The Regiospecific *p*-Deiodination of 2,4-Di-iodo Phenols; a New Synthesis of Aflatoxin B_2

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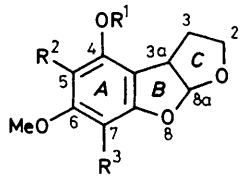
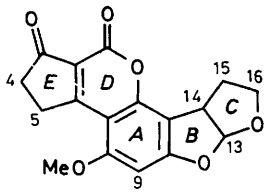
An *o*-iodinated phenolic tetrahydrofurobenzofuran intermediate has been prepared with the correct regiochemistry and converted into aflatoxin B_2.

In a recent publication[1] we disclosed a simple route to the furobenzofuran (**1**), the *ABC* segment of aflatoxin B_2 (**2**). Since (**1**) had already been converted[2] into (**2**) in rather low yield by a von Pechmann reaction, our work constituted a formal synthesis of this mycotoxin. Improvements we had envisaged[1] in the transformation of (**1**) to (**2**) required a further element of regiocontrol, specifically the presence of an iodine atom at C-5 as a handle for attachment of rings *D* and *E* of (**2**). We now report the adaptation of our earlier synthesis of (**1**) to provide the desired monoiodo *ABC* intermediate (**3**) (6.4% overall) by a new, general phenol *p*-deiodination procedure and its conversion to (**2**), thus completing a total synthesis of aflatoxin B_2 in 2.3% overall yield from 3,5-dimethoxyphenol.

The di-iodo intermediate (**4**) prepared before[1] in 20% overall yield was tosylated selectively at the phenolic hydroxy group (tosyl chloride, K_2CO_3) and cyclised as before with lead tetra-acetate (LTA)–I_2 to provide the tricyclic furofuran (**5**). Removal of the tosyl group [NEt_4OH, aqueous tetrahydrofuran (THF)] gave (**6**) which was regiospecifically deiodinated at the *para* position to furnish (**7**) in 70% yield by treatment with one molar proportion of sodium hydride at 0 °C (to form the phenate) followed by one molar proportion Bu^nLi at −100 °C for 15 min.

These are appropriate conditions for the deiodination of other 2,4-di-iodo phenols (Scheme 1, Table 1). It is clear from such experiments that, firstly, the phenate ion must be pre-formed and, secondly, the negative charge localised on that oxygen atom for regioselectivity to be observed in the lithium–iodine exchange. Thus if the reaction is attempted without prior sodium hydride treatment but with two moles of butyl lithium instead, regioselectivity is poor, presumably because the rate of exchange even at −100 °C competes successfully with deprotonation of the phenol. The lack of regioselectivity observed with methyl di-iodo salicylate (Table 1, entry 5) relates to the second conclusion. We believe that the charge on the phenate oxygen atom is extensively delocalised (as shown in Scheme 1) and support this view in that the corresponding acid, when reacted as its dianion, gives the expected result (Table 1, entry 4). Di-iodo phenols are easily obtainable, but a good general method for *o*-iodination of phenols[3] does not exist. We expect that our deiodination procedure will prove to be a useful alternative to the methoxymethylation, *o*-deprotonation–iodination, hydrolysis sequence now available.[4] We have observed that in many instances, with more activated phenols in particular, polyiodination and phenol-formaldehyde condensations are frequent problems in the latter three step procedure.

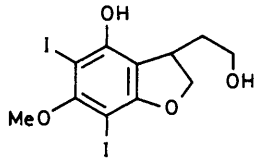




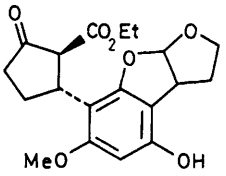
(1) $R^1 = R^2 = R^3 = H$
(3) R^1 = Bn, $R^2 = I$, $R^3 = H$
(5) R^1 = Ts, $R^2 = R^3 = I$
(6) $R^1 = H$, $R^2 = R^3 = I$
(7) $R^1 = R^3 = H$, $R^2 = I$
(8) $R^1 = R^2 = H$, $R^3 = I$

(Bn = benzyl; Ts = $SO_2C_6H_4Me$-*p*)

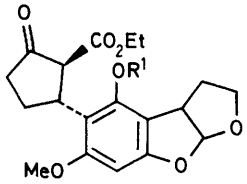
(2)



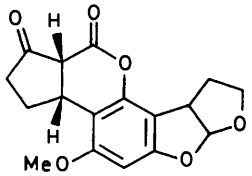
(4)



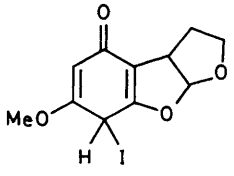
(13)



