Synthesis of pyrrolidine homoazasugars and 3,4-dihydroxy-5-hydroxymethylprolines using aldol additions of metalated bislactim ethers to 2,4-*O*-ethylidene-D-erythroses

Olga Blanco, Cristina Pato, María Ruiz* and Vicente Ojea*

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A strategy for the synthesis of 2,5-dideoxy-2,5-iminohexitols and 2,5-dideoxy-2,5-iminoglyconic acids is described by using diastereoselective aldol additions of metalated bislactim ethers to 2,4-*O*-ethylidene-D-erythroses and intramolecular *N*-alkylation as key steps. The nature of the metal fragment of the azaenolate and the β-alkoxy protecting group for the erythrose moiety were varied to modulate the level and the direction of the asymmetric induction in the aldol addition. The contrasting stereochemical results of the tin(II)-mediated aldol reactions have been rationalized with the aid of density functional theory calculations (B3LYP/cc-pVDZ-PP). DFT calculations indicate that boat-shaped transition structures that allow the formation of a stabilizing hydrogen bond can account for the unusual *anti*,*syn*-stereoselectivity of the aldol addition to β-protected 2,4-*O*-ethylidene-erythroses. In the addition to the "unprotected" 2,4-*O*-ethylidene-erythrose, the preference for chair-shaped transition structures in which the erythrose moiety is involved in a six-membered chelate ring is consistent with the experimentally observed *syn*,*anti*-stereochemical outcome. The preparative utility of the aldol-based approach was demonstrated by application in concise routes for the synthesis of glycosidase inhibitors 2,5-dideoxy-2,5-iminogalactitol and 2,5-dideoxy-2,5-imino-D-glucitol (DGADP and DGDP) and 3,4-dihydroxy-5-hydroxymethylprolines (2,5-dideoxy-2,5-imino-L-gulonic acid and 2,5-dideoxy-2,5-imino-L-galactonic acid) that may be useful for glycosidase and glycuronidase inhibition.

Introduction

Imino sugars are powerful and specific inhibitors of glycosidases and glycosiltransferases due to their mimicry of the transition state of the enzymatic reactions. Accordingly, they are useful tools for the study of the biological functions of oligosaccharides and constitute an excellent platform for the development of new drugs against diabetes, cancer metastasis and viral infections.[1] To date, several piperidine imino sugars have already reached the market (see Zavesca and Glyset in Fig. 1) or are undergoing clinical trials.[2] Piperidine imino acids, a particular subset of the imino sugar family, also have a similarly appealing pharmacological potential. For example, naturally occurring 2,6-dideoxy-2,6-imino-L-gulonic acid (**1**) [3] inhibits α-D-glucosidases,[4] and its diastereoisomer with L-galacto configuration **2** is a potent inhibitor of α-galactosidases.[5] Both acids can be also considered as 1,5-dideoxy-1,5-imino analogues of glycuronic acids and have been shown to act as competitive inhibitors of β-D-glucuronidases.[6] Inhibitors of human β-D-glucuronidase are clinically important since they suppress side-effects induced by the antitumor camptotecin derivative CPT-11.[7] In addition, imino acid **1** has displayed α-L-iduronidase [6] and anti-metastatic activity,[8] and imino acid **2** also proved to be active against several galacturonidases.[5]

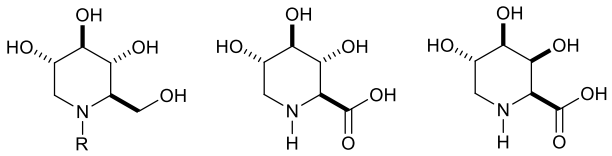


Fig. 1

Pyrrolidine imino sugars have also shown promising biological activity. Among them, those having a hydroxymethyl group or a polyhydroxylated carbon chain linked to the carbon adjacent to nitrogen, the so-called homoazasugars (aza-*C*-glycosides), have gained special importance. Homoazasugars present high stability towards chemical and enzymatic degradation, usually retain the same type of enzymatic inhibition activity of the lower homologues and, in some cases, exhibit higher selectivity and potency. In particular, 2,5-dideoxy-2,5-imino-D-glucitol (DGDP, see Fig. 2) and its C-4 epimer, 2,5-dideoxy-2,5-iminogalactitol (DGADP), are potent inhibitors of several galactosidases and glucosidases [9] and, consequently, significant efforts have been devoted to their synthesis.[10,11] Moreover, *N*-adamantanyl alkyl amide derivatives of DGDP have been found to act as pharmacological chaperones for Gaucher disease,[12a] while *N*-acetyl analogues of DGDP **3** are hexosaminidase inhibitors, which may offer new therapeutic options in the treatment of osteoarthritis.[12b] Imino acids of the pyrrolidine family are

likewise interesting. As polyhydroxylated proline derivatives, they are key constituents of natural bioactive molecules,[13] useful building blocks for the construction of peptide-mimetics with improved pharmacological profile,[14] and also have been shown as efficient organocatalysts in asymmetric synthesis.[15] Furthermore, related imino amides, like **6**, have been identified as inhibitors of glucosylceramide synthase, a Gaucher's disease target.[16] Despite their synthetic utility [17] and potential as glycosidase and glycuronidase inhibitors, routes to five-membered imino acids of the homoazasugar family (2,5-dideoxy-2,5-iminoglyconic acids), like **4** and **5**, are notably scarce in the literature. Thus, only very recently, Lundt, Wrodnigg *et al.* have reported the synthesis of 2,5-dideoxy-2,5-imino-L-gulonic acid (**4**) by ring closure of 2-amino-6-bromo-2,6-dideoxy-D-1,4-mannonolactone.[10a]

In this area, our group has developed a general methodology for the synthesis of piperidine imino sugars, which involves the aldol reaction between metalated bislactim ethers and tetrose acetonides as the key step.[18] In an early paper we have shown the flexibility of this strategy and reported its application to the synthesis of the pyrrolidine homoazasugar DGDP.[19] Herein we present a further extension of our aldol-based methodology for the synthesis of the pyrrolidine homoazasugar DGADP and also introduce its applicability for the synthesis of five-membered imino acids of the homoazasugar family. Thus, in this paper we also report novel routes to 2,5-dideoxy-2,5-imino-L-gulonic acid (**4**) and the previously unknown 2,5-dideoxy-2,5-imino-L-galactonic acid (**5**).

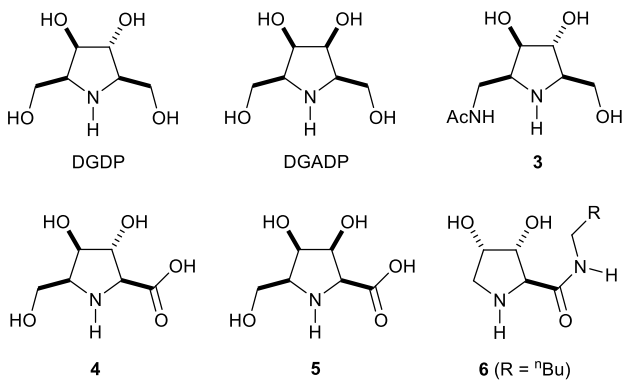
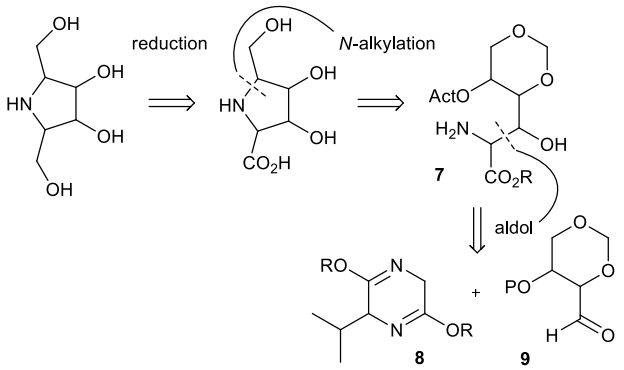


Fig. 2

In formulating the synthetic plan, we recognized that polyhydroxy amino esters **7** might be valuable key intermediates, since the targeted five-membered imino acids would originate by cyclization, *via* nucleophilic substitution of an activated hydroxyl group (see Scheme 1). In addition, the corresponding homoazasugars would be accessible by simple reduction of the carboxylic acid function. We envisaged preparing key intermediates **7** by stereocontrolled aldol additions between metalated bislactim ethers **8** and suitably protected tetrose derivatives **9**. Bislactim ethers were sought as appropriate precursors, as aldol additions of metalated bislactims to matched α-alkoxyaldehydes have been reported to proceed with high levels of *syn,anti*-selectivity,[20] which has been rationalized by invoking chair-like pericyclic transition structures [21] with Felkin-Anh or Cornforth-like conformations for the aldehyde moiety. Moreover, 2,4-alkylidene-tetroses have been commonly used in stereoselective synthesis,[22] and their reactions with different nucleophilic reagents were reported to afford moderate to high *anti*-selectivity.[23]



Scheme 1

In contrast with these precedents, we have recently found that tin(II)-mediated aldol reaction between bislactim ether (*R*)-**10** and matched 3-*O*-silylated-D-erythrose ethylidene **11a** takes place with an unusual stereochemical course and affords adduct **12a**, with 3,1´-*anti*-1´,2´-*syn* configuration, with high selectivity (see Scheme 2 and Table 1, entry 1).[24] Due to the potential effect that the tin(II) counterion and the silyl group may have on the stereoselection of the aldol addition, we were interested in evaluating the influence of different metal fragments and β-alkoxy protecting groups on the process. Thus, in this paper, we report the dependence of the level and the sense of the asymmetric induction of the aldol reaction on the nature of the metallic counterion of the azaenolate and on the β-alkoxy protecting group for the D-erythrose ethylidene derivative. To gain more insight into the origins of the stereoinduction, we have also carried out computational studies of the diastereomeric pathways, and transition-state models consistent with the stereoselectivity of the aldol additions are also put forward. Finally, we describe the efficient transformation of the addition products into the targeted homoazasugars and 2,5-dideoxy-2,5-iminoglyconic acids that may result in useful pharmacological tools for the study of glycosidase and glycuronidase inhibition.

