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STEREOSPECIFIC ADDITION OF NUCLEOPHILES TO ENAMINONES AND THE SYNTHESIS OF MYRTINE AND 4-EPIMYRTINE.

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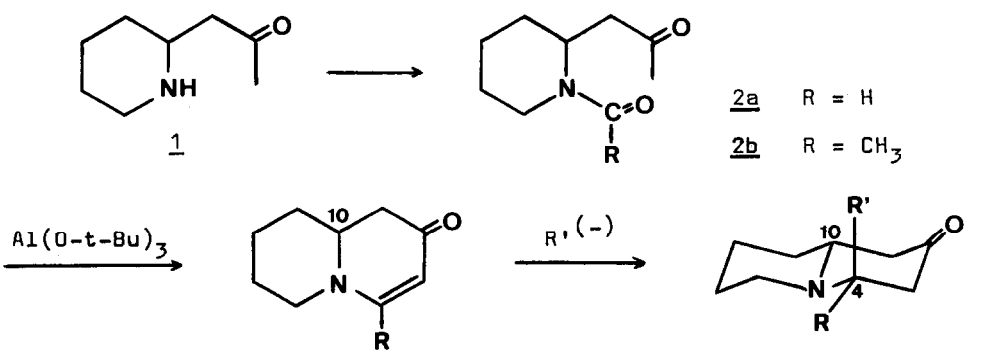
Summary: Stereospecific syntheses of the quinolizidine alkaloid myrtine and its 4-epimer are accomplished by 1,4-nucleophilic addition to the enaminones 3.

In a previous communication[1] we reported the isolation and structure determination (including the absolute configuration) of myrtine 4a, a new quinolizidine alkaloid from Vaccinium myrtillus (Ericaceae). Myrtine 4a and its 4-epimer 4b were synthesized -albeit in low yield- through Mannich condensation of pelletierine 1 with acetaldehyde in acetic acid.

We now wish to report a convenient route -that should be capable of extension to related systems- for the stereochemically controlled syntheses of racemic 4a and 4b starting from pelletierine. The approach employed is based on the finding that in the 1,4-additions to the cyclic enaminones 3 there is a cis-relationship between the entering nucleophile and the hydrogen at C-10.



From dl-pelletierine[2] 1, 4-methyl-3,4-dehydroquinolizidin-2-one 3b was obtained by the procedure described[3]. Treatment of this compound with $LiAlH_4$ (3 equiv., THF, 0°) led to the stereospecific introduction of the hydride ion at C-4 in axial position: it afforded epimyrtine 4b (yield 50%; ir, pmr, cmr, ms, gc, picrate m.p. 177-179° with dec.) and a mixture of the saturated corresponding secondary alcohols consisting (pmr) of 90% equatorial isomer (picrate m.p. 159-161°; pmr ($CDCl_3$): δ 1.1 (d., J = 7 Hz: CH_3) and 3.6 ppm (m.: CHOH) and 10% axial isomer (1.05 (d., J = 7 Hz) and 4.1 ppm).

Myrtine in turn was obtained through the following sequence:

Treatment of dl-pelletierine 1 with acetic-formic anhydride in pyridine solution yielded N-formylpelletierine 2a (pmr (C_2Cl_4): δ 1.96 and 2.0 (2 s.: CH_3), 7.76 and 7.88 ppm (2 s. (40:60): CHO; coalescence at 85°). Cyclisation of N-formylpelletierine in refluxing toluene in the presence of aluminum t-butoxide furnished the enaminone 3a (m.p. 69-70°; $\lambda_{max.}^{EtOH}$ 320 nm (ε = 15,600); ir (KBr): 1580 and 1630 cm^{-1}; pmr ($CDCl_3$): δ 4.92 (C-3 H) and 6.84 ppm (C-4 H) (2 d., J = 8 Hz). Addition of methylmagnesium iodide to 3a in benzene proceeded stereospecifically by axial introduction of the entering methyl group, leading to dl-myrtine 4a in 70% yield (ir, pmr, cmr[4], ms, gc, picrate m.p. 190-192° with dec.)

(+)-Myrtine ($[\alpha]_D^{23}$ +11.3° ($CHCl_3$, c = 2.7), m.p. 41-43°) was obtained from the racemic base by resolution with (-)-tartaric acid (fractional crystallization from acetone).

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References and notes.

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2. (a) J. Quick and R. Oterson, Synthesis, 745 (1976).
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3. Y. Ban, M. Kimura and T. Oishi, Chem. Pharm. Bull., 24, 1490 (1976).
4. The cmr chemical shifts previously assigned to C-4 and C-10 have to be interchanged for 57.2 and 53.6 ppm respectively[1].