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A formal synthesis of (−)-swainsonine from a chiral aziridine

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ABSTRACT

A formal synthesis of enantiomerically pure (−)-swainsonine was successfully achieved using intramolecular cyclization of the amino alcohol **4** which was derived from a readily available 1-(*R*)-α-methylbenzylaziridine-2-carboxylic acid (−)-menthol ester **6**.

(−)-Swainsonine, first isolated from the fungus *Rhizoctonia leguminicola* in 1973,[1] is well known as an anti-cancer drug with potential for treating glioma[2] and gastric carcinoma.[3] A number of synthetic studies have been reported[4] and efficient syntheses of (−)-swainsonine still draw much attention from organic and medicinal chemists due to its biological activities.[5] Among many available methods, the synthesis of (−)-swainsonine **1** via dihydroxylation of the bicyclic intermediate **2** elaborated from RCM is quite attractive. This intermediate was originally prepared from sequential reactions including Borono-Mannich reaction of a chiral hydroxyaldehyde as the key step. Recently, Dewey et al. elaborated the same intermediate **2** from piperidine compound **3** obtained from a gold(III)-catalyzed allene cyclization.[6] We were interested in developing an efficient synthetic method for (−)-swainsonine via the synthetic intermediate **3** using recently developed aziridine chemistry. In this Letter, we would like to introduce the synthetic method for the desired substituted chiral piperidine **3** starting from a readily available enantiomerically pure 1-(*R*)-α-methylbenzylaziridine-2-carboxylic acid (−)-menthol ester **6** (Scheme 1).

Two stereogenic centers in the compound **3** can be easily constructed via stereoselective reduction of the 2-acylaziridine **5** to provide for the piperidine ring to have the relative *erythro* configuration. In addition to the stereoselective reduction of **5**, homologation of the lateral chain is needed to isolate the target olefin. Compound **5** is readily available by application of general synthetic methods from the (2*S*)-aziridine carboxylic acid (−)-menthol ester **6**, via the Weinreb amide.[7] The reaction of *N*,*O*-dimethylhydroxylamine hydrochloride and enantiomerically pure **6** in the presence of *i*-PrMgCl in THF provides the corresponding Weinreb amide in 95% yield. The Weinreb amide was reacted with magnesium and commercially available (3-bromopropoxy)-*tert*-butyl-dimethylsilane in THF to provide the corresponding ketone **5** in 67% yield. The chelation-controlled reduction of the 2-acylaziridine[8] **5** by $NaBH_4$ in the presence of $ZnCl_2$ was followed by protection of the secondary alcohol moiety to provide **7** in 99% yield. The regioselective ring-opening reaction of the resulting protected diol **7** with AcOH in CH_2Cl_2 at room temperature provided the ring-opening product **8** in 88% yield. We previously reported that the nucleophile, AcO^-, attacks the aziridine ring at the less sterically hindered C(3) position and the aziridine ring C(3)–N bond was regioselectively cleaved.[9] Then, deprotection of the primary silyl ether **8** was selectively achieved by reaction with AcOH/H_2O/THF (3:1:1) at room temperature, to give **4**.[10] The primary alcohol of **4** was activated, after which the mesylate was transformed into the substituted piperidine **9** in 61% yield via intramolecular cyclization under the reaction conditions (Scheme 2).[11]

The α-methylbenzyl group of **9** was replaced by the Boc group by applying a two-step reaction sequence: hydrogenation in the presence of 30% $Pd(OH)_2$ followed by reaction of the resulting disubstituted piperidine with $(Boc)_2O$ in methanol.[12] Then the acetyl group was quantitatively hydrolyzed by KOH in methanol at room temperature to provide 2-hydroxymethyl-*N*-Boc-piperidine.[13] The Swern oxidation[14] of the primary alcohol provided the piperidine-2-carbaldehyde which, by Wittig olefination with methylenetriphenylphosphorane at 0 °C, provided the desired vinyl piperidine **3** in 46% overall yield (from **9**).[15] We compared the data of the 2-vinylpiperidines **3** with those reported previously and confirmed that they were identical to the same intermediate described by Dewey et al. upon occasion of the synthesis of (−)-swainsonine (Scheme 3).

