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A Six-Step Asymmetric Synthesis of (+)-Hyperaspine

Daniel L. Comins* and James J. Sahn

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

daniel_comins@ncsu.edu

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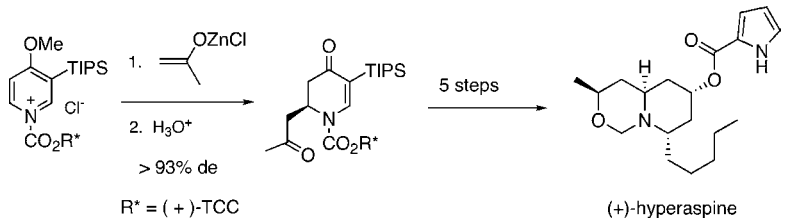
ABSTRACT



The ladybird alkaloid, (+)-hyperaspine, has been synthesized in a concise and highly stereoselective manner. The total synthesis was accomplished in six steps and 21% overall yield.

The isolation of hyperaspine (**1**, Figure 1) from the European Coccinellidae *Hyperaspis campestris* was reported by Braekman and co-workers in 2001.[1] This natural product was the first of a new type of ladybird alkaloid containing a 3-oxaquinolizidine ring system, a novelty that has prompted synthesis efforts. Studies by Ma and Zhu resulted in a synthesis of (−)-8-epihyperaspine[2a] and (+)-hyperaspine[2b] in 12 and 9 steps, respectively. Braekman and co-workers recently reported a racemic synthesis of **1** in 15 steps via a protected piperidine-4-one.[3]

As part of a program centered on expanding the utility of dihydropyridones as synthetic intermediates,[4,5] a study was initiated to develop a concise synthesis of **1**.

The addition of a metallo enolate to a chiral, nonracemic 1-acylpyridinium salt[6] seemed to be an attractive reaction to begin the synthesis of **1**. To the 1-acylpyridinium salt **2**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine and (+)-TCC chloroformate,[7] the zinc enolate of acetone (LDA; $ZnCl_2$) was added to provide 72% yield of the *N*-acyldihydropyridone **3** on acidic workup.[6a] Reduction of the ketone carbonyl of **3** with LS-Selectride (Aldrich) and treatment with K_2CO_3/MeOH provided alcohol **4** in 80% yield (98% de). The relative stereochemistry of **4** was confirmed by NOESY experiments on the bicyclic carbamate **5**. Unlike previous approaches to **1**, we decided to form the bicyclic aminal early in the synthesis. After considerable effort, it was found that the desired cyclization of **4** could be effectively carried out using phase-transfer catalysis.[8] Treatment of **4** with K_2CO_3, CH_2Br_2, and Aliquat 336

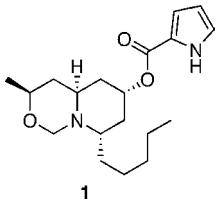


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Figure 1. Structure of natural (+)-hyperaspine.

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(2) (a) Ma, D.; Zhu, W. *Tetrahedron Lett.* **2003**, *44*, 8609. (b) Zhu, W.; Ma, D. *Org. Lett.* **2003**, *5*, 5063.

(3) Dooms, C.; Laurent, P.; Daloze, D.; Pasteels, J.; Nedved, O.; Braekman, J.-C. *Eur. J. Org. Chem.* **2005**, 1378.

(4) For recent and leading references, see: (a) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5219. (b) Comins, D. L.; Kuethe, J. T.; Miller, T. M.; Février, F. C.; Brooks, C. A. *J. Org. Chem.* **2005**, *70*, 5221.

(5) Reviews: (a) Joseph, S.; Comins, D. L. *Curr. Opin. Drug Discov. Devel.* **2002**, *6*, 870. (b) Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491. (c) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press, Inc.: Greenwich, CT, 1996; Vol. 2, p 251.

