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Environmentally benign and stereoselective formation of β-mannosidic linkages utilizing 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-protected mannopyranosyl phosphite and montmorillonite K-10

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Abstract

An environmentally benign and stereoselective β-mannopyranosylation has been developed employing 4,6-*O*-benzylidene-protected mannopyranosyl diethyl phosphite as a glycosyl donor and montmorillonite K-10 as an activator.

Keywords: Glycosidation; Glycosyl phosphite; β-Mannopyranoside; Solid acid; Montmorillonite K-10

Glycosubstances, including glycoconjugates and oligosaccharides, continue to be a central focus of research both in chemistry and biology (for reviews on *O*-glycosidation see Ref. 1) Although β-mannopyranosidic linkages frequently appear in many biologically important natural products, such as asparagine-linked glycoproteins and certain antibiotics, the stereoselective construction of β-mannopyranosides has proved particularly difficult to achieve, because the axial β-hydroxy group at C-2 and the anomeric effect strongly block access to the β face (for review on β-mannosylation, see Ref. 2). To overcome this problem, a number of indirect methods have been developed and their high potency demonstrated.[3] However, it is clear that a direct method would be ideal in terms of efficiency and practicality.[4] Paulsen reported pioneering work on the direct construction of this linkage using an α-mannopyranosyl halide and silver silicate.[5] Notable recent work in this area is Crich's method using a 4,6-*O*-benzylidene-protected mannopyranosyl sulfoxide or thioglycoside as the glycosyl donor and a Lewis acid, triflic anhydride, or benzensulfonyl triflate, as a promoter.[6] However, a practical and environmentally benign method not using a heavy metal or a Lewis acid (components not reusable and contaminating the reaction solvent) is urgently needed both in the laboratory and in industry. Such 'greening' of chemical glycosidation could include the use of a heterogeneous and reusable solid acid as an activator. A direct and stereoselective construction of β-mannopyranosidic linkages in a practical and environmentally friendly manner is thus of particular interest. Herein we report a direct and β-stereoselective glycosidation of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-protected mannopyranosyl diethyl phosphite with several alcohols, using a heterogeneous and reusable solid acid, namely montmorillonite K-10 (Fig. 1).

In our previous studies, we demonstrated[7,8] with nonparticipating groups the stereoselective β-glycosidation of benzyl-protected glucopyranosyl and 2-deoxy-arabino-hexopyranosyl diethyl phosphites with alcohols, using montmorillonite K-10. As a challenging extension of our studies, we first examined the glycosidation of the 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl diethyl phosphite (**1**) and an sugar alcohol **2** using montmorillonite K-10[9] under various conditions. These results are summarized in Table 1. First, it was found that the glycosidation of **1** and **2** proceeded smoothly in CH_2Cl_2 to give the disaccharide **9** in high yield with good β-stereoselectivity. Other solvents examined such as PhMe, Et_2O, and MeCN, were less effective than CH_2Cl_2 with respect to both the chemical yield and the β-stereoselectivity (entries 1–4 in

