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REACTION OF 2,3-ANHYDRO-4,6-O-BENZYLIDENE-α-D-HEXOPYRANOSIDES WITH PROPENYLMAGNESIUM CHLORIDES. REGIOSELECTIVE CARBON CHAIN EXTENSION AT THE C-2 POSITION OF HEXOPYRANOSIDES[1)]

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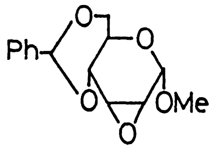
The reaction of 2-propenylmagnesium chlorides with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (1) or -gulopyranoside (6) exclusively afforded the corresponding 2-deoxy-2-C-(2-propenyl)-α-D-hexopyranosides (4b, 8a, and 8b).

Carbohydrates have been utilized as starting materials for the construction of carbon frameworks of chiral natural products.[2)] Although a number of successful approaches to carbon chain extension of carbohydrates have been reported so far, there still exists difficulty to differenciate sharply between hydroxyl groups at C-2 and C-3 positions on furanosides and pyranosides.[3)] In most cases, therefore, new carbon chains are introduces at the C-1 position and/or at the terminal carbon atom of furanosides (C-5 position), pyranosides (C-6 position), or their degradation products.

In connection with our interest in the synthesis of macrolides, it has become necessary to introduce a carbon chain having a carbonyl equivalent functional group on the C-2 position of pyranosides. One possible approach to discriminate the C-2 position from C-3 position is the use of a locked 2,3-anhydropyranoside, since a clear pattern has emerged in their oxirane ring-opening.[4)] Thus the reaction of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (1) with organolithium- or organosodium reagents has reported to give the corresponding 2-C-substituted 2-deoxyaltropyranosides.[5)] On the other hand, the reaction of 1 with alkylmagnesium halides resulted in the formation of 4,6-O-benzylidene-1,2-dideoxy-D-ribo-hex-1-enopyranoside (2) and methyl 2-deoxy-D-ribo-α-hexopyranoside (3) rather than 2-C-alkyl-2-deoxy-α-D-altropyranoside (4).[6)]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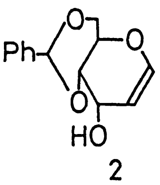
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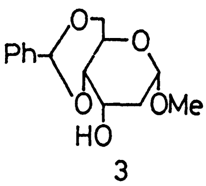
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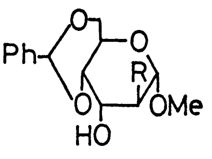
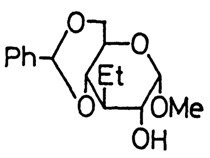

4a: $R = C_2H_5-$
b: $R = CH_2{=}\underset{CH_3}{C}{-}CH_2-$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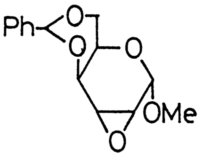
It has been demonstrated that 2 and 3 are produced by the reaction of excess Grignard reagent with initially formed methyl 4,6-O-benzylidene-2-deoxy-2-halo-α-D-altropyranoside (4; R = halogen).6) In order to introduce a carbon chain on the C-2 position of 1, it would be essential to remove halide ion from the reaction system.7)

At the outset, we attempted the reaction of 1 with diethylmagnesium.8) When diethylmagnesium was treated with 1 in ether under reflux for 6 h, virtually no reaction took place and 90% of 1 was recovered. It was found, however, the reaction proceeded smoothly by the use of dichloromethane as co-solvent (refluxed for 6 h) giving expected methyl 4,6-O-benzylidene-2-deoxy-2-C-ethyl-α-D-altropyranoside (4a) in 76% yield along with 3-C-ethyl isomer (5; 16% yield) and 2 (3% yield).9)

Contrary to the case of 1, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-gulopyranoside (6) did not react with diethylmagnesium under the same conditions (97% recovery). This result suggests that, although undesirable formation of 2 and 3 is practically surpressed, dialkylmagnesiums are not so reactive as to be utilized in the C-C bond formation at the C-2 position of 1 and 6.



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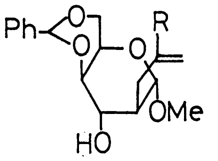
$CH_2{=}CR{-}CH_2{-}MgCl$

7a: R = CH_3
b: R = H

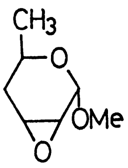


8a: R = CH_3
b: R = H

Since the electronegativity of magnesium is higher than those of alkali metals, the magnesium-carbon bond of simple alkylmagnesium halides may have appreciable covalent charactor.10) It would be reasonable to assume that Grignard reagents having magnesium-carbon bond of increased ionic charactor can transfer organic group rather than halide ion to 1 and 6.

