ORGANIC LETTERS 1999 Vol. 1, No. 2 229–231

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

Daniel L. Comins,* Clinton A. Brooks, Rima S. Al-awar, and R. Richard Goehring

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

daniel_comins@ncsu.edu

Received April 9, 1999

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 syntheses² of 1, and one enantioselective route³ 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

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

10.1021/ol990028j CCC: \$18.00 © 1999 American Chemical Society Published on Web 06/11/1999

1-acylpyridinium salt **2**, would be converted to 1,2-dihydropyridine **4**. Intramolecular Diels-Alder (IMDA) and sub-



^{(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.

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)pyridine⁵ and the chloroformate of (+)*trans*-2-(α -cumyl)cyclohexanol (TCC),^{6,7} to give *N*-acyldihydropyridone **8** in 80% yield⁸ (Scheme 2). One-pot removal



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's⁹ 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-



Mannich ring opening (10 LDA, 10 *i*-Pr₂NH, 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



⁽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 SnCl₄ 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 procedure¹¹ to give

(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 $^{1}\mathrm{H}$ and $^{13}\mathrm{C}$ NMR spectra and elemental analysis or high-resolution mass spectra.

(+)-luciduline (1) in high yield $[[\alpha^{23}_D] + 85.3$ (*c* 0.15, MeOH); lit⁴ $[\alpha_D] + 87$ (*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.

Acknowledgment. We express appreciation to the National Institutes of Health (Grant GM 34442) for financial support of this research. C.B. and R.A. also thank the Burroughs Wellcome Fund for graduate fellowships.

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.

OL990028J

⁽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.