(silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3400 (OH, m), 3000 (COOH, b), 2950 (s), 2930 (s), 2860 (s), 1715 (acid, s), 1455 (m), 1405 (m), 1375 (m), 1290 (s), 1270 (s), 1175 (m), 1110 (s), 1010 (m), 965 (m), 905 (w), 730 (m), 695 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.38 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.59 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.00 (b, 3 H, OH), 5.95 (q, J = 7 Hz, 1 H, H-15), 6.18 (q, J = 9 Hz, 1 H, H-11), 6.66 (q, J = 9 Hz, 1 H, H-9), 6.90 (m, 1 H, H-6), 7.33-9.00 (m, 22 H), 9.12 (m, 3 H, CH_3). **36a**: white solid, mp 107-109 °C; R_f = 0.09 (silica, 10% methanol in methylene chloride); IR ($CHCl_3$) ν_{max} 3400 (OH, w), 3100 (COOH, b), 2960 (s), 2930 (s), 2860 (s), 1710 (acid, s), 1455 (m), 1405 (w), 1375 (w), 1310 (m), 1280 (m), 1260 (m), 1205 (m), 1125 (s), 1035 (w), 1005 (w), 970 (m), 900 (w), 815 (w), 725 (s) cm^{-1}; ^1H NMR (360 MHz, acetone-d_6) τ 4.43 (m, 2 H, olefinic), 6.00 (q, J = 7 Hz, 1 H, H-15), 6.07 (q, J = 8 Hz, 1 H, H-11), 6.48 (q, J = 9 Hz, 1 H, H-9), 7.77 (m, 1 H, H-6), 7.87-9.00 (m, 25 H), 9.12 (m, 3 H, CH_3).

Acknowledgment. We wish to thank Professors J. Bryan Smith and Allan M. Lefer of Thomas Jefferson University for the biological and stability investigations of the prostacyclins and the Ono Pharmaceutical Co., Japan, for generous samples of prostaglandin intermediates. Financial support for this work was provided by Merck Sharp and Dohme, U.S.A., and the National Institutes of Health (Heart, Lung and Blood Institute, Contract No. HV-E2931). The 360-MHz ^1H NMR spectra were recorded at the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the Medical School of the University of Pennsylvania.

A New Synthesis of Aflatoxin M_1

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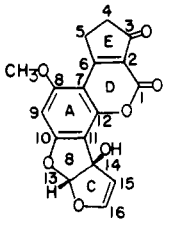
Abstract: Starting with the known and readily available phloroglucinol monobenzenesulfonate (**4**) and 1,4-anhydroerythritol (**7**), we prepared aflatoxin M_1 (**1**) in 13 steps with an overall yield of 5%. The critical features of this second synthesis of aflatoxin M_1 (**1**) include a novel approach to the tricyclic phenol **21** containing the ABC ring system, a regioselective hydrogenolysis of the benzyl protecting group at C_6 in **16**, and removal of the second benzyl group in **20** by Birch reduction. Neither the 1,3,5-trialkoxy-substituted benzene ring nor the vinyl ether function present in **20** were affected in the latter operation.

As soon as the toxic and carcinogenic properties of the naturally occurring aflatoxins[4] had been established questions were raised concerning the presence of toxic derivatives in edible products when animals ingest fodder containing aflatoxin. Lactating cattle fed sublethal doses of aflatoxin B_1 excrete in their milk a metabolite which has been named aflatoxin M_1 (milk toxin).[5] The same metabolite has also been identified in the urine of rats, sheep, monkeys, and humans.[6] A careful search for minor constituents in the original *Aspergillus flavus* mold also led to the isolation of aflatoxin M_1, and its dihydro derivative, which lacks the olefinic bond.[7] Two independent structural studies revealed aflatoxin M_1 to be 14-hydroxyaflatoxin B_1[8,9] (**1**). To probe the toxic and carcinogenic properties of M_1, substantial quantities of this metabolite are required, and the severely limited supply of natural material made it a worthwhile target for synthesis. After efforts to introduce the missing hydroxyl group into B_1 by chemical means failed, attention was focused on total synthesis. The first synthesis, published in 1971,[10] served to prepare approximately 50 mg of racemic aflatoxin M_1 for biological studies.[11] It is not an organic synthesis type of preparation! Two of the intermediates were found to be unstable, and difficult to handle, particularly on scales larger than those described; some had to be purified by chromatography, and finally, the synthesis suffered from a low overall yield.



1

A superior synthesis is detailed in this paper. The basic strategy for the production of the final pentacyclic framework, a modified von Pechmann condensation of the monocyclic bromoester **23** containing ring E with a tricyclic phenol comprising the ABC portion of the molecule, was retained from the first synthesis. However, the successive annulations of the B and C rings to a derivative of phloroglucinol were replaced by a more convergent route in which a ring A component was condensed with a second, *monocyclic* intermediate representing ring C.

The first phase of the synthesis was concerned with the preparation of a suitably protected derivative of phloroglucinol (**2**). Partial alkylations, as well as acylations, of polyhydric phenols are known to be nonselective. The isolation of pure products is tedious, and usually accompanied by losses of material. Contrary to the base hydrolysis of polyesters, which again proceeds with little specificity, the partial hydrolysis of phloroglucinol triarylsulfonates was found to be an efficient process.[12,13] The presence of electron-withdrawing groups on the benzene ring increases the

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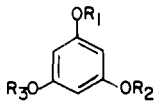
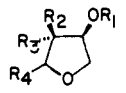
acidity of the phenol liberated, and the creation of phenoxides in basic media thus assures large rate differences in the heterolysis of the three sulfonate esters. Combined with standard and novel methods[14] for ether formation this sequence proved to be efficient, allowing us to prepare a variety of phloroglucinol derivatives containing O-methyl, benzyl, and allyl substituents. In practice the benzyl sequence proved to be superior, and details are presented only for intermediates containing this protecting group. Phloroglucinol monobenzenesulfonate (**4**), prepared in one step by base hydrolysis of the tribenzenesulfonate (**3**), was transformed to the dibenzyl ether **5** by O-alkylation. Basic hydrolysis afforded crystalline phenol **6**.



