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A Short, Organocatalytic Formal Synthesis of (−)-Swainsonine and Related Alkaloids

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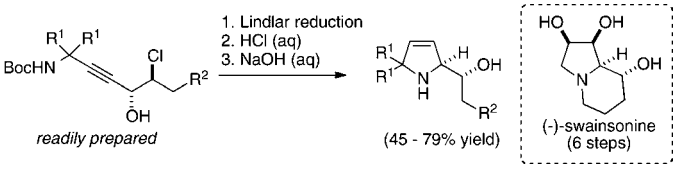
ABSTRACT



A short synthesis of hydroxyalkyl dihydropyrroles has been developed that involves the coupling of propargylamines with α-chloroaldehydes, followed by Lindlar reduction and a one-pot epoxide formation/opening sequence. The application of this process to the synthesis of unnatural iminosugars and a formal synthesis of (−)-swainsonine is described.

Swainsonine (**1**) is an indolizidine alkaloid that was originally isolated from the fungal plant pathogen *Rhizoctonia leguminicola* and structurally assigned as the piperidine **2** (Scheme 1).[1] Several years later, the correct structural assignment for **1** was reported following its reisolation from the Australian flowering plant *Swainsona canescens*,[2] and it was shown to be the causative agent of a livestock disease clinically similar to mannosidosis.[2] Subsequently, it was found that swainsonine is a potent inhibitor of lysosomal α-mannosidase[3a] and Golgi α-mannosidase II,[3b] and **1** has been implicated as a lead candidate for the treatment of a variety of diseases.[4] Most notably, in preclinical models, swainsonine suppressed the growth of several carcinoma xenografts,[5a] and GD0039 (the HCl salt of **1**) progressed as far as phase II clinical trials for the treatment of renal cell carcinoma.[5b] It is not surprising then that swainsonine has been the subject of numerous synthetic efforts.[6−9] In fact, swainsonine has become a classic target for the demonstration of new synthetic methods and/or strategies relevant to pyrrolidine, piperidine, or indolizidine synthesis.[7] Presently, more than 40 syntheses of swainsonine have been reported that range in length from 8 to >20 steps (average approximately 14 steps), the most recent of which was a 14-step synthesis that originates with L-glutamic acid.[9s] Based on the importance of swainsonine as a biological tool and potential therapeutic and the ongoing need for selective Golgi α-mannosidase II inhibitors,[5] we endeavored to develop a short and flexible synthesis of **1** that does not rely on chiral pool starting materials. Specifically, our efforts in the synthesis of *trans*-epoxides[10] and various heterocycles[11] from chlorohydrins suggested that optically enriched aminoepoxides of general structure **5** should be readily available and may well serve as precursors to the pyrrolidine core (e.g., **6**) of the indolizidine alkaloids via a 5-*exo*-*tet* epoxide opening reaction[12] and subsequently iminosugars following alkene oxidation. Elaboration of

(1) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055.
(2) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257.
(3) (a) Dorling, P. R.; Huxtable, C. R.; Colegate, S. M. *Biochem. J.* **1980**, *191*, 649. (b) Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7393.
(4) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579.
(5) (a) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (b) Shaheen, P. E.; Stadler, W.; Elson, P.; Knox, J.; Winquist, E.; Bukowski, R. M. *Invest. New Drugs* **2005**, *23*, 577.
(6) For early syntheses of swainsonine, see: (a) Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, *7*, 447. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29. (c) Adams, C. E.; Walker, F. J.; Sharpless, B. K. *J. Org. Chem.* **1985**, *50*, 420. (d) Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948.
(7) For reviews of swainsonine syntheses, see: (a) Pyne, S. G. *Curr. Org. Synth.* **2005**, *2*, 39. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (c) Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579.
(8) For a large-scale synthesis of swainsonine, see: Sharma, P. K.; Shah, R. N.; Carver, J. P. *Org. Process Res. Dev.* **2008**, *12*, 831.

