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Synthesis and L-fucosidase inhibitory activity of a new series of cyclic sugar imines—in situ formation and assay of their saturated counterparts

Jean-Bernard Behr *

Institut de Chimie Moléculaire de Reims (ICMR), UMR 6229, UFR Sciences—CNRS, BP 1039, 51687 Reims Cedex 2, France

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ABSTRACT

The synthesis of a series of aryl-substituted cyclic sugar imines was performed via a tandem nucleophilic addition/substitution reaction. The so-obtained ketimines displayed fucosidase inhibitory activities (IC_{50} = 46–556 μM). Their reduced counterparts were prepared and assayed after addition of sodium borohydride to the enzymatic assay stock solution. The pyrrolidines strongly inhibit fucosidase (IC_{50} = 0.65–150 μM).

Iminosugars have emerged as an important class of potential therapeutic agents because of their great power of inhibition towards glycoenzymes.[1] Typically, iminosugars are analogues of pyranoses or furanoses in which the endocyclic oxygen has been replaced by a nitrogen atom. The strong affinity of iminosugars for glycosidases or glycosyltransferases is generally attributed to their resemblance to the intermediate oxocarbenium ion assumed to occur during the enzymatic process.[2] Thus, potent inhibitors of fucosidase[3] or fucosyltransferases[4] from the literature are mainly pyrrolidines or piperidines which feature the hydroxyl configuration of the parent fucosyl intermediate **1**. Due to the potential of these compounds as anti-inflammatory,[5] anti-viral[6] or contraceptive agents,[7] the search for new structures is still the subject of extensive interest. Some attempts were made recently to design more fine-tuned inhibitors with a flattened heterocyclic ring, in the aim of imitating the distorted half-chair conformation of **1**.[8] Promising results were obtained with pyrroline **2** featuring a C=N unsaturation, which displayed potent inhibition of α-L-fucosidase (K_i = 9.8 μM, IC_{50} = 268 μM).[9] In addition, it was demonstrated that the incorporation of an aromatic substituent in place of the aglycon leaving group in the structure of a fucosidase inhibitor adds binding energy, which greatly improves the activity.[10] We therefore sought to design a new series of transition state analogues (compounds **3a–e**, Fig. 1) that would feature (i) the fucose-like configuration at C-3, C-4, C-5 (ii) a C=N bond to force the cycle to adopt the required conformation and (iii) a hydrophobic group at C-2. Fucosidase inhibitory activity of a small library of such compounds was evaluated and the reduction of the ketimines was also carried out on the enzymatic assay stock solutions to test the corresponding pyrrolidines.

Despite their structural resemblance with the putative oxocarbenium intermediate, little or no attention has been given to sugar ketimines. Very few polyhydroxypyrrolines have been reported in the literature and assayed against glycosidases, due to the lack of general synthetic methods available.[11] We have recently described a simple and straightforward synthesis of polyhydroxypyrrolines, which was based on the tandem addition/cyclization reaction of Grignard reagents to easily available

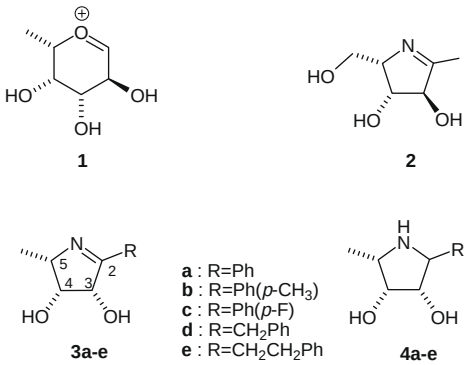

Figure 1. Structures of compounds **1**–**4**.

