STEREOSELECTIVE SYNTHESIS OF (±)-DIHYDROCORYNANTHEOL VIA ENAMINE ANNELATION

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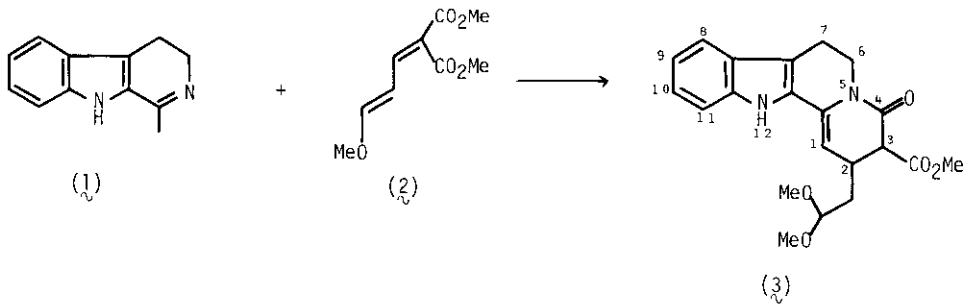
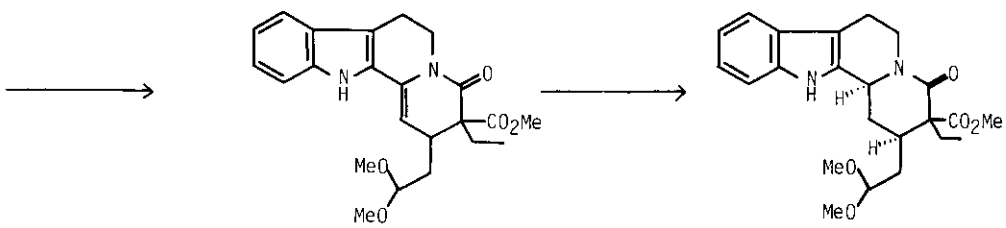
Abstract —— A facile stereoselective synthesis of (±)-dihydrocorynantheol (8) was achieved *via* the key step of enamine annelation using 3,4-dihydro-1-methyl-β-carboline (1) and dimethyl 3-methoxyallidenemalonate (2).

We recently developed a facile synthesis of benzo[*a*]quinolizines[1] and indolo[*a*]-quinolizines[2] *via* the reaction of a 3,4-dihydro-1-methylisoquinoline and a 3,4-dihydro-1-methyl-β-carboline with α,β-unsaturated esters. The enamine character of the above dihydro bases was utilised in these annelations. Employing this reaction, (±)-emetine[3] and its analogues,[4,5] and (±)-camptothecin[6] were synthesised. We here wish to report a facile stereoselective synthesis of (±)-dihydrocorynanteol[7] (8) using the same methodology.

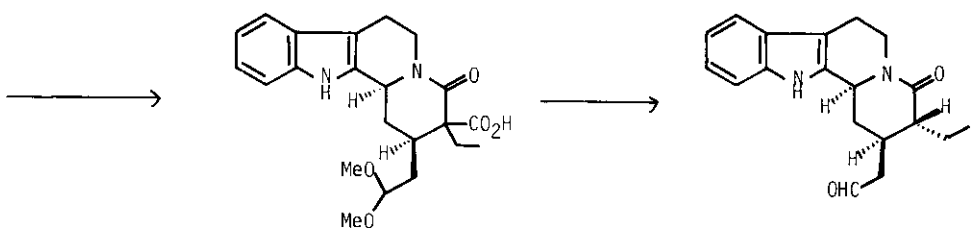
Stirring 3,4-dihydro-1-methyl-β-carboline (1) and dimethyl 3-methoxyallylidene-malonate (2)[8] in methanol for 3 days at room temperature, followed by refuxing the mixture for 24 h produced the indolo[*a*]quinolizine (3), *m/e* 384 (M^+); ν_{max} ($CHCl_3$) 3470 (NH), 1740 and 1660 cm^{-1} (C=O); δ ($CDCl_3$) 1.67 (2H, t, J = 6 Hz, C_2-CH_2), 3.30 (6H, s, 2 x OMe), 3.70 (3H, s, OMe), 4.53 (1H, t, J = 6 Hz, $CH(OMe)_2$), 5.57 (1H, d, J = 5 Hz, C_1-H), 6.97 - 7.50 (4H, m, 4 x Ar-H) and 8.70 p.p.m. (1H, s, NH), in 77 % yield. Treatment of 3 with ethyl iodide in the presence of one equivalent sodium hydride in dry dimethylformamide at 0°C generated the ethyl compound (4), *m/e* 412 (M^+); δ 1.00 p.p.m. (3H, t, J = 6 Hz, $CH_2\underline{CH_3}$), in 89.8 % yield. On hydrogenation of 4, in the presence of Adams catalyst in methanol, the amide (5), *m/e* 413 (M^+-1); δ ($CDCl_3$) 0.90 p.p.m. (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), was obtained in 95.7 % yield. In each of the above three reactions a single stereoisomer was produced,



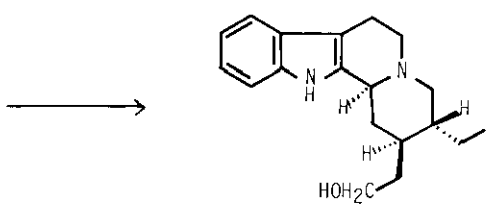
(1) (2) (3)



(4) (5)



(6) (7)



(8)

although the relative configuration at the C_2 and C_3 positions remains obscure. The partial stereochemistry of amide (5) was assigned on the assumption that hydrogen selectively attacked the C_{12b} carbon from the side opposite to bulky substituent at the C_2 position.[3] When the reduction of 4 was carried out in the presence of 10 % palladium on carbon two stereoisomers, including 5, were formed.

After hydrolysis of the ester (5) with sodium methoxide in hot aqueous methanol, the resulting carboxylic acid (6) was heated in dimethyl sulfoxide at 160°C to give a mixture of the aldehyde (7) and the corresponding acetal, which on treatment with p-toluenesulfonic acid in acetone at 0°C lead to the pure aldehyde (7), m/e 310 (M^+); δ ($CDCl_3$) 0.90 (3H, t, J = 7 Hz, CH_2CH_3) and 9.70 p.p.m. (1H, s, CHO), obtained in 92 % yield from 5. Conversion of the aldehyde (7) into (±)-dihydrocorynantheol (8) was achieved in 54.5 % yield by reduction with lithium aluminium hydride in hot ether-tetrahydrofuran. The spectral data of this synthetic compound, mp 178.5 - 180°C (lit.,[9a] mp 178 - 180.5°C; lit.,[9b] mp 180 - 182°C) were consistent with those reported.[7] That the three other possible stereoisomers were not formed, i.e. that the reaction sequence was stereoselective, was demonstrated by t.l.c. comparison of the final reaction product with authentic samples of these isomers.[10]

Extension of this method for the synthesis of other indole alkaloids is in progress in this laboratory.

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