Environmentally Benign and Stereoselective Construction of 2-Deoxy and 2,6-Dideoxy-β-glycosidic Linkages Employing 2-Deoxy and 2,6-Dideoxyglycosyl Phosphites and Montmorillonite K-10

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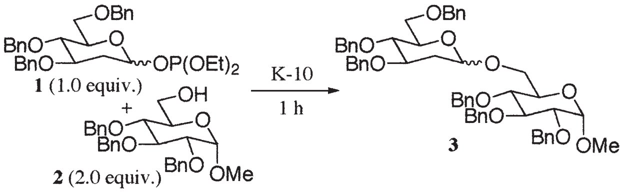
The β-stereoselective glycosidations of 2-deoxy- and 2,6-dideoxyglycosyl diethyl phosphites with alcohols using a heterogeneous and environmentally benign solid acid, montmorillonite K-10, have been developed.

Highly effective, simple and environmentally benign glycosidations have attracted considerable attention in current synthetic organic chemistry related to both biomolecules and functional materials.[1] Some of the challenges for the greening of chemical glycosidations may include the use of a heterogeneous and reusable solid acid as the activator. On the other hand, deoxy sugars frequently appear in the glycosidic components of the bioactive substances.[2,3] Among them, 2-deoxyglycosides including 2,6-dideoxyglycosides are some of the most common and important, and found in many biologically attractive natural products. However, the direct and stereoselective β-glycosidation of a 2-deoxy sugar is quite difficult due to the anomeric effect and the lack of the stereodirecting anchimeric assistance from the C-2 position.[1c,4,5] The most extensively developed strategy for the synthesis of 2-deoxy-β-glycosides utilizes donors with equatorial C-2 heteroatom substituents that are reductively removed after the glycosidation event. Furthermore, most of these methods use a homogeneous Lewis acid as the activator, which contaminates the reaction solvent and can not be reused. Therefore, the development of direct and stereoselective β-glycosidations of 2-deoxy sugar in an environmentally compatible manner is of particular interest. Herein, we report the direct and stereoselective glycosidations of the 2-deoxy- and 2,6-dideoxyglycosyl diethyl phosphites[6,7] with alcohols using a heterogeneous and environmentally friendly solid acid, montmorillonite K-10, for the stereoselective synthesis of the 2-deoxy- and 2,6-dideoxy-β-glycosides.

In our previous studies, we have demonstrated the novel and stereoselective β-glycosidations of a benzyl-protected glucopyranosyl diethyl phosphite and alcohols using montmorillonite K-10 with a non-participating group.[8] Therefore, based on these results, we first examined the glycosidations of the totally benzylated 2-deoxyglucopyranosyl diethyl phosphite **1** and an alcohol **2** using montmorillonite K-10[9] under several conditions. These results are summarized in Table 1. It was unfortunately found that the glycosidation of **1** ($\alpha/\beta = 80/20$) and **2** under the conditions similar to the optimized conditions[8] for the benzylated glucopyranosyl diethyl phosphite gave the 2-deoxyglucopyranoside **3** in low yield with low stereoselectivity (entry 1 in Table 1). However, when the glycosidation was performed at a lower temperature, $-78\,^{\circ}$C, a better yield and β-stereoselectivity were obtained (entry 2 in Table 1). In addition, it was found that the glycosidations of **1** and **2** in Et_2O at $-78\,^{\circ}$C effectively proceeded to afford **3** in high yield with good β-stereoselectivity (entry 7 in Table 1). Et_2O was shown to be superior to the other solvents (entries 3–7 in Table 1) with respect to both the chemical yield and unusual β-stereoselectivity. Moreover, it was confirmed that the chemical yield and β-stereoselectivity were highly dependent on the amount of montmorillonite K-10 and the reaction temperature. Thus, the highest chemical yield and β-stereoselectivity were realized when 100 wt% montmorillonite K-10 was used in Et_2O at $-78\,^{\circ}$C for 1 h (entries 7–12 in Table 1). The optimized conditions for selectively giving the 2-deoxy-β-glucopyranoside significantly differed from that for the previously reported β-stereoselective glucosylation.

Table 1. Glycosidations of **1** and **2** using montmorillonite K-10 under several conditions

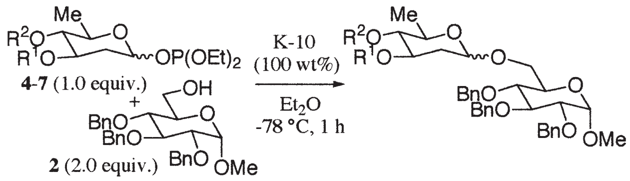


Entry	K-10 /wt%	Solvent	Temp. /°C	Yield /%	α/β Ratio[a]
1	100	CH_2Cl_2/MeCN=10:1	-20	58	43/57
2	100	CH_2Cl_2/MeCN=10:1	-78	78	26/74
3	100	CH_2Cl_2	-78	87	23/77
4	100	EtCN	-78	81	32/68
5	100	PhMe	-78	69	25/75
6	100	THF	-78	84	47/53
7	100	Et_2O	-78	87	19/81
8	200	Et_2O	-78	82	24/76
9	50	Et_2O	-78	80	21/79
10	20	Et_2O	-78	63	21/79
11	100	Et_2O	-50	80	31/69
12	100	Et_2O	-20	77	44/56

[a] α:β Ratios were determined by HPLC analysis.

