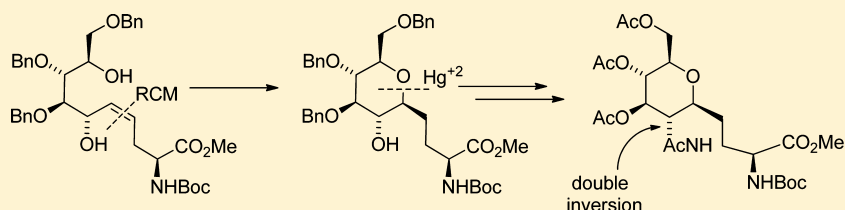


Synthesis of β -C-GlcNAc Ser from β -C-Glc Ser

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S Supporting Information



ABSTRACT: The glycosylation of proteins, specifically installation of *O*-GlcNAc on Ser/Thr residues, is a dynamic control element for transcription repression, protein degradation, and nutrient sensing. To provide homogeneous and stable structures with this motif, the synthesis of a C-linked mimic, *C*-GlcNAc Ser, has been prepared from the *C*-Glc Ser by a double inversion strategy using azide to insert the C-2 nitrogen functionality. The *C*-Glc Ser was available by a ring-closing metathesis and hydroalkoxylation route.

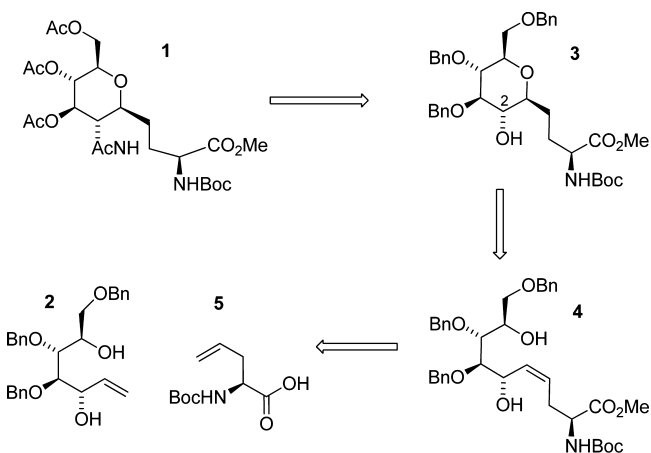
The syntheses of biochemically robust glycosyl amino acids that may be incorporated into peptide constructs are important for the development of tools to assist in glycobiological studies. Because protein glycosylation is a post-translational event and thus beyond the direct governance of DNA control, and because some glycosylations are highly dynamic, access to pure and stable glycopeptides has been of synthetic interest since 1975¹ and a review of artificial glycopeptides by Dondoni in 2000² generated considerable attention.

One of the most common glycoprotein motifs is a β -*O*-GlcNAc Ser/Thr linkage found on a wide variety of nuclear and cytoplasmic proteins.^{3,4} This single carbohydrate modification exhibits a reciprocal relationship with phosphorylation for the regulation of protein activity and degradation, and nutrient sensing.^{5–7} In view of these biochemical activities, the misregulation of *O*-GlcNAc has been implicated in cancer, neurodegenerative disorders, and type-II diabetes.

Although the interplay between phosphorylation and *O*-GlcNAc-ylation has been established, it is surprising that phosphorylation is mediated by over 650 enzymes,⁸ while *O*-GlcNAc is maintained by only two: *O*-GlcNAc transferase and *O*-GlcNAc-ase. Due to the widespread deployment of these enzymes with multiple physiological roles, inhibition of the *O*-GlcNAc enzymes, while illustrative, is of limited therapeutic use due to likely side effects. Therefore, the development of more localized downstream mimetics, such as targeted mimics of *O*-GlcNAc modified peptides, may prove useful. For this reason, we have directed our attention to the synthesis of the metabolically more stable β -*C*-GlcNAc Ser 1.

