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Effect of Anomeric Configuration on Stereocontrolled α-Glycosylation of L-Fucose

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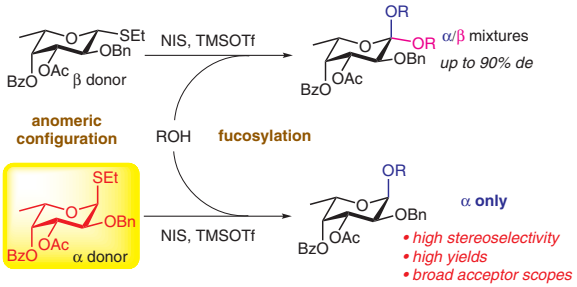

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Abstract In this letter, we report an approach to the stereoselective α-glycosylation of L-fucose that is exemplified by effect of anomeric configuration. The neighboring group participation is not compatible with α-glycosylation of L-fucose, therefore the remote participation by 4-*O*-Bz was employed to control the formation of 1,2-*cis*-glycosidic bond. Furthermore, we found the anomeric configuration of fucose donor is crucial to stereoselectivity of the glycosylated products. The α/β-mixed products were generated by using β-anomeric donor while the glycosyl donor in α configuration yielded products in high α-selectivity possibly due to the distinct pathway to forming the key intermediates. This phenomenon supplies the basis for the synthesis of complicated natural carbohydrates containing fucose α-glycoside, such as fucoidans, fucosylated *N*-glycans, and fucosylated chondroitin sulfates, etc.

Key words α-L-fucoside, stereoglycosylation, thioglycoside donor, anomeric configuration, remote participation

Carbohydrates widely exist in nature as oligosaccharides, polysaccharides, and glycoconjugates in the form of biomolecules such as peptides, proteins, lipids, etc.[1] Natural carbohydrates play crucial roles in versatile biological processes from cell adhesion to chemical signaling in terms of their structural complexity and diversity related to anomeric configurations, ring substituents, and conformational variations.[2] To obtain pure carbohydrate substrates, versatile types of innovative approaches have been developed, such as extraction from natural sources,[3] chemical,[4] enzymatic synthesis,[5] and automated synthesis[6] of oligosaccharides from fundamental building blocks. Currently, increasingly complex carbohydrates are being successfully obtained through chemical approaches dedicated to the applications in pharmaceutics, biomaterials, and food additives, as well as cosmetics and other fields.

Glycosylation is considered as the central reaction in carbohydrate chemistry.[7] Robust glycosylation commonly possesses the properties of high yields, and excellent regio- and stereoselectivities, which supply fundamental building blocks for accessing complex carbohydrates. Among these, regioselectivity is usually achieved by the selective protection–deprotection process on acceptors. However, stereoselective glycosylation is more challenging because of the flexible formation of a pair of diastereoisomers during glycosylation. The neighboring group participation is the most effective strategy to construct the 1,2-*trans* glycosides;[8] furthermore, solvent effects[9] and specific donors[10] were also employed to carry out high stereoselective glycosylation. The catalytic glycosylation with glycosyl imidate, halide, carbamate donors, and thioglycosides have been recently reviewed with a focus on the development and application of natural carbohydrates.[11] Representative L-hexose, such as L-fucose and L-iduronic acid, are mainly in the form of α-glycosides in the nature.[12] The glycosylation of α-L-iduronic acid could be achieved by neighboring group participation for assembly of heparin, heparan sulfate, and dermatan sulfate oligosaccharides.[13] However, it is still a challenge to form 1, 2-*cis* α-glycosides, especially for L-fucose.[14] The fucose-containing glycans and glycoconjugates (Figure 1), such as fucoidans,[15] fucosylated *N*-glycans,[16] as well as fucosylated chondroitin sulfates,[17] mostly exist in the form of α-fucosides, which play multiple biological functions, including anticancer, antiviral, and anticoagulant activities, etc. Carbohydrate chemists have devoted considerable efforts to the synthesis of complex fucose-containing carbohydrates. Type I and II fucoidan oligosaccharides were chemically synthesized from di- to hexasaccharides. The stereoselective blockwise synthesis and acid-promoted sulfation were developed by Nifantiev and co-workers to prepare fucoidan fragments.[18] Toshima's group

