Aflatoxins Revisited: Convergent Synthesis of the ABC-Moiety

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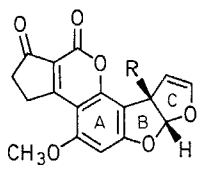
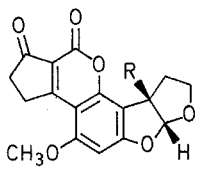
After appropriate model studies, two methods of current preparative interest, namely radical-initiated 5-*exo-trig* cyclization and palladium/formate anion mediated intramolecular hydroarylation, were confronted and optimized for the convergent synthesis of the oxygenated ABC-moiety of aflatoxin B_1.

The aflatoxin B_1 molecule **1a** is a ubiquitous natural toxicant, which has featured prominently as logo of the Sixth International Symposium on Mycotoxins and Phycotoxins.[1] Common to synthetic approaches to the series **1a–d** is the annulation of a suitable ABC building block by a modified von Pechmann reaction,[2] **2** → **1**. An efficient synthesis of aflatoxin B_1 (**1a**) requires controlled access to 3a,8a-dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-ones **3**. In the pioneering work of Buechi,[2–4] **3** was obtained by a β-formyllactone rearrangement. For comparison, aflatoxin B_2 (**1c**), which lacks the double bond in ring C, proved to be a simpler target.[5,6]

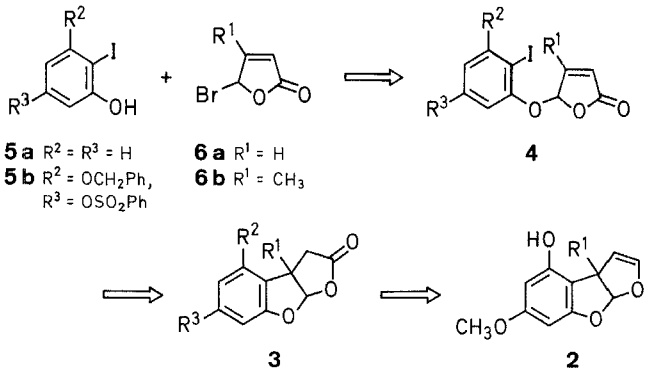


1a R = H
1b R = OH



1c R = H
1d R = OH

Our basic strategy for the construction of tricyclic oxoacetal **3** is outlined in Scheme **A**. Combination of a suitably protected, iodinated phloroglucinol **5** with a reactive 5-bromobutenolide **6** is expected to provide the functionalized, unsaturated acetal **4**, which has to be cyclized intramolecularly to **3**. The 5-*exo-trig* addition of the phenyl-radical, to be generated by iodine



5a $R^2 = R^3 = H$
5b $R^2 = OCH_2Ph$, $R^3 = OSO_2Ph$

6a $R^1 = H$
6b $R^1 = CH_3$

4

3

2

3,4	R^1	R^2	R^3
a	H	H	H
b	CH_3	H	H
c	H	OCH_2Ph	OSO_2Ph

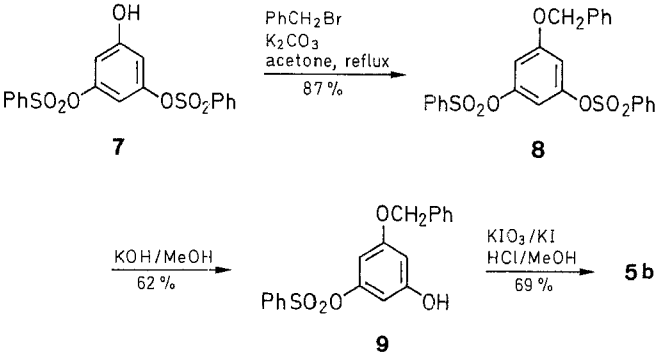
Scheme **A**

abstraction from **4**, into the internal Michael acceptor should allow, at least in principle, selective formation of the B-ring. It is not clear, however, to what extent the desired cyclization is stereoelectronically and thermodynamically feasible and whether the tri-*n*-butyltin hydride method[7,8] is compatible with the high level of oxygenation of the target molecule **3c**. Because of the tendency towards formation of strong tin-oxygen bonds, side reactions could be expected in this case.

