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IMDA/Retro-Mannich Approach to *cis*-Perhydroquinoline *Lycopodium* Alkaloids: Asymmetric Synthesis of (+)-Luciduline

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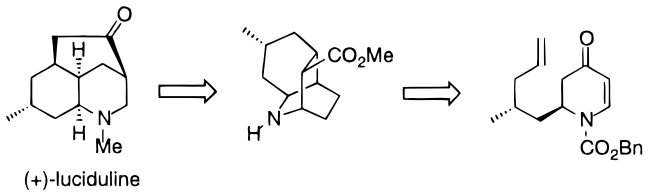
ABSTRACT

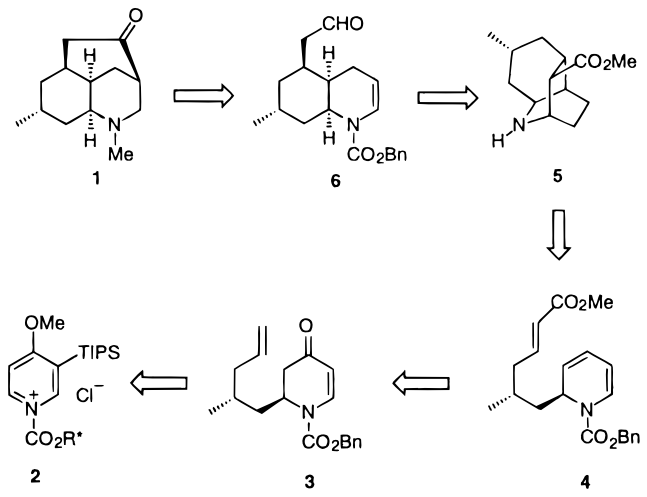


The first chiral auxiliary mediated asymmetric synthesis of the naturally occurring *Lycopodium* alkaloid (+)-luciduline has been accomplished. Key steps include an IMDA reaction of a chiral dihydropyridine, a subsequent retro-Mannich ring opening, and a novel cationic reductive cyclization reaction.

The *Lycopodium* alkaloids are diverse in structure and have provided challenging targets for total synthesis.[1] Luciduline (**1**) is a *cis*-perhydroquinoline alkaloid isolated from *Lycopodium lucidulum*.[2] The presence of a cyclohexanone ring in its skeleton makes **1** unique among this group of naturally occurring alkaloids. Four racemic syntheses[2] of **1**, and one enantioselective route[3] starting from (+)-pulegone, have appeared in the literature. We report in this Letter the first chiral auxiliary mediated asymmetric synthesis of (+)-luciduline, which features new strategies and methods for the stereoselective construction of *cis*-perhydroquinoline-containing alkaloids.

Our strategy for the total synthesis of **1** is shown in Scheme 1. The enantiopure dihydropyridone **3**, prepared from chiral 1-acylpyridinium salt **2**, would be converted to 1,2-dihydropyridine **4**. Intramolecular Diels−Alder (IMDA) and sub-

Scheme 1



(1) (a) Ayer, W. A.; Trifonov, L. S. *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: San Diego, 1994; Vol. 45, pp 233−274. (b) Blumenkopf, T. A.; Heathcock, C. H. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 185−240.

(2) (a) Schumann, D.; Naumann, A. *Liebigs Ann. Chem.* **1984**, 1519. (b) Szychowski, J.; MacLean, D. B. *Can. J. Chem.* **1979**, *57*, 1631. (c) Scott, W. L.; Evans, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 4779. (d) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722.

(3) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755.

