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Abstract: While studying the opening of an epoxide on a sugar-derived aziridine, we observed an unexpected formation of bicyclic compounds. The structure of these bicycles depends on the nature of the protecting group on the amine of the aziridine. This compounds appeared to be weak glycosidase inhibitors.

Glycosidases, enzymes that catalyse the hydrolysis of oligosaccharides, are involved in many therapeutic phenomena.[1] Searching for new and efficient inhibitors of such enzymes is thus the object of extensive research. Iminosugars, sugar analogs in which the endocyclic oxygen is replaced by a nitrogen atom, have been thoroughly studied and demonstrated high inhibition potential.[2] Several applications of iminosugars for the treatment of lysosomal storage disorder,[3] HIV infection,[4] viral infection,[5] Alzheimer disease[6] or cancer[7] have already been approved. Today, three drugs have been marketed, Zavesca[@], Glyset[@] and Galafold[@] for the treatment of Gaucher , type II-diabetes and Fabry diseases respectively.[8] Our group has focused on the synthesis and evaluation of original five- (**A**),[9] six-(**B**),[10] seven-(**C**)[11] and unnatural ether-bridged iminosugars (**D**, **E**).[12] Some of them have proven to be interesting molecules notably as inhibitors of *N*-acetyl-glycosaminidases.[9-11] Numerous original molecules were disclosed exploiting one key building block, the tribenzylated azacycloheptene **F**, due to its ability to be further functionalized either through dihydroxylation or epoxidation at the double bond. Thus, we have synthesized numerous potent glycosidases inhibitors using a nucleophilic opening of epoxyazepanes. We have previously synthesized β, γ-*trans*-typed pentahydroxylated azepanes via epoxide opening with water under harsh acidic or basic conditions.[11] However, disappointing results both in terms of yields and stereoselectivity hampered the use of this transformation to access iminosugars. Hence, the improvement of this reaction is of interest. As the carbamate-based protecting group at the *N*-endocyclic position is not compatible with the use of hydroxide or harsh basic conditions, we reasoned that activation of the epoxide by a Lewis acid should lower the

activation energy of the reaction and favor the formation of products under milder conditions. A similar approach has been reported by Behr et al.[13]

Bismuth triflate ($Bi(OTf)_3$) has been used as Lewis acid catalyst in many organic transformations and is very attractive due to its strong Lewis acidity together with low toxicity, low cost and good stability.[14] Taking into account that $Bi(OTf)_3$ has been used as catalyst for epoxide opening,[15] we envisaged using $Bi(OTf)_3$ in the presence of water to prepare 1,2-*trans* diols.

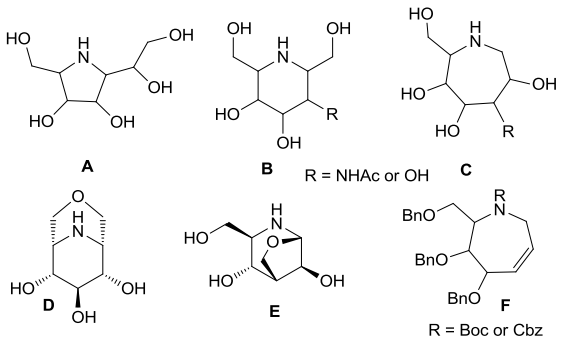
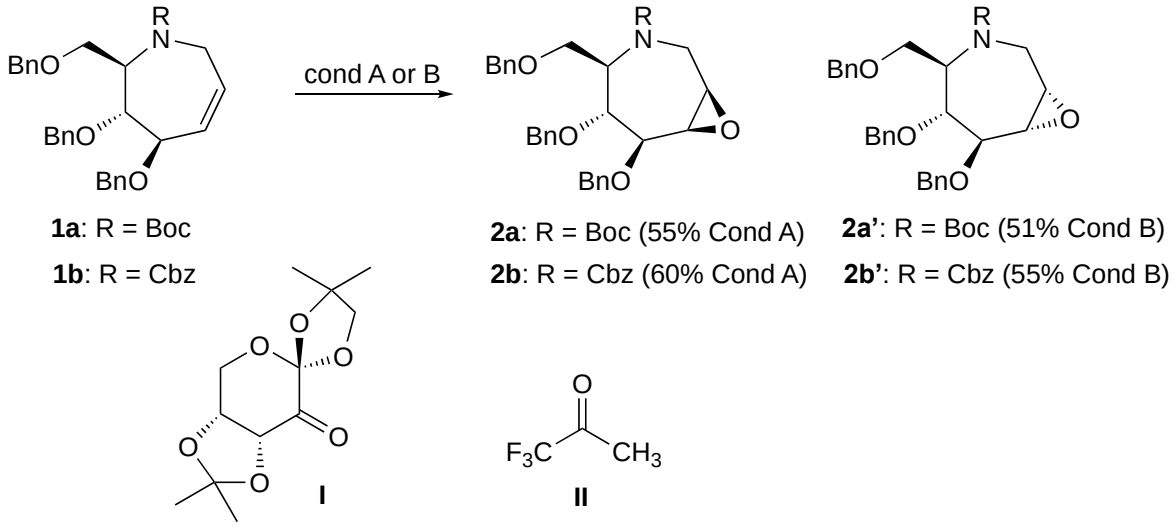