* Tel.: +33 326 91 32 38; fax: +33 326 91 31 66.
E-mail address: jb.behr@univ-reims.fr

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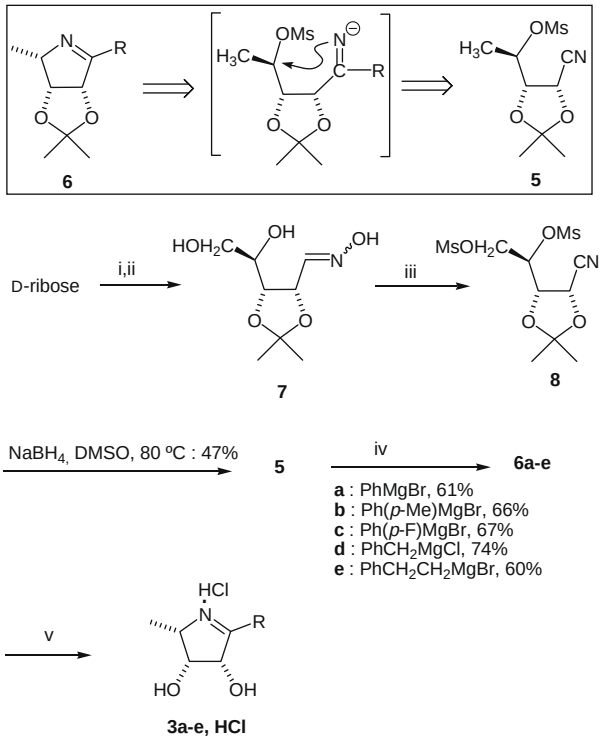
methanesulfonylglyconononitriles.[12] We applied this methodology to the synthesis of the fucose-configured pyrrolines **3a–e**. As depicted in Scheme 1, the targeted compounds **3** might result from the addition of a Grignard reagent to the nitrile **5**, after subsequent in situ displacement of the mesylester by the intermediate imide salt. The key substrate **5** was prepared in only four steps from D-ribose. Firstly, acetonation of ribose was performed according to the conditions described in the literature (acetone, cat. sulfuric acid)[13] and the resulting oil was treated with an aqueous ethanol solution of pre-formed hydroxylamine (NH_2OH–HCl + $NaHCO_3$). The partially water-soluble hydroxylamine **7** was extracted with ethyl acetate and was directly taken to the next step, without purification.

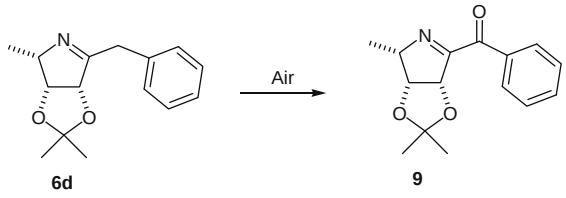
The treatment of **7** with a threefold excess of methanesulfonyl chloride simultaneously allowed dehydration of the oxime and activation of the free hydroxyl groups into the corresponding sulfonate esters **8** in 78% yield.

At this point, the selective reductive removal of the primary mesylate was required to furnish the targeted deoxyribononitrile **5**. The most efficient methods generally employ a metal hydride to generate a hydride anion as a displacement nucleophile.[14] In our case, the presence of the sensitive nitrile function limits the repertoire of such reagents to those having a low reducing ability. A set of experiments were conducted with $NaBH_4$, $LiBH_4$, $NaBH_3CN$ or $LiBHEt_3$ as the hydride donors, in DMSO, HMPT, DMF or THF as the possible solvents, according to established protocols.[15] In most attempts, no reaction occurred, even at 80 °C. Only sodium borohydride proved to be efficient for this transformation. Nitrile **5** was obtained in 40% yield after reaction of bis-mesylate **8** with $NaBH_4$ in anhydrous DMSO at 80 °C for 1.5 h. Moreover, the addition of an excess of *tert*-butyl alcohol minimized the formation of by-products, presumably by quenching the in situ generated borane.[16]

