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Phytochemical medicinal agents. A quinone-based route to pterocarpins

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Abstract—The synthesis of 6,9 di-demethoxy kushecarpin A has been achieved by the coupling of a benzofuran anion with a quinone monoketal followed by a regioselective cyclization and a stereoselective hydrogenation reaction.
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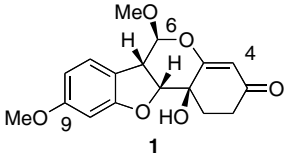
Kushecarpin A (**1**) was recently isolated from *Sophora flavescens* by methanol extraction of the roots. This novel pterocarpin exhibited significant antibacterial activities against the Gram-positive bacteria Staphylococcus aureus, Bacillus subtilis, S. epidermidis, and Propionibacterium acnes.[1] Related compounds **2a** and **3** have been reported.[2,3] The benzofuran **4** has been reported to be a constituent of *Lespedeza* species.[4] Despite their novel structures and potentially valuable biological activity, no synthetic approaches to **1** or **2** have been reported. As part of a program to identify useful plant medicinal agents,[5] we report herein a convenient and direct preparation of **2b** featuring the addition of the anion of a benzofuran to a synthetic equivalent of methoxy-1,4-benzoquinone.



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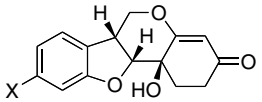
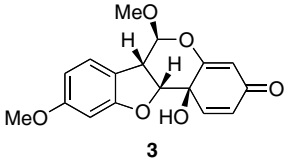


2a: X = OMe
2b: X = H



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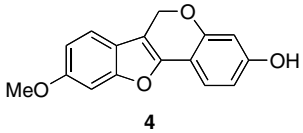
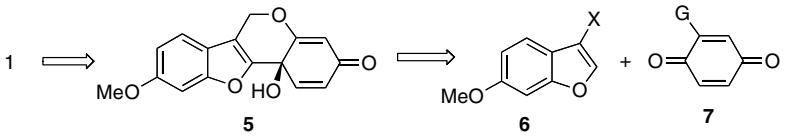


4

Cyclohexadienone **5** was viewed as a key intermediate because hydroxyl-directed hydrogenation[6] was expected to install the dihydrobenzofuran unit with the methine hydrogens on the same face of the molecule as the hydroxyl group. Compound **5** in turn would be synthesized from readily available benzofuran **6** and benzoquinone **7**.[7] If G represents an electron-donating substituent, regioselective reaction of an organolithium reagent with the benzoquinone at the carbonyl required for the synthesis of **5** has good precedent.[8]

In order to test this hypothesis, we metalated benzofurans **8a** and **8b** with *n*-butyl lithium (THF, 0 °C, 1 h) and treated the resulting anion with benzoquinones. Unfortunately, neither methoxybenzoquinone nor phenylthiobenzoquinone reacted with **8a** or **8b** to generate the desired hydroxy cyclohexadienone. Transmetalation with zirconium salts, a strategy used effectively in a related system,[9] did not result in the formation of an adduct. However, **8a** and **8b** reacted with benzoquinone to afford **9a** and **9b**, respectively, in 96% and 71% yields.[10]



5 **6** **7**

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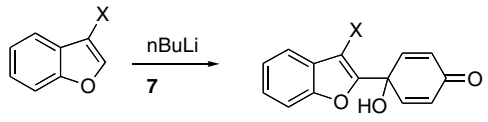
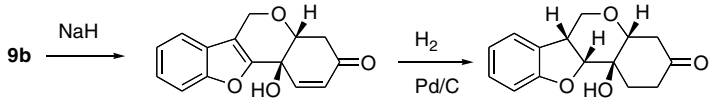


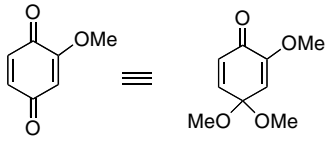
8a: X = H
8b: X = CH_2OH
8c: X = CH_2OEVE

9a: X = H
9b: X = CH_2OH

The next step was to transform benzofuran **9b**. Compound **9b** reacted readily under basic conditions to afford alcohol **10**. The most convenient conditions for scale up involved sodium hydride in THF at 25 °C. With the tetracyclic system in hand, the reduction of the benzofuran was examined. Surprisingly, alcohol **10** did not react using the iridium-based directed hydrogenation conditions. Catalytic hydrogenation using Pd/C afforded a single stereoisomer based on the proton and carbon NMR spectra. The structure of **11** was determined by X-ray crystallography.[11]



Attempts to introduce the C-4–C-4a double bond (see **1** for numbering) in ketone **10** by enol silyl ether formation and subsequent oxidation were unsuccessful because the enol silyl ether could not be formed (2 TMSOTf, Et_3N; TMSCl, DBU). The efforts to oxidize **10** had become necessary because the benzofuran anions failed to react with methoxybenzoquinone. We next synthesized quinone monoketal **12**[12] as a synthetic equivalent of methoxybenzoquinone.



