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Synthesis and biological evaluation of the first example of an eight-membered iminoalditol

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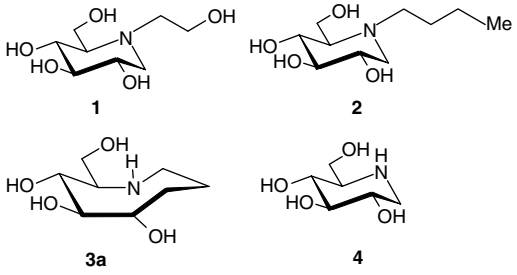
Abstract—The synthesis of the first examples of eight-membered iminoalditols has been achieved from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose by way of a ring-closing metathesis. The (2*R*,3*R*,4*R*,5*S*)-2-hydroxymethyl-azocane-3,4,5-triol (**3a**), which has the D-*gluco* configuration for C-2–C-5 and appears to exist predominantly in a boat–chair conformation, is a weak inhibitor of glycosidases.

It may seem paradoxical that such diverse, ubiquitous, and important biomolecules as carbohydrates are used by Nature almost exclusively in the furanose or pyranose form. This structural feature is shared by iminosugars, one of the most fascinating classes of glycomimetics reported so far. Despite the spectacular development of these modified sugars in which the ring oxygen is replaced by nitrogen, few examples of synthetic seven-membered azacyclitols have been reported.[1] To our knowledge, no eight-membered iminoalditol has been isolated or synthesized to date. Owing to their properties as carbohydrate-processing enzyme inhibitors,[2] iminosugars have recently entered the clinical field for assessment of their therapeutic potential in a wide range of diseases including tumor metastasis, viral infection, and lysosomal storage disorders.[3] Two iminosugars have been approved as drugs: *N*-hydroxyethyl-1-deoxynojirimycin (Glyset™) **1**[4] to treat complications associated with type II diabetes since 1996 and *N*-butyl-1-deoxynojirimycin **2**[5] (Zavesca™) for the treatment of Gaucher's disease since 2003. Considering the high potential of iminosugars for drug discovery,[3,6] it seemed important to explore original structural frameworks, such as medium-sized rings, in order to access new spatial distribution of the hydroxyl groups and to increase conformational flexibility. The main objectives are thus to find more potent/selective inhibitors and to provide new insights into the mechanism of carbohydrate-processing enzymes by probing further their binding specificity.[7]



In this context, our current work on iminosugars and olefin metathesis reactions[8] led us to design a concise synthesis of the eight-membered iminoalditol **3a**, a higher homolog of 1-deoxynojirimycin **4**. The key step of our synthetic strategy is the ring-closing metathesis (RCM) reaction of the 1,8-diene **B** obtained in four steps from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**) by way of a reductive amination (Scheme 1). Although RCM reactions have been widely used to form five-, six-, and seven-membered heterocycles, the synthesis of eight-membered rings still remains challenging due to entropic

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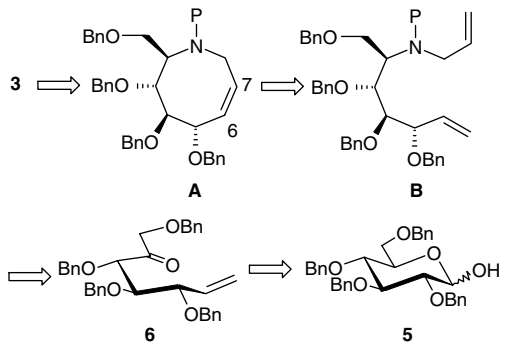
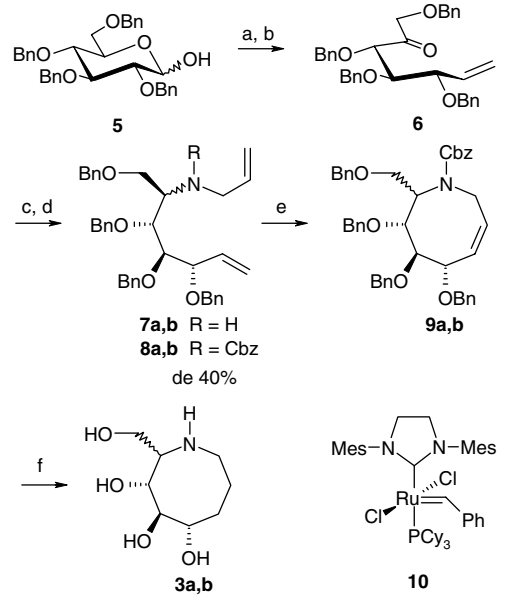


