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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 307–310

Ring-closing double reductive amination route to aza-heteroannulated sugars

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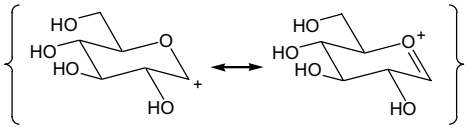
Received 8 October 2004; revised 3 November 2004; accepted 8 November 2004
Available online 25 November 2004

Abstract—1,4-Dicarbonyl derivatives of glycosides are produced by ozonolysis or Wacker oxidation. A stable ozonide is isolated and a carbonyl group reduced whilst maintaining the ozonide functionality. The 1,4-dicarbonyl compounds are converted to various *N*-substituted pyrrolidines by diastereoselective double reductive amination The resulting aza-heteroannulated sugars no significant inhibition of any glycosidase, with the exception of compound **12g**, which is a weak inhibitor of β-galactosidase.

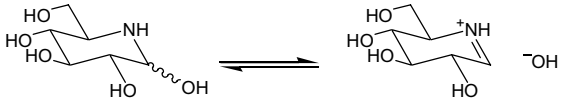
Polyhydroxylated aza-heterocycles and aminosugars are of interest because they evince a wide range of biological activity.[1–3] Particular attention has been paid to their ability to inhibit glycoside-processing enzymes, with resulting potential therapeutic applications in treatment of cancer, HIV and diabetes.[4,5]

The mechanism of glycosidases has been extensively studied, and is now thought to proceed via protonation of the *exo*-cyclic oxygen, which after bond cleavage gives rise to an oxo-carbonium ion intermediate such as **1**.[1]



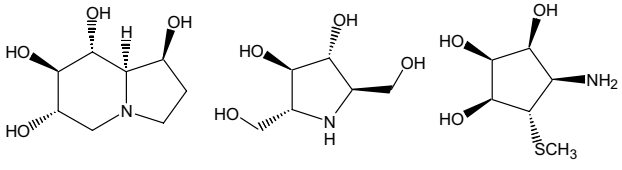
1

Design of inhibitors has subsequently focused upon mimicking the shape and charge of the transition state that leads to intermediate **1**. Potent naturally-occurring inhibitors such as nojirimycin (**2**) are thought to work via formation of an iminium ion (**3**), which is an aza-analogue of oxonium ion **1**.



2 **3**

Other potent inhibitors, such as castanospermine (**4**) and (2*R*,5*R*,3*R*,4*R*)-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (**5**), lack an hydroxyl group adjacent to the *endo*-cyclic heteroatom, and therefore cannot form an iminium ion analogous to **3**.[6] In these compounds the presence of a nitrogen that can be protonated is sufficient to give high glycosidase inhibitory activity.[1] Mannostatin A (**6**) is a potent inhibitor without obvious resemblance to the proposed transition state. This illustrates the importance of a basic amino group being present.[7a] Acetylation of this amino group has been found to destroy inhibitory activity.[7b]



4 **5** **6**

Keywords: Pyrrolidines; Carbohydrate annulation; Amino sugars; Stable ozonide decomposition; Glycosidase inhibitors.
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doi:10.1016/j.tetlet.2004.11.032

The synthesis of such compounds has therefore attracted considerable interest, with routes to enantiopure materials of special importance.

Previous work within this group has focused on the use of carbohydrates as scaffolds for stereoselective construction of various cyclic compounds.[8,9] Extension of this approach to include aza-heterocycles was expected to provide a facile route to substituted pyrrolidines. Production of the desired compounds by double reductive amination of a 1,4-dicarbonyl precursor was envisaged. Several examples of highly stereoselective double reductive amination ring-closures indicated the broad applicability of the intended approach.[10,11] The potential to create a diverse range of derivatives by altering the substituent on the nitrogen of the resulting pyrrolidine was also attractive, as it allows for possible optimisation of any biological activity, which is found.

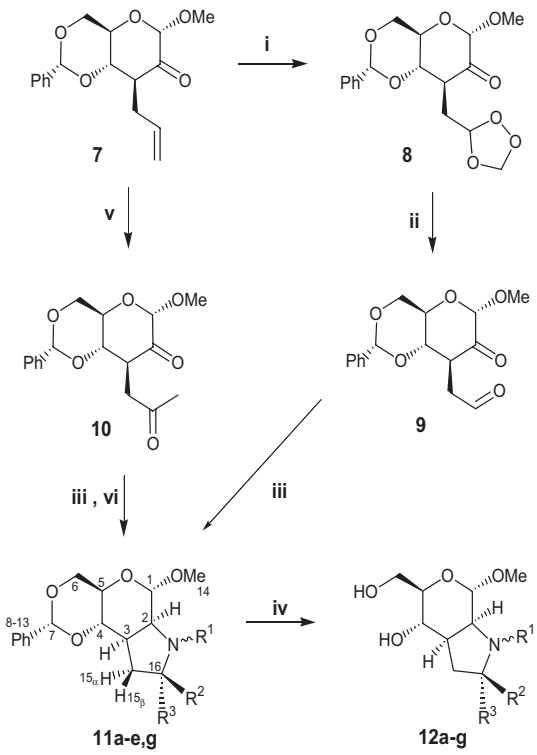
The transformation of the known alkene **7**[8] to a 1,4 dicarbonyl compound can be achieved by various methods in which oxidation of the alkene bond is a common feature. The simplest route was expected to be the ozonolysis of the double bond.

