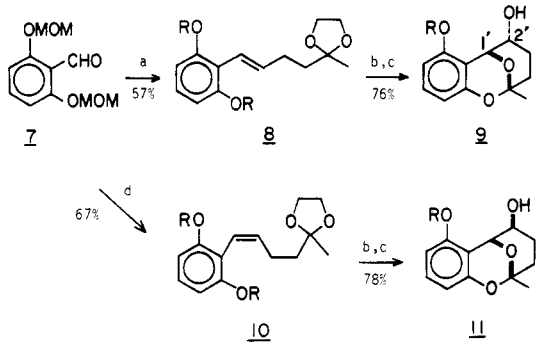
Scheme II[a,b]



[a] R = MOM. [b] Conditions: (a) $Ph_3P^+(CH_2)_3C(OCH_2CH_2O)(CH_3)$, Br^- (i)/LDA (1 equiv)/THF, 0 °C; addition of **7**, −78 °C, 30 min; LDA (1 equiv), −40 °C → −30 °C, 1 h; MeOH (excess), −30 °C → room temperature, overnight; (b) OsO_4, *N*-methylmorpholine *N*-oxide/THF/H_2O, room temperature, overnight; (c) aqueous 1 N HCl/THF, room temperature, 40 h; (d) phosphonium bromide i, $KN(SiMe_3)_2$ (1 equiv)/THF, room temperature, 20 min; addition of **7** at −78 °C, 10 min; −78 °C → room temperature, overnight.

empirical means,[15] a sample of optically active averufin has been synthesized and thereby the 1′*S* configuration assigned to the natural product. This configuration is in accord with that predicted on the basis of a biogenetic proposal[5] relating the linear side chain of averufin through a chain-branching step to generate ultimately the bisfuran of aflatoxin in the correct absolute stereochemical sense.

Acknowledgment. The National Institutes of Health are gratefully acknowledged for financial support of this research (UM, ES 02851; JHU, ES 01670). The high-field FT NMR spectrometers used were acquired with the assistance of major instrumentation grants (UM, NSF CHE 79-09108; JHU, NSF PCM 83-03176 and NIH RR 01934).

Registry No. **4**, 14016-29-6; **7**, 79834-12-1; **8**, 98634-98-1; (±)-**8** (glycol), 98635-00-8; **9** (R = H), 98635-06-4; **9** (phenylthionocarbonate), 98635-05-3; (±)-**9**, 98635-02-0; (+)-**9**, 98675-11-7; (+)-**9** (MTPA ester), 98635-03-1; (−)-**9**, 98675-12-8; (−)-**9** (MTPA ester), 98717-30-7; **10**, 98634-99-2; (±)-**10** (glycol), 98635-01-9; (±)-**11**, 98675-10-6; **12**, 98635-04-2; **13**, 98675-13-9; i, 5944-33-2; $Br(CH_2)_3COCH_3$, 3884-71-7; (±)-3-acetyldihydro-2(3*H*)-furanone, 98634-97-0; 2-methyl-2-(3-bromopropyl)-1,3-dioxolane, 24400-75-7.

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Received August 22, 1985

A Cationic Model of the Chain-Branching Step in Aflatoxin Biosynthesis

Summary: The 2′-mesylates of 6,8-di-*O*-methylnidurufin and 6,8-di-*O*-dimethylpseudonidurufin and simple benzenoid models of these compounds have been treated in 2,2,2-trifluoroethanol to give furanoid products of potential relevance to aflatoxin B_1 biosynthesis.

Sir: Initiation of averufin (**1**, R = H) biosynthesis by hexanoic acid necessitates a sequence of otherwise seemingly redundant redox steps in its formation.[1] In so doing, however, a template is generated whose latent chemistry is revealed in a series of oxidative rearrangement reactions that lead ultimately to the unusual bisfuran of the potent mycotoxin aflatoxin B_1 (**6**). Fermentive incorporation studies of aflatoxin using specifically labeled samples of averufin[2] have led to the proposal that a pinacol-like rearrangement may be initiated by oxidation at C-2′ in **1** (R = H) to achieve the side-chain branching and redox changes required for bisfuran formation[3] (Scheme I). Against expectation, however, nidurufin (**1**, R = OH)[4] and its 2′-epimer, pseudonidurufin, failed to incorporate label into aflatoxin B_1 (**6**) under conditions where averufin (**1**, R = H) was efficiently utilized.[2] In noteworthy juxtaposition, however, [1′-^{18}O,5′-^{13}C]averufin was converted in vivo into versiconal acetate (**5**) with ca. 80% of the ^{18}O-label (●) found at the carbonyl oxygen bound to C-5′ (■). This boundary condition and consideration of stereoelectronic effects,[4] which are supported by the absolute configuration of averufin,[5] in one of a limited number of mechanistic interpretations may argue for direct oxidation at C-2′ and rearrangement through the closed form of the ketal side chain.[4] Of several interesting possibilities that can be advanced for the detailed course of such a transformation, one is fundamentally cationic and may be approximated by the reactions described herein.

