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Regioselective Methylation of the C-1 and C-3 Positions of 1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-D-*ribo*-hex-1-enitol by the Reaction with Methylmagnesium Bromide or Methyl Cuprates

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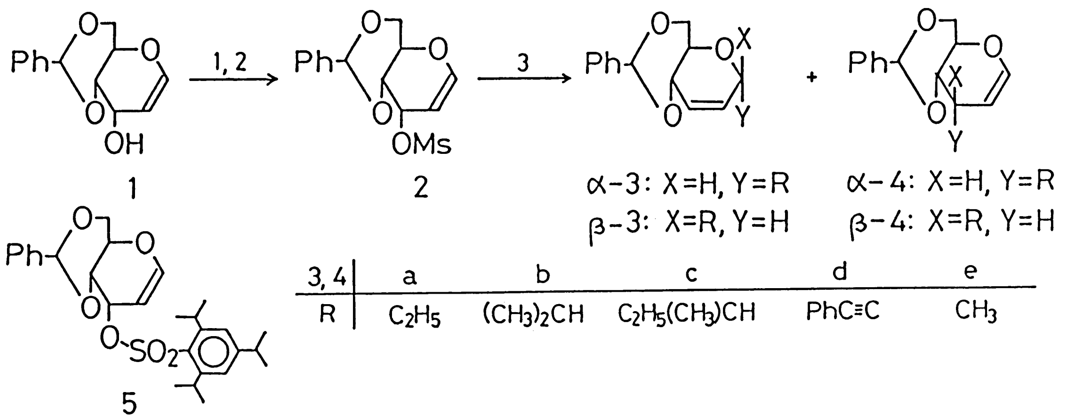
1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-D-*ribo*-hex-1-enitol reacted with alkylmagnesium bromides (RMgBr: R = C_2H_5-, $(CH_3)_2CH$-, or $C_2H_5(CH_3)CH$-) to give the corresponding 1-β-*C*-glycopyranosides and 3-*C*-alkyl-D-*arabino*-hex-1-enitols, while the reaction with methylmagnesium bromide afforded 1-α-*C*- and 1-β-*C*-methyl-glycosides in a ratio of 1 : 1.5-2. On the other hand, when the reaction was carried out in the presence of CuI or CuBr-$S(CH_3)_2$, substitution took place at the C-3 position to afford the corresponding 3-*C*-methyl-D-*arabino*-hex-1-enitol.

Carbohydrates have been utilized as versatile starting materials for the synthesis of natural products having multiple centers of chirality.$^{1)}$ Although many elegant approaches have been reported so far, there is still need to develop convenient methods for introducing a carbon chain, especially methyl group, on the carbohydrate frameworks. Of many carbohydrate derivatives, glycals have attracted attentions because of inherent reactivity. Although glycals are ambident electrophiles, the reaction of glycals with organometallic reagents in the presence of Lewis acids generally takes place at the C-1 position.$^{2)}$ In this communication, we wish to report regioselective introduction of a methyl group at the C-1 or C-3 position of 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*ribo*-hex-1-enitol (**1**).

When 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-D-*ribo*-hex-1-enitol (**2**) prepared by the successive reaction of **1** with lithium diisopropylamide (LDA)$^{3)}$ and mesyl chloride was allowed to react in situ with a variety of alkylmagnesium bromides, RMgBr with R = CH_3-, C_2H_5-, $(CH_3)_2CH$-, or $C_2H_5(CH_3)CH$-, in tetrahydrofuran (THF), the corresponding 1-β-*C*-alkyl-glycopyranosides (β-**3**) and 3-*C*-alkyl-D-*arabino*-hex-1-enitol (β-**4**) were obtained except for the case of methylmagnesium bromide (Table 1, entries 1, 3, 4).

The reaction of methylmagnesium bromide with **2** took place at the C-1 position to give 1-α-*C*-methyl-glycoside (α-**3e**) and its β-isomer (β-**3e**) (Table 1, entry 8) which were separated by silica gel chromatography and identified by ^{1}H-NMR (270 MHz) including NOE experiments.$^{4)}$ In the hope of preventing the formation of α-**3e**, 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2,4,6-triisopropylbenzenesulfonyl)-D-*ribo*-hex-1-enitol (**5**) was allowed to react with methylmagnesium bromide under the same conditions. Contrary to our expectation, however, α-3e and β-3e were again formed in a ratio of 1 : 2 (Table 1, entry 9). When phenylethynylmagnesium bromide reacted with 2, 1-β-C-phenylethynyl-glycoside (β-3d) was exclusively formed in nearly quantitative yield (Table 1, entry 5).



3, 4	a	b	c	d	e
R	C_2H_5	$(CH_3)_2CH$	$C_2H_5(CH_3)CH$	PhC≡C	CH_3

1) LDA, -78 °C, 0.5 h. 2) MsCl, -78 °C ⟶ 0 °C, 1.5 h.
3) R-Metal, -78 °C ⟶ room temp.

