recristallized from ethanol (91%); mp 154 °C. Anal. Calcd for $C_{10}H_{11}N_3O_2Cl$ (mol wt 241.67): C, 49.69; H, 5.00; N, 17.38; Cl, 14.66. Found: C, 49.68; H, 5.14; N, 17.36; Cl, 15.02.

4-(Benzylamino)-6-methyl-7-(2,3-dihydroxypropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (6a). A solution of **6c** (1 g, 4.1 mmoles) in 2-methoxyethanol (40 mL) was stirred for 4 h under reflux with 877 mg (8.2 mmol) of benzylamine. After evaporation of the mixture under reduced pressure, the residue was cristallized twice in water yielding **6a**: 66%; mp 155 °C. Anal. Calcd for $C_{17}H_{20}N_4O_2$ (mol wt 312.36): C, 65.36; H, 6.45; N, 17.94. Found: C, 65.34; H, 6.34; N, 18,23.

7-Benzyl-6-methyl-4-[(2,3-dihydroxypropyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidine (6b). A solution of **6d**[9] in 2-methoxyethanol was treated as described above with 3-amino-1,2-propanediol. An analytical sample of **6b** was obtained by crystallization from ethanol, giving colorless crystals: mp. 194 °C; 74%. Anal. Calcd for $C_{17}H_{20}N_4O_2$ (mol wt 312.34): C, 65.36; H, 6.45; N, 17.94. Found: C, 65.18; H, 6.38; N, 18.04.

Acknowledgment. This investigation was supported in part by funds from the "Institut National de la Santé et de la Recherche Médicale" (CRL No. 813013.

Registry No. 1a, 27382-01-0; **1d**, 35636-10-3; **2a**, 27382-09-8; **2a**·HCl, 80765-61-3; **3a**, 80765-62-4; **3a**·HCl, 80765-63-5; **2b**, 80765-64-6; **2b**·HCl, 80765-65-7; **3b**, 80765-66-8; **3b**·HCl, 80765-67-9; **2c**, 80765-68-0; **2c**·HCl, 80765-69-1; **3c**, 80765-70-4; **3c**·HCl, 80765-71-5; **2d**, 35801-12-8; **2d**·HCl, 80765-72-6; **3d**·HCl, 80765-73-7; **5**, 46802-94-2; **6a**, 80765-74-8; **6b**, 80765-75-9; **6c**, 80765-76-0; **6d**, 26035-89-2; 5-acetonyl-4,6-dichloropyrimidine, 26035-69-8; 3-amino-1,2-propanediol, 616-30-8.

Bufadienolides. 32. Selenium Dioxide Dehydrogenation of 14-Dehydrobufalin[1a]

