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Enantiopure *N*-Acyldihydropyridones as Synthetic Intermediates: Asymmetric Synthesis of (−)-Slaframine

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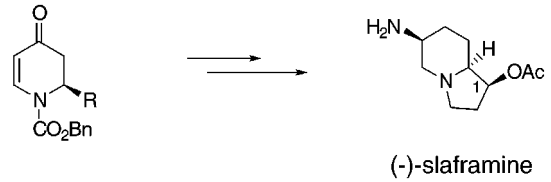
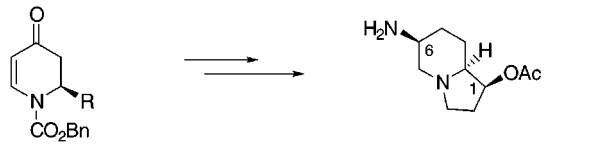
ABSTRACT



(-)-slaframine

An asymmetric synthesis of (−)-slaframine and *N*-acetylslaframine has been accomplished starting from an enantiopure dihydropyridone building block. The oxygen−carbon bond at C-1 was incorporated with complete stereoselectivity by using an efficient phenylselenocyclocarbamation reaction.

The synthetic transformation of readily available chiral building blocks is an attractive method for the preparation of enantiopure natural products and bioactive compounds.[1] *N*-Acyldihydropyridones **1** are easily prepared as either antipode using chiral 1-acylpyridinium salt chemistry.[2] As part of a program directed at expanding the scope of heterocycles **1** as synthetic intermediates, we began a study on the total synthesis of the indolizidine alkaloid (−)-slaframine (**2**). Alkaloid **2** is a metabolite of the fungus *Rhizoctonia leguminicola*, which can infest ruminant forages.[3] Due to the presence of slaframine, excessive salivation in animals occurs after consumption of the infested vegetation. The biological activity of (−)-slaframine may make it clinically useful for the treatment of disease arising from chlolinergic dysfunctions,[4] and slaframine has been proposed as a possible drug candidate for treatment of the symptoms of cystic fibrosis sufferers.[5] The alkaloid's biological activity has stimulated considerable synthetic effort.[6] Herein we describe a novel asymmetric synthesis of **2** that utilizes an enantiopure *N*-acyl-2,3-dihydro-4-pyridone as a chiral building block.



1 **2** (-)-slaframine

The synthesis proceeded as shown in Scheme 1. The alkenylcuprate **3** was added to a mixture of 4-methoxy-3-(triisopropylsilyl)pyridine[7] and the chloroformate of (−)-

(1) (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; Wiley: New York, 1987. (b) Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: New York, 1995.

(2) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651 and references therein.

(3) Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940 and references therein.

(4) For a review, see: Croom, W. J.; Hagler, W. M.; Froetschel, M. A.; Johnson, A. D. *J. Anim. Sci.* **1995**, *73*, 1499.

(5) Aust, S. D. *Biochem. Pharmacol.* **1969**, *18*, 929.

(6) (a) Sibi, M. P.; Christensen, J. W. *J. Org. Chem.* **1999**, *64*, 6434. (b) Knight, D. W.; Sibley, A. W. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2179 and references therein.

