ORGANIC LETTERS

2001
Vol. 3, No. 2
201−203

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

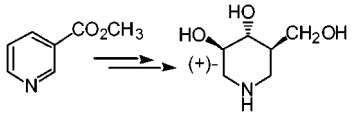
Guohua Zhao, Urmila C. Deo, and Bruce Ganem*

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

bg18@cornell.edu

Received October 31, 2000

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

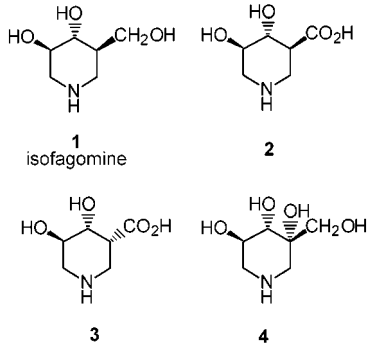


Figure 1. Representative examples of 1-azasugars

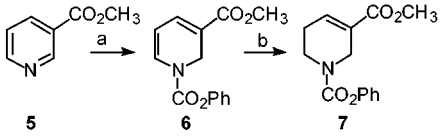
(1) Heightman, T. D.; Vasella, A. T. *Angew Chem., Int. Ed.* **1999**, *38*, 750−770.
(2) Jesperson, T. M.; Dong, W.; Skrydstrup, T.; Sierks, M. R.; Lundt, I.; Bols, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1778−1779.
(3) Ichikawa, Y.; Igarashi, Y. *Tetrahedron Lett.* **1995**, *36*, 4585−4586.
(4) Ruoslahti, E. *Sci. Am.* **1996**, *275*(3), 72−77.
(5) Roden, L. In *The Biochemistry of Glycoproteins and Proteoglycans*; Lennarz, W. G., Ed.; Plenum Press: New York, 1980; pp 267−271.
(6) Ichikawa, M.; Igarashi, Y.; Ichikawa, Y. *Tetrahedron Lett.* **1995**, *36*, 1767−1770.

10.1021/ol006810x CCC: $20.00
Published on Web 12/21/2000

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



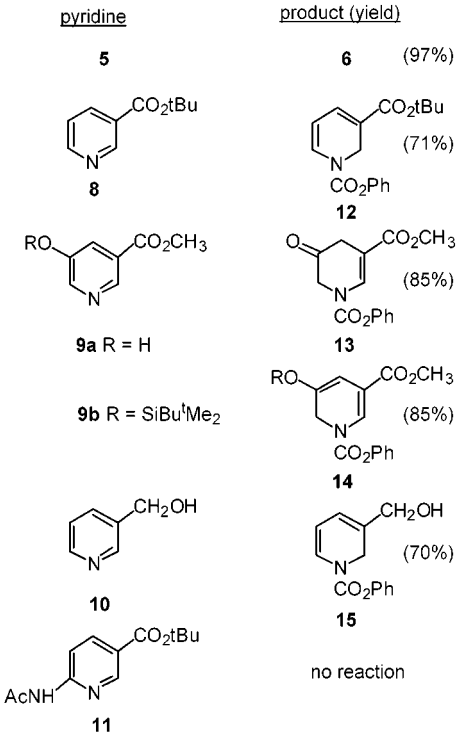
(a) $NaBH_4$, PhOCOCl, CH_3OH, -78 °C, 97%; (b) $NaBH_4$-TFA, C_6H_6, 5 °C, 99%.

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.

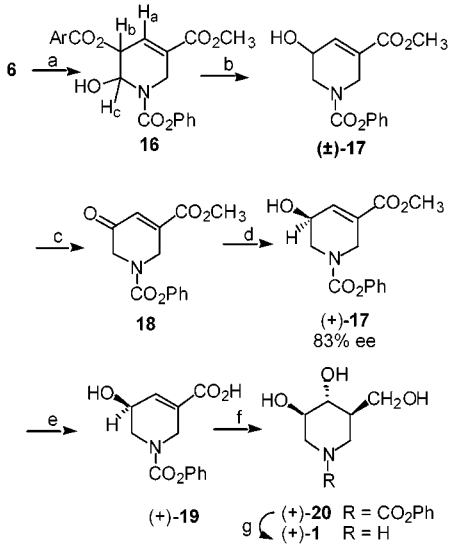
The utility of such 1,2-dihydropyridines in assembling 1-azasugars was illustrated in the following synthesis of isofagomine. Reaction of **6** with *m*-chloroperoxybenzoic acid (MCPBA) afforded hydroxyester **16** regioselectively and in 92% yield (Scheme 2). The regiochemistry of **16** was assigned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

(7) Recent reviews: (a) Bols, M. *Acc. Chem. Res.* **1997**, *31*, 1-8. (b) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007−3018.

(8) (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321−1323. (b) Keay, J. G. In *Comprehensive Organic Synthesis*; 1991; Vol. 8, pp 579−602.

(9) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51*, 3672−3679.

(10) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836−4842.

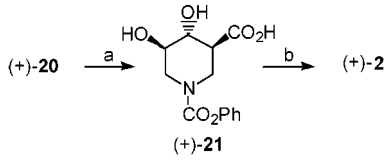
(11) Liberatore, F.; Carelli, V.; Cardellini, M. *Tetrahedron Lett.* **1968**, 4735−4738.

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



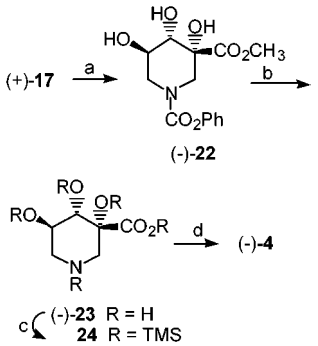
(a) Pt-O_2, 80%; (b) LiOH, 95%.

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.

Acknowledgment. We thank the National Institutes of Health (GM 35712, GM 08500) for generous financial assistance and for training grant support (to U.C.D.). Support of the Cornell NMR Facility by the NSF and NIH is gratefully acknowledged.

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.

OL006810X

(12) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* **1984**, 239−242.

(13) Klein, J.; Dunkelblum, E. *Tetrahedron* **1968**, *24*, 5701−5710.

(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%).