Synthesis of Novel 3-Amino(Hydroxy)methyl-L-*fuco*-Azafagomines as Leads for Selective Inhibitors of α-L-Fucosidases

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Abstract: The synthesis of 3-substituted L-*fuco*-azafagomines from D-lyxose is reported. They represent the first example of aza-*C*-glycosides having a biimino (–NH–NH–) moiety. The key step of the synthesis is the introduction of the hydrazine moiety by reductive hydrazination of a 1-deoxy-ketohexose with *tert*-butyl carbazate. Their glycosidase inhibitory properties are also reported.

Key words: azasugars, glycosidases, fucosidase inhibitors, azafagomines, *C*-glycosides

α-L-Fucosidase is an exoglycosidase involved in the trimming of nonreducing terminal L-fucose units during the biosynthetic processing of fucose-containing glycoconjugates.[1] This enzyme, in common with other glycosidases, has glycosyl transfer activity and, therefore, can be also used in the synthesis of fucosyl glycans.[2] α-L-Fucosidase is associated with a great variety of physiological and pathological events. For example, aberrant distribution of fucose on fucose-containing glycoconjugates is found in inflammation processes, cancer, and cystic fibrosis.[3] Inhibitors of α-L-fucosidase can provide useful information about the functions of the enzyme and the basis for the development of potential therapeutic agents.[4]

Among the most powerful α-L-fucosidase inhibitors are L-*fuco* hydroxylated piperidines such as L-fuconojirimycin (FNJ, **1**),[5] although the intrinsic instability caused by the lability of the N,O-acetal function prevents its biological use. The 1-hydroxymethyl-FNJ[6] and 1-aminomethyl-FNJ,[7] which have a C–C bond at C-1, are stable *C*-glycosyl analogues[8] that have been used to generate potent inhibitors of α-L-fucosidases.[9]

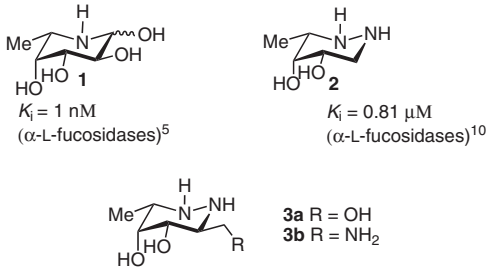
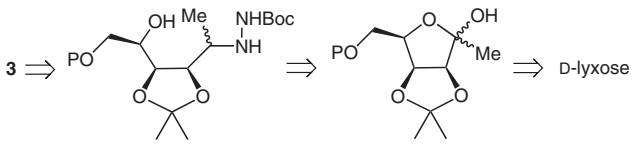


Figure 1

On the other hand, Bols and co-workers have described the preparation of (3*S*,4*R*,5*S*)-3-methylhexahydropyridazine-4,5-diol (**2**), the so-called '*fuco*-azafagomine' (Figure 1) that showed interesting inhibitory properties.[10] To the best of our knowledge, **2** is the only reported example of a L-*fuco* polyhydroxylated hexahydropyridazine.

We report herein for the first time the synthesis and the glycosidase inhibitory properties of the C-3 substituted *fuco*-azafagomines **3a** and **3b**. Both compounds can be used as new leads in the search for selective and potent inhibitors of α-L-fucosidases. The hydroxylated L-*fuco*-hexahydropyridazine moiety can be used as core structure to mimic the fucosyl cation generated in the enzymatic hydrolysis. Besides, the hydroxymethyl or aminomethyl groups at C-3 can be further functionalized giving a library of derivatives by a diversity-oriented synthesis. These compounds could contribute to a better understanding of the inhibition mechanisms of fucosidases in terms of structural and conformational changes, charge dislocation, and protonation as it has been made with azafagomine analogues in glucosidases.[11]

The retrosynthetic analysis for the preparation of compounds **3a** and **3b** is indicated in Scheme 1. The key steps imply cyclization of 2-methyl glycosylhydrazines, which were obtained by reductive hydrazination of a 1-deoxyketohexose easily prepared from D-lyxose, which contains the correct configuration at C-4 and C-5 of our target compounds.



