139.14867, found M_r (mass spectrum) 139.14796 ($M^+ - C_8H_5O$).

3-Methylpentynyl Ether 2d. This compound was obtained as described above for **2e** (tri-*sec*-butylborane in place of triphenylborane). Ether **2d**: $[\alpha]^{19}_D$ −61° (*c* 1.1, cyclohexane); IR (film) 2950, 2260, 1475, 1370, 1250, 1235, 1215, 1150, 1100, 1090, 965, 950, 915, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.8–1.0 (m, 12 H), 1.10 (d, *J* = 7 Hz, 3 H), 1.1–1.8 (m, 9 H), 2.3 (m, 3 H), 3.71 (m, 1 H); mass spectrum (chemical ionization), *m/e* 237 (M + 1, 5%), 156 (100%), 139 (25%).

Acknowledgment. We thank Dr. Luche for his interest in our work and the CNRS (UA 332) for financial support. A.M. is grateful to NATO for a post-doctoral fellowship.

Registry No. **1**, 2216-51-5; **2a**, 108167-50-6; **2b**, 108167-51-7; **2c**, 108266-28-0; **2d**, 108167-59-5; **2e**, 108167-60-8; **3**, 34857-28-8; **4**, 108167-52-8; **5**, 6169-06-8; **6**, 108167-53-9; **7**, 57-88-5; **8**, 108167-54-0; **9**, 108167-55-1; **9** (dichloro enol ether), 108167-61-9; **10a**, 108167-56-2; **10b**, 108167-57-3; **11**, 79547-82-3; **12**, 108167-58-4; CH_3I, 74-88-4; C_2H_5I, 75-03-6; n-C_3H_7I, 107-08-4; CH_2=$CHCH_2I$, 556-56-9; triphenylborane, 960-71-4; tri-*sec*-butylborane, 1113-78-6; trichloroethylene, 79-01-6.

An Efficient Synthesis of Partially Protected α-D-Ribofuranosides from D-Ribose by Way of a Unique Selective Debenzylation Reaction

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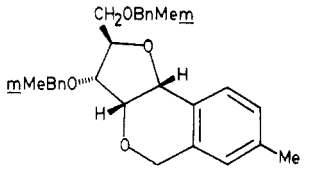
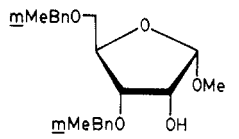
Selectively protected D-ribofuranose derivatives constitute highly useful synthetic precursors of modified nucleosides such as, for example, (2-deoxy-2-halo-D-arabinofuranosyl)cytosine and -uracil.[1-3] Differentiation of the two secondary positions is, however, a difficult problem, which has precluded a more extensive use of such derivatives: thus, benzylation[4] of methyl 2,3-*O*-dibutylstannylene-α- and -β-D-ribofuranoside, partial de-*O*-acylation[5] of the corresponding peracetates, and mild hydrolysis[6] of 2,3-*O*-(dimethylamino)alkylidene acetals proceed indeed with a modest degree of regioselectivity. There are only two processes of preparative value that allow the formation of partially protected ribofuranoses from the parent sugar: the simultaneous protection of positions 3 and 5 of the furanosides using a tetraisopropyldisiloxane-1,3-diyl group[7,8] and the hydrolysis of tri-*O*-benzoyl-β-D-ribofuranosyl bromide, a reaction that affords 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose in good yield.[9] In spite of its limited stability and its susceptibility to acyl group migration, the latter compound has been used successfully as an intermediate in the synthesis of a few arabino nucleosides.[3,10] However, most of the partially protected ribofuranose derivatives used in nucleoside synthesis (2-*O*-methyl,[11] 2-*O*-benzyl,[12] 3-*O*-benzyl,[4] 3,5-di-*O*-benzyl[1a,2]) have been prepared from other sugars (D-arabinose, D-xylose, or D-glucose) by way of lengthy procedures involving, at some stage, an inversion of configuration or a chain-shortening step. We report, in this paper, a novel reaction that makes selectively protected α-D-ribofuranosides readily available from D-ribose; the resulting derivatives are ideally suited for conversion into 2-substituted arabinofuranosides and the corresponding nucleosides.

During previous investigations on the behavior of benzylated sugars in the presence of a Lewis acid,[13] we had observed that two different reactions occurred when methyl 2,3,5-tri-*O*-(3-methylbenzyl)-β-D-ribofuranoside was treated with tin(IV) chloride: intramolecular alkylation[14] of the 2-*O*-benzyl group, to form an internal *C*-glycoside (30%) (compound **1**), and cleavage of this group with anomerization, to give methyl 3,5-di-*O*-(3-methylbenzyl)-α-D-ribofuranoside (**2**) as the major product (50%).



