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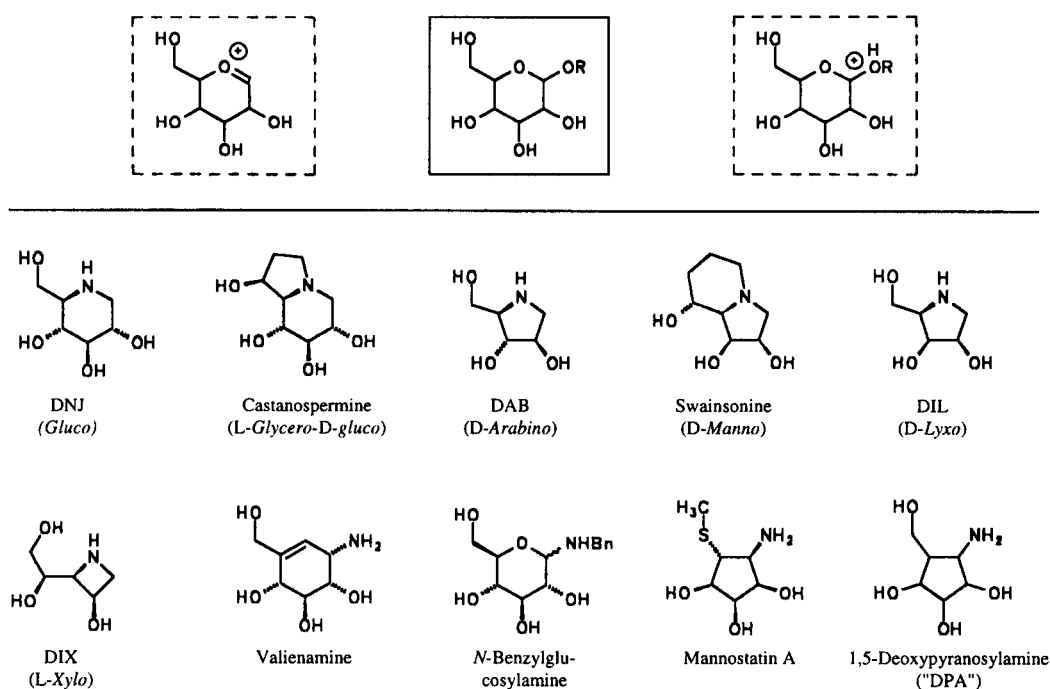
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## A. Introduction.

Mono- and bicyclic iminopolyols like deoxynojirimycin or castanospermine represent classic examples of strong and selective glycosidase inhibitors. Likewise, many pyrrolidine derivatives (1,4-iminopolyols) with these or other interesting bio-activities are known (Scheme 1) [1].

the enzymatic protein part of the respective active site [5]. Thus, as depicted in Scheme 2, *N*-oxy compounds like cyclic hydroxylamines, *N*-oxides, nitrones, or bicyclic isoxazolidines were considered as interesting candidates, as well as the hydrazine derivatives shown. Incidentally, another type of structure, that of the tetrahydro-1,2-oxazine,

Scheme 1  
Glycosidase Inhibition, Structural Types



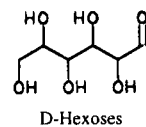
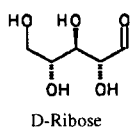
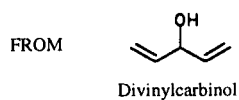
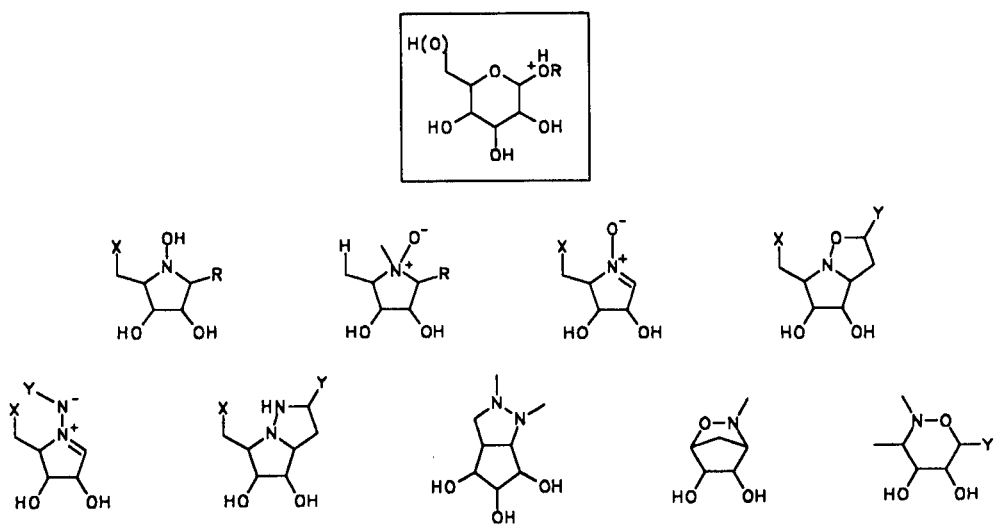
We have developed several approaches to this group of compounds earlier [2-4], and now report on facile routes to a variety of "non-classical" structures (Scheme 2), based on cyclization of unsaturated oximes and the like (Scheme 3). The new structures were all designed with the simple view of imitating the main features of *exo*-protonated glycosidases: (i) Several hydroxy groups, whose configuration would be responsible for selectivity toward the corresponding series of glycosidases; (ii) A basic nitrogen function in or at the ring which would readily be protonated, or nitrogen already positively charged, and (iii) An additional heteroatom, nitrogen or oxygen, which might form additional hydrogen bonds on interaction with

was obtained also in the course of these studies (*vide infra*). The new structures were derived from unsaturated nitrogen derivatives of unsaturated polyols, in turn accessible from divinylcarbinol, D-ribose and D-hexoses. The cyclizations would mostly generate a terminal halomethyl or methyl group, so mainly  $\alpha$ -L-fucosidases would be the enzymes to be assayed with the new structures.