Scheme 1

Thus, starting from D-lyxose, tri-O-protected D-lyxonolactone **5** could be easily obtained following a similar procedure to that described in the literature[12] (Scheme 2). Addition of MeLi[13] afforded the protected 1-deoxy-ketohexose **6** as a 3:1 mixture of anomers. Reductive hydrazination of **6** using *tert*-butyl carbazate, $NaBH_3CN$, and acetic acid in MeOH at 65 °C afforded the mixture of hydrazines **7** in 82% yield. Reaction of **7** with benzyl chloroformate, followed by mesylation and selective Boc deprotection gave crude monohydrazides that were treat-

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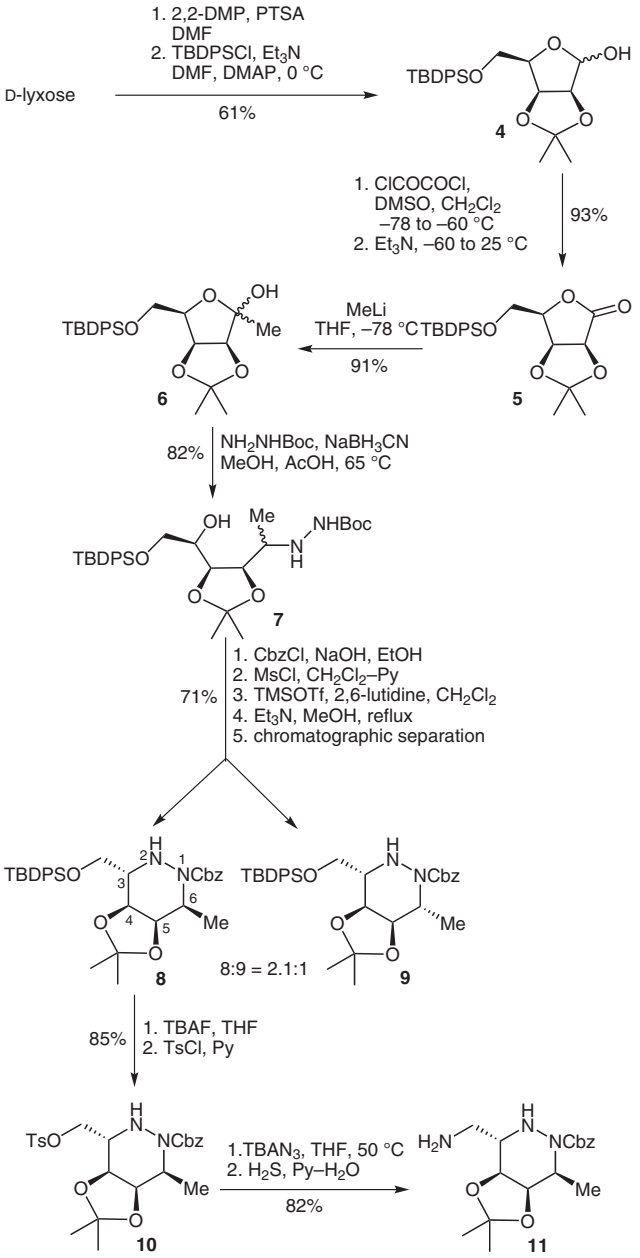
ed with Et_3N in MeOH at reflux to afford cyclic derivatives **8** and **9** as a 2.1:1 mixture of diastereomers. This sequence could be efficiently carried out without intermediate purification, affording the corresponding hexahydropyridazines in 71% overall yield after chromatographic separation.



