

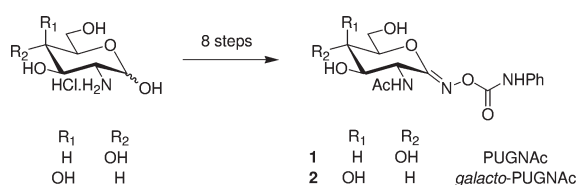
## An Improved Route to PUGNac and Its Galacto-Configured Congener

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Received March 31, 2010



An efficient, scalable, and reliable synthesis of PUGNac and its galacto-configured congener is reported.

The *exo*- $\beta$ -*N*-acetylglucosaminidases, a group of glycoside hydrolases (glycosidases) responsible for the hydrolysis of 2-deoxy-2-acetamido- $\beta$ -D-glucopyranosides, are essential for the catabolism of a wide range of glycoproteins, glycolipids, and oligosaccharides. An almost universal requirement to process such biomacromolecules renders these enzymes ubiquitous in Nature. Anomalous *exo*- $\beta$ -*N*-acetylglucosaminidase activity is the cause of several genetic disorders,<sup>1</sup> and appears to play a role in the propagation of other diseases.<sup>2–8</sup> These enzymes are also involved in bacterial cell-wall processing.<sup>9,10</sup>

Thus, it is no surprise that considerable efforts have been invested into the development of a range of *exo*- $\beta$ -*N*-acetylglu-

cosaminidase inhibitors.<sup>8,11–20</sup> One of these inhibitors, *O*-(2-acetamido-2-deoxy-D-glucopyranosylidene)-amino *N*-phenylcarbamate **1**, commonly known as PUGNac, has demonstrated excellent and broad inhibitory potency for *exo*- $\beta$ -*N*-acetylglucosaminidases, irrespective of the fact that some of these enzymes operate via different catalytic mechanisms. PUGNac was first prepared by Vasella and co-workers,<sup>12</sup> and found to be a potent competitive inhibitor of  $\beta$ -*N*-acetylglucosaminidases from *Canavalia ensiformis* ( $K_i = 100$  nM),<sup>12</sup> *Mucor rouxii* ( $K_i = 40$  nM),<sup>12</sup> and bovine kidney ( $K_i = 110$  nM).<sup>12</sup>

It was subsequently determined to be a competitive inhibitor of the human enzymes *O*-GlcNAcase ( $K_i = 46$  nM),<sup>21</sup> HEXB ( $K_i = 46$  nM),<sup>21</sup> HEXD ( $K_i \approx 100$   $\mu$ M),<sup>22</sup> the prokaryotic enzyme NagZ ( $K_i = 48$  nM),<sup>23</sup> and even an  $\alpha$ -*N*-acetylglucosaminidase ( $K_i = 6$   $\mu$ M).<sup>24</sup>

Indeed, the inhibitory potency of PUGNac has prompted the suggestion that it may be a transition state analogue,<sup>12</sup> although this assertion has yet to be rigorously substantiated. Indeed, in the case of human *O*-GlcNAcase, PUGNac does not appear to possess all of the properties expected of a genuine transition state analogue.<sup>25</sup>

The broad-spectrum inhibitory activity of PUGNac arguably limits its utility as a tool for probing biological systems that contain multiple  $\beta$ -*N*-acetylglucosaminidases.<sup>21,26</sup> For example, PUGNac continues to be used as a probe for studying the mechanisms that give rise to insulin resistance in tissue culture,<sup>6,27</sup> despite its established off-target effects, which have prompted questions about the mechanism by which such a phenotype arises.<sup>28</sup> As a result, several measures have been

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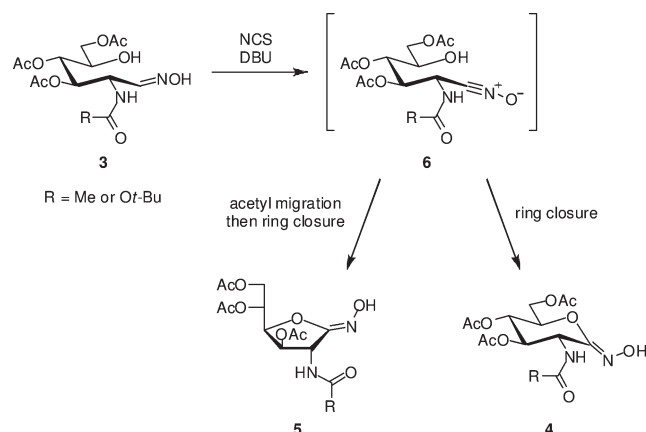
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## SCHEME 1. Rationalization of the Oxidative Ring Closure



