Regiocontrol by Remote Substituents. An Enantioselective Total Synthesis of Frenolicin B via a Highly Regioselective Diels–Alder Reaction

George A. Kraus* and Jun Li

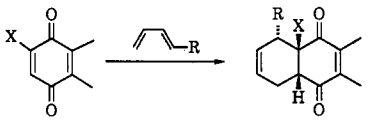
Department of Chemistry
Iowa State University
Ames, Iowa 50011

Mark S. Gordon and Jan H. Jensen

Department of Chemistry and
Ames Laboratory US-DOE
Ames, Iowa 50011

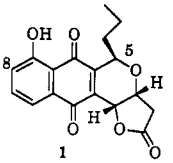
Received March 22, 1993

The quinone subunit is contained in a broad range of biologically important natural products.[1] This subunit is present in anticancer agents such as the anthracyclines, antibiotics such as the rifamycins, antifungal agents such as kalafungin, and anticoccidial agents such as frenolicin B.[2] The latter two compounds are members of the pyranonaphthoquinone family. The diverse biological activity of quinones has led to the development of several new synthetic methods for quinones. A number of methods involving cycloadditions,[3] carbanion-mediated annulations,[4] and nucleophilic and electrophilic reactions[5] have been reported. Among the pathways featuring a cycloaddition reaction, one of the most general methods for the regiospecific synthesis of substituted quinones was pioneered by Rapoport and others.[6] This method involves the Diels–Alder reaction of a substituted quinone and is depicted below. The X group is usually chlorine or bromine, but nitriles and sulfoxides[7] can also be employed.



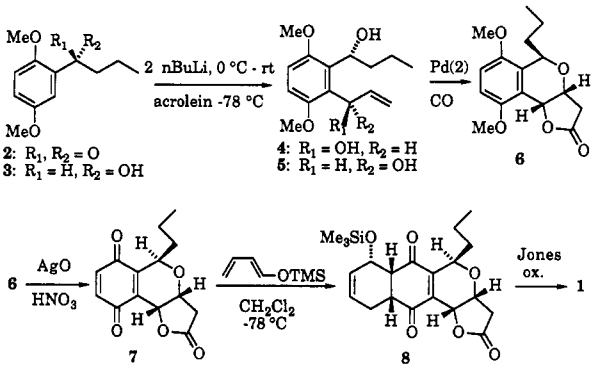
However, the requirement for a directing group can sometimes complicate the synthesis of the dienophile.

As part of a program to evaluate the directing effects of functional groups not directly attached to the atoms undergoing Diels–Alder cycloaddition,[8] we now report that remote substituents on a dienophile can confer excellent regioselectivity in Diels–Alder reactions. This work has led to an extremely direct synthesis of the pyranonaphthoquinone framework and to the first synthesis of frenolicin B (**1**).



The synthesis of **1**, shown in Scheme I, began with the reduction of ketone **2**. The alcohol **3** was generated in 100% yield by

Scheme I



treatment of **2** with (+)-Ipc_2BCl according to the method of Brown.[9] Analysis of the Mosher ester of **3** indicated an enantiomeric excess of approximately 93% on the basis of NMR. In contrast, the reaction of 2,5-dimethoxybenzaldehyde with di-*n*-propylzinc and quinine proceeded in 83% yield and afforded alcohol **3** with an enantiomeric excess of only 70%. Metalation[10] of benzylic alcohol **3** using 2 equiv of *n*-butyllithium in ether to generate the dianion followed by reaction with acrolein at −78 °C afforded diols **4** and **5** in a combined yield of only 44%. The major product appeared to be derived from metalation either meta or para to the benzylic alcohol. When the reaction was conducted in 1:10 ether:pentane solution, the alcohols **4** and **5** were isolated in 56% yield, with only 11% of the undesired isomeric product. Diols **4** and **5** were synthesized in a 1:1.5 ratio and could be separated by flash chromatography. Cyclization of alcohol **5** with palladium acetate and CO in THF in analogy with the work of Semmelhack[11] provided lactone **6** in 65% yield. The reaction of the isomeric diol **4** under the same reaction conditions afforded a mixture of **6** and its C-5 epimer. Oxidation of **6** with the standard Rapoport conditions (AgO and nitric acid)[12] provided benzoquinone **7** in 95% yield.

