Racemic and Chiral Syntheses of Some Indolo[2,3-a] Quinolizidine Alkaloids Through a "Lactim Etherroute"

RACEMIC AND CHIRAL SYNTHESES OF SOME INDOLO[2,3-*a*]QUINOLIZIDINE ALKALOIDS THROUGH A "LACTIM ETHER ROUTE"†

Tozo Fujii* and Masashi Ohba

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

Abstract — The racemic and/or chiral syntheses of some *Corynanthe*-type indoloquinolizidine alkaloids and related bases, accomplished through a "lactim ether route" by the present authors' group, are reviewed with 107 reference citations. As a result of these syntheses, the structures and/or absolute configurations of the *Neisosperma* alkaloid ochromianine [(–)-**35**], the *Ophiorrhiza* alkaloid ophiorrhizine [(–)-**46**], and the *Neisosperma* and *Ochrosia* alkaloid ochropposinine [(–)-**49**] have been unequivocally established.

CONTENTS

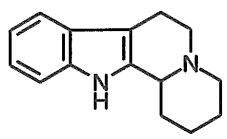
I. Introduction

The indole alkaloids, a large and complex group of natural products bearing the indole or 2,3-dihydroindole (indoline) ring in their structures, include a number of indolo[2,3-*a*]quinolizidine alkaloids (*e. g.*, **1**), often referred to as indoloquinolizidine alkaloids.[1] Although the chemical structures of most of the known indoloquinolizidine alkaloids have

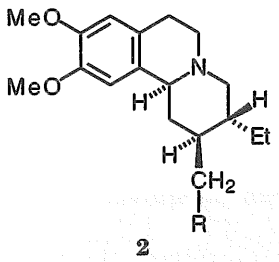
†This review article is dedicated to Professor Koji Nakanishi (Columbia University) on the occasion of his 75th birthday.

been unequivocally established, there are some structural problems still remaining even in this new era of highly sophisticated spectroscopic studies.[1c] Solutions to these problems could come with the racemic and/or chiral syntheses of compounds possessing the candidate structures, and the syntheses might be feasible *via* extensions of the "lactim ether route",[2,3] which has been developed in our laboratory as the best available vehicle for unified racemic and chiral syntheses of the structurally analogous benzo[*a*]-quinolizidine-type *Alangium* alkaloids (types **2**–**5**[4]).[3,5] This synthetic route features the introduction of an adequate phenethyl skeleton into the key intermediate *trans*-lactim ether (**7**), which is readily available in any of the (±)-,[6] (+)-,[2c,7] and (–)-forms.[7]

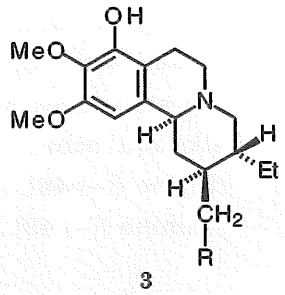
The aim of this article is to give an overview of the synthetic results obtained by us *via* such approach to the above problems, with coverage of the literature through the late part of 1996.



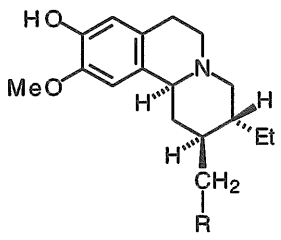
1



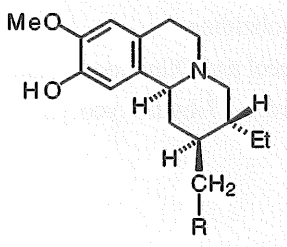
2



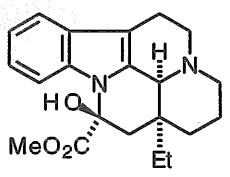
3



4

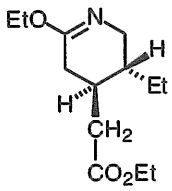


5

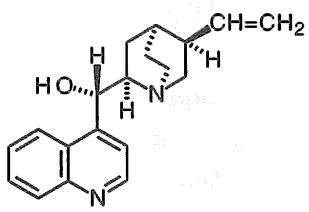


6

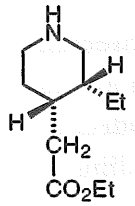
R = CH_2OH, CO_2H, or a heterocyclic ring



(+)-**7**



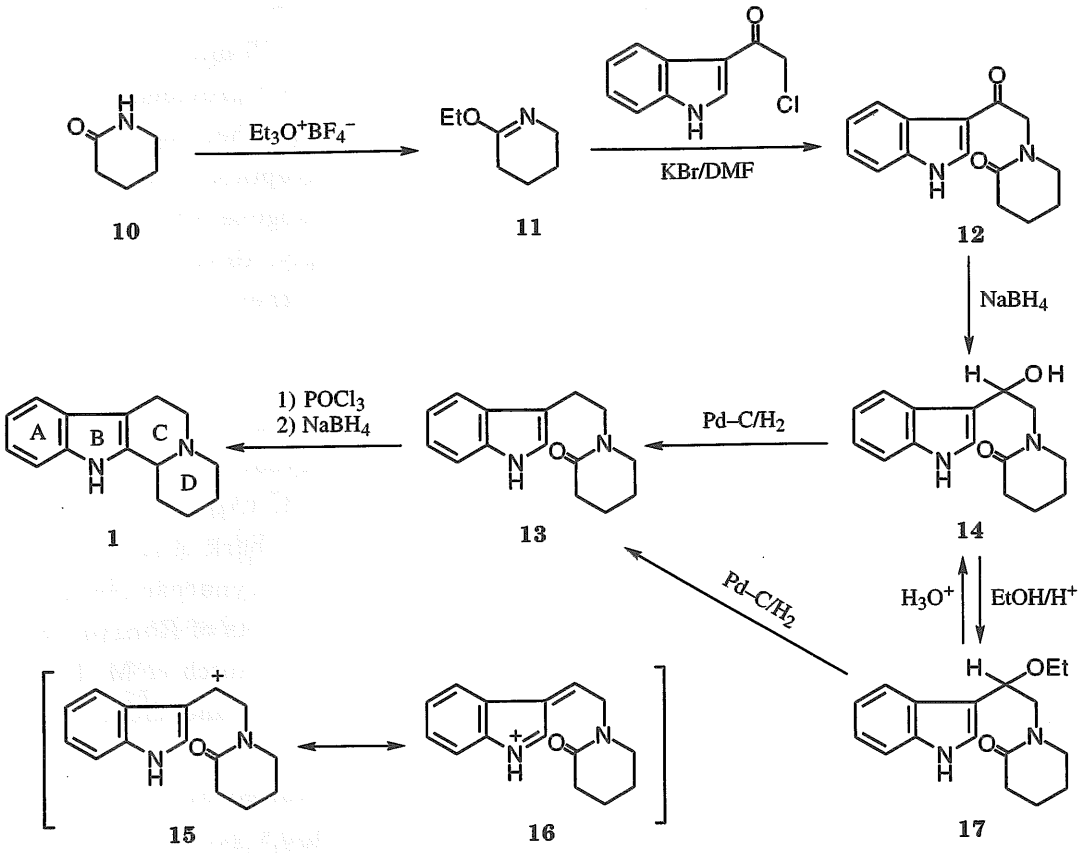
(+)-**8**



(+)-**9**

II. Indolo[2,3-*a*]quinolizidine

The tetracyclic base (**1**) is the simplest member of the indoloquinolizidine alkaloids: Its (–)-isomer, yet unnamed, has been isolated[8] in partially racemized form from the leaves of a New Guinea tree, *Dracontomelum mangiferum* Bl., belonging to the family Anacardiaceae. Although more than 40 synthetic routes to this parent framework (**1**) had been reported,[9,10] the feasibility of the above "lactim ether route" approach was tested by Fujii's group in the racemic synthesis of **1** (Scheme 1).[11]



