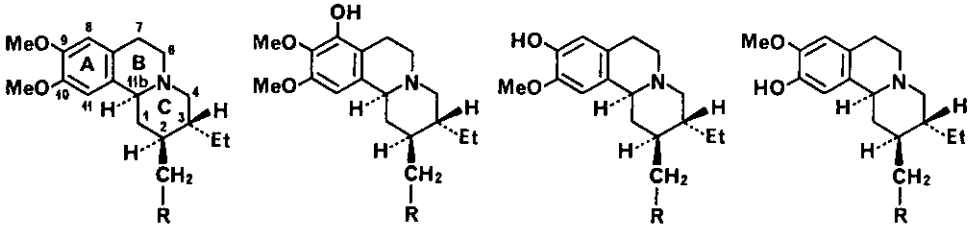
QUINOLIZIDINES. XXIII.[1] AN ALTERNATIVE SYNTHETIC ROUTE TO BENZO[a]QUINOLIZIDINE-TYPE ALANGIUM ALKALOIDS FROM ETHYL CINCHOLOIPONATE

Tozo Fujii,* Masashi Ohba, and Kaori Shimohata
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan
Shigeyuki Yoshifuji
School of Pharmacy, Hokuriku University, Kanagawa-machi, Kanazawa 920-11, Japan

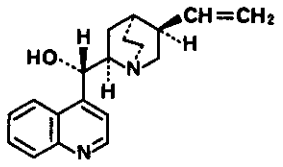
Abstract —— The trans lactam acid (+)-XX was isolated in good yield in the form of the 4-methoxybenzyl ester (+)-XXV from an equilibrated 66 : 34 mixture of the trans and cis isomers [(+)-XX and (+)-XIX], which was obtained by thermal cis–trans isomerization of the cis lactam acid (+)-XIX at 190°C for 15 min. Catalytic hydrogenolysis of (+)-XXV with 10% Pd–C and H_2 gave (+)-XX in 97% yield. This made it possible to establish an alternative synthetic route to all of the I–IV-type Alangium alkaloids from ethyl cincholoiponate [(+)-XVI], a degradation product of the Cinchona alkaloid cinchonine [(+)-V].

The Indian medicinal plant Alangium lamarckii Thwaites (Alangiaceae) is a rich source of alkaloids: Eighteen benzo[a]quinolizidine alkaloids[2,3] and 14 other alkaloids[2,4] have so far been isolated from various parts of this plant. These benzo[a]quinolizidine-type Alangium alkaloids fall into four categories according to their substitution patterns in the aromatic ring A:[5] (i) 9,10-dimethoxy type (I),

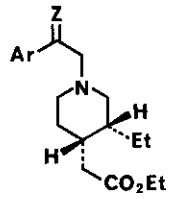


I II III IV

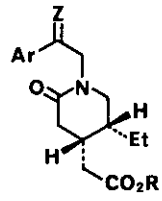
R = CH_2OH, CO_2H or a heterocyclic ring



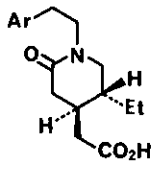
(+)-V



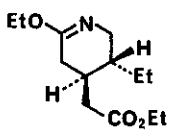
VI: Z = O
VII: Z = H, OH



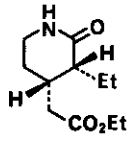
VIII: R = Et; Z = H, OH
IX: R = Et; Z = H_2
X: R = H; Z = H_2
XI: R = Et; Z = O



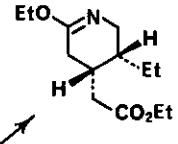
XII



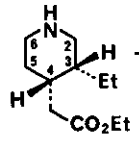
(+)-XIII



(−)-XIV

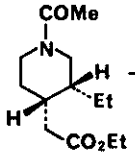


(−)-XV



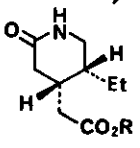
(+)-XVI

MeCOCl
Na_2CO_3



(+)-XVII

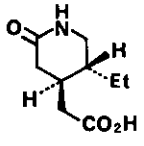
1) RuO_4
2) Al_2O_3



(+)-XVIII: R = Et
(+)-XIX: R = H

$Et_3O^+BF_4^-$

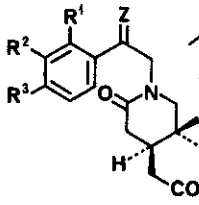
Δ (R = H)