In order to determine whether the lactone moiety might influence the regioselectivity of the Diels–Alder reaction, we examined a Diels–Alder reaction of **7**. Treatment of benzoquinone **7** with 1-((trimethylsilyl)oxy)butadiene afforded a Diels–Alder adduct which was immediately treated with excess Jones reagent[13] to provide frenolicin B in 81% isolated yield from **7**. We did not isolate any fractions containing an isomeric quinone. Our product was identical by proton NMR, IR, TLC, and ^{13}C NMR analyses to an authentic sample of frenolicin B supplied by Hoffmann-LaRoche. In order to be absolutely certain, we also determined the structure of our compound by X-ray crystallography.

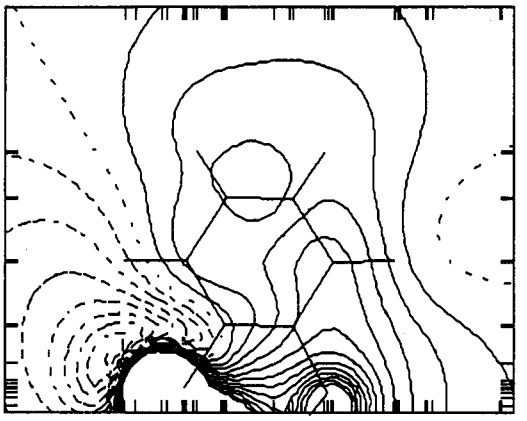
We did not anticipate the excellent regioselectivity. In order to better understand the origins of the selectivity, the molecular geometry of **7** was fully optimized at the AM1[14] level of theory and verified as a minimum by calculating the Hessian numerically. Interestingly, the propyl group on the dihydropyran ring is equatorial. Steric factors do not appear to be an issue here.

The RHF/6-31G(d) wave function[15] was then evaluated at this geometry and used to calculate molecular electrostatic potentials (MEPs).[16] Here, a MEP is defined as the potential felt by a positive test charge due to the molecular charge density, evaluated over a grid of points in a given plane of the molecule.

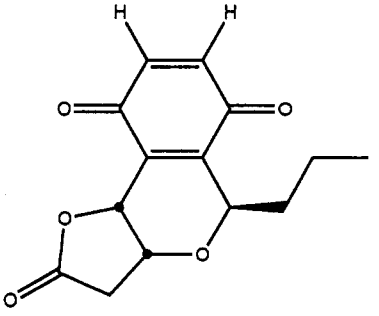
(1) Thomson, R. H. *Naturally Occurring Quinones*; Chapman and Hall: New York, 1987.
(2) Frenolicin B: Iwai, Y.; Kora, A.; Takahashi, Y. *J. Antibiot.* **1978**, *31*, 959.
(3) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.
(4) Krohn, K. *Prog. Chem. Nat. Prod.* **1989**, *55*, 37–88.
(5) Krohn, K. *Tetrahedron* **1990**, *46*, 291–318.
(6) Bauman, J. G.; Hawley, R. C.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1569. McNamara, J. M.; Kishi, Y. *Tetrahedron* **1984**, *40*, 4685. Gesson, J. P.; Jacquesy, J. C.; Renoux, B. *Tetrahedron* **1984**, *40*, 4743.
(7) Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1986**, *51*, 114.
(8) Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 283.
(9) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.
(10) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195.
(11) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.
(12) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.
(13) Kraus, G. A.; Li, C. *J. Org. Chem.* **1991**, *56*, 5098.
(14) Dewar, M. J.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(15) Harihanan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
(16) *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981.

