An Efficient Method for Catalytic Stereoselective Synthesis of α-L-Fucopyranosides

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A new efficient method for the catalytic stereoselective synthesis of various α-L-fucosides by using an easily available and stable glycosyl donor, 2,3,4-tri-*O*-benzyl-L-fucopyranosyl methoxyacetate, is established. Also, trimethylsilyl trifluoroacetate and lithium perchlorate are found to be effective additives in the synthesis of Fucα1-3GlcNAc and Fucα1-4GlcNAc linkages.

Carbohydrates and their conjugates have recently attracted much attention due to their important roles in many complex biological processes.[1] Especially in a cell adhesion phenomenon, the role of saccharide chain was well recognized as a ligand of the endotherial leukocyte adhension molecule such as sialyl Lewis X.[2] Since sialyl Lewis X is considered to have high potential as an anti-inflammatory drug, many synthetic approaches to sialyl Lewis X and its novel mimetics were reported in these years.[3] In those reports, all mimetics have relatively simple structures with necessary L-fucose residue because 2,3,4-OH groups of L-fucose are essential for the inhibition of cell adhesion process (E-selectin recognition). In addition, an uncommon L-fucose-threonine linkage was found in the growth factor domains of several coagulation/fibrinolytic proteins,[4] though the role of L-fucose moiety is not yet made clear.[5] Since various L-fucose containing glycoconjugates showed a wide variety of biological functions, development of more efficient methods for the synthesis of α-L-fucoside was strongly desired. Then, various glycosyl donors were employed in the syntheses of α-L-fucosides such as thioglycosides,[6] glycosyl halides[7] and glycosyl trichloroacetimidates[8] and so on. However, each glycosyl donor had some problems; that is, its instability in storage, multi steps needed in synthesis and so on. Moreover, stoichiometric amount of activator was required for the completion of L-fucoside linkage formations in most cases. Thus, development of an efficient method by using a simple and easily available glycosyl donor, 1-*O*-acyl-L-fucoside, was investigated. In this communication, we would like to report a useful method for glycosylation of 1-*O*-acyl-L-fucoside with several glycosyl acceptors affording valuable α-L-fucosides in high yields with high stereoselectivities by using Lewis acid catalyst.

Firstly, the reaction of 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl acetate[9] **1a** with D-glucose derivative **2** was examined in the presence of a catalytic amount of $Sn(OTf)_2$. However, desired L-fucoside **3a** having Fucα1-3Glc linkage was obtained in a very poor yield. Then, more reactive glycosyl donor,[10] 2,3,4-tri-*O*-benzyl-L-fucopyranosyl methoxyacetate **1b** (α/β=75/25) which was easily prepared from 2,3,4-tri-*O*-benzyl-L-fucopyranose and methoxy acetyl chloride in almost quantitative yield, was employed. This glycosyl donor was smoothly activated by using 20 mol% of $Sn(OTf)_2$ at room temperature in the coexistence of 1500 mg/mmol (vs **1b**) of MS3A to give the corresponding L-fucoside **3** in good yield. Then several solvents were screened and the desired L-fucoside **3** was obtained in moderate yield with high stereoselectivity in benzene or toluene. When

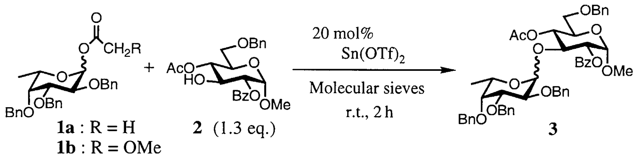


Table 1. Effect of solvents

Entry	Donor	Solvent	MS (mg/mmol)	Yield / %	α / β
1	**1a**	CH_2Cl_2	3A (1500)	14	α only
2	**1b**	CH_2Cl_2	3A (1500)	85	93 / 7
3	**1b**	Benzene	3A (1500)	67	97 / 3
4	**1b**	Toluene	3A (1500)	62	97 / 3
5	**1b**	THF	3A (1500)	22	98 / 2
6	**1b**	$EtNO_2$	3A (1500)	67	88 / 12
7	**1b**	Benzene	None	74	89 / 11
8	**1b**	Benzene	3A (500)	92	96 / 4

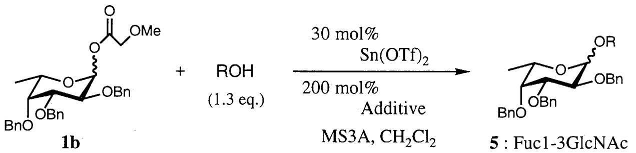
Table 2. Effect of molecular sieves

Entry	MS (mg/mmol)	Solvent	Yield / %	α / β
1	5A (500)	Benzene	89	95 / 5
2	4A (500)	Benzene	42	98 / 2
3	3A (500)	Benzene	92	96 / 4

dichloromethane was used, the yield was improved but the stereoselectivity was slightly decreased. Further, the amount of molecular sieves effected on the yield and stereoselectivity; that is, **3** was obtained in high yield with high stereoselectivity when the amount of molecular sieves was reduced to 500 mg/mmol. The effect of the kinds of molecular sieves (3A,4A and 5A) was also examined and molecular sieves 3A gave the best results.

