ORGANIC LETTERS

2012
Vol. 14, No. 15
4022–4025

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

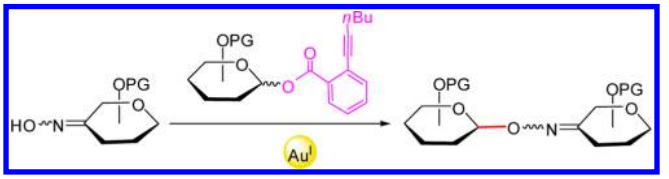
Jun Yu,[†] Jiansong Sun,*[,‡] and Biao Yu*[,‡]

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

Received July 6, 2012

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.

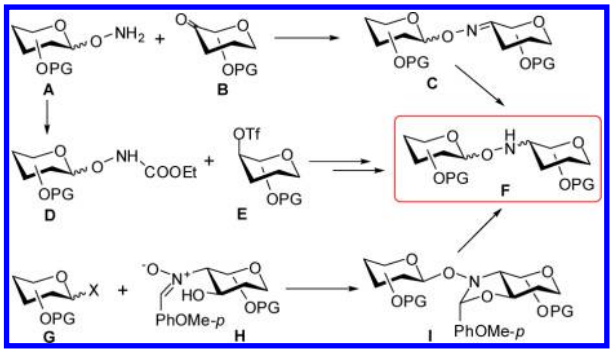
(6) (a) Yang, D.; Kim, S.-H.; Kahne, D. *J. Am. Chem. Soc.* **1991**, *113*, 4715. (b) Halcomb, R. L.; Wittman, M. D.; Olson, S. H.; Danishefsky, S. J.; Golik, J.; Wong, H.; Vyas, D. *J. Am. Chem. Soc.* **1991**, *113*, 5080.

(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.

