A Reaction Cascade Leading to 1,6-Didehydro[10]annulene → 1,5-Dehydronaphthalene Cyclization Initiated by Thiol Addition

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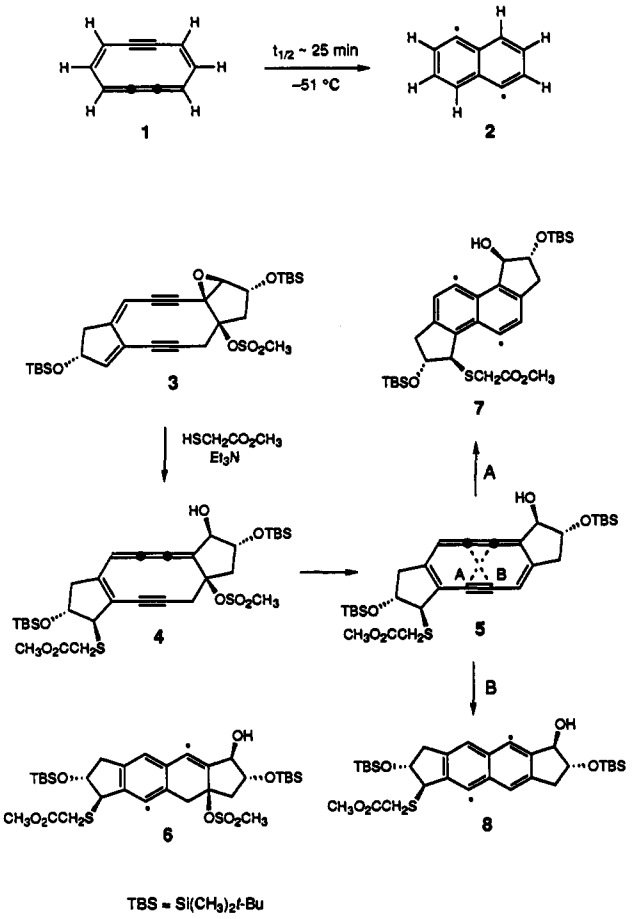
The simple aromatic hydrocarbon 1,6-didehydro[10]annulene (**1**) has recently been prepared and characterized spectroscopically at low temperature (≤ −90 °C). At −60 °C and above, **1** undergoes a rapid first-order cyclization to form the biradical 1,5-dehydronaphthalene (**2**) as evidenced by the production of naphthalene and, in deuteriated solvents, 1,5-dideuterionaphthalene. The half-life for the transformation of **1** to **2** is ~25 min at −51 °C making this the most rapid biradical-forming cycloaromatization now known.[1] As a first step toward the development of agents for the cleavage of DNA mediated by 1,5-dehydronaphthalene biradical intermediates, we report an enantioselective synthesis of the epoxy dienediyne **3** and evidence for its transformation to such biradicals upon treatment with methyl thioglycolate.

The epoxy dienediyne structure **3** arose from consideration of the mechanism of thiol activation of neocarzinostatin chromophore[2] and a desire to achieve synthetic simplification by the use of symmetry. Substrate **3** was envisioned to undergo thiol addition to form the cumulene **4** and, after elimination of methanesulfonic acid, the 1,6-didehydro[10]annulene intermediate **5** (Scheme I). Previous experience with an intermediate related to **4** suggested that the elimination reaction that forms **5** would be rapid relative to the potentially competitive cyclization of **4** to the biradical **6**.[1] An interesting feature of the 1,6-didehydro[10]annulene intermediate **5** is the fact that, by virtue of the lower symmetry of **5** versus **1**, the two modes of 1,5-dehydronaphthalene formation from **5** are not degenerate, as is the case with **1** (pathways A and B, affording **7** and **8**, respectively, Scheme I). The synthesis of **3** and the details of its thiol-induced transformations are described below.

