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Stereoselective synthesis of (−)-8-*epi*-swainsonine starting with a chiral aziridine

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ABSTRACT

An efficient synthesis of (−)-8-*epi*-swainsonine, starting from a commercially available 1-(*R*)-α-methylbenzylaziridine-2-methanol, was developed. The synthetic route utilizes stereocontrolled Sharpless asymmetric dihydroxylation governed by AD-mix-β followed by an aziridine ring opening-cyclization sequence to generate the five membered N-heterocyclic ring system present in the bicyclic target. A subsequent stereoselective allylation and piperidine ring forming cyclization then produced a precursor that was converted into (−)-8-*epi*-swainsonine.

Polyhydroxylated indolizidine alkaloids, such as (+)-castanospermine (**1**), (+)-lentiginosine (**2**), and (−)-swainsonine (**3**) in Figure 1, have received great attention owing to their interesting biological properties.[1] For example, (+)-castanospermine[2] (**1**) is known to have antiviral activity and (+)-lentiginosine[3] (**2**) is an amyloglucosidase inhibitor. (−)-Swainsonine (**3**), first isolated from the fungus *Rhizoctonia leguminicola*,[4] displays potent activities against lysosomal α-D-mannosidase[5] and Golgi mannosidase II.[6] Moreover, this indolizidine alkaloid possesses anti-proliferative activity[7] and, as a result, it has been subjected to clinical investigation for the treatment of cancer.[8] It has also been reported[9] that (−)-swainsonine stimulates bone marrow cell proliferation and differentiation.

Owing to these interesting biological and pharmacological properties, various routes[1c,10] for the synthesis of (−)-swainsonine and its analogs have been developed since the time of its first preparation in 1984.[11]

As exemplified by those devised by Richardson[11d] and Fleet,[11a] most of the approaches employ carbohydrate starting materials as chirality sources. Additional efforts in this area have focused on the preparation of stereoisomers of (−)-swainsonine, including (+)-swainsonine[12] and (−)-8-*epi*-swainsonine,[13] with the aim of obtaining more highly bioactive substances. Interestingly, the (+)-swainsonine was found to be a selective and potent inhibitor of naringinase (L-rhamnosidase) with a K_i value of 0.45 μM, whereas its enantiomer is not an inhibitor of this enzyme.[14] Several groups have described the syntheses of (−)-8-*epi*-swainsonine (**4**) that rely on stereoselective addition of allenes to chiral sulfinylimine,[15] aza-pinacol rearrangements of polyhydroxylated pyrrolidines,[16] nitrone cycloaddition to pyrrolo[1,2-*a*]azepine,[17a] RCM using Grubbs catalyst,[13b,17] and stereoselective dihydroxylations of α,β-unsaturated lactams.[18]

In recent studies, described below, we have developed an efficient and stereoselective synthesis of (−)-8-*epi*-swainsonine, which begins with a commercially available chiral aziridine that

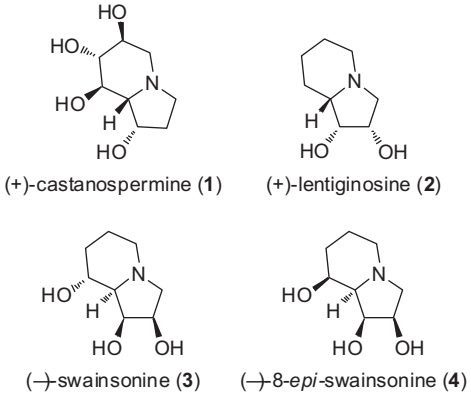

Figure 1. Indolizidine alkaloids' analogs.

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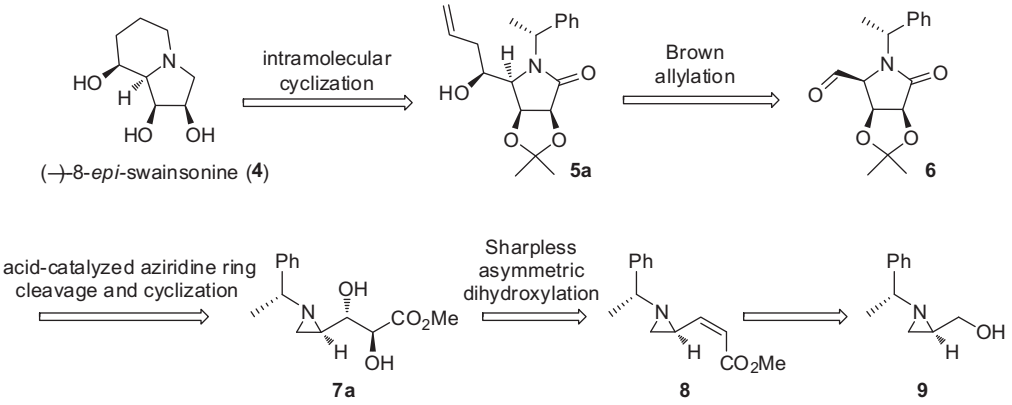


