Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6453–6457

TETRAHEDRON LETTERS

A stereocontrolled construction of 2-azido-2-deoxy-1,2-*trans*-β-glycosidic linkages utilizing 2-azido-2-deoxyglycopyranosyl diphenyl phosphates

Toshifumi Tsuda, Seiichi Nakamura and Shunichi Hashimoto*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

Received 3 June 2003; revised 21 June 2003; accepted 23 June 2003

Abstract—A high-yielding and stereocontrolled construction of 2-azido-2-deoxy-1,2-*trans*-β-glycosidic linkages has been achieved by exploiting TMSOTf-promoted 1,2-*trans*-glycosidation of 2-azido-2-deoxyglycopyranosyl diphenyl phosphates with various glycoside alcohols in propionitrile at −78°C. The present method exhibits the highest levels of 1,2-*trans*-β-selectivity reported to date for this type of glycosidation.

2-Acetamido-2-deoxy-D-glycopyranosides are ubiquitous constituents of biologically significant oligosaccharides and glycoconjugates including glycolipids, glycoproteins, proteoglycans, and peptidoglycan. Most 2-acetamido-2-deoxy-D-glycopyranosides are present in these molecules in 1,2-*trans*-β-glycosidic linkages.

In terms of efficiency and practicality, direct glycosidation using 2-acetamido-2-deoxyglycosyl donors should constitute an ideal procedure for the stereocontrolled construction of 2-acetamido-2-deoxy-1,2-*trans*-β-glycosidic linkages.[1] In practice, however, reaction of these donors generally leads to the predominant formation of oxazoline derivatives via neighboring group participation and subsequent abstraction of an amide proton. To overcome this problem, a number of different 2-amino protecting groups with an anchimeric assistance have been investigated,[2,3] though this method requires two additional synthetic steps: deprotection and subsequent replacement by an acetyl group. The phthaloyl group[2a] has been most widely used for this purpose, and results in high yields and virtually complete β-selectivity with most glycosyl acceptors as has been demonstrated by a number of syntheses of complex oligosaccharides. However, removal of the phthaloyl group requires relatively harsh conditions which often cause partial decomposition of the product.

An alternative approach to 2-acetamido-2-deoxy-β-glycopyranosides involves the use of 2-azido-2-deoxyglycopyranosyl donors. Although the azido group as a latent amino functionality is incapable of neighboring group participation, the glycosidation of 2-azido-2-deoxyglycosyl trichloroacetimidates[4] in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2–hexane[5] or TMSOTf in acetonitrile[6] has proven to be the method of choice for a highly stereocontrolled construction of 2-azido-2-deoxy-β-glycosides. Modest to good levels of β-selectivity were observed with the corresponding *S*-xanthates,[7] isopropenyl carbonate,[8] 2-pyridinecarboxylates,[9] and phenylthio glycosides.[10]

We have recently developed glycosyl donors incorporating a variety of phosphorus-containing leaving groups, the glycosidations of which constitute mild and efficient methods for the highly stereocontrolled construction of 1,2-*trans*-β- and 1,2-*cis*-α-glycosidic linkages with or without a participating group at C-2.[11,12] A recent report by Seeberger and co-workers concerning TMSOTf-promoted glycosidations of 2-azido-2-deoxyglucosyl dibutyl phosphate[13] with modest β-selectivity has prompted us to report our efforts toward the stereocontrolled construction of 2-azido-2-deoxy-β-glycosides from 2-azido-2-deoxyglycosyl donors carrying phosphorus-containing leaving groups.

At the outset of this study, we explored glycosidations of 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl diphenyl phosphate **1**[14] (α:β = 72:28 or 2:98) and tetramethylphosphorodiamidate **2**[16] (α:β = 65:35) with 6- or

Keywords: 2-azido-2-deoxyglycopyranosyl diphenyl phosphate; β-selective glycosidation; α-nitrilium ion.
* Corresponding author. Tel.: +81-11-706-3236; fax: +81-11-706-4981; e-mail: hsmt@pharm.hokudai.ac.jp

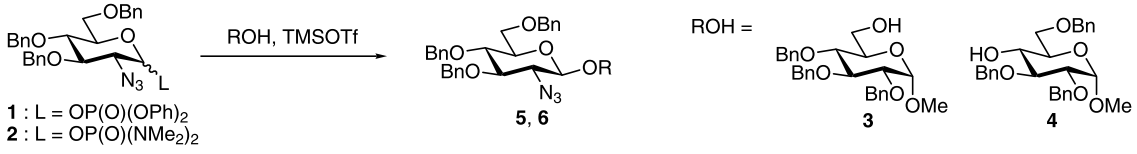
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01557-0

4-*O*-unprotected glycosides **3** or **4** (1.1 equiv. each) as highly reactive and less reactive acceptor alcohols, respectively. Some representative results are summarized in Table 1, from which several features have been noted.

