Tetrahedron Letters No. 50, pp 4413 - 4416, 1977. Pergamon Press. Printed in Great Britain.

STEREOSPECIFIC SYNTHESIS OF (6R)- AND (6S)-[6-$^{2}H_{1}$]-D-GLUCOSES

Katsumi Kakinuma
Laboratory of Chemistry for Natural Products
Tokyo Institute of Technology
Nagatsudacho, Midori-ku, Yokohama 227, Japan

(Received in Japan 21 September 1977; received in UK for publication 20 October 1977)

Although carbohydrate metabolisms have been well studied and importance of carbohydrates as precursors of various natural products is widely understood, little attention has been paid from the stereochemical viewpoints for the fates of a prochiral hydroxymethyl group of D-glucose or other carbohydrates in biological systems. To facilitate the stereochemical studies on the enzyme reactions, it is desirable to use stereospecifically labeled carbohydrates with hydrogen isotopes (^{2}H and/or ^{3}H) on the hydroxymethyl group.[1] So far, carbohydrates containing a chiral hydroxymethyl group have been prepared only by enzymic procedures, e.g. D-glucose with a hydrogen isotope on C-1 can be converted by phosphoglucose isomerase to D-fructose labeled in a stereospecific manner at the C-1 hydroxymethyl group,[2] which is further manipulated to various compounds such as phosphoenolpyruvate, dihydroxyacetone phosphate, etc., by glycolytic enzymes.[3]

This communication describes, to the best of author's knowledge, the first chemical synthesis of D-glucose having the stereospecifically labeled chiral hydroxymethyl group, which posseses high usefulness and generality for preparation of quantities of such carbohydrate derivatives to provide a new tool for studies of the stereochemistry of carbohydrate metabolisms.

An aldehyde 1, prepared by known methods from D-glucose, was converted to 3-O-benzyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose 2, $[\alpha]_{D}^{24}$ -50.8° (c 1.0, $CHCl_3$), $\delta_{CDCl_3}^{TMS}$ 1.34 (3H, s), 1.52 (3H, s), 4.02 (1H d, J=3.2 Hz, H-3), 4.58 (1H d, J=4.0 Hz, H-2), 4.50 (1H d, J=13 Hz), 4.64 (1H d, J=13 Hz), 4.78 (1H dd, J=3.2 and 8.0 Hz, H-4), 5.92 (1H d, J=4.0 Hz, H-1), 6.66 (1H d, J=8.0 Hz, H-5) and 7.36 (5H, br.s), in 91 % yield by a method of Corey et al,[4] as shown in the Scheme. The dibromoolefin 2 was then treated with n-butyllithium in THF at -75°C, followed by quenching an intermedial acetylide with $^{2}H_{2}O$, to afford in 56 % yield an acetylene, [6-$^{2}H_{1}$]-3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-ynofuranose 3,[5,6] $[\alpha]_{D}^{25}$ +7.0° (c 1.0, $CHCl_3$), ν_{max}^{neat} 2650, 1980 cm^{-1} ($^{2}HC{\equiv}C$-), $\delta_{CDCl_3}^{TMS}$ 1.30 (3H, s), 1.47 (3H, s), 4.00 (1H d, J= 3.2 Hz, H-3), 4.59 (1H d, J=3.8 Hz, H-2), 4.73 (1H d, J=12 hz), 4.81 (1H d, J=12 Hz), 4.83 (1H d, J=3.2 Hz, H-4), 5.98 (1H d, J=3.8 Hz, H-1) and 7.35 (5H, br.s). During this reaction, a competitive deprotonation at the benzylic methylene group took place, though the stoichiometric amount of the base was used, and the anion formed was attacked by n-butyl bromide generated by the initial lithioolefin formation to give a minor product 4, M^{+}-15: m/e 316, $C_6H_5(C_4H_9)CH^{+}$: m/e 147, ν_{max}^{neat} 2650, 1980 cm^{-1}, $\delta_{CDCl_3}^{TMS}$ 0.83 (3H t, J=7 Hz), 1.34 (3H, s), 1.43 (3H, s), 1.20-1.90 (6H, m), 3.80 (1H d, J=3.5 Hz, H-3), 4.40 (1H dd, J=5.6 and 7.5 Hz, benzylic methine), 4.60 (1H d, J= 3.8 Hz, H-2), 4.73 (1H d, J=3.5 Hz, H-4), 6.01 (1H d, J=3.8 Hz, H-1) and 7.36 (5H, m).

