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Concise and stereocontrolled syntheses of phosphonate *C*-glycoside analogues of β-D-ManNAc and β-D-GlcNAc 1-*O*-phosphates ☆

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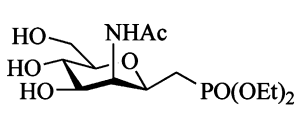
Abstract—Diethyl *C*-(2-deoxy-2-acetamido-β-D-mannopyranosyl)methylphosphonate and dimethyl *C*-(2-deoxy-2-acetamido-β-D-glucopyranosyl)methylphosphonate were stereoselectively prepared from *N*-acetyl D-glucosamine. Routes to such compounds starting from D-GlcNAc have been problematic, but we have found short and efficient implementations of this highly desirable transformation.

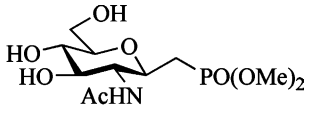
C-Glycosyl analogues of sugar 1-*O*-phosphates have recently attracted attention due to their potential as glycosyltransferase inhibitors.[1] Convenient routes to *C*-glycosyl analogues of *N*-acetyl D-mannosamine 1-*O*-phosphate and *N*-acetyl D-glucosamine 1-*O*-phosphate are particularly desirable[2] because carbohydrate phosphates are key intermediates in the assembly of oligo- and polysaccharides in bacteria and higher organisms.

Although many routes to *C*-glycosides exist, few are applicable to the preparation of 2-deoxy-2-acetamido β-*C*-glycosides.[3–8] Even less has been reported on the preparation of 2-deoxy-2-acetamido *C*-glycosylphosphonates. In fact, the difficulties associated with the 2-acetamido group have induced most researchers to employ other hexose or pentose starting materials, and to install the acetamido group after the key C–C bond forming reaction. Such approaches have typically entailed many steps and low overall yields.[2a–c]

Given the availability and low cost of *N*-acetyl-D-glucosamine, we were convinced that expeditious routes directly from this inexpensive material could be devised, and this has proven to be the case. Here we report the syntheses of analogues **1** and **2**, of *N*-acetyl β-D-mannosamine- and *N*-acetyl β-D-glucosamine 1-*O*-phosphates.[9] We have found particularly concise and attractive routes, beginning from well-known, simple, and readily-made derivatives of D-GlcNAc.



1



2

The synthesis of D-mannosyl analogue **1** started from *N*-acetyl glucosamine derivative **3**[10] (Scheme 1). Treatment of compound **3** with $(EtO)_2P(O)CHLiP(O)(OEt)_2$ in the presence of $ZnBr_2$ gave α,β-unsaturated phosphonate **4** in good yield. In the absence of $ZnBr_2$, a compound identified by NMR as **8**[11] was obtained instead, presumably from retro-aldol reaction of **3** followed by a Wittig reaction. This was caused by the stronger basicity of the lithium diphosphonate compared to the zinc diphosphonate. Similar retro-aldol/Wittig products have been observed when reducing sugars were treated with nonstabilized ylides.[12]

Compound **4** underwent Michael cyclization upon treatment with K_2CO_3/EtOH, to give the β-*C*-mannopyranosyl product **7**. We noted that **5** was formed first, and could in fact be recovered in impure form from incomplete reactions. Intermediate **5** disappeared over time with concurrent formation of **7**, presumably via the

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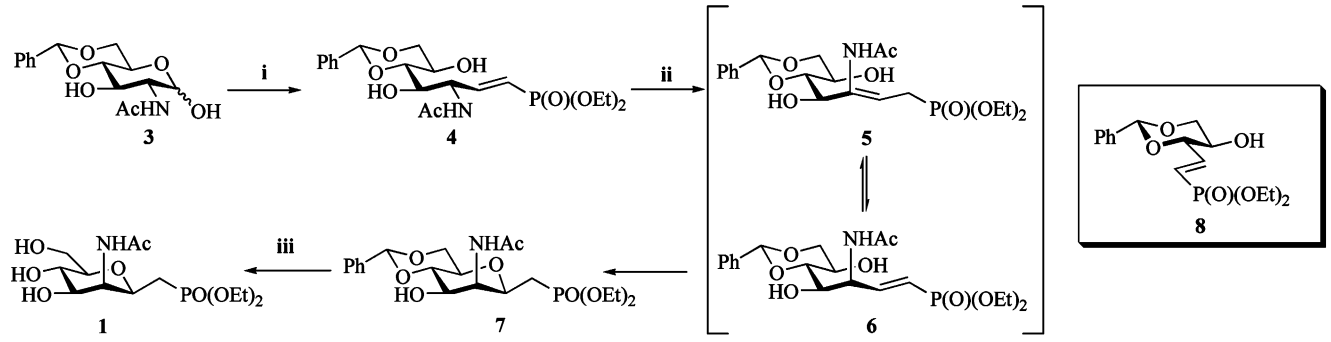


