

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

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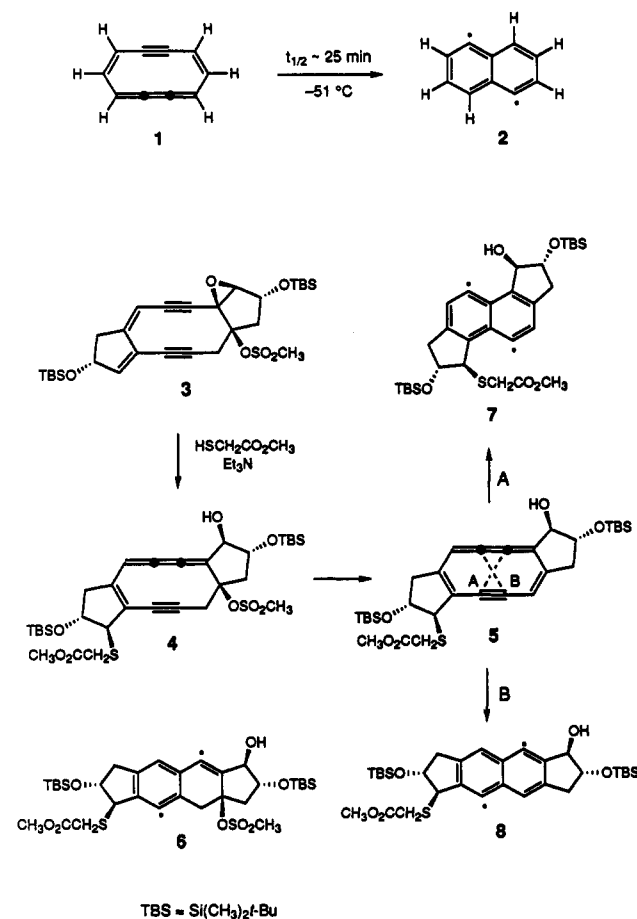
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The simple aromatic hydrocarbon 1,6-didehydro[10]annulene (**1**) has recently been prepared and characterized spectroscopically at low temperature ( $\leq -90^\circ\text{C}$ ). At  $-60^\circ\text{C}$  and above, **1** undergoes a rapid first-order 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  $\sim 25$  min at  $-51^\circ\text{C}$  making this the most rapid biradical-forming cycloaromatization now known.<sup>1</sup> 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<sup>2</sup> 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**.<sup>1</sup> 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**.<sup>3</sup> 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  $23^\circ\text{C}$  for 2 h provided the iodide **10** in 93% yield after workup and flash column chromatography.<sup>4</sup> Treatment of **10** with allenylmagnesium bromide (4.0 equiv)<sup>5</sup> in ethyl ether at  $23^\circ\text{C}$  afforded the diastereomeric alcohols **11** and **12** in 36 and 62% yield, respectively, after chromatography on silica gel. The stereochemistry of diastereomer **12** (mp  $57-61^\circ\text{C}$ ) was established

Scheme I



by X-ray crystallography.<sup>6</sup> Treatment of diastereomer **11** with neat (diethylamino)trimethylstannane (3.0 equiv) at  $23^\circ\text{C}$  for 3.5 h provided the trimethylstannylacetylene **13** in 95% crude yield following concentration and aqueous workup (required to hydrolyze the tertiary trimethylstannyl ether).<sup>7</sup> This product was dimerized in the presence of tetrakis(triphenylphosphine)-palladium(0) (0.20 equiv) in deoxygenated benzene ( $70^\circ\text{C}$ , 12 h) affording the  $C_2$ -symmetric diol **14** in 34% yield.<sup>8</sup> Attempts to produce **14** directly from **11** employing palladium/copper-catalyzed coupling procedures<sup>9</sup> formed only the Glaser-type acetylene dimerization product, in accord with literature precedent.<sup>8b</sup> Treatment of a solution of **14** in dichloromethane at  $0^\circ\text{C}$  with dimethyldioxirane ( $\sim 1.0$  equiv)<sup>10</sup> afforded the epoxide **15** in 41% yield after purification by flash column chromatography.<sup>11,12</sup> Exposure of **15** to 4-(dimethylamino)-pyridine (20 equiv) and methanesulfonic anhydride (10 equiv)

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

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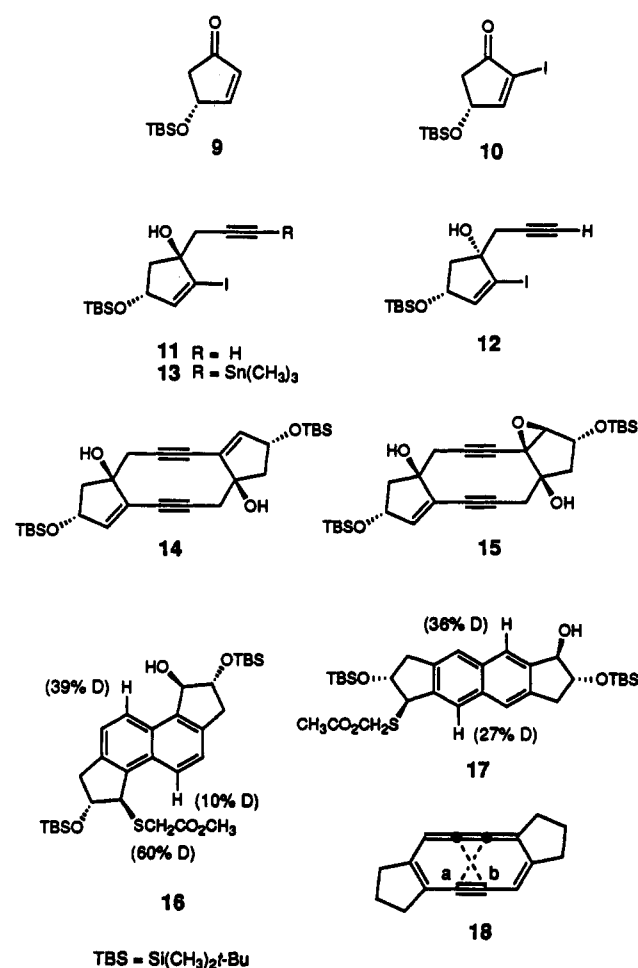
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Chart I



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

(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).

16 and 17 in 67 and 20% yield, respectively.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15</sup>

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, <sup>1</sup>H NMR, and high-resolution mass spectral data and reproductions of <sup>1</sup>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.

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

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(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.