Tetrahedron Letters, Vol.31, No.22, pp 3101-3104, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

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

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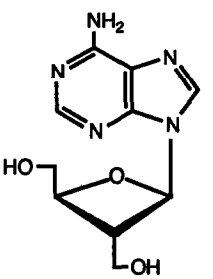
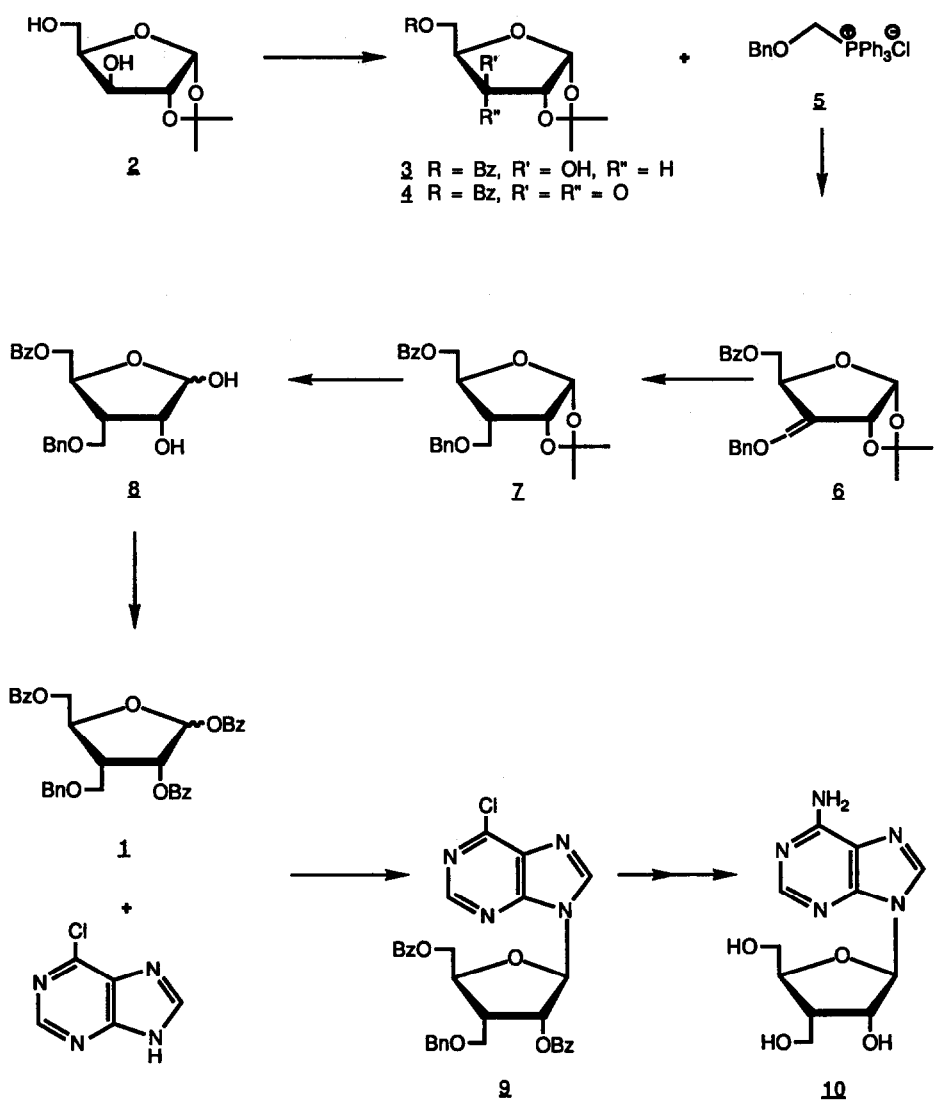
Summary: The synthesis of 1,2,5 tri-O-benzoyl-3-deoxy-3-[(benzyloxy)methyl]-α,β-D-ribofuranose (1) from 1,2-O-isopropylidene-α-D-xylofuranose (2) has been achieved in an overall yield of 37%. Compound 1 is a properly substituted intermediate for the synthesis of novel 3'-"branched" nucleoside analogs.