Scheme 1.

(probability of terminal olefins meeting) and enthalpic influences (transition-state strains).[9] Nevertheless, a few recently published examples have demonstrated that it is possible to synthesize efficiently substituted azocanes by way of RCM using conformational constraints or a stereoelectronic effect.[10] It is noteworthy that the unsaturated iminosugar **A** with a double bond tactically positioned at C(6)–C(7) is potentially an advanced intermediate in the preparation of various glycomimetics.

Commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**5**) was converted to the heptenulose **6** by Wittig methylenation[11] followed by oxidation of the resulting secondary alcohol with PCC[12] (Scheme 2). The convergent introduction of the allylamino group at C-6 was performed by way of a reductive amination.[13] The



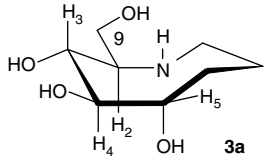
Scheme 2. Reagents and conditions: (a) $Ph_3P^+CH_3Br^-$ (3 equiv), *n*-BuLi (6 equiv), THF, 24 h; 90%; (b) PCC (1.8 equiv), molecular sieves 3 Å, CH_2Cl_2, 1 h; 89%; (c) allylamine (10 equiv), AcOH (5.2 equiv), $NaBH_3CN$ (5 equiv), molecular sieves 3 Å, MeOH, 0–40 °C, 5 days; 98%; (d) CBzCl (3.7 equiv), K_2CO_3 (3 equiv), THF, 16 h; 78%; (e) **10** (6 mol%), CH_2Cl_2, 40 °C, 30 h; 73%; (f) H_2, Pd/C, MeOH/HCl 1 N, 24 h; 82%.

reaction of **6** with allylamine and acetic acid in the presence of $NaBH_3CN$ afforded an inseparable mixture of D-*gluco* and L-*ido* aminoheptenitols **7a** and **7b** in excellent yield (ratio 2.3:1). As a prelude to the RCM reaction, the secondary amines **7** were derivatized as carbamates in order to avoid detrimental chelation of the metal center of the ruthenium–carbene catalyst.[8,14] The epimeric mixture of **7a** and **7b** was reacted with benzyl chloroformate in the presence of K_2CO_3 to produce the protected dienes **8a**,**b** in good yield. Although no conformational constraints were effective in our system, the RCM reaction using catalyst **10** proceeded smoothly to give the epimeric mixture of azocanes **9a**,**b** in 73% yield. Finally, the one-step removal of protecting groups and reduction of the endocyclic double bond was conducted using hydrogen over palladium on carbon to complete the synthesis of the eight-membered iminosugars **3a**,**b**. After various attempts, careful purification of the mixture of epimers **3a**,**b** by ion-exchange chromatography[15] allowed the isolation of a pure sample of (2*R*,3*R*,4*R*,5*S*)-2-hydroxymethyl-azocane-3,4,5-triol **3a** according to ^1H NMR spectra (de > 98%).[16] The ^1H and ^{13}C NMR signals of **3a** were assigned by 2D experiments (COSY and HMQC) (for selected data see Table 1). The definite NOE interaction between H-4 and H-2 indicated that these two protons were on the same side of the ring and thus that **3a** had a pseudo D-*gluco* configuration.

