Hz, 14β-H), 3.98 (1 H, m, 3α-H), 5.73 (1 H, m, 15β-H), 6.35 (1 H, d, J = 10.5 Hz, 23-H), 7.67 (1 H, d, J = 3 Hz, 21-H), 7.67 (1 H, dd, J = 10.5, 3 Hz, 22-H), 7.80–7.94 (3 H), 8.03–8.16 (1 H, m, phenyl H); mass spectrum, m/e 589 (M^+), 559, 529 (M^+ – AcOH), 422 (M^+ – o-nitrobenzoic acid ≡ RCO_2H), 407 (M^+ – RCO_2H – CH_3), 404, 380, 362 (M^+ – RCO_2H – AcOH), 347 (M^+ – RCO_2H – AcOH – CH_3), 300.

Anal. Calcd for $C_{33}H_{35}O_9N$: C, 67.21; H, 5.98; N, 2.38. Found: C, 67.21; H, 6.07; N, 2.35.

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Registry No. 5a, 4029-66-7; **6a**, 4029-64-5; **6b**, 36615-18-6; **7a**, 7439-77-2; **7b**, 22612-50-6; **8a**, 80753-84-0; **8b**, 80753-85-1; **10**, 80753-86-2; **11**, 80753-87-3; **12**, 80753-88-4; SeO_2, 7446-08-4.

Improved Synthesis of α-D-Ribofuranosides via Stereoselective Alkylation of a Dibutylstannylene Derivative for Ready Access to the 2-Substituted 2-Deoxyarabinofuranosides[1]

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Benzylation of the dibutylstannylene derivative of 3,5-di-*O*-benzyl-D-ribofuranose (**2**) gives 1,3,5-tri-*O*-benzyl-α-D-ribofuranose (**5**) as the major product (83%) together with some 2,3,5-tri-*O*-benzyl-D-ribofuranose (**6**, 13%). Formation of the β anomer of **5** was not observed. Methylation of **2** was found to be less regioselective but still stereospecific for the α-methylribofuranoside **3**. Several new 2-substituted benzyl 2-deoxy-α-D-arabinofuranosides (**10a–e**) were prepared by the trifluoromethanesulfonylation of **5** followed by treatment of triflate **9** with the lithium, sodium, or tetrabutylammonium salts of varios nucleophiles (F^-, Cl^-, Br^-, I^-, N_3^-).

Recent studies in our laboratory have been directed toward the development of improved methods for the synthesis of 2-modified 2-deoxyarabinofuranoside derivatives to be used as key intermediates in the preparation of several arabinosylpyrimidine nucleosides of biomedical interest. Among these are 1-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)cytosine[2] (2′-F-ara-C) and 1-(2′-chloro-2′-deoxy-β-D-arabinofuranosyl)cytosine[3] (2′-Cl-ara-C), which have exhibited pronounced inhibitory activity against several mouse leukemic cell lines in culture, and 1-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (FIAC) which exhibited powerful antiherpetic activity in vitro and in vivo.[4,5]

As part of these studies, we have reported recently[6] that methyl 3,5-di-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-α-D-ribofuranoside (**7**) could be readily converted into the corresponding 2-halogeno (and 2-azido) arabinosyl derivatives **8a–e** in high yields via nucleophilic displacement of the secondary 2-triflate group. Under similar conditions, the β anomer of **7** afforded the corresponding 2-substituted 2-deoxy-β-D-arabinofuranosides in poor yields together with the methyl ether of 3-(benzyloxy)-2-furanmethanol as the predominant product. Both **3** and its β anomer were obtained from the acid-catalyzed methanolysis of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose. This reaction, however, afforded predominantly the less desirable β isomer.[3] Several attempts to increase the proportion of the α anomer by varying the concentration of hydrogen chloride in methanol or by using mixed solvents (e.g., methanol in tetrahydrofuran[7]) were unsuccessful. Since the unfavorable anomeric ratio seriously limited accessibility to derivatives such as **8**,[6] it became necessary to develop a stereoselective synthesis of **3** or of comparably useful α-ribofuranosides (e.g., **5**).

