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Construction of Interglycosidic N–O Linkage via Direct Glycosylation of Sugar Oximes

Jun Yu,[†] Jiansong Sun,*[,‡] and Biao Yu*[,‡]

Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, China, and State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

jssun@mail.sioc.ac.cn; byu@mail.sioc.ac.cn

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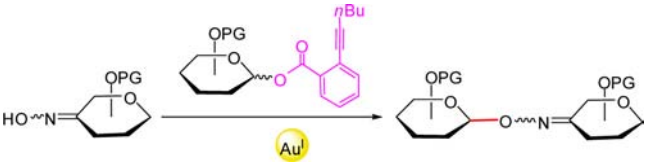
ABSTRACT



Direct glycosylation of sugar oximes and HONHFmoc has been realized for the first time by using glycosyl *ortho*-hexynylbenzoates as donors under the catalysis of PPh_3AuOTf, providing an effective approach to the synthesis of N–O linked saccharides, which are of great biological interest.

The peculiar three-bond glycosidic –N–O– linkage is a prominent structural feature of calicheamicin-esperamicin antibiotics,[1,2] providing a conformational control element that allows selective binding of the antibiotics to specific DNA sequences.[3,4] Heroic efforts toward the synthesis of this type of saccharide and the intact antibiotics have led to three alternatives for the construction of this important glycosidic linkage (Scheme 1).[5–7] The first approach employs condensation of glycosyloxyamine **A** with sugar ketone **B** to provide oxime disaccharide **C** which is then subjected to reduction to afford the target disaccharide **F**.[5] The second one applies S_N2 displacement of a sugar trifluoromethanesulfonate **E** with the sodium salt of glycosyl urethane **D**, and a removal of the *N*-COOEt group, to furnish disaccharide **F**.[6] The third alternative employs glycosylation of sugar nitrone **H** with a glycosyl bromide or trichloroacetimidate **G** and subsequent removal of the resulting *N*,*O*-benzylidene group to provide disaccharide **F**.[7] However, an obvious approach to the construction of the interglycosidic N–O linkage would be via the direct glycosylation of sugar oximes (i.e., **2a**).

[†] University of Science and Technology of China.
[‡] Chinese Academy of Sciences.

(1) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

(2) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

(3) Walker, S.; Cange, D.; Gupta, V.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 3197.

(4) For example, see: (a) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198. (b) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697. (c) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888. (d) Walker, S.; Landovitz, R.; Ding, W. D.; Ellestad, G. A.; Kahne, D. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 4608.

(5) (a) Nicolaou, K. C.; Groneberg, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4085. (b) Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W.; Schreiner, E. P.; Suzuki, T.; Iwabuchi, Y.; Smith, A. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7593. (c) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625.

(6) (a) Yang, D.; Kim, S.-H.; Kahne, D. *J. Am. Chem. Soc.* **1991**, *113*, 4715. (b) Halcomb, R. L.; Wittman, M. D.; Olson, S. H.; Danishefsky, S. J.; Golik, J.; Wong, H.; Vyas, D. *J. Am. Chem. Soc.* **1991**, *113*, 5080.

(7) (a) Bamhaoud, T.; Lancelin, J.-M.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1992**, 1494. (b) Da Silva, E.; Prandi, J.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1994**, 2127. (c) Moutel, S.; Prandi, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 305.

(8) Glycosylation of isatine 3-oximes with α-D-glucosaminyl chloride peracetate under phase transfer conditions was reported; see: Kuryanov, V. O.; Chupakhina, T. A.; Shapovalova, A. A.; Katsev, A. M.; Chirva, V. Ya. *Russ. J. Bioorg. Chem.* **2011**, *37*, 231.

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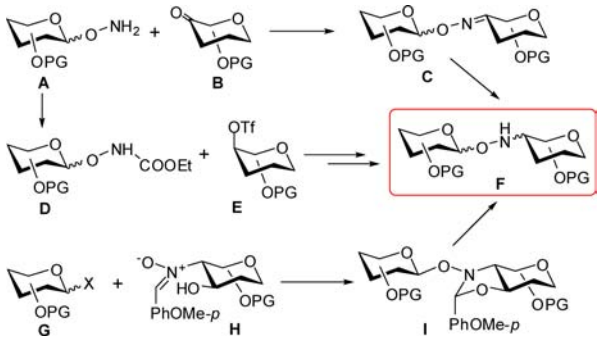
Scheme 1. Known Approaches to the Synthesis of the N–O Linked Saccharides