The well-established prostaglandin intermediate **9**, synthesized in 96% ee following literature procedures, served as starting material for the preparation of **3**.[3] Slow addition of a solution of iodine (1.7 equiv) in a mixture of dichloromethane and pyridine (1:1) to an ice-cooled solution of **9** in the same solvent followed by stirring at 23 °C for 2 h provided the iodide **10** in 93% yield after workup and flash column chromatography.[4] Treatment of **10** with allenylmagnesium bromide (4.0 equiv)[5] in ethyl ether at 23 °C afforded the diastereomeric alcohols **11** and **12** in 36 and 62% yield, respectively, after chromatography on silica gel. The stereochemistry of diastereomer **12** (mp 57–61 °C) was established by X-ray crystallography.[6] Treatment of diastereomer **11** with neat (diethylamino)trimethylstannane (3.0 equiv) at 23 °C for 3.5 h provided the trimethylstannylacetylene **13** in 95% crude yield following concentration and aqueous workup (required to hydrolyze the tertiary trimethylstannyl ether).[7] This product was dimerized in the presence of tetrakis(triphenylphosphine)-palladium(0) (0.20 equiv) in deoxygenated benzene (70 °C, 12 h) affording the C_2-symmetric diol **14** in 34% yield.[8] Attempts to produce **14** directly from **11** employing palladium/copper-catalyzed coupling procedures[9] formed only the Glaser-type acetylene dimerization product, in accord with literature precedent.[8b] Treatment of a solution of **14** in dichloromethane at 0 °C with dimethyldioxirane (~1.0 equiv)[10] afforded the epoxide **15** in 41% yield after purification by flash column chromatography.[11,12] Exposure of **15** to 4-(dimethylamino)-pyridine (20 equiv) and methanesulfonic anhydride (10 equiv)

Scheme I



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(6) Diastereomer **12** was converted into the enantiomer of diastereomer **11** in 67% yield by the following sequence: desilylation with tetrabutylammonium fluoride in THF (23 °C, 45 min, 98%); oxidation with pyridinium chlorochromate (88%); reduction with sodium borohydride in methanol at 0 °C (91%); and silylation with *tert*-butyldimethylsilyl chloride, triethylamine, and catalytic 4-(dimethylamino)pyridine (85%).

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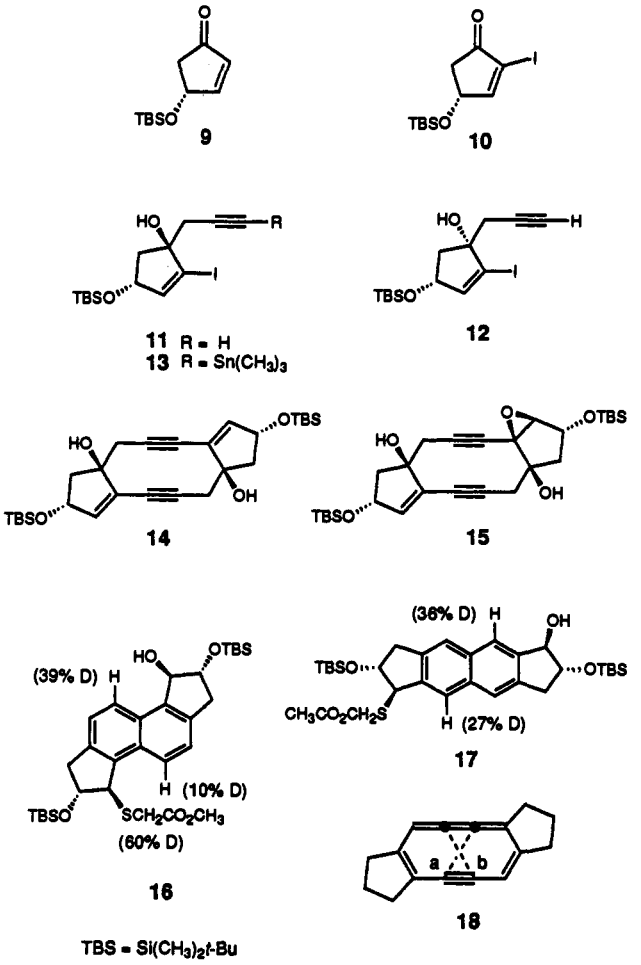
Chart I



in dichloromethane at 23 °C for 7 h then provided the mesylate **3** in 70% yield. Mesylate **3** is stable toward purification by flash column chromatography and in solution in the presence of a free-radical inhibitor.

