ORGANIC LETTERS

2007
Vol. 9, No. 17
3473−3476

A General Approach to the Synthesis of 1-Deoxy-L-iminosugars

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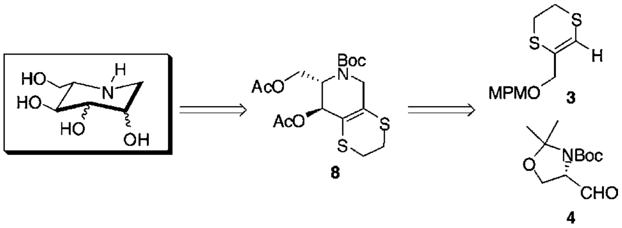
Received June 21, 2007

ABSTRACT



A stereoselective procedure for the preparation of non-naturally occurring deoxy iminosugars belonging to L-series has been developed. The synthesis involves the construction of the key intermediate bicycle pyperidine 8, available in few steps by the coupling of the heterocyclic synthon 3 and the readily available Garner aldehyde 4.

Polyhydroxylated piperidines (commonly known as iminosugars or azasugars) represent sugar analogues with the nitrogen atom in place of the ring oxygen of the corresponding carbohydrate. Since their first discovery over 40 years ago, iminosugars have gained a great deal of attention as inhibitors of carbohydrate-processing enzymes glycosidases and glycosyltransferases. As extensively described,[1] their inhibitory aptitude has been linked with their structural resemblance to the glycone moiety of glycosides that interact with such enzymes.

As alterations in biosynthesis and function of these enzymes are implicated in a wide variety of diseases, the significant inhibitory properties of iminosugars make them excellent targets for medical intervention. Their prospective therapeutical uses range from diabetes[2] through cancer[3] and viral diseases[4] to metabolic and neurological disorders.[5] As a result, α-glucosidase inhibitors 1-deoxynojirimycin (DNJ, **1**) and *N*-butyl-1-deoxynojirimycin (*N*B-DNJ, Zavesca **2**) (Figure 1) have been shown to inhibit human immunodeficiency virus (HIV) replication and HIV-mediated syncytium formation in vitro.[6] Moreover, *N*B-DNJ has been the first iminosugar medicine to receive approval, in 2002 in the European Union and in 2003 in the United States, for use in patients with mild to moderate type 1 Gaucher disease.

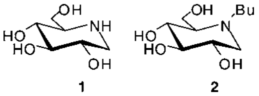


Figure 1. Bioactive iminosugars DNJ and *N*B-DNJ.

The principal advances in total and stereoselective syntheses of such compounds have recently been reviewed.[7] As reported, most syntheses have focused attention on the

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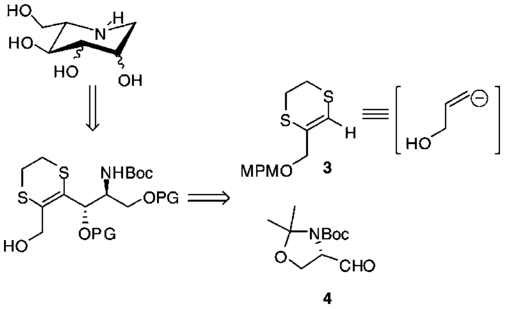
10.1021/ol7014847 CCC: $37.00

preparation of iminosugars with D-configuration, whereas few routes are available for the synthesis of their corresponding L-analogues.[8] This fact is evidently due to the larger commercial availability of D-series sugars as starting materials, as well as to the fact that glycosides belonging to D-series are the natural substrates of almost all glycosidases. However, it is worth recalling that iminosugars mimicking the sugar moiety structure of the natural substrate are not always inhibitors of the corresponding glycosidase. D-*manno*-DNJ (DMJ) is known as a much better inhibitor of α-L-fucosidase than α-D-mannosidase; on the other hand L-*allo*-DNJ is a better inhibitor of α-D-mannosidase than D-DMJ.[9] As recently shown,[10] an explanation of this behavior could be found considering that D-enantiomers are competitive inhibitors of D-glycosidases, whereas their L-enantiomers are noncompetitive inhibitors of the same enzymes.

