Effect of the nature of protecting group at O-4 on stereoselectivity of glycosylation by 4-O-substituted 2,3-di-*O*-benzylfucosyl bromides

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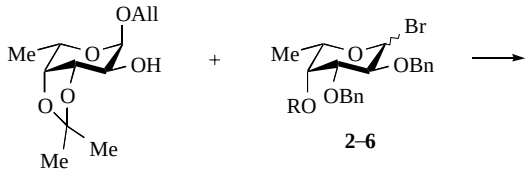
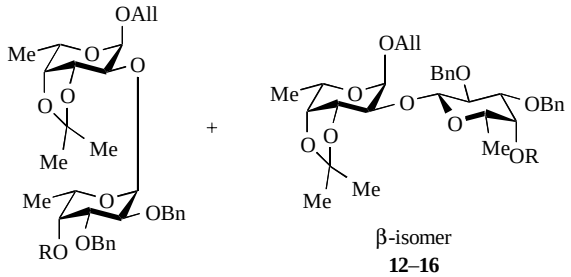
The effect of the nature of the substituent at O-4 on the stereoselectivity of glycosylation by 2,3-di-*O*-benzylfucosyl bromides was studied by direct chemical experiments and computer modelling.

Within the synthesis of fucoidan fragments[1] we performed glycosylation of acetonide **1** by 2,3-di-O-benzylated L-fucosyl bromides **2** and **3** with benzyl and benzoyl protecting groups at O-4 (Scheme 1). In case of 4-O-benzoylated bromide **3** glycosylation was more stereoselective than in case of **2** (Table 1). Similar data on the stereoselectivity of fucosylation were reported before,[2,3] but the origin of the dependence of the stereoselectivity of fucosylation on the structure of fucosyl donor remains unclear.



1 **2–6**



7–11 **12–16**

All = $CH_2CH=CH_2$

R	bromide	α-isomer	β-isomer
Bn	**2**	**7**	**12**
Bz	**3**	**8**	**13**
p-$NO_2C_6H_4CO$	**4**	**9**	**14**
p-$MeOC_6H_4CO$	**5**	**10**	**15**
$AcNHCH_2CO$	**6**	**11**	**16**

Scheme 1

To explain the predominance of the α-product in case of glycosylation by **3** we supposed the formation of intermediate cation II (Scheme 2), in which the carbonyl group of benzoate provides intramolecular 'stabilisation' of the cationic centre. Cation II is hindered from the β-side for a nucleophilic attack leading to the formation of the α-glycoside product.

To evaluate the ability of the substituent at O-4 in fucosyl bromide **3** to 'stabilise' the cationic centre at C-1, the difference (Δ*E*) between the total energy of 'non-stabilised' glycosyl cation I and 'stabilised' glycosyl cation II was calculated using the MM+ force field.[4] Partial charges were calculated on the AM1 level[5] of approximation. Both molecular-mechanics and semi-empirical calculations were performed using the HyperChem software[†] (version 5.02). The starting conformations of cations I and II were built using standard geometric parameters and setting the torsion angle H(4)–C(4)–O(4)–C equal to 0° for cation I and to 180° for cation II. The total geometry optimisation was performed using the Polak–Ribiere conjugate gradient algorithm until the gradient value reached 0.1 kcal mol^{-1} $Å^{-1}$. The Δ*E* value for 4-O-benzylated compound **2** (Table 1) was close to zero, but it was positive for 4-benzoate **3**, thus confirming the stabilisation hypothesis and explaining the difference in the stereoselectivities of fucosylation by bromides **2** and **3**. Note that all glycosylation reactions were performed in CH_2Cl_2,[‡] which solvates all mentioned cations in a similar manner. This permitted us to neglect solvation effects in the calculations.

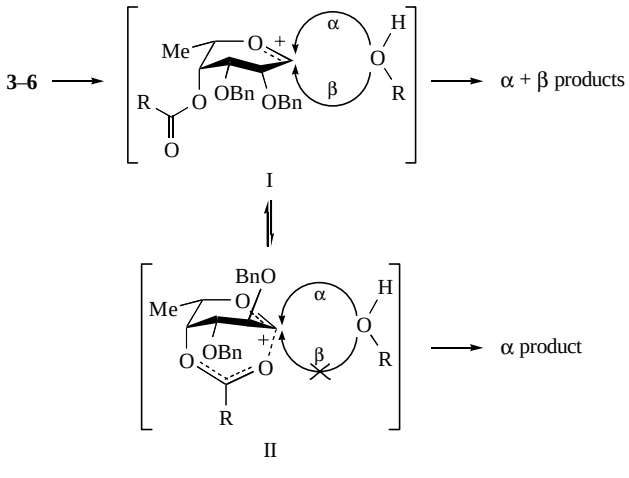
[†] HyperChem™, Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601, USA.