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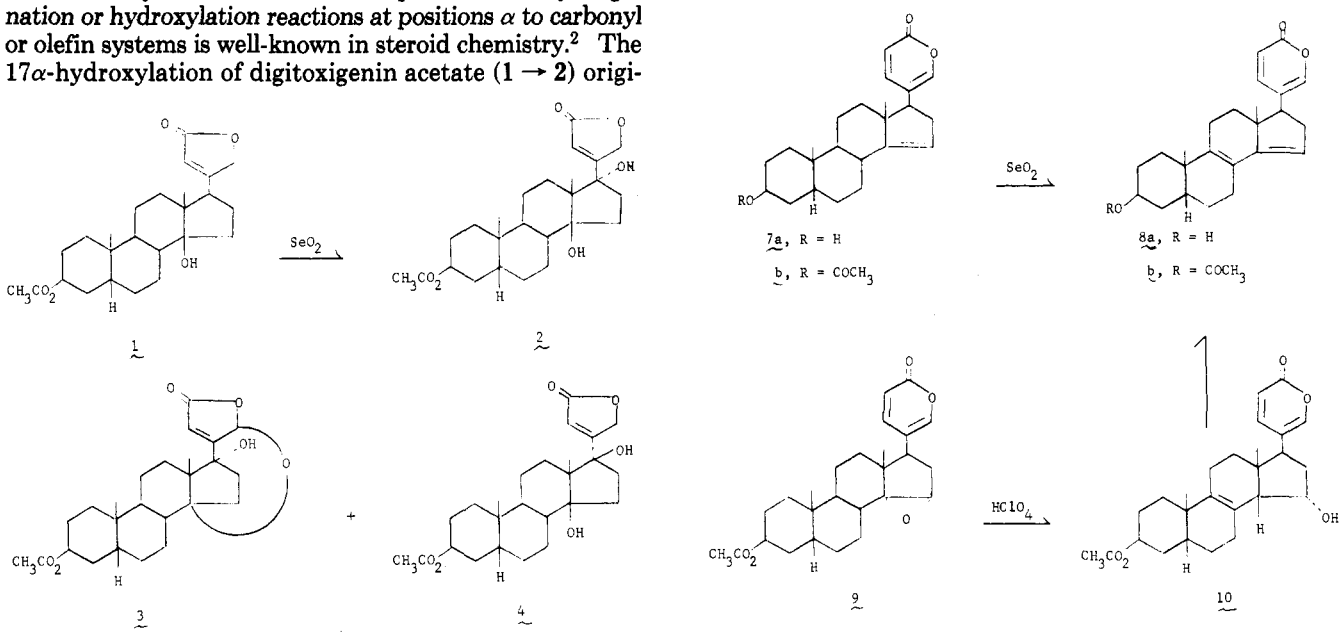
Unlike digitoxigenin acetate (**1**), bufalin acetate (**5a**), resibufogenin acetate (**6a**), and cinobufagin acetate (**6b**) were found to be resistant to selenium dioxide hydroxylation (e.g., **1** → **2**). However, under similar conditions selenium dioxide was found to dehydrogenate 14-dehydrobufalin (**7a**) to 3β-hydroxy-5β-bufa-8,14,20,22-tetraenolide (**8a**). An analogous dehydrogenation reaction was observed by employing 14-dehydrobufalin acetate (**7b** → **8b**). The structure of tetraene **8** was confirmed by dehydration of alcohol **10** to yield the same tetraene (**8b**). In turn, the structure of alcohol **10** prepared from α-epoxide **9** was substantiated by an X-ray crystallographic study of *o*-nitrobenzoate derivative **11**.

The utility of selenium dioxide promoted dehydrogenation or hydroxylation reactions at positions α to carbonyl or olefin systems is well-known in steroid chemistry.[2] The 17α-hydroxylation of digitoxigenin acetate (**1** → **2**) originally observed by Sondheimer and colleagues[3] provides an interesting illustration of such reactions. Subsequently, strophanthidin acetate was found to undergo the same 17α-hydroxylation reaction,[4] and the allyl oxidation of digitoxigenin acetate (**1**) with selenium dioxide was studied in detail by the Repke group.[5] In the latter investigation,

Scheme I



(1) (a) For part 31 and "Steroids and Related Natural Products. 98" refer to Y. Kamano, G. R. Pettit, M. Inoue, M. Tozawa, and Y. Komeichi, *J. Chem. Res., Miniprint*, *M*, 0837 (1977); G. R. Pettit, E. G. Thomas, and C. L. Herald, *J. Org. Chem.*, **46**, 4167 (1981). (b) Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Fukazawa, Setagaya Ku, Tokyo 158, Japan. (c) Department of Physical Chemistry, University of Cape Town, Cape Town, South Africa.

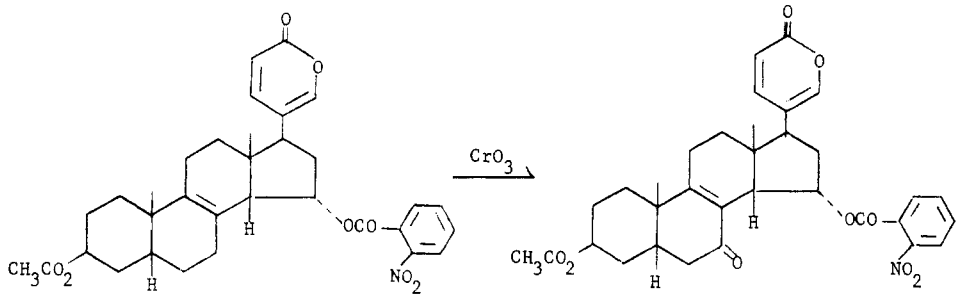
(2) cf. C. Djerassi, "Steroid Reactions", Holden-Day, San Francisco, 1963.