In the context of our ongoing program directed toward the achievement of a new synthetic methodology for the preparation of polyhydroxylated molecules, we have developed a versatile strategy for the synthesis of non-naturally occurring deoxy-iminopyranoses belonging to L-series, through a non-carbohydrate based route.

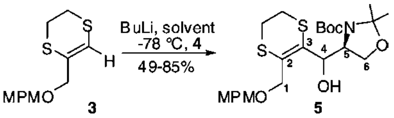
Scheme 1. Retrosynthetic Path



As outlined in Scheme 1, the synthesis involves the use of an heterocyclic synthon, the 5,6-dihydro-1,4-dithiin-2-yl-[(4-methoxybenzyl)oxy]methane[11] (**3**), a reagent capable of three-carbon homologation of electrophiles by the introduction of a fully protected allylic alcohol moiety, already devoted to the preparation of several polyhydroxylated compounds.[12]

The synthesis began with the coupling of the in situ prepared *C*-3 lithiated carbanion of **3** with the Garner[13] aldehyde **4** (Table 1) to afford a syn/anti diastereomeric mixture of alcohols **5**. As highlighted in Table 1, the best stereoselectivity was achieved by the use of Et$_2$O without catalyst, providing *anti*-**5** in good stereoselectivity (91:9 dr). Interestingly, the stereochemical outcome of the reaction seemed to be mainly influenced by the nature of the solvent,[14] whereas any significant stereoselective induction was not observed in the presence of the catalysts.[15]

Table 1. Three-Carbon Homologation



solvent	catalyst (20%)	(anti/syn) dr	yield(%)
THF	none	60:40	83
THF	Ti(*O*-*i*-Pr)$_4$	60:40	80
THF	Cp$_2$TiCl$_2$	60:40	85
Et$_2$O	Cp$_2$TiCl$_2$	70:30	49
Et$_2$O	ZnBr$_2$	82:18	73
Et$_2$O	none	91:9	72

The secondary alcohol[16] *anti*-**5**, obtained by the coupling reaction, was separated from its diastereomer by flash chromatography; the stereochemical assignment at the newly generated *C*-4 was clearly deduced by X-ray analysis (Figure 2).

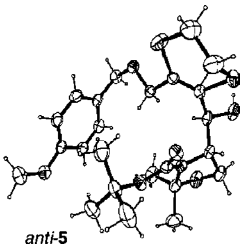


Figure 2. X-ray analysis of *anti*-**5**.

With the educt **5** in hand, our interest was focused on the achievement of key intermediate **9** (Scheme 2). To this purpose, we converted the alcohol **5** in its diacetate **6** by deprotection of the oxazolidine ring and acetylation of the

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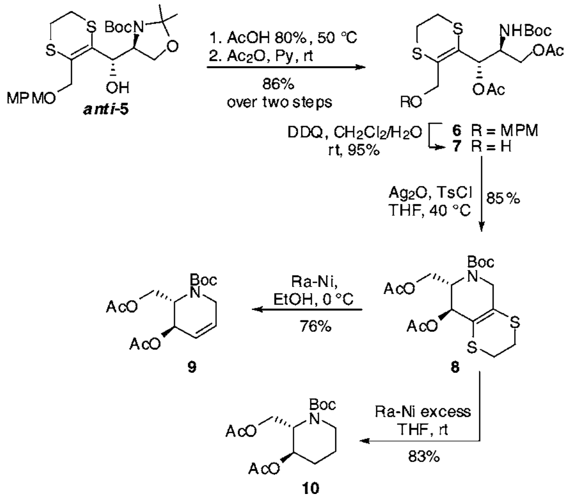
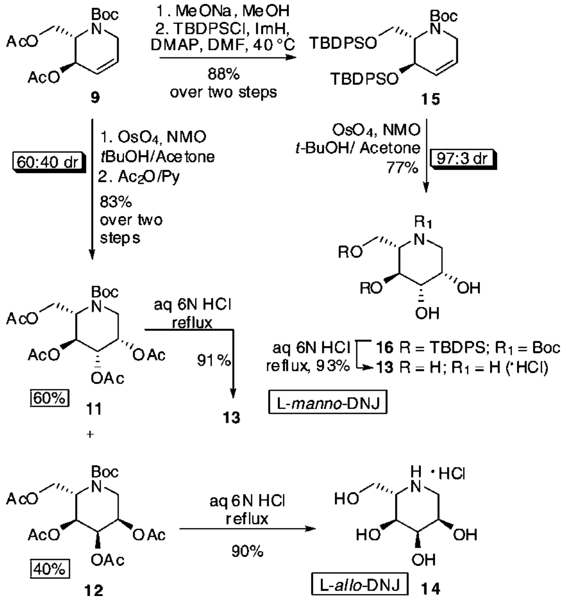
Scheme 2. Synthesis of the Key Intermediate **9**



