Nitrogen substituted cyclic enediynes: synthesis, thermal reactivity and complexation with metal ions

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Received (in Cambridge, UK) 3rd February 2000, Accepted 5th April 2000
Published on the Web 31st May 2000

A number of *N*-substituted cyclic enediynes (azaenediynes) have been synthesized *via* Pd(0)-catalysed ene–yne coupling followed by *N*-alkylation. The simplest of them, a 10-membered monocyclic enediyne **1**, underwent Bergman cyclization (BC) at 23 °C with a half-life of 72 h. The kinetics of BC slowed down considerably by fusing a benzene ring onto the enediyne. Several novel bis(azaenediyne)s and bis(diazaenediyne)s **3**–**6** have been synthesized. Their onset temperatures for BC were lowered under metal ion complexation conditions.

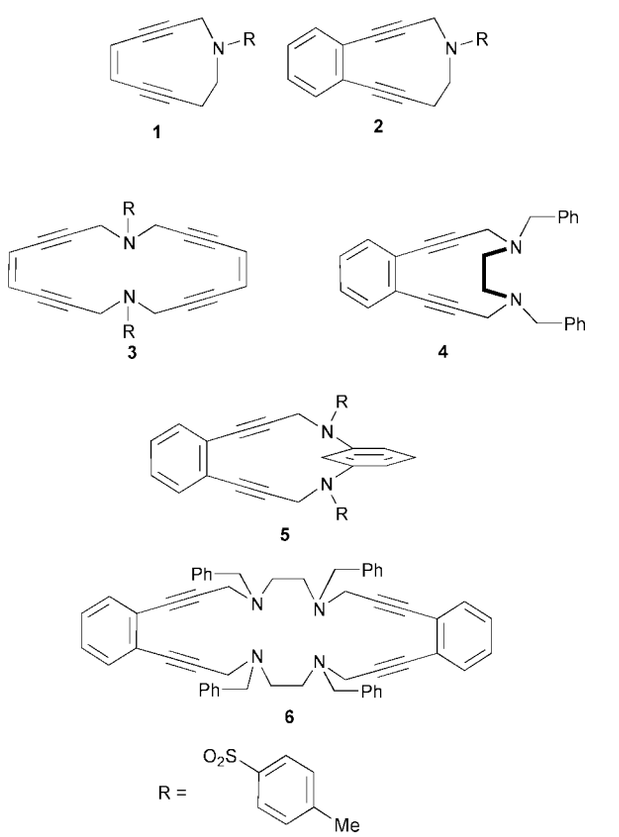
Introduction

The enediyne class of natural products,[1] discovered more than a decade ago, continues to draw the attention of chemists working in various fields. One important aspect of the chemistry of the enediynes is the design and synthesis of simple model systems.[2] Several of these possess antitumour activity by virtue of their DNA-cleaving ability and have shown promise as anticancer agents.[3] Over the past few years we have been trying to understand the behaviour of cyclic enediynes with one or more nitrogen atoms constituting a part of the ring. The rationale behind such an interest involves the following: 1) the shorter C–N bond length may help in speeding up the kinetics of BC[4] compared to the C or S analogs,[5,6] 2) the ease of attachment of DNA binding agents[7] onto the nitrogen atom, 3) the possible decrease of torsional strain[8] compared to the all carbon analogs, thus reducing the activation barrier for BC and 4) probable perturbation of the kinetics of BC upon complexation to metal ions[9] *via* chelation through N. At the very outset it is pertinent to mention that although the synthesis and reactivity of the bicyclic azaenediyne core related to dynemicin were previously described prior to this work,[10] the synthesis of simple monocyclic azaenediynes and the influence of the nitrogen atom on the reactivity towards cycloaromatization had not been investigated. In fact, we are one of the first groups to report the synthesis of such analogs.[11,12] In the present article, we wish to report in detail the synthesis of these molecules, their comparative thermal reactivities under neat and metal complexation conditions.

In our design, two types of enediynes were considered: (a) systems with a single N-atom (monoaza) and (b) systems with multiple N-atoms. In the latter category we have concentrated on molecules with either two (diaza) or four (tetraaza) N-atoms. In order to get an idea about the distances between the reacting acetylenic atoms (c,d distance), molecular mechanics calculations were carried out on all these systems using the MM2 force field (Table 1). The energy minimised conformations of the pertinent species are shown in Fig. 1. The c,d-distance for the monocyclic enediyne **1** came out to be 3.22 Å which is within the critical range of 3.31–3.20 Å proposed by Nicolaou *et al.*[13] for spontaneous cyclization at ambient temperature. The aromatic fused analog **2**, like the carbocyclic counterparts,[14] is expected to exhibit better stability. However, a c,d-distance of 3.24 Å based on MM2 calculations would predict similar behaviour to **1**. For the other enediynes **3**–**6**, the c,d-distance expectedly came out much higher (>3.6 Å) because of the presence of larger rings (18, 12, 13 and 24

Table 1 MM2 results for enediynes **1**–**6**

Molecule	'Calculated' c,d-distance/Å
1	3.22
2	3.24
3	4.08
4	3.68
5	3.86
6	4.0, 4.17



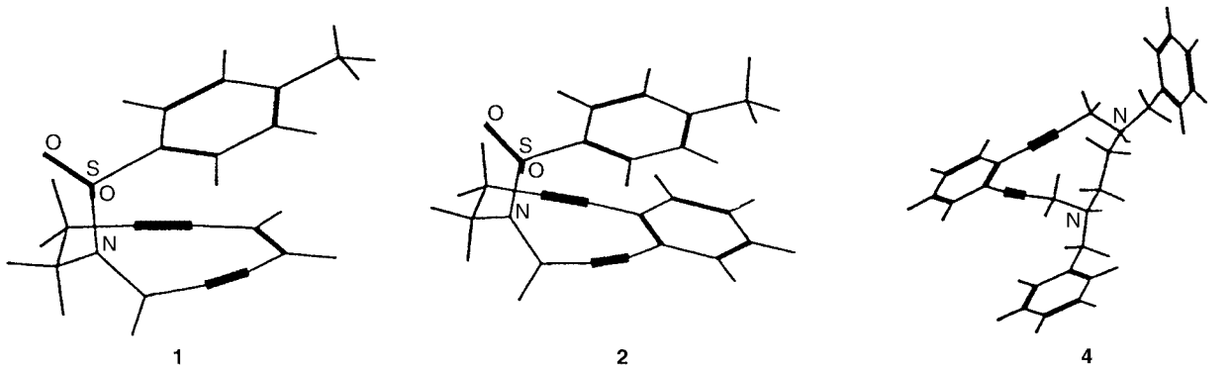
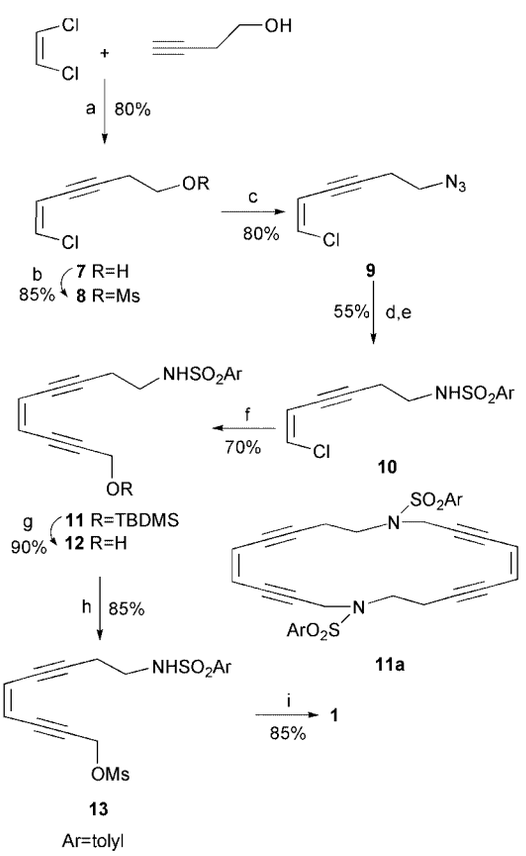


Fig. 1 Energy minimized conformations of azaenediynes.

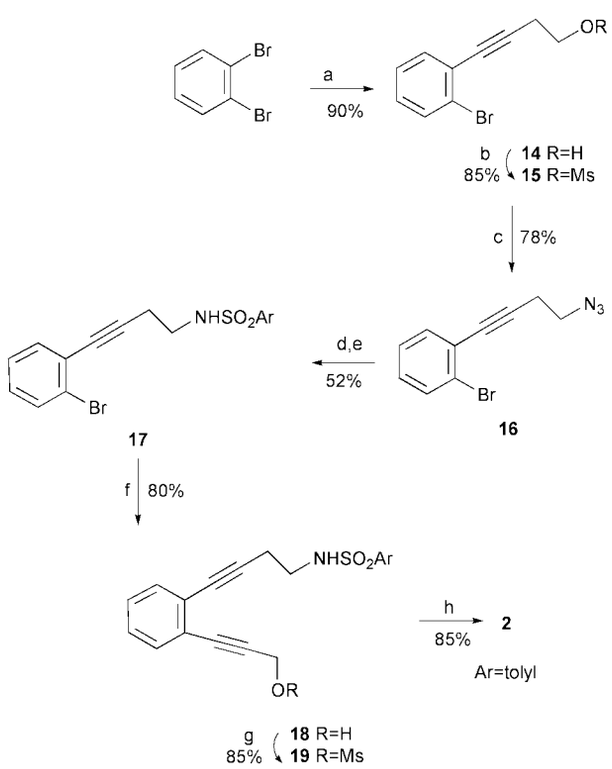
respectively) and these should undergo BC at a much higher temperature. Complexation to metal ions, however, would lead to a change of ring size and should alter the kinetics of BC.

