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Synthesis of a new class of iminosugars based on constrained azaspirocyclic scaffolds by way of catalytic C-H amination†

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Pierre-Antoine Nocquet,[a] Raphaël Hensienne,[a] Joanna Wencel-Delord,‡[a] Eric Wimmer,[a] Damien Hazelard[a] and Philippe Compain*[a,b]

The synthesis of the first examples of a new class of iminosugars based on constrained spirocyclic scaffolds has been achieved *via* Rh-catalyzed C(sp^3)-H amination. In this process, the needed electronic control in securing high regioselectivity from substrates with a high density of activated C-H bonds was achieved by using a combination of activating and electron-withdrawing groups.

Fifty years after their discovery, sugars in which the endocyclic oxygen is replaced by a nitrogen atom, the so-called iminosugars, have established themselves as the most fascinating class of glycomimetics reported so far.[1,2] The main skeletal framework of iminosugars may be classified into five structural classes: pyrrolidines, piperidines, indolizidines, pyrrolizidines and nortropanes (Figure 1). Firstly known as potent glycosidase inhibitors in the 70's, iminosugars have been shown over the years to have a wide range of inhibitory activities against various carbohydrate-processing enzymes including glycosyltranferases and glycogen phosphorylases.[1-4] Remarkably, in the early 2000's, the scope of their biological activity was extended to metalloproteinases,[5] protein kinases[6] and cholinesterases[7] which are enzymes that act on non-sugar substrates. Because of the pivotal roles played by the above-mentioned enzymes in numerous biological mechanisms, iminosugars have logically demonstrated a range of promising activities that span a wide cross section of diseases such as diabetes, viral diseases, psoriasis or misfolded protein disorders.[1,8] The number of structures involved in clinical trials and the two drugs currently on the market further highlight the high therapeutic interest of iminosugars.[1,8] The approval of Zavesca (*N*Bu-DNJ, **1**) as the first oral treatment for Gaucher and Niemann-Pick diseases and its recent evaluation in phase II clinical trials for cystic fibrosis are spectacular demonstrations of the importance of iminosugars as medicines for unmet medical needs.[8]

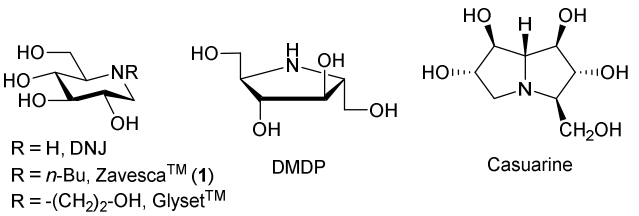


Fig. 1 Some representative examples of iminosugars

Despite these successes, several issues are facing the development of iminosugars as credible medicines, the most important one being their potential lack of selectivity. Iminosugars may indeed appear as "dirty drugs" for medicinal chemists due to their capability to strike several intracellular targets.[9] In this context, the development of truly original iminosugar analogues with unprecedented skeletons is more than ever highly needed. In connection with our recent work on new classes of glycomimetics,[10] we turned our attention to spirocyclic systems of type **I** incorporating small rings (Figure 2). The main objective was to rigidify the conformation of the potential iminosugar-based inhibitors, a strategy widely used in drug discovery,[11] while exploring unfrequented regions of chemical and intellectual property spaces.[12,13] In addition, such structures with several contiguous asymmetric centres, two small cycles, an azaspiranic skeleton and a high density of functional groups represent a number of attractive synthetic challenges. Although four-membered ring-containing spirocycles are witnessing a rapidly growing interest in organic and medicinal chemistry, only very few examples of relatively complex, polysusbtituted heteraspiro[3.n]alkanes have been reported so far. [12,13] Herein we report the synthesis of the first members of a new class of iminosugars based on a 5-azaspiro[3.4]octane framework. The *trans-trans* relative configuration of the three secondary hydroxyl groups in **I** has been chosen since it represents an important

