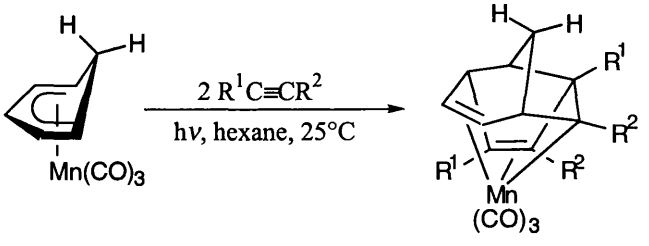


325 **326**

Scheme 2.6

Thus, the Fischer carbene **326** was designed as the precursor for such a strategy, bearing the correct functionalisation. We hoped that by performing the Cope rearrangement with a dialkynylcyclopropane we would be able to access products with a higher degree of unsaturation (*vide infra*), thereby avoiding the oxidation sequence.

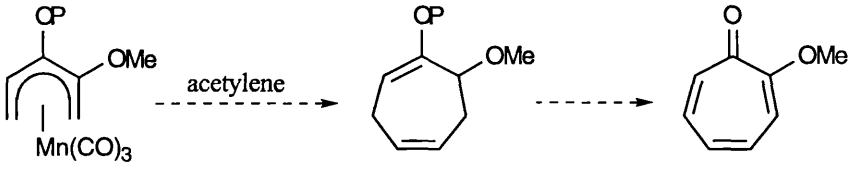
The second approach owes its origin to the observation by Sheridan of an unusual product formed from the photoassisted, metal-mediated higher order cycloaddition reaction between two alkynes and a co-ordinated cyclohexadienyl group.[255] The products formed from this reaction (**328**) are derived from one alkyne adding to the dienyl ligand in a [5+2] fashion and the second adding in a [3+2] process (scheme 2.7). The reaction conditions are very mild, requiring only 3-6 hours at room temperature under irradiation to afford the product in 90% yield.



327 **328**

Scheme 2.7

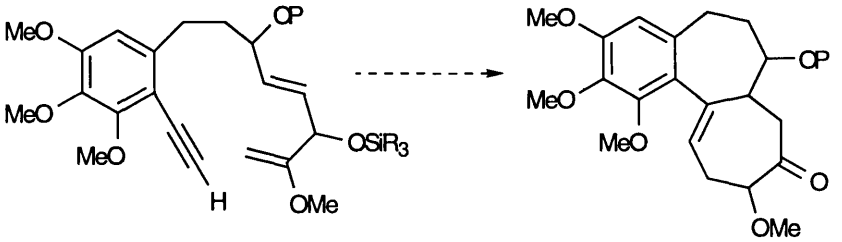
This was the first example of a [5+2] cycloaddition reaction and shows the potential for a η^5-bonded polyene such as a pentadienyl group to add to an alkene or alkyne, forming a seven-membered ring system. This prompted us to ask the question as to whether a suitably functionalised pentadiene, such as **329** may add in a [5+2] fashion to an alkyne to afford a tropolonic product.



329 **330** **331**

Scheme 2.8

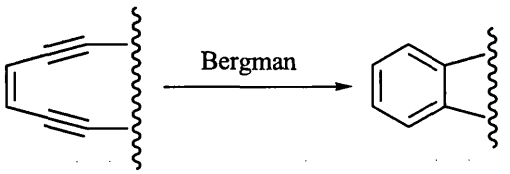
To test this hypothesis we designed **332** as our target structure. It was hoped that an intramolecular metal-mediated [5+2] cycloaddition of **332** would give rise to the desired tricyclic system **333**, which could then be elaborated to the natural product.



332 **333**

Scheme 2.9

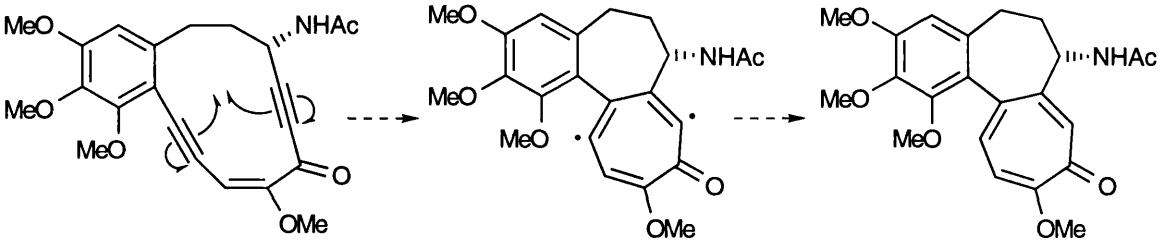
The third strategy was inspired by the fascinating chemistry of the enediyne antibiotics, such as calicheamicin, dynemicin and neocarzinostatin. As we have seen in the introduction, these natural products undergo a cycloaromatisation of the enediyne unit to form the more stable 6-membered aromatic structure (scheme 2.10).



334 **335**

Scheme 2.10

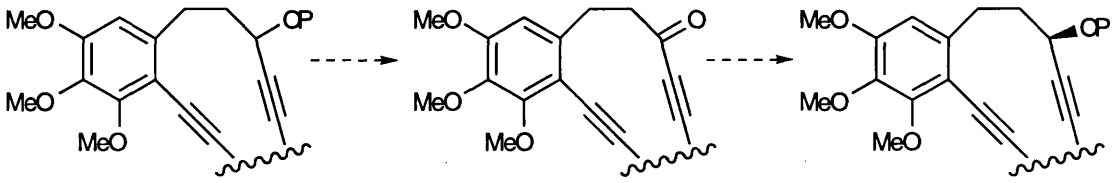
For this approach we pose the question as to the existence of a similar cycloaromatisation of the 12-membered macrocycle **336** occurring to generate the tropolonyl C-ring. Although the Bergman cycloaromatisation has been used extensively for the formation of five- and six-membered aromatic rings (*vide supra*), very little attention has been focused upon the potential for formation of aromatic rings of other sizes.



336 **337** **285**

Scheme 2.11

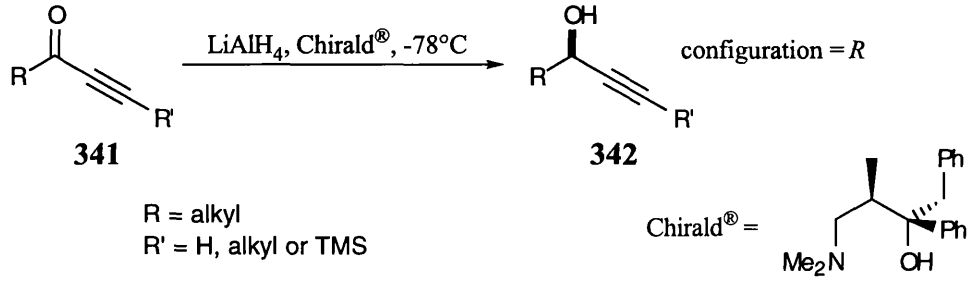
These three approaches were developed concurrently, although for ease of discussion we shall consider each in a separate section. It is also worth noting at this stage that each strategy appears to ignore our second objective in that the acetamido function is not installed and no stereoselectivity at C-7 is observed. Since the C-7 acetamido function can be introduced *via* a nucleophilic displacement of an oxygen-based leaving group (as in Banwell's synthesis), it was decided that the protected secondary alcohol **338** would be synthesised in each case.



338 **339** **340**

Scheme 2.12

Moreover, it has been reported that α-alkynones can be reduced enantiospecifically to secondary alcohols by the use of lithium aluminium hydride with (2*S*,3*R*)-(+)-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (Chirald®) as an auxiliary (scheme 2.13).[256]



341 **342**

R = alkyl
R' = H, alkyl or TMS

Scheme 2.13

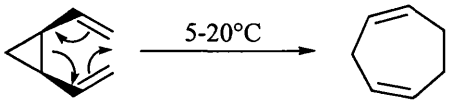
Hence we envisaged that the alcohol **340** could be generated from an α-alkynone, such as **339**. In this manner, our second objective can be fulfilled.

2.3 Investigation of the Cope Rearrangement Approach

2.3.1 Background and Strategy

2.3.1.1 The Cope Rearrangement of Divinylcyclopropanes

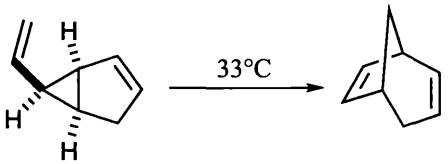
The Cope rearrangement of *cis*-divinylcyclopropanes is thermally allowed and offers an attractive stereoselective approach to the formation of cycloheptadienes. The presence of the cyclopropane lowers the activation energy of the rearrangement by virtue of the release of strain on opening the three-membered ring. For example, *cis*-1,2-divinylcyclopropane **343** undergoes a spontaneous Cope rearrangement below room temperature to afford the less-strained 1,4-cycloheptadiene **344**.[257]



343 **344**

Scheme 2.14

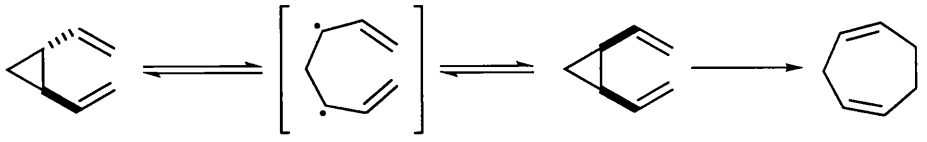
This rearrangement still occurs readily when the 1,2-divinylcyclopropane moiety is part of a bicyclic ring system, as in **345**. This rearranges at just above room temperature to the bicyclo[3.2.1]octadiene **346**.[258,259]



345 **346**

Scheme 2.15

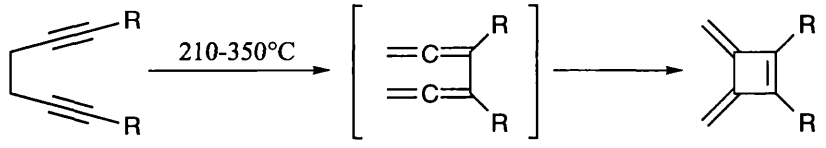
It is worth noting that *trans*-1,2-divinylcyclopropanes will give the same products at a higher temperature. This result is claimed to involve isomerisation *via* the diradical intermediate **348** to the corresponding *cis* isomer.[260,261]



347 **348** **343** **344**

Scheme 2.16

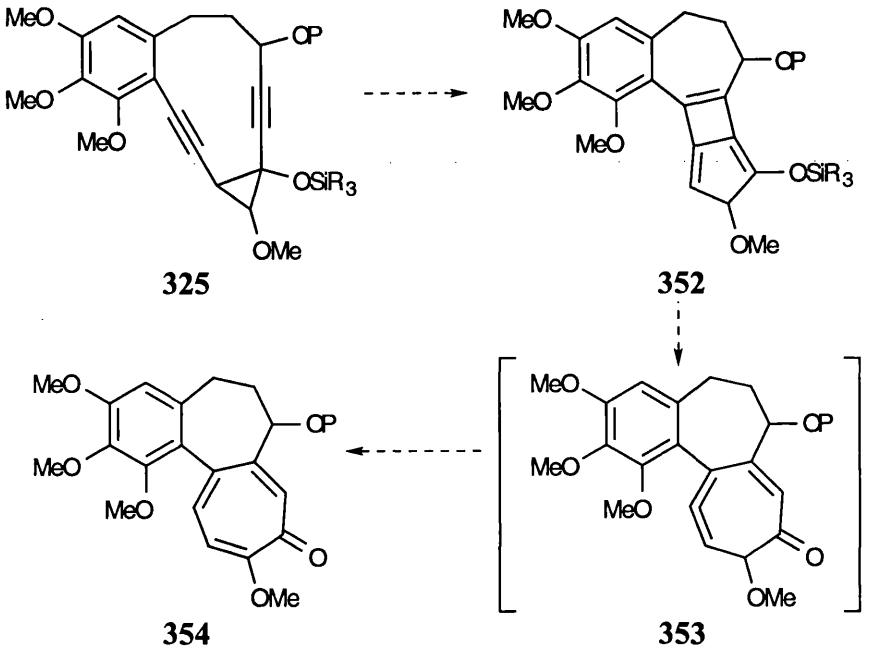
Although it may appear geometrically impossible for a linear alkyne bond to fit into the constraints of a six-membered transition state, the Cope rearrangement of 1,5-enynes and 1,5-diynes is known and provides a route to allenes. The simple 1,5-diyne **349** undergoes a Cope rearrangement upon heating to afford the bis-allene **350**. Under the high temperatures involved in the reaction, this allene performs a rapid [2+2] cycloaddition, affording the cyclobutene derivative **351**.[262,263]



349 **350** **351**

Scheme 2.17

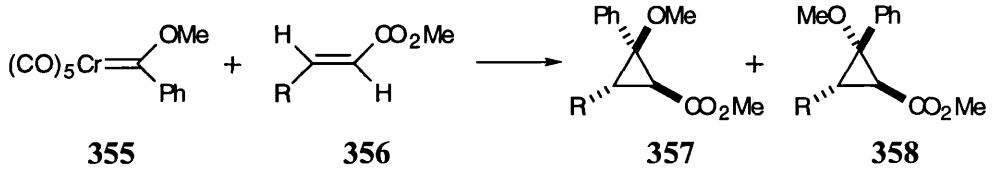
Dialkynylcyclopropane **325** may be formally expected to undergo a similar process, forming the tetracyclic compound **352**, which may be hydrolysed and ring-opened to form a tropolone.



Scheme 2.18

2.3.1.2 Cyclopropanation by Fischer Carbenes

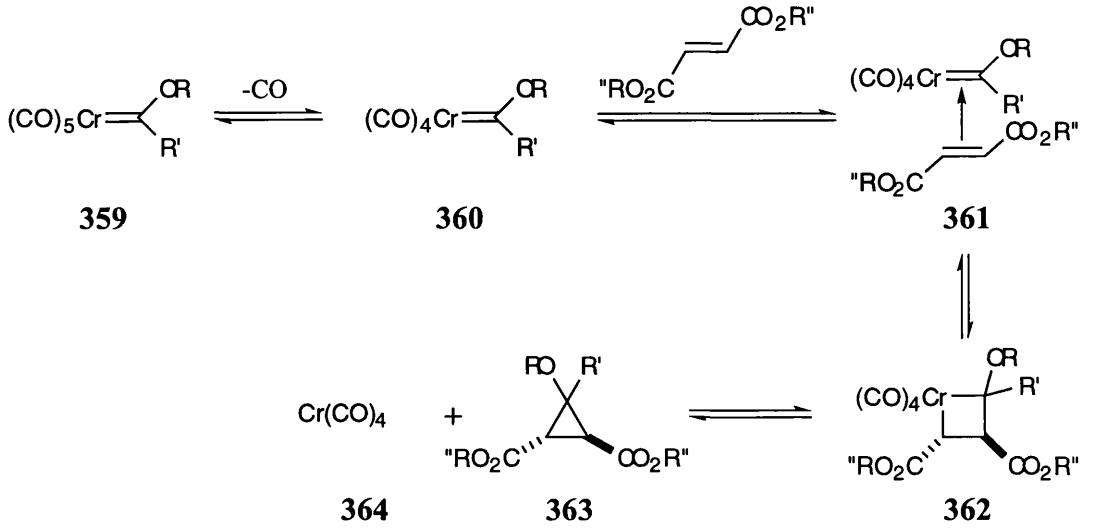
The cycloaddition of alkenes with heteroatom carbene complexes is reported to proceed only with activated alkenes.[264,265] Dötz and Fischer demonstrated the formation of the highly functionalised cyclopropanes (**357** and **358**) when α,β-unsaturated ester **356** was treated with a chromium carbene (**355**) (scheme 2.19).[266]



Scheme 2.19

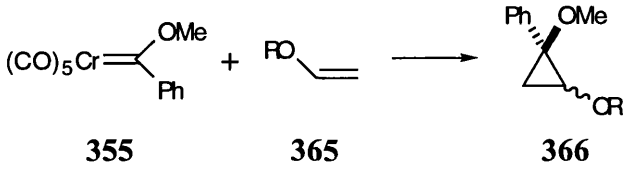
Carbene complexes of chromium, molybdenum and tungsten have been treated with *trans*-methyl crotonate under similar conditions, which showed that the relative rate of cyclopropanation is Mo > Cr > W. The mechanism of this cyclopropanation

reaction is shown in scheme 2.20.[265] Initial loss of a CO ligand from the chromium is followed by co-ordination to the activated alkene. A [2+2] cycloaddition affords the metallocycle **362** which then loses chromium tetracarbonyl to form the cyclopropane (**363**).



Scheme 2.21

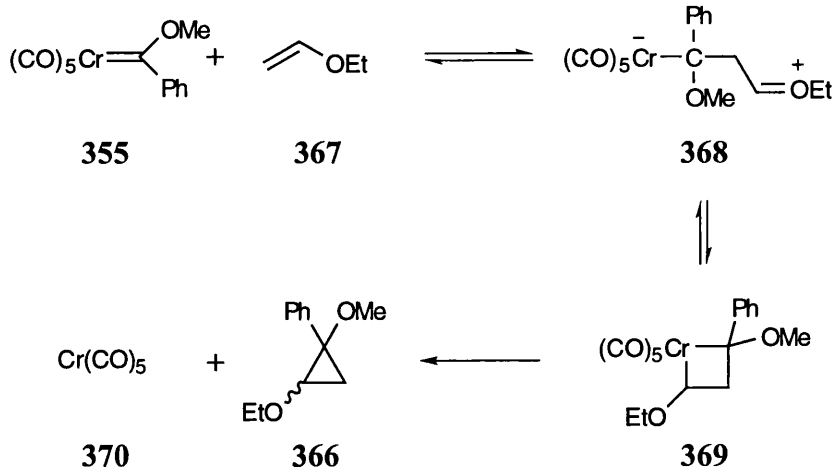
Under high pressures of carbon monoxide, however, vinyl ethers also react with carbenes to afford cyclopropane products.[267] Thus, treatment of ethyl vinyl ether (**365**) with [(phenyl)(methoxy)carbene]chromium pentacarbonyl (**355**) under 100 atmospheres of CO, affords **366** in 60% yield.



Scheme 2.21

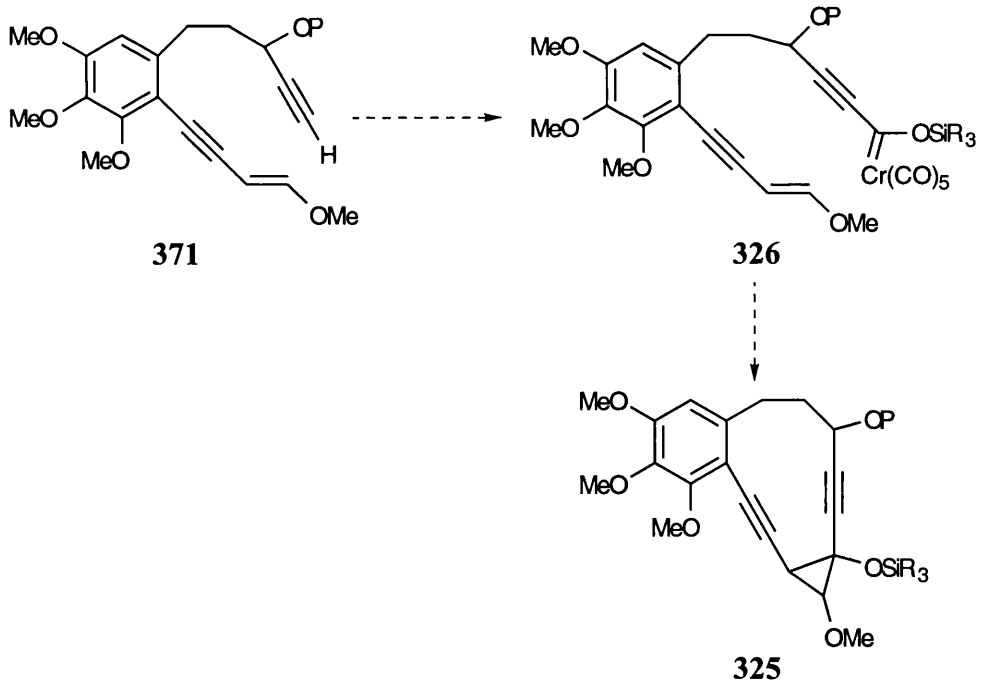
However, the mild reaction conditions and the nucleophilic nature of vinyl ethers suggest a different mechanism from that postulated for the reaction with α,β-unsaturated esters. Since a vacant co-ordination site on the metal should not be available under the reaction conditions, the first step of the transformation could be

nucleophilic attack by the vinyl ether on the carbene carbon.[265] This initial adduct (**368**) could then rearrange to the seven-co-ordinate metallocyclobutane (**369**) which would be favoured by high CO pressures. Reductive elimination would then result in formation of the cyclopropane (**366**).



355 **367** **368** **370** **366** **369**

Scheme 2.22



371 **326** **325**

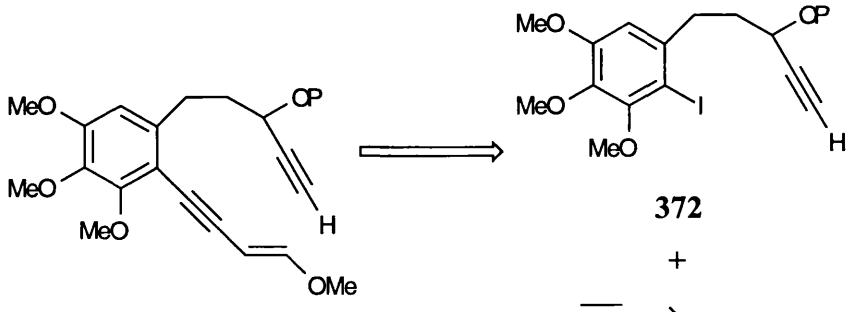
Scheme 2.23

The cyclopropanated macrocycle **325** can be disconnected to the acyclic precursor **371** bearing both methyl vinyl ether and acetylene functionality. Formation of the

Fisher carbene on the acetylide anion and quenching with a suitable electrophile, such as trimethylsilyl chloride would give us **326**. If cyclopropanation onto the double-bond of the methyl vinyl ether can then be achieved, we would have a regiocontrolled formation of the cyclopropane, bearing the correct functionality for the proposed Cope rearrangement.

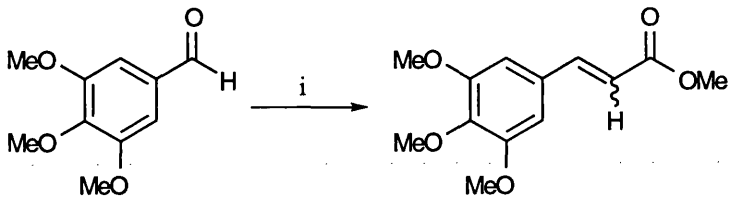
2.3.2 Synthesis of the Fischer Carbene Precursor

Our target compound **371** may be disconnected to the protected propargyl alcohol **372** and the methyl vinyl ether **373**. The propargyl alcohol was chosen as it is also an important intermediate in the construction of the macrocycle for the Bergman cyclisation strategy (*vide infra*).



Scheme 2.24

The first approach to the construction of **371** was to perform the Wittig addition of (carbomethoxymethyl)triphenylphosphonium bromide to 3,4,5-trimethoxy benzaldehyde (**374**) (scheme 2.25). Addition of 1.5 equivalents of the phosphonium salt in aqueous sodium hydroxide solution to a dichloromethane solution of the benzaldehyde followed by rapid stirring gave the product in 64% yield as a 2:1 mixture of (*E*) and (*Z*) isomers. This result was in contrast to that previously obtained in the group,[268] where the product formed was exclusively the anticipated *trans*-cinnamic ester. However, repeating the reaction with freshly prepared rather than commercially purchased phosphonium salt had no effect on the results obtained.

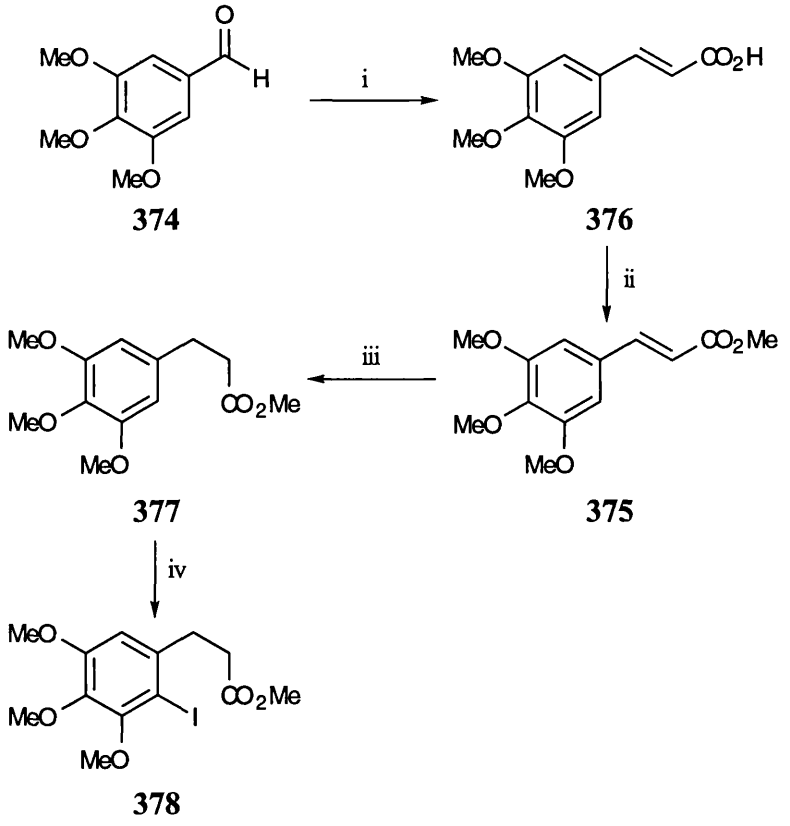


374 **375**

i) $MeO_2CCH_2PPh_3Br$ (1.5eq), 1M NaOH, DCM, r.t. (64%)

Scheme 2.25

As an alternative strategy, we considered the use of a Knoevenagel condensation with malonic acid followed by esterification to afford the same cinnamic ester **375**. Using the procedure described by Koo *et al.*,[269] **376** was isolated in 88% yield as the (*E*)-isomer exclusively.



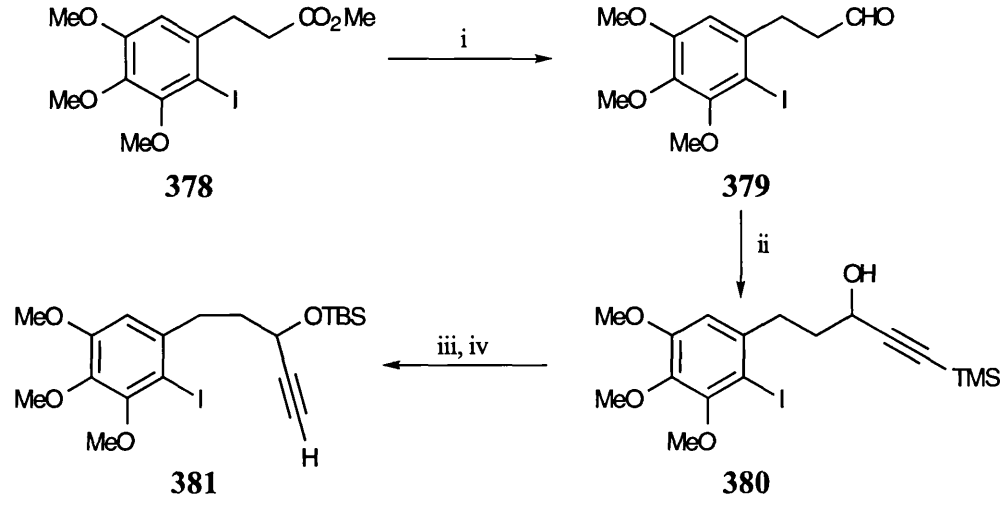
374 **376** **375** **377** **378**

i) Malonic acid (2eq), piperidine (15mol%), pyridine, reflux (88%); ii) AcCl (2.2eq), MeOH, reflux (87%); iii) H_2, Pd/C, MeOH, r.t. (87%); iv) CF_3CO_2Ag (1.1eq), I_2 (1.1eq), DCM, r.t. (86%).

Scheme 2.26

Elaboration to the methyl ester was achieved by heating in a methanolic solution of hydrogen chloride produced from acetyl chloride and methanol to afford **375**. The saturated ester **377** was furnished by hydrogenation over 10% palladium on carbon, and monoiodination of the phenyl ring proceeded smoothly using silver trifluoroacetate and elemental iodine.[270,271] This approach allowed the synthesis of multigram quantities of **378** without incurring any loss in yield. Indeed, the highest yields were obtained for the larger scale reactions.

Concentrating initially on the northern half of the Fischer carbene precursor, DIBAL-H reduction of **378** gave the desired aldehyde (**379**) in 73% yield. It was found that over-reduction to the alcohol could be avoided by keeping the reaction mixture at -78°C until pouring onto the hydrochloric acid. Allowing the reaction mixture to warm at all before work-up results in the formation of some alcohol. Addition of the alkynylmagnesium bromide, formed *in situ*, to the aldehyde gave alcohol **380** in 82% yield. Protection of the alcohol as the TBS ether was followed by deprotection of the acetylene with potassium carbonate in methanol to afford **381** in an excellent overall yield of 57% from **378**.

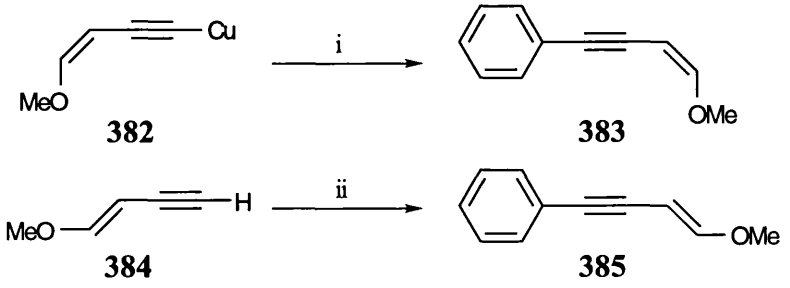


378 **379** **380** **381**

i) DIBAL-H (1.1eq), DCM, -78°C (73%); ii) HC≡CTMS (2eq), EtMgBr (2eq), -78°C to r.t. (82%); iii) TBSCl, imidazole, cat. DMAP, r.t. (87%); iv) K_2CO_3, MeOH, r.t. (100%).

Scheme 2.27

With the acetylene (**381**) in hand, we turned to the incorporation of the enyne fragment. Kraus and Frazier prepared (*Z*)-phenylenyne **383** by heating copper acetylide **382** with iodobenzene in pyridine at 120°C after vigorous exclusion of oxygen (scheme 2.28).[272] It was considered doubtful that **381** would survive such reaction conditions, but (*E*)-enyne **384** was also available and could be prepared according to the literature procedure.[273] This was coupled with iodobenzene in a Heck/Castro-type reaction using palladium(II) acetate and copper(I) iodide as catalysts to afford the (*E*)-phenylenyne (**385**) in good yield.

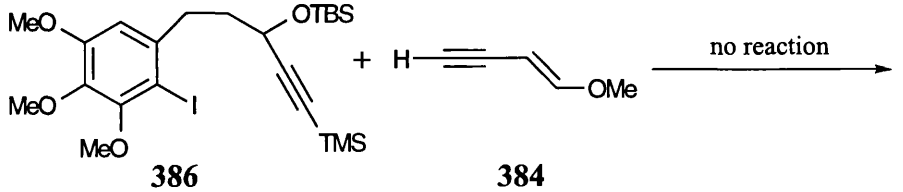


382 **383** **384** **385**

i) iodobenzene, pyridine, 120°C (63%); ii) iodobenzene (0.83eq), $Pd(OAc)_2$ (5mol%), CuI (5mol%), PPh_3 (20mol%), Et_2NH, reflux (92% based on iodobenzene)

Scheme 2.28

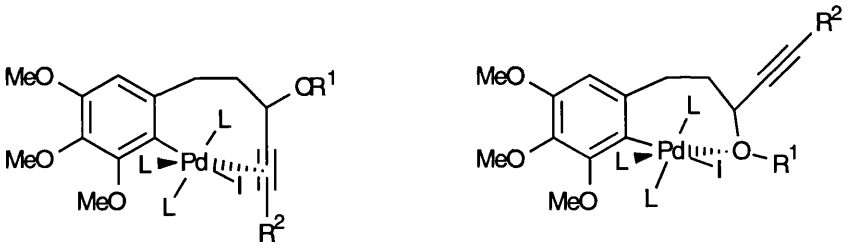
Although the starting enyne is acid sensitive the product is, as reported by Kraus and Frazier, sufficiently stable to be purified by chromatography on silica gel. However, when the same reaction conditions were applied to the coupling of enyne **284** to the protected acetylene **286** no addition products were observed. The reaction was repeated with different combinations of catalyst and base, but in our hands the starting material appeared inert.



