Vinylquinone Ketals as Diels-Alder Dienes. Construction of Functionalized Naphthalenes and Nonlinear Polycyclic Aromatics

Kathlyn A. Parker* and Suzanne M. Ruder

Department of Chemistry, Brown University
Providence, Rhode Island 02912

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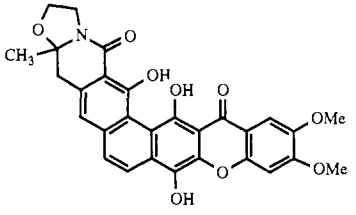
Aromatic polyketide antibiotics generally fall into two structural classes, the linear polyketides, a group which includes the anthracyclines and the nanoamycins, and the nonlinear polyketides, a group which includes a number of benzanthracene and benznaphthacene quinones.[1] The structure of cervinomycin A_1 (**1**),[2] one of the polycyclic xanthone antibiotics,[3] is representative of the nonlinear polyketide antibiotics, a rapidly growing class of compounds.

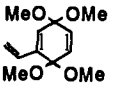
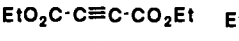
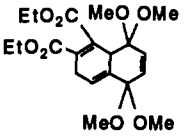
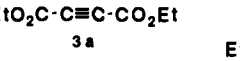
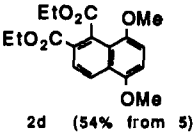
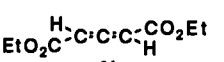
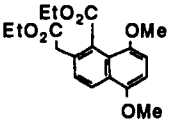
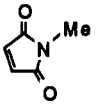
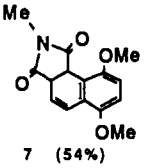
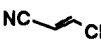
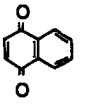
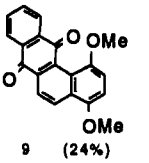
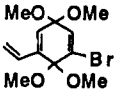
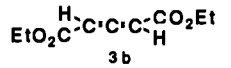
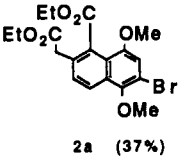


1, Cervinomycin A_1

Although enormous efforts have been devoted to the synthesis of the linear polyketides,[4] the nonlinear aromatic polyketides have received relatively little attention.[5] The key construction problems which must be addressed in the preparation of any member of the latter series are the "elbow bend" in the ring system (i.e., the phenanthrene substructure) and the oxygenation pattern of the region immediately adjacent to the bend.

A classical solution to the preparation of phenanthrene building blocks and one which might be considered for structures similar to **1** is a Diels-Alder condensation in which a styrene acts as the diene and a quinone acts as the dienophile.[6] Such condensations have been used in synthesis, but they suffer from low yields. Styrenes are not very reactive dienes, and they may undergo polymerization at rates competitive with simple cycloaddition.[7] Furthermore, in condensations involving substituted styrenes, there may be a lack of regiocontrol.[8] One would anticipate a regio-

Table I

Vinyl Quinone Ketal	Dienophile and Conditions	Product (Yield)
 5	 3a 160°, benzene, sealed tube, 3.5 d	 6 (83%)
	 3a 1) 160°, benzene, sealed tube, 3 d. 2) anh. TsOH, 1 h, room temp.	 2d (54% from 5)
	 3b 1) 160°, benzene, sealed tube, 4.5 d. 2) anh. TsOH, 30 min, room temp.	 2b (48%)
	 1) 160°, benzene, sealed tube, 3.5 d. 2) TsOH, Et_2O, 23h, room temp.	 7 (54%)
	 1) 160°, benzene, 3.5 d. 2) TsOH. 3) PtO_2, 150°, benzene, 24 h.	 8 (40%)
	 1) 160°, benzene, 6 d. 2) TsOH, 45 min, room temp. 3) PtO_2, 18 h.	 9 (24%)
 10	 3b 160°, benzene, sealed tube, 5 d.	 2a (37%)