2, $R_1=R_2=R_3=H$
3, $R_1=R_2=R_3=SO_2Ph$
4, $R_1=R_2=H$, $R_3=SO_2Ph$
5, $R_1=R_2=CH_2Ph$, $R_3=SO_2Ph$
6, $R_1=R_2=CH_2Ph$, $R_3=H$

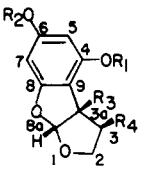


7, $R_1=R_3=R_4=H$, $R_2=OH$
8, $R_3=R_4=H$, $R_1=Ac$, $R_2=OH$
9, $R_1=Ac$, $R_2=R_3=O$, $R_4=H$
10, $R_1=Ac$, $R_2=R_3=O$, $R_4=Br$

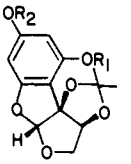
The ring C portion of the molecule was projected to be a 2-bromo-3-oxotetrahydrofuran containing an additional functionality capable of being transformed into a double bond. Compound **10** proved to be the most accessible of the candidates considered and was prepared in 37% overall yield as follows. Monoacetate **8**, available from 1,4-anhydroerythritol (**7**)[15] via the ortho ester (triethyl orthoacetate followed by aqueous oxalic acid), was oxidized to the ketone **9**, which on bromination with *N*-bromosuccinimide gave the bromide **10**. Spectral measurements indicated the presence of two diastereomers, but no efforts were made to separate them.

Initial attempts to condense **10** with **6** by heating the two components, with or without solvents, gave only poor yields of tricyclic substances. Addition of acid scavengers to the reaction media gave no improvement. However, when performed in methylene chloride that had been saturated with anhydrous hydrobromic acid at 25 °C the condensation was complete within 20 min and afforded 42% of a single, crystalline bromide **11**, rather than the corresponding carbinol, which surely must have been the initial tricyclic intermediate. In earlier experiments performed with phloroglucinol methyl benzyl, rather than dibenzyl ether, two isomeric tricyclic alcohols were actually isolated, and transformed to the corresponding bromides on exposure to hydrogen bromide in methylene chloride. Phloroglucinol dibenzyl ether (**6**), incidentally, was found to suffer some ether cleavage under the conditions of the condensation, and yields, perhaps, could be improved by using excess **6** and/or acids, less apt to cleave the two protecting groups. The tricyclic bromide **11** was converted to the diol **12** in quantitative yield by successive treatments with aqueous oxalic acid, and with aqueous hydroxide without isolation of the intermediate diolmonoacetate. The more stable of the two diastereomeric benzyl alcohols should have been created in this solvolysis reaction, and the two hydrofuran rings consequently must be cis oriented. Facile formation of the acetonide **16** established the presence of a cis diol.

At some stage in the synthesis, prior to the von Pechmann condensation, the two benzyl protecting groups had to be removed—one at a time, in a regioselective manner. It was felt that the steric shelter provided to one of the benzyl substituents by the geminal dimethyl group of the acetonide should allow a selective, hydrogenolytic removal of the other. Indeed, hydrogenolysis of **16** over 5% palladium on barium sulfate in ethyl acetate gave 82% of phenol **17**, which crystallized on addition of hexane to the filtered solution. Methylation of phenol **17** gave ether **18**. The structure of **18** was verified by comparison with

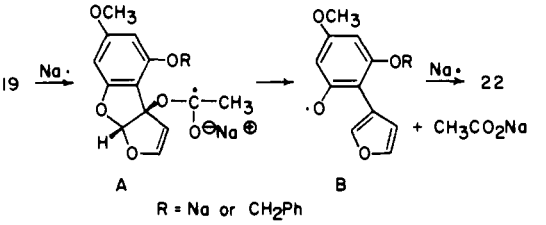


11, $R_1=R_2=CH_2Ph$, $R_3=Br$, $R_4=OAc$
12, $R_1=R_2=CH_2Ph$, $R_3=R_4=OH$
13, $R_1=CH_2Ph$, $R_2=CH_3$, $R_3=R_4=OH$
14, $R_1=CH_2Ph$, $R_2=CH_3$, $R_3=OH$, $R_4=SO_2p\text{-}C_6H_4Br$
15, $R_1=CH_2Ph$, $R_2=CH_3$, $R_3=OAc$, $R_4=SO_2p\text{-}C_6H_4Br$



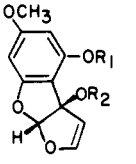
16, $R_1=R_2=CH_2Ph$
17, $R_1=CH_2Ph$, $R_2=H$
18, $R_1=CH_2Ph$, $R_2=CH_3$

a compound, prepared in a nonregiospecific manner from phloroglucinol methyl benzyl ether, which had previously been converted by P.F.S. to the Weinreb intermediate **21**[10] with known regiochemistry. Hydrolysis of the acetonide **18** to the diol **13** was fast in hot aqueous acetic acid, and to create a leaving group for olefin formation the diol **13** was transformed to the *p*-bromobenzenesulfonate **14**. Contrary to the acetylation of **13** in which intramolecular acyl transfer led to the formation of a diacetate, no transsulfonylations were observed, and various monosulfonate esters were prepared in high yields. A number of experiments aimed at converting such diolmonosulfonates to an olefin, using a wide spectrum of bases, gave disappointing results. Since the tertiary hydroxyl function appeared to be involved, it was protected by esterification with acetic anhydride–triethylamine in the presence of 4-dimethylaminopyridine.[16] Exposure of **15** to hot diazabicycloundecene furnished a 2:1 mixture of the highly crystalline acetate **19** and the much less stable alcohol **20**. To facilitate the isolation of a pure product the crude mixture was reacetylated, and crystallization afforded acetate **19** in 70% overall yield. Removal of the benzyl protecting group in the presence of a vinyl ether function was accomplished with sodium in liquid ammonia.[17] Initially, when performed on the acetate **19** the major product was not the anticipated phenol **21**, but the furan **22**. This finding can be rationalized if the radical A formed by electron transfer to the ester undergoes fragmentation to B, followed by further reduction to **22**.

