"A NEW AND NOVEL APPROACH TOWARDS THE SYNTHESIS OF 3'-DEOXY-3'-HYDROXYMETHYL RIBOFURANOSIDES"

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Summary: The synthesis of 1,2,5 tri-O-benzoyl-3-deoxy-3-[[(benzyloxy)methyl]-α,β-D-ribofuranose (1) from 1,2-O-isopropylidene-α-D-xylofuranose (2) has been achieved in an overall yield of 37%. Compound 1 is a properly substituted intermediate for the synthesis of novel 3'-"branched" nucleoside analogs.

3'-Deoxy-3'-hydroxymethyl ribofuranosides (3'-branched nucleosides) are a known class of compounds, but there has been a paucity of reports regarding synthetic approaches for the preparation of these analogs. To the best of our knowledge, only the 3'-branched analog of adenosine (10) is known. This nucleoside (10) was synthesized and evaluated for its potential as an antitumor agent. A renewed interest in this specific class of compounds has been generated by the close structural similarity of the 3'-hydroxymethyl sugar moiety of this branched nucleoside to some recently developed antiviral agents such as 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG) and oxetanocin. Antiviral agents that exhibit anti-HIV activity such as AZT, ddT, and ddA seem to be dependent upon sugar ring conformation and also the polarity of the 3'-substituent (as indicated by the inactivity of 2',3'-dideoxy-3' cyanothymidine (CNT)). It was envisioned that substitution of the hydroxyl group at the 3'-position of ribose with an hydroxymethyl group may satisfy both the apparent 3'-exo sugar ring conformation and the polarity requirements. Although the methodology for the synthesis of these branched nucleosides had been previously reported, it was obvious that a new and more efficient synthetic route would
facilitate research in this area. This prompted us to initiate studies designed for the facile synthesis of a properly substituted sugar amenable to a glycosylation of appropriate aglycones.

Commercially available 1,2-\(\beta\)-isopropylidene-\(\alpha\)-D-xylofuranose\(^6\) (2) served as our starting material and was selectively monobenzoylated (pyridine/\(\text{CH}_2\text{Cl}_2\), 1/4, BzCl, room temp., 12 h, 93\%) at the primary hydroxyl group to yield 5-\(\beta\)-benzoyl-1,2-\(\beta\)-isopropylidene-\(\alpha\)-D-xylofuranose (3). Oxidation of the remaining 3-hydroxyl group in refluxing \(\text{CH}_2\text{Cl}_2\)^7 (PDC, Ac"O, 2 h, 81\%) provided 5-\(\beta\)-benzoyl-1,2-\(\beta\)-isopropylidene-\(\alpha\)-D-ribofuranos-3-ulose (4). Treatment of 4 with the Wittig salt of benzyloxymethylchloro ether \(^5\)\(^8\) furnished 5-\(\beta\)-benzoyl-1,2-\(\beta\)-isopropylidene-3-C-[(benzxyloxy)methylene]-\(\alpha\)-D-ribofuranose (6) (\(n\)-BuLi, THF, \(-40^\circ\text{C}, 80\%\)) and subsequent reduction of the vinyl group with 5\% Pd/C (EtOH, 50 psi \(\text{H}_2\), 4 h, 91\%) yielded 5-\(\beta\)-benzoyl-3-deoxy-3-[(benzxyloxy)methylene]-1,2-\(\beta\)-isopropylidene-\(\alpha\)-D-ribofuranose (7). The presence of the isopropylidene group on the \(\alpha\)-face served to effectively block the catalyst access to this face assuring hydrogen delivery to the \(\beta\)-face resulting in a steroselective reduction. Orientation of the benzyloxymethyl substituent of 7 was confirmed by \(^1\text{H}\) NMR techniques. The coupling constants \(J_{1,2}=3.7\) Hz and \(J_{2,3}=4.8\) Hz indicated an all \(\text{cis}\) relationship of H-1, H-2, and H-3\(^9\) with further proof being provided by NOE experiments. Irradiation of H-3 resulted in an enhancement of the C-2 proton resonance further indicating a \(\text{cis}\) relationship between these two protons. Similarly, irradiation of H-2 resulted in an enhancement of H-1 and H-3.

