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Enediyne antibiotics and their models: new potential of acetylene chemistry

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Abstract. Structures and chemical properties of enediynes, *viz*., compounds comprising a system of conjugated double and triple bonds, are surveyed. The presence of this system in the molecules of enediyne antitumour antibiotics ensures their high activity. The mechanism of biological action of enediynes is discussed based on cycloaromatisation of the enediyne chromophore resulting in highly active benzenoid 1,4-diradicals, which selectively cleave DNA. The key strategies of enediyne synthesis are analysed. The bibliography includes 291 references.

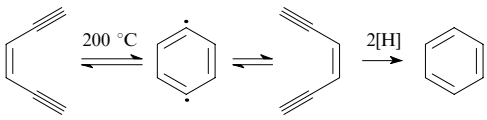
I. Introduction

The role of antibiotics in nature and in the human life can hardly be overestimated. Compounds with conjugated double and triple carbon – carbon bonds occupy a special place among them. Compounds with acetylene, vinylacetyle and acetylene – allene type systems of bonds were first found in the late 19 century in some plants and mushrooms. Since molecules containing these fragments are most often unstable, their presence in natural objects appeared unusual. However, as experimental facts have been accumulated, it turned out that compounds of this type are characteristic of the living nature, are widely represented and perform important functions, in particular, act as antibiotics, fungicides and insecticides. By the early 1970s, more than 600 natural acetylene derivatives have been isolated and studied. The studies published by that time were summarised in the fundamental monograph by Kucherov, Mavrov and Derzhinskii.[1]

The first representatives of enediyne antibiotics, natural antitumour compounds, were discovered in the second half of the 20th century.[2–6] This was preceded by a discovery by Bergman of the thermal cycloaromatisation of (*Z*)-3-ene-1,5-diyne systems (enediynes), which was later named after him.[7]

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The diradical intermediates formed upon cyclisation of enediynes were found [8] to attack selectively the DNA regions responsible for cell functioning.

By the end of the 20th century, the structure of the enediyne antitumour antibiotics has been studied in outline, but many important details, especially those concerning their synthesis, reactivity and the mechanism of physiological action remained unknown. Therefore, the attention of researchers to the development of new approaches to their synthesis and construction of functional models does not decline. The success in the design of enediyne systems gave a large number of synthetic analogues of known natural antibiotics of this class.

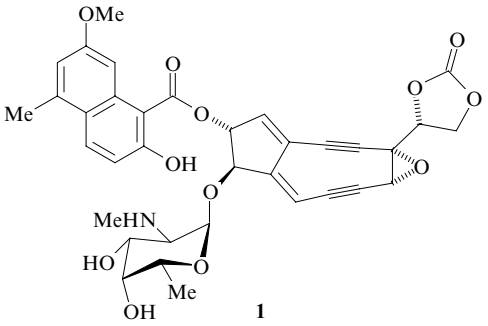
Study of the factors that influence cycloaromatisation of enediynes resulted in the development of a simple model of DNA cleavage induced by the benzenoid † diradicals formed (see, for example, Ref. 8). The second and third generations of enediyne antibiotics appeared, which are more active towards tumour cells than the natural products. The present review is devoted to the studies along this line carried out mainly over the last decade.

II. Typical representatives of enediyne antibiotics

1. Neocarzinostatin

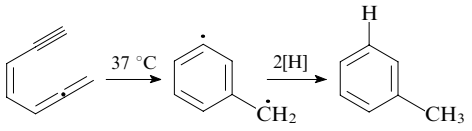
Neocarzinostatin was isolated in 1965 from the culture *Streptomyces carzinostaticus* var. F-41.[2] This was the first natural enediyne antibiotic to be described. This is a 1 : 1 complex of an apoprotein (a 113 amino-acid peptide) with chromophore **1**. Later, it has been shown that the chromophore component (generally designated as NCS in the modern literature on this subject) has a bicyclic dienediyne core.[2,8–11]

† The systematic name of the parent compound of this diradical series is 1,4-phenylene or 1,4-didehydrobenzene; however, for compliance with the term generally used in the literature, below they are referred to as benzenoid diradicals.



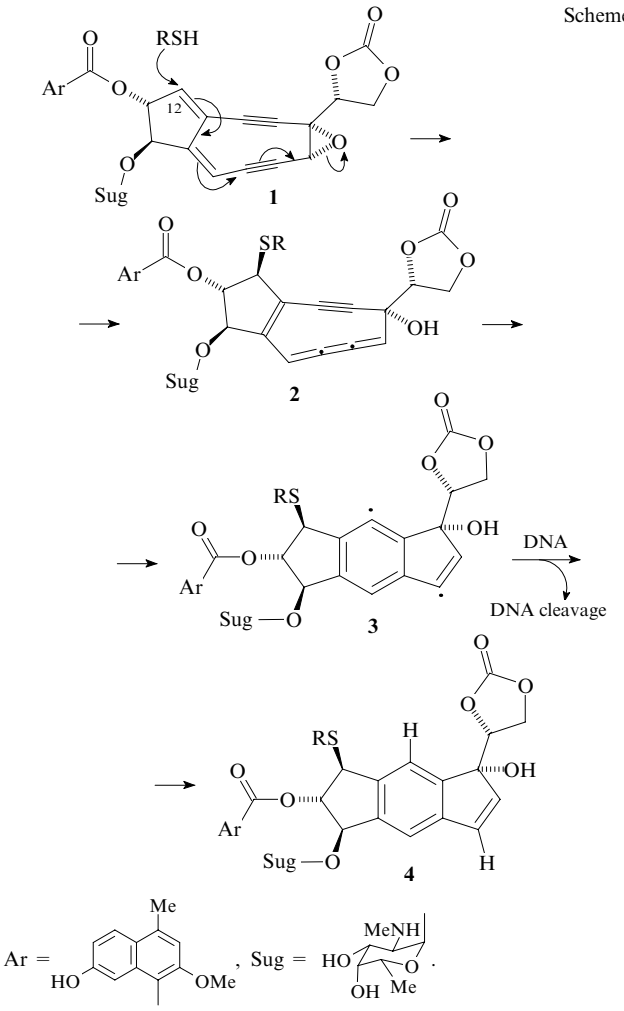
1

The biological activity of NCS is due to the Myers–Saito cycloaromatisation of the *Z*-enyne–allene system:[9]



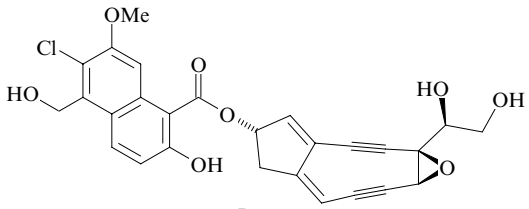
The mechanism of DNA destruction by the neocarzinostatin chromophore[2,8] is shown in Scheme 1. The cascade of reactions resulting in DNA cleavage is initiated by the specific nucleophilic attack on the C(12) carbon atom. The addition of a nucleophile (for example, a free sulfide group from the chromophore-surrounding proteins) induces bond rearrangement in the ring accompanied by oxirane opening giving rise to cumulene **2**. (In model syntheses, activation is due to an external nucleophile, for example, methyl thioglycolate.) The unstable intermediate **2** rapidly undergoes cycloaromatisation to give diradical **3**. The latter abstracts hydrogen from DNA, thus inducing its destruction and being converted into compound **4**. The cumulene intermediate **2** is detectable in the NMR spectra at low temperatures.[2,12,13]

Scheme 1



The reaction of the diradical with DNA starts with the elimination of the hydrogen atom from position C(5) of the deoxyribose fragment (the major reaction route).[14] The subsequent stages result in cleavage of the DNA chain.

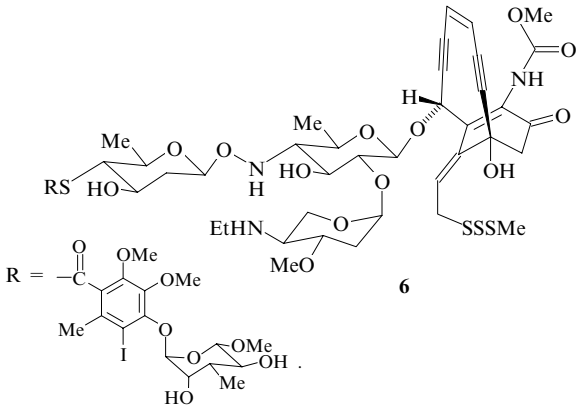
A unique analogue of neocarzinostatin, *i.e.*, the non-protein antibiotic N 1999 A2, which is a potent growth inhibitor for tumour cells and bacteria, was isolated from *Streptomyces* sp. AJ 9493.[15–20] The cytotoxic properties of this analogue with respect to some types of tumours are superior to the action of neocarzinostatin. The molecule of N 1999 A2 (**5**) also contains a nine-membered enediyne ring, but, unlike neocarzinostatin, it has neither a concomitant peptide nor a sugar residue.[18]



5

2. Calicheamicins, namenamicin, shishijimicin

Calicheamicins are a family of antibiotics isolated from *Micromonospora echinospora* ssp. *calichensis*.[2,21] The structure of one of them, calicheamicin γ_1^I (**6**), is shown below.

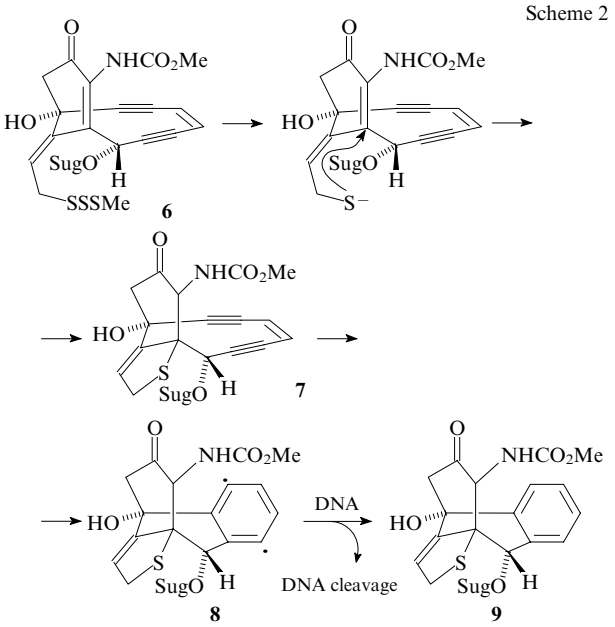


6

Representatives of this family of antibiotics are active with respect to Gram-positive and Gram-negative bacteria in concentrations below 1 μg ml^{-1} (Refs 2–6 and 22) and with respect to malignant tumours in concentrations of 0.15–5 μg ml^{-1}. The biological activity of these compounds is manifested as selective cleavage of double-stranded DNA *in vivo*; moreover, the carbohydrate part of the molecule was found to be responsible for selective coordination to the DNA minor groove (preferably, it binds to pyrimidine-rich regions).[3,6,23–29]

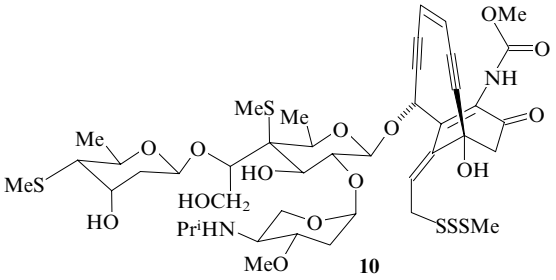
The calicheamicin aglycon has a rigid bicyclic core. The enediyne fragment incorporated in a ten-membered ring is able to undergo the Bergman cyclisation. The allylic trisulfide fragment activates the process (Scheme 2).[8,23] An attack by a nucleophile on the central sulfur atom of the trisulfide fragment gives a thiol group, which adds intramolecularly to the double bond (the Michael reaction) giving enediyne **7**, which is highly prone to cycloaromatisation to give highly reactive 1,4-benzenoid diradical **8**. This diradical abstracts a hydrogen atom from DNA, thus inducing its cleavage. The aromatic compound **9** formed upon the addition of hydrogen atoms was identified[21] based on low-temperature NMR spectra.[23,30]

Scheme 2



Sug is the carbohydrate fragment.

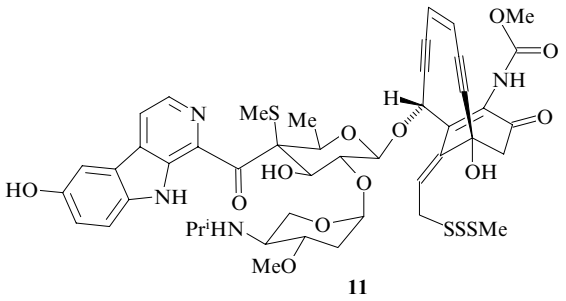
Namenamicin (**10**) is isolated from the marine ascidian *Polysyncraton lithostrotum* (Didemnidae, the Fiji Islands). From 1 kg of the frozen ascidian, one can obtain 1 mg of the antibiotic. Its structure and the cytotoxic properties are similar to those of calicheamicin and esperamicin.[16, 31]



Namenamicin exhibits a cytotoxic activity *in vitro* with an average IC_{50} value of $\sim$3.5 ng ml^{-1}, an antitumour activity *in vivo* with respect to the model leukemia P388 in rats (a 40% increase in the life time at doses of 3 mg kg^{-1}) and an antimicrobial action (see below). Its lower activity with respect to DNA destruction and higher selectivity compared to that of calicheamicin are due to differences in the structure of the carbohydrate fragment.[16]

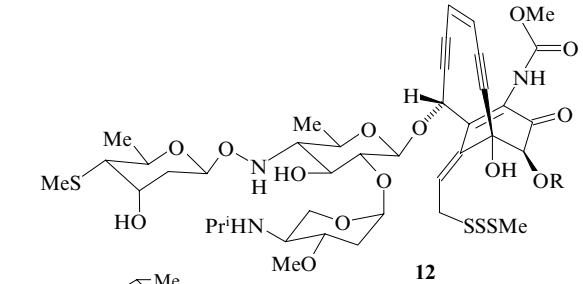
Organisms	Minimum inhibitory concentration /mg ml^{-1}		
	namenamicin	calicheamicin	penicillin G
Bacillus subtilis	0.03	0.00005	0.25
Candida albicans	0.25	0.03	>128

Shishijimicin (**11**) can be isolated from a methanolic or ethanolic extract of ascidian.[9, 32] Its carbohydrate moiety contains a 6-hydroxy-β-carboline fragment, while the aglycon is represented by 13-(2-methyltrisulfanylethylidene)bicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-11-one derivative. This compound is much more cytotoxic than namenamicin, which is devoid of the β-carboline heterocycle.