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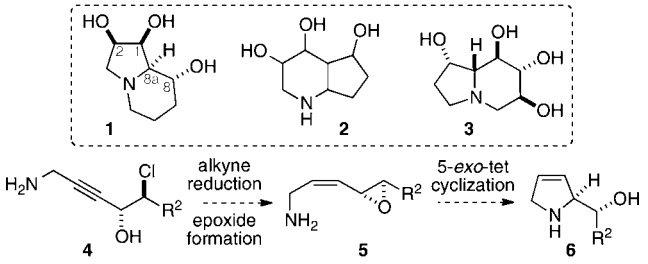
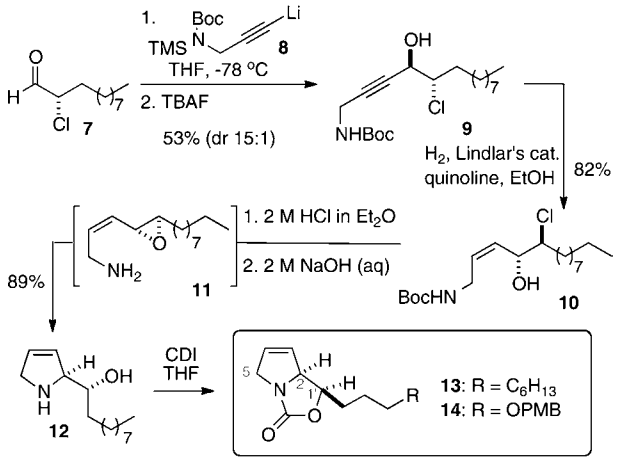
these later substances into swainsonine (**1**), analogues of **1**, or other inhibitors of carbohydrate-processing enzymes (e.g., castanospermine (**3**)[13]) would then involve a second annulation event. The development of this methodology, as well its application in a short formal synthesis of (−)-swainsonine (**1**) and several structurally related alkaloids, are discussed below.

Scheme 1. Natural Products Swainsonine (**1**), Castanospermine (**3**), and a Synthetic Strategy to Access Dihydropyrroles (e.g., **6**)



As depicted in Scheme 2, our initial efforts focused on defining a concise synthesis of 1,2-*anti*-chlorohydrins that incorporate a *cis*-allylamine functionality. It was anticipated that this would be accomplished through the addition of an alkynyllithium[10] derived from propargylamine to an α-chloroaldehyde[11e,14] followed by partial hydrogenation. Toward this goal, α-chloroundecanal (**7**) was prepared in good yield from undecanal[14b] and treated with the dianion generated from the reaction of propargylamine with 2 equiv of *n*-BuLi. Although these conditions provided the desired chlorohydrin (not shown) as a single stereoisomer, this compound was produced in modest yield (22%) and proved difficult to isolate and purify by flash chromatography. In an effort to improve the yield of this reaction and generate a more tractable product, the addition of lithium anions derived from a variety of protected propargylamines to the α-chloroaldehyde **7** was explored. While reaction of the dianion derived from commercially available *N*-Boc-propargylamine with **7** afforded the chlorohydrin **9** in improved yield (44%), addition of the monoanion **8**[15] to this aldehyde consistently provided the desired chlorohydrin **9** in yields >50%.[16] Notably, this latter material proved stable to flash chromatography and underwent smooth reduction to provide

Scheme 2. Synthesis of 2-Hydroxyalkyldihydropyrrole **12**



the desired *cis*-alkenylchlorohydrin **10** in excellent yield. After surveying conditions to promote a sequence of reactions involving deprotection, epoxide formation, and epoxide opening, we found that treating the alkenylchlorohydrin **10** with aqueous acid effected removal of the Boc protecting group and that direct basification of the reaction mixture then promoted epoxide formation followed immediately by epoxide opening, furnishing the dihydropyrrole **12** in excellent overall yield. The relative stereochemistry of the vicinal amino alcohol function in **12** was confirmed following its conversion to the cyclic carbamate **13** and comparison of spectral data derived from **13** to that reported for the related dihydropyrrole **14**.[17]

(9) For syntheses of swainsonine that have been reported since the 2005 review by Pyne (ref 7a), see: (a) Martin, R.; Murruzzu, C.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (c) Tinarelli, A.; Paolucci, C. *J. Org. Chem.* **2006**, *71*, 6630. (d) Au, C. W. G.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097. (e) Ceccon, J.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 4739. (f) Dechamps, I.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082. (g) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J.-H.; Kang, S. H. *Chem.—Eur. J.* **2008**, *14*, 1023. (h) Hakansson, A. E.; van Ameijde, J.; Horne, G.; Nash, R. J.; Wormald, M. R.; Kato, A.; Besra, G. S.; Gurcha, S.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 179. (i) Shi, G. F.; Li, J. Q.; Jiang, X. P.; Cheng, Y. *Tetrahedron* **2008**, *64*, 5005. (j) Alam, M. A.; Kumar, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 4972. (k) Tian, Y.-S.; Joo, J.-E.; Kong, B.-S.; Pham, V.-T.; Lee, K.-Y.; Ham, W.-H. *J. Org. Chem.* **2009**, *74*, 3962. (l) Bates, R. W.; Dewey, M. R. *Org. Lett.* **2009**, *11*, 3706. (m) Choi, H. G.; Kwon, J. H.; Kim, J. C.; Lee, W. K.; Eum, H.; Ha, H.-J. *Tetrahedron Lett.* **2010**, *51*, 3284. (n) Chooprayoon, S.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2011**, *9*, 531. (o) Louvel, J.; Chemla, F.; Demont, E.; Ferreira, F.; Perez-Luna, A. *Org. Lett.* **2011**, *13*, 6452. (p) Chen, M.-J.; Tsai, Y.-M. *Tetrahedron* **2011**, *67*, 1564. (q) Bates, R. W.; Dewey, M. R.; Tang, C. H.; Safii, S. b.; Hong, Y.; Hsieh, J. K. H.; Siah, P. S. *Synlett* **2011**, *14*, 2053. (r) Wardrop, D. J.; Bowen, E. G. *Org. Lett.* **2011**, *13*, 2376. (s) Archibald, G.; Lin, C. P.; Boyd, P.; Barker, D.; Caprio, V. *J. Org. Chem.* **2012**, *77*, 7968.