With compound **5** in our hands, we focused on the key tandem reaction. In view of SAR studies, we planned to prepare a small library of ketimines, 'armed' at C-2 with aromatic residues or homoanalogues covering various electronic and steric characteristics. Thus, nitrile **5** was reacted with PhMgBr (1.5 equiv from a 3 M ethereal solution) in toluene at 70 °C. After 1 h, the starting material had disappeared, yielding a less polar product. The reaction mixture was treated according to an optimized procedure: THF was added and the mixture was allowed to stir at 20 °C for 1 h.[9] The crude mixture was quenched at 0 °C with ammonium chloride and the ketimine **6a** was purified by silica gel chromatography (Et_2O/petroleum ether, 1:1, v/v, 61% yield).[17,18] Compounds **6b–e** were prepared by reaction of **5** with *p*-tolylMgBr (66% yield), 4-fluorophenylMgBr (67%), benzylMgCl (74%) and phenethylMgBr (60%), respectively, following the same procedure.[17,18] The particular structure of the benzyl derivative **6d** was responsible for its low degradation on air, affording the conjugated ketone **9** (Scheme 2).[18] Thus, **6d** was kept under argon to avoid this side reaction. The other ketimines proved to be stable on air at room temperature.



Scheme 1. Reagents and conditions: (i) H_2SO_4, acetone, 96%; (ii) NH_2OH–HCl, $NaHCO_3$, 100%; (iii) MsCl, pyr, 78%; (iv) RMgX, PhMe, 1 h, 70 °C then THF, rt, 1 h; (v) 1 M HCl, rt, 24 h (40–99%).



Scheme 2. Formation of conjugated ketone **9**.

Final deprotection of the isopropylidene group was achieved efficiently by treatment of **6a–e** with a 1 M HCl solution (Scheme 1). The so-obtained hydrochloride salts **3·HCl** were isolated as colourless oils after elution through a PTFE microfilter and lyophilization. Polyhydroxyketimines **3·HCl** were characterized by NMR and HRMS and their purity was estimated by analytical HPLC (RP-HPLC purity >95%; C18 Nucleodur® column, 20 °C, 254 nM, flow-rate 0.8 mL min^{-1}, eluent: MeOH/water 40:60) as exemplified in Figure 2.[18]

Finally, 10 mM stock solutions of each compound were prepared for the enzymatic assays by dissolving the ketimines **3·HCl** in de-ionized water. These dilutions were also used as working solutions for the preparation of the free ketimines **3a–e** and the corresponding pyrrolidines **4a–e** (Fig. 3). Thus, neutralization of a 500 µL sample of each solution (natural pH 4) with Amberlyst® A-26 (OH^-) (30 mg) gave a 10 mM solution of the corresponding free imine **3** (natural pH 7). In a same manner, we intended to prepare the pyrrolidines **4** by treatment of the stock solution of **3·HCl**

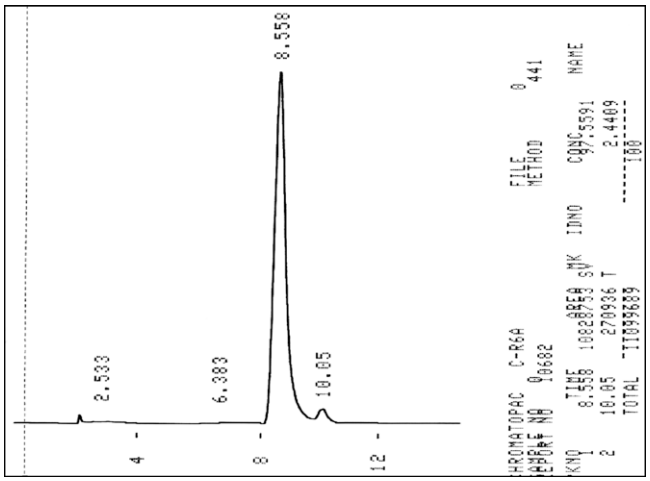


Figure 2. RP-HPLC trace of compound **3b**·HCl (2 mM aqueous solution, 254 nM, MeOH/water 40:60).

