A Formal Synthesis of Aflatoxin B_2

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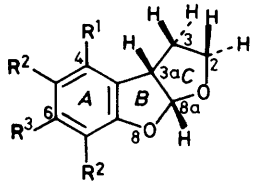
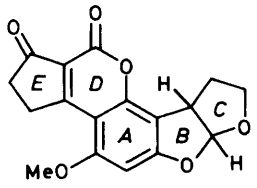
A brief synthesis of a ring *A* differentiated tetrahydrofurobenzofuran intermediate previously converted into Aflatoxin B_2 is described.

The aflatoxins are a well known group of acutely toxic and highly carcinogenic metabolites of various *Aspergillus* species. Long-standing problems associated with the synthesis of these mycotoxins have been identified and discussed.[1] A recent preparation[2] of the furo[2.3-*b*]benzofuran (**1**), constituting rings *A*, *B*, and *C* of Aflatoxin B_2 (**2**) with correctly differentiated oxygen substituents on the phloroglucinol (ring *A*) moiety, represents a formal synthesis of (**2**) and 'state of the art' in aflatoxin synthesis. We now report a simple synthesis of (**1**) in *ca.* 4% overall yield from commercially available 3,5-dimethoxy phenol (**4**).

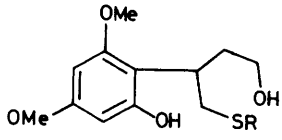
During our initial investigations, the dihydrobenzofuran (**6**) was prepared in two steps from *ortho*-iodophenol *via* the crotonate (**5**) by the intramolecular conjugate addition procedure we had recently developed.[3] Reduction to the alcohol (**7**) and treatment of the latter with lead tetra-acetate (LTA),



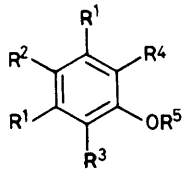
(1) R^1 = OH, R^2 = H, R^3 = OMe
(3) R^1 = OBn, R^2 = H, R^3 = OMe
(8) R^1 = R^2 = R^3 = H
(14) R^1 = R^3 = OMe, R^2 = I
(21) R^1 = OBn, R^2 = I, R^3 = OMe
(22) R^1 = OH, R^2 = I, R^3 = OMe
Bn = $PhCH_2$, benzyl



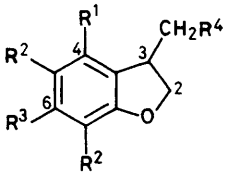
(2)



(16) R = Et
(17) R = CMe_3



(4) R^1 = OMe, R^2 = R^3 = R^4 = R^5 = H
(5) R^1 = R^2 = R^3 = H, R^4 = I, R^5 = $CH_2CH{=}CHCO_2Et$
(9) R^1 = OMe, R^2 = R^5 = H, R^3 = R^4 = I
(10) R^1 = OMe, R^2 = H, R^3 = R^4 = I, R^5 = $CH_2CH{=}CHCO_2Et$



(6) R^1 = R^2 = R^3 = H, R^4 = CO_2Et
(7) R^1 = R^2 = R^3 = H, R^4 = CH_2OH
(11) R^1 = R^3 = OMe, R^2 = H, R^4 = CO_2Et
(12) R^1 = R^3 = OMe, R^2 = H, R^4 = CH_2OH
(13) R^1 = R^3 = OMe, R^2 = I, R^4 = CH_2OH
(15) R^1 = OH, R^2 = H, R^3 = OMe, R^4 = CH_2OH
(18) R^1 = OMe, R^2 = H, R^3 = OH, R^4 = CH_2OH
(19) R^1 = OAc, R^2 = H, R^3 = OMe, R^4 = CH_2OAc
(20) R^1 = OBn, R^2 = I, R^3 = OMe, R^4 = CH_2OH

