A concise enantioselective synthesis of iminosugar derivatives†

Wei-Wei Liao, Ismail Ibrahem and Armando Córdova*

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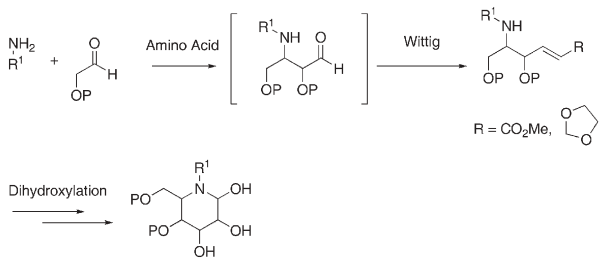
The concise *de novo* synthesis of amino- and iminosugar derivatives is presented; the four stereocenters of the iminosugar derivatives are created in two-steps with high chemoselectivity and excellent enantioselectivity.

Glycobiology is a rapidly growing research area uncovering multiple biological processes wherein carbohydrates play a major role. Moreover, this research area is also used in the finding of selective carbohydrate based inhibitors with different therapeutic areas.[1] Among these, glycosidase inhibitors are the most important,[2] being extensively studied in the treatment of metabolic disorders such as diabetes[3] and Gaucher disease[4] and as antiviral or anticancer agents.[5,6] An important type of glycosidase inhibitor are sugar-like compounds with an easily protonated basic N-atom replacing the ring oxygen atom of the carbohydrate (iminosugars). There is a plethora of approaches to their synthesis and they usually rely on monosaccharide transformations.[2c,7] Moreover, the development of efficient catalytic enantioselective methods for the preparation of iminosugars constitutes an important active area of research.[8] However, existing catalytic enantioselective routes usually require extensive protective group strategies and more than six steps.

Organocatalysis is a rapidly growing research field in organic synthesis.[9] In this context, amino acid catalysis was recently added to the synthetic repertoire of carbohydrate synthesis.[10] For example, organocatalysis has been employed to the *de novo* synthesis of aldoses and ketoses.[11] Organocatalysis has the advantages of being highly selective and reducing synthetic manipulations. However, amino acid catalysis has not yet been applied to the synthesis of iminosugars.

Triggered by the importance and pharmaceutical activity of iminosugars, we became interested in finding a short enantioselective route for their preparation based on asymmetric catalysis. Thus, we envisioned an expeditious amino- and iminosugar synthesis based on one-pot tandem organocatalytic asymmetric Mannich–Wittig-olefination reactions utilizing an α-oxyaldehyde as the aldehyde component followed by diastereoselective hydroxylation [eqn (1)].



(1)

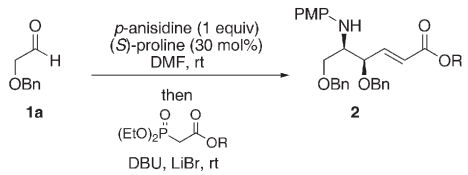
Herein, we describe the short *de novo* synthesis of amino- and iminosugar derivatives, where the newly formed stereocenters are created in two-steps with high stereocontrol.

In initial experiments, we investigated the possibility of developing a one-pot tandem organocatalytic Mannich–(Horner–Wittig–Emmons) (HWE) reaction (Table 1). Thus, we reacted α-benzyloxyacetaldehyde **1a** (3 equiv.) with *p*-anisidine (1 equiv.) in the presence of a catalytic amount of (*S*)-proline (30 mol%) in DMF.[12] After 48 h of stirring at room temperature, LiBr (2.2 equiv.), the alkyl diethylphosphonoacetate (2.2 equiv.) and DBU (2.2 equiv.) were added to the reaction mixture. The reaction was quenched after 1.5 h and the desired orthogonally protected vicinal amino alcohols **2a** and **2b** where isolated in 64 and 51% yield, respectively, with 4:1 dr and 95% ee.

Encouraged by these results we investigated our tandem catalytic asymmetric Mannich–HWE protocol for a set of different aldehyde donors and acceptors (Table 2). In all cases tested, the desired *p*-methoxyphenyl (PMP) protected vicinal amino alcohols **2a–2e** were furnished with good to high dr [4:1–(>19):1 dr] and high enantiomeric excesses (95–96% ee).

