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Synthesis and glycosidase inhibitory activity of new penta-substituted C8-glycomimetics

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Abstract—The syntheses of new C8-carbasugars and -aminocyclitols related to miglitol and voglibose are described. The key step involves the ring closing metathesis of 1,9-dienes derived from D-mannitol. Chemical transformations of the newly created double bond of the resulting cyclooctenes involved notably hydroboration and reductive amination. The inhibitory activity of the glycomimetics so-obtained has been evaluated towards 24 commercially available glycosidases.

1. Introduction

The biological importance of oligosaccharides was first recognized for their role in metabolism and energy storage. More recently, it became clear that complex oligosaccharides also regulate a large number of biological processes. Most important are the oligosaccharides formed on the surface of cells and their role on protein and glycoprotein conformation. The cell-surface oligosaccharides are the 'words' used by cells to communicate with the outer world.[1–4] They guide their social behavior such as cell/cell interactions, cell/invader interactions, including HIV/cell penetration.[5] These oligosaccharides are conjugated with proteins (*N*-linked, *O*-linked glycoproteins), with phosphatidylinositol (GPI-anchored proteins) or with glycolipids.[5–10] Carbohydrate mimetics are potential tools to study the mechanisms of cellular interactions, the biosynthesis of glycoproteins, the catabolism of glycoconjugates,[11,12] and the mechanisms of digestions.[13,14] Inhibition of intestinal α-glucosidases can be used to treat diabetes through the lowering of blood glucose levels, and α-glucosidase inhibitors[1–3] are being marketed against type 2 (non-insulinodependent mellitus) diabetes (Fig. 1).[15–17]

The naturally occurring acarbose (**1**)[18] and voglibose (or AO-128) (**2**),[19] the synthetic piperidine derivatives such as **3** (miglitol)[20] and **4** (1-deoxynojirimycin)[21] or pyrrolidine derivatives such as **5** (nectrisine)[22,23] can have their amino moiety protonated. The corresponding ammonium ions mimick the charge of the presumed transition states or intermediates of the enzymatic glycoside hydrolyses.[21,22]

Furthermore, it has to be pointed out that carbasugars such as valienamine (**6**) and its derivative **7**[24] (Fig. 2), or polyol **8**[25] and C7-aminocyclitols **9**[26] (Fig. 2) can also present potent glycosidase inhibitory activity.

In that context, new C8-glycomimetics[27] have been targeted

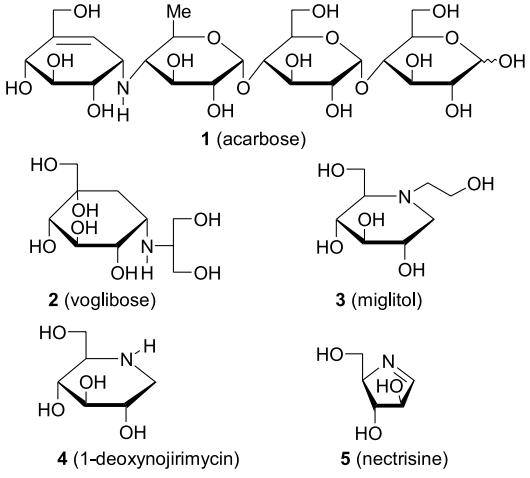

Figure 1. Examples of glycosidase inhibitors.

Keywords: Carbasugars; Aminocyclitols; Glycomimetics; Ring closing metathesis; Reductive amination; Glycosidases.
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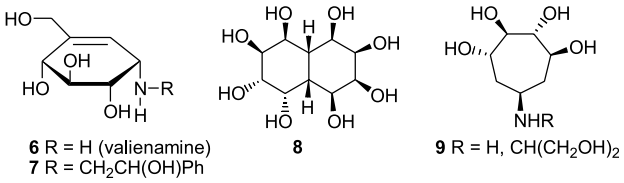


Figure 2. Examples of glycosidase inhibitors.

in order to study the effect of the enhanced flexibility and of the new spatial distribution displayed by these structures on their adaptability in the active site of the enzymes.

2. Results and discussion

Our retrosynthetic analysis (Fig. 3) involves the carbacyclisation of enantiomerically pure polyhydroxylated C_2-symmetric 1,9-dienes **13** by ring closing metathesis (RCM) leading to a cyclooctenic structure **11**.[28] The synthetic potentialities of the newly created double bond are then explored to reach pentasubstituted C8-carbasugars and their apparented aminocyclitols (**10**). Due to the different configurations available, (D-*manno* and L-*ido*) of corresponding presented bis-epoxides **14**, the approach allows access to various glycomimetics. Furthermore, the pinacolic coupling (PC) of 1,8-dialdehyde **12**, resulting from oxidative cleavage of dienes **13**, is proposed as a complementary approach towards related hexasubstitued C8-carbasugars of type **10**.