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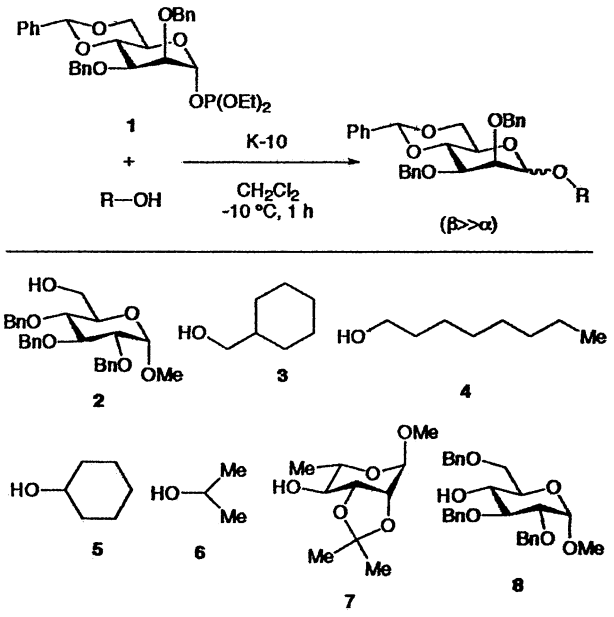
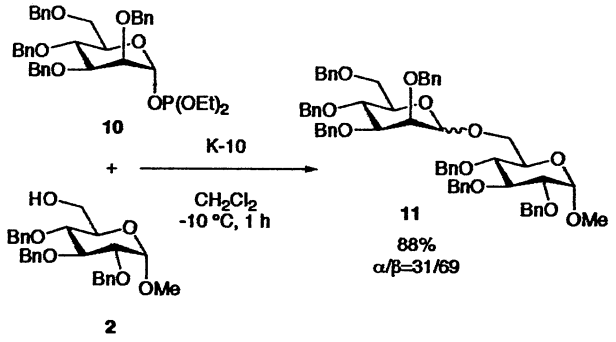


Fig. 1. Overview of synthesis.

Table 1). Furthermore, it was confirmed that a lower reaction temperature, < -30 °C, significantly decreased the chemical yield, while the stereoselectivity was not changed (entries 5 and 6). However, the use of 200 wt.% montmorillonite K-10 increased the chemical yield with good β-stereoselectivity (entries 5, 7–9 in Table 1). Thus, the glycosidation of **1** and **2** was best effected by using 200 wt.% montmorillonite K-10 in CH_2Cl_2 at -10 °C for 1 h to give **9** in 93% yield with an α/β ratio of 15/85. The optimized conditions for stereoselectively in obtaining the β-mannopyranoside significantly differed from those for the previously reported β-stereoselective glycosidations of glucopyranosyl and 2-deoxy-arabino-hexopyranosyl diethyl phosphites.[7,8] It was noted that the chemical yields for glycosidation of **1** and **2** using homogeneous Lewis acid, Me_3SiOTf, and the protic acid, TfOH, under similar conditions, were much lower than that with montmorillonite K-10 because of partial hydrolysis[10] of the benzylidene acetal group of **1** (entries 10 and 11 in Table 1). Moreover, although the manno-pyranosyl triflate, which is the key intermediate for obtaining high β-stereoselectivity in Crich's method,[6] was not present in this case, the 4,6-*O*-benzylidene functionality of **1** was found to be helpful for achieving good β-stereoselectivity.[11] Indeed, a modest α/β ratio of 31/69 was observed in the glycosidation of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl diethyl phosphite **10** and **2** under similar conditions (Scheme 1).

Armed with these favorable results, our attention then turned to the generality of this reaction. The glycosidation of **1** with other primary and secondary alcohols **3**–**8** were next examined. From the results summarized in Table 2, it is clear that all the glycosidations of **1** and **3**–**8** using 200 wt.% montmorillonite K-10 in CH_2Cl_2 at -10 °C for 1 h, as well as that of **2**, effectively produced the corresponding β-mannopyranosides in good to high yields, with good stereoselectivities. It is noteworthy that acid-sensitive groups, such as benzylidene and isopropylidene acetals, were not cleaved under these conditions. Furthermore, the poorly reactive acceptor **8** also underwent smooth coupling with **1** to furnish the corresponding β-mannopyranoside in good yield and high stereoselectivity.



Scheme 1.

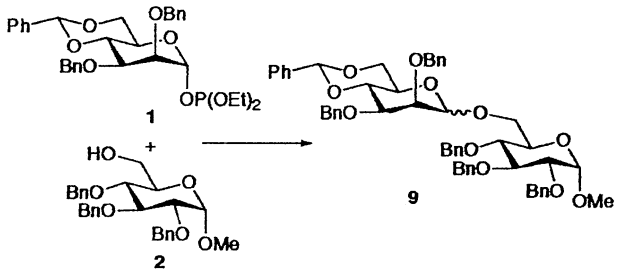
Finally, we tested recycling of the solid acid for the glycosidation of **1** and **3**. After filtration, washing with chloroform and methanol, and heating at 100 °C/1 mm Hg for 12 h, the montmorillonite K-10 could be reused for at least three times and showed similar high yields and stereoselectivities as shown in Table 3.

