Carbohydrate Research, 27 (1973) 363–372

DERIVATIVES OF 6-DEUTERIO-D-GLUCOSE, ABSOLUTE CONFIGURATION AT C-6, AND STERIC DISPOSITION OF AN ACETOXYMETHYL GROUP

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(Received October 14th, 1972, accepted November 29th, 1972)

ABSTRACT

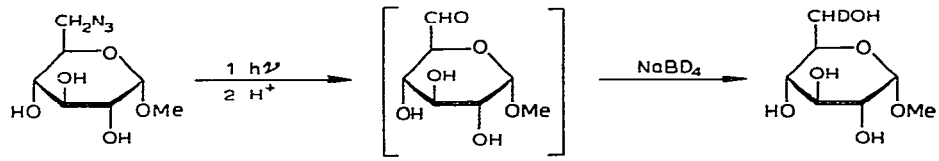
Borodeuteride reduction of methyl D-*gluco*-hexodialdo-1,5-pyranoside (**2**) gave a 3 2 mixture of the 6(*S*) and 6(*R*) methyl 6-deuterio-α-D-glucopyranosides (**3**), converted into other products having the same epimeric distribution at C-6, including the tetraacetate (**5**) of **3**, 6-deuterio-D-glucitol hexaacetate (**6**), 3,5,6-tri-*O*-acetyl-6-deuterio-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**), and methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-6-deuterio-α-D-glucopyranoside (**4**) The deuterium-decoupled p m r spectrum of **4** permitted differentiation of the 6-epimers and assignment of configuration at C-6 for the complete series of derivatives The favored, but not exclusive, disposition of the 5-acetoxymethyl group in compounds **5–7** has the acetoxyl group antiparallel to C-4

INTRODUCTION

The individual assignment of the n m r signals of nonequivalent protons in a methylene group adjacent to an asymmetric center remains a controversial problem In studies of the series of dihydrofurfuryl and tetrahydrofurfuryl alcohols[1], sugar derivatives[2–4], and in nucleoside systems[5], the majority of investigators have resorted to arbitrary assignments based on comparison of values of vicinal coupling with an adjacent proton, some of the interpretations have been contradictory In an elegant synthesis affording ethanol-*1-d* of known absolute configuration, Lemieux and Howard[6] prepared 5-deuterio-β-D-xylopyranose tetraacetate by a route involving reduction of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose with lithium aluminum deuteride, and they showed by p m r spectroscopy that the product contained 65% of the 5(*R*) isomer Perlin and co-workers[7] have recently described the synthesis of specifically 4-deuterated L-threofuranose derivatives In neither study were signal assignments made for a methylene group that is free to rotate

The present study developed from a common interest in our two laboratories in the synthesis of specifically deuterated carbohydrates[8] and in the biosynthesis of deuterated, bacterial cellulose[9]. Work from the Ohio State laboratories[10] has

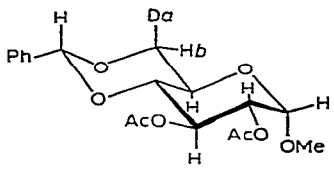
established a simple route, by photolysis of methyl 6-azido-6-deoxy-α-D-glucopyranoside (**1**), to the corresponding 6-aldehyde **2** Reduction of **2** with borodeuteride should afford methyl α-D-glucopyranoside (**3**) monodeuterated at H-6 or H-6′



1 2 3

Inasmuch as this reduction might present some stereoselectivity leading to unequal yields of the 6(*R*) and 6(*S*) isomers, the reaction offered the possibility for unequivocal differentiation of the n m r signals for the two methylenic sites, by conversion of **3** into a fused, bicyclic [4 4 0] system for which the n m r assignments are unambiguous ($J_{ax,ax} \neq J_{eq,ax}$)

