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Solvent-induced anomeric diastereoselectivity switching using a single glycosyl donor

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ABSTRACT

Highly diastereoselective glycosylation reactions have been developed; however, not all glycosylation reactions are diastereoselective and these reactions have probably not been reported. For some fucosylation reactions, unusually low or abnormally opposite selectivities have been demonstrated. In the present study, the fucosylation reaction of long-chain hydrocarbon alcohols, ethyl 9-hydroxynonanoate and decanol using a series of the 2-*O*-benzyl-protected fucopyranosyl donors were investigated. The resulting products demonstrated the solvent-induced diastereoselectivity switching using diethyl ether (Et_2O) or dichloromethane (CH_2Cl_2). Practical α-selectivities were observed using ether solvents. In contrast, practical β-selectivities were observed using CH_2Cl_2. The anomeric diastereoselectivity switching was similarly observed in the alcohol galactosylation reaction. The larger spin-lattice relaxation time constant (T_1) actually indicated that molecular motion of ethyl 9-hydroxynonanoate was more vigorous in Et_2O than in CH_2Cl_2, suggesting its dissociation in Et_2O and association in CH_2Cl_2. The bulkiness of the associated alcohols is most likely responsible for the observed diastereoselectivity.

1. Introduction

The central synthetic focus of naturally occurring glycoconjugates is the diastereoselective glycosylation of an aglycon with a suitably protected glycon donor.[1–4] Glycon and aglycon protecting groups may significantly influence the yield and diastereoselectivity of glycosylation reactions.[5] If a 1,2-cis glycopyranosidic α linkage is required in a D-gluco-, D-galacto-, and L-fucopyranosyl series, then the presence of a non-participating group (e.g., benzyl) at the C-2 of a glycon donor is essential for their diastereoselectivity. Thus, the formation of a 1,2-cis glycosidic bond can predominantly be produced through the use of a promoter, which is able to generate an α- and a β-form intermediate equilibrium with a good leaving group (i.e., a halide,[6] perchlorate,[7] or triflate[7]). The α-glycosylation preferentially occurs because the β-form intermediate is much reactive than the α-form and is stabilized by the anomeric effect. However, unexpected β-L-fucosylation,[8] β-selective L-fucosylation,[9] and β-selective D-galactosylation[10] that results from using 2-*O*-benzyl-glycosyl donors have been found in the literature.

Whereas, a significant biological role for O-L-fucosylation of epidermal growth factor repeats in the Notch receptor has been revealed.[11–15] The expression of Fringe, which is a β-1,3-*N*-acetylglucosaminyltransferase, inhibits the activation of Notch by Serrate and increases the activation of Notch by Delta.[16,17] However, not only the Notch receptor, but also the Notch ligands (*Drosophila* Delta and Serrate, Human Jagged 1, and Rat Delta-like 1) are fucosylated and elongated by Fringe.[18] Consequently, antibodies against *O*-L-fucosyl saccharides were required to elucidate the complex Notch signaling modulation mechanism. We attempted to synthesize the α-L-fucosyl lipid antigens.

In this paper, we studied the influence of solvents on the anomeric ratio of fucosylation reactions using 2-*O*-benzyl-L-fucosyl thioglycosides as the glycosyl donors and *N*-iodosuccinimide (NIS) and silver triflate (AgOTf) as the promoters. In addition, the influence of substituent effects on the fucosylation of a simple long-chain alcohol, decanol, and the L-fucosylation of a D-galactose derivative was also investigated. We then hypothesized why two solvents (Et_2O and CH_2Cl_2) switched the anomeric selectivity of the glycosylation reactions.

2. Results and discussion

The diastereoselectivities of the iodonium-assisted coupling reactions between ethyl 9-hydroxynonanoate[19] (**1**) and the L-fucosyl donor **2** in the presence of NIS and AgOTf were investigated in different solvents. Conclusions regarding the solvent-induced diastereoselectivity switching are summarized in Table 1.

The coupling reaction in toluene afforded L-fucopyranoside **3** with a poor diastereoselectivity of 10% de (entry 1). The similar coupling reaction in Et_2O afforded unusual but interesting results.

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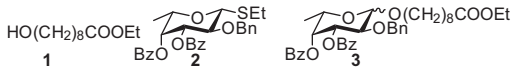
Table 1
Fucosylation[a] of ethyl 9-hydroxynonanoate (**1**) with fucosyl donor **2**



Entry	Solvent	Temp (°C)	Yield[b] (%)		% de[c]
			3α	**3β**	
1	$PhCH_3$	−40	41	50	10
2	Et_2O	−60	50	44	6
3	Et_2O	−40	66	29	39
4	Et_2O	−10	78	15	68
5	Et_2O	0	72	20	57
6	Et_2O	rt	73	19	59
7	PME	0	80	19	62
8	PME	−10	82	13	73
9	THF	0	53	44	9
10	CH_2Cl_2	−60	18	63	−56
11	CH_2Cl_2	−40	23	66	−48
12	CH_2Cl_2	0	50	50	0
13	CH_3CN	−40	34	61	−28