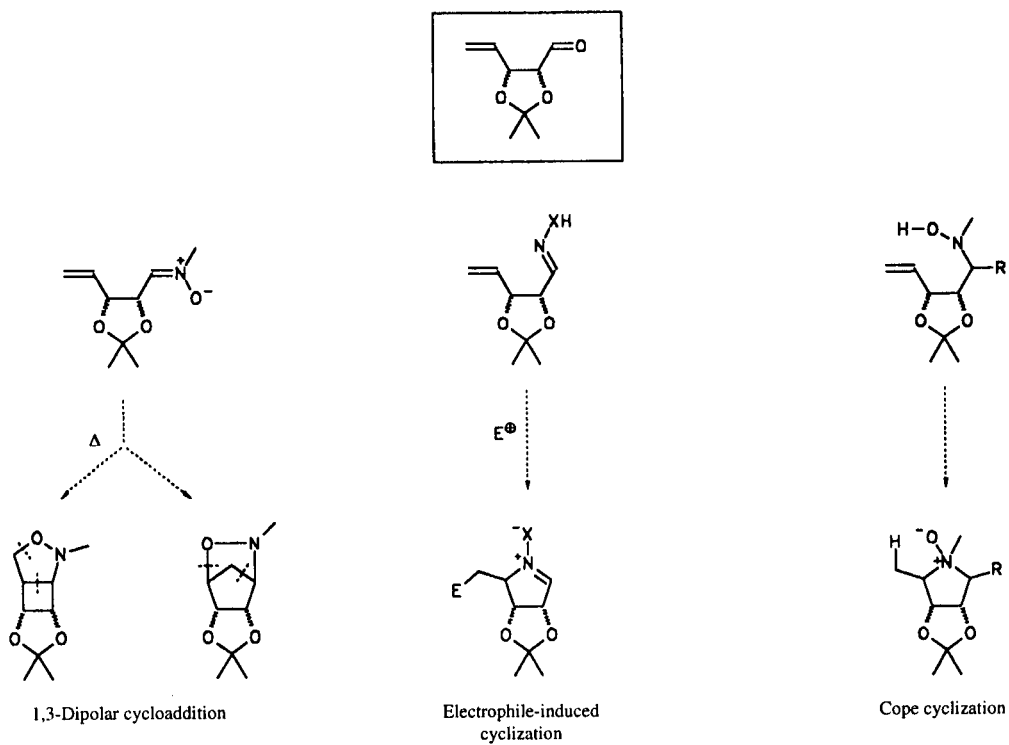
## B. Halocyclization of Pentenose Oximes.

The cyclization of unsaturated oximes upon action of electrophiles was first reported by Grigg *et al.*, (Scheme 4). The substrate we have worked with mostly, the *erythro*-pentenose oxime derived from D-ribose, was chosen also by Wightman *et al.* very recently, and cyclization was

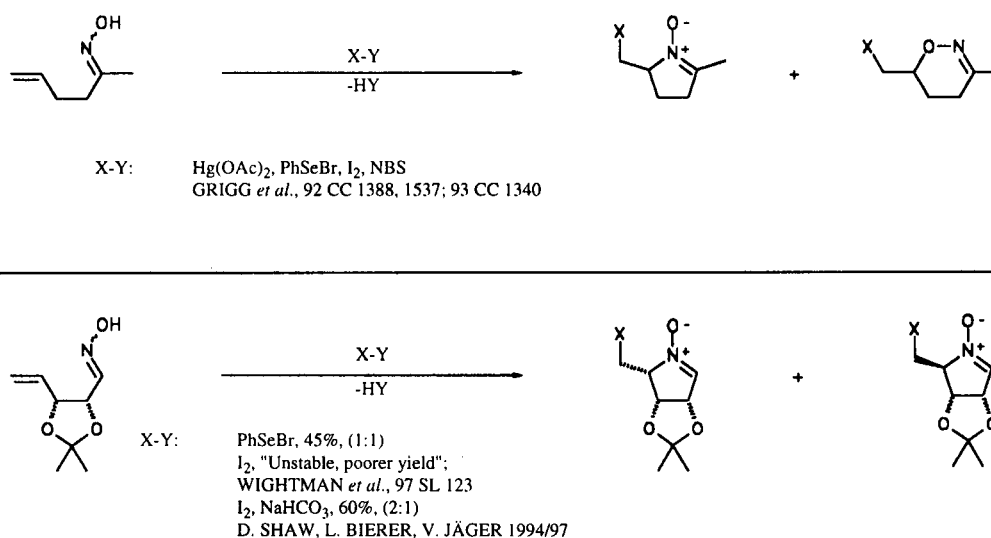
Scheme 2  
New Heterocyclic Structures for Glycosidase Inhibition



Scheme 3  
Possibilities for Cyclic Products from *erythro*-4-Pentose



Scheme 4  
Cyclization of Alkenyl Oximes



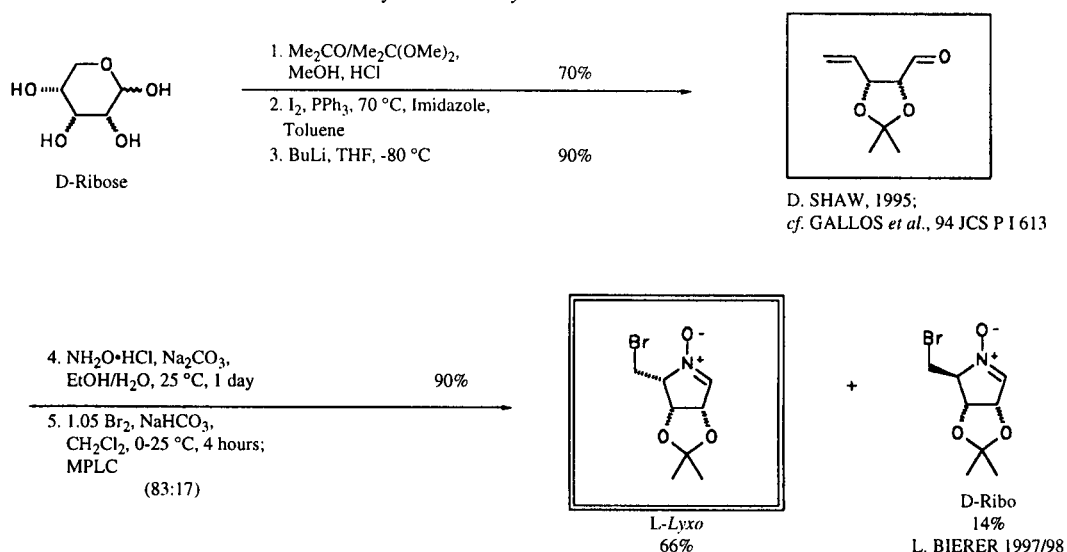
induced with phenylselenenyl bromide. With iodine some cyclization was reported to occur also. In our hands, *ca.* 60% of a 2:1 mixture of stereoisomeric nitrones (pyrroline *N*-oxides) was obtained, but separation proved tedious and subsequent reactions not as clean as desired.

The project became more enjoyable when we succeeded to effect bromocyclization. The route started with D-ribose, which was smoothly transformed to the protected pentenose, with highly effective formation of the 5-iodo compound and reductive elimination with butyllithium at low temperature (Scheme 5). The oxime underwent cyclization with the simplest reagent on the shelf, with bromine [6]. The major isomer, the *L-lyxo* compound, was formed with better diastereoselectivity than seen in

the iodo case, and, after separation, turned out crystalline and stable. And it became a marvellous source for plenty of different structures with the *L-lyxo* configuration at the last three stereocenters, identical with those of *L*-fucose!

