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

Tozo Fujii,* Masashi Ohba, Takeshi Tachinami, and Hisae Miyajima

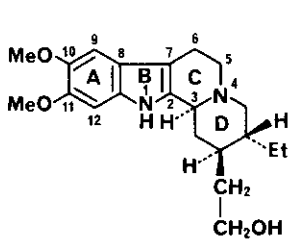
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

Michel Koch and Elisabeth Seguin

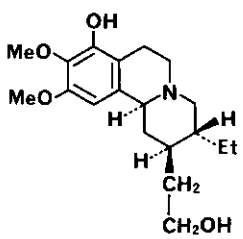
Département de Pharmacognosie de l'Université René Descartes, U.A. au C.N.R.S. n° 484, Faculté des Sciences Pharmaceutiques et Biologiques, 4 avenue de l'Observatoire, 75270 Paris, France

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.

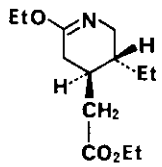
(−)-Ochropposinine is an indoloquinolizidine alkaloid isolated from the trunk bark of Ochrosia oppositifolia (Lmk) K. Schum. (Apocynaceae).[1,2] It also occurs in the bark of two other species of the same genus, Ochrosia vieillardii and Ochrosia moorei, together with many other indole alkaloids.[3] The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



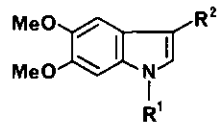
(±)-I
(−)-I



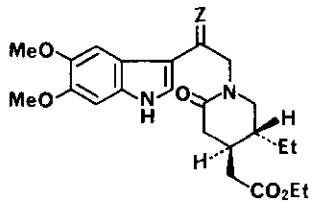
(−)-II



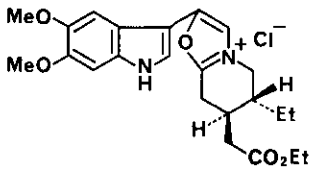
(±)-III
(+)-III



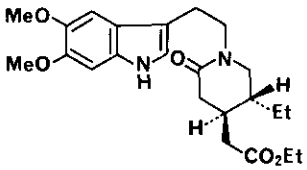
IV: $R^1 = R^2 = H$
V: $R^1 = H$; $R^2 = COCH_2Cl$
VI: $R^1 = COCH_2Cl$; $R^2 = H$



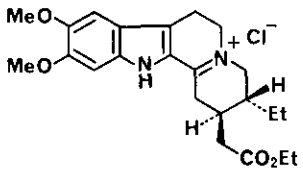
(±)-VII: Z = O
(+)-VII: Z = O
(±)-VIII: Z = H,OH



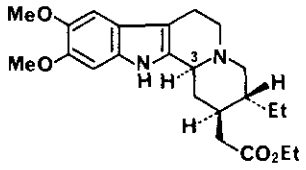
(±)-IX
(+)-IX



(±)-X
(+)-X



XI



(±)-XII
(−)-XII

figuration shown[4]) 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 (−)-forms[6] 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 (±)-VII with a large excess of $NaBH_4$ (EtOH, room temp., 3 h) furnished a diastereomeric mixture of the lactam alcohol (±)-VIII in 97% yield. However, hydrogenolysis of (±)-VIII using H_2 and Pd–C catalyst under various conditions failed to give the desired lactam ester (±)-X.[14] On treatment with $POCl_3$ (boiling toluene, 1 h), (±)-VII produced the oxazolium salt (±)-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 (±)-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 (±)-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 (±)-XII [mp 161–162°C; ir $\nu_{max}^{CHCl_3}$ 2835, 2805, and 2755 cm^{-1} (trans-quinolizidine[16])] in 60% overall yield [from (±)-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 (±)-XII with $LiAlH_4$ (tetrahydrofuran, room temp., 3 h) gave the desired alcohol (±)-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 (±)-I were identical with those of a natural sample of ochropposinine, establishing the structure and relative stereochemistry of this alkaloid.