[a] *Laboratoire de Synthèse Organique et Molécules Bioactives (SYBIO), Université de Strasbourg/CNRS (UMR 7509), Ecole Européenne de Chimie, Polymères et Matériaux (ECPM), 25 rue Becquerel, 67087 Strasbourg, France. E-mail:philippe.compain@unistra.fr*
[b] *Institut Universitaire de France, 103 Bd Saint-Michel, 75005 Paris, France.*
‡ Present address: SynCat, Université de Strasbourg/CNRS (UMR 7509), Ecole Européenne de Chimie, Polymères et Matériaux (ECPM), 25 rue Becquerel, 67087 Strasbourg, France
† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

structural feature of bioactive iminosugars including DNJ analogues, castanospermine and iminoxylitols.[1,2,14] Our retrosynthetic analysis hinges on protected cyclobutanol **2**, an advanced intermediate synthesized recently in our group from vitamin C.[10a] The key step of our synthetic strategy is the stereocontrolled formation of the pivotal C-N bond at C4 by way of intramolecular Rh-catalyzed C-H amination, a powerful insertion process occurring with retention of configuration.[15] Applying such a reaction to polyoxygenated substrates represents however an attractive challenge in terms of regioselectivity since electron-donating groups generally activate α-C-H bond towards insertion.[15] Because of the strong bias of carbamates for 5-membered ring formation,[15] this functional group was chosen to generate the transient metal nitrene to secure a high level of stereocontrol. Less control was indeed expected from sulfamate esters for which the panel of cycles generated may span from 5- to 10-membered rings.[15,16] The carbamate function, as an electron-withdrawing group, was directly introduced on the cyclobutane ring and not on the carbon side-chain at C4 to deactivate the α-oxygenated C-H bond at C3 (Figure 2). To further discriminate between cyclobutane C-H bonds, a vinylic group was introduced at C4 since C-H insertion into allylic C-H bonds has been described to be favoured over α-oxygenated C-H bonds.[17] In addition to direct the C-H bond insertion at C4, the vinylic group is involved in the subsequent key step of our strategy which is the ring-closing metathesis of *N*-allyl carbamate **III**. Although RCM reaction has been widely used to form nitrogen-containing heterocycles,[18,19] its application to constrained substrates such as **III** represents an additional challenge. One advantage of combining C-H amination and RCM is that no additional steps are required to prevent unwanted coordination events between the metathesis catalyst and the nitrogen atom since the latter is deactivated by an electron-withdrawing group.[18]

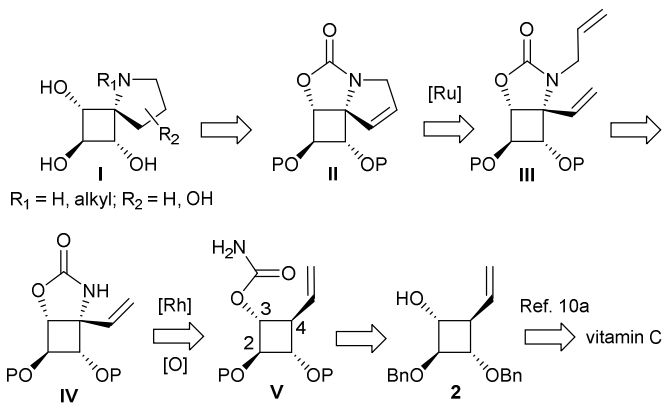
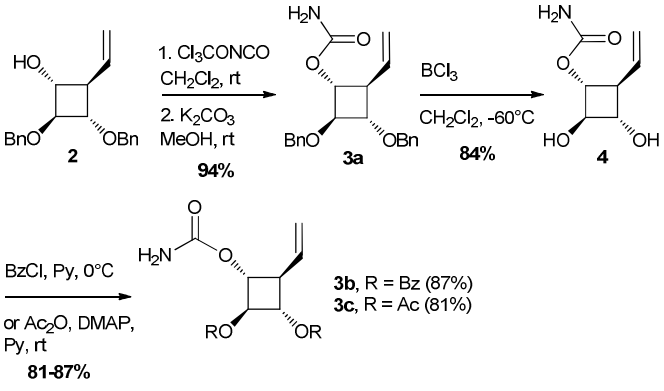