The bromomethyl-*L-lyxo*-nitronone could be reduced in three different ways (Scheme 6): (1) With sodium borohydride only the C=N bond was reduced, to furnish the bromomethyl hydroxylamine; (2) Lithium aluminium hydride additionally removed the bromide, but let intact the N-OH moiety; (3) All of these then were reduced by catalytic hydrogenation, to provide 1,4-iminopentitol as the third member of the series. Equally well C-C formation at the nitronone carbon occurred, with Grignard reagents **4**, but also cyanide when employed in the form

Scheme 5  
Bromocyclization of *erythro*-Pentenose Oxime

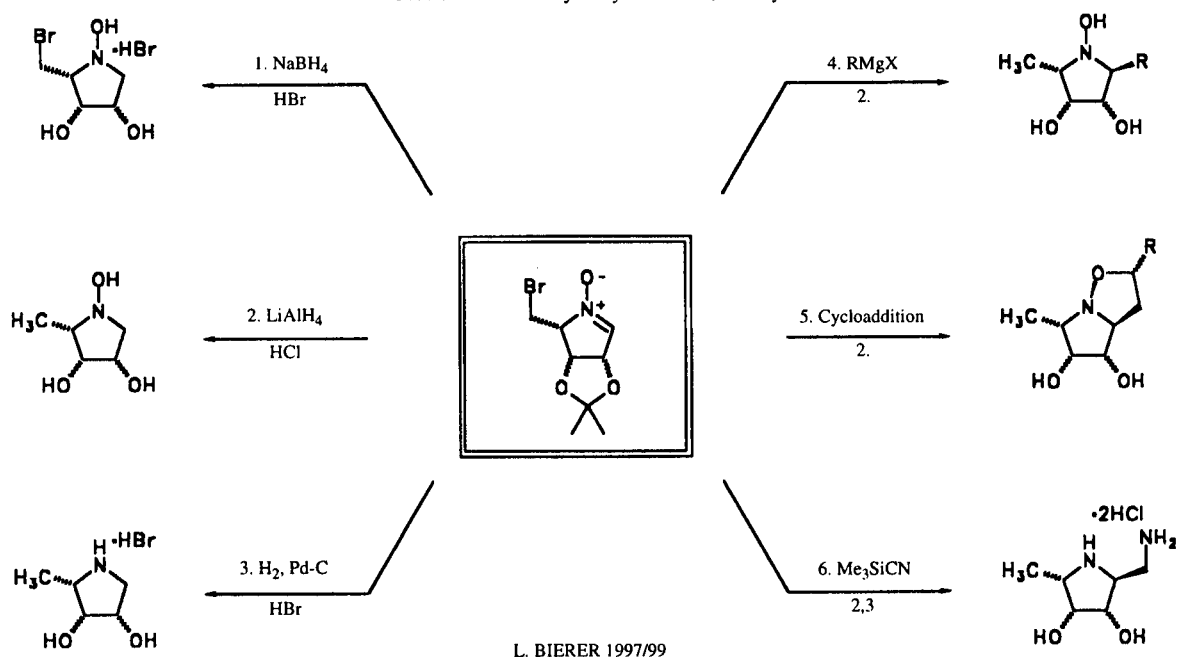


of trimethylsilyl derivative **6**. 1,3-Dipolar cycloaddition, well-known with other nitrones, led to the bicyclic isoxazolidines. All of these C-C-forming reactions proceeded with high diastereoselectivity, the acetonide clamp serving as an effective shield for the  $\alpha$ -diastereoface. Applying one or both of the reduction methods seen above, the

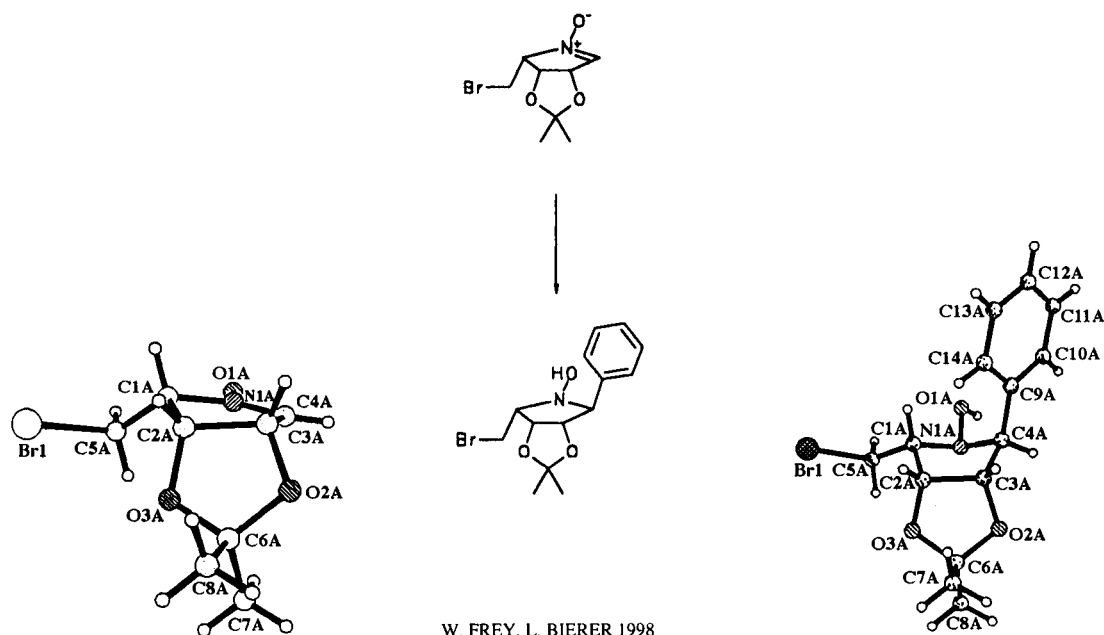
methyl compounds were obtained from all three types of products, with a carbon substituent at C2 of the pyrrolidine [6].

