

PREPARATION OF A DEOXYNOJIRIMYCIN ANALOG CONTAINING AN IMIDAZOLE RING

Kevin Burgess* and David A. Chaplin

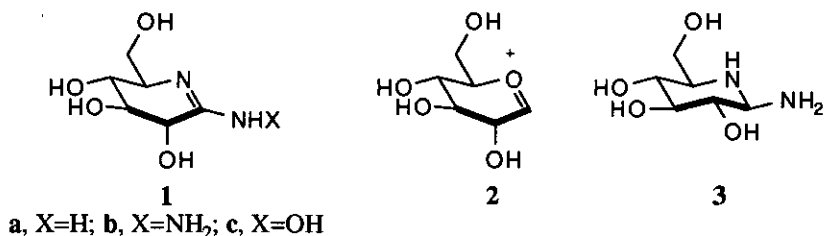
Department of Chemistry, Texas A & M University, College Station, TX 77843,
U.S.A.

Alan D. Elbein and Yucheng Zeng

Department of Biochemistry, University of Arkansas for Medical Sciences
4301 W. Markham, Little Rock, AK 72205, U.S.A.

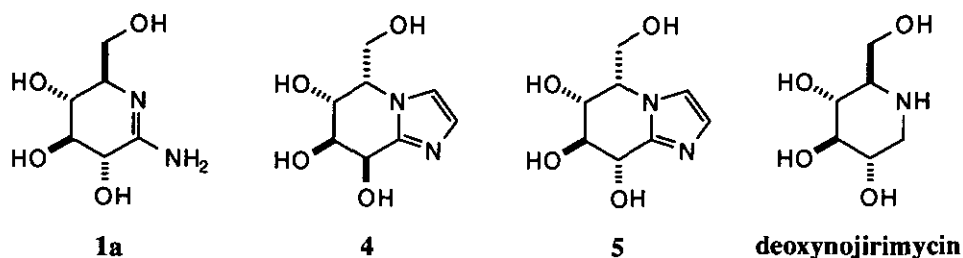
Abstract - The deoxynojirimycin analogs (4) and (5) were prepared *via* addition of a metallated imidazole to an aldehyde; these compounds were screened for inhibition of glycosidase enzymes and anti-HIV activities.

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



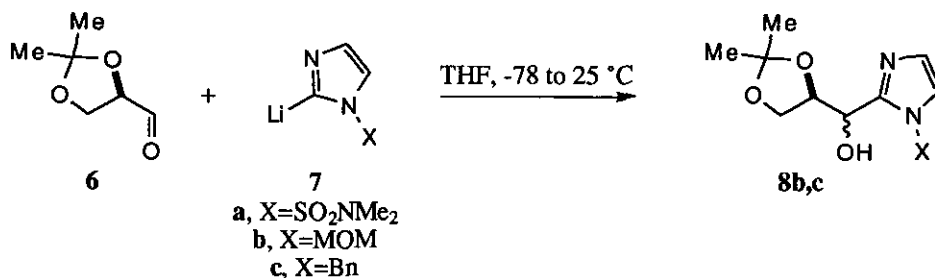
This idea is supported by the observation that the saturated analog (**3**) is not a good glycosidase inhibitor.² Extensive structure/activity and modeling studies have led others to conclude that the charged half-chair

