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

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Selectively protected $\alpha$-D-ribofuranoside derivatives constitute highly useful synthetic precursors of modified nucleosides such as, for example, (2-deoxy-2-halo-D-arabinofuranosyl)cytosine and -uracil.\(^1\)\(^2\) Differentiation of the two secondary positions is, however, a difficult problem, which has precluded a more extensive use of such derivatives: thus, benzylolation\(^3\) of methyl 2,3-D-dibutylstannylene-$\alpha$- and $\beta$-D-ribofuranoside, partial de-O-acylation\(^4\) of the corresponding peracetates, and mild hydrolysis\(^5\) of 2,3-D-(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 ribofuranosides from the parent sugar: the simultaneous protection of positions 3 and 5 of the furanoside using a tetraisopropylboronate, and mild hydrolysis of tri-O-benzyl-$\beta$-D-ribofuranosyl bromide, a reaction that affords 1,3,5-tri-O-benzyl-$\alpha$-D-ribofuranoside in good yield.\(^6\) In

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

As it is likely that the two processes involve a common intermediate, 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 3,5-di-O-(3-methylbenzyl)-$\alpha$-D-ribofuranoside under standard conditions, afforded almost exclusively methyl 3,5-di-O-(4-chlorobenzyl)-D-ribofuranoside\(^7\) on reaction with tetravinyl chloride (Scheme 1). This remarkable action thus brings about the cleavage of the 4-chlorobenzyl group at O-2 specifically and the simultaneous inversion of the anomeric configuration. As $\alpha$-ribofuranosides constitute much better substrates for nucleophilic displacements at C-2 than the corresponding $\beta$-isosomers,\(^8\) amidonization 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\(^9\) and the azido group reduced by hydrogenolysis, thus providing methyl 2-amino-2-deoxy-$\alpha$-D-arabinofuranoside\(^9\) in four steps only from 3.

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As previously suggested,\(^10\) formation of 4 might involve initially a tetravinyl-mediated amidonization of the $\beta$-glyco-
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 12 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)-α-L-arabinofuranoside 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 anomeration 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 arabinoglycosides 3 and 10 may be explained by the ability of the arabinose 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-CH3 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-arabinose configuration of 8 are fully supported by their NMR parameters, in particular by the ring $^{3}$J$_{HH}$ coupling constants 21 and the chemical shifts of the anomic carbon (δ 13C-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 (Δδ 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 anomic 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) 1:3, (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 dimethyl sulfoxide was prepared by adding pentane-washed sodium hydride (1.40 g, 58.4 mmol) to dry Me$_2$SO (20 mL) and heating the magnetically stirred suspension to 60 °C for 45 min. A solution of methyl β-d-ribofuranoside 12 (β/α ~10:1) (1.03 g, 6.29 mmol) in dry Me$_2$SO (50 mL) was then added dropwise to the cooled solution of dimethyl sulfoxide. After 4 hr, 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$_2$SO$_4$) and concentrated, and the residue was submitted to flash chromatography (solvent A), which afforded 2.74 g (81%) of pure, syrupy 3: [α]$_{D}^{20}$ +26.4° (c 1.39, MeOH); R$_f$ 0.66 (solvent C); IR (film) 2920, 2860, 1595, 1480, 1462, 1405, 1355, 1200, 1010-1140 cm$^{-1}$; 'H NMR (50 MHz, CDCl$_3$) δ 3.33, 3.60, 3.63, 3.79 (12 H, 2 CH$_2$, 4 CH$_3$, 3, 4, 5); 4.97 (1 H, H-4); 5.45 (1 H, H-1); 7.30 and 7.40 (12 H, 2 C,H$_2$); 13C NMR (20 MHz) δ 106.32, 106.68, 110.50, 123.65, 136.58, 136.66, 149.30, 150.40, 160.10, 165.60; Anal. Calcd for C$_{27}$H$_{27}$Cl$_3$O$_5$: 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, 0.58 mmol) in dry CH$_3$Cl (5 mL) was added 10% (v/v) solution of tin(IV) chloride-dry CH$_3$Cl (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$_2$SO$_4$) and concentrated, and the residue was submitted to flash chromatography (solvent C), which afforded 0.32 g (79%) after hydrolysis. Further investigations are in progress to identify the nature of the initial reagent-substrate complex in these reactions. 

