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SYNTHETIC STUDIES ON THE ESPERAMICIN/CALICHEAMICIN ANTITUMOR ANTIBIOTICS. CONJUGATE ADDITION OF THIOL TO INITIATE 1,4-DIYL FORMATION

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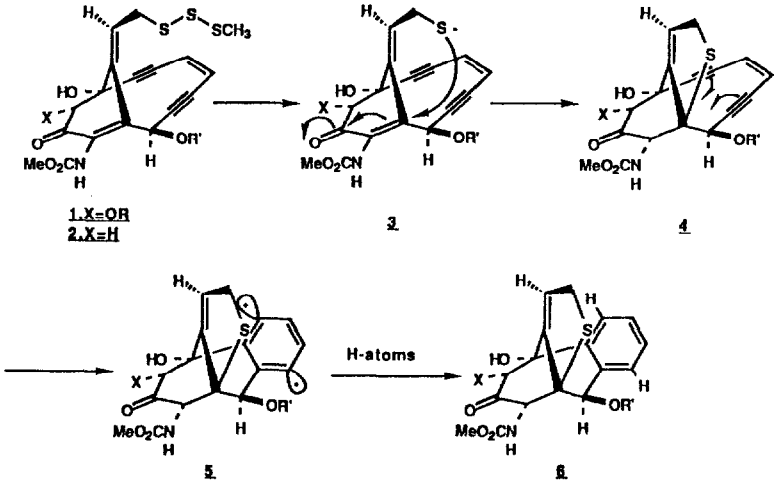
Abstract: Intermolecular thiol addition to the bicyclo[7.3.1]diynenone **9** allows access to the C-1 sp^3 hybridized derivative **9a**, which in turn undergoes cycloaromatization to give the bicyclo[3.3.1]system **10.**

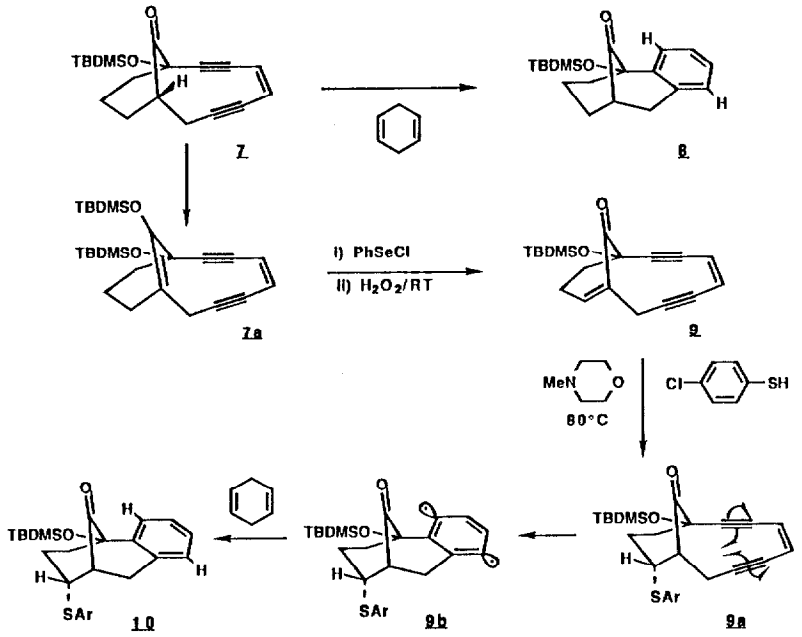
The recent discovery and structural elucidation of the potent antitumor antibiotics esperamicin **1** and its 4-deoxy analog calicheamicin **2**[2] has generated immediate interest in their synthesis and mechanism of action.[3] It has been proposed that a bioreductive process produces the allylic sulfide **3**, which undergoes intramolecular conjugate addition to C-1 to give **4** (C-1 now sp^3 hybridized), thus allowing access to a [3.3.1]type transition state leading to the putative 1,4-diyl **5**.[2] Hydrogen atom abstraction affords the aromatic adduct **6**. In this letter we show that it is necessary to change the hybridization at C-1 from trigonal to tetrahedral by conjugate addition in order to provide an energetically reasonable route to the 1,4-diyl.[4]

We have shown that the saturated ketone **7** cyclizes to the [3.3.1]system **8** when heated at 80°C for 48h in 1,4-cyclohexadiene.[3] Treatment of **7** with KHMDS/TBDMSOT*f* gave the bridgehead enol ether **7a** (89%). It should be noted that the C-1 hydrogen atom in **7** is axial and therefore correctly aligned for ready enolization. When **7a** was treated with phenylselenenyl chloride followed by H_2O_2 the bridgehead enone **9** was isolated in 83% yield.

The α,β-unsaturated ketone **9** is a stable compound relative to **7**. Heating a mixture of **7** and **9** in 1,4-cyclohexadiene at 80°C converted **7** into **8**, but left **9** unchanged. However, heating **9** at 110°C in 1,4-cyclohexadiene in the presence of 4-chlorothiophenol and *N*-methylmorpholine gave the aromatized adduct **10** (50%). Decoupling of the C-3 hydrogens allows measurement of the H-1 to H-2 coupling constant (2Hz), and the indicated nOe's demonstrate that the 4-chlorothiophenol group is in an axial configuration.[5]



SCHEME 1



This result convincingly demonstrates that the formation of the putative 1,4-diyl can be triggered intermolecularly by thiol addition to C-2, and provides an alternative triggering device that may be exploited in the design of so-called rational analogs.[6]

References and Footnotes:

1. Correspondence to the author should be addressed: Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712.
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3. P. Magnus and P.A. Carter, *J. Am. Chem. Soc.*,1988, *110*, 1626. P. Magnus, R.T. Lewis and J.C. Huffman, *J. Am. Chem. Soc.*, 1988, *110*, 6921. S.J. Danishefsky, N.B. Mantlo and D.S. Yamashita, *J. Am. Chem. Soc.*, 1988, *110*, 6890. K.C. Nicolaou, G. Zuccarello, Y. Ogawa, E.J. Schweiger, and T. Kumazawa, *J. Am. Chem. Soc.*, 1988, *110*, 4866. A.S. Kende and C.A. Smith, *Tetrahedron Lett.*, 1988, *29*, 4217.
4. The prototype 1,4-diyl system was studied by Bergman: R.G. Bergman, *Acc. Chem. Res.*, 1973, *6*, 25.
5. Spectral data for **10**: ^{1}H NMR (500MHz, $CDCl_3$) δ 0.24(3H, s), 0.29(3H, s), 1.00(9H, s), 1.75-1.93(3H, m), 2.54(1H, m), 2.96(1H, m), 3.09(1H, d, J = 17.8Hz), 3.50(1H, dd, J's = 7.7 and 17.8Hz), 3.73(1H, m), 7.04(1H, dd, J's = 0.8 and 7.6Hz), 7.21(1H, dt, J's = 1.4 and 7.4Hz), 7.28(1H, m), 7.32(2H, d, J = 7Hz), 7.41(2H, d, J = 8.7Hz), 7.60(1H, dd, J's = 1.3 and 7.9Hz). ^{13}C (125MHz, $CDCl_3$) δ -2.28(q), -2.32(q), 18.91(s), 26.29(q), 25.04(t), 38.30(t), 41.20(t), 49.98(d), 55.12(d), 80.30(s), 127.52(d), 129.40(d), 131.80(s), 133.23(s), 134.26(s), 134.94(d), 142.90(s), 208.81(s).

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