Communications to the Editor

Design and Synthesis of a System for Enediyne Formation by Anthraquinone Reductive Activation

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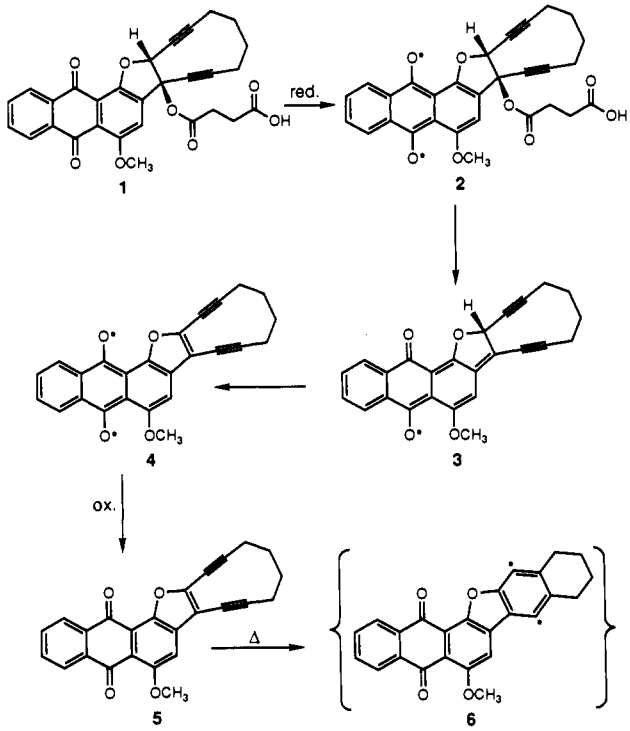
In vitro experiments conducted with the natural antitumor agents calichemicin, esperamicin, and dynemicin support, as a common mechanistic feature, the cyclization of a carbocyclic (*Z*)-enediyne to form a highly reactive 1,4-dehydrobenzene intermediate (Bergman reaction).[1,2] In each case, a chemical activation step leads to a structural change within the antibiotic that accelerates Bergman cyclization. In an alternative strategy for formation of a 1,4-dehydrobenzene intermediate by reductive activation, we have synthesized the anthraquinone–cyclic diacetylene conjugate **1** as a masked (*Z*)- enediyne. This compound was envisioned to enter the reaction cascade outlined in Scheme I upon reduction of the anthraquinone ring. Central to this plan is the notion that spontaneous elimination of succinic acid from **1** will be slow due to strain considerations. Reductive elimination (**1** → **2** → **3**) and tautomerization (**3** → **4**), steps related to initial events in mitomycin C activation,[3] then provide a pathway for generation of the strained (*Z*)-enediyne **4**.[4]

The primary challenge in the synthesis of **1** is to devise a scheme for construction of the strained cyclodecadiyne ring that is compatible with the anthraquinone functional group. Initial efforts to close the diacetylene ring in the presence of the anthraquinone were abandoned in favor of a more convergent approach wherein the preformed cyclodecadiynone **10** was coupled with the anthraquinone precursor **11** to form **12** (Chart I). Metalation of 1,7-octadiyne with *n*-butyllithium (2.0 equiv) in tetrahydrofuran (THF) at 0 °C followed by addition of *N*,*N*-dimethylformamide (DMF, 5.0 equiv), also at 0 °C, and warming to 23 °C for 12 h affords the dialdehyde **7** in 69% yield after flash column chromatography. In an unusual application of the Pedersen pinacolic coupling procedure, dialdehyde **7** (2.0 M in CH_2Cl_2) is added by syringe pump over 3 h to a solution of $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (1.2 equiv, 0.2 M) and DMF (6.0 equiv) in dichloromethane at 23 °C to provide the diol **8** as a 4:1 mixture of cis and trans isomers, respectively, in 40% yield.[5,6] Limited exposure of this diastereomeric mixture of diols to methoxytrityl chloride (2.0 equiv) in dichloromethane containing triethylamine (3.0 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.25 equiv) affords methoxytrityl ether **9** as a 9:1 mixture of cis and trans isomers, respectively, in 79% yield after flash column chromatography. Oxidation of diastereomers **9** with the Dess–Martin periodinane (2.5 equiv, CH_2Cl_2, 23 °C) forms the acetylenic ketone **10** in >90% yield and >90% purity.[7] Due to the sensitivity of this product toward silica gel, the subsequent coupling reaction is performed using crude material. Anthracene derivative **11** is prepared by treatment of 2-bromo-1,4-dimethoxyanthraquinone[8] with zinc dust (2.2 equiv) and *tert*-butyldimethylsilyl chloride (2.2 equiv) in deoxygenated pyridine at 60 °C (95% yield). Subjection of **11** (1.1 equiv) to conditions of metal–halogen exchange (1.05 equiv of *n*-butyllithium, THF, −78 °C, 20 min) followed by addition of acetylenic ketone **10** (1 equiv) affords the corresponding 1,2-addition product as a single diastereomer.[9] This product is isolated by extraction and is oxidized directly with ceric ammonium nitrate (2.0 equiv) in aqueous THF (4:1, 23 °C) providing, after flash column chromatography, the anthraquinone **12** in 40% overall yield from **9**. The methoxytrityl protecting group

