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Efficient access to azadisaccharide analogues

Christine Gravier-Pelletier, William Maton, Thomas Lecourt and Yves Le Merrer*

Université René Descartes, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 CNRS, 45, rue des Saints-Pères, 75270 Paris Cedex 06, France

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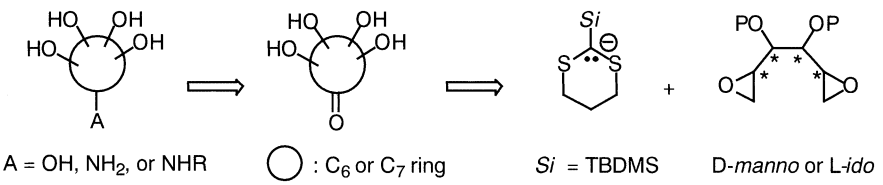
Abstract—The synthesis of various aminocyclitols as pseudo-azadisaccharide candidates for glycosidase inhibition is described. The strategy involves the reductive amination with several amines of polyhydroxycycloheptanones resulting from a tandem alkylation–cyclisation of C_2-symmetrical bis-epoxides derived from D-mannitol.

As part of an ongoing program[1,2] directed towards the design and synthesis of new glycosidases and glycosyltransferases inhibitors, our goal was to develop a short and convergent route to carbasugars and aminocyclitols. Indeed, due to protonation of the nitrogen atom at physiological pH, aminocyclitols can be considered as mimics of the positively charged transition state which is claimed to arise during these enzymatic reactions.[3] The charge can be localised either at anomeric oxygen or carbon atoms, or at the exocyclic oxygen atom, depending on the nature, α or β, of the glycosidase, thus giving rise to the rational design of potent transition state analogues as competitive inhibitors of these enzymes. Therapeutic applications of such inhibitors can be directed towards diabetes, cancer or viral infections,[4] justifying the intense synthetic efforts devoted to these challenging compounds.[5,6] Furthermore, in order to improve the selectivity of the interaction between the enzyme and the potent inhibitor, it has been shown that it is often beneficial to also mimic the aglycone part of the di- or poly-saccharide to enhance the observed inhibition; so that many current strategies deal with access to pseudo-azadisaccharides.[2,7,8]

In this context, we have been aiming at developing a new route to enantiomerically pure aminocyclitols displaying various sizes and configurations, the nitrogen atom being either substituted or not. It is noteworthy that such a structure may be exemplified by voglibose[9] or acarbose,[10] which are both already used as antidiabetics.

The retrosynthesis of the target compounds is outlined in Scheme 1 and relies on a strategy we recently described,[11] which involves a one-pot tandem alkylation–cyclisation of C_2-symmetrical bis-epoxides derived from D-mannitol.

Carbasugars or aminocyclitols can result from the reduction or the reductive amination of the corresponding polyhydroxycycloalcanones, which are first masked as their dithioketals. We have shown that by selecting appropriate protective groups for the secondary alcohol functions of the starting bis-epoxide, the carbocyclisation involving 1,4-Brook[12] rearrangement could be directed towards the major formation of enantiomerically pure dithioketals of either cyclohexanone or cycloheptanone. Thus, for P = methylethylidene, C_6 rings are mainly formed, while for P = benzyl, C_7 rings predominate whether the configuration of the bis-epoxide is D-*manno* or L-*ido* (Scheme 2). The overall yield ranges from 63 to 82%.



Scheme 1.

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

* Corresponding author. Tel.: +33(0)142862176; fax: +33(0)142868387; e-mail: yves.le-merrer@biomedicale.univ-paris5.fr

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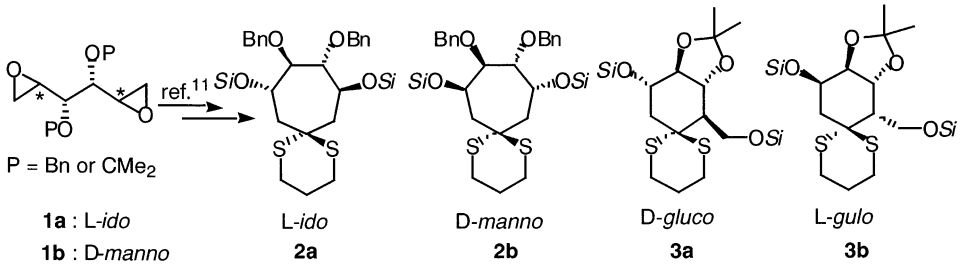


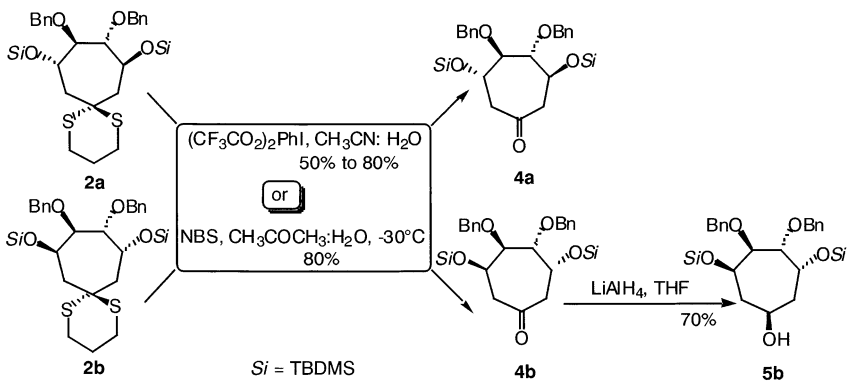
Scheme 2. Major cyclitols available from either **1a** or **1b** (Si = TBDMS).