Scheme 1

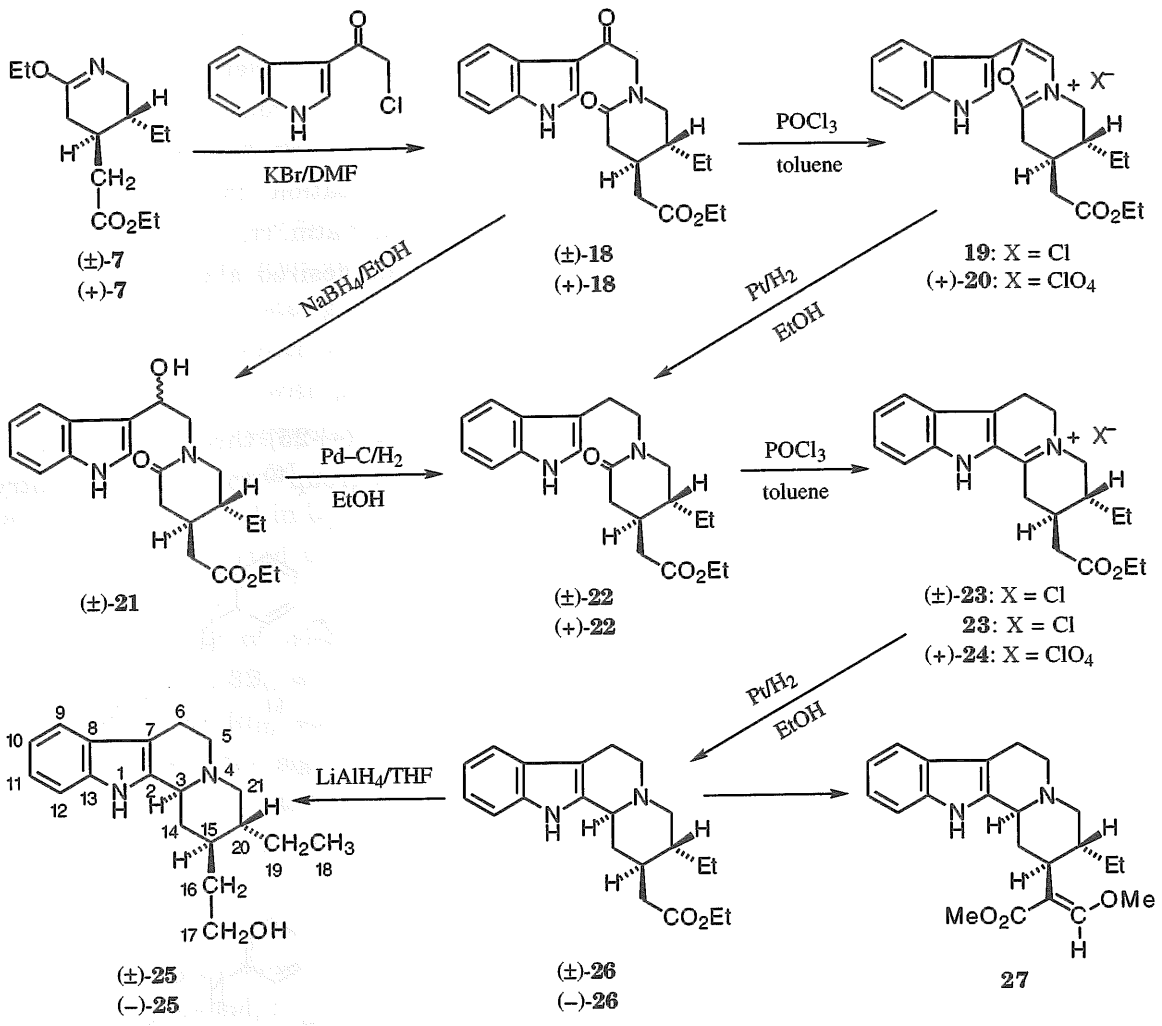
Thus, alkylation of the lactim ether (**11**), obtained in 84% yield from 2-piperidone (**10**) according to the literature procedure,[2a,12] with 3-(chloroacetyl)indole[13] in DMF at 60°C in the presence of KBr for 24 h furnished the lactam ketone (**12**) in 71% yield. In the absence of KBr, the progress of alkylation was extremely slow, suggesting the intermediary formation of 3-(bromoacetyl)indole in the above alkylation. Reduction of **12** with $NaBH_4$ in aqueous EtOH at rt for 20 h gave the lactam alcohol (**14**) (96% yield), which was then hydrogenolyzed (10% Pd–C/H_2, 1 atm, 20°C, 50 min) in EtOH containing a small amount of 70% aqueous $HClO_4$ to afford the known lactam (**13**) in 96% yield. The hydroxy group of **14** at the indolylcarbinyl carbon was found to be considerably

reactive. On treatment with EtOH in the presence of a catalytic amount of HCl at 25°C for 1 h, **14** produced the ethoxy derivative (**17**) in 94% yield. Conversely, treatment of **17** with H_2O in MeCN containing a catalytic amount of HCl at 17°C for 1 h reproduced the lactam alcohol (**14**) in 86% yield. These transformations reflect the acid-catalyzed formation of the reactive "3-indolylcarbinyl system"[14] (**15**↔**16**) from **14** and from **17**. Catalytic hydrogenolysis of **17** to give **13** was smoothly effected under reaction conditions similar to those employed for the above conversion of **14** into **13**, but the result was less satisfactory when the reaction was carried out in the absence of $HClO_4$. Bischler–Napieralski cyclization of **13** ($POCl_3$, boiling benzene, 75 min)[9] and reduction of the resulting quaternary iminium salt ($NaBH_4$, MeOH, 1 h)[9] provided the desired tetracycle (**1**) in 95% overall yield from **13**. Thus, this "lactim ether route" may be of value, not only in preparing the alkaloid material (**1**) in an acceptable overall yield but also in the design and execution of the total syntheses of analogous alkaloids carrying substituents in ring A and/or ring D (*vide infra*). Interestingly, Govindachari's group has synthesized (±)-vincamine [(±)-**6**] *via* an analogous "lactim ether route".[15]

