[Chem. Pharm. Bull.
33(10)4314—4319(1985)]

Quinolizidines. XV.[1] A Racemic Synthesis of 10-Demethyltubulosine, an Alkaloid from *Alangium lamarckii*

TOZO FUJII* and MASASHI OHBA

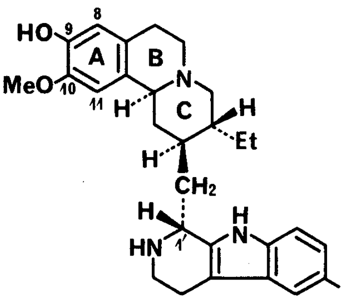
*Faculty of Pharmaceutical Sciences, Kanazawa University,
Takara-machi, Kanazawa 920, Japan*

(Received March 6, 1985)

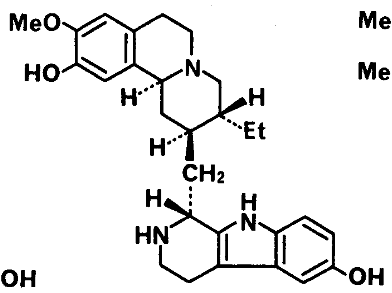
The racemic synthesis of the *Alangium lamarckii* alkaloid 10-demethyltubulosine (**2**) has been accomplished for the first time *via* a "lactim ether route," which included the intermediates (±)-**7**, (±)-**8**, (±)-**10**, and (±)-**9**. The 1′α-H isomers (±)-**12** and (±)-**11** were also obtained through this synthetic route. The assignments of the configuration at C-1′ of (±)-**2**, (±)-**9**, (±)-**11**, and (±)-**12** were based on four criteria, namely, the ratio of products from the catalytic reduction of (±)-**10**, thin-layer chromatographic mobility, and ^{1}H and ^{13}C nuclear magnetic resonance spectral features. The identity of synthetic (±)-**2** with (−)-demethyltubulosine from *A. lamarckii* unequivocally established the structure of this alkaloid.

Keywords——*Alangium lamarckii* alkaloid 10-demethyltubulosine; diethyl phosphorocyanidate amide formation; Bischler–Napieralski cyclization; carbon–nitrogen double bond catalytic reduction; benzyl ether catalytic hydrogenolysis; TLC epimer differentiation; NMR epimer differentiation

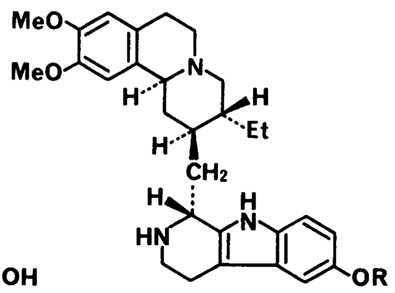
A number of benzo[*a*]quinolizidine alkaloids have been isolated from various parts of the Indian medicinal plant *Alangium lamarckii* THWAITES (Alangiaceae),[2] a deciduous shrub or small tree widely distributed throughout India, Burma, Ceylon, South China, Malaya, and the Philippines.[3,4] In 1966, Popelak *et al.*[5] reported the isolation of a new phenolic benzoquinolizidine alkaloid, designated as demethyltubulosine, from the stem- and root-bark of this plant. One year later, Pakrashi and Ali[6] also reported its isolation from the root-bark of the same plant. The German group[5] put forward two possible alternative structures (**1** and **2**) for this alkaloid on the basis of its two-step methylation to *O*-methyltubulosine (**4**) through tubulosine (**3**), as well as mass spectral evidence. With the aim of determining which structure is correct, we recently synthesized racemic 9-demethyltubulosine [(±)-**1**] and found that it did not match the *A. lamarckii* alkaloid demethyltubulosine.[1,7,8] This indicated the alternative 10-demethyl structure (**2**) to be the complete expression for the natural base. In the present paper, we detail our further efforts directed toward the synthesis of (±)-**2**, which have



1



2



3: R=H
4: R=Me

confirmed the correctness of the above indication. A brief account of the results described here has been published in a preliminary form.[9)]