Synthesis of the azaenediynes 1–6

Zerovalent Pd-catalysed Sonogashira coupling[15] is the key reaction used to synthesize the target enediynes **1**–**6**. For the construction of the simple 10-membered azaenediyne **1**, (*z*)-1,2-dichloroethylene was first monocoupled with homopropargyl† alcohol (Scheme 1). The resulting 6-chlorohex-5-en-3-ynol **7** was converted to the azide **9**, which upon reduction with PPh_3–H_2O produced the amine, isolated as the toluene-*p*-sulfonamide **10**. Another round of Pd(0)-catalysed coupling with propargyl† *tert*-butylsilyl ether gave the acyclic enediyne **11** which was deprotected to the alcohol **12**. Intramolecular *N*-alkylation of the mesylate **13** using K_2CO_3–DMF under high dilution (0.006 M) proceeded smoothly to produce the 10-membered azaenediyne **1**. Carrying out the reaction at a higher concentration (*e.g.* >0.06 M) produced a substantial amount of the dimer **11a**. The benzene-fused enediyne **2** was synthesized in a similar fashion (Scheme 2). However, in this case the Pd(0)-based coupling had to be carried out in the absence of CuI, addition of which led to extensive oxidative dimerization of the acetylene in our hands. An attempt to prepare a 9-membered analog failed; the initial intermolecular *N*-alkylation product **26a** underwent intramolecular cyclization leading to the 18-membered bis(azaenediyne) **3** (Scheme 3). Just and Singh[16a] and Konig *et al.*[16b] had previously reported the formation of a similar molecule starting from the dimesylate **28** or dibromide **29** and a primary amine. The other bis(azaenediyne)s **4** and **5** were prepared in a single step from the dimesylate **28** by double *N*-alkylation with *N*,*N*′-dibenzylethylenediamine and *N*,*N*′-bis(*p*-tolylsulfonyl)-*m*-phenylenediamine respectively (Scheme 4). It must be pointed out here that in both the cases we ended up getting only the 1 : 1 adducts. We did not see the formation of any higher adducts; the dilute conditions employed might be responsible for this observation. The mass spectra of both the adducts are in accord with the proposed structures (appearance

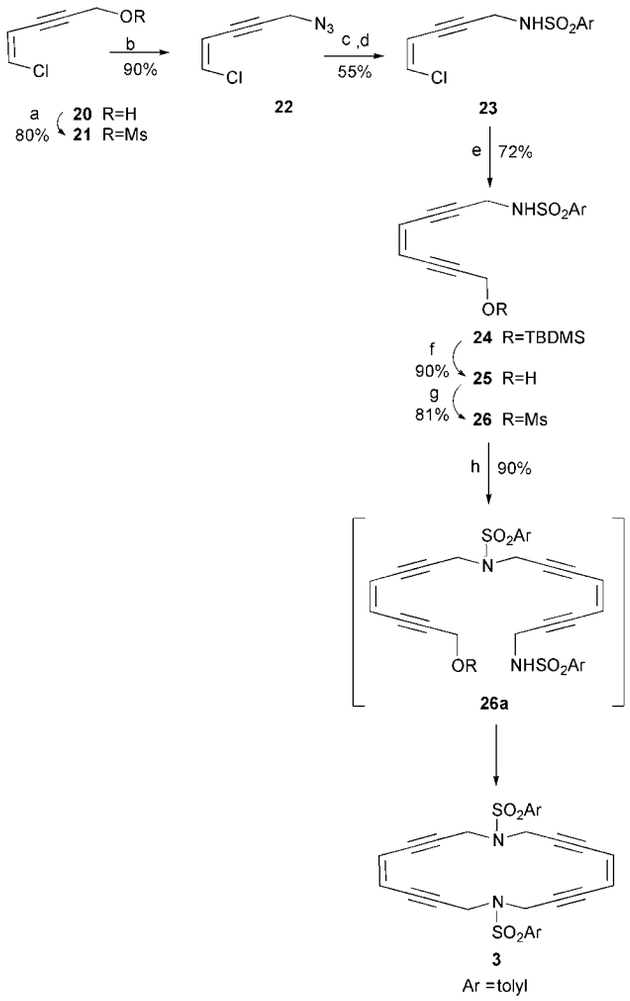


Scheme 1 *Reagents and conditions*: a, $Pd(PPh_3)_4$, *n*-$BuNH_2$, CuI, PhH, rt; b, MsCl, NEt_3; c, NaN_3, DMF; d, PPh_3–H_2O; e, TsCl, DMAP; f, propargyl *tert*-butyldimethylsilyl ether, $Pd(PPh_3)_4$, *n*-$BuNH_2$, CuI, PhH, rt; g, CsF, MeCN; h, MsCl, NEt_3; i, K_2CO_3, DMF.



Scheme 2 *Reagents and conditions*: a, But-3-yn-1-ol, $Pd(PPh_3)_4$, *n*-$BuNH_2$, 80 °C; b, MsCl, NEt_3; c, NaN_3, DMF; d, PPh_3–H_2O; e, TsCl, DMAP; f, propargyl alcohol, $Pd(PPh_3)_4$, *n*-$BuNH_2$, 80 °C; g, MsCl, NEt_3; h, K_2CO_3, DMF.

† IUPAC name for homopropargyl is but-3-ynyl; IUPAC name for propargyl is prop-2-ynyl.



Scheme 3 *Reagents and conditions*: a, MsCl, NEt_3; b, NaN_3, DMF; c, PPh_3–H_2O; d, TsCl, DMAP; e, propargyl *tert*-butyldimethylsilyl ether, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$; f, CsF, MeOH; g, MsCl, NEt_3; h, K_2CO_3, DMF.

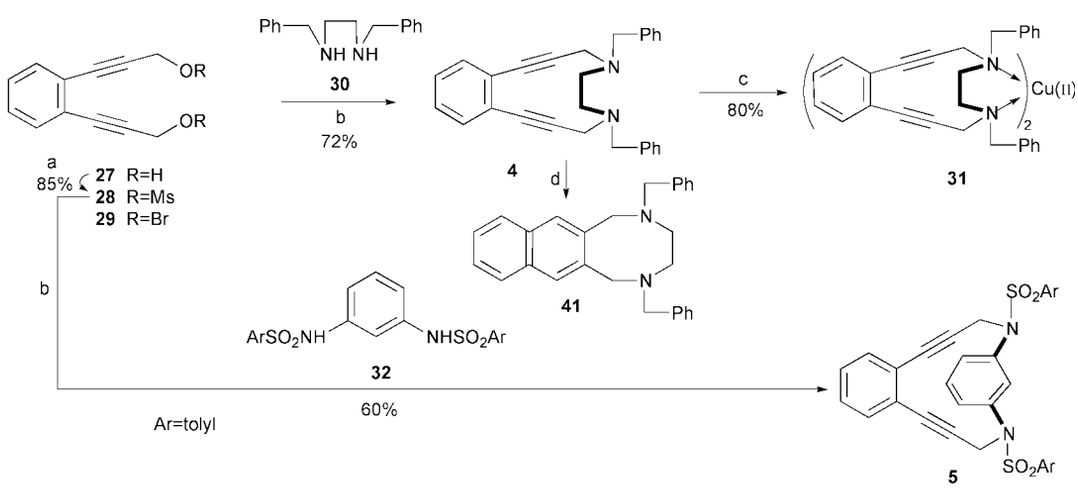
of molecular ion peaks at 390 and 566). No peak corresponding to a higher mass was observed in the mass spectrum. Single crystal X-ray diffraction data on the enediyne **4** confirmed the formation of a 1:1 coupling product.‡ Our initial attempt to prepare the bis(diazaenediyne) **6** from the dibromo dienediyne **35** *via* Pd(0)-catalyzed coupling with propargyl alcohol followed by mesylation and bis-*N*-alkylation with *N*,*N*′-dibenzylethylenediamine failed. Gratifyingly, however, **6** could be prepared in moderate yield in a single step from the diyne **35** by a novel Pd(0)-catalyzed macrocyclization (Scheme 5).

‡ The X-ray structure along with all the parameters are, as yet, unpublished results.