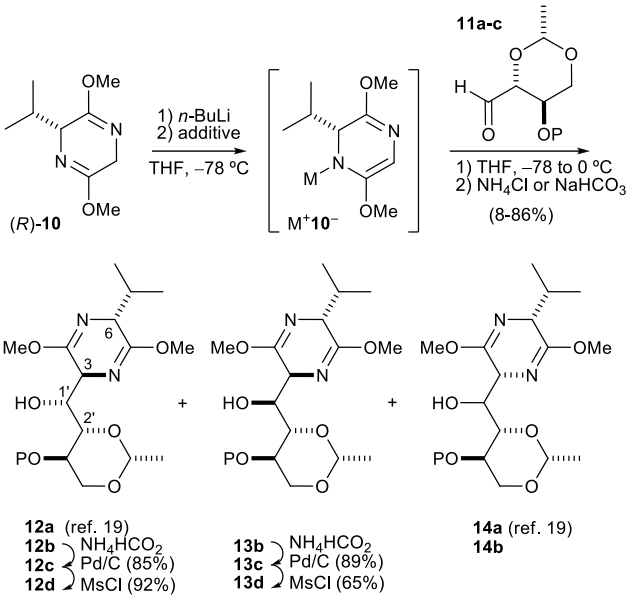
Results and discussion

1. Aldol additions of metalated bislactim ethers to 2,4-*O*-ethylidene-D-erythroses

To investigate the effect of the β-alkoxy protecting groups in the addition of metalated bislactim ethers to the erythrose ethylidenes, we decided to employ the aldehydes **11b** and **11c** (see Scheme 2). Benzyl group was selected to protect the β-oxygen atom due to its common use in synthesis design and their significant steric and electronic differences with the *terc*-butyldiphenylsilyl group that was used in our previous work. On the basis of the complete azaenolate control (and *syn*-

selectivity) reported by Schöllkopf and Kobayashi in the reactions of tin(II), zinc(II) or titanium(IV) salts of bislactim ethers with either matched or mismatched polyhydroxylated aldehydes,[20b,e] we decided to examine the behaviour of the corresponding metalated azaenolates M^+**10**$^-$ as the aldol counterparts of the erythrose derivatives.

Consequently, 3-*O*-benzyl-2,4-*O*-ethylidene-D-erythrose was readily obtained from D-glucose, following the reported procedure.[25] The benzylated aldehyde **11b** underwent stereoselective aldol additions of metalated azaenolates M^+**10**$^-$, in an analogous fashion to that previously reported for the 3-*O*-*tert*-butyldiphenylsilyl derivative **11a**. Thus, slow addition of *n*-BuLi to a solution of bislactim ether (*R*)-**10** in THF at −78 ºC was followed 1 h later by the addition of freshly distilled benzylated aldehyde **11b**. Reaction took place within 4 h, and after quenching with NH_4Cl, aqueous workup, and removal of the excess of (*R*)–**10** by chromatography,[26] a mixture containing adducts 3,6-*trans*-3,1´-*anti*-1´,2´-*syn* **12b**, 3,6-*trans*-3,1´-*syn*-1´,2´-*anti* **13b** and a 3,6-*cis* diastereoisomer **14b** was isolated in 75% combined yield. Integration of the pairs of doublets corresponding to the isopropyl groups in the ^{1}H NMR spectrum of this mixture revealed a 50:37:13 ratio between adducts **12b**/**13b**/**14b** (see Table 1, entry 2). The yield and the stereoselectivity of this aldol addition could be increased by using the tin(II) azaenolate, as previously reported for other aldol reactions with bislactim ethers.[18a,20b] To this end, the lithium azaenolate was allowed to react with $SnCl_2$ for 1 h to produce the transmetalated azaenolate $SnCl^+$**10**$^-$, prior to the addition of the aldehyde **11b**. Reaction of the tin(II) azaenolate was also complete within 4 h at −78 ºC and, after quenching with $NaHCO_3$, aqueous workup, and removal of the excess of (*R*)-**10**, led to a mixture of adducts **12b**/**13b** in a 72:28 ratio with 86% yield (see entry 3). Attempting to further improve the diastereoselectivity of the process we also performed the reaction of $SnCl^+$**10** and **11b** in the presence of an excess of $SnCl_2$,[27] but in this conditions the diastereomeric ratio between **12b**/**13b** was almost unchanged and the yield was lower (see entry 4). It should be noticed that adducts **12a,b**, with an unusual *anti*,*syn*-configuration, were obtained as the major products in the additions of the tin(II) azaenolate $SnCl^+$**10**$^-$ to either the silylated or the benzylated erythrose derivatives **11a** and **11b**. Nevertheless, the lower steric requirement and the different electronic nature of the benzyl group in **11b** with respect to the *tert*-butyldiphenylsilyl one in **11a** led to an increased *trans*-selectivity and a markedly reduced *anti*,*syn*-stereoselection in the reaction with $SnCl^+$**10**$^-$.



Scheme 2. Legend: **a**, P = TBDPS; **b**, P = Bn; **c**, P = H; **d**, P = Ms.

Prompted by the moderate stereoselectivity achieved in the reaction of $SnCl^+$**10**$^-$ and the benzylated aldehyde **11b**, we tested the addition process in the presence of other metallic counterions. Thus, we prepared the zinc(II) and the titanium(IV) azaenolates from Li^+**10**$^-$ and $ZnCl_2$ or $Ti(O^iPr)_2Cl_2$ (in THF at −78ºC for 1 h), prior to the addition of **11b**. Switching the metal of the azaenolate from lithium or tin(II) to zinc(II) or titanium(IV) changed the stereochemical outcome of the process, and thus, additions to the benzylated aldehyde took place with moderate *syn*,*anti*-selectivity in both cases. In this manner, by using $Ti(O^iPr)_2Cl^+$**10**$^-$, the reaction with **11b** was also complete under the standard conditions (4 h at −78 ºC) and furnished a mixture of adducts **12b**/**13b**/**14b** in a 10:66:24 ratio, with 81% yield (see Table 1, entry 5). Neither the selectivity nor the yield could be significantly changed when this reaction was performed with a larger excess of $Ti(O^iPr)_2Cl_2$ (see entry 6). In a different manner, the reaction of the zinc(II) azaenolate resulted in a very low conversion to products, which could not be increased with longer reaction times or higher temperatures (12 h at 0 ºC). Thus, by using $ZnCl^+$**10**$^-$, the reaction with **11b** gave a mixture of adducts **12b**/**13b** in a 36:64 ratio that was isolated in 8% yield (see entry 7). Finally, all the mixtures of the addition products could be separated by flash chromatography, and the benzylated adducts **12b** and **13b** were isolated as single diastereoisomers in yields up to 62% and 53%, respectively.

Table 1. Aldol additions of M^+10^- to D-erythrose ethylidenes 11a-c

entry	D-erythrose ethylidene (P)	(*R*)-**10** equiv	additive (equiv)	yield (%)[a]	ratio [b] **12/13/14**
1	**11a** (TBDPS)	1.2	$SnCl_2$ (1.5)	80 [c]	92:–:08
2	**11b** (Bn)	1.5	–	75 [d]	50:37:13
3	**11b** (Bn)	1.5	$SnCl_2$ (1.9)	86 [d]	72:28:–
4	**11b** (Bn)	1.5	$SnCl_2$ (3.8)	73 [d]	69:31:–
5	**11b** (Bn)	1.5	$Ti(O^iPr)_2Cl_2$ (1.9)	81 [d]	10:66:24
6	**11b** (Bn)	1.5	$Ti(O^iPr)_2Cl_2$ (3.8)	83 [d]	10:65:25
7	**11b** (Bn)	1.5	$ZnCl_2$ (1.9)	8 [d]	36:64:–
8	**11c** (H)	3.2	$SnCl_2$ (3.8)	88 [e]	06:94:–

[a] Isolated yield of mixtures of diastereomeric adducts, after flash chromatography. [b] Determined by integration of the ^{1}H NMR spectra of the crude mixtures. [c] Data obtained from reference 19. [d] Reaction conducted at −78 ºC in THF. [e] Reaction conducted from −78 to 0 ºC in THF.

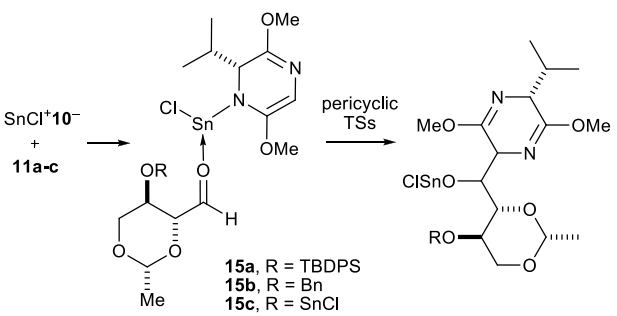
To further explore the effect of the β-protecting group on the stereochemical outcome of the aldol addition, 2,4-*O*-ethylidene-D-erythrose (**11c**),[22] with an "unprotected" hydroxyl group, was found attractive. As was previously found for the azaenolate additions to erythrose acetonides with an "unprotected" γ-hydroxyl group,[18a,b] we reasoned that an initial deprotonation of **11c** by the azaenolate M^+**10**$^-$ would lead to an oxyanion at β-position, which should be able to coordinate with the metal cation to form a temporary ring that could enhance 1´,2´-*anti*-selectivity in the subsequent aldol addition. To this end, aldehyde **11c** was added to a solution of 3.8 equiv of $SnCl^+$**10**$^-$ at −78 ºC. As the addition was not observed at this temperature, the reaction mixture was gradually warmed to 0 ºC. Reaction was completed 4 h later, and after quenching with $NaHCO_3$, aqueous work-up and removal of the excess of (*R*)-**10** by chromatography, a mixture of adducts **12c**/**13c** was obtained in 88% yield. Integration of the ^{1}H NMR of this mixture revealed a 6:94 ratio between adducts **12c** and **13c** (see Table 1, entry 8). Thus, with the use of the matched "unprotected" erythrose ethylidene, addition of the tin(II) azaenolate proceeded in the expected way, with remarkable 3,6-*trans*-3,1´-*syn*-1´,2´-*anti*-stereoselection. In this manner, the major adduct **13c** could be obtained with high purity (d.e higher than 98%) and 83% yield after purification by flash chromatography.

