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# Highly Selective Formation of β-Glycosides of *N*-Acetylglucosamine Using Catalytic Iron(III) Triflate

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Efficient and highly selective glycosylation reactions of peracetylated β-D-*N*-acetylglucosamine are described using catalytic iron(III) triflate and 2,4,6-tri-*tert*-butylpyrimidine (TTBP) under microwave conditions. We have demonstrated that the formation of β-(1→6) and β-(1→3) linked disaccharides are obtained in high yields in the presence of various protecting groups.

## Introduction

Glycosylation with glycosyl acetate donors, one of the simplest methods, was earlier discovered by Helferich and Schmitz-Hillerbrecht.[1] It consists of a convenient direct anomeric oxygen exchange under a typical acid-catalyzed acetal formation reaction. This glycosylation method is particularly straightforward in comparison with numerous glycosylation methods.[2] *O*-Acetylglycosyl donors of glucopyranose, galactopyranose, *N*-acetylglucosamine, and *N*-acetylgalactosamine, examples of biorelevant hexoses, are easily accessible and were used earlier extensively in glycosylation reactions upon activation with various acidic activators, in most cases in stoichiometric amounts {recent uses of promoters: TfOH,[3] $Sc(OTf)_3$,[4] $Yb(OTf)_3$,[5] $Yb[N(Tf)_2]_3$,[6] [$BF_3$·$OEt_2$ + $Bi(OTf)_3$],[7] [TsOH + $Yb(OTf)_3$]}[8] and at high temperatures to form simple aryl or alkyl glycosides, disaccharides, and glycoconjugates. The α/β selectivity of the reactions depends on the nature of the promoter and the reaction conditions. Recently, stoichiometric cupric salts ($CuCl_2$, $CuBr_2$),[9] 30 mol-% $Yb(OTf)_3$,[10] 15 mol-% rare earth metal triflates [$Sc(OTf)_3$, $Sm(OTf)_3$, $La(OTf)_3$, $Dy(OTf)_3$, $Nd(OTf)_3$],[11] $H_2SO_4$/silica under microwave conditions,[12] and TsOH[13] were used as promotors in the synthesis of glycosides of *N*-acetylglucosamine (GlcNAc), directly or via the isolated oxazolines. Activation using $FeCl_3$ was also previously described for anomeric ester donors incorporating a C-2 amide functionality (*N*-acetyl-, *N*-phthaloyl-, *N*-(chloroacetyl)-glycosyl acetate donors)[14] through reactive oxazolinium cations, as for other non-C2-amide donors[15] having a C-2 ester participatory group. It involved the use of a large excess of both $FeCl_3$ and the glycosyl donors.[16] Numerous other β-selective glycosylation methods[2,17] have been developed using elaborated glucosamine donors possessing appropriate leaving groups at C-1 (trichloroacetimidate, phosphite, thio groups) and temporary participating groups[18] of the 2-amino function. The reactions generally proceeded at low temperatures with high yields but required separate steps for the introduction of the protecting groups and the post-coupling conversion to the 2-acetamido substituent found in natural products.

## Results and Discussion

Previous studies reported mild conditions by using triflates of rare earth metals.[2a,11] This development was based on the better Lewis acid properties of the catalysts, their ready availability, and their ease of handling. Iron has a number of advantages over other metals typically used in catalysis, as it is cheap, nontoxic, environmentally friendly, and abundant. Accordingly, an increasing number of publications describe novel applications of iron catalysts in organic synthesis.[19] In carbohydrate chemistry, iron(III) triflate has only been used for oxidative C–C bond cleavage[20] and the thioglycosylation of peracetylated glycosides.[21] In our recent effort to identify efficient and step-saving processes in carbohydrate chemistry,[22] we now present a glycosylation procedure using catalytic amounts of stable and nonhygroscopic $Fe(OTf)_3$·6.2DMSO[23] or $Fe(OTf)_3$ as new activators of the stable and commercially available glucosaminyl donor **1β**[24] or oxazoline **2**[25] easily prepared from **1** (Table 1).