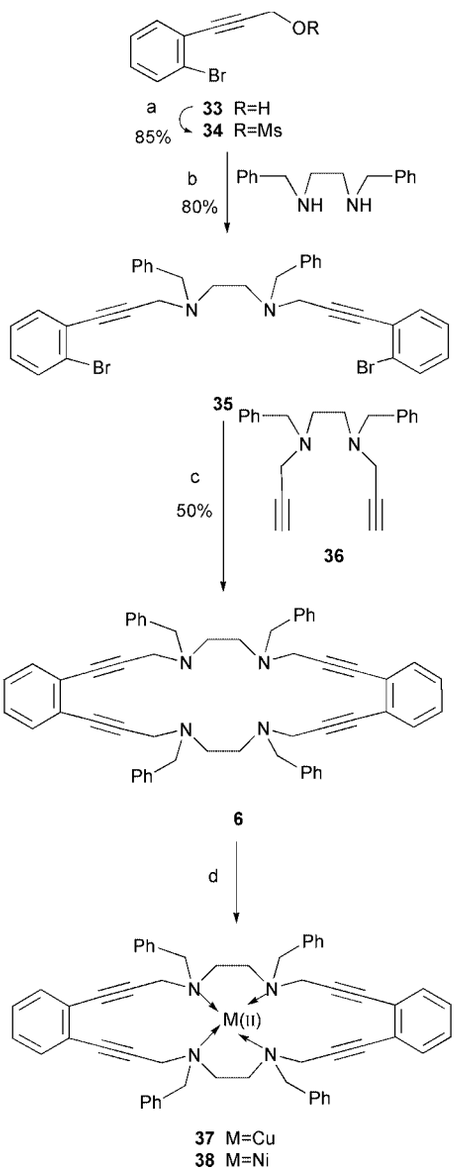
Results and discussion

The enediyne **1** was found to be sufficiently stable at ambient temperature to allow us to record its ^1H, ^{13}C and correlation NMR spectra. The molecule, however, slowly underwent cycloaromatization (BC) in $CDCl_3$ at room temperature resulting in the formation of a tetrahydroisoquinoline system **39a**. The $t_{\frac{1}{2}}$ at 23 °C for such a cyclization was found to be around 72 h ($E_a \sim 18$ kcal mol^{-1}). The Bergman cyclization could be monitored by keeping a solution of the sample in $CDCl_3$ at a constant temperature and checking the ^1H-NMR at different points in time. Interestingly, the characteristic peaks at δ 5.84, 4.09, 3.53 and 2.77 for **1** diminished while new peaks at δ 4.22, 3.33 and 2.91 appeared, corresponding to the tetrahydroisoquinoline system. Differential scanning calorimetric (DSC)[17] measurements on **1** in the neat liquid state showed the onset temperature for BC to be around 50 °C. The benzene-fused enediyne **2**, on the other hand, is stable at room temperature. The cyclized product, a tetrahydrobenzoisoquinoline derivative **40a**, could be isolated by refluxing a chloroform solution of **2** for 3 days followed by chromatography. The $t_{\frac{1}{2}}$ for the cycloaromatization was found to be ~ 52 h at 65 °C. The molecule showed an onset temperature for BC of ~110 °C when checked by DSC. Thus, fusion of an aromatic ring on to the 10-membered azaenediyne caused a significant elevation of the activation barrier to cycloaromatization. A similar slowing down of kinetics has been observed by Semmelhack *et al.*[14a] and by Nicolaou *et al.*[14b] for carbocyclic systems. One would expect that the larger ene bond length (1.39 Å) possibly led to an increase in the distance between the reacting acetylenic carbons in **2** thereby slowing down the kinetics of BC. However, as indicated earlier, MM2 calculations showed the c,d-distance in **2** to be 3.24 Å, well within Nicolaou's proposed critical range for spontaneous cyclization at room temperature thus possibly ruling out the above proposition. A more plausible explanation is based on the lower gain of resonance energy in the naphthalene-like transition state (TS) for the BC of **2**, acting as weaker driving force compared to an isolated benzenoid TS for cyclization of **1**.

The onset temperature for BC in the case of bis(azaenediyne)s **3**, **4** and **5** were, as expected, quite high, 130, 210 and 275 °C respectively. We failed to prepare any well-defined metal complex from **3** probably because of the weak ligation by $NHSO_2Ar$, which has a delocalized N-lone pair. However, when an acetonitrile solution containing equimolar quantities of **3** and AgOAc was evaporated and the resulting brown solid was checked for DSC measurement, the exothermic rise now started



Scheme 4 *Reagents and conditions*: a, MsCl, NEt_3; b, K_2CO_3, DMF; c, $Cu(OAc)_2$ MeOH, reflux; d, chlorobenzene, cyclohexa-1,4-diene, 240 °C.



Scheme 5 *Reagents and conditions*: a, MsCl, NEt_3; b, K_2CO_3, DMF; c, $Pd(PPh_3)_4$, *n*-$BuNH_2$, 80 °C; d, $Cu(OAc)_2$ or $Ni(ClO_4)_2$, MeOH, reflux.

at a temperature of 110 °C, a decrease of about 20 °C from the parent enediyne **3**, probably induced by a weakly complexing Ag^+ which lowers the transannular repulsion between the N-lone pairs. The other bis(azaenediyne) **4** formed a brown solid, possibly containing the complex **31**, when a methanolic solution of **4** and $Cu(OAc)_2$ in a 2 : 1 molar ratio was refluxed for 10 h and

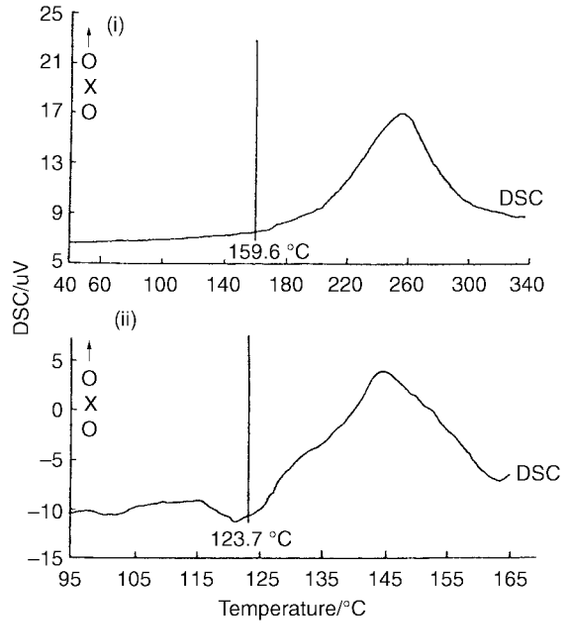
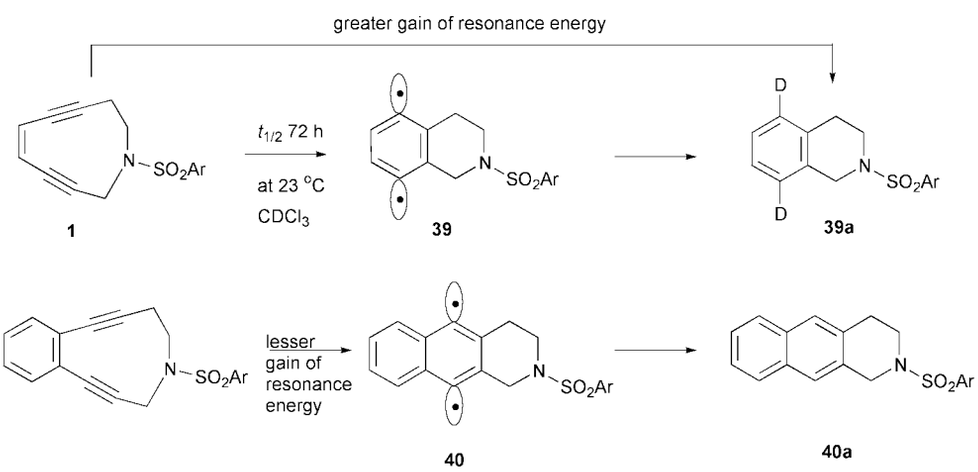


Fig. 2 DSC curve of i) tetraazaenediyne (**6**) and ii) its Ni(II)-complex (**38**).

the solvent was evaporated. Like all the other Cu(II)-complexes, compound **31** also exhibited extremely broad signals in its ^{1}H-NMR spectrum due to the paramagnetism of Cu(II). DSC measurements on the complex showed an onset temperature for BC at 110 °C, indicating a considerable reduction of the activation barrier for BC upon complexation, attributable to the formation of a smaller 11-membered metallocycle in the complex compared to the 12-membered parent enediyne **4**. The cycloaromatization of **4** to the diazacyclooctene **41** could be followed by heating a degassed chlorobenzene solution of **4** in the presence of a large excess of cyclohexa-1,4-diene (1,4-CHD) to 240 °C for 24 h. The presence of an equivalent amount of copper acetate enhanced the rate of disappearance of starting enediyne **4** probably due to complexation.

For the tetraazaenediyne, in addition to the Cu(II)-complex, the Ni(II)-complex was also prepared as a brown solid from Ni(II) perchlorate and methanol. The ^{1}H-NMR spectrum of the Ni(II) complex taken in d_6-DMSO showed three broad singlets corresponding to the three sets of methylenes at δ 3.24 (NCH_2CH_2), 3.94 (NCH_2CC) and 4.09 (CH_2Ph); each methylene undergoing a downfield shift of ~δ 0.4 upon complexation. As expected, DSC measurements on the two complexes showed considerable reduction in the activation barrier for BC, exemplified by a lowering of onset temperature for the cyclization in both the cases (Fig. 2). Presumably, complexation with



Scheme 6

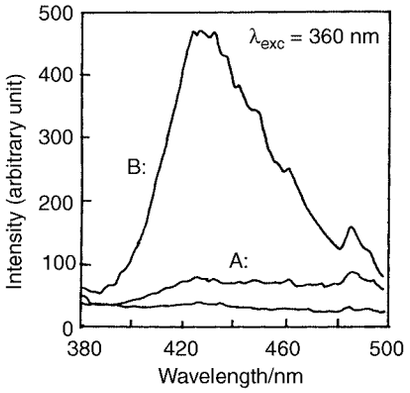


Fig. 3 Emission spectra of (A) cyclic azaenediyne **6**, (B) its Ni(II)-complex and (C) DMSO at excitation wavelength λ 360 nm. Slit widths used are: excitation, 5 mm and emission, 3 mm.