Scheme I. Proposed Transformation of Anthraquinone **1** to (*Z*)-Enediyne **5** and Cyclization of the Latter to Biradical **6**[a]



[a] Asterisks are used to accommodate the possible involvement of either semiquinone or hydroquinone intermediates.

(1) Calichemicin: (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. Esperamicin: (c) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (d) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462. Dynemicin: (e) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. Review: (f) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

(2) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (c) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091.

(3) (a) Iyer, V. N.; Szybalski, W. *Science* **1964**, *145*, 55. (b) Review: Franck, R. W.; Tomasz, M. In *Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie: Glasgow, 1990; p 379.

(4) This proposed reductive activation is also related to chemistry occurring in dynemicin and the anthracycline antibiotics; see refs 1e and 12, respectively.

(5) (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Raw, A. S.; Pedersen, S. F. *J. Org. Chem.* **1991**, *56*, 830. (c) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28.

(6) Use of hexamethylphosphoric triamide (6.0 equiv) in place of DMF gives rise to a 10:1 ratio of cis and trans isomers, in comparable yield. The cis stereoisomer is assigned on the basis of its facile conversion to the corresponding acetonide.

(7) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(8) Prepared in 56% yield by bromination of quinizarin (5 equiv of Br_2, HOAc, reflux, 6 h) followed by methylation under phase-transfer conditions (4 equiv of NaOH, 80 equiv of CH_3I, 4 equiv of n-Bu_4NBr, 2:1 CH_2Cl_2:H_2O, 23 °C, 2 days).

(9) The stereochemistry of **12** is assigned tentatively as shown, on the basis of the presumption that aryllithium attack on **10** occurs opposite the bulky MMT group.

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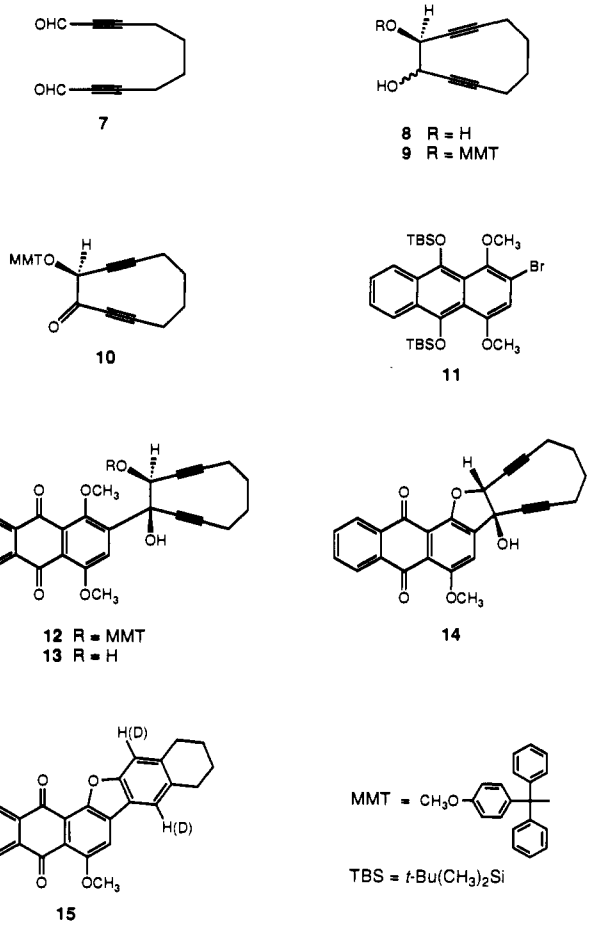
Chart I



is removed by treatment of **12** with 0.1 N hydrochloric acid in 10% aqueous acetonitrile at 0 °C to produce the diol **13** (mp 135–136 °C) in 71% yield. Treatment of **13** with trifluoromethanesulfonic anhydride (2.0 equiv) and 2,6-lutidine (3.0 equiv) in dichloromethane at −78 °C forms the cyclic ether **14** (mp 124 °C dec) in 85% yield after purification on silica gel.[10] Transformation of **14** to the succinate ester **1** is accomplished by treatment of **14** with succinic anhydride (10 equiv), triethylamine (10 equiv), and DMAP (0.25 equiv) in dichloromethane for 2 h at 23 °C (83% yield, mp 115 °C dec). Succinate ester **1** is stable to routine handling and purification (silica gel chromatography) and is soluble in aqueous buffer solutions (pH 8.0) where control experiments establish that it is stable for at least several hours at 23 °C.

