Novel Stereocontrolled Glycosidations Using a Solid Acid, SO_4/ZrO_2, for Direct Syntheses of α- and β-Mannopyranosides

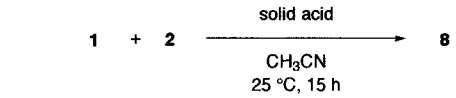
Kazunobu Toshima,* Ken-ichi Kasumi, and Shuichi Matsumura
Department of Applied Chemistry, Faculty of Science and Technology,
Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223, Japan
Received 27 February 1998

Abstract: Novel stereocontrolled glycosidations using an environmentally friendly solid acid, sulfated zirconia (SO_4/ZrO_2), for direct syntheses of α- and β-mannopyranosides have been developed. The glycosidations of the totally benzylated mannopyranosyl fluoride **1** and various alcohols using SO_4/ZrO_2 in CH_3CN at 40 °C for 15 h exclusively gave the corresponding α-mannopyranosides. On the other hand, the corresponding β-mannopyranosides were selectively obtained by the glycosidations of **1** and various alcohols employing SO_4/ZrO_2 in the presence of molecular sieves 5Å in Et_2O at 25 °C for 15 h.

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 formation of α- and β-mannopyranosides is of considerable importance in synthetic organic chemistry.[1] The stereospecific and direct formation of β-mannopyranoside has proved particularly difficult to achieve, in spite of considerable effort, because the axial β-hydroxy group at the C2 position and the anomeric effect blocks access to the β-face.[1,2,3] On the other hand, a practical and environmentally benign glycosidation protocol without using a heavy metal or a Lewis acid, which is not reusable and would make the reaction solvent dirty, is also needed both in the laboratory and in industry.[4] Therefore, a highly stereocontrolled synthesis of α- and β-mannopyranosides by an environmentally friendly manner is of particular interest. In this communication, we now report the novel stereocontrolled glycosidations of a mannopyranosyl fluoride using an environmentally compatible solid acid, sulfated zirconia (SO_4/ZrO_2), for the direct syntheses of both α- and β-mannopyranosides in high yields (Figure 1).

In our first experiments, we examined the glycosidations of the totally benzylated α-mannopyranosyl fluoride **1**[5] and cyclohexylmethanol (**2**) using several solid acids such as montmorillonite K-10,[6] Nafion-H[7] and SO_4/ZrO_2,[8] all of which could be recovered from the reaction mixture by only filtration and then reused. These results are summarized in Table 1. It was found that these glycosidations in CH_3CN at 25 °C for 15 h smoothly proceeded to afford the mannopyranoside **8** in high yields. Furthermore, SO_4/ZrO_2 was shown to be superior to the others with respect to both chemical yield and α-stereoselectivity. These results clearly indicated that the solid acid, SO_4/ZrO_2,[9,10] was very useful for the environmentally acceptable glycosidation of the mannopyranosyl fluoride **1**.

Table 1. Glycosidations of **1** and **2** by several solid acids in CH_3CN[a]



Entry	Solid acid	Wt% of solid acid	Yield (%)[b]	α/β Ratio[c]
1	Montmorillonite K-10	20	89	76 : 24
2	Nafion-H	20	92	89 : 11
3	SO_4/ZrO_2	20	93	91 : 9

[a] All reactions were carried out by use of 2.0 equiv. of **2** to **1**. [b] Isolated yields after purification by column chromatography. [c] $\alpha:\beta$ Ratios were determined by ^{1}H-NMR (270 MHz) spectroscopy and / or isolation of pure isomers

Our attention next turned to the solvent effect on this novel glycosidation. Therefore, we tested the glycosidations of **1** and **2** using SO_4/ZrO_2 in various solvents. From the results shown in Table 2, CH_3CN was found to be the best solvent to selectively obtain the α-mannopyranoside **8**α, and the use of 5 wt% of the present activator was sufficient to perform this reaction at 40 °C with quite satisfactory chemical yield and α-stereoselectivity (entries 1 and 6 in Table 2). Moreover, interestingly, the stereoselectivity of the glycosidation was

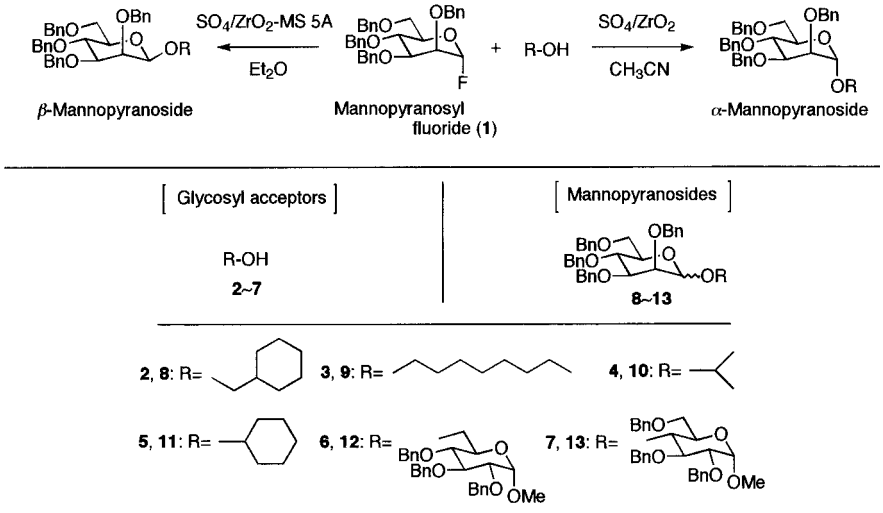
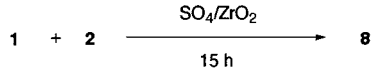


