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Total synthesis of (+)-swainsonine and (+)-8-*epi*-swainsonine

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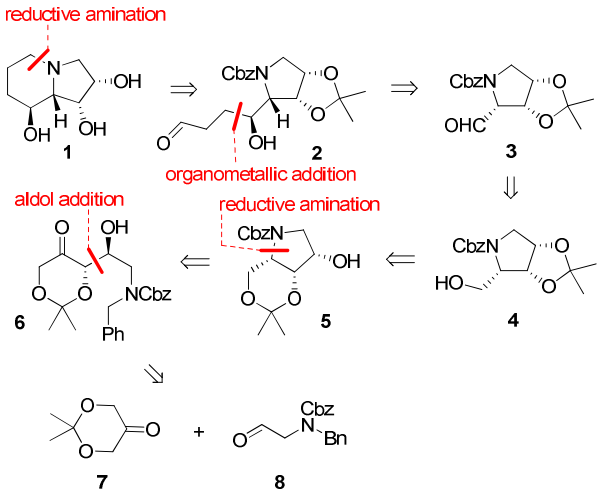
Enantioselective synthesis of (+)-swainsonine was achieved in 9 steps, with 24% overall yield. The key feature of the synthesis is the tactical combination of reactions: organocatalyzed aldolization/reductive amination, which allows for a rapid construction of highly functionalized heterocyclic systems. In a similar way (+)-8-*epi*-swainsonine was synthesized (7 steps, 28%).

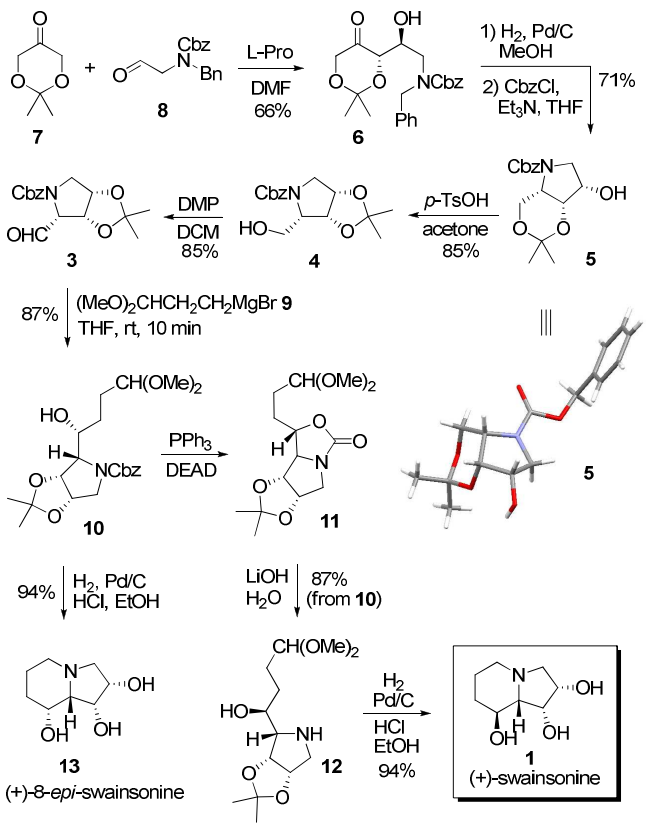
Iminosugars, also known as azasugars, or iminocyclitols, are a class of alkaloids that has attracted considerable attention from the scientific community, due to their promising biological activity.[1] These compounds inhibit enzymes involved in carbohydrate processing, which may have therapeutic potential for treatment of various deseases, such as cancer, diabetes, obesity, or viral infections.[1c] Indolizidine alkaloids are an important subclass of this family,[2] where swainsonine (*ent*-**1**)[3] occupies a prominent place. This alkaloid, first isolated in 1973,[4] was found to be a potent inhibitor of mannosidases,[5] and has entered in phase II clinical trials for the treatment of renal carcinoma.[6] It was also found to be a potent and strain-selective inhibitor of infection by prions – infectious agents responsible for neurodegenerative disorders such as Creutzfeldt-Jacob disease and kuru.[7] Intensive synthetic efforts toward this compound have resulted in more than 50 syntheses, most of them relying on a chiron approach, using sugars, amino acids, or hydroxy acids as starting compounds.[8,9] Of interest is not only swainsonine, but also its structural analogues (including the optical antipode, which is a strong and specific inhibitor of naringinase),[9i,10] for the studies of structure activity relationship.[11]

We set out to develop an enantioselective synthesis of swainsonine that would start from achiral precursors, using a catalytic asymmetric approach. The retrosynthetic blueprint is represented in Scheme 1. Disconnection of the piperidine ring in **1** by reductive amination gives pyrrolidine derivative **2**, which would be obtained by homologation of aldehyde **3**. The synthetic predecessor of **3** – dioxolane **4** – should be a thermodynamically more stable isomer of 1,3-dioxane **5**, on its turn obtainable by reductive amination of aldol **6**. This latter compound would be assembled by an organocatalyzed[12] aldol addition of dioxanone (**7**)[13] to amino aldehyde **8**. The key feature of this synthetic concept would be the tactical combination of reactions: organocatalyzed aldolization/reductive amination, which we recently applied in the synthesis of hyacinthacine analogues.[14] Both enantiomers of swainsonine would be available from the same starting compounds, using enantiomeric organocatalysts.



