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2-Acetamido-2-deoxy-D-iminosugar C-glycosides: recent synthetic approaches and perspectives

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Whereas **iminosugars** are ranking among the most **powerful glycosidase inhibitors**,¹ their promising C-glycoside derivatives have not yet shown their full potential as glycosidase or glycosyltransferase inhibitors. One of the **main drawbacks associated with iminosugar-C-glycosides is their multistep synthesis sequence**. This is even **more obvious with 2-acetamido-2-deoxy-D-iminosugars**, due to the presence of the sensitive NHAc moiety.

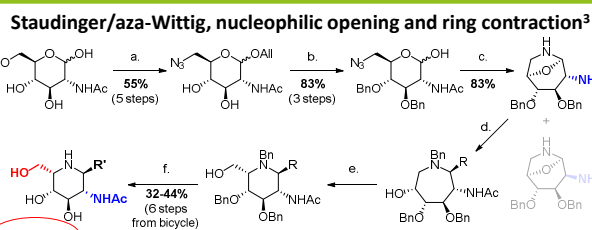
Because of the **key biological role of GlcNAc and GalNAc** and the valuable potential of relevant iminosugar analogues able to interfere with enzymes of high therapeutic interest,² developing new strategies for the synthesis of this class of compounds is still worth investigating.

(1) O. R. Martin, P. Compain (2007), *Iminosugars: From synthesis to therapeutic applications*, Wiley-VCH: Weinheim
(2) N. E. Clark et al. (2012), *PNAS* (43) 17400-17405



2-acetamido-2-deoxy-D-iminosugar C-glycoside

Context of the study



a. i) Al(OH)₃, AcCl ii) Ac₂O, pyr. iii) tBuOK, MeOH iv) TsCl, pyr. v) Na₂S₂O₈, DMF, b. i) BnBr, BaO, DMF, Ba(OH)₂·8H₂O ii) Ir complex, THF iii) I₂, THF/H₂O, c. PMe₃, THF, 75°C, 1h. d. i) RMgCl, THF ii) BnBr, K₂CO₃, DMF, e. i) TFAA ii) aq. NaOH, f. i) H₂, Pd black, 10% Pd/C, MeOH, 1M HCl ii) Amberlite resin

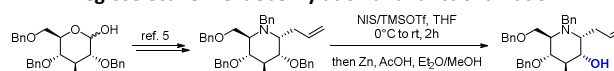


- ✓ NHAc moiety already in place
- ✓ Highly diastereoselective opening of the bicyclic hemiaminal
- ✓ Robust ring contraction strategy

BUT → only L-series
→ many steps
→ C-2 epimerisation during Staudinger/Aza-Wittig

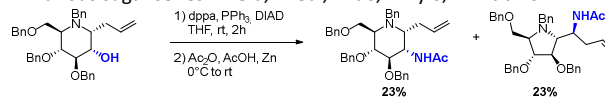
(3) N. Fontelle et al. (2018), *Eur. J. Org. Chem.* (2018) 5477-5488

Regioselective 2-O-debenzylation and functionalization⁴



This C-2 regioselective debenzylative cycloetherification/reductive elimination sequence was applied on several iminosugars substrates:

- various ring size: piperidine, azepane or pyrrolidine
- various sugar series: D-Glu, D-Gal, L-Ido, D-Xylo, D-Arabino...



- ✓ Access to 2-acetamido-2-deoxy-D-gluco iminosugar C-glycoside
- ✓ Large scope for 2-O-debenzylation step
- ✓ Short sequence

BUT → modest yields
→ mixture of piperidine and pyrrolidine
→ limited to C-allyl iminosugars

(4) Q. Foucart et al. (2019), *Org. Lett.* (21) 4821-4825
(5) L. Cipolla et al. (2000), *Chem. Commun.* (2000) 1289-1290

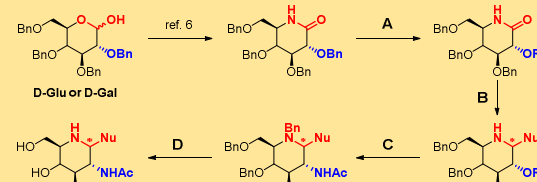
Former strategies

New strategy

O-protected sugar lactams are readily obtained from the corresponding 2,3,4,6-tetra-O-benzylated pyranoses.⁶ The following steps will then provide 2-acetamido-2-deoxy-D-iminosugar C-glycosides:

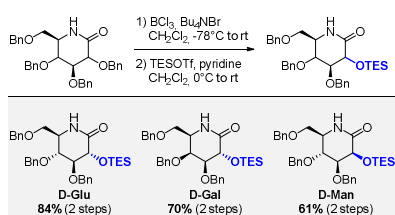
- Regioselective O-2 debenzylation and orthogonal protection
- Lactam reduction and nucleophilic addition
- O-2 deprotection and acetamidation
- Full deprotection

This strategy allows the use of various nucleophiles and late acetamide introduction.

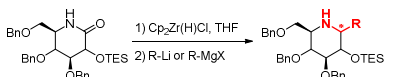


(6) T. Stauffert et al. (2016), *Synthesis* (48) 1177-1180

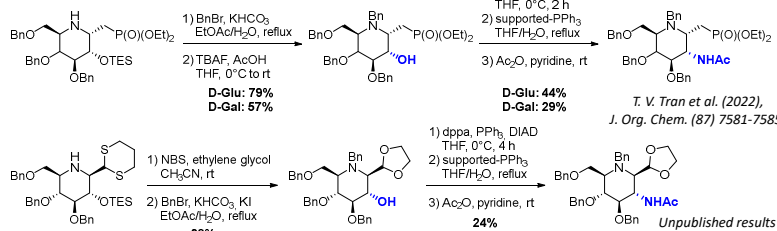
A. Regioselective O-2 debenzylation and silylation



B. Lactam reduction and nucleophilic addition⁷

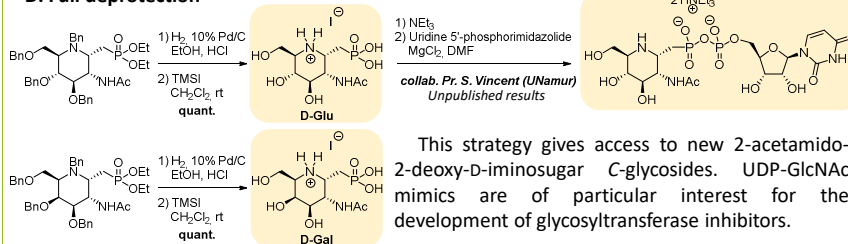


C. O-2 deprotection and acetamidation



N-benylation is required to perform stereoretentive azidation via aziridinium intermediate. Minor formation of pyrrolidine ring is also observed.

D. Full deprotection



This strategy gives access to new 2-acetamido-2-deoxy-D-iminosugar C-glycosides. UDP-GlcNAc mimics are of particular interest for the development of glycosyltransferase inhibitors.

Shortened synthetic sequence

Stereoselective synthesis of new and valuable 2-acetamido-2-deoxy-D-iminosugar C-glycosides
Access to various C-glycosides allows adaptability to biological targets

(7) P. Szczesniak et al. (2014), *Tetrahedron* (70) 1880-1888

Results