1



2

As it is likely that the two processes involve a common intermediate,[15] we considered that it might be possible to increase the effectiveness of the unusual selective debenzylation pathway by using benzyl groups less prone to electrophilic substitution. Replacement of the 3-methylbenzyl groups by 4-chlorobenzyl groups indeed effectively suppressed the C-glycosidation component of the reaction: compound **3**, prepared from methyl D-ribofuranoside under standard conditions, afforded almost exclusively[16] methyl 3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside **4**[17] on reaction with tin(IV) chloride (Scheme I). This remarkable reaction thus brings about *the cleavage of the 4-chlorobenzyl group at O-2 specifically and the simultaneous inversion of the anomeric configuration.* As α-ribofuranosides constitute much better substrates for nucleophilic displacements at C-2 than the corresponding β-isomers,[2] anomerization is a particularly fortunate feature of this reaction: for example, we have obtained D-arabino azido sugar **8** from compound **4** by way of triflate **7** in 77% overall yield. The remaining 4-chlorobenzyl groups were then cleaved[18] and the azido group reduced by hydrogenolysis, thus providing methyl 2-amino-2-deoxy-α-D-arabinofuranoside **9**[19] in four steps only from **3**.

As previously suggested,[15] formation of **4** might involve initially a tin(IV)-mediated anomerization of the β-glyco-

(1) (a) Ritzmann, G.; Klein, R. S.; Hollenberg, D. H.; Fox, J. J. *Carbohydr. Res.* **1975**, *39*, 227. (b) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21. (c) Su, T.-L.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 151.

(2) (a) Su, T.-L.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 1790. (b) Su, T.-L.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1982**, *47*, 1506.

(3) Tann, C. H.; Brodfuehrer, P. R.; Brundidge, S. P.; Sapino, C., Jr.; Howell, H. G. *J. Org. Chem.* **1985**, *50*, 3644.

(4) Schmidt, R. R.; Gohl, A.; Karg, J. *Chem. Ber.* **1979**, *112*, 1705.

(5) Ishido, Y.; Sakairi, N.; Sekiya, M.; Nakazaki, N. *Carbohydr. Res.* **1981**, *97*, 51.

(6) Hanessian, S.; Moralioglu, E. *Can. J. Chem.* **1972**, *50*, 233.

(7) (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932. (b) Schaumberg, J. P.; Hokanson, G. C.; French, J. C.; Smal, E.; Baker, D. C. *J. Org. Chem.* **1985**, *50*, 1651.

(8) This group has been used primarily for the selective protection of nucleosides: Markiewicz, W. T. *Natural Products Chemistry 1984*; Zalewski, R. I., Skolik, J. J., Eds.; Elsevier: Amsterdam, 1985; p 275.

(9) (a) Ness, R. K.; Fletcher, H. J. *J. Am. Chem. Soc.* **1956**, *78*, 4710. (b) Chavis, C.; Dumont, F.; Imbach, J.-L. *J. Carbohydr., Nucleosides, Nucleotides* **1978**, *5*, 133. (c) Brodfuehrer, P. R.; Sapino, C., Jr.; Howell, H. G. *J. Org. Chem.* **1985**, *50*, 2598.

(10) Chavis, C.; Dumont, F.; Wightman, R. H.; Ziegler, J. C.; Imbach, J.-L. *J. Org. Chem.* **1982**, *47*, 202.

(11) Haines, A. H. *Tetrahedron* **1973**, *29*, 2807.

(12) Schmidt, R. R.; Gohl, A. *Chem. Ber.* **1979**, *112*, 1689.

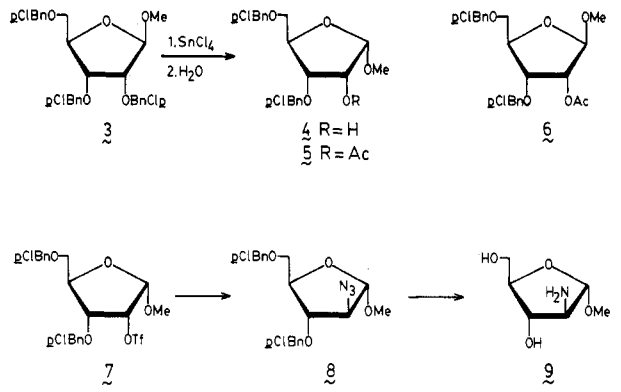
(13) (a) Martin, O. R. *Tetrahedron Lett.* **1985**, *26*, 2055. (b) Martin, O. R.; Mahnken, R. E. *J. Chem. Soc., Chem. Commun.* **1986**, 497.

(14) Intramolecular C-arylation is the exclusive reaction of the corresponding benzylated D-ribofuranosyl *acetates*.

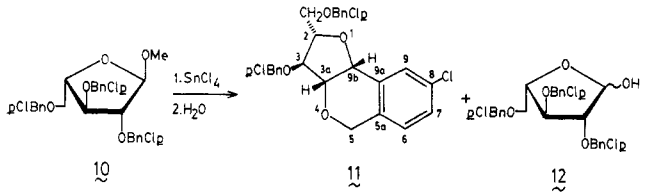
(15) Martin, O. R. *Carbohydr. Res.*, in press. We have observed a geminal coupling constant of the same magnitude in related compounds lacking normal *O*-benzyl ethers; this corroborates our assignment of the "larger" J_{gem} value to the ring-methylene group of **11**.