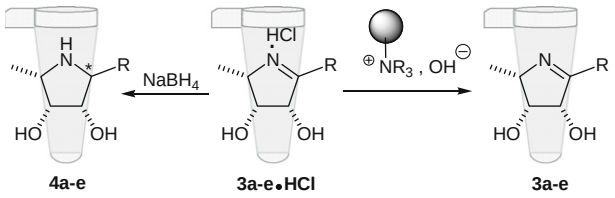


Figure 3. Neutralization and reduction of the stock solution of compounds **3**·**HCl**.

with polymer-supported borohydride. However, unsatisfactory results were obtained with this reductant as well as with $NaBH_3CN$. Alternately, the addition of 4 equiv of $NaBH_4$ to the stock solution of **3**·**HCl** allowed the reduction to take place in 30 min (HPLC monitoring) to afford a 10 mM solution of the corresponding pyrrolidine **4**. The formation of **4** was ascertained by mass spectrometry analysis.[18] The configuration of the newly generated stereocenter in the structure of **4** remained unknown at this stage.[19] Nevertheless, enzymatic assay of the reduction products thus obtained would give a first insight into their potential.

Imines **3**·**HCl** and **3** as well as pyrrolidines **4** were assayed against α-L-fucosidase (Table 1). Enzyme activity was determined at 35 °C (acetate buffer, pH 5.6) after incubation of 2 mM *p*-nitrophenyl fucoside for 15 min and quenching the reaction by addition of 1 M sodium bicarbonate. The *p*-nitrophenolate formed was quantified at 400 nm. Inhibitors were pre-incubated at 35 °C for 5 min with the fucosidase before addition of the substrate to start the standard assay. At least five concentrations of each compound were tested and IC_{50}'s were determined using Dixon plots, as exemplified in Figure 4.

The new cyclic sugar imines **3**·**HCl** displayed some inhibition towards α-L-fucosidase. The phenethyl derivative **3e**·**HCl** was the most potent of the series with IC_{50} = 46 μM. By comparing compounds **3a**·**HCl** (312 μM) and **3b,c**·**HCl** (157 and 181 μM, respectively) it appeared that the introduction of a lipophilic substituent in the aromatic ring resulted in an increase of the inhibition potency. The free imines **3a–e** showed an identical inhibition profile, though they were slightly less active. After reduction with $NaBH_4$, we also assayed the so-obtained pyrrolidines. Initial assays with an aqueous solution of sodium borohydride allowed us to exclude any effect of this reagent towards fucosidase at the highest concentration used (4 mM). Nevertheless, pyrrolidines **4** displayed potent inhibition of fucosidase with IC_{50} in the micromolar range. Best results were obtained with **4b** (IC_{50} = 0.65 μM).

Table 1
IC_{50} of pyrrolines **3**·**HCl**, **3** and pyrrolidines **4**

Entry	Compound	IC_{50} (μM)		
		3·**HCl**	**3**	**4**
1	**a** (R = Ph)	312	813	2.7
2	**b** (R = PhMe)	157	262	0.65
3	**c** (R = PhF)	181	381	1.2
4	**d** (R = CH_2Ph)	556	1360	150
5	**e** (R = CH_2CH_2Ph)	46	142	2.3

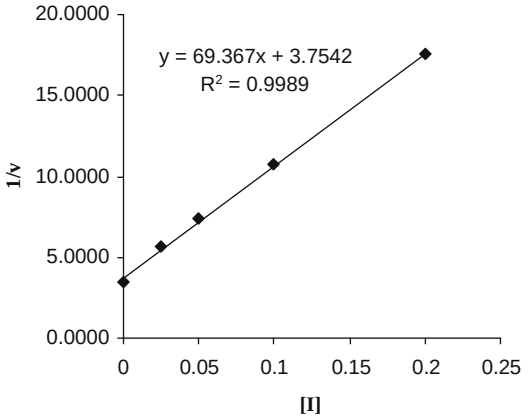


Figure 4. IC_{50} determination of compound **3e**·HCl.