Scheme 1. Retrosynthetic analysis used to design the synthesis of (−)-8-*epi*-swainsonine (**4**).

until now has not been used as a starting material for the synthesis of this target.

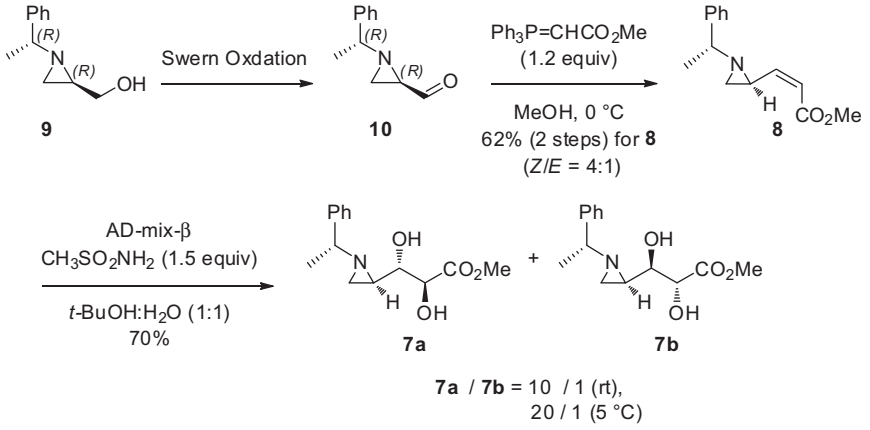
The plan we devised is outlined in a retrosynthetic manner in Scheme 1. In the route, the bicyclic indolizidine ring system of the target is prepared by piperidine ring forming cyclization of **5a**, which is produced from pyrrolidinone **6** by using an asymmetric Brown allylation process. In addition, we hypothesized that **6** would be formed from aziridine **7a** by employing a sequence involving acid-catalyzed aziridine ring-opening and subsequent pyrrolidinone ring forming cyclization. Finally, a Sharpless asymmetric dihydroxylation of the aziridine-acrylate **8**, arising from a commercially available 1-(*R*)-α-methylbenzylaziridine-2-methanol **9**, would be utilized to generate **7a**.

Studies aimed at the synthesis of (−)-8-*epi*-swainsonine commenced with Swern oxidation of 1-(*R*)-α-methylbenzylaziridine-2-methanol **9** that generates the corresponding aldehyde **10** (Scheme 2). Wittig olefination of **10** with carbomethoxymethylene-triphenylphosphorane afforded the desired aziridine-acrylate as a 4:1 mixture of (*Z*)- and (*E*)-isomers, which are readily separated by using column chromatography to afford (*Z*)-enoate **8** in 62% yield. It has been reported that (*Z*)-enoates bearing C-4 chiral centers undergo AD-mix-*β* promoted dihydroxylations to produce (2*S*,3*R*)-2,3-dihydroxyester independent of the configuration at the C4 center. Based on this precedent, (*Z*)-enoate **8** was subjected to Sharpless asymmetric dihydroxylation using AD-mix-β. Importantly, although requiring a long time period (1 day), this process resulted in highly diastereoselective formation of the (2*S*,3*R*)-2,3-dihydroxyester **7a**. Accordingly, the dihydroxylation reaction performed at room temperature gives **7a** and **7b** in a 10:1 ratio (by ^{1}H NMR analysis), whereas the process carried out at 5 °C is extremely sluggish (7 days) but it occurs with a higher level of diastereoselectivity (**7a**:**7b** = 20:1). Importantly, subjection of the mixture formed in the room temperature reaction to flash column chromatography provided **7a** as a single diastereomer in 70% yield. Finally, the stereochemical assignment of **7a** rests on its conversion to the pyrrolidinone-2-one acetonide **12** (see below).

