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New azadisaccharide analogs as potential antidiabetics

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Abstract—The synthesis of various aminocyclitols displaying a *N*-substituted (or unsubstituted) polyhydroxycyclohexylamine structure is described. The strategy relies on two key steps: a tandem alkylation–cyclization of a C_2-symmetrical bis-epoxide derived from D-mannitol and a reductive amination with several amines of the resulting polyhydroxycyclohexanone. Reduction of the latter also allows a rapid access to the corresponding carbasugars. © 2002 Published by Elsevier Science Ltd.

Due to the potential therapeutic applications of glycosidases or glycosyltransferases inhibitors[1] in diabetes, cancer or viral infections, we have developed an intensive program[2] concerning the synthesis of carbohydrate mimics. Our attention has first been focused on heterocyclic compounds such as imino-,[3] thio-,[4] guanidinosugars[5] or azadisaccharide analogs[6] and we are now interested in the design and the synthesis of aminocyclitols displaying various size for the ring. Thus, we recently described access to C_8-cyclitols via metathesis of 1,9-diene[7] and to C_7-aminocyclitols.[8] Considering the powerful α-glucosidase inhibitory activity of both voglibose and acarbose (Fig. 1) which are used in the treatment of non-insulino-dependant diabetes *mellitus*,[9] our goal is now to develop straightforward routes to C_6-aminocyclitols analogous to these compounds.

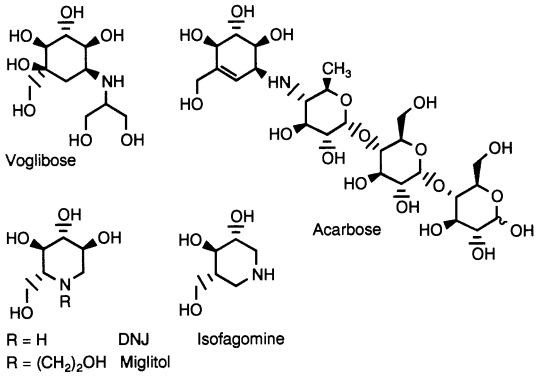

Figure 1.

Due to their potential activity, intensive synthetic efforts[10] have been directed towards carbohydrate mimics and their biological activity is believed to arise from their ability to be protonated at physiological pH allowing them to fit with the putative oxocarbenium ion-like transition state. The charge can be localized either at endocyclic oxygen atom as mimicked (Fig. 1) by deoxynojirimycin (DNJ) or miglitol (another antidiabetic compound),[11] or at anomeric carbon atom as illustrated by isofagomine or finally at the exocyclic oxygen atom as exemplified by voglibose or acarbose.

The retrosynthesis of the target compounds is outlined in Fig. 2 and relies on either the reduction or the reductive amination of the enantiopure polyhydroxycyclohexanone resulting from a tandem alkylation–cyclization reaction of C_2-symmetrical bis-epoxide coming from D-mannitol. According to the strategy we recently described,[12] the later reaction which involves Brook rearrangement can be directed to the major formation of either dithioketal of cyclohexanone or cycloheptanone depending on the nature of the protective group for the central diol of the bis-epoxide. Thus, benzyl ethers preferentially led to C_7-rings while an acetonide moiety mainly furnished the C_6-ring. We already described access to C_7-aminocyclitols from C_7-rings[8] and we now wish to report our results concerning the synthesis of C_6-carbasugars and C_6-aminocyclitols from C_6-rings.

Keywords: glycosidases; pseudo-azasaccharide; carbasugars; aminocyclitols; reductive amination.

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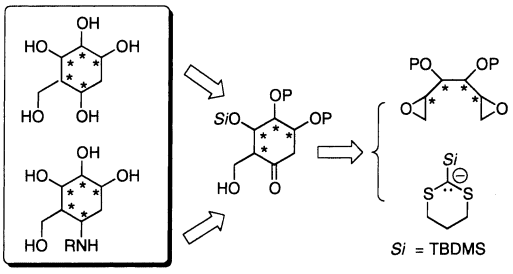


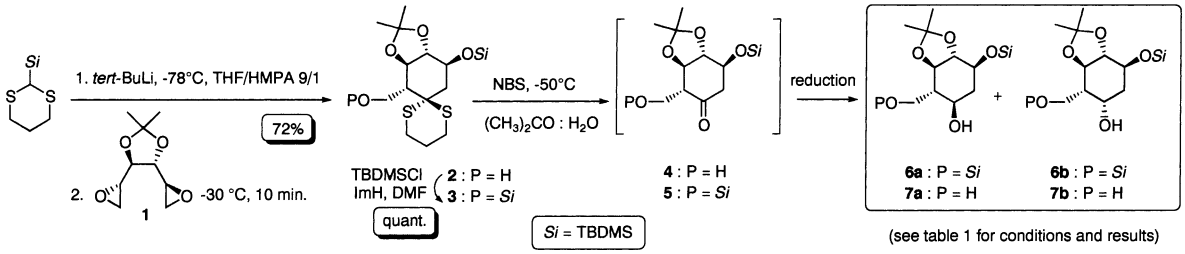
Figure 2. Retrosynthetic analysis.