In summary, a series of aryl-substituted cyclic sugar imines were successfully synthesized and their biological activity was evaluated. The most potent inhibitor displayed an IC_{50} of 46 μM. The corresponding pyrrolidines proved to be much more active with IC_{50}'s in the micromolar range. Based on these results, the pyrrolidine ring seems to reflect more favourably the half-chair conformation of the fucosyl cation than its unsaturated counterpart. Further structure–activity relationship and biological evaluation of these series of sugar analogues are currently underway, in particular the preparation of the six-membered derivatives.

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Supplementary data

^{1}H NMR spectra for compounds **6a–e** and **3a–e,HCl** and mass spectra of pyrrolidines **4a–e**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.075.

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17. *Compound* **6a**, yellow oil; R_f = 0.45 [petroleum ether/Et_2O (50:50)]; $[\alpha]_D^{20}$ −156 (*c* 0.22, $CHCl_3$); IR (film) 2995, 2926, 1612, 1446, 1381, 1371 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.04–7.99 (m, 2H, Ar-H), 7.49–7.42 (m, 3H, Ar-H), 5.50 (d, 1H, *J* = 5.5 Hz, H-3), 4.79 (t, 1H, *J* = 5.5 Hz, H-4), 4.14 (dq, 1H, *J* = 5.5 7.1 Hz, H-5), 1.48 (d, 3H, *J* = 7.1 Hz, 5-CH_3), 1.44 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.2 (C=N), 130.7 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 112.3 ($C(CH_3)_2$), 86.6 (C-3), 79.9 (C-4), 67.8 (C-5), 26.9 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 14.2 (5-CH_3); ESI-HRMS: calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$ 232.1338; found 232.1333. Compound **6b**, yellow oil; R_f = 0.47 [petroleum ether/Et_2O (50:50)]; $[\alpha]_D^{20}$ −182 (*c* 0.4, $CHCl_3$); IR (film) 2986, 2934, 1612, 1372 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.91 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.23 (d, 2H, *J* = 8.0 Hz, Ar-H), 5.49 (d, 1H, *J* = 5.5 Hz, H-3), 4.78 (t, 1H, *J* = 5.5 Hz, H-4), 4.12 (dq, 1H, *J* = 5.5 7.1 Hz, H-5), 2.40 (s, 3H), 1.53 (d, 3H, *J* = 7.1 Hz, 5-CH_3), 1.40 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.1 (C=N), 140.9 (Ar-C), 129.7 (Ar-C), 129.1 (Ar-C), 128.2 (Ar-C), 112.1 ($C(CH_3)_2$), 86.4 (C-3), 79.8 (C-4), 67.6 (C-5), 26.9 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 21.4 (Ar-CH_3), 14.2 (5-CH_3); ESI-HRMS: calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1494; found 246.1491. Compound **6c**, white foam; R_f = 0.32 [petroleum ether/Et_2O (50:50)]; $[\alpha]_D^{20}$ −140 (*c* 0.32, $CHCl_3$); IR (film) 2988, 2979, 2934, 1617, 1601, 1513, 1375 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.05–7.98 (m, 2H, Ar-H), 7.10 (t, 2H, *J* = 8.6 Hz, Ar-H), 5.51 (d, 1H, *J* = 5.7 Hz, H-3), 4.70 (t, 1H, *J* = 5.7 Hz, H-4), 4.12 (dq, 