0022-3263/87/1952-2922$01.50/0

Scheme I



Scheme II



side **3** into the corresponding cis α-glycoside: the α-anomer is favored owing to its ability to form a chelated structure with the tin(IV) atom linked to O-1 and O-2; this tin(IV) complex specifically activates the 2-*O*-benzyl ether function and promotes its cleavage to give a 2-*O*-trichlorostannyl intermediate in which the metal atom is still coordinated to O-1, thereby further stabilizing the α-configuration of the substrate. Other factors, however, must contribute to the success of this reaction: surprisingly, no trace of 2-O-debenzylation product was obtained from methyl 2,3,5-tri-*O*-(4-chlorobenzyl)-α-L-arabinofuranoside **10** under the same conditions. This compound reacts very slowly with tin(IV) chloride to give, after 2 days at room temperature and aqueous processing, internal *C*-glycosides **11** (14%), tri-*O*-(4-chlorobenzyl)-L-arabinofuranose **12** (26%), and recovered starting material (55%) (Scheme II). Furthermore, the lyxo isomer of **3** (α-anomer) yielded a mixture of at least three major products! These results indicate that the relative orientation of the alkoxy groups on the substrate plays an important role, probably by defining the site of precomplexation of the reagent. As in the case of the titanium(IV) chloride mediated anomerization of benzylated D-glucopyranosides,[20] it is likely that the substrate forms initially a bidentate complex with the Lewis acid, the structure of which determines the outcome of the reaction. Thus, the diverging behavior of the ribo and arabino glycosides **3** and **10** may be explained by the ability of the arabino derivative to form a tin(IV) complex involving O-1 and O-3 (cis in **10**, trans in **3**): this complex could promote both intramolecular C-arylation (to give **11**) and cleavage of the O-1–CH_3 bond (to give **12** after hydrolysis). Further investigations are in progress to identify the nature of the initial reagent–substrate complex in these reactions.

The α-ribo configuration of **4** and **5** and the α-arabino configuration of **8** are fully supported by their NMR parameters, in particular by the ring $^3J_{H,H}$ coupling constants[21] and the chemical shifts of the anomeric carbon (δ ^{13}C-1: **3**, 106.32; **4**, 102.97; **8**, 107.09).[22] The position of the free hydroxyl function in **4** was readily established on the basis of the shift of δ H-2 upon acetylation ($\Delta\delta$ H-2 = 0.56 ppm). Furthermore, 2-*O*-acetyl derivative **5** was anomerized upon brief treatment with titanium(IV) chloride at low temperature, to give the more stable β-D-ribofuranoside **6**; comparison of the NMR characteristics of **4** and **5** with those of **6** confirmed our assignment of anomeric configuration. Interestingly, internal *C*-glycoside **11** exhibits an H,H-geminal coupling constant for the ring-methylene group (14.8 Hz) substantially larger (in absolute value) than that of the acyclic benzyl ethers (12.1 Hz): this feature, which we already observed previously,[15] appears to be a consistent indication of the incorporation of the *O*-benzyl function into a cyclic structure.

In conclusion, the tin(IV) chloride mediated reaction of **3** constitutes the first example of a preparatively useful selective debenzylation of a carbohydrate derivative at a secondary position and provides a very short approach to partially protected α-D-ribofuranosides from D-ribose.

Experimental Section

For general methods, see ref 15. The following solvent systems were used for analytical thin-layer (TLC), flash, and column chromatography: (A) 1:6, (B) 5:2, (C) 5:3, (D) 1:1 ether–hexane; (E) 3:1 $CHCl_3$–MeOH; (F) 4:1, (G) 9:1 toluene–ethyl acetate.

Methyl 2,3,5-Tri-*O*-(4-chlorobenzyl)-β-D-ribofuranoside (3). A solution of dimsyl sodium was prepared by adding pentane-washed sodium hydride (1.40 g, 58.4 mmol) to dry Me_2SO (20 mL) and heating the magnetically stirred suspension to 60 °C for 45 min. A solution of methyl D-ribofuranoside[23] (β/α ~10:1) (1.03 g, 6.29 mmol) in dry Me_2SO (50 mL) was then added dropwise to the cooled solution of dimsyl sodium. After 4 h, 4-chlorobenzyl chloride (9.6 g, 59.6 mmol) was added slowly, and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of methanol (5 mL) and then water (65 mL); the mixture was extracted with chloroform (3 × 50 mL), the combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was submitted to flash chromatography (solvent A), which afforded 2.74 g (81%) of pure, syrupy **3**: $[\alpha]^{20}_D$ +26.4° (*c* 1.39, MeOH); R_f 0.66 (solvent C); IR (film) 2920, 2860, 1595, 1480, 1462, 1405, 1355, 1200, 1010–1140 (br), 942, 835, 801 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.33 (s, 3 H, OCH_3), 3.58 (m, 2 H, H-5A,5B), 3.86 (d, 1 H, $J_{1,2}$ < 1 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 4.05 (dd, 1 H, $J_{3,4}$ = 6.5 Hz, H-3), ~4.35 (m, 1 H, H-4), 4.49, 4.53, and 4.62 (3 s, 3 × 2 H, 3 OCH_2Ar), 4.97 (s, 1 H, H-1), 7.30 and 7.40 (2 s, 12 H, 3 C_6H_4); ^{13}C NMR (20 MHz) δ 106.32 (C-1).

