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Novel Cyclic Sugar Imines: Carbohydrate Mimics and Easily Elaborated Scaffolds for Aza-Sugars

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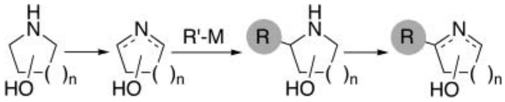
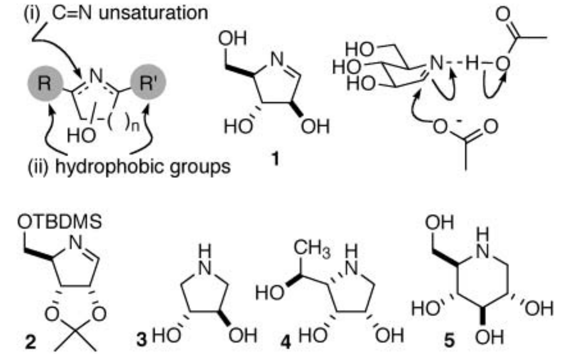
ABSTRACT



Representative simple or polyhydroxylated, pyrrolidine (e.g, DRAM) or piperidine (e.g., DNJ) imines not only are potential carbohydrate-processing enzyme inhibitors that may be formed as regioisomeric variants but also are scaffolds that may be rapidly elaborated to diversely functionalized aza-sugars through highly diastereoselective organometallic additions.

Polyhydroxylated nitrogen heterocycle aza-sugars may be considered to be mimics of sugars in which the ring oxygen has been substituted for a nitrogen atom.[1] The often potent inhibitory activity of many of these compounds toward carbohydrate-processing enzymes has suggested their use in a wide range of potential therapeutic strategies including the treatment of viral infections,[2] cancer,[3] diabetes,[4] tuberculosis,[5] lysosomal storage diseases,[6] and parasitic protozoa.[7] Moreover, aza-sugar transition state analogues have proved themselves to be invaluable tools in the study of the mechanism of action of carbohydrate-processing enzymes.[8] We have chosen to investigate two structural motifs that may offer generally enhanced inhibitory potency in aza-sugars: (i) C=N unsaturation and (ii) additional hydrophobic substituents.



Remarkably, despite their direct resemblance to the putative flattened transition states or intermediates of car-

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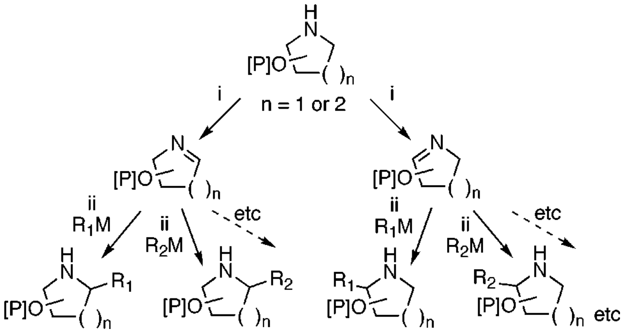
bohydrate-processing enzyme mechanisms and their potential to act as suicide inhibitors, few sugar imines are known. In the few cases that sugar imines have been synthesized they have shown enhanced inhibitory properties over their fully reduced counterparts.[9] Indeed, nectrisine (FR-900483) **1** isolated from *Nectria lucida* is a known potent α-mannosidase and glucosidase inhibitor.[10] The introduction of hydrophobic aromatic or alkyl groups has also given rise to novel sugar mimetics with enhanced potency (through interaction with hydrophobic protein residue side chains) and bioavailability (through altered membrane permeability) in carbohydrate-processing systems.[11] Typically the synthesis of sugar mimetics bearing such additional substituents often requires their introduction at an early stage in the synthesis; however the synthesis of diverse arrays of aza-sugars would ideally involve the elaboration of a late stage intermediate. To address this problem and with the aim of creating libraries for high throughput screening, we set ourselves the goal of developing just such a late stage diversification. As our synthetic strategy we have successfully combined (i) regioselective C=N imine formation with (ii) the irreversible addition of organometallics to these late stage cyclic imine intermediates (Scheme 1).