Access to aminocyclitols requires dithioketal hydrolysis. It was first carried out on cycloheptanone **2a** or **2b** according to smooth Stork conditions[13] involving bis(trifluoro acetoxy)iodobenzene (BTI) in aqueous acetonitrile at 20°C to afford the expected cycloheptanone **4a** or **4b** in good yield (Scheme 3).[14] However, depending on the assays, the yield happened to decease to 50% in a few cases. It seems that this difficulty could be overcome by careful monitoring of the quantity of water introduced since excess of water could lead to decomposition of BTI.[15] Alternatively, this dethioketalisation could be achieved in the presence of *N*-bromosuccinimide (NBS) in aqueous acetone[16] at −30°C to give the corresponding cycloheptanone in 80% reproducible yield. Further $LiAlH_4$ reduction of the cycloheptanone **4b** cleanly afforded the expected carbasugar **5b** in 70% yield.

NBS conditions were best for allowing recovery of cyclohexanones from their dithioketals in reasonable yield. Indeed, most of the classical methods (Table 1) to complete this hydrolysis on C_6 rings failed, leading either to unreacted starting material or to degradation products.[17]

In order to limit side reactions, NBS dithioketal hydrolysis of the cyclohexane **3a** was achieved at −30°C and was followed by sodium borohydride reduction of the resulting ketone **6a** immediately after its isolation, without intermediate purification, thus affording a 82:18 mixture of the alcohols *R*-**7a**/*S*-**7a** in 80% overall yield (Scheme 4).[14] Conditions of this reaction are now being studied to improve the diastereoselectivity towards the formation of a single isomer, either *R*-**7a** or *S*-**7a**.[18]

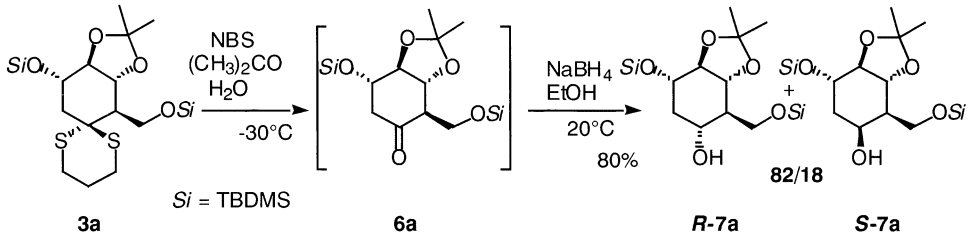
With cycloalcanones in hand, we next turned to the preparation of the targeted aminocyclitols via their reductive amination with various amines in order to reach pseudo-azadisaccharides displaying both functional and configurational diversity. The reductive amination was carried out under Mattson et al. conditions[19] involving the mild and effective titanium-(IV) isopropoxide as Lewis acid to catalyze imine



Scheme 3.

Table 1. Summary of typical assays of dithioketal hydrolysis of the cyclohexanone **3a**

Reagent	Solvent	Temperature (°C)	Result
Et_3OBF_4	CH_2Cl_2	20	Degradation
$HgCl_2$, K_2CO_3	$(CH_3)_2CO/H_2O$	Reflux	Starting material
$HgCl_2$, K_2CO_3	CH_3CN/H_2O	Reflux	Starting material
$Hg(ClO_4)_2$, K_2CO_3	THF/H_2O	20	28% of **6a**
DDQ, H_2O traces	CH_3CN	Reflux	Degradation
NBS	$(CH_3)_2CO/H_2O$	20	34% of **6a**



