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Quinone Approaches toward the Synthesis of Aflatoxin B_2

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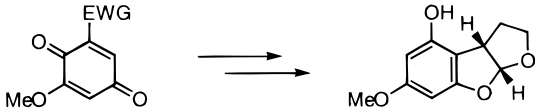
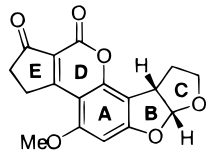
ABSTRACT



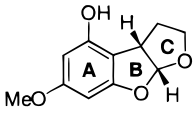
EWG = CHO or S*(O)-*p*-tolyl

Quinones bearing electron-withdrawing groups can serve as useful precursors to furobenzofuran ring systems through their reaction with 2,3-dihydrofuran. Formal racemic and stereoselective syntheses of the fungal metabolite aflatoxin B_2 are described that utilize this approach to construct the tricyclic ABC-ring core of the molecule.

The aflatoxins are a group of compounds produced in spoiling foodstuffs by the molds *Aspergillus flavus*, *Aspergillus versicolor*, and *Aspergillus parasiticus*. These molds, and hence the aflatoxins, can occur on a wide variety of common food items.[1] The aflatoxins are extremely toxic, causing acute liver damage in a variety of animals,[2] and are also powerful carcinogens.[3] Aflatoxin B_2 (**1**) is one of four key members of the aflatoxin family of compounds.



aflatoxin B_2 (**1**)



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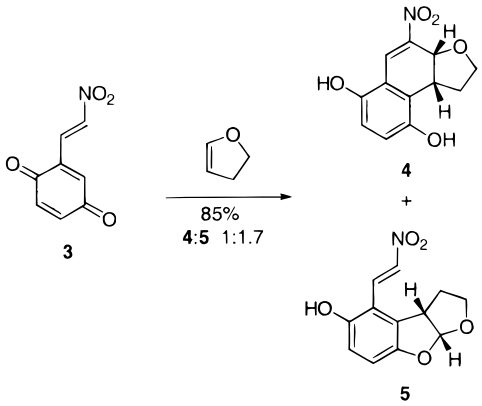
The potent biological activity of the aflatoxins, along with their wide distribution, has translated into considerable synthetic interest over the last several decades. Numerous syntheses of aflatoxin B_2 have been reported.[4] Most syntheses rely on the formation of the tricyclic intermediate **2**, containing the ABC-ring core of the molecule. The D and E rings are then efficiently appended via a von Pechmann reaction to complete the syntheses.[4k,l] The furo[2,3-*b*]-benzofuran intermediate (**2**) has proven to be somewhat challenging to construct and continues to inspire new approaches to its synthesis.

In the course of studying the [4 + 2] cycloadditions of 2-(2-nitrovinyl)-1,4-benzoquinone (**3**) with 2,3-dihydrofuran, an interesting side product (**5**) was observed (Scheme 1).

Scheme 1



Two products were obtained, the cycloaddition product **4** and the furo[2,3-*b*]benzofuran product **5**, in 85% combined yield and in a 1:1.7 ratio, respectively.[5]

(1) Schuda, P. F. *Top. Curr. Chem.* **1980**, *91*, 75.
(2) Butler, W. H.; Clifford, J. I. *Nature* **1965**, *206*, 1045.
(3) (a) Lilly, L. J. *Nature* **1965**, *207*, 433. (b) Butler, W. H. *Brit. J. Cancer* **1964**, *18*, 756.

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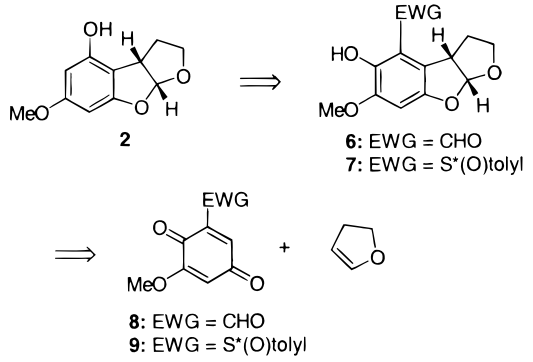
Inspired by the facile formation of **5**, we decided to explore the use of quinones bearing electron-withdrawing groups (EWG) for synthesizing aflatoxin B_2, which contains a similar furo[2,3-*b*]benzofuran ring system. We were also encouraged by a previous report of 2-acetyl-1,4-benzoquinone reacting similarly with dihydrofuran[6] and by the work of Brimble and co-workers on the reactivity of 2-(4-methylbenzenesulfinyl)-1,4-benzoquinone with 2-trimethylsiloxyfuran.[7] Our approach to aflatoxin B_2 is summarized in Scheme 2, where the electron-withdrawing group is an