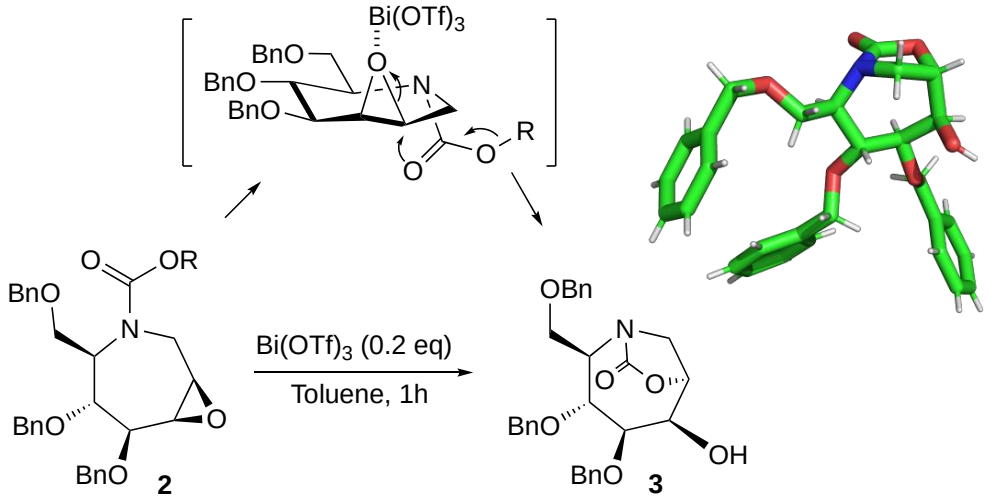
Figure 1. Iminosugars reported by our groups

Epoxidation of azacycloheptenes **1a**[10] and **1b**[11] were first studied. We recently reported[10] that modified Shi's procedure[16] with slow addition of ketone **I** gave epoxide **2a**[10] in a stereoselective manner (55%). This optimized procedure was also applied successfully on **1b** furnishing **2b**[11] in 60% yield. Interestingly, CF_3COCH_3/Oxone[17] could also stereoselectively mediate the epoxidation but in favor of epoxides **2a'** (51%) and **2b'** (55%).



Scheme 1. Epoxidation of Azacycloheptenes **1a** and **1b**. Conditions A: Oxone, ketone **I**, Bu_4NOH, $NaHCO_3$, $CH_3CN/10^{-4}$ M Na_2EDTA, 0°C. Conditions B : Oxone, ketone **II**, $NaHCO_3$, $CH_3CN/4x10^{-4}$ M Na_2EDTA, 0°C.

With these epoxides in hand, we treated them with $Bi(OTf)_3$ (10 mol %) in a mixture of Toluene/water (9/1). Epoxide **2a** was totally consumed after 1 h of stirring at 100 °C. Interestingly, the expected β,γ-dihydroxy azepanes were not observed, but a bicyclic carbamate **3** was produced in 50% yield along with non-isolable side products. The structure of **3** was confirmed by X-ray crystallography (CCDC 1015485) and its formation can be rationalized by the nucleophilic addition of the carbamate on the closest carbon of the epoxide. Indeed, similar intramolecular epoxide opening has been reported by Hayes using $Ti(O\mathit{i}Pr)_4$ in stoichiometric quantity.[18] Rather than problematic, this unexpected product is of interest as it demonstrated the possibility for regioselective epoxide opening leading to β,γ-*trans*-dihydroxyazepane. Better yields (60%) were obtained when the reaction was performed in dried toluene (table 1, entry 1). The same product was isolated when the reaction was performed with epoxide **2b** but in lower yields (30%, entry 2). Lowering the temperature provided a satisfying 78% yield (entry 3). Only traces of product were observed when the reaction was carried out at room temperature despite long reaction times.



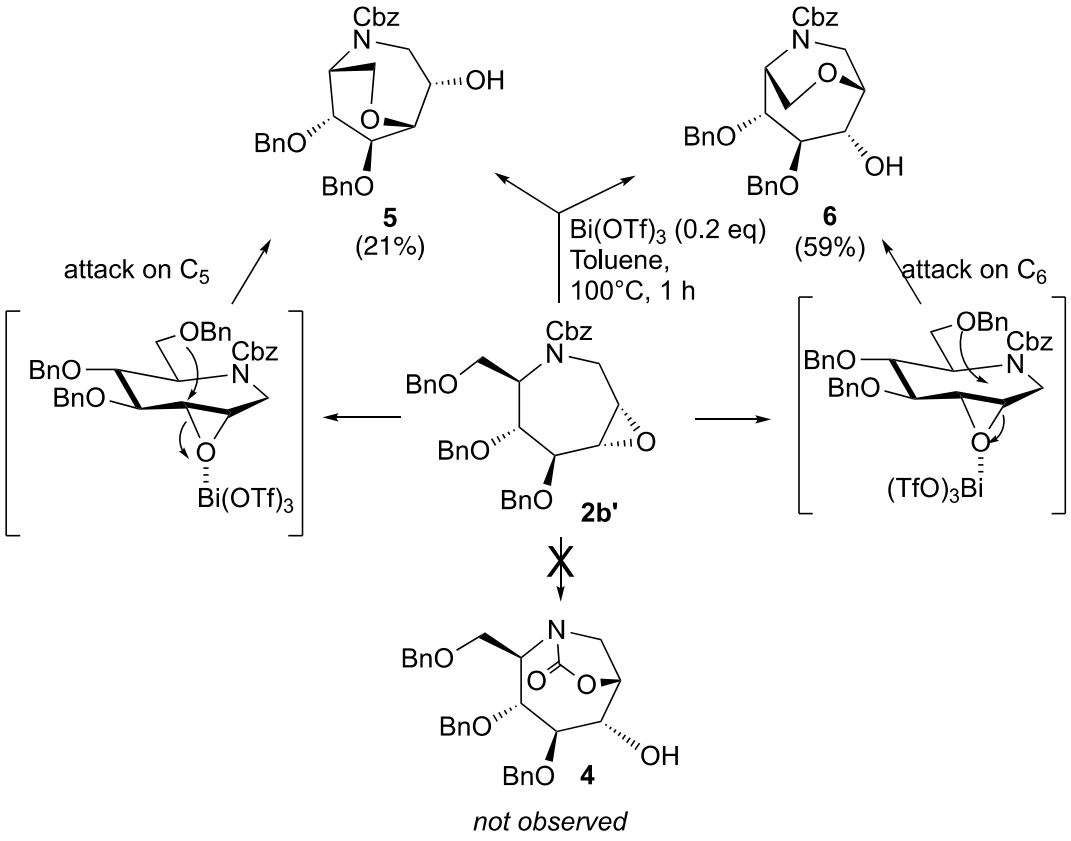
Entry	Compound	R	Temperature (°C)	Yield of **3** (%)[a]
1	**2a**	t-Bu	100	60
2	**2b**	Bn	100	30
3	**2a**	t-Bu	60	78
4	**2a**	t-Bu	RT	Traces[b]

