Highly Stereoselective Synthesis of 1,2-*trans*-Glycosides Using *p*-Chlorobenzylated Glycosyl Carbonate as Glycosyl Donor

Teruaki Mukaiyama, Kazuo Miyazaki, and Hiromi Uchiro
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

(Received February18, 1998; CL-980116)

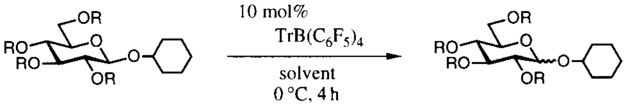
A new and efficient method for catalytic stereoselective synthesis of 1,2-*trans*-glycosides was successfully established by use of 2,3,4,6-tetra-*O*-*p*-chlorobenzyl-β-D-glucopyranosyl phenyl carbonate as a stable and easily-available glycosyl donor. Several β-D-glucopyranosides were prepared in good yields with high stereoselectivities.

In recent years, many cell surface-associated glycoconjugates have been discovered in various biological processes such as antigen recognition, cell adhesion, and so on.[1] Several types of glycoside linkages are contained in those biomolecules, and 1,2-*trans*-glycosides are widespread constituents and many useful methods for the construction of these glycoside linkages have been developed.[2] Of these methods, glycosylation reaction using benzyl protected glycosyl donors are employed in the syntheses of both 1,2-*cis* and 1,2-*trans*[3] glycosides. However, the stereoselectivities obtained in 1,2-*trans*-selective glycosylations are slightly lowered compared with that of traditional methods of using 2-*O*-acyl protected glycosyl donors due to the absence of a neighboring participation. Therefore, a method for the efficient synthesis of 1,2-*trans*-glycoside with high setereoselectivity is strongly desired. In this communication, we would like to report a new and efficient method for highly 1,2-*trans*-selective glycosylation by use of *p*-chlorobenzyl-protected glycosyl carbonate as a stable and easily-available glycosyl donor.

In our previous papers, highly stereoselective syntheses of several 1,2-*cis*-glycosides from easily-available and stable 1-hydroxy sugars were described.[4] High stereoselectivities achieved by those new methods were dependent on their anomerization steps activated by the combined use of Lewis acid catalyst and lithium salt. During the process of the above experiment, an interesting behavior of *p*-chlorobenzylated glycoside was observed, that is, *p*-chlorobenzyl-protected glycoside was highly resistant to anomerization even in the presence of Lewis acid compared with that observed by using common benzyl protected one.[5]

Cyclohexyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside anomerized to produce the α-anomer (α/β=49/51) in the presence of 10 mol% of trityl tetrakis(pentafluorophenyl)borate in dichloromethane at 0 °C for 4h (Table 1, Entry 1). On the other hand, anomerization of cyclohexyl 2,3,4,6-tetra-*O*-*p*-chloro benzyl-β-D-glucopyranoside proceeded slightly (α/β=7/93) under the same condition (Table 1, Entry 2). This phenomenon found in anomerization of *p*-chlorobenzyl-protected glycoside was also observed when pivalonitrile-dichloromethane (5/1) was used as a solvent (Table 1, Entry 3,4). In the above solvent, 1,2-*trans*-selective glycosylation had taken place preferentially was already demonstrated.[6] Then, a new and effective method for highly 1,2-*trans*-selective glycosylation was expected to be developed by using *p*-chlorobenzyl-protected glycosyl donor.

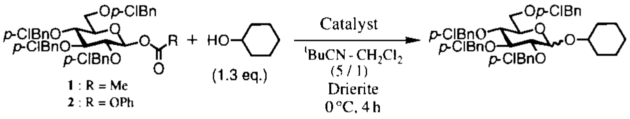
Table 1. Effect of *p*-chlorobenzyl group on anomerization of glycoside



Entry	R	Solvent (v / v)	α / β	
			Initial ratio	Final ratio
1	Bn	CH_2Cl_2	1 / >99	49 / 51
2	*p*-ClBn	CH_2Cl_2	1 / >99	7 / 93
3	Bn	$^tBuCN-CH_2Cl_2$ (5 / 1)	1 / >99	13 / 87
4	*p*-ClBn	$^tBuCN-CH_2Cl_2$ (5 / 1)	1 / >99	1 / 99

