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Stereoselective Synthesis of (±)-Epibatidine Analog : (±)-2β-(2-Chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane

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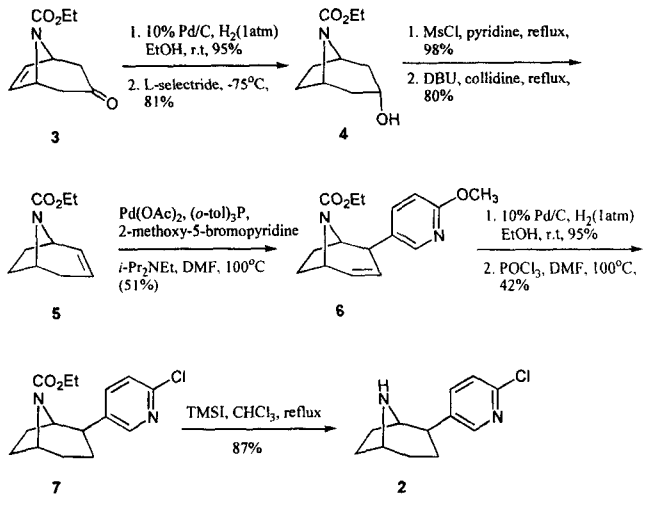
Stereoselective synthesis of (±)-epibatidine analog **2**, which contains the 8-azabicyclo[3.2.1]octane ring system, was achieved by using palladium-catalyzed Heck-type coupling reaction from **3**.

Key words : Alkaloids, Analgesics, Palladium, Stereocontrol

Epibatidine (**1**), which was isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers (Spande *et al.*, 1992), has been reported to be a highly potent, non-opioid analgesic and nicotinic acetylcholine receptor agonist (Fisher *et al.*, 1994). A number of its synthetic approaches have been reported (Bai *et al.*, 1996; Pandy *et al.*, 1998) due to its unusual structure and its interesting biological activity. It has been found that the desirable activity is accompanied by high toxicity. This has generated interest in the preparation of analogs for 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 regio- and stereocontrolled synthesis of (±)-epibatidine analog, (±)-2β-(2-chloro-5-pyridinyl)-8-aza-bicyclo[3.2.1]octane(**2**).

The synthesis of (±)-epibatidine analog **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). The conversion of **3** to **5** was accomplished by the efficient four step sequences. Hydrogenation of **3** in the presence of Pd/C followed by sequential L-selectride reduction, mesylation of the resulting alcohol and then DBU treatment afforded **5** in 60% overall yield in four steps. The pyridinyl group was then introduced into the 8-azabicyclo[3.2.1]octane ring system by a palladium catalyzed coupling reaction. In case of the 5-Iodo-2-chloropyrine, dechlorination was occurred in subsequent catalytic hydrogenation. To avoid this problem, the 2-methoxy-5-bromopyridine was prepared (Sirisoma *et al.*, 1998) and reacted with **5** under standard conditions (15 mol% palladium acetate, 4 equiv. diisopropylethylamine, and 30 mol% tri-*o*-tolylphosphine) in dry DMF at 80°C to give **6** (Sonesson *et al.*, 1997). We were delighted to find that **6** was found to be completely regio- and stereoselective as the only desired exo-isomer could be isolated. The exo-orientation of 2-methoxy pyridinyl group

1 **2**



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was determined on the basis of ^{1}H NMR coupling constant (J=6.5Hz), which is in agreement with the reported value (Zhang *et al.*, 1997).

The conversion of **6** into **7** was achieved by hydrogenation and subsequent treatment with $POCl_3$ in DMF at 100°C (Sirisoma *et al.*, 1998). Deprotection of ethoxycarbonyl group in **7** with iodotrimethylsilane produced compound **2** from **5** in 18% overall yield.

In summary, a stereoselective synthesis of (±)-epibatidine analog was accomplished by palladium-catalyzed coupling reaction.

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