Pergamon

Tetrahedron Letters, Vol. 37, No. 9, pp. 1463-1466, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00042-1

Total Synthesis of (±) Epibatidine

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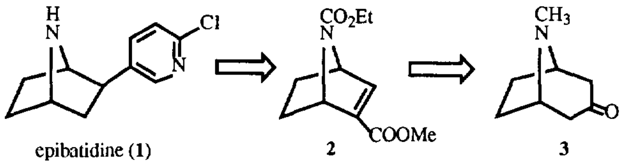
Abstract: *An efficient total synthesis of the non-opiate antinociceptive alkaloid epibatidine is described. Distinctly different from the previously published approaches it features the novel synthesis of the 7-azabicyclo[2.2.1]heptane ring system by contraction of the tropinone skeleton via Favorskii rearrangement.*

Epibatidine(**1**), which was isolated in trace amounts from the skin of the Ecuadorian poison frog *Epipedobates tricolor*,[1] represents a new class of alkaloid possessing a 7-azabicyclo[2.2.1]heptane (7-azanorbornane) structure to which is attached, in an *exo*-orientation, a 2-chloro-5-pyridyl substituent. It was reported to be a highly potent, non-opioid analgesic and nicotinic acetylcholine receptor agonist.[2-4]

Due to its unique structure, remarkable pharmacological activity and scarcity in nature, the total synthesis of **1** has attracted considerable attention. Several approaches have been reported to the synthesis of **1** with two different methodologies for the preparation of the azabicyclic system: (1) Diels-Alder reaction of *N*-protected pyrroles with activated dienophiles,[5-8] or (2) intramolecular nucleophilic ring closure of aminocyclohexane derivetives.[9-17] In this communication we wish to report our successful total synthesis of **1** by adopting a novel methodology to construct the 7-azabicyclo[2.2.1]heptane framework.

Retrosynthetic analysis of the target molecule suggested that the α,β–unsaturated ester **2** would be a valuable precursor (Scheme 1). Conjugate addition of a pyridyl anion to **2** followed by decarboxylation and deprotection would generate epibatidine. It was further expected that the ester **2** would be obtained from the readily available tropinone by contraction of its azabicyclo[3.2.1]octane ring through Favorskii rearrangement.

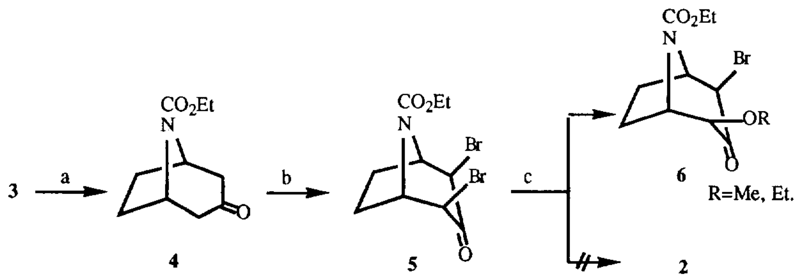
Scheme 1



The Favorskii reaction has been widely used for ring contraction in the synthesis of strained and monocyclic ring systems. With α,α'- dihaloketones, the rearrangment is accompanied by dehydrohalogenation to yield an α,β–unsaturated ester. However, this rearrangement in bicyclic systems has been studied to a less extent, especially for the substrates having halogen at a position other than a bridgehead.[18] To our knowledge, this type of rearrangement has not been reported yet for any non-bridgehead halogenated heterobicycloketones.

First we attempted to prepare **2** in a single step from the α,α'- dihaloketone **5**. Commercially available tropinone **3** was used as the starting material. Tropinone **3** was converted into *N*-carbethoxy tropinone **4** by treatment with ethyl chloroformate.[19] Bromination of **4** with bromine in ether gave the dibromide **5**. However, all attempts to carry out the Favorskii rearrangement on **5** under various basic conditions to achieve the α,β–unsaturated ester **2** were unsuccessful. In most cases the monosubstituted compound **6** was the main product (Scheme 2).

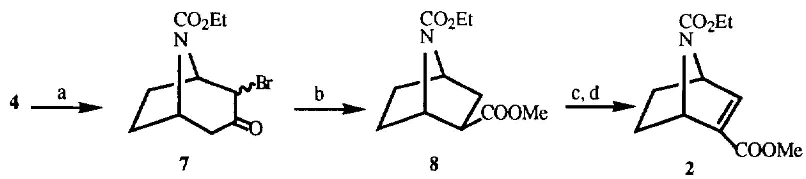
Scheme 2



(a) $ClCO_2Et$ (2 equiv.), K_2CO_3 (cat.), toluene, reflux, 3h, 86% yield; (b) Br_2 (2 equiv.), Et_2O, rt, 10 min, 66% yield; (c) NaOMe/DME or PhH or CH_2Cl_2; Et_3N/MeOH or EtOH.

Preparation of the ester **8** was then tried. Bromination of **4** with cupric bromide[20] afforded the monobromide **7**, which was subjected to rearrangement reaction without purification by treatment with sodium methoxide,[21] yielding the expected ester **8** (56% overall yield from **4**). The configuration of carbomethoxy is exclusively *exo* based on careful analysis of ^{1}HNMR spectra.[27] The key intermediate **2** was then easily obtained in 68% yield through α–selenation of **8** followed by selenoxide elimination as shown in Scheme 3.