III. Dihydrocorynantheol and Dihydrocorynantheine

(–)-Dihydrocorynantheol (corynan-17-ol) [(–)-**25**] has been isolated from the bark[16] and stem bark[17] of *Aspidosperma marcgravianum* Woodson (Apocynaceae); the bark of *A. auriculatum*;[18] the leaves of *Amsonia tabernaemontana* Walt. (Apocynaceae);[19] the leaves of *Mitragyna parvifolia* (Roxb.) Korth (Rubiaceae);[20] the bark of *Hunteria zeylanica* (Apocynaceae);[21] the trunk bark of *Ochrosia moorei* (Apocynaceae);[22] the root bark and trunk bark of *Aspidosperma marcgravianum*;[23] the roots of *Rhazya stricta* Decsne. (Apocynaceae);[24] the stem bark of *Strychnos johnsonii* Hutch *et* M. B. Mass (Loganiaceae);[25] the stem bark of *Ochrosia alyxioides* Guillaumin;[26] and the aerial part of *Aspidosperma oblongum*.[27]

Although racemic dihydrocorynantheol [(±)-**25**] had been synthesized by many research groups,[28] its racemic synthesis from (±)-**7** was tested by Fujii's group[11] in order to evaluate the applicability of the "lactim ether route". Thus, treatment of (±)-**7** with 3-(chloroacetyl)indole[13] in DMF at 60°C in the presence of KBr for 38 h gave the lactam ketone [(±)-**18**] in 70% yield (Scheme 2). Reduction of (±)-**18** with $NaBH_4$ (EtOH, 22–25°C, 3 h) furnished a diastereomeric mixture of the lactam alcohol [(±)-**21**] in 70% yield. The diastereomeric mixture [(±)-**21**] was then submitted to catalytic hydrogenolysis (10% Pd–C/H_2, EtOH, 1 atm, 21–22°C, 1 h) in the presence of a small amount of 70% aqueous $HClO_4$, affording the (±)-*trans*-lactam ester [(±)-**22**] in 74% yield. The lactam ester [(±)-**22**] has been converted into (±)-**25**[28b] and (±)-dihydrocorynantheine [(±)-**27**][29,30] through the quaternary iminium salt [(±)-**23**] and the tetracyclic ester [(±)-**26**]. Consequently, the above results [(±)-**7**→(±)-**18**→(±)-**21**→(±)-**22**] imply that an alternative racemic synthesis of each of these *Corynanthe*-type alkaloids has now been completed in a formal sense.



Scheme 2

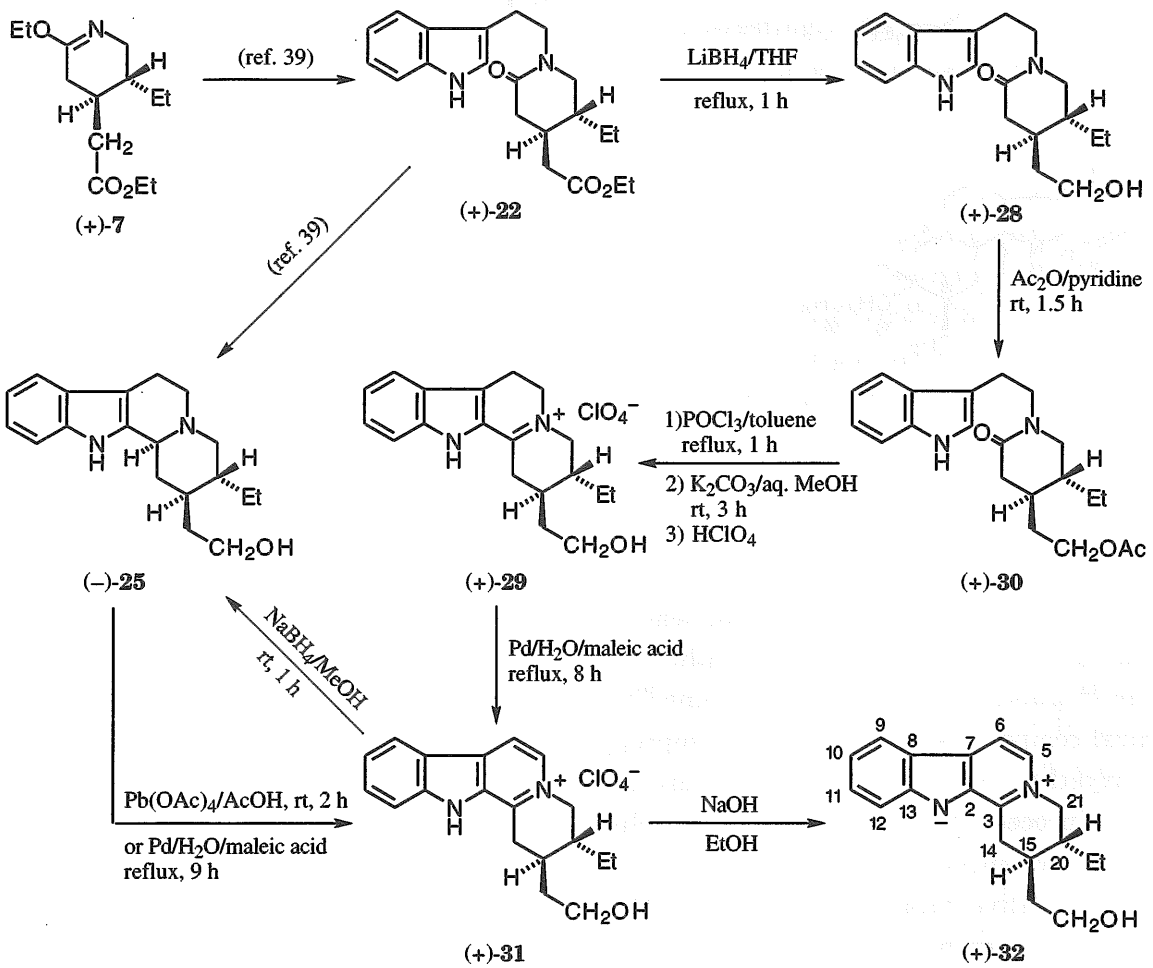
As regards the synthesis of (–)-**25**, semisynthetic (–)-**25** has been prepared from various alkaloids such as dihydrocorynantheine (**27**),[10h,31] geissoschizol,[32] quinine,[33] ajmalicine,[34] guettardine,[35] and yohimbine.[36] The total syntheses of (–)-**25** by starting from chiral compounds, such as (*R*)-1,2-isopropylideneglyceraldehyde[37] and (4*S*,5*R*)-4-(2-benzyloxyethyl)-5-ethyl-3,4,5,6-tetrahydro-2-pyrone,[36] and by utilizing an asymmetric synthesis process[38] have also been accomplished. The latter asymmetric total synthesis[38] also allows entry into dihydrocorynantheine (**27**).

