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TRANSFORMATION OF PROTOBERBERINES INTO BENZINDENOAZEPINES. STEREOSELECTIVE SYNTHESIS OF (±)-FUMARITRINE

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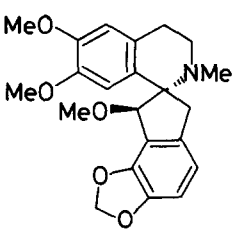
Summary: Treatment of the 8,14-cycloberbine (16), derived from dihydroepiberberine (13), with *p*-toluenesulfonic acid in methanol effected regioselective ring cleavage to afford stereoselectively the *cis*-benzindenoazepine (17) after *N*-methylation. Mesylation and subsequent sodium borohydride reduction of 17 furnished (±)-fumaritrine (2) in a good yield.

Fumaritrine, isolated from *Fumaria rostellata* Knaf and *F. officinalis* L., had been shown to possess the spirobenzylisoquinoline structure 1,[1] however, the intriguing benzindenoazepine structure 2 was recently proposed for fumaritrine instead of 1 on the basis of the careful consideration of its ^{1}H-NMR spectrum and the conversion of dihydroparfumidine (3) to fumaritrine.[2]

During our continuous studies on the transformation of protoberberines into related alkaloids, we have developed a novel method for the preparation of benzindenoazepine system (6)[3,4] through regioselective C_{14}-N bond cleavage



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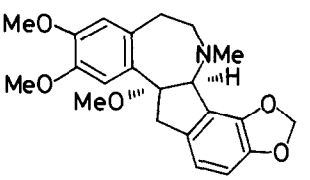

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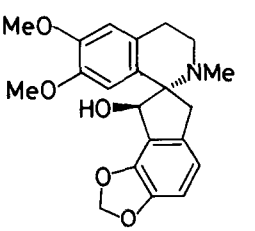

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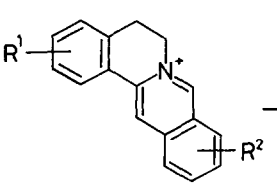

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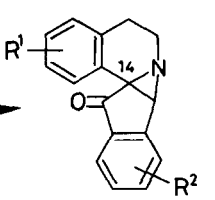

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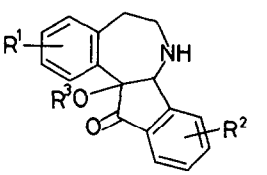
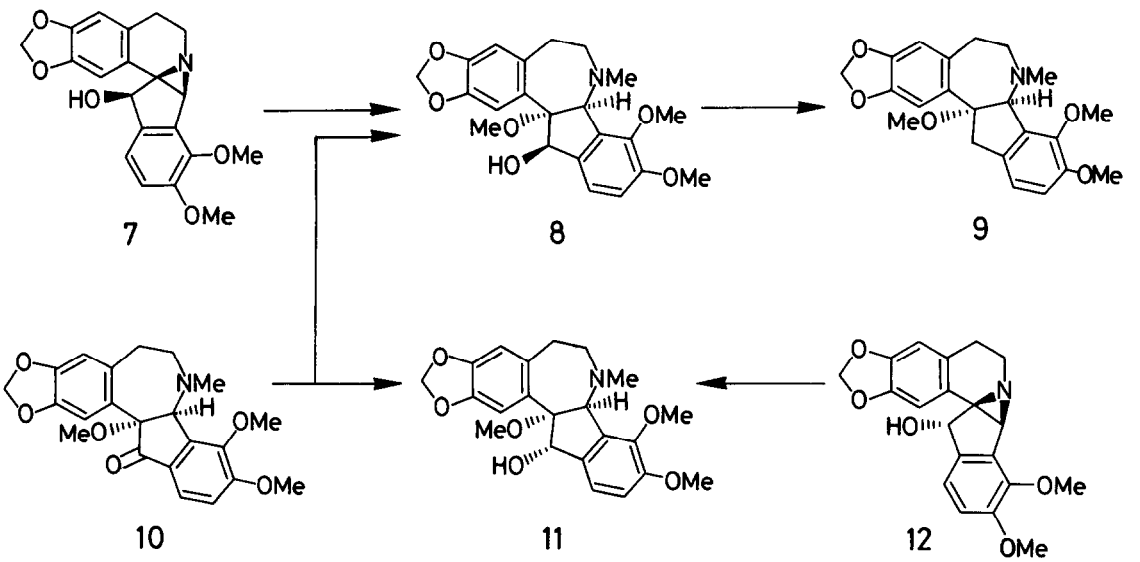