reported that both natural fucoidan and 3,4-*O*-sulfated tetrafucoside exhibited apoptosis-inducing activities through activation of caspase-8 on MCF-7 cells.[19] Synthesis of fucoidan-mimetic glycopolymers with well-defined sulfation patterns via emulsion ring-opening metathesis polymerization was recently developed by Cai and co-workers.[20] However, the stereocontrolled fucosylation of versatile acceptors with different nucleophilicities have not yet been well studied.

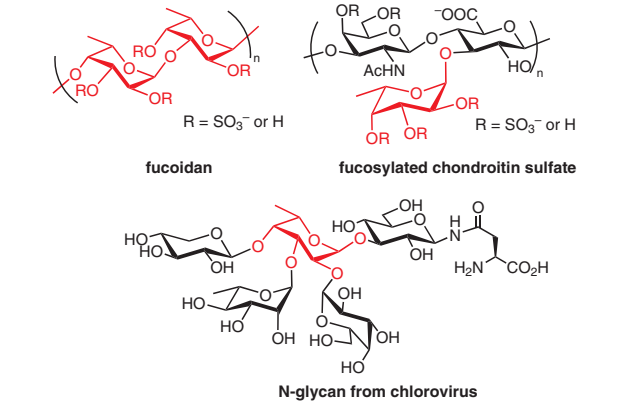
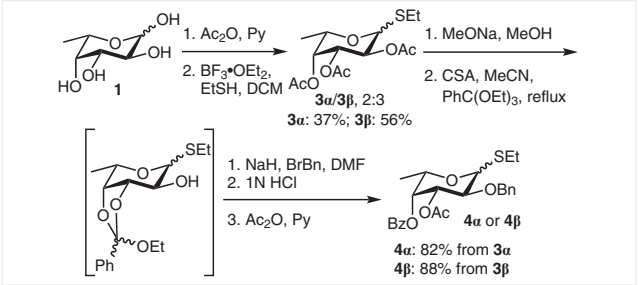


Figure 1 The representative structures of natural carbohydrates containing α-fucosides

The influence of anomeric configuration on the stereoselective formation of α-fucosides is reported here. The leaving group on β face of the fucoside donor preferred to form oxocarbenium ions, leading to α- and β-mixed products upon attack by strong nucleophiles. On the contrary, the high α-selective fucosidic bonds were promoted by the fucoside donor in α configuration and prior remote participation during the fucosylation for a wide range of acceptors.

The remote participation of 4-*O*-benzyl group on fucose donors was reported to assist the formation of α-fucosidic linkage;[21] moreover, the ether groups attached at C2 could facilitate α-anomer selectivity as well. However, these multiple effects were still not powerful enough to control the complete formation of α-fucosides, especially with strong nucleophiles as acceptors. Thioglycoside is one of the most commonly used donors due to its concise preparation and better stability.[22] Therefore, the thioglycoside **4** with 3,4-*O*-diacyl group was synthesized as a donor for fucose glycosylation. As shown in Scheme 1, fucose was peracetylated under Ac_2O/Py conditions followed by treatment with EtSH in the presence of $BF_3{\cdot}OEt_2$ to realize thioglycoside **3** as an α/β mixture. Notably, the mixture of anomers could be separated completely by a silica gel column to furnish the alternative anomers **3α** and **3β** (2:3), respectively. Compound **3α**/**3β** was deacetylated and protected with cyclic 3,4-*O*-orthobenzoate subsequently followed by 2-*O*-benzylation. The regioselective ring opening of the orthoester and 3-*O*-acetylation afforded thioglycoside donors **4α** and **4β** in one-pot with high yields (82% for **4α** from compound **3α**, 88% for **4β** from compound **3β**).