Anal. Calcd for $C_{27}H_{27}Cl_3O_5$: C, 60.29; H, 5.06; Cl, 19.78. Found: C, 60.15; H, 5.23; Cl, 19.98.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside (4). To a cold (0 °C) solution of **3** (0.53 g, 0.98 mmol) in dry CH_2Cl_2 (5 mL) was added a 10% (v/v) solution of tin(IV) chloride in dry CH_2Cl_2 (1.09 mL, 0.94 mmol). The mixture was stirred at 0 °C until TLC analysis (solvent B) indicated the absence of starting material (4–6 h). Saturated aqueous $NaHCO_3$ (5 mL) was then added, the organic phase separated, and the aqueous phase extracted with $CHCl_3$ (3 × 5 mL); the combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was submitted to flash chromatography (solvent C), which afforded 0.32 g (79%)

(16) Isolated yields varied between 79% and 83%. Excess tin(IV) chloride decreases the yield of the reaction. A byproduct of higher polarity was isolated (1.6%) and identified as 3,5-di-*O*-(4-chlorobenzyl)-D-ribofuranose. See Experimental Section.

(17) The overall yield of **4** from D-ribose (three steps, without isolation of the intermediates) was 55%.

(18) 4-Chlorobenzyl groups are readily cleaved by hydrogenolysis. See: Koto, S.; Inada, S.; Morishima, N.; Zen, S. *Carbohydr. Res.* **1980**, *87*, 294.

(19) (a) Buchanan, J. G.; Clark, D. R. *Carbohydr. Res.* **1977**, *57*, 85. (b) Montgomery, J. A.; Thorpe, M. C.; Clayton, S. D.; Thomas, H. J. *Carbohydr. Res.* **1974**, *32*, 404.

(20) Koto, S.; Morishima, N.; Kawahara, R.; Ishikawa, K.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1092.

(21) For reference data, see: Serianni, A. S.; Barker, R. *J. Org. Chem.* **1984**, *49*, 3292.

(22) For reference data, see: Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27.

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

of pure, syrupy α-D-ribofuranoside **4**: $[\alpha]^{20}_D$ +111.9° (*c* 1.2, MeOH); R_f 0.40 (solvent C); IR (film) 3550 (sh) and 3500 (br) (OH), 2920, 2860, 1595, 1487, 1403, 1300, 1010–1130 (br), 832, 800 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 3.48 (m) and 3.51 (s) (5 H, H-5A,5B, OCH_3), 3.80 (dd, 1 H, $J_{2,3}$ = 7 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.22 (m, 2 H, H-2, H-4), 4.51 (s, 2 H) and 4.67 (AB, 2 H) (2 OCH_2Ar), 4.96 (d, 1 H, $J_{1,2}$ = 4.5 Hz, H-1), 7.37 (s, 8 H, 2 C_6H_4); ^{13}C NMR (20 MHz) δ 102.97 (C-1).

Anal. Calcd for $C_{20}H_{22}Cl_2O_5$: C, 58.12; H, 5.37; Cl, 17.16. Found: C, 58.16; H, 5.21; Cl, 17.29.

Further elution afforded a small amount (6 mg, 1.6%) of a more polar byproduct (R_f 0.14, solvent C), which was acetylated under standard conditions; the resulting product was identified as 1,2-di-*O*-acetyl-3,5-di-*O*-(4-chlorobenzyl)-β-D-ribofuranose: syrup; IR (film) 3020, 2920, 2860, 1740 (C=O), 1595, 1490, 1365, 1215, 1085, 1010, 950, 800, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.87 and 2.05 (2 s, 2 × 3 H, 2 $OCOCH_3$), 3.45 (dd, 1 H, $J_{4,5A}$ = 4.0 Hz, $J_{5A,5B}$ = 10.8 Hz, H-5A), 3.59 (dd, 1 H, $J_{4,5B}$ = 2.9 Hz, H-5B), 4.13 (m, 1 H, $J_{3,4}$ = 7.6 Hz, H-4), 4.17 (dd, 1 H, $J_{2,3}$ = 4.0 Hz, H-3), 4.32 and 4.51 (2 d, 2 H, J_{AB} = 11.7 Hz, OCH_2Ar), 4.36 and 4.43 (2 d, 2 H, J_{AB} = 12.3 Hz, OCH_2Ar), 5.23 (d, 1 H, $J_{1,2}$ < 0.5 Hz, H-2), 6.05 (s, 1 H, H-1), 7.11–7.23 (m, 8 H, 2 C_6H_4).

