

[1,2]-HYDRIDE SHIFTS IN THE REACTION OF METHYL 5,6-O-CYCLOHEXYLIDENE-
3-O-MESYL- α -AND β -D-ALLOFURANOSIDE WITH METHYLMAGNESIUM IODIDE¹

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Despite the extensive amount of research on nonenzymatic [1,2]-hydride shifts,² there have been particularly few reports on similar transfers related to carbohydrates.³ We wish to report here the novel example of the stereoselective [1,2]-hydride shifts which occurred in the reactions of methyl 3-O-mesyl-D-allofuranoside derivatives with MeMgI. These reactions will serve to prepare not only specifically labeled sugars but also branched-chain deoxy sugars.

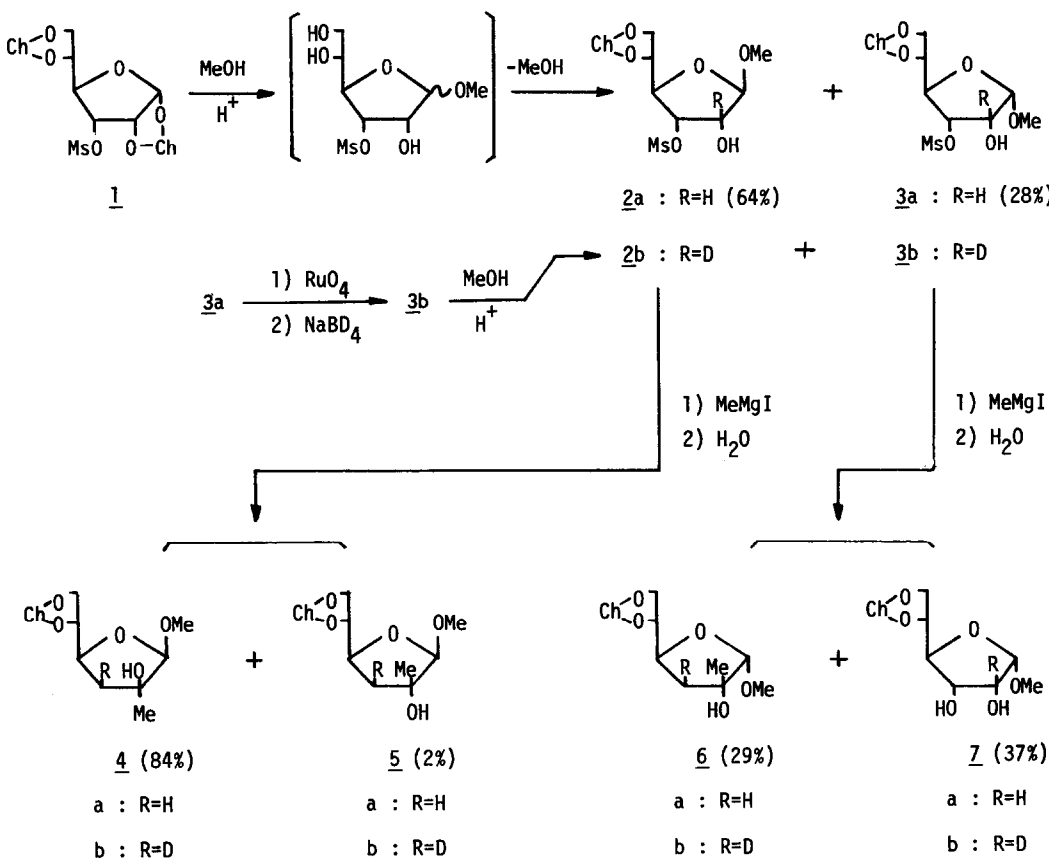
Treatment of 1,2:5,6-di-O-cyclohexylidene- α -D-allofuranose⁴ with mesyl chloride gave the corresponding mesylate 1 [88%; mp 119.5-121.5°; $[\alpha]_D^{23} +82.2^\circ$ (c 1.3, CHCl₃)]. A suspension of 1 in absolute methanol was gently refluxed in the presence of sulfuric acid for 3 hr. The methanol was removed by repeated coevaporation with dry benzene to give, after neutralization with calcium hydroxide, an anomeric mixture of methyl 5,6-O-cyclohexylidene-3-O-mesyl- β -D-allofuranoside 2a [needles; mp 138-140°; $[\alpha]_D^{24} -44.6^\circ$ (c 1, CHCl₃); mass m/e 352 (M⁺), 141 (the 5,6-O-cyclohexylidene group)] and its α -anomer 3a [prisms; mp 118-119°; $[\alpha]_D^{22} +97.7^\circ$ (c 1, CHCl₃); mass m/e 352 (M⁺), 141] in a ratio of 2:1. Each anomer could be separated by fractional crystallization from isopropyl ether-benzene.