As expected from previous work,[11a] TMSOTf-promoted glycosidations of the diphenyl phosphate **1** with **3** or **4** in propionitrile at −78°C proceeded smoothly to give disaccharides **5** and **6** in high yields with excellent β-selectivity regardless of the anomeric composition of the donor (entries 1–4).[17] A solvent survey revealed that propionitrile was the optimal solvent for this glycosidation, bringing about a beneficial effect on the stereoselectivity as well as the reaction rate (entries 1 and 3 versus 5–8). As is consistent with the proposal by Schmidt,[6] an exceptionally high order of β-selectivity observed with both **3** and **4** may be explained by assuming the predominant formation of an intermediate 2-azido-2-deoxy-α-D-glucosyl-nitrilium ion associated with triflate as a gegenion[18] followed by the backside attack of acceptor alcohols on this intermediate. Not unexpectedly, an increase in the reaction temperature was accompanied by a significant decrease in stereoselectivity (entries 1 and 3 versus 9–11). As would be expected if the reactions proceed via a common mechanism, TMSOTf-promoted glycosidations of phosphorodiamidate **2** under the identical conditions exhibited virtually the same β-selectivities as those with **1** (entries 12 and 13), albeit with a slightly lower yield in the case of **4**.

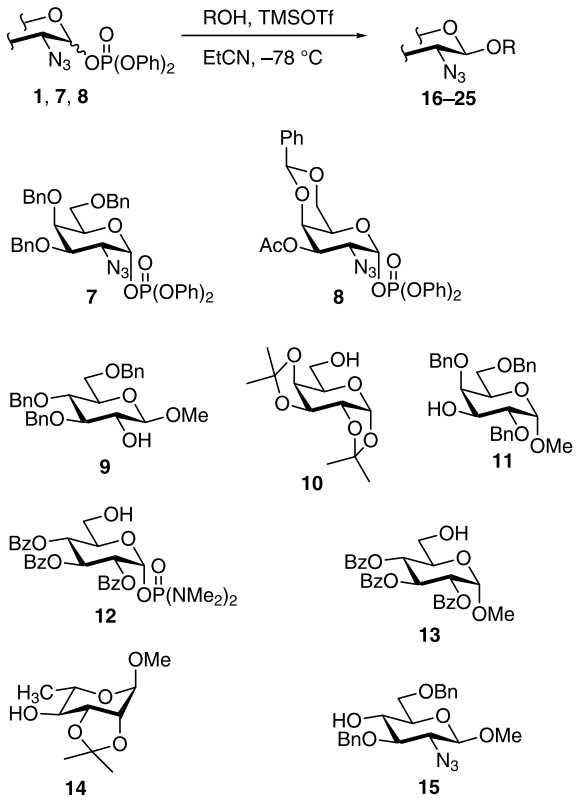
Next, we selected the phosphate method for ease of preparation of this type of donor, and explored glycosidations of 2-azido-2-deoxyglycosyl phosphates **1** (α:β = 72:28), **7**[14] (α:β = 95:5), and **8**[14] (α:β = 95:5) in the D-gluco and D-galacto series with a range of suitably protected glycoside alcohols of different reactivities (Scheme 1). The examples highlighted in Table 2 deserve some comments. In all cases, TMSOTf-promoted glycosidations in propionitrile at −78°C were found to offer a facile and high-yielding entry to 1,2-*trans*-β-linked disaccharides, in which the α:β ratios ranged from 9:91 to 1:>99. As touched on above, Seeberger and co-workers reported that TMSOTf-promoted coupling of 2-azido-2-deoxyglucosyl dibutyl phosphate with glycoside alcohols **9** or **10** in acetonitrile at −40°C produced disaccharides **16** and **17** in modest yields with α:β ratios of 1:4 and 1:5, respectively.[13] Clearly, the present method is superior to the dibutyl phosphate method in terms of both product yield and stereoselectivity (entries 1 and 2). It is also noteworthy that glucosylation of *O*-3-unprotected galactose derivative **11** led to the exclusive formation of disaccharide **18**, which constitutes a building block of gangliosides such as sialyl Lewis^x (entry 3). As might be expected from the fact that the fully benzoylated glucosyl tetramethylphosphorodiamidate is unaffected at temperatures below −5°C by such reaction conditions,[19] chemoselective glycosidation was uneventfully realized by using *O*-6-unprotected glucosyl phosphorodiamidate **12** as a disarmed acceptor (entry 4). It is interesting to note that 2-azido-2-deoxygalactosyl diphenyl phosphate **7** is even more reactive than the corresponding glucosyl