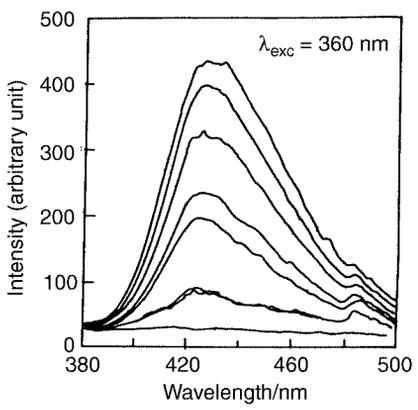


Fig. 4 Emission spectra of the Ni(II)-complex of **6** at λ_{exc} = 360 nm at various concentrations. (A) The topmost spectrum is for 9.0 mM concentration with each successive spectrum representing two-fold dilutions. The lowest spectrum is that of the solvent DMSO.

metal ions brings the reacting acetylenic carbon atoms closer, thus making the BC more favourable. Heating a solution of **6** in chlorobenzene in the presence of 1,4-CHD led to disappearance of the starting material leading to a complex mixture of cyclization products. Again the disappearance of **6** was faster in the presence of Cu^{2+} or Ni^{2+} ions.

Fluorescence studies

Fluorescence measurements[18] also showed that the enediyne **6** was able to form complexes with divalent metal ions. Thus the fluorescence spectra of the parent enediyne **6** in DMSO showed extremely weak excitation and emission at λ_{max} 360 and 426 nm respectively (Fig. 3). However, the Ni(II)-complex of **6** displayed a broad but intense maximum at λ 426 nm in the emission spectrum when the excitation λ was fixed at 360 nm (Fig. 3) at a concentration at which neither the starting enediyne nor pure DMSO showed any detectable maxima. In this and in all the other fluorescence studies, DMSO was selected as the solvent because of its high polarity and low background fluorescence intensity at the above mentioned λ for excitation and emission spectra. Increasing the concentration of **6** by up to ten times failed to show any detectable maxima in the emission spectrum at a fixed excitation λ of 360 nm. Also the intensity of the maximum of the Ni-complex of **6** was enhanced gradually as the concentration of the complex was increased (Fig. 4). Thus, there is a modest (more than two-fold) increase in intensity as the concentration of the Ni-complex is raised from 0.45 to 9 mM. Moreover, the complex also exhibited a maximum at 360 nm in the excitation spectrum, when the λ for emission was kept fixed at its maximum value of 426 nm. However the intensity of this fluorescence was much less pronounced compared to the emission spectrum. Here again the starting material **6** did not

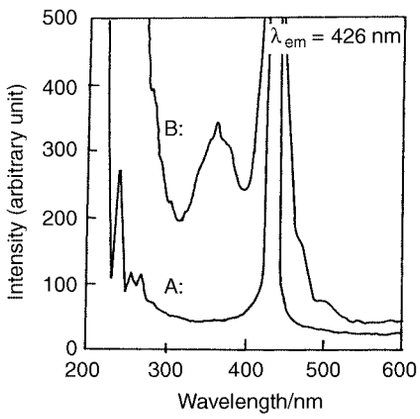


Fig. 5 Excitation spectra of (A) enediyne **6** and (B) its Ni(II)-complex at λ_{ems} = 426 nm.

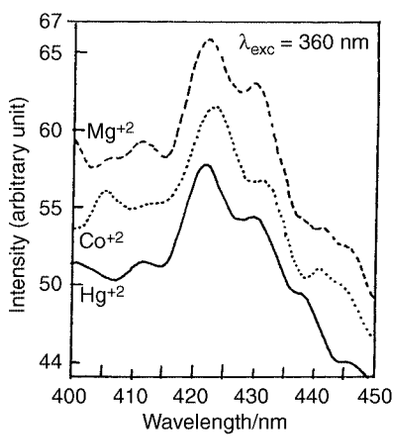


Fig. 6 Emission spectra of **6** in the presence of various metal ions at identical concentration levels.

show any detectable fluorescence maximum at identical concentrations (Fig. 5). Again, a dose-dependent increase in intensity of excitation maximum was observed for the Ni-complex (Figure not shown). These fluorescence data clearly suggested that the enediyne **6** does indeed form a complex with Ni^{2+}. In fact, **6** is capable of forming complexes with various other transition and alkaline-earth metal ions. These metal ions showed a major maximum peak at anywhere ranging from 418 to 435 nm in their emission spectra with the excitation wavelength fixed at 360 nm (Fig. 6). This observation of a shift to higher or lower wavelengths or an increase in fluorescence intensity in either excitation or emission spectra, upon treatment with metal ions,[19] also suggests complex formation.

Conclusion

We have successfully synthesized several novel and interesting azaenediynes. The monocyclic enediyne **1** has the ability to undergo spontaneous cyclization at room temperature, thus making it a logical target for elaboration into a selective DNA-cleaving agent. The effect of existing aromaticity is to slow down the rate of BC, while complexation with metal ions tends to accelerate the cyclization rate. The DNA-cleaving properties of the bis(azaenediyne)s and bis(diazaenediyne)s, complexed to various metal ions are now being studied in our laboratory. Because of the ability of the azaenediyne **6** to bind alkaline-earth as well as transition metal ions (many of which are known to regulate the proteolytic activity of enzymes like proprotein convertases (PC's), subtilisin/kexin-like serine proteases,[20] we are currently conducting studies to examine the potential enzyme inhibitory properties of these molecules. The development of selective inhibitors of PC's are of prime importance in view of the clinical relevance of these proteases.[21] Studies pertaining to these results will be presented in the near future.

Experimental

General

All solvents were dried prior to use. Methylene chloride, triethylamine and DMF were distilled from calcium hydride. All reactions were carried out under nitrogen. IR spectra were recorded on a Perkin-Elmer model 883 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ (unless mentioned otherwise) on a Bruker AC 200 spectrometer. Melting points were determined in open capillaries and are uncorrected. Anhydrous Na_2SO_4 was used for drying organic extracts after reaction workup. DSC measurements were done using a NETZSCH 40 Thermal Analyzer Instrument.

Fluorescence studies

All fluorescence studies were conducted in 96-well plate format; typical sample volume is 100 µl. DMSO was used as the solvent and the fluorescence measurements were carried out using a Perkin-Elmer MPF-3L spectrofluorimeter. The slit widths used were 5 and 3 mm for the excitation and emission spectra respectively. All experiments were performed in duplicate. For all metal ion binding studies, a 4.2 mM stock solution of **6** in DMSO was prepared and 95 µl of this solution was treated with 5 µl of the solution of the metal salt in a well plate. The solution was shaken vigorously at ambient temperature for times ranging from 6 h to overnight, depending upon the nature of cation used. The following metal salts were employed for the study: $CoCl_2$, $NiCl_2{\cdot}6H_2O$, $CaCl_2$, $CuCl_2$, $ZnSO_4$ and $Hg(OAc)_2$. A stock solution of 100 mM of each salt in an aqueous medium of pH 7.0 was used. Thus the final concentration of **6** and each metal salt was kept very near to 5 mM. For fluorescence measurements of **6** and its Ni-complex, a 100 µl solution was used with the fluorescence parameters as described earlier.

Synthesis of (*Z*)-6-chlorohex-5-en-3-yn-1-ol (7)

To a dry degassed benzene (15 ml) solution of (*z*)-1,2-dichloroethylene (305 µl, 4 mmol), $Pd(PPh_3)_4$ (185 mg, 0.16 mmol) and *n*-butylamine (1.75 ml, 16 mmol) were added and stirred for 5 min under argon. CuI (152 mg, 0.8 mmol) was added and stirred for 20 min followed by addition of but-3-yn-1-ol (330 µl, 4.4 mmol). Stirring was continued for 3 h at room temperature. A mixture of EtOAc and saturated NH_4Cl (15 ml each) was added and stirred for a further 10 min. The organic layer was washed with water (3 × 20 ml), dried and filtered. Evaporation afforded an oil from which the title compound **7** was isolated by column chromatography (Si-gel, hexane–EtOAc 1 : 1) as an orange–yellow oil (418 mg, 80%); ν_{max} ($CHCl_3$) 3340, 1800, 1340, 1060, 850 cm^{-1}; δ_H 2.15 (1H, br s), 2.67 (2H, dt, J = 1.8, 6.0 Hz), 3.79 (2H, t, J = 6.0 Hz), 5.88 (1H, dd, J = 1.8, 7.4 Hz), 6.35 (1H, d, J = 7.4 Hz); δ_C 23.8, 60.7, 76.2, 90.9, 112.0, 127.6; MS (EI) 132, 130 (M^+); HRMS: calcd for $C_6H_7{}^{35}ClO$ 130.0185, found 130.0186.