The preparation of polyhydroxycyclohexanes (Scheme 1) involved the regiospecific opening of the 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-L-iditol **1** by the *tert*-butyllithium generated lithio derivative of 2-*tert*-butyldimethylsilyl-1,3-dithiane in a 9:1 mixture of THF:HMPA at −30°C, followed by in situ Brook rearrangement and carbocyclization which led to the dithioketal of cyclohexanone **2** in 72% yield. It has to be noted that the choice of L-*ido* bis-epoxide was directed by the absolute configuration of the asymmetric carbon atoms of the resulting cyclohexane closed to that of the compounds displaying interesting antidiabetic properties. Protection of the primary alcohol function of **2** (*tert*-butyldimethylsilylchloride, DMF) afforded the *O*-silylated derivative **3** in quantitative yield. Then the dithioketal hydrolysis of **3** in the presence of *N*-bromosuccinimide in aqueous acetone[13] at −50°C, to avoid side reactions, gave the corresponding cyclohexanone **5**[14] which was submitted to the next reduction without purification (see Table 1 for the various conditions used for the reduction of the carbonyl moiety of **5**).

Thus, in the presence of sodium borohydride in EtOH, at 20°C, a 82/18 mixture of the alcohols **6a**/**6b**[15] was obtained in 80% yield. These products were easily separated by flash chromatography and the absolute configuration at the newly created chiral carbon atom was assigned by ^{1}H NMR studies.[16] The same reaction done at −78°C for 3 hours led to a slight increase in **6a**/**6b** to 96/4 in an identical yield. This result is in good agreement with the described major formation of an equatorial hydroxyl group promoted by $NaBH_4$.[17] Attempts to reverse the observed diastereoselectivity in the presence of bulky hydride were then examined. Surprisingly, DIBAL-H in THF at −78°C furnished the same major compound as previously (**6a**/**6b** = 78/22, 43% yield), however L-Selectride® and K-Selectride® (−78°C, 30 min) in THF allowed the expected inversion of the diastereoselectivity of the reaction and led to the major formation of **6b** (**6a**/**6b** up to 39/61, 50% yield). The lower yield observed with DIBAL-H and L- or K-Selectride® compared to that obtained with $NaBH_4$ can be explained by the partial decomposition of intermediate ketone **5**. It has to be noted that the reduction with K-Selectride® was also carried out on an isolated pure cyclohexanone **5** sample and led to the same isolated yield of **6a**/**6b** (4/6, respectively, 50% yield).

In order to examine an eventual induction by the free alcohol function of the compound **2** during the reduction step, hydrolysis of its dithioketal moiety was carried out in the same conditions as previously (NBS, acetone–H_2O, −50°C) but gave the corresponding ketoalcohol **4** in only 10% yield revealing that these conditions were not suitable with the free alcohol. Alternatively, the alcohol **4** could be obtained by deprotection of the silyl ether **5** with HF–pyridine in 40% non-optimized yield. However, the reduction of this ketoalcohol **4** with $NaBH_4$ in EtOH, at −78°C afforded a 75/25 mixture of the corresponding diols **7a**/**7b** revealing no modification of the diastereoselectivity of the reduction.

We next turned to the preparation of the targeted aminocyclitols via the reductive amination of the *O*-silylated keto-alcohol **5** (Scheme 2) in the presence of

