Stereoselective α-Glycosylation with 3-O-Acetylated D-*Gluco* Donors

Nadezhda Ustyuzhanina,[a] Bozhena Komarova,[a] Natalya Zlotina,[b] Vadim Krylov,[b] Alexey Gerbst,[a] Yury Tsvetkov,[a] Nikolay Nifantiev*[a]

[a] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prospect 47, 119991 Moscow B-334, Russia

[b] Higher Chemical College, Russian Academy of Sciences, Miusskaya sq., 125047 Moscow, Russia
Fax +7(95)1358784; E-mail: nen@ioc.ac.ru

Received 14 December 2005

Abstract: The effect of a 3-*O*-acetyl group on the stereoselectivity of α-glycosylation with 2-O-benzylated D-*gluco* glycosyl donors was studied. It was shown that 3-O-acetylated donors gave α-anomers predominantly or exclusively, whereas glycosylation with the corresponding per-O-benzylated donors afforded mixtures of comparable amounts of α- and β-anomers. The higher α-stereoselectivity in the first case was accounted for by the remote anchimeric assistance of the 3-*O*-acetyl group, which was confirmed by theoretical calculations.

Key words: carbohydrates, glycosylations, remote participation, stereoselectivity, α-glucosylation

Although the glycosylation reaction has been known for more than a century, the stereoselective formation of the 1,2-*cis* glycoside bond is still considered a challenging problem in synthetic chemistry.[1] The major principle of the strategy is the use of a non-participating substituent on C-2 to avoid formation of the acyloxonium intermediate.[2] A number of factors should be taken into account, for instance, the nature of leaving and protecting groups, solvent, promoting system, the structure of the glycosyl acceptor, and temperature.[3,4] There are a few communications where the anchimeric assistance of remote substituents was used to improve the stereoselectivity of 1,2-*cis* glycosylation. Noteworthy are the examples with 6-O-acylated D-glucosyl and D-galactosyl donors,[5,6] 4-O-acylated D-galactosyl,[7] L-fucosyl,[8,9] D-mannosyl,[10] and L-rhamnosyl[11] donors, and fully benzylated glucuronyl donors bearing a participating COOAlk group at C-5.[12,13] The anchimeric participation of a remote 3-*O*-acyl substituent was also reported for the glycosylation with 2-deoxy-*ribo*-hexopyranosyl donors.[14–16] Recently we have shown that glycosylation with 3-*O*-benzoyl-2,4-di-*O*-benzyl-fucosyl bromide proceeded with high α-stereoselectivity.[17] Moreover, the stereoselectivity of the glycosylation with the latter donor was higher than that with the 4-O-benzoylated isomer, indicating that the anchimeric assistance of the 3-*O*-benzoyl group is more efficient than that of 4-*O*-benzoyl. These results were in good correlation with theoretical calculations on the 'stabilization energy' of the glycosyl cations formed due to the participation of a benzoyl group.

To investigate the scope of this stereochemical effect, we studied the influence of a 3-*O*-acetyl group on the stereoselectivity of glycosylation with D-*gluco* donors, such as fully benzylated and 3-O-acetylated D-glucosyl *N*-phenyl trifluoroacetimidates **1**[18] and **2**,[18] D-glucuronyl bromides **3**[14] and **4**, and D-xylosyl trichloroacetimidates **5** and **6**. All these compounds have the same configuration at C-2, C-3, and C-4 (for this reason the xylosyl donors were included in the D-*gluco* series) but vary in the C-5 substituent and the leaving group at the anomeric center. Glycosylations of acceptors **7**–**9** with donors **1**–**6** were performed as steps within the syntheses of several substances: glycoforms of the outer core of the *Pseudomonas aeruginosa* lipopolysaccharide,[18] heterosaccharide fragments of fucoidans, and probes for the elucidation of xylosyltransferase activity. The synthesis of compounds **4**, **5**, and **6** will be reported elsewhere.