This fact is nicely seen from the respective crystal structures determined by X-ray diffraction. In Scheme 7, the nitron and the respective 2-phenyl addition product

Scheme 6  
Uses of Bromomethyl-L-lyxo-nitron, Survey



Scheme 7  
X-ray Crystal Structure Determination of Phenyl Adduct



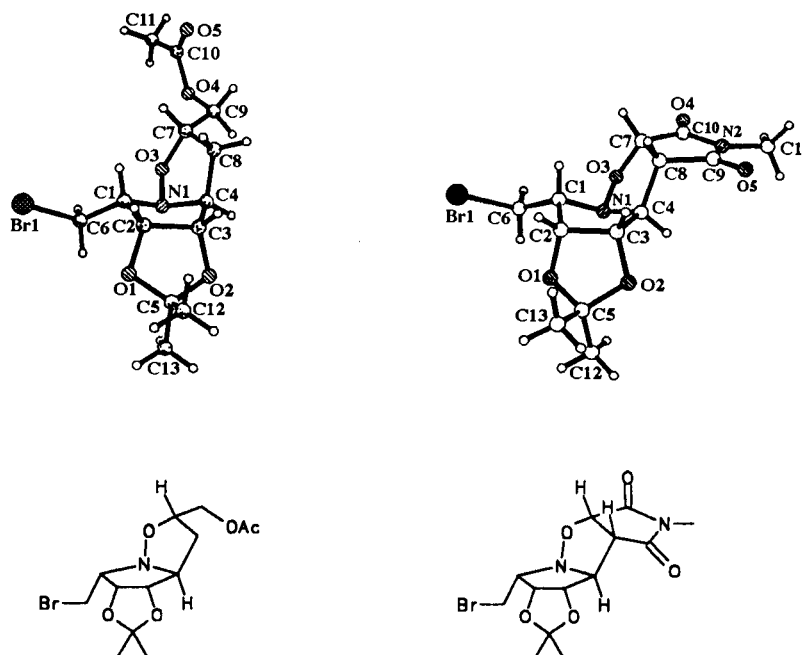
are shown. In the latter, the formerly near-flat ring of the pyrroline *N*-oxide now is a distinct envelope, with phenyl quasi-axial, and bromomethyl and *N*-hydroxy groups oriented in pseudo-equatorial positions.

Similarly, the products from 1,3-dipolar cycloadditions could safely be assigned the respective relative configura-

tions. The cases of the allyl acetate and *N*-methyl-maleimide products are shown in Scheme 8, with like arrangements of the three substituents at C-N-C [6].

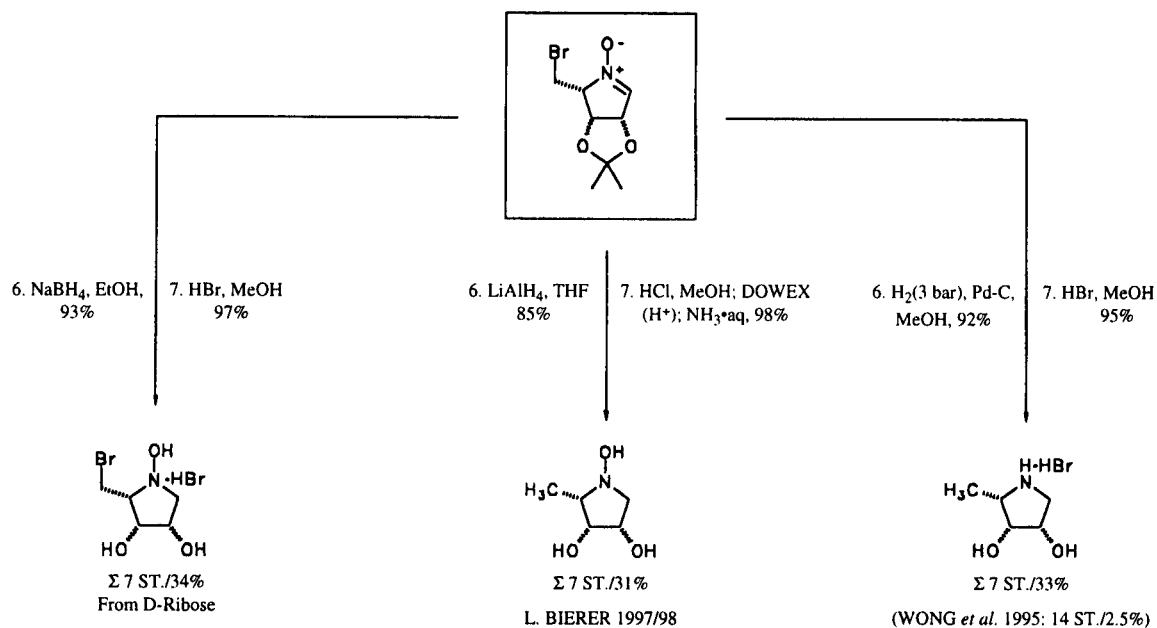
The *N*-oxy products from the various additions to the bromomethyl-*L*-lyxo-nitrone were all transformed into the free pyrrolidine diols or *N*-hydroxy compounds, in order

Scheme 8  
XCSD of Cycloadducts with *L*-lyxo Nitrone



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Scheme 9  
Synthesis of 1,4-Iminopolyols I; *L*-lyxo Series



to have samples suitable for the test of enzyme inhibition. Examples are given for the parent compounds, *i.e.*, the structures obtained by direct reduction of the parent nitron. Thus, the bromomethyl-*N*-hydroxy compound was obtained in the form of the hydrobromide (Scheme 9). The other new structure to examine the hypothesis advanced at the outset, the *N*-hydroxy-1,4-imino-L-lyxitol or, correctly: -2,5-imino-L-arabinitol), was obtained as the free base from ion exchange purification after acid-catalyzed hydrolysis of the respective acetonide. Finally, from catalytic reduction, acetal hydrolysis and hydrobromide formation the pyrrolidine diol was produced, a known compound prepared earlier in Wong's group. The virtues of the approach elaborated now are clearly seen with this Scheme and comparison: Diversity and efficiency.

### C. Halocyclization of Pentenose Hydrazones.

Hydrazones had not yet been taken as the nucleophilic component in additions induced by electrophiles such as halogen, as far as we are aware. If proceeding in analogy with the oxime cases, then cyclic azomethine imines should result. Indeed, with several hydrazones of the *erythro*-pentenose a reaction occurred on treatment with bromine or iodine, as had been successful above. However, mixtures of products formed which were difficult to analyze. Again, crystallization and ensuing analyses by X-ray diffraction shed light on what was going on. From iodine treatment of the phenylhydrazone a hydrazide was isolated in low yield, the structure of which is depicted in Scheme 10. This is rationalized by a reaction proceeding as hoped for, but the azomethine ylide had reacted with water.