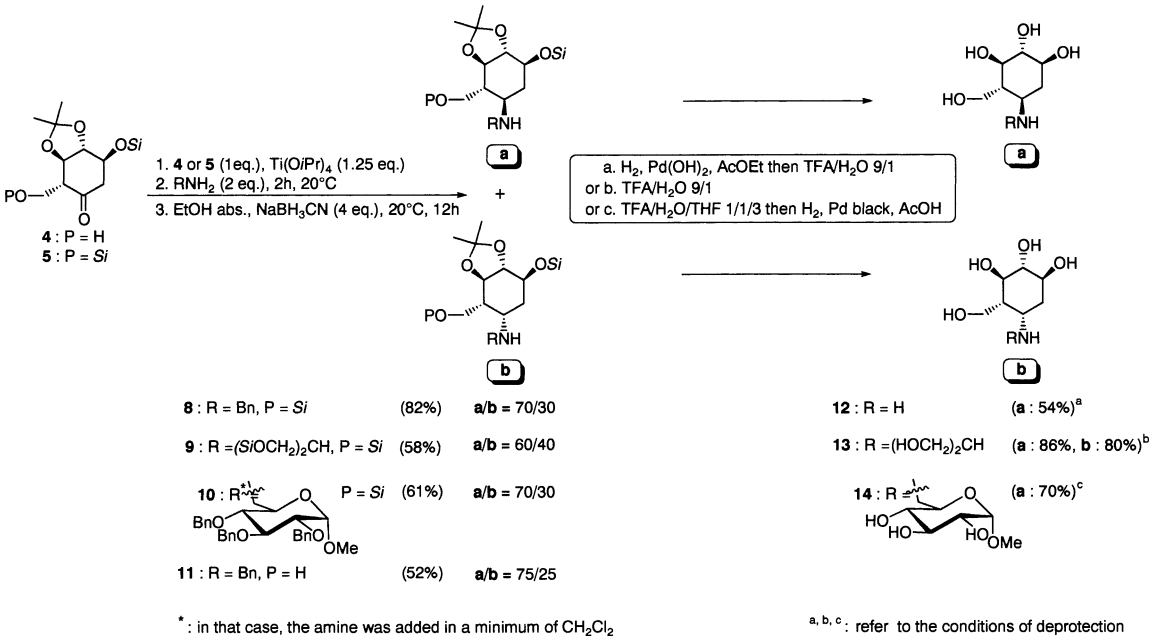


Scheme 1.

Table 1. Reduction of ketone **4** or **5** with hydride reagents

Substrate	Reagents and conditions	Ratio[a]	Yield (%)
5	$NaBH_4$, EtOH, 20°C, 20 h	**6a**/**6b** = 82/18	80
5	$NaBH_4$, EtOH, −78°C, 3 h	**6a**/**6b** = 96/4	80
5	DIBAL-H, THF, −78°C, 1.5 h	**6a**/**6b** = 78/22	43
5	L-Selectride®, THF, −78°C, 30 min	**6a**/**6b** = 39/61	50
5	K-Selectride®, THF, −78°C, 30 min	**6a**/**6b** = 36/64	50
4	$NaBH_4$, EtOH, −78°C, 3 h	**7a**/**7b** = 75/25	40

[a] The **a**/**b** ratio was determined by ^{1}H NMR spectrum of the crude mixture prior to flash chromatographic separation.



Scheme 2. Reductive amination and deprotections on the major compounds.

various primary amines such as benzylamine, 1,3-di-*tert*-butyldimethylsilyloxy-2-propylamine or methyl 6-amino-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside,[18] respectively, chosen to afford unsubstituted C_6-aminocyclitol, an analog of voglibose and an analog of disaccharide displaying partial acarbose structure. Thus, the reductive amination was carried out under Mattson et al. conditions[19] and involved imine formation catalyzed by the mild and effective titanium(IV) isopropoxide as Lewis acid followed by its in situ reduction with sodium cyanoborohydride in EtOH.[15] A mixture of the two possible aminocyclitols (**8a**/**8b**, **9a**/**9b** and **10a**/**10b**, respectively) was obtained in moderate to good yield (82, 58 and 61%, respectively). In all cases, the ratio of the diastereomeric mixture (60/40 to 70/30) was in favor of the amino group in equatorial position,[20] as precedently observed for the $NaBH_4$ reduction of the cyclohexanone **5**. Again, to examine the possible induction of a free alcohol on the diastereoselectivity of the reductive amination, the keto-alcohol **4** was submitted to reductive amination with benzylamine and afforded a 75/25 mixture of the corresponding aminocyclitols **11a**/**11b** in 52% yield, thus revealing no modification in the diastereoselectivity of the reductive amination.

The deprotection of the aminocyclitols **9a** or **9b** was easily achieved in a single step in the presence of a 9/1 mixture of trifluoroacetic acid/H_2O to afford the expected aminocyclitols **13a** or **13b** in good yield (86 or 80%, respectively). Hydrogenolysis of the *N*-benzyl bond of the compound **8a** in the presence of Pearlman catalyst (H_2, $Pd(OH)_2$, 20°C) was followed by acidic hydrolysis (TFA/H_2O = 9/1) to give the *N*-unsubstituted aminocyclitol **12a** (54% yield). Deprotection of the disaccharide analog **10a** required first, acidic hydrolysis (TFA/H_2O/THF = 1/1/3, 20°C) of both the acetonide moiety and the silyl ethers followed by hydrogenolysis of the benzyl ethers in the presence of palladium black in acetic acid to lead to the pseudo-azadisaccharide **14a** (70% yield). All compounds were purified by ion exchange chromatography (Dowex 50X8-100).

