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Enantiopure 2,3-Dihydro-4-pyridones as Synthetic Intermediates: A Concise Asymmetric Synthesis of (+)-Allopumiliotoxin 267A

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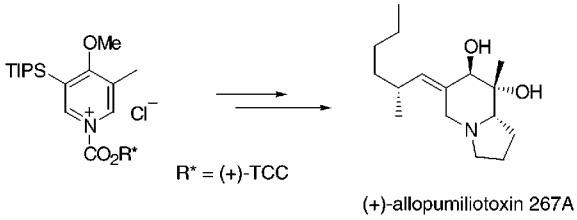
ABSTRACT

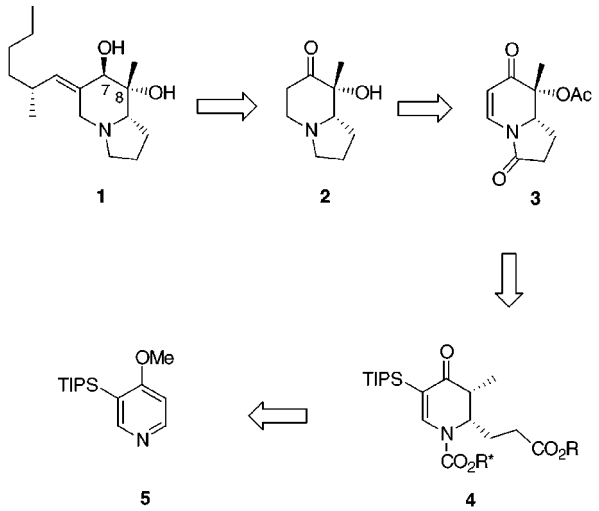


A concise asymmetric synthesis of (+)-allopumiliotoxin 267A has been accomplished using an enantiopure dihydropyridone building block. The synthesis is highly stereoselective and requires 10 steps from readily available material.

The skin secretions of neotropical frogs of the family Dendrobatidae have been a fruitful source of biologically active indolizidine alkaloids.[1] One group of these alkaloids, the allopumiliotoxins, has stimulated considerable synthetic efforts due to their unique structures and biological activities.[2] These studies have resulted in numerous new synthetic methodologies and novel strategies for the construction of indolizidines.

In our laboratories we have been exploring the utility of enantiopure *N*-acyl-2,3-dihydro-4-pyridones as chiral building blocks for the stereocontrolled synthesis of various alkaloids.[3] As part of this program, we developed a novel strategy (Scheme 1) for a concise synthesis of the indolizidine core **2** which is Overman's intermediate[2a] for the preparation of various allopumiliotoxins. The key intermediate **3** was to

Scheme 1



(1) For reviews, see: (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 13, Chapter 1. (b) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162. (c) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids* **1993**, *43*, 185−288.

(2) (a) Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505−522. (b) Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984. (c) Tan, C.-H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1397. (d) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950.

(3) (a) Huang, S.; Comins, D. L. *Chem. Commun.* **2000**, 569. (b) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855 and references therein.

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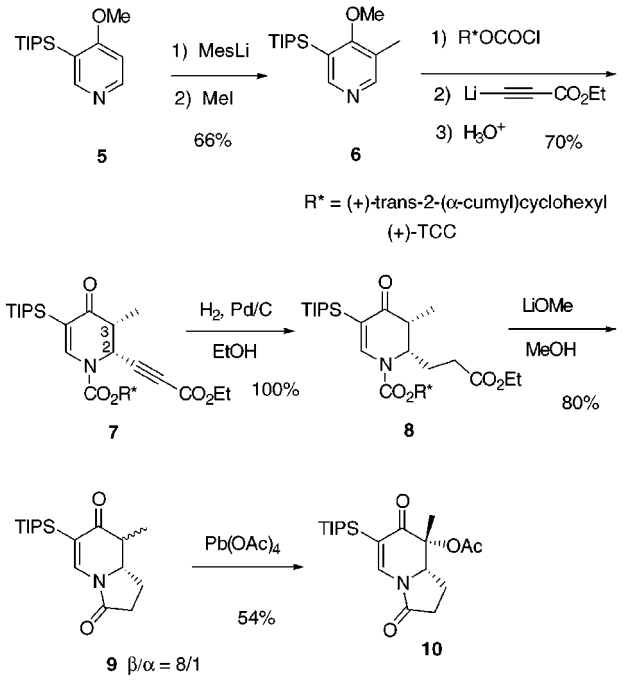
be prepared in six steps from readily available pyridine **5**. It was anticipated that **3** could be converted to known **2** in two steps. Our strategy proved successful, and we now report a concise and highly stereocontrolled asymmetric synthesis of **2** and (+)-allopumiliotoxin 267A (**1**).

