THE TOTAL STEREOSELECTIVE RETRO MASS SPECTRAL SYNTHESIS OF (±)-EMETINE

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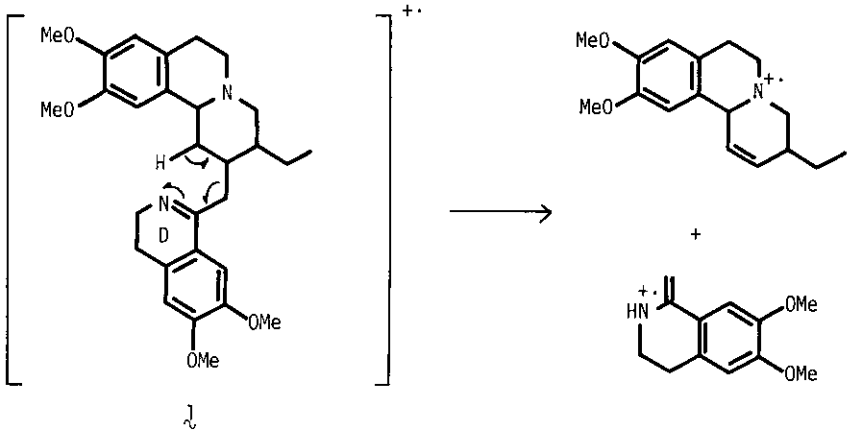
Abstract —— A new route to (±)-emetine (18) via the Michael addition product (4A) is described. Addition of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (3) to the α,β-unsaturated ester (2) afforded 2-(3',4'-dihydro-6',7'-dimethoxy-1'-isoquinolinyl-methyl)-3-methoxycarbonyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-benzo[a]quinolizin-4-one (4A) which was converted to (±)-emetine in 6 steps.

Although one of the most synthesised natural products known[1], there is continuing interest in developing a practical and efficient route to the ipecac alkaloid emetine, as a consequence of its medicinal value.[2] In view of the success with which the Retro-Mass Spectral method has been applied to the synthesis of a wide range of alkaloids,[3] it was decided to investigate a Retro Mass Spectral synthesis of emetine.

In accord with the method, it has been observed that the main mass spectral fragmentation process for the emetine bases in which ring D is incorporated in a 3,4-dihydroisoquinoline moiety, e.g. O-methylpsychotrine (1), is as shown in Scheme 1.[4]

Scheme 1

It was thus envisaged that utilisation of the feasible synthetic equivalents of these mass spectral fragments, α,β-unsaturated ester (2) and the 3,4-dihydro-1-methylisoquinoline (3), in a Michael reaction would enable a synthesis of emetine via the Retro Mass Spectral adduct (4), as outlined in Scheme 2.



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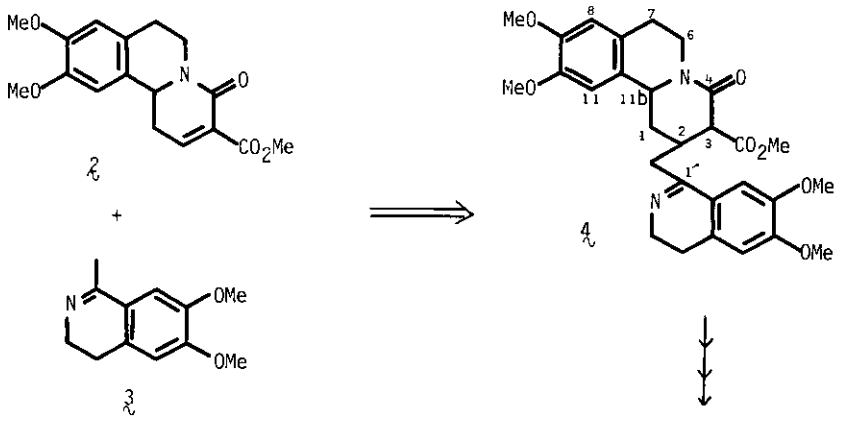
Scheme 1