Evidence supporting the relative configurations of the addition products was obtained from NMR analysis and chemical correlation. For the 3,6-*trans* diastereoisomers (**12b,c** and **13b,c**) the H-6 resonance appears between 3.86 and 4.08 ppm, as a triplet with ^5J(H-3,H-6) close to 3.5 Hz, which is general of the *trans* relationship of substituents at the bislactim ethers. Conversely, the ^{1}H NMR spectrum of adduct **14b** shows the absorption corresponding to H-6 at 3.97 ppm, as a doublet of doublets with a ^5J(H-3,H-6) of 6.0 Hz, which is typical of a 3,6-*cis* relationship at the bislactim ethers.[28] Furthermore, the configurations of the major adducts were unambiguously confirmed through their conversion into known pyrrolidine alkaloids. Thus, adducts **12b,c** were transformed into DGDP and adducts **13b,c** were used in the preparation of DGADP, as will be described below (see Schemes 2, 4 and 5).

In summary, the experimental results obtained in the additions of metalated bislactim ethers to erythrose ethylidenes indicate that the level and the direction of the stereoinduction is markedly dependent on the presence of a free or a protected β-hydroxyl group. With the use of tin(II) azaenolates, addition to the "unprotected" erythrose ethylidenes takes place with high *syn,anti*-stereoselection, while additions to the β-protected erythrose derivatives results in an unusual *anti,syn*-stereoselectivity. Finally, this unusual stereochemical result was found to be characteristic for the reactions with lithium and tin(II) azaenolates, and could be reverted to the expected one by switching the metal fragment to titanium(IV).

2. Models for diastereoselective aldol additions of tin(II) azaenolates of bislactim ethers to erythrose ethylidenes.

We have studied the kinetically controlled tin(II)-mediated aldol additions of bislactim ethers to glyceraldehyde and erythrose acetonides by computational methods, and reported that these reactions proceed by the exothermic formation of an intermediate complex which subsequently reorganizes to the diastereomeric aldolates in the rate-determining step, through competitive six-membered, pericyclic transitions structures (TSs). We analyze herein the extension of this model to the reactions of $SnCl^+$**10**$^-$ with "unprotected" and benzylated erythrose ethylidenes **11b** and **11c** (see Scheme 3) and show that DFT calculations provide some insight to rationalize the contrasting stereochemical results. Since these reactions are performed under conditions of kinetic control, the analysis can be performed from comparison of the competing TSs for the reorganization step, in which the new stereocenters are formed. To this end, geometry optimizations were performed using B3LYP procedure 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 Computational methods and ESI for further details). We reported in early contributions that this computational methodology has performed well in providing predictions of diastereoselectivity that are in line with the experimental values encountered in the tin(II)-mediated aldol additions of Schöllkopf´s bislactim ethers.[18a,19]



Scheme 3.

We first analyzed the reaction of $SnCl^{+}$**10**$^{-}$ and the benzylated erythrose ethylidene **11b**. Pericyclic TSs connecting the intermediate complex **15b** to the corresponding aldolates with either *cis*,*anti*,*anti*, *cis*,*syn*,*syn*, *trans*,*anti*,*syn* or *trans*,*syn*,*anti* configuration were grouped into four diastereomeric pathways designated as **caa**, **css**, **tas** and **tsa**, respectively. In each diastereomeric pathway, different geometries were constructed and subjected to optimization, considering (1) boat-like and chair-like conformations for the pericyclic ring [29] (denoted "B" and "C", respectively), (2) Felkin-Anh,[30] modified-Cornforth,[31] and non-Anh [32] conformations for the erythrose moiety (denoted "F", "M" and "N", respectively, see Fig. S2 of the ESI), and (3) *R* and *S* configurations for the tetrahedral tin(II) cation. Most stable diastereomeric TSs located for the reorganization of the benzylated complex **15b** were analogous to those previously computed from the silylated intermediate **15a**.[19] In agreement with the experimental result, the *trans*,*anti*,*syn*-diastereomeric pathway offered the lowest energy profile for the reaction between $SnCl^{+}$**10**$^{-}$ and **11b**. The most favourable TS, designated as **tas**-BN**b,** was characterized by a boat-like conformation for the pericyclic ring and a non-Anh conformation for the erythrose moiety. In the *trans*,*syn*,*anti*-diastereomeric pathway, the most stable TS was **tsa**-CM**b**, which showed chair-like and Cornforth-like conformations for the pericyclic ring and the erythrose moiety, respectively, and was calculated to be 0.6 kcal mol^{-1} higher in energy than **tas**-BN**b** (see Fig. 3). Other competitive TSs in the *cis*-pathways were also calculated higher in energy (see Fig. S3 of the ESI). In **tas**-BN**b**, the distance between the oxygen atom at α-position of the erythrose moiety and one of the methoxy hydrogen atoms of the bislactim ether was 2.26 Å, indicating the presence of a hydrogen bond interaction (represented as a doted line in Fig. 3). The magnitude of this interaction was assessed by natural bond order (NBO) analysis of the optimized structure. Thus, in **tas**-BN**b,** the energy associated with oxygen lone pair donation into the C-H σ* is 1.8 kcal mol^{-1}. This interaction was not present in the competing TSs, and therefore could contribute to the unusual preference for the *trans*,*anti*,*syn*-pathway.

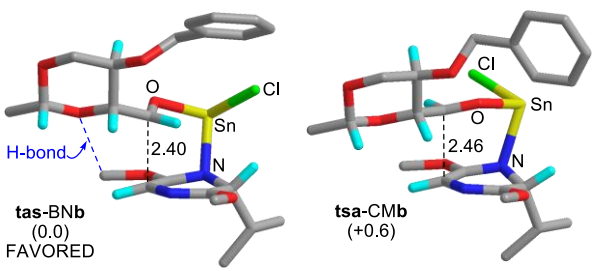


Fig. 3. Chem3D representations of the most favoured TSs located in the gas phase (at B3LYP/cc-pVDZ-PP level) for the reaction between azaenolate $SnCl^{+}$**10**$^{-}$ and benzylated erythrose ethylidene **11b**. Relative energies in THF (at B3LYP(SCRF)/cc-pVTZ-PP level using the PCM method) are shown in parenthesis in kcal mol^{-1}. Distances are in angstroms. The hydrogen atoms are omitted for clarity except at chiral and reaction centers.

We next studied the reaction of $SnCl^{+}$**10**$^{-}$ and the "unprotected" erythrose ethylidene **11c**. Most stable TS located in the rearrangement of the intermediate complex **15c** was found in the *trans*,*syn*,*anti*-diastereomeric pathway, also in agreement with the experimental result. This TS was designated as **tsa**-CM**c**, and was characterized by the presence of two pseudotetrahedral, tricoordinated tin(II) cations, a chair-like conformation for the pericyclic ring, and a Cornforth-like for the erythrose moiety, which was also involved in a six-membered chelate ring (see Fig. 4). Thus, in **tsa**-CM**c**, the carbonyl oxygen acts as a bidentate ligand, which binds to the tin(II) cation of the azaenolate and also to the tin(II) cation of the erythrose moiety. Most stable TS in the *trans*,*anti*,*syn*-pathway was **tas**-BN**c**, which showed a 6,8 ring system, boat-like conformation for the pericyclic ring and non-Anh conformation for the erythrose moiety. The additional eight-membered ring in **tas**-BN**c** originates from the interaction of the chlorine of the tin(II) azaenolate with the tin(II) cation of the erythrose moiety. Although **tas**-BN**c** showed a hydrogen bond interaction between the oxygen atom at α-position of the erythrose moiety and one of the methoxy hydrogens of the bislactim ether, it was calculated 4.4 kcal mol^{-1} higher in energy than **tsa**-CM**c**. Other competitive TSs in the *cis*-pathways were also computed higher in energy (see Fig. S4 in the ESI).

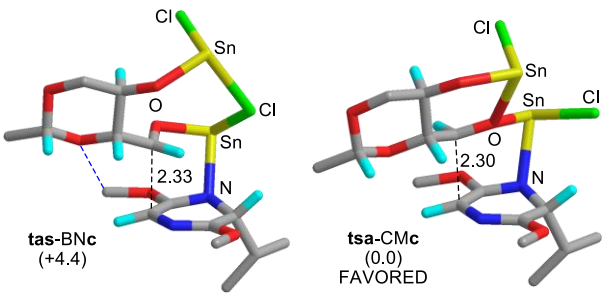


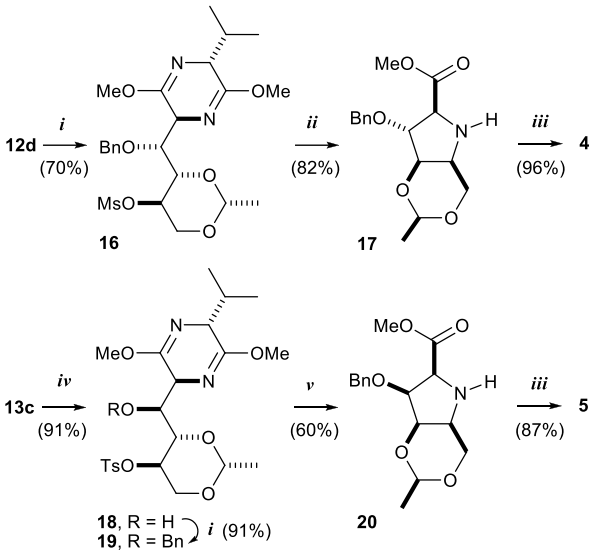
Fig. 4. Chem3D representations of the most favoured TSs located in the gas phase (at B3LYP/cc-pVDZ-PP level) for the reaction between azaenolate $SnCl^{+}$**10**$^{-}$ and "unprotected" erythrose ethylidene **11c**. Relative energies in THF (at B3LYP(SCRF)/cc-pVTZ-PP level using the PCM method) are shown in parenthesis in kcal mol^{-1}. Distances are in angstroms. The hydrogen atoms are omitted for clarity except at chiral and reaction centers.

In summary, the computational models reproduce the sense and degree of stereoselection in the reactions of $SnCl^{+}$**10**$^{-}$ with the erythrose ethylidenes **11a-c**. When the β-oxygen atom of the aldehyde is protected, *trans*,*anti*,*syn* TSs were favoured over the *trans*,*syn*,*anti*-counterparts, and the calculated energy gap between the competitive TSs was greater for the silylated derivatives (1.2 kcal mol^{-1}, see ref. 19) than for the benzylated ones (0.6 kcal mol^{-1}, see Fig. 3) in agreement with the experimentally observed ratios (see Table 1). Calculations indicate that the unusual *anti*,*syn*-selectivity in the aldol additions to the β-protected erythrose ethylidenes originate from the kinetic preference for boat-shaped TSs in which a stabilizing hydrogen-bond exist between the α-oxygen atom of the erythrose and an alkoxy hydrogen of the bislactim ether. Conversely, the enhanced *syn*,*anti*-

stereoselectivity in the addition of the tin(II) azaenolate to "unprotected" erythrose ethylidene can be explained in terms of the preference for chair-shaped TSs in which the erythrose moiety is involved in a six-membered chelate ring. Thus, in this case, DFT calculations indicate that chelation may play a key role in both activating the "unprotected" erythrose ethylidene towards the aldol addition and also directing facial selectivity.

