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Regioselective Introduction of Allylic Groups into the C-2 or C-3 Position of Furanoside Rings

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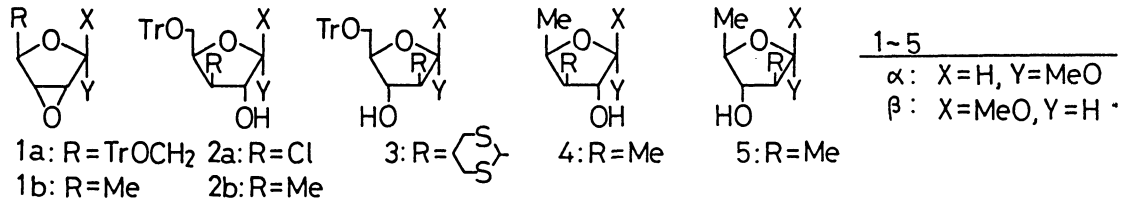
The reaction of α-anomers of methyl 2,3-anhydro-D-ribo- and D-allo-furanosides with allylic Grignard reagents predominantly gave the corresponding 2-deoxy-2-C-alkenylfuranosides. In contrast, their β-anomers selectively gave 3-C-alkenyl derivatives. Preparation of a synthon of the C-4～C-9 fragment common to various 16-member macrolide antibiotics is also described.

Carbohydrates have been extensively utilized as starting materials for the synthesis of natural products with multiple centers of chirality.[1] One of the most fundamental processes encountered in this approach is regioselective activation of the specific carbon atom of the substrate in the form amenable to introducing a desired substituent. Anhydropyranosides with locked conformation such as 4,6-O-alkylidene-2,3-anhydrohexopyranosides have oftentimes used as activated sugars, because the position of nucleophilic attack is generally predictable in terms of diaxial opening of oxiran ring.[2] In contrast, prediction of the reaction sites of 2,3-anhydrofuranosides is not easy. For example, either α- or β-anomer of methyl 2,3-anhydro-5-O-trityl-D-ribofuranoside (α- and β-1a) reacts with MeMgCl to give the corresponding 3-chloroxylofuranosides (α- and β-2a) and 3-C-methyl-xylofuranosides (α- and β-2b) irrespective of anomeric configuration,[3] while predominant C-2 attack takes place in the reaction of α-1 with 1,3-dithian-2-yl-lithium giving 2-deoxy-2-C-(1,3-dithian-2-yl) derivative (α-3).[4] Lithium dimethylcuprate reacts with 2,3-anhydro-5-deoxy-α-D-ribofuranoside (α-1b) to yield 3-C-methyl and 2-C-methyl derivatives (α-4 and α-5) in a ratio of 1 : 5.4, while the corresponding β-isomer (β-1b) does not react with the cuprate (Scheme 1).[5]

