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Synthesis of New Aminocyclitols as Potent Enzymatic Inhibitors

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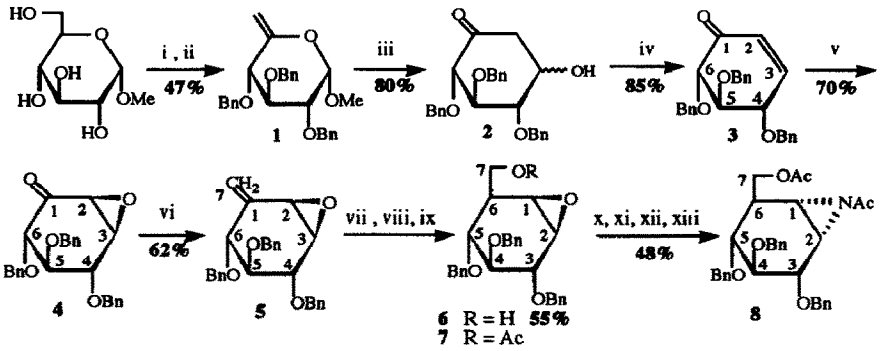
Abstract **: The syntheses of new *pseudo*-saccharides having an allylic amino moiety or an aziridine group are reported starting from methyl-α–D-glucopyranoside. To enhance the hydrophilic / lipophilic balance, *pseudo*-saccharides 9 and 10 were linked with a glycosyl derivative.**

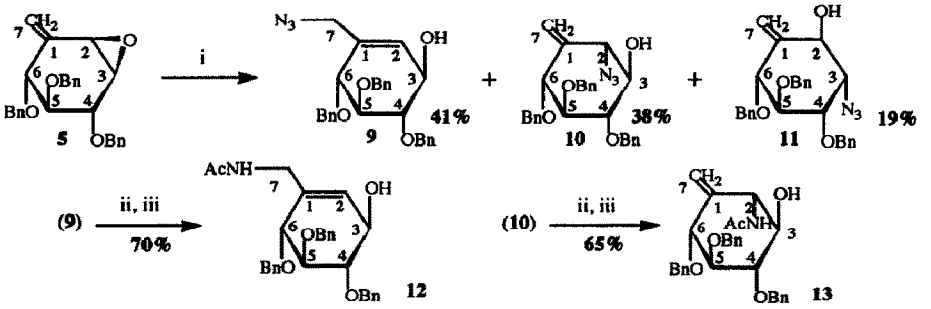
Among natural inhibitors of glycosidases [1], cyclitol epoxides [2] and aminocyclitols [3] were synthesized starting from carbohydrate derivatives [4] or *endo*-adduct of furan and acrylic acid [5]. As part of a program to synthesize potential enzyme inhibitors [6], we were concerned with the preparation of new aminocyclitols.

To obtain the carbocyclic skeleton, methyl-α–D-glucopyranoside was transformed in three steps into **3**. Methyl-α–D-glucopyranoside was chlorinated at the primary carbon with mesyl chloride in DMF, at 65°C. Then, both hydrogen chloride elimination and protection of the secondary hydroxy groups with benzyl bromide were carried out in the presence of sodium hydride in excess, to afford **1** in 47 % yield. During this one pot reaction, methyl 3,6 anhydro-2,4-di-O-benzyl-α-D-glucopyranoside is obtain in 18% yield [7]. Treated with $HgCl_2$ (1.25 eq., acetone-water 2/1, 70°C), **1** led to *pseudo*-saccharide **2**, by the classical Ferrier transposition [8], in 80% yield. Dehydration of **2** with mesyl chloride (14 eq.) and 4-*N,N*-dimethylaminopyridine (0,1 eq.) in pyridine, resulted in 85% yield of cyclohexenone derivative **3**. Epoxidation of **3** with *t*-butyl hydroperoxide (70% in dichloromethane) occurred stereospecifically from the less hindered side, to give the epoxy ketone **4** [9]. Olefination of **4** with triphenylphosphonium methylide (1.5 eq., THF, 0°C to r.t.) afforded **5** (62%). Diborane, generated *in situ*, reacted with **5** in THF, then the organoborane was converted into the epoxy alcohol **6** which was acetylated into **7**. A coupling constant of 7.4 Hz for $J_{5,6}$ involves a C-5,C-6 *anti* methyne configuration. Nucleophilic ring opening of **7** by sodium azide (3.5 eq. , 2- methoxyethanol / water 8 / 2) in the presence of ammonium chloride (3.5 eq.) yielded two azido isomers resulting from nucleophilic attack at C-2 (70%) and C-1 (20%). The ^1H nmr spectrum of the former shows a *trans e,e* coupling constant $J_{1,2} = 3.4$ Hz and a *cis a,e* coupling constant $J_{2,3} = 2.5$ Hz, resulting from an inversion of configuration at the C-2. Mesylation of the free hydroxy group of the azido isomers, followed by reduction with lithium aluminium hydride (0.7 eq., Et_2O, r.t.) gave, after acetylation, the aziridine **8** in 48 % overall yield .



