EFFICIENT SYNTHESIS OF (±)-EMETINE AND (±)-PROTOEMETINOL BY THE STEREOSELECTIVE INTRAMOLECULAR MICHAEL REACTION

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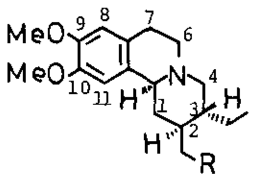
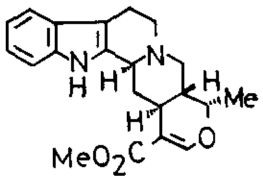
Abstract —— The intramolecular Michael Reaction of **8** and **12** gave stereoselectively **9** and **13**, which were converted to the emetine precursor (**11**) and (±)-protoemetinol (**2**).

Although a variety of approaches for the synthesis of emetine (**1**) have hitherto been reported[1], considerable attention to the new methods for the constraction of its ring system is still being paid from the view point of the medicinal activity and the structural similarity with various indol alkaloids, e.g., ajmalicine (**3**) and corynantheine (**4**).[2] In this communication we describe an efficient synthesis of (±)-emetine (**1**) and (±)-protoemetinol (**2**) by the stereoselective intramolecular Michael reaction.[3]





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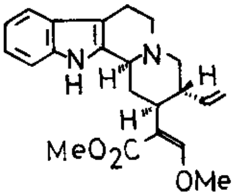

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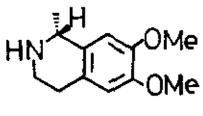
1 R = 

