Total Synthesis of (±)-Vertaline

Vertaline, an alkaloid of Decodon verticillatus (L.) ELL. (Lythraceae), possesses a cis-fused quinolizidine ring with a biphenyl ether and a fourteen-membered lactone in its structure (I). Its epimeric alkaloid decaline (II) having a trans-fused quinolizidine ring was already synthesized. We now report the total synthesis of (±)-vertaline.

Previously we reported that condensation of isopelletierine with 6-bromoisoovanillin in aqueous sodium hydroxide afforded only the trans-quinolizidine (III) whereas the reaction with benzaldehyde was reported to give a mixture of cis- and trans-4-phenylquinolizidine-2-one. The complete stereoselectivity in the former case would be interpreted as follows: this condensation reaction gave also a mixture of cis- and trans-isomer and then the resulting cis-isomer isomerized to trans-isomer under this reaction condition. The stereoselectivity in these condensation reactions would depend on solvents and solubilities of the starting aldehydes and the products.

Condensation of isopelletierine (IV) with 6-bromoveratraldehyde in tetrahydrofuran in the presence of aqueous sodium hydroxide gave the cis-quinolizidine (V) [m/e: 369, 367 (M+ 1:1), \text{CH$_{max}$ cm}^{-1}: 1712 (C=O), no Bohmann bands, \text{δ}: 4.87 (1H, t, J=6.5 Hz, CHAr)] and the trans-quinolizidine (VI) in the ratio of 3:2 in 42% yield. The latter was identified with the authentic specimen derived from III. The former (V) isomerized to VI by treatment with aqueous sodium hydroxide in methanol. The stereochemistry of V was verified from its spectral data and especially the presence of a cis-quinolizidine ring was confirmed by the lower chemical shift of the proton at C$_4$ in the nuclear magnetic resonance (NMR) spectrum of V.

Reduction of the cis-quinolizidine (V) with sodium borohydride in methanol afforded the axial alcohol (VII) [m/e: 371, 369 (M+, 1:1), \text{δ}: 4.79 (1H, t, J=5.5 Hz, CHAr)] and the

7) All the compounds except VI described for the synthesis of (±)-vertaline lack the Bohmann bands due to trans-quinolizidine in their infrared (IR) spectra.
equatorial alcohol (VIII) \([m/e: 371, 369 \ (M^+, 1:1), \delta: 4.51 \ (1H, d-d, J=11.5; 3 \ Hz, CHAr)]\) in the ratio of 3:1 in 96% yield. Both alcohols (VII and VIII) were acetylated with acetic anhydride in pyridine to give quantitatively the axial acetyl derivative (IX) \(\delta: 5.16 \ (1H, quin, J=4.5 \ Hz, CHOAc), 4.76 \ (1H, d-d, J=8; 4.5 \ Hz, CHAr), 2.11 \ (3H, s, OC\text{CH}_3)\) and the equatorial acetyl derivative (X) \(\delta: 5.14 \ (1H, m, W_H=24 \ Hz, CHOAc), 4.57 \ (1H, d-d, J=11.5; 3 \ Hz, CHAr), 2.04 \ (3H, s, OC\text{CH}_3)\), respectively.

Ullmann condensation of IX with methyl 4-hydroxyhydrocinnamate\(^9\) in pyridine using copper oxide furnished the biphenyl ether (XI) \([m/e: 511 \ (M^+), \nu_{\text{CH}} \text{cm}^{-1}: \ 1727 \ (C=O), \delta: 5.20 \ (1H, m, W_H=14 \ Hz, CHOAc), 4.62 \ (1H, t, J=6 \ Hz, CHAr), 3.98, 3.84, 3.73 \ (each 3H, s, OC\text{CH}_3 \times 3), 1.99 \ (3H, s, OC\text{CH}_3)\] which, on hydrolysis with aqueous sodium hydroxide, afforded the carboxylic acid (XII) \([m/e: 455 \ (M^+), \nu_{\text{CH}} \text{cm}^{-1}: \ 2460 \ br. \ (N=O), 1590 \ (COO^-)]\) in 28% yield from IX. A solution of XII in benzene was heated with \(p\)-toluenesulfonic acid to provide (±)-veratraline (I) \([\text{mp \ 224-225^\circ}, \ m/e: 437 \ (M^+), \nu_{\text{CH}} \text{cm}^{-1}: \ 1720 \ (C=O), \delta: 4.96 \ (1H, m, W_H=9 \ Hz, CHOCO), 3.97, 3.93 \ (each 3H, s, OC\text{CH}_3 \times 2), 3.48 \ (1H, d-d, J=11; 3.5 \ Hz, CHAr)\]) in 41% yield.

The synthetic (±)-veratraline was proved to be identical with natural veratraline by IR (in CHCl\(_3\)), NMR and mass spectral comparison and thin-layer chromatographic behaviour.

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10) The proton at C\(_4\) of (±)-veratraline appeared ca. 1 ppm higher than the corresponding protons of other compounds. The diamagnetic shift of this proton was caused by the anisotropy of the benzene ring in the lactonized hydrocinnamate moiety.