Synthesis of the Enantiomeric Furobenzofurans, Late Precursors for the Synthesis of (+)- and (−)-Aflatoxins B_1, B_2, G_1, and G_2

Edgar R. Civitello and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received February 22, 1994®

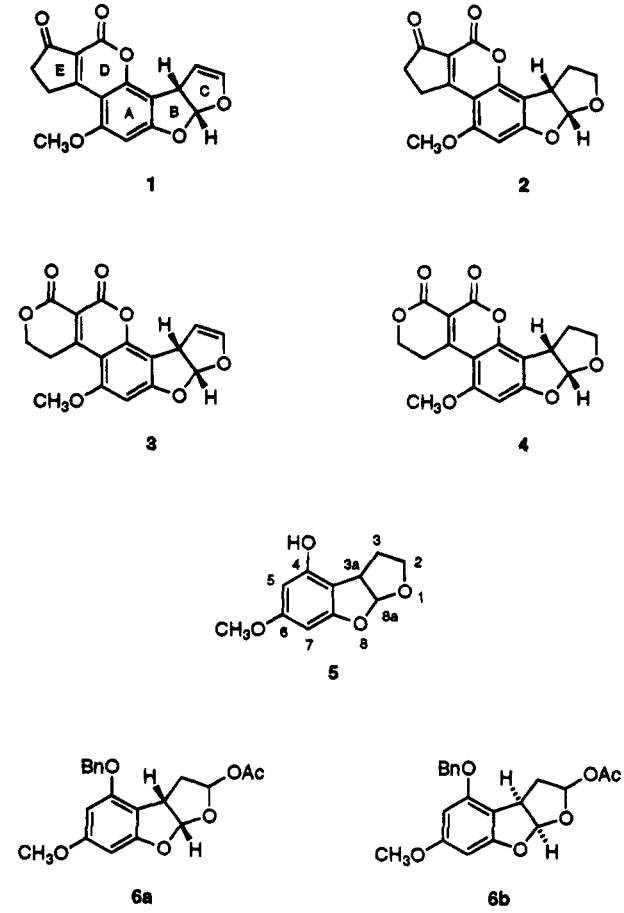
Enantiomeric tetrahydrofuro[2,3-*b*]benzofurans, representing the ABC tricyclic portion of aflatoxins B_1, B_2, G_1, and G_2, were generated from the oxaza-Cope rearrangement of a suitably functionalized *O*-aryloxime. The *O*-aryloxime was, in turn, made from the condensation of an enantiomerically pure aldehyde derived from glutamic acid and a substituted phenoxyamine. High regioselectivity with respect to the A-ring substituents of the ABC tricycle was achieved through the use of electrochemistry. The regioselective electrochemical cleavage of 4,6-bis(tosyloxy)-2-(methoxycarbonyl)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (**22**) resulted in a 97/3 mixture of regioisomeric phenols. The regiochemical assignments of the resulting phenols were determined by 2D NOESY NMR. The enantiomeric ratio of the final product was determined to be 96/4 by NMR analysis of diastereomers resulting from the coupling of **31a** to (+)- and (±)-phenethylamine.

Introduction

Aflatoxins B_1 (**1**), B_2 (**2**), G_1 (**3**), and G_2 (**4**) are metabolites of the mold *Aspergillus flavus* belonging to the large family of mycotoxins. Since their discovery in 1961 as the cause of the Turkey X disease, aflatoxins have been the subject of extensive biological studies because of their high toxicity and carcinogenicity.[1] Their threat as food contaminants and their unique structure have made them popular synthetic targets. Several published total syntheses have resulted.[2]

All these previous syntheses of the aflatoxins **1**–**4** (Chart 1) were accomplished in two major stages: first, the furo[2,3-*b*]benzofuran ring systems (ABC tricycle) were formed starting with a phloroglucinol nucleus; second, annulation of the D and E rings was effected through a modified von Pechmann reaction. These elegant early racemic syntheses were limited by low yields and regioisomeric mixtures associated primarily with the regiochemical requirements of the A-ring. In previous work we had successfully addressed these difficulties with the synthesis of tricycle **5** which represents a formal total synthesis of racemic aflatoxin B_2.[3] At the core of this synthesis is an oxaza-Cope rearrangement of an appropriately derivatized *O*-aryloxime which affords the dihydrobenzofuran moiety. As an extension of this earlier work, we now report the enantioselective synthesis of tricycles **6a** and **6b**. Since the conversion of racemic **6** to the racemic aflatoxins has been effectively accomplished,[2b,c] together with these previous reports, this constitutes a formal total synthesis of (−)- and (+)-aflatoxins **1**–**4**, respectively.

Chart 1



Results and Discussion

Our general route to the tetrahydrofuro[2,3-*b*]benzofuran tricycle is outlined in Scheme 1. The basic plan was to use a chiral auxiliary to obtain stereochemical selectivity in the oxaza-Cope rearrangement of oxime **7**. With the stereochemistry at the benzylic 3a position established, the second chiral center would then be controlled by the geometric constraints of the 5-5 fused-ring juncture. The chiral auxiliary was to serve two purposes: first, to induce asymmetry through a diastereomeric effect in the rearrangement; and second, to

® Abstract published in *Advance ACS Abstracts,* June 1, 1994.

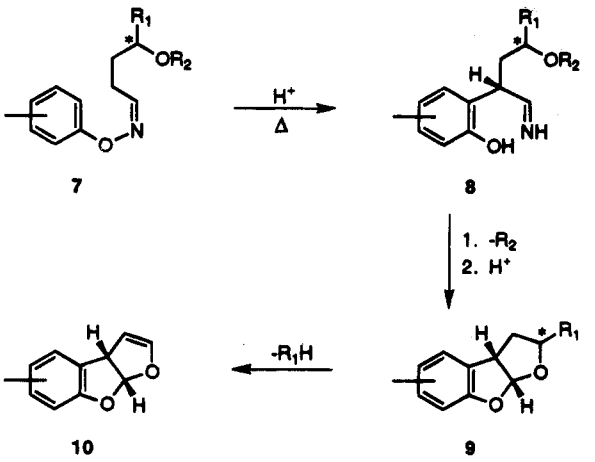
(1) Reviewed by Busby, W. F., Jr.; Wogan, G. N. In *Chemical Carcinogens*, 2nd ed.; Searle, C., Ed.; American Chemical Society: Washington, DC, 1984; Vol. 182, pp 945–1136.

(2) (a) Reviewed by Schuda, P. F. *Top. Curr. Chem.* **1980**, *91*, 75. (b) Büchi, G.; Weinreb, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 746. (c) Büchi, G.; Foulkes, D. M.; Kurono, M.; Mitchell, G. F.; Schneider, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 6745. (d) Roberts, J. C.; Sheppard, A. H.; Knight, J. A.; Roffey, P. *J. Chem. Soc.* **1968**, 22. (e) Knight, J. A.; Roberts, J. C.; Roffey, P. *J. Chem. Soc.* **1966**, 1308. (f) Sloan, C. P.; Cuevas, J. C.; Quesnelle, C.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 4685. (g) Weeratunga, G.; Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1988**, 721.

(3) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1006.

0022-3263/94/1959-3775$04.50/0

Scheme 1. Furobenzofurans from *O*-Aryloximes



provide a handle for introduction of the 2,3-double bond in the C-ring of tricycle **10**.

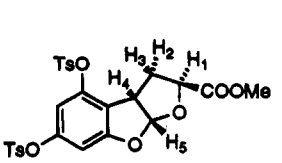
The requisite enantiomerically pure *O*-aryloxime **19** would arise from condensation of the suitably functionalized aldehyde **17** with 3,5-bis(tosyloxy)phenoxyamine (**18**),[4] and its synthesis is outlined in Scheme 2. The start of selectivity in this sequence was the monoesterification of glutamic acid.[5] We found the regioselectivity of this reaction to be ≥98/2 in favor of γ-esterification by high-resolution NMR analysis using dibenzyl glutamate to determine the limits of detection. The nitrous acid deamination of γ-benzyl glutamate that follows was expected to pose the largest potential for loss of enantiomeric purity. Thus the enantiomeric purity of the deamination reaction was assessed after formation of methyl ester **13**. 5-Benzyl 1-methyl 2-hydroxyglutarate (**13**) was coupled with (+)- and (±)-*N*-(phenylsulfonyl)-prolyl chloride.[6] Analysis of the (+)-prolyl ester **14** with high-resolution NMR established the enantiomeric ratio of **13** to be ≥98/2. The limits of detection were determined to be ±1% by doping studies with the (±)-prolyl ester. Continuation of the sequence was straightforward, proceeding by benzoylation of hydroxyglutarate **13** to triester **15**, hydrogenolytic liberation of the γ-acid and its reduction to δ-alcohol **16**, and oxidation to hydroxy aldehyde ester **17**.