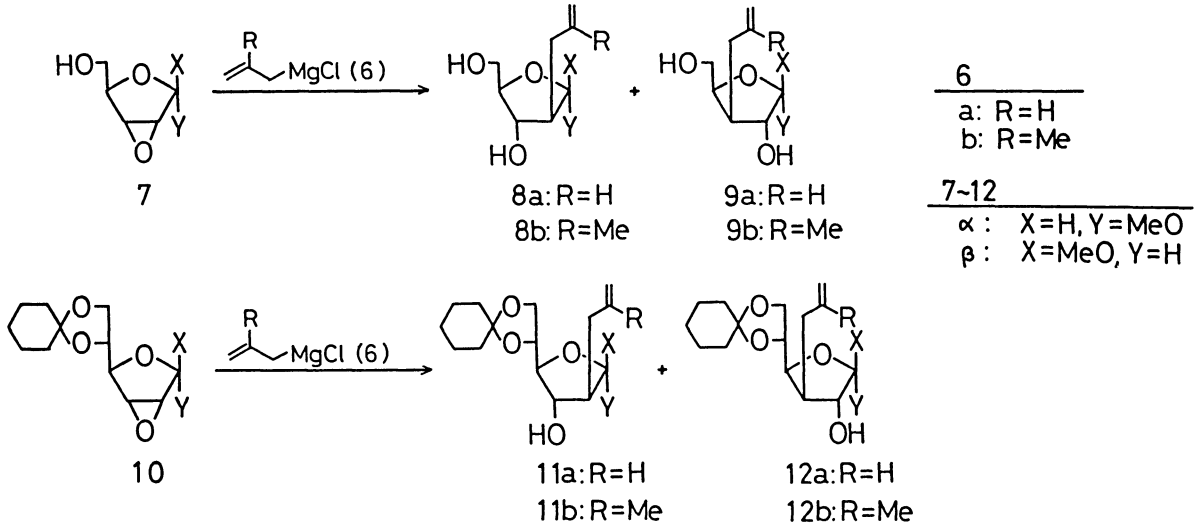


Scheme 1.

In this communication, we wish to report the regioselective reaction of α- and β-anomers of methyl 2,3-anhydro-D-ribofuranoside and methyl 2,3-anhydro-5,6-O-

cyclohexylidene-D-allofuranoside with 2-propenyl- or 2-methyl-2-propenyl-magnesium chloride leading to branched-chain sugars having allylic substituents,[6] which can be converted into various oxygenated carbon chains.[7]

The reaction of methyl 2,3-anhydro-α-D-ribofuranoside (α-7) with 2-propenylmagnesium chloride (6a) or 2-methyl-2-propenylmagnesium chloride (6b) in tetrahydrofuran (THF) at 0 °C for 2 h selectively afforded the corresponding 2-deoxy-2-C-alkenylarabinofuranosides (α-8a and α-8b) in good yields. The reaction of methyl 2,3-anhydro-5,6-O-cyclohexlidene-α-D-allofuranoside (α-10)[9] with 6a or 6b again occurred exclusively at the C-2 position to yield altrofuranoside derivatives (α-11a and α-11b) in nearly quantitative yields (Table 1, entries 1, 2, 5, 6).[8] In these reactions, no detectable amount of the corresponding regioisomers (α-9a, α-9b, α-12a, and α-12b) were formed.



Scheme 2.

Table 1. Reaction of 2,3-anhydrofuranosides with allylic Grignard reagents in THF

Entry	Reactants	Reaction conditions[a] temp/°C	time	Product (isolated yield/%)		Recovery/%
1	α-7 + 6a	0	2 h	α-8a (89)	α-9a (0)	-
2	α-7 + 6b	0	2 h	α-8b (89)	α-9b (0)	-
3	β-7 + 6a	rt	1 d	β-8a (0)	β-9b (90)[b]	-
4	β-7 + 6b	rt	1 d	β-8b (0)	β-9b (62)[b]	27
5	α-10 + 6a	rt	1 d	α-11a (95)	α-12a (0)	-
6	α-10 + 6b	0	2 h	α-11b (100)	α-12b (0)	-
7	β-10 + 6b	rt	1 d	β-11b (0)	β-12b (37)[b]	61
8	β-10 + 6b	rt	1 d	β-11b (0)	β-12b (96)[c]	-

a) rt = Room temperature. b) A trace of impurity was included. c) Reaction was carried out in diethyl ether.

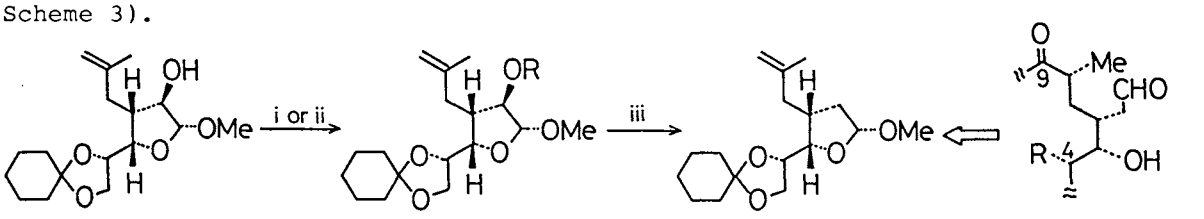
Contrary to the cases of α-anomers, the reactions of the corresponding β-anomers (β-7, β-10) with allylic Grignard reagents resulted in the predominant

cleavage at the C-3 position to give xylo- and gluco-furanosides (β-9a, β-9b, and β-12b; Table 1, entries 3, 4, 7, 8).[8] In the reaction of β-anomers, thin layer chromatography (tlc) of crude reaction mixture indicated the formation of a trace of by-product which could not be identified. The yield of β-12b increased to 96% when the reaction of β-10 with 6b was carried out in diethyl ether, where neither side product nor starting material (β-10) could be detected as indicated by tlc of the crude reaction mixture.