In conclusion, we described powerful routes to new carbasugars or aminocyclitols via respective stereoselective reduction or reductive amination of an enantiomerically pure polyhydroxycyclohexanone easily obtained by a tandem alkylation–cyclization of a bis-epoxide derived from D-mannitol followed by careful dithioketal hydrolysis. According to this strategy, the synthetized aminocyclitols can be *N*-substituted by various R-groups, such as R = $CH(CH_2OH)_2$ or methyl α-D-glucoside as, respectively, voglibose or acarbose analogs or unsubstituted to serve as a reference concerning the eventual biological effect of *N*-substitution of such derivatives. The biological activity of the synthetized aminocyclitols towards various glycosidases and especially α-glucosidase will be evaluated soon and the results of biological evaluation will be published later on.

Acknowledgements

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References

1. (a) For recent reviews on carbohydrates and glycobiology, see: Hurtley, S.; Service, R.; Szuromi, P. *Science* **2001**, *291*, 2337 and references cited therein; (b) Mc Carther, J. D.; Withers, S. G. *Curr. Opin. Struc. Biol.* **1994**, *4*, 885–892; (c) Ly, H. D.; Withers, S. G. *Annu. Rev.*

Biochem. **1999**, *68*, 487–522; (d) Elbein, A. D.; Molyneux, R. J. *Comprehensive Natural Products Chemistry*; Pinto, B. M., Ed.; Barton, D. H. R.; Nakanishi, K.; Meth-Cohn, O., Ser. Eds.; Elsevier: UK, 1999; Vol. 3, Chapter 7.

2. Le Merrer, Y.; Gravier-Pelletier, C.; Depezay, J.-C. *Recent Res. Devel. Org. Chem.* **2001**, *5*, 257–278 and references cited therein.
3. (a) Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett*. **1994**, *35*, 3293–3296; (b) Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem*. **1997**, *5*, 519–533.
4. Le Merrer, Y.; Fuzier, M.; Depezay, J.-C.; Dosbaa, I.; Foglietti, M.-J. *Tetrahedron* **1997**, *53*, 16731–16746.
5. Le Merrer, Y.; Gauzy, L.; Gravier-Pelletier, C.; Depezay, J.-C. *Bioorg. Med. Chem*. **2000**, *8*, 307–320.
6. Le Merrer, Y.; Sanière, M.; McCort, I.; Dupuy, C.; Depezay, J.-C. *Tetrahedron Lett*. **2001**, *42*, 2661–2663.
7. Gravier-Pelletier, C.; Andriuzzi, O.; Le Merrer, Y. *Tetrahedron Lett*. **2002**, *43*, 245–248.
8. Gravier-Pelletier, C.; Maton, W.; Lecourt, T.; Le Merrer, Y. *Tetrahedron Lett*. **2001**, *42*, 4475–4478.
9. (a) Balfour, J. A.; Mc Tavish, D. *Drugs* **1993**, *46*, 1025–1054; (b) Shapiro, J. A.; Seaton, T. B. *Arch. Inter. Med.* **1994**, *154*, 2442–2448; (c) Cheng, X.-M. In *Annu. Rep. Med. Chem*.; Bristol, J. A., Ed.; Academic Press: San Diego, 1995; Vol. 30, p. 313.
10. (a) *Carbohydrate Mimics, Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: New York, 1998; (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265–295; (c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (d) *Iminosugars as Glycosidases Inhibitors: Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: New York, 1999.
11. Gaudillière, B. In *Annu. Rep. Med. Chem*.; Doherty, A. M., Ed.; Academic Press: San Diego, 1999; Vol. 34, p. 325.
12. Le Merrer, Y.; Gravier-Pelletier, C.; Maton, W.; Numa, M.; Depezay, J.-C. *Synlett* **1999**, 1322–1324.
13. Corey, E. J.; Erickson, B. W. *J. Org. Chem*. **1971**, *36*, 3553–3560.
14. Due to the instability of the cyclohexanone **5** in basic conditions, it is necessary to avoid basic conditions during work-up.
15. Satisfactory analytical and/or spectroscopic data were obtained on all new compounds.
16. For **6a**: $J_{1,2}=9.1$ Hz and for **6b**: $J_{1,2}<2$ Hz.
17. Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449–462.
18. This amine was prepared according to known routes. See: Whistler, R. L.; Wolfrom, M. L. *Methods Carbohydr. Chem*. **1963**, *2*, 244–245.
19. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem*. **1990**, *55*, 2552–2554.
20. For **8a**: $J_{1,2}=11.8$ Hz and for **8b**: $J_{1,2}<2$ Hz.