(+)-XX

1) MeO-C6H4-CH_2OH
DCC/DMAP
2) crystn. from hexane–AcOEt

I–IV-type alkaloids

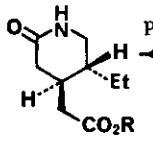


XXIa–d: Z = O
XXIIa–d: Z = H, OH
XXIIIa–f: Z = H_2

$ArCOCH_2Br$

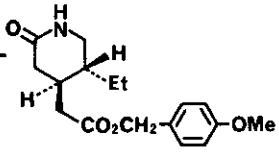
(+)-XIII

$Et_3O^+BF_4^-$



(+)-XX: R = H
(+)-XXIV: R = Et

Pd-C/H_2



(+)-XXV

a: R^1 = H; R^2 = R^3 = OMe
b: R^1 = OCH_2Ph; R^2 = R^3 = OMe
c: R^1 = H; R^2 = OCH_2Ph; R^3 = OMe
d: R^1 = H; R^2 = OMe; R^3 = OCH_2Ph
e: R^1 = H; R^2 = OH; R^3 = OMe
f: R^1 = H; R^2 = OMe; R^3 = OH

(ii) 8-hydroxy-9,10-dimethoxy type (II), (iii) 9-hydroxy-10-methoxy type (III), and (iv) 10-hydroxy-9-methoxy type (IV).[6] We have already shown that the racemic syntheses of all of these types of alkaloids are possible through the "lactim ether route"[7] or "3-acetylpyridine route"[1,5] and the chiral syntheses, through the "cincholoipon-incorporating route"[7] or "lactim ether route".[8] (−)-Ankorine (II: R = CH_2OH) was originally synthesized by us[9] from cincholoipon ethyl ester [(+)-XVI], obtainable from commercially available cinchonine [(+)-V] in 50% overall yield according to the classical degradation procedure, through a reaction sequence [(+)-XVI→VI→VII→VIII→IX→X→XII→XXIIIb→II] involving the following five main operations: (i) introduction of an appropriate phenethyl skeleton into (+)-XVI at N(1), (ii) generation of the lactam carbonyl function at C(6) (by utilizing the mercuric acetate–EDTA oxidation method for the step VII→VIII), (iii) epimerization at C(4) to produce the 3,4-trans configuration that must match the relative and absolute configurations of the I–IV-type alkaloids at the 3- and 2-positions, (iv) ring closure to complete the benzo[a]quinolizidine system, and (v) modification of the acetate side chain. In quite a recent alternative synthesis of (−)-II (R = CH_2OH),[8] the RuO_4 oxidation method and lactim ether method were utilized for operations (ii) and (i), respectively, inverting the original order of operations (i) and (ii). Thus, the N-acetyl derivative (+)-XVII, obtained from (+)-XVI by acetylation, was oxidized with a mixture of RuO_2 and 10% aqueous $NaIO_4$ to give the 6-piperidone (+)-XVIII and the 2-piperidone (−)-XIV in 55% and 27% yields, respectively. Alkaline hydrolysis of (+)-XVIII and thermal cis–trans isomerization of the resulting cis lactam acid (+)-XIX at 190°C for 15 min produced an equilibrated 66 : 34 mixture of (+)-XX and (+)-XIX. However, separation of the desired trans isomer [(+)-XX] from the mixture was so difficult that the alteration of stereochemistry in (+)-XVIII had to be done at a later stage. This led us to follow the synthetic route (+)-XVIII→(−)-XV→XI→VIII→IX→X→XII→II (R = CH_2OH).[8]

In the present study, an extension of such a hybrid of the original "cincholoipon-incorporating route" and "lactim ether route" to the chiral syntheses of the remaining I-, III-, and IV-type Alangium alkaloids was achieved with some alteration in the order of the above main operations, together with improvement in the cis–trans isomerization procedure. The preparation of the intermediate cis lactam acid (+)-XIX from (+)-XVI [through (+)-XVII and (+)-XVIII] and thermal isomerization of (+)-XIX was carried out as described previously,[8] giving a 66 : 34 mixture of the trans [(+)-XX] and cis [(+)-XIX] isomers. After many unsuccessful trials for separating the trans isomer [(+)-XX] from the mixture in the carboxylic acid level[10] or in the derivative (salt or ester) level, we found that the separation in the form of the 4-methoxybenzyl ester was very effective. Thus, the mixture of the two isomeric lactam acids was treated with 4-methoxybenzyl alcohol in CH_2Cl_2 in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP), and crystallization of the resulting oily ester fraction from hexane–AcOEt gave the 4-methoxybenzyl ester [(+)-XXV] of the trans lactam acid. The yield of (+)-XXV reached 73% [from (+)-XIX] when the following three-step procedure was repeated twice: (i) de-