(10) Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083.

(11) (a) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717. (b) Draper, J. A.; Britton, R. *Org. Lett.* **2010**, *12*, 4034. (c) Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716. (d) Chang, S.; Britton, R. *Org. Lett.* **2012**, *14*, 5844. (e) Britton, R.; Kang, B. *Nat. Prod. Rep.* **2013**, *30*, 227.

(12) For examples of intramolecular epoxide opening reactions that form 5-membered ring heterocycles, see: (a) Shankaraiah, G.; Kumar, R. S. C.; Poornima, B.; Babu, K. S. *Tetrahedron Lett.* **2011**, *52*, 4885. (b) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129. (c) Medjahdi, M.; Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 7859. (d) Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526.

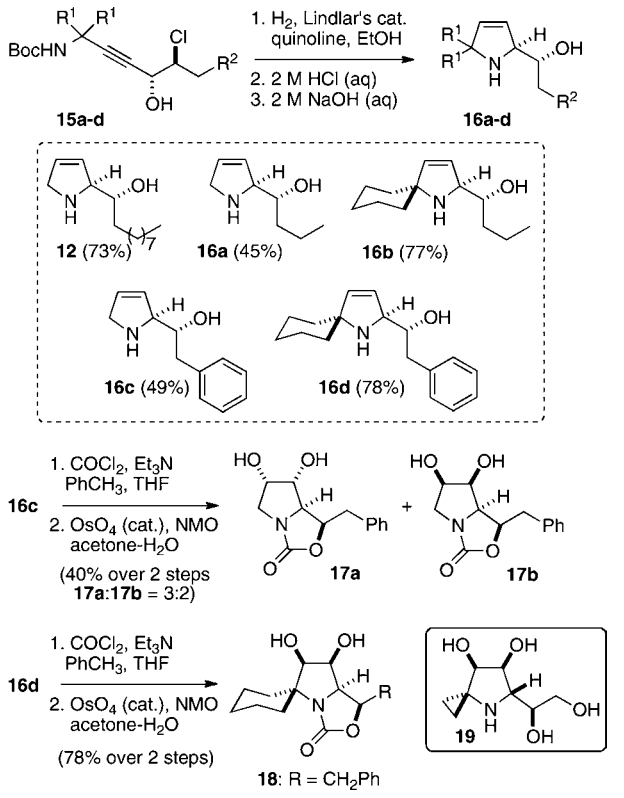
(13) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.

(14) (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (c) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121. (d) Dekeukeleire, S.; D'hooghe, M.; Tornroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 5934.

(15) Azzarelli, J. M.; Lumb, J.-P.; Trost, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 740.

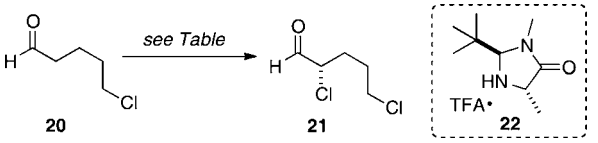
(16) Reaction of the lithium anion derived from *N,N*-bis(trimethylsilyl)-propargylamine or *N,N*-bis(Boc)propargylamine with the chloroaldehyde **7** also provided the desired chlorohydrin, albeit in lower (<45%) yield.