Synthesis of 6-chlorohex-5-en-3-ynyl methanesulfonate (8)

To a solution of **7** (400 mg, 3.1 mmol) in CH_2Cl_2 (20 ml), methanesulfonyl chloride (265 µl, 3.3 mmol) and triethylamine (470 µl, 3.37 mmol) were added at 0 °C. The mixture was stirred for 15 min at room temperature after which it was poured into water and CH_2Cl_2 (50 ml each). The organic layer was washed with water (2 × 50 ml), dried and then evaporated. Chromatography of the residue over Si-gel, furnished the title compound **8** as a pale brown oil (540 mg, 85%); δ_H 2.16 (1H, br s), 2.49 (3H, s), 2.69 (2H, dt, J = 1.8, 6.0 Hz), 4.82 (2H, t, J = 6.0 Hz), 5.89 (1H, dd, J = 1.8, 7.3 Hz), 6.36 (1H, d, J = 7.3 Hz); MS (EI) 210, 208 (M^+); HRMS: calcd for $C_7H_9{}^{35}ClO_3S$ 207.9961, found 207.9965.

Synthesis of 1-azido-6-chlorohex-5-en-3-yne (9)

To a solution of the mesylate **8** (500 mg, 2.4 mmol) in dry DMF (20 ml), NaN_3 (625 mg, 4 equiv.) was added and stirred for 4 h at room temperature. The mixture was then partitioned between EtOAc and water (50 ml each). The organic layer was thoroughly washed with water (3 × 50 ml), dried, filtered and then evaporated. The title compound **9** was isolated by chromatography (Si-gel, hexane–EtOAc 1 : 1) as a pale brown oil (220 mg, 80%); δ_H 2.37 (2H, dt, J = 2.0, 6.8 Hz), 3.14 (2H, t, J = 6.8 Hz), 5.54 (1H, dt, J = 2.1, 7.4 Hz), 5.89 (1H, dd, J = 1.8, 7.3 Hz), 6.36 (1H, d, J = 7.3 Hz); δ_C 20.54, 49.53, 94.34, 96.04, 111.76, 127.92; MS (EI) 157, 155 (M^+); HRMS: calcd for $C_6H_6{}^{35}ClN_3$ 155.0250, found 155.0252.

Synthesis of 1-(4-methylphenylsulfonamido)-6-chlorohex-5-en-3-yne (10)

To a solution of the azide **9** (200 mg, 1.28 mmol) in THF (15 ml), PPh_3 (370 mg, 1.4 mmol) and water (200 µl) were added and stirred at room temperature for 20 h. It was then partitioned between EtOAc and water (50 ml each). The organic layer was dried, filtered and evaporated. The oily residue was dissolved in CH_2Cl_2 (15 ml) and toluene-*p*-sulfonyl chloride (267 mg, 1.4 mmol) and DMAP (172 mg, 1.4 mmol) were added. The mixture was stirred for 3 h. After partitioning between CH_2Cl_2 and water (50 ml each), the organic layer was dried (Na_2SO_4), filtered and evaporated. From the oily residue, the title compound **10** was isolated in pure form by chromatography (Si-gel, hexane–EtOAc 1 : 1) as a pale brown oil (200 mg, 55%); δ_H 2.38 (3H, s), 2.94 (2H, t, J = 6.6 Hz), 3.08 (2H, dd, J = 6.6, 13.2 Hz), 5.46 (1H, br s), 5.74 (1H, dd, J = 2.0, 5.7 Hz), 6.27 (1H, d, J = 7.4 Hz), 7.25 (2H, d, J = 8.1 Hz), 7.72 (2H, d, J = 8.1 Hz); δ_C 20.83, 21.38, 41.57, 76.70, 96.0, 111.89, 126.95, 127.74, 129.58, 137.03, 143.14; MS (EI) 285, 283 (M^+); HRMS: calcd for $C_{13}H_{14}{}^{35}ClNO_2S$ 283.0435, found 283.0436.

Synthesis of 1-*tert*-butyldimethylsilyloxy-9-(4-methylphenylsulfonamido)non-4-ene-2,6-diyne (11)

To a degassed solution of the chlorosulfonamide **10** (200 mg, 0.71 mmol) in benzene (10 ml), $Pd(PPh_3)_4$ (33 mg, 0.0284 mmol) and *n*-butylamine (310 µl, 2.84 mmol) were added and stirred for 5 min. CuI (27 mg, 0.142 mmol) was added and stirred for 20 min after which *tert*-butyldimethylsilyl propargyl ether (140 mg, 0.82 mmol) dissolved in degassed benzene (1 ml) was added and the reaction mixture was stirred at 40 °C for 3 h. EtOAc (20 ml) and saturated. NH_4Cl (10 ml) were added and stirred for a further 10 min. The organic layer was washed with water, dried and evaporated. The title compound **11** was isolated by chromatography (Si-gel, hexane–EtOAc 4 : 1) and isolated as a yellow oil (210 mg, 70%); δ_H 0.05 (6H, s), 0.83 (9H, s), 2.36 (3H, s), 2.42 (2H, t, J = 6.6 Hz), 3.06 (2H, dd, J = 6.6, 13.6 Hz), 4.46 (2H, s), 5.05 (1H, t, J = 6.2 Hz), 5.68–5.87 (2H, *m*), 7.22 (2H, d, J = 8.2 Hz), 7.69 (2H, d, J = 8.2 Hz); δ_C 5.08, 18.29, 21.05, 21.51, 25.86, 41.58, 52.22, 80.45, 82.21, 93.49, 95.63, 119.13, 119.20, 127.08, 129.60, 137.44, 143.10; MS (CI) 418 (MH^+); HRMS: calcd for $C_{22}H_{31}NO_3SSi+H^+$ 418.1872, found 418.1874.

Synthesis of 9-(4-methylphenylsulfonamido)non-4-ene-2,6-diyn-1-ol (12)

Caesium fluoride (152 mg, 1 mmol) was added to a solution of **11** (250 mg, 0.92 mmol) in CH_3CN (10 ml) and the mixture was stirred for 4 h at room temperature. The mixture was filtered through Si-gel and evaporated. The title compound **12** was isolated in pure form by chromatography (Si-gel, hexane–EtOAc 1 : 1) as a pale brown oil (160 mg, 90%); δ_H 2.41 (3H, s), 2.49 (2H, t, J = 6.6 Hz), 3.12 (2H, dd, J = 6.3, 12.2 Hz), 4.49 (2H, s), 5.80 (3H, *m*), 7.30 (2H, d, J = 8.2 Hz), 7.75 (2H, d, J = 8.2 Hz); δ_C 20.96, 21.58, 41.43, 51.19, 80.88, 82.62, 93.93,

95.94, 119.51, 119.63, 127.18, 129.73, 137.21, 143.37; MS (EI) 303 (M^+); HRMS: calcd for $C_{16}H_{17}NO_3S$ 303.0930, found 303.0935.

Synthesis of 1-Methylsulfonyloxy-9-(4-methylphenylsulfonamido)non-4-ene-2,6-diyne (13)

To a solution of **12** (150 mg, 0.5 mmol) in CH_2Cl_2 (10 ml), methanesulfonyl chloride (43 µl, 0.55 mmol) and triethylamine (76 µl, 0.55 mmol) were added and stirred at rt for 15 min. After partitioning between water and CH_2Cl_2, the organic layer was dried and evaporated. The title compound **13** was isolated by chromatography (Si-gel, hexane–EtOAc 1:1) as an oil (160 mg, 85%); δ_H 2.44 (3H, s), 2.56 (2H, t, J = 6.2 Hz), 3.11–3.17 (5H, br m), 5.08 (2H, s), 5.14 (1H, t, J = 8.4 Hz), 5.80–5.92 (2H, m), 7.30 (2H, d, J = 8.2 Hz), 7.76 (2H, d, J = 8.2 Hz); δ_C 21.27, 21.59, 38.92, 41.45, 58.19, 80.13, 82.62, 89.50, 95.44, 117.82, 122.27, 127.20, 129.75, 137.36, 143.33; MS (EI) 381 (M^+); HRMS: calcd for $C_{17}H_{19}NO_5S_2$ 381.0705, found 381.0709.

Synthesis of 1-(4-Methylphenylsulfonyl)-1-azacyclodec-5-ene-3,7-diyne (1)

To a solution of the mesylate **13** (50 mg, 0.13 mmol) in DMF (20 ml), K_2CO_3 (90 mg, 0.66 mmol) was added and stirred at rt for 3 h. EtOAc was added and the organic layer was washed with water (3 × 25 ml), dried and evaporated. Si-gel chromatography (hexane–EtOAc 2:1) furnished the title compound **1** as an oil (30 mg, 85%); δ_H 2.45 (3H, s), 2.77 (2H, t, J = 5 Hz), 3.53 (2H, t, J = 5 Hz), 4.09 (2H, s), 5.84 (2H, br s), 7.30 (2H, d, J = 8.1 Hz), 7.76 (2H, d, J = 8.1 Hz); δ_C 21.58, 22.45, 42.16, 51.15, 83.82, 89.53, 94.39, 96.54, 122.18, 124.48, 127.39, 129.75, 136.11, 143.46; MS (EI, $CHCl_3$) 321 ($MHCl^+$), 287 (MH_2^+), 286 (MH^+), 285 ($M^{+\cdot}$), 155, 130 ($M^+ - CH_3C_6H_4SO_2$), 104, 102; HRMS: calcd for $C_{16}H_{15}NO_2S$ 285.0824, found 285.0828.