Scheme 1[a]



[a] Strategic stages: (i) regioselective imine formation; (ii) irreversible addition of R_1M, R_2M, ...

Thus, this Letter describes the synthesis of novel sugar imines of double utility not only as attractive inhibitor targets in their own right but also as scaffolds that may be readily and diversely elaborated. In this way we have been able to construct sugar mimics bearing one or both of two structural elements of potentially enhanced potency: (i) endocyclic C=N unsaturation and (ii) a hydrophobic group.[12]

Remarkably, although the irreversible addition of organometallics to acyclic imines has been widely exploited,[13] its application to cyclic imines has been scarce.[14] Indeed, such additions to polyhydroxylated imines have to date been limited solely to iminoribitol **2**. These elegant studies[15] have highlighted the synthetic potential of this method through the addition of a variety of nucleophiles to **2** that allowed the preparation of "immucillin" nucleoside analogues as potential antimalarials.[7] However the generality of this methodology and in particular the scope of the imine electrophile is unexplored. This communication reveals the wide scope of this methodology, including its application to the elaboration of **3** to prepare nectrisine analogues, the elaboration of known model glycosidase inhibitors 1-deoxynojirimycin (**4**, DNJ)[16] and 1,4-deoxy-1,4-imino-L-rhamnitol (**5**, DRAM),[17] and the first examples of such additions to cyclic ketimines.

To probe the breadth of (i) imines that could be synthesized and (ii) the imine addition methodology we chose imine targets **10**, **11**, **15**, **18**, **21**, **22**, **25** and **26** (Scheme 2). Simple piperidinoimines **10** and **11** were readily prepared by elimination of HCl with diazabicycloundecene (DBU) from their corresponding *N*-chloro derivatives **8** and **9**, which were themselves prepared using *N*-chlorosuccinimide (NCS) in Et_2O. Polyhydroxylated sugar imines **15**, **18**, **21**, **22**, **25**, and **26** were prepared in three contrasting ways to illustrate ready preparation from different sources.

First, to illustrate the construction of a complete aza-sugar motif from an unfunctionalized scaffold, racemic dihydroxy iminothreitol **15** was prepared from 3-pyrroline **12** in seven steps. Thus, *N*-protection, epoxidation,[18] and hydrolysis gave *trans*-diol **13**,[19] which after protecting group manipulation afforded protected amine **14** in 36% overall yield. Chlorination of **14** using NCS followed by elimination with diazabicycloundecene (DBU) gave target iminothreitol **15**. The

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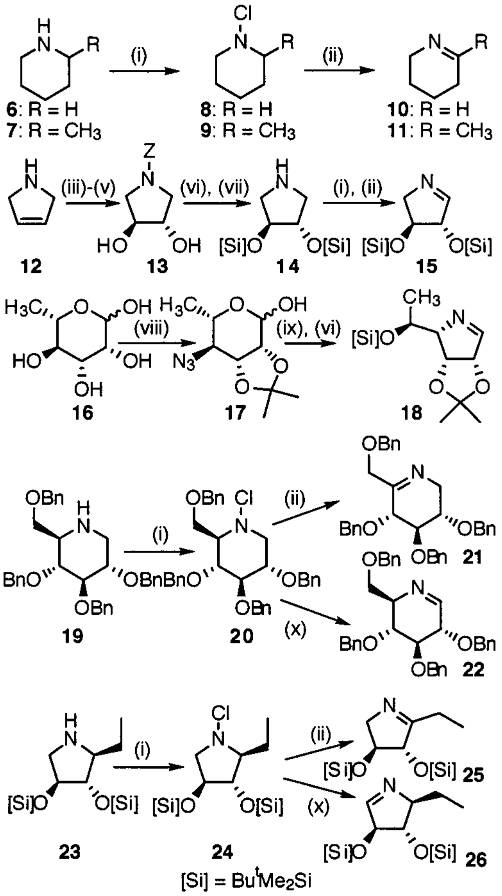
Scheme 2[a]