Finally, removal of the isopropylidene group under acidic conditions (1N HCl, dioxane, 3 h, 70\%) provided 5-\(\beta\)-benzoyl-3-deoxy-3-[(benzxyloxy)methylene]-\(\alpha\),\(\beta\)-D-ribofuranose (8) which was benzoylated (pyridine, BzCl, room temp., 90 min, 95\%) to furnish an \(\alpha\):\(\beta\) anomic mixture\(^10\) (2:3) of 1,2,5-tri-\(\beta\)-benzoyl-3-deoxy-3-[(benzxyloxy)methylene]-\(\alpha\),\(\beta\)-D-ribofuranose (11). To demonstrate the utility of 11, the anomic mixture was subjected to a Vorbruggen-type glycosylation\(^11\) with 6-chloropurine to yield 9-[(3'-deoxy-3'-(benzxyloxy)methylene]-2,5-di-\(\beta\)-benzoyl-\(\beta\)-D-ribofuranosyl]-6-chloropurine (9). Anomeric purity of 9 was provided by the \(^1\text{H}\) NMR spectrum. The resonance corresponding to the anomeric proton appeared as a singlet indicating that only the \(\beta\)-anomer was present. The absence of any detectable amount of the \(\alpha\)-anomer was not surprising due to the well-known neighboring group participatory effect of the 2'-acyl group. Compound 9 was then converted into the known branched adenosine analog (10) in two steps by a removal of the benzyl group (\(\text{BCl}_3\), \(-40^\circ\), \(\text{CH}_2\text{Cl}_2\), 85\%) followed by a removal of the benzoyl groups and concurrent ammination by treatment with methanolic ammonia (100\%, 3.5 h, 73\%). This provided a product with spectral data (UV, \(^1\text{H}\) NMR) identical to the data reported by Rosenthal\(^1\).
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REFERENCES

6) Obtained from Pfansteihl, Waukegan, IL, I-105.

10) \( ^1 \text{H NMR} \)

\( \delta \) (CDCl\(_3\)) 3.14 (m, 1.7 H, H-3); 3.75-3.94 (m, 3.4 H, C-3-CH\(_2\)); 4.48-4.80 (m, 8.5 H, H-4, Bn, H-5)
5.80 (t, 0.7 H, H-2 \( \alpha \)); 5.85 (d, 1 H, H-2 \( \beta \)); 6.57 (s, 1 H, H-1 \( \beta \)); 6.89 (d, 0.7 H, H-1 \( \alpha \)); 7.28-8.17 (m, 34 H, Bz).

\( \delta \) (CDCl\(_3\)) 1.38 (s, 3 H, CH\(_3\)); 1.53 (s, 3 H, CH\(_3\)); 4.50-4.67 (m, 2 H, H-5); 4.84 (dd, 2 H, Bn); 5.01 (d, 1 H, H-2); 4.25 (bs, 1 H, H-4); 5.91 (d, J=4.1 Hz, 1 H, H-1); 6.51 (s, 1 H, H-3'); 7.27-8.02 (complex, 10 H, Bn, Bz).

\( \delta \) (CDCl\(_3\)) 1.34 (s, 3 H, CH\(_3\)); 1.51 (s, 3 H, CH\(_3\)); 2.35 (m, 1 H, H-3); 3.62 (dd, 1 H, H-3'); 3.84 (dd, 1 H, H-3'); 4.24-4.36 (m, 2 H, H-4, 5); 4.54 (s, 2 H, Bn); 4.68-4.77 (m, 2 H, H-2, 5); 5.87 (d, J=3.7 Hz, 1 H, H-1); 7.27-8.07 (complex, 11 H, Bn, Bz).

\( \delta \) (DMSO-\( d_6 \)) 2.47 (m, 1 H, H-3); 3.51 (dd, 1 H, H-3'); 3.73 (dd, 1 H, H-3'); 3.92 (t, J=4.5 Hz, 1 H, H-2); 4.07-4.25 (m, 2 H, H-4, 5); 4.47 (dd, 2 H, Bn); 5.01 (d, J=4.5 Hz, 1 H, H-1); 5.12 (d, 1 H, D\(_2\)O exchangeable, 2-OH); 6.30 (d, 1 H, D\(_2\)O, exchangeable, 1-OH); 7.24-8.00 (complex, 10 H, Bn, Bz).

11) The heterocycle (6-chloropurine, 0.93 g, 6.01 mmol) was suspended in MeCN (20 mL) and heated to 80°C (external). BSA (2.0 mL, 8.1 mmol) was added and the solution stirred for 30 min. Compound \( 8 \) (2.85 g, 5.03 mmol) in MeCN (2 mL) and TMSTf (2.9 mL, 15 mmol) was added to this solution. The reaction mixture was then stirred for 60 min., cooled, and worked up to provide \( 2 \) (2.36 g, 78%).

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