Scheme 2

Compounds **8** and **9** were fully characterized by their spectroscopic data[14] but the configuration of C-6 was difficult to assign. Fortunately, deprotection of **8** followed by tosylation afforded crystalline tosyl derivative **10**, the structure of which was unambiguously confirmed by X-ray crystallography (Figure 2).[15] The ^{1}H NMR spectrum of **9** showed a large coupling constant (J = 9.3 Hz) between H-3 and H-4 and no coupling constant between H-5 and H-6. These results together with a coupling constant of 5.0 Hz between H-4 and H-5 indicated that **9** had a chair conformation with the C-3 substituent in equatorial and the Me-6 in axial positions. However, although the X-ray structure of **10** indicated a chair conformation, its ^{1}H NMR spectrum[16] showed coupling constant values of 4.5, 5.5 and 5.5 Hz for $J_{3,4}$, $J_{4,5}$, and $J_{5,6}$, respectively. These values were also observed for compound **8**, which indicates that a conformational equilibrium for both derivatives takes place in solution.

Reaction of **10** with $TBAN_3$ followed by reduction of the azido group with H_2S afforded protected aminomethyl derivative **11**.

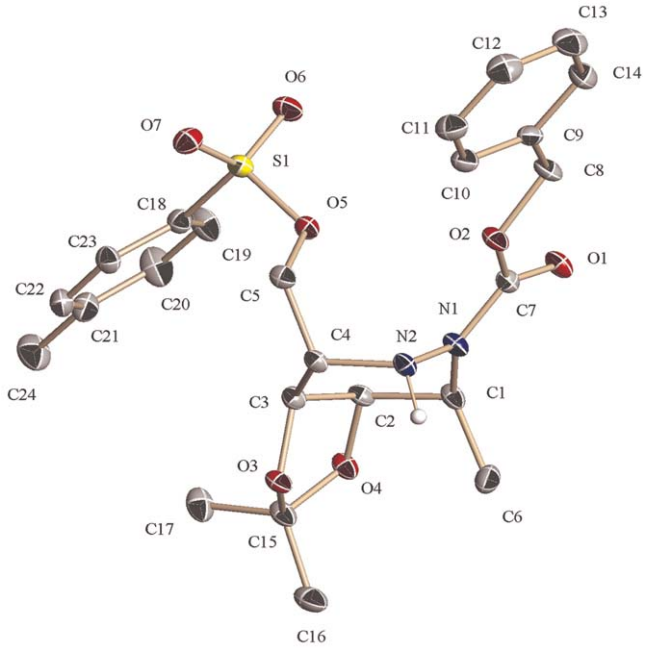
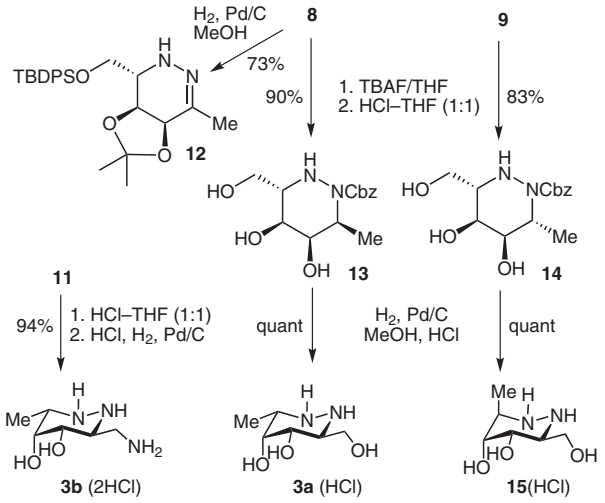


Figure 2 X-ray crystallographic structure for compound **10**

Hydrogenation of compound **8** afforded hydrazone **12** in good yield. The formation of this product can be explained by oxidation of the hydrazine to the corresponding azo compound, followed by isomerization of the double bond to the more stable hydrazone.[17] Then, deprotection of compounds **8** and **9** was attempted by treatment with TBAF, followed by acidic removal of the acetonide affording N-protected alcohols **13** and **14** in good to excellent yields. Final hydrogenation of these compounds under acidic conditions afforded desired hydroxylated hexahydropyridazines **3a** and **15**,[18] in quantitative yields as the corresponding hydrochloride salts. Acidic treatment of **11** and subsequent catalytic hydrogenation furnished compound **3b** as hydrochloride salt in excellent overall yield (Scheme 3). Hydrogenation under acidic conditions is critical to avoid undesired oxidation.