In initial experiments, the glycosylation of menthol (**3**) or glucose derivative **4** was studied. $Fe(OTf)_3$ solvate (15 mol-%) efficiently catalyzed the exclusive formation of β-glycoside **5** in refluxing $CH_2Cl_2$ in 61% yield (Table 1,

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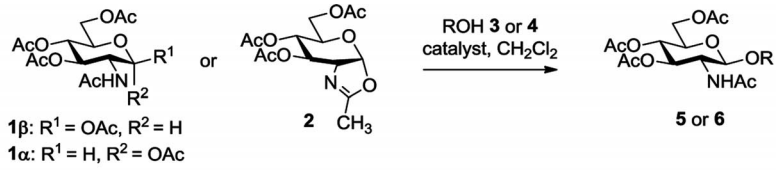
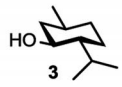
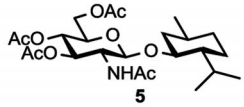
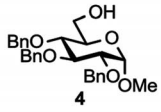
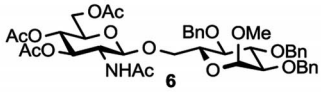
Table 1. Iron triflate catalyzed glycosylation of alcohols **3** and **4** with **1** and **2** under various conditions.




**1β**: $R^1$ = OAc, $R^2$ = H
**1α**: $R^1$ = H, $R^2$ = OAc

**2**

**5 or 6**

| Entry | Donor (D) | Acceptor (A) | Product | D/A | Conditions (mol-% catalyst) | Time [min] | Yield [%][f] |
|---|---|---|---|---|---|---|---|
| 1[a] | **1β** |  **3** |  **5** | 1:2 | A[a] (15) | 1440 | 61 |
| 2 | **1β** | **3** | **5** | 1:2 | B[b] (15) | 20 | 85 |
| 3 | **1α** | **3** | – | 1:2 | B[b] (15) | 20 | – |
| 4 | **1β** |  **4** |  **6** | 1:2 | B[b] (15) | 30 | 82 |
| 5 | **1β** | **4** | **6** | 2:1 | $Sc(OTf)_3$[c] (15) | 180 | 62 (75)[11a] |
| 6 | **1β** | **4** | **6** | 2:1 | B[b] (15) | 30 | 92 |
| 7 | **1β** | **4** | **6** | 2:1 | C[d] (15) | 30 | 90 |
| 8 | **1β** | **4** | **6** | 2:1 | $FeCl_3$[c] (15) | 30 | 31 |
| 9 | **1β** | **4** | **6** | 1:2 | D[e] (15) | 30 | 51 |
| 10 | **1β** | **4** | **6** | 2:1 | TfOH[c] (0.45 equiv.) | 30 | 47 |
| 11 | **1β** | **4** | **6** | 2:1 | TfOH[c] (0.45 equiv.), TTBP (2 equiv.) | 30 | 70 |
| 12 | **1β** | **4** | **6** | 2:1 | B[b] (15), TTBP (1 equiv.) | 45 | 76 |
| 13 | **1β** | **4** | **6** | 2:1 | B[b] (15), TTBP (2 equiv.) | 45 | 98 |
| 14 | **1β** | **4** | **6** | 2:1 | B[b] (5), TTBP (2 equiv.) | 45 | 66 |
| 15 | **2** | **4** | **6** | 2:1 | B[b] (15), TTBP (2 equiv.) | 30 | 99 |

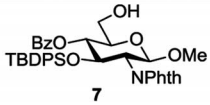
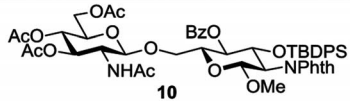
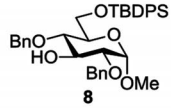
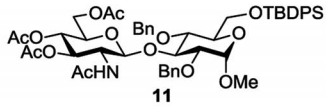
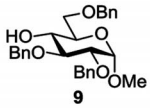
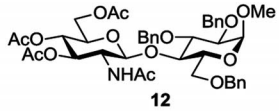
[a] A = $Fe(OTf)_3$·6.2DMSO in $CH_2Cl_2$ under reflux at 50 °C. [b] B = $Fe(OTf)_3$·6.2DMSO in $CH_2Cl_2$ under microwave irradiation at 80 °C. [c] In $CH_2Cl_2$ under microwave irradiation at 80 °C. [d] C = $Fe(OTf)_3$ in $CH_2Cl_2$ (microwave at 80 °C). [e] D = $Fe(NTf_2)_3$·6.2DMSO in $CH_2Cl_2$ (microwave at 80 °C). [f] Yield after silica gel chromatography.