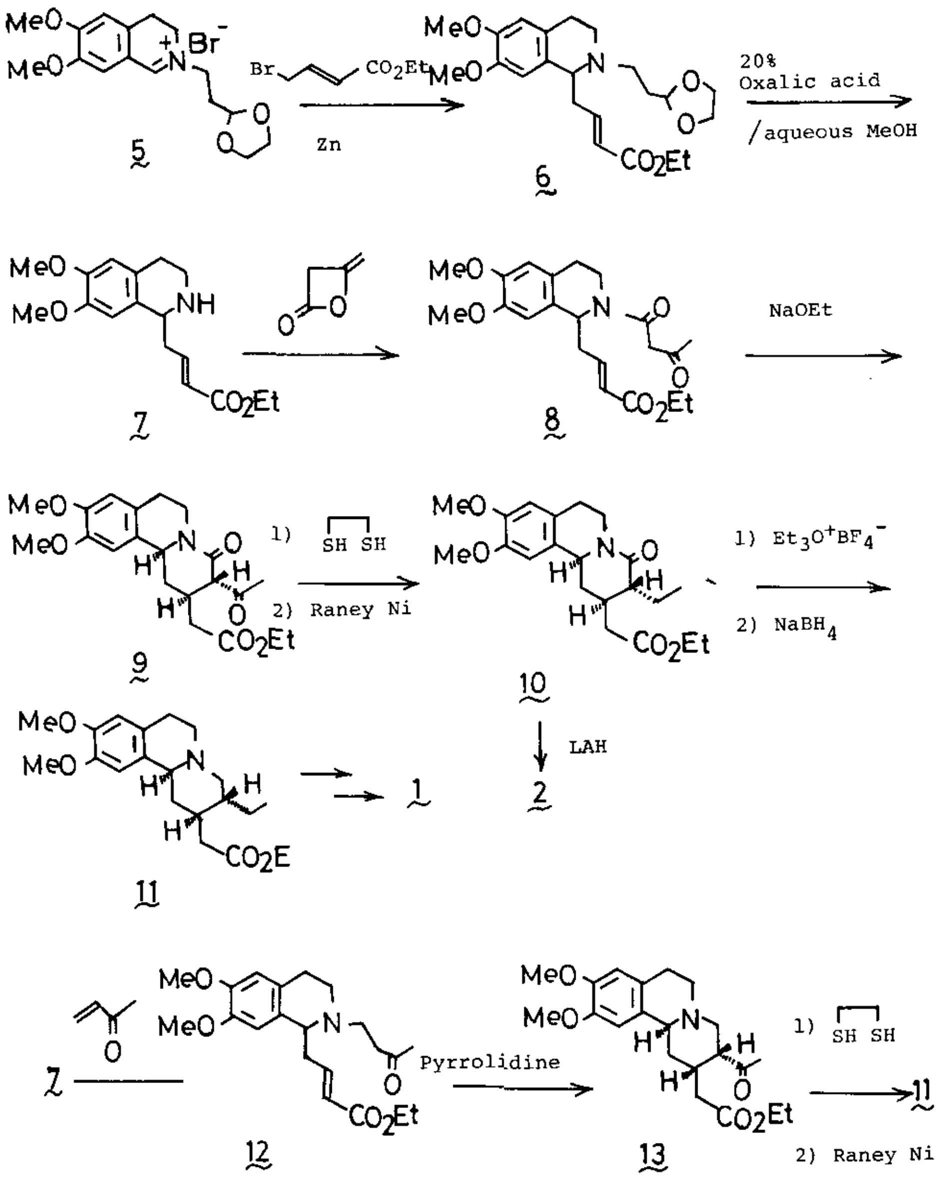
2 R = CH_2OH

The iminium salt (5), easily obtained in 98% yield from 3,4-dihydro-6,7-dimethoxyisoquinoline and 2-(2-bromoethyl)-1,3-dioxolane, was condensed with ethyl 4-bromocrotonate in acetonitrile containing zinc powder for 12 h at room temperature[4] to give the amine (6)[5] in 90% yield. Hydrolysis of 6 was effected by heating with a 20% solution of oxalic acid in methanol for 20 h to give the secondary amine (7) as an oil in 80% yield. Treatment of 7 with diketene in dry ether for 2 h at room temperature afforded the ketoamide (8) in 80% yield. Cyclization reaction of 8 was carried out by treating with sodium methoxide in dry methanol at room temperature to yield the tricyclic compound (9) in 63% yield.[6] The proton nmr of 9 suggested trans reationship between C_2-H and C_3-H.[7,8] Spectral and chromatographical analyses verified that only one stereoisomer was obtained.

Conversion of the tricyclic compound (9) to (±)-protoemetinol (2) and (±)-emetine (1) was carried out as follows. A mixture of 9 and ethanedithiol in trifluoroacetic acid was heated under reflux to afford a thioketal (71%), which was treated with Raney nickel in ethanol for 2 h to afford the lactam ester (10) in 65% yield. The lactam ester (10) was reduced with lithium aluminum hydride[9] to (±)-protoemetinol (2) in 67% yield.[10] The lactam ester (10) was then treated with triethyloxonium fluoroborate in dry CH_2Cl_2 at room temperature, and the reaction mixture was subjected to sodium borohydride reduction[11] to afford the emetine precursor (11)[12,13] in 54% yield. Since 11 has been converted to emetine,[1,14] this constitutes a formal synthesis of (±)-emetine (1).

A simpler preparation of 11 was also examined. Treatment of 7 with methyl vinyl ketone in dry CH_2cl_2 at room temperature afforded 12 (92%), which was cyclized to the tricyclic compound (13) in 80% yield in tetrahydrofuran containing pyrrolidine.[6] Compound (13) was converted to the ester (11) in 52.5% yield via its thioketal.[15]

Applications of the above methods to other ipecac and indole alkaloids are now in progress.



