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Note

Some stereochemical characteristics of C-^{1}H–C-^{2}H exchange-reactions with Raney nickel catalyst in deuterium oxide

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C-Deuterated carbohydrates are utilized[1] in a wide variety of chemical and biochemical applications. A facile method[2,3] for the introduction of deuterium atoms bonded to carbon consists of exchange between an appropriate carbohydrate derivative and deuterium oxide at 100° in the presence of Raney nickel catalyst. In using this method to prepare *C*-deuterated analogs of a number of compounds, we[4,5] have made a series of observations on regio- and stereo-selective aspects of the isotope-exchange reaction that are summarized here.

Influence of substituents on the rate of ^1H-^2H *exchange.* — It has been shown[2-4] that methyl α-D-glucopyranoside (**1**) may be *C*-deuterated to the extent of >95% at C-2, -3, -4, -6, and -6'. However, the rate at which the isotope is incorporated into different positions differs notably. Thus, on lowering the proportion of Raney nickel in the reaction mixture by a factor of 1/2.5, we have found that H-2 and H-4 were fully replaced, as before, whereas only ~50% of deuterium exchange occurred at C-3 and -6*. Furthermore, one of the primary protons was exchanged several times as rapidly as the other; this was apparent from the ^{1}H-n.m.r. spectrum of the per-acetate of the product of incomplete deuteration (see Fig. 1A). The spectrum consists of a mixture of overlapping signals: there are two sharp doublets of doublets due to H-6_S and -6_R of molecules in the sample that had not reacted at C-6 [as shown by the H-6_S and -6_R signals[7] of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (**2**) (see Fig. 1B)], and also two broadened signals due to H-6_S and -6_R of molecules in which either one or the other 6-proton had been exchanged. From the relative intensities of these two doublets, obtained by subtracting spectrum 1B from 1A, H-6_S was found to have been exchanged about three times as rapidly as H-6_R. Overall, therefore, the relative rates of exchange were H-2 ≃ H-4 > H-6_S > H-3 > H-6_T.

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*The quantity of deuterium incorporated at various positions in this and other compounds was estimated from the degree of diminution in the intensity of signals in the ^{1}H-n.m.r. spectra of the compounds, as well as of those in their ^{13}C-n.m.r. spectra; that is, the resonance signals of ^{13}C atoms bonded to ^{2}H atoms were broadened so markedly as to be virtually undetected[6].

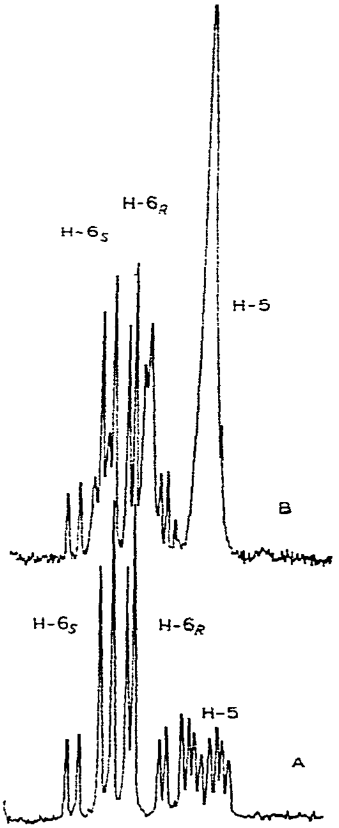

Fig. 1. 90-MHz, ^{1}H-n.m.r. spectrum of (A) methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside in C_6D_6, and (B) an analog partially deuterated at C-6, showing the signals of H-6(*S*), H-6(*R*), and H-5.

These characteristics suggest, as one possibility, that the interaction between methyl α-D-glucopyranoside and the catalytic surface occurs as in Fig. 2. That is, deuteration at C-2 and C-4 is envisaged as a result of substitution from the less-hindered side of the molecule. The OH-2 and OH-4 groups, which probably serve as efficient, chemisorption groups* on the catalyst, in initiating the reactions, should be suitably oriented, as are H-2 and H-4 that ultimately undergo exchange. Another possibility, suggested by observations on side reactions leading to inversion (see later), is that the isotope is not introduced at C-2 and -4 simultaneously, but in successive steps.

