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SYNTHESIS OF A SULFUR-CONTAINING 10-MEMBERED ENEDIYNE MODEL COMPOUND RELATED TO THE ESPERAMICIN/CALICHEAMICIN/DYNEMICIN AGLYCONES

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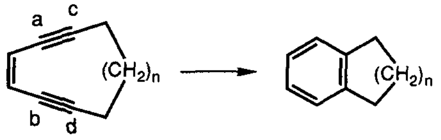
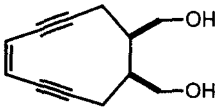
Summary: Synthesis of the 10-membered heterocyclic enediyne **4** and its conversion to the benzenoid adduct **10** via the Bergman reaction are described.

The DNA damaging antitumor antibiotics calicheamicins,[1] esperamicins,[2] dynemicin A,[3] and neocarzinostatin[4] have attracted considerable attention due to their very high biological activity. Except for neocarzinostatin, the mechanism of action of these antibiotics is believed to be due to the generation of a phenylene biradical which is responsible for DNA cleavage.[1,2,5] The reactive biradical intermediate arises thermally from a conjugated enediyne moiety by the Bergman reaction.[6] During the past three years several synthetic investigations of the model compounds[7] as well as total synthetic effort[8] of the title antibiotics have been reported. These studies have stimulated investigations aimed at understanding factors that control biradical formation.[9] Nicolaou and coworkers have proposed that a spontaneous conversion of an enediyne system (e.g. **1** → **2**) takes place only over a crucial interatomic cd distance of less than 3.31 - 3.20 Å as suggested by MM2 calculations and the synthesis of **1**.[9b] The same authors showed that the synthetic enediyne **3** (calculated cd distance is 3.25 Å) was sufficiently stable for isolation, but cyclized with a half life of 11.8 h at 37°C and caused scission of double-stranded DNA.[9d] Here we report the synthesis of a novel thioenediyne system **4** that is relatively stable, crystalline, and undergoes similar transformation by heating to a benzenoid adduct **10** in 58% yield.[10]



1 **2**



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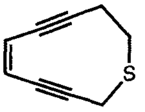

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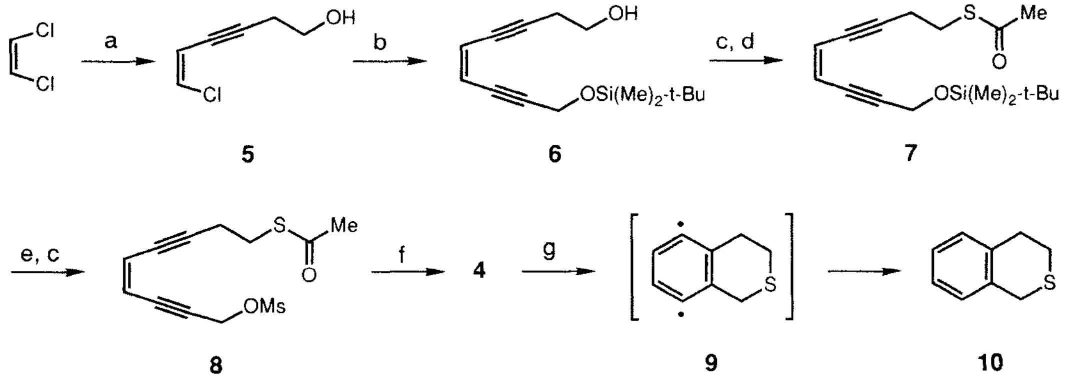

a) 3-Butyn-1-ol, Pd(0)$(Ph_3P)_4$, CuI, n-BuNH_2, PhH, 25°, 4h. b) HC≡CCH_2OTBS, Pd(0)$(Ph_3P)_4$, CuI, n-BuNH_2, PhH, 25°, 12h. c) MsCl, NEt_3, CH_2Cl_2, 0°, 0.5h. d) KSCOCH_3, acetone, reflux, 2h. e) 1N HCl, acetone, 25°, 2h. f) NaOMe, MeOH, 25°, 36h. g) 1,4-Cyclohexadiene, PhH, 80°, 18h.