benzylation of the cis lactam ester, recovered from the crystallization mother liquor, with hydrogen and 10% Pd–C catalyst, (ii) thermal isomerization of the resulting cis lactam acid at 190°C for 15 min, and (iii) esterification of the isomerized mixture with 4-methoxybenzyl alcohol as described above. Hydrogenolysis of (+)-XXV in EtOH with hydrogen and 10% Pd–C catalyst smoothly produced the trans lactam acid (+)-XX (97% yield), which was identical with an authentic sample prepared by the previously reported[11] optical resolution method. Since (+)-XX has already been converted into (−)-ankorine (II: R = CH_2OH)[8,9] and other II-type alkaloids[3b,c,12,13] through (+)-XXIV,[11] (+)-XIII,[11] (+)-XXIb,[8] XXIIb,[8] and (+)-XXIIIb,[9] the above synthesis of (+)-XX through the route (+)-XVI→(+)-XVII→(+)-XVIII→(+)-XIX→(+)-XXV→(+)-XX is formally tantamount to alternative syntheses of these II-type Alangium alkaloids from ethyl cincholoiponate [(+)-XVI].

For the chiral syntheses of the I-type Alangium alkaloids, the trans lactim ether (+)-XIII was treated with 3,4-dimethoxyphenacyl bromide as in the case of the previously reported[14] racemic series, affording (+)-XXIa in 89% yield. Reduction of (+)-XXIa with $NaBH_4$ in EtOH gave XXIIa as a diastereomeric mixture (98% yield), which furnished the known lactam ester (+)-XXIIIa[15] (92% yield) on catalytic hydrogenolysis using hydrogen and 10% Pd–C catalyst.

Two parallel sequences of conversions starting from condensations of (+)-XIII with 3-benzyloxy-4-methoxyphenacyl bromide and with 4-benzyloxy-3-methoxyphenacyl bromide produced (+)-XXIc (95% yield) and (+)-XXId (92%), XXIIc[16] (96%) and XXIId[16] (97%), and (+)-XXIIIe (96%) and (+)-XXIIIf (95%), respectively. In view of the intermediary functions of (+)-XXIIIa,[15] (+)-XXIIIe [and (+)-XXIIIc[17] obtainable from (+)-XXIIIe by O-benzylation], and (+)-XXIIIf [and (+)-XXIIId[18] obtainable from (+)-XXIIIf by O-benzylation] in the previous syntheses of the I-,[15] III-,[17,19-21] and IV-type[19,21] Alangium alkaloids by us, the above syntheses of these three intermediates represent alternative formal syntheses of such alkaloids.

In summary, the present work has thus shown that chiral syntheses of all of the I–IV-type alkaloids are possible from ethyl cincholoiponate [(+)-XVI] through the synthetic route which may be regarded as a hybrid of our original "cincholoipon-incorporating route"[7] and "lactim ether route".[7]

EXPERIMENTAL

General Notes —— All melting points are corrected. See ref. 8 for details of instrumentation and measurements. The organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, m = multiplet, q = quartet, s = singlet, t = triplet.

(4R,5R)-5-Ethyl-2-oxo-4-piperidineacetic Acid 4-Methoxybenzyl Ester [(+)-XXV] —— The cis lactam