The racemic *exo*- and *endo*-mesylates **7** and **8**, respectively (Table I), were easily prepared from the corresponding 2′-alcohols, which were in turn available as described in the accompanying paper.[5] While the attempted rearrangement of **7** and **8** in dipolar aprotic solvents under a variety of conditions led to complex mixtures of products, the use of 2,2,2-trifluoroethanol (TFE)[6] met with encouraging results. The *exo*-mesylate **7**, analogous in its relative configuration to nidurufin (**1**, R = OH) as correctly constituted,[7] when heated to reflux in TFE, rearranged in 10 min to benzofuran **7a** in 50% yield (Table I, entry 1). Buffering the reaction mixture with sodium bicarbonate or triethylamine resulted in the formation of **7b** and **7c**, mixed acetals/ketals of TFE (entries 2 and 3). In marked contrast, the endo isomer **8** failed to react under the same conditions. The deoxy analogue of **7**, compound **9**, was prepared by a similar route from salicylaldehyde and found to rearrange in like fashion (entries 6 and 7).

To more directly mimic the biogenetic hypothesis illustrated in Scheme I, close models of nidurufin (**1**, R = OH) and pseudonidurufin, its 2′-epimer, were synthesized by modification of the route used earlier.[4,7] 5,7-Dimeth-

(1) Townsend, C. A.; Christensen, S. B.; Trautwein, K. *J. Am. Chem. Soc.* **1984**, *106*, 3868–3869.
(2) Townsend, C. A.; Christensen, S. B.; Davis, S. G. *J. Am. Chem. Soc.* **1982**, *104*, 6152–6153. Simpson, T. J.; deJesus, A. E.; Vleggaar, R.; Steyn, P. S. *J. Chem. Soc., Chem. Commun.* **1982**, 631–632. Townsend, C. A.; Davis, S. G. *Ibid.* **1983**, 1420–1421.
(3) Townsend, C. A.; Christensen, S. B. *Tetrahedron* **1983**, *39*, 3575–3582. For an independent related proposal, see: Sankawa, Y.; Shimada, H.; Kobayashi, T.; Ebizuka, Y.; Yamamoto, Y.; Noguchi, H.; Seto, H. *Heterocycles* **1982**, *19*, 1053–1058.
(4) Townsend, C. A.; Christensen, S. B. *J. Am. Chem. Soc.* **1985**, *107*, 270–271.
(5) Koreeda, M.; Hulin, B.; Yoshihara, M.; Townsend, C. A.; Christensen, S. B. *J. Org. Chem.*, previous communication in this issue.
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(7) For a discussion of the correct structure of nidurufin, see ref 4 and the first citation in ref 3.

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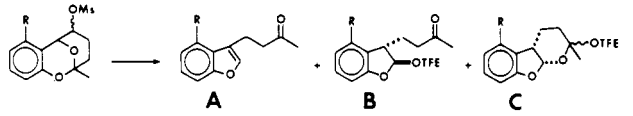
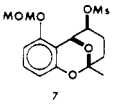
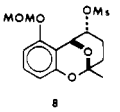
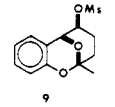
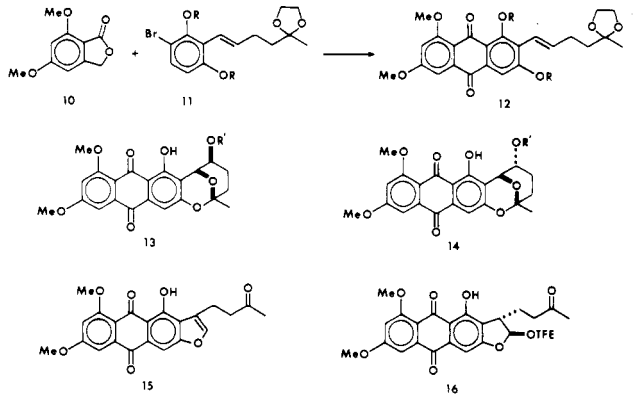
Table I. Results for Solvolytic Rearrangement Reactions of Nidurufin and Pseudonidurufin Model Compounds



