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# Total Synthesis of (+)-Swainsonine, (–)-Swainsonine, (+)-8-*epi*-Swainsonine and (+)-Dideoxy-Imino-Lyxitol by an Organocatalyzed Aldolization/Reductive Amination Sequence

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**Abstract**

A tactical combination of either (*S*)- or (*R*)-proline catalyzed aldol reaction followed by intramolecular reductive amination enabled the synthesis of a chiral pyrrolidine derivative with 3 contiguous stereocenters in only 2 synthetic steps, starting from achiral precursors. This product, obtainable in both enantiomeric forms, was further exploited as a common intermediate in total syntheses of the biologically active iminosugars: (+)-swainsonine, (–)-swainsonine, (+)-8-*epi*-swainsonine, and (+)-dideoxy-imino-lyxitol.

**Keywords**

iminosugars, organocatalyzed aldol reaction, reductive amination, glycosidase inhibitors, indolizidines, pyrrolidines

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(–)-Swainsonine (*ent*-**1**, Figure 1)[1] is a biologically active polyhydroxylated indolizidine iminosugar,[2–4] with high potential for application in pharmacy and medicine, due to its diverse biological activities: swainsonine inhibits Golgi α-mannosidase II,[5–8] exhibits anticancer[9,10] and anti-prion[11] activity and has been tested as a therapeutic option for immunological disorders.[12,13] It has attracted significant attention from the synthetic community, resulting in more than 50 total syntheses.[14–21] Additionally, in order to enhance the biological activity, several structural analogs of (–)-swainsonine (*ent*-**1**) have also been synthesized.[22–27] Over the past several years, we have successfully utilized tactical combination of organocatalyzed aldolization and reductive amination as a key step in asymmetric synthesis of several iminosugars.[28–32] The main advantages of our approach include good to excellent reagent-controlled stereoselectivity in aldol addition, as well as substrate-controlled stereoselectivity in reductive amination thus allowing preparation of both natural and unnatural iminosugar stereoisomers. Previously, we reported a concise synthesis of (+)-swainsonine (**1**) and (+)-8-*epi*-swainsonine (**18**) based on this synthetic concept[16]; herein, we provide a full account on this research.

## Results and Discussion

Our retrosynthetic strategy for the enantioselective synthesis of (+)-swainsonine (**1**) is outlined in Figure 1. The piperidine ring in **1** could be constructed by reductive amination from pyrrolidine derivative **2**, which in turn could be obtained by organometallic addition to aldehyde **3**. Aldehyde **3** might arise from 1,3-dioxane **5**, through an epimerization/oxidation sequence (via dioxolane **4**). Disconnection of the pyrrolidine ring in compound **5** by reductive amination gives aldol **6**—a compound which could be produced enantioselectively by proline-catalyzed aldol addition of 2,2-dimethyl-1,3-dioxan-5-one (**7**, dioxanone) to amino aldehyde **8**.[33–37] As our synthesis starts from achiral precursors, both enantiomers of swainsonine and 8-*epi*-swainsonine would be available simply by switching from (*S*)- to (*R*)-proline as a catalyst in the aldol reaction.

The synthesis started with asymmetric aldol reaction between dioxanone **7** and double-protected amino aldehyde **8** (Figure 2). When (*S*)-proline was employed as a catalyst, a