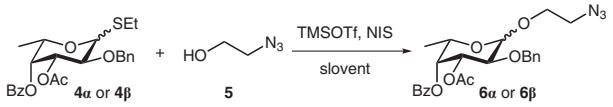
Scheme 1 Synthetic route of fucoside donor **4α**/**4β**

To study the diastereoselectivity of the coupling reaction between thiofucoside donor and acceptors, a common acceptor **5** was synthesized from 2-chloroethanol.[23] Compound **4β** was first chosen as a donor attributed to its high isolate yield from the anomer mixture. The coupling reaction that participated with thioglycoside was generally conducted through an iodonium-assisted pathway. Thus, the glycosylation system was handled with the promotion of NIS/TMSOTf in CH_2Cl_2 to afford **6**. However, α/β-mixed products obtained subsequently were difficult to separate by silica gel column, and only a very small amount of **6α** was isolated. To analyze the ratio of **6α** to **6β** directly, a high throughput reverse-phase high-performance liquid chromatograph (RP-HPLC) assay was applied for each coupling reaction (Figure S1). Owing to the obstacles to the separation of **6β**, we synthesized **6β** (74% from compound **7**) by Fisher glycosylation between compounds **2** and **5** (Scheme S1) as a standard for RP-HPLC assay.

Moreover, the results of the coupling reaction between **4β** and **5** under various conditions are summarized in Table 1. The glycosylation reactions were performed at –20 °C in various solvents (Table 1, entries 1–3). We found that the reaction in Et_2O showed remarkable α selectivity of 86% de, while CH_3CN as a solvent showed relatively good β selectivity of –38% de. In addition, CH_2Cl_2 showed low anomeric selectivity that was mainly affected by the intrinsic properties of donor and acceptor. The primary solvent effects were obviously observed in that ether solvent facilitated α selectivity compared with β selectivity in CH_3CN. The observed solvent-induced diastereoselectivity could account for the molecular motion of dissociation and association in different solvents.[24] To improve the α selectivity of the coupling reaction, we raised the temperature to 0 °C (Table 1, entries 4–6). The ratios of **6α**/**6β** in different types of solvents were all advanced due to the increase of reaction temperature. This phenomenon could be attributed to the improved formation of remote participation and anomeric effect under thermodynamic control. These results demonstrate that reaction in Et_2O at high reaction temperature could promote

the formation of α-fucosidic linkage. Upon further increasing the reaction temperature to even higher, however, room temperature resulted in increased decomposition of thioglycoside **4β** (Table 1, entry 7). Therefore, the optimum condition for the formation of α-fucosidic linkage could be 0 °C in Et_2O.

Table 1 Glycosylations of Fucose Donor with Alkyl Alcohol under Varying Conditions



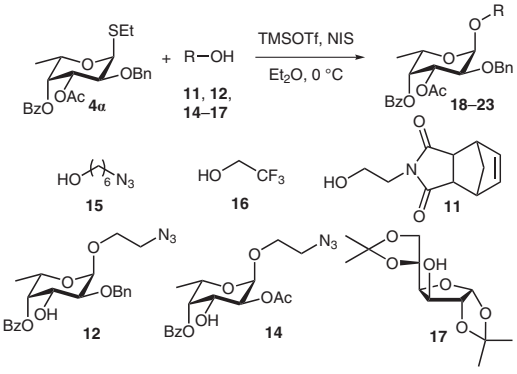
Entry	Donor	Solvent	T (°C)	α/β[a]	de (%)[b]
1	**4β**	DCM	–20	3.2:1	52
2	**4β**	Et_2O	–20	13.2:1	86
3	**4β**	CH_3CN	–20	1:2.2	–38
4	**4β**	DCM	0	4.5:1	64
5	**4β**	Et_2O	0	18.2:1	90
6	**4β**	CH_3CN	0	1:1.4	–17
7	**4β**	Et_2O	r.t.	decomposed	–
8	**4α**	Et_2O	0	1:0	100