386 **384**

Scheme 2.29

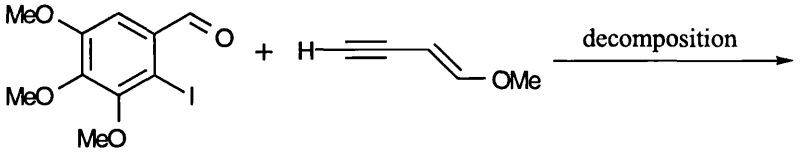
The cause for this may be that when the palladium has inserted into the carbon-iodine bond, compounds such as **387** and **388** are formed. These seven-membered cyclic species are so strongly chelated that the palladium atom cannot dissociate and then participate in the catalytic cycle and, as a result, no coupling occurs.



387 **388**

Figure 2.7

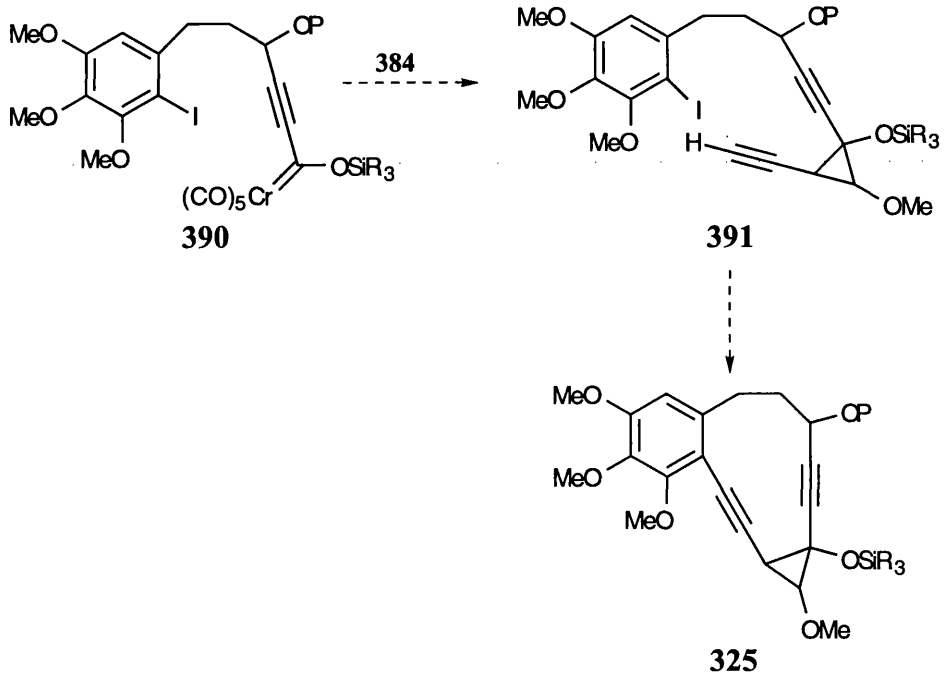
Attempts were therefore made to perform the Heck/Castro-type coupling at an earlier stage in the synthesis. In this case, coupling of the (*E*)-enyne to the aldehyde (**389**) using palladium(II) acetate and copper(I) iodide, however, gave only decomposition products and the desired phenylenyne could not be isolated.



389 **384**

Scheme 2.30

At this stage we decided to study the formation of some model Fischer carbenes in the hope that an intermolecular cyclopropanation of the enyne fragment **384** by carbene **390** might lead to our desired dialkynyl cyclopropane. This may then undergo a more favourable intramolecular Heck/Castro coupling to the aryl iodide to furnish the macrocycle **325**.

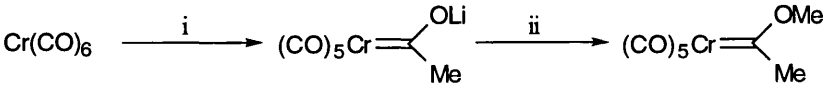


Scheme 2.31

Fischer carbenes may be synthesised by the action of an alkyllithium[274] or alkyl Grignard reagent[275] on chromium hexacarbonyl and then quenching with an electrophile. We hoped that formation of the acetylide anion of **381** and addition of chromium hexacarbonyl would allow access to the desired carbene products. We were later to discover (*vide infra*) that the formation of an acetylide anion in the presence of an aryl iodide led simply to deiodination of our starting material *via* metal halogen exchange (scheme 2.55). These results forced us to study a different approach.

It has been reported that treatment of [(methyl)(methoxy)carbene]chromium pentacarbonyl (**394**) with butyllithium results in the formation of an anionic species which may be converted to an α,β-unsaturated carbene by the addition of an aldehyde.[276] This approach would permit the formation of a vinylalkynyl-cyclopropane and so a model for the cyclopropanation reaction was devised.

Formation of [(methyl)(methoxy)carbene]chromium pentacarbonyl followed the literature procedure[274] to afford the product as bright yellow crystals. The product is partially air-sensitive and was observed to turn slowly brown when not stored under nitrogen.

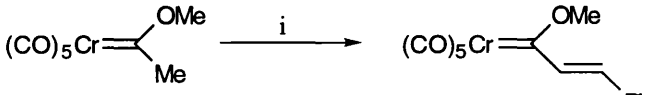


392 **393** **394**

i) MeLi, Et_2O, reflux; ii) $Me_3O^+BF_4^-$, H_2O, r.t. (33%).

Scheme 2.32

Condensation of the anion of **394** with benzaldehyde, following the procedure reported by Casey and Brunsvold, gave a poor yield (12%) of the desired [(styryl)(methoxy)carbene]chromium pentacarbonyl (**395**) as deep red crystals.[276]

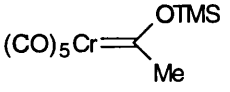


394 **395**

i) ^{n}BuLi (1.1eq), Et_2O, -78°C, then benzaldehyde, -78°C to 0°C (12%).

Scheme 2.33

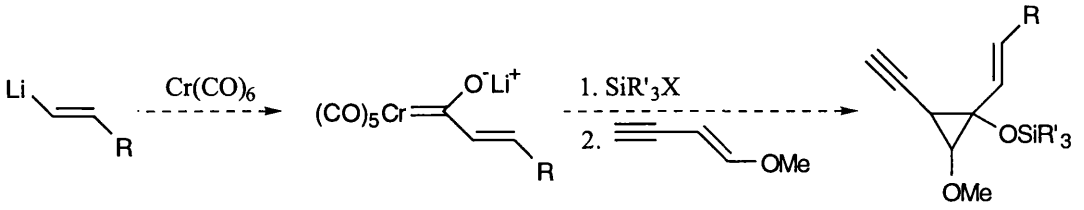
The formation of a silylated carbene (**396**) has been reported,[277] but in our hands it was found to be very unstable to the work-up procedure described and decomposed rapidly upon exposure to neutral solutions and air.



396

Figure 2.8

Although this approach was not pursued any further, the potential for the formation of tropolones *via* the cyclopropanation of vinyl ethers is certainly worthy of further study. It is interesting to note that the intermediate lithium salt of the alkoxide (**393**) is stable to air, and the trimethyloxonium tetrafluoroborate is added to its aqueous solution. Synthesis of the carbene formed between a vinyllithium and chromium hexacarbonyl may therefore allow isolation of **398**. Such a compound could then be treated sequentially with a silylating agent and the alkene in a single pot to afford the desired cyclopropane products (**399**) without the need for isolation of the unstable silylated carbenes.



397 **398** **399**

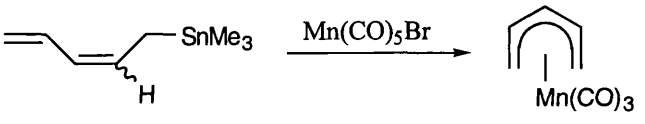
Scheme 2.34

It is also worth noting, however, that chromium carbenes are well known for the Dötz benzannulation reaction with alkynes.[278] In our substrate we have both an alkyne and a methyl vinyl ether and so the problem of competition between the two modes of reaction of the carbene would have to be carefully controlled, perhaps through protection of the acetylene as its dicobalthexacarbonyl complex.

2.4 Investigation of the [5+2] Cycloaddition Approach

2.4.1 Background and Strategy: The Formation of η^5-Pentadienyl Metal Complexes

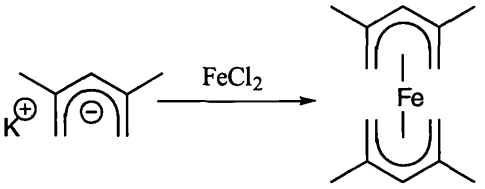
It has been shown that η^5-$Mn(CO)_3$ complexes may be formed by the addition of pentacarbonylmanganese bromide to a pentadienyl tin in THF (scheme 2.35).[279]



400 **401**

Scheme 2.35

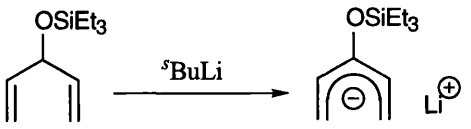
Alternatively, if the potassium salt of the pentadiene can be isolated, then this may be complexed to titanium or iron(II) in a titanocene or ferrocene open structure (scheme 2.36).[280]



402 **403**

Scheme 2.36

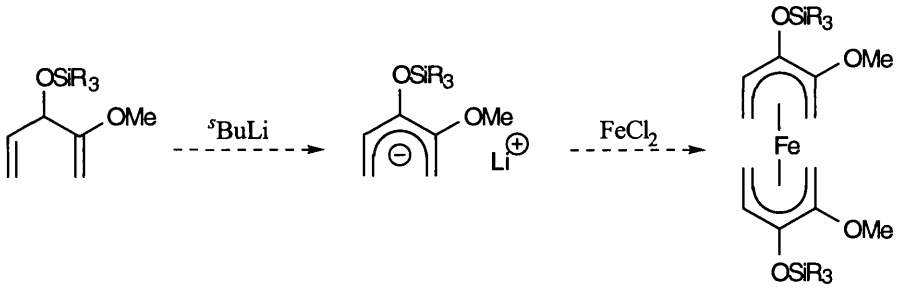
Yamada found that either 1,3 or 1,4-dienes react with alkali metals dispersed in THF in the presence of triethylamine to afford the alkali metal salt.[281,282] Oppolzer *et al.* have since shown that the addition of *sec*-butyllithium to **404** resulted in the formation of the lithium salt **405**.[283]



404 **405**

Scheme 2.37

From these observations and in the knowledge that methyl vinyl ethers are stable to basic media, we hoped that treatment of **406** with *sec*-butyllithium and iron(II) would result in the formation of the open ferrocene structure **408**. This would then permit a study of the proposed metal-mediated [5+2] cycloaddition.

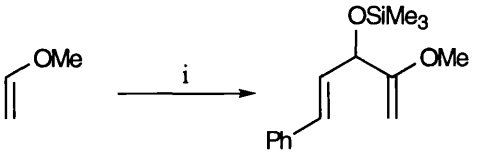


406 **407** **408**

Scheme 2.38

2.4.2 Approaches Towards the Synthesis of a Model [5+2] Precursor

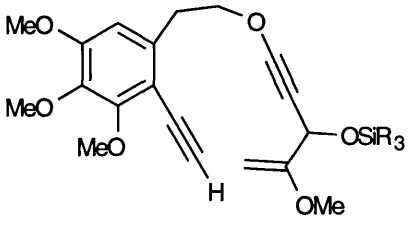
The synthesis of a model of the desired pentadiene was achieved by treating the vinyllithium formed from the reaction of *tert*-butyllithium and methyl vinyl ether (**409**) at -78°C with cinnamaldehyde. Quenching the reaction mixture with trimethylsilylchloride afforded the pentadiene, which was found to be stable to chromatography on silica, in 52% yield.



409 **410**

i) ^{t}BuLi, THF, -78°C, then *trans*-cinnamaldehyde, THF, -20°C to r.t., then TMSCl, r.t. (52%).

Scheme 2.39

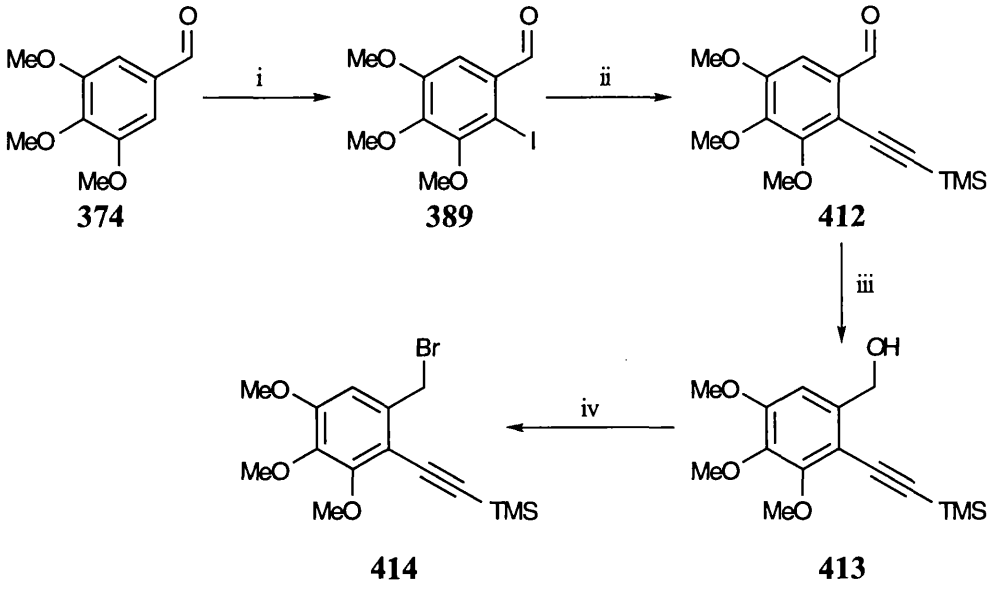


411

Figure 2.9

The ether analogue **411** was designed as the target for our [5+2] cyclisation studies. This contains a pentenyne structure, thereby permitting formation of a product with a higher degree of unsaturation. The starting material for the synthesis of **411** is 3,4,5-trimethoxybenzaldehyde, which was converted to the aldehyde **389** using iodine and stoichiometric silver trifluoroacetate, as before. A Heck/Castro type coupling reaction between the aldehyde (**389**) and trimethylsilylacetylene using palladium(II) acetate and copper(I) iodide as catalysts afforded aldehyde **412** in 70% yield. As with

other Heck-type palladium-mediated couplings, the active catalyst is believed to be a palladium(0) species, formed *in situ* from the palladium(II) acetate by reduction and co-ordination with triphenylphosphine. The aldehyde **412** was reduced to the alcohol **413** in excellent yield (94%) using lithium aluminium hydride, and conversion to the bromide **414** was achieved by reaction with carbon tetrabromide and triphenylphosphine. The use of freshly sublimed carbon tetrabromide and recrystallised triphenylphosphine was found to be essential for the clean conversion of **413** to **414**.

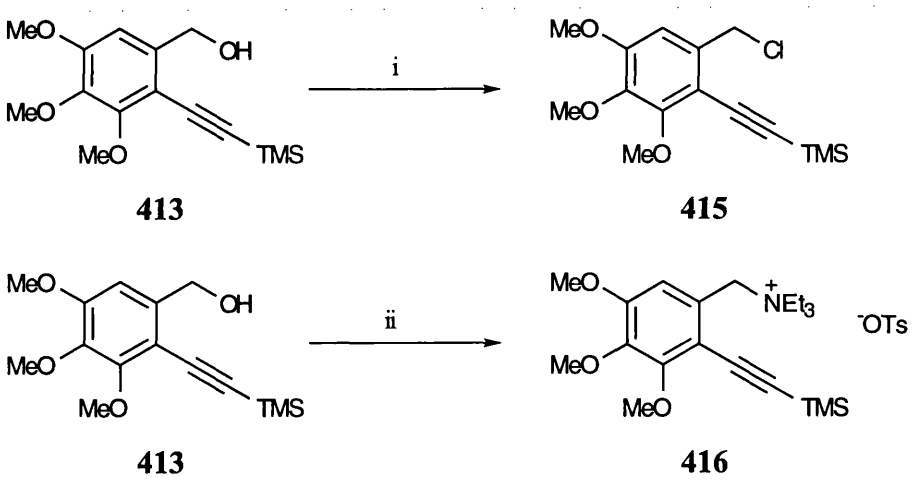


i) $AgOCOCF_3$, I_2, DCM, r.t. (85%); ii) TMSC≡CH (4eq), $Pd(OAc)_2$ (5mol%), CuI (5mol%), PPh_3 (20mol%), Et_2NH, reflux (70%); iii) $LiAlH_4$ (1.4eq), Et_2O, reflux (94%); iv) CBr_4 (2.2eq), PPh_3 (2.2eq), Et_2O, r.t. (94%).

Scheme 2.40

To our initial surprise, all attempts to convert the alcohol (**413**) to other leaving groups led to unexpected products. Reaction of **413** with methanesulfonyl chloride and triethylamine gave rise to an unusually efficient chloride anion displacement of the intermediate mesylate to afford the chloride **415**. A similar result was obtained when **413** was treated with *p*-toluenesulfonyl chloride and triethylamine, but in this

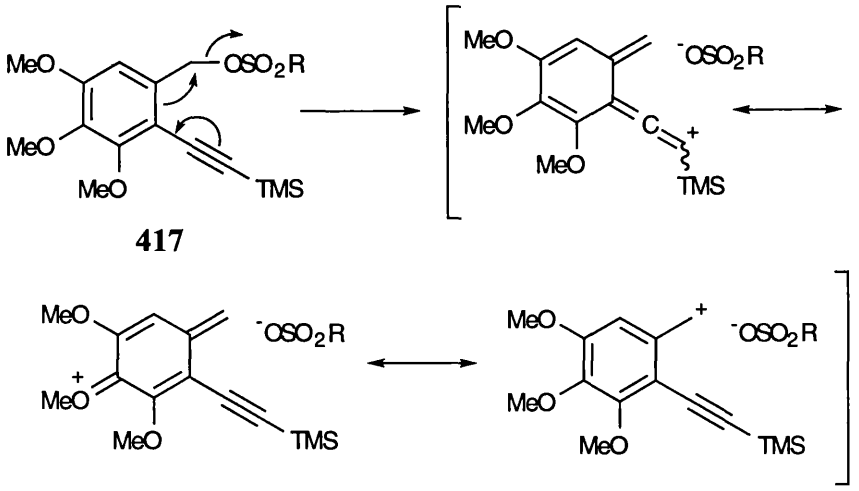
case the product appeared to be the result of displacement of the tosylate by triethylamine to afford the ammonium salt **416**.



i) MsCl, Et_3N, DCM (41%); ii) TsCl, Et_3N, DMAP, DCM (78%)

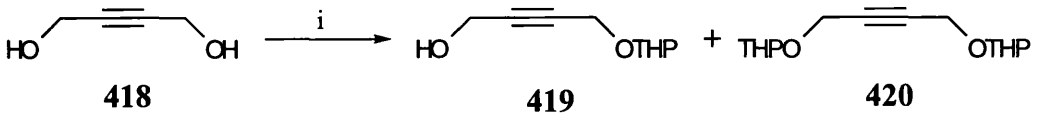
Scheme 2.41

These observations suggest that the high electron density around the aromatic ring will stabilise the formation of a benzylic cation. Furthermore, the acetylinic residue *ortho* to the benzylic alcohol can also be responsible for this stabilisation by π participation, as indicated in scheme 2.42.



Scheme 2.42

Reaction of 2-butyne-1,4-diol with 1.2 equivalents of dihydropyran and 10mol% of pyridinium *p*-toluenesulfonate afforded the alcohol **419** in 49% yield together with 37% of the bis-protected compound **420**.

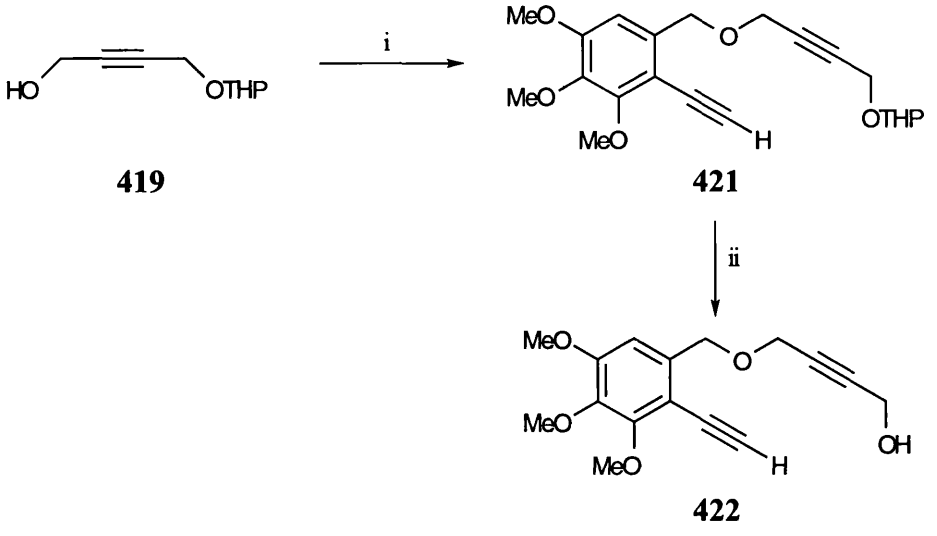


418 **419** **420**

1) dihydropyran (1.2eq), ppts (10mol%), DCM, r.t. (**419** 49%, **420** 37%).

Scheme 2.43

Alcohol **419** was then treated with sodium hydride and the bromide (**414**) to give ether **421**, in which the trimethylsilyl group has been removed. Since a "catalytic" amount of hydroxide ion might be generated by the reaction of sodium hydride with the residual water in the solvent, removal of the TMS group is feasible. Removal of the THP protecting group was then achieved in excellent yield (98%) by the addition of catalytic *p*-toluenesulfonic acid to afford the alcohol **422**.



419 **421** **422**

i) NaH, DMF, r.t., then **414** (0.72eq), DMF r.t. (55%, based on **414**); ii) *p*-TsOH (0.4eq), MeOH, r.t. (98%).

Scheme 2.44

It was anticipated that oxidation of **422** to the aldehyde would permit formation of our target molecule **411**, using the same conditions devised for the synthesis of the pentadiene **410** (see scheme 2.39). However, due to the very small quantities of **422** that were available and its relative instability we were unable to complete this synthesis. Further study may permit the construction of the [5+2] precursor and complexation to a suitable metal, although this was a purely speculative approach and may benefit from the study of much simpler systems. In the light of concurrent ongoing work in the enediyne ketone Bergman approach however (*vide infra*), no further work was carried out on these systems.

2.5 Investigation of the Cycloaromatisation Approach

The third approach to the synthesis of colchicine *via* a novel variant of the Bergman cyclisation was the focus of the majority of our work. As such, this approach will constitute the largest section of this chapter.

2.5.1 Background and Strategy

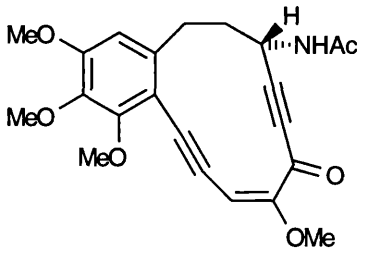
The cycloaromatisation of enediynes and enyne-allenes is known for the construction of five and six-membered ring systems (*vide supra*). However, less attention has been focused on the construction of rings of other sizes. Appropriately, Meyer and Sondheimer, in the first observation of the cycloaromatisation of highly unsaturated macrocycles, reported the formation of the tricyclic compound **2** which embodies the seven-membered ring azulene system.[2]

423 **2**

Scheme 2.45

Based on this observation, construction of the appropriate macrocycle would therefore allow formation of other seven-membered aromatic structures, such as tropones and tropolones. Inspired by this thought, and also with an interest in preparing novel unnatural enediyne-like compounds, we decided to approach colchicine by using a Bergman-type cycloaromatisation to construct the tropolonyl C-

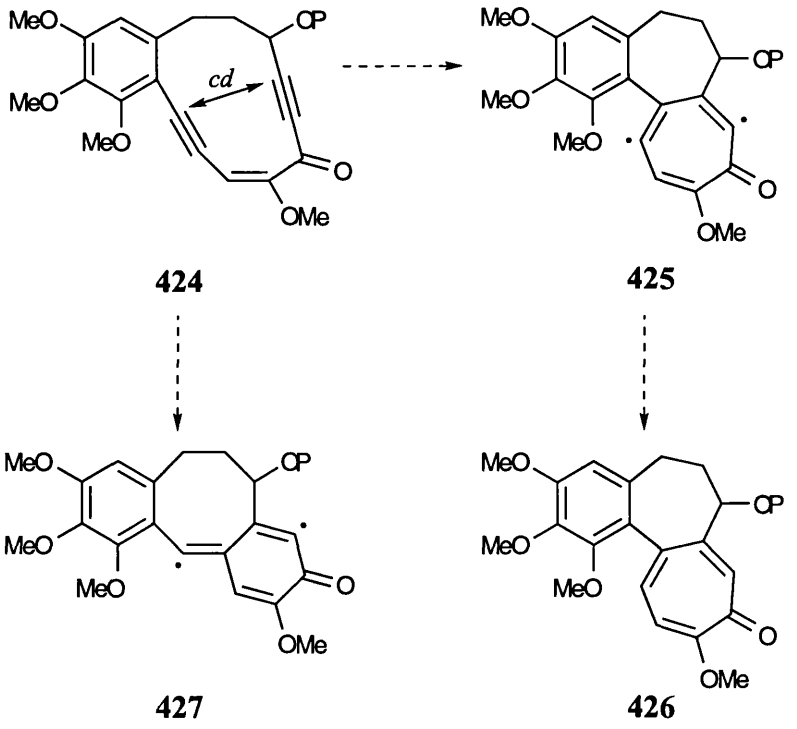
ring. Thus, the 12-membered macrocycle **336** was designed as the target precursor for such a cyclisation.



336

Figure 2.10

Inspection of molecular models suggested that the introduction of an additional benzylic (*Z*)-double bond would increase the proximity of the two acetylenic termini and also confer additional rigidity to the macrocyclic framework. However, it should be noted that the presence of this double bond was found to cause problems in the synthesis of the macrocycle.[268]

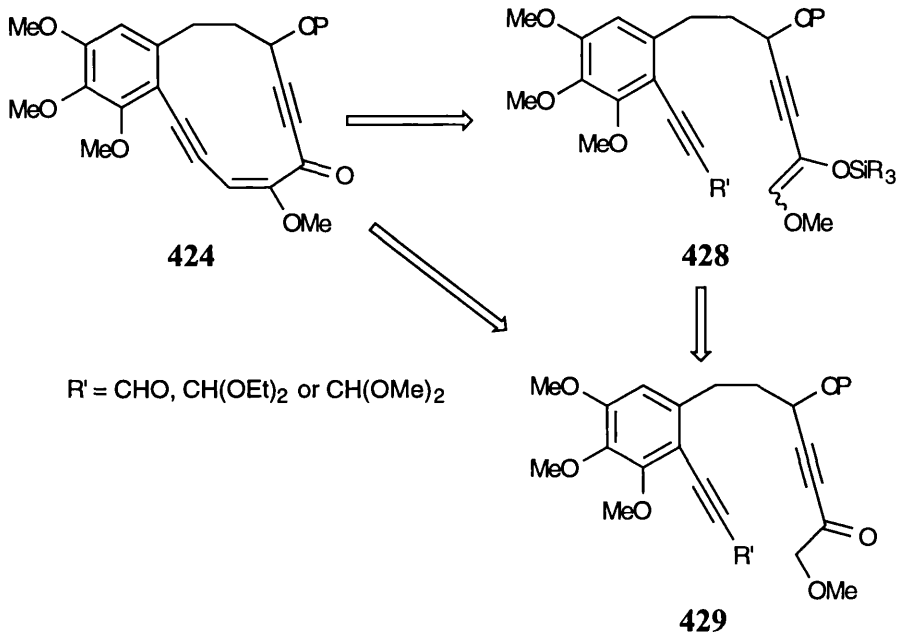


Scheme 2.46

Calculations (MM2, Macromodel 4.0) showed that the *cd* distance of **336** is 3.20Å and that addition of a benzylic (*Z*)-double bond would only increase the strain energy by 17kJ mol^{-1}. Considering the precedent reported by Sondheimer that Bergman cyclisation can give rise to a seven-membered ring (scheme 2.45),[2] and the requirement that the *cd* distance be less than 3.3Å for spontaneous cyclisation at 25°C,[6,7] we anticipated that macrocycle **424** would undergo facile cycloaromatisation either to the desired diradical **425**, or to the doubly benzenoid system **427**.

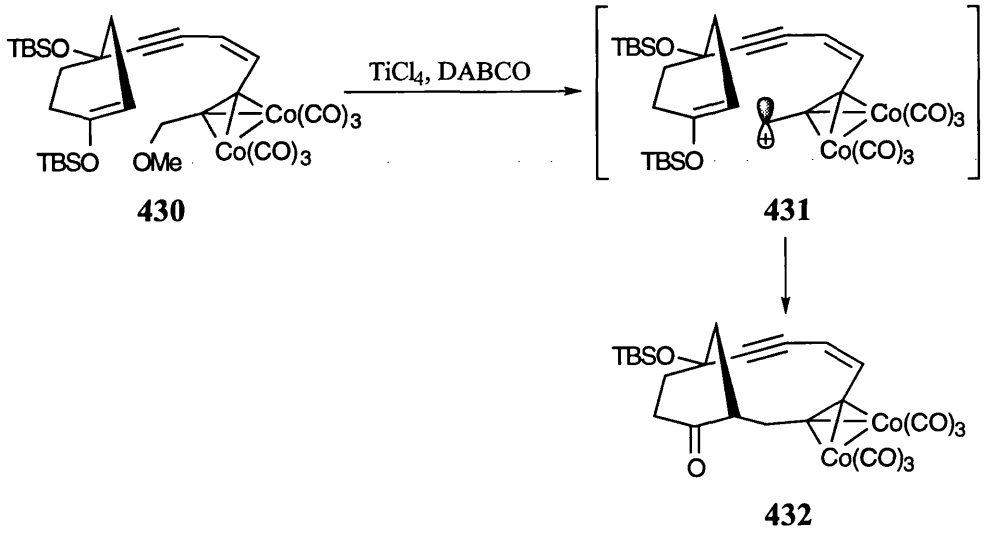
2.5.2 Construction of the Macrocyclic Framework

If we are to consider the macrocycle **424** as our Bergman precursor then several disconnections may be made. As we have seen in the introduction, the prominence of the aldol reaction and its variants in performing macrocyclic ring closures is overwhelming. Thus, we considered the Lewis acid-mediated aldol condensation of **429**, either directly or *via* an isolable silyl enol ether (**428**), as the best option.



Scheme 2.47

It was anticipated that this aldol condensation may be best performed using the dicobalthexacarbonyl complex of the propargyl aldehyde (i.e. R' = CHO). Magnus and co-workers have used extensively titanium(IV) chloride and 4-diazabicyclo-[2.2.2]octane (DABCO) to achieve the cyclisation of dicobalthexa-carbonyl complexes such as **430** using the TBS enol ether moiety to give the macrocyclic ketone **432**.[168-170]

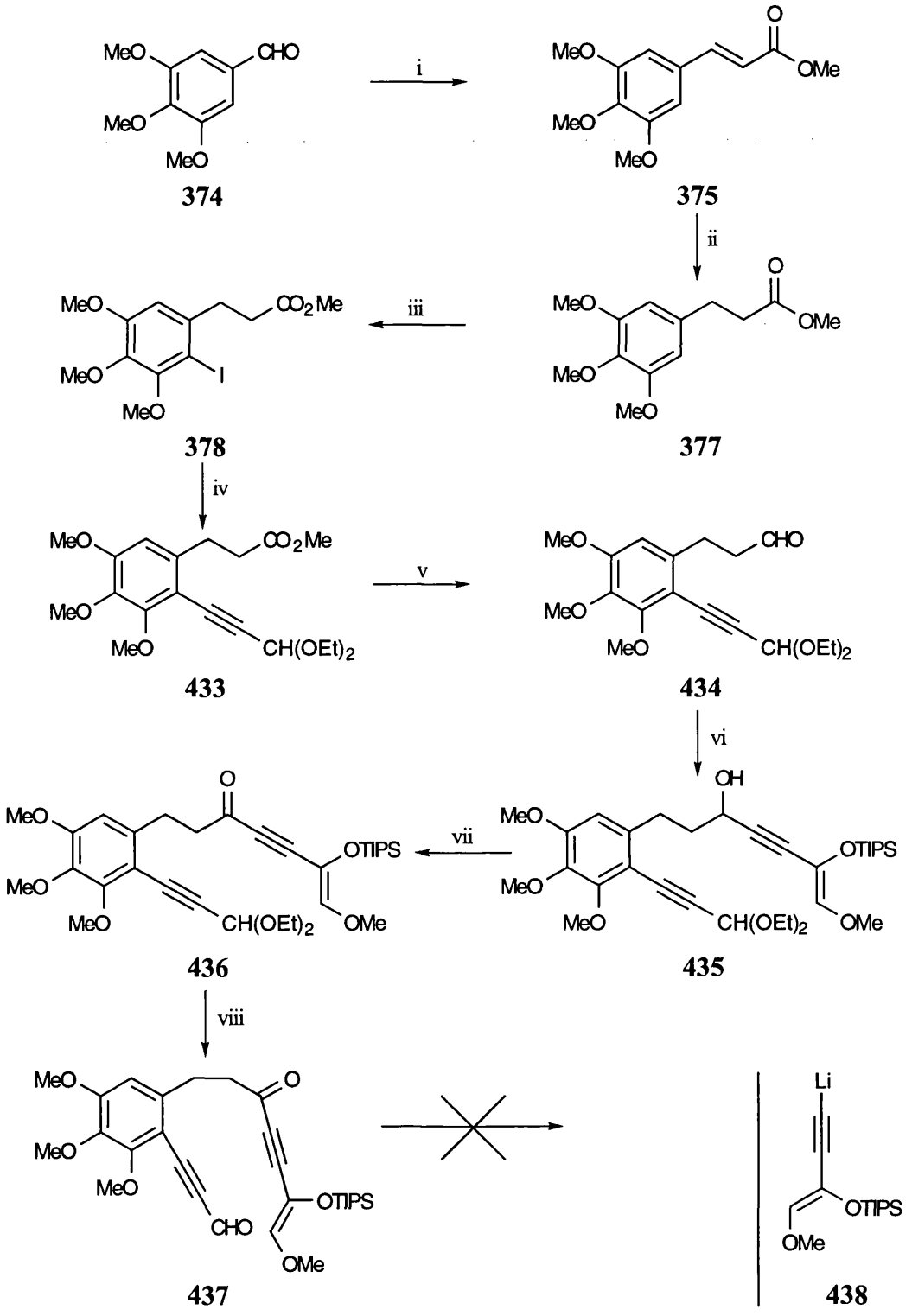


430 **431** **432**

Scheme 2.48

Alternatively the ketone itself may undergo a direct transformation to the macrocyclic enediyne upon treatment with dibutylboron triflate and triethylamine (see scheme 1.67).[176,177] In each case, however, Magnus reports that the corresponding reaction in the absence of the dicobalthexacarbonyl complex does not proceed.