Table 1. Reaction of 2 with Methylmagnesium Bromide or Methyl Cuprates

			Products (yield/% and ratio)[a]	
Entry	R-Metal	equiv	3 (α : β)	4 (α : β)
1	C_2H_5MgBr	5	61 (1 : 10)	14 (β)
2	C_2H_5MgBr/CuI	5/2.5	-	24 (β)
3	$(CH_3)_2CHMgBr$	5	21	60 (β)
4	$C_2H_5(CH_3)CHMgBr$	5	10 (β)	72 (β)
5	PhC≡CMgBr	5	95 (β)	-
6	PhC≡CMgBr/CuI	5/2.5	-	47 (19 : 1)[b]
7	PhC≡CMgBr/CuBr-S$(CH_3)_2$	5/2.5	-	46 (13 : 1)[b]
8	CH_3MgBr	5	65 (1 : 1.5-2)	d)
9	CH_3MgBr[c]	5	54 (1 : 2)	-
10	CH_3MgBr/CuI	5/2.5	d)	72 (β)
11	$CH_3MgBr/CuBr\text{-}S(CH_3)_2$	5/2.5	d)	63 (β)
12	$(CH_3)_2CuLi$	5	d)	62 (β)

a) Yields are average of three experiments carried out under the same conditions. b) Result of single experiment. c) Compound 5 was used d) A trace of regioisomer was formed.

It has been proposed that the reaction site of 3-O-acyl-glycals in substitution reaction with nucleophiles could be rationalized by the principle of "hard and soft acids and bases (HSAB)". Thus, the C-1 position is suggested to be harder than the C-3 position.[5)] HSAB principle would also be capable of correlating some of the reactivity we observed, i.e. the softer anionoid reagents attack the C-3 position of 2 more readily than the hard ones.

Since organo cuprates are known to be softer nucleophiles than Grignard reagents, the reactions of 2 with methylmagnesium bromide in the presence of CuI or CuBr-$S(CH_3)_2$ was examined, where, as expected, 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-D-*arabino*-hex-1-enitol (β-4e) was formed rather than 3e (Table 1, entries 10, 11). Although thin layer chromatography (TLC) of the crude reaction mixture indicated the formation of a trace of 3e, it was practically negligible. Similar result was obtained in the reaction of 2 with lithium dimethyl cuprate (Table 1, entry 12). Ethylmagnesium bromide also reacted with 2 in the presence of CuI to give 3-*C*-ethyl derivative with D-*arabino*-configuration (β-4a). Although the yield of β-4a was low, no detectable amount of 3a was formed (Table 1, entry 2).

While the reaction of phenylethynylmagnesium bromide with 2 in the presence of CuI or CuBr-$S(CH_3)_2$ again afforded 3-*C*-phenylethynyl derivative, the isomer having D-*ribo*-configuration (α-4d) was formed in preference to the *arabino*-isomer (β-4d) (45% and 2.4%, or 43% and 3.2% isolated yields, respectively: Table 1, entries 6, 7).

The stereochemistry of the substitution reactions at the C-3 position was complete inversion with the exception of phenylethynylation and the structures of 3-*C*-alkylated products obtained were determined as depicted in Scheme 1 by ^{1}H-NMR studies.

The work described in this paper demonstrates that the regioselectivity of the reaction of 2 with Grignard reagents can be controlled by the addition of Cu (I) salts.6) The regioselectivity of these reactions could be rationalized by HSAB principle, while the origin of the stereoselectivity at the respective reaction sites has not yet been elucidated. Since the reaction of methylmagnesium bromide with 2 in the presence of Cu(I) salts took place at the C-3 position with high regio- and stereoselectivities and the procedure makes 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-D-*arabino*-hex-1-enitol (β-4e) readily available.

The following procedure is representative. Reaction of 2 with methylmagnesium bromide in the presence of CuI: A solution of 1 (234 mg, 1.0 mmol) in THF (3 ml) was added to LDA (1.1 equiv) at -78 °C under an argon atmosphere and stirred for 30 min. Mesyl chloride (3.45 mg, 3.02 mmol) in THF (5 ml) was added and the temperature was slowly raised to 0 °C. After stirring for 90 min, the mixture was added to a mixture of CuI (2.5 mmol) and methylmagnesium bromide (5 mmol in THF). The reaction mixture was allowed to warm to room temperature and stirred for 17 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution and filtered through Hyflo super cel. The filtrate was extracted with ether (50 ml x 3). The combined organic layers were successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and filtered, and the residue was purified by silica gel layer chromatography (petroleum ether/ether = 8 : 1) to give β-4e; mp 65-67 °C (Table 1, entry 10). ^{1}H-NMR ($CDCl_3$): δ = 1.11 (d, CH_3, $J_{3,Me}$ = 6.6 Hz), 2.35-2.55 (m, 3-H), 3.42 (t, 4-H), 3.73 (t, 6-H_{ax}, $J_{5,6a}$ = $J_{6a,6e}$ = 10 Hz), 3.75-3.86 (m, 5-H), 4.37 (dd, 6-H_{eq}, $J_{5,6e}$ = 3.9 Hz), 4.55 (dd, 2-H, $J_{2,3}$ = 2.0 Hz), 6.27 (dd, 1-H, $J_{1,2}$ = 5.9 Hz, $J_{1,3}$ = 2.3 Hz).7)

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