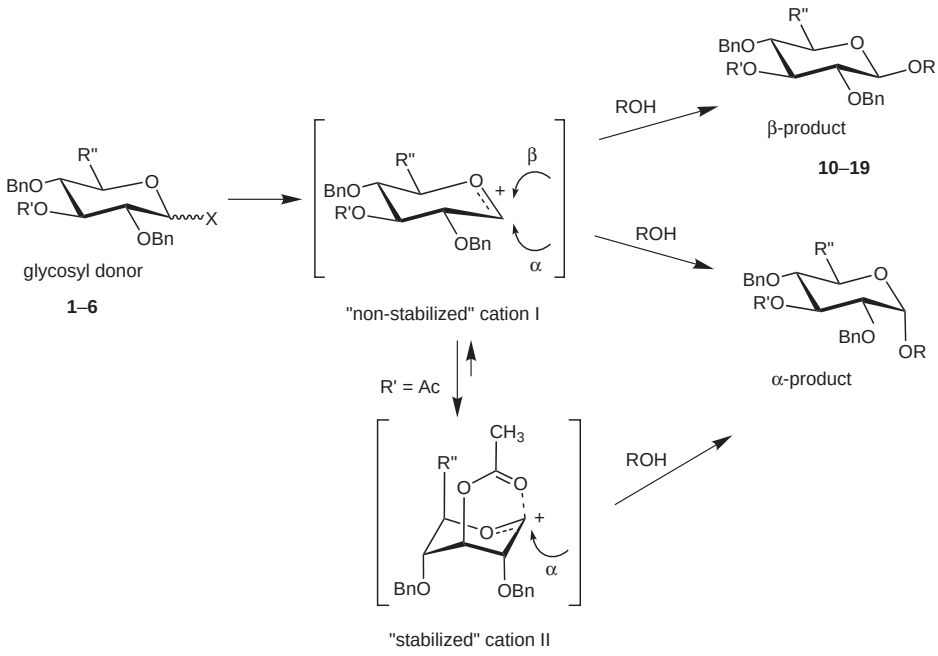
Methyl 2-azido-2-deoxy-D-galactoside **7**[18] was used as a glycosyl acceptor in reactions with glucosyl donors **1** and **2**. AgOTf-promoted glycosylation with fully benzylated *N*-phenyltrifluoroacetimidate **1** (Table 1, entry 1) afforded a 2:1 mixture of α- and β-isomers **10** and **11** in 95% yield.[19] The reaction of 3-O-acetylated donor **2** (Table 1, entry 2) demonstrated a notably higher α-stereoselectivity (**12**/**13**, α/β ratio, 4:1).[20]

A more pronounced stereochemical effect was observed in the case of glucuronyl donors **3** and **4**. The reaction of per-O-benzylated bromide **3** with acetonide **8**[21] in the presence of AgOTf (Table 1, entry 3) led to a 2:1 mixture of α- and β-anomers **14** and **15** (89%), whereas the use of 3-O-acetylated bromide **4** (Table 1, entry 4) strongly enhanced the stereoselectivity of the reaction and gave the α-isomer **16** exclusively (90%).[22]

Xylosyl donors **5** and **6** also provided evidence for the stereocontrolling effect of the 3-*O*-acetyl group. Glycosylation of allyl xyloside **9**[23] with 2,3,4-tri-O-benzylated trichloroacetimidate **5** (Table 1, entry 5) proceeded with relatively low stereoselectivity (**17**:**18**, 2.5:1), while the coupling of compounds **6** and **9** (Table 1, entry 6) afforded only α-linked disaccharide **19** in 80% yield.[24]

We assumed that the higher stereoselectivity of reactions with D-*gluco* donors **2**, **4**, and **6** is regulated by the remote stereocontrolling effect of the 3-*O*-acetyl group resulting in the formation of stabilized cation **II** (Scheme 1). Nucleophilic attack on cation **II** is favored from the α-side. To evaluate this possibility we calculated the energy

SYNLETT 2006, No. 6, pp 0921–0923
Advanced online publication: 14.03.2006
DOI: 10.1055/s-2006-939037; Art ID: G38605ST



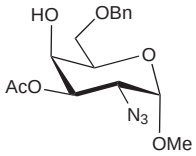
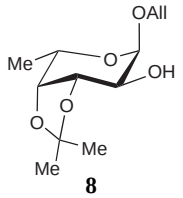
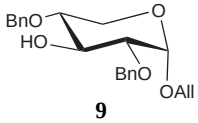
Scheme 1

difference between the stabilized and non-stabilized forms **I** and **II**, which is referred to as the 'stabilization energy' (Table 1).

