



Intramolecular radical cyclizations onto quinones. A direct synthesis of Bauhinoxepin J

George A. Kraus*, Aniket Thite, Feng Liu

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

ARTICLE INFO

Article history:

Received 12 May 2009

Revised 23 June 2009

Accepted 26 June 2009

Available online 16 July 2009

ABSTRACT

Bauhinoxepin J has been synthesized in four steps using an intramolecular persulfate-mediated radical addition to a quinone as the key step.

© 2009 Elsevier Ltd. All rights reserved.

In recent years natural products scientists have discovered a number of biologically active natural products bearing the dibenz[*b,f*]oxepin skeleton. Representative structures are depicted in Figure 1. Tournefoliac acid B (**1**) was isolated from *Tournefortia sarmentosa* Lam. (Boraginaceae) and exhibits potent anti-LDL-peroxidative activity.¹ Bauhiniastatin 1 (**2**) was isolated from *Bauhinia purpurea* by Pettit et al. It exhibits significant growth inhibition against a mini-panel of human cancer cell lines, including the P388 cancer cell line.² Bauhinoxepin J (**3**) is a dihydrodibenz[*b,f*]oxepin that was isolated from *B. purpurea*. It exhibited cytotoxicity toward KB and BC cell lines with IC₅₀ values of 10.5 and 12.1 μM, antimycobacterial activity with an MIC value of 24.4 μM, and antimalarial activity with IC₅₀ value of 5.8 μM.³ Relatively few syntheses of dibenz[*b,f*]oxepins have been reported. Notable examples include the synthesis of bulbophylol-B by Yao using an intramolecular Ullmann cyclization and the Snieckus synthesis of dibenz[*b,f*]oxepinones using an innovative lateral metalation/cyclization protocol.⁴

Our approach to the synthesis of **3** is depicted below in Figure 2. We had previously synthesized colutequinone A (**4**) by way of an intermolecular persulfate-mediated radical addition to a benzoquinone.⁵ For the synthesis of quinone **3**, we planned an intramolecular radical cyclization. To the best of our knowledge, intramolecular radical additions to quinones to form carbon–carbon bonds have not previously been reported.

The synthesis of **3** is shown in Scheme 1 and began with the reduction of **5** with LAH to afford diol **7**⁶ in 85% yield. This diol was deprotonated using potassium carbonate in DMF and treated with bromoquinone **6**.⁷ The resulting alcohol (produced in 90% yield from **6**) was oxidized with Jones reagent at 0 °C to provide acid **8** in 73% yield from **7**. The reduction/alkylation/oxidation sequence was necessary because the dianion derived from hydrolysis

of **5** reacted with **6** to provide a 30% yield of **8**, but the reaction was not reproducible.

First, we attempted to use phenyliodoso diacetate^{8,9} to generate the radical from **8**. To our disappointment, it provided a meager 4% yield of the target compound. We next employed the Barton ester^{10,11} protocol. Unfortunately, this method did not provide any of the desired products. We then examined the silver (I)-catalyzed persulfate method developed by Torsell and by Minisci.^{12,13} Fortunately, the use of ammonium persulfate with equivalent proportions of the silver salt afforded **3** in 30% isolated yield as the only

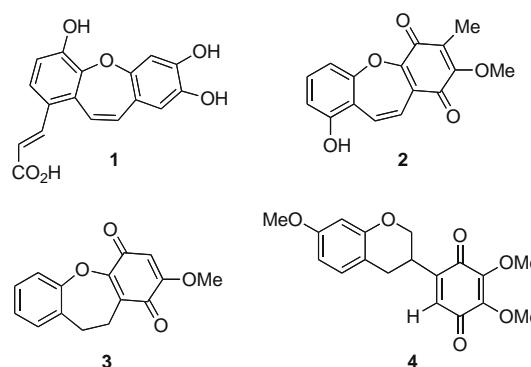


Figure 1. Natural products containing quinone or hydroquinone subunits.

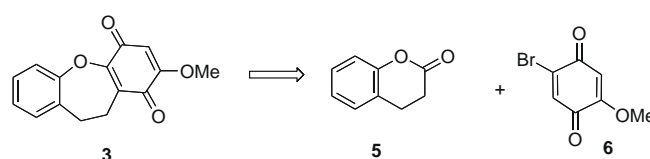
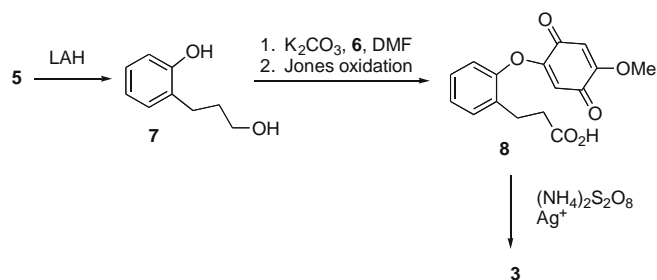


Figure 2. Retrosynthetic analysis.