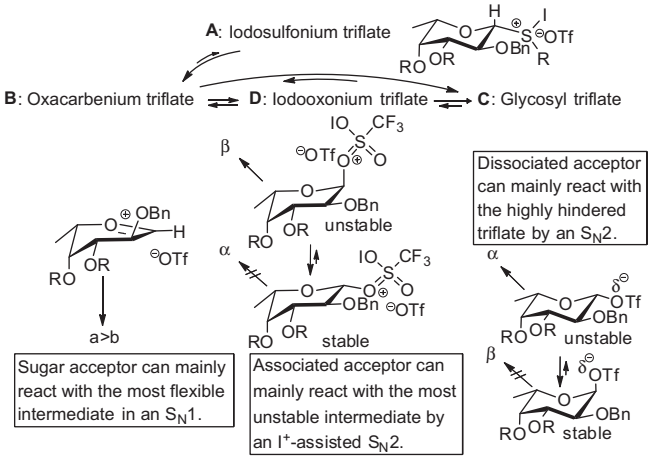
[a] All reactions were continued for 1–2 h.
[b] Isolated yield based on the donor.
[c] Diastereomeric excess (% de) = [ratio of α anomer (%)] − [ratio of β anomer (%)].

Good α-selectivities of L-fucopyranoside **3** were observed at high reaction temperatures of −10 °C to rt (entries 4, 5, and 6). Additionally, the diastereoselectivity almost disappeared at a low reaction temperature of −60 °C (entry 2). The temperature dependence found would not be accounted for by the stabilities of the intermediates and suggested an influence of a phase conversion. The highest α-selectivity (73% de) was performed using cyclopentyl methyl ether, which was also investigated at a high temperature of −10 °C (entry 8). However, in the case of using a cyclic ether solvent (i.e., THF), the selectivity was drastically decreased to 9% de (entry 9). This solvent effect of the cyclic ether was completely different from the reported α-directional effect of dioxane,[20,21] indicating that the observed ether-induced selectivity was due to neither participation of the ether oxygen atom with a glycosyl oxacarbenium ion[7] nor anomeric effect potentiation in low-polar ether solvents.[22] In contrast, the highest β-selectivity (−56% de) for fucopyranoside **3** was observed in CH_2Cl_2 at a low reaction temperature of −60 °C (entry 10); β-selectivity disappeared at a high reaction temperature of 0 °C (entry 12).

Because it has been reported that $FeCl_3$ readily anomerizes β-glycopyranosides to their corresponding α-anomers in good yields and selectivities,[23] the isolated β-anomer of **3** was exposed to the initial (NIS/AgOTf, 4 Å MS) or final (I_2, MeSSMe, TfOH, 4 Å MS) reaction conditions for three days, which indicated that the β-anomer was completely stable under these conditions examined. Therefore, it was confirmed that both anomers were formed under kinetic control.

The reaction pathways shown in Scheme 1 were formulated from these results. A thioglycoside reacts with iodotriflate to produce the iodosulfonium triflate ion-pair **A**, which is converted to resonance-stabilized oxacarbenium triflate ion-pair **B**. Intermediate **B** reacts with iodotriflate or triflate to generate resonance-stabilized iodooxonium triflate ion-pair **D** or glycosyl triflate **C**, respectively. The iodooxonium triflate ion-pair **D** can also be generated by iodonium activation of the glycosyl triflate **C**. The glycosyl triflate generation from an oxacarbenium cation and triflate anion has been well identified.[24]

Although slight β-selectivity (−6% de) in the coupling reaction with ethyl 3,4-di-*O*-acetyl-2-*O*-benzyl-1-thio-β-L-fucopyranoside and decanol in CH_2Cl_2 has been reported, the α-selectivities (24% de or 40% de) of fucosylations with the same donor and allyl alcohol or 3-bromopropanol have also been reported using similar reaction



Scheme 1. Possible pathways for anomeric diastereoselectivity under kinetic control.

conditions.[8] A simple alcohol (e.g., allyl alcohol and 3-bromopropanol) can react with glycosyl triflate **C** via an S_N2 mechanism to predominantly form the α-linkage from the more reactive β-triflate due to the anomeric effect. In contrast, long-chain alcohols (e.g., decanol and ethyl 9-hydroxynonanoate), which may be slightly hindered by an association such as partial micelles in CH_2Cl_2, do not react with triflate **C**. The alcohols react with less sterically hindered iodooxonium triflate ion-pair **D** in an I^+-assisted S_N2 mechanism. Consequently, it is reasonable that the β-linkage is predominantly formed from the more reactive α-orientated iodooxonium triflate ion-pair **D** due to the inverse anomeric effect.[22]

The carbon-13 T_1 values of **1** in the solvents $CDCl_3$, rather than CH_2Cl_2, and Et_2O-d_{10}, were measured to demonstrate molecular assembly because T_1 is nearly equal to T_2 in the molecular weight range of **1**. All T_1 values in Et_2O-d_{10} were larger than those in $CDCl_3$. These results indicate that the molecular motion of **1** was more vigorous in Et_2O than in CH_2Cl_2, suggesting the dissociation and association of **1** in Et_2O and CH_2Cl_2, respectively (Fig. 1).

