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Synthesis of a constrained polyfunctional bicyclic iminocyclitol scaffold from L-sorbose via a tandem sequence including stereoselective intramolecular Huisgen cycloaddition

Ciaran O'Reilly [a], Colin O'Brien [a], Paul V. Murphy [a,b,*]

[a] UCD School of Chemistry and Chemical Biology and Centre for Synthesis and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland
[b] School of Chemistry, National University of Ireland, Galway, Ireland

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This Letter is dedicated to Professor R. N. Butler on the occasion of his 65th birthday

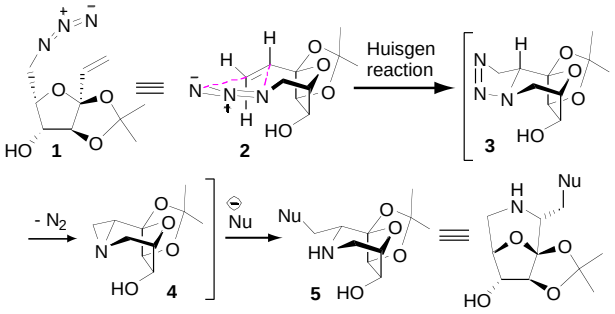
ABSTRACT

The synthesis of a functionalized (azido, amino, and hydroxy) 8-oxa-3-azabicyclo[3.2.1]octane framework and its conversion into a protected sugar amino acid and a tricyclic framework is described. The sequence includes a one-pot Huisgen 1,3-dipolar cycloaddition, with decomposition to an aziridine and subsequent ring opening by azide. The stereoselectivity observed in the Huisgen cycloaddition reaction is attributed to minimization of allylic strain.

A variety of scaffolds have been investigated in medicinal chemistry, including monosaccharides and related compounds.[1] The use of carbohydrate scaffolds in bioactive compound generation has been a success in part because the inherent pyran or furan framework contains multiple sites (alcohol, amine, and carboxylic acid) to which pharmacophoric groups can be attached. Polyhydroxylated piperidines, also known as iminosugars or iminocyclitols, are analogues of monosaccharides. The use of iminosugars as scaffolds[2] for bioorganic and medicinal chemistry offers the possibility, not available to pyranosides, of incorporating a charged hydrogen bond donor through protonation of the ring nitrogen atom. In addition, pharmacophoric groups can be grafted to the nitrogen atom. Iminocyclitols have been of significant interest as glycosidase inhibitors[3] prompting the development of a range of syntheses of these and their related compounds. Herein we describe the synthesis of a polyfunctionalized bicyclic iminocyclitol from L-sorbose. The product contains azide, amino, and hydroxy groups that would facilitate its exploitation in medicinal chemistry.

Recently the intramolecular 1,3-dipolar cycloaddition reactions[4] of azides and alkenes (Huisgen reaction)[5] were used in a sequence of reactions for the synthesis of 1-deoxynojirimycin (DNJ) and close structural analogues from a sugar lactone percursor.[6] As an extension, it was envisaged that the azide–alkene cycloaddition of substrate **1**, obtained from readily available L-sorbose, would provide access to the protected polyfunctional bicyclic scaffold **5**.

As in the DNJ synthesis it was anticipated that an intermediate (Scheme 1) of the type **2** would be favored as it would minimize allylic strain and provide a single triazoline stereoisomer **3**. The intermediate triazoline would be expected to lose nitrogen, possibly giving the aziridine **4**[7] which on reaction with a nucleophile would give the polyfunctional bicyclic compound **5**.



Scheme 1. Synthesis of functionalized scaffold **5** from L-sorbose.

The synthesis of **9** (Scheme 2) began from **7**, which was available from L-sorbose **6** (furanose form) as described previously.[8] The regioselective ring opening of the more labile isopropylidene group was carried out by treatment of **7** with 60% acetic acid at 60 °C for 2 h giving the diol **8** in good yield. With this diol in hand, the exchange of the primary alcohol with an azide and subsequent Huisgen reaction[9] were next investigated. Diol **8** was thus treated with thionyl chloride and pyridine in dichloromethane at 0 °C for 2 h giving a cyclic sulfite. This intermediate was treated with excess sodium azide in DMF at 110 °C. The crystalline bicyclic product **9** was isolated in 40% yield; other by-products were not obtained. The formation of **9** is explained by the cascade sequence

* Corresponding author. Fax: +353 91 525700.
E-mail address: paul.v.murphy@nuigalway.ie (P.V. Murphy).