Monocoupling of dichloroethylene with 3-butyn-1-ol proceeded by application of the standard Stephens-Castro procedure[11] at room temperature to provide the (Z)-vinyl chloride **5** in 90% yield. A second coupling of **5** with *tert*-butyldimethylsilyl propargyl ether furnished the enediyne **6** in 87% yield. Sulfur was introduced by mesylation of **6** followed by nucleophilic substitution with potassium thioacetate to provide **7** in 81% overall yield from **6**. Desilylation of **7** under acid conditions and subsequent mesylation of the resulting alcohol afforded the thioacetate **8** in 87% yield. Simultaneous slow addition of methanolic solutions of **8** (7.4 mmol) and sodium methoxide (7.4 mmol) via a syringe pump into MeOH (500 ml) over a period of 36 h at room temperature gave the cyclic enediyne **4** in 61% yield. Purification of **4** by column chromatography furnished the pure compound in crystalline form (mp 59 - 61°C, from *iso*-PrOH), which provided us the opportunity to examine its structure by X-ray crystallographic analysis. The results are shown in Figure 1.

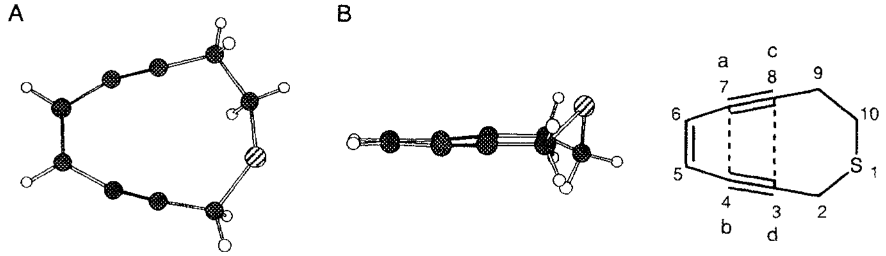

Figure 1. The molecular structure **4**: A, top view; B, side view.

The distance between carbons C3 and C8 (cd distance) was found to be 3.30 Å,[13] which is very close to our calculated values for **4** by MM2[10] and falls in the critical range (3.31 - 3.20 Å) for ring closure proposed by Nicolaou.[9b] It is worthnoting that the bond angles C3-C4-C5 and C6-C7-C8 (a and b carbons) in **4** are substantially bent, 165° and 163°, respectively, whereas those of C2-C3-C4 and C7-C8-C9 (c and d carbons) are almost linear, 176°. This finding (θ a,b < θ c,d) is the reverse of what was reported for bicyclic 10-membered enediyne antibiotics[14] and their model compounds[7c,h,k] as shown for **11**[7c] in Figure 2.

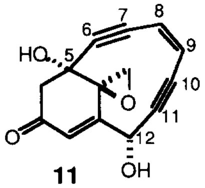

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Figure 2. Synthetic enediyne model. [7c]
Angles: C5-C6-C7 = 165.7°; C6-C7-C8 = 169.6°
C9-C10-C11 = 168.1°; C10-C11-C12 = 165.4°.

Above data strongly suggested that cd bond formation is feasible. Indeed, when the enediyne **4** was heated in benzene (2 mM solution) in the presence of 1,4-cyclohexadiene at 80°C for 18 h, isothiochromane **10** was isolated in 58% yield. Structure proof for this compound was derived by a synthesis according to literature procedure.[15,16]

Current efforts are aimed at designing of **4** that would undergo cyclization at body temperature and at useful rates to cause DNA cleavage.