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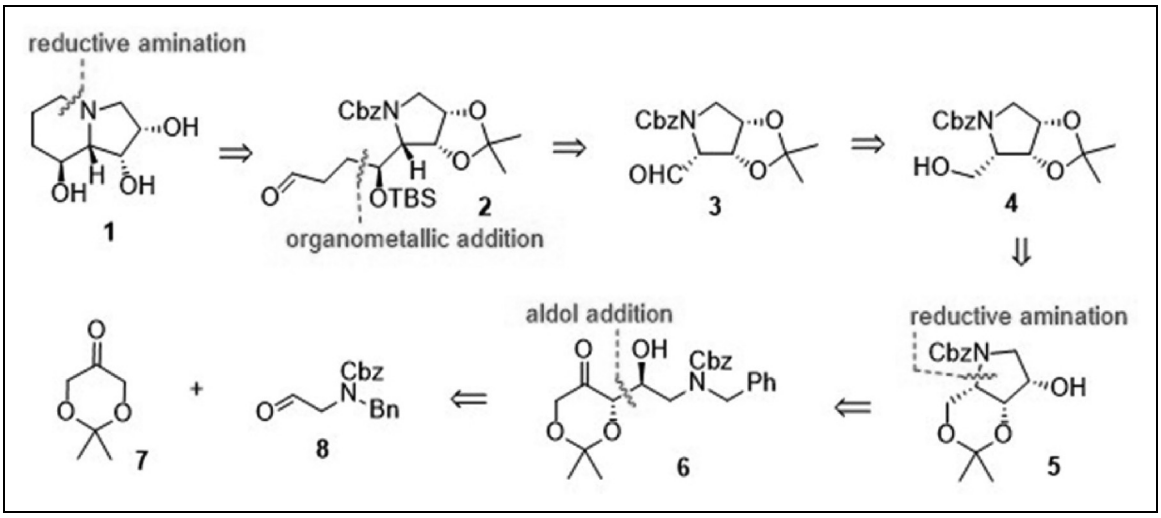