Table 1 The ratios between α- and β-disaccharide products in the glycosylation of acceptor **1** with bromides **2–6** (Scheme 2) and the Δ*E* values for corresponding cations of type II.

Fucosyl bromide	Substituent at O-4	Δ*E*/kcal mol^{-1}	α- and β-disaccharide products	Ratio between α- and β-products
2	Bn	–0.1	**7** and **12**	1:1[a]
3	Bz	3.6	**8** and **13**	3.5:1[a]
4	*p*-$NO_2C_6H_4CO$	2.1	**9** and **14**	2:1
5	*p*-$MeOC_6H_4CO$	4.7	**10** and **15**	5:1
6	$AcNHCH_2CO$	1.6 (19.3[b])	**11** and **16**	2:1

[a]Experimental ratios of α:β isomers were determined by integration of respective ^1H signals of Fuc residues at the 'non-reducing' end. [b]Δ*E* value for intermediate III.

To elucidate in more details the stabilising effect of protecting group at O-4, which favours the α-selectivity of fucosylation, we also calculated Δ*E* for cations with *p*-nitrobenzoyl, *p*-methoxybenzoyl and *N*-acetylaminoacetyl groups at O-4. The Δ*E* values for *p*-nitrobenzoate **4** and 4-*O*-(*N*-acetylaminoacetyl) derivative **6** (Table 1) were lower than that for benzoylated compound **3**. On the contrary, the Δ*E* value for *p*-methoxybenzoate **5** was higher than that for benzoate **3**. According to these calculation data, we expected that the α-selectivity of fucosylation should decrease in the order **5** > **3** > **4** > **6** > **2**. These results were later

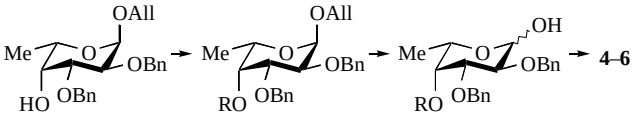


Scheme 2

Table 2 ^{1}H NMR data[a] for monosaccharides **17**–**23** and disaccharides **9**–**11** and **14**–**16**.

Compound	Fucose residue[b]	Chemical shifts, δ/ppm						Coupling constants,[e] *J*/Hz			
		1-H	2-H	3-H	4-H	5-H	6-H	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{5,6}$
9	R	4.99	3.87	4.39	4.09	n/d[c]	1.05–1.50[d]	3.5	7.9	5.7	n/d
	N	5.02	3.86	4.28	5.68	4.53	1.05–1.50[d]	3.5	9.9	3.1	n/d
10	R	4.98	3.86	4.38	4.09	n/d	1.05–1.50[d]	3.1	7.9	5.5	n/d
	N	5.01	3.91	4.25	5.66	4.48	1.05–1.50[d]	3.5	10.0	3.2	n/d
11	R	4.94	3.82	4.34	4.03	n/d	1.05–1.50[d]	2.9	7.7	5.2	n/d
	N	5.01	3.71	4.12	5.31	4.39	1.05–1.50[d]	3.2	10.0	3.0	n/d
14	R	5.09	3.91	4.45	4.09	n/d	1.05–1.50[d]	3.2	8.0	5.1	n/d
	N	4.81	3.69–3.74		4.54	3.76	1.05–1.50[d]	6.5	n/d	2.9	n/d
15	R	5.11	3.90	4.45	4.09	n/d	1.05–1.50[d]	3.9	7.5	5.1	n/d
	N	4.75	3.65	3.75	5.58	3.72	1.05–1.50[d]	7.1	7.1	3.2	n/d
16	R	5.08	3.88	4.40	4.03	n/d	1.05–1.50[d]	3.1	8.5	4.9	n/d
	N	4.74	3.60–3.63		5.46	3.62	1.05–1.50[d]	6.9	n/d	3.5	n/d
17		4.85	3.81	4.05	3.79	n/d	1.20	3.9	9.5	3.1	6.0
18		4.95	3.89	4.13	5.65	4.25	1.19	3.5	9.5	3.5	7.5
19		4.95	3.93	4.12	5.62	4.21	1.20	3.9	9.1	3.0	6.0
20		n/d	3.83	4.07	5.52	4.16	1.20	4.0	10.0	3.9	6.8
21	α	5.35	3.87	4.10	5.65	4.42	1.22	3.2	10.0	3.4	6.9
	β	n/d	3.65	3.71	5.59	3.82	1.31	7.4	9.8	3.1	6.3
22	α	5.28	3.89	4.01	5.58	4.31	1.18	3.6	10.0	2.9	6.5
	β	5.24	4.09	3.63	5.51	3.73	1.21	n/d	7.8	2.8	6.0
23	α	5.23	4.06	3.76	5.48	4.33	1.15	3.5	9.0	4.0	6.7
	β	n/d	3.48	3.73	5.43	3.84	1.25	8.0	9.5	3.1	6.7