In the first place, 1-*O*-acetyl-2,3,4,6-tetra-*O*-*p*-chlorobenzyl-β-D-glucopyranose **1**[7] was stereoselectively prepared as a glycosyl donor and the glycosylation of cyclohexanol with **1** was examined in the presence of 10 mol% of trityl tetrakis (pentafluorophenyl)borate in the mixed solvent of pivalonitrile-dichloromethane (5/1)[10] at 0 °C for 4h. The glycosylation proceeded smoothly and the desired glycoside was obtained with high stereoselectivity (α/β=7/93) in a fairly good yield at relatively high reaction temperature (Table 2, Entry 1). In this reaction, 11% yield of the glycosyl donor was recovered as an anomerized α-anomer. This result indicated that the activation of glycosyl donor by trityl catalyst was a reversible process and caused the lowering of yield by the formation of less reactive α-anomer of glycosyl donor. Then, 2,3,4,6-tetra-*O*-*p*-chlorobenzyl-β-D-glucopyranosyl phenyl carbonate **2**[7] was prepared as a glycosyl donor which should be irriversively activated to form carbon dioxide and phenol by the subsequent decomposition of the leaving group.[11] Expectedly, the reaction of cyclohexanol with donor **2** under the above condition proceeded smoothly and the desired glycoside was obtained in high yield (86%) with high stereoselectivity (α/β=7/93) (Table 2, Entry 2). The use of 5 mol% of trityl tetrakis(pentafluorophenyl)borate also promoted the glycosylation while trimethylsilyl trifrate was quite ineffective for the catalytic glycosylation (Table 2, Entry 3-5).

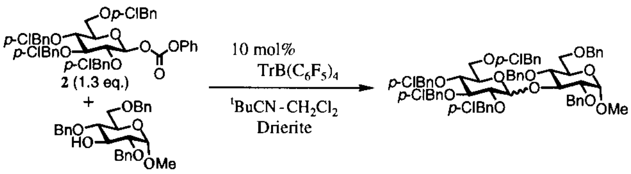
Table 2. Glycosylations of cyclohexanol with *p*-chlorobenzylated glycosyl donors



Entry	R	Catalyst (mol%)	Yield / %	α / β
1	Me	$TrB(C_6F_5)_4$ (10)	77	7 / 93
2	OPh	$TrB(C_6F_5)_4$ (10)	86	7 / 93
3	OPh	$TrB(C_6F_5)_4$ (5)	83	7 / 93
4	OPh	Me_3SiOTf (10)	33	31 / 69
5	OPh	Me_3SiOTf (100)	86	26 / 74

Next, the reaction temperature was examined by taking the glycosylation of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside with donor **2** as a model (Table 3). At lower temperatures, the stereoselectivity was clearly improved and reached to α/β=4/96 at -28 °C.

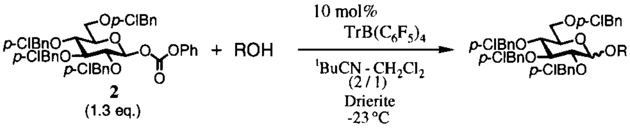
Table 3. Effect of reaction temperature on stereoselectivity

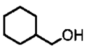
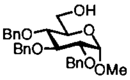
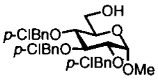
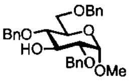
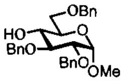


Entry	Temp.	Solvent (v / v)	Time / h	Yield / %	α / β
1	0 °C	5 / 1	4	88	11 / 89
2	-10 °C	3 / 1	6	92	9 / 91
3	-15 °C	3 / 1	6	92	7 / 93
4	-23 °C	2 / 1	20	97	6 / 94
5	-28 °C	2 / 1	30	88	4 / 96
6	-35 °C	2 / 1	12	72	4 / 96

Several examples of the present glycosylation reaction are demonstrated in Table 4. In every case, the desired β-D-glucopyranoside was obtained in high yield with high stereoselectivity. Especially, perfect stereoselections were achieved when sugar derivatives having a primary hydroxyl group were employed as glycosyl acceptors. Such high compatibility of yield and stereoselectivity has not yet been reported in the glycosylation utilizing benzyl protected glycosyl donors.

Table 4. Synthesis of β-D-glucopyranosides



Entry	ROH	Time / h	Yield / %	α / β
1		9	98	3 / 97
2		9	93	only β
3		9	97	only β
4		20	97	6 / 94
5^a		30	88	4 / 96
6		20	80	6 / 94
7^b		20	92	6 / 94

^{a} The reaction was carried out at -28 °C.
^{b} 2.0 eq. of donor was used.