An alternative total synthesis of (–)-**25**, adaptable to its preparation on a gram-size scale, has been achieved by Fujii's group *via* a "lactim ether route" (Scheme 2).[39] The initial step was coupling of the lactim ether [(+)-**7**] with 3-(chloroacetyl)indole, which proceeded in DMF at 60°C in the presence of KBr for 72 h to give the lactam ketone [(+)-**18**] in 68% yield. Treatment of (+)-**18** with $POCl_3$ in boiling toluene for 3 h afforded the oxazolium chloride (**19**), which was characterized as the crystalline perchlorate salt

[(+)-**20**]. The crude chloride salt (**19**) was then reduced by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, rt, 3 h) to furnish the lactam [(+)-**22**] in 52% overall yield [from (+)-**18**]. Conversion of (+)-**22** into the tetracyclic ester [(–)-**26**] through the quaternary iminium salt (**23**) [characterized as the crystalline perchlorate salt [(+)-**24**]] was effected in 91% overall yield by means of Bischler–Napieralski cyclization ($POCl_3$, boiling toluene, 1 h) followed by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, rt, 1 h). On reduction with $LiAlH_4$ in THF at rt for 30 min, (–)-**26** produced the desired alkaloid [(–)-**25**] in quantitative yield.

IV. 3,4,5,6-Tetradehydro-17-hydroxycorynanium

The gram-scale total synthesis of (–)-dihydrocorynantheol [(–)-**25**] through the "lactim ether route"[39] described above (Section III) allowed Fujii's group[40] to make their entry



Scheme 3

into the synthesis of 3,4,5,6-tetradehydro-17-hydroxycorynanium [(+)-**32**], the zwitterionic structure assigned[23] to an alkaloid from *Aspidosperma marcgravianum* Woodson (family Apocynaceae).

Thus, selective reduction of (+)-**22** with $LiBH_4$ in boiling THF for 1 h gave the lactam alcohol [(+)-**28**] (84% yield), which was then converted into the acetate [(+)-**30**] (100% yield) by treatment with acetic anhydride in pyridine at rt for 1.5 h (Scheme 3). Bischler–Napieralski cyclization of (+)-**30** with $POCl_3$ in boiling toluene for 1 h, followed by hydrolysis of the ester group with K_2CO_3 in aqueous MeOH at rt for 3 h, produced a tetracyclic alcohol, which was isolated in the form of the perchlorate salt [(+)-**29**] (86% yield). On treatment with palladium black and maleic acid in boiling H_2O for 8 h, (+)-**29** afforded the dehydrogenated product [(+)-**31**] in 91% yield. Alternatively, dehydrogenation of synthetic (–)-**25** with lead tetraacetate in AcOH at rt for 2 h or with palladium black and maleic acid in boiling H_2O for 9 h also gave (+)-**31** (in 8% or 72% yield, respectively), which reverted to (–)-**25** in quantitative yield when reduced with $NaBH_4$ in MeOH at rt for 1 h.

Finally, treatment of (+)-**31** with aqueous NaOH in EtOH furnished the target anhydronium base [(+)-**32**], which was characterized as a hydrate [(+)-**32**·2/5H_2O] [mp 161–162.5°C (decomp); $[\alpha]_D^{18}$ +50.0° (*c* 0.53, MeOH)]. Unfortunately, however, the ^1H NMR spectral data and the sign of specific rotation for the synthetic (+)-**32** were in disagreement with those reported[23] for a natural sample, leaving the chemistry of this *A. marcgravianum* alkaloid incomplete.

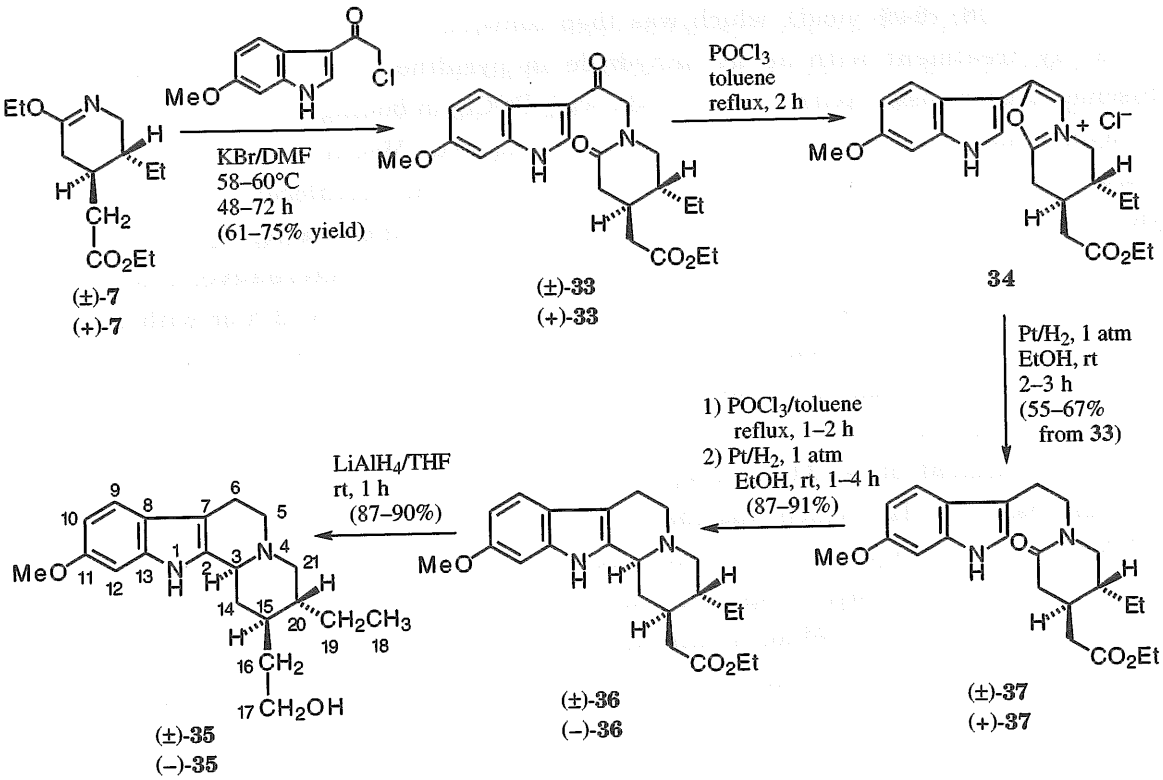
V. Ochromianine

In 1974, Koch and co-workers[41] reported the isolation of (–)-ochromianine, a new *Corynanthe*-type alkaloid, from the bark of a New Caledonian plant named *Ochrosia miana* H. Bn. ex Guill. (family Apocynaceae) at that time. The name of the plant was later revised to *Neisosperma miana* (Baillon ex-White) Boiteau.[42] The French research group deduced the structure and absolute configuration of (–)-ochromianine to be (–)-**35** (11-methoxydihydrocorynantheol) on the basis of spectral analysis as well as chiroptical and biosynthetic rationales.[41] The correctness of this structure assignment was confirmed by Fujii's group as a result of the racemic and chiral syntheses of the candidate structure (**35**), which followed a "lactim ether route" as delineated in Scheme 4.[43]

