New Building Blocks for Tackling the Synthesis of Polyhydroxylated Piperidines: Expeditious Synthesis of Amino Derivatives in the 1-Deoxynojirimycin Series

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A remarkable range of polyhydroxylated piperidine and indolizidine alkaloids isolated from living systems belongs to the important family of azasugars. Many of them exhibit specific and potent inhibitory activity against glycosidases, and as a consequence have a great potential as drugs against diabetes, cancer, and viruses.[1]

Among them, 1-deoxynojirimycin[2] and castanospermine[2c,3] have received much attention in recent years as representatives of this class of compounds (Figure 1) and led to an impressive number of review articles dealing with their multistep syntheses.

Most of the numerous synthetic approaches in these series are based upon carbohydrates as a predetermined source of chirality for a given synthetic target.[2a,4] The heterocyclizations are achieved after introduction of an amino group at the last stages of multistep routes.

The need for an easy access to this type of molecules led us to conceive a new trihydroxylated chiral nonracemic building block **1** (Figure 1) for the development of our own approach based upon the general and versatile CN(*R,S*) method.[5,6]

In this preliminary note, we disclose the facile synthesis of **1** from commercially available starting materials and its straightforward transformation into the new 6-amino-1,6-dideoxy-5-*epi*-nojirimycin as a first application.

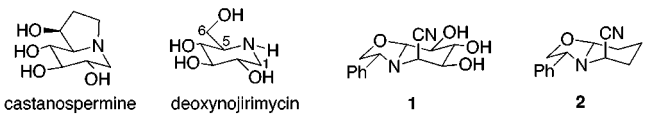

Figure 1.

The preparation of **1** parallels the double condensation of *R*-(−)-phenylglycinol **3** as the nitrogen source, chirality inducer, and iminium stabilizer,[6] with glutaraldehyde into building block **2**.[7] Taking advantage of carbohydrate precursors to establish three of the five contiguous stereogenic centers, our approach employed the *meso*-trihydroxylated glutaraldehyde **4**, easily prepared[8] from the commercialy available isopropylidene-α-D-glucofuranose by periodate oxidation and acidic deprotection (Scheme 1).

Thus, condensation of **3** and **4** in the presence of potassium cyanide in aqueous citric acid buffer afforded a crude material which was equilibrated to the more thermodynamically stable derivatives in the presence of zinc bromide. After flash chromatography (yield: 45%), compound **1** was crystallized from tetrahydrofuran while its diastereomer **5** was obtained as a minor byproduct (≈5−15%). Thus, two new stereogenic centers were created at the same time and concomitant desymmetrization of the "sugar moiety" included in the new structure was achieved.

Careful NMR studies (2D-experiments: COSY, HETCOR, and NOESY) of piperidine **1** established the structure and stereochemistry as depicted in Scheme 1 (hexahydro-3-phenyl-6,7,8-trihydroxy-3*R*-[3α,5*β*,6*β*,7α,8*β*,-8a*β*]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile). In particular, the coupling constant $J_{H-6/H-5} = 7.5$ Hz was significative of an axial relationship between H-6 and H-5, while $J_{H-2/H-3} = 5.5$ Hz was in favor of an equatorial/axial relationship between H-2 and H-3. These results were confirmed by H-6/H-8, H-6/H-4 as well as H-2/H-3 correlations in the NOESY spectrum.

The same NMR experiments performed on isomer **5** gave support for an axial position of the three hydroxyl groups. This surprising feature was confirmed by a X-ray study.

In principle, formation of eight configurationally different cyclization products was possible since selective recognition of the aldehyde functions by phenylglycinol was not expected.

It has been shown for the formation of **2** (85% yield) in equilibrating conditions, that there is a stereoelectronic preference for a *trans*-diaxial relationship for CN-addition on iminium salts and the developing nitrogen lone pair

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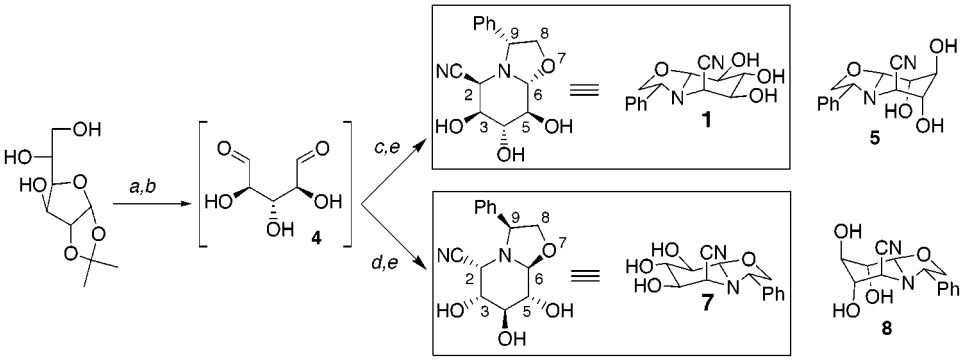
Scheme 1. Synthesis of Building Blocks 1 and 7



Reagents and conditions: *a*, $NaIO_4$, $NaHCO_3$; *b*, H_2O, DOWEX H^+; *c*, (*R*)-(-)-Phenylglycinol **3**, H_2O citric buffer, KCN; *d*, (*S*)-(+)-Phenylglycinol **6**, H_2O citric buffer, KCN; *e*, $ZnBr_2$, MeOH (2 steps, 45 %).

