A NOVEL SYNTHESIS OF (±)-FUMARICINE

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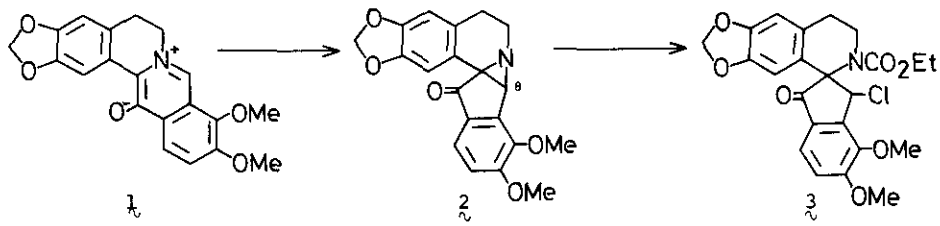
Abstract — A novel synthesis of (±)-fumaricine (9) from the phenolbetaine (5) *via* the 8,14-cycloberbine (6), the photochemical valence tautomer of 5, is described.

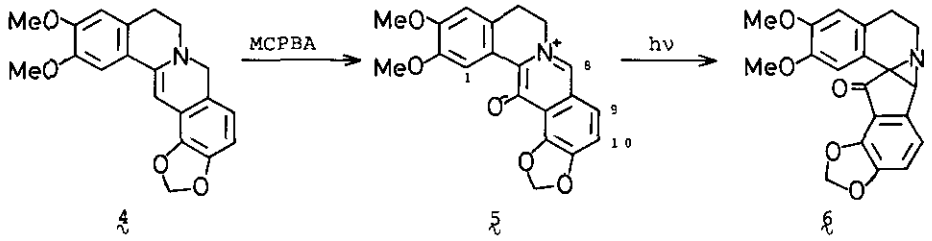
Previously, we reported a novel method for a synthesis of the spirobenzylisoquinoline (3) from berberinephenolbetaine (1) by photochemical valence tautomerization and subsequent regioselective C_8-N bond cleavage of the valence tautomer, the 8,14-cycloberbine (2).[1] This communication deals with the first application of this method to a novel synthesis of a spirobenzylisoquinoline alkaloid, (±)-fumaricine (9).[2]

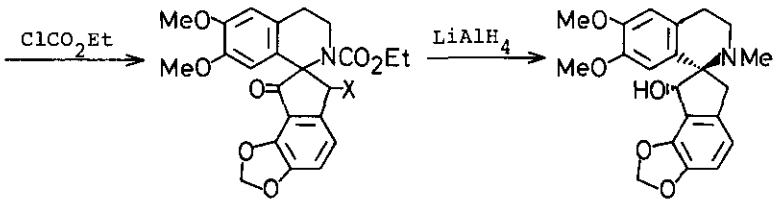


1 2 3

Oxidation of the dehydroberbine (4)[3] with *m*-chloroperbenzoic acid in CH_2Cl_2 in a stream of N_2 at -20∿ -30° gave the phenolbetaine (5) [69%, mp 142-143°, δ[4] 9.15 (1H, s, H-8), 7.36 (1H, s, H-1), 7.05 (2H, s, H-9 and H-10), 6.48 (1H, s, H-4)]. Irradiation (100W high pressure Hg lump, with Pyrex filter) of 5 in MeOH in a stream of N_2 for 1.5 hr at room temperature effected valence tautomerization leading to the 8,14-cycloberbine (6) [36%, ν[4] 1710, δ 3.78 (1H, s, H-8)]. Regioselective C_8-N bond cleavage of 6 with $ClCO_2Et$ afforded the spirobenzylisoquinoline (7) [65%, mp 110-111°, *m/e*: 459, 461 (M^+), ν 1730, 1680, δ 7.06 (2H, s, H-11 and H-12), 6.58 (1H, s, H-4), 6.11 (1H, s, H-1), 5.91 (1H, s, H-13)], which was hydrogenolyzed over 5% Pd-C to give the dechlorination product (8) in

90% yield. Reduction of 8 with $LiAlH_4$[5] in THF afforded (±)-fumaricine (9) [37%, mp 148-150° (lit.[2] mp 147.5-149°), *m/e*: 369 (M^+), ν 3550, δ 6.67 (2H, s, H-11 and H-12), 6.54 (1H, s, H-4), 6.35 (1H, s, H-1), 5.88 (2H, s, OCH_2O), 5.40 (1H, s, H-8), 3.79 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.28 (2H, s, H-13), 2.39 (3H, s, $N-CH_3$)], which was proved to be identical with the authentic sample of (±)-fumaricine by IR and NMR spectra. The present synthesis will provide a general synthetic method for the spirobenzylisoquinoline alkaloids.





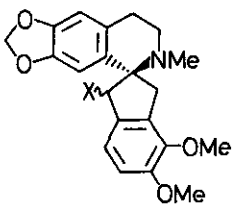
7: X= Cl
8: X= H

9

Acknowledgement: The authors are grateful to Professor H. Irie, Kyoto University, for sending the IR and NMR spectra of (±)-fumaricine.

REFERENCES AND FOOTNOTES

1. M. Hanaoka, S. Yasuda, K. Nagami, K. Okajima, and T. Imanishi, *Tetrahedron Letters*, 1979, 3749.
2. A synthesis of (±)-fumaricine has been accomplished; T. Kishimoto and S. Uyeo, *J. Chem. Soc. (C)*, 1969, 2600.
3. The synthesis of 4 will be described in a future paper.
4. All IR and NMR spectra were measured in $CHCl_3$ and $CDCl_3$, respectively.
5. Hydrogenation of 3 over 5% Pd-C followed by $LiAlH_4$ reduction[6] gave stereoselectively the alcohol (a), while the diastereoisomeric alcohol (b) was stereoselectively derived from 2 by the following reaction sequence; i) $NaBH_4$, ii) $ClCO_2Et$, iii) H_2/Pd-C, iv) $LiAlH_4$.
6. *cf.* H. Irie, S. Tani, and H. Yamane, *J. Chem. Soc. Perkin I*, 1972, 2986.



a: X= ···OH
b: X= ◀OH

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