Regioselective Introduction of 2-Propynyl Groups into the C-2 or C-3 Position of Furanoside Ring

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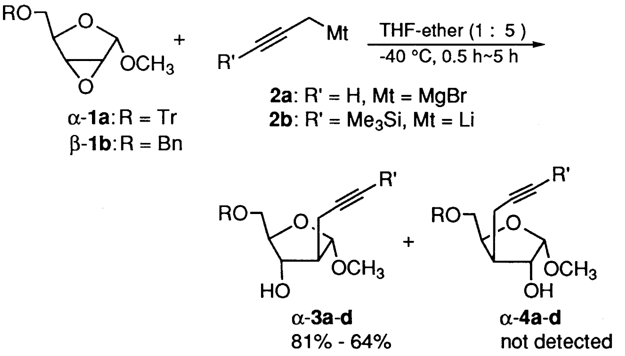
The reaction of methyl 2,3-anhydro-α-D-ribofuranoside or methyl 2,3-anhydro-5,6-*O*-cyclohexylidene-α-D-allofuranoside with 2-propynyl metallic reagents exclusively gave the corresponding 2-*C*-(2-propynyl)-*arabino*-pentofuranosides and 2-*C*-(2-propynyl)-*altro*-hexofuranosides, respectively. In contrast, the β-anomers were selectively attacked at the position 3 to afford the corresponding 3-*C*-(2-propynyl)furanosides.

Carbohydrates have attracted attention 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 a carbohydrate. In this context, anhydropyranosides with locked conformation have been widely utilized in organic synthesis because the reaction site attacked by nucleophiles could be predicted in terms of diaxial oxirane-ring opening.[2] On the other hand, the reactions of 2,3-anhydrofuranosides with nucleophiles are more complicated, the reaction site being difficult to predict.[3] In view of the clean regioselectivity observed in the reaction of α- and β-furanosides with allylic Grignard reagents,[3] the same trend would be expected in the reaction of the furanosides with 2-propynyl metallic reagents. In this communication, we wish to report regioselective introduction of 2-propynyl groups into furanoside frameworks.

At the outset, methyl 2,3-anhydro-5-*O*-trityl-α-D-ribofuranoside (α-**1a**) was allowed to react with 2-propynylmagnesium bromide (**2a**)[4] in THF-ether (1 : 5) at -40 °C for 1.5 h to give methyl 2-deoxy-2-*C*-(2-propynyl)-5-*O*-trityl-α-D-*arabino*-pentofuranoside (α-**3a**) in 64% yield. Under similar conditions, the reaction of methyl 2,3-anhydro-5-*O*-benzyl-α-D-ribofuranoside (α-**1b**) with **2a** gave the expected 2-*C*-(2-propynyl)-5-*O*-benzyl-α-D-*arabino*-pentofuranoside (α-**3b**) in 69% yield. In these reactions, no detectable formation of regioisomers α-**4a** and α-**4b** could be observed (Scheme 1; Table 1, entries 1 and 2).



Scheme 1. (For α-**3a-d** and α-**4a-d**, see Table 1).

3-Trimethylsilyl-2-propynyllithium (**2b**)[5] reacted smoothly with α-**1a** and with α-**1b** to give the corresponding 2-deoxy-2-*C*-(3-trimethylsilyl-2-propynyl)-*arabino*-pentofuranosides α-**3c** and α-**3d** in 81% and 76% yields, respectively. In these reactions, no regioisomer α-**4c** or α-**4d** was again detected (Scheme 1; Table 1, entries 3 and 4).