As a second mode of cyclization we visualized a palladium-induced hydroarylation,[9,10] which in our case, however, had to be *intra*molecular. Such a reaction would complement the well-known Heck olefination, and a further question is whether the α,β-unsaturated oxoacetal in ring C will stay intact, i.e. without being cleaved to a π-allyl palladium complex and phenolate anion. The various strategies and methodologies have first been developed and applied to the model systems **3a, b** and then to the electronrich, condensed heterocycle **3c** itself.

1. Preparation of Starting Materials

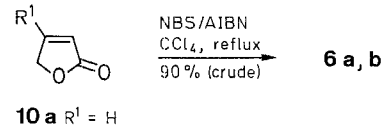
Regiocontrolled differentiation of the three hydroxy groups of phloroglucinol is necessary for obtaining an A-ring precursor suitable for aflatoxin synthesis.[4,11] Bis(benzenesulfonyl) derivative **7**[11] was monobenzylated to **8** and then selectively monodesulfonylated to give **9**. The required iodine atom was introduced site-selectively by generating an electrophilic iodine species[12] in the presence of **9**. Aside from some diiodinated product and recovered starting material **9**, the desired iodophloroglucinol derivative **5b** was formed as major product (Scheme **B**).



7 **8** **9**

Scheme **B**

The C-ring precursors were obtained by bromination of butenolides **10a, b** with *N*-bromosuccinimide under free radical conditions. The sensitive bromobutenolides **6a, b** (90% crude yield) were not isolated as such, but used directly in the acetal forming step.



10a $R^1 = H$
10b $R^1 = CH_3$

Convergent coupling of ring A and C to **4a–c** was accomplished under mild, two-phase liquid-liquid conditions at room temperature (Table 1).

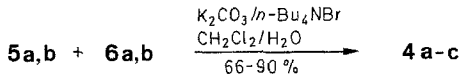


Table 1. 2-Iodophenylacetals **4a–c** Prepared

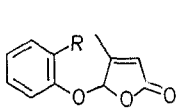
Starting Compounds	Product	Yield[a] (%)	mp (°C) (solvent)[b]	Molecular Formula[c]
5a + 6a	**4a**	90	80–81 (ether/PE)	$C_{10}H_7IO_3$ (302.1)
5a + 6b	**4b**	77	78–79 (ether/PE)	$C_{11}H_9IO_3$ (316.1)
5b + 6a	**4c**	66	140 (ether/CH_2Cl_2)	$C_{23}H_{17}IO_7S$ (564.4)

[a] Yield of isolated product.
[b] PE = petroleum ether (30–50 °C).
[c] Satisfactory microanalyses obtained: C ±0.15, H ±0.27.

2. Intramolecular Cyclization

a) The Tributyltin Hydride Method: Generally, radical-initiated 5-*exo*-*trig* cyclizations of 5-hexenyl halides have been carried out in refluxing benzene, in the presence of catalytic amounts of azobis(isobutyronitrile) (AIBN) with slow addition of tri-*n*-butyltin hydride.[7,8] In the present instance, photochemical activation in benzene solvent with a mercury high-pressure lamp, proved to be convenient for preparing the model compound **3a**. Even tricycle **3b** was formed in respectable yield (58%) (Table 2), although in this case, the *ortho*-stannylated phenolic acetal **11a** was isolated as a by-product (13%). The NMR data of **3a–c** and **4a–c** are given in Table 3.

Tricyclic oxoacetyl **3b** contains a quaternary bridgehead carbon which is not found in natural aflatoxins and which is expected to block metabolism to the M-series (cf. **1b, 1d**).