Spectral data for 1,11-bis(4-methylphenylsulfonyl)-1,11-diazacycloicosa-5,15-diene-3,7,13,17-tetrayne (11a)

The title compound was obtained when the previous reaction was carried out at a concentration of 0.06 M. Isolated as a pale brown oil (30%); δ_H 2.40 (3H, s), 2.67 (2H, dt, J = 2.0, 7.5 Hz), 3.27 (2H, t, J = 7.5 Hz), 4.40 (2H, s), 5.48 (2H, s), 5.70 (1H, d), 7.30 (2H, d, J = 8.2 Hz), 7.72 (2H, d); MS (EI) 570 (M^+); HRMS: calcd for $C_{32}H_{30}N_2O_4S_2$ 570.1648, found 570.1651.

Synthesis of 2-bromo-1-(4-hydroxybut-1-yn-1-yl)benzene (14)

1,2-Dibromobenzene (500 µl, 4.2 mmol), homopropargyl alcohol (350 µl, 4.62 mmol) and $Pd(PPh_3)_4$ (194 mg, 0.169 mmol) were added to degassed *n*-butylamine (15 ml) and the solution was refluxed for 10 h. It was then poured into EtOAc (50 ml) and the organic layer was washed with 0.1 M HCl, then with water (50 ml each) and dried. Evaporation *in vacuo* gave an oil from which the title compound **15** was isolated by chromatography (Si-gel, hexane–EtOAc 1:1) as a brown oil (850 mg, 90%); δ_H 2.90 (2H, t, J = 6.1 Hz), 4.01 (2H, t, J = 6.1 Hz), 7.26–7.44 (2H, *m*), 7.60 (1H, dd, J = 1.8, 7.7 Hz), 7.73 (1H, dd, J = 1.3, 7.9 Hz); MS (EI) 226, 224 (M^+); HRMS: calcd for $C_{10}H_9{}^{79}BrO$ 223.9837, found 223.9840.

Synthesis of 2-bromo-1-(4-methylsulfonyloxybut-1-yn-1-yl)-benzene (15)

Prepared from the corresponding alcohol **14** (200 mg, 0.89 mmol) following the procedure as described for the preparation of **8.** Isolated as a brown oil (230 mg, 85%); δ_H 2.95 (2H, t, J = 6.8 Hz), 3.06 (3H, s), 4.42 (2H, t, J = 6.8 Hz), 7.14–7.28 (2H, *m*), 7.43 (1H, dd, J = 1.9, 7.6 Hz), 7.56 (1H, dd, J = 1.4, 9.3 Hz); MS (EI) 304, 302 (M^+); HRMS: calcd for $C_{11}H_{11}{}^{79}BrO_3S$ 301.9612, found 301.9614.

Synthesis of 2-bromo-1-[4-azidobut-1-yn-1-yl)]benzene (16)

The title compound **16** was prepared following the same procedure as described for **9**. Isolated as a pale brown oil (78%); δ_H 2.76 (2H, t, J = 6.9 Hz), 3.51 (2H, t, J = 6.9 Hz), 7.08–7.27 (2H, m), 7.43 (1H, d, J = 7.5 Hz), 7.55 (1H, d, J = 7.8 Hz); MS (EI) 251, 249 (M^+); HRMS: calcd for $C_{10}H_8{}^{79}BrN_3$ 248.9902, found 248.9905.

Synthesis of 2-bromo-1-[4-(4-methylphenylsulfonamido)but-1-yn-1-yl]benzene (17)

The title compound was prepared from the azide **16** (120 mg, 0.48 mmol) *via* reduction with Ph_3P (126 mg, 0.45 mmol) and water (200 µl), followed by protection with toluene-*p*-sulfonyl chloride and Et_3N (each 1.2 equiv.); isolated as a pale brown oil (90 mg, 52%); δ_H 2.42 (3H, s), 2.61 (2H, t, J = 6.4 Hz), 3.23 (2H, dd, J = 6.4, 12.8 Hz), 5.25 (1H, t, J = 6.2 Hz), 7.09–7.23 (2H, m), 7.28 (2H, d, J = 8.0 Hz), 7.38 (1H, dd, J = 1.4, 7.5 Hz), 7.55 (1H, dd, J = 1.4, 7.8 Hz), 7.79 (2H, d, J = 8.0 Hz); MS (EI) 379, 377 (M^+); HRMS: calcd for $C_{17}H_{16}{}^{79}BrNO_2S$ 377.0086, found 377.0088.

Synthesis of 2-(3-hydroxyprop-1-yn-1-yl)-1-[4-(4-methylphenylsulfonamido)but-1-yn-1-yl]benzene (18)

The bromotosylate **17** (80 mg, 0.22 mmol), dissolved in degassed *n*-butylamine (8 ml), was treated with $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) and propargyl alcohol (10 µl, 0.27 mmol). The mixture was refluxed for 20 h after which it was partitioned between EtOAc and 0.1 M HCl (30 ml each). The organic layer was dried, filtered and evaporated. The title compound was isolated by chromatography (Si-gel, hexane–EtOAc 1:1) as a pale yellow oil (60 mg, 80%); δ_H 2.41 (3H, s), 2.59 (2H, t, J = 5.8 Hz), 3.21 (2H, t, J = 5.8 Hz), 4.56 (2H, s), 5.52 (1H, t, J = 1.5 Hz), 7.33–7.36 (2H, d, J = 8.3 Hz), 7.44–7.48 (2H, m), 7.80 (2H, d, J = 8.3 Hz); MS (EI) 353 (M^+); HRMS: calcd for $C_{20}H_{19}NO_3S$ 353.1086, found 353.1088.

Synthesis of 2-(1-methylsulfonyloxyprop-1-yn-1-yl)-1-[4-(4-methylphenylsulfonamido)but-1-yn-1-yl]benzene (19)

The title compound was prepared from the alcohol **18** following the same procedure as described for **7.** Isolated as a brown oil (85%); δ_H 2.40 (3H, s), 2.63 (2H, t, J = 5.9 Hz), 3.10 (3H, s), 3.17 (2H, t, J = 5.9 Hz), 5.17 (2H, s), 5.75 (1H, t, J = 1.5 Hz), 7.20–7.40 (5H, m), 7.43–7.53 (1H, m), 7.78 (2H, d, J = 8.1 Hz); MS (EI) 431 (M^+); HRMS: calcd for $C_{21}H_{21}NO_5S_2$ 431.0861, found 431.0863.

Synthesis of 5-(4-methylphenylsulfonyl)-5-azabicyclo[8.4.0]-tetradeca-1(10),11,13-triene-2,8-diyne (2)

The mesylate **19** (50 mg, 0.12 mmol), dissolved in dry DMF (20 ml) was treated with K_2CO_3 (85 mg, 0.61 mmol) and the mixture was stirred for 3 h at room temperature. It was then partitioned between EtOAc and water (50 ml each). The organic layer was further washed with water (3 × 50 ml), dried and evaporated. From the residue the title compound was isolated by chromatography (Si gel, hexane–EtOAc 4:1) as a pale brown oil (30 mg, 80%); δ_H 2.40 (3H, s), 2.80 (2H, t, J = 5 Hz), 3.58 (2H, t, J = 5 Hz), 4.15 (2H, s), 7.24–7.29 (6H, m), 7.75 (2H, d, J = 8.3 Hz); MS (EI) 335 (M^+); HRMS: calcd for $C_{20}H_{17}NO_2S$ 335.0981, found 335.0982.

Synthesis of 5-chloropent-4-en-2-yn-1-ol (20)

The title compound **20** was prepared from (*Z*)-1,2-dichloroethylene and propargyl alcohol *via* a Pd(0)-catalysed coupling following the same procedure as described for the preparation of **7**. Isolated as a brown oil (yield 65%); δ_H 2.22 (1H, br s), 4.23 (2H, s), 5.89 (1H, dt, J = 2, 7.5 Hz), 6.37 (1H, d, J = 7.5 Hz); MS (EI) 118, 116 (M^+); HRMS: calcd for $C_5H_5{}^{35}ClO$ 116.0029, found 116.0031.

Synthesis of 5-chloropent-4-en-2-ynyl methanesulfonate (21)

Prepared from the corresponding alcohol **20** (232 mg, 2 mmol) following the procedure as described for the preparation of **8**. Isolated as a brown oil (310 mg, 80%); δ_H 3.13 (3H, s), 5.01 (2H, d, $J = 2$ Hz), 5.91 (1H, dt, $J = 1.8$, 7.5 Hz), 6.49 (1H, d, $J = 7.5$ Hz); MS (EI) 196, 194 (M^+); HRMS: calcd for $C_6H_7{}^{35}ClO_3S$ 194.1234, found 194.1236.