While several methods for the stereoselective synthesis of certain α-glycosides of cis-1,2 configuration have been reported involving either nucleophilic displacement of halogeno or other good leaving groups at C-1[7,8] or direct C-1 O-alkylation of appropriately metalated furanose or pyranose derivatives,[9-11] none were directly applicable to the synthesis of glycosides similar to **3** or **5**. An alternative approach to the stereoselective synthesis of α-ribofuranosides from ribofuranose derivative **1** was suggested by the reported utilization of cyclic dibutylstannylene derivatives of several ribofuranosyl nucleosides[12] and py-

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Table I[a]

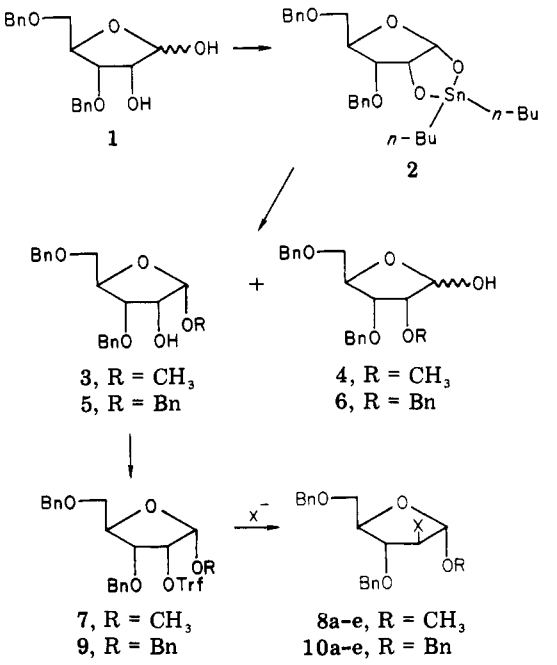
compd	X	reagent	time, h	yield, %	selected ^{1}H NMR data ($CDCl_3$) δ (H-1)	$J_{1,2}$, Hz
10a	F	$(n\text{-Bu})_4NF$	3	50	5.25 (d)	<1.0[b]
10b	Cl	LiCl	20	64	5.20 (s)	<1.0
10c	Br	LiBr	5	72	5.33 (d)	1.2
10d	I	NaI	20	90	5.44 (d)	1.8
10e	N_3	LiN_3	3	84	5.08 (d)	1.8

[a] Satisfactory analytical values (C, H, X or C, H, N) were obtained for all compounds in the table. [b] $J_{1,F}$ = 12.8 Hz.

ranosides[13,14] for the regioselective (and sometimes regiospecific) alkylation, sulfonylation, or acylation of *one* of the hydroxyl groups of the vicinal diol functions of such systems. These studies have shown that the dibutylstannylene function can serve as an activating group for the selective monosubstitution of one of the 2-oxy functions involved in the cyclic stannylene derivative, even in the presence of other unblocked hydroxy groups.[12,14] The observed regioselectivity of such reactions seems to be determined largely by steric factors as demonstrated by substitution at the equatorial oxygen of vicinal axial–equatorial dibutylstannylene-derivatized hydroxy groups[13] and by the importance of additional coordination of the tin atom with other neighboring oxy functions.[14] Similar regioselective acylation of several glycopyranosides and disaccharides via their tributylstannyl derivatives have also been reported.[15]