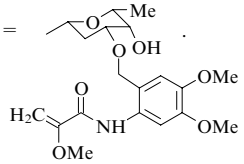


3. Esperamicins

Esperamicin is an exceptionally active broad-spectrum natural antibiotic. It was isolated from *Actinomadura verrucosospora Pto Esperanza* in 1985.[9] Its structure is similar to that of calicheamicin. The esperamicin molecule contains a bicyclic enediyne core. The absolute configurations of esperamicin A_1 (**12**) and calicheamicins were determined simultaneously.[33] Esperamicins and calicheamicins are the strongest known antitumour drugs. They are active against several model tumours in concentrations of $\sim$0.1 μg ml^{-1}.

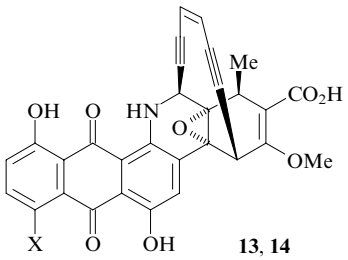


R =



4. Dynemicins

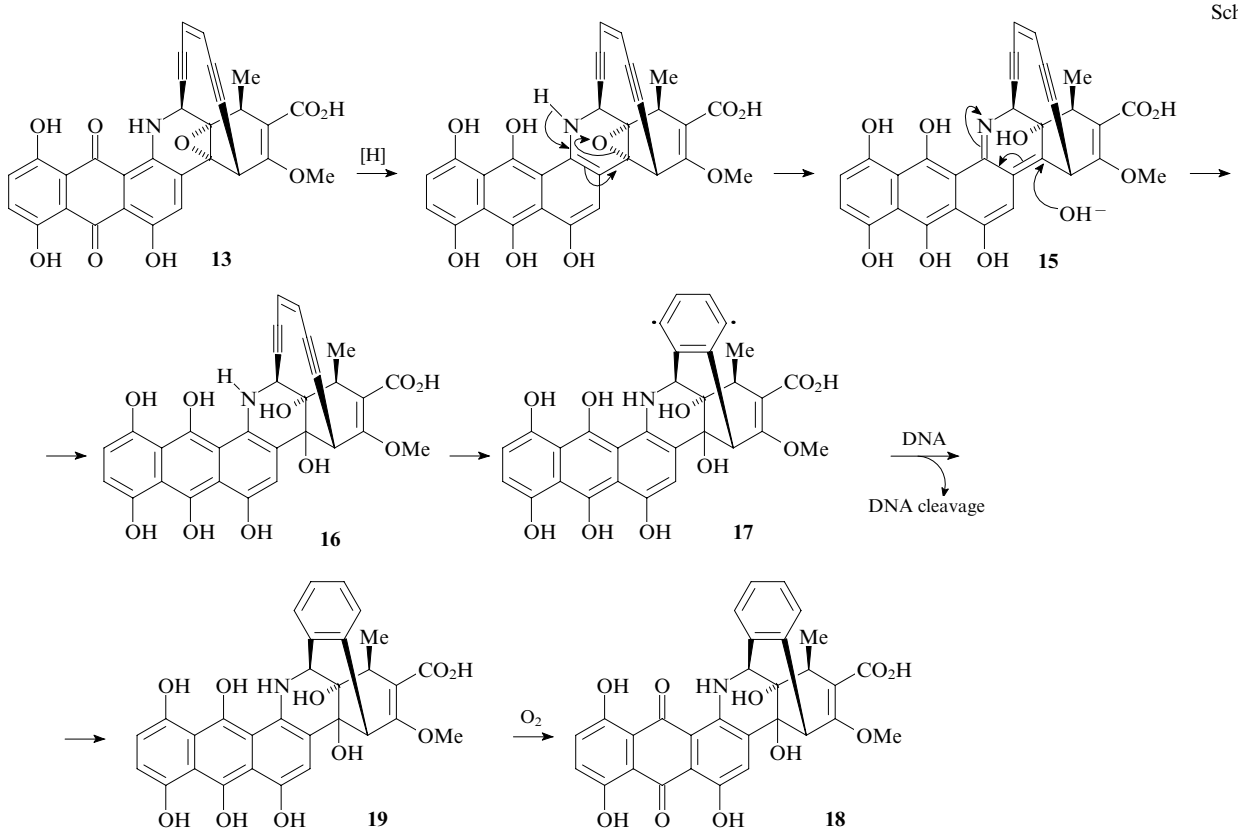
Dynemicin A (**13**), the first discovered representative of this family of antibiotics, was isolated from *Micromonospora chersina*.[9, 34–36] It exhibits high activity against many types of tumours and increases the life span of rats infected by leukemia P388 and melanoma B16. Its high activity is combined with low toxicity.[35] Yet another member of this family is deoxydynemicin (**14**) isolated from *Micromonospora globosa* MG331-hF6.[2]



X = OH (**13**), H (**14**).

A distinctive feature of dynemicins is the combination of a ten-membered bridging enediyne ring with an anthraquinone fragment. X-Ray diffraction analysis has shown that the anthraquinone moiety of the molecule is bevel with respect to the enediyne ring.[36–40]

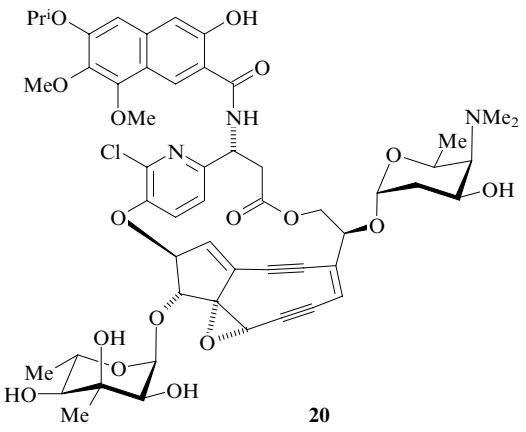
Scheme 3



The tentative mechanism of DNA cleavage under the action of dynemicin A involves initial reduction of quinone **13** (Scheme 3).[8,9] This is followed by opening of the epoxide ring to give intermediate **15**. Under the action of a nucleophile (for example, the hydroxide anion), **15** is converted into diol **16** with an unstable polycyclic system of multiple bonds, which undergoes fast cycloaromatisation to give 1,4-benzenoid diradical **17**, which cleaves DNA. The final product **18** is formed upon oxidation of polyol **19**.[2,41,42]

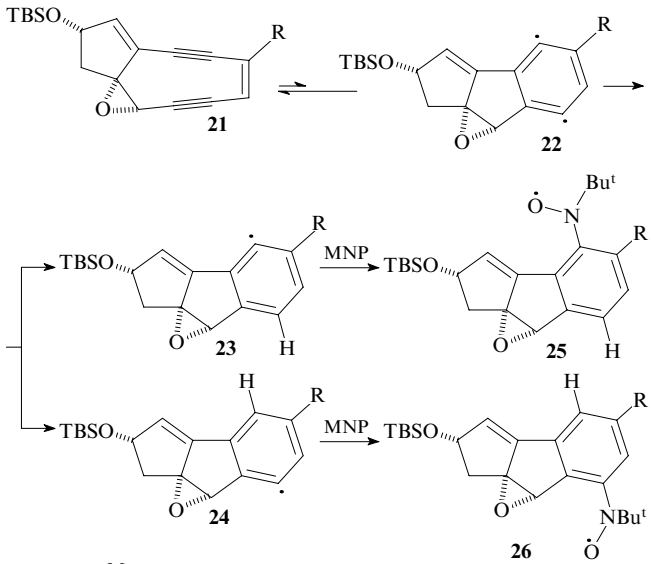
5. Kedarcidin, C-1027, maduropeptin

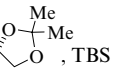
Studies of neocarcinostatin and the mechanism of its action demonstrated that a whole group of enediyne antibiotics represent non-covalent complexes formed by unstable chromophores and proteins that stabilise them. This resulted in the discovery of the kedarcidin,[2,8,9,43–51] C-1027[2,8,9,52–55] and maduropeptin[2,56,57] chromophores. The kedarcidin chromophore (**20**) was first described in 1991.[2] Antitumour preparations based on kedarcidin, like many other enediyne antibiotics, are also active with respect to Gram-positive bacteria.[43]



The kedarcidin apoprotein exists in a number of forms.[2] The main form contains 114 amino acid residues with predominance of alanine and serine. Whereas for neocarcinostatin the apoprotein : chromophore molar ratio is 1 : 1, in the case of kedarcidin, this ratio is equal 18 : 1. Cleavage of DNA by kedarcidin resembles the action of neocarcinostatin.[43]

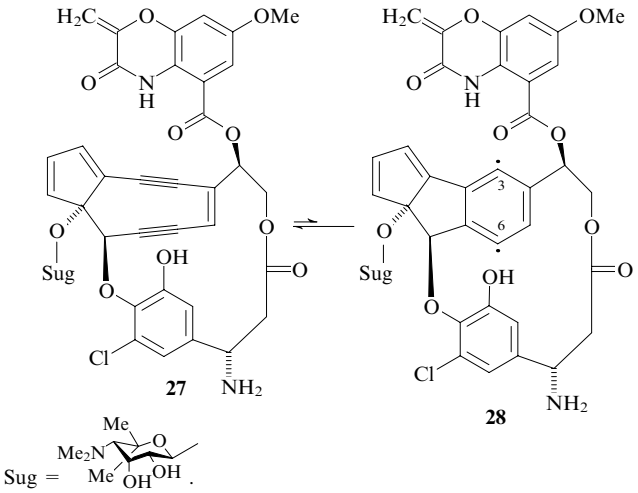
An analogue of the kedarcidin chromophore **21** exists as an equilibrium mixture with the cycloaromatisation product, 1,4-didehydrobenzene **22**. This system was studied by the spin trap method[58,59] using 2-methyl-2-nitrosopropane (MNP), which allowed identification of intermediate monoradicals **23** and **24** having different reactivities.



R = , TBS = Bu^tMe_2Si.

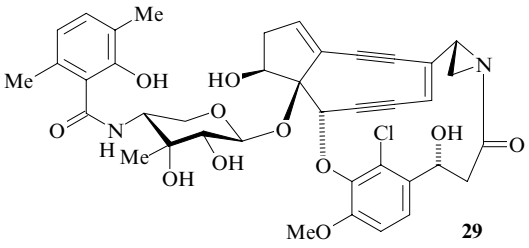
Spin adducts **25** and **26** formed in 2 : 1 ratio were characterised by EPR and mass spectrometry.[59]

An exceptionally active antitumour antibiotic C-1027 containing a polypeptide and a dienediyne chromophore **27** was isolated from the culture broth of *Streptomyces globisporus*.[2] To date, this is the most labile nine-membered enediyne chromophore.[9] Chromophore **27** is stable only when bonded to the apoprotein. In the free state, it undergoes rapid cycloaromatisation even at room temperature.[60–72] Unlike other representatives of this subfamily, compound **27** can be cycloaromatised without the thiol activation.[9]



A two-stage mechanism of hydrogen atom abstraction from DNA by diradical **28** was established. First, one hydrogen atom adds slowly to position 6 giving free monoradical and then the second H atom rapidly adds at position 3 to give the aromatic structure.[73] The radical intermediates formed upon DNA cleavage by the antibiotic C-1027 were captured by spin traps, and the spin adducts were identified by EPR spectroscopy and mass spectrometry.[60, 73] These data provide an insight into the mechanism of antibiotic action in DNA cleavage processes.[59, 73]

The antibiotic maduropeptin, which possesses bactericidal and antitumour activities, was isolated in 1990 from *Actinomadura madurae*.[2, 9, 56, 57] It is a 1 : 1 complex of a water-soluble protein comprising 32 amino acids and enediyne chromophore **29**.



Maduropeptin is also capable of forming diradicals without activation.[9]

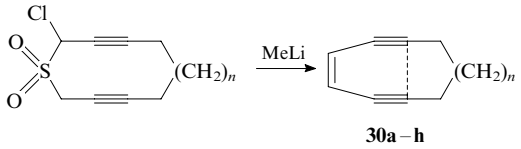
III. Cycloaromatisation of enediynes

Cycloaromatisation reactions of enediynes have attracted considerable attention due to their high synthetic potential and the possible use in pharmaceutical chemistry,‡ as indicated by numerous publications: monographs,[2, 6] reviews[8, 9, 74, 75] and original papers (see, for example, Refs 76–79). Below we consider the results of experimental studies and quantum-chemical simulation of enediyne systems. Note that apart from the thermal Bergman reaction, other (homolytic and heterolytic) ways to initiate cycloaromatisation are also possible.

‡ It was proved that the antitumour activity of natural antibiotics is directly related to their susceptibility to cycloaromatisation.[80–90]

1. Susceptibility to cycloaromatisation

The first theory that relates the susceptibility of a enediyne system to cycloaromatisation to the distance between the acetylenic bonds belongs to Nicolaou, who studied cycloaromatisation of monocyclic enediynes **30a**–**h**.[91]



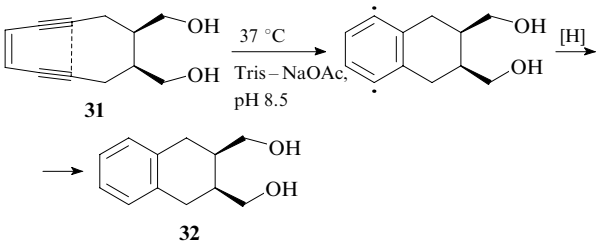
30a–**h**

n = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**), 5 (**e**), 6 (**f**), 7 (**g**), 8 (**h**).