Interestingly, the $^3J_{H,H}$-coupling constants observed for **3a** appear to indicate that this compound exists predominantly in a boat–chair conformation with most substituents adopting a pseudo equatorial position. This result is in agreement with the NMR conformational study of Anet et al.[17] on azocane, the simplest example of an azacyclooctane.

Eight-membered alditol **3a** was assayed toward a panel of nine glycosidases (Table 2). Despite its pseudo D-*gluco* configuration, **3a** was found to be a very weak inhibitor of glucosidases and to display better inhibition

Table 1. Selected ^{13}C and ^1H NMR data for compound **3a** in D_2O[16]



Position	^{13}C[a]	J (Hz)[b]
2	61.4	$J_{2,3} = 10.5$
3	73.7	$J_{3,4} = 9.2$
4	81.6	$J_{4,5} = 3.7$
5	72.9	$J_{5,6a} = 1.0$
6	29.0	$J_{5,6b} = 8.7$
7	26.9	$J_{2,9a} = 9.2$
8	42.5	$J_{2,9b} = 3.7$
9	62.9	

[a] Recorded at 125 MHz in D_2O (ppm from TSP[c]).
[b] Recorded at 500 MHz in D_2O (ppm from TSP[c]).
[c] TSP = sodium 3-(trimethylsilyl)propionate.

Table 2. Inhibition values of **3a** toward selected glycosidases

Enzyme	Inhibition rate at 1 mM
α-Glucosidase	
Rice	33%
Yeast	22.1%
Rat intestinal maltase	28.8%
Rat intestinal isomaltase	33.9%
Rat intestinal sucrase	NI[a]
β-Glucosidase	
Sweet almond	37%
α-Fucosidase	
Bovine epididymis	NI[a]
Human placenta	28.3%
α-L-Rhamnosidase	
Penicillium decumbens	(110)[b]

[a] NI: no inhibition at $[I] = 1$ mM.
[b] IC_{50} (μM).

activity toward α-L-rhamnosidase with an IC_{50} value of 110 μM. No significant inhibition of α-fucosidases was observed.

In conclusion, we have achieved a rapid synthesis of the first examples of eight-membered iminoalditols **3** by way of RCM. Preliminary biological evaluation of (2*R*,3*R*,4*R*,5*S*)-2-hydroxymethyl-azocane-3,4,5-triol (**3a**) indicates that this compound is a weak inhibitor of glycosidases. This result may be explained in part by the absence of hydroxyl groups at C-6 and C-7 (corresponding to OH-3 and OH-2 in the parent glucosides). Future work will focus on the improvement and the extension of our synthetic strategy to other eight-membered alditols functionalized at C-6 and C-7.

Acknowledgements

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15. The mixture of epimers **3** was chromatographed over a Dowex 1-X2 (OH^- form) with H_2O as the eluant. A further chromatography on Amberlite CG-50 column (NH_4^+ form) (H_2O then 0.5 M NH_4OH elution) gave a sample of pure **3a**.
16. Selected data for iminoalditol **3a**: ^1H NMR (500 MHz, D_2O–TSP): δ 1.58 (m, 1H, H-7a), 1.72–1.81 (m, 2H, H-7b, H-6a), 1.92 (m, 1H, H-6b), 2.69 (m, 1H, H-8a), 2.81 (m, 1H, H-8b), 2.84 (ddd, 1H, $J = 3.7$, 9.2, 10.5 Hz, H-2), 3.60 (dd, 1H, $J = 3.7$, 9.2 Hz, H-4), 3.67 (dd, 1H, $J = 9.2$, 10.5 Hz, H-3), 3.69 (dd, 1H, $J = 9.2$, 11.5 Hz, H-9a), 3.88 (dd, 1H, $J = 3.7$, 11.5 Hz, H-9b), 3.98 (ddd, 1H, $J = 1.0$, 3.7, 8.7 Hz, H-5); $[\alpha]_D^{20}$ +10.5 (*c* 0.2, H_2O); HRMS (CI) *m/z* 192.1235 $[M+H]^+$ ($C_8H_{18}NO_4$ requires 191.1236).
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