Synthesis and reactivity of a 9-membered azaenediyne: importance of proximity effect in *N*-alkylation†

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Synthesis of a 9-membered azaenediyne has been achieved for the first time *via* intramolecular *N*-alkylation; the importance of proximity of the reacting centres *via* cobalt carbonyl complexation of the acetylenic moiety and not the activation of propargylic carbon has been demonstrated.

Natural product chemistry that includes isolation, structure elucidation, synthesis and property evaluation has regained its momentum in recent years after a temporary slump in the mid eighties.[1] This revival has been primarily possible because of the discovery in the late eighties of molecules with intricate structural features and fascinating modes of biological action. The enediyne class of natural products[2] certainly belongs to that group. In 1987 researchers at Lederle[3] and Bristol Myers[4] reported the exciting and unprecedented structures of calicheamicins and esperamicins. This was soon followed by the discovery of related molecules like dynemicin,[5] kedercidin[6] and C-1027.[7] All these molecules show their biological activity (cytotoxicity) *via* Bergman cyclization (BC)[8] after an initial triggering. It is interesting to note that molecules like kedercidin and C-1027 have a more reactive 9-membered enediyne[9] as compared to the comparatively more stable 10-ring system present in calicheamicin, esperamicin and dynemicin. Thus, not only are these products of Nature complex but they are also unstable. It is this instability factor that has translated into a constant tussle against the inherent decomposition processes and as such has stretched the bounds of contemporary organic synthesis and the skills of the researcher at the bench. Right after the unraveling of structures of natural enediynes with a 9-membered ring system, the development of methodology for the synthesis of this key ring system has become an active area of research. Seminal contributions have appeared from the laboratories of Magnus[10] and Hirama.[11] Over the past few years, we have also been interested in the synthesis of a 9-membered enediyne system containing a nitrogen atom as a replacement for the nonenediynyl carbons. It may be mentioned that nitrogen containing cyclic enediynes have assumed significant importance in recent years.[9,12] The key step in the synthesis of such a system (10-membered or more) is the intramolecular *N*-alkylation of an acyclic substrate, which worked nicely to give the cyclic product in high yield.[13]

However, our attempt to extend the same methodology to prepare the 9-membered analogue **1** failed and we could only isolate a dimeric macrocyclic enediyne **2** *via* initial intermolecular *N*-alkylation (Fig. 1).[14] This change of reactivity was attributed to the stereoelectronic constraint imposed by the severely strained 9-membered enediynyl system. Recently we reported[15] the synthesis of two macrocyclic enediynes **4** and **5** (Fig. 2). Compound **5**, which has the ability to form a 10-membered ring *via* an intramolecular nucleophilic attack, was found to be unstable and thus underwent BC after the initial transannular reaction which the compound **4** cannot undergo because that would involve the formation of a 9-membered ring.

Encouraged by the reported success of the Magnus group in synthesizing a 9-membered carbocyclic enediyne[10] *via* intramolecular Nicholas reaction,[16] we envisioned that a similar complexation of the alkynyl functionality with cobalt carbonyl might facilitate the intramolecular attack by the nitrogen on to the activated propargylic centre. Proximity of the reacting centres due to bending of the otherwise linear C(sp)–C(sp)–C(sp^3) axis and the extra flexibility offered by the slight elongation of the triple bond after complexation[1,16] might also aid the cyclization. With the above logic, we went ahead with efforts to synthesize for the first time a 9-membered N-containing enediyne **14** in complexed form. Our success in doing so is reported herein.

In order to reach our target, the acyclic enediynyl alcohol **7** was first synthesized following our published procedures.[13,17] The synthesis includes sequential Sonogashira coupling[18] and functional group manipulation. Realizing that conversion of hydroxyl into a good leaving group might be difficult after cobalt complexation, compound **7** was first converted into a stable mesylate **8**, which was then treated with dicobalt octacarbonyl (2.2 eq).[19] The isolated bis-alkyne complex **9**[20] was subjected to ring closure conditions (K_2CO_3/DMF, 3 h) followed by

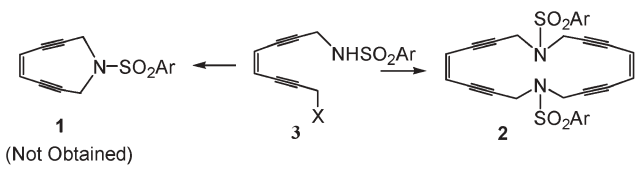

Fig. 1 Attempted synthesis of 9-membered azaenediyne by direct *N*-alkylation.

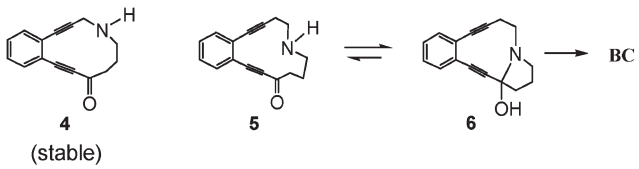

Fig. 2 Fate of macrocyclic enediynyl amino ketones.