With these favorable new results, next our attention turned to the glycosidations of a typical 2,6-dideoxy sugar, olivose, because β-olivoside is a very common and important 2,6-dideoxyglycoside.[2,3] Therefore, we examined the glycosidations of the benzylated olivosyl diethyl phosphites **4** ($\alpha/\beta = 86/14$), **5** ($\alpha/\beta = 72/28$), **6** ($\alpha/\beta = 89/11$) and **7** ($\alpha/\beta = 79/21$) with **2**. These results are summarized in Table 2. It was found, in this

Table 2. Glycosidations of **4–7** and **2** using montmorillonite K-10



Entry	Donor	R^1	R^2	Yield /%	α/β Ratio[a]
1	**4**	Bn	Bn	76	20/80
2	**5**	Bn	Bz	92	10/90
3	**6**	Bz	Bn	72	22/78
4	**7**	Bz	Bz	68	16/84

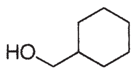
[a] α:β Ratios were determined by HPLC analysis.

Table 3. Glycosidations of **1** and **5** with **2**, **8–13** using montmorillonite K-10

$$\underset{(1.0\text{ equiv.})}{\mathbf{1}\text{ or }\mathbf{5}} + \underset{(2.0\text{ equiv})}{\mathbf{2},\mathbf{8}\text{-}\mathbf{13}} \xrightarrow[\text{Et}_2\text{O},\ -78\,^\circ\text{C},\ 1\text{ h}]{\text{K-10 (100 wt\%)}} \text{2-Deoxy or 2,6-dideoxyglycosides}$$

Entry	Donor	Accepter	Yield /%	α/β Ratio[a]
1	**1**	**2**	87	19/81
2	**1**	**8**	93	17/83
3	**1**	**9**	94	14/86
4	**1**	**10**	97	22/78
5	**1**	**11**	96	23/77
6	**1**	**12**	88	21/79
7	**1**	**13**	70	29/71
8	**5**	**2**	92	10/90
9	**5**	**8**	86	14/86
10	**5**	**9**	90	10/90
11	**5**	**10**	95	19/81
12	**5**	**11**	86	17/83
13	**5**	**12**	89	17/83
14	**5**	**13**	82	15/85

[c] α:β Ratios were determined by HPLC analysis.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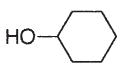
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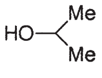
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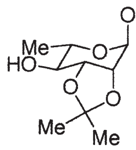
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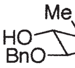
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case, that the chemical yield and stereoselectivity were significantly dependent on the protecting groups of the C-3 and 4 hydroxy groups of the donors, and the C-4 acyl group significantly assisted the β-stereoselectivity by the participating effect.[10] Thus, the glycosidations of **5** and **2** using 100 wt% montmorillonite K-10 in Et_2O at $-78\,^\circ C$ for 1 h effectively proceeded to furnish the corresponding olivosides in high yield with high β-stereoselectivity (entry 2 in Table 2).

Based on these results, the glycosidations of **1** and **2** using other primary and secondary alcohols **8–13** were next examined. From the results summarized in Table 3, it was found that all the glycosidations of **1** and **5** with **8–13** using 100 wt% montmorillonite K-10 in Et_2O at $-78\,^\circ C$ for 1 h, as well as that of **2**, effectively proceeded to give the corresponding 2-deoxy-β-glucopyranosides and β-olivosides, respectively, in high yields with good stereoselectivities.

Finally, we tested the solid acid recycling in the glycosidations of **1** and **8**. After filtration, washing with chloroform and methanol, and heating at 100 °C/1 mmHg for 12 h, the montmorillonite K-10 was reused for at least three times and showed high yields and stereoselectivities; 1st (93%, 17/83), 2nd (89%, 17/83), 3rd (89%, 17/83), and 4th (87%, 17/83).

A general experimental procedure: To a stirred solution of the glycosyl phosphite **1** ($\alpha/\beta = 80/20$, 0.1 mmol) or **5** ($\alpha/\beta = 72/28$, 0.1 mmol) and an alcohol (0.2 mmol) in dry Et_2O (1 ml) was added montmorillonite K-10 (100 wt% to the glycosyl donor **1** or **5**). After stirring for 1 h at $-78\,^\circ C$, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography gave the 2-deoxyglucopyranosides or the olivosides.

References and Notes

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9 Montmorillonite K-10 was purchased from Aldrich Chemical Company, Inc. and dried at 200 °C/1 mmHg for 12 h before use.

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