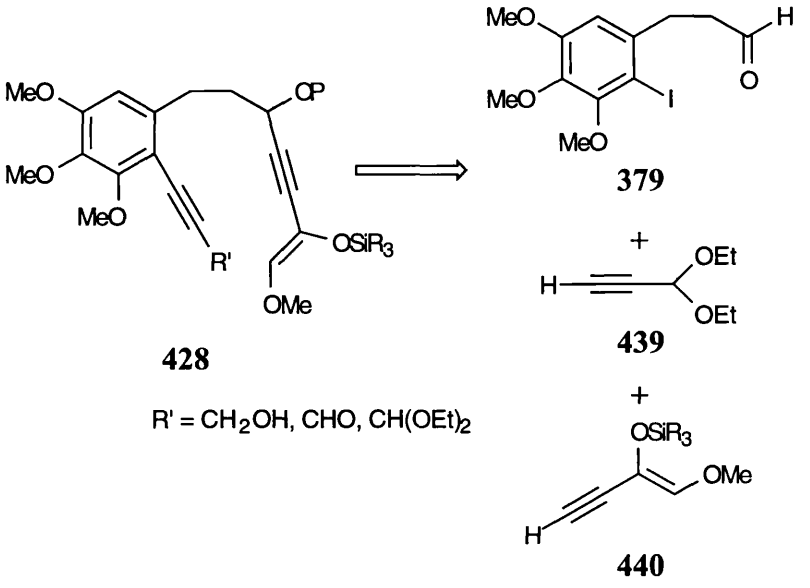
Work already performed in this group developed a synthesis of an advanced precursor to the macrocyclisation (**437**) (scheme 2.49).[268] Unfortunately, all attempts to perform the vital ring-closure were unsuccessful, but this gave a valuable outline of the route which we expected to take.



i) $MeO_2CCH_2PPh_3Br$, 1M NaOH, DCM (93%); ii) H_2, Pd/C, MeOH (97%); iii) CF_3CO_2Ag, I_2, DCM (97%); iv) $Pd(OAc)_2$, CuI, PPh_3, $HC{\equiv}CCH(OEt)_2$, Et_2NH (75%); v) DIBAL-H, PhMe (87%); vi) **438**, THF (83%); vii) MnO_2, DCM (79%); viii) Amberlyst® 15 resin, acetone (48%).

Scheme 2.49

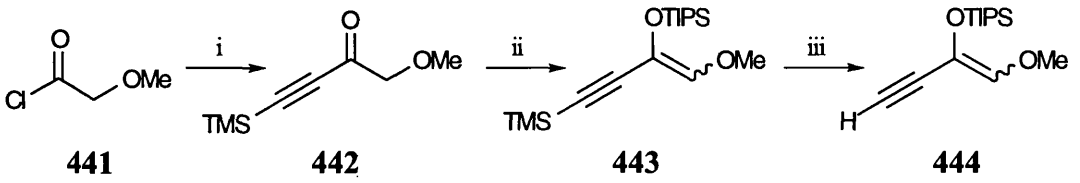
In order to make maximum use of common intermediates it was decided to use the silyl enol ether (**428**) as our aldol precursor. Aldol precursor **428** may be disconnected into three principal fragments, the aldehyde (**379**), the silyl enol ether (**440**) and commercially available propargyl aldehyde diethyl acetal (**439**).



Scheme 2.50

Iodo aldehyde **379** was synthesised in a highly efficient sequence, as previously described in schemes 2.26 and 2.27. For the preparation of the silyl enol ether fragment (**440**), commercially available methoxyacetyl chloride was coupled to tributyl(trimethylsilylethynyl)stannane in the presence of bis-(triphenylphosphine) palladium(II) chloride to afford the alkynone **442** in 74% yield. Formation of the silyl enol ether followed the procedure described by Corey.[284] Thus, the alkynone **442** was treated with triisopropylsilyl triflate (TIPSOTf) and triethylamine to afford **443** as a pair of stereoisomers in 92% yield with a ratio of 20:1 (scheme 2.51). The TIPS group was selected in the anticipation that the trimethylsilyl group at the acetylene terminus could be selectively removed without affecting the silyl enol ether moiety. Indeed, when the silyl enol ether was treated with potassium carbonate in methanol, the trimethylsilyl group was successfully removed to afford the desired terminal

alkyne **444** in excellent yield (91%). However, this terminal acetylene was found to decompose rapidly, and hence was used very soon after preparation.

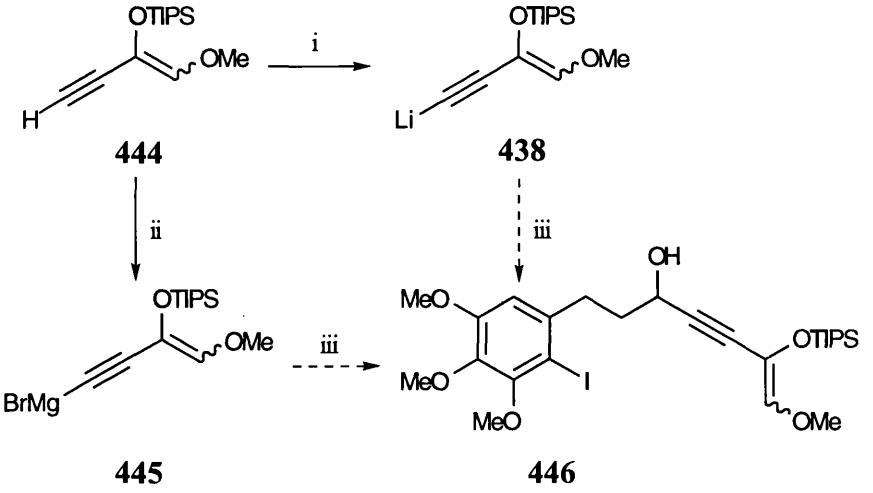


441 **442** **443** **444**

i) $^{n}Bu_3SnC{\equiv}CTMS$ (1.1eq), $Pd(PPh_3)_2Cl_2$ (5mol%), 1,2-DCE, 50°C (74%); ii) TIPSOTf (1.1eq), Et_3N (1.5eq), PhH, r.t. (92%); iii) K_2CO_3, MeOH, r.t. (91%).

Scheme 2.51

The lithium acetylide (**438**) is reported to be generated by treatment of alkyne **444** with *n*-butyllithium at -78°C in THF. The addition of aldehyde **379** at -78°C should then provide the desired alcohol **446**. However, in our hands only decomposition of the starting materials was observed, and attempted syntheses of **446** *via* the alkynyl Grignard **445** also proved unsuccessful.



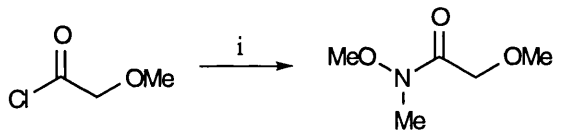
444 **438** **445** **446**

i) ^{n}BuLi, THF, -78°C; ii) EtMgBr, THF, r.t.; iii) **379**, -78°C

Scheme 2.52

As we were to discover later (*vide infra*), addition of a lithium or magnesium base to the aryl iodide results in a deiodination process, and therefore unwanted product mixtures. From these observations, ketone **429** should be installed in a stepwise process, *via* the previously described acetylene (**381**). Synthesis of the ketone might be achieved by formation of the stannyl acetylene and a palladium-mediated coupling of this to methoxyacetyl chloride, as used in the construction of alkynone **442**. However, owing to the presence of an aryl iodide in the molecule, we could expect competitive palladium insertion into the carbon iodine bond giving rise to the highly chelated seven-membered complexes discussed earlier (figure 2.7).

It has been reported that *N*-methoxy-*N*-methylamides combine cleanly with both Grignard reagents and organolithium species in THF to form ketones, without the formation of tertiary alcohols, even when a large excess of organometallic is used.[285] Accordingly, formation of the *N*-methoxy-*N*-methylamide (**447**) was achieved by treatment of methoxyacetyl chloride (**441**) with *N,O*-dimethylhydroxylamine hydrogen chloride salt in the presence of pyridine (scheme 2.53).

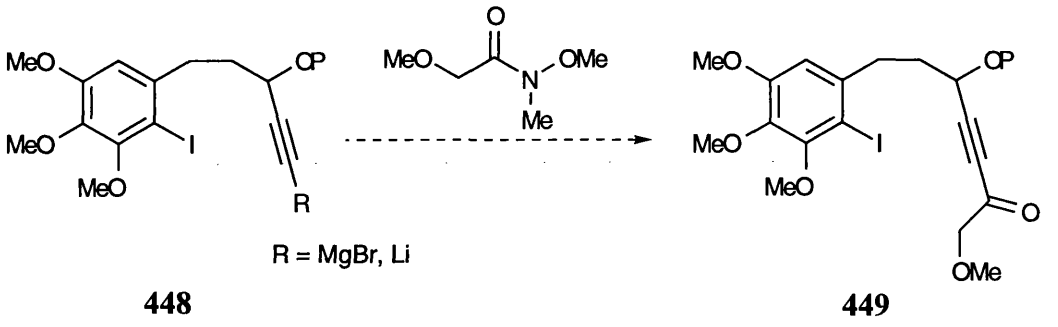


441 **447**

i) *N,O*-dimethylhydroxylamine.HCl (1.1eq), pyridine (2eq), DCM, 0°C to r.t. (58%)

Scheme 2.53

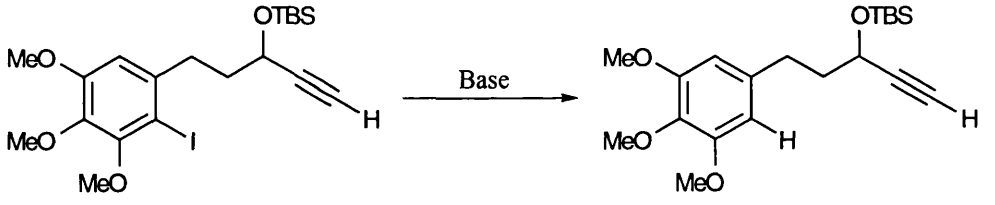
At this stage, it was anticipated that conversion of **381** to the lithiated acetylene with butyllithium or LHMDS would permit addition to the *N*-methoxy-*N*-methylamide (**447**) affording the desired ketone (**449**).



448 **449**

Scheme 2.54

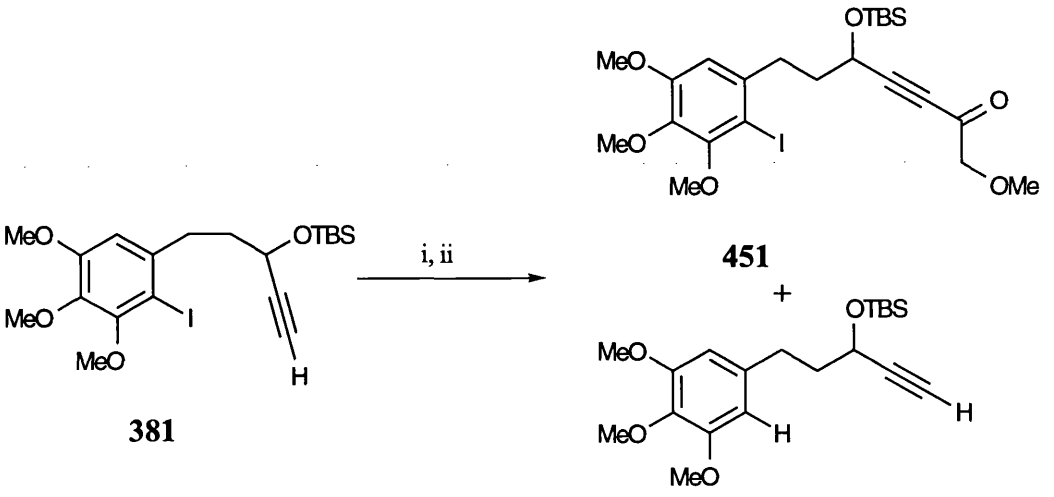
However, using any lithium base, including LDA, resulted in the formation of a new compound, identified as **450**, and performing the reaction at lower temperatures showed that the preferential mode of attack for these bases is a lithium-halogen exchange process. Indeed, none of the desired alkynyllithium was formed in the reaction mixture.



381 **450**

Scheme 2.55

After various reaction conditions had been attempted, it was discovered that treatment of **381** with ethylmagnesium bromide at -10°C and quenching with the amide gave a small quantity of the desired ketone (scheme 2.56). Lowering the temperature to -20°C suppressed any alkynyl Grignard formation, whereas only the deiodinated product was observed at 0°C.



381 **450**

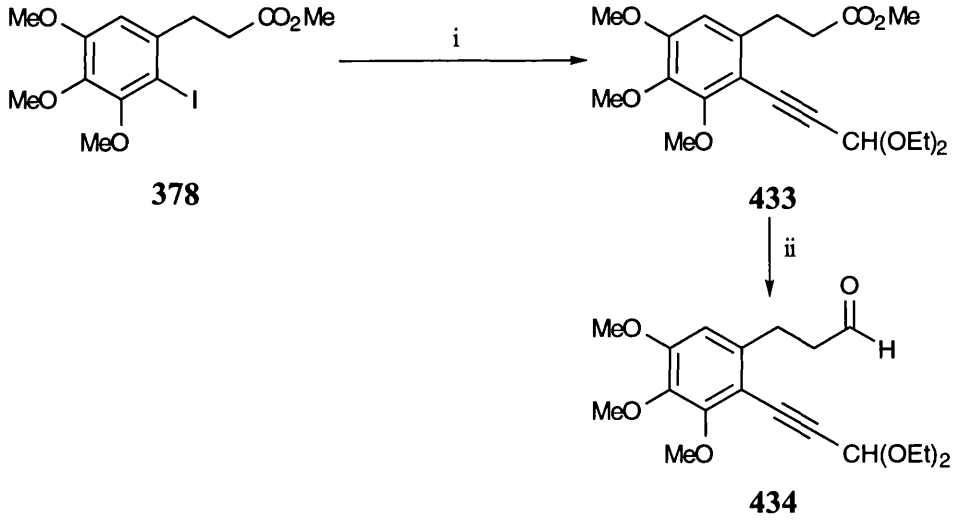
i) EtMgBr (1.1eq), THF, -10°C; ii) **447**, THF, -70°C to r.t. (**450** 14%, **451** 18%)

Scheme 2.56

It was obvious, therefore, that the presence of the iodine at this stage was hindering any useful progress. Efforts were made to couple compound **381** with propargylaldeyde diethyl acetal using a Heck/Castro-type reaction. However, despite attempted utilisation of various palladium catalysts and reaction conditions, no desired coupling products were obtained from the silyl ether (**381**), alcohol **380** or aldehyde **379**. Partial recovery of the starting material was observed if the reaction conditions were mild. As reported in section 2.3.2, the proposed reason for this is the formation of a highly stable seven-membered palladium complex, preventing participation in the catalytic cycle.

It was decided, therefore, to perform the Heck/Castro-type coupling of the acetylene to the aryl iodide at an earlier stage. The commercially available diethyl acetal of propargyl aldehyde was chosen for this addition since the aldol cyclisation onto acetals is well known. In addition, mild conditions exist for the liberation of the aldehyde and subsequent conversion to the alcohol, were this to have proved to be necessary.

Coupling of **439** with aryl iodide **378** gave the highest yield (83%) of the desired ester **433** when performed in the presence of copper(I) iodide, 5mol% of palladium(II) acetate and 20mol% of triphenylphosphine. DIBAL-H reduction at -78°C then afforded the aldehyde (**434**) in 98% yield.

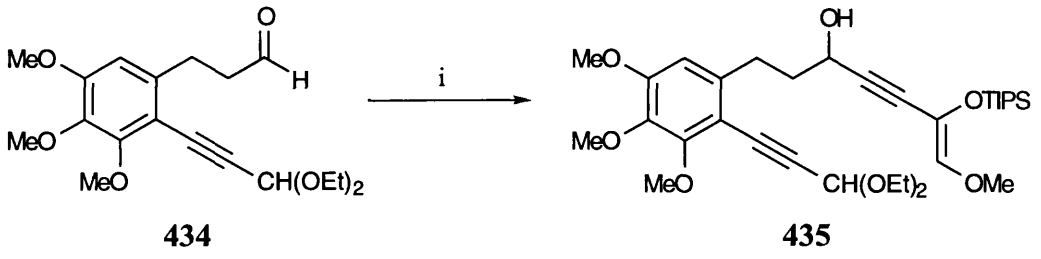


378 **433** **434**

i) $HC{\equiv}CCH(OEt)_2$ (2eq), $Pd(OAc)_2$ (5mol%), CuI (5mol%), PPh_3 (20mol%), Et_2NH, reflux (83%); ii) DIBAL-H (1.1eq), DCM, -78°C (98%);

Scheme 2.57

The key secondary alcohol (**435**), incorporating all the necessary carbon atoms, was then obtained in good yield by treating the aldehyde (**434**) with 1.1 equivalents of alkynyl Grignard **445**.

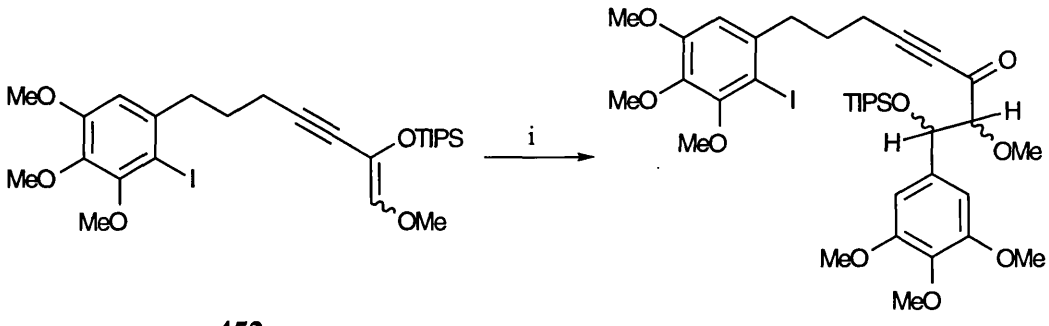


434 **435**

i) **445** (1.1eq), THF, -78°C (82%)

Scheme 2.58

Previous work had shown that reaction of silyl enol ether **452** with titanium(IV) chloride and 3,4,5-trimethoxybenzaldehyde in DCM at -78°C gave an aldol adduct, albeit in low yield (scheme 2.59).[268]



452 **453**

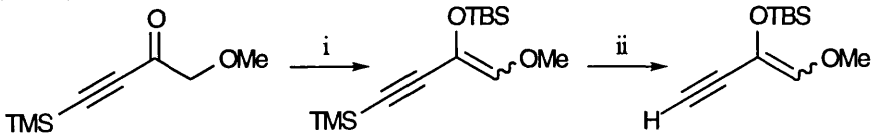
i) **374** (1eq), $TiCl_4$ (1eq), DCM, -78°C; Na_2CO_3 (28%).

Scheme 2.59

It is well documented that acetals may also undergo Lewis acid-promoted aldol reactions with silyl enol ethers[179-181,286-289] and hence attempts were made to cyclise **435** directly. However, treatment of the acetal with TMSOTf at -78°C or -55°C afforded no cyclisation products. The acetal (**435**) decomposed rapidly even at -94°C when titanium(IV) chloride was used as the Lewis acid.

A close examination of the literature revealed, however, that the TIPS enol ether is remarkably stable, whereas the corresponding aldol reactions with TBS enol ethers are commonplace. We therefore decided to alter our tactics by forming the TBS enol ether since this would be more amenable to the conditions we wished to use for the aldol macrocyclisation. Hence, treatment of alkynone **442** with *tert*-butyldimethylsilyl triflate (TBSOTf) in the presence of triethylamine gave the silyl enol ether **454** in 88% yield. In contrast to the results observed with the TIPS enol ether, the product formed in this reaction was a single stereoisomer, although it was not possible to assign the configuration of the double bond. This was successfully

deprotected by the addition of potassium carbonate in methanol to afford a moderate yield (60%) of the unstable terminal alkyne **455**.

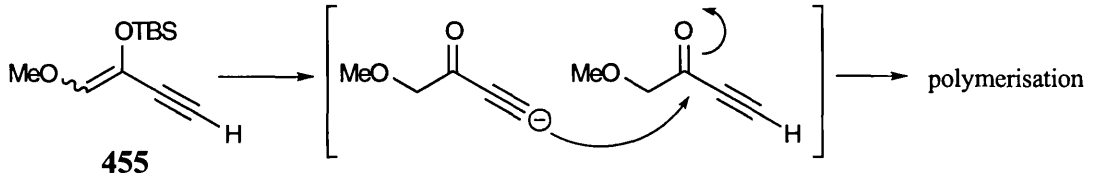


442 **454** **455**

i)TBSOTf (1.1eq), Et_3N (1.5eq), PhH, r.t. (88%); ii) K_2CO_3, MeOH, r.t. (60%).

Scheme 2.60

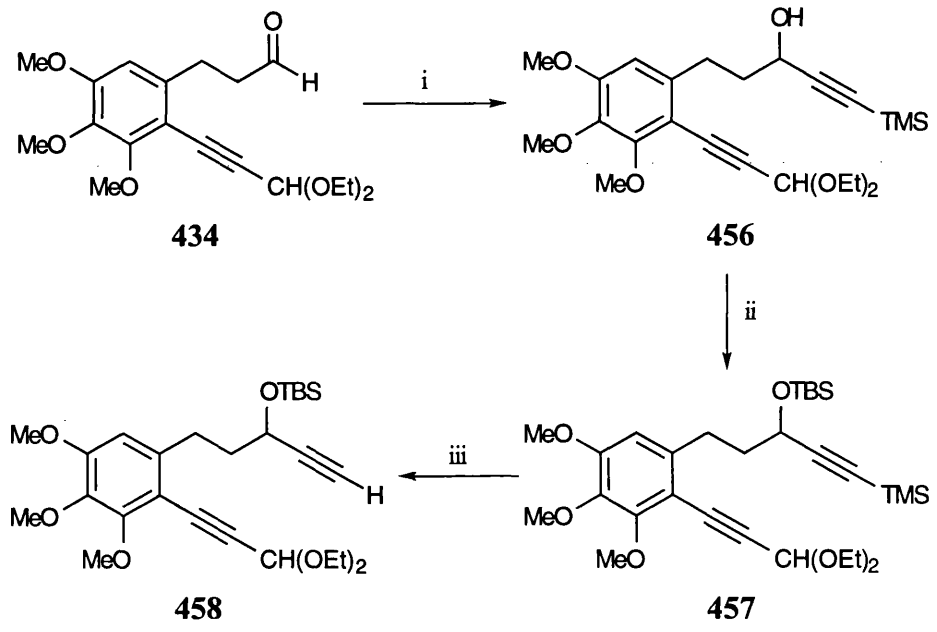
Unfortunately, treatment of the terminal alkyne (**455**) with *n*-butyllithium at -78°C resulted in rapid decomposition of the starting material. This is probably due to the relative lability of the TBS enol ether compared to the TIPS enol ether (**444**). The 'naked' acetylide anion might undergo 1,2-addition to the parent alkynone immediately after generation leading to polymerisation (scheme 2.61).



455

Scheme 2.61

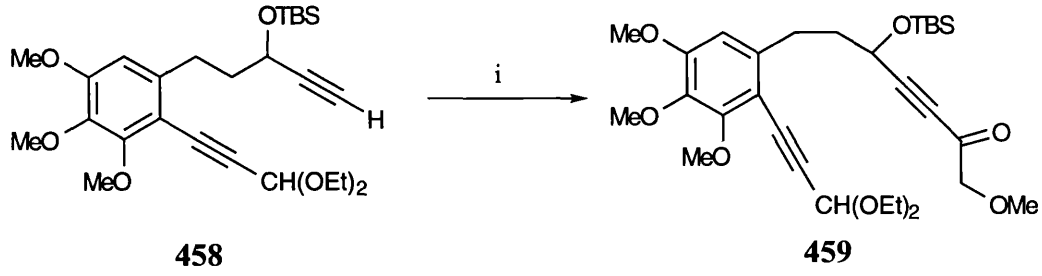
These results led us back to our linear strategy for the formation of the aldol precursor *via* the *N*-methoxy-*N*-methylamide (**447**). Addition of TMS acetylide to the aldehyde **434** was followed by protection and deprotection as before, to afford the target terminal acetylene (**458**) in 69% yield from **434**.



i) BrMgC≡CTMS (2eq), -78°C to r.t. (77%); ii) TBSCl, imidazole, cat. DMAP, r.t. (93%); iii) K_2CO_3, MeOH, r.t. (97%).

Scheme 2.62

Conversion of **458** to the alkynylmagnesium bromide at room temperature followed by addition of the *N*-methoxy-*N*-methylamide **447** proceeded smoothly to afford the desired alkynyl ketone **459** in good yield (76%).

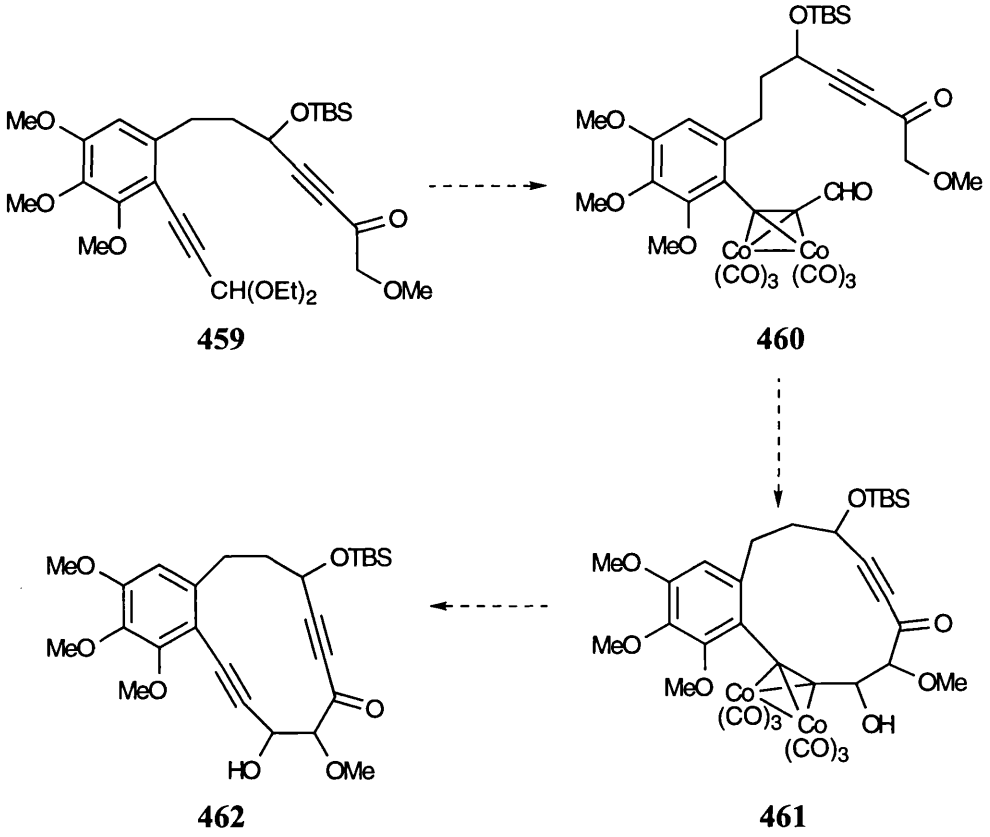


i) EtMgBr (1.2eq), THF, -78°C to r.t., then **447**, THF, -78°C to r.t. (76%).

Scheme 2.63

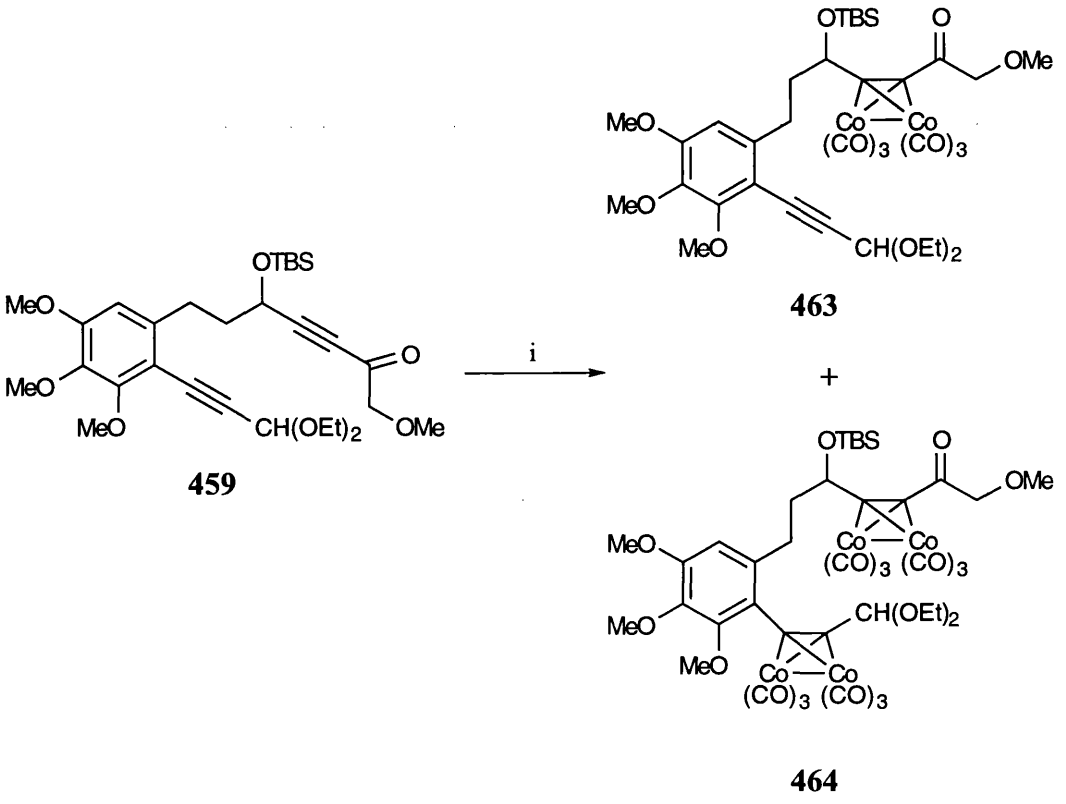
The stage was now set for a study of the proposed aldol ring closure upon which our synthetic strategy depended. Initially, we wished to construct the macrocycle in a manner as close to the literature methods as possible and therefore we selected the η^2-

dicobalthexacarbonyl assisted aldol ring closures pioneered by Magnus (*vide supra*). We anticipated that complexation of the least hindered alkyne to cobalt carbonyl followed by conversion to the aldehyde would permit the aldol cyclisation shown in scheme 2.64. The major difference between our substrate and those reported by Magnus (see scheme 1.67) is the presence of the methoxy group α- to the ketone. Dehydration of **462** would then furnish our desired Bergman cyclisation precursor.



Scheme 2.64

In the event, however, treatment of the ketone **459** with cobalt carbonyl afforded a mixture of two complexed products. Identification was hindered by the fact that the infra-red absorption bands of the two alkynes in the starting material overlap and so the disappearance of only one is very hard to observe. However, both alkynes have a single proton in the α-position, which resonated at slightly lower field when the alkyne was complexed. This permitted the identification of the two products as **463** and **464**, afforded in 58% and 33% yield respectively.



