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The Synthesis and Reactivity of a Novel 10-Membered Azaenediyne

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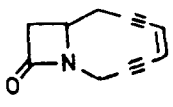
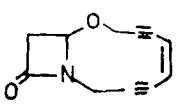
Abstract : Monocyclic azaenediyne **6** have been synthesized and has a half life of ~36 h in $CDCl_3$ at 30°C.

Enediyne antitumor antibiotics have been the subject of intense research in recent years[1]. Amongst the various synthetic designs, the azaenediynes have certain advantages over the carbon[2] or sulphur[3] containing enediynes. These include (i) the possible incorporation of side chains onto the nitrogen that may provide triggering mechanisms[4] for enediyne activation or act as DNA-binding appendages[5] and (ii) the possible enhancement of reactivity towards Bergman cyclization[6] for the azaenediynes as C-N bond (1.47 A°) is less than C-C (1.54 A°) or C-S (1.81 A°). Energy minimized calculation using DTMM (version 87) showed the distance between the reacting acetylenic carbon atoms to be 3.24 A° (Fig.1) which is within the critical range required for such molecules to undergo BC under ambient conditions.

Recently, we have described the synthesis of 1,4-β-lactam fused enediynes **1** and **2** and bis-propargyl sulphone[8] **3** and demonstated the ability of the β-lactam ring to act as a molecular lock[9] in stabilizing these systems. Banfi and Guanti[10] also synthesized a 3,4-β-lactam fused 10-membered enediyne **4** and showed that opening of the β-lactam ring triggered the Bergman cyclization. Since 1,4-fused systems resemble the natural bicyclic β-lactams, our model seemed more likely to be recognized by penicillin binding proteins including transpeptidase or β-lactamase compared to the 3,4-fused ones. However before we proceed further, we require a thorough knowledge of the reactivity profile of azaenediynes. In this communication we report for the first time the synthesis and reactivity of a novel 10-membered azaenediyne **6**.



1



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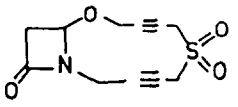

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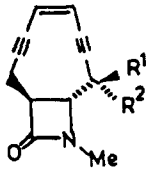
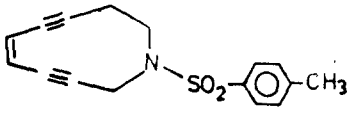
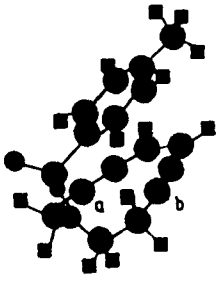