(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 (16%) 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 65%.


of pure, syrpy α-D-ribofuranoside 4: \([\text{a}]_D^{20} +111.9^\circ\) (c 1.2, MeOH); \(R_f\) 0.40 (solvent C; IR (film) 3500 (sh) and 3500 (br), (OH), 2920, 2860, 1595, 1487, 1403, 1010–1130 (br), 852, 800 cm\(^{-1}\)); \(^1\)H NMR (60 MHz, CDCl\(_3\)) \(\delta\) 3.48 (m and 3.51 (s (5, H-5A,5B, OCH\(_3\)), 3.80 (dd (1, H, J\(_{4,5A}\) = 7 Hz, J\(_{4,5B}\) = 3.5 Hz, H-3)), 4.22 (m, 2, H-5A,5B), 4.67 (AB, 2 H) (2-OCH\(_2\)OH), 4.86 (dd (1, H, J\(_{1,2}\) = 4.5 Hz, H-1)), 7.57 (s, 8, H-2), 2, CH\(_2\)), 31C NMR (20 MHz) 102.9 (C-1). Anal. Calcd for C\(_9\)H\(_{18}\)O\(_4\): C, 54.81; H, 4.83; 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 0.240 g (60%) of pure 9: mp 73.4–73.5°C (lit. 75–75°C); \([\text{a}]_D^{20} +94.9^\circ\) (c 0.77, CHCl\(_3\)) (lit.\(^{[4]}\) \([\text{a}]_D^{20} +100^\circ\) (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 solution of 11 (0.65 g) in 6 mL of dry THF at room temperature. The residue was submitted to flash chromatography (solvent G), which afforded 0.65 g (77% from 11), syrup; \([\text{a}]_D^{20} +29.8^\circ\) (c 1.1, CHCl\(_3\)); \(R_f\) 0.75 (solvent F; IR (film) 3050, 2900, 2860, 1600, 1490, 1465, 1410, 1360, 1190, 1090, 1060, 1010, 945, 840, 800 cm\(^{-1}\)); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 3.39 (s, 3, H, OCH\(_3\)), 3.60 (M, 2, H-5A,5B), 3.86 (s, 3, H, OCH\(_3\)), 3.90 (dd (1, H, J\(_{1,2}\) = 7.1 Hz, H-1)), 4.11 (q, 1, H-4, 4.53 and 4.43 (2 d, 2 H, J\(_{1,2}\) = 12.2 Hz, OCH\(_3\)), 4.27 and 4.25 (2 H, J\(_{1,2}\) = 12.2 Hz, OCH\(_3\)), 5.23 (d, 1, H, J\(_{1,2}\) = 0.5 Hz, H-2), 6.05 (s, 1, H-1), 7.11–7.25 (m, 8, H, 2, C\(_6\)H\(_5\)).

An analysis of crystallization of α-galactose 5 was anomerized by treatment with trichloroacetonitrile (1 equiv) in CH\(_2\)Cl\(_2\) at -78°C for 2 min, then quenched 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): syrpy \(\delta\) \(\text{[a]}_D^{20} +23.8^\circ\) (c 1.96, CHCl\(_3\)), \(R_f\) 0.40 (solvent C; IR (film) 3290, 2870, 1760 (C=O), 1600, 1495, 1365, 1255, 1100, 1085 (br), 1095, 895 (c 1.93, CHCl\(_3\)); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 2.10 (s, 3, H, OCH\(_3\)), 3.27 (dd (1, H, J\(_{4,5A}\) = 4.2 Hz, J\(_{4,5B}\) = 10.5 Hz, H-5A), 3.37 (dd (1, H, J\(_{4,5A}\) = 3.9 Hz, H-5B), 3.38 (s, 3, H, OCH\(_3\)), 3.90 (dd (1, H, J\(_{1,2}\) = 7.1 Hz, H-1)), 4.11 (q, 1, H-4, 4.53 and 4.43 (2 d, 2 H, J\(_{1,2}\) = 12.2 Hz, OCH\(_3\)), 4.35 and 4.54 (2, 2 H, J\(_{1,2}\) = 12.7 Hz, OCH\(_3\)), 4.80 (dd (1, H, J\(_{1,2}\) = 4.6 Hz, H-2), 5.05 (d, 1, H, J\(_{1,2}\) = 7.10–7.26 (m, 8, H, 2, CH\(_2\)).