'Stabilization energy' calculations (Table 1) were performed with an MM+Molecular mechanics force field (HyperChem, Version 7.0). Electrostatic interactions were considered in charge-charge approximation, the values of partial atomic charges were obtained from AM1 single point calculations. Calculated energy data were in good agreement with experimental results. Thus, the 'stabilization energy' of –11.3 kcal/mol for the donor **2** corresponds to the α/β ratio of 4:1. 'Stabilization energies' –15.3 kcal/mol for xylosyl donor **6** and –21.6 kcal/mol in the case of glucuronyl donor **4** are in accordance with the increase in α-stereoselectivity.

In conclusion, a series of D-*gluco* donors was studied as α-glycosylating agents. It was found that the reactions with donors bearing an acetyl group at O-3 provided remarkably higher stereoselectivity than those with per-O-benzylated analogues. This finding can be applied to the efficient synthesis of α-glucosides.

Table 1 Glycosylation and the 'Stabilization Energy' of the Cationic Intermediates II

Glycosyl donor				Glycosyl acceptor	α-Product	β-Product	Yield	Ratio α/β	Stabilization energy (kcal/mol)
	X	R′	R″						
1	α/β-OC(=NPh)CF_3	Bn	CH_2OBn	 **7**	**10**	**11**	95%	2:1	–
2	α/β-OC(=NPh)CF_3	Ac	CH_2OBn			**13**	90%	4:1	–11.3
3	α-Br	Bn	COOMe	 **8**	**14**	**15** not observed	89%	2:1	–
4	α-Br	Ac	COOMe		**16**		90%	–	–21.6
5	α/β-OC(=NH)CCl_3	Bn	H	 **9**	**17**	**18** not observed	85%	2.5:1	–
6	α/β-OC(=NH)CCl_3	Ac	H		**19**		80%	–	–15.3

Acknowledgment

This work was supported by the Russian Foundation for Basic Research (grants 03-03-32-556 and 05-03-08107) and the 1st Program of the Division of Chemistry and Material Sciences. We thank Mr. A. A. Grachev for recording NMR spectra.

