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Reaction of Hex-1-enopyranose-3-uroses with Organometallic Reagents. Regio- and Stereoselective Introduction of Allylic Substituents on Pyranose Ring

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4,6-O-Benzylidene-1,2-dideoxy-D-threo-hex-1-enopyranose-3-urose reacted with allylic organometallic reagents, $CH_2=CR-CH_2$-Metal [R = H or CH_3; Metal = MgCl, $AlEt_2$, or $Ti(OPr^i)_3$], to selectively give 4,6-O-benzylidene-1,2-dideoxy-3-C-(2-propenyl- or 2-methyl-2-propenyl)-D-lyxo-hex-1-enopyranose. On the other hand, the erythro isomer gave 3-C-(2-propenyl- or 2-methyl-2-propenyl)-D-arabino-hex-1-enopyranose and the corresponding ribo isomer in a ratio ranging from 1 : 1 to 10 : 1.

Carbohydrates have been extensively utilized as starting materials for the preparation of natural products with multiple centers of chirality.[1)] The activation of the particular position of carbohydrate skeleton and control the course of the subsequent reaction with incoming reagents would be the crucial problem for the regio- and stereoselective transformation of carbohydrates.

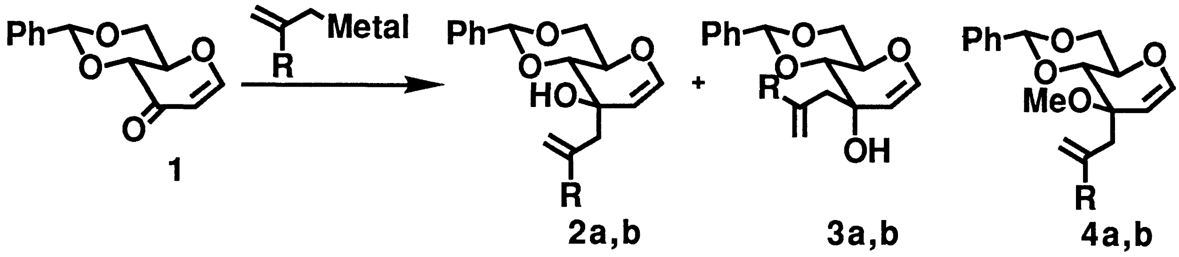
Previous papers describe highly regio- and stereoselective reaction of allylic Grignard reagents with 2,3-anhydropyranosides,[2)] 2,3-anhydrofuranosides,[3)] and 3-O-mesylglycals.[4)] In this communication, we wish to report the reaction of 2-propenyl- or 2-methyl-2-propenyl-metallic reagents with 4,6-O-benzylidene-1,2-dideoxy-D-erythro-hex-1-enopyranose-3-urose (**1**) and its threo isomer **5**. Since hex-1-enopyranose-3-uroses **1** and **5** are ambident electrophiles, four products are possible in the reaction with anionoid reagents. It would therefore be important to find out the conditions where only one of four possible diastereomers is formed.[5)]

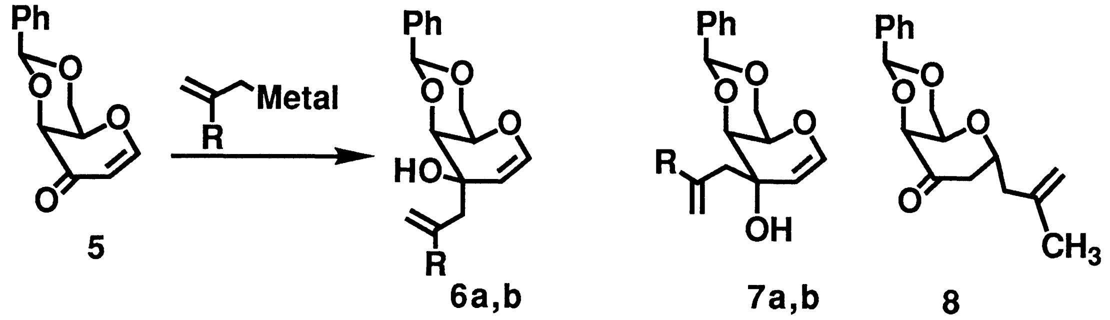
The reaction of **1** with 2-propenylmagnesium chloride in tetrahydrofuran (THF) proceeded smoothly at -78 °C to give 4,6-O-benzylidene-1,2-dideoxy-3-C-(2-propenyl)-D-arabino-hex-1-enopyranose (**2a**) and ribo isomer **3a**. Similarly, 2-methyl-2-propenylmagnesium chloride selectively reacted at the carbonyl group of **1** to afford arabino isomer **2b** and ribo isomer **3b** (Table 1; entries 1 and 5). The configuration of C-3 of **2a** and **2b** was determined by NMR including NOE experiment on 3-O-methyl derivatives **4a** and **4b**. Although the yields of products were good in both cases, the reaction was essentially non-stereoselective.

The reaction of **1** with allylic aluminium and allylic titanium reagents again occurred at the carbonyl group and exhibited moderate to good levels of π-facial selectivity.[6)] Thus, diethyl-(2-propenyl)aluminium, prepared by the reaction of 2-propenylmagnesium chloride with diethylaluminium chloride,[7)] was allowed to react in situ with **1** at -78 °C, **2a** and **3a** being obtained in

93% isolated yield in a ratio of 5 : 1 (Table 1, entry 2). The reaction of diethyl(2-methyl-2-propenyl)aluminium with **1** afforded **2b** and **3b** in a ratio of 4 : 1 (Table 1, entry 6).