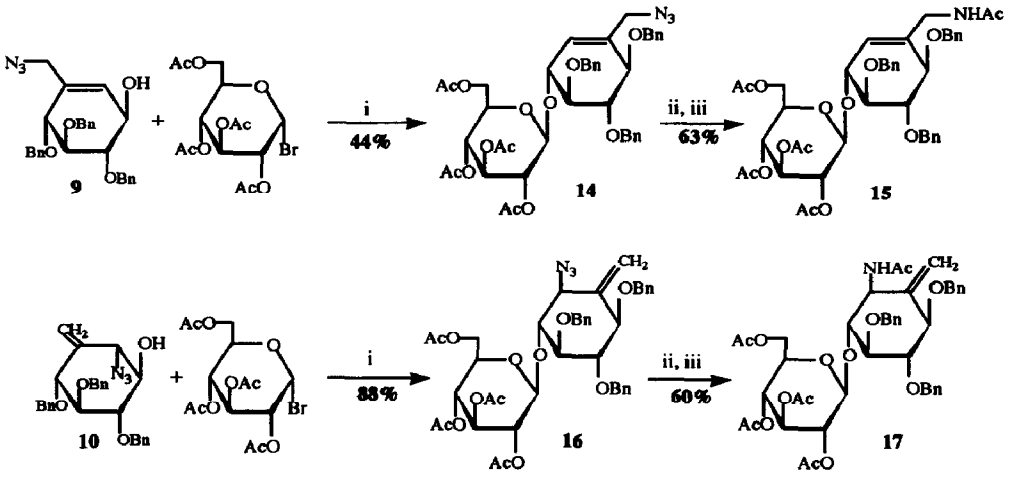
i) MsCl, DMF, 65°C ii) NaH, BnBr, DMF, 50°C iii) $HgCl_2$, acetone-water, reflux iv) MsCl, DMAP, pyridine ; v) tBuOOH , triton, B, CH_2Cl_2, R.T. vi) Ph_3PCH_3Br , nBuLi, THF, R.T. vii) B_2H_6 , THF viii) H_2O_2 , OH^- ix) Ac_2O / pyridine x) NaN_3, NH_4Cl, 16h reflux xi) MsCl, pyridine xii) $LiAlH_4$, Et_2O xiii) Ac_2O, pyridine

To introduce an amino group in the allylic position, as in valienamine [10], **5** was treated with sodium azide / ammonium chloride (3.5 / 3.5 eq.). A mixture of three azido derivatives **9**, **10** and **11** was obtained in 41, 38 and 19 % yield respectively. Reduction of the azido derivative **9** with lithium aluminium hydride, (0.7 eq.) followed by *N*-acetylation, led to **12** in 70 % yield. Similar treatment transformed **10** in **13**, in 65 % yield.



i) NaN_3, NH_4Cl ii) $LiAlH_4$ iii) Ac_2O / pyridine

To enhance the hydrophilic / lipophilic balance of 3S-(3,5/4,6)-1-acetamidomethyl-4,5,6-tri-O-benzyl-1-ene-cyclohexane-3,4,5,6-tetrol **12** and 2R(2,4,6/3,5)-2-acetamido-4,5,6-tri-O-benzyl-1-methylene-cyclohexane-3,4,5,6-tetrol **13**, we have coupled **9** and **10** with a glycosyl derivative. The coupling of azido derivatives with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (3 eq.) was carried out by nucleophilic displacement in the presence of silver trifluoromethanesulphonate (AgOTf, 3 eq.) and 1,1,3,3-tetramethylurea (TMU, 3 eq.) in dichloromethane (-30°C to r.t.) [11]. The β-stereoselective glycosylation of **9** ($J_{1'2'}$ = 7.8 Hz) led to the *pseudo*-disaccharide **14** in 44 % yield, accompanied with 30 % of **9** acetylated on the allylic hydroxy group by *trans*-esterification with the peracetylated sugar. Analogous treatment applied to **10** afforded the *pseudo*-disaccharide **16** in 88 % yield. The anomeric hydrogen signal in the ^1H nmr spectrum of **16** being masked, the anomeric configuration of this product was deduced indirectly. A very slow rearrangement of **16** into **14** at room temperature, involving an allylic azido group migration, was observed and allowed us to confirm a β-configuration. Reduction of both **14** and **16** by $LiAlH_4$, followed by acetylation, led to **15** and **17** in 63% and 60 % yield respectively [12].



i) AgOTf , TMU , CH_2Cl_2 ii) $LiAlH_4$, Et_2O iii) Ac_2O / pyridine

Biological assays *in vitro* of **12** and **13** have shown interesting inhibitor activity on chitin synthase. In *in vivo* assays, they have an insect antifeedant activity. Assays of **15** and **17** are in progress.