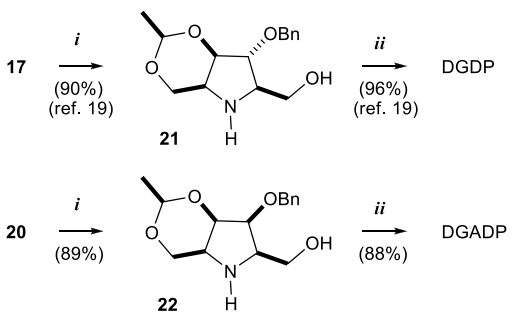
3. Transformation of aldol adducts into proline derivatives and pyrrolidine homoazasugars.

Conversion of the aldol adducts **12c** and **13c** into the targeted polyhydroxylated proline derivatives required, in addition to the removal of the chiral auxiliary, a selective activation of the hydroxyl group at C-3' that would enable the cyclization by intramolecular *N*-alkylation. To this end, additional amounts of the required diols were obtained by catalytic hydrogenation of the benzylated adducts **12b** and **13b**. Thus, heating of **12b** or **13b** with ammonium formate and palladium catalyst in MeOH furnished **12c** and **13c** in high yield (see Scheme 2). By following our recently reported methodology,[19] diols **12c** and **13c** were efficiently transformed into gulonate **17** and galactonate **20**, respectively, as depicted in Schemes 2 and 4. In this manner, treatment of diol **12c** with MsCl, Et_3N and a catalytic amount of dimethylaminopyridine in CH_2Cl_2 at 0 ºC led to the regioselective mesylation of the equatorial hydroxyl group at position 3´, and afforded the mesylate **12d** in good yield.[33] Conversely treatment of diol **13c** in the same conditions gave rise to a mixture of mesylate **13d** along with the corresponding dimesylated derivative, in a 3:1 ratio and 88% combined yield (see Scheme 2). Nevertheless, tosylation of **13c** by treatment with TsCl, Ag_2O and a catalytic amount of KI in toluene at rt was completely regioselective at equatorial hydroxyl group and gave **18** in 91% yield (see Scheme 4). As was previously observed for other bislactim ether derivatives with free hydroxyl groups, protection of mesylate **12d** and tosylate **18** was necessary to achieve acceptable yields in the hydrolysis of the bislactim ethers. In this way, reaction of **12d** and **18** with sodium hydride and benzyl bromide in the presence of a catalytic amount of tetrabutylammonium iodide led to the corresponding benzyl ethers **16** and **19** in good yields. Selective hydrolysis of the bislactim ether ring in the presence of the ethylidene acetal was achieved on the benzyl ethers **16** and **19** with 0.25 M HCl in MeOH at room temperature. Under these conditions, cyclization of the amino mesylate intermediate to afford the corresponding gulonate **17** was observed. In the other hand, complete cyclization of the corresponding amino tosylate intermediate to galactonate **20** required heating in DMSO, in the presence of Et_3N as auxiliary base. Finally, deprotection of **17** and **20** by catalytic hydrogenation and hydrolysis in hydrochloric acid, followed by purification by ion-exchange and reversed-phase chromatography, furnished 2,5-dideoxy-2,5-imino-L-gulonic acid (**4**) and 2,5-dideoxy-2,5-imino-L-galactonic acid (**5**) in high yields.



Scheme 4 *Reagents and conditions:* ***i.*** NaH, BnBr, Bu_4NI, THF. ***ii.*** 0.25M HCl/MeOH 1:3, rt. ***iii.*** (a) 0.25M HCl/THF 1:1, H_2, Pd/C, rt; (b) 1M HCl, Δ. ***iv.*** TsCl, Ag_2O, KI, toluene, rt. ***v.*** (a) 0.25M HCl/MeOH 1:3, rt; (b) DMSO, Et_3N, Δ.

Pyrrolidine homoazasugars DGADP and DGDP were readily accessible from the gulonate **17** and galactonate **20**, respectively, as depicted in Scheme 5. Reduction of the ester group in **17** and **20** by treatment with lithium triethylborohydride proceeded cleanly, and gave the protected homoazasugars **21** and **22** in excellent yields. Thus, under the conditions employed for the deprotection of the prolinates, **21** and **22** gave rise to DGDP and DGADP, respectively, in high yields after ion-exchange and reversed-phase chromatography. Specific rotations and spectral data obtained for imino acid **4**, DGDP and DGADP were consistent with the literature values.[10,11]



Scheme 5 *Reagents and conditions:* ***i.*** $LiEt_3BH$, THF, 0 ºC. ***ii.*** (a) 0.25M HCl/THF 1:1, H_2, Pd/C, rt; (b) 1M HCl, Δ.

Conclusions

Stereoselective aldol additions of bislactim ethers to matched 2,4-*O*-ethylidene-erythroses coupled with an intramolecular *N*-alkylation step gave an easy access to the synthesis of biologically active homoazasugars (DGADP and DGDP) and 3,4-dihydroxy-5-hydroxymethylprolines **4** and **5** with potential glycuronidase inhibition activity. It has been shown that the stereochemical outcome of these aldol additions can be modulated (1) by varying the metal fragment of the

azaenolate or (2) with the presence of a free or a protected β-hydroxyl group at the erythrose ethylidene. An additional interesting feature of the described methodology lays in its inherent flexibility, since a variety of pyrrolidine homoazasugars and 2,5-iminoglyconic acids could become accessible by simply altering the stereochemistry or the chain length in the starting aldehyde. The combined experimental/theoretical investigations of the aldol additions of metalated bislactim ethers to matched and mismatched 2,4-*O*-ethylidene-threoses and their adaptation to the synthesis of biologically active compounds are currently underway.

Experimental

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Reagents and solvents were purchased and used without further purification unless otherwise stated. $Ti(OiPr)_2Cl_2$ was prepared in situ by reaction of equimolecular amounts of $TiCl_4$ and $Ti(OiPr)_4$ in THF at room temperature.[34] THF was distilled from sodium/benzophenone, CH_2Cl_2 was distilled from calcium hydride and toluene and Et_3N were distilled from sodium. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent and cerium sulfate/ammonium molybdate in 10% sulfuric acid or ninhydrin in a 3% HOAc/*n*-BuOH solution as developing agents. E. Merck Silica gel and RP-18 (both 230-400 mesh) were used for liquid chromatography separations and Dowex 50W-X8 resin (H^+ form, 100-200 mesh) was used for ion-exchange chromatography. Melting points, determined with Bibby SM3P apparatus, are uncorrected. IR spectra were recorded on a Bruker Vector 22 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE spectrometers (300 MHz or 500 MHz). Coupling constants were measured in Hz. Chemical shifts were given in δ (ppm) relative to internal $CDCl_3$ (δ 7.27), to HOD in D_2O (δ 4.79) or to Me_4Si in MeOD (δ 0.00) for ^1H, relative to internal $CDCl_3$ (δ 77.0) for ^{13}C. ^1H or ^{13}C assignments were made on the basis of NOESY, COSY, HSQC and HMBC experiments. FABMS spectra were recorded on a Thermo Finnigan MAT95XP spectrometer using thioglycerol as a matrix. Optical rotations were taken at the Na_D-line using a Jasco DIP-1000 polarimeter. $[a]_D$ Values are given in units 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed at Servizos Xerais de Apoio á Investigación of Universidade da Coruña.

Synthetic intermediates

3-[3-Benzyloxy-2,4-ethylidenedioxybutyl-1-hydroxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (12b and 13b)

A solution of *n*-BuLi (2.5 M in hexane, 0,4 mL, 1.0 mmol) was added to a stirred solution of Schöllkopf´s bislactim ether **10** (176 mg, 0.96 mmol) in THF (6 mL) at −78 °C and the mixture was stirred for 1 h. Then, a 0.5 M solution of the additive ($SnCl_2$, $Ti(O^iPr)_2Cl_2$ or $ZnCl_2$) in THF (1.9 or 3.8 equiv) was added dropwise. The mixture was stirred for 1 h, and a solution of freshly distilled aldehyde **11b** (150 mg, 0.63 mmol) in THF (1 mL) was added dropwise. After being stirred at −78 °C for 4 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution. The crude reaction mixture was warmed to rt. The solids were removed by filtration and the filtrate was concentrated in *vacuo*. The resulting material was diluted with water and extracted with ether. The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 1:6) to yield the corresponding addition products **12b** and **13b**.

(3*S*,6*R*,1´*R*,2´S,3´*R*)-3-[3-Benzyloxy-2,4-ethylidenedioxybutyl-1-hydroxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (**12b**): colorless oil; *Rf* = 0.45 (silica gel, EtOAc/hexanes 1:3); $[\alpha]^{24}_D$ +13.5 (*c* 0.6 in CH_2Cl_2); (Found: C, 62.93; H, 7.69; N, 6.58. Calc. for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66%); ν_{max}/cm^{-1} 2943, 1695, 1239, 1094; δ_H (300 MHz, $CDCl_3$) 0.70 (3H, d, *J* = 6.9), 1.07 (3H, d, *J* = 6.9), 1.23 (3H, d, *J* = 5.0), 2.29 (1H, dsp, *J* = 6.8 and 3.4), 3.38 (1H, t, *J* = 10.5), 3.47 (1H, d, *J* = 9.6), 3.51 (1H, dd, *J* = 9.3 and 1.2), 3.70 (3H, s), 3.74 (3H, s), 3.73-3.81 (1H, m), 3.87 (1H, t, *J* = 3.4), 4.10 (1H, dd, *J* = 10.7 and 5.2), 4.18 (1H, ddd, *J* = 9.5, 6.5 and 1.3), 4.37 (1H, dd, *J* = 6.5 and 3.8), 4.56 (1H, q, *J* = 5.0), 4.58 (1H, AB system, *J* =11.6), 4.68 (1H, AB system, *J* =11.6), 7.29–7.38 (5H, m), δ_C (75 MHz, $CDCl_3$) 16.5 (CH_3), 19.1 (CH_3), 20.4 (CH_3), 31.4 (CH), 52.5 (CH_3), 52.6 (CH_3), 57.7 (CH), 61.1 (CH), 68.2 (CH), 68.5 (CH), 69.1 (CH_2), 72.8 (CH_2), 79.7 (CH), 98.4 (CH), 127.7 (CH), 128.4 (CH), 138.2 (C), 161.8 (C), 163.8 (C); FABMS (thioglycerol) *m/z* 421 (MH^+, 100). HRMS 421.2334. $C_{22}H_{33}N_2O_6$ requires 421.2339.