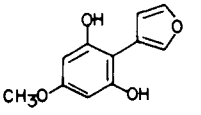


A B
R = Na or CH_2Ph

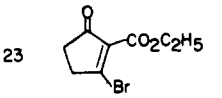
To avoid this reductive fragmentation the Birch reduction was performed on crude samples of alcohol **20**, available by methanolysis of acetate **19**, giving the tricyclic phenol **21** in nearly quantitative yield. This observation again demonstrates the rate-retarding effect of electron-donating alkoxy groups on the reduction of benzene rings by dissolving metals.



19, $R_1=CH_2Ph$, $R_2=Ac$
20, $R_1=CH_2Ph$, $R_2=H$
21, $R_1=R_2=H$



22



23

As in the earlier synthesis, aflatoxin M_1[10] was prepared by condensation of phenol **21** with bromide **23** in methylene chloride

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solution containing suspended zinc carbonate and sodium bicarbonate.

Experimental Section

The following spectrometers were used: IR, Perkin-Elmer 397; NMR, Varian T-60, Jeol FXQ, Bruker wm 250; UV, Hitachi Perkin-Elmer 200; mass spectrum, Varian Mat 44. Boiling points and melting points done on a Reichert microscope melting apparatus are uncorrected. Microanalyses were performed by the Robertson Laboratory, Florham Park, N.J.

Phloroglucinol Monobenzenesulfonate (4). Phloroglucinol tribenzenesulfonate (**3**) (77.3 g, 0.141 mol) was suspended in methanol (235 mL) at 25 °C. Potassium hydroxide (47.3 g, 0.843 mol) in water (23.5 mL) diluted to 235 mL with methanol was added dropwise to the triester over a period of 10 min. Addition was accompanied by a rise in temperature from 25–55 °C. The solution was then heated at reflux for 0.5 h. After the solution had been diluted to 2500 mL with water it was acidified to pH 0–1 with concentrated hydrochloric acid and decolorized with a few grains of solid sodium thiosulfate. The solution was then stirred for 6 h at 25 °C to assist deposition of a white crystalline solid. After storage at 0 °C overnight the crystals were filtered, washed with water, air dried, and azeotroped with benzene (345 mL) to remove water. As soon as 275 mL of azeotrope had distilled, the remaining slurry was allowed to cool to 25 °C overnight and the solid filtered to give 20.4 g (55%) of **4**: mp 158–165 °C; ^{1}H NMR (acetone-d_6) 6.00 (d, J = 2 Hz, 2), 6.25 (t, J = 2 Hz, 1), 7.75 (m, 5), 8.50 (br, 2) ppm.

Phloroglucinol Dibenzyl Ether Monobenzenesulfonate (5). Phloroglucinol monobenzenesulfonate (**4**) (29.0 g, 0.109 mol) was dissolved in dry *N,N*-dimethylformamide (390 mL). Powdered, anhydrous potassium iodide (46.5 g, 0.280 mol) and powdered, anhydrous potassium carbonate (93.7 g, 0.678 mol) were then added followed by benzyl chloride (32.5 mL, 35.5 g, 0.282 mol). The slurry was stirred overnight at 25 °C under a nitrogen atmosphere. After 12 h the reaction mixture was diluted with methylene chloride (800 mL) and filtered through Celite. The filtrates were concentrated in vacuo. The residue was dissolved in ethyl acetate (800 mL) and washed with water (300 mL) and saturated, aqueous sodium chloride solution (200 mL) and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave 48.6 g (100%) of **5** as a light-colored crystalline solid, mp 58.5–62.5 °C. This material was pure enough to be used in the next step of the synthesis. Trituration of this solid with methanol gave crystals with the following: mp 63.5–64.5 °C; IR ($CHCl_3$) 3030, 1621, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.82 (s, 4), 6.18 (d, J = 2.2 Hz, 2), 6.38 (t, J = 2.2 Hz, 1), 7.23 (s, 10), 7.10–7.90 (m, 5) ppm; m/e (rel intensity) 446 (M^+, 1.44). Anal. Calcd for $C_{26}H_{22}O_5S$: C, 69.94; H, 4.97. Found: C, 69.73; H, 5.00.

Phloroglucinol Dibenzyl Ether (6). Phloroglucinol dibenzyl ether monobenzenesulfonate (**5**) (49.1 g, 0.110 mol) was suspended in methanol (245 mL). Potassium hydroxide (184.1 g, 3.282 mol) in water (92 mL) diluted to 920 mL with methanol was added and the suspension heated at reflux for 18 h. The reaction mixture was cooled and concentrated to half volume in vacuo and then diluted to 2500 mL with water and acidified to pH 1–4 with concentrated hydrochloric acid. The solution was stirred at room temperature for 12 h to assist deposition of a light tan solid. After storage at 0 °C for 12 h the crystalline solid was filtered and washed with water. After drying in vacuo there was obtained 32 g (95%) of **6**: mp 90–92 °C (lit.[18] mp 91–91.5 °C); IR ($CHCl_3$) 3623 (s, OH), 3279 (br, OH), 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.97 (s, 4), 5.15 (s, 1 exch. w/D_2O), 6.12 (d, J = 2.4 Hz, 2), 6.24 (t, J = 2.4 Hz, 1), 7.35 (s, 10) ppm; m/e (rel intensity) 306 (M^+, 17.22). Recrystallization from carbon tetrachloride gave an analytically pure sample of **6**. Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.67; H, 6.03.