A typical experimental procedure is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (9.0 mg, 0.0098 mmol) and Drierite (200 mg) in a mixed solvent (pivalonitrile/dichloromethane=5/1, 3 ml) was successively added a mixed solvent (1.5 ml) solution of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (45.3 mg, 0.098 mmol) and 2,3,4,6-tetra-*O*-*p*-chlorobenzyl-β-D-glucopyranosyl phenyl carbonate **2** (101.3 mg, 0.13 mmol) at -23 °C. The reaction mixture was stirred for 20h at -23 °C, then it was quenched by adding saturated aqueous sodium hydrogen carbonate (20 ml). The mixture was diluted with dichloromethane (30 ml) and filtered through Celite. The organic layer was separated and successively washed with water and brine (each of 20 ml). After drying and evaporation, the resulted residue was purified by preparative TLC (silica gel) and methyl 3-*O*-(2,3,4,6-tetra-*O*-*p*-chlorobenzyl-β-D-glucopyranosyl) -2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (100.5 mg, 92% yield) was isolated. The ratio of the anomers was determined by ^{1}H-NMR and HPLC analysis.

Thus, a new and efficient method for highly 1,2-*trans*-selective glycosylation was successfully developed by using *p*-chlorobenzylated glycosyl carbonate as a glycosyl donor. It is noted that this new glycosylation has great advantages over the conventional glycosylation methods in its efficiency and high stereoselectivity brought by the influence of anomerization-resistant *p*-chlorobenzylated glycoside.

The present research is partially supported by Grant-in-Aids for Scientific Research from Ministry of Education, Science and Culture.

References and Notes

1 A. Varki, *Glycobiology*, **3**, 97(1993); R. A. Dewk, *Biochem. Soc. Trans.*, **23**, 1(1995).
2 K. Toshima and K. Tatsuta, *Chem. Rev.*, **93**, 1503 (1993).
3 S. Hashimoto, M. Hayashi, and R. Noyori, *Tetrhedron. Lett.*, **25**, 1379 (1984); S. Hashimoto, T. Honda, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, **1989**, 685; R. R. Schmidt, M. Behrendt, and A. Toepfer, *Synlett*, **1990**, 694; Y. D. Vankar, P. S. Vankar, M. Behrendt, and R. R. Schmidt, *Tetrahedron*, **47**, 9985 (1991); K. Koide, M. Ohno, and S. Kobayashi, *Tetrahedron Lett.*, **32**, 7065 (1992); H. Kondo, S. Aoki, Y. Ichikawa, R. L. Halcomb, H. Ritzen, and C. H. Wong, *J. Org. Chem.*, **59**, 864(1994); S. Hashimoto, K. Umeo, A. Sano, N. Watanabe, M. Nakajima, and S. Ikegami, *Tetrahedron Lett.*, **36**, 2251(1995); K. Fukase, I. Kinoshita, T. Kanoh, Y. Nakai, A. Hasuoka, and S. Kusumoto, *Tetrahedron*, **52**, 3897 (1996).
4 H. Uchiro and T. Mukaiyama, *Chem. Lett.*, **1996**, 271; H. Uchiro, K. Miyazaki, and T. Mukaiyama, *Chem. Lett.*, **1997**, 403.
5 Quite recently, oligosaccharide synthesis utilizing chemical stability of *p*-chlorobenzylated glycoside under the acidic condition was reported: N. L. Pohl and L. L. Kiessling, *Tetrahedron Lett.*, **40**, 6985(1997).
6 H. Uchiro and T. Mukaiyama, *Chem. Lett.* **1997**, 121.
7 Donors **1** and **2** were easily and stereoselectively prepared from the corresponding 1-hydroxy sugars[8] with acetyl chloride or phenyl chloroformate by Bols's stereoselective acylation method.[9]
8 S. Koto, S. Inada, N. Morishima, and S. Zen, *Carbohydr. Res.*, **87**, 294(1980).
9 M. Bols and H. C. Hansen, *Acta Chem. Scand.*, **47**, 818 (1993).
10 Since the melting point of pivalonitrile is 15 °C, a mixed solvent was applied to the reaction at lower temperature.
11 Examples of glycosylation utilizing phenylcarbonate-type glycosyl donors have been reported: R. Ishido, I. Takai, and K. Shibasaki, *Japanese Patent*, JP 9409674(1994); T. Mukaiyama, T. Sasaki, E. Iwashita, and K. Matsubara, *Chem. Lett.* **1995**, 455.