Access to pyrrolidine imino sugars *via* tin(II)-mediated aldol reactions of bislactim ethers: synthesis of 2,5-dideoxy-2,5-imino-D-glucitol

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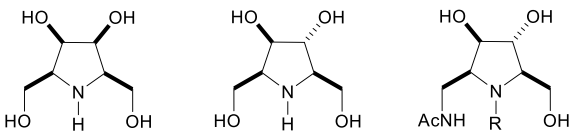
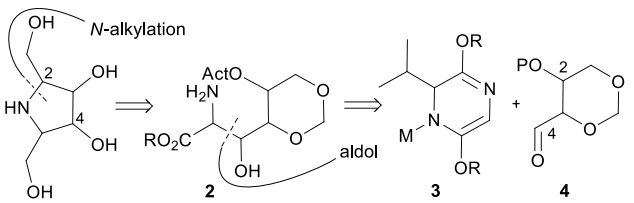
2,5-Dideoxy-2,5-imino-D-glucitol has been synthesized *via* tin(II)-mediated *anti*-selective aldol reaction of bislactim ether 5 and 2,4-ethylidene-D-erythrose derivative 6. Computed boat-like transition structures with a stabilizing hydrogen bond can account for the unexpected stereoselection.

Given the potent and specific inhibitory activity toward carbohydrate processing enzymes, polyhydroxylated piperidines and pyrrolidines have emerged in recent years as highly promising candidates for the development of new drugs against diabetes, cancer metastasis and viral infections.[1] In particular, pyrrolidine imino sugar 2,5-dideoxy-2,5-iminogalactitol (DGADP) and its C-4 epimer, 2,5-dideoxy-2,5-iminoglucitol (DGDP), recently isolated from Thai medicinal plants, are potent inhibitors of several galactosidases and glucosidases.[2] In addition, *N*-adamantanyl alkyl amide derivatives of DGDP have been found to act as pharmacological chaperones for Gaucher disease,[3a] while *N*-acetyl analogues of DGDP **1** are hexosaminidase inhibitors which may offer new therapeutic options in the treatment of osteoarthritis.[3b]

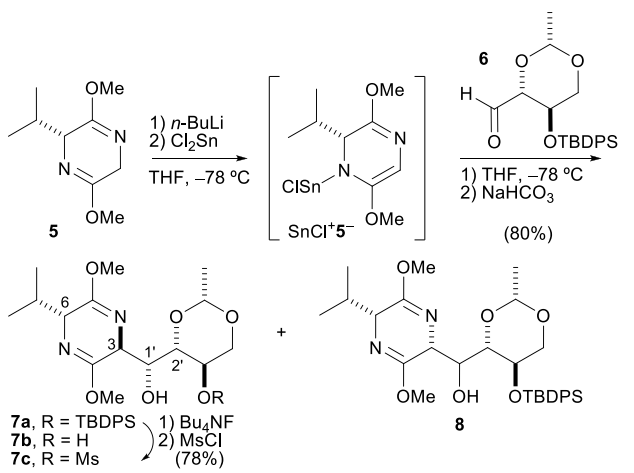


Consequently with the huge pharmacological potential of polyhydroxylated pyrrolidines,[4] significant efforts have been devoted to their synthesis. To date, DGDP have been mostly synthesized through stereoselective transformations of readily available carbohydrate precursors.[5] Alternative approaches have relied on annulation of α–amino acid derivatives,[6a] chemoenzymatic processes,[2a,6b] or asymmetric aminohydroxylations[6c]. We have recently described a general strategy for the synthesis of piperidine imino sugars, by using an aldol reaction between metalated bislactim ethers and threose or erythrose acetonides in the key-step.[7] In this communication, we introduce an extension of this methodology to the synthesis of pyrrolidine imino sugars. In adaptating the synthetic plan we recognized that amino esters **2** might be valuable intermediates since the targeted pyrrolidines would originate by cyclization *via* nucleophilic substitution of an activated hydroxyl group, followed by reduction of the carboxylic acid group (see Scheme 1).



Scheme 1

We envisaged preparing key intermediates **2** by stereocontrolled aldol additions between four-carbon building blocks and a chiral glycine equivalent. Alkylidene-tetroses like **4** were sought as appropriate precursors, delivering various configurations and being suitable functionalized at positions 2 and 4. Although commonly used in stereoselective synthesis,[8] to the best of our knowledgement, 2,4-alkylidene-threoses or erythroses had not been previously employed as aldol acceptors.[9] In addition, aldol reactions of metalated bislactim ethers **3** with matched α–alkoxyaldehydes have been reported to proceed with high levels of *syn,anti*-selectivity, which has been rationalized by invoking chair-like pericyclic transition structures with a Felkin-Anh or a Cornforth-like conformation for the aldehyde moiety.[7,11] Thus, double asymmetric induction of the 3,1´-*syn*-1´,2´-*anti* configuration was expected in the reaction of D-valine and D-erythrose derivatives **5** and **6** (see Scheme 2), which could enable the selective access to a convenient precursor of pyrrolidine imino sugar DGADP.