The deuteroacetylene 3 was stereospecifically reduced by $Cr^{II}SO_4$ in aq. DMF to give only a trans-olefin, [6-$^2H_1$]-3-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose 5, $[\alpha]_D^{25}$ -66.5° (c 1.3, $CHCl_3$), $\delta_{CDCl_3}^{TMS}$ 1.32 (3H, s), 1.50 (3H, s), 3.89 (1H d, J=3.0 Hz, H-3), 4.56 (1H d, J=12 Hz), 4.64 (1H dd, J=3.0 and 7.0 Hz, H-4), 4.64 (1H d, J=3.8 Hz, H-2), 4.65 (1H d, J=12 Hz), 5.42 (1H d, J=17 Hz, H-6), 5.96 (1H d, J=3.8 Hz, H-1), 6.00 (1H dd, J=7.0 and 17 Hz, H-5) and 7.32 (5H, br.s), in 47 % yield.[7] No cis-olefin was detected by pmr analysis. The n-butylated acetylene 4 was little reduced by this method to a corresponding trans-olefin, since the reduction requires a both-side attack of the metal ligands to the acetylenic bond which is sterically hindered in 4 by the bulky n-butyl group.[7]

An attempt to get a cis-deuteroolefin by catalytic hydrogenation of 3 using Pd-$BaSO_4$ in pyridine resulted in affording an undesidable mixture of cis- and trans-olefins.

To affect trans-dihydroxylation of the double bond, 5 was treated with an excess amount of m-chloroperbenzoic acid to give quantitatively a mixture of (6S)-[6-$^2H_1$]-5,6-anhydro-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose 6a, $[\alpha]_D^{25}$ -48.5° (c 1.06, $CHCl_3$), $\delta_{CDCl_3}^{TMS}$ 1.32 (3H, s), 1.45 (3H, s), 2.76 (1H d, J=2.5 Hz, pro-R H-6), 3.30 (1H dd, J=2.5 and 7.2 Hz, H-5), 3.78 (1H dd, J=3.4 and 7.2 Hz, H-4), 4.09 (1H d, J=3.4 Hz, H-3), 4.65 (1H d, J=3.8 Hz, H-2), 4.66 (1H d, J=12 Hz), 4.73 (1H d, J=12 Hz), 5.96 (1H d, J=3.8 Hz, H-1) and 7.33 (5H, br.s), and an L-ido counterpart 6b in a ratio of 6:5. The deuterium enrichment of 6a was confirmed to be more than 96 % by mass spectrometry.

Chromatographic separation of 6a, followed by hydrolysis with dil. NaOH in aq. dioxane, provided a glycol, (6R)-[6-$^2H_1$]-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose 7a, $[\alpha]_D^{25}$ -38.9° (c 1.08, $CHCl_3$), $\delta_{CDCl_3}^{TMS}$ 1.30 (3H, s), 1.48 (3H, s), 3.23 (2H br.s, D_2O exchangable), 3.77 (1H d, J=3.0 Hz, pro-S H-6), 3.95-4.20 (3H m, H-3, H-4 and H-5), 4.56 (1H d, J=12 Hz), 4.58 (1H d, J=3.9 Hz, H-2), 4.69 (1H d, J=12 Hz), 5.92 (1H d, J=3.9 Hz, H-1) and 7.33 (5H, br.s), in 90 % yield with inversion at C-6 position.

