CHEMISTRY LETTERS, pp. 1373-1376, 1993.

Catalytic Stereoselective Synthesis of α- or β-Glucosides Using a Single Glycosyl Donor, 1-O-2'-(2'-Methoxyethoxy)acetyl-Glucopyranose Derivative

Koki MATSUBARA, Takenori SASAKI, and Teruaki MUKAIYAMA
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

In the presence of a catalytic amount of active acidic species generated from $SnCl_4$ and $AgClO_4$, various α-glucosides are stereoselectively synthesized in excellent yields from 1-O-2'-(2'-methoxyethoxy)acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose and alkyl trimethylsilyl ethers. β-Glucosides are also selectively prepared by using a catalyst, generated from $SiCl_4$ and $AgClO_4$, in the above reaction.

Stereoselective glycosylation reaction is currently one of the most important problems in carbohydrate chemistry. Several methods for the preparation of both anomers of glucosides have been reported,[1] however, there are few examples that achieved a convenient and a highly stereoselective procedure for the preparation of both anomers separately using the catalytic amount of activators. Therefore, it is one of challenging topics to achieve the preparation of α- or β-anomers distinctively from a single glycosyl donor by a catalytic process. In this communication, we would like to describe an efficient method for the selective preparation of α- or β-anomers starting from a single glycosyl donor having 2-(2-methoxyethoxy)acetoxy group at an anomeric center, that is 1-O-2'-(2'-methoxyethoxy)acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose, by choosing a suitable catalyst.

Recently, we have reported a method for the preparation of α-glucosides from 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose (**1**) by the use of a catalytic amount of active species generated from tin(IV) chloride and silver perchlorate (1:1).[2] In the first place, glycosylation reaction of **1** with cyclohexyl trimethylsilyl ether (**2**) was attempted at 0 °C in dichloromethane instead of ether in the above mentioned experiment and it was found that the ratio of the produced β-glucoside increased up to 51/49(yield = 94%). Next, the reaction was tried at -23 °C with a view to achieving higher β-selectivity and α/β-selectivity increased up to 17/83 (yield = 48%) as expected. Furthermore, yield increased up to 85% (α/β = 24/76) when $SnCl_2(ClO_4)_2$, generated from tin(IV) chloride and twofold of silver perchlorate, was used as a catalyst. Several other leaving groups at an anomeric position of the glycosyl donor were screened by taking the above mentioned reaction as a model (see Table 1).

It was shown that the corresponding β-glucoside was obtained in a good yield with high stereoselectivity when 2-(2-methoxyethoxy)acetoxy group was employed as a leaving group. Furthermore, after screening various catalysts and solvents, the best result was obtained when $SiCl_2(ClO_4)_2$, generated in situ from silicon(IV) chloride and silver perchlorate, was used as a catalyst in acetonitrile (see Table 2).

Several examples of the present glycosylation reaction of 1-O-2'-(2'-methoxyethoxy)acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose (**3**; α/β=4/1)[3] with alkyl trimethylsilyl ethers are summarized in Table 3.

Thus, **3** was also employed as a glycosyl donor in the synthesis of α-glucosides since 2-(2-

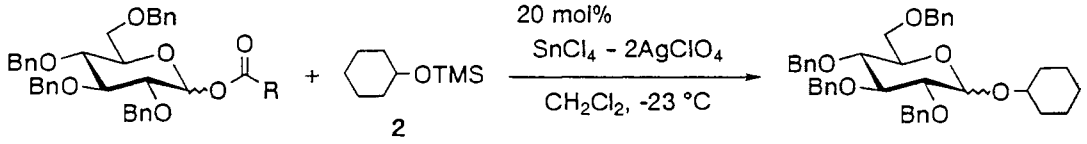
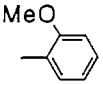
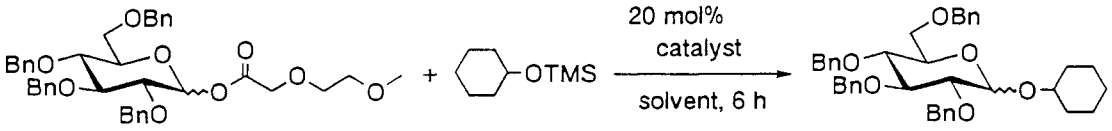


