CONVERSION OF ETHYL CINCHOLOIPONATE INTO A TRICYCLIC INTERMEDIATE ADAPTABLE TO CHIRAL SYNTHESES OF 10-DEMETHYLATED ALANGIUM ALKALOIDS

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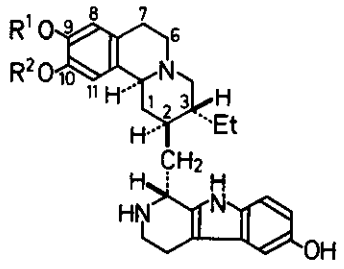
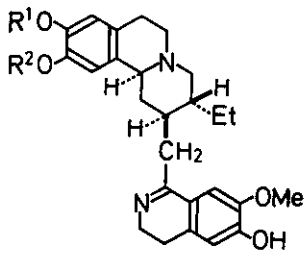
Abstract —— The title (−)-tricyclic amino ester VII has been synthesized by means of an initial condensation of 4-benzyloxy-3-methoxyphenacyl bromide with (+)-ethyl cincholoiponate (VIII), derived from the Cinchona alkaloid cinchonine, and succeeding steps proceeding through the intermediates (+)-IX, X, XI, (−)-XIII, (−)-XIV, (+)-XV, (+)-XVI, (+)-XVII, and XVIII.

It has recently been shown in this laboratory that the Alangium alkaloid (−)-demethyltubulosine[1,2] is not the 9-demethylated base (I),[3] but 10-demethyltubulosine (II),[4] whereas (+)-desmethylpsychotrine, another Alangium alkaloid,[2] has the 9-demethyl structure (III).[5] (−)-Demethylcephaeline is yet another alkaloid that has been assigned the alternative of the 9-demethyl (V) or the 10-demethyl structure (VI).[6] For chiral syntheses of these 10-demethylated bases, the tricyclic amino ester VII (absolute configuration shown) would be a convenient key intermediate since the corresponding racemic form [(±)-VII] has already been converted into (±)-10-demethyltubulosine [(±)-II][4] and (±)-10-demethylpsychotrine [(±)-IV].[7] We now report the first synthesis of the (−)-antipode VII, which represents an extension of our "cincholoipon-incorporating method"[5,8−11] to the 10-benzyloxybenzo[a]quinolizidine series.

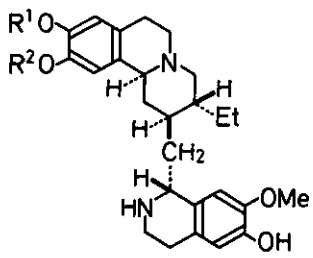
Treatment of (+)-ethyl cincholoiponate (VIII), prepared[12] from the Cinchona alkaloid cinchonine in 50% overall yield, with 4-benzyloxy-3-methoxyphenacyl bromide[13] and K_2CO_3 in benzene (50−55°C, 7 h) gave the (+)-amino ketone IX [98% yield; $[\alpha]_D^{16}$ +3.7° (c 2.71, EtOH)],[14] which was then reduced ($NaBH_4$, EtOH, 0°C, 2 h, room temp., 6 h) to afford a diastereomeric mixture of the amino alcohol X [97%; $[\alpha]_D^{18}$ −1.6° (c 2.55, EtOH)]. Oxidation of the mixture X with $Hg(OAc)_2$–EDTA (1% aq. AcOH, reflux, 1.5 h)[15,16] followed by column chromatography (silica gel or alumina, AcOEt–hexane or $CHCl_3$–hexane) furnished the 6-piperidone XI as a diastereomeric mixture [53% yield; $[\alpha]_D^{25}$ −9.6° (c 2.00, EtOH); ir ($CHCl_3$): 3350 (OH), 1726 (ester CO), 1618 cm^{-1} (lactam CO)] and an oily substance [15% yield; $[\alpha]_D^{18}$ +10.3° (c 2.00, EtOH); ir ($CHCl_3$): 3350 (OH), 1726 (ester CO), 1610 cm^{-1} (lactam CO)] presumed[8] to



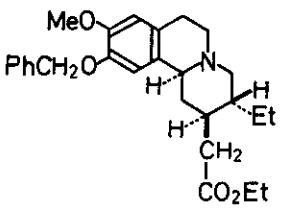
I: R^1 = H; R^2 = Me
II: R^1 = Me; R^2 = H



