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Novel stereocontrolled α- and β-glycosidations of mannopyranosyl sulfoxides using environmentally benign heterogeneous solid acids

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Abstract—The environmentally benign and stereocontrolled glycosidations of mannopyranosyl sulfoxides and alcohols using a heterogeneous solid acid, Nafion-H or sulfated zirconia (SO_4/ZrO_2) as a new activator for the direct syntheses of both the α- and β-mannopyranosides have been developed.

Glycosubstances including glycolipids, glycoproteins and many antibiotics continue to be the central focus of research both in chemistry and biology. Since α- and β-mannopyranosides frequently appear in many naturally occurring bioactive substances, the stereocontrolled construction of α- and β-mannopyranosides is of considerable importance in synthetic organic chemistry.[1] The stereoselective and direct formation of β-mannopyranoside has proved particularly difficult to achieve because the axial β-hydroxy group at the C2 position and the anomeric effect blocks access to the β-face.[2] On the other hand, a practical and environmentally benign glycosidation method without using a heavy metal or a Lewis acid, which is not reusable and would make the reaction solvent dirty, is urgently needed both in the laboratory and in industry. Therefore, the highly stereocontrolled synthesis of both the α- and β-mannopyranosides in an environmentally friendly manner is of particular interest. In a previous paper, we demonstrated the stereocontrolled mannopyranoside formation with mannopyranosyl fluoride using a heterogeneous promoter, sulfated zirconia (SO_4/ZrO_2).[3] Recently, glycosyl sulfoxide has been paid considerable attention as an effective glycosyl donor (as Kahne's glycosidation)[4] as well as glycosyl fluoride, because glycosyl sulfoxide can be easily prepared from another glycosyl donor, thioglycoside, and converted into the other glycosyl donor, sulfonylglycoside.[1,2] In this context, the intermolecular β-stereoselective mannopyranosylation of 4,6-*O*-benzylidene protected mannopyranosyl sulfoxides using a homogeneous activator, triflic anhydride (Tf_2O), was announced by Crich.[5] In this letter, we now report the novel stereocontrolled glycosidations of mannopyranosyl sulfoxides **1** and **2** with several alcohols using an environmentally compatible heterogeneous solid acid,

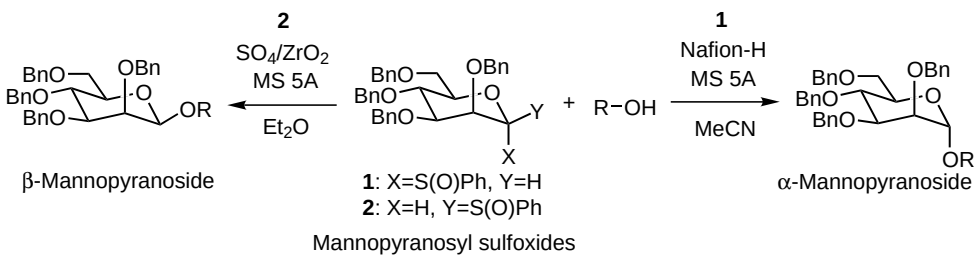

Figure 1. Stereocontrolled mannosylations using heterogeneous solid acids.

Keywords: sulfoxide glycosidation; heterogeneous solid acid; Nafion-H; sulfated zirconia; α- and β-mannopyranosides.
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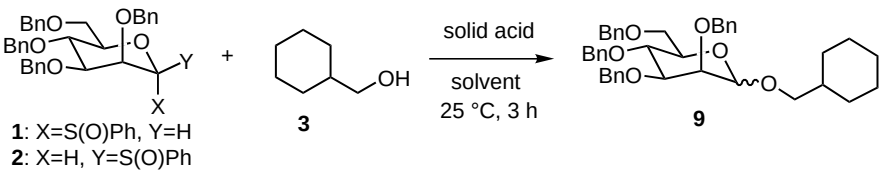
Nafion-H or SO_4/ZrO_2, as a new activator for the direct syntheses of both the α- and β-mannopyranosides in high yields (Fig. 1).

