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A Stereoselective α-Fucosylation Reaction Using 1-Hydroxy 2,3,4-tri-*O*-benzyl-L-fucose Donor for the Practical Synthesis of Selectin Blocker

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Abstract: A 1-hydroxy 2,3,4-tri-*O*-benzyl-L-fucose donor affords a high stereoselectivity of glycosylation in the presence of TMSOTf and is a very useful substrate for the preparation of an α-L-fucosyl dipeptide in a stereoselective manner. The donor will be a key component in the preparation of an attractively biological selectin blocker **1**.

α-L-Fucopyranosyl derivatives are a series of the most attractive compounds in the field of glycobiology. For instance, sialyl Lewis X antigenic determinant (Neuα2-3Galβ1-4(Fucα1-3)GlcNAcβ1-R, sLe^X) is a native ligand of selectins, and both 2- and 3- hydroxy groups of the fucose part are essential moiety for the Ca^{2+} dependent binding to selectins. Many studies indicated that the sLe^X/selectin interaction plays an important role in the migration of inflammatory cells from the blood stream to inflammatory sites, and the interaction participates in various inflammatory diseases[1-5] such as asthma, rheumatoid arthritis, ischemia/reperfusion injury, and cutaneous inflammatory disorders. Recently, a number of selectin blockers were reported as new type of anti-inflammatory agents. Most of these compounds contain an α-L-fucopyranosyl moiety, *e.g.* liner alkyl-, cycloalkyl-, and aryl-α-fucopyranoside groups.[6-10] Since the fucose part of these compounds play a crucial role in the blocking activity, the development of the practical and stereoselective α-fucosylation reaction has been desired. So far, the fucosylation reaction on the synthesis of these selectin blockers were mainly performed using fucopyranose derivatives bearing active leaving group at the C-1 position. However, such glycosylation reactions might involve several problems, *i. e.* (i) the instability of the fucose donor, (ii) the use of expensive reagents for the activation of the fucose donor, (iii) the necessity of the leaving group introduction. Accordingly, the development of the practical α-fucosylation reaction has been still desired.

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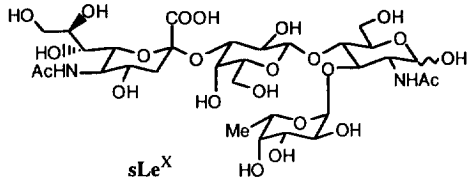
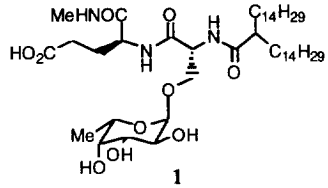
We have also reported significant selectin blocker **1**, having *O*-(α-L-fucopyranosyl)serine scaffold which is 20-100 fold more potent inhibitor than sLe^x. An important step in the preparation of compound **1** was the coupling of L-fucose donor, 2,3,4-tri-*O*-benzyl-L-fucopyranosyl fluoride, with the dipeptide acceptor.[11] This



sLe^X



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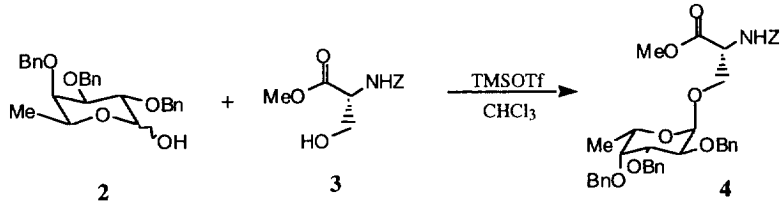
glycosylation reaction proceeded in stereoselective manner (α/β = 4/1), the stereoselectivity, however, was not enough for the practical synthesis of **1**. In addition, the fucosylation reaction is not suitable for the glycosylation in a large scale synthesis, because the activation of the leaving group to construct the glycosyl bond requires the expensive reagents such as AgOTf. Therefore, to establish a practical synthesis of compound **1**, we need the establishment of stereoselective α-L-fucosylation using a more simplified fucose donor.

In a series of investigation to address the problems mentioned above, we found that the reaction of 1-hydroxy 2,3,4-tri-*O*-benzyl-L-fucopyranose (**2**), a precursor of the fucopyranosyl fluoride mentioned above, with Z-D-serine methyl ester **3** proceeded in the presence of TMSOTf at room temperature to afford the corresponding fucosylated serine derivative **4** in high stereoselectivity, especially TMSOTf was a useful activator for our purpose (Table 1 and Scheme 1)[12]. This is the first method in which the sugar peptide has been synthesized with a 1-hydroxy sugar donor in the presence of TMSOTf at high stereoselectivity[13].



