A Novel Diels–Alder Approach To Heavily Substituted Azasugars

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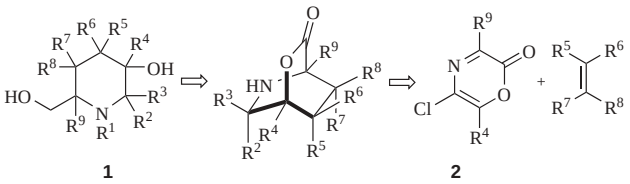
Received 29 August 2003

Abstract: Diels–Alder cycloaddition of an appropriately substituted 1,4-oxazin-2-one with vinylene carbonate followed by the chemical manipulation of the bridged bicyclic lactone cycloadduct affords a heavily functionalised azasugar ring.

Key words: Diels–Alder, cycloaddition, 2*H*-1,4-oxazin-2-one, azasugar

'Azasugars' (also known as 'iminosugars') are structural analogues of pyranose carbohydrates in which the ring oxygen atom is replaced by a nitrogen atom. It has been postulated that because of their structural similarity to 'true' sugars, azasugars are recognized by carbohydrate handling enzymes and receptors, which are nevertheless incapable of chemically transforming them. The resulting inhibition of the enzymes or antagonism of the receptors leads to the numerous pharmacological properties which are associated with azasugars.[1] The opportunity they provide for 'rational' design of inhibitors and their already proven ability to interfere with the biological processes involving binding or turn-over of native polysaccharides has made azasugars important biological tools and medicinal targets. This is demonstrated with the recent launch of Zavesca (miglustat) for the treatment of Gaucher's disease.[2] Crucial to these investigations are the development of general as well as specific synthetic methods for the preparation of azasugars. Indeed, the preparation and biological properties of a number of naturally occurring and synthetic azasugars are already documented in the literature (Figure 1).[3–8]

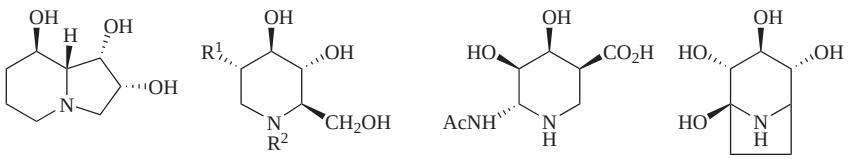
These examples typify the many routes to azasugars already reported in the literature. The vast majority of these involve a ring forming reductive amination of an in situ generated ω-aminoaldehyde or ketone and have been applied to aza analogues of furanose as well as pyranose sugars.[9] The starting materials for these syntheses are readily available carbohydrate molecules of the chiral pool which results in the formation of the products in an enantiomerically pure form. However, the requirement for functional group protection makes the synthesis of certain analogues laborious and inefficient, particularly those with a more elaborate pattern of substituents.



Scheme 1

Therefore, other methods have also been investigated including ring contraction of azepanes,[10] photocyclisation,[11] ring closure metathesis[12] and ruthenium catalysed ring rearrangement,[13] oxidation of a pyridone[14] and oxidation of aminomethylfurans,[15] to name a few. Combinatorial synthesis of libraries of azasugars are also reported.[16] The 'aza' concept has been further expanded to 'double aza'[16b] analogues and amino aza sugars.[17]

Here, we report a new approach to the synthesis of azasugars. The key advantage of this route is that it allows a short, very efficient method for the controlled synthesis of heavily and diversely substituted piperidines e.g. **1**, in



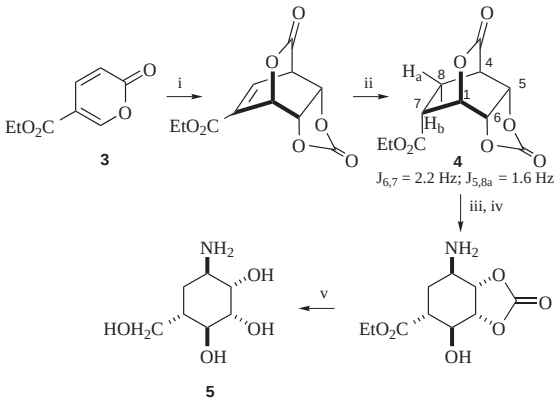
Swainsonine[2] $R^1 = R^2 = H$; Fagomine[3] $R^1 = OH$; $R^2 = H$; Deoxynojirimycin[4] $R^1 = OH$; $R^2 = n$-Bu; Zavesca (Miglustat) $R^1 = OH$; $R^2 = CH_2CH_2OH$; Miglitol[5]

Siastatin B[6]

calystegin B_2[7]

Figure 1

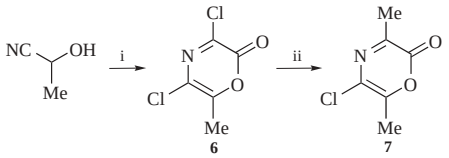
SYNLETT 2003, No. 15, pp 2341–2344
Advanced online publication: 21.11.2003
DOI: 10.1055/s-2003-43336; Art ID: D21703ST