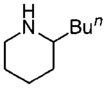
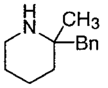
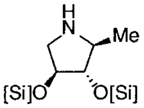
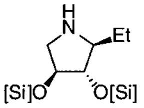
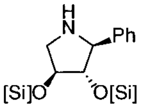
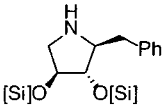
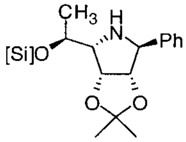
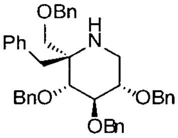


[a] Reagents and conditions: (i) NCS, Et$_2$O, 70%, 75%, 96%, 97%, 93% from **6**, **7**, **14**, **19**, **23**; (ii) DBU, DCM for **11**, 77% from **7**; DBU, THF, 67%, 90%, 52% for **15**, **21**, **25**; (iii) ZCl, 3 M, NaOH (aq), toluene, 97%; (iv) mCPBA, DCM, 46%; (v) 2 M H_2SO_4 (aq), Et$_2$O, 96%; (vi) TBDMSOTf, py, DCM, 92% for **14**, 61% for **18**; (vii) H_2, Pd−C, MeOH, 92%; (viii) see ref 20, 36% from **16**; (ix) PPh$_3$, DCM, 0 °C, 96%; (x) LiTMP, THF, 90%, 83% for **22**, **26**.

presence of an imine C=N bond was confirmed by characteristic IR (υ_{max} 1645 cm^{-1}), ^{1}H NMR (δ_H (CDCl$_3$) 7.44 (d, 1H, $J_{2,3}$ 2.8 Hz)), and ^{13}C NMR (δ_C 169.0) resonances. Second, as an alternative strategy for the preparation of sugar imines we utilized a Staudinger aza-Wittig cyclization. Iminorhamnitol **18** was prepared from protected azidolactol **17**, which was itself prepared from parent carbohydrate L-rhamnose **16** in six steps.[20] Thus, treatment of **17** with solid-supported PPh$_3$ led to intramolecular imine formation. Protection of the secondary alcohol gave **18** in 57% overall yield. Finally, we elaborated commercially available azasugar arcehtype tetra-Bn-DNJ **19** and were pleased to discover that through the appropriate choice of conditions the regioselectivity of the elimination of **20** could be controlled. Thus, treatment of **20** with DBU afforded ketimine **21**, whereas elimination with lithium tetramethylpiperidide (LiTMP) gave aldimine **22**. This adaptable elimination method also allowed the synthesis of the two nectrisine analogues **25** and protected 5-methyl-5-deoxynectrisine **26** from iminothreitol **23**.[21]

With a representative selection of aldimine or ketimine, pyrrolidino- or piperidino-, simple or polyhydroxylated substrates **10**, **11**, **15**, **18**, and **21** in hand, we investigated the introduction of hydrophobic substituents through organometallic addition (Table 1).[22] Simple imines **10** and **11** reacted sluggishly with a variety of organometallics in only moderate yield. Interestingly, under the conditions of the Grignard reaction, dimerization products were obtained alongside the expected addition products.[23] However, we were delighted to observe that the addition methodology

Table 1. Results of Organometallic Additions to Cyclic Imines

imine	RM[a]	yield[d] (%)	products[d]
10	BuLi[b]	11	 **27**
11	BnMgCl[c]	39	 **28**
15	MeMgBr	58[e,f]	 **29**
15	EtMgBr	45[e]	 **23**
15	PhMgBr	44[e]	 **30**
15	BnMgCl	48[e]	 **31**
18	PhMgBr	67	 **32**
21	BnMgCl	19[e]	 **33**

[a] Conditions unless stated otherwise: Et$_2$O, rt. [b] THF, rt. [c] Et$_2$O, dioxane, rt. [d] Product stereochemistry established by NOESY NMR at >98% de unless stated otherwise. [e] Yield over two steps from chloramine. [f] 72% de.

