Tetrahedron Letters, Vol.32, No.47, pp 6887-6890, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Highly Stereoselective Glycosylation by Conformational Assistance of Glycosyl Donor

Kazunobu Toshima, Yuko Nozaki, and Kuniaki Tatsuta*

Department of Applied Chemistry, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223, Japan

Key Words: *stereoselective glycosylation; 2-deoxy-D-fucose; conformational assistance; anomeric effect; 1,3-diaxial interaction.*

Abstract: *Highly α-stereoselective glycosylation of 2-deoxy-D-fucose was achieved by use of the conformational assistance of the rigid glycosyl donor* **2**. *The selectivity of the glycosylation of* **2** *was much higher than that of* **3** *which had a normal chair conformation.*

In numerous glycosylation studies for long time, new and efficient functional groups at anomeric position of glycosyl donor and activating reagents were developed to control stereoselectivity of glycosylation reaction[1]. Also, solvent effect[2] was frequently used as a significant factor as well as an activator, while the mechanism of induction of selectivity due to the solvent was not clear. On the other hand, little attention has been turned to the conformation of glycosyl donor in glycosylation. We reported previously the highly α-stereoselective glycosylation for 2,6-dideoxy sugar by use of C-1 activated 2,6-anhydro-2-thio sugar as a very rigid glycosyl donor[3]. In this communication, we wish to announce some preliminary results on the glycosylation selectivity in relation to the conformation of glycosyl donor in glycosylation and demonstrate a novel strategy for a highly α-stereoselective glycosylation of 2-deoxy-D-fucose by use of phenyl 2-deoxy-3,4-O-isopropylidene-1-thio-D-fucopyranoside (**2**).

In general, in the glycosylation of the sugar which exists in chair conformation, anomeric effect influenced glycosylation selectivity to predominantly produce the corresponding α-glycoside[4]. However, it is well known that conformation of sugar (glycosyl donor) is changed subtly by substituents in the sugar in different solvent systems[5]. On the other hand, we expected that, in the glycosyl donor such as **1** which had a rigid and unusual boat conformation, 1,3-diaxial interaction between C-3 substituent and the approaching alcohol which was generated from its conformational assistance would strongly assist α-selectivity in the glycosylation, although selectivity of glycosylation would not be effectively affected by anomeric effect because of its unusual structure (Fig. 1). To assay this hypothesis, we designed both the rigid 2,6-dideoxy glycosyl donor **2** and the flexible 2,6-dideoxy glycosyl donor **3** and examined the effect of the conformational assistance of the glycosyl donor in glycosylation by comparing the glycosylation selectivities of **2** with those of **3** under the several same conditions.

Phenyl α-thioglycosides **2**[6,7] and **3**[6] were synthesized from 2-deoxy-D-fucopyranose[8] in 2 steps [for **2**: (a) Bu_3P/PhSSPh/THF/25°C/4h/70%; (b) $Me_2CO/BF_3{\cdot}Et_2O$/25°C/1h/70%(α/β=3/2); for **3**: (a) Bu_3P/

