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Communications

Synthetic Studies of the Angucyline Antibiotics. Reaction of a Quinone Methide Produced from a Benz[*a*]anthracene with Molecular Oxygen

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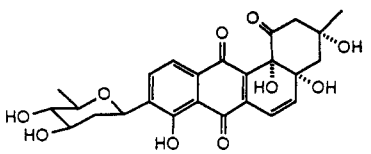
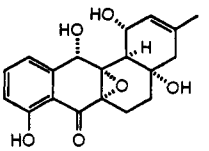
Summary: Molecular oxygen-based procedures for the stereocontrolled introduction of oxygen functionality present in the antitumor antibiotics aquayamycin (1) and SF 2315B (2) are described.

The angucyclines[1] and isotetracenones[2] are two families of antibiotics which possess the aglycon aquayamycin (1)[3] as a common structural feature. These antibiotics are reported to exhibit a variety of biological activity including antitumor and enzyme inhibitory.[4,5] More recently the structure of SF 2315B, an antibiotic which also contains a benz[*a*]anthracene carbon skeleton, has been confirmed through single-crystal X-ray analysis.[6]

The development of a unified synthetic strategy directed toward the angucyclines and related antitumor antibiotics, such as SF 2315B (2), is of current interest in our laboratory. During the course of preliminary investigations, we observed a unique oxidation process which resulted in the stereocontrolled introduction of key oxygen functionality. This unusual oxidation has contributed toward the further refinement of our synthetic strategy.



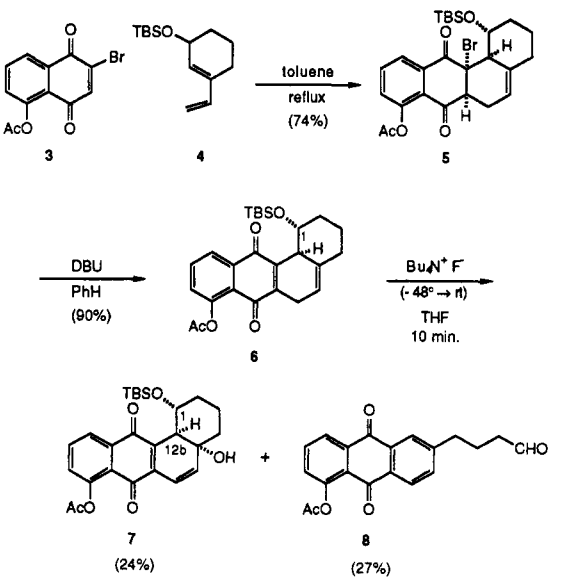
aquayamycin (1)



SF2315B (2)

Our approach to the angucyclines relies upon a stereo- and regiocontrolled Diels–Alder reaction between a bromojuglone derivative and an appropriately functionalized diene. To evaluate the feasibility of this reaction, we chose

Scheme I



to examine the Diels–Alder reaction between 2-bromo-5-acetoxyjuglone (3)[7] and 3-[(*tert*-butyldimethylsilyl)oxy]-

† Author to whom correspondence regarding the X-ray crystal structure should be addressed.

(1) (a) Drautz, H.; Zahner, H.; Rohr, J.; Zeeck, A. *J. Antibiot.* **1986**, *39*, 1657. (b) Rohr, J.; Beale, J. M.; Floss, H. G. *J. Antibiot.* **1989**, *42*, 1151. (c) Rohr, J.; Zeeck, A.; Floss, H. G. *J. Antibiot.* **1988**, *41*, 126. (d) Rohr, J.; Zeeck, A. *J. Antibiot.* **1987**, *40*, 459. (c) Synthesis of urdamycinone B: Yamaguchi, M.; Okuma, T.; Horiguchi, A.; Ikeura, C.; Minami, T. *J. Org. Chem.* **1992**, *57*, 1647.

(2) (a) Hayakawa, Y.; Iwakiri, T.; Imamura, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 960. (b) Hayakawa, Y.; Furihata, K.; Seto, H.; Otake, N. *Tetrahedron Lett.* **1985**, *26*, 3475.

