New Synthetic Technology for the Construction of Oxocenes

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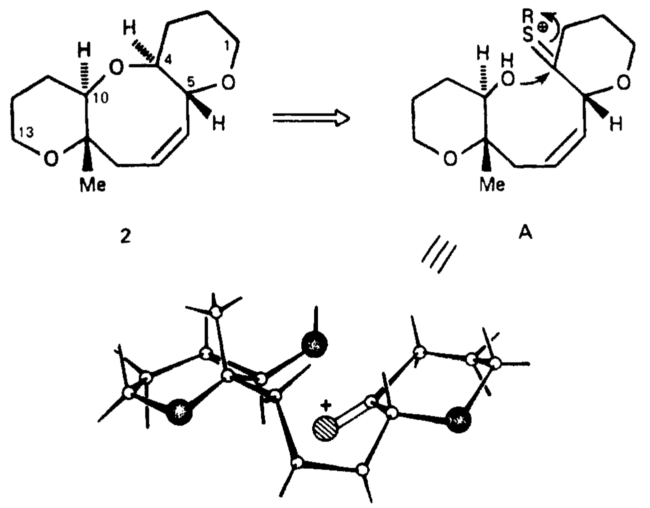
The oxocene and oxocane ring systems are often-encountered structural units in naturally occurring substances such as the brevetoxins[1,2] and other marine natural products.[3] Due to increasing interest in these bioactive molecules and the well-recognized problems in building midsize rings, the synthesis of such systems becomes a challenging synthetic objective. In this paper we report new, practical, and efficient synthetic technologies for the construction and chemical manipulation of oxocenes[4] as part of polycyclic frameworks similar to brevetoxin B[5] and related compounds.

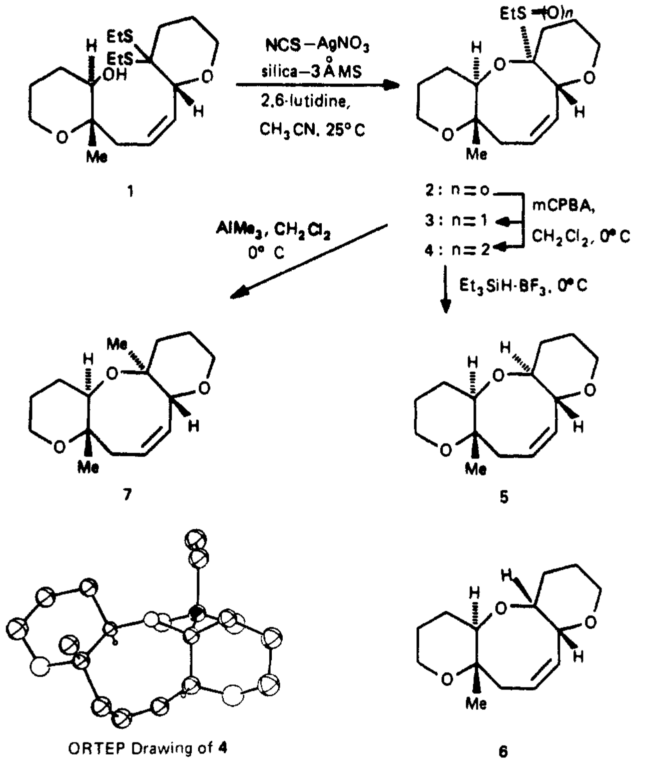
Because of the severe difficulties involved in synthesizing medium-size rings by cyclization reactions attributed to entropic disfavor, angle deformations, bond opposition forces, and transannular interactions,[6] our design for an entry into these systems postulated intramolecular capture of a reactive intermediate such as the sulfonium[7] ion represented by structure A (Scheme I) or its equivalent. Computer-generated and Dreiding molecular models indicated that a relatively strain-free conformation could be realized in which the p-orbital of the electrophilic sp^2 carbon of A is appropriately oriented for intramolecular capture by the nearby nucleophilic oxygen, giving rise to the fused oxocene system **2** (Scheme I). The attractiveness of such a method is enhanced when one considers the ease by which sulfonium ions (or their equivalents) can be generated from diothioketals and the synthetically rich chemistry of the expected thio group.

