ORGANIC LETTERS

2001
Vol. 3, No. 10
1427−1429

Total Synthesis of Himandravine

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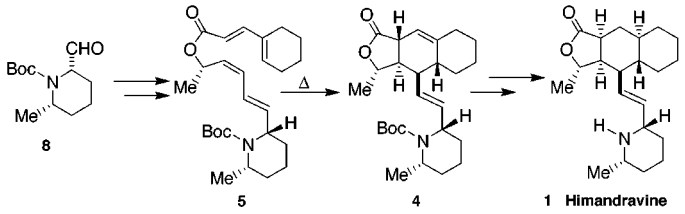
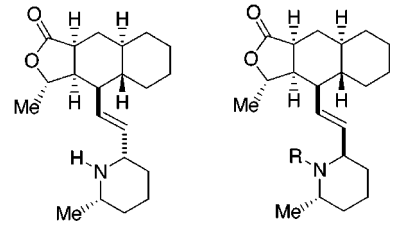
Received February 28, 2001

ABSTRACT



The first total synthesis of (+)-himandravine (1) is described, starting from (2*S*,6*S*)-*cis*-2-formyl-6-methyl-*N*-Boc-piperidine (8) in 11 linear steps and 17% overall yield. The key step involves a highly diastereoselective intramolecular Diels–Alder reaction of the key intermediate 5 that contains the entire latent carbon framework and functional group substitution of himandravine.

Himandravine (**1**) is a complex tetracyclic piperidine alkaloid isolated from the bark of *Galbulimima baccata*, a species of the magnolia family found in New Guinea and northern Queensland regions of Australia.[1] Himandravine shares its



structural traits with its congeners himbacine and himbeline in that these alkaloids possess the same tricyclic perhydronaphthofuranone ring system and a 2,6-disubstituted piperidine ring, connected to each other via a *trans*-ethylene unit. Himandravine is diastereomeric to himbeline, being epimeric at the carbon bearing the alkenyl unit of piperidine. While himbacine has enjoyed much synthetic[2] and medicinal chemistry attention lately by virtue of its potent antimuscarinic activity,[3] the synthetic and biological properties of himandravine remain unexplored.[4] It has been postulated that

(1) (a) Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem*. **1961**, *14*, 106. (b) Brown, R. F. C.; Drummond, R.; Fogerty, A. C.; Hughes, G. K.; Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem*. **1956**, *9*, 283. (c) Ritchie, E.; Taylor, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 529.

(2) For the total synthesis of himbacine, see: (a) Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D. *J. Org. Chem*. **1999**, *64*, 1932. Also see: Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc*. **1996**, *118*, 9812. (b) Hart, D. J.; Wu, W.-L.; Kozikowski, A. P. *J. Am. Chem. Soc*. **1995**, *117*, 9369. Also see: Hart, D. J.; Li, J.; Wu, W.-L.; Kozikowski, A. P. *J. Org. Chem*. **1997**, *62*, 5023. (c). Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron Lett*. **1999**, *40*, 3399. For studies directed toward the total synthesis of himbacine, see: (d) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett*. **1995**, *36*, 9551. (e) Hofman, S.; De Baecke, G.; Kenda, B.; De Clercq, P. J. *Synthesis* **1998**, 479.

(3) (a) Darroch, S. A.; Taylor, W. C.; Choo, L. K.; Mitchelson, F. *Eur. J. Pharmacol*. **1990**, *182*, 131. (b) Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 61 and references therein. (c) Kozikowski, A. P.; Fauq, A. H.; Miller, J. H.; McKinney, M. *Bioorg. Med. Chem. Lett*. **1992**, *2*, 797.

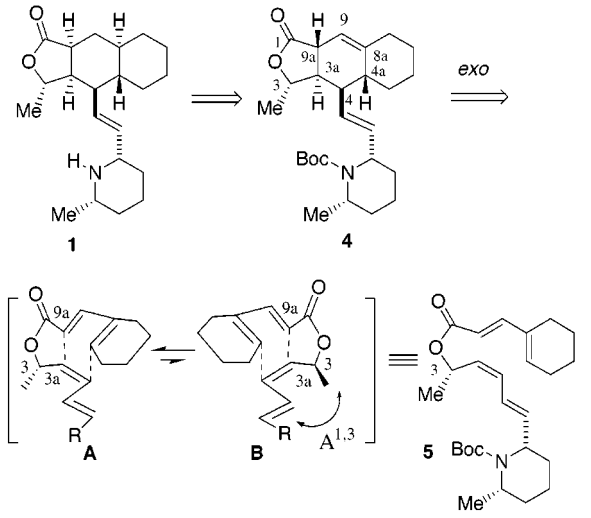
(4) Himandravine and *N*-methylhimandravine are reportedly less active in guinea-pig ileal longitudinal muscle and electrically stimulated left atrium.[3a] However, the K_i value for himandravine in cloned human muscarinic M2 receptors has not been reported, which is required for a meaningful comparison.