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[21] Compound **23** is in fact a product of the novel addition reactions described below (see Table 1).

[22] This range of imines allowed us to successfully demonstrate representative additions to both aldimines **10**, **15**, **18** and ketimines **11**, **21**. Additions to other aldimines **22**, **26** and ketimine **25** are now underway.

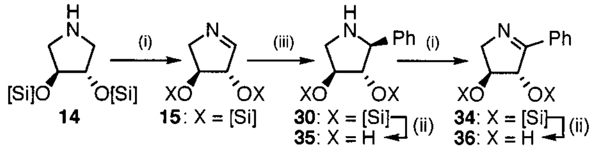
[23] Tentatively characterized as addition product of exocyclic enamine tautomer of **10** to **10** itself, which was catalyzed by Mg salts; the synthetic utility of this dimerization is currently being explored.

could be applied to ketimines; reaction of BnMgCl with **11** gave the corresponding adduct **28** in a moderate 39% yield, which to the best of our knowledge is the first such addition to a cyclic ketimine. The reactions of polyhydroxylated imines **15**, **18**, and **21** with nucleophiles were more efficient, proceeded more rapidly than for the corresponding simple imines **10** and **11,** and were compatible with a variety of protecting groups (Bn, TBDMS, isopropylidene). Moreover, in all cases good to excellent diastereoselectivities were observed in a sense consistent with steric approach control, which only drifted from >98% de for delivery of the small methyl substituent to **15** to give **29**. It should be noted that even hindered imines such as **21** are effective reactants using this strategy and provided another rare example of an addition to cyclic ketimines. Best yields were obtained with **18**, and this may be due to an inherently greater stability of this fused [4.4.0] bicyclic system. This is supported by the recovery of **18** as the balance of mass in its reaction (based on recovered starting material reaction yield of **32** was 97%) and by the isolation of pyridine elimination products and benzyl alcohol as side products in reactions of less rigid **21**.

In summary, we have successfully demonstrated that both sugar-derived imines and diversely functionalized aza-sugars, as potential carbohydrate-processing enzyme inhibitors, may be rapidly synthesized as a representative range of simple or polyhydroxylated, pyrrolidine or piperidine scaffolds by regioselective imine formation and highly diastereoselective irreversible addition. A wide variety of novel aza-sugars have been prepared in this way including aromatic, alkyl, and C═N functionalized analogues of deoxynojirimycin (DNJ), 1,4-imino-L-rhamnitol (DRAM), and nectrisine. This ready elaboration of known and commercially available aza-sugar scaffolds lends itself well to the rapid development of aza-sugar libraries through parallel synthesis methods (Scheme 1) and hence to structure−activity relationship studies.

Scheme 3 illustrates that different advantageous C═N or hydrophobic motifs may be sequentially installed, e.g., into **15**, **30**, and **34**, at each stage in routes that may generate potential inhibitors, e.g., **35** and **36**, at each such iterative stage.[24] Although in some cases the efficiencies of additions are only modest, the overall yield of this strategy compares well with alternative synthetic routes. For example, we successfully synthesized protected 5-methyl-5-deoxy-nectrisine (**26**) in 10 steps and 12% overall yield, which compares favorably to the synthesis of the only similar analogue 5-deoxynectrisine (16 steps, 10% yield).[10] The mechanism of these useful organometallic additions is unclear. Interestingly, side products consistent with both radical and polar additions have been isolated, and further investigation of the mechanism is in progress. Testing of the novel aza-sugars synthesized here and their deprotection products for biological activity, including the inhibition of carbohydrate-processing enzymes, is underway, the results of which will be presented in due course.

Scheme 3[a]



[a] Reagents and conditions: (i) NCS, Et_2O then DBU, 59%, 79% for **15**, **34**; (ii) 25−50% TFA (aq); 63%, 34% for **35**, **36**; (iii) PhMgBr, Et_2O, 44%.

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Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Other complementary methods exist for creating potentially electrohphilic azomethine carbons, e.g., nitrones or acyl immoniums, However, these require additional steps to both introduce and remove additional functionality.