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REFERENCES AND NOTES

1. M. Shamma, 'The Isoquinoline Alkaloids', Academic Press, New York, 1972, pp. 426-457; M. Shamma and J. L. Moniot, 'Isoquinoline Alkaloids Research, 1972-1977', Plenum Press, New York, 1978, pp. 355-363; T. Fujii and M. Ohba, 'The Alkaloids', Vol. XXII, ed by Brossi, Academic Press, New York, 1983, pp. 1-50.
2. Recently several interesting syntheses of emetine were reported. S. Takano, S. Hatakeyama, and K. Ogasawara, *Tetrahedron Lett.*, 1978, 2519; T. Kametani, Y. Suzuki, H. Terasawa, and M. Ihara, *J. Chem. Soc. Perkin 1*, 1979, 1211; T. Fujii, M. Ohba, and S. Akiyama, *Heterocycles*, 1983, **22**, 159; R. T. Brown and M. F. Jones, *Tetrahedron Lett.*, 1984, **25**, 3127.
3. A part of this work was presented at the 62th Meeting of the Hokuriku Branch of the Pharmaceutical Society of Japan, Kanazawa, Novemver 1983.
4. T. Shono, H. Hamaguchi, M. Sasaki, S. Fujita, and K. Nagami, *J. Org. Chem.*, 1983, **48**, 1621.
5. Satisfactory elemental analyses were obtained for new compounds. Selected data. **6** : ^{1}H-nmr ($CDCl_3$) δ 3.86 (4H, br s, OCH_2CH_2O); 5.00 (1H, t, *J* = 5Hz, ), 5.85 (1H, dt, *J* = 16 and 1Hz, =CHCO), 7.13 (1H, dt, *J* = 16 and 7Hz, CH_2CH=); **7** : ir (Nujol) cm^{-1} 3325 (NH), 1710 (CO_2Et); ^{1}H-nmr ($CDCl_3$) δ 1.83 (1H, br s, NH), 5.93 (1H, dt, *J* = 16 and 1Hz, =CHCO), 7.03 (1H, dt, *J* = 16 and 7Hz, CH_2CH=); **10** : ir (Nujol) cm^{-1} 1730 (CO_2Et), 1632 (NCO-); ^{1}H-nmr ($CDCl_3$) δ 0.90 (3H, t, *J* = 7Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, *J* = 7Hz, $CO_2CH_2\underline{Me}$), 4.20 (2H, q, *J* = 7Hz, $CO_2C\underline{H}_2Me$), 3.88 (6H, s, OCH_3), 6.22 (1H, s, ArH), 6.64 (1H, s, ArH); **12** : ^{1}H-nmr ($CDCl_3$) δ 2.26 (3H, s, $COCH_3$), 5.17 (1H, dt, *J* = 16 and 1Hz, =CHCO), 7.00 (1H, dt, *J* = 16 and 7Hz, $CH_2C\underline{H}$=); **13** : ^{1}H-nmr ($CDCl_3$) δ 1.91 (3H, s, $COCH_3$).
6. During our studies,[3] synthesis of (-)-ajmalicine was reported by the similar intramolecular Michael reaction by G. Massiot and T. Mulamba [*J. Chem. Soc., Chem. Comm.*, 1984, 715].
7. The signal for the proton on C_3 was observed at δ 3.53 (1H, d, *J* = 10Hz) in addition to the signals at 2.43 (3H, s, $COCH_3$), 3.89 (6H, s, OCH_3), 4.70 (2H, m, C_{11b}-H and C_6-equatorial H), 6.80 (1H, s, ArH), and 6.82 (1H, s, ArH) in the nmr spectrum ($CDCl_3$).
8. F. A. Bovey, 'NMR Data Tables for Organic Compounds', Vol. 1, John Wiley & Sons, Inc., New York, 1967, pp. 230.
9. A. W. Burgstahler and Z. J. Bithos, *J. Am. Chem. Soc.*, 1960, **82**, 5466.
10. Compound (**2**) was identified by ir ($CHCl_3$) and nmr ($CDCl_3$) with an authentic sample.
11. R. F. Borch, *Tetrahedron Lett.*, 1968, 61; K. Mashimo and Y. Sato, *Tetrahedron*, 1970, **26**, 803.
12. The stereochemistry of this product was established by direct comparison (nmr and ir) with the optically active compound(-) of (**11**).
13. H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1963, 1461; T. Fujii and S. Yoshifuji, *Chem Pharm. Bull.*, 1979, **27**, 1486.
14. A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, 1960, 717.
15. E. E. van Tamelen, C. Placeway, G. P. Schiemenz, and I. G. Wright, *J. Am. Chem. Soc.*, 1969, **91**, 7359.

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