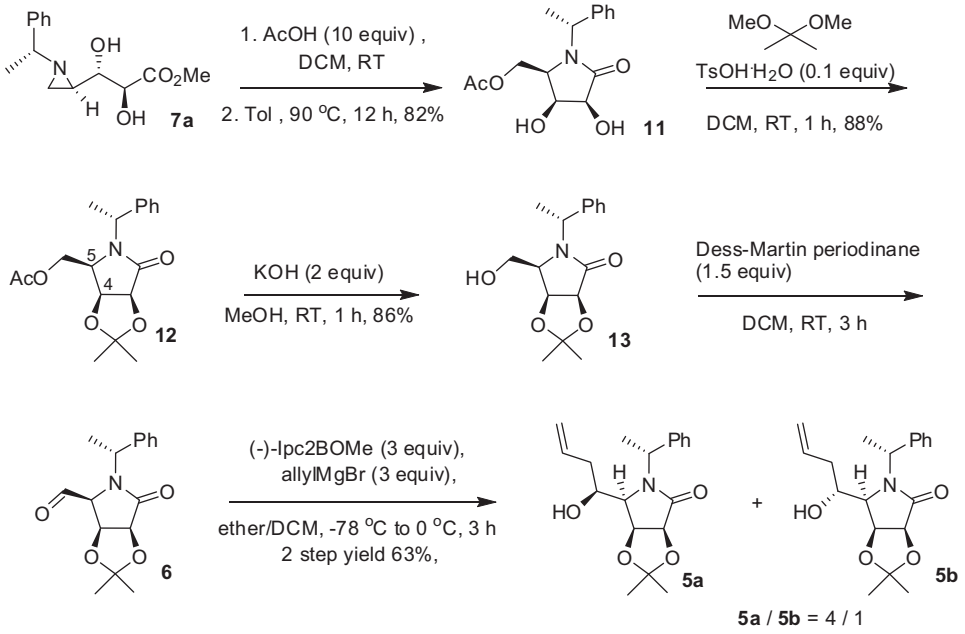
Further studies of the dihydroxylation reaction of the *N*-(*R*)-1-phenylethyl-protected (*Z*)-enoate **8** showed that treatment with osmium tetraoxide in the absence of $(DHQD)_2PHAL$ leads to non-stereoselective (1:1 dr) production of a mixture of **7a** and **7b**. It is noteworthy that (*Z*)-2-alkenyl-1-[(*R*)-1-phenylethyl]aziridines[19] and (*E*)-3-(aziridin-2-yl)acrylates,[20] *N*-protected with carbamate groups (ethyl or *tert*-butyl), have been found to undergo stereoselective (ca., 9:1 dr) dihydroxylation when reacted with osmium tetroxide alone and that *N*-unprotected (*E*)-3-(aziridin-2-yl)acrylates[20] undergo non-stereoselective (1:1 dr) osmium tetroxide promoted dihydroxylations.

In continuing efforts aimed at the synthesis of (−)-8-*epi*-swainsonine, we observed that regioselective aziridine ring-opening[21] of aziridine-diol **7a** takes place when it is treated with acetic acid in CH_2Cl_2 and that the crude product of this process is directly transformed to pyrrolidinone **11** (82% yield, 2 steps) when heated in toluene at 90 °C (Scheme 3).

Acetonide protection of the diol in **11** occurs smoothly to afford **12** (88%). The relative C4 and C5 stereochemistry in pyrrolidinone-2-one **12** and, consequently, that of diol **7a** was determined by using ^{1}H NMR spectroscopy and NOESY experiments. The coupling constants between *cis* protons at C4 and C5 of the pyrrolidinone-



