values for k within experimental error. The decay profiles followed single exponential kinetics. Given the decay times and the concentrations used, $1-2 \times 10^{-4}$ M, the first-order kinetics show that the reactions are intramolecular in nature.

The quantity $\Delta E_{1/2}$ is related to the free energy change for intramolecular electron transfer by including the electrostatic term in eq 3. The expression in eq 3 assumes spherical ions of the same size separated by a distance d in a solvent of static dielectric constant D_s.[8] In eq 3, e is the unit electron charge and κ is the

$$-\Delta G = \Delta E_{1/2} - \frac{e^2}{D_s d}\left(\frac{1}{1+\kappa d}\right) \quad (3)$$

Debye-Hückel inverse length, which is proportional to the square root of the ionic strength. From standard bond lengths and angles, it can be estimated that d can vary from ca. 4 to 12 Å, depending upon the relative orientation of the PTZ group around the $-CH_2-$ link.[5] The comparison in Figure 1A between the data in DCE and the data in DCE that is 0.1 M in $[N(n\text{-}C_4H_9)_4](PF_6)$ shows that ionic strength effects do play a role in the intramolecular electron transfer.

In Figure 1B is shown a plot of ln k_{nr} vs emission energy, E_{em}, for nonradiative decay in the related series of excited states $[(4,4'\text{-}(X)_2\text{-bpy}^{\bullet-})Re^{II}(CO)_3(4\text{-Etpy})]^+$ (4-Etpy = 4-ethylpyridine).

$$[(4,4'\text{-}(X)_2\text{-bpy}^{\bullet-})Re^{II}(CO)_3(4\text{-Etpy})]^{+*} \rightarrow [(4,4'\text{-}(X)_2\text{-bpy})Re^{I}(CO)_3(4\text{-Etpy})]^+ \quad (4)$$

The preparation and characterization of the complexes are described elsewhere.[9] The nonradiative decay rate constants, k_{nr}, were calculated from emission lifetimes (τ) and quantum yields for emission, which varied from 0.002 to 0.4, by using the equation $k_{nr} = 1/\tau(1 - \phi_{em})$.

The linear *decreases* in ln k_{elt} or ln k_{nr} with energy gap are predicted qualitatively by the "energy gap law", eq 5.[10,11] In eq

$$\ln k_{nr} \propto -\frac{\gamma E}{\hbar\omega} \quad (5)$$

$$\gamma = \left(\ln \frac{E}{S\hbar\omega}\right) - 1 \quad (5a)$$

5, E is the energy gap between the excited and ground states and $\hbar\omega = h\nu$ is the average vibrational spacing of the acceptor modes. The quantity S is the electron-vibrational coupling constant. It is proportional to the square of the difference in equilibrium displacements in the acceptor modes between the excited and ground states. For bpy-based MLCT excited states, the energy acceptor role is played by seven ν(bpy) modes which can be approximated by an average mode having $\hbar\omega \sim 1300-1400$ cm^{-1}.[11,12] For intramolecular electron transfer, the energy acceptor role is expected to be played by a combination of $\nu(4,4'\text{-}(X)_2\text{-bpy})$ and ν(PTZ) ring stretching modes.[13]

The decrease in slope for electron transfer compared to nonradiative decay is predicted qualitatively by eq 5. For MLCT excited states, S increases with the energy gap since the extent of charge transfer increases with the energy gap.[11,12] For intramolecular electron transfer between $PTZ^{\bullet+}$ and $4,4'\text{-}(X)_2\text{-bpy}^{\bullet-}$, a complete electron transfer occurs, leading to an increase in S, a decrease in γ, eq 5a, and the decrease in slope.

The quality of the fit to the electron transfer data is impressive. It must be a consequence of the relatively minor perturbations caused by the changes in substituents and points to a common electron transfer distance. The linear correlation verifies the applicability of the energy gap law to electron transfer in the inverted region and points to a close, fundamental relationship between electron transfer in this region and nonradiative decay.