**Figure 1.** Retrosynthetic analysis of (+)-swainsonine (1).

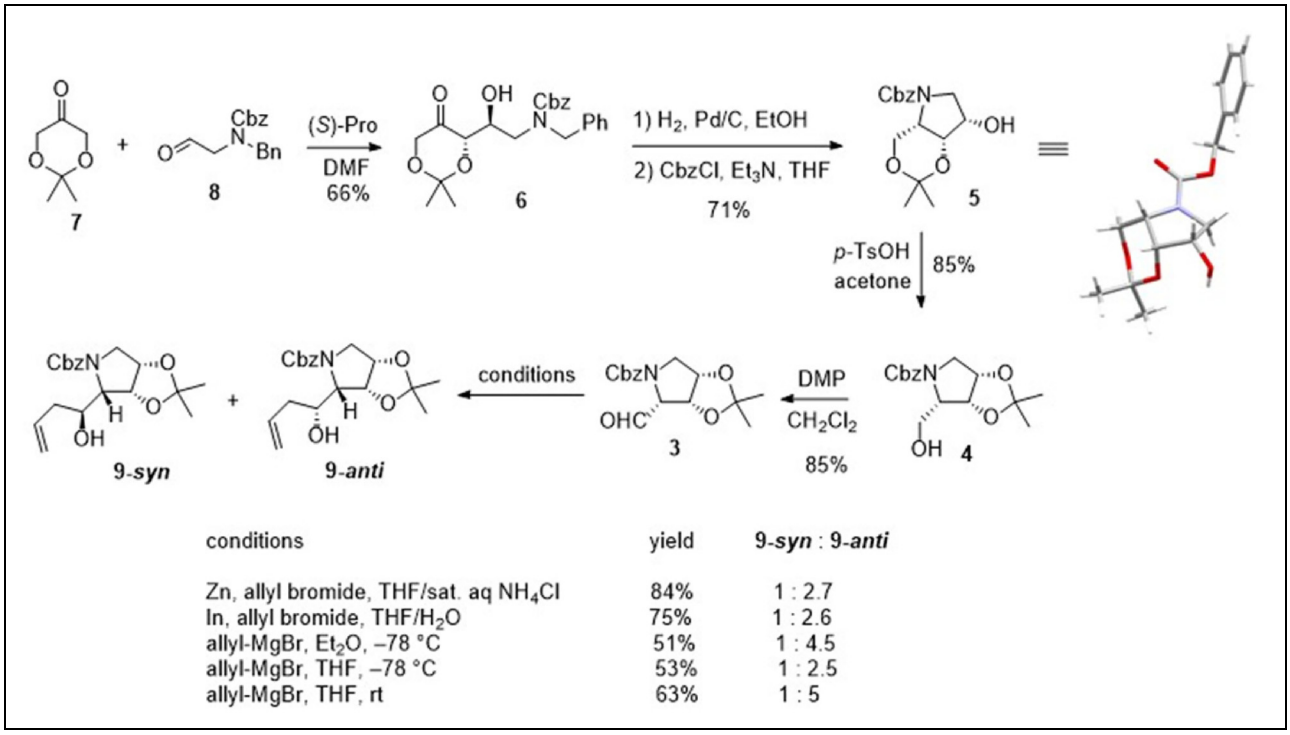


**Figure 2.** Synthesis of pyrrolidine derivative 3 and subsequent allylation reaction.

smooth reaction occurred and *anti*-aldol **6** was obtained in good yield (66%), as a single diastereoisomer. An attempt to perform the aldol reaction with a single-protected Cbz-aminoacetaldehyde resulted in a prolonged reaction time, incomplete conversion of the starting material, low diastereoselectivity and poor yield (20%-30%). Exposure of aldol **6** to hydrogenation conditions led to deprotection and subsequent reductive amination in situ; after reprotection, the pyrrolidine derivative **5** was obtained. As a consequence of the bicyclic structure of the imine intermediate, the reductive amination proceeded with good substrate-controlled diastereoselectivity (12/1). As a result of a tactical combination of the aldolization and reductive amination, the trisubstituted pyrrolidine derivative **5**, with the required configuration at all 3 newly formed contiguous stereocenters, was expeditiously synthesized in optically pure form. The absolute configuration of this compound was confirmed by a single-crystal x-ray analysis.[38]

A greater thermodynamic stability of dioxolane **4** (with respect to 1,3-dioxane **5**) was exploited as a driving force for the epimerization of dioxane **5** under acidic conditions, and