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References and Notes :

1. Legler, G. *Adv. Carbohydr. Chem. and Biochem.* **1990**,*48*, 319-384 and references therein
2. a) Herrchen, M.; Legler, G. *Eur. J. Biochem.* **1984**, *138*, 527-531 ; b) Hozel, W.; Banz, W. *Eur. J. Biochem.* **1975**, *57*, 607-616 ; c) Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett.* **1990**, *31*,1171-1172 ; d) Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Carbohydr. Res.* **1991**, *222*, 189-203 ; e) Akiyama, T.; Ohnari, M.; Shima, H.; Ozaki, S. *Synlett* **1991**, 11, 831-832 ; f) Lee, K.J.; Boyd, S.A.; Radin, N.S. *Carbohydr. Res.* **1985**, *144* , 148-154 ; g) Jaramillo, C.; Fernandez de la Pradilla, R.; Martin-Lomas, M. *Carbohydr Res.* **1991** , 296-298 ; h) Jaramillo, C.; Martin-Lomas, M. *Tetrahedron Lett.* **1991**, *32*,2501-2504
3. a) Horii, S.; Fukase, H. *Carbohydr. Res.* **1985**, *140*, 185-200 ; b) Ogawa, S.; Shibata, Y.; Nose, T.; Suami, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3387-88 ; c) Junge, B.; Boeshagen, H.; Stoltefuss, J.; Müller, L. *Enzymes inhibitors, Proc. Meet.* (Edited by Brodbech, Urs.) Verlag Chem.: Weinheim 1980, pp123-137 ; d) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L. *Angew. Chem. Int. Ed. Engl.* **1981**, *20* , 744-761 ; e) Paulsen, H.; Mielke, B. *Liebigs Ann. Chem.* **1990**, 169-180
4. a) Fukase, H.; Horii, S. *J. Org. Chem.* **1992**, *57*, 3642-3650 and 3651-3658 ; b) Madi-Puskas, M.; Pelyvas, I.; Bognar, R. *J. Carbohydr. Chem.* **1985**, *4*, 323-331 ; c) Meszanos, P.; Pinter, I.; Messmer, A.; Toth, G.; Géro, S.D. *Carbohydr. Res.* **1990**, *197*, 302-309 ; d) Corbett, F.; Dean, D.K.; Robinson, S.R. *Tetrahedron Lett.* **1993**, *34*, 1525-1528
5. a) Ogawa, S. *Studies in Natural Products Chemistry* **1993**, *13*, 187-255 ; b) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21-90
6. a) Beaupère, D.; Stasik, B.; Uzan, R.; Demailly, G. *Carbohydr. Res.* **1989**, *191*, 163-166 ; b) Dheilly, L.; Fréchou, C.; Beaupère, D.; Uzan, R.; Demailly, G. *Carbohydr. Res.* **1992**, *224*, 301-306 ; c) Benazza, M.; Uzan, R.; Beaupère, D.;

Demailly, G. *Tetrahedron Lett.* **1992**, 33, 3129-3132 ; d) Mbongo, A.; Fréchou, C.; Beaupère, D.; Uzan, R.; Demailly, G. *Carbohydr. Res.* **1993**, *246*, 361-370

7. a) Chrétien, F. *Synthetic Communications* **1989**, *19*, 1015-1024 ; b) Dubreuil, D.; Cléophax, J.; Loupy, A. *Carbohydr. Res.* **1994**, *252*, 149-157
8. Ferrier, R.J.; Middelton, S. *Chem. Rev.* **1993**, 2779-2831
9. a) Grieco, P.A.; Nishizawa, M.; Oguri, T.; Burke, S.D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773-8 ; b) Vass, G.; Krausz, P.; Quiclet-Sire, B.; Delaumeny, J.M.; Cléophax, J.; Géro S. *C. R. Acad. Sci. Série II*, **1985**, *301*, 1345-1346
10. Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038-1046
11. Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13-C16
12. **RMN ^{1}H (300MHz, $CDCl_3$)** :