Formation of ozonide **8** in 85% yield was achieved by bubbling O_3 through a solution of alkene **7** in DCM at −78 °C.[12,13] Decomposition of ozonide **8** was initially attempted by treatment with excess DMS at rt overnight.[12] Removal of the DMS and DCM resulted in a clear syrup that was identified as a mixture of two diastereoisomers of ozonide **8** by ^{1}H NMR (Scheme 1).[13] Further attempts at reduction of the ozonide were made using thiourea, which also failed. Reduction using powdered zinc in acetic acid, which has been reported in the literature as reducing ozonides impervious to reduction with DMS[14] gave a complex mixture of products that did not have the Ph or OMe ^{1}H NMR signals of the starting material, indicating loss of the protecting groups. Direct conversion of the ozonide to an amine was also attempted without success.[15] Reaction of ozonide **8** with $NaCNBH_3$ in 2:1 THF–DCM at rt resulted in the reduction of the ketone functional group without decomposition of the ozonide moiety to afford ozonide **13** (Scheme 2); indicating an unusually stable ozonide.[16]

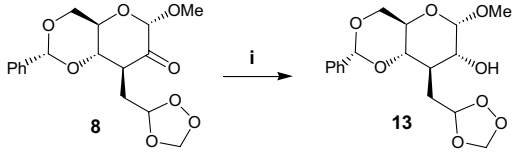
Decomposition of ozonide **8** was eventually achieved by treatment with 1 equiv of PPh_3 in DCM at rt to afford the dicarbonyl compound **9** in 62% yield.[17,18] Difficulties in removal of the Ph_3PO from **9** were overcome by use of a polymer-bound reagent (Scheme 1).[19]

An alternative approach for the conversion of ketone **7** to a 1,4-dicarbonyl compound makes use of the Wacker oxidation. This involves the oxidation of a terminal alkene to a methyl ketone using $PdCl_2$.[20] The desired diketone **10** was produced according to the literature procedure in 85% yield as a colourless syrup and identified by ^{1}H and ^{13}C NMR.[8]

Ring closure of the dicarbonyl compound **9** was achieved by treatment with an excess of amine with a catalytic amount of AcOH in THF at rt, followed by addition of $NaCNBH_3$ (Scheme 1). We were encouraged by the initial success with aliphatic amines, in which only one diastereoisomer was formed, in moderate yields (Table 1).[21] The configuration and stereochemistry of the ring junction was confirmed by single-crystal X-ray crystallography (Fig. 1)[22] and ^{1}H NMR NOESY experiments. For example, NOE interactions were observed between H-3 and H-5 for **11d**, and between H-4, H-15$_\beta$ and H-16$_\beta$ and H-2, H-15$_\alpha$ and H-16$_\alpha$ for **12a**.



Scheme 1. Reagents and conditions: (i) O_3, DCM, rt, 1 h, 85%; (ii) polymer-bound PPh_3, PhMe, 90 °C, 1 h, 62%; (iii) R^1NH^2, AcOH, THF, then $NaCNBH_3$, rt, 2 h (Table 1); (iv) 80% AcOH aq, reflux, 4 h or 80% AcOH in EtOH, reflux, 30 h (Table 1); (v) $PdCl_2$, $CuCl_2$, O_2, 1:1 DMF–H_2O, rt, 4 h, 85%; (vi) chromatographic separation.



Scheme 2. Reagents and conditions: (i) $NaCNBH_3$, THF–DCM, rt, 1 h, 83%.

Table 1. Structures and yields of compounds **11a–e**, **g** and **12a–g**

	R^1	R^2	R^3	% Yield of **11**	% Yield of **12**
11a, **12a**	Pr^i	H	H	49	78
11b, **12b**	Pr^i	Me	H	29	83
11c, **12c**	Pr^i	H	Me	15	67
11d, **12d**	$CH_2CH_2CH_2OH$	H	H	45	94
11e, **12e**	CH_2CO_2Et	H	H	42	65
12f	CH_2CO_2H	H	H	—	80
11g, **12g**	OH	H	H	57	77