taken to confer inhibitory selectivity upon derivatives of PUGNAc: a PUGNAc analogue with an *N*-butyryl group, instead of an *N*-acetyl group, is selective for *O*-GlcNAcase16 as well as for the bacterial enzyme NagZ,<sup>23,29</sup> while the *D*-galacto-configured congener, *galacto*-PUGNAc **2**, only recently reported, can selectively inhibit human HEXA and HEXB in cells, owing to the ability of these enzymes to process  $\beta$ -glycosides of *N*-acetyl-*D*-galactosamine.<sup>17</sup>

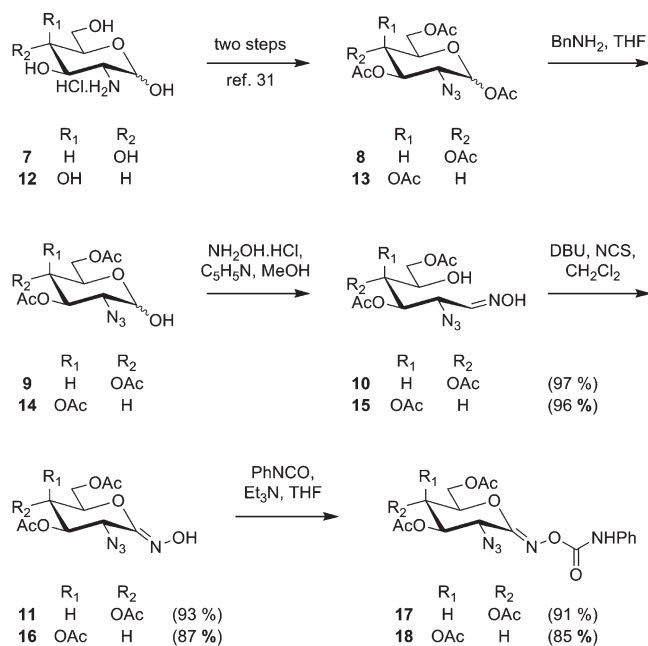
A key step in the best syntheses of PUGNAc<sup>16,30</sup> is the NCS-mediated oxidative ring closure of an oxime **3** to give the corresponding oximinolactone **4** (Scheme 1). This reaction is problematic, in that it provides a variable yield (at best 60%, but often worse), is acutely temperature sensitive, and is accompanied by the formation of another compound, the oximinolactone **5** (a difficult to remove byproduct).<sup>30</sup> A solution to this “bottleneck” in these syntheses would be most welcome, given that large quantities of PUGNAc and its analogues continue to be used in research. It was reasoned that problems associated with this ring closure could be ascribed to the amide/carbamate group at C-2, which may reversibly capture the presumed nitrile oxide intermediate **6**, delaying ring closure and enabling acetyl migration to be a competitive process. Thus, it seemed logical that replacement of the group at C-2 with a nonparticipating amino group surrogate, such as an azido group, might minimize or obviate the formation of the troublesome byproduct **5**, and invariably increase the overall yield and operational convenience of the reaction.

To explore the merits of this idea, *D*-glucosamine hydrochloride **7** was converted into the corresponding peracetylated azido sugar **8**,<sup>31</sup> then treated with benzylamine to afford the lactol **9** (Scheme 2).<sup>32</sup> This product was condensed with hydroxylamine to provide the oxime **10** as a mixture of stereoisomers.

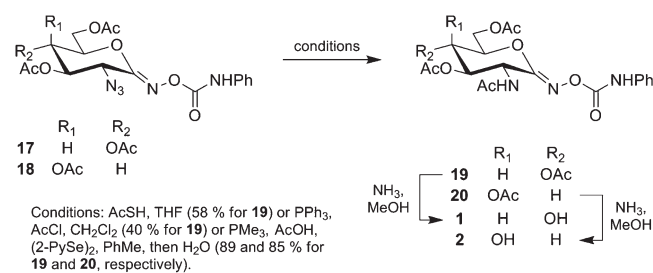
Addition of DBU to a mixture containing NCS and the oxime **10** in dichloromethane at  $-40$  °C provided the desired ring-closed material **11** exclusively, and in an excellent yield (93%).