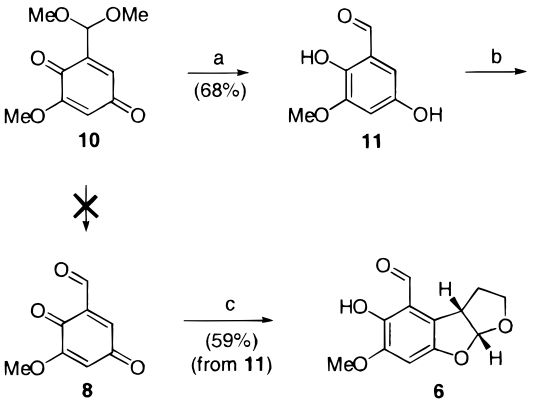
Scheme 2



aldehyde or optically pure sulfoxide, leading to formal racemic and stereoselective syntheses of aflatoxin B_2, respectively.

Synthesis of Racemic 2. The synthesis of methoxy-substituted quinone aldehyde **8** and its subsequent reaction with dihydrofuran, giving **6**, is outlined in Scheme 3. The

Scheme 3[a]

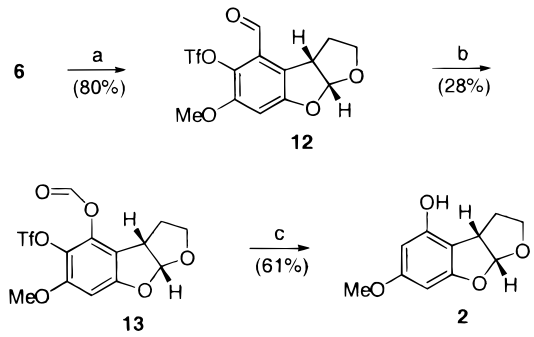


[a] Key: (a) (i) H_2 (1 atm), 10% Pd−C, EtOAc, (ii) 6 N HCl, Et_2O; (b) DDQ, PhH; (c) dihydrofuran, CH_3CN, 0 °C, 2 h, then rt, 2 h.

quinone acetal **10** was synthesized in two steps from commercially available *o*-vanillin as described by Hibino and Weinreb.[8] Attempts were made to deprotect the acetal of **10** leading directly to **8**, but this resulted in decomposition. To circumvent the difficulties associated with direct deprotection of **10**, a reduction, deprotection, and reoxidation strategy was used. Quinone **10** was converted to hydroquinone **11** by a modification of the Hibino and Weinreb procedure.[8] Oxidation of **11** using DDQ in benzene gave the unstable quinone **8**, which was isolated and used in the next step without further purification. The reaction of **8** with dihydrofuran in acetonitrile gave the tricycle **6** in 59% overall yield in two steps from **11**. Solvent choice was significant in this reaction, with the polar solvent acetonitrile giving the best results.

With the completion of the racemic furobenzofuran core (**6**) of aflatoxin B_2, it remained to deoxygenate the existing phenolic hydroxyl and replace the aldehyde with a phenolic hydroxyl (Scheme 4).

Scheme 4[a]



[a] Key: (a) Tf_2O, DMAP, pyridine, CH_2Cl_2, 0 °C; (b) urea·H_2O_2, TFAA, CH_2Cl_2, rt; (c) Raney Ni, MeOH, rt.

To deoxygenate the phenolic hydroxyl group of **6**, it was first converted to the trifluoromethanesulfonate ester (triflate, TfO) using triflic anhydride in pyridine and methylene chloride with catalytic DMAP, giving **12** in 80% yield. Baeyer−Villiger oxidation of aldehyde **12** using urea−hydrogen peroxide and trifluoroacetic anhydride[9] gave the aryl formate **13** in 28% yield.