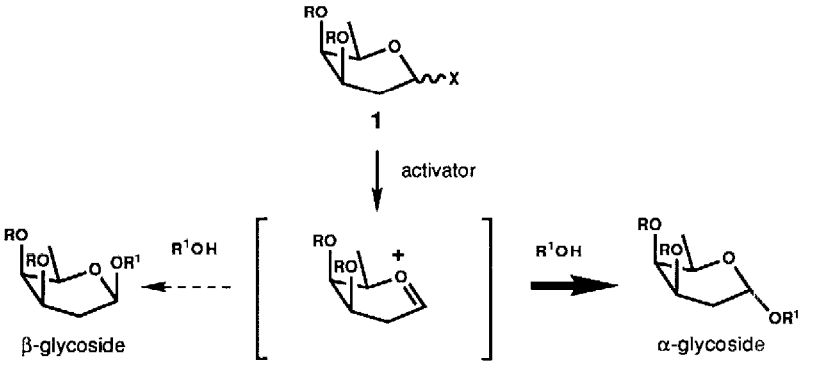


Fig. 1

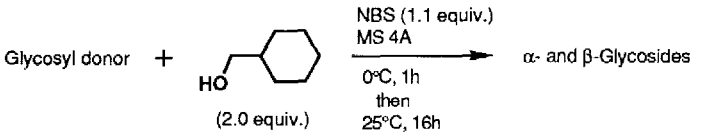
PhSSPh/THF/25°C/4h/70%; (b) Ac_2O/DMAP/Py/25°C/0.5h/99%(α/β=3/2), respectively] and used for the following glycosylations according to Nicolaou's glycosylation method[9]. We first examined the glycosylation of **2** and **3** by using cyclohexylmethanol as the glycosyl acceptor in several solvents respectively. The results in Table 1 showed sharp contrast in glycosylation selectivities of **2** and **3**. Each yields of the produced glycosides were not quite different, but selectivities of the glycosylation of **2** were much higher than those of **3** especially in nonpolar solvents. Remarkably, in CH_2Cl_2 and $(CH_2Cl)_2$, stereoselectivities of the glycosylations were quite α-specific. On this stage, we contacted the question whether the high α-selectivities really came from conformational assistance, not from the isopropylidene group itself. So, we examined the glycosylation of **4**[6,7] and **5**[6] under the same conditions which were used for **2** and **3**. Phenyl thioglycoside **4** (α/β=2/1) was synthesized from methyl 2,6-dideoxy-α-D-ribo-hexopyranoside[10] in 2 steps [(a) Ac_2O/DMAP/Py/25°C/0.5h/99%; (b) Me_3SiSPh/TMSOTf/CH_2Cl_2/25°C/1h/86%.] and **5** (α/β=2/1) from **4** in 2 steps [(a) NaOMe/MeOH/25°C/10 min/92%; (b) $Me_2CO/BF_3{\cdot}Et_2O$/25°C/5h/85%.]. In these cases, we expected that both selectivities of the glycosylations of **4** and **5** would be almost the same, because the isopropylidene group in **4** would not generate the aforementioned 1,3-diaxial interaction due to the configurations at C-3 and 4 positions. The experimental results in Table 1 showed good agreements with our expectations. Indeed, both yields and stereoselectivities were very similar and the significant differences due to the protecting groups were not observed in the glycosylations of **4** and **5**. Finally, we examined the glycosylation of **2** with several alcohols in CH_2Cl_2 at 25°C for 2h. The results in Table 2 showed an additional efficiency of the present conformationally assisted glycosylation. Selectivities of the glycosylations of **2** were highly independent of alcohols and the corresponding α-glycosides were obtained with high stereocontrol in good yields.

In conclusion, These results suggested that conformational assistance of glycosyl donor was an important factor in glycosylation selectivity and could be used for controlling the selectivity. Further, this work showed an effficient method with high stereocontrol for synthesis of 2-deoxy-α-D-fucosides which were found as components in the antibiotics such as olivomycin[11].

Acknowledgement

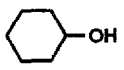
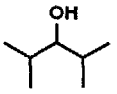
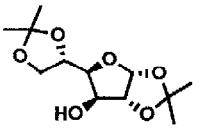
We are grateful to the Institute of Microbial Chemistry for the generous support of our program. Financial supports by the Ministry of Education, Science and Culture (Grant-in-Aid Scientific Research) and the Kawakami Memorial Foundation are gratefully acknowledged.

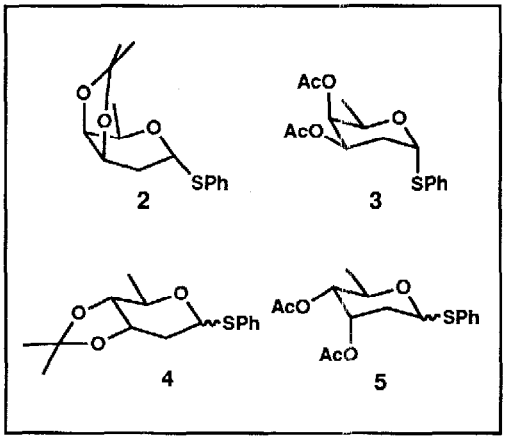
Table1. Stereoselectivities of the glycosylations of **2, 3, 4** and **5** with cyclohexylmethanol.



Glycosyl donors	**2**		**3**		**4**		**5**	
Glycosides / Solvents	α/β[a)]	yields(%)[b)]	α/β[a)]	yields(%)[b)]	α/β[a)]	yields(%)[b)]	α/β[a)]	yields(%)[b)]
CH_3CN	8/1	80	2/1	79	1/1.2	80	1/1	78
THF	15/1	87	2/1	95	1.3/1	82	1/2.3	93
Et_2O	9/1	75	13/1	81	1.3/1	88	1/1.4	95
CH_2Cl_2	>99/1	99	11/1	97	1.2/1	78	1/1	91
$(CH_2Cl)_2$	>99/1	71	14/1	82	1/1.6	86	1.2/1	86
PhMe	40/1	77	3/1	88	1/1.4	84	1/1.4	96

Table2. Glycosylations of **2** with several alcohols (2.0 equiv.) by use of NBS (1.1 equiv.) in CH_2Cl_2.