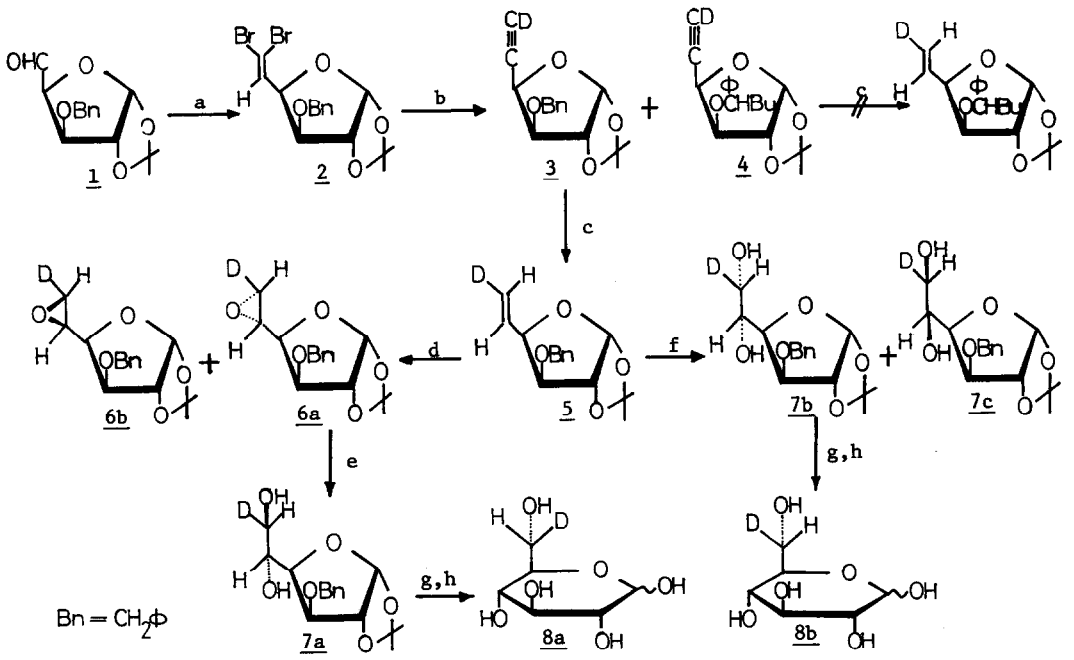
On the other hand, OsO_4 oxidation of 5 gave rise to a cis-glycol, (6S)-[6-$^2H_1$]-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose 7b, $[\alpha]_D^{26}$ -40.2° (c 1.2, $CHCl_3$), $\delta_{CDCl_3}^{TMS}$ 3.66 (1H d, J=4.5 Hz, pro-R H-6), together with very small amount of 7c with L-ido configuration, which were able to be separated chromatographically.

The glycols, 7a and 7b, were converted quantitatively to (6R)-, 8a, and (6S)-[6-$^2H_1$]-D-glucose 8b, respectively, by known procedures of hydrogenolysis and acid hydrolysis.

The L-ido derivatives obtained as by-products may be transformed to the corresponding deuterated D-glucose by conventional displacement reactions.