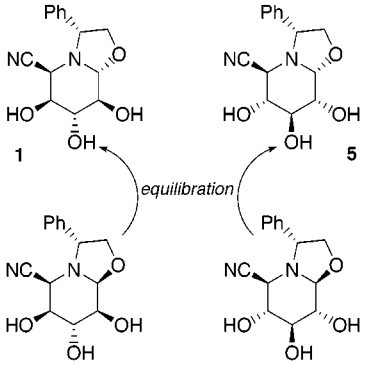
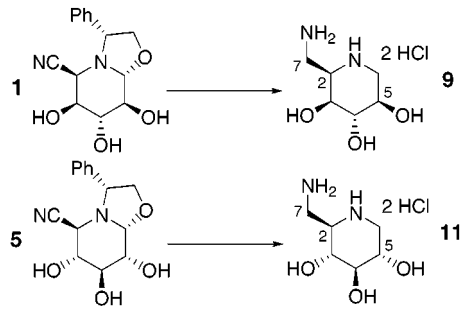


Figure 2. Preferred stereomers.

Scheme 2. Synthesis of 9 and 11



Reagent and conditions: H_2, Pd/C, 10 bars, EtOH,HCl (90 %).

of electrons. Furthermore a *trans* relative stereochemistry between C-2 and C-6 substituents is observed. Moreover, the absolute configuration of the C-2 stereogenic center is the result of a 1,3-transfer of chirality from the phenyl substituent involving addition of CN^- from the upper face of Δ^1-piperidinium chair transition state.

The four isomers wherein the cyano group is equatorial can be disregarded because they do no profit from the combined influence of a stabilizing anomeric effect between the nitrogen lone pair of electrons and the *peri*-antiplanar cyano group.[9] Since only two cyclization products **1** and **5** were isolated (the remaining products ≈50% decompose during purification), mechanistic arguments for their formation might be inspired from the above-mentioned considerations. As far as the four isomers with an axial cyano group are concerned (Figure 2), after equilibration to the more thermodynamically stable *trans*-oxazolidines, one obtains compound **1** as the major compound wherein the three hydroxyl groups are equatorial and a themodynamically less-stable all-axial compound **5**.

As expected, similar results were obtained by the condensation of (*S*)-phenylglycinol **6** with glutaraldehyde, leading to the enantiomer of **1** (**7**) as well as a minor compound **8**, enantiomeric with **5** (Scheme 1).

A general synthetic strategy for the preparation of the polyhydroxylated piperidines and indolizidines from building block **1** would be very attractive acccording to the following considerations:

(1) *R* or *S* phenylglycinols are the source of nitrogen and chirality at α and α′ position of the nitrogen atom. Consequently, control of the configuration at these newly created asymmetric centers would allow synthesis of enantiomeric series.

(2) Access to indolizidines should be possible through alkylation with suitable side chains and subsequent cyclization on the nitrogen after elimination of the chiral appendage.

(3) Compound **1** can be considered as a 1,4-dihydropyridine equivalent since α-aminonitrile and α-aminoether functions are both precursors of iminium salts and tautomeric enamines.[5] Thus, differentiated ketones could be selectively generated *β* or *β*′ to the nitrogen, permitting inversion of the configuration of hydroxyl groups or introduction of new functions.

(4) In addition to reduction in a primary amine, the nitrile itself could be hydrolyzed in acid or transformed in aldehyde or alcohol under controlled reductions.

Interestingly, all this transformations should not require the protection of the hydroxyl groups.

One example of the numerous synthetic possibilities of compound **1** is given by the easy preparation of a new amino derivative (**9**) which is an isomer of the two amino analogues of 1-deoxynojirimycin previously reported.[10] Catalytic hydrogenation of **1** (Scheme 2) implying simultaneous reduction of the cyano group and hydrogenolysis of the chiral appendage afforded **9** in a single operation (three steps, 40% overall yield, $[\alpha]^{20}_D = -9.5$ [c = 1.5, H_2O, 2 HCl salt]). The relative configuration of **9** was ascertained by NMR analysis in comparison with 6-amino-1,5-imino-1,5,6-trideoxy-D-mannitol **10**,[10] and 6-amino-

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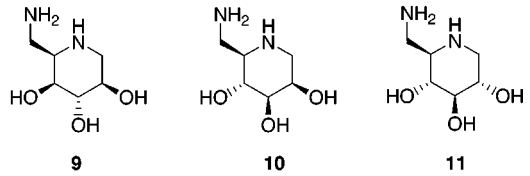

9 **10** **11**

Figure 3.