While these previous observations had been done on stannylene complexes involving only nonanomeric hydroxyl groups (that is, hydroxyl groups of predetermined configurations), they suggested a possible application to the stereoselective functionalization of anomeric hydroxyl groups as well. Thus, dialkylstannylene derivatives of **1** (e.g., **2** in Scheme I) may serve as useful intermediates in the synthesis of the desired α-ribofuranosides because of the anticipated α configuration of the now-fixed anomeric stannyloxy function at C-1. We have now found that treatment of 3,5-di-*O*-benzyl-D-ribofuranose (obtained by mild acid hydrolysis of its 1,2-*O*-isopropylidene derivative) with dibutyltin oxide in methanol affords a noncrystalline complex (**2**) which, upon direct methylation with methyl iodide in dimethylformamide, gives two products. After chromatographic separation on silica gel, these were identified as methyl 3,5-di-*O*-benzyl-α-D-ribofuranoside (**3**, 49% yield from **1**) and 3,5-di-*O*-benzyl-2-*O*-methyl-D-ribofuranose (**4**, 43%). Alkylation of **2** with benzyl bromide in dimethylformamide was more regioselective and afforded 3,5-di-*O*-benzyl-α-D-ribofuranoside **5** as the predominant product (83% from **1**) together with some 2,3,5-tri-*O*-benzyl-D-ribofuranose (**6**, 13%). On attempted chromatography on silica gel, stannylene derivative **2** reverted to ribofuranose **1**. Characterization by NMR techniques was complicated by its poorly resolved spectra. Similar observations have been reported for several dibutylstannylene derivatives.[12] Our observation that neither β isomer of **3** or **5** was formed upon alkylation of **2** however, is strong supportive evidence for the thermodynamically favored formation of the cis-fused bicyclic stannylene structure as shown for **2** in Scheme I and its intermediacy in subsequent alkylation steps. The enhanced regioselectivity favoring 1-*O*-alkylation in the case of benzyl bromide is also consistent with the observed dependence of similar reactions to steric constraints.[13-15]

Scheme I[a]



[a] X^-: a, F^-; b, Cl^-; c, Br^-; d, I^-; e, N_3^-. Trf = Trifluoromethanesulfonyl; Bn = benzyl; Bu = butyl.

While these studies were in progress, Srivastava and Schuerch[16] reported the stereoselective conversion of 3,4,6-tri-*O*-benzyl-D-mannopyranoside into the corresponding methyl and allyl β-pyranosides via a similar 1,2-*O*-dibutylstannylene complex. Their observation that methylation of the 1,2-*O*-dibutylstannylene derivative of 3,4,6-tri-*O*-benzyl-D-glucopyranoside with methyl iodide in DMF afforded both the 2-OMe derivative and the methyl α-pyranoside (albeit in a 7:3 ratio) but apparently none of the β-anomer parallels our own findings.[17]

Ribofuranoside **5** could be readily converted into the colorless crystalline triflate **9** (89%) by treatment with trifluoromethanesulfonic anhydride and dry pyridine in methylene chloride at −15 °C under nitrogen. Nucleophilic substitution of the triflate function to afford the corresponding 2-deoxy-2-substituted derivatives **10a–e** (see Table I) was carried out by the general procedures we described previously[6] for conversions of **7** into **8a–e**. Thus,

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(14) R. M. Munavu and H. H. Szmant, *J. Org. Chem.*, **41**, 1832 (1976).
(15) T. Ogawa and M. Matsui, *Carbohydr. Res.*, **56**, C1 (1977).
(16) V. S. Srivastava and C. Schuerch, *Tetrahedron Lett.*, **35**, 3269 (1979).
(17) It should be noted, however, that these same authors reported that methylation of the dibutylstannylene derivative of 3,4,6-tri-*O*-benzyl-D-mannopyranoside with methyl *p*-toluenesulfonate and dimethyl sulfate afforded substantial amounts of the α-glycoside. This might be the result of the higher reaction temperatures used with these less reactive methylating agents.

treatment of **9** with a slight excess of lithium chloride or bromide or of sodium iodide or azide in dimethyl sulfoxide containing 1.5 equiv of hexamethylphosphorotriamide afforded the corresponding 1-*O*-benzyl-α-D-arabinofuranosyl derivatives **10b–d** in generally good yields (see Table I). As we had previously observed with **7**,[6] α-benzylribofuranoside **9** also failed to react with lithium fluoride under a variety of conditions but was readily converted to **10a** (50% yield) when treated with tetra-*n*-butylammonium fluoride (TBAF) in dry tetrahydrofuran at −10 °C.

