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A NEW APPROACH TO (±)-APOVINCAMINE

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Summary: *(±)-Apovincamine (2) is synthesized by dehydration of the β-hydroxyester (7) obtained by alkylation of the aldehyde (6) with methyl chloroacetate.*

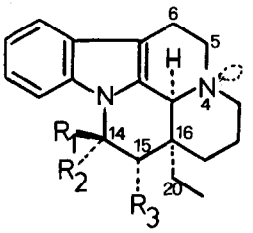
The potent pharmacological properties as cerebral vasodilators of eburnane alkaloids [e.g., vincamine (1) and apovincamine (2)] have prompted intensive efforts culminating in several syntheses.[1] We report a new high-yielding and feasible approach to (±)-apovincamine (2) which bypasses the intermediacy of vincamine (1).

The readily available Wenkert's enamine perchlorate (3)[2] upon treatment with 40% aq formaldehyde (25 equiv) in refluxing MeCN in the presence of Hünig's base (3 equiv) for 2 hr, gave in almost quantitative yield the pure (1R*,5R*,12bR*)-alcohol (4)[3], m.p. 222° (MeOH) [1] [δ_C ($CDCl_3$) 7.35 (C_{14}), 19.8 (C_3), 21.6-21.8 (C_2/C_7), 30.15 (C_{15}), 54.6-54.8 (C_4/C_6), 68.1 (C_{13}), 69.9 (C_{12b})].

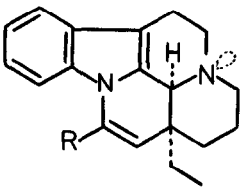
The oxidation of (4) with DMSO-oxalyl chloride-Et_3N[4] in CH_2Cl_2 (-78° → 0°, 4 hr) or with DMSO-DCC-orthophosphoric acid[5] (r.t., 3 hr) smoothly afforded (5), m.p. 110° (hexane) [1] [δ_C ($CDCl_3$) 8.4 (C_{14}), 20.5 (C_3), 21.1-21.9 (C_2/C_7), 29.0 (C_{15}), 53.2 (C_1), 53.8-55.9 (C_4/C_6), 62.6 (C_{12b})], in 83% and 85%, respectively. By treatment with t-BuOK in diglyme (40°, 30 min), (5) underwent retro-Mannich reaction leading quantitatively to a (1:1) mixture of (5) and the stereochemically suitable (1R*, 5S*, 12bS*)-aldehyde (6), m.p. 150° (Et_2O) [1] [δ_C ($CDCl_3$) 8.0 (C_{14}), 21.9-22.1 (C_3/C_7), 26.1 (C_2), 29.5 (C_{15}), 52.3 (C_1), 53.3-56.2 (C_4/C_6), 65.3 (C_{12b})]. This diastereomeric mixture was easily resolved by crystallisation or medium pressure chromatography and thence the 'wrong' aldehyde (5) recycled. When an equimolecular mixture of (6) and methyl chloroacetate was allowed to react at r.t. for 2 hr in the presence of t-BuOK (4.2 equiv) in benzene, (±)-apovincamine (2), identical in all respects with an authentical sample, was isolated in 84% yield. A plausible mechanism for the formation of (2) involves the regiospecific alkylation at N_a by methyl chloroacetate followed by aldol cyclization to give the intermediate threo β-hydroxyester (7), m.p. 190° (Et_2O), isolable

in 81% yield by quenching the reaction after 20 min. The (3R*, 4 S*,14R*,15R*,16S*)-configuration for (7) is based on its well-defined and predictable spectroscopic data : devoid of *trans*-quinolizidine Bohlmann bands in i.r. spectrum, magnitude of ^{3}J(9.0Hz) between $C_{14}H$(δ4.51) and $C_{15}H$(δ4.19), presence of $^{4}J_{15,20}$(1.5Hz) ('W'pathway). (7) was converted quantitatively into (2) by exposure to t-BuOK in benzene for 1.5 hr at r.t.

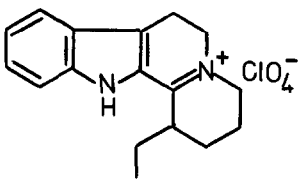
A parallel sequence with ethyl chloroacetate gave, via the intermediacy of β-hydroxyester, the clinically useful apovincamine analogue (+)-(8,Cavinton®)[6],m.p.135° (EtOH) in 73% yield.



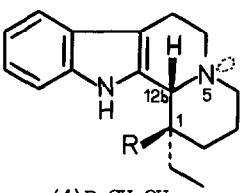
(1) R_1:OH;R_2:CO_2Me;R_3:H
(7) R_1:CO_2Me;R_2:H;R_3:OH



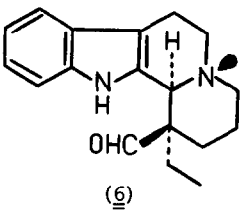
(2) R:CO_2Me
(8) R:CO_2Et



(3)



(4) R:CH_2OH
(5) R:CHO



(6)

References and Notes

1 J.L.Herrman,R.J.Cregge,J.E.Richman,G.R.Kieczykowski,S.N.Normandin,M.L.Quesada,C.L.Semmelhack, A.J.Poss,and R.H.Schlessinger, J.Am.Chem.Soc.,101,1540(1979) and references cited therein.

2 B.Danieli,G.Lesma, and G.Palmisano, J.C.S.Chem.Commun.,109(1980); ibid.,861(1980).

3 The formation of (4) is viewed as proceeding via the intermediate iminium salt followed by its reduction with steric approach control by formaldehyde in a crossed-Cannizzaro reaction.

4 K.Omura and D.Swern, Tetrahedron, 34,1651(1978).

5 K.E.Pfitzner and J.G.Moffatt, J.Am.Chem.Soc.,85,3027(1963)

6 We thank Professor Cs. Szántay,Budapest, for a generous gift of (8).

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