Fig. 2 Retrosynthetic analysis

The C-H amination substrate **3a** was obtained in high yield by treatment of cyclobutanol **2**[10a,20] with $CCl_3C(O)NCO$ followed by K_2CO_3 (Scheme 1). The first attempts to perform the intramolecular C-H insertion reaction led to reverse regioselectivity as compared with acyclic or pyran substrates.[17] Treatment of carbamate **3a** with 2 mol% of $Rh_2(esp)_2$ and stoichiometric amounts of $PhI(OAc)_2$ and MgO afforded the desired C-H amination product **5a** in only 1% yield, whereas the unwanted regioisomer **6a**, corresponding to the insertion at C2, was obtained in 32% yield (Table 1, entry 1). Increasing the amount of catalyst to 20 mol% led to complete conversion of **3a** and provided the allylic C-H insertion product **5a** in 17% yield, compound **6a** being still the major product (56% yield, entry 2). Structure of **5a** was unambiguously determined by ^1H NMR, mainly by the disappearance of the allylic C-H proton at C4, whereas structure **6a** was confirmed by the presence in ^{13}C NMR of a signal at δ 91.1 ppm corresponding to the quaternary hemiaminal ether carbon C2 (see ESI). Since the nature of the catalyst may have a profound influence on the regioselectivity of the C-H amination reaction, several catalytic systems were evaluated.[15,21] Unfortunately, no improvements were observed with $Rh_2(O_2CCF_3)_4$, $Rh_2(OAc)_4$, or $Rh_2(tpa)_4$ catalysts or using silver-based catalytic systems[15e] in the presence of bathophenanthroline and of $PhI(OAc)_2$ (entries 3-7).

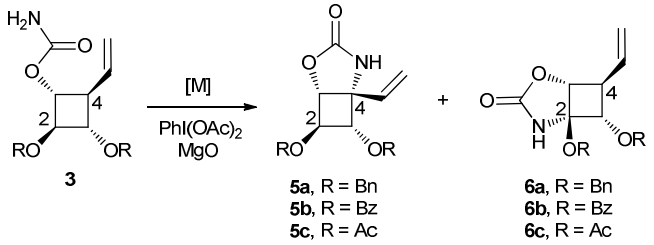


Scheme 1 Synthesis of C-H amination substrates **3**

To disfavour the formation of the unwanted regioisomer **6a**, we switched the benzyloxy protecting groups by much more electron-withdrawing protecting groups to reduce the electronic density of the C-H bond at C2. Deprotection of the benzyloxy groups with BCl_3 followed by treatment with BzCl or Ac_2O in the presence of pyridine afforded the desired esters **3b,c** in high yields for the two steps (Scheme 1). The electron-withdrawing protecting group strategy was found to be successful since it completely prevented the formation of the unwanted regioisomer (entries 8-10). The best results were obtained with benzoate **3b**, the allylic C-H amination product being obtained in 40% yield (entry 10). However, the use of benzoate groups is a double-edge sword since the presence of two electron-withdrawing protecting groups on the cyclobutane ring may also reduce the reactivity of the allylic C-H bond as shown by the modest C-H insertion yield obtained. As a prelude to RCM reaction, *N*-allyl carbamate **7** was prepared in one step from **5b** in the presence of NaH and allylbromide (Scheme 2). Despite the large additional ring strain generated by the 5-membered ring closure, the second key step of our synthetic strategy led to the expected tricyclic spirocycle derivative **8** in high yield under classical conditions using 5 mol% of Grubbs II catalyst. Having in hands the 5-azaspiro[3.4]octane skeleton of our targets, we first reduced the endocyclic double bond using hydrogen over palladium on charcoal and then performed the one-step basic hydrolysis of the benzoate protecting groups and the cyclic carbamate. The latter step proved difficult mainly because of solubility problems during the work-up and purification process. Treatment of **9** with a basic anion

exchange resin[22] provided **10**, the simplest representative of the new class of iminosugars targeted.[23]

Table 1. C-H amination of carbamates **3**[a]



