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THE TRANSFORMATION OF METHYL 1,2-trans-GLYCOFURANOSIDES TO THEIR RESPECTIVE cis-ANOMERS WITH GRIGNARD REAGENTS

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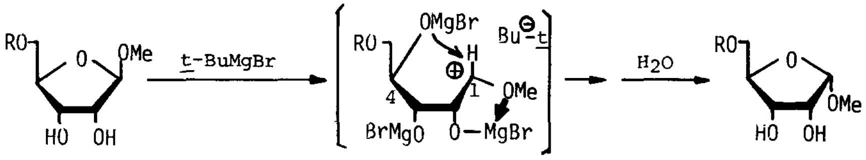
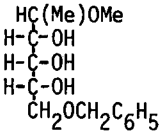
It is known that methyl glycosides do not undergo anomerization in the absence of acidic catalysts, because they possess acetal structures in their anomeric portions.[1] Although acetals and ketals are generally stable under Grignard reaction conditions, certain cyclic derivatives are cleaved by Grignard reagents in boiling benzene.[2] The anomeric regions of the glycofuranosides, therefore, will be able to become the target of attack of the Grignard reagents under appropriate conditions to give rise to open their furanose rings. In the course of our work on the synthesis of sugar derivatives with Grignard reagents,[3] we found a new method for the stereocontrolled anomerization without the acidic catalysts as described in the following scheme.



1 a:R= $-CH_2C_6H_5$ 2 b:R= $-C(C_6H_5)_3$ 3

The starting material, methyl 5-O-benzyl-β-D-ribofuranoside 1a [syrup; $[\alpha]_D^{21}$ -49.6° (c 1.5, $CHCl_3$)],[4] and its α-anomer 3a [syrup; $[\alpha]_D^{21}$ +96.5° (c 0.86, $CHCl_3$)] were isolated from the corresponding anomeric mixture[5] by column chromatography on silica gel with benzene-ethyl acetate. In a typical experiment for the present anomerization, a solution of 1a (238 mg, 0.94 mmol) in benzene (3 ml) was added to a stirred solution of t-butylmagnesium bromide (ca. 8 mmol) in ether (10 ml) and benzene (15 ml), and the mixture was heated at 70-75 °C (bath-temperature) under a dry nitrogen atmosphere for 2.5 hr. During this period the ether was distilled from the reaction mixture. The usual workup gave 3a (225 mg, 95%) as the sole product along with a trace amount of the starting material.

This reaction is considered to proceed *via* a posturated intermediate 2, in which the non-bonded pair of electrons on the methoxy oxygen coordinated to the magnesium cation bound to the oxygen at C-2 to form a stable five-membered ring. The subsequent cyclization of the oxygen at C-4 to the C-1 carbon stereoselectively gave the α-anomer 3a. Under similar conditions a 5-O-trityl derivative 1b[6] could be transformed into its α-anomer 3b [mp 104-105 °C; $[\alpha]_D^{21}$ +82.7° (c 1.0, CHCl$_3$)] in moderate yield. When methylmagnesium iodide was used in place of *t*-butylmagnesium bromide in this reaction, 1a yielded 3a and a C-1 methylated ribitol derivative 4 in a ratio of approximately 1:1.



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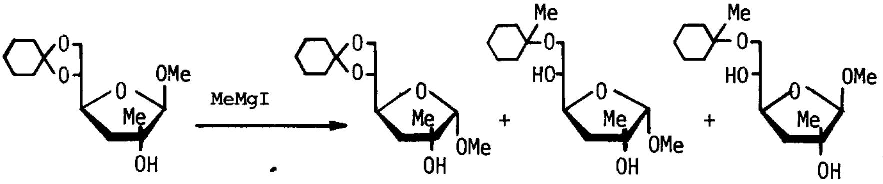

5 6 7 8

Methyl 5,6-O-cyclohexylidene-3-deoxy-2-C-methyl-β-D-*ribo*-hexofuranoside 5[3a] having both the acetal and ketal structures in one molecule was subjected to a similar Grignard reaction with methylmagnesium iodide to afford its α-anomer 6[3a] (6%), methyl 3-deoxy-2-C-methyl-6-O-(1'-methylcyclohexyl)-α-D-*ribo*-hexofuranoside 7 (38%) [syrup; $[\alpha]_D^{20}$ +66.2° (c 1.1, CHCl$_3$)], and its β-anomer 8 (18%) [syrup; $[\alpha]_D^{22}$ -75.4° (c 0.74, CHCl$_3$)]. In this case the 5,6-O-cyclohexylidene group was also cleaved by the Grignard reagent. When the reaction time was reduced, 6 (42%) was obtained as a main product.

The present anomerization would be potentially useful as a means of synthesizing certain 1,2-*cis*-glycofuranosides that are difficult to prepare by other methods. The application of this method to other glycosides, as well as the cleavage of 1,3-dioxolane rings of other sugar derivatives are currently under investigation.

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