Scheme 2 i) Vinylene carbonate, 100 °C, 83%; ii) H_2, EtOAc, Pd/C, 100%; iii) NH_3 Dioxane, 78%; iv) $(CF_3CO_2)_2IPh$, $MeCN/H_2O$, 92%; v) $LiAlH_4$, pyridine, 88%

general, and azasugars, in particular. Our methodology is based on Diels–Alder cycloadditions of appropriately substituted 1,4-oxazin-2-ones, e.g. **2**, as an azadiene component of the [4+2] cycloaddition to regio and stereoselectively bring together the heterocyclic ring which through further chemo- and stereoselective transformations would afford target molecules (Scheme 1).

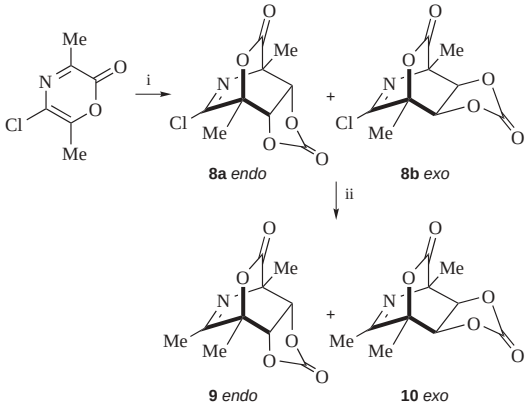
This approach is particularly relevant to us due to the close analogy between the 1,4-oxazin-2-ones and the 2*H*-pyran-2-one rings. We have previously shown that the Diels–Alder cycloaddition of appropriately substituted 2*H*-pyran-2-ones, such as **3**, is an excellent starting point for the synthesis of heavily functionalised carbocyclic six-membered rings, and in particular carbasugars. This has been exemplified by the conversion of **3** to epi-validamine via its chemical manipulation of intermediates **4** and **5** (Scheme 2).[18] Carbasugars, naturally occurring or synthetic analogues of pyranose sugars in which the ring oxygen atom is replaced by a methylene group, have a similar biological relevance as azasugars.[19] We expected that our experience with the cycloadditions of 2*H*-pyran-2-one would be very beneficial to addressing the issues raised by this proposed methodology.



Scheme 3 i) Toluene, reflux, 24 h, $(COCl)_2$; ii) Toluene, reflux, 24 h, $SnMe_4$, $Pd(PPh_3)_4$

Surprisingly, a general and reliable method for the preparation of substituted 1,4-oxazin-2-ones was lacking until Hoornaert published a straightforward route in 1989.[20] Starting from cyanohydrins, Hoornaert prepared various 6-substituted 3,5-dichloro-1,4-oxazin-2-ones and subsequently demonstrated that they undergo [4+2] cycloaddition with concomitant loss of CO_2 or cyanogen to afford pyridines[21] and 2*H*-pyran-2-ones, respectively.[22] Later, Hoornaert demonstrated that 2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one cycloadducts can also be isolated from the cycloadditions[23] and reported on their chemical manipulation.[24]

These observations by Hoornaert encouraged us to consider a route to substituted piperidines from the cycloaddition of 1,4-oxazin-2-ones. The key advantage of such an approach is the diversity of the substituents that can be introduced into the piperidine nucleus (Scheme 1). In particular, this approach is expected to allow control over the relative configuration of every carbon substituent on the azasugar ring (Scheme 1).



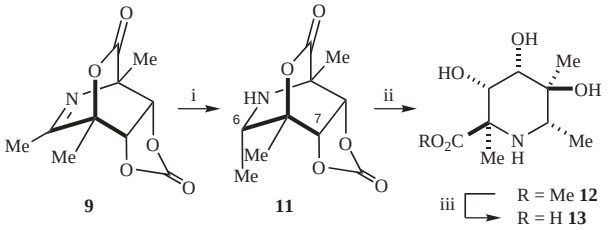
Scheme 4 i) Toluene, reflux, 24 h, vinylene carbonate (74%); ii) Toluene, reflux, 48 h, Me_4Sn, $Pd(PPh_3)_4$ (92%)

3,5-Dichloro-6-methyl-1,4-oxazin-2-one (**6**) was prepared according to a previously published route by Hoornaert.[20] Under palladium catalysed conditions, the 3-chloro substituent was selectively substituted with a methyl group to afford **7** (Scheme 3). There was no evidence of substitution of the 5-chloro substituent in the NMR data of the crude product. This azadiene underwent efficient cycloaddition with vinylene carbonate to afford a 2.5:1 *endo*/*exo* ratio of cycloadducts **8a** and **8b**, which could not be separated. The chloro substituents in each of the cycloadducts **8a** and **8b** were replaced with methyl groups using palladium catalysed Stille coupling. At this stage, the *endo* and *exo* products **9** and **10** could be separated by chromatography and were isolated in 65% and 27% yields respectively (Scheme 4).