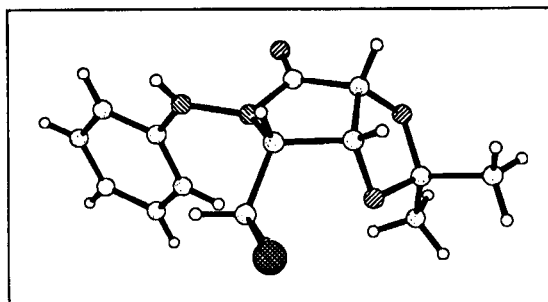
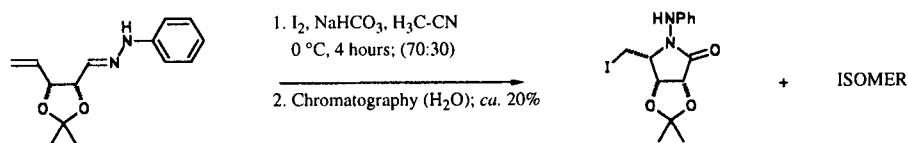
With the Boc-hydrazone, another type of products was obtained: a cleaner reaction gave 61% of a mixture of two stereoisomers in a ratio of *ca.* 3:2. From the nmr data we first were led to believe that this would be the 1,3-dipoles, but the ir data did not fit, and from the literature reports it seemed probable that any azomethine imine formed would rather combine and settle as a dimer. Again, X-ray diffraction gave the answer for one of the products: a pentacyclic dimer with a central perhydropyridazine ring of  $C_2$  symmetry had been built! And the reaction then must have been as given in Scheme 11. The intriguing structure of the product is seen in Scheme 12. Reactions of this dimer, which may be induced to split, will be reported separately.

With unsaturated hydrazones, in principle, intramolecular 1,3-dipolar cycloadditions might occur, if protropy to the *N*-H azomethine imine were possible and the chain length suitable. This idea was tested with several hexanose products obtained on treatment with mono- and *N,N'*-disubstituted hydrazines. On heating, all of them led to bicyclic pyrazolidines from which a number of promising candidates for glycosidase inhibition will be derived. Some of these cycloaddition products are gathered in Scheme 13.

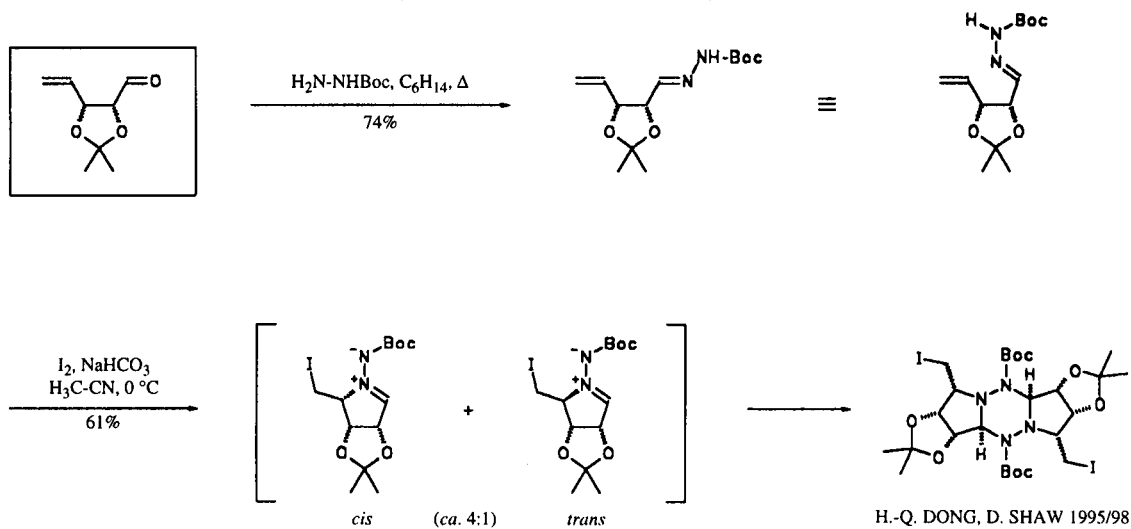
### D. Cope Cyclization (Retro-Cope Elimination, House Reaction).

Another, promising and versatile possibility to secure cyclic *N*-oxy structures of interest for glycosidase inhibition might take advantage of the cyclization of alkenyl-substituted hydroxylamines. This would nicely complement and extend the structure variations opened by bro-

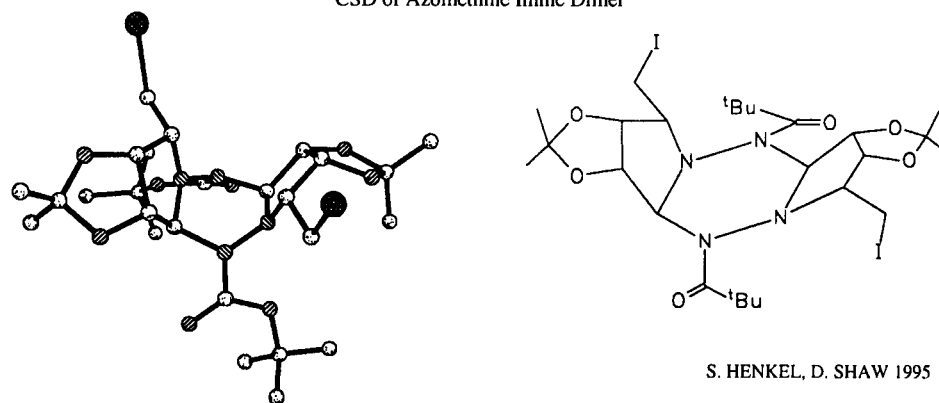
Scheme 10  
Halocyclization of *erythro*-4-Pentenose Hydrazones II



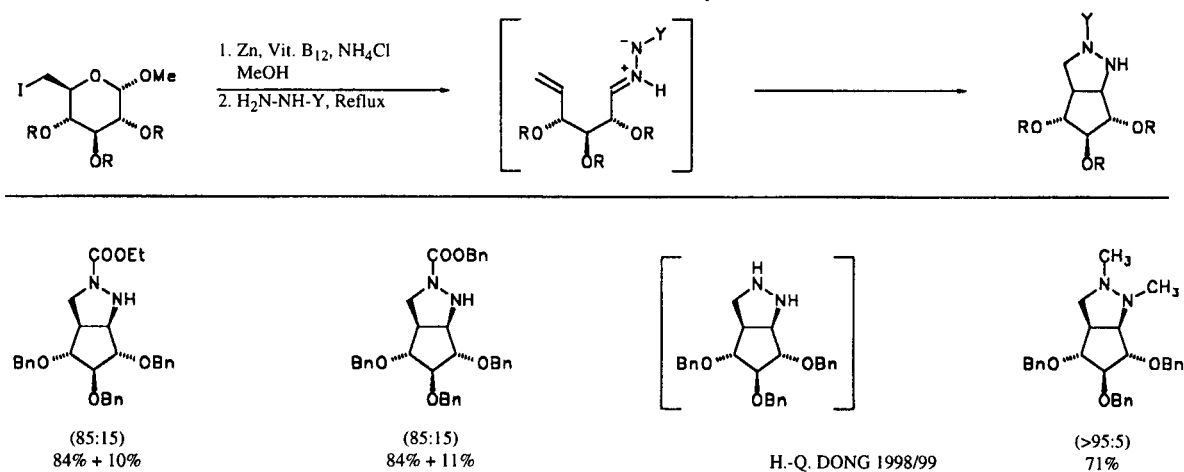
Scheme 11  
Halocyclization of erythro-4-Pentenose Hydrazones I