10.1021/ol301863j
Published on Web 07/25/2012

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

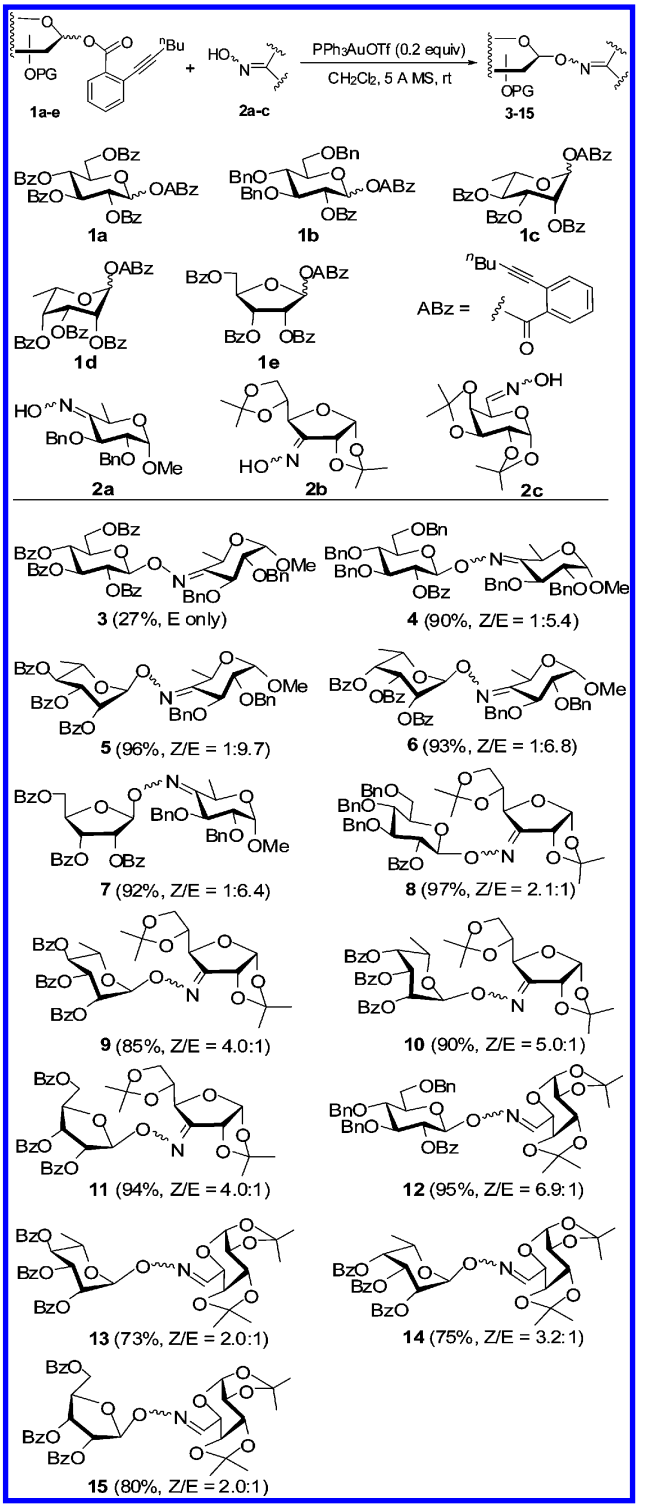


To date, this approach has never been accomplished,[7a,8] due to the lability of the oximes toward the Lewis acids required for the glycosylation reaction. In this regard, the newly developed glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors, and a gold(I) complex as the catalyst,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

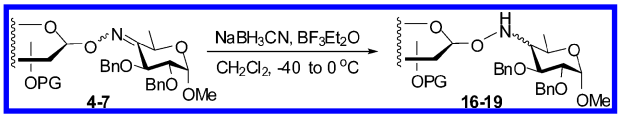
(10) For glycosylation of acid labile substrates with *ortho*-alkynylbenzoates, see: (a) Yang, W.; Sun, J.; Lu, W.; Li, Y.; Shan, L.; Han, W.; Zhang, W.-D.; Yu, B. *J. Org. Chem.* **2010**, *75*, 6879. (b) Li, Y.; Sun, J.; Yu, B. *Org. Lett.* **2011**, *13*, 5508. (c) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang,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

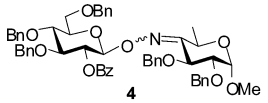
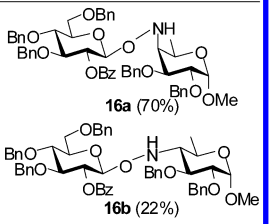
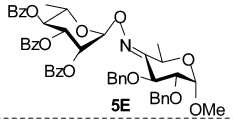
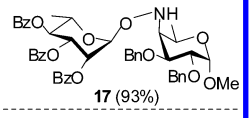
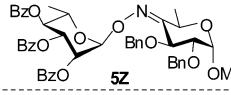
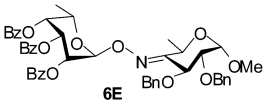
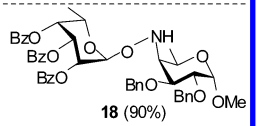
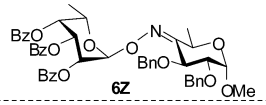
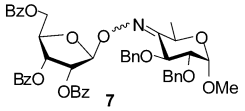
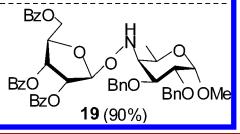
(11) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2107.