In the coupling reaction using Et_2O, the dissociation of the solvated long-chain hydrocarbon and OH group activation may account for the adverse diastereoselectivity. Moreover, dissociation and activation by Et_2O are generally facilitated at higher temperatures. Thus, a dissociated and activated long-chain alcohol can react with glycosyl triflate **C** in an S_N2 mechanism to predominantly yield the α-linkage. The drastic diastereoselectivity decrease in THF was probably due to its weak hydrophobic interaction ability because of its narrow hydrophobic face.

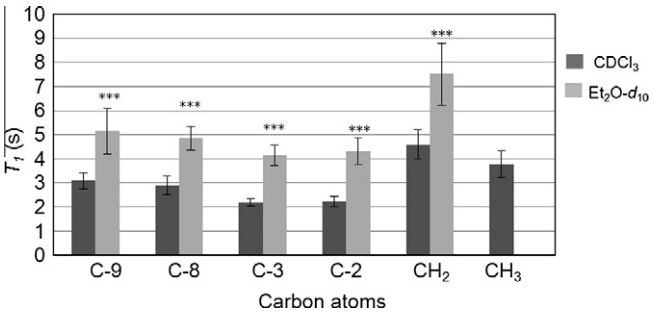
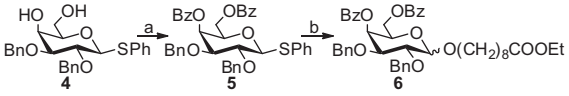


Figure 1. Carbon-13 T_1 of ethyl 9-hydroxynonanoate in solvents $CDCl_3$ and Et_2O-d_{10}. All samples were measured at a concentration similar to that of glycosylation reaction and 23 °C. Each value represented the average of three samples ± SD. The differences were significant between $CDCl_3$ and Et_2O-d_{10} (***p <0.0005).



Scheme 2. Reagents and conditions: (a) BzCl, pyridine, 93%; (b) ethyl 9-hydroxynonanoate, NIS, AgOTf, solvent, MS 4 Å.

Predictably, moderate β-selectivity (−28% de) was observed in CH_3CN. This observation may be exerted by the occurrence of the nitrilium–nitrile intermediate, which has often been used to discuss anomeric selectivity (entry 13).[25]

We then focused on the application of different protecting groups and other sugar series donors. Diastereoselectivity switching was investigated for the coupling reactions with donor (fucosyl: **2**, **9**, and **10**[26] or galactosyl: **5**, which was derived from **4**,[27] Scheme 2) and acceptor (**1** or **7**) combinations. However, the switching was not investigated for all combinations involving per-benzylated fucosyl donor **11**[28] or sugar acceptor **8**.[29] These results are summarized in Table 2.

The solvent-induced diastereoselectivity switching by Et_2O (α) and CH_2Cl_2 (β) occurred in the coupling reaction of acceptor **1** with donors **9** (3-*O*-benzyl-4-*O*-benzoyl donor), **10** (3,4-*O*-isopropylidene-donor), or **5** (galactosyl donor) to produce each anomer of **12**, **13,** and **6**, respectively (entries 14–19). The reaction of **2** or **7** and a long-chain alcohol that does not contain an acyl group (decanol) exerted similar selectivity as **1** in Et_2O (α: 60% de) and CH_2Cl_2 (β: −55% de) to afford each anomer of **14** (entries 20 and 21). The glycosylation β-selectivity was decreased in EtOAc similar to that observed in CH_3CN because of the large polarity influence (entry 13 and 22).

The first exception of the switching was demonstrated in the coupling reaction of **7** and **11**. The β-selective production of **15** was even observed in Et_2O, and the selectivity was higher than that in CH_2Cl_2. It was considered that donor **11**, only possessing ether protecting groups, is an ether molecule type that associates with long-chain hydrocarbons. Thus, the sterically hindered decanol can react with iodooxonium triflate **D** in an I^+-assisted S_N2-reaction to afford a β-linkage even in Et_2O (entries 23 and 24).

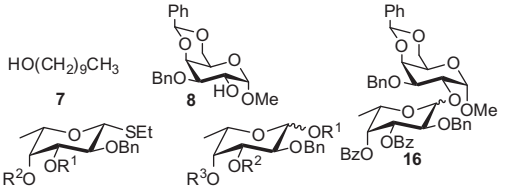
For the second exception, the reaction of a bulky alcohol (sugar acceptor **8**) and **2** may proceed only via flat oxacarbenium triflate ion-pair **B** in an S_N1 mechanism so that the α-anomer of **16** is predominantly obtained even in CH_2Cl_2 by means of the anomeric effect (entry 26). The α-selectivity was extremely improved using Et_2O that contained 12 equivalents of CH_2Cl_2 (based on the donor) because the anomeric effect has more of a critical influence in a less polar solvent, such as Et_2O (entry 25). This type of solvent effect may be similar to the one reported.[20,21]

3. Experimental

3.1. General methods

The optical rotations were measured at 25 °C using a JASCO DIP-370 polarimeter. The ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker DRX-600 spectrometer at 600 and 125 MHz, respectively. The δ_H-value in $CDCl_3$ is relative to internal Me_4Si, and the δ_C-value is referenced to the solvent [δ_C ($CDCl_3$) 77.0]. Assignments were aided by COSY, TOCSY, and ^1H- and ^{13}C correlation spectroscopy. The inversion–recovery method was used to measure the T_1 values with prior determination of the 180° pulse for some samples. The elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer. All reactions were monitored using TLC with aluminum sheets that were coated with Silica Gel $60F_{254}$ (0.2 mm thickness, E. Merck, Darmstadt, Germany). Column