Treatment of oxime **19** with excess HCl in THF at 80–85 °C in a sealed vessel resulted in several products, the major one of which was dihydrobenzofuran **20** (Scheme 3). The 4-chlorobutyl moiety in **20** arises from HCl cleavage of THF and serves as a protecting group to prevent the aromatization of the initially formed dihydrobenzofuran. It was subsequently demonstrated that **20** could be cyclized to the diastereomeric furobenzofuran tricycles **22a** and **22b** which could be separated by routine liquid chromatography. However, the ratio of **22a** to **22b** was determined to be 60/40, indicating that little chiral induction had occurred in the oxaza-Cope rearrangement.

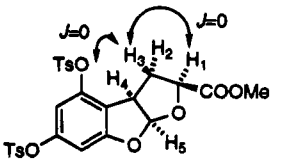
The byproducts in the oxaza-Cope rearrangement of oxime **19** were phenol **23** and nitrile **24**, resulting from Beckmann fragmentation of the oxime. It was possible to partially control this competitive rearrangement by lowering the reaction temperature to 70–75 °C and extending the reaction time. Under improved conditions, the amount of **19** lost to Beckmann fragmentation was estimated to be 10–15%. Another significant problem with the oxaza-Cope rearrangement was the formation of large amounts of chlorobutanol from the HCl cleavage of THF, which contributed to isolation difficulties.

To circumvent these problems we investigated solvents other than THF, e.g., dimethoxyethane (DME) which is known to be much more stable than THF to ether cleavage. When oxime **19** was heated with excess HCl in DME at 75 °C, only traces of a dihydrobenzofuran were seen. The major product was the tricyclic lactam **25** (Scheme 3). In the absence of a trapping agent, such as chlorobutanol, the hemiaminal intermediate in the oxaza-Cope rearrangement formed a δ-lactam by cyclization on the methyl ester. In none of these rearrangements did we see any indication of the fully aromatic benzofuran which would result from the elimination of ammonia.

The significance of lactam **25** was realized when we found that it could be converted to the methyl acetal **26** by simple treatment with HCl in methanol under reflux. It was not possible, however, to cyclize and form the C-ring from methyl acetal **26** by the same method used for the chlorobutyl acetal **21**. Apparently, the acid-catalyzed equilibrium in the cyclization of debenzoylated **26** favored the ring-opened form while that of **21** favored the ring-closed form. This equilibrium could be driven to the ring-closed form by removing the released methanol under acidic conditions. Thus methyl acetal **26** was converted directly to the diastereomeric tricycles **22a** and **22b** by quenching the transesterification reaction of **26**



22a



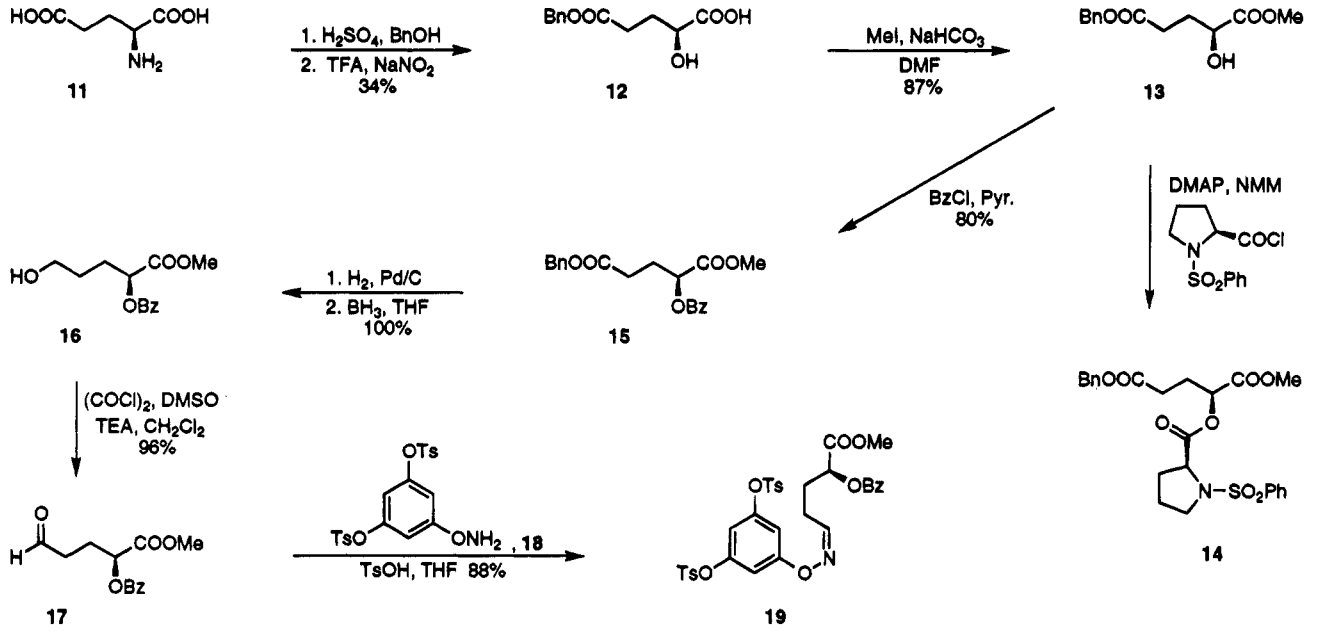
22b

with an excess of anhydrous HCl and then evaporating the acidic mixture to dryness under reduced pressure. The sequence **19** → **25** → **26** → **22a/22b** shown in Scheme 3 could be accomplished in 50–55% overall yield with only one purification. The ratio of **22a/22b** from this sequence was the same as proceeding through **19** → **20** → **21** → **22a/22b**. It was not possible to combine into one step the sequence **19** → **25** → **26** by conducting the oxaza-Cope rearrangement in methanol. All attempts at this resulted in the near quantitative recovery of oxime **19**. It would seem that the activity of HCl in methanol is insufficient in promoting the necessary prearrangement tautomerization of the oxime moiety.

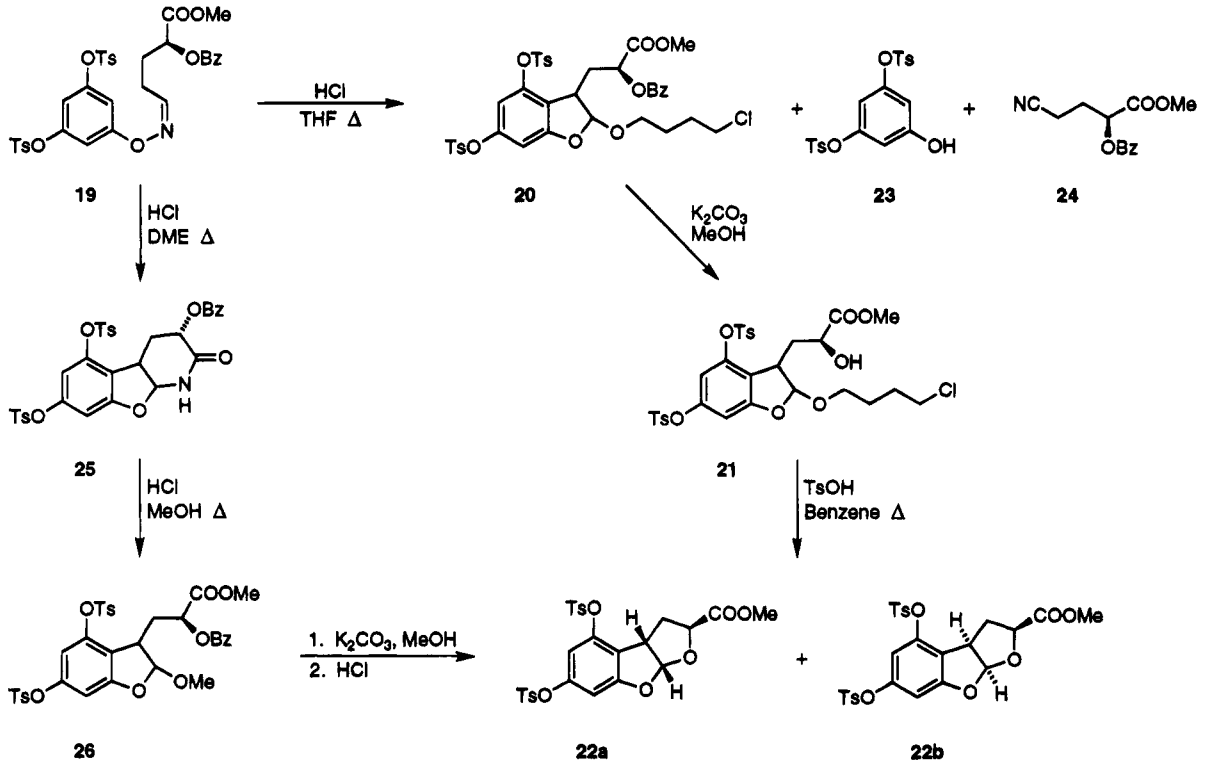
The stereochemical assignments of tricycles **22a** and **22b** were easily determined by 2D phase-sensitive NOE spectroscopy (NOESY), owing much to the fact that the tricycles are conformationally constrained and that the entire aliphatic region of both spectra are first order. It was also possible, in this case, to assign the stereochemistry based solely on the 1D NMR spectra. Proton H_3 for one of the stereoisomers of **22** appeared as a large doublet (J = 13 Hz), indicative of geminal coupling, while for the other isomer, proton H_3 appeared as a complex doublet-of-doublet-of-doublets. A single large doublet for H_3 could only arise from a conformation where the dihedral angles between H_3–H_4 and H_3–H_1 were simultaneously ~90° and the J coupling ~0 Hz. On the basis of molecular models, such a conformation is only possible with **22b**.