[a)]isolated yield, [b)] reaction was carried out for 24h

Table 1. Synthesis of bicyclic carbamate **3**

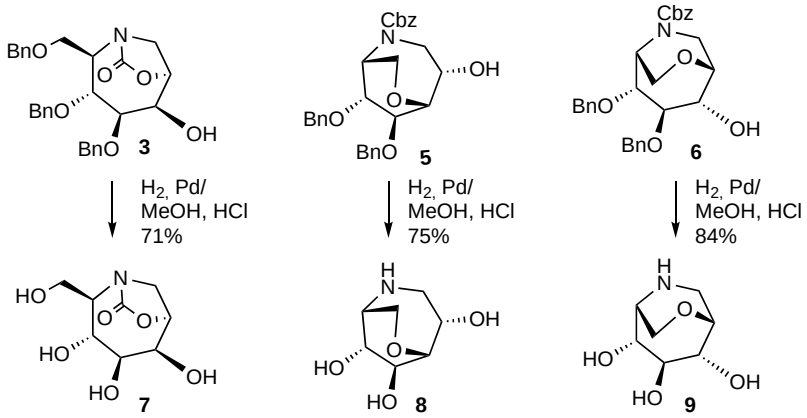
Subsequently, the $Bi(OTf)_3$-mediated intramolecular epoxide opening was also studied with epoxides **2a'** and **2b'**. Using the optimized conditions, the expected cyclic carbamate **4** was not observed. While **2a'** gave an inseparable mixture of compounds, reaction of **2b'** afforded two ether-bridged compounds **5** (21%) and **6** (59%) (Scheme 2). The formation of these

compounds probably results from the S_N2 nucleophilic addition of C_8 benzylether on both carbons of the epoxide. We can suppose that nucleophilic attack occurres preferentially on the sterically less hindered position (C_6) leading the formation of the major product. The intramolecular epoxide opening was also reported by Nemoto et al.[19]



Scheme 2. $Bi(OTf)_3$-mediated epoxide opening on compound **2b'**

Hydrogenolysis of compounds **3**, **5**, **6** gave unprotected bicyclic compounds **7**, **8**, **9**. (Scheme 3) These three structurally original bicylic compounds were evaluated as inhibitors of a panel of glycosidases. Interestingly, derivatives **8** and **9** show weak but surprising specific inhibition activity toward β-glucuronidase from *E.*coli with IC_{50} are 372 and 368 μM respectively (table 2).



Scheme 3. Hydrogenolysis of **3**, **5**, and **6**.

	IC_{50} (μM)		
Enzyme	**7**	**8**	**9**
α-Glucosidase			
Yeast	[a]NI [b](3.6 %)	NI (31.7 %)	NI (34.7 %)
Rice	NI (5.2 %)	NI (10.3 %)	NI (28.7 %)
Rat intestinal maltase	NI (0 %)	NI (0 %)	NI (29.0 %)
β-Glucosidase			
Almond	NI (0 %)	NI (10.4 %)	NI (5.1 %)
Bovine liver	NI (43.4 %)	NI (29.4 %)	NI (33.9 %)
α-Galactosidase			
Coffee beans	NI (2.3 %)	NI (28.1 %)	NI (21.3 %)
β-Galactosidase			
Bovine liver	NI (12.1 %)	NI (11.3 %)	NI (27.0 %)
α-Mannosidase			
Jack bean	NI (0 %)	NI (4.7 %)	NI (0 %)
β-Mannosidase			
Snail	NI (0 %)	NI (2.5 %)	NI (0 %)
α-L-Fucosidase			
Bovine kidney	NI (9.4 %)	NI (28.4 %)	NI (23.2 %)
α-L-Rhamnosidase			
Penicillium decumbens	NI (0 %)	NI (0 %)	NI (12.4 %)
β-Glucuronidase			
E.coli	NI (11.1 %)	372	368
α,α-Trehalase			
Porcine kidney	NI (5.1 %)	NI (0 %)	NI (3.6 %)
Amyloglucosidase			
Aspergillus niger	NI (6.5 %)	NI (0 %)	NI (0.1 %)
	[a] NI : No inhibition (less than 50 % inhibition at 1000 μM).		
	[b] ( ) : inhibition % at 1000 μM		

Table 2. Inhibitory activity of **7**, **8**, and **9**.

In summary, $Bi(OTf)_3$ can be used to access a variety of bicyclic compounds from epoxy-azepanes, which happen to be relatively weak glycosidase inhibitors when deprotected. Other Lewis acids may now be tried to assess the generality of this reactivity.

Acknowledgements
We thank Chinese Scholarship Council (CSC) for a PhD grant (SZ) and Lise-Marie Chamoreau for X-ray diffraction.