Nine-membered cyclic enediyne **30a** (n = 1) has not been synthesised, but the products of its cycloaromatisation have been identified. Other compounds have been isolated in a free state. Of these, only the ten-membered enediyne **30b** undergoes cycloaromatisation at moderate temperatures, while compounds **30c**–**h** do not cyclise under these conditions.

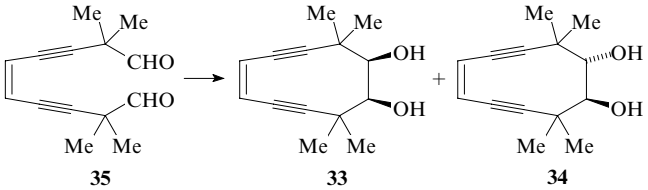
Thus, it can be seen that the ease of cycloaromatisation of the enediyne macrocycle depends on the distance between the terminal acetylenic carbon atoms. The range of 3.2–3.3 Å is critical; in this case, the reaction proceeds at a noticeable rate at moderate temperature. The transition state energy for this reaction was estimated based on calculations and kinetic data.[91]

In diol **31**, the distance between the terminal acetylenic atoms is equal to 3.20 Å; this compound cyclises at 37 °C. Diol **31** readily cleaves DNA, while the final product **32** does not react with DNA under the same conditions.[91]

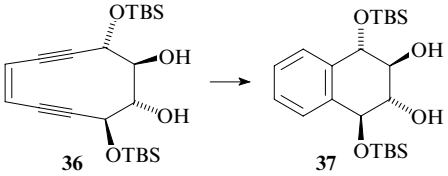


Tris = $HOCH_2C(CH_2OH)(NH_2)CH_2OH$.

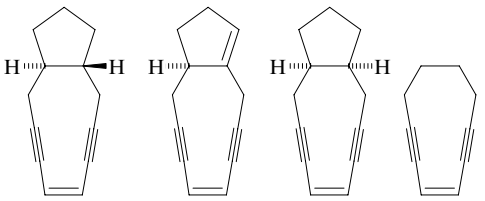
Diols **33** and **34** prepared from dialdehyde **35** cleave DNA *in vitro* (Tris–acetate buffer, pH 8.5); the half-conversion time is 4 h at 50 °C.[92]



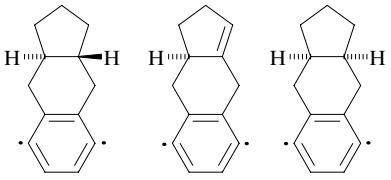
The synthesis of enantiomerically pure ten-membered cyclic tetrahydroxyenediynes from L-tartrates has been reported.[93, 94] The introduction of silyl protecting groups allows one to control the cycloaromatisation rate in compound **36** (deprotection accelerates the process). The half-conversion time for compound **36** into product **37** is 2 h at 50 °C and pH 8.5.[94]



Determination of the distance between the acetylenic bonds is the easiest method for predicting the tendency of a enediyne system to aromatisation. A more fundamental approach is to estimate the heat of formation of the diradical. For enediynes **38**–**40**, which mimic the chromophores of the calicheamicin antibiotics, the distances between the terminal carbon atoms of the acetylenic fragments and the enthalpies of formation of the respective diradicals **41**–**43** were determined by semiempirical calculations (AM1)[95]



38 **39** **40** **44**



41 **42** **43**

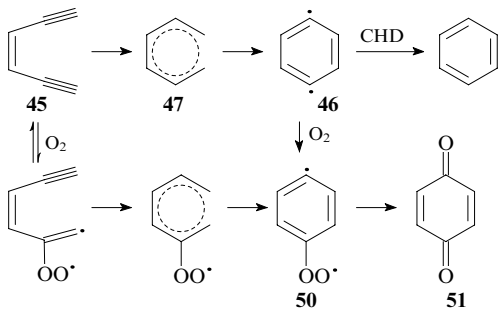
Compound	Distance /Å	Diradical	ΔH_f/kcal mol^{-1}
38	3.24	**41**	48.2
39	3.09	**42**	40.9
40	2.98	**43**	38.1

The calculations predict a decrease in the susceptibility to cycloaromatisation (**40** > **39** > **38**) from the *cis*-fused to *trans*-fused bicyclic structure, which is correlated with the variation of the distance between the acetylenic carbon atoms. Compound **38** is expected to be much less reactive than the simplest ten-membered monocyclic enediyne **44**, which is cycloaromatised very slowly at 25 °C (the calculated heat of formation of the corresponding diradical is 45.2 kcal mol^{-1}).[2]

2. The diradical pathway of enediyne cyclisation

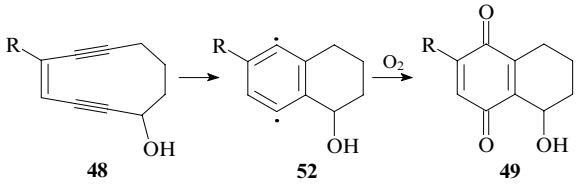
The simplest example of the Bergman cyclisation is the transformation of hex-3-ene-1,5-diyne (**45**) into 1,4-didehydrobenzene (**46**) through transition state **47** accompanied by hydrogen atom abstraction from 1,4-cyclohexadiene (CHD) to give benzene (Scheme 4).

Scheme 4



45 **47** **46** **50** **51**

Recently, it has been found[96] that cyclisation of enediyne **48** in an aqueous medium (in the presence of traces of oxygen) gives quinone **49**, its yield being proportional to the concentration of dissolved oxygen.



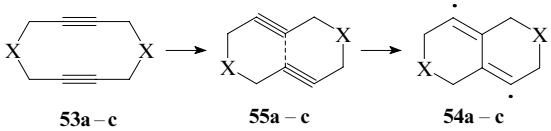
48 **52** **49**

R = $CH_2NHC(O)CF_3$.

In this connection, one more radical pathway for cyclisation of enediyne **45** was proposed, involving oxidation with oxygen to give peroxide diradical **50** and then quinone **51**. The possible radical pathways of cyclisation of enediyne **45** (see Scheme 4) were studied theoretically (DFT calculations, 6-31 G* basis set).[86,96–98] For triplet and singlet diradicals and neutral species formed during cyclisation of compounds **45** and **48**, geometry optimisation was carried out and the relative energies and reaction barriers were estimated. To take into account the solvent effects, some calculations were repeated using the polarised continuum model (PCM).

It was shown that diradical **52** cannot react with O_2 in the gas phase. The assumption of direct reaction of enediyne **48** with oxygen is also not confirmed.[86] To elucidate the nature of the intermediate diradical, gas-phase thermolysis of 1,6-cyclodecadiyne has been studied.[99,100]

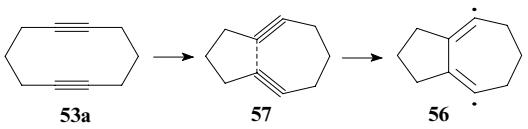
Molecular orbital calculations [CASSCF(8,8)/6-31 G*] have been carried out for the gas-phase transannular ring closure in ten-membered cyclic diynes **53a**–**c** to give bicyclo[4.4.0]deca-1,6-diene-2,7-diyls **54a**–**c**.[99]



53a–**c** **55a**–**c** **54a**–**c**

X = CH_2 (**a**), NH (**b**), O (**c**).

The geometries were optimised for the ground states **53a**–**c**, transition states **55a**–**c** and intermediates **54a**–**c**. The activation energy for the transition **53** → **54** was found to depend on the distance between the triple bonds. The transition along the route **53a** → **57** → **56** has higher activation energy than **53a** → **55a** → **54a**.[99]



53a **57** **56**

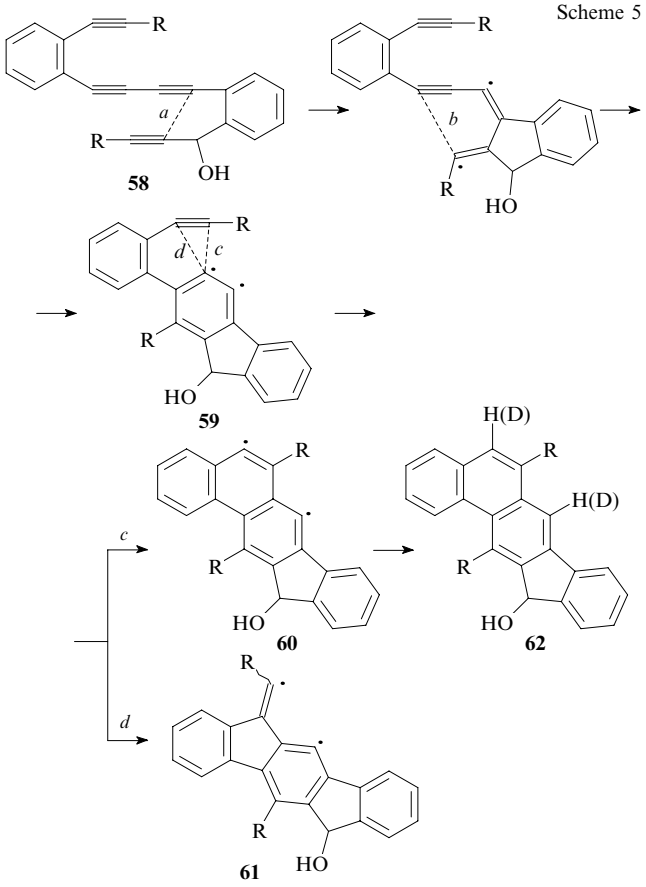
Aromatic enediynes **58** cyclise at 25 °C to give fused systems (Scheme 5).[8,101]

Thermolysis of compounds **58** initiates the cycloaromatisation of acetylenic bonds along the pathway *a* and is accompanied by the tandem radical cyclisation along the pathway *b* to give σ,σ-dehydrobenzene diradicals **59**.[101] Subsequently, thermal radical cyclisation of diradicals **59** (along pathway *c* or *d*) gives two types of diradicals, **60** and **61**, respectively.

In particular, product **62** was obtained by this method in 10% yield from tetrayne **58** (R = C≡CSiMe$_3$). Synthesis of compounds **62** is accompanied by the formation of large amounts of by-products. Thermolysis of the same tetraacetylene in methanol-d_4 gives **62**-d_2 containing deuterium only in positions 5 and 7 (see Scheme 5).[101]

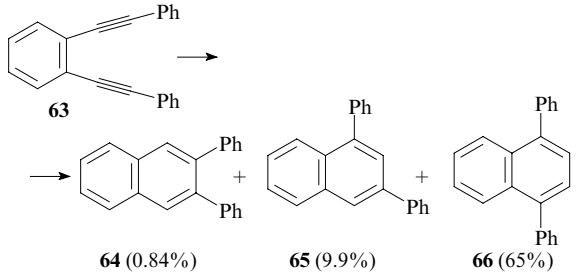
Upon thermal cyclisation (320 °C, 3 h) of 1,2-bis(phenylethynyl)benzene (**63**), the expected 1,2-diphenylnaphthalene **64** was detected in trace amounts (0.84%).[102] The isomeric naphtha-

Scheme 5



R = H, $SiMe_3$, Ph, $C{\equiv}CSiMe_3$.

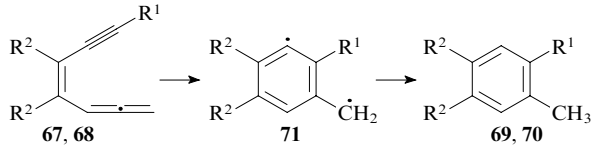
lenes **65** and **66** resulting from migration of the phenyl groups were the major cyclisation products.



64 (0.84%) **65** (9.9%) **66** (65%)

Analysis of the thermodynamics of these transformations is carried out using quantum-chemical calculations (DFT). Cycloaromatisation of these enediynes in the presence of tellurium proceeds under mild conditions.[103]

Cyclisation of allene enynes **67** and **68** into benzene (**69**) and naphthalene (**70**) compounds occurs at 50–100 °C through diradicals **71**.[50, 104, 105]

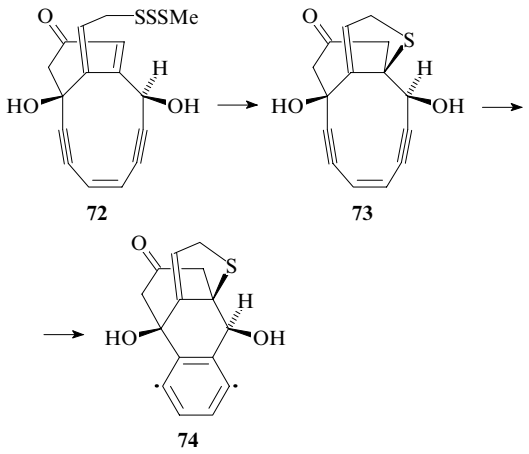


67, **68** **71** **69**, **70**

R^1 = H, Alk, Ph; R^2_2 = H_2 (**67**, **69**), $(CH)_4$ (**68**, **70**).

