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Synthesis of C8-glycomimetics as potential glycosidases inhibitors

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Abstract—The synthesis of C8-glycomimetics is described from C_2-symmetrical polyhydroxylated cyclooctenes derived from carbocyclisation of enantiomerically pure 1,9-dienes by ring closing metathesis. Their obtention notably involved either hydroboration followed by oxidation to carbasugars or to cyclooctanones then reductive amination, or formation of a *cis*-cyclic sulfate followed by successive introduction of an azido group, reduction and subsequent reductive amination. The biological activity of the C8-carbasugars and related aminocyclitols, analogous to voglibose, has been evaluated towards several commercially available glycosidases.

Glycosidases, enzymes responsible for the formation and the cleavage of glycosidic bonds, are involved in numerous biological processes such as the catabolism of glycoconjugates or the degradation of polysaccharides. Their inhibition therefore displays diverse therapeutical applications such as diabetes[1] and cancer,[2] thus glycosidases inhibitors with various structures, iminosugars or aminocyclitols[3] and carbasugars[4] have been highlighted (Fig. 1). Among them, miglitol (Glyset®)[5] and voglibose (Basen®)[6] are used in non-insulino dependant diabetes treatment.

As part of a programme aimed at the synthesis of potential glycosidases inhibitors,[7] we focused on the access to eight-membered carbasugars and related aminocyclitols to study the effect of the enhanced flexibility and of the new spatial distribution of the hydroxyl groups displayed by these structures on their adaptability in the active site of the enzyme. The versatile described approach allows access to various configurations at chiral centres. Furthermore, in order to mimic the aglycon part encountered, for example, in voglibose, alkylation of the amine functionality can also be carried out. The retrosynthesis of the targeted compounds (Fig. 2) relies on a strategy we recently reported,[8] based on a key step of carbocyclisation by ring closing metathesis involving a 1,9-diene, easily available from the C_2-symmetrical D-*manno*- or L-*ido*-bis-epoxide.

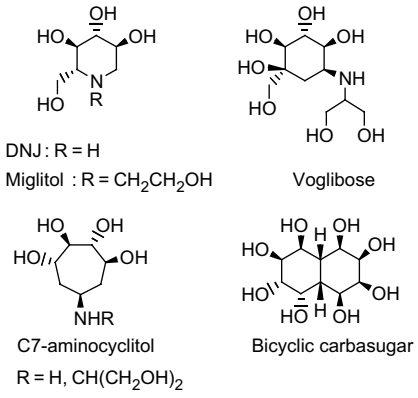

Figure 1. Examples of α-D-glucosidase inhibitors.

The synthetic potentialities of the newly created double bond in the cyclooctenic structure were then explored to reach the targeted glycomimetics.

For this purpose, the most straightforward approach to the C8-aminocyclitols unsubstituted in the C2-position (A = H) seemed to be a double bond hydroboration followed by oxidation or aminolysis, whereas to the C8-aminocyclitols hydroxylated in the C2-position

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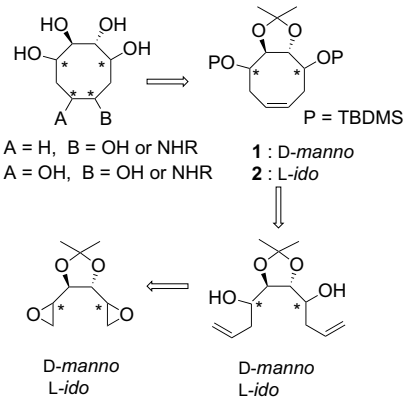


Figure 2. Retrosynthetic analysis.

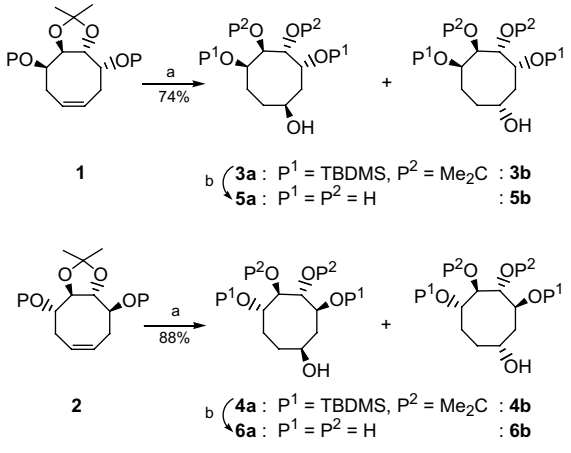
(A = OH) it seemed to be an epoxidation followed by the nucleophilic opening of the epoxide moiety by a primary amine or another nitrogen nucleophile.