iodine, and solid calcium carbonate in refluxing benzene[4] provided rapid access to the parent furobenzofuran (**8**) in four steps and 25% overall yield from *ortho*-iodophenol. In order to test the LTA–iodine cyclisation with a substrate possessing the activated phloroglucinol ring *A* of aflatoxin, the preparation of (**12**) was undertaken by the same method. Iodination[5] of 3,5-dimethoxy phenol (**4**) with KI–KIO_3 produced the symmetrical (^{1}H n.m.r.) di-iodo derivative (**9**), which was converted into the crotonate (**10**) and cyclised with concomitant deiodination with two molar equivalents of n-butyllithium at −100 °C. Reduction of (**11**) with di-isobutyl(aluminium) hydride (DIBAL-H) produced the desired alcohol (**12**) in 23.2% overall yield. When the LTA–iodine reaction was attempted with (**12**), aromatic iodination rather than cyclisation resulted and when two molar equivalents of the reagent were used, the di-iodo derivative (**13**) was isolated from among a mixture of products. However, when (**13**) was purified and resubjected to the cyclisation, the furobenzofuran (**14**) was formed and its presence indicated by the appearance of H-8a as a doublet at δ 6.35 (*J* 5.7 Hz) in the ^{1}H n.m.r. spectrum of the product.

The differentiation of the oxygen substituents on ring *A* was always a major difficulty that had been addressed in the initial stages of the early syntheses[1] of the aflatoxins. Our preference for a method of intramolecular discrimination between the methoxy groups in an intermediate like (**11**) or (**12**) was enhanced by a recent study[6] of hydroxyl directed demethylation of various methoxylated aromatic substrates by the ethyl mercaptide anion. As it happened, the application of this method to (**12**) did result in retention of the C-6 methoxy group and demethylation at C-4 [(**15**) 8%], but a concurrent reaction at C-2 gave a second product identified as (**16**) (16%). Much better results ensued with t-butyl mercaptide [in dimethylformamide (DMF), 110 °C, 3 h]; the selectivity and yield were both vastly improved [(**15**) 61 and (**17**) 13%] and at no time was any of the 6-demethylated product† found. The two products were easily separated by column chromatography on silica gel. Iodination of (**15**) with KI–KIO_3, followed by benzylation (benzyl bromide–potassium carbonate), provided the 5,7-di-iodo-4-*O*-benzyl derivative (**20**), which was cyclized with LTA–I_2 to (**21**). Hydrogenolysis of this compound under a variety of conditions gave no worthwhile result; neither (**1**),(**3**) nor (**22**) could be obtained cleanly. However, deiodination of (**21**) was effected (Bu^nLi, −100 °C; H_2O) and the product (**3**) characterized‡ by 500 MHz ^{1}H n.m.r. As before,[2] transfer hydrogenolysis (cyclohexa-1,4-diene, Pd–charcoal) provided (**1**) with melting point and ^{1}H n.m.r. data identical with literature values, thus completing a formal synthesis of Aflatoxin B_2. We are making progress towards the synthesis of (**22**) which we expect to employ as an *ABC* intermediate for the attachment of rings *D* and *E*.

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† The identity of (**15**) was provisionally inferred by comparison of the ^{1}H n.m.r. spectra of (**15**) and its diacetate (**19**). The *meta* coupled (*J* 2.1 Hz) aromatic protons of (**15**) at δ 5.99 and 6.02 were shifted to δ 6.16 and 6.28 (*J* 2.1 Hz) in (**19**). If (**18**) had been formed by demethylation at C-6, both aromatic protons H-5 and H-7 should have been equally affected by acetylation.[7]

‡ *Spectral data* for (**3**): ^{1}H n.m.r. (500 MHz, $CDCl_3$), δ 2.10—2.15 (1H, m, H-3β), 2.205 and 2.23 (1H, dd, H-3α), 3.63—3.68 (1H, dq, H-2α), 3.74 (3H, s, OMe), 4.01 and 3.99 (1H, dd, H-3a), 4.05 (1H, t, H, 2β), 4.30 (2H, s, OCH_2Ph), 6.07, 6.09 (1H each, d each, H-5 and -7), 6.30 (1H, d, H-8a), 7.40 (5H, m, OCH_2Ph). Coupling constants *J*(Hz): 2α,2β 8.6; 2α,3α 5.0; 2α,3β 12.0; 2β,3α ~0; 2β,3β 8.1; 3α,3β 12.2; 3α,3a ~0; 3β,3a 8.1; 3a,8a 5.7; and H-5,H-7 2.0.