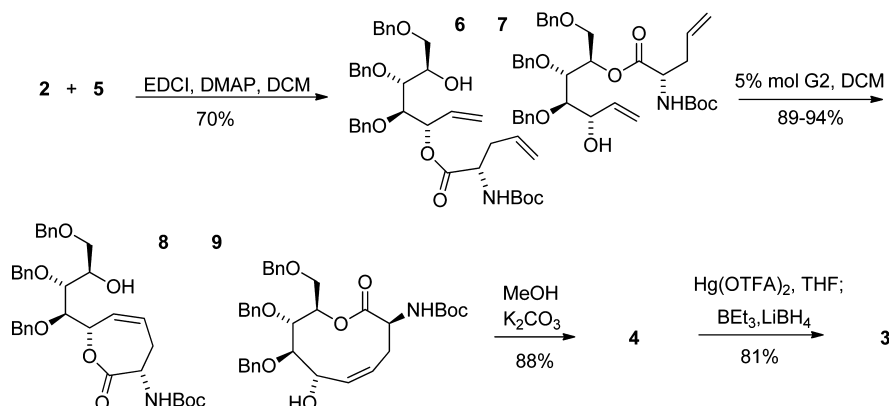
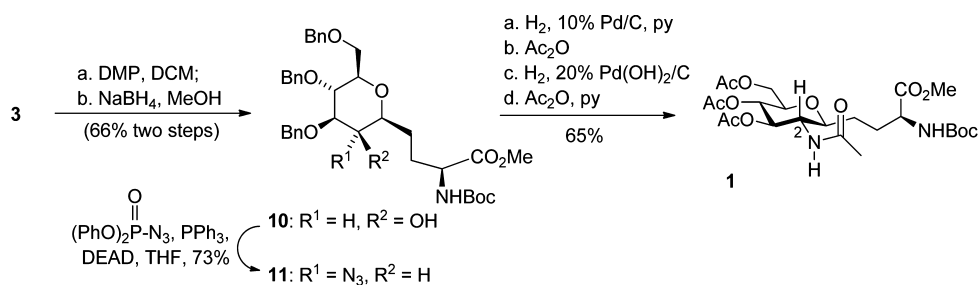
Three previous syntheses of β -*C*-GlcNAc Ser 1 have been reported and all began with a C-2 nitrogen (glycoside numbering) functionality in place prior to the elaboration of the carbon-linkage to the amino acid moiety by a Wittig,⁹ a Ramberg–Bäcklund rearrangement,¹⁰ and an ethynylation.¹¹

Our initial strategy to forge an all-carbon linkage was developed around an olefin cross-metathesis (CM) approach,¹² but *C*-vinyl glycosides have low reactivity with vinyl glycines,¹³ although related CMs have been successful.^{14,15} We then envisioned a repositioning of the alkene to allow for greater metathesis reactivity, as found in the heptenitol 2 (Scheme 1).

Scheme 1. Retrosynthetic Analysis of β -C-GlcNAc Ser via β -C-Glc Ser

Thus, our retrosynthetic plan derives the β -*C*-GlcNAc Ser 1 from a double inversion with the C-2 acetamido introduced onto β -*C*-Man Ser as the azide. The axial hydroxyl of the manno-isomer would itself be the product of an inversion of the C-2 equatorial hydroxyl of β -*C*-Glc Ser 3. Structure 3 represents a stable mimic of β -*O*-Glc Ser, a core carbohydrate

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Scheme 2. Synthesis of β -C-Glc SerScheme 3. Synthesis of β -C-GlcNAc Ser

found in the epidermal growth factor (EGF)-like domain associated with blood clotting factors, in fetal antigen-1, and in Notch1;^{16,17} also, stability issues of β -O-Glc Ser peptides have been reported to be troublesome.¹⁸ The β -C-Glc Ser 3 was prepared according to our previously reported method¹⁹ via an intramolecular mercury-mediated hydroalkoxylation on the (Z)-alkene 4 obtained from esterification and RCM, by way of the heptenitol 2 and (S)-allyl glycine 5.

