# The enediyne and dienediyne based antitumour antibiotics. Methodology and strategies for total synthesis and construction of bioactive analogues. Part 1

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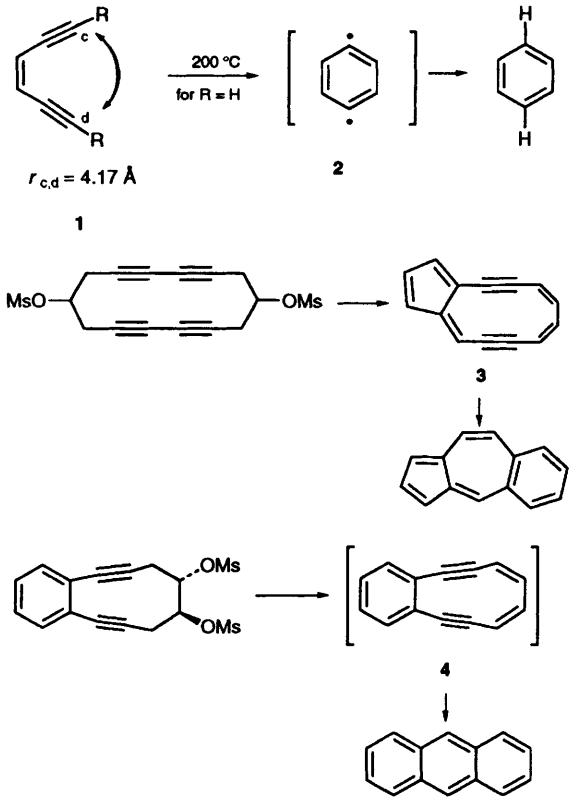
Reviewing the literature published up to 15 October 1995



## 1 Introduction

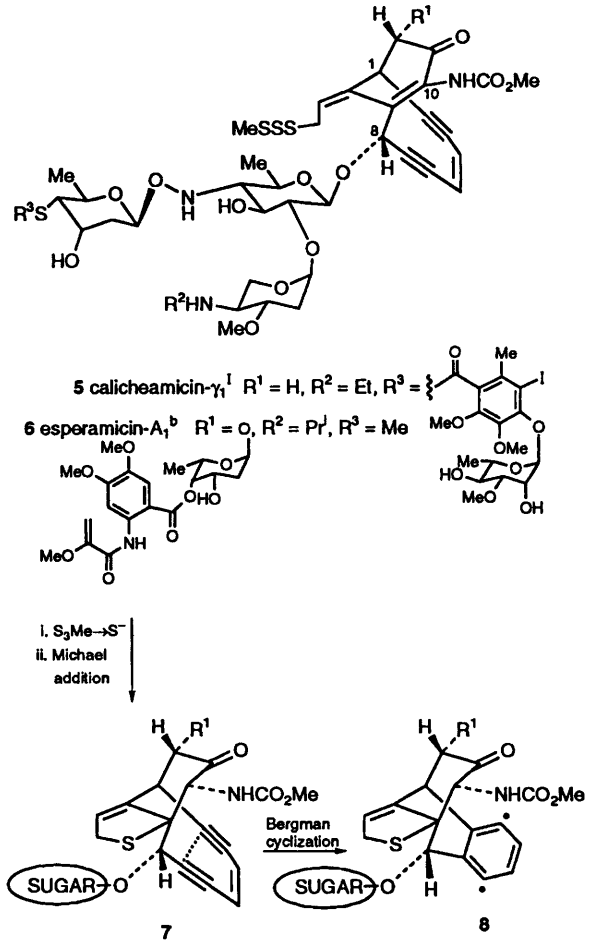
In a key contribution to the study of aromatic systems and aromaticity, Bergman and collaborators carried out experiments nearly twenty-five years ago to define the physical existance, structure, bonding properties and reactivity of 1,4-dehydrobenzene **2**.[1] In one particularly elegant experiment the scrambling of the deuterium label in the acyclic enediyne **1** (R = D) provided convincing evidence for the intermediacy of phenylene diradical **2** (**Scheme 1**). This result, further, offered a coherent mechanistic rationale for a number of unexpected transformations, including the tendency of molecules such as the dehydro-azulene **3** and the 1,5-dehydro[10]annulene **4** to undergo rapid cycloaromatization.[2,3] As important as these studies remain today from a fundamental point of view, the human spirit was a long way at that time from imagining the creative way in which nature has for eons enabled microorganisms to employ this same process in a controlled and lethal manner to assure their proper defence. However, our awareness of this situation changed in the mid 1980s with the structure elucidation of the complex and extraordinary novel antibiotics calicheamicin **5**,[4] esperamicin **6**[5] and the neocarzinostatin chromophore **9**,[6] the first three members of a family




**Scheme 1**

of naturally occurring and highly potent cytotoxic agents.

The most notable features in the common core structure of (−)-calicheamicin $\gamma_1^1$ and (−)-esperamicin $A_1$ (**Scheme 2**) are the presence of a contiguous yne-ene-yne (or 'enediyne') system incorporated into a bicyclo[7.3.1]tridecane framework, an allylic trisulfide unit, and an enone system in which the double bond occupies the bridgehead position. Chemical and biochemical investigations have shown that these entities react in concert to generate the highly reactive 1,4-phenylene diradical intermediate **8** which cause cell destruction through single and double strand

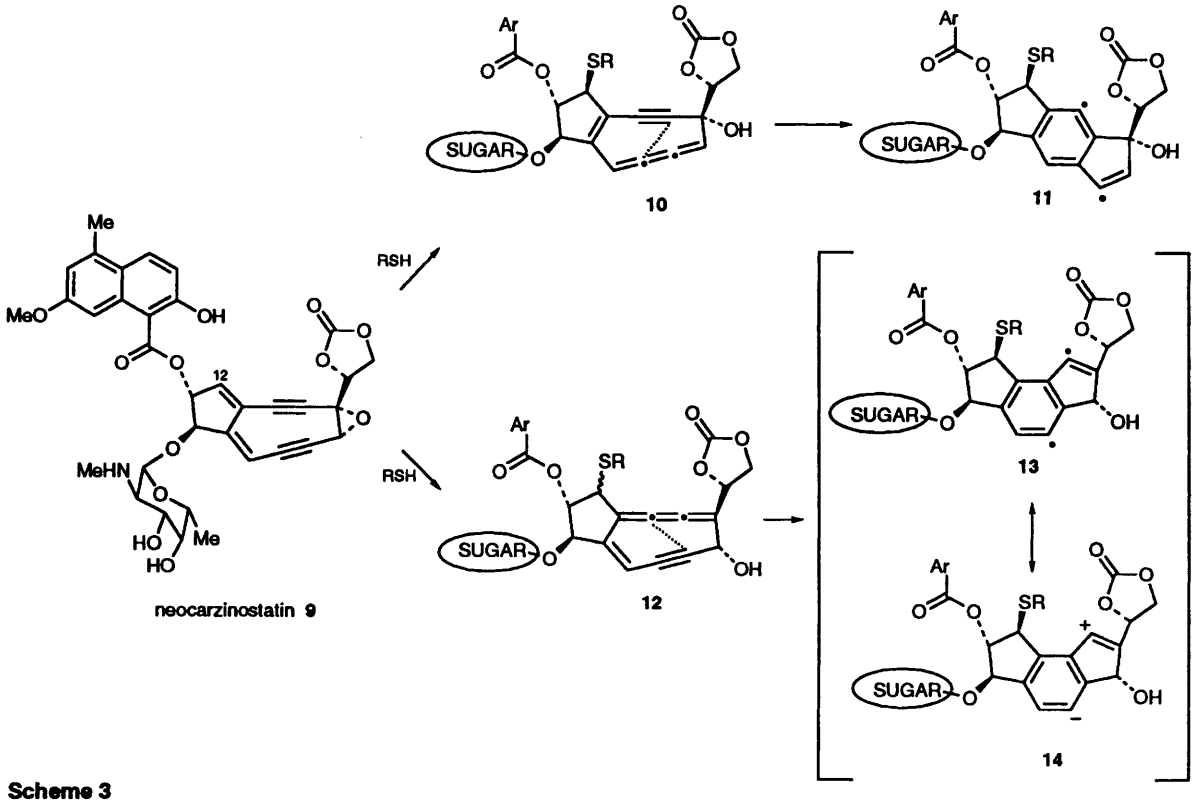



Scheme 2

cleavage of duplex DNA.[7–9] This is brought about by an unprecedented multistep mechanism involving the aryl oligosaccharide mediated association of the antibiotic with its intracellular target, cleavage (reduction) of the trisulfide bond, and Michael addition of the resulting thiolate anion to the enone double bond to produce the highly strained intermediate **7** lacking the crucial C-9,10 bridgehead double bond. This latter structural modification activates, or unlocks, the molecule with respect to spontaneous Bergman type cycloaromatization to diradical **8**.

The neocarzinostatin chromophore **9**, a very heat-, light- and pH-sensitive 9-membered bicyclic dienediyne, exists in nature in association with an apoprotein.[10] With the knowledge that **9** is activated towards DNA cleavage through reaction with thiols,[8–10] Myers proposed a mechanism whereby thiol addition at C-12 initiates epoxide ring opening and formation of the yne-ene-cumulene **10** (**Scheme 3**).[11] This strained and very highly reactive intermediate then undergoes a cycloaromatization reaction, analogous to that for the enediynes, giving the diradical **11** which cleaves DNA through hydrogen atom abstraction. In an elegant series of NMR experiments Myers both confirmed the formation of the thioglycolate derivative of **10**, measured its stability ($t_{\frac{1}{2}} = 2$ h at $-38$ °C), and deduced the absolute stereochemistry of **9**.[12,13] Recently, it has been shown that the alternative pathway, leading to the diradical **13** or its zwitterionic resonance form **14** via cumulene **12**, is also operative in aqueous buffered solution.[14]

In 1990, Konishi and Clardy reported the structure of another enediyne antibiotic,



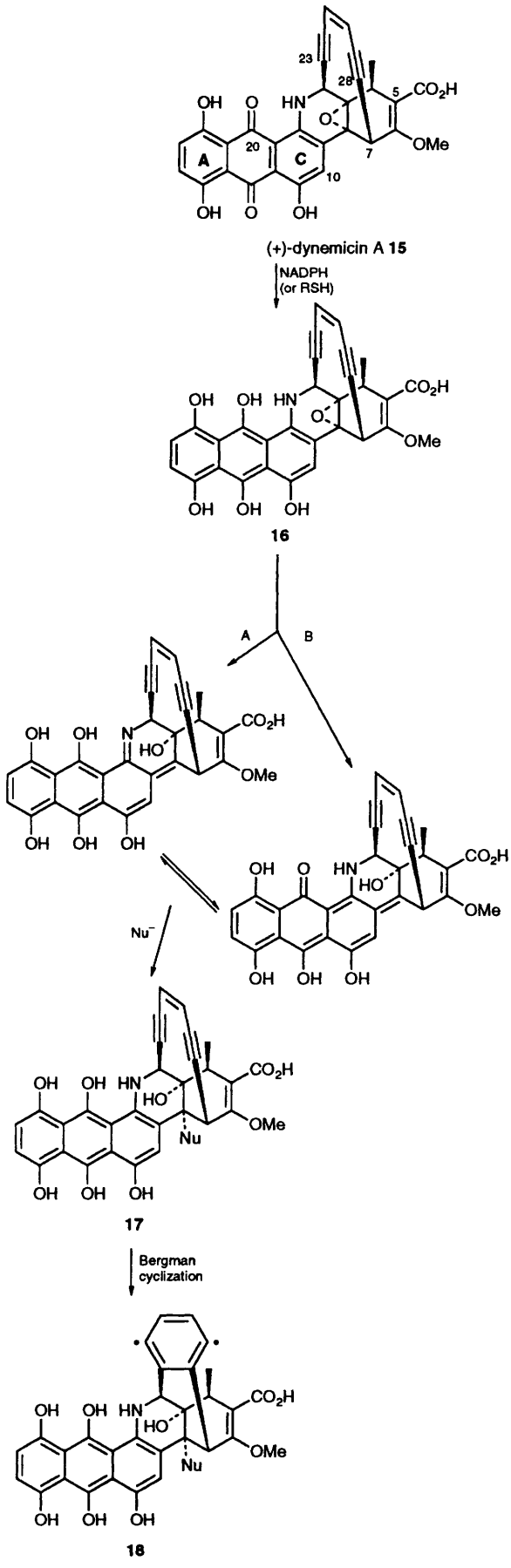

Scheme 3

(+)-dynemicin A **15** (**Scheme 4**).[15] This unique hybrid molecule is essentially composed from an enediyne core as found in calicheamicin/esperamicin, and an anthraquinone unit typical of the anthracyclines which can associate with DNA through intercalation.[8,9,16,17] Between these two halves of the molecule is an angular epoxide function which acts as the triggering device. Bioreduction of the paraquinone system of **15** giving **16** activates the molecule toward epoxide opening according to pathway B, or through participation of the electrons on nitrogen (pathway A). As discussed further on, the latter mechanism has, in particular, been exploited to activate simplified analogues of dynemicin A. Reaction of either intermediate with the $OH^-$ ($Nu^-$) ion giving **17** alters the shape and strain energy of the D/E rings promoting spontaneous Bergman cyclization to diradical **18**. The highly strained nature of dynemicin A is readily apparent from the X-ray crystal structure of its triacetate derivative.[15] In this molecule the alkyne substituents are bent by up to 20° from linearity, and the distance between the two acetylene terminal carbons 23 and 28 is 3.54 Å, *i.e.* considerably less than the 4.17 Å separation observed between the same carbons in **1**.

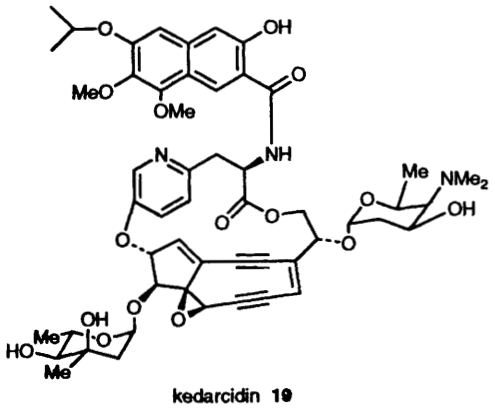
Over the past three or four years three new molecules have been added to the list of enediyne based antitumor agents. These include kedarcidin **19**[18] and C-1027 **20**[19] which both possess an enediyne unit within a 9-membered bicyclic framework related to the neocarzinostatin chomophore (**Scheme 5**). Certain elements are still undetermined concerning the structure of the third and extremely labile molecule named maduropeptin.[20] However, from the structure of the artifact **21**, one perceives a new mechanism of activation involving $S_N2'$ displacement of $X^-$ and generation of the central enediyne double bond in **22**.