A sample of acetylated α-galactose 5 was anomerized by treatment with trichloroacetonitrile (1 equiv) in CH\(_2\)Cl\(_2\) at -78°C for 2 min, then quenched 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): syrpy \(\delta\) \(\text{[a]}_D^{20} +23.8^\circ\) (c 1.96, CHCl\(_3\)), \(R_f\) 0.40 (solvent C; IR (film) 3290, 2870, 1760 (C=O), 1600, 1495, 1365, 1255, 1100, 1085 (br), 1095, 895 (c 1.93, CHCl\(_3\)); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 2.10 (s, 3, H, OCH\(_3\)), 3.27 (dd (1, H, J\(_{4,5A}\) = 4.2 Hz, J\(_{4,5B}\) = 10.5 Hz, H-5A), 3.37 (dd (1, H, J\(_{4,5A}\) = 3.9 Hz, H-5B), 3.38 (s, 3, H, OCH\(_3\)), 3.90 (dd (1, H, J\(_{1,2}\) = 7.1 Hz, H-1)), 4.11 (q, 1, H-4, 4.53 and 4.43 (2 d, 2 H, J\(_{1,2}\) = 12.2 Hz, OCH\(_3\)), 4.35 and 4.54 (2, 2 H, J\(_{1,2}\) = 12.7 Hz, OCH\(_3\)), 4.80 (dd (1, H, J\(_{1,2}\) = 4.6 Hz, H-2), 5.05 (d, 1, H, J\(_{1,2}\) = 7.10–7.26 (m, 8, H, 2, CH\(_2\)).
... 379 (1) and 381 (0.7) (M⁺ – C₇H₆Cl'), 504 (0.5) and 506 (0.4) (M⁺). Anal. Calcd for C₃₇H₂₃ClO₄: 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 (2): recrystallized from ether–hexane; mp 87–88°C; [α]D₂₅ +108.0 (c 1.8, CHC₁₇); Rr 0.25 (solvent F); recrystallized from ether–hexane; mp 87-88°C, 77 (3), 90 (3), 128 (12): recrystallized from ether-hexane; mp 87-88°C.

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 labile to cleavage and reaction with DNA bases.1 We have discovered that aromatic hydroxylamines react with acetyl cyanide to afford in almost quantitative yield the O-acylated derivatives: of obvious interest in carcinogenesis. More recently it became possible to observe directly,4 by using 1H and 13C 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.

Results and Discussion

When 15N-labeled 1a is mixed with 2 at 215 K in acetonitrile solution of 50% (v/v) CDC1₃/CDCN: (a) at 215 K immediately after mixing, corresponding to formation of 4c; (b) warming to 285 K, corresponding to 3c; (c) recolling to 215 K, showing the presence of both 3c and 4c. Key carbon atoms referred to in the text are indicated by an asterisk. Peaks at δ 77.0 and 31.0 are due to CDC1₃ and MeOCOCN, respectively.

Scheme I

Ar

Figure 1. 13C NMR spectra at 62.93 MHz for the reaction between 2 and 1c in 50% (v/v) CDC1₃/CDCN: (a) at 215 K immediately after mixing, corresponding to formation of 4c; (b) warming to 285 K, corresponding to 3c; (c) recolling to 215 K, showing the presence of both 3c and 4c. Key carbon atoms referred to in the text are indicated by an asterisk. Peaks at δ 77.0 and 31.0 are due to CDC1₃ and MeOCOCN, respectively.