Derivatives **3a**, **3b**, and **15** have been analyzed for their inhibitory activities towards twelve commercially available glycosidases (Table 1).[19] Compound **3a** was a selective and competitive inhibitor of α-L-fucosidase from bovine kidney (97% at 1 mM concentration, K_i = 4.2 μM) which



Scheme 3

Table 1 Inhibitory Activities of 3-substituted L-*fuco*-azafagomines[a–c]

Compound	α-L-Fucosidase (%)
3a	97 (K_i = 4.2 μM)
3b	44
15	17

[a] For measurement conditions, see ref. 19.
[b] The mode of inhibition for given K_i is competitive.
[c] Percentage of inhibition at 1 mM, K_i in μM, when measured. Optimal pH, 37 °C.

is a comparable value to that reported for *fuco*-azafagomine **2**,[10] showing that the C-3 substituent is not detrimental for the inhibition. It is worth noting that compound **3a** did not inhibit any of the other enzymes assayed: α-galactosidases from coffee beans, β-galactosidases from *Escherichia coli* and *Aspergillus orizae*, α-glucosidases from yeast and from rice, amyloglucosidase from *Aspergillus niger*, β-glucosidases from almonds, α-mannosidases from Jack beans, β-mannosidases from snail, β-xylosidases from *Aspergillus niger*, and β-*N*-acetylglucosaminidases from Jack beans. Compounds **3b** and **15** are much weaker inhibitors of α-L-fucosidases from bovine kidney (44% for **3b** and 17% for **15**, at 1 mM concentration) and did not inhibit the other enzymes. Compound **15**, epimer of **3a** at C-6, showed a weak inhibition towards α-L-fucosidases indicating the importance of the *S* configuration at Me-6 to bind the enzyme.

In summary, the synthesis of new C-3-substituted *fuco*-configurated hydroxylated hexahydropyridazines from D-lyxose is reported. They can be considered as the first examples of aza-*C*-glycosides having a biimino (–NH–NH–) moiety and constitute interesting lead compounds for the search of new α-L-fucosidase inhibitors. In spite of that compound **3b** is a weak inhibitor of α-L-fucosidases, its triamino functionality makes it a promising candidate for the discovery of fucosidase inhibitors by combinatorial procedures through the approach of dynamic libraries of imines[20] or through the in situ evaluation of libraries of amides.[7]

The use of lead compounds **3a** and **3b** in the synthesis of new derivatives, the conformational analysis and the corresponding biological studies are currently in progress in our laboratory and will be reported in due course.

Acknowledgment

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References and Notes

(1) (a) Ma, B.; Simala-Grant, J. L.; Taylor, D. E. *Glycobiology* **2006**, *16*, 158R. (b) Vocadlo, D.; Davies, G. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 539. (c) Davies, G. J.; Ducros, V. M.-A.; Varrot, A.; Zechel, D. L. *Biochem. Soc. Trans.* **2003**, *31*, 523. (d) Benesova, E.; Markova, M.; Lipovova, P.; Kralova, B. *Chem. Listy* **2005**, *99*, 324.

(2) (a) Berteau, O.; Bielicki, J.; Kilonda, A.; Delphine Machy, D.; Anson, D. S.; Kenne, L. *Biochemistry* **2004**, *43*, 7881. (b) Osanjo, G.; Dion, M.; Drone, J.; Solleux, C.; Tran, V.; Rabiller, C.; Tellier, C. *Biochemistry* **2007**, *46*, 1022.