The racemic synthesis of **35** started with coupling of (±)-**7** with 3-chloroacetyl-6-methoxyindole to give the lactam ketone [(±)-**33**]. Conversion of (±)-**33** into the lactam [(±)-**37**] through the oxazolium salt (**34**), cyclization of (±)-**37** to form the tetracyclic ester [(±)-**36**], and $LiAlH_4$ reduction of the ester group to give (±)-**35** were carried out as in the case of the above synthesis of dihydrocorynantheol (**25**) (Section III).

For the chiral synthesis of (–)-**35**, a parallel sequence of conversions starting with (+)-**7** was followed. The UV, IR, and ^1H NMR spectra and MS of the synthetic (–)-**35** [mp 162–

169°C (decomp); $[\alpha]_D^{25}$ –28.0° (*c* 1.00, EtOH)] were virtually identical with those of natural (–)-ochromianine, and the chiral identity of (–)-**35** with the alkaloid was shown by their virtually identical CD spectra.



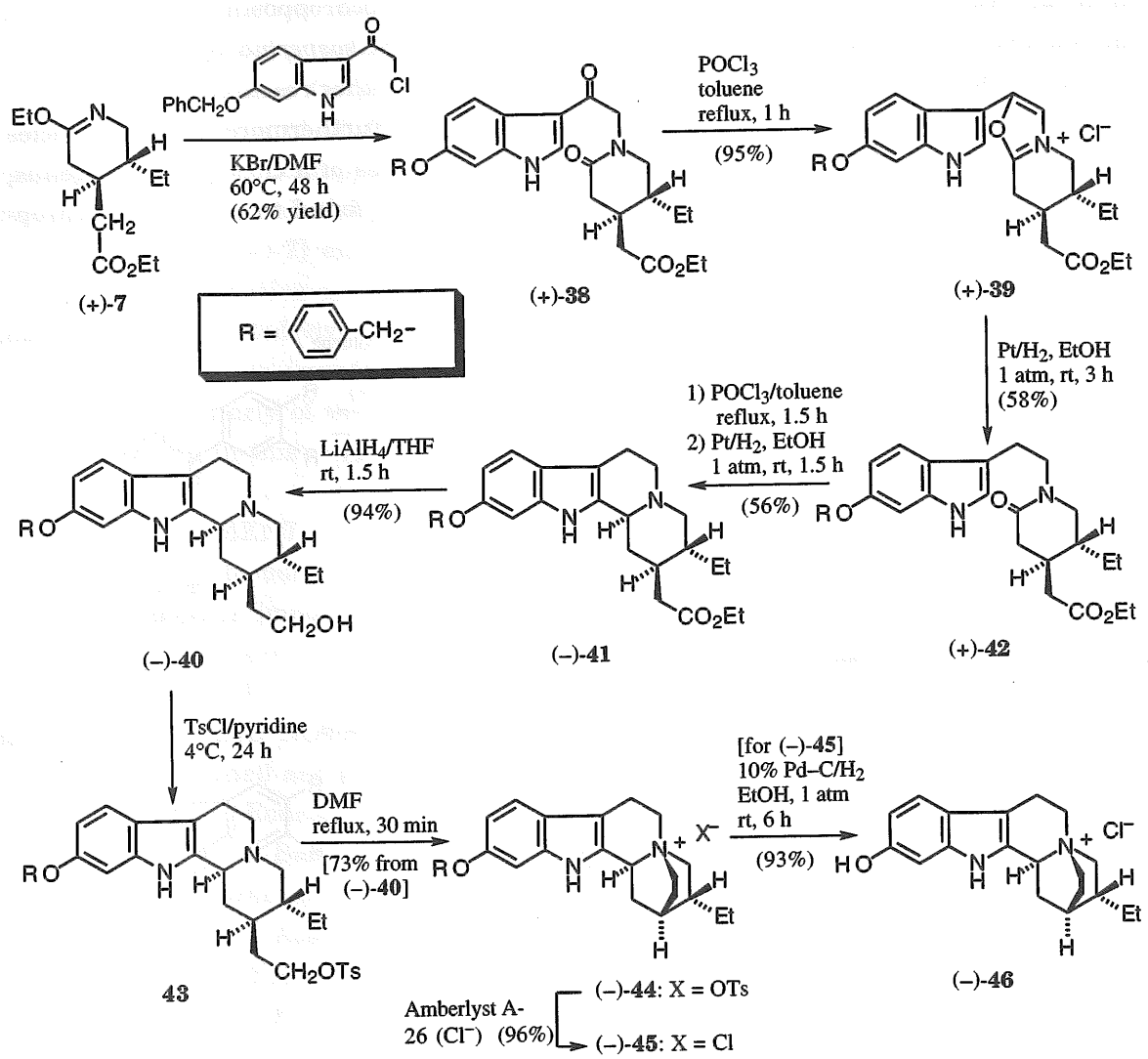
Scheme 4

VI. Ophiorrhizine

In 1992, Arbain *et al.*[44] reported the isolation of a new C_{19} pentacyclic quaternary indole alkaloid, named ophiorrhizine, from the fresh aerial parts of the medicinal plant *Ophiorrhiza major* Ridl. (family Rubiaceae). They established the structure and relative stereochemistry of ophiorrhizine as **46** on the basis of its spectral properties and X-ray molecular structure.[44] However, its absolute stereochemistry has only been inferred to be (–)-**46** from the negative sign and magnitude of the specific rotation of this alkaloid.[44]

The correctness of this inference was verified by Fujii's group as a result of the chiral synthesis of the target compound with the candidate structure [(–)-**46**].[45] The synthesis featured an adaptation of their favorite "lactim ether route" [(+)-**7**→(+)-**38**→(+)-**39**→(+)-**42**→(–)-**41**→(–)-**40**→**43**→(–)-**44**→(–)-**45**→(–)-**46**], as shown in Scheme 5, and the reaction sequence from (+)-**7** to the tetracyclic alcohol [(–)-**40**] was similar to

those employed for the syntheses of (–)-**25** (Section III), (–)-**35** (Section V), and (–)-ochropposinine [(–)-**49**] (Section VII). The route beyond (–)-**40** included treatment of (–)-**40** with *p*-toluenesulfonyl chloride in pyridine at 4°C for 24 h and heating of the resulting *O*-tosyl derivative (**43**) in boiling DMF for 30 min, which gave the 4,17-cyclocorynanium tosylate [(–)-**44**] in 73% overall yield [from (–)-**40**]. Anion exchange of (–)-**44** was effected with Amberlyst A-26 (Cl^-) in aqueous MeOH to furnish the chloride salt [(–)-**45**] in 96% yield.