(3*S*,6*R*,1´*S*,2´S,3´*R*)-3-[3-Benzyloxy-2,4-ethylidenedioxybutyl-1-hydroxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (**13b**): colorless oil; *Rf* = 0.55 (silica gel, EtOAc/hexanes 1:3); $[\alpha]^{24}_D$ −37.5 (*c* 1.0 in CH_2Cl_2); (Found: C, 62.77; H, 7.71; N, 6.87. Calc. for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.67; N, 6.66%); ν_{max}/cm^{-1} 2943, 1697, 1236, 1091; δ_H (300 MHz, $CDCl_3$) 0.72 (3H, d, *J* = 6.9), 1.05 (3H, d, *J* = 6.9), 1.33 (3H, d, *J* = 5.0), 2.26 (1H, dsp, *J* = 6.8 and 3.5), 3.10 (1H, d, *J* = 5.8), 3.48 (1H, t, *J* = 10.1), 3.70 (3H, s), 3.72-3.78 (1H, m), 3.76 (3H, s), 3.87-3.93 (1H, m), 4.00 (1H, t, *J* = 3.5), 4.22-4.28 (3H, m), 4.57 (1H, AB system, *J* = 11.4), 4.61 (1H, AB system, *J* = 11.4), 4.72 (1H, q, *J* = 5.0), 7.29–7.38 (5H, m); δ_C (75 MHz, $CDCl_3$) 16.8 (CH_3), 19.1 (CH_3), 20.5 (CH_3), 31.7 (CH), 52.4 (CH_3), 52.6 (CH_3), 55.6 (CH), 60.9 (CH), 68.4 (CH_2), 72.0 (CH_2), 73.4 (CH), 74.7 (CH_2), 76.1 (CH), 98.8 (CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 137.1 (C), 162.0 (C), 165.5 (C); FABMS (thioglycerol) *m/z* 421 (MH^+, 100).

3-[2,4-Ethylidenedioxybutyl-1,3-dihydroxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (12c and 13c)

A solution of *n*-BuLi (2.5 M in hexane, 5.5 mL, 13.75 mmol) was added to a stirred solution of Schöllkopf´s bislactim ether **10** (2.42 g, 13.14 mmol) in THF (60 mL) at −78 °C and the mixture was stirred for 1 h. Then, a 0.5 M solution of $SnCl_2$ (2.96 g, 15.62 mmol) in THF was added dropwise. The mixture was stirred for 1 h, and a solution of aldehyde **11c** (600 mg, 4.11 mmol) in THF (11 mL) was added dropwise. The reaction mixture was gradually warmed to 0 °C for 4 h

and quenched with aqueous saturated $NaHCO_3$ solution. The solids were removed by filtration and the filtrate was concentrated in *vacuo*. The resulting material was diluted with water and extracted with ether. The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 1:1) to yield adduct **12c** (70 mg, 5%) and adduct **13c** (1.12 g, 83%).

Compounds **12c** and **13c** were also prepared by hydrogenation of **12b** and **13b** respectively: A solution of adduct **12b** or **13b** (1 equiv) in MeOH (15 mL/mmol) was added to a mixture of HCO_2NH_4 (2.4 equiv) and 10% Pd/C (75% w/w). The mixture was heated to 70 ºC in a sealed flask for 1.5 h. The solids were removed by filtration through a short pad of Celite and the filtrate was concentrated in *vacuo*, and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 2:3) to give the corresponding diols. Hydrogenation of compound **12b** (314 mg, 0.75 mmol) gave 210 mg of **12c** (85%). Hydrogenation of compound **13b** (210 mg, 0.5 mmol) gave 146 mg of **13c** (89%).

(3*S*,6*R*,1´*R*,2´S,3´*R*)-3-[2,4-Ethylidenedioxybutyl-1,3-dihydroxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (**12c**): colorless oil; *Rf* = 0.35 (silica gel, EtOAc/hexanes 1:1); $[\alpha]^{22}_D$ –4.1 (*c* 1.0 in CH_2Cl_2); (Found: C, 54.28; H, 8.06; N, 8.52. Calc. for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48%); ν_{max}/cm^{-1} 3429, 2951, 1749, 1239 and 1206; δ_H (300 MHz, CD_3OD) 0.69 (3H, d, *J* = 6.8), 1.07 (3H, d, *J* = 6.8), 1.22 (3H, d, *J* = 5.0), 2.30 (1H, dsp, *J* = 6.8 and 3.4), 3.20–3.50 (2H, m), 3.67–3.75 (1H, m), 3.72 (6H, s), 3.87 (1H, t, *J* = 3.4), 3.98-4.05 (2H, m), 4.32 (1H, dd, *J* = 6.2 and 3.4), 4.62 (1H, q, *J* = 5.0); δ_C (75 MHz, CD_3OD) 16.9 (CH_3), 19.8 (CH_3), 20.9 (CH_3), 32.1 (CH), 53.2 (CH_3), 53.6 (CH_3), 59.9 (CH), 61.9 (CH), 62.0 (CH), 71.0 (CH), 72.1 (CH_2), 82.1 (CH), 100.1 (CH), 164.3 (C), 166.9 (C). FABMS (thioglycerol) *m/z* 331 (MH^+, 100%). HRMS 331.1882. $C_{15}H_{27}N_2O_6$ requires 331.1869.

(3*S*,6*R*,1´*S*,2´S,3´*R*)-3-[2,4-Ethylidenedioxybutyl-1,3-dihydroxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (**13c**): white solid; m.p. 155 °C; *Rf* = 0.50 (silica gel, EtOAc/hexanes 1:1); $[\alpha]^{22}_D$ –24.7 (*c* 1.0 in CH_2Cl_2); (Found: C, 54.69; H, 7.66; N, 8.61. Calc. for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48%); ν_{max}/cm^{-1} 3399, 3152, 1698, 1228, 1196, 1079, 1042, 1007; δ_H (300 MHz, $CDCl_3$) 0.70 (3H, d, *J* = 6.8), 1.08 (3H, d, *J* = 6.8), 1.5 (3H, d, *J* = 5.1), 2.10 (1H, brd, *J* = 4.6), 2.32 (1H, dsp, *J* = 6.8 and 3.5), 3.44 (1H, t, *J* = 10.7), 3.54 (1H, dd, *J* = 8.9 and 3.1), 3.73 (3H, s), 3.76 (3H, s), 3.85 (1H, ddd, *J* = 10.1, 9.0 and 5.5), 4.08 (1H, t, *J* = 3.5), 4.15 (1H, brd, *J* = 3.6), 4.22 (1H, dd, *J* = 10.7 and 5.5), 4.41–4.43 (1H, m), 4.73 (1H, q, *J* = 5.1), 6.81 (1H, brs), δ_C (75 MHz, $CDCl_3$) 16.5 (CH_3), 19.1 (CH_3), 20.5 (CH_3), 31.6 (CH), 52.9 (CH_3), 53.4 (CH_3), 56.5 (CH), 59.5 (CH), 60.7 (CH), 70.0 (CH_2), 73.4 (CH), 83.1 (CH), 98.6 (CH), 160.5 (C), 167.6 (C); FABMS (thioglycerol) *m/z* 331 (MH^+, 100). HRMS 331.1876. $C_{15}H_{27}N_2O_6$ requires 331.1869.

(3*S*,6*R*,1´*R*,2´*S*,3´*R*)-3-[2,4-Ethylidenedioxybutyl-1-hydroxy-3-methanesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (12d)

A solution of diol **12c** (340 mg, 1.03 mmol), Et_3N (0.28 mL, 2.02 mmol) and DMAP (21 mg, 0.17 mmol) in CH_2Cl_2 (15 mL) at 0 ºC was treated with MsCl (0.12 mL, 1.55 mmol) and the mixture was stirred for 2 h at rt. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 2:3) to give mesylate **12d** (386 mg, 92%) as a colorless oil; *Rf* = 0.50 (silica gel, EtOAc/hexanes 1:1); $[\alpha]^{23}_D$ –22.5 (*c* 1.0 in CH_2Cl_2); (Found: C, 47.15; H, 7.03; N, 6.58; S, 7.71. Calc. for $C_{16}H_{28}N_2O_8S$: C, 47.05; H, 6.91; N, 6.86; S, 7.85%); ν_{max}/cm^{-1} 2952, 2873, 1697, 1382, 1245, 1180 and 995; δ_H (300 MHz, $CDCl_3$) 0.71 (3H, d, *J* = 6.7), 1.07 (3H, d, *J* = 6.7), 1.25 (3H, d, *J* = 5.0), 2.27 (1H, dsp, *J* = 6.7 and 3.5), 3.15 (3H, s), 3.56-3.78 (2H, m), 3.70 (3H, s), 3.76 (3H, s), 3.89 (1H, t, *J* = 3.5), 3.95-4.01 (1H, m), 4.33–4.43 (2H, m), 4.58 (1H, q, *J* = 5.0), 4.74 (1H, ddd, *J* = 14.6, 9.8 and 5.3); δ_C (75 MHz, $CDCl_3$) 16.6 (CH_3), 19.1 (CH_3), 20.2 (CH_3), 31.6 (CH), 37.4 (CH_3), 52.6 (CH_3), 52.7 (CH_3), 56.3 (CH), 61.3 (CH), 67.6 (CH), 68.5 (CH_2), 68.9 (CH), 78.1 (CH), 99.0 (CH), 161.1 (C), 164.0 (C). FABMS (thioglycerol) *m/z* 409 (MH^+, 100%). HRMS 409.1652. $C_{16}H_{29}N_2O_8S$ requires 409.1645.

Mesylation of diol 13c

A solution of diol **13c** (100 mg, 0.30 mmol), Et_3N (0.083 mL, 0.60 mmol) and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was treated with MsCl (0.025 mL, 0.33 mmol) and the mixture was stirred for 12 h at rt. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2 1:19) to give monomesylate **13d** (79 mg, 65%) along with dimesylated derivative (33 mg, 23%).