Contrary to the cases of the α-anomers, the reactions of the corresponding β-anomers with either **2a** or **2b** were complicated. Thus, no reaction took place when β-**1a** was treated with **2a** in

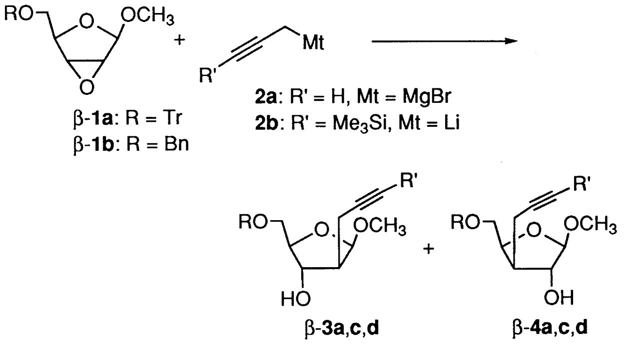
Table 1. Reaction of 2,3-anhydrofuranosides with 2-propynyl metallic reagents

Entry	Substituents of substrate, reagent, and product R	R'	Substrate	Reagent	Solvent[a]	Temp/°C	Time/h	Product: yield/%[b]		Recovery of substrate/%
1	Tr	H	α-**1a**	**2a**	T-E	-40	1.5	α-**3a**: 64	α-**4a**: nd	nd
2	Bn	H	α-**1b**	**2a**	T-E	-40	2.0	α-**3b**: 69	α-**4b**: nd	nd
3	Tr	TMS	α-**1a**	**2b**	T-E	-40	0.5	α-**3c**: 81	α-**4c**: nd	nd
4	Bn	TMS	α-**1b**	**2b**	T-E	-40	5.0	α-**3d**: 76	α-**4d**: nd	nd
5	Tr	H	β-**1a**	**2a**	T	-10	24	β-**3a**: nd	β-**4a**: nd	90
6	Tr	H	β-**1a**	**2a**	E	-10	24	β-**3a**: nd	β-**4a**: 36	63
7	Tr	H	β-**1a**	**2a**	E	rt	24	β-**3a**: nd	β-**4a**: 99	nd
8	Tr	TMS	β-**1a**	**2b**	E	-20	6	β-**3c**: nd	β-**4c**: nd	74
9	Bn	TMS	β-**1b**	**2b**	E	-20	6	β-**3d**: nd[c]	β-**4d**: nd	nd
10	-	H	α-**5**	**2a**	T-E	-40	2	α-**6a**: 62	α-**7a**: nd	nd
11	-	TMS	α-**5**	**2b**	T-E	-40	0.25	α-**6b**: 75	α-**7b**: nd	nd
12	-	H	β-**5**	**2a**	E	-10	24	β-**6a**: nd	β-**7a**: 89	nd
13	-	TMS	β-**5**	**2b**	E	-20	6	β-**6b**: nd	β-**7b**: nd	14

[a] T-E = THF : ether = 1 : 5. T = THF. E = ether. [b] nd = Could not be detected. [c] Although an unstable single product was obtained, the structure could not be determined.

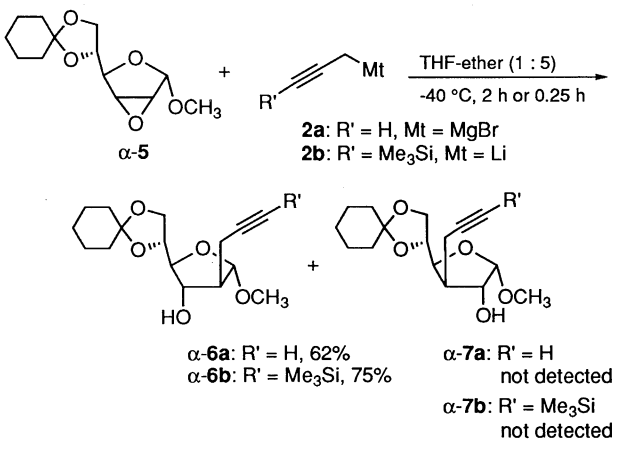
THF at -10 °C for 24 h (Table 1, entry 5), while, in ether at -10 °C, methyl 3-deoxy-3-*C*-(2-propynyl)-β-D-*xylo*-pentofuranoside (β-**4a**) was obtained in 36% yield with 63% recovery of β-**1a** (Scheme 2, Table 1, entry 6). When the reaction of β-**1a** with **2a** was carried out in ether at room temperature for 24 h, β-**4a** was obtained in nearly quantitative yield (Scheme 2, Table 1, entry 7).