Table 1. TMSOTf-promoted glycosidation of 2-azido-2-deoxyglucosyl donors **1**[a] and **2**[b]



Entry	Donor		ROH	Solvent	Temp. (°C)	Time (h)	Glycoside		
		α:β[c]						Yield (%)[d]	α:β[e]
1	**1**	72:28	**3**	EtCN	−78	1.5	**5**	84	1:99
2	**1**	2:98	**3**	EtCN	−78	1.5	**5**	85	1:99
3	**1**	72:28	**4**	EtCN	−78	2	**6**	90	6:94
4	**1**	2:98	**4**	EtCN	−78	2	**6**	92	7:93
5	**1**	72:28	**3**	CH_2Cl_2	−78	4	**5**	88	1:99
6	**1**	72:28	**3**	PhMe	−65	2	**5**	90	4:96
7	**1**	72:28	**4**	CH_2Cl_2	−78	8	**6**	84	10:90
8	**1**	72:28	**4**	PhMe	−65	8	**6**	81	24:76
9	**1**	72:28	**3**	EtCN	−45	0.5	**5**	89	3:97
10	**1**	72:28	**4**	EtCN	−45	0.5	**6**	88	13:87
11	**1**	72:28	**3**	EtCN	−10	0.1	**5**	92	8:92
12	**2**	65:35	**3**	EtCN	−78	2.5	**5**	81	2:98
13	**2**	65:35	**4**	EtCN	−78	3	**6**	81	7:93

[a] Donor **1**/ROH/TMSOTf molar ratio = 1.0/1.1/1.5.
[b] Donor **2**/ROH/TMSOTf molar ratio = 1.0/1.1/1.8.
[c] Determined by 109 MHz ^{31}P NMR using 85% H_3PO_4 as an external standard.
[d] Isolated yield based on the donor used.
[e] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17% ethyl acetate in hexane; flow rate 1.0 mL/min).



Scheme 1.

donor **1** (entries 5–8), displaying slightly higher β-selectivity than that of **1** (entry 5 versus entry 3 in Table 1). In accordance with a general trend,[20] the 4,6-*O*-benzylidene protective group in **8** significantly reduced its reactivity compared with the fully benzylated galactosyl donor **7**, yet had little effect on either product yield or stereoselectivity (entries 9 and 10).

In conclusion, we have demonstrated that TMSOTf-promoted glycosidations of 2-azido-2-deoxyglycopyranosyl diphenyl phosphates with a variety of glycoside alcohols give 1,2-*trans*-β-linked disaccharides in high yields. Furthermore, these reactions proceed with the highest levels of stereoselectivity reported to date for this type of glycosidation, regardless of the anomeric configuration of the donor, in which the key to the success of the present protocol lies in a smooth coupling in propionitrile at −78°C. This method has the advantages of operational simplicity and practical value, and thus should be a potent alternative to Schmidt's trichloroacetimidate procedure.[21]

Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.T. is grateful to the JSPS for a graduate fellowship. We thank Ms. H. Matsumoto, A. Maeda, S. Oka, and M. Kiuchi of the Center for Instrumental Analysis, Hokkaido University, for technical assistance in MS and elemental analysis.

References

1. For reviews, see: (a) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195; (b) Debenham, J.; Rodebaugh, R.; Fraser-Reid, B. *Liebigs Ann. Recueil* **1997**, 791–802.
2. (a) Phthaloyl group: Lemieux, R. U.; Takeda, T.; Chung, B. Y. *ACS Symp. Ser.* **1976**, *39*, 90–115; (b) 2,2,2-trichloroethoxycarbonyl group: Imoto, M.; Yoshimura, H.; Shimamoto, T.; Sakaguchi, N.; Kusumoto, S.; Shiba,

Table 2. Glycosidation of 2-azido-2-deoxyglycosyl diphenyl phosphates **1**, **7** and **8**[a,b]