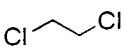
Table 1. Effect of leaving groups

Entry	-R	Time / h	Yield / %	α / β
1	-Me	10	85	24 / 76
2	$-CH_2Br$	14	79	22 / 78
3	$-CH_2I$	11	91	24 / 76
4	$-CH_2OMe$	10	82	18 / 82
5	$-CH_2CH_2OMe$	20	66	19 / 81
6	$-CH_2SMe$	5	40	15 / 85
7	$-CH_2OCH_2CH_2OMe$	6	90	16 / 84
8		8	90	19 / 81

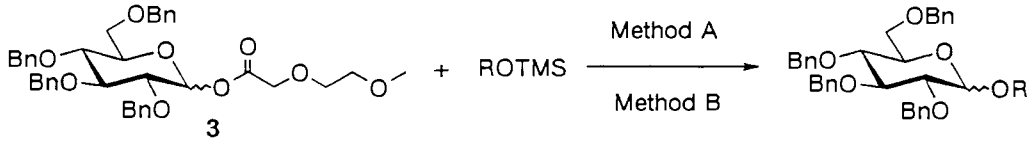


3 2

Table 2. Effect of catalysts and solvents

Entry	Catalyst	Solvent	Temp / °C	Yield / %	α / β
1	$SnCl_4$ - $2AgClO_4$	CH_2Cl_2	-23	90	16 / 84
2	$SnCl_4$ - 2AgOTf	〃	〃	26	22 / 78
3	$TiCl_4$ - $2AgClO_4$	〃	〃	14	19 / 81
4	$SiCl_4$ - $2AgClO_4$	〃	〃	90	15 / 85
5	$SnCl_2$ - $2AgClO_4$	〃	〃	trace	——
6	$Sn(OTf)_2$	〃	〃	trace	——
7	$SiCl_4$ - $2AgClO_4$		〃	99	10 / 90
8	〃	Toluene	〃	45	44 / 56
9	〃	$MeNO_2$	〃	23	36 / 64
10 a)	〃	MeCN	-10	98	5 / 95

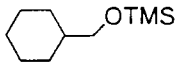
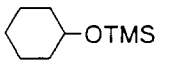
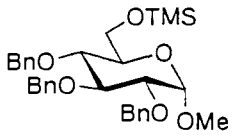
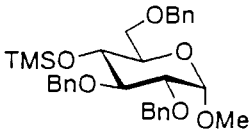
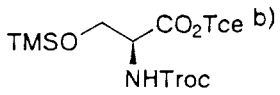
a) Reaction time = 12 h.



Method A : catalyst = $SiCl_4$ - $2AgClO_4$ (20 mol%), solvent = MeCN, time = 12 h

Method B : catalyst = $SnCl_4$ - $AgClO_4$ (10 mol%), solvent = Et_2O, temp = -5 °C, time = 12 h

Table 3. Synthesis of α- and β-glucosides

			Method A			Method B	
Entry	ROTMS (1.2 equiv.)	Temp / °C [a]	Yield / %	α / β		Yield / %	α / β
1		-10	quant.	3 / 97		quant.	98 / 2
2		-10	98	5 / 95		98	97 / 3
3	3β-CholestanylOTMS	-10	97	5 / 95		98	97 / 3
4		-10	99	1 / 99		quant.	98 / 2
5		-5	85	9 / 91		95	96 / 4
6		-10	98	3 / 97		95	97 / 3

a) Alkyl trimethylsilyl ethers were added at -23 °C, and then warmed up to -10 or -5 °C.

b) Troc = 2,2,2-Trichloroethoxycarbonyl, Tce = 2,2,2-Trichloroethyl.

methoxyethoxy)acetoxy group was superior to acetoxy group as a leaving group (see Table 3).

When the glucopyranose **3** was used as a glycosyl donor, all of the selectivities of the produced glucosides were superior to those obtained by using **1**. Thus, high yields and selections of either α- or β-anomers are dependent on the high reactivity of **3** compared with the other glycosyl donors mentioned above (see Table 1).