We have concluded from the studies outlined above that stereoselective alkylation of stannylene complexes such as **2** to suitably protected α-D-ribofuranosides followed by the facile nucleophilic displacement of a C-2 triflate function provides a useful general strategy for the synthesis of various 2-substituted 2-deoxyarabinofuranosides in generally good overall yields. The approach is potentially quite flexible and probably capable of further improvement by the utilization of other stannylating agents and/or more selective alkylators.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover Unimelt apparatus (capillary method) and are uncorrected. NMR spectra were obtained on a JEOL PFT-100 spectrometer. Optical rotations were measured on a P&I digital photoelectric polarimeter, Model A. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Column chromatography was performed in E. Merck silica gel 60 (70–230 mesh ASTM). Preparative TLC was carried out on 500-μm silica gel GF precoated plates (Analtech, Inc.).

3,5-Di-*O*-benzyl-β-D-ribofuranose (1). To a solution of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose[3] (19 g, 0.051 mmol) in 600 mL of dioxane was added 15 g of Dowex 50W-X8 (H^+) cation-exchange resin, and the magnetically stirred suspension was heated at 80 °C for 24 h. After filtration, the clear solution was treated with a small amount of Amberlite IR-45 (OH^-) anion-exchange resin, filtered, and evaporated to dryness. The residue was crystallized from petroleum ether (bp 30–60 °C)–diethyl ether (1:1) to give 12.87 g (78%) of ribofuranose **1**: mp 78–79 °C (lit.[18] 84–86 84–86 °C cor); ^1H NMR ($CDCl_3$) δ 7.31–7.33 (10H, m, arom H), 5.23 (1 H, d, $J_{1,OH}$ = 7.0 Hz, $J_{1,2}$ < 1 Hz, H-1), 4.39–4.67 (4 H, m, $2CH_2$), 3.90–4.32 (3 H, m, H-2, H-3, H-4), 3.65 (1 H, dd, $J_{4,5}$ = 2.7 Hz, $J_{5,5'}$ = 10.1 Hz, H-5),3.43 (1 H, dd, $J_{4,5'}$ = 2.7 Hz, $J_{5,5'}$ = 10.1 Hz, H-5'), 3.59 (1 H, d, $J_{1,OH}$ = 7.0 Hz, D_2O exchange, C_1OH), 2.75 (1 H, d, $J_{2,OH}$ = 3.3 Hz, D_2O exchange, C_2OH).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.32; H, 6.49.

Methyl 3,5-Di-*O*-benzyl-α-D-ribofuranoside (3) and 3,5-Di-*O*-benzyl-2-*O*-methyl-D-ribofuranose (4). To a solution of 3,5-di-*O*-benzyl-β-D-ribofuranose (660 mg, 2 mmol) in methanol (80 mL) was added dibutyltin oxide (548 mg, 2 mmol), and the suspension was heated to reflux for 1.5 h. The clear solution was evaporated to dryness, and the crude dibutylstannylene derivative (**2**, clear syrup) thus obtained was methylated directly by dissolving in dry DMF (3 mL) and adding an excess of methyl iodide (5 mL). After being stirred for 15 h at ambient temperature, the mixture was warmed at 38 °C for 5 h and then evaporated to dryness. The residue was dissolved in $CHCl_3$ (40 mL), washed with water, and then dried over anhydrous Na_2SO_4. After solvent evaporation in vacuo, the residue which contained **3** and **4** was chromatographed on a silica gel column (4 × 30 cm) with $CHCl_3$ as the eluent. Ribofuranoside **3**, which eluted first, was obtained as a clear syrup: 338 mg (49%); $[\alpha]^{23}_D$ +67° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29 (10 H, M, arom H), 4.88 (1 H, d, $J_{1,2}$ = 4.6 Hz, H-1), 4.64 (2 H, m, CH_2), 4.47 (2 H, m, CH_2), 4.01–4.24 (2 H, m, H-2 and H-4), 3.78 (1 H, m, H-3), 3.39 (2 H, ddd, $J_{4,5}$ = 2.4 Hz, $J_{4,5'}$ = 2.7 Hz, $J_{5,5'}$ = 10.3 Hz, H-5), 3.47 (3 H, s, OCH_3), 2.96 (1 H, d, $J_{2,OH}$ = 11.2 Hz, D_2O exchange, OH).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.57; H, 7.02. Found: C, 69.55; H, 6.96.