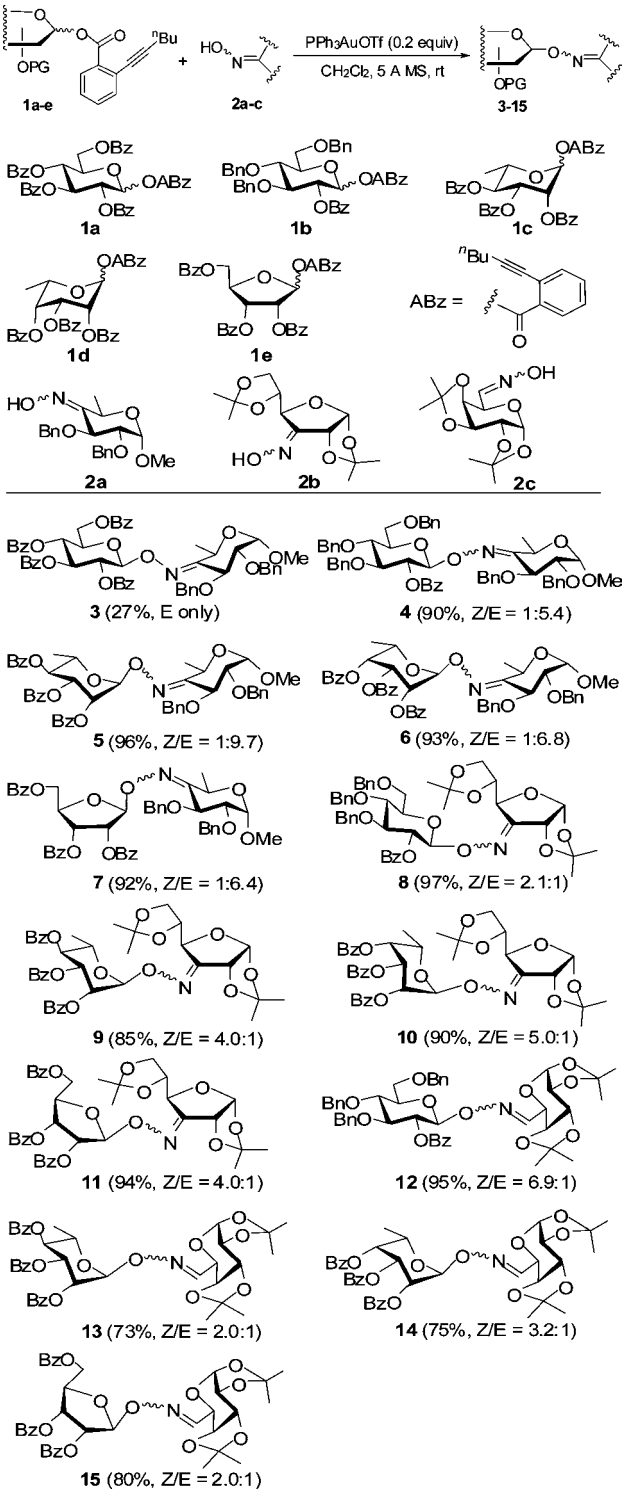


To date, this approach has never been accomplished,[7a,8] due to the lability of the oximes toward the Lewis acids required for the glycosylation reaction. In this regard, the newly developed glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors, and a gold(I) complex as the catalyst, which performs under neutral conditions might solve this problem.[9,10]

The glycosylation of 6-deoxy-glucopyranoside 4-oxime **2a** was first examined, which failed to be glycosylated previously,[7a] with perbenzoyl glucopyranosyl *ortho*-hexynylbenzoate **1a**[9] (1.2 equiv) under standard conditions (0.2 equiv of PPh_3AuOTf, 5 Å MS, CH_2Cl_2, rt) (Scheme 2). The reaction led to the desired disaccharide **3**(*E*) in 27% yield as a single isomer, with the major product being the corresponding orthoester. Thus, more reactive glucopyranosyl *ortho*-hexynylbenzoate **1b**, which is equipped with a super-armed protecting pattern,[11] was used as a glycosyl donor to couple with **2a**. Under identical conditions, disaccharide **4** was obtained in a high 90% yield as a pair of the *Z*/*E* isomers (*Z*/*E* = 1:5.4). Similarly, the 6-deoxy perbenzoyl pyranose donors, L-rhamnosyl and L-talosyl *ortho*-hexynylbenzoates **1c** and **1d**, coupled with **2a** to provide the corresponding disaccharides **5** (96%, *Z*/*E* = 1:9.7) and **6** (93%, *Z*/*E* = 1:6.8) in excellent yields in favor of the *E* isomers. In addition, perbenzoyl D-ribosyl *ortho*-hexynylbenzoate **1e**, a furanose donor, was also shown to be suitable for direct glycosylation of **2a**, providing disaccharide **7** cleanly (92%, *Z*/*E* = 1:6.4).

