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Biomimetic Total Synthesis of (+)-Himbacine

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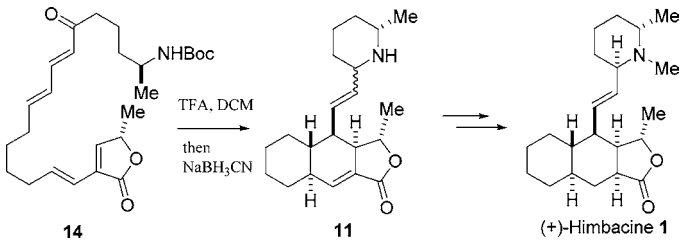
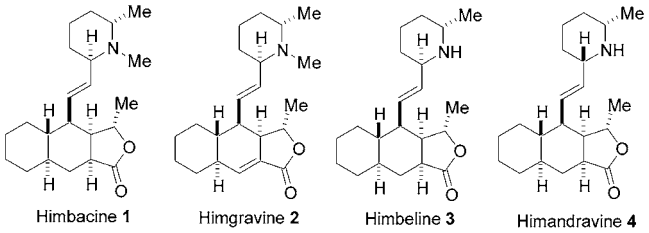
ABSTRACT



On treatment with trifluoroacetic acid butenolide 14 undergoes *N*-Boc deprotection and condensation followed by an iminium ion activated intramolecular Diels–Alder cycloaddition to give the (+)-himbacine precursor 11 on reductive work up. Compound 11 was converted into (+)-himbacine in four synthetic steps.

In 1956, Ritchie and Taylor reported isolation of the *Galbulimina* family alkaloids from the bark of *Himantandra baccata*.[11] Overall 28 new alkaloids were isolated, which were divided into 4 classes. Class 1 consisted of four tetracyclic lactones.



Within its class, himbacine (**1**) was the first and major isolated representative. It was originally shown to exhibit anti-spasmodic activity with low toxicity and few side effects.[2] More recently though, himbacine has been shown to be a selective muscarinic antagonist and thus a potential new lead in the treatment of Alzheimer's disease.[3] Consequently himbacine **1** has attracted much synthetic attention,[4] and three successful total syntheses of this molecule have been reported to date.[5−7] Quite remarkably an intramolecular Diels−Alder reaction was involved in the construction of the tricyclic core unit of himbacine in all the synthetic efforts published, however these approaches do not describe a

(1) 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*, 284. Ritchie, E.; Taylor, W. C. The Galibulimina Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 529. Ritchie, E.; Taylor, W. C. The Galibulimina Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 13, p 227.

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(4) De Baecke, G.; De Clercq, P. J. *Tetrahedron Lett.* **1995**, *36*, 7515. Hofman, S.; De Baecke, G.; Kenda, B.; De Clercq, P. J. *Synthesis* **1998**, 479. Hofman, S.; Gao, L.-J.; Van Dingenen, H.; Hosten, N. G. C.; Van Haver, D.; De Clercq, P. J.; Milanesio, M.; Viterbo, D. *Eur. J. Org. Chem.* **2001**, 2851. Wong, L. S.-M.; Sherburn, M. S. *Org. Lett.* **2003**, *5*, 3603.

(5) Hart, D. J.; Wu, W.-L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1995**, *117*, 9369. Hart, D. J.; Li, J.; Wu, W.; Kozikowski, A. P. *J. Org. Chem.* **1997**, *62*, 5023.

(6) Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc.* **1996**, *118*, 9812. Chakalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D. *J. Org. Chem.* **1999**, *64*, 1932.

(7) Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron Lett.* **1999**, *40*, 3399. Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron* **2002**, *58*, 9903.

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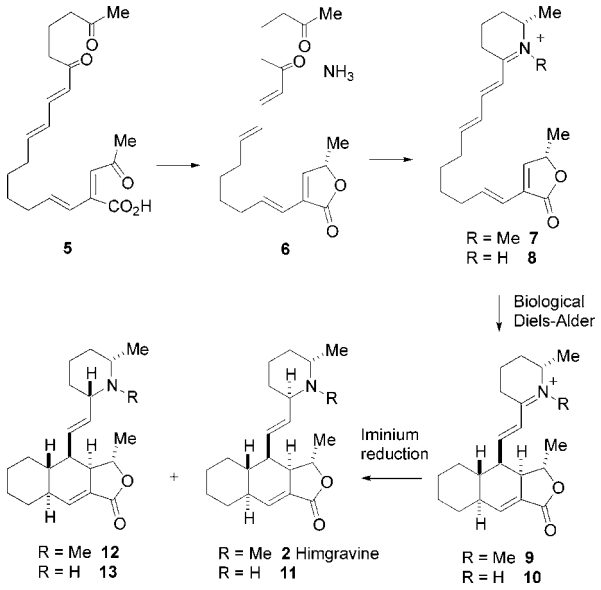
general biomimetic synthesis for all members of the class 1 *Galbulimina* alkaloids.