This excellent result encouraged further investigations; the analogous route for *D*-galactosamine hydrochloride **12** was explored. The results were similarly impressive: the azidosugar **13**<sup>31</sup> was converted to the lactol **14** and thence oxime **15**.

## SCHEME 2



## SCHEME 3



Oxidative ring closure then provided the desired oximinolactone **16** exclusively and in high yield (87%).

Treating the oximinolactones **11** and **16** with phenyl isocyanate, under basic conditions, yielded the corresponding carbamates **17** and **18**, respectively, in excellent yields after purification by flash chromatography.

Several approaches were taken to the reductive acylation of the azido group. To begin with, the carbamate **17** was treated with a slight excess of thioacetic acid<sup>33</sup> to return the desired acetamide **19** in moderate yield (Scheme 3).

Other protocols for the reductive acylation of azides were explored to improve upon this result. Treatment of the azide **17** with triphenylphosphine, to form the presumed phosphazene, followed by acetyl chloride,<sup>34,35</sup> gave the acetamide **19** in modest yield. A slightly different approach to this transformation, reported by Vilarrasa and co-workers, utilizes carboxylic acids, trimethylphosphine, and a catalytic quantity of 2,2'-dipyridyl diselenide.<sup>36</sup> This method proved to be

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most satisfactory; when applied to compounds **17** and **18** it affected their smooth conversion into the amides **19** and **20**, respectively, in excellent yield.

Deprotection of **19** and **20** with ammoniacal methanol, in accordance with literature procedure,<sup>30</sup> provided PUGNAc **1** and *galacto*-PUGNAc **2**, respectively. These compounds were spectroscopically identical with samples that had been prepared by literature methods,<sup>17,37</sup> thus confirming that both oxidative ring closures had provided the desired *Z*-stereoisomers.

This alternative route to PUGNAc and its analogues greatly simplifies the preparation of these useful molecules. The more facile conversion of  $\alpha$ -azido- $\delta$ -hydroxy-aldoximes to the corresponding oximinolactones, relative to the analogous transformation for  $\alpha$ -amido- $\delta$ -hydroxy-aldoximes, is noteworthy. Regardless of whether or not the rationalization and original motivation for using an azido group (rather than an amide or carbamate) in these syntheses was correct, azidosugars are evidently useful and readily accessible syntheses for the preparation of PUGNAc and its analogues.

## Experimental Section

**(E)- and (Z)-3,4,6-Tri-O-acetyl-2-azido-2-deoxy-D-glucose Oxime (10).** Hydroxylamine hydrochloride (1.0 g, 14 mmol) was added to the hemiacetal **9**<sup>32</sup> (3.0 g, 9.0 mmol) and pyridine (2.0 mL, 25 mmol) in MeOH (30 mL) and the resulting solution was stirred at reflux (2 h). The solution was concentrated and coevaporated with toluene (2  $\times$  20 mL). The residue was taken up in EtOAc and washed with water (2  $\times$  50 mL) and brine (50 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated. The residue was subjected to flash chromatography (EtOAc/hexanes, 2:3) to give the presumed oxime **10** (3.0 g). *R<sub>f</sub>* 0.35 (EtOAc/hexanes, 1:1).

**(Z)-3,4,6-Tri-O-acetyl-2-azido-2-deoxy-D-glucono-hydroxime-1,5-lactone (11).** DBU (1.50 mL, 10 mmol) was added to the crude oxime **10** (3.0 g, 8.7 mmol) and *N*-chlorosuccinimide (1.3 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at -45 °C in such a way that the temperature did not go above -40 °C and the resulting mixture was stirred for 60 min at this temperature, then left to warm to room temperature over 3 h. Water was added (10 mL), and the mixture was diluted with EtOAc (100 mL). The organic layer was separated and washed with water (2  $\times$  50 mL) and brine (1  $\times$  50 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated. Flash chromatography of the residue (EtOAc/hexanes, 2:3) gave compound **11** as a colorless oil (2.8 g, 93%): *R<sub>f</sub>* 0.40 (EtOAc/hexanes, 1:1); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +89 (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.20–7.10 (br s, 1H), 5.15 (dd, *J* = 6.0, 12.0 Hz, 1H), 5.06 (dd, *J* = 6.0 Hz, 1H), 4.56 (ddd, *J* = 3.0, 4.8, 12.0 Hz, 1H), 4.38 (dd, *J* = 4.8, 13.0 Hz, 1H), 4.34 (dd, *J* = 3.0, 13.0 Hz, 1H), 4.28 (d, *J* = 6.0 Hz), 2.14 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 169.4, 169.3, 148.5, 74.2, 72.2, 68.2, 61.4, 58.3, 20.7, 20.6, 20.5. Anal. Calcd for C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>8</sub>: C, 41.86; H, 4.68. Found: C, 41.72; H, 4.65. HRMS *m/z* 345.1053 [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>17</sub>N<sub>4</sub>O<sub>8</sub> 345.1046.