Following our earlier report (Scheme 2), the readily available Glc-configured heptenitol 2 was esterified with *N*-Boc-allyl glycine 5 to give a nonselective esterification, along with ~6% diester formation. The monoesters 6 and 7, taken as a mixture, were treated with 5 mol % of the Grubbs second generation catalyst to afford the ring-closing metathesis products in 89–94% yield. The resulting lactone mixture, 8 and 9, underwent methanolysis to converge on the identical Z-alkene 4 in 88% yield, as we had reported previously. The stereoselective cyclization to the pyran was accomplished with mercury(II) trifluoroacetate, followed by *in situ* demercuration using LiBH_4 ²⁰ and BEt_3 .²¹ These improved conditions consistently furnished consistent results (>80% yields) by avoiding workup of the organomercury intermediate and the procedural simplicity of adding LiBH_4 as a solution versus our previous attempts to add solid NaBH_4 to a -78°C reaction mixture. The stereochemical outcome is driven by allylic 1,3-strain from the Z-alkene and overrides the inside-alkoxy effect commonly observed in electrophilic cyclizations with an allylic hydroxyl.^{19,22}

With β -C-Glc Ser 3 in hand, we explored an oxime route to introduce the nitrogen functionality. Oxidation of the C-2 hydroxyl and benzyloxime formation went smoothly, but reduction with NaCNBH_3 and $\text{BF}_3\cdot\text{OEt}_2$ ^{23,24} gave the axial benzyloxyamine product with the mannose-configuration. Other attempts to overcome this substrate-controlled stereo-

chemical preference met with failure. So, we turned our attention to a double-inversion strategy to introduce the C-2 acetamido group (Scheme 3). Toward that end, the β -C-Glc Ser 3 was oxidized with Dess-Martin periodane, and following workup it was reduced directly with NaBH_4 to give β -C-Man Ser 10 with complete stereocontrol.²⁵ Reducing agents such as L-selectride, known to add by an equatorial approach also worked, but care had to be taken not to reduce the methyl ester as well. Although purification of the intermediate ketone was possible, this carbonyl had a tendency to hydrate and form the *gem*-diol during chromatography unnecessarily complicating its purification, so this material was telescoped into the reduction step.

Activation of the axial C-2 hydroxyl was required to allow for an inversion by azide. Unfortunately, triflic anhydride led to loss of the *N*-Boc protecting group either directly²⁶ or by advantageous acid, and formation of the mesylate gave incomplete reactions. Gratifyingly the diphenylphosphoryl azide under Mitsunobu conditions²⁷ gave a clean reaction leading to a 73% yield of the azide 11. Global deprotection of the benzyl ethers with concomitant reduction of the azide was initially problematic even when taking care to acetylate the catalyst-poisoning amine at an early stage of the process before attempting the exhaustive hydrogenolysis.¹⁰ Use of methanol as a solvent or cosolvent in the initial reduction of the azide led to small amounts of *N*-methylation easily observed by MALDI analysis of the crude reaction mixture. Optimized conditions required initial hydrogenation using 10% Pd/C in pyridine to selectively reduce the azide only.²⁸ Partial acetylation of the newly generated amine and subsequent hydrogenolysis using 20% $\text{Pd}(\text{OH})_2/\text{C}$ Degussa type in *t*BuOH/ H_2O led overnight to complete debenzilation. Following acetylation in pyridine, the target β -C-GlcNAc Ser 1 was formed in 65% yield over the four steps. It is important to note the ability to selectively

reduce the azide in the presence of the benzyl ethers so as to afford the opportunity to acylate the amino at this point. Several groups have successfully produced labeled variants of O-GlcNAc for biochemical assays through alternative acylations on the C-2 amine,^{29,30} hence, this work allows the opportunity to tag the amine of our more robust C-linked isostere.

The C-linked GlcNAc- β -Ser clearly resides in the 4C_1 chair conformation like its O-linked counterpart judged by triplet coupling patterns for H-3 and H-4 due to axial–axial couplings with neighboring protons. Most interestingly, H-2 is an apparent quartet ($J = 9.8$ Hz) due to the axial couplings and to the approximate 180°-dihedral relation to the NH of the acetamide. Conformational work, both NMR^{31,32} and X-ray,³³ on O-GlcNAc all highlight this general orientation of the acetamide, which may be a key presentation mode for this carbohydrate. A recent report on the X-ray structure of OGT as a binary and ternary complex with UDP and a peptide is noteworthy, but therein the authors regret that no complex with O-GlcNAc was achieved due to hydrolysis of the substrate.³⁴

