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A SIMPLE SYNTHESIS OF (*1R* and *1S*)-[1-$^{2}H_{1}$]-1,5-ANHYDRO-D-GLUCITOL AND [1-$^{2}H_{2}$]-1,5-ANHYDRO-D-GLUCITOL

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As a basic study of metabolism of 1,5-anhydro-D-glucitol, which has recently been identified in both human cerebrospinal fluid and plasma, the title compounds were conveniently synthesized as preliminary targets not only for multideuteration but for tritium labelling.

1,5-Anhydro-D-glucitol 1 (poligalitol), which had been known as a component of some plants,[1] has recently been recognized in human cerebrospinal fluid[2] from diabetic and uremic patients as well as in human plasma[3] from healthy persons of various ages. In a very recent paper,[4] Yoshioka and his coworkers suggested that this minor sugar might be a candidate of metabolic indexes for insulin-dependent diabetes mellitus.

These facts, therefore, drove us to prepare both cold and hot labelled derivatives of 1 for the purpose of clarifing the unknown metabolism of this sugar.

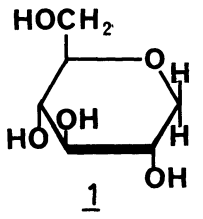
In the present communication, we wish to describe simple and versatile, mono- and dideuteration at C-1 of 1 as a preliminary synthesis not only for multideuteration but for tritium introduction into 1.

(*1S*)-[1-$^{2}H_{1}$]-1,5-Anhydro-D-glucitol 3a was first of all prepared as follows (Scheme 1) : 2,3,4,6-tetra-*o*-acetyl-α-D-glucopyranosyl bromide 2 was reduced with excess amount of lithium aluminum deuteride (LAD) in dry ether to yield 3a [mp 143-144 °C, $[\alpha]_{D}^{13}$ +39.0° (c 1.0, H_2O)] stereospecifically in a good yield. The stereochemistry of 3a was unambiguously demonstrated from the analysis of ^{1}H-NMR of the corresponding tetraacetate 3b [syrup, $[\alpha]_{D}^{13}$ +38.8° (c 1.0, $CHCl_3$)] : H_1 equatorial

proton at 4.15 ppm disappeared and a doublet of H_1 axial proton ($J_{1,2}$ =10.9 Hz) at 3.30 ppm was observed.

Interestingly, in the case of reduction of 2 with equimolar amount of tributyltin deuteride in refluxing benzene, retention of stereochemistry at C-1 was predominantly confirmed and the ratio of *1R* and *1S* derivatives was estimated to be ca. 5 : 1 from the integral curve of the NMR.

On the other hand, we tried an alternative route to get *1S* derivative 3a in order to economize mainly LAD : 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride[5] 5 was reduced with equimolar amount of LAD in a similar manner described as above to give (*1S*)-[1-$^2H_1$]-2,3,4,6-tetra-*O*-benzyl-1,5-anhydro-D-glucitol 6 [syrup, $[\alpha]_D^9$ +7.2° (c 0.87, $CHCl_3$)] in a 64% yield. Hydrogenolysis of 6 in the presence of Pd/C (10%) was effected in acetic acid to give 3a in 84% yield. As for the total yields of 3a from D-glucose, however, the former method was rather better than the latter one requiring longer steps.



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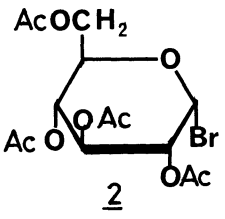

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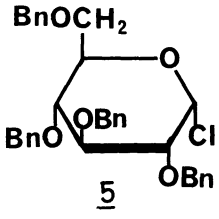

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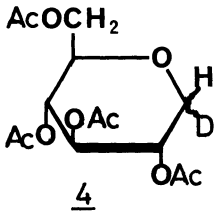

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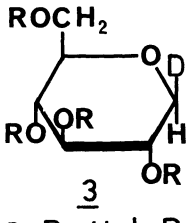

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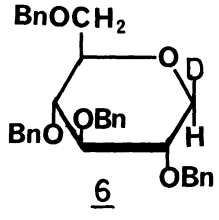
a: R = H, b: R = Ac



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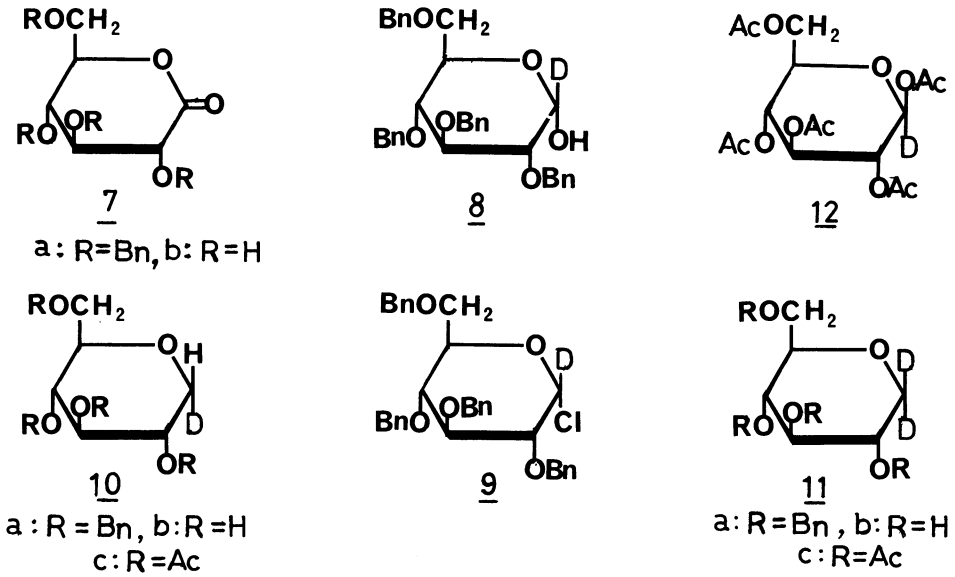
Scheme 1.