Methyl 2-*O*-Acetyl-3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside (5). Compound **4** was acetylated under standard conditions and purified by flash chromatography (solvent C); syrup; $[\alpha]^{20}_D$ +92.6° (*c* 1.2, $CHCl_3$); R_f 0.37 (solvent C); IR (film) 2920, 2860, 1740 (C=O), 1595, 1487, 1370, 1233, 1120, 1082, 1060, 1040, 1010, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3 H, $OCOCH_3$), 3.27 (dd, 1 H, $J_{4,5A}$ = 4.2 Hz, $J_{5A,5B}$ = 10.5 Hz, H-5A), 3.37 (dd, 1 H, $J_{4,5B}$ = 3.9 Hz, H-5B), 3.38 (s, 3 H, OCH_3), 3.90 (dd, 1 H, $J_{2,3}$ = 7.1 Hz, $J_{3,4}$ = 4.2 Hz, H-3), 4.11 (q, 1 H, H-4), 4.33 and 4.41 (2 d, 2 H, J_{AB} = 12.2 Hz, OCH_2Ar), 4.35 and 4.54 (2 d, 2 H, J_{AB} = 12.7 Hz, OCH_2Ar), 4.80 (dd, 1 H, $J_{1,2}$ = 4.6 Hz, H-2), 5.05 (d, 1 H, H-1), 7.10–7.26 (m, 8 H, 2 C_6H_4); MS, *m/z* 125 (100) and 127 (35)($C_7H_6Cl^+$), 43 (61), 89 (10), 126 (9), 82 (8), 115 (7), 103 (6), 211 (6), 99 (5), ..., 423 (0.1) ($M^{\bullet+}$ – $OCH_3^{\bullet}$), 329 (0.1) ($M^{\bullet+}$ – $C_7H_6Cl^{\bullet}$).

A sample of acetylated α-glycoside **5** was anomerized by treatment with titanium(IV) chloride (1 equiv) in CH_2Cl_2 at −78 °C for 2 min, then quenching with saturated aqueous sodium bicarbonate at low temperature, to give compound **6**, namely, methyl 2-*O*-acetyl-3,5-di-*O*-(4-chlorobenzyl)-β-D-ribofuranoside, in 61% yield after flash chromatography (solvent D): syrup; $[\alpha]^{22}_D$ +23.5° (*c* 1.96, $CHCl_3$); R_f 0.40 (solvent C); IR (film) 2930, 2870, 1750 (C=O), 1600, 1495, 1365, 1235, 1100, 1085 (br), 1005, 895, 800 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.10 (s, 3 H, $OCOCH_3$), 3.33 (s, 3 H, OCH_3), 3.50 (dd, 1 H, $J_{4,5A}$ = 5.5 Hz, $J_{5A,5B}$ = 10.6 Hz, H-5A), 3.59 (dd, 1 H, $J_{4,5B}$ = 3.4 Hz, H-5B), 4.12 (dd, 1 H, $J_{2,3}$ = 4.5 Hz, $J_{3,4}$ = 7.6 Hz, H-3), 4.18 (ddd, 1 H, H-4), 4.36 and 4.53 (2 d, 2 H, J_{AB} = 11.5 Hz, OCH_2Ar), 4.50 (AB, 2 H, J_{AB} = 12.1 Hz, OCH_2Ar), 4.88 (s, 1 H, $J_{1,2}$ < 0.5 Hz, H-1), 5.20 (d, 1 H, H-2), 7.16–7.20 and 7.23–7.31 (m, 8 H, 2 C_6H_4).

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-*O*-[(trifluoromethyl)sulfonyl]-α-D-ribofuranoside (7). To a cold (−15 °C) solution of compound **4** (0.79 g, 1.91 mmol) in a mixture of dry CH_2Cl_2 (27 mL) and pyridine (2 mL) was added trifluoromethanesulfonic anhydride (0.39 mL, 2.31 mmol) in dry CH_2Cl_2 (1.4 mL). After having been stirred for 3 h at −15 °C, the reaction mixture was quenched by the addition of a cold saturated aqueous solution of $NaHCO_3$ (50 mL), and the organic phase was separated, washed with water (5 mL), dried (Na_2SO_4), and evaporated to dryness to afford a nearly quantitative yield of triflate **7**; compound **7** thus obtained was used without further purification in subsequent steps: syrup; R_f 0.62 (solvent C); IR (film) 1205 and 1410 cm^{-1} (SO_2); ^1H NMR (60 MHz) δ 3.53 (s and m, 5 H, OCH_3 and H-5A,5B), 4.20 (m, 2 H, H-3, H-4), 4.50 (s, 2 H, OCH_2Ar), 4.48 and 4.77 (2 d, 2 H, J_{AB} = 12 Hz, OCH_2Ar), 5.16 (m, 2 H, H-1, H-2), 7.38 (s, 8 H, 2 C_6H_4); MS, *m/z* 125 (100) and 127 (32) ($C_7H_6Cl^+$), 82 (15), 126 (10), 57 (8), 222 (7), 69 (7), 141 (7), 43 (7), 89 (6), ..., 419 (5) and 421 (3) ($M^{\bullet+}$ – $C_7H_6Cl^{\bullet}$).