Entry 1). Due to the low reactivity of the acetate donor, the reaction proceeded better under microwave irradiation[11] for this example and in all other following cases, with a more efficient and faster glycosylation (20 min, 85% yield compared to a 61% yield at reflux for 24 h; Table 1, Entries 1 and 2). The best catalytic charge of $Fe(OTf)_3$·6.2DMSO or $Fe(OTf)_3$ was 15 mol-% with an irradiation time varying between 20 and 45 min (Table 1, Entries 2, 6, 7, 13). The reagent[26] was far superior to $FeCl_3$, $Fe(NTf_2)_3$,[23] TfOH, or TfOH/TTBP (2,4,6-tri-*tert*-butylpyrimidine)[27] in the formation of glycoside **6** (92–90% vs. 31–70%; Table 1, Entries 6, 7 vs. 8–11) and compare well with the conditions of Jensen[11a] (62% in our hands; Table 1, Entry 5). The lower efficiency of TfOH (with or without the hindered base TTBP; Table 1, Entries 10 and 11) verify that the catalysis, although occurring at an acceptable level, is not only provided by the liberated acid in the course of the reaction (together with AcOH). No reaction occurred with more stable donor **1α** (Table 1, Entry 3). The addition of TTBP (2 equiv.) provided the optimized procedure to perform the glycosylation (98% yield of **6**; Table 1, Entry 13). Lowering the loading of catalyst to 5 mol-% (Table 1, Entry 14) or TTBP to 1 equiv. resulted in lower yields (66 and 76%, respectively; Table 1, Entry 12). Interestingly, under the optimized conditions, oxazoline **2** also gave disaccharide **6** in high yield (99%; Table 1, Entry 15). In a limited study, these conditions were extended to other glycosyl acceptors (Table 2). The use of TTBP allowed the glycosylation of a silylated acceptor (TBDPS protecting group, compound **7**[22e]), without degradation (Table 2, Entry 1). Formation of β-(1→3) linked disaccharide **11** was also obtained in 70% yield from donor **1β** and acceptor **8** (Table 2, Entry 2). The method was tested in the challenging synthesis of a β-1,4-glycosidic linkage between two D-glucopyranosyl units (Table 2, Entries 3 and 4). Under all the conditions attempted,[28] very moderate yields were obtained (20–25%), although with quantitative recovery of the acceptor (Table 2, Entry 3).

In the direct synthesis of β-glycopyranosides starting from *N*-acetylglucosamine derivatives, oxazoline **2** is generally considered as the intermediate, thus explaining the high β-stereoselectivity. Excellent results in the glycosylation of 6-OH acceptor **4** with oxazoline **2** would support this mechanism (Table 1, Entry 15). This possibility was, however, not corroborated by the glycosylation results of the less nucleophilic 4-OH acceptor **9** by **2** vs. β-acetate **1β** (13 vs. 20% yield; Table 2, Entry 5 vs. 3).

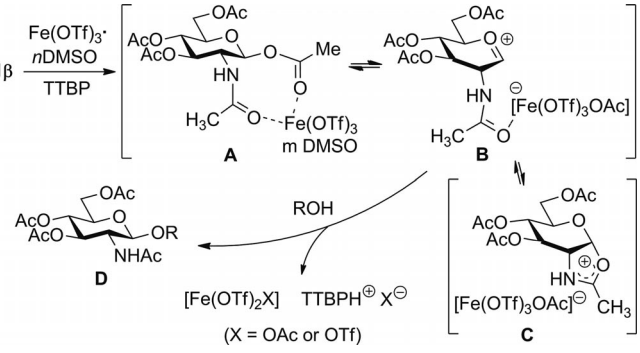
  

Table 2. Iron triflate catalyzed glycosylation using **1β** and **2** with $Fe(OTf)_3$·6.2DMSO (15 mol-%) and TTBP (2 equiv.) in $CH_2Cl_2$ under microwave irradiation at 80 °C.