In view of the large possibilities of designing and discovering new anticancer agents based upon the novel structure and mechanism of action of the enediyne–dienediyne antibiotics, intense efforts have been made to both achieve their total synthesis, and to access simpler and more stable biologically active analogues. Work toward both goals has necessitated the development of new synthetic methodology for the efficient construction of the enynes and enediynes, and for the incorporation of these entities into strained mono- and polycyclic structures under conditions where adventitious cycloaromatization, and/or other undesired rearrangements are avoided. It has similarly required the invention of novel triggering devices, and experiments to establish the different factors which permit Bergman and Myers type electrocyclization of enediyne, yne-ene-allene and yne-ene-cumulene systems to occur at physiological temperatures.

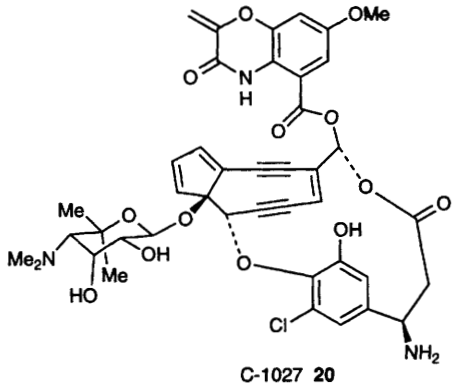
These, and many other challenging aspects of the chemistry in this field, are described in this two-part review. In Part 1, synthetic approaches, and the reactivity of simple enediynes and neocarzinostatin analogues are described. In Part 2,[20a] the discussion



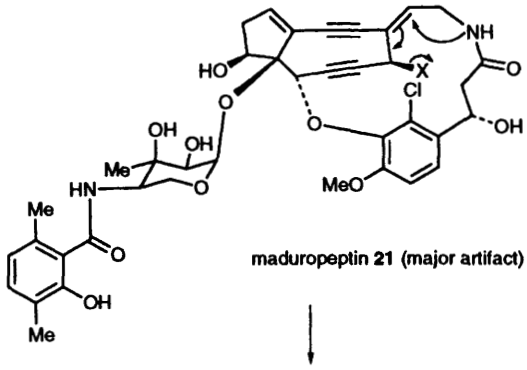

**Scheme 4**



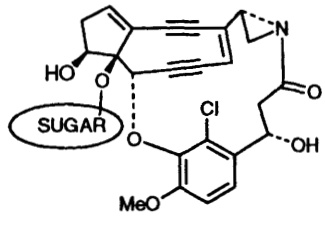
kedarcidin **19**



C-1027 **20**



maduropeptin **21** (major artifact)



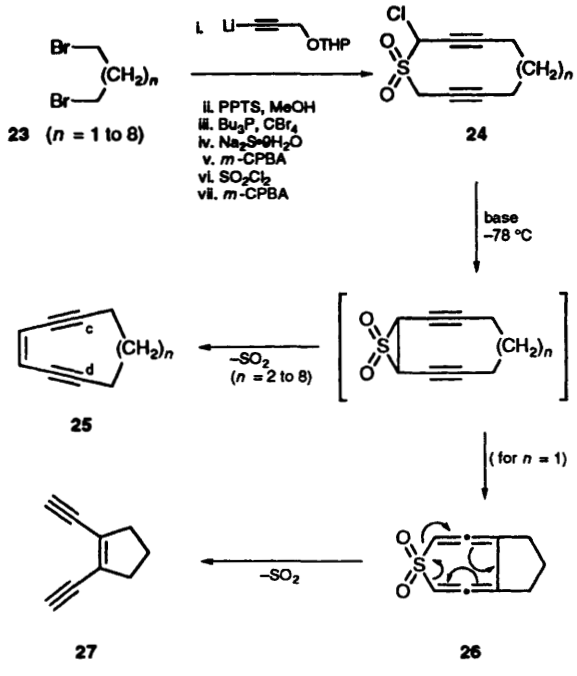
**22**

**Scheme 5**

centres more specifically upon the strategies developed for the total synthesis of the neocarzinostatin chromophore, calicheamicin $\gamma_1^I$, esperamicin $A_1$ and dynemicin A. Several earlier reviews have appeared treating the chemistry and/or biological properties of the enediyne–diendiyne antibiotics.[8,9,21–25]

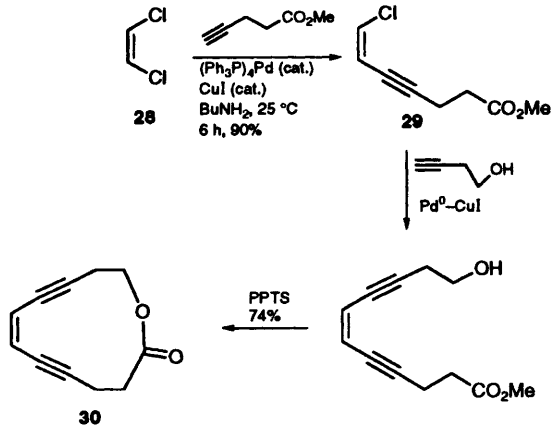
## 2 Enediyne construction and simple monocyclic and bicyclic enediynes

The seminal investigations by Bergman on the cycloaromatization of simple acyclic enediynes demonstrated that heating to approximately 200 °C is required in order to surmount the activation barrier ($\Delta E_{act}$ = 28–32 kcal mol$^{-1}$) to transformation of **1** to the 1,4-phenylene diradical **2**.[1,26,27] In contrast, calicheamicin, dynemicin A and the other enediynes undergo almost instantaneous ambient temperature cycloaromatization upon activation, indicating that incorporation of the enediyne system into a cyclic structure lowers $\Delta E_{act}$ significantly (21–24 kcal mol$^{-1}$ range). To systematically examine the influence of ring size, and hence the distance $r_{c,d}$ between the acetylene terminal carbon atoms, on cycloaromatization rates, Nicolaou devised a route to the monocyclic enediynes **25** ($n$ = 2–8) starting from the appropriate dibromides **23**.[28–30] In this approach the key step was the Ramberg–Bäcklund ring contraction of the sulfone intermediates **24** (**Scheme 6**).[31] These studies showed that for the 10-membered all carbon monocyclic enediyne **25** ($n$ = 2), $r_{c,d}$ falls in the range (3.20–3.30 Å; MMX calculations) where Bergman cyclization can occur at an appreciable rate at 37 °C ($t_{1/2}$ = 11.8 h). Interestingly, attempts to prepare the 9-membered enediyne **25** ($n$ = 1) by this route resulted in formation of enediyne **27**, presumably by a Cope type rearrangement of **26** and $SO_2$ extrusion. Magnus and Snyder further showed that for more highly functionalized cyclic enediynes, $\Delta E_{act}$ is primarily determined by factors influencing the strain energy (i) of the ground state structure and (ii) at the transition state for the cycloaromatization reaction.[26,32]



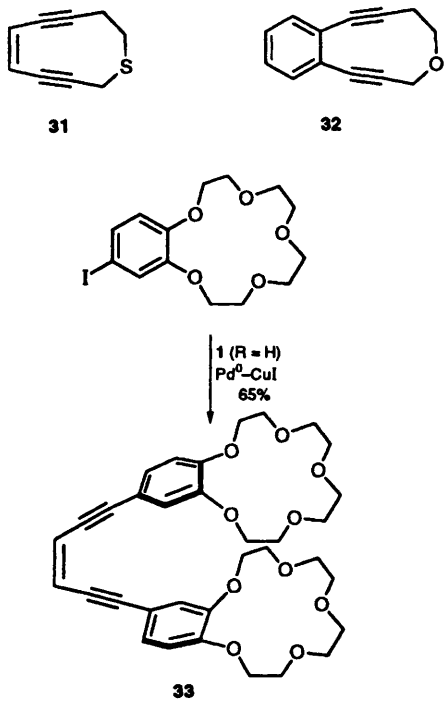

**Scheme 6**

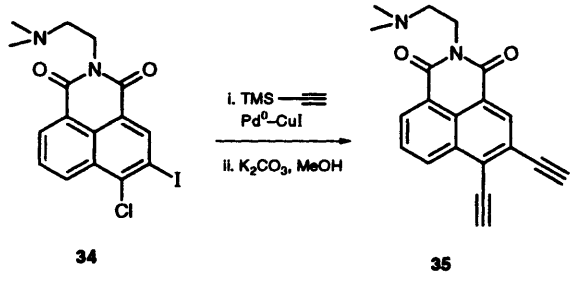
Of major impact to all subsequent syntheses of the enediyne and neocarzinostatin type systems has been the existence of modern palladium(0) based coupling methodology permitting assembly of the key ene-yne motif from a wide variety of olefin and acetylene precursors under operationally simple, exceptionally mild, and high yielding conditions. The generality of this approach is nicely illustrated by the construction of the parent 3-ene-1,5-diyne **1** (R = TMS) by Vollhardt,[33,34] and the stable 12-membered ring lactone **30** by Linstrumelle (**Scheme 7**).[35,36] In this latter synthesis, described two years prior to the discovery of calicheamicin/esperamicin, the species produced by oxidative addition of *cis*-dichloroethene **28** to Pd(0) reacts with an *in situ* generated copper acetylide intermediate, and the resulting vinyl-alkynyl palladium derivative undergoes a reductive elimination to liberate the ene-yne product **29** and the Pd(0) catalyst. Various amine bases ($Et_2NH$, $Et_3N$, $Pr^iNH_2$, $BuNH_2$) can be employed in this reaction,[37] and, as described by Sonogashira, $(Ph_3P)_4Pd^0$ can be replaced by $(Ph_3P)_2PdCl_2$ when a slight excess of the acetylene component is used to effect reduction of Pd(II).[38] Vinyl and alkynyl tin, zinc and boron reagents can also be employed in these palladium couplings.[39–42] Recently it has been shown that Pd(0) coupling of terminal acetylenes with vinyl bromides, iodides and triflates does not require added CuI when pyrrolidine or piperidine is used as the base.[43]




**Scheme 7**

Following the Linstrumelle strategy the more strained 10-membered monocyclic enediyne **31** has been prepared,[44] and by replacing *cis*-dichloroethene by *o*-dibromobenzene the related benzodiyne **32** was also obtained.[45] These compounds undergo Bergman cyclization at temperatures higher than the parent enediyne **25** ($n = 2$). $Pd^0$–CuI mediated coupling of aryl iodides with enediyne **1** (R = H) is similarly efficient, and has been used to prepare the novel crown ether **33**.[46] The reaction threshold for this molecule is apparently lower than for **1** (R = H). However, the 2:1 sandwich complex with the $K^+$ ion is less reactive. In the search for new enediyne systems which can intercalate with DNA, the acyclic benzodiyne **35** was constructed from the naphthalimide derivative **34** through reaction with two molecules of trimethylsilyl acetylene.[47]

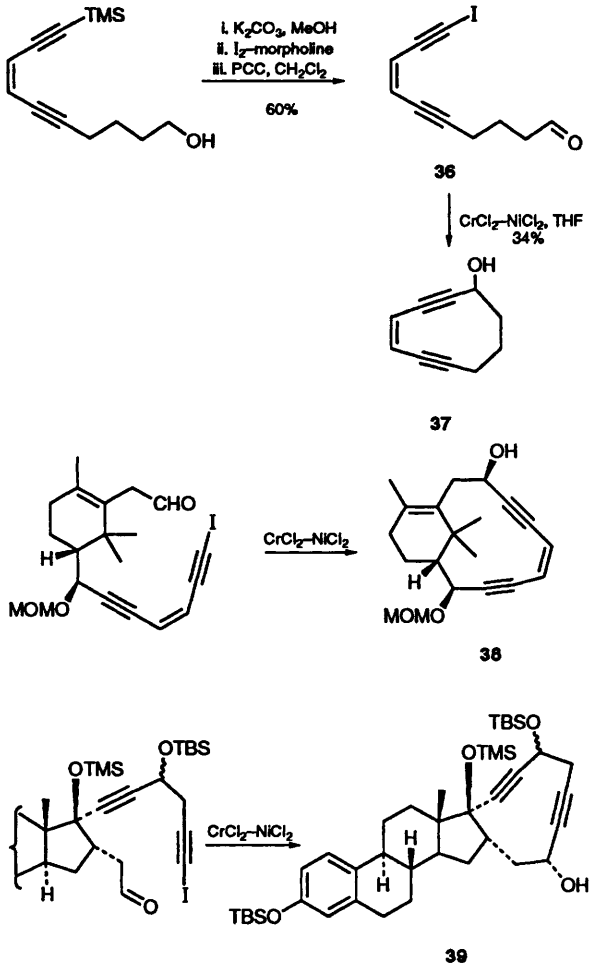


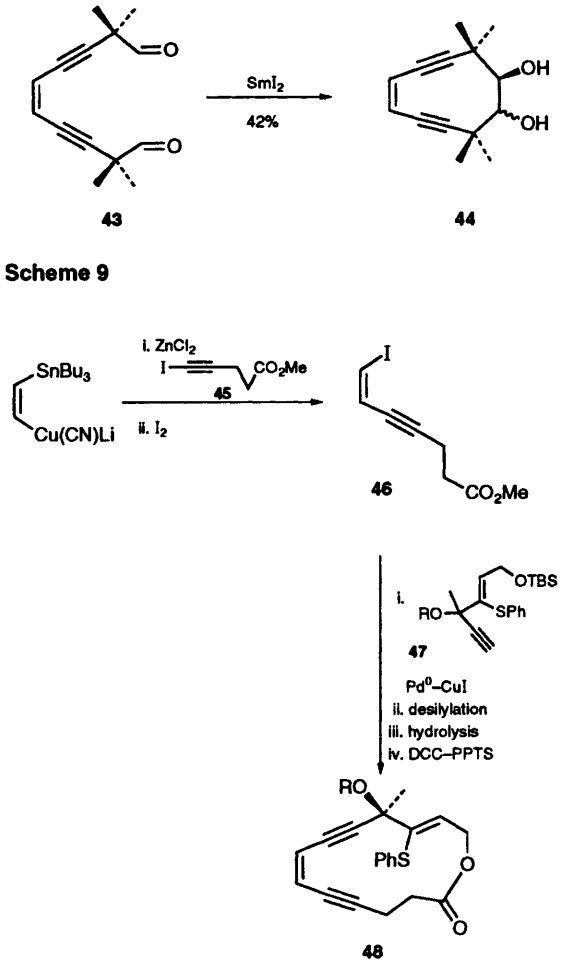

Beau and co-workers have demonstrated the power of the Nozaki–Kishi reaction ($CrCl_2$–$NiCl_2$) between an acetylenyl iodide and an aldehyde to effect ring closure of **36** to the 10-membered enediyne **37** bearing a prop-2-ynylic alcohol substituent (**Scheme 8**).[48,49] This reaction is similarly a key step in the conceptually interesting synthesis by Fallis of the 'taxamycin' **38** (an enediyne–taxol hybrid),[50] and the equally novel enediyne–estradiol hybrid **39** by De Clercq.[51]

Boger *et al.* on the other hand, found that the benzodiyne **40** undergoes ring closure to **41** on treatment with lithium amide base, albeit in modest yield (21%).[52] This compound was coupled to $CDPI_3$, a synthetic non-covalent DNA minor groove binder, and the resulting conjugate **42** was shown to display potent capacity to interact with and cleave supercoiled DNA.