2 + 3 ⟹ 4

Scheme 2

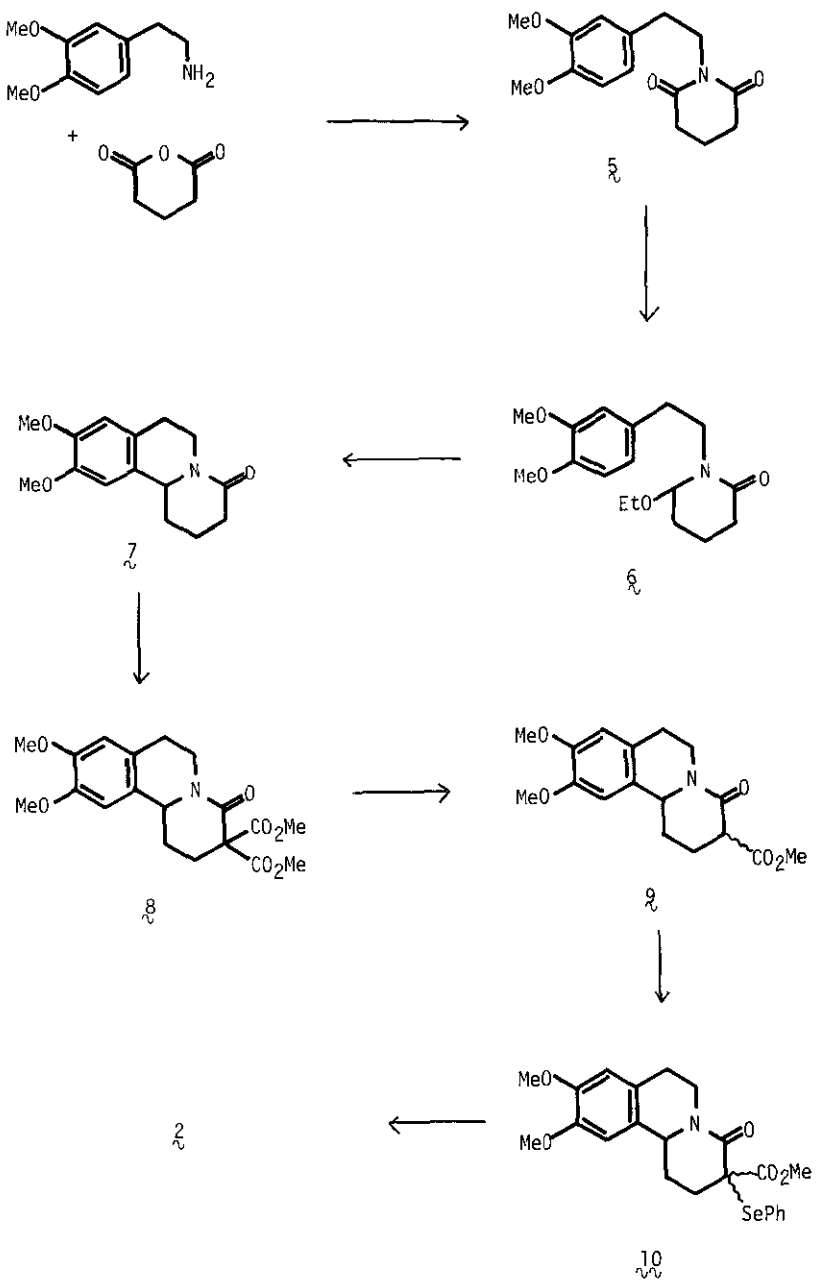
Scheme 2

With this then as the key step, a synthesis of emetine was undertaken as follows. The requisite α,β-unsaturated ester (2) was prepared via the known benzoquinolizinone (7).[5,6]

