

Published in final edited form as:

Org Lett. 2011 May 6; 13(9): 2376–2379. doi:10.1021/ol2006117.

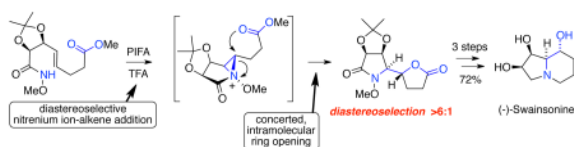
Nitrenium Ion-Mediated Alkene Bis-Cyclofunctionalization: Total Synthesis of (-)-Swainsonine

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Abstract



The total synthesis of (-)-swainsonine from 2,3-*O*-isopropylidene-D-erythrose in 12 steps and an overall yield of 28% is reported. The pivotal transformation in our route to this indolizidine alkaloid is the formation of the pyrrolidine ring and C-8a/8 stereodias through the diastereoselective, bis-cyclofunctionalization of an γ,δ -unsaturated *O*-alkyl hydroxamate. This transformation is believed to proceed via the intramolecular capture of an *N*-acyl-*N*-alkoxyaziridinium ion generated by the diastereoselective addition of a singlet acylnitrenium ion to the pendant alkene.

(-)-Swainsonine (**1**), an alkaloid isolated first from the fungal plant pathogen *Rhizoctonia leguminicola*¹ and subsequently from a range of other sources,² has become one of the most keenly studied of all naturally occurring azasugars (Scheme 1). Interest in this indolizidine stems principally from its role as an inhibitor of Golgi α -mannosidase II (GMII)^{3,4} and, to a lesser extent, lysosomal α -mannosidase (LM).⁵ While the latter enzyme is involved in the catabolism of *N*-linked oligosaccharides, GMII plays a key role in the biosynthesis of glycoproteins, specifically in the formation of their trimannose core.⁶ Since alterations in the normal glycosylation patterns of such proteins are often found on the surface of tumor cells and are associated with metastasis and disease progression, inhibition of GMII offers potential as a cancer treatment. In this context, swainsonine is notable as being the first glycoprotein processing inhibitor selected for clinical evaluation.⁷ Most recently, **1** has also been found to be a strain-selective inhibitor of infectious mammalian prions,⁸ which are associated with a variety of neurodegenerative disorders including Creutzfeldt-Jakob disease and kuru.⁹ Although the mechanism of action in this case awaits clarification, swainsonine's activity does not appear to be associated with its glycosidase inhibitory properties.

Since its isolation, swainsonine has proven a highly popular target of both total¹⁰ and formal syntheses.^{11,12} Furthermore, the search for more potent glycosidase inhibitors, which display improved GMII vs. LM selectivity has spurred the preparation of a large number of

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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>.

analogs.¹³ That swainsonine has recently been the subject of a process research study, further underscores the continued relevance of this natural product as a synthetic target.¹¹ⁿ

As part our ongoing study of the chemistry of nitrenium ions,¹⁴ we recently reported a versatile method for the preparation of α -hydroxyalkyl lactams involving the intramolecular addition of acylnitrenium ions to alkenes.¹⁵ Having successfully utilized this methodology in the stereocontrolled synthesis of the piperidine core of the azasugar castanospermine,¹⁶ we were prompted to consider whether this chemistry might also be brought to bear on (-)-swainsonine. Herein we report the successful development of an efficient route to this indolizidine alkaloid, in which the pyrrolidine ring and C-8a/8 *threo* stereodiad of the target are simultaneously established in a substrate-controlled nitrenium ion oxamidation reaction. Furthermore, we demonstrate that interception of the putative bicyclic aziridinium ion in this key transformation by a proximate carboxylate group offers a novel means of alkene bis-cyclofunctionalization.