A samarium iodide induced Pinacol type reaction has also been used by Nicolaou to effect ring

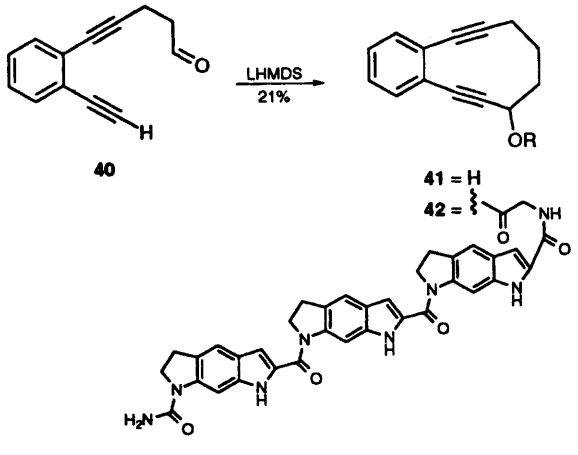



**Scheme 8**




**Scheme 9**

**Scheme 10**

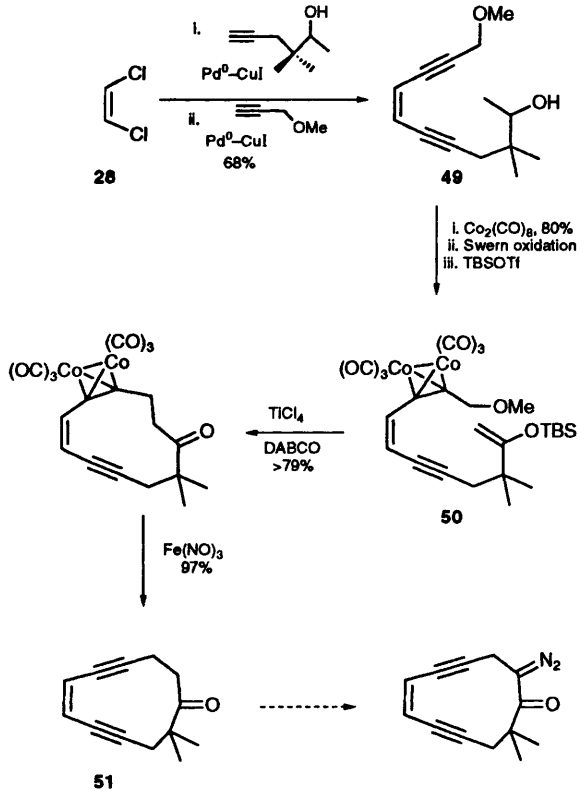



closure of the readily accessible dialdehyde **43** to the 10-membered enediyne **44** (42%) (**Scheme 9**).[53]

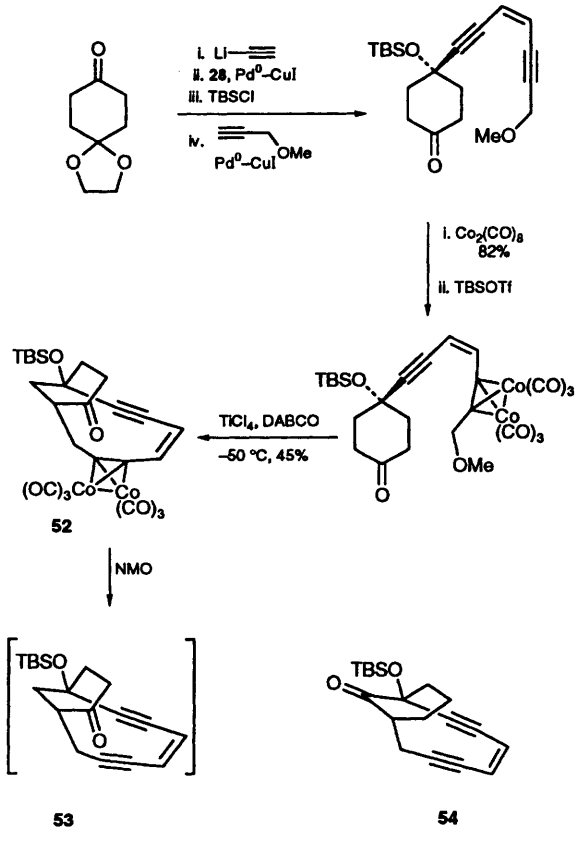
Working along different lines, Magriotis *et al.* plan to exploit the facility with which the enediyne antibiotics undergo cycloaromatization to promote tandem Ireland–Claisen rearrangement–Bergman cyclization of the 14-membered lactone **48** to tetrahydronaphthalene systems (**Scheme 10**).[54] The enyne intermediate **46** was prepared by reaction of a stannyl vinyl cuprate with iodoacetylene **45** in the presence of $ZnCl_2$, followed by iododestannylation. Subsequent $Pd^0$–CuI mediated coupling of **46** with the acetylene derivative **47** and macrocyclization gave **48**. Note the compatibility of this palladium coupling reaction with the presence of the vinyl sulfide unit in the acetylene derivative **47**.

With the idea of ring contracting larger stable cyclic enediynes to more reactive 10-membered monocyclic forms, Maier and Brandstetter devised a route to compound **51** (**Scheme 11**).[55] The acyclic enediyne intermediate **49** was again obtained in two steps from *cis*-dichloroethene **28**. The key cyclization of **50** was achieved via a Nicholas reaction.[56] Under these conditions ($TiCl_4$, DABCO) a carbocation species is generated adjacent to the dicobalt hexacarbonyl complexed triple bond which reacts with the electron rich enol ether system at the other extremity of the chain.

This ring closure strategy was first introduced to the enediyne field by Magnus and co-workers as part of a systematic study to prepare bicyclic enediynes which have different ring sizes and substituent patterns (**Scheme 12**).[57] As illustrated by the preparation of enediyne **53**, the interest in this approach resides in the fact that, compared to the




**Scheme 11**

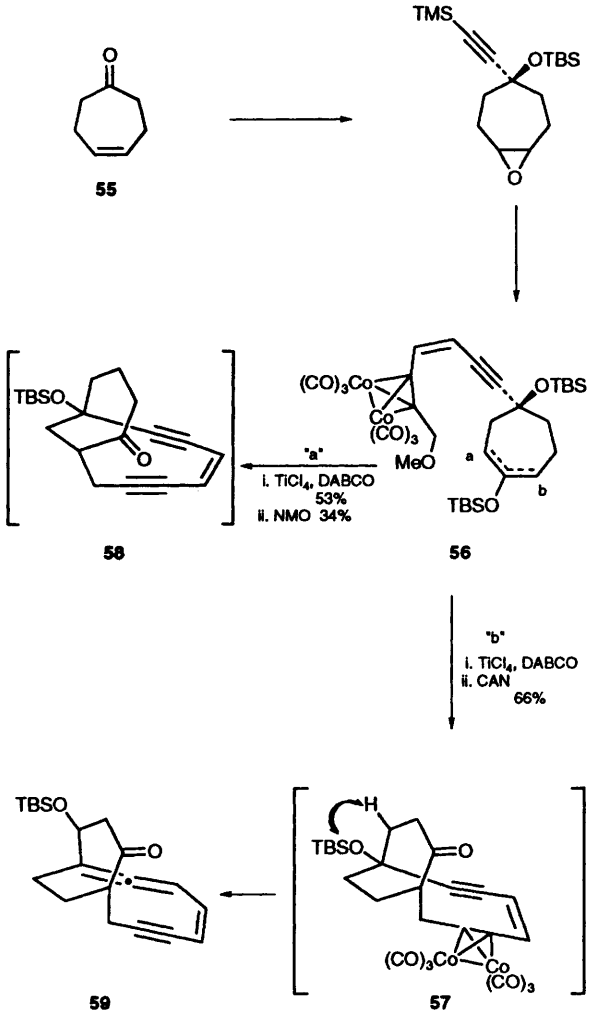



**Scheme 12**

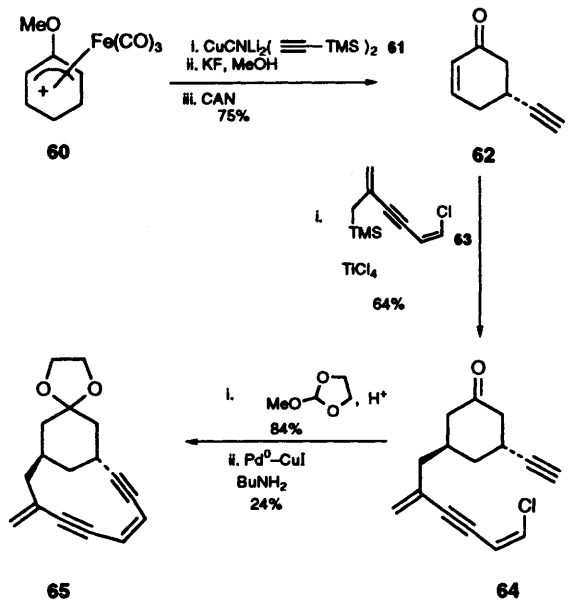
parent linear enediyne system, the alignment of the reacting centres in the cobalt complex are optimized, and the distance between them is significantly less. This results from the altered 145° bond angles in the masked (complexed) triple bond. In addition, cobalt complexation stabilizes the derived bicyclic product **52**, facilitating its isolation and handling. Indeed, on decomplexation of **52** enediyne **53** was observed to cycloaromatize spontaneously. In contrast, the isomeric bicyclic enediyne **54**, described in further detail in Scheme 18 of Part 2 of this review,[20a] was found to be stable.

Using Magnus's methodology, compound **58** and yne-ene-allene **59** were prepared by Maier from 5-cycloheptenone **55** (**Scheme 13**).[58] Enediyne **58** cycloaromatizes spontaneously. However, it is remarkable that the yne-ene-allene product **59** – issuing from the cyclization of **56**, dyotopic rearrangement of **57** and decomplexation – is stable.

Schinzer and Kabbara were the first to have completed the synthesis of a 11-membered enediyne possessing a 1,3-*trans* bicyclic ring junction (**Scheme 14**).[59,60] To obtain ketone **62** the acetylenyl cuprate reagent **61** was added to the cyclohexadienyl iron



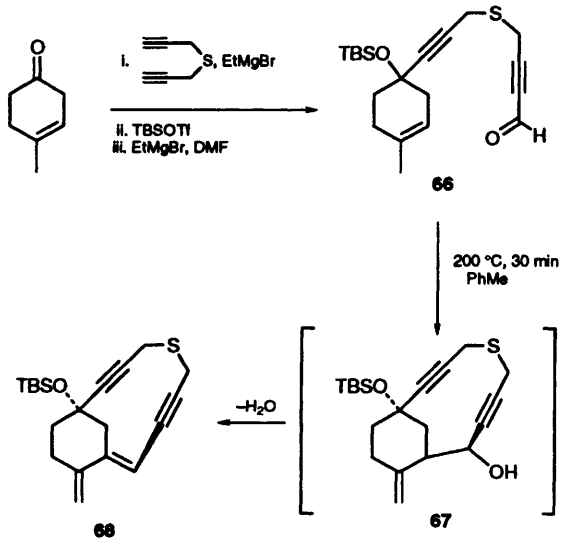

**Scheme 13**




**Scheme 14**

complex **60** (98% yield), followed by desilylation and oxidative demetallation. Lewis acid promoted Sakurai reaction[61,62] of **62** with allyl silane **63** then proceeded regio- and stereospecifically to produce compound **64**. The intramolecular $Pd^0$–CuI coupling of the acetal derived from **64** to give enediyne **65** is remarkable, despite the only moderate yield observed.

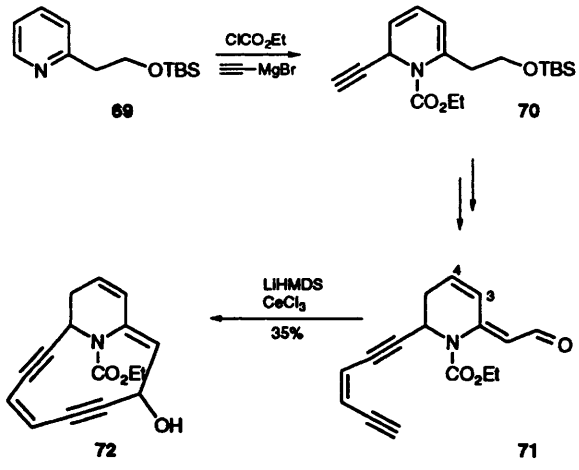
Mikami has explored a novel approach involving an ene reaction to create the crucial bond between the enediyne containing chain and the 6-membered ring 'platform' component of the calicheamicin/esperamicin core structure.[63] This involved conversion of the readily accessible alkynyl aldehyde intermediate **66** to the 11-membered bicycle **67** (**Scheme 15**). A subsequent Nicolaou type




**Scheme 15**

Ramberg–Bäckland ring contraction step could then be exploited to introduce the central double bond. However, at present, the thermal conditions employed (200 °C, 30 min) effect dehydration of the desired product to the enediyne containing compound **68**.