(4) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1348.
(5) Benoiton, L. *Can. J. Chem.* **1962**, *40*, 570.
(6) Mauer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

Scheme 2. Synthesis of Enantiomerically Pure *O*-Aryloxime 19



Scheme 3. Rearrangement of *O*-Aryloxime to Dihydrobenzofuran and Cyclization to Tetrahydrofurobenzofuran



With the synthesis of tricycle **22** completed, the two major tasks remaining were to functionalize the A-ring substituents with the correct regiochemistry and to provide for the introduction of the enol ether moiety in the C-ring through an oxidative decarboxylation process. The regiochemistry in the A-ring substituents would be established by selectively cleaving one of the tosyl protecting groups. This was most effectively accomplished by electrochemical reduction. Previously we had demonstrated the chemoselective and regioselective properties of the electrochemical reductive cleavage of aryl tosylates.[7] Applying this method to the detosylation of tricycle **22** resulted in a mix of regioisomeric phenols in a ratio of 93/7, with the methyl ester in **22** being preserved by this process (Scheme 4). The crude product from the electrochemical reduction, **27**, was then immediately protected as the corresponding benzyl ether **28**. Removal of the second tosyl group and ester hydrolysis to **29** was accomplished by alkaline hydrolysis, and subsequent methylation afforded tricycle ether esters **30a** and **30b**. It was not possible to cleave the second tosyl group by electrochemical reduction due to the competitive cleavage of the benzyl ether. The chromatographic separation of the tricyclic diastereomers **30** was found to be much easier than at the stage of tricycle **22**, and it

(7) (a) Civitello, E. R.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 834. (b) Roemmele, R. C.; Rapoport, J. *J. Org. Chem.* **1988**, *53*, 2367.

Scheme 4. Differentiation of Ring-A Tosylates and Acetoxylation of Ring-C

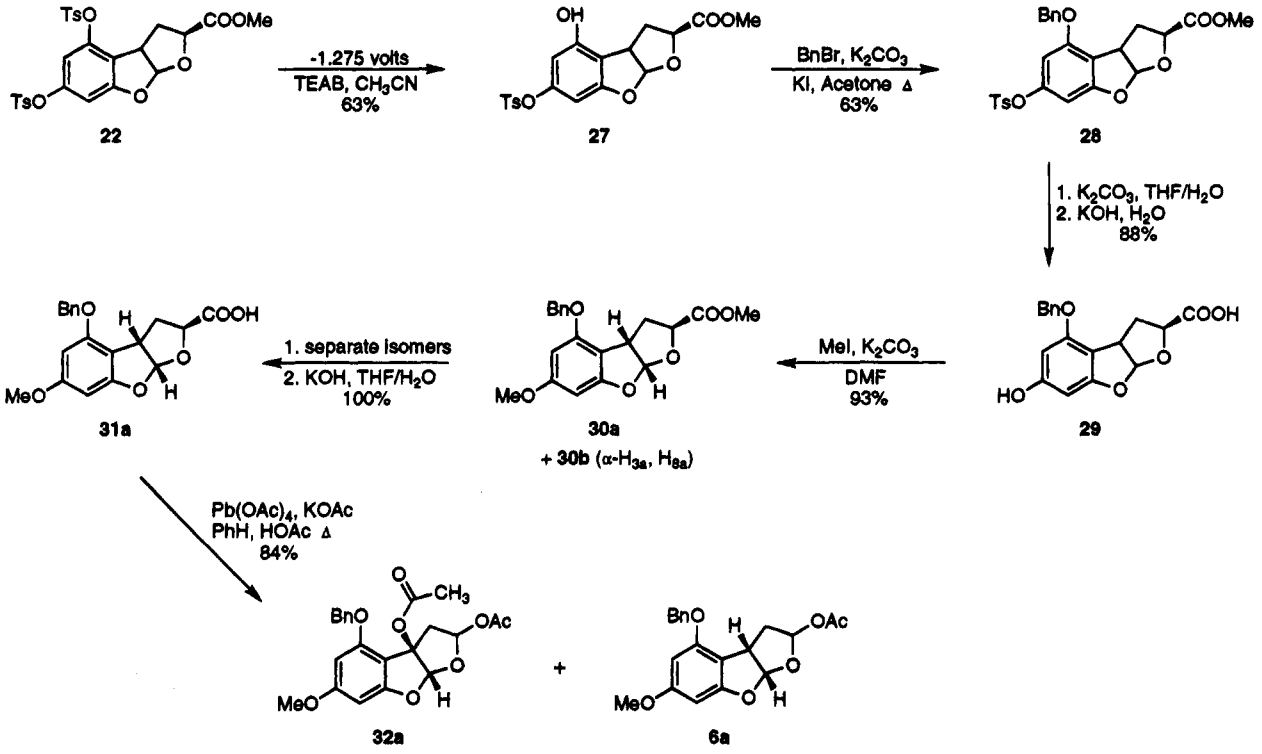
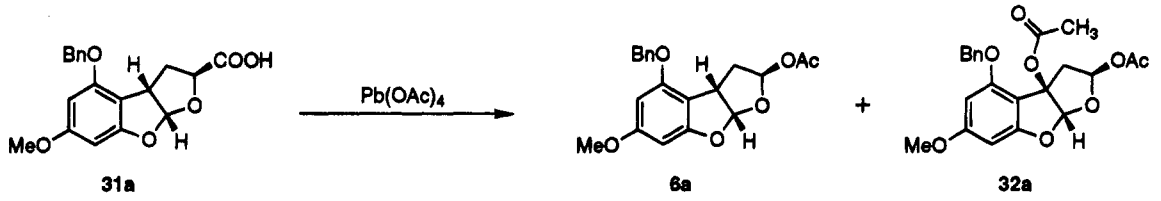


Table 1. $Pb(OAc)_4$ Oxidative Decarboxylation of Acid 31



31a, mg	solvent	$Pb(OAc)_4$ mole%	temp, °C	ratio, 6a / 32a	% yield 6a + 32a
122	PhCl	280	120	<1/99	52
151	PhCl	215	100	45/55	79
136	PhH	125	70	76/24	67
338	PhH	100	55	88/12	84

was also possible to remove the trace amounts of the A-ring regioisomer during this separation.

Since separation of the tricyclic diastereomers was effected best at compound **30**, the conditions for the hydrolysis of the tosylate and methyl ester of **28** to phenolic acid **29** had to be nonracemizing at C-2. This was accomplished using a two-step process whereby the ester was hydrolyzed first under mild conditions and the resulting carboxylate anion then serves to prevent racemization at C-2 during the more vigorous hydrolysis of the tosyl group. The enantiomeric ratio in the *O*-benzyl *O*-methyl acid **31** was determined to be 98/2 by amide formation with (+)- and (±)-phenethylamine and NMR analysis by a method analogous to that used for hydroxy ester **13**.