Methyl 2-Azido-3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-α-D-arabinofuranoside (8). To a solution of crude triflate **7** (1.91 mmol) in Me_2SO (3 mL) was added sodium azide (0.15 g, 2.1 mmol), and the mixture was stirred for 5 h at room temperature. Ice–water (10 g) was then added and the mixture extracted with petroleum ether (bp 35–60 °C) (6 × 5 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated, and the residue was submitted to flash chromatography (solvent C), which afforded 0.65 g (77% from **4**) of pure **8**: syrup; $[\alpha]^{20}_D$ +71.3° (*c* 1.7, MeOH); R_f 0.77 (solvent C); IR (film) 2910, 2860, 2090 (N_3), 1600, 1492, 1360, 1250, 1080 (br), 1005, 835, 800 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.38 (s, 3 H, OCH_3), 3.55 (dd, 1 H, $J_{4,5A}$ = 4.6 Hz, $J_{5A,5B}$ = 10.6 Hz, H-5A), 3.60 (dd, 1 H, $J_{4,5B}$ = 3.6 Hz, H-5B), 3.85 (dd, 1 H, $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 6.3 Hz, H-3), 3.89 (dd, 1 H, $J_{1,2}$ = 1,2 Hz, H-2), 4.17 (q, 1 H, H-4), 4.45 and 4.51 (2 d, 2 H, J_{AB} = 12.1 Hz, OCH_2Ar), 4.45 and 4.58 (2 d, 2 H, J_{AB} = 12.5 Hz, OCH_2Ar), 4.89 (d, 1 H, H-1), 7.17–7.20 and 7.25–7.29 (2 AA'BB', 8 H, 2 C_6H_4); ^{13}C NMR (20 MHz) δ 55.30 (OCH_3), 69.25, 70.82, 71.85, 72.82, 81.14, 83.29, 107.09 (C-1), 128.63, 128.73, 129.04, 129.21 and 134.05 (Ar C); MS, *m/z* 125 (100) and 127 (33) ($C_7H_6Cl^+$), 89 (8), 126 (8), 197 (7), 90 (4), 45 (3), 128 (3), 77 (3), 99 (3), 114 (3), ..., 312 (0.7, $M^{\bullet+}$ – $C_7H_6Cl^{\bullet}$).

Anal. Calcd for $C_{20}H_{21}Cl_2N_3O_4$: C, 54.81; H, 4.83; Cl, 16.18; N, 9.59. Found: C, 54.83; H, 4.98; Cl, 16.46; N, 9.59.

Methyl 2-Amino-2-deoxy-α-D-arabinofuranoside (9). A solution of azide **8** (1.09 g, 2.49 mmol) in glacial acetic acid (100 mL) was hydrogenated at 50 psi on a Parr hydrogenator in the presence of 10% palladium on charcoal as the catalyst (0.71 g) for 24 h. The catalyst was then removed by filtration, the solid carefully washed with acetic acid, and the filtrate evaporated to dryness. The crude amino sugar was purified by column chromatography (solvent E), which afforded 0.204 g (60%) of pure **9**: mp 74.3–76.5 °C (lit.[19a] 75–77 °C); $[\alpha]^{20}_D$ +94.9° (*c* 0.77, $CHCl_3$) (lit.[19a] $[\alpha]^{20}_D$ +100.8° (*c* 0.75, $CHCl_3$)).

Methyl 2,3,5-Tri-*O*-(4-chlorobenzyl)-α-L-arabinofuranoside (10). Sodium hydride (0.88 g as a 50% dispersion in mineral oil), carefully washed with petroleum ether, was added to a magnetically stirred solution of methyl α-L-arabinofuranoside[24] (0.6 g, 3.6 mmol) in anhydrous DMF (30 mL). After 1 h, 4-chlorobenzyl chloride (2.4 g, 15 mmol) was added and the mixture stirred overnight at room temperature. The reaction was quenched by the addition of methanol (10 mL) and then water (100 mL); the mixture was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic phases were washed with water, dried (Na_2SO_4), and concentrated. The residue was submitted to flash chromatography (solvent G), which afforded 1.6 g (81%) of pure, syrupy **10**: $[\alpha]^{20}_D$ −29.8° (*c* 1.1, $CHCl_3$); R_f 0.75 (solvent F); IR (film) 3050, 2900, 2860, 1600, 1490, 1465, 1410, 1360, 1190, 1090, 1050, 1010, 945, 840, 800 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.39 (s, 3 H, OCH_3), 3.60 (AB, 2 H, $J_{4,5A}$ = 4.9 Hz, $J_{4,5B}$ = 4.0 Hz, $J_{5A,5B}$ = 10.8 Hz, H-5A,5B), 3.86 (dd, 1 H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 6.5 Hz, H-3), 3.95 (d, 1 H, H-2), 4.17 (m, 1 H, H-4), 4.39–4.56 (3 AB's, 6 H, 3 OCH_2Ar), 4.93 (s, 1 H, H-1), 7.15–7.32 (m, 12 H, 3 C_6H_4).

Anal. Calcd for $C_{27}H_{27}Cl_3O_5$: C, 60.29; H, 5.06; Cl, 19.78. Found: C, 60.55; H, 5.11; Cl, 19.99.

Reaction of 10 with Tin(IV) Chloride. To a solution of **10** (1.6 g, 2.9 mmol) in anhydrous CH_2Cl_2 (30 mL) was added a 1 M solution of tin(IV) chloride in CH_2Cl_2 (6 mL, 6 mmol), and the mixture was stirred for 48 h at room temperature. Water (100 mL) was then added, the organic layer was separated, the aqueous phase was washed with CH_2Cl_2 (2 × 20 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated. The residue was submitted to flash chromatography (solvent G), which afforded, in order of elution, compounds **11** (130 mg, 14%), **10** (900 mg, 55%), and **12** (400 mg, 26%).

