A Highly Efficient Total Synthesis of (+)-Himbacine

Samuel Chackalamannil,* Robert J. Davies,
Theodros Asberom, Darío Doller, and Daria Leone

Schering-Plough Research Institute
2015 Galloping Hill Road
Kenilworth, New Jersey 07033

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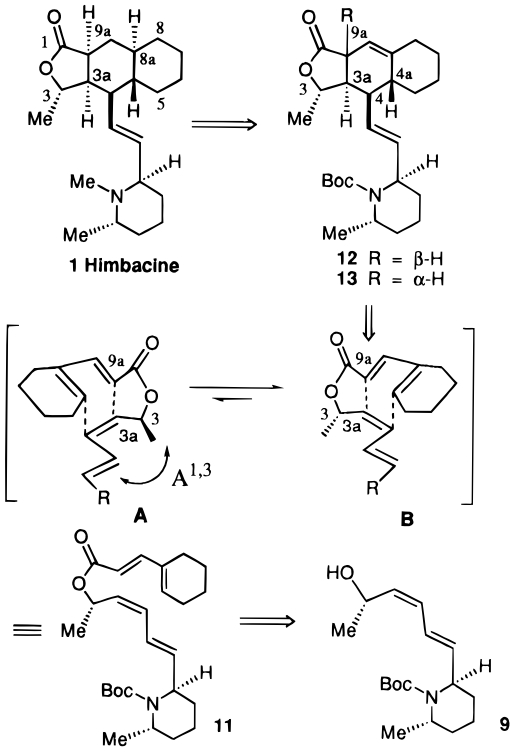
Himbacine (**1**), a tetracyclic piperidine alkaloid isolated from the bark of the Australian pine tree of *Galbulimima* species,[1,2] has attracted considerable attention due to its interesting structural features and promising biological property as a muscarinic receptor antagonist.[3] Positive modulation of synaptic acetylcholine levels by selective inhibition of presynaptic muscarinic receptors is a promising therapeutic approach for the treatment of senile dementia associated with Alzheimer's disease.[4] Himbacine is a potent inhibitor of the muscarinic receptor of M_2 subtype with 20-fold selectivity toward the M_1 receptor.[5] However, the paucity of natural himbacine as well as the inherent structural complexity of this molecule has precluded exhaustive optimization of its biological properties by structural modification. Hart, Wu, and Kozikowski have published a total synthesis of himbacine in 20 linear steps.[6a] A short, practical synthesis of himbacine would greatly facilitate research in the therapeutic application of this compound. We wish to report a highly convergent and concise synthesis of (+)-himbacine (Scheme 2) in 11 linear steps and 9.7% yield starting from readily accessible (*S*)-2-methylpiperidine L-tartrate (**3**).

Our approach envisions, as the key step, an enantioselective, all-encompassing intramolecular Diels−Alder reaction[7] of the appropriately functionalized molecular ensemble **11**, which bears the entire latent carbon framework and functional group substitution of himbacine (Scheme 1). Several points are worth noting regarding this approach. First, we expected that the vinylcyclohexenyl region of **11** would act as the diene moiety in the intramolecular Diels−Alder reaction in preference to the piperidinyl substituted diene, since it is more likely to adopt the required cisoid conformation. The methyl group at C_3 would serve to confer the *s-cis* orientation to the ester linkage, thereby facilitating the cyclization.[8] The face selectivity of the C_{3a}−C_{9a} bond formation in the intramolecular Diels−Alder reaction would be dictated by the preferred conformation **B** of the intermediate **11**, which avoids $A^{1,3}$ strain. During the Diels−Alder process, the absolute chirality at C_3 would be translated to *R*-configuration at C_{3a} which, in turn, would engender the required absolute configurations at C_4 and C_{4a} and, after epimerization, at C_{9a}.[9] Finally, considering the fact that the pendent *trans* double bond is sterically encumbered by the presence of the tricyclic ring system and the *N*-Boc-substituted piperidine, we expected to achieve regioselective reduction of the internal double bond.[10] This reduction would occur stereoselectively from the less hindered α-face to produce the required *R*-configuration at C_{8a}.