The reaction scope was further investigated with 1,2;5,6-di-*O*-isopropylidene glucofuranoside 3-oxime **2b**[12] and 1,2;3,4-di-*O*-isopropylidene galactopyranoside **2c**[13] as

Scheme 2. Direct Glycosylation of Sugar Oximes (**2a**–**c**) with Glycosyl *ortho*-Hexynylbenzoates (**1a**–**e**)



acceptors. The glycosylation of furanose oxime **2b** with donors **1b**–**1e** proceeded smoothly under standard conditions, affording the desired disaccharides **8**–**11** in excellent yields (85%–97%). In contrast to the previous reaction with oxime **2a** as the acceptor, the coupling with **2b** favored the formation of the *Z* isomer (*Z*/*E* = 2.1:1 to 5.0:1). Under

(9) (a) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604. (b) Li, Y.; Yang, X. Y.; Liu, Y. P.; Zhu, C. S.; Yang, Y.; Yu, B. *Chem.—Eur. J.* **2010**, *16*, 1871. (c) Zhu, Y.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 8329.

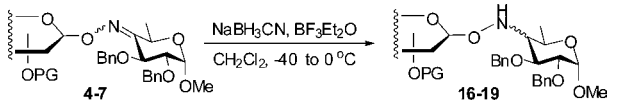
(10) For glycosylation of acid labile substrates with *ortho*-alkynylbenzoates, see: (a) Yang, W.; Sun, J.; Lu, W.; Li, Y.; Shan, L.; Han, W.; Zhang, W.-D.; Yu, B. *J. Org. Chem.* **2010**, *75*, 6879. (b) Li, Y.; Sun, J.; Yu, B. *Org. Lett.* **2011**, *13*, 5508. (c) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 4933.

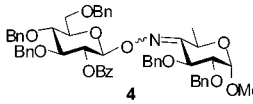
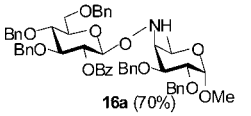
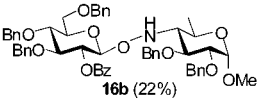
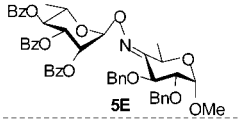
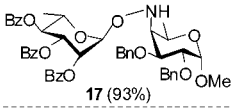
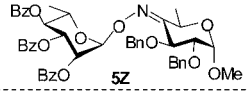
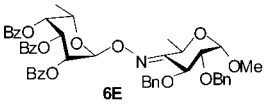
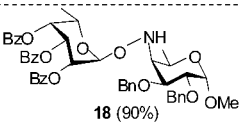
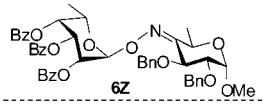
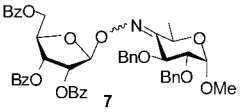
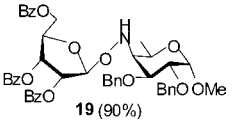
(11) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2107.

(12) (a) Tronchet, J. M. J.; Habashi, F.; Fasel, J.-P.; Zosimo-Landolfo, G.; Barbalat-Rey, F.; Moret, G. *Helv. Chim. Acta* **1986**, *69*, 1132. (b) Hall, A.; Bailey, P. D.; Rees, D. C.; Rosair, G. M.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 329.

(13) Mishra, R. C.; Tewari, N.; Verma, S. S.; Tripathi, R. P.; Kumar, M.; Shukla, P. K. *J. Carbohydr. Chem.* **2004**, *23*, 353.