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10. Molecular mechanics calculations (MM2) indicated that the cd distance of **4** was 3.31Å. Parameters used about sulfur atom were corrected so as the results reproduce the known geometrical structure of dimethylsulfide.
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12. Compound **4**, crystallized in monoclinic space group ($P2_1/c$) with a = 12.408 (2)Å, b = 4.589 (3)Å, c = 13.724 (2)Å, β = 94.62 (1)°, z = 4, Dc = 1.264g/cm^3. All measurements were made on a Rigaku AFC5S diffractometer with graphite monochromated Mokα radiation. The data were collected using the ω - 2θ scan technique to a maximum 2θ value of 50.0°. Of the 1645 reflections which were collected, 1570 were unique. The intensities of three representative reflections which were measured after every 150 reflections declined during X-ray exposure. A linear correction factor was applied to the data to account for this phenomena. The data were corrected for Lorents and polarization effects. The structure was solved by direct methods [TEXSAN - TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985)]. The resulting E map revealed the positions of all non-H atoms. All H atom positions were calculated after anisotropic refinement of the non-H atoms. The refinement of atomic parameters was carried out by a full-matrix least-squares refinement. Thermal parameters were refined anisotropically for all non-H atoms. Convergence on 401 reflections [$I > 3\sigma(I)$] and 91 parameters resulted in R = 0.077 (Rw = 0.078).
13. Found values for geometrical parameters of compound **4** : Bond angles (°), S1-C2-C3 = 113.3(9), C2-C3-C4 = 176(2), C3-C4-C5 = 165(2), C4-C5-C6 = 120(1), C5-C6-C7 = 119(1), C6-C7-C8 = 163(2), C7-C8-C9 = 176(2), C8-C9-C10 = 114(1), C9-C10-S1 = 117(1), C10-S1-C2 = 102.6(7); Bond lengths (Å), S1-C2 = 1.85(1), C2-C3 = 1.43(2), C3-C4 = 1.16(2), C4-C5 = 1.42(2), C5-C6 = 1.33(2), C6-C7 = 1.43(2), C7-C8 = 1.20(2), C8-C9 = 1.42(2), C9-C10 = 1.52(2), C10-S1 = 1.82(1), C3-C8 = 3.30(2), C4-C7 = 2.73(2).
14. X-Ray crystallographic analysis of Dynemicin A was recently reported and was shown that there were two independant molecules with different conformations in the asymmetric unit. One of them has the same tendency of bond angles (θ a,b < θ c,d) as that for **4**, whereas the other has the reverse (θ a,b > θ c,d); see, M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G.D. VanDuyne, and J. Clardy, *J. Amer. Chem. Soc.*, **112**, 3715 (1990).
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16. Selected data, **5**: IR ($CHCl_3$) 3340, 1800, 1340, 1060, and 850 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$): δ 2.15 (1H, br), 2.67 (2H, dt, J=6.0 and 1.8), 3.79 (2H, d, J=6.0), 5.88 (1H, dd, J=7.4 and 1.8), and 6.35 (1H, d, J=7.4). **6**: IR ($CHCl_3$) 3350 and 2220 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 0.15 (6H, s), 0.92 (9H, s). 2.58 (1H, br), 2.70 (2H, t, J=6.0), 3.80 (2H, t, J=6.0) 4.50 (2H, s), and 5.80 (2H, s). **7**: IR ($CHCl_3$) 2220, 1700, 1100, and 840 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$): δ 0.15 (6H, s), 0.92 (9H, s), 2.35 (3H, s), 2.67 (2H, dt, J=6.9 and 1.0), 3.07 (2H, t, J=6.9), 4.35 (2H, d, J=1.0), and 5.80 (2H, s). **8**: IR ($CHCl_3$) 2230, 1690, 1350, and 1190 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$): δ 2.36 (3H, s), 2.68 (2H, dt, J=7.1 and 2.0), 3.07 (2H, t, J=7.1), 3.18 (3H, s), and 5.07 (2H, d, J=2.0). **9**: mp 59~61°C; IR ($CHCl_3$) 2180 and 1655 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.66 (2H, t, J=5.5), 3.14 ~ 3.19 (4H, m), 3.46 (2H, s), and 5.80 ~ 5.90 (2H, m); ^{13}C NMR (50MHz, $CDCl_3$) δ 23.0, 23.8, 34.9, 82.3, 83.9, 99.2, 101.4, 122.5, and 124.0; CI-MS (*iso*-butane) (m/z) 149 (M^+ + 1).

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