No reaction took place between **2b** and β-**1a** (Scheme 2, Table 1, entry 8). On the other hand, **2b** reacted with β-**1b** to afford a single product which could not be identified because of instability (Scheme 2, Table 1, entry 9).



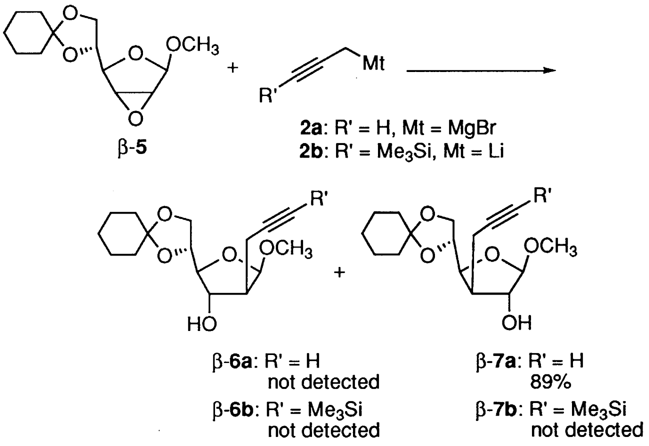
Scheme 2. (For β-**3a,c,d** and β-**4a,c,d**, see Table 1).

Reaction of methyl 2,3-anhydro-5,6-*O*-cyclohexylidene-α-D-allofuranoside (α-**5**) with **2a** and with **2b** in THF-ether (1 : 5, v/v) at -40 °C for 2 h gave methyl 5,6-*O*-cyclohexylidene-2-deoxy-2-*C*-(2-propynyl)-α-D-*altro*-hexofuranoside (α-**6a**) and methyl 5,6-*O*-cyclohexylidene-2-deoxy-2-*C*-(3-trimethylsilyl-2-propynyl)-α-D-*altro*-hexofuranoside (α-**6b**) in 62% and 75% yields, respectively, without any detectable formation of regioisomers α-**7a** and α-**7b** (Scheme 3, Table 1, entries 10 and 11).



Scheme 3.

Although β-**5** reacted smoothly with the Grignard reagent **2a** in ether at -10 °C to give β-**7a** in 89% yield, the reaction with the lithium reagent **2b** resulted in the formation of a complex mixture of products (Scheme 4, Table 1, entries 12 and 13).



Scheme 4.

The observed regioselectivity may be rationalized on the bases of steric and electrostatic effects.[3]

The procedures described in this paper make 2-*C*-(2-propynyl)furanosides and 3-*C*-(2-propynyl)furanosides readily available. These compounds would be expected to have versatile utilities in synthetic organic chemistry.

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References and Notes

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3 J. Ohmori, T. Shiotani, and O. Mitsunobu, *Chem. Lett.*, **1990**, 303, and references cited therein.

4 See for example, P. Deslongchamps, D. D. Rowan, N. Pothier, T. Sauvé, and J. K. Saunders, *Can. J. Chem.*, **59**, 1105 (1981).

5 3-Trimethylsilyl-2-propynyllithium (**2b**) was generated by the treatment of 1-trimethylsilyl-1-propyne with *tert*-butyllithium at -78 °C and then stirred at 0 °C for 1 h. a) E. J. Corey and C. Rücker, *Tetrahedron Lett.*, **23**, 719 (1982). b) K. Furuta, M. Ishiguro. R. Haruta, N. Ikeda, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **57**, 2768 (1984).

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 70th birthday.