Scheme 1



The implementation of the above plan is outlined in Scheme 2. Commercially available 2-methylpiperidine was resolved using L-tartaric acid.[11,12] The tartrate salt **3** was directly converted to *N*-Boc-protected (*S*)-2-methylpiperidine by treatment with excess of Boc anhydride in 96% yield.[13] Treatment of piperidine derivative **4** with *sec*-butyllithium followed by quenching with dimethylformamide according to the Beak procedure[14] yielded the *trans*-substituted piperidinyl aldehyde **5** in 86% yield. Homologative iodovinylation of aldehyde **5**

(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 X-ray crystallographic studies on himbacine, see: Fridrichsons, J.; Mathieson, A. M. *Acta Crystallogr*. **1962**, *15*, 119.

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

(4) (a) Miller, J. H.; Aagaard, P. J.; Gibson, V. A.; McKinney, M. *J. Pharmacol. Exp. Ther*. **1992**, *263*, 663. (b) Dodds, H. N. *Drugs Future* **1995**, *20*, 157.

(5) Five muscarinic receptor subtypes have been reported. See: Levey, A. I. *Life Sci*. **1993**, *52*, 441 and references cited therein. Himbacine has been reported to bind to M_2 receptor with a Ki value of 4.6 nM and with 20-fold selectivity against M_1 receptor (ref 3b).

(6) For the total synthesis of himbacine, see: (a) Hart, D. J.; Wu, W.-L.; Kozikowski, A. P. *J. Am. Chem. Soc*. **1995**, *117*, 9369. For studies directed toward the total synthesis of himbacine, see: (b) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett*. **1995**, *36*, 9551. (c) Baecke, G. D.; De Clercq, P. *Tetrahedron Lett*. **1995**, *36*, 7515.

(7) For reviews on intramolecular Diels−Alder reactions, 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, Inc.: 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.

(8) For a discussion of the substituent effect on intramolecular Diels−Alder reactions of enoates, see: Jung, M. E. *Synlett* **1990**, *4*, 186.

(9) (a) For a discussion of $A^{1,3}$ strain induced facial selectivity of intermolecular Diels−Alder reactions, see: Adam, W.; Glaser, J.; Peters, K.; Prein, M. *J. Am. Chem. Soc*. **1995**, *117*, 9190 and references cited therein. (b) For a review on $A^{1,3}$ strain induced stereoselectivity, see: Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841.

(10) It has been reported that reduction of himbacine to dihydrohimbacine required catalytic hydrogenation over platinum oxide in glacial acetic acid for 16 h (ref 1a).

(11) The resolution of 2-methylpiperidine was carried out according to the procedure given by Marckwald. Marckwald, W. *Ber*. **1896**, *29*, 43. Also, see: (a) Craig, J. C.; Roy, S. K. *Tetrahedron* **1965**, *21*, 401. (b) Munchof, M. J.; Meyers, A. I. *J. Org. Chem*. **1995**, *60*, 7084. (c) Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc*. **1955**, *77*, 6361.

(12) The optical purity of (*S*)-2-methylpiperidine was measured using *O*-acetylmandelic acid as a chiral solvating agent. Integration of the methyl doublet indicated >99% optical purity after four recrystallizations. See: Parker, D.; Taylor, R. J. *Tetrahedron* **1987**, *43*, 5451.

(13) The workup procedure involved addition of excess of ammonium hydroxide. This step converted the unreacted reagent, which coeluted with the product, to more polar *tert*-butylurethane.