***cis*-3-Acetoxy-4-hydroxytetrahydrofuran (8).** A solution of 3,4-dihydroxytetrahydrofuran (**7**)[19] (104 g, 0.999 mol), triethyl orthoacetate (275 mL, 243 g, 1.50 mol), and trifluoroacetic acid (1 mL) in anhydrous tetrahydrofuran (500 mL) was heated at reflux for 48 h under argon. After cooling, the solvent was evaporated in vacuo. The residual oil was dissolved in a mixture of acetone (350 mL) and 5% aqueous oxalic acid (35 mL) and stirred at 25 °C for 0.5 h. Anhydrous sodium sulfate (10 g, 0.07 mol) and potassium bicarbonate (2 g, 0.02 mol) were added and the slurry stirred for 0.25 h. Filtration through a 1-cm layer of silica gel and concentration of the filtrates in vacuo gave an oil, which after vacuum distillation gave 126.5 g (87%) of **8**: bp 86–87 °C (0.3 mmHg); IR (film) 3410 (br, OH), 2940, 2860, 1735 (s, O_2CCH_3), 1250, 1065, 940, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.12 (s, 3), 2.40 (d, J = 6 Hz, 1), 3.84 (m, 4), 4.38 (m, J = 6 Hz, 1), 5.06 (q, J = 6 Hz, 1) ppm. Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.54; H, 6.68.

4-Acetoxytetrahydrofuran-3-one (9). A solution of the alcohol **8** (80.7 g, 0.552 mol) in methylene chloride (150 mL) was added dropwise to a mechanically stirred slurry of Celite (59 g) which had been dried overnight at 110 °C and pyridinium chlorochromate[20] (237.7 g, 1.103 mol) in methylene chloride (1500 mL). After being stirred for 49 h at 25 °C under argon, diethyl ether (1500 mL) was added and the slurry stirred overnight (16 h). The solution was decanted and filtered from a black semisolid which was washed with ether (375 mL). The combined decantates were concentrated in vacuo to a dark oil which was dissolved in ether (150 mL) and filtered through a plug of Woelm SiO_2 (63–200 μm) packed in a 350-mL fritted glass disk funnel. After washing the plug with ether (500 mL), the combined filtrates were concentrated in vacuo to an oil which was vacuum distilled to give 51.3 g (64%) of **9** [bp 82–84 °C (0.18–0.2 mmHg)] and 3.8 g of unreacted starting material. The yield of **9** after recovering starting material was 68%: IR (film) 2925, 2855, 1780 (s, C=O), 1750 (s, O_2CCH_3), 1430, 1375, 1230, 1080, 1065, 1020, 935 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.16 (s, 3), 3.87 (t, J = 8 Hz, 1), 4.05 (s, 2), 4.52 (t, J = 8 Hz, 1), 5.20 (t, J = 8 Hz, 1) ppm; m/e (rel intensity) 144 (M^+, 0.47), 43 (acylium ion, 100). Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 50.16; H, 5.71.

4-Acetoxy-2-bromotetrahydrofuran-3-one (10). To a solution of **9** (2.2 g, 0.015 mol) in carbon tetrachloride (76 mL) distilled from phosphorus pentoxide was added recrystallized *N*-bromosuccinimide (3.0 g, 0.017 mol) which had been dried in vacuo over phosphorus pentoxide. A 100-W light was placed next to the reaction vessel and the solution stirred under nitrogen. After 1.25 h the solution temperature had risen to 35 °C and a white solid had floated to the top of the solution. The solution was then cooled, filtered, and concentrated in vacuo at temperatures less than 35 °C to give 3.4 g (100%) of **10** as a mixture of diastereomers which was unstable to silica gel and alumina and tends to decompose upon distillation: IR (film) 3300, 3010, 2920, 1780 (s, C=O), 1750 (s, O_2CCH_3), 1725 (w), 1380, 1225, 1080, 1060, 920, 885, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.18 (s, 1.5), 2.23 (s, 1.5), 4.15 (m, 1), 4.70 (m, 1), 5.34 (m, 1), 6.65 (s, 1) ppm. Short path vacuum distillation of a 2-g sample of the crude **10** gave 1.5 g (75%) of **10**: bp 80 °C (0.01 mmHg).

3-Acetoxy-3a-bromo-4,6-bis(benzyloxy)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (11). Dry methylene chloride (300 mL) was saturated for 5 min at 25 °C with a vigorous stream of HBr gas. Phloroglucinol dibenzyl ether (**6**) (25.1 g, 0.0819 mol) was then added in a single portion followed by dry methylene chloride (70 mL). Bromide **10** (28.7 g, 0.129 mol) in dry methylene chloride (80 mL) was then added dropwise over a period of 5 min. The solution was stirred for an additional 20 min at 25 °C under nitrogen and was then filtered through 100 g of Woelm SiO_2 (63–200 μm) packed in methylene chloride in a 350 mL (c) fritted disk funnel. The SiO_2 was washed with methylene chloride (500 mL) and the filtrates were concentrated in vacuo to ~300 mL and washed with 2 × 70 mL of saturated, aqueous sodium bicarbonate and sodium chloride solutions. After drying over anhydrous magnesium sulfate, filtration and concentration in vacuo gave 30.0 g of material which was dissolved in 110 mL of chloroform and chromatographed on 300 g of Woelm SiO_2 (63–200 μm). Elution with 5:1 hexane–ethyl acetate gave 17.6 g (42%) of **11** as a crystalline solid: mp 146–147 °C; IR ($CHCl_3$) 3030, 1745 (vs, O_2CCH_3), 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.20 (s, 3), 4.00 (m, 2), 5.05 (s, 2), 5.15 (s, 2), 5.95 (br, 1), 6.25 (s, 2), 6.35 (s, 1), 7.40 (s, 10) ppm; m/e (rel intensity) 510, 512 (M^+, 0.33, 0.35), 91 (tropylium, 100). Anal. Calcd for $C_{26}H_{23}BrO_2$: C, 61.07; H, 4.53. Found: C, 60.82; H, 4.61.