crude residue (86% overall yield). Removal of MPM group by treatment of **6** with DDQ in a CH_2Cl_2/H_2O (9:1) emulsion gave the primary alcohol **7** with an excellent yield (95%). Intramolecular cyclization was then carried out under mild conditions by treatment of **7** with Ag_2O/TsCl in THF at 40 °C (85%). Finally, removal of the dithioethylene bridge on intermediate **8** was achieved by treatment with Raney-Ni in ethanol at 0 °C for 2 h leading to the olefin **9**. Moreover, when the reaction was carried out with a Raney-Ni excess in THF, at room temperature, the over-reduction product was obtained with a satisfactory yield (83%), affording the 1,2,3-trideoxy-L-iminosugar **10**.

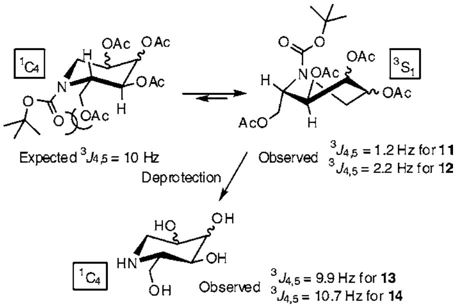
With the promising olefin **9** in hand our interest was directed to the stereoselective double-bond dihydroxylation (Scheme 3). Exposure of **9** to the common Upjohn conditions (OsO_4/NMO) followed by acetylation of the crude residue yielded a fully separable mixture of the protected L-*manno*-DNJ **11** and L-*allo*-DNJ **12** in low diastereomeric ratio (6:4). Both diastereomers were deprotected by means of refluxing aq 6 N HCl solution, obtaining deoxy-L-mannojirimycin (**13**) and deoxy-L-allonojirimycin (**14**) in remarkable yields (91% and 90%, respectively). Further attempts to improve the stereoselectivity of dihydroxylation reaction (i.e., using the bidentate complex OsO_4/TMEDA[17] and the Sharpless catalysts[18]) showed no significant effects.[19] The observed low selectivity in the above dihydroxylation reactions might be attributed to the relatively small size of the C-4 acetyl group and thus both faces of the double bond were almost equally hindered. As a matter of fact, the replacement of the Ac groups of **9** with the much bigger TBDPS ethers (**15**, 88% overall yield, Scheme 3), afforded after dihydroxylation of **15**, under Upjohn conditions, the protected L-*manno*-DNJ **16** with a high stereoselectivity (97:3 dr). Then, treatment with aq 6 N HCl allowed removal of all protective groups to obtain deoxy-L-mannojirimycin (**13**) in 93% yield.

Scheme 3. Syn Dihydroxylation of **9**



It is noteworthy to recall that the stereochemistry of compounds **13** and **14** is consistent with X-ray analysis of the *anti*-**5** compound and with the spectroscopic data. However, observing the coupling constant values in the ^1H NMR spectra (Scheme 4), it is evident that the *N*-Boc compounds **11** and **12** do not conform to the expected $^1C_4$ chair conformation, typical of L-sugars adopting a conformation close to $^3S_1$.[20]

Scheme 4. Preferred Conformations for Compounds **11**, **12**



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(14) The solvent-dependent stereoselective effect should be related to the nature of the organolithium intermediate: as already reported (see farther on), a "nude" and more reactive ionic couple prevails in THF, while a less reactive non-ionized species is formed in Et_2O, driving the reaction towards a better stereoselective outcome: (a) Seyferth, D.; King, R. B. *Annual Surveys of Organometallic Chemistry*, Vol. 1−3, Elsevier Publishing Co.: Amsterdam, 1965−1967. (b) Maercker, A.; Roberts, J. D. *J. Am Chem. Soc*. **1966**, *88*, 1742−1759.