As expected, 1 reacted smoothly with 2-methyl-2-propenylmagnesium chloride (7a) in tetrahydrofuran (THF) at room temperature to give methyl 4,6-O-benzylidene-2-deoxy-2-C-(2-methyl-2-propenyl)-α-D-altropyranoside (4b) in nearly quantitative yield. Acid hydrolysis of 4b afforded methyl 2-deoxy-2-C-(2-methyl-2-propenyl)-α-D-altropyranoside which consumed 98% of theoretical amount of periodate supporting the structure of 4b. Similarly, the reaction of 6 with 7a and with allylmagnesium chloride (7b) resulted in the formation of the corresponding 2-deoxy-2-C-(2-propenyl)-α-D-idopyranosides, 8a and 8b, in good yields.11) The structure were confirmed by periodate titration of the debenzylidenated products.

In contrast with locked pyranosides, no regioselectivity was observed in the reaction of a flexible pyranoside. Thus the reaction of methyl 2,3-anhydro-4,6-dideoxy-D-ribo-hexopyranoside (9) with 7a or 7b gave rise to 2-C- and 3-C-(2-propenyl)-pyranosides (10a and 11a, 81% total yield; 10b and 11b, 97% total yield) in a ratio of about 1 : 1.12)



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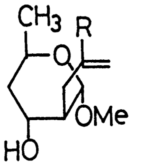
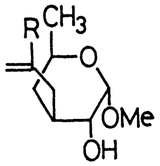


10a: R= CH3
b: R= H



11a: R= CH3
b: R= H

The work described in this paper makes 4b, 8a, and 8b readily available. These compounds have different kinds of reactive sites and, therefore, provide efficient and versatile intermediates for the synthesis of chiral natural products.

The following procedure is representative. To a solution of 7a prepared by the reaction of 2-methyl-2-propenyl chloride (905 mg, 10 mmol) and magnesium (243 mg, 10 mmol) in THF (2 ml) was added 1 (264 mg, 1 mmol) in THF (50 ml) at room temperature under argon. After the mixture had been stirred for 16 h at room temperature, saturated aqueous NH_4Cl (20 ml) was added and filtered. The filtrate was extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated to give crude 4b which was recrystallized from hexane (250 mg, 78%); mp 98-100 °C, $[\alpha]_D$ +66° (c 0.5, $CHCl_3$). NMR (60 MHz, $CDCl_3$), δ 1.77 (br s, $C\underline{H}_3$-C=CH_2), 1.9-2.6 (m, $C\underline{H}_2$-C(CH_3)=CH_2 and H-2), 3.4 (s, CH_3O-), 3.5-4.5 (m, H-3, H-4, H-5, H-6), 4.52 (s, H-1), 4.65-4.9 (m, $C\underline{H}_2$=C<), 5.6 (s, PhC$\underline{H}$<), 7.2-7.8 (m, aromatic H). Anal. Found C, 67.50; H, 7.52%. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55%.

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7) Foster and coworkers have reported that the reaction of diethylmagnesium with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside where methyl 4,6-O-benzylidene-3-deoxy-3-C-ethyl-α-D-altropyranoside was exclusively formed. A. B. Foster, W. G. Overend, M. Stacey, and G. Vaughan, J. Chem. Soc., 1953, 3308.

8) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessey, J. Am. Chem. Soc., 78, 1221 (1956).

9) The products were obtained as a mixture by preparative layer chromatography (ether-petroleum ether = 1 : 1). The respective yield was determined by gas chromatographic analysis (OV-1, 1 m, 155 °C, FID) assuming the weight-responce factors are not different for **2**, **4a**, and **5**.

10) E. Negishi, "Organometallics in Organic Synthesis", Vol. 1, John Wiley & Sons, New York (1980).

11) For **8a**; mp 80.5-82 °C (from hexane), $[\alpha]_D$ +38° (c 0.5, $CHCl_3$). NMR ($CDCl_3$) δ 1.71 (s, $C\underline{H}_3\text{-}\overset{}{C}{=}CH_2$), 1.9-2.7 (m, $C\underline{H}_2\text{-}C(CH_3){=}CH_2$ and H-2), 3.4 (s, CH_3O-), 3.6-4.4 (m, H-3, H-4, H-5, H-6), 4.75 (br one peak, $C\underline{H}_2{=}C\langle$ and H-1), 5.6 (s, PhCH⟨), 7.1-7.7 (aromatic H).

For **8b**; mp 86-87 °C (from hexane), $[\alpha]_D$ +44° (c 0.5, $CHCl_3$). NMR ($CDCl_3$) δ 2.0 (br q, H-2), 2.46 (br t, $C\underline{H}_2\text{-}CH{=}CH_2$), 3.4 (s, CH_3O-), 3.5-4.65 (m, H-3, H-4, H-5, H-6), 4.8 (s, H-1), 4.8-5.3 (m, $C\underline{H}_2{=}CH$-), 5.5 (s, PhCH⟨), 5.57-6.23 (m, $\text{-}C\underline{H}{=}CH_2$), 7.23-7.85 (m, aromatic H).

12) The isomers could not be separated, the structures being assigned by NMR spectrum of the mixture. The ratio was determined by the integration of the NMR spectrum and peak areas of gas chromatogram.

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