(2*S*,3*S*,3a*S*,9b*R*)-8-Chloro-3-[(4-chlorobenzyl)oxy]-2-[[(4-chlorobenzyl)oxy]methyl]-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran (11): syrup; $[\alpha]^{20}_D$ −4.8° (*c* 1.0, $CHCl_3$); R_f 0.8 (solvent F); IR (film) 3030, 2900, 2860, 1600, 1580, 1490, 1410, 1370, 1200, 1100 (br), 1010, 880, 860, 840, 800, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.57 and 3.61 (AB, 2 H, $J_{2,2'A}$ = 5.4 Hz, $J_{2,2'B}$ = 6.1 Hz, $J_{2'A,2'B}$ = 10.1 Hz, H-2'A,2'B), 3.95 (d, 1 H, $J_{2,3}$ = 5.4 Hz, $J_{3,3a}$ = 0 Hz, H-3), 4.16 (m, 2 H, $J_{3a,9b}$ = 3.4 Hz, H-2, H-3a), 4.49 (AB, 2 H, *J* = 12.1 Hz, OCH_2Ar), 4.57 and 4.62 (2 d, 2 H, *J* = 12.1 Hz, OCH_2Ar), 4.58 (d, 1 H, $J_{5A,5B}$ = 14.8 Hz, H-5A), 4.69 (d, 1 H, H-9b), 4.72 (d, 1 H, H-5B), 7.00 (d, 1 H, $J_{6,7}$ = 8.8 Hz, H-6), 7.20–7.32 (m, 9 H, H-7, 2 C_6H_4), 7.47 (d, 1 H, $J_{7,9}$ = 2.0 Hz, H-9); MS, *m/z* 125 (100) and 127 (32) ($C_7H_6Cl^+$), 165 (16), 89 (10), 167 (9), 126 (9), 166 (7), 139 (7), 103 (5), 90 (5),

(24) Martin, M. G.; Ganem, B.; Rasmussen, J. *Carbohydr. Res.* **1983**, *123*, 332.

..., 379 (1) and 381 (0.7) ($M^{\cdot+} - C_7H_6Cl^{\cdot}$), 504 (0.5) and 506 (0.4) ($M^{\cdot+}$).

Anal. Calcd for $C_{26}H_{23}Cl_3O_4$: C, 61.72; H, 4.55; Cl, 21.07. Found: C, 61.71; H, 4.66; Cl, 21.02.

2,3,5-Tri-*O*-(4-chlorobenzyl)-α- and -β-L-arabinofuranose (12): recrystallized from ether–hexane; mp 87–88 °C; $[\alpha]^{22}_D$ −3.3° (*c* 1.8, $CHCl_3$); R_f 0.25 (solvent F); IR (CCl_4) 3450 (OH), 3020, 2910, 2860, 1600, 1550, 1490, 1410, 1360, 1250, 1210, 1090, 1060, 1020, 970, 800 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, α/β ~1:1) δ 3.51 and 3.57 (2 m, 2 H, $J_{4\alpha,5A\alpha} = J_{4\alpha,5B\alpha} = 4.7$ Hz, $J_{4\beta,5A\beta} = J_{4\beta,5B\beta} = 4.0$ Hz, $J_{5A,5B} = 10.1$ Hz, H-5Aα,β, H-5Bα,β), 3.87 (dd, 0.5 H, $J_{2\alpha,3\alpha}$ ~ 1.5 Hz, $J_{3\alpha,4\alpha} = 4.0$ Hz, H-3α), 3.95 (d, 0.5 H, H-2α), 3.99 (t, 0.5 H, $J_{1\beta,2\beta} = 4.0$ Hz, $J_{2\beta,3\beta}$ ~ 5 Hz, H-2β), 4.08 (m, 0.5 H, H-4β), 4.10 (q, 0.5 H, H-4α), ~4.42 (m, 0.5 H, H-3β), 4.40–4.55 (m, 5.5 H) and 4.63 (d, 0.5 H) (3 OCH_2Ar), 5.33 (d, 0.5 H, H-1β), 5.39 (s, 0.5 H, H-1α), 7.18–7.35 (m, 12 H, 3 C_6H_4); MS, *m/z* 125 (100) and 127 (32) ($C_7H_6Cl^+$), 126 (8), 69 (8), 115 (7), 89 (7), 141 (4), 77 (3), 90 (3), 128 (3), ..., 397 (2) and 399 (1) ($M^{\cdot+} - C_7H_6Cl^{\cdot}$).

Anal. Calcd for $C_{26}H_{25}Cl_3O_5$: C, 59.59; H, 4.77. Found: C, 59.71; H, 4.83.

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Registry No. 3, 108008-65-7; 4, 108008-66-8; 5, 108008-67-9; 6, 108008-68-0; 7, 108008-69-1; 8, 108008-70-4; 9, 52706-45-3; 10, 108008-71-5; 11, 108008-72-6; 12, 108008-73-7; methyl β-D-ribofuranoside, 7473-45-2; methyl α-D-ribofuranoside, 52485-92-4; methyl α-L-arabinofuranoside, 3795-68-4.