Ribofuranose **4** was eluted next, and, after evaporation of the appropriate fractions in vacuo, it was obtained as a clear syrup (301 mg, 43%); ^1H NMR indicated the presence of an α–β anomeric mixture in which the α anomer predominates: ^1H NMR ($CDCl_3$) δ 7.31–7.38 (10 H, m, arom H), 5.33 (1 H, dd, $J_{1,2}$ = 3.9 Hz, $J_{1,OH}$ = 11.3 Hz, α-H-1, superimposed over the β-H-1 signal), 4.65 (2 H, m, CH_2), 4.52 (2 H, s, CH_2), 3.40–4.40 (6 H, m, H-2, H-3, H-4, H-5,5', and 1-OH), 3.46 and 3.48 (3 H, 2 s, α- and β-OCH_3).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.63; H, 6.89.

1,3,5-Tri-*O*-benzyl-α-D-ribofuranose (5) and 2,3,5-Tri-*O*-benzyl-D-ribofuranose (6). To a solution of the dibutylstannylene **2** [prepared as described above from 8.26 g (25 mmol) of **1** and 8.71 g (35 mmol) of dibutyltin oxide] in 30 mL of anhydrous DMF was added 11 g of potassium carbonate. Benzyl bromide (8 mL) was then added dropwise to the rapidly stirred suspension at room temperature. After 12 h, the mixture was filtered through a pad of celite which was then washed with small portions of $CHCl_3$, and the combined filtrates were evaporated to a syrup. The residue was then dissolved in 300 mL of $CHCl_3$, washed with water, and dried over anhydrous Na_2SO_4. Evaporation to dryness in vacuo afforded a syrup shown to contain only two components by TLC. Column chromatography on silica gel (5 × 27 cm, toluene) afforded first the α-D-ribofuranoside **5**: 8.48 g (83%); clear syrup; $[\alpha]^{23}_D$ +72.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.29–7.33 (15 H, m, arom H), 5.09 (1 H, d, $J_{1,2}$ = 4.3 Hz, H-1), 4.88 and 4.55 (2 H, 2 d, *J* = 12.2 Hz, CH_2), 4.72 and 4.59 (2 H, 2 d, *J* = 12.2 Hz, CH_2), 4.49 (2 H, s, CH_2), 4.04–4.25 (2 H, m, H-2 and H-4), 3.88 (1 H, dd, $J_{2,3}$ = 7.0 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 3.44 (2 H, m, H-5), 3.04 (1 H, d, $J_{2,OH}$ = 11.3 Hz, D_2O exchange, C_2OH).

Anal. Calcd for $C_{26}H_{28}O_5$: C, 74.26; H, 6.7. Found: C, 74.21; H, 6.69.

The known tri-*O*-benzyl-D-ribofuranose[19] **6** was eluted next and obtained as a colorless syrup, 1.37 g (13%).

Anal. Calcd for $C_{26}H_{28}O_5 \cdot 0.5H_2O$: C, 72.71; H, 6.81. Found: C, 72.93; H, 6.77.

