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SHORT COMMUNICATION

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Double Reductive Amination and Selective Strecker Reaction of a D-Lyxaric Aldehyde: Synthesis of Diversely Functionalized 3,4,5-Trihydroxypiperidines

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A D-mannose-derived aldehyde with the D-*lyxo* configuration is a versatile key intermediate to functionally and stereochemically diversified piperidines. It allowed the synthesis of natural 3,4,5-trihydroxypiperidines and new analogs through a double reductive amination strategy and the synthesis of novel 2-cyanotrihydroxypiperidines through a highly regio- and diastereoselective Strecker reaction.

Introduction

3,4,5-Trihydroxypiperidines **1**–**3** (Figure 1) were isolated in 1995 from *Eupatorium fortunei* TURZ,[1] a plant used in folk medicine for the treatment of several pathologies. They have been synthesized by Ganem[2] and others either by the "chiral pool" strategy[3] or by enantioselective syntheses[4] and behave as selective inhibitors of glycosidases. These molecules, also referred to as 1-*N*-iminosugars together with their relative isofagomine (**4**), have shown potential therapeutic applications for the treatment of several pathologies such as energy utilization diseases, viral infections, and lysosomal storage disorders.[5] During our studies on the synthesis of polyhydroxylated alkaloids and their unnatural analogs,[6] our attention was drawn to aldehyde **5** (Scheme 1), whose synthesis from D-mannose has been recently reported.[7]

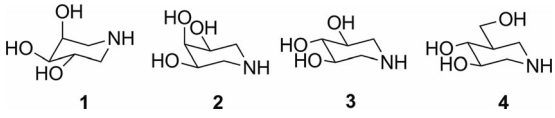
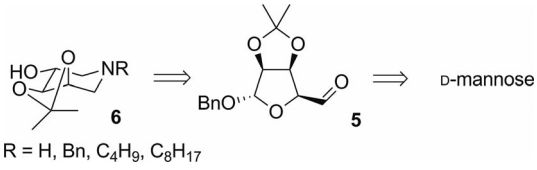


Figure 1. Natural glycosidase inhibitor trihydroxypiperidine alkaloids.



Scheme 1. Retrosynthetic strategy.

We envisaged in "masked" dialdehyde **5**, with the configuration of D-lyxose, a versatile building block for the synthesis of trihydroxypiperidines and their unnatural congeners (Scheme 1). In particular, the introduction of lipophilic chains on the nitrogen atom was appealing to improve the ability of the iminosugars to penetrate the cell membrane and their chaperoning activity.[8] The most direct approach conceivable for the synthesis of piperidines **6** was double reductive amination with a primary amine. While many examples of this reaction have been reported starting from diketones or ketoaldehyde derivatives,[9] the same approach from dialdehydes has been less exploited, apart from Bols' synthesis of isofagomine[10] and a few recent reports.[11] We describe here the results obtained with aldehyde **5** that led to the synthesis of natural **2**, *ent*-**1**, and some new unnatural *N*-alkylated piperidines. Preliminary results on the Strecker reaction with **5** (and its debenzylated derivative) are also reported.

Results and Discussion

Aldehyde **5** was synthesized in four steps from D-mannose, following a slight modification of the published procedure[7] (see the Supporting Information). We initially sought to access piperidines **6** by one-pot double reductive amination of **5** with hydrogen as the reducing agent, in view of the required removal of the benzyl protecting group at the anomeric position. Compound **5** was treated with benzylamine (1 equiv.) in MeOH in the presence of 3 Å molecular sieves (Scheme 2). After 40 min, the imine was formed (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture), then $Pd(OH)_2/C$ was added, and the mixture was stirred under an atmosphere of H_2 (balloon) for 25 h to afford compound **7**[12a] in 69% yield. Treatment of **7** with methanolic HCl followed by ion-exchange resin afforded unnatural *ent*-**1**,[12,4a,2,3b,3c] quantitatively. The spectroscopic data and physicochemical proper-