(3*S*,6*R*,1´*S*,2´*S*,3´*R*)-3-[2,4-Ethylidenedioxybutyl-1-hydroxy-3-methanesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine **13d**: colorless oil; *Rf* = 0.25 (silica gel, MeOH/CH_2Cl_2 1:19); $[\alpha]^{25}_D$ –18.3 (*c* 1.0 in CH_2Cl_2); (Found: C, 47.01; H, 6.99; N, 6.68; S, 7.91. Calc. for $C_{16}H_{28}N_2O_8S$: C, 47.05; H, 6.91; N, 6.86; S, 7.85%); ν_{max}/cm^{-1} 2946, 2872, 1696, 1349, 1237, 1174, 1134, 1112, 1052, 1002; δ_H (300 MHz, $CDCl_3$) 0.74 (3 H, d, *J* = 6.8), 1.03 (3 H, d, *J* = 6.8), 1.33 (3 H, d, *J* = 5.0), 2.11 (1 H, d, *J* = 10.6), 2.23 (1 H, dsp, *J* = 6.8 and 3.8), 3.08 (3 H, s), 3.64 (1 H, dd, *J* = 11.1 and 9.9), 3.73 (3 H, s), 3.74 (3 H, s), 3.93-3.99 (1 H, m), 4.01 (1 H, t, *J* = 3.8), 4.19 (1 H, ddd, *J* = 10.3, 8.1 and 2.1), 4.26 (1 H, dd, *J* = 3.6 and 2.2), 4.40 (1 H, dd, *J* = 11.1 and 5.5), 4.64 (1 H, td, *J* = 9.5 and 5.5), 4.73 (1 H, q, *J* = 5.0); δ_C (75 MHz, $CDCl_3$) 17.0 (CH_3), 19.0 (CH_3), 20.4 (CH_3), 32.3 (CH), 38.3 (CH_3), 52.7 (CH_3), 52.8 (CH_3), 55.2 (CH), 61.3 (CH), 68.3 (CH_2), 72.7 (CH), 73.4 (CH), 75.6 (CH), 98.8 (CH), 161.6 (C), 167.0 (C). FABMS (thioglycerol) *m/z* 409 (MH^+, 100%). HRMS 409.1645. $C_{16}H_{29}N_2O_8S$ requires 409.1645.

(3*S*,6*R*,1´*S*,2´*S*,3´*R*)-3-[2,4-Ethylidenedioxybutyl-1,3-dimethanesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine: white solid; m.p. 129-130 °C; *Rf* = 0.45 (silica gel, MeOH/CH_2Cl_2 1:19); $[\alpha]^{25}_D$ +8.5 (*c* 0.5 in CH_2Cl_2); ν_{max}/cm^{-1} 2960, 1705, 1676, 1336, 1248, 1168, 1135, 1060, 1010; δ_H (300 MHz, $CDCl_3$) 0.68 (3 H, d, *J* =

6.8), 1.06 (3 H, d, *J* = 6.9), 1.35 (3 H, d, *J* = 5.0), 2.33 (1 H, dsp, *J* = 6.9 and 3.3), 2.99 (3 H, s), 3.15 (3 H, s), 3.75 (6 H, s), 3.77 (1 H, dd, *J* = 11.4 and 9.0), 3.99 (1 H, t, *J* = 3.6), 4.33 (1 H, dd, *J* = 8.5 and 6.1), 4.44–4.50 (1 H, m), 4.55 (1 H, dd, *J* = 11.4 and 5.1), 4.80 (1 H, q, *J* = 5.0), 4.87 (1 H, td, *J* = 8.8 and 5.1), 5.08 (1 H, dd, *J* = 6.1 and 3.0); δ_C (75 MHz, $CDCl_3$) 16.4 (CH_3), 19.1 (CH_3), 20.4 (CH_3), 31.4 (CH), 38.4 (CH_3), 38.8 (CH_3), 52.7 (CH_3), 52.9 (CH_3), 55.3 (CH), 60.7 (CH), 67.8 (CH_2), 71.3 (CH), 75.7 (CH), 80.7 (CH), 98.8 (CH), 159.8 (C), 165.4 (C). FABMS (thioglycerol) *m/z* 487 (MH^+, 49%), 391 (100%). HRMS 487.1418. $C_{17}H_{31}N_2O_{10}S_2$ requires 487.1420.

(3*S*,6*R*,1´*R*,2´*S*,3´*R*)-3-[1-Benzyloxy-2,4-ethylidenedioxybutyl-3-methanesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimetoxypyrazine (16)

A solution of mesylate **12d** (340 mg, 0.83 mmol) in THF (2 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) in THF (10 mL) at 0 °C. After 1 h, NBu_4I (107 mg, 0.30 mmol) and BnBr (0.12 mL, 1.0 mmol) were added, and the resulting solution was stirred at rt for 3 h. The reaction mixture was cooled to 0 °C and quenched by the addition of CH_3OH (2.5 mL). The solvents were removed in *vacuo* and the resulting material was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 1:3) to give compound **16** (291 mg, 70%) as a colorless oil; *Rf* = 0.40 (silica gel, EtOAc/hexanes 1:2); $[\alpha]^{22}_D$ +13.7 (*c* 1.0 in CH_2Cl_2); (Found: C, 55.48; H, 6.69; N, 5.73; S, 6.52. Calc. for $C_{23}H_{34}N_2O_8S$: C, 55.41; H, 6.87; N, 5.62; S, 6.43%); ν_{max}/cm^{-1} 1691, 1357, 1237, 1176 and 1098; δ_H (300 MHz, $CDCl_3$) 0.69 (3H, d, *J* = 6.8), 1.08 (3H, d, *J* = 6.8), 1.31 (3H, d, *J* = 5.0), 2.35 (1H, dsp, *J* = 6.8 and 3.2), 2.89 (3H, s), 3.59 (1H, t, *J* = 10.5), 3.71 (3H, s), 3.72 (3H, s), 3.85–3.96 (3H, m), 4.41 (1H, dd, *J* =10.8 and 5.4), 4.55 (1H, dd, *J* = 5.7 and 3.6), 4.64 (1H, q, *J* = 5.0), 4.66 (1H, AB system, *J* = 11.0), 4.73 (1H, AB system, *J* = 11.0), 4.95 (1H, ddd, *J* = 14.8, 9.6 and 5.4), 7.26–7.42 (5H, m); δ_C (75 MHz, $CDCl_3$) 16.4 (CH_3), 19.2 (CH_3), 20.3 (CH_3), 30.9 (CH), 38.3 (CH_3), 52.6 (CH_3), 52.7 (CH_3), 55.9 (CH), 60.4 (CH), 68.3 (CH_2), 69.2 (CH), 72.8 (CH_2), 77.4 (CH), 77.5 (CH), 99.4 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 137.9 (C), 161.9 (C), 165.0 (C). FABMS (thioglycerol) *m/z* 499 (MH^+, 16%), 242 (100). HRMS 499.2094. $C_{23}H_{35}N_2O_8S$ requires 499.2114.

Methyl 3-benzyloxy-4,6-ethylidenedioxy-2,5-dideoxy-2,5-imino-D-gulonate (17)

A solution of compound **16** (265 mg, 0.53 mmol) in MeOH (13 mL) and 0.25 M HCl (4.25 mL, 1.06 mmol) was stirred at rt for 9 h. Then, the solution was diluted with water (10 mL) and concentrated to one-third its initial volume. The aqueous solution was made basic (pH~10) by the addition of $NaHCO_3$ followed by concentrated ammonia. The aqueous layer was extracted with CH_2Cl_2 (7 x 12 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The crude was purified by flash chromatography (silica gel, EtOAc) to give gulonate **17** (134 mg, 82%) as a colorless oil; *Rf* = 0.35 (silica gel, EtOAc); $[\alpha]^{19}_D$ +22.6 (*c* 0.8 in CH_2Cl_2); (Found: C, 62.71; H, 6.75; N, 4.60. Calc. for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56%); ν_{max}/cm^{-1} 2910, 1739 and 1109; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* = 5.0, CHC*H*$_3$), 2.60 (1H, brs, NH), 3.11 (1H, m, 5-H), 3.78 (3H, s, OCH_3), 3.89 (1H, d, *J* = 2.1, 2-H), 3.98 (1H, dd, *J* = 12.5 and 2.4, 6-H), 4.04 (1H, d, *J* = 2.1, 3-H), 4.08 (1H, d, *J* = 2.1, 4-H), 4.18 (1H, d, *J* = 12.5, 6'-H), 4.59 (1H, AB system, *J* = 11.9, C*H*$_2$Ph), 4.64 (1H, q, *J* = 5.0, CH_3C*H*), 4.68 (1H, AB system, *J* = 11.9, C*H*$_2$Ph), 7.28-7.38 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.0 (*C*H_3CH), 52.4 (OCH_3), 55.4 (C-5), 65.5 (C-6), 66.7 (C-2), 71.7 (*C*H_2Ph), 79.4 (C-4), 87.9 (C-3), 97.6 (*C*HCH$_3$), 127.7 (CH), 127.8 (CH), 128.4 (CH), 137.4 (C), 172.0 (C=O). FABMS (thioglycerol) *m/z* 308 (MH^+, 77%), 154 (100). HRMS 308.1500. $C_{16}H_{22}NO_5$ requires 308.1498.