Experimental

Material and methods

All commercial reagents were used as supplied. TLC plates (Macherey-Nagel, ALUGRAM® SIL G/UV_{254}, 0.2 mm silica gel 60 Å) were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 3 g of phosphomolybdic acid in 100 mL of ethanol followed by heating with a heat gun. Flash column chromatography was performed using Macherey-Nagel silica gel 60 (15-40 μm). NMR experiments were recorded with a Bruker AM- 400 spectrometer at 400 MHz for ^{1}H nuclei and at 100 MHz for ^{13}C nuclei. The chemical shifts are expressed in part per million (ppm) using residual $CHCl_3$ signal as internal reference (δ (^{1}H) =7.26 ppm and δ(^{13}C) =77.16 ppm) and the coupling constant *J* in hertz (Hz). NMR multiplicities are reported using the following abbreviations: b = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. HRMS were recorded on a Bruker microTOF spectrometer, using Tuning-Mix as reference. Optical rotations were measured on a Perkin–Elmer 341 digital polarimeter or a Jasco P-2000 polarimeter with a path length of 1 dm.

Compound 3 To a solution of **2a** (136 mg, 0.25 mmol) and $Bi(OTf)_3$ (33 mg, 0.05 mmol) in dry toluene (12 mL) was stirred at 60°C for 1 hour. After cooling to room temperature, the solvent was evaporated and the residue was purified by chromatography (cyclohexane/AcOEt: 100/0 to 80/20) to give **3** (95 mg, 78%) as white solid. Recrystallization with CH_2Cl_2/Cyclohexane allowed obtaining the crystal which was analyzed by X-ray analysis. Mp = 139°C. $[\alpha]^{24}_D$ = +10.8 (c = 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.19 (m, 13H, H_{ar}), 7.11-7.09 (m, 2H, H_{ar}), 4.79 (d, 1H, ^{2}J = 10.5 Hz, C$\underline{H}_2$Ph), 4.75 (d, 1H, ^{2}J = 10.5 Hz, C$\underline{H}_2$Ph), 4.56-4.53 (m, 2H, C$\underline{H}_2$Ph, H_6), 4.41 (d, 1H, ^{2}J = 10.5 Hz, C$\underline{H}_2$Ph), 4.32-4.29 (m, 2H, 2xC$\underline{H}_2$Ph), 4.17 (t, 1H, $J_{H3\text{-}H4}$ = $J_{H3\text{-}H2}$ = 9.5 Hz, H_3), 4.06-4.04 (m, 1H, H_5), 3.68-3.58 (m, 5H, H_{8a}, H_{8b}, H_2, H_4, H_{7a}), 3.34 (ddd, 1H, $J_{H7b\text{-}H5}$ = 1.0 Hz, $J_{H7b\text{-}H6}$ = 5.0 Hz, $J_{H7b\text{-}H7a}$ = 13.0 Hz, H_{7b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (C$\underline{O}$), 138.0, 137.9, 137.5 (C_{ipso}), 128.5, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6 (C$\underline{H}_{ar}$), 81.8 (C_4), 77.6 (C_6), 75.5 (C$\underline{H}_2$Ph), 74.9 (C_3), 75.0, 73.2 (C$\underline{H}_2$Ph), 69.6 (C_8), 69.4 (C_5), 61.2 (C_2), 44.9 (C_7). HRMS calcd for $C_{29}H_{31}NO_6$: $[MH]^+$: 490.2230 found 490.2222.

Compound 5 and 6. A mixture of **2b'** (90 mg, 0.155 mmol) and $Bi(OTf)_3$ (20 mg, 0.031 mmol) in dry toluene (8.0 mL) was stirred at 100°C for 1 hour. After cooling to room temperature, the solvent was evaporated and the residue was purified by chromatography (cyclohexane/AcOEt: 8/2 - 7/3 to 80) to give **5** (16 mg, 21%) as clear oil and **6** (44 mg, 59%). Compound **5** $[\alpha]^{16}_D$ = -28.5 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers in 1:0.8 ratio) δ 7.38-7.23 (m, 27H, H_{ar}), 5.17 (s, 2H, C$\underline{H}_2$Ph), 5.15 (s, 1.6H, C$\underline{H}_2$Ph), 4.83-4.81 (m, 1H, H_2), 4.68-4.61 (m, 3H, C$\underline{H}_2$Ph), 4.57-4.45 (m, 5H, C$\underline{H}_2$Ph, $H_{2'}$), 4.37 (dd, 0.8H, $J_{H7a'\text{-}H6'}$ = 6.5 Hz, $J_{H7a'\text{-}H7b'}$ = 14.0 Hz, $H_{7a'}$) 4.20 (dd, 1H, $J_{H7a\text{-}H6}$ = 6.0 Hz, $J_{H7a\text{-}H7b}$ = 14.0 Hz, H_{7a}),

