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Enantioselective synthesis of 1-deoxy-D-gulonojirimycin from a phenylglycinol-derived lactam

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Dedicated to Professor Dr. José Luis Soto on the occasion of his retirement

Abstract—Cyclocondensation of (*R*)-phenylglycinol with appropriately γ-substituted δ-oxo acid derivatives provides bicyclic lactams from which the enantioselective synthesis of 1-deoxy-D-gulonojirimycin has been reported.

Azasugars (also called iminosugars) are compounds in which the ring O-atom of a carbohydrate is replaced by nitrogen.[1] They constitute an important class of glycosidase inhibitors that are receiving a great deal of attention because of their therapeutic potential in the treatment of viral infections including HIV,[2] cancer,[3] diabetes,[4] and other metabolic disorders.[5] In particular, inhibitory activities have been reported for many naturally occurring polyhydroxylated piperidines (deoxynojirimycin, isofagomine),[6] whereas miglitol,[7] a synthetic glucose-mimic piperidine, is commercially available in several countries for the treatment of diabetes (Fig. 1).

Although traditionally enantiopure azasugars have been synthesized through multistep transformations of readily available carbohydrate precursors, recent interest has increasingly focused on the synthesis of this class of compounds from non-carbohydrate sources.[8]

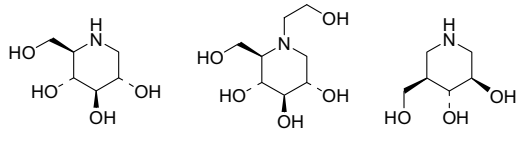

Figure 1. Natural and synthetic azasugars.

In the context of our studies on the enantioselective synthesis of piperidine derivatives from phenylglycinol-derived bicyclic lactams,[9] we have recently reported a synthetic route to 3,4,5-trihydroxypiperidines, in which the key step was an unprecedented stereoselective oxidative hydroxylation of *N*-(1-phenyl-2-hydroxyethyl)-2-pyridone.[10] We present here a different approach to enantiopure 3,4,5-trihydroxypiperidines that additionally bear a hydroxymethyl substituent at the 2-position, which is a structural feature characteristic of most piperidine containing azasugars.

Our approach consists of two well-differentiated phases: (i) the assembling of an enantiopure bicyclic δ-lactam **B** by cyclocondensation of (*R*)-phenylglycinol with an appropriately functionalized (and protected) δ-oxo acid derivative (**A**), and (ii) functional group transformations, with removal of the chiral auxiliary (Scheme 1). To illustrate the usefulness of the methodology we present here the synthesis of 1-deoxy-D-gulonojirimycin (**1**; 1-deoxy-3,4-diepi-nojirimycin; 1,5-dideoxy-1,5-imino-D-gulitol),[11] a piperidine-derived azasugar, whose isolation from the bark of *Anglylocalyx pynaertii* (Leguminosae) has recently been reported.[12]

For the generation of the required enantiopure bicyclic δ-lactam we initially planned to operate from a racemic

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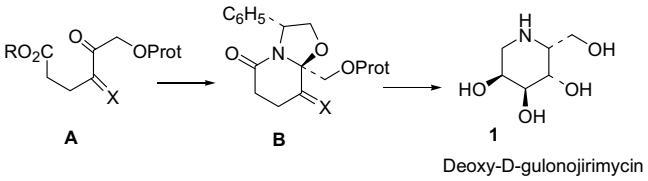
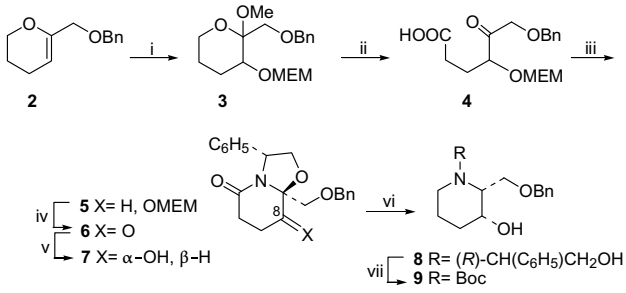


Scheme 1. Synthetic strategy.

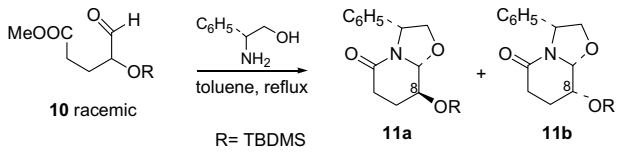


Scheme 2. Reagents and conditions: (i) *m*-CPBA, MeOH, 0 °C, 2 h then DIPEA, ClMEM, rt, 20 h, 77%; (ii) Jones reagent, acetone, rt, 5 h, 40%; (iii) (*R*)-phenylglycinol, toluene, reflux, 12 h, 72%; (iv) NaI, $CeCl_3{\cdot}7H_2O$, MeCN, reflux, 6 h, then Jones reagent, acetone, rt, 1 h, 66%; (v) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, EtOH, THF, rt, 1.5 h, 87%; (vi) BH_3–THF, THF, rt, 24 h, 57%; (vii) H_2, $(t\text{-BuOCO})_2O$, $Pd(OH)_2/C$, AcOEt, 25 °C, 72%.