By analogy with the stereochemistry depicted in Fig. 2, the interaction of **1** with the catalyst should favor an orientation for H-6$_S$ in which the proton is coplanar with H-2 and H-4, as depicted by rotamer A. The latter, it may be noted, is not a

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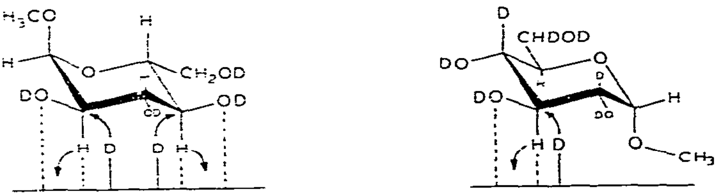
*One prerequisite for exchange is a hydroxyl group geminal to the C–H bond; indeed, the presence in a compound of at least two hydroxyl groups, not necessarily contiguous, appears to be essential for occurrence of a reaction with the catalyst.



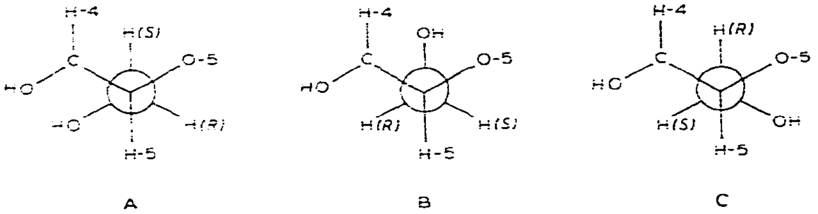


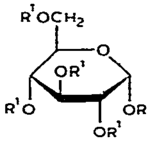
Fig. 2. Representation of exchange (left) of H-2 and H-4 of methyl α-D-glucopyranoside adsorbed on deuterated, Raney nickel catalyst, and (right) of H-3 of methyl α-D-glucopyranoside-2,4-$^2H_2$, following desorption and readsorption of the latter on the catalytic surface.

significant contributor to the conformation of the molecule in the ground state, in which rotamers **B** and **C** preponderate[7,8]. Nevertheless, a preference for **A** in the exchange reaction might be determined by optimum contact with the catalyst, offsetting the lower free-energies of **B** and **C**.

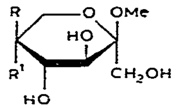
Interaction of the nickel surface with H-3 and OH-3 of **1** must take place at the face of the molecule opposite to H-2 and H-4 (see Fig. 2). Hence, the comparatively low reactivity at C-3 may be related to the absence of other, suitably positioned CHOH groups, as well as to interference by the axial 1-methoxyl group. That the latter factor is important was suggested by the finding that, when the aglycon was bulkier, as in ethyl α-D-glucopyranoside (**3**), there was relatively less reactivity at C-3. That is, under the conditions leading to 50% deuteration at C-3 of **1**, H-3 of **7** was not perceptibly affected, whereas H-2 and H-4 were almost fully exchanged, as before.

Also consistent with these observations were results obtained with methyl α-L-sorbopyranoside (**4**) which, like **1**, contains three contiguous, potentially exchangeable, axial protons (H-3, -4 and -5). In this instance, H-4 bears a *syn*-diaxial relationship with respect to the anomeric methoxyl group and, accordingly, was exchanged far more slowly than H-3 and H-5.

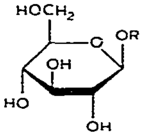
Essentially complete deuteration (>95%) was effected under standard conditions at C-2, -3, -4, -6, and -6′ of methyl β-D-glucopyranoside (**6**). By examining the reaction mixture at intervals, however, H-2 was observed to undergo exchange at the lowest rate; this appears to be associated with the relatively close proximity between *gauche* H-2 and the 1-methoxyl group, because deuteration at C-2 proved to be even more difficult to effect with the corresponding isopropyl glycoside (**7**). Similarly, in the exchange reaction of methyl β-D-galactopyranoside (**8**), C-2 was



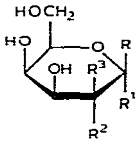
1 R = Me, R^1 = H
2 R = Me, R^1 = Ac
3 R = Et, R^1 = H



4 R = OH, R^1 = H
5 R = H, R^1 = OH



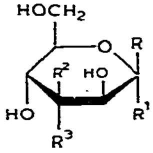
6 R = Me
7 R = Ip



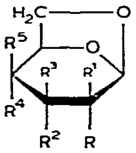
8 R = OMe, R^1 = H, R^2 = OH, R^3 = H
9 R = H, R^1 = OMe, R^2 = OH, R^3 = H
10 R = OMe, R^1 = H, R^2 = H, R^3 = OH

deuterated more slowly than C-3, -4, or -6. It is worth noting also that H-2′ of methyl β-cellobioside was strongly resistant to ^{1}H–^{2}H exchange under the same conditions[5], although the glycosidic linkage at C-4′ may have caused a further diminution in access to the catalyst by C-2′. The C-2′ atom of methyl β-maltoside was also the slowest to undergo exchange.