Preliminary studies indicated that incorporation of the C-8 methyl group late in the synthesis would be problematic. To circumvent this potential problem, the needed methyl group was introduced during the first step as shown in Scheme 2. Methylation at the C-5 position of 4-methoxy-

Scheme 2



3-(triisopropylsilyl)pyridine[4] occurred via lithiation with mesityllithium[5] (THF, −23 °C, 3 h) and treatment with methyl iodide to give **6**. To a 1-acylpyridinium salt, prepared in situ from **6** and (+)-TCC chloroformate,[6] was added lithiated ethyl propiolate[7] (THF, −78 °C) followed by acidic workup to provide dihydropyridone **7** in 70% yield. The diastereoselectivity of this reaction was determined to be >96% by HPLC and NMR analysis of the crude product. The stereochemistry at C-2 of **7** was assigned *R* by analogy to similar reactions reported from these laboratories.[4] The configuration at C-3 was determined to be *R* on the basis of ^{1}H NMR coupling constants (J_{H2-3} = 5.5 Hz; calcd cis J_{H2-3} = 3.8 Hz, trans J_{H2-3} = 1.0 Hz).[8] The observed stereochemistry at C-3 is likely a result of axial protonation of the intermediate enol ether during workup. With the TIPS group protecting the enone system, catalytic hydrogention of **7** gave **8** in quantitative yield. Treatment of **8** with lithium methoxide (MeOH, reflux, 18 h) effected removal of the chiral auxiliary (95% recovery) and cyclization to afford indolizidinone **9** as an 8:1 mixture of diastereomers. Acetoxylation of mixture **9** proceeded in a stereocontrolled manner on treatment with $Pb(OAc)_4$ in refluxing AcOH/*m*-hexafluoroxylene to give **10**.[9] The stereoselectivity can be explained by invoking an intramolecular acetate transfer from an enol−lead triacetate intermediate (Figure 1). Because of stereoelectronic control,[10]

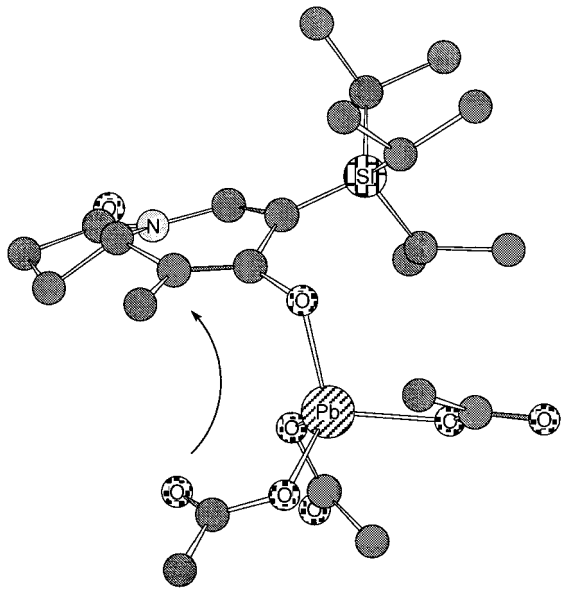


Figure 1. Axial acetoxylation of **9** with $Pb(OAc)_4$. The hydrogens have been removed for clarity.

