Moisture Stable Promoters for Selective α-Fucosylation Reactions: Synthesis of Antigen Fragments

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Abstract: Moisture stable reagents $Yb(OTf)_3$ and acid washed molecular sieves (AW 300 MS) can act as mild promoters for selective α-fucosylation reactions. Using a combination of $Yb(OTf)_3$ and AW 300 MS a good stereocontrol is achieved with a perbenzylated fucosyl *N*-phenyl trifluoroacetimidate donor by exploiting the directing effect of ether solvents. With the AW 300 MS alone the selectivity can be obtained with partially acetylated donors by exploiting a long-range participation effect. Both systems proved suitable for the synthesis of fragments contained in important antigen sequences, included the Lewis X trisaccharide.

Key words: carbohydrates, synthesis of oligosaccharides, stereoselectivity in fucosylation reactions, acid-washed molecular sieves, ytterbium triflate

L-Fucose residues with α-anomeric configuration are commonly found in biologically important oligosaccharidic sequences, many antigen domains included.[1] Thus, a wide interest has been elicited toward the development of methodologies aimed at the α-stereoselective construction of this glycosidic linkage, a particularly difficult problem in oligosaccharide synthesis.[2] In fact, fucosyl donors are quite reactive and amenable to decomposition so that excess amounts are often required to achieve high glycosidation yields, especially with poorly reactive glycosyl acceptors.[2,3,4a] In addition, the α-fucosylation reactions lead to 1,2-*cis*-glycosides whose stereoselective construction cannot be guaranteed by an approach as efficient as the neighboring participation effect exerted by acyl protecting groups in position 2 in the stereocontrolled synthesis of 1,2-*trans*-glycosides.

To face these problems several tactics were described over the last years such as the use of the inverse procedure proposed by Schmidt with trichloroacetimidate donors,[5] or the adoption of fucosyl donors benzylated at the O-2 and acylated at O-3 and O-4. This latter strategy entails an increased number of steps for preparing the donor, but glycosidation yields are generally improved as the partially acylated donors appear relatively less prone to degradation than their perbenzylated counterparts,[2,6] and guarantee an improved α-selectivity because of the ability of O-4 acyl groups to give a long range participation effect. A good control of stereoselectivity can also be attained by procedures based on the 'in situ' generation of highly reactive β-glycosyl halides on which a mechanism of direct displacement can occur with alcoholic acceptors, although long reaction times are generally required.[7]

Recently, especially mild glycosidation promoters such as $LiClO_4$ have been tested to modulate the reactivity of some fucosyl donors (fucosyl trichloroacetimidates or fluorides). Moderate yields and selectivities were generally observed.[4]

In pursuing our investigations aimed at developing glycosylation procedures relying on convenient moisture stable promoters, we have recently reported[8] the feasible use of catalytic $Yb(OTf)_3$ for the activation of both armed and disarmed glycosyl trichloro-[9] and *N*-phenyltrifluoroacetimidates.[10] A good stereocontrol was achieved even with a perbenzylated glucosyl donor devoid of neighbouring participating groups through the appropriate choice of the reaction solvent. In particular, satisfying α-selectivities were obtained with secondary acceptors in ternary mixtures containing diethyl ether and dioxane.[8b,11] Even better results in terms of stereocontrol (exclusive formation of α-glucosides) were registered by using these mixtures in combination with an armed glucosyl trifluoroacetimidate equipped at 6-OH with the sterically bulky dimethoxytrityl group.[8c] Unfortunately this strategy cannot be directly applied to sugars deoxygenated at their primary position such as fucose. More recently, 4 Å acid washed molecular sieves (commercially known as AW 300 MS) were also found to efficiently activate glycosyl trihaloacetimidates, although in this case glycosidations did not exhibit a satisfying stereocontrol with donors devoid of participating groups.[12]

