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George A. Kraus
Iowa State University, gakraus@iastate.edu

Jianmin Shi
Iowa State University

Don Reynolds
Iowa State University

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A versatile intermediate for the synthesis of pyranoquinone antibiotics

Abstract
As a result of the sophisticated detection and isolation procedures developed by Omural and others, the family of biologically active pyranoquinones continues to grow rapidly. As a consequence of their interesting structures and useful activity, several synthetic approaches have already appeared.2

Disciplines
Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

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A Versatile Intermediate for the Synthesis of Pyranoquinone Antibiotics

George A. Kraus* and Jianmin Shi

Department of Chemistry, Iowa State University, Ames, Iowa 50011

Don Reynolds

Veterinary Medical Research Institute, Iowa State Univeristy, Ames, Iowa 50011

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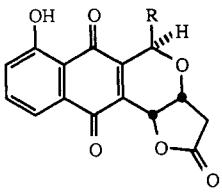
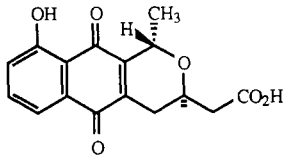
As a result of the sophisticated detection and isolation procedures developed by Omura[1] and others, the family of biologically active pyranoquinones continues to grow rapidly. As a consequence of their interesting structures and useful activity, several synthetic approaches have already appeared.[2] Its members include the antimycoplasmal antibiotics frenolicin B (**1**)[3] and nanaomycin A (**2**),[4] the antifungal agent kalafungin (**3**),[5] the antibiotics medermycin (**4**)[6] and mederrhodin (**5**),[7] and the novel C-glycoside SCH 38519 (**6**),[8] which inhibits the growth of Gram-negative and Gram-positive microorganisms. It is clear from an examination of their structures depicted below that the primary difference lies in the substitution pattern on the naphthoquinone subunit. Since an acid such as **2** can be converted into a lactone in high yield under mild conditions,[4] our interest in developing a common intermediate for the synthesis of all of these natural products led us to embark on the preparation of quinone **7**, wherein X could be a phenylthio group or a bromide or chloride.

A direct route to **7** coupled with the annulation methodology developed by Rapoport[9] could provide a general synthesis of **1**–**6**. The key to solving this problem came from our earlier report[2] that the reaction of naphthoquinones with electron-rich dienes in a Diels–Alder reaction followed by a fluoride-induced retro-Claisen reaction afforded excellent yields of advanced intermediates for the synthesis of pyranoquinones. Ester **8a** was available from acetylbenzoquinone via the one-pot Diels–Alder–retro-Claisen (DARC) reaction in 91% yield (Scheme I).

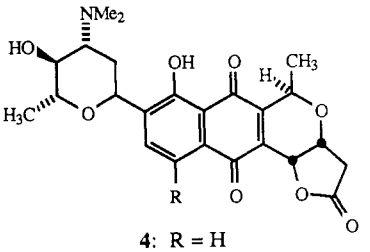
Bromination of *o*-hydroxyacetophenones using bromine/$TiCl_4$ has been shown to be selective for bromination



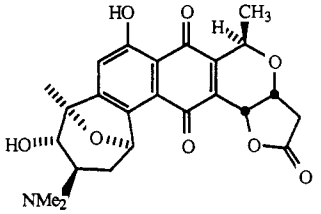
1: R = Pr
3: R = Me



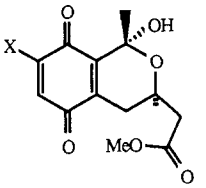
2



4: R = H
5: R = OH



6



7

ortho to the phenol.[10] Bromination of **8a** with 1 equiv of bromine afforded *only* bromophenol **8b**, as evidenced by TLC and the proton NMR of the unpurified material. Support for the regiochemical assignment came from an NOE study of the methyl ether of **8b**. Irradiation of the methyl group of the ether did not cause an enhancement of the aromatic ring proton, which is consistent with the structure of **8b**. Interestingly, bromination and oxidation with 2 equiv of bromine and $TiCl_4$ in methylene chloride at 0 °C afforded quinone **9** in 82% yield, presumably via the intermediacy of bromophenol **8b**. Initially, quinone **9** was treated with 1-methoxy-1-(trimethylsilyloxy)butadiene at −78 °C to afford a complex product mixture as evidenced by thin-layer chromatography. Fortunately, reductive removal of the hydroxyl group provided the quinone **10**, which did react in 34% yield to yield **11**, an advanced intermediate in our previous synthesis of nanaomycin A.[2]

In summary, the sequence **8a** → **9** → **10** produces a common intermediate by which the more complex pyranonaphthoquinones can be prepared. Since highly oxygenated dienes are readily available,[9] this extremely convergent approach will permit the direct synthesis of biologically active analogues and may also aid in the structure identification of quinone natural products.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes–ethyl acetate solvent mixtures for TLC. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis.