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The Timing of Aromatic Deoxygenation in Aflatoxin Biosynthesis

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Deoxygenation of phenols is a difficult reaction to execute synthetically. Yet among polyketide-derived natural products many instances can be found where such reactions appear to occur in the course of their biosynthesis. Of these the majority may be characterized by the absence of an "expected" hydroxyl group at a position (e.g., C-4 in **2**) where hypothetical polyketide intermediates are proposed to turn back on themselves leading to self-condensation reactions and aromatization. In the classic study of this behavior experiments with 6-methylsalicylic acid synthase[1] demonstrated that, in fact, preparatory to formation of **2** a *pre*aromatic reduction/dehydration sequence takes place to give a cis double bond, e.g., **1**. However, exceptions involving *post*-aromatic deoxygenation have emerged that cannot be rationalized according to this model. Among these, two may be cited. The first is the apparent reduction of emodin (**3**) to chrysophanol (**4**) at an early stage of ergochrome biosynthesis reported by Franck.[2] In an important advance at the cell-free level this transformation was unambiguously shown by Anderson and Scott to be mediated by NADPH.[3] Reasoning by analogy to a second system, they suggested (quite persuasively) that deoxygenation of versicolorin A (**5**, R = OH) could occur at C-6 to provide a necessary reduction in the course of its conversion to sterigmatocystin (**6**), a late intermediate in aflatoxin B_1 (**7**) biosynthesis.[4] We record in this communication three lines of evidence that indicate 6-deoxy-

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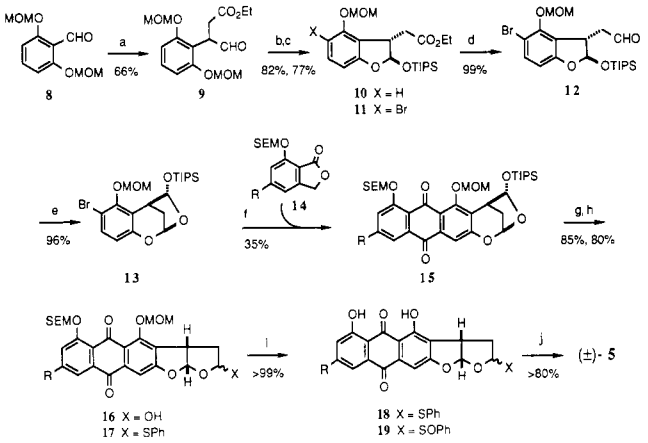
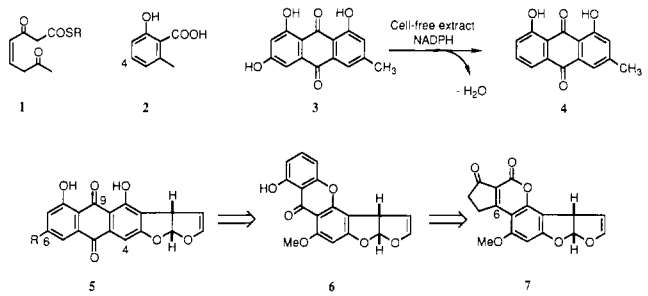
0002-7863/89/1511-8306$01.50/0

Scheme I[a]



[a] Conditions: (a) ref 9; (b) Et_3N (1.5 equiv), TIPSOTf (1.1 equiv), THF, 0 °C; (c) 3 Å MS, NBS (3 equiv), $CHCl_3$, 20 °C; (d) DIBAL (1.5 equiv), ether, −95 °C, 15 min; (e) TIPSOTf (0.1 equiv), Et_2AlCl (0.1 equiv), CH_2Cl_2, −43 °C, 5 min; (f) i. LiTMP (5 equiv), **14** (1 equiv), **13** (1.5 equiv), −43 °C; ii. AcOH; iii. O_2; (g) $(n\text{-}Bu)_4NF$ (1.1 equiv), THF, −78 °C → −20 °C; (h) PBu_3 (2 equiv), *N*-(phenylthio)-succinimide (2 equiv), THF, −100 °C → 0 °C; (i) AcOH, catalyst 6 N HCl, THF, H_2O, 60 °C; (j) i. *m*-CPBA (2 equiv), then excess Me_2S, EtOAc, −15 °C; ii. 1:1 toluene/DMSO reflux, 1 h.

versicolorin A (**5**, R = H), while a known *Aspergillus* metabolite[5] is not an intermediate in the formation of aflatoxin B_1.