From a retrosynthetic perspective, we initially envisioned that the indolizidine skeleton of **1** could be generated from α -hydroxyalkyl lactam **2** through a sequence of functional group reductions and *N*-alkylative ring closure (Scheme 1). In turn, this compound would be accessed through the intramolecular oxamidation of unsaturated hydroxamate **6**. On the basis of our earlier studies,¹⁷ we anticipated that this reaction would proceed via aziridinium ion **3**, which upon regioselective ion-pair collapse at the external (α) position¹⁸ and hydrolysis of the resulting trifluoroacetate ester adduct would provide δ -lactam **2**, thereby establishing the C-8/8a stereodiad of the natural product. With regard to the diastereoselectivity of the addition process, we anticipated that cyclization of the singlet nitrenium ion generated from **6** would preferentially proceed via a transition state resembling pseudo-chair **4**, thereby avoiding the 1,3-allylic strain¹⁹ present in boat-like conformer **5**.²⁰

Our route to (-)-swainsonine (**1**) began from 2,3-*O*-isopropylidene-D-erythronolactone (**7**), which is readily available from the oxidative cleavage of sodium D-isoascorbate with hydrogen peroxide (Scheme 2).²¹ Following a sequence of reactions developed by Pearson and Hembre during their synthesis of **1**,^{10c} reduction of **7** with DIBAL-H yielded the corresponding D-erythrose derivative,²² which through stereoselective addition of vinylmagnesium bromide²³ and selective *O*-silylation of the primary alcohol, was converted to allylic **8** alcohol in excellent overall yield. Upon heating with trimethyl orthoacetate in the presence of propionic acid, compound **8** underwent Johnson-Claisen rearrangement to provide β,γ -unsaturated ester **9** as the *E*-isomer.²⁴

Removal of the TBS ether from **9** using TBAF provided primary alcohol **10**, which through a sequence of Dess-Martin and Pinnick oxidations was transformed to the corresponding carboxylic acid. Conversion of this material to methyl hydroxamate **6** was accomplished by treatment with isobutyl chloroformate, to generate the corresponding mixed anhydride, and coupling with methoxyamine.

Employing our previously reported oxamidation conditions,¹⁵ cyclization of substrate **6** was now accomplished by treatment with phenyliodine(III) bis(trifluoroacetate) (PIFA, 1.2 equiv) and trifluoroacetic acid (1 equiv) in methylene chloride at 0 °C (Scheme 3). After 9 h, the reaction was simply concentrated to provide a 6:1 mixture of bis-cyclization products **12** and **13**. Notably, no products arising from alkene trifluoroacetoxyamidation were observed in this mixture suggesting that interception of aziridinium ion **11** (in the case of product **12**) by the proximate carboxylate group occurs significantly faster than ion pair collapse.²⁵ Fortuitously, separation of **12** from unwanted diastereomer **13** was readily accomplished by flash chromatography on silica gel.

The relative stereochemistry at the C6 position of the cyclization products was established by nOe analysis. In the case of compound **12**, the 2D NOESY spectrum displayed a strong correlation between H-6 and H-3a, which was conspicuously absent in the spectrum of **13** (Scheme 3). Further confirmation of the desired *cis-cis* stereochemistry of the lactam ring in **12** was gleaned from the vicinal coupling constant between H6 and H6a (6.4 Hz), which is diagnostic of the *cis* relationship between these protons.²⁶ At this point, assignment of the relative C2' stereochemistry in **12** was made difficult by the conformational freedom of the C6-C2' bond, although was assumed to be *R* in view of the stereospecificity of the oxamidation process with respect to alkene geometry.¹⁵

In order to progress towards swainsonine, we now sought to globally reduce **12** to gain compound **14** (Scheme 4). While treatment of **12** with excess LiAlH₄ in THF heated at reflux led to lactam and lactone reduction, cleavage of the N-O bond under these conditions proved to be rather sluggish.²⁷ Fortunately, reaction of **12** with LiAlH₄ at higher temperature, in 1,4-dioxane at reflux (b.p. 101 °C), proved to be more fruitful and lead to the reduction of all three functional groups and formation of 1-amino-2,5-diol **14** in excellent yield.

