PREPARATION OF A DEOXYNOJIRIMYCIN ANALOG CONTAINING AN IMIDAZOLE RING

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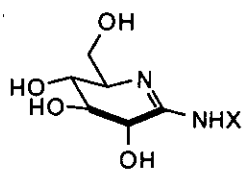
Abstract - The deoxynojirimycin analogs (**4**) and (**5**) were prepared *via* addition of a metallated imidazole to an aldehyde; these compounds were screened for inhibition of glycosidase enzymes and anti-HIV activities.

The amidine (**1a**) is a potent inhibitor of glycosidases, apparently because the planarity of the protonated form of this molecule closely resembles the putative half-chair intermediate (**2**) in the enzymatic hydrolysis.[1]



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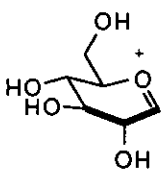
a, X=H; **b**, X=NH_2; **c**, X=OH



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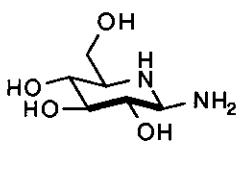
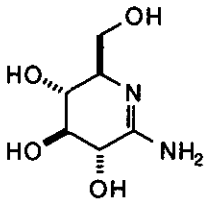


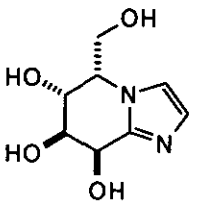
3

This idea is supported by the observation that the saturated analog (**3**) is not a good glycosidase inhibitor.[2] Extensive structure/activity and modeling studies have led others to conclude that the charged half-chair

conformation of **1** is more important than the stereochemistry of the hydroxymethine carbons with respect to glycosidase inhibition.[3,4]



1a



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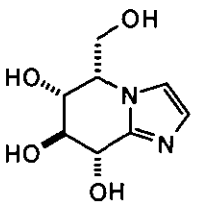

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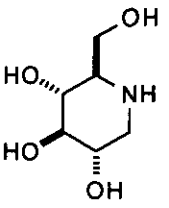
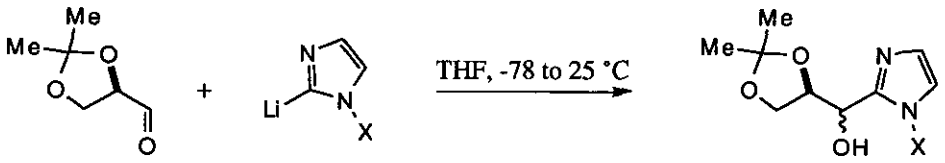


deoxynojirimycin

Unfortunately, compound (**1a**) is too easily hydrolysed to be useful for most practical applications.[4] More robust derivatives have been prepared, *eg* **1b** and **1c**,[5] but hydrolytic stability is still an issue. This paper describes a synthesis and preliminary biological tests of imidazole derivatives (**4**)and (**5**). Motivation for this particular effort was four-fold: (i) the imidazole functionality enforces a half-chair conformation on the six-membered ring; (ii) the imidazole could be protonated in the enzyme active site; (iii) hydrolytic stability; and, (iv) compounds (**4**) and (**5**) resemble the bicyclic compound deoxynojirimycin, which is known to strongly inhibit glycosidase enzymes and the *N*-butyl form has appreciable anti-HIV activity.[6] Stereoisomers (**4**) and (**5**) were chosen as initial targets because the starting material (aldehyde **9**, *vide infra*) is readily available.

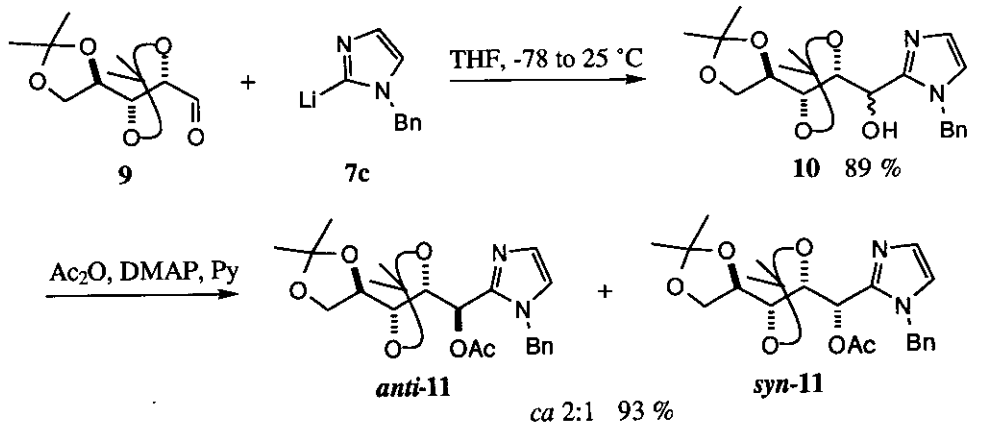
Syntheses of compounds (**4**) and (**5**) could be achieved *via* addition of a metallated imidazole derivative to an aldehyde. This reaction is less straight-forward than might be expected. Trial experiments using 2,3-isopropylideneglyceraldehyde (**6**) as the substrate revealed the choice of *N*-protecting group was critical.[7-9] The dimethylsulfamoyl masked system (**7a**) was too basic, and only deprotonated the aldehyde. Lithiated, methoxymethyl protected imidazole (**7b**) gives the desired addition reaction, but removal of the MOM-group later in the synthesis was problematic. Eventually, the *N*-benzylimidazole (**7c**) was selected.