0002-7863/93/1515-5859$04.00/0

a



b



c

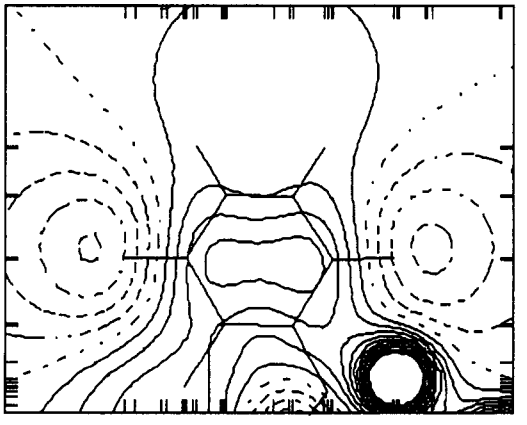


Figure 1. MEPs of 7 evaluated in planes 2 Å below (a) and above (c) the benzoquinone ring. (b) Schematic orientation of 7 in the MEPs.

The contour map thus generated identifies relative positive and negative parts of the molecule and can be used, for example, to indicate likely sites for electrophilic and nucleophilic attack. All calculations were performed with the parallel version of the electronic structure program GAMESS.[17] Figure 1 shows two MEPs of 7 evaluated in planes 2 Å below (Figure 1a) and above (Figure 1c) and parallel with the benzoquinone ring.[18] Figure 1b schematically depicts the orientation of 7 in the MEPs. Both MEPs show a positive center region (solid lines) with negative regions (dotted lines) at either side. The plane above the ring shows an almost equal negative charge distribution on either side. The plane below the ring shows more negative charge on one side, presumably due mostly to the lactone ring, and only one negative contour on the other side. Thus, these MEPs indicate that an incoming diene with one electronegative substituent should prefer to react with 7 from below the plane with the substituent away from the butyrolactone ring. This preference is dictated by the unequal charge distribution and the molecular geometry.[19]

In order to probe this hypothesis, the Diels–Alder adduct 8 was isolated and its structure evaluated by both decoupling experiments and a 2D-NOESY experiment. The significant feature of the NOESY experiment was an NOE interaction between the methine proton at C-5 and the methyls of the (trimethylsilyl)oxy group. This interaction could only be observed if the diene had reacted by an endo transition state from the face opposite the propyl group, supporting the theoretical analysis.

Frenolicin B, an anticoccidial agent, has been synthesized in six steps from ketone 2. The key step, a regioselective Diels–Alder reaction, proceeds with complete regiocontrol and in excellent yield. A rationale for the remarkable regiocontrol is advanced. The approach to the control of regioselectivity described herein should be applicable to many other natural product systems.

Acknowledgment. G.A.K. thanks Hoffmann-LaRoche for financial support. M.S.G. thanks the National Science Foundation (CHE-89-11911). Parallel SCF calculations were performed on the Cal Tech Intel Delta, under a joint study agreement with DARPA.

Supplementary Material Available: Experimental procedures and characterization data (2 pages). Ordering information is given on any current masthead page.

(17) (a) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Jensen, J. H.; Koseki, S.; Gordon, M. S.; Nguyen, K. A.; Windus, T. L.; Elbert, S. T. *QCPE Bull.* **1990**, *10*, 52. (b) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.*, submitted for publication.

(18) (a) The distance from the benzoquinone ring (2 Å) was chosen to roughly match the distance between the diene and dienophile in the transition state for the prototypical Diels–Alder cycloaddition reaction, 1,3-butadiene + ethene. (b) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1991**, *31*, 682.

(19) These results are consistent with the prediction by Kahn and Hehre (Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663) that regioselectivity is driven by electrostatic interactions between the diene and dienophile. The electrostatic interpretations provide a more general view than Frontier MO arguments (e.g., Rozeboom, M. D.; Tegmo-Larsson, I.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338).