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De Novo Asymmetric Synthesis of D- and L-Swainsonine

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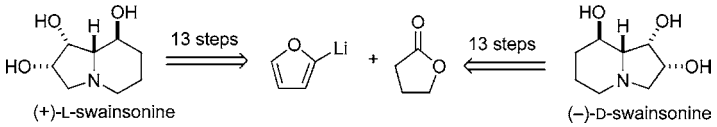
ABSTRACT



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 an 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] Suami,[6] and Sharpless[7] 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 Cha[8] and Pearson[3f,9] are the most practical. Cha's route is considered the shortest (eight 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, Hirama was the first to prepare the enantiomer of swainsonine (***ent*)-1**.[10] Hirama 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) (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1645−1680. (b) Michael, J. P. *Nat. Prod. Rep*. **1997**, *14*, 619−636.

(2) For a review of iminosugars, see: (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed*. **1999**, *38*, 2300−2324. (b) Tyler, P. C.; Winchester, B. G. *Iminosugars as Glycosidase Inhibitors* **1999**, 125−156. (c) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045−66. (d) Fellows, L. E.; Kite, G. C.; Nash, R. J.; Simmonds, M. S. J.; Scofield, A. M. *Rec. Adv. Phytochem.* **1989**, *23*, 395−427.

(3) For a review of swainsonine syntheses, see: (a) Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579−8629. For more recent syntheses, see: (b) Martin, R.; Murruzzu, C.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325−2328. (c) Heimgaertner, G.; Raatz, D.; Reiser, O. *Tetrahedron* **2005**, *61*, 643−655. (d) Song, L.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2004**, *69*, 7284−7293. (e) Lindsay, K. B.; Pyne, S. G. *Aust. J. Chem.* **2004**, *57*, 669−672. (f) Pearson, W. H.; Ren, Y.; Powers, J. D. *Heterocycles* **2002**, *58*, 421−430. (g) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem*. **2002**, *67*, 7774−7780. (h) Buschmann, N.; Rueckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329. (i) Zhao, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem*. **2001**, *66*, 1761−1767.

(4) Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447−448.

(5) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853−1856.

(6) Suami, T.; Tadano, K.; Iimura, Y. *Chem. Lett.* **1984**, 513−516.

(7) Adams, C. E.; Walker, F. J.; Sharpless. K. B. *J. Org. Chem.* **1985**, *50*, 420−422.

(8) Bennett, R. B.; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580−2582.

(9) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217−7221.

(10) (a) Oishi, T.; Iwakuma, T.; Hirama, M.; Ito, S. *Synlett* **1995**, 404−406. (b) Davis, B.; Bell, A. A.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. J. *Tetrahedron Lett.* **1996** *37*, 8565−8568.

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1).[10] Typically, the naturally occurring mannose exists in its D-form, and the naturally occurring 6-deoxymannose, rhamnose, exist in its L-form.

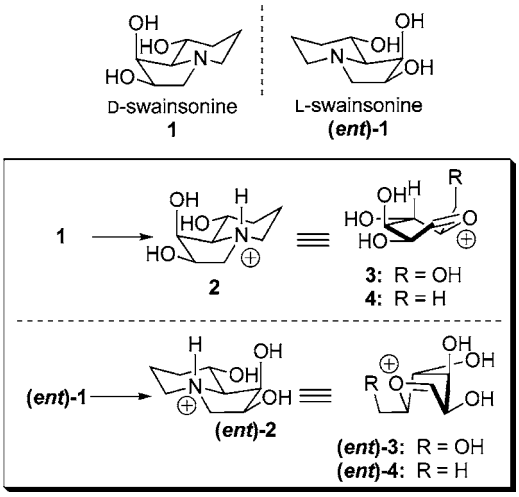
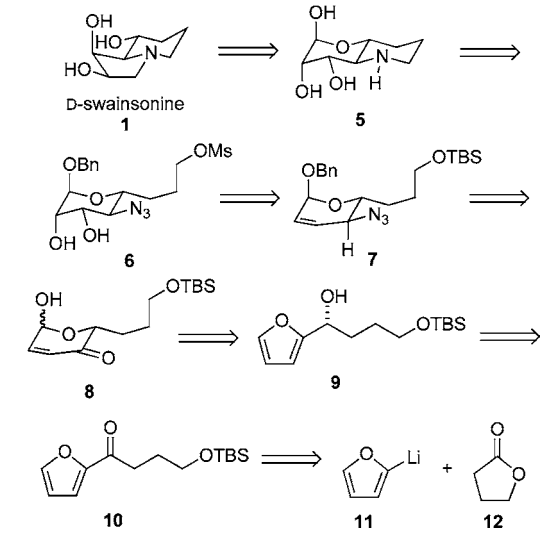