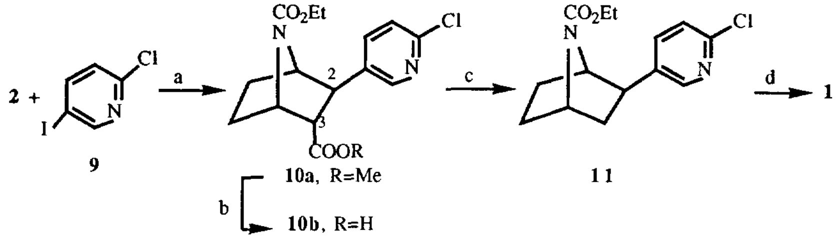
Scheme 3

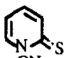


(a) $CuBr_2$ (2 equiv.), $CHCl_3$, EtOAc, reflux, 1 h; (b) NaOMe (3 equiv.), DME, rt, 0.5 h; (c) LDA, THF, -78°C, 20 min, then PhSeBr; (d) 30% H_2O_2, CH_2Cl_2, rt, 15 min.

With α,β–unsaturated ester **2** in hand, conjugate addition of a 5-pyridyl cuprate to **2** was investigated. However, our efforts failed probably due to the low reactivity of the α,β–disubstituted unsaturated ester. Fortunately, reductive palladium-catalyzed coupling reaction[6,23,24] between **2** and 2-chloro-5-iodo-pyridine **9**[22] at room temperature furnished the coupled product **10a** stereoselectively in 56% yield. The *trans* relationship between H-2 and H-3 and *exo*-orientation of 2-chloropyridyl group in **10a** were determined on the basis of [1]HNMR coupling constants,[27] which is in agreement with the reported values of epibatidine ring system.[25] Hydrolysis of **10a** with LiOH provided the acid **10b** in 92% yield. Finally, radical decarboxylation of **10b** was achieved using Barton's method,[26] giving **11** in 75% yield, and subsequent deprotection of **11** with iodotrimethyl silane led to epibatine **1** in a yield of 83% after chromatography (Scheme 4).

Scheme 4



(a) $(Ph_3P)_2Pd(OAc)_2$ (cat.), Et_3N, HCO_2H, DMF, rt, 4 d; (b) $LiOH{\cdot}H_2O$, $MeOH$-H_2O(3:2), 45°C, 1h; (c) $(COCl)_2$,  (1.2equiv.), *t*-BuSH, benzene, reflux, 3 h; (d) Me_3SiI (1.1 equiv.), $CHCl_3$, reflux, 4 h.

In conclusion, we have developed a concise and versatile approach for the synthesis of epibatidine and analogs. Starting from the commercially available tropinone, this approach features two crucial steps: a) novel method to prepare 7-azabicyclo[2.2.1]heptane ring system by contraction of tropinone skeleton through Favorskii rearrangement; b) stereoselective introduction of 2-chloropyridyl to C-2 position by Heck-type coupling reaction *via* the α,β–unsaturated ester **2**.

Acknowledgement. We acknowledge the financial support of this work by the National Key Laboratory of New Drug Research.

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27. Selected spectroscopic data of compound **8**, **10a**, **11** and **1**:

8: MS (EI) m/z 227 (M^+), 198, 168, 154, 140. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.52 (1H, m), 4.33 (1H, br s), 4.06 (2H, q, J=7.0Hz), 3.70 (3H, s), 2.55 (1H, dd, J=8.5Hz, 4.9Hz), 2.22 (1H, m), 1.77 (2H, m), 1.60 (1H, dd, J=12.2Hz, 9.0Hz), 1.42 (2H, m), 1.19 (3H, t, J=7.1Hz).

10a: MS (EI) m/z 338/340 (M^+), 307/309, 199, 141. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.30 (1H, d, J=2.5Hz), 7.62 (1H, dd, J=8.3Hz, 2.5Hz), 7.24 (1H, d, J=8.3Hz), 4.64 (1H, m), 4.30 (1H, br s), 4.12 (2H, q, J=7.1Hz), 3.71 (3H, s), 3.29 (1H, d, J=5.4Hz), 2.99 (1H, dd, J=5.4Hz, 5.0Hz), 1,40-1.95 (4H, m), 1.23 (3H, t, J=7.1Hz).

11: MS (EI) m/z 280/282 (M^+), 205, 199, 141. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.22 (1H, d, J=2.3Hz), 7.60 (1H, dd, J=8.3Hz, 2.3Hz), 7.23 (1H, d, J=8.3Hz), 4.42 (1H, m), 4.19 (1H, br s), 4.08 (2H, q, J=7.1Hz), 2.87 (1H, dd, J=8.5Hz, 5.2Hz), 2.00 (1H, dd, J=11.9Hz, 9.1Hz), 1.5-1.9 (3H, m), 1.21 (3H, t, J=7.1Hz).

1: MS (EI) m/z 208/210 (M^+), 179/181, 140/142, 69. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.26 (1H, d, J=2.4Hz), 7.77 (1H, dd, J=8.3Hz, 2.4Hz), 7.23 (1H, d, J=8.3Hz), 3.83 (1H, m), 3.59 (1H, br s), 2.79 (1H, dd, J=8.8Hz,.5.3Hz), 1.92 (1H, dd, J=12.2Hz, 9.1Hz), 1,4-1.8 (5H, m).

(*Received in China* 28 *September* 1995; *accepted* 7 *December* 1995)