In order to demonstrate the hydride shift, the deuterated (at C-2) analogues of 2a and 3a were prepared. Thus, 3a was oxidized with RuO₄, followed by reduction with NaBD₄ to give exclusively a monodeuterated "D-allo" analogue 3b [mass m/e 353 (M⁺); nmr (CDCl₃) δ 4.92 (1H, s, H₁)]; the use of NaBH₄ instead of NaBD₄ had resulted in the formation of 3a. Treatment of 3b with refluxing methanol in the presence of sulfuric acid gave 2b [mass m/e 353 (M⁺); nmr (CDCl₃) δ 4.87 (1H, s, H₁)].

An ethereal solution of MeMgI (6 mol. equiv.)⁵ was added to a stirred suspension of 2a in dry ether at 0-5° over a period of 40 min, and the mixture was stirred at room temperature for

3 hr. After the usual work-up, the crystallization of crude products from water-ethanol led to the isolation of methyl 5,6-*O*-cyclohexylidene-3-deoxy-2-*C*-methyl- β -D-arabino-hexofuranoside 4a [mp 69-70°; $[\alpha]_D^{25}$ -69.4° (c 1, CHCl₃); nmr (CDCl₃) δ 2.09 (1H, q, $J_{3a,3b}$ =11.5 Hz, $J_{3b,4}$ =6.5 Hz, H_{3b}), δ 1.88 (1H, bq, $J_{3a,3b}$ =11.5 Hz, $J_{3a,4}$ =8.0 Hz, H_{3a})]; chromatographic purification of the residual material on silica gel with *n*-hexane-ether gave another crop of 4a and a very small amount of the corresponding C-2 epimer 5a [mp 90-92°; $[\alpha]_D^{20}$ -80.2° (c 0.3, CHCl₃); nmr (CDCl₃) δ 2.09 (1H, q, $J_{3a,3b}$ =13.1 Hz, $J_{3b,4}$ =6.6 Hz, H_{3b}), δ 1.91 (1H, q, $J_{3a,3b}$ =13.1 Hz, $J_{3a,4}$ =8.6 Hz, H_{3a})]. Under similar conditions, 2b yielded 4b [mass m/e 273 (M⁺); nmr (CDCl₃) δ 2.09 (1H, bd, $J_{3b,4}$ =ca. 5 Hz, H_{3b})] and 5b [mass m/e 273 (M⁺); nmr δ 2.08 (1H, bd, $J_{3b,4}$ =6.5 Hz, H_{3b})]. Both 4b and 5b were exclusively labeled by the deuteriums at C-3 (*S*-configurations).

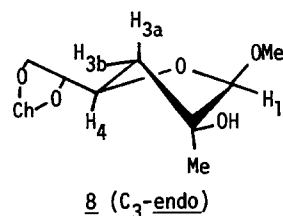
On the other hand, 3a gave, in a similar experiment, methyl 5,6-*O*-cyclohexylidene-3-deoxy-



2-C-methyl- α -D-ribo-hexofuranoside **6a** [syrup; bp 128-130° (bath-temperature)/2 mmHg; $[\alpha]_D^{21} +75.2^\circ$ (c 1, CHCl₃); nmr (CDCl₃) δ 2.11 (1H, q, $J_{3a,3b}=12.4$ Hz, $J_{3b,4}=7.0$ Hz, H_{3b}),⁶ 1.93 (1H, q, $J_{3a,3b}=12.4$ Hz, $J_{3a,4}=6.4$ Hz, H_{3a})] and methyl 5,6-O-cyclohexylidene- α -D-allofuranoside **7a** [syrup; $[\alpha]_D^{21} +100^\circ$ (c 1, CHCl₃)]. In this case, no epimer of **6a** could be detected. Similarly **3b** gave **6b** [mass m/e 273 (M⁺); nmr (CDCl₃) δ 2.08 (1H, bd, $J_{3b,4}=6$ Hz, H_{3b})] and **7b** [mass m/e 275 (M⁺); nmr (CDCl₃) δ 4.90 (1H, s, H₁)]. The transfer of the deuterium again took place stereoselectively to give the S-configuration at C-3 in **6b**.

The structures of the newly synthesized branched-chain deoxy sugars **4** - **6** were assigned on the basis of their spectroscopic data, elemental analyses, and chemical transformations. The nmr spectra of **4a** - **6a** showed singlets due to the anomeric protons and quartets characteristic of the AB parts of ABX systems, which were assignable to H_{3a} (A),

H_{3b} (B), and H₄ (X);⁶ the spectra of the deuterated analogues revealed no signals due to H_{3a}. The relatively large values (8.6-6.4 Hz) of the coupling constants for H_{3a}-H₄ and H_{3b}-H₄ in **4a** - **6a** suggested that these compounds favorably existed in C₂-exo or C₃-endo conformations.⁷ For example, the C₃-endo conformation of **4a** can be depicted as in **8**, in which H_{3a} and the methyl group at C-2 as well as H_{3a} and H₄ constitutes an axial-quasi axial pair. Spin-spin decoupling experiments demonstrated that the methyl protons in the former pair were coupled to H_{3a} ($J=0.8$ Hz) because of their W-shaped arrangement.