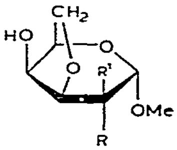
The orientation of the alcohol group may be an additional factor. Hence, H-2 of methyl β- and α-D-mannopyranoside (**11** and **12**, respectively) was exchanged relatively more rapidly than H-2 of **6**, although this proton is *gauche* with respect to the 1-methoxyl group in each molecule (*e*,*e*, *e*,*a*, and *a*,*e*, respectively). Possibly, then, the equatorial protons (axial OH) at C-2 of **11** and **12** are more reactive than axial H-2 (equatorial OH) of **6**. Analogously, the equatorial protons (axial OH groups) at C-2, -3, and -4 of 1,6-anhydro-β-D-glucopyranose (**14**), which are all *gauche* with respect to neighboring C–O bonds, were fully exchanged under the conditions leading to only partial deuteration at C-2 of **6**. In the exchange reaction of methyl 3,6-anhydro-α-D-galactopyranoside (**18**), deuteration occurred much more rapidly at C-2 (axial OH) than at C-4 (equatorial OH): *i.e.*, in a reaction time of 2 h, the intensity of the C-2 signal was lessened by ~60%, whereas that of C-4 appeared to be virtually unaffected[4]. Also, the fact that H-3 of methyl α-D-mannofuranoside (**20**) was exchanged much more rapidly than H-2 may, by analogy, be ascribed, at least partly, to the likelihood[9] that OH-3 tends to be *quasi*-axial, and OH-2 *quasi*-equatorial.



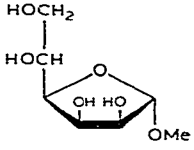
1 R = OMe, R^1 = H, R^2 = OH, R^3 = H
2 R = H, R^1 = OMe, R^2 = OH, R^3 = H
3 R = OMe, R^1 = H, R^2 = H, R^3 = OH



14 R = R^3 = R^4 = OH
15 R = R^2 = R^5 = OH
16 R = R^2 = R^5 = OH
17 R = R^2 = R^4 = OH



18 R = OH, R^1 = H
19 R = H, R^1 = OH



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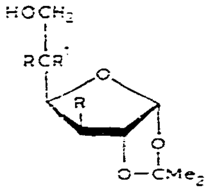
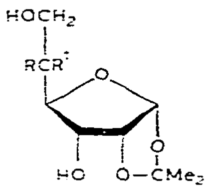
Access to the catalytic surface may account for differences in behavior between some other furanose derivatives. Hence, whereas 1,2-*O*-isopropylidene-α-D-glucofuranose (**21**) was deuterated[3] solely and completely at C-5 and C-6, its C-3 epimer, 1,2-*O*-isopropylidene-α-D-allofuranose (**23**) incorporated ~30% of deuterium at C-2,



21 R = OH, R' = H

22 R = H, R' = OH



23 R = OH, R' = H

24 R = H, R' = OH

as well as ~ 100% at C-5 and C-6. Presumably, H-3 of **23** experiences less interference from the *O*-isopropylidene group, whereas, in **21**, the latter group and H-3 are in much closer proximity.

Isomerization reactions. — Configurational inversion of carbon atoms bearing hydroxyl groups (in carbohydrates) in the presence of hydrogenation catalysts is well known[10-14] and, as noted earlier[2-4], is observed under the conditions of the ^1H–^2H exchange-reactions. Although most of the isomerizations detected in our studies were found to occur at positions where exchange was facile, deuteration was generally much more rapid than isomerization. Consequently, Raney nickel permits high levels

