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Access to iminosugars by aldol additions of metalated bis-lactim ethers to L-erythrose derivatives

María Ruiz,* Vicente Ojea, Tania M. Ruanova and José M. Quintela

Departamento de Química Fundamental, Facultade de Ciencias, Universidade da Coruña, Campus da Zapateira, s/n, 15071 A Coruña, Spain

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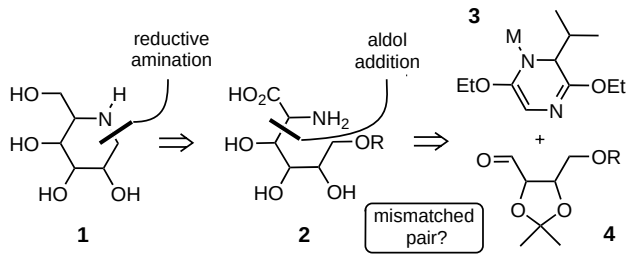
Abstract—Aldol additions of metalated bis-lactim ethers derived from *cyclo*-[Gly-D-Val] **3A**–**E*** to mismatched L-erythrose-derivatives **4a** and **4b** have been studied. Reactions of titanium(IV) and tin(II) azaenolates with the lactol derivative **4b** allow direct and moderate (*syn*,*syn*)- or highly (*anti*,*anti*)-selective access to polyhydroxy amino acids that have been efficiently transformed into 1-deoxy-D-gulonojirimycin or 1-deoxy-D-allonojirimycin.

Natural and synthetic alkaloid sugar mimics with a nitrogen in the ring (iminosugars) have shown the ability to inhibit important glycoconjugate processing enzymes in a reversible and competitive manner.[1] Glycosidase inhibitors have received a great deal of attention because of their value in basic biochemical research[2] and their therapeutic potential in the treatment of prominent diseases, such as viral infections, cancer, diabetes and other metabolic disorders.[3] As a consequence, a variety of synthetic approaches have been used to assemble this class of compounds ranging from chemical to enzymatic methods, and employing a wide range of starting materials from sugars to benzene.[1c] Although, traditionally, iminosugars have been synthesized through multistep transformations of readily available carbohydrate precursors, recent interest has increasingly focused on the synthesis of this class of compounds from non-carbohydrate sources.[4] Prominent among these strategies are cycloaddition-based routes,[5a,b] chemoenzymatic functionalization of carbocyclic intermediates,[5c,d] aldolase-catalyzed condensation reactions[5e] and stereoselective elongation of homochiral short chain precursors exploiting different chemical procedures.[5f]

Recent efforts in our laboratory directed toward the synthesis of bioactive amino polyols led to the development of a convergent route to the polyhydroxylated piperidine derivatives **1** (see Scheme 1). Our strategy relies on cyclization of the polyhydroxy amino acid precursors **2** that can be direct and stereoselectively prepared by aldol reactions between homochiral glycine equivalents and readily accessible enantiopure hydroxyaldehydes.[6] Based on this methodology, we have previously succeeded in the synthesis of 1-deoxy-D-talonojirimycin and 1-deoxy-D-galactonojirimycin, by using highly (*syn*,*anti*)-selective aldol additions of the stannous azaenolate **3**, derived from a Schöllkopf's bis-lactim ether, to matched 1,3-dioxolane-4-carboxaldehyde derivatives **4**.[7]

In addition, the reactions of metalated bis-lactim ethers with mismatched cyclohexylidene glyceraldehyde[8] and an α,β-*syn*-dihydroxy aldehyde,[9] have been studied by Schöllkopf and Kobayashi, respectively. Although the stereochemical outcome of these additions was markedly dependent on the metal counterpart, using titanium(IV) or tin(II) and zinc(II) salts, the reactions



Scheme 1. Amino acid based approach to piperidine alkaloids.