Glycosides / Alcohols	α/β[a)]	yields(%)[b)]
$C_8H_{17}OH$	>99/1	84
	>99/1	87
	98/2	79
	96/4	95



a) α/β Ratios were determined by ^{1}H-NMR spectroscopy and/or isolation of pure isomers[12].

b) Isolated yields after purification by column chromatography.

References and Notes

1) For recent reviews of glycosylation, see: (a) K. Krohn, *Nachr. Chem. Tech. Lab.*, **35**, 930 (1987); (b) R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, **25**, 212 (1986); (c) H. Paulsen, *Angew. Chem. Int. Eng.*, **21**, 155 (1982); (d) S. Hanessian, D. M. Dixit, and T. J. Liak, *Pure Appl. Chem.*, **53**, 129 (1981); (e) H. Tsutsumi and Y. Ishida, *J. Syn. Org. Chem. Jpn.*, **38**, 473 (1980); (f) A. F. Bochkov and G. E. Zaikov, "*Chemistry of the O-Glycosidic Bond: Formation and Cleavage*", Pergamon Press, Oxford, 1979; (g) P. Sinay, *Pure Appl. Chem*, **50**, 1437 (1978); (h) K. Igarashi, *Adv. Carbohydr. Chem. Biochem.*, **34**, 243 (1977); (i) S. Hanessian and J. Banoub, *Adv. Chem. Ser.*, **39**, 36 (1976); (j) G. Wulff and G. Rohle, *Angew. Chem.*, **86**, 173 (1974).

2) For some selective glycosylations by using solvent effect, see: (a) R. R. Schmidt, M. Behrendt, and A. Toepter, *Synlett*, **1990**, 694, and references therein; (b) K. Suzuki, H. Maeta, T. Suzuki, and T. Matsumoto, *Tetrahedron Lett.*, **30**, 6879 (1989); (c) M. Perez and J-M. Beau, *Tetrahedron Lett.*, **30**, 75 (1989); (d) T. Matsumoto, H. Maeta, K. Suzuki, and G. Tuchihashi., *Tetrahedron Lett.*, **29**, 3567 (1988); (e) K. C. Nicolaou, T. Ladduwahetty, J. L. Randall, and A. Chucholowski, *J. Am. Chem. Soc.*, **108**, 2466 (1986); (f) S. Hashimoto, M. Hayashi, and R. Noyori, *Tetrahedron Lett.*, **25**, 1379 (1984).

3) (a) K. Toshima, S. Mukaiyama, T. Ishiyama, and K. Tatsuta, *Tetrahedron Lett.*, **31**, 3339 (1990); (b) K. Toshima, S. Mukaiyama, T. Ishiyama, and K. Tatsuta, *Tetrahedron Lett.*, **31**, 6361 (1990); (c) K. Toshima, S. Mukaiyama, T. Yoshida, T. Tamai, and K. Tatsuta, *Tetrahedron Lett.*, in press.

4) P. Deslongchamps, "*Stereoelectronic Effects in Organic Chemistry*", Pergamon Press: Oxford, 1983.

5) (a) P. L. Durette and D. Horton, *Adv. Carbohydr. Chem. Biochem.*, **26**, 49 (1971). (b) R. U. Lemieux, *Pure Appl. Chem.*, **27**, 527 (1971).