4.14 (brs, 1.8H, H_5, $H_{5'}$), 4.05-3.95 (m, 4.6H, H_{8a}, H_4, $H_{4'}$, H_6, $H_{6'}$), 3.92-3.79 (m, 4.4H, $H_{8a'}$, H_{8b}, $H_{8b'}$, H_3, $H_{3'}$), 3.29 (dd, 1H, $J_{H7b\text{-}H6}$ = 9.5 Hz, $J_{H7b\text{-}H7a}$ = 14.0 Hz, H_{7b}), 3.22 (dd, 0.8H, $J_{H7b'\text{-}H6'}$ = 10.0 Hz, $J_{H7b'\text{-}H7a'}$ = 14.0 Hz, $H_{7b'}$). 2.12 (s, 1.8H, O<u>H</u>, O<u>H</u>'); ^{13}C NMR (100 MHz, $CDCl_3$, 2 rotamers in 1:0.8 ratio) δ 155.8, 155.7 (<u>C</u>O, Cbz), 137.7, 137.7, 137.4, 137.3, 136.3, 136.3 (C_{ipso}), 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, (<u>C</u>H_{ar}), 78.6 ($C_{4'}$), 78.5 (C_4), 77.6 ($C_{3'}$), 77.2 (C_3), 77.2 (C_5), 77.1 ($C_{5'}$), 70.9, 70.7, 70.6 (C_6, $C_{6'}$, 4x<u>C</u>H_2Ph), 67.7, 67.6 (CH_2Ph), 66.1 (C_8), 65.6 ($C_{8'}$), 50.4 ($C_{2'}$), 50.0 (C_2), 45.3 (C_7), 44.9 ($C_{7'}$). HRMS calcd for $C_{29}H_{31}NNaO_6$: $[MNa]^+$: 512.2049 found 512.2052. Compound **6** $[\alpha]^{19}_D$ = -29.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers in 1:0.7 ratio) δ 7.44-7.20 (m, 25.5H, H_{ar}), 5.25 (d, 1H, ^2J = 12.5 Hz, C<u>H</u>$_2$Ph), 5.21-5.17 (m, 1.7H, C<u>H</u>$_2$Ph), 5.12 (d, 0.7H, ^2J = 12.5 Hz, C<u>H</u>$_2$Ph), 5.07-5.01 (m, 1.7H, C<u>H</u>$_2$Ph), 4.87 (d, 1H, ^2J = 11.0 Hz, C<u>H</u>$_2$Ph), 4.70-4.61 (m, 3.4H, C<u>H</u>$_2$Ph, H_2), 4.56 (d, 1H, ^2J = 11.5 Hz, C<u>H</u>$_2$Ph), 4.49 (d, 0.7H, ^2J = 11.5 Hz, C<u>H</u>$_2$Ph), 4.41 (d, 1H, J = 2.5 Hz, $H_{2'}$), 4.17-4.09 (m, 1.7H, H_{8a}, $H_{8a'}$), 3.97-3.96 (m, 0.7H, $H_{6'}$), 3.90-3.88 (m, 1H, H_6), 3.84-3.56 (m, 10.2H, H_{8b}, $H8_{b'}$, H_3, $H_{3'}$, H_4, $H_{4'}$, H_5, $H_{5'}$, H_{7a}, $H_{7a'}$, H_{7b}, $H_{7b'}$); ^{13}C NMR (100 MHz, $CDCl_3$, 2 rotamers in 1:0.7 ratio) δ 158.8, 158.2 (<u>C</u>O, Cbz), 138.8, 138.7, 137.7, 137.6, 136.5, 136.4 (C_{ipso}), 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.1, 128.0, 127.9, 128.0, 127.9, 127.9, 127.8, (<u>C</u>H_{ar}), 85.3 ($C_{4'}$), 85.2 (C_4), 83.6 (C_5), 83.5 ($C_{5'}$), 75.7 ($C_{3'}$), 75.6 (C_3), 75.4, 75.3, 71.6, 71.5 (4x<u>C</u>H_2Ph), 71.3 ($C_{6'}$), 70.8 (C_6), 67.6 ($C_{8'}$), 67.5 (C_8), 51.3 ($C_{2'}$), 51.0 (C_2), 42.9 (C_7), 42.7 ($C_{7'}$); HRMS calcd for $C_{29}H_{31}NNaO_6$: $[MNa]^+$: 512.2049 found 512.2042.

Compound 7. To a solution of **3** (11 mg, 0.022 mmol) in MeOH (2 mL) was added aqueous HCl (1M, 0.1 mL) under argon. After adding Pd/C (10%, 10 mg), the argon was removed. The H_2 was introduced and the mixture was bubbled for 5 minutes. After stirring the solution for 24 under H_2 atmosphere, the mixture was filtered on micro-filter 0.3 µm). The solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2/MeOH: 8.5/1.5) to give the desired product (3.5 mg, 71%). $[\alpha]^{22}_D$ = +2.8 (c = 0.55, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 4.61 (t, 1H, $J_{H6\text{-}H7a}$ = $J_{H6\text{-}H5}$ = 4.5 Hz, H_6), 4.05 (ddd, 1H, $J_{H5\text{-}H7b}$ = 1.0 Hz, $J_{H5\text{-}H4}$ = 2.5 Hz, $J_{H5\text{-}H6}$ = 4.5 Hz, H_5), 3.93 (t, 1H, $J_{H3\text{-}H2}$ = $J_{H3\text{-}H4}$ = 9.5 Hz, H_3), 3.86 (dd, 1H, $J_{H8a\text{-}H2}$ = 3.0 Hz, $J_{H8a\text{-}H8b}$ = 11.5 Hz, H_{8a}), 3.74 (dd, 1H, $J_{H8b\text{-}H2}$ = 6.5 Hz, $J_{H8b\text{-}H8a}$ = 11.5 Hz, H_{8b}), 3.56 (d, 1H, $J_{H7a\text{-}H7b}$ = 12.5 Hz, H_{7a}), 3.53 (dd, $J_{H4\text{-}H5}$ = 2.5 Hz, $J_{H4\text{-}H3}$ = 9.5 Hz, H_4), 3.41-3.34 (m, 2H, H_2, H_{7b}). ^{13}C NMR (100 MHz, MeOD) δ 168.0 (<u>C</u>O), 80.2 (C_6), 72.8 (C_4), 71.4 (C_5), 68.5 (C_3), 66.3 (C_2), 62.8 (C_8), 44.8 (C_7) HRMS calcd for $C_8H_{14}NO_6$: $[MH]^+$: 220.0821 found 220.0820.