* Corresponding author. Tel.: 34-981167000; fax: 34-981167065; e-mail: ruizpr@udc.es

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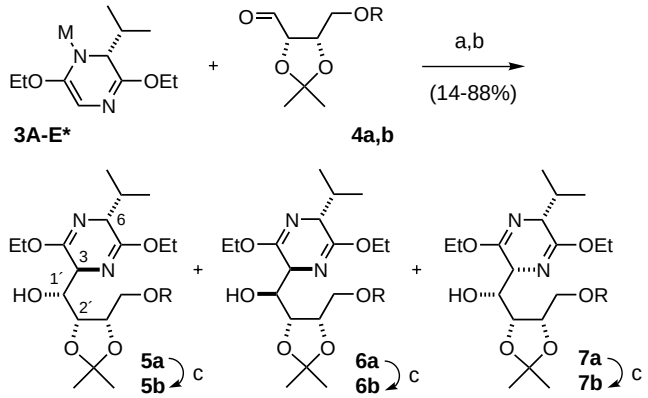
proceeded under almost complete azaenolate control, affording the (*syn*,*syn*)-adducts with excellent diastereoselectivities. The high level of π-facial discrimination found in these processes prompted us to explore the additions of metalated Schöllkopf's bis-lactim ethers to mismatched erythrose derivatives, that could result in a stereocontrolled route to (*syn*,*syn*)-polyhydroxy amino acids, thus extending the applicability of our iminosugar approach to the gulo series.[10]

We first examined the aldol additions of azaenolates derived from (3*R*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine[11,12] to 4-*O*-benzyl-2,3-*O*-isopropylidene-L-erythrose **4a**[13] (see Scheme 2). Addition of aldehyde **4a** to 1 equiv. of azaenolates **3A**–**E** at −78°C in THF, afforded, after quenching and aqueous work-up, mixtures of adducts **5a**/**6a**/**7a** in good yields except for the reaction of **3B** (see Table 1). The reaction with the lithium azaenolate **3A** proceeded with very low selectivity, giving rise to a 4.7:3.7:1.6 mixture of adducts **5a**/**6a**/**7a**.[14] The configuration of the major adduct, **5a**, was determined as 3,6-*trans*–3,1′-*anti*–1′,2′-*anti*, instead of the expected 3,6-*trans*–3,1′-*syn*–1′,2′-*syn*, which was assigned to adduct **6a**, the secondary one.[15]



Scheme 2. Aldol additions of azaenolates **3A**–**E*** to mismatched L-erythrose derivatives **4a**,**b**. *Reagents and conditions*: (a) THF, −78°C, 2 h for **4a**; THF, −78–0°C, 12 h for **4b**. (b) NH_4Cl or phosphate buffer. (c) H_2, Pd/C, THF, rt, 6 h. Legends. For compound **3**: **A**, M = Li; **B**, M = ZnCl; **C**, M = SnCl; **D**, M = MgBr; **E**, M = $Ti(NEt_2)_3$; **E***, M = $Ti(OiPr)_3$. For compounds **5**–**7**: **a**, R = Bn; **b**, R = H.

Table 1. Selectivity and yields in the aldol additions of metalated bis-lactims **3A**–**E** to mismatched aldehyde **4a**

Case	Additive	Equiv.	Yield (%)[a]	**5a**/**6a**/**7a**[b]
A	–	–	60	4.7:3.7:1.6
B	$ZnCl_2$	2.0	14	4.6:2.8:2.5
C	$SnCl_2$	1.0	65	5.7:3.8:0.5
C*	$SnCl_2$	2.0	65	6.5:3.1:0.3
D	$MgBr_2{\cdot}OEt_2$	2.0	60	6.4:2.2:1.4
E	$Ti(NEt_2)_3Cl$	1.0	60	6.4:2.7:0.9

[a] Isolated yield of mixtures of diastereoisomers.
[b] Ratios determined by ^1H NMR analysis of the mixtures of adducts.

To evaluate the counterion dependence of the stereochemical outcome, the lithium azaenolate **3A** was allowed to react, at −78°C in THF, with $ZnCl_2$, $SnCl_2$, $Ti(NEt_2)_3Cl$, or $MgBr_2{\cdot}OEt_2$, to produce the transmetalated azaenolates **3B**–**E**,[8,9,16] prior to addition of the aldehyde. Reaction of **4a** with the zinc azaenolate **3B** resulted in a very low conversion to a mixture of adducts **5a**/**6a**/**7a** with almost the same ratio observed for the lithium salt. Surprisingly, switching the metal to Sn(II), Ti(IV) or Mg(II) did not change the stereochemical course of the addition, and led to the (*trans*,*anti*,*anti*)-adduct **5a** as the major product with only slightly higher selectivity.

