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De Novo Asymmetric Synthesis of D- and L-Swainsonine

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Abstract

The enantioselective syntheses of both enantiomers of the indolizidine natural product swainsonine have been achieved in 13 steps from furan. The indolizidine ring system is installed by a one-pot hydrogenolysis of both an azide and O-Bn group along with an intramolecular reductive amination reaction. The asymmetry of swainsonine was introduced by Noyori reduction of an acylfuran. This route relies upon an Achmatowicz rearrangement, a diastereoselective palladium catalyzed glycosylation, Luche reduction and a dihydroxylation reaction.

Over the years the indolizidine class of alkaloid natural products has attracted a lot of attention from the synthetic community because of their interesting structures and potent biological activities.¹ A unique subset of the indolizidine natural products is noteworthy because of their ability to serve as potent glycosidase inhibitors and as such they have received attention from both the synthetic and carbohydrate communities.² The potent mannosidase inhibitor, swainsonine **1** has probably received most of this attention.³

Since the first syntheses by Richardson,⁴ Fleet,⁵ Suami⁶ and Sharpless⁷ in 1984, there have been over 30 syntheses of swainsonine. Most routes to swainsonine draw their asymmetry from carbohydrate starting materials (e.g. Richardson and Fleet). Of the syntheses, the routes by Cha⁸ and Pearson^{9,3f} are most practical. Cha's route is considered the shortest (8 steps from D-erythrose), whereas, the 15-step synthesis of swainsonine by Pearson provided material on a multigram scale. Key to the success of the Pearson synthesis is the use of highly diastereoselective transformations.

In 1995, Hiram was the first to prepare the enantiomer of swainsonine (*ent*)-**1**.¹⁰ Hiram synthesized L-swainsonine in 20 steps from butyrolactone.^{10a} A year later, Fleet synthesized L-swainsonine for its evaluation as a glycosidase inhibitor.^{10b} Fleet's study of L-swainsonine showed that it is a potent inhibitor of naringinase, an L-rhamnosidase enzyme. That is to say, a protonated L-swainsonine (*ent*)-**2** functions as a transition state mimic for the enzymatic hydrolysis of both L- α -mannose (*ent*)-**3** and L-rhamnose (*ent*)-**4** (Figure 1).¹⁰ Typically the naturally occurring mannose exists in its D-form and the naturally occurring 6-deoxy-mannose, rhamnose, exist in its L-form.

As a continuation of our efforts aimed at the *de novo* synthesis of oligosaccharides, we wanted to prepare swainsonine-containing *manno*-oligosaccharides. The goal of these efforts is to develop more selective glycosylation inhibitor, with the hope that it would display better antitumor and antiviral activity than swainsonine.¹¹ Thus, we became interested in a practical

synthesis of swainsonine. In particular, we desired a route that was shorter and as practical as the Pearson approach. Since we wanted access to both the D- and L-swainsonine, we planned to synthesize swainsonine by a *de novo* route.

Retrosynthetically, we envisioned that we could establish the D/L stereochemistry by a Noyori reduction of acylfuran **10**, which can be prepared in one step from furan and γ -butyrolactone. An Achmatowicz reaction should convert the furyl alcohol **9** into a C-6 substituted pyranone **8**.¹² A stereoselective protection of the anomeric alcohol followed by ketone reduction and a palladium catalyzed allylic substitution should convert **8** into **7**. With the C-1,4,5 stereochemistry established in **7** a diastereoselective dihydroxylation reaction should install the *manno*-stereochemistry in **6**.

Finally, we planned on a global hydrogenolysis/alkylation/reductive amination sequence to convert azidosugar **6** into swainsonine **1** via imine **5**. This one-pot transformation would initially involve an azide reduction to form the aminosugar **13**, which after an intramolecular alkylation would undergo hydrogenolysis to free up the anomeric hydroxyl group to form **14**. Finally, under the same reaction conditions **14** should undergo a reductive amination reaction to form swainsonine.¹³ Herein we describe our successful efforts to implement this strategy for the *de novo* synthesis of swainsonine.

As outlined in Scheme 3, our approach to both D- and L-swainsonine began with commercially available furan and γ -butyrolactone **12**.¹⁴ Treatment of γ -butyrolactone **12** with a THF solution of 2-lithiofuran **11** gave furyl ketone **16** in good yield (74%). The primary alcohol of **16** was protected as a TBS-ether using TBSCl/imid. in DMF providing **10** in an excellent yield (98%). The asymmetric reduction of acylfuran **10** under modified Noyori conditions¹⁵ afforded the desired furyl alcohol (*ent*)-**9** in 89% yield with high enantiomeric purity (> 96% ee). Exposing furyl alcohol (*ent*)-**9** to the typical Achmatowicz conditions (NBS in THF/H₂O) gave the ring-expanded product pyranone (*ent*)-**8** in good yield (84%).