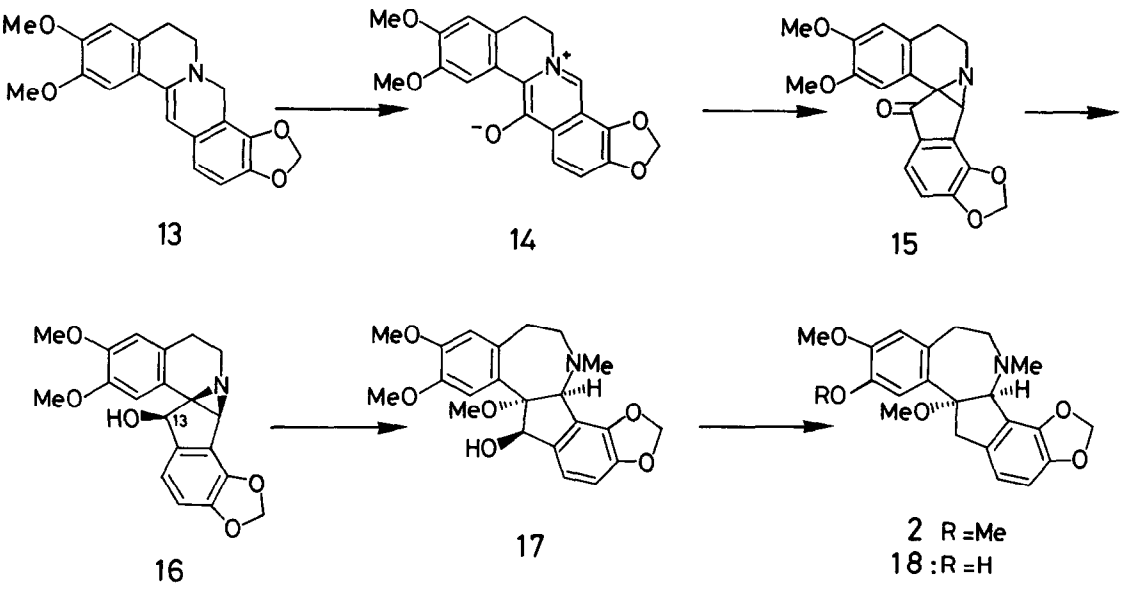
6

of the 8,14-cycloberbine (5),[5] derived from the protoberberine (4). Our endeavor was now focused on the synthesis of fumaritrine utilizing this synthetic method for benzindenoazepines. This communication deals with an efficient stereoselective synthesis of a benzindenoazepine alkaloid fumaritrine (2) from a protoberberine.

Prior to a synthesis of fumaritrine (2), we investigated a transformation of the 13-hydroxy-8,14-cycloberbine (7),[6] readily available from berberine, into fumaritrine analogue (9) as a preliminary examination. Treatment of 7