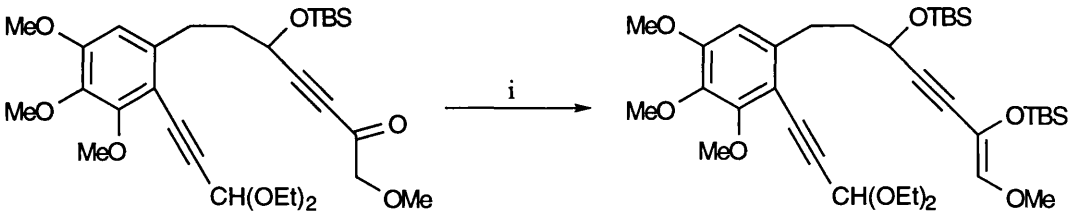
i) $Co_2(CO)_8$ (1.1eq), benzene, r.t. (**463** 58%, **464** 33%).

Scheme 2.65

We were disappointed that the preferential site of attack for the cobalt carbonyl appeared to be the undesired northern alkyne. We therefore decided to construct the silyl enol ether prior to complexation, in the hope that the increased steric bulk and reversed electronics around the northern alkyne would direct complexation to the benzylic triple bond. Alkynone **442** readily formed the TBS enol ether upon addition of triethylamine and TBSOTf, but these conditions resulted in no reaction of **459**. Butyllithium was found to be too strong a base, resulting in decomposition of the starting material. Treatment of **459** with LDA and quenching with TBSCl gave a novel material which has yet to be identified.

However, it was found that by treating **459** with one equivalent of potassium bis(trimethylsilyl)amide (KHMDS) the potassium enolate was successfully formed

and could be quenched by the addition of TBSCl to afford a 77% yield of the desired silyl enol ether (**465**).

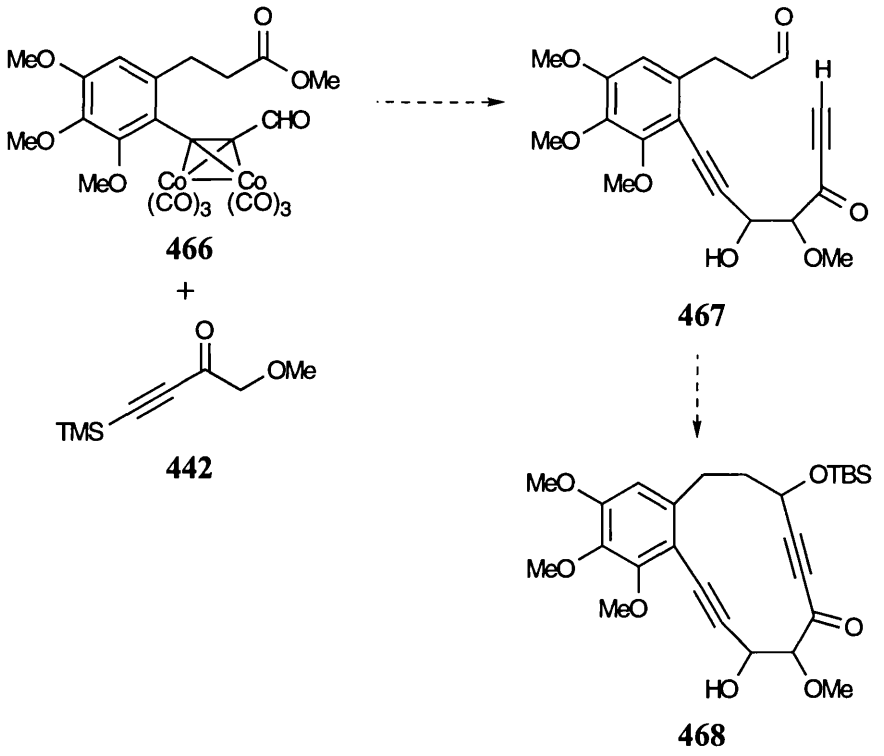


459 **465**

i) KHMDS, Et_2O, -78°C, then TBSCl, Et_2O, r.t. (77%)

Scheme 2.66

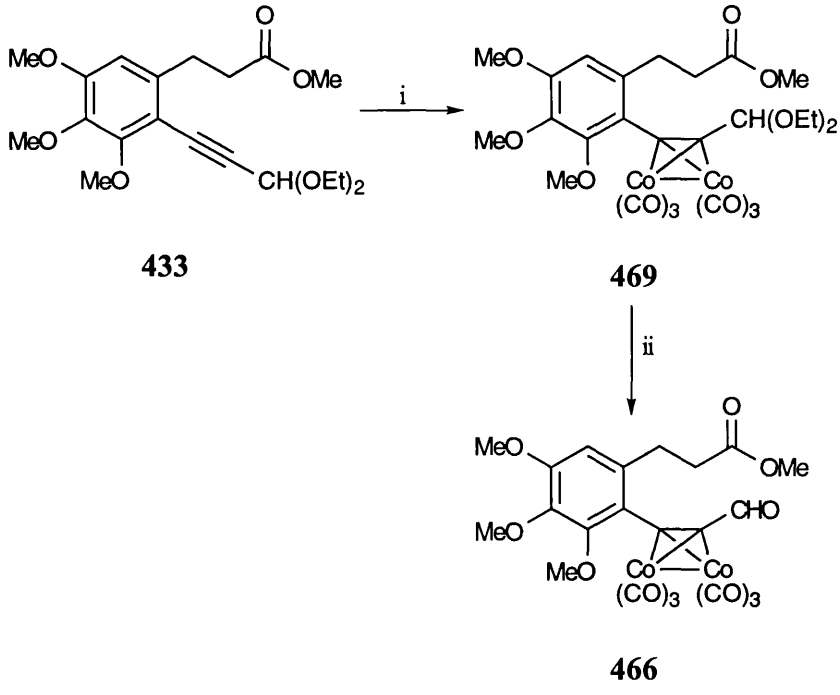
Unfortunately, treatment of **465** with dicobalt octacarbonyl again resulted in a mixture of products, although the presence of the cobalt in the mixture caused broadening of the proton signals in the ^1H NMR, and so the products could not be identified. Adapting the approach, we decided to concentrate on performing the



Scheme 2.67

intermolecular η^2-dicobalthexacarbonyl assisted aldol condensation between **466** and **442**. Ring-closure could then be performed by an intramolecular cyclisation of an acetylide onto an aldehyde. Precedent for such a macrocyclic ring closure may be found in schemes 1.69 to 1.72 (*vide supra*).

Treatment of **433** with dicobalt octacarbonyl in benzene at room temperature afforded the desired complex **469** in excellent yield (97%). This could then be deprotected to the aldehyde by stirring in acetone over Amberlyst® 15 resin (scheme 2.68).

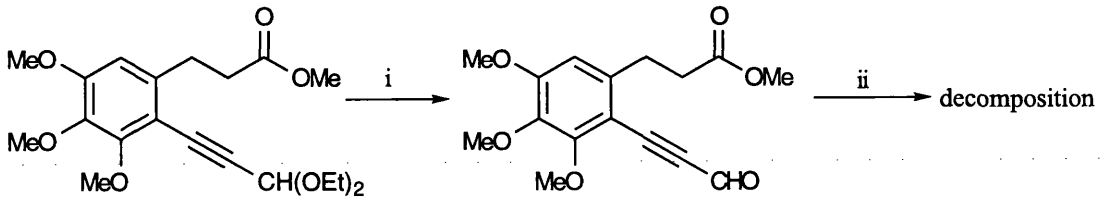


433 **469** **466**

i) $Co_2(CO)_8$ (1.1eq), benzene, r.t. (97%); ii) Amberlyst® 15 resin, acetone, r.t. (89%).

Scheme 2.68

It is interesting to note that deprotection of **433** with Amberlyst® 15 resin afforded the aldehyde in a more modest 60% yield. Attempted complexation of **470** resulted in the formation of a complex mixture from which no identifiable products could be isolated.

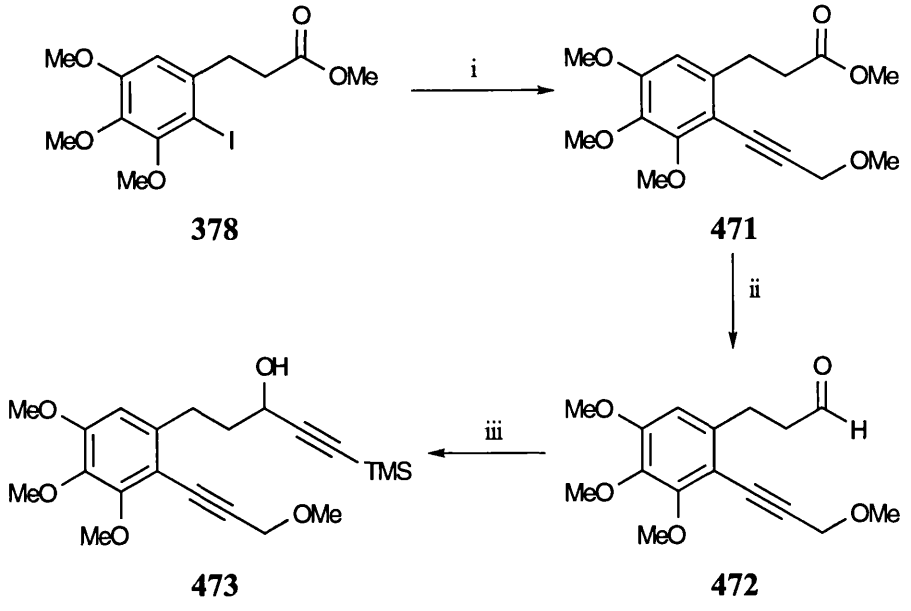


433 **470**

i) Amberlyst® 15 resin, acetone, r.t. (60%); ii) $Co_2(CO)_8$ (1.1eq), benzene, r.t. (see text).

Scheme 2.69

We also wished to explore the potential of the aldol condensation of a ketone or silyl enol ether onto a dicobalthexacarbonyl-complexed methyl propargyl ether. Thus, palladium-mediated coupling of methyl propargyl ether with aryl iodide **378**, afforded the aryl acetylene (**471**) in 73% yield. This was reduced to the aldehyde and converted to the propargyl alcohol as shown in scheme 2.70. It should be noted, however, that the yields from these reactions were not as high as those achieved for the diethyl acetal and so the product was not taken any further at this stage.

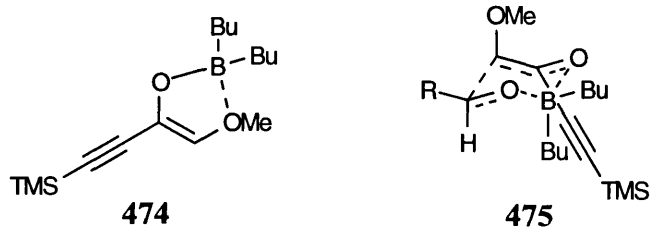


378 **471** **472** **473**

i) HC≡CCH$_2$OMe (2eq), Pd(OAc)$_2$ (5mol%), CuI (5mol%), PPh$_3$ (20mol%), Et$_2$NH, reflux (73%); ii) DIBAL-H (1.1eq), DCM, -78°C (83%); iii) BrMgC≡CTMS (2eq), -78°C to r.t. (59%).

Scheme 2.70

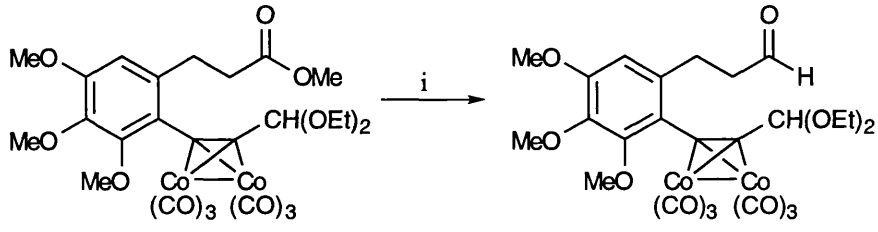
The intermolecular aldol condensation of **466** with the alkynone **442** followed the procedure reported for the intramolecular reaction by Magnus.[175] Formation of the boron enolate was performed by addition of the ketone to a solution of dibutylboron triflate and triethylamine at -78°C. After 5 minutes a solution of the aldehyde was added, but no reaction was observed. Leaving the ketone to stir for longer and at elevated temperatures had no effect on the outcome of this reaction. It is reasoned that the boron enolate formed in the reaction mixture is "locked" by the α-methoxy group as shown in figure 2.11. The co-ordination sites on the boron are then all occupied, preventing co-ordination to the aldehyde and thus hindering the formation of the necessary six-membered transition state for the aldol reaction (**475**).



474 **475**

Figure 2.11

As the cobalt complexes appeared to be relatively stable it was decided to investigate the construction of the remainder of the aldol precursor from **469**. Although it was possible to perform the DIBAL-H reduction of the ester moiety in the presence of the dicobalthexacarbonyl complex, the yield was very low (26%) and isolation of the product proved difficult.

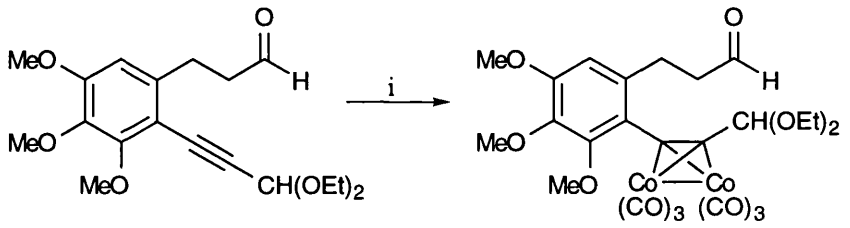


469 **476**

i) DIBAL-H (1.1eq), DCM, -78°C (26%).

Scheme 2.71

Although complexation of aldehyde **434** to dicobalt octacarbonyl proceeded in higher yield (68%), difficulties were experienced in product isolation and the reactions were giving more complex mixtures. This may be a result of the decomposition of cobalt carbonyl over time, but at this stage we decided to attempt the cyclisation of **465** without the electronic and geometrical assistance of the dicobalthexacarbonyl complex.

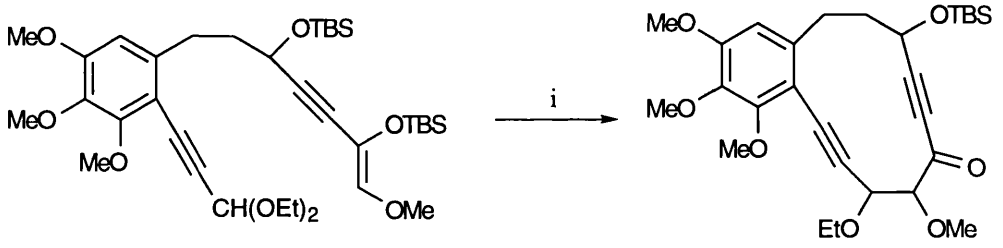


434 **476**

i) $Co_2(CO)_8$, benzene, r.t. (68%).

Scheme 2.72

Gratifyingly, treatment of a highly dilute DCM solution of the silyl enol ether with one equivalent of titanium(IV) chloride gave the macrocycle **477** in good yield (67%).



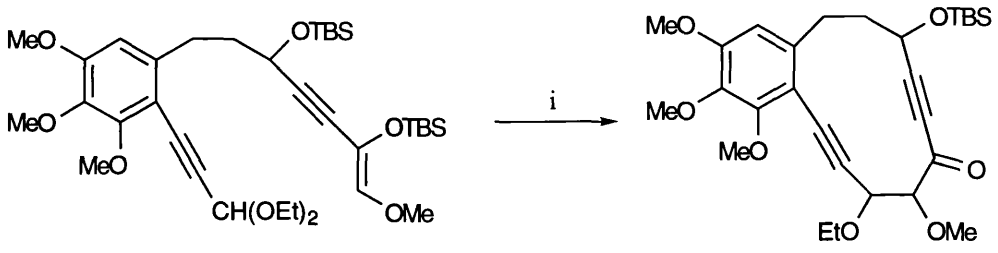
465 **477**

i) $TiCl_4$ (1eq), DCM, -78°C; Na_2CO_3 (67%).

Scheme 2.73

Noyori *et al.* have reported that trimethylsilyl triflate (TMSOTf), a milder Lewis acid then titanium(IV) chloride, can also be used as a catalyst in the aldol reaction between acetals and TMS enol ethers.[182,290] Treatment of a dilute ethereal solution of **465**

with 10mol% of TMSOTf at -40°C was therefore attempted and afforded the desired macrocycle **477** in an excellent 88% yield, thus establishing the complete outer carbon connectivity required.



465 **477**

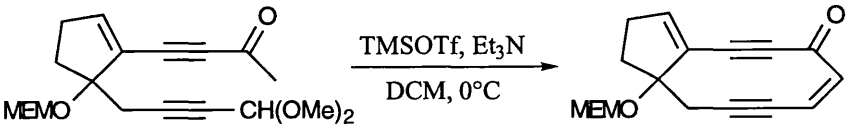
i) TMSOTf (10mol%), Et_2O, -40°C; H_2O (88%).

Scheme 2.74

Four pairs of diastereomers are created in this reaction and initial study of the ^1H NMR data for **477** shows that there is no selectivity. This was not unexpected, but made identification of the product somewhat problematic. The appearance of a strong absorption band at 1679cm^{-1} in the infra red spectrum was encouraging, and the presence of new resonances at 4.61-4.52ppm in the ^1H NMR spectrum are indicative of the protons at C-4 and C-5. The molecular composition is confirmed by both high resolution mass spectrometry and combustion analysis. Given the remarkably high yield from this macrocyclisation no attempts have yet been made towards its optimisation, although the reaction has proved to be reproducible on three occasions.

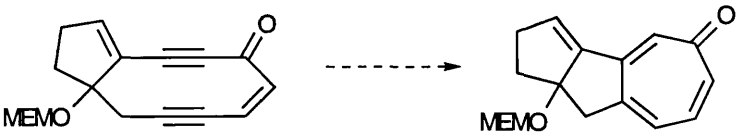
It was interesting to note that the reaction of ketone **478** with 1.5 equivalents of TMSOTf in the presence of 1.1 equivalents of triethylamine at 0°C is reported by Krebbs *et al.* to afford the α,β-unsaturated enediyne ketone macrocycle **479**.[178] The enediyne ketone is an important intermediate in the synthesis of dienediyne models of neocarzinostatin, and as such was not the subject of an cyclisation studies itself. However, it would be of interest to our approach to colchicine to discover whether

479 may be cycloaromatised to the tricyclic tropone-containing structure **480** (scheme 2.76).



478 **479**

Scheme 2.75



479 **480**

Scheme 2.76

Unfortunately, treatment of **459** with 1.5 equivalents of TMSOTf in the presence of 1.1 equivalents of triethylamine at 0°C only gave decomposition products. The proposed mechanism for this reaction involves the aldol reaction affording the macrocycle, followed by spontaneous elimination of methanol under the reaction conditions. However, treatment of **465** with 1.1 equivalents of TMSOTf at 0°C gave rise to a new product which could not be visualised at 254nm but showed clearly at 366nm on the tlc plate.

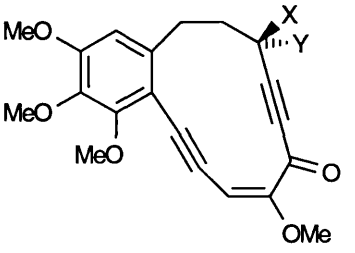
The mass spectrum of this new compound indicates a clear molecular ion with a mass of 342, which would correspond with the loss of ethanol, as anticipated, but also loss of the methyl vinyl ether and the TBS protecting group. Under the very acidic reaction conditions it might be expected that the methyl vinyl ether would be cleaved, and concentration of the compound under these acidic conditions prior to column chromatography may lead to alcohol deprotection. The infra-red spectrum also supports this structure, with strong absorption bands at 3416cm^{-1}, indicating an alcohol, and 1644cm^{-1}, indicating increased unsaturation around the carbonyl. The

formation of a tropolone structure may be ruled out by the lack of absorption at 350nm in the UV spectrum.

To our dismay, the ^{1}H NMR spectrum shows that the compound is not purified satisfactorily by simple column chromatography, and the presence of resonances at 3.90, 3.83, 3.80 and 3.39ppm would suggest that there are still four distinct methoxy groups, indicating that the methyl vinyl ether is still intact, and contradicting the mass spectrum. Unfortunately, HPLC was not able to provide a suitably pure sample for detailed ^{1}H NMR analysis. It appears that we have a jigsaw for which the pieces do not match, thus obscuring our view of the complete picture, so it is with regret that we report no definitive answer as to the structure of this intriguing compound.

2.5.3 Conclusions

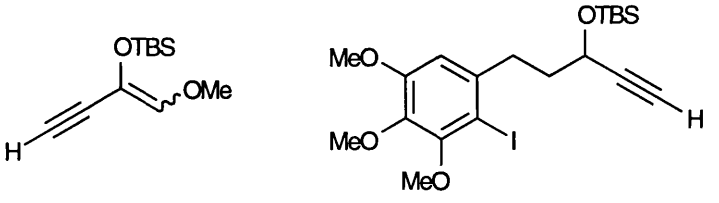
The above section constitutes the major studies which were undertaken on the investigation of the synthesis of colchicine. Although the synthesis of the macrocycles **336** and **424** was not completed the results obtained give a valuable insight into the construction of the macrocyclic framework. These results are summarised briefly below, and the optimised route to the macrocycle can therefore be set out as shown in scheme 2.77.



336 X = H, Y = NHAc
424 X,Y = H, O, OH, NHAc

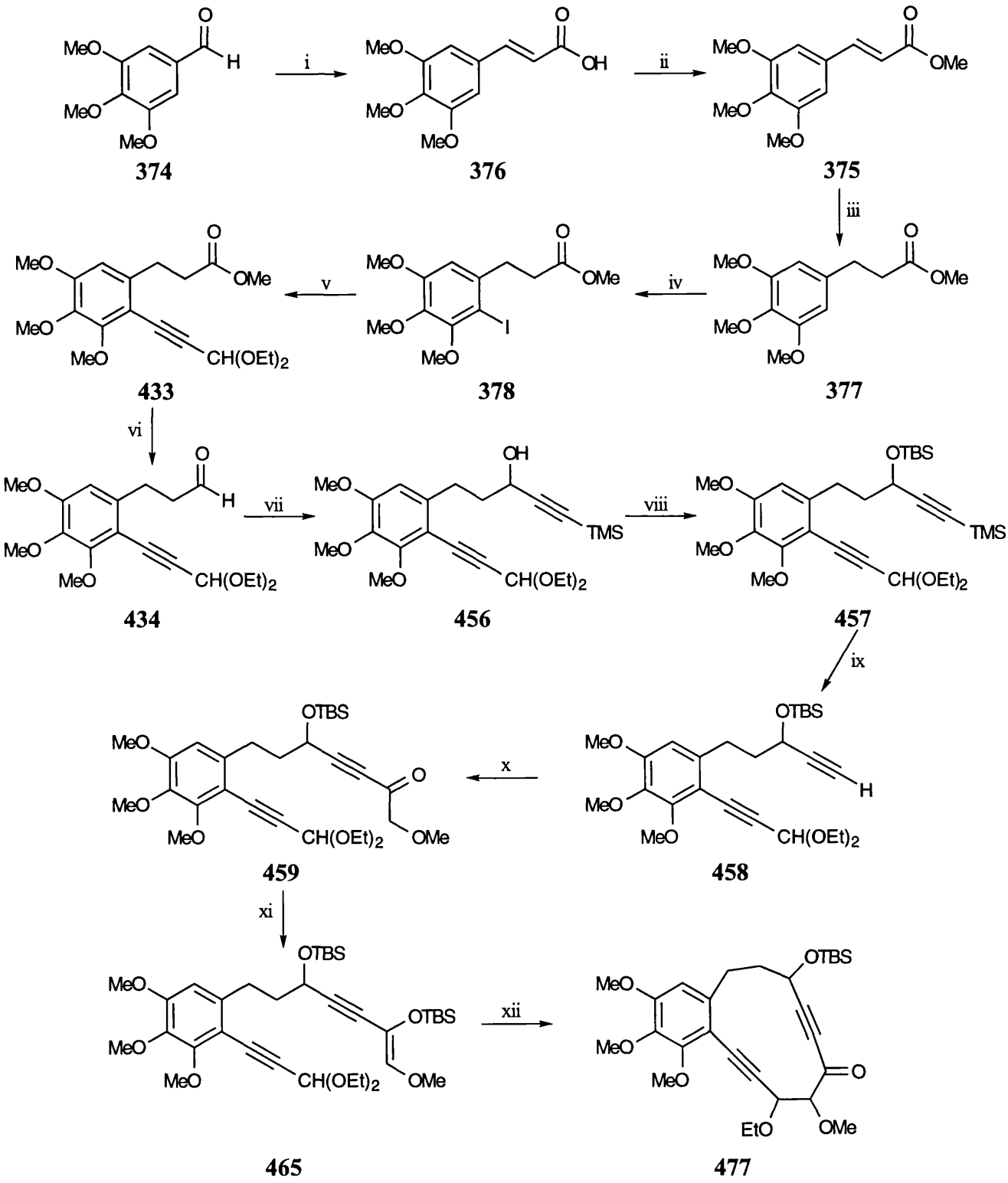
Figure 2.12

Problems were encountered with the construction of the northern half of the macrocyclic framework, particularly in the formation of acetylide anions **444** and **381**. This was overcome by employing a more linear strategy for construction of the macrocyclic precursor and performing the palladium-mediated coupling with propargyl aldehyde diethyl acetal prior to incorporation of the other alkyne group.



444 **381**

Figure 2.13

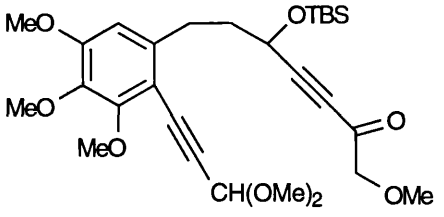


i) Malonic acid, cat. piperidine, pyridine, reflux (88%); ii) AcCl, MeOH, reflux (87%); iii) H_2, Pd/C, MeOH, r.t. (87%); iv) CF_3CO_2Ag, I_2, DCM, r.t. (86%); v) $HC{\equiv}CH(OEt)_2$, cat. $Pd(OAc)_2$, cat. CuI, cat. PPh_3, Et_2NH, reflux (83%); vi) DIBAL-H, DCM, -78°C (98%); vii) $BrMgC{\equiv}CTMS$, -78°C to r.t. (77%); viii) TBSCl, imidazole, cat. DMAP, r.t. (93%); xi) K_2CO_3, MeOH, r.t. (97%); x) EtMgBr, THF, -78°C to r.t., then **447**, THF, -78°C to r.t. (76%); xi) KHMDS, Et_2O, -78°C, then TBSCl, Et_2O, r.t. (77%); xii) cat. TMSOTf, Et_2O, -40°C, then H_2O (88%).

Scheme 2.77

Careful study of the literature gave us concern that a TIPS enol ether is notoriously stable and would not be suitable for the aldol condensation. We have, however, demonstrated the successful construction of an unsaturated 12-membered ring system (**477**) *via* an intramolecular Noyori type aldol condensation of a *tert*-butyldimethylsilyl enol ether onto a diethyl acetal in very high yield.

The formation of a new compound bearing aromatic protons gave encouragement to our proposed cycloaromatisation of enediyne ketones to afford tropolonic products. It is obvious that in order to prove the existence of such a cyclisation, the intermediate enediyne ketone must first be isolated and fully characterised. Based on work presented in the literature, the intramolecular aldol condensation of a ketone onto a dimethyl acetal may provide a cleaner route to the enediyne ketone. Thus, the construction of dimethyl acetal **481** and its cyclisation should be the focus of any future work.



481

Figure 2.14

The analogous aldol condensation onto the free aldehyde to afford an alcohol product should also not be overlooked. This would permit conversion of the alcohol into a suitable leaving group, such as a mesylate, which, upon elimination, could afford the enediyne ketone (**424**).

CHAPTER THREE

EXPERIMENTAL

3.1 General Procedures

^{1}H and ^{13}C NMR spectra were recorded at 400MHz and 100MHz respectively on a Varian VXR-400 instrument. Residual protic solvent, i.e. $CHCl_3$ (δ_H=7.26ppm; δ_C=77.0ppm), was used as the internal standard. Coupling constants were measured in Hertz (Hz) and chemical shifts in ppm relative to the internal reference. Infra red spectra were recorded in wavenumbers (cm^{-1}), using sodium chloride plates or a potassium bromide disc as appropriate, on a Perkin Elmer 1605 FT-IR spectrophotometer. Mass spectra were recorded on VG 12 253 and VG ZAB-e instruments by EI and CI with NH_3 carrier gas, by the EPSRC mass spectrometry service. FAB spectra were run on a VG 7070 instrument at UCL, or on a VG ZAB-SE double focusing spectrometer by the ULIRS. Accurate mass measurements were recorded by the ULIRS on a VG micromass 305 instrument by EI and on a VG ZAB-SE double focusing spectrometer by FAB. Microanalyses were performed by the UCL chemistry department microanalytical laboratory. Melting points were recorded on a Kofler hot stage or on a Gallenkamp melting point apparatus using sealed capillary tubes, and are uncorrected.

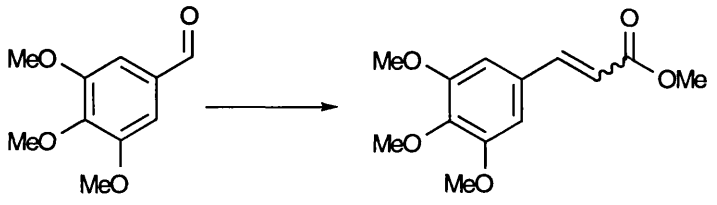
Analytical thin layer chromatography (tlc) was performed on pre-coated glass or aluminium-backed plates (Merck Kieselgel 60 F_{254}, 2mm) and visualised using ultra violet light (254 or 366nm), iodine, potassium permanganate [add 62.5g of Na_2CO_3 in water (1.25L) to 12.5g of $KMnO_4$ in water (1.25L)], or acidic ammonium molybdate(IV) [concentrated H_2SO_4 (250mL), ammonium molybdate.$4H_2O$ (125g), water (2.25L)] as appropriate. Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh).

'Petrol' refers to petroleum ether, boiling range 40-60°C, which was distilled prior to use. Diethyl ether (referred to as ether)and tetrahydrofuran, where used as solvents,

were distilled from sodium-benzophenone ketyl. Dichloromethane was distilled from phosphorus pentoxide; acetone from 4Å molecular sieves; *N,N*-dimethylformamide, trimethylsilyl chloride, diethylamine, and triethylamine from calcium hydride; pyridine from sodium hydroxide; methanol and ethanol from magnesium turnings; and toluene and benzene from sodium. Unless specified, all reactions were performed under a dry nitrogen atmosphere, and removal of solvents was carried out under reduced pressure (15-20mmHg). All glassware was flame dried under a stream of nitrogen immediately prior to use. Purchased chemicals are named as indicated on the labels and used without further purification.

3.2 Preparation of Individual Compounds

Preparation of methyl 3-(3,4,5-trimethoxyphenyl)propenoate[246] (375).



374 **375**

To a 1M solution of sodium hydroxide (10mL) was added (carbomethoxymethyl) triphenylphosphonium bromide (782mg, 1.88mmol) and a solution of 3,4,5-trimethoxybenzaldehyde (400mg, 1.24mmol) in dichloromethane (10mL). The reaction mixture was stirred at room temperature for 5 hours, then poured onto water (30mL) and extracted with dichloromethane (2 ×10mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 50% ether in petrol) afforded the product (300mg, 64%) as an inseparable mixture of the *E* and *Z*-isomers (2:1 by ^1H NMR).

m.p. 97-98°C (ether/DCM) (lit. 95.5-97°C[246]);

R_f (ether) 0.48;

ν_{max} (KBr)/cm^{-1} 2944, 2838, 1700, 1634, 1582, 1506, 1460, 1421, 1338, 1287, 1249, 1128, 1005, 818;

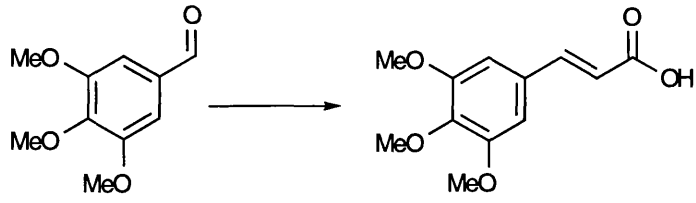
δ_H(400MHz; $CDCl_3$) 7.57 (1H, d, J=15.4Hz, ArC*H*CH), 6.72 (2H, s, aromatic), 6.30 (1H, d, J=15.4Hz, ArCHC*H*), 3.85 (6H, s, MeO), 3.78 (3H, s, MeO), 3.68 (3H, s, MeO);

δ_C(100MHz; $CDCl_3$) 167.4, 153.4, 144.8, 144.5, 129.8, 117.0, 105.2, 60.9, 56.1, 51.7;

LRMS (FAB mode): *m/z* 252 (100%, M^+), 237, 221;

HRMS (FAB mode): Found: M^+, 252.0998. $C_{13}H_{16}O_5$ requires *M*, 252.0994.