acid (+)-XIX[8] (3.33 g, 18 mmol) was heated neat in an oil bath at 190°C for 15 min.[8] On cooling, the oily reaction mixture solidified. A mixture of this solid, dicyclohexylcarbodiimide (4.12 g, 20 mmol), 4-dimethylaminopyridine (220 mg, 1.8 mmol), and 4-methoxybenzyl alcohol (2.76 g, 20 mmol) in CH_2Cl_2 (80 ml) was stirred at room temperature in an atmosphere of N_2 for 4 h. The precipitate that resulted was removed by filtration, and the filtrate was washed successively with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a pale yellow oil. Purification of the oil by means of flash chromatography[22] [silica gel 60 (E. Merck, No. 9385), $CHCl_3$–EtOH (40 : 1, v/v)] afforded a mixture (5.05 g) of the esters of the trans and cis lactam acids [(+)-XX and (+)-XIX] as a colorless oil. The mixture was crystallized from hexane–AcOEt (2 : 1, v/v) to give the trans lactam ester (+)-XXV (2.91 g). The ^{13}C nmr spectroscopic analysis[23] of this sample indicated that it was free from the cis isomer. The mother liquor of the above crystallization was concentrated in vacuo to leave a slightly yellow oil, which was dissolved in EtOH (60 ml). The ethanolic solution was hydrogenated over 10% Pd–C (700 mg) at atmospheric pressure and 22°C for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The semicrystalline residue was washed with Et_2O to recover crude (+)-XIX as a colorless solid (1.05 g). Repetition of the above sequence of conversions starting from this solid was then carried out twice, giving further crops (0.82 g and 0.27 g) of (+)-XXV. The total yield of (+)-XXV was 4.00 g [73% from (+)-XIX]. Further recrystallization of (+)-XXV from hexane–AcOEt (2 : 1, v/v) afforded an analytical sample as colorless needles, mp 79.5–80.5°C; $[\alpha]_D^{25}$ +49.0° (c 0.50, EtOH); ms m/z: 305 (M^+); ir ν_{max}^{Nujol} cm^{-1}: 3210 (NH), 1721 (ester CO), 1675 (lactam CO); ^1H nmr ($CDCl_3$) δ: 0.88 (3H, t, J = 7 Hz, CCH_2Me), 3.81 (3H, s, OMe), 5.06 (2H, s, CO_2CH_2), 6.43 (1H, br, NH), 6.8–7.0 [2H, m, H(3') and H(5')], 7.2–7.4 [2H, m, H(2') and H(6')];[24] ^{13}C nmr ($CDCl_3$) δ: 11.0 (CCH_2Me), 23.5 (CCH_2Me), 33.5 [C(4)], 35.8 (CH_2CO_2), 38.1 [C(5)], 38.3 [C(3)], 44.6 [C(6)], 55.2 (OMe), 66.3 (CO_2CH_2), 114.0 [C(3') and C(5')], 127.8 [C(1')], 130.2 [C(2') and C(6')], 159.7 [C(4')], 171.8 [C(2) and CO_2CH_2].[24] Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.93; H, 7.73; N, 4.64.

(4R,5R)-5-Ethyl-2-oxo-4-piperidineacetic Acid [(+)-XX] —— A solution of (+)-XXV (4.58 g, 15 mmol) in EtOH (150 ml) was hydrogenated over 10% Pd–C (1.5 g) at an atmospheric pressure and 23°C for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The resulting semicrystalline solid was triturated with Et_2O, and the insoluble material was collected by filtration to yield (+)-XX (2.69 g, 97%) as a colorless solid, mp 122.5–124°C. Recrystallization of the solid from EtOH afforded a pure sample as colorless prisms, mp 123–124°C; $[\alpha]_D^{25}$ +82.8° (c 0.50, EtOH). This sample was identical [by mixture melting point test and comparison of ir (Nujol) and ^1H nmr (Me_2SO-d_6) spectra and specific rotation] with authentic (+)-XX.[11]

(4R,5R)-1-(3,4-Dimethoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-XXIa] —— A solution of (+)-XIII[11] (362 mg, 1.5 mmol) and 3,4-dimethoxyphenacyl bromide[25] (428 mg, 1.65 mmol) in $HCONMe_2$ (1 ml) was stirred at 60–65°C for 8 h. For removal of the excess bromide, the reaction mixture, after addition of pyridine (0.5 ml), was stirred at room temperature overnight and then concentrated in vacuo. The oily residue was partitioned by extraction with a mixture of benzene (40 ml) and H_2O (10 ml). The benzene extracts were washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a pale yellow oil. The oil was purified by means of flash chromatography[22] [silica gel 60 (E. Merck, No. 9385), AcOEt–hexane (2 : 1, v/v)] to give (+)-XXIa (523 mg, 89%) as a colorless oil, $[\alpha]_D^{22}$ +29.7° (c 0.50, EtOH); ms m/z: 391 (M^+). The ir (neat) and ^1H nmr ($CDCl_3$) spectra of this sample were identical with those of authentic (±)-XXIa.[14]