Scheme 1. Reagents and conditions: (i) BuLi, $ZnBr_2$ (3 equiv), $(EtO)_2P(O)CH_2P(O)(OEt)_2$ (6 equiv), THF, −78 °C to rt, 2 h, 85%; (ii) K_2CO_3, EtOH, overnight; (iii) 80% HOAc, 80 °C, 1 h, 60% over the last two steps.

intermediate **6**. We were unable to detect **6**. More strongly basic conditions (KO*t*-Bu/THF, EtONa/EtOH, or NaOH/EtOH) gave low yields of the desired product. Acid hydrolysis of the benzylidene protecting group in **7** furnished the D-*manno* analogue **1**[13] in 60% yield from **4**.

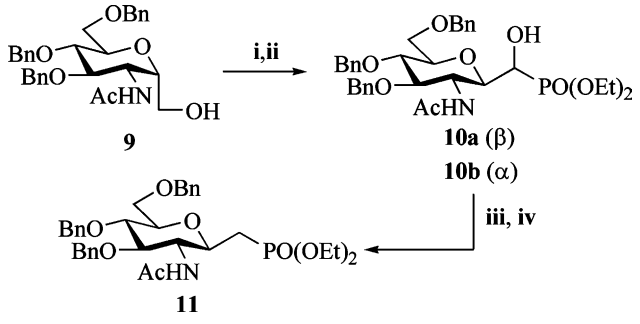
The origin of the *manno*-stereoselectivity in the transformation of **4** to **7** is unclear. There is literature precedent for the formation of both cyclic and acyclic ManNAc products from the olefination of GlcNAc derivatives.[14] However, calculations and equilibration studies by Davis and co-workers[14b] confirm that β-GlcNAc-*C*-pyranosides are the thermodynamically favored ring forms. We attempted to rationalize the apparent preference for **6** over **4** using molecular mechanics, but the results of these preliminary calculations were not illuminating.

Our initial approach to the synthesis of D-*gluco* analogue **2** began with the known alcohol **9**[2e] (Scheme 2). Swern oxidation of **9** afforded two aldehydes in a 5:1 ratio (as judged by TLC and NMR). The addition of $(EtO)_2POLi$ to the crude aldehydes gave hydroxy phosphonate **10a** in 66% yield, along with 13% of an isomeric product that appeared by NMR to be **10b** (both were single diastereomers at C-1, but the stereochemistry at this center was not identified). *C*-Glycosidic aldehydes may be epimerized under the basic conditions of the Swern oxidation, favoring an equatorial orientation.[15] Arbuzov-type addition to this isomer would afford **10a**. We have not optimized the oxidation of **9**, but we note the possibility that either **10a** or **10b** might be obtained by optimal choice of reaction conditions.

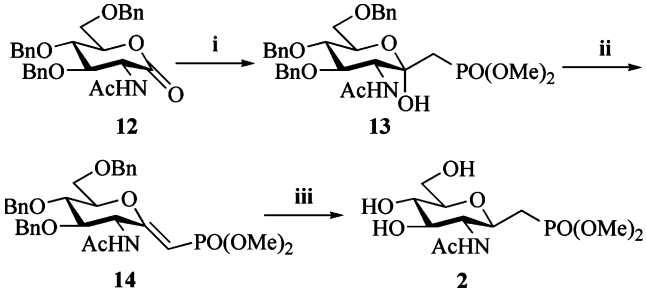
Deoxygenation of compound **10** also turned out to be problematic. Attempted reduction using Zn/HOAc, $NaBH_4$/TFA, or SmI_2/Ac_2O/THF failed to produce any significant amount of **11**. Attempts to convert **10a** to an olefin by treatment of its mesylate derivative with DBN were also unsuccessful. Finally, **10a** was converted to the xanthate, which was reduced by Bu_3SnH to give the desired product **11** in 46% yield from **10a**.

The strategy shown in Scheme 2 suffered from the low yield of the deoxygenation step, as well as the fact that starting compound **9** required several steps to prepare from *N*-acetyl glucosamine.[2e] Therefore, we decided to pursue a more efficient synthetic route.