(3*S*,6*R*,1´*S*,2´*S*,3´*R*)-3-[2,4-Ethylidenedioxybutyl-1-hydroxy-3-*p*-toluenesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimethoxypyrazine (18)

A solution of diol **13c** (750 mg, 2.27 mmol), Ag_2O (789 mg, 3.40 mmol), KI (75 mg, 0.45 mmol) and TsCl (477 mg, 2.50 mmol) in toluene (30 mL) was stirred for 11 h at rt. The reaction mixture was filtrated through a short pad of Celite, the filtrate was concentrated in *vacuo* and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 1:4) to give tosylate **18** (1.0 g, 91%) as a white solid; *Rf* = 0.50 (silica gel, EtOAc/hexanes 3:7); mp 48 – 50 ºC; $[\alpha]^{27}_D$ +3.4 (*c* 1.0 in MeOH); (Found: C, 54.83; H, 6.47; N, 5.65; S, 6.90. Calc. for $C_{22}H_{32}N_2O_8S$: C, 54.53; H, 6.66; N, 5.78; S, 6.62%); ν_{max}/cm^{-1} 3553, 2945, 1698, 1365, 1238, 1176; δ_H (300 MHz, $CDCl_3$) 0.72 (3H, d, *J* = 6.9), 1.04 (3H, d, *J* = 6.9), 1.30 (3H, d, *J* = 5.0), 2.23 (1H, dsp, *J* = 6.9 and 3.6), 2.30 (1H, d, *J* = 8.9), 2.45 (3H, s), 3.56 (1H, dd, *J* = 11.1 and 9.7), 3.69 (3H, s), 3.73 (3H, s), 3.94-4.00 (2H, m), 4.05–4.10 (2H, m), 4.13 (1H, dd, *J* = 11.0 and 5.2), 4.19 (1H, dd, *J* = 3.6 and 2.7), 4.65-4.73 (1H, m), 4.70 (1H, q, *J* = 5.0), 7.34 (2H, d, *J* = 8.2), 7.82 (2H, d, *J* = 8.2); δ_C (75 MHz, $CDCl_3$) 16.9 (CH_3), 19.0 (CH_3), 20.4 (CH_3), 21.7 (CH_3), 32.0 (CH), 52.5 (CH_3), 52.6 (CH_3), 55.4 (CH), 61.1 (CH), 67.6 (CH_2), 72.4 (CH), 72.8 (CH), 76.6 (CH), 98.7 (CH), 128.1 (CH), 129.8 (CH), 133.3 (C), 145.2 (C), 161.7 (C), 166.1 (C); FABMS (thioglycerol) *m/z* 485 (MH^+, 100). HRMS 485.1976. $C_{22}H_{33}N_2O_8S$ requires 485.1958.

(3*S*,6*R*,1´*R*,2´*S*,3´*R*)-3-[1-Benzyloxy-2,4-ethylidenedioxybutyl-3-*p*-toluenesulfonyloxy]-3,6-dihydro-6-isopropyl-2,5-dimetoxypyrazine (19)

A solution of tosylate **18** (927 mg, 1.90 mmol) in THF (10 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 93 mg, 2.3 mmol) in THF (28 mL) at 0 °C. After 1 h, NBu_4I (249 mg, 0.67 mmol) and BnBr (0.27 mL, 2.3 mmol) were added, and the resulting solution was stirred at rt for 3 h. The reaction mixture was cooled to 0 °C and quenched by the addition of MeOH (6 mL). The solvents were removed in *vacuo* and the resulting material was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes 1:9) to give compound **19** (1.0 g, 91%) as a white solid; *Rf* = 0.35 (EtOAc/hexanes 1:9); mp 79–81 ºC;

$[\alpha]^{27}_D$ +32.7 (*c* 1.0 in CH_2Cl_2); (Found: C, 60.79; H, 6.69; N, 4.95; S, 5.53. Calc. for $C_{29}H_{38}N_2O_8S$: C, 60.61; H, 6.66; N, 4.87; S, 5.58%); ν_{max}/cm^{-1} 1694, 1361, 1191, 1176, 1071; δ_H (300 MHz, $CDCl_3$) 0.66 (3H, d, *J* = 6.8), 1.04 (3H, d, *J* = 6.8), 1.31 (3H, d, *J* = 5.0), 2.26 (1H, dsp, *J* = 6.8 and 3.3), 2.39 (3H, s), 3.55 (1H, dd, *J* = 11.3 and 8.9), 3.62 (3H, s), 3.71 (3H, s), 3.85 (1H, t, *J* = 3.3), 4.03–4.12 (3H, m), 4.31 (1H, dd, *J* = 3.9 and 1.5), 4.36 (1H, d, *J* = 11.0), 4.63 (1H, d, *J* = 11.0), 4.71 (1H, q, *J* = 5.0), 4.77-4.84 (1H, m), 7.17 (2H, d, *J* = 8.3), 7.21–7.33 (5H, m), 7.65 (2H, d, *J* = 8.3); δ_C (75 MHz, $CDCl_3$) 16.4 (CH_3), 19.1 (CH_3), 20.5 (CH_3), 21.6 (CH_3), 31.1 (CH), 52.2 (CH_3), 52.4 (CH_3), 55.6 (CH), 60.3 (CH), 67.4 (CH_2), 73.0 (CH), 73.2 (CH_2), 76.1 (CH), 80.6 (CH), 98.4 (CH), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.1 (CH), 129.6 (CH), 134.0 (C), 138.1 (C), 144.7 (C), 161.7 (C), 164.3 (C); FABMS (thioglycerol) *m/z* 575 (MH^+, 100). HRMS 575.2429. $C_{29}H_{39}N_2O_8S$ requires 575.2427.

Methyl 3-benzyloxy-4,6-ethylidenedioxy-2,5-dideoxy-2,5-imino-D-galactonate (20)

A solution of compound **19** (941 mg, 1.64 mmol) in MeOH (50 mL) and 0.25 M HCl (13 mL, 3.2 mmol) was stirred at rt for 9 h. Then, the solution was diluted with water (50 mL) and concentrated to one-third its initial volume. The aqueous solution was made basic (pH~10) by the addition of $NaHCO_3$ followed by concentrated ammonia. The aqueous layer was extracted with CH_2Cl_2 (7 x 12 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was dissolved in DMSO (19 mL), Et_3N (0.45 mL, 3.2 mmol) was added and the mixture was heated to 70 ºC for 1.5 h. The reaction mixture was cooled to rt, diluted with brine and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated. The crude was purified by reversed-phase flash chromatography (RP-18, MeOH/H_2O 1:1) to give galactonate **20** (302 mg, 60%) as a colorless oil; *Rf* = 0.15 (silica gel, AcOEt); $[\alpha]^{25}_D$ +10.3 (*c* 1.0 in CH_2Cl_2); (Found: C, 62.35; H, 6.94; N, 4.57. Calc. for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56%); ν_{max}/cm^{-1} 1737, 1206, 1102, 955; δ_H (300 MHz, $CDCl_3$) 1.40 (3H, d, *J* = 5.1), 2.68 (1H, brs), 3.81 (3H, s), 3.98 (1H, dd, *J* = 12.4 and 2.5), 4.00 (1H, d, *J* = 9.0), 4.05 (1H, dd, *J* = 3.8 and 2.1), 4.12 (1H, dd, *J* = 12.4 and 0.8), 4.23 (1H, dd, *J* = 9.0 and 3.8), 4.65 (1H, AB system, *J* = 12.6), 4.71 (1H, AB system, *J* = 12.6 4.69), (1H, q, *J* = 5.1), 7.29–7.36 (5H, m); δ_C (75 MHz, $CDCl_3$) 21.1 (CH_3), 52.1 (CH_3), 53.9 (CH), 61.7 (CH), 65.8 (CH_2), 72.5 (CH_2), 74.8 (CH), 82.0 (CH), 97.8 (CH), 127.5 (CH), 127.7 (CH), 128.3 (CH), 137.8 (C), 171.1 (C); FABMS (thioglycerol) *m/z* 308 (MH^+, 100). HRMS 308.1487. $C_{16}H_{22}NO_5$ requires 308.1498.

4-Benzyloxy-1,3-ethylidenedioxy-2,5-dideoxy-2,5-imino-D-glucitol (21)

$LiEt_3BH$ (1 M in THF, 1.5 mL, 1.5 mmol) was dropwise added to a solution of gulonate **17** (150 mg, 0.49 mmol) in THF (9 mL) at 0 °C and the mixture was stirred at this temperature for 1 h. The reaction mixture was quenched by the addition of aqueous saturated NH_4Cl solution, the solvents were removed in *vacuo* and the residue was diluted with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated, and the crude was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2 1:20), to give pyrrolidine **21** (123 mg, 90%) as a colorless oil; *Rf* = 0.30 (silica gel, MeOH/CH_2Cl_2 1:20), $[\alpha]^{22}_D$ + 35.1 (*c* 0.8 in CH_2Cl_2); (Found: C, 64.39; H, 7.57; N, 5.11. Calc. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01%); ν_{max}/cm^{-1} 3277, 2990, 2862 and 1069; δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* = 5.0, CHC*H*$_3$), 2.71 (1H, brs, NH), 3.11 (1H, brs, 2-H), 3.35-3.37 (1H, m, 5-H), 3.73 (1H, d, *J* = 2.7, 4-H), 3.74-3.80 (2H, m, 6-H and 6'-H), 4.00 (1H, dd, *J* = 12.5 and 2.5, 1-H), 4.15 (1H, d, *J* = 12.5, 1'-H), 4.17 (1H, d, *J* = 2.7, 3-H), 4.57 (1H, AB system, *J* = 11.8, C*H*$_2$Ph), 4.61 (1H, AB system, *J* = 11.8, C*H*$_2$Ph), 4.69 (1H, q, *J* = 5.0, CH_3C*H*), 7.28–7.37 (5H, m); δ_C (75 MHz, $CDCl_3$) 21.0 (*C*H_3CH), 55.1 (C-2), 63.3 (C-6), 66.4 (C-1), 66.9 (C-5), 72.0 (*C*H_2Ph), 80.1 (C-3), 86.8 (C-4), 97.9 (*C*HCH$_3$), 127.6 (CH), 127.8 (CH), 128.5 (CH), 137.8 (C). FABMS (thioglycerol) *m/z* 280 (MH^+, 88%), 154 (78), 147 (89), 136 (100). HRMS 280.1546. $C_{15}H_{22}NO_4$ requires 280.1549.

4-Benzyloxy-1,3-ethylidenedioxy-2,5-dideoxy-2,5-imino-D-galactitol (22)

$LiEt_3BH$ (1 M in THF, 1.20 mL, 1.20 mmol) was dropwise added to a solution of galactonate **20** (123 mg, 0.40 mmol) in THF (6 mL) at 0 °C and the mixture was stirred at this temperature for 1 h. The reaction mixture was quenched by the addition of aqueous saturated NH_4Cl solution, the solvents were removed in *vacuo* and the residue was diluted with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated, and the crude was purified by flash chromatography (silica gel, MeOH/CH_2Cl_2 1:20), to give pyrrolidine **22** (99 mg, 89%) as a colorless oil; *Rf* = 0.25 (silica gel, MeOH/CH_2Cl_2 1:20), $[\alpha]^{27}_D$ –66.7 (*c* 1.0 in CH_2Cl_2); (Found: C, 64.44; H, 7.62; N, 5.10. Calc. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01%); ν_{max}/cm^{-1} 2879, 1408, 1155, 1080; δ_H (300 MHz, $CDCl_3$) 1.38 (3H, d, *J* = 5.0), 2.75 (1H, brs), 2.83 (2H, brs), 3.35–3.48 (1H, m), 3.70 (1H, dd, *J* = 11.6 and 4.0), 3.92 (1H, dd, *J* = 11.7 and 2.4), 3.98 (1H, dd, *J* = 12.3 and 2.3), 4.05–4.25 (3H, m), 4.49 (1H, AB system, *J* = 11.7), 4.70 (1H, AB system, *J* = 11.7), 4.73 (1H, q, *J* = 5.0), 7.27-7.36 (5H, m); δ_C (75 MHz, $CDCl_3$) 21.1 (CH_3), 53.3 (CH), 60.7 (CH), 60.8 (CH_2), 66.5 (CH_2), 72.5 (CH_2), 74.3 (CH), 82.1 (CH), 97.8 (CH), 127.6 (CH), 127.9 (CH), 128.5 (CH), 137.8 (C); FABMS (thioglycerol) *m/z* 280 (MH^+, 100). HRMS 280.1553. $C_{15}H_{22}NO_4$ requires 280.1549.

