Quinolizidines. XIII. Syntheses of (±)-and (-)-Alangimarckines

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Quinolizidines. XIII.[1] Syntheses of (±)- and (−)-Alangimarckines

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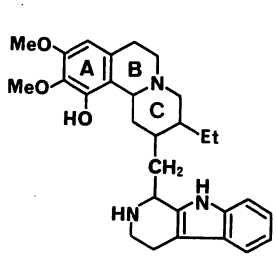
The first total synthesis of the *Alangium* alkaloid alangimarckine (**8**) has been accomplished in the form of a racemic modification by means of an initial coupling of the (±)-tricyclic amino acid **6** with tryptamine and succeeding steps proceeding through the intermediates (±)-**7**, (±)-**10**, and (±)-**9**. The 1′-epimers (±)-**12** and (±)-**11** were also produced in this reaction sequence. A parallel sequence of conversions starting with the (−)-tricyclic amino acid **6** yielded the chiral molecule (−)-**8** *via* the intermediates (+)-**7**, (+)-**10**, and (+)-**9**, together with the 1′-epimer (−)-**11** *via* (−)-**12**. The identity of the synthetic (−)-**8** with natural alangimarckine unequivocally established the structure and absolute configuration of this alkaoid. The assignments of the configuration at C-1′ of **8**, **9**, **11**, and **12** were based on five criteria, namely, the ratio of products from the $NaBH_4$ reduction of (±)-**10**, thin-layer chromatographic mobility, and proton and carbon-13 nuclear magnetic resonance and circular dichroism spectroscopic features.

Keywords——*Alangium* alkaloid alangimarckine; diethyl phosphorocyanidate amide formation; Bischler–Napieralski cyclization; sodium borohydride reduction; catalytic hydrogenolysis; TLC epimer differentiation; NMR epimer differentiation; CD epimer differentiation

The isolation of alangimarckine, a phenolic benzo[*a*]quinolizidine alkaloid, from the leaves of the Indian medicinal plant *Alangium lamarckii* THWAITES (Alangiaceae)[2] was first reported by Battersby *et al.*[3] in 1966. They put forward the planar structure **1** for this new alkaloid, largely on the basis of mass spectral evidence.[3] The exact location of the hydroxy and methoxy groups in ring A, however, and the stereochemistry about ring C and another heterocyclic moiety remained to be determined. This paper describes the details of our synthetic work in both the racemic and chiral series, which permitted the assignment of the complete expression **8** (absolute configuration shown[4]) to alangimarckine. Preliminary accounts of this work have appeared.[5,6]



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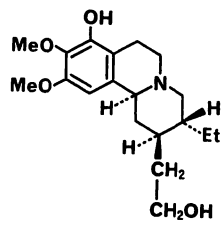

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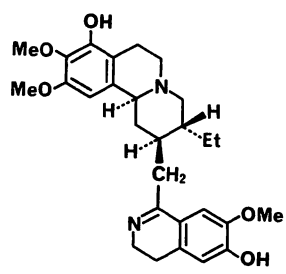

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At the time when the present study was initiated, the structures and absolute configurations of ankorine[3,7] and alangicine,[8] co-occurring *Alangium* alkaloids, had already been established by us as **2**[9] and **3**,[10] respectively. Assuming the structure of the benzo-

uinolizidine moiety to be the same in both alangimarckine and ankorine (**2**) or alangicine **3**), we first selected the two alternative, racemic target molecules (±)-**8** and (±)-**11** for ynthesis with a view to establishing the structure and relative stereochemistry of alangimarkine. This selection of the epimeric pair at the 1′-position was based on the fact that ubulosine (**15**)[11] and isotubulosine (**18**),[12] an analogous epimeric pair, have also been solated from *A. lamarckii*. The starting material in the synthesis of (±)-**8** and (±)-**11** was the ±)-tricyclic amino acid **6**, which had already been prepared from the (±)-lactam ester **4** *via* in eight-step route[9a,b,10a,c] and used for the synthesis of (±)-alangicine (**3**)[10a,c] in our aboratory. The coupling of (±)-**6** with tryptamine was effected in *N*,*N*-dimethylformamide DMF) at 30 °C *via* the agency of diethyl phosphorocyanidate[13] in the presence of Et_3N,