Reductive activation of **1** at pH 8.0 (0.1 M aqueous HEPES buffer, 23 °C) proceeds rapidly and cleanly with a flavin-based enzymatic system (ferredoxin reductase, glucose oxidase, isocitrate dehydrogenase, and catalase in the presence of glucose, NADPH, isocitrate, and $MnSO_4$, anaerobic incubation) to form the (*Z*)-enediyne **5** in 75% yield following extraction and flash column chromatography.[11] Control experiments show that ferredoxin reductase is the primary reductant; enediyne formation is slow in its absence and does not occur when both ferredoxin reductase and NADPH are omitted. NADPH alone induces clean formation of **5** from **1**, albeit more slowly than the enzyme-mediated reaction. The efficacy of this activation method is significant in that flavin-based enzymatic reductants have been implicated as potential in vivo activation factors for the clinically important quinone-containing antitumor agents mitomycin, adriamycin, and daunomycin.[3,11,12] As anticipated in light of ample precedent,[13] (*Z*)-enediyne **5** cyclizes slowly at 37 °C ($t_{1/2} \approx 2$ days) to form, in the presence of 1,4-cyclohexadiene, the aromatic product **15**.[14] Deuterium is incorporated quantitatively within the newly formed aromatic ring when the cyclization is conducted in THF-d_8, consistent with the intermediacy of biradical **6** in the transformation **5** → **15**.

In summary, we have demonstrated a new strategy for the generation of a reactive (*Z*)-enediyne by anthraquinone reductive activation in water. The efficiency of the enzymatic reduction system discussed above bodes well for potential in vivo activation of synthetic systems of this type.

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Supplementary Material Available: Reproductions of high-resolution ^{1}H NMR and IR spectral data for all synthetic intermediates (21 pages). Ordering information is given on any current masthead page.

(10) This product is believed to arise by nucleophilic displacement of the secondary triflate by methoxyl, followed by nucleophilic demethylation of the resulting oxonium ion. The corresponding secondary mesylate also forms **14** upon warming in DMF (70 °C).

(11) (a) Fisher, J.; Abdella, B. R. J.; McLane, K. E. *Biochemistry* **1985**, *24*, 3562. (b) Gutteridge, J. M. C.; Toeg, D. *FEBS Lett.* **1982**, *149*, 228.

(12) Reviews of anthracycline antibiotics: (a) *Anthracycline and Anthracenedione-Based Anticancer Agents*; Lown, J. W., Ed.; Elsevier: Amsterdam, 1988. (b) Fisher, J. F.; Aristoff, P. A. *Prog. Drug Res.* **1988**, *32*, 411.

(13) (a) Darby, N.; Kim, C. U.; Salaün, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1971**, 1516. (b) Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217. (c) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. (d) Nicolaou, K. C.; Hong, Y.-P.; Torisawa, Y.; Tsay, S.-C.; Dai, W.-M. *J. Am. Chem. Soc.* **1991**, *113*, 9878. See also ref 1f.

(14) Cyclization of **5** at 80 °C (2 M 1,4-cyclohexadiene, dimethylsulfoxide-d_6) proceeds with a half-life of ~20 min forming **15** in 75% yield.

Thermodynamically Controlled Electrochemical Formation of Thiolate Monolayers at Gold: Characterization and Comparison to Self-Assembled Analogs

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Thiolate monolayers self-assembled from dilute solutions of $X(CH_2)_nSH$ at gold[1] have emerged as attractive models of organic interfaces. We report herein the discovery of a new route for the preparation of thiolate monolayers that provides enhanced control of monolayer formation. The finding stems from our studies of the reductive desorption of these monolayers in alkaline solution via reaction 1.[2] We show that (1) the reverse of reaction 1 can

$$X(CH_2)_nSAu + e^- \rightarrow Au + X(CH_2)_nS^- \qquad (1)$$

be used for the electrodeposition of thiolate monolayers, (2) the electrodeposited monolayers have structures and interfacial

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(1) For a general overview of self-assembled monolayers, see: (a) Ulman, A. *An Introduction to Ultrahigh Organic Films: From Langmuir-Blodgett to Self-Assembly*; Academic Press: Boston, 1991. (b) Whitesides, G. M.; Laibinis, P. E. *Langmuir* **1990**, *6*, 87–96.

(2) (a) Widrig, C. A.; Chung, C.; Porter, M. D. *J. Electroanal. Chem.* **1991**, *310*, 335–59. (b) Walczak, M. M.; Popenoe, D. D.; Deinhammer, R. S.; Lamp, B. D.; Chung, C.; Porter, M. D. *Langmuir* **1991**, *7*, 2687–93.

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