1,5-imino-1,5,6-trideoxy-D-glucitol **11**[11] (Figure 3). These 6-amino analogues of 1-deoxymannojirimycin and 1-deoxynojirimycin were obtained in multistep syntheses. While the δ values for C-2, C-3, C-5, C-6, and C-7 are very close in the ^{13}C NMR spectra of both **9** and **11**, the shift difference for C-4 (**9**: 69.3 ppm, **11**: 77.4 ppm) is suggestive of an 1,3-diaxial relationship between the amino chain at C-2 and the proton attached at C-4 in compound **9**. Furthermore, a direct comparison of the ^1H NMR spectra of the HCl salts of **9** and **10** was very informative. Indeed, the H-2 resonance at 3.75 ppm (3.46 ppm for **10**)[12] was a strong argument for an equatorial proton as well as the coupling constants (td, $J = 6$ and 3 Hz). The signal at 4.27 ppm for the equatorial proton H-5 in the spectrum of **9**,[11] was observed at 3.92 ppm for **9** as a result of an axial position. This (2*R*,3*S*,4*S*,5*R*)-2-(aminomethyl)piperidine-3,4,5-triol **9** obtained in a two-step synthesis constitutes a new stereomer of the amino analogue (**11**, (2*R*,3*R*,4*R*,5*S*)-2-(aminomethyl)piperidine-1,3,5-triol)[12] of natural 1-deoxynojirimycin (Figure 1).[2]

Finally, the same reaction was performed on the minor compound **5** in order to synthesize the amino derivative **11** related to the parent azasugar deoxynojirymicine.[2] Indeed, compound **11** was obtained quantitatively from **5** and showed identical physical data to those previously reported.[11b] Although performed on a minor reaction compound, this short synthesis favorably compares with the already published method[11b] which needs 11 steps for the same yield approximately.

Among the multiple ways for synthesizing polyhydroxylated piperidines alkaloids and analogues, the well-established CN(*R,S*) method could provide a short and efficient strategy toward the synthesis of a wide range of azasugars. In this respect, the new building block **1** constitutes an ideal starting material for natural product synthesis and design of new glycosidase inhibitors. The potential flexibility of our approach is currently being studied.

Experimental Section

All new compounds were characterized by 2D ^1H and ^{13}C NMR as well as IR spectra, [α] values, simple and high-resolution mass spectrometry, or elemental analysis.

Hexahydro-3-phenyl-6,7,8-trihydroxy-3*R*-[3α,5*β*,6*β*,7α,8*β*,-8a*β*]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (1): (*R*)-(−)-phenylglycinol **3** (1.5 g, 11 mmol) was dissolved in 4% citric acid buffer (50 mL). A solution of **4** (3 g, 20 mmol) in citric buffer (50 mL) was added followed by potassium cyanide (1 g, 15 mmol). After stirring overnight, the reaction mixture was neutralized with $NaHCO_3$ and concentrated under reduced pressure. The residue was dissolved in boiling MeOH, the resulting suspension filtered over a pad of silica gel, and the filtrate evaporated. The oily crude mixture was dissolved in MeOH and treated, under vigorous stirring, with $ZnBr_2$ (500 mg) for 3 h before being evaporated in vacuo and submitted to a flash chromatography. Elution with CH_2Cl_2/MeOH (95:5) gave 1.5 g (45%) of compound **1** and small amounts of diasteromer **5** (175 mg, 5%). Compound **1** crystallized from THF: mp = 182−185 °C; $[\alpha]^{25}_D$ –139 ($c = 1$ in MeOH); ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6 2:1, 25 °C): δ 3.5−3.6 (m, 1H), 3.66 (t, $J = 8$ Hz, 1H), 3.76 (d, $J = 5.5$ Hz, 1H), 3.88 (t, $J = 8$ Hz, 1 H), 4.02 (d, $J = 7.5$ Hz, 1H), 4.23 (t, $J = 8$ Hz, 1H), 5.03 (d, $J = 3.5$ Hz, 1H), 5.20 (d, $J = 4$ Hz, 1H), 5.46 (d, $J = 4$ Hz, 1H), 7.2−7.4 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD, 25 °C) δ 51.7, 64.0, 71.1, 74.7, 75.1, 75.7, 92.9, 114.9, 128.4, 129.5, 129.8, 137.1; MS (CI, CH_4) *m/z* 277 $(M + 1)^+$; HRMS (CI, CH_4) *m/z* $(M + 1)^+$; Calcd for $C_{14}H_{17}N_2O_4$: 277.1188, Found: 277.1176. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N,10.14. Found: C, 60.70; H, 5.71; N, 10.20.