6) All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means. Significant ^{1}H-NMR(270MHz, $CDCl_3$) spectra [δ (TMS), J(Hz)] are the following. **2**: 1.25 (3H, d, J=6.8, H-6), 1.35 (3H, s, $C\underline{H}_3CCH_3$), 1.48 (3H, s, $CH_3C\underline{C}H_3$), 1.87 (1H, ddd, J=15.6, 8.8 and 3.9, H-2), 2.40 (1H, ddd, J=15.6, 6.2 and 4.3, H-2'), 4.02 (1H, dd, J=7.9 and 2.0, H-4), 4.04 (1H, dq, J=6.8 and 2.0, H-5), 4.50 (1H, ddd, J=7.9, 4.3 and 3.9, H-3), 5.56 (1H, dd, J=8.8 and 6.2, H-1), 7.2-7.6 (4H, m, SPh); **3**: 1.15 (3H, d, J=6.4, H-6), 2.00 (3H, s, OAc), 2.05 (1H, ddd, J=12.8, 4.6 and 0.4, H-2), 2.16 (3H, s, OAc), 2.47 (1H, ddd, J=12.8, 12.8 and 5.9, H-2'), 4.55 (1H, dq, J=6.4 and 0.5, H-5), 5.22 (1H, dd, J=3.4 and 0.5, H-4), 5.28 (1H, ddd, J=12.8, 4.6 and 3.4, H-3), 5.73 (1H, dd, J=5.9 and 0.4, H-1), 7.2-7.5 (4H, m, SPh); **4**: 1.29 (1/3 X 3H, d, J=6.4, β-H-6), 1.30 (2/3 X 3H, d, J=6.4, α-H-6), 1.36 (1/3 X 3H, s, β-$C\underline{H}_3CCH_3$), 1.38 (2/3 X 3H, s, α-$C\underline{H}_3C$-CH_3), 1.47 (1/3 X 3H, s, β-$CH_3C\underline{C}H_3$), 1.57 (2/3 X 3H, s, α-$CH_3C\underline{C}H_3$), 2.08 (1/3H, ddd, J=15.6, 12.0 and 4.4, β-H-2), 2.25 (2/3H, ddd, J=15.2, 5.0 and 5.0, α-H-2), 2.41 (1/3H, ddd, J=15.6, 2.4 and 2.4, β-H-2'), 2.49 (2/3H, ddd, J=15.2, 7.0 and 4.8, α-H-2'), 3.48 (1/3H, dq, J=9.0 and 6.4, β-H-5), 3.65 (1/3H, dd, J=9.0 and 4.9, β-H-4), 3.79 (2/3H, dd, J=9.0 and 5.8, α-H-4), 4.21 (2/3H, dq, J=9.0 and 6.4, α-H-5), 4.32 (2/3H, ddd, J=5.8, 5.0 and 4.8, α-H-3), 4.38 (1/3H, ddd, 4.9, 4.4 and 2.4, β-H-3), 5.01 (1/3H, dd, J=12.0 and 2.4, β-H-1), 5.45 (2/3H, dd, J=7.0 and 5.0, α-H-1), 7.2-7.5 (4H, m, SPh); **5**: 1.22 (2/3 X 3H, d, J=6.2, α-H-6), 1.23 (1/3 X 3H, d, J=6.2, β-H-6), 1.95-2.2 (1/3 X 2H, m, β-H-2 and β-H-2'), 2.01 (1/3 X 3H, s, β-OAc), 2.05 (2/3 X 3H, s, α-OAc), 2.10 (1/3 X 3H, s, β-OAc), 2.20 (2/3 X 3H, s, α-OAc), 2.32 (2/3H, ddd, J=15.2, 3.9 and 2.0, α-H-2), 2.44 (2/3H, ddd, J=15.2, 6.2 and 3.0, α-H-2'), 3.98 (1/3H, dq, J=10.0 and 6.2, β-H-5), 4.5-4.75 (4/3H, m, α-H-4, 5 and β-H-4), 5.09 (1/3H, dd, J=11.6 and 4.6, β-H-1), 5.36 (2/3H, br ddd, J=3.9, 3.0 and 3.0, α-H-3), 5.42 (1/3H, br ddd, J=3.6, 3.6 and 3.6, β-H-3), 5.47 (2/3H, dd, J=6.2 and 2.0, α-H-1), 7.2-7.5 (4H, m, SPh).

7) The ^{1}H-NMR analyses of **2** and **4** indicated that they had the unusual boat-like confromations depicted in the figure which were different from the normal chair conformations such as **3** and **5**. See ref. 6.

8) B. Iselin and T. Reichstein, *Helv. Chim. Acta*, **27**, 1203 (1944).

9) K. C. Nicolaou, S. P. Seitz, and D. P. Papahatjis, *J. Am. Chem. Soc.*, **105**, 2430 (1983).

10) M. Haga, M. Chonan, and S. Tejima, *Carbohydr. Res.*, **16**, 486 (1971).

11) (a) Yu. A. Berlin, S. E. Esipov, M. N. Kolosov, M. M. Shemyakin, and M. G. Brazhnikova, *Tetrahedron Lett.*, **1964**, 3513; (b) Yu. A. Berlin, S. E. Esipov, M. N. Kolosov, and M. M. Shemyakin, *Tetrahedron Lett.*, **1966**, 1431.

12) In the isopropylidene glycosides, the configurations of the anomeric positions were confirmed by ^{1}H-NMR analyses of the corresponding di-O-acetyl glycosides which were obtained by standard deisopropylidenation (75%AcOH) followed by acetylation (Ac_2O/DMAP/Py).

(Received in Japan 23 August 1991)