8 2.70 (d, $J_{1,2}$ =5.5Hz, H-1), 2.75 (dd, $J_{2,3}$ = 3.4Hz, H-2), 3.75 (dd, $J_{3,4}$ = 6Hz, H-3), 3.58 (dd, $J_{4,5}$ = 10.3Hz, H-4), 3.43 (dd, $J_{5,6}$ = 7.9Hz, H-5), 2.89 (dd, $J_{6,7}$ =10.2Hz, H-6), 4.25 (t, $J_{7,7'}$ = 10.2Hz, H-7), 4.55 (dd, $J_{6,7'}$ = 3.7Hz, H-7'), 4.7 to 5.2 (6H, $C\underline{H}_2Ph$), 7.2 to 7.4 (15H, 3 C_6H_5), 2.0 (3H, $C\underline{H}_3CO$), 2.1 (3H, $C\underline{H}_3CNO$)

12 5.55 (s, H-2), 4.25 (t, $J_{3,4}$ = 6.4Hz, H-3), 3.5 (t, $J_{4,5}$ = 9.5Hz, H-4) 3.75 (dd, H-5), 4.15 (d, $J_{5,6}$ = 6.8Hz, H-6), 3.9 (dd, $J_{7,7'}$ = 14.5Hz, $J_{7,NH}$ = 6.9Hz, H-7), 3.65 (dd, $J_{7',NH}$ = 3.6Hz, H-7') 3.65 (m, $N\underline{H}$Ac ; 1.75 3H, s, $C\underline{H}_3CNO$), 4.55 to 4.9 (6H, $C\underline{H}_2Ph$), 7.2 to 7.3 (15H, 3 C_6H_5), 2.55 (1H, s, O$\underline{H}$)

13 4.42 (t, $J_{2,3}$ = 8.3Hz, H-2) 3.36, (t, H-3), 3.6 (t, $J_{3,4}$ = $J_{4,5}$ = 8.3Hz , H-4) 3.51 (t, H-5), 4.05 (d, $J_{5,6}$ = 8.3Hz, H-6), 5.15 (s, H-7) 5.35 (s, H-7'), 6.32 (d, $J_{NH,1}$ =8.3Hz, N$\underline{H}$), 4.55 to 5.0 (6H, $C\underline{H}_2Ph$), 7.25 to 7.35 (15H, 3 C_6H_5), 2.0 (3H, $C\underline{H}_3CO$), 4.5 to 5.0 (s, O$\underline{H}$)

15 5.51 (s, H-2), 4.43 (d, $J_{3,4}$ = 6.6Hz, H-3), 3.55 to 3.75 (4H, H-4, H-5, H-5', H-7'), 4.15 (d, $J_{5,6}$ =5.4Hz, H-6) 3.9 (dd, $J_{7,7'}$ =14.5Hz, $J_{7,NH}$ = 6.9Hz, H-7), 4.68 (d, $J_{1',2'}$ = 7.8Hz, H-1'), 4.95 (t, H-2'), 5.15 (t, $J_{2',3'}$ = $J_{3',4'}$ = 9.6Hz, H-3'), 5.10 (t, $J_{4',5'}$ = 9.6Hz, H-4'), 4.20 (dd, $J_{5',6'}$ = 3.8Hz, $J_{6',6''}$ = 12.3Hz, H-6'), 4.0 (dd, $J_{5',6''}$ = 1.9Hz, H-6''), 5.50 (m, N$\underline{H}$), 4.6 to 5.0 (6H, $C\underline{H}_2Ph$), 7.2 to 7.4 (15H, 3 C_6H_5), 1.9 to 2.1 (15H, $C\underline{H}_3COO$ et $C\underline{H}_3CNO$)

17 4.50 (t, $J_{2,3}$ = 7.5Hz, H-2), 3.70 (t, H-3), 3.60 (t, $J_{3,4}$ = 7.6Hz, H-4), 3.55 (t, $J_{4,5}$ = $J_{5,6}$ = 7.8Hz, H-5), 4.0 (d, H-6), 5.3 (s , H-7), 5.1 (s, H-7'), 4.95, (2H, H-1', H-2') 5.15 (m, $J_{2',3'}$ = $J_{3',4'}$ = 9.4Hz), 5.0 (t, $J_{4',5'}$ = 9.4Hz, H-4'), 3.65 (m, H-5') 4.15 (dd, $J_{6',6''}$ = 12.5Hz, $J_{6',5'}$ = 3.9Hz, H-6'), 4.0 (dd, $J_{5',6''}$ =2.2Hz, H-6''), 4.55 to 4.9 (6H, $C\underline{H}_2Ph$), 7.2 to 7.3 (15H, 3 C_6H_5), 6.18 (d, $J_{NH,1}$ = 8.3Hz, N$\underline{H}$), 1.9 to 2.1(15H, $C\underline{H}_3COO$ and $C\underline{H}_3CNO$).

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