**(E)- and (Z)-3,4,6-Tri-O-acetyl-2-azido-2-deoxy-D-galactose Oxime (15).** The hemiacetal **14**<sup>32</sup> (2.5 g, 7.5 mmol) was treated in the same manner as for the preparation of **10**. The presumed oxime **15** (2.5 g) was used in the next step without further purification. *R<sub>f</sub>* 0.30 (EtOAc/hexanes, 1:1).

**(Z)-3,4,6-Tri-O-acetyl-2-azido-2-deoxy-D-galactonohydroxime-1,5-lactone (16).** The crude oxime **15** (2.5 g, 7.2 mmol) was treated in the same manner as for the preparation of **11** to give compound **16** as a colorless oil (2.2 g, 87%). *R<sub>f</sub>* 0.33 (EtOAc/

hexanes, 1:1); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +123 (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.05–8.00 (br s, 1H), 5.55 (dd, *J* = 1.5, 2.9 Hz, 1H), 5.04 (dd, *J* = 2.9, 10.0 Hz, 1H), 4.46 (d, *J* = 10.0 Hz, 1H), 4.44 (ddd, *J* = 1.5, 5.3, 6.6 Hz, 1H), 4.29–4.24 (m, 2H), 2.16 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.4, 169.6, 169.5, 148.9, 74.9, 70.7, 65.9, 61.0, 56.0, 20.6, 20.5, 20.4. Anal. Calcd for C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>8</sub>: C, 41.86; H, 4.68. Found: C, 41.81; H, 4.61. HRMS *m/z* 345.1039 [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>17</sub>N<sub>4</sub>O<sub>8</sub> 345.1046.

**(Z)-O-(3,4,6-Tri-O-acetyl-2-azido-2-deoxy-D-glucopyranosylidene)amino N-Phenylcarbamate (17).** Phenyl isocyanate (0.35 mL, 3.2 mmol) was added to the lactone **11** (1.0 g, 2.9 mmol) and Et<sub>3</sub>N (0.81 mL, 5.8 mmol) in THF (30 mL) and the solution was stirred (rt, 3 h). Concentration of the mixture and flash chromatography of the residue (EtOAc/hexanes, 1:4) yielded the carbamate **17** as a colorless oil (1.2 g, 91%). *R<sub>f</sub>* 0.70 (EtOAc/hexanes, 2:3); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +30 (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.88 (br s, 1H), 7.47 (m, 2H), 7.34 (m, 2H), 7.12 (m, 1H), 5.14 (dd, *J* = 4.8, 12.0 Hz, 1H), 5.06 (dd, *J* = 4.8 Hz, 1H), 4.70 (ddd, *J* = 3.6, 4.8, 12.0 Hz, 1H), 4.46 (d, *J* = 4.8 Hz, 1H), 4.39–4.35 (m, 2H), 2.14 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 169.3, 169.2, 151.9, 151.0, 136.8, 129.2, 124.3, 119.4, 74.8, 72.0, 68.1, 60.4, 57.9, 20.7, 20.6, 20.5. Anal. Calcd for C<sub>19</sub>H<sub>21</sub>N<sub>5</sub>O<sub>9</sub>: C, 49.25; H, 4.57. Found: C, 49.30; H, 4.61. HRMS *m/z* 464.1423 [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>N<sub>5</sub>O<sub>9</sub> 464.1418.