To test the feasibility of this strategy, a potential progenitor to intermediate A, hydroxy dithioketal **1** (Scheme II) was synthesized.[8] Exposure of **1** to *N*-chlorosuccinimide (NCS, 1.1 equiv) in acetonitrile (CH_3CN) and in the presence of 2,6-lutidine (2.0 equiv), silver nitrate ($AgNO_3$, 1.1 equiv),[9] molecular sieves (MS 3A), and silica gel[10] at 25 °C led, in 5 min, to a 95% yield of **2**. Oxidation of **2** with 1.1 equiv of mCPBA (CH_2Cl_2, 0 °C) led to sulfoxide **3** (95%, single stereoisomer), whereas further oxidation (1.1 equiv of additional *m*CPBA, CH_2Cl_2, 0 °C) furnished sulfone **4** (92%) as colorless rods, mp 97–98.5 °C (ether–hexane). An X-ray crystallographic analysis[11] confirmed the expected stereochemistry for this compound and its pregenitors **3** and **2** (ORTEP plot, Scheme II).

Scheme I

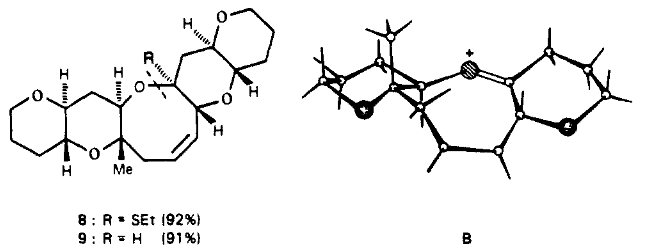


Scheme II



ORTEP Drawing of 4

Chart I



In designing the present technology for the construction of oxocenes, we were projecting that replacement of the remaining sulfur group, via homo[12] or heterolytic[13] carbon–sulfur bond clevage, would lead to the desired trans ring juncture. It was

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(1) Lin. Y. Y.; Risk, M.; Ray, M. S.; Van Engen, D.; Clardy, J.; Golik. J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.

(2) Shimizu, Y.; Chou, H.-N.; Bando, H.; Van Duyne, G.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 514.

(3) Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1.

(4) For a recent and elegant method for the synthesis and elaboration of oxocenones, see: Schreiber, L. S.; Kelly, S. E. *Tetrahedron Lett.* **1984**, 1757.

(5) For ring-selective synthetic technology for the construction of the tetrahydropyran systems of brevetoxin B and the synthesis of the ABC ring system of this molecule see: Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.: Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359.

(6) Eliel, E. L. *Stereochemistry of Carbon Compounds*, McGraw-Hill: New York, 1962: Chapter 2. Sicher, J. *Prog. Stereochem.* **1982**, *3*, 202.

(7) For previous intramolecular cyclizations involving dithioketals, see. C–C bond formation: Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *1078* 719. C–O bond formation: Hanessian, S. K.; Sato, K., Liak, T. J.; Danh, N.; Dixit, D.; Cheney, B. V. *J. Am. Chem. Soc.* **1984**, *106*, 6114.

(8) The hydroxy dithioketals utilized in this work were synthesized from the corresponding dithioketal aldehyde and the *tert*-butyldimethylsilyloxyylide. These intermediates are in turn prepared by standard chemistry and the methods described in ref 5.

(9) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(10) The addition of silica (Kieselgel 60, 230–400 mesh) leads to ca. 3–5-fold rate increase of cyclization, presumably due to absorption resulting in breaking up a tight ion pair and/or conformational change in favor of ring closure.

(11) We thank Dr. Patrick J. Carroll of this department for his assistance in solving this X-ray structure.

(12) Treatment of **2** with *n*-Bu_3SnH–AIBN (toluene, Δ) led to **5** in 85% yield but only in ca. 60% conversion. See: Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984**, *25*, 1349.

(13) For the use of sulfones as leaving groups in the presence of Lewis acids, see: Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260.