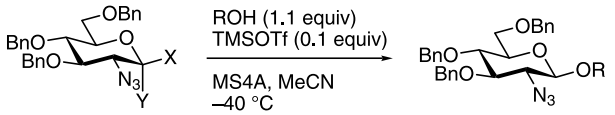
Entry	Donor[c]	ROH	Time (h)	Glycoside		
					Yield (%)[d]	α:β[e]
1	**1**	**9**	2	**16**	91	9:91
2	**1**	**10**	1.5	**17**	79	2:98
3	**1**	**11**	2	**18**	89	1:>99
4[f]	**1**	**12**	2	**19**	88	7:93[g]
5	**7**	**4**	0.5	**20**	93	4:96
6	**7**	**13**	0.2	**21**	85	5:95
7	**7**	**14**	0.3	**22**	82	6:94
8	**7**	**15**	0.5	**23**	86	8:92
9	**8**	**3**	3	**24**	78	3:97
10	**8**	**4**	3	**25**	90	4:96

[a] The reaction was carried out on 0.1 mmol scale.
[b] Donor/ROH/TMSOTf molar ratio = 1.0/1.1/1.5.
[c] The anomeric α:β ratio of the phosphates: **1**, 72:28; **7**, 95:5; **8**, 95:5.
[d] Isolated yield based on the donor used.
[e] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17% ethyl acetate in hexane or 14–17% THF in hexane; flow rate 1.0 mL/min), unless otherwise stated.
[f] The reaction was performed with 2.0 equiv. of TMSOTf.
[g] Determined by 500 MHz ^{1}H NMR.

T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2205–2214; (c) allyloxycarbonyl and benzyloxycarbonyl groups: Boullanger, P.; Jouineau, M.; Bouammali, B.; Lafont, D.; Descotes, G. *Carbohydr. Res.* **1990**, *202*, 151–164; (d) trichloroacetyl group: Blatter, G.; Beau, J.; Jacquinet, J. *Carbohydr. Res.* **1994**, *260*, 189–202; (e) tetrachlorophthaloyl group: Debenham, J. S.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 3302–3303; (f) dithiasuccinoyl group: Meinjohanns, E.; Meldal, M.; Paulsen, H.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 405–415; (g) *N*,*N*-diacetyl group: Castro-Palomino, J. C.; Schmidt, R. R. *Tetrahedron Lett.* **1995**, *36*, 6871–6874; (h) 4,5-dichlorophthaloyl group: Shimizu, H.; Ito, Y.; Matsuzaki, Y.; Iijima, H.; Ogawa, T. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 73–76; (i) dimethylmaleoyl group: Aly, M. R. E.; Castro-Palomino, J. C.; Ibrahim, E.-S. I.; El-Ashry, E.-S. H.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 2305–2316; (j) *N*,*N*-dibenzyl group: Jiao, H.; Hindsgaul, O. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 346–348; (k) thiodiglycoloyl group: Castro-Palomino, J. C.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 629–632.