| Entry | Donor (D) | Acceptor (A) | Product | D:A | Time [h] | Yield [%][a] |
|---|---|---|---|---|---|---|
| 1[a] | **1β** |  **7** |  **10** | 2:1 | 0.75 | 76 |
| 2 | **1β** |  **8** |  **11** | 2:1 | 1 | 70 |
| 3 | **1β** |  **9** |  **12** | 2:1 | 3 | 20 (100)[b] |
| 4 | **1β** | **9** | **12** | 4:1 | 16 | 25 |
| 5 | **2** | **9** | **12** | 2:1 | 3 | 13 |

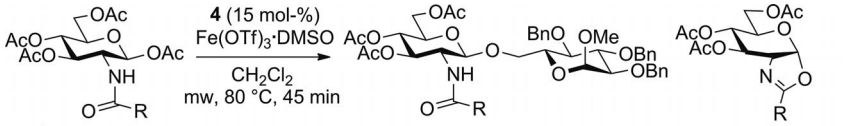
[a] Yield after silica gel chromatography. [b] Yield based on recovered acceptor. Donor was recovered as a mixture of anomers (**1α/1β** = 1:1; 24% combined yield).

Taking glycosylation of **4** under the optimized conditions (Table 1, Entry 13) as a reference test, further experiments with other D-glucosaminyl donors **13**–**15** were performed to clarify the mechanism (Table 3). Similarly to **1β**, tolylamide **13** provided expected glycoside **6**, whereas trichloroacetamide **14** and pivaloyl amide **15** were unexpectedly completely ineffective. Further, without the nucleophile, oxazolines **2**, **20**,[29] and **21** were not formed except for oxazoline **19** from tolylamide **13**. These experiments suggest that efficient glycosylation would not require the formation of the "mandatory" oxazolinium intermediate.[30] Preferably, glycosylation would necessitate not only the activation of the anomeric acetate but also effective precomplexation of the catalyst by a suitable amide group as found in **1β** (see **A**, Scheme 1) or **13**. Electronic (NHTCA, donor **14**) or steric (NHPiv, donor **15**) factors would prevent effective amide complexation of $Fe(OTf)_3$ and thus glycoside formation. Glycosylation from the β face, through α-ionic pair **B** from **1β** instead of oxazolinium ion **C**, would then be favored in the formation of glycoside **D**.




Scheme 1. Possible mechanism for the iron(III) triflate catalyzed glycosylation using 2-acetamido-2-deoxyglucosyl donor **1β**.

Table 3. Iron triflate catalyzed glycosylation of **4** using **1β** and **13**–**15** (2 equiv.) with $Fe(OTf)_3$·6.2DMSO (15 mol-%) in $CH_2Cl_2$ under microwave irradiation at 80 °C.




**1β**: R = $CH_3$; **13**: R = $PhCH_3$; **14**: R = $CCl_3$; **15**: R = $C(CH_3)_3$

**6**: R = $CH_3$; **16**: R = $PhCH_3$; **17**: R = $CCl_3$; **18**: R = $C(CH_3)_3$

**2**: R = $CH_3$; **19**: R = $PhCH_3$; **20**: R = $CCl_3$; **21**: R = $C(CH_3)_3$

| Entry | Donor | Acceptor | Product (% Yield)[a] |
|---|---|---|---|
| 1 | **1β** | **4** | **6** (98)[b] |
| 2 | **1β** | none | **1α/1β** (100)[c] |
| 3 | **13** | **4** | **16** (82)[b] |
| 4 | **13** | none | **19** (62)[b] |
| 5 | **14** | **4** | **17** (<5)[b] |
| 6 | **14** | none | nr[b,d] |
| 7 | **15** | **4** | nr[b,d] |

[a] Yield after silica gel chromatography. [b] Reaction performed in the presence of TTBP (2 equiv.). [c] **1β/1α** ratio of 4:1. [d] No reaction.

## Conclusions

We have developed a new catalytic procedure for the glycosylation of peracetylated β-*N*-acetylglucosamine using an inexpensive and environmentally friendly promoter system composed of iron(III) triflate and TTBP. It is highly effective in the direct synthesis of GlcNAc β-glycosides. This procedure should prove useful in the synthesis of bioactive oligosaccharides for biological research. Work is ongoing to study the detailed mechanism of the process.

