# Enantioselective Access to the Mycotoxin, Aflatoxin $B_2$

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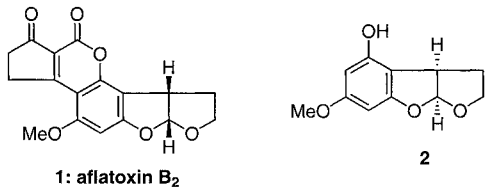
**Abstract:** Enantiomerically enriched tetrahydrofuro[2,3-*b*]benzofuran (**2**), a penultimate intermediate in the synthesis of optically active aflatoxin $B_2$, has been synthesized employing the lipase-catalyzed asymmetric acetylation of the prochiral diol as the key step.

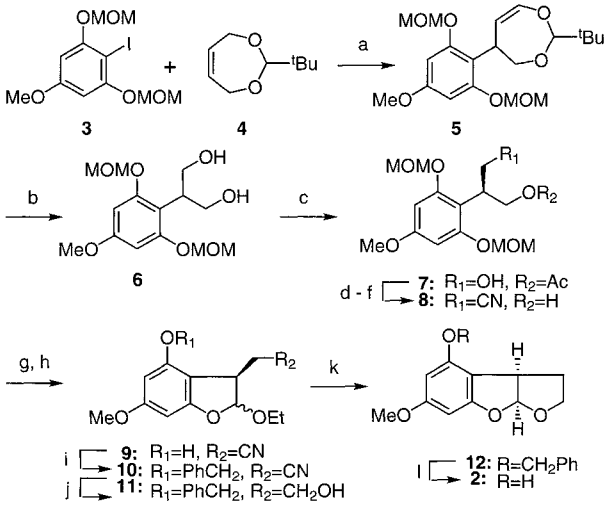
Aflatoxin $B_2$ (**1**) is a member of the toxic metabolite aflatoxins produced by *Aspergillus flavus*.[1] This mycotoxin is the less toxic dihydroderivative of aflatoxin $B_1$, which is one of the most potent environmental mutagens and carcinogens known.[2] The remarkable biological properties, coupled with their unique structural features, have made these mycotoxins desirable targets for total synthesis. Although many stimulating synthetic efforts including total synthesis have been focused on aflatoxins,[3] only one example of chiral synthesis has been reported by Rapoport[3l] in 1994. We now report here an enantioselective synthesis of the tricyclic tetrahydrofuro[2,3-*b*]benzofuran (**2**), which is a penultimate intermediate[3c,d] in the synthesis of the unnatural enantiomer of aflatoxin $B_2$, employing the lipase-mediated asymmetric acetylation[4] of the prochiral diol (**6**) in organic solvent. (**Figure**)




**1: aflatoxin $B_2$** **2**

**Figure**

Preparation of a σ-symmetrical 2-aryl-1,3-propanediol (**6**) for the substrate of chemoenzymatic conversion[5] was started with the Heck reaction[6] of the iodide (**3**), derived from methoxymethylation of 2, 6-dihydroxy-4-methoxyiodobenzene,[7] with the acetal (**4**)[8] to afford the coupled product (**5**). Ozonolytic cleavage of the double bond in **5** followed by reductive workup with $NaBH_4$ provided the diol (**6**) in 49% yield for the 2 steps. It should be noted that the procedure is simple and efficient and appears to be suitable for the preparation of such type of prochiral diols.[9] With the requisite diol in hand, we examined the optimum conditions for the conversion to the optically active monoacetate (**7**) using a wide variety of lipases. Of these, lipase AL, originated from *Achromobacter* sp., mediated transesterification using vinyl acetate as an acetyl donor in $Et_2O$ at room temperature; this proved to be the best choice, and the optically enriched **7** was obtained in 72% yield. The enantiomeric excess was 89% as determined by HPLC on a Chiralcel OD column. The absolute configuration of a stereogenic center was deduced to be *S* in terms of the empirical rule[10] based on the chemical shift of the corresponding (*S*)-MTPA ester, prepared from **7** with (*R*)-MTPA chloride, and the configuration was confirmed by the eventual synthesis of **2**. The optically active alcohol (**7**) thus obtained was converted to the cyanide (**8**) via a three-step reaction sequence. Oxidation of **8** with tetra-n-propylammonium perruthenate (TPAP)[11] in the presence of *N*-methylmorpholine *N*-oxide (NMO), followed by treatment of the resulting hemiacetal with triethyl orthoformate in the presence of catalytic *p*-toluenesulfonic acid (*p*-TsOH) yielded the cyclic acetal (**9**). After protection of the phenolic hydroxyl function as benzyl ether, the cyanide (**10**) generated was hydrolyzed and the resulting carboxylic acid was reduced immediately with a borane dimethylsulfide complex to produce the alcohol (**11**). When the alcohol (**11**) was subjected to the internal transacetalization conditions, the desired tricycle (**12**) was generated in 43% yield from **10**. Finally, transfer hydrogenolysis[12] of **12** using 1, 4-cyclohexadiene as hydrogen donor yielded quantitatively the tetrahydrofuro[2,3-*b*]benzofuran (**2**), $[\alpha]_D$ +136 ° (*c* 0.1, $CHCl_3$) {lit.[3a] for the enantiomer; $[\alpha]_D$ -155 ° (*c* 0.24, $CHCl_3$)}, as colorless prisms, mp 150-151 °C. The $^1H$ NMR and mass spectra obtained from synthetic **2** compared favorably with the data reported in the literature. Since the compound (**2**) has successfully been converted to aflatoxin $B_2$,[3c,d] the present synthesis means the formal total synthesis of its unnatural enantiomer has been achieved.




**Scheme.** ***Reagents and Conditions***: a, $Pd(OAc)_2$, $Ph_3P$, $^iPr_2NEt$, DMF; b, $O_3$ then $NaBH_4$, MeOH (49% from **3**); c, Lipase AL, vinyl acetate, $Et_2O$ (72%); d, MsCl, $^iPr_2NEt$, 4-DMAP, $CH_2Cl_2$ (89%); e, KCN, 18-Crown-6, DMSO (72%); f, LiOH, THF:$H_2O$=3:1 (90%); g, TPAP, NMO, 4A MS, $CH_2Cl_2$; h, $(EtO)_3CH$, EtOH, HCl; i, $PhCH_2Cl$, $K_2CO_3$, DMF (50% from **8**); j, KOH, EtOH:$H_2O$=4:1 then $BH_3$•$SMe_2$, THF; k, p-TsOH, $CH_2Cl_2$ (43% from **10**); l, 1,4-cyclohexadiene, Pd-C, MeOH (100%).

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