References and Notes

(1) Demchenko, A. V. *Lett. Org. Chem.* **2005**, *2*, 580.
(2) Nukada, T.; Berces, A.; Zgierski, M.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291.
(3) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
(4) Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35.
(5) Ishikawa, T.; Fletcher, H. G. *J. Org. Chem.* **1969**, *34*, 563.
(6) Fletcher, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1972**, *94*, 604.
(7) Demchenko, A. V.; Rousson, E.; Boons, G.-J. *Tetrahedron Lett.* **1999**, *40*, 6523.
(8) Dejter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1972**, *23*, 41.
(9) Dejter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1973**, *28*, 61.
(10) De Meo, C.; Kamat, M. N.; Demchenko, A. V. *Eur. J. Org. Chem.* **2005**, 706.
(11) Yamanoi, T.; Nakamura, K.; Takeyama, H.; Yanagihara, K.; Inazu, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1359.
(12) Kováč, P.; Palovčík, R. *Carbohydr. Res.* **1977**, *54*, C11.
(13) Hirsch, J.; Koóš, M.; Kovač, P. *Carbohydr. Res.* **1998**, *310*, 145.
(14) Wiesner, K.; Tsai, T. Y. R.; Ren, A.; Kumar, R.; Tsubuki, V. *Helv. Chim. Acta* **1983**, *66*, 2632.
(15) Tsai, T. Y. R.; Jin, H.; Wiesner, K. *Can. J. Chem.* **1984**, *62*, 1403.
(16) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 284.
(17) Gerbst, A. G.; Ustuzhanina, N. E.; Grachev, A. A.; Khatuntseva, E. A.; Tsvetkov, D. E.; Whitfield, D. M.; Berces, A.; Nifantiev, N. E. *J. Carbohydr. Chem.* **2001**, *20*, 821.
(18) Komarova, B.; Tsvetkov, Y.; Knirel, Y.; Zähringer, U.; Pier, G.; Nifantiev, N. *Tetrahedron Lett.* **2006**, in press.
(19) A mixture of donor **1** (53 mg, 0.069 mmol), acceptor **7** (17 mg, 0.048 mmol), and MS AW-300 (76 mg) in CH_2Cl_2 (0.8 mL) was treated with a soln of AgOTf (9 mg, 0.034 mmol) in toluene (110 μL) overnight at r.t. under argon. The reaction mixture was filtered through celite, the filtrate was washed with 1 M $Na_2S_2O_3$, a sat. soln of $NaHCO_3$, and concentrated. After purification by chromatography (silica gel, toluene–EtOAc, 12:1) a mixture of α- and β-anomers **10** and **11** (40 mg, 0.045 mmol, 95%, 2:1) was obtained. The ratio of **10**/**11** was determined by the integration of the H-3 signal intensities (α, 5.21 ppm; β, 5.32 ppm) in the ^{1}H NMR spectra. Selected signals for **10**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.82 (d, 1 H, $J_{1',2'}$ = 4.0 Hz, H-1′), 4.88 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 5.21 (dd, 1 H, $J_{2,3}$ = 11.2 Hz, $J_{3,4}$ = 2.7 Hz, H-3). Selected signals for **11**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.39 (d, 1 H, $J_{1',2'}$ = 9.4 Hz, H-1′), 4.90 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H-1), 5.32 (dd, 1 H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 2.8 Hz, H-3).
(20) To a stirred mixture of acceptor **7** (33 mg, 0.095 mmol), donor **2** (50 mg, 0.075 mmol), and MS AW-300 (140 mg) in anhyd CH_2Cl_2 (2 mL) a soln of AgOTf (10 mg, 0.039 mmol) in anhyd toluene (0.1 mL) was added. The reaction was monitored by TLC, when donor **2** was consumed, a further portion of the donor (29 mg, 0.044 mmol) in anhyd CH_2Cl_2 and AgOTf (6 mg, 0.023 mmol) were added. The reaction mixture was stirred at r.t. for 2 d and then filtered through celite. The filtrate was washed with 1 M $Na_2S_2O_3$, a sat. soln of $NaHCO_3$, and concentrated. After purification by column chromatography (silica gel; toluene–EtOAc, 12:1) and gel-permeation chromatography (BioBeads SX-3, toluene) a mixture of α- and β-isomers **12** and **13** (71 mg, 90%, 4:1) was obtained. The α/β ratio was determined by the integration of the H-3′ signals (α, 5.58 ppm; β, 5.18 ppm) in the ^{1}H NMR spectra. Selected signals for **12**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.83 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 4.87 (d, 1 H, $J_{1',2'}$ = 3.3 Hz, H-1′), 5.18 (dd, 1 H, $J_{2,3}$ = 11.3 Hz, H-3), 5.58 (t, 1 H, $J_{2',3'}$ = 9.8 Hz, H-3′). Selected signals for **13**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.90 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 5.18 (t, 1 H, $J_{2',3'}$ = 10.0 Hz, H-3′).