Preparation of *(E)* 3-(3,4,5-trimethoxyphenyl)propenoic acid (376).



374 **376**

In a 500mL round-bottomed flask fitted with a condenser and thermometer was placed 3,4,5-trimethoxybenzaldehyde (25g, 0.13mol), malonic acid (26.5g, 0.25mol) and pyridine (50mL). This was heated with stirring until the malonic acid had dissolved (~50°C) and then piperidine (1.9mL, 0.02mmol) was added. The resultant solution was heated to 80°C for 1 hour and then to reflux for 4 hours. On cooling, the reaction mixture was poured onto water (500mL) and precipitated with concentrated hydrochloric acid (62.5mL). The product was removed by filtration and dried in benzene (250mL) under Dean and Stark conditions to give *(E)* 3-(3,4,5-trimethoxyphenyl) propenoic acid (27.3g, 88%) as white crystals.

m.p.126-127°C (ether/petrol);

R_f (ether) 0.31;

ν_{max} (KBr)/cm^{-1} 3069, 2654, 1686, 1625, 1578, 1501, 1448, 1396, 1343, 1278, 1114, 990, 826;

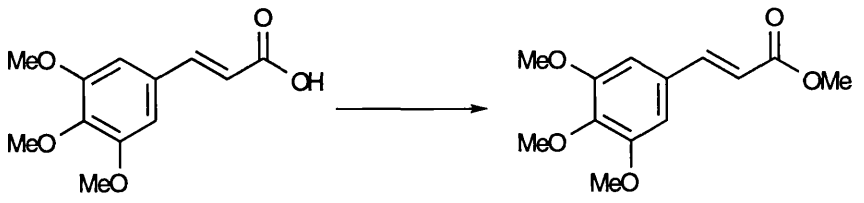
δ_H(400MHz; $CDCl_3$) 7.78 (1H, d, J=16.5Hz, ArC*H*CH), 6.85 (2H, s, aromatic), 6.44 (1H, d, J=16.5Hz, ArCHC*H*), 3.90 (9H, s, MeO);

δ_C(100MHz; $CDCl_3$) 173.5, 171.6, 153.4, 147.0, 129.4, 116.3, 105.5, 61.0, 56.2;

LRMS (FAB mode): *m/z* 238 (75%, M^+), 221, 176, 154, 136, 107;

HRMS (FAB mode): Found: M^+, 238.0841. $C_{12}H_{14}O_5$ requires *M*, 238.0845.

Preparation of *(E)* methyl 3-(3,4,5-trimethoxyphenyl)propenoate (375).



376 **375**

Acetyl chloride (20mL, 0.28mol) was added over a period of 5 minutes to methanol (125mL) with rapid stirring at room temperature (CARE: vigorous reaction, very exothermic). To this solution was added *(E)* 3-(3,4,5-trimethoxyphenyl)propenoic acid (27.3g, 0.11mol) and the resultant solution heated to reflux for 2 hours. On cooling the reaction mixture was concentrated *in vacuo* and the product recrystallised from ethyl acetate / petrol to give (*E*) methyl 3-(3,4,5-trimethoxyphenyl)propenoate (24g, 87%) as white crystals.

m.p. 97-98°C;

R_f (ether) 0.48;

ν_{max} (KBr)/cm^{-1} 2944, 2838, 1700, 1634, 1582, 1506, 1460, 1421, 1338, 1287, 1249, 1128, 1005, 818;

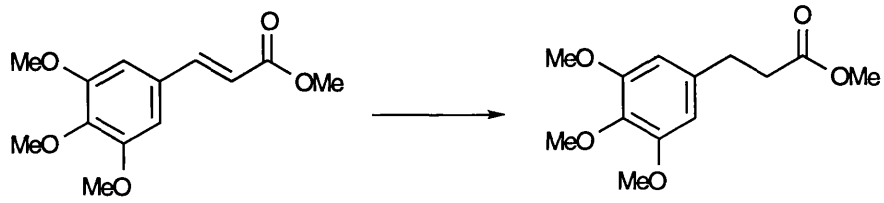
δ_H(400MHz; $CDCl_3$) 7.57 (1H, d, J=15.4Hz, ArC*H*CH), 6.72 (2H, s, aromatic), 6.30 (1H, d, J=15.4Hz, ArCHC*H*), 3.85 (6H, s, MeO), 3.78 (3H, s, MeO), 3.68 (3H, s, MeO);

δ_C(100MHz; $CDCl_3$) 167.4, 153.4, 144.8, 144.5, 129.8, 117.0, 105.2, 60.9, 56.1, 51.7;

LRMS (FAB mode): *m/z* 252 (100%, M^+), 237, 221;

HRMS (FAB mode): Found: M^+, 252.0998. $C_{13}H_{16}O_5$ requires *M*, 252.0994.

Preparation of methyl 3-(3,4,5-trimethoxyphenyl)propanoate[242] (377).



375 377

Methyl 3-(3,4,5-trimethoxyphenyl)propenoate (20.0g, 79.4mmol) was added to methanol (210mL) and warmed until it completely dissolved. Under a purge of nitrogen, 10% palladium on carbon (500mg) was added and then hydrogen passed through the vessel for 30 minutes. The reaction mixture was stirred at room temperature under a low positive pressure of hydrogen for 1.5 hours, flushed with nitrogen and then filtered. Concentration *in vacuo* afforded a yellow oil (17.6g, 87%) which crystallised on standing.

m.p. 42-45°C (ether/petrol) (lit. oil[242]);

R_f (ether) 0.50;

ν_{max} (KBr)/cm^{-1} 3008, 2940, 2840, 1733, 1593, 1509, 1462, 1424, 1370, 1332, 1285, 1244, 1124, 1003, 832;

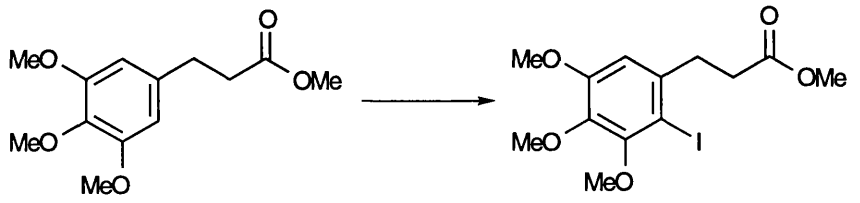
δ_H(400MHz; $CDCl_3$) 6.42 (2H, s, aromatic), 3.85 (6H, s, MeO), 3.82 (3H, s, MeO), 3.68 (3H, s, MeO), 2.90 (2H, t, J=8.7Hz, Ar$CH_2$$CH_2$), 2.63 (2H, t, J=8.7Hz, Ar$CH_2$$CH_2$);

δ_C(100MHz; $CDCl_3$) 173.2, 153.1, 136.3, 105.3, 105.1, 60.8, 56.0, 51.7, 35.8, 31.3;

LRMS (FAB mode): *m/z* 254 (100%, M^+), 240, 223, 181, 176, 154, 136, 107;

HRMS (FAB mode): Found: M^+, 254.1154. $C_{13}H_{18}O_5$ requires *M*, 254.1150.

Preparation of methyl 3-(2-iodo-3,4,5-trimethoxyphenyl)propanoate (378).



377 **378**

To a suspension of the ester (**377**) (17.6g, 69.1mmol) and silver trifluoroacetate (16.8g, 76.1mmol) in dichloromethane (150mL) at room temperature was added, dropwise with stirring, a solution of iodine (19.3g, 76.1mmol) in dichloromethane (350mL) over 3 hours. The red solution obtained was filtered and the filtrate washed successively with saturated sodium thiosulfate solution (100mL), water (100mL) and saturated sodium bicarbonate solution (100mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give a yellow oil (22.5g, 86%), which crystallised on standing overnight.

m.p. 40-42°C (ether/petrol);

R_f (80% ether in petrol) 0.71;

ν_{max} (KBr)/cm^{-1} 2940, 2844, 1736, 1562, 1479, 1381, 1280, 1171, 1097, 851, 804;

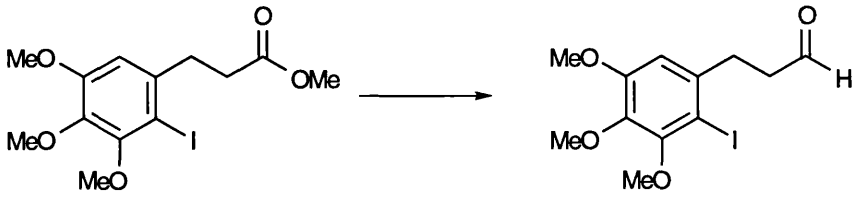
δ_H(400MHz; $CDCl_3$) 6.66 (1H, s, aromatic), 3.85 (3H, s, MeO), 3.82 (3H, s, MeO), 3.81 (3H, s, MeO), 3.68 (3H, s, MeO), 3.03 (2H, t, J=7.9Hz, $ArCH_2CH_2$), 2.59 (2H, t, J=7.9Hz, $ArCH_2CH_2$);

δ_C(100MHz; $CDCl_3$) 173.0, 153.6, 153.1, 140.5, 138.7, 108.9, 87.8, 60.9, 60.7, 56.1, 51.7, 36.2, 34.4;

LRMS (EI mode 70eV): *m/z* 380 (58%, M^+), 307, 253, 211;

HRMS (EI mode 70eV): Found: M^+, 380.0121. $C_{13}H_{17}IO_5$ requires *M*, 380.0125.

Preparation of 3-(2-iodo-3,4,5-trimethoxyphenyl)propanal (379).



378 **379**

Ester (**378**) (1.51g, 4.0mmol) was dissolved in dichloromethane (20mL) and cooled to -78°C. To this was added, dropwise, DIBAL-H (2.9mL of a 1.5M solution in toluene, 4.4mmol) and the resultant solution stirred at -78°C for 75 min. The reaction mixture was poured onto 2M hydrochloric acid (20mL) and extracted with dichloromethane (3 ×10mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, 50% ether in petrol) to afford the aldehyde (**379**) (1.01g, 73%) as a pale yellow oil.

R_f (70% ether in petrol) 0.47;

ν_{max} (thin film)/cm^{-1} 2936, 2846, 2722, 1722, 1582, 1561, 1480, 1387, 1330, 1240, 1199, 1105, 1006, 924, 804;

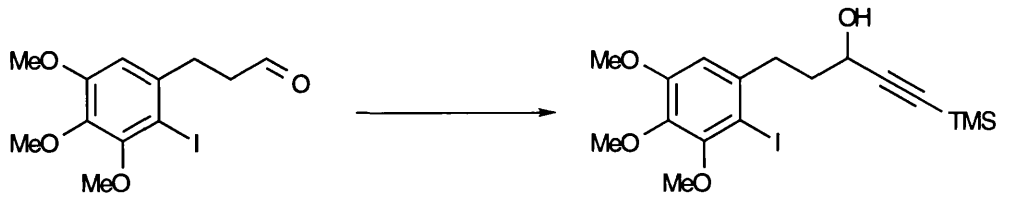
δ_H(400MHz; $CDCl_3$) 9.80 (1H, s, C*H*O), 6.64 (1H, s, aromatic), 3.83 (3H, s, MeO), 3.81 (6H, s, MeO), 3.03 (2H, t, J=7.0Hz, Ar$CH_2$$CH_2$), 2.76 (2H, t, J=7.0Hz, Ar$CH_2$$CH_2$);

δ_C(100MHz; $CDCl_3$) 201.5, 153.6, 153.2, 140.5, 138.7, 109.1, 109.0, 87.7, 60.9, 56.1, 44.1, 33.4;

LRMS (FAB mode): *m/z* 350 (32%, M^+), 333, 321, 307, 224, 207, 195, 181, 165, 151, 136, 121;

HRMS (FAB mode): Found: M^+, 350.0015. $C_{12}H_{15}IO_4$ requires *M*, 350.0010.

Preparation of 3-hydroxy-5-(2-iodo-3,4,5-trimethoxyphenyl)-1-trimethylsilyl-1-pentyne (380).



379 **380**

Trimethylsilyl acetylene (0.4mL, 2.8mmol) in THF (10mL) was cooled to -78°C and treated with ethyl magnesium bromide (2.5mL of a 1.0M solution in THF, 2.5mmol). The reaction mixture was allowed to warm to room temperature, refluxed for 30 minutes, then cooled to room temperature. In a separate flask, aldehyde **379** (496mg, 1.4mmol) in THF (10mL) was cooled to -78°C and then treated with the alkynyl Grignard solution, dropwise, until the reaction was shown to be complete by tlc. The reaction mixture was then allowed to warm to room temperature and poured onto saturated ammonium chloride solution (20mL), extracted with ether (3 × 20mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 50% ether in petrol) afforded the propargyl alcohol (**380**) (518mg, 82%) as a yellow oil.

R_f (70% ether in petrol) 0.51;

ν_{max} (thin film)/cm^{-1} 3410, 2957, 2853, 2171, 1582, 1562, 1480, 1427, 1387, 1334, 1249, 1199, 1164, 1105, 1008, 843, 760;

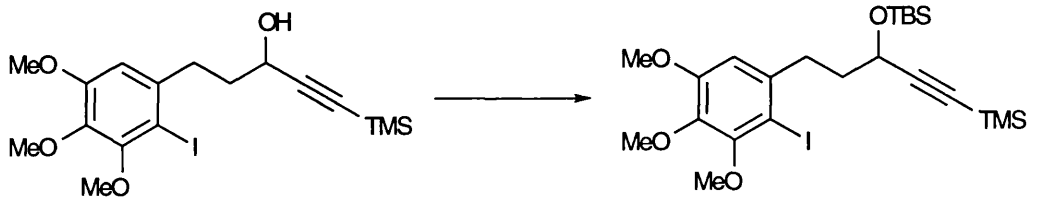
δ_H(400MHz; $CDCl_3$) 6.65 (1H, s, aromatic), 4.38 (1H, dd, J=6.3, 10.8Hz C*H*OH), 3.85 (3H, s, MeO), 3.82 (6H, s, MeO), 2.89 (2H, dd, J=5.7, 9.1 Ar$CH_2$$CH_2$), 1.98-1.92 (2H, m, Ar$CH_2$$CH_2$), 1.83, (1H, m, OH), 0.17 (9H, s, Me_3Si);

δ_C(100MHz, $CDCl_3$) 153.5, 153.1, 140.4, 139.6, 108.9, 106.2, 90.0, 88.0, 65.8, 62.1, 60.7, 56.1, 37.8, 36.7, 15.2;

LRMS (EI mode 70eV): *m/z* 449 (11%, $[M+H]^+$), 321, 308, 181, 73;

HRMS (EI mode 70eV): Found: M^+, 448.0567. $C_{17}H_{25}IO_4Si$ requires *M*, 448.0562.

Preparation of 3-*tert*-butyldimethylsilyloxy-5-(2-iodo-3,4,5-trimethoxyphenyl)-1-trimethylsilyl-1-pentyne (386).



380 **386**

A solution of alcohol (**380**) (104mg, 0.23mmol) in dichloromethane (5mL) was treated with *tert*-butyldimethylsilyl chloride (38mg, 0.25mmol), imidazole (17mg, 0.25mmol) and *N,N*-dimethylaminopyridine (10mg), and stirred at room temperature for 18 hours. The reaction mixture was then poured onto saturated ammonium chloride solution (10mL) and extracted with ether (3 × 20mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 20% ether in petrol) afforded **386** (114mg, 87%) as a pale yellow oil.

R_f (60% ether in petrol) 0.88;

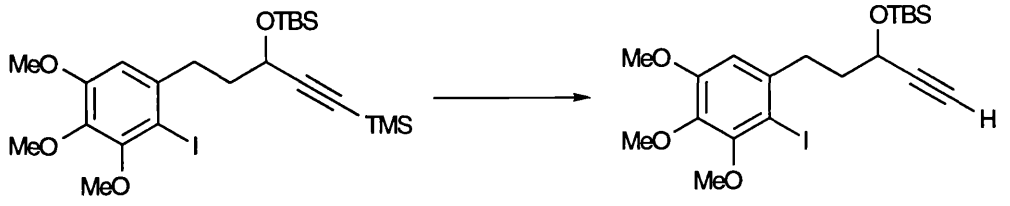
ν_{max} (thin film)/cm^{-1} 2957, 2856, 2120, 1563, 1480, 1387, 1335, 1250, 1106, 841;

δ_H(400MHz; $CDCl_3$) 6.63 (1H, s, aromatic), 4.38 (1H, t, J=5.5Hz, C*H*OSi), 3.84 (3H, s, MeO), 3.82 (6H, s, MeO), 2.98-2.70 (2H, m, ArCH_2CH_2), 1.93 (2H, q, J=7.6Hz, ArCH_2CH_2), 0.91 (9H, s, ^{t}BuSi), 0.14 (12H, s, MeSi), 0.10 (3H, s, MeSi);

LRMS (EI mode 70eV): *m/z* 562 (3%, M^+), 506, 436, 364, 306, 181, 73;

HRMS (EI mode 70eV): Found: M^+, 562.1436. $C_{23}H_{39}IO_4Si_2$ requires *M*, 562.1432.

Preparation of 3-*tert*-butyldimethylsilyloxy-5-(2-iodo-3,4,5-trimethoxyphenyl)-1-pentyne (381).



386 **381**

Trimethylsilyl alkyne (**386**) (200mg, 0.35mmol) in methanol (5mL) was treated with potassium carbonate (73mg, 0.53mmol) and the resultant solution stirred at room temperature for 2 hours. The solution was then concentrated *in vacuo*, taken up in dichloromethane (5mL) and absorbed onto silica (3g). The crude product was then purified by column chromatography (SiO_2, 15% ether in petrol) to afford the acetylene (**381**) (174mg, 100%) as a clear colourless oil.

R_f (20% ether in petrol) 0.42;

ν_{max} (thin film)/cm^{-1} 3290, 2932, 2856, 2120, 1563, 1480, 1386, 1335, 1251, 1199, 1105, 1007, 924, 837, 778;

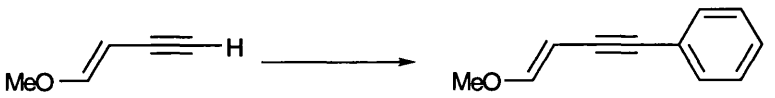
δ_H(400MHz; $CDCl_3$) 6.62 (1H, s, aromatic), 4.44 (1H, dt, J=2.3, 9.4Hz, C*H*OSi), 3.84 (3H, s, MeO), 3.82 (6H, s, MeO), 2.95-2.73 (2H, m, ArCH_2CH$_2$), 2.43 (1H, d, J=2.3Hz, C≡C*H*), 1.94 (2H, dt, J=9.4, 9.2Hz, ArCH$_2$CH_2), 0.91 (9H, s, ^{t}BuSi), 0.14 (3H, s, MeSi), 0.10 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 153.5, 153.1, 140.0, 108.7, 88.0, 85.1, 72.6, 62.2, 61.0, 60.7, 56.1, 38.8, 36.8, 25.8, 18.3, -4.5, -5.0;

LRMS (FAB mode): *m/z* 490 (4%, M^+), 434, 364, 307, 291, 232, 181;

HRMS (FAB mode): Found: M^+, 490.1036. $C_{20}H_{31}IO_4Si$ requires *M*, 490.1032.

Preparation of (*E*)-(4-methoxy-3-buten-1-ynyl)benzene (385).



384 **385**

To a stirred mixture of (*E*)-1-methoxy-1-buten-3-yne[273] (**384**) (4.82g, 58.8mmol), palladium(II) acetate (45mg, 0.2mmol), copper(I) iodide (40mg, 0.2mmol) and triphenylphosphine (440mg, 1.7mmol) in diethylamine (60mL) at 0°C was added, dropwise, iodobenzene (10g, 49mmol). The reaction mixture was heated to reflux for 30 minutes and then cooled to room temperature. After absorbing onto silica gel (30g), the reaction mixture was purified by column chromatography (SiO_2, 3% ether in petrol) to afford **385** (7.14g, 92% based on iodobenzene) as a colourless oil, which readily turned brown at room temperature.

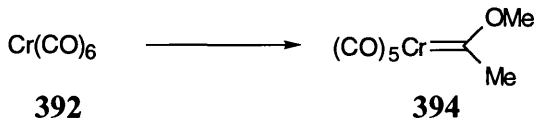
ν_{max} (thin film)/cm^{-1} 2935, 2835, 2203, 1623, 1594, 1299, 1214;

δ_H(400MHz; $CDCl_3$) 7.34 (5H, m, aromatic), 6.98 (1H, d, J=12.7Hz, C*H*CHOMe), 5.09 (1H, d, J=12.7Hz, CHC*H*OMe), 3.65 (3H, s, MeO);

LRMS (FAB mode): *m/z* 158 (35%, M^+), 129;

HRMS (FAB mode): Found: M^+, 158.0741. $C_{11}H_{10}O$ requires *M*, 158.0732.

Preparation of [(methyl)(methoxy)carbene]chromium pentacarbonyl[274] (394).



392 **394**

A stirring suspension of chromium hexacarbonyl (592mg, 2.69mmol) in ether (60mL) at room temperature was treated with methyllithium (1.68mL of a 1.6M solution in

ether, 2.69mmol), dropwise over a period of 10 minutes. The reaction mixture was then heated to reflux for 2 hours, cooled to room temperature and concentrated *in vacuo*. The dark brown residual solid was taken up in water (40mL) (in air) and trimethyloxonium tetrafluoroborate (398mg, 2.69mmol) was added over a 15 minute period with stirring. The reaction mixture was extracted with cold, degassed pentane (5 ×30mL), the combined organic layers were dried ($MgSO_4$) and filtered through a pad of celite. The solution was concentrated *in vacuo* to approximately 5 mL and cooled to -20°C under nitrogen. After 24 hours the bright yellow crystals were collected and dried at 25°C under reduced pressure for 10 minutes to afford **394** (224mg, 33%).

m.p. 34-36°C (lit. 34-35°C[291]);

R_f (petrol) 0.60;

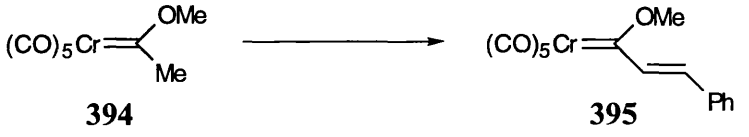
ν_{max} (KBr)/cm^{-1} 2062, 1950, 1913, 1452, 1254, 1104, 1020, 896;

δ_H(400MHz; $CDCl_3$) 4.70 (3H, br s, MeO), 2.93 (3H, s, Me);

δ_C(100MHz; $CDCl_3$) 334.2, 223.2, 216.4, 211.5, 65.9, 15.3;

LRMS (FAB mode): *m/z* 273 (3%, $[M+Na]^+$), 176, 154, 136, 120, 107;

Preparation of [(styryl)(methoxy)carbene]chromium pentacarbonyl[276] (395).



394 **395**

n-Butyllithium (60μL of a 10M solution in hexanes, 0.60mmol) was added to a solution of **394** (151mg, 0.60mmol) in ether (20mL) at -78°C. After 2 minutes, benzaldehyde (61μL, 0.60mmol) was added at -78°C. The resultant solution was stirred at 0°C for 15 minutes, washed with water (50mL), dried ($MgSO_4$), filtered and

concentrated *in vacuo*. Column chromatography (SiO_2, petrol) afforded the product (**395**) (11mg, 6%) as deep red crystals.

m.p. 72-74°C (lit. 73-76°C[276]);

R_f (petrol) 0.60;

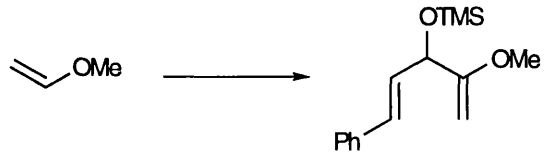
ν_{max} (thin film)/cm^{-1} 2958, 2057, 1985, 1922, 1593, 1572, 1448, 1328, 1227, 1172, 1078, 990, 663;

δ_H(400MHz; $CDCl_3$) 7.95 (1H, d, J=15.4Hz, C*H*=CHPh), 7.58-7.39 (5H, m, aromatic), 6.95 (2H, d, J=15.4Hz, CH=C*H*Ph), 4.81 (3H, s, MeO);

δ_C(100MHz; $CDCl_3$) 333.6, 235.9, 224.2, 216.7, 139.6, 134.4, 130.8, 129.4, 66.4;

LRMS (FAB mode): *m/z* 338 (6%, M^+), 282, 230, 131, 115;

Preparation of (*E*) 4-methoxy-1-phenyl-3-trimethylsilyloxypent-1,4-diene (410).



409 **410**

Methyl vinyl ether (1mL) was condensed into a flask at -78°C and then transferred, *via* a cannula, to another flask containing THF (10mL) at -78°C. To this solution was added, dropwise over a period of 12 minutes, *tert*-butyllithium (3.7mL of a 1.28M solution in pentane, 4.8mmol) and the reaction mixture was allowed to slowly warm to -20°C. *Trans*-cinnamaldehyde (0.69mL, 5.0mmol) was added and the reaction mixture was allowed to warm further to 0°C, when the reaction was quenched by addition of trimethylsilyl chloride (0.64mL, 5.0mmol). The resulting solution was absorbed onto silica (6g) and purified by column chromatography (SiO_2, 5-15% ether in petrol) to afford the product (**410**) (644mg, 52%) as a clear, colourless oil.

R_f (5% ether in petrol) 0.60;

ν_{max} (thin film)/cm^{-1} 2958, 2873, 2844, 1664, 1623, 1497, 1450, 1380, 1299, 1252, 1114, 1072, 966, 904, 883, 843, 746, 693;

δ_H(400MHz; $CDCl_3$) 7.39-7.20 (5H, m, aromatic), 6.59 (1H, d, J=16.0Hz, ArC*H*CH), 6.28 (1H, dd, J=16.0, 5.9Hz, ArCHC*H*), 4.66 (1H, d, J=5.9Hz, C*H*OSi), 4.26 (1H, d, J=2.1Hz, C=CH_2), 3.99 (1H, d, J=2.1Hz, C=CH_2), 3.56 (3H, s, MeO), 0.16 (9H, s, Me_3Si);

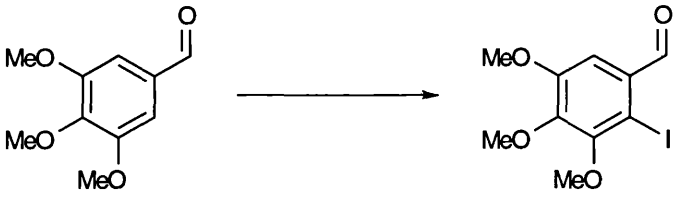
δ_C(100MHz; $CDCl_3$) 164.3, 136.9, 130.2, 130.0, 128.4, 127.4, 126.5, 80.9, 73.9, 55.0, 0.1;

LRMS (FAB mode): *m/z* 263 (18%, $[M+H]^+$), 262 (13%, M^+), 261 (47%, $[M-H]^+$), 247, 231, 205, 189, 173, 131;

HRMS (FAB mode): Found: $[M+H]^+$, 263.1460. $C_{15}H_{23}O_2Si$ requires *M*, 263.1467.

Found: $[M-H]^+$, 261.1320. $C_{15}H_{21}O_2Si$ requires *M*, 261.1311.

Preparation of 2-iodo-3,4,5-trimethoxybenzaldehyde[270,271] (389).



374 **389**

3,4,5-Trimethoxybenzaldehyde (3.66g, 18.7mmol) and silver trifluoroacetate (4.12g, 18.7mmol) were suspended in dichloromethane (25mL). A saturated solution of iodine (5.22g, 20.6mmol) in dichloromethane was added dropwise over 2.5 hours with vigorous stirring at room temperature. The red suspension obtained at the end of addition was stirred for a further hour before filtering, and then washed successively with saturated sodium thiosulfate solution, water and saturated sodium bicarbonate solution (50mL of each). The organic layer was dried ($MgSO_4$), filtered and

concentrated *in vacuo* to give a yellow solid, which was recrystallised from petrol at -78°C to give **389** (5.14g, 85%) as pale yellow needles.

m.p.68-69°C (lit. 66-67°C[270], 66-66.5°C[271]);

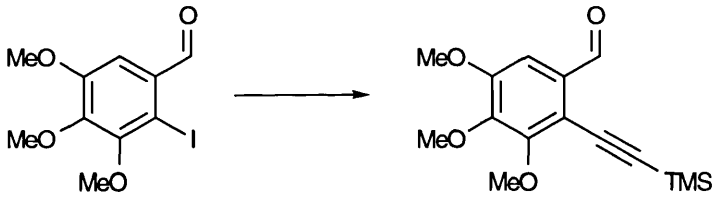
R_f (10% ether in petrol) 0.25;

ν_{max} (thin film)/cm^{-1} 3345, 2936, 2850, 1688, 1569;

δ_H(400MHz; $CDCl_3$) 10.05 (1H, s, ArC*H*O), 7.35 (1H, aromatic), 3.97 (3H, s, MeO), 3.92 (3H, s, MeO), 3.90 (3H, s, MeO);

LRMS (FAB mode): *m/z* 322 (100%, M^+);

Preparation of 2-trimethylsilylethynyl-3,4,5-trimethoxybenzaldehyde (412).



389 **412**

A mixture of 2-iodo-3,4,5-trimethoxybenzaldehyde (3.00g, 9.3mmol), palladium(II) acetate (104mg, 0.46mmol), triphenylphosphine (488mg, 1.83mmol), copper(I) iodide (90mg, 0.47mmol) and trimethylsilyl acetylene (5.25mL, 37.2mmol) in diethylamine (45mL) was gently heated to reflux for 2 hours. On cooling, the solution was concentrated *in vacuo* and the resultant oil extracted with 10% ether in petrol and absorbed onto silica (5g). Column chromatography (SiO_2, 10% ether in petrol) gave **412** (1.91g, 70%) as pale yellow crystals.

m.p. 70-71°C.

R_f (10% ether in petrol) 0.17;

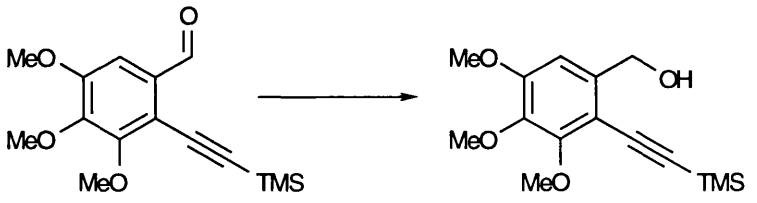
ν_{max} (KBr)/cm^{-1} 2944, 2850, 2146, 1694, 1582, 1486, 1331, 1245, 1202, 1128, 1072, 1036, 848;

δ_H(400MHz; $CDCl_3$) 10.42 (1H, s, C*H*O), 7.20 (1H, s, aromatic), 3.97 (3H, s, MeO), 3.95 (3H, s, MeO), 3.91 (3H, s, MeO), 0.27 (9H, s, Me_3Si);

LRMS (EI mode 70eV): *m/z* 292 (52%, M^+), 277, 219

HRMS (EI mode 70eV): Found: $[M+H]^+$, 293.1204. $C_{15}H_{20}O_4Si$ requires *M*, 293.1209.

Preparation of 2-trimethylsilylethynyl-3,4,5-trimethoxybenzyl alcohol (413).



412 **413**

A solution of 2-trimethylsilylethynyl-3,4,5-trimethoxybenzaldehyde (174mg, 0.6mmol) in ether (5mL) was added, dropwise, to a stirred suspension of lithium aluminium hydride (33mg, 0.87mmol) in ether (5mL) at room temperature. When addition was complete, the reaction mixture was warmed to gentle reflux. After 5 minutes the reaction mixture was cooled to room temperature and slowly added to 2M hydrochloric acid (40mL). The resultant mixture was extracted with ether (2 ×20mL), the combined extracts washed with water (2×20mL), dried ($MgSO_4$) and filtered. Concentration *in vacuo* gave **413** (165mg, 94%) as yellow needles.

m.p. 82-84°C.

R_f (50% ether in petrol) 0.11;

ν_{max} (KBr)/cm^{-1} 3464, 2945, 2841, 2148, 1596, 1489, 1461, 1405, 1327, 1250, 1197, 1131, 1048, 1021, 973, 896, 844;

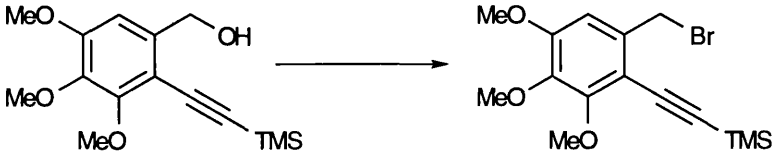
δ_H(400MHz; $CDCl_3$) 6.74 (1H, s, aromatic), 4.72 (2H, s, ArCH_2), 3.95 (3H, s, MeO), 3.87 (3H, s, MeO), 3.83 (3H, s, MeO), 0.25 (9H, s, Me_3Si);

δ_C(100MHz; $CDCl_3$) 155.3, 154.1, 141.1, 140.0, 108.3, 106.5, 102.6, 98.5, 64.0, 61.2, 61.1, 56.1, -0.0;

LRMS (FAB mode): *m/z* 294 (100%, M^+), 277;

HRMS (FAB mode): Found: M^+, 294.1280. $C_{15}H_{22}O_4Si$ requires *M*, 294.1287.