3,3a-Dihydroxy-4,6-bis(benzyloxy)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]-benzofuran (12) from 11. The tricyclic bromide **11** (14.4 g, 0.0282 mol) was dissolved in acetone (500 mL) to which 5% aqueous oxalic acid (215 mL) was then added. The solution was heated at reflux for 0.5 h. After cooling, the solution was evaporated to dryness in vacuo and the residual solids were dissolved in 1:1 tetrahydrofuran–water (v/v) (600 mL). The solution was made basic with 50% aqueous sodium hydroxide solution and solid sodium hydroxide (34.1 g, 0.853 mol) was added. The reaction mixture was stirred at 25 °C for 23.5 h and the solution was acidified to pH 0–1 with concentrated hydrochloric acid and evaporated to dryness in vacuo. The residual solids were extracted with ethyl acetate (4 × 250 mL) and the combined extracts were filtered and dried over magnesium sulfate to give 11.4 g (99%) of **12** as a white crystalline solid: mp 132–133 °C; IR ($CHCl_3$) 3584 (br, OH), 3030 (m, unsat. CH), 1631 (s, C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.15 (br, 2), 3.75–3.95 (dd, J_{AB} = 10.4 Hz, J_{AX} = 2 Hz, 1), 4.05–4.25 (d, J_{BA} = 10.4 Hz, 1), 4.45 (m, 1), 5.00 (s, 2), 5.10 (s, 2), 5.95 (s, 1), 6.15 (d, J = 1.8 Hz, 1), 6.25 (d, J = 1.8 Hz, 1), 7.40 (s, 10) ppm; m/e (rel intensity) 406 (M^+, 5.90), 91 (tropylium, 100). Recrystallization from ethyl acetate/*n*-hexane gave analytically pure **12**. Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.93; H, 5.47. Found: C, 70.83; H, 5.54.

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3,3a-Acetonide-4,6-bis(benzyloxy)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (16). Diol **12** (19.6 g, 0.0482 mol) was dissolved in distilled 2,2-dimethoxypropane (920 mL) and fused *p*-toluenesulfonic acid (0.13 g, 0.77 mmol) was added. The solution was stirred for 3 h at 25 °C under a nitrogen atmosphere and was then evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate (800 mL), and the solution was washed with a saturated, aqueous sodium bicarbonate solution and dried over magnesium sulfate. Filtration and concentration in vacuo gave 21.0 g (98%) of **16** as a crystalline solid: mp 145–146 °C; IR ($CHCl_3$) 3030 (m, unsatd. CH), 1631 (s, C=C), 1602 (s, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 1.28 (s, 3), 1.50 (s, 3), 3.95 (dd, J_{AB} = 9.5 Hz, J_{AX} = 2.0 Hz, 1), 4.28 (d, J_{BA} = 9.5 Hz, 1), 4.76 (d, J_{XA} = 2.0 Hz, 1), 5.02 (s, 2), 5.07 (s, 2), 5.99 (s, 1), 6.20 (q, J = 2.6 Hz, 2), 7.39 (s, 10) ppm; *m/e* (rel intensity) 446 (M^+, 0.97), 91 (tropylium, 100). Recrystallization from carbon tetrachloride gave analytically pure **16**. Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.42; H, 5.86.

3,3a-Acetonide-4-(benzyloxy)-6-hydroxy-2,3,3a,8a-tetrahydrofuro[8,3-*b*]benzofuran (17). The tricyclic acetonide **16** (7.0 g, 0.016 mol) dissolved in ethyl acetate (400 mL) was stirred with 5% Pd–$BaSO_4$ (5.0 g), under 1 atm of hydrogen at 25 °C. After approximately 1 h TLC revealed only traces of starting material and the first traces of the product lacking both benzyl groups. The reaction mixture was filtered and concentrated in vacuo. The recovered catalyst could be used for further hydrogenations. Seven equal sized batches were pooled and concentrated in vacuo to give 41.8 g of crude crystalline solid. The solid was dissolved in 90–100 mL of boiling ethyl acetate and diluted to 300 mL with *n*-hexane. After being stirred for 0.5 h at room temperature and storage at −18 °C overnight, the solid was filtered, washed with 50 mL of ice cold 5:1 hexane–ethyl acetate and dried in vacuo to give 33.8 (88%) of **17**. The mother liquors were chromatographed to give another 2.7 g of **17**. This material was sufficiently pure for the methylation step. IR ($CHCl_3$) 3600 (s, OH), 3400 (broad, OH) cm^{-1}; ^1H NMR (acetone-d_6) 1.27 (s, 3), 1.43 (s, 3), 3.42–3.60 (dd, J_{AB} = 11 Hz, J_{AX} = 2 Hz, 1), 4.10–4.30 (d, J_{BA} = 11 Hz, 1), 4.75 (d, J_{XA} = 2 Hz, 1), 5.15 (s, 2), 5.90 (s, 1), 5.95 (d, J = 1.8 Hz, 1), 6.20 (d, J = 1.8 Hz, 1), 7.45 (m, 5) ppm; *m/e* (rel intensity) 356 (M^+, 3.40), 91 (tropylium, 100). Recrystallization of a small sample gave analytically pure **17**: mp 186–188 °C. Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.13; H, 5.79.