(21) Takeo, K.; Aspinall, G. O.; Brennan, P.; Chatterjee, D. *Carbohydr. Res.* **1986**, *150*, 133.
(22) **Glycosylation with Glucuronyl Donors 3 and 4; General Procedure.** A mixture of glucuronyl bromide (0.052 mmol; 28 mg for **3**, 26 mg for **4**), acceptor **8** (12 mg, 0.05 mmol) and MS 4 Å (200 mg) in anhyd CH_2Cl_2 (2 mL) was stirred at r.t. for 30 min. Then AgOTf (15 mg, 0.057 mmol) was added at –30 °C. The mixture was stirred for 15 min at –30 °C, then quenched with Et_3N (0.1 mL), and filtered through celite. The filtrate was washed with 1 M $Na_2S_2O_3$, H_2O, dried over Na_2SO_4, and concentrated. Column chromatography (toluene–EtOAc, 15:1) of the residue afforded disaccharides. The α/β ratios were determined by integration of the signals corresponding to H-1′ in the ^{1}H NMR spectra. Selected signals for **14**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.92 (d, 1 H, $J_{1,2}$ = 3.1 Hz, H-1), 5.25 (d, 1 H, $J_{1'2'}$ = 3.5 Hz, H-1′). Selected signals for **15**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.98 (s, 1 H, H-1), 5.56 (d, 1 H, $J_{1',2'}$ = 8.5 Hz, H-1′). Selected signals for **16**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (d, 3 H, 3 × H-6), 1.98 (s, 3 H, $COCH_3$), 3.52 (dd, 1 H, $J_{1',2'}$ = 3,6 Hz, $J_{2',3'}$ = 10.0 Hz, H-2′), 3.73 (s, 3 H, CH_3), 3.76 (m, 2 H, H-2, H-4′), 4.04–4.22 (m, 5 H, H-3, H-4, H-5, CH_2CH=CH_2), 4.42–4.80 (m, 5 H, H-5′, 2 × CH_2Ph), 4.88 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 5.20 and 5.35 (2 dd, 2 H, CH_2CH=CH_2), 5.30 (d, 1 H, $J_{1',2'}$ = 3.6 Hz, H-1′), 5.56 (t, 1 H, $J_{2',3'}$ = $J_{3',4'}$ = 9.6 Hz, H-3′), 5.92 (m, 1 H, CH_2C*H*=CH_2), 7.24–7.35 (m, 10 H, 2 × Ph).
(23) Fukase, K.; Hase, S.; Ikenaka, T.; Kusumoto, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 436.
(24) **Glycosylation with Xylosyl Donors 5 and 6; General Procedure.** A mixture of xylosyl trichloroacetimidate (0.071 mmol; 40 mg for **5**: 36 mg for **6**), acceptor **9** (26 mg, 0.07 mmol) and MS 4 Å (200 mg) in anhyd CH_2Cl_2 (2 mL) was stirred at r.t. for 30 min. Then a 0.1 M solution of TMSOTf in anhyd CH_2Cl_2 (10 μL) was added at –30 °C. The mixture was stirred for 15 min at –30 °C, then quenched with Et_3N (0.1 mL), and filtered through celite. The filtrate was washed with H_2O, dried over Na_2SO_4, and concentrated. Column chromatography (toluene–EtOAc, 10:1) of the residue afforded disaccharides. The α/β ratios were determined by integration of the signals corresponding to H-1′ in the ^{1}H NMR spectra. Selected signals for **17**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.58 (d, 1 H, $J_{1',2'}$ = 3.5 Hz, H-1′). Selected signals for **18**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.93 (d, 1 H, $J_{1',2'}$ = 9.5 Hz, H-1′). ^{1}H NMR data for **19**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.36 (dd, 1 H, $J_{1',2'}$ = 3.3 Hz, $J_{2',3'}$ = 9.6 Hz, H-2′), 3.43–3.74 (m, 7 H, H-2, H-4, H-4′, 2 × H-5, 2 × H-5′), 3.91–4.20 (m, 3 H, H-3, CH_2CH=CH_2), 4.31–4.79 (m, 9 H, 4 × CH_2Ph, H-1), 5.20–5.35 (m, 2 H, CH_2CH=CH_2), 5.54 (t, 1 H, $J_{2',3'}$ = $J_{3',4'}$ = 9.6 Hz, H-3′), 6.67 (d, $J_{1',2'}$ = 3.3 Hz, H-1′), 5.92 (m, 1 H, CH_2C*H*=CH_2), 7.08–7.50 (m, 20 H, 4 × Ph).