In order to expand the scope of these approaches to biologically relevant oligosaccharide sequences we have now investigated the feasible application of such promoters in the difficult task of α-fucosylations. For this purpose fucosyl *N*-(phenyl)trifluoroacetimidates **1** and **2** (Figure 1) were prepared by standard procedures. In order to reconcile this methodological investigation with the possibility to prepare useful disaccharide building blocks to be elaborated into structures of biological interest (such as the Lewis A, B, X, and Y sequences), secondary model acceptors **3**–**5** were chosen. Initial efforts were dedicated to the feasible synthesis of α-fucosides by adopting the readily prepared perbenzylated donor **1**. In this case the activation of $Yb(OTf)_3$ was examined in combination with α-directing solvents. Thus, several conditions were tested for the coupling of **1** with acceptor **3**, starting from

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those previously[8b] reported for a perbenzylated glucosyl donor [–10 °C to r.t., 0.1 equiv of $Yb(OTf)_3$, toluene/Et_2O/dioxane 4:1:1 as the solvent]. As shown in Table 1 (entries 1 and 2) fucosyl donor **1** proved to be reactive even at –30 °C in the presence of 0.1 equivalent of $Yb(OTf)_3$ and the ternary mixture dichloromethane/Et_2O/dioxane 4:1:1 represented the solvent of choice due to the best solubility of the acceptor at low reaction temperature. Under these conditions a good yield was achieved for disaccharide **6** together with a good control of stereoselectivity. The established conditions of activation were then tested in the α-fucosylation of the glucosamine acceptors **4** and **5**, and also in these cases synthetically useful results in terms of both yield and selectivity were smoothly obtained (entries 3 and 4). Encouraged by these results, some effort was dedicated to ascertain whether α-selective fucosylations might be achieved with the simple activation of acid washed molecular sieves taking advantage of a long range participation effect. For this purpose the activation of **2** was initially tested in the attempted fucosylation of acceptor **4**. As a matter of fact the reaction proceeded at room temperature in 24–36 hours to afford the desired disaccharide **9** in good yield and high α-selectivity. Both toluene and dichloroethane proved suitable solvents for this reaction, comparable results being obtained (entries 5 and 6). The procedure was then tested on acceptors **3** and **5** and afforded the corresponding disaccharides in good yield and notably high α-selectivity (entries 7 and 8). Having demonstrated the applicability of these alternative fucosylation protocols to the synthesis of several disaccharides, their extension to even more complex structures, containing less reactive fucosylation sites, was attempted.

We chose the Lewis X trisaccharide as a representative target to demonstrate the practical applicability of the reported procedures.[13] Thus, poorly reactive glucosamine acceptor **5** was initially β-galactosylated with donor **12**[8b] under the exclusive activation of acid washed molecular