Compound 8. To a solution of **5** (13 mg, 0.027 mmol) in MeOH (3 mL) was added aqueous HCl (1M, 0.2 mL) was added under argon. After adding Pd/C (10%, 13 mg), the argon was removed. The H_2 was introduced and the mixture was bubbled for 5 minutes. After stirring the solution for 24h under H_2 atmosphere, the mixture was filtered on micro-filter 0.3 µm). The solvent was evaporated to give the desired product (4.2 mg, 75%). $[\alpha]^{22}_D$ = +7.0 (C = 0.3, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.32 (ddd, $J_{H6\text{-}H5}$ = 3.0 Hz, $J_{H6\text{-}H7a}$ = 5.5 Hz, $J_{H6\text{-}H7b}$ = 9.0 Hz, H_6), 4.22-4.12 (m, 4H, H_{8a}, H_{8b}, H_3, H_4), 4.10 (d, 1H, $J_{H5\text{-}H6}$ = 3.0 Hz, H_5), 4.00 (t, $J_{H2\text{-}H8a}$ = $J_{H2\text{-}H3}$ = 4.0 Hz, H_2), 3.54 (dd, 1H, $J_{H7a\text{-}H6}$ = 5.5 Hz, $J_{H7a\text{-}H7b}$ = 13.5 Hz, H_{7b}), 3.15 (dd, 1H, $J_{H7b\text{-}H6}$ = 9.0 Hz, $J_{H7b\text{-}H7a}$ = 13.5 Hz, H_{7b}); ^{13}C NMR (100 MHz, D_2O) δ 80.3 (C_5), 71.3 (C_4),

70.1 (C_3), 67.5 (C_6), 62.4 (C_1), 53.5 (C_2), 42.8 0 (C_7); HRMS calcd for $C_7H_{14}NO_4$: $[MH]^+$: 176.0917 found 176.0920.

Compound 9. To a solution of **6** (15 mg, 0.031 mmol) in MeOH (3 mL) was added aqueous HCl (1M, 0.2 mL) under argon. After adding Pd/C (10%, 15 mg), the argon was removed. The H_2 was introduced and the mixture was bubbled for 5 minutes. After stirring the solution for 24 under H_2 atmosphere, the mixture was filtered on micro-filter 0.3 µm). The solvent was evaporated to give the desired product (5.5 mg, 84%). $[\alpha]^{22}_D$ = -15.8 (C = 0.3, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.24 (dd, J_{H8a-H2} = 3.0 Hz, $J_{H8a-H8b}$ = 12.5 Hz, H_{8a}), 4.16-4.08 (m, 3H, H_{8b}, H_3, H_6), 3.88 (ddd, 1H, J_{H5-H7a} = 1.0 Hz, J_{H5-H6} = 2.5 Hz, J_{H5-H4} = 9.0 Hz, H_5), 3.83-3.78 (m, 2H, H_{7a}, H_2), 3.69 (t, 1H, J_{H4-H3} = J_{H4-H5} = 9.0 Hz, H_4), 3.62 (dd, 1H, J_{H7b-H6} = 1.0 Hz, $J_{H7b-H7a}$ = 14.5 Hz, H_{7b}); ^{13}C NMR (100 MHz, D_2O) δ 74.3 (C_4), 74.2 (C_5), 72.6 (C_3), 69.4 (C_6), 62.2 (C_8), 55.6 (C_2), 39.0 (C_7); HRMS calcd for $C_7H_{14}NO_4$: $[MH]^+$: 176.0917 found 176.0914.

Crystal data for **3**. Colorless needles : $C_{29}H_{31}NO_6$, orthorhombic, *P* $2_12_12_1$, a = 6.1055(3), b = 13.7134(6), c = 30.6466(16) Å, V = 2566.0(2) Å^3, Z = 4, T = 200(2) K, μ□= 5.233 mm^{-1}, 10288 reflections measured, 4467 independent (R_{int}= 0.0401), 3363 observed [I≥2σ(I)], 326 parameters, final R indices R_1 [I≥2 σ (I)] = 0.0482 and wR_2 (all data)= 0.1178, GOF on F^2 = 1.042, max/min residual electron density = 0.13/-0.19 e.Å^{-3}. CCDC 1015485 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

A single crystal of the compound was mounted onto a cryoloop. Intensity data were collected at 200K with a BRUKER Kappa-APEXII diffractometer with micro-focused Cu-Kα radiation (λ = 1.54178 Å). Data collection and data reduction were performed within APEX2 suite, with SAINT and SADABS programs (BRUKER). In the WinGX suite of programs[20], the structure was solved with Sir92[21] program and refined by full-matrix least-squares methods using SHELXL-97[22].

References

[1] (a) Horne, H.; Wilson, F. X. Therapeutic Applications of Iminosugars: Current Perspectives and Future Opportunities. *Prog. Med. Chem.* **2011,** *50,* 135-176. DOI: 10.1016/B978-0-12-381290-2.00004-5. (b) Horne, G.; Wilson, F. X.; Tinsley, J. D.; Williams H.; Storer, R. Iminosugars Past, Present and Future: Medicines for Tomorrow. *Drug Discov. Today* **2011,** *16,* 107-118. DOI: 10.1016/j.drudis.2010.08.017.