(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**



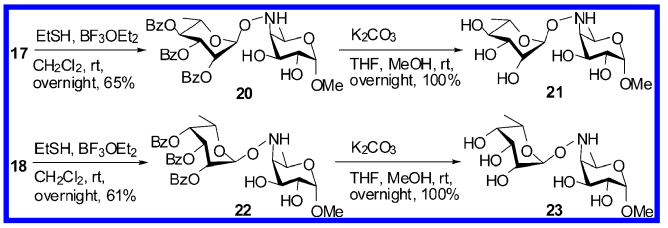
entry	oxime disaccharide	product (isolated yield)
1	 **4**	 **16a** (70%) **16b** (22%)
2	 **5E**	 **17** (93%)
3	 **5Z**	**17** (86%)
4	 **6E**	 **18** (90%)
5	 **6Z**	**18** (85%)
6	 **7**	 **19** (90%)

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



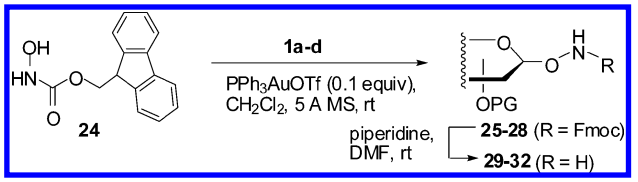
accordance with the determination of the *Z*/*E* isomer of acceptor **2b** (*Z*/*E* = 4.5:1, H4 of the *Z* isomer: δ 4.70 ppm; H4 of the *E* isomer: δ 5.19 ppm, in $CDCl_3$)[12b] and is further corroborated by the X-ray diffraction of compound **8E**. The *Z*/*E* isomers of disaccharides **12**–**15** 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]

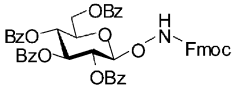
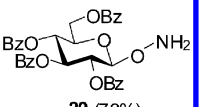
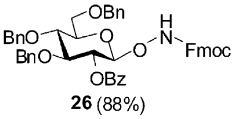
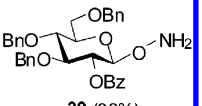
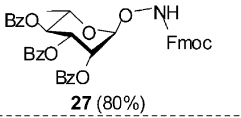
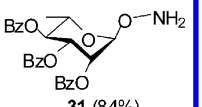
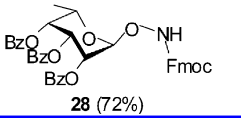
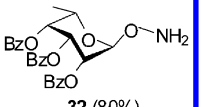
The interglycosidic oxime C=N bond has been reduced with borane complexes (e.g, $BH_3 \cdot Et_3N$)[5a,14] or $NaBH_3CN$,[5b,c] and the stereoselectivity of the reduction is largely dependent on the oxime sugar unit.[5,14] The reduction of disaccharides **4**–**7** bearing a methyl 2,3-di-*O*-benzyl-6-deoxy-α-D-gluco/galactopyranoside 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.

Acknowledgment. This work was financially supported by the Ministry of Science and Technology of China (2012ZX09502-002) and the National Natural Science Foundation of China (20932009 and 20921091).

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.

(16) Daly, S. M.; Armstrong, R. W. *Tetrahedron Lett.* **1989**, *30*, 5713.

(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.

(18) For example, see: (a) Rodriguez, E. C.; Winans, K. A.; King, D. S.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 9905. (b) Rodriguez, E. C.; Marcaurelle, L. A.; Bertozzi, C. R. *J. Org. Chem.* **1998**, *63*, 7134. (c) Hudak, J. E.; Yu, H. H.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2011**, *133*, 16127. (d) Chen, W.; Xia, C.; Cai, L.; Wang, P. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3859.

(19) Andersson, M.; Oscarson, S. *Glycoconjugate J.* **1992**, *9*, 122. (b) Cao, S.; Tropper, F. D.; Roy, R. *Tetrahedron* **1995**, *51*, 6679. (c) Andreana, P. R.; Xie, W.; Cheng, H. N.; Qiao, L.; Murphy, D. J.; Gu, Q.-M.; Wang, P. G. *Org. Lett.* **2002**, *4*, 1863.

(20) (a) Grochowski, E.; Jurczak, J. *Carbohydr. Res.* **1976**, *50*, C15. (b) Renaudet, O.; Dumy, P. *Tetrahedron Lett.* **2001**, *42*, 7575.

(21) Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311.

The authors declare no competing financial interest.