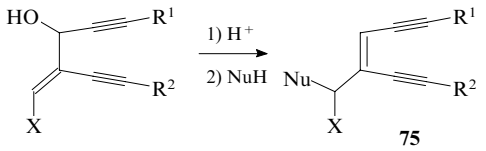
To elucidate the reaction mechanism, quantum-chemical calculations were carried out, and the geometric parameters of radicals **71** and thermodynamic parameters of their formation reactions were determined.[104]

As noted above, an important feature of natural enediynes is the fact that some chemical reactions convert them from a stable form (*e.g.*, **72**) into a reactive form (**73**), which is rapidly converted into benzenoid diradical (**74**).[106–109]



72 **73** **74**

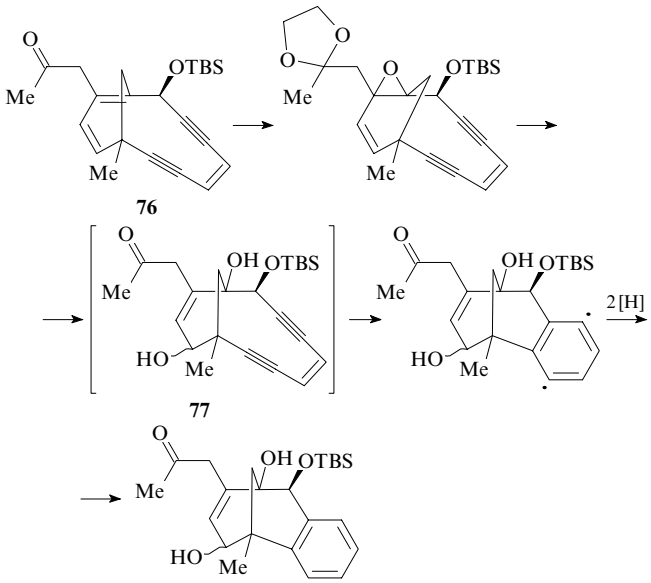
The synthesis of *cis*-enediynes **75** by acid-catalysed rearrangement of 1,2-dialkynylprop-2-en-1-ols in the presence or in the absence of nucleophilic reagents (alcohols or thiols) can serve as an example of chromophore activation through isomerisation of double bonds.[110]



75

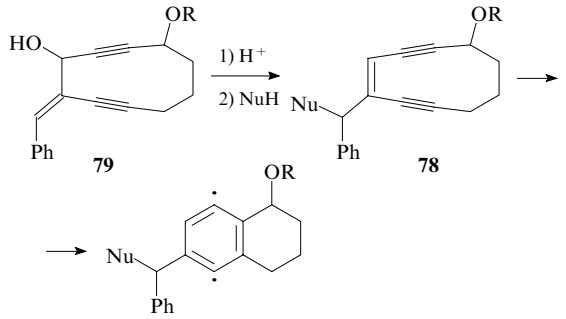
X = H, Ar; Nu = OH, OMe, SMe; R^1 = CH_2SPh; R^2 = $(CH_2)_4OMe$.

The activation of the enediyne bond system in compound **76**, which mimics calicheamicin, through the rearrangement of multiple bonds, resulting in structure **77** more prone to cycloaromatisation, was studied experimentally and by quantum-chemical calculations.[111] The diradical formed in the cycloaromatisation of enediyne **77** is converted upon reduction into the corresponding ketodiol in a high yield.



76 **77**

Cycloaromatisation of the 10-membered highly strained enediyne **78**, prepared from thermally stable precursor **79**, has been carried out.[112, 113]



Nu = OH, OEt; R = anthraquinone-2-carbonyl.

Acid-catalysed dehydration of alcohol **79** affords allylic intermediate, which is attacked by the nucleophile exclusively on the γ-carbon atom to give enediyne **78** prone to cycloaromatisation.[114–116] The same allylic rearrangement presumably takes place on heating alcohol **79** in a weakly basic medium in the presence of DNA.[117]

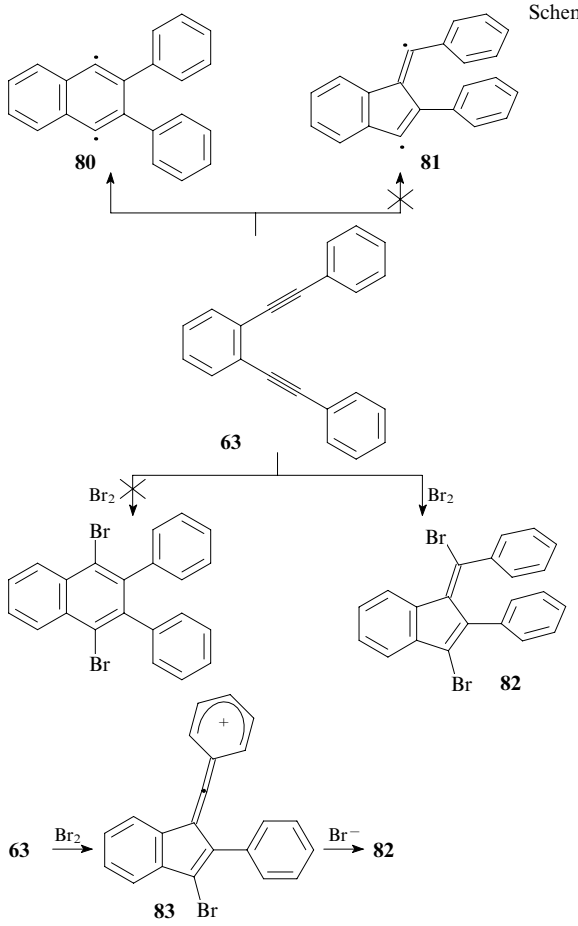
The formation of reactive enediynes upon allylic rearrangement obviously underlies the mechanism of action of the maduropeptin [118, 119] and kedarcidin [58] chromophores.

3. Electrophilic activation of the cyclisation

As an alternative to the C(1)–C(6) cyclisation of enediynes such as *o*-bis(2-phenylethynyl)benzene (**63**), which proceeds through diradical **80**, C(1)–C(5) cyclisation proceeds through diradical **81** to yield benzopentafulvenes (Scheme 6).[120]

The energy barrier to the formation of naphthalene diradical **80** is rather high (40 kcal mol^{-1}, according to UBS-B3LYP/6-31 G* calculations). It was found that, unlike the homolytic reaction resulting in naphthalene derivatives, the reaction of the enediyne **63** with bromine results in fulvene **82**.[120] The cyclisation of compound **63** induced by bromine proceeds through cation **83**.

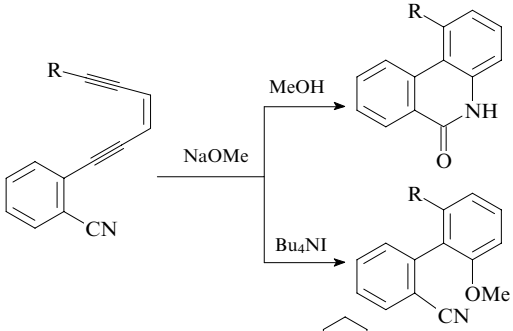
Scheme 6

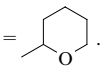


4. Cyclisation under the action of nucleophiles

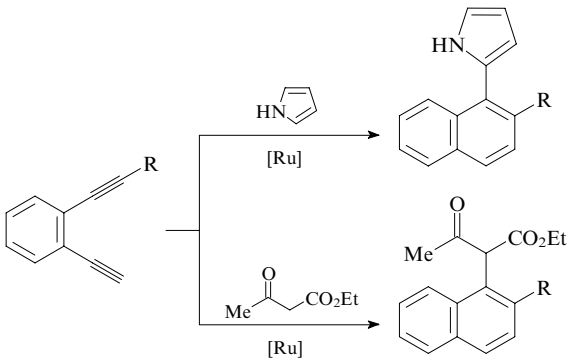
Cyclisation of non-functionalised enediynes along the diradical pathway and through electrophilic addition gives benzene derivatives and functionalised fulvenes, respectively.[121] Base-induced aromatisation of enediynes (the Bergman anionic cyclisation) can be used for functionalisation of the benzene nucleus by nucleophiles.[122–124]

A general method for the preparation of functionalised aromatic compounds from enediynes has been developed; the key stage of the method is cycloaromatisation of the enediyne fragment induced by nucleophiles.[122] Depending on the reaction conditions and the substrate structure, either benzo[*c*]phenanthridinone or biaryls are formed. If the methoxide anion attacks the nitrile function, cycloaromatisation resulting in phenanthridinones takes place. If the attack is directed on the acetylenic C(2) atom of the enediyne system, biaryls are formed.[122]



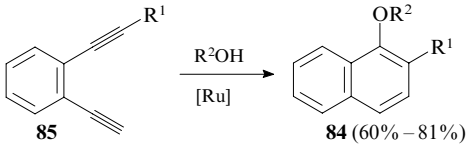
R = Pr^n, Bu^n, $(CH_2)_3$OTHP, THP = .

The cyclisation of enediynes with a terminal acetylene group induced by neutral nucleophiles (water, alcohols, aniline, acetylacetone, pyrroles, dimethyl malonate) and catalysed by the ruthenium complex $[TpRu(PPh_3)\cdot(MeCN)_2]\cdot PF_6$ [Tp is hydrotris(pyrazol-1-yl) borate] can serve as a general method for the synthesis of functionalised benzenes and naphthalenes.



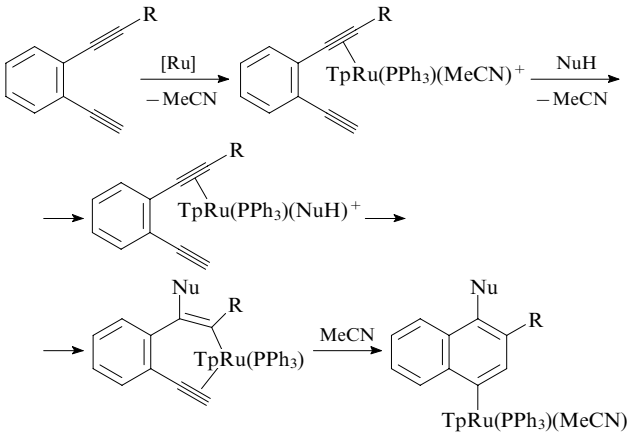
R = H, Me; [Ru] = $[TpRu(PPh_3)(MeCN)_2]PF_6$.

In particular, this method was used to prepare 1-alkoxy-2-substituted naphthalenes **84** by treatment of enediynes **85** with water or an alcohol (n-butyl, isobutyl or *tert*-butyl alcohol).[121]



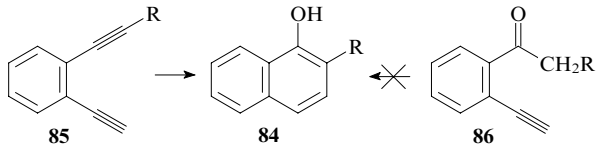
R^1 = H, Me, Et; R^2 = H, Bu^n, Bu^i, Bu^s, Bu^t.

In this case, the addition of nucleophiles to the substituted triple bond and spontaneous cyclisation of the enediyne system take place in the coordination sphere of ruthenium.[121, 125–128]



Presumably, the reaction involves vinylruthenium and vinylideneruthenium intermediates.[121]

This type of enediyne cycloaromatisation is quite unusual, because electrophilic metal complexes can catalyse hydration of terminal alkynes **85** to ketones **86**.[129] It was shown that the latter are not intermediates of cycloaromatisation, because they do not form naphthols under the conditions studied.[130]

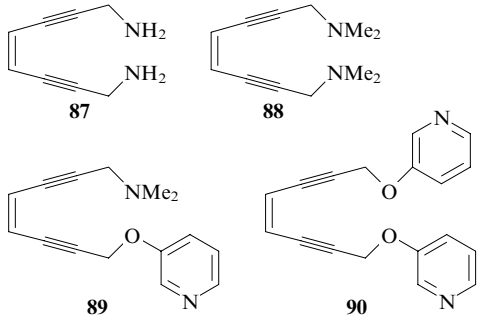


5. Cycloaromatisation of heteroatomic enediynes

It is expedient to consider the cycloaromatisation of enediynes containing heteroatoms taking nitrogen-containing derivatives as examples, as they attract most interest.[131–133]

a. Acyclic nitrogen-containing enediynes

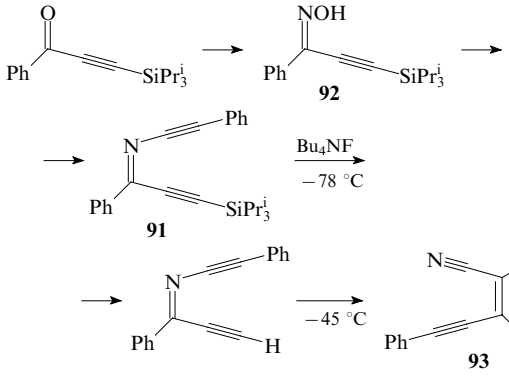
The thermal cyclisation of enediynes **87**–**90** in the presence of CHD is affected by steric factors.[131–133]



This is believed[131] to be caused by hindered rotation of substituents about the acetylene groups of the enediyne fragment. Enediyne **88** cyclises only at 186 °C, whereas the cyclisation temperature for 3-hydroxypyridine derivative **90** is 149 °C, which is attributable to the easier rotation of substituents. The cycloaromatisation temperature of 1,6-bis(3-pyridyl)hex-3-ene-1,5-diyne in which the pyridine rings are directly bound to the acetylene groups increases to 195 °C.