The synthesis of the target molecule (±)-**2** proceeded from the *trans*-lactam ester (±)-**5** through a "lactim ether route,"[10)] which paralleled that employed for our recent synthesis[1,7)] of the 9-demethyl isomer (±)-**1**. The key intermediate was the tricyclic amino acid (±)-**7**, and it was obtained from (±)-**5** in eight steps *via* the lactim ether (±)-**6** according to the previously reported procedure.[11)] Application of the diethyl phosphorocyanidate method[12)] to the condensation of (±)-**7** with 5-benzyloxytryptamine in *N*,*N*-dimethylformamide (DMF) produced the amide (±)-**8** (96% yield), which was then cyclized with $POCl_3$ in boiling toluene to afford the dihydro-β-carboline (±)-**10** in 59% yield. Catalytic hydrogenation of (±)-**10** in dioxane over Adams catalyst and subsequent chromatographic separation of the products gave (±)-*O*,*O*-dibenzyl-10-demethyltubulosine [(±)-**9**] and its 1′-epimer [(±)-**12**] in 25% and 54% yields, respectively.

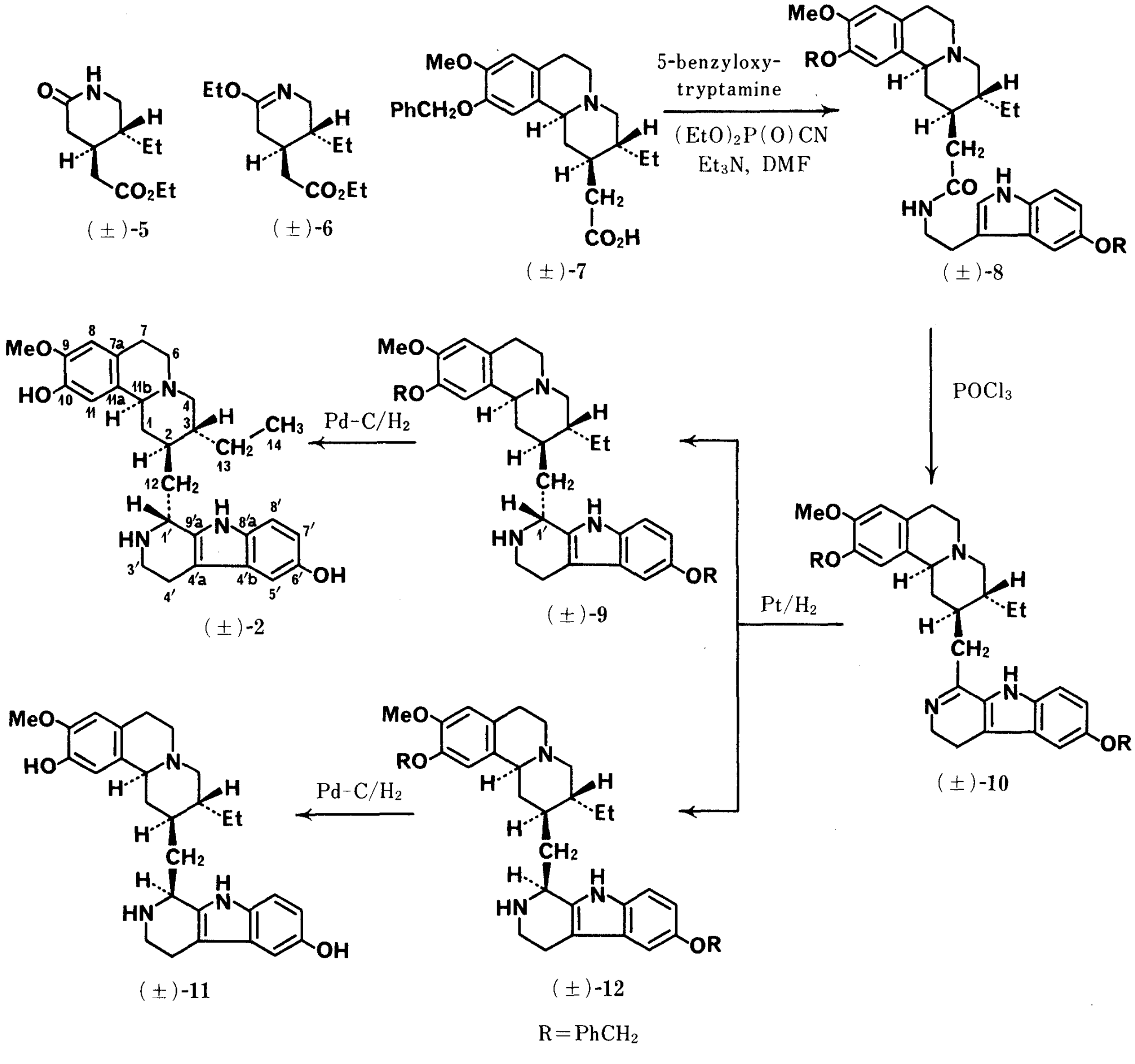


Chart 1

The assignments of the relative configuration at C-1′ of (±)-**9** and (±)-**12** were based on the following evidence. In the catalytic reduction of (±)-**10**, the formation of (±)-**12** predominated over that of (±)-**9** in a 2.2:1 molar ratio. On thin-layer chromatography