To carry out the experiments described in this and the following paper, a new, general route to aryl-fused dihydro- and tetrahydrobisfurans was developed[6] and applied in the first syntheses of versicolorin A (**5**, R = OH) and 6-deoxyversicolorin A (**5**, R = H). The anthraquinone nucleus was assembled by reaction of an appropriately substituted phthalide **14** (R = H or OSEM) and an aryl bromide **13** containing the dihydrobisfuran in a masked form stable to lithium tetramethylpiperidide used in the benzyne annulation[7,8] of these two entities. The aldehyde **8** was elaborated to **9** by using the geminal disubstitution method of Martin[9] and converted to the differentially protected hemiacetal **10**.[10] Regioselective bromination and DIBAL reduction gave **12**, which could be induced to undergo a critical rearrangement and closure to **13** (40% overall yield from **8**) in the presence of a catalytic amount of triisopropylsilyl(TIPS)triflate and diethylaluminum chloride.[11] Following anthraquinone formation, the dihydrobisfuran was revealed in a series of conventional steps to afford versicolorin A and 6-deoxyversicolorin A in 8% and 9% overall yields from **8**, respectively. The phthalide **14** could be labeled from $Ba^{13}CO_3$ to give the corresponding [9-^{13}C]anthraquinones.

[9-^{13}C]Versicolorin A and [9-^{13}C]-6-deoxyversicolorin A were administered to mycelial suspensions of *A. parasiticus* (SU-1) as previously described.[8] The aflatoxin B_1 produced in each experiment was isolated, and the extent of stable isotope incorporation was examined by mass spectrometry and $^{13}C\{^1H\}$ NMR spectroscopy. [9-^{13}C]Versicolorin A gave a substantial incorporation (20%) of ^{13}C specifically at C-6 (δ 177.0 ppm). In contrast, [9-^{13}C]-6-deoxyversicolorin A failed to give any detectable incorporation into aflatoxin B_1.

The negative incorporation of 6-deoxyversicolorin A was further examined in experiments with a blocked mutant of wild-type *A. parasiticus*. *Avr-1*[12] accumulates averufin, an earlier intermediate of aflatoxin B_1 biosynthesis[8,13] than versicolorin A. It is, however, a leaky mutant, and small amounts of aflatoxins accumulate during its growth.[14] Addition of 6-deoxyversicolorin A to mycelial suspensions of this mutant did not support enhanced synthesis of the mycotoxin in triplicate runs (0.8 × control), whereas versicolorin A, a known intermediate in aflatoxin biosynthesis,[16] in parallel experiments gave markedly higher amounts of the toxin (85 × control). Finally, attempted cell-free reduction of versicolorin A to 6-deoxyversicolorin A in the presence of NADH/NADPH failed to proceed.[17]

In conclusion, [9-^{13}C]versicolorin A and [9-^{13}C]-6-deoxyversicolorin A have been prepared and tested for their conversion in vivo into aflatoxin B_1. While the former gave a highly efficient (20%) and specific incorporation into the mycotoxin,[18] the latter gave no detectable incorporation of stable isotope. This outcome was further substantiated by the failure of 6-deoxyversicolorin A to support aflatoxin synthesis in an *A. parasiticus* mutant

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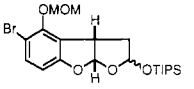
(11) A full discussion of these syntheses and the silyltriflate-induced cyclizations used in the formation of **10** and **13** will be presented elsewhere. The isomeric protected form (**i**) of the bisfuran **13** could not be used in the benzyne annulation owing to an elimination reaction and rapid decomposition to polar material in the presence of LiTMP, even at −78 °C (Graybill, T. L.; Pal, K.; Whittamore, P. R. O.; McGuire, S. M.; Townsend, C. A., unpublished).