Methyl (4-Acetyl-2,3-dihydro-5-hydroxybenzofuran-2-yl)acetate (8a). To a solution of acetylbenzoquinone (2.30 g, 15.3 mmol) in 60 mL of dry CH_2Cl_2 at −78 °C was added 1-(*tert*-butyldimethylsilyloxy)-1-methoxybutadiene (6.52 g, 30.6 mmol). The solution was stirred at −78 °C for 30 min and then allowed to warm to ambient temperature for 1 h. The solution

(1) Omura, S. *Microbiol. Rev.* **1986**, *50*, 259–279.
(2) For leading references to syntheses of pyranoquinone antibiotics, see: Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568 and references therein.
(3) Omura, S.; Tsuzuki, K.; Iwai, Y. *J. Antibiot.* **1985**, *38*, 1447.
(4) Omura, S.; Tanaka, H.; Okada, Y.; Marumo, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320.
(5) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454.
(6) Ogura, H.; Furuhata, K. *Abst. 9th Int. Congr. Heterocyclic Chem.* **1983**, 114.
(7) Hopwood, D. A.; Malpartida, F.; Kieser, H. M.; Ikeda, H.; Duncan, J.; Fujii, I.; Rudd, B. A. M.; Floss, H. G.; Omura, S. *Nature (London)* **1985**, *314*, 642.
(8) Hegde. V. R.; King, A. H.; Patel, M. G.; Puar, M. S.; McPhail, A. T. *Tetrahedron Lett.* **1987**, *28*, 4485.
(9) Bauman, J. G.; Hawley, R. C.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1569.
(10) Cresp, T. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Chem. Commun.* **1972**, 214.

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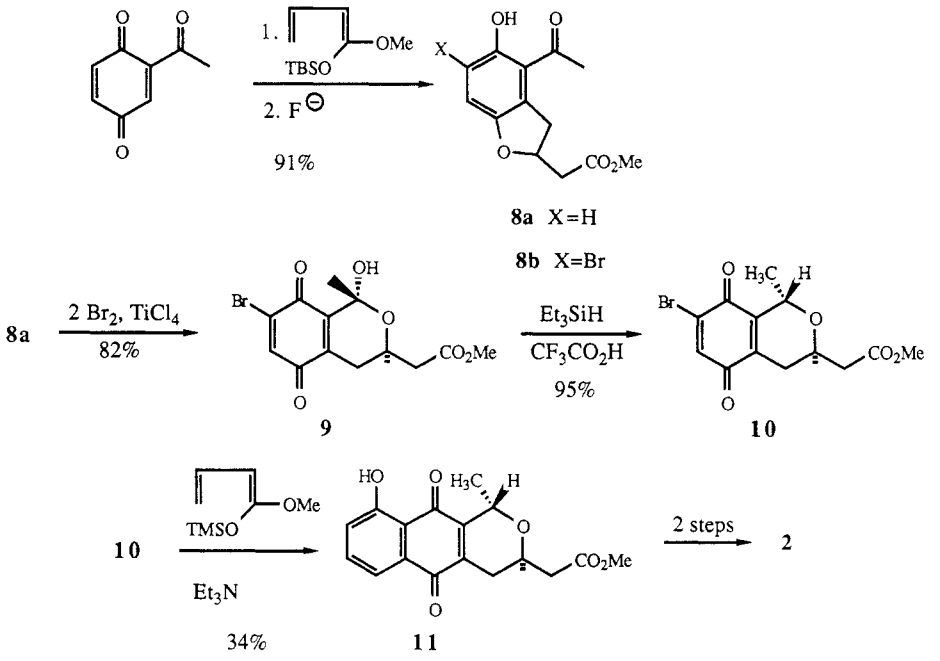
Scheme I



was cooled to 0 °C, and 40 mL of acetonitrile, 20 mL of pH 7.2 phosphate buffer, and 35 mL of tetra-*n*-butylammonium fluoride (1 M in THF) was added. The solution was allowed to warm to ambient temperature and acidified with 3 N HCl. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried, concentrated, and then purified by flash chromatography using 3:1 hexanes–ethyl acetate to provide 3.49 g (91% yield) of phenol **8a**. Phenol **8a** was a clear liquid: HRMS calcd for $C_{13}H_{14}O_5$ 250.08413, found 250.08439; IR (film) 3020, 1736, 1580, 1474, 1215, 827 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (s, 3 H), 2.72 (dd, J = 16.2, 6.6 Hz, 1 H), 2.91 (dd, J = 16.2 and 6.3 Hz, 1 H), 3.23 (dd, J = 16.2, 7.2 Hz, 1 H), 3.71 (dd, J = 16.5, 8.7 Hz, 1 H), 3.74 (s, 3 H), 5.17 (m, 1 H), 6.79 (d, J = 9 Hz, 1 H), 6.95 (d, J = 9 Hz, 1 H), 12.16 (s, 1 H); TLC (3:1 H:EA) R_f = 0.30.