[a]NMR spectra were recorded on a Bruker AM-300 instrument (300 MHz) in $CDCl_3$ at 303 K. Assignment was performed by 2D ^{1}H–^{1}H correlation spectroscopy. [b]R is the 'reducing' end (*i.e.*, a fucose residue attached to allyl aglycon), N is the 'non-reducing' end (*i.e.*, a fucose residue attached to fucose aglycon). [c]n/d = not determined. [d]Signals of 6-H in all Fuc residues in the specta of mixtures of disaccharide pairs (**9**,**14**), (**10**,**15**) and (**11**,**16**) were not assigned because of overlapping. [e]For all compounds, $J_{4,5} < 1$ Hz.

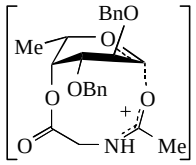


17

All = $CH_2CH{=}CH_2$

R		
p-$NO_2C_6H_4CO$	**18**	**21**
p-$MeOC_6H_4CO$	**19**	**22**
$AcNHCH_2CO$	**20**	**23**

Scheme 3



III

‡ *Preparation of bromides* **4**–**6**. Esters **18** {$[\alpha]_D$ –134° (*c* 2, $CHCl_3$)} and **19** {$[\alpha]_D$ –162° (*c* 1, $CHCl_3$)} were prepared in 80–90% yields by acylation of compound **7** (1 mmol) with a corresponding acylchloride (4 mmol) in 40 mmol of pyridine in the presence of a catalytic amount of *N*,*N*-dimethylaminopyridine. Amide **20** {$[\alpha]_D$ –62° (*c* 1, $CHCl_3$)} was obtained in 75% yield by reaction of **7** with equimolar amounts of *sym* anhydride of *N*-acetylglycine and *N*,*N*-dimethylaminopyridine. Deallylation of esters **18**–**20** in the presence of $PdCl_2$ (0.4 mmol) in methanol gave semiacetals **21**–**23** with 75–80% yields. The bromination with CBr_4 and Ph_3P (1.1 mmol each) in 5 ml of boiling methylene chloride resulted in formation of bromides **4**–**6** in almost quantitative yields. Fucosyl bromides were used directly in glycosylation reactions without special purification.

Glycosylation with bromides **2**–**6** (*typical procedure*). A solution of 1 mmol of acetonide **1**, 1.5 mmol of $Hg(CN)_2$, 10–20 mg of $HgBr_2$ and 1.4 g of molecular sieves 4 Å were stirred for 1 h at room temperature under Ar, and a solution of 1.5 mmol of a corresponding fucosyl bromide was added portionwise within 1 h at room temperature. The mixture was additionally stirred for 24 h at room temperature, then filtered through Celite, diluted with CH_2Cl_2, washed with saturated aqueous KBr and $NaHCO_3$ solutions, filtered through cotton wool and concentrated *in vacuo*. The residue was subjected to flash column chromatography to separate a mixed fraction of α- and β-disaccharide products. The ratio between the products was determined from the ^{1}H NMR spectra (Tables 1 and 2). The anomeric configurations of Fuc residues in disaccharides **7**–**16** at the 'non-reduced' end were confirmed by characteristic values of $J_{1,2}$, which were 3–3.5 Hz for α-anomers and 7–7.5 Hz for β-anomers.

proven experimentally by chemical glycosylations (Table 1), except for the coincidence of stereochemical outcomes in glycosylations with compounds **4** and **6**.

For compound **6** which comprises a carbonyl of the amido group along with the ester carbonyl, the hypothetical intermediate III can also be expected in addition to cation II. The Δ*E* value for III is higher (Table 1) than that for ester-stabilised cations of the type II.

Taking into account too high Δ*E* value for intermediate III, we can expect high α-stereoselectivity of fucosylation with bromide **6**. However, the ratio between α- and β-disaccharides in the glycosylation with bromide **6** was as low as 2:1. This result argues that the glycosylation proceeds preferentially *via* cation II rather than cation III.

In conclusion, the data obtained show the mechanism of the influence of the substitutent at O-4 on the α-stereoselectivity of glycosylation by 2,3-di-*O*-benzylfucosyl donors. Molecular-mechanics calculations according to the described procedure can be successfully applied to the estimation of the stereoselectivity of glycosylation.

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