As mentioned above, 2-propenyl groups could be selectively introduced into either C-2 or C-3 position of furanosides depending on the anomeric configuration, i.e., α-anomers gave 2-C-alkenyl derivatives while β-anomers afforded 3-C-alkenyl derivatives. The regioselectivity observed would be explained by cooperation of steric and electrostatic effects. Thus, for β-anomers, electrostatic repulsion between β-OMe group and incoming anionoid reagents would play an important role for C-3 selectivity.

In order to convert β-12b into a common precursor (14) corresponding to the C-4~C-9 fragments (15) of various kinds of 16-member macrolide antibiotics such as carbomycin, rosaramicin, and tylosin, deoxygenation of the C-2 position was examined. When 2-O-mesyl derivative of β-12b (13a) was allowed to react with $LiAlH_4$ or $LiEt_3BH$, demesylation occurred regenerating β-12b. Treatment of 13a with Na in liquid ammonia afforded the expected deoxygenated product (14) in 17% yield and β-12b was again formed in 66% yield.[10]

The deoxygenation of the C-2 position was successfully carried out by Barton procedure.[11] Thus, β-12b was converted into the phenyl thiocarbonate (13b), followed by the reaction with tri-n-butyltin hydride to give 14 in 66% overall yield (Scheme 3).



i) MsCl, i-Pr_2EtN, Et_3N, $CHCl_3$, rt, 3 d (91%).
ii) PhOC(S)Cl, Py, rt, 2 d (78%). iii) n-Bu_3SnH, AIBN, toluene, reflux, 4 h (84%).

Scheme 3.

General procedure: Allyl chloride (8.42 g, 0.11 mol) or 2-methyl-2-propenyl chloride (9.96 g, 0.11 mol) was slowly added to Mg (2.43 g, 0.10 mol) in THF (50 ml) at 0 °C (ice bath) under Ar. 2,3-Anhydrofuranoside (7 or 10; 1.0 mmol) in THF (1 ml) was treated with a portion (5 equiv.) of the Grignard reagent under the conditions shown in Table 1. The reaction mixture was diluted with $CHCl_3$ (30 ml), followed by the addition of H_2O (1 ml), dried with anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was separated by silica-gel chromatography yielding desired product.

The work described in this paper demonstrates the regioselective introduction of allylic substituents on C-2 or C-3 position of furanosides and suggests a number of interesting possibilities for further work.[7)]

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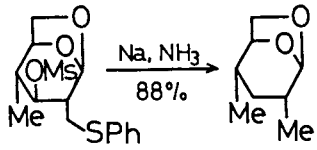
7) See for example, T. Mikami, A. Katoh, and O. Mitsunobu, Tetrahedron Lett., in press.

8) The structural elucidation of the products was made by NMR spectral data.

9) A mixture of methyl 5,6-O-cyclohexylidene-3-O-mesyl-α- and -β-D-glucofuranosides was prepared according to the procedure reported by Kawana and Emoto; M. Kawana, and S. Emoto, Tetrahedron Lett., 1975, 3395. The anomeric mixture was treated with sodium methoxide at room temperature for 2 d to give 2,3-anhydro-α-allofuranoside (α-10) and the β-anomer (β-10) in 25% and 41% isolated yields, respectively. When the β-isomer of 3-O-mesyl derivative was isolated and subjected to epoxidation, β-10 was obtained in 67% yield. Epoxidation via 3-O-tosylate gave β-10 in 59% yield under practically identical conditions.

10) This procedure could be successfully utilized in the deoxygenation of sterically hindered position. O. Mitsunobu, T. Moroboshi, and H. Tsutsui, unpublished.



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