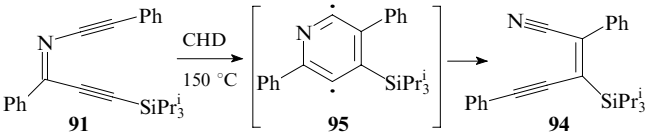
b. C,N-Dialkynylimines (aza-enediynes)

The replacement of the sp^2 carbon atom of an enediyne by a nitrogen atom results in C,N-dialkynylimines **91**. These compounds are synthesised from acetylenic ketoximes **92**.[134]



Deprotection of the acetylene fragment in compound **91** destabilises the molecule, and rearrangement takes place at −45 °C giving rise to β-phenylethynylacrylonitrile derivative **93** (yield 89%).[135]

Thermolysis of protected aza-enediyne **91** (heating in chlorobenzene in the presence of 20 equiv. of CHD in a sealed tube at 150 °C for 3 days) resulted in 2,5-diphenyl-3-triisopropylsilylpent-2-en-4-ynenitrile (**94**) (yield 35%).[135]

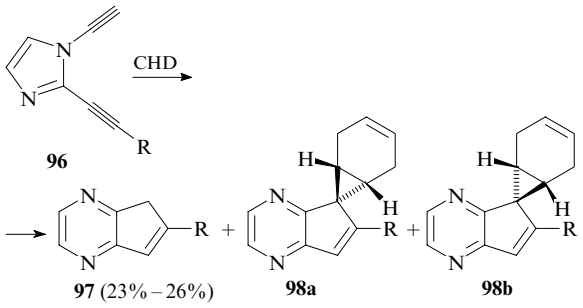


The reaction proceeds presumably *via* 2,5-didehydropyridine intermediate **95** (the aza-Bergman cyclisation), which undergoes fast ring opening (the retro-aza-Bergman cyclisation).[135] Diradical intermediates have not been isolated, although GC/MS analysis detected the formation of pyridine type products upon the thermolysis of aza-enediynes in acidic media.[135]

The synthesis and transformations of dialkynyldiazenes (diaza-enediynes) that possess antitumour action have been described.[136]

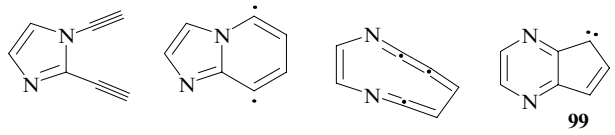
c. Hetarenediynes

The Bergman-type thermal cyclisation of 1,2-dialkynylimidazoles **96** (heating in a sealed tube with CHD at 75–100 °C for 2–4 days) gives, in addition to 5*H*-cyclopentapyrazine (**97**), spirobicyclo[4.1.0]heptane-7,5-5*H*-cyclopentapyrazines **98a**,**b**.[137, 138]



R = H, Alk, Ar.

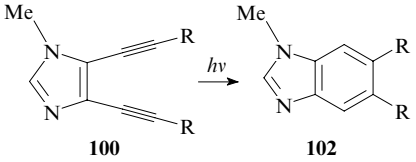
Quantum-chemical calculations (B3LYP/6-31G*) of the relative energies of the possible intermediates of this process indicate that cyclopentapyrazinecarbene intermediates **99** are most favourable.[138]



99

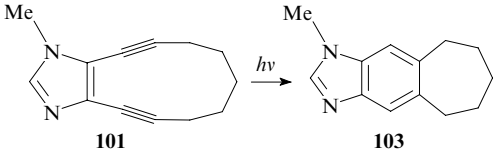
E_{rel} /kcal mol^{-1}	0	+15.1	−12.9	−12.9

The photoinduced (irradiation with a 450 W lamp) cyclisation of a number of 1-methyl-2,3-diethynylimidazoles **100** and their macrocyclic analogue **101** to give benzimidazoles **102** and **103** has been studied.[139, 140]



100 **102**

R = Me, Bu^n, Ph.

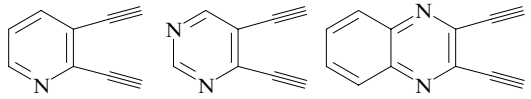


101 **103**

The cycloaromatisation products **102** are formed in good yields. Bicyclic compound **101** cleaves plasmid DNA at low temperatures.[140]

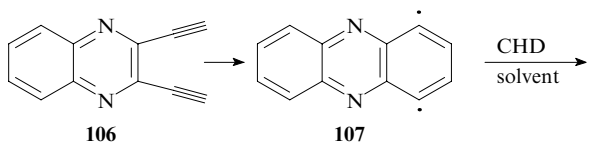
Although the distance between the terminal acetylene atoms is the major factor affecting the cyclisation of enediynes,[141, 142] electronic effects also play a role.[143–145]

The influence of the electronic factors and the medium on the cyclisation of hetarenediynes **104**–**106** has been studied.[143]

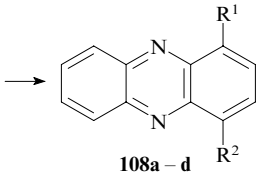


104 **105** **106**

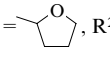
It was shown that the presence of the electron-deficient hetarene fragment decreases the activation energy of the reaction.[146] Using cyclisation of 2,3-diethynylquinoxaline (**106**) as an example, it was shown that the reaction kinetics depends appreciably on the nature of the solvent (acetonitrile, methanol, benzene, dioxane, carbon tetrachloride, THF); the half-conversion time may vary from 361 to 16 min.[143] Cyclisation in each solvent was carried out both in the presence and in the absence of CHD (*i.e.*, either CHD or the solvent served as the hydrogen source). The removal of CHD from the reaction mixture did not exert pronounced influence on the structures and yields of the cyclisation products. Less polar solvents ensured higher yields of the cyclisation products. In most solvents, phenazine **108a** was formed as the major product, while in benzene and carbon tetrachloride, the products formed in the reaction of diradical **107** with the solvent (**108b**–**d**) predominated.[143]



106 **107**



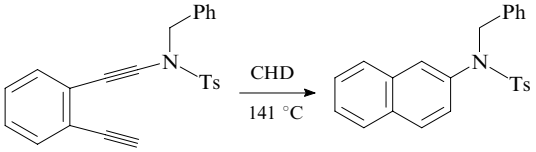
108a–**d**

R^1 = R^2 = H (**a**), Ph (**b**), Cl (**c**); R^1 = , R^2 =  (**d**).

Solvent	Half-life /min	Cyclisation products	Yield (%)
Acetonitrile	361	**108a**	7
Methanol	312	**108a**	2
Benzene	96	**108b**	58
Dioxane	60	**108a**	15
CCl_4	14	**108c**	81
THF	16	**108a** + **108d**	36, 9

d. Enediyne sulfonamides

A study of the thermal cyclisation of *N*-benzyl-*N*-(2-ethynylphenyl)ethynyl-*p*-toluenesulfonamide (**109**) (141 °C, benzene : CHD = 2 : 1) to naphthalene derivative **110** has shown that the half-conversion time of this compound (44 min) is much shorter than that for the parent compound of the series, 1,2-diethynylbenzene.[147] This is indicative of the activating effect of the sulfonamido group on the cyclisation; simultaneously, this group decreases the hydrolysability of the ynamine fragment.[148]



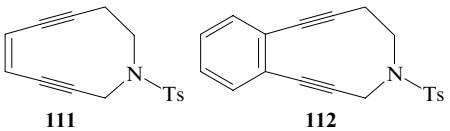
109 **110**

Ts = $SO_2C_6H_4Me$-4.

This example confirms once again the general trend, namely, that σ-withdrawing substituents at the terminal acetylenic carbon atom of an enediyne increases the susceptibility of the compound to cycloaromatisation.

The synthesis and reactivity of cyclic enediyne sulfonamides are considered in a number of publications.[149–153]

Enediyne sulfonamides have certain advantages as regards cycloaromatisation over the carbon and sulfur analogues. In particular, the presence of a short C−N bond (1.47 Å), which is shorter than the C−C (1.54 Å) or C−S (1.81 Å) bonds in the corresponding analogues, results in a decrease in the distance between the terminal acetylenic carbon atoms. Indeed, in sulfonamide **111** this distance is only 3.24 Å,[91] *i.e.*, corresponds to the critical distance that ensures easy cyclisation.

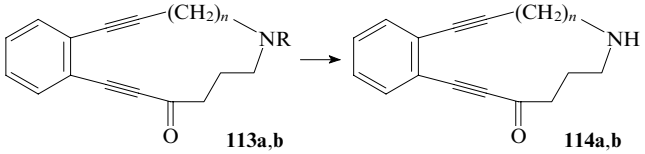


111 **112**

Heterocyclic compound **111** slowly undergoes cycloaromatisation even at 25 °C in $CDCl_3$ to give tetrahydroisoquinoline.[152] In acetonitrile, its half-life at 23 °C is 72 h, which implies an activation energy of 18 kcal mol^{-1}.

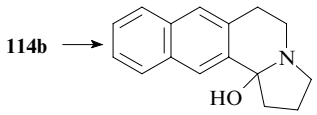
Cycloaromatisation of sulfonamide **112** occurs at 62 °C with a half-life of 52 h. Its low reactivity compared to that of enediyne **111** was attributed to less pronounced resonance energy stabilisation of the transition state and to different degrees of pyramidalisation of the nitrogen atom.[152]

N-Deprotection of the 12-membered enediyne **113a** results in a quite stable cyclic amino ketone **114a**. Meanwhile, its 13-membered homologue, amino ketone **114b**, proved to be unstable, being rapidly converted into cycloaromatisation product **115**.[153] In this case, the Bergman cyclisation is stimulated by the parallel transannular cyclisation involving the amine and carbonyl function.



113a,**b** **114a**,**b**

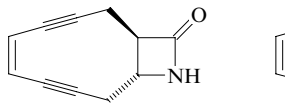
R = $SO_2C_6H_4NO_2$-4; n = 1 (**a**), 2 (**b**).



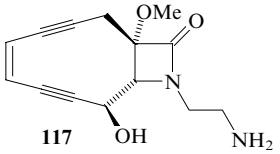
115

e. Lactenediynes

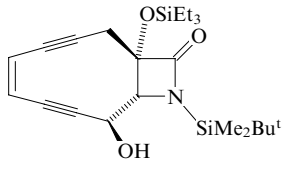
This is the name for ten-membered enediynes fused to β-lactam.[154–156] The presence of *trans*-fused rings in the molecules of compounds **116**–**118** makes them rather thermostable. Cycloaromatisation is initiated by β-lactam ring opening.[155] N-Protected compound **118** is unable to cleave DNA, however after deprotection, the enediyne becomes reactive.[155] The parent compound of the series of substituted lactenediynes, bicyclic compound **116**, easily undergoes cycloaromatisation (the half-conversion time is 36 h at 30 °C).[154]



116



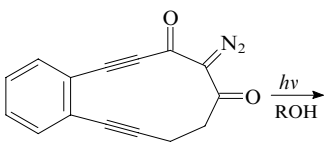
117



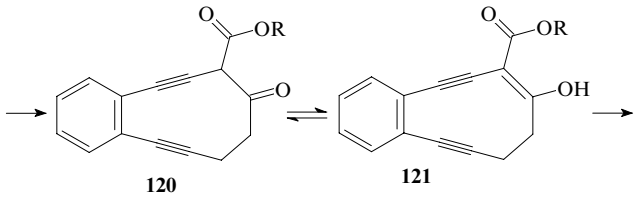
118

f. Cyclic enediynes with a diazocarbonyl fragment

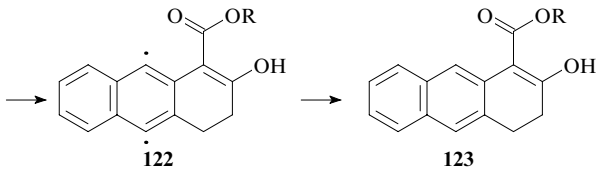
Irradiation of 11-membered enediynes with a diazo-β-dicarbonyl fragment results (through the Wolf rearrangement) in reactive ten-membered structures. Indeed, photolysis of enediyne **119** induces its rearrangement into oxo ester **120**,[157] which is in equilibrium with enol **121**. The latter undergoes fast cycloaromatisation to give reactive diradical **122**, which is converted into dihydroanthracene **123** in the presence of hydrogen donors. These reactions served as the basis for the development of a new concept of activation of enediyne antibiotics based on photochemical transformations of functional groups adjacent to the enediyne chromophore.



119



120 **121**



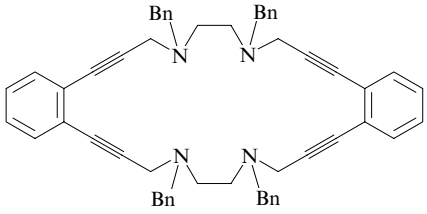
122 **123**

* * *

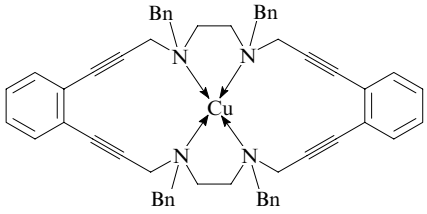
It is impossible to cover all types of cycloaromatisation of heteroatomic enediynes in a brief review. Note only that along with nitrogen-containing enediyne compounds, compounds with other heteroatoms adjacent to the enediyne system, in particular a sulfur atom, are also under study.[158–160]

6. Metal complex enediynes

The thermal cycloaromatisation of enediynes is affected by complexation. For instance, the formation of a complex of enediyne **124** with copper decreases the distance between the acetylenic carbon atoms; as a result, the cycloaromatisation temperature for complex **125** is 70° lower than that for the starting ligand **124**.[161]



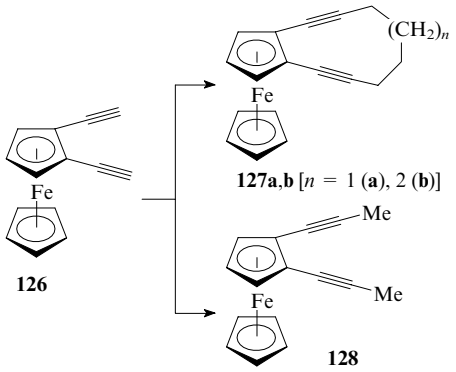
124



125

Synthesis of a number of enediyne macrocyclic ligands and their complexes with copper and zinc salts and DSC estimation of their relative reactivities towards cycloaromatisation have been reported.[162]

Deprotonation of diethynylferrocene (**126**) with butyllithium and treatment of the resulting dianion with diiodobutane (or diiodopentane) results in enediyne complexes **127a**,**b**.[163]



126 **127a**,**b** [n = 1 (**a**), 2 (**b**)] **128**

Methyl derivative **128** was prepared in a similar way. One can observe a correlation between the ring strain in compounds **127a**,**b** (based on *ab initio* calculations) and their susceptibility to electrochemical oxidation:

128 (+0164V) < **127b** (+0.152V) < **127a** (+0.123V).