(4R,5R)-1-(3-Benzyloxy-4-methoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-XXIc] —— A mixture of (+)-XIII[11] (362 mg, 1.5 mmol), 3-benzyloxy-4-methoxyphenacyl bromide[25b] (553 mg, 1.65 mmol), and $HCONMe_2$ (1 ml) was stirred at 60–65°C for 8 h. After cooling, pyridine (0.5 ml) was added and the mixture was stirred at room temperature overnight. The reaction mixture was worked up as described above for (+)-XXIa, affording (+)-XXIc (663 mg, 95%) as a colorless oil, $[\alpha]_D^{22}$ +23.8° (c 0.50, EtOH); ms m/z: 467 (M^+). The ir ($CHCl_3$) and ^1H nmr ($CDCl_3$) spectra of this specimen were identical with those of authentic (±)-XXIc.[26]

(4R,5R)-1-(4-Benzyloxy-3-methoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-XXId] —— A stirred mixture of (+)-XIII[11] (483 mg, 2.0 mmol) and 4-benzyloxy-3-methoxyphenacyl bromide[27] (737 mg, 2.2 mmol) in $HCONMe_2$ (1 ml) was heated at 60–65°C for 8 h. After cooling, the reaction mixture was diluted with pyridine (0.5 ml), stirred at room temperature overnight, and worked up as described above for (+)-XXIa, giving (+)-XXId (862 mg, 92%) as a slightly yellow solid, mp 84–86°C. Recrystallization of the solid from hexane–AcOEt (2 : 1, v/v) afforded an analytical sample as colorless prisms, mp 86–87°C; $[\alpha]_D^{22}$ +25.6° (c 0.50, EtOH); ms m/z: 467 (M^+); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727 (ester CO), 1688 (ArCO), 1638 (lactam CO). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.33; H, 7.14; N, 3.19.

(4R,5R)-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (XXIIa) —— A solution of (+)-XXIa (470 mg, 1.2 mmol) in EtOH (10 ml) was stirred under ice-cooling, and $NaBH_4$ (45 mg, 1.2 mmol) was added portionwise. After the mixture had been stirred at room temperature for 4 h, acetone (0.5 ml) was added. The resulting mixture was further stirred at room temperature for 15 min and then concentrated in vacuo. The residual oil was partitioned by extraction with a mixture of benzene and H_2O. The benzene extracts were washed with saturated aqueous

NaCl, dried, and concentrated to leave a diastereomeric mixture of XXIIa (461 mg, 98%) as a colorless oil, $[\alpha]_D^{26}$ +56.9° (c 0.50, EtOH); ms m/z: 393 (M^+); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1729 (ester CO), 1620 (lactam CO); ^1H nmr ($CDCl_3$) δ: 0.78 and 0.82 (3H, t each, J = 7 Hz, diastereomeric $CCH_2\underline{Me}$'s), 1.26 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.87 and 3.90 (3H each, s, two OMe's), 4.14 (2H, q, J = 7 Hz, $O\underline{CH_2}$-Me), 4.85–5.05 [1H, m, $ArC\underline{H}(OH)$], 6.75–7.05 (3H, m, aromatic protons).

(4R,5R)-1-[2-(3-Benzyloxy-4-methoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (XXIIc) —— A solution of (+)-XXIc (608 mg, 1.3 mmol) in EtOH (10 ml) was stirred under ice-cooling, and $NaBH_4$ (50 mg, 1.3 mmol) was added portionwise. The mixture was then stirred at room temperature for 4 h and worked up as described above for XXIIa to give a diastereomeric mixture of XXIIc (587 mg, 96%) as a colorless oil, $[\alpha]_D^{26}$ +46.1° (c 0.50, EtOH); ms m/z: 469 (M^+). This sample was identical [by comparison of ir ($CHCl_3$) and ^1H nmr ($CDCl_3$) spectra] with authentic (±)-XXIIc.[26]