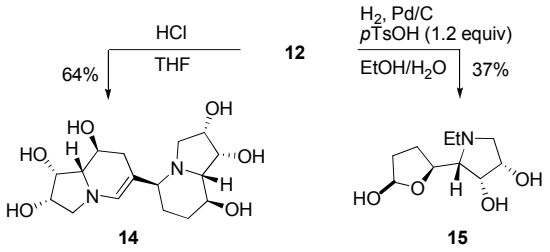
Scheme 1. Retrosynthetic analysis of (+)-swainsonine (**1**).

The synthesis commenced with (*S*)-proline-catalyzed aldol addition of dioxanone (**7**) to aminoacetaldehyde derivative **8**, which produced the desired adduct **6** in 66% yield, as a single diastereoisomer (Scheme 2). For the reasons of atom-economy, we also attempted to



Scheme 2. Total synthesis of (+)-swainsonine (**1**) and (+)-8-*epi*-swainsonine (**13**).

perform the aldol addition with a single-protected Cbz-aminoacetaldehyde (i.e., substituting hydrogen for benzyl in compound **8**). These attempts gave inferior results: lower diastereoselectivity, extended reaction time, incomplete conversion and the low yield (20-30%); in addition, the corresponding aldol product was unstable and decomposed on purification. Upon exposure to a hydrogen atmosphere in the presence of palladium on charcoal, aldol **6** underwent double deprotection followed by a reductive amination, to give a pyrrolidine derivative which was reprotected *in situ* and isolated as a Cbz-derivative **5**. The product was obtained as a mixture of two easily separable diastereoisomers with the predominance of the desired one (**5**: 71%; ***epi*-5** (not represented): 6%), corresponding to the hydrogen delivery from the sterically less shielded, convex face of the bicyclic imine intermediate. The absolute configuration of this compound was confirmed by a single-crystal X-ray analysis.[15] Acetone-derived dioxolanes are known to be more stable than the corresponding dioxanes; therefore, **5** was isomerized in the presence of a catalytic amount of *p*-TsOH to primary alcohol **4**, which was further oxidized with Dess-Martin periodinane to aldehyde **3**. Homologation of **3** was accomplished in high yield via addition of Grignard reagent **9**, with the formation of a single diastereoisomer **10**. The observed stereochemical outcome of the reaction can be explained by the coordination of the metal with the carbamate oxygen followed by the nucleophilic attack from the sterically less shielded face.[16,11d,e] Exposure of **10** to the hydrogenation conditions in 2M HCl resulted in reductive amination and produced (+)-8-*epi*-swainsonine (**13**) in high yield. The configurational inversion of the newly created secondary alcohol stereocenter in **10**, as required for the synthesis of **1**, was accomplished under modified Mitsunobu conditions: the Cbz group served as an internal nucleophile, thus obviating the need for the addition of carboxylic acid, which is usually used as an external nucleophile in the reactions of this type. After the hydrolysis of cyclic carbamate **11**, aminoacetal **12** was subjected to the hydrogenation conditions in highly acidic medium, to provide in excellent yield (+)-swainsonine (**1**) identical to the natural product in all respect (except for the sense of optical rotation). It is of note that for the cyclization of **12** to occur, a fine balance between the acidity and the reducing power of the reaction medium is required. An attempt to hydrolyze the acetal functionality in **12** by treatment with 2M HCl resulted in the formation of dimeric compound **14** (64%, Scheme 3).[17] To our surprise, catalytic hydrogenation of **12** under mildly acidic conditions gave *N*-ethylated product **15** (37%, Scheme 3).[18]



Scheme 3. Side reactions during attempted reductive amination of **12**.

Conclusions

To summarize, total synthesis of (+)-swainsonine (**1**) was achieved from the commercially available achiral precursors in 9 steps with 24% overall yield, which compares favorably (in terms of yield and step-economy) with all previous asymmetric syntheses of this compound. In addition, (+)-8-*epi*-swainsonine was also synthesized by the shortest route reported so far (7 steps, 28% overall yield). The key feature of the syntheses described is the tactical combination of reactions: organocatalyzed aldolization/reductive amination, which allows for an expedient entry into optically pure heterocycles.

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [experimental procedures, spectral data and copies of NMR spectra for all compounds, CIF file for compound **5**]. See DOI: 10.1039/c000000x/

1 Citations here in the format A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523; A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523.

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Enantioselective total synthesis of (+)-swaisonine that hinges on a combination of organocatalyzed aldolization and reductive amination, affords the title compound in 9 steps, with 24% overall yield.