Total 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), which was isolated in a trace amount 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. Subsequent studies showed that the analgesic activity of epibatidine is attributed to its distinctive property as an extremely potent agonist of the nicotinic acetylcholine receptor (Qian et al., 1993; Fisher et al., 1994). Due to its unique structure and remarkable pharmacological 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 accompanied 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-

![Chemical structures](image)

Epibatidine (1)  Homoeopibatidine (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 Bu₄SnH (Rasmussen et al., 1998). Finally, cleavage of the carboxethoxy group in 7 with iodos(trimethyl)silane 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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