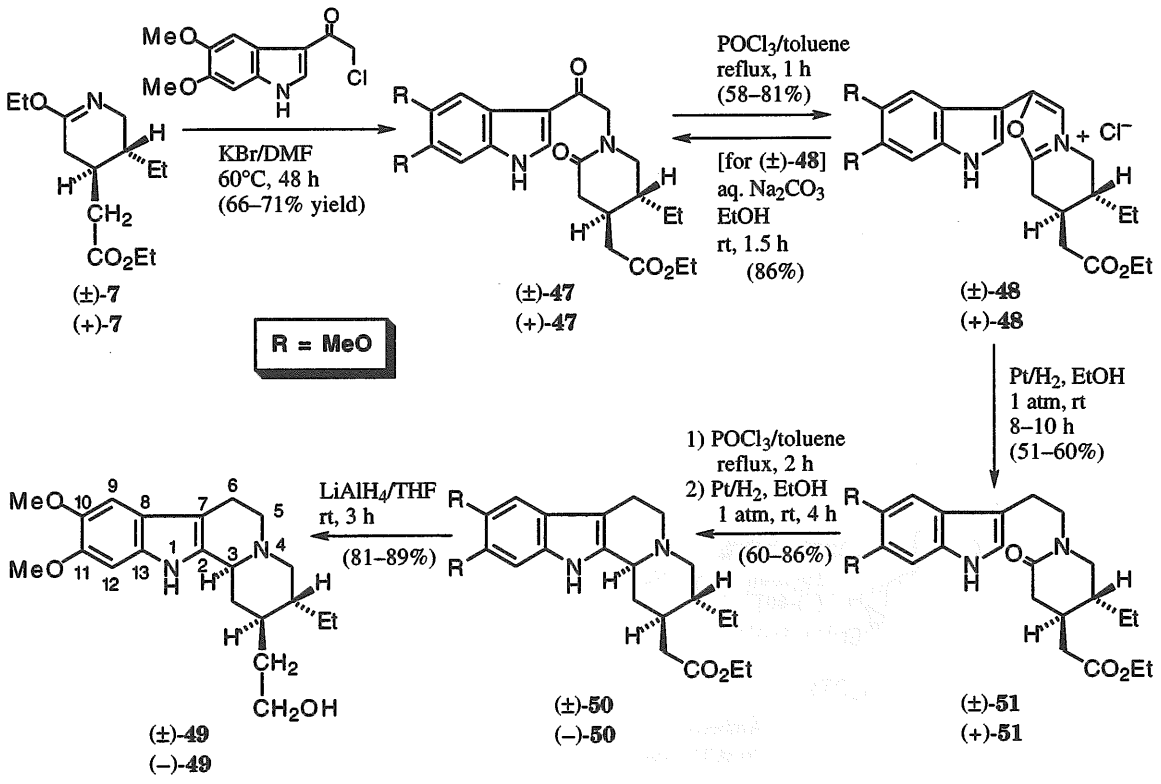
Scheme 5

Finally, debenzylation of (–)-**45** by means of catalytic hydrogenolysis (10% Pd–C/H_2, EtOH, 1 atm, rt, 6 h) gave the target compound [(–)-**46**·H_2O] [mp 282–285°C (decomp); $[\alpha]_D^{30}$ –102° (*c* 0.209, MeOH)] in 93% yield. The UV (MeOH), IR (KBr), ^1H NMR (CD_3OD),

and ^{13}C NMR (CD_3OD) spectra and TLC mobility of the synthetic (–)-**46**·H_2O were virtually identical with those of natural (–)-ophiorrhizine. More importantly, the chiral identity of the synthetic (–)-**46**·H_2O with the alkaloid was established on the basis of the same sign of their specific rotations in MeOH as well as their virtually superimposable CD spectra in MeOH.

VII. Ochropposinine

In 1972, Peube-Locou *et al.*[46] reported the isolation of (–)-ochropposinine, a member of the indoloquinolizidine alkaloids, from the trunk bark of *Neisosperma oppositifolia* (Lamarck) Fosberg *et* Sachet (Apocynaceae).[47] Later on, two other research groups also reported isolations of this alkaloid from the same plant.[48] Furthermore, another species of the same genus, *Neisosperma glomerata*, and two species of a closely related genus, *Ochrosia vieillardii* and *Ochrosia moorei*, have so far been found to contain (–)-ochropposinine, together with many other indole alkaloids.[22,49]



Scheme 6

The structure including the absolute configurations of three stereogenic centers of (–)-ochropposinine has been proposed to be (–)-**49** (10,11-dimethoxydihydrocorynantheol) on the basis of a combination of spectral analysis and a biosynthetic rationale.[22,46b] Une-

quivocal confirmation of the correctness of this proposal came with the syntheses of the racemic and chiral target molecules [(±)-**49** and (–)-**49**] by Fujii's group, which were also accomplished through their favorite "lactim ether route" (**7**→**47**→**48**→**51**→**50**→**49**) as shown in Scheme 6.[50]

VIII. Conclusions

The syntheses of the candidate target molecules described above enhance the usefulness of our "lactim ether route", originally designed for unified racemic and chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids (types **2**–**5**),[3,5] for racemic and chiral syntheses of *Corynanthe*-type indoloquinolizidine alkaloids. Interestingly, the chiral syntheses of dihydrocorynantheol [(–)-**25**], ochromianine [(–)-**35**], ophiorrhizine [(–)-**46**], and ochropposinine [(–)-**49**] described above are equivalent to chemical correlations of these alkaloids with the *Cinchona* alkaloid cinchonine [(+)-**8**], because the lactim ether [(+)-**7**] employed as a starting material can be prepared from (+)-**8** through its degradation product, cincholoipon ethyl ester [(+)-**9**].[2c,51] It is hoped that this review has quoted vivid examples in support of the statement[3b] that chemical synthesis can still be an important and powerful tool for structure elucidation of natural products (particularly of those isolated only in minute quantity, unstable, and hard to crystallize) even in this new era of highly refined spectroscopic studies.

ACKNOWLEDGMENT

We are grateful to our co-workers, whose names appear in the individual reference citations, for their important contributions to the development of this research program.

