A NEW FORMAL TOTAL SYNTHESIS OF (±)-VINCAMINE

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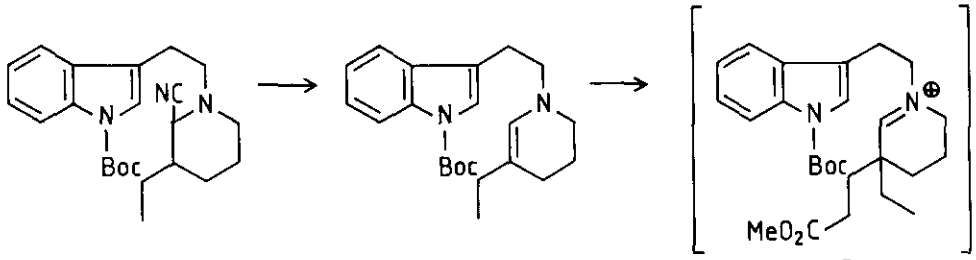
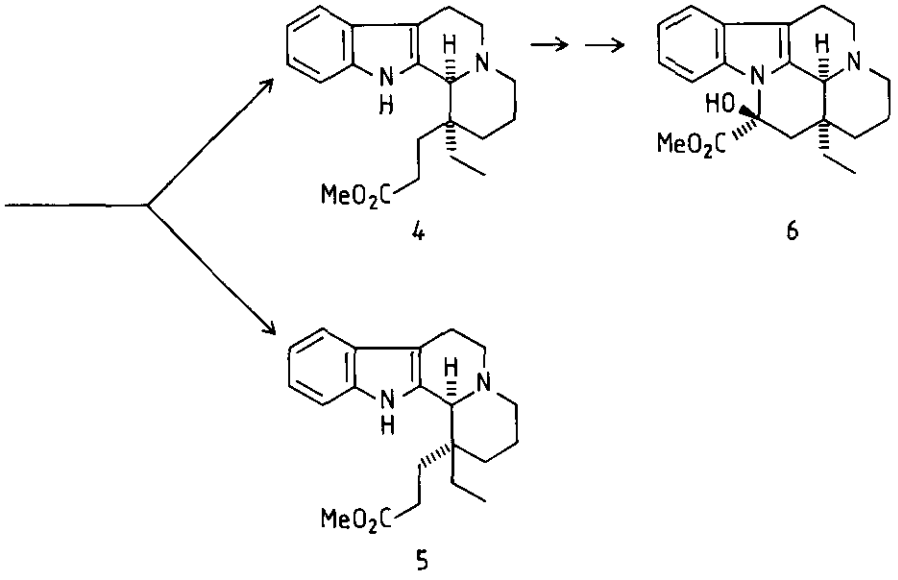
Abstract - A new "one-pot" method was developed to transform the easily accessible enamine 2 to the crucial vincamine intermediate 4.

The significant therapeutical value of several vincamine derivatives[1-3] has prompted an intensive search for feasible total syntheses of these compounds.[4-7] We report here a new "one-pot" method to transform the easily accessible enamine 2 to the crucial vincamine intermediate 4.[8-9]





Compound 1[10] was treated with $AgBF_4$ in 1,2-dichloroethane. The solution was washed with dilute aq NH_4OH, dried over Na_2SO_4 and the solvent was carefully evaporated under vacuum. The relatively unstable Boc-protected enamine 2 in CH_2Cl_2 was alkylated with methyl acrylate to yield the intermediate 3. Evaporation of the solvent was followed by acid treatment, which cleaved the protecting group (Boc) and permitted nucleophilic attack to take place, leading to the cyclized products 4 and 5 (1:1, ca. 25% overall yield).

The transformation of 4 to (±)-vincamine 6 has been described earlier.[4,5,11] Thus a new formal total synthesis of (±)-vincamine is in hand and a new flexible method available for the preparation of tetracyclic indoloquinolizidines.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 Spectrophotometer using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimeters (cm^{-1}) using polystyrene calibration. Bands yielding structural information are reported. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS as internal standard δ=0) on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS where s, d, t, q and m designate singlet, doublet, triplet, quartet and multiplet, respectively. Mass spectrometry was performed on a Jeol DX 303/DA 5000 apparatus.