The assignment of the *endo* and *exo* isomers proved to be non-trivial. Based on our extensive expertise in the cycloadditions of 2*H*-pyran-2-ones, we did expect the major isomer to have *endo* configuration. However, the primary evidence for this is deduced from the coupling constants of the bridgehead protons in the NMR of the cycloadducts, using empirical rules set out previously.[25] Since neither cycloadduct contains a bridgehead proton (i.e. both positions 1 and 4 are substituted), the assignment could not be made. We therefore had to resort to a different criterion for this assignment. Fortunately, Tomisawa[26] and Posner[24] had earlier demonstrated that in pyrone cycloadducts, magnetic anisotropy due to the double bond

significantly lowers the chemical shifts of the protons at *endo* positions. Indeed, the chemical shifts for H-7 and H-8 protons in the assigned *endo* product are at 4.74 ppm and 4.78 ppm whereas the chemical shifts for H-7 and H-8 protons in the assigned *exo* product are at 4.51 ppm. Further evidence of the *endo* configuration of the major cycloadduct was obtained after the next step.

Hydride reduction of the imine functionality of the *endo* bridged ester **9** selectively gave amine **11**. The stereochemistry of the reduction is based on our earlier observations during hydrogenolysis of the structurally related compound **4**.[18] The lower face of the imine is sterically encumbered by the carbonate bridge and therefore, the reducing agent is introduced from the lactone bridge face (Scheme 5). Furthermore, close analysis of the NMR of compound **11** revealed a fine coupling (1.3 Hz) between H-6 and H-7. This W coupling, is also a feature of reduction of cycloadducts of 2*H*-pyran-2-ones and is observed, for instance, in compound **5** (Scheme 2). The presence of this W coupling strongly supports the proposed configuration of the reduction product.

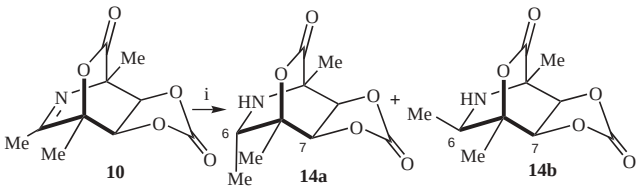


9 **11**

Scheme 5 i) HOAc, $NaBH(OAc)_3$, r.t., 24 h (67%); ii) MeONa (1 equiv), MeOH, reflux, 30 min (49%); iii) 2 M NaOH, r.t., 1 h (quant.)

Basic aqueous hydrolysis of the amine **11** was not efficient, however, methanolysis of **11** to methyl ester **12** followed by basic hydrolysis of compound **12** gave a very good yield of azasugar **13**.

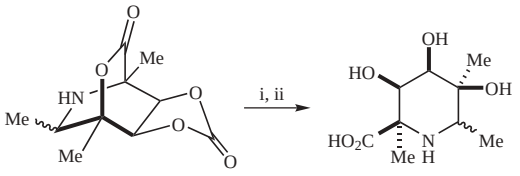
In contrast to the stereoselective reduction of imine **9**, hydride reduction of the imine functionality of the *exo* bridged ester **10** gave a mixture of two amines **14a** and **14b** in a 3:1 ratio which could not be separated (Scheme 6). The lack of selectivity in the reduction of **10** is again consistent with our previous observations that *exo* cycloadducts of 2*H*-pyran-2-ones undergo non-stereoselective hydrogenation of their alkene function.[18] In the case of reduction of **10**, there are no steric encumbrance to either face of the imine and therefore, the reducing agent is introduced from either face. Interestingly, close analysis of the NMR of compounds **14a** and **14b** revealed no fine W coupling between H-6 and H-7. The absence of this W coupling supports the proposed *exo* configuration of the starting material.



10 **14a** **14b**

Scheme 6 i) HOAc, $NaBH(OAc)_3$, r.t., 24 h (79%)

As before, methanolysis of **14a** and **14b** followed by basic hydrolysis of the two isomers gave azasugars **15a** and **15b** (Scheme 7).



14ab **15ab**

Scheme 7 i) MeONa (1 equiv), MeOH, reflux, 30 min; ii) 2 M NaOH, r.t., 30 min (51%)

In conclusion, we have demonstrated that azasugars can be prepared with control of relative stereochemistry via the Diels–Alder cycloaddition of an appropriately substituted 1,4-oxazin-2-one with vinylene carbonate followed by the chemical manipulation of the bridged bicyclic lactone cycloadduct. We are currently working to expand the scope of this novel methodology and to synthesise other azasugars.

Acknowledgement

We thank Oxford GlycoSciences Ltd. (now part of Celltech R&D Ltd.) for financial support.

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