Targeted pyrrolidine derivatives

2,5-Dideoxy-2,5-imino-L-gulonic acid (4)

A solution of gulonate **17** (238 mg, 0.77 mmol) in THF (15 mL) and 0.25 M HCl (15 mL, 3.75 mmol) was stirred with 10% Pd/C (24 mg) under H_2 (1 atm) for 12 h at rt. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated in *vacuo*. The residue was dissolved in HCl 1 M (2 mL) and the mixture was heated to 100 ºC for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was diluted with 1% aqueous NH_3 solution and was evaporated again. The residue was purified by ion-exchange chromatography (Dowex 50W–X8, H^+ form, eluting with 4% aqueous NH_3 solution) followed by reversed-

phase flash chromatography (RP-18, using H_2O as eluent) to give imino acid **4** (131 mg, 96 %) as a white solid; *Rf* = 0.10 (silica gel, BuOH/AcOH/H_2O 12:3:5); mp 216-217 ºC (decomp.), (lit.,[10a] m.p. 216 °C (decomp)); $[\alpha]^{24}_D$ –13.5 (*c* 1.0 in H_2O), (lit.,[10a] $[\alpha]^{20}_D$ EQ/S –14.3 (*c* 1.0 in H_2O)); (Found: C, 40.49; H, 6.52; N, 7.86. Calc. for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91%); ν_{max}/cm^{-1} 3443, 3183, 1631, 1564, 1347, 1058; δ_H (500 MHz, D_2O + DCl) 3.96–4.06 (3 H, m), 4.32 (1 H, dd, *J* = 3.0 and 1.6), 4.37 (1 H, brs), 4.62 (1 H, brs); δ_C (75 MHz, D_2O + DCl) 58.1 (CH_2), 64.9 (CH), 67.1 (CH), 75.1 (CH), 79.1 (CH), 170.5 (C); FABMS (thioglycerol) *m/z* 178 (MH^+, 100%). HRMS 178.0710. $C_6H_{12}NO_5$ requires 178.0715.

2,5-Dideoxy-2,5-imino-L-galactonic acid (5)

A solution of galactonate **20** (150 mg, 0.49 mmol) in THF (10 mL) and 0.25 M HCl (10 mL, 2.50 mmol) was stirred with 10% Pd/C (15 mg) under H_2 (1 atm) for 12 h at rt. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated in *vacuo*. The residue was dissolved in HCl 1 M (2 mL) and the mixture was heated to 100 ºC for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was diluted with 1% aqueous NH_3 solution and was evaporated again. The residue was purified by ion-exchange chromatography (Dowex 50W–X8, H^+ form, eluting with 2% aqueous NH_3 solution) followed by reversed-phase flash chromatography (RP-18, using H_2O as eluent) to give imino acid **5** (76 mg, 87%) as a white solid; *Rf* = 0.10 (silica gel, BuOH/AcOH/H_2O 12:3:5); mp 228 ºC (decomp.); $[\alpha]^{26}_D$ +47.1 (*c* 0.5 in H_2O); (Found: C, 40.72; H, 6.37; N, 7.87. Calc. for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91%); ν_{max}/cm^{-1} 3196, 3113, 1624, 1559, 1132, 1019; δ_H (500 MHz, D_2O) 3.82–3.90 (1H, m), 3.92–3.97 (2H, m), 4.15 (1H, d, *J* = 5.3), 4.46–4.56 (2H, m); δ_C (125 MHz, D_2O) 57.4 (CH_2), 60.8 (CH), 62.7 (CH), 70.1 (CH), 70.6 (CH), 170.2 (C); FABMS (thioglycerol) *m/z* 178 (MH^+, 100). HRMS 178.0719. $C_6H_{12}NO_5$ requires 178.0715.

2,5-Dideoxy-2,5-imino-D-glucitol (DGDP)

A solution of pyrrolidine **21** (86 mg, 0.31 mmol) in THF (5 mL) and 0.25 M HCl (3 mL, 0.75 mmol) was stirred with 10% Pd/C (18 mg) under H_2 (1 atm) for 12 h at rt. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated in *vacuo*. The residue was dissolved in HCl 1 M (3 mL) and the mixture was heated to 100 ºC for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was diluted with 1% aqueous NH_3 solution and was evaporated again. The residue was purified by ion-exchange chromatography (Dowex 50W–X8, H^+ form, eluting with 2% aqueous NH_3 solution) followed by reversed-phase flash chromatography (RP-18, using H_2O as eluent) to give DGDP (48 mg, 96%) as a white solid; m.p. 136-138 °C (from H_2O), (lit.,[10d] m.p. 138-140 °C); *Rf* = 0.20 (silica gel, BuOH/AcOH/H_2O 12:3:5), $[\alpha]^{22}_D$ + 24.2 (*c* 0.7 in H_2O), (lit.,[10d] $[\alpha]_D$ + 25.1 (*c* 1.5 in H_2O)); (Found: C, 44.34; H, 8.12; N, 8.43. Calc. for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58%); ν_{max}/cm^{-1} 3274, 3272, 3198, 2905, 1318 and 1033; δ_H (300 MHz, D_2O) 3.14 (1H, app q, *J* = 5.3), 3.44 (1H, app q, *J* = 6.0), 3.69–3.91 (4H, m), 3.93 (1H, dd, *J* = 5.0 and 2.8), 4.17 (1H, dd, *J* = 5.0 and 2.8); δ_C (75 MHz, D_2O) 62.8 (CH_2), 64.1 (CH), 64.9 (CH_2), 68.1 (CH), 80.1 (CH), 81.8 (CH). FABMS (thioglycerol) *m/z* 164 (MH^+, 100%). HRMS 164.0920. $C_6H_{14}NO_4$ requires 164.0923.

2,5-Dideoxy-2,5-imino-D-galactitol (DGADP)

A solution of pyrrolidine **22** (45 mg, 0.16 mmol) in THF (2.5 mL) and 0.25 M HCl (1.6 mL, 0.4 mmol) was stirred with 10% Pd/C (9 mg) under H_2 (1 atm) for 12 h at rt. The catalyst was removed by filtration through a short pad of Celite and the filtrate was concentrated in *vacuo*. The residue was dissolved in HCl 1 M (2 mL) and the mixture was heated to 100 ºC for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was diluted with 1% aqueous NH_3 solution and was evaporated again. The residue was purified by ion-exchange chromatography (Dowex 50W–X8, H^+ form, eluting with 2% aqueous NH_3 solution) followed by reversed-phase flash chromatography (RP-18, using H_2O as eluent) to give DGADP (23 mg, 88%) as colorless oil; *Rf* = 0.25 (silica gel, BuOH/AcOH/H_2O 12:3:5); (Found: C, 44.22; H, 8.10; N, 8.62. Calc. for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58%); ν_{max}/cm^{-1} 3303, 1668, 1190, 1126; δ_H (300 MHz, D_2O) 3.28–3.46 (2H, m), 3.72 (2H, dd, *J* = 11.5 and 6.3), 3.83 (2H, dd, *J* = 11.5 and 5.4), 4.34 (2H, d, *J* = 5.7); δ_C (75 MHz, D_2O) 60.2 (CH_2), 63.6 (CH), 72.4 (CH); FABMS (thioglycerol) *m/z* 164 (MH^+, 100). HRMS 164.0919. $C_6H_{14}NO_4$ requires 164.0923.

Computational

Electronic structure calculations were performed using the Kohn-Sham formulation of the density functional theory (DFT) with the hybrid exchange functional of Becke [35] and the Lee, Yang, and Parr correlation functional [36] (B3LYP) and the cc-pVDZ basis set [37] with a small-core relativistic pseudopotential for Sn [38] (referred as B3LYP/cc-pVDZ-PP level). All transition structures were obtained by unconstrained optimization and frequency calculations have been performed to check the presence of a single negative eigenvalue in their diagonalized force constant matrices. The associated eigenvectors were inspected with the aid of the visualization program GaussView 3.0 to confirm that they correspond to the expected reaction coordinate. All the intermediate complexes have positive defined Hessian matrices. All the energies reported are free energies and thus contain zero-point energy corrections (using frequencies scaled by 0.97) [39] and thermal and entropy effects at reaction temperature (195 or 273 K) and 1 atm pressure calculated at B3LYP/cc-pVDZ-PP level. Finally, single point energy calculations considering solvent effects were computed at B3LYP(SCRF)/cc-pVTZ-PP level for the gas-phase stationary points using the self-consistent reaction field method [40] based on the polarizable continuum model of Tomasi´s group [41] with a permittivity of 7.52 for THF. All optimizations and frequency calculations reported in this article were performed using Gaussian03 program package.[42] cc-pVDZ-PP and cc-pVTZ-PP basis sets and ECP parameters for Sn were obtained from Basis Set Exchange (BSE) software and the EMSL Basis Set Library (https://bse.pnl.gov/bse/portal).[43] NBO

delocalization energies were calculated using second-order perturbation theory with the NBO 3.1 program [44] as implemented in Gaussian03 program package. See ESI for further details.

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Notes and references

Departamento de Química Fundamental, Facultade de Ciencias, Universidade da Coruña, Campus da Zapateira s/n, 15071 A Coruña, Spain. Fax: +34 981167065; Tel: +34 981167000; E-mail: ojea@udc.es

† Electronic Supplementary Information (ESI) available: Computational details, Cartesian coordinates and absolute energies for the models reported and NMR spectra of new compounds. See

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