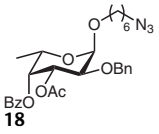
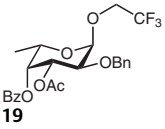
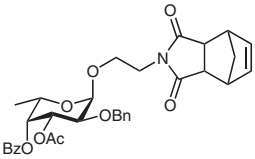
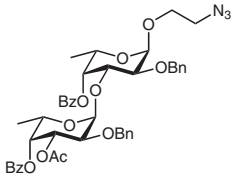
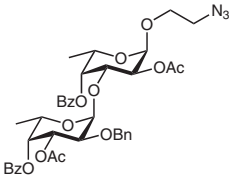
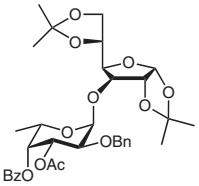
[a] Anomeric ratio determined by RP-HPLC analysis.
[b] Diastereomeric excess (% de) = [ratio of α anomer (%)] – [ratio of β anomer (%)]

With the thioglycoside **4α** in hand as well, we further investigated the glycosylation reaction under optimum conditions, and interesting results were observed (Table 1, entry 8). An impressive α selectivity of nearly 100% de was obtained and no β-fucosidic products were isolated. Thus, we speculated that the anomeric configuration of thioglycoside could also be a critical factor influencing stereoselectivity during formation of α-L-fucosides.

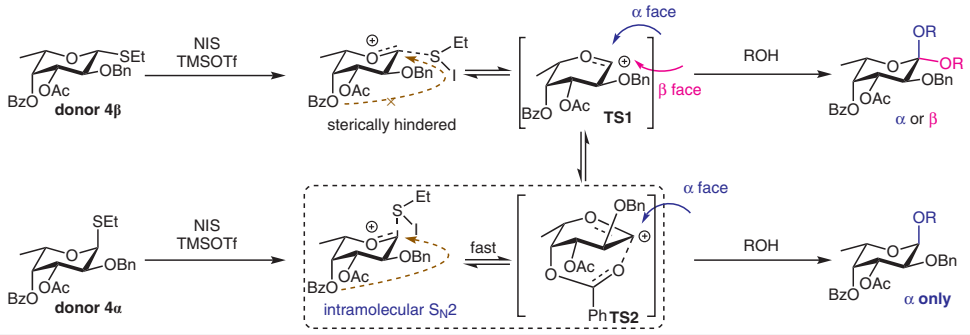
Next, we investigated the efficiency and stereoselectivity of donor **4α** by using a series of coupling reactions with six acceptors from simple alcohols as strong nucleophiles to versatile carbohydrate acceptors for the potential synthesis of natural products.[25] Among these acceptors, compounds **16** and **17** were commercially available, while the other substrates **11**, **12**, **14**, and **15** were synthesized as depicted in Scheme S2. Acceptor **11** containing norbornene was prepared by heating **10** and 2-aminoethanol in toluene. Terminal azide containing alcohol **15** was furnished from 6-chlorohexanol by treatment with sodium azide under alkaline conditions. Compound **12** was procured through selective removal of acetyl groups on **6α** with 4% acetyl chloride in methanol. Furthermore, **6α** was successfully debenzylated under mild oxidative conditions ($NaBrO_3/Na_2S_2O_4$) and deacylated to afford compound **13**. Subsequent transformation into the cyclic 3,4-*O*-orthobenzoate, acetylation, and regioselective ring opening of orthoester gave acceptor **14**.

