Synthesis of (±)-Emetine from Protoberberine Precursor *via* the α-Diketone Monothioketal Intermediate

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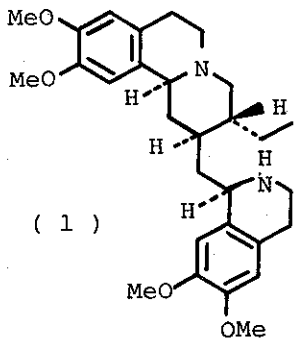
A synthesis of (±)-emetine(1) is accomplished using 2,3,11-trimethoxytetrahydroprotoberberine(3) as a starting material *via* the α-diketone monothioketal intermediate(8). Compound(3) was converted to the α-diketone monothioketal derivative(8) through a 4 step-sequence. The intermediate(8) upon treatment with potassium hydroxide, followed by desulfurization yielded the protoemetine derivative(11). (±)-Emetine(1) was obtained from 11 by a series of classical methods.

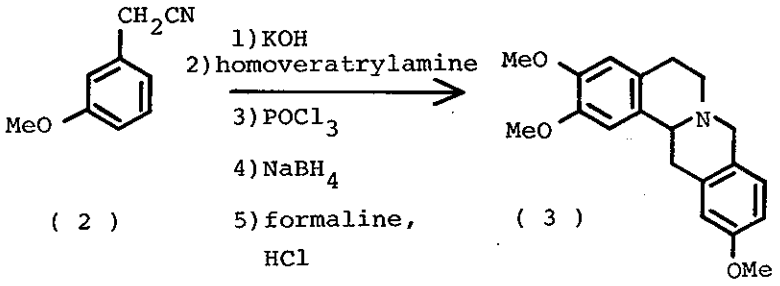
Emetine(1) is the one of the most highly synthesized alkaloids[1] because of its pharmacological activity. Since the first synthesis has been reported by Preobrazhenskii in 1950, more than a dozen syntheses of emetine(1) were made by various investigators.[1] We report here a synthesis of (±)-emetine (1) by a completely new approach starting from a protoberberine precursor(3) using the Marshall cleavage reaction[2] in the



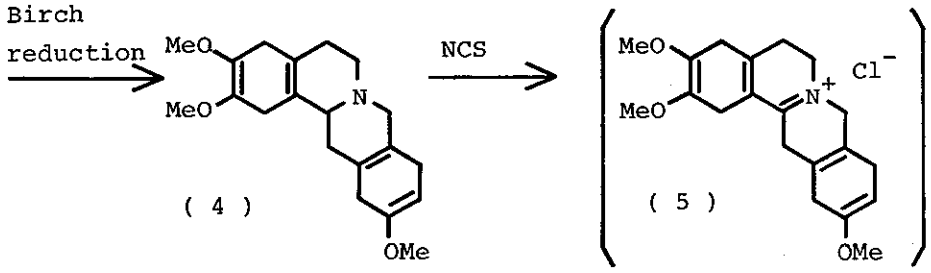
(1)

key stage.

