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otal Synthesis of (±)-Homoepibatidine

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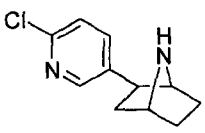
Total synthesis of (±)-homoepibatidine (**2**), which contains the 8-azabicyclo[3.2.1] octane ring system, was achieved by using palladium-catalyzed Heck-type coupling reaction from **3**.

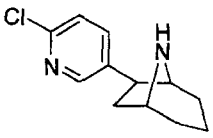
Key words : Alkaloids, Analgesics, Palladium, Stereocontrol

A new class of amphibian alkaloid epibatidine (**1**), vhich was isolated in a trace amount from the skin of he Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers (Spande *et al.*,1992), has been eported to be a highly potent non-opioid analgesic. Subsequent studies showed that the analgesic activity of epibatidine is attributed to its distinctive property as an extremely potent agonist of the nicotinic acetylcholine eceptor (Qian *et al.*, 1993; Fisher *et al.*, 1994). Due to its unique structure and remarkable pharmarcological activity, epibatidine has been the subject of many synthetic studies (Bai *et al.*, 1996; Pandy *et al.*, 1998; Malpass and Cox., 1999; Koren *et al.*, 1999). It has been found that this desirable activity is accom-panied by high toxicity. This has generated interest in the preparation of analogs which may be selective nicotinic receptor analgesics with reduced toxicity.

Remarkably, in spite of the intense activity, there exist few examples of epibatidine analogs with different ring system (Bai *et al.*, 1996; Malpass *et al.*, 1996; Zhang *et al.*, 1997). In this communication, we wish to report a simple, efficient stereocontrolled synthesis of (±)-homo-epibatidine (**2**).



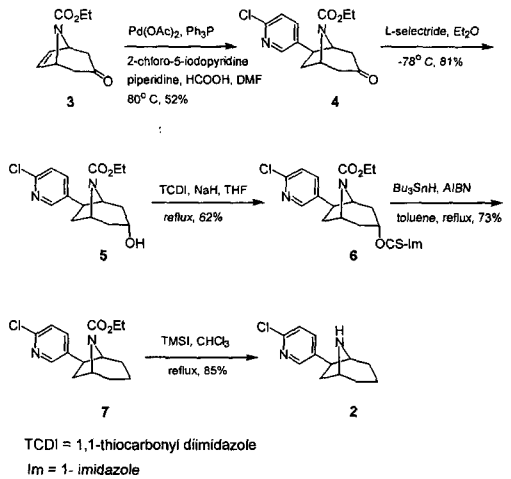
Epibatidine (**1**)



Homoepibatidine (**2**)

Total synthesis of (±)-homoepibatidine (**2**) was started from 8-carboethoxy-8-azabicyclo[3.2.1]oct-6-ene-3-one (**3**), which was early synthesized according to the efficient method developed by Barbosa et al (Mann *et al.*, 1992). **3** was heated at 80°C for 24 h in DMF containing piperidine (3.5 equiv.), formic acid (2.6 equiv.), palladium acetate (10 mol%) and triphenylphosphine (20 mol%) (Bai *et al.*, 1996). The desired reductively-coupled product (**4**) was formed in a moderate yield (52%) after flash chromatography. **4** was treated with L-selectride at -78°C to afford the corresponding alcohol (**5**). Deoxygenation was accomplished by way of the imidazolyl thionoester, followed by treatment with Bu_3SnH(Rasmussen *et al.*, 1998). Finally, cleavage of the carboethoxy group in **7** with iodotrimethylsilane gave (±)-homoepibatidine (**2**) in 16% overall yield from **3**.

In summary, total synthesis of (±)-homoepibatidine was



Scheme 1. Synthetic scheme

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accomplished by palladium-catalyzed coupling reaction.

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