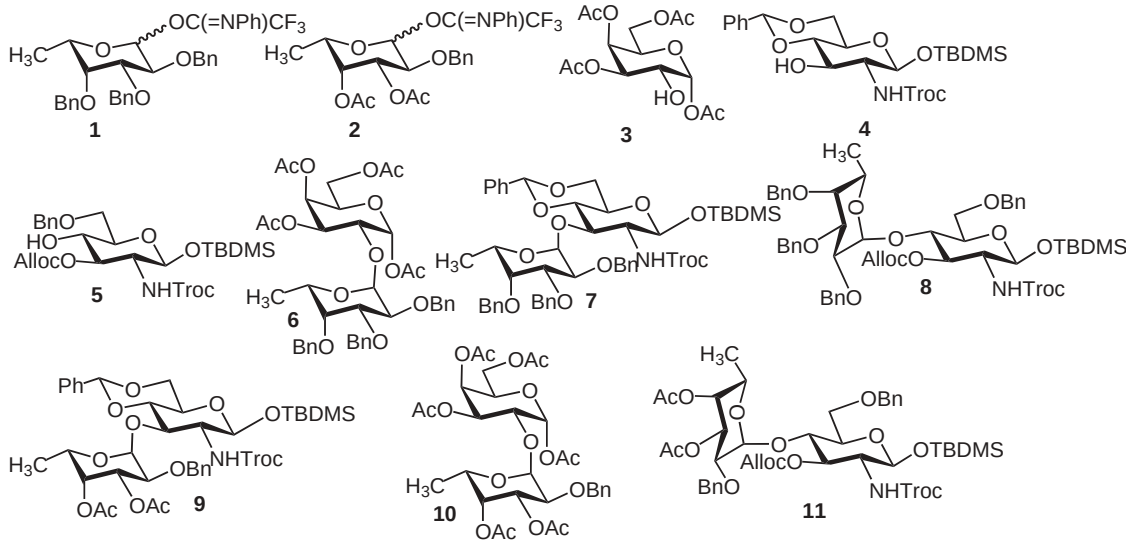
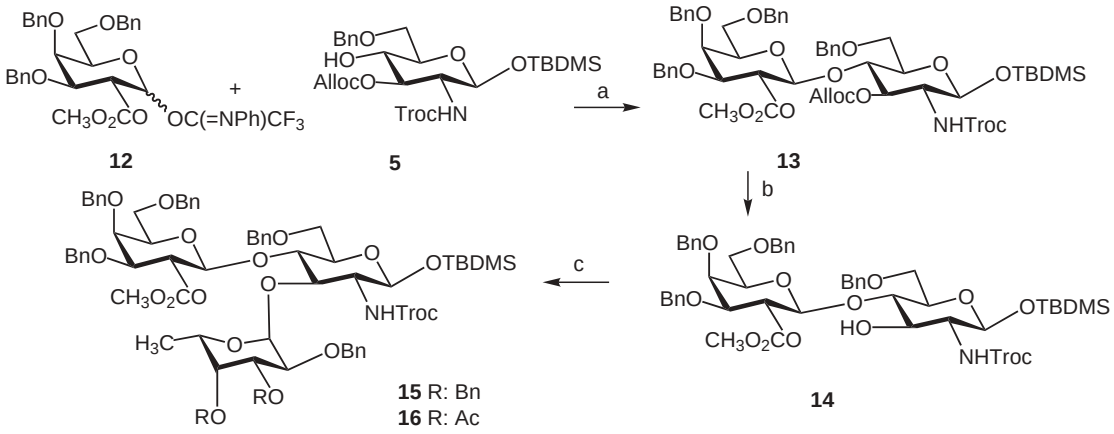


Figure 1

Table 1 α-Selective Fucosylation of Acceptors **3**–**5** under the Agency of $Yb(OTf)_3$ or 4 Å AW 300 MS

Entry	Donor (equiv)	Acceptor	Product	Solvent	Procedure[a]	Yield (%)	α:β
1	**1** (1.4)	**3**	**6**	4:1:1 toluene/Et_2O/dioxane	A	66	9:1
2	**1** (1.4)	**3**	**6**	4:1:1 CH_2Cl_2/Et_2O/dioxane	A	79	8:1
3	**1** (3.0)	**4**	**7**	4:1:1 CH_2Cl_2/Et_2O/dioxane	A	83	> 10:1
4	**1** (2.5)	**5**	**8**	4:1:1 CH_2Cl_2/Et_2O/dioxane	A	75	> 10:1
5	**2** (2.0)	**4**	**9**	Toluene	B	61	10:1
6	**2** (2.0)	**4**	**9**	Dichloroethane	B	66	10:1
7	**2** (2.0)	**3**	**10**	Dichloroethane	B	78	only α
8	**2** (2.0)	**5**	**11**	Toluene	B	58	only α

[a] Procedure A: $Yb(OTf)_3$ (0.1 equiv), 4 Å AW 300 MS, –30 °C, 1–3 h; Procedure B: 4 Å AW 300 MS, from 0 °C to r.t., 24–36 h.