Scheme 2

To this end, *n*-BuLi was added to a solution of bislactim ether **5** in THF at −78 ºC, and the corresponding lithium azaenolate was allowed to react with Cl_2Sn for 1 h to produce the transmetalated azaenolate $SnCl^+\mathbf{5}^-$. Upon addition of freshly distilled aldehyde **6**,[12] reaction took place within 4 h at −78 ºC and, after quenching and aqueous workup, a crude mixture containing adducts **7a**/**8** in 12:1 ratio [13] was isolated in 80% combined yield. The separation of the components of this mixture could be achieved by flash chromatography to provide **7a** with high purity (d.e. higher than 98%) and 74% yield. Surprisingly, the configuration of the major adduct **7a** was determined as 3,1´-*anti*-1´,2´-*syn* instead of the expected 3,1´-*syn*-1´,2´-*anti* one.[14]

To gain more insight into the origins of the unexpected *anti*,*syn*-selectivity in the reaction between $SnCl^+\mathbf{5}^-$ and **6**, we have computed the competing diastereomeric transition structures (TSs) for the aldol process.[15] In agreement with the experimental outcome, most favorable TS was located in the *trans*,*anti*,*syn*-diastereomeric pathway. This TS, designated as ***tas***-BN in Figure 1, was characterized by a boat-like conformation for the pericyclic ring and a non-Anh conformation [16] for the erythrose moiety. In the *trans*,*syn*,*anti*-diastereomeric pathway, most stable TS was ***tsa***-CM, which showed chair-like and Cornforth-like conformations for the pericyclic and the erythrose moieties and was calculated 1.2 kcal/mol higher in energy than ***tas***-BN. Other competitive TSs in the *cis*-pathways were also computed higher in energy. It should be noted that in ***tas***-BN the distance between the oxygen atom at α−position of the erythrose moiety and one of the methoxy hydrogens of the bislactim ether was reduced to 2.22 Å, which indicated a hydrogen bond interaction (represented as a blue doted line in Figure 1). This interaction was not present in the competing TSs and therefore could contribute to the unexpected kinetic preference for the *trans*,*anti*,*syn*-pathway.[17]

Conversion of adduct **7a** to the targeted imino sugar was straightforward. After deprotection of silyl ether, mesylation of diol **7b** (by treatment with MsCl, Et_3N and a catalytic amount of dimethylaminopyridine in CH_2Cl_2 at 0 ºC) was completely regioselective at equatorial hydroxyl group (see Scheme 2).[18] Protection of mesylate **7c** was found necessary to achieve acceptable yields in the hydrolysis of the pyrazino moiety, as was previously reported for other bislactim ethers with free hydroxyl groups.[19] After benzylation, the selective cleavage of the bislactim ether in the presence of the ethylidene acetal took place with concomitant cyclization (see Scheme 3). In this manner, hydrolysis of **9** in acidic media gave rise to glucuronate **10** in 82% yield after removing the auxiliary D-valine by flash chromatography. Reduction of the ester group of **10** with $LiBEt_3H$ proceeded cleanly, as previously described for other pyrrolidine derivatives.[5e] Final deprotection of pyrrolidine **11**, by catalytic hydrogenation and hydrolysis of the acetal in hot HCl, followed by purification of the crude mixture by ion-exchange chromatography (Dowex, H^+ form) and reversed-phase chromatography led to DGDP in excellent yield.[20]

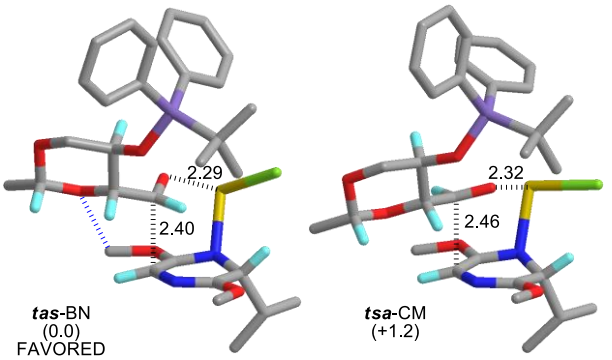
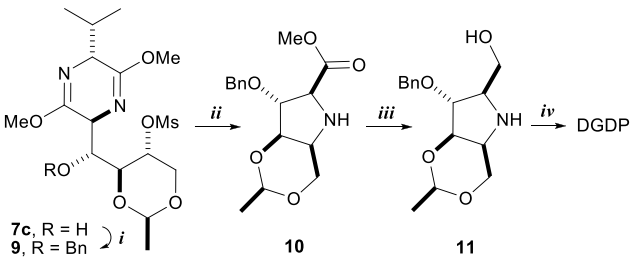