12

The reaction of the anion of **8c** with quinone monoketal **12** followed by acetic acid-mediated hydrolysis of the ethyl vinyl ether (EVE) protecting group afforded adduct **13** in 80% yield. Cyclization of **13** with DBU in THF at 140 °C afforded **14** plus isomer **15** in a ratio of 5:1. The use of sodium hydride at 25 °C generated only **15**. The use of triethylamine at 140 °C resulted in returned starting material. The use of acid catalysts such as BF_3–Et_2O afforded only **15**. Attempts to convert **15** into **14** using base catalysis were unsuccessful.

Catalytic hydrogenation of **14** using palladium on carbon followed by treatment of the reduced product with trifluoroacetic acid in toluene at 110 °C provided **2b** in 71% overall yield.[13] The structure of **2b** is supported by proton and carbon NMR and mass spectrometry. A 2D NOE experiment on the acetate of **2b** showed interactions between the methyl group of the acetate and hydrogens on C-1, C-11a, and C-6, supporting the relative stereochemistry assigned to **2b**. The hydrogen on C-6a showed NOE interactions with hydrogens on C-6, C-7 and C-11a.

The route to **2b** from **8c** requires only five steps and should be compatible with considerable structural variation. The use of quinone monoketal **12** as a synthetic equivalent of methoxybenzoquinone extends the range of quinols that can be produced by carbanion reactions. Certain heterocyclic quinol adducts show promising in vivo antitumor activity.[10]

Acknowledgements

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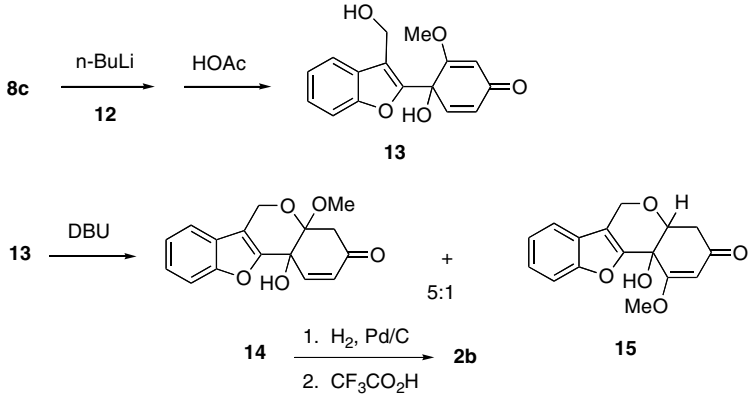

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13. **2b** data: ^{1}H NMR (300 MHz, CD_3COCD_3) δ 2.03 (m, 1H), 2.27 (m, 1H), 2.73 (m, 2H), 4.04 (m, 1H), 4.30 (d, 1H, $J = 10.8$ Hz), 4.84 (dd, 1H, $J = 10.8$ Hz, $J = 4.2$ Hz), 4.97 (d, 1H, $J = 10.8$ Hz), 5.25 (s, –OH), 5.42 (s, 1H), 6.73 (d, 1H, $J = 8.1$ Hz), 6.92 (t, 1H, $J = 7.5$ Hz), 7.15 (t, 1H, $J = 8.1$ Hz), 7.37 (d, 1H, $J = 7.5$ Hz).
CMR (75 MHz, CD_3COCD_3) δ 32.1, 32.2, 40.6, 67.3, 67.7, 82.4, 108.2, 109.1, 121.4, 125.0, 128.7, 129.1, 159.5, 171.6, 197.1. MS: *m/z* 258, 257, 172, 131, 130, 117. HRMS: *m/z* for $C_{15}H_{14}O_4$ calcd. 258.0892; measured 258.0897. TLC (ethyl acetate/hexane = 2:1) $R_f = 0.25$. Mp 198–200 °C.