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.[1] 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



Oxetanocin

branched nucleoside to some recently developed antiviral agents such as 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine (DHPG) and oxetanocin.[2] Antiviral agents that exhibit anti-HIV activity such as AZT, ddT, and ddA seem to be dependent upon sugar ring conformation[3,4] and also the polarity of the 3'-substituent (as indicated by the inactivity of 2',3'-dideoxy-3' cyanothymidine (CNT)[5]). 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[1], it was obvious that a new and more efficient synthetic route would


HO
OH
O
O
2
RO
R'
R"
3 R = Bz, R' = OH, R" = H
4 R = Bz, R' = R" = O
BnO
PPh3Cl
5
BzO
BnO
6
7
8
OH
1
OBz
Cl
N
H
9
NH2
HO
10

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-O-isopropylidene-α-D-xylofuranose[6] (2) served as our starting material and was selectively monobenzoylated (pyridine/CH_2Cl_2, 1/4, BzCl, room temp., 12 h, 93%) at the primary hydroxyl group to yield 5-O-benzoyl-1,2-O-isopropylidene-α-D-xylofuranose (3). Oxidation of the remaining 3-hydroxyl group in refluxing CH_2Cl_2[7] (PDC, Ac_2O, 2 h, 81%) provided 5-O-benzoyl-1,2-O-isopropylidene-α-D-ribofuranos-3-ulose (4). Treatment of 4 with the Wittig salt of benzyloxymethylchloro ether (5)[8] furnished 5-O-benzoyl-1,2-O-isopropylidene-3-C-[(benzyloxy)methylene]-α-D-ribofuranose (6) (*n*-BuLi, THF, -40°C, 80%) and subsequent reduction of the vinyl group with 5% Pd/C (EtOH, 50 psi H_2, 4 h, 91%) yielded 5-O-benzoyl-3-deoxy-3-[(benzyloxy)methyl]-1,2-O-isopropylidene-α-D-ribofuranose (7). The presence of the isopropylidene group on the α-face served to effectively block the catalyst access to this face assuring hydrogen delivery to the β-face resulting in a stereoselective reduction. Orientation of the benzyloxymethyl substituent of 7 was confirmed by ^1H NMR techniques. The coupling constants $J_{1,2}$=3.7 Hz and $J_{2,3}$=4.8 Hz indicated an all 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 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-O-benzoyl-3-deoxy-3-[(benzyloxy)methyl]-α,β-D-ribofuranose (8) which was benzoylated (pyridine, BzCl, room temp., 90 min, 95%) to furnish an α:β anomeric mixture[10] (2:3) of 1,2,5-tri-O-benzoyl-3-deoxy-3-[(benzyloxy)methyl]-α,β-D-ribofuranose (1). To demonstrate the utility of 1, the anomeric mixture was subjected to a Vorbruggen-type glycosylation[11] with 6-chloropurine to yield 9-[3'-deoxy-3'-[(benzyloxy)methyl]-2,5-di-O-benzoyl-β-D-ribofuranosyl]-6-chloropurine (9). Anomeric purity of 9 was provided by the ^1H NMR spectrum. The resonance corresponding to the anomeric proton appeared as a singlet indicating that only the β-anomer was present. The absence of any detectable amount of the α-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 (BCl_3, -40°, CH_2Cl_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, ^1H NMR) identical to the data reported by Rosenthal[1].

Acknowledgement: This research was supported by funds from the Department of Health and Human Services research grant number NO1-AI-25739 and the National Institutes of Health Training grant number 5-T32-GM-07767. We would also like to thank Ms. Rae Miller for her expert preparation of this manuscript.

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10) ^{1}H NMR

1: ($CDCl_3$) δ 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 α); 5.85 (d, 1 H, H-2 β); 6.57 (s, 1 H, H-1 β); 6.89 (d, 0.7 H; H-1 α); 7.28-8.17 (m, 34 H, Bz).

6: ($CDCl_3$) δ 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).

7: ($CDCl_3$) δ 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, 1 H, Bn, Bz).

8: (DMSO-d_6) δ 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_2O exchangeable, 2-OH); 6.30 (d, 1 H, D_2O, 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 9 (2.36 g, 78%).

(Received in USA 9 February 1990)