Scheme 3

Thus, heating a mixture of 3,4-dimethoxyphenylethylamine and glutaric anhydride at 100°C and treatment of the crude product with refluxing acetyl chloride afforded the imide (5) in 71 % yield. By the method of Speckamp,[7] this imide was converted to 1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[a]quinolizin-4-one (7). Namely, low temperature sodium borohydride reduction of imide (5) in ethanol in the presence of hydrochloric acid yielded the ethoxypiperidine (6), which on treatment with toluene-p-sulphonic acid in refluxing benzene produced the benzoquinolizinone (7)[8] in 98 % overall yield. Conversion to the diester derivative (8) was achieved by treatment of this lactam in tetrahydrofuran with 2 equivalents of LDA and excess methyl chloroformate. The diester, thus produced in 93.3 % yield after recrystallisation, was hydrolysed using 1 equivalent of potassium hydroxide in methanol to afford the monoester (9), in 93.8 % yield, as a non-crystalline diastereoisomeric mixture.[9] Introduction of α,β-unsaturation was brought about through an α-selenation/oxidative elimination sequence.[10] Namely, treatment of the diastereoisomeric mixture of monoesters (9) in benzene-dimethylformamide with 1 equivalent of sodium hydride followed by addition of 1 equivalent of phenylselenyl chloride yielded a diastereoisomeric mixture[11] of the α-phenylseleno derivative (10) as a viscous oil in 90.4 % yield. Oxidative elimination proceeded smoothly on treatment of the above mixture with 2 equivalents of sodium metaperiodate in aqueous methanol at room temperature. Short-column chromatography ($SiO_2/CHCl_3$) of the resulting product afforded, in 90 % yield, the required 3-methoxycarbonyl-1,6,7,11b-tetrahydro-9,10-dimethoxybenzo[a]-quinolizin-4-one (2) as a pale yellow oil [IR($CHCl_3$) ν_{max} 1740, 1665, 1620 cm^{-1}; NMR($CDCl_3$) δ 7.50 (1H, d, J 3 Hz, C_2-H), 6.70 & 6.63 (2H, 2 x s, arom.), 3.90 (9H, s, 3 x OMe)].