Table 2
Glycosylation[a] of alcohols **1**, **7**, and **8** using glycosyl donor **2**, **5**, or **9**–**11**



9: R^1 = Bn, R^2 = Bz
10: R^1, R^2 = $(CH_3)_2C$=
11: R^1 = R^2 = Bn
12: R^1 = $(CH_2)_8COOEt$, R^2 = Bn, R^3 = Bz
13: R^1 = $(CH_2)_8COOEt$, R^2, R^3 = $(CH_3)_2C$=
14: R^1 = $(CH_2)_9CH_3$, R^2 = R^3 = Bz
15: R^1 = $(CH_2)_9CH_3$, R^2 = R^3 = Bn

Entry	Alcohol	Donor	Solvent	Temp (°C)	Product	Yield[b] (%)		% de[c]
						α	β	
14	**1**	**9**	Et_2O	−10	**12**	65	29	38
15	**1**	**9**	CH_2Cl_2	−40	**12**	20	70	−56
16	**1**	**10**	Et_2O	0	**13**	49	33	20
17	**1**	**10**	CH_2Cl_2	−60	**13**	18	49	−46
18	**1**	**5**	Et_2O	−10	**6**	68	13	68
19	**1**	**5**	CH_2Cl_2	−40	**6**	20	64	−52
20	**7**	**2**	Et_2O	−10	**14**	71	18	60
21	**7**	**2**	CH_2Cl_2	−40	**14**	21	73	−55
22	**7**	**2**	EtOAc	−60	**14**	32	60	−30
23	**7**	**11**	Et_2O	−5	**15**	19	76	−60
24	**7**	**11**	CH_2Cl_2	−60	**15**	28	64	−39
25	**8**	**2**	Et_2O/ CH_2Cl_2[d]	−10	**16**	85	0	100
26	**8**	**2**	CH_2Cl_2	−40	**16**	85	11	77

[a] All reactions were continued for 1–2 h.
[b] Isolated yield based on the donor.
[c] Diastereomeric excess (% de) = [ratio of α anomer (%)] − [ratio of β anomer (%)].
[d] Et_2O-containing CH_2Cl_2 (12 equiv based on the donor); **2** was not soluble in Et_2O and partially dissolved by addition of CH_2Cl_2 to afford fucal in a 15% yield as a byproduct.

Table 3
^{1}H NMR data of L-fucopyranosides

	Chemical shifts (δ), multiplicities, and coupling constants (Hz)						
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6	Others[a]
2	4.86d (10.6)	3.92t (9.8)	5.44dd (3.4)	5.66dd (0.8)	3.99dq (6.4)	1.30d	4.67, 4.64 Bn, 2.9–2.8, 1.38 SEt
9	4.51d (9.4)	3.69t (9.4)	3.73dd (3.4)	5.63dd (0.8)	3.78dq (6.4)	1.27d	4.84, 4.82, 4.77, 4.57 Bn, 2.9–2.8, 1.35 SEt
3α	4.10d (3.4)	4.2–4.1 (7.2)	5.73dd (3.4)	5.67dd (0.8)	4.32dq (6.4)	1.18d	4.69, 4.63 Bn, 4.2–4.1, 1.26 OEt, 2.30 CH_2CO, 3.72, 3.49 OCH_2, 1.8–1.3 CH_2
3β	4.58d (7.6)	3.85dd (10.2)	5.37dd (3.4)	5.58dd (0.8)	3.96dq (6.4)	1.29d	4.87, 4.70 Bn, 4.12, 1.25 OEt, 2.28 CH_2CO, 4.04, 3.60 OCH_2, 1.8–1.3 CH_2
12α	4.84d (3.8)	4.09dd (10.2)	3.90dd (3.8)	5.63dd (1.1)	4.2–4.1 (6.8)	1.17d	4.82, 4.81, 4.66, 4.60 Bn, 4.2–4.1, 1.26 OEt, 2.29 CH_2CO, 3.65, 3.49 OCH_2, 1.7–1.3 CH_2
12β	4.41d (7.8)	3.67m	3.67m (3.0)	5.56dd (0.8)	3.74dq (6.4)	1.27d	4.91, 4.79, 4.75, 4.58 Bn, 4.12, 1.25 OEt, 2.27 CH_2CO, 3.99, 3.54 OCH_2, 1.7–1.2 CH_2
13α	4.72d (3.4)	3.50dd (7.9)	4.32dd (5.7)	4.04dd (2.6)	4.10m (6.4)	1.4–1.3	4.79, 4.70 Bn, 1.40, 1.35 CH_3, 4.12, 1.25 OEt, 2.28 CH_2CO, 3.62, 3.37 OCH_2, 1.7–1.3 CH_2
13β	4.28d (7.9)	3.38t (7.9)	4.2–4.1 (5.3)	4.00dd (1.9)	3.83dq (6.4)	1.41d	4.87, 4.81 Bn, 1.39, 1.36 CH_3, 4.2–4.1, 1.28 OEt, 2.30 CH_2CO, 3.95, 3.49 OCH_2, 1.7–1.3 CH_2
14α	4.95d (3.4)	4.11dd (10.6)	5.73dd (3.4)	5.66dd (1.3)	4.32dq (6.4)	1.19d	4.69, 4.63 Bn, 0.89 CH_3, 3.72, 3.50 OCH_2, 1.7–1.2 CH_2
14β	4.58d (7.3)	3.85dd (10.6)	5.37dd (3.4)	5.58dd (0.8)	3.96dq (6.0)	1.29d	4.87, 4.70 Bn, 0.88 CH_3, 4.05, 3.60 OCH_2, 1.8–1.2 CH_2
15β	4.31d (7.6)	3.80dd (9.8)	3.50dd (2.6)	3.55dd (0.8)	3.43dq (6.4)	1.17d	4.98, 4.94, 4.79, 4.76, 4.72, 4.69 Bn, 3.93, 3.46 OCH_2, 1.7–1.2 CH_2, 0.87 CH_3