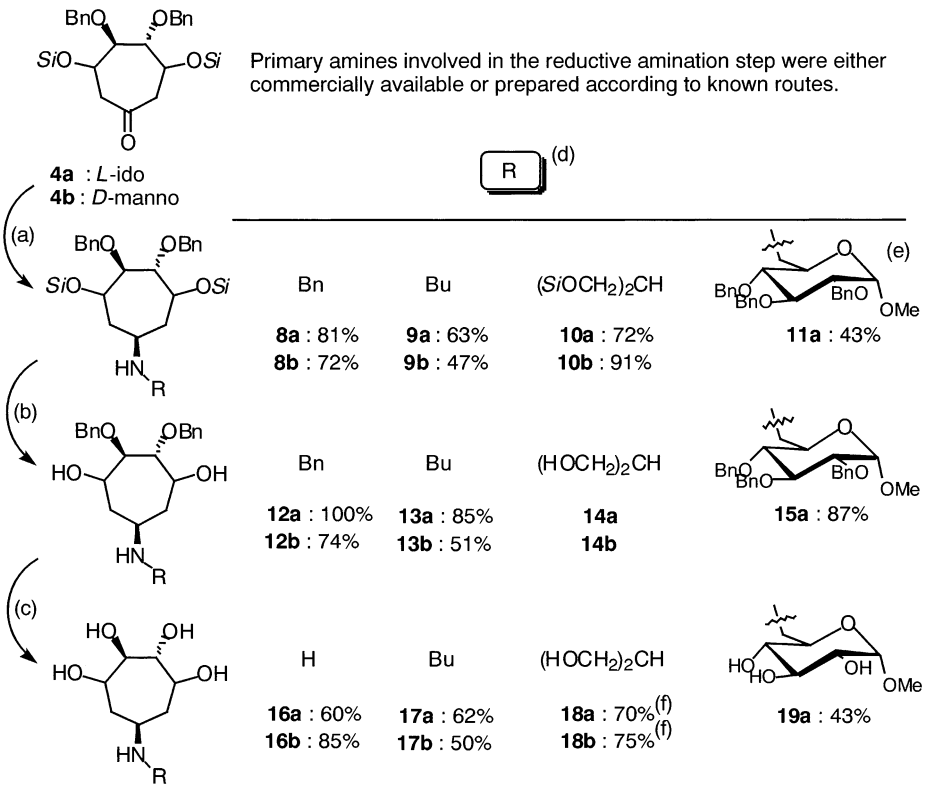
Scheme 4.

formation followed by its in situ reduction in the presence of sodium cyanoborohydride (Table 2).[14] Thus, the imine formation efficiently occurred at 20°C by addition of neat amine (benzylamine, butylamine, 1,3-di-*tert*-butyldimethylsilyloxy-2-propylamine or methyl 6-amino-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside,[20] 2 equivalents), to a mixture of the cycloheptanone **4a** or **4b** (1 equivalent) with $Ti(OiPr)_4$ (1.25 equivalent) and was followed by successive addition of absolute ethanol and $NaBH_3CN$ (4 equivalents) to afford the expected *N*-substituted aminocycloheptanol (**8**–**11**) in yields ranging from 47 to 91%.

Removal of the *tert*-butyldimethylsilyl protective groups was easily achieved in the presence of an excess of *n*-tetrabutylammonium fluoride in THF to give the corresponding alcohol (**12**–**15**). The deprotection of benzyl ethers, and *N*-benzyl amines for **12a** and **12b**, involved hydrogenolysis in the presence of palladium black in acetic acid. For the compound **15a**, this reaction was carried out by sodium in liquid ammonia. Subsequent purification by ion-exchange chromatography afforded the targeted pseudo-azadisaccharides (**16**–**19**).

In summary, various aminocyclitols were obtained in a straightforward manner via reductive amination of enantiomerically pure cycloheptanones resulting from a one-pot tandem alkylation–cyclisation of C_2-symmetrical bis-epoxides derived from D-mannitol. According to

Table 2. Summary of the various aminocyclitols obtained.[14] Yield is given for each step



(a) Cycloheptanone **4a** or **4b** respectively (1eq.), $Ti(OiPr)_4$ (1.25eq.) then neat amine RNH_2 (2eq.), 2 hours, 20°C then absolute ethanol, $NaBH_3CN$ (4eq.), 20°C, 12h. (b) $(nBu)_4NF$ excess, THF, 20°C. (c) H_2, Pd black, AcOH (except for **15a** : Na/NH_3 liquid) then purification by ion exchange chromatography (Dowex 50X8-100). (d) **a** and **b** are respectively related to *L*-ido and *D*-manno configuration. (e)The glucosamine was diluted in CH_2Cl_2 prior to its addition to the cycloheptanone. (f) Overall yield from **10a** or **10b**, respectively.

this strategy, the synthesised aminocyclitols have been *N*-substituted by several R groups: R = *n*-Bu, $(HOCH_2)_2CH$ and methyl α-D-glucoside as respectively *N*-butyl-1-deoxynojirimycin,[21] voglibose[9] and azadisaccharide analogues. Their biological activity towards various glycosidases will be evaluated and compared to that of the corresponding aminocyclitol (R = H). Access to aminocyclitol analogues from C_6 derivatives is now in progress and will be reported in due course.

Acknowledgements

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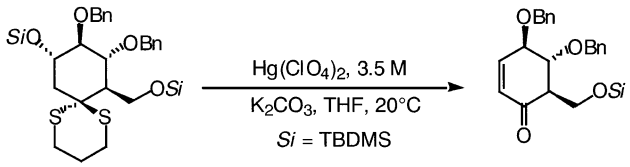
17. Instability of such compounds was emphasised by the isolation of an α,β-ethylenic ketone resulting from β-elimination of *tert*-butyldimethylsilyl ether in the following case:



18. The respective absolute configurations of *R*-**7a** and *S*-**7a** were unambiguously attributed by ^1H NMR studies. For *R*-**7a**: $J_{1,6} = 9.1$ Hz and for *S*-**7a**: $J_{1,6} < 2$ Hz.
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