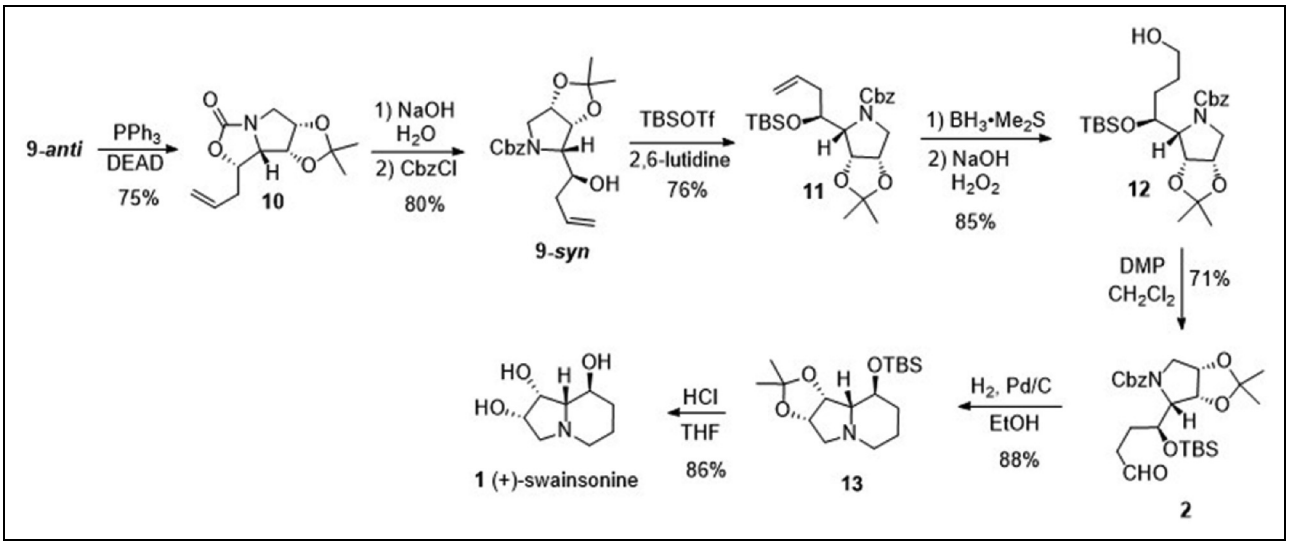


**Figure 3.** Epimerization of 9-*anti* to 9-*syn* and completion of the synthesis of (+)-swainsonine (1).

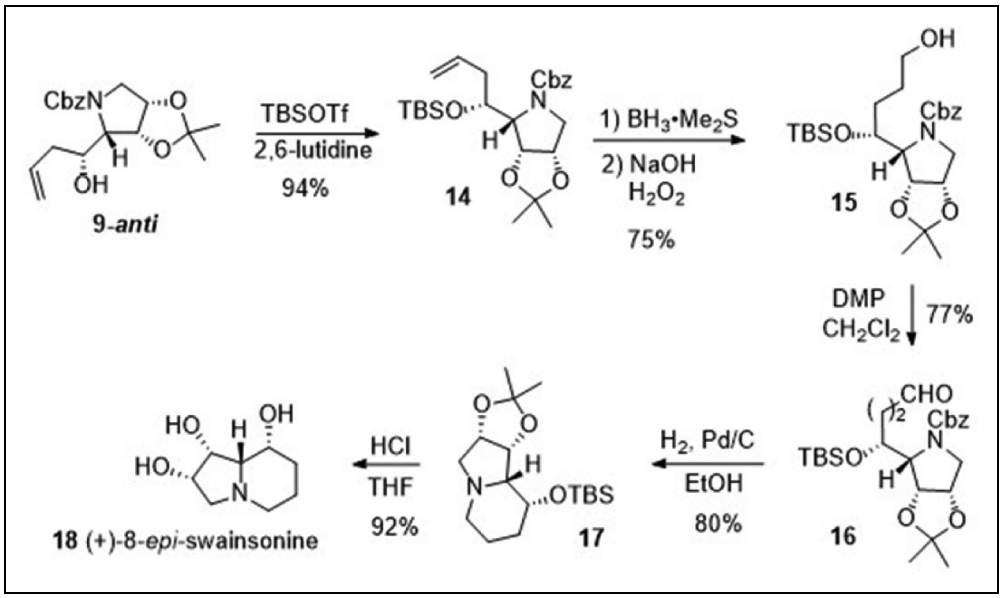


**Figure 4.** Completion of the synthesis of (+)-8-*epi*-swainsonine (18).

after subsequent oxidation of primary alcohol **4** with Dess-Martin periodinane, the aldehyde **3** was isolated in good yield (72% over 2 steps). Aldehyde **3** served as a substrate for the planned organometallic allyl addition. The Zn- and In-mediated reactions afforded the homoallylic alcohol **9** in good yields; however, it was obtained as a mixture of 2 diastereoisomers with the predominance of the undesired one (**9-*anti***), which would not lead to swainsonine, but to its 8-epimer. Predominant formation of the **9-*anti*** isomer can be rationalized by the coordination between metal and carbamate oxygen, resulting in the attack of allyl nucleophile from the less hindered face of the molecule.[39–41] Thus, the inversion of the stereochemical outcome would be unlikely even with a different protecting group on nitrogen.