**(Z)-O-(3,4,6-Tri-O-acetyl-2-azido-2-deoxy-D-galactopyranosylidene)amino N-Phenylcarbamate (18).** The crude oxime **16** (1.1 g, 3.2 mmol) was treated in the same manner as for the preparation of **17** to give the title compound **18** as a colorless oil (1.3 g, 85%). *R<sub>f</sub>* 0.65 (EtOAc/hexanes, 2:3); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +43 (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.08–8.03 (br s, 1H), 7.48 (m, 2H), 7.33 (m, 2H), 7.11 (m, 1H), 5.60 (dd, *J* = 1.6, 3.0 Hz, 1H), 5.09 (dd, *J* = 3.0, 9.9 Hz, 1H), 4.64 (d, 9.9 Hz, 1H), 4.59 (ddd, *J* = 1.7, 6.8 Hz, 1H), 4.32–4.26 (m, 2H), 2.18 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.2, 169.4, 169.3, 152.7, 151.0, 136.8, 129.1, 124.3, 119.3, 76.1, 69.9, 65.3, 60.6, 55.8, 20.6, 20.5, 20.4. Anal. Calcd for C<sub>19</sub>H<sub>21</sub>N<sub>5</sub>O<sub>9</sub>: C, 49.25; H, 4.57. Found: C, 49.40; H, 4.60. HRMS *m/z* 464.1428 [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>N<sub>5</sub>O<sub>9</sub> 464.1418.

**(Z)-O-(3,4,6-Tri-O-acetyl-2-acyl-2-deoxy-D-glucopyranosylidene)amino N-Phenylcarbamate (19).** **Procedure A:** Thioacetic acid (50  $\mu$ L, 0.60 mmol) was added to the carbamate **17** (0.23 g, 0.50 mmol) in THF (5 mL) at 0 °C and the solution was stirred (2 h). Concentration of the mixture gave a yellow residue, which was dissolved in EtOAc (30 mL) and washed with water (2  $\times$  20 mL) and brine (1  $\times$  20 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated. Flash chromatography (EtOAc/hexanes, 7:3) of the residue gave **19** as a colorless oil (58%), which had a <sup>1</sup>H NMR spectrum consistent with that found in the literature.<sup>37</sup>

**Procedure B:** Triphenylphosphine (0.16 g, 0.60 mmol) was added to the carbamate **17** (0.23 g, 0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0 °C and the solution was stirred (1 h). Acetyl chloride (0.11 mL, 1.5 mmol) was then added and the mixture refluxed (5 h). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with water (2  $\times$  20 mL) and brine (1  $\times$  20 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated. Flash chromatography (EtOAc/hexanes, 7:3) of the residue gave **19** as a colorless oil (40%), which had a <sup>1</sup>H NMR spectrum consistent with that found in the literature.<sup>37</sup>

**Procedure C:** A solution of Me<sub>3</sub>P (1.0 M in toluene, 0.50 mL, 0.50 mmol) was added to a mixture of acetic acid (30  $\mu$ L, 0.5 mmol), **17** (0.23 g, 0.50 mmol), and 2,2'-dipyridyl diselenide<sup>38</sup> (30 mg, 0.10 mmol) in toluene (5 mL) at 0 °C under nitrogen. A few minutes later, after the evolution of bubbles had ceased, the ice bath was removed and the reaction was stirred at room

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temperature (2 h). Water (1 mL) was added and the mixture was stirred (10 min). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with aqueous NaHCO<sub>3</sub> (2 × 20 mL), water (2 × 20 mL), and brine (1 × 20 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated. Flash chromatography (EtOAc/hexanes, 7:3) of the residue gave **19** as a colorless oil (89%), which had a <sup>1</sup>H NMR spectrum consistent with that found in the literature.<sup>37</sup>

(*Z*)-*O*-(3,4,6-Tri-*O*-acetyl-2-acetamido-2-deoxy-*D*-galactopyranosylidene)amino *N*-Phenylcarbamate (**20**). Using procedure C, **18** was used to prepare compound **20**, which was obtained as a colorless oil (85%). The material had a <sup>1</sup>H spectrum consistent with that found in the literature.<sup>17</sup>

**Acknowledgment.** K.A.S. acknowledges the support of the Australian Research Council.

**Note Added after ASAP Publication.** Configuration annotations of some of the molecules were incorrect in the version published ASAP May 5, 2010; the correct version reposted May 7, 2010.

**Supporting Information Available:** <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **11**, **16**, **17**, and **18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.