Accordingly, treatment of the *O*-protected polyhydroxylated cyclooctene **1** in diethyl ether by borane–tetrahydrofuran complex[9] was followed by oxidative cleavage with alkaline hydrogen peroxide (Scheme 1). The mixture of the two epimers **3a** and **3b** in a 2/1 ratio[10] was isolated in 74% yield, and each isomer was isolated as a pure compound[11] by flash chromatography. The structure of the major isomer **3a** was unambiguously assigned by 2D-NMR studies. This structure is in agreement with the hydroboration of the double bond opposite to the *tert*-butyldimethylsilyloxy group in β position. Acidic hydrolysis (TFA/H_2O) of each compound, **3a** and **3b**, afforded the corresponding C8-carbasugars **5a** and **5b**. In the same manner, hydroboration of the L-*ido*-cyclooctene **2** gave the protected cyclitols **4a** and **4b** in 88% yield. However, in that case the diastereoselectivity decreased (3/2) and mainly led to an hydroboration on the same side as the *tert*-butyldimethylsilyloxy group in β position. As above, acidic hydrolysis of **4a** and **4b** cleanly led to the deprotected C8-carbasugars **6a** and **6b**.

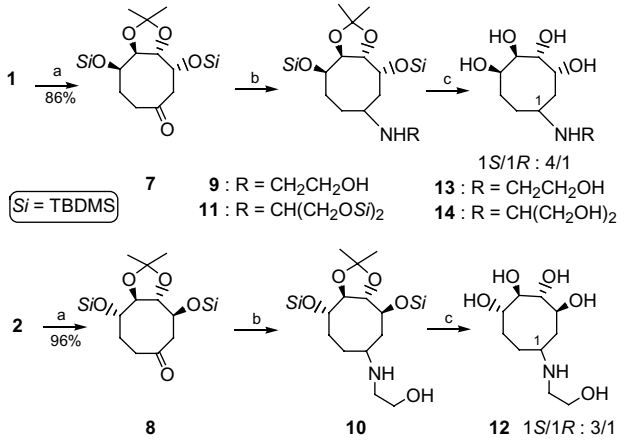
In order to reach the corresponding aminocyclitols, we turned to the hydroboration of **1** or **2** followed by aminolysis with sulfamic acid,[12] however this reaction revealed unsuccessful. Alternative activation of the alcohol function as its triflate (Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C) followed by treatment with NaN_3 or ethanolamine (DMF, −78 °C to rt) led to recover the initial cyclooctene as a result of β elimination.

Nevertheless, the targeted compounds could be efficiently obtained through oxidation of the precedent mixture **3a** and **3b** followed by reductive amination (Scheme 2).

Thus, hydroboration of **1** and alkaline hydrogen peroxide treatment as above, followed by oxidation with pyridinium chlorochromate efficiently led to the corresponding fully *O*-protected polyhydroxylated cyclooctanone **7** in 86% overall yield. Reductive amination[13] of **7** by ethanolamine in the presence of titanium(IV) tetraisopropoxide followed by the cyanoborohydride reduction of the imine intermediate gave the expected *N*-substituted derivative **9** displaying the aglycon part of miglitol. In the same way, the reductive amination was carried out with the bis-*O*-*tert*-butyldimethylsilylserinol[14] to introduce the aglycon part of voglibose, and afforded the corresponding compound **11**. Acidic hydrolysis of **9** and **11** gave, after purification by ion-exchange chromatography, the expected glycomimetics **13** and **14** in 60% and 63% overall yield, respectively. ^{1}H NMR studies (500 MHz) revealed that **13** and **14** were mixtures of epimers in a 4/1 ratio.[15] The absolute configuration at the newly created chiral centre for the major stereoisomer is the same as for the previous hydroboration reaction (**1** → **3a**, **3b**). Starting from the L-*ido*-cyclooctene **2**, the ketone **8** was obtained in 96% yield as previously described, and subsequent reductive amination with ethanolamine was followed by acidic hydrolysis to afford the miglitol mimetic **12**. This aminocyclitol isolated in 45% overall yield was also identified by ^{1}H NMR (500 MHz) as a mixture of epimers in a 3/1 ratio



