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ANOTHER SYNTHESIS OF (±)-MESEMBRINE USING A SYMMETRIC STARTING MATERIAL

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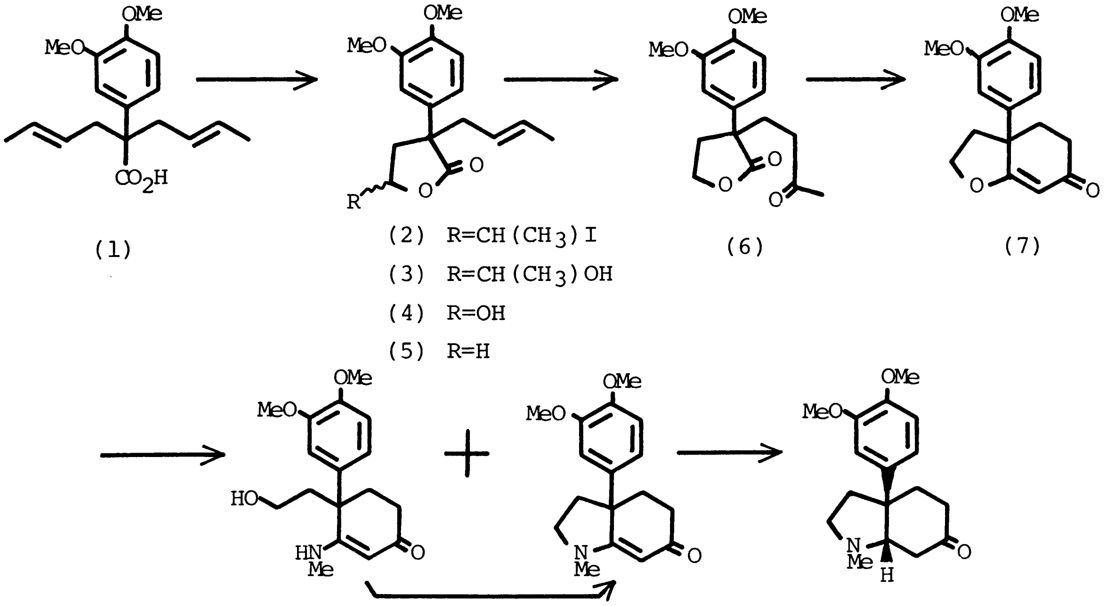
(±)-Mesembrine(10) has been synthesized efficiently via the vinylogous amide(9) using the symmetric substrate(1) as starting material.

Considerable efforts have been focused on the synthesis of the mesembrine alkaloids because of their being convenient testing targets for many new synthetic methodologies[1]. We now report here another synthesis of (±)-mesembrine(10) based on new methodology.

Exposure of the symmetric acid[2](1), prepared in 87 % overall yield from 3,4-dimethoxyphenylacetonitrile via two steps((i) crotyl bromide, LDA, (ii) saponification), to a mixture of iodine and potassium iodide in saturated sodium hydrogencarbonate[3] gave the iodolactone(2), which on sequential treatment with aqueous sodium hydroxide(20 %) and hydrochloric acid(36 %) afforded the diastereomeric γ-lactone(3) quantitatively. The compound(3), on successive treatment with aqueous sodium hydroxide(20 %) and then sodium periodate in the same flask, gave the hydroxylactone(4) which gave the γ-butyrolactone(5)(85.5 % yield from (3)) on reduction with sodium borohydride. Palladium catalyzed oxidation[4] of the γ-lactone (5) furnished the methyl ketone(6) predominantly in 73 % yield. Treatment of (6) with potassium tert-butoxide in tetrahydrofuran brought smooth intramolecular cyclization to give the tricyclic enone(7) quantitatively. Condensation of (7) with aqueous methylamine(40 %)(sealed tube, 180 °C) afforded a mixture of the vinylogous amides, (8) and (9), in yields of 40 and 7 %, respectively. Although conversion of the former into the latter proved to be difficult, intramolecular alkylation could be accomplished by using diethyl azodicarboxylate(DEAD) and triphenylphosphine[5] with extreme ease. Thus, treatment of (8) with DEAD(1 equiv.) and triphenylphosphine(1 equiv.) in tetrahydrofuran gave (9) almost quantitatively within an hour at room temperature. Conversion of (9) into (±)-mesembrine[6](10) was accomplished excellently by employing the dissolving metal procedure[7](Li(2 equiv.), liq. NH_3).



(1)

(2) R=CH(CH_3)I
(3) R=CH(CH_3)OH
(4) R=OH
(5) R=H

(6)

(7)

(8)

(9)

(10)

References

1) Pertinent review: R.V. Stevens, In "The Total Synthesis of Natural Products"; J. ApSimon, Ed., John Wiley & Sons: New York, 1977; vol. 3, pp. 443-453. See also, S.F. Martin, T.A. Puckette, and J.A. Colapret, J. Org. Chem., 44, 3391 (1979) and references cited therein.

2) Satisfactory analytical(canbustion or high-resolution mass spectrum) and spectral (IR, NMR, MS) data have been obtained for all new compounds.

3) Cf. M.D. Dowle and D.I. Davies, Chem. Soc. Reviews, 8, 171(1979).

4) (a) J. Tsuji, I. Shimizu, and K. Yamamoto, Tetrahedron Lett., 1976, 2975; (b) S. Takano, C. Kasahara, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1981, 637.

5) Cf. O. Mitsunobu, M. Wada, and T. Sano, J. Am. Chem. Soc., 94, 679(1972).

6) Nmr spectrum was completely identical to that reported: T. Oh-ishi and H. Kugita, Chem. Pharm. Bull., 18, 299(1970).

7) S. Takano, K. Shishido, M. Sato, K. Yuta, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1978, 943 and S. Takano, K. Shishido, J. Matsuzaka, and K. Ogasawara, Heterocycles, 13, 307(1979).

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