with *p*-toluenesulfonic acid in methanol at room temperature followed by methylation with methyl iodide afforded the benzindenoazepine (8)[82%; mp 191.5-193°; *m/z* 399 (M^+); ν 3300; δ 7.27, 6.94 (2H, AB-q, *J*=8), 7.12, 6.63 (each 1H, each s), 5.99, 5.96 (2H, AB-q, *J*=1.5), 4.91 (1H, d, *J*=1.5), 4.83 (1H, s), 3.94, 3.89, 3.01, 2.12 (each 3H, each s)] as a sole product. Its stereochemistry of the *cis*-fused benzindenoazepine was elucidated by an alternative synthesis from the known *cis*-benzindenoazepine (10).[3,4] Namely, sodium borohydride reduction of 10 gave two diastereoisomeric alcohols, one of which was identical with 8 and the other was identical with 11 derived from the isomeric alcohol (12).[7,8] The alcohol (8) was subsequently mesylated with methanesulfonyl chloride in methylene chloride at room temperature and the resulting mesylate was without purification treated with sodium borohydride in refluxing dimethoxyethane to furnish the fumaritrine analogue (9) [77%; mp 147-148°; *m/z* 383 (M^+); δ 6.94 (1H, s), 6.93, 6.91 (2H, AB-q, *J*=8), 6.66 (1H, s), 5.93, 5.92 (2H, AB-q, *J*=1), 4.67 (1H, s), 3.93, 3.86 (each 3H, each s), 3.40 (2H, s), 3.03, 2.12 (each 3H, each s)], which exhibited ^{1}H-NMR



spectrum similar to that of fumaritrine (2).

On the basis of the above preliminary results, a synthesis of fumaritrine (2) was efficiently achieved as follows. Epiberberinephenolbetaine (14), obtained from dihydroepiberberine (13)[9] by oxidation with *m*-chloroperbenzoic acid, was irradiated[5] in methanol with a high-pressure mercury lamp to produce the 8,14-cycloberbine (15)[62%; mp 157-159°; *m/z* 351 (M^+); ν 1710; δ 7.46, 6.85 (2H, AB-q, *J*=8), 7.36, 6.68 (each 1H, each s), 6.11, 6.09 (2H, AB-q, *J*=1.2), 3.95 (1H, s), 3.91, 3.88 (each 3H, each s)]. Sodium borohydride reduction of the ketone (15) in methanol afforded stereoselectively the alcohol (16)[quant.; mp 172-174°; *m/z* 353 (M^+); ν 3300; δ 7.14 (1H, s), 6.94, 6.75 (2H, AB-q, *J*=8), 6.67 (1H, s), 5.99, 5.96 (2H, AB-q, *J*=1.5), 5.71 (1H, br s), 3.92, 3.88 (each 3H, each s), 3.63 (1H, s)], the stereochemistry of which was confirmed as depicted by appearance of the signal due to H-13 at downfield (δ 5.71) similar to that of 7 (δ 5.63)[10] in the ^{1}H-NMR spectrum.[7,8] Upon treatment with methanol containing a small amount of *p*-toluenesulfonic acid, followed by methylation with methyl iodide, 16 produced stereoselectively the *cis*-benzindenoazepine (17)[92%; mp 212-213°; *m/z* 399 (M^+); ν 3400; δ 7.14 (1H, s), 7.06, 6.84 (2H, AB-q, *J*=7.5), 6.65 (1H, s), 6.05, 5.98 (2H, AB-q, *J*=1.5), 4.99, 4.70 (each 1H, each s), 3.94, 3.90, 3.07, 2.30 (each 3H, each s)]. Finally (±)-fumaritrine (2)[mp 164.5-166°; *m/z* 383 (M^+); δ 6.99 (1H, s), 6.74 (2H, s), 6.67 (1H, s), 6.02, 5.93 (2H, AB-q, *J*=1.5), 4.61 (1H, s), 3.91, 3.89 (each 3H, each s), 3.41 (2H, s), 3.10, 2.32 (each 3H, each s)] was obtained in 71% yield by successive mesylation and reduction of 17 according to the procedure described for the preparation of 9. The synthetic fumaritrine was proved to be identical with authentic fumaritrine derived from natural fumaritridine (18)[1,11] by comparison with IR, ^{1}H-NMR, and Mass

spectra, and thin-layer chromatographic behavior. Thus we have accomplished a synthesis of fumaritrine from the protoberberine (13) and its structure (2) has unambiguously been established by this synthesis.

The present efficient and stereoselective synthesis of a benzindeno-azepine alkaloid fumaritrine (2) will provide a general method for the preparation of the benzindenoazepine alkaloids.

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