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STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-3-ISO-19-EPIAJMALICINE

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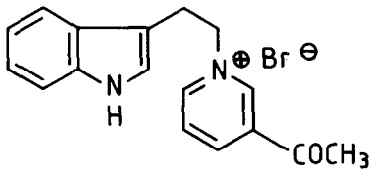
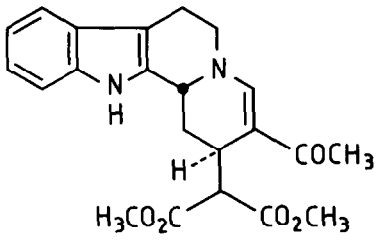
Summary: A new stereoselective three-step total synthesis of (±)-3-iso-19-epiajmalicine 4 starting from the easily accessible compound 1 is described.

The synthesis of the eight basic heteroyohimbine alkaloids has been described by different authors.[1-12] However, the stereoselectivity and/or total yields are mostly poor. Our new rapid three-step route starting from salt 1[13] constitutes an easy and highly specific method for the preparation of (±)-3-iso-19-epiajmalicine 4, a heteroyohimbine alkaloid possessing the pseudo configuration.



1



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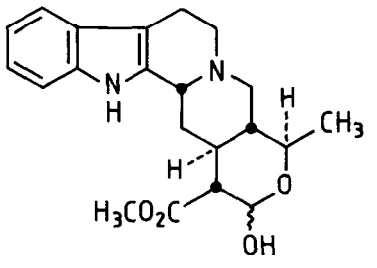
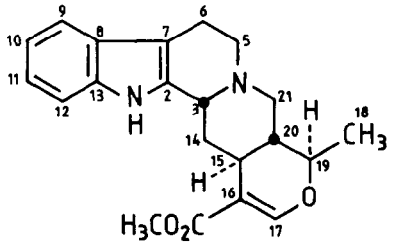


3 a OH = α
3 b OH = β



4

Pyridinium salt 1 was alkylated according to our modification (dimethyl sodiomalonate, THF, DME, -15°C) of the Kröhnke procedure.[14] Without isolation, the intermediate dihydropyridine was cyclized to compound 2[6] (yield 1→2 ~40%). $NaBH_4$ reduction of 2 in acidic media (abs. AcOH) followed by treatment with excess methanol and addition of more $NaBH_4$ afforded 3a[16] (containing a small amount of 3b) in ~50% yield. Polyphosphoric acid treatment of 3a yielded racemic 4[17] almost quantitatively. Thus a new rapid total synthesis of (±)-3-iso-19-epiajmalicine 4 was accomplished in about 20% overall yield.

The earlier accomplished conversion[4] of (±)-3-iso-19-epiajmalicine 4 into (±)-formosanine and (±)-isoformosanine means that the present procedure constitutes a formal total synthesis of these oxindole alkaloids as well.

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16. 3a: Y ~50%, ir 3300, 1730, pmr 1.17 (3H, d), 3.74 (3H, s), 6.72 (1H, br s), 7.06-7.53 (arom. H), 8.54 (1H, br s), cmr 16.49 (t), 18.51 (q), 22.27 (d), 30.78 (t), 43.31 (d), 45.84 (t), 50.32 (t), 51.88 (q), 53.37 (d), 65.59 (d), 73.57 (d), 90.64 (d), 107.14 (s), 111.68 (d), 117.91 (d), 119.60 (d), 121.87 (d), 127.13 (s), 130.64 (s), 136.36 (s), 171.48 (s), m/z 370 (M^+), 369, 352, 339, 225, 223, 184, 169, 156. Found: 370.1896 (mass spectrometry). Calc. for $C_{21}H_{26}N_2O_4$: 370.1894.
17. Analytical data (ir, pmr, cmr, ms) were identical with the data given in refs. 4, 6 and 18.
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