A general experimental procedure[†]: To a stirred solution of the glycosyl phosphite **1** ($\alpha/\beta \Rightarrow 99/1$, 0.1 mmol) and an alcohol (0.2 mmol) in dry CH_2Cl_2 (1 mL) was added montmorillonite K-10 (200 wt.% to the glycosyl donor **1**). After stirring for 1 h at -10 °C, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography gave the mannopyranosides.

In summary, we have developed an environmentally benign and stereoselective strategy for the direct synthesis of β-mannopyranosides from mannopyranosyl diethyl phosphite and alcohols using a heterogeneous and reusable solid acid. This simple protocol, affording high yield and stereoselectivity, should find wide application in the synthesis of biomolecules and functional materials. Further studies along this line are currently underway.

[†] All α- and β-mannopyranosides were purified by column chromatography on silicagel and were fully characterized by spectroscopic means. The anomeric configuration was determined by comparison with authentic samples with the aid of ^1H NMR analysis.

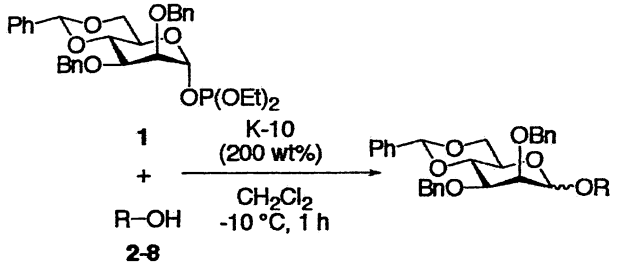
Table 1
Glycosidation of **1** and **2** under various conditions[a]



Entry	Activator	Amount of activator	Solvent (0.1 M)	Temperature (°C)	Time (h)	Yield (%)[b]	α/β ratio[c]
1	K-10	150 wt.%	CH_2Cl_2	0	1	89	16/84
2	K-10	150 wt.%	PhMe	0	1	85	38/62
3	K-10	150 wt.%	Et_2O	0	1	74	37/63
4	K-10	150 wt.%	MeCN	0	1	12	42/58
5	K-10	100 wt.%	CH_2Cl_2	−10	1	84	16/84
6	K-10	100 wt.%	CH_2Cl_2	−30	1	74	17/83
7	K-10	50 wt.%	CH_2Cl_2	−10	1	61	19/81
8	K-10	150 wt.%	CH_2Cl_2	−10	1	91	16/84
9	K-10	200 wt.%	CH_2Cl_2	−10	1	93	15/85
10	TMSOTf	0.3 mol.%	CH_2Cl_2	−10	1	50	17/83
11	TfOH	0.3 mol.%	CH_2Cl_2	−10	1	60	18/82

[a] All reactions were carried out by use of **2** to **1**.
[b] Isolated yields after purification by column chromatography.
[c] a:b Ratios were determined by 300 MHz 1H-NMR analysis.

Table 2
Glycosidation of **1** and several alcohols **2**–**8** by montmorillonite K-10



Entry	Alcohols[a]	Yield (%)[b]	α/β ratio[c]
1	**2**	93	15/85
2	**3**	92	11/89
3	**4**	84	13/87
4	**5**	85	12/88
5	**6**	86	10/90
6	**7**	92	15/85
7	**8**	78	13/87

[a] All reactions were carried out by use of 2.0 equiv. of alcohol.
[b] Isolated yields after purification by column chromatography.
[c] a:b Ratios were determined by 300 MHz 1H-NMR analysis.

Table 3
Recycling of montomorillonite K-10 in glycosidation of **1** and **3**

Recycling number	0	1st	2nd	3rd
Yield (%)	92	91	86	82
α/β ratio	11/89	12/88	10/90	9/91

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