11a R = Sn(*n*-Bu)$_3$
11b R = H

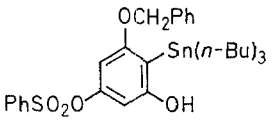


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Table 2. 3a,8a-Dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-ones **3a–c** Prepared by the Tri-*n*-butyltin Hydride Method

Starting Material	Product	Yield[a] (%)	mp (°C) (solvent)[b]	Molecular Formula[c] or Lit. mp (°C)
4a[d]	**3a**	86[e]	122 (ether/PE)	124–126[13]
4b	**3b**	58[e]	85–86 (ether/PE)	$C_{11}H_{10}O_3$ (190.2)
4c	**3c**	~28	142–143 (CH_2Cl_2/ether)	$C_{23}H_{18}O_7S$ (438.5)

[a] Yield of isolated product.
[b] PE = Petroleum ether (30–50 °C).
[c] Satisfactory microanalyses obtained: C ±0.25, H ±0.11.
[d] The corresponding bromoderivative could also be cyclized to **3a** in up to 50% yield.
[e] Photochemically induced cyclization.

Table 3. NMR Data of **3a–c** and Their Precursors **4a–c**

Compound	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ
3a	2.82, 3.12 (dd, 2H, AB part of ABX, $J_{A,B}$ = 18.5, $J_{A,X}$ = 2, $J_{B,X}$ = 9, H-3); 4.24 (m, 1H, X part of ABX, H-3a); 6.55 (d, 1H, $J_{4,5}$ = 6, H-8a); 6.93–7.32 (m, 4H$_{arom}$)	34.57 (t, C-3); 42.39 (d, C-3a); 107.77 (d, C-8a); 110.84, 122.94, 124.81, 129.85 (d, C$_{arom}$); 126.84, 157.26 (s, C$_{arom}$); 173.73 (s, C-2)
3b	1.54 (s, 3H, CH_3); 2.89 (ABq, 2H, J = 18, H-3); 6.11 (s, 1H, H-8a); 6.85–7.22 (m, 4H$_{arom}$)	23.93 (q, CH_3); 41.52 (t, C-3); 49.82 (s, C-3a); 111.02, 112.66, 123.08, 123.33, 129.77 (d, C$_{arom}$ + C-8a); 131.57, 156.56 (s, C$_{arom}$); 173.26 (s, C-2)
3c	2.94 (m, 2H, H-3); 4.18 (m, 1H, H-3a); 4.97 (s, 2H, $CH_2C_6H_5$); 6.15, 6.37 (d, 2H$_{arom}$, J = 2); 6.49 (d, 1H, J = 6, H-8a); 7.3–7.9 (m, 10H$_{arom}$)	32.47 (t, C-3); 40.63 (d, C-3a); 70.60 (t, $CH_2C_6H_5$); 98.72, 101.29 (d, C$_{arom}$); 108.25 (d, C-8a); 112.71 (s); 128.48, 127.43, 128.45, 128.79, 129.28, 134.42 (d, 10C$_{arom}$); 135.30, 135.54, 151.64, 155.62, 158.02 (s, C$_{arom}$); 173.68 (s, C-2)
4a	6.34 (t, 1H, $J_{3,5}$ = $J_{4,5}$ = 1.5, H-5); 6.36 (dd, 1H, $J_{3,4}$ = 5.5, $J_{3,5}$ = 1.5, H-3); 6.85–7.84 (m, 4H$_{arom}$); 7.50 (dd, 1H, $J_{3,4}$ = 5.5, $J_{4,5}$ = 1.5, H-4)	88.04 (s, C-I); 101.65 (d, C-5); 117.93, 125.55, 126.02, 129.92, 139.39 (d, C$_{arom}$ + C-3); 149.57 (d, C-4); 155.66 (s); 168.54 (s, C-2)
4b	2.33 (dd, 3H, $J_{5,6}$ = 0.7, $J_{3,6}$ = 1.6, CH_3); 6.02 (dq, 1H, $J_{3,5}$ = 0.5, $J_{5,6}$ = 1.6, H-3); 6.78 (bs, 1H, H-5); 6.83–7.83 (m, 4H$_{arom}$)	14.10 (q, CH_3); 79.10 (s, C-I); 102.31 (d, C-5); 116.63, 119.47, 125.55, 129.92, 139.65 (d, C$_{arom}$ + C-3); 155.72 (s); 162.99 (s, C-4); 169.85 (s, C-2)
4c	5.07 (s, 2H, $CH_2C_6H_5$); 6.14 (t, 1H, $J_{3,5}$ = $J_{4,5}$ = 1.5, H-5); 6.34 (dd, 1H, $J_{3,4}$ = 1.5, $J_{3,5}$ = 5.5, H-3); 6.44, 6.52 (d, 2H$_{arom}$, J = 2.2); 7.34–7.92 (m, 10H$_{arom}$ + H-4)	71.48 (t, CH_2); 78.66 (s, C-I); 100.92 (d, C-5); 103.26, 104.23 (d, 2C$_{arom}$); 125.62 (d); 128.22 (d); 127.12, 128.54, 128.63, 129.42 (8C$_{arom}$); 134.70 (d); 134.98 (s); 135.54 (s); 149.09 (d, C-4); 151.31, 156.64, 159.01 (s); 169.10 (s, C-2)