The one-pot tandem organocatalytic asymmetric Mannich–HWE reaction protocol is readily performed with other donor and acceptor aldehydes than protected α-oxyaldehydes,[13] which allows for structural variation at the C-6 and C-4 positions of the products **2**. For example, the PMP protected chiral amine **2d** was assembled in an asymmetric manner in 88% yield with >19:1 dr and 96% ee (Entry 4). We next assembled in an asymmetric manner the desired galactolactam **4a** with excellent stereocontrol (Scheme 1). Thus, tandem catalytic asymmetric Mannich–HWE

Table 1 One-pot asymmetric assembly of **2a** and **2b**



Entry	R	Product	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	Me	**2a**	64	4:1	95
2	Et	**2b**	51	4:1	95

[a] Isolated yield of the pure products after silica-gel chromatography. [b] *syn*:*anti* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses, Bn = benzyl, PMP = *p*-methoxyphenyl.

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Sweden. E-mail: acordova1a@netscape.net; acordova@organ.su.se; Fax: +46 8 15 49 08; Tel: +46 8 162479
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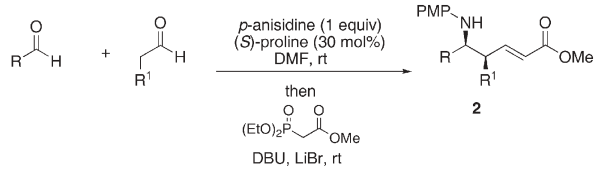
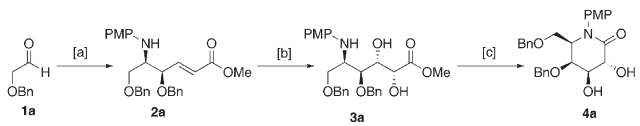
Table 2 One-pot tandem catalytic Mannich–HWE reactions



Entry	R	R^1	Product	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	CH_2OBn	OBn	**2a**	64	4:1	95
2	CO_2Et	OBn	**2c**	45	10:1	96
3	CO_2Et	OBn	**2c**	51[d]	10:1	96
4	*p*-ClC_6H_4	Me	**2d**	88	>19:1	96

[a] Isolated yield of the pure products after silica-gel chromatography. [b] *syn*:*anti* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses, Bn = benzyl, PMP = *p*-methoxyphenyl. [d] Preformed imine was used as the acceptor.



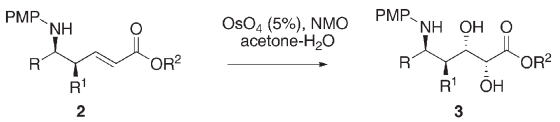
Scheme 1 *Reagents and conditions*: [a] *p*-anisidine, (*S*)-proline, DBU, LiCl, $(EtO)_2POCH_2COOMe$, DMF, rt, 64% for **2a**; [b] cat. OsO_4, NMO, acetone–H_2O 9:1, rt, 67% for **3a**; [c] AcOH, MeOH, reflux, 74% for **4a**.

reaction with protected glycoaldehyde **1a** gave **2a**, which was catalytically dihydroxylated[14] to furnish galactonic acid **3a**. The subsequent ring-closure of **3a** yielded the desired galactolactam **4a** with 95% ee (Scheme 1).

In addition, we also asymmetrically assembled other galactonic acids than **3a**. Thus, catalytic diastereoselective dihydroxylation of the chiral vicinal amino alcohols **2** furnished the corresponding orthogonally protected 5-deoxy-5-aminogalactonic acids **3a–3c** in good yield with good dr (6:1–8:1 dr) and high ees (95–96% ee) (Table 3).

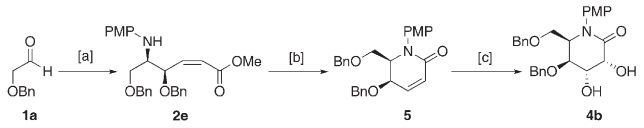
The dihydroxylation of α,β-unsaturated ester **2d** proceeded with moderate diastereoselectivity. Thus, the size of the C-4 substituent of the chiral amines **2** was important in the shielding of the *Re*-face of the olefinic bond. The galactonic acids **3** are structurally varied at the C-6, and C-4 positions, which makes them highly modular chiral synthons and scaffolds for the synthesis of polyhydroxylated compounds.

