

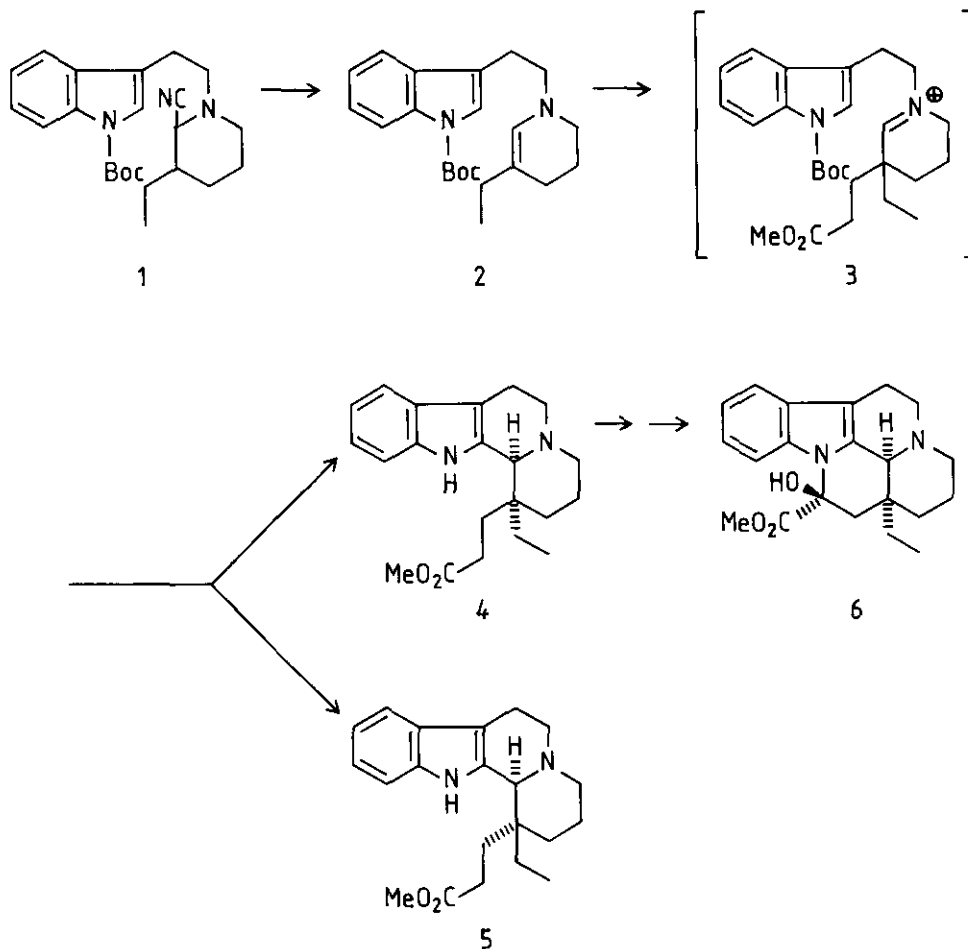
A NEW FORMAL TOTAL SYNTHESIS OF (±)-VINCAMINE

Mauri Lounasmaa* and Reija Jokela

Technical University of Helsinki, Department of Chemistry,
Laboratory for Organic and Bioorganic Chemistry, SF-02150 Espoo, Finland

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 derivatives¹⁻³ 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 1¹⁰ was treated with AgBF₄ in 1,2-dichloroethane. The solution was washed with dilute aq NH₄OH, dried over Na₂SO₄ and the solvent was carefully evaporated under vacuum. The relatively unstable Boc-protected enamine 2 in CH₂Cl₂ 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 ¹³C NMR spectra were recorded in CDCl₃ (TMS as internal standard δ=0) on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (¹H NMR) and 15.04 MHz (¹³C 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 PF₂₅₄₊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). AgBF₄ (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 NH₄OH (10%) and twice with H₂O. After drying with Na₂SO₄ and evaporation of the solvent enamine 2 was obtained. Abs. CH₂Cl₂ (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 NaHCO₃ in CH₂Cl₂. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. After preparative TLC on silica (10% MeOH/CHCl₃) 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/CHCl₃).

Compound 4. mp 142-143°C (lit. 144-145°C^{4,5} (see also ref. 8), 144-145°C⁸, 138-140°C⁹). IR (CHCl₃): 3430 (NH), 2830, 2770 (Bohlmann bands), 1730 cm⁻¹ (ester C=O). ¹H NMR (CDCl₃): δ 1.10 (3H, t, J = 7.0 Hz, -CH₂CH₃), 3.55 (3H, s, -CO₂CH₃), 6.97-7.58 (4H, m, arom. H), 9.21 (1H, br s, NH). ¹³C NMR (CDCl₃): δ 7.7 (-CH₂CH₃), 22.0 (C-3), 22.0 (C-7), 28.6 (C-2), 28.7 (β-C), 30.6 (-CH₂CH₃), 32.8 (α-C), 39.5 (C-1), 51.6 (-CO₂CH₃), 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 (-CO₂CH₃). 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°C⁸, 146-147°C⁹). IR (CHCl₃): 3350 (NH), 2830, 2770 (Bohlmann bands), 1720 cm⁻¹ (ester C=O). ¹H NMR (CDCl₃): δ 0.66 (3H, t, J = 7.0 Hz, -CH₂CH₃), 3.80 (3H, s, -CO₂CH₃), 6.97-7.58 (4H, m, arom. H), 8.85 (1H, br s, NH). ¹³C NMR (CDCl₃): δ 7.2 (-CH₂CH₃), 22.0 (C-3), 22.0 (C-7), 25.4 (β-C), 28.2 (C-2), 31.9 (-CH₂CH₃), 33.1 (α-C), 39.5 (C-1), 52.2 (-CO₂CH₃), 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 (-CO₂CH₃). MS: m/z 340 (M⁺), 325, 309, 267 (100%), 170, 169.

REFERENCES

1. J. Le Men, *Chim. Thér.*, 1971, 137.
2. *Arzneim.-Forsch.* (Drug Res.), 1976, 26, 1905.
3. *Arzneim.-Forsch.* (Drug Res.), 1977, 27(1), 1237.
4. M.E. Kuehne, *J. Am. Chem. Soc.*, 1964, 86, 2946.
5. M.E. Kuehne, *Lloydia*, 1964, 27, 435.
6. W. Döpke in "The Alkaloids", eds. R.H.F. Manske and R.G.A. Rodrigo, vol. 20, Academic Press, New York 1981, pp. 297-332.
7. J.E. Saxton in "The Monoterpenoid Indole Alkaloids", ed. J.E. Saxton, J. Wiley, New York 1983, pp. 439-465.
8. Gy. Kalas, P. Györy, M. Kajtár, L. Radics, L. Szabó and Cs. Szántay, *Chem. Ber.*, 1981, 114, 1476; see also Cs. Szántay, L. Szabó, Gy. Kalas, P. Györy, J. Sági and K. Nógrádi in "Organic Synthesis Today and Tomorrow", eds. B.M. Trost and C.R. Hutchinson, Pergamon Press, Oxford 1981, pp. 295-298.
9. K. Irie and Y. Ban, *Heterocycles*, 1982, 18, 255.
10. R. Jokela, T. Tamminen and M. Lounasmaa, *Heterocycles*, 1985, 23, 1707.
11. Roussel-Uclaf, Belg. Pat. 765.006.

Received, 14th February, 1986