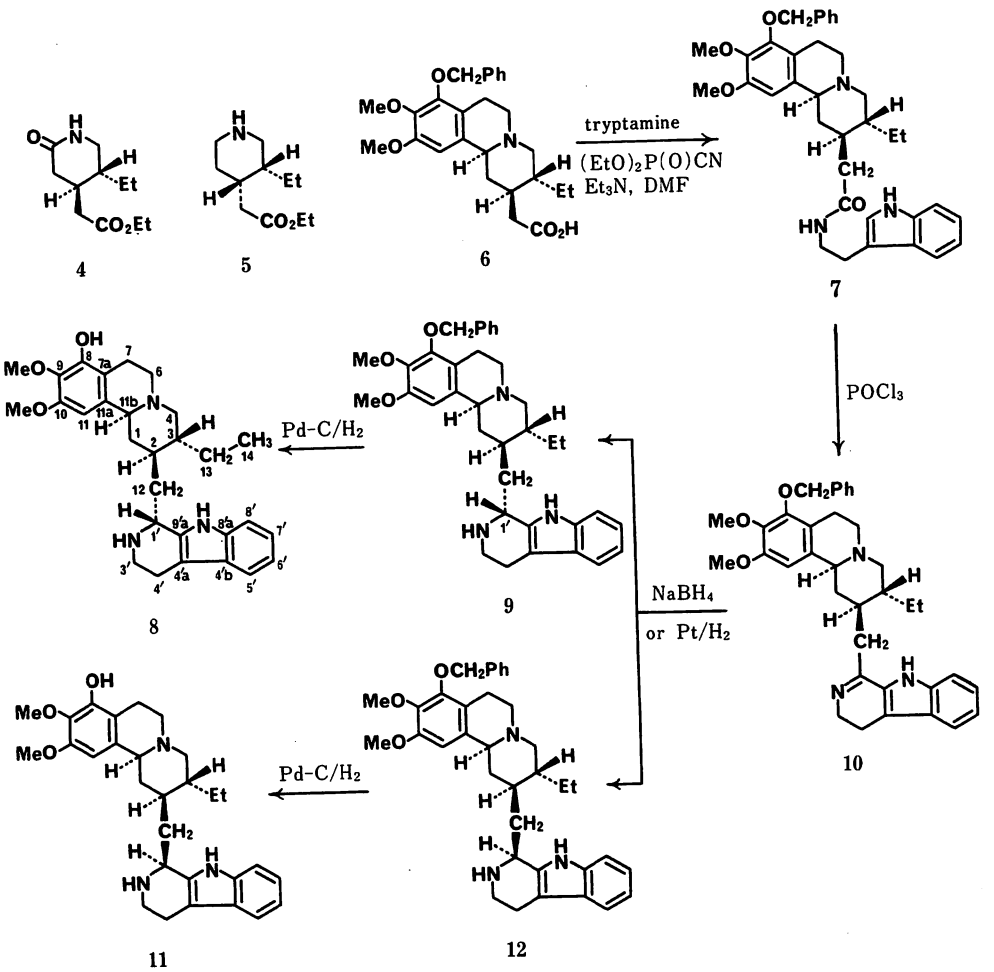
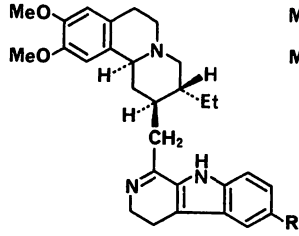


Chart 1

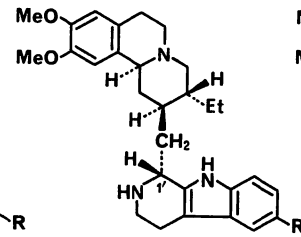
producing the (±)-tryptamide **7** in 93% yield. Bischler–Napieralski cyclization of (±)-**7** with $POCl_3$ in boiling toluene gave the (±)-dihydro-β-carboline base **10**, which was isolated in 75% yield in the form of the dihydrobromide monohydrate. Reduction of this salt with $NaBH_4$ in MeOH and chromatographic separation of the products furnished (±)-8-benzyloxydeoxytubulosine (**9**) and its 1′-epimer [(±)-**12**] in 18% and 59% yields, respectively. On debenzylation with hydrogen activated on Pd–C catalyst, (±)-**9** afforded (±)-8-hydroxydeoxytubulosine (**8**) (95% yield), one of the desired compounds, which was charac-

terized as a crystalline hydrate. Similar hydrogenolysis of (±)-**12** gave the other epimeric target (±)-**11** in 95% yield.

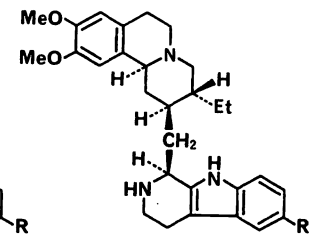
Proof of the correctness of the assigned configuration at C-1′ of (±)-**8**, (±)-**9**, (±)-**11**, and (±)-**12** was provided by the following findings. The formation of a 1 : 3.3 mixture of (±)-**9** and (±)-**12** in the $NaBH_4$ reduction of (±)-**10** was comparable to that [14] of a 1 : 3.5 mixture of *O*-benzyltubulosine (**14**) and *O*-benzylisotubulosine (**17**) in the analogous reduction of the dihydro-β-carboline base **13**. On thin-layer chromatographic (TLC) analysis, (±)-**8** and (±)-**9** moved faster than their 1′-epimers (±)-**11** and (±)-**12**, respectively, and this TLC behavior



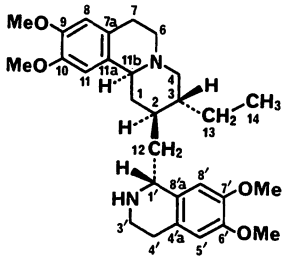
13: R = OCH_2Ph



14: R = OCH_2Ph
15: R = OH
16: R = H



17: R = OCH_2Ph
18: R = OH



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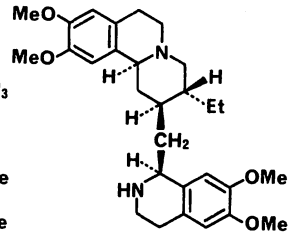

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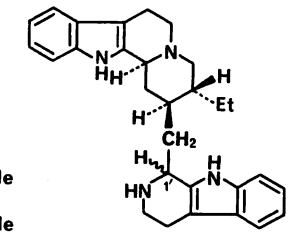