4 R^1= OH, R^2=H

5 R^1= H, R^2=OH

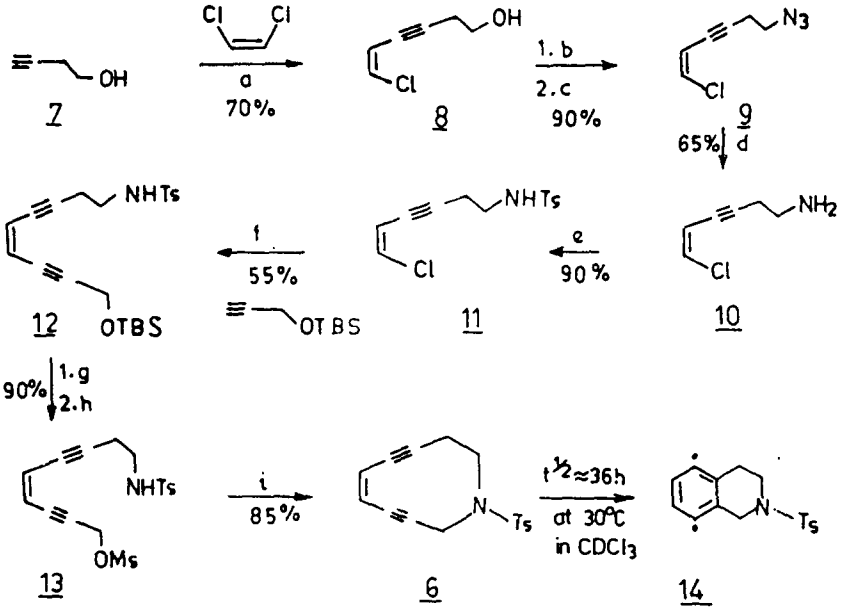


6



$d_{a,b}$ = 3.24 Å

Fig.1



a = $Pd(PPh_3)_2Cl_2$, n-$BuNH_2$, CuI, PhH. Ms = CH_3SO_2

b = MsCl, Et_3N, c = NaN_3, DMF, d = PPh_3, THF-H_2O Ts = CH_3-⟨⟩-SO_2

e = TsCl, DMAP, f = $Pd(PPh_3)_4$, n-$BuNH_2$, CuI, PhH. 45°C.

g = CsF, MeOH, h = MsCl, Et_3N, i = K_2CO_3, DMF

SCHEME 1

Our synthesis started with the mono coupling of cis-dichloroethylene with 3-butyn-1-ol (7) under a modified Stephen-Castro procedure[11] at room temperature. The resulting Z-vinyl chloride 8 was converted to the azide 9 via mesylation followed by displacement with NaN_3. Subsequent reduction with PPh_3 in $THF-H_2O$[12] produced the amine 10 which was isolated as the p-toluenesulphonamide 11. A second Pd (0) coupling of 11 with t-butyldimethylsilyl propargyl ether furnished the enediyne 12. Removal of the silyl protection with CsF in methanol followed by treatment with $MsCl/Et_3N$ afforded the mesylate 13. Final intramolecular ring closer was achieved in 85% yield by treating the mesylate 13 with K_2CO_3 in DMF at room temperature. The entire synthesis is shown in Scheme - 1.

The enediyne 6 is sufficiently stable at room temperature which enabled us to record its ^1H, ^{13}C, DEPT and correlation spectra. However it slowly undergoes Bergman cyclization in the NMR tube in $CDCl_3$ at the room temperature of 30°C (half life ~36h). This is revealed by the disappearance of the characteristic peaks of 6 at δ 5.84 (CH=CH), 4.09 (≡-CH_2N), 3.53 (NCH_2CH_2) and 2.77 (NCH_2CH_2) and appearance of new peaks at δ 4.22, 3.88 and 2.95 corresponding to the tetrahydroisoquinoline system. The Differential Scanning Calorimetric (DSC) measurement[13] showed the onset temperature for Bergman cyclization in neat liquid state to be ~50°C. On the other hand, the acyclic enediyne 13 expectedly showed exothermic rise at ~90°C in the DSC. The mass spectrum of 6 is consistent with its structure[14].

In conclusion, we have demonstrated that 10-membered azaenediyne is an ideal candidate for further elaboration into a suitable anticancer drug. Current studies are aimed towards incorporating novel enzyme-triggerable appendages onto the N.

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14. Selected spectra data for 6 : δ_H ($CDCl_3$, 200 MHz) 7.73 (2H,d,J=8.11 Hz), 7.30 (2H,d,J=8.11 Hz), 5.84 (2H, *bs*), 4.09 (2H, *s*); 3.53 (2H, t, J=5.0 Hz), 2.77 (2H, t, J=5.0 Hz), 2.45 (3H, *s*) δc ($CDCl_3$, 50 MHz) 143.46, 136.11, 129.75, 127.39, 124.48, 122.18, 96.54, 94.39, 89.53, 83.82, 51.15, 42.16, 22.45, 21.58. Mass (El, $CHCl_3$) 321 ($MHCl^+$), 287 (MH_2^+), 286 (MH^+), 285 (M^+), 155 ($CH_3C_6H_4SO_2^+$), 130 (M^+-$CH_3C_6H_4SO_2$), 104, 102.

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