Figure 1. Chem3D representations of the most favored TSs located in the gas phase (at B3LYP/cc-pVDZ-PP level) for the reaction between $SnCl^+\mathbf{5}^-$ and **6**. Relative energies in THF (at B3LYP(SCRF)/cc-pVTZ-PP level using the PCM method) are shown in parenthesis in kcal/mol. Distances are in angstromgs. The hydrogen atoms are omitted for clarity except at chiral and reaction centers. Legend: carbon = gray, nitrogen = blue, oxygen = red, hydrogen = turquoise, tin = yellow, chlorine = green, silicon = mauve.



Scheme 3 *Reagents and conditions:* ***i***. NaH, BnBr, Bu_4NI, THF (70%). ***ii***. 0.25M HCl:MeOH 1:3 (82%). ***iii***. $LiEt_3BH$, THF, 0 ºC (90%). ***iv***. (a) 0.25M HCl:THF 1:1, H_2, Pd/C; (b) 1M HCl, Δ (96%).

In summary, with the efficient preparation of DGDP we have traced the utility of tin(II)-mediated aldol reactions between bislactim ethers and 2,4-ethylidene-tetroses for the synthesis of pyrrolidine imino sugars. Additional studies to extend this aldol-based strategy to the synthesis of other biologically active 2,5-iminohexitols are currently under progress and will be reported in due course.

Acknowledgments

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization of new compounds and computational methods, Cartesian coordinates and absolute energies for the models reported. See DOI: 10.1039/B810878A

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12 Aldehyde **6** was easily prepared from D-glucose. See: D. Crich, M. A. de la Mora and R. Cruz, *Tetrahedron*, 2002, **58**, 35–44 and reference 8.

13 The ratio between diastereoisomers was determined by integration of the baseline resolved doublets corresponding to the methyl groups of the dioxane moiety in the ^{1}H NMR spectrum of the crude mixture.

14 Evidence supporting the relative configurations of the addition products was obtained from NMR analysis and chemical correlation to DGDP (see Scheme 3). For bislactim **7a** 6-H resonance appears at 3.86 ppm, as a triplet with ^{5}J(3-H,6-H) close to 3.4 Hz, which is general of the 3,6-*trans* configuration. Conversely, for **8** the absorption corresponding to 6-H appears at 3.95 ppm, as a doublet of doublets with ^{5}J(3-H,6-H) of 5.0 Hz, which is typical of a 3,6-*cis* relationship at the bislactim ether ring. Thus, configuration of **8** must be *cis*,*syn*,*syn* or *cis*,*anti*,*anti*.

15 Geometry optimizations were performed using B3LYP proccedure with the cc-pVDZ basis set and a small-core relativistic pseudopotential (PP) for Sn. Single-point energy calculations were performed at the B3LYP/cc-pVTZ-PP level in THF solution using the PCM method (see Supplementary Information for full details). This computational methodology has performed well in providing predictions of diastereoselectivity in line with the experimental values reported for tin(II)-mediated aldol additions of Schöllkopf´s bislactim ethers and tetrose acetonides (see reference 7).

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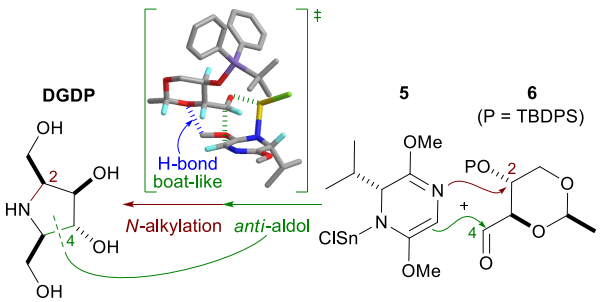
20 Optical rotation for 2,5-dideoxy-2,5-imino-D-glucitol: $[\alpha]^{22}_{D}$ + 24.2 (*c* 0.7 in H_2O), (lit.,[5d] $[\alpha]^{20}_{D}$ + 25.1 (*c* 1.5 in H_2O)). Spectral data obtained for this material were also consistent with the literature values [5] (see Supplementary Information).

Graphical Abstract



Unexpected *anti*-selective aldol reaction of metalated bislactim ether **5** and matched 2,4-ethylidene-D-erythrose derivative **6** enabled a direct and efficient access to pyrrolidine imino sugar DGDP.