2 **3** **4**

Scheme 1

A similar glycosylation has been reported,[14] however, there is no report concerning the sufficiently stereoselective fucosylation using the 1-hydroxy sugar donor in the presence of TMSOTf as activator with the practical yield, in addition with the glycosylation reaction for the syntheses of useful compounds as in pharmaceutical field.

To optimize the α-selective fucosylation, we studied several reaction conditions, *e.g.*, the reaction temperature, the molecular sieves effect, and the amount of TMSOTf (Table 1). First, various reaction temperatures were investigated (entry 1-4). The stereoselectivity of α-anomer increased with decreasing reaction temperature, however, the reactivity was decreased at lower temperature (entry 4). Next, we

investigated the effect of molecular sieves on this reaction (entry 3 and 5). As a result, the existence of molecular sieves did not affect the yield and the stereoselectivity of the fucosylation. In addition, this reaction did not require any anhydrous operations, *i.e.* the substitution of the atmosphere with an inert gas and

Table 1. Coupling Reaction of Fucose Donor**2** and Serine Acceptor**3** in the presence of TMSOTf

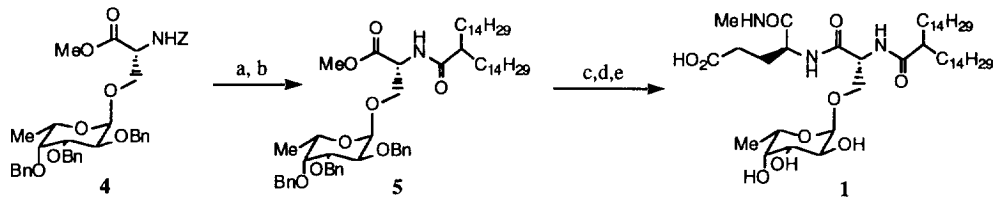
Entry	**2** (eq.)	**3** (eq.)	TMSOTf (eq.)	Temp. (°C)	Time (h)	MS[a] 4A	stereoselectivity[b] (α/β)	Yield[c] (α–anomer, %)
1	1.5	1.0	2.0	reflux	2	+	71/29	67
2	1.5	1.0	2.0	r.t.	2	+	81/19	65
3	1.5	1.0	1.7	-20	3	+	95/5	74
4	1.5	1.0	2.0	-70	3	+	96/4	9
5	1.5	1.0	1.7	-20	3	-	94/6	75
6	1.5	1.0	1.5	-20	3	+	94/6	72
7	1.5	1.0	1.0	-20	3	+	92/8	48
8	1.5	1.0	0.5	-20	6	+	86/14	6

a) MS = Molecular Sieves. b)Ratio was determined by HPLC. c)Isolated yield.

particular purification of the solvent. Finally, to elucidate the role of TMSOTf in this reaction, we examined the amounts of TMSOTf. When the excess or equal amount of TMSOTf against compound **2** was used at -20°C, both the stereoselectivity and the isolated yield of compound **4** were not influenced (entry 3 and 6). On the other hand, when the amount of TMSOTf was diminished to 2/3 based on that of compound **2**, it was of interest to note that the isolated yield of compound **4** also decreased to 48 % (entry 7).

These results indicate that the hydroxy group of C-1 position on compound **2** would be first activated with TMSOTf to form the oxocarbenium ion, followed by the nucleophilic attack of the acceptor **3** to afford the α-L-fucosyl serine derivative **4** in high stereoselective manner because of the kinetic control, anomeric effect. As a result, the stereoselectivity and the isolated yield were improved to 95/5 (α/β ratio[15]) and 75 % yield, respectively.

A key intermediate **4** prepared successfully was a useful component for the construction of biologically attractive selectin blocker **1** as shown in Scheme 2. Thus, selective deprotection of amino group of compound **4** was performed by Pd-C catalyzed hydrogenation and followed by the introduction of lipophilic chain to afford compound **5**. Then, the coupling with glutamic acid component followed by the debenzylation to give the desired compound **1**. Compound **1** is now under investigation for anti-inflammatory drug because of its strong activity as a selectin blocker and the facility in the synthesis.



(a)H_2/10%Pd-C, 100%; (b)$(C_{14}H_{29})_2CHCO_2H$, WSC, HOBt, 60%; (c)LiI, pyridine, 91%; (d)Glu(OBn)NHMe, WSC, HOBt, 77%; (e)H_2/$Pd(OH)_2$, 97%.

Scheme 2

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15. The stereoselectivity (α/β ratio) was determined by HPLC. Chromatographic condition: wavelength (nm); 254, mobile phase; CH_3CN:0.1%TFA=7:3, flow rate; 1ml/min, column; inertsil ODS-2, HPLC system; Waters model 150, retention time (min); 17.2 for α, 18.2 for β.