Pergamon

Tetrahedron Letters 40 (1999) 3399–3402

TETRAHEDRON LETTERS

A Novel Total Synthesis of (+)-Himbacine, A Potent Antagonist of the Muscarinic Receptor of M_2 Subtype

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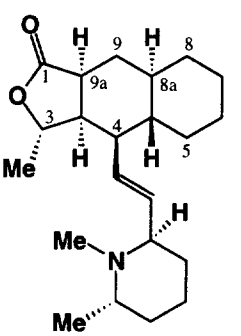
Received 8 February 1999; accepted 26 February 1999

Abstract

The title total synthesis was achieved by a method featuring highly stereoselective intermolecular Diels–Alder reaction of the tetrahydroisobenzofuran **5** with the chiral butenolide **6** as the key step. The cycloadduct **4** was converted to the title alkaloid by way of the known sulfone **2** in 17 steps.

Keywords: alkaloids; stereocontrol; Diels–Alder reaction; natural products

(+)-Himbacine (**1**) is a piperidine alkaloid isolated from the bark of *Galbulimima Baccata* collected in North Queensland and New Guinea in 1956 [1]. This alkaloid (**1**) bears a charactaristic structural feature in which the tricyclic part, consisting of *cis*-fused γ-lactone and *trans*-fused decaline moieties, is connected with *trans*-disubstituted piperidine via an (*E*)-double bond. It is reported that **1** behaves as a potent antagonist of the muscarinic receptor of M_2 subtype with 20-fold selectivity toward the M_1 receptor [2]. Thus, blockage of the presynaptic muscarinic receptor of M_2 subtype leads to an elevation of the synaptic levels of acetylcholine, possibly offsetting some of the losses in the cholinergic system that occurs in Alzheimer's disease [3]. Accordingly, **1** has attracted much interest from medicinal and synthetic organic chemists, and two total syntheses of **1** have hitherto been achieved by Hart–Kozikowski [4] and



(+)-himbacine (1)

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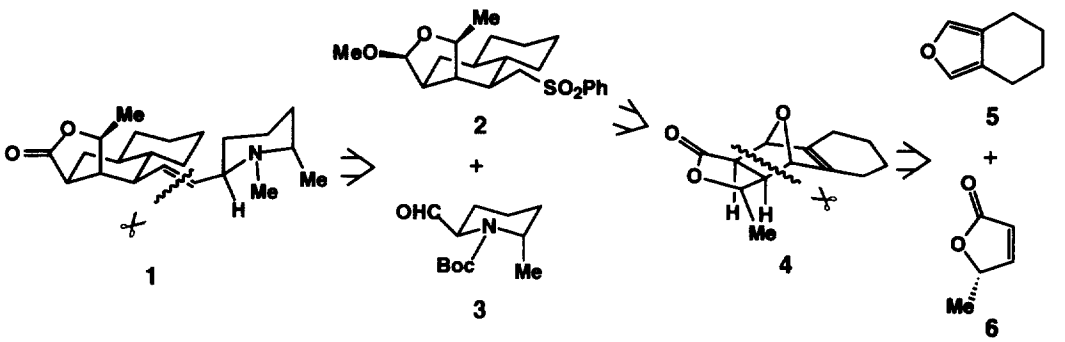
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00473-6

Scheme 1. Synthetic design of **1** featuring intermolecular Diels–Alder reaction.



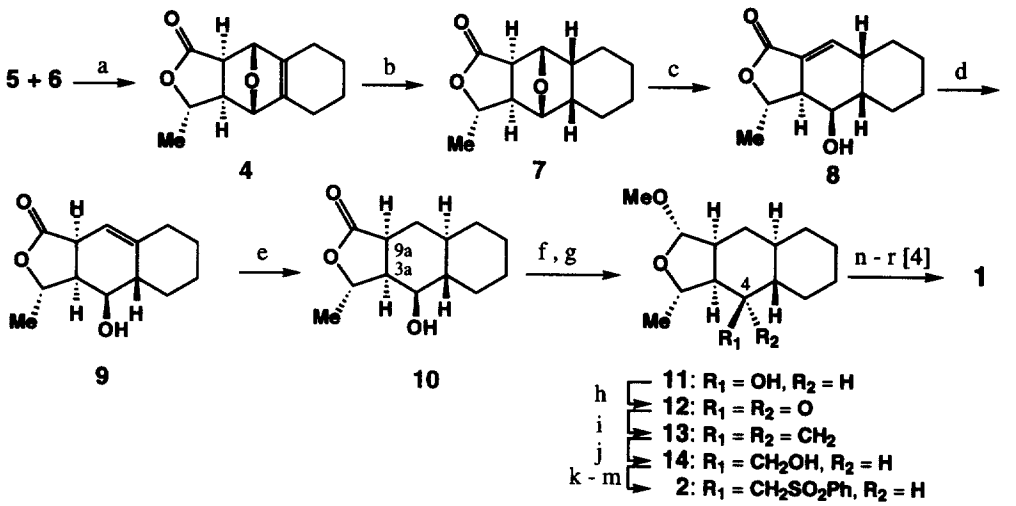
Chackalamannil [5] by employing an intramolecular Diels–Alder reaction as the key step. In order to disclose novel aspects of the structure-activity relationships of **1** and, moreover, to explore the promising congeners of **1** which may show more improved M_2 subtype selectivity, an efficient synthetic route to **1** was sought which is more convergent and flexible than those reported [4, 5]. Here, we wish to report a novel total synthesis of **1** accomplished by featuring an intermolecular Diels–Alder reaction as the key step.