21: 1′β-H
22: 1′α-H

corresponded to that reported[12] for tubulosine (**15**) and isotubulosine (**18**) as well as to that observed for emetine (**19**) and isoemetine (**20**) (Table I). In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of (±)-**8** and (±)-**11** in Me_2SO-d_6 or in $CDCl_3$, the difference in chemical shift between two methoxy groups in the same molecule is smaller for (±)-**8** (Δ = 0.08 ppm) than for (±)-**11** (Δ = 0.16 or 0.34 ppm) (Table II), and such a relationship has been observed by Popelak *et al.*[12] for tubulosine (**15**) and isotubulosine (**18**). This may be explained by the assumption that the methoxy group at the 10-position of isotubulosine (**18**) overhangs the indole system in a preferred conformation, so that it is more shielded than that of tubulosine (**15**).[12] This view is supported by the observation of a 0.32- or 0.35-ppm upfield shift of the $C_{(11)}$-H signal of (±)-**11**, relative to that of (±)-**8**, as shown in Table II. The fourth criterion employed for the stereochemical assignments was the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectral data, which proved to be the most conclusive. It may be seen from Table III that the C-1, C-2, and C-1′ carbons of emetine (**19**) resonate at higher field than do the corresponding carbons of isoemetine (**20**) by 1.9—3.3 ppm, whereas the differences in the chemical shifts of the other corresponding carbons of the two isomers are insignificant. A similar feature has been found and discussed by Wenkert and co-workers[15] for ochrolifuanine A (**21**) and ochrolifuanine B (**22**). As shown in Table III, such a relationship holds for (±)-**8** and (±)-**11**.

TABLE I. TLC Mobility of the Epimeric Pairs (±)-**8**—(±)-**11** and Emetine (**19**)—Isoemetine (**20**)

Plate	Solvent[b]	*Rf* value[a]			*Rf* value[a]		
		(±)-**8**	(±)-**11**	(**11**/**8**)[c]	**19**	**20**	(**20**/**19**)[c]
SiO_2[d]	A	0.76	0.60	(0.79)	0.74	0.53	(0.72)
	B	—	—	—	0.59	0.48	(0.81)
	C	0.69	0.61	(0.88)	0.62	0.52	(0.84)
	D	0.76	0.61	(0.80)	0.44	0.35	(0.80)
	E	0.72	0.56	(0.78)	—	—	—
	F	0.49	0.36	(0.73)	—	—	—
	G	0.28	0.21	(0.75)	—	—	—
Al_2O_3[e]	H	0.78	0.56	(0.72)	—	—	—
	I	—	—	—	0.72	0.38	(0.53)
	J	0.73	0.59	(0.81)	0.62	0.36	(0.58)
	K	0.69	0.41	(0.59)	—	—	—
	L	0.53	0.36	(0.68)	—	—	—
	M	—	—	—	0.72	0.40	(0.56)
	N	0.32	0.18	(0.56)	—	—	—

a) Chromatograms were developed in the usual manner at 25 °C, and spots were located under ultraviolet light (254 nm) and by means of the I_2—KI reagent spray. *b*) The letter A designates the solvent system $CHCl_3$–MeOH–pyridine (6:1:1, v/v); B, $CHCl_3$–MeOH–pyridine (10:1:1, v/v); C, $CHCl_3$–MeOH (5:1, v/v); D, AcOEt–EtOH–DMF (5:1:1, v/v); E, $CHCl_3$–acetone–Et_3N (16:8:3, v/v); F, Et_2O–EtOH (5:1, v/v); G, AcOEt–EtOH–MeCN (5:2:2, v/v); H, CH_2Cl_2–EtOH (200:1, v/v); I, CH_2Cl_2–EtOH (70:1, v/v); J, AcOEt–hexane–EtOH (20:20:1, v/v); K, $CHCl_3$–acetone (5:1, v/v); L, CCl_4–acetone (2:1, v/v); M, CCl_4–acetone (3:1, v/v); N, $CHCl_3$–hexane–Et_3N (6:5:2, v/v). *c*) Relative value. *d*) Silica gel GF_{254} (type 60, E. Merck) was used after activation at 110 °C for 1 h. *e*) Aluminum oxide GF_{254} (E. Merck) was used after activation at 110 °C for 1 h.

TABLE II. Chemical Shifts for Methoxy Protons and $C_{(11)}$-H

Compound	Solvent	Chemical shift (δ)			
		$C_{(11)}$-H	9-OMe	10-OMe	Δ(OMe)[a]
Tubulosine (**15**)	Me_2SO-d_6[b]	—[c]	3.73	3.73	0
Isotubulosine (**18**)	Me_2SO-d_6[b]	—[c]	3.69	3.49	−0.20
(±)-**8**	Me_2SO-d_6	6.40	3.72	3.64	−0.08
	$CDCl_3$	6.35	3.89	3.81	−0.08
(±)-**11**	Me_2SO-d_6	6.08	3.64	3.48	−0.16
	$CDCl_3$	6.00	3.82	3.48	−0.34

a) $\Delta(\text{OMe}) = \delta(\text{10-OMe}) - \delta(\text{9-OMe})$. *b*) Taken from ref. 12. *c*) Not recorded in ref. 12.