Synthesis of 5-chloro-1-azidopent-4-en-2-yne (22)

The title compound **22** was prepared from the mesylate **21** (194 mg, 1 mmol) following the same procedure as described for **9**. Isolated as a pale brown oil (127 mg, 90%); δ_H 4.10 (2H, s), 5.92 (1H, dt, $J = 2$, 7.5 Hz), 6.45 (1H, d, $J = 7.5$ Hz); MS (EI) 143, 141 (M^+): HRMS: calcd for $C_5H_4{}^{35}ClN_3$ 141.0094, found 141.0097.

Synthesis of 5-chloro-1-(4-methylphenylsulfonamido)pent-4-en-2-yne (23)

The title compound **22** was prepared from the corresponding azide **22** *via* reduction with PPh_3–H_2O followed by protection as the sulfonamide (55%); δ_H 2.42 (3H, s), 4.04 (2H, dd, $J = 2$, 6.1 Hz), 4.60 (1H, t, $J = 5.6$ Hz), 5.64 (1H, dt, $J = 2$, 7.4 Hz), 6.32 (1H, d, $J = 7.4$ Hz), 7.30 (2H, d, $J = 8.1$ Hz), 7.78 (2H, d, $J = 8.1$ Hz); MS (EI) 271, 269 (M^+); HRMS: calcd for $C_{12}H_{12}{}^{35}ClNSO_2$ 269.0277, found 269.0279.

Synthesis of 1-*tert*-butyldimethylsilyloxy-8-(4-methylphenylsulfonamido)oct-4-ene-2,6-diyne (24)

The title compound **23** was synthesized from the chloroenyne **23** *via* Pd(0)-mediated coupling as described for **11** (yellow oil, 72%); δ_H 0.13 (6H, s), 0.91 (9H, s), 2.42 (3H, s), 4.01 (2H, dd, $J = 2$, 6 Hz), 4.48 (2H, d, $J = 2$ Hz), 4.49 (1H, t, $J = 5.6$ Hz), 5.54 (1H, d, $J = 10.9$ Hz), 5.78 (1H, d, $J = 10.9$ Hz), 7.30 (2H, d, $J = 8.1$ Hz), 7.77 (2H, d, $J = 8.1$ Hz); MS (EI) 403 (M^+); calcd for $C_{21}H_{29}NO_3SSi$ 403.1637, found 403.1639.

Synthesis of 1-hydroxy-8-(4-methylphenylsulfonamido)oct-4-ene-2,6-diyne (25)

The title compound **25** was synthesized from the silyl protected compound **24** by deprotection with CsF (nearly colourless oil, 90%); δ_H 2.41 (3H, s), 3.39 (1H, t, $J = 6.8$ Hz), 3.96 (2H, s), 4.45 (2H, s), 5.62 (1H, d, $J = 10$ Hz), 5.72 (1H, d, $J = 10$ Hz), 7.28 (2H, d, $J = 8.1$ Hz), 7.78 (2H, d, $J = 8.1$ Hz); HRMS: calcd for $C_{15}H_{15}NO_3S$ 289.0773, found 289.0775.

Synthesis of 1-methylsulfonyloxy-8-(4-methylphenylsulfonamido)oct-4-ene-2,6-diyne (26)

The title compound **26** was prepared from the alcohol following the same procedure as described for **8**; isolated as a pale brown oil (81%); δ_H 2.41 (3H, s), 3.14 (3H, s), 3.99 (1H, dd, $J = 1.3$, 6.0 Hz), 5.12 (1H, t, $J = 5.6$ Hz), 5.76 (2H, m), 7.29 (2H, d, $J = 7.5$ Hz), 7.78 (2H, d, $J = 7.5$ Hz); MS (EI) 367 (M^+); HRMS: calcd for $C_{16}H_{17}NO_5S_2$ 367.0548, found 367.0549.

Synthesis of 1,10-bis(4-methylphenylsulfonyl)-1,10-diazacyclooctadeca-5,14-diene-3,7,12,16-tetrayne (3)

To a solution of **26** (50 mg, 0.14 mmol) in dry DMF (5 ml), K_2CO_3 (95 mg, 0.68 mmol) was added and the mixture was stirred for 3 h at room temperature. It was then partitioned between EtOAc and water (50 ml each). The organic layer was washed with water (3 × 50 ml), dried and evaporated. The residue on chromatography (Si-gel, hexane–EtOAc 2 : 1) furnished the title compound **3** as a viscous oil (35 mg, 90%); ν_{max} (KBr) 3438, 2925, 1633, 1162, 670 cm^{-1}; δ_H 2.41 (6H, s), 4.34 (8H, s), 5.58 (4H, s),7.29 (4H, d, $J = 8.3$ Hz), 7.69 (4H, d, $J = 8.3$ Hz); δ_C 21.51, 36.85, 83.10, 88.93, 120.25, 127.94, 129.51, 135.10, 143.99; MS (EI) 542 (M^+); HRMS: calcd for $C_{30}H_{26}N_2O_4S_2$ 542.1335, found 542.1339.

Synthesis of 1,2-bis(3-hydroxyprop-1-yn-1-yl) benzene (27)

To a degassed solution of 1,2-dibromobenzene (500 µl, 4.2 mmol) and propargyl alcohol (513 µl, 8.83 mmol) in *n*-butylamine (5 ml), $Pd(PPh_3)_4$ was added and refluxed for 20 h. It was then partitioned between EtOAc and 0.1 M HCl (50 ml each). The organic layer was dried and evaporated to leave a residue from which **27** was isolated by chromatography (Si-gel, hexane–EtOAc 1 : 2) as a brown oil (625 mg, 80%); ν_{max} ($CHCl_3$) 3413, 3022, 2929, 2858, 1642, 1450, 1215, 1025, 910, 758 cm^{-1}; δ_H 4.54 (4H, s), 7.24–7.29 (2H, m), 7.37–7.44 (2H, m); HRMS: calcd for $C_{12}H_{10}O_2$ 186.0681, found 186.0683.

Synthesis of 1,2-bis-(1-methylsulfonyloxyprop-1-yn-1-yl) benzene (28)

The title compound was prepared *via* mesylation following the same procedure as described for **8** (yield 85%); ν_{max} 3448, 2927, 2857, 2244, 1742, 1646, 1449, 1359, 1171, 999, 934, 803, 762 cm^{-1}; δ_H 3.15 (6H, s), 5.13 (4H, s), 7.33–7.40 (2H, m), 7.44–7.51 (2H, m); MS (EI) 342 (M^+); HRMS: calcd for $C_{14}H_{14}O_6S_2$ 342.0232, found 342.0234.

Synthesis of 5,8-dibenzyl-5,8-diazabicyclo[10.4.0]hexadeca-1(12),13,15-triene-2,10-diyne (4)

To a solution of the mesylate **28** (117 mg, 0.44 mmol) in DMF (30 ml), *N*,*N*′-dibenzylethylenediamine **30** (104 µl, 0.44 mmol) and K_2CO_3 (243 mg, 1.76 mmol) were added and stirred at room temperature for 3 h. The solution was then partitioned between EtOAc and water (50 ml each). The organic layer was further washed with water (3 × 50 ml), dried and evaporated. The residue, on chromatography (Si-gel, hexane–EtOAc 1 : 1) furnished **4** as a white solid, crystallized from hexane–CH_2Cl_2 as needles (125 mg, 72%); mp 123 °C, ν_{max} 3445, 3030, 2916, 2846, 2360, 1704, 1479, 1440, 1372, 1332, 1131, 1072, 736, 696 cm^{-1}; δ_H 3.04 (2H, s), 3.56 (2H, s), 3.68 (2H, s), 7.22–7.42 (14H, m); δ_C 43.22, 51.77, 60.66, 84.81, 89.95, 126.99, 127.10, 127.63, 128.24, 128.95, 130.45, 138.5; MS (CI) 391 (MH^+), 300, 299, 152, 91; HRMS calcd. for $C_{28}H_{26}N_2 + H^+$ 391.2176, found 391.2180.

Synthesis of the copper(II) complex (31)

To a solution of **4** (80 mg, 0.2 mmol) in MeOH (4 ml), a methanolic solution of $Cu(OAc)_2 \cdot 2H_2O$ (20 mg, 0.1 mmol) was added dropwise and then refluxed for 10 h. The Cu(II)-complex **31** was collected as a brown precipitate and dried under vacuum (75 mg, 80%); ν_{max} 3425, 3061, 2927, 1567, 1435, 1082, 1030, 746, 696 cm^{-1}; MS (ES) 453 (M^+).

Synthesis of bisazaenediyne (5)

To a solution of the mesylate **28** (100 mg, 0.37 mmol) in DMF (5 ml), *N*,*N*′-bis(*p*-tolylsulfonyl)-1,3-phenylenediamine **32** (158 mg, 0.37 mmol) and K_2CO_3 (207 mg, 1.50 mmol) were added and stirred at room temperature for 3 h. It was then partitioned between EtOAc and water (50 ml each). The organic layer was further washed with water (3 × 50 ml), dried and evaporated. The residue, on chromatography (Si-gel, hexane–EtOAc 1 : 1) furnished **5** as a white solid, crystallized from hexane–CH_2Cl_2 as needles (125 mg, 60%); mp 142 °C, ν_{max} 3445, 3030, 2916, 2846, 2360, 1704, 1479, 1440, 1372, 1332, 1131, 1072, 736, 696 cm^{-1}; δ_H 3.04 (2H, s), 3.56 (2H, s), 3.68 (2H, s), 7.22–7.42 (14H, m); MS (EI) 566 (M^+); HRMS: calcd for $C_{32}H_{26}N_2O_4S_2$ 566.1335, found 566.1336.

