Total Syntheses of (+)-Himbacine and (+)-Himbeline

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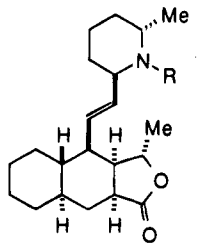
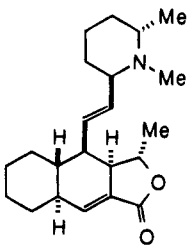
Received June 19, 1995

(+)-Himbacine (**1**) is a piperidine alkaloid isolated from the Australian pine *Galbulimima baccata*.[1,2] It is a potent muscarinic antagonist that displays selectivity for M2 or M4 receptors and, as such, has become a leading compound for identifying possible new drug candidates for the treatment of Alzheimer's dementia.[3,4] For example, blockage of presynaptic inhibitory muscarinic receptors leads to an elevation of synaptic levels of acetylcholine, thus possibly offsetting some of the losses in the cholinergic system that occurs in Alzheimer's disease. Limited SAR studies suggest that the *trans*-decalin substructure of himbacine may play an important role in conferring its selective binding properties.[4] Thus, it was desired to develop a synthesis of himbacine that would couple a decalin substructure to an appropriately substituted piperidine. This paper describes the first total synthesis of (+)-himbacine (**1**) via the related alkaloid (+)-himbeline (**2**).



1 R = Me
2 R = H



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The initial target for synthesis was aldehyde **14**. It was hoped that this would be available via an intramolecular Diels–Alder reaction of a substrate such as **9**. Indeed, the presence of himgravine (**3**) as a congener with himbacine has led to the suggestion that an intramolecular cycloaddition might be involved in the biosynthesis of these alkaloids.[5] The synthesis of **9** is shown in Scheme 1. Ozonolysis of cycloheptene according to the procedure of Schreiber provided aldehyde **5**, and subsequent Wittig olefination gave **6** as a 2:1 mixture of geometrical isomers in 72% overall yield.[6,7] Addition of the dienolate derived from **6** to the tetrahydropyranyl ether of (*S*)-2-hydroxypropanal,[8] followed by acetal hydrolysis and lactonization using *p*-toluenesulfonic acid in methanol and dehydration (MsCl, Et_3N, CH_2Cl_2), provided diene **8** as an 8:1 mixture of geometrical isomers.[9] The *E*:*Z* ratio was improved to 32:1 by allowing the mixture to stand in sunlight in the presence of iodine.[10] Acetal hydrolysis was followed by Wittig olefination to afford unsaturated thioester **9** in 67% yield.[11] Thermal cyclization of **9** at 110 °C in toluene for 16 h gave a 3:2 mixture of **12** and the corresponding exo cycloadduct, respectively. It was eventually found, however, that the endo:exo selectivity improved to 20:1 when a promoter prepared from diethylaluminum chloride and silica gel was used and the reaction was conducted at 40 °C for 96 h.[12] In this manner, crystalline **12** (mp 72–73 °C) was isolated in 67% yield. It is notable that ester **10** and alcohol derivative **11** failed to provide the stereoselectivity required for development of an efficient synthesis of himbacine.[13–15] Treatment of **12** with Raney nickel gave **13** (81%), and oxidation of the primary alcohol using Swern conditions completed the synthesis of aldehyde **14** (80–90%).[16,17]

Unfortunately, extensive efforts to couple sulfone **15** (Scheme 2) with aldehyde **14** met with failure.[18] Presumably, the aldehyde was simply too hindered to participate in the Julia–Lythgoe coupling.[19] Thus, it was decided to reverse the polarity of the coupling partners and attempt the coupling of sulfone **18** with aldehyde **23**. Conversion of **13** to the corresponding tosylate, followed by a displacement reaction using potassium thiophenoxide, gave **16** in 89% yield (Scheme 1). Reduction of **16** with diisobutylaluminum hydride in ether–hexane, followed by treatment of the resulting lactol with boron trifluoride etherate and methanol in dichloromethane, gave **17** in 94% yield. Oxidation of **17** with *m*-chloroperoxybenzoic acid gave sulfone **18** (94%).[20] Aldehyde **23** was prepared from (*R*)-piperidine-2-carboxylic acid as outlined in Scheme 2.[21] Thus, reduction of the amino acid with borane–dimethyl sulfide, followed by protection of the amine using di-*tert*-butyl dicarbonate, gave **19** in 88% yield.[22] Protection of the primary alcohol afforded **20** (96%), and application of the Beak