Table 2 Synthetic Scope Between α-Fucosidic Donor with Different Types of Acceptors



Entry	Donor	Acceptor	α/β	Yield (%)[a]	Product
1	**4α**	**15**	α only	98	 **18**
2	**4α**	**16**	α only	96	 **19**
3	**4α**	**11**	α only	98	 **20**
4	**4α**	**12**	α only	94	 **21**
5	**4α**	**14**	α only	95	 **22**
6	**4α**	**17**	α only	96	 **23**

[a] Isolated yield.



Scheme 2 Proposed mechanism for the stereoglycosylation controlled by effect of anomeric configuration.

As shown in Table 2, the coupling reactions between donor **4α** and six acceptors demonstrate excellent stereoselectivity, in which only α-fucosidic products were isolated with high yields. The straight-chain alkane acceptor **15** possesses strong nucleophilicity as similar as possible to acceptor **5**, and high anomeric selectivities were found for both coupling reactions. The decrease of nucleophilicity on an acceptor by introducing fluorine atoms (Table 2, entry 2) did not change the stereoselectivity obviously. Therefore, the anomeric configuration of **4α** was supposed to be the crucial factor for the stereocontrolled fucosylation. Furthermore, acceptor **11** showed a similar α selectivity compared with the above-mentioned substrates,[26] which could be applied for the ring-opening metathesis polymerization (ROMP) to access multivalent glycopolymers.[27] Condensation with secondary hydroxyl groups on carbohydrate acceptors also exhibited excellent α selectivity. For example, although the presence of 2-*O*-acetyl group on **14** decreased nucleophilicity compared to 2-*O*-benzyl group on **12**, the high α selectivity during the coupling reactions was still consistent. These representative acceptors (**12** and **14**) were more favorable for the synthesis of oligofucosides with defined sulfation patterns. Thus, it would be very helpful to reveal their structure–activity relationship.[18] Furthermore, disaccharide **23**[28] was a fragment related to the distinct *N*-glycans of chloroviruses, and the protocol presented here promoted the access to chemical synthesis of the *N*-glycans recently observed.[16] Overall, the coupling reactions of donor **4α** with simple and complicated acceptors could all give the products in α configuration. We speculated that the α anomer of the thioglycoside donor facilitates the formation of remote participation, leading to the desired products with α configuration only.

Furthermore, the β thioglycosides commonly in higher isolated yields were also used as donors for the preparation of α-fucosidic linkages. According to the recent reports, the coupling of β-thioglycoside donors with carbohydrate acceptors generally afforded α-configuration products in terms of their low nucleophilicity.[29] The results in our study show that the preference of α-configuration products could be attributed to the high portion of remote participation among reaction intermediates, while the strong nucleophilic acceptor was bound to oxocarbenium ions immediately which showed lower stereoselectivity.

Based on the obtained results, the proposed mechanism for the stereoselective glycosylation of donor **4α**/**4β** is depicted in Scheme 2. The ethylthio and 4-*O*-benzoyl group on donor **4β** located at the same orientation which hindered the remote participation initially through the formation of oxocarbenium cation **TS1**. Thus, the acceptors could attack the anomeric position from α and β faces, respectively. The acceptors with strong nucleophilicity rapidly react with **TS1** to achieve lower α selectivity. However, **TS1** is mainly transformed into **TS2**, while the acceptors with weak nucleophilicity are employed to afford moderate α selectivity. Furthermore, the ethylthio and 4-*O*-benzoyl groups on donor **4α** are present at the opposite orientation, thus possessing low steric hindrance. Remote participation with the cleavage of the ethylthio group under an intramolecular S_N2 pathway forms **TS2** quickly, which avoids the formation of **TS1**. Therefore, the acceptors attack the anomeric position only from the α face which gives pure product in α configuration for both strong and weak nucleophiles. Increasing the reaction temperature could improve the formation of **TS2** along with the higher α selectivity of the anomeric effect.