In our first experiments, we examined the glycosidations of the totally benzylated α- and β-mannopyranosyl sulfoxides **1** and **2** with cyclohexylmethanol (**3**) using several heterogeneous solid acids such as montmorillonite K-10,[6] Nafion-H[7] and SO_4/ZrO_2,[8] all of which are well known as environmentally benign solid acids because they could be recovered from the reaction mixture only by filtration and then reused. These results are summarized in Table 1. It was found that the glycosidation of α-mannopyranosyl sulfoxide **1** using Nafion-H smoothly proceeded to give the mannopyranoside **9** in moderate yield (entry 3). It was also confirmed that MeCN was shown to be superior to the other solvents such as CH_2Cl_2, PhMe and Et_2O (entries 3–6). However, when the reaction was performed in MeCN, considerable amounts of the corresponding 1-hydroxy sugar was produced, while the unreacted glycosyl donor was recovered in CH_2Cl_2, PhMe and Et_2O. The use of 5 Å molecular sieves (5 Å MS)[9] as an additive in MeCN led to the high chemical yield and stereoselectivity for the α-mannopyranoside **9α** (entry 7). Thus, the glycosidation of α-mannopyranosyl sulfoxide **1** and **3** using 100 wt% Nafion-H and 100 wt% 5 Å MS in MeCN at 25°C for 3 h exclusively gave the α-mannopyranoside **9α** in high yield with high stereoselectivity. On the other hand, after many attempts for the successful β-stereoselective mannopyranosylation, we finally found that the glycosidation of β-mannopyranosyl sulfoxide **2** using SO_4/ZrO_2 in Et_2O proceeded to selectively give the β-mannopyranoside **9β** (entry 9). Furthermore, it was confirmed that the β-mannopyranosyl sulfoxide **2** is a better glycosyl donor than the α-anomer **1** with respect to both the chemical yield and β-stereoselectivity (entries 8 and 9), and only the use of SO_4/ZrO_2 in Et_2O provided β-stereoselectivity among the examined conditions (entries 9–14). Moreover, the use of 300 wt% SO_4/ZrO_2 in the presence of an equal amount of 5 Å MS[9] led to the satisfactory result for the β-stereoselective mannopyranosylation (entry 15). Thus, the glycosidation of β-mannopyranosyl sulfoxide **2** and **3** using 300 wt% SO_4/ZrO_2 and 300 wt% 5 Å MS in EtO_2 at 25°C for 3 h selectively furnished the β-mannopyranoside **9β** in high yield with high stereoselectivity.

To enhance the synthetic utility of this novel and environmentally benign protocol, the glycosidations using other primary and secondary alcohols **4–8** including sugar derivatives were examined next. Based on the results summarized as entries 1–6 in Table 2, all the glycosidations of **1** and **4–8** using 100 wt% Nafion-H in MeCN at 25°C for 3 h, as well as that of **3**, effectively proceeded to give the corresponding α-mannopyranosides **10α–14α**, respectively, in high yields with high stereoselectivity. On the other hand, the β-stereoselective mannopyranosylation using **2** with **4–8** are outlined as entries 7–12 in Table 2. Although the β-mannopyranoside **14β** was produced from **2** and **8** with moderate stereoselectivity, other β-mannopyranosides **10β–13β** were obtained in high yield with good stereoselectivity by the glycosidations of **2** and **4–7** under the conditions similar to that for **9β**. Since the configuration of the anomeric position was not epimerized by exposure of the isolated single anomer of the *O*-mannopyranoside

Table 1. Glycosidations of **1** and **2** with cyclohexylmethanol (**3**) using solid acids[a]