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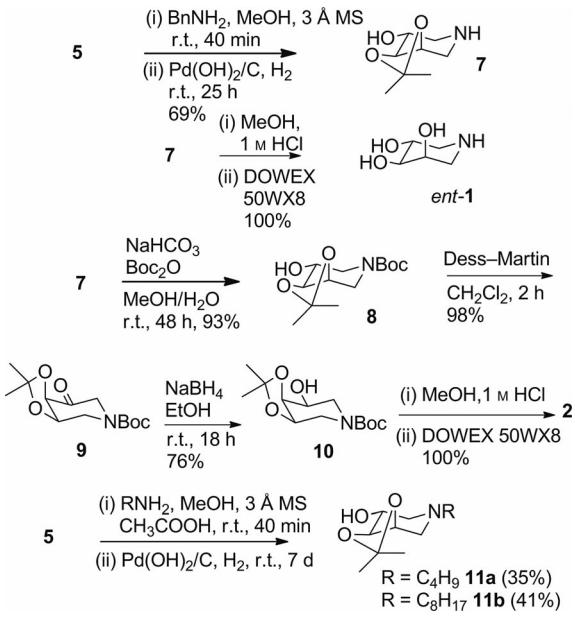
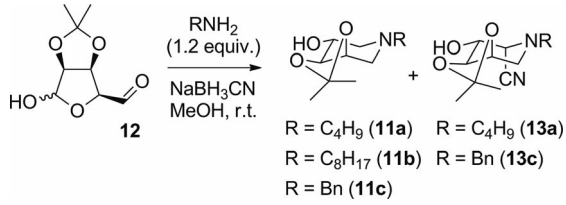
ties of *ent*-**1** are in agreement with the literature data.[12b,4a] Synthetic *ent*-**1** showed a specific optical rotation {$[\alpha]_D^{26}$ = –65.7 (*c* = 1.0, MeOH)} that was opposite to that reported for the natural sample {$[\alpha]_D$ = +66.7 (*c* = 0.3, MeOH)}.[1] This compound was shown to be a selective inhibitor of α-L-fucosidase from human placenta.[12b] In order to access natural **2**, the configuration at C5–OH in **7** had to be inverted. However, the Mitsunobu reaction under standard conditions[13] failed both on **7** and on *N*-Boc-protected piperidine **8**, which was obtained in 93% yield from **7** under standard conditions. We then turned to an oxidation–reduction procedure. In the final reduction, the expected favored axial attack of hydride to C=O at C-5 *anti* to the vicinal C–O bond according to a Felkin–Anh model would install the desired all-*cis* relative configuration of the final product. Oxidation of **8** with Dess–Martin periodinane[14] gave ketone **9** in 98% yield, and subsequent reduction with $NaBH_4$ afforded stereoselectively alcohol **10**, as expected, in 76% yield. Final treatment with methanolic HCl followed by ion-exchange resin afforded **2**[3a,3c–3e,4a] in quantitative yield (Scheme 2). The spectroscopic data and physicochemical properties of **2** were in agreement with those reported in the literature.[3a,3e,4a] Compound **2** was shown to inhibit β-glucosidase and α- and β-galactosidase.[3a,3d] The double amination protocol on **5** employing butylamine and octylamine afforded piperidines **11a** and **11b** in moderate yields (Scheme 2). Obviously, *N*-benzyl-substituted piperidine could not be achieved through this catalytic hydrogenation procedure.



Scheme 2. Synthesis of *ent*-**1** and **2**.

Alternatively, deprotection of the benzyl anomeric group by catalytic hydrogenation afforded dialdehyde **12** in 100% yield (see the Supporting Information). This compound, which can be viewed (in its open-chain form) as a 2,3-di-*O*-protected D-lyxaric aldehyde or as a 3,4-di-*O*-protected D-arabinaric aldehyde, could be a suitable substrate for the double reductive amination reaction by using $NaBH_3CN$ as the reducing agent. This procedure would also allow the synthesis of *N*-benzyl-substituted piperidines. Martin and co-workers reported related examples on different carbohydrate-derived aldehydes, and the yields varied from very low to excellent.[11b] While this work was in progress, Crich and co-workers described the double reductive amination of a 1,5-dialdehyde to afford isofagomine (**4**).[15] Our results on dialdehyde **12** are shown in Table 1.