## Experimental Section

**Typical Procedure for the Glycosylation:** Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**; 30 mg, 0.065 mmol), TTBP (32 mg, 0.129 mmol, 2 equiv.), and $Fe(OTf)_3$·6.2DMSO (9 mg, 0.010 mmol, 15 mol-%) were added to **1β** (50 mg, 0.129 mmol, 2 equiv.) in $CH_2Cl_2$ (1 mL). The reaction mixture was heated to 80 °C under microwave conditions for 45 min then poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3× 20 mL). The combined organic layers were washed with brine (10 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel (heptane/EtOAc, 8:2 to 4:6) to give **6** (50 mg, 98%) as an amorphous white solid.

**Supporting Information** (see footnote on the first page of this article): General methods, experimental procedures, characterization data, and copies of the $^1H$ NMR and $^{13}C$ NMR spectra of all new compounds.

## Acknowledgments

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[1] B. Helferich, E. Schmitz-Hillebrecht, *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 378–383.
[2] a) For a review see A. V. Demchenko (Ed.), *Handbook of Chemical Glycosylation*, Wiley-VCH, Weinheim, **2008**, pp. 116–122; b) for a recent discussion on the mechanism, see: L. K. Mydock, A. V. Demchenko, *Org. Biomol. Chem.* **2010**, *8*, 497–510.
[3] K. Sasaki, S. Matsumura, K. Toshima, *Tetrahedron Lett.* **2006**, *47*, 9039–9043.
[4] T. Yamanoi, Y. Oda, I. Yamazaki, M. Shinbara, K. Morimoto, S. Matsuda, *Lett. Org. Chem.* **2005**, *2*, 242–246.
[5] a) T. Yamanoi, I. Yamazaki, *Tetrahedron Lett.* **2001**, *42*, 4009–4011; b) for a review, see: S. Kobayashi, M. Sugiura, H. Kitagawa, W. W. L. Lam, *Chem. Rev.* **2002**, *102*, 2227–2302.
[6] T. Yamanoi, S. Nagayama, H. Ishida, J. Nishikido, T. Inazu, *Synth. Commun.* **2001**, *31*, 899–903.
[7] K. Ikeda, Y. Torisawa, T. Nishi, J. Minamikawa, K. Tanaka, M. Sato, *Bioorg. Med. Chem.* **2003**, *11*, 3073–3076.
[8] F. Ponticelli, A. Trendafilova, M. Valoti, S. Saponara, G. Sgaragli, *Carbohydr. Res.* **2001**, *330*, 459–468.
[9] V. Wittmann, D. Lennartz, *Eur. J. Org. Chem.* **2002**, 1363–1367.
[10] C. F. Crasto, G. B. Jones, *Tetrahedron Lett.* **2004**, *45*, 4891–4894.
[11] a) H. Christensen, M. S. Christiansen, J. Petersen, H. H. Jensen, *Org. Biomol. Chem.* **2008**, *6*, 3276–3283; b) J. Krag, M. S. Christiansen, J. G. Petersen, H. H. Jensen, *Carbohydr. Res.* **2010**, *345*, 872–879.
[12] S. Mandal, N. Sharma, B. Mukhopadhyay, *Synlett* **2009**, 3111–3114.
[13] Y. Cai, C.-C. Ling, D. R. Bundle, *Org. Lett.* **2005**, *7*, 4021–4024.
[14] a) M. Kiso, L. Anderson, *Carbohydr. Res.* **1985**, *136*, 309–323; b) F. Dasgupta, L. Anderson, *Carbohydr. Res.* **1990**, *202*, 239–255.
[15] a) S. K. Chatterjee, P. Nuhn, *Chem. Commun.* **1998**, 1729–1730; b) S. Koto, M. Hirooka, T. Tashiro, M. Sakashita, M. Hatachi, T. Kono, M. Shimizu, N. Yoshida, S. Kurasawa, N. Sakuma, S. Sawazaki, A. Takeuchi, N. Shoya, E. Nakamura, *Carbohydr. Res.* **2004**, *339*, 2415–2424; c) J. Seibel, L. Hillringhaus, R. Moraru, *Carbohydr. Res.* **2005**, *340*, 507–511.