This article[11] demonstrates that the reduction of **2** with sodium borodeuteride is indeed stereoselective, giving a 3 2 mixture (**3**) of the 6(*S*) and 6(*R*) monodeuterated derivatives, these were individually differentiated and assigned by examination of the derived mixture (**4**) of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-6-deuterio-α-D-



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glucopyranosides The glycosides **3** provided the starting point for synthesis of regio- and stereo-specifically defined derivatives (including D-glucose, D-glucitol hexaacetate, and 1,2-*O*-isopropylidene-α-D-glucofuranose triacetate) all monodeuterated at C-6 and having the 6(*S*) and 6(*R*) forms present in the ratio of 3 2, and permitted the favored steric disposition of the primary acetoxymethyl group in methyl α-D-glucopyranoside tetraacetate to be determined

DISCUSSION

The procedure already reported[10] for photolytic conversion of the azide **1** into the "aldehyde" **2** (presumably a mixture of hemiacetalic forms) was followed, and the product was reduced with aqueous sodium borodeuteride to give the 6-epimeric methyl 6-deuterio-α-D-glucopyranosides (**3**) The mass spectrum of the tetraacetates (**5**) of **3** (see Experimental) confirmed that a single deuterium atom had been incorporated into the methyl α-D-glucopyranoside molecule.

Benzylidenation of the deuterated glycosides 3 followed by acetylation gave the 6-epimeric methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-6-deuterio-α-D-glucopyranosides (**4**), whose n m r spectrum in benzene-d_6 was analyzed completely by the program T-LAOCOON after deuterium decoupling (to suppress the H–D couplings and thus afford sharp signals for the protons originally coupled with the deuterium atom) That part of the spectrum containing the H-5 and H-6 signals (and also the H-4 pattern) is shown in Fig 1 The spectrum differs from that of its non-deuterated analog[12] in that (*a*) the signals of H-6*b* (signal *b*) and H-6*a* (signal *a*) appeared as doublets instead of 4-line patterns, and (*b*) the integrated intensity for H-6*b* plus H-6*a* totalled one proton instead of two, the proton intensity of the H-5 pattern, which was more complex, remained at unity The H-6*b* signal was of intensity 0 60 proton and showed a spacing $J_{5\ 6b} = 5\ 0$ Hz, and the H-6*a* signal had intensity 0 40 proton and showed a spacing $J_{5,6a} = 11$ Hz, the H-6*b* and H-6*a* signals are separated by 62 Hz and are well separated from the H-5 signal, indicating that the first-order spacings correspond closely to the true coupling-constants

The n m r data for **4** permit the following conclusions (*a*) monodeuteration at C-6 to the extent of >95% had been effected, and there was no detectable incorporation (<5%) of deuterium at C-5, (*b*) the reduction with borodeuteride proceeded stereoselectively, giving 60% of one C-6 epimer and 40% of the other, and (*c*) the major 6-epimer had the (*S*) co figuration at C-6, and the minor 6-epimer, the (*R*) configuration at C-6

The third conclusion follows from the observed spectral integrals and $J_{5\ 6}$ couplings for the H-6 silgnas, and the well established[12 13] *Cl* (D) conformation of the locked, *trans*-decalin type of ring system in derivatives such as **4** The low-field

