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Selective Fowler Reductions: Asymmetric Total Syntheses of Isofagomine and Other 1-Azasugars from Methyl Nicotinate

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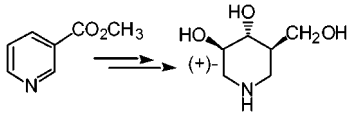
ABSTRACT



An efficient, high-yielding strategy has been developed for the asymmetric synthesis of 1-*N*-iminosugars (1-azasugars), a new class of glycosidase inhibitors with promising biomedical applications. A highly regioselective procedure for the 1,2-reduction of substituted pyridines was employed to transform methyl nicotinate into several representative 1-azasugars.

Interest continues to mount in new applications of natural and synthetic glycosidase inhibitors to basic research and medicine.[1] Linkage- and configuration-specific inhibitors may be useful in treating lysozomal storage diseases, diabetes, viral infection, and metastatic cancer. In the past few years, 1-*N*-iminosugars, or 1-azasugars, have emerged as a major new family of monosaccharide mimics worthy of further development. The prototype 1-azasugar **1**, named isofagomine (Figure 1), was first conceived by Bols et al. as an apparent transition state analogue mimicking equatorial glycoside cleavage.[2] Ichikawa et al. found that 1-*N*-iminosugars **2** and **3** inhibited glucuronidase and iduronidase,[3] two enzymes that promote the invasion of basement membrane components during tumor cell metastasis.[4,5] Since then, several other 1-*N*-iminosugars have been studied, including hydroxylated isofagomine derivative **4**.[6] Besides being potent, such 1-azasugars are anomer-selective inhibitors. For example, **1** exhibited 780-fold greater potency against β-glu than against the corresponding α-glu.[7]

Here we report short, enantioselective synthetic routes to iminosugars **1**, **2**, and **4** in high overall yields from methyl nicotinate **5**. Our synthetic strategy relied on a regioselective

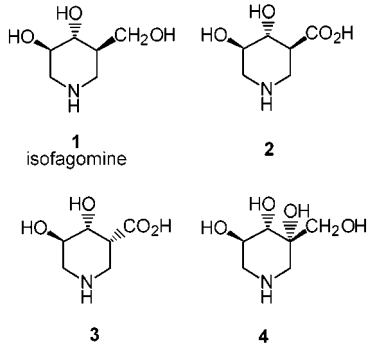


Figure 1. Representative examples of 1-azasugars

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(2) Jesperson, T. M.; Dong, W.; Skrydstrup, T.; Sierks, M. R.; Lundt, I.; Bols, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1778−1779.
(3) Ichikawa, Y.; Igarashi, Y. *Tetrahedron Lett.* **1995**, *36*, 4585−4586.
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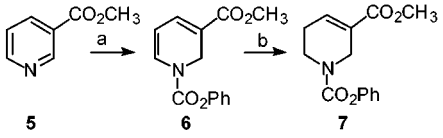
and high-yielding reduction of **5**, together with efficient and stereoselective functionalizations of the resulting 1,2-dihydropyridine system. This methodology should also facilitate the synthesis of other 1-*N*-iminosugars having substituents and stereochemistry designed for, and tailored to, specific biological targets.

Several methods have been described for the partial reduction of pyridines using hydride sources.[8] In a detailed study, Sundberg et al. noted that reductions of **5** using combinations of borohydride reagents with ethyl or benzyl chloroformate afforded mixtures of the 1,2-, 1,4-, and 1,6-reduction products.[9] No reductions of **5** using phenyl chloroformate were reported, although that reagent had been used earlier to achieve the clean reduction of pyridine to *N*-phenoxycarbonyl-1,2-dihydropyridine.[10] We observed that reduction of **5** with $NaBH_4$ and phenyl chloroformate afforded 2,3-dihydropyridine **6** in 90% yield (Scheme 1).