Scheme 12  
CSD of Azomethine Imine Dimer

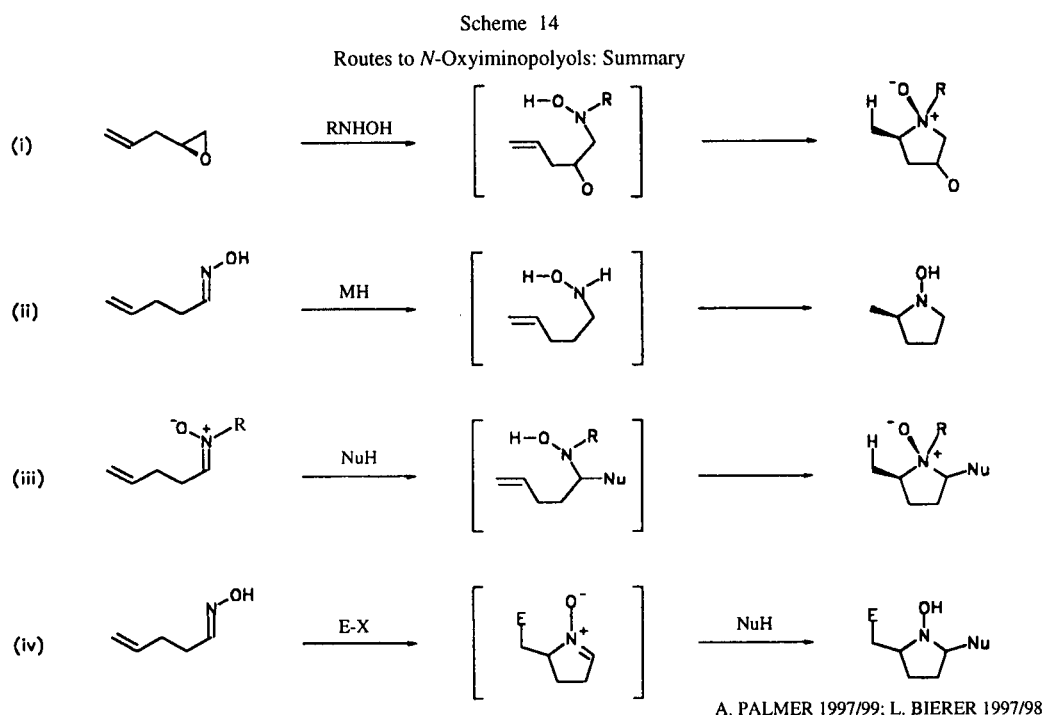


Scheme 13  
Intramolecular Azomethine Imine Cycloadditions



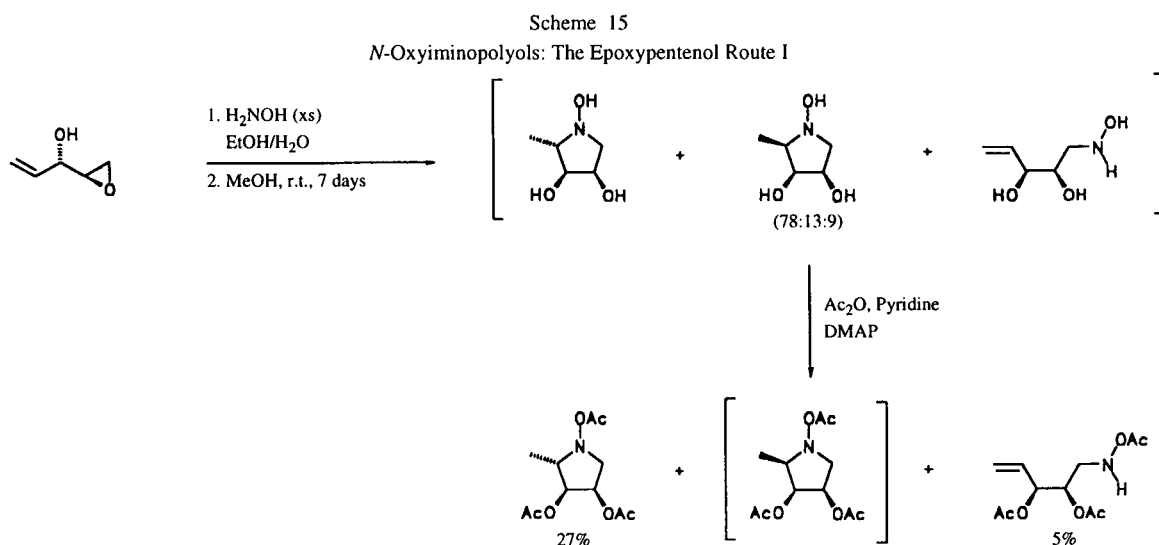
mocyclization of oximes. This, with most promising variants for access to and Cope cyclization of *N*-alkenyl hydroxylamines are combined in Scheme 14. All of these have been successful in our hands, and are presented at this conference separately in poster form, so that only a few points may be detailed here.

carbinol occurs with high diastereo- and enantioselectivity, to produce highly versatile, optically active building blocks that we – also, independently, Takano's group, and many others afterwards – have used for various transformations since. For example, a large number of aminodiols was prepared then from these epoxides by reaction with



The simplest access to an unsaturated hydroxylamine of a structure appropriate for Cope cyclization is shown with the epoxypentenol accessible from divinylcarbinol in just two steps. As we had shown in 1985 (at the 10th ICHC in Waterloo), the asymmetric Sharpless epoxidation of divinyl-

amines. Hydroxylamine was also employed then, but the products could not be identified since a mixture had resulted and the retro-Cope elimination at that time was not common knowledge. This particular reaction then was reconsidered in the last years, and the products could be





analyzed and separated, after acetylation (Scheme 15). The cyclization preferably is performed by keeping the initial hydroxylamine adduct in methanol at room temperature.

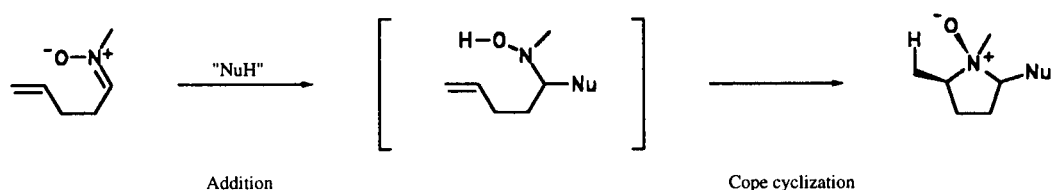
While further results from this and other routes are presented separately, an unexpected result opening the access to novel "azasugars" (correct naming) shall be detailed here. The sequence we had devised is shown in Scheme 16 (a recent paper by Knight *et al.* presents the same approach with the same starting material albeit a rather different access to another nitronone substrate). Addition of a nucleophile to a pentenal-derived nitronone could produce the Cope substrate, and henceforth the cyclic *N*-oxide (Scheme 16).

nor products of a subsequent cycloaddition. This reaction took place only with heating as we could verify (Scheme 18).