Table 3 Catalytic conversion of chiral α,β-unsaturated esters **2** to galactonic acids

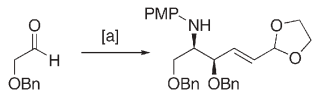


Entry	R	R^1	R^2	Product	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	CH_2OBn	OBn	Me	**3a**	67	7:1	95
2	CH_2OBn	OBn	Et	**3b**	71	8:1	95
3	CO_2Et	OBn	Me	**3c**	74	6:1	96
4	*p*-ClC_6H_4	Me	Me	**3d**	86	2:1	96

[a] Isolated yield of the pure products after silica-gel chromatography. [b] *syn*:*anti* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses, Bn = benzyl, PMP = *p*-methoxyphenyl.



Scheme 2 *Reagents and conditions*: [a] i. *p*-anisidine, (*S*)-proline, DMF, rt, ii. $(Ph)_3P{=}CH_2COOMe$, DMF, rt, 56% for **2e**; [b] AcOH, MeOH, reflux, 82% for **5**. [c] cat. OsO_4, NMO, acetone–H_2O 9:1, rt, 80% for **4b**.



Scheme 3 *Reagents and conditions*: [a] *p*-anisidine, (*S*)-proline, LiOEt, (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide, DMF, rt, 31% for **6**.

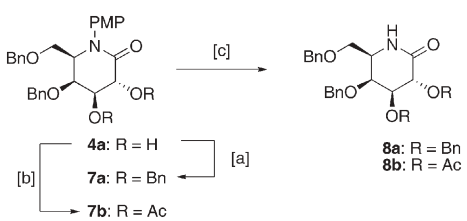
The catalytic asymmetric Mannich reaction of **1a** was also linked with Wittig olefination to furnish protected vicinal amino alcohol **2e** with a 4:1 *Z*:*E* (**2e**: 92% ee; **2a**: 95% ee) ratio (Scheme 2). The subsequent ring-closure of **2e** was followed by catalytic diastereoselective dihydroxylation of lactam **5** to furnish the desired gulolactam **4b** as a single diastereomer with high enantiomeric excess (92% ee).

Thus, iminosugar derivatives with a gulose configuration can also be prepared in few chemical manipulations. Moreover, the one-pot catalytic asymmetric Mannich–Wittig reaction can also be applied to the synthesis of other excellent precursors of iminosugars. For example, starting from aldehyde **1a** chiral protected aldehyde **6** was asymmetrically assembled exclusively as the *trans*-isomer with 90% ee in one-pot (Scheme 3).

The PMP protective groups of galactolactams **7a** and **7b** were readily removed with CAN (cerium ammonium nitrate) to yield the corresponding galactolactams **8a** and **8b**, respectively (Scheme 4).

Comparison of the known galactolactam **8a** with the literature established that the absolute and relative stereochemistry of the iminosugar was that of (+)-D-galactolactam ($[\alpha]_D^{25}$ = +62.0 (*c* = 0.1, $CHCl_3$); literature $[\alpha]_D^{25}$ = +68.0 (*c* = 0.38, $CHCl_3$)[15]). Thus, starting the *de novo* synthesis with (*S*)-proline asymmetrically assembles the corresponding D-iminosugars with excellent stereoselectivity. This is in accordance with established transition state theory for proline-catalyzed Mannich reactions.[12,13]

In summary, we have developed a short protocol for the *de novo* synthesis of amino- and iminosugar derivatives. The new stereocenters are set in two steps: a one-pot catalytic asymmetric Mannich–HWE or Mannich–Wittig olefination reaction and a



Scheme 4 *Reagents and conditions*: [a] BnBr, NaH, *n*-Bu_4NI, THF, 0–4 °C, 34% for **7a**; [b] Ac_2O, cat. DMAP, CH_2Cl_2, rt, 96% for **7b**. [c] CAN, CH_3CN–H_2O 9:1, 0 °C, 36% for **8a** and 40% for **8b**.

subsequent catalytic diastereoselective dihydroxylation. For example, orthogonally protected galactolactams were prepared with high stereoselectivity. The short synthetic protocol allows for structural variation at the C-4, and C-6 positions of the iminosugar. Thus, both enantiomeric forms of several natural as well as non-natural iminosugars can be prepared in few steps, which reduces extensive protective group manipulations and the generation of waste products. We are currently applying our synthetic methodology in the asymmetric assembly of several novel enzyme inhibitors as well as linking the one-pot tandem asymmetric Mannich–Wittig reaction with other catalytic asymmetric oxidations.

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