In conclusion, we have demonstrated that the ring-closing metathesis and pyran cyclization approach can take advantage of the free C-2 hydroxyl for the synthesis of a C-linked analogue of the biochemically important O-GlcNAc and that initial NMR indications corroborate it as a true isosteric mimic.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under an argon atmosphere using oven-dried glassware. Anhydrous THF, toluene, and dichloromethane were obtained from activated commercial columns. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was achieved with UV light (254 nm) and an acidic phosphomolybdic acid, cerium(IV) sulfate stain. Preparative chromatographic separations were performed on silica gel (0.040–0.063 mm). Optical rotations were measured using a polarimeter at ambient temperature in chloroform in a 0.25 dm cell and are reported in 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. Infrared (IR) spectra were recorded as a chloroform solution. All NMR spectral assignments were determined by ${}^1\text{H}$ (400 MHz), ${}^{13}\text{C}$ (100 MHz) attached proton tests, COSY, and HMQC 2D techniques in CDCl_3 . Peaks were referenced to residual chloroform signals (δH 7.26 ppm, or δC 77.0 ppm). High resolution mass spectra were recorded on an ESI-TOF instrument.

(S)-Methyl 4-((2S,3S,4R,5R,6R)-4,5-di(benzyloxy)-6-((benzyloxy)methyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-2-((tert-butoxycarbonyl)amino)butanoate, 10. To a solution of alcohol **3**¹⁹ (666 mg, 1.03 mmol) in 10 mL DCM was added Dess-Martin Periodinane (873 mg, 2.05 mmol) and the mixture was stirred under Ar at rt for 12 h. Then a 1:1:0.5 solution of aqueous saturated NaHCO_3 , aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ and DI H_2O (20 mL) was added. This biphasic mixture was stirred for an additional 30 min. After separation, the aqueous phase was extracted with DCM (2×10 mL); the combined organics were washed with saturated aqueous NaHCO_3 , water, and brine and then dried over Na_2SO_4 . Flash chromatography using 20% EtOAc/hexanes provided 550 mg of a colorless solid, 83% or the crude material could be carried through to the next step.

To a solution of crude ketone (96 mg, 0.15 mmol) in methanol (3.7 mL) at -10°C was added solid NaBH_4 (11 mg, 0.29 mmol). After 1 h, the reaction was quenched with a small amount of acetic acid and concentrated. The residue was taken up in DCM and washed with water, brine, and dried over Na_2SO_4 . Flash chromatography with 20 to 30% EtOAc/hexanes afforded 77 mg (80%) of an oily residue of **10**, giving a 66% yield over two steps.

Intermediate Ketone. Mp = 103–105 $^\circ\text{C}$. $[\alpha]_{\text{D}} -26$ (c 2.5, CHCl_3). ${}^1\text{H}$ NMR (CDCl_3) δ 7.5–7.2 (m, 15H, 3 \times Bn), 5.12 (bd, $J = 8.8$ Hz, 1H, NH), 5.01 (d, $J = 11.3$ Hz, 1H, Bn), 4.86 (d, $J = 10.9$ Hz, 1H, Bn), 4.68–4.52 (4 \times d, 4H, 2 \times Bn), 4.33 (m, 1H, H- α), 4.19 (d, J

= 8.8 Hz, 1H, H-3), 3.89 (t, $J = 9.2$ Hz, 1H, H-4), 3.84 (m, 1H, H-1), 3.8–3.7 (m, 3H), 3.74 (s, 3H, OMe), 1.95 (bm, 2H), 1.80 (bm, 2H), 1.46 (s, 9H, tBu). ${}^{13}\text{C}$ NMR (CDCl_3) δ 202.7, 173.1, 155.5, 137.9, 137.8, 137.6, 129.0–127.7, 86.6, 80.0, 79.9, 79.8, 79.1, 75.0, 73.8, 73.5, 68.9, 53.0, 52.3, 28.3, 28.0, 24.3. IR 3438, 1740, 1710 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{37}\text{H}_{45}\text{NO}_9\text{Na}$ 670.2992; found 670.2988.