Scheme 1



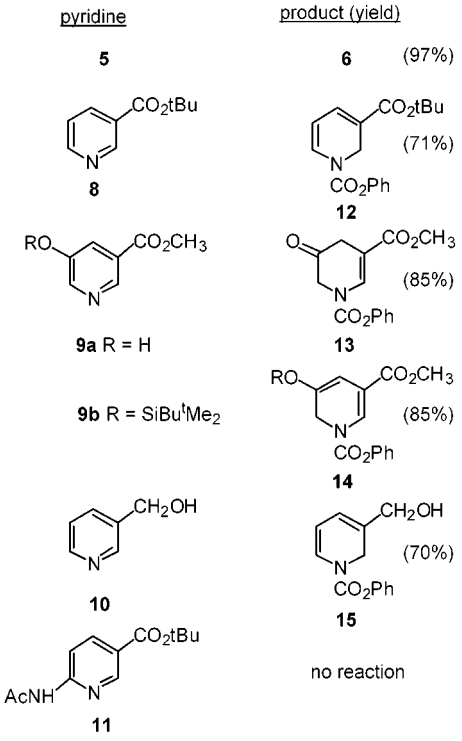
(a) $NaBH_4$, PhOCOCl, CH_3OH, -78 °C, 97%; (b) $NaBH_4$-TFA, C_6H_6, 5 °C, 99%.

Using $NaBH_4$−trifluoroacetic acid, **6** could further be reduced to the tetrahydropyridine **7** in virtually quantitative yield, thus providing a superior route to tetrahydropyridines of the arecoline family.[11]

The use of $NaBH_4$ and phenyl chloroformate proved generally applicable in the selective 1,2-reduction of a range of substituted pyridines, as indicated in Table 1. Reduction of the more sterically hindered *tert*-butylnicotinate **8** paralleled that of **5**. In the case of **9a** and **9b**, smooth reduction to the corresponding 1,6-dihydropyridines **13** and **14** was observed, with regiocontrol arising from the oxygen substituent. The selective 1,2-reduction of 3-hydroxymethylpyridine **10** afforded **15** in good yield, indicating that the reaction was not limited to nicotinic esters. Acetamidonicotinate **11** was inert to reduction.

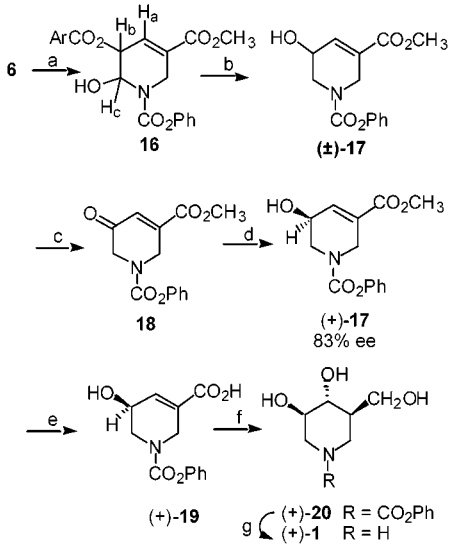
The utility of such 1,2-dihydropyridines in assembling 1-azasugars was illustrated in the following synthesis of isofagomine. Reaction of **6** with *m*-chloroperoxybenzoic acid (MCPBA) afforded hydroxyester **16** regioselectively and in 92% yield (Scheme 2). The regiochemistry of **16** was assigned on the basis of an ^1H NMR decoupling experiment.

Table 1. Selective Fowler Reductions of Substituted Pyridines



Irradiation of the resonance at δ 5.70 corresponding to H_b caused the vinylic hydrogen resonance for H_a at δ 7.25 to collapse to a singlet. Since the resonances for H_b and H_c were broad, the relative stereochemistry in **16** could not be assigned unambiguously. Reduction of **16** with trimethylsilyl

Scheme 2



(a) MCPBA, CH_2Cl_2, -70 to 0 °C, 92%; (b) TMSOTf, BH_3-THF, -70 to 0 °C, 77%; (c) CrO_3, acetone; (d) $LiAlH_4$, (-)-N-Me-ephedrine, 85%; (e) 1 *N* HCl, reflux, 99%; (f) BH_3-THF, H_2O_2, NaOAc, 70%; (g) LiOH, 95%.

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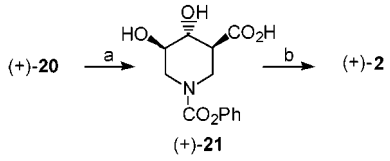
triflate (TMSOTf) and borane−THF complex gave rise to allylic alcohol (±)-**17**.