Attempted photocyclization of **4c** gave none of the desired **3c**. Instead, acetal cleavage and formation of the stannylated phloroglucinol **12** was observed. Standard cyclization of **4c** with slow addition of tri-*n*-butyltin hydride gave a mixture of tin-containing compounds and also **3c** (28%), which, however, could not be obtained pure.

b) Intramolecular Palladium/Formate Anion-Mediated Hydroarylation: In searching for an alternative method of cyclization we first of all tried standard Heck olefination conditions[14] on the model precursor **4a** and obtained **3a** in 11% yield. While our work was in progress, examples of *inter*molecular palladium-assisted hydroarylation reactions were described.[9,10] With tetrakis(triphenylphosphine)palladium(0) and triethylamine in dimethylformamide at 80 °C,[10] precursor **4c** suffered reductive removal of iodine and also acetyl cleavage to **9**. Cacchi conditions[9] proved to be more successful, giving tricyclic **3a** (68%), **3b** (16%), but none of the desired **3c**. In the latter case, cleavage of the unsaturated oxoacetal occurred again, giving **5b**. We finally used $Pd(CH_3CN)_2Cl_2$ (up to 10 mol%) and preformed triethylammonium formate at 35–50 °C, obtaining the series of compounds **3a–c** in good to very good yields (Table 4). By-product **11b**, which was formed from the sterically hindered precursor

4b, corresponds to **11a** formed in the tributyltin hydride-induced cyclization. Addition of silver nitrate as a cocatalyst[15] gave no further improvement.

Table 4. Benzoannulated Oxoacetals **3a–c** Prepared by Intramolecular Palladium-Promoted Hydroarylation

Product	Yield (%)	Concentration (mmol/mL) of **4** in Solvent DMF	Mol % of Pd-catalyst	Temp. (°C)	Reaction Time (h)
3a	68[b]	0.63	2[d]	50	3.5
	91[c]	0.25	20[d]	50	1.5
	86[c]	0.25	4[e]	50	3.0
3b	42[b,f]	0.5	4[e]	50	3.5
	16[b]	0.5	2[d]	50	4.0
3c	46[b]	0.5	20[d]	50	2.25
	51[c]	0.2	10[e]	35	1.0

[a] Yield of isolated product.
[b] Purified by flash column chromatography (silica, light petroleum/*tert*-butyl methyl ether).
[c] Purified by column filtration and recrystallization (see Table 2).
[d] $Pd(OAc)_2[PPh_3]_2$.
[e] $Pd(CH_3CN)_2Cl_2$.
[f] **11b** (5%) was isolated as a by-product.
^{1}H-NMR ($CDCl_3$/TMS): *inter alia* δ = 7–7.4 (m, 5 H_{arom}).
MS (70 eV) *m/z* (%) = 190 (M^+, 35).