With this in mind, we focused on searching for the most selective method for the production of "undesired" diastereoisomer **9-*anti***, which would be subsequently isomerized into the required **9-*syn*** stereoisomer. After some experimentation, the highest diastereoselectivity was obtained with allyl-Grignard reagent at rt in THF (dr = 5:1). Notably, under Mitsunobu conditions ($Ph_3P$, DEAD), an intramolecular substitution at the newly created stereocenter in **9-*anti*** occurred, to give the cyclic carbamate **10**; in this modified Mitsunobu protocol the Cbz group served as an internal nucleophile (Figure 3). After hydrolysis of cyclic carbamate **10** and nitrogen reprotection, the desired **9-*syn*** product was obtained in 60% yield from **9-*anti***. The secondary hydroxyl group in **9-*syn*** was then protected as a TBS-ether, and the terminal alkene **11** was

converted to primary alcohol **12** by an hydroboration/oxidation protocol. Oxidation of **12** with Dess-Martin periodinane afforded aldehyde **2**, which upon exposure to hydrogenation conditions gave the bicyclic product of a reductive amination, **13**. A global deprotection under acidic conditions provided (+)-swainsonine (**1**), identical to the natural product in all respects. The same reaction sequence was used for the preparation of (+)-8-*epi*-swainsonine **(18)**, starting from **9-*anti*** stereoisomer (Figure 4).

After completing the synthesis of both (+)-swainsonine (**1**) and (+)-8-*epi*-swainsonine (**18**), further efforts were made in order to increase the efficiency of both syntheses, by introducing the already oxygenated fragment, instead of the allyl group, to aldehyde **3**: in addition to improving the overall redox-economy of the synthesis, the addition of the modified Grignard reagent **19** was expected to be diastereoselective, obviating the separation of isomers. Indeed, the reaction of **3** with **19** produced the expected adduct **20**, as a single stereoisomer in 87% yield (Figure 5). The increased diastereoselectivity of the reaction (as compared to allyl magnesium bromide) can be explained by the internal coordination of the Grignard reagent **19**, which increases steric bulk and further disfavors nucleophilic attack on the aldehyde from the *Si*-face. In addition, the addition of allyl magnesium bromide can proceed with allylic rearrangement (which may decrease stereoselectivity of the reaction), which is not possible for **19**. Finally, hydrogenation of **20** under acidic conditions led to one pot total deprotection and reductive amination to afford (+)-8-*epi*-swainsonine (**18**) in excellent yield (94%), thus shortening the first-generation synthesis by as much as 4 steps.

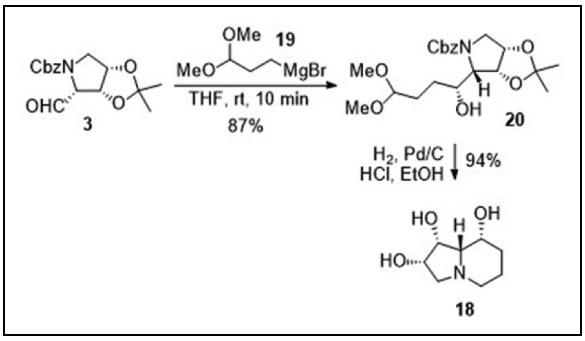


**Figure 5.** The improved synthesis of (+)-8-*epi*-swainsonine (18).

The synthesis of (+)-swainsonine (**1**) required the epimerization of the secondary alcohol **20**, which was accomplished under Mitsunobu conditions (Figure 6), as previously described for **9-*anti***. Surprisingly, the hydrolysis/hydrogenation protocol which was successfully applied for the synthesis of 8-*epi*-swainsonine (**18**), was not useful for the diastereoisomer **21**. An attempt to hydrolyze the acetal functionality in **21** by treatment with 2 M HCl resulted in the formation of dimeric compound **22**; this transformation proceeds *via* an interesting sequence involving the Mannich reaction of the swainsonine-derived iminium ion with the corresponding enamine, as previously described by Nagasawa, Asakawa and collaborators.[26] In addition, catalytic hydrogenation under mildly acidic conditions gave *N*-ethylated product **23**.[42,43] Apparently, intramolecular hydrogen bonding induced considerable changes in the conformation and reactivity of **21** (with respect to **20**); for the cyclization of **21** to occur, it was crucial to finely tune the acidity and the reducing power of the reaction medium. After some experimentation, we found that catalytic hydrogenation in the presence of excess HCl affords (+)-swainsonine (**1**) in excellent yield.