Preparation of 2-trimethylsilylethynyl-3,4,5-trimethoxybenzyl bromide (414).



413 **414**

To a stirred solution of alcohol (**413**) (160mg, 0.5mmol) in ether (5mL) was added carbon tetrabromide (365mg, 1.1mmol) and triphenylphosphine (287mg, 1.1mmol). The reaction mixture was stirred at room temperature for 5 hours, filtered and washed with ether. The filtrate was absorbed onto silica (5g) and purified by column chromatography (SiO_2, 20% ether in petrol) to give **414** (184mg, 94%) as yellow needles.

m.p. 57-58°C.

R_f (20% ether in petrol) 0.34;

ν_{max} (KBr)/cm^{-1} 2940, 2150, 1593, 1491, 1460, 1405, 1338, 1248, 1194, 1126, 1077, 1037, 993, 844;

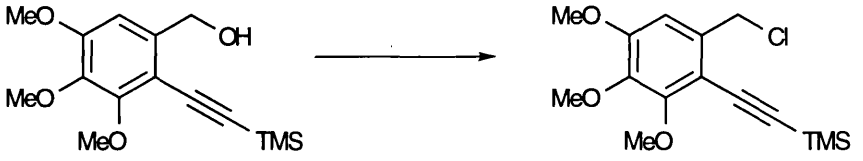
δ_H(400MHz; $CDCl_3$) 6.70 (1H, s, aromatic), 4.60 (2H, s, ArCH_2), 3.95 (3H, s, MeO), 3.86 (3H, s, MeO), 3.83 (3H, s, MeO), 0.27 (9H, s, Me_3Si);

δ_C(100MHz; $CDCl_3$) 155.1, 153.9, 142.1, 136.0, 110.8, 108.6, 103.6, 97.9, 61.2, 61.1, 56.1, 32.2;

LRMS (FAB mode): *m/z* 359, (24%, M^+), 357 (22%, M^+), 277, 263;

HRMS (FAB mode): Found: M^+, 357.0530. $C_{15}H_{22}O_3Si^{79}Br$ requires *M*, 357.0522.

Preparation of 1-Chloromethyl-2-trimethylsilylethynyl-3,4,5-trimethoxybenzene (415).



413 **415**

Alcohol **413** (0.41g, 1.39mmol) was stirred in dichloromethane (10mL) at 0°C, to which was added methanesulfonyl chloride (0.35g, 3.06mmol) and triethylamine (0.41g, 0.39mmol). The reaction mixture was stirred at room temperature for 30 minutes and then poured onto 1M hydrochloric acid (10mL) The aqueous layer was extracted with dichloromethane (10mL) and the combined layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 20% ether in petrol) afforded the chloride (0.18g, 41%) as a white solid.

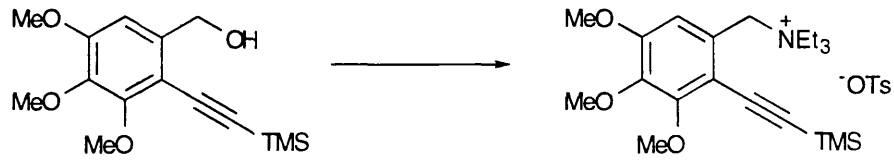
m.p. 69-71°C

ν_{max} (film)/cm^{-1} 3989, 3582, 2933, 1736, 1656, 1480, 1388, 1105;

δ_H(400MHz; $CDCl_3$) 6.91 (1H, s, Ar*H*), 4.70 (2H, s, ArCH_2Cl), 3.89 (3H, s, MeO), 3.88 (6H, s, MeO);

LRMS (FAB mode): *m/z* 312 (M^+), 277;

Preparation of (2-trimethylsilylethynyl-3,4,5-trimethoxybenzyl)triethyl-ammonium *p*-toluenesulfonate (416).



413 **416**

To a solution of alcohol **413** (150mg, 0.51mmol) in dichloromethane (5mL) was added *p*-toluenesulonyl chloride (116mg, 0.61mmol), triethylamine (0.41mL), 1.02mmol) and a catalytic quantity of *N*,*N*-dimethylaminopyridine (10mg). The resulting mixture was stirred for 48 hours at room temperature and then poured onto water (20mL), and extracted with dichloromethane (2× 20mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **416** (219mg, 78%) as a brown oil.

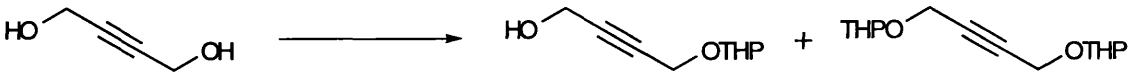
R_f (petrol) 1.0;

ν_{max} (thin film)/cm^{-1} 3454, 2957, 2150, 1650, 1592, 1460, 1404, 1337, 1223, 1123, 1081, 1034, 850, 680;

δ_H(400MHz; $CDCl_3$) 7.81 (2H, d, J=8.5Hz, Ar*H*), 7.35 (2H, d, J=8.5Hz, ArH), 6.63 (1H, s, aromatic), 4.83 (2H, s, ArCH_2), 3.92 (3H, s, MeO), 3.86 (3H, s, MeO), 3.88 (3H, s, MeO), 3.54 (6H, q, J=6.7Hz, CH_2CH_3), 2.31 (3H, s, *p*-ArCH_3), 1.37 (9H, t, j=6.7Hz, CH_2CH_3), 0.26 (9H, s, Me_3Si)

LRMS (FAB mode): *m/z* 447 (13%, M^+), 312, 235;

Preparation of 4-tetrahydropyranyloxybut-2-yn-1-ol (419) and 1,4-bis-(tetrahydropyranyloxy)-but-2-yne (420).



418 **419** **420**

To a stirring solution of 2-butyne-1,4-diol (2.00g, 23mmol) in dichloromethane (50mL) at 50°C was added dihydropyran (2.55mL, 28mmol) and pyridinium *p*-toluenesulfonate (578mg, 2.3mmol). The reaction mixture was stirred at room temperature for 2 hours, after which the starting material remained unreacted by tlc. To the reaction mixture was added dihydropyran (1mL, 13mmol) and stirring continued for a further hour. The resultant yellow solution was poured into semi-saturated brine (100mL), the organic layer separated, and the aqueous layer extracted with dichloromethane (2 ×30mL). The combined organic extracts were dried ($MgSO_4$), filtered and chromatographed (SiO_2, 50-65% ether in petrol) to give **420** (2.17g, 37%), and **419** (1.90g, 49%), both as pale yellow oils.

4-tetrahydropyranyloxybut-2-yn-1-ol (419).

R_f (70% ether in petrol) 0.53;

ν_{max} (thin film)/cm^{-1} 3420, 2943, 2869, 1443, 1389, 1345, 1265, 1204, 1116, 1032, 971, 902, 871, 813;

δ_H(400MHz; $CDCl_3$) 4.78 (1H, t, J=3.3Hz, THP), 4.35-4.21 (4H, m, $CH_2C{\equiv}CCH_2$), 3.84-3.78 (1H, m, THP), 3.54-3.48 (1H, m, THP), 1.95 (1H, s, OH), 1.83-1.48 (6H, m, THP);

δ_C(100MHz; $CDCl_3$) 96.8, 84.3, 81.8, 62.0, 54.3, 51.0, 60.2, 25.3, 19.0;

LRMS (FAB mode): *m/z* 171 (100%, M+H), 154, 137, 123;

HRMS (FAB mode): Found: $[M+H]^+$, 171.1030. $C_9H_{15}O_3$ requires *M*, 171.1021.

1,4-bis-(tetrahydropyranyloxy)-but-2-yne (420).

R_f (70% ether in petrol) 0.26;

ν_{max} (thin film)/cm^{-1} 2945, 2870, 1730, 1443, 1388, 1344, 1265, 1204, 1118, 1026, 971, 947, 904, 872, 816;

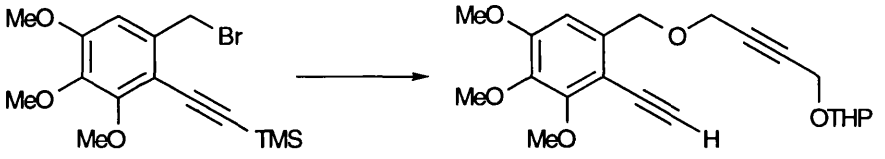
δ_H(400MHz; $CDCl_3$) 4.77 (2H, m, THP), 4.33-4.21 (4H, m, $CH_2C{\equiv}CCH_2$), 3.82-3.77 (2H, m, THP), 3.51-3.47 (2H, m, THP), 1.81-1.49 (12H, m, THP);

δ_C(100MHz; $CDCl_3$) 96.8, 81.9, 61.9, 54.3, 30.2, 25.3, 19.0;

LRMS (FAB mode): *m/z* 255 (5.5%, M+H), 167, 137, 113;

HRMS (FAB mode): Found: $[M+H]^+$, 255.1590. $C_{14}H_{23}O_4$ requires *M*, 255.1596.

Preparation of 1-(2-ethynyl-3,4,5-trimethoxyphenyl)-2-oxo-6-tetrahydopyranyl-oxyhex-4-yne (421).



414 **421**

To a stirring solution of 4-tetrahydropyranyloxybut-2-yn-1-ol (**419**) (100mg, 0.58mmol) in *N,N*-dimethylformamide (3mL) at room temperature was added sodium hydride (24.4mg of a 60% dispersion in mineral oil, 0.58mmol) and stirring was continued for 10 minutes. To this was added, dropwise *via* a cannula, a solution of bromide (**414**) (150mg, 0.42mmol) in *N,N*-dimethylformamide (2mL). After 3 hours, the solution was partitioned between ether and water (10mL of each) and the organic layer washed with water (10mL), dried ($MgSO_4$) and filtered. Concentration *in vacuo* gave a yellow oil which was chromatographed (SiO_2, 40-50% ether in petrol) to give **421** (87mg, 55%) as a clear oil.

R_f (50% ether in petrol) 0.26;

ν_{max} (thin film)/cm^{-1} 3289, 2941, 2852, 2103, 1595, 1492, 1456, 1406, 1332, 1128, 1023, 735;

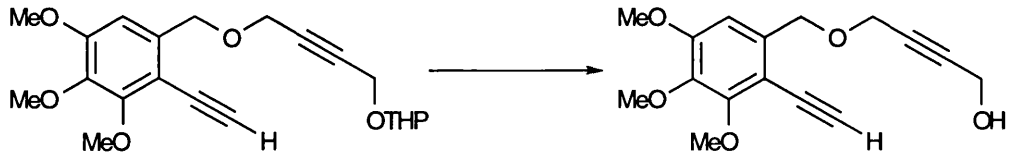
δ_H(400MHz; $CDCl_3$) 6.79 (1H, s, aromatic), 4.80 (1H, t, J=3.3Hz, THP), 4.67 (2H, s, ArCH_2O), 4.33-4.24 (4H, m, CH_2C≡CCH_2), 3.94 (3H, s, MeO), 3.87 (3H, s, MeO), 3.85-3.78 (1H, s, THP), 3.83 (3H, s, MeO), 3.54-3.47 (1H, m, THP), 3.42 (1H, s, ArC≡C*H*), 1.85-1.50 (6H, m, THP);

δ_C(100MHz; $CDCl_3$) 155.3, 154.3, 141.2, 136.7, 108.0, 106.9, 96.8, 84.5, 82.7, 81.8, 77.1, 69.6, 62.0, 61.3, 61.0, 58.2, 56.1, 54.3, 30.2, 25.3, 19.0;

LRMS (FAB mode): *m/z* 374 (9%, M^+), 307, 289, 273, 221;

HRMS (FAB mode): Found: M^+, 374.1720. $C_{21}H_{26}O_6$ requires *M*, 374.1729.

Preparation of 1-(2-ethynyl-3,4,5-trimethoxyphenyl)-2-oxohex-4-yn-6-ol (422).



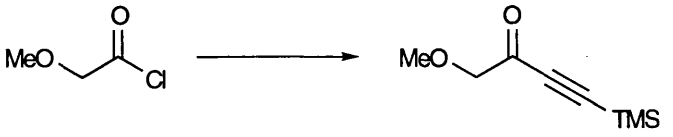
421 **422**

To a solution of THP ether (**421**) (50mg, 0.13mmol) in methanol (5mL) was added *p*-toluenesulfonic acid (5mg, 0.03mmol) and the resultant solution was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue dissolved in ether (10mL). This solution was washed with water (10mL), dried ($MgSO_4$) and filtered. Concentration *in vacuo* gave the alcohol (**422**) (37mg, 98%) as a yellow oil, which decomposed rapidly at room temperature.

R_f (50% ether in petrol) 0.11;

δ_H(400MHz; $CDCl_3$) 6.80 (1H, s, aromatic), 4.68 (2H, s, ArCH_2O), 4.33-4.27 (4H, m, $CH_2C{\equiv}CCH_2$), 3.95 (3H, s, MeO), 3.88 (3H, s, MeO), 3.84 (3H, s, MeO), 3.43 (1H, s, Ar$C{\equiv}CH$);

Preparation of 1-methoxy-4-trimethylsilylbut-3-yn-2-one (442).



441 **442**

To a solution of methoxyacetyl chloride (500μL, 5.46mmol) in 1,2-dichloroethane (25mL) was added bis-(triphenylphosphine)palladium(II) chloride (190mg, 0.28mmol) and a solution of tributyl(trimethylsilylethynyl)stannane (2.32g, 6.00mmol) in 1,2-dichloroethane (5mL). The resultant suspension was heated to 50°C with stirring for 3 hours and was then allowed to cool to room temperature. The reaction mixture was filtered through a pad of celite, washed with copious amounts of dichloromethane, and absorbed onto silica (5g). Column chromatography (SiO_2, 0-10% ether in petrol) gave the product (**442**) (688mg, 74%) as a yellow oil.

R_f (2% ether in petrol) 0.24;

ν_{max} (thin film)/cm^{-1} 2961, 2200, 1694, 1253;

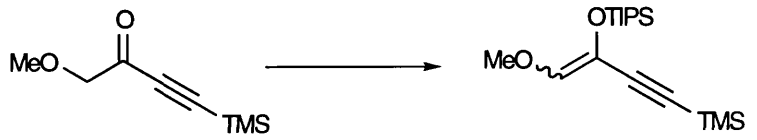
δ_H(400MHz; $CDCl_3$) 4.17 (2H, s, CH_2OMe), 3.44 (3H, s, MeO), 0.24 (9H, s, Me_3Si);

δ_C(100MHz; $CDCl_3$) 184.5, 101.2, 99.5, 78.4, 59.5, -0.9;

LRMS (FAB mode): *m/z* 171 (100%, M+H), 167, 154, 136, 125;

HRMS (FAB mode): Found: M^+, 170.0762. $C_8H_{14}O_2Si$ requires *M*, 170.0763.

Preparation of 1-methoxy-2-tri-*iso*-propylsilyloxy-4-trimethylsilylbut-1-en-3-yne (443).



442 **443**

To a stirred solution of triethylamine (1.00mL, 8.8mmol) and ketone (**442**) (1.00g, 5.9mmol) in benzene (25mL) at 0°C was added, dropwise, tri-*iso*-propylsilyl trifluoromethanesulfonate (1.75mL, 6.5mmol). The reaction mixture was stirred at room temperature for 8 hours, then poured onto water (30mL) and extracted with ether (2 ×20mL). The combined organic extracts were dried ($MgSO_4$), filtered and chromatographed (SiO_2, 2% ether in petrol) to give a mixture of the major and minor isomers (20:1 by ^1H NMR) (1.76g, 92%) as a colourless oil.

R_f (2% ether in petrol) 0.71;

ν_{max} (thin film)/cm^{-1} 2945, 2867, 2139, 1754, 1694, 1652, 1464, 844;

δ_H(400MHz; $CDCl_3$) 5.89 (1H, s, C*H*OMe), 3.61 (3H, s, MeO), 1.3-1.0 (21H, m, $^iPr_3Si$), 0.13 (9H, s, Me_3Si);

δ_C(100MHz; $CDCl_3$) 140.5, 118.7, 102.0, 94.3, 60.2, 17.9, 17.7, 12.7;

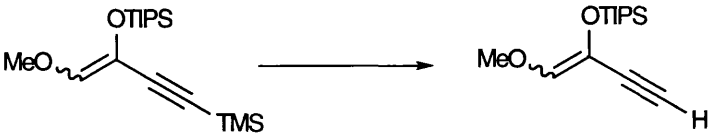
LRMS (FAB mode): *m/z* 326 (27%, M^+), 311, 299, 269, 157, 115, 73;

HRMS (FAB mode): Found: M^+, 326.2098. $C_{17}H_{34}O_2Si_2$ requires *M*, 362.2097.

Partial data for minor isomer:

δ_H(400MHz; $CDCl_3$) 7.37 (1H, s, C*H*OMe), 3.40 (3H, s, MeO), 1.3-1.0 (21H, m, $^iPr_3Si$), 0.13 (9H, s, Me_3Si);

Preparation of 1-methoxy-2-tri-*iso*-propylsilyloxybut-1-en-3-yne (444).



443 **444**

A suspension of silyl acetylene (**443**) (360mg, 1.10mmol) and anhydrous potassium carbonate (168mg, 1.21mmol) in methanol (10mL) was stirred at room temperature for 3 hours. Concentration *in vacuo* gave a yellow oil, which was partitioned between ether and water (10mL of each) and the aqueous layer further extracted with ether (2 ×10mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give the product (254mg, 91%) as a pale yellow oil.

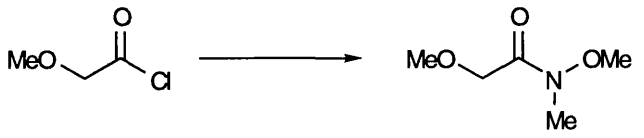
R_f (2% ether in petrol) 0.56;

ν_{max} (thin film)/cm^{-1} 3308, 2945, 2868, 1656, 1463, 1343, 1231, 1136, 1014, 908, 733, 650;

δ_H(400MHz; $CDCl_3$) 5.90 (1H, s, C*H*OMe), 3.64 (3H, s, MeO), 2.95 (1H, s, C≡C*H*), 1.18-1.06 (21H, m, $^iPr_3Si$);

LRMS (EI mode 70eV): *m/z* 254 (27%, M^+), 237, 211;

Preparation of *N*-methoxy-*N*-methyl-2-methoxyacetamide (447).



441 **447**

To a stirred suspension of methoxyacetyl chloride (5mL, 54.7mmol) and *N,O*-dimethylhydroxylamine hydrogen chloride salt (5.6g, 57.4mmol) in dichloromethane (60mL) at 0°C was added, dropwise, pyridine (9.1mL, 113mmol). The resultant dense white suspension was occasionally shaken during the addition in order to maintain stirring. When the addition was complete the mixture was stirred at 0°C for 30 minutes and then at room temperature for 1 hour. The mixture was then washed successively with water (30mL) and brine (2 ×25mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give a pale yellow oil, which was then distilled (15mmHg, 90°C) to afford the product (**447**) (4.3g, 58%) as a pale yellow liquid.

ν_{max} (thin film)/cm^{-1} 3586, 2940, 2822, 1682, 1458, 1334, 1201, 1135, 994, 937;

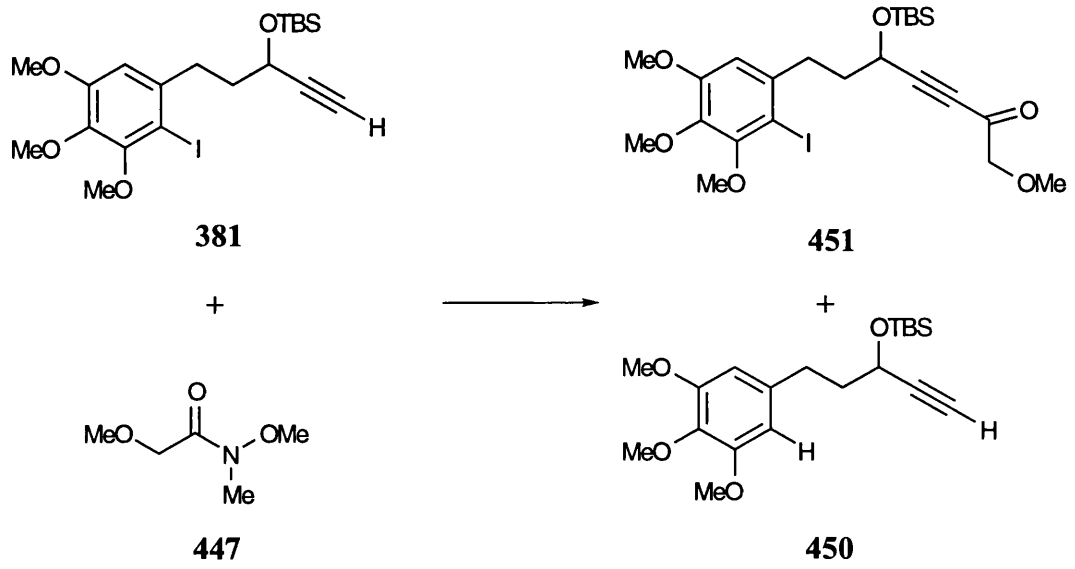
δ_H(400MHz; $CDCl_3$) 4.05 (2H, s, CH_2OCH_3), 3.53 (3H, s, $NOCH_3$), 3.29 (3H, s, CH_2OCH_3), 3.02 (3H, s, NCH_3);

δ_C(100MHz; $CDCl_3$) 170.6, 69.6, 61.3, 59.2, 32.1;

LRMS (FAB mode): *m/z* 134 (100%, $[M+H]^+$);

HRMS (FAB mode): Found: $[M+H]^+$, 134.0810. $C_5H_{12}NO_3$ requires *M*, 134.0817.

Preparation of 5-*tert*-butyldimethylsilyloxy-7-(2-iodo-3,4,5-trimethoxyphenyl)-1-methoxy-2-oxohept-3-yne (451) and 3-*tert*-butyldimethylsilyloxy-5-(3,4,5-trimethoxyphenyl)-1-pentyne (450).



Amide **447** (45mg, 0.34mmol) was stirred in THF (2mL) over 3Å molecular sieves at room temperature for 1 hour. In a separate flask, aryl iodide **381** (165mg, 0.34mmol) in THF (3mL) was cooled to -10°C and ethyl magnesium bromide (135μL of a 3.0M solution in ether, 0.41mmol) was added. This solution was stirred at -10°C for 30 minutes and then further cooled to -70°C. To this cold solution was added the solution of the amide, *via* a cannula, and the mixture allowed to warm slowly to room temperature over a period of 3.5 hours. The reaction mixture was then poured onto saturated ammonium chloride solution (20mL), extracted with ether (3× 20mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 10-30% ether in petrol) afforded the starting acetylene (**381**) (100mg, 61%), de-iodinated starting material (**450**) (17mg, 14%) and the product ynone (**451**) (34mg, 18%) all as pale yellow oils.

3-*tert*-butyldimethylsilyloxy-5-(3,4,5-trimethoxyphenyl)-1-pentyne (450).

R_f (30% ether in petrol) 0.31;

ν_{max} (thin film)/cm^{-1} 3309, 2955, 2930, 2857, 2112, 1590, 1509, 1464, 1420, 1336, 1240, 1131, 1098, 1010, 837, 778, 668;

δ_H(400MHz; $CDCl_3$) 6.39 (2H, s, aromatic), 4.35 (1H, dt, J=2.1, 9.1Hz, C*H*OSi), 3.82 (6H, s, MeO), 3.80 (3H, s, MeO), 2.76-2.60 (2H, m, ArCH_2CH$_2$), 2.41 (1H, d, J=2.1Hz, C≡C*H*), 2.02 (2H, m, ArCH$_2$CH_2), 0.90 (9H, s, ^{t}BuSi), 0.13 (3H, s, MeSi), 0.10 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 153.1, 137.4, 136.1, 105.2, 85.2, 72.5, 62.1, 60.9, 60.8, 56.0, 40.2, 31.8, 26.0, 25.8, 18.2, -4.5, -5.0;

LRMS (FAB mode): *m/z* 364 (37%, M^+), 333, 307, 233, 181;

HRMS (FAB mode): Found: M^+, 364.2060. $C_{20}H_{32}O_4Si$ requires *M*, 364.2070.

5-*tert*-butyldimethylsilyloxy-7-(2-iodo-3,4,5-trimethoxyphenyl)-1-methoxy-2-oxohept-3-yne (451).

R_f (30% ether in petrol) 0.20;

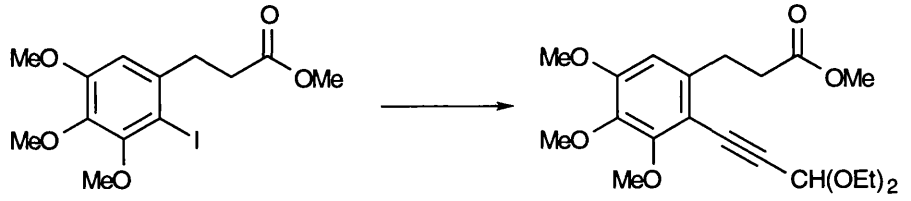
ν_{max} (thin film)/cm^{-1} 2931, 2856, 2209, 1698, 1562, 1481, 1388, 1335, 1252, 1200, 1164, 1105, 1008, 926, 838, 779;

δ_H(400MHz; $CDCl_3$) 6.63 (1H, s, aromatic), 4.60 (1H, t, J=6.2Hz, C*H*OSi), 4.17 (2H, s, CH_2OMe), 3.87 (3H, s, MeO), 3.85 (3H, s, MeO), 3.84 (3H, s, MeO), 3.46 (3H, s, MeO), 2.95-2.78 (2H, m, ArCH_2CH$_2$), 2.16-1.97 (2H, m, ArCH$_2$CH_2), 0.94 (9H, s, ^{t}BuSi), 0.18 (3H, s, MeSi), 0.15 (3H, s, MeSi);

LRMS (FAB mode): *m/z* 585 (67%, $[M+Na]^+$), 562 (35%, M^+), 431, 416, 307, 181;

HRMS (FAB mode): Found: $[M+Na]^+$, 585.1140. $C_{23}H_{35}IO_6SiNa$ requires *M*, 585.1145.

Preparation of methyl 3-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl) propanoate (433).



378 **433**

To a solution of ester (**378**) (3.00g, 7.9mmol) in diethylamine (100mL) was added copper(I) iodide (75mg, 0.4mmol), palladium(II) acetate (89mg, 0.4mmol), triphenylphosphine (410mg, 1.6mmol) and then propargyl aldehyde diethyl acetal (2.8mL, 19.0mmol). The reaction mixture was heated to reflux for 6 hours and then allowed to cool to room temperature. Silica (15g) was added and the solution concentrated *in vacuo*. Column chromatography (SiO_2, 30-40% ether in petrol) afforded the product (2.50g, 83%) as an orange oil.

R_f (30% ether in petrol) 0.11;

ν_{max} (thin film)/cm^{-1} 2975, 2226, 1738, 1595, 1493, 1458, 1407, 1324, 1101, 1051;

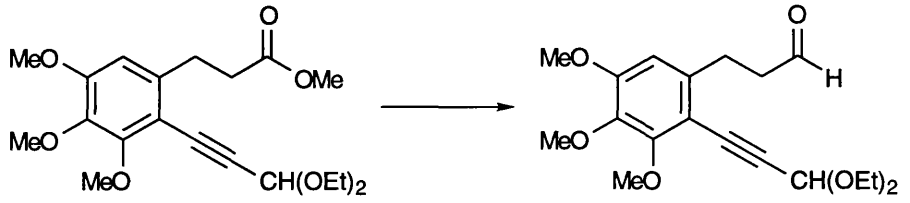
δ_H(400MHz; $CDCl_3$) 6.51 (1H, s, aromatic), 5.51 (1H, s, C*H*$(OEt)_2$), 3.91 (3H, s, MeO), 3.83-3.76 (2H, m, OC*H*$_2$$CH_3$), 3.82 (3H, s, MeO), 3.80 (3H, s, MeO), 3.69-3.61 (2H, m, OC*H*$_2$$CH_3$), 3.01 (2H, t, J=7.6Hz, ArC*H*$_2$$CH_2$), 2.63 (2H, t, J=7.6Hz, $ArCH_2$C*H*$_2$), 1.24 (6H, t, J=7.0Hz, OCH_2C*H*$_3$);

δ_C(100MHz; $CDCl_3$) 173.2, 155.3, 154.0, 140.3, 139.5, 108.6, 108.0, 92.0, 91.3, 79.5, 61.2, 61.0, 60.8, 55.9, 53.4, 51.6, 34.6, 30.0, 27.3, 15.1;

LRMS (EI mode 70eV): *m/z* 380 (30%, M^+), 335, 305, 275, 205, 115;

HRMS (EI mode 70eV): Found: M^+, 380.1830. $C_{20}H_{28}O_7$ requires *M*, 380.1835.

Preparation of 3-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)propanal (434).



433 **434**

To a stirred solution of ester (**433**) (1.00g, 2.64mmol) in dichloromethane (60mL) at -78°C was added dropwise DIBAL-H (1.76mL of a 1.5M solution in toluene, 2.64mmol) to give a yellow solution. The reaction mixture was stirred at this temperature for 10 minutes and then poured onto 1M hydrochloric acid (50mL) and extracted with dichloromethane (2× 20mL). The combined extracts were dried ($MgSO_4$), filtered and chromatographed (SiO_2, 40-60% ether in petrol) to afford the aldehyde (**434**) (902mg, 98%) as a pale yellow oil.

R_f (50% ether in petrol) 0.15;

ν_{max} (KBr)/cm^{-1} 2976, 2936, 2885, 2723, 2226, 1723, 1595, 1494, 1459, 1408, 1324, 1236, 1196, 1103, 1051, 1007. 928, 863;

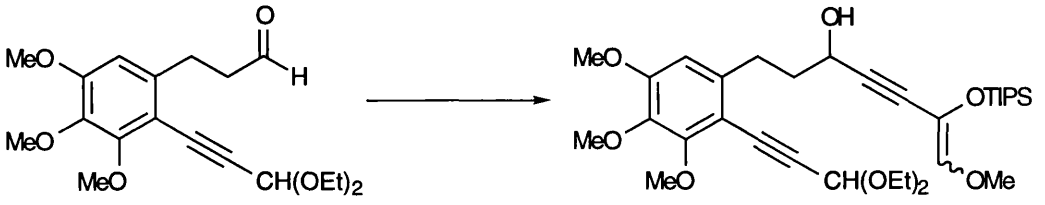
δ_H(400MHz; $CDCl_3$) 9.79 (1H, t, J=1.3Hz, C*H*O), 6.50 (1H, s, aromatic), 5.51, (1H, C*H*$(OEt)_2$), 3.92 (3H, s, MeO), 3.83 (3H, s, MeO), 3.83-3.76 (2H, m, OC*H*$_2$$CH_3$), 3.81 (3H, s, MeO), 3.68-3.63 (2H, m, OC*H*$_2$$CH_3$), 3.01 (2H, t, J=7.4Hz, ArC*H*$_2$$CH_2$), 2.79 (2H, dt, J=1.3, 7.2Hz, $ArCH_2$C*H*$_2$), 1.25 (6H, dt, J=2.4, 7.1Hz, OCH_2C*H*$_3$);

δ_C(100MHz; $CDCl_3$) 201.4, 155.4, 154.1, 140.5, 139.5, 108.6, 108.1, 92.0, 91.6, 79.6, 61.3, 61.0, 60.9, 56.0, 51.5, 34.4, 29.9, 27.3, 15.2;

LRMS (FAB mode): *m/z* 373 (M+Na), 350 (19%, M^+), 305, 277, 233;

HRMS (FAB mode): Found: M^+, 350.1720. $C_{19}H_{26}O_6$ requires *M*, 350.1729.

Preparation of 5-hydroxy-7-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-methoxy-2-tri-*iso*-propylsilyloxyhept-1-en-3-yne (435).



434 **435**

A solution of 1-methoxy-2-tri-*iso*-propylsilyloxybut-1-en-3-yne (**444**) (114mg, 0.49mmol) in THF (10mL) at -78°C was treated with ethyl magnesium bromide (163μL of a 3.0M solution in ether, 0.49mmol). The reaction mixture was allowed to warm to room temperature, stirred for 2 hours, cooled to -78°C, and then a solution of aldehyde **434** (105mg, 0.30mmol) in THF (3mL) was added. The reaction mixture was then poured onto saturated ammonium chloride solution (20mL) and extracted with ether (2 ×15mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 70% ether in petrol) gave the product (**435**) (149mg, 82%) as a pale yellow oil.