Figure 1. Stereocontrolled mannosylations using SO_4/ZrO_2

Downloaded by: Universite Laval. Copyrighted material.

dramatically changed by the solvent, and β-mannopyranoside **8β** was predominately produced when Et_2O was used as the solvent (entry 5 in Table 2).[11] Furthermore, it was found that the use of molecular sieves 5Å (MS 5Å)[12] as an additive in the glycosidation in Et_2O led to the high chemical yield and stereoselectivity for β-mannopyranoside **8β** (entry 8 in Table 2). Thus, the glycosidation of **1** and **2** using 5 wt% of SO_4/ZrO_2 in CH_3CN at 40 °C for 15 h exclusively gave the α-mannopyranoside **8α**, while the glycosidation employing 100 wt% of the same activator in the presence of equal amounts of MS 5Å in Et_2O at 25 °C for 15 h afforded the β-mannopyranoside **8β** in high yield with high stereoselectivity.

Table 2. Glycosidations of **1** and **2** by SO_4/ZrO_2 under several conditions[a]



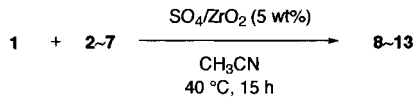
Entry	Solvent	Additive	Wt% of solid acid	Temp. (°C)	Yield (%)[b]	α/β Ratio[c]
1	CH_3CN	None	20	25	93	91 : 9
2	CH_2Cl_2	None	20	25	74	69 : 31
3	PhH	None	20	25	7	51 : 49
4	THF	None	20	25	2	52 : 48
5	Et_2O	None	20	25	24	34 : 66
6	CH_3CN	None	5	40	99	97 : 3
7	Et_2O	None	100	25	32	24 : 76
8	Et_2O	MS 5A	100	25	99	17 : 83

[a] All reactions were carried out by use of 2.0 equiv. of **2** to **1**. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^{1}H-NMR (270 MHz) spectroscopy and / or isolation of pure isomers

To enhance the synthetic utility of this novel and unusual reaction, the glycosidations using other primary and secondary alcohols **3**~**8** were next examined. Based on the results summarized in Table 3, all glycosidations of **1** and **3**~**8** using 5 wt% of SO_4/ZrO_2 in CH_3CN at 40 °C for 15 h, as well as that of **2**, effectively proceeded to give the corresponding α-mannopyranosides **9α**~**13α**, respectively, in high yields with high stereoselectivity. On the other hand, stereoselective syntheses of the corresponding β-mannopyranosides by the present glycosidation are outlined in Table 4. Although only β-mannopyranoside **13β** was produced in moderate yield with low stereoselectivity, other β-mannopyranosides **9β**~**12β** were obtained in high yield with good stereoselectivity by the glycosidations of **1** and **3**~**6** under the conditions similar to that for **8β**.

General experimental protocols for the preparations of the α- and β-mannopyranosides:[13] α-Mannopyranosides: To a stirred solution of the glycosyl fluoride **1** (0.5 mmol) and a glycosyl acceptor (1.0 mmol) in dry CH_3CN (5.0 ml) was added SO_4/ZrO_2 (5 wt% to the glycosyl donor **1**). After stirring for 15 h at 40 °C, the mixture was filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography gave mannopyranosides which predominately contained its α-anomer. β-Mannopyranosides: To a stirred solution of **1** (0.5 mmol) and a glycosyl acceptor (1.0 mmol) in dry Et_2O (5.0 ml) were added powdered MS 5Å (100 wt% to **1**) and SO_4/ZrO_2 (100 wt% to **1**). After stirring for 15 h at 25 °C, the similar workup and purification mentioned above gave mannopyranosides which included its β-anomer as a major product. In conclusion, we have presented a novel and stereocontrolled strategy for the direct synthesis of both α- and β-mannopyranosides from a mannopyranosyl fluoride and an alcohol using an environmentally acceptable solid acid. Moreover, the results including the simple protocol, high yield and stereoselectivity should be instructive for further research that employs solid acids in glycosidation reactions. Further studies along this line are currently underway.