3,3a-Acetonide-4-(benzyloxy)-6-methoxy-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (18). The phenol **17** (28.9 g, 0.0811 mol) was dissolved in dry *N,N*-dimethylformamide (160 mL). Anhydrous potassium carbonate (23.6 g, 0.171 mol) was added followed by methyl iodide (5.10 mL, 11.6 g, 0.0819 mol). The slurry was stirred at 25 °C under a nitrogen atmosphere for 24 h. The slurry was filtered and ethyl acetate (1800 mL) was added to the solution which was then filtered through Celite. The filtrates were washed with saturated aqueous sodium bicarbonate solution (1 × 500 mL) and brine (1 × 500 mL). The combined aqueous phases were re-extracted with ethyl acetate (1 × 300 mL) and the combined organic phases were dried over magnesium sulfate. Filtration and concentration in vacuo gave a brown gum which crystallized on trituration with 1:1 petroleum ether–ether to give 29.5 g (98%) of **18** as a light tan crystalline solid: mp 99.5–101 °C; IR ($CHCl_3$) 3100, 1610, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) 1.27 (s, 3), 1.50 (s, 3), 3.74 (s, 3), 3.93 (dd, J_{AB} = 10.7 Hz, J_{AX} = 2.4 Hz, 1), 4.27 (d, J_{BA} = 10.7 Hz, 1), 4.78 (d, J_{XA} = 2.4 Hz, 1), 5.07 (s, 2), 5.99 (s, 1), 6.12 (dd, 2), 7.39 (s, 5) ppm; *m/e* (rel intensity) 370 (M^+, 3.75), 91 (tropylium ion, 100). Recrystallization from carbon tetrachloride gave analytically pure **18**. Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.22; H, 6.03.

3,3a-Dihydroxy-4-(benzyloxy)-6-methoxy-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (13). The acetonide **18** (7.6 g, 0.021 mol) was heated at reflux for 1 h with glacial acetic acid (567 mL) and water (310 mL). The reaction mixture was cooled and evaporated in vacuo to an oil which crystallized when triturated with 1:1 petroleum ether–ether (2 × 15 mL) to give 6.1 g (90%) of **13** as a white crystalline solid: mp 125–126 °C; IR ($CHCl_3$) 3496 (br, OH), 3030 (m, unsat. C–H), 1623, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) 3.33 (br s, 2), 3.73 (s, 3), 3.88 (dd, J_{AB} = 10 Hz, J_{AX} = 2.3 Hz, 1), 4.09 (d, J_{BA} = 10 Hz, 1), 4.45 (d, J_{XA} = 2.3 Hz, 1), 5.10 (s, 2), 5.91 (s, 1), 6.11 (q, J = 1.6 Hz, 2), 7.38 (s, 5) ppm; *m/e* (rel intensity) 330 (M^+, 4.00), 91 (tropylium ion, 100). Recrystallization from ethyl acetate–hexane gave analytically pure **13**. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.20; H, 5.43.

3-((*p*-Bromobenzenesulfonyl)oxy)-3a-hydroxy-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (14). The diol **13** (6.0 g, 0.018 mol) was dissolved in dry pyridine (55 mL) and cooled to 0 °C under a nitrogen atmosphere. *p*-Bromobenzenesulfonyl chloride (9.4 g, 0.037 mol) was added in a single portion and the stirred solution was allowed to warm to 25 °C under nitrogen for 24 h. The reaction was poured into ice water (360 mL) and the mixture was shaken in a separatory funnel. The aqueous phase was extracted with ethyl acetate (2 × 200 mL, 1 × 150 mL, 1 × 100 mL), and the combined extracts were washed with ice cold 1:1 concentrated hydrochloric acid–water (2 × 230 mL), saturated, aqueous sodium bicarbonate solution (1 × 125 mL), and brine (1 × 125 mL). After being dried over magnesium sulfate, filtered, and concentrated in vacuo, 9.7 g of a light pink foam was obtained. Trituration with 1:1 petroleum ether–ether gave 8.4 g (86%) of **14** as a crystalline solid. Chromatography of the filtrates gave an additional 1.1 g of **14** for a total of 9.5 g (95%): mp 114.5–115.5 °C; IR ($CHCl_3$) 3550 (w, OH), 3100–3030 (w, unsat. CH), 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) 2.90 (s, 1), 3.65 (s, 3), 3.70–3.90 (dd, J_{AB} = 11 Hz, J_{AX} = 2 Hz, 1), 4.00–4.20 (d, J_{BA} = 11 Hz, 1), 4.96 (s, 2), 5.23 (d, J_{XA} = 2 Hz, 1), 5.78 (s, 1), 5.95 (d, J = 1.8 Hz, 1), 6.00 (d, J = 1.8 Hz, 1), 7.30 (s, 5), 7.43 (s, 4) ppm; *m/e* (rel intensity) 312 ($C_{18}H_{16}O_5$, 0.70). Anal. Calcd for $C_{24}H_{21}BrO_8S$: C, 52.47; H, 3.85. Found: C, 52.71; H, 4.09.

