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## POLYHYDROXYAZEPANES MIMICKING MONOSACCHARIDES : SYNTHESIS OF AN $\alpha$ -D-GALACTO-LIKE IMINOHEPTITOL

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*Dedicated to Prof. Pierre Potier on the occasion of his 70<sup>th</sup> birthday*

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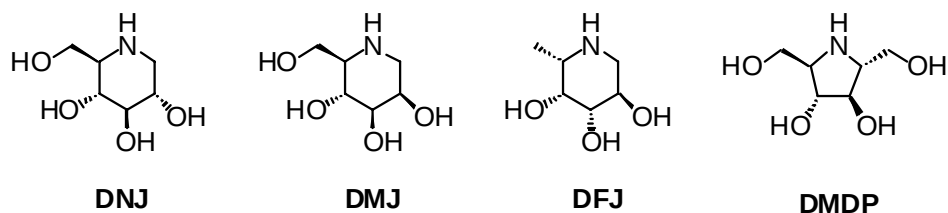
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**Abstract** - The synthesis of three new examples of seven-membered ring iminoalditols, displaying an extra hydroxymethyl group on the ring compared to the previously reported polyhydroxylated azepanes, has been achieved from D-lyxonolactone. None of them, including the  $\alpha$ -D-galacto-like azepane (7), showed significant glycosidase inhibition on green coffee bean  $\alpha$ -galactosidase and other commercially available hydrolases.

## INTRODUCTION

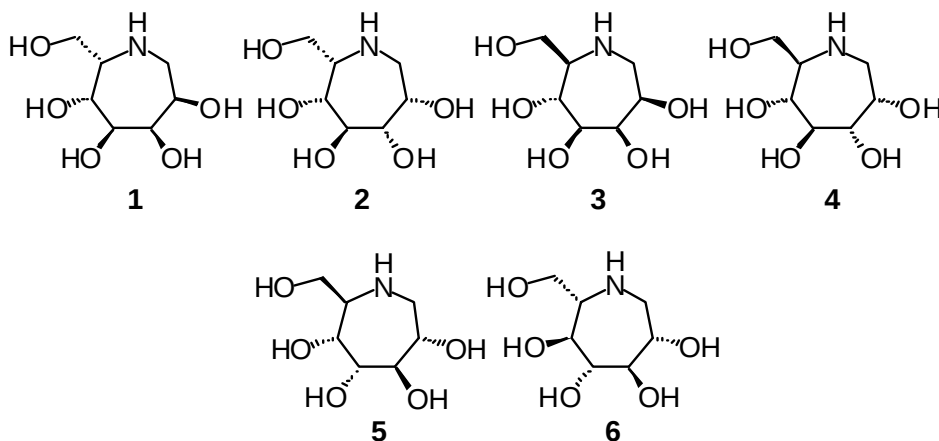
The quest for potent and selective glycosidase inhibitors is mainly due to their therapeutic potential<sup>1</sup> and several glycosidase inhibitors have already been tested or approved in the treatment of diabetes,<sup>2</sup> Gaucher's disease,<sup>3</sup> HIV infection,<sup>4</sup> viral infections,<sup>5</sup> or cancer.<sup>6</sup> These compounds have also been used as chemical probes, in combination with protein crystallography and kinetics studies, to provide new insights into glycosidase mechanism.<sup>7</sup>

Extensive synthetic work has been achieved to design five- and six-membered ring azasugars,<sup>8</sup> including deoxynojirimycin (DNJ), deoxymannojirimycin (DMJ), deoxyfuconojirimycin (DFJ) and 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) (Figure 1) which mimic the ring size of their parent sugar, but only a few syntheses of higher homologues with seven-<sup>9</sup> or eight-membered rings<sup>10</sup> have been reported so far.



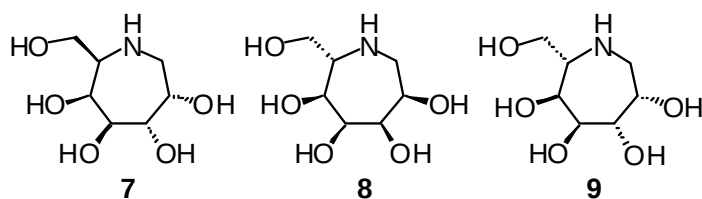
**Figure 1** : Structures of DNJ, DMJ, DFJ and DMDP

As part of an ongoing project on the design of new carbohydrates mimetics, we published the synthesis and biological evaluation of 1,6-dideoxy-1,6-iminoheptitols (**1-4**).<sup>11</sup> Dhivale *et al.* reported recently the synthesis of two other epimers (**5-6**) (Figure 2).<sup>12</sup>