(3) N. Danieli, Y. Masur, and F. Sondheimer, *Tetrahedron*, **23**, 715 (1967).

(4) R. K. Ruzieva, M. B. Gorovits, and N. K. Abubakirov, *Khim. Prir. Soedin.*, 57 (1968).

0022-3263/82/1947-1503$01.25/0

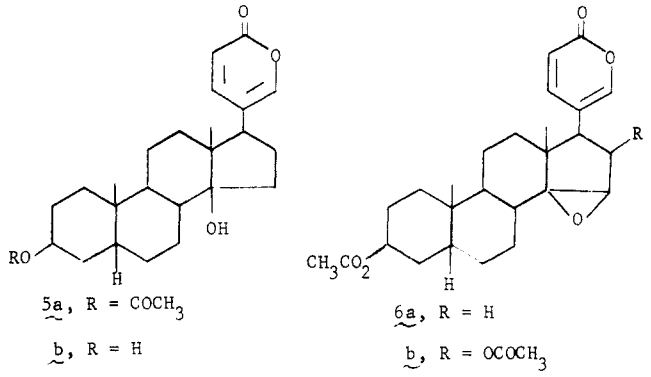
Scheme II



11 12

cardenolide 1 upon oxidation with selenium dioxide in dioxane solution was found to provide 17α-alcohol **2**, 14,21-epoxy 17α-alcohol **3**, and 17β-alcohol **4** in yields of 59%, 7%, and 0.6% respectively. In addition, further selenium dioxide oxidation of cardenolide **2** was found to give tetrahydropyran **3** in 44% yield.

The need for a rapid and convenient route to 17α-hydroxybufadienolides led us to explore the selenium dioxide oxidation of bufalin acetate (**5a**), resibufogenin



5a, R = $COCH_3$
b, R = H

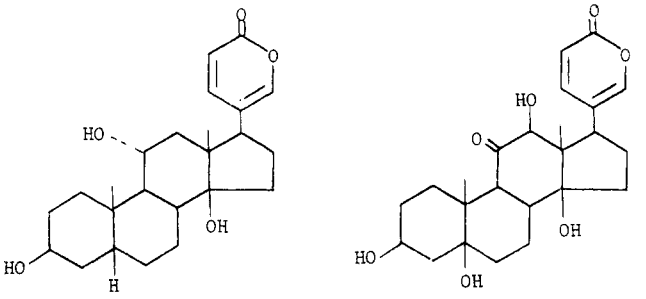
6a, R = H
b, R = $OCOCH_3$

acetate (**6a**), and cinobufagin acetate (**6b**). Interestingly, only starting materials were recovered, and no oxidation products were detected. However, when 14-dehydrobufalin (**7a**) was subjected to the same reaction with selenium dioxide (Scheme I) a new substance (**8a**) was obtained in good yield (75–80%). Acetylation of the product (**8a**) gave monoacetate **8b** which was also obtained by selenium dioxide dehydrogenation of 14-dehydrobufalin acetate (**7b**).

The selenium dioxide dehydrogenation products **8a** and **8b** gave mass spectra and elemental analyses which suggested a simple one-step dehydrogenation of 14-dehydrobufalin. Furthermore, the results of ultraviolet, infrared, and NMR spectral studies confirmed preservation of the 2-pyrone ring and introduction of a 8,14-diene system. The presence of the 8,14-diene was suggested by the slight downfield NMR shift of the 19-methyl protons from δ 0.97 to 1.12 and 1.14, respectively, for alcohol **8a** and acetate **8b** and appearance of absorption at 246 and 247 nm in the ultraviolet spectra of both products.

The assignment of structure **8** to the 14-dehydrobufalin dehydrogenation product was confirmed as follows. In an earlier study, opening of 14α,15α-epoxide **9** with 72% perchloric acid was found to afford 8-ene **10**.[6] While stereochemical assignments at positions 14 and 15 could not be made in our earlier investigation of alcohol **10**, the overall structure was firmly established. Therefore, if the selenium dioxide dehydrogenation product **8** was as assigned, then dehydration of alcohol **10** should yield the same 8,14-diene. Nice agreement with this proposal was realized when alcohol **10** was treated with *p*-toluenesulfonyl chloride in pyridine or with *p*-toluenesulfonic acid in refluxing benzene. Both procedures converted alcohol **10** to diene **8b**.