Table 1. Double reductive amination of dialdehyde **12**.

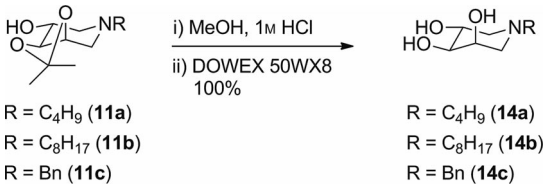


Entry	RNH_2	$NaBH_3CN$ [equiv.]	Time [d]	**11**/**13**[a]	Yield of **11** [%][b]
1	$BnNH_2$	3	3	2:1[c]	23[d]
2	$BnNH_2$	3	2	3.5:1[c]	51[d]
3	$BnNH_2$	2	5	6:1	32
4	$C_4H_9NH_2$	2	5	3:1	43
5[e]	$BnNH_2$	3	3	>98:2	93
6[e]	$C_4H_9NH_2$	3	7	>98:2	48
7[e]	$C_8H_{17}NH_2$	3	7	>98:2	56

[a] Determined by ^1H NMR spectroscopic analysis of the crude mixture. [b] Isolated yield after flash column chromatography. [c] Determined after acetylation of the crude mixture. [d] Yield refers to isolation of the acetate of **11**. [e] Anhydrous MeOH, 3 Å molecular sieves, R–NH_2 (0.9 equiv.), AcOH (2 equiv.).

Initially, **12** was treated with benzylamine (1.2 equiv.) in MeOH, and after 3 d, a 2:1 mixture of the desired **11c** together with the unexpected amine **13c** was recovered (Table 1, Entry 1). Formation of cyano-substituted compounds as byproducts during reductive amination reactions under neutral or basic conditions has been occasionally reported.[16] Remarkably, 2-cyano-substituted piperidine **13c** was formed completely regio- and stereoselectively. The structure of **13c** was assigned on the basis of 1D and 2D NMR spectra of its acetate derivative, which showed for 3-H a dd with *J* = 8.4 and 4.8 Hz, in agreement with an *ax*–*ax* relationship with 4-H and an *ax*–*eq* relationship with 2-H, respectively. Rationalization of the observed selectivity is currently under investigation. The amount of **13c** formed could be reduced by shortening the reaction time (Table 1, Entry 2 vs. 1) or by reducing the number of equivalents of $NaBH_3CN$ (Table 1, Entry 3 vs. 1). The formation of 2-cyanopiperidine **13a** was also observed with the use of $BuNH_2$ (Table 1, Entry 4). By employing anhydrous MeOH and AcOH (2 equiv.),[11b] the formation of the 2-cyano adduct was completely suppressed and *N*-alkyl piperidines **11a**–**c** were formed in good to excellent yields (Table 1, En-

tries 5–7). Final treatment with methanolic HCl followed by ion-exchange resin afforded unnatural *N*-alkylated piperidines **14a**–**c** (Scheme 3) in quantitative yields.

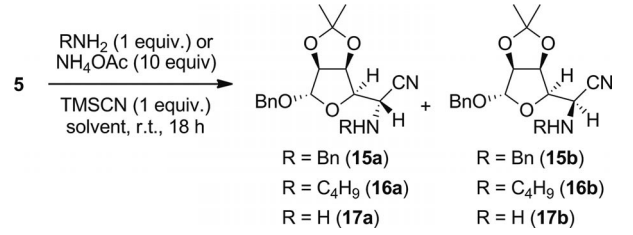


Scheme 3. Synthesis of unnatural *N*-alkylated piperidines.