3. For methods involving azaglycosidation of glycals, see: (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811–5819; (b) Liu, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9789–9797.
4. For reviews, see: (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235; (b) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123; (c) Schmidt, R. R.; Jung, K.-H. In *Carbohydrates in Chemistry and Biology*, Ernst, B.; Hart, G. W.; Sinaÿ, P. Eds.; Wiley-VCH: Weinheim, 2000; pp. 5–59.
5. Kinzy, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 1537–1545. High levels of β-selectivity achieved by this method are mostly limited to the use of α-trichloroacetimidates. See also Refs. 4a and 4b.
6. Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694–696. In this paper, it was demonstrated that β-selectivities are practically independent of the anomeric configuration of the starting trichloroacetimidates.
7. Marra, A.; Gauffeny, F.; Sinaÿ, P. *Tetrahedron* **1991**, *47*, 5149–5160.
8. Marra, A.; Esnault, J.; Veyrières, A.; Sinaÿ, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354–6360.
9. Furukawa, H.; Koide, K.; Takao, K.; Kobayashi, S. *Chem. Pharm. Bull.* **1998**, *46*, 1244–1247.
10. Codée, J. D.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519–1522.
11. (a) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685–687; (b) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259–1260 and references cited therein. See also: http://www.glycoforum.gr.jp/science/word/glycotechnology/GT-A01E.html.
12. Recently, we have reported the selective construction of β-mannosidic linkages capitalizing on 4,6-*O*-benzylidene-protected D-mannopyranosyl diethyl phosphite. See: Tsuda, T.; Sato, S.; Nakamura, S.; Hashimoto, S. *Heterocycles* **2003**, *59*, 509–515.
13. Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2000**, *2*, 3841–3843.
14. 2-Azido-2-deoxyglycosyl diphenyl phosphates were prepared from the corresponding glycopyranoses according to the method of Sabesan[15a] [$ClP(O)(OPh)_2$, DMAP, CH_2Cl_2, 0°C] except the donor **1** of α:β ratio of 2:98 which was obtained by the reaction of 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate (**26**α)[5] with $HOP(O)(OPh)_2$ in CH_2Cl_2.[15b] The crude diphenyl phosphates **1**, **7** and **8** were purified by column chromatography (silica gel, 2:1–3:1 hexane/AcOEt with 2% Et_3N).
15. (a) Sabesan, S.; Neira, S. *Carbohydr. Res.* **1992**, *223*, 169–185; (b) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1984**, *23*, 680–691.
16. The donor **2** was prepared from the corresponding glucopyranose according to the literature procedure [BuLi, THF, −78°C, then $(Me_2N)_2P(O)Cl$, HMPA, −20°C], see: Hashimoto, S.; Yanagiya, Y.; Honda, T.; Harada, H.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 3523–3526.
17. *Typical procedure for the glycosidation of 2-azido-2-deoxyglycopyranosyl diphenyl phosphate* (Table 1, entry 3): TMSOTf (1.0 M in CH_2Cl_2, 0.15 mL, 0.15 mmol) was added to a stirred solution of donor **1** (70.8 mg, 0.1 mmol) and acceptor **4** (51.1 mg, 0.11 mmol) in EtCN (1.5 mL) at −78°C under an argon atmosphere. After stirring at this temperature for 2 h, the reaction was quenched with Et_3N (0.1 mL). The mixture was poured into a two-layer mixture of AcOEt (5 mL) and H_2O (5 mL), and the whole was extracted with AcOEt (15 mL). The organic layer was successively washed with 10% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by flash column chromatography (silica gel, 5:1 hexane/AcOEt) afforded disaccharide **6** (82.6 mg, 90%, α:β = 6:94) as a colorless oil. The α:β ratio was determined by HPLC (column, Zorbax® Sil, 4.6×250 mm; eluent, 17% ethyl acetate in hexane; flow rate 1.0 mL/min; t_R α-disaccharide, 18.0 min; t_R β-disaccharide, 25.1 min).
18. Sakamoto, H.; Nakamura, S.; Tsuda, T.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 7691–7695.
19. Hashimoto, S.; Sakamoto, H.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 5181–5184.
20. (a) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942; (b) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51–65; (c) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753.
21. For comparison, TMSOTf-promoted glycosidation of 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranosyl trichloroacetimidate (**26**)[5] with **3** or **4** was investigated under 'Schmidt's standard conditions' [TMSOTf (0.1 equiv.), MS 4 Å, MeCN, −40°C].[6,22] The results are summarized in the table. Glycosidation of **26** with 6-*O*-unprotected glycoside **3** was found to give nearly the same β-selectivities as those obtained by the diphenyl phosphate method, regardless of the anomeric configuration of the donor (entries 1 and 2). However, coupling of **26** with 4-*O*-unprotected glycoside **4** resulted in diminished β-selectivities (entries 3 and 4), in which the use of α-imidate **26**α gave less satisfactory yield (entry 3) due to

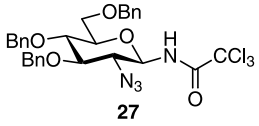
the inevitable formation (35%) of trichloroacetamide **27**.[23]



26α X=H, Y=OC(NH)CCl_3
26β X=OC(NH)CCl_3, Y=H

5, **6**

Entry	Donor	ROH	Time h	Glycoside	Yield, %	α:β
1	**26**α	**3**	0.1	**5**	88	2:98
2	**26**β	**3**	0.1	**5**	92	3:97
3	**26**α	**4**	0.3	**6**	51	12:88
4	**26**β	**4**	0.3	**6**	84	12:88



27

22. Greilich, U.; Zimmermann, P.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1993**, 859–864.
23. For examples of the formation of *N*-glycosyl trichloroacetamides as by-products, see: (a) Sadozai, K. K.; Nukada, T.; Ito, Y.; Nakahara, Y.; Ogawa, T.; Kobata, A. *Carbohydr. Res.* **1986**, *157*, 101–123; (b) Kinzy, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1987**, 407–415; (c) Nunomura, S.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 5681–5684; (d) Kobayashi, M.; Yamazaki, F.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *201*, 51–67; (e) Lindberg, J.; Öhberg, L.; Garegg, P.; Konderson, P. *Tetrahedron* **2002**, *58*, 1387–1398.