1,3,5-Tri-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-α-D-ribofuranose (9). To a solution of 1,3,5-tri-*O*-benzyl-α-D-ribofuranose(**5**; 4.2 g, 10 mmol) and anhydrous pyridine (7 mL) in 200 mL of dry CH_2Cl_2 was added dropwise trifluoromethanesulfonic anhydride (2 mL, 12 mmol) in 20 mL of CH_2Cl_2 at −20 °C. The mixture was magnetically stirred at this temperature for 1.5 h and then allowed to reach ambient temperature. The solution was washed with ice-cold saturated aqueous $NaHCO_3$, and then with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was recrystallized from petroleum ether–diethyl ether (1:1) to afford 4.95 g (89.7%) of the pure triflate **9**: mp 33–34 °C; ^1H NMR ($CDCl_3$) 7.29–7.33 (15 H, m, arom H), 5.25 (1 H, d, $J_{1,2}$ = 4.3 Hz, H-1), 5.01 (1 H, dd, $J_{1,2}$ = 4.3 Hz, $J_{2,3}$ = 5.8 Hz, H-2), 4.90 and 4.64 (2 H, 2 d, *J* = 12.5 Hz, CH_2), 4.76 and 4.45 (2 H, 2 d, *J* = 11.9 Hz, CH_2), 4.52 and 4.36 (2 H, 2 d, *J* = 12.2 Hz, CH_2), 4.03–4.26 (2 H, m, $J_{3,4}$ = 5.8 Hz, H-3, H-4), 3.46 (2 H, ddd, $J_{4,5}$ = 2.7 Hz, $J_{4,5'}$ = 3.0 Hz, $J_{5,5'}$ = 11.0 Hz, H-5).

Anal. Calcd for $C_{27}H_{27}F_3H_7S$: C, 58,69; H, 4.93; F, 10.31; S, 5.80. Found: C, 58.80; H, 4.88; F, 10.12; S, 5.73.

2-Fluoro-1,3,5-tri-*O*-benzyl-α-D-arabinofuranose (10a). To a solution of triflate **9** (552.5 mg, 1 mmol) in 20 mL of dry THF was added TBAF (1.3 g, 5 mmol) at −10 °C. After being stirred in an ice bath for 3 h, the mixture was allowed to warm to ambient temperature and was evaporated to dryness. Preparative TLC of the residue (petroleum ether–diethyl ether, 95:5 v/v) afforded 2-fluoroarabinofuranoside **10a**: 210 mg (50%); clear syrup; ^1H NMR ($CDCl_3$) δ 7.29–7.33 (15 H, m, arom H), 5.25 (1 H, d, $J_{1,2}$ < 1 Hz, $J_{1,F}$ = 12.8 Hz, H-1), 5.03 (1 H, dd, $J_{2,F}$ = 51.2 Hz, $J_{2,3}$ = 2.4 Hz, H-2), 4.86–4.44 (6 H, m, $3CH_2$), 4.36–3.86 (2 H, m, $J_{3,4}$

(18) M. Haga, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1810 (1968). These authors concluded that this crystalline material was the β anomer on the basis of its dextromutarotation in aqueous dioxane. This assignment is consistent with its NMR spectrum.

(19) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

= 7.3 Hz, H-3, H-4), 3.63 (2 H, m, H-5).

Anal. Calcd for $C_{26}H_{27}FO_4$: C, 73.91; H, 6.44; F, 4.49. Found: C, 73.77; H, 6.38; F, 5.00.

General Method for the Preparation of 2-Substituted 2-Deoxy-1,3,5-tri-*O*-benzyl-α-D-arabinofuranosides 10b–e. To a mixture of triflate **9** (552.5 mg, 1 mmol) and anhydrous HMPA (269 mg, 1.5 mmol) in dry Me_2SO (2 mL) was added 1.1 mmol of the salt (LiCl, LiBr, NaI, or LiN_3). After vigorous stirring (see Table I for reaction time) at room temperature, ice–water (30 mL) was added, and the product was extracted with petroleum ether (bp 30–60 °C) several times. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo. The products were isolated by silica gel column chromatography with petroleum ether (bp 30–60 °C)–acetone (98:2) as the eluent and characterized (see Table I) by ^1H NMR and elemental analysis.