δ-oxo acid **4**, which bears two differently protected hydroxy groups at the ketone α and α′ positions. Our hope was that, by analogy with related cyclocondensation reactions from racemic γ-aryl (or alkyl) δ-oxo acids,[13] a dynamic kinetic resolution of the stereocenter α to the ketone carbonyl group would occur during cyclocondensation with (*R*)-phenylglycinol, stereoselectively leading to a bicyclic lactam with a well-defined configuration at the piperidine α- and β-positions. The required δ-oxo acid **4** was readily prepared from the dihydropyran derivative **2**,[14] by *m*-CPBA oxidation followed by protection of the resulting α-hydroxy ketal and finally Jones oxidation (Scheme 2). However, cyclocondensation of **4** with (*R*)-phenylglycinol led to a C-8 epimeric mixture (3:2 ratio) of lactams **5**[15] in 74% yield, thus revealing that dynamic kinetic resolution had only occurred to a small extent.

To investigate if the above result could be attributed to the presence of the benzyloxymethyl substituent on the ketone carbonyl, we studied the cyclocondensation reaction from racemic O-protected hydroxy-aldehyde **10**,[16] from which the imine ⇋ enamine equilibrium required for deracemization would necessarily involve the epimerizable stereocenter at the aldehyde α-position (Scheme 3). A C-8 epimeric mixture of bicyclic lactams **11a** and **11b** (50%, 3:2 ratio)[15] was again obtained, thus indicating that cyclocondensation reactions take place with low stereoselectivity when there is an oxygenated substituent on the epimerizable stereocenter α to the aldehyde or ketone carbonyl group.

In spite of the above results, the approach depicted in Scheme 2 proved to be synthetically useful for the preparation of enantiopure 3-hydroxypiperidines bearing a hydroxymethyl substituent at the 2-position. Thus,



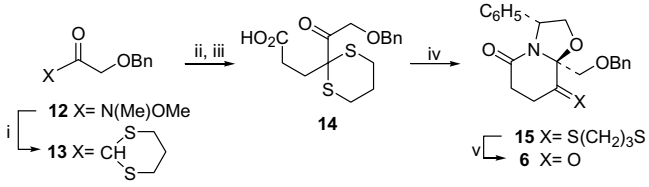
Scheme 3.

the above epimeric mixture of lactams **5** was satisfactorily converted to alcohol **7** by deprotection of the hydroxy function, followed by Jones oxidation and subsequent stereoselective Luche reduction of the resulting ketone **6**. Then, treatment of **7** with BH_3–THF brought about both the reduction of the lactam carbonyl group and the stereoselective reductive opening of the oxazolidine ring, with retention of configuration,[17] to give the *cis* piperidine **8**. Finally, removal of the chiral auxiliary by chemoselective hydrogenolysis of the *N*-benzylic substituent in the presence of di-*tert*-butyl dicarbonate led to the protected 3-hydroxypiperidine **9**.[18]

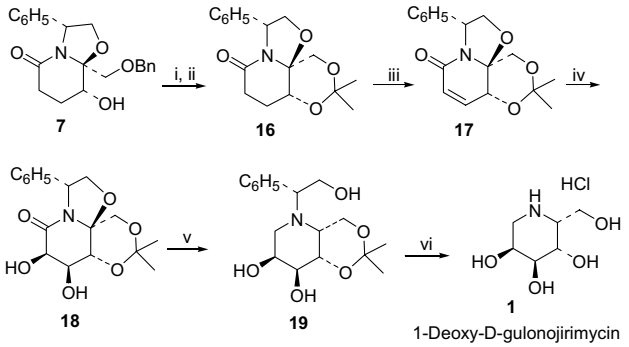
An alternative synthetic route to the key enantiopure intermediate **6**, also based on a cyclocondensation reaction, is depicted in Scheme 4. The required δ-oxo acid **14**, incorporating a dithioacetal function at the ketone α position, was prepared from the Weinreb amide **12**,[19] by reaction with the lithium salt of 1,3-dithiane followed by alkylation of the resulting dithioacetal **13** with ethyl 3-bromopropionate and subsequent hydrolysis of the ester group. Cyclocondensation of **14** with (*R*)-phenylglycinol took place in satisfactory yield to give lactam **15**,[15] which was then desulfurized to ketone **6** by treatment with NBS in acetone–water.

The synthesis of the target azasugar **1** from bicyclic lactam **7** simply required the introduction of two additional hydroxy groups by stereoselective *syn* dihydroxylation, after generation of a conjugated carbon–carbon double bond. The synthetic sequence is illustrated in Scheme 5. Debenzylation of **7** followed by protection of the resulting diol with dimethoxypropane under acidic conditions gave acetal **16**, which was then converted to α,β-unsaturated lactam **17** via a sulfoxide. As expected, dihydroxylation of **17** with catalytic OsO_4 and NMO occurred on the most accessible *endo* face, in contrast with other related *exo* dihydroxylations,[10,17] to give diol **18** as a single stereoisomer.