(3) (a) Becker, D. J.; Lowe, J. B. *Glycobiology* **2003**, *13*, 41R. (b) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (c) Springer, T. A.; Lasky, L. A. *Nature (London)* **1991**, *349*, 196. (d) Ayude, D.; Fernández-Rodríguez, J.; Rodríguez-Berrocal, F. J.; Martínez-Zorzano, V. S.; De Carlos, A.; Gil, E.; De la Cadena, M. P. *Oncology* **2000**, *59*, 310. (e) Michalski, J. C.; Klein, A. *Biochim. Biophys. Acta* **1999**, *1455*, 69. (f) Glick, M. C.; Kothari, V. A.; Liu, A.; Stoykova, L. I.; Scanlin, T. F. *Biochimie* **2001**, *83*, 743.

(4) (a) Kajimoto, T.; Node, M. *Curr. Top. Med. Chem.* **2009**, *9*, 13. (b) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Med. Chem.* **2009**, *16*, 473. (c) Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *Mini-Rev. Med. Chem.* **2006**, *6*, 1043. (d) Robina, I.; Moreno-Vargas, A. J.; Carmona, A. T.; Vogel, P. *Curr. Drug Metabol.* **2004**, *5*, 329.

(5) Dubernet, M.; Defoin, A.; Tarnus, C. *Bioorg. Med. Chem. Lett.* **2006**, *61*, 1172.

(6) (a) Fleet, G. W. J.; Namgoong, S. K.; Barker, C.; Baines, S.; Jacob, G. S.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 4439. (b) Andrews, D. M.; Bird, M. I.; Cunningham, M. M.; Ward, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2533. (c) Beacham, A. R.; Smelt, K. H.; Biggadike, K.; Britten, C. J.; Hackett, L.; Winchester, B. G.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron Lett.* **1998**, *39*, 151.

(7) Wu, C.-Y. i.; Chang, C.-F.; Chen, J. S.-Y.; Wong, C.-H.; Lin, C.-H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4661.

(8) (a) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645. (b) *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P.; Martin, O. R., Eds.; Wiley-VCH: Weinheim, **2007**. (c) Robina, I.; Vogel, P. *Synthesis* **2005**, 675.

(9) (a) Ho, C.-W.; Lin, Y.-N.; Chang, C.-F.; Li, S.-T.; Wu, Y.-T.; Wu, C.-Y.; Chang, C.-F.; Liu, S.-W.; Li, Y.-K.; Lin, C.-H. *Biochemistry* **2006**, *45*, 5695. (b) Chang, C.-F.; Ho, C.-W.; Wu, C.-Y.; Chao, T.-A.; Wong, C.-H.; Lin, C.-H. *Chem. Biol.* **2004**, *11*, 1301.

(10) Jensen, H. H.; Jensen, A.; Hazzel, R. G.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1190.

(11) (a) Hansen, S. U.; Bols, M. *J. Chem. Soc., Perkin Trans. 2* **2000**, 665. (b) Bülow, A.; Plesner, I. W.; Bols, M. *J. Am. Chem. Soc.* **2000**, *122*, 8567. (c) Lohse, A.; Hardlei, T.; Jensen, A.; Plesner, I. W.; Bols, M. *Biochem. J.* **2000**, *349*, 211. (d) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, *8*, 1218. (e) Sivertsen, A. C.; Gasior, M.; Bjerring, M.; Hansen, S. U.; López López, O.; Nielsen, N. C.; Bols, M. *Eur. J. Org. Chem.* **2007**, 1735. (f) G loster, T. M.; Meloncelli, P.; Stick, R. V.; Zechel, D.; Vasella, A.; Davies, G. J. *J. Am. Chem. Soc.* **2007**, *129*, 2345.