(1) (a) Benzanthracenes. For aquayamycin derivatives, see: Omura, S.; Nakagawa, A.; Fukamachi, N.; Miura, S.; Takehashi, Y.; Komiyama, K.; Kobayashi, B. *J. Antibiot.* **1988**, *41*, 812 and references therein. Also, Rohr, J.; Zeeck, A.; Floss, H. G. *J. Antibiot.* **1988**, *41*, 126. For related interesting compounds, see: Wilton, J. H.; Cheney, D. C.; Hokanson, G. C.; French, J. C.; He, C.-H.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 3936. Irie, H.; Mizuno, Y.; Kouno, I.; Nagasawara, T.; Tani, Y.; Yamada, H.; Osaki, K. *J. Chem. Soc., Chem. Commun.* **1983**, 174. Kern, D. L.; Schaumberg, J. P.; Hokanson, G. C.; French, J. C. *J. Antibiot.* **1986**, *39*, 469. Rasmussen, R. P.; Nuss, M. E.; Scherr, M. H.; Mueller, S. L.; McAlpine, J. B.; Mitscher, L. *J. Antibiot.* **1986**, *39*, 1515. Otake, N.; Hayakawa, Y.; Iwakiri, T.; Jpn Kokai Tokyo Koho J.P., 61, 263, 971 (86, 263, 971); *Chem. Abstr.* **1987**, *107*, 5727e. (b) Benznaphthacenes. Tanabe, A.; Nakashima, H.; Yoshida, O.; Yamamoto, N.; Tenmyo, O.; Oki, T. *J. Antibiot.* **1988**, *41*, 1708. Gomi, S.; Sezaki, M.; Kondo, S.; Takeuchi, T.; Hara, T.; Naganawa, H. *J. Antibiot.* **1988**, *41*, 1019; Yasuzawa, T.; Yoshida, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 1111. Rickards, R. W. *J. Antibiot.* **1989**, *42*, 336.

(2) Nakagawa, A.; Omura, S.; Kushida, K.; Shimizu, H.; Lukacs, G. *J. Antibiot.* **1987**, *40*, 301. Omura, S.; Nakagawa, A.; Kushida, K.; Lukacs, G. *J. Am. Chem. Soc.* **1986**, *108*, 6088.

(3) See also: (a) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Mikawa, T.; Shiobara, Y.; Kodama, M. *J. Antibiot.* **1988**, *41*, 741 and references therein. (b) For the corrected structures of albogungin and chloroalbogungin, see: Onaprienko, V. V.; Koz'min, Yu. P.; Kolosov, M. N. *Bioorg. Khim.* **1978**, *4*, 1418; *Chem. Abstr.* **1979**, *90*, 54885u.

(4) Many of these approaches are described in Tetrahedron *Symposium*-in-Print Number 17, Recent Aspects of Anthracyclinone Chemistry. Kelly, T. R., Ed.; *Tetrahedron* **1984**, *40*, 4537-4793.

(5) (a) Guigant, A.; Barreto, M. M. *Tetrahedron Lett.* **1987**, *28*, 3107 and references therein. (b) For a recently completed synthesis of cervinomycins A_1 and A_2, see: Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522.

(6) (a) A review: Wagner-Jauregg, T. *Synthesis* **1980**, 769. (b) Manning, W. B. *Tetrahedron Lett.* **1981**, *22*, 1571. (c) Manning, W. B.; Wilbur, D. J. *J. Org. Chem.* **1980**, *45*, 733. (d) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798. (e) Rosen, B. I.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 3463.

(7) The problem of styrene diene reactivity has been addressed previously by Kita et al. who demonstrated that enforced coplanarity of the potential diene system promotes the Diels-Alder condensation. These workers isolated modest yields of several perihydroxylated products which were aromatized adducts. See: Kita, Y.; Yasuda, H.; Tamura, O.; Tamura, Y. *Tetrahedron Lett.* **1984**, *25*, 1813.

(8) For example, 3-methoxystyrene added to benzoquinone to afford 7-methoxy-1,4-phenanthraquinone and not the 5-methoxy isomer (see ref 6e). A different problem is encountered with a 3,5-disubstituted styrene which can give two regioisomeric products.