6 + **7** → **8b,c**

a, X=SO_2NMe_2
b, X=MOM
c, X=Bn

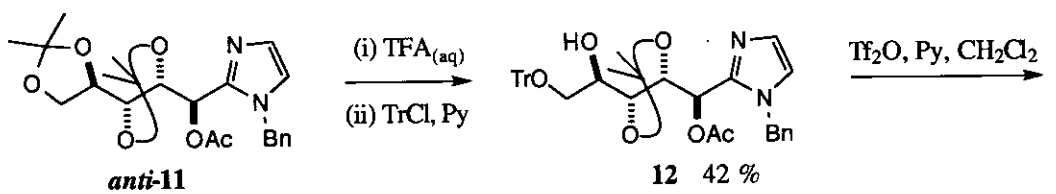
Aldehyde (**9**), derived from arabinose *via* a literature procedure,[10] was used as the starting point for the synthesis of **4** and **5**. Reaction of this with lithiated *N*-benzyl imidazole gave the addition product (**10**) as a *ca* 2:1 mixture of epimers. Later it was shown that the Felkin-Anh product predominates, but at this stage we were unable to confirm this or separate the stereoisomers. Acylation and chromatographic separation of ***anti*-11** and ***syn*-11** was possible, however; the rest of this description outlines manipulation of the major stereoisomer ***anti*-11**. Aqueous TFA cleaved the terminal acetonide without hydrolyzing the acetate group, and the terminal hydroxyl functionality was protected with a trityl group giving **12**. Triflation of the remaining hydroxy group facilitated cyclization to **4** *via* global deprotection using prolonged hydrogenolysis in aqueous TFA.



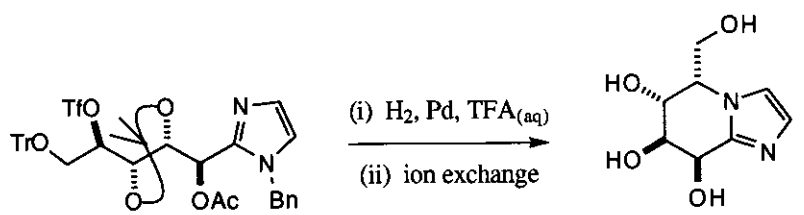
9 **7c** **10** 89 %

***anti*-11** ***syn*-11**

ca 2:1 93 %



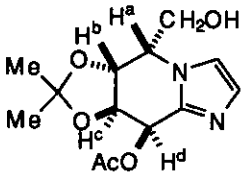
***anti*-11** **12** 42 %



13

4
54 % from **12**

Stereoisomer (**5**) was produced *via* a route which exactly parallels that shown above, but starting with ***syn*-11**. Hydrogenolysis of triflate (**13**) in a non-acidic solvent facilitated cyclization without removal of the acetate or acetonide functionalities, to give compound (**14**). Proton nmr analyses of this compound were the basis of the stereochemical assignments indicated above. Specifically, strong NOE enhancements were observed between protons H^a and H^b, and between H^c and H^d. Moreover, the J^{ab} and J^{cd} coupling constants were measured as 3.6 Hz and 6.4 Hz, respectively as might be expected for protons oriented in an axial/*pseudo*-equatorial relationship.



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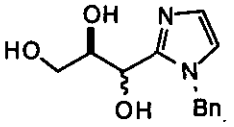

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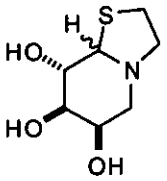
In preliminary screens, compound **4** at a concentration of 100 μg/ml caused 50 % inhibition of hydrolysis by glucosidase I, whereas castanospermine[6] at concentrations of 100 μg/ml and of 10 μg/ml completely inhibited this enzyme in the same assay. Compound (**5**) and the triol (**15**) (*ca* 3:1 mixture of stereoisomers) formed by removing the acetonide protecting group from **8c**, were inactive against glycosidase I. All the compounds tested were inactive against glucosidase II, and none showed any appreciable anti-HIV activity in a cellular assay.

After this synthesis was initiated, modeling studies were published which indicate the stereochemistry of the carbon bearing the CH_2OH functionality is important with respect to glycosidase inhibition.[4] This stereocenter is inverted in compounds (**4**) and (**5**), *ie* they do not correspond to **1** - **3** or deoxynojirimycin. Consequently, we are optimistic that appropriate stereoisomers of **4** and **5** will show the desired activity.

Finally, there have been some relevant observations reported while this work was in progress. Compounds (**16**) and (**17**) have been prepared and show appreciable glycosidase activities,[11,12] and the former had anti-HIV properties.[13] No biological data has been reported yet for deprotected forms of the pyrrole derivative **18** which was synthesized recently,[14] but it is obviously related to the target compounds in the present paper.



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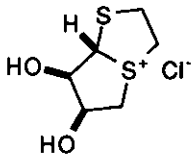

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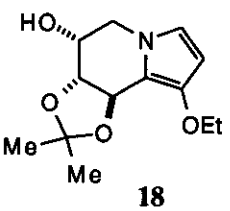

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