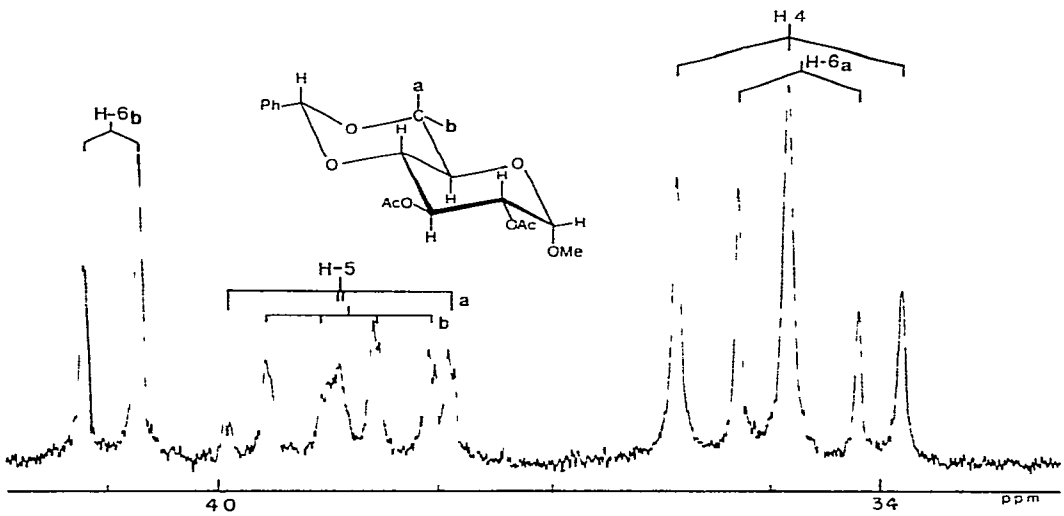
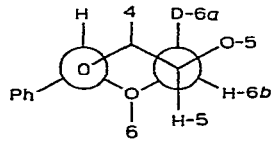
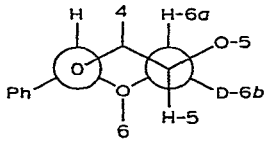


Fig 1 The deuterium-decoupled, 100-MHz n m r spectrum of the mixture 6*R*(a) and 6*S*(b) of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-6-deuterio-α-D-glucopyranoside isomers (**4**) in benzene-d_6, in the region showing the H-4, H-5, and H-6 signals

proton (H*b*) at C-6 shows a small coupling with H-5, and evidently is gauche disposed to H-5, this isomer is preponderant. The high-field proton (H*a*) at C-6 has a large coupling with H-5, and is antiparallel to H-5, this is the minor isomer The conformations of the two isomers may be depicted in the Newman projection as follows



6(*S*) configuration (60%)

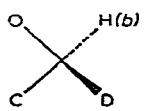


6(*R*) configuration (40%)

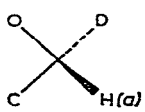
Physical differences arising from isotopic substitution are so slight that separation of these isomers by any physical technique at present available is out of the question (as with the other 6-epimeric pairs reported here), but the two isomers are clearly differentiated by n m r spectroscopy

Fine structure observed in the H-5 signal of compound **4**, a splitting of about 0 6 Hz of each principal peak in the pattern, appears to result from a long-range coupling of H-5, most probably with H-1 This coupling ($J \sim 0$ 6 Hz) is in accord with literature values[14] for a long-distance coupling across four bonds, through an oxygen atom, between an axial and an equatorial proton

From the foregoing results for compound **4**, it was possible to make firm assignments for the individual methylene protons in derivatives, prepared from **4**, in which the methylene group was no longer spatially fixed in a locked, 6-membered ring-system In each example, the major (60%) isomer (protonated at the position designated *b*) is the 6(*S*) form, and the minor (40%) isomer (protonated at the position designated *a*) is the 6(*R*) form

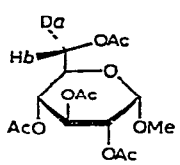


(*S*)



(*R*)

Acetylation of compound **3** gave the 6-epimeric methyl 2,3,4,6-tetra-*O*-acetyl-6-deuterio-α-D-glucopyranosides (**5**) The n m r spectrum of **5** in benzene-d_6 was analyzed completely, and the assignments previously made[12] by proton decoupling with the non-deuterated analog were fully substantiated, notably as concerns the



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independent attribution of the H-3 and H-4 signals, by use of theoretical spectra calculated for 7 spins with the aid of the LAOCOON iteration program The lowest-field signal is that of H-3

That portion of the spectrum of compound **5** showing the H-5 and H-6 signals, under deuterium decoupling, is shown in Fig 2 Again, the result of monodeuteration at C-6 is evident, with the 6-epimers being present in the ratio of 3 2. In this example, the product in which the 6-proton exhibits the larger coupling with H-5 is the major one First-order values show $J_{5\,6b}$ [major product, 6(*S*)] = 4 6 Hz and $J_{5,6a}$ [minor product, 6(*R*)] = 2 4 Hz, the separation of the two H-6 signals is 16.6 Hz Once again, there is evidence of a small (0 6 Hz), long-distance coupling of H-5.