Formation of the indolizidine ring system was now accomplished through use of an Appel reaction.²⁸ Thus, selective bromination of the primary alcohol in **14** was accompanied by spontaneous cyclization to generate **15**. Finally, removal of the acetone group, using 6 M HCl,^{10c} provided (-)-swainsonine (**1**), after purification by ion exchange chromatography. The ¹H and ¹³C NMR spectral data obtained from this material were identical to those reported for the natural product.^{1b} In addition, the optical rotation of synthetic **1** ([α]_{24D} -86.0; *c* 0.1, MeOH) closely matched that of the natural product ([α]_{25D} -87.2; *c* 2.1, MeOH).^{1b}

In conclusion, we have developed a 12-step, azide-free synthesis of (-)-swainsonine (**1**) in which the C-8/8a stereodiad and pyrrolidine ring of the target are simultaneously established through the diastereoselective bis-cyclization of an unsaturated *O*-alkyl hydroxamate. Although lost through reduction in our current synthesis, the bis-cyclic lactone-lactam framework accessible through this nitrenium ion cyclization is present in a number of alkaloids, most recognizably in the tuberostemospironine subgroup of the *Stemona* alkaloid family,²⁹ their biogenetic relatives, the pandamarilactonines,³⁰ and the *Securinega* alkaloid (-)-norsecurinine.³¹ Extension of this type of transformation to the preparation of these alkaloids is now in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

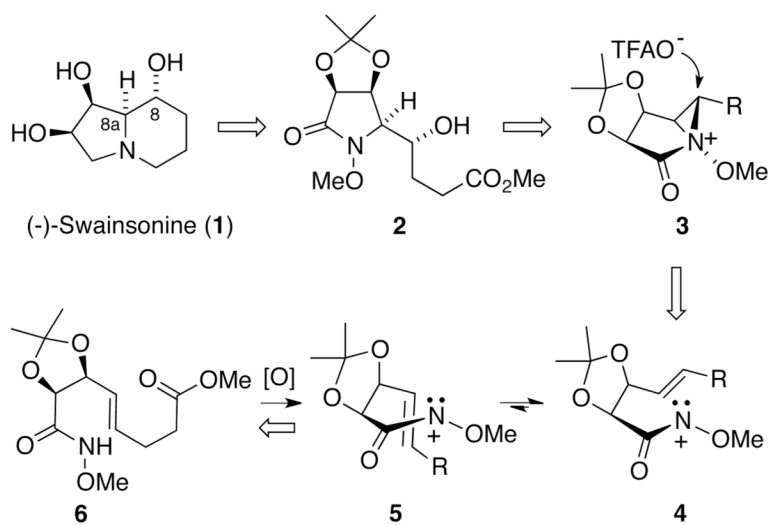
We thank the National Institutes of Health (GM-67176) and the University of Illinois at Chicago for financial support of this work.