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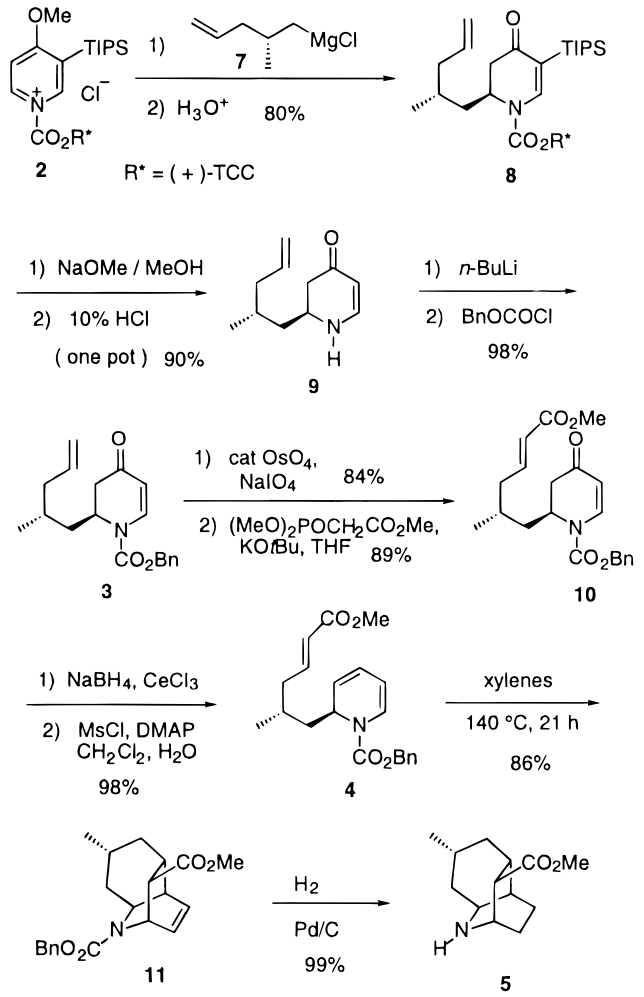
sequent reduction leads to **5**, which after retro-Mannich ring opening is converted to enecarbamate **6**. Completion of the synthesis requires a novel tandem cationic alkylation/reduction cyclization reaction.

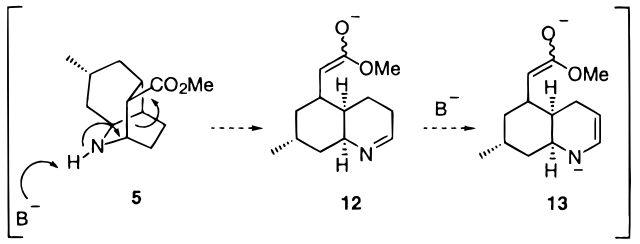
The enantiopure Grignard reagent **7**[4] was added to 1-acylpyridinium salt **2**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[5] and the chloroformate of (+)-*trans*-2-(α-cumyl)cyclohexanol (TCC),[6,7] to give *N*-acyldihydropyridone **8** in 80% yield[8] (Scheme 2). One-pot removal

Scheme 2



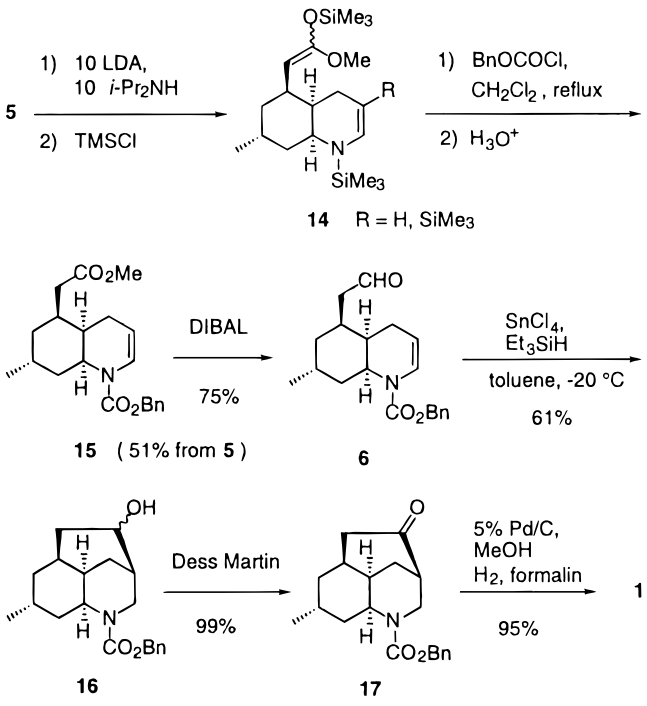
of the chiral auxiliary and TIPS group provided a high yield of enantiopure dihydropyridone **9** with 95% recovery of the chiral auxiliary, (+)-TCC. Deprotonation with *n*-BuLi and addition of benzyl chloroformate gave a near quantitative yield of intermediate **3**. Oxidative cleavage of the terminal alkene in **3** and subsequent Horner−Wadsworth−Emmons olefination provided ester **10**. The 1,2-dihydropyridine **4** was efficiently prepared in two steps (98%) by Luche reduction of **10** and subsequent dehydration with Furukawa's[9] reagent. Intramolecular Diels−Alder reaction of **4** in refluxing xylene provided an 86% yield of the tricyclic carbamate **11**.[10] Catalytic hydrogenation of **11** gave a near quantitative yield of amino ester **5**. The structure of **5** was confirmed by single-crystal X-ray analysis. On the basis of our model studies,[10] ring opening of **5** was anticipated to occur on treatment with excess base (i.e., LDA) as depicted in Scheme 3. Retro-