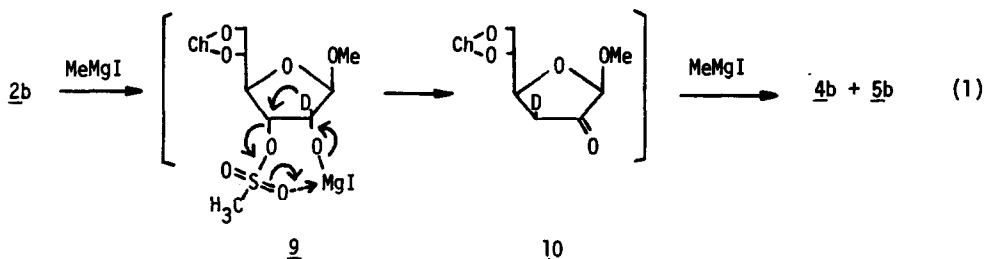
formation of **4a** can be depicted as in **8**, in which H_{3a} and the methyl group at C-2 as well as H_{3a} and H₄ constitutes an axial-quasi axial pair. Spin-spin decoupling experiments demonstrated that the methyl protons in the former pair were coupled to H_{3a} ($J=0.8$ Hz) because of their W-shaped arrangement.

In the ir spectra (in CCl₄) of **4a** - **6a**, only **5a** showed a broad band near 3250 cm⁻¹ due to polymeric intermolecular hydrogen-bonds. This observation was consistent with the trans, rather than cis, relationship between the methoxy and hydroxy groups in **5a**.

When **4a** was treated with cyclohexanone in the presence of sulfuric acid, 1,2:5,6-di-O-cyclohexylidene-3-deoxy-2-C-methyl- β -D-arabino-hexofuranose [syrup; $[\alpha]_D^{23} -21.0^\circ$ (c 1, CHCl₃)] was obtained, whereas both **5a** and **6a** gave, under similar conditions, the corresponding α -D-ribo-hexofuranose [syrup; $[\alpha]_D^{22} +10.3^\circ$ (c 1, CHCl₃)]. Furthermore, **4a** was treated in aqueous dioxane with Dowex 50W-X8 (H⁺ form), followed by oxidation with KMnO₄ to give the known S-(+)-2-methyl-malic acid⁸ after chromatographic purification with Dowex 50W-X8 (H⁺ form), thus indicating the S-configuration at C-2 in **4a**.

A possible mechanism of formation of **4b** and **5b** is shown in Eq. 1. The cyclic intermediate **9** undergoes the stereoselective [1,2]-deuteride shift and the elimination of a molecule of

mesyloxymagnesium iodide in a concerted manner to give the uloside derivative 10, which, in turn, is suffered from the attack of MeMgI to yield the products.⁵ The formation of 6b can also be explained in terms of the same mechanism, but that of the α -anomer of 9 will be suppressed probably because of the competitive chelation of the magnesium with the oxygen atom of the methoxy group. The β -elimination of the mesyloxy group and the deuterium from 2b may lead to the formation of the nondeuterated analogue of 10,⁹ but this is not the case in the present reaction. The anomeric configurations of 10 and its α -anomer influence significantly the determination of the stereochemistry at C-2 in 4b - 6b.¹⁰



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REFERENCES AND NOTES

1. Presented in part at the 32nd Annual meeting of the Japan Chemical Society, Tokyo, April 1975.
2. For example, see "Organic Reaction Mechanisms 1973", ed. by A. R. Butler and M. J. Perkins, John Wiley & Sons, London (1975) and its preceding series.
3. W. B. Gleason and R. Barker, *Can. J. Chem.*, **49**, 1433 (1971); D. W. Harris and M. S. Feather, *J. Amer. Chem. Soc.*, **97**, 178 (1975).
4. M. Kawana, H. Ohruji, and S. Emoto, *Bull. Chem. Soc. Japan*, **41**, 2199 (1968).
5. Recent experiments indicated that the use of ca. 2.5 mol. equiv. of MeMgI brought about the same products in similar yields. When 2a was treated with MeMgI at elevated temperature, a dimeric compound [mp 155-156°; $[\alpha]_D^{25}$ -83.2° (c 1, CHCl₃)] containing a carbon-carbon bond between furanose rings was found to be formed in ca. 40% yield.
6. The configurational relation among H_{3a}, H_{3b}, and H₄ is the same as that among the corresponding protons in 8.
7. C. D. Jardetzky, *J. Amer. Chem. Soc.*, **84**, 62 (1962).
8. P. A. Stadler, A. J. Frey, and A. Hofmann, *Helv. Chim. Acta*, **46**, 2300 (1963); they have quoted the results of G. Settimo, H. Weber, and D. Arigoni.
9. T. Sasaki, K. Minamoto, and K. Hattori, *Tetrahedron*, **30**, 2689 (1974), and references cited therein.
10. M. Miljković, M. Gligorićević, and D. Miljković, *J. Org. Chem.*, **39**, 2118 (1974).