Our synthetic design of **1** is outlined in **Scheme 1** in which the intermolecular Diels–Alder reaction of the tetrahydroisobenzofuran **5** with the chiral butenolide **6** is employed as the key step. Stereoselective production of the *exo*-cycloadduct **4** was expected based on the result reported for the reaction of **5** with maleic anhydride [6]. It is generally accepted that an intermolecular Diels–Alder reaction is more convergent and flexible than an intramolecular one, especially for the synthesis of complex natural products. Therefore, our approach was anticipated to be not only more advantageous for the total synthesis of **1** itself but also more useful for the exploration of the novel congeners of **1**.

Following the designed synthetic scheme, our approach to **1** commenced with the intermolecular Diels–Alder reaction of **5** with **6**,[2] both of which are readily obtainable following the reported procedures with some modifications [7, 8]. As shown in **Scheme 2**, treatment of **5** with **6** in ether containing $LiClO_4$ (5M solution) was found to undergo the expected intermolecular Diels–Alder reaction [9], giving rise to **4** as the sole isolable product in 71% yield.[3] It appeared evident that, probably due to steric and electronic reasons, the intermolecular Diels–Alder reaction takes place in a highly stereoselective manner, exclusively producing **4**. To the best of our knowledge, this is the first example of Diels–Alder reaction of **6** with furan derivatives.[4] Hydrogenation of the double bond in **4** from the sterically less-hindered convex face was effected under conventional conditions, affording the saturated

2. The specific rotation of **6** was $[\alpha]_D^{24}$+86.2° (*c* 0.65, $CHCl_3$) [lit. $[\alpha]_D^{20}$+93.8° (*c* 0.50, $CHCl_3$) [8]].
3. The stereochemistry of **4** was confirmed by single crystal X-ray crystallographic analysis of **7** produced by hydrogenation of **4**. Diastereoselectivity of the Diels–Alder reaction (de >95%) was estimated based on the 400 MHz ^{1}H-NMR spectrum of the crude reaction product. Details of the X-ray analysis will be reported in a separate paper.
4. It is reported that the enantiomer of **6** is inert toward furan under a variety of conditions [10].

Scheme 2. Synthesis of (+)-himbacine (**1**)



a) 5M $LiClO_4$ in Et_2O, rt, 3 d, 71%; b) H_2, 10% Pd-C, EtOH, rt, 8 h, 73%; c) $LiN(TMS)_2$, THF, −78 ~ −30 °C, 4 h; d) DBU, PhMe, 100 °C, 4 h, 80% (2 steps); e) H_2, PtO_2, EtOH, rt, 12 h, 88%; f) DIBAL-H, Et_2O, −78 °C, 1 h; g) $BF_3{\cdot}Et_2O$, MeOH, CH_2Cl_2, −78 °C ~ rt, 12 h, 94% (2 steps); h) Dess–Martin reagent, CH_2Cl_2, rt, 1 h, 97% or TPAP, NMO, MS4A, CH_2Cl_2, rt, 1.5 h, 95%; i) Ph_3PCH_3I, $NaN(TMS)_2$, Et_2O, 0 °C, 1.5 h, 91%; j) $BH_3{\cdot}THF$, THF, −78 °C, 3 h, then 30% H_2O_2 aq., 10% NaOH aq., 0 °C, 0.5 h, 73%; k) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 3 h; l) PhSH, ^{t}BuOK, DMSO, rt, 12 h; m) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 3.5 h, 95% (3 steps); n) **3** [4b], BuLi, DME, −78 °C, 100% (a mixture of the diastereomers, corrected for the recovery of **2**); o) 5% Na-Hg, Na_2HPO_4, MeOH, rt, 2.5 h, 66%; p) Jones reagent, Me_2CO, rt, 0.5 h; q) TFA, CH_2Cl_2, rt, 1.5 h; r) $NaBH_3CN$, 37% HCHO aq., MeOH, rt, 0.5 h, 91% (3 steps).