In order to diastereoselectively protect the anomeric position as benzyl ether; we employed a two-step acylation/Pd-catalyzed glycosylation (Scheme 4). Diastereoselective acylation of hemiacetal (*ent*)-**8** with (Boc)₂O provided the Boc-protected pyranone **17** (8:1 α/β ratio) in excellent yield (85%). Coupling of pyranone **17** with benzyl alcohol in presence of 2.5% palladium(0) and 5% triphenylphosphine gave Bn-protected pyranone **18** as a single diastereomer in excellent yield (88%).^{12b,16}

With pyranone **18** suitably protected at the anomeric position, we next investigated the stereoselective azide incorporation at C-4 using palladium catalysis (Scheme 5). The C-4 ketone in **18** was diastereoselectively reduced with NaBH₄ (CH₂Cl₂/MeOH, -78 °C) forming the equatorial allylic alcohol **19** in excellent yield (94%). In order to convert the allylic alcohol of **19** into a better leaving group it was acylated with methyl chloroformate to form the mixed carbonate **20** (72%). Exposing carbonate **20** to the conditions developed by Sinou¹⁷ (TMSN₃, (Pd(allyl)Cl)₂/1,4-bis(diphenylphosphino)butane) afforded a single regio- and stereo-isomeric allylic azide (*ent*)-**7** in a good yield (77%).¹⁸

Before the one-pot reductive cyclization could be attempted the TBS-protected primary alcohol needed to be converted into a good leaving group and the C-2/C-3 diol needed to be introduced (Scheme 6). Deprotection of TBS-ether (*ent*)-**7** with a THF solution of TBAF gave the primary alcohol **21** in near quantitative yield (99%). The primary alcohol in **21** was converted to a mesylate (MeSO₂Cl, Et₃N, 0 °C), forming **22** in similarly excellent yield (99%). The *manno*-stereochemistry in diol (*ent*)-**6** was stereoselectively installed by dihydroxylation of allylic azide **22** under Upjohn conditions (OsO₄/NMO, 93%).¹⁹ Finally, L-swainsonine (*ent*)-**1** was obtained by exhaustive hydrogenation of an ethanol solution of diol (*ent*)-**6** with Pd(OH)₂/C in excellent yield 88% (100 psi, 3 days).²⁰

Similarly, a protected form of L-Swainsonine **29** could also be synthesized from (*ent*)-**7** by incorporating an acetonide protection (Scheme 7). Once again a stereoselective dihydroxylation of allylic azide (*ent*)-**7** was performed (OsO₄/NMO) yielding diol **24** (92%). Protecting diol **24** with 2,2-dimethoxypropane and acid catalyst *p*-TsOH, afforded acetonide **25** (97%), whose TBS group was deprotected (TBAF) to provide primary alcohol **26**. Mesylation of **26** (MeSO₂Cl, Et₃N, 0 °C) gave mesylate **28** in excellent yield (99%). Once again, exhaustive hydrogenation/hydrogenolysis of a THF/ethanol solution of azide **28** (100 psi, 4 days) afforded the protected swainsonine **29**, which was easily deprotected (95%) to give L-swainsonine (*ent*)-**1**. This alternative sequence gave L-swainsonine (*ent*)-**1** in similarly excellent overall yield (70% from allylic azide (*ent*)-**7** in 6 steps).²⁰ Swainsonine prepared by either of these two methods provided material with physical and spectral data (melting point, ¹H NMR, ¹³C NMR, IR, and optical rotation), which matched that of the natural material.^{3–10}

In conclusion, two short *de novo* asymmetric syntheses of swainsonine (**1**) and its enantiomer (*ent*)-**1** have been developed. This highly enantio- and diastereocontrolled route illustrates the utility of the Noyori reduction, Achmatowicz reaction and a palladium catalyzed glycosylation for natural product synthesis. This approach provided both enantiomers of swainsonine in 17% overall yields from furan **11**, respectively. It is also worth noting that this route provided swainsonine in comparable efficiency to the previous carbohydrate based approach;^{3–10} however, this *de novo* approach started from achiral sources and required the use of only two protecting groups. Further application of this approach to the synthesis of swainsonine containing oligosaccharides and biological testing is ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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20. By simply switching the (*S, S*)-Noyori reagent for the reduction of 10 to (*ent*)-9 to the (*R, R*)-Noyori reagent (10 to 9), D-swainsonine was prepared from 9 in nearly identical overall yield.

Figure 1.
Swainsonine (**1**) and L-enantiomer (**ent-1**)

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

Scheme 2.
Key reductive cyclization to swainsonine (1)

Scheme 3.
Enantioselective synthesis of pyranone (*ent*)-8

Scheme 4.
Palladium catalyzed C-1 protection

Scheme 5.
Palladium catalyzed C-4 azide incorporation

Scheme 6.
Diastereoselective C-2/3 dihydroxylation and reductive cyclization to L-swainsonine (*ent*-1)

Scheme 7. Synthesis of swainsonine (*ent*)-1 via a protected swainsonine (**29**)