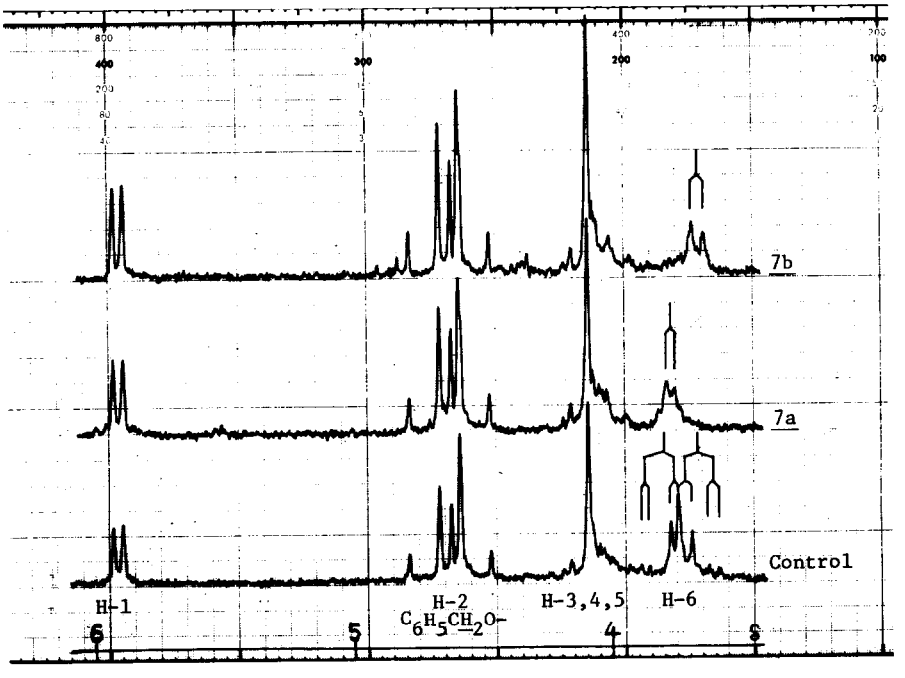
A portion of the pmr spectra of 7a, 7b and the non-labeled control are illustrated in the Figure. A non-deuterated methylene group at C-6 appeares as 8 lines of a part of ABX system, which is reduced to a broad doublet in 7a and 7b, though deuterium is not decoupled, and the coupling constants between H-5 and pro-R H-6 or pro-S H-6 are determined to be 4.5 Hz and 3.0 Hz, respectively. These results are quite consistent with a previous report by Horton et al,[8] in which, an unseparable diastereoisomeric mixture of 6-monodeutero derivatives of D-glucose was

Scheme



Reagents : a, CBr_4, $(C_6H_5)_3P$, Zn ; b, n-BuLi, ^2H_2O ; c, $Cr^{II}SO_4$; d, MCPBA ; e, NaOH ; f, OsO_4 ; g, H_2/Pd-C ; h, aq. AcOH.

Figure



obtained by $NaBD_4$ reduction of a 6-aldehyde intermediate prepared by photolysis of a 6-azido-6-deoxy-D-glucose derivative.

As a result, it now becomes possible to differentiate unambiguously the hydrogens on C-6 of D-glucose and derivatives thereof. Furthermore, since D-erythrose can be prepared from D-glucose in a few steps,[9] the above synthesis constitutes a synthesis of (4S)- and (4R)-[4-$^2H_1$]-D-erythrose. D-erythrose is known to be a precursor of shikimic acid biosynthesis.

Acknowledgement

A part of this study was supported by a grant from the Ministry of Education.

References

1) J. E. G. Barnett and D. L. Corina "Adv. Carbohyd. Chem. & Biochem." R. S. Tipson and D. Horton Ed., Vol. 27, 127 (1972).

2) I. A. Rose and F. L. O. O'Connell, Biochem. Biophs. Acta, 42, 159 (1960).

3) H. G. Floss, D. K. Onderka and M. Carroll, J. Biol. Chem., 247, 736 (1972); M. C. Summers and I. A. Rose, J. Am. Chem. Soc., 99, 4475 (1977).

4) E. J. Corey and P. L. Fuchs., Tetrahedron Lett., 1972, 3769.

5) Similarly, hydrolysis of the lithium acetylide with H_2O gave a non-deuterated acetylene, ν_{max}^{neat} 3280 cm^{-1}, $\delta_{CDCl_3}^{TMS}$ 2.60 (1H d, J=2.0 Hz, acetylenic H-6).[6]

6) J. M. J. Tronchet, A. Gonzalez, J. B. Zumwald and F. Perret, Helv. Chim. Acta, 57, 1505 (1974).

7) C. E. Castro and R. D. Stephens, J. Am. Chem. Soc., 86, 4358 (1964).

8) D. Gagnaire, D. Horton and F. R. Taravel, Carbohyd. Res., 27, 363 (1973).

9) A. S. Perlin "Methods Carbohyd. Chem." R. L. Whistler and M. L. Wolfrom Ed., Vol. I, 64 (1962).