Table 1. Stereoselective Reduction of Oxime Disaccharides **4**–**7**



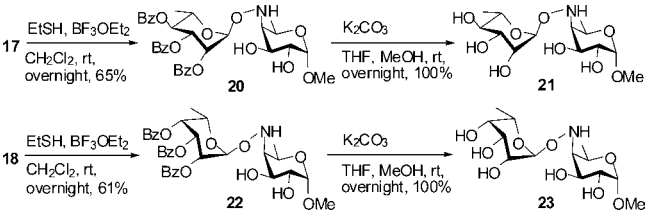
entry	oxime disaccharide	product (isolated yield)
1	 **4**	 **16a** (70%)  **16b** (22%)
2	 **5E**	 **17** (93%)
3	 **5Z**	**17** (86%)
4	 **6E**	 **18** (90%)
5	 **6Z**	**18** (85%)
6	 **7**	 **19** (90%)

similar conditions, the glycosylation of aldehyde oxime **2c** led to disaccharides **12**–**15** in slightly lower yields (73%–95%) in favor of the *Z* isomer (*Z*/*E* = 2.0:1 to 6.9:1). Clearly, the *Z*/*E* outcome of the present reaction is mainly determined by the structure of the coupling oximes. Interconversion between the coupled disaccharide *Z*/*E* isomers was not found during purification, structure analysis, and storage.

The *Z*/*E* geometries of the oxime disaccharides (i.e., **3**–**7**) derived from **2a** were determined by the diagnostic quartet H5 signals of the acceptor residue.[14] The H5 signal in a *Z* isomer appears at δ 4.60–4.70 ppm (in $CDCl_3$), while in the *E* counterpart it appears evidently downfield (δ ~5.0 ppm) due to the shielding of the proximal donor residue. This conclusion is validated by the X-ray diffraction of **6Z**, whose H5 signal appears at δ 4.65–4.70 ppm. The *Z*/*E* geometries of the oxime disaccharides **8**–**11** were assigned according to the chemical shift of H4 in the acceptor (**2b**) residue. The H4 signal appeared at δ 4.7–4.9 ppm (in $CDCl_3$) for the *Z* isomer, while it appears above δ 4.9 ppm for the *E* counterpart due to the shielding effect of the donor residue. This assignment is in good

(14) Renaudet, O.; Dumy, P. *Tetrahedron* **2002**, *58*, 2127.

Scheme 3. Deprotection of the Benzyl and Benzoyl Groups in the Presence of the Interglycosidic N–O Linkage



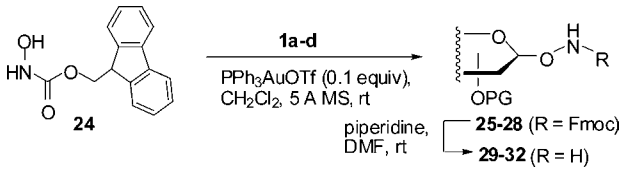
accordance with the determination of the *Z*/*E* isomer of acceptor **2b** (*Z*/*E* = 4.5:1, H4 of the *Z* isomer: δ 4.70 ppm; H4 of the *E* isomer: δ 5.19 ppm, in $CDCl_3$)[12b] and is further corroborated by the X-ray diffraction of compound **8E**. The *Z*/*E* isomers of disaccharides **12**–**15** were discriminated by the imino H6 signals. The H6 signal in an *E* isomer appears at > δ 7.0 ppm with a *J*-value > 6.0 Hz, while the H6 in the Z counterpart is < δ 7.0 ppm with *J*-value < 5.0 Hz. Such an assignment has been applied in the determination of the *Z*/*E* isomer of acceptor **2c** (*Z*/*E* = 1.2:1).[13]

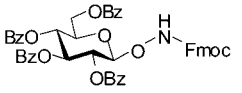
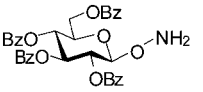
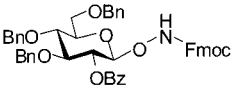
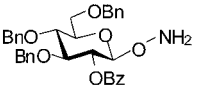
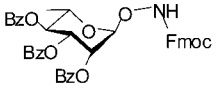
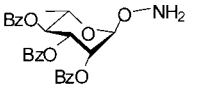
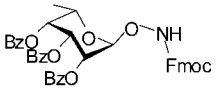
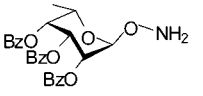
The interglycosidic oxime C=N bond has been reduced with borane complexes (e.g, $BH_3 \cdot Et_3N$)[5a,14] or $NaBH_3CN$,[5b,c] and the stereoselectivity of the reduction is largely dependent on the oxime sugar unit.[5,14] The reduction of disaccharides **4**–**7** bearing a methyl 2,3-di-*O*-benzyl-6-deoxy-α-D-gluco/galactopyranoside 4-oxime unit with $NaBH_3CN$/$BF_3 \cdot Et_2O$ (CH_2Cl_2, −40 to 0 °C) was examined, and the results are shown in Table 1. Thus, reduction of oxime disaccharide **4** led to the N–O linked galactose derivative **16a** (70%) and glucose derivative **16b** (22%) in an excellent overall yield (entry 1). The configurations of the resulting C4-amino group in **16a** and **16b** were easily identified by the H4 NMR signal (H4 in **16a**: δ 3.97 ppm, dd, $J_{3,4}$ = 5.2 Hz; H4 in **16b**: δ 4.12 ppm, dd, $J_{3,4}$ = 10.0 Hz; in $CDCl_3$). Reduction of oximes **5E** and **5Z** afforded the galactose derivative **17** in 93% and 86% yield, respectively, without detection of the corresponding glucose diastereoisomer (entries 2 and 3). Similar results were attained with the pair **6E** and **6Z** as the substrates (entries 4 and 5); the galactose diastereoisomer **18** was isolated in high yield (90% and 85%, respectively). Treatment of oxime disaccharide **7** (*Z*/*E* = 1:6.4) under similar conditions also afforded only the galactose derivative **19** in 90% yield (entry 6). These results demonstrate clearly that the stereoselectivity of the present reduction is independent of the geometry of the oxime and its *O*-substituted sugar residue.