In summary, we have developed a new methodology for a formal synthesis of (−)-swainsonine starting from a readily available chiral aziridine-2-carboxylate **6** by making use of an intramolecular cyclization to access the key intermediate **9** in reasonably good yields.

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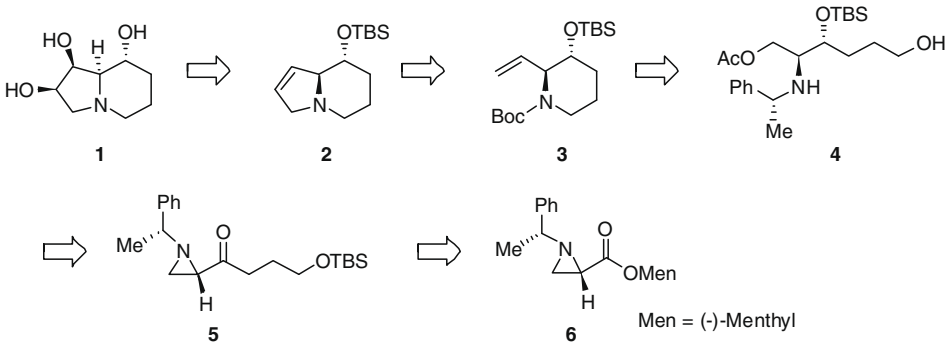
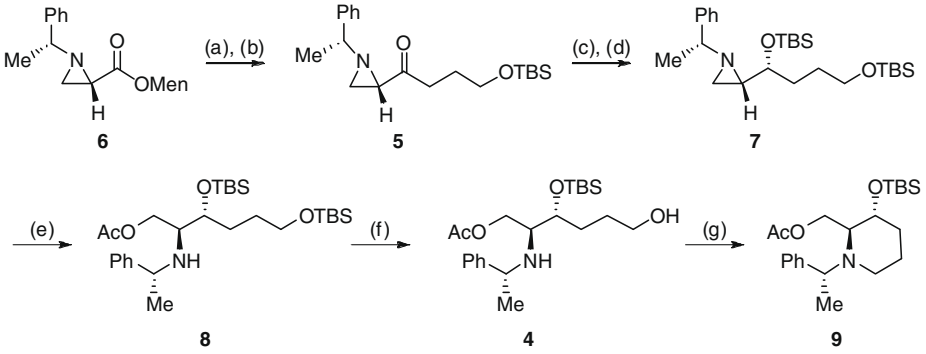
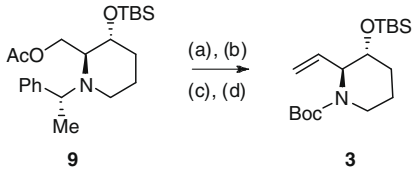


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) *N,O*-dimethylhydroxylamine hydrochloride, *i*-PrMgCl, THF, 0 °C, 95%; (b) Mg, (3-bromopropoxy)-*tert*-butyl-dimethylsilane, THF, reflux, 67%; (c) $NaBH_4$, $ZnCl_2$, MeOH, −78 °C, 94% (>99:1); (d) TBSCl, DMAP, CH_2Cl_2, 0 °C to rt, 99%; (e) AcOH, CH_2Cl_2, rt, 88%; (f) AcOH/H_2O/THF = 3:1:1, rt, 90%; (g) MsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 61%.



Scheme 3. Reagents and conditions: (a) H_2, $Pd(OH)_2$, $(Boc)_2O$, MeOH, rt; (b) KOH, MeOH, rt; (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (d) $MePPh_3Br$, LHMDS, THF, 0 °C, 46% (four steps yield).

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Supplementary data

Supplementary data (detailed experimental procedures, optical rotations, ^1H and ^{13}C NMR spectra and high resolution mass spectra of compounds **3**, **4**, **5**, **7**, **8** and **9**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.069.

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