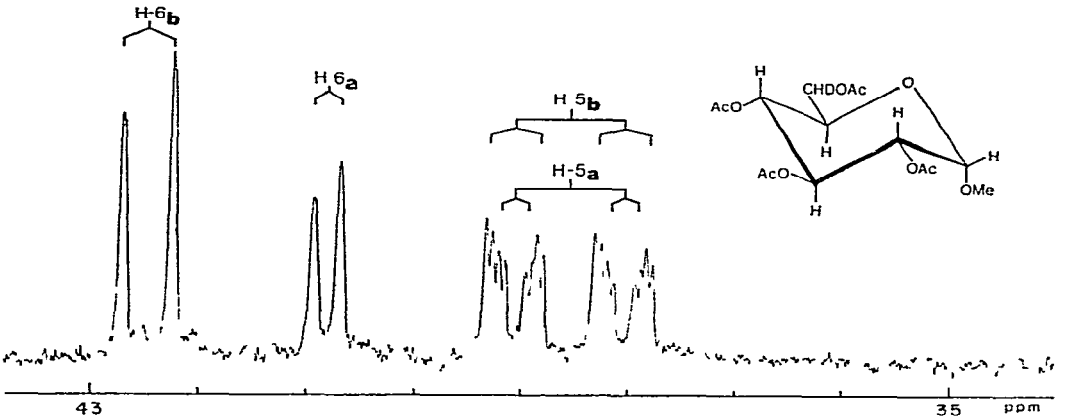
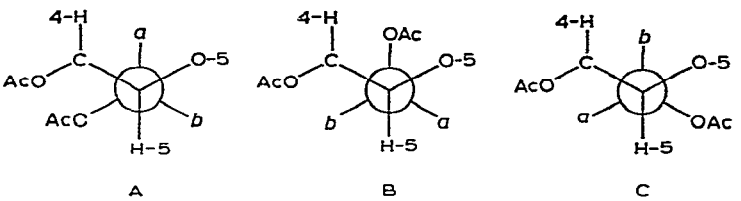


Fig 2 The deuterium-decoupled, 100-MHz n m r spectrum of the mixture 6*R*(a) and 6*S*(b) of methyl 2,3,4,6-tetra-*O*-acetyl-6-deuterio-α-D-glucopyranoside isomers (**5**) in benzene-d_6, in the region showing the H-5 and H-6 signals

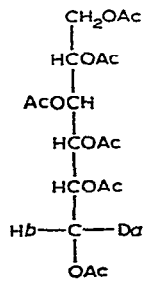
Free rotation about C-5–C-6 in compound **5** allows, in principle, the existence of the three limiting rotamers possible Rotamer A can be excluded as a significant contributor to the conformational population, because of the minimal value (2 4 Hz) of $J_{5\,6a}$; this exclusion would be expected as this rotamer has the acetoxyl groups at



C-4 and C-6 in eclipsed orientation The magnitudes of the couplings observed accord with an equilibrium in which rotamers B and C both contribute significantly; rotamer C has the 6-acetoxyl group antiparallel to C-4, whereas rotamer B has this group bisecting the C-4–O-5 angle The minor, 6(*R*) isomer has the proton at position *a* in

gauche orientation to H-5 in both rotamer B and C, so that $J_{5,6a}$ is small, whereas the major, 6(*S*) isomer, having the proton at position *b*, has the 5- and 6-protons *gauche*-disposed in rotamer B and antiparallel in rotamer C, and the observed $J_{5\ 6b}$ value of 4 6 Hz reflects contributions from the two rotamers