β -C-Man Ser 10. $[\alpha]_{\text{D}} +1.6$ (c 2.5, CHCl_3). ${}^1\text{H}$ NMR (CDCl_3) δ 7.5–7.2 (m, 15H, 3 \times Bn), 5.12 (bd, $J = 8.3$ Hz, 1H, NH), 4.86 (d, $J = 10.8$ Hz, 1H, Bn), 4.75 (d, $J = 11.6$ Hz, 1H, Bn), 4.69 (d, $J = 11.6$ Hz, 1H, Bn), 4.63 (d, $J = 12.2$ Hz, 1H, Bn), 4.56 (d, $J = 12.2$ Hz, 1H, Bn), 4.54 (d, $J = 10.8$ Hz, 1H, Bn), 4.34 (m, 1H, H- α), 3.90 (m, 1H, H-2), 3.85–3.66 (m, 3H), 3.74 (s, 3H, OMe), 3.61 (dd, $J = 3.3$, 9.1 Hz, 1H, H-3), 3.40 (ddd, $J = 1.9$, 4.96, 9.8 Hz, 1H, H-5), 3.36 (m, 1H, H-1), 2.39 (bs, 1H, OH), 1.93 (m, 3H), 1.64 (m, 1H), 1.46 (s, 9H, tBu). ${}^{13}\text{C}$ NMR (CDCl_3) δ 173.2, 155.4, 138.2, 138.2, 137.7, 128.5–127.5, 83.3, 79.8, 79.1, 77.1, 75.1, 74.6, 73.4, 71.6, 69.3, 68.3, 53.1, 52.3, 28.9, 28.3, 26.7. IR 3566, 3440, 1736, 1710 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{37}\text{H}_{47}\text{NO}_9\text{Na}$ 672.3148; found 672.3150.

(S)-Methyl 4-((2S,3S,4R,5S,6R)-3-azido-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)-2-((tert-butoxycarbonyl)amino)butanoate, 11. At rt, diphenylphosphoryl azide (178 μL , 0.82 mmol) was added over 15 min to a solution of the alcohol **10** (162 mg, 0.25 mmol), DEAD (131 μL , 0.82 mmol), triphenylphosphine (215 mg, 0.82 mmol) in THF (3.5 mL) and stirred 26 h. The reaction mixture was concentrated onto SiO_2 and flash chromatographed (10 to 30% EtOAc/hexanes) to yield 119 mg (73%) as a cloudy oil. $[\alpha]_{\text{D}} -26$ (c 2.5, CHCl_3). ${}^1\text{H}$ NMR (CDCl_3) δ 7.5–7.2 (m, 15H, 3 \times Bn), 5.12 (d, $J = 8.4$ Hz, 1H, NH), 4.91 (d, $J = 10.7$ Hz, 1H, Bn), 4.87 (d, $J = 10.7$ Hz, 1H, Bn), 4.81 (d, $J = 10.9$ Hz, 1H, Bn), 4.62 (d, $J = 12.2$ Hz, 1H, Bn), 4.59 (d, $J = 10.9$ Hz, 1H, Bn), 4.54 (d, $J = 12.2$ Hz, 1H, Bn), 4.37 (m, 1H, H- α), 3.75 (s, 3H, OMe), 3.75–3.62 (m, 2H, H-6), 3.66 (t, $J = 9.4$ Hz, 1H, H-4), 3.57 (t, $J = 9.1$ Hz, 1H, H-3), 3.37 (dt, $J = 3.0$, 9.7 Hz, 1H, H-5), 3.22 (t, $J = 9.5$ Hz, 1H, H-2), 3.09 (bdd, $J = 8.3$, 9.5 Hz, 1H, H-1), 1.91 (m, 3H), 1.59 (m, 1H), 1.47 (s, 9H, tBu). ${}^{13}\text{C}$ NMR (CDCl_3) δ 173.2, 155.4, 138.1, 137.9, 137.8, 128.5–127.7, 85.4, 79.9, 79.0, 78.3, 77.3, 75.6, 74.9, 73.5, 68.7, 66.5, 53.1, 52.3, 28.3, 28.3. IR 3440, 2110, 1740, 1710 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{37}\text{H}_{46}\text{N}_4\text{O}_8\text{Na}$ 697.3213; found 697.3214.