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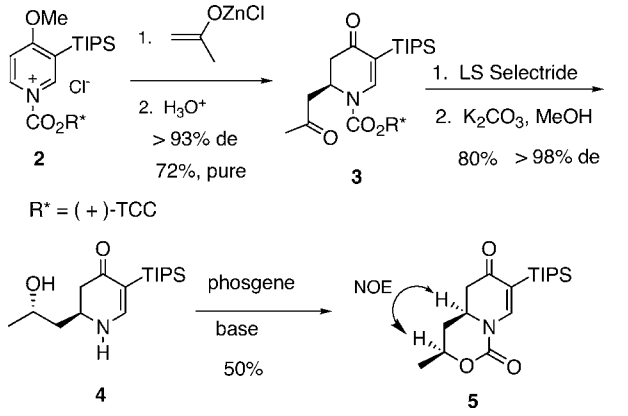
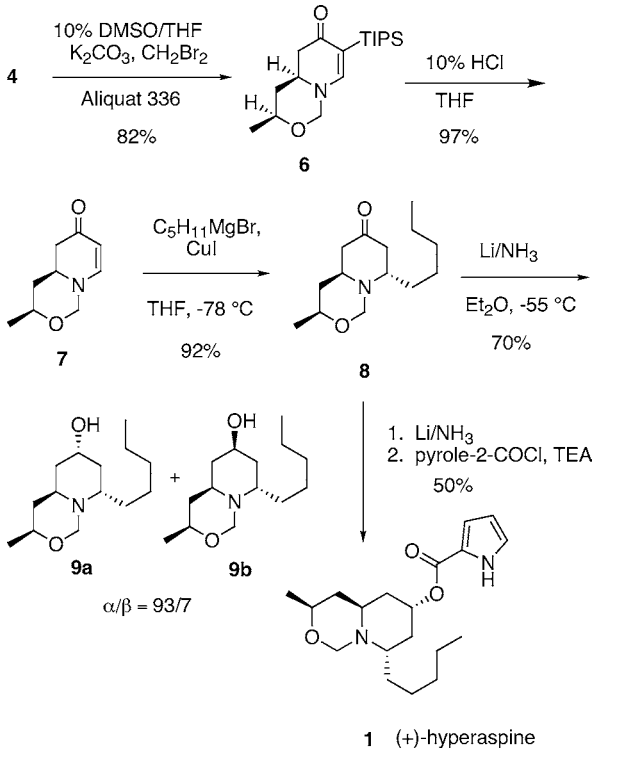
Scheme 1



Scheme 2



(Aldrich) in DMSO/THF afforded an 82% yield of the bicyclic dihydropyridone **6** (Scheme 2). Protodesilylation occurred with aqueous 10% HCl in THF to give **7** in excellent yield. Conjugate addition of a dialkylcuprate, prepared from pentylmagnesium bromide and CuI, to **7** provided nearly complete (>96% de) facial selectivity affording a 92% yield of piperidone **8**. This stereochemical outcome was anticipated on the basis of stereoelectronic arguments[9] and literature precedent.[3,6b] Ma and Zhu reported that bicyclic ketone **8** is reduced with LS-Selectride to give alcohol **9b**, which was esterified with inversion via the Mitsunobu reaction to provide hyperaspine.[2b] Braekman and co-workers reduced racemic **8** with $NaBH_4$ to give a 1:1 mixture of the two inseparable epimeric alcohols.[3] Since a stereoselective reduction of (+)-**8** to the aminal alcohol **9a** is advantagous, we investigated the use of a dissolving metal reduction. To our delight, treatment of **8** with Li/NH_3 in Et_2O afforded a good yield of the desired alcohol **9a** as the major diastereomer (dr 93:7 by NMR). As reported,[3] the epimeric alcohols are difficult to separate, so conditions were developed to acylate the alcohols in situ without isolation. On workup of the Li/NH_3 reduction, addition of pyrrole 2-carbonyl chloride to the reaction mixture provided a 50% yield of (+)-hyperaspine directly from ketone **8**. The spectral properties of our (+)-**1** are in agreement with reported data.[1−3]

In summary, a highly stereocontrolled synthesis of (+)-hyperaspine has been accomplished in six steps and 21% overall yield. This synthesis represents another example of the versatile utility of chiral dihydropyridones as building blocks for the enantioselective preparation of piperidine containing natural products.[5]

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Supporting Information Available: Characterization data for compounds **1** and **3**−**8** and comparison tables of NMR data for synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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