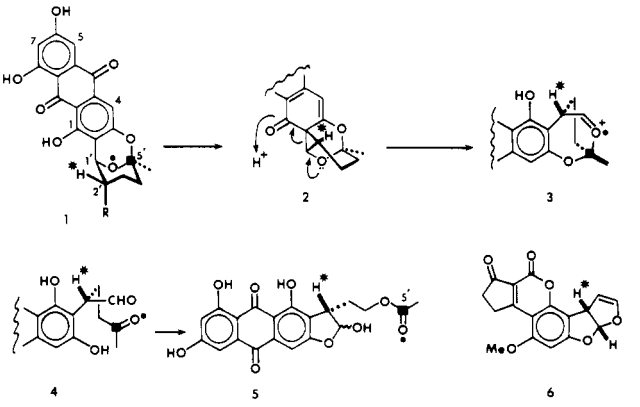
entry	substrate	reactn condns	product(s)	R	yield, %
1	 7	TFE, reflux, 10 min	A	OMOM	50
2	7	TFE, $NaHCO_3$ (1.3 equiv), 50 C, 9 h	B (trans:cis, 7:1)	OH	45
			B (trans)	OMOM	20
3	7	TFE:H_2O (100:1), Et_3N, r.t., 48 h	C (anomeric mixture, 2:1)	OMOM	71
4	 8	TFE, reflux	no reactn		
5	8	TFE, $NaHCO_3$, reflux	no reactn		
6	 9	TFE, reflux, 30 min	A	H	73
7	9	TFE, $NaHCO_3$ (1.5 equiv), reflux, 30 min	B	H	60

oxyphthalide (**10**)[8,9] and aryl bromide **11**[10] were reacted through a benzyne intermediate[8] to give the anthraquinone **12** in 42% isolated yield after chromatography on silica gel. By way of the epoxide[11] or diol,[12] **12** was converted to 6,8-di-*O*-methylnidurufin (**13**, R = H) [establishing that this natural product[13] shares with nidurufin (**1**, R = OH) the same relative stereochemistry at [C-2′] and 6,8-di-*O*-methylpseudonidurufin (**14**, R = H).



The 2′-acetates and -trifluoroacetates of **13** and **14** were unreactive in refluxing TFE, apart from gradual oxidative decomposition. The mesylate of **13**, however, underwent rearrangement in TFE at 80 °C showing clean first-order kinetics ($t_{1/2}$ = 3.7 ± 0.1 h) to give a 1:4 mixture of fused furan **15** and the acetal **16** ($^3J_{1'2'}$ = 1.2 Hz) in 54% isolated yield. Paralleling the behavior of *endo*-mesylate **8** (Table I), the mesylate of 6,8-di-*O*-methylpseudonidurufin (**14**, R′ = Ms) underwent no reaction on prolonged heating in TFE. It is interesting (cf. Table I) that reaction of **13** (R′ = Ms) in TFE containing 2% triethylamine proceeded more rapidly than that in TFE alone ($t_{1/2}$ = ca. 100 min, 45 °C) to give not the rearranged products **15** and **16** but two comparatively less polar compounds identified as **13** (R′ = CH_2CF_3, H-1′: 5.16 ppm, $^3J_{1'2'}$ = 2.5 Hz) and **14** (R′ = CH_2CF_3, H-1′: 5.18 ppm, $^3J_{1'2'}$ = 4.8 Hz) in a ratio of 8.8:1. The *endo*-mesylate **14** (R′ = Ms) under identical conditions again failed to react.