(4R,5R)-1-[2-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (XXIId) —— A mixture of (+)-XXId (561 mg, 1.2 mmol) and EtOH (10 ml) was stirred under ice-cooling, and $NaBH_4$ (45 mg, 1.2 mmol) was added portionwise. After stirring was continued at room temperature for 4 h, the reaction mixture was worked up as described above for XXIIa, giving a diastereomeric mixture of XXIId (549 mg, 97%) as a colorless oil, $[\alpha]_D^{26}$ +47.6° (c 0.50, EtOH); ms m/z: 469 (M^+). The ir (neat) and ^1H nmr ($CDCl_3$) spectra of this sample were identical with those of authentic (±)-XXIId.[26]

(4R,5R)-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-XXIIIa] —— A solution of XXIIa (393 mg, 1.0 mmol) in EtOH (20 ml) containing 70% aqueous $HClO_4$ (0.2 ml) was hydrogenated over 10% Pd–C (300 mg) at 3.6–3.8 atmospheric pressure and room temperature for 16 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to leave an almost colorless oil, which was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated to give (+)-XXIIIa (345 mg, 92%) as a colorless oil, $[\alpha]_D^{22}$ +66.4° (c 1.00, EtOH). This sample was identical [by comparison of ir (neat) and ^1H nmr ($CDCl_3$) spectra and specific rotation] with authentic (+)-XXIIIa.[15]

(4R,5R)-5-Ethyl-1-(3-hydroxy-4-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-XXIIIe] —— A solution of XXIIc (470 mg, 1.0 mmol) in EtOH (20 ml) containing 70% aqueous $HClO_4$ (0.2 ml) was hydrogenated over 10% Pd–C (300 mg) at atmospheric pressure and room temperature for 20 h. The reaction mixture was worked up in a manner similar to that described above for (+)-XXIIIa, giving (+)-XXIIIe (350 mg, 96%) as a colorless oil, $[\alpha]_D^{27}$ +69.8° (c 0.50, EtOH). This sample was identical

[by comparison of ir ($CHCl_3$) and ^1H nmr ($CDCl_3$) spectra and specific rotation] with authentic (+)-XXIIIe.[17]

(4R,5R)-5-Ethyl-1-(4-hydroxy-3-methoxyphenethyl)-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-XXIIIf] —— A solution of XXIId (470 mg, 1.0 mmol) in EtOH (20 ml) containing 70% aqueous $HClO_4$ (0.2 ml) was hydrogenated over 10% Pd-C (300 mg) at atmospheric pressure and room temperature for 16 h. The reaction mixture was worked up as described above for (+)-XXIIIa, affording (+)-XXIIIf (347 mg, 95%) as a colorless oil, $[\alpha]_D^{27}$ +64.3° (c 0.50, EtOH). The oil was identical [by comparison of ir ($CHCl_3$) and ^1H nmr ($CDCl_3$) spectra and specific rotation] with authentic (+)-XXIIIf.[18]

ACKNOWLEDGMENT We are pleased to acknowledge the support of this work by a Grant-in-Aid for Scientific Research (No. 61570997) from the Ministry of Education, Science and Culture, Japan.

REFERENCES

1. Paper XXII in this series, T. Fujii, M. Ohba, and J. Sakaguchi, Chem. Pharm. Bull., in press.
2. For recent reviews, see (a) T. Fujii and M. Ohba, 'The Alkaloids,' Vol. XXII, ed. by A. Brossi, Academic Press, New York, Chapter 1, 1983; (b) T. Fujii, Yakugaku Zasshi, 1983, 103, 257; (c) W. Wiegrebe, W. J. Kramer, and M. Shamma, J. Nat. Prod., 1984, 47, 397.
3. For alancine, see (a) S. K. Chattopadhyay, D. J. Slatkin, P. L. Schiff, Jr., and A. B. Ray, Heterocycles, 1984, 22, 1965; (b) T. Fujii, M. Ohba, A. Yonezawa, J. Sakaguchi, S. K. Chattopadhyay, D. J. Slatkin, P. L. Schiff, Jr., and A. B. Ray, ibid., 1986, 24, 345; (c) T. Fujii, M. Ohba, A. Yonezawa, and J. Sakaguchi, Chem. Pharm. Bull., in press.
4. (a) S. C. Pakrashi, R. Mukhopadhyay, R. R. Sinha, P. P. Ghosh Dastidar, B. Achari, and E. Ali, Indian J. Chem., 1985, 24B, 19; (b) A. Bhattacharjya, R. Mukhopadhyay, and S. C. Pakrashi, Tetrahedron Lett., 1986, 27, 1215; (c) For the revised absolute configuration of venoterpine, see T. Ravao, B. Richard, M. Zeches, G. Massiot, and L. Le Men-Olivier, ibid., 1985, 26, 837.
5. T. Fujii, M. Ohba, and S. Akiyama, Chem. Pharm. Bull., 1985, 33, 5316.
6. Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations. The optical rotation descriptors (+) and (−) are omitted in the cases where the optically active compounds are mixtures of diastereoisomers or they are represented by general formulas.
7. For this synthetic route, see ref. 8 and references cited therein.
8. T. Fujii, M. Ohba, K. Yoneyama, H. Kizu, and S. Yoshifuji, Chem. Pharm. Bull., 1986, 34, 669.
9. (a) S. Yoshifuji and T. Fujii, Tetrahedron Lett., 1975, 1965; (b) T. Fujii and S. Yoshifuji, J. Org. Chem., 1980, 45, 1889.
10. In contrast to this difficulty in the chiral series, the easy separation of a mixture of the

