

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

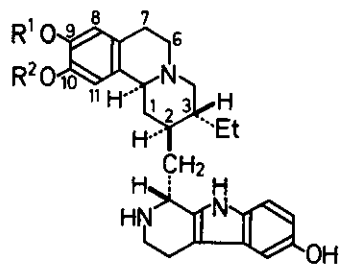
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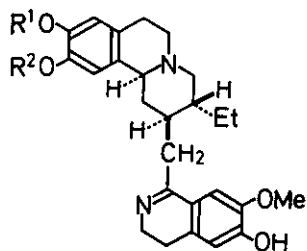
Abstract — The title (–)-tricyclic amino ester VII has been synthesized by means of an initial condensation of 4-benzyloxy-3-methoxyphenacyl bromide with (+)-ethyl cincholoiponate (VIII), derived from the Cinchona alkaloid cinchonine, and succeeding steps proceeding through the intermediates (+)-IX,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

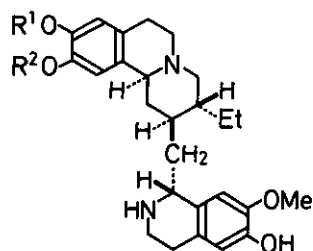
Treatment of (+)-ethyl cincholoiponate (VIII), prepared¹² from the Cinchona alkaloid cinchonine in 50% overall yield, with 4-benzyloxy-3-methoxyphenacyl bromide¹³ and K₂CO₃ in benzene (50–55°C, 7 h) gave the (+)-amino ketone IX [98% yield; [α]_D¹⁶ +3.7° (c 2.71, EtOH)],¹⁴ which was then reduced (NaBH₄, EtOH, 0°C, 2 h, room temp., 6 h) to afford a diastereomeric mixture of the amino alcohol X [97%; [α]_D¹⁸ –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 CHCl₃–hexane) furnished the 6-piperidone XI as a diastereomeric mixture [53% yield; [α]_D²⁵ –9.6° (c 2.00, EtOH); ir (CHCl₃): 3350 (OH), 1726 (ester CO), 1618 cm⁻¹ (lactam CO)] and an oily substance [15% yield; [α]_D¹⁸ +10.3° (c 2.00, EtOH); ir (CHCl₃): 3350 (OH), 1726 (ester CO), 1610 cm⁻¹ (lactam CO)] presumed⁸ to



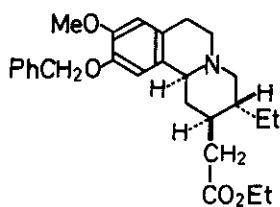
I: $R^1 = H; R^2 = Me$
 II: $R^1 = Me; R^2 = H$



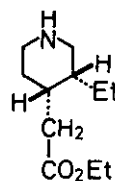
III: $R^1 = H; R^2 = Me$
 IV: $R^1 = Me; R^2 = H$



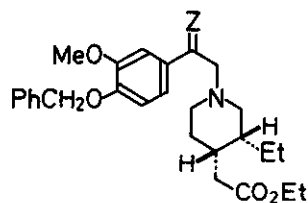
V: $R^1 = H; R^2 = Me$
 VI: $R^1 = Me; R^2 = H$



VII

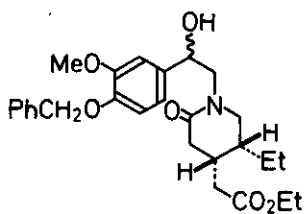


VIII

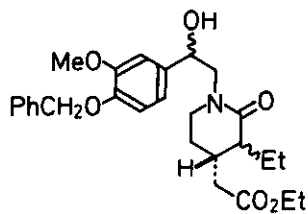


IX: $Z = O$

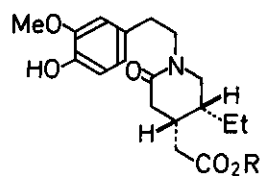
X: $Z = H, OH$



XI

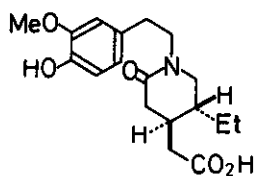


XII

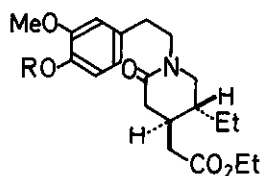


XIII: $R = Et$

XIV: $R = H$

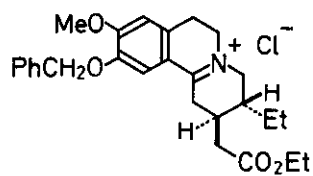


XV



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/H₂, EtOH-70% aq. HClO₄, 1 atm, 35°C, 16 h), the major product XI of the above oxidation yielded the (-)-lactam phenol XIII [99%; [α]_D²⁵ -5.7° (c 2.00, EtOH)], which was then hydrolyzed (2N aq. NaOH-EtOH, 25°C, 24 h) to give the (-)-*cis*-lactam acid XIV [98%; [α]_D²⁴ -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; [α]_D¹⁶ +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%; [α]_D¹⁶ +66.8° (c 0.50, EtOH)], which was benzylated (PhCH₂Br + K₂CO₃, boiling acetone, 26 h) to furnish the (+)-benzyl ether XVII [96%; [α]_D¹⁵ +55.0° (c 0.50, EtOH)]. Compound (+)-XVII was then cyclized (POCl₃, toluene, reflux, 1.5 h) and the resulting iminium salt (XVIII) was hydrogenated (Pt/H₂, 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; [α]_D¹⁶ -46.0° (c 0.50, EtOH); ir (CHCl₃): 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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