Upon comparison with the results reported by Kobayashi,[9] it appears that the *anti* diastereofacial preference of the 1,3-dioxolane-4-carboxaldehyde **4a** is reinforced by the *cis*-substituent,[17] and the *syn*-selectivity characteristic for the additions of metalated bis-lactims is overridden. In spite of such moderate substrate control, the influence of the chiral azaenolate still determines the *trans* configuration in the two major bis-lactim ethers **5a** and **6a**.

Prompted by the unexpected change of stereochemical control from azaenolate to aldehyde in the reactions of **3A**–**E** with **4a**, we decided to investigate the potential of such mismatched situations for the selective construction of (*anti*,*anti*)-aminodiol fragments. For this purpose, 2,3-*O*-isopropylidene-L-erythrose **4b** was sought as an appropriate precursor, as has been shown to react with organometallic reagents in a highly stereoselective fashion.[18] Furthermore, reactions of organometallic reagents with lactols are usually more selective than reactions with the corresponding aldehydes.[19] Based on these precedents and aimed at the development of a stereocontrolled approach to the β-galactosidase inhibitor 1-deoxy-D-allonojirimycin,[20] the additions of metalated Schöllkopf's bis-lactim ethers **3A**–**E*** to the lactol **4b** were examined,[21] the most salient results being summarized in Table 2.

Table 2. Selectivity and yields in the aldol additions of metalated bis-lactims **3A**–**E*** to mismatched lactol **4b**

Case	Additive	Equiv.	Yield (%)[a]	**5b**/**6b**/**7b**[b]
A	–	–	52	6.2:3.8:0.0
B	$ZnCl_2$	6.0	–	–:–:–
C	$SnCl_2$	3.0	78	7.7:0.3:2.0
C*	$SnCl_2$	6.0	89	9.1:0.9:0.0
D	$MgBr_2{\cdot}OEt_2$	3.0	70	3.3:0.6:6.1
E	$Ti(NEt_2)_3Cl$	3.0	70	3.0:7.0:0.0
E*	$Ti(OiPr)_3Cl$	3.0	78	6.6:3.3:1.0

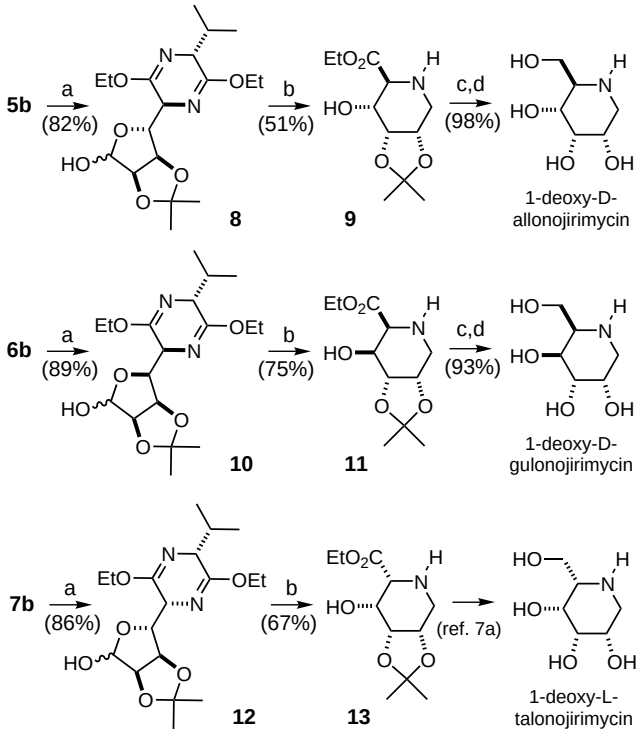
[a] Isolated yield of mixtures of diastereoisomers.
[b] Ratios determined by ^1H NMR analysis of the mixtures of adducts.

To this end, lactol **4b**[22] was slowly added to THF solutions of 3 equiv. of the azaenolates **3A**–**E*** at −78°C and the reaction mixtures were gradually warmed to 0°C during 12 h. After quenching, aqueous work-up and removal the excess of bis-lactim ether,[23] mixtures of diastereomeric adducts **5b**/**6b**/**7b** (see Scheme 2) were