Figure 1. Swainsonine (**1**) and L-enantiomer (***ent*)-1**.

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 a more selective glycosylation inhibitor, with the hope that it will 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.

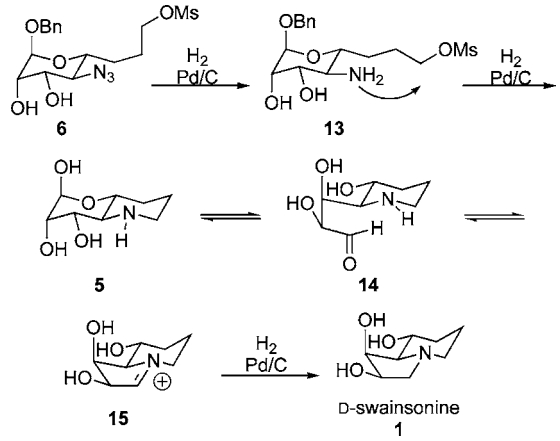
Retrosynthetically, we envisioned that we could establish the D/L stereochemistry by a Noyori reduction of acylfuran **10**, which can be prepared in one step from furan and γ-butyrolactone (Scheme 1). An Achmatowicz reaction should convert the furyl alcohol **9** into a *C*-6-substituted pyranone **8**.[12] 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**.

Scheme 1. Retrosynthetic Analysis of Swainsonine (**1**)



Finally, we planned on a global hydrogenolysis/alkylation/reductive amination sequence to convert azidosugar **6** into swainsonine **1** via imine **5** (Scheme 2). 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.

Scheme 2. Key Reductive Cyclization to Swainsonine (**1**)



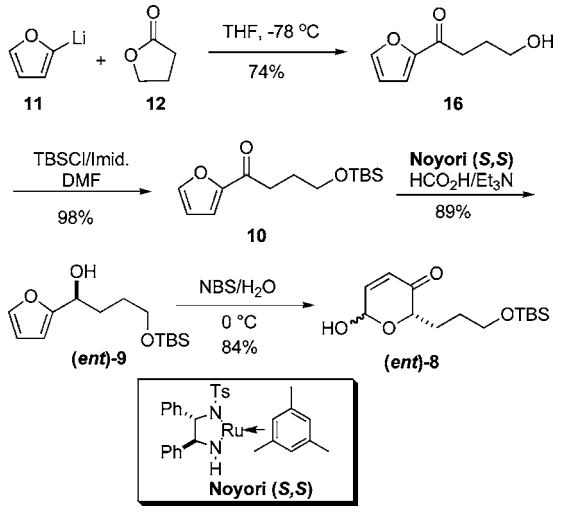
As outlined in Scheme 3, our approach to both D- and L-swainsonine began with commercially available furan and

(11) For the bioactivities of swainsonine, see: (a) Elbein, A. D. *FASEB J.* **1991**, *5*, 3055−3063. (b) Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer Res.* **1997**, *3*, 11077−11086. (c) Galustian, C.; Foulds, S.; Dye, J. F.; Guillou, P. J. *Immunopharmacol.* **1994**, *27*, 165−172. (d) Grzegorzewski, K.; Newton, S. A.; Akiyama, S. K.; Sharrow, S.; Olden, K.; White, S. L. *Cancer Commun.* **1989**, *1*, 373−279. (e) Elbein, A. D. *Annu. Rev. Biochem* **1987**, *56*, 497−534. (f) Cenci Di Bello, I.; Fleet, G.; Namgoong, S. K.; Tadano, K.; Winchester, B. *Biochem. J.* **1989**, *259*, 855−861.(g) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199−210. (h) Tulsiani, D. R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936−7939. (i) Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1985**, *38*, 936−940.