Scheme I



Several points bear comment. First, for both the simple model systems in Table I and the anthraquinones **13** and **14**, a sharp dichotomy exists where the *exo*-mesylates as a group rearranged under solvolytic conditions to give branched chain products while the *endo*-substrates were toally unreactive. In keeping with a substantial literature,[14] these observations support participation of the adjacent π-system in the transition state leading to products. The latter can be readily achieved by an exo leaving group but is stereoelectronically prohibited in the endo series by the orthogonal orbital relationship of the migrating and departing groups. Second, the rearrangement of the close nidurufin analogue **13** is significantly less facile than the simple benzenoid compound **7**. This diminished migrating

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(9) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835–1838.
(10) 2,6-Bis-*O*-(methoxymethyl)benzaldehyde[8] was reacted with the appropriate phosphorane: Crombie, L.; Hemesley, P.; Pattenden, G. *J. Chem. Soc. C* **1969**, 1016–1024.
(11) Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267–2268.
(12) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.
(13) Kingston, D. G. I.; Chen, P. N.; Vercellotti, J. R. *Phytochem.* **1976**, *15*, 1037–1039.
(14) Murphy, W. S.; Wattanasin, S. *Chem. Soc. Rev.* **1983**, *12*, 213–250. Lancelot, C. J.; Cram, D. J.; Schleyer, P. v. R. In "Carbonium Ions"; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972; Vol. 3, pp 1347–1483.

ability owes to the reduced electron density of the anthraquinone nucleus noted earlier[15] and is further manifested in a fine balance of product distribution where in the presence of triethylamine, solvent capture of TFE supplants rearrangement as the observed reaction path. Third, the 1′-oxygen in averufin, which might be supposed to stabilize the developing positive charge at C-1′ in the transition state, in fact, almost certainly retards the rearrangement process through powerful inductive effects.[16] In summary, these factors may provide a thermodynamic basis for why nidurufin (1, R = OH) is bypassed in the biosynthesis of aflatoxin B_1 (6),[4] although oxidation at C-2′ of averufin without hydroxylation would lead in the cationic regime to furanoid products. For the moment, however, any more definitive connection between the in vivo chemistry and these model systems must await further experiments to evaluate other valid mechanistic possibilities.

Acknowledgment. The National Institutes of Health are gratefully acknowledged for their support of the work at Hopkins (ES 01670) and Michigan (ES 02851). The high-field NMR spectrometers used were acquired with the assistance of major instrumentation grants (JHU, NSF PCM 83-03176 and NIH RR 01934; UM, NSF CHE 79-09108).

Registry No. 7, 98652-28-9; 7A (R = OMOM), 98652-30-3; *cis*-7B (R = OH), 98652-31-4; *trans*-7B (R = OH), 98652-32-5; *trans*-7B (R = OMOM), 98677-59-9; 7C (R = OMOM) (isomer 1), 98719-06-3; 7C (R = OMOM) (isomer 2), 98652-33-6; 8, 98757-09-6; 9, 98652-29-0; 9A, 98652-34-7; 9B, 98652-35-8; 10, 3465-69-8; 11 (R = H), 98652-36-9; 12 (R = H), 98652-37-0; 13 (R′ = H), 98717-44-3; 13 (R′ = CH_2CF_3), 98652-41-6; 13 (R′ = Ms), 98652-38-1; 14 (R′ = H), 98717-45-4; 14 (R′ = CH_2CF_3), 98717-46-5; 15, 98652-39-2; 16, 98652-40-5; aflatoxin B_1, 1162-65-8.

† Research Fellow of the Alfred P. Sloan Foundation 1982–1986; Camille and Henry Dreyfus Teacher–Scholar 1983–1988.

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(16) Martin, J. C.; Bartlett, P. D. *J. Am. Chem. Soc.* **1957**, *79*, 2533–2541. Paquette, L. A.; Dunkin, I. R. *Ibid.* **1972**, *95*, 3067–3068. For an interesting discussion of the effects of methoxyl on carbonium ion rearrangements and an entry into the earlier literature, see: Van Cantfort, C. K.; Coates, R. M. *J. Org. Chem.* **1981**, *46*, 4331–4339.

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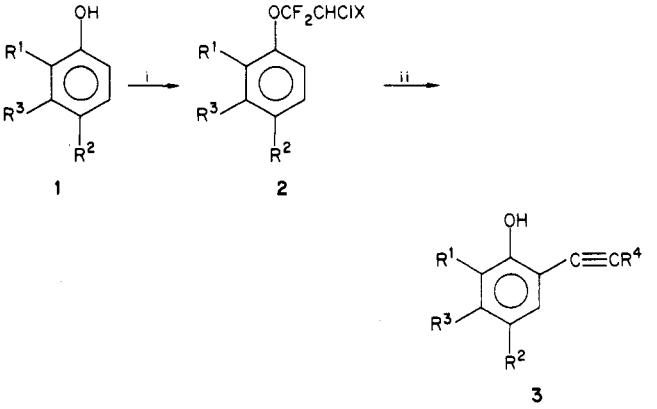
Received August 22, 1985