3. Conclusion

We have described flexible and efficient methods for constructing ABC-precursors of aflatoxins, and are able to compare directly two methods of current synthetic interest. A drawback of tri-*n*-butyltin hydride, aside from high molecular weight (291) and toxicity, are difficulties on work-up. Note also that the tributyltin hydride method requires dilution of reagents by solvent down to 0.02 M. Nonetheless, both **3a** and **3b** have been obtained readily by either method of cyclization. For the preparation of the oxygenated target molecule **3c**, the palladium-catalyzed intramolecular hydroarylation is superior with respect to yield and isolation of product.

1,3-Bis(benzenesulfonyloxy)-5-benzyloxybenzene (8):
A mixture of phloroglucinol dibenzenesulfonate[11] (**7**; 25.9 g, 64 mmol), K_2CO_3 (17.9 g, 0.13 mol) and benzyl bromide (11.1 g, 65 mmol) is refluxed in acetone (100 mL) for 3.5 h and cooled to room temperature. After evaporation of the solvent, the residue is taken up in EtOAc (50 mL), and filtered. The organic phase is washed with water (3 × 20 mL), dried (Na_2SO_4), and the solvent is evaporated to leave a light yellow solid, which is recrystallized from MeOH to give **8** as a colorless solid; yield: 27.6 g (87%); mp 92–93°C.

$C_{25}H_{20}O_7S_2$	calc.	C 60.47	H 4.06
(496.6)	found	60.38	4.02

IR ($CHCl_3$): ν = 1610, 1590, 1450, 1380 cm^{-1}.
^{1}H-NMR ($CDCl_3$/TMS): δ = 4.88 (s, 2 H, CH_2); 6.24 (t, 1 H, J = 2 Hz, H-2); 6.57 (d, 2 H, J = 2 Hz, H-4, H-6); 7.3–7.81 (m, 15 H_{arom}).

1-Benzenesulfonyloxy-3-benzyloxy-5-hydroxybenzene (9):
To a stirred suspension of **8** (27 g, 54 mmol) in MeOH (150 mL) is added slowly a 20% methanolic solution of KOH at room temperature. After stirring for 4 h, the mixture is diluted with water (200 mL), adjusted to pH 4 with 10% HCl and extracted with EtOAc (5 × 60 mL). The combined organic phase is washed with water (2 × 50 mL), dried (Na_2SO_4), and the solvent is removed to leave a viscous brown oil, which is purified by flash chromatography on silica (light petroleum/ether/CH_2Cl_2, 2:1:1), giving **9** as colorless, waxy oil; yield: 11.9 g (62%).

Exact mass calc. for $C_{19}H_{16}O_5S$		356.0718474
	found	356.0718911

IR ($CHCl_3$): ν = 3500 (br, OH); 1620; 1600; 1450; 1375 cm^{-1}.
^{1}H-NMR ($CDCl_3$/TMS): δ = 4.82 (s, 2 H, CH_2); 6.14 (t, 1 H, J = 2 Hz); 6.17 (t, 1 H, J = 2 Hz); 6.36 (t, 1 H, J = 2 Hz); 6.75 (s, 1 H, OH); 7.3–7.9 (m, 10 H_{arom}).

1-Benzenesulfonyloxy-3-benzyloxy-5-hydroxy-4-iodobenzene (5b):
A solution of **9** (710 mg, 2 mmol) in MeOH (10 mL) is acidified with conc. HCl (0.17 mL, 2 mmol) and a solution of KI (220 mg, 1.34 mmol) and KIO_3 (140 mg, 0.66 mmol) in water (4 mL) is vigorously stirred in during 15 min, such that the transient color of iodine does not persist. After stirring for a further 45 min, the mixture is diluted with water (50 mL) and extracted with EtOAc (4 × 20 mL). The combined organic phase is washed with brine (2 × 30 mL), dried (Na_2SO_4), and evaporated. The resulting brown oil is purified by flash chromatography on silica ($CHCl_3$/light petroleum/ether, 10:10:1) to give some **9** (~ 200 mg), diiodinated product and the desired **5b** as a colorless oil which turned yellow on standing; yield: 460 mg (48%, 69% based on recovered **9**).