REFERENCES AND NOTES

1. (a) G. A. Cordell and J. E. Saxton, 'The Alkaloids,' Vol. 20, ed. by R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1981, Chapter 1; (b) Atta-ur-Rahman and A. Basha, 'Biosynthesis of Indole Alkaloids,' Clarendon Press, Oxford, 1983; (c) C. Szántay, G. Blaskó, K. Honty, and G. Dörnyei, 'The Alkaloids,' Vol. 27, ed. by A. Brossi, Academic Press, New York, 1986, Chapter 2.
2. (a) T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Pharm. Bull.*, 1978, **26**, 2071; (b) T. Fujii, M. Ohba, K. Yoneyama, H. Kizu, and S. Yoshifuji, *ibid.*, 1986, **34**, 669, and references cited therein; (c) T. Fujii, M. Ohba, K. Shimohata, and S. Yoshifuji, *Heterocycles*, 1987, **26**, 2949.
3. For reviews, see (a) T. Fujii, M. Ohba, and S. Yoshifuji, *Heterocycles*, 1988, **27**, 1009; (b) T. Fujii, *Yakugaku Zasshi*, 1996, **116**, 335.
4. Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations.

5. For reviews, see (a) T. Fujii and M. Ohba, 'The Alkaloids,' Vol. 22, ed. by A. Brossi, Academic Press, New York, 1983, Chapter 1; (b) T. Fujii, *Yakugaku Zasshi*, 1983, **103**, 257.
6. (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.
7. T. Fujii, M. Ohba, K. Yoneyama, and H. Kizu, *Chem. Pharm. Bull.*, 1985, **33**, 358.
8. (a) S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Chem. Commun.*, 1966, 421; (b) *Idem*, *Aust. J. Chem.*, 1966, **19**, 1951.
9. M. Nakagawa, M. Kiuchi, M. Obi, M. Tonozuka, K. Kobayashi, T. Hino, and Y. Ban, *Chem. Pharm. Bull.*, 1975, **23**, 304.
10. (a) Ref. 10 in ref. 9; (b) S. Yamada and T. Kunieda, *Chem. Pharm. Bull.*, 1967, **15**, 499; (c) L. Novák and C. Szántay, *Chem. Ber.*, 1969, **102**, 3959; (d) C. A. Scherer, C. A. Dorschel, J. M. Cook, and P. W. Le Quesne, *J. Org. Chem.*, 1972, **37**, 1083; (e) G. W. Gribble, *ibid.*, 1972, **37**, 1833; (f) H.-P. Husson, L. Chevolot, Y. Langlois, C. Thal, and P. Potier, *J. Chem. Soc., Chem. Commun.*, 1972, 930; (g) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 2614; (h) E. E. van Tamelen, J. Webber, G. P. Schiemenz, and W. Barker, *Bioorg. Chem.*, 1976, **5**, 283; (i) S. Yamada, K. Murato, and T. Shioiri, *Tetrahedron Lett.*, 1976, 1605; (j) S. J. Martinez and J. A. Joule, *Tetrahedron*, 1978, **34**, 3027; (k) E. Yamanaka, K. Nakayama, N. Yanagishima, K. Nagashima, M. Yamauchi, and S. Sakai, *Chem. Pharm. Bull.*, 1980, **28**, 2527; (l) J. E. Johansen, B. D. Christie, and H. Rapoport, *J. Org. Chem.*, 1981, **46**, 4914; (m) T. Fujii, M. Ohba, and N. Sasaki, *Heterocycles*, 1984, **22**, 1805; (n) A. I. Meyers, T. Sohda, and M. F. Loewe, *J. Org. Chem.*, 1986, **51**, 3108; (o) G. W. Gribble and D. A. Johnson, *Tetrahedron Lett.*, 1987, **28**, 5259; (p) S. B. Mandal, V. S, Giri, M. S. Sabeena, and S. C. Pakrashi, *J. Org. Chem.*, 1988, **53**, 4236; (q) M. Salas, I. K. Al-Khawaja, M. J. Thomas, and J. A. Joule, *J. Chem. Res. (S)*, 1988, 218; (r) M. Lounasmaa and R. Jokela, *Tetrahedron*, 1989, **45**, 3975; (s) G. Massiot and A. Cherif, *Bull. Soc. Chim. Fr.*, 1990, **127**, 648; (t) D. H. Hua, S. N. Bharathi, J. A. K. Panangadan, and A. Tsujimoto, *J. Org. Chem.*, 1991, **56**, 6998; (u) R. C. Bernotas and R. V. Cube, *Tetrahedron Lett.*, 1991, **32**, 161; (v) H. Waldmann, M. Braun, M. Weymann, and M. Gewehr, *Tetrahedron*, 1993, **49**, 397; (w) F. A. Farés, H. Virelizier, K. Jankowski, and G. W. Gribble, *J. Heterocycl. Chem.*, 1995, **32**, 1389; (x) E. Cheng, J. Botzem, M. J. Wanner, B. E. A. Burm, and G.-J. Koomen, *Tetrahedron*, 1996, **52**, 6725.
11. (a) T. Fujii, S. Yoshifuji, and H. Ito, *Heterocycles*, 1977, **7**, 149; (b) *Idem*, *Chem. Pharm. Bull.*, 1988, **36**, 3348.
12. T. Oishi, M. Nagai, T. Onuma, H. Moriyama, K. Tsutae, M. Ochiai, and Y. Ban, *Chem. Pharm. Bull.*, 1969, **17**, 2306.
13. (a) J. Bergman, *J. Heterocycl. Chem.*, 1970, **7**, 1071; (b) J. Bergman, J.-E. Bäckvall, and J.-O. Lindström, *Tetrahedron*, 1973, **29**, 971.