The complete structure of alcohol **10** was unequivocally established by X-ray crystallographic methods. For this purpose as well as anticipated use in a synthetic approach to gamabufotalin (**13**, from the toad *Bufo marinus*)[7] and



13

14

the firefly lucibufagins (e.g., **14**, a defensive bufadienolide of *Photinus ignitus* and *P. marginellus*),[8,9] the 15α-alcohol **10** was converted to *o*-nitrobenzoate **11**. A considerable number of attempts were made to selectively oxidize 8-ene **11** at the 11-position to afford a useful gamabufotalin-type precursor. But the usual product of allylic oxidation was 7-ketone **12** (also established by X-ray crystal structure determination).[10] Application of a different (e.g., sterically smaller) protecting group at the C-15 position (**10**) may eventually allow an efficient and selective oxidation at C-11. However, benzoate **11** did prove quite useful for X-ray crystal structure determination,[10,11] and the 14β-H[12] 15α-*o*-nitrobenzoate relationship of this potentially useful intermediate was unequivocally established.

Experimental Section

Each of the naturally occurring bufadienolides (before acetylation, e.g., bufalin **5b**) employed in this study were isolated from the Chinese toad venom preparation Ch'an Su. Analytical

(5) C. Lindig, P. Franke, and K. R. H. Repke, *J. Prakt. Chem.*, **317**, 17 (1975).
(6) Y. Kamano, G. R. Pettit, P. Brown, and M. Inoue, *Tetrahedron*, **31**, 2359 (1975).
(7) K. Shimada and T. Nambara, *Chem. Pharm. Bull.*, **27**, 1881 (1979).
(8) M. Goetz, D. F. Wiemer, L. W. Haynes, J. Meinwald, and T. Eisner, *Helv. Chim. Acta*, **62**, 1396 (1979).
(9) J. Meinwald, D. F. Wiemer, and T. Eisner, *J. Am. Chem. Soc.*, **101**, 3055 (1979).
(10) L. R. Nassimbeni, M. L. Niven, G. R. Pettit, M. Inoue, Y. Kamano, and J. J. Einck, to be submitted for publication in *Acta Crystallogr.*
(11) T. Debaerdemaeker, U. Thewalt, W. Kreiser, and H. A. F. Heinemann, *Chem. Ber.*, **112**, 423 (1979).
(12) M. Anastasia, A. Fiecchi, P. Gariboldi, and G. Galli, *J. Org. Chem.*, **45**, 2528 (1980).

thin-layer chromatographic plates (0.25-mm thickness of silica gel supplied by E. Merck) were developed with the solvent system acetone–chloroform–*n*–hexane (3:3:4), and substances were developed with ultraviolet light (254 nm) and detected by spraying with concentrated sulfuric acid and heating (hot plate). Silica gel supplied by E. Merck was also emloyed for column chromatography by using a dry-loading technique. All melting points are uncorrected, and other general experimental techniques and instrumental methods have been summarized in the preceding part of this series.[1a].

3β-Hydroxy-5β-bufa-8,14,20,22-tetraenolide (8a). Method A. A mixture composed of 14-dehydrobufalin (0.10 g),[13] selenium dioxide (0.20 g), and dry dioxane (16 mL) was heated at reflux for 12 h, filtered, poured into ice–water, and extracted with chloroform. The combined extract was washed with 5% sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and concentrated to a 99-mg residue which was chromatographed on a column of silica gel. Elution with ligroin–acetone (5:1) provided tetraenolide **8a** (75 mg) as needles (from acetone): mp 188–190 °C; TLC R_f 0.35 (color with sulfuric acid, purple to bluish green); UV (CH_3OH) λ_{max} 300 nm (log ε 4.22), 246 (4.23); IR (KBr) ν_{max} 3500 (OH), 1718, 1700 (conjugated CO), 1685, 1637, 1540 (conjugated C=C), 1130, 1065 (CO), 955, 910, 843, 805, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (3 H, s, 18-CH_3), 1.12 (3 H, s, 19-CH_3), 3.90 (1 H, m, 3α-H), 5.45 (1 H, br s, 15-H), 6.27 (1 H, d, J = 10 Hz, 23-H), 7.31 (1 H, d, J = 3 Hz, 21-H), 7.34 (1 H, dd, J = 3, 10 Hz, 22-H); mass spectrum, m/e 366 (M^+), 351 ($M^+ - CH_3$), 348 ($M^+ - H_2O$), 333 ($M^+ - H_2O - CH_3$), 307.

Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.71; H, 8.23.

In an analogous experiment with bufalin acetate (**5a**, 10 mg), selenium dioxide (10 mg), and dry dioxane (2 mL) at reflux temperature for 24 h, examination of the product by thin-layer chromatography showed only starting material. In another experiment using dioxane–acetic acid–water (50:25:1.5) as the solvent, the same observation was made. Again, no reaction was observed on employing resibufogenin acetate (**6a**, 10 mg) or cinobufagin acetate (**6b**, 10 mg).

Method B. When 8 mL of dioxane–acetic acid–water (50:25:1.5), selenium dioxide (0.10 g), and 14-dehydrobufalin (**7a**, 50 mg) were stirred at 80 °C for 5 h, isolation of the product as described in method A led to 39 mg of tetraenolide **8a** as needles (from acetone), mp 187–190 °C. The product was found to be identical[14] with a specimen obtained by method A.

3β-Acetoxy-5β-bufa-8,14,20,22-tetraenolide (8b). Method A. By Acetylation of Alcohol 8a. An 80-mg specimen of tetraenolide **8a** was acetylated with pyridine (1.6 mL)–acetic anhydride (1.1 mL) for 24 h at room temperature. Acetate **8b** (73 mg) was recrystallized to afford needles: mp 176–179 °C (from acetone–*n*-hexane); TLC R_f 0.57 (color with sulfuric acid, yellowish brown to bluish green); UV (CH_3OH) λ_{max} 300 nm (log ε 4.01), 247 (4.20); IR (KBr) ν_{max} 1740, 1718, 1700 (ester CO and conjugated CO), 1690, 1638, 1540 (conjugated C=C), 1270, 1260, 1240 (ester CO), 1130, 1068 (CO), 954, 910, 845, 805, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 (3 H, s, 18-CH_3), 1.14 (3 H, s, 19-CH_3), 2.05 (3 H, s, 3-$OCOCH_3$), 4.97 (1 H, m, 3α-H), 5.47 (1 H, br s, 15-H), 6.28 (1 H, d, J = 10 Hz, 23-H), 7.32 (1 H, d, J = 3 Hz, 21-H), 7.36 (1 H, dd, J = 3, 10 Hz, 22-H); mass spectrum, m/e 408 (M^+), 393 ($M^+ - CH_3$), 348 ($M^+ - AcOH$), 333 ($M^+ - AcOH - CH_3$), 307.

Anal. Calcd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.59; H, 7.97.

Method B. From 14-Dehydrobufalin Acetate (7b). Selenium dioxide (0.10 g) dehydrogenation of 14-dehydrobufalin acetate (**7b**, 50 mg) in dry dioxane (18 mL) was conducted as described above (method A) for preparation of tetraene **8a**.. The product was eluted from the silica gel column with 9:1 ligroin–acetone and recrystallized from acetone–*n*-hexane to afford 33 mg of tetraene acetate **8b** as needles, mp 176–178 °C.

The preceding reaction was repeated for 5 h at 80 °C with 8 mL of dioxane–acetic acid–water (50:25:1.25) as the solvent. Recrystallization of the product from acetone–*n*-hexane yielded 31 mg of tetraenolide acetate **8b** as needles, mp 176–179 °C.

Method C. From 15α-Alcohol 10. To a solution of 3β-acetoxy-15α-hydroxy-5β,14β-bufa-8,20,22-trienolide (**10**, 50 mg)[6] in pyridine (0.8 mL) was added 35 mg of *p*-toluenesulfonyl chloride. The mixture was allowed to remain at room temperature for 2 days, and the product was isolated by preparative thin-layer chromatography on silica gel with acetone–chloroform–*n*-hexane (3:3:4) as the eluant. The product corresponding to R_f 0.57 was located with the aid of ultraviolet light and extracted with chloroform–methanol (4:1). Recrystallization of the product from acetone–*n*-hexane provided tetraenolide acetate **8b** (37 mg) as needles, mp 177–179 °C.