Scheme 3. Synthesis of Hydroxyalkyldihydropyrroles **16a**–**d** and the Protected Aminotriols **17a**, **17b**, and **18**



As depicted in Scheme 3, this strategy for dihydropyrrole synthesis was further explored through the preparation of compounds **16a**–**d**. Toward this end, the alkynyl chlorohydrins **15a**–**d** were synthesized following addition of the requisite Boc-protected propargylamine to 2-chloropentanal or 2-chlorohydrocinnamaldehyde.[14b,18] Pleasingly, Lindlar reduction of the alkynylchlorohydrins followed by direct treatment of the crude reduction products with aqueous acid then base (a one-pot procedure) afforded hydroxyalkyldihydropyrroles **16a**–**d** in good overall yield.[19] Considering the brevity of the entire reaction sequence (four steps), this strategy should serve as an efficient means to access a wide variety of natural and unnatural iminosugars. For example, the dihydropyrroles **16c** and **16d** were converted into the protected iminosugar analogues **17a/17b** and **18**, respectively, via reaction with phosgene followed by dihydroxylation. The relative stereochemistry of these new iminosugars was assigned based on analysis of 1D NOESY spectra (see the Supporting Information for details). Structurally, this latter spirocyclic compound resembles the pyrrolidine **19**, which is a selective inhibitor of α-L-fucosidase.[20]

Table 1. Asymmetric α-Chlorination of Aldehyde **20**[a]



entry	catalyst (mol %)	conditions	temp (°C)	yield (%)	ee[b] (%)
1	L-proline (20)	A	0 to rt	49	0
2	L-prolinamide (20)	A[c]	0 to rt	58	62
3	**22** (20)	B[d]	0 to rt	61	30
4	**22** (20)	B[e]	−25	62	58
5	**22** (20)	B[f]	−35	75	82

[a] Conditions: (A) NCS, CH_2Cl_2, 4 h; (B) $Cu(TFA)_2$, LiCl, $Na_2S_2O_8$, H_2O, MeCN. [b] Determined by chiral HPLC analysis (see the Supporting Information for details). [c] 24 h. [d] 4 h. [e] 3 days. [f] 19 days.

Having established a four-step synthesis of hydroxyalkyl dihydropyrroles, we focused on applying this process to a short synthesis of swainsonine (**1**). For this purpose, it was envisaged that a second annulation event involving displacement of a primary alkyl chloride would secure the indolizidine core of **1**.[21] Toward this end, L-prolinamide-catalyzed chlorination of 5-chloropentanal (**20**)[22] using the procedure reported by Jørgensen[14b] provided the dichloroaldehyde **21** in modest yield and enantioselectivity (Table 1, entry 2). For comparison purposes, using identical reaction conditions the chlorination of pentanal is complete in 4 h (>97% yield) and proceeds with much higher enantioselectivity (85% ee).[10] Unfortunately, when repeated at 0 °C, the extended reaction time corresponded with an erosion in enantioselectivity, presumably through prolinamide-catalyzed racemization of the chloroaldehyde **21**. Considering these challenges, we next explored the use of MacMillan's SOMO-activated aldehyde α-chlorination procedure,[14c] as the imidazolidinone catalyst **22** does not effect racemization of chloroaldehyde products.[14c] Unfortunately, using these conditions (entry 3), the α-chloroaldehyde **21** was prepared in only modest optical purity (30% ee). At lower temperatures, the reaction rate decreased substantially (e.g., entries 4 and 5); however, racemization of the chloroaldehyde product was not observed. Ultimately, chlorination at −35 °C afforded the desired α-chloroaldehyde **21** in good yield and enantioselectivity (82% ee).

(17) Key ^{1}H NMR data for compounds **13** ($CDCl_3$, 600 MHz) and **14** ($CDCl_3$, 300 MHz). H1′: δ 4.72 (**13**), δ 4.70 (**14**); H2: δ 4.72 (**13**), δ 4.70 (**14**); H5α: δ 3.75 (**13**), δ 3.75 (**14**); H5β: δ 4.42 (**13**), δ 4.39 (**14**). For spectral data for compound **14**, see: Lindsay, K. B.; Pyne, S. G. *Aust. J. Chem.* **2004**, *57*, 669.

(18) See the Supporting Information for details.