Scheme 1 a) 4 Å AW 300 MS, dichloroethane, 24 h at 5 °C, 24 h at r.t., 76%; b) $Pd(PPh_3)_4$, dimedone, THF, 1.5 h at r.t., 70%; c) for **15**: donor **1** (3 equiv), procedure A as in Table 1, 81%; for **16** donor **2** (2.5 equiv), procedure B as in Table 1, 42%.

sieves in good yield (65–76%, Scheme 1). Disaccharide **13** was smoothly deprotected at position 3[14] of the glucosamine to provide acceptor **14** that was submitted to the fucosylation procedures previously established. Coupling with excess of **1** in the presence of catalytic $Yb(OTf)_3$ afforded the trisaccharide **15** in high yield and complete α-selectivity (81%). Remarkably, the synthesis of the Lewis X trisaccharide **16** based on the exclusive activation with AW MS in all the glycosidation steps turned out to be feasible although the final fucosylation proceeded in average yield (42%) but with complete selectivity.

In conclusion, in this paper we have reported the use of two alternative moisture stable and mild activating systems of *N*-phenyltrifluoroacetimidate donors for the stereocontrolled synthesis of α-fucosides. In a first approach catalytic $Yb(OTf)_3$ was found to provide good yields and α-selectivity in short reaction times when used in combination with solvent mixtures containing diethyl ether and dioxane.[15] In an alternative approach, synthetically useful results were achieved by activating a partially acylated fucosyl donor with AW 300 MS.[16] In this case a high stereocontrol could be obtained exploiting a long-range participation effect of the acyl groups installed at the fucose residues. Both these approaches were used in the synthesis of several fragments[17] contained in biologically interesting sequences, including the Lewis X trisaccharide. The results reported demonstrate that important oligosaccharidic sequences can be accessed by using promoters, which – in contrast to those adopted in standard glycosidation procedures – show moisture stability and remarkable mildness.

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(15) **Procedure A:** A mixture of acceptor (0.2 mmol) and donor **1** (see Table 1 for relative amounts) were coevaporated three times in anhyd toluene and the residue was kept under vacuum for 1 h. Acid washed molecular sieves (4 Å AW 300 MS, pellets, 200 mg) were then added and the mixture was dissolved at 0 °C with CH_2Cl_2 (2.8 mL), and Et_2O (700 μL). After cooling at –30 °C, a solution of $Yb(OTf)_3$ (12.5 mg, 0.02 mmol) in dioxane (700 μL) was added drop-wise. The mixture was kept under stirring at this temperature until complete consumption of the fucosyl donor (1–3 h, TLC) and then few drops of Et_3N were added. The mixture was filtered on a short pad of silica gel, concentrated, and the residue purified by silica gel chromatography (eluent: hexane/EtOAc mixtures).

(16) **Procedure B:** A mixture of acceptor (0.2 mmol) and donor **2** (see Table 1 for relative amounts) were coevaporated three times in anhyd toluene and the residue was kept under vacuum for 1 h. Acid washed molecular sieves (4 Å AW 300 MS, pellets, 1.5–2 g) were then added and the solvent (dichloroethane or toluene, 2–4 mL) was added at 0 °C. The mixture was kept at 0 °C under stirring for 30 min and then temperature was left to rise spontaneously. After complete consumption of the donor (24–36 h), the mixture was filtered through a cotton pad and concentrated. The residue was purified by silica gel chromatography (eluent: hexane/EtOAc mixtures).