Although borane reduction of **18**, as in the above model series, provided a 3:2 mixture of the expected piperidine



Scheme 4. Reagents and conditions: (i) 1,3-dithiane, BuLi, −78 °C, 1 h, then 0 °C, 2 h, 64%; (ii) LDA, THF, −78 °C, 1 h, then ethyl 3-bromopropionate, rt, 24 h, 61%; (iii) 20% aq KOH, MeOH, 0 °C, 1 h, 2 N HCl, 60%; (iv) (*R*)-phenylglycinol, toluene, reflux, 36 h, 57%; (v) NBS, acetone-H_2O, −30 °C, 15 min, 68%.



Scheme 5. Reagents and conditions: (i) BF_3Et_2O, SMe_2, rt, 12 h, 81%; (ii) $MeC(OMe)_2Me$, *p*-TsOH, CH_2Cl_2, rt, 3 h, 75%; (iii) KH, THF, $PhSO_2Me$, rt, then toluene, reflux, 15 h, 76%; (iv) 2.5% OsO_4 *t*-BuOH, NMO, MeCN, 72 h, 82%; (v) $LiAlH_4$, THF, rt, 15 h, 90%; (vi) H_2, $Pd(OH)_2$/C, MeOH, HCl, 72 h, 40%.

19 and its C-2 epimer, reduction with $LiAlH_4$ took place with retention of configuration at C-2, stereoselectively affording piperidine **19** in excellent yield. Finally, hydrogenolysis under acidic conditions with simultaneous hydrolysis of the acetonide ring, led to polyhydroxylated piperidine **1** as the hydrochloride.[20]

Both the ^1H and ^{13}C NMR data of **1** hydrochloride coincided with those previously reported[20d,e] for 1-deoxy-gulonojirimycin hydrochloride, whereas the specific rotation of our synthetic product, $[\alpha]_D^{22}$ +2.0 (*c* 0.2, MeOH), agreed with that reported[20d] for the hydrochloride of this azasugar, $[\alpha]_{589}$ +2.6 (*c* 1.6, MeOH).

Kinetic measurements with **1** were performed on β-galactosidase, α-amylase and α-glucosidase. In our conditions only α-glucosidase was significantly inhibited with an IC_{50} of 0.25 mM. The assay was performed with *Saccharomyces cerevisiae* α-glucosidase acting on *p*-nitrophenyl-α-D-glucopyranoside, a synthetic substrate analogous for α-glucosidases, which was routinely used at 1.5 mM concentration for the IC_{50} standard assays. Reactions were carried out at pH 6.8 and 37 °C. Under these conditions the K_M for *p*-nitrophenyl-α-D-glucopyranoside was 0.6 mM, and the K_i for **1**, assayed in a range of concentrations of inhibitor going from 0.025 to 0.25 mM in front of different amounts of substrate ranging from 0.4 to 1.5 mM, was 0.15 mM. Finally it has to be underscored that in our conditions the inhibition of this enzyme by deoxynojirimycin displayed a 5 fold higher IC_{50} of 1.25 mM and hence this natural product is a weaker inhibitor than **1**.

Taking into account that (*S*)-phenylglycinol is also commercially available, the methodology here reported provides access to azasugars in both enantiomeric series.

Acknowledgements

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18. Compound (**9**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 1.45–1.60 (m, 2H, H-4 and H-5), 1.67 (dm, J =12.8 Hz, 1H, H-5), 1.90 (dm, J =12.4 Hz, 1H, H-4), 2.66 (td, J =13.2 and 2.8 Hz, 1H, H-6ax), 2.93 (d, J = 6.4 Hz, 1H, OH), 3.65 (dd, J = 9.6 and 6.0 Hz, 1H, H-1′), 3.83 (m, 1H, H-3), 3.90 (masked, 1H, H-6eq), 3.90 (dd, J =9.6 and 8.0 Hz, 1H, H-1′), 4.53 (d, J =12.0 Hz, 1H, OCH_2), 4.56 (d, J =12.0 Hz, 1H, OCH_2), 4.63 (m, 1H, H-2), 7.33 (m, 5H, C_6 H_5); ^{13}C NMR ($CDCl_3$) δ 24.0 (C-5), 28.4 (CH_3), 28.9 (C-4), 39.0 (C-6), 53.0 (C-2), 66.7 (C-1′), 69.6 (C-3), 73.3 (OCH_2), 79.8 (C), 127.6 (2 CH), 127.7 (*p*-C), 128.4 (2 CH), 137.6 (*ipso*-C), 154.9 (CO). For spectroscopic data of related enantiopure *N*-Boc-3-hydroxy-2-(hydroxy-methyl)piperidines, see: (a) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3673; (b) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603.
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