(12) An Achmatowicz reaction is the oxidative rearrangement of furyl alcohols to 2-substituted 6-hydroxy-2*H*-pyran-3(6*H*)-ones; see: (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165−176. For its recent use in carbohydrate synthesis, see: (b) Guo, H.; O'Doherty, G. A. *Org. Lett*. **2005**, *7*, 3921−3924 and references therein.

(13) In the Fleet synthesis of swainsonine a similar reductive amination was employed; see ref 5.

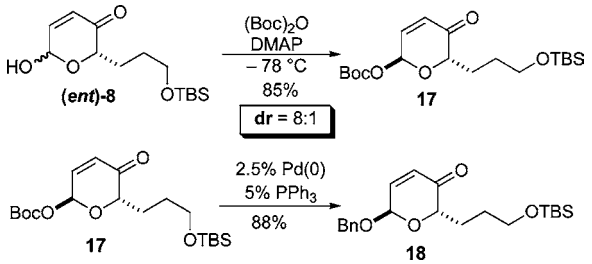
Scheme 3. Enantioselective Synthesis of Pyranone (*ent*)-8



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/imidazole in DMF, providing **10** in an excellent yield (98%). The asymmetric reduction of acylfuran **10** under modified Noyori conditions[15] 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/H_2O) gave the ring-expanded product pyranone **(*ent*)-8** in good yield (84%).

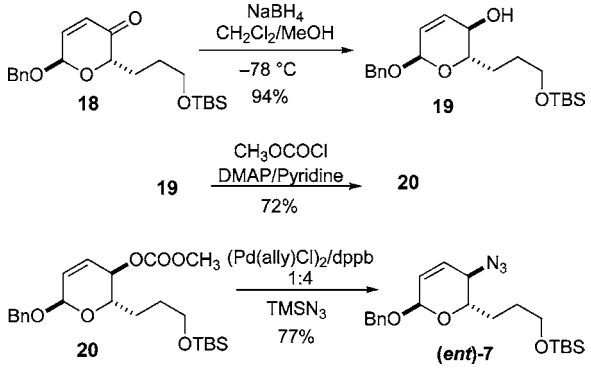
To diastereoselectively protect the anomeric position as an *O*-benzyl ether, we employed a two-step acylation/Pd-catalyzed glycosylation (Scheme 4). Diastereoselective acylation of hemiacetal **(*ent*)-8** with $(Boc)_2O$ provided the Boc-protected pyranone **17** (8:1 α/β ratio) in excellent yield (85%). Coupling of pyranone **17** with benzyl alcohol in the presence of 2.5% palladium(0) and 5% triphenylphosphine gave Bn-protected pyranone **18** as a single diastereomer in excellent yield (88%).[12b,16]

Scheme 4. Palladium-Catalyzed *C*-1 Protection



With pyranone **18** suitably protected at the anomeric position, we next investigated the stereoselective azide incorporation at *C*-4 using palladium catalysis (Scheme 5).

Scheme 5. Palladium-Catalyzed *C*-4 Azide Incorporation



The *C*-4 ketone in **18** was diastereoselectively reduced with $NaBH_4$ (CH_2Cl_2/MeOH, −78 °C) forming the equatorial allylic alcohol **19** in excellent yield (94%). 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 Sinou[17] ($TMSN_3$, $(Pd(allyl)Cl)_2$/1,4-bis(diphenylphosphino)butane) afforded a single regio- and stereoisomeric 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 ($MeSO_2Cl$, Et_3N, 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 (OsO_4/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 an excellent yield of 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

(14) While we have prepared both D- and L-swainsonine, for simplicity herein we only show the L-enantiomer.