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expected that oxidation to the sulfoxide and/or sulfone to enhance leaving and complexing ability[13] would facilitate such processes, particularly in the presence of the neighboring ring oxygen lone pair of electrons. These expectations were fully realized and led to a number of new and highly effective transformations as shown in Scheme II. Thus, treatment of either sulfoxide **3** or sulfone **4**[14] with $BF_3 \cdot Et_2O$ (1.0 equiv) in the presence of excess Et_3SiH (5.0 equiv) in CH_2Cl_2 at 0 °C (2 h) led in excellent yield (>90%) to the 4,5-trans tricyclic system **5**.[15] Trimethylaluminum ($AlMe_3$, 2.0 equiv) reacted with either **3** or **4**[15] with equal ease and effectiveness (CH_2Cl_2 0–25 °C, 2 h) to afford compound **7**[16] in 92% yield. The observed retention of stereochemistry in these reactions implicates oxonium species B (Chart I) as an intermediate. Molecular models demonstrate severe nonbonding interactions of the incoming nucleophile with 8β-H and 9-Me, as well as torsional strain[17] with 3β-H and 5-H in the transition state leading to the 4,5-cis oxocene by β-attack on B. In contrast, α-attack may proceed via a significantly less congested transition state leading to the observed 4,5-trans product.[18] Interestingly, DIBAL, a stronger hydride donor, reacted rapidly (−78 °C, 15 min) with sulfone **4** to afford a mixture of **5** and its cis isomer **6**[15] in ca. 1:1 ratio (90% yield), presumably by a dual pathway involving direct S_N2-type displacement of the SO_2Et group or attack on a tight ion pair (inversion) and via oxonium species B (retention).

The versatility and usefulness of this technology was tested in a number of more demanding situations involving polycyclic systems of higher rigidity such as the one depicted in Chart I.[19] Thus the oxocene-containing system **8** was constructed from the corresponding hydroxyl dithioketal[8] (retrosynthetically derived by opening the ring at the dotted line, Chart I) according to the above procedure and in high yield. Whereas formation of **2** was complete in less than 5 min at 0 °C (20 min without silica),[10] the cyclization leading to **8** required 30 min (2 h without silica)[10] indicating a more highly strained eight-membered ring transition state for the later system as anticipated. Finally, oxidation (2.2 equiv, mCPBA) followed by in situ reduction (Et_2SiH–BF_3) resulted in compound **9** in excellent yield (see Chart I).[15]

The chemistry described above sets the stage for the construction of the complex naturally occurring brevetoxins and simple structural analogues of them for neurobiological investigations. It may also prove useful in other areas of organic synthesis including glycoside and medium- and large-ring construction.[20]

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Supplementary Material Available: Listing of ^1H NMR data for compounds **1**, **2**, and **5–13**, ^{13}C NMR data for compounds **2** and **5**, experimental section for compounds **2**, **4**, and **5–7**, and X-ray crystallographic analysis data for **4** (11 pages). Ordering information is given on any current masthead page.

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[14] This transformation is more conveniently carried out directly from sulfide **2** without isolation of the intermediates **3** and/or **4** in one pot and with equal efficiency.

[15] Stereochemical assignments were made on the basis of ^1H decoupling and NOE studies. The trans compounds **5**, **9**, **11**,[19] and **13** exhibited a *J* value for H-4,5 of ca. 9.2 Hz while the corresponding value for the cis compound **6** was 3.7 Hz.

[16] The syn relationship of the C-4 methyl and the C-10 proton was assigned on the basis of NOE experiments. Thus, irradiation of the C-4 methyl (δ 1.22, C_6D_6, 50.3 MHz) resulted in a 30% enhancement of the C-10 proton signal (δ 3.91).

[17] Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.

[18] This stereochemical outcome is also in accord with the recent proposal of Cieplak favoring axial (β) attack of the "cyclohexanone-like" portion of oxonium B by two-electron stabilization of the developing antibonding orbital ($\sigma_{\#}^*$) with the C-3β–H and C-5–H occupied orbitals: Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

[19] For the construction of a number of other related systems (**10–13**), see the supplementary material.