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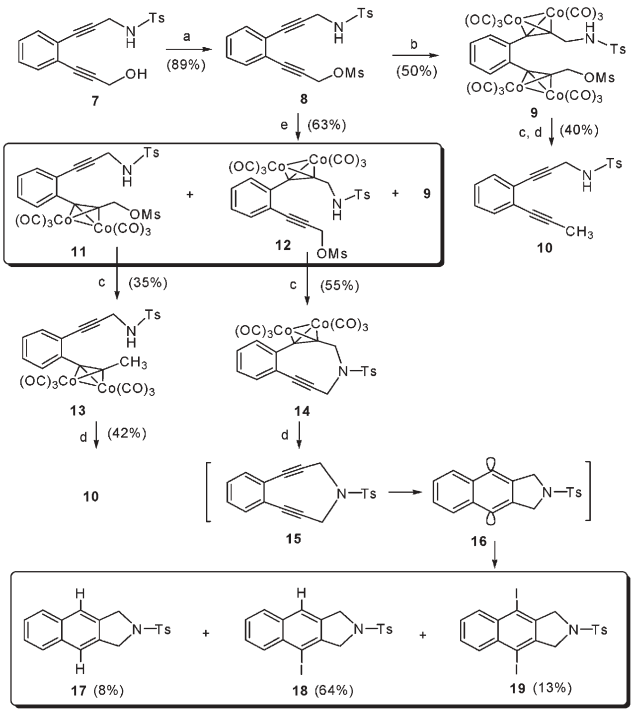
deprotection with iodine/THF.[1,21] A new product **10** was isolated by Si-gel chromatography (hexane–ethyl acetate 7 : 1 as eluent). Its ^{1}H-NMR spectrum[22] showed complete consumption of the mesylate as revealed by the absence of the three-proton singlet at δ 3.17; instead, a new 3-proton singlet appeared at δ 2.04, characteristic of an acetylenic methyl. The spectrum also contained a 2-proton doublet at δ 3.98, which was coupled to a triplet at δ 8.14; the latter signal got exchanged with D_2O. The characteristic peaks for the tosylate (aromatic protons as well as the aromatic methyl) were also present in the NMR spectrum. The compound was finally assigned the structure **10**, which was based on ^{13}C (four acetylenic carbons) as well as mass spectral data (Scheme 1). A similar observation was also reported by Magnus *et al.*[1] in their attempt to induce intramolecular Nicholas reaction.[16]

Having failed to induce the intramolecular alkylation, we realized that the propargylic carbon in the acetylenic arm containing the mesylate **8** becomes too strongly electrophilic after complexation and possibly abstracts hydride from the solvent. This prompted us to focus our attention on preparing compound **12** in which the acetylenic arm containing the sulfonamide moiety is complexed to cobalt (Scheme 1). Thus the mesylate **8** was treated with 1.1 equivalent of cobalt octacarbonyl for 5 min at 0 °C. This produced a mixture of complexes **9**, **11** and **12** in the ratio of ~ 1 : 1 : 2. Complexes **9** and **11**, which were inseparable in tlc, were subjected to an alkylation–decomplexation protocol which led to the reduced product **10** like the previous reaction. The other isomeric cobalt complex **12**,[22] to our delight, underwent smooth intramolecular alkylation to afford the target 9-membered enediyne **14**[22] in the complexed form. The reaction was actually much faster (40 min) as compared to the formation of the



Scheme 1 Synthesis and reactivity of 9-membered azaenediyne.

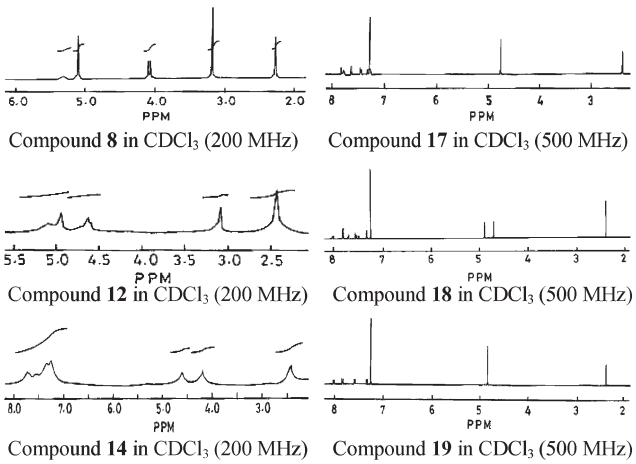


Fig. 3 ^{1}H NMR spectra.

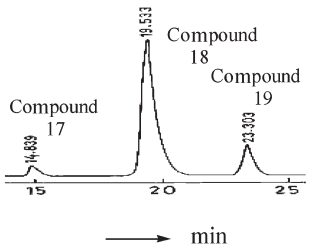


Fig. 4 HPLC trace of cyclized products using a C18 reverse phase column and MeOH as mobile phase.