(2R,3S,4R,5S,6S)-5-Acetamido-2-(acetoxymethyl)-6-((S)-3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl)tetrahydro-2H-pyran-3,4-diyl diacetate, 1. The catalyst Pd/C (10%, 1 \times weight of the starting material) was added to a solution of the tri-O-benzyl azido C-glucoside **11** (24 mg, 0.034 mmol) in pyridine (3.5 mL) under Ar. The reaction flask was evacuated and saturated with H_2 (by means of a H_2 -filled balloon) three times. The suspension was rapidly stirred for 2 h. MALDI analysis indicated complete consumption of the azide. The mixture was filtered through a polytetrafluoroethylene (PTFE) syringe filter (25 mm diameter, 0.2 μm pore size) and washed with pyridine. The solvent was coevaporated with toluene and dried *in vacuo* for several hours. The residue was stirred with Ac_2O (0.5 mL) for 1 h and then concentrated. The mixture was placed back under hydrogenation conditions as above, but with $\text{Pd}(\text{OH})_2/\text{C}$ (20%, 1 \times weight of the starting material) in $\text{tBuOH}:\text{H}_2\text{O}$ (6:1, 2.8 mL) and left to stir 18 h. MALDI analysis confirmed the loss of all benzyl protecting groups. The mixture was filtered through a PTFE syringe filter and washed. Solvents were coevaporated with toluene and dried *in vacuo*. A solution of the crude product in Ac_2O (0.4 mL) and pyridine (0.8 mL) was stirred 12 h. This mixture was concentrated onto SiO_2 and chromatographed (75% EtOAc/hexanes to 100% EtOAc) to give a 12 mg (65%) as a white solid. Mp = 177–180 $^\circ\text{C}$. $[\alpha]_{\text{D}} -23$ (c 1.9, CHCl_3). ${}^1\text{H}$ NMR (CDCl_3) δ 5.49 (bd, $J = 9.5$ Hz, 1H, NHAc), 5.21 (bd, $J = 8.3$ Hz, 1H, NHBoc), 5.08 (t, $J = 9.5$ Hz, 1H, H-4), 5.02 (t, $J = 9.5$ Hz, 1H, H-3), 4.23 (dd, $J = 5.2$, 12.2 Hz, 1H, H-6a), 4.22 (m, 1H, H- α), 4.11 (dd, $J = 2.3$, 12.2 Hz, 1H, H-6b), 4.05 (q, $J = 9.8$ Hz, 1H, H-2), 3.76 (s, 3H, OMe), 3.61 (m, 1H, H-5), 3.42 (bdd, $J = 7.9$, 8.4 Hz, 1H, H-1), 2.11 (s, 3H, OAc), 2.05 (bs, 6H, 2 \times OAc), 2.01 (m, 1H, H- β a), 1.96 (s, 3H, NHAc), 1.76 (m, 2H, H- β b and H- γ a), 1.60 (m, 1H, H- γ b), 1.46 (s, 9H, tBu). ${}^{13}\text{C}$ NMR (CDCl_3) δ 173.2, 171.6,

170.8, 170.1, 169.3, 155.8, 79.8, 77.7, 75.7, 74.5, 68.5, 62.5, 53.2, 52.6, 52.3, 28.4, 27.8, 27.0, 23.3, 20.7, 20.6. IR 3427, 1742, 1708 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{38}\text{N}_2\text{O}_{12}\text{Na}$ 569.2322; found 569.2332.