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

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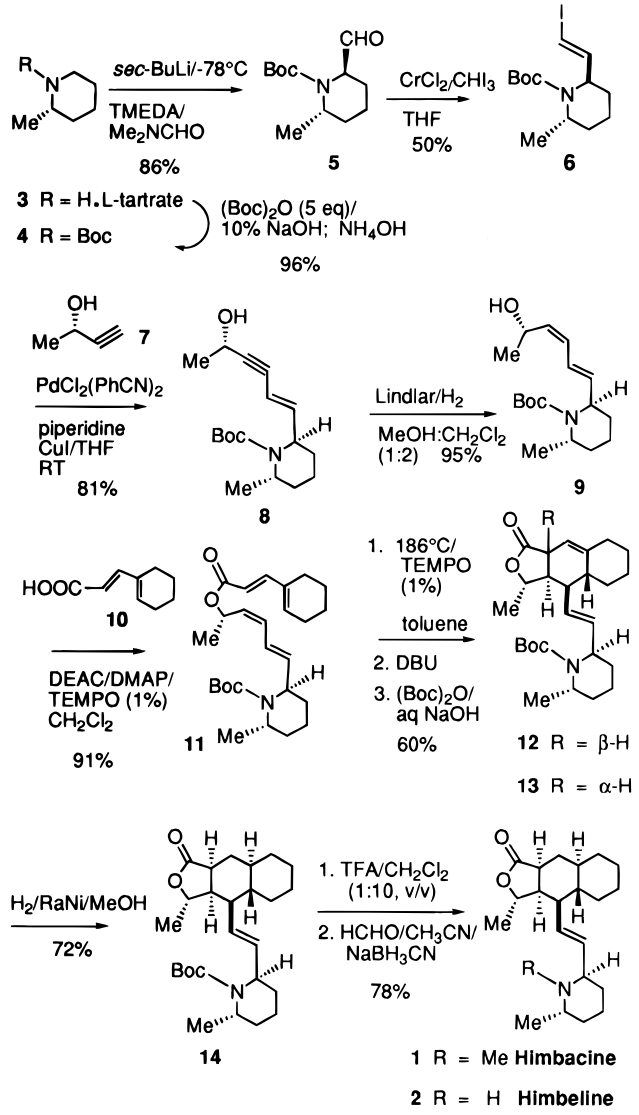
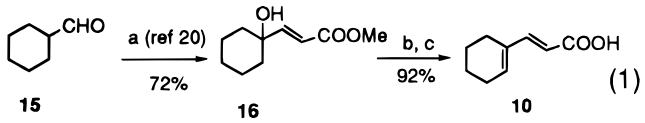
Scheme 2



according to the Takai protocol[15] using chromous chloride[16] and iodoform yielded the vinyl iodide **6** in 50% yield. Palladium-mediated coupling[17] of vinyl iodide **6** with commercially available[18] (*S*)-3-butyn-2-ol (**7**) gave the enyne derivative **8** in 81% yield. Selective reduction of the triple bond of **8** was achieved using catalytic hydrogenation over Lindlar catalyst in the presence of quinoline.[19]

The carboxylic acid derivative **10** was readily prepared from cyclohexane carboxaldehyde in an overall 66% yield in three steps according to the reported procedure[20] (eq 1). Esterification



a. (4-Cl-C_6H_4)S(O)CH_2COOMe/piperidine/CH_3CN/rt
b. Ac_2O/AcCl/heat c. NaOH/EtOH/reflux; H_3O^+

of alcohol **9** with the acid **10** yielded the Diels−Alder precursor **11** in 91% yield.[19] Thermal cyclization of a solution of compound **11** in toluene at 186 °C for 8 h generated exclusively the *exo* adduct **12** which, under reaction conditions, underwent partial isomerization to the *cis* lactone **13**.[21]

A brief treatment of the reaction mixture with excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected complete isomerization of **12** to the *cis* lactone **13**. Regioselective reduction of the internal double bond of **13** occurred stereoselectively from the less hindered α-face under catalytic hydrogenation over Raney nickel[22] to yield the previously reported *N*-Boc-himbeline derivative **14**.[6a,23] N-Deprotection of compound **14** yielded (+)-himbeline (**2**). Direct conversion of compound **14** to (+)-himbacine was achieved in a one-pot procedure by deprotection with trifluoroacetic acid followed by reductive methylation[6a] using aqueous formaldehyde and sodium cyanoborohydride. Both synthetic himbeline and himbacine showed spectroscopic properties identical to those reported for the natural products as well as comparable optical rotations.[24,25]