An anhydrous sample of (±)-**8** was prepared by dissolving the above hydrate in $CHCl_3$ and evaporating the resulting solution to dryness. Its ultraviolet (UV) (in 95% aqueous EtOH), infrared (IR) (in $CHCl_3$), ^{1}H-NMR (in $CDCl_3$), and mass spectra (MS) were found to match those of natural (−)-alangimarckine. Thus, the structure and relative stereochemistry of this alkaloid have been unambiguously established as **8** or its mirror image.

We next tried to solve the problem of the absolute stereochemistry of alangimarckine by synthesis again. For the same reason as mentioned above for the synthesis in the racemic series, the absolute stereoformula **8** rather than its mirror image was selected as the synthetic target. The chiral synthesis of **8** started with the (−)-tricyclic amino acid **6**, our (+)-alangicine (**3**) precursor available from cincholoipon ethyl ester [(+)-**5**] by an eleven-step synthesis,[9c,d,10b,c] and proceeded through essentially the same reaction sequence as used for

TABLE III. ^{13}C Chemical Shifts of Emetine (**19**), Isoemetine (**20**), (±)-Alangimarckine [(±)-**8**], and (±)-**11** in $CDCl_3$

Carbon	Chemical shift[a]			
	Emetine (**19**)[b]	Isoemetine (**20**)	(±)-**8**	(±)-**11**
C(1)	37.0	39.3	36.8	38.6
C(2)	36.9	38.8	36.5	38.0
C(3)	41.8	42.8	41.6	42.7
C(4)	61.4	61.5	61.4	61.6
C(6)	52.3	52.5	51.9	52.2
C(7)	29.4	29.1	23.5	23.4
C(7a)	126.9	126.5	115.1	114.7
C(8)	111.6[c]	111.4	150.2	150.2
C(9)	147.1[d]	147.0	134.2[e]	133.7
C(10)	147.3[d]	147.0	146.6	146.5
C(11)	108.7	108.2	100.5	100.0
C(11a)	130.3	130.0	133.9[e]	133.7
C(11b)	62.4	62.7	62.5	62.9
C(12)	40.2[f]	40.7	38.9	38.6
C(13)	23.6	23.9	23.5	24.0
C(14)	11.2	11.3	11.2	11.4
C(1′)	51.9	55.2	49.3	52.2
C(3′)	40.8[f]	41.2	42.1	43.1
C(4′)	29.4	29.5	22.9	22.9
C(4′a)	126.9	127.0	108.9	108.9
C(4′b)	—	—	127.6	127.6
C(5′)	111.9[c]	111.8	117.9	117.9
C(6′)	147.3[d]	147.0	121.5	121.6
C(7′)	147.5[d]	147.0	119.4	119.5
C(8′)	109.3	109.5	110.7	110.8
C(8′a)	132.1	131.9	136.5	136.5
C(9′a)	—	—	135.6	135.6
9-OMe	55.8[g]	55.7	60.9	60.8
10-OMe	55.8[g]	55.7	56.0	55.6
6′-OMe	56.0[g]	55.7	—	—
7′-OMe	56.3[g]	55.7	—	—

a) In ppm downfield from internal Me_4Si. *b*) Assignments were made largely on the basis of those reported in ref. 15. *c*—*g*) Assignments indicated by a given superscript may be interchanged or exchanged.

the above racemic synthesis (Chart 1). Condensation of (−)-**6** with tryptamine in DMF by the diethyl phosphorocyanidate method[13] furnished the (+)-tryptamide **7** (92% yield), which was then cyclized with $POCl_3$ in boiling toluene to give the (+)-dihydro-β-carboline base **10** in 82% yield. Catalytic hydrogenation of (+)-**10** in dioxane over Adams catalyst followed by column chromatography produced (+)-8-benzyloxydeoxytubulosine (**9**) (25% yield) and its 1′-epimer [(−)-**12**] (48% yield). Catalytic hydrogenolysis of (+)-**9** provided the desired compound, (−)-8-hydroxydeoxytubulosine (**8**) (96% yield), which was characterized as a hydrate. The epimeric base (−)-**12** was similarly debenzylated to give the corresponding (−)-phenolic base **11** in 95% yield. The stereochemistry at C-1′ of (−)-**8** and (−)-**11** was confirmed by the identity of their solution IR and NMR spectra and TLC mobility with those of the racemic modifications (±)-**8** and (±)-**11**, respectively. Moreover, we found that (−)-**8** exhibited a negative circular dichroism (CD) curve in EtOH or 0.1 N aqueous HCl, whereas (−)-**11** showed a positive CD curve, as recorded in our preliminary report.[6] Similar chiroptical properties found for the 1′-epimeric pairs of emetine (**19**)–isoemetine (**20**),[6]

ochrolifuanine A (**21**)–ochrolifuanine B (**22**),[16] and certain structural analogs[17] of tubulosine (**15**) thus afforded an additional proof of the correctness of the configuration assigned to C-1′ of (−)-**8** and (−)-**11**.

Since the melting point, specific rotation, and UV (in 95% aqueous EtOH), IR (in $CHCl_3$), ^{1}H-NMR (in $CDCl_3$), and MS of the synthetic (−)-**8** have been found to match those of natural (−)-alangimarckine, the above results prove that the stereoformula **8** is a complete expression for alangimarckine. It follows that alangimarckine is the 8-hydroxy relative of deoxytubulosine (**16**),[14,18] which had been isolated by Battersby *et al.*[18] from the fruits of the same plant, *Alangium lamarckii*.

Experimental

General Comments——All melting points are corrected. See ref. 10*c* for details of instrumentation and measurements. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, m = multiplet, s = singlet, sh = shoulder.

Materials——The free base of emetine (**19**) was prepared from a commercially available sample of the dihydrochloride salt in the usual manner. Isoemetine (**20**) was prepared in the free base form from the di(hydrogen oxalate) salt[19] of *O*-methylpsychotrine according to the directions of Karrer *et al.*,[20] but with some modification.[19]

(±)-8-Benzyloxy-3α-ethyl-1,3,4,6,7,11bα-hexahydro-*N*-[2-(indol-3-yl)ethyl]-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2β-acetamide [(±)-7]——Diethyl phosphorocyanidate[13,21] (1.57 g, 9.6 mmol) and Et_3N (810 mg, 8 mmol) were successively added to a chilled, stirred solution of (±)-**6**[10a,c] (1.76 g, 4 mmol) and tryptamine (960 mg, 6 mmol) in $HCONMe_2$ (10 ml). The mixture was stirred at 30 °C for 6 h and extracted, after addition of H_2O (100 ml), with AcOEt. The AcOEt extracts were washed successively with 10% aqueous Na_2CO_3 and H_2O, dried, and concentrated to dryness. Trituration of the residue with a little AcOEt and collection of the insoluble solid by filtration gave (±)-**7** (2.17 g, 93%), mp 169—171 °C. Recrystallization from AcOEt yielded an analytical sample as colorless pillars, mp 170—171 °C; MS *m/e*: 581 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3390 and 3270 (NH's), 1667 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 3.74 and 3.84 (3H each, s, two MeO's), 4.96 (2H, s, $PhC\underline{H}_2O$), 5.5—5.7 (1H, br, CONH), 6.50 (1H, s, $H_{(11)}$), 6.85—7.7 (10H, m, aromatic protons), 8.34 (1H, br, indole NH). *Anal.* Calcd for $C_{36}H_{43}N_3O_4$: C, 74.33; H, 7.45; N, 7.22. Found: C, 74.37; H, 7.61; N, 7.17.

(2*R*,3*R*,11b*S*)-(+)-8-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-*N*-[2-(indol-3-yl)ethyl]-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetamide [(+)-7]——The tricyclic amino acid (−)-**6**[10b,c] (879 mg, 2 mmol) was allowed to react with tryptamine (481 mg, 3 mmol) in $HCONMe_2$ (10 ml) at 28 °C for 6 h in the presence of diethyl phosphorocyanidate[13,21] (816 mg, 5 mmol) and Et_3N (404 mg, 4 mmol). The reaction mixture was worked up as described above for the racemic modification, giving (+)-**7** (1.07 g, 92%) as a colorless solid, mp 175—177 °C. Recrystallization from AcOEt afforded an analytical sample as colorless needles, mp 176.5—177.5 °C; $[\alpha]_D^{28}$ +0.95° (*c* = 2.0, EtOH); MS *m/e*: 581 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3380 and 3280 (NH's), 1631 (amide CO); ^{1}H-NMR ($CDCl_3$), identical with that of (±)-**7**. *Anal.* Calcd for $C_{36}H_{43}N_3O_4$: C, 74.33; H, 7.45; N, 7.22. Found: C, 74.33; H, 7.54; N, 7.12.

(±)-8-Benzyloxy-2β-[(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine [(±)-10]——A solution of (±)-**7** (1.00 g, 1.72 mmol) and $POCl_3$ (2 ml) in toluene (40 ml) was heated under reflux for 2.5 h. The reaction mixture was concentrated *in vacuo*, and 10% aqueous KOH (100 ml) was added to the residue under ice-cooling. The resulting mixture was then extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave crude (±)-**10** as a reddish-brown glass, which was dissolved in EtOH (20 ml). The ethanolic solution was acidified (pH 3—4) with a slight excess of 47% aqueous HBr and kept, after addition of ether (15 ml), in a refrigerator. The yellowish prisms that resulted were filtered off and dried to give the dihydrobromide salt (953 mg, 75%), mp 201—202 °C (dec.). Recrystallization of the salt from MeOH and drying over P_2O_5 at 2 mmHg and 50 °C for 8 h yielded an analytical sample (in the form of the monohydrate) as yellow prisms, mp 201—202 °C (dec.); ^{1}H-NMR (Me_2SO-d_6) δ: 3.42 and 3.80 (3H each, s, two MeO's), 5.06 (2H, s, $PhC\underline{H}_2O$), 6.62 (1H, s, $H_{(11)}$), 7.2—8.0 (9H, m, aromatic protons). *Anal.* Calcd for $C_{36}H_{41}N_3O_3 \cdot 2HBr \cdot H_2O$: C, 58.15; H, 6.10; N, 5.65. Found: C, 57.86; H, 5.88; N, 5.42.