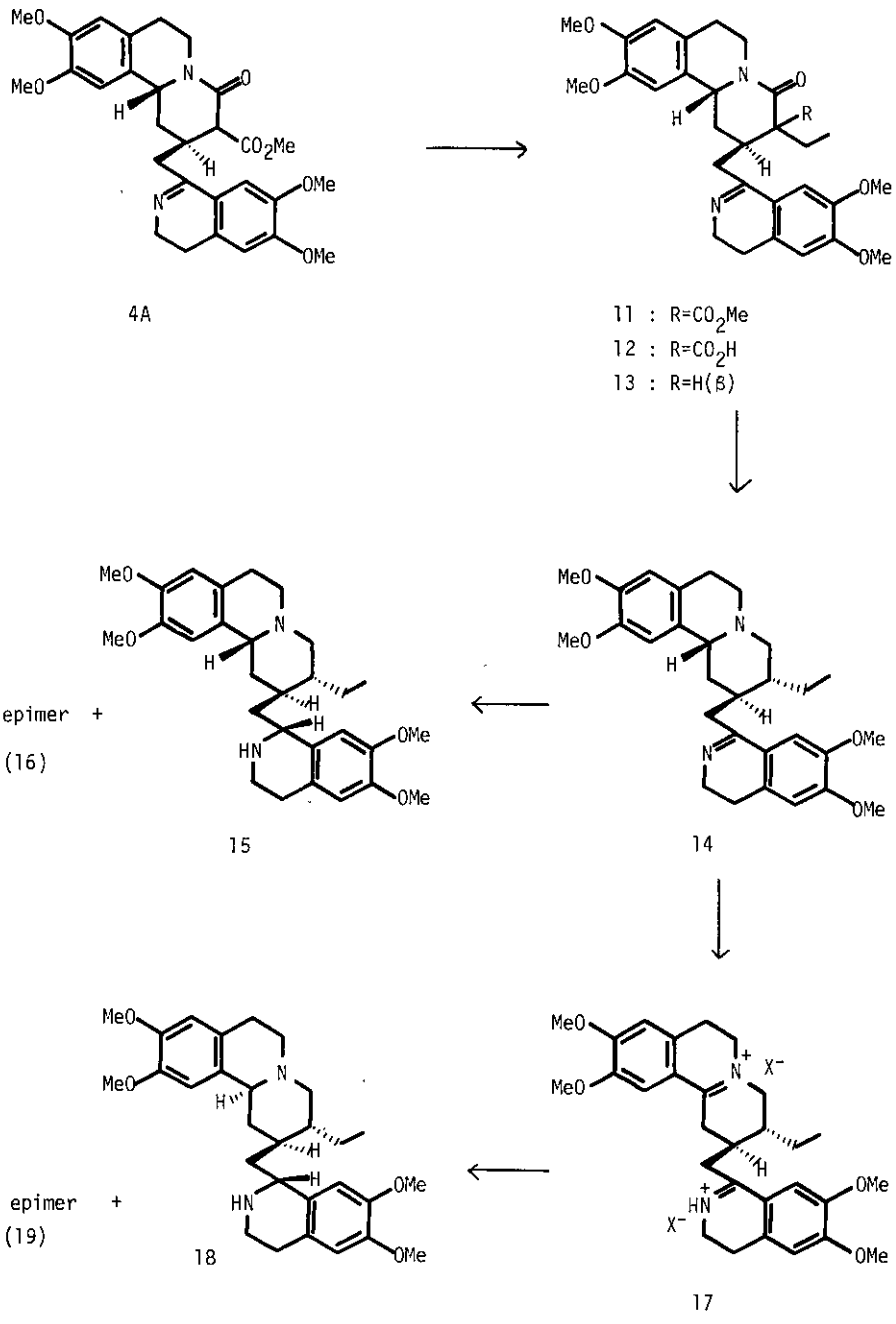
Scheme 4



Scheme 3

When a mixture of the above product (2) and two equivalents of the other Retro Mass Spectral synthon, 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline,[12] in dry methanol solution was maintained under nitrogen at room temperature for 94 h, a single diastereoisomer of the Michael adduct (4A) was produced as a fine white precipitate in 56 % yield [IR($CHCl_3$) ν_{max} 1740, 1640, 1605, 1570 cm^{-1}; NMR($CDCl_3$) δ 7.28, 7.03, 6.67 & 6.58 (4H, 4 x s, arom.), 3.87 (6H, s, 2 x OMe), 3.78 (3H, s, OMe), 3.70 (6H, s, 2 x OMe)]. As is to be expected of a Retro Mass Spectral product, this adduct showed only a very small molecular ion peak in its mass spectrum, with the largest peaks corresponding to the molecular weights of the two synthons. That the partial stereochemistry of this product is as represented in formula (4A) of Scheme 4 was shown by the subsequent reactions.

Treatment of (4A), in THF-DMF solution at room temperature, with 1 equivalent of sodium hydride and 1 equivalent of ethyl iodide afforded the 3-ethyl derivative (11) in 77.5 % yield [IR($CHCl_3$) ν_{max} 1740, 1640, 1620 cm^{-1}; NMR ($CDCl_3$) δ 6.93 & 6.72 (2H, 2 x s, arom.), 6.59 (2H, s, arom.), 3.93, 3.81 & 3.72 (9H, 3 x s, 3 x OMe), 3.86 (6H, s, 2 x OMe), 0.59 (3H, t, J 7.5 Hz, $-CH_2\underline{CH}_3$)]. Hydrolysis in refluxing methanolic potassium hydroxide gave an almost quantitative yield of the carboxylic acid (12) [IR($CHCl_3$) ν_{max} 2800 - 2200, 1730, 1650, 1600, 1560 cm^{-1}; NMR(d_6-DMSO) δ 7.37, 7.18, 6.73 & 6.62 (4H, 4 x s, arom.), 3.93, 3.79, 3.72 & 3.51 (12H, 4 x s, 4 x OMe), 0.53 (3H, t, J 7.5 Hz, $-CH_2\underline{CH}_3$)]. Although the relative configuration at C_2 and C_3 in these compounds (4A, 11 & 12) remains obscure, a single diastereoisomer was obtained in each case. Heating the acid (12) in DMF at 180 - 185°C for 30 min furnished the decarboxylated product (13) as a single compound in 79 % yield [IR($CHCl_3$) ν_{max} 1620, 1570 cm^{-1}; NMR($CDCl_3$) δ 7.03 & 6.77 (2H, 2 x s, arom.), 6.65 (2H, s, arom.), 4.02, 3.97, 3.90 & 3.84 (12H, 4 x s, 4 x OMe), 0.92 (3H, t, J 7.5 Hz, $-CH_2\underline{CH}_3$) . Reduction to the emetine-type base was carried out in two straightforward steps.[13] Namely, room temperature Red-al reduction of the lactam (13) in benzene afforded a quantitative yield of the amine (14) as a pale yellow oil, [NMR($CDCl_3$) δ 7.05 & 6.74 (2H, 2 x s, arom.), 6.57 (2H, s, arom.), 3.96, 3.89, 3.83 & 3.71 (12H, 4 x s, 4 x OMe), 0.85 (3H, t, J 7 Hz, $-CH_2\underline{CH}_3$)], and sodium borohydride reduction of this derivative produced, again in quantitative yield, an approximately 1 : 1 mixture of the emetine isomers (15 & 16) which was separated by silica gel chromatography. Although the higher Rf isomer was indistiguishable from authentic (±)-emetine by *t.l.c. analysis*,[14] *comparison of its NMR spectrum* [($CDCl_3$) δ 6.74 (1H, s, arom.) 6.54 (3H, br s, arom.), 3.84 (12H, s, 4 x OMe), 0.86 (3H, t, J 5.7 Hz,