The necessary functionality in ring-C was introduced with a $Pb(OAc)_4$ oxidative decarboxylation of carboxylic acid **31a** (Table 1). This method was found to be superior to both the decarbonylation of the corresponding acid chloride[8] and the decarboxylative rearrangement of the corresponding thiohydroxamic ester.[9] Tricycle acetate **6a** (as well as **6b**) was found to be a 78/22 mixture of diastereomers at C-2, the major isomer having the acetate moiety on the convex face of the tricycle as shown by 1D and 2D NMR analysis. While it is known that a direct acid-to-alkene conversion is possible in the Pb^{IV} reaction with the addition of $Cu(OAc)_2$,[10] only traces of the tricyclic enol ether were realized when these conditions were applied to **31**. The major byproduct in the Pb^{IV} reaction was the C-3a acetoxy compound **32** resulting from benzylic oxidation. It was possible to control the ratio of **6** to **32** with temperature and stoichiometry as shown in Table 1. Tricycle **32**, however, is of current interest since it potentially can lead to a synthesis of optically-active aflatoxin M_1.

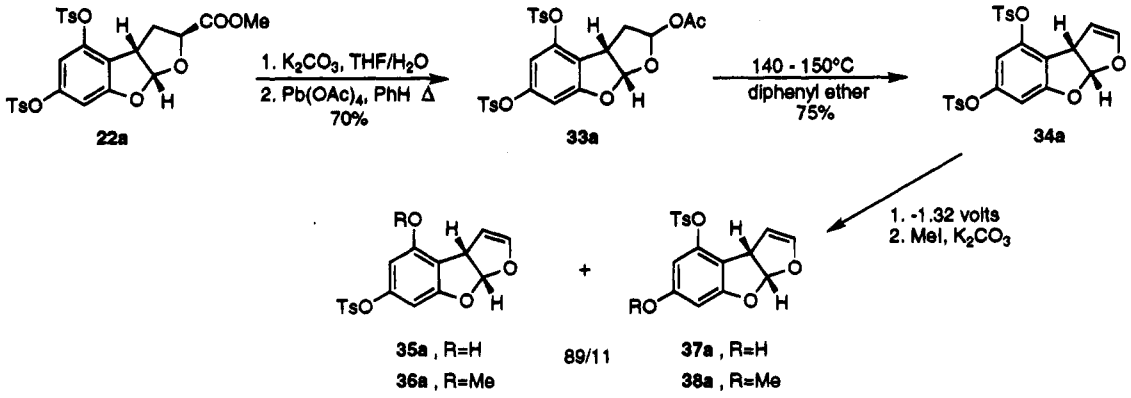
As an alternative to the above route, we investigated the feasibility of introducing the enol ether moiety of the

(8) Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157.

(9) (a) Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733. (b) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1987**, *43*, 4297.

(10) (a) Ogibin, Y. N.; Katzin, M. I.; Nikishin, G. I. *Synthesis* **1974**, 889. (b) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215.

Scheme 5. Alternative Route to the Dihydrofurobenzofuran Ring System



C-ring before establishing the correct regiochemistry in the A-ring substituents (Scheme 5). Beginning with the single diastereomer **22a**, the ester moiety was oxidatively cleaved following the previously described method. It is of interest to note that there was no indication of benzylic oxidation in this case. This absence was attributed to the mild electron-withdrawing character of the tosyloxy substituents as compared to the electron-donating ether substituents of acid **31**. The pyrolytic elimination from acetoxy derivative **33a** was conducted at 140–150 °C in diphenyl ether/20% biphenyl. It was necessary to flush the reaction vessel continually with a stream of nitrogen to remove the HOAc as produced, otherwise substantial decomposition resulted. The electrochemical reduction of **34a** afforded an 89/11 mixture of phenols **35a** and **37a** in favor of **35a**. Although it would have been possible to complete the synthesis of the A-ring substitution pattern along this route, it was not pursued further since (1) the regioselectivity in the electrochemical reduction of **34a** was less than that for **22** and (2) it was appreciably more difficult to separate the diastereomers of **22** than those of **30** on a large scale.

The regiochemical assignments of phenols **27** and **35a** were determined by 2D NOESY NMR. In previous work[7a] we had determined that it was possible to observe an NOE correlation between the methyl group of anisole and its two ortho aromatic protons. This phenomenon was used to assign the regiochemistry of the A-ring substituents of tricycles **36a** and **38a**, resulting from the electrochemical reduction of **34a** and subsequent methylation. For the major isomer, compound **36a**, only one cross-peak was seen between the methyl ether and the aromatic protons, while for the minor isomer, **38a**, cross-peaks were seen for both aromatic signals. The exact reason for the high selectivity for reduction at the 4-position remains unclear; however, the same selectivity was observed in the base-catalyzed hydrolysis of **22**, resulting in an 85/15 mix of phenolic products.

Conclusion. We have developed a method for the synthesis of tetrahydrofuro[2,3-*b*]benzofurans with an enantiomeric ratio of 96/4 as advanced synthetic intermediates to (+)- and (−)-aflatoxins B_1, B_2, G_1, and G_2. We have demonstrated selectivity with respect to diastereomer formation and high levels of enantiomeric purity of the tricyclic intermediates and control of the regiochemistry of the A-ring substituents. This work, combined with previous reports,[2b,c] represents the first formal total synthesis of optically-active aflatoxins.

Experimental Section

General. Tetraethylammonium bromide (TEAB), $Pb(OAc)_4$, and all solvents were purified prior to use.[11] Solutions of HCl in DME were prepared by bubbling anhydrous HCl through DME for approximately 1 h, and then the solutions were titrated with standard NaOH(aq) to a phenolphthalein endpoint. ^1H NMR spectra, for which chemical shifts are reported in ppm downfield from internal tetramethylsilane (TMS), were determined in $CDCl_3$ unless otherwise noted, as were ^{13}C NMR spectra. Significant ^1H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s), *J*, in hertz. Elemental analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley, CA.

γ-Benzyl (2*S*)-2-Hydroxyglutaric Acid (12).[5] To 200 mL of anhydrous Et_2O was added, very slowly with stirring, 20 mL of concentrated H_2SO_4 (375 mmol) followed by BnOH (200 mL, 1.9 mol). The warm solution was concentrated to a thick clear colorless oil by rotary evaporation and glutamic acid (**11**, 29.6 g, 201 mmol) was added in several portions with stirring. After the complete addition of **11**, the thick cloudy solution was left stirring overnight at rt; then 400 mL of 95% EtOH and 100 mL of pyridine were added. The solution was cooled in an ice/water bath and a white precipitate formed which was collected by filtration and triturated with Et_2O. This white crystalline γ-benzyl glutamic acid was used directly without further purification (23.8 g, 50% yield): ^1H NMR (D_2O/D_2SO_4) δ 2.36–2.43 (2H, m), 2.76 (2H, dt, *J* = 7, 3), 4.29 (1H, t, *J* = 7), 5.20 (2H, s), 7.43–7.5 (5H, m). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.8; H, 6.4; N, 5.9. Found: C, 60.6; H, 6.3; N, 5.9.

A solution of γ-benzyl glutamic acid (23.8 g, 100 mmol) in 130 mL of 1 M TFA (130 mmol) was diluted with 250 mL of H_2O and a solution of $NaNO_2$ (10.3 g, 149 mmol) in 100 mL of H_2O was added dropwise over 4 h at rt. The reaction mixture was stirred for an additional 2 h and was then extracted with 3/1 $CHCl_3$/2-propanol (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried, and evaporated to give crude **12** (16.2 g, oil, 68% yield). The unstable crude product was used immediately without further purification: ^1H NMR ($CDCl_3/CD_3OD$) δ 1.9–2.1 (2H, m), 2.1–2.3 (2H, m), 4.26 (1H, dd, *J* = 8, 4), 5.10 (2H, s), 6.3–7.0 (-OH, br), 7.33 (5H, s).