Our preferred route to **2** is shown in Scheme 3. The synthesis started from lactone **12**,[16] available from D-GlcNAc in three simple steps. Addition of $(MeO)_2POCH_2Li$ to **12** generated β-hydroxy phosphonate **13** in excellent yield. Direct reductive deoxygenation of compound **13** also proved to be difficult. Attempted reductions with $Et_3SiH/BF_3{\cdot}Et_2O$, Et_3SiH/TFA, Et_3SiH/TMSOTf, Ph_3SiH/Et_2AlCl, and $NaBH_4$/TFA did not afford **2**. However, when compound **13** was treated with Ac_2O/NaOAc at 100 °C, olefin **14**[17] could be obtained in good yield. Other elimination conditions (oxalyl chlo-



Scheme 2. Reagents and conditions: (i) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 30 min; (ii) $HOP(OEt)_2$, BuLi, THF, −78 °C to rt, 2.5 h, 66% of **10a**+13% of **10b**; (iii) CS_2, NaH, MeI, THF, rt, overnight; (iv) Bu_3SnH, AIBN, toluene, 80 °C, 20 min, 46% over the last two steps.



Scheme 3. Reagents and conditions: (i) $(MeO)_2POCH_2Li$, THF, −78 °C, 96%; (ii) Ac_2O, AcONa, 100 °C, 70%; (iii) H_2 (g), Pd/C, HOAc, quant.

ride/pyridine, $SOCl_2$/pyridine, $POCl_3$/pyridine) only afforded complex mixtures. Hydrogenation of olefin **14** quantitatively furnished the product **2**. Efficient methods for the conversion of *C*-glycosylphosphonate diesters similar to **1** and **2** to the corresponding phosphonate monoesters or phosphonic acids have been reported.[18]

We have established completely stereoselective and highly efficient routes to the β *C*-glycosyl analogues of *N*-acetyl mannosamine 1-*O*-phosphate and *N*-acetyl glucosamine 1-*O*-phosphate, starting from well-known and readily prepared derivatives of the inexpensive D-GlcNAc. These are not only useful as structural components of potential glycosyltransferase inhibitors, but they may also serve as precursors to more elaborate 2-amino β-*C*-glycosides via Horner–Emmons reaction of the phosphonate groups.

Supplementary data. Experimental procedures and spectroscopic data for compounds **1**, **2**, **4**, **10a**, **11**, **13**, and **14**. The supplementary data are available online with the paper in ScienceDirect.

Acknowledgements

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11. Compound **8** was obtained under a variety of reaction conditions. It was identified as diethyl (3*S*,4*R*)-3,5-*O*-benzylidene-4-hydroxy-(*E*)-1-pentene-1-phosphonate from the following data, supported by DEPT, COSY, HSQC, and NOE experiments: $[\alpha]_D$ −54.5° (*c* 1.05, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (dt, 6H, *J* = 0.8 and 7.1), 3.62 (dddd, 1H, *J* = 10.1, 4.1, 5.0, and 8.8, H-4), 3.68 (dd, 1H, *J* = 10.1 and 10.1, H-5), 4.00–4.14 (m, 4H), 4.23 (dd, 1H, *J* = 8.8, 3.2, and 2.0, H-3), 4.32 (dd, 1H, *J* = 10.1 and 4.1, H-5), 5.44 (d, 1H, *J* = 5.0, OH), 5.58 (s, 1H), 6.11 (ddd, 1H, *J* = 21.6, 17.2, and 2.0, H-1), 7.26 (ddd, 1H, *J* = 3.2, 17.2, and 23.3, H-2), 7.34–7.57 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.64 (d, *J* = 6.5), 62.44 (d, *J* = 5.6), 62.46 (d, *J* = 5.5), 65.36 (d, *J* = 1.9), 72.00 (s), 81.36 (d, *J* = 20.5), 101.10 (s), 116.36 (d, *J* = 188.9), 149.99 (d, *J* = 6.7); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 20.41; ESI-MS (*m*/*z*): 343.34.
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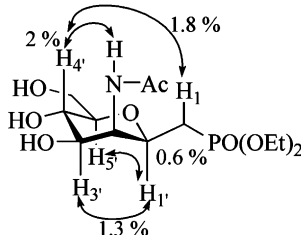
13. Compound **1** was obtained as a glassy solid. Its configuration was confirmed by NOE correlations between H_{NH}–$H_{4'}$, H_1–$H_{4'}$, $H_{1'}$–$H_{2'}$, and $H_{1'}$–$H_{3'}$.



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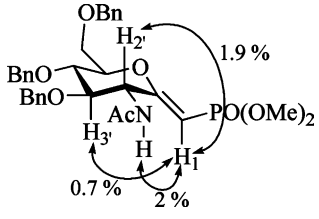
17. Compound **14** was obtained as white needles. Only one isomer of **14** was observed. An NOE experiment showed correlations between H_1–NH, H_1–$H_{2'}$, and H_1–$H_{3'}$.



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