10.1021/ol010038w CCC: $20.00
Published on Web 04/21/2001

the chirality of the substituted piperidine moiety might be important to the potency and receptor selectivity of himbacine.[3a] Since himandravine has the (*S*)-absolute chirality at the C_2 piperidine carbon, which is opposite to that of himbacine, its synthesis constitutes an important step in the structure−activity relationship study (SAR) of this important class of molecules. Reported here is the first total synthesis of (+)-himandravine in 11 linear steps and 17% overall yield starting form (*S*)-2-methyl-*N*-Boc-piperidine (**6**). Also, this total synthesis confirms the structure as well as the absolute stereochemistry of himandravine.

The retrosynthetic analysis is presented in Scheme 1 which bears close analogy to our previously reported synthesis of

Scheme 1



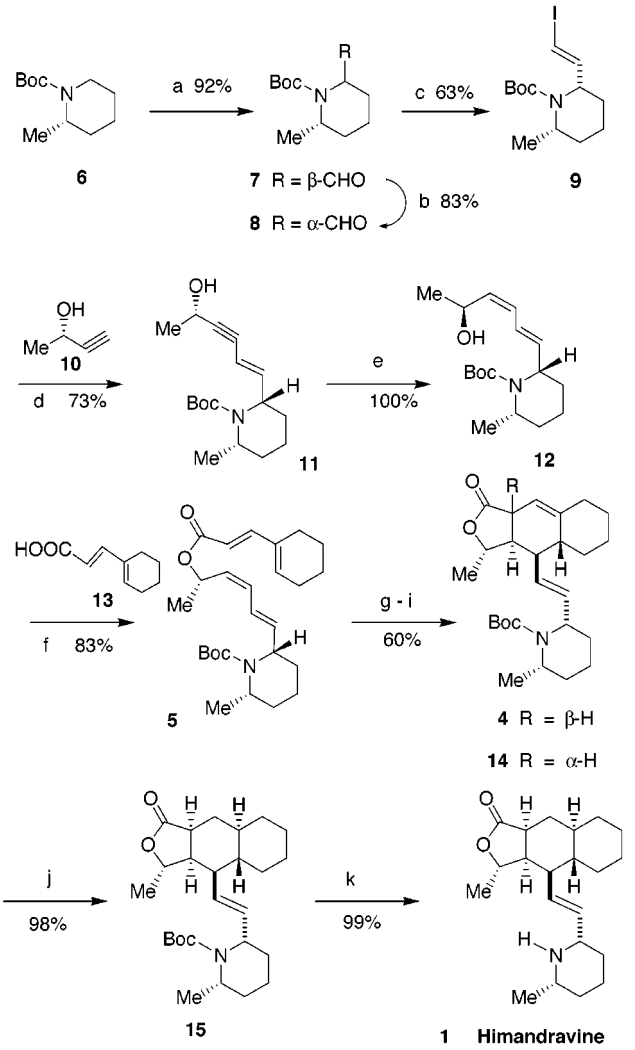
himbacine. The key step of the synthesis is a highly enantioselective intramolecular Diels−Alder reaction[5] of tetra-ene intermediate **5** which bears the entire latent carbon framework of himandravine and functional group substitution. The facial selectivity of the C_{3a}−C_{9a} bond formation in the intramolecular Diels−Alder reaction is dictated by the preferred conformation **A** of the intermediate **5** which minimizes $A^{1,3}$ strain.[6] The preexisting absolute chirality at C_3 would be translated into the *R*-configuration at C_{3a} which, in turn, would produce the required absolute configurations at C_4 and C_{4a} and, after epimerization, at C_{9a}. The stereoselective reduction of the internal double bond from the convex face was expected to produce the required *R*-configuration at C_{8a} as reported before.[2a]

(5) For reviews on intramolecular Diels−Alder reaction, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 513. (b) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984; Vol. 32, p 1. (c) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 87. (d) Weinreb, S. W. *Acc. Chem Res.* **1985**, *18*, 16. (e) For a discussion of the substituent effect on intramolecular Diels−Alder reactions of enoates, see: Jung, M. E. *Synlett* **1990**, *4*, 186.

(6) (a) Hoffmann, R. W.*Chem. Rev.* **1989**, *89*, 1841. (b) Adam, W.; Glaser, J.; Peters, K.; Prein, M. *J. Am. Chem. Soc.* **1995**, *117*, 9190 and references therein. (c) Mulzer, J.; Bock, H.; Eck, W.; Buschman, J.; Lugar, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 414.