(3) (a) Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H. *Tetrahedron* **1970**, *26*, 5171. (b) Uchida, T.; Imoto, M.; Watanabe, Y.; Miura, K.; Dobashi, T.; Matsuda, N.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1171.

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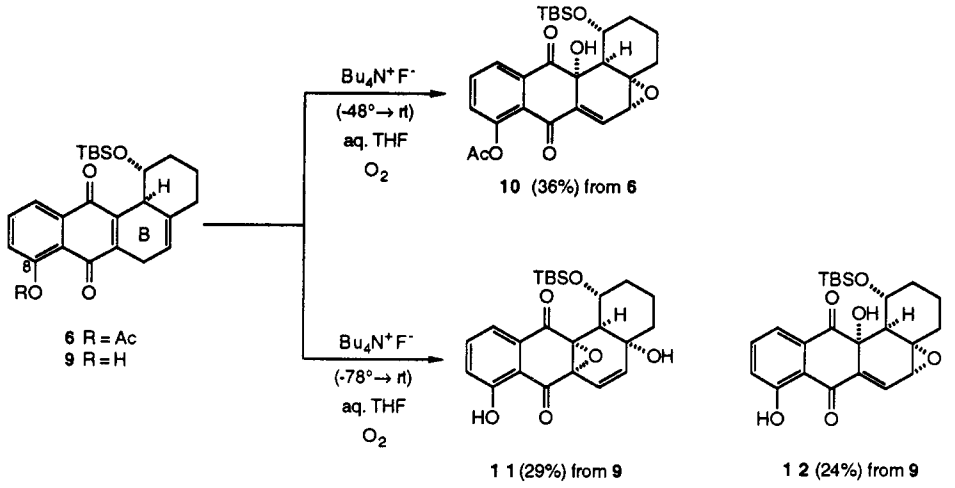
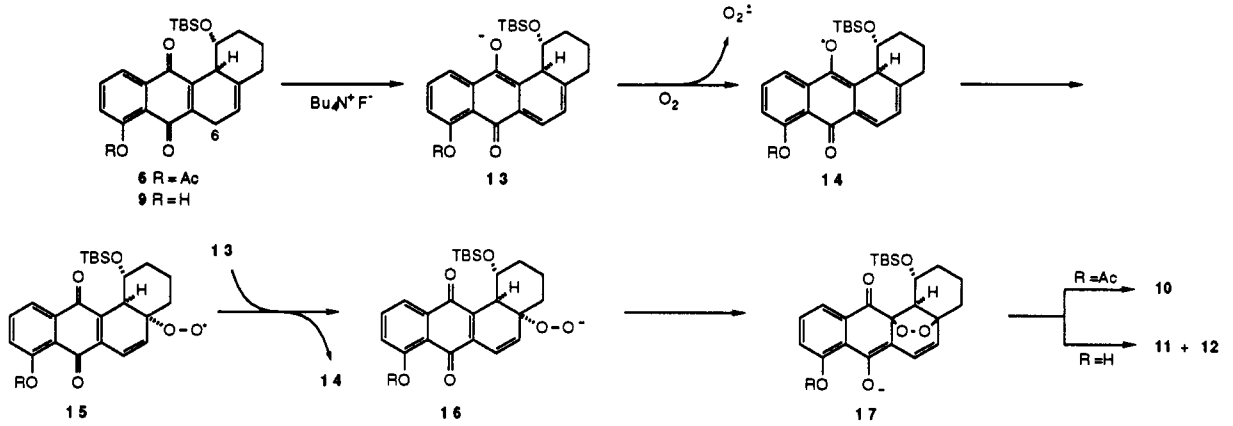
Scheme II