TABLE I. ^{13}C-NMR Data for (±)-10-Demethyltubulosine (**2**), (±)-*O*,*O*-Dibenzyl-10-demethyltubulosine (**9**), and the 1′α-H Isomer (±)-**12**

Carbon[b]	Chemical shift[a] (±)-**2**[c]	(±)-**9**[d]	(±)-**12**[d]
C(1)	36.3	36.8	38.9[k]
C(2)	35.8	36.3	38.4
C(3)	—[e]	41.8	42.7
C(4)	61.1	61.3	61.4
C(6)	52.1	52.5	52.5
C(7)	28.8	29.2	29.1
C(7a)	124.7	127.5	127.5
C(8)	111.9[f]	111.9[h]	111.9[l]
C(9)	144.2[g]	148.2[i]	148.2[m]
C(10)	145.7[g]	146.1[i]	146.2[m]
C(11)	112.1[f]	112.3[h]	111.7[l]
C(11a)	130.5	130.2	129.8
C(11b)	62.0	62.2	62.5
C(12)	—[e]	38.7	39.2[k]
C(13)	22.9	23.5	23.9
C(14)	11.0	11.1	11.3
C(1′)	48.7	49.3	52.3
C(3′)	41.6	42.2	42.6
C(4′)	22.4	23.0	22.9
C(4′a)	106.1	108.7	108.6
C(4′b)	127.8	128.0	127.9
C(5′)	101.7	102.2	102.1
C(6′)	150.0	153.2	153.2
C(7′)	110.0	112.1[h]	111.9[l]
C(8′)	110.9	111.3	111.4
C(8′a)	130.0	131.0	130.9
C(9′a)	138.3	137.5[j]	137.3[n]
9-OMe	55.5	56.0	55.9
10-O$\underline{\text{C}}$H$_2$Ph	—	71.7	71.5
6′-O$\underline{\text{C}}$H$_2$Ph	—	71.0	70.9
OCH$_2\underline{\text{Ph}}$	—	137.8[j]	137.7[n]
	—	—	137.6[n]
	—	128.4	128.3
	—	127.6	127.6
	—	127.2	127.5

a) In ppm downfield from internal Me$_4$Si. *b*) See formula (±)-**2** in Chart 1 for the numbering system. The carbon(s) indicated by underscoring in the partial structures is that to which the signal has been assigned. *c*) Measured in Me$_2$SO-d_6. *d*) Measured in CDCl$_3$. *e*) Overlapped with the signals of the solvent, Me$_2$SO-d_6. *f*—*n*) Assignments indicated by a given superscript may be interchanged.

TABLE II. ^{1}H-NMR Data for (±)-*O*,*O*-Dibenzyl-10-demethyltubulosine (**9**) and Its 1′α-H Isomer (±)-**12** in CDCl$_3$

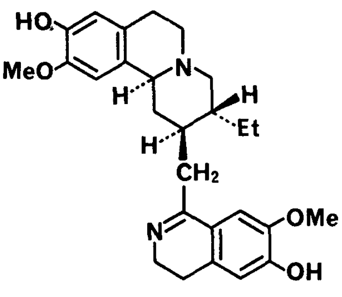
Proton[a]	Chemical shift (δ) (±)-**9**	(±)-**12**
CH$_2\underline{\text{Me}}$	0.86 (t)[b]	0.91 (t)[c]
C(9)OMe	3.83 (s)	3.80 (s)
C(1′)H	4.08 (d)[d]	4.08 (t)[e]
C(10)OC$\underline{\text{H}}_2$Ph	5.08 (s)	4.92 (s)
C(6′)OC$\underline{\text{H}}_2$Ph	5.08 (s)	5.01 (s)
C(8)H	6.59 (s)	6.56 (s)[f]
C(11)H	6.72 (s)	6.58 (s)[f]
C(5′)H	7.04 (d)[g]	7.01 (d)[h]
C(7′)H	6.85 (dd)[i]	6.82 (dd)[j]
C(8′)H	7.16 (d)[k]	7.17 (d)[l]
OCH$_2\underline{\text{Ph}}$	7.1—7.5 (m)	7.15—7.5 (m)
N(9′)H	7.80 (s)	7.97 (s)