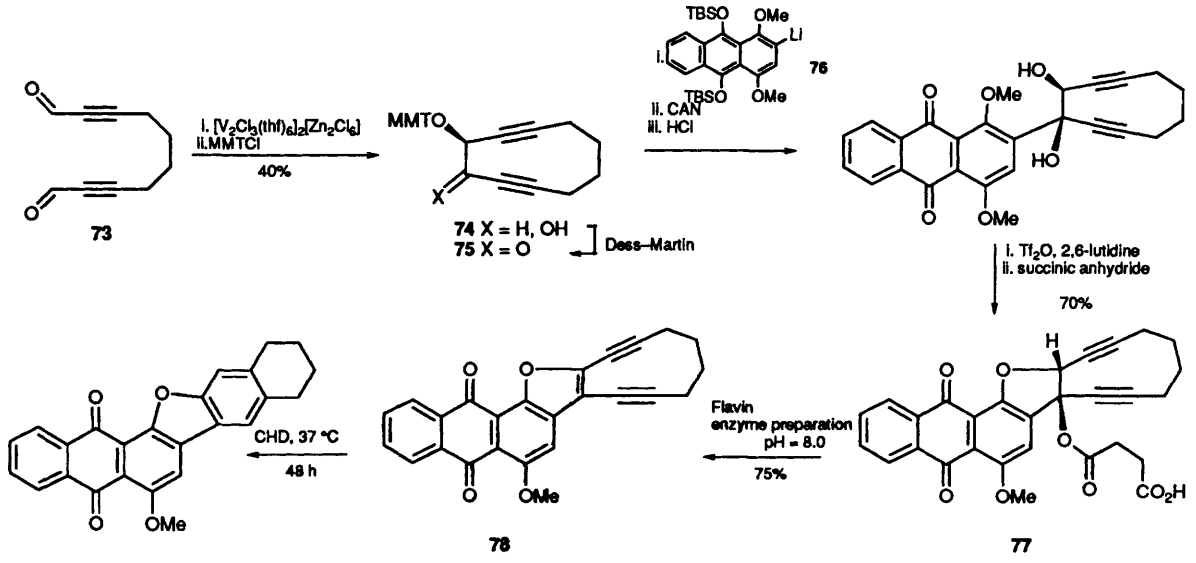
Brana and co-workers prepared the novel dynemicin analogue **72** in which the enediyne unit is built across a tetrahydropyridine backbone (**Scheme 16**).[64] Thus, reaction of pyridine **69** with ethylchloroformate and ethynylmagnesium bromide (Yamaguchi conditions[65]) led to formation of the 1,2-addition product **70** which was elaborated to the $\Delta^{3,4}$-piperideine aldehyde **71** (and its $\Delta^{4,5}$ isomer; 2:1 mixture). Reaction of **71** with LHMDS/$CeCl_3$ at low temperature produced compound **72** in 35% yield.




**Scheme 16**

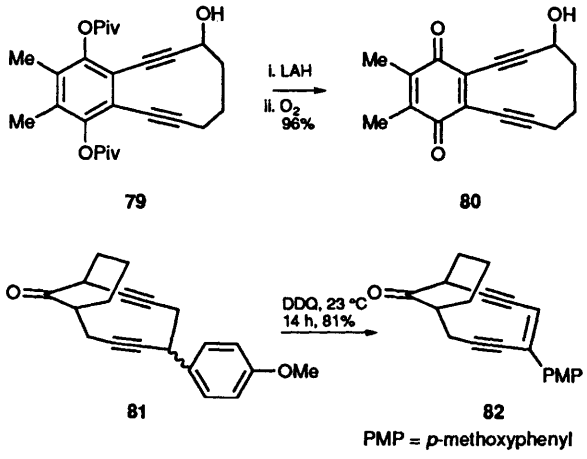
### 3 Monocyclic and bicyclic enediynes with novel activating devices

Several concepts have been evaluated which have potential application for the *in vivo* transformation of stable or latent enediyne systems to more reactive forms. One interesting strategy, which in a sense was a prelude to the discovery of maduropeptin **21**, involves introduction of the central enediyne double bond as the triggering step toward cycloaromatization. For instance, Myers and Dragovich envisaged that, by analogy to dynemicin A, bioreduction of anthraquinone **77** would lead to loss of the succinate residue and formation of the 10-membered enediyne **78** (**Scheme 17**).[66] Key synthetic operations in the preparation of **77** include the modified Pedersen pinacolic coupling[67] to convert dialdehyde **73** to a mixture of *cis* and *trans* diols **74** (4:1; 40%), and reaction of the derived ketone **75** with the anthracenyllithium reagent **76**. Reductive activation of **77** with a flavin-based enzyme system at pH 8.0 proceeded rapidly to give enediyne **78** (75%), which slowly cycloaromatizes at 37 °C in the presence of cyclohexadiene (CHD) ($t_{\frac{1}{2}}$ = 2 d).




**Scheme 17**

Taking advantage of the slower cycloaromatization rate of benzodiynes compared to enediynes, Nicolaou and Semmelhack have independently studied the differential reactivity of hydroquinone based diynes and their corresponding quinone forms (*cf.* **79** and **80**; **Scheme 18**).[68–70]



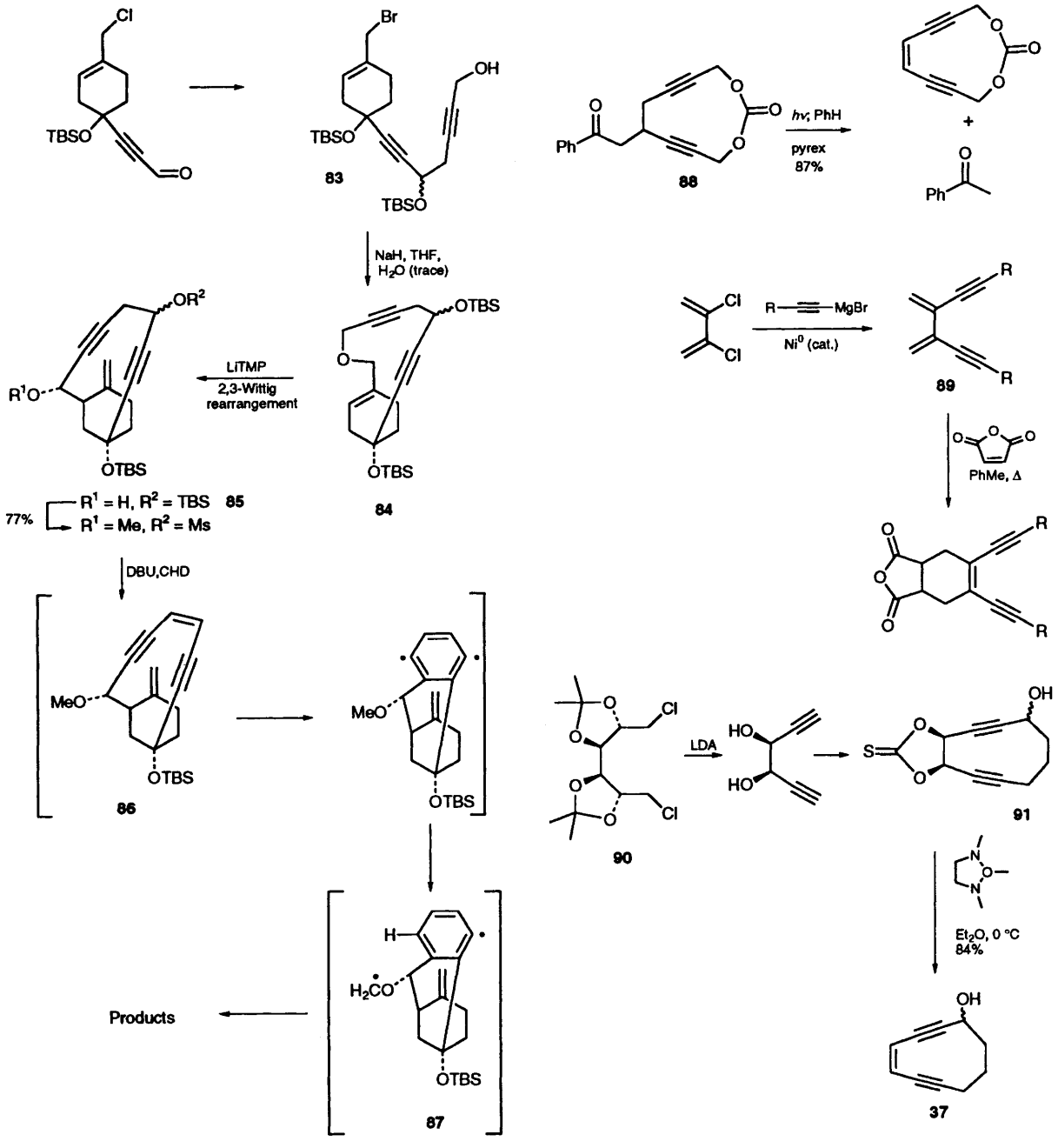

**Scheme 18**

Maier has also shown that the enediyne double bond can be introduced via benzylic oxidation in bicyclic 1,5-diyne systems functionalized at the 3 position by a *p*-methoxyphenyl substituent (**81**→**82**; **Scheme 18**).[71]

In the course of work on an approach to the bicyclic core structure of calicheamicin/esperamicin, Grierson and co-workers constructed the unstrained 13-membered macrocyclic ether **84** by cyclization of **83**, and studied its 2,3-Wittig rearrangement to **85** under basic conditions (**Scheme 19**).[72,73] As anticipated from the calculated $r_{c,d}$ distance (3.20 Å; MMX calculations) and observations by Magnus on the related compound **53**, the *in situ* generated enediyne **86** underwent spontaneous Bergman cycloaromatization. Interestingly, this was accompanied by a 1,5-hydrogen translocation to give the more stable diradical **87**, which evolved to a number of products. A similar radical translocation was observed earlier by Wender during studies on neocarzinostatin chromophore analogues.[74] Such studies may have relevance to internal radical quenching reactions suspected to occur on cycloaromatization of neocarzinostatin **9** and esperamicin **6**.

Other strategies through which the central double bond of the enediyne system is generated include the Norrish type II photochemical fragmentation of aromatic ketone **88**,[75] and the Diels–Alder reaction of dienediynes **89**.[76] Semmelhack has similarly devised methodology for introduction of this double bond based upon the Corey–Winter reaction of thionocarbonate **91** (**Scheme 20**).[77] Note also that the two acetylene functions in **91** were elaborated by reaction of the chlorohydrin derivative **90** with excess LDA. Interestingly, the conjugate **92**, formed by joining **37** to a truncated netropsin derivative via a four carbon (crotonate) tether, is 2000 times more effective as a DNA cleaving agent than **37** itself.[78]

Glycoside bond cleavage, which would convert the sugar derived enediyne **98** to the 10-membered monocycle **99**, has also been envisaged as a triggering mechanism for cycloaromatization (**Scheme 21**).[79] To access this bicyclic acetal the ketone **93** (obtained from D-xylose) was reacted with lithium trimethylsilylacetylide in the presence of $CeCl_3$. This preferentially gave the $\beta$-substituted product **94**, which was converted in three steps to alcohol **95**. Attempts to achieve ring closure of aldehyde **96** under strongly basic conditions failed. However, compound **98** was obtained from the corresponding iodoalkyne intermediate **97** under Nozaki–Kishi conditions ($CrCl_2$–$NiCl_2$; 26%).[49]

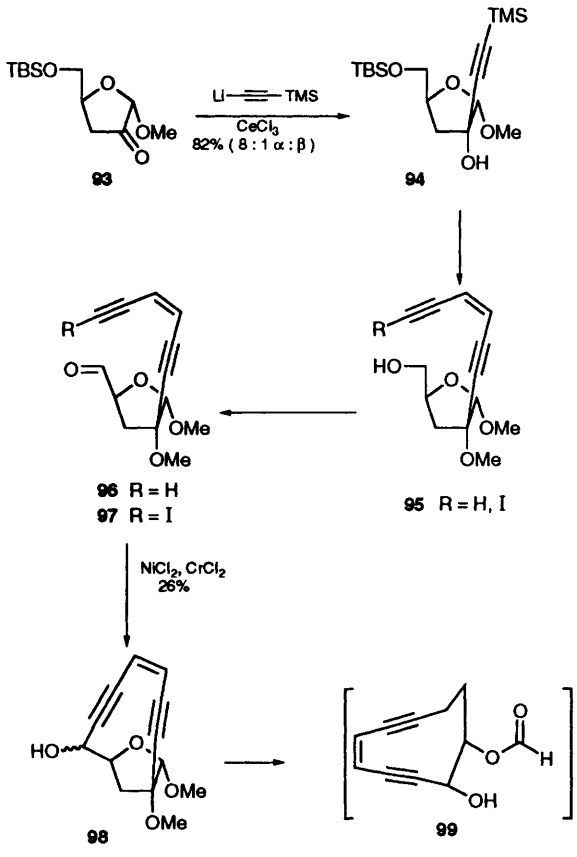



**Scheme 19**

**Scheme 20**

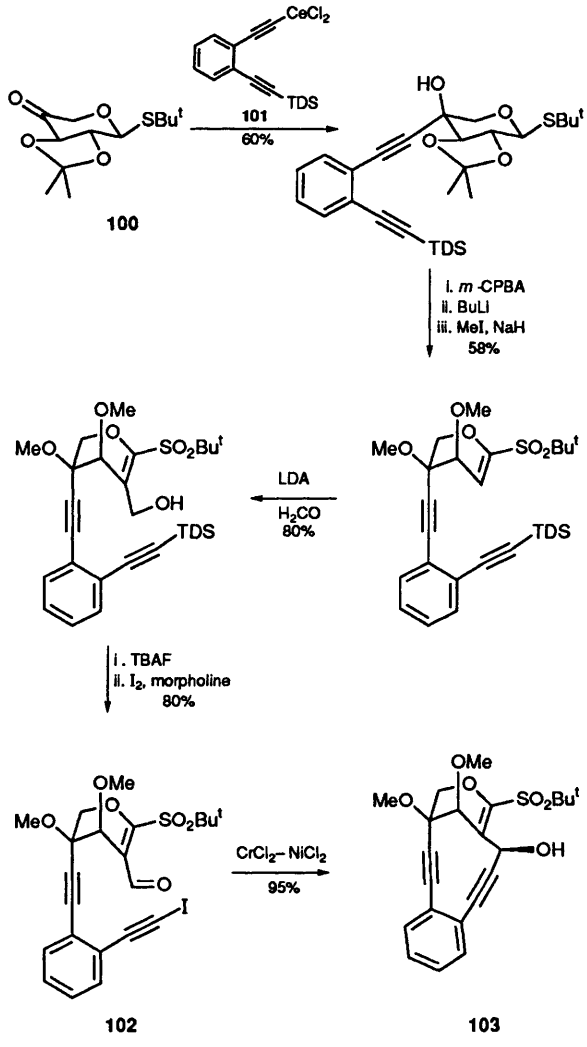
Similarly it was conceived that enol ether hydrolysis of the benzodiyne **103** would give a monocyclic enediyne susceptible to undergo the Bergman reaction (**Scheme 22**).[80] Preparation of **103** involved condensation of the ketone **100** (prepared in two steps from 1-*tert*-butylthio-D-xylopyranoside) with the acetylenyl cerium(III) reagent **101**, followed by elaboration of aldehyde **102** and chromium mediated ring closure (95% yield!).