14. R. J. Sundberg, 'The Chemistry of Indoles,' Academic Press, New York, 1970, pp. 93–107.
15. T. R. Govindachari and S. Rajeswari, *Indian J. Chem.*, 1983, **22B**, 531.
16. B. Gilbert, L. D. Antonaccio, and C. Djerassi, *J. Org. Chem.*, 1962, **27**, 4702.
17. R. Verpoorte, C. L. M. Ruigrok, and A. B. Svendsen, *Planta Med.*, 1982, **46**, 149.
18. B. Gilbert, A. P. Duarte, Y. Nakagawa, J. A. Joule, S. E. Flores, J. Aguayo Brissolese, J. Campello, E. P. Carrazzoni, R. J. Owellen, E. C. Blossey, K. S. Brown, Jr., and C. Djerassi, *Tetrahedron*, 1965, **21**, 1141.
19. J.-M. Panas, A.-M. Morfaux, L. Olivier, and J. Le Men, *Ann. Pharm. Fr.*, 1972, **30**, 273.
20. E. J. Shellard and P. J. Houghton, *Planta Med.*, 1973, **24**, 13.
21. L. S. R. Arambewela and F. Khuong-Huu, *Phytochemistry*, 1981, **20**, 349.
22. 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.
23. G. M. T. Robert, A. Ahond, C. Poupat, P. Potier, C. Jollès, A. Jousselin, and H. Jacquemin, *J. Nat. Prod.*, 1983, **46**, 694.
24. Atta-ur-Rahman and K. Zaman, *Planta Med.*, 1986, 73.
25. G. Massiot, P. Thépenier, M.-J. Jacquier, L. Le Men-Olivier, R. Verpoorte, and C. Delaude, *Phytochemistry*, 1987, **26**, 2839.
26. N. Boughandjioua, L. Bengaouer, F. Hotellier, E. Seguin, F. Tillequin, M. Koch, and T. Sevenet, *J. Nat. Prod.*, 1989, **52**, 1107.
27. G. M. T. Robert, A. Ahond, C. Poupat, P. Potier, H. Jacquemin, and S. K. Kan, *J. Nat. Prod.*, 1983, **46**, 708.
28. (a) F. E. Ziegler and J. G. Sweeny, *Tetrahedron Lett.*, 1969, 1097; (b) C. Szántay and M. Bárczai-Beke, *Chem. Ber.*, 1969, **102**, 3963; (c) Ref. 10h; (d) T. Kametani, N. Kanaya, H. Hino, S.-P. Huang, and M. Ihara, *Heterocycles*, 1980, **14**, 1771; (e) *Idem*, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3168; (f) S. Takano, K. Shibuya, M. Takahashi, S. Hatakeyama, and K. Ogasawara, *Heterocycles*, 1981, **16**, 1125; (g) B. Danieli, G. Lesma, G. Palmisano, and S. Tollari, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1237; (h) R. T. Brown, M. F. Jones, and M. Wingfield, *J. Chem. Soc., Chem. Commun.*, 1984, 847; (i) M. Ihara, N. Taniguchi, K. Fukumoto, and T. Kametani, *ibid.*, 1987, 1438; (j) M. Lounasmaa, R. Jokela, B. Tirkkonen, J. Miettinen, and M. Halonen, *Heterocycles*, 1992, **34**, 321; (k) A. Diez, C. Vila, M.-E. Sinibaldi, Y. Troin, and M. Rubiralta, *Tetrahedron Lett.*, 1993, **34**, 733; (l) A. Diez, C. Vila, M.-E. Sinibaldi, Y. Troin, P. Forns, J. Castells, D. S. Grierson, H.-P. Husson, and M. Rubiralta, *An. Quim.*, 1993, **89**, 149.
29. (a) E. E. van Tamelen and J. B. Hester, Jr., *J. Am. Chem. Soc.*, 1959, **81**, 3805; (b) *Idem*, *ibid.*, 1969, **91**, 7342.
30. J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. Douglas, *Tetrahedron Lett.*, 1965, 3457.

31. C. Vamvacas, W. v. Philipsborn, E. Schlittler, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1957, **40**, 1793.
32. N. J. Dastoor, A. A. Gorman, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 213.
33. (a) Y. K. Sawa and H. Matsumura, *Chem. Commun.*, 1968, 679; (b) *Idem*, *Tetrahedron*, 1969, **25**, 5329.
34. J. Le Men, M. Zèches, and F. Sigaut, *Heterocycles*, 1982, **19**, 1807.
35. M. H. Brillanceau, C. Kan-Fan, S. K. Kan, and H.-P. Husson, *Tetrahedron Lett.*, 1984, **25**, 2767.
36. M. Ihara, N. Taniguchi, K. Yasui, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2771.
37. (a) T. Suzuki, E. Sato, K. Unno, and T. Kametani, *Heterocyles*, 1985, **23**, 835; (b) *Idem*, *Chem. Pharm. Bull.*, 1986, **34**, 1584.
38. R. L. Beard and A. I. Meyers, *J. Org. Chem.*, 1991, **56**, 2091.
39. M. Ohba, T. Ohashi, and T. Fujii, *Heterocycles*, 1991, **32**, 319.
40. T. Fujii, M. Ohba, and T. Ohashi, *Tetrahedron,* 1993, **49**, 1879.
41. (a) N. Preaux, M. Koch, and M. Plat, *Phytochemistry*, 1974, **13**, 2607; (b) N. Preaux, Ph. D. Dissertation, Université Pierre et Marie Curie–Paris VI, June 1976.
42. F. R. Fosberg, P. Boiteau, and M.-H. Sachet, *Adansonia Ser. 2*, 1977, **17**, 23.
43. (a) T. Fujii, M. Ohba, T. Tachinami, T. Ohashi, M. Koch, and E. Seguin, *Heterocycles,* 1989, **29**, 1037; (b) T. Fujii, M. Ohba, T. Tachinami, and T. Ohashi, *Chem. Pharm. Bull.*, 1991, **39**, 75.
44. D. Arbain, L. T. Byrne, D. P. Putra, M. V. Sargent, B. W. Skelton, and A. H. White, *J. Chem. Soc., Perkin Trans. 1*, 1992, 663.
45. (a) M. Ohba, S. Seto, T. Fujii, M. V. Sargent, and D. Arbain, *Heterocycles*, 1994, **38**, 1741; (b) T. Fujii, M. Ohba, and S. Seto, *Chem. Pharm. Bull.*, 1995, **43**, 49.
46. (a) N. Peube-Locou, M. Koch, M. Plat, and P. Potier, *Ann. Pharm. Fr.*, 1972, **30**, 821; (b) *Idem*, *Phytochemistry*, 1972, **11**, 2109.
47. This plant was formerly named *Ochrosia oppositifolia* (Lmk) K. Schum. For the change of name, see ref. 42.
48. (a) A. S. Amarasekera and L. S. R. Arambewela, *Fitoterapia*, 1986, **57**, 55; (b) A. A. L. Gunatilaka, H. C. Fernando, Atta-ur-Rahman, M. M. Qureshi, and S. Balasubramaniam, *Heterocycles*, 1989, **28**, 999.
49. (a) E. Seguin, M. Koch, and T. Sevenet, *J. Nat. Prod.*, 1982, **45**, 738; (b) E. Seguin, F. Hotellier, M. Koch, and T. Sevenet, *ibid.*, 1984, **47**, 687; (c) J. Bruneton, T. Sevenet, and A. Cavé, *Phytochemistry*, 1972, **11**, 3073.
50. (a) T. Fujii, M. Ohba, T. Tachinami, H. Miyajima, M. Koch, and E. Seguin, *Heterocycles,* 1986, **24**, 1215; (b) T. Fujii, M. Ohba, T. Tachinami, and H. Miyajima, *Chem. Pharm. Bull.*, 1990, **38**, 1200.
51. For the preparation of cincholoipon ethyl ester [(+)-**9**] from cinchonine [(+)-**8**], see (a) A. Kaufmann, E. Rothlin, and P. Brunnschweiler, *Ber. Dtsch. Chem. Ges.*, 1916,

49, 2299; (b) V. Prelog and E. Zalán, *Helv. Chim. Acta*, 1944, **27**, 535; (c) T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.*, 1975, **23**, 2094; (d) T. Fujii and S. Yoshifuji, *Tetrahedron*, 1980, **36**, 1539.

Received, 5th December, 1996