**Figure 2** : Structure of 1,6-dideoxy-1,6-iminoheptitols synthesized by us (**1-4**) and Dhivale (**5-6**)

Unlike previously reported polyhydroxylated azepanes, compounds (**1-6**) possess an extra hydroxymethyl group in order to mimick the parent sugar more closely. These compounds can be considered as higher homologues of nojirimycin and insertion of a methylene group between the nitrogen atom and the pseudo-anomeric hydroxyl group ensures chemical stability unlike nojirimycin. We anticipated that the relative flexibility of such structures associated with the unusual spatial distribution of the hydroxyl groups might generate an atypical inhibition profile for these molecules. This was indeed the case and the analogue (**4**), although having an  $\alpha$ -D-gluco structure, was found to be a rather potent and selective green coffee bean  $\alpha$ -galactosidase inhibitor ( $K_i$  2.2  $\mu$ M). A step further towards the understanding of this unexpected inhibition result would be the evaluation of the  $\alpha$ -D-galacto-like 1,6-dideoxy-1,6-iminoheptitol. In this paper we disclose the synthesis and the biological evaluation of three new 1,6-dideoxy-1,6-iminoheptitols (**7**, **8**, and **9**), displaying an  $\alpha$ -D-galacto,  $\alpha$ -L-allo and  $\beta$ -L-altro configuration respectively (Figure 3).

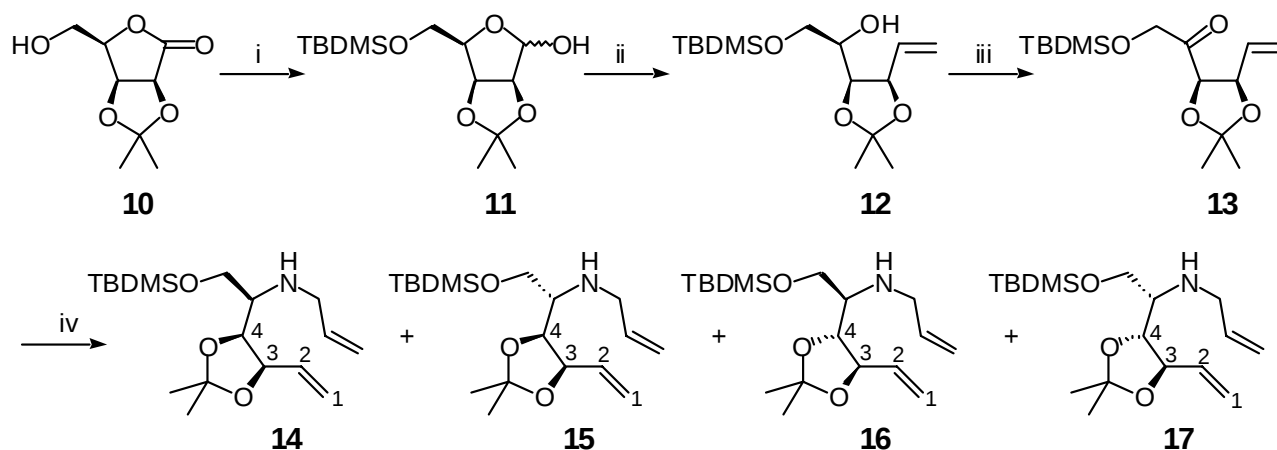


**Figure 3 :** Structure of the synthesized 1,6-dideoxy-1,6-iminoheptitols (7-9)

## RESULTS AND DISCUSSION

Our strategy, based on the RCM<sup>13</sup> of a suitable iminodiene, is very similar to the one described in our previous paper.<sup>11</sup> The only modification is the use of D-lyxonolactone as starting material and orthogonal protecting groups which should enable us to selectively decorate these azepanes.

Our synthesis starts from the known and easily available 1,2-O-isopropylidene-D-lyxonolactone (**10**).<sup>14</sup> Silylation of the primary alcohol and subsequent reduction with DIBAL gave lactol (**11**) in 87 % yield over two steps. Wittig olefination of (**11**) yielded the acyclic alcohol (**12**) which was then oxidized to the corresponding ketone (**13**) in 60% over two steps. Reductive amination of the ketone (**13**) with allylamine and acetic acid in the presence of NaBH(OAc)<sub>3</sub> gave the D-lyxo (12%) and L-ribo (17%) aminohexenitols (**14**) and (**15**) (Scheme 1).



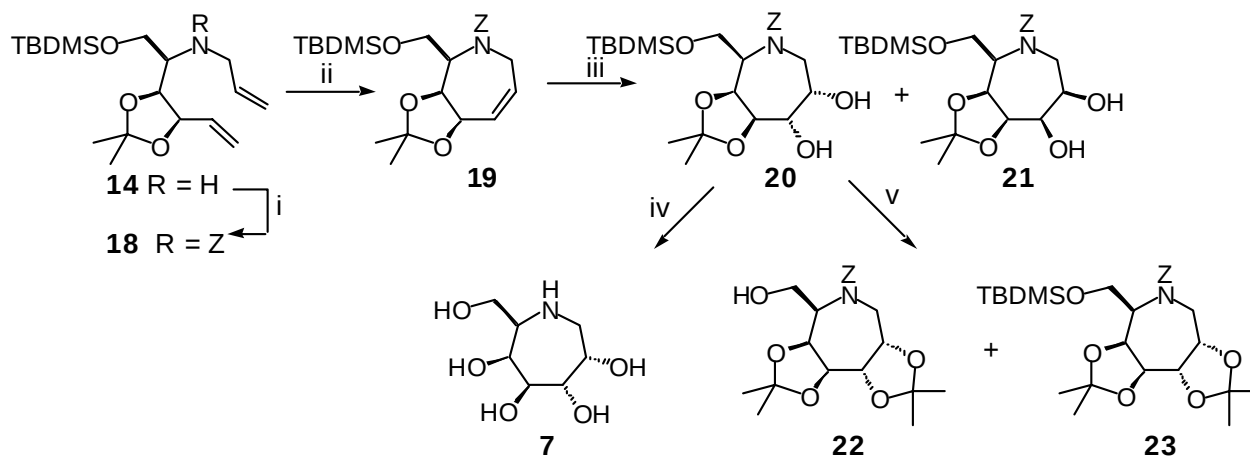
**Conditions :** i) TBDMSCl, pyridine, 95% yield then DIBAL-H, toluene, -40°C, 92% yield ; ii) Ph<sub>3</sub>PCH<sub>2</sub>Br, n-BuLi, THF, 77% yield ; iii) PCC, 4Å MS, CH<sub>2</sub>Cl<sub>2</sub>, 78% yield ; iv) allylamine, AcOH, NaBH(OAc)<sub>3</sub>, 4Å MS, CH<sub>2</sub>Cl<sub>2</sub>, 40°C, 52% yield.

**Scheme 1 :** Synthesis of the aminohexenitols (14-17)

Surprisingly, two other compounds could be isolated and were identified as the D-arabino (**16**) (18%) and L-xylarbo (**17**) (6%) aminohexenitols. Compounds (**15**) and (**16**) could not be separated at this stage. This indicates that epimerisation occurred at the 4 position during this reductive amination step. Work is in progress to improve the yield of this step and circumvent this problem.

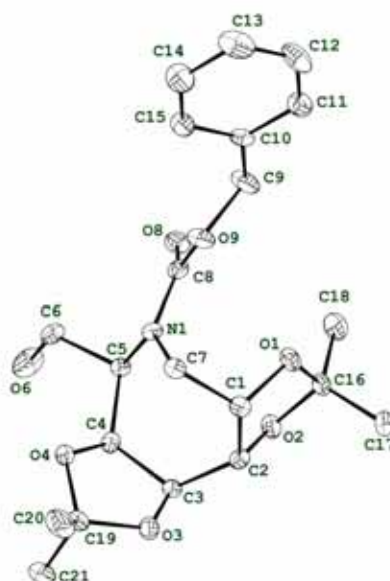
The secondary amine of the D-lyxo aminodiene (**14**) was then protected with a Z group in 82% yield to afford the carbamate derivative (**18**), in order to suppress chelation of the amine on the ruthenium of the

catalyst in the forthcoming RCM step. Ring closing metathesis of diene (**18**) proceeded in excellent yield to afford azacycloheptene (**19**) in 99% yield. Dihydroxylation of (**19**) using OsO<sub>4</sub> proceeded smoothly and afforded almost exclusively the *cis*-diol (**20**) as the main product in 91% yield with only a trace of diol (**21**) (3%). Hydrogenolysis followed by acidic deprotection of compound (**20**) afforded the polyhydroxylated azepane (**7**) in quantitative yield (Scheme 2). The stereochemistry of compound **7** was confirmed by solving the X-Ray structure of its diacetonide derivative (**22**)(Figure 4)<sup>15</sup> obtained in 51% yield from compound (**20**) along with the fully protected compound (**23**) (obtained in 45% yield).