(15) In all our experiments the reported syn stereoselection [Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136−2157] was never observed. Because of the chemical characteristics of compound **5**, such discrepancy could be rationalized assuming that in the reaction medium the catalyst does not complex Garner aldehyde, but it can be sequestrated by the negatively-charged heterocyclic system, without induction of stereoselectivity.

(16) An alternative numbering reported on the carbon skeleton has been employed to identify carbon atoms that will belong to the carbohydrate-like ring (see Table 1).

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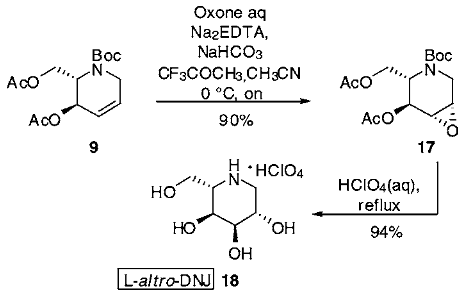
The above successes led us to consider the anti dihydroxylation of the key olefin **9**. Treatment of this latter with in situ generated[21] DMDO (oxone/trifluoroacetone) afforded exclusively the *anti*-epoxide **17** in 90% yield (Scheme 5).

Scheme 5. Anti Dihydroxylation of **9**



Ring opening[22] of the 2,3-anhydro derivative **17** along with the removal of all protecting groups by means of refluxing $HClO_4$ gave the deoxy-L-altronojirimycin (**18**) in 94% yield.

In summary, a versatile pathway for the synthesis of L-deoxyiminosugars belonging to L-series has been opened up in this paper. Together with L-*manno*-, L-*allo*-and L-*altro*-deoxyiminosugars **13**, **14**, and **18**, whose synthesis has been described, this path will be profitably employed for the synthesis of all the epimers with *galacto* configuration, simply applying the same procedure on the *syn*-**5** diastereomer. Furthermore, the whole synthetic procedure so far described, carried out from **3** and the *ent*-**4** (prepared from D-serine) enables the preparation of D-series iminosugars as well.

Acknowledgment. This research has been supported by a Regione Campania grant to A.G. (L.R. 5/2002). ^1H and ^{13}C NMR spectra and X-ray analysis were performed at Centro Interdipartimentale di Metodologie Chimico-Fisiche (CIMCF), Università di Napoli Federico II. Varian Inova 500 MHz instrument is property of Consorzio Interuniversitario Nazionale La Chimica per l'Ambiente (INCA) and was used in the frame of a project by INCA and M.I.U.R. (L. 488/92, Cluster 11-A). We are grateful to Dr Umberto Ciriello (ICI International Chemical Industry S.p.A.) for his collaboration to this work. We also thank Prof. Angela Tuzi (Dept. of Chemisty, University of Napoli) for X-ray analysis of *anti*-**5** compound.

Supporting Information Available: Experimental procedures, analytical data, X-ray crystallographyc data (cif file) for *anti*-**5**, ^1H and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) In the $^1C_4$ chair form, a downward orientation is imposed on the *N*-Boc substituent owing to the nature of the ring nitrogen atom, resulting in a strong repulsive interaction with the nearly coplanar *C*-6 methylene group. An upward movement of the ring nitrogen relieves such repulsion leading to a $^3S_1$ conformation. For similar results see: (a) Kilonda, A.; Compernolle, F.; Hoornaert, G. J. *J. Org. Chem.* **1995**, *60*, 5820−5824. (b) Kazmaier, U.; Grandel, R. *Eur. J. Org. Chem.* **1998**, 1833−1840.

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(22) On the basis of ^1H NMR coupling constant values we established that also **17** essentially exists in a $^3S_1$ conformation and that the formation of *trans*-diaxial ring opening product **18** could be explained assuming that the $HClO_4$ first removes the *N*-Boc group, allowing the chair inversion from $^3S_1$ to $^1C_4$, and then leads to the epoxide cleavage.