3-((*p*-Bromobenzenesulfonyl)oxy)-3a-acetoxy-4-(benzyloxy)-6-methoxy-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (15). The sulfonate **14** (7.6 g, 0.014 mol) was suspended in dry triethylamine (47 mL) and 4-(*N,N*-dimethylamino)pyridine (0.33 g, 0.0027 mol) was added followed by distilled acetic anhydride (7.9 mL, 8.5 g, 0.084 mol). The solution was stirred at 25 °C under a nitrogen atmosphere for 24 h. Excess acetic anhydride was destroyed with methanol (95 mL) at 0 °C. The solution was evaporated to dryness and the residue dissolved in ethyl acetate (490 mL). The organic phase was washed with 2 N aqueous hydrochloric acid (2 × 175 mL), saturated, aqueous sodium bicarbonate solution (1 × 175 mL), and brine (1 × 175 mL) and dried over magnesium sulfate. Filtration and concentration in vacuo gave 8.2 g (100%) of **15**: mp 134–136 °C; IR ($CHCl_3$) 3100–3025 (m, unsat. CH), 1750 (vs, O_2CCH_3) cm^{-1}; ^1H NMR ($CDCl_3$) 1.60 (s, 3), 3.67 (s, 3), 3.67–3.90 (dd, J_{AB} = 10 Hz, J_{AX} = 2 Hz, 1), 4.05–4.20 (d, J_{BA} = 10 Hz, 1), 4.99 (s, 2), 5.50 (d, J_{XA} = 2 Hz, 1), 6.00 (s, 2), 6.18 (s, 1), 7.35 (s, 5), 7.45 (m, 4) ppm; *m/e* (rel intensity) 329 ($C_{18}H_{17}O_6$, 4.16), 238 ($C_6H_5Br^{81}O_3S$, 11.50), 236 ($C_6H_5Br^{79}O_3S$, 11.79), 91 (tropylium, 100), 43 (acylium, 77.59). Recrystallization from ethyl acetate–hexane gave analytically pure **15**. Anal. Calcd for $C_{26}H_{23}BrO_9S$: C, 52.80; H, 3.92. Found: C, 52.69; H, 4.05.

3a-Acetoxy-4-(benzyloxy)-6-methoxy-3a,8a-dihydrofuro[2,3-*b*]benzofuran (19). The sulfonate **15** (4.2 g, 0.0072 mol) was heated for 5 h in 1,8-diazabicyclo[5.4.0]undec-7-ene (14 mL) at 105–110 °C under a nitrogen atmosphere. The solution was cooled, diluted with ethyl acetate (570 mL), and washed with ice cold 1:4 concentrated hydrochloric acid–water (2 × 200 mL), saturated, aqueous sodium bicarbonate solution (1 × 130 mL), and brine (1 × 130 mL) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave 2.5 g of a crude crystalline solid, which was dissolved in dry methylene chloride (14 mL) and triethylamine (14 mL). Acetic anhydride (3.9 mL, 4.2 g, 0.041 mol) was added followed by 4-(*N,N*-dimethylamino)pyridine (0.097 g, 0.00079 mol). The solution was kept at 25 °C for 2 h under a nitrogen atmosphere. The reaction was quenched with methanol (10 mL) at 0 °C and the solution was evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate (270 mL) and washed with 2 N aqueous hydrochloric acid (2 × 100 mL), saturated, aqueous sodium bicarbonate solution (1 × 100 mL), and brine (1 × 100 mL) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave a crude solid, which was dissolved in a small amount of ethyl acetate and filtered through a plug of silica gel. The filtrates were concentrated in vacuo and the resultant crystalline solid (2.2 g) was recrystallized from ethyl acetate–hexane to give 1.4 g (56%) of **19**. The mother liquors were chromatographed to give an additional 0.4 g of **19**: total yield 1.8 g (70%); mp 154–156 °C; IR ($CHCl_3$) 3100 (m, unsat. CH), 1740 (vs, O_2CCH_3), 1630, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) 2.00 (s, 3), 3.70 (s, 3), 5.00 (s, 2), 5.45 (d, J = 3 Hz, 1), 6.00 (d, J = 1.8 Hz, 1), 6.10 (d, J = 1.8 Hz, 1), 6.50 (d, J = 3 Hz, 1), 6.70 (s, 1), 7.30 (s, 5) ppm; *m/e* (rel intensity) 354 (M^+, 4.62), 221 ($C_{11}H_9O_5$, 10.67), 91 (tropylium ion, 100), 43 (acylium ion, 25.35). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.89; H, 5.25.

3a,4-Dihydroxy-6-methoxy-3a,8a-dihydrofuro[2,3-*b*]benzofuran (21). Acetate **19** (1.0 g, 0.0028 mol) was dissolved in dry tetrahydrofuran (20 mL) and absolute methanol (12 mL). A solution of 1 M sodium methoxide in methanol (7 mL) was added and the solution was stirred at 25 °C for 0.5 h under a nitrogen atmosphere. The solution was evaporated to dryness in vacuo and the residue dissolved in anhydrous diethyl ether (20 mL) and liquid ammonia (160 mL). Sodium metal (0.45 g, 0.019 mol) was added in portions over a period of 10 min at a rate to just maintain a blue colored solution. The blue solution was then allowed to stir for an additional 5 min after which excess sodium metal was destroyed with small portions of solid ammonium chloride. The residue was dissolved in water (105 mL) and washed with benzene 2 × 40 mL). The aqueous phase was acidified with 1:4 concentrated hydrochloric acid–water (30 mL) and extracted with ethyl acetate (4 × 105 mL). The combined extracts were washed with brine (3 × 80 mL) and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo gave

0.63 g of an oil which could be used for the final step as is. For characterization, 0.2 g of the oil was chromatographed on an analtech 2000 μm, SiO_2 plate. Elution with 10% methanol in chloroform gave 0.19 g (98%) of **21** as an oil which was identical with an authentic sample prepared by Weinreb[10] as judged by TLC, ^1H NMR, IR, MS, and UV comparisons. UV_{max} (95% EtOH) 213 nm (ε 22 500), 242 (ε 6100), 270 (sh, ε 660); IR ($CHCl_3$) 3550 (m, OH), 3500–3200 (br, OH), 1625 (vs, unsat. C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 3.69 (s, 3), 5.53 (d, J = 3 Hz, 1), 5.96 (d, J = 1.8 Hz, 1), 6.04 (d, J = 1.8 Hz, 1), 6.25 (s, 1), 6.51 (d, J = 3 Hz, 1) ppm; m/e (rel intensity) 223 (M + 1, 0.94), 222 (M^+, 4.90), 83 ($C_4H_3O_2$, 100).