Enol ether hydrolysis has also been exploited as an alternative means to destroy the bridgehead double bond in the bicyclic calicheamicin/esperamicin system (**Scheme 23**).[81] To obtain analogue **108** the aldehyde **104** was converted to acetylene **105** by reaction wth $(MeO)_2POCHN_2$,[82] and from there to enediyne **106** by coupling with 1-chloro-4-trimethylsilyl-(*Z*)-but-1-en-3-yne.[35] Final cyclization was achieved by treatment of **107** with LiHMDS. The hydrolysis product, ketone **109**, is



Scheme 21

stable enough to be isolated (compare with **53**), but does cycloaromatize fairly rapidly [$t_{\frac{1}{2}}$ = 35–53 min (R = H, TBS) at 37 °C].



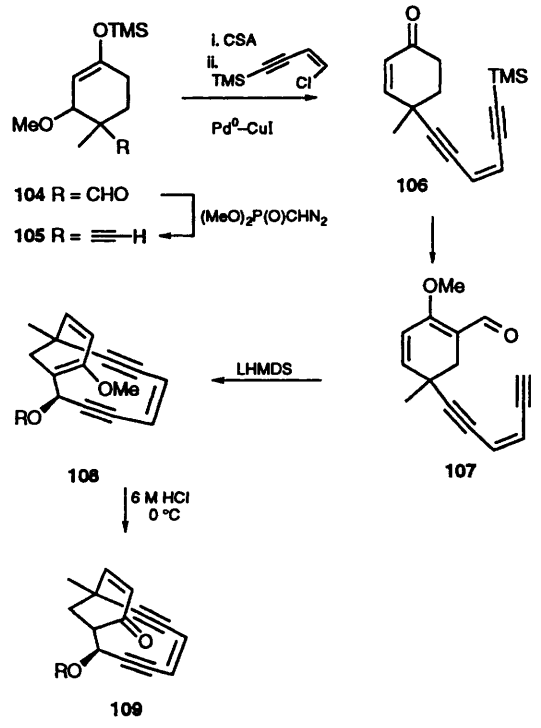
Scheme 22

## 4 Simple yne-ene-allenes and yne-ene-cumulenes

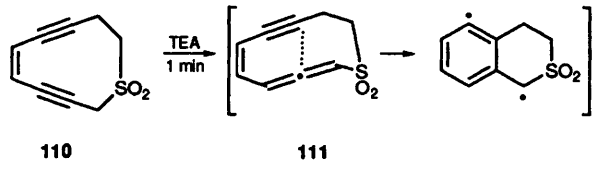
A clear demonstration of the much greater propensity of yne-ene-allenes and yne-ene-cumulenes to cycloaromatize to diradical intermediates compared to enediynes was provided by the simple experiment wherein the 10-membered sulfone **110** was either heated in the presence of cyclohexadiene as the only additive, or treated at room temperature with triethylamine base (**Scheme 24**). Under the first set of conditions Bergman cyclization occurred progressively (80 °C, 18 h). However, in the presence of $Et_3N$ a very rapid cycloaromatization reaction (< 1 min) was observed via the yne-ene-allene intermediate **111** generated by proton rearrangement.[83,84]

Koga *et al.* have attributed the difference in reactivity of these two conjugated systems to less favourable orbital interactions created during enediyne electrocyclization.[85,26] A decrease in the $r_{c,d}$ distance between the reacting centres in yne-ene-allene systems compared to enediynes most probably also contributes to their higher reactivity. In any event, containment of yne-ene-cumulenes in strained rings is not an obligatory requirement for these systems to undergo Myers type cycloaromatization at ambient temperatures. For instance, the unstrained acyclic yne-ene-allenes **114** and **115** both cycloaromatize smoothly at 37 °C ($t_{\frac{1}{2}}$ = 1.5 to 8 h) and effect cleavage of supercoiled DNA. These compounds were prepared by [2,3]-sigmatropic rearrangement of the *in situ* formed phosphinite derivatives of enediyne **112** and prop-2-ynylic alcohol **113**, respectively (**Scheme 25**).[86–88] As illustrated by the reactivity of **116**, substituents on the terminal acetylene carbon C-1 have a considerable influence on the mode of cycloaromatization; *i.e.* in the presence of cyclohexadiene (CHD) **116** (R = H) cycloaromatizes in the Myers mode ($C_1$–$C_6$ bond formation) to produce **118**, whereas **116** (R = tolyl) reacts to give **117** as a consequence of $C_2$–$C_6$ bond formation.[89] This may be due to steric hindrance, and/or ground state stabilization of the acetylene moiety.

In a more sophisticated experiment compound **119** was constructed, and shown to undergo an intramolecular $S_N2'$ reaction giving **120** directly (75% yield) (**Scheme 26**).[90]



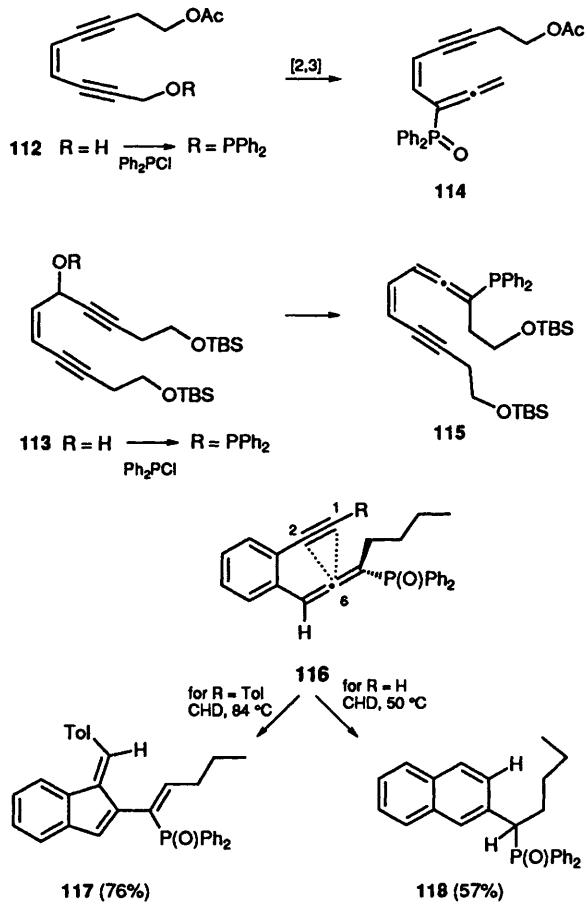

**Scheme 23**



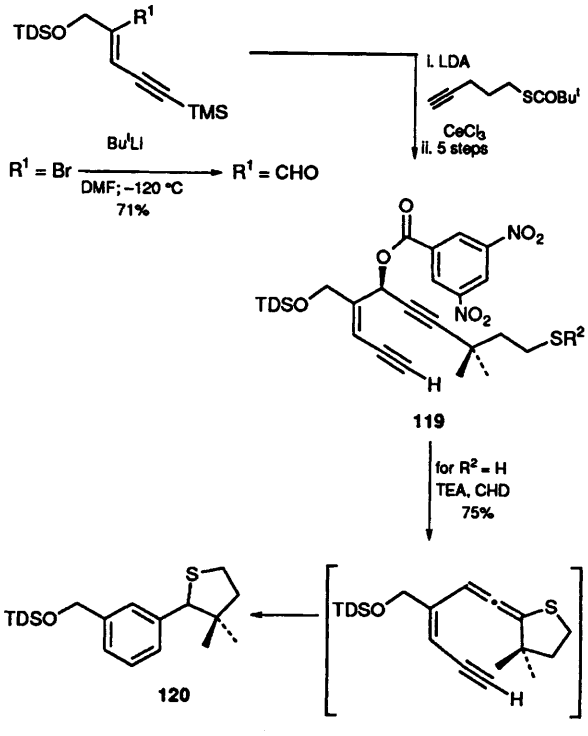

**Scheme 24**

The parent unsubstituted (*Z*)-1,2,4-heptatrien-6-yne system **124** has been synthesized by either Zn–Cu reduction of mesylate **121**,[86] or via a sigmatropic rearrangement initiated by oxidation of prop-2-ynylic hydrazine **122** to the unstable diazene **123** at 0 °C (**Scheme 27**).[91,92] Interestingly, these unsubstituted yne-ene-allenes cycloaromatize relatively slowly ($t_{\frac{1}{2}} \approx 24$ h). NMR evidence suggests that this may result from a preference for them to adopt the less hindered s-*trans* conformation.

Saito and co-workers made use of their experience on the [2,3]-sigmatropic rearrangement of prop-2-ynylic phosphinites to prepare phosphine oxide **125** and react it with aldehyde **126** (**Scheme 28**).[93] This permitted them to construct the acyclic yne-ene-cumulene derivative **127** related to the thiol addition product **10** of the neocarzinostatin chromophore. Alternatively, Wang showed that mesylate **129**, obtained by reaction of **126** with lithium acetylide **128**, undergoes very mild conversion to **127** on treatment with TBAF.[94,95] Like the above acyclic allenes this compound could be isolated by flash column chromatography or HPLC and characterized.

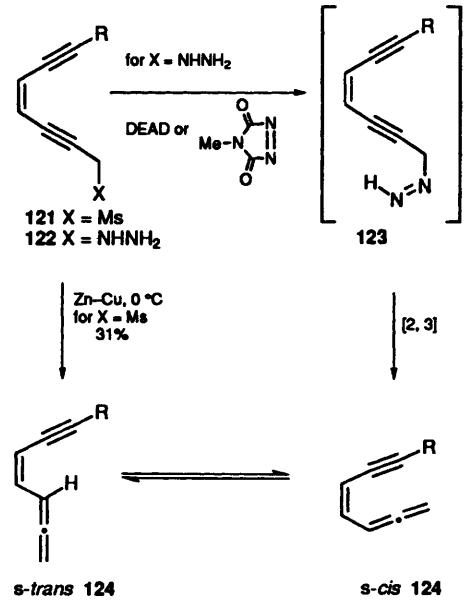



**Scheme 25**

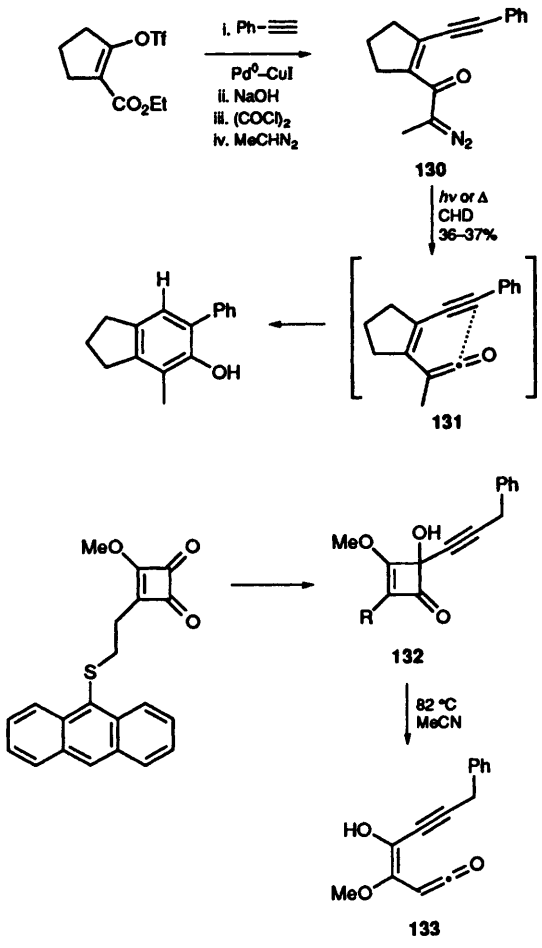



**Scheme 26**

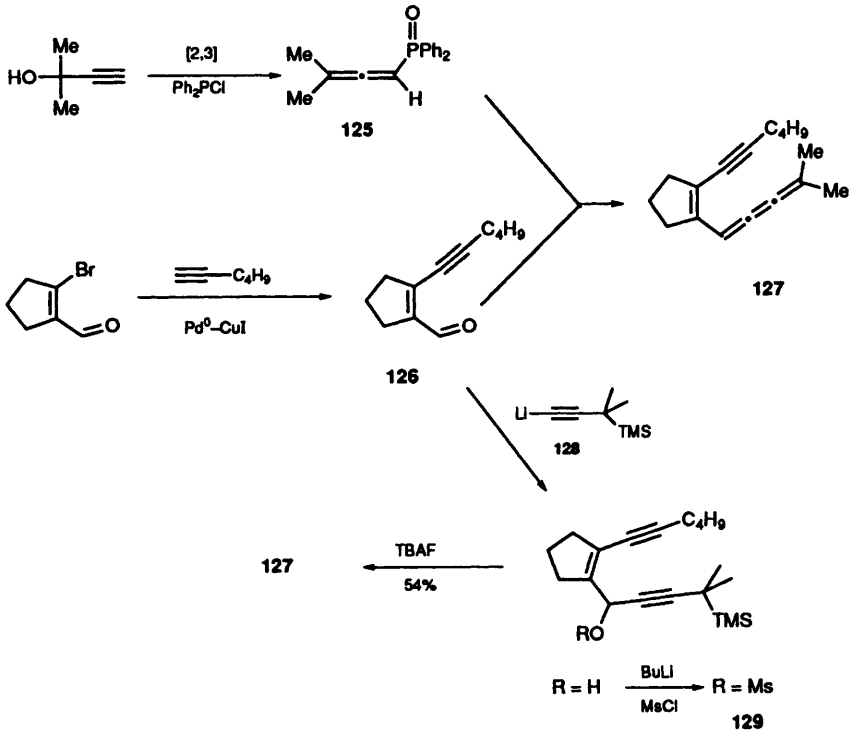
Two strategies for the preparation of acyclic yne-ene-ketene analogs of cumulene **10** have also been reported. On the one hand, ketene **131**, which cycloaromatizes spontaneously, was generated by heating or photolysing (254 nm) diazoketone **130** (**Scheme 29**).[96] In the second study, Moore *et al.* showed that cyclobutenone **132** fragments on mild heating ($CH_3CN$; 82 °C) to the ketene **133**.[97] Cyclization of this intermediate to a diradical