2-Cyanopiperidines **13** obtained as byproducts would be valuable synthetic intermediates.[17] Thus, we reasoned that such compounds could be obtained regioselectively by Strecker reaction[18] of aldehyde **5**, followed by deprotection at the anomeric carbon atom and cyclization. The Strecker reaction has been extensively used for the synthesis of α-aminonitriles from aldehydes, also in its enantioselective version,[17,19] and due to the chirality of **5**, we envisaged that a diastereoselective Strecker reaction could be accomplished. Aldehyde **5** was first treated with benzylamine (1.0 equiv.) and TMSCN (1.0 equiv.) in dry acetonitrile with the addition of 1.0 mol-% of $Cu(OTf)_2$ as catalyst.[20] We were delighted to observe that mainly one diastereoisomer was formed, in remarkable diastereomeric excess (>95:5; Table 2, Entry 1). A similar result was observed with $BuNH_2$ as the amine source (Table 2, Entry 2). However, the presence of a Lewis acid catalyst was found unnecessary (Table 2, Entries 1 and 2), with cleaner products obtained under these conditions that did not require further purification by flash column chromatography. By employing 10 equiv. of NH_4OAc[21] as source of ammonia in acetonitrile (Table 2, Entry 3), adduct **17a** was obtained in 62:38 diastereoselectivity. A change to EtOH led to an improvement in the diastereoselectivity (81:19; Table 2, Entry 4) and a quite good isolated yield (61%) of **17a** was also achieved. Configuration at the new stereocenter was assigned on the basis of X-ray analysis of a single crystal of **17a** (see the Supporting Information).[22] The stereochemical outcome of the reaction can be rationalized by considering the approach of the cyanide nucleophile through a Cram model of a chelation-controlled transition state (Figure 2), where the iminium proton is involved in a five-membered chelate ring. According to this model, the cyanide ion would attack from the less-hindered *Si* face of the double bond to give diastereomers with the *S* absolute configuration at the newly formed stereocenter as major products **15**–**17a**. This stereochemical outcome is in agreement with the one recently reported for acyclic polyhydroxylated aldehydes.[21]

Even more intriguing, the direct Strecker reaction of dialdehyde **12**,[23] followed by cyclization and in situ reduction of the iminium ion intermediate by $NaBH_3CN$ afforded 2-cyanopiperidine **13c** with high regio- and stereoselectivity (Scheme 4) in 50% yield after purification over silica gel.[24] The structure of **13c** was ascertained by acetylation (see the

Table 2. Strecker reaction on aldehyde **5**.



Entry	RNH_2/$AcONH_4$	Solvent	**a**/**b**[a]	Yield of **a** [%][b]
1	$BnNH_2$	MeCN[c]	>95:5	100[d] (80)[e]
2	$BuNH_2$	MeCN[c]	>95:5	100[d] (75)[e]
3[f]	$AcONH_4$	MeCN	62:38	–
4[f]	$AcONH_4$	EtOH	81:19	61

[a] Determined by ^1H NMR spectroscopic analysis of the crude mixture. [b] Isolated yield after flash column chromatography. [c] Anhydrous solvent and 3 Å MS added. [d] Yield of the crude, >95% purity as evaluated by ^1H NMR spectroscopy. [e] Addition of 1.0 mol-% of $Cu(OTf)_2$. [f] 1.2 equiv. of TMSCN.

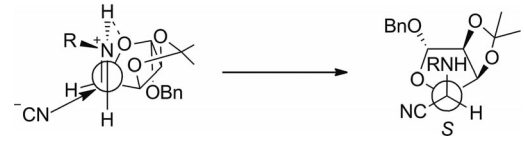
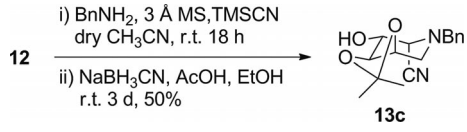


Figure 2. Cram chelate model for the Strecker reaction.

Supporting Information), which gave a sample identical to the one formed during the reductive amination of **12** (Table 1). From this result, we may also infer that the regio- and stereoselective formation of compounds **13** from **12** during the reductive amination is derived from a Strecker reaction occurring at the more reactive aldehyde at C-5 followed by intramolecular reductive amination at C-1.



Scheme 4. Regio- and stereoselective Strecker reaction.