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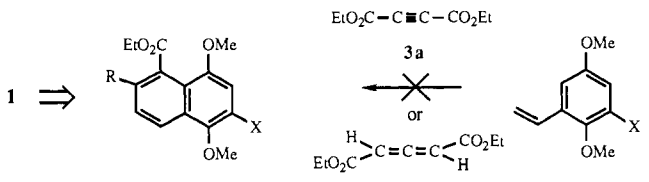
chemistry problem in styrene–quinone additions directed at the oxygenated 1,4,10-phenanthrene system required for the polycyclic xanthones.

Naphthalenes of general structure **2**, in which the eventual "elbow bend" is implicit in the 1,2,5,8-substitution pattern, might be elaborated to phenanthrenes with the desired oxygenation pattern. Naphthalenes **2** are themselves, formally, the Diels–Alder products of styrenes **4** and diethyl acetylenedicarboxylate (**3a**) or diethyl allenedicarboxylate (**3b**). Not surprisingly,[9] attempts to effect these condensations led to complex mixtures.



2a R=CH_2CO_2Et, X=Br
2b R=CH_2CO_2Et, X=H
2c R=CO_2Et, X=Br
2d R=CO_2Et, X=H

4a X=H
4b X=Br

Consideration of the reactivity problems inherent in a styrene diene led us to attempt the preparation and Diels–Alder reactions of the synthetically equivalent but nonaromatic vinylquinone bis-ketals. The results of these studies and selected transformations of the adducts are summarized in Table I.

The facile electrochemical procedure developed by Swenton[10] was found to effect the oxidation of 2,5-dimethoxystyrene to diene substrate **5** in 91% yield. Likewise, the electrochemical oxidation of bromostyrene **4b** afforded the substituted vinylquinone bis-ketal **10** in 63% yield.

Heating a mixture of diene **5** and diethyl acetylenedicarboxylate (**3a**) in benzene in a sealed tube afforded a high yield of the remarkably stable adduct **6**.[11] Acid-catalyzed aromatization gave the substituted naphthalene dicarboxylic ester **2d** (54% from **5**).[12]

Under similar conditions, diene **5** added to diethyl allenedicarboxylate (**3b**) to give a mixture which contained partially aromatized material; treatment of this mixture with anhydrous toluenesulfonic acid completed the aromatization, affording diester **2b** (48% from **5**). The expected regiochemistry of the Diels–Alder reaction of **5** with **3b** was supported by nuclear Overhauser difference experiments on **2b**: irradiation of the C-3 proton (7.44 ppm) resulted in enhancement of the methylene signal (AB at 3.75 and 3.76 ppm); irradiation at 3.78 or at 3.71 ppm resulted in enhancement of the signal at 7.44 ppm. Additional confirmation of the substitution pattern in **2b** was obtained by a long-range heteronuclear cosy experiment[13] in which three-bond proton-carbon couplings between the C-3 aromatic proton and the benzylic methylene carbon and also between the benzylic protons and the C-3 aromatic carbon were observed.[14]

Condensation of vinylquinone acetal **5** with monounsaturated dienophiles gave adducts which could be isolated and characterized or converted to dihydronaphthalenes. For example, diene **5** added to *N*-methylphthalimide to give the stable Diels–Alder adduct in 76% yield (see Supplementary Material for details). Treatment of this adduct with toluenesulfonic acid effected its conversion to the 1,2-dihydronaphthalene-1,2-dicarboxylic acid derivative **7**.

Adducts derived from monounsaturated dienophiles could also be converted to naphthalenes. Thus, the crude reaction mixture from diene **5** and fumaronitrile was subjected to oxidative aromatization (TsOH, PtO_2) to afford naphthalene 1,2-dicarbonitrile **8**. Similarly, the mixture obtained from the reaction of diene **5** and naphthoquinone was converted to benzanthracenedione **9**.

We considered naphthalene **2a**, functionalized on both rings of the naphthalene, to be a particularly desirable intermediate for regiospecific elaboration to the cervinomycins and to other nonlinear polyketides. Condensation of diene **10** with allene dicarboxylate **3b** gave naphthalene **2a** directly in 37% yield.