Exact mass calc. for $C_{19}H_{15}O_5IS$		481.9684979
	found	481.968669

IR ($CHCl_3$): ν = 3500 (br, OH); 1720 (br w, C=O); 1600; 1380 cm^{-1}.
^{1}H-NMR ($CDCl_3$/TMS): δ = 5.1 (s, 2 H, CH_2); 5.68 (s, 1 H, OH); 6.24 (d, 1 H, J = 2 Hz); 6.28 (d, 1 H, J = 2 Hz); 7.34–7.93 (m, 10 H_{arom}).

5-Bromo-2(5*H*)-furanones 6a, b; General Procedure:
A two-necked, pre-dried flask equipped with reflux condenser is charged with anhydrous *N*-bromosuccinimide (890 mg, 5 mmol). Butenolide **10a, b**[16] (5 mmol) in CCl_4 (10 mL) and AIBN (16 mg, 0.1 mmol) are added under N_2, and the resulting mixture is refluxed until after ca 1 h, succinimide has appeared as a floating yellow solid. The mixture is cooled in an ice bath, filtered, and the filter residue is washed with cold CCl_4 (5 mL). The combined filtrate is evaporated to leave a yellow oil, which is used directly in the next step; yield: ~ 90%. Spectroscopic data of **6a** (Ref. 17) and **6b** (Ref. 18).

General Procedure for Coupling of 5 and 6; Preparation of 4:
A solution of **5** (2 mmol) in CH_2Cl_2 (5 mL) is mixed with a solution of K_2CO_3 (280 mg, 2 mmol) and tetra-*n*-butylammonium bromide (65 mg, 0.2 mmol) in water (10 mL). After vigorous stirring for 10 min at room temperature, a solution of bromobutenolide **6** (~ 2.5 mmol) in CH_2Cl_2 (5 mL) is added during 15 min. The two phase mixture is stirred vigorously for a further 1 h, and the progress of the reaction is monitored by TLC (ether/light petroleum). The organic phase is separated, and the aqueous phase is washed with CH_2Cl_2 (3 × 5 mL). The combined organic phase is dried (Na_2SO_4), concentrated, and filtered through a column of alumina (Woelm neutral, activity II-III), using CH_2Cl_2 as eluent. After evaporation of the solvent the remaining pale yellow solid is purified by (i) recrystallization, and (ii) flash column chromatography on silica (ether/light petroleum). Both methods of purification give comparable yields (cf. Table 1).

Tributyltin Hydride-Induced Cyclization; General Procedure:
A solution of iodinated precursor **4** (2 mmol) and *n*-Bu_3SnH (0.6 mL, 2.2 mmol) in dry benzene (80 mL) is irradiated with a Hg high-pressure lamp (Philips HPK 125 W) for 20 h under N_2. The benzene is evaporated to leave an oil which is purified by two methods.

4a: the oil is taken up in acetonitrile (20 mL) and extracted with light petroleum (4 × 10 mL). After evaporation of the solvent a light yellow solid remains which is recrystallized (ether/light petroleum).

4b, c: the oil is flash chromatographed on silica (ether/light petroleum) (Tables 2 and 3).

Palladium-Promoted Cyclization of 4; General Procedure:
The reaction is carried out on a 0.2–2 mmol scale, the concentration of **4** varies from 0.2–0.63 mmol/mL.

A solution of **4** (1 mmol) in DMF (1 mL) is kept at room temperature under N_2, while $Pd(CH_3CN)_2Cl_2$ (10 mg, 0.04 mmol) and then Et_3N (100 mg, 1 mmol) are added. The mixture is stirred for 5 min to dissolve the Pd-catalyst, and a solution of Et_3N (220 mg 2.2 mmol) and formic acid (0.07 mL, ca. 2.2 mmol) in DMF (1 mL) is added. The resulting mixture is stirred under conditions as indicated in Table 4. The progress of the reaction is monitored by TLC (ether/light petroleum). After being cooled to room temperature, the mixture is diluted with brine (20 mL)

and extracted with EtOAc or CH_2Cl_2 (4 × 10 mL). The organic phase is washed with water (2 × 10 mL) and dried (Na_2SO_4). After removal of the solvent the remaining oil is purified (cf. Table 4).

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