(17) All compounds were identified by ^1H NMR and ^{13}C NMR analyses. Spectroscopic selected data of representative compounds are reported. Compound **15**: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.20 (aromatic protons), 5.10 (1 H, d, $J_{1,2}$ = 3.9 Hz, H-1 Fuc), 5.07 (1 H, d, $J_{1,2}$ = 8.2 Hz, H-1 GlcN), 5.03 (1 H, dd, $J_{1,2}$ = 7.4 Hz, $J_{2,3}$ = 10.2 Hz, H-2 Gal), 4.62 (1 H, d, H-1 Gal), 4.90–4.34 (17 H, Troc CH_2, 7 × benzyl CH_2 and H-5 Fuc), 4.18 (1 H, t, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3 GlcN), 4.04–3.26 (12 H, H-3 Gal, H-4 Gal, H-5 Gal, H_2-6 Gal, H-4 GlcN, H-5 GlcN, H_2-6 GlcN, H-2 Fuc, H-3 Fuc, and H-4 Fuc), 3.81 (3 H, s, -OCH_3), 3.03 (1 H, m, H-2 GlcN), 1.13 (3 H, d, $J_{5,6}$ = 6.2 Hz, H_3-6 Fuc), 0.86 [9 H, s, -$SiC(CH_3)_3$], 0.08 and 0.03 [6 H, 2 × s, -$Si(CH_3)_2$]. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.0 and 153.4 (-NH-CO-OCH_2CCl_3, -O-CO-OMe), 139.3, 139.2, 138.8, 138.6, 138.4, 137.9, and 137.8 (aromatic C), 128.8–127.0 (aromatic CH), 99.5, 97.3, and 94.4 (C-1 Gal, GlcN, Fuc), 95.1 (-NH-CO-OCH_2CCl_3), 55.0 (-OCH_3), 25.6 [-$SiC(CH_3)_3$], 17.9 [-$SiC(CH_3)_3$], 16.2 (C-6 Fuc), –4.2 and –5.3 [-$Si(CH_3)_2$]; other signals at δ = 80.9, 79.6, 78.8, 76.6, 76.0, 75.4, 75.0, 74.7, 73.8, 73.4, 73.2, 72.8, 72.4, 72.3, 68.2, 67.6, 66.4, 61.8. Compound **16**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.15 (aromatic protons), 5.27 (1 H, dd, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.2 Hz, H-3 Fuc), 5.21 (1 H, bd, H-4 Fuc), 5.15 (1 H, d, $J_{1,2}$ = 3.6 Hz, H-1 Fuc), 5.11 (1 H, d, $J_{1,2}$ = 7.8 Hz, H-1 GlcN), 5.00–4.96 (2 H, m, H-2 Gal and H-5 Fuc), 4.59 (1 H, d, $J_{1,2}$ = 8.0 Hz, H-1 Gal), 4.72–4.40 (12 H, Troc CH_2, 5 × benzyl CH_2), 4.20 (1 H, t, $J_{2,3}$ = $J_{3,4}$ = 9.4 Hz, H-3 GlcN), 3.98–3.28 (10 H, H-3 Gal, H-4 Gal, H-5 Gal, H_2-6 Gal, H-4 GlcN, H-5 GlcN, H_2-6 GlcN, and H-2 Fuc), 3.78 (3 H, s, -OCH_3), 2.91 (1 H, m, H-2 GlcN), 2.09 and 1.98 (6 H, 2 × s, 2 × acetyl CH_3), 0.93 (3 H, d, $J_{5,6}$ = 6.2 Hz, H_3-6 Fuc), 0.84 [9 H, s, -$SiC(CH_3)_3$], 0.06 and 0.01 [6 H, 2 × s, -$Si(CH_3)_2$]. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.4 and 169.4 (2 × -$COCH_3$), 155.1 and 154.0 (-NH-CO-CH_2CCl_3, -O-CO-OMe), 138.6, 138.3, 138.3, 138.1, and 138.1 (aromatic C), 129.0–127.2 (aromatic CH), 99.4, 97.5, 93.9 (C-1 Gal, GlcN, and Fuc), 55.0 (-OCH_3), 25.6 [-$SiC(CH_3)_3$], 20.9 and 20.7 (2 × -$COCH_3$), 17.9 [-$SiC(CH_3)_3$], 15.2 (C-6 Fuc), –4.2 and –5.3 [-$Si(CH_3)_2$]; other signals at δ = 80.5, 74.8, 74.6, 74.4, 73.6, 73.2, 73.1, 72.3, 72.0, 71.8, 70.3, 67.9, 67.8, 64.5, 61.8.