(7) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

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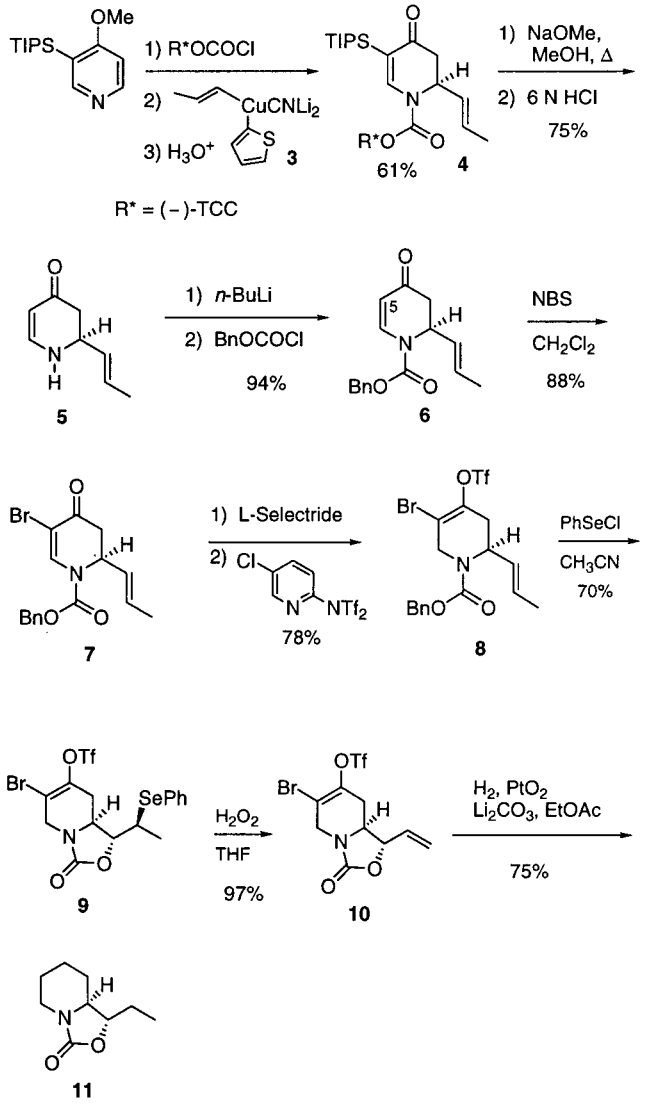
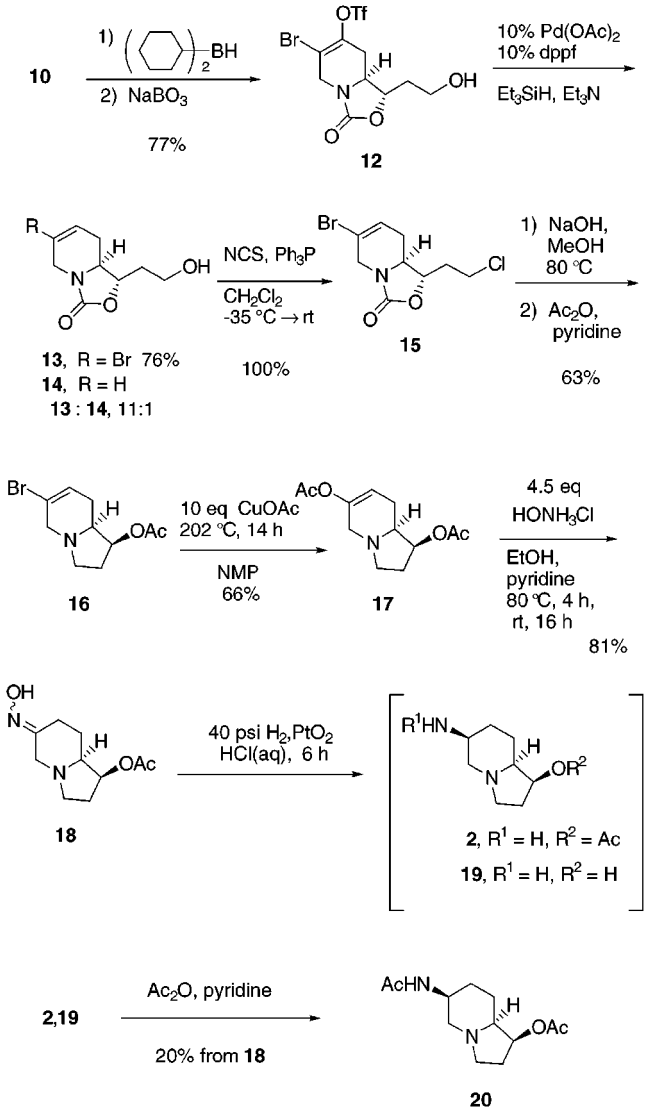
Scheme 1



TCC[8] to give *N*-acyldihydropyridone **4** in 61% yield.[9] One-pot removal of the chiral auxiliary and TIPS group provided enantiopure dihydropyridone **5** in 75% yield along with 95% recovery of the chiral auxiliary (−)-TCC. Deprotonation with *n*-BuLi and addition of benzyl chloroformate gave a 94% yield of intermediate **6**. In preparation for the eventual introduction of the required C-6 amino group of slaframine, the C-5 position of dihydropyridone **6** was functionalized. Treatment of **6** with NBS gave bromide **7** in high yield.[10] Conjugate reduction of **7** with L-Selectride and trapping the intermediate enolate with *N*-(5-chloro-2-pyridyl) triflimide[11] provided bromovinyl triflate **8**. At this stage, the synthetic plan called for incorporation of a C-1 acetoxy precursor with control of stereochemistry. This was accomplished by using a phenylselenocyclocarbamation reaction.[12] Addition of PhSeCl to **8** gave a 70% yield of carbamate **9**. The reaction appears to be completely stereoselective as no other isomers were found on purification. The stereochemistry of **9** was tentatively assigned as shown on the basis of ^{1}H NMR data and transition state analysis. Oxidation of **9** with hydrogen peroxide gave the alkene **10** in excellent yield. The stereochemical assignment was confirmed by reducing **10** to the known cyclic carbamate **11**.[13] Hydroboration−oxidation of the terminal olefin in **10** provided the alcohol **12** (Scheme 2). Prior to hydrolysis of the cyclic carbamate, the labile

Scheme 2



bromovinyl triflate[11] needed to be selectively reduced to a vinyl bromide. After considerable effort, a modification of Kotsuki's procedure[14] for reduction of enol triflates was found to effect the required transformation. Treatment of **12**

(8) (a) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. (b) Both (+)- and (−)-TCC alcohols are available from Aldrich Chemical Co.