(12) Jiang, S.; Rycroft, A. D.; Singh, G.; Wang, X.-Z.; Wu, Y.-L. *Tetrahedron Lett.* **1998**, *39*, 3809; compound **5** was reported but not characterized

Characterization Data for 5

$[\alpha]_D^{22}$ –34.9 (*c* 0.74, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.65 (m, 4 H, H_{arom}), 7.47–7.37 (m, 6 H, H_{arom}), 4.82–4.78 (m, 2 H, H-2, H-3), 4.58 (td, 1 H, $J_{4,5a} = J_{4,5b} = 6.4$ Hz, $J_{4,3} = 2.6$ Hz, H-4), 4.08–3.93 (m, 2 H, H-5a, H-5b), 1.36 [s, 6 H, $C(CH_3)_2$], 1.07 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 173.9 (C=O), 135.8, 133.2, 133.0, 130.0, 128.0, 127.9 (C arom.), 114.2 [$C(CH_3)_2$], 79.5 (C-4), 76.2, 75.9 (C-2, C-3), 61.7 (C-5), 26.9 [$C(CH_3)_3$], 26.1 [$C(CH_3)_2$], 19.4 [$C(CH_3)_3$] ppm. MS (CI): *m/z* (%) = 427 (5) $[M + H]^+$. HRMS (CI): *m/z* calcd for $C_{24}H_{31}O_5Si$ $[M + H]^+$: 427.1941; found 427.1927.

(13) Jones, N. A.; Jenkinson, S. F.; Soengas, R.; Fanefjord, M.; Wormald, M. R.; Dwek, R. A.; Kiran, G. P.; Devendar, R.; Takata, G.; Morimoto, K.; Izumoric, K.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 774.

(14) **Analytical Data for 8**

$[\alpha]_D^{25}$ –18.2 (*c* 1.19, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.61–7.58 (m, 4 H, H_{arom}), 7.48–7.38 (m, 6 H, H_{arom}), 7.28–7.26 (m, 5 H, H_{arom}), 5.18 (br d, 1 H, $J_{NH,3} = 3.2$ Hz, NH), 5.05 (d, 1 H, $^2J_{H,H} = 12.7$ Hz, CH_2 of Cbz), 5.02 (d, 1 H, CH_2 of Cbz), 4.08 (dd, 1 H, $J_{5,4} = 5.5$ Hz, $J_{5,6} = 4.8$ Hz, H-5), 3.97 (qd, 1 H, $J_{6,Me\text{-}6} = 7.2$ Hz, H-6), 3.96 (t, 1 H, $J_{4,3} = 5.5$ Hz, H-4), 3.65 (d, 2 H, $J_{1',3} = 6.7$ Hz, H-1′), 3.05 (m, 1 H, H-3), 1.34 (d, 3 H, Me-6), 1.33, 1.24 [2 s, 3 H each, $C(CH_3)_2$], 0.99 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 156.0 (C=O of Cbz), 136.7, 135.0, 132.7, 129.9, 128.2, 127.9, 127.8, 127.6, 127.3 (C_{arom}), 108.0 [$C(CH_3)_2$], 72.6 (C-5), 70.8 (C-4), 66.2 (CH_2 of Cbz), 63.7 (C-1′), 58.7 (C-3), 50.9 (C-6), 26.8, 25.7 [$C(CH_3)_2$], 26.5 [$C(CH_3)_3$], 18.7 [$C(CH_3)_3$], 15.9 (Me-6) ppm. MS–FAB: *m/z* (%) = 597 (40) $[M + Na]^+$, 575 (8) $[M + H]^+$. HRMS–FAB: *m/z* calcd for $C_{33}H_{42}N_2O_5NaSi$ $[M + Na]^+$: 597.2761; found: 597.2780.