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

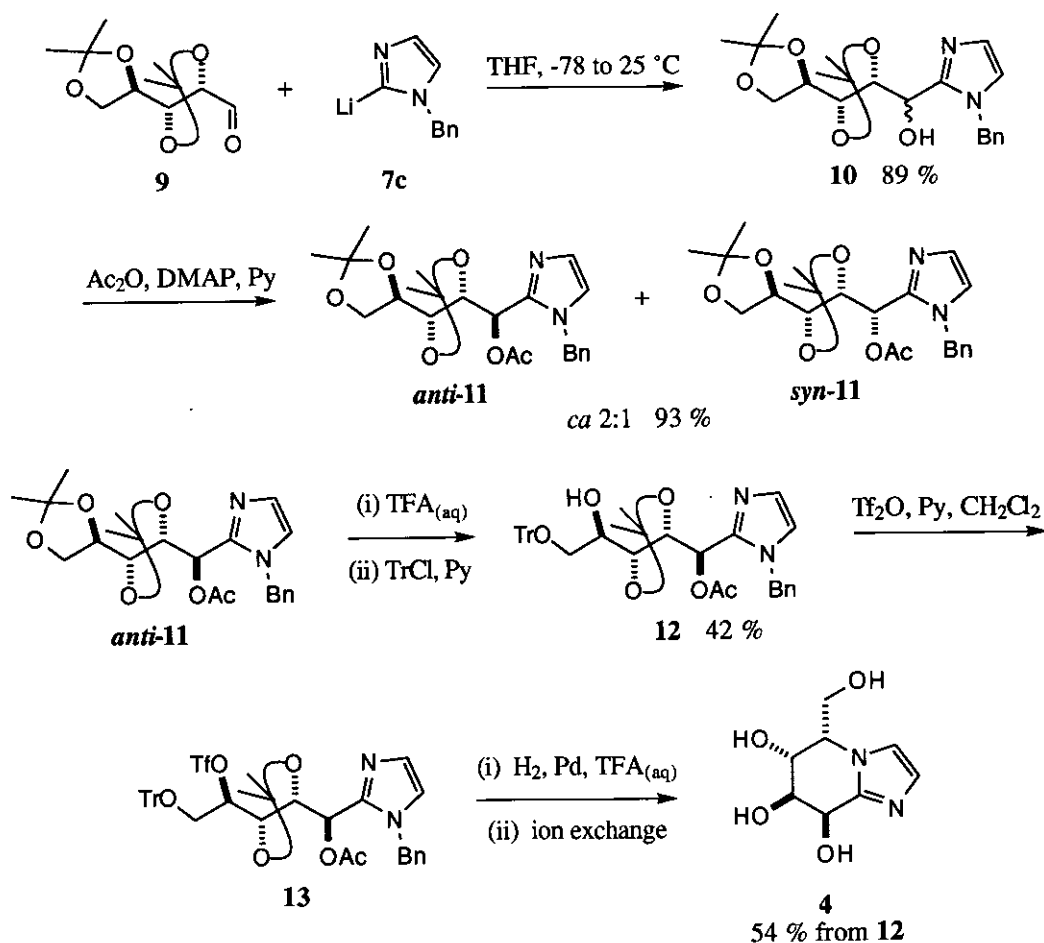


Unfortunately, compound (**1a**) is too easily hydrolysed to be useful for most practical applications.⁴ More robust derivatives have been prepared, *eg* **1b** and **1c**,⁵ but hydrolytic stability is still an issue. This paper describes a synthesis and preliminary biological tests of imidazole derivatives (**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.

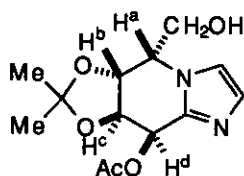
Syntheses of compounds (**4**) and (**5**) could be achieved *via* addition of a metallated imidazole derivative to an aldehyde. This reaction is less straight-forward than might be expected. Trial experiments using 2,3-isopropylidenglyceraldehyde (**6**) as the substrate revealed the choice of *N*-protecting 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.



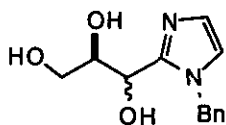
Aldehyde (**9**), derived from arabinose *via* a literature procedure,¹⁰ was used as the starting point for the synthesis of **4** and **5**. Reaction of this with lithiated *N*-benzyl imidazole gave the addition product (**10**) as a *ca* 2:1 mixture of epimers. Later it was shown that the Felkin-Anh 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.



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.

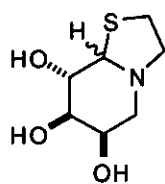


14

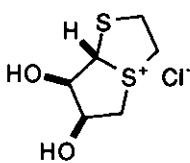


15

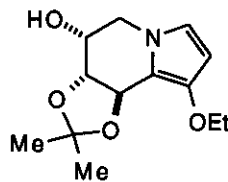
In preliminary screens, compound 4 at a concentration of 100 $\mu\text{g/ml}$ caused 50 % inhibition of hydrolysis by glucosidase I, whereas castanospermine⁶ at concentrations of 100 $\mu\text{g/ml}$ and of 10 $\mu\text{g/ml}$ completely inhibited this enzyme in the same assay. Compound (5) and the triol (15) (*ca* 3:1 mixture of stereoisomers) formed by removing the acetonide protecting group from 8c, were inactive against glucosidase 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 CH₂OH 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.



16



17



18

ACKNOWLEDGMENTS

We thank Dr D. Montefiori (Duke University) for performing preliminary tests for anti-HIV activities. Financial support for this work was obtained from the National Institutes of Health. KB thanks the NIH for a Research Career Development Award, and the Alfred P. Sloan Foundation for a scholarship.

This paper is dedicated to Professor Katritzky, with gratitude and respect.

REFERENCES AND NOTES

1. M. K. Tong, G. Papandreou, and B. Ganem, *J. Am. Chem. Soc.*, 1990, **112**, 6137.
2. H. Yoon, S. B. King, and B. Ganem, *Tetrahedron Lett.*, 1991, **32**, 7199.
3. K. K.-C. Liu, T. Kajimoto, L. Chen, Z. Zhong, Y. Ichikawa, and C.-H. Wong, *J. Org. Chem.*, 1991, **56**, 6280.
4. T. Kajimoto, K. K.-C. Liu, R. L. Pederson, Z. Zhong, Y. Ichikawa, J. A. Porco, and C.-H. Wong, *J. Am. Chem. Soc.*, 1991, **113**, 6187.
5. B. Ganem and G. Papandreou, *J. Am. Chem. Soc.*, 1991, **113**, 8984.
6. G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tynms, S. Petursson, S. K. Namgoong, N. G. Ramsden, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob, and T. W. Rademacher, *Febs Lett.*, 1988, **237**, 128.
7. K. L. Kirk, *J. Org. Chem.*, 1978, **43**, 4381.
8. N. J. Curtis and R. S. Brown, *J. Org. Chem.*, 1980, **45**, 4038.
9. D. J. Chadwick and R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. I*, 1984, 481.
10. H. Zinner, E. Wittenburg, and G. Rembarz, *Chem. Ber.*, 1959, **92**, 1614.
11. A. H. Siriwardena, A. Chiaroni, C. Riche, and D. S. Grierson, *J. Org. Chem.*, 1992, **57**, 5661.
12. A. H. Siriwardena, A. Chiaroni, C. Riche, S. El-Daher, B. Winchester, and D. S. Grierson, *J. Chem. Soc., Perkin Trans I*, 1992, 1531.
13. D. C. Montefiori, W. E. Robinson, S. S. Schuffman, and W. M. Mitchell, *J. Clinical Microbiology*, 1988, **26**, 231.
14. P. Kefalas and D. S. Grierson, *Tetrahedron Lett.*, 1993, **34**, 3555.

Received, 26th August, 1993