In another experiment 15α-alcohol **10** (30 mg), *p*-toluenesulfonic acid (6 mg), and benzene (1 mL) were heated at reflux for 30 min. The product was isolated by preparative thin-layer chromatography as described in the preceding paragraph and recrystallized from acetone–*n*-hexane to afford 9.4 mg of tetraene acetate **8b** as needles, mp 175–178 °C.

The samples of tetraene acetate **8b** prepared by methods A–C were found to be identical.[14]

3β-Acetoxy-15α-[(*o*-nitrobenzoyl)oxy]-5β,14β-bufa-8,20,22-trienolide (11). *o*-Nitrobenzoyl chloride (2.2 mL) was added to 15α-alcohol **10** (0.20 g) in 5 mL of dry pyridine at ice-bath temperature. After 20 h at room temperature the mixture was poured into ice–water and extracted with chloroform. The combined extract was washed consecutively with water, 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. Removal of solvent yielded a light brown oil (0.28 g) which was chromatographed on a column of slica gel. The fractions eluted by 7:1 ligroin–acetone were found to be ester **11** (0.24 g, 85% yield). Recrystallization from acetone yielded a pure specimen; mp 177–179 °C; TLC R_f 0.39 (deep green color with sulfuric acid); UV (CH_3OH) λ_{max} 295 nm (log ε 3.96); IR (KBr) ν_{max} 1710 (ester CO and conjugated CO), 1610, 1525 (conjugated C=C and NO_2), 1280, 1240 (ester CO), 1210, 1125, 1080, 1030, 955, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (3 H, s, 18-CH_3), 0.97 (3 H, s, 19-CH_3), 1.96 (3 H, s, 3β-$OCOCH_3$), 2.16 (1 H, d, J = 5 Hz, 14β-H), 4.12 (1 H, m, 3α-H), 5.65 (1 H, m, 15β-H), 6.29 (1 H, d, J = 11 Hz, 23-H), 7.34 (1 H, d, J = 2 Hz, 21-H), 7.6–7.95 (4 H, s and m, phenyl H), 7.72 (1 H, dd, J = 2, 11 Hz, 22-H); ^1H NMR (acetone-d_6) δ 0.75 (3 H, s, 18-CH_3), 1.00 (3 H, s, 19-CH_3), 1.90 (3 H, s, 3β-$OCOCH_3$), 4.15 (1 H, m, 3α-H), 5.67 (1 H, m, 15β-H), 6.25 (1 H, d, J = 10.5 Hz, 23-H), 7.54 (1 H, d, J = 2.5 Hz, 21-H), 7.56 (1 H, dd, J = 10.5, 2.5 Hz, 22-H), 7.86–8.00 (4 H, s and m, phenyl H); mass spectrum, m/e 575 (M^+), 560, 516, 502, 425, 424, 408 (M^+ – *o*-nitrobenzoic acid ≡ RCO_2H), 366 ($M^+ - RCO_2H - CH_2CO$), 348 ($M^+ - RCO_2H - AcOH$), 333 ($M^+ - RCO_2H - AcOH - CH_3$), 294 ($M^+ - RCO_2H - AcOH - C_4H_6$).

Anal. Calcd for $C_{33}H_{37}O_8N$: C, 68.85; H, 6.48; N, 2.43. Found: C, 68.32; H, 6.41; N, 2.41.