A similar trend can be followed in the variation of their ionisation potentials in both the liquid and gas phases.[163]

IV. Synthesis of enediyne antibiotics and their analogues

Total syntheses of enediyne antibiotics and their analogues cannot be described within the limits of this paper; therefore, we only briefly consider the general approaches.

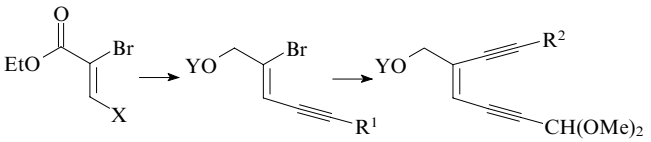
The Sonogashira cross-coupling of vinyl or aryl dihalides with terminal acetylenes catalysed by Pd(0) or Cu(I) complexes is used most often to prepare enediynes.[164] Good results are obtained in the Pd(0)-catalysed reaction of (*Z*)-1,2-bis(trimethylstannyl)-ethenes with iodoalkynes (the Stille cross-coupling).[165,166] A large number of methods of *cis*-enediyne synthesis are based on the introduction of a double bond into 1,5-diyne systems. These are based on reductive elimination [167] and acid-catalysed [168] and base-catalysed [169] elimination of alcohols or diols,[170] the Diels–Alder reaction [171] and rearrangements of allylic alcohols.[116–118,172] Numerous studies along this line are devoted to the synthesis of the neocarzinostatin chromophore [2,51,173–176] and its analogues.[177,178]

Typical strategies for the construction of enediyne system are described in brief below.

1. Construction of the bicyclic dienediyne system

The functionalised bicyclic system of enediyne antibiotics can be constructed by aldol condensation.[179,180] In the synthesis of NCS chromophore- and kedarcidin-related systems, dihydroxylated cyclopentenone often serves as the starting structural block.[181–184] Early approaches to the synthesis of the bicyclic nucleus of NCS have been described by Myers *et al.*[185,186] A recent paper by Hirama and co-workers [187] presents an advanced approach to the construction of the molecule of this chromophore based on the convergent synthetic scheme. In some syntheses, cobalt carbonyls have been used to protect triple bonds.[42,188–190]

A typical synthesis of a bicyclic enediyne system includes: (i) construction of the enediyne fragment from simple starting compounds; (ii) its conjugate addition to the enone to form a cyclopentene fragment; (iii) closure of the second ring by aldol reaction.[180] Bromoiodoethylene **129** obtained from ethyl propiolate is coupled with trimethylsilylacetylene, and the resulting enyne ester **130** is reduced to alcohol **131**. The protection of the hydroxy group by *tert*-butylchlorodipropylsilane (compound **132**) and deprotection of the acetylene function yield terminal alkyne **133**. Compound **133** is converted into acetal **134**. This is followed by cross-coupling with trimethylsilylacetylene in the presence of Pd(II) to give compound **135** and by removal of the TMS-protection, which results in enediyne **136**.[180]

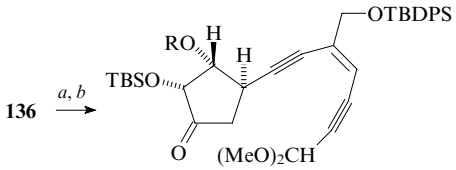


129: X = I;
130: X = $C\equiv CSiMe_3$

131: Y = H, R^1 = $SiMe_3$;
132: Y = $SiPr^n_2Bu^t$, R^1 = $SiMe_3$;
133: Y = $SiPr^n_2Bu^t$, R^1 = H;
134: Y = $SiPr^n_2Bu^t$, R^1 = $CH(OMe)_2$

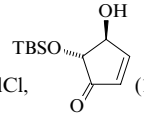
135: Y = $SiPr^n_2Bu^t$, R^2 = $SiMe_3$;
136: Y = $SiPr^n_2Bu^t$, R^2 = H

Conjugate addition of enediyne **136** to enone **137** is carried out *via* the alkynylaluminium derivative.[180] The yield of product **138** is 51%.

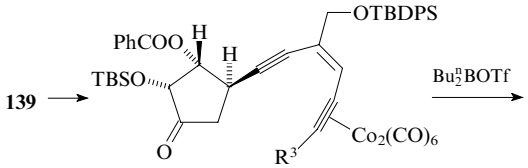


138 (R = H);
139 (R = COPh)

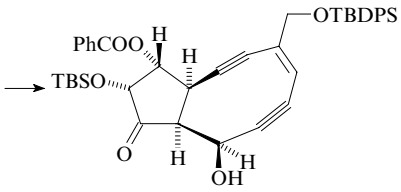
TBDPS = $SiPr^n_2Bu^t$;
(*a*) BuLi, THF, from 0 to −78 °C, 30 min; (*b*) Et_2AlCl, (**137**).



The elaboration of adduct **138** requires benzoate protection (conversion into compound **139**) and protection of one triple bond with cobalt carbonyl to give complex **140** (84%).[191] Acetal **140** is transformed into aldehyde **141**; its cyclisation (on treatment with di-n-butylboryl triflate and triethylamine) yields enediyne **142** (yield 75%). This route ensures high stereoselectivity of enediyne synthesis.



140 [R^3 = $CH(OMe)_2$];
141 (R^3 = CHO)



142

Most of chromophores of the enediyne antibiotics contain a ten-membered ring.[2,4] Some studies dealing with the construction of the bicyclic core of enediyne antibiotics are directed at preparation of larger rings (as they are formed more easily) followed by their contraction. A classical example of this approach has been demonstrated by Mayer and Sondheimer,[192] who were the first to use electrocyclisation to form diradicals.

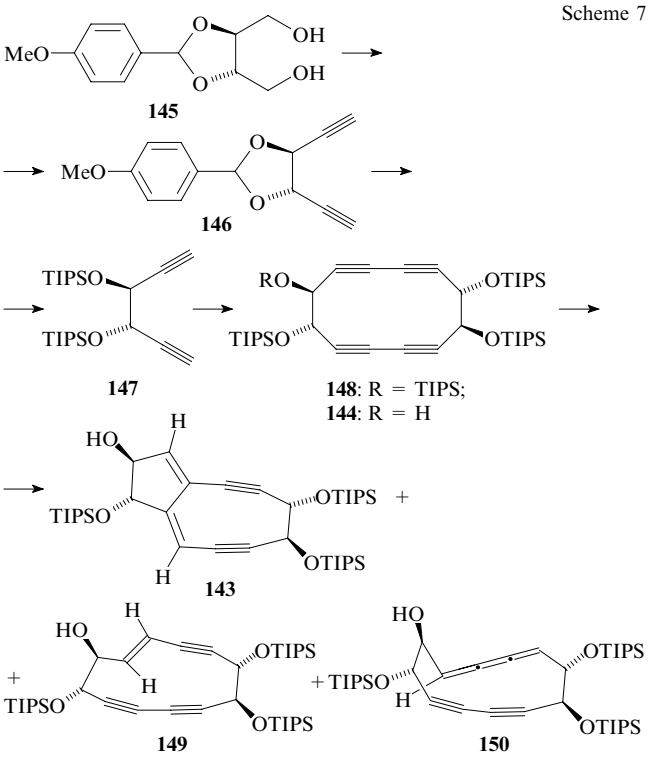
The synthesis of the bicyclic core of enediyne **143** by reductive cyclisation of the 12-membered tetrayne precursor **144** has been described [193] (Scheme 7).

Diol **145** synthesised from L-tartrate is converted into bis(dibromoalkene) by oxidation followed by methylenation. Treatment of this product with n-butyllithium (4 equiv.) affords diyne **146**. Deacetalation followed by *O*-triisopropylsilylation (**146** → **147**) and oxidative dimerisation in the presence of copper derivatives converts this diyne into symmetrical cyclic tetrayne **148**.[193]

The key step of the synthesis is the reductive cyclisation of non-symmetric tetrayne **144** on treatment with $NaAlH(OCH_2CH_2NMe_2)_3$ and KHMDS, which yields bicyclic compound **143** and two isomeric products: *trans*-alkene **149** and cumulene **150**.[193]

The interest in the neocarzinostatin chromophore stimulated the search for its stable analogues and development of numerous new synthetic procedures. In a number of papers, the McMurry reaction [coupling of carbonyl compounds under the action of

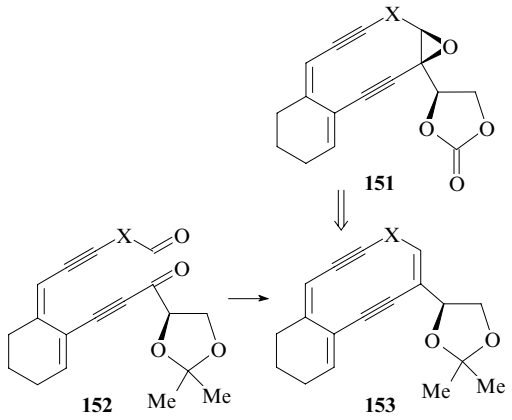
Scheme 7



TIPS = $SiPr^i_3$.

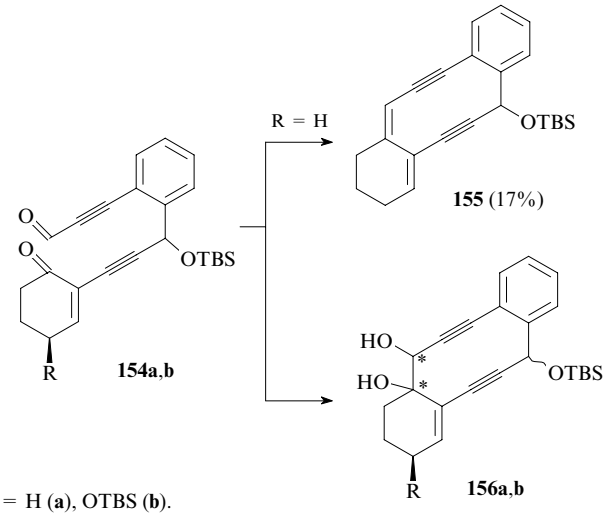
titanium(0) complexes] was shown to be promising for dienediyne ring closure.[194–200]

On the way to NCS models containing an epoxy group and a carbonate ring (compound **151**), researchers[195–198] prepared dienediynic oxo aldehydes **152** and successfully carried out the McMurry ring closure to obtain trienediyne products **153**.



X = CH_2CH_2, CMe_2.

An alternative retro synthesis of this type of bicyclic systems implies scission of the diyne ring at its second double bond. This approach was implemented using cyclisation induced by titanium complexes.[199] In this case, oxo aldehydes **154a**,**b** were involved in the reaction. Olefination was possible only for unsibstituted compound **154a**.

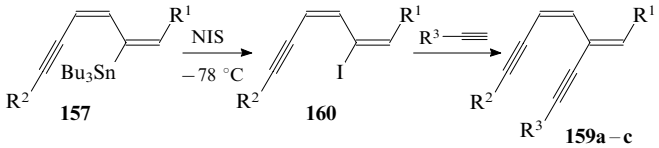


R = H (**a**), OTBS (**b**).

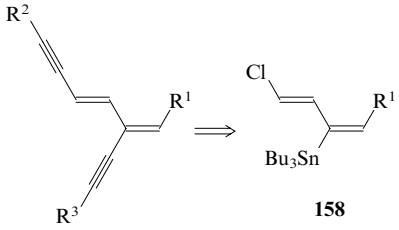
In the case of bis-silylated oxo aldehyde **154b**, pinacone coupling (carried out with the same titanium reagent but at −20 °C) proved to be efficient. Note that both pinacone couplings, **154a** → **156a** and **154b** → **156b**, are diastereoselective. The yields of diols **156a**,**b** (60% and 40%) are much higher than that of alkene **155**.[199]

Analogues of natural antibiotics having a dienediyne fragment[200–202] are also synthesised from α-bromocyclopentenone,[203–205] bis(enol triflates)[206–208] and xylitol.[209]

A stereocontrolled and flexible strategy for the synthesis of acyclic (*Z*,*E*)- and (*E*,*E*)-dienediynes from readily available organotin compounds **157** and **158** has been proposed.[210]



159a: R^1 = R^2 = Ph, R^3 = CH(OH)Me;
159b: R^1 = Ph, R^2 = $SiMe_3$, R^3 = CH(OH)Me;
159c: R^1 = Ph, R^2 = $SiMe_3$, R^3 = $(CH_2)_2OH$.



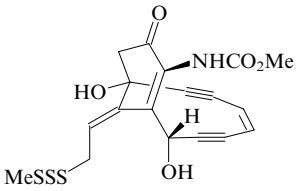
For example, the synthesis of (*Z*,*E*)-dienediynes **159a**–**c** starts from dienynes **157**.[210] The use of *N*-iodosuccinimide allows stereoselective preparation of derivatives **160**, which yield dienediynes **159a**–**c** upon cross-coupling with terminal alkynes in the presence of a Pd/Cu-catalyst. The workup and concentration of the reaction mixtures on deactivated silica gel yields pure (*Z*,*E*)-dienediynes **159a**–**c** (yields 49%–51%).[210]

2. Calicheamicin and related molecules

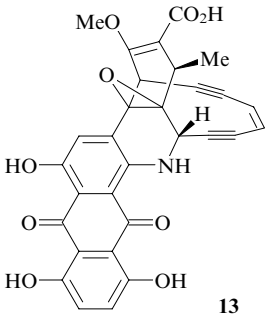
Following the first publications dealing with the structure of calicheamicin, publications concerning the construction of its enediyne core appeared.[21,23,30,211–216] The total synthesis of calicheamicin-aglycone (calicheamicinone) and its analogues was carried out by Danishefsky and co-workers.[217] They also compared the behaviour of calicheamicin γ^I_1 and calicheamicinone in DNA cleavage and demonstrated the importance of the presence

of carbohydrate fragments in the natural product.[23] The total synthesis of calicheamicin γ_1^1 carried out by Nicolaou and coworkers[218] includes 28 stages (1.4% overall yield).