(4) (a) Bando, Toshikazu, Shishido, Kozo *Synlett* **1997**, 665. (b) Pirrung, M. C.; Lee, Y. R. *Tetrahedron Lett.* **1996**, *37*, 2391. (c) Rapoport, H.; Civitello, E. R. *J. Org. Chem.* **1994**, *59*, 3775. (d) Koreeda, M.; Dixon, L. A.; Hsi, J. D. *Synlett* **1993**, 555. (e) Kraus, G. A.; Johnston, B. E.; Applegate, J. M. *J. Org. Chem.* **1991**, *56*, 5688. (f) Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1990**, 39. (g) Wolff, S.; Hoffmann, H. M. R. *Synthesis* **1988**, 760. (h) Sloan, C. P.; Cuevas, J. C.; Quesnelle, C.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 4685. (i) Weeratunga, G.; Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1988**, 721. (j) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1006. (k) Roberts, J. C.; Sheppard, A. H.; Knight, J. A.; Roffey, P. *J. Chem. Soc. C* **1968**, 22. (l) Büchi, G.; Weinreb, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 746. (m) Büchi, G.; Foulkes, D. M.; Kurono, M.; Mitchell, G. F.; Schneider, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 6745. (n) Knight, J. A.; Roberts, J. C.; Roffey, P. *J. Chem. Soc. C* **1966**, 1308.

(5) Noland, W. E.; Kedrowski, B. L. *J. Org. Chem.* **1999**, *64*, 596.

(6) Kuser, P.; Frauenfelder, E. F.; Eugster, C. H. *Helv. Chim. Acta* **1971**, *54*, 969.

(7) (a) Brimble, M. A.; Elliott, R. J. R. *Tetrahedron* **1997**, *53*, 7715. (b) Brimble, M. A.; Duncalf, L. J.; Reid, D. C. W. *Tetrahedron: Asymmetry* **1995**, *6*, 263. (c) Brimble, M. A.; Brimble, M. T.; Gibson, J. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 179. (d) Brimble, M. A.; Gibson, J. J. *Tetrahedron Lett.* **1987**, *28*, 4891.

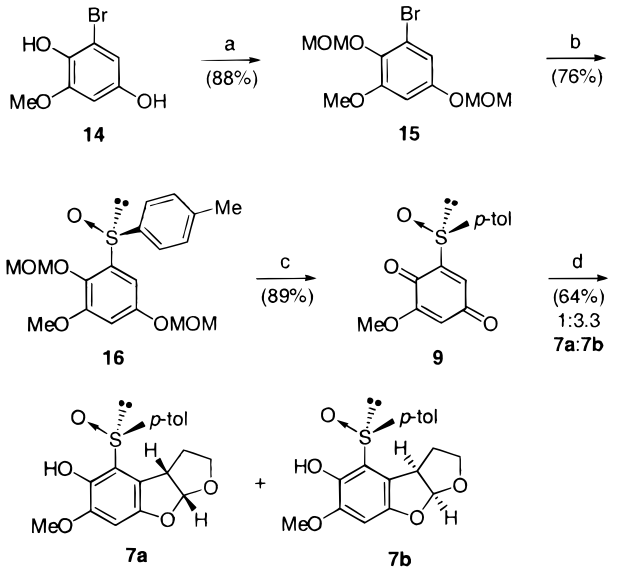
(8) Hibino, S.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 1175.

(9) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.

Other milder oxidants were examined in this reaction, such as *m*-CPBA, but these were less effective. Treatment of **13** with Raney nickel in methanol hydrogenolyzed the aryl triflate and cleaved the formate ester, giving the desired compound **2** in 61% yield. Other more standard methods for this reduction were attempted, including palladium-catalyzed formate reduction, but these failed to hydrogenolyze the aryl triflate. Reversing the order of the final two steps of the synthesis was also explored. Hydrogenolysis of the triflate in **12** proceeded smoothly, but all attempts at the subsequent Baeyer−Villiger oxidation of the product failed. The formation of **2** proceeds in nine steps from commercially available *o*-vanillin and, from here, constitutes a formal synthesis of (±)-aflatoxin B_2, as previously reported.