TABLE I

ISOMERIZATION PRODUCTS FROM REACTIONS OF CARBOHYDRATE DERIVATIVES WITH RANEY-Ni IN WATER AT 100°

Substrate	*Product*[a] *(%)*
Methyl α-D-glucopyranoside (**1**)	methyl α-D-mannopyranoside (10%)
	methyl α-D-galactopyranoside (15%)
Methyl α-D-galactopyranoside (**9**)	methyl α-D-glucopyranoside (32%)
	methyl α-D-mannopyranoside (2%)
Methyl α-D-mannopyranoside (**12**)	methyl α-D-glucopyranoside (15%)
	unknown (~ 4%)
Methyl β-D-galactopyranoside (**8**)	methyl β-D-glucopyranoside (9%)
	methyl β-D-talopyranoside (18%)[b]
Methyl β-D-mannopyranoside (**11**)	methyl β-D-glucopyranoside (4%)
	methyl β-D-altropyranoside (18%)[b]
Methyl β-D-glucopyranoside (**6**)	methyl β-D-galactopyranoside (5%)
	unknown (15%)
Methyl α-L-sorbopyranoside (**4**)	methyl β-D-fructopyranoside (38%)
Methyl 3,6-anhydro-β-D-galactopyranoside (**18**)	methyl 3,6-anhydro-β-D-talopyranoside (20%)
1,6-Anhydro-β-D-glucopyranose (**14**)	1,6-anhydro-β-D-idopyranose (26%)
	1,6-anhydro-β-D-gulopyranose (10%)
	1,6-anhydro-β-D-allopyranose (14%)
1,2-*O*-Isopropylidene-α-D-glucofuranose (**21**)	1,2-*O*-isopropylidene-α-L-idofuranose (25%)
1,2-*O*-Isopropylidene-α-D-allofuranose (**23**)	1,2-*O*-isopropylidene-α-L-talofuranose (25%)[b]

[a] Identified by comparison of ^{13}C-n.m.r. spectrum, or g.l.c. retention-time (Me_3Si derivative), with that of the known compound; yield determined by g.l.c. analysis of Me_3Si derivatives of reaction mixture. (The enantiomeric designation was assumed.) [b] Tentative identification.

of isotope (tritium as well as deuterium[4]) to be incorporated, with relatively little contamination by isomeric by-products.

In examining features of the isomerization process, a standardized set of reaction conditions was selected. Water was used as the solvent instead of deuterium oxide, and quantitative measurements were made by g.l.c., as well as by ^{13}C-n.m.r. spectroscopy. Diastereoisomeric aldohexopyranosides were found to exhibit substantial differences in yields of isomerization products (*cf.*, ref. 14). For example, methyl α-D-galactopyranoside (**9**) gave 32% of methyl α-D-glucopyranoside (**1**), whereas the same product was obtained from methyl α-D-mannopyranoside (**12**) in only 15% yield (see Table I); other isomerization products were minor. In each instance, the epimerization entailed the inversion of an axial hydroxyl to an equatorial one: at C-4 of **9**, and at C-2 of **12**. However, both **9** and **12** were formed, in almost equal yield, in the reaction between **1** and Raney nickel in water (see Table I), representing equatorial-to-axial inversions at C-2 and C-4, respectively. As the *talo* diastereoisomer was not detected, simultaneous inversions at C-2 and -4 did not occur. Furthermore, although **12** or **9** was epimerized to **1**, the isomeric product arising from inversions at *both* C-2 and C-4 was not significant in either instance.

The data given in Table I for **1** and **9** appear to be close to equilibrium values. That is, the product compositions were essentially unchanged by extending the reaction time from 24 to 72 h, or, alternatively, with **9**, by employing three successive, 24-h treatments, each with fresh Raney nickel. Both reaction mixtures contained the same three compounds in common, but in widely different proportions: for **1**, *gluco*:*galacto*:*manno* was 15:3:2, whereas, for **9**, the corresponding ratio was 16:33:1. Consequently, as the two systems did not tend towards a common position of equilibrium, the isomerization processes were not controlled by the thermodynamic stability of the products.

In the β-anomeric series, both the *galacto* (**8**) and *manno* (**11**) isomers produced glucoside **6**, whereas the latter gave galactoside **8**, all in low yield (see Table I). Other products, characterized tentatively*, were methyl β-D-altropyranoside (**13**) from **11**, and methyl β-D-talopyranoside (**10**) from **8**.

