

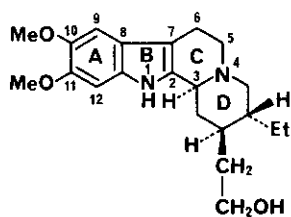
STRUCTURE DETERMINATION OF THE OCHROSIA ALKALOID OCHROPPOSININE:
SYNTHESES OF (±)- AND (-)-OCHROPPOSININE

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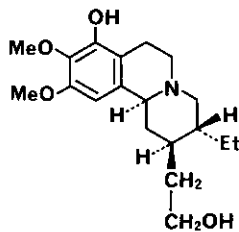
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Abstract — The tetracyclic alcohols (±)-I and (-)-I have been synthesized from the lactim ethers (±)-III and (+)-III via the intermediates (±)-VII and (+)-VII, (±)-IX and (+)-IX, (±)-X and (+)-X, XI, and (±)-XII and (-)-XII. The identity of the synthetic (-)-I with natural ochropposinine unequivocally established the structure and absolute stereochemistry of this Ochrosia alkaloid.

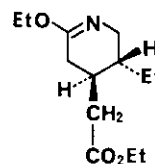
(-)-Ochropposinine is an indoloquinolizidine alkaloid isolated from the trunk bark of Ochrosia oppositifolia (Lmk) K. Schum. (Apocynaceae).^{1,2} It also occurs in the bark of two other species of the same genus, Ochrosia vieillardii and Ochrosia moorei, together with many other indole alkaloids.³ The structure and absolute stereochemistry of (-)-ochropposinine have been inferred to be (-)-I (absolute con-



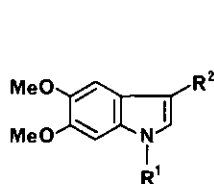
(±)-I
(-)-I



(-)-II



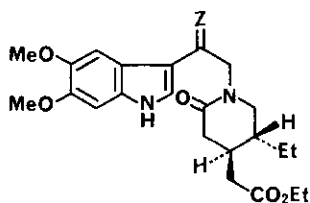
(±)-III
(+)-III



IV: $R^1 = R^2 = H$

V: $R^1 = H$; $R^2 = COCH_2Cl$

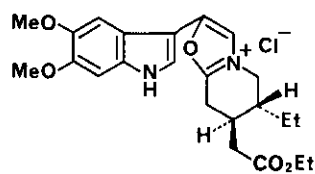
VI: $R^1 = COCH_2Cl$; $R^2 = H$



(±)-VII: $Z = O$

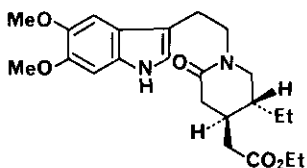
(+)-VII: $Z = O$

(±)-VIII: $Z = H, OH$



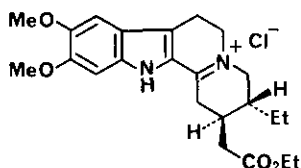
(±)-IX

(+)-IX

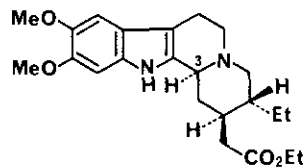


(±)-X

(+)-X



XI



(±)-XII

(-)-XII

figuration shown⁴) on the basis of spectral evidence, the negative sign of specific rotation, and biogenetic considerations.^{2,3b} With a view to verifying the correctness of this inference, we accomplished both the racemic and chiral syntheses of the target molecule I in the present work.

Among the various routes conceivable for the synthesis of I in the racemic and chiral forms, the one utilizing the lactim ether III as a starting material to form ring D in I seemed most attractive since III was readily available in any of the (±)-,⁵ (+)-,⁶ and (-)-forms⁶ and had already been shown to be able to serve as a key intermediate in the stereospecific syntheses of structurally related alkaloids, representatively in the synthesis of the *Alangium* alkaloid ankorine [(-)-II]⁷ as well as its (±)-⁸ and (+)-modifications,⁷ by a "lactim ether route".⁹ Another starting material, derived from the tricyclic synthon (rings A, B, and C in I), was 3-chloroacetyl-5,6-dimethoxyindole (V)¹⁰ [mp 229–230°C (dec.)], and it was prepared in 51% yield from 5,6-dimethoxyindole (IV)¹¹ by treatment with chloroacetyl chloride and pyridine in toluene (55–60°C, 40 min) according to a general 3-chloroacetylation procedure.¹² The 1-acylated isomer VI [7% yield; mp 149–150°C (dec.)] was a by-product in this reaction.