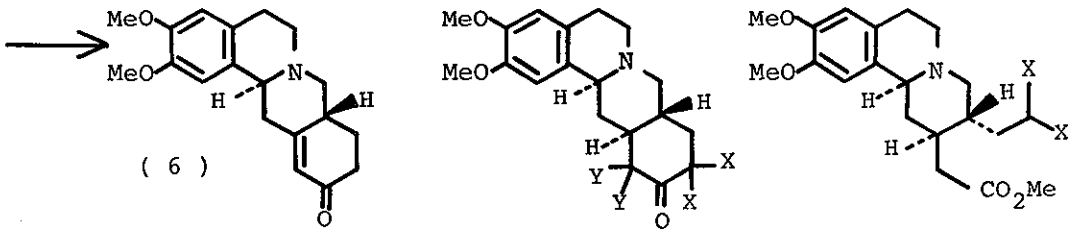
2,3,11-Trimethoxytetrahydroprotoberberine(5)[3], mp 99-100°C, δ^{CDCl_3} 3.77(3H, s), 3.87(3H, s), 3.90(3H, s), m/e 325(M^+), 134(base peak), prepared from *m*-methoxybenzyl cyanide(2)[4] in 47 % total yield by the method shown, was reduced with lithium in liquid ammonia in the presence of *ter*.butyl alcohol to afford the enol ether(4), mp 108.5°C, ν_{max}^{Nujol} 1660, δ^{CDCl_3} 3.50(3H, s), 3.60(3H, s), 3.62(3H, s), 4.60(1H, br.s), m/e 329(M^+, base peak), in 76 % yield. On treatment of 4 with an equivalent molar amount of *N*-chlorosuccinimide in methylene chloride at 0° for 10 h, the aromatic α,β-unsaturated ketone(6)[5], mp 187-189°C(lit,[5] 189-191°C), ν_{max}^{Nujol} 1660, 1605, δ^{CDCl_3} 3.88(3H, s), 3.89(3H, s), 6.05(1H, br.s), 6.68(1H, s), 6.70(1H, s), m/e 313(M^+), 282(base peak), was obtained in 63 % yield. In this conversion, an iminium salt(5) could be formed initially and concurrent hydrolysis of the enol group and isomerization of double bonds could furnish the thermodynamically more stable compound (6). Catalytic hydrogenation of 6 on 10 % palladized carbon in methanol brought about a highly stereospecific reduction to give the C/D trans compound(7), mp 139-140°C, ν_{max}^{Nujol} 1700, δ^{CDCl_3} 3.81(6H, s), 6.53(1H, s), 6.61(1H, s), m/e 315(M^+), 205(base peak) exclusively in 89 % yield. Enamine formation of 7 with pyrrolidine in boiling benzene for 2 h, followed by treating with trimethylene dithiotosylate[6,7] in boiling acetonitrile in the presence of triethylamine afforded the α-diketone monothioketal(8), mp 202-204°C, ν_{max}^{Nujol} 1690, δ^{CDCl_3} 2.95-3.24(5H, m), 3.66(1H, dd, J=12 and 3Hz), 3.84(6H, s), 6.52(1H, s), 6.60(1H, s), m/e 419(M^+), 205(base peak), in 65 % yield and the undesired isomer(9),



(2) (3)



(4) (5)



(6)

(7) X=Y=H

(8) X=-S(CH$_2$)$_3$S-, Y=H

(9) X=H, Y=-S(CH$_2$)$_3$S-

(10) X=-S(CH$_2$)$_3$S-

(11) X=H

mp 225.5-227°C, ν_{max}^{Nujol} 1690, δ^{CDCl_3} 3.84(6H, s), 6.57(1H, s), m/e 419(M^+, base peak), in 9 % yield. Cleavage of α-diketone monothioketal group of 8 by treating with potassium hydroxide[2] in the mixture of *ter*.butyl alcohol and THF(1 : 1) at 60° for 5 h, followed by esterification with diazomethane gave rise to the tricyclic thioacetal(10), pale yellow glass, ν_{max}^{Nujol} 1710, δ^{CDCl_3} 3.75(3H, s), 3.87(6H, s), 6.58(1H, s), 6.67(1H, s), m/e 451(M^+), 206(base peak), in 94 % yield, which on desulfurization with Raney nickel(W-2) in boiling methanol for 20 h gave the known protoemetine derivative (11)[8], mp 77.0-78.5°C(lit.[8] 79.0-81.0°C), ν_{max}^{Nujol} 1710, δ^{CDCl_3} 0.92 (3H, s), 6.56(1H, s), m/e 347(M^+), 246(base peak), in 92 % yield. By following the established methods,[8,9] 11 was converted into (±)-emetine(1) which was identical spectroscopically and chromatographically with the authentic material.

REFERENCES AND NOTES

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3 Satisfactory analytical data were obtained for all new compounds.

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