5-Benzyl 1-Methyl (2*S*)-2-(Benzoyloxy)glutarate (15). To α-hydroxy acid **12** (16.2 g, 68 mmol) dissolved in 100 mL of DMF was added $NaHCO_3$ (11.4 g, 136 mmol) with stirring followed by CH_3I (21.5 mL, 345 mmol). The heterogeneous mixture was stirred at rt under N_2 for 2 days and then was filtered into EtOAc (50 mL) and concentrated to a yellow residue. Residual DMF was removed by Kugelrohr distillation at ≤30 °C/0.05 Torr. The residue was partitioned between 75 mL of H_2O and 75 mL of EtOAc, the aqueous layer was extracted with EtOAc (2 × 30 mL), the combined EtOAc layers

(11) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press, Inc.: New York, 1980.

were washed with 5% aqueous $Na_2S_2O_3$ (2 × 30 mL), satdurated $NaHCO_3$ (2 × 30 mL), and brine (50 mL), and the solution was dried and evaporated to give crude 5-benzyl 1-methyl 2-hydroxyglutarate (**13**, 14.8 g, oil, 87% yield). This product was used without further purification: $[\alpha]^{23}_D$ +2.0° (*c* 6.04, $CHCl_3$); ^1H NMR δ 1.9–2.0 (1H, m), 2.14–2.23 (1H, m), 2.45–2.6 (2H, m), 3.09 (-OH, d, *J* = 6), 3.76 (3H, s), 4.21–4.26 (1H, m), 5.12 (2H, s), 7.25–7.35 (5H, m). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.9; H, 6.4. Found: C, 61.8; H, 6.2.

To a solution of diester **13** (14.8 g, 59 mmol) in 50 mL of pyridine was added 4-(dimethylamino)pyridine (DMAP, 0.72 g, 5.9 mmol), and the solution was cooled to 0 °C under N_2. Benzoyl chloride (BzCl, 14.0 mL, 121 mmol) was added via syringe and the reaction mixture was stirred at 0 °C for 1 h and then at rt for 24 h after which glycine (0.5 g) in 50 mL of H_2O was added. The mixture was stirred for 6 h and then filtered and evaporated at ≤40 °C to a red-orange oil. This oil was partitioned between 75 mL of Et_2O and 75 mL of water, and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined ether layers were washed with 0.1 M HCl (3 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and brine (50 mL), dried, and evaporated to a yellow-orange oil (19.3 g, 92% crude yield). Purification by LPC (175 g SiO_2, 4/1 → 2/1 hexanes/EtOAc) afforded pure **15** (16.7 g, oil, 80% yield): $[\alpha]^{23}_D$ −7.1° (*c* 3.23, $CHCl_3$); ^1H NMR δ 2.33–2.41 (2H, m), 2.57–2.64 (2H, m), 3.74 (3H, s), 5.11 (2H, s), 5.32 (1H, dd, *J* = 8, 5), 7.29–7.35 (5H, m), 7.43 (2H, t, *J* = 8), 7.57 (1H, t, *J* = 8), 8.06 (2H, d, *J* = 8); ^{13}C NMR δ 26.4, 29.9, 52.5, 66.5, 71.6, 128.3, 128.5, 128.9, 129.2, 129.9, 133.5, 135.7, 165.8, 170.0, 172.1. Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.4; H, 5.7. Found: C, 67.2; H, 5.7.

Methyl (2*S*)-2-(Benzoyloxy)-5-hydroxypentanoate (16). Gaseous N_2 was bubbled through a solution of benzyl ester **15** (23.4 g, 65.8 mmol) in 150 mL of dry MeOH for 5 min, then 10% palladium on charcoal (2.25 g) was added, the flask was attached to a Parr shaker, and the mixture was shaken at 30 °C overnight at 50 psi of H_2 and was then filtered through a 10-cm column of Celite under vacuum. The filtrate was evaporated to give α-methyl 2-(benzoyloxy)glutaric acid (18.6 g, oil): $[\alpha]^{23}_D$ −10.4° (*c* 2.40, $CHCl_3$); ^1H NMR δ 2.28–2.41 (2H, m), 2.56–2.63 (2H, m), 3.78 (3H, s), 5.33 (1H, dd, *J* = 7, 5), 5.8–6.8 (-COOH, br), 7.46 (2H, t, *J* = 8), 7.57 (1H, t, *J* = 8), 8.07 (2H, d, *J* = 8). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.7; H, 5.3. Found: C, 58.9; H, 5.3.

A solution of the α-methyl 2-(benzoyloxy)glutaric acid from the previous reaction in 250 mL of THF was cooled to −5 °C and BH_3·THF (1.0 M in THF, 73 mL, 111 mol %) was added over 30 min via cannula. After the addition, the reaction mixture was allowed to slowly warm to rt overnight; then it was stirred overnight with 100 mL of MeOH before evaporation. The residue was taken up in 100 mL of EtOAc and washed with saturated $NaHCO_3$ (2 × 30 mL) and brine (50 mL), then dried and evaporated to give alcohol **16** (17.3 g, oil): $[\alpha]^{23}_D$ 2.2° (*c* 1.28, $CHCl_3$); ^1H NMR δ 1.72–1.79 (2H, m), 2.01–2.13 (2H, m), 2.2–2.4 (-OH, br), 3.69 (2H, t, *J* = 6), 3.76 (3H, s), 5.28 (1H, dd, *J* = 7, 5), 7.44 (2H, t, *J* = 8), 7.58 (1H, t, *J* = 8), 8.08 (2H, d, *J* = 8); ^{13}C NMR δ 37.8, 28.3, 52.3, 62.1, 72.5, 128.4, 129.5, 133.3, 166.0, 170.6. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.9; H, 6.4. Found: C, 61.5; H, 6.4.

Methyl (2*S*)-2-(Benzoyloxy)-5-oxopentanoate (17).[12] To a solution of $(COCl)_2$ (6.2 mL, 72.7 mmol) in 40 mL of CH_2Cl_2, cooled to −60 °C, was added a solution of DMSO (10.2 mL, 144 mmol) in 20 mL of CH_2Cl_2 dropwise via syringe with stirring over 15 min. Alcohol **16** (16.6 g, 65.8 mmol) in 60 mL of CH_2Cl_2 was then added slowly over 15 min, stirring was continued for 30 min at −60 °C, triethylamine (40 mL, 288 mmol) was added, and the cold bath was removed. After 30 min, 50 mL of $CHCl_3$ and 150 mL of H_2O were added, the aqueous layer was separated and extracted with $CHCl_3$ (1 × 50 mL), and the combined organic layers were washed with 0.5 M TFA (3 × 100 mL), saturated $NaHCO_3$ (2 × 50 mL), and brine (50 mL) and then dried and evaporated to give aldehyde **17** (15.8 g, oil, 96% yield): $[\alpha]^{23}_D$ −6.1° (*c* 3.47, $CHCl_3$); ^1H NMR δ 2.32–2.38 (2H, m), 2.68–2.71 (2H, m), 3.78 (3H, s), 5.30 (1H, dd, *J* = 7, 5), 7.46 (2H, t, *J* = 7), 7.58 (1H, t, *J* = 7), 8.06 (2H, d, *J* = 7), 9.83 (1H, s); ^{13}C NMR δ 23.6, 28.1, 39.1, 52.2, 128.3, 129.1, 129.7, 133.3, 165.6, 169.8, 200.0. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.5; H, 5.7.