For the synthesis of (±)-I, (±)-III was treated with V in $HCONMe_2$ at 60°C in the presence of KBr for 48 h to give the lactam ketone (±)-VII (mp 156–157°C)¹³ in 71%

yield. Reduction of ($\pm$)-VII with a large excess of NaBH_4 (EtOH, room temp., 3 h) furnished a diastereomeric mixture of the lactam alcohol ($\pm$)-VIII in 97% yield. However, hydrogenolysis of ($\pm$)-VIII using H_2 and Pd-C catalyst under various conditions failed to give the desired lactam ester ($\pm$)-X.¹⁴ On treatment with POCl_3 (boiling toluene, 1 h), ($\pm$)-VII produced the oxazolium salt ($\pm$)-IX [81% yield; mp 261–263°C (dec.)], which was then reduced (Pt/ H_2 , EtOH, 1 atm, room temp., 10 h) to the lactam ($\pm$)-X in 51% yield. This reduction of the carbonyl group has a precedent in which an *N*-phenacyl amide was reduced to the corresponding *N*-phenethyl amide through an oxazole derivative.¹⁵ Bischler-Napieralski cyclization of ($\pm$)-X (POCl_3 , boiling toluene, 2 h) and catalytic hydrogenation of the resulting quaternary iminium salt XI (Pt/ H_2 , EtOH, 1 atm, room temp., 4 h) afforded the tetracyclic ester ($\pm$)-XII [mp 161–162°C; ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 2835, 2805, and 2755 cm^{-1} (*trans*-quinolizidine¹⁶)] in 60% overall yield [from ($\pm$)-X]. Since catalytic hydrogenation of similar systems provides the more stable isomer,¹⁷ the hydrogen at C-3 was assigned the α configuration. Reduction of ($\pm$)-XII with LiAlH_4 (tetrahydrofuran, room temp., 3 h) gave the desired alcohol ($\pm$)-I (mp 199–200°C)¹⁸ in 89% yield. The uv (EtOH), ir (CHCl_3), ^1H nmr (CDCl_3), ^{13}C nmr (CDCl_3), and mass spectra and tlc mobility of ($\pm$)-I were identical with those of a natural sample of ochroprosinine, establishing the structure and relative stereochemistry of this alkaloid.

A parallel sequence of reactions starting with (+)-III and V afforded (+)-VII [66% yield; $[\alpha]_{\text{D}}^{16} +36.8^\circ$ (c 0.50, EtOH)], (+)-IX [58%; mp 261.5–263.5°C (dec.); $[\alpha]_{\text{D}}^{23} +70.8^\circ$ (c 0.52, EtOH)], (+)-X [60%; $[\alpha]_{\text{D}}^{25} +62.2^\circ$ (c 0.61, EtOH)], (–)-XII [86% from (+)-X; $[\alpha]_{\text{D}}^{17} -6.3^\circ$ (c 0.50, EtOH)], and (–)-I [81%; $[\alpha]_{\text{D}}^{17} -15.9^\circ$ (c 1.00, CHCl_3); $[\alpha]_{577}^{17} -15.7^\circ$ (c 1.00, CHCl_3)]. The synthetic (–)-I was identical (by comparison of uv, ir, nmr, and mass spectra, tlc behavior, and specific rotation) with a natural sample of ochroprosinine [$[\alpha]_{578}^{20} -18^\circ$ (c 1, CHCl_3)].¹⁻³

Thus, the above results unequivocally establish the structure of the *Ochrosia* alkaloid ochroprosinine as 10,11-dimethoxydihydrocorynantheol [(–)-I]. In addition, they also represent an example of the extension of the "lactim ether route"⁹ to indoloquinolizidine alkaloids.

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