R_f (70% ether in petrol) 0.29;

ν_{max} (thin film)/cm^{-1} 3447, 2939, 2868, 2226, 1655, 1595, 1491, 1460, 1406, 1338, 1232, 1133, 1050, 1007, 883;

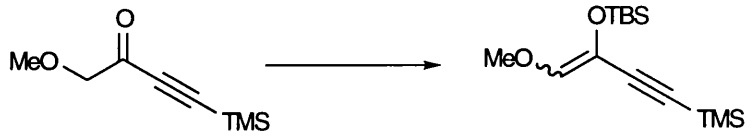
δ_H(400MHz; $CDCl_3$) 6.52 (1H, s, aromatic), 5.85 (1H, s, C*H*OMe), 5.53 (1H, s, C*H*(OEt)$_2$), 4.51-4.46 (1H, m, C*H*OH), 3.94 (3H, s, MeO), 3.86 (3H, s, MeO), 3.83 (3H, s, MeO), 3.72-3.60 (4H, m, OC*H*$_2$CH$_3$), 3.62 (3H, s, MeO), 2.97-2.80 (2H, m, ArC*H*$_2$CH$_2$), 2.62 (1H, d, J=6.6Hz, OH), 2.11-1.93 (2H, m, ArCH$_2$C*H*$_2$), 1.27 (6H, dt, J=2.0, 7.1Hz, OCH$_2$C*H*$_3$), 1.14-1.04 (21H, m, ^{i}Pr$_3$Si);

δ_C(100MHz; $CDCl_3$) 155.0, 154.1, 141.1, 140.1, 118.1, 108.5, 108.2, 92.0, 91.0, 89.6, 81.6, 80.4, 65.8, 61.8, 61.3, 61.0, 60.9, 60.1, 56.0, 38.7, 30.6, 17.9, 15.3, 15.1, 12.7;

LRMS (FAB mode): *m/z* 587 (6%, M-CH_3), 559, 543, 307, 233, 205, 115;

HRMS (FAB mode): Found: $[M+Na]^+$, 627.3325. $C_{33}H_{52}O_8SiNa$ requires *M*, 627.3329.

Preparation of 1-methoxy-2-*tert*-butyldimethylsilyloxy-4-trimethylsilylbut-1-en-3-yne (454).



442 **454**

To a stirred solution of triethylamine (1.06mL, 7.61mmol) and ketone (**442**) (863mg, 5.08mmol) in benzene (50mL) at room temperature was added, dropwise, *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.28mL, 5.58mmol). The reaction mixture was stirred at room temperature for 20 hours, then poured onto water (30mL) and extracted with ether (2 ×25mL). The combined organic extracts were dried ($MgSO_4$), filtered and chromatographed (SiO_2, 10% ether in petrol) to give the product (1.27g, 88%) as a colourless oil.

R_f (5% ether in petrol) 0.57;

ν_{max} (thin film)/cm^{-1} 2957, 2897, 2956, 2139, 1654, 1465, 1406, 1338, 1226, 1135, 1013, 843, 784, 694;

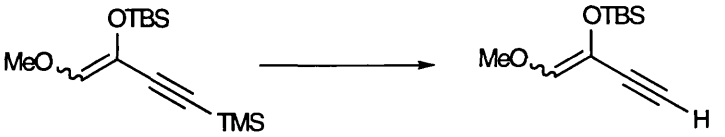
δ_H(400MHz; $CDCl_3$) 5.94 (1H, s, C*H*OMe), 3.62 (3H, s, MeO), 0.93 (9H, s, ^{t}BuSi), 0.16 (6H, s, MeSi), 0.15 (9H, s, Me_3Si);

δ_C(100MHz; $CDCl_3$) 141.0, 117.6, 80.6, 60.3, 30.3, 29.7, 25.6, 18.3;

LRMS (FAB mode): *m/z* 269 (71%, $[M-CH_3]^+$), 147, 125;

HRMS (FAB mode): Found: $[M-CH_3]^+$, 269.1390. $C_{12}H_{25}O_2Si_2$ requires *M*, 269.1393.

Preparation of 1-methoxy-2-*tert*-butyldimethylsilyloxybut-1-en-3-yne (455).



454 **455**

A solution of silyl enol ether (**454**) (256mg, 0.90mmol) in methanol (20mL) was treated with potassium carbonate (138mg, 1.00mmol) and the resulting solution stirred at room temperature for 2 hours. The reaction mixture was then partitioned between ether and water (20mL of each) and the aqueous layer extracted with ether (3 ×20mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the product (**455**) (115mg, 60%) as a clear colourless oil.

R_f (5% ether in petrol) 0.51;

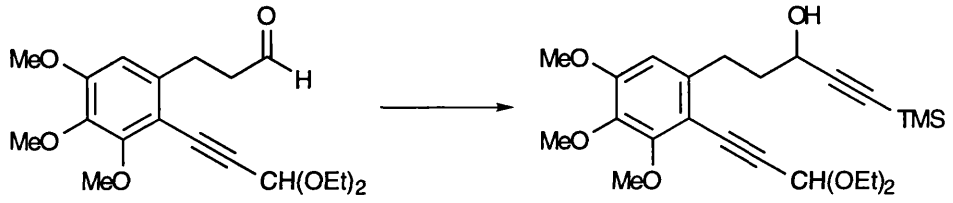
ν_{max} (thin film)/cm^{-1} 3309, 2934, 2858, 2093, 1657, 1464, 1340, 1230, 1134, 1009, 962, 834, 784;

δ_H(400MHz; $CDCl_3$) 5.94 (1H, s, C*H*OMe), 3.63 (3H, s, MeO), 2.94 (1H, s, C≡C*H*), 0.93 (9H, s, ^{t}BuSi), 0.16 (6H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 141.0, 117.5, 80.6, 60.2, 30.3, 29.7, 25.6, 18.2;

LRMS (FAB mode): *m/z* 213 (14%, $[M+H]^+$), 175, 154, 142, 136, 126;

Preparation of 3-hydroxy-5-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-trimethylsilyl-1-pentyne (456).



434 **456**

Trimethylsilyl acetylene (188μL, 1.33mmol) in THF (5mL) was cooled to -78°C and treated with ethyl magnesium bromide (1.33mL of a 3.0M solution in THF, 1.33mmol). The resultant solution was allowed to warm to room temperature and then heated to reflux for 15 minutes, after which it was allowed to cool back to room temperature. In a separate flask, aldehyde (**434**) (232mg, 0.66mmol) in THF (5mL) was cooled to -78°C. To this was added the Grignard solution, *via* a cannula, and the mixture was allowed to warm to room temperature. The reaction mixture was poured onto saturated ammonium chloride solution (25mL) and extracted with ether (2 ×20mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 60% ether in petrol) afforded the product (229mg, 77%) as a pale yellow oil.

R_f (70% ether in petrol) 0.37;

ν_{max} (thin film)/cm^{-1} 3456, 2974, 2227, 2171, 1595, 1565, 1494, 1462, 1408, 1322, 1250, 1196, 1103, 1050, 1004, 844, 761, 700;

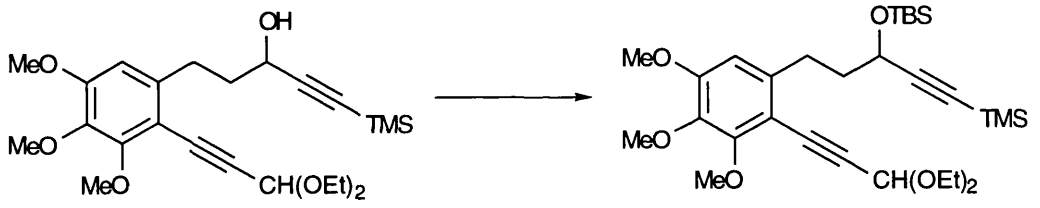
δ_H(400MHz; $CDCl_3$) 6.51 (1H, s, aromatic), 5.51 (1H, s, C*H*$(OEt)_2$), 4.35-4.29 (1H, m, OH), 3.92 (3H, s, MeO), 3.84-3.77 (2H, m, OC*H*$_2$CH$_3$), 3.83 (3H, s, MeO), 3.80 (3H, s, MeO), 3.89-3.60 (2H, m, OC*H*$_2$CH$_3$), 2.97-2,88 (1H, m, C*H*OH), 2.83-2.73 (2H, m, ArC*H*$_2$CH$_2$), 2.10-1.91 (2H, m, ArCH$_2$C*H*$_2$), 1.25 (6H, dt, J=3.3, 7.1Hz, OCH$_2$C*H*$_3$), 0.13 (9H, s, Me_3Si);

δ_C(100MHz; $CDCl_3$) 155.0, 154.1, 141.0, 140.1, 108.4, 108.2, 106.9, 91.9, 90.9, 88.7, 80.4, 65.8, 61.8, 61.3, 61.1, 61.0, 60.9, 55.9, 38.9, 30.6, 15.2, 15.1;

LRMS (FAB mode): *m/z* 471 (10%, $[M+Na]^+$), 419, 403, 233, 219, 191, 181, 154, 136;

HRMS (FAB mode): Found: $[M+Na]^+$, 471.2170. $C_{24}H_{36}O_6SiNa$ requires *M*, 471.2179.

Preparation of 3-*tert*-butyldimethylsilyloxy-5-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-trimethylsilyl-1-pentyne (457).



456 **457**

Alcohol (**456**) (742mg, 1.66mmol) in dichloromethane (20mL) was treated with *tert*-butyldimethylsilyl chloride (275mg, 1.82mmol), imidazole (124mg, 1.82mmol) and catalytic *N,N*-dimethylaminopyridine (30mg). The resultant suspension was stirred at room temperature for 24 hours, then poured onto saturated aqueous ammonium chloride solution (50mL) and extracted with dichloromethane (3 ×30mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 40% ether in petrol) gave the silyl ether (**457**) (868mg, 93%) as a clear, colourless oil.

R_f (50% ether in petrol) 0.42;

ν_{max} (thin film)/cm^{-1} 2958, 2932, 2857, 2227, 2172, 1595, 1565, 1493, 1463, 1408, 1325, 1251, 1196, 1100, 1052, 1007, 841, 778, 761;

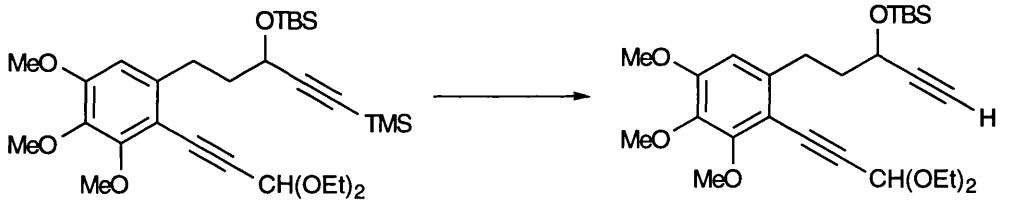
δ_H(400MHz; $CDCl_3$) 6.48 (1H, s, aromatic), 5.51 (1H, s, C*H*$(OEt)_2$), 4.34 (1H, t, J=6.6Hz, C*H*OSi), 3.91 (3H, s, MeO), 3.83 (3H, s, MeO), 3.81 (3H, s, MeO), 3.88-3.62 (4H, m, OC*H*$_2$$CH_3$), 2.89-2.71 (2H, m, ArC*H*$_2$$CH_2$), 2.03-1.92 (2H, m, $ArCH_2$C*H*$_2$), 1.25 (6H, t, J=7.1Hz, OCH_2C*H*$_3$), 0.90 (9H, s, ^{t}BuSi), 0.14 (9H, s, Me_3Si), 0.13 (3H, s, MeSi), 0.11 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 155.3, 153.9, 140.9, 140.0, 108.7, 107.9, 107.4, 92.0, 91.0, 88.9, 79.9, 63.0, 61.2, 61.0, 60.8, 55.9, 39.0, 30.9, 30.3, 25.9, 25.8, 15.3, 15.2, -0.2;

LRMS (FAB mode): *m/z* 585 (7%, $[M+Na]^+$), 561, 533, 517, 387, 311, 189;

HRMS (FAB mode): Found: $[M+Na]^+$, 585.3040. $C_{30}H_{50}O_6Si_2Na$ requires *M*, 585.3044.

Preparation of 3-*tert*-butyldimethylsilyloxy-5-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-pentyne (458).



457 **458**

Silyl acetylene (**457**) (468mg, 0.83mmol) in methanol (20mL) was treated with potassium carbonate (127mg, 0.92mmol) and the resultant solution stirred at room temperature for 18 hours. Concentration *in vacuo* afforded a yellow gum, to which was added water (20mL) and the product was extracted with ether (2 ×25mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give the product (**458**) (392mg, 97%) as a clear, colourless oil.

R_f (50% ether in petrol) 0.43;

ν_{max} (thin film)/cm^{-1} 3284, 2932, 2857, 2227, 1595, 1493, 1462, 1408, 1325, 1252, 1196, 1101, 1052, 1006, 838, 779;

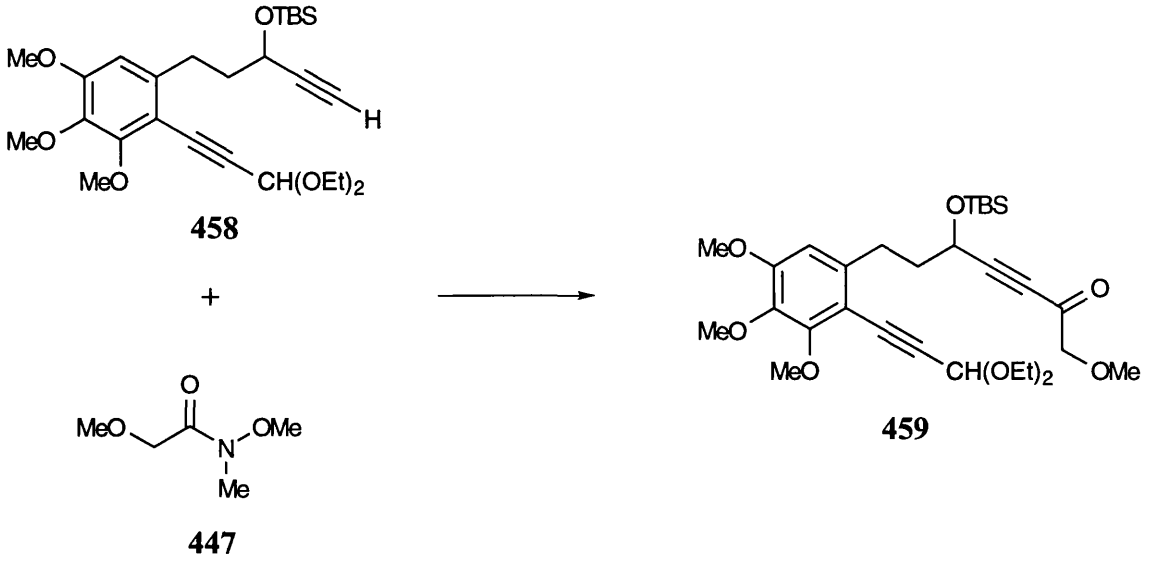
δ_H(400MHz; $CDCl_3$) 6.50 (1H, s, aromatic), 5.53 (1H, s, C*H*(OEt)$_2$), 4.39 (1H, dt, J=2.1, 6.5Hz, C*H*OSi), 3.93 (3H, s, MeO), 3.85 (3H, s, MeO), 3.83 (3H, s, MeO), 3.67 (4H, ddq, J=0.6, 9.4, 7.1Hz, OC*H*$_2$CH$_3$), 2.90-2.78 (2H, m, ArC*H*$_2$CH$_2$), 2.42 (1H, d, J=2.1Hz, C≡C*H*), 2.03-1.96 (2H, m, ArCH$_2$C*H*$_2$), 1.27 (6H, t, J=7.1Hz, OCH$_2$C*H*$_3$), 0.91 (9H, s, ^{t}BuSi), 0.15 (3H, s, MeSi), 0.12 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 155.3, 153.9, 140.8, 140.1, 108.7, 107.8, 92.0, 91.1, 85.2, 79.9, 72.5, 62.5, 61.2, 61.1, 60.8, 56.0, 39.1, 30.6, 25.8, 18.2, 15.2, -4.5, -5.0;

LRMS (FAB mode): *m/z* 513 (11%, [M+Na]$^+$), 489, 461, 445, 239, 205, 189;

HRMS (FAB mode): Found: [M+Na]$^+$, 513.2640. $C_{27}H_{42}O_6SiNa$ requires *M*, 513.2648.

Preparation of 5-*tert*-butyldimethylsilyloxy-7-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-methoxy-2-oxohept-3-yne (459).



Amide (**447**) (45mg, 0.34mmol) was stirred over 3Å molecular sieves in THF (2mL) at room temperature for 2 hours. In a separate flask, acetylene (**458**) (83mg,

0.17mmol) in THF (3mL) was cooled to -78°C and treated with ethyl magnesium bromide (83μL of a 3.0M solution in ether, 0.25mmol). The resultant solution was stirred at room temperature for 1.5 hours and then cooled to -78°C. To this was added the solution of amide, *via* a cannula, and the mixture was allowed to warm to room temperature over a period of 1.5 hours. The reaction mixture was then poured onto saturated aqueous ammonium chloride solution (20mL) and extracted with ether (2 ×10mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo.* Column chromatography (SiO_2, 50% ether in petrol) gave the product (**459**) (73mg, 76%) as a clear, colourless oil.

R_f (50% ether in petrol) 0.22;

ν_{max} (thin film)/cm^{-1} 2933, 2858, 2223, 1698, 1680, 1595, 1494, 1462, 1408, 1326, 1253, 1197, 1100, 1051, 1006, 838, 780;

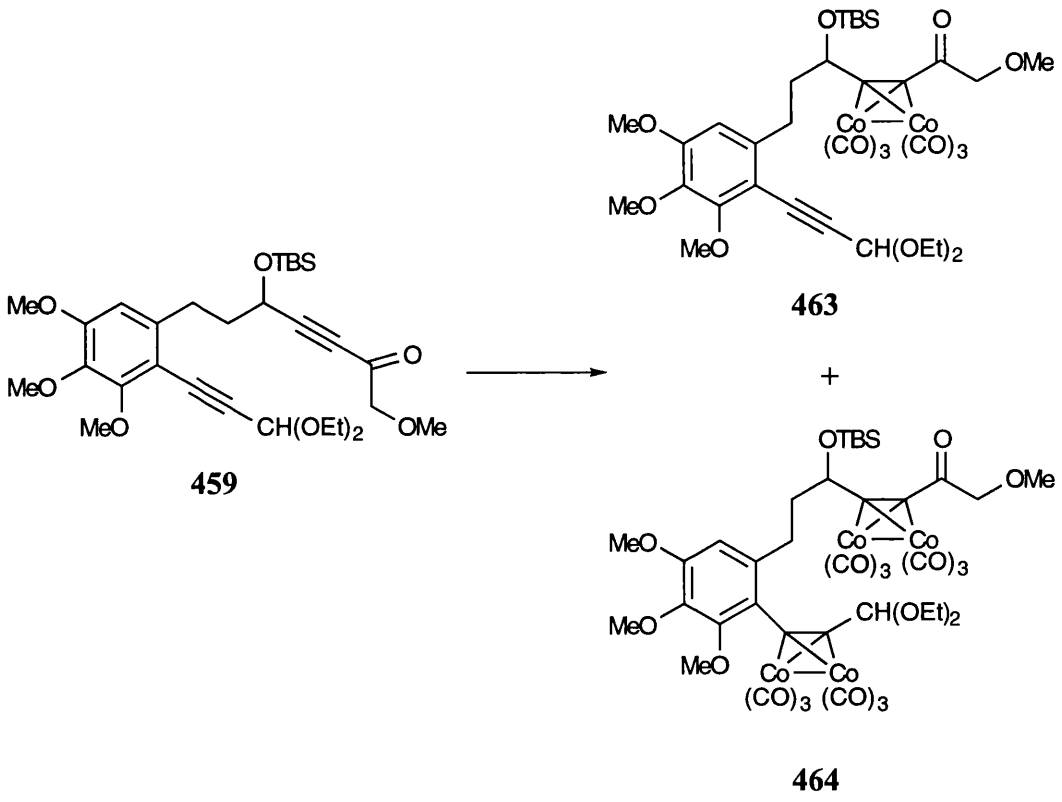
δ_H(400MHz; $CDCl_3$) 6.46 (1H, s, aromatic), 5.49 (1H, s, C*H*(OEt)$_2$), 4.51 (1H, t, J=6.2Hz, C*H*OSi), 4.12 (2H, s, C*H*$_2$OMe), 3.90 (3H, s, MeO), 3.82 (3H, s, MeO), 3.79 (3H, s, MeO), 3.67-3.59 (4H, m, OC*H*$_2$CH$_3$), 3.41 (3H, s, MeO), 2.88-2.74 (2H, m, ArC*H*$_2$CH$_2$), 2.11-1.96 (2H, m, ArCH$_2$C*H*$_2$), 1.23 (6H, t, J=7.0Hz, OCH$_2$C*H*$_3$), 0.89 (9H, s, ^{t}BuSi), 0.12 (3H, s, MeSi), 0.10 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 184.4, 155.4, 154.0, 140.2, 140.0, 108.7, 107.9, 95.7, 92.0, 91.3, 81.1, 79.7, 78.3, 65.8, 62.4, 61.2, 61.1, 61.0, 60.8, 59.5, 56.0, 38.2, 30.6, 25.7, 18.2, 15.2;

LRMS (FAB mode): *m/z* 585 (75%,[M+Na]$^+$), 562, 517, 233, 205, 189;

HRMS (FAB mode): Found: [M+Na]$^+$, 585.2865. $C_{30}H_{46}O_8SiNa$ requires *M*, 585.2860.

Preparation of 5-*tert*-butyldimethylsilyloxy-7-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-methoxy-2-oxohept-3-(3,4-η^2-dicobalthexacarbonyl)-yne (463) and 5-*tert*-butyldimethylsilyloxy-7-(2-(3,3-diethoxypropyn(1,2-η^2-dicobalthexacarbonyl)yl)-3,4,5-trimethoxyphenyl)-1-methoxy-2-oxohept-3-(3,4-η^2-dicobalthexacarbonyl)-yne (464).



A solution of bis-acetylene **459** (52mg, 0.09mmol) in benzene (5mL) was treated with a solution of dicobalt octacarbonyl (35mg, 0.10mmol) in benzene (5mL) and the resultant solution was stirred at room temperature for 2 hours. Silica (2g) was added and the mixture concentrated *in vacuo*. Column chromatography (SiO_2, 30% ether in petrol) gave $Co_2(CO)_6$-acetylene complex (**463**) (44mg, 58%) and bis-$Co_2(CO)_6$-acetylene complex (**464**) (34mg, 33%) as black solids.

5-*tert*-butyldimethylsilyloxy-7-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-methoxy-2-oxohept-3-(3,4-η^2-dicobalthexacarbonyl)-yne (463)

R_f (50% ether in petrol) 0.36;

ν_{max} (thin film)/cm^{-1} 2933, 2226, 2099, 2069, 2035, 1668, 1594, 1494, 1464, 1408, 1322, 1253, 1197, 1116, 838, 776;

δ_H(400MHz; $CDCl_3$) 6.48 (1H, s, aromatic), 5.50 (1H, s, C*H*$(OEt)_2$), 4.93-4.90 (1H, m, C*H*OSi), 4.28 (2H, s, C*H*$_2$OMe), 3.91 (3H, s, MeO), 3.89-3.76 (2H, m, OC*H*$_2$CH$_3$), 3.81 (3H, s, MeO), 3.78 (3H, s, MeO), 3.67-3.61 (2H, m, OC*H*$_2$CH$_3$), 3.43 (3H, s, MeO), 2.85-2.75 (1H, m, ArC*H*$_2$CH$_2$), 2.56-2.48 (1H, m, ArC*H*$_2$CH$_2$), 2.20-2.10 (1H, m, ArCH$_2$C*H*$_2$), 1.84-1.75 (1H, m, ArCH$_2$C*H*$_2$), 1.30-1.17 (6H, m, OCH$_2$C*H*$_3$), 0.88 (9H, s, ^{t}BuSi), 0.11 (3H, s, MeSi), 0.08 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 200.8, 198.8, 198.7, 198.6, 155.4, 154.1, 140.2, 140.0, 108.5, 107.5, 105.0, 92.1, 91.2, 82.6, 79.7, 72.9, 72.8, 61.1, 61.0, 60.9, 60.8, 58.8, 41.7, 30.7, 30.6, 29.4, 25.9, 25.8, 25.7, 18.0, 15.3, 15.2, 15.1;

5-*tert*-butyldimethylsilyloxy-7-(2-(3,3-diethoxypropyn(1,2-η^2-dicobalthexacarbonyl)yl)-3,4,5-trimethoxyphenyl)-1-methoxy-2-oxohept-3-(3,4-η^2-dicobalthexacarbonyl)-yne (464)

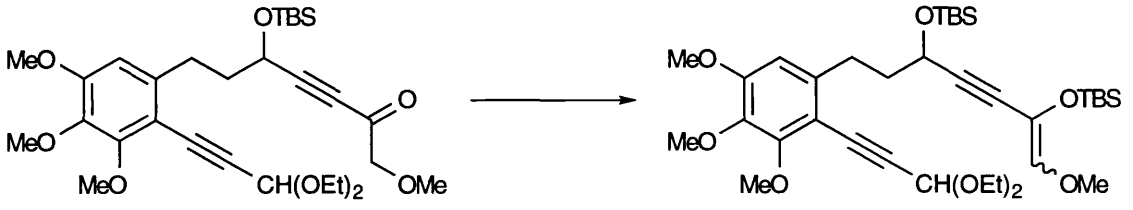
R_f (50% ether in petrol) 0.54;

ν_{max} (thin film)/cm^{-1} 2932, 2100, 2029, 1669, 1589, 1465, 1388, 1340, 1252, 1198, 1114, 837, 776;

δ_H(400MHz; $CDCl_3$) 6.58 (1H, s, aromatic), 5.68 (1H, s, C*H*$(OEt)_2$), 5.08 (1H, t, J=6.4Hz, C*H*OSi), 4.27 (2H, d, J=4.0Hz, C*H*$_2$OMe), 4.00 (3H, s, MeO), 3.85 (3H, s, MeO), 3.84-3.79 (2H, m, OC*H*$_2$CH$_3$), 3.77 (3H, s, MeO), 3.64-3.59 (2H, m, OC*H*$_2$CH$_3$), 3.41 (3H, s, MeO), 3.48-3.39 (1H, m, ArC*H*$_2$CH$_2$), 2.82-2.73 (1H, m, ArC*H*$_2$CH$_2$), 2.14-2.10 (1H, m, ArCH$_2$C*H*$_2$), 2.01-1.95 (1H, m, ArCH$_2$C*H*$_2$), 1.30-1.12 (6H, m, OCH$_2$C*H*$_3$), 0.86 (9H, s, ^{t}BuSi), 0.01 (3H, s, MeSi), 0.00 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 200.6, 200.2, 200.1, 198.4, 153.7, 139.2, 138.7, 119.6, 107.9, 104.8, 102.6, 102.5, 71.2, 64.2, 63.9, 60.7, 60.6, 60.5, 60.4, 58.8, 55.8, 55.7, 42.6, 29.8, 29.7, 29.5, 29.4, 27.9, 26.1, 26.0, 25.9, 18.1, 15.3, 15.1;

Preparation of 5,2-di-*tert*-butyldimethylsilyloxy-7-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)-1-methoxy-hept-1-en-3-yne (465).



459 **465**

A stirred solution of ketone (**459**) (43mg, 0.08mmol) in ether (8mL) was cooled to -78°C, treated with potassium bis(trimethylsilyl)amide (153μL of a 0.5M solution in toluene, 0.08mmol) and then warmed to room temperature. To this was added a solution of *tert*-butyldimethylsilyl chloride (12mg, 0.08mmol) in ether (2mL) and the resultant solution was stirred at room temperature for 1 hour. The reaction mixture was then poured onto saturated ammonium chloride solution (20mL) and extracted with ether (2 ×15mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 50% ether in petrol) gave the product (**465**) (40mg, 77%) as a clear, colourless oil.

R_f (50% ether in petrol) 0.44;

ν_{max} (thin film)/cm^{-1} 2933, 2859, 2227, 1655, 1595, 1492, 1462, 1406, 1338, 1251, 1196, 1133, 1101, 1051, 1006, 838, 781;

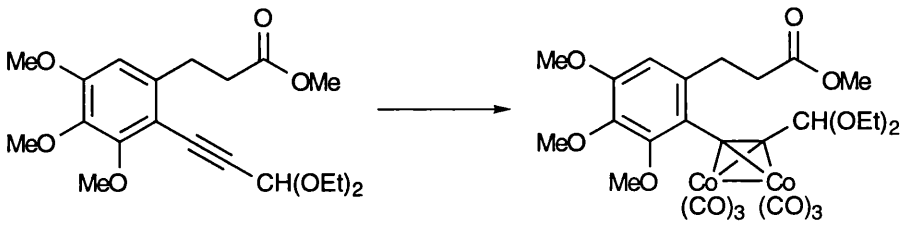
δ_H(400MHz; $CDCl_3$) 6.48 (1H, s, aromatic), 5.85 (1H, s, C*H*OMe), 5.50 (1H, s, C*H*(OEt)$_2$), 4.45 (1H, t, J=6.7, C*H*OSi), 3.91 (3H, s, MeO), 3.82 (3H, s, MeO), 3.80 (3H, s, MeO), 3.69-3.62 (4H, m, OC*H*$_2$CH$_3$), 3.60 (3H, s, MeO), 2.87-2.73 (2H, m, ArC*H*$_2$CH$_2$), 2.04-1.90 (2H, m, ArCH$_2$C*H*$_2$), 1.24 (6H, t, J=7.0Hz, OCH$_2$C*H*$_3$), 0.91 (9H, s, ^{t}BuSi), 0.88 (9H, s, ^{t}BuSi), 0.14 (6H, s, MeSi), 0.11 (3H, s, MeSi), 0.09 (3H, s, MeSi);

δ_C(100MHz; $CDCl_3$) 155.3, 153.9, 140.9, 140.0, 118.1, 108.7, 107.8, 92.0, 91.0, 90.0, 81.2, 79.8, 62.9, 61.2, 61.0, 60.8, 60.1, 55.9, 39.0, 30.8, 25.8, 25.7, 18.2, 15.2;

LRMS (FAB mode): *m/z* 699 (4%, $[M+Na]^+$), 676 (8%, M^+), 631, 587, 501, 355, 263, 233, 205, 189, 175;

HRMS (FAB mode): Found: $[M+Na]^+$, 699.3730. $C_{36}H_{60}O_8Si_2Na$ requires *M*, 699.3724.

Preparation of methyl 3-(2-(3,3-diethoxypropyn(1,2-η^2-dicobalthexacarbonyl)yl) -3,4,5-trimethoxyphenyl)propanoate (469).



433 **469**

To a solution of dicobalt octacarbonyl (51mg, 0.15mmol) in benzene (5mL) at room temperature was added, *via* a cannula, a solution of ester **433** (51mg, 0.13mmol) in benzene (5mL) and the resultant solution was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 30% ether in petrol) to afford **469** (87mg, 97%) as a black solid.

m.p. 64-66°C.

Rf (50% ether in petrol) 0.39;

ν_{max} (KBr)/cm^{-1} 2930, 2089, 2051, 2027, 1739, 1590, 1488, 1390, 1118;

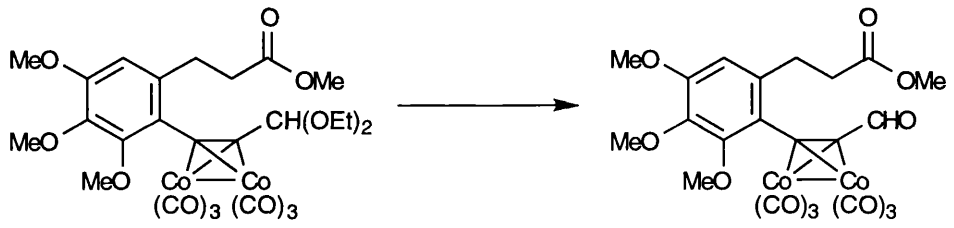
δ_H(400MHz; $CDCl_3$) 6.46 (1H, s, aromatic), 5.69 (1H, s, C*H*$(OEt)_2$), 4.00 (3H, s, MeO), 3.85 (3H, s, MeO), 3.77 (3H, s, MeO), 3.69 (3H, s, MeO), 3.46 (4H, q, J=7.0Hz, OC*H*$_2$$CH_3$), 3.26 (2H, t, J=7.9Hz, ArC*H*$_2$$CH_2$), 2.68 (2H, t, J=7.9Hz, $ArCH_2$C*H*$_2$), 1.19 (6H, t, J=7.0Hz, OCH_2C*H*$_3$);

δ_C(100MHz; $CDCl_3$) 200.1, 173.3, 153.6, 139.2, 137.0, 120.1, 106.2, 102.7, 65.9, 64.0, 60.6, 60.3, 55.8, 51.7, 34.5, 31.9, 29.7, 29.4, 27.8, 22.7, 15.3, 15.1;

LRMS (FAB mode): *m/z* 488 (7%, M-$(CO)_6$), 454, 394, 335 (M^+ not observed);

Elemental analysis: Found: C, 46.70; H, 4.14. $C_{26}H_{28}Co_2O_{13}$ requires C, 46.86; H, 4.24%.