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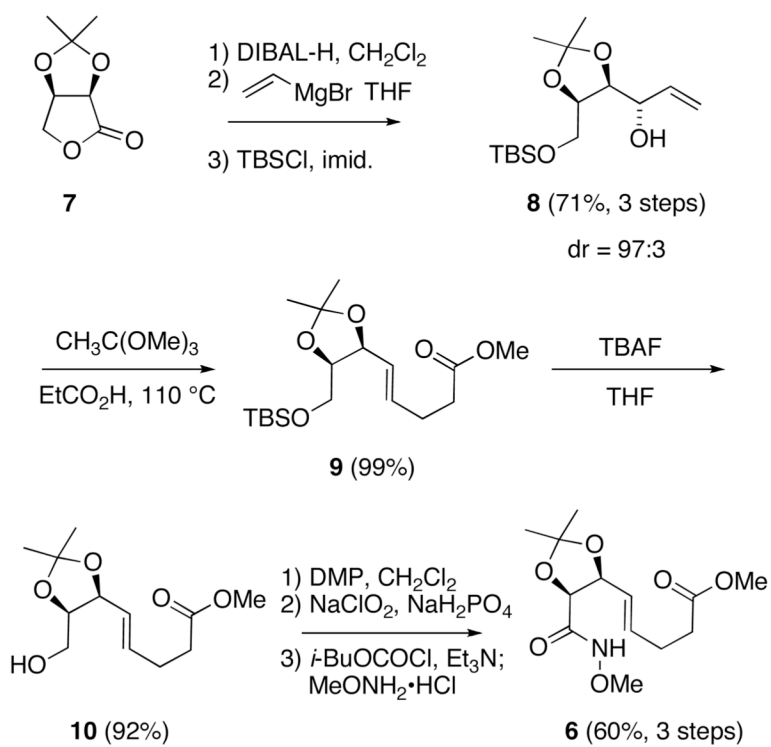
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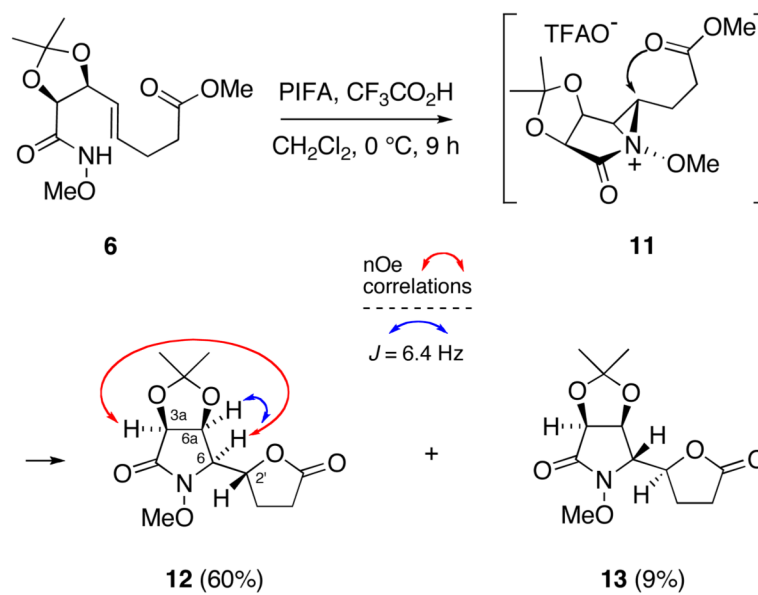
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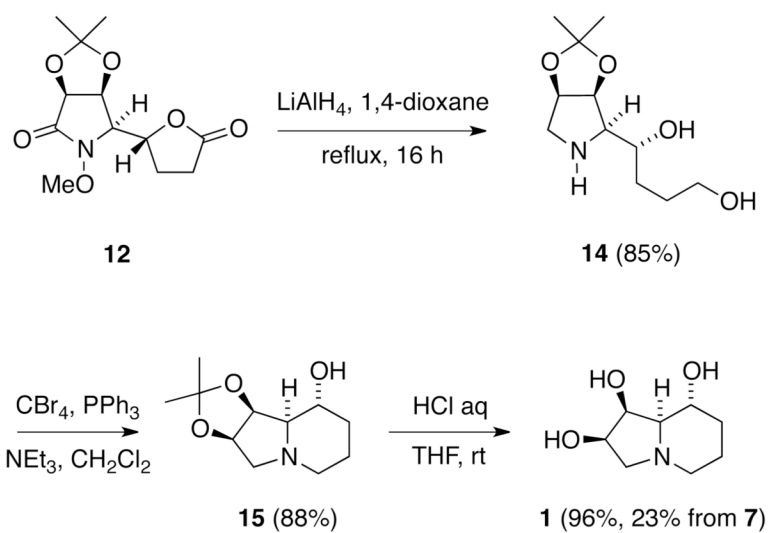
Scheme 1. Retrosynthetic Analysis of (-)-Swainsonine (1)



Scheme 2.
Preparation of Oxamidation Substrate **6**.



Scheme 3.
Bis(cyclofunctionalization) of Substrate **6**.



Scheme 4.
Total Synthesis of (-)-Swainsonine (**1**).