Halocarbon Chemistry. 1. (2-Hydroxyaryl)acetylenes from Haloethyl Aryl Ethers. A New O to C Rearrangement

Summary: A new base-induced (BuLi) oxygen-to-carbon rearrangement is described which involves the direct conversion of phenyl tetra(or tri)haloethyl ethers and the related intermediate phenoxyalkynes to the corresponding 1-(2-hydroxyphenyl)alkynes in good to excellent yield.

Sir: We report a new base-induced rearrangement which we believe has potentially broad synthetic utility. The general reaction is shown below (**2** → **3**) and was discovered

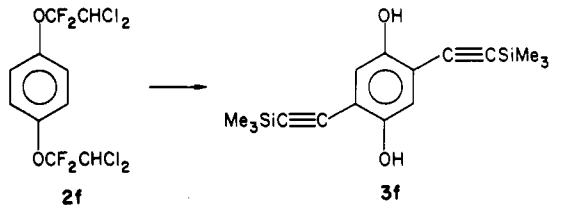


reagents: i, CF_2CClX/40%KOH/$Bu_4{}^+N^-OH$/CH_2Cl_2; ii, 4 equiv of BuLi/THF/−78 °C to 25 °C

in the course of investigations on the use of simple haloalkyl groups as protecting agents for phenols. It proceeds in good yield in all cases examined so far.

Methods for the synthesis of haloalkyl ethers using, principally, based-catalyzed additions of haloalkenes to phenols have been reported[1] previously but yields were found to be capricious.[2] We have now developed an adaptation[3] of this reaction using phase-transfer catalysis and this generates the required ethers (**2**; X = Cl, F, or H) from the corresponding phenols (**1**) consistently and in high yields in all of the cases studied. In this paper we deal only with examples (**2**) where X = Cl.

The acetylenic phenols (**3**; R^4 = H) themselves appear to be somewhat sensitive to aerial oxidation and although they may be isolated as such, they are frequently more conveniently obtained as the C-acetylenic trimethylsilyl derivatives (**3**; R^4 = $SiMe_3$). The latter are formed directly in situ simply by quenching the reaction mixture with $(CH_3)_3SiCl$ followed by flash chromatography. The generality of the procedure can be seen from Table I but its versatility perhaps is better illustrated by example **2f** in which the bis(1,1-difluoro-2,2-dichloroethyl) ether of hydroquinone gives the corresponding bisacetylene **3f**.[6]



(1) Hanford, W. R.; Rigby, G. W. U.S. Pat. 2 409 274 (Oct 15, 1946); *Chem. Absts.* **1947**, *41*, 982b. (b) McBee, E. T.; Bolt, R. G. *Ind. Eng. Chem.* **1947**, *29*, 412. (c) Park, J. D.; Vail, D. K.; Lea, K. R.; Lacher, J. R. *J. Am. Chem. Soc.* **1951**, *73*, 1781. (e) England, D. C.; Melby, L. R.; Dietrich, M. A.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 5116. (f) Sauvetre, R.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1972**, 3202.

(2) In general the use of an homogeneous solution containing a strong base to effect the addition exposes the desired product **2** to dehydrohalogenation and formation of some phenoxyhalo olefin, which we found frequently contaminated the product. Although we have observed that these olefins also are intermediates in the production of **3** from **2**, their presence was a nuisance with regard to obtaining good analytical data.

(3) A general procedure for the preparation of phenolic 1,1-difluoro-2,2-dichloroethyl ethers is as follows: The phenol (50 mequiv) is dissolved in 40% KOH solution (14 mL) to which is added an aqueous solution of 40% $Bu_4N^+OH^-$ (2 mL). To this mixture at 0 °C is added 1,1-dichloro-2,2-difluoroethylene (75 mequiv) and methylene chloride (35 mL). The flask is tightly capped and shaken vigorously at 25 °C for 16 h. Isolation of the product using a normal procedure gives the desired ether in 90% yield.

(4) Satisfactory analytical data were obtained for all new compounds reported.

(5) Compound **3d** was not trapped as the trimethylsilyl derivative because of problems arising out of lithiation ortho to the methoxy group in the product.

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