One of the secondary products, " $\beta$ -X", then could be induced to form crystals suitable for structural analysis by X-ray diffracton (once more!). The result is depicted in Scheme 19: it turned out a 6-hydroxylamino-1,2-tetrahydrooxazine, with the *N*-oxy group positioned axially and forming an intramolecular hydrogen bond with the ring nitrogen atom.

A possible pathway to account for the formation of "X" is given in Scheme 20; it is initiated by the (second) addition of hydroxylamine to the nitronone and Cope cyclization of the bis(hydroxylamine). The *N*-oxide products may

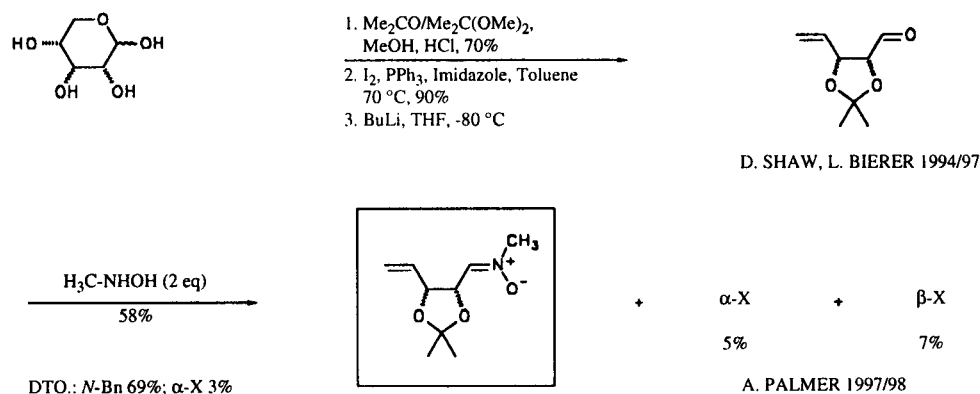
Scheme 16  
*N*-Oxyiminopolyols via Nitronones: Strategy



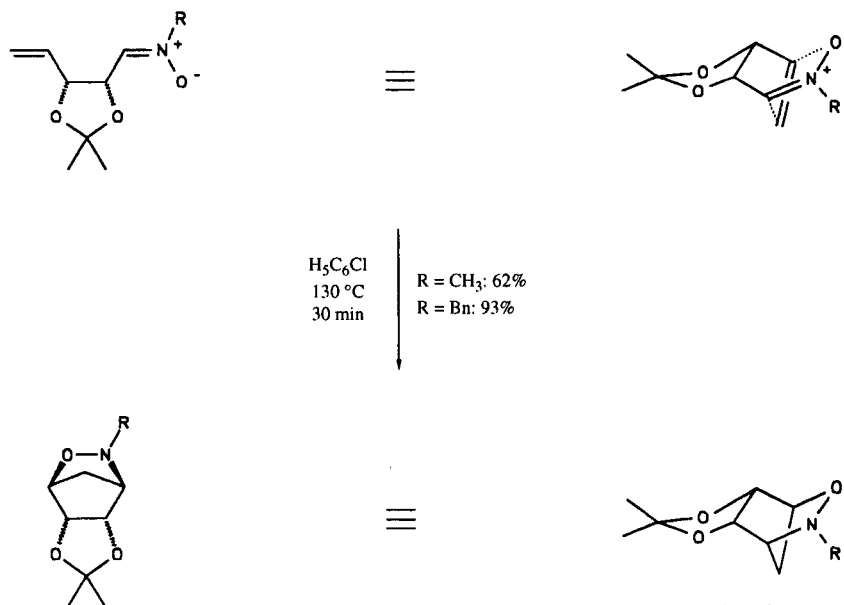
A nitronone derivative of our favorite building block, the *erythro*-pentenose drawn upon above, was known from the literature [12], was prepared in the usual way. Indeed, the expected nitronone was isolated with a decent yield (58%), but two low yield by-products were observed also, and subsequently isolated by chromatographic separation. The structure of these " $\alpha$ -X" and " $\beta$ -X" (Scheme 17), however, was difficult to deduce. From all data it was clear that these were neither stereoisomers of the nitronone

undergo elimination forming the nitronone moiety again, but the former C=C-bond now bears the *N*-attached hydroxylamino group. Recyclization with the oxygen atom then ends the cascade to afford the two 4-epimers of X. These 1,2-tetrahydrooxazines may be regarded as pyranose analogues, with C5 replaced by nitrogen, therefore constituting a new (the true) kind of azasugars. The above mechanistic interpretation which involves a Meisenheimer-type rearrangement, was transformed into practicality, *i.e.*, treat-

Scheme 17  
Key Intermediates: Nitronones of *D*-*erythro*-Pentenose



Scheme 18  
*erythro*-Pentenose Nitron: Intramolecular Cycloaddition



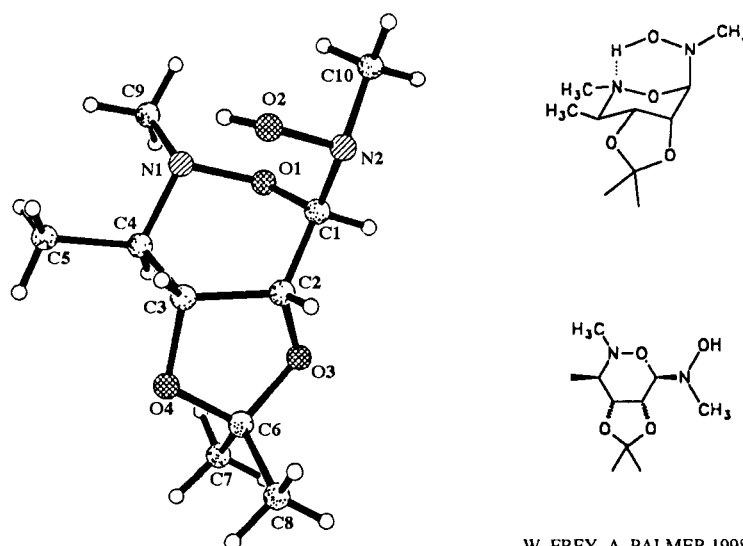
ment of such nitrones with excess hydroxylamine, and, satisfyingly, led to high yields of such azasugars, to be detailed elsewhere. The development of the chemistry of this new class of carbohydrate derivatives will be a future adventure in itself.