the acetate transfer occurs from the axial direction to maintain a chairlike transition state. Protodesilylation of **10** using formic acid (reflux, 2 h) provided a 93% yield of enantiopure **3** (Scheme 3). A one-pot reduction using K-Selectride followed by $LiAlH_4$ gave diol **11** in high yield. The reduction was completely stereoselective at C-7, providing the equatorial alcohol (J_{H7-6} = 11.0, 5.1 Hz). Oxidation under Swern conditions[11] afforded Overman's intermediate **2** which was converted in 48% overall yield to (+)-allopumiliotoxin 267A using a modified literature procedure.[12] Lithiation of **2** with tritylllithium (2.0 equiv), addition of chiral aldehyde **12** (1.2 equiv), and dehydration was effected by a one-pot process

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(5) For lithiation of methoxypyridines with mesityllithium, see: Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1998**, *29*, 773.
(6) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.
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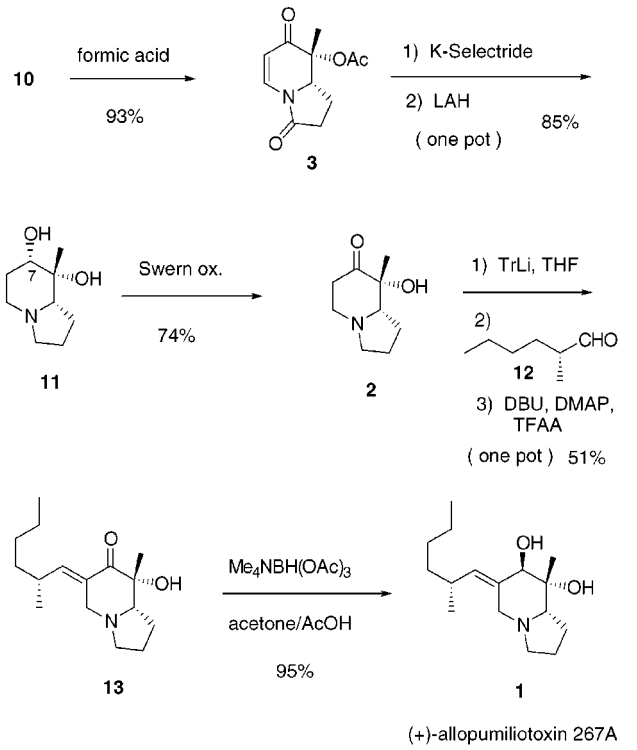
(8) Calculations of coupling constants were performed using PCMODEL (v 7.0), Serena Software, Bloomington, IN.
(9) For acetoxylation of C-3 unsubstituted *N*-acyl-2,3-dihydro-4-pyridones with $Pb(OAc)_4$, see: Comins, D. L.; Stolze, D. A.; Thakker, P.; McArdle, C. L. *Tetrahedron Lett.* **1998**, *39*, 5693.
(10) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 6. (b) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 0. 7445.
(11) (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) The C-7 epimer of **11** has been oxidized to **2** under Swern conditions, see ref 2c.
(12) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179.

Scheme 3



to give keto alcohol **13**. Reduction with $Me_4NBH(OAc)_3$ provided the natural product **1** in excellent yield. The ^1H and ^{13}C NMR data and the optical rotation of **1** [$[\alpha]_D^{25}$ +30.0 (*c* 0.50, $CHCl_3$)] are in agreement with literature values.[12,13]

A concise and highly stereocontrolled asymmetric synthesis of (+)-allopumiliotoxin 267A (**1**) has been carried out in 10 steps from readily available materials. Key steps in the synthesis include (1) a regio- and stereospecific addition of an alkynyllithium to a 1-acylpyridinium salt of trisubstituted pyridine **6**, (2) an axial acetoxylation of indolizidinone **9** with $Pb(OAc)_4$, and (3) a one-pot reduction of intermediate **3** to provide diol **11**. Our synthesis compliments earlier work in this area[1,2] and expands the considerable utility of enantiopure *N*-acyl-2,3-dihydro-4-pyridones as synthetic intermediates.

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Supporting Information Available: Characterization data for compounds **1**−**3**, **6**−**11**, and **13** and comparison tables of NMR data for synthetic **1**. ^1H and ^{13}C NMR spectra of **3**, **8**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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