(15) Previously, we have shown that a lower ratio of HCO_2H/Et_3N (1:1 instead of 2:1) was required for the Noyori reduction of compounds with primary TBS groups; see: Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett*. **2004**, *45*, 1005−1009.

(16) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc*. **2003**, *125*, 12406−12407. (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc*. **2004**, *126*, 3428−3429. (c) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem*. **2005**, *24*, 169−177.

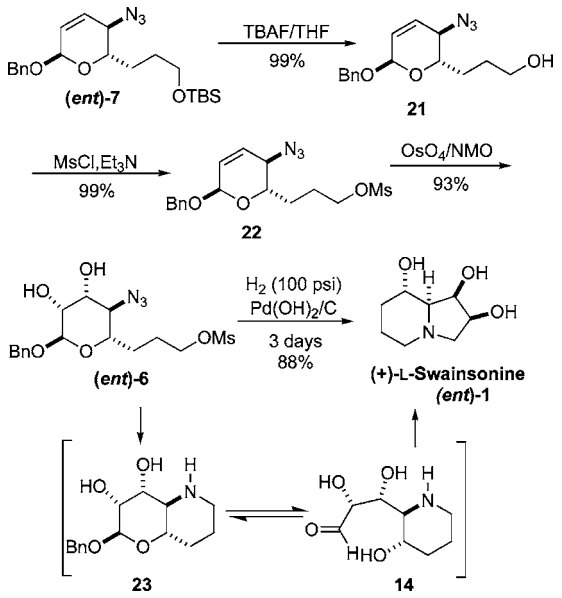
(17) de Oliveira, R. N.; Cottier, L.; Sinou, D.; Srivastava, R. M. *Tetrahedron* **2005**, *61*, 8271−8281.

(18) Presumably, because of the rigid nature of the **7** and the equatorial nature of the allylic azide no [3,3] sigmatropic rearrangement was observed; see: Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc*. **2005**, *127*, 13444−13445.

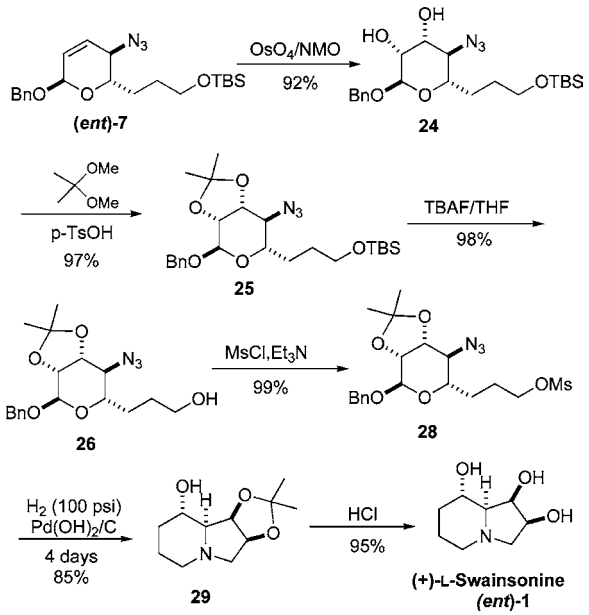
(19) (a) Hudlicky, T.; Abboud, K. A.; Bolonick, J.; Maurya, R.; Stanton, M. L.; Thorpe, A. J. *Chem. Commun*. **1996**, 1717−1718. (b) Takao, K.-I.; Hara, M.; Tsujita, T.; Yoshida, K.-I.; Tadano, K.-I. *Tetrahedron Lett*. **2001**, *42*, 4665−4668.

(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.

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**)



protection (Scheme 7). Once again, a stereoselective dihydroxylation of allylic azide **(*ent*)-7** was performed (OsO_4/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** ($MeSO_2Cl$, Et_3N, 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 six steps).[20] Swainsonine prepared by either of these two methods provided material with physical and spectral data (melting point, ^{1}H NMR, ^{13}C 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, the 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.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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