(*E*)- and (*Z*)-Methyl (2*S*)-2-(Benzoyloxy)-5-oxopentanoate *O*-((3,5-Bis(tosyloxy)phenyl)oxime (19). Phenoxyamine **18**[4] (964 mg, 2.14 mmol) was added to a solution of aldehyde **17** (557 mg, 2.23 mmol) in 50 mL of THF, and this was followed by the addition of TsOH·H_2O (0.04 g, 0.21 mmol). The reaction mixture was flushed with N_2 and allowed to stir at rt overnight, after which excess solid $NaHCO_3$ was added, the mixture was stirred for 30 min and filtered, and the filtrate was evaporated. The residue was partitioned between 50 mL of Et_2O and 50 mL of 50% saturated $NaHCO_3$, and the organic layer was separated and washed with 30 mL of brine and then dried and evaporated to an orange oil (1.40 g, 96% crude yield). Purification by LPC (40 g SiO_2, 3/1 hexanes/EtOAc) afforded pure oxime **19** (1.192 g, oil, 82% yield). The cis/trans ratio was determined to be 1/3 by NMR integration of the oxime proton: $[\alpha]^{23}_D$ −3.0° (*c* 2.51, $CHCl_3$); ^1H NMR δ 2.25–2.35 (2H, m), 2.45 (6H, s), 2.5–2.8 (2H, m), 3.79 (0.75H (cis), s), 3.80 (2.25H (trans), s), 5.32 (0.25H (cis), t, *J* = 6), 5.37 (0.75H (trans), dd, *J* = 7, 5), 6.23 (0.25H (cis), t, *J* = 2), 6.25 (0.75H (trans), t, *J* = 2), 6.45 (0.5H (cis), d, *J* = 2), 6.76 (1.5H (trans), d, *J* = 2), 7.04 (0.25H (cis), t, *J* = 6), 7.31 (4H, d, *J* = 8), 7.4–7.5 (2H, m), 7.58 (1H, t, *J* = 7), 7.6–7.7 (4H, m), 7.75 (0.75H (trans), t, *J* = 6), 8.07 (2H, d, *J* = 8); ^{13}C NMR δ 21.6, 25.5, 27.8, 52.5, 71.6, 107.4, 107.8, 109.8, 128.5, 129.2, 129.7, 132.3, 133.6, 145.6, 150.2, 153.9, 160.0, 165.8, 169.9. Anal. Calcd for $C_{33}H_{31}NO_{11}S_2$: C, 58.1; H, 4.6. Found: C, 58.4; H, 4.6.

(3*S*)-3-(Benzoyloxy)-5,7-bis(tosyloxy)-2-oxo-1,2,3,4,4a,-9a-hexahydropyrido[2,3-*b*]benzofuran (25). A pressure flask was charged with oxime **19** (5.09 g, 7.46 mmol) in 150 mL of DME and to the solution was added 8.0 mL of a 3.7 M solution of anhydrous HCl in DME (29.6 mmol). The flask was sealed under N_2 and heated in an oil bath regulated at 70 °C overnight; then it was cooled and the reaction mixture was poured into 75 mL of H_2O, 75 mL of saturated $NaHCO_3$, and 75 mL of EtOAc. The organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried, and evaporated to a brown foam (4.76 g, 98% crude yield). Crude **25** was used without further purification.

(*E*)- and (*Z*)-2-Methoxy-3-[(2*S*)-2-(benzoyloxy)-2-(methoxycarbonyl)ethyl]-4,6-bis(tosyloxy)-2,3-dihydrobenzofuran (26). A pressure flask was charged with crude lactam **25** (4.76 g, 7.33 mmol) in 150 mL of dry MeOH. To the stirring solution was added 5.0 mL of a 3.7 M solution of anhydrous HCl in DME (18.5 mmol). The flask was sealed under N_2 and heated in an oil bath at 65 °C. After 2 days the reaction was quenched with an excess of solid $NaHCO_3$. The mixture was concentrated to a paste by rotary evaporation and the residue was partitioned between 50 mL of EtOAc and 50 mL of 50% saturated $NaHCO_3$, adding 20 mL of brine to separate the layers. The aqueous layer was extracted with EtOAc (2 × 25 mL) and the combined organic layers were washed with brine, dried, and evaporated to a yellow paste (4.75 g, 93% mass recovery). Crude **26**, as a mixture of four diastereomers, was used without further purification.

(2*S*)-4,6-Bis(tosyloxy)-2-(methoxycarbonyl)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (22). To a solution of crude **26** (4.47 g, 6.42 mmol) in 175 mL of dry MeOH was added K_2CO_3 (0.44 g, 3.18 mmol), and the mixture was stirred at 35 °C for 24 h and then acidified with 5.0 mL of 3.7 M HCl in DME (18.5 mmol). Stirring for 2 h at rt and evaporating left an oily residue which was taken up in 100 mL of DME, 2.5 mL of 3.7 M HCl in DME was added, the solution was evaporated and chased twice with 50 mL of DME, and the crude residue was partitioned between 75 mL of EtOAc and 75 mL of saturated $NaHCO_3$. The aqueous layer was extracted with another portion of EtOAc (25 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and then dried and evaporated to a brown foam. Purification by LPC (200 g SiO_2; 3/1 hexanes/EtOAc)

(12) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

afforded pure fractions of both diastereomers **22a** (867 mg) and **22b** (540 mg) along with a third fraction consisting of a mixture of the two (994 mg). The overall yield of **22** was 67% from crude **26** and 57% from oxime **19**.

22a: ^{1}H NMR δ 2.28 (1H, ddd, J = 13, 11, 8), 2.47 (3H, s), 2.49 (3H, s), 2.51 (1H, dd, J = 13, 8), 3.77 (3H, s), 3.94 (1H, dd, J = 8, 6), 4.33 (1H, dd, J = 11, 6), 6.26 (1H, d, J = 2), 6.32 (1H, d, J = 2), 6.37 (1H, d, J = 6), 7.34 (2H, d, J = 8), 7.38 (2H, d, J = 8), 7.69 (2H, d, J = 8), 7.72 (2H, d, J = 8).

22b: ^{1}H NMR δ 2.46 (3H, s), 2.49 (3H, s), 2.56 (1H, dt, J = 13, 9), 2.78 (1H, d, J = 13), 3.37 (3H, s), 3.95 (1H, dd, J = 8, 6), 4.73 (1H, d, J = 8), 6.15 (1H, d, J = 2), 6.28 (1H, d, J = 2), 6.31 (1H, d, J = 6), 7.35 (2H, d, J = 9), 7.37 (2H, d, J = 9), 7.67 (2H, d, J = 8), 7.72 (2H, d, J = 8). Anal. Calcd for $C_{26}H_{24}O_{10}S_2$: C, 55.7; H, 4.3. Found: C, 55.7; H, 4.6.

Electrolysis of 22: Synthesis of (2*S*)-2-(Methoxycarbonyl)-4-hydroxy-6-(tosyloxy)-2,3,3a,8a-tetrahydrofuro-[2,3-*b*]benzofuran (27).[7] A standard H-electrolysis cell (length, 15.0 cm; o.d., 5.0 cm) was equipped with a platinum foil anode, mercury pool cathode, silver wire reference electrode, and nitrogen bubbler. Both chambers were charged with 100 mL of CH_3CN saturated with TEAB and the apparatus was preelectrolyzed at −1.50 V for 20 min to a background current of ~0.8 mA. Current to the cell was then shut off while **22** (2.03 g, 3.62 mmol) was added to the cathode chamber, and it was dissolved with the help of bubbling nitrogen. The electrolysis was conducted at −1.275 V and the initial current was ~65 mA. After 20 h the reaction was stopped with the current measuring ~3 mA. The cathode solution was separated, 50 mL of 1 M KH_2PO_4, 75 mL of H_2O, and 50 mL of EtOAc were added, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with 1 M $Na_2S_2O_3$ (2 × 25 mL), saturated $NaHCO_3$ (2 × 25 mL), and brine (50 mL) and then dried and evaporated. Purification of the residue by LPC (100 g of SiO_2, 3/1 → 1/1 hexanes/EtOAc) afforded pure **27** as a 1/1 mixture of diastereomers (920 mg oil, 63% yield) and 10% recovered **22**. The ratio of regioisomers with respect to the A-ring substituents was estimated to be 93/7 by high resolution NMR.

27a: ^{1}H NMR δ 2.27 (1H, dt, J = 11, 8), 2.46 (3H, s), 2.61 (1H, dd, J = 13, 5), 3.78 (3H, s), 4.09 (1H, dd, J = 8, 5), 4.40 (1H, dd, J = 11, 5), 5.91 (1H, d, J = 2), 6.27 (1H, d, J = 2), 6.40 (1H, d, J = 5), 7.33 (2H, d, J = 8), 7.72 (2H, d, J = 8).

27b: ^{1}H NMR δ 2.45 (3H, s), 2.52 (1H, dt, J = 13, 8), 2.92 (1H, d J = 13), 3.38 (3H, s), 4.02 (1H, dd, J = 8, 5), 4.75 (1H, d, J = 11), 5.97 (1H, d, J = 2), 6.19 (1H, d, J = 2), 6.33 (1H, d, J = 5), 6.85−6.95 (1H, OH, br), 7.33 (2H, d, J = 8), 7.72 (2H, d, J = 8).