[2] Martin, O. R.; Compain, P. *Iminosugars: From Synthesis to Therapeutic Applications;* Wiley-VCH: Weinheim, 2007.
[3] Parenti, G. Treating Lysosomal Storage Diseases with Pharmacological Chaperones: from Concept to Clinics. *EMBO Mol. Med.* **2009,** *1*, 268-279. DOI: 10.1002/emmm.200900036.
[4] (a) Groopman, J. E. Current Advances in the Diagnosis and Treatment of AIDS: an Introduction. *Rev. Infect. Dis.* **1990,** *12*, 908-911. (b) Jacob, G. Glycosylation Inhibitors in Biology and Medicine. *Curr. Opin. Struct. Biol.* **1995,** *5*, 605-611. DOI: 10.1016/0959-440X(95)80051-4. (c) Papandreou, M. J.; Barbouche, R.; Guieu, R. Kieny, M. P.; Fenouillet, E. The α-Glucosidase Inhibitor 1-Deoxynojirimycin Blocks Human Immunodeficiency Virus Envelope Glycoprotein-Mediated Membrane Fusion at the CXCR4 Binding Step. *Mol. Pharmacol.* **2002,** *61*, 186-193. DOI: 10.1124/mol.61.1.186.
[5] (a) Wu, S.-F.; Li, C. -J.; Liao, C. -L.; Dwek, R. A.; Zitzmann, N.; Lin, Y. -L. Antiviral Effects of an Iminosugar Derivative on Flavivirus Infections. *J. Virol.* **2002,** *76*, 3596-3604. DOI: 10.1128/JVI.76.8.3596-3604.2002. (b) Mehta, A.; Ouzounov, S.; Jordan, R.; Simsek, E.; Lu, X. -Y.; Moriarty, R. M.; Jacob, G.; Dwek, R. A.; Block, T. M. Imino Sugars That are Less Toxic but More Potent as Antivirals, *In Vitro*, Compared with N-n-Nonyl DNJ. *Antivir. Chem. Chemother.* **2002,** *13*, 299-304. DOI: 10.1177/095632020201300505. (c) Greimel, P.; Spreitz, J.; Stütz, A. E.; Wrodnigg, T. M. Iminosugars and Relatives as Antiviral and Potential Anti-infective Agents. *Curr. Top. Med. Chem.* **2003,** *3*, 513-523. DOI: 10.2174/1568026033452456.
[6] Mecozzi, V. J.; Berman, D. E.; Simoes, S.; Vetanovetz, C.; Awal, M. R.; Patel, V. M.; Schneider, R. T.; Petsko, G. A.; Ringe, D.; Small, S. A. Pharmacological Chaperones Stabilize Retromer to Limit APP Processing. *Nat. Chem. Biol.* **2014,** *10*, 443-449. DOI: 10.1038/nchembio.1508.
[7] Oh, M.; Lee, J. H.; Wang, W.; Lee, H. -S.; Leeb, W. S.; Burlakd, C.; Im, W.; Hoang, Q. -Q.; Lima, H. -S. Potential Pharmacological Chaperones Targeting Cancer-associated MCL-1 and Parkinson Disease-associated α-Synuclein. *Proc. Natl. Acad. Sci. USA.* **2014,** *111*, 11007-11012. DOI: 10.1073/pnas.1320556111.
[8] (a) Jacob, G. S. Glycosylation Inhibitors in Biology and Medicine. *Curr. Opin. Struct. Biol.* **1995,** *5*, 605-611. DOI: 10.1016/0959-440X(95)80051-4. (b) McCormack, P. L.; Goa, K. L. Miglustat. *Drugs* **2003,** *63*, 2427. DOI: 10.2165/00003495-200363220-00006. (c) Germain, D. P.; Hughes, D.; Nicholls, K.; Bichet, D.; Giugliani, R.; Wilcox, W.; Feliciani, C.; Shankar, S.; Ezgu, F.; Amartino, H.; et al. *N. Engl. J. Med.* Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat. **2016,** *375*, 545-555. DOI: 10.1056/NEJMoa1510198.
[9] (a) Jagadeesh, Y.; Tran, A. T.; Luo, B.; Auberger, N.; Désiré, J.; Nakagawa, S.; Kato, A.; Zhang, Y.; Sollogoub, M.; Blériot, Y. γ-Aminoalcohol Rearrangement Applied to Pentahydroxylated Azepanes Provides Pyrrolidines Epimeric to HomoDMDP. *Org. Biomol. Chem.* **2015,** *13*, 3446-3456. DOI: 10.1039/c5ob00050e. (b) Tran, A. T.; Luo, B.; Jagadeesh, Y.; Auberger, N.; Désiré, J.; Nakagawa, S.; Kato, A.; Zhang, Y.; Blériot, Y.; Sollogoub, M. Synthesis of Pyrrolidine-based Analogues of 2-Acetamidosugars as N-Acetyl-D-glucosaminidase Inhibitors. *Carbohydr. Res.* **2015,** *409*, 56-62. DOI: 10.1016/j.carres.2015.02.014.
[10] (a) Blériot, Y.; Auberger, N.; Jagadeesh, Y.; Gauthier, C.; Prencipe, G.; Tran, A. T.; Marrot, J. M.; Désiré, J.; Yamamoto, A.; Kato, A.; Sollogoub, M. Synthesis of 1,2-*cis*-Homoiminosugars Derived from GlcNAc and GalNAc Exploiting a β-Amino Alcohol Skeletal Rearrangement. *Org. Lett.* **2014,** *16*, 5512-5515. DOI: 10.1021/ol502926f. (b) Blériot, Y.; Tran, A.; Prencipe, G.; Jagadeesh, Y.; Auberger, N.; Zhu, S.; Gauthier, C.; Zhang, Y.; Désiré, J.; Adachi, I.; Kato, A.; Sollogoub, M. Synthesis of 1,2-trans-2-Acetamido-2-deoxyhomoiminosugars. *Org. Lett.* **2014,** *16*, 5516-5519. DOI: 10.1021/ol502929h.
[11] (a) Li, H.; Blériot, Y.; Chantereau, C.; Mallet, J.; Sollogoub, M.; Zhang, Y.; Rodríguez-García, E.; Vogel, P.; Jiménez-Barbero, J.; Sinaÿ, P. The First Synthesis of Substituted Azepanes Mimicking Monosaccharides: a New Class of Potent Glycosidase Inhibitors. *Org. Biomol. Chem.* **2004,** *2*, 1492-1499. DOI: 10.1039/b402542c. (b) Li, H.; Schütz, C.; Favre, S.; Zhang, Y.; Vogel, P.; Sinaÿ, P.; Blériot, Y. Nucleophilic Opening of Epoxyazepanes: Expanding the Family of Polyhydroxyazepane-based Glycosidase Inhibitors. *Org. Biomol. Chem.* **2006,** *4*, 1653-1662. DOI: 10.1039/b518117h. (c) Li, H.; Zhang, Y.; Favre, S.; Vogel, P.; Sollogoub, M.; Blériot, Y. Synthesis of Branched Seven-membered 1-N-Iminosugars and Their Evaluation as Glycosidase Inhibitors. *Carbohydr. Res.* **2012,** *356*, 110-114. DOI: 10.1016/j.carres.2011.10.039. (d) Li, H.; Blériot, Y.; Mallet, J.; Rodriguez-Garcia, E.; Vogel, P.; Zhang, Y.; Sinaÿ, P. New 1-Amino-1-deoxy- and 2-Amino-2-deoxy-polyhydroxyazepanes: Synthesis and Inhibition of Glycosidases. *Tetrahedron: Asymmetry* **2005,** *16*, 313-319. DOI: 10.1016/j.tetasy.2004.12.005. (e) Li, H.; Marcelo, F.; Bello, C.; Vogel, P.; Butters, T.; Sollogoub, M.; Rauter, A.; Blériot, Y. Design and Synthesis of Acetamido tri- and tetra-hydroxyazepanes: Potent and Selective beta-N-Acetylhexosaminidase Inhibitors. *Bioorg. Med. Chem.* **2009,** *17*, 5598-5604. DOI: 10.1016/j.bmc.2009.06.022. (f) Marcelo, F.; He, Y.; Yuzwa, S.; Nieto, L.; Jiménez-Barbero, J.; Sollogoub, M.; Vocadlo, D.; Davies, G.; Blériot, Y. Molecular Basis for Inhibition of GH84 Glycoside Hydrolases by Substituted Azepanes: Conformational Flexibility Enables Probing of Substrate Distortion. *J. Am. Chem. Soc.* **2009,** *131*, 5390-5392. DOI: 10.1021/ja809776r.