2-Propenyl- and 2-methyl-2-propenyltitanium triisopropoxides were prepared by the procedure reported by Reetz et al.[8)] Reaction of **1** with 2-propenyltitanium triisopropoxide proceeded smoothly at -78 °C to afford **2a** and **3a** in a ratio of 4 : 1 (Table 1, entry 3). In the reaction with 2-methyl-2-propenyltitanium triisopropoxides, π-facial selectivity rose to 10 : 1, favoring again bottom face attack (Table 1, entry 7). The reaction of magnesium chlorotetrakis(2-propanolato)-2-propenyltitanate[8)] with **1** afforded **2a** and **3a** in a ratio of 5 : 1 (Table 1, entry 4).[9)]





	2, 3, 4, 6, 7 a	2, 3, 4, 6, 7 b
R	H	CH3

Metal = MgCl, $\mathrm{AlEt_2}$, $\mathrm{Ti(OPr^i)_3}$, or $\mathrm{[Ti(OPr^i)_4]^-}$

Table 1. Reaction of **1** with organometallic reagents (5 equiv.) at -78 °C for 1 h

Entry	$\mathrm{CH_2{=}CR{-}CH_2{-}Metal}$	Solvent[a)]	Product 2, 3; R	Yield/% (2 + 3)	Ratio (2 : 3)
1	$\mathrm{CH_2{=}CHCH_2{-}MgCl}$	T[b)]	H	>99	1 : 1
2	$\mathrm{CH_2{=}CHCH_2{-}AlEt_2}$	T-H-DCM[c)]	H	93	5 : 1
3	$\mathrm{CH_2{=}CHCH_2{-}Ti(OPr^i)_3}$	T-DCM	H	96	4 : 1
4	$\mathrm{CH_2{=}CHCH_2{-}Ti(OPr^i)_4MgCl}$	T-DCM	H	95	5 : 1
5	$\mathrm{CH_2{=}C(CH_3)CH_2{-}MgCl}$	T-DCM	$\mathrm{CH_3}$	90	1.2 : 1
6	$\mathrm{CH_2{=}C(CH_3)CH_2{-}AlEt_2}$	T-H-DCM	$\mathrm{CH_3}$	95	4 : 1
7	$\mathrm{CH_2{=}C(CH_3)CH_2{-}Ti(OPr^i)_3}$	T-DCM	$\mathrm{CH_3}$	>99	10 : 1

a) T = Tetrahydrofuran; H = n-Hexane; DCM = Dichloromethane. b) Reaction in T-DCM gave practically same result. c) Reaction was carried out for 1.5 h.

4,6-O-Benzylidene-1,2-dideoxy-D-threo-hex-1-enopyranose-3-urose (**5**) also reacted with allylic organometallic reagents. In these reactions, the anionoid reagents exclusively attacked the bottom face of carbonyl group to afford the corresponding lyxo isomer **6a** or **6b** in good to excellent yields without any detectable formation of xylo isomers **7**. In the reaction with 2-methyl-2-propenylmagnesium chloride, a small amount of conjugate addition product **8** was isolated in addition to **6b**.[9)] The results are summarized in Table 2.[10)]

Table 2. Reaction of **5** with allylic organometallic reagents (5 equiv.) in THF-CH_2Cl_2 at -78 °C for 1 h

Entry	CH_2=CRCH_2-Metal	Product	Yield/%
1	CH_2=CHCH_2-MgCl	**6a**	90
2	CH_2=CHCH_2-AlEt_2[a)]	**6a**	80
3	CH_2=CHCH_2-Ti(OPr^i)$_3$	**6a**	97
4	CH_2=C(CH_3)CH_2-MgCl[b)]	**6b**	87[c)]
5	CH_2=C(CH_3)CH_2-AlEt_2[a, b)]	**6b**	97
6	CH_2=C(CH_3)CH_2-Ti(OPr^i)$_3$	**6b**	>99

a) Reaction was carried out in THF-CH_2Cl_2-n-hexane.
b) 3 Equiv. of the organometallic reagents were used.
c) Compound **8** was isolated in 7% yield.

Although the origin of stereoselectivity observed in the reaction of **5** with allylic organometallic reagents has not yet been elucidated, the results suggest that steric and/or electrostatic repulsion between the axial oxygen at the C-4 and incoming anionoid reagents are responsible rather than chelation-directed diastereoselection.[11)]

The procedure developed in this paper makes functionalized cyclic enol ethers having a chiral tertiary carbinol center readily available and suggests a number of interesting possibilities for the synthesis of chiral natural products.

The following experimental procedure is representative. To a solution of **5** (0.5 mmol; 116 mg) in CH_2Cl_2 (3 ml) was added 2-methyl-2-propenylmagnesium chloride (1.09 ml; 1.37 M THF solution) at -78 °C under nitrogen atmosphere. After the mixture was stirred for 1h, the reaction was quenched by the addition of saturated aqueous NH_4Cl and warmed to room temperature. The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. The residue was separated by silica gel column chromatography (n-hexane-AcOEt = 4: 1) to give **6b** (125 mg, 87%) and **8** (10 mg, 7%).

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9) The configuration of the C-3 position of **6a**, **6b** and C-1 of **8** was determined by NMR experiment involving NOE measurement.

10) The Lewis acid mediated addition of allylsilanes and allylstannanes to **1** or **5** has not been examined. For a review of allylsilanes, see; A. Hosomi, *Acc. Chem. Res.*, **21**, 200 (1988). For a review of allylstannanes, see; Y. Yamamoto, *Acc. Chem. Res.*, **20**, 243 (1987).

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