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# SYNTHETIC STUDIES ON THE ESPERAMICIN/CALICHEAMICIN ANTITUMOR ANTIBIOTICS. SELENIUM DIOXIDE OXIDATION OF A BRIDGEHEAD TRIALKYLSILYL ENOL ETHER

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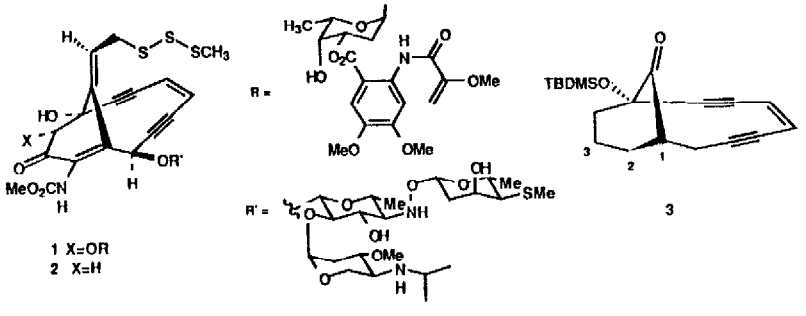
**Abstract:** Oxidation of the bridgehead *t*-butyldimethylsilyl enol ether **4** with selenium dioxide at 25°C produces the stable hemihydrate **6**, which on further oxidation gave the allylic alcohol **8**.

The strategy we have adopted for the synthesis of the aglycone portion of the potent antitumor agents esperamicin $A_2$/calicheamicin $\gamma_1$ **1/2** allows systematic exploration of the intrinsic chemistry of the bicyclo[7.3.1]diynene core.[1] Multigram quantities of the ketone **3** are available and its conversion into more highly functionalized analogs is being studied in order to define, at least to some extent, what transformations can be carried out on the intact bicyclo[7.3.1]diynene system.[2] Here we describe some unexpected results involving selenium dioxide oxidations. On the basis of the Sharpless[3] mechanism for the allylic oxidation of alkenes using selenium dioxide it can be predicted that the *t*-butyldimethylsilyl enol ether derived from **3**, namely **4**, would give the alcohol **5**.[4]




Treatment of the ketone **3** with *t*-$BuMe_2SiOTf$/KHMDS/THF at -78°C for 0.5h gave the derived enol ether **4** (≥90%). When **4** was treated with Se $O_2$(1.1 equiv)/dioxane/25°C for 3h the major isolated product is the hemiketal **6** (53%)[3] along with the enone **7** (14%). The hemiketal **6** proved to be a surprisingly stable adduct, and crystals suitable for single crystal X-ray crystallography could be grown from aqueous ethanol (FIGURE 1 shows an ORTEP representation).[7] A plausible mechanistic explanation for the observed products **6/7** is shown in Scheme 1. Electrophilic substitution by $SeO_2$ at the bridgehead (C-1) leads to **4a**, which can close to the selenooxetane **4b** only when the cyclohexane ring is in a boat conformation. The selenooxetane **4b** can collapse by elimination to give **6/7**.