[a] Phenyl proton signals commonly appeared at δ 7.1–8.2.

Table 4
^{13}C NMR data of L-fucopyranosides

	Chemical shifts (δ)						
	C-1	C-2	C-3	C-4	C-5	C-6	Others[a]
2	85.0	77.6	81.2	70.5	73.3	16.9	75.8, 71.7 Bn, 24.8, 15.0 SEt
9	85.3	76.2	75.1	71.8	73.3	16.7	75.5 Bn, 25.2, 15.0 SEt
3α	97.6	73.6	70.8	72.6	64.8	16.3	72.8 Bn, 68.8 C-9^N, 29.6, 29.4, 29.3, 26.3, 25.1 CH_2, 34.5 C-2^N, 60.3, 14.4 OEt
3β	104.0	76.1	73.2	71.7	69.3	16.4	74.5 Bn, 70.6 C-9^N, 29.7, 29.3, 29.1, 26.1, 25.0 CH_2, 34.4 C-2^N, 60.2, 14.3 OEt
12α	97.8	76.5	75.2	71.6	64.8	16.3	73.3, 71.9 Bn, 68.4 C-9^N, 29.5, 29.3, 29.1, 26.2, 25.0 CH_2, 34.4 C-2^N, 60.2, 14.3 OEt
12β	103.8	78.9	79.3	70.4	69.3	16.6	75.3, 71.9 Bn, 70.5 C-9^N, 29.8, 29.3, 29.2, 29.1, 26.1, 25.0, CH_2, 34.4 C-2^N, 60.2, 14.3 OEt
13α	97.0	76.4	75.9	76.3	63.0	16.3	72.2 Bn, 108.7, 28.2, 26.1 iPr, 68.3 C-9^N, 29.4, 29.3, 29.2, 29.1, 26.4, 25.0 CH_2, 34.4 C-2^N, 60.2, 14.3 OEt
13β	102.9	79.5	79.2	76.5	68.7	16.6	73.6 Bn, 109.6, 27.9, 26.1 iPr, 69.7 C-9^N, 29.7, 29.3, 29.2, 29.1, 26.4, 25.0 CH_2, 34.4 C-2^N, 60.2, 14.3 OEt
14α	97.5	73.4	72.5	70.7	64.7	16.1	72.7 Bn, 68.7 OCH_2, 31.9, 29.7, 29.5, 29.5, 29.4, 26.2, 22.7 CH_2, 14.2 CH_3
14β	104.0	76.1	73.2	71.7	69.3	16.4	74.5 Bn, 70.6 OCH_2, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 26.2, 22.7, CH_2, 14.2 CH_3
15β	103.9	79.5	82.6	76.3	70.2	16.9	75.1, 74.5, 73.2 Bn, 69.9 OCH_2, 31.9, 29.8, 29.6, 29.6, 29.5, 29.4, 26.2, 22.7 CH_2, 14.2 CH_3

[a] Carbonyl- and phenyl carbon signals commonly appeared at δ 175–165 and 140–125, respectively. 'N' designates signals belonging to the ethyl 9-hydroxynonanoate (**1**).

chromatography was conducted using Wako Gel C-300E (Wako). The solvent extracts were dried with anhydrous $MgSO_4$ unless otherwise specified.

3.2. Ethyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-1-thio-β-L-fucopyranoside (2)

To a solution of ethyl 2-*O*-benzyl-1-thio-β-L-fucopyranoside[30] (54.9 g, 184 mmol) in pyridine (510 mL) was added BzCl (210 mL, 1.81 mol) at 0 °C. The mixture was stirred at rt for 3 h. The mixture was then diluted with CH_2Cl_2 and washed with 2 M aq HCl, satd aq $NaHCO_3$, and NaCl, dried, concentrated *in vacuo*, and purified using flash column chromatography (1:8 EtOAc–hexane) to afford **2** (87.0 g, 93%) as a colorless syrup: $[\alpha]_D$ −152 (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{29}H_{30}O_6S$ (506.61): C, 68.75; H, 5.97; S, 6.33. Found: C, 68.99; H, 5.93; S, 6.25. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.3. Phenyl 4,6-di-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (5)