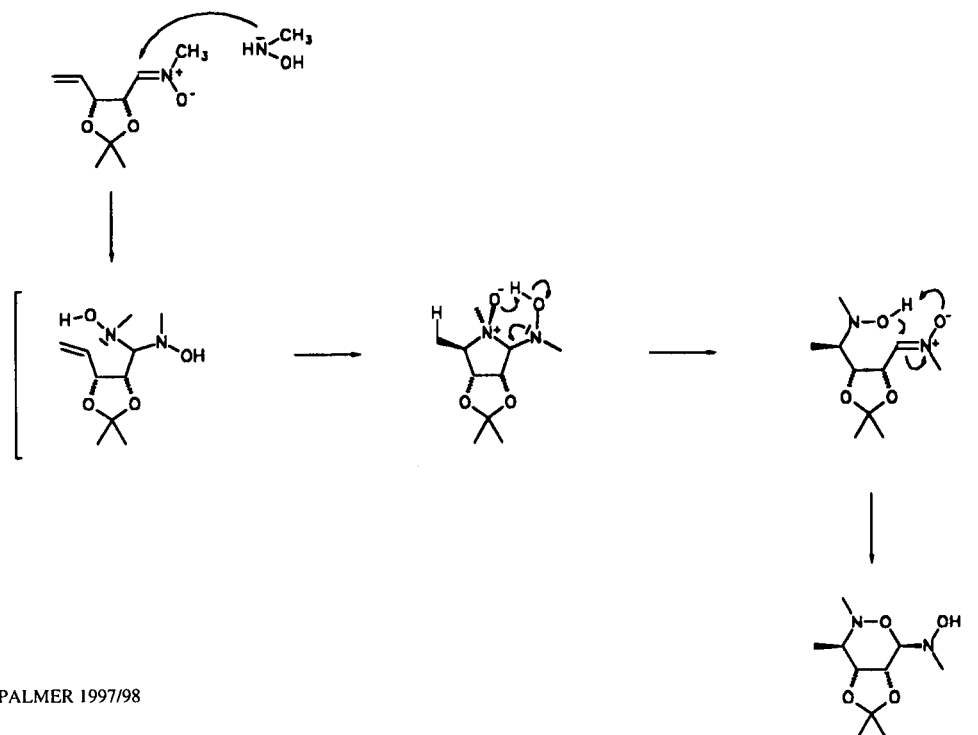
#### E. Conclusion.

Following the concept outlined, the various cyclization modes for unsaturated nitrogen derivatives were examined and given for the most part, products expected or hoped for. Since optically active starting materials were used – mostly derived from the *erythro*-pentenose avail-

able from *D*-ribose, enantiomerically pure compounds were obtained. The major objective here was to explore new structures mimicking  $\alpha$ -*L*-fucosides, and indeed very active compounds with  $K_i$  values down to  $0.04\ \mu\text{M}$  were found (details will appear elsewhere). Besides this, the various routes to prepare pyrrolidines and the like, with a wide array of structures, will also be useful for syntheses of related compounds active in other fields. Of the new compounds seen, the unexpected, facile access to 5-azapyranoses may be of particular significance, permitting to explore now the new field of azasugar chemistry.

Scheme 19



Scheme 20  
5-Azapyranoses II

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## REFERENCES AND NOTES

- [\*] E-mail address: jager.ioc@po.uni-stuttgart.de
- [1a] G. Legler, *Adv. Carbohydr. Chem. Biochem.*, **48**, 319 (1990); [b] B. Winchester and G. W. Fleet, *J. Glycobiology*, **2**, 199 (1992); [c] A. E. Stütz, *Iminosugars as Glycosidase Inhibitors*, Wiley VCH, Weinheim, 1999; [d] Y. Chapleur, *Carbohydrate Mimics*, Wiley-VCH, Weinheim, 1998.
- [2a] V. Jäger, R. Müller, T. Leibold, M. Hein, M. Schwarz, M. Fengler, L. Jaroskova, M. Pätzelt and P.-Y. LeRoy, *Bull. Soc. Chim. Belg.*, **103**, 491 (1994); [b] V. Jäger, T. Gracza, E. Dubois, T. Hasenöhl, W. Hümmer, U. Kautz, B. Kirschbaum, A. Lieberknecht, L. Remen, D. Shaw, U. Stahl and O. Stephan, in *Organic Synthesis via Organometallics (OSM 5)*; G. Helmchen, ed, Proc. 5th Symp. Heidelberg, 1996; Vieweg, Braunschweig, pp 321-360 (1997); [c] Cf. V. Jäger, R. Öhrlein, V. Wehner, P. Poggendorf, B. Steuer, J. Raczko, H. Griesser, F.-M. Kiess and A. Menzel, *Enantiomer*, **4**, 205 (1999).
- [3] Cf. B. Krämer, T. Franz, S. Picasso, P. Pruscek and V. Jäger, *Synlett*, 295 (1997).
- [4] V. Jäger and S. Picasso, The 16th ICHC, Montana State University, Bozeman, August 10-15, 1997, Abstr. IL-VI-2.
- [5] T. D. Heightman and A. T. Vasella, *Angew. Chem. Int. Ed.*, **38**, 750 (1999).
- [6] L. Bierer, Dissertation, Universität Stuttgart, 1999.
- [7a] H. O. House, D. T. Manning, D. G. Melillo, L. F. Lee, O. R. Haynes and B. E. Wilkes, *J. Org. Chem.*, **41**, 855 (1976); [b] W. Oppolzer, A. C. Spivey and C. G. Bochet, *J. Am. Chem. Soc.*, **116**, 3139 (1994); [c] E. Ciganek, J. M. Read, Jr. and J. C. Calabrese, *J. Org. Chem.*, **60**, 5795 (1995).
- [8] V. Jäger, I. Müller, R. Schohe, M. Frey, R. Ehrler, B. Häfele and D. Schröter, *Lect. Heterocyclic Chem.*, **8**, 79 (1985).
- [9] V. Jäger and T. Gracza, unpublished results 1988.
- [10a] A. M. Palmer, Diplomarbeit, Universität Stuttgart, 1998; [b] A. M. Palmer, Dissertation, Universität Stuttgart, in preparation.
- [11] J. R. Hanrahan and D. W. Knight, *J. Am. Chem. Soc., Chem. Commun.*, 2231 (1998).
- [12] J. K. Gallos, E. G. Goga and A. E. Koumbis, *J. Chem. Soc. Perkin Trans. I*, 613 (1994).
- [13a] S. Takahashi, T. Kusumi, Y. Sato, Y. Inouye and H. Kakisawa, *Bull. Chem. Soc. Japan*, **54**, 1777 (1981); [b] M. B. Gravestock, D. W. Knight and S. R. Thornton, *J. Chem. Soc., Chem. Commun.*, 169 (1993).