It was noted earlier that H-4 of methyl α-L-sorbopyranoside (**4**) is exchanged by deuterium more slowly than H-3 and H-5. By contrast, isomerization proved to be confined to C-4, resulting in a 38% yield of the D-fructoside isomer (**5**). Also, only one epimeric product was detected in the reaction mixture obtained from methyl 3,6-anhydro-α-D-galactopyranoside (**18**), which yielded the 2-epimer, *i.e.*, the *talo* derivative (**19**). Examples of isomerization at exocyclic positions were afforded by 1,2-*O*-isopropylidene-α-D-glucofuranose (**21**) and -allofuranose (**23**), which were epimerized at C-5 to yield the *ido* (**22**)[3] and *talo* (**24**) derivatives, respectively.

In these isomerization reactions, each product represented inversion at a single carbon atom. However, 1,6-anhydro-D-glucopyranose (**14**) provided an example in

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*These configurational assignments were based on evidence that the isomerization products contained more axial hydroxyl groups than **8** and **11**; *i.e.*, in comparison with **8** and **11**, several of their ^{13}C-nuclei were more shielded[15,16], and their g.l.c. retention-times[17] were shorter.

which epimerization occurred at two, and three, positions, giving the *gulo* (**15**) and *ido* (**16**) isomers, respectively, as well as at C-3 only, to give the *allo* (**17**) epimer. In view of the results obtained with the other compounds, it appears more likely that **15** and **16** represent successive single inversions, rather than two and three simultaneous inversions. As noted earlier, this characteristic may apply to the exchange process, as well.

Various possibilities may be envisaged for an inversion reaction. One type of mechanism, proposed[18] to account for inversion, as well as retention, of configuration, in the hydrogenolysis of derivatives of 2-phenyllactate on Raney nickel, regards the accessibility of chemisorption groups in a molecule to the catalytic surface as the main factor determining delivery of a hydrogen atom from "above" or "below" the plane of the molecule. Another possibility is an initial dehydrogenation, whereby a ketone[19] or an enol[20], or both, is formed, and is then hydrogenated. Exchange reactions of (—)-inositol on platinum have been evaluated[21] in this context in relation to the known propensity of platinum catalyst to dehydrogenate axial, secondary alcohol groups more readily than equatorial ones. By analogy, however, the formation of carbonyl intermediates in the present isomerization-reactions appears to have been less likely, as there was no marked selectivity with respect to the orientations of hydroxyl groups in the compounds studied. Although orientational preferences were observed in the *exchange* reactions, as already mentioned, this aspect of the catalytic process was necessarily obscured in water.

Conclusions. — In *C*-deuteration of carbohydrate derivatives with Raney nickel in deuterium oxide, the following reaction-characteristics have been observed: (*a*) at least two hydroxyl groups, not necessarily contiguous, are required for ^1H–^2H exchange to occur; (*b*) the rate of isotope incorporation into alkyl glycopyranosides is relatively slow when the C–H bond undergoing exchange is *syn*-axial with respect to an alkoxyl group, or (*c*) when the bond is axial and vicinal to an equatorial alkoxyl group; (*d*) an increase in the size of the alkoxyl substituent leads to further diminution in the rate of exchange; (*e*) an equatorial hydrogen atom undergoes exchange more readily than an axial one; (*f*) isotope exchange proceeds primarily with retention of configuration, although some degree of isomerization is almost always observed; (*g*) the isomerization process is not controlled by the thermodynamic stability of the products; and (*h*) in isomerization reactions, inversion probably occurs at only one carbon atom at a time, rather than at two or three centers simultaneously.

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 50° under diminished pressure. Gas–liquid chromatography was conducted with a Hewlett–Packard FEM 402 gas chromatograph using a silicone column (4% of OV-1) on Chromosorb W, and helium as the carrier gas; compounds were analyzed as their per(trimethylsilyl) derivatives. Proton magnetic resonance spectra were recorded with a Bruker WH-90 spectrometer. The same instrument, operating at 22.6 MHz, was used to record ^{13}C-n.m.r. spectra, using a sweep-width of 1.5 kHz, an acquisition time of 1.4 s, and pulse width of 12.5 μs.

Preparation, and handling, of deuterated Raney nickel, and its removal from reaction mixtures. — Raney nickel catalyst, prepared from nickel–aluminum alloy by the procedure of Pavlic and Adkins[23], or acquired from W. R. Grace and Co., was washed 4–5 times with deuterium oxide[3], and stored under the same solvent. The weight of catalyst used in a reaction was estimated ("wet weight") by centrifuging the catalyst suspension and then transferring an appropriate portion of it, as a solidly packed sediment, to the weighed reaction–flask. Whatman No. 42 paper coated with diatomaceous earth was used to filter the used catalyst from the reaction mixture. When the filtrate was to be examined by n.m.r. spectroscopy, it was passed through a short column of Chelex ion-exchange resin, in order to minimize interference by paramagnetic metal ions.

Methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside-2,3,4,6,6′-$^2H_5$. Standard conditions for deuteration. — A mixture of methyl α-D-glucopyranoside (5.0 g) and deuterated Raney nickel catalyst (24.0 g; ~5 parts by weight) in deuterium oxide (30 mL) was boiled under reflux for 24 h. The catalyst was filtered off, the filtrate evaporated, and the residue acetylated with 2:3 acetic anhydride–pyridine, affording the title compound; m.p. 101–102°. The ^{1}H-n.m.r. spectrum showed that the product contained ~95% of deuterium at C-3 and -6, and >95% at C-2 and -4.

Partial deuteration of methyl α-D-glucopyranoside. — A mixture of methyl α-D-glucopyranoside (3.0 g) and deuterated Raney nickel catalyst (6.5 g; ~2 parts by weight) in deuterium oxide (20 mL) was boiled under reflux for 24 h. As before, acetylation of the product afforded a crystalline tetraacetate, the ^{1}H-n.m.r. spectrum of which (see Fig. 1) showed >90% incorporation of deuterium at C-2 and C-4, and ~50% at C-3 and C-6.

Ethyl α-D-glucopyranoside-2,4,6,6′-$^2H_4$. — A mixture of ethyl α-D-glucopyranoside[24] (0.30 g) and deuterated Raney nickel catalyst (1.5 g; ~5 parts by weight) in deuterium oxide (20 mL) was boiled under reflux for 24 h. The catalyst was then filtered off, and the filtrate was evaporated. The ^{13}C-n.m.r. spectrum of the product in deuterium oxide showed that the signals for C-1, C-3, and C-5 were intact, whereas there were no detectable signals for C-2 and C-4, and only a small, residual signal for C-6.

Partial deuteration of methyl 3,6-anhydro-α-D-galactopyranoside. — When methyl 3,6-anhydro-α-D-galactopyranoside (**18**) (0.13 g) was boiled under reflux for 2 h with deuterated Raney nickel catalyst (1.4 g; ~10 parts by weight) in deuterium oxide (10 mL), the product was found by ^{13}C-n.m.r. spectroscopy to be ~60% deuterated at C-2. After a 24-h reaction-time, signals for C-2 and C-4 were virtually absent from the spectrum; ^{13}C-n.m.r. data for **18** (D_2O): δ 99.4 (C-1), 82.2 (C-3), 78.5 (C-5), 71.3 (C-4), 70.4 (C-2), 70.2 (C-6), and 58.9 (Me).

Representative, isomerization reactions. (a) Isomerization of methyl β-D-glucopyranoside. — Methyl β-D-glucopyranoside (1.1 g) in water (25 mL) was boiled under reflux with Raney nickel catalyst (5.7 g; ~5 parts by weight). Analysis of the products (as Me$_3$Si derivatives) by g.l.c. showed the presence of methyl β-galactopyranoside (5%) and an unidentified compound (~15%), in addition to starting material.

(*b*) *Isomerization of 1,2-O-isopropylidene-α-D-allofuranose*. A solution of 1,2-*O*-isopropylidene-α-D-allofuranose (23) (0.43 g) in water (25 mL) containing Raney nickel catalyst (2.1 g; ~5 parts by weight) was boiled under reflux for 24 h. The ^{13}C-n.m.r. spectrum of the product showed the presence of intact **23**, and ~25% of 1,2-*O*-isopropylidene-α-L-talofuranose (**24**) (tentative identification); ^{13}C-n.m.r. data for **23** (D$_2$O): δ 114.8 (OCO), 105.0 (C-1), 80.9 (C-2,4), 72.2 (C-5), 71.4 (C-3), 63.5 (C-6), and 27.1 and 26.9 (2 Me); ^{13}C-N.m.r. data for **24** (D$_2$O): δ 114.8 (OCO), 105.2 (C-1), 80.4 (C-2,4), 71.8 (C-5), 70.8 (C-3), 64.6 (C-6), and 27.1 and 26.9 (2 Me).

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