(2*S*)-2-(Methoxycarbonyl)-4-(benzyloxy)-6-(tosyloxy)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (28). To **27** (1.62 g, 3.97 mmol) dissolved in 60 mL of acetone was added K_2CO_3 (0.66 g, 4.8 mmol) followed by NaI (0.71 g, 4.7 mmol) and BnBr (570 μL, 4.79 mmol). The reaction mixture was stirred overnight at reflux, excess glycine (0.5 g) was added and after 1 h at reflux, the mixture was evaporated to a paste, and the residue was partitioned between 75 mL of EtOAc and 150 mL of H_2O. The aqueous layer was extracted with EtOAc (1 × 50 mL), the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), and the solution was dried and evaporated. Purification by LPC (30 g SiO_2, 2/1 → 3/2 hexanes/EtOAc) afforded pure **28** (1.88 g, oil, 95% yield) as a 50/50 mixture of diastereomers and a 93/7 mixture of regioisomers. The NMR spectra were determined on pure samples obtained by prep TLC.

28a: ^{1}H NMR δ 2.24 (1H, ddd, J = 13, 11, 9), 2.46 (3H, s), 2.57 (1H, dd, J = 13, 5), 3.77 (3H, s), 4.08 (1H, dd, J = 8, 6), 4.39 (1H, dd, J = 11, 5), 4.97 (1H, d, AB), 5.00 (1H, d, AB), 6.00 (1H, d, J = 2), 6.35 (1H, d, J = 2), 6.38 (1H, d, J = 6), 7.31 (2H, d, J = 8), 7.34−7.43 (5H, m), 7.71 (2H, d, J = 8); ^{13}C NMR δ 21.7, 35.2, 44.6, 52.4, 70.3, 97.6, 100.3, 111.9, 112.4, 127.4, 128.3, 128.5, 128.7, 129.8, 132.4, 135.9, 145.5, 151.2, 155.3, 160.1, 170.9.

28b: ^{1}H NMR δ 2.45 (3H, s), 2.49 (1H, dt, J = 13, 9), 2.88 (1H, d, J = 13), 3.33 (3H, s), 3.99 (1H, dd, J = 8, 6), 4.71 (1H, d, J = 8), 4.97 (2H, s), 6.02 (1H, d, J = 2), 6.25 (1H, d, J = 2), 6.31 (1H, d, J = 6), 7.32 (2H, d, J = 8), 7.34−7.42 (5H, m), 7.70 (2H, d, J = 8); ^{13}C NMR δ 21.7, 33.6, 44.1, 52.1, 70.3, 78.2, 97.8, 100.1, 112.5, 127.3, 128.2, 128.5, 128.7, 129.8, 132.4, 136.0, 145.4, 151.3, 155.3, 160.1, 171.8; HRMS calcd for $C_{26}H_{25}O_8S$ (MH^+) 497.1270, found 497.1253.

(2*S*)-4-(Benzyloxy)-2-carboxy-6-hydroxy-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (29). To **28** (860 mg, 1.73 mmol) dissolved in 75 mL of THF was added 75 mL of H_2O followed by K_2CO_3 (240 mg, 1.73 mmol), and the solution was stirred at rt for 24 h at which time 1 M KOH (6.0 mL, 6.0 mmol) was added. The mixture was then heated overnight at 65 °C and then cooled and washed with EtOAc (50 mL), discarding the organic layer. The aqueous layer was acidified with 3 M H_2SO_4 to pH 2 and extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine (50 mL), dried, and evaporated to give crude **29** (502 mg, 88% yield) as a ~50/50 mixture of diastereomers: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 2.20−2.24 (0.5H, m), 2.53 (0.5H, dt, J = 13, 9), 2.88 (0.5H, d, J = 13), 4.00 (0.5H, t, J = 6), 4.11 (0.5H, t, J = 6), 4.40 (0.5H, dd, J = 11, 6), 4.63 (0.5H, d, J = 9), 5.06 (1H, AB), 5.94 (0.5H, d, J = 2), 5.98 (0.5H, d, J = 2), 6.00 (0.5H, d, J = 2), 6.10 (0.5H, d, J = 2), 6.28 (0.5H, d, J = 5), 6.34 (0.5H, d, J = 6), 7.3−7.5 (5H, m).

(2*S*)-4-(Benzyloxy)-6-methoxy-2-(methoxycarbonyl)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (30). To a solution of **29** (242 mg, 0.77 mmol) in 15 mL of DMF was added K_2CO_3 (0.48 g, 3.47 mmol) followed by MeI (720 mL, 11.6 mmol), and the mixture was stirred at rt for 2 days. After filtering, the orange filtrate was evaporated, removing residual DMF by Kugelrohr distillation at ≤30 °C/0.05 Torr. The residue was partitioned between 50 mL of H_2O and 50 mL of EtOAc, the aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with 5% $Na_2S_2O_3$ (2 × 25 mL), saturated $NaHCO_3$(2 × 5 mL), and brine (25 mL) and then dried and evaporated to give crude **30b** as a yellow oil (192 mg, 93% crude yield). Purification by LPC (15 g SiO_2, 2/3 EtOAc/hexanes) afforded both diastereomers, **30a** (71 mg, oil, 35% yield) and **30b** (92 mg, oil, 45% yield).

30a: ^{1}H NMR δ 2.22 (1H, dt, J = 8, 12), 2.60 (1H, dd, J = 12, 5), 3.74 (3H, s), 3.77 (3H, s), 4.10 (1H, dd, J = 8, 6), 4.45 (1H, dd, J = 11, 5), 5.03 (1H, d, J = 12), 5.07 (1H, d, J = 12), 6.09 (1H, d, J = 2), 6.11 (1H, d, J = 2), 6.41 (1H, d, J = 6), 7.3−7.45 (5H, m); ^{13}C NMR δ 35.6, 44.6, 52.2, 55.5, 69.8, 76.4, 88.3, 92.9, 105.6, 111.6, 127.1, 127.9, 128.5, 136.5, 155.7, 160.8, 162.2, 171.1.

30b: ^{1}H NMR δ 2.48 (1H, dt, J = 13, 9), 2.92 (1H, d, J = 13), 3.36 (3H, s), 3.72 (3H, s), 4.00 (1H, dd, J = 8, 6), 4.72 (1H, d, J = 9), 5.05 (2H, s), 6.04 (1H, d, J = 2), 6.09 (1H, d, J = 2), 6.32 (1H, d, J = 6), 7.3−7.45 (5H, m); ^{13}C NMR δ 33.9, 43.9, 51.9, 55.4, 70.0, 78.0, 88.4, 92.8, 105.5, 112.3, 127.4, 127.8, 128.5, 136.6, 155.8, 160.9, 162.2, 172.1. Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.4; H, 5.7. Found C, 67.3; H, 5.6.

(2*S*,3a*S*,8a*R*)-4-(Benzyloxy)-2-carboxy-6-methoxy-2,3,-3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (31a). To a solution of **30a** (720 mg, 2.02 mmol) in 60 mL of THF was added 70 mL of H_2O followed by K_2CO_3 (0.66 g, 4.8 mmol), and the solution was stirred at rt for 2 days. The aqueous layer was acidified to pH 2 with 1 M TFA and extracted with EtOAc (1 × 50 mL, 3 × 25 mL), and the combined organic layer was washed with brine (50 mL), dried, and evaporated to give crude **31a** (689 mg, 100% yield): ^{1}H NMR δ 2.18−2.31 (1H, m), 2.64 (1H, dd, J = 12, 5), 3.75 (3H, s), 4.12 (1H, dd, J = 8, 6), 4.43 (1H, dd, J = 12, 5), 5.1 (2H, s), 6.1 (1H, d, J = 2), 6.15 (1H, d, J = 2), 6.4 (1H, d, J = 6), 7.3−7.5 (5H, m).

(3a*S*,8a*S*)-2-Acetoxy-4-(benzyloxy)-6-methoxy-2,3,3a,-8a-tetrahydrofuro[2,3-*b*]benzofuran (6a). To a solution of **31a** (338 mg, 0.99 mol) in 25 mL of benzene were added 1.5 mL of HOAc, one spatula tip full of KOAc, and $Pb(OAc)_4$ (0.44 g, 0.99 mol). Nitrogen was bubbled through the solution for 20 min with stirring; then the reaction mixture was heated overnight at 55 °C. It was then poured into 75 mL of H_2O and 75 mL of EtOAc, the aqueous layer was extracted with EtOAc (25 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (2 × 30 mL) and brine (50 mL) and then dried and evaporated. The crude reaction product was filtered through a 5-cm column of gravity silica gel in 2/1 hexanes/EtOAc and the filtrate was evaporated to give a clean

mixture of **6a** and **32a** in a ratio of 88/12 (186 mg, 84% yield based on 129 mg of recovered **31a**, 62% conversion) as indicated by ^{1}H NMR analysis. Purification by LPC (25 g SiO_2; 3/2 hexanes/ EtOAc) afforded pure fractions of both **6a** and **32a**. The combined aqueous solutions were acidified to pH 1 and extracted with EtOAc (2 × 30 mL), and the EtOAc layers were washed with brine (50 mL), dried, and evaporated to afford recovered acid **31a** (129 mg, 38% recovery). The ratio of the diastereomers at C-2 was measured by ^{1}H NMR to be 78/22 in favor of the *R* configuration.