Analytical Data for 9

$[\alpha]_D^{26}$ –64.5 (*c* 0.82, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.63–7.61 (m, 4 H, H_{arom}), 7.49–7.30 (m, 11 H, H_{arom}), 5.18 (br s, 2 H, CH_2 of Cbz), 5.09 (br s, 1 H, NH), 4.56 (q, 1 H, $J_{6,Me\text{-}6} = 7.2$ Hz, H-6), 3.99 (d, 1 H, $J_{5,4} = 5.0$ Hz, H-5), 3.80 (dd, 1 H, $J_{4,3} = 9.4$ Hz, H-4), 3.77 (dd, 1 H, $^2J_{1'a,1'b} = 10.7$ Hz, $J_{1'a,3} = 3.0$ Hz, H-1′a), 3.59 (dd, 1 H, $J_{1'b,3} = 9.0$ Hz, H-1′b), 2.89 (m, 1 H, H-3), 1.28 (d, 3 H, Me-6), 1.20 [s, 6 H, $C(CH_3)_2$], 0.98 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 155.2 (C=O of Cbz), 136.9, 135.0, 132.6, 129.9, 128.2, 127.9, 127.8, 127.7, 127.1 (C_{arom}), 108.0 [$C(CH_3)_2$], 75.0 (C-5), 70.0 (C-4), 66.3 (CH_2 of Cbz), 63.3 (C-1′), 59.9 (C-3), 49.1 (C-6), 27.8, 26.3 [$C(CH_3)_2$], 26.5 [$C(CH_3)_3$], 18.7 [$C(CH_3)_3$], 16.1 (Me-6) ppm. MS–FAB: *m/z* (%) = 597 (50) $[M + Na]^+$, 575 (10) $[M + H]^+$. HRMS–FAB: *m/z* calcd for $C_{33}H_{42}N_2O_5NaSi$ $[M + Na]^+$: 597.2761; found: 597.2802.

(15) **Crystal Data for 10**

$C_{24}H_{30}N_2O_7S$, $M_r = 490.56$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 5.9856$ (3) Å, $b = 16.5688$ (8) Å, $c = 24.4976$ (11) Å, $V = 2429.5$ (2) Å^3, $Z = 4$, $\rho_{calcd} = 1.341$ g cm^{-3}, λ (Mo Kα1) = 0.71073 Å, $F(000) = 1040$, $\mu = 0.180$ mm^{-1}, $T = 173$ (2) K, 34818 reflections measured, 4999 unique ($R_{int} = 0.0847$) which were used in all calculations. The final $R1 = 0.0430$ [$I > 2\sigma(I)$], $wR2 = 0.1047$ (all data). Flack parameter = –0.02 (8). Full crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 764937. These data can obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or e-mail: deposit@ccdc.cam.ac.uk.

(16) **Analytical Data for 10**

Mp 130–132 °C (EtOAc–PE). $[\alpha]_D^{23}$ –6.4 (*c* 0.45, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.76 (d, 2 H, $^3J_{H,H} = 8.0$ Hz, H-Ts), 7.46 (d, 2 H, H-Ts), 7.37–7.30 (m, 5 H, H_{arom}), 5.17 (br s, 1 H, NH), 5.04 (d, 1 H, $^2J_{H,H} = 12.7$ Hz, CH_2 of Cbz), 5.01 (d, 1 H, CH_2 of Cbz), 4.16 (t, 1 H, $J_{5,4} = J_{5,6} = 5.5$ Hz, H-5), 4.04–3.97 (m, 3 H, H-6, H-1′a, H-1′b), 3.83 (dd, 1 H, $J_{4,3} = 4.5$ Hz, H-4), 3.10 (m, 1 H, H-3), 2.41 (s, 3 H, CH_3 of Ts), 1.28 (d, 3 H, $J_{6,Me\text{-}6} = 7.0$ Hz, Me-6), 1.31, 1.23 [2 s, 3 H each, $C(CH_3)_2$] ppm. ^{13}C NMR (125.7 MHz, DMSO-d_6, 353 K): δ = 156.1 (C=O of Cbz), 145.1, 136.7, 132.0, 130.2, 128.3, 127.8, 127.6, 127.5 (C_{arom}), 108.1 [$C(CH_3)_2$], 72.2 (C-5), 70.0, 69.9 (C-4, C-1′), 66.3 (CH_2 of Cbz), 56.1 (C-3), 50.1 (C-6), 26.6, 25.6 [$C(CH_3)_2$], 21.1 (Me of Ts), 15.7 (Me-6) ppm. MS–FAB: *m/z* (%) = 513 (100) $[M + Na]^+$, 491 (10) $[M + H]^+$. HRMS–FAB: *m/z* calcd for $C_{24}H_{30}N_2O_7SNa$ $[M + Na]^+$: 513.1671; found: 513.1678. Anal. Calcd for $C_{24}H_{30}N_2O_7S$: C, 58.76; H, 6.16; N, 5.71; S, 6.54. Found: C, 58.75; H, 6.11; N, 5.82; S, 6.50.