Scheme III



1-vinylcyclohexene (4) (Scheme I).[8] Toward this end, a reaction mixture consisting of a 1:1 ratio of 3 and 4 in toluene was heated at reflux for 12 h. Following purification, a single isomeric product (5)[9a] was isolated in 74% yield. Dehydrohalogenation of bromo ketone 5 under standard conditions provided quinone 6.[9] It is important to note that quinone 6 displays no tendency to undergo air oxidation to the corresponding anthraquinone. Thus we were provided the opportunity to examine the introduction of oxygen functionality required for the synthesis of aquayamycin (1) and SF 2315B (2). We next turned our attention to the removal of the *tert*-butyldimethylsilyl protecting group of the C1 hydroxyl. Exposure of silyl ether 6 to an anhydrous solution of tetrabutylammonium fluoride in tetrahydrofuran for 10 min resulted in the production of two products, in addition to recovered starting material (25%), which were separated by flash chromatography. The slower eluting product was assigned structure 7[9] (24%) and the second product was identified as anthraquinone 8 (27%).[9a] The structure of 7 was independently confirmed by a separate four-step conversion of bromo ketone 5 to carbinol 7 [(i) n-$Bu_4N^+OH^-$, THF; (ii) *m*-CPBA; (iii) K_2CO_3, MeOH; and (iv) Ac_2O, pyridine]. The product of the latter reaction sequence was identical in all respects to that obtained from treatment of silyl ether 6 with tetrabutylammonium fluoride. One possible scenario for the formation of anthraquinone 8 is oxidation of 6 to 7 followed by desilylation resulting in fragmentation of the C1–C12b carbon–carbon bond (7 → 8). Treatment of a tetrahydrofuran solution of quinone 7 with 4 equiv of tetrabutylammonium fluoride resulted in the comparatively slow production of anthraquinone 8. Due to the significant differences in the rates of formation of anthraquinone 8 from quinones 6 and 7, we surmise that desilylation–fragmentation precedes oxidation in the conversion of 6 to 8.

Assuming that molecular oxygen is the oxidant in this reaction, we attempted to optimize this process by treatment of quinone 6 with tetrabutylammonium fluoride in tetrahydrofuran at low temperature under an atmosphere of oxygen without employing any precautions to exclude moisture from the reaction (Scheme II). The reaction mixture was allowed to warm to room temperature and provided a mixture of starting material (26%) plus two new products. Upon examination of the ^1H and ^{13}C NMR we assigned the major product (36%) as epoxy alcohol 10.[9,10]

(4) (a) Henkel, T.; Zeeck, A. *J. Antibiot.* **1990**, *43*, 830. (b) Hayakawa, Y.; Iwakiri, T.; Imamura, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 957.

(5) (a) Okazaki, H.; Ohta, K.; Kanamura, T.; Ishimura, T.; Kishi, T. *J. Antibiot.* **1981**, *34*, 1355. (b) Ohta, K.; Mizuta, E.; Okazaki, H.; Kishi, T. *J. Antibiot.* **1984**, *32*, 4350. (c) Ohta, K.; Kamiya, K. *J. Chem. Soc., Chem. Commun.* **1981**, 154.

(6) (a) Sasaki, T.; Gomi, S.; Sezaki, M.; Takeuchi, Y.; Kodama, Y.; Kawamura, K. *J. Antibiot.* **1988**, *41*, 843. (b) Sasaki, T.; Yoshida, J.; Itoh, M.; Gomi, S.; Shomura, T.; Sezaki, M. *J. Antibiot.* **1988**, *41*, 835.

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(8) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472.

(9) (a) The structure assigned to each new compound was in accord with its infrared, 200-MHz ^1H NMR, and 50-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. (b) In addition, an analytical sample of this new compound gave satisfactory C and H combustion analysis.

This assignment was subsequently confirmed by single-crystal X-ray analysis.[11] Interestingly, treatment of the corresponding phenol 9 under identical reaction conditions resulted in the production of epoxy alcohols 11 and 12 in approximately equal yield in addition to recovered 9 (26%).[9a,12] The structural assignment of 11 was also confirmed by single-crystal X-ray analysis.[11] *This result is of particular significance in that epoxy alcohol 11 possesses the correct connectivity and four of the five stereogenic centers present in SF 2315B (2).*[11]