The stereospecific synthesis of *1R* derivative 10a was also achieved via different processes shown in the scheme 2 : 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[6] 7a was firstly treated with LAD (10-13 molar amount) in the presence of large amount of borontrifluoride etherate (60 molar amount) in dry ether in an ice-bath to give the corresponding [1-^{2}H]-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose 8 [mp 151-152 °C, $[\alpha]_D^{12}$ +14.0° (c 1.0, $CHCl_3$)][7] in 90% yield. The compound 8 was then chlorinated with methanesulfonyl chloride in 2,4,6-collidine[5] to yield

[1-^{2}H]-2,3,4,6-tetra-*o*-benzyl-α-D-glucopyranosyl chloride 9 which was then promptly treated without purification with lithium aluminum hydride in dry ether to give , stereospecifically the inversion product, (1*R*)-[1-$^2H_1$]-2,3,4,6-tetra-*o*-benzyl-1,5-anhydro-D-glucitol 10a [syrup, $[\alpha]_D^{14}$ +7.5° (c 0.42, $CHCl_3$)] in a yield of 58% from 8. The stereochemistry at C-1 was similarly demonstrated from the analysis of ^{1}H-NMR of the corresponding tetraacetate[8] 10c [syrup, $[\alpha]_D^9$ +40.7° (c 0.87, $CHCl_3$)] obtained from 10a by successive hydrogenation and acetylation processes : H_1 axial proton at 3.30 ppm completely disappeared and a doublet of H_1 equatorial proton at 4.15 ppm ($J_{1,2}$ = 5.6 Hz) was observed.



Scheme 2.

As for 1-$^2H_2$ derivative of 1, a similar reduction of 9 with LAD was conducted in dry ether to yield the corresponding [1-$^2H_2$]-2,3,4,6-tetra-*o*-benzyl-1,5-anhydro-D-glucitol 11a [syrup, $[\alpha]_D^{15}$ +7.0° (c 0.5, $CHCl_3$)] in a 63% yield. Conventional hydrogenation of 11a in the presence of Pd/C (10%) in acetic acid, followed by acetylation with acetic anhydride in pyridine gave tetraacetate 11c [syrup, $[\alpha]_D^9$ +38.5° (c 0.72, $CHCl_3$) in 72% yield from 11a. Double deuteration at C-1 of 1 was clearly confirmed by the ^{1}H-NMR spectrum of 11c, in which both H_1 axial proton at 3.30 ppm and H_1 equatorial proton at 4.15 ppm completely disappeared. ^{13}C-NMR spectrum of 11c also showed the absence of C-1 signal at 66.86 ppm, supporting the result of ^{1}H-NMR. An alternative route to the compound 11b[9] was also successfully effected in the same procedure as was described in the first synthesis of 3a, via [1-^{2}H]-1,2,3,4,6-penta-*o*-acetyl-β-D-glucopyranose 12[10] obtained in two conventional steps (hydrogenation and acetylation) from 8. The total yields of both

routes were comparable with each other.

References

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7) The ^{1}H-NMR spectrum of the monoacetate obtained by acetylation of 8 with acetic anhydride and pyridine indicated disappearence of both axial and equatorial H_1 protons at 5.60 and 6.35 ppm. The both signals were observed in the corresponding light compound, namely, 1-*o*-acetyl-2,3,4,6-tetra-*o*-benzyl-α,β-D-glucopyranose.

8) Deacetylation of 10c with sodium methoxide in methanol or hydrogenolysis of 10a with Pd/C (10%) in acetic acid gave (*1R*)-[1-$^{2}H_1$]-1,5-anhydro-D-glucitol 10b in a good yield ; mp 143-144 °C, $[\alpha]_D^9$ +43.2° (c 1.0, H_2O).

9) Mp 144 °C , $[\alpha]_D^{12}$ +40.5° (c 1.0, H_2O).

10) The compound 12 [mp 131-132 °C, $[\alpha]_D^{14}$ +3.8° (c 1.0, H_2O)] could be independently prepared in a yield of 38% by reducing D-glucono-1,5-lactone 7b with $NaBD_4$ in a range of pH 5-6 and by acetylating the resulting free sugar with acetic anhydride and sodium acetate. The details will be described elsewhere.

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