(9) The yield is of diastereomerically pure **4** isolated by radial preparative layer chromatography. The reaction proceeded in 87% de.

(10) (a) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435. (b) Comins, D. L.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141.

(11) (a) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

with triethylsilane in the presence of a catalytic amount of a palladium catalyst (10% $Pd(OAc)_2$, 10% dppf) gave a 11:1 mixture of the desired vinyl bromide **13** and over-reduced alkene **14**. After conversion of **13** to chloride **15**, hydrolysis with NaOH, in situ cyclization, and subsequent acylation provided indolizidine **16**. Several attempts to convert the vinyl bromide moiety of **16** to a ketone were unsuccessful; however, reaction with freshly prepared CuOAc[15] in *N*-methylpyrrolidone at 202 °C gave the diacetate **17** in good yield.[16] The diacetate **17** could be converted directly to oxime **18** under mild conditions. The oxime **18** is an intermediate in previous slaframine syntheses; a highly stereoselective reduction via catalytic hydrogenation gives slaframine.[17] One attempt at this known conversion on a small scale afforded a mixture of (−)-slaframine (**2**) and deacetylslafamine **19**. The crude mixture was acylated with acetic anhydride and purified to yield *N*-acetylslaframine **20**. Our synthetic **20** exhibited spectral data in agreement with reported data for authentic material.[18] The optical rotation [$[\alpha]^{25}_D$ −10.0 (*c* 0.06, EtOH)] also agrees with the literature value [$[\alpha]^{25}_D$ −11.2 (*c* 1.45, EtOH)].[18]

An asymmetric synthesis of (−)-slaframine and *N*-acetylslaframine has been carried out starting from an enantiopure dihydropyridone building block.[19] Although the synthetic route is not as short as some others,[6] it is highly stereocontrolled and represents the first asymmetric synthesis of slaframine using a recyclable chiral auxiliary. Key transformations in the synthesis include (1) a highly stereoselective phenylselenocyclocarbamation reaction to give **9**, (2) a chemoselective reduction of a 1,2-bromovinyl triflate to provide vinyl bromide **13**, and (3) the use of CuOAc to convert **16** in two steps to known slaframine intermediate **17**. The phenylselenocyclocarbamation reaction of dihydropyridone derivatives should be useful for the synthesis of other hydroxyindolizidines and related biologically active alkaloids.

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research. We are grateful to Dr. H. Wasserman for an ^{1}H NMR spectrum of a slaframine intermediate. NMR and mass spectra were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grants CHE-9121380 and CHE-9509532).

Supporting Information Available: Characterization data for compounds **4**−**10**, **12**−**18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For other examples of phenylselenocyclocarbamation reactions, see: (a) Berkowitz, D. B.; Pedersen, M. L.; Jahng, W. *Tetrahedron Lett.* **1996**, *37*, 4309. (b) Takano, S.; Hatakeyama, S. *Heterocycles* **1982**, *19*, 1243.

(13) This conversion was carried out on racemic **10**. The product **11** exhibited NMR spectra in agreement with literature values, see: Kano, S.; Yokomatsu, T.; Yuasa, Y.; Shibuya, S.; *Heterocycles* **1986**, *24*, 621.

(14) Kotsuki, H.; Datta, P. K.; Hayakawa, H.; Suenaga, H. *Synthesis* **1995**, 1348.

(15) Edwards, D. A.; Richards, R. *J. Chem. Soc., Dalton Trans.* **1973**, 2463. Method g was used to prepare fresh copper(I) acetate.

(16) For previous preparations of vinyl acetates from vinyl bromides using copper(I) acetate, see: (a) Klumpp, G. W.; Bos, H.; Schakel, M.; Schmitz, R. F.; Vrielink, J. J. *Tetrahedron Lett.* **1975**, *16*, 3429. (b) Lewin, A. H.; Goldberg, N. L. *Tetrahedron Lett.* **1972**, *13*, 491.

(17) (a) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3843. (b) Wasserman, H. H.; Vu, C. B. *Tetrahedron Lett.* **1994**, *35*, 9779.

(18) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977.

(19) The structure assigned to each new compound is in accord with its IR and ^{1}H and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra.