Quinolizidines. VIII. Structure and Synthesis of the Alangium Alkaloid Alangicine : Syntheses of (±)- and (+)-Alangicines

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Quinolizidines. VIII.[1] Structure and Synthesis of the *Alangium* Alkaloid Alangicine: Syntheses of (±)- and (+)-Alangicines

TOZO FUJII,* KOICHIRO YAMADA, SHINZABURO MINAMI, SHIGEYUKI YOSHIFUJI, and MASASHI OHBA

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

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The first total synthesis of alangicine (**3**), an *Alangium lamarckii* alkaloid, has been achieved in the form of a racemic modification by means of an initial alkaline hydrolysis of the (±)-tricyclic ester **6** and succeeding steps proceeding through the intermediates (±)-**7**, (±)-**10**, and (±)-**9**. A parallel synthetic route starting with the (−)-tricyclic ester **6**, derived from (+)-cincholoipon ethyl ester (**8**), produced the chiral target molecule (+)-**3** *via* the intermediates (−)-**7**, (−)-**10**, and **9**. The identity of the synthetic (+)-**3** with alangicine unequivocally established the structure and absolute stereochemistry of this alkaloid. The ^{13}C nuclear magnetic resonance spectra of (±)-alangicine (**3**) and the ipecac and *Alangium* alkaloid psychotrine (**18**) confirmed their endocyclic double bond structures in the dihydroisoquinoline moiety. Catalytic reductions of **11**, (±)-**12**, and **15** using hydrogen and Pd-C were investigated, and the results have shown that hydrogenolysis of the benzyloxy group proceeds much faster than saturation of the endocyclic C=N bond.

Keywords——alangicine; psychotrine; structure; absolute configuration; stereoselective synthesis; ^{13}C NMR; CD; benzyl ether; hydrogenolysis

In 1967, Pakrashi and Ali reported the isolation of alangicine, a phenolic benzoquinolizidine alkaloid, from the Indian medicinal plant *Alangium lamarckii* THWAITES (family *Alangiaceae*) and proposed the gross structure **1** for this base largely on the basis of mass spectral evidence and biogenetic considerations.[2] However, the exact location of the phenolic hydroxyl group in ring A and the stereochemistry about ring C remained to be determined. In this paper, we present the details of our synthetic work in both the racemic and chiral series, proving that the structure **3** (absolute configuration shown[3]) is a complete expression for alangicine. Brief accounts of the results recorded here have been published in preliminary form.[4,5]

Prior to the commencement of the present study, the originally proposed gross structure **2**[6] for ankorine, a co-occurring alkaloid,[6,7] had already been altered to the complete expression **4** as a result of the synthesis of the target molecules (±)-**4**[8,9] and (−)-**4**.[10] On the basis of the assumption that the structure of the benzoquinolizidine moiety is the same in both alangicine and ankorine, we first selected the racemic target molecule (±)-**3** for synthesis with a view to establishing the structure and relative stereochemistry of alangicine. The key intermediate in the synthesis of (±)-**3** was the (±)-tricyclic ester **6**, and it was certainly convenient that a seven-step synthesis of this ester from the (±)-lactam ester **5** had already been developed during our recent synthetic study of (±)-ankorine (**4**).[8] On hydrolysis with aqueous NaOH in EtOH at 20 °C, (±)-**6** produced the (±)-amino acid **7** in 99% yield. Condensation of (±)-**7** with 3-benzyloxy-4-methoxyphenethylamine in dimethylformamide (DMF) at 20 °C using the coupling reagent[11] diethyl phosphorocyanidate[12] in the presence of Et_3N furnished the (±)-amide **10** in 79% yield. On the other hand, application of the dicyclohexylcarbodiimide method to this condensation gave an unsatisfactory result. The (±)-amide **10** was then subjected to Bischler–Napieralski cyclization with polyphosphate

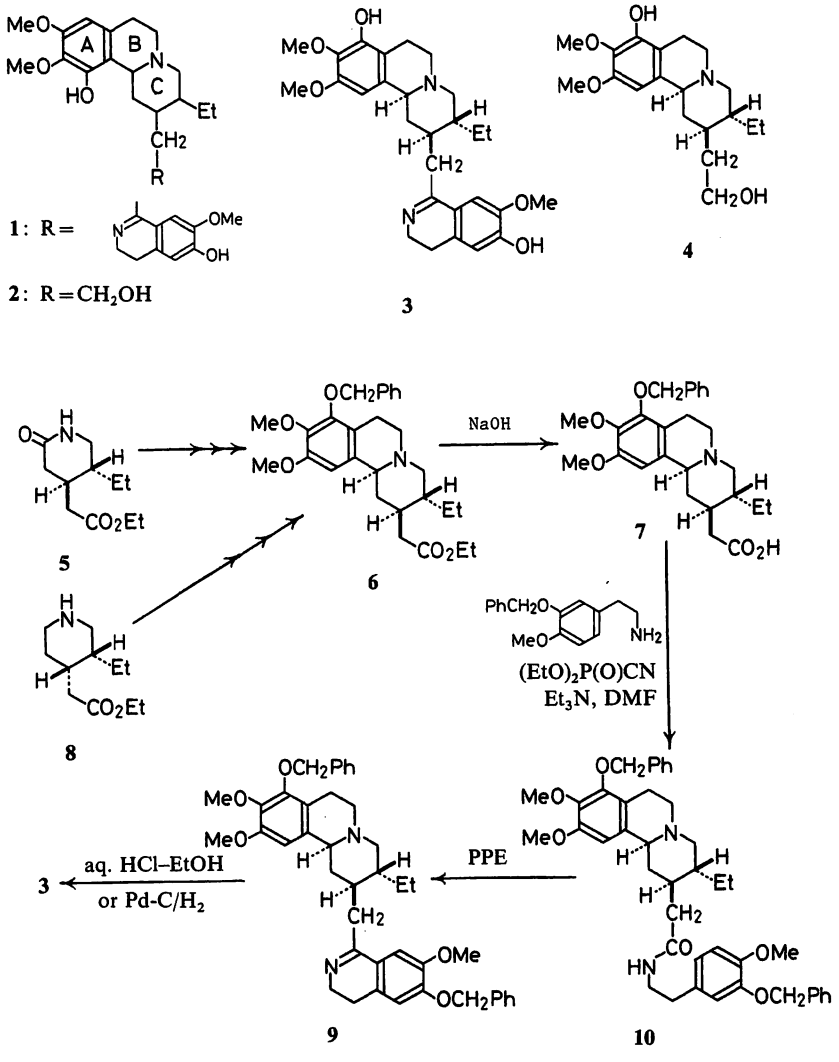
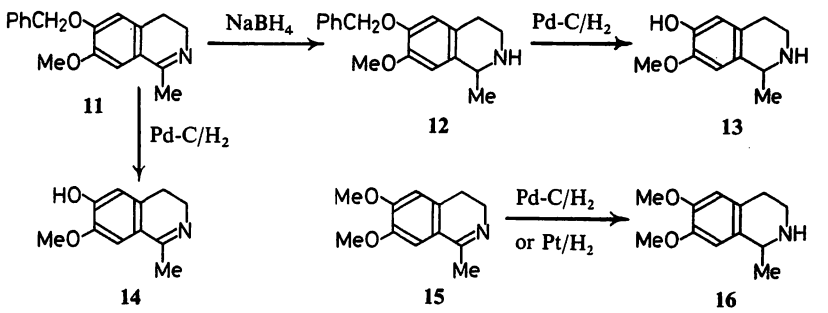


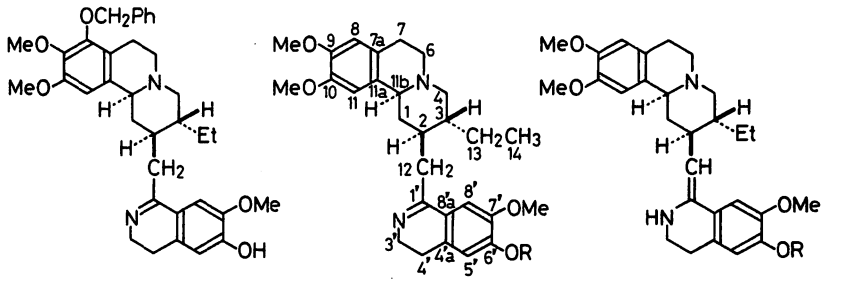
Chart 1

ester (PPE)[13,14] in boiling $CHCl_3$ to afford the (±)-base **9** in 94% yield. Finally, debenzylation of (±)-**9** by refluxing in 10% aqueous HCl–EtOH for 15 h gave the desired compound (±)-**3** (74% yield), which was characterized as the triethanolate after recrystallization from EtOH.

An alternative way to debenzylate (±)-**9** to (±)-**3** would be catalytic hydrogenolysis using hydrogen and Pd-C as a catalyst, if the C=N bond in the dihydroisoquinoline moiety could be kept intact during the reaction. In order to test the feasibility of this method catalytic reductions of the model compounds **11**, (±)-**12**, and **15** were investigated. When the (±)-tetrahydroisoquinoline **12**, prepared by $NaBH_4$ reduction of **11**, was hydrogenated in EtOH over 10% Pd-C at 1 atm and 20 °C for 40 min, the debenzylated product (±)-**13** was obtained in 89% yield. A similar hydrogenation of **15** gave the corresponding tetrahydroisoquinoline (±)-**16** in 97% yield but required 250 min for completion, whereas the use of Adams catalyst in this hydrogenation shortened the reaction time to 20 min. These results suggested that preferential debenzylation in **11** over saturation of the C=N bond might occur

under similar conditions. Indeed, this proved to be the case: debenzylation of **11** in EtOH with hydrogen and 10% Pd-C at 1 atm and 22 °C was completed within 12 min to give **14** as a sole product in 97% yield.

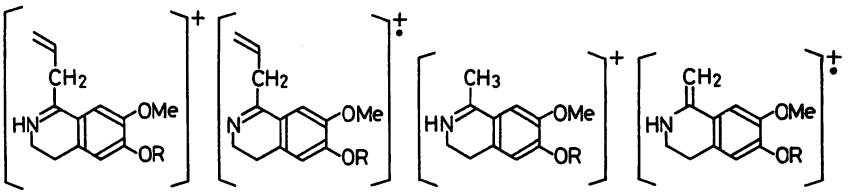




17

18: R=H
19: R=Me

20: R=H
21: R=Me



22: R=H (*m/e* 216)	**25**: R=H (*m/e* 215)	**28**: R=H (*m/e* 192)	**31**: R=H (*m/e* 191)
23: R=Me (*m/e* 230)	**26**: R=Me (*m/e* 229)	**29**: R=Me (*m/e* 206)	**32**: R=Me (*m/e* 205)
24: R=PhCH$_2$ (*m/e* 306)	**27**: R=PhCH$_2$ (*m/e* 305)	**30**: R=PhCH$_2$ (*m/e* 282)	**33**: R=PhCH$_2$ (*m/e* 281)

Chart 2

When the free base (±)-**9** was hydrogenated similarly at 19—30 °C for 2 h, uptake of hydrogen was incomplete owing to precipitation of a yellow solid during the reaction, and the desired product (±)-**3** was obtained in only 3% yield with recovery of 14% of (±)-**9**. The main product was the monodebenzylated derivative (±)-**17** (48% yield), which yielded (±)-**3** on treatment with boiling 2 N aqueous HCl for 5 h. The 6′-hydroxy structure of the monodebenzylated product was assigned on the basis of the following mass spectral study. Psychotrine (**18**) and *O*-methylpsychotrine (**19**) are among the seven alkaloids isolated from the ipecac roots,[15] and the former has also been found in *A. lamarckii*.[16] A detailed discussion of the mass spectra of the two alkaloids has been given by Budzikiewicz *et al.*,[16] who detected the

fragments **22**, **25**, **28**, **31**, **23**, **26**, **29**, and **32** originated from their dihydroisoquinoline moieties. Paralleling this fragmentation pattern, the mass spectrum of (±)-**9** showed peaks at *m/e* 306, 305, 282, and 281 corresponding to the fragments **24**, **27**, **30**, and **33**, respectively. On the other hand, (±)-**17** derived from the above hydrogenolysis of (±)-**9** failed to show these four peaks, indicating its debenzylated site to be in the dihydroisoquinoline moiety. The solubility problem encountered during the above hydrogenolysis of the free base (±)-**9** was then overcome by substituting the hydrochloride salt for the base: the crude hydrochloride, presumed to be (±)-**9**·2HCl, was hydrogenated in EtOH over 10% Pd-C at 1 atm and 19—50 °C for 9 h, and (±)-**3** was obtained in 70% yield together with a small amount (9% yield) of the monodebenzylated product (±)-**17**.

The ultraviolet (UV) (in EtOH or 0.1 N aqueous NaOH) and mass spectra of the triethanolate of (±)-**3** described above were found to match those of natural alangicine. An ethanol-free sample of (±)-**3** was prepared by dissolving the triethanolate in $CHCl_3$ and evaporating the solution to dryness. Comparison of the infrared (IR) (in $CHCl_3$), nuclear magnetic resonance (NMR) (in $CDCl_3$, after treatment with D_2O), and mass spectra and thin-layer chromatographic (TLC) behavior of the solvent-free samples of (±)-**3** and natural alangicine[17] confirmed their identity. Thus, the structure and relative stereochemistry of alangicine have been rigorously established to be **3**.

At this stage, the problem of the position of the double bond in the dihydroisoquinoline moiety of alangicine and psychotrine deserves consideration. Psychotrine and *O*-methylpsychotrine have been assigned the structures **18** and **19**, respectively, in which the double bond in the dihydroisoquinoline moiety is endocyclic.[15] However, Schuij *et al.*[18] recently claimed the double bond to be exocyclic, as in **20** and **21**, on the basis of their mass spectral study. On the contrary, Fujii *et al.*[1] have more recently presented ^1H and ^{13}C NMR and UV spectroscopic evidence that *O*-methylpsychotrine has the genuine 3,4-dihydroisoquinoline structure **19**, not the exocyclic double bond structure **21**, both in its free base and protonated forms. By analogy, they considered that psychotrine and alangicine also have the genuine 3,4-dihydroisoquinoline structures as shown in formulas **18** and **3**.[1] We now present ^{13}C NMR spectroscopic evidence in support of their view. Table I lists the chemical shifts for all carbons of natural (+)-psychotrine and (±)-alangicine, which have been assigned as in the case[1] of *O*-methylpsychotrine (**19**).[19] It may be seen that (±)-alangicine has fifteen sp^3 carbons and thirteen sp^2 carbons. This differs from the exocyclic double bond structure (type **20**) in having one more sp^3 carbon and one less sp^2 carbon. The di(hydrogen oxalate) [(±)-**3**·2($CO_2H)_2$] has also been found to have carbons similar in kind and in number, aside from the carboxyl carbons. These spectral data, therefore, are consistent with the endocyclic double bond structure **3** of alangicine, both in its free base and protonated forms. Although the signals assignable to the three methoxyl carbons are not differentiated in the case of (+)-psychotrine, other carbon signals have been found to correspond to those of (±)-**3**, indicating that the double bond in psychotrine is also endocyclic, as in structure **18**.

With the structure and relative stereochemistry of alangicine unequivocally established as **3**, we proceeded to the problem of its absolute stereochemistry. The assumption that the absolute configuration of all three asymmetric centers in alangicine is the same as that in the co-occurring alkaloids ankorine (**4**) and psychotrine (**18**) was supported by the observation of a close resemblance between the circular dichroism (CD) curves of alangicine and its 8-deoxy congener psychotrine (**18**), which are shown in Fig. 1. In order to confirm this, we selected for synthesis the target stereoformula **3** (absolute configuration shown) rather than its mirror image. The chiral synthesis of **3** started with the (−)-tricyclic ester **6**, our (−)-ankorine precursor[5,10] available from ethyl cincholoiponate [(+)-**8**] by a ten-step synthesis, and followed essentially the same route as adopted for the racemic series (Chart 1). Treatment of (−)-**6** in EtOH with 2 N aqueous NaOH at 25 °C gave the (−)-amino acid **7** in 96% yield. The

TABLE I. ^{13}C Chemical Shifts of (+)-Psychotrine (**18**) and (±)-Alangicine (**3**)

Carbon	Chemical shift[a]			
	(+)-Psychotrine (**18**)	(±)-Alangicine (**3**)		
	Free base	Free base		Di(hydrogen oxalate)[b]
	in $CDCl_3$	in $CDCl_3$	in $(CD_3)_2SO$	in $(CD_3)_2SO$
C (1)	37.2	36.6	37.0	33.7
C (2)	40.2	40.7	39.2	38.0[h]
C (3)	42.4	42.1	41.8	38.4[h]
C (4)	61.1	61.0	60.7	56.9
C (6)	52.4	51.7	51.4	48.9
C (7)	29.1	23.6	23.6	21.0
C (7a)	126.6	115.1	115.1	112.8
C (8)	111.4	146.8	147.0[e]	147.2[i]
C (9)	147.0[c]	133.5[d]	133.4[f]	134.1[j]
C (10)	147.1[c]	150.1	150.4	151.4
C (11)	108.2	100.0	99.0	99.8
C (11a)	129.9	134.0[d]	134.0[f]	128.3
C (11b)	62.3	62.3	62.2	60.4
C (12)	38.6	37.7	38.4	35.2
C (13)	23.7	23.6	23.0	22.2
C (14)	11.3	11.2	11.0	10.2
C (1′)	167.5	169.1	165.5	174.5
C (3′)	45.0	43.0	45.0	41.0
C (4′)	26.3	26.6	25.7	24.7
C (4′a)	133.4	134.7[d]	132.5	135.2[j]
C (5′)	115.4	117.0	115.3	115.4
C (6′)	155.9	163.1	154.0	155.9
C (7′)	147.4[c]	148.9	147.1[e]	147.4[i]
C (8′)	109.1	109.8	110.1	113.4
C (8′a)	117.5	112.8	117.5	116.2
OMe at C (9)	55.8	60.7	60.1	60.2
OMe at C (10)	55.8	55.6	55.7[g]	56.1[k]
OMe at C (7′)	55.8	55.6	55.2[g]	55.5[k]
CO_2H	—	—	—	164.9

a) In ppm downfield from internal Me_4Si.
b) Prepared *in situ* by adding two equivalent moles of anhydrous oxalic acid to a solution of (±)-**3** in $(CD_3)_2SO$.
c—*k*) Assignments indicated by a given superscript may be reversed.

next coupling of (−)-**7** with 3-benzyloxy-4-methoxyphenethylamine was effected in DMF at 25 °C *via* the agency of diethyl phosphorocyanidate[11] in the presence of Et_3N, giving the (−)-amide **10** in 88% yield. Cyclization of (−)-**10** with PPE in boiling $CHCl_3$ and debenzylation of the resulting base **9** in boiling 10% aqueous HCl–EtOH furnished the desired product (+)-**3** in 67% overall yield from (−)-**10**. The synthetic (+)-**3** was identical with a sample of natural (+)-alangicine.

The results of the above synthetic and ^{13}C NMR spectroscopic studies have thus proved that the stereoformula **3** is the unique and complete expression for alangicine. Interestingly, alangicine has turned out to be the 8-hydroxy congener of psychotrine (**18**).

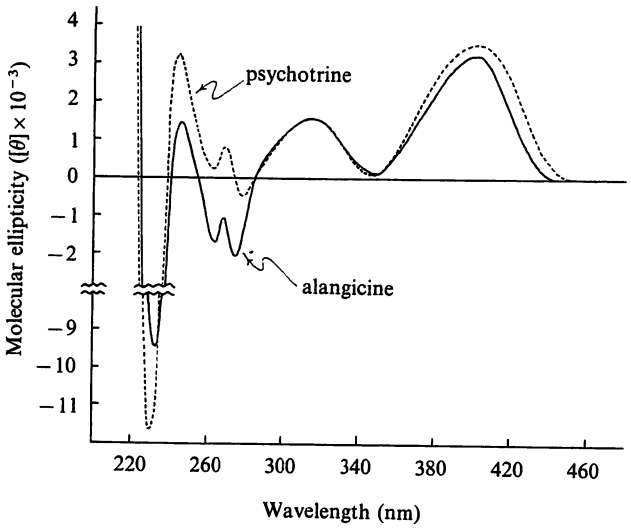


Fig. 1. CD Curves of Alangicine (**3**) and Psychotrine (**18**) in EtOH at 26 °C

Experimental

General Comments——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. CD spectra were measured with a JASCO J-20 ORD-CD spectrometer. See refs. 1 and 10*b* for details of other instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet.

(±)-8-Benzyloxy-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2β-acetic Acid [(±)-7]——A solution of (±)-**6**[8] (424 mg, 0.91 mmol) and 2 N aqueous NaOH (2 ml) in EtOH (4 ml) was kept at 20 °C for 24 h. The reaction mixture was concentrated *in vacuo*, and H_2O (10 ml) was added to the residue. The resulting aqueous solution was neutralized with 2 N aqueous HCl (2 ml) and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to leave (±)-**7** (394 mg, 99%) as slightly greenish plates, mp 156—163 °C. Recrystallizations from EtOH–hexane (1 : 1, v/v) gave an analytical sample as colorless plates, mp 168—169 °C; MS *m/e*: 439 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200—2560 (weak, N^+H), 1695 (b, COOH and COO^-); ^1H NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.84 and 3.87 (6H, s each, two MeO's), 4.99 and 5.07 (1H each, AB type d's, J=11 Hz, $PhC\underline{H}_2O$), 6.56 (1H, s, $H_{(11)}$), 7.24—7.60 (5H, m, $\underline{Ph}CH_2O$), 13.2 (1H, b, COOH). *Anal.* Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19. Found: C, 70.83; H, 7.82; N, 3.29.

The picrolonate of (±)-**7**: A small portion of (±)-**7** was dissolved in EtOH, and a saturated solution of picrolonic acid in EtOH was added. After the mixture had been kept in a refrigerator overnight, the yellow precipitate that resulted was filtered off and recrystallized from EtOH to yield the picrolonate as yellow prisms, mp 230—232 °C (dec.). *Anal.* Calcd for $C_{36}H_{41}N_5O_{10}$: C, 61.44; H, 5.87; N, 9.95. Found: C, 61.41; H, 6.15; N, 9.76.

(2*R*,3*R*,11b*S*)-(−)-8-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid [(−)-7]——The tricyclic ester (−)-**6**[5,10] was hydrolyzed at 25 °C as described above for the racemic series, and the resulting crude acid (mp 183—184 °C; 96% yield) was recrystallized from EtOH to produce an analytical sample as colorless prisms, mp 189—192 °C; $[\alpha]_D^{16}$ −37.2±0.3° (*c*=0.6, EtOH); IR ($CHCl_3$) and ^1H NMR ($CDCl_3$), identical with those of (±)-**7**. *Anal.* Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19. Found: C, 71.33; H, 7.68; N, 3.49.

(±)-8-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2β-acetamide [(±)-10]——To a chilled, stirred solution of (±)-**7** (358 mg, 0.814 mmol) and 3-benzyloxy-4-methoxyphenethylamine[20] (334 mg, 1.3 mmol) in $HCONMe_2$ (5 ml) were added successively diethyl phosphorocyanidate[12] (261 mg, 1.6 mmol) and Et_3N (162 mg, 1.6 mmol). The mixture was stirred at 20 °C for 7 h and extracted with $CHCl_3$ after addition of H_2O (10 ml). The $CHCl_3$ extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, leaving a pale brownish solid. The solid was recrystallized from 70% (v/v) aqueous EtOH to give (±)-**10** (439 mg, 79%), mp 156—159 °C. Two recrystallizations from 70% (v/v) aqueous EtOH yielded an analytical sample as colorless prisms, mp 157—159 °C; MS *m/e*: 678 (M^+); IR ν_{max}^{KBr} cm^{-1}: 3310 (CONH), 2800, 2750 (*trans*-quinolizidine ring),[21] 1635 (CONH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (CONH), 2840, 2760 (*trans*-quinolizidine ring),[21] 1658 (CONH); ^1H NMR ($CDCl_3$) δ: 3.84, 3.90, and 3.92 (9H, s each, three MeO's), 5.06 and 5.18 (4H, s each, two $PhC\underline{H}_2O$'s), 5.6—5.8 (1H, b, CONH), 6.64 (1H, s, $H_{(11)}$), 6.80—7.04 (3H, m, aromatic protons),

7.36—7.66 (10H, m, two PhCH$_2$O's). *Anal.* Calcd for $C_{42}H_{50}N_2O_6$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.27; H, 7.47; N, 4.15.

(2*R*,3*R*,11b*S*)-(−)-8-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetamide [(−)-10]——The tricyclic acid (−)-**7** (440 mg, 1 mmol) was allowed to react with 3-benzyloxy-4-methoxyphenethylamine[20] (386 mg, 1.5 mmol) in $HCONMe_2$ (5 ml) at 25 °C for 3 h in the presence of diethyl phosphorocyanidate[12] (326 mg, 2 mmol) and Et_3N (202 mg, 2 mmol) in a manner similar to that described above for (±)-**10**. The reaction mixture was also worked up as described above for the racemic series, and crude (−)-**10** (600 mg, 88%) was obtained as a colorless solid, mp 156—157.5 °C. Two more recrystallizations from 70% (v/v) aqueous EtOH gave an analytical sample as colorless needles, mp 156.5—158 °C; $[\alpha]_D^{17}$ −9.3±0.1° (c=0.601, EtOH); IR ($CHCl_3$) and ^{1}H NMR ($CDCl_3$), identical with those of (±)-**10**. *Anal.* Calcd for $C_{42}H_{50}N_2O_6$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.55; H, 7.51; N, 4.14.

(±)-8-Benzyloxy-2β-(6-benzyloxy-3,4-dihydro-7-methoxy-1-isoquinolyl)methyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine [(±)-9]——A solution of (±)-**10** (286 mg, 0.42 mmol) and PPE[13] (2.60 g) in $CHCl_3$ (15 ml) was heated under reflux for 3 h. The reaction mixture was concentrated *in vacuo*, and H_2O (10 ml) was added to the residue. After being stirred at room temperature for 2 h, the aqueous mixture was made alkaline by adding 10% aqueous NaOH (10 ml) under ice-cooling. The resulting mixture was stirred at room temperature for 30 min and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a brown oil (262 mg, 94%). A portion of the oil was purified by preparative TLC [alumina, hexane–AcOEt (10:7, v/v)], giving (±)-**9** as a faintly yellowish, viscous oil, MS *m/e* (relative intensity): 660 (M^+) (4), 570 (13), 480 (4), 380 (11), 379 (22), 378 (36), 350 (22), 306 (2), 305 (2), 298 (3), 297 (3), 296 (4), 289 (25), 288 (100), 282 (31), 281 (10), 260 (12), 192 (30), 191 (20); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2840, 2750 (*trans*-quinolizidine ring),[21] 1621 (C=N); ^{1}H NMR ($CDCl_3$) δ: 3.76, 3.86, and 3.92 (9H, s each, three MeO's), 5.01 and 5.21 (4H, s each, two PhC$\underline{H}_2$O's), 6.36 (1H, s, $H_{(11)}$), 6.78 (1H, s, $H_{(5')}$),[22] 7.08 (1H, s, $H_{(8')}$),[22] 7.3—7.6 (10H, m, two $\underline{Ph}CH_2O$'s).

(±)-2β-(3,4-Dihydro-6-hydroxy-7-methoxy-1-isoquinolyl)methyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine [(±)-Alangicine] [(±)-3]——i) By Acid Hydrolysis of (±)-**9**: A solution of (±)-**9** (143 mg, 0.216 mmol) in a mixture of 10% aqueous HCl (5 ml) and EtOH (2 ml) was heated under reflux for 15 h. After cooling, the reaction mixture was washed with benzene, neutralized (pH 7) with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to leave a yellow oil (101 mg). The oil was purified by column chromatography [silica gel (10 g), $CHCl_3$, $CHCl_3$–MeOH (8:1, v/v)] to yield (±)-**3** (77 mg, 74%) as a yellow glass, which crystallized from EtOH. Recrystallizations from EtOH produced an analytical sample (in the form of the triethanolate) as pale yellowish pillars, mp 145—147 °C; MS *m/e* (relative intensity): 480 (M^+) (68), 302 (24), 290 (33), 289 (94), 288 (76), 274 (29), 260 (100), 258 (10), 216 (15), 207 (14), 206 (24), 192 (52), 191 (35), 190 (24), 178 (12); UV λ_{max} (99% aqueous EtOH) 271.5 nm (sh) (log ε 4.00), 276 (4.02), 312.5 (3.65), 408 (4.34); UV λ_{max} (0.1 N aqueous HCl) 244.5 (4.21), 285 (sh) (3.63), 306.5 (3.98), 354.5 (3.99); UV λ_{max} (0.1 N aqueous NaOH) 239 (4.27), 293.5 (3.97), 327 (4.22); ^{1}H NMR ($CDCl_3$) δ: 1.24 (9H, t, J=7 Hz, three $\underline{Me}CH_2OH$'s), 3.72, 3.85, and 3.88 (9H, s each, three MeO's), 3.73 (6H, q, J=7 Hz, three $MeC\underline{H}_2OH$'s), 6.11 (1H, s, $H_{(11)}$), 6.77 (1H, s, $H_{(5')}$),[22] 7.01 (1H, s, $H_{(8')}$).[22] *Anal.* Calcd for $C_{28}H_{36}N_2O_5 \cdot 3C_2H_5OH$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.31; H, 8.50; N, 4.75. An ethanol-free sample of (±)-**3** was prepared by dissolving the triethanolate in $CHCl_3$ and evaporating the solution to dryness. The UV, IR (in $CHCl_3$), ^{1}H NMR (in $CDCl_3$, after treatment with D_2O), and mass spectra and TLC behavior of this sample (see Table I for ^{13}C NMR data) were identical with those of a solvent-free sample of natural alangicine.[17]

ii) By Hydrogenolysis of (±)-**9**: A solution of (±)-**9** (174 mg, 0.263 mmol) in EtOH (10 ml) was hydrogenated over 10% Pd-C (50 mg) at atmospheric pressure and 19—30 °C for 2 h, during which time uptake of hydrogen was incomplete owing to precipitation of a yellow solid. The catalyst was filtered off and washed with hot EtOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a yellow solid (134 mg), which was chromatographed on preparative TLC plates [silica gel, $CHCl_3$–MeOH (8:1, v/v)] to give the following three substances: the starting material [(±)-**9**] (24 mg, 14%); (±)-8-benzyloxy-2β-(3,4-dihydro-6-hydroxy-7-methoxy-1-isoquinolyl)methyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine [(±)-**17**] as a yellowish solid (72 mg, 48%) [mp 103—105 °C; MS *m/e* (relative intensity): 570 (M^+) (7), 480 (9), 380 (8), 379 (17), 378 (13), 350 (20), 298 (2), 297 (2), 296 (2), 289 (33), 288 (100), 260 (24), 192 (35), 191 (23); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 2840, 2750 (*trans*-quinolizidine ring);[21] ^{1}H NMR ($CDCl_3$) δ: 3.73, 3.82, and 3.83 (9H, s each, three MeO's), 4.08 (1H, b, OH), 4.96 (2H, s, PhC$\underline{H}_2$O), 6.29 (1H, s, $H_{(11)}$), 6.68 (1H, s, $H_{(5')}$),[22] 6.94 (1H, s, $H_{(8')}$),[22] 7.2—7.5 (5H, m, $\underline{Ph}CH_2O$)]; (±)-**3** (4 mg, 3%) as the triethanolate (mp 143—145 °C), identical with a sample obtained by method (i). When a solution of (±)-**17** (12 mg) in 2 N aqueous HCl (5 ml) was refluxed for 5 h and worked up as described above under method (i), (±)-**3** was obtained as the triethanolate (3 mg) (mp 145—147 °C) and shown to be identical with an authentic sample.

iii) By Hydrogenolysis of (±)-**9**·2HCl: A solution of crude (±)-**9**·2HCl (150 mg, 0.204 mmol), prepared by dissolving (±)-**9** in 10% ethanolic HCl and evaporating the resulting solution to dryness, in EtOH (15 ml) was hydrogenated over 10% Pd-C (50 mg) at ordinary pressure and 19—50 °C for 9 h. Removal of the catalyst by

filtration and concentration of the filtrate under reduced pressure afforded a pale yellowish solid, which wa partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SC and concentrated *in vacuo* to leave a yellowish solid (94 mg). Preparative TLC [silica gel, $CHCl_3$–MeOH (5 : 1, v/v)] c the solid gave (±)-**17** (11 mg, 9%) and (±)-**3** (69 mg, 70%), which were shown to be identical with the above authent samples, respectively.

(2*R*,3*R*,11b*S*)-(+)-2-(3,4-Dihydro-6-hydroxy-7-methoxy-1-isoquinolyl)methyl-3-ethyl-1,3,4,6,7,11b-hexahydro-1 hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (Alangicine) [(+)-3]——A solution of (−)-**10** (100 mg, 0.147 mmo and PPE[13] (1.0 g) in $CHCl_3$ (10 ml) was heated under reflux for 3 h. The reaction mixture was concentrated *in vacu* and 10% ethanolic HCl (4 ml) and 10% aqueous HCl (8 ml) were added to the residue. The resulting mixture wa refluxed for 15 h, washed with benzene, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extrac were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to leave a reddish-brown oil. The oil was crystallize from EtOH to furnish (+)-**3** as pale yellowish granules (47.2 mg, 67%, after being dried over P_2O_5 at 80 °C an 3 mmHg for 24 h), mp 144—145 °C (dec.). Repeated recrystallizations from EtOH and drying as above gave a analytical sample as light yellow granules, mp 145—147 °C (dec.); $[\alpha]_D^{16}$ +67±2° (*c*=0.113, MeOH); MS *m/e* (relativ intensity): 480 (M^+) (52), 302 (31), 290 (39), 289 (100), 288 (71), 274 (25), 260 (100), 258 (14), 216 (15), 207 (15), 20 (19), 192 (52), 191 (54), 190 (35), 178 (15); UV λ_{max} (99% aqueous EtOH) 271 nm (sh) (log ε 3.99), 276 (4.02), 31 (3.65), 407 (4.36); UV λ_{max} (0.1 N aqueous NaOH) 239 (4.18), 293 (3.86), 326 (4.10). *Anal.* Calcd for $C_{28}H_{36}N_2O_5$: C 69.98; H, 7.55; N, 5.83. Found: C, 69.57; H, 7.47; N, 5.83. This sample was identical [by mixture melting point te (mp 146—148 °C (dec.)) and comparison of UV, IR ($CHCl_3$), ^1H NMR, and mass spectra, TLC behavior, an specific rotation] with a natural sample of alangicine [mp 146—148 °C (dec.); $[\alpha]_D$ +64.1° (*c*=0.26, MeOH)].[2]

(±)-6-Benzyloxy-1,2,3,4-tetrahydro-7-methoxy-1-methylisoquinoline (12)——To a chilled (to 0 °C), stirred sc lution of **11**[23] (150 mg, 0.53 mmol) in EtOH (10 ml) was added portionwise $NaBH_4$ (20 mg, 0.53 mmol). After th mixture had been stirred at 0 °C for 3 h, acetone (2 ml) was added. The resulting mixture was concentrated *in vacuc* and the residue was partitioned between H_2O and benzene. The benzene extracts were dried over anhydrous Na_2SO and concentrated *in vacuo* to leave (±)-**12** (150 mg, 99%) as a faintly yellowish oil, IR ν_{max}^{film} cm^{-1}: 3330, 3270 (NH) ^1H NMR ($CDCl_3$) δ: 1.43 (3H, d, *J*=7 Hz, $C_{(1)}$-Me), 1.68 (1H, s, NH), 3.6—4.5 (4H, $H_{(3)}$'s and $H_{(4)}$'s), 3.86 (3H, s MeO), 4.03 (1H, q, *J*=7 Hz, $H_{(1)}$), 5.10 (2H, s, $PhCH_2O$), 6.61 (1H, s, $H_{(5)}$), 6.66 (1H, s, $H_{(8)}$), 7.2—7.6 (5H, m, Ph CH_2O).

The picrate of (±)-**12**: This was prepared in the usual manner and recrystallized from EtOH to furnish yello plates, mp 181—182.5 °C (dec.). *Anal.* Calcd for $C_{24}H_{24}N_4O_9$: C, 56.25; H, 4.72; N, 10.93. Found: C, 56.16; H, 4.73 N, 10.66.

Hydrogenolysis of (±)-12——A solution of (±)-**12** (149 mg, 0.53 mmol) in EtOH (15 ml) was hydrogenated ove 10% Pd-C (50 mg) at atmospheric pressure and 20 °C for 40 min. Removal of the catalyst by filtration an concentration of the filtrate under reduced pressure left (±)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-1-methyl isoquinoline (**13**) (91 mg, 89%) as a pale yellowish solid, mp 209—213 °C (dec.). Recrystallization from MeOH pro vided colorless plates, mp 219—219.5 °C (dec.) (lit.[24] mp 225—226 °C); IR ν_{max}^{KBr} cm^{-1}: 3450, 3280 (OH, NH); ^1H NMR (Me_2SO-d_6) δ: 1.30 (3H, d, *J*=7 Hz, $C_{(1)}$-Me), 2.6—3.6 (6H, NH, OH, $H_{(3)}$'s, and $H_{(4)}$'s), 3.73 (3H, s, MeO) 3.84 (1H, q, *J*=7 Hz, $H_{(1)}$), 6.44 (1H, s, $H_{(5)}$), 6.63 (1H, s, $H_{(8)}$).

Hydrogenolysis of 11——A solution of **11**[23] (350 mg, 1.24 mmol) in EtOH (17 ml) was hydrogenated over 10% Pd-C (80 mg) at atmospheric pressure and 22 °C for 12 min. The catalyst was filtered off and washed with hot EtOH The filtrate and washings were combined and concentrated *in vacuo* to leave a yellow solid (229 mg, 97%), mp 210—240 °C (dec.). Recrystallization of the solid from EtOH afforded 3,4-dihydro-6-hydroxy-7-methoxy-1 methylisoquinoline (**14**) as yellow prisms, mp 261—265 °C (dec.) [lit.[23b] mp *ca.* 270 °C (dec.)]; UV λ_{max} (99% aqueous EtOH) 226 nm (log ε 4.13), 268.5 (sh) (4.03), 273.5 (4.05), 311 (3.70), 401 (4.36); UV λ_{max} (0.1 N aqueous HCl 242.5 (4.22), 300 (3.96), 346 (3.94); UV λ_{max} (0.1 N aqueous NaOH) 241.5 (4.04), 302 (sh) (3.95), 325.5 (4.18); IR ν_{max}^{Nujol} cm^{-1}: 3240 (OH), 1620 (C=N).

The hydrochloride of **14**: A small sample of the above free base was dissolved in 10% ethanolic HCl and th solution was concentrated *in vacuo*. The residual solid was recrystallized from 90% (v/v) aqueous EtOH to giv **14**·HCl as slightly yellowish prisms, mp 254—256 °C (dec.) (lit.[23b] mp 261—263 °C); IR ν_{max}^{Nujol} cm^{-1}: 3430, 336 (OH), 1646 (C=N^+); ^1H NMR (Me_2SO-d_6) δ: 2.78 (3H, s, $C_{(1)}$-Me), 2.8—3.1 (2H, m, $H_{(4)}$'s), 3.2—3.7 (2H, b, N^+H OH), 3.6—3.9 (2H, m, $H_{(3)}$'s), 3.88 (3H, s, MeO), 6.96 (1H, s, $H_{(5)}$), 7.45 (1H, s, $H_{(8)}$). This sample was identical witl that obtained by hydrolysis of **11** with boiling 20% aqueous HCl.[23b]

Hydrogenation of 15——i) With Adams Catalyst: A solution of **15**[25] (1.00 g, 4.87 mmol) in EtOH (30 ml) wa hydrogenated over Adams catalyst (100 mg) at atmospheric pressure and 29 °C for 20 min. Removal of the catalyst b filtration and concentration of the filtrate under reduced pressure left a pale yellowish oil, which was dissolved i benzene. The benzene solution was dried over anhydrous K_2CO_3 and evaporated *in vacuo* to leave a slightly yellowis solid (968 mg, 96%), mp 40—43 °C. Recrystallization of the solid from hexane afforded (±)-1,2,3,4-tetrahydro-6,7 dimethoxy-1-methylisoquinoline (**16**) as colorless needles, mp 48—50 °C (lit.[26] mp 53—53.5 °C); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3320 (NH); ^1H NMR ($CDCl_3$) δ: 1.42 (3H, d, *J*=7 Hz, $C_{(1)}$-Me), 1.92 (1H, s, NH), 2.6—3.4 (4H, $H_{(3)}$'s and $H_{(4)}$'s) 3.87 (6H, s, two MeO's), 4.04 (1H, q, *J*=7 Hz, $H_{(1)}$), 6.58 and 6.64 (2H, s each, $H_{(5)}$ and $H_{(8)}$).

The picrate of (±)-**16**: This was prepared from the above free base in the usual manner and recrystallized from EtOH to yield yellow prisms, mp 201—202 °C (dec.) (lit.[26] mp 201—202 °C).

ii) With 10% Pd-C: A solution of **15**[25] (1.00 g, 4.87 mmol) in EtOH (30 ml) was hydrogenated over 10% Pd-C (100 mg) at atmospheric pressure and 27 °C for 250 min. The reaction mixture was worked up as described above under method (i), giving (±)-**16** (978 mg, 97%) as a pale yellowish solid, mp 40—45 °C, identical with a sample obtained by method (i). The picrate [mp 201—202 °C (dec.)] prepared from the free base was also identical with that described above under method (i).

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References and Notes

1) Paper VII in this series, T. Fujii, M. Ohba, O. Yonemitsu, and Y. Ban, *Chem. Pharm. Bull.*, **30**, 598 (1982).
2) S. C. Pakrashi and E. Ali, *Tetrahedron Lett.*, **1967**, 2143.
3) Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configuration.
4) T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *Tetrahedron Lett.*, **1976**, 2553.
5) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, **8**, 175 (1977).
6) A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, *Tetrahedron Lett.*, **1966**, 4965.
7) B. Dasgupta, *J. Pharm. Sci.*, **54**, 481 (1965).
8) *a*) T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron Lett.*, **1975**, 1527; *b*) *Idem*, *Tetrahedron*, **36**, 965 (1980).
9) C. Szántay, E. Szentirmay, L. Szabó, and J. Tamás, *Chem. Ber.*, **109**, 2420 (1976).
10) *a*) S. Yoshifuji and T. Fujii, *Tetrahedron Lett.*, **1975**, 1965; *b*) T. Fujii and S. Yoshifuji, *J. Org. Chem.*, **45**, 1889 (1980).
11) *a*) S. Yamada, Y. Kasai, and T. Shioiri, *Tetrahedron Lett.*, **1973**, 1595; *b*) S. Yamada, N. Ikota, T. Shioiri, and S. Tachibana, *J. Am. Chem. Soc.*, **97**, 7174 (1975); *c*) T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, *Tetrahedron*, **32**, 2211 (1976).
12) A. Takamizawa, Y. Sato, and S. Tanaka, *Yakugaku Zasshi*, **85**, 298 (1965).
13) *a*) G. Schramm, H. Grötsch, and W. Pollmann, *Angew. Chem., Internat. Ed.*, **1**, 1 (1962); *b*) W. Pollmann and G. Schramm, *Biochim. Biophys. Acta*, **80**, 1 (1964); *c*) Y. Kanaoka, M. Machida, O. Yonemitsu, and Y. Ban, *Chem. Pharm. Bull.*, **13**, 1065 (1965).
14) *a*) Y. Kanaoka, E. Sato, O. Yonemitsu, and Y. Ban, *Tetrahedron Lett.*, **1964**, 2419; *b*) Y. Kanaoka, E. Sato, and Y. Ban, *Chem. Pharm. Bull.*, **15**, 101 (1967); *c*) Y. Kanaoka, E. Sato, and O. Yonemitsu, *Tetrahedron*, **24**, 2591 (1968); *d*) M. P. Cava, M. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem.*, **34**, 2665 (1969); *e*) R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *ibid.*, **36**, 2409 (1971); *f*) I. Ribas, J. Sáa, and L. Castedo, *Tetrahedron Lett.*, **1973**, 3617.
15) For reviews, see *a*) H. T. Openshaw, "Chemistry of the Alkaloids," ed. by S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, Chapter 4; *b*) A. Brossi, S. Teitel, and G. V. Parry, "The Alkaloids," Vol. XIII, ed. by R. H. F. Manske, Academic Press, New York, 1971, Chapter 3; *c*) M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, 1972, Chapter 23; *d*) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research, 1972—1977," Plenum Press, New York, 1978, Chapter 27.
16) H. Budzikiewicz, S. C. Pakrashi, and H. Vorbrüggen, *Tetrahedron*, **20**, 399 (1964).
17) The solvent-free sample was prepared from a natural sample of alangicine (mp 146—148 °C), a gift from Dr. S. C. Pakrashi (Calcutta), by the same method as used for the triethanolate of synthetic (±)-**3**. The natural sample had been crystallized from acetone–MeOH and was found by ^{1}H NMR spectroscopy to contain *ca.* one equivalent mole of MeOH of crystallization.
18) C. Schuij, G. M. J. Beijersbergen van Henegouwen, and K. W. Gerritsma, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 970.
19) The present ^{13}C NMR assignments were also facilitated by many examples from the isoquinoline alkaloids recently reviewed by D. W. Hughes and D. B. MacLean in "The Alkaloids," Vol. XVIII, ed. by R. H. F. Manske and R. G. A. Rodrigo, Academic Press, New York, 1981, Chapter 3.
20) M. Tomita and H. Yamaguchi, *Yakugaku Zasshi*, **72**, 1219 (1952).
21) *a*) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); *b*) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

22) The same numbering system as employed for formula **18** is adopted for convenience of designating the atoms in the dihydroisoquinoline moiety.
23) *a*) M. B. Moore, H. B. Wright, M. Vernsten, M. Freifelder, and R. K. Richards, *J. Am. Chem. Soc.*, **76**, 3656 (1954); *b*) H. Bruderer and A. Brossi, *Helv. Chim. Acta*, **48**, 1945 (1965).
24) T. Kametani, S. Takano, and F. Sasaki, *Yakugaku Zasshi*, **87**, 191 (1967).
25) *a*) E. Späth and N. Polgar, *Monatsh. Chem.*, **51**, 190 (1929); *b*) T. Fujii, M. Tashiro, K. Ohara, and M. Kumai, *Chem. Pharm. Bull.*, **8**, 266 (1960).
26) C. Viel, *Ann. Chim.* (Paris), **8**, 515 (1963) [*Chem. Abstr.*, **60**, 11982*b* (1964)].