Conclusions

In conclusion, we have reported ready access to valuable 3,4,5-trihydroxypiperidines, including natural alkaloids and analogs, by reductive amination of a D-lyxaric/D-arabinaric aldehyde derived from D-mannose. Highly regio- and stereoselective Strecker reaction of the same key intermediate allowed access to 2-cyano-substituted piperidine adducts. These latter are valuable intermediates for the synthesis of pipecolic acid analogs and other natural compounds.[25]

Experimental Section

General Procedure for the Synthesis of *N*-Alkyl Piperidines 11a–c by Double Reductive Amination: A solution of dialdehyde **12** (0.06 M in dry MeOH) was stirred in the presence of powdered 3 Å molecular sieves for 15 min under a nitrogen atmosphere. Then, $NaBH_3CN$ (3.0 equiv.) was added, and the reaction mixture was cooled to 0 °C. Finally, RNH_2 (R = Bn, Bu, octyl, 0.9 equiv.) and AcOH (2.0 equiv.) were added, and the mixture was warmed to room temperature and stirred for a total of 3–7 d under a nitrogen atmosphere. The molecular sieves were removed by filtration through Celite, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (CH_2Cl_2/MeOH or CH_2Cl_2/MeOH/6% NH_4OH) to afford **11a–c** in 48–93% yield.

General Strecker Reaction Procedure: A 0.2 M solution of compound **5** and the appropriate amine source ($BuNH_2$, $BnNH_2$, 1.0 equiv., or NH_4OAc, 10.0 equiv.) in dry CH_3CN was stirred at room temperature for 40 min and then trimethylsilyl cyanide (1.0 or 1.2 equiv.) was added. The resulting reaction mixture was stirred at room temperature for 18 h, then diluted with EtOAc and washed with water and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude products, which were purified by flash chromatography (PE/EtOAc) to afford major diastereoisomers **15**–**17a** in 61–100% yield.

Supporting Information (see footnote on the first page of this article): Procedures and characterization data of all key compounds, X-ray structure of **17a**, and copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

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[22] Full details will be given in a forthcoming Full Paper.
[23] The ^1H NMR spectrum of **12** showed the presence of a complex mixture of different forms.
[24] No other isomers were detectable in the crude mixture.

[25] Selected examples: a) A. Fadel, N. Lahrache, *J. Org. Chem.* **2007**, *72*, 1780–1784; b) S. Shahane, F. Louafi, J. Moreau, J.-P. Hurvois, J.-L. Renaud, P. van de Weghe, T. Roisnel, *Eur. J. Org. Chem.* **2008**, 4622–4631; c) T. Kanemitsu, Y. Yamashita, K. Nagata, T. Itoh, *Synlett* **2006**, 1595–1597; d) N. Blank, T. Opatz, *J. Org. Chem.* **2011**, *76*, 9777–9784; e) Y. Nakamura, A. M. Burke, S. Kotani, J. W. Ziller, S. D. Rychnovsky, *Org. Lett.* **2010**, *12*, 72–75; f) S. Takayama, R. Martin, J. Wu, K. Laslo, G. Siuzdak, C.-H. Wong, *J. Am. Chem. Soc.* **1997**, *119*, 8146–8151; g) A. Peer, A. Vasella, *Helv. Chim. Acta* **1999**, *82*, 1044–1065; h) E. Poupon, B.-X. Luong, A. Chiaroni, N. Kunesch, H.-P. Husson, *J. Org. Chem.* **2000**, *65*, 7208–7210.

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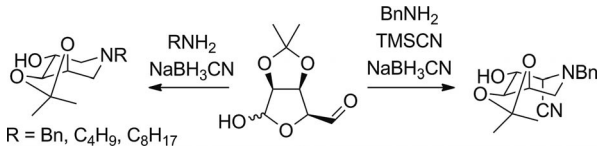

The synthesis of natural 3,4,5-trihydroxypiperidines and non-natural *N*-alkylated derivatives from a dialdehyde possessing the D-*lyxo* configuration is presented herein. The highly regio- and diastereoselective Strecker reaction on the same key aldehyde allowed access to important precursors of pipecolic acids and diaminopiperidine compounds.

Azasugars

Keywords: Total synthesis / Alkaloids / Azasugars / Amination / Strecker reaction