a) See formula (±)-**2** in Chart 1 for the numbering system. The protons indicated by underscoring in the partial structures are those to which the signal has been assigned. *b*) With $J=6.8$ Hz. *c*) With $J=6.4$ Hz. *d*) With $J=10.5$ Hz. *e*) Dull triplet with $J=5.0$ Hz. *f*) Assignments indicated by this superscript may be reversed. *g*) With $J=2.4$ Hz. *h*) With $J=2.2$ Hz. *i*) With $J=8.6$ and 2.4 Hz. *j*) With $J=8.8$ and 2.2 Hz. *k*) With $J=8.6$ Hz. *l*) With $J=8.8$ Hz.

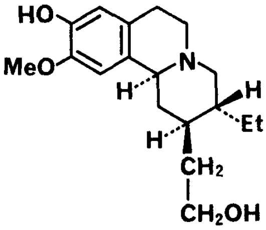
(TLC), (±)-**9** moved faster than (±)-**12**. In the ^{13}C nuclear magnetic resonance (^{13}C-NMR) spectra in CDCl$_3$ (see Table I), the C(1), C(2), and C(1′) carbon signals of (±)-**9** resonated at higher field than the corresponding carbon signals of (±)-**12** by 2.1—3.0 ppm. In the ^{1}H-NMR spectra in CDCl$_3$ (see Table II), the methylene protons of the C(10)-benzyloxy group in (±)-**12** were more shielded than those in (±)-**9** by 0.16 ppm. A similar upfield shift of the C(11)H proton signal of (±)-**12**, relative to that of (±)-**9**, was also observed. Furthermore, the C(1′)H proton signal of (±)-**9** appeared as a doublet with $J=10.5$ Hz, whereas that of (±)-**12** appeared as a dull triplet with $J=5.0$ Hz. These chemical, TLC, and ^{13}C-NMR and

^{1}H-NMR spectral features of (±)-**9** and (±)-**12** fulfilled all the recently reported[1,13] criteria for the 1′β-H and 1′α-H isomers, which had been shown to function satisfactorily in analogous ring systems.

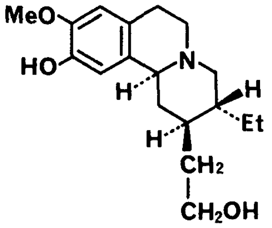
On hydrogenolysis using hydrogen and Pd–C catalyst, (±)-**9** furnished the target molecule (±)-**2** (79% yield), which was characterized as a dihydrate, mp 199—201 °C (dec.). A similar debenzylation of the epimeric base (±)-**12** afforded the corresponding phenolic base (±)-**11** in 88% yield. The ultraviolet (UV) (MeOH, 0.1 N aqueous NaOH, or 0.1 N aqueous HCl), infrared (IR) (Nujol), ^{1}H-NMR (Me$_2$SO-d_6), and mass spectra and TLC mobility of the synthetic (±)-**2**·2H$_2$O were found to be identical with those of natural (−)-demethyltubulosine dihydrate [mp 198—200 °C (dec.)].



13



14



15

Thus, the above results, together with the previous chemical correlation,[5] establish the structure of the *Alangium lamarckii* alkaloid demethyltubulosine as 10-demethyltubulosine [**2** (absolute configuration shown)]. Interestingly, the positions of the methoxy and the hydroxy groups in ring A of this base are just the reverse of those of desmethylpsychotrine (**13**),[6,11,14] a co-occurring alkaloid.[6] However, this turned out to be not uncommon when Pakrashi and co-workers[15] quite recently isolated from the seeds of *A. lamarckii* two new alkaloids inferred to be 9-demethylprotoemetinol (**14**) and 10-demethylprotoemetinol (**15**), the structure and stereochemistry of the latter having been confirmed by us *via* synthesis.[16]

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 11*b* for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