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Registry No. **1**, 54429-44-6; **2**, 80765-77-1; **3**, 80795-53-5; **4**, 80765-78-2; **5**, 80795-54-6; **6**, 54623-25-5; **9**, 80765-79-3; **10a**, 80765-80-6; **10b**, 80765-81-7; **10c**, 80765-82-8; **10d**, 80765-83-9; **10e**, 80765-84-0; 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose, 55735-86-9.

Biogenesis of Epidithiadioxopiperazines. Nucleophilic Additions to Benzene Oxide and *sym*-Oxepin Oxide

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The additions of amine nucleophiles to benzene oxide (**10**) and to *sym*-oxepin oxide (**14**) serve as models for the biogenesis of the epidithiadioxopiperazines of the gliotoxin and aranotin family. Also reported are the additions of a thiolate and an amide anion to *sym*-oxepin oxide (**14**).

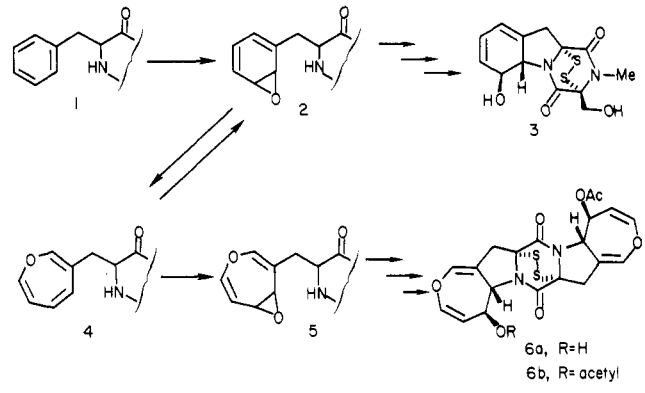
The biogenesis of the fungal metabolites gliotoxin[2] (**3**, Scheme I) and aranotin[2e-g,3] (**6a**) from phenylalanine (see **1**) occurs through oxidative elaboration of the amino acid. Neuss and co-workers[2e,f] have suggested that an enzyme-bound arene oxide, **2**, serves as a direct precursor to the dihydroarene ring of gliotoxin (**3**). Valence tautomerization of oxide **2** (**2** ⇄ **4**) and further enzymatic oxidation (**4** → **5**) would provide oxepin oxide **5**, the proposed[2e,f] precursor of the aranotins (see **6**).

Though plausible, Neuss' scheme has remained without chemical precedent. Arene oxides are prone to rearrangement, and consequently their "nucleophilic susceptibility"[4] is low. Thus, 3-(β-aminoethyl)benzene oxide (**7**), a model for enzyme-bound oxide **2**, fails to cyclize (**7** → **8**) under a variety of conditions.[5] Rather, conditions which might facilitate ring closure also accelerate the rearrangement of **7** to phenol **9**.

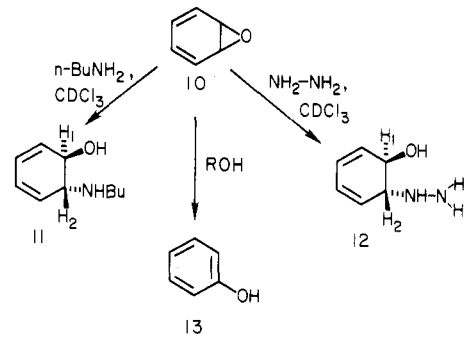
The reactivity of oxepin oxides toward nucleophiles has not been reported previously. Upon contact with untreated glassware or protic solvents, the parent, *sym*-oxepin oxide (**14**), undergoes rapid ring contraction (**14** → **20**).[6] A priori, the lability of the ring system might preclude successful nucleophilic reactions of **14** in a biogenetic fashion (see **5** → **6**). Certainly, *sym*-oxepin oxide (**14**) is incompatible with the protic conditions which facilitate nucleophilic additions to simple epoxides.[7]

Herein we present chemical precedent for both epoxide-opening steps of Neuss' scheme, **2** → **3** and **5** → **6**. Under appropriate conditions benzene oxide (**10**, Scheme

Scheme I



Scheme II



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