(*i*)

(12) Same as ATCC 24551: Donkersloot, J. A.; Mateles, R. I.; Yang, S. S. *Biochem. Biophys. Res. Commun.* **1972**, *47*, 1051–1055.

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(17) This cell-free system has been shown (unpublished) to be capable of carrying out several transformations in the aflatoxin biosynthetic pathway some of which are described in the following paper.

(18) While once controversial, versicolorin A is now generally accepted as a probable intermediate in the biosynthesis of aflatoxin.[16] This is, however, the first unambiguous demonstration of its intact incorporation into the toxin.

blocked several steps earlier in the pathway and by the absence of a cell-free activity capable of reducing versicolorin A to 6-deoxyversicolorin A. Therefore, unlike the seemingly closely related case of emodin reduction to chrysophanol,[3] the deoxygenation that occurs between versicolorin A (**5**, R = OH) and sterigmatocystin (**6**) must proceed by means other than direct reduction of an anthraquinone. The metabolic events whereby the anthraquinone nucleus is cleaved, deoxygenated, and rearranged to a xanthone provide entry into the final stages of the aflatoxin biosynthetic pathway and are the object of current investigation.

Acknowledgment. Drs. P. R. O. Whittamore and S. G. Davis are thanked for many preliminary studies that made possible development of the bisfuran synthesis described above. We are grateful to the National Institutes of Health for financial support of this research (ES 01670). Major analytical instrumentation used was acquired with funds from the NIH and NSF (NMR: RR01934 and PCM 83-03176; MS: RR02318).

Registry No. 5 (R = OH), 6807-96-1; (±)-**5** (R = OH), 122741-51-9; **6**, 10048-13-2; **7**, 1162-65-8; **8**, 79834-12-1; **9**, 122623-60-3; **10**, 122623-61-4; **11**, 122623-62-5; **12**, 122623-63-6; **13**, 122623-64-7; **14** (R = H), 122623-65-8; **14** (R = OSEM), 122647-58-9; **15** (R = H), 122647-57-8; **15** (R = OSEM), 122623-70-5; **16** (R = H), 122623-66-9; **16** (R = OSEM), 122623-71-6; **17** (R = H), 122623-67-0; **17** (R = OSEM), 122647-59-0; **18** (R = H), 122623-68-1; **18** (R = OSEM), 122623-72-7; **19** (R = H), 122623-69-2; **19** (R = OSEM), 122623-73-8; [9-^{13}C]versicolorin A, 122623-74-9; 6-deoxyversicolorin A, 30517-65-8.

Partitioning of Tetrahydro- and Dihydrobisfuran Formation in Aflatoxin Biosynthesis Defined by Cell-Free and Direct Incorporation Experiments

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The fused dihydrobisfuran of the mycotoxin aflatoxin B_1 (**9**) contains an electron-rich double bond that undergoes metabolic activation in vertebrates to an epoxide which is capable of generating covalent lesions upon intercalation with doubly stranded DNA.[1] This structural element is formed from the six-carbon side chain of averufin (**1**) in three efficient oxidative steps leading to versicolorin A (**5**, Scheme I).[2] In addition to the dihydrobisfuran series of metabolites a family of tetrahydrobisfurans co-occurs in generally lesser amounts typified by aflatoxin B_2 (**7**). There is disagreement as to whether these two series are interconvertible in vivo or in fact arise from separate pathways.[3] We demonstrate here that partitioning between these two bisfuran groups takes place at the point of their formation in versicolorin B (**4**) and versicolorin A (**5**).