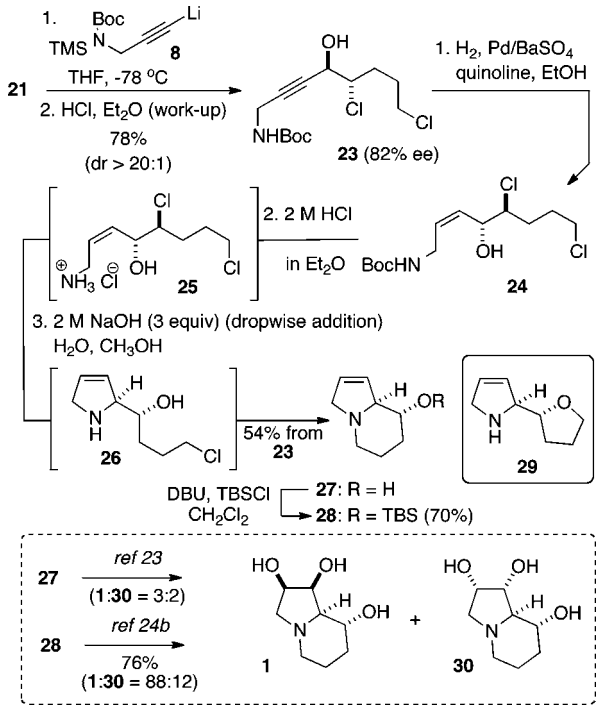
(19) The lower overall yields for **16a** and **16c** reflect difficulties associated with the isolation and purification of these substances rather than the efficiency of the reaction sequence.

(20) Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Schutz, C.; Vogel, P.; Plantier-Royon, R. *Bioorg. Med. Chem.* **2006**, *14*, 4047.

(21) (a) Dudot, B.; Micouin, L.; Baussanne, I.; Royer, J. *Synthesis* **1999**, *4*, 688. (b) St-Denis, Y.; Chan, T. H. *J. Org. Chem.* **1992**, *57*, 3078. (c) Dieter, R. K.; Chen, N.; Watson, R. T. *Tetrahedron* **2005**, *61*, 3221. (d) Dieter, R. K..; Lu, K. *J. Org. Chem.* **2002**, *67*, 847.

(22) 5-Chloropentanal is available from the oxidation of 5-chloro-1-pentanol; see: Brodfuehrer, P. R.; Chen, B.-C.; Sattelberg, T. R.; Smith, P. R.; Reddy, J. P.; Stark, D. R.; Quinlan, S. L.; Reid, J. G.; Thottathil, J. K.; Wang, S. *J. Org. Chem.* **1997**, *62*, 9192.

Scheme 4. Formal Synthesis of (−)-Swainsonine (**1**)



With the α-chloroaldehyde **21** in hand, treatment of this material with the lithium anion derived from the protected propargylamine **8** afforded the 1,2-*anti*-chlorohydrin **23** in good yield and diastereoselectivity (dr > 20:1) (Scheme 4). Initial attempts to effect dihydropyrrole formation from **23** through the sequence of reactions described in Scheme 3 afforded **29** as the major product. After some experimentation, however, it was found that when both the equivalents and rate of addition of NaOH to the alkenylchlorohydrin **25** were strictly controlled, formation of the undesired tetrahydrofuran **29** could be largely avoided. Thus, slow addition of 3 equivalents of aqueous NaOH to **25** in MeOH reproducibly afforded the indolizidine **27** in good yield (54% over three steps from **23**) accompanied by minor amounts (< 10%) of **29**. As expected,[23] dihydroxylation of the indolizidine **27** provided an inseparable mixture of trihydroxyindolizidines **1** and **30**, in which (−)-swainsonine (**1**) was the major component (dr = 3:2). To improve the facial selectivity of the dihydroxylation, the unprotected indolizidine **27** was also converted into the corresponding TBS ether **28**, which undergoes selective dihydroxylation (dr ~8:1) to provide swainsonine (**1**) following deprotection.[24] The spectral data (^{1}H NMR, ^{13}C NMR, MS, IR, $[\alpha]_D$) recorded on the TBS ether **28** were in agreement with that reported for this material by Pyne.[9d] Notably, preparation of the indolizidine **27** in five steps from commerically available 5-chloropentanol constitutes a six-step formal synthesis of (−)-swainsonine, the shortest of all reported routes.

In summary, we have developed a concise asymmetric synthesis of hydroxyalkyldihydropyrroles and demonstrated the utility of this process in a formal synthesis of the α-mannosidase inhibitor swainsonine (**1**). While there are more than 40 reported syntheses of swainsonine ranging in length from 8 to over 20 steps (average length of 14 steps) our unique approach provides access to this potentially important natural product in six steps from 5-chloropentanol, does not rely on chiral pool starting materials, and employs an organocatalytic asymmetric α-chlorination as the basis for the controlled introduction of each stereogenic center. Based on its operational simplicity and reliance on readily available starting materials, this process should be adaptable to the production of a range of indolizidine, pyrrolidine, and pyrrolizidine natural products, efforts that are currently ongoing in our laboratory.

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

(23) De Vicente, J.; Arrayas, R. G.; Canada, J.; Carretero, J. C. *Synlett* **2000**, *1*, 53.

(24) (a) Buschmann, N.; Ruckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325. (b) Mukai, C.; Sugimoto, Y.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281.

The authors declare no competing financial interest.