(2*R*,3*R*,11b*S*)-(+)-8-Benzyloxy-2-[(4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine [(+)-10]——The tryptamide (+)-**7** was cyclized as described above for the racemic series, producing crude (+)-**10** as a reddish-brown glass. Purification of the base by column chromatography [silica gel, benzene–EtOH (10 : 1, v/v)] furnished a yellow glass (82% yield), $[\alpha]_D^{18}$ +9.6° (*c* = 0.50, EtOH); MS *m/e*: 563 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 2800 (sh) and 2760 (*trans*-quinolizidine ring);[22] ^{1}H-NMR ($CDCl_3$) δ: 3.50 and 3.80 (3H each, s, two MeO's), 4.96 (2H, s, $PhC\underline{H}_2O$), 6.22 (1H, s, $H_{(11)}$), 7.0—7.8 (9H,

m, aromatic protons), 8.48 (1H, s, NH).

[2*R-[2α(*S**),3β,11bβ]]- and [2*R**-[2α(*R**),3β,11bβ]]-8-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-[(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-2*H*-benzo[*a*]quinolizines [(±)-9 and (±)-12]**——A solution of (±)-**10**·2HBr·H_2O (815 mg, 1.1 mmol) in MeOH (25 ml) was stirred under ice-cooling, and $NaBH_4$ (415 mg, 11 mmol) was added portionwise. After stirring had been continued at 25 °C for 1.5 h, acetone (3 ml) was added and the mixture was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O and CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated to leave a solid, which was shown to be a mixture of two components on TLC analysis. The solid was chromatographed on a column packed with silica gel (100 g). Earlier fractions eluted with $CHCl_3$–EtOH (15 : 1, v/v) gave (±)-**9** (109 mg, 18%) as an unstable, yellowish glass, MS *m/e*: 565 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 2760 (*trans*-quinolizidine ring).[22] Later fractions eluted with the same solvent system afforded (±)-**12** (365 mg, 59%) as a colorless solid, mp 211—212 °C. Recrystallization of the solid from EtOH produced an analytical sample as colorless prisms, mp 212—213 °C; MS *m/e*: 565 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 2760 (*trans*-quinolizidine ring);[22] ^{1}H-NMR ($CDCl_3$) δ: 1.75 (1H, br, $N_{(2')}$-H), 3.52 and 3.84 (3H each, s, two MeO's), 5.00 (2H, s, $PhC\underline{H}_2O$), 6.28 (1H, s, $H_{(11)}$), 7.0—7.65 (9H, m, aromatic protons), 7.92 (1H, br, indole NH). *Anal.* Calcd for $C_{36}H_{43}N_3O_3$: C, 76.43; H, 7.66; N, 7.43. Found: C, 76.38; H, 7.85; N, 7.62.

[2*S*-[2α(*S),3β,11bβ]]- and [2*S*-[2α(*R**),3β,11bβ]]-8-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-[(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-2*H*-benzo[*a*]quinolizines [(+)-9 and (−)-12]**——A solution of (+)-**10** (543 mg, 0.96 mmol) in dioxane (5 ml) was hydrogenated over Adams catalyst (100 mg) at atmospheric pressure and 19 °C for 40 min. Removal of the catalyst by filtration and evaporation of the filtrate under reduced pressure left a yellowish oil, which was partitioned by extraction with a mixture of H_2O and CH_2Cl_2. The CH_2Cl_2 extracts were washed successively with 5% aqueous NaOH and H_2O, dried, and concentrated to leave a yellow glass (505 mg). This material was then chromatographed on a 75-g silica gel column using $CHCl_3$–EtOH (15 : 1, v/v) as eluent. Earlier fractions furnished (+)-**9** (134 mg, 25%) as an unstable, yellowish glass, $[\alpha]_D^{18}$ +25.2° (*c*=0.25, EtOH); MS *m/e*: 565 (M^+); IR ($CHCl_3$), identical with that of (±)-**9**; ^{1}H-NMR ($CDCl_3$) δ: 2.7 (1H, br, $N_{(2')}$-H), 3.82 and 3.86 (3H each, s, two MeO's), 5.00 (2H, s, $PhC\underline{H}_2O$), 6.60 (1H, s, $H_{(11)}$), 7.0—7.6 (9H, m, aromatic protons), 7.92 (1H, br, indole NH). Later fractions of the above chromatography gave (−)-**12** (261 mg, 48%) as a yellowish glass, $[\alpha]_D^{18}$ −31.2° (*c*=0.50, EtOH); MS *m/e*: 565 (M^+); IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$), identical with those of (±)-**12**.