The asymmetric epoxidation or osmylation of **6** was explored under a variety of conditions. Although these transformations were highly regioselective for the disubstituted alkene in **6**, only modest (20−25%) enantioselectivities were achieved. As an alternative, oxidation of racemic **17** using Jones reagent gave the achiral enone **18**, which was immediately subjected to asymmetric $LiAlH_4$ reduction using (−)-*N*-methylephedrine as the chiral auxiliary[12] to afford optically active alcohol (+)-**17** in 85% yield and 83% ee, based on Mosher ester analysis. Hydrolysis of (+)-**17** afforded unsaturated hydroxyacid (+)-**19** in near-quantitative yield. The hydroboration of (+)-**19**, following a protocol for other β-substituted α,β-cyclohexenones,[13] was performed using BH_3−THF (5 molar equiv) followed by oxidative workup, affording *trans,trans*-triol (+)-**20** as the exclusive product in 65% yield. Hydrolysis of (+)-**20** afforded (+)-isofagomine **1** in 95% yield, thus confirming the assigned absolute configuration of (+)-**17**.[14] Overall, the synthesis of isofagomine required eight steps and gave (+)-**1** in 41% yield from methyl nicotinate.

Intermediate (+)-**20** also afforded ready access to glucuronidase inhibitor (+)-**2** (Scheme 3). Oxidation of (+)-**20**

Scheme 3



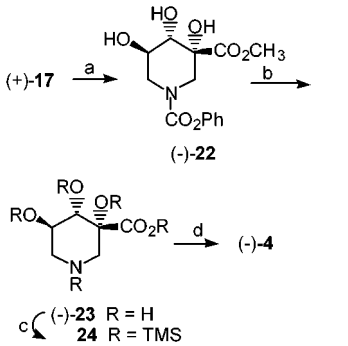
(a) $Pt\text{-}O_2$, 80%; (b) LiOH, 95%.

with platinum and oxygen furnished carboxylic acid (+)-**21** (80%), which was deprotected in base to give (+)-**2**[14] in a total of nine steps and 33% overall yield from methyl nicotinate.

Allylic alcohol (+)-**17** was also useful in synthesizing tetraol (−)-**4**, a hydroxylated analogue of isofagomine that is also a potent and highly selective β-glucosidase inhibitor.[6]

Osmylation of (+)-**17** afforded triol (−)-**22** with excellent *anti*-selectivity. Alkaline hydrolysis of the urethane and methyl ester groups in (−)-**22** afforded triol−amino acid (−)-**23**, an hydroxylated analogue of **2** and prospective glucuronidase inhibitor (Scheme 4). All attempts to reduce the carboxyl

Scheme 4



(a) OsO_4, NMO, 81%; (b) LiOH (2 equiv), 95%; (c) hexamethyldisilazane-pyridine, 110 °C; (d) $LiAlH_4$, THF, 83%.

group in (−)-**23** (or its methyl ester, not shown) proved fruitless. Therefore, to improve its poor solubility in organic solvents, (−)-**23** was transformed to the moisture-sensitive persilylated ester **24**, which was smoothly reduced to the desired aminotetraol (−)-**4** in good yield.[14]

In summary, an efficient and flexible route to 1-azasugars has been developed from a readily available and inexpensive starting material.[15] As part of that strategy, an improved procedure has been devised for the 1,2-reduction of substituted pyridines with high regioselectivity. Taken together, the methodology reported herein should provide access to other new 1-*N*-iminosugars for use as anomer-specific glycosidase inhibitors.

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Supporting Information Available: Detailed experimental procedures for **16**, (±)-**17** **18**, and (+)-**17**, along with ^1H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Spectroscopic, chiroptical, and physical characterization data for this compound matched literature values.

(15) **Representative procedure for the Fowler reduction:** To a suspension of methyl nicotinate **5** (10 g, 72.6 mmol) and sodium borohydride (2.89 g, 72.6 mmol) in methanol (200 mL) at −78 °C was added phenyl chloroformate (9.11 mL, 72.6 mmol) in a dropwise manner, over an interval of 40 min. The mixture was stirred for 3 h and then poured onto 800 mL of distilled water to give a yellow precipitate. The precipitate was filtered, washed with distilled water (150 mL), and dried under vacuum to give **6** (18 g, 97%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.35 (m, 2 H), 7.28−7.21 (m, 1 H), 7.18−7.13 (m, 3 H), 7.02 (d, 1 H, J = 3.0 Hz), 5.44−5.37 (m, 1 H), 4.77 (s, 1 H), 4.63 (s, 1 H), 3.77 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.1 and 165.7, 150.9 and 150.8, 132.7, 131,2. 129.8 and 129.7, 126.5−126.4, 121.7 and 121.6, 120.4, 118.5, 105.1 and 105.0, 52.1 and 51.9, 43.4 and 43.0; IR (CH_2Cl_2) 2950, 1740, 1720, 1230, 1190 cm^{-1}; EIMS m/z 259 (M^+, 87%), 77 (100%).