6a (major diastereomer): ^{1}H NMR δ 2.06 (3H, s), 2.37–2.48 (2H, m), 3.73 (3H, s), 4.04–4.08 (1H, m), 5.03 (1H, d, J = 12), 5.05 (1H, d, J = 12), 6.10–6.12 (2H, m), 6.34–6.37 (2H, m), 7.32–7.44 (5H, m); ^{13}C NMR δ 21.1, 37.0, 42.6, 55.6, 69.8, 89.0, 93.3, 98.3, 107.7, 111.5, 127.2, 127.5, 128.6, 136.6, 155.6, 159.8, 162.2, 169.7.

32a (major diastereomer): ^{1}H NMR δ 2.04 (3H, s), 2.11 (3H, s), 2.73 (1H, dd, J = 11, 5), 3.03 (1H, dd, J = 11, 5), 3.75 (3H, s), 5.08 (2H, s), 6.11 (1H, d, J = 2), 6.13 (1H, d, J = 2), 6.28 (1H, t, J+5), 6.41 (1H, s), 7.32–7.41 (5H, m); ^{13}C NMR δ 21.0, 21.3, 41.9, 55.6, 69.7, 89.0, 90.4, 93.8, 97.4, 111.4, 113.0, 126.8, 128.0, 128.6, 136.6, 146.5, 155.9, 162.0, 164.3, 169.7.

(3a*S*,8a*R*)-2-Acetoxy-4,6-bis(tosyloxy)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (33a). To a solution of **22a** (1.19 g, 2.12 mmol) in 400 mL of 1/1 THF/H_2O was added K_2CO_3 (0.73 g, 5.28 mmol) with stirring, and the solution was stirred at rt for 18 h before adding 40 mL of 1 M KH_2PO_4 and 50 mL of brine. The pH was adjusted to 3 with 3 M H_2SO_4, the mixture was extracted with EtOAc (3 × 50 mL), and the combined EtOAc extracts were washed with brine (2 × 30 mL), dried, and evaporated to a light yellow solid (1.12 g, 97% crude yield). To this crude solid was added 100 mL of benzene followed by glacial HOAc (5 drops) and $Pb(OAc)_4$ (1.82 g, 4.10 mmol), and the reaction mixture was heated at reflux under N_2. An additional 1.84 g of $Pb(OAc)_4$ was added after 12 h, and another 1.98 g of $Pb(OAc)_4$ was added after a total of 24 h. After 33 h, 25 drops of ethylene glycol were added, and the mixture was stirred for 1 h and filtered and the filtrate was evaporated. The residue was partitioned between 100 mL of EtOAc and 100 mL of 50% saturated $NaHCO_3$, the aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed in saturated $NaHCO_3$ (30 mL) and brine (30 mL) and then dried and evaporated. Chromatography of the residue by LPC (25 g SiO_2; 2/1 hexanes/EtOAc) afforded **33a** as a light yellow foam/oil (830 mg, 72% yield, 80/20 mixture of diastereomers favoring the *R* configuration at C-2): ^{1}H NMR (major diastereomer) δ 2.08 (3H, s), 2.32 (1H, dt, J = 14, 5), 2.40–2.45 (1H, m), 2.47 (3H, s), 2.50 (3H, s), 4.06 (1H, dt, J = 10, 6), 6.22 (1H, d, J = 2), 6.28–6.31 (2H, m), 6.33 (1H, d, J = 2), 7.34 (2H, d, J = 8), 7.38 (2H, d, J = 8), 7.69 (2H, d, J = 8), 7.73 (2H, d, J = 8).

(3a*S*,8a*R*)-4,6-Bis(tosyloxy)-3a,8a-dihydrofuro[2,3-*b*]-benzofuran (34a). Acetate **33a** (394 mg, 0.70 mmol) was covered with 10 mL of diphenyl ether containing 20 wt % of biphenyl. A pipet was fixed in the neck of the flask through which a N_2 stream was forced directly onto the stirring solution as it was heated in an oil bath at 140 °C for a total of 8 h. Then the cooled reaction mixture was added to a column of SiO_2 (20 g) and flushed with hexanes until no UV-active material could be detected in the eluate. Pure **34a** was then eluted with 3/1 → 2/1 hexanes/EtOAc (265 mg oil, 75% yield). **34a**: $[\alpha]^{23}_D$ −108.5° (*c* 6.91, $CHCl_3$). **34b** from a separate reaction starting with **33b**: $[\alpha]^{23}_D$ +109.1° (*c* 3.62, $CHCl_3$). ^{1}H NMR δ 2.45 (3H, s), 2.50 (3H, s), 4.47 (1H, dt, J = 7, 2), 5.23 (1H, t, J = 3), 6.20 (1H, d, J = 2), 6.38 (1H, d, J = 2), 6.41 (1H, t, J = 2), 6.60 (1H, d, J = 7), 7.33 (2H, d, J = 8), 7.38 (2H, d, J = 8), 7.68 (2H, d, J = 8), 7.73 (2H, d, J = 8).

Electrolysis of 34a: Synthesis of (3a*S*,8a*R*)-4-Hydroxy-6-(tosyloxy)-3a,8a-dihydrofuro[2,3-*b*]benzofuran (35a). A standard H-electrolysis cell (length, 10.0 cm; o.d., 2.5 cm) was equipped with a platinum foil anode, mercury pool cathode, silver wire reference electrode, and nitrogen bubbler. Both chambers were charged with 15 mL of CH_3CN saturated with TEAB. The apparatus was preelectrolyzed at −1.40 V for 20 min to a background current of ~0.6 mA. Current to the cell was then shut off while compound **34a** (248 mg, 0.495 mmol) was added to the cathode chamber, and it dissolved with the help of bubbling nitrogen. The electrolysis was conducted at −1.32 V and the initial current was ~8 mA. The reaction was stopped after 12 h with the current measuring ~3 mA and to the separated cathode solution were added 30 mL of 1 M KH_2PO_4, 30 mL of H_2O, and 25 mL of EtOAc. The aqueous layer was extracted with EtOAc (25 mL), and the combined organic layers were washed with 1 M $Na_2S_2O_3$ (1 × 25 mL), saturated $NaHCO_3$ (2 × 25 mL), and brine (30 mL) and then dried and evaporated, leaving a residue of 163 mg. The ratio of regioisomers was estimated to be 89/11. Purification by LPC (20 g SiO_2, 3/1 → 2/1 hexanes/EtOAc) afforded pure **35a** (130 mg oil, 83% based on recovered **34a**, 21 mg): ^{1}H NMR δ 2.46 (3H, s), 4.56 (1H, dt, J = 7, 2), 5.32 (1H, t, J = 3), 5.8–5.9 (OH, br), 5.99 (1H, d, J = 2), 6.23 (1H, d, J = 2), 6.43 (1H, t, J = 2), 6.65 (1H, d, J = 7), 7.32 (2H, d, J = 8), 7.73 (2H, d, J = 8).

Acknowledgment. The expert technical assistance of undergraduate research participants Steven D. Knight and Andrew K. Shiau is gratefully acknowledged.

Supplementary Material Available: Comparison of tosyloxy compounds **22** and **25** with their corresponding mesyloxy analogues; NMR analysis and assignments for **22**, **26**, **27**, **29a**, **29b**, **31a**, **32a**, **33a**, **34a**, **35a**, and **36a**; enantiomeric ratio determinations for **13** and **31a**; original ^{1}H NMR spectra of **26**, **27a**, **27b**, **29a**, **29b**, **31a**, **32a**, **33a**, **34a**, **35a**, **36a**, **38a**, **38**, **39a**, and **40a**; NOESY spectra of **36a**, **38a**, and **39a** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.