Racemic Aflatoxin M_1 (1). The phenol **18** (0.15 g, 0.00086 mol) was dissolved in dry methylene chloride (35 mL) and anhydrous, powdered sodium bicarbonate (10.5 g, 0.125 mol) and zinc carbonate[10] (7.0 g, 0.0558 mol) were added, followed by the bromide **19** (0.28 g, 0.0012 mol) in methylene chloride (35 mL). The slurry was stirred for 24 h at 25 °C under a nitrogen atmosphere and was then transferred to a Soxhlet thimble and continuously extracted for 24 h with 2% methanol in chloroform (500 mL). The extract was washed with saturated, aqueous sodium bicarbonate solution (2 × 150 mL) and brine (1 × 150 mL) and dried over anhydrous sodium sulfate. The solid in the thimble was treated with 1:4 concentrated hydrochloric acid–water (250 mL) and the suspension was extracted with chloroform (3 × 100 mL). The combined extracts were washed with sodium bicarbonate solution (2 × 100 mL) and brine (1 × 100 mL), dried, and combined with the chloroform solution of the Soxhlet extraction. Filtration and concentration in vacuo gave 0.17 g of residue which was triturated with methanol (5 × 1 mL) to give 0.06 g (27%) of **1** as a light yellow crystalline solid. The methanol washes were chromatographed on an analtech 2000 μm, SiO_2 plate. Elution with 10% methanol in chloroform gave an additional crop of 0.01 g (5%) of **1** bringing the total yield to 32%. Aflatoxin M_1 (**1**) was identical with an authentic sample as judged by chromatographic and spectral comparisons: UV_{max} (95% EtOH) 228 nm (ε 23 200), 260 (sh, ε 10 900), 266 (ε 11 800), 358 (ε 18 500); IR ($CHCl_3$) 1760 (br, C=O), 1630 (C=C), 1620 (aromatic C=C) cm^{-1}; ^1H NMR (pyridine-d_5) 2.53 (m, 2), 3.07 (m, 2), 3.82 (s, 3), 6.05 (d, J = 2.9 Hz, 1), 6.63 (s, 1), 6.91 (d, J = 2.9 Hz, 1), 6.95 (s, 1) ppm; m/e (rel intensity) 328 (M^+, 67.38), 299 ($C_{14}H_9O_6$, 75.89), 271 ($C_{13}H_9O_5$, 100).

Acknowledgment. This investigation was supported by a National Research Service Award (2 T32 CA09112) from the National Cancer Institute, DHEW; the National Institutes of Health (GM09868); and the Hoffmann-LaRoche Foundation. We wish to thank Mr. T. Holler for having prepared some of the intermediates.

Complete Retention in Substitution and Stereospecificity in Transannular Reactions of *cis*- and *trans*-3-*tert*-Butylcyclooctyl Tosylates

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Abstract: The stereochemistry of solvolysis reactions including 1,5 hydride shifts is investigated with 3-*tert*-butylcyclooctyl compounds. The hitherto undetected epimeric alcohols can be differentiated by ^{13}C NMR but not by the nearly identical ^1H NMR and IR spectra. Their configuration, confirmed by an unpublished X-ray analysis, is compared to the stereoselectivity of corresponding ketone reductions. Solvolysis of the epimeric tosylates in aqueous acetone, acetic acid, and trifluoroethanol is accompanied by at least 99% retention; the precursor configuration is retained too in the transannular 1,5 hydride shift reaction products. These amount to approximately 50%, as found by ^{13}C and ^2H NMR spectroscopic analysis of ^2H distribution in solvolysis products of C^α-deuterated tosylates. Solvolysis rates of the epimeric tosylates differ by a factor of 15, which is attributed not to different degrees of transannular hydrogen participation but to strain energy variations. Other isomerization products such as 1- and 2-*tert*-butylcyclooctanols are not observed.

Although almost 3 decades have passed since Cope, Prelog, and their schools discovered the unique transannular reactions of medium-ring compounds,[1] very little is known about the stereochemistry of the corresponding substitutions. With 5-methyl-,[2a] 5-phenyl-,[2b] and 5-*tert*-butylcyclooctyl tosylates,[2c] Allinger, Cope, and their co-workers showed that only the cis epimer undergoes solvolysis with a transannular 1,5 hydride shift; the stereochemistry of the substitution was not investigated, and it was not clear whether the solvolysis rate was enhanced by participation of the migrating hydrogen. Arguments against a hydrogen participation have been put forward earlier;[1,2b] a more recent isotope effect study of Parker and Watt,[3] however, demonstrates definite, although perhaps small, participation in cyclooctyl sulfonate solvolysis. The high solvolysis rates of medium-ring compounds have been attributed by Brown[4] to I strain relief and not to transannular participation, and we recently[5] could show that trifluoroethanolysis rates of cycloalkyl tosylates indeed are quantitatively predicted by force field calculated strain energy differences between multiple-ring conformations containing an sp^3 or sp^2 hybridized carbon. Harris, Raber, et al. have found particularly low solvent assistance in cyclooctyl sulfonate solvolysis rates and have attributed this to the inherent strain of the ring;[6] steric shielding by different hydrogens against solvent attack or hydrogen participation might offer an alternative and preferable explanation.

Cyclooctyl sulfonates bearing an alkyl group in the 3-position are particularly intriguing systems as here 1,5 hydride shifts can lead to structurally identical products. Introduction of deuterium

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