Preparation of methyl 3-(2-(3-oxopropyn(1,2-η^2-dicobalthexacarbonyl)yl)-3,4,5-trimethoxyphenyl)propanoate (466).



469 **466**

A solution of diethyl acetal (**469**) (76mg, 0.11mmol) and Amberlyst® 15 resin (100mg) in acetone (5mL) was stirred at room temperature for 1.5 hours. The reaction mixture was filtered and concentrated *in vacuo* to afford a black solid which was then purified by column chromatography (SiO_2, 40% ether in petrol) to give the aldehyde (**466**) (60mg, 98%).

m.p. 235°C (dec.).

R_f (50% ether in petrol) 0.30;

ν_{max} (KBr)/cm^{-1} 2952, 2096, 2059, 2028, 1739, 1667, 1589, 1489, 1391, 1197, 1133, 1088;

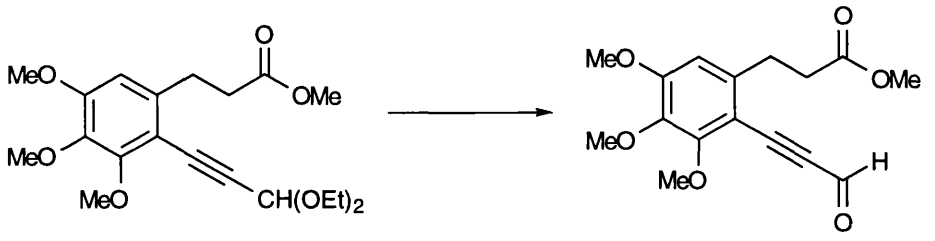
δ_H(400MHz; $CDCl_3$) 10.31 (1H, s, C*H*O), 6.53 (1H, s, aromatic), 3.89 (3H, s, MeO), 3.86 (3H, s, MeO), 3.80 (3H, s, MeO), 3.67 (3H, s, MeO), 3.21 (2H, t, J=7.8Hz, Ar$CH_2$$CH_2$), 2.69 (2H, t, J=7.8Hz, Ar$CH_2$$CH_2$);

δ_C(100MHz; $CDCl_3$) 198.4, 190.3, 172.8, 154.6, 151.9, 139.6, 118.8, 107.0, 60.8, 60.3, 55.9, 51.8, 34.3, 29.7, 27.7, 27.6;

LRMS (FAB mode): *m/z* 509, 480, 452, 305 (46%, M-$HCo_2(CO)_6$), (M^+ not observed);

Elemental analysis: Found: C, 45.05; H, 4.47. $C_{22}H_{18}Co_2O_{12}$ requires C, 44.62; H, 3.06%.

Preparation of methyl 3-(2-(3-oxopropynyl)-3,4,5-trimethoxyphenyl)propanoate (470).



433 **470**

A solution of acetal (**433**) (149mg, 0.39mmol) in acetone (5mL) was treated with Amberlyst® 15 resin (30mg) and stirred at room temperature for 1 hour. The resultant solution was filtered, diluted with ether (20mL) and washed with water (3 ×10mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 50% ether in petrol) gave the aldehyde (**470**) (71mg, 60%) as a pale yellow oil.

R_f (50% ether in petrol) 0.28;

ν_{max} (thin film)/cm^{-1} 2939, 2862, 2361, 2338, 1734, 1653, 1591, 1559, 1496, 1456, 1405, 1340, 1240, 1198, 1139, 1093, 1050, 998;

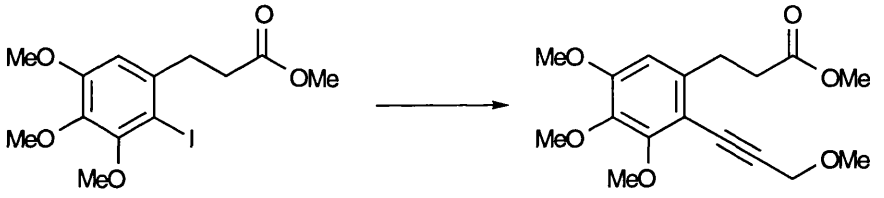
δ_H(400MHz; $CDCl_3$) 9.43 (1H, s, C*H*O), 6.58 (1H, s, aromatic), 3.97 (3H, s, MeO), 3.86 (3H, s, MeO), 3.81 (3H, s, MeO), 3.65 (3H, s, MeO), 3.06 (2H, t, J=7.6Hz, Ar$CH_2$$CH_2$), 2.64 (2H, t, J=7.6Hz, Ar$CH_2$$CH_2$);

δ_C(100MHz; $CDCl_3$) 176.4, 172.9, 156.7, 156.6, 142.4, 140.3, 108.3, 105.9, 96.0, 91.0, 61.7, 61.1, 56.1, 51.7, 34.6, 29.8;

LRMS (FAB mode): *m/z* 306 (100%, M^+), 247, 217, 115;

HRMS (FAB mode): Found: M^+, 306.1107. $C_{16}H_{18}O_6$ requires *M*, 306.1103.

Preparation of methyl 3-(2-(3-methoxy-1-propynyl)-3,4,5-trimethoxyphenyl) propanoate (471).



378 **471**

To a solution of ester **378** (1.00g, 2.63mmol) in diethylamine (40mL) was added copper(I) iodide (25mg, 0.13mmol), palladium(II) acetate (29mg, 0.13mmol), triphenylphosphine (139mg, 0.53mmol) and then methyl propargyl ether (444μL, 5.26mmol). This was heated to reflux for 24 hours and then allowed to cool to room temperature. Silica (10g) was added and the solution concentrated *in vacuo*. Column chromatography (SiO_2, 50% ether in petrol) afforded the starting ester (230mg, 23%) and the product (**471**) (614mg, 73%) as a yellow oil.

R_f(50% ether in petrol) 0.17;

ν_{max} (thin film)/cm^{-1} 2938, 2841, 2252, 2220, 1737, 1595, 1493, 1407, 1337, 1196, 1136, 1099, 1044, 997, 912, 733;

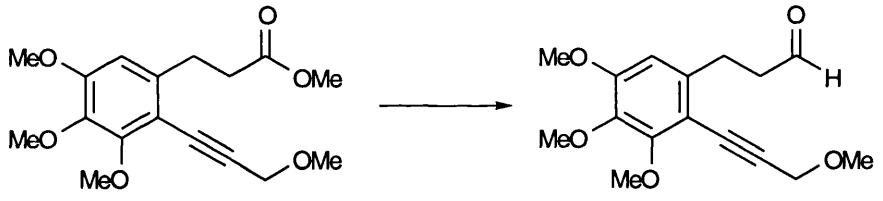
δ_H(400MHz; $CDCl_3$) 6.51 (1H, s, aromatic), 4.36 (2H, s, CH_2OMe), 3.91 (3H, s, MeO), 3.81 (3H, s, MeO), 3.80 (3H, s, MeO), 3.64 (3H, s, MeO), 3.43 (3H, s, MeO), 3.01 (2H, t, J=7.6Hz, $ArCH_2CH_2$), 2.62 (2H, t, J=7.6Hz, $ArCH_2CH_2$);

δ_C(100MHz; $CDCl_3$) 173.2, 155.0, 153.7, 140.4, 139.2, 109.3, 108.0, 91.7, 80.4, 65.8, 61.2, 61.0, 60.5, 57.4, 55.9, 51.6, 34.6, 30.0, 15.2;

LRMS (FAB mode): *m/z* 322 (74%, M^+), 291, 231, 219, 136;

HRMS (FAB mode): Found: M^+, 322.1410. $C_{17}H_{22}O_6$ requires *M*, 322.1416.

Preparation of 3-(2-(3-methoxy-1-propynyl)-3,4,5-trimethoxyphenyl)propanal (472).



471 **472**

To a stirred solution of ester (**471**) (250mg, 0.78mmol) in dichloromethane (15mL) at -78°C was added dropwise DIBAL-H (533μL of a 1.5M solution in toluene, 0.80mmol) to give a yellow solution. The reaction mixture was stirred at this temperature for 30 minutes, then quenched by pouring onto 1M hydrochloric acid (15mL) and extracted with dichloromethane (2 ×20mL). The combined extracts were dried ($MgSO_4$), filtered and chromatographed (SiO_2, 50% ether in petrol) to afford the aldehyde (**472**) (189mg, 83%) as a pale yellow oil.

R_f (50% ether in petrol) 0.09;

ν_{max} (KBr)/cm^{-1} 2934, 2840, 2726, 2221, 1722, 1594, 1493, 1456, 1406, 1334, 1236, 1195, 1136, 1099, 1050, 996, 901, 841;

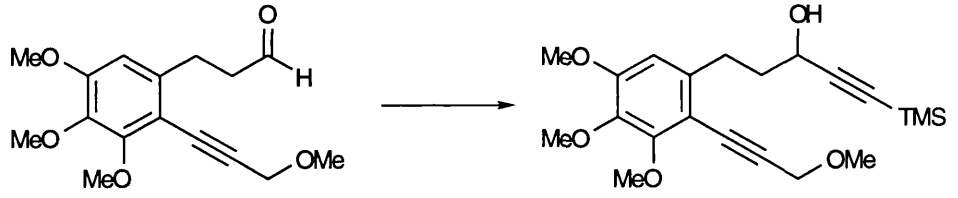
δ_H(400MHz; $CDCl_3$) 9.79 (1H, t, J=1.3Hz, C*H*O), 6.51 (1H, s, aromatic), 4.36 (2H, s, CH_2OMe), 3.92 (3H, s, MeO), 3.83 (3H, s, MeO), 3.81 (3H, s, MeO), 3.43 (3H, s, MeO), 3.01 (2H, t, J=7.4Hz, ArCH_2CH_2), 2.78 (2H, dt, J=1.3, 7.2Hz, ArCH_2CH_2);

δ_C(100MHz; $CDCl_3$) 201.5, 155.1, 153.8, 140.4, 139.2, 109.2, 108.1, 91.9, 80.5, 61.2, 61.0, 60.6, 57.5, 56.0, 44.4, 27.2;

LRMS (FAB mode): *m/z* 292 (100%, M^+), 261, 233, 219, 203, 189;

HRMS (FAB mode): Found: M^+, 292.1316. $C_{16}H_{20}O_5$ requires *M*, 292.1311.

Preparation of 3-hydroxy-5-(2-(3-methoxypropynyl)-3,4,5-trimethoxyphenyl)-1-trimethylsilyl-1-pentyne (473).



472 **473**

Trimethylsilyl acetylene (99μL, 0.70mmol) in THF (5mL) was cooled to -78°C and treated with ethyl magnesium bromide (233μL of a 3.0M solution in THF, 0.70mmol). The resultant solution was heated to room temperature and then to reflux for 1 hour, after which it was allowed to return to room temperature. In a separate flask, aldehyde (**472**) (102mg, 0.35mmol) in THF (5mL) was cooled to -78°C, to which was added the Grignard solution, *via* a cannula. On warming to room temperature the reaction mixture was poured onto saturated ammonium chloride solution (20mL) and extracted with ether (2× 20mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2,

60% ether in petrol) gave the starting aldehyde (21mg, 21%) and the product (**473**) (80mg, 59%) as pale yellow oils.

R_f (70% ether in petrol) 0.39;

ν_{max} (thin film)/cm^{-1} 3424, 2936, 2869, 2222, 2171, 1636, 1593, 1492, 1461, 1407, 1337, 1250, 1194, 1134, 1101, 1065, 1004, 902, 843, 761;

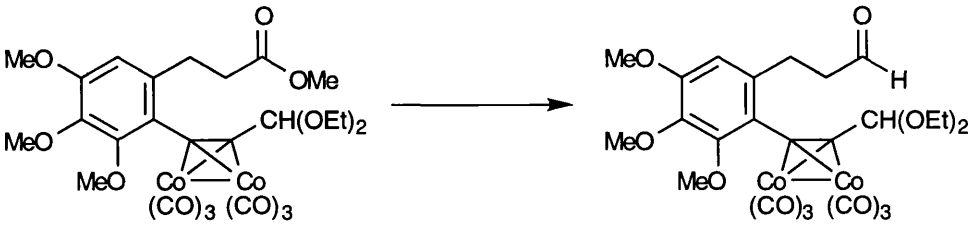
δ_H(400MHz; $CDCl_3$) 6.54 (1H, s, aromatic), 4.39 (2H, d, C*H*$_2$OMe), 4.38-4.34 (1H, m, OH), 3.95 (3H, s, MeO), 3.86 (3H, s, MeO), 3.84 (3H, s, MeO), 3.47 (3H, s, MeO), 2.96-2,82 (2H, m, ArC*H*$_2$CH$_2$), 2.30-2.24 (1H, m, C*H*OH), 2.11-1.95 (2H, m, ArCH$_2$C*H*$_2$), 0.17 (9H, s, Me_3Si);

δ_C(100MHz; $CDCl_3$) 154.9, 153.8, 140.4, 140.2, 109.3, 108.2, 106.6, 105.2, 91.5, 89.4, 81.0, 62.0, 61.3, 61.1, 60.8, 57.7, 56.0, 38.5, 30.5;

LRMS (FAB mode): *m/z* 390 (42%, M^+), 359, 343, 250, 231, 189, 128;

HRMS (FAB mode): Found: M^+, 390.1870. $C_{21}H_{30}O_5Si$ requires *M*, 390.1863.

Preparation of 3-(2-(3,3-diethoxypropyn(1,2-η^2-dicobalthexacarbonyl)yl)-3,4,5-trimethoxyphenyl)propanal (476).



469 **476**

To a stirred solution of ester (**469**) (60mg, 0.09mmol) in dichloromethane(10mL) at -78°C was added dropwise DIBAL-H (66μL of a 1.5M solution in toluene, 0.10mmol) and the resultant solution was stirred at this temperature for 2.5 hours. The reaction was quenched by pouring onto 2M hydrochloric acid (10mL) and

extracted with dichloromethane (2× 15mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography of the crude material (SiO_2, 50% ether in petrol) gave the starting ester (**469**) (14mg, 23%) and the product aldehyde (**476**) (15mg, 26%) as black solids.

m.p. 220°C (dec.).

R_f(50% ether in petrol) 0.26;

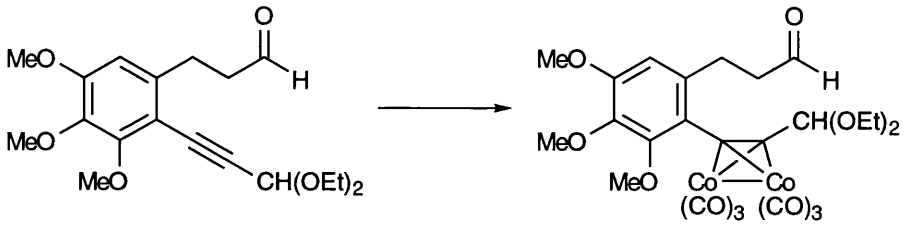
ν_{max} (KBr)/cm^{-1} 2929, 2088, 2048, 2014, 1726, 1589, 1487, 1388, 1321, 1197, 1107, 1059;

δ_H(400MHz; $CDCl_3$) 9.86 (1H, t, J=1.5Hz, C*H*O), 6.43 (1H, s, aromatic), 5.69 (1H, s, C*H*$(OEt)_2$), 4.01 (3H, s, MeO), 3.86 (3H, s, MeO), 3.77 (3H, s, MeO), 3.64-3.60 (4H, m, O*CH*$_2$$CH_3$), 3.28-3.25 (2H, m, ArC*H*$_2$$CH_2$), (2H, m, $ArCH_2$C*H*$_2$), 1.32-1.15 (6H, m, OCH_2C*H*$_3$);

δ_C(100MHz; $CDCl_3$) 201.5, 200.1, 200.0, 136.9, 106.5, 102.9, 64.1, 60.6, 60.3, 55.8, 44.4, 21.3, 15.1;

Elemental analysis: Found: C, 46.17; H, 4.06. $C_{25}H_{26}Co_2O_{12}$ requires C, 47.19; H, 4.12%.

Preparation of 3-(2-(3,3-diethoxypropyn(1,2-η^2-dicobalthexacarbonyl)yl)-3,4,5-trimethoxyphenyl)propanal (476).



434 **476**

To a solution of aldehyde (**434**) (64mg, 0.18mmol) in benzene (10mL) at room temperature was added, *via* a cannula, a solution of dicobalt octacarbonyl (75mg,

0.22mmol) in benzene (5mL) and the resultant solution was stirred at room temperature for 2.5 hours. After this time the reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, 50% ether in petrol) to afford the product (**476**) (78mg, 68%) as a black solid.

m.p. 220°C (dec.).

R_f (50% ether in petrol) 0.26;

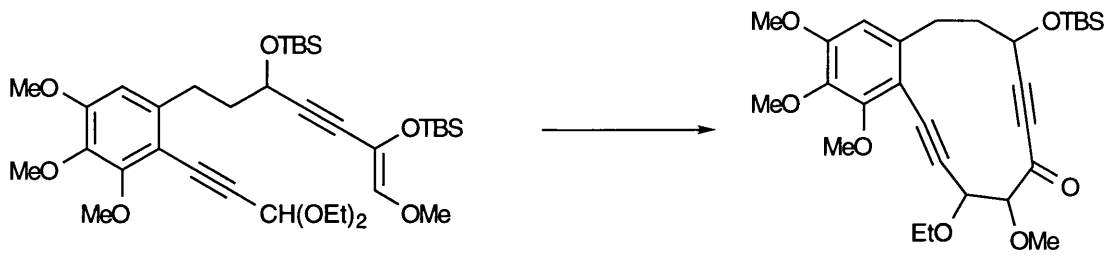
ν_{max} (KBr)/cm^{-1} 2929, 2088, 2048, 2014, 1726, 1589, 1487, 1388, 1321, 1197, 1107, 1059;

δ_H(400MHz; $CDCl_3$) 9.86 (1H, t, J=1.5Hz, C*H*O), 6.43 (1H, s, aromatic), 5.69 (1H, s, C*H*$(OEt)_2$), 4.01 (3H, s, MeO), 3.86 (3H, s, MeO), 3.77 (3H, s, MeO), 3.64-3.60 (4H, m, OC*H*$_2$$CH_3$), 3.28-3.25 (2H, m, ArC*H*$_2$$CH_2$), (2H, m, $ArCH_2$C*H*$_2$), 1.32-1.15 (6H, m, OCH_2C*H*$_3$);

δ_C(100MHz; $CDCl_3$) 201.5, 200.1, 200.0, 136.9, 106.5, 102.9, 64.1, 60.6, 60.3, 55.8, 44.4, 21.3, 15.1;

Elemental analysis: Found: C, 46.17; H, 4.06. $C_{25}H_{26}Co_2O_{12}$ requires C, 47.19; H, 4.12%.

Preparation of 1,12,13,14,15,16-dehydrobicyclo[10.4.0]-4-ethoxy-5,14,15,16-tetramethoxy-6-oxo-9-*tert*-butyldimethylsilyloxyhexadec-2,7-diyne (477).



465 **477**

A solution of silyl enol ether (**465**) (35mg, 5.2×10^{-5}mol) in dichloromethane (50mL) at -78°C was treated, dropwise, with a solution of titanium(IV) chloride (52μL of a

1.0M solution in dichloromethane, 5.2×10^{-5}mol) and the resultant solution stirred at -78°C for 5 minutes. Saturated aqueous sodium carbonate (1mL) was added and the mixture was allowed to warm to room temperature. The reaction mixture was poured onto water (20mL) and extracted with dichloromethane (2 ×20mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo.* Column chromatography (SiO_2, 50% ether in petrol) afforded the macrocycle (**477**) (18mg, 67%) as a pale yellow oil.

R_f (50% ether in petrol) 0.30;

ν_{max} (thin film)/cm^{-1} 2932, 2857, 2217, 2180, 1679, 1595, 1563, 1492, 1460, 1434, 1407, 1339, 1253, 1196, 1119, 1093, 987, 913, 839, 780, 732;

δ_H(400MHz; $CDCl_3$) 6.49-6.47 (1H, m, aromatic), 4.61-4.52 (2H, m), 4.18-3.93 (1H, m), 3.92-3.87 (3H, m, MeO), 3.84-3.82 (3H, m, MeO), 3.81-3.78 (3H, m, MeO), 3.63-3.53 (1H, m), 3.47-3.42 (3H, m, MeO), 3.24-3.10 (1H, m), 2.97-2.89 (1H, m), 2.86-2.76 (1H, m), 2.14-1.79 (2H, m), 1.24-1.17 (3H, m, OCH_2CH_3), 0.85-0.84 (9H, m, ^{t}BuSi), 0.10-0.06 (6H, m, MeSi);

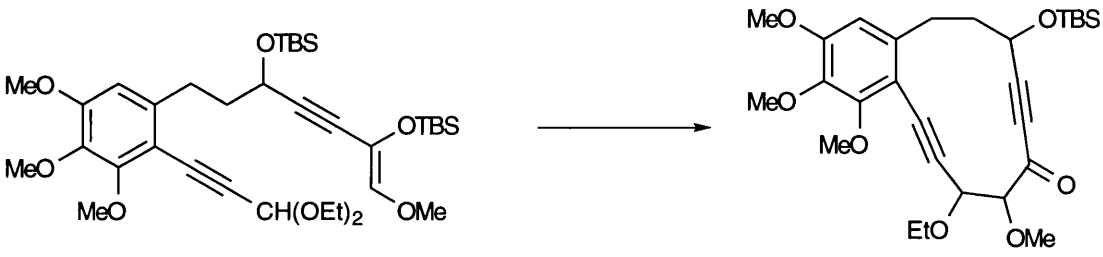
δ_C(100MHz; $CDCl_3$) 186.1, 155.2, 154.1, 153.0, 141.1, 140.6, 140.2, 107.8, 107.6, 98.3, 90.5, 90.2, 90.0, 87.6, 87.4, 84.0, 83.1, 83.0, 82.4, 71.2, 71.1, 69.8, 69.7, 65.1, 64.7, 62.8, 62.6, 61.2, 61.2, 61.1, 61.0, 58.9, 58.8, 58.5, 56.0, 55.9, 40.2, 40.0, 33.6, 30.3, 29.7, 29.5, 29.3, 25.7, 25.6, 25.5, 18.1, 14.9, 14.8;

LRMS (FAB mode): *m/z* 539 (55%, $[M+Na]^+$), 515, 501, 485, 471, 443, 357, 233, 207, 181;

HRMS (FAB mode): Found: $[M+Na]^+$, 539.2450. $C_{28}H_{40}O_7SiNa$ requires *M*, 539.2441.

Elemental analysis: Found: C, 64.93; H, 7.97. $C_{28}H_{40}O_7Si$ requires C, 65.09; H, 7.80%.

Preparation of 1,12,13,14,15,16-dehydrobicyclo[10.4.0]-4-ethoxy-5,14,15,16-tetramethoxy-6-oxo-9-*tert*-butyldimethylsilyloxyhexadec-2,7-diyne (477).

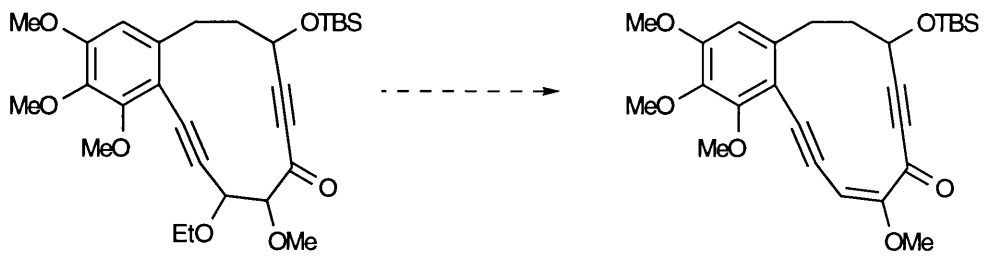


465 **477**

To a solution of silyl enol ether (**465**) (105mg, 0.155mmol) in dichloromethane (30mL) at -40°C was added a solution of trimethylsilyl trifluoromethanesulfonate (20μL of a 1.0M solution in dichloromethane, 2× 10^{-5}mol). The resultant blue solution was stirred at this temperature for 30 minutes. The reaction was then quenched by the addition of water (1mL) and allowed to warm to room temperature. The purple solution obtained was poured onto saturated ammonium chloride solution (20mL) and extracted with dichloromethane (2 ×10mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 50% ether in petrol) proved unsuccessful in separating the diastereomers but afforded the product (71mg, 88%) as a pale yellow oil.

Spectral data as for procedure above.

Attempted Preparation of 1,12,13,14,15,16-dehydrobicyclo[10.4.0]-5,14,15,16-tetramethoxy-6-oxo-9-*tert*-butyldimethylsilyloxyhexadec-4-en-2,7-diyne (481).



477 **481**

A solution of **477** (81mg, 0.16mmol) in dichloromethane (3mL) at 0°C was treated with trimethylsilyl trifluoromethanesulfonate (240μL of a 1M solution in dichloromethane, 0.24mmol). After 5 minutes the reaction mixture was poured onto water (10mL) and extracted with dichloromethane (3× 15mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo.* Column chromatography (SiO_2, ether) gave an impure sample of the product (34mg) as a dark yellow oil.

R_f (ether) 0.30;

ν_{max} (thin film)/cm^{-1} 3415, 2923, 1645, 1594, 1464, 1409, 1322, 1197, 1098, 1033;

δ_H(400MHz; $CDCl_3$) unassignable, except for signals at 3.90, 3.83, 3.80 and 3.39ppm;

LRMS (EI mode 70eV): *m/z* 342 (100%), 220, 205, 181, 152;

λ_{max} (EtOH)/nm 221 and 368.

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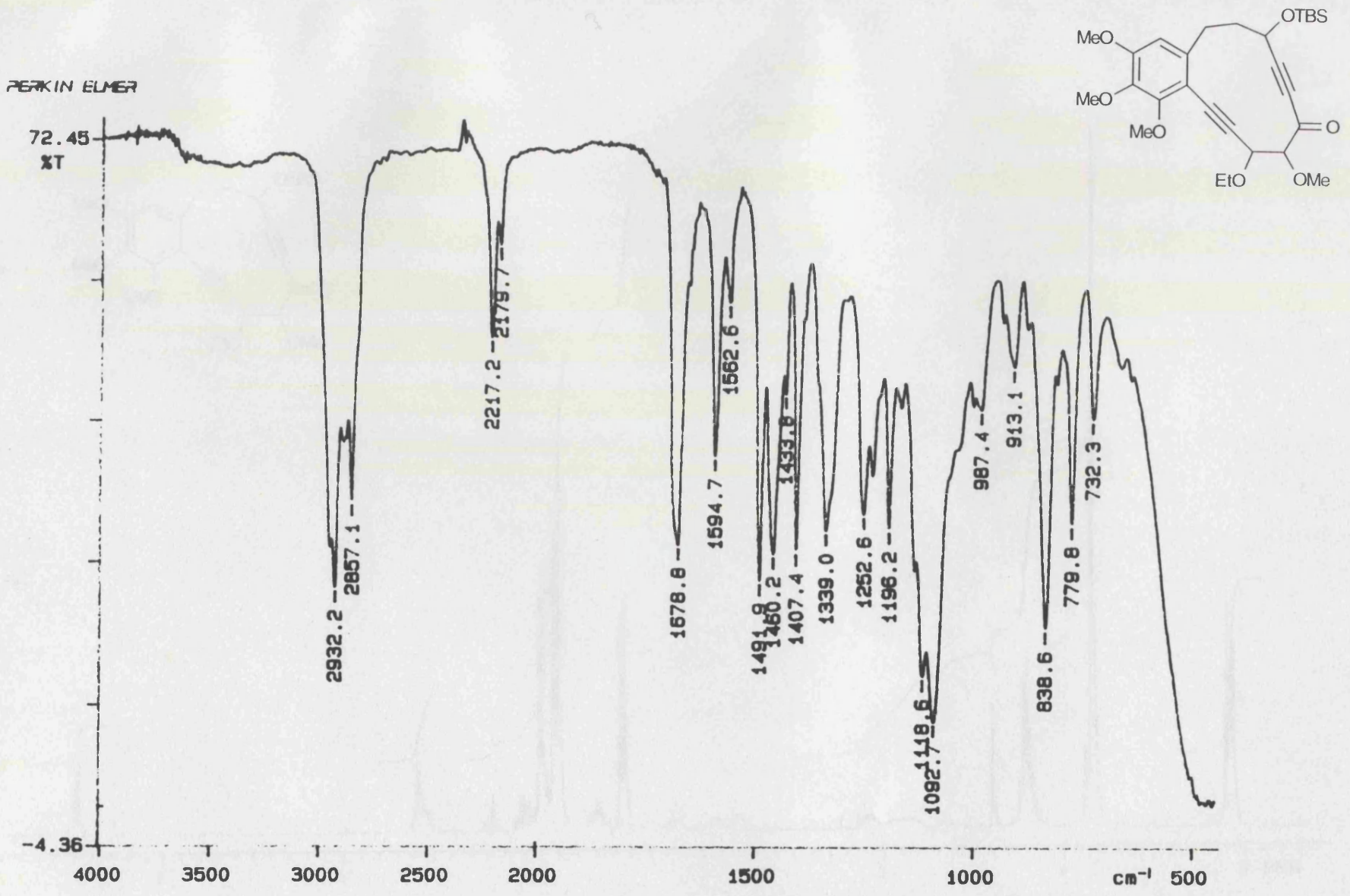
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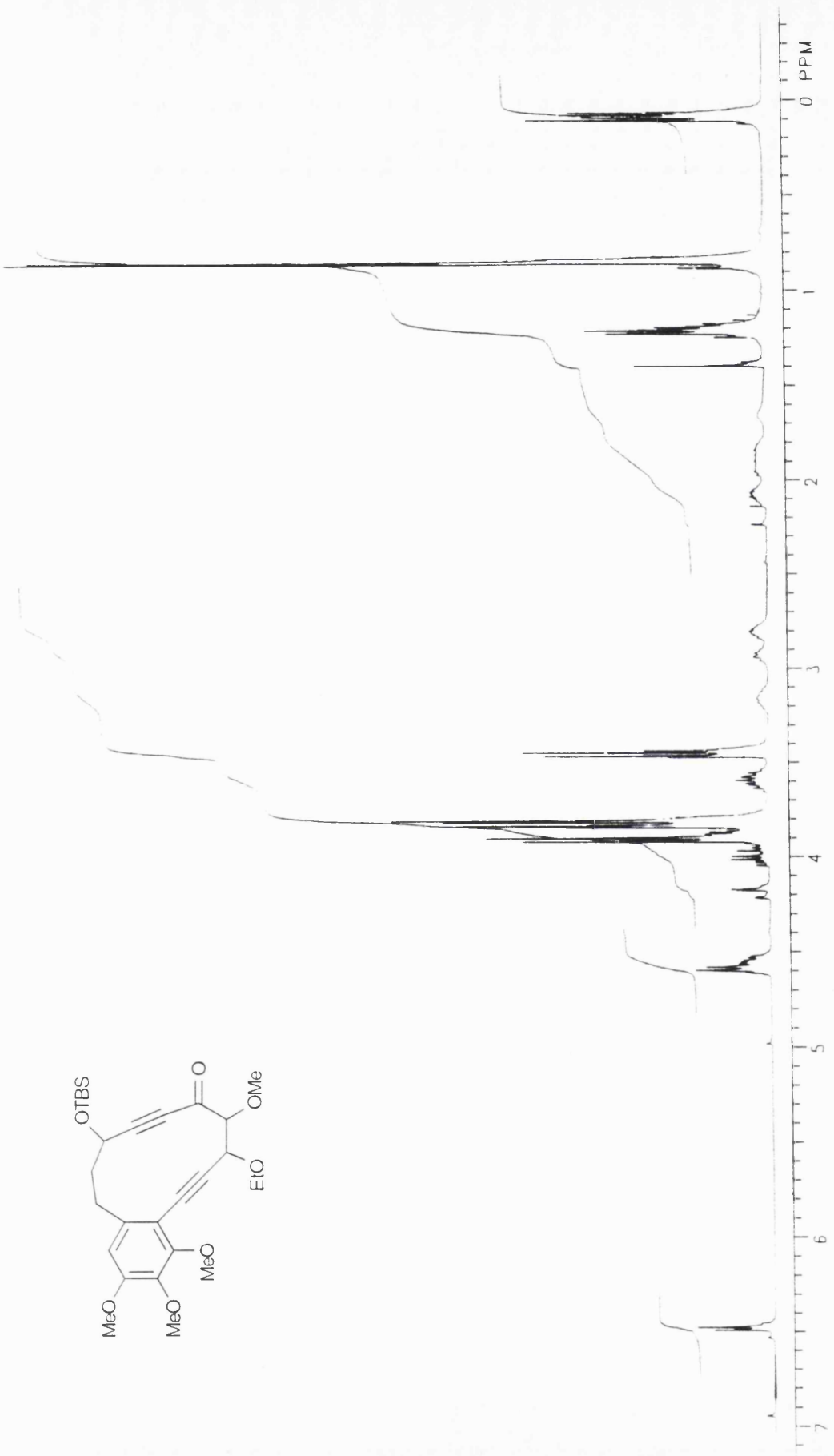
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