Next, syntheses of Fucα1-3GlcNAc and Fucα1-4GlcNAc linkages were investigated (see Table 3). The reactions proceeded much slower than that of D-glucose derivative **2** and then, several attempts concerning additives were made in order to improve the yield. Lithium perchlorate and trimethylsilyl trifluoroacetate were consequently found to be quite effective for the promotion of the above reactions. It was assumed that these additives interact toward acetamide moiety of GlcNAc in competition with $Sn(OTf)_2$ and prevent the lowering of its Lewis acidity. When 3-OH GlcNAc **4** was used as a glycosyl acceptor, the addition of several trimethylsilyl compounds gave better results than that of lithium perchlorate. On the contrary, lithium perchlorate was more effective when 4-OH GlcNAc **6** was used as an acceptor. Details of the synthesis of Fucα1-4GlcNAc linkage are shown in Table 4. It is noted that 50 mol% of lithium perchlorate was enough to promote the reaction. On the other hand, the yield was decreased slightly when an excessive amount of lithium perchlorate was used, because thus formed L-fucoside linkage was more sensitive under acidic conditions compared with other L-fucosides leading to the formation of 2,3,4-tri-*O*-benzyl-L-fucopyranose and 4-OH GlcNAc **6** on quenching.

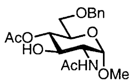
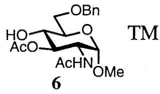
The present fucosylation reaction was further applied to the



1b

5 : Fuc1-3GlcNAc
7 : Fuc1-4GlcNAc

Table 3. Effect of additives

Entry	ROH	Additive	MS3A(mg/mmol)	Yield / %	α / β
1		None	50	19	96 / 4
2		$LiClO_4$	50	66	97 / 3
3		TMSCl	50	85	95 / 5
4		TMSBr	50	80	92 / 8
5	**4**	Me_2SiCl_2	50	75	95 / 5
6		TMSOC(O)CF_3	50	85	96 / 4
7		TMSOC(O)CF_3	150	62	93 / 7
8[a]	**6**	$LiClO_4$	150	72	94 / 6

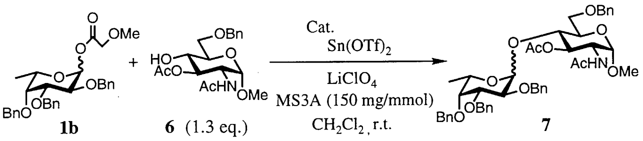
[a] The reaction was carried out for 15 h.

synthesis of Fucα1-Thr linkage[3a,4,5] as shown in scheme 1. The appropriately protected threonines (**8** or **10**) reacted smoothly with fucosyl donor **1b** using 30 mol% of $Sn(OTf)_2$ in a mixed solvent (benzene/dichloromethane=3/1) with coexistence of MS3A (150 mg/mmol). In this reaction, benzene was suitable solvent to achieve high stereoselectivity, but both protected threonines were not sufficiently soluble in this medium. Then, some examinations concerning the ratio of mixed solvents were studied and the above ratio gave best results for the compatibility of high yield and selectivity. The amount of MS3A also influenced the reaction as shown in Table 1. In the absence of MS3A, the fucoside was obtained in 85% yield with slightly decreased stereoselectivity (α/β = 86/14) while addition of a large amount of MS3A led to poor yielding of the desired fucoside.

The typical experimental procedure is as follows: to a stirred suspension of tin(II) triflate (12.5 mg, 0.03 mmol), trimethylsilyl trifluoroacetate (37.2 mg, 0.2mmol), and MS3A (5 mg) in dichloromethane (3 ml) was successively added a dichloromethane (1.5 ml) solution of 2,3,4-tri-*O*-benzyl-L- fucopyranosyl methoxyacetate (50.7mg, 0.1 mmol) and GlcNAc derivative **4** (47.8 mg, 0.13 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature, then it was quenched by adding saturated aqueous sodium hydrogen carbonate. By usual work-up and purification with preparative TLC (silica gel), the desired fucoside **5** (66.7 mg, 85% yield) was isolated. The ratio of anomers was determined by HPLC analysis.

Thus, a catalytic and stereoselective synthesis of various α-L-fucosides by using easily available and stable glycosyl donor, 2,3,4-tri-*O*-benzyl-L-fucopyranosyl methoxyacetate, was successfully developed. It was noted that trimethylsilyl trifluoroacetate and lithium perchlorate were quite effective as additives for the promotion of the glycosylation when less reactive GlcNAc derivatives were used as glycosyl acceptor.

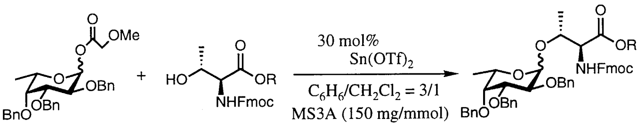
Further study on the syntheses of several valuable oligosaccharide according to the present procedure is now in progress.



1b **6** (1.3 eq.) **7**

Table 4. Effect of the amount of $LiClO_4$

Entry	Cat. / mol%	$LiClO_4$ / mol%	Time / h	Yield / %	α / β
1	30	30	20	64	94 / 6
2	30	50	20	80	94 / 6
3	30	100	15	73	93 / 7
4	30	200	15	72	94 / 6
5	50	50	2.5	80	94 / 6
6	100	50	0.5	83	94 / 6



1b

8 : R = Me
10 : R = Bn
(1.3 eq.)

9 : R = Me
98% yield, α/β = 92/8
11 : R = Bn
87% yield, α/β = 93/7

Scheme 1. Synthesis of Fucose-Threonine linkage.

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