isolated in good yields for all the cases except for the reaction of **3B**, that was not observed under such conditions or with longer reaction times and higher temperatures. The additions to the lactol **4b** generally proceeded with improved diastereoselectivity relative to the same reactions with aldehyde **4a**. In sharp contrast to the results obtained with the aldehyde, the stereochemical course of the additions to the lactol was found to be markedly dependent on the nature of the metal salt.[15] In this way, the (*trans*,*anti*,*anti*)-adduct **5b** was predominantly obtained with either the lithium or the tin azaenolates. As expected, Sn(II) azaenolate reacted with higher diastereoselectivity and better yield than the lithium azaenolate. Remarkably, on using an excess of $SnCl_2$, **5b** was formed with a diastereomeric excess higher than 80% and could be isolated with a yield of 81%.[24] Surprisingly, the (*cis*,*syn*,*anti*)-adduct **7b** was predominantly obtained with the Mg(II) azaenolate,[25] while tuning the ligand for the Ti(IV) azaenolate enabled the modulation of the stereochemical course of the addition. In this manner, the (*trans*,*syn*,*syn*)-adduct **6b** was favored using $Ti(NEt_2)_3Cl$ as additive, while the (*trans*,*anti*,*anti*)-adduct **5b** was mainly obtained with $Ti(OiPr)_3Cl$. It can be concluded that the diastereofacial preference of the lactol **4b** overwhelms the stereochemical bias imposed by the azaenolate in a higher extension than previously observed for the related aldehyde **4a**. Moderate reagent control was observed only for the titanium azaenolate **3E** in the reactions with the lactol.

Conversion of adducts **5**, **6** and **7** into 1-deoxy-D-allonojirimycin,[26] 1-deoxy-D-gulonojirimycin[27] and 1-deoxy-L-talonojirimycin[28] was straightforward, involving chemoselective oxidation of the primary hydroxyl group to enable reductive amination after removal of the chiral auxiliary, as depicted in Scheme 3.

Debenzylation of adducts **5a**, **6a**, and **7a** by catalytic hydrogenation gave the corresponding diols **5b**, **6b**, and **7b** in quantitative yields (see Scheme 1), which were subsequently oxidized to the γ-lactols **8**, **10** and **12**, respectively, by using a slight modification of Corey's conditions.[29] In this way, when a solution of compounds **5b**, **6b** or **7b** was treated with a solution of *o*-iodoxybenzoic acid (IBX)[30] a 62–68% conversion to the desired lactols **8**, **10** or **12** was achieved.[31] Selective hydrolysis of the bis-lactim ether in the presence of the isopropylidene ketal and subsequent intramolecular reductive amination were achieved in a one-pot procedure. Stirring the lactols **8**, **10** or **12** in a 1:2 mixture of 0.25 M HCl and EtOH under a hydrogen atmosphere and palladium catalyst afforded the piperidine esters **9**, **11** or **13** in good yields. Reduction of **9** or **11** with $LiBEt_3H$ proceeded cleanly, as previously described for other piperidine derivatives with acidic functions.[7] Filtering the crude reduction products through Dowex (H^+ form) and subsequent purification by reverse-phase flash chromatography (H_2O, RP-18, 230–400 mesh) afforded 1-deoxy-D-allonojirimycin or 1-deoxy-D-gulonojirimycin in excellent yields.[32] The stereochemical assignment for piperidine ester **13**, derived from adducts **7a**,**b**, was made by comparing its specific rotation and spectral data with those of its enantiomer, which has been previously prepared as an intermediate in the synthesis of 1-deoxy-D-talonojirimycin.[7a]



Scheme 3. Transformation of adducts **5**–**7b** into iminosugars. *Reaction and conditions*: (a) IBX, DMSO/THF (1:1), 8°C, 24 h. (b) 0.25 M HCl/EtOH (1:2), H_2, Pd/C, rt, 3 h. (c) $LiBEt_3H$, THF, rt, 5 h. (d) Dowex-H^+.

In conclusion, aldol additions of metalated bis-lactim ethers derived from *cyclo*-[Gly-D-Val] to 2,3-*O*-isopropylidene-L-erythrose allow a direct and highly (*anti*,*anti*)- or moderate (*syn*,*syn*)-selective access to polyhydroxy amino acids that have been efficiently transformed into 1-deoxy-D-allonojirimycin and 1-deoxy-D-gulonojirimycin. Study of the corresponding aldol additions to mismatched threose derivatives for the synthesis of piperidine alkaloids in the ido and altro series is currently under progress.

Acknowledgements

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32. Specific rotations and spectral data obtained for these iminosugars were in accordance with the literature values.