The synthesis of (+)-himandravine is outlined in Scheme 2. We have previously reported an efficient synthesis of

Scheme 2[a]



[a] Reagents and conditions: (a) (i) *sec*-BuLi, Et_2O, TMEDA, −78 °C; (ii) DMF; (b) silica gel, Et_3N:EtOAc:hexane (3:10:90, v/v/v), 22 h; (c) $CrCl_2$, CHI_3, THF; (d) $PdCl_2(PhCN)_2$, CuI, piperidine, THF **10**, rt; (e) Lindlar, H_2, MeOH:CH_2Cl_2 (1:4, v/v), quinoline (45 wt % equiv); (f) **13**, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMAP, TEMPO (1 wt % equiv), CH_2Cl_2; (g) toluene, TEMPO (1 wt % equiv), 186 °C, 8 h; (h) DBU; (i) $(Boc)_2O$, NaOH (20%);(j) RaNi, H_2, MeOH; (k) TFA:CH_2Cl_2 (1:10, v/v).

(2*R*,6*S*)-*trans*-2-formyl-6-methyl-*N*-Boc-piperidine[2a] (**7**) from (*S*)-2-methylpiperidine[7] (**6**) using Beak's method.[8] The corresponding (2*S*,6S)-*cis*-2-formyl-6-methyl-*N*-Boc-piperidine (**8**) needed for the total synthesis of (+)-himandravine was efficiently generated from *trans*-substituted piperidine **7** by triethylamine-catalyzed epimerization on silica gel in 83% yield. Homologative iodovinylation of formyl derivative

(7) Doller, D.; Davies, R.; Chackalamannil, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1275.

(8) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

8 using Takai protocol gave the *trans*-vinyl iodide **9** in 63% yield.[9] Sonogashira coupling[10] of vinyl iodide **9** and commercially available propargylic alcohol **10** gave the ene-ynol **11** in 73% yield. Selective reduction of the alkyne unit of **11** using Lindlar catalyst followed by esterification with dienoic acid **13**[2a,11] gave the Diels−Alder precursor **5** in a combined 83% yield. Intramolecular Diels−Alder reaction of tetra-ene derivative **5** at 186 °C, followed by in situ epimerization at C_{9a} by treatment with DBU, and reprotection of the partially deprotected piperidine nitrogen, gave tricyclic intermediate **14** in 60% isolated yield. Selective hydrogenation[12] of the internal double bond of **14** mediated by Raney nickel followed by hydrolytic removal of the Boc protecting group gave (+)-himandravine which showed spectroscopic properties identical to those of a sample of natural product and a comparable optical rotation.[13,14] Definitive proof of the structure of synthetic himandravine was derived from the X-ray crystallographic analysis of its hydrochloride salt (Figure 1).

In conclusion, the first total synthesis of (+)-himandravine has been accomplished in 11 linear steps and 17% overall yield. The current synthesis corroborates the reported structure and absolute chirality of himandravine. The biological data of himandravine and related compounds will be published in the future.

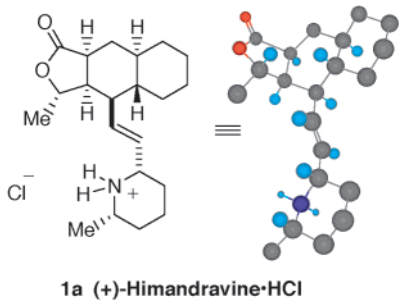


Figure 1. X-ray crystallographic structure of himandravine hydrochloride. Chloride anion not shown.

Acknowledgment. The authors thank Drs. Ashit Ganguly, William J. Greenlee, and Michael Czarniecki for helpful discussions. We also thank Dr. Pradip Das for mass spectral data, Dr. Mohindar Puar for NMR data, and Prof. W. C. Taylor, University of Sydney, Australia for an authentic sample of (+)-himandravine.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **5**, **8**, **9**, **11**, **14**, and **15**. Tables of crystal data, fractional coordinates and thermal parameters, and interatomic distances with standard deviation for the hydrochloride of himandravine (**1a**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc*. **1986**, *108*, 7408.

(10) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Alami, M.; Linstrumele, G. *Tetrahedron Lett.* **1991**, 6109. For reviews on the Sonogashira reaction, see: (d) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*(2), 127. (e) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 521.

(11) Tanikaga, R.; Nozaki, Y.; Tamura, T.; Kaji, A. *Synthesis* **1983**, 134.

(12) The hydrogenation product **15** was contaminated with a trace amount of side product, presumed to be the C_{8a} epimer, that could not be separated by flash chromatography.

(13) Specific rotation of himandravine: $[\alpha]_D^{20}$ +19.8 (*c* 1.08, $CHCl_3$); lit.[1b] +23 (*c* 1.89, $CHCl_3$). Himandravine hydrochloride melted at 218−220 °C (dec).

(14) All intermediates were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopic methods.