Scheme 1. Reagents and conditions: (a) i. BH_3·THF, Et_2O, ii. NaOH, H_2O_2; (b) TFA, H_2O.



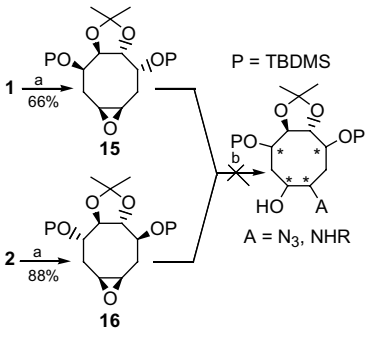
Scheme 2. Reagents and conditions: (a) i. BH_3·THF, Et_2O, ii. NaOH, H_2O_2, iii. PCC; (b) $H_2NCH_2CH_2OH$ or $H_2NCH(CH_2OTBDMS)_2$, $Ti(Oi\text{-}Pr)_4$, $NaBH_3CN$, CH_2Cl_2; (c) TFA, H_2O.

in favour of the 1*S* stereoisomer, as for hydroboration (**2** → **4a**, **4b**).

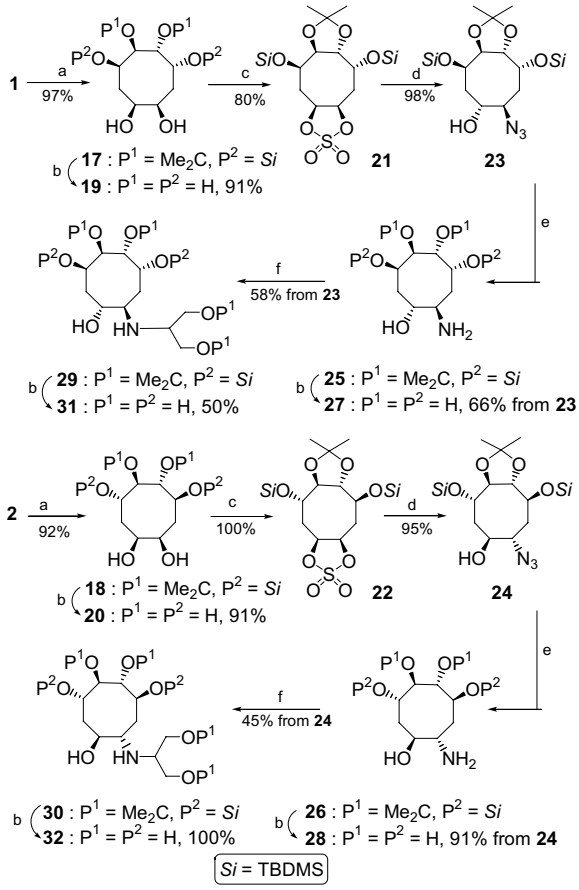
Now, to reach the 2-hydroxylated glycomimetics (A = OH) we turned to the epoxidation[16] of cyclooctenes **1** and **2** (Scheme 3) by *meta*-chloroperbenzoic acid in the presence of sodium hydrogenocarbonate, which efficiently afforded the epoxides **15** and **16**[17] in 66% and 88% yield, respectively. Surprisingly, all attempts involving various nucleophiles (sodium azide, benzylamine, *n*-butylamine or serinol), and different experimental conditions (protic or aprotic solvent, presence or absence of a Lewis acid catalyst such as ytterbium triflate) to open the epoxide ring revealed unsuccessful, only leading to recover the starting material.