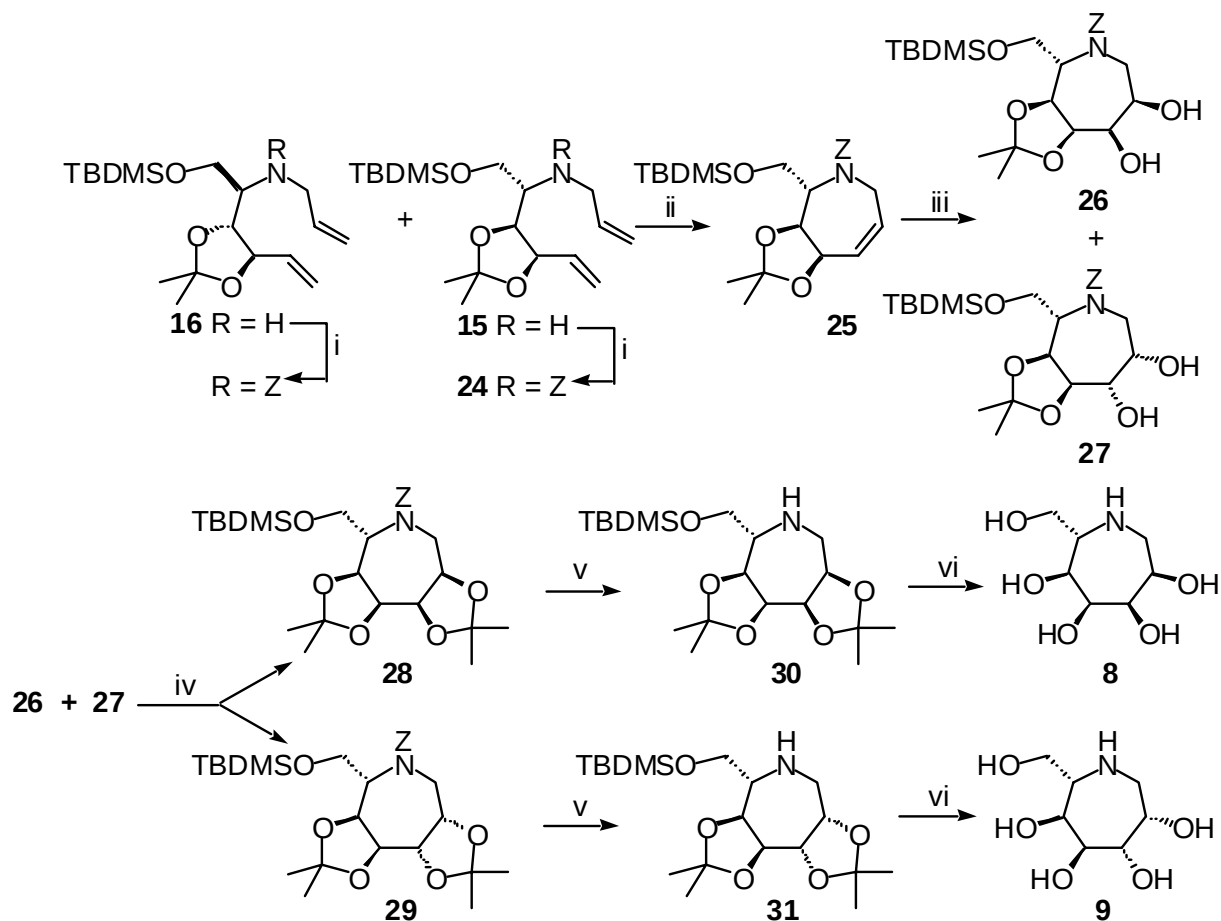
**Conditions :** i) ZCl, KHCO<sub>3</sub>, ethyl acetate/water, 82% yield ; ii) first generation Grubbs' catalyst , DCM, 1 day, 99% yield ; iii) OsO<sub>4</sub>, NMO, acetone/water, 94% yield ; iv) H<sub>2</sub>, 10% Pd/C, AcOH, then 50% aq. TFA quant. ; v) 2,2-dimethoxypropane, CSA, acetone.