Although these Diels–Alder/aromatization procedures proceed in modest overall yield, they are easily performed, and they provide valuable synthetic intermediates which are essentially inaccessible by other methods. The elaboration of these intermediates and the exploration of other strategies for the preparation of nonlinear polyketides are the subjects of further study.

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Supplementary Material Available: Description of experimental procedures including spectroscopic data (^1H NMR, ^{13}C NMR, IR, and HRMS) and a heteronuclear COSY plot (8 pages). Ordering information is given on any current masthead page.

(9) Low yields of 1:1 adducts have been obtained for β-substituted styrenes with maleates and with diethyl acetylenedicarboxylate; however, attempts to effect similar addition reactions with β-unsubstituted styrenes afforded polymeric materials. (a) Diment, J. A.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1969**, *22*, 1721. (b) Hudson, B. J. F.; Robinson, R. *J. Chem. Soc.* **1941**, *143*, 715.

(10) (a) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369. (b) Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6182.

(11) All new compounds were characterized by IR, NMR, and high resolution mass spectrometry or combustion analysis.

(12) Yields represent chromatographed, homogeneous materials.

(13) Sato, Y.; Geckle, M.; Gould, S. J. *Tetrahedron Lett.* **1985**, *26*, 4019.

(14) For full NMR data, see Supplementary Material.

2,4,6-Tri-*tert*-butylselenobenzaldehyde, the First Stable Selenoaldehyde

Renji Okazaki,* Naoko Kumon, and Naoki Inamoto

Department of Chemistry, Faculty of Science
The University of Tokyo, Hongo, Tokyo 113, Japan

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In recent years much attention has been paid to the chemistry of multiple bond compounds containing heavier typical elements.[1] Some years ago we reported the isolation of the first stable aromatic[2] and aliphatic[3] thioaldehydes.[4] Since selenocarbonyl compounds are much less stable than thiocarbonyl compounds,[1i-k] selenoaldehydes have eluded isolation so far, although some heterocyclic selenoaldehydes stabilized by mesomeric effect of heteroatoms such as nitrogen and sulfur have been synthesized.[5]

(1) For reviews on multiple bond compounds containing group 14–16 elements, see the following. Group 14: (a) Raabe, G.; Michl, J. *Chem. Rev.* **1985**, *85*, 419. (b) West, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1201. (c) Brook, A. G.; Baines, K. M. *Adv. Organomet. Chem.* **1986**, *25*, 1. (d) Wiberg, N. *J. Organomet. Chem.* **1984**, *273*, 141. Group 15: (e) Cowley, A. H.; Norman, N. C. *Prog. Inorg. Chem.* **1986**, *34*, 1. (f) Lochschmidt, S.; Schmidtpeter, A. *Phosphorus Sulfur* **1986**, *29*, 73. (g) Regitz, M.; Binger, P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1484. Group 16: (h) Duus, F. *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 3, pp 373–487. (i) Magnas, P. D. *Ibid.* Vol. 3, Part 12. (j) Jensen, K. A.; Kjaer, A. *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1986; Vol. 1, Chapter 1. (k) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986; Chapter 3. (l) Okazaki, R. *Yuki Gosei Kagaku Kyokai Shi* **1988**, *46*, 1149.

(2) (a) Okazaki, R.; Ishii, A.; Fukuda, N.; Oyama, H.; Inamoto, N. *J. Chem. Soc., Chem. Commun.* **1982**, 1187. (b) Okazaki, R.; Ishii, A.; Fukuda, N.; Oyama, H.; Inamoto, N. *Tetrahedron Lett.* **1984**, *25*, 849. (c) Okazaki, R.; Fukuda, N.; Oyama, H.; Inamoto, N. *Chem. Lett.* **1984**, 101.

(3) Okazaki, R.; Ishii, A.; Inamoto, N. *J. Am. Chem. Soc.* **1987**, *109*, 279.

(4) For an aliphatic thioaldehyde stable in solution, see: Vedejs, E.; Perry, D. A.; Wilde, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 2985.

(5) Reid, D. H.; Webster, R. G.; McKenzie, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2334.

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