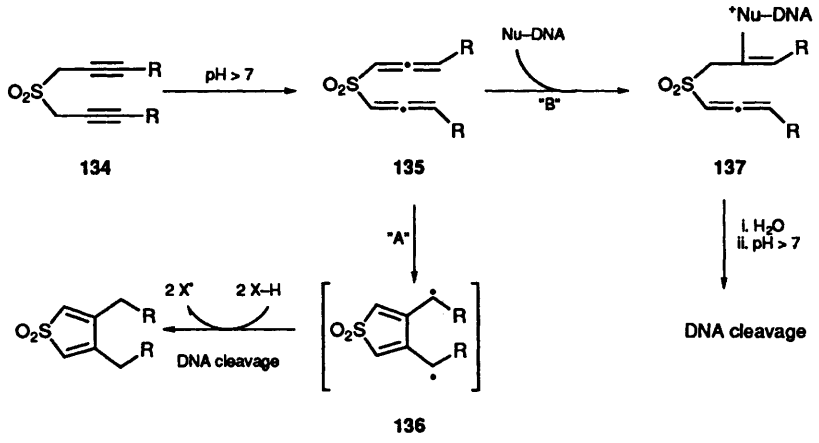

**Scheme 27**




**Scheme 29**




**Scheme 28**




**Scheme 30**

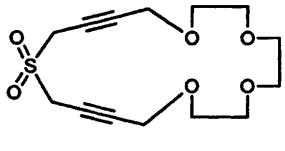
accounts at least partially for the capacity of this intermediate to cleave DNA.

Returning to the reactivity of bis(prop-2-ynylic) sulfones, Nicolaou has suggested that Myers cycloaromatization is not the only route through which these systems can potentially cut DNA (**Scheme 30**).[98] Indeed, on pH dependent conversion of **134** to the corresponding bis(allenic) sulfone **135**, further reaction can occur giving the diradical **136** (pathway A), or through direct reaction with a DNA-nucleophile to give adduct **137** (pathway B). Studies of the reactivity of a series of mono and bis(prop-2-ynylic) sulfones, as well as the novel crown ethers **138** and **139** and compounds **140**, has provided convincing evidence for the polar reaction pathway in DNA cleavage (note **138**→**141**).[99–102]

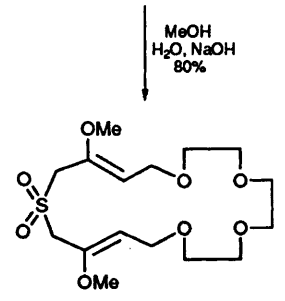
Similarly, it was observed that the 10-membered ring sulfide **143**, obtained by dehydration of **142**, is converted to the conjugated allene **144** in a basic medium. This intermediate reacts via both polar and radical mechanisms (**Scheme 31**).[103] Attachment of aromatic ester residues to these monocycles increased their ability to interact with DNA through intercalation. Somewhat of a surprise, oxidation of sulfide **145** with *m*-CPBA led to formation of the enyne-allene sulfone **146** as a stable compound.[104] Cycloaromatization of the allene-cumulene **147** generated by elimination of HOR from **146** was also split between polar and radical pathways.

The Pd(0) coupling and ring closure technology developed during the study of enediyne–dienediyne systems was brought to bear by Myers to construct the fully conjugated 'aromatic' 1,6-didehydro-[10]annulene **151** (**Scheme 32**).[105] This was achieved by coupling vinyl iodide **148** with a but-3-ynylic alcohol derivative (79%), followed by Wittig olefination, and ring closure of **149** under Nozaki–Kishi conditions to the alcohol **150**. Subsequent triflate elimination to give **151** had to be conducted at −90 °C! The half-life for cyclization of **151** at −51 °C is ≈ 25 min, making this the most rapid diradical-forming cycloaromatization yet recorded (*c.f.* **10**→**11**; $t_{\frac{1}{2}}$ = 2 h at −38 °C).

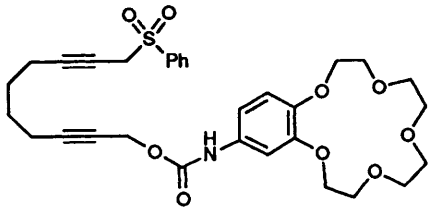
In a synthetically economic and astute way Myers then went on to incorporate the 1,6-didehydro-



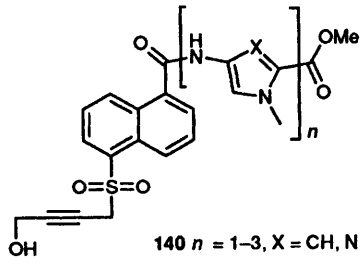
**138**




**141**

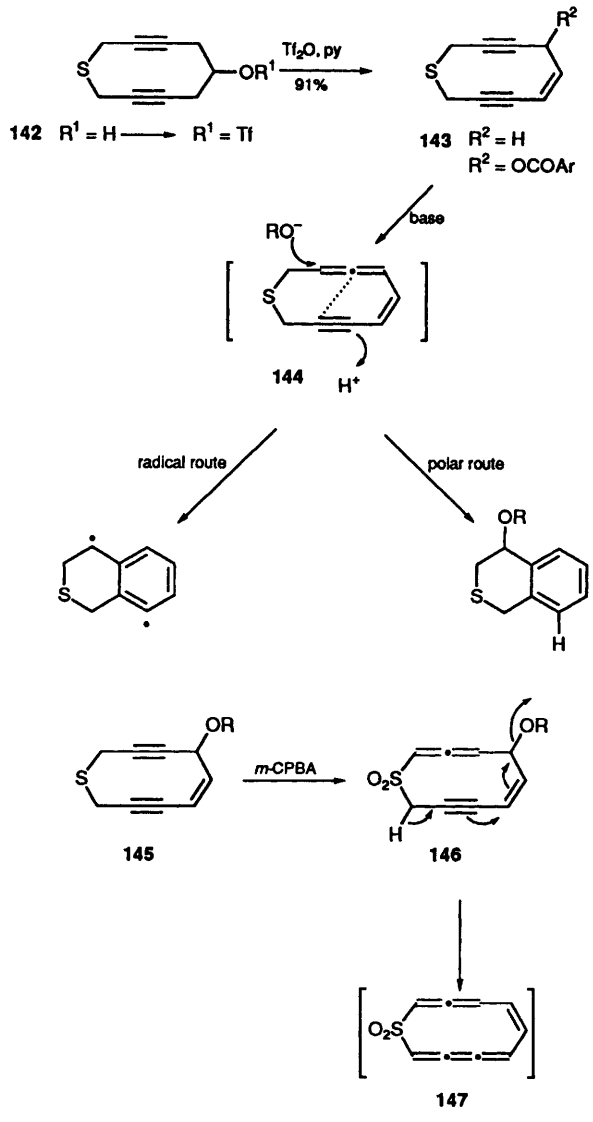



**139**



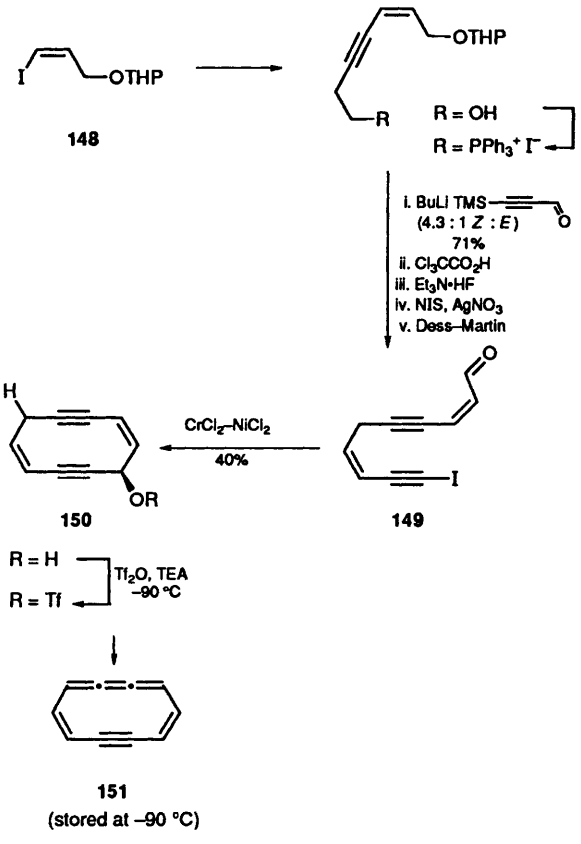

**140** *n* = 1–3, X = CH, N

[10]annulene system in latent form into the neocarzinostatin analogue **155** (**Scheme 33**).[106] Compound **155** was prepared starting by reaction of enantiomerically pure **152** with allenylmagnesium

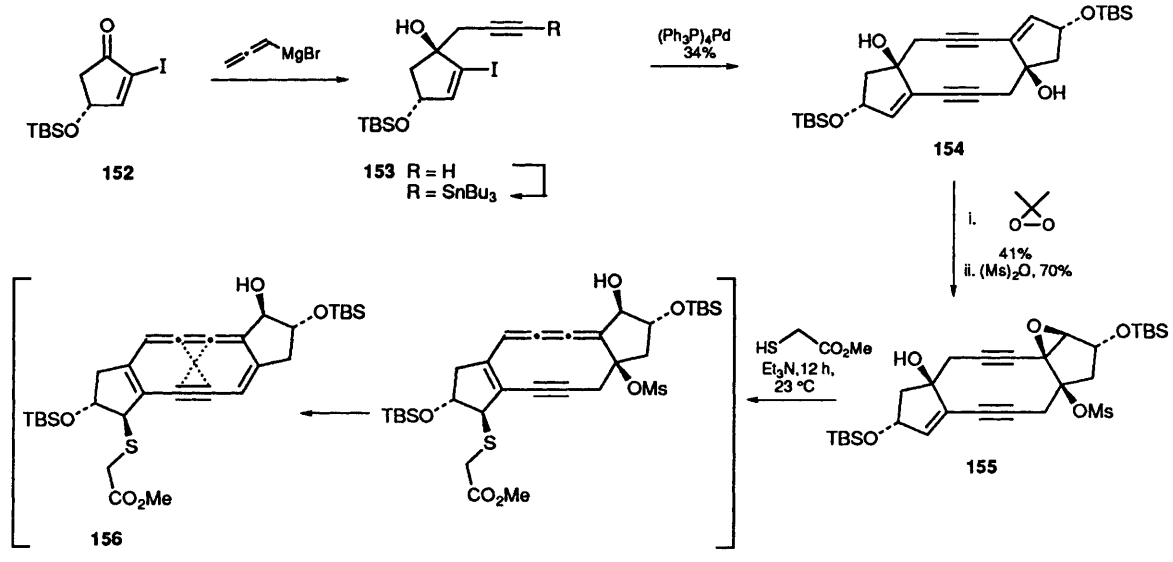



Scheme 31

bromide, followed by stannylation of acetylene **153**. This product was dimerized under Pd(0) conditions, affording the $C_2$-symmetric alcohol **154** in 34% yield. Mesylation of **154** gave the target molecule **155**, which proved to be stable with respect to column purification. However, treatment of this compound with methyl thioglycolate and $Et_3N$ led to



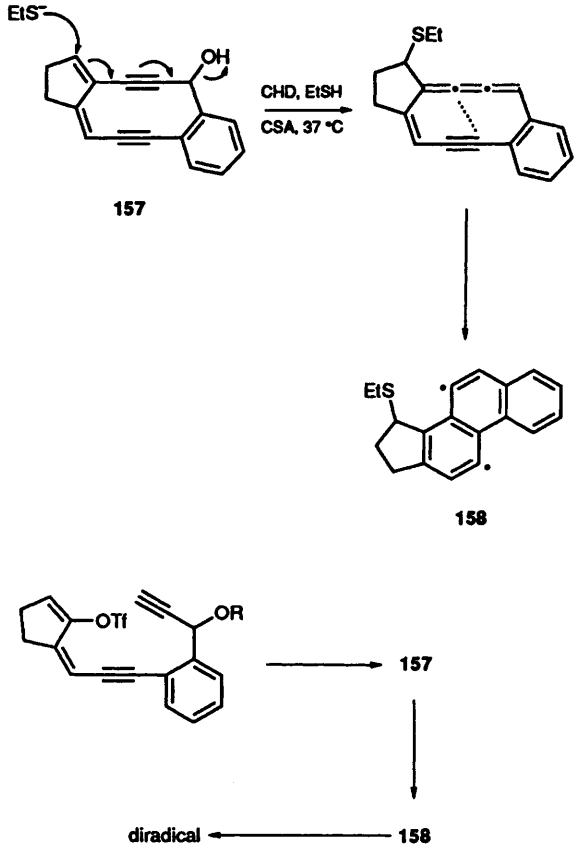

Scheme 32




Scheme 33

cycloaromatized products whose formation may imply **156** as an intermediate.