Our proposed biogenesis of all members of the class 1 *Galbulimina* alkaloids[8] is outlined in Scheme 1.

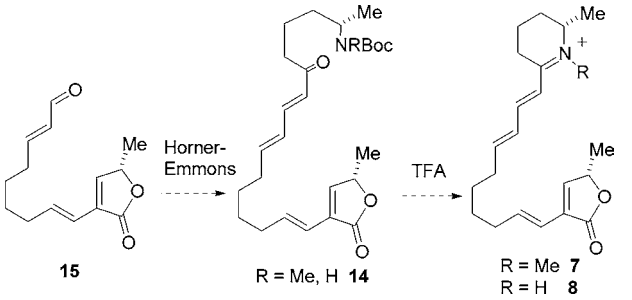
Scheme 1. Biogenesis of the Class 1 *Galbulimina* Alkaloids



The polyketide derivative **5**[9] would undergo reductive lactonisation to produce the butenolide **6**, which on reductive amination followed by methylation or protonation would give the iminium species **7** or **8**. Intramolecular Diels−Alder reaction via the *endo* transition state would afford tricycles **9** or **10**, which on hydride reduction of the iminium ion from either α or *β* face would finish the *cis*- or *trans*-piperidine rings of the himbacine precursor **2**, himbeline precursor **11** and himandravine precursor **13**. It was previously shown that mild reduction affords quantitative conversion of himgravine into himbacine,[1010] which coupled with the fact that himgravine is found in significantly smaller quantities leads to a proposal that himgravine is a precursor on the biosynthetic pathway to himbacine.

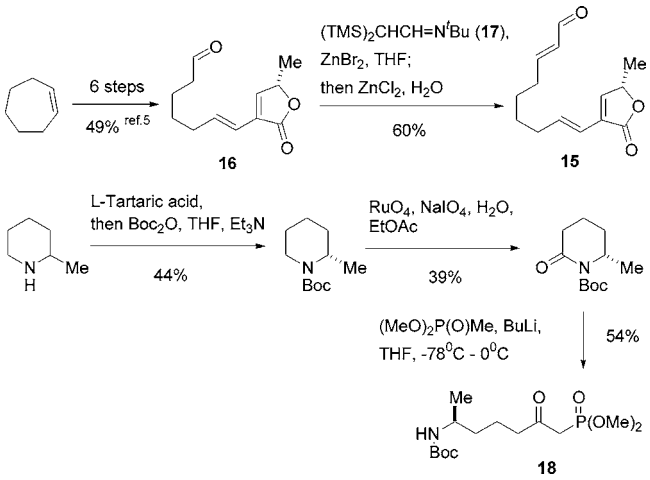
Previously[8] we have demonstrated evidence of the possibility of an iminium ion activated biological Diels−Alder reaction of the type shown above. The core tricyclic unit of himgravine was constructed via a Gassman-type[11] oxonium ion activated Diels−Alder cycloaddition. To obtain unambiguous evidence in support of our iminium ion proposal we decided to investigate the reaction of the dienone **14**, which on Boc removal should provide after condensation the iminium species **7** or **8**. The compound **14** would be obtained from a known aldehyde **15** via a Horner-Emmons type olefination as outlined in Scheme 2.

Scheme 2. Synthetic Plan



Probably the most elegant approach to the aldehyde **15** was reported by Hart[5] and we have adopted this sequence in our synthesis. According to the published procedures cycloheptene was converted into the aldehyde **16** in six synthetic steps and 49% overall yield (Scheme 3). A number

Scheme 3. Synthesis of the Horner−Emmons Precursors



of different homologation methods in order to obtain the aldehyde **15** were tried, including the use of commercially available stabilized phosphorane $Ph_3P{=}CHCHO$ and arsenic ylide $Ph_3As{=}CHCHO$,[5] which was prepared according to published procedure.[12] In our hands, these Wittig-type procedures resulted in low yields of the product, which was always contaminated with small amounts of over homologated material. On the contrary, the use of the aldimine **17**[13] gave a satisfactory isolated yield of the homologated aldehyde **15** (Scheme 3).