(±)-10-Benzyloxy-*N*-[2-(5-benzyloxy-1*H*-indol-3-yl)ethyl]-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine-2β-acetamide [(±)-8]——Diethyl phosphorocyanidate[17] (1.31 g, 8.03 mmol) and Et$_3$N (810 mg, 8.00 mmol) were successively added to an ice-cooled, stirred solution of (±)-**7**·H$_2$O[11] (1.71 g, 4.00 mmol) and 5-benzyloxytryptamine[18] (1.60 g, 6.01 mmol) in HCONMe$_2$ (20 ml). The mixture was stirred at room temperature for 6 h and extracted with CHCl$_3$ after addition of H$_2$O (30 ml). The CHCl$_3$ extracts were combined, washed with H$_2$O, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo* to leave an orange glass, which crystallized from AcOEt to afford (±)-**8** (2.53 g, 96%) as almost colorless, minute prisms, mp 148.5—150 °C. Recrystallization from AcOEt gave an analytical sample as colorless prisms, mp 150.5—152 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 and 3460 (NH's), 2820 and 2760 (*trans*-quinolizidine ring),[19] 1658 (amide CO); ^{1}H-NMR (CDCl$_3$) δ: 0.88 (3H, t, J= 6.6 Hz, CCH$_2\underline{Me}$), 3.84 (3H, s, OMe), 4.97 and 5.04 (2H, AB type d's, J= 11.6 Hz, OC$\underline{H}_2$Ph), 5.06 (2H, s, OC$\underline{H}_2$Ph), 5.53 (1H, t, J= 5.5 Hz, CONH), 6.60 (1H, s, H$_{(8)}$ or H$_{(11)}$), 6.74 (1H, s, H$_{(11)}$ or H$_{(8)}$), 6.88 (1H, dd, J= 8.6 and 2.2 Hz, H$_{(6')}$), 6.90 (1H, d, J= 2.0 Hz, H$_{(2')}$), 7.09 (1H, d, J= 2.2 Hz, H$_{(4')}$), 7.11 (1H, d, J= 8.6 Hz, H$_{(7')}$), 7.15—7.5 (10H, m, two OCH$_2\underline{Ph}$'s), 8.18 (1H, br, indole NH).[20] *Anal.* Calcd for C$_{42}$H$_{47}$N$_3$O$_4$: C, 76.68; H, 7.20; N, 6.39. Found: C, 76.54; H, 7.21; N, 6.41.

(±)-10-Benzyloxy-2β-[(6-benzyloxy-4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-3α-ethyl-1,3,4,6,7,11bα-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizine [(±)-10]——A solution of (±)-**8** (2.17 g, 3.3 mmol) and POCl$_3$ (5.06 g, 33 mmol) in dry toluene (100 ml) was heated under reflux in an atmosphere of nitrogen for 2.5 h. The reaction mixture was evaporated *in vacuo* to leave an orange gum, which was treated with a mixture of CH$_2$Cl$_2$ (80 ml) and 5%

aqueous KOH (80 ml) under ice-cooling and stirring for 10 min. The CH_2Cl_2 layer was separated from the aqueous layer, which was further extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a dark orange glass. The glass was purified by means of column chromatography [silica gel (40 g), benzene–EtOH (10 : 1, v/v)] to furnish (±)-**10** (1.24 g, 59%) as a yellow glass, MS *m/e*: 639 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (NH), 2760 (*trans*-quinolizidine ring);[19] ^1H-NMR ($CDCl_3$) δ: 0.92 (3H, t, $J=6.6$ Hz, $CCH_2\underline{Me}$), 3.80 (3H, s, OMe), 4.82 and 5.03 (2H each, s, two $OC\underline{H}_2Ph$'s), 6.48 (1H, s, $H_{(8)}$ or $H_{(11)}$), 6.54 (1H, s, $H_{(11)}$ or $H_{(8)}$), 6.9—7.5 (13H, m, $H_{(5')}$, $H_{(7')}$, $H_{(8')}$, and two $OCH_2\underline{Ph}$'s), 8.25 (1H, br, NH).

