

AN ALTERNATIVE ROUTE TO (+)-EMETINE AND (+)-DIHYDROCORYNANTHEINE

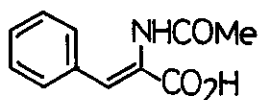
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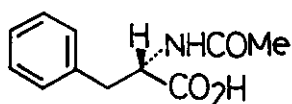
Abstract-----An alternative synthesis of (+)-emetine(11) and (+)-dihydrocorynantheine(13) has been developed in formal sense starting from methyl 3-formylhexanoate(3).

Highly enantioselective reduction of certain enamides has been demonstrated using a rhodium-chiral bisphosphine complex as catalyst¹(e.g. eq. 1). Relating to our attempting chiral reduction of different enamide system to yield chiral lactam (eq. 2), we preliminarily examined transformation of two racemic lactams, (2a) and (2b), into the natural products hoping to apply the results to the corresponding chiral substrates.

Condensation of methyl 3-formylhexanoate²(3) with 2-(3,4-dimethoxyphenyl)ethylamine at 50~60 °C yielded the Schiff base³(4a), quantitatively, which gave the cyclic enamide(1a) in 95 % yield on heating at 160 °C. Medium pressure hydrogenation of (1a) over 5 % palladized carbon at room temperature gave the lactam(2a), bp 164~168 °C(0.16 Torr), in nearly quantitative yield. The lactam(2a) was also obtained from the Schiff base(4a) in 88 % yield by reduction with sodium borohydride.



(1)a, b



(2)a, b

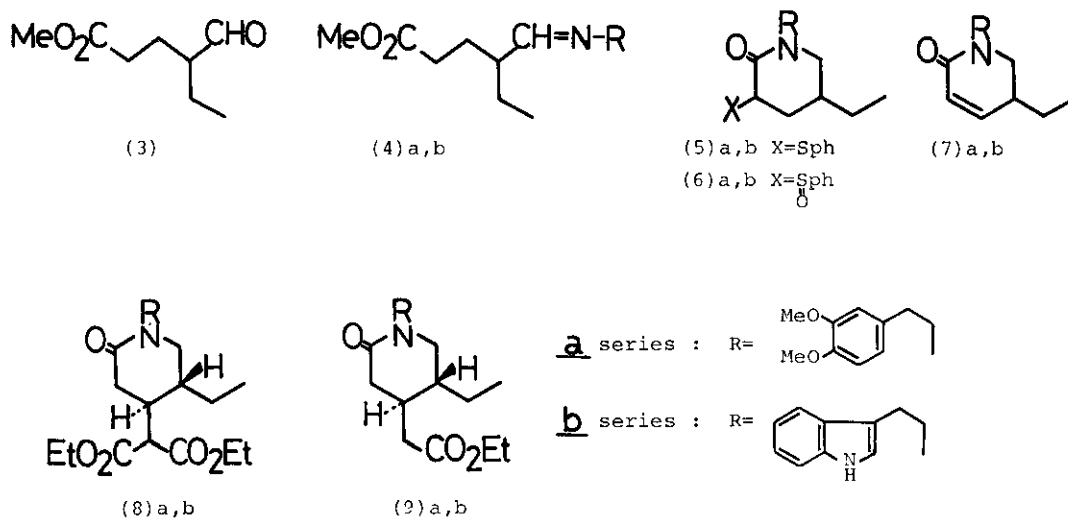
eq. 1

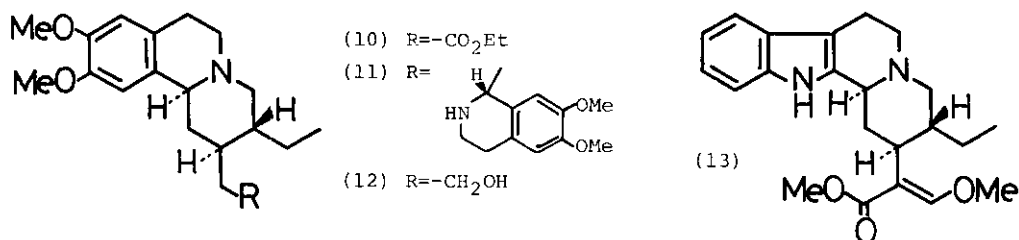
eq. 2

Treatment of the lactam(2a) with diphenyldisulfide at -78 °C in the presence of lithium diisopropylamide^{4,5} gave the sulfide(5a) in 89 % yield. Oxidation of the sulfide(5a) by *m*-chloroperbenzoic acid⁵(MCPBA), or sodium metaperiodate⁴, or N,N,N-

trimethylbenzylammonium metaperiodate⁶ gave the sulfoxide(6a), excellently in each case, which on pyrolysis in refluxing toluene in the presence of calcium carbonate⁴ furnished about 70 % overall yield of the known α,β -unsaturated lactam(7a), bp 170~175 °C(0.20 Torr), which has been obtained by Battersby and Turner⁷ employing fundamentally different approach. The Michael adduct(8a), obtained stereoselectively in 73 % yield from (7a) and diethyl sodiomalonate, upon reflux with magnesium chloride hexahydrate⁸ in moist dimethyl sulfoxide induced smooth decarbethoxylation to give the monoester⁷(9a) in 91 % yield. The monoester(9a), on Bischler-Napieralski reaction, followed by reduction with sodium borohydride afforded the amino-ester^{7, 9,10}(10), in 49 % yield, which has been converted into (+)-emetine^{7,10}(11).

Employing the same methodology above *N*-2-(3-indolyl)ethyl lactam(2b), mp 158 °C, was prepared from (3) and tryptamine in 51 % overall yield through the Schiff base (4b). The lactam(2b) was converted into the α,β -unsaturated lactam(7b) in 60 % yield through the sulfide(5b), mp 118~121 °C, and the sulfoxide(6b) as above. Although the addition of diethyl sodiomalonate to (7b) to form the diester(8b) could not be performed in a satisfactory yield(34 %), subsequent decarbethoxylation was accomplished efficiently using the magnesium salt as above to give 90 % yield of the known lactam ester^{11,12}(9b), which has been synthesized by completely different approach by van Tamelen and Hester, Jr.¹² Since (9b) has been transformed into (+)-dihydrocorynantheine(13) by the same authors¹², the present synthesis constitutes a formal synthesis.





ACKNOWLEDGMENT

We thank Mr. K. Kawamura, Misses Y. Enomoto, and C. Koyanagi for spectral measurements and microanalyses.

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Received, 2nd February, 1981