**Scheme 2 :** Synthesis of the seven-membered ring iminoheptitol (**7**)



**Figure 4 :** X-Ray structure of compound (**22**)

The same sequence was now applied to the L-xylo aminohexenitol (**15**). Separation of compounds (**15**) and (**16**) was achieved during the protection of the nitrogen to afford the corresponding carbamates. The carbamate of compound (**16**) with the D-arabino stereochemistry was not further processed. Carbamate (**24**) was subjected to ring closing metathesis to afford azacycloheptene (**25**) in 97% yield. Dihydroxylation of (**25**) using OsO<sub>4</sub> afforded an inseparable mixture of the two *cis*-diols (**26**) and (**27**) in 96% yield and in a 1/6 ratio respectively. Compounds (**26**) and (**27**) were separated as their di-O-isopropylidene derivatives (**28**) and (**29**). Hydrogenolysis of the benzyloxycarbonyl group yielded compounds (**30**) and (**31**) in quantitative yield. Treatment with aqueous TFA quantitatively afforded the polyhydroxylated azepanes (**8**) and (**9**) (Scheme 3).



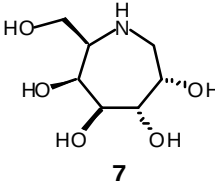
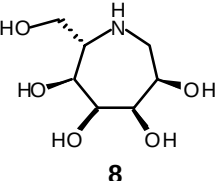
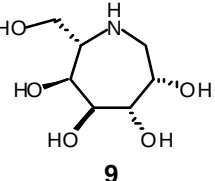
**Conditions :** i) ZCl, K<sub>2</sub>CO<sub>3</sub>, ethyl acetate/water, 93% yield ; ii) first generation Grubbs' catalyst, DCM, 45°C, 24 h, 97% yield ; iii) OsO<sub>4</sub>, NMO, acetone/water, 96% yield ; iv) 2,2-dimethoxypropane, acetone, CSA, 90% ; v) H<sub>2</sub>, 10% Pd/C, AcOH, quant ; vi) 50% aq. TFA, quant.

**Scheme 3 :** Synthesis of seven-membered ring iminoheptitols (**8**) and (**9**)

The stereochemistry of compounds (**8**) and (**9**) was deduced from the structure of the diacetone derivative (**22**) and from their respective NMR spectra.<sup>16</sup>

## INHIBITION ON GLYCOSIDASES

These iminoheptitols have been assayed for their inhibitory activity toward 24 commercially available glycosidases.<sup>17</sup> They did not inhibit the following enzymes at 1 mM:  $\alpha$ -L-fucosidase from bovine epididymis,  $\alpha$ -galactosidases from *Aspergillus niger* and *E. coli*,  $\beta$ -galactosidases from *E. coli*,  $\alpha$ -glucosidases from yeast and rice, amyloglucosidases from *Aspergillus niger* and *Rhizopus mold*,  $\beta$ -mannosidase from *Helix pomatia*,  $\beta$ -xylosidase from *A. niger*,  $\beta$ -N-acetylglucosaminidases from jack bean and bovine epididymis A and B. For other enzymes the results are shown in Table 1.

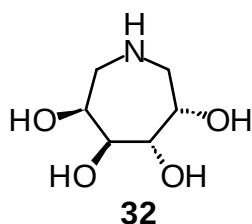
|                                          |                                                                                        |                                                                                        |                                                                                         |
|------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
|                                          | <br>7 | <br>8 | <br>9 |
| Relative configuration                   | $\alpha$ -D-galacto                                                                    | $\alpha$ -L-allo                                                                       | $\beta$ -L-altro                                                                        |
| <i><math>\alpha</math>-galactosidase</i> |                                                                                        |                                                                                        |                                                                                         |
| Coffee beans                             | 50%                                                                                    | NI                                                                                     | 27%                                                                                     |
| <i><math>\beta</math>-galactosidase</i>  |                                                                                        |                                                                                        |                                                                                         |
| Bovine liver                             | NI                                                                                     | 68%                                                                                    | NI                                                                                      |
| <i>Aspergillus niger</i>                 | NI                                                                                     | 50%                                                                                    | NI                                                                                      |
| <i><math>\alpha</math>-mannosidase</i>   |                                                                                        |                                                                                        |                                                                                         |
| Jack beans                               | NI                                                                                     | 56%                                                                                    | NI                                                                                      |
| Almonds                                  | NI                                                                                     | 40%                                                                                    | NI                                                                                      |
| <i><math>\beta</math>-glucosidase</i>    |                                                                                        |                                                                                        |                                                                                         |
| almonds                                  | NI                                                                                     | 53%                                                                                    | NI                                                                                      |
| <i>Saccharomyces cerevisiae</i>          | NI                                                                                     | 72%                                                                                    | NI                                                                                      |

**Table 1** : Inhibitory activity of compounds (7, 8 and 9)

Percentage of inhibition at 1 mM concentration, optimal pH, 35°C, NI = no inhibition at 1 mM concentration of the inhibitor

Compound (7) is a selective albeit weak inhibitor of  $\alpha$ -galactosidase from green coffee beans. This a surprising result regarding the structure of 7, which mimicks  $\alpha$ -D-galactopyranose more closely than the potent  $\alpha$ -D-glucopyranose analogue (4). Interestingly, a polyhydroxylated azepane (32), analogue of compound (7) but lacking the hydroxymethyl group, was previously synthesized by Painter et al. and shown to be a

potent inhibitor of green coffee beans  $\alpha$ -galactosidase (Figure 5).<sup>9n</sup> This means that, in compound (7), unlike compound (4), the presence of an hydroxymethyl group appears to be detrimental to the inhibition. Compound (8) is a weak and non selective glycosidase inhibitor, inhibiting similarly  $\alpha$ -mannosidases,  $\beta$ -galactosidases and  $\alpha$ -glucosidases. Compound (9) behaves as compound (7), displaying a selective but weak inhibition on  $\alpha$ -galactosidase from coffee beans. These results emphasize the difficulty to predict the inhibition profile for this family of compounds adopting unusual conformations.



**Figure 5 :** Tetrahydroxyazepane (32) synthesized by Painter *et al.*

## CONCLUSION

We have synthesized three new seven-membered ring iminoheptitols (7-9) using RCM methodology and displaying an  $\alpha$ -D-galacto,  $\alpha$ -L-allo and  $\beta$ -L-altro configuration respectively. None of them displayed significant glycosidase inhibition, especially on green coffee bean  $\alpha$ -galactosidase. These data emphasize the potent inhibition obtained for the  $\alpha$ -D-gluco analog (4) on this enzyme. We recently rationalized this result invoking a pseudoaxial orientation of the OH-3 in compound (4) mimicking closely the axial OH-4 of galactopyranoside.<sup>18</sup> A conformational study of compounds (7-9) is underway to provide insights into their lack of inhibition.

## ACKNOWLEDGEMENTS

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## REFERENCES

1. V.H. Lillelund, H.H. Jensen, X. Liang, and M. Bols, *Chem. Rev.*, 2002, **102**, 515; O.R. Martin, and P. Compain, *Curr. Top. Med. Chem.*, 2003, **3**, i-iv.
2. A. Mitrakou, N. Tountas, A.E. Raptis, R.J. Bauer, H. Schulz, and S.A. Raptis, *Diab. Med.*, 1998, **15**, 657.