[2*R-[2α(*S**),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2-[(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-2*H*-benzo[*a*]quinolizine [(±)-Alangimarckine] [(±)-8]**——A solution of (±)-**9** (200 mg, 0.354 mmol) in MeOH–AcOH (1 : 1, v/v) (20 ml) was hydrogenated over 10% Pd–C (100 mg) at atmospheric pressure and 20 °C for 1.5 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was heated at 90 °C after addition of H_2O (10 ml), and the mixture was filtered. The aqueous filtrate was made alkaline with 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to leave (±)-**8** (159 mg, 95%) as a faintly orange solid. Recrystallization of the solid from EtOH and drying over P_2O_5 at 2 mmHg and 75 °C for 3 h provided an analytical sample (in the form of a hydrate) as colorless pillars, mp 157—159 °C (dec.); TLC mobility (Table I); MS *m/e* (relative intensity): 475 (M^+) (66), 291 (62), 290 (47), 289 (43), 288 (83), 262 (100), 260 (49), 221 (41), 208 (53), 207 (34), 206 (37), 192 (35), 191 (35), 185 (84), 184 (63), 183 (62), 171 (91), 144 (22), 130 (19); UV λ_{max} (99% aqueous EtOH) 282.5 nm (log ε 3.99), 292 (3.88); UV λ_{max} (95% aqueous EtOH) 282 (3.96), 291 (3.85); UV λ_{max} (0.1 N aqueous NaOH) 283 (4.03); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 3480 (NH), 2800 (sh) and 2760 (*trans*-quinolizidine ring);[22] ^{1}H-NMR ($CDCl_3$) δ: 3.81 (3H, s, 10-OMe), 3.89 (3H, s, 9-OMe), 6.35 (1H, s, $H_{(11)}$), 7.05—7.6 (4H, m, aromatic protons), 7.84 (1H, br, indole NH); ^{1}H-NMR (Me_2SO-d_6) (Table II); ^{13}C-NMR ($CDCl_3$) (Table III). *Anal.* Calcd for $C_{29}H_{37}N_3O_3 \cdot 3/4H_2O$: C, 71.21; H, 7.93; N, 8.59. Found: C, 71.42; H, 7.64; N, 8.66. See the text for the preparation of an anhydrous sample of (±)-**8** and confirmation of its spectral identity with natural (−)-alangimarckine.

[2*S*-[2α(*S),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2-[(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-2*H*-benzo[*a*]quinolizine [(−)-Alangimarckine] [(−)-8]**——The benzyl ether (+)-**9** was debenzylated as described above for the racemic series, and crude (−)-**8** was obtained in 96% yield as a faintly reddish solid, mp 140—143 °C (dec.). Recrystallization of the solid from isopropyl ether–AcOEt (20 : 1, v/v) and drying over P_2O_5 at 2 mmHg and 75 °C for 3 h furnished an analytical sample (in the form of a hydrate) as colorless needles, mp 185—187 °C (dec.); $[\alpha]_D^{18}$ −68.5±0.6° (*c*=0.34, pyridine); UV λ_{max} (99% aqueous EtOH) 282.5 nm (log ε 3.97), 292 (3.87); UV λ_{max} (95% aqueous EtOH) 282 (3.95), 291 (3.85); UV λ_{max} (0.1 N aqueous NaOH) 283 (4.02); CD (*c*=6.14×10^{-5} M, 99% aqueous EtOH) $[\theta]^{22}$ (nm): 0 (302), −650 (292) (neg. max.), 0 (289), +330 (283) (pos. max.), 0 (281), −240 (279) (neg. max.), 0 (276) (pos. max.), −1630 (256) (neg. max.), −1140 (253) (pos. max.), −1300 (250);[23] CD (*c*=6.27×10^{-5} M, 0.1 N aqueous HCl) $[\theta]^{22}$ (nm): 0 (300), +160 (298) (pos. max.), 0 (295), −160 (292) (neg. max.), 0 (290) (pos. max.), −640 (282) (neg. max.), −480 (280) (pos. max.), −1280 (276) (neg. max.), −720 (268) (pos. max.), −1120 (261) (neg. max.), 0 (253), +800 (250);[23] TLC mobility, MS, IR ($CHCl_3$), and ^{1}H-NMR ($CDCl_3$), identical with those of (±)-**8**. *Anal.* Calcd for

$C_{29}H_{37}N_3O_3 \cdot 1/2H_2O$: C, 71.87; H, 7.90; N, 8.67. Found: C, 71.61; H, 7.93; N, 8.81. The synthetic (−)-**8** was identical [by comparison of melting point, specific rotation, and UV (in 95% aqueous EtOH), IR (in $CHCl_3$), ^{1}H-NMR (in $CDCl_3$), and mass spectra] with natural (−)-alangimarckine [lit.[3] mp 184—186 °C; $[\alpha]_D^{25}$ −67.7° (pyridine)].

[2*R-[2α(*R**),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2-[(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-2*H*-benzo[*a*]quinolizine [(±)-11]**——Debenzylation of (±)-**12** and work-up of the reaction mixture were carried out as described above for (±)-**8**, giving (±)-**11** (95% yield) as a yellowish solid, mp 199—201 °C (dec.). Recrystallization of the solid from MeCN and drying over P_2O_5 at 2 mmHg and 95 °C for 4.5 h yielded an analytical sample, which contained 0.5 molar equivalent of MeCN, as colorless prisms, mp 202—203 °C (dec.); TLC mobility (Table I); MS *m/e* (relative intensity): 475 (M^+) (59), 291 (51), 290 (41), 289 (32), 288 (63), 262 (100), 260 (35), 221 (31), 208 (65), 207 (25), 206 (28), 192 (26), 185 (87), 184 (29), 183 (26), 171 (63), 144 (15), 130 (7); UV λ_{max} (99% aqueous EtOH) 282.5 nm (log ε 3.97), 292 (3.87); UV λ_{max} (0.1 N aqueous NaOH) 283 (4.02); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 3480 (NH), 2800 (sh) and 2760 (*trans*-quinolizidine ring);[22] ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, 10-OMe), 3.82 (3H, s, 9-OMe), 6.00 (1H, s, $H_{(11)}$), 7.0—7.6 (4H, m, aromatic protons), 7.88 (1H, br, indole NH); ^{1}H-NMR (Me_2SO-d_6) δ: 2.08 (s, MeCN), other protons (Table II); ^{13}C-NMR ($CDCl_3$) (Table III). *Anal.* Calcd for $C_{29}H_{37}N_3O_3 \cdot 1/2CH_3CN$: C, 72.62; H, 7.82; N, 9.88. Found: C, 72.51; H, 7.96; N, 9.66.