Tetrahedral Intermediates Formed by Nitrogen and Oxygen Attack of Aromatic Hydroxylamines on Acetyl Cyanide

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Aromatic hydroxylamines **1** have been postulated as intermediates in the carcinogenic process induced by some aromatic amines. The necessary chemical activation of **1** for the latter stages of this process can subsequently be achieved by O-acylation, rendering the N–O bond labile for cleavage and reaction with DNA bases.[2] We have discovered that aromatic hydroxylamines react with aroyl cyanides at room temperature to afford in almost quantitative yield the O-aroylated derivatives,[3] of obvious interest in carcinogenesis. More recently it became possible to observed directly,[4] by using ^1H and ^{13}C NMR spectroscopy, an O-tetrahedral intermediate **3a** formed in the reaction between *N*-phenylhydroxylamine (**1a**) and acetyl cyanide (**2**) (Scheme I) and to demonstrate its base-catalyzed decomposition to the *O*-acyl derivative **5a**. We present in this paper evidence that O-tetrahedral intermediates such as **3** result from thermodynamic control and that under kinetic control N-tetrahedral intermediates such as **4** are formed instead.

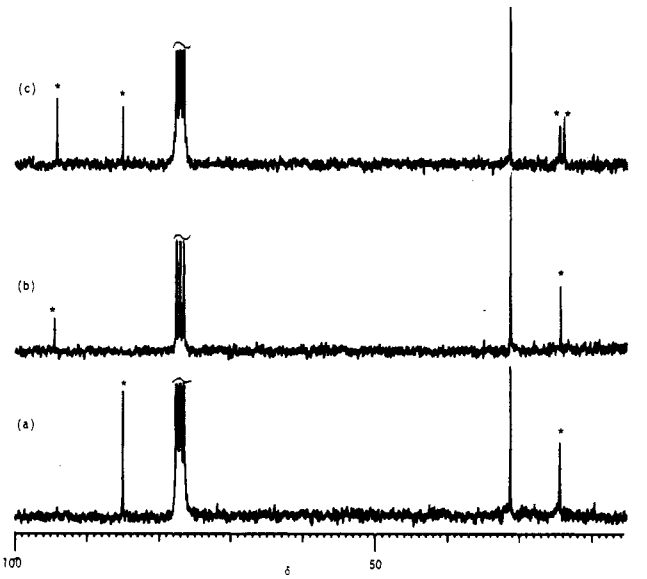
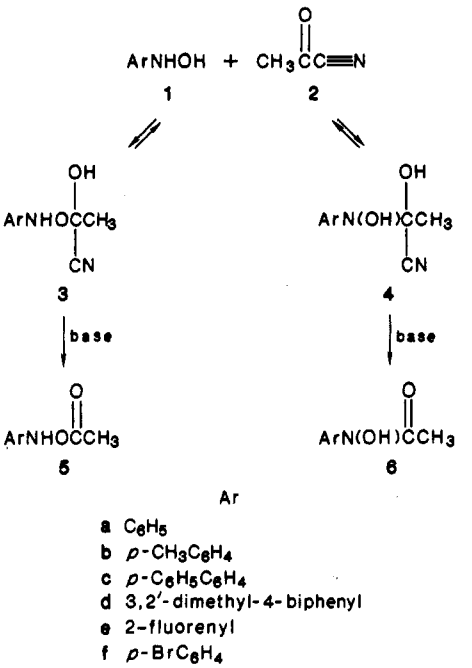


Figure 1. ^{13}C NMR spectra at 62.93 MHz for the reaction between **2** and **1c** in 50% (v/v) $CDCl_3/CD_3CN$: (a) at 215 K immediately after mixing, corresponding to formation of **4c**; (b) warming to 285 K, corresponding to **3c**; (c) recooling to 215 K, showing the presence of both **3c** and **4c**. Key carbon atoms referred to in the text are indicated with an asterisk. Peaks at δ 77.0 and 31.0 are due to *C*DCl_3 and *Me*COCN, respectively.

Scheme I



Results and Discussion

When ^{15}N-labeled **1a** is mixed with **2** at 215 K in acid-free solution[5] of 50% (v/v) $CDCl_3/CD_3CN$, the formation of a single new species can be observed with ^1H and ^{13}C NMR spectroscopy. This is attributed to **4a** on the following basis: The new sp^3 carbon resonance[4] appears as a doublet [δ 85.0 ($^1J_{^{15}N-^{13}C} = 1.3$ Hz)],[6] as does the new

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(2) Lotlikar, P. D.; Hong, Y. S.; Baldy, W. J. In *Biological Oxidation of Nitrogen*; Gorrod, J. W., Ed.; Elsevier: Oxford, 1978; p 185.

(3) Prabhakar, S.; Lobo, A. M.; Marques, M. M. *Tetrahedron Lett.* **1982**, 1391.

(4) Lobo, A. M.; Marques, M. M.; Prabhakar, S.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1985**, 1113.

(5) Our previous study[4] was carried out in $CDCl_3$ solutions containing traces of DCl. Under these conditions, **3** was found to dcompose rapidly to **5** at room temperature. If rigorously purified $CDCl_3$ or mixtures of $CDCl_3/CD_3CN$ are used, no decomposition of the tetrahedral intermediate **3** is observed over a period of several hours at temperatures up to 290 K.

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