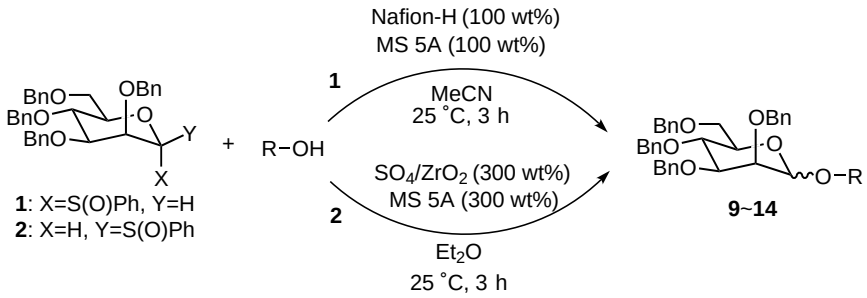


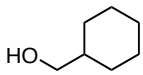
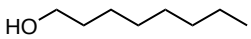
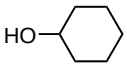
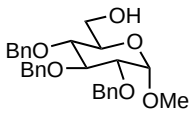
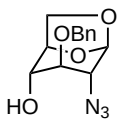
Entry	Glycosyl donor	Solid acid (wt%)	Additive	Solvent	Yield (%)	α/β Ratio[b]
1	**1**	Montmorillonite K-10 (100)	–	MeCN	6	60/40
2	**1**	SO_4/ZrO_2 (100)	–	MeCN	38	57/43
3	**1**	Nafion-H (100)	–	MeCN	64	77/23
4	**1**	Nafion-H (100)	–	CH_2Cl_2	Trace	–
5	**1**	Nafion-H (100)	–	PhMe	Trace	–
6	**1**	Nafion-H (100)	–	Et_2O	Trace	–
7	**1**	Nafion-H (100)	5 Å MS (100)	MeCN	97	97/3
8	**1**	SO_4/ZrO_2 (100)	–	Et_2O	2	39/61
9	**2**	SO_4/ZrO_2 (100)	–	Et_2O	17	32/68
10	**2**	SO_4/ZrO_2 (100)	–	MeCN	52	64/36
11	**2**	SO_4/ZrO_2 (100)	–	CH_2Cl_2	4	75/25
12	**2**	SO_4/ZrO_2 (100)	–	PhMe	4	74/26
13	**2**	Nafion-H (100)	–	Et_2O	21	67/33
14	**2**	Montmorillonite K-10 (100)	–	Et_2O	8	58/42
15	**2**	SO_4/ZrO_2 (300)	5 Å MS (300)	Et_2O	99	19/81

[a] All reactions were carried out using 2.0 equiv. of **3** to the glycosyl donor.

[b] α:β Ratios were determined by HPLC analysis (column, CrestPack C18S®, 4.6×150 mm; eluent, 10% H_2O in MeCN; flow rate, 1.0 ml/min, 40°C; detection, UV 250 nm).

Table 2. α- and β-Stereoselective glycosidations of **1** and **2** with several alcohols[a]



			1		2	
Entry	Alcohol	Product	Yield (%)	α/β Ratio[b]	Yield (%)	α/β Ratio[b]
1, 7	 **3**	**9**	97	97/3	99	19/81
2, 8	 **4**	**10**	99	96/4	99	21/79
3, 9	 **5**	**11**	94	97/3	95	20/80
4, 10	 **6**	**12**	94	97/3	93	23/77
5, 11	 **7**	**13**	90	98/2	85	26/74
6, 12	 **8**	**14**	80	96/4	70	38/62

[a] All reactions were carried out by use of 2.0 equiv. of the alcohol to the glycosyl donor.
[b] α:β Ratios were determined by HPLC analysis (column, CrestPack C18S®, 4.6 x 150 mm; eluent, 10% H_2O in MeCN; flow rate, 1.0 mL/min, 40 °C; detection, UV 250 nm).

for both reaction conditions, the predominant α- and β-stereoselectivities observed in the present glycosidations must occur kinetically.

The general experimental protocols for the preparations of the α- and β-mannopyranosides.[10] α-Mannopyranosides: To a stirred solution of the α-mannopyranosyl sulfoxide **1** (0.5 mmol) and an alcohol (1.0 mmol) in dry MeCN (5.0 ml) were added powdered 5 Å MS (100 wt% to **1**) and Nafion-H (100 wt% to **1**). After stirring for 3 h at 25°C, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography gave the mannopyranosides, which predominately contained its α-anomer. β-Mannopyranosides: To a stirred solution of the β-mannopyranosyl sulfoxide **2** (0.5 mmol) and an alcohol (1.0 mmol) in dry Et_2O (5.0 ml) were added powdered 5 Å MS (300 wt% to **1**) and SO_4/ZrO_2 (300 wt% to **1**). After stirring for 3 h at 25°C, a similar workup and purification mentioned above gave the mannopyranosides which included its β-anomer as the major product.

In conclusion, we have described the novel and stereocontrolled strategy for the direct syntheses of both α- and β-mannopyranosides from mannopyranosyl sulfoxides and alcohols using an environmentally acceptable heterogeneous solid acid. Moreover, the results including the simple protocol, high yield and stereoselectivity should find wide application in the synthesis of biomolecules and functional materials. Further studies along this line are currently underway.

Acknowledgements

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6. Montmorillonite K-10 was purchased from Aldrich Chemical Company, Inc. and dried at 200°C/1 mmHg for 12 h before using.
7. Nafion-H was purchased from Aldrich Chemical Company, Inc. as Nafion® perfluorinated ion-exchange powder and dried at 25°C/1 mmHg for 2 h before using.
8. SO_4/ZrO_2 was purchased from Wako Pure Chemical Industries, Ltd. and dried at 200°C/1 mmHg for 12 h before using.
9. 5 Å MS was shown to be slightly superior to other MS such as 3 Å MS and 4 Å MS.
10. All α- and β-mannopyranosides were purified by silica gel column chromatography and were fully characterized by spectroscopic means. The anomeric configuration was assigned in each case with the aid of ^{1}H NMR analysis and confirmed by the comparison with the authentic samples, see: Ref. 3 and references cited therein.