Stereoselective Synthesis. The synthesis of methoxy-substituted quinone sulfoxide **9** and its subsequent reaction with dihydrofuran to give **7a** and **7b** is outlined in Scheme 5. The hydroquinone **14** was synthesized from vanillin in two steps by known methods.[10] Hydroquinone **14** was protected as its bis(methoxymethyl) ether **15** by a phase-transfer method in 88% yield.[11] The sulfoxide auxiliary was installed via Andersen's method,[12] by first treating **15** with *n*-butyllithium and adding the resulting anion to a solution of (−)-menthyl (*S*)-*p*-toluenesulfinate, giving **16** in 76% yield. Oxidative demethylation of **16** with ceric ammonium nitrate (CAN) gave the quinone sulfoxide **9** in 89% yield. The use of methoxymethyl (MOM) protecting groups[11a] was critical to the success of this reaction, which gave very poor results when the hydroquinone was protected with the more typical methyl ether groups.

Scheme 5[a]



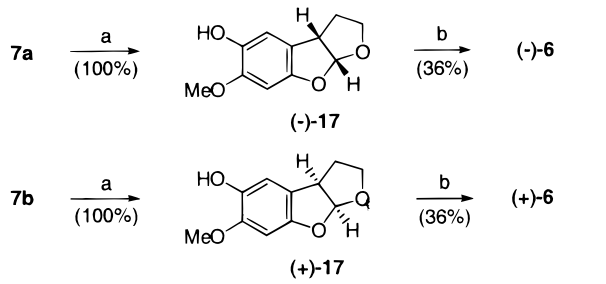
[a] Key: (a) MOMCl, NaOH, $BnEt_3NCl$, THF, 0 °C; (b) *n*-BuLi, THF, −78 °C, **15**; then add to (−)-menthyl (*S*)-*p*-toluenesulfinate, THF, −78 °C; (c) CAN, CH_3CN, H_2O; (d) $TiCl_4$ (5 equiv), $Ti(OiPr)_4$ (5 equiv), CH_2Cl_2, rt, 30 min, then −78 °C; **9**, CH_2Cl_2; then dihydrofuran, 1 h, −78 °C.

Treatment of the quinone **9** with 10 equiv of the chelating Lewis acid $TiCl_2(O\text{-}i\text{-}Pr)_2$ in methylene chloride at −78 °C, followed by dihydrofuran, gave a mixture of **7a** and **7b**. These diastereomers were separated by column chromatography and crystallized, giving a 64% yield of **7a** and **7b** in 1:3.3 ratio. The stereochemical assignment of **7b** was confirmed by single-crystal X-ray diffraction.[13]

The sequence in Scheme 5 was also carried out in the enantiomeric series using the (+)-menthyl (*R*)-*p*-toluenesulfinate auxiliary, giving similar yields of *ent*-**7a** and *ent*-**7b**, respectively.

The completion of the stereoselective synthesis is described in Scheme 6. Both **7a** and **7b** could be efficiently desulfurized in essentially quantitative yield by treatment with Raney nickel in ethanol and acetone, leading to (−)- and (+)-**17**. Duff formylation of (−)- and (+)-**17** with hexamethylenetetramine gave (−)- and (+)-**6**, respectively, in 36% yield. It was shown above that **6** could be converted to **2** in the racemic series.

Scheme 6[a]



[a] Key: (a) Raney Ni, EtOH, acetone; (b) hexamethylenetetramine, AcOH, 110 °C.

In summary, the synthesis of furobenzofuran ring systems, such as those found in the natural product aflatoxin B_2, can be achieved by the reactions of quinone-aldehydes or quinone-sulfoxides with dihydrofuran.

Acknowledgment. B.L.K. wishes to thank the Wayland E. Noland Research Fellowship Fund of the University of Minnesota Foundation for a research fellowship.

Supporting Information Available: Full experimental details for all new reactions, including full characterization of new compounds, ^1H NMR spectra for **13** and **2**, and X-ray crystallographic data for **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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