The final two compounds examined were prepared from 6-deuterio-D-glucose by standard reactions Reduction and acetylation gave 6-deuterio-D-glucitol (1-deuterio-L-gulitol) hexaacetate (**6**), whose deuterium-decoupled n m r spectrum



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(see Fig 3) yielded the first-order values $J_{5,6a}$ 3 8 Hz and $J_{5\ 6b}$ 5 8 Hz, the separation

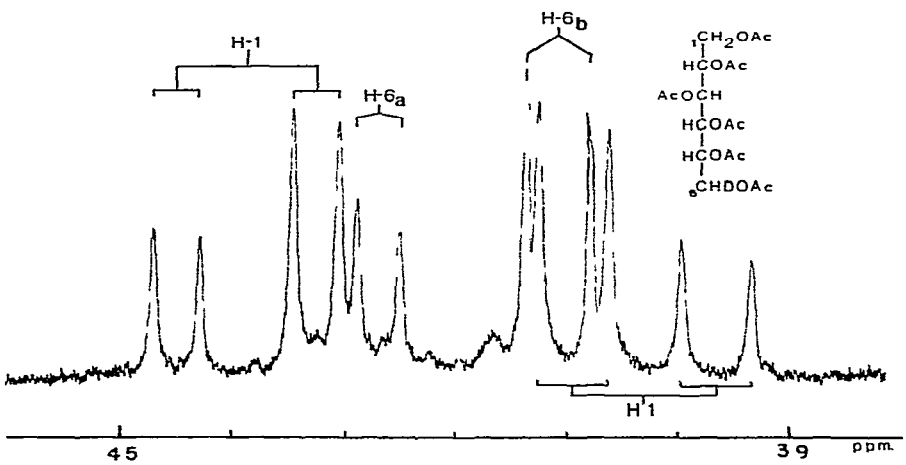
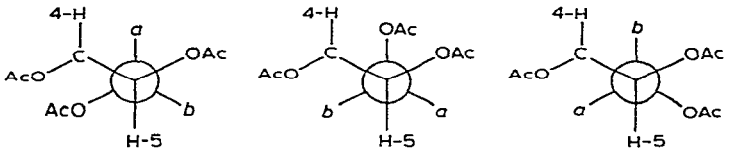


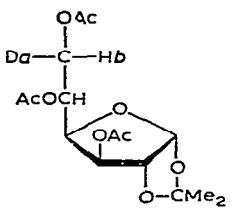
Fig 3 The deuterium-decoupled, 100-MHz n m r spectrum of the mixture 6*R*(a) and 6*S*(b) of 6-deuterio-D-glucitol hexaacetate isomers (**6**) in chloroform-*d*, in the region showing the 1-CH_2 and 6-CHD proton-signals

of the H-6*a* and H-6*b* signals was 16 Hz The major product (*S*) was the form having the larger coupling Three C-5–C-6 rotamers are, in principle, possible Rotamer A can be excluded because of the low value of $J_{5\ 6a}$ This rotamer has a parallel interaction between O-4 and O-6, such interactions are known to be unfavored in alditol acetates[15] and other acyclic sugar systems[16] Rotamer C appears to be the favored,

but not exclusive, rotamer, substantial contribution from rotamer B (having the 6-acetoxyl group bisecting the C-4–OAc-5 angle) is evidently also involved Another possible explanation for the $J_{5\ 6b}$ value observed would be the existence of a favored orientation arising from slight torsional distortion of conformer C



The final example, namely, 3,5,6-tri-*O*-acetyl-6-deuterio-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**), analyzed similarly, showed $J_{5\ 6a}$ 2 5 Hz and $J_{5\ 6b}$ 6 5 Hz, and the H-6*b* signal was 60 Hz upfield of the H-6*a* signal, the 6-epimer having the large