3β-Acetoxy-7-oxo-15α-[(*o*-nitrobenzoyl)oxy]-5β,14β-bufa-8,20,22-trienolide (12). A solution of benzoate **11** (60 mg) in methylene chloride (1 mL)–glacial acetic acid (6mL)–water (0.5 mL) was heated to 47–48 °C, 40 mg of chromium trioxide was added, and the temperature was maintained at 47–48 °C for 2 h. After cooling (ice bath), methanol was added, and the solution was poured into ice–water and extracted with chloroform. The organic phase was washed with 5% sodium bicarbonate and water. Removal of solvent gave a pale yellow amorphous solid (63 mg) which was purified by preparative thin-layer chromatography on silica gel with ligroin–chloroform–acetone (4:3:3) as the mobile phase. The product eluted with chloroform–methanol (9:1) was recrystallized from acetone to give 49 mg of ketone **12** as needles: mp 224–227 °C; TLC R_f 0.31 (pink to light brown color with sulfuric acid); UV (CH_3OH) λ_{max} 252 nm (log ε 4.02), 300 (4.11); IR (KBr) ν_{max} 1730 (ester CO and conjugated CO), 1660, 1610, 1530 (conjugated C=C and NO_2), 1280, 1240 (ester CO), 1210, 1160, 1115, 1060, 1030, 1015, 945, 860, 785, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (3 H, s, 18-CH_3), 1.16 (3 H, s, 19-CH_3), 1.96 (3 H, s, 3β-$OCOCH_3$), 2.75 (1 H, dd, J = 5, 18 Hz, 6β-H), 2.76 (1 H, dd, J = 6 Hz, 17α-H), 3.09 (1 H, d, J = 7 Hz, 14β-H), 3.86 (1 H, m, 3α-H), 5.74 (1 H, m, 15β-H), 6.37 (1 H, d, J = 10 Hz, 23-H), 7.38 (1 H, d, J = 2 Hz, 21-H), 7.65–7.75 (4 H), 7.80–7.95 (1 H, m, 22-H and phenyl-H); ^1H NMR (acetone-d_6) δ 0.82 (3 H, s, 18-CH_3), 1.24 (3 H, s, 19-CH_3), 1.96 (3 H, s, 3β-$OCOCH_3$), 3.12 (1 H, d, J = 7

(13) G. R.. Pettit, Y. Kamano, F. Bruschweiler, and P. Brown, *J. Org. Chem.*, **36**, 3736 (1971).

(14) The identical composition of both products was confirmed by mixture melting point determination, infrared spectral comparison, and thin-layer chromatographic behavior.

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.

Acknowledgment. We are grateful for support of this investigation by Grants No. CA-16049-01-04 and -07 awarded by the National Cancer Institute, DHW, by Mrs. Mary Dell Pritzlaff, by the Olin Foundation (Spencer T. and Ann W.), by the Fannie E. Rippel Foundation, by Mrs. Eleanor W. Libby, and by the Donald Ware Waddell Foundation. We also thank Dr. Gordon M. Cragg for other assistance.

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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(2) J. A. Wright, D. T. Wilson, and J. J. Fox, *J. Med. Chem.*, **13**, 269 (1970); U. Reichman, K. A. Watanabe, and J. J. Fox, *Carbohydr. Res.*, **42**, 233 (1975).

(3) G. Ritzmann, R. S. Klein, D. H. Hollenberg, and J. J. Fox, *Carbohydr. Res.*, **39**, 227 (1975).

(4) K. A. Watanabe, U. Reichman, K. Hirota, C. Lopez, and J. J. Fox, *J. Med. Chem.*, **22**, 21 (1979).

(5) C. Lopez, K. A. Watanabe, and J. J. Fox, *Antimicrob. Agents Chemother.*, **17**, 803 (1980); J. J. Fox, C. Lopez, and K. A. Watanabe, "Antiviral Chemotherapy: Design of Inhibitors of Viral Functions", K. K. Gauri, Ed., Academic Press, 1981, p 219.

(6) T.-L. Su, R. S. Klein, and J. J. Fox, *J. Org. Chem.*, **46**, 1790 (1981).

(7) G. Wulff, U. Schröder, and J. Wichelhaus, *Carbohydr. Res.*, **72**, 280 (1979).

(8) R. Eby and C. Schuerch, *Carbohydr. Res.*, **39**, 33 (1975), and references therein.

(9) A. H. Haines and K. C. Symes, *J. Chem. Soc. C*, 2331 (1971).

(10) H. Bredereck, G. Hageldoch, and E. Haurbsh, *Chem. Ber.*, **87**, 35 (1954).

(11) R. R. Schmidt and M. Reichrath, *Angew. Chem., Int. Ed. Engl.*, **18**, 466 (1979).

0022-3263/82/1947-1506$01.25/0