[2*S*-[2α(*R),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2-[(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-2*H*-benzo[*a*]quinolizine [(−)-11]**——Debenzylation of (−)-**12** was effected as described above for (±)-**8**, and crude (−)-**11** was obtained in 95% yield as a faintly orange solid, mp 122—130 °C (dec.). Recrystallization of the solid from MeCN and drying over P_2O_5 at 2 mmHg and 60 °C for 24 h produced an analytical sample (in the form of a hydrate) as colorless needles, mp 130—132 °C (dec.); $[\alpha]_D^{19}$ −112.0±0.5° (*c* = 0.41, pyridine); UV λ_{max} (99% aqueous EtOH) 282.5 nm (log ε 3.94), 292 (3.84); UV λ_{max} (0.1 N aqueous NaOH) 283 (4.00); CD ($c = 6.06 \times 10^{-5}$ M, 99% aqueous EtOH) $[\theta]^{18}$ (nm): 0 (310), +3140 (300), +5780 (294) (pos. max.), +3300 (289) (neg. max.), +7100 (285) (pos. max.), +6110 (281) (neg. max.), +8090 (270) (pos. max.), +1650 (250);[23] CD ($c = 5.63 \times 10^{-5}$ M, 0.1 N aqueous HCl) $[\theta]^{18}$ (nm): 0 (306), +3020 (292) (pos. max.), +1600 (287) (neg. max.), +6390 (282) (pos. max.), +5860 (280) (neg. max.), +12600 (264) (pos. max.), +10650 (260), +8520 (255), +3900 (250);[23] TLC mobility, MS, IR ($CHCl_3$), and ^{1}H-NMR ($CDCl_3$), identical with those of (±)-**11**. *Anal.* Calcd for $C_{29}H_{37}N_3O_3 \cdot 1/3H_2O$: C, 72.32; H, 7.88; N, 8.72. Found: C, 72.62; H, 7.75; N, 8.94.

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References and Notes

1) Paper XII in this series, T. Fujii, M. Ohba, and H. Suzuki, *Chem. Pharm. Bull.*, **33**, 1023 (1985).
2) For recent reviews on the *Alangium* alkaloids, see *a*) T. Fujii and M. Ohba, "The Alkaloids," Vol. XXII, ed. by A. Brossi, Academic Press, New York, 1983, Chapter 1; *b*) T. Fujii, *Yakugaku Zasshi*, **103**, 257 (1983).
3) A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, *Tetrahedron Lett.*, **1966**, 4965.
4) Unless otherwise stated, the structural formulas of optically active compounds in this paper represent their absolute configurations.
5) T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Lett.*, **1977**, 3477.
6) T. Fujii, H. Kogen, and M. Ohba, *Tetrahedron Lett.*, **1978**, 3111.
7) B. Dasgupta, *J. Pharm. Sci.*, **54**, 481 (1965).
8) S. C. Pakrashi and E. Ali, *Tetrahedron Lett.*, **1967**, 2143.
9) *a*) T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron Lett.*, **1975**, 1527; *b*) *Idem, Tetrahedron*, **36**, 965 (1980); *c*) S. Yoshifuji and T. Fujii, *Tetrahedron Lett.*, **1975**, 1965; *d*) T. Fujii and S. Yoshifuji, *J. Org. Chem.*, **45**, 1889 (1980).
10) *a*) T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *Tetrahedron Lett.*, **1976**, 2553; *b*) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, **8**, 175 (1977); *c*) T. Fujii, K. Yamada, S. Minami, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, **31**, 2583 (1983).
11) *a*) S. C. Pakrashi, *Indian J. Chem.*, **2**, 468 (1964); *b*) J. D. Albright, J. C. Van Meter, and L. Goldman, *Lloydia*, **28**, 212 (1965); *c*) A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Lett.*, **1966**, 1081; *d*) S. C. Pakrashi and B. Achari, *Experientia*, **26**, 933 (1970).
12) A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Lett.*, **1966**, 5077.
13) T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, *Tetrahedron*, **32**, 2211 (1976).
14) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.* (*C*), **1969**, 91.

15) M. C. Koch, M. M. Plat, N. Préaux, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and E. Wenkert, *J. Org. Chem.*, **40**, 2836 (1975).
16) M. Koch, M. Plat, and N. Préaux, *Bull. Soc. Chim. Fr.*, **1973**, 2868.
17) F. Sigaut-Titeux, L. Le Men-Olivier, and J. Le Men, *Heterocycles*, **6**, 1895 (1977).
18) A. R. Battersby, J. R. Merchant, E. A. Ruveda, and S. S. Salgar, *Chem. Commun.*, **1965**, 315.
19) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, **1963**, 1461.
20) P. Karrer, C. H. Eugster, and O. Rüttner, *Helv. Chim. Acta*, **31**, 1219 (1948).
21) A. Takamizawa, Y. Sato, and S. Tanaka, *Yakugaku Zasshi*, **85**, 298 (1965).
22) *a*) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); *b*) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).
23) See ref. 6 for the graphic presentation.