A number of synthetic routes to calicheamicinone (**161**) (see Refs 211–216 and 219) and dynemicin (**13**) having a similar bicyclic core have been reported.[214–216]



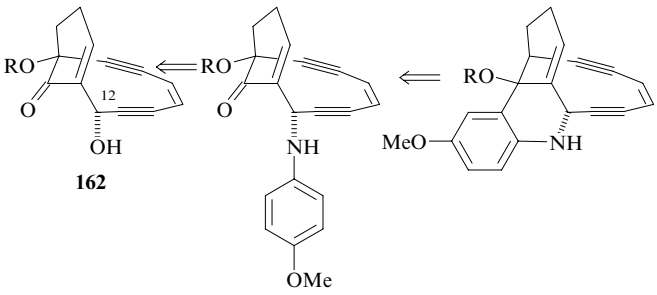
161



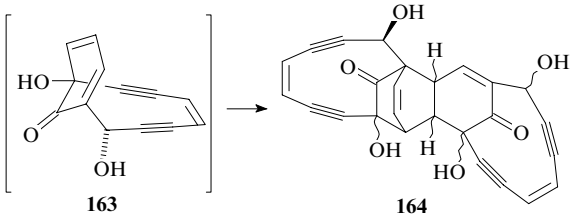
13

An attempt[213] to carry out interconversion of calicheamicinone and dynemicin analogues prompted by the obvious structural similarity of these two molecules deserves mention. A possible way of this transformation is the replacement of the 12-hydroxy group in compound **162** by an aniline fragment with retention of the configuration followed by intramolecular arylation.

However, the intermediate bicyclic ketones **163** formed underwent dimerisation through [2 + 4]-cycloaddition. Deprotection of the oxo group gave dimers **164** with different stereochemistry of ring fusion.[213]



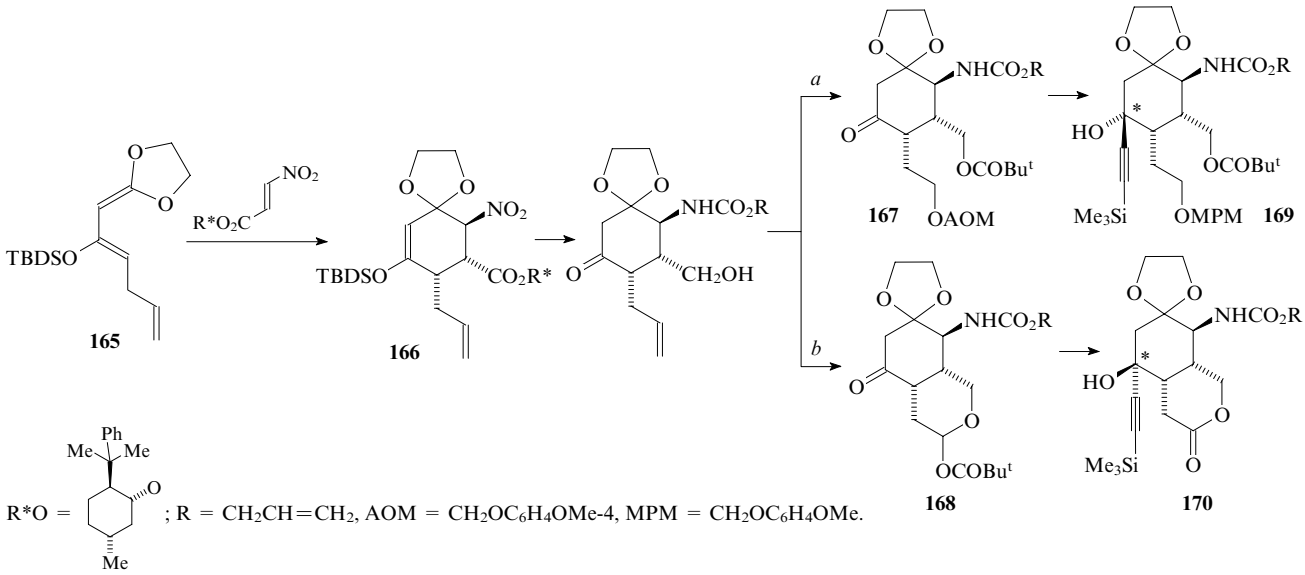
162



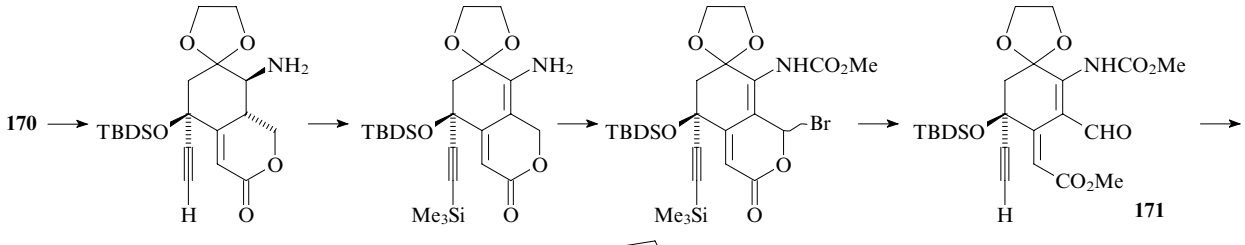
163 **164**

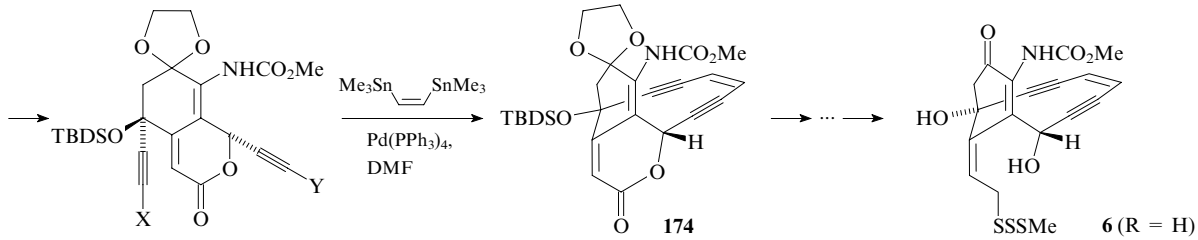
Detailed synthesis of optically pure calicheamicinone has been reported.[220–222] The synthesis starts with stereoselective Diels–Alder reaction of ketene acetal **165** with chiral R*-3-nitropropе-

Scheme 8



R*O = ; R = $CH_2CH{=}CH_2$, AOM = $CH_2OC_6H_4OMe$-4, MPM = $CH_2OC_6H_4OMe$.





172 (X = H, Y = $SiMe_3$);
173 (X = Y = I)

174

6 (R = H)

noate containing a (−)-8-phenylmenthol residue (Scheme 8).[222] Thus, the desired stereochemistry of the skeleton is founded in the initial stage. Then adduct **166** is converted, along two pathways, into ketones **167** (pathway *a*) and **168** (pathway *b*). These ketones add lithium trimethylsilylacetylide to give *syn*- and *anti*-addition products, *viz*., alcohols **169** and **170**, respectively.

During the transformation of alcohols **169** and **170** into (−)-calicheamicinone, the stereogenic centres, except for C*, are racemised, both diastereomers giving the same final product.[222]

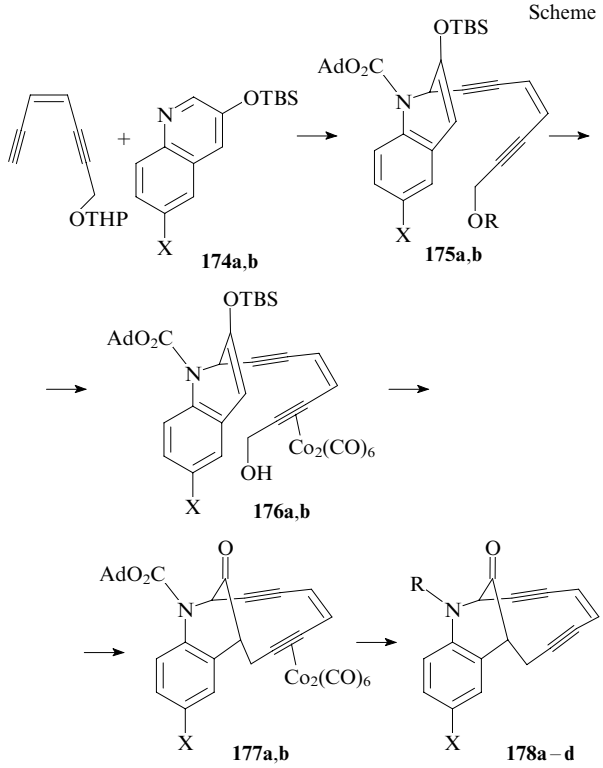
The subsequent series of oxidation stages (for introduction of double bonds), protecting group manipulations, halogenation and hydrolysis give aldehydo ester **171**, which stereoselectively adds lithium trimethylsilylacetylide to give diyne **172**. Calicheamicinone ring closure was accomplished by the reaction of diiodide **173** with *cis*-bis(trimethylstannyl)ethene to give precursor **174**. Nine more stages it took to introduce the trisulfide substituent and attain (after removal of the protecting group) the required functionalisation.[223, 224]

3. Dynemicin and its analogues

Structural features, the activation mechanism and total synthesis of the dynemicin chromophore are considered in the papers by Nicolaou and Smith,[2] Danishefsky *et al*.,[217] Myers *et al*.[225, 226] and other researchers.[35, 227, 228]

The synthesis of the enediyne fragment of dynemicin is shown in Scheme 9.[42] *O*-Tetrahydropyranyl ether of hept-4-ene-2,6-diyn-1-ol reacted with protected 3-hydroxyquinolines **174a**,**b** to give adducts **175a**,**b**. The removal of the tetrahydropyranyl protection and the reaction with $Co_2(CO)_8$ yield complexes **176a**,**b**, which cyclise to give bicyclic structures **177a**,**b**. Decomplexation of the latter affords products **178**. The structure of enediyne **178b** was proved by X-ray diffraction.[229]

Scheme 9

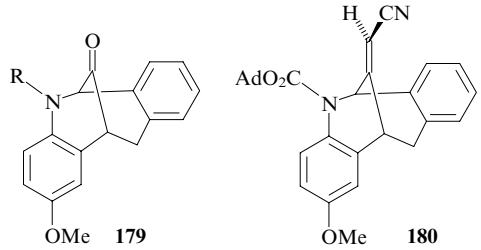


178a: X = H, R = AdO_2C;
178b: X = OMe, R = AdO_2C;
178c: X = H, R = H;
178d: X = OMe, R = H.

X = H (**a**), OH (**b**);

Ad = .

The aromatisation rates of the synthesised enediynes were considerably different, although the distances between the acetylenic bonds in them are approximately the same. The determination of the cycloaromatisation rate of enediyne **178b** to give compound **179** in the temperature range from 65 to 114 °C allowed calculation of thermodynamic parameters of the reaction.[42] The experimental data extrapolated to 37 °C show that **178b** is stable under physiological conditions.

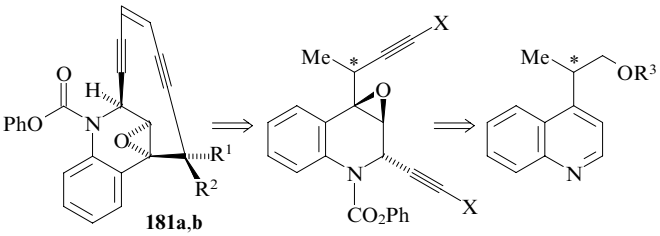


Amine **178d** undergoes cycloaromatisation in THF on heating to 51–67 °C. The cycloaromatisation rate of amine **178d** increases with temperature faster than that of carbamate **178b**. At 37 °C, amine **178d** cyclises 1.6 times faster than carbamate **178b**, while at 65 °C these rates differ by a factor of 20. The cycloaromatisation of nitrile obtained from ketone **178b** results in compound **180**. At 37 °C, this reaction proceeds 500 times faster than cycloaromatisation of ketone **178b**, although the distances between the acetylenic bonds in these compounds are almost the same.[42]

The synthesis of the naphtho[2,3-*h*]quinoline part of the dynemicin molecule has been reported.[42, 230, 231]

The subsequent development of the dynemicin chemistry[232–236] confirmed that its specific antitumour properties are related to the presence of the 10-membered enediyne ring.[237–242] Therefore, investigation into the synthesis of second-generation dynemicin analogues becomes topical.

The total synthesis of two diastereomeric dynemicin analogues (**181a**,**b**) was carried out and their activities with respect to DNA cleavage was studied.[243–246] The retro-synthetic analysis is presented below.

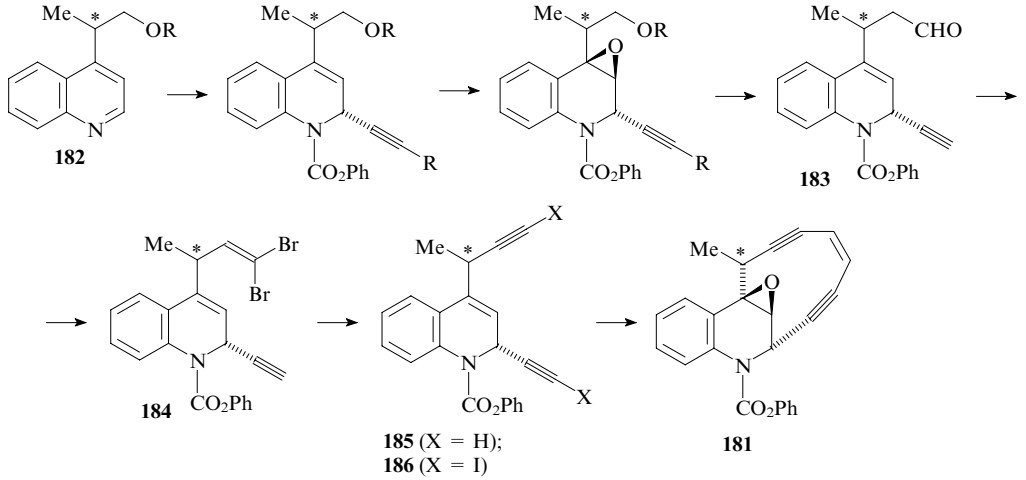


R^1 = H, R^2 = Me (**a**); R^1 = Me, R^2 = H (**b**).