TLC plates were coated with Silica gel 60 $PF_{254+366}$ from Merck. Dragendorff-Munier reagent was used to locate reaction components.

Compounds 4 and 5

Compound 1 (0.60 g, 2.4 mmol) was dissolved in 1,2-dichloroethane (80 ml). $AgBF_4$ (0.80 g, 2 equiv) in 1,2-dichloroethane (20 ml) was added during 20 min and stirring was continued for 90 min (Ar-atm.). The solution was washed thoroughly with NH_4OH (10%) and twice with H_2O. After drying with Na_2SO_4 and evaporation of the solvent enamine 2 was obtained. Abs. CH_2Cl_2 (30 ml), methanol (0.2 ml) and freshly distilled methyl acrylate (560 mg, 4 equiv) were immediately added and the mixture was left standing for 3 d. After evaporation of the solvent, methanol presaturated with HCl gas was added and the solution was stirred for 40 h. It was then poured into a suspension of $NaHCO_3$ in CH_2Cl_2. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. After preparative TLC on silica (10% MeOH/$CHCl_3$) a mixture of 4 and 5 (~1:1) was obtained, Y: 130 mg (24.3%). The two isomers were separated by TLC (silica, 5% MeOH/$CHCl_3$).

Compound 4. mp 142-143°C (lit. 144-145°C[4,5] (see also ref. 8), 144-145°C[8], 138-140°C[9]). IR ($CHCl_3$): 3430 (NH), 2830, 2770 (Bohlmann bands), 1730 cm^{-1} (ester C=O). ^1H NMR ($CDCl_3$): δ 1.10 (3H, t, J = 7.0 Hz, $-CH_2\underline{C}H_3$), 3.55 (3H, s, $-CO_2CH_3$), 6.97-7.58 (4H, m, arom. H), 9.21 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 7.7 ($-CH_2\underline{C}H_3$), 22.0 (C-3), 22.0 (C-7), 28.6 (C-2), 28.7 (β-C), 30.6 ($-\underline{C}H_2CH_3$), 32.8 (α-C), 39.5 (C-1), 51.6 ($-CO_2\underline{C}H_3$), 54.1 (C-6), 56.8 (C-4), 66.4 (C-12b), 110.7 (C-11), 111.9 (C-7a), 117.8 (C-8), 119.2 (C-9), 121.4 (C-10), 126.7 (C-7b), 133.4 (C-12a), 136.1 (C-11a), 175.8 ($-\underline{C}O_2CH_3$). MS: m/z 340 (M^+), 325, 309, 267 (100%), 170, 169.

Compound 5. m.p. 150-152°C (lit. 149-150°C[4,5] (see also ref. 8), 151-152°C[8], 146-147°C[9]). IR ($CHCl_3$): 3350 (NH), 2830, 2770 (Bohlmann bands), 1720 cm^{-1} (ester C=O). ^1H NMR ($CDCl_3$): δ 0.66 3H, t, J = 7.0 Hz, $-CH_2\underline{C}H_3$, 3.80 (3H, s, $-CO_2CH_3$), 6.97-7.58 (4H, m, arom. H), 8.85 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 7.2 ($-CH_2\underline{C}H_3$), 22.0 (C-3), 22.0 (C-7), 25.4 (β-C), 28.2 (C-2), 31.9 ($-\underline{C}H_2CH_3$), 33.1 (α-C), 39.5 (C-1), 52.2 ($-CO_2\underline{C}H_3$), 54.1 (C-6), 56.9 (C-4), 66.4 (C-12b), 110.9 (C-11), 112.0 (C-7a), 117.7 (C-8), 119.1 (C-9), 121.4 (C-10), 126.4 (C-7b), 133.2 (C-12a), 136.3 (C-11a), 175.8 ($-\underline{C}O_2CH_3$). MS: m/z 340 (M^+), 325, 309, 267 (100%), 170, 169.

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