Synthesis of 2-bromo-1-(3-hydroxyprop-1-yn-1-yl) benzene (33)

The title compound was prepared from 1,2-dibromobenzene (500 µl, 4.2 mmol), propargyl alcohol (270 µl, 4.62 mmol)

following the procedure as described for **14**. Isolated as a light brown oil (90%); ν_{max} 3379, 3021 2929, 2860, 1676, 1470, 1435, 1343, 1216, 1151, 1027, 910, 851, 758, 651 cm^{-1}; δ_H 4.53 (2H, s), 7.15–7.29 (2H, m), 7.46 (1H, dd, J = 7.5, 1.9 Hz), 7.57 (1H, dd, J = 7.5, 1.9 Hz); MS (EI) 212, 210 (M^+); HRMS: calcd for $C_9H_7{}^{79}BrO$ 209.9680, found 209.9682.

Synthesis of 2-bromo-1-(3-methylsulfonyloxyprop-1-yn-1-yl) benzene (34)

The title compound was prepared from the corresponding alcohol following the same procedure as described for **8**. Isolated as a pale brown oil (85%); ν_{max} 3026, 2932, 2861, 2236, 1742, 1633, 1467, 1360, 1177, 1054, 990, 936, 805, 758, 655 cm^{-1}; δ_H 3.19 (3H, s), 5.13 (2H, s), 7.35–7.18 (2H, m), 7.49 (1H, dd, J = 2.0, 7.4 Hz), 7.60 (1H, dd, J = 1.9, 7.4 Hz); δ_C 38.5, 57.9, 85.7, 88.0, 122.85, 124.2, 128.1, 130.2, 132.0, 133.9; MS (EI) 290, 288 (M^+); HRMS: calcd for $C_{10}H_9{}^{79}BrO_3S$ 287.9455, found 287.9458.

Synthesis of *N*,*N*′-dibenzyl-*N*,*N*′-bis[3-(2-bromophenyl)prop-2-ynyl]ethylene diamine (35)

To a solution of **34** (333 mg, 0.735 mmol) in DMF, *N*,*N*′-dibenzylethylenediamine (86 µl, 0.38 mmol) and K_2CO_3 were added and stirred at room temperature for 3 h. It was then poured into EtOAc (50 ml) and washed with water (3 × 50 ml). The organic layer was dried and evaporated to leave a brown solid from which the title compound **35** was isolated by chromatography (Si-gel, hexane–EtOAc 10 : 1) as a brown solid (550 mg, 80%); ν_{max} (KBr) 3448, 3032, 2922, 2840, 1632, 1498, 1457, 1374, 1235, 1078, 938, 833, 746, 694 cm^{-1}; δ_H 2.93 (4H, s), 3.67 (4H, s), 3.80 (4H, s), 7.14–7.56 (18H, m); δ_C 42.4, 51.4, 58.3, 84.1, 89.7, 125.4, 126.8, 127.0, 128.2, 129.2, 132.2, 133.4, 138.6; HRMS: calcd for $C_{34}H_{30}{}^{79}Br_2N_2$ 624.0777, found 624.0779.

Synthesis of bis(diazaenediyne) (6)

To a solution of **33** in degassed *n*-butylamine, *N*,*N*′-dibenzyl-*N*,*N*′-di(prop-2-yn-1-yl)ethylenediamine (**36**) (34 mg, 0.17 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.0085 mmol) were added and refluxed for 24 h. The mixture was then poured into EtOAc (30 ml) and the organic layer was washed with 0.1 M HCl (50 ml), then water (2 × 50 ml) and dried. Filtration followed by evaporation gave a residue from which the title compound **6** was isolated by chromatography (Si-gel, hexane–EtOAc 10 : 1) as a solid (40 mg, 50%); ν_{max} (KBr) 3069, 3025, 2921, 2830, 1969, 1603, 1545, 1442, 1318, 1112, 1075, 983 cm^{-1}; δ_H 2.87 (8H, s), 3.65 (8H, s), 3.74 (8H, s), 7.21–7.49 (28H, m); δ_H (d_6-DMSO) 2.77 (8H, s), 3.59 (8H, s), 3.68 (8H, s), 7.21–7.54 (28H, m); δ_C 42.5, 51.3, 58.3, 84.8, 88.3, 125.7, 127.1, 127.7, 128.2, 129.2, 132.3, 138.7; MS (EI) 780 (M^+); HRMS calcd. for $C_{56}H_{52}N_4$ 780.4196, found 780.4195.

Synthesis of Cu(II)-complex (37)

To a solution of the enediyne **6** (78 mg, 0.1 mmol) in methanol (10 ml), a methanolic solution of Cu(II) acetate (20 mg, 0.1 mmol) was added and then refluxed for 4 h. The solution was evaporated and the complex was collected as a brown solid which was dried under vacuum; ν_{max} 2933, 2454, 2355, 1981, 1569, 1428, 1234, 1119, 1026, 749, 693, 614 cm^{-1}; MS (ES) 843 (M^+).

Synthesis of the Ni(II)-complex (38)

To a solution of the enediyne **6** (39 mg, 0.05 mmol) in methanol (5 ml), a methanolic solution of Ni(II) perchlorate (19 mg, 0.05 mmol) was added and then refluxed for 1 h. The Ni(II)-complex was collected as a brownish white solid; ν_{max} (KBr) 3069, 2867, 1927, 1638, 1470, 1306, 1169, 1092, 1010, 922, 718, 634 cm^{-1}; δ_H (d_6-DMSO) 3.24 (8H, s), 3.94 (8H, s), 4.09 (8H, s), 7.39–7.60 (28H, m); MS (ES) 838 (M^+).

Bergman cyclization of the enediynes

For enediyne 1. A solution of **1** (10 mg) in $CDCl_3$ (0.5 ml) was kept at a constant temperature of 23 °C with occasional shaking. The ^{1}H-NMR was checked at different points in time. After 7 days, the solution was evaporated and the cyclized product, *N*-(4-methylphenylsulfonyl)-5,8-dideuterio-1,2,3,4-tetrahydroisoquinoline **39a** was isolated by chromatography (6 mg); δ_H 2.40 (3H, s), 2.91 (2H, t), 3.33 (2H, t, J = 6.0 Hz), 4.22 (2H, s), 7.30 (2H, d, J = 8.0 Hz), 7.39 (1H, d, J = 8.0 Hz), 7.70 (2H, d, J = 8.0 Hz), 7.92 (1H, d, J = 8.0 Hz); MS (EI) 289 (M^+); HRMS: calcd for $C_{16}H_{15}D_2NO_2S$ 289.1103, found 289.1105.

For enediyne 2. A solution of **2** (20 mg) in $CHCl_3$ (2 ml) was refluxed under argon. Aliquots (200 µl) were taken at different points in time and the extent of conversion was checked by ^{1}H-NMR. When the reaction was almost complete (96 h), the solution was cooled, evaporated and then chromatographed to give the *N*-(4-methylphenylsulfonyl)-1,2,3,4-tetrahydrobenzo-[*g*]isoquinoline **40a**; δ_H 2.39 (3H, s), 3.11 (2H, t, J = 6.2 Hz), 3.49 (2H, t, J = 6.1 Hz), 4.43 (2H, s), 7.29 (2H, d, J = 8.0 Hz), 7.38 (2H, m), 7.51 (1H, br s), 7.54 (1H, br s), 7.70 (2H, m), 7.73 (2H, d, J = 8.2 Hz); MS (EI) 337 (M^+); HRMS calcd for $C_{20}H_{19}NO_2S$ 337.1138, found 337.1142.

For enediyne 4. A degassed solution of **4** (20 mg) and cyclohexa-1,4-diene (10 equiv.) in chlorobenzene (2 ml) was heated in a sealed tube in a sand bath kept at 240 °C for 24 hours. After cooling, the solution was evaporated *in vacuo* and the residue, upon chromatography, furnished 5,8-dibenzyl-5,8-diazatricyclo[10.4.0.0^{3,10}]hexadeca-1(12),2,10,13,15-pentaene **41** in 85% yield; δ_H 2.76 (2H, s), 3.65 (2H, s), 4.15 (2H, s), 7.28–7.38 (10H, m), 7.45 (2H, dd, J = 3.2, 6.2 Hz), 7.57 (2H, m), 7.79 (2H, dd, J = 3.2, 6.2 Hz); MS (EI) 392 (M^+), 301, 155; HRMS: calcd for $C_{28}H_{28}N_2$ 392.2255, found 392.2257.

Acknowledgements

A. B. thanks Council of Scientific and Industrial Research (CSIR), Government of India, for partially financing this project. We are grateful to Professor Craig A. Townsend, Johns Hopkins University, Baltimore, USA, for providing spectral and computer facilities and for helpful discussions. We also thank Professor Michel Chretien for his interest in the work.

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