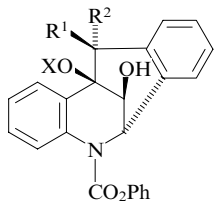
Chiral quinoline derivatives prepared[247, 248] in an optically pure state by enantiomer resolution or by a microbiological procedure were used as the starting compounds. The stereoselective addition of protected acetylide to quinolines **182** and the subsequent modification of the alcohol function leads to aldehydes **183** (Scheme 10). To introduce the second triple bond, aldehydes **183** were converted into dibromoalkenes **184** and then into alkynes **185**.[243] The macrocycle was closed by treatment with *cis*-bis(trimethylstannyl)ethene. For cross-coupling, diyne **185** was converted into diiodide **186**.

Epoxide ring opening (on treatment with *p*-toluenesulfonic acid) in the target enediynes **181a**,**b** was accompanied by their fast Bergman cyclisation.[249, 250] After neutralisation of the acid with triethylamine and stirring for 24 h in the presence of CHD (as a

Scheme 10



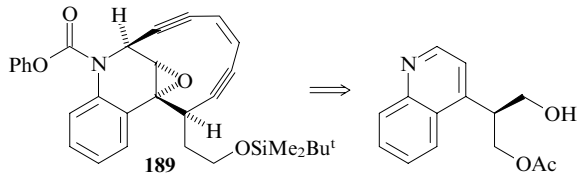
hydrogen atom donor), diol **187** and mono-*p*-toluenesulfonate **188** were isolated.



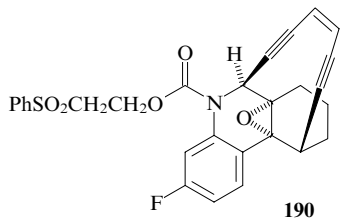
187 (R^1 = Me, R^2 = X = H);
188 (R^1 = H, R^2 = Me, X = Ts)

Biological tests revealed high activity of enediynes **181a**,**b** with respect to the plasmid DNA.[251]

The stereoselective synthesis of the simplest dynemicin analogue **189**, which is active against plasmid DNA, has been described.[252]



The susceptibility to cycloaromatisation and the biological activity of tricyclic enediyne **190** have been studied.[253]



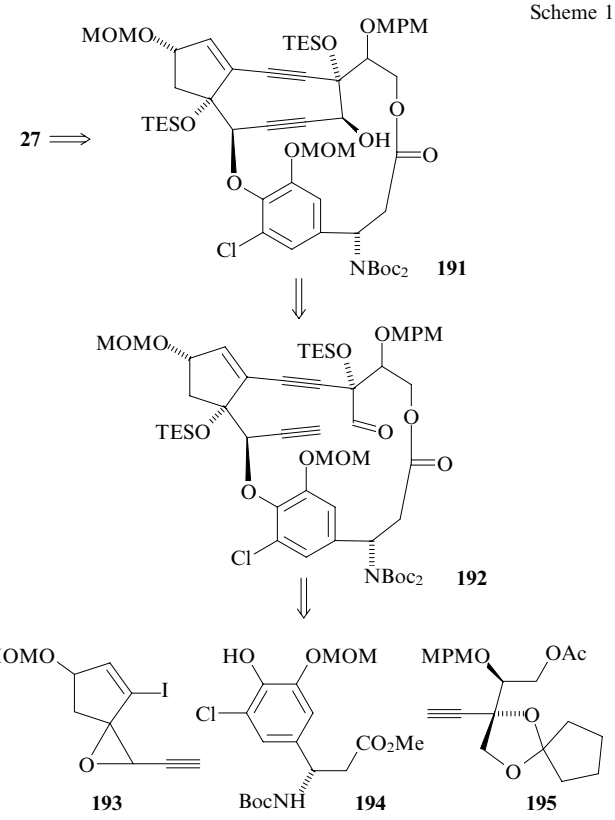
4. Antibiotic C-1027

The high biological activity of the enediyne antibiotic C-1027 stimulated the studies aimed at the construction of its nine-membered ring [254, 255] and its total synthesis.[60, 256–265]

The retro-synthetic analysis [60] of the chromophore macrolide **27** is shown in Scheme 11.

The total synthesis of molecule **27** is completed by introducing of an amino sugar and benzoxazine into the core **191** with simultaneous formation of two double bonds. Since diyne **191** is unstable (this is confirmed by experiments on model compounds),

Scheme 11



MOM = $MeOCH_2$, TES = Et_3Si.

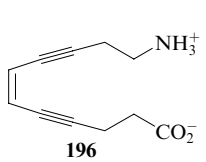
it is necessary to construct the macrolactone system prior to construction of the nine-membered ring. Diyne **191** is formed upon cyclisation of aldehyde **192** under the action of the $LiN(SiMe_3)_2-CeCl_3$ system. In turn, aldehyde **192** is prepared by the convergent coupling of three fragments, **193**, **194** and **195**.[60]

V. Introduction of the enediyne fragment into other classes of organic compounds

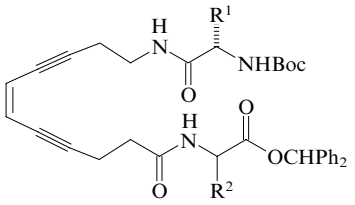
Studies of enediynes have long been concentrated on their synthesis and reactivity. However, when it became clear that the biological activity of this class of compounds is correlated with the presence of (*Z*)-1,5-diyn-3-ene fragment,[266–271] attempts were undertaken to introduce this structural unit into other classes of biologically active and natural compounds. A number of typical examples are given below.

1. Enediyne tripeptides

The synthesis of amino acid **196** and peptides **197a–c**, promising compounds *en route* to new enediyne antibiotics, has been reported.[272]



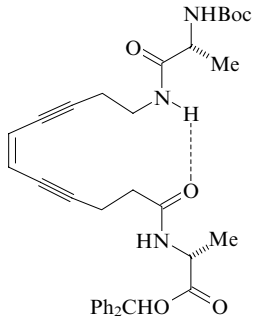
196



197a–c

$R^1 = R^2 = Me$ (**a**), Bn (**b**); $R^1 = Me$, $R^2 = CH_2OH$ (**c**).

Cycloaromatisation of protected enediyne peptides **197a–c** yields polymers. A DSC study has shown [272] that the reaction has an isothermal peak typical of the Bergman cyclisation. Peptide **197b** cyclises more easily (135 °C) than peptide **197a** (180 °C), which is related to the presence of the hydrogen bond in the latter.

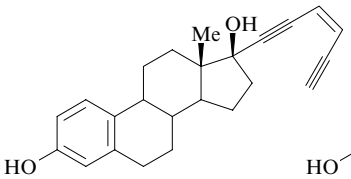


197a

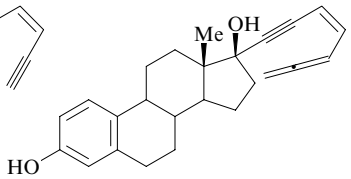
Analysis of changes in the NMR spectra of peptide **197a** depending on temperature suggests stabilisation of its conformations owing to hydrogen bonds (a similar situation is observed for free amino acid **196**).[273]

2. Enediyne estrogens

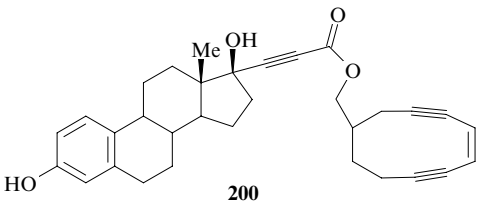
By introduction of substituents containing an enediyne system into the estradiol molecule, a family of steroid hormones **198–201** has been obtained.[274, 275]



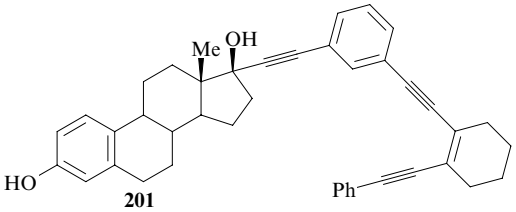
198



199



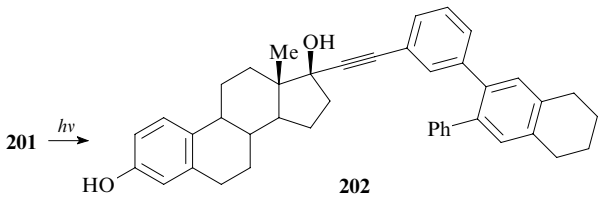
200



201

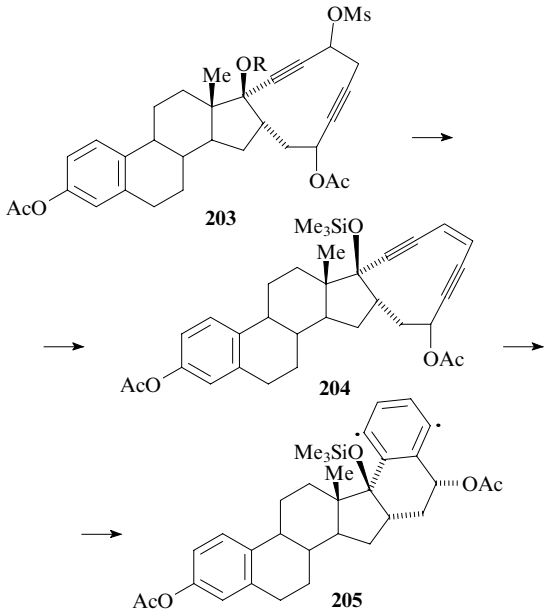
Enediynyl- and enyneallenylestrogens **198** and **199** were actually found to produce diradicals in the Bergman or Myers cycloaromatisation processes.[276–281] The diradicals abstract hydrogen from DNA and proteins, which results in their degradation and agglomeration.

Compound **201** undergoes the Bergman photocycloaromatisation to give product **202**.[274, 282–284] A series of estrogen–enediyne conjugates have been prepared and their affinity with respect to the hERα receptor has been determined.



202

Estradiol derivatives of the type **203** § eliminate methanesulfonic acid to be converted into enediyne steroids **204**, which cyclise to give benzenoid diradical **205** at 25 °C (half-conversion time is 108 min).[287]



203

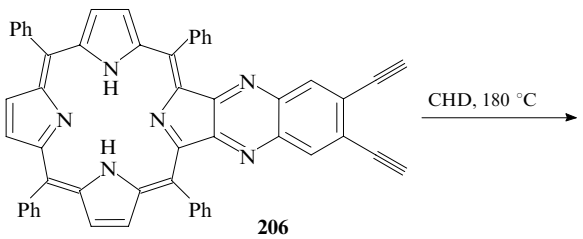
204

205

R = H, $SiMe_3$; Ms = $MeSO_2$.

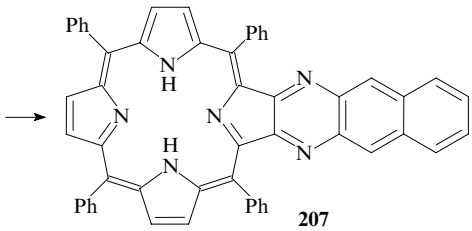
3. Porphyrin enediynes

The synthesis of porphyrin **206** containing an enediyne fragment has been reported.[288] Heating (180 °C) of derivative **206** in the presence of CHD results in cycloaromatisation to give porphyrin **207**.



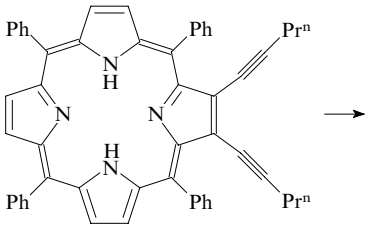
206

§ The synthesis of derivatives **203** has been described.[285–287]

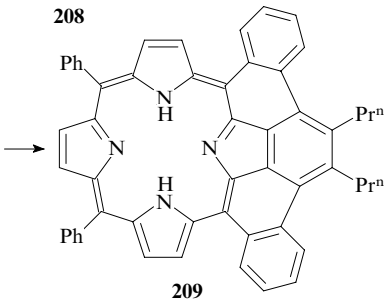


207

Porphyrin enediyne **208** with disubstituted triple bonds cyclises in a peculiar way, namely, with participation of neighboring phenyl groups to give a polyaromatic fragment in the porphyrin system **209**.[289]



208



209

Photoreactive porphyrin enediynes, which undergo cycloaromatisation on exposure to radiation, have been described.[290, 291]

VI. Conclusion

During the last decade, a substantial progress in the enediyne chemistry has been achieved and information flow concerning these peculiar acetylenic derivatives has grown. The structures of the natural and synthetic compounds described above, which actively destroy cancer cells and suppress bacteria and microbes, are characterised by great diversity, but the presence of the (*Z*)-3-ene-1,5-diyne fragment is a common feature of all these derivatives. Its key chemical property and the cause for the unique biological action is the ability to undergo cycloaromatisation involving two acetylenic bonds, resulting in 1,4-benzenoid diradicals. Currently, this reaction is the subject of active theoretical and experimental research not merely due to the fact that this contributes to the understanding of the chemistry of enediyne antibiotics, but also because this is a new, exceptionally powerful synthetic method of organic chemistry as a whole[121] and, in particular, acetylene chemistry.

The search for new types of enediyne structures active with respect to DNA cleavage remains topical; nitrogen-containing enediynes (dialkynyldiazenes) appear to be especially promising.[136]

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