An additional concern was the feasibility of removal of the benzyl and benzoyl groups in the presence of the interglycosidic N–O linkage. Although there is a precedent,[15] subjection of **17** or **18** to hydrogenolysis (over Pd/C, $Pd(OH)_2$/C, or Raney Ni) led unavoidably to cleavage of the N–O linkage. Fortunately, the benzyl groups in **17**/**18** could be removed selectively with $EtSH/BF_3 \cdot OEt_2$

(15) Hornyák, M.; Sztaricskai, F.; Pelyvás, I. F.; Batta, G. *Carbohydr. Res.* **2003**, *338*, 1787.

Table 2. Efficient Preparation of Glycosyloxyamines



entry	donor	sugar-ONHFmoc	sugar-ONH$_2$
1	**1a**	 **25** (62%)	 **29** (78%)
2	**1b**	 **26** (88%)	 **30** (88%)
3	**1c**	 **27** (80%)	 **31** (84%)
4	**1d**	 **28** (72%)	 **32** (80%)

(CH_2Cl_2, rt, overnight, 61% and 65%; Scheme 3).[16,17] The remaining benzoyl groups were then cleaved cleanly with K_2CO_3 in MeOH/THF (rt, 100%).

As mentioned, glycosyloxyamines (**A**) are key precursors in the previous syntheses of glycosidic N−O linkages (Scheme 1). In addition, glycosyloxyamines have been used effectively for attaching glycans onto proteins/lipids bearing a ketone/aldehyde group under bioorthogonal conditions.[18]

The preparation of glycosyloxyamines has employed glycosylation of *N*-hydroxy-succinimide,[19] HONPhth,[5,20] and *N*-pentenoyl hydroxamate[18c] under a variety of the glycosylation reactions, followed by removal of the *N*-protecting groups. Considering the mild glycosylation conditions in the present oxime glycosylation, we envisioned the use of *N*-Fmoc-hydroxylamine **24**[21] as the coupling acceptor to ensure a mild and selective removal of the *N*-Fmoc group afterward to liberate the glycosyloxyamines. Expectedly, subjection of **24** to glycosylation with glycosyl *ortho*-hexynylbenzoates **1a**−**d** (1.2 equiv) (0.1 equiv of PPh_3AuOTf, 5 Å MS, CH_2Cl_2, rt) led to the desired glycosides **25**−**28** in good 62−88% yields (Table 2).[17] Subsequent removal of the *N*-Fmoc group in **25**−**28** with piperidine (DMF, rt) met with no difficulty, affording the desired glycosyloxyamines **29**−**32** in high yield (78%−88%),[17] with the anomeric configuration unchanged.

In summary, direct glycosylation of sugar oximes has been realized for the first time by using glycosyl *ortho*-hexynylbenzoates as donors under catalysis by PPh_3AuOTf. Reduction of the resulting oxime with $NaBH_3CN/BF_3\cdot Et_2O$ leads to the N−O linked saccharides stereoselectively. Glycosylation of HONHFmoc has also been achieved under similar conditions, providing glycosyloxyamines conveniently after an easy removal of the *N*-Fmoc group. These results shall facilitate greatly the synthesis of N−O linked saccharides, which are of considerable interest in biomedical studies.

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Supporting Information Available. Experimental details, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) See Supporting Information. The crystallographic data for compounds **6Z** and **8E** (CCDC 875774 and 876961) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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