Hexahydro-3-phenyl-6,7,8-trihydroxy-3*R*-[3α,5*β*,6α,7*β*,8α,-8a*β*]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (**5**): crystallization from THF; mp = 156−158 °C; $[\alpha]^{25}_D$ –155 ($c = 1$ in MeOH); ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ 3.63 (t, $J = 7.5$ Hz, 1H), 3.75−3.85m, 2H), 3.85−4.00 (m, 3H), 4.25 (t, $J = 7.5$ Hz, 1H), 4.49 (d, $J = 1$ Hz, 1H), 4.80 (d, $J = 6$ Hz, 1H), 5.09 (d, $J = 8$ Hz, 1H), 5.46 (d, $J = 3.5$ Hz, 1H), 7.2−7.4 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD, 25 °C) δ 51.9, 64.3, 70.5, 71.8, 74.6, 89.2, 115.5, 129.0, 129.6, 130.0, 137.7; MS (CI, CH_4) *m/z* 277 $(M + 1)^+$.

Hexahydro-3-phenyl-6,7,8-trihydroxy-3*S*[3*β*,5α,6α,7*β*,8α,-8aα]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (7): identical procedure as for **1**. $[\alpha]^{25}_D$ +134 ($c = 1$ in MeOH).

Hexahydro-3-phenyl-6,7,8-trihydroxy-3*S*[3*β*,5α,6*β*,7α,8*β*,-8aα]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile (8): identical procedure as for **5**. $[\alpha]^{25}_D$ +150 ($c = 1$ in MeOH); MS (CI) *m/z* 163 $(M + 1)^+$; HRMS (FAB+, Na^+) *m/z* $(M + Na)^+$; calcd for $C_6H_{15}N_2O_3Na$: 299.1007, found: 299.1001.

(2*R*,3*S*,4*S*,5*R*)-2-(Aminomethyl)piperidine-3,4,5-triol (9): a solution of **1** (100 mg, 0.36 mmol) in ethanol (18 mL) was added to a 1 N HCl ethanolic solution (2 mL) and hydrogenated at 10 bar over Pd/C/10% for 2 days. After filtration the mixture was evaporated to dryness. The residue was triturated in THF/Et_2O (1:1) to remove phenylethanol.The remaining precipitate was dried to give the hygroscopic hydrochloride salt of compound **9** (77 mg, 90%) as a yellowish powder: $[\alpha]^{20}_D$ –9.5 ($c = 1.5$ in H_2O); ^1H NMR (300 MHz, D_2O, 25 °C): δ 3.15−3.45 (m, 4H), 3.75 (td, $J = 6$, 3 Hz, 1H), 3.85−43.95 (m, 3H); ^{13}C NMR (75 MHz, D_2O, 25 °C) δ 40.4; 48.2, 54.8, 68.0, 69.3, 69.9; MS (CI) *m/z* 163 $(M + 1)^+$; HRMS (FAB+) *m/z* $(M + 1)^+$; calcd for $C_6H_{15}N_2O_3$: 163.1083, found: 163.1078.

(2*R*,3*R*,4*R*,5*S*)-2-(Aminomethyl)piperidine-3,4,5-triol (11): dichlorhydrate obtained by the same procedure as for **9**: $[\alpha]^{25}_D$ +8 ($c = 1$ in H_2O); ^1H NMR (400 MHz, D_2O, 25 °C): δ 2.88 (t, $J = 11.5$ Hz, 1H), 3.10−3.25 (m, 2H), 3.28 (m, 1H), 3.36 (m, 2H), 3.46 (t, $J = 10$ Hz, 1H), 3.59 (ddd, $J = 5$, 9, 11.5 Hz, 1H); ^{13}C NMR (75 MHz, D_2O, 25 °C) δ 42.40; 49.0, 57.9, 69.3, 73.8, 78.5; MS (CI) *m/z* 163 $(M + 1)^+$; HRMS (FAB+) *m/z* $(M + 1)^+$; calcd for $C_6H_{15}N_2O_3$: 163.1083, found: 163.1078.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **5**, **7**, **9**, **11**, and their NMR spectra viz. ^1H, ^{13}C, 2D experiments, ORTEP plots, and X-ray data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The numbering of compound **9** follows the usual nomenclature while nojirimycin, mannojirimycin, and several analogues are numbered by some authors according to the sugar nomenclature.