In conclusion, facial-selective nucleophilic attack of a glycosyl acceptor is attributed to steric and electronic properties of the oxocarbenium intermediate as well as stabilization of the intermediate formed by remote participation. The cleavage of the ethylthio group on α face followed by successive 4-remote participation affords fucosides in a high α configuration through the intramolecular S_N2 pathway. The present study is of great significance for the assembly of complex natural carbohydrates and glycoconjugates containing α-L-fucosides.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611311.

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(25) **General Procedure for Fucosylation of 4α with Acceptors**
To a solution of compound **4α** (10 mg, 0.0225 mmol, 1 equiv) and acceptor (0.0248–0.225 mmol, 1.1–10 equiv) in 500 μL anhyd Et_2O with argon protection was added 4 Å MS. The mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C, then NIS (10.1 mg, 0.045 mmol, 2 equiv) and TMSOTf (0.4 μL, 0.00225 mmol, 0.1 equiv) were added. The mixture was stirred for 0.5 h after which TLC indicated full conversion and quenched with Et_3N. The mixture was filtered, evaporated, and purified by column chromatography to afford product.

(26) **Analytical Data for Product 20**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.1 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.33–7.27 (m, 5 H), 6.23 (s, 2 H), 5.50 (d, *J* = 3.0 Hz, 1 H), 5.35 (dd, *J* = 10.5, 3.2 Hz, 1 H), 4.93 (d, *J* = 3.4 Hz, 1 H), 4.60 (dd, *J* = 27.2, 12.1 Hz, 2 H), 4.26 (q, *J* = 6.5 Hz, 1 H), 3.91 (dd, *J* = 10.5, 3.5 Hz, 1 H), 3.85–3.80 (m, 1 H), 3.78–3.70 (m, 3 H), 3.26 (s, 1 H), 3.19 (s, 1 H), 2.60 (dd, *J* = 23.4, 7.0 Hz, 2 H), 1.91 (s, 3 H), 1.42 (d, *J* = 10.0 Hz, 1 H), 1.36 (d, *J* = 10.1 Hz, 1 H), 1.16 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.98, 177.95, 170.01, 165.98, 138.13, 137.82, 137.68, 133.22, 129.77, 129.67, 128.48, 128.34, 127.75, 127.69, 97.27, 73.49, 72.98, 72.15, 70.02, 65.02, 63.58, 47.83, 45.19, 42.89, 37.81, 20.83, 16.03. HRMS: *m/z* calcd for $[C_{33}H_{35}NNaO_9]^+$: 612.2204; found: 612.2201.

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(28) **Analytical Data for Product 23**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.3 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 7.37–7.30 (m, 5 H), 5.82 (d, *J* = 3.6 Hz, 1 H), 5.53 (d, *J* = 2.6 Hz, 1 H), 5.37 (dd, *J* = 10.6, 3.2 Hz, 1 H), 5.01 (d, *J* = 3.5 Hz, 1 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.60 (d, *J* = 5.6 Hz, 1 H), 4.56 (d, *J* = 12.2 Hz, 1 H), 4.41–4.36 (m, 1 H), 4.34 (d, *J* = 3.6 Hz, 1 H), 4.31 (d, *J* = 3.1 Hz, 1 H), 4.17 (dd, *J* = 8.6,

6.2 Hz, 1 H), 4.11 (dd, *J* = 9.1, 3.1 Hz, 1 H), 4.03–3.99 (m, 2 H), 1.96 (s, 3 H), 1.50 (s, 3 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.29 (s, 3 H), 1.14 (d, *J* = 6.5 Hz, 3 H).^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.12, 166.05, 138.16, 133.28, 129.80, 129.72, 128.53, 128.49, 127.97, 127.68, 111.93, 109.22, 105.38, 96.00, 82.31, 81.08, 78.34, 73.80, 73.53, 72.20, 72.09, 70.43, 67.97, 65.27, 26.95, 26.87, 26.24, 25.36, 20.87, 15.88. HRMS: *m/z* calcd for $[C_{34}H_{42}NaO_{12}]^+$: 665.2568; found: 665.2565.

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