The synthesis of the chiral phosphonate **18** was accomplished in three steps. 2-Methyl piperidine was resolved

(8) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551.

(9) **5** itself would most probably be derived from nine acetates and one pyruvate by standard polyketide biosynthesis, as previously postulated by Mander et al.; see: Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1705.

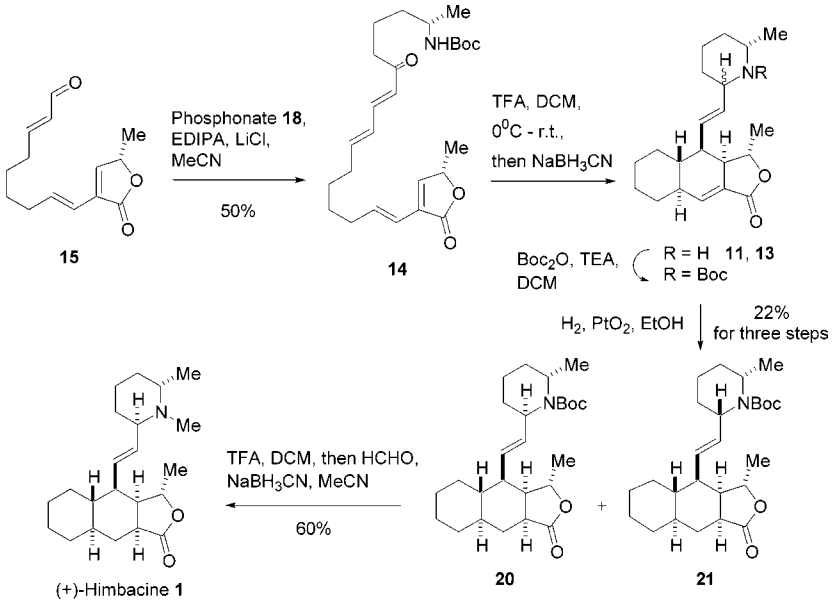
(10) Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1961**, *14*, 106.

(11) Gassman, P. G.; Singleton, D. A.; Wilwending, J. J.; Chavan, S. P. *J. Am. Chem. Soc.* **1987**, *109*, 2182.

(12) Huang, Y.-Z.; Shi, L.; Yang, J.; Cai, Z. *J. Org. Chem.* **1987**, *52*, 3558.

(13) Bellasoued, M.; Majidi, A. *J. Org. Chem.* **1993**, *58*, 2517.

Scheme 4. Completion of Synthesis



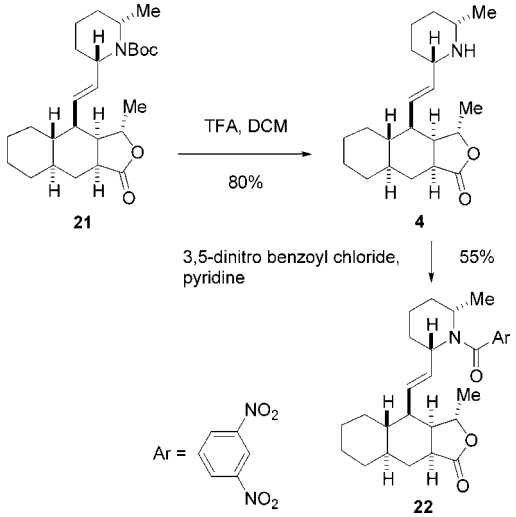
via crystallization with L-tartaric acid,[14] which was followed by Boc protection and oxidation.[15] Treatment of the piperidinone with a small excess of the lithiated dimethyl methylphosphonate produced the desired Horner−Emmons reagent **18** in 54% yield after column chromatography (Scheme 3).