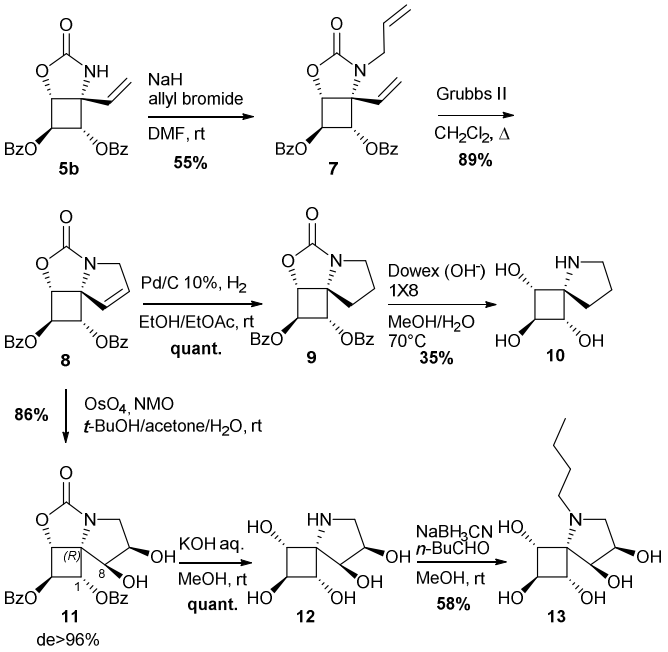
Entry	Cat. (mol%)	Solvant	T	R	5[b]	6[b]	3[c]
1	**$Rh_2(esp)_2$ (2)**	**CH_2Cl_2**	**Δ**	**Bn**	**1%**	**32%**	**23%**
2	$Rh_2(esp)_2$ (20)	CH_2Cl_2	Δ	Bn	17%	56%	-
3	$Rh_2(O_2CCF_3)_2$ (23)	CH_2Cl_2	Δ	Bn	5%	56%	15%
4	$Rh_2(OAc)_4$ (10)	C_6H_6	60°C	Bn	8%	43%	9%
5	$Rh_2(OAc)_4$ (30)	CH_2Cl_2	Δ	Bn	9%	56%	-
6	$Rh_2(tpa)_4$ (5)	CH_2Cl_2	Δ	Bn	-	14%	24%
7[d]	AgOTf (50)[d]	CH_3CN	Δ	Bn	2%	14%	29%
8	$Rh_2(OAc)_4$ (20)	CH_2Cl_2	Δ	Ac	12%	-	-
9	$Rh_2(esp)_2$ (15)	CH_2Cl_2	Δ	Ac	31%	-	-
10	**$Rh_2(esp)_2$ (20)**	**CH_2Cl_2**	**Δ**	**Bz**	**40%**	**-**	**10%**

[a]See ESI for experimental conditions. [b]Isolated yields.[c]Recovered after purification on silica gel.[d]Reaction performed in the presence of bathophenanthroline in the absence of MgO.

To access more water soluble compounds with additional OH groups, alkene **8** was converted into the corresponding diol **11** under Upjohn reaction conditions in 86% yield and high diastereoselectivity. The absolute configuration of the two new stereogenic centres was determined in part by NOE interactions between H-1 and H-8 (see ESI for the NOESY NMR of **11**). Thus dihydroxylation has occurred on the concave face of the pyrrolo[1,2-c]oxazol-3-one moiety. Such high level of stereoselectivity has been already observed with simpler bicyclic oxazolidine derivatives and has been rationalized by stereoelectronic effects involving the carbamate nitrogen lone pair.[24] The use of aqueous KOH in MeOH instead of basic anion exchange resin led to the one-step hydrolysis of the oxazolidinone ring and the benzoate protecting groups to provide **12** in high yield. A prevalent structural feature of many pyrrolidine- or piperidine-based bioactive iminosugars is the presence of an *N*-alkyl chain.[1,8] To evaluate the feasibility of alkylating the nitrogen atom of unprotected spiranic iminosugar of type **I**, compound **12** was subjected to reductive amination with butanal and sodium cyanoborohydride. The reaction provided the expected product **13** which may be seen as a constrained analogue of *N*Bu-DNJ (**1**).

Conclusions

In conclusion, we have synthesized the first examples of a new class of iminosugars based on a constrained azaspiranic framework. The 5-azaspiro[3.4]octane skeleton was built by way of C-H amination and RCM. Despite the high density of reactive C-H bonds and the fact that the cyclobutane ring imparts unusual regioselectivity, high level of regiocontrol could be achieved for the C-H amination key step by using a tactical combination of activating and electron-withdrawing groups**.** Future work will focus on the extension of our synthetic strategy to access a diversity of biologically relevant spiro iminosugars.



Scheme 2 Synthesis of spiranic iminosugars

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