As an additional benefit of the represented synthetic approach, the optical antipode of intermediate **5** was separately synthesized by the same procedure, but using (*R*)-proline as a

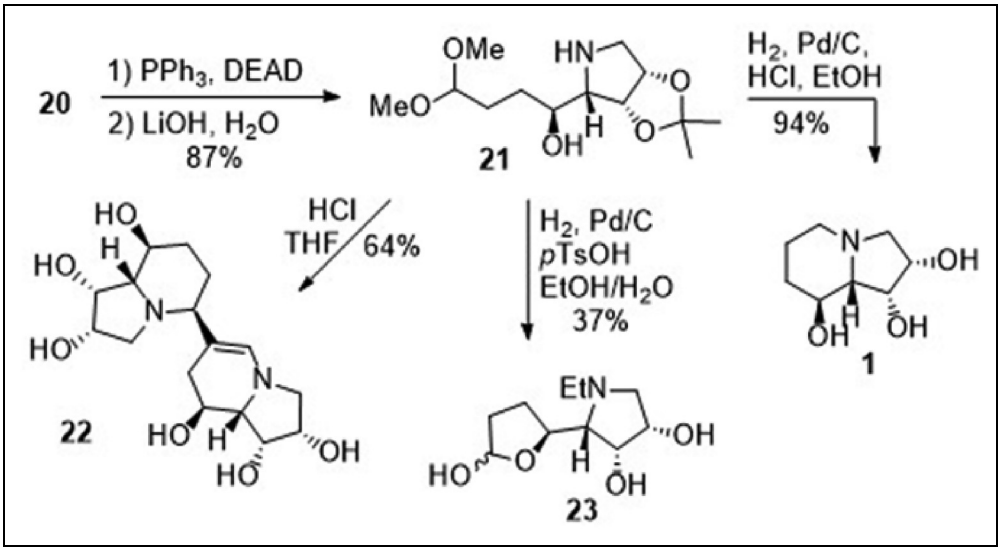


**Figure 6.** The improved synthesis of (+)-swainsonine (1).

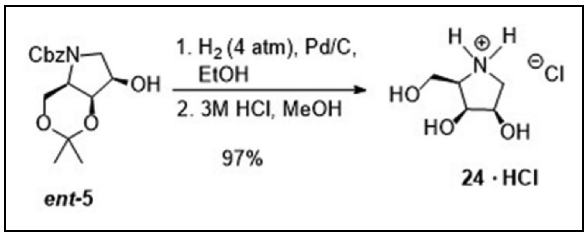


**Figure 7.** Synthesis of (+)-dideoxy-imino-lyxitol (24).

catalyst. This pyrrolidine derivative was then converted to (+)-dideoxy-imino-lyxitol (**24**, DIL) in 2 steps (Figure 7). DIL (**24**) is another member of a class of biologically active pyrrolidine iminosugars: it was found to inhibit Golgi α-mannosidase II[44] and β-galactocerebrosidase.[45]

## Conclusions

In summary, the catalytic enantioselective synthesis of 3 biologically active iminosugars was accomplished from 2 commercially available, achiral precursors. The synthesis hinges on a tactical combination of 2 reactions: organocatalyzed aldol addition which proceeds as a catalytic asymmetric reaction, and reductive amination. This approach allows for a quick assembly of the pyrrolidine core with a defined absolute configuration of 3 newly formed stereocenters, resulting in highly efficient total synthesis of (+)-swainsonine (**1**), (–)-swainsonine (***ent*-1**) (9 steps, 24% overall yield), (+)-8-*epi*-swainsonine (**18**) (7 steps, 28% overall yield) and (+)-dideoxy-imino-D-lyxitol **24** (5 steps, 45% overall yield).

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### Supplemental Material

Supplemental material for this article is available online.

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