Olefination of the aldehyde **15** and Horner-Emmons reagent **18** was achieved in acetonitrile using Hünig's base and an excess of lithium chloride.[16] The cyclization precursor **14** was then treated with trifluoroacetic acid in dichloromethane at 0 °C and the reaction was allowed to slowly warm to room temperature. After stirring for an hour it was quenched by addition of an access of sodium cyanoborohydride almost immediately followed by addition of saturated aqueous sodium bicarbonate. To our delight the crude NMR spectrum of the reaction mixture showed complete conversion of the starting material along with the appearance of two characteristic peaks at 6.62 and 6.69 ppm corresponding to the resonances of the protons of the α,β-unsaturated double bond of two epimeric products **11** and **13** derived from consecutive *N*-Boc deprotection, condensation, cycloaddition and iminium ion reduction (Scheme 4).

The reduction proved to be nonfacial selective and both proton peaks had identical integration in the 500 MHz 1H NMR. We found that direct separation of the diastereomeric mixture of **11** and **13** from the complex crude reaction mixture was impossible and required *N*-Boc protection followed by a highly selective reduction of the trisubstituted double bond[10] in order to separate the *N*-Boc protected himbeline **20** and himandravine **21** derivatives. Boc deprotection and *N*-methylation[5] of **20** afforded the synthetic (+)-himbacine (Scheme 4), whose structure was confirmed via a doping NMR experiment with an authentic sample[17] of the natural product.

The structure of the himandravine precursor **21** was established after Boc deprotection followed by formation of a dinitrobenzoate derivative **22** (Scheme 5) (which was crystallized by a slow evaporation of an ethyl acetate solution). The results of the single-crystal X-ray analysis of **22** are presented in Figure 1.

Scheme 5. Preparation of the Himandravine Analogue **22**



It is notable that all four representatives of the class 1 *Galbulimina* alkaloids can be accessed from the cyclization products **11** and **13**.

(14) Doller, D.; Davies, R.; Chackalamannil, S. *Tetrahedron: Asymmetry* **1997,** *7*, 1275.
(15) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728.
(16) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183.

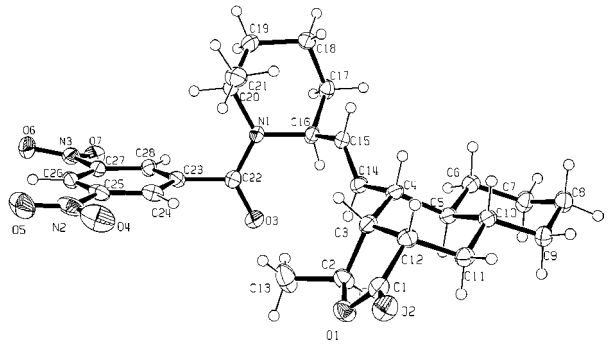


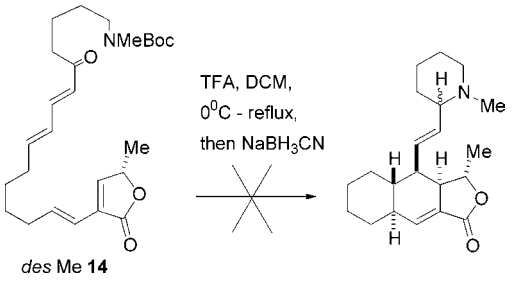
Figure 1. Crystal structure of the himandravine analogue **22**.

Interestingly, in an earlier model study on an analogue of **14** lacking the stereogenic center α to the nitrogen, cyclization was not achieved when the Boc-protected nitrogen was methylated; higher temperatures and longer reaction times did not lead to the formation of the tetracycle (Scheme 6). This is consistent with a more facile condensation from a primary rather than a secondary amine in order to access a key iminium ion intermediate.

In summary, we have demonstrated a single step biomimetic transformation of **14** into a tetracyclic himbacine precursor **11**, which was transformed into the natural product in four simple steps. We believe this proceeds via a consecutive *N*-Boc deprotection, condensation and iminium ion activated intramolecular Diels−Alder cycloaddition process. This provides support for our proposed biogenesis of the class 1 *Galbulimina* alkaloids.

(17) The ref 1 mg sample was obtained from Fisher Scientific UK (Acros cat. no. 32912 0010).

Scheme 6. Attempted Cyclization of Des-methyl **14**



des Me **14**

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **4**, **14**, **18**, and **20**−**22**. Tables of crystal data, fractional coordinates and thermal parameters, and interatomic distances with standard deviation for the himandravine derivative **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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