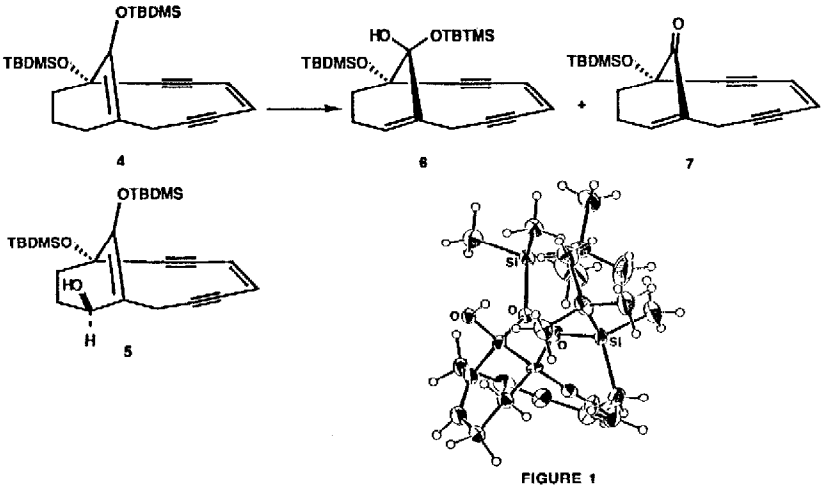
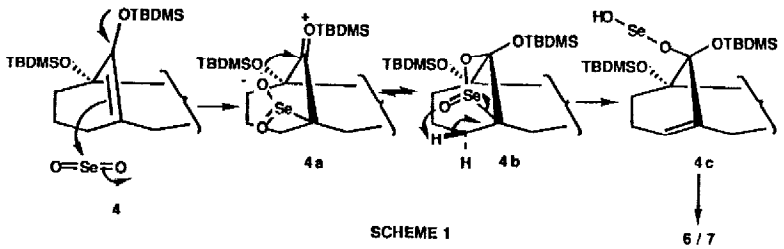
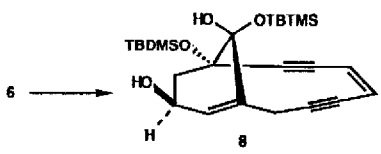



FIGURE 1




SCHEME 1

Further exposure of **6** to $SeO_2$/dioxane/40°-50°C for 90h gave the crystalline diol **8** (52%)[7] along with starting material (23%). The structure and relative stereochemistry of **8** was confirmed by single crystal X-ray crystallography (*FIGURE 2*).[8]



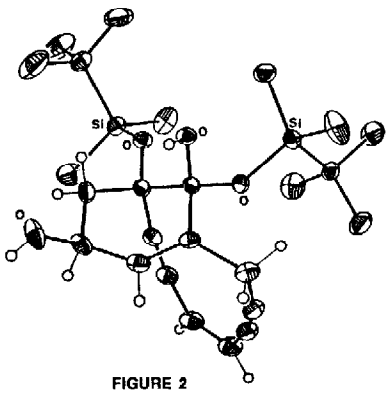
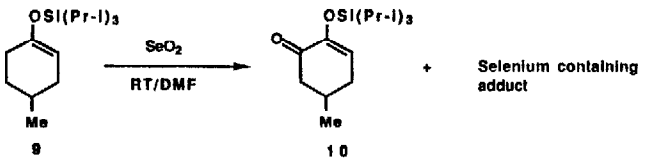




FIGURE 2



Since there are no reports of the treatment of simple trialkylsilyl enol ethers with selenium dioxide we briefly examined the reaction of **9**. Treatment of **9** with $SeO_2$/DMF/25°Cgave the α-diketone monotriisopropylsilyl enol ether **10** (40%) along with a selenium containing adduct whose structure has yet to be completely established. We are currently examining the scope and mechanism of this potentially useful transformation, and in particular, questions concerning regiochemistry.

In summary, the direct oxidation of the bridgehead trialkylsilyl enol ether **4** with selenium dioxide provides immediate access to the derivative **8** where C-1, C-2 and C-3 of the bicyclo[7.3.1]diynene have been oxidized.[9]

**References and Footnotes:**


1. J. Golik, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, and T. W. Doyle, *J. Am. Chem. Soc.*, 1987, *109*, 3462. M. D. Lee, T. S. Dunne, M. M. Seigel, C. C. Chang, G. O. Morton, and D. B. Borders, *J. Am. Chem. Soc.*, 1987, *109*, 3464. M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Seigel, G. O. Morton, W. J. McGahren, and D. B. Borders, *J. Am. Chem. Soc.*, 1987, *109*, 3466.