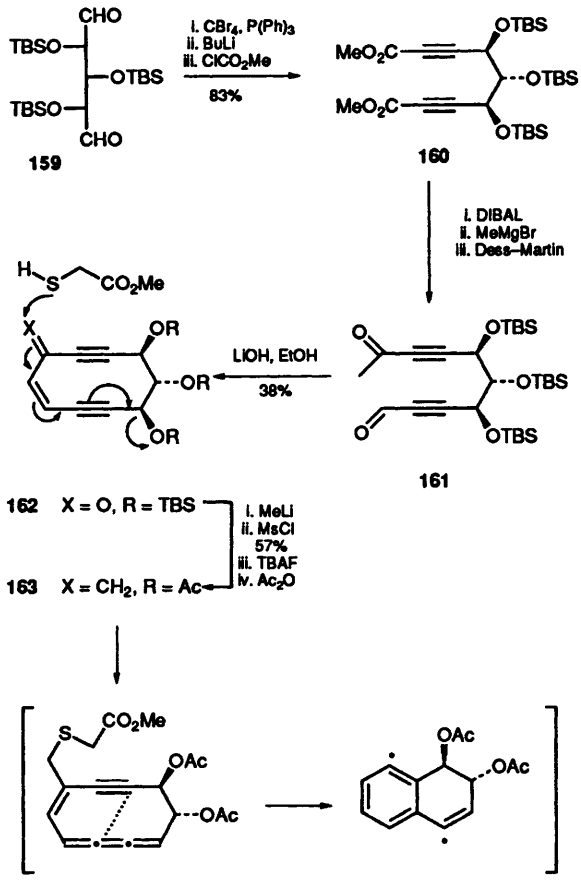
Applying techniques described later in Scheme 37, Suffert showed that upon $EtS^-$ addition the benzodienediyne **157** rearranges to a didehydro-[10]annulene. This intermediate cycloaromatized spontaneously to **158** (**Scheme 34**)[107] in an analogous fashion to the Saito pathway[14] for the neocarzinostatin chromophore.




**Scheme 34**

The simple monocycle **163** (**Scheme 35**) was designed by Toshima *et al.* to undergo cycloaromatization through thiol–acetate addition elimination in a manner closely analogous to neocarzinostatin **9**.[108] In four steps, D-xylitol was converted to the dialdehyde **159**. According to the Corey–Fuchs procedure[109] this compound was elaborated to the diester **160**, and from there to the keto-aldehyde **161**. An intramolecular Aldol reaction then gave **162**, whose conversion to **163** could not be achieved directly under Wittig conditions.

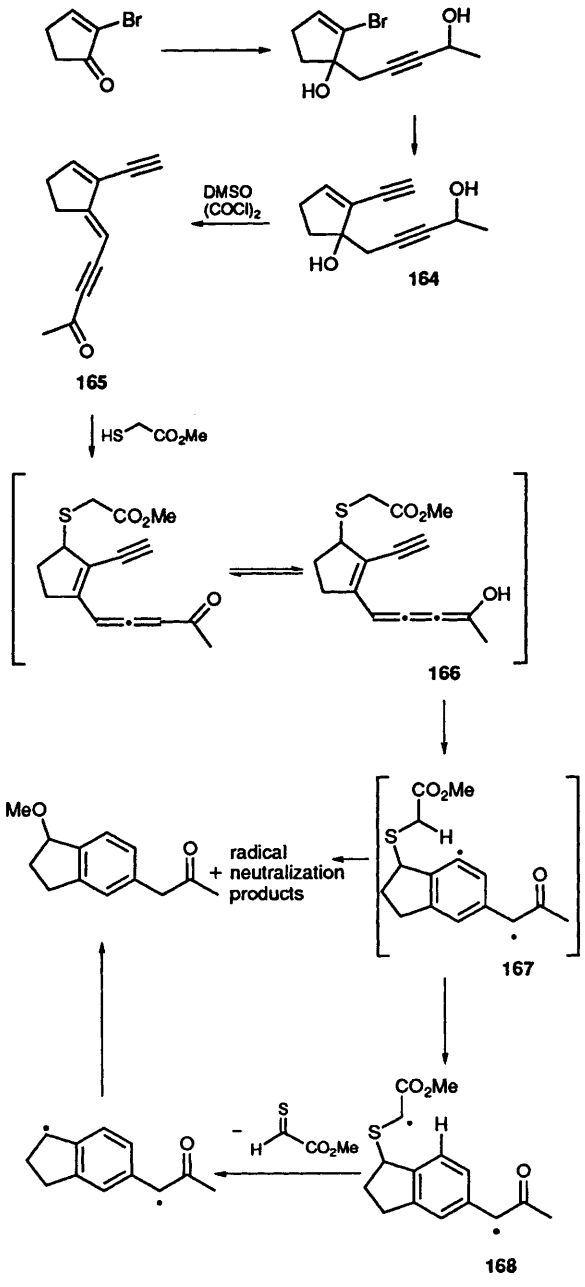
In conjunction with their pioneering work on the neocarzinostatin chromophore skeleton, Wender and Tebbe designed the monocyclic *E*-configured dienediynes **165** which react as Michael acceptors in the presence of thiols (**Scheme 36**).[74,110,111] Although MsOH elimination from **164** produces the less hindered thermodynamic product, the reactive s-*cis*



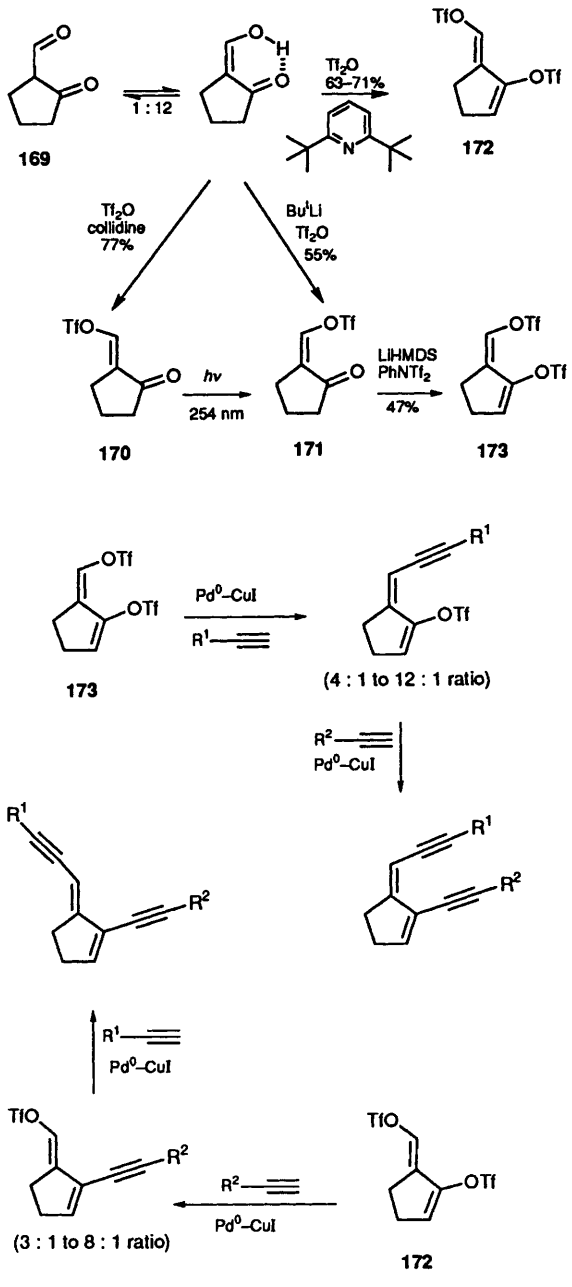

**Scheme 35**

conformation can easily be adopted in the tetraene **166**. A thorough study of the Myers type cycloaromatization chemistry of **165** was made, which both demonstrated that **166** cyclizes spontaneously and also brought to light an internal radical quenching process involving 1,5-hydrogen transfer (**167**→**168**).

Suffert and Terashima have further defined methodology for stereospecific construction of monocyclic *Z*- and *E*-dienediynes from *Z*- and *E*-monoenol triflate and dienol triflate precursors (**Scheme 37**).[112,113] The essential challenge in their work was to establish conditions for controlled preparation of compounds **170** and **171**, as well as **172** and **173**, from 2-formylcyclopentanone **169**. It was found that the *Z*-enol form of **169** reacts with triflic anhydride and amine base to give the *E*-configured monoenol triflate **170**, whereas reaction of the lithium enolate of **169** with the same reagent gives the *Z*-monoenol triflate **171**. Alternatively, partial conversion of **170** to **171** could be achieved photochemically (254 nm). Similarly, 2-formylcyclopentanone was converted directly to the *E*-dienol ditriflate **172** (63–71%), and compound **171** was converted to **173** in 47% yield through treatment with LHMDS and $PhNTf_2$. It is interesting that reaction of the lithium enolate of **169** with $PhNTf_2$ led to the *E*- rather than the *Z*-monoenol triflate, and that there is a loss of




**Scheme 36**

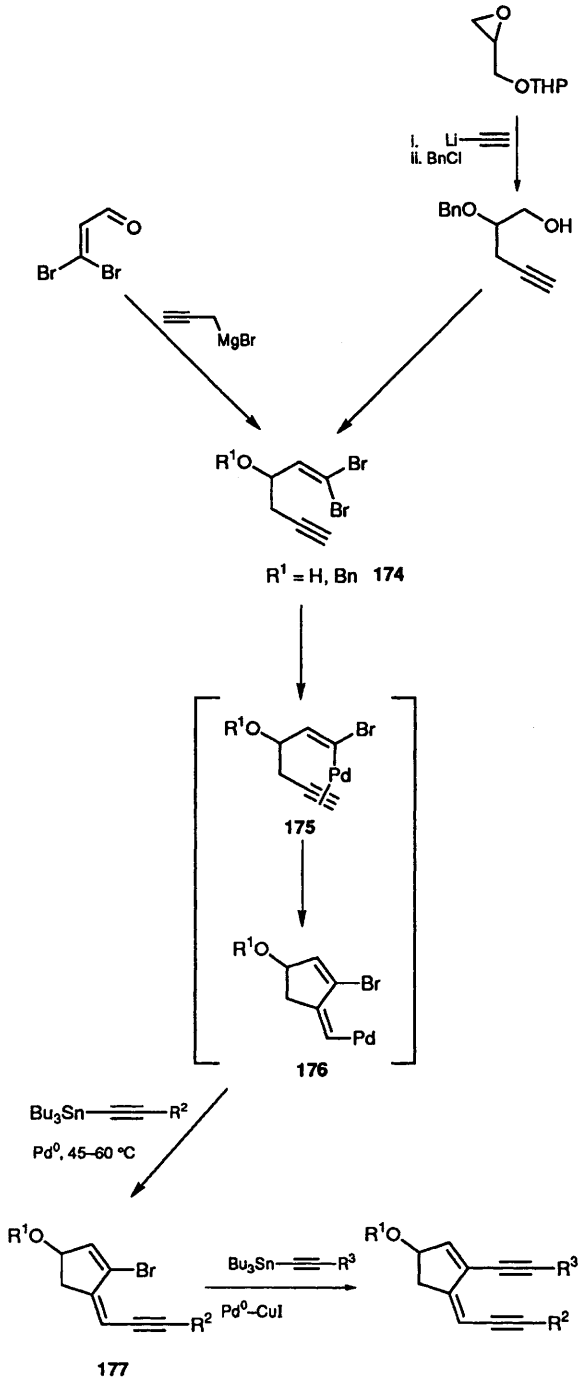



**Scheme 37**

stereochemistry on treatment of monoenol triflate **171** with $Tf_2O$ (**171**→**172**).

The subsequent $Pd^0$–CuI bis-coupling of dienol ditriflates **172** and **173** with >2 equivalents of diversely substituted terminal acetylenes provided open chain *E*- and *Z*-dienediyne systems respectively with common acetylene functions [*Z*-series: 36–73% yields; *E*-series: 79–98% yields]. However, sequential addition of two different acetylene units can also be accomplished. As one might expect, for *Z*-compound **173** there is preferential reaction at the more accessible exocyclic enol triflate function (4:1 to 12:1). However, for *E*-**172** it is the endocyclic position which is substituted first (3:1 to 8:1). In this latter instance, the order of introduction of two different acetylene units can be inversed by first coupling with monotriflate **170**.

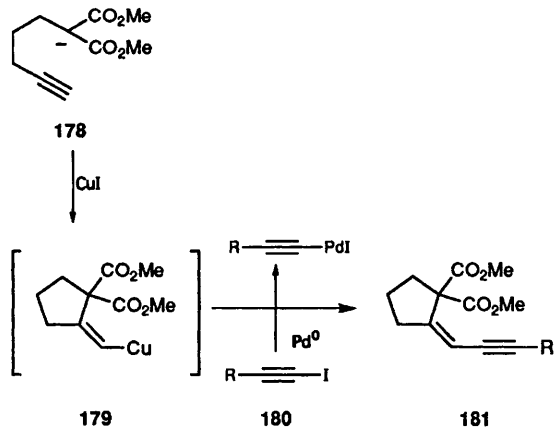
A strategy based upon a Pd(0) catalysed insertion–cross coupling sequence has been developed which permits both creation of the cyclopentene ring from an acyclic precursor and introduction of an acetylene appendage with control of the exocyclic $C_8$–$C_9$ olefin geometry (**Scheme 38**).[114,115] In the experiment, Pd(0) reacts with dibromo (or diiodo) **174** via π-complexation and selective oxidative addition to the more hindered proximal *Z*-1-Br bond to give the critical Pd–C σ-bonded species **175**. In a solvent dependant reaction, this intermediate then undergoes rapid carbometallation of the precoordinated alkyne, resulting in formation of the *Z*-vinyl organometallic



Scheme 38

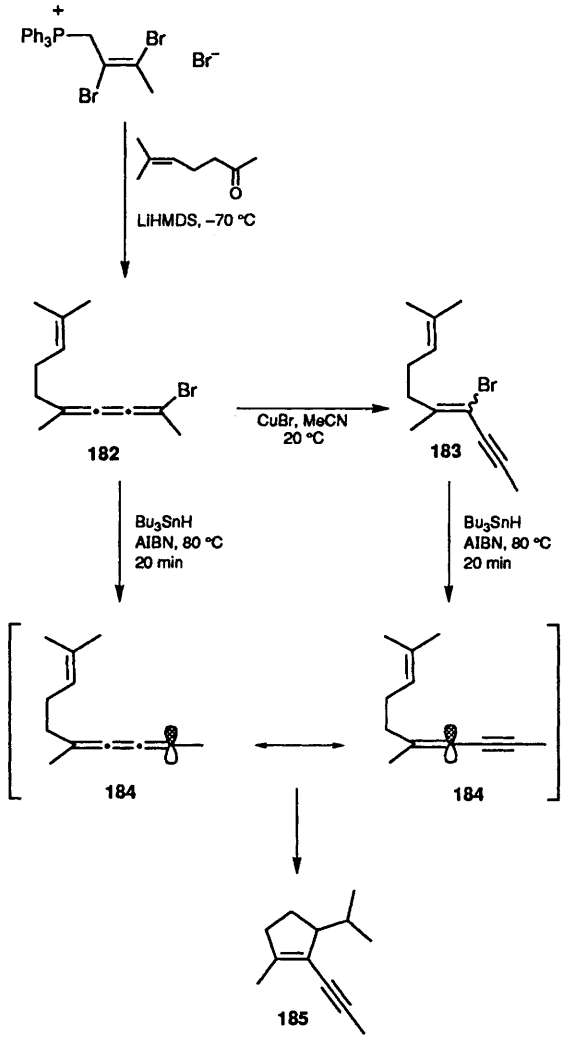
176. Reaction of **176** with the stannylacetylene reagent present in the medium gives the product diene-yne **177**. The presence of the vinyl bromide functionality can subsequently serve for introduction of a second acetylene unit.