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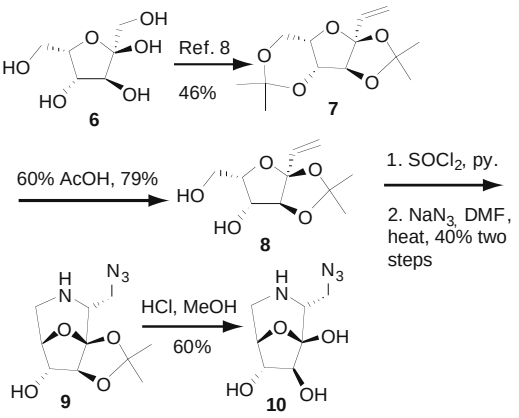


Scheme 2.

described in Scheme 1, where, under the reaction conditions, it was not possible to observe the triazoline or aziridine intermediates.[10] Efforts to improve the yield of **9** from the one-pot reaction were not successful. The X-ray crystal structure of **9** (Fig. 1) confirmed the structure of the bicyclic compound and the configuration of the newly generated stereocenter. Removal of the isopropylidene from **9** was effected using 0.2 M HCl in MeOH to give polyhydroxylated compound **10**.

Treatment of **9** with ethyl bromoacetate in THF along with a catalytic amount of tetrabutylammonium iodide gave **11** (61%), which can be considered to be a protected sugar amino acid.[11] Catalytic hydrogenation of **11** caused reduction of the azide to the amine which led to spontaneous lactam formation; subsequent removal of the acetonide from the intermediate gave tricyclic derivative **12** in 58% yield over two steps (Scheme 3).

In summary, iminocyclitols with an ether bridge have been prepared in a concise and stereoselective manner from L-sorbose. The

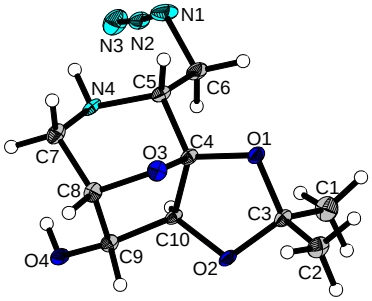
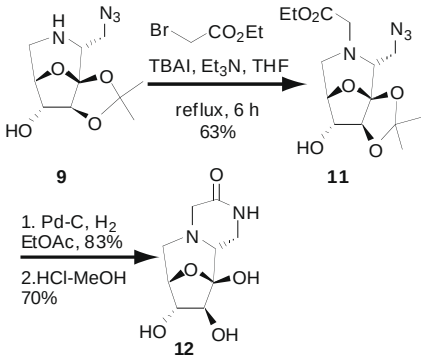


Figure 1. ORTEP representation of the X-ray crystal structure of **9**. The atomic displacement parameters are at the 50% level. CCDC 731460.



Scheme 3.

one-pot sequence included azide incorporation, Huisgen cycloaddition, triazoline decomposition, aziridine formation, and its subsequent reaction with azide. The 8-oxa-3-azabicyclo[3.2.1-]octanes are of medicinal interest. For example, achiral 8-oxa-3-azabicyclo[3.2.1]octane[12,13] has analgesic and anti-inflammatory effects in vivo[14] and analogues have been prepared.[15] The protected amino acid **10** could have application in peptidomimetic development.[16] Sorbose derivative **9** can be considered a conformationally constrained morpholine derivative[17] and is structurally related to bicyclic alkaloids with nortropane skeletons, which have been found to have biological activity as glycosidase inhibitors.[18] Lactam **12** contains a tricyclic framework.[19] A recent analysis of scaffolds investigated in organic chemistry showed that a small number of frameworks are found in a large number of all known compounds.[20] The approach described herein using readily available carbohydrate precursors has potential to be applied to generating new functional frameworks for organic chemistry.

Acknowledgments

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Supplementary data

Supplementary (general experimental methods, experimental procedures, analytical data, ^{1}H and ^{13}C NMR spectra, crystallographic information file for **9**) data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.060.

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