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

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ABSTRACT

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

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. Tournefolic 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 IC_{50} values of 10.5 and 12.1 μM, antimycobacterial activity with an MIC value of 24.4 μM, and antimalarial activity with IC_{50} 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 Torssell 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

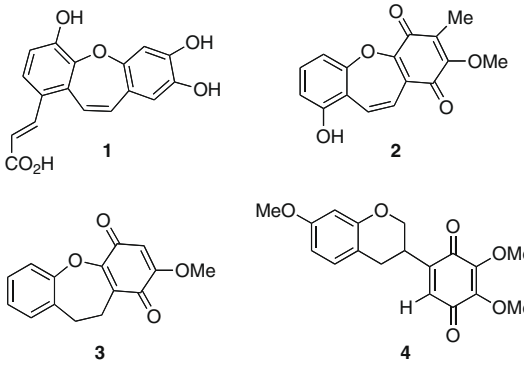

Figure 1. Natural products containing quinone or hydroquinone subunits.

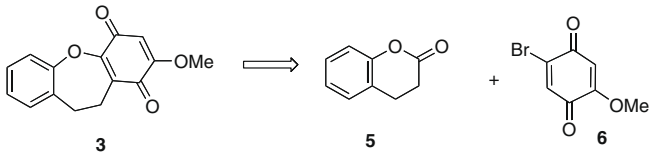

Figure 2. Retrosynthetic analysis.

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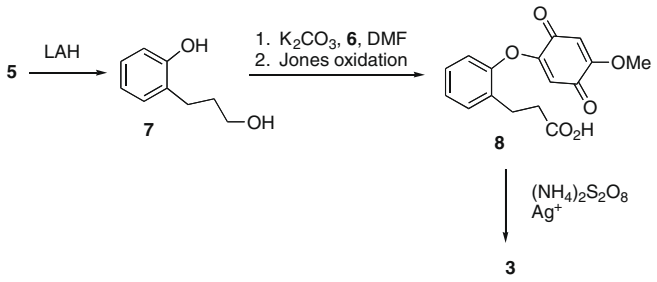

Scheme 1. Synthesis of **3**.

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 Bauhinoxepin J. The identity of synthetic Bauhinoxepin J (**3**) was confirmed by comparison of our ^{1}H NMR, ^{13}C 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

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15. To a stirred solution of acid **8** (16 mg, 0.053 mmol) in 6 mL of 30% aq CH_3CN 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 CH_3CN 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 CH_3CN 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 Na_2SO_4, 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}. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{12}O_4$: 256.0736, found: 256.0740.