The benzoylation of **4**[27] (2.23 g, 4.92 mmol) with pyridine (21.8 mL) and BzCl (6.30 mL, 54.3 mmol) was performed as described for **2**, which was then purified using flash column chromatography (1:8 EtOAc–hexane) to afford **5** (3.00 g, 93%) as a colorless amorphous product: $[\alpha]_D$ +2.3 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.01–7.49 (m, 25H, 5Ph), 5.90 (dd, 1H, $J_{4,5}$ 0.8 Hz, H-4), 4.75–4.85 (m, 3H, C*H*HPh), 4.75 (d, 1H, $J_{1,2}$ 9.4 Hz, H-1), 4.56 (dd, 1H, H-6a), 4.55 (d, 1H, C*H*HPh), 4.43 (dd, 1H, H-6b), 4.08 (m, 1H, $J_{5,6a}$ 7.4 Hz, $J_{5,6b}$ 5.5 Hz, H-5), 3.80 (dd, 1H, $J_{3,4}$ 3.0 Hz, H-3), 3.76 (q, 1H, $J_{2,3}$ 9.1 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 166.2, 165.7, 133.4, 133.3, 132.9, 132.9, 130.1, 129.8, 129.6, 129.5, 128.9, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 87.4 (C-1), 81.2 (C-3), 76.6 (C-2), 75.8 (*C*H$_2$Ph), 74.9 (C-5), 72.0 (*C*H$_2$Ph), 67.4 (C-4), 63.1 (C-6). Anal. Calcd for $C_{40}H_{36}O_7S$ (660.78): C, 72.71; H, 5.49; S, 4.85. Found: C, 72.50; H, 5.63; S, 4.82.

3.4. Ethyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-β-L-fucopyranoside (9)

The benzoylation of ethyl 2,3-di-*O*-benzyl-1-thio-β-L-fucopyranoside[31] (2.10 g, 5.40 mmol) with pyridine (21.0 mL) and BzCl (3.10 mL, 26.7 mmol) was performed as described for **2**, which was then purified using flash column chromatography (1:8 EtOAc–hexane) to afford **9** (1.63 g, 61%) as a colorless syrup: $[\alpha]_D$ –49.4 (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{29}H_{32}O_5S$ (492.63): C,

70.70; H, 6.55; S, 6.51. Found: C, 70.54; H, 6.67; S, 6.44. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.5. General glycosylation procedure

A mixture of donor (1.00 mmol) and alcohol (1.50 mmol) in dry solvent (for dehydration, 5.0 mL) was dried by azeotropic dehydration under Ar for 2 h and was then concentrated. The mixture was dissolved in dry solvent (reaction, 5.0 mL) and cooled to the presented temperature (Tables 1 and 2). Molecular sieves (4 Å, 0.50 g), NIS (2.70 mmol), and AgOTf (0.10 mmol) were added to the mixture, and the reaction was stirred at the same temperature for 1–2 h. The reaction was quenched with Et_3N. The precipitate was filtered through a pad of Celite. The filtrate and washings were combined, and the solution was successively washed with satd aq $NaHCO_3$, 1 M $Na_2S_2O_3$, and satd aq NaCl, dried and concentrated. The residue was purified by flash column chromatography to yield the products.

3.6. 8-Ethoxycarbonyloctyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranoside (3α) and 8-ethoxycarbonyloctyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-β-L-fucopyranoside (3β)

Compound **1** (322 mg, 1.59 mmol), **2** (532 mg, 1.06 mmol), NIS (640 mg, 2.86 mmol), and AgOTf (27.0 mg, 0.110 mmol) were reacted as described in Section 3.5. The anomers were then purified using flash column chromatography (1:8 EtOAc–hexane) to afford **3α** (562 mg, 82%) and **3β** (89.0 mg, 13%) as colorless syrups.

3.6.1. Analytical data for 3α

$[\alpha]_D$ −143 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{38}H_{46}O_9$ (646.77): C, 70.57; H, 7.17. Found: C, 70.77; H, 7.21. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.6.2. Analytical data for 3β

$[\alpha]_D$ −132 (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{38}H_{46}O_9$ (646.77): C, 70.57; H, 7.17. Found: C, 70.52; H, 6.75. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.7. 8-Ethoxycarbonyloctyl 4,6-di-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-galactopyranoside (6α) and 8-ethoxycarbonyloctyl 4,6-di-*O*-benzoyl-2,3-di-*O*-benzyl-β-D-galactopyranoside (6β)

Compound **1** (462 mg, 2.28 mmol), **10**[26] (378 mg, 1.52 mmol), NIS (920 mg, 4.10 mmol), and AgOTf (39.0 mg, 0.150 mmol) were reacted as described in Section 3.5. The anomers were then purified using flash column chromatography (1:8 EtOAc–hexane) to afford **13α** (356 mg, 49%) and **13β** (240 mg, 33%) as colorless syrups.