Scheme 3



Mannich ring opening (10 LDA, 10 *i*-Pr_2NH, THF, −50 °C) and quenching with chlorotrimethylsilane provided a crude mixture of polysilylated derivatives **14** (Scheme 4). Without purification, the mixture was N-acylated with benzyl chloroformate in refluxing methylene chloride to give the enecarbamate **15** in 51% yield. Completion of the synthesis required a cyclization at the β-position of the enecarbamate

Scheme 4



(4) The Grignard reagent was prepared from the chloride, which was derived from the known enantiopure alcohol, see: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

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

(6) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.

(7) The (+)- and (−)-TCC alcohols are available from Aldrich Chemical Co.

(8) The yield is for diastereomerically pure **8** isolated by radial preparative layer chromatography. The stereoselectivity ranged from 85 to 90%.

olefin. After several unsuccessful attempts at intramolecular acylations, the ester **15** was reduced to the aldehyde **6** with DIBAL. The desired ring formation was obtained via a cationic reductive cyclization reaction. On treatment of **6** with $SnCl_4$ in the presence of triethylsilane, a 61% yield of alcohol **16** was obtained. The reactive *N*-acyliminium ion formed during the cyclization step is rapidly reduced by triethylsilane to give the desired tricyclic carbamate. The ketone **17** was obtained from **16** in near quantitative yield using Dess−Martin oxidation. Finally, deprotection and reductive methylation were carried out using a one-pot procedure[11] to give (+)-luciduline (**1**) in high yield [[α^{23}_D] +85.3 (*c* 0.15, MeOH); lit[4] [α_D] +87 (*c* 2.05, MeOH)]. Our synthetic **1** is identical in all respects to the natural material.[4]

In summary, the first chiral auxiliary mediated asymmetric synthesis of (+)-luciduline has been accomplished from readily available materials in 14 steps (10% overall) with a high degree of stereocontrol.[12] The IMDA/retro-Mannich strategy should be amenable to the synthesis of other *cis*-decahydroquinoline alkaloids, and work is in progress toward this goal.

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Supporting Information Available: Characterization data for compounds **1**, **3**−**6**, **8**−**11**, and **15**−**17** and X-ray data for **5** . This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 440.

(10) Onyl a single Diels−Alder product was observed. For model studies on related IMDA reactions and subsequent ring opening, see: Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098.

(11) Rosenberg, S. H.; Spina, K. P.; Condon, S. L.; Polakowski, J.; Yao, Z.; Kovar, P.; Stein, H. H.; Cohen, J.; Barlow, J. L.; Klinghofer, V.; Egan, D. A.; Tricarico, K. A.; Perun, T. J.; Baker, W. R.; Kleinert, H. D. *J. Med. Chem.* **1993**, *36*, 460.

(12) 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.