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Asymmetric Synthesis of 1-Hydroxyindolizidines, Biosynthetic Precursors to the Toxic Indolizidine Alkaloids Slaframine and Swainsonine

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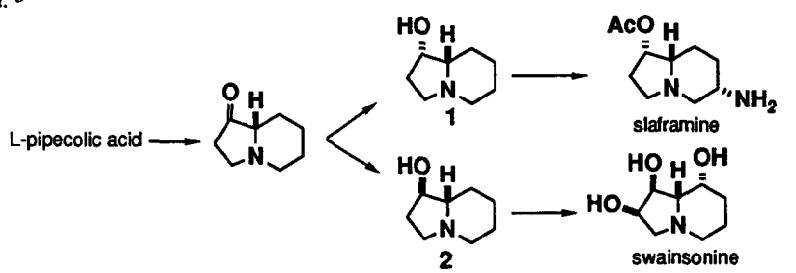
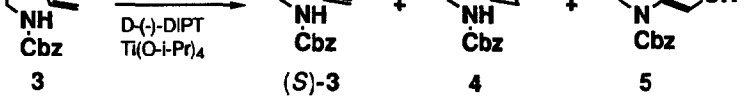
Abstract: An enantioselective synthesis of 1-hydroxyindolizidines (**1** and **2**) from racemic *N*-benzyloxycarbonyl-3-hydroxy-4-pentenylamine (**3**) by following the Sharpless kinetic resolution, intramolecular amidomercuration, and radical Michael addition as key steps is described.

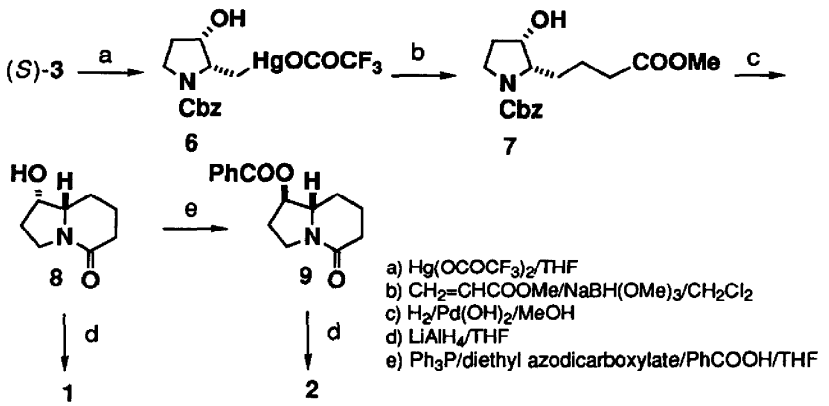
During the course of our program directed toward the design and development of new strategies for the asymmetric synthesis of biologically active nitrogen-containing compounds, we have recently reported an efficient synthesis of chiral pyrrolidine alkaloids by a highly stereoselective intramolecular amidomercuration.[1,2] Our interest has been turned to the synthesis of indolizidine alkaloids by application of the intramolecular amidomercuration followed by a radical Michael addition. Herein we wish to communicate a practical, stereoselective synthesis of chiral 1-hydroxyindolizidines (**1** and **2**) recognized as key precursors for the biosynthesis of the toxic indolizidine alkaloids, slaframine and swainsonine, in the fungus *Rhizoctonia leguminicola*.[3]



Harris and co-workers already reported the synthesis of optically active 1-hydroxyindolizidines (**1** and **2**) from pipecolic acid.[4] However, their procedure had certain drawbacks such as tedious fractional recrystallization for the optical resolution and separation of a mixture of diastereomers. Our synthesis of **1** and **2** began with the Sharpless kinetic resolution of *N*-benzyloxycarbonyl-3-hydroxy-4-pentenylamine (**3**). The kinetic resolution and asymmetric epoxidation of racemic **3** capitalizing on a Sharpless reagent was performed according to the our recent procedure[2] reported for *N-tert*-butoxycarbonyl analogue of **3**, providing three kinds of products, (*S*)-**3** (44%),[5] the epoxy alcohol **4** (33%), and the pyrrolidine (2*R*,3*R*)-**5** (14%).[6]



Stereoselective intramolecular amidomercuration of (*S*)-**3** with mercuric trifluoroacetate in THF followed by the radical Michael addition[7] with excess methyl acrylate in the presence of $NaBH(OMe)_3$ provided the *cis*-3-hydroxy-2-(methoxycarbonylpropyl)pyrrolidine **7** with no isolation of the *trans* isomer in 37% overall yield from (*S*)-**3**. Exposure of **7** to palladium hydroxide under an atmosphere of hydrogen in methanol caused debenzyloxycarbonylation followed by spontaneous annulation, providing the indolizidinone **8** in 78% yield. Reduction of **8** with lithium aluminum hydride gave the desired (1*S*,8a*S*)-1-hydroxyindolizidine (**1**) [bp 100-105 °C/3.2 mmHg, $[\alpha]^D_{25}$ +30.7 (*c* 2.335, EtOH), lit.[4] $[\alpha]^D_{27}$ +27 (*c* 0.95, EtOH)] in 81% yield, whose spectral data (^{1}H- and ^{13}C-NMR) were identical with the values reported.[4] Finally, conversion of **8** to (1*R*,8a*S*)-1-hydroxyindolizidine (**2**) [bp 90 °C/0.3 mmHg, $[\alpha]^D_{25}$ -49.7 (*c* 0.50, EtOH), lit.[4] $[\alpha]^D_{27}$ -49 (*c* 0.90, EtOH)] was achieved by the inversion of the hydroxyl in **8** employing the Mitsunobu reaction[8] followed by reduction in 61% yield. Spectral data for **2** were also consistent with the values reported.[4]



In summary, we have developed a short, efficient, and highly enantioselective synthesis of 1-hydroxyindolizidines (**1** and **2**) from racemic **3** *via* the diastereoselective intramolecular amidomercuration induced by an allylic hydroxyl group. Extensions of this methodology to the synthesis of other indolizidine alkaloids such as indolizidinediol and slaframine are the subjects of active investigations in our laboratory, the results of which will be reported in due course.

References and notes

1) Takahata, H.; Takehara, H.; Ohkubo, N.; Momose, T. *Tetrahedron: Asymmetry* **1990**, *1*, 561.
2) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* in press.
3) For an elegant biosynthetic investigation of slaframine and swainsonine in the fungus *Rhizoctonia leguminicola*, see Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940.
4) Harris, C. M.; Harris, T. M. *Tetrahedron Lett.* **1987**, *28*, 2559.
5) The enantiomeric excess of (*S*)-**3** was determined on the basis of ^{1}H NMR analysis for the corresponding (+)-α-methoxy-α-trifluorophenyl acetic ethyl ester, which indicated the optical purity to be 92%ee.
6) The pyrrolidine **5** was also obtained by treatment of **4** with catalytic D-10-camphorsulfonic acid and would serve as chiral building block for the synthesis of biologically active nitrogen-containing compounds. a) Heffner, R. J.; Joullie, M. M. *Tetrahedron Lett.* **1989**, *30*, 7021. b) Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.* **1990**, *51*, 4827. c) ref. 2.
7) Giese, B., "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds" Baldwin, J. E., Ed., Pergamon Press, Oxford, 1986, p. 36.
8) Mitsunobu, O. *Synthesis* **1981**, 1.