3.7.1. Analytical and spectral data for 6α

$[\alpha]_D$ +40.3 (*c* 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.06–7.22 (m, 20H, 4Ph), 5.90 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 0.8 Hz, H-4), 4.90 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.85 (d, 1H, C*H*HPh), 4.83 (d, 1H, C*H*HPh), 4.66 (d, 1H, C*H*HPh), 4.62(d, 1H, C*H*HPh), 4.46 (m, 1H, H-6a), 4.38–4.33 (m, 2H, H-5, H-6b), 4.12 (m, 3H, H-3, CH_2CH_3), 3.94 (dd, 1H, $J_{2,3}$ 10.2 Hz, H-2), 3.65 (m, 1H, OC*H*HCH$_2$), 3.48 (m, 1H, OC*H*HCH$_2$), 2.27 (t, 2H, CH_2CH_2COO), 1.66–1.56 (m, 4H, OCH_2CH_2, CH_2CH_2COO), 1.32–1.21 (m, 8H, $4CH_2CH_2CH_2$), 1.25 (t, 3H, OCH_2CH_3,); ^{13}C NMR ($CDCl_3$): δ 173.9, 166.1, 165.8, 138.5, 138.1, 133.2, 133.2, 130.0, 129.8, 129.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 97.8 (C-1), 76.4 (C-2), 75.2 (C-3), 73.5 (CH_2Ph), 72.1 (CH_2Ph), 68.8 (C-4), 68.6 ($COCH_2CH_2$), 67.1 (C-5), 63.3 (C-6), 60.2, 34.4 (CH_2CH_2COO), 29.4, 29.2, 29.1, 26.1, 25.0, 14.3 (OCH_2CH_3). Anal. Calcd for $C_{45}H_{52}O_{10}$ (752.89): C, 71.79; H, 6.96. Found: C, 71.57; H, 6.97.

3.7.2. Analytical data and spectral data for 6β

$[\alpha]_D$ +16.6 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.14–7.21 (m, 20H, 4Ph), 5.84 (dd, 1H, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 1.1 Hz, H-4), 4.90 (d, 1H, C*H*HPh), 4.83 (d, 1H, C*H*HPh), 4.74 (d, 1H, C*H*HPh), 4.59 (dd, 1H, H-6a), 4.59 (d, 1H, C*H*HPh), 4.47 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 4.36 (dd, 1H, H-6b), 4.12 (q, 2H, OCH_2CH_3), 4.00–3.96 (m, 2H, H-5, OC*H*HCH$_2$), 3.74–3.68 (m, 2H, H-2, H-3), 3.57 (m, 1H, OC*H*HCH$_2$), 2.27 (t, 2H, CH_2CH_2COO), 1.74–1.57 (m, 4H, OCH_2CH_2, CH_2CH_2COO), 1.45–1.24 (m, 8H, $4CH_2CH_2CH_2$), 1.25 (t, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 173.9, 166.2, 165.9, 138.5, 137.8, 133.3, 130.1, 129.8, 129.7, 128.5, 128.3, 128.1, 128.0, 127.6, 104.0 (C-1), 79.3 (C-3), 79.0 (C-2), 75.4 (CH_2Ph), 72.2 (CH_2Ph), 71.0 (C-5), 70.6 ($COCH_2CH_2$), 67.4 (C-4), 62.6 (C-6), 60.2 (CH_2CH_3), 34.4 (CH_2CH_2COO), 29.7, 29.3, 29.1, 26.1, 25.0, 14.3 (OCH_2CH_3). Anal. Calcd for $C_{45}H_{52}O_{10}$ (752.89): C, 71.79; H, 6.96. Found: C, 71.55; H, 6.93.

3.8. 8-Ethoxycarbonyloctyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-α-L-fucopyranoside (12α) and 8-ethoxycarbonyloctyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-β-L-fucopyranoside (12β)

Compound **1** (186 mg, 0.92 mmol), **9** (302 mg, 0.61 mmol), NIS (370 mg, 1.65 mmol), and AgOTf (16.0 mg, 61.5 μmol) were reacted as described in Section 3.5. The anomers were then purified using flash column chromatography (1:8 EtOAc–hexane) to afford **12α** (251 mg, 65%) and **12β** (113 mg, 29%) as colorless syrups.

3.8.1. Analytical data for 12α

$[\alpha]_D$ −77.0 (*c* 0.92, $CHCl_3$). Anal. Calcd for $C_{38}H_{48}O_8$ (632.78): C, 72.13; H, 7.65. Found: C, 72.18; H, 7.72. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.8.2. Analytical data for 12β

$[\alpha]_D$ −60.9 (*c* 1.06, $CHCl_3$). Anal. Calcd for $C_{38}H_{48}O_8$ (632.78): C, 72.13; H, 7.65. Found: C, 72.02; H, 7.69. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.9. 8-Ethoxycarbonyloctyl 2-*O*-benzyl-3,4-*O*-isopropylidene-α-L-fucopyranoside (13α) and 8-ethoxycarbonyloctyl 2-*O*-benzyl-3,4-*O*-isopropylidene-β-L-fucopyranoside (13β)

Compound **1** (462 mg, 2.28 mmol), **10**[26] (378 mg, 1.52 mmol), NIS (920 mg, 4.10 mmol), and AgOTf (39.0 mg, 0.150 mmol) were reacted as described in Section 3.5. The anomers were then purified using flash column chromatography (1:8 EtOAc–hexane) to afford **13α** (356 mg, 49%) and **13β** (240 mg, 33%) as colorless syrups.