***trans*-Methyl (7-Bromo-3,4-dihydro-5,8-dioxo-1-methyl-1*H*-2-benzopyran-3-yl)acetate (10).** To a solution of phenol **8a** (0.75 g, 3.0 mmol) in 15 mL of CH_2Cl_2 at 25 °C was added 10.5 mL of a 1 M solution of $TiCl_4$ in CH_2Cl_2, followed by bromine (0.948 g, 6.0 mmol). The solution was stirred for 1.5 h. Water (10 mL) was carefully added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution and then with brine. The organic layer was dried and concentrated. The crude product was purified by flash chromatography using 3:1 hexanes–ethyl acetate to provide 0.85 g (82% yield) of **9**.

In practice, **9** was reduced directly to afford **10**. To a solution of **9** (0.280 g, 0.81 mmol) at −78 °C in 8 mL of CH_2Cl_2 was added triethylsilane (0.174 g, 1.5 mmol) followed by BF_3Et_2O (0.1 mL). After 30 min, the reaction was warmed to 25 °C and the solvent was removed. The crude product was immediately purified by flash chromatography using 3:1 hexanes–ethyl acetate to afford a 95% yield of **10**. Quinone **10** was an oil: HRMS calcd for $C_{13}H_{13}BrO_5$ 327.99463, found 327.99502; IR (film) 3061, 2982, 1738, 1668, 1655, 1595, 1259 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (d, J = 6.6 Hz, 3 H), 2.24 (ddd, J = 18.3, 10.4, 4.0 Hz, 1 H), 2.58 (dd, J = 15.8, 5.7 Hz, 1 H), 2.66–2.75 (m, 2 H), 3.73 (s, 3 H), 3.85–3.94 (m, 1 H), 4.69–4.78 (m, 1 H), 7.26 (s, 1 H); TLC (3:1 H:EA) R_f = 0.17.

***trans*-Methyl (3,4-Dihydro-5,10-dioxo-9-hydroxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (11).** To a solution of **10** (0.098 g, 0.3 mmol) in 5 mL of CH_2Cl_2 was added dropwise 1-(trimethylsiloxy)-1-methoxy-1,3-butadiene (0.103 g, 0.6 mmol). The solution was stirred at −78 °C for 1 h and then allowed to warm to ambient temperature. Triethylamine (0.070 g, 0.7 mmol) was added, and the solution was stirred for 5 min. The solvent was removed in vacuo, and the residue was dissolved in acetonitrile. A 5% solution of HF in acetonitrile was added, and the solution was stirred for 5 min (TLC). The solvent was removed in vacuo, and the residue was partitioned between water and CH_2Cl_2. The crude product was purified by silica gel chromatography using 5:1 hexanes–ethyl acetate to provide 0.032 g (34%) of **11**. This compound was identical with that produced in our previous synthesis:[2] HRMS calcd for $C_{17}H_{16}O_5$ 300.0998, found 300.0993; IR (film) 3018, 2990, 1742, 1663, 1624, 1595, 1296, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (d, J = 6.6, Hz, 3 H), 2.34 (ddd, J = 18.5, 10.5, 4.0 Hz, 1 H), 2.63 (dd, J = 16.5, 5.4 Hz, 1 H), 2.75 (dd, J = 15.6, 7.5 Hz, 1 H), 2.88 (dt, J = 18.3, 2.7 Hz, 1 H), 3.74 (s, 3 H), 3.91–3.99 (m, 1 H), 4.86–4.90 (m, 1 H), 7.71–7.79 (m, 1 H), 8.04–8.10 (m, 1 H); TLC (3:1 H:EA) R_f = 0.47.

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Registry No. **2**, 52934-83-5; **8a**, 124287-42-9; **8b**, 124287-45-2; **9**, 124287-43-0; **10**, 124287-44-1; **11**, 124438-93-3; CH_2=CHCH=C(OMe)TBSO, 119582-47-7; CH_2=CHCH=C(OMe)-TMS, 124287-46-3; acetylbenzoquinone, 1125-55-9.

Transformation of α- and β-Ionones into α- and β-Damascone and β-Damascenone Using Allylsilane Chemistry

Elisabetta Azzari, Cristina Faggi, Nedo Gelsomini, and Maurizio Taddei*

Dipartimento di Chimica Organica "U. Schiff", Università di Firenze, Via G. Capponi 9, I-50121 Firenze, Italy

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The damascones and damascenones are flavor components present in *Rosa damascena* and in several varieties of fruits, grapes, and wines.[1] Their importance as essences for perfumes, cosmetics, and foods has justified the large number of syntheses reported recently in the literature.[2]

(1) See for example: Weeks, W. W. In *Biogeneration of Aromas*; Parlamient, T. H., Croteau, R., Eds.; ACS Symposium Series 317; American Chemical Society: Washington, DC, 1986; p 157.

(2) For the more recent syntheses, see: Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909. Snowden, R. L.; Linder, S. M.; Muller, B. L.; Shulte-elte, K. H. *Helv. Chim. Acta* **1987**, *70*, 1868. Zaidlewicz, M. *Tetrahedron Lett.* **1986**, *27*, 5135. Noef, F.; Decarzant, R. *Tetrahedron* **1986**, *42*, 3245. Uneyama, K.; Fujibayashi, S.; Torii, S.; *Tetrahedron Lett.* **1985**, *27*, 4637.

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