MeO
MeO
N
O
H
CO2Me
H
N
OMe
OMe
4A
R
11 : R=CO2Me
12 : R=CO2H
13 : R=H(β)
HN
C1 epimer +
(16)
15
14
X−
17
C1 epimer +
(19)
18

Scheme 4

-$CH_2\underline{CH}_3$)] with that of emetine [($CDCl_3$) δ 6.73 (1H, s, arom.), 6.54 (2H, br s, arom.), 6.47 (1H, s, arom.), 3.84 (9H, s, 3 x OMe), 3.80 (3H, s, OMe), 0.90 (3H, t, J 5.7 Hz, -$CH_2\underline{CH}_3$)] showed this product to be a diastereoisomer of (±)-emetine. That it was the C_{11b} epimer, as illustrated in formula (15), was demonstrated by subsequent work. Treatment of the compound (14), the C_{11b} epimer of O-methylpsychotrine, with mercuric acetate in aqueous acetic acid[15] furnished the dehydrogenation product (17) which was isolated as the perchlorate salt. Sodium borohydride reduction of this derivative afforded, in good yield, an approximately 1 . 1 mixture of (±)-emetine (18) and (±)-isoemetine (19) which was separated by silica gel chromatography. Comparison with an authentic sample demonstrated the higher Rf synthetic compound to be identical to (±)-emetine. The medicinally useless isoemetine can of course be converted, via O-methylpsychotrine, to emetine.[15] This last reaction sequence described above, dehydrogenation/reduction, shows that compound (14) is the thermodynamically less stable cis-quinolizinine, and therefore that the preceeding compounds back to the original Michael adduct also have the β C_{11b}-H configuration as represented in the formulae (4A to 16, Scheme 4).

We have thus achieved a simple and efficient synthesis of (±)-emetine based on the Retro Mass Spectral method.

ACKNOWLEDGEMENTS

We wish to thank the Japan Society for the Promotion of Science for the award of a Post-Doctoral Fellowship to one of us (S.A.S.) during the period 1978 to 1980.

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8. Although the melting point (116 - 118°C) of this compound differs from that already reported (Ref. 5; m.p. 87.5 - 90.5°C, Ref. 6; oil, b.p. 193°C/ 0.02 mm), mass spectral and microanalytical data are in agreement with the proposed structure.

9. By chromatography ($SiO_2/CHCl_3$) a sample of a single isomer was obtained as a crystalline solid and fully characterised.

10. D. L. J. Clive, Tetrahedron, 1978, 34, 1049; H. J. Reisch, Accs. Chem. Res., 1979, 12, 22.

11. Again a crystalline sample of a single diastereoisomer was obtained by careful chromatography and characterised.

12. E. Späth, Ber., 1938, 71, 113.

13. Reduction of such derivatives to the emetine-type base has previously been carried out in one step using lithium aluminium hydride, A. W. Burgstahler and Z. J. Bithos, J. Amer. Chem. Soc., 1960, 82, 5466.

14. In t.l.c. analysis of a mixture of emetine and isoemetine, emetine is the faster moving component. Also, the β C_1'-H epimer in a range of C_1' diastereoisomeric pairs was shown to have the higher Rf, T. Fujii, S. Yoshifuji, and H. Kogen, Tetrahedron Letters, 1977, 3477.

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Received, 21st January, 1980