In 1980 Hsieh[4] and Dutton[5] independently reported the preparation of cell-free systems from *Aspergillus parasiticus* capable of carrying out the conversion of versiconal acetate (**3**) to versicolorin A (**5**). In the former a time course study revealed, surprisingly, at least four apparent intermediates in this process. With the intention of determining their structures, several protocols for cell breakage and spheroplast generation were surveyed in an effort to duplicate this conversion. Cell-free systems prepared by several methods, notably rapid disruption with glass powder in phosphate buffer,[6] gave clean, time-dependent reactions of versiconal acetate (**3**) to form not versicolorin A (**5**) but versicolorin B (**4**)[7,8] by way of the diol corresponding to hydrolysis of the acetate in **3**.[9] Complete conversion of **3** to **4** was readily achieved indicating that racemization of the former is rapid relative to the rate of selective enzymic processing of the (*S*)-antipode to bisfuran. Versicolorin A hemiacetal (**10**) was prepared from versicolorin A by acid-catalyzed hydration of the terminal double bond.[11] To test its potential intermediacy in dihydrobisfuran formation, incubation of this substrate with the cell-free extract above and in the presence of NAD^+, NADH, $NADP^+$, or NADPH gave only *reduction* to versicolorin B and no detectable dehydration to versicolorin A.

The unexpected results of these cell-free experiments led directly to the hypothesis shown in Scheme I that versicolorin B (**4**), first, was an intermediate in versicolorin A (**5**) formation, and, second, played a pivotal role in aflatoxin biosynthesis serving as the point of partition between tetrahydro- and dihydrobisfuran-containing products. In a direct test of this proposal averufin (**1**), an earlier

Scheme I

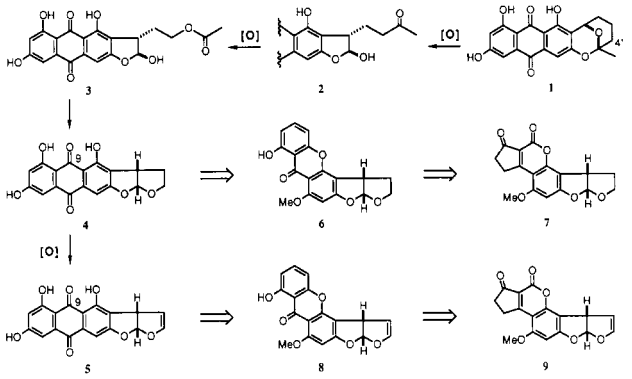

Table I. Incorporation of ^{13}C-Labeled Substrates into Aflatoxin B_1 and B_2

substrate	% incorp (SU-1) AFB_1	% incorp (SU-1) AFB_2
(±)-[4′-^{13}C]averufin	9	10
(±)-[9-^{13}C]versicolorin B(C)	9	25
(±)-[9-^{13}C]versicolorin A hemiacetal	8	15
(±)-[9-^{13}C]versicolorin A	20	0

(1) For entry into the recent literature, see: Shimada, T.; Guengerich, F. P. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 462-465. Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929-7931. Benasutti, M.; Efadi, S.; Whitlow, M. D.; Loechler, E. L. *Biochemistry* **1988**, *27*, 472-481. Wood, W. L.; Lindsay-Smith, J. R.; Garner, R. C. *Mutation Res.* **1987**, *176*, 11-20.

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(6) Mycelial pellets of SU-1 were homogenized by using a "Bead-Beater" (Biospec, Bartlesville, OK) with 3.3 × their wet weight of glass powder (0.10-0.11 mm diamter) in 0.2 M potassium phosphate buffer (pH 7.5 at 22 °C) precooled in an ice/water bath. Duty cycles of 1 min were alternated with 1 min at rest for a total of 20 min. The homogenate was decanted and centrifuged (20 000 × g, 25 min at 0 °C); the supernatant was taken as the cell-free extract. See also ref 4.

(7) The identity of versicolorin B was established by HPLC comparisons to authentic materials (vide infra and accompanying paper) and by ^{1}H NMR and MS analyses.

(8) Versicolorin B and A are relatively difficult to separate chromatographically. Some of the conflicting claims in the literature may stem from this technical problem leading to product misidentification and/or radiochemical contamination.

(9) For comparison the diol (the name versiconal has been proposed for this compound by Gorst-Allman,[10] although it has not been isolated or synthesized and characterized prior to the present work) was prepared by saponification of versiconal acetate and independently correlated to other known structures (Brobst, S. W.; McGuire, S. M.; Townsend, C. A., unpublished).

(10) Gorst-Allman, C. P.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 163-168.

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