(10) R^1 = Bn
(11) $R^1 = H$

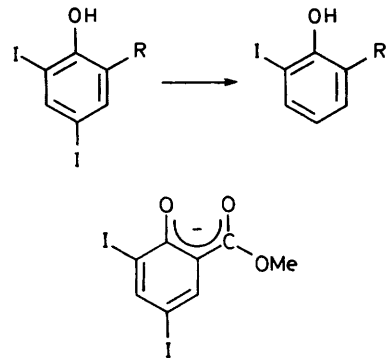


(12)



(9)

Returning to the aflatoxin synthesis, we also found that (**1**) could be di-iodinated[5] (benzyltrimethyammonium dichloroiodate, methanol, dichloromethane) to produce (**6**) so that other synthetic routes[2,6] to (**1**) become compatible with our *DE* annelation *via* (**6**) and the 5-iodo isomer (**7**). The latter compound is interesting for another reason; it was converted completely to its *p*-iodo isomer (**8**) by treatment with trifluoroacetic acid in dichloromethane. This reaction is formally an iodine migration which must occur by opening of ring *B* at the acetal carbon C-8a and recyclisation at the C-4 hydroxy group. We do not understand why such an equilibrium should favour the *p*-iodo phenol (**8**) so exclusively over the *ortho* isomer (**7**); it may be related to the well recognised tendency[7] of phloroglucinols to exist as quinonoid tautomers. Presumably the *p*-quinonoid tautomer (**9**) [derived from (**8**)] is more stable than the *o*-quinonoid tautomer derivable from (**7**). The structure of (**8**) is supported by its mass spectrum, its ^{1}H NMR spectrum, which is very similar to that of (**7**), and by the 'upfield anion shift' observed for the aromatic protons [$\Delta\delta$ for H-7 in (**7**) = −0.83 p.p.m., $\Delta\delta$ for H-5 in (**8**) = −0.54 p.p.m.]. These values are characteristic[8] for the shifts of *para* and *ortho* protons, respectively, of phenol/phenate pairs. The benzylation of (**7**) (benzyl bromide, potassium carbonate) then provided the desired *ABC* fragment (**3**) suitably iodinated and regio-differentiated for the *DE* annelation sequence.



Scheme 1

Table 1.

Entry	R	Isolated yield/%
1	Me	70
2	$CH(OMe)_2$	77[a]
3	OMe	90
4	CO_2H	82[b]
5	CO_2Me	76[c]

[a] Isolated as aldehyde after hydrolysis of acetal. [b] Two moles of NaH. [c] A 1 : 1 mixture of *ortho* and *para* isomers was formed in this case.

The attachment of the cyclopentanone-2-carboxylate representing rings *D* and *E* at C-5 of (**3**) was achieved by a one-pot three step procedure in 60% yield. Exchange of the C-5 iodine with one equivalent of n-butyl-lithium at −78 °C was followed by treatment with lithium 2-thienylcyano cuprate[9] (−78 to 0 °C) and after recooling to −78 °C, addition of the Michael acceptor, ethyl cyclopentenone-2-carboxylate[10] (−78 to 25 °C) provided the *trans* adduct (**10**) as a mixture of diastereoisomers. Hydrogenolysis with 0.5 equiv. of 30% palladium/charcoal at 200 psi in ethyl acetate for 9 h, gave the free phenol (**11**) which is somewhat unstable. It was immediately cyclised with trifluoroacetic acid (TFA) in dichloromethane at room temperature to the diastereoisomeric *cis*-lactones (**12**) (60% for both steps). A second product (M^+ = 362), with a ^{1}H NMR spectrum very similar to (**11**) was also found in the reaction mixture. In view of the earlier rearrangement of (**7**) to (**8**) under the same conditions it is likely that this by-product is (**13**). Cyclisation under basic conditions was also attempted without much success. Thus with sodium hydride in dry THF for example a <50% yield of (**12**) was obtained, but in this case decomposition of the β-ketoester moiety of (**11**) seemed to intervene. Dehydrogenation of (**12**) to aflatoxin B_2[11]† was both instantaneous and quantitative with dichloro dicyano benzoquinone in dioxane at room temperature.‡ Further applications of the deiodina-

† (**2**); m.p. 300—303 °C (decomp.), lit.[11] 303—306 °C (decomp.); electron impact (EI) MS calcd. for $C_{17}H_{14}O_6$: 314.0790, found 314.0792; IR ($CHCl_3$) 1760, 1689, 1628, 1599 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23—2.30 (m, 2H, H-15), 2.64 (apparent t, 2H, H-4), 3.39—3.41 (m, 2H, H-5), 3.61—3.66 (apparent q, 1H, H-16 α), 3.95 (s, 3H, OMe), 4.14—4.18 (m, 2H, H-14 and H-16 β), 6.34 (s, 1H, H-9), 6.48 (d, 1H, H-13, $J_{13,14}$ 5.6 Hz).

‡ Full experimental details will be published later.

tion reaction to natural product synthesis are being actively pursued.

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