Ring closing metathesis is a widespread method[29] to reach carba- or hetero-cyclic compounds and has been largely applied to the synthesis of five to seven-membered rings. It is less used for the preparation of eight-membered ring systems,[30] perhaps due to unfavorable thermodynamic factors.[31]

The synthesis of protected polyhydroxylated cyclooctenes is outlined in Scheme 1. First, the double opening of the C_2-symmetrical 3,4-*O*-methylethylidene-L-*ido*-bis-epoxide **15**[32] by an excess of lithium divinylcyanocuprate[33] at −78 °C cleanly afforded diene **16** in 92% yield. Thanks to the stability of commercially available ruthenium Grubbs catalyst and to its potential compatibility with free hydroxyl groups, the RCM was first applied to unprotected diene-diol **16**. Thus, up to 13 mol% of ruthenium catalyst

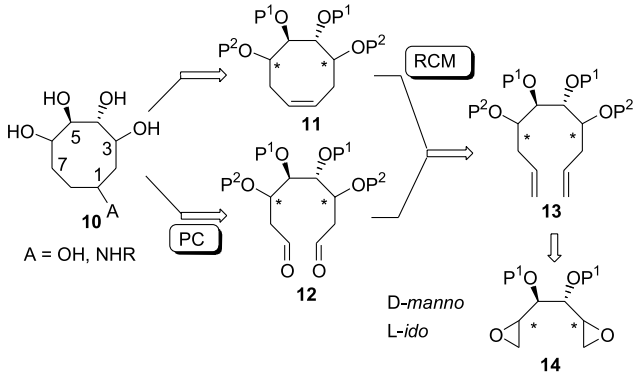
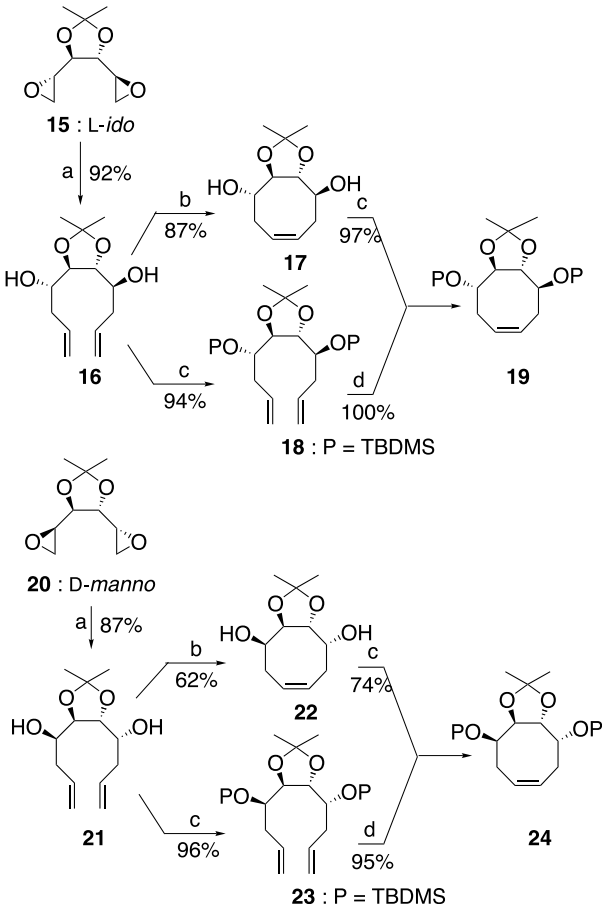


Figure 3. Retrosynthetic analysis.



Scheme 1. Reagents and conditions: (a) $(CH_2{=}CH)_2CuCNLi_2$, THF, −78 °C to 20 °C; (b) Grubbs I cat. 13 mol%, CH_2Cl_2, rt, 96 h; (c) TBDMSCl, DMF, ImH, 50 °C; (d) Grubbs I cat. 2 mol%, CH_2Cl_2, rt, 30 min.

[$(PCy_3)_2Cl_2Ru{=}CHPh$] in dichloromethane (20 °C, 96 h) gave the expected cyclooctene **17** in 87% yield. In order to avoid subsequent side reactions of the free alcohol functions, they were protected as their *O*-silylated derivative **19**. The alternative way involving double-*O*-protection prior to RCM was also carried out. In that case, the cyclisation involving the di-*O*-silylated dienetetrol **18** was realized in quantitative yield with 2 mol% of catalyst in much shorter time (20 °C, 30 min).

The same sequence of reactions was applied to the D-manno bis-epoxide **20** and afforded the protected cyclooctenetetrol **24**. However, it has to be pointed out that the route involving protection of the diol (**21**→**23**) followed by RCM (**23**→**24**) was both more efficient and easier to carry out than that involving first RCM (**21**→**22**→**24**) due to incomplete reaction.

We explored further the efficiency of RCM with diene **26** and with the alcohol protected derivative **27** (Scheme 2) resulting from opening of 3,4-di-*O*-benzyl-D-manno-bis-epoxide **25**[34] by lithium divinylcyanocuprate (30% yield)[35] and subsequent *O*-silylation. Under the same reaction conditions as above the expected cyclooctene **28** was obtained in 95% yield.