In conclusion, we have completed the total synthesis of himbacine in 11 linear steps from readily accessible (*S*)-2-methylpiperidine L-tartrate (**3**) in 9.7% yield. With this practical synthesis of himbacine now in hand, the continuing exploration of the promising biological property of this class of compounds will be aided.

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Supporting Information Available: Spectral data and procedures for compounds **1**, **2**, **5**, **6**, **8**, **9**, **11**, **13**, and **14** and ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of compounds **1**, **2**, **6**, **13**, and **14**, and ^{1}H NMR (400 MHz) for natural (+)-himbacine (19 pages). See any current masthead page for ordering and Internet access instructions.

JA962542F

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

(16) The technical grade chromous chloride (95%) available from Aldrich was used. Chromous chloride of high purity (99.9%), purchased from Strem Chemicals, gave inferior yields.

(17) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Alami, M.; Linstrumele, G. *Tetrahedron Lett.* **1991**, 6109. For reviews on Sonogashira reaction, see: (d) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. 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.

(18) (*S*)-3-Butyn-2-ol was purchased from Chiroscience Ltd, Cambridge Science Park, Milton Rd, Cambridge, CB4 4WE, England. It is also available from DSM Fine Chemicals, 217 Rte 46 W., Saddle Brook, NJ 07663-6253.

(19) The crude product, which was used for the next step without further purification, was contaminated with a small amount (5−10%) of saturated alcohol generated from the over-reduction of dienol **9**. This side product underwent esterification at the next step to generate the corresponding ester which coeluted with the desired product **11**. However, the presence of this side product did not affect the subsequent intramolecular Diels−Alder reaction.

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

(21) Prolonged reaction time resulted in substantial amount of N-deprotection of **12**. The corresponding free amine could be readily converted to **13** by treatment of the crude reaction mixture with Boc anhydride in the presence of 20% aqueous sodium hydroxide. Thermolytic deprotection of *tert*-butoxycarbonyl protecting group on indoles and pyrroles has been reported: Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

(22) Large excess (8−12 wt equivs) of Raney nickel was necessary. Commercially available (Aldrich) Raney nickel was washed four times with water and four times with methanol prior to use.

(23) *N*-Boc-(+)-himbeline showed ^{1}H and ^{13}C NMR data identical to those reported.[6a] Specific rotation: $[\alpha]_D^{20}$ +66.7 (*c* 0.19, $CHCl_3$); lit.[6a] $[\alpha]_D^{20}$ +60.6 (*c* 0.55, $CHCl_3$).

(24) The ^{13}C and ^{1}H NMR spectra of himbeline were identical to those reported (ref 6a, supporting information). The melting point of synthetic himbeline hydrochloride was 261−263 °C (dec) (lit.[1b] 265−266 °C) and the specific rotation was $[\alpha]_D^{20}$ + 22.4 (*c* 0.33, $CHCl_3$); lit.[6a,1b] [+17.1 (*c* 0.56, $CHCl_3$)[6a], +19 (2.4% in $CHCl_3$)[1b]].

(25) Synthetic himbacine was identical to the natural product by ^{1}H NMR, ^{13}C NMR, and TLC. Synthetic himbacine melted at 129−130 °C (lit.[6a] 129−130 °C). A 1:1 mixture of synthetic himbacine and authentic natural himbacine melted undepressed. Specific rotation: $[\alpha]_D^{20}$ +59.4 (*c* 0.35, $CHCl_3$); lit.[6a,1b] [+51.4 (*c* 1.01, $CHCl_3$)[6a], +63 (1.04% in $CHCl_3$)[1b]].