[20] All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

Stability of Buckminsterfullerene and Related Carbon Clusters

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Under appropriate collisional conditions the mass spectrum of carbon fragments produced by laser vaporization of graphite is dominated by C_{60} and (to a lesser extent) C_{70} clusters.[1] The discoverers of this phenomenon have noted that the carbon valence requirements can be satisfied in closed, hollow structures. For C_{60} they suggest an icosahedral soccerball network, which they call buckminsterfullerene and we abbreviate as BF.[2] Experimental support has come from studies with lanthanum-impregnated graphite.[1b] The resulting mass spectra show intense $C_{60}La$ peaks, but no C_nLa_2 or C_nLa_3 peaks. Subsequent experiments have demonstrated the inertness of C_{60} and, indeed, other large C_{2n} clusters under NO attack.[1c]

We report here the results of quantum calculations which were prompted by the experiments cited above and other earlier work.[3] Our purpose has been to test the intrinsic stability of BF and related polyhedral species and to compare their stability with that of planar graphite fragments. The latter have the advantage of being strain free, but suffer from dangling valences on their perimeters. We also make comparisons with linear carbon chains.

Preliminary Hückel level results are shown in the central columns of Table I. Like BF the other polyhedra included in the table have closed-shell Hückel wave functions and multiple Kekulē structures. Note that *all* have resonance energies that are comparable with graphite[4] and 50–70% greater than that of benzene.[5] Note also, however, that in contrast to graphite, the bond orders of the polyhedra exhibit considerable variation from bond to bond, suggesting a parallel variation in bond length.

In order to account realistically for angle strain, we carried out MNDO[6,7] calculations, with full geometry optimization. This method has been shown to be reliable (ΔH_f per C good to ~1 kcal/mol) for hydrocarbons containing five- and six-membered rings. A highly pertinent and satisfactory test is provided by corannulene ($C_{20}H_{10}$),[8] which consists of five six-membered rings fused about a pentagon (i.e., one sector of BF): all calculated angles are within 2° of X-ray values, and the bond lengths are correctly ordered, with a 0.01-Å mean error.

For large planar fragments, we employed Benson's empirical group equivalents[9] (accurate to better than 0.5 kcal/mol per C for unstrained aromatic systems).[10]

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[1] (a) Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E. *Nature (London)* **1985**, *318*, 162–163. (b) Heath, J. R.; O'Brien, S. C.; Zhang, Q.; Liu, Y.; Curl, R. F.; Kroto, H. W.; Tittel, F. K.; Smalley, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 7779–7780. (c) Zhang, Q. L.; O'Brien, S. C.; Heath, J. R., Liu, Y.; Curl, R. F.; Kroto, H. W.; Smalley, R. E. *J. Phys. Chem.* **1986**, *90*, 525–528.

[2] See also: Stanlevich, I. V.; Nikerov, M. V.; Bochvar, D. A. *Russ. Chem. Rev. (Engl. Transl.)* **1984**, *53*, 640–654.

[3] (a) Rohlfing; E. A.; Cox, D. M.; Kaldor, A. *J. Chem. Phys.* **1984**, *81*, 3322–3330. (b) Bloomfield, L. A.; Geusic, M. E.; Freeman, R. R.; Brown, W. L. *Chem. Phys. Lett.* **1985**, *121*, 33–37.

[4] Anno, T.; Coulson, C. A. *Proc. R. Soc. London, Ser. A* 1961, *264*, 165–175.

[5] See also: Haymet, A. D. J. *J. Am. Chem. Soc.* **1986**, *168*, 319–321.

[6] Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907.

[7] Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907–4917.

[8] (a) Barth, W. E.; Lawton, R. G. *J. Am. Chem. Soc.* 1971, *93*, 1230–1745. (b) Hanson, J. C.; Nordman, C. E. *Acta Crystallogr., Sect. B* **1976**, *B32*, 1147–1153. (c) Gleicher, G. J. *Tetrahedron* **1967**, *23*, 4257–4263.

[9] (a) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976; Appendix. (b) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S., Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279–323.

0002-7863/86/1508-2469$01.50/0