■ ASSOCIATED CONTENT

● Supporting Information

^1H and ^{13}C NMR spectra for new and title compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Rosenthal, A.; Brink, A. J. *J. Carbohydr., Nucleosides, Nucleotides* **1975**, *2*, 343–356.
- (2) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395–4421.
- (3) Zachara, N. E.; Hart, G. W. *Biochim. Biophys. Acta* **2006**, *1761*, 599–617 and references cited therein.
- (4) Wells, L.; Vosseller, K.; Hart, G. W. *Science* **2001**, *291*, 2376–2378.
- (5) Whisenhunt, T. R.; Yang, X.; Damon, B. B.; Paterson, A. J.; Van Tine, B. A.; Kudlow, J. E. *Glycobiology* **2006**, *16*, 551–563.
- (6) Zhang, F.; Su, K.; Yang, X.; Bowe, D. B.; Paterson, A. J.; Kudlow, J. E. *Cell* **2003**, *115*, 715–725.
- (7) Kim, E. J.; Amorelli, B.; Abdo, M.; Thomas, C. J.; Love, D. C.; Knapp, S.; Hanover, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14854–14855.
- (8) Forrest, A. R.; Ravasi, T.; Taylor, D.; Huber, T.; Hume, D. A.; Grimmond, S. *Genome Res.* **2003**, *13*, 1443–1454.
- (9) Fuchss, T.; Schmidt, R. R. *Synthesis* **1998**, 753–758.
- (10) Dondoni, A.; Mariotti, G.; Marra, A.; Massi, A. *Synthesis* **2001**, 2129–2137.
- (11) Ohnishi, Y.; Ichikawa, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 997–999.
- (12) Nolen, E. G.; Kurish, A. J.; Wong, K. A.; Orlando, M. D. *Tetrahedron Lett.* **2003**, *44*, 2449–2453.
- (13) McGarvey, G. J.; Benedum, T. E.; Schmidtman, F. W. *Org. Lett.* **2002**, *4*, 3591–3594.
- (14) Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett.* **2004**, *6*, 4077–4080.
- (15) Kulkarni, S. S.; Gervay-Hague, J. *Org. Lett.* **2006**, *8*, 5765–5768.
- (16) Nishimura, H.; Takao, T.; Hase, S.; Shimonishi, Y.; Iwanaga, S. *J. Biol. Chem.* **1992**, *267*, 17520–17525.
- (17) Ishimizu, T.; Sano, K.; Uchida, T.; Teshima, H.; Omichi, K.; Hojo, H.; Nakahara, Y.; Hase, S. *J. Biochem. (Tokyo, Jpn.)* **2007**, *141*, 593–600 and references cited therein.
- (18) Sjölin, P.; Kihlberg, J. *J. Org. Chem.* **2001**, *66*, 2957–2965.
- (19) Nolen, E. G.; Donahue, L. A.; Greaves, R.; Daly, T. A.; Calabrese, D. R. *Org. Lett.* **2008**, *10*, 4911–4914.
- (20) Kang, S. H.; Kim, M. *J. Am. Chem. Soc.* **2003**, *125*, 4684–4685.
- (21) Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59–62.
- (22) Nolen, E. G.; Kurish, A. J.; Potter, J. M.; Donahue, L. A.; Orlando, M. D. *Org. Lett.* **2005**, *7*, 3383–3386 and references cited therein.
- (23) 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*, 7593–7611.
- (24) Banaszek, A.; Karpiesiuk, W. *Carb. Res.* **1994**, *251*, 233–242.
- (25) Lichtenthaler, F. W.; Schneider-Adams, T. *J. Org. Chem.* **1994**, *59*, 6728–6734.
- (26) Schüler, P.; Fischer, S. N.; Marsch, M.; Oberthür, M. *Synthesis* **2013**, *45*, 27–39.
- (27) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977–1980.
- (28) Venot, A.; Swayze, E. E.; Griffey, R. H.; Boons, G. J. *ChemBioChem* **2004**, *5*, 1228–1236.
- (29) Gross, B. J.; Kraybill, B. C.; Walker, S. *J. Am. Chem. Soc.* **2005**, *127*, 14588–14589.
- (30) Witte, M. D.; Florea, B. I.; Verdoes, M.; Adeyanju, O.; Van der Marel, G. A.; Overkleeft, H. S. *J. Am. Chem. Soc.* **2009**, *131*, 12064–12065.
- (31) Mobli, M.; Almond, A. *Org. Biomol. Chem.* **2007**, *5*, 2243–2251.
- (32) Fernandez-Tejada, A.; Corzana, F.; Busto, J. H.; Jimenez-Oses, G.; Jimenez-Barbero, J.; Avenzoa, A.; Peregrina, J. M. *Chem.—Eur. J.* **2009**, *15*, 7297–7301.
- (33) Glithero, A.; Tormo, J.; Haurum, J. S.; Arsequell, G.; Valencia, G.; Edwards, J.; Springer, S.; Townsend, A.; Pao, Y.-L.; Wormald, M.; Dwek, R. A.; Jones, E. Y.; Elliott, T. *Immunity* **1999**, *10*, 63–74.
- (34) Lazarus, M. B.; Nam, Y.; Jiang, J.; Sliz, P.; Walker, S. *Nature* **2013**, *469*, 564–567.