3.9.1. Analytical data for 13α

$[\alpha]_D$ −75.8 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{27}H_{42}O_7$ (478.62): C, 67.76; H, 8.84. Found: C, 67.90; H, 8.79. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.9.2. Analytical data for 13β

$[\alpha]_D$ −47.6 (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{27}H_{42}O_7$ (478.62): C, 67.76; H, 8.84. Found: C, 68.04; H, 8.71. For ^{1}H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.10. Decyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranoside (14α) and decyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-β-L-fucopyranoside (14β)

Compound **7** (147 mg, 0.93 mmol), **2** (298 mg, 0.59 mmol), NIS (370 mg, 1.67 mmol), and AgOTf (15.0 mg, 58.4 μmol) were reacted as described in Section 3.5. The anomers were then purified using flash column chromatography (1:20 EtOAc–hexane) to afford **14α** (250 mg, 71%) as a colorless syrup and **14β** (62 mg, 18%) as a colorless syrup.

3.10.1. Analytical data for 14α

$[\alpha]_D$ −157 (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{37}H_{46}O_7$ (602.76): C, 73.73; H, 7.69. Found: C, 73.78; H, 7.79. For ^1H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.10.2. Analytical data for 14β

$[\alpha]_D$ −129 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{37}H_{46}O_7$ (602.76): C, 73.73; H, 7.69. Found: C, 73.90; H, 7.44. For ^1H and ^{13}C NMR data see Tables 3 and 4, respectively.

3.11. Decyl 2,3,4-tri-*O*-benzyl-β-L-fucopyranoside (15β)

Compound **7** (103 mg, 0.65 mmol), **11**[28] (228 mg, 0.43 mmol), NIS (260 mg, 1.16 mmol), and AgOTf (12 mg, 45.5 μmol) were reacted as described in Section 3.5. The product was then purified using flash column chromatography (3:80 EtOAc–hexane) to afford **15β** (189 mg, 76%) as a colorless syrup. $[\alpha]_D$ +78.8 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{37}H_{50}O_5$ (574.79): C, 77.31; H, 8.77. Found: C, 77.27; H, 8.59. For ^1H and ^{13}C NMR data see Tables 3 and 4, respectively. Pure **15α** was not obtained and was only detected by ^1H NMR spectroscopy.

3.12. Methyl 3,4-di-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benylidene-α-D-galactopyranoside (16α)

Compound **8**[28] (265 mg, 0.71 mmol), **2** (240 mg, 0.47 mmol), NIS (290 mg, 1.29 mmol), and AgOTf (12 mg, 47.5 μmol) were reacted as described in Section 3.5. The product was then purified using flash column chromatography (2:5 EtOAc–hexane) to afford **16α** (331 mg, 85%) as a colorless syrup. $[\alpha]_D$ −64.0 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.93–7.10 (m, 25H, 5Ph), 5.82 (dd, 1H, $J_{3,4}$ 3.4 Hz, H-3^{II}), 5.68 (dd, 1H, $J_{4,5}$ 1.1 Hz, H-4^{II}), 5.52 (s, 1H, C*H*Ph), 5.30 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1^{II}), 5.01 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1^{I}), 4.82 (d, 1H, C*H*HPh), 4.79 (d, 1H, C*H*HPh), 4.62 (d, 1H, C*H*HPh), 4.53 (d, 1H, C*H*HPh), 4.46 (dq, 1H, $J_{5,6}$ 6.4 Hz, H-5^{II}), 4.25 (dd, 1H, H-6a^{I}), 4.23 (dd, 1H, $J_{2,3}$ 10.2 Hz, H-2^{I}), 4.17 (dd, 1H, $J_{4,5}$ 0.8 Hz, H-4^{I}), 4.08 (dd, 1H, $J_{2,3}$ 10.6 Hz, H-2^{II}), 4.03 (dd, 1H, H-6b^{I}), 3.99 (dd, 1H, $J_{3,4}$ 3.4 Hz, H-3^{I}), 3.61 (d, 1H, $J_{5,6}$ 6.4 Hz, H-5^{I}), 3.43 (s, 3H, OC*H*$_3$), 1.19 (d, 3H, H-6^{II}); ^{13}C NMR ($CDCl_3$): δ 166.0, 165.7, 139.1, 137.9, 133.2, 132.9, 129.9, 129.8, 129.7, 129.0, 128.5, 128.3, 128.2, 128.2, 127.9, 127.7, 127.5, 127.4, 126.5, 126.4, 101.3 (*C*HPh), 100.1 (C-1^{I}), 99.8 (C-1^{II}), 77.4 (C-2^{I}), 75.3 (C-4^{I}), 74.2 (C-3^{I}), 72.8 (C-2^{II}), 72.4 (C-4^{II}), 71.8 (*C*H$_2$Ph), 70.4 (C-3^{II}), 69.4 (C-6^{I}), 65.0 (C-5^{II}), 62.4 (C-5^{I}), 55.3 (O*C*H$_3$), 16.3 (C-6^{II}). Anal. Calcd for $C_{48}H_{48}O_{12}$ (816.89): C, 70.57; H, 5.92. Found: C, 70.66; H, 5.94. Pure **16β** was not obtained and was only detected by ^1H NMR spectroscopy.

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