Pure α- and β-anomers of **3** were employed respectively under the above reaction conditions in order to ascertain whether the ratio of α- and β-isomers of produced glucosides was dependent on the ratio of starting α- and β-anomers of **3** or not.[4] The same α/β-selectivity was observed in both reactions, indicating that the reactions proceeded via S_N1 process through the common oxocarbenium cation.

The followings are typical procedures for the preparation of both anomers of methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-α-D-glucopyranoside. β-Anomer: a solution of silicon(IV) chloride (0.06 mmol) in toluene(0.1 ml) was added to a solution of silver perchlorate (0.12 mmol) in acetonitrile (6 ml) at room temperature, and the mixture was shielded from the light and stirred for 1 h. To this mixture was added a solution of **3** (0.3 mmol) and methyl 2,3,4-tri-O-benzyl-6-O-trimethylsilyl-α-D-glucopyranoside (0.36

mmol) in acetonitrile (4 ml) at -23 °C, and the mixture was then warmed up to -10 °C. After stirring for an additional 12 h, aqueous sodium hydrogen carbonate was added. Usual work up and separation by TLC afforded β-anomer (98%) and α-anomer (1%). α-Anomer: a solution of tin(IV) chloride (0.03 mmol) in toluene (0.1 ml) was added to a solution of silver perchlorate (0.03 mmol) in ether (6 ml) at room temperature, and the mixture was shielded from the light and stirred for 1 h. To this mixture was added a solution of **3** (0.3 mmol) and methyl 2,3,4-tri-O-benzyl-6-O-trimethylsilyl-α-D-glucopyranoside (0.36 mmol) in ether (4 ml) at -5 °C. After stirring for an additional 12 h, aqueous sodium hydrogen carbonate was added. Usual work up and separation by TLC afforded α-anomer (98%) and β-anomer (2%).

Thus, highly stereoselective synthesis of α- or β-glucosides starting from a single glycosyl donor is successfully carried out by using glucopyranose having 2-(2-methoxyethoxy)acetoxy group at an anomeric center with $SnCl_3(ClO_4)$ or $SiCl_2(ClO_4)_2$ as a catalyst. The present glycosylation method is superior to conventional ones[1,2] with regard to the synthesis of α-glucosides, and has a wide applicability to various substrates except for those that are very sensitive to acidic conditions. Whereas, in the case of the synthesis of β-glucosides, the selectivity decreases when hindered nucleophiles are employed, therefore, the imidate procedure is more preferable.[5]

References

1) S. Hashimoto, M. Hayashi, and R. Noyori, *Tetrahedron Lett.*, **25**, 1379 (1984); T. Matsumoto, H. Maeta, and K. Suzuki, *ibid.*, **29**, 3567, 3571, 3575 (1988); K. Suzuki, H. Maeta, and T. Matsumoto, *ibid.*, **30**, 4853 (1989); S. Kobayashi, K. Koide, and M. Ohno, *ibid.*, **31**, 2435 (1990); K. Koide, M. Ohno, and S. Kobayashi, *ibid.*, **32**, 7065 (1991); K. Fukase, A. Hasuoka, I. Kinoshita, and S. Kusumoto, *ibid.*, **33**, 7165 (1992).

2) T. Mukaiyama, T. Takashima, M. Katsurada, and H. Aizawa, *Chem. Lett.*, **1991**, 533; T. Mukaiyama, M. Katsurada, and T. Takashima, *ibid.*, **1991**, 985.

3) ^1H NMR ($CDCl_3$) Spectral data of H-1; α-isomer: δ 6.46 (d, J=3.30 Hz), β-isomer: δ 5.68 (d, J=7.92 Hz).

4) β-Anomer of **3** was prepared in the similar manner to that reported by H. Kunz. H. Kunz, R. Kullmann, P. Wernig, and J. Zimmer, *Tetrahedron Lett.*, **33**, 1969 (1992).

5) R. R. Schmidt, M. Behrendt, A. Toepfer, *Synlett*, **1990**, 694.

(Received May 7, 1993)