compound **7** in 73% yield. This was subjected to base-induced β-elimination of the oxygen bridge [11] followed by double bond isomerization, providing the unsaturated alcohol **9** as the sole product in 80% combined yield.[5] Catalytic reduction of **9** over PtO_2 smoothly gave the saturated tricyclic alcohol **10** in 88% yield.[6] Thus, stereoselective construction of the decahydronaphtho[2,3-*c*]furan system involved in **1** was readily furnished in 4 steps from the Diels–Alder *exo*-cycloadduct **4**.

After the lactone carbonyl group in **10** was protected by sequential reduction and acetalization,[7] the hydroxy group in the acetal **11** was oxidized with either the Dess–Martin reagent or the tetrapropylammonium perruthenate (TPAP) – 4-methylmorpholine *N*-oxide (NMO) system [12], affording the cyclohexanone **12** in high yield. Methylenation of **12** provided the *exo*-methylene compound **13** in 91% yield. Sequential hydroboration and oxidation of **13** gave rise to the β-methyl alcohol **14** in 73% yield along with the undesired

5. Highly stereoselective formation of **9** may be due to the thermodynamic control.
6. When the hydrogenation was carried out over $Rh\text{-}Al_2O_3$, a 1:1 mixture of **10** and its C-3a, 9a-epimer (the himbacine numbering) was produced quantitatively. The structure of the C-3a, 9a-epimer was determined by single crystal X-ray crystallographic analysis.
7. This sequence of the reactions gave rise to thermodynamically more stable **11** as an almost sole product.
8. When the sequential reactions were carried out at 0 °C, the ratio of desired **14** to the undesired C-4-epimer (the himbacine numbering) was found to be 5.3:1.

α-methyl alcohol (8%).[8] The structure of **14** carrying all of the desired chiral centers in the tricyclic part of **1** was rigorously confirmed as shown by single crystal X-ray crystallographic analysis.[9] Selective formation of **14** may reflect the increased steric hindrance of the β-face of **13**.

Next, **14** was transformed to the known sulfone **2**[10] in 95% combined yield by a three-step sequence [4] involving mesylation of the hydroxy group, replacement of the mesylate with a phenylsulfide group, and oxidation of the resulting sulfide. According to the Hart–Kozikowski protocol [4b], **2** was finally converted to **1** in 5 steps. Physical and spectral properties of the synthetic sample of **1**[11] were found to be identical to those reported [4b].

In summary, we have developed a novel synthetic route to (+)-himbacine (**1**), a potent antagonist of the muscarinic receptor of M_2 subtype, by employing an intermolecular Diels–Alder reaction of **5** with **6** as the key step. The explored synthetic scheme which is anticipated to be highly convergent and flexible, may be amenable to the large-scale preparation as well as applicable to the synthesis of various structural types of the novel congeners of **1**.

Acknowledgments

We are grateful to Dr. H. Ohkubo, Kyorin Pharmaceutical Co., Ltd., for his encouragement and many valuable suggestions.

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9. Details of the X-ray analysis will be reported in a separate paper.

10. Physical data for **2** are as follows; $[\alpha]_D^{20}$+104° (*c* 0.35, $CHCl_3$) [lit. $[\alpha]_D^{20}$+100° (*c* 0.35, $CHCl_3$) [4b]] and mp. 136~137 ℃ (recrystallized from hexane–EtOAc) [lit. mp. 127~128 ℃ (measured for a sample purified by column chromatography on SiO_2) [4b]]. Spectral (^{1}H-NMR,^{13}C-NMR, and IR) data of **2** was identical to those reported [4b].

11. Physical data of the synthetic sample are as follows ; $[\alpha]_D^{24}$+54.7° (*c* 0.21, $CHCl_3$) [authentic sample, $[\alpha]_D^{24}$+55.7° (*c* 0.21, $CHCl_3$): lit. $[\alpha]_D^{20}$+51.4° (*c* 1.01, $CHCl_3$) [4b]] and mp. 127~128 ℃ (recrystallized from hexane) [authentic sample, mp. 128~129 ℃ (recrystallized from hexane): lit. mp. 129~130 ℃ [4b]]. An authentic sample of **1** was purchased from Sigma Chemical Co., Ltd., and purified by recrystallization from hexane.