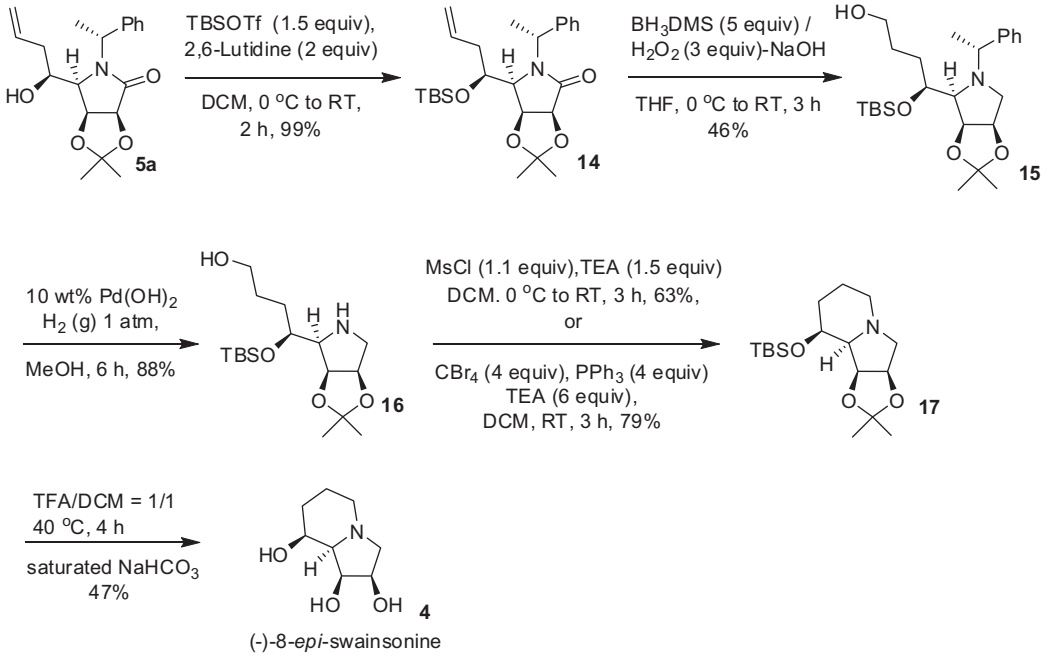
Scheme 2. Route for the preparation of **7a**.



Scheme 3. Synthesis of **5a**.

2-ones are known to be larger than those of the corresponding *trans* protons (J_{cis} = 3.7-4.2 Hz, J_{trans} = 0 Hz).[22] The observation that $J_{4,5}$ = 5.0 and 3.4 Hz for **11** and **12**, respectively, clearly demonstrates that these substances possess *cis* C4–C5 stereochemistry and, as a result, the absolute configuration of C4 is *S* in both **11** and **12**. Lastly, base promoted hydrolysis of the acetate group in **12** furnishes the corresponding primary alcohol **13** in 86% yield. Primary alcohol **13** was converted by Dess–Martin periodinane oxidation for 3 h into the corresponding aldehyde **6**, which in its crude form was subjected to asymmetric Brown allylation[23] to install the homoallylic alcohol side chain containing the final stereogenic center of the polyhydroxylated-indolizidine target. Reaction of **6** with (−)-Ipc$_2$BOCH$_3$ and allylmagnesium bromide at −78 °C gives the desired adduct in 63% yield with a moderate level of diastereoselectivity (**5a**:**5b** = 4:1). Isomer **5a**, needed in the synthetic route, was acquired in diastereomerically pure form by using column chromatography (63% yield, 2 steps). It is worth noting that Brown allylation of **6** using (+)-Ipc$_2$BOCH$_3$, carried out in order to form **5b** as a potential intermediate for (−)-swainsonine synthesis, results in the formation of an unknown substance.

As described in Scheme 4, protection of the allylic alcohol **5a** with TBSOTf gives TBS-ether **14** (99%), which is treated with the



Scheme 4. Synthesis of (−)-8-*epi*-swainsonine.

borane–dimethyl sulfide complex (0 °C to room temperature), followed by oxidation with H_2O_2 to yield the desired primary alcohol containing pyrrolidine **15** in 46% yield.

Cleavage of the phenylethyl group in **15** by using $Pd(OH)_2$ under a hydrogen atmosphere at room temperature affords the aminoalcohol **16**. Treatment of this substance with methanesulfonyl chloride promotes piperidine ring forming cyclization to afford indolizidine **17**. This process can also be accomplished in a higher yield (79%) by using CBr_4/PPh_3. Finally, removal of the TBS and acetonide groups takes place simultaneously and effectively upon reaction of **17** with TFA/CH_2Cl_2 (1/1) to furnish (−)-8-*epi*-swainsonine (**4**).

In summary, the enantioselective synthesis of (−)-8-*epi*-swainsonine, using the route described above, was successfully accomplished in 13 steps. The synthesis of (−)-8-*epi*-swainsonine starting from a chiral aziridine has not been reported to the best of our knowledge. Several interesting features of the approach include the first application of Sharpless dihydroxylation with AD-mix-β to a (*Z*)-3-(aziridin-2-yl)acrylate and the use of a novel, one-pot, aziridine ring-opening/pyrrolidinone ring forming cyclization process. The general strategy employed above has the potential of being applicable to enantioselective synthetic routes targeted at swainsonine analogs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.087.

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