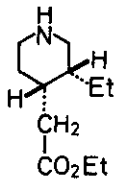
III: R^1 = H; R^2 = Me
IV: R^1 = Me; R^2 = H



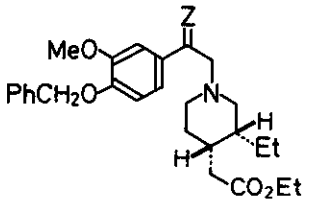
V: R^1 = H; R^2 = Me
VI: R^1 = Me; R^2 = H



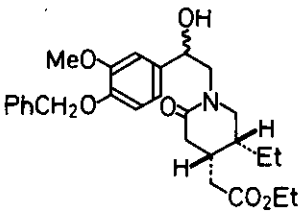
VII



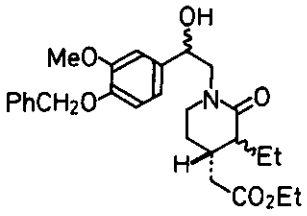
VIII



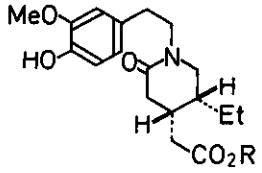
IX: Z = O
X: Z = H,OH



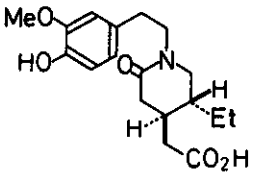
XI



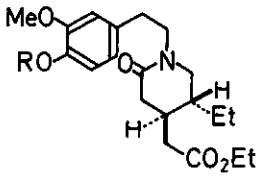
XII



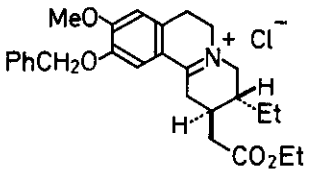
XIII: R = Et
XIV: R = H



XV



XVI: R = H
XVII: R = $PhCH_2$



XVIII

be a diastereomeric mixture of the cis- and the trans-2-piperidones XII. On catalytic hydrogenolysis (10% Pd-C/H_2, EtOH–70% aq. $HClO_4$, 1 atm, 35°C, 16 h), the major product XI of the above oxidation yielded the (–)-lactam phenol XIII [99%; $[\alpha]_D^{25}$ –5.7° (c 2.00, EtOH)], which was then hydrolyzed (2 N aq. NaOH–EtOH, 25°C, 24 h) to give the (–)-cis-lactam acid XIV [98%; $[\alpha]_D^{24}$ –0.2° (c 2.00, EtOH)]. Thermal isomerization (180°C, 1.5 h) of the (–)-cis-lactam acid XIV to the (+)-trans-lactam acid XV [74% yield; mp 122.5–123°C; $[\alpha]_D^{16}$ +68.0° (c 0.50, EtOH)] was effected in a manner similar to that[5,8,9,17] described previously for structurally analogous systems. When esterified with ethanolic HCl (15°C, 24 h), (+)-XV gave the (+)-lactam ester XVI [99%; $[\alpha]_D^{16}$ +66.8° (c 0.50, EtOH)], which was benzylated ($PhCH_2Br + K_2CO_3$, boiling acetone, 26 h) to furnish the (+)-benzyl ether XVII [96%; $[\alpha]_D^{15}$ +55.0° (c 0.50, EtOH)]. Compound (+)-XVII was then cyclized ($POCl_3$, toluene, reflux, 1.5 h) and the resulting iminium salt (XVIII) was hydrogenated (Pt/H_2, EtOH, 1 atm, room temp., 1 h) to produce the desired (–)-tricyclic amino ester VII [70% overall yield from (+)-XVII; mp 99–99.5°C; $[\alpha]_D^{16}$ –46.0° (c 0.50, EtOH); ir ($CHCl_3$): 2820, 2765 (trans-quinolizidine ring),[18] 1725 cm^{-1} (ester CO)]. The tlc behavior and the solution ir and nmr spectra of (+)-XVI, (+)-XVII, and (–)-VII thus obtained were identical with those of the corresponding racemic variety,[7] substantiating the assigned structure and stereochemistry.

In conclusion, the key intermediate (–)-VII for chiral syntheses of the 10-demethylated Alangium alkaloids has now become available through the above reaction sequence, and the synthesis of 10-demethylcephaeline (VI) from (–)-VII is currently under way in our laboratory.

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14. Satisfactory spectral data and/or elemental analyses were obtained for all the new compounds described.

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