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coupling was preponderant By arguments analogous to those presented for the rotamers about C-5–C-6 of compounds **5** and **6**, rotamer C appears favored, with significant contribution from rotamer B, from conclusions drawn for acyclic systems, rotamer A (in this instance, having the ring-oxygen atom, instead of an acetoxyl group,

TABLE I

P.M R -SPECTRAL PARAMETERS FOR COMPOUNDS **4**, **5**, **6**, AND **7**

Major product [6(S) *configuration*]	*Solvent*	*Chemical shifts* (δ)		*Coupling constants* (*Hz*)	
		H-6b	*H-6a*	$J_{5\ 6b}$	$J_{5\ 6a}$
Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-6-deuterio-α-D-glucopyranoside (**4**)	C_6D_6	4 1	3 48	5 0	11
Methyl 2,3,4,6-tetra-*O*-acetyl-6-deuterio-α-D-gluco-pyranoside (**5**)	C_6D_6	4 25	4 08	4 6	2 4
6-Deuterio-D-glucitol hexa-acetate (**6**)	$CDCl_3$	4 11	4 27	5 8	3 8
3,5,6-Tri-*O*-acetyl-6-deuterio-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**)	C_6D_6	3 95	4 55	6 5	2 5

at C-4) would be disfavored, because of interactions between O-6 and the oxygen atom of the furanose ring

These results, listed in Table I, permit the following conclusions to be made From the stereoselectivity of the reduction of compound **2**, and the spectral analysis of compound **4**, the signals of the proton sites at C-6 are assigned unambiguously for compounds **4**, **5**, **6**, and **7**; the absolute chirality at C-6 of these compounds is likewise established.

These assignments of individual protons in the methylene group of an exocyclic $-CH_2OAc$ group are in accord with those suggested (without evidence from specific deuteration) by Lemieux and Stevens[2] and Horton and coworkers[3], the proposals made by Hall and co-workers[4] are not in accord with these results, and their argument in favor of the overriding influence of an electronegative substituent on a proton antiparallel to it does not appear valid

It may be noted that, in each case, the preponderant isomer shows the larger coupling, except for the fused-ring derivative **4**, for which the reverse is true In the latter compound, free rotation about C-5–C-6 is not possible, and O-4 and O-6 are forced by the ring into a 1,3-parallel orientation The other derivatives, in which free rotation about C-5–C-6 is possible, evidently do not assume this rotameric form

Finally, the structural component –CHOAc–CHDOAc, which is present in compounds **6** and **7** but absent from **4** and **5**, appears to be a factor in determining the relative field-positions of the two protons examined, H-6*a* resonates upfield of H-6*b* for **4** and **5**, and downfield for **6** and **7**

EXPERIMENTAL

Spectra — P m r. spectra were obtained with a Varian HA-100 spectrometer for 10–30% solutions, with tetramethylsilane as the internal reference-standard Deuterium decoupling at the 15 3 MHz irradiating frequency was performed with an "NMR Specialties" HD-60B heteronuclear spin decoupler Observed coupling-constants and chemical shifts may not be definitive values, as calibration of each signal was not performed Exact values of these parameters for the non-deuterated products have been reported[12 15,19], variations through isotopical substitution may be expected to be very minor, but the effect of concentration or of temperature modification may be appreciable, and the temperature of the probe is markedly increased by deuterium irradiation

Mass spectra were recorded with an A E I MS-9 spectrometer.