2. For the synthesis of **3**, see: P. Magnus, R. T. Lewis, and J. C. Huffman, *J. Am. Chem. Soc.*, 1988, *110*, 6910. For other synthetic studies, see: P. Magnus and P. A. Carter, *J. Am. Chem. Soc.*, 1988, *110*, 1626: 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. S. L. Schreiber and L. L. Kiessling, *Tetrahedron Lett.*, 1989, 433: K. Tomioka, H. Fujita, and K. Koga, *Tetrahedron Lett.*, 1989, 851.

3. K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, 1972, *94*, 7154; D. Arigoni, A. Vasella, K. B. Sharpless and H. P. Jensen, *J. Am. Chem. Soc.*, 1973, *95*, 7917. H. P. Jensen and K. B. Sharpless, *J. Org. Chem.*, 1975, *40*, 264. For the oxidation of ketones to α-diketones, see: K. B. Sharpless and K. M. Gordon, *J. Am. Chem. Soc.*, 1976, *98* 300.

4. Trialkylsilyl enol ethers have been treated with a wide range of oxidizing agents, see: W. P. Weber, "Silicon Reagents for Organic Synthesis", Springer-Verlag, New York, 1983, p.228-233, but there are no reports of $SeO_2$ oxidation.

5. Data for **6** m.p. 114°-116°C (ethanol-water). $^1$H NMR (500MHz, $CDCl_3$) δ 0.19(3H, s), 0.21(3H, s), 0.24(3H, s), 0.34(3H, s), 0.93(9H, s), 0.94(9H, s), 2.02-2.20(3H, m), 2.34-2.41(1H, m), 2.98(1H, dt, J's = 16.8 and 0.7Hz), 3.30(1H, d, J = 16.8Hz), 3.87(1H, s), 5.71(1H, ddd, J's = 9.53, 0.90 and 0.70Hz), 5.76(1H, dt, J's = 9.5 and 0.8Hz), 5.82(1H, dd, J's = 5.4 and 2.9Hz). $^{13}$C NMR -2.88, -2.61, -2.45, -0.31, 18.08, 18.24, 23.10, 25.61, 26.06, 26.32, 34.56, 76.21, 85.34, 85.91, 98.39, 99.34, 103.78, 121.52, 123.18, 129.30 and 140.04. HRMS $C_{25}H_{40}O_3Si_2$ requires $M^+$ 444.2516. Found 444.2481. Stable hydrates of bridged ketones have been

isolated, the most recent being: J. Bonjoch, J. Quirante, I. Serret and J. Bosch, *Tetrahedron Lett.*, 1989, 1861 and references cited therein.

6. The complete details of the single-crystal X-ray structural determination of **6** may be obtained from Dr. John C. Huffman, Molecular Structure Center, Indiana University, Bloomington, Indiana 47405. Request structure report No. 88199.

7. Data for **8** m.p. 143°-145°C (dioxane-water). $^1$H NMR (300MHz, $CDCl_3$) δ 0.17(3H, s), 0.20(3H, s), 0.23(3H, s), 0.34(3H, s), 0.918(9H, s), 0.920(9H, s), 1.60(1H, bs), 2.10(1H, dd, J's = 14.4 and 4.5Hz), 2.64(1H, dd, J = 14.4 and 7.6Hz), 3.01(1H, dd, J's = 16.6 and 1.4Hz), 3.32(1H, d, J = 16.6Hz), 4.16(1H, ddd, J's = 7.6, 5.9 and 4.5Hz), 4.20(1H, bs), 5.71(1H, dd, J's = 9.5 and 1.4Hz), 5.76(1H, d, J = 9.5Hz).

8. The single-crystal X-ray structural determination of **8** was carried out by Dr. Vince Lynch, Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712.

9. The National Institutes of Health are thanked for their financial support. Dr. Benjamin B. Mugrage is thanked for carrying out the conversion of **9** into **10**.

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