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(13) For example, ester **10** gave a 1:4 mixture of **12** (R = CO_2Et) and the corresponding exo cycloadduct in 77% yield at 200 °C (3 h) in toluene. Small amounts of what appear to be two other isomers (perhaps cycloaddition syn to the methyl group) were present in the mixture, based on signals in the olefinic region of the ^{1}H-NMR spectrum. When the temperature was dropped to 110 °C (toluene, 24 h), the yield dropped to 58% (87% conversion), the endo:exo ratio became 1:1, and only one minor cycloadduct was detected. The endo:exo ratio improved to 3:1 upon treatment with SiO_2–Et_2AlCl at 40 °C in toluene, but the yield was only 36% (50% conversion) after 96 h. Substrate **11** gave a 1:4 mixture of **12** (R = CH_2-OTBS) and the corresponding exo cycloadduct, respectively, upon heating in toluene at 210 °C for 18 h. Small amounts of another isomer were detected in this product mixture. Treatment of **9**, **10**, or **11** with Et_2AlCl in dichloromethane at room temperature failed to provide cycloaddition products.

(14) For some Diels–Alder reactions of unsaturated thioesters, see: Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840. Byeon, C.-H. Ph.D. Thesis, The Ohio State University, Columbus, OH, 1994. Wu, H. J.; Pan, K. *J. Chem. Soc., Chem. Commun.* **1987**, 898. Wu, H. J.; Huang, F. J.; Lin, C. C. *J. Chem. Soc., Chem. Commun.* **1991**, 770. Wladislaw, B.; Marzorati, L.; Gruber, J. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *59*, 479.

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(16) The structure of **13** was proven by X-ray crystallography. We thank Dr. Judith Gallucci of Department of Chemistry Crystallography Facility for providing this service.

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(18) The preparation of sulfone **15** from (*R*)-piperidine-2-carboxylic acid will be described elsewhere.

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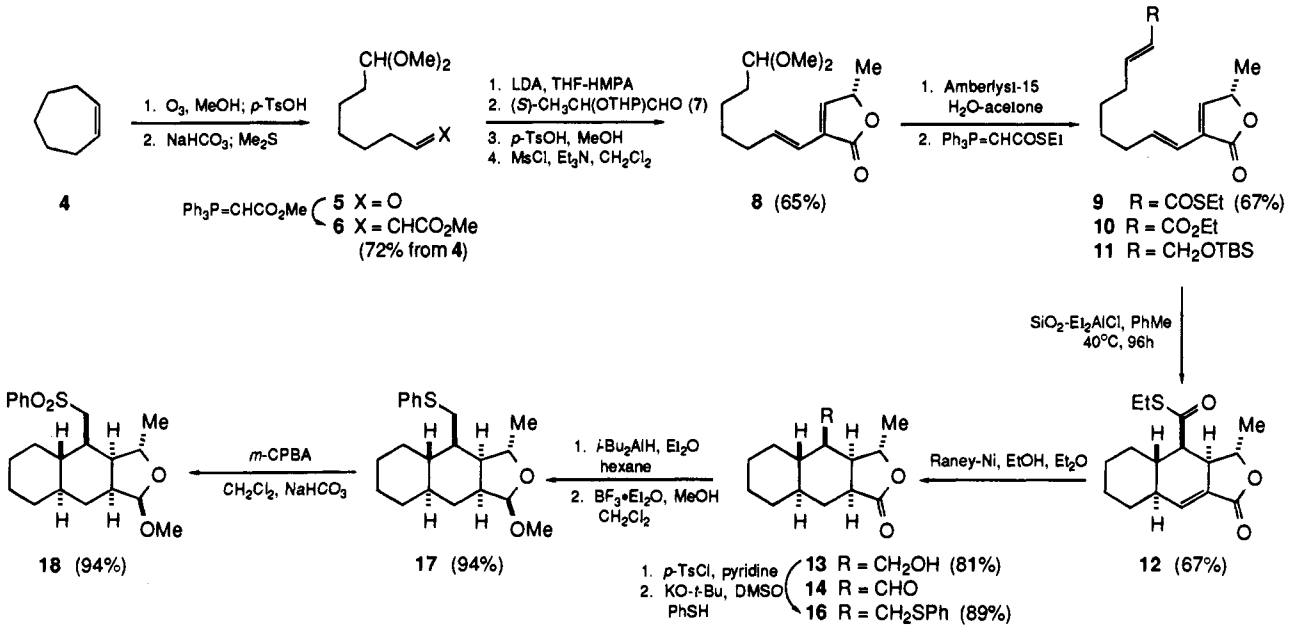
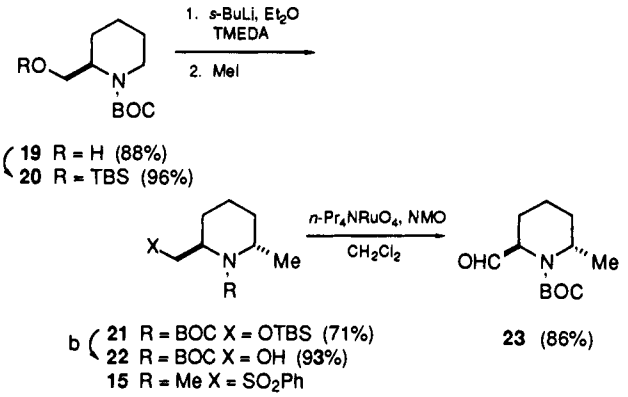
Scheme 1