1H, *J* = 5.7 7.1 Hz, H-5), 1.53 (d, 3H, *J* = 7.1 Hz, 5-CH_3), 1.43 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.1 (C=N), 163.3 (d, C–F), 129.4 (d, Ar-C), 127.8 (d, Ar-C), 114.5 (Ar-C), 111.3 ($C(CH_3)_2$), 85.5 (C-3), 79.0 (C-4), 66.7 (C-5), 25.9 ($C(CH_3)_2$), 25.1 ($C(CH_3)_2$), 13.9 (5-CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) −109.76; ESI-HRMS: calcd for $C_{14}H_{17}NO_2F$ $[M+H]^+$ 250.1243; found 250.1241. Compound **6d**, yellow oil; R_f = 0.45 [CH_2Cl_2/Et_2O (70:30)]; IR (film) 2986, 2933, 1641, 1381, 1372, 1078 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H, Ar-H), 4.90 (d, 1H, *J* = 5.6 Hz, H-3), 4.56 (t, 1H, *J* = 5.6 Hz, H-4), 3.90 (m, 1H, H-5), 2.40 (br s, 2H, CH_2), 1.42 (d, 3H, 5-CH_3), 1.40 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.1 (C=N), 136.8 (Ar-C), 130.1 (Ar-C), 129.5 (Ar-C), 127.6 (Ar-C), 112.9 ($C(CH_3)_2$), 86.6 (C-3), 80.5 (C-4), 68.3 (C-5), 38.2 ($C(CH_3)_2$), 27.7 ($C(CH_3)_2$), 27.0 (Ar-CH_3), 15.5 (5-CH_3); ESI-HRMS: calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1494; found 246.1498. Compound **6e**, yellow oil; R_f = 0.50 [CH_2Cl_2/Et_2O (70:30)]; IR (film) 2986, 2933, 1642, 1380, 1371, 1078 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H, Ar-H), 4.90 (d, 1H, *J* = 5.6 Hz, H-3), 4.61 (t, 1H, *J* = 5.6 Hz, H-4), 3.91 (m, 1H, H-5), 3.00 (t, 2H, *J* = 7.8 Hz, CH_2), 2.73 (m, 2H, CH_2), 1.42 (d, 3H, *J* = 7.3 Hz, 5-CH_3), 1.38 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.3 (C=N), 141.7 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 126.5 (Ar-C), 112.5 ($C(CH_3)_2$), 87.9 (C-3), 80.2 (C-4), 67.9 (C-5), 32.5 (2 × CH_2), 27.3 ($C(CH_3)_2$), 26.6 ($C(CH_3)_2$), 15.2 (5-CH_3); ESI-HRMS: calcd for $C_{16}H_{22}NO_2$ $[M+H]^+$ 260.1651; found 260.1644. Compound **9**, yellow oil; R_f = 0.60 [petroleum ether/Et_2O (40:60)]; IR (film) 2987, 2935, 1664, 1597, 1373, 1233, 1073 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.22 (d, 2H, *J* = 5.6 Hz 7.25 (m, 5H, Ar-H), 4.90 (d, 1H, *J* = 5.6 Hz, H-3), 4.61 (t, 1H, *J* = 5.6 Hz, H-4), 3.91 (m, 1H, H-5), 3.00 (t, 2H, *J* = 7.8 Hz, CH_2), 2.73 (m, 2H, CH_2), 1.42 (d, 3H, *J* = 7.3 Hz, 5-CH_3), 1.38 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 190.7 (C=O), 170.5 (C=N), 135.8 (Ar-C), 134.3 (Ar-C), 130.8 (Ar-C), 128.9 (Ar-C), 112.7 ($C(CH_3)_2$), 86.8 (C-3), 79.2 (C-4), 70.5 (C-5), 27.4 ($C(CH_3)_2$), 25.9 ($C(CH_3)_2$), 15.0 (5-CH_3); ESI-HRMS: calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.1287; found 260.1278.
18. See Supplementary data.
19. The $NaBH_4$ reduction of such ketimines is usually not selective (see Ref. 9); thus, we assume that the two possible stereoisomers are formed during the reaction. Indeed, preliminary NMR analysis of a sample of **4b** revealed the presence of the two possible isomers (two doublets at 1.3 ppm, 2 × 5-Me).