10-membered ring system (3 h).[23] The ^{1}H NMR (Fig. 3) showed two separate two-proton broad singlets corresponding to the two NCH_2 protons. The methylene adjacent to the acetylene complexed to cobalt appeared downfield at δ 4.61 compared to the methylene adjacent to the uncomplexed acetylene, which resonated at δ 4.20. The mass spectrum showed a molecular ion peak at *m*/*z* 607. The peak at *m*/*z* 523 indicated the loss of three CO molecules. The formation of the 9-membered system was further confirmed by a decomplexation–BC protocol. Upon deprotection (I_2/THF, 0 °C, 1 h), the compound immediately underwent BC to produce three distinct products resulting from abstraction of either H (compound **17**) or iodine (compound **19**) or both (compound **18**) (ratio 3 : 5 : 25) (Scheme 1). All three cyclization products were separated by HPLC (Fig. 4) and their structures confirmed by NMR and mass spectral analysis.[22] From our observations, it can be concluded that for the formation of a 9-membered ring by intramolecular alkylation, proximity of the reacting centres is more important than the activation of the propargylic carbon with a good nucleofugal group like mesyl by complexation.

In conclusion, we have developed a synthetic route to an N-based 9-membered cyclic enediyne *via* a cobalt complexation route. The importance of the proximity of reacting centers rather than the activation of the propargyl centre has been shown. The facile BC of the 9-membered ring system which is similar to that of the carbocyclic counterpart under ambient conditions has also been successfully demonstrated.

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20 The bis alkyne complex **9**, after close inspection, was found to be contaminated with the reduced product **10** which implied that the reduction was occurring during the complexation step. The proportion of the mesylate and the reduced product was dependent upon the duration of the reaction. After 1 h, the bis cobalt complex is only that of the reduced product.

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22 Selected spectral data: For **10**: (200 MHz, [D_6]DMSO): δ = 8.14 (d, ^3J (H,H) = 6.0 Hz, 1H; NH), 7.72 (d, ^3J (H,H) = 8.2 Hz, 2H; aryl-H), 7.35–7.20 (m, 5H; aryl-H), 6.97 (m, 1H; aryl-H), 3.98 (d, ^3J (H,H) = 6.0 Hz, 2H; CH_2N), 2.29 (s, 3H; Ts-CH_3), 2.04 ppm (s, 3H; aliphatic-CH_3). For **12**: (200 MHz, $CDCl_3$): δ = 7.82 (bd, ^3J (H,H) = 8.0 Hz, 2H; aryl-H), 7.26–7.49 (6H, bm, aryl-H), 5.06 (bm, 1H; NH), 4.93 (bs, 2H; CH_2OMs), 4.61 (bm, 2H; CH_2NH), 3.08 (bs, 3H; Ms-CH_3), 2.43 ppm (bs, 3H; Ts-CH_3). For **14**: (200 MHz, $CDCl_3$): δ = 7.73–7.26 (bm, 8H; aryl-H), 4.61 (bs, 2H; $CoCCH_2N$), 4.20 (bs, 2H; $CCCH_2N$), 2.44 ppm (bs, 3H; Ts-CH_3); HRMS calcd for $C_{25}H_{15}O_8NSCo_2$ (MH^+) 607.9256, found 607.9559. For **17**: (500 MHz, $CDCl_3$): δ = 7.79 (d, ^3J (H,H) = 3.2 Hz, 2H; aryl-H), 7.76 (q, ^3J (H,H) = 1.2 Hz, 2H; aryl-H), 7.62 (s, 1H; aryl-H), 7.43 (q, ^3J (H,H) = 1.2 Hz, 2H; aryl-H), 7.31 (d, ^3J (H,H) = 3.2 Hz, 2H; aryl-H), 7.26 (s, 1H; aryl-H), 4.74 (s, 4H; CH_2NCH_2), 2.38 ppm (s, 3H; Ts-CH_3); HRMS calcd for $C_{19}H_{17}O_2NS$ (MH^+) 324.1054, found 324.1072. For **18**: (500 MHz, $CDCl_3$): δ = 8.02 (d, ^3J (H,H) = 3.1 Hz, 1H; aryl-H), 7.82 (d, ^3J (H,H) = 3.2 Hz, 2H; aryl-H), 7.70 (d, ^3J (H,H) = 3.1 Hz, 1H; aryl-H), 7.56–7.48 (m, 3H; aryl-H), 7.33 (d, ^3J (H,H) = 3.2 Hz, 2H; aryl-H), 4.88 (s, 2H; $CICCH_2N$), 4.07 (s, 2H; $CHCCH_2N$), 2.39 ppm (s, 3H; Ts-CH_3); HRMS calcd for $C_{19}H_{16}O_2NSI$ (MH^+) 450.0021, found 450.0034. For **19**: (500 MHz, $CDCl_3$): δ = 8.02 (q, ^3J (H,H) = 1.2 Hz, 2H; aryl-H), 7.83 (d, ^3J (H,H) = 3.2 Hz, 2H; aryl-H), 7.58 (q, ^3J (H,H) = 1.2 Hz, 2H; aryl-H), 7.34 (d, ^3J (H,H) = 3.2 Hz, 2H; aryl-H), 4.84 (s, 4H; CH_2NCH_2), 2.39 ppm (s, 3H; Ts-CH_3); HRMS calcd for $C_{19}H_{15}O_2NSI_2$ (MH^+) 575.8988, found 575.8964.

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