[16] G. H. Wei, X. Lv, Y. U. Du, *Carbohydr. Res.* **2008**, *343*, 3096–3099.
[17] X. Zhu, R. R. Schmidt, *Angew. Chem.* **2009**, *121*, 1932; *Angew. Chem. Int. Ed.* **2009**, *48*, 1900–1934.
[18] For a review, see: A. F. G. Bongat, A. V. Demchenko, *Carbohydr. Res.* **2007**, *342*, 374–406.
[19] a) A. Correa, O. G. Mancheno, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108–1117; b) E. B. Bauer, *Curr. Org. Chem.* **2008**, *12*, 1341–1369; c) S.-K. Xiang, L.-H. Zhang, N. Jiao, *Chem. Commun.* **2009**, 6487–6489.
[20] S. Ichikawa, I. Tomita, A. Hosaka, T. Sato, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 513–520.
[21] S. S. Weng, *Tetrahedron Lett.* **2009**, *50*, 6414–6417.
[22] a) N. Grenouillat, B. Vauzeilles, J. J. Bono, E. Samain, J.-M. Beau, *Angew. Chem.* **2004**, *116*, 4744; *Angew. Chem. Int. Ed.* **2004**, *43*, 4644–4646; b) S. Zameo, B. Vauzeilles, J.-M. Beau, *Angew. Chem.* **2005**, *117*, 987; *Angew. Chem. Int. Ed.* **2005**, *44*, 965–969; c) A. Malapelle, Z. Abdallah, G. Doisneau, J.-M. Beau, *Angew. Chem.* **2006**, *118*, 6162; *Angew. Chem. Int. Ed.* **2006**, *45*, 6016–6020; d) A. Français, D. Urban, J.-M. Beau, *Angew. Chem.* **2007**, *119*, 8816; *Angew. Chem. Int. Ed.* **2007**, *46*, 8662–8665; e) A. Stevenin, F.-D. Boyer, J.-M. Beau, *J. Org. Chem.* **2010**, *75*, 1783–1786; f) J.-F. Soulé, A. Mathieu, S. Norsikian, J.-M. Beau, *Org. Lett.* **2010**, *12*, 5322–5325; g) Y. Bourdreux, A. Lemetais, D. Urban, J.-M. Beau, *Chem. Commun.* **2011**, *47*, 2146–2148.
[23] It is easily obtained by oxidative dissolution of iron powder in DMSO under an atmosphere of $O_2$ at atmospheric pressure in the presence of triflic acid: S. Antoniotti, E. Duñach, *Chem. Commun.* **2008**, 993–995; see the Supporting Information.
[24] β-D-GlcNAc tetraacetate (**1β**) was prepared on a large scale by *N*-acetylation using $Ac_2O$ in pyridine from the β-D-glucosaminylammonium chloride tetraacetate (90%): H. Myszka, D. Bednarczyk, M. Najder, W. Ç. Kaca, *Carbohydr. Res.* **2003**, *338*, 133–141.
[25] S. Nakabayashi, C. D. Warren, R. W. Jeanloz, *Carbohydr. Res.* **1986**, *150*, C7–C10.
[26] Due to the cost of $Fe(OTf)_3$ (≈27 €/g) and the simplicity to obtain large quantities of $Fe(OTf)_3$·6.2DMSO by the method of Antoniotti and Duñach[23] (≈4 €/g), we performed the glycosylation reactions with this last reagent.
[27] D. Crich, M. Smith, Q. J. Yao, J. Picione, *Synthesis* **2001**, 323–326.
[28] This included changes in solvent, additives, or concentration.
[29] Trichloroacetamide **14** is well known for its efficiency as a β-glycosyl donor through the formation of oxazoline **20**: G. Blatter, J.-M. Beau, J.-C. Jacquinet, *Carbohydr. Res.* **1994**, *260*, 189–202.
[30] For previous work suggesting that glycosylation with certain 2-acetamido-2-deoxy donors does not proceed via an oxazolinium intermediate, see: a) A. Lubineau, J. L. Gallic, A. Malleron, *Tetrahedron Lett.* **1987**, *28*, 5041–5044; b) R. Arihara, S. Nakamura, S. Hashimoto, *Angew. Chem.* **2005**, *117*, 2285; *Angew. Chem. Int. Ed.* **2005**, *44*, 2245–2249.

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