In another $Pd^0$–CuI based approach, reaction of the *in situ* generated organocopper species **179** with the $\sigma$-ethynylpalladium species **180** produces the *Z*-ene-yne product **181** (**Scheme 39**).[116] This is achieved by slow addition of iodide **180** to a solution of the preformed potassium enolate **178** in the presence of $(Ph_3P)_4Pd$ and CuI.

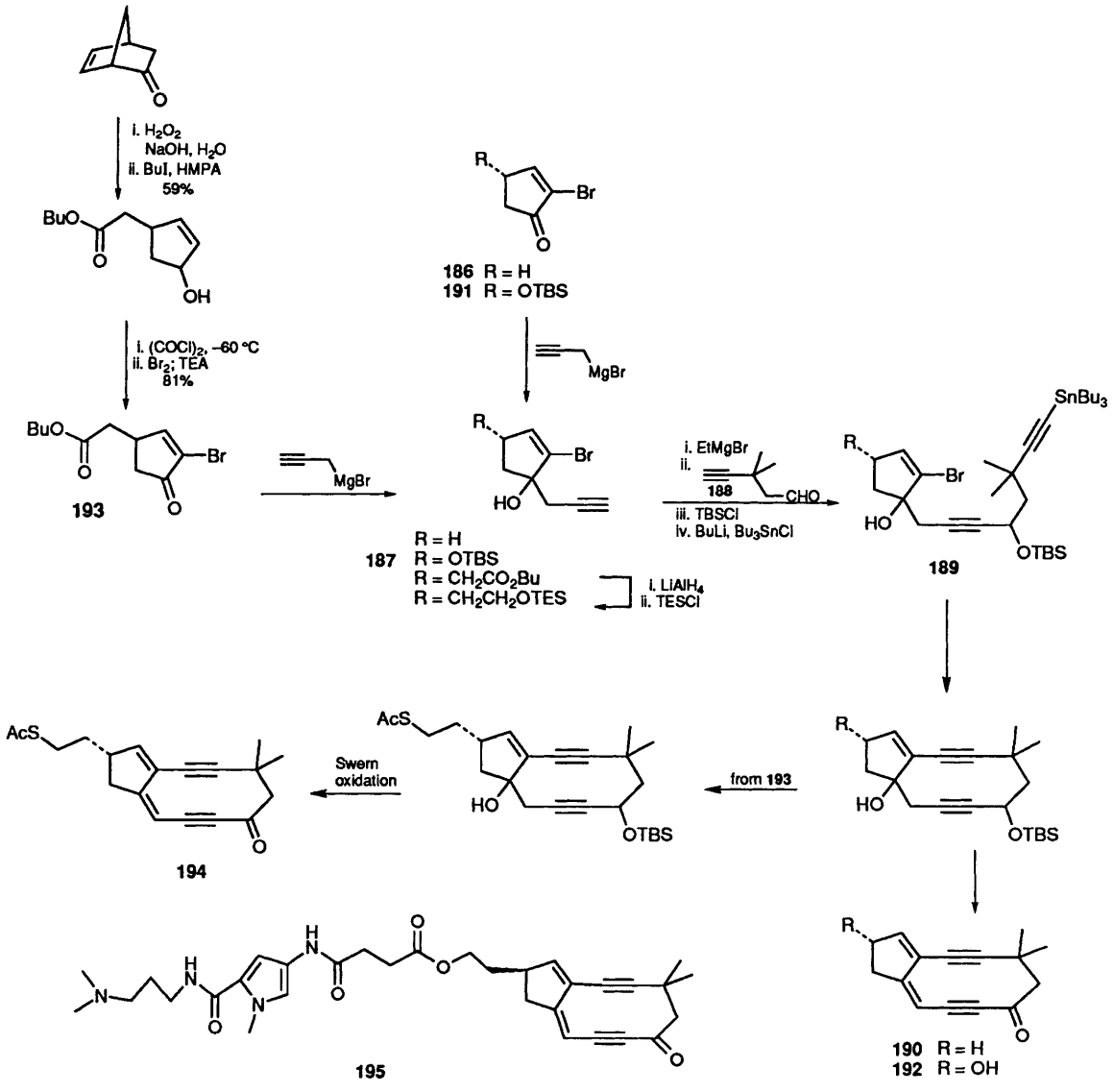


Scheme 39

Ziegler has shown that the cyclopentenynes such as **185** can be constructed by $Bu_3SnH$ induced radical cyclization of either bromo[3]cumulene **182** or the bromoenyne precursor **183**, since both systems produce the same delocalized radical intermediate **184** (**Scheme 40**).[117]



Scheme 40



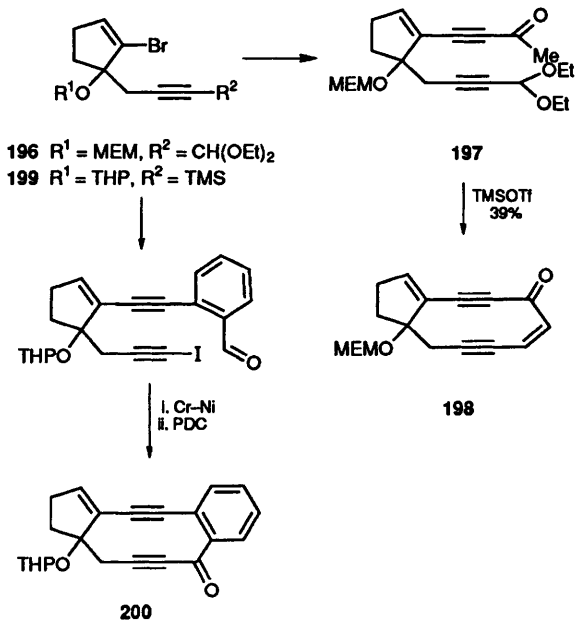
**Scheme 41**

## 5 Ten-membered ring and higher neocarzinostatin chromophore analogues

Calculations made by Hirama and collaborators suggest that 10-membered neocarzinostatin chromophore analogues should be more stable than **9** due to reduced ring strain, but at the same time retain the capacity to undergo Myers type cycloaromatization to a diradical intermediate (small difference in the $r_{c,d}$ distance). They thus prepared the conjugated ketone **190** from 2-bromocyclopent-2-enone **186** (**Scheme 41**) via reaction of the Grignard reagent derived from intermediate **187** with aldehyde **188**, followed by Pd(0) catalysed ring closure of the stannane **189** (72%) and Swern oxidation.[118,119] By the same route compound **192** (R = OH, OCOAr) was prepared from monochiral ketone **191**.[120] This 10-membered dienediyne ketone cleaves supercoiled DNA with a very marked selectivity for purine bases (G > A). Incorporation of an internal thiol triggering device as in **194** was also achieved starting from the readily available ketone **193**.[121] As expected, methanolysis of thioacetate **194** at room temperature resulted in spontaneous thiol addition and Myers type cycloaromatization. Finally, the conjugate **195** was prepared which displayed potent DNA cleaving capacity.[122]

Krebs *et al.* have also constructed the cross-conjugated 10-membered dienediyne ketone **198** from acetylene **196** (**Scheme 42**).[123] The key step in their approach is the Noyori type intramolecular aldol reaction between the acetal and silyl enol ether moieties in the intermediate generated from **197**. More recently, Ueda has also described the elaboration of **199** to the isomeric ketone **200**, in which a phenyl group replaces the double bond α to the carbonyl function.[124]

In an extension of work on the regio- and stereoselective introduction of acetylene containing side chains onto 2-formylcyclopentanone derived enol triflates (Scheme 37), Terashima has described

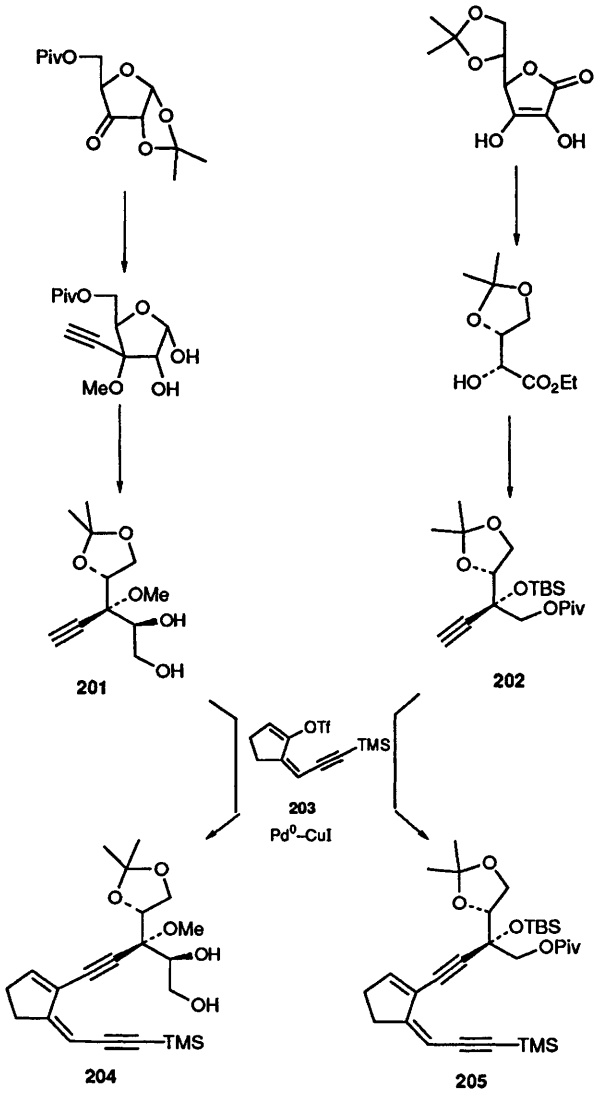



Scheme 42

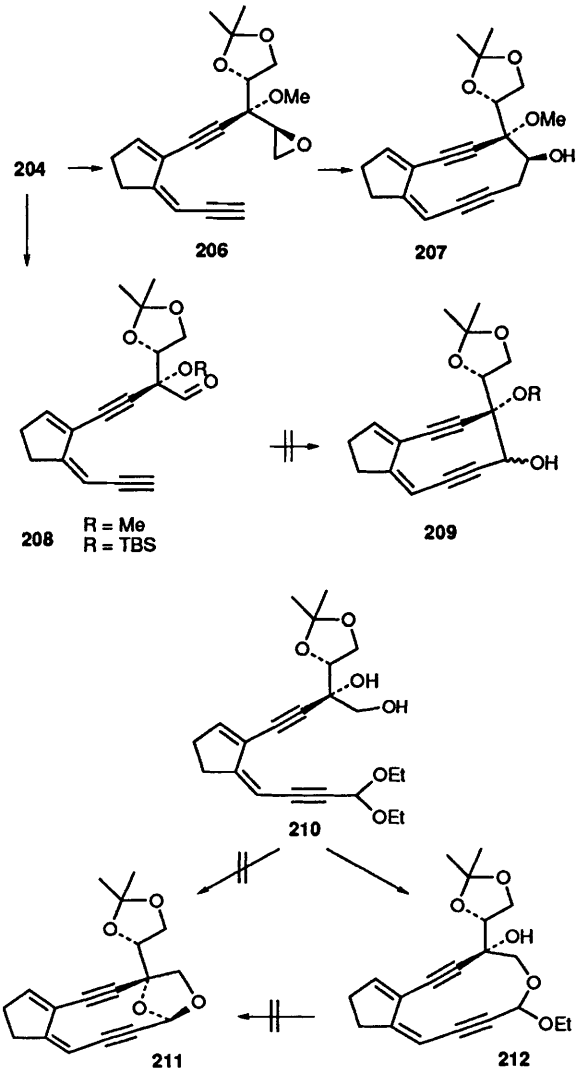
the preparation of the two chiral acetylene derivatives **201** and **202**, and their coupling to enol triflate **203** (**Schemes 43 and 44**).[113,125] Further conversion of compound **204** to epoxide **206** provided the possibility of obtaining the 10-membered bicycle **207**. However, the 9-membered neocarzinostatin analogue **209** was not accessible from the corresponding epoxide prepared from **205**. Similar efforts to prepare this compound by intramolecular acetylide condensation in **208** were also unsuccessful. Interestingly, attempted assembly of the novel 10-membered 1,3-dioxolane **211** through intramolecular transketalization of the polyhydroxylated intermediate **210** led instead to formation of the 11-membered bicycle **212**.

## 6 Conclusion

Much of the methodology used to access both the neocarzinostatin analogues and the enediyne systems described so far has either been applied to, or been developed during, efforts to achieve the




Scheme 43




Scheme 44

total synthesis of the three major enediyne–dienediyne antibiotics: the neocarzinostatin chromophore **9**, calicheamicin $\gamma_1^I$ **5**/esperamicin $A_1$ **6** and dynemicin A **15**. The outstanding achievements in this direction are analysed in Part 2 of this review, which will appear in the next issue of *Contemporary Organic Synthesis* (H. Lhermitte and D. S. Grierson, *Contemp. Org. Synth.*, 1996, **3**, 93).

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