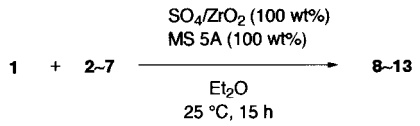
Table 3. α-Stereoselective glycosidations of **1** and several alcohols[a]



Entry	Alcohol	Product	Yield (%)[b]	α/β Ratio[c]
1	**2**	**8**	99	97: 3
2	**3**	**9**	97	98 : 2
3	**4**	**10**	96	98 : 2
4	**5**	**11**	96	97 : 3
5	**6**	**12**	88	97 : 3
6	**7**	**13**	75	98 : 2

[a] All reactions were carried out by use of 2.0 equiv. of the alcohol to **1**. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^{1}H-NMR (270 MHz) spectroscopy and / or isolation of pure isomers

Table 4. β-Stereoselective glycosidations of **1** and several alcohols[a]



Entry	Alcohol	Product	Yield (%)[b]	α/β Ratio[c]
1	**2**	**8**	99	17 : 83
2	**3**	**9**	96	20 : 80
3	**4**	**10**	97	19 : 81
4	**5**	**11**	95	16 : 84
5[d]	**6**	**12**	84	27 : 73
6[d]	**7**	**13**	55	56 : 44

[a] All reactions were carried out by use of 2.0 equiv. of the alcohol to **1**. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^{1}H-NMR (270 MHz) spectroscopy and / or isolation of pure isomers. [d] This reaction was carried out by use of SO_4/ZrO_2 (200 wt%) and MS 5A (200 wt%) to **1**

References and Notes

(1) For a recent review, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503-1531.

(2) For recent selective and direct syntheses of β-mannnopyranosides, see: (a) Kim, W.-S.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 7797-7800. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506-4507. (c) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198-1199. (d) Tatsuta, K.; Yasuda, S. *Tetrahedron Lett.* **1996**, *37*, 2453-2456. (e) Hodosi, G.; Kovac, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335-2336. (f) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435-436.

Downloaded by: Universite Laval. Copyrighted material.

(3) For elegant syntheses of β-mannnopyranosides by intramolecular approaches, see: (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc*. **1991**, *113*, 9376-9377. (b) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759-761. (c) Stork, G.; Kim, G. *J. Am. Chem. Soc*. **1992**, *114*, 1087-1088. (d) Stork, G.; La Clair, J. *J. Am. Chem. Soc*. **1996**, *118*, 247-248. (e) Ito, Y.; Ogawa, T. *Angew. Chem*. **1994**, *106*, 1843-1845; *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 1765-1767. (f) Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem*. **1995**, *60*, 4680-4681. (g) Ziegler, T.; Lemanski, G.; Rakoczy, A. *Tetrahedron Lett*. **1995**, *36*, 8973-8976. (h) Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem*. **1996**, *61*, 605-615. (i) Crich, D.; Hwang, J.-T.; Yuan, H. *J. Org. Chem*. **1996**, *61*, 6189-6198. (j) Iimori, T.; Ohtake, H.; Ikegami, S. *Tetrahedron Lett*. **1997**, *38*, 3415-3418.

(4) For glycosidations using a reusable solid acid, see: (a) Florent, J.-C.; Monneret, C. *J. Chem. Soc., Chem. Commun*. **1987**, 1171-1172. (b) Fukase, K.; Winarno, H.; Kusumoto, S. *Chem. Express* **1993**, *8*, 409-411. (c) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Synlett* **1995**, 306-308. (d) Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M.; Matsumura, S. *Chem. Commun*. **1996**, 1379-1380.

(5) The fluoride **1** was prepared from the corresponding 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose and DAST as previously described in the literature, see; Posner, G. H.; Haines, S. R. *Tetrahedron Lett*. **1985**, *26*, 5-8.

(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 Wako Pure Chemical Industries, Ltd. as Nafion® NR-50 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) The study on glycosidation using SO_4/ZrO_2-$CaCl_2$ has been quite recently announced. Nishimura, S.; Matsuda, M. *The Abstract of XIXth Japanese Carbohydrate Symposium*, A3-10, 1997.

(10) For the use of zirconia species for glycosidations of glycosyl fluorides, see; (a) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett*. **1988**, *29*, 3567. (b) Suzuki, K.; Maeta, H.; Suzuki, T.; Matsumoto, T. *Tetrahedron Lett*. **1989**, *30*, 6879.

(11) For a pioneering work on β-mannosylation using a heterogenic catalyst, see; Paulsen, H.; Lockhoff, O. *Chem. Ber*. **1981**, *114*, 3102.

(12) MS 5Å was shown to be slightly superior to other MS such as MS 3Å and MS 4Å.

(13) All mannopyranosides were purified by silica gel column chromatography and were fully characterized by spectroscopic means. The anomeric configuration is assigned in each case with the aid of ^{1}H-NMR analysis and confirmed by comparison with the authentic samples which were reported in ref. 2 or 3.

Downloaded by: Universite Laval. Copyrighted material.