* Corresponding author. Tel.: +1 515 294 7794; fax: +1 515 294 0105.
E-mail address: gakraus@iastate.edu (G.A. Kraus).

Scheme 1. Synthesis of **3**.

identifiable product. We also tried using potassium persulfate instead of ammonium persulfate; however, it provided only a 13% yield of **3**. The conditions of DeKimpe,¹⁴ wherein both the silver salt and the persulfate were added in two portions,¹⁵ afforded **3** in 40% isolated yield. This constitutes a 25% overall yield of Bauhinnoxepin J. The identity of synthetic Bauhinnoxepin J (**3**) was confirmed by comparison of our ¹H NMR, ¹³C NMR, LRMS, and HRMS data with the published spectra.

This represents the first total synthesis of quinone **3**. This synthesis features the first intramolecular radical addition to a quinone. This flexible and direct synthetic pathway will facilitate further biological evaluation of this little studied class of natural products.

Acknowledgment

We thank the Department of Chemistry at Iowa State University for partial support of this work.

References and notes

- Lin, Y.-L.; Chang, Y.-Y.; Kuo, Y.-H.; Shiao, M.-S. *J. Nat. Prod.* **2002**, *65*, 745–747.
- Pettit, G. R.; Numata, A.; Iwamoto, C.; Usami, Y.; Yamada, T.; Ohishi, H.; Cragg, G. M. *J. Nat. Prod.* **2006**, *69*, 323–327.
- Boonphong, S.; Puangsombat, P.; Baramée, A.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. *J. Nat. Prod.* **2007**, *70*, 795–801.
- Lin, J.; Zhang, W.; Jiang, N.; Niu, Z.; Bao, K.; Zhang, L.; Liu, D.; Pan, C.; Yao, X. *J. Nat. Prod.* **2008**, *71*, 1938–1941; MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem.* **2008**, *73*, 9710–9719.
- Kraus, G. A.; Kim, I. *Tetrahedron* **2003**, *59*, 7935–7937.
- Botta, M.; Quici, S.; Pozzi, G.; Marzanni, G.; Pagliarini, R.; Barra, S.; Crich, S. G. *Org. Biomol. Chem.* **2004**, *2*, 570–577.
- Tohma, H.; Morioka, H.; Harayama, Y.; Hashizume, M.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6899–6902.
- Togo, H.; Katohgi, M. *Synlett* **2001**, 565.
- Togo, H.; Aoki, M.; Kuramochi, T.; Yokoyama, M. *Perkin Trans. 1* **1993**, 2417.
- Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1989**, *45*, 2615–2626.
- Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 5307–5314.
- Jacobsen, N.; Torssell, K. *Justus Liebigs Ann. Chem.* **1972**, *763*, 135–147.
- Coppa, F.; Fontana, F.; Lazzarini, E.; Minisci, F. *Chem. Lett.* **1992**, 1299.
- DeKimpe, Norbert, private communication.
- To a stirred solution of acid **8** (16 mg, 0.053 mmol) in 6 mL of 30% aq CH₃CN under argon was added silver nitrate (0.3 equiv). The mixture was heated to 65 °C and a solution of ammonium persulfate (1.3 equiv) in 2 mL of 30% aq CH₃CN was added dropwise for 20 min. The mixture was then stirred at 70 °C for 3 h. The mixture was cooled to 65 °C. An additional amount of silver nitrate (0.3 equiv) was added and a solution of ammonium persulfate (1.3 equiv) in 2 mL of 30% aq CH₃CN was added dropwise for 20 min. After an additional 3 h at 70 °C, the reaction mixture was cooled to rt and extracted with dichloromethane. The organic extracts were washed with brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified using flash chromatography on silica gel (1:1 hexanes:ethyl acetate) to obtain **3** (5.5 mg, 40% yield).
IR (thin film): 2915, 2849, 1661, 1607, 1582, 1488, 1463, 1380, 1228, 1193 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.22–7.25 (m, 2H), 7.13–7.17 (m, 2H), 5.90 (s, 1H), 3.83 (s, 3H), 3.06–3.09 (m, 2H), 2.81–2.85 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 182.8, 181.9, 158.9, 155.7, 152.9, 133.2, 129.6, 128.0, 126.0, 123.7, 121.2, 105.4, 56.7, 29.9, 26.5; LRMS (EI): *m/z* 256 (M⁺, 100%), 241, 115, 69; HRMS (EI) calcd for C₁₅H₁₂O₄: 256.0736, found: 256.0740.