3. T.D. Butters, R.A. Dwek, and F.M. Platt, *Curr. Top. Med. Chem.*, 2003, **3**, 561.
4. J.E. Groopman, *Rev. Infect. Dis.*, 1990, **12**, 908; I. Robina, A.J. Moreno-Vargas, A.T. Carmona, and P. Vogel, *Current Drug Metabolism*, 2004, **5**, 329.
5. W.G. Laver, N. Bischofberger, and R.G. Webster, *Sci. Am.*, 1999, *Jan*, 78; P. Greimel, J. Spreitz, A.E. Stütz, and T.M. Wrodnigg, *Curr. Top. Med. Chem.*, 2003, **3**, 513.
6. N. Zitzmann, A.S. Mehta, S. Carrouée, T.D. Butters, F.M. Platt, J. McCauley, B.S. Blumberg, R.A. Dwek, and T.M. Block, *PNAS*, 1999, **96**, 11878.
7. T.D. Heightman and A.T. Vasella, *Angew. Chem. Int. Ed.*, 1999, **38**, 750; A. Vasella, G.J. Davies, and M. Böhm, *Curr. Op. Chem. Biol.*, 2002, **6**, 619.
8. A. Stütz : *Iminosugars as glycosidase inhibitors : Nojirimycin and Beyond* ; Wiley-VCH : Weinheim, 1999.
9. For tetrahydroxyazepanes see : a) H. Paulsen and K. Todt, *Chem. Ber.*, 1967, **100**, 512; b) R. Dax, B. Gaigg, B. Grassberger, B. Koelblinger, and A.E. Stütz, *J. Carb. Chem.*, 1990, **9**, 479; c) B.B. Lohray, Y. Jayamma, and M. Chatterjee, *J. Org. Chem.*, 1995, **60**, 5958; d) X.-H. Qian, F. Moris-Varas, and C.-H. Wong, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1117; e) F. Moris-Varas, X.-H. Qian, and C.-H. Wong, *J. Am. Chem. Soc.*, 1996, **118**, 7647; f) X.-H. Qian, F. Moris-Varas, M.C. Fitzgerald, and C.-H. Wong, *Bioorg. Med. Chem.* 1996, **4**, 2055; g) Y. Le Merrer, L. Poitout, J.-C. Depezay, I. Dosbaa, S. Geoffroy, and M.-J. Foglietti, *Bioorg. Med. Chem.*, 1997, **5**, 519; h) B.B. Lohray, V. Bhushan, G. Prasuna, Y. Jayamma, M.A. Raheem, P. Papireddy, B. Umadevi, M. Premkumar, N.S. Lakshmi, and K. Narayanareddy, *Indian J. Chem., Sect. B*, 1999, **38B**, 1311; i) G.F. Painter and A. Falshaw, *J. Chem. Soc., Perkin Trans 1*, 2000, 1157; j) H.A. Johnson and N.R. Thomas, *Bioorg. Med. Chem. Chem. Lett.*, 2002, **12**, 237; k) P.R. Andreana, T. Sanders, A. Janczuk, J.I. Warrick, and P.G. Wang, *Tetrahedron Lett.*, 2002, **43**, 6525; l) C.C. Joseph, H. Regeling, B. Zwanenburg, and G.J.F. Chittenden, *Tetrahedron*, 2002, **58**, 6907; m) J. Fuentes, C. Gasch, D. Olano, M. A. Pradera, G. Repetto, and F.J. Sayago, *Tetrahedron : Asymmetry*, 2002, **13**, 1743; n) G.F. Painter, P.G. Eldridge, and A. Falshaw, *Bioorg. Med. Chem.*, 2004, **12**, 225.
10. G. Godin, E. Garnier, P. Compain, O.R. Martin, K. Ikeda, and N. Asano, *Tetrahedron Lett.*, 2004, **45**, 579.
11. H. Li, Y. Blériot, C. Chantereau, J.-M. Mallet, M. Sollogoub, Y. Zhang, E. Rodriguez-Garcia, P. Vogel, J. Jimenez-Barbero, and P. Sinaÿ, *Org. Biomol. Chem.*, 2004, **2**, 1492.
12. D.D. Dhivale, S.D. Markad, N.S. Karanjule, and J. PrakashaReddy, *J. Org. Chem.*, 2004, **69**, 4760.
13. For recent reviews on olefin metathesis, see : A. Fürstner, *Angew. Chem.*, 2000, **112**, 3140; *Angew. Chem., Int. Ed.*, 2000, **39**, 3012; T.M. Trnka and R.H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18; R.H. Grubbs, *Tetrahedron*, 2004, **60**, 7117.