Gaudiano and Koch have reported that the quinone methide of daunomycin reacts with molecular oxygen resulting in several products of oxidation.[13] On the basis of their work, and others,[14] the reaction mechanism we propose, outlined in Scheme III, accounts for the various products obtained upon treatment of quinones 6 and 9 with tetrabutylammonium fluoride. The initial step is loss of a proton from the C6 position of quinone 6 or 9, resulting in generation of the corresponding quinone methide 13. Subsequent electron transfer to molecular oxygen then produces semiquinone methide 14 which traps molecular oxygen to provide peroxy radical 15.[15] One-electron transfer from quinone methide 13 to peroxy radical 15 then serves to produce peroxide 16 and generate additional semiquinone methide 14. Intramolecular Michael addition of the peroxide group generates endoperoxide 17 and subsequent 1,3-elimination generates either epoxy alcohol 10 or 11 as the major product, depending upon the identity of the C8 substituent. In the case of acetate 17 (R = Ac), γ,δ-epoxide 10 is produced while phenol 17 (R = H) results in α,β-epoxide 11. The observed difference in product distribution may be attributed to the generation of a dianionic species in the case of phenol 17. Finally, we note reduction of the oxygen–oxygen bond at the stage of peroxide 16 accounts for production of carbinol 7.

In summary, we have described an oxidation procedure which will find application in the total synthesis of SF 2315B. Currently, we are conducting labeling experiments to support our proposed mechanism and continue to direct our efforts toward the total synthesis of SF 2315B and related antibiotics.

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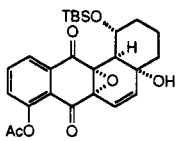
Supplementary Material Available: Experimental procedures and spectral data for all compounds including the four-step conversion of 5 to 7 (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered form the ACS; see any current masthead page for ordering formation.

(10) A minor product (<10%), tentatively assigned the isomeric epoxy alcohol i, was also observed.



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(11) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1 EZ, UK.

(12) Since we have observed the isomerization of epoxy alcohol 11 to 12 during attempted recrystallizations, the actual kinetic product of this reaction may very well be 11 which isomerizes to 12 under the reaction conditions. The details of this rearrangement are currently under investigation and will be reported in a full account of this work.

(13) Gaudiano, G.; Koch, T. H. *J. Am. Chem. Soc.* **1990**, *112*, 9423.

(14) (a) Dowd, P.; Ham, S. W. *J. Am. Chem. Soc.* **1991**, *113*, 9403. (b) Lai, M.-T.; Liu, H.-W. *J. Am. Chem. Soc.* **1992**, *114*, 3160.

(15) In regard to the stereoselectivity of this process, examination of molecular models provides no evidence for a preferred steric approach of molecular oxygen to the α face of 13. While we have no explanation for the observed stereoselectivity at this time, we note that epoxidation of the topologically similiar phenol 9 also occurs exclusively from the α face.

Synthesis and Reactivity of Enyne- and Dienyne-Tethered Molybdenum Carbene Complexes: Precursors to Polycyclic Frameworks

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Summary: Thermolysis of several enyne and dienyne tethered molybdenum–carbene complexes has been found to provide direct access to tricyclic ring systems.

Recently, studies from our group have demonstrated that the thermolysis of alkyne-tethered molybdenum carbene complexes in the presence of electron-poor olefins results in the formation of cyclopentenylcyclopropanes in good yield.[1] Work in our laboratories[2] and elsewhere[3] has shown that properly functionalized enynes will react with Fischer carbene complexes via a similar pathway to efficiently produce vinylcyclopropanes. Treatment of dienynes with Fischer carbene complexes has been demonstrated to smoothly produce hexahydroazulene systems via the [3,3]-sigmatropic rearrangement of *cis*-divinylcyclopropane intermediates.[4] All of these processes occur via the cyclopropanation of an alkene by an in situ generated vinylcarbene complex. Described herein are our initial investigations of the fully intramolecular version of this

(1) (a) Harvey, D. F.; Brown, M. F. *J. Am. Chem. Soc.* **1990**, *112*, 7806–7807. (b) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett.* **1991**, *32*, 5223–5226.

(2) (a) Harvey, D. F.; Lund, K. P.; Neil, D. A. *Tetrahedron Lett.* **1991**, *32*, 6311–6314. (b) Harvey, Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.*, in press.

(3) (a) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676–2678. (b) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1989**, *8*, 2070–2071. (c) Hoye, T. R.; Rehberg, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 2841–2842.

(4) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066–5068.

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