[12] Luo, B.; Marcelo, F.; Désiré, J.; Zhang, Y.; Sollogoub, M.; Kato, A.; Adachi, I.; Canada, F. J.; Jiménez-Barbero, J.; Blériot, Y. Synthesis, Conformational Analysis, and Evaluation as Glycosidase Inhibitors of Two Ether-Bridged Iminosugars. *J. Carbohydr. Chem.* **2011,** *30,* 641-654. DOI: 10.1080/07328303.2011.630547.
[13] Taghzouti, H.; Goumain, S.; Harakat, D.; Portella, C.; Behr, J. B.; Plantier-Royon, R. Synthesis of 2-Carboxymethyl Polyhydroxyazepanes and Their Evaluation as Glycosidase Inhibitors. *Bioorg. Chem.* **2015,** *58,* 11-17. DOI: 10.1016/j.bioorg.2014.11.003.
[14] Salvador, J. A. R.; Pinto, R. M. A.; Silvestre, S. M. Recent Advances of Bismuth(III) Salts in Organic Chemistry: Application to the Synthesis of Aliphatics, Alicyclics, Aromatics, Amino Acids and Peptides, Terpenes and Steroids of Pharmaceutical Interest. *Mini-Rev. in Org. Chem.* **2009,** *6,* 241-274. DOI: 10.2174/157019309789371587.
[15] Ollevier, T.; Lavie-Compin, G. Bismuth triflate-catalyzed Mild and Efficient Epoxide Opening by Aromatic Amines Under Aqueous Conditions. *Tetrahedron Lett.* **2004,** *45,* 49-52. DOI: 10.1016/j.tetlet.2003.10.129.
[16] Tu, Y.; Wang, Z.-X.; Shi, Y. An Efficient Asymmetric Epoxidation Method for *trans*-Olefins Mediated by a Fructose-Derived Ketone. *J. Am. Chem. Soc.* **1996,** *118,* 9806-9807. DOI: 10.1021/ja962345g.
[17] Yang, D.; Wong, M.-K.; Yip, Y. C. Epoxidation of Olefins Using Methyl(trifluoromethyl)dioxirane Generated in Situ. *J. Org. Chem.* **1995,** *60,* 3887-3889. DOI: 10.1021/jo00117a046.
[18] Hameed, A.; Blake, A. J.; Hayes, C. J. A Second Generation Formal Synthesis of (−)-Cephalotaxine. *J. Org. Chem.* **2008,** *73,* 8045-8048. DOI: 10.1021/jo801540q.
[19] Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H. Concise and Highly Stereocontrolled Synthesis of 1-Deoxygalactonojirimycin and Its Congeners Using Dioxanylpiperidene, a Promising Chiral Building Block. *Org. Lett.* **2003,** *5,* 2527-2529. DOI: 10.1021/ol034886y.
[20] Farrugia, L. J. *WinGX* Suite for Small-molecule Single-crystal Crystallography. *J. Appl. Crystallogr.* **1999**, *32,* 837-838. DOI: 10.1107/S0021889899006020.
[21] Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *SIR*92 - a Program for Automatic Solution of Crystal Structures by Direct Methods. *J. Appl. Crystallogr.* **1994**, *27,* 435-435. DOI: 10.1107/S002188989400021X.
[22] Sheldrick, G. M. A Short History of *SHELX*. *Acta Cryst. A* **2008**, *64,* 112-122. DOI: 10.1107/S0108767307043930.