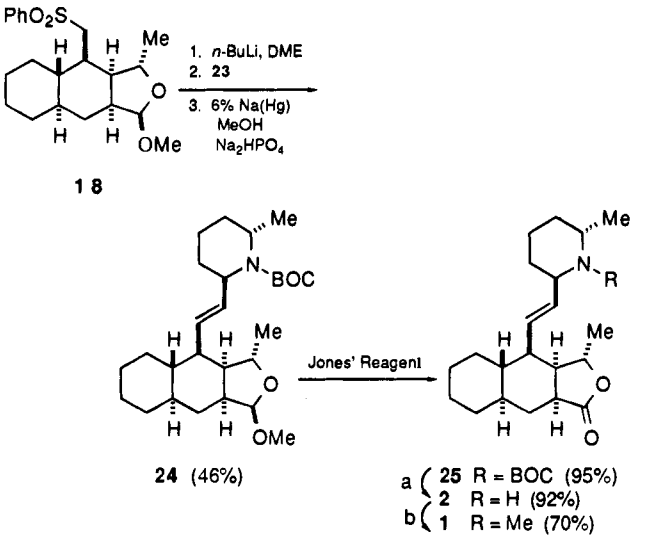


Scheme 2[a]



[a] (a) *t*-BuMe$_2$SiCl, DMF, imidazole; (b) *n*-Bu$_4$NF, THF.

Scheme 3[a]



[a] (a) TFA, CH_2Cl_2; (b) 37% aqueous CH_2O, CH_3CN, $NaBH_3CN$.

alkylation procedure gave **21** (71%),[23,24] Deprotection of the primary alcohol with tetra-*n*-butylammonium fluoride and oxidation of **22** (93%) using the Ley procedure gave **23** (86%),[25]

The synthesis was completed as described in Scheme 3, Treatment of sulfone **18** with *n*-butyllithium in glyme, followed by addition of aldehyde **23**, afforded a mixture of diastereomeric β-hydroxy sulfones which, upon treatment with sodium amalgam, gave **24** in 46% overall yield,[18] Oxidation of the acetal to lactone **25** was accomplished in 95% yield using Jones' reagent.[26] Treatment of **25** with trifluoroacetic acid gave (+)-himbeline (**2**),[27] and methylation of himbeline completed the synthesis of (+)-himbacine (**1**),[28]

In summary, an efficient convergent total synthesis of (+)-himbacine has been achieved via a longest linear sequence of 20 steps. The synthesis provides a protocol for conducting analog studies either via total synthesis or via intermediates that should be available through oxidative degradation of (+)-himbacine itself. From the standpoint of chemistry, the synthesis features an intramolecular thioester Diels–Alder reaction and suggests that this little-explored family of dienophiles might find some general use in synthesis,

Acknowledgment. We thank Interneuron Pharmaceuticals for a generous gift that supported this research and acknowledge instrumentation support from the Campus Chemical Instrumentation Center at The Ohio State University.

Supporting Information Available: Spectral data for all compounds in reaction sequence leading to **1** and **2**, procedures for the preparation of **8**, **12**, **24**, and **1**, and ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra of synthetic and authentic **1** and synthetic **2** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9519748

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(27) Synthetic (+)-himbeline gave a melting point (97.5–98.5 °C; lit.[1] mp 100 °C) and specific rotation α_D +17.1° in chloroform; lit.[1] α_D +19° in chloroform) in agreement with those reported for the natural product.
(28) Synthetic (+)-himbacine was identical to a sample of the natural product by TLC, mp (129–130 °C; authentic sample 129–130 °C; lit.[1] mp 132 °C), IR, ^{1}H-NMR, and ^{13}C-NMR. A 1:1 mixture of synthetic and authentic **1** melted undepressed. The synthetic himbacine displayed a specific rotation at the sodium D line of 51.4° (chloroform), identical to the specific rotation of a sample of the natural product recorded on the same instrument (lit.[1] α_D 63° in chloroform). We thank Professors Viresh Rawal and Micheal Cava for kindly supplying a sample of the natural product.