14. G.W.J. Fleet, S. Petursson, A.L. Campbell, R.A. Müller, J.R. Behling, K.A. Babiak, J.S. Ng, and M.G. Scarosc, *J. Chem. Soc. Perkin Trans 1*, 1989, 665; M. Godskesen, I. Lundt, and I. Sotofte, *Tetrahedron : Asymmetry*, 2000, **11**, 567.
15. Selected crystal structure data for compound (**22**); crystal system orthorhombic; Space Group P 2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>; Z=4; cell parameters: a=9.7399(5), b=10.8579(6), c=19.195(11),  $\alpha=90^\circ$ ,  $\beta=90^\circ$ ,  $\gamma=90^\circ$ ; radiation (MoK $\alpha$ )  $\lambda = 0.71073 \text{ \AA}$ ; 263 variables for 2619 reflections; final R=0.0476, R<sub>w</sub>=0.0502; Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 250899. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)].
16. Selective data for compounds (**7**, **8** and **9**):  
 Compound (**7**) :  $[\alpha]_D + 54^\circ$  (c = 1.07 in MeOH/H<sub>2</sub>O 1 : 1) ; <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz): 4.28 (m, 1H, H-1), 4.07 (app. d, 1H, J = 2.3 Hz, H-4), 3.81 (dd, 1H, J = 2.2 Hz, J = 5.0 Hz, H-2), 3.80 - 3.70 (m, 3H, H-3, H-6, H-6'), 3.61 (app. dd, 1H, J = 6.0 Hz, J = 8.5 Hz, H-5), 3.36 (m, 2H, H-7, H-7'); <sup>13</sup>C NMR (D<sub>2</sub>O, 100 MHz): 74.08 (C-3), 73.75 (C-2), 69.34 (C-4), 68.47 (C-1), 61.63 (C-6), 57.61 (C-5), 45.73 (C-7); m/z (CI, NH<sub>3</sub>) : 194 (M+H<sup>+</sup>, 100%); HRMS (CI, NH<sub>3</sub>) : Calcd for C<sub>7</sub>H<sub>16</sub>NO<sub>5</sub> (M+H<sup>+</sup>): 194.1028, Found 194.1024.  
 Compound (**8**) :  $[\alpha]_D - 13^\circ$  (c = 0.49 in H<sub>2</sub>O) ; <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz): 4.10 - 4.05 (m, 2H, H-3, H-1), 3.95 (dd, 1H, J = 2.7 Hz, J = 5.8 Hz, H-2), 3.93 (dd, 1H, J = 3.4 Hz, J = 12.4 Hz, H-6), 3.80 (m, dd, 1H, J = 2.4 Hz, J = 9.0 Hz, H-4), 3.69 (dd, 1H, J = 7.9 Hz, J = 12.1 Hz, H-6'), 3.30 (dd, 1H, J = 3.3 Hz, J = 10.2 Hz, H-7), 3.26 (ddd, 1H, J = 3.0 Hz, J = 8.3 Hz, J = 11.3 Hz, H-5), 3.11 (dd, 1H, J = 7.6 Hz, J = 13.9 Hz, H-7'); <sup>13</sup>C NMR (D<sub>2</sub>O, 100 MHz): 77.89 (C-3), 72.14 (C-4), 68.31 (C-1), 67.84 (C-2), 60.06 (C-5), 59.55 (C-6), 44.98 (C-7); m/z (CI, NH<sub>3</sub>) : 194 (M+H<sup>+</sup>, 100%); HRMS (CI, NH<sub>3</sub>) : Calcd for C<sub>7</sub>H<sub>16</sub>NO<sub>5</sub> (M+H<sup>+</sup>): 194.1028, Found 194.1030.  
 Compound (**9**) :  $[\alpha]_D + 4^\circ$  (c = 1.0 in MeOH /H<sub>2</sub>O 1 : 1) ; <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz): 4.18 (ddd, 1H, J = 2.5 Hz, J = 5.2 Hz, J = 6.8 Hz, H-1), 4.07 (dd, 1H, J = 2.2 Hz, J = 8.2 Hz, H-4), 4.05 (dd, 1H, J = 2.2 Hz, J = 8.9 Hz, H-3), 3.99 (dd, 1H, J = 4.0 Hz, J = 12.1 Hz, H-2), 3.86 (dd, 1H, J = 4.0 Hz, J = 12.1 Hz, H-6), 3.73 (dd, 1H, J = 7.3 Hz, J = 12.1 Hz, H-6'), 3.28 (dd, 1H, J = 6.9 Hz, J = 14.1 Hz, H-7), 3.18 (ddd, 1H, J = 4.0 Hz, J = 7.1 Hz, J = 11.0 Hz, H-5), 3.11 (dd, 1H, J = 2.5 Hz, J = 14.0 Hz, H-7'); <sup>13</sup>C NMR (D<sub>2</sub>O, 100 MHz): 71.55 (C-3), 71.37 (C-2), 69.21 (C-4), 67.69 (C-1), 61.16 (C-5), 61.11 (C-6), 46.93 (C-7); m/z (CI, NH<sub>3</sub>) : 194 (M+H<sup>+</sup>, 100%); HRMS (CI, NH<sub>3</sub>) : Calcd for C<sub>7</sub>H<sub>16</sub>NO<sub>5</sub> (M+H<sup>+</sup>): 194.1028, Found 194.1021.
17. A known protocol was applied : R. Saul, J.P. Chambers, R.J. Molyneux, and A.D. Elbein, *Arch. Biochem. Biophys.*, 1983, **221**, 593; A. Brandi, S. Cicchi, F.M. Cordero, B. Frignoli, A. Goti, S.

Picasso, and P. Vogel, *J. Org. Chem.*, 1995, **60**, 6806. We verified that the delay of inhibitor/enzyme incubation did not affect the inhibition measurements. Under standard conditions, optimal inhibitory activities were measured after five minutes of incubation.

18. K. Martinez-Mayorga, J.L. Medina-Franco, S. Mari, F.J. Canada, E. Rodriguez-Garcia, P. Vogel, H. Li, Y. Blériot, P. Sinaÿ, and J. Jiménez -Barbero, *Eur. J. Org. Chem.*, 2004, **20**, 4119.