(17) This process of oxidation–isomerization has been previously studied for hydrazines and some examples are reported, see: Stone, K. J.; Greenberg, M. M.; Blackstock, S. C.; Berson, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 3659; see also ref. 11a.

(18) **Analytical Data for 3a**

$[\alpha]_D^{22}$ –44.6 (*c* 0.6, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.85–3.82 (m, 2 H, H-5, H-1′a), 3.74 (dd, 1 H, $^2J_{1'b,1'a} = 11.6$ Hz, $J_{1'b,3} = 5.5$ Hz, H-1′b), 3.63 (dd, 1 H, $J_{4,3} = 10.3$ Hz, $J_{4,5} = 2.8$ Hz, H-4), 3.35 (qd, 1 H, $J_{6,Me\text{-}6} = 6.8$ Hz, $J_{6,5} = 1.2$ Hz, H-6), 3.24 (ddd, 1 H, $J_{3,1'a} = 2.9$ Hz, H-3), 1.28 (d, 3 H, Me-6) ppm. ^{13}C NMR (125.7 MHz, CD_3OD): δ = 69.6 (C-5), 68.1 (C-4), 60.1 (C-1′), 58.0 (C-6), 57.5 (C-3), 14.0 (Me-6) ppm. MS (CI): *m/z* (%) = 163 (40) $[M + H]^+$. HRMS (CI): *m/z* calcd for $C_6H_{15}N_2O_3$ $[M + H]^+$: 163.1083; found: 163.1083.

Analytical Data for 15

$[\alpha]_D^{22}$ –12.3 (*c* 0.85, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.85 (dd, 1 H, $^2J_{1'a,1'b} = 11.5$ Hz, $J_{1'a,3} = 3.7$ Hz, H-1′a), 3.81 (dd, 1 H, $J_{4,3} = 7.4$ Hz, $J_{4,5} = 2.9$ Hz, H-4), 3.77 (dd, 1 H, $J_{1'b,3} = 6.9$ Hz, H-1′b), 3.71 (m, 1 H, H-5), 3.51 (qd, 1 H, $J_{6,Me\text{-}6} = 6.9$ Hz, $J_{6,5} = 5.4$ Hz, H-6), 3.36 (td, 1 H, H-3), 1.34 (d, 3 H, Me-6) ppm. ^{13}C NMR (125.7 MHz, CD_3OD): δ = 70.1 (C-5), 65.4 (C-4), 60.5 (C-3), 60.2 (C-1′), 56.6 (C-6), 13.2 (Me-6) ppm. MS (CI): *m/z* (%) = 163 (65) $[M + H]^+$. HRMS (CI): *m/z* calcd for $C_6H_{15}N_2O_3$ $[M + H]^+$: 163.1083; found: 163.1087.

(19) For the conditions used in the biological tests, see: (a) Saul, R.; Chambers, J. P.; Molyneux, R. J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1983**, *221*, 593. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806.

(20) Gerber-Lemaire, S.; Popowycz, F.; Rodriguez-Garcia, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *ChemBioChem* **2002**, *3*, 466.