To overcome this difficulty, we turned to a more electrophilic sulfate moiety[18] (Scheme 4). So, *syn*-dihydroxylation[19] of cyclooctenes **1** and **2** by a 5 mol% aqueous solution of osmium(IV) tetroxide in acetone in the presence of *N*-methylmorpholine oxide and *tert*-butanol cleanly led to the expected *cis*-diols **17** and **18**.[17] On the first hand, acidic hydrolysis of the *O*-protective groups furnished the expected cyclooctanic carbasugars **19** and **20**. On the other hand, treatment of these diols **17** and **18** with thionyl chloride in the presence of triethylamine followed by subsequent oxidation with sodium periodate in the presence of ruthenium trichloride gave the cyclic sulfates **21** and **22**. As expected, nucleophilic opening of the cyclic sulfate moiety was efficiently carried out by sodium azide in DMF at 80 °C,[20] and was followed by acidic hydrolysis of the resulting acyclic sulfate ester to afford the respective azido-alcohol **23** and **24**, isolated as a single stereoisomer in excellent yield (≥95%).

However, it has to be pointed out that more hindered nucleophiles, such as primary amines, revealed unable to open the sulfate **21** or **22**. Next, reduction of each azido-alcohol **23** and **24** by dihydrogen in the presence of palladium black in ethyl acetate led to the corresponding amines **25** and **26**. Acidic hydrolysis of the *O*-protective groups on the cyclooctylamines **25** and **26** by aqueous trifluoroacetic acid furnished, after purification by ion-exchange chromatography, the targeted C8-glycomimetics **27** and **28** with a free amine functionality. Alternatively, to obtain analogues of voglibose, the amine function of **25** and **26** could be alkylated via reductive amination[13] with a dihydroxyacetone derivative. Thus, treatment of the amines **25** and **26** by the commercially available 2,2-dimethyl-1,3-dioxan-5-one in the presence of titanium(IV) tetra-isopropoxide followed by the cyanoborohydride reduction of the imine intermediate gave the expected *N*-alkylated derivatives **29** and **30**. Then, simultaneous acidic hydrolysis of all protective groups led to the C8-voglibose mimetics **31** and **32**.



Scheme 3. Reagents and conditions: (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (b) NaN_3 or $PhCH_2NH_2$, *n*-$BuNH_2$ or serinol in protic or aprotic solvent.



Scheme 4. Reagents and conditions: (a) OsO_4 5 mol%, NMO, acetone/*tert*-BuOH; (b) TFA/H_2O; (c) i. $SOCl_2$, Et_3N, CH_2Cl_2, ii. $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$; (d) i. NaN_3, DMF, 80 °C, ii. H_2SO_4, H_2O/THF; (e) H_2, Pd black, EtOAc; (f) i. $O{=}C(CH_2O)_2CMe_2$, $Ti(Oi\text{-}Pr)_4$, ii. $NaBH_3CN$, EtOH.

The biological activity of carbasugars **5a**, **5b**, **6a**, **6b**, **19** and **20**, and unsubstituted or *N*-substituted aminocyclitols **12**, **13**, **14**, **27**, **28**, **31** and **32** was evaluated at 1 mM concentration, as previously described,[21] towards four commercially available glycosidases: α-D-glucosidase from *Bacillus stearothermophilus*, β-D-glucosidase from almonds, α-D-mannosidase from Jack beans and α-L-fucosidase from bovine kidney. Each of these new compounds revealed a poor inhibitor of the tested enzymes (<20%). However as these structures are closely related to that of voglibose, their potential activity on other glycosidases is currently studied, and the results will be reported in due course.

In conclusion, we have developed an efficient and versatile synthetic strategy for the preparation of C8-glycomimetics. The described routes involved cyclisation by ring closing metathesis of 1,9-diene and subsequent exploitation of the synthetic potentialities of the newly created double bond, for example: either hydroboration followed by oxidation and reductive amination, or formation of a *cis*-cyclic sulfate, then introduction of an azido group by opening of the sulfate followed by reduction and eventual alkylation of the resulting amine. The spatial distribution of the hydroxyl groups can be chosen according to the D-*manno* or L-*ido* configuration of the starting bis-epoxide. Moreover, the general strategy we describe can be extended to other *N*-substituted C8-glycomimetics according to the ketone or amine involved in the final reductive amination step.

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