Treatment of the mesylate **3** (1.7 mM) with methyl thioglycolate (10 equiv) and triethylamine (10 equiv) in a deoxygenated mixture of dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF, 4:1, respectively) containing 1,4-cyclohexadiene (1.0 M) for 12 h at 23 °C produced the isomeric naphthalene derivatives **16** and **17** in 67 and 20% yield, respectively.[13] A similar experiment conducted in deuteriated solvents (1,4-cyclohexadiene, DMSO, and THF, natural abundance methyl thioglycolate) afforded **16** and **17** with the indicated levels of deuterium incorporation at the sites anticipated from a consideration of their putative biradical precursors, **7** and **8**. Not surprisingly, intermediate **7** undergoes a particularly efficient intramolecular hydrogen atom transfer from the methylene group of the methyl thioglycolate appendage.[14] As mentioned above, the intermediate **5** may be envisioned to undergo two nondegenerate cyclization reactions to form the 1,5-dehydronaphthalene biradicals **7** and **8**. While the origin of the product **17** is mechanistically ambiguous, potentially arising from **5** and/or **6**, the origin of product **16** is not. That we observe both products argues strongly for the intermediacy of the annulene **5**. The unequal distribution of **16** and **17**, with **16** favored ~3:1 over **17**, is clearly a manifestation of substitution upon the cyclization reaction. In this regard, it is interesting to note that distances a and b within structure **18** are determined to be 3.04 and 3.10 Å, respectively, by MM2* calculations, suggesting that a predisposition exists for cyclization along pathway A within the ground-state structure.[15]

In summary, a system for thiol-induced formation of a 1,6-didehydro[10]annulene intermediate and thence the corresponding 1,5-dehydronaphthalene biradicals is described. Present goals are to modify structure **3** so as to confer an affinity for double helical DNA and DNA cleaving activity.

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Supplementary Material Available: Tabulations of IR, ^{1}H NMR, and high-resolution mass spectral data and reproductions of ^{1}H NMR spectra for compounds **3** and **10–17** and an ORTEP diagram with crystal structure data for compound **12** (23 pages). Ordering information is given on any current masthead page.

(11) Epoxidation of **14** with *m*-CPBA (1.0 equiv) in dichloromethane at 0 °C produced the identical epoxide, albeit in lower yield (~20%). The stereochemistry of **15** was assigned as shown based on the assumption that the *m*-CPBA-mediated epoxidation proceeds with direction from the hydroxyl group.

(12) The analogous dimerization of alcohol **12** and subsequent epoxidation of the resulting diol proceeded in substantially lower yields (20 and 5%, respectively).

(13) The stereochemistry of **16** and **17** was assigned on the basis of ^{1}H NMR coupling constants and with the presumption that the thiol addition occurs opposite the bulky *tert*-butyldimethylsilyloxy group.

(14) For related observations, see: (a) Wender, P. A.; Tebbe, M. J. *Tetrahedron Lett.* **1991**, *32*, 4863. (b) Chin, D.-H.; Goldberg, I. H. *J. Am. Chem. Soc.* **1992**, *114*, 1914.

(15) Computer modeling was performed using the MM2* force field (see: Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982) as part of the program Macromodel V3.5X: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. This modeling study is intended to be suggestive only since the analysis does not examine the relevant transition-state energies of the two biradical-forming pathways.