A parallel sequence of reactions starting with (+)-III and V afforded (+)-VII [66% yield; $[\alpha]_D^{16}$ +36.8° (c 0.50, EtOH)], (+)-IX [58%; mp 261.5–263.5°C (dec.); $[\alpha]_D^{23}$ +70.8° (c 0.52, EtOH)], (+)-X [60%; $[\alpha]_D^{25}$ +62.2° (c 0.61, EtOH)], (−)-XII [86% from (+)-X; $[\alpha]_D^{17}$ −6.3° (c 0.50, EtOH)], and (−)-I [81%; $[\alpha]_D^{17}$ −15.9° (c 1.00, $CHCl_3$); $[\alpha]_{577}^{17}$ −15.7° (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 ochropposinine [$[\alpha]_{578}^{20}$ −18° (c 1, $CHCl_3$)].[1-3]

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

ACKNOWLEDGMENT We are grateful to Dr. P. Potier, Institut de Chimie des Substances Naturelles de C. N. R. S., Paris, for his help and interest. This work was supported by a Grant-in-Aid for Scientific Research (No. 58570869 to T. F.) from the Ministry of Education, Science and Culture, Japan.

REFERENCES

1. N. Peube-Locou, M. Koch, M. Plat, and P. Potier, Ann. Pharm. Fr., 1972, 30, 821.
2. N. Peube-Locou, M. Koch, M. Plat, and P. Potier, Phytochemistry, 1972, 11, 2109. Since the isolation of ochropposinine, the name of this species has been revised to Neisosperma oppositifolia (Lamarck) Fosberg & Sachet [F. R. Fosberg, P. Boiteau, and M.-H. Sachet, Adansonia Ser. 2, 1977, 17, 23].
3. (a) J. Bruneton, T. Sevenet, and A. Cavé, Phytochemistry, 1972, 11, 3073; (b) A. Ahond, H. Fernandez, M. Julia-Moore, C. Poupat, V. Sánchez, P. Potier, S. K. Kan, and T. Sévenet, J. Nat. Prod., 1981, 44, 193.
4. Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations.
5. (a) T. Fujii and S. Yoshifuji, Chem. Pharm. Bull., 1979, 27, 1486; (b) J. Gutzwiller, G. Pizzolato, and M. R. Uskoković, Helv. Chim. Acta, 1981, 64, 1663.
6. T. Fujii, M. Ohba, K. Yoneyama, and H. Kizu, Chem. Pharm. Bull., 1985, 33, 358.
7. T. Fujii, M. Ohba, K. Yoneyama, H. Kizu, and S. Yoshifuji, Chem. Pharm. Bull., in press.
8. T. Fujii, S. Yoshifuji, and K. Yamada, Tetrahedron, 1980, 36, 965.
9. For the "lactim ether route" leading to the benzo[a]quinolizidine and indolo-[2,3-a]quinolizidine systems, see (a) T. Fujii and M. Ohba, Chem. Pharm. Bull., 1985, 33, 144, and references cited therein; (b) T. Fujii, S. Yoshifuji, and H. Ito, Heterocycles, 1977, 7, 149; (c) T. R. Govindachari and S. Rajeswari, Indian J. Chem., 1983, 22B, 531.
10. S. Sakai, N. Saito, N. Hirose, and E. Yamanaka, Heterocycles, 1982, 17, 99.
11. A. K. Sinhababu and R. T. Borchardt, J. Org. Chem., 1983, 48, 3347.
12. J. Bergman, J.-E. Bäckvall, and J.-O. Lindström, Tetrahedron, 1973, 29, 971.
13. Satisfactory microanalytical and/or spectroscopic data have been obtained for all new compounds described herein.
14. This failure is probably owing to the high reactivity at the benzylic position.
15. A. P. Kozikowski and A. Ames, J. Org. Chem., 1980, 45, 2548.
16. (a) F. Bohlmann, Chem. Ber., 1958, 91, 2157; (b) E. Wenkert and D. K. Roychaudhuri, J. Am. Chem. Soc., 1956, 78, 6417.
17. E. E. van Tamelen and J. B. Hester, Jr., J. Am. Chem. Soc., 1969, 91, 7342.
18. The elemental analysis pointed to the formula $C_{21}H_{30}N_2O_3 \cdot 1/2\,H_2O$.

Received, 7th January, 1986