corresponding racemic modifications [(±)-XX and (±)-XIX] into its components by fractional crystallization from EtOH has been reported: (a) T. Fujii, Chem. Pharm. Bull., 1958, 6, 591; (b) T. Fujii, S. Yoshifuji, and M. Tai, ibid., 1975, 23, 2094.

11. T. Fujii, M. Ohba, K. Yoneyama, and H. Kizu, Chem. Pharm. Bull., 1985, 33, 358.
12. (a) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, Heterocycles, 1977, 8, 175; (b) T. Fujii, K. Yamada, S. Minami, S. Yoshifuji, and M. Ohba, Chem. Pharm. Bull., 1983, 31, 2583.
13. (a) T. Fujii, H. Kogen, and M. Ohba, Tetrahedron Lett., 1978, 3111; (b) T. Fujii, H. Kogen, S. Yoshifuji, and M. Ohba, Chem. Pharm. Bull., 1985, 33, 1946.
14. T. Fujii and S. Yoshifuji, Chem. Pharm. Bull., 1979, 27, 1486.
15. (a) T. Fujii and S. Yoshifuji, Tetrahedron Lett., 1975, 731; (b) Idem, Tetrahedron, 1980, 36, 1539.
16. Obtained as a diastereomeric mixture.
17. (a) T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, Tetrahedron Lett., 1979, 4955; (b) T. Fujii and M. Ohba, Chem. Pharm. Bull., 1985, 33, 583.
18. (a) T. Fujii, M. Ohba, and H. Suzuki, Heterocycles, 1982, 19, 705; (b) Idem, Chem. Pharm. Bull., 1985, 33, 1023.
19. (a) T. Fujii and M. Ohba, Heterocycles, 1982, 19, 857; (b) Idem, Chem. Pharm. Bull., 1985, 33, 5264.
20. (a) T. Fujii, M. Ohba, H. Hatakeyama, C. Kan-Fan, and H.-P. Husson, Heterocycles, 1986, 24, 317; (b) T. Fujii, M. Ohba, and H. Hatakeyama, Chem. Pharm. Bull., 1987, 35, 2355.
21. (a) T. Fujii, M. Ohba, H. Suzuki, S. C. Pakrashi, and E. Ali, Heterocycles, 1982, 19, 2305; (b) T. Fujii, M. Ohba, E. Ali, H. Suzuki, and J. Sakaguchi, Chem. Pharm. Bull., 1987, 35, 2755.
22. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 1978, 43, 2923.
23. T. Fujii, M. Ohba, S. Yoshifuji, and S. Akiyama, Chem. Pharm. Bull., 1985, 33, 1062, and references cited therein.
24. For convenience, each position of the aromatic ring is indicated by a primed number.
25. (a) C. Mannich and F. L. Hahn, Ber. Dtsch. Chem. Ges., 1911, 44, 1542; (b) T. Fujii, S. Yoshifuji, and M. Ohba, Chem. Pharm. Bull., 1978, 26, 3218.
26. T. Fujii and M. Ohba, Chem. Pharm. Bull., 1985, 33, 144.
27. B. Leopold, Acta Chem. Scand., 1950, 4, 1523 (Chem. Abstr., 1951, 45, 7049g).

Received, 13th July, 1987