*Methyl 6-deuterio-α-*D*-glucopyranoside* (**3**) — Following the procedure already described[10], methyl α-D-glucopyranoside was converted, by way of its 6-chloro-6-deoxy and 6-azido-6-deoxy (**1**) analogs, by photolysis and mild hydrolysis, into methyl 6-*aldehydo*-α-D-*gluco*-hexodialdo-1,5-pyranoside (**2**) This product was reduced as described[10], but with sodium borodeuteride instead of sodium borohydride, to give the title compound **3**, isolated crystalline in a yield comparable to that for the non-labeled compound, the material had the same m p and $[\alpha]_D$ as the non-labeled

product Compound **3** was exclusively monodeuterated at C-6, and was a 3 2 mixture of the 6(*S*) and 6(*R*) isomers (see Discussion section)

*Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-6-deuterio-α-*D*-glucopyranoside* (**4**) — By the standard procedure, compound **3** was condensed with benzaldehyde in the presence of zinc chloride, and the crystalline product was acetylated (acetic anhydride–pyridine) to give crystalline **4**, identical by mixed m p. with non-deuterated **4** (see ref 12), it contained the 6(*S*) and 6(*R*) isomers in the ratio of 3 2 (see Discussion section)

*Methyl 2,3,4,6-tetra-*O*-acetyl-6-deuterio-α-*D*-glucopyranoside* (**5**) — Acetylation of **3** with acetic anhydride–pyridine gave **5** having the same m p as non-deuterated **5** (see ref 12), *m/e* 332 (25%, $M^+ - OCH_3$), 303 (9%, $M^+ - HOAc$), 289 (11%, $M^+ - CHDOAc$), 244 (85%, $M^+ - OAc - HOAc$), the 6(*S*) and 6(*R*) isomers were present in the ratio of 3 2

*1,2,3,4,5,6-Hexa-*O*-acetyl-6-deuterio-*D*-glucitol* (*1,2,3,4,5,6-hexa-*O*-acetyl-1-deuterio-*L*-gulitol*) (**6**) — The glycoside **3** (600 mg) was heated in 3M hydrochloric acid (15 ml) for 15 h at 80°, the decolorized solution was de-ionized with Amberlite IR-45 (OH^-) ion-exchange resin, and the solution was evaporated The product, which was indistinguishable from D-glucose by chromatography [g l c of the per-*O*-(trimethylsilyl) derivative on 20% SE-30 at 190°], was reduced with aqueous sodium borohydride The product was isolated and acetylated (acetic anhydride–pyridine) in the conventional way to give **6**, m p 97–98° (lit [17] value for the non-deuterated analog, m p 99°), chromatographically homogeneous (g l c on 20% SE-30 at 190°) It contained the 6(*R*) and 6(*S*) deuterated isomers in the ratio of 3 2

*3,5,6-Tri-*O*-acetyl-1,2-*O*-isopropylidene-6-deuterio-α-*D*-glucofuranose* (**7**) — The foregoing procedure was interrupted before the reduction step, and the 6-deuterio-D-glucose was converted[18] into 6-deuterio-1,2-*O*-isopropylidene-α-D-glucofuranose, this was acetylated (acetic anhydride–pyridine) to give **7**, which, crystallized from chloroform, had m p 74–75°, identical by mixed m p with an authentic, non-deuterated sample[19] The product was a 3 2 mixture of the 6(*S*) and 6(*R*) isomers N m r data (benzene-d_6, 100 MHz) δ 5 6 d ($J_{1\,2}$ 3 5 Hz, H-1), 4 05 d ($J_{2\,3}$ 0 5 Hz, H-2), 5 55 d ($J_{3\,4}$ 3 0 Hz, H-3), 4 35 dd ($J_{4,5}$ 9 0 Hz, H-4), 5 3 (two quadruplets, $J_{5\,6a}$ 2 5 Hz, $J_{5\,6b}$ 6 5 Hz, H-5), 4 55 d (H-6*a*), 3 95 d (H-6*b*)

ACKNOWLEDGMENTS

We thank Mr R Nardin for kindly recording deuterium-decoupled, double-resonance spectra The iterative calculations were made at the Laboratory for Numerical Calculations of the Centre d'Études Nucléaires de Grenoble We thank Mrs M Taieb and F Csakvary for providing us with a modified version of the T-LAOCOON program We are grateful to Mr B Bouhet for determining the mass spectra, under the direction of Mr Ulrich in the Service de Chimie Analytique du C E N G

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