[2*R-[2α(*S**),3β,11bβ]]- and [2*R**-[2α(*R**),3β,11bβ]]-10-Benzyloxy-2-[(6-benzyloxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-3-ethyl-1,3,4,6,7,11b-hexahydro-9-methoxy-2*H*-benzo[*a*]quinolizines [(±)-9 and (±)-12]**——A solution of (±)-**10** (1.00 g, 1.56 mmol) in dioxane (25 ml) was hydrogenated over Adams catalyst (120 mg) at atmospheric pressure and 19 °C for 1.5 h. Removal of the catalyst by filtration with the aid of EtOH (30 ml) and concentration of the filtrate under reduced pressure left an orange oil, which was dissolved in $CHCl_3$ (80 ml). The $CHCl_3$ solution was washed successively with 5% aqueous NaOH and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*, leaving a dark orange glass (995 mg). The glass was then chromatographed on a Merck Lobar column (LiChroprep Si 60) using $CHCl_3$–EtOH (10 : 1, v/v) as eluent. Earlier fractions yielded (±)-*O*,*O*-dibenzyl-10-demethyltubulosine [(±)-**9**] (254 mg, 25%) as a pale yellow glass, TLC *Rf* 0.57 [silica gel, $CHCl_3$–EtOH (10 : 1, v/v)]; MS *m/e*: 641 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (indole NH), 3390 [N(2′)H], 2820 and 2760 (*trans*-quinolizidine ring);[19] ^1H-NMR (Table II); ^{13}C-NMR (Table I). This sample crystallized from EtOH, and further recrystallizations from EtOH and drying over P_2O_5 at 2 mmHg and 40 °C for 18 h produced an analytical sample of (±)-**9**·1/2EtOH as colorless needles, mp 89—91 °C; IR ν_{max}^{Nujol} cm^{-1}: 2760 (*trans*-quinolizidine ring);[19] ^1H-NMR ($CDCl_3$) δ: 0.88 (3H, t, $J=6.8$ Hz, $CCH_2\underline{Me}$), 1.23 (1.5H, t, $J=7.1$ Hz, $\underline{Me}CH_2OH$), 3.71 (1H, q, $J=7.1$ Hz, $MeC\underline{H}_2OH$), 3.86 (3H, s, OMe), 4.11 (1H, d, $J=10.5$ Hz, $H_{(1')}$), 5.11 (4H, s, two $OC\underline{H}_2Ph$'s), 6.60 (1H, s, $H_{(8)}$), 6.71 (1H, s, $H_{(11)}$), 6.88 (1H, dd, $J=8.8$ and 2.4 Hz, $H_{(7')}$), 7.05 (1H, d, $J=2.4$ Hz, $H_{(5')}$), 7.22 (1H, d, $J=8.8$ Hz, $H_{(8')}$), 7.1—7.5 (10H, m, two $OCH_2\underline{Ph}$'s), 7.57 (1H, br, NH). *Anal.* Calcd for $C_{42}H_{47}N_3O_3 \cdot 1/2C_2H_5OH$: C, 77.68; H, 7.58; N, 6.32. Found: C, 77.53; H, 7.42; N, 6.53.

Later fractions obtained from the above chromatography gave the 1′α-H isomer (±)-**12** (541 mg, 54%) as a yellow glass, TLC *Rf* 0.48 [silica gel, $CHCl_3$–EtOH (10 : 1, v/v)]; MS *m/e*: 641 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (indole NH), 3390 [N(2′)H], 2820 and 2760 (*trans*-quinolizidine ring);[19] ^1H-NMR (Table II); ^{13}C-NMR (Table I).

[2*R-[2α(*S**),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-10-hydroxy-2-[(6-hydroxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-9-methoxy-2*H*-benzo[*a*]quinolizine [(±)-10-Demethyltubulosine] [(±)-2]**——A solution of (±)-**9**·1/2EtOH (166 mg, 0.25 mmol) in MeOH–AcOH (1 : 1, v/v) (12 ml) was hydrogenated over 10% Pd–C (160 mg) at atmospheric pressure and 18 °C for 3 h. The catalyst was removed by filtration and washed with MeOH (15 ml). The filtrate and washings were combined and concentrated *in vacuo*, and H_2O (3 ml) was added to the oily residue. The aqueous mixture was filtered and the filtrate was made alkaline with 10% aqueous Na_2CO_3. The crystals that resulted were filtered off, washed with H_2O, and dried to yield (±)-**2**·$2H_2O$ (98 mg, 79%). Recrystallization from MeOH–CH_2Cl_2 (1 : 1, v/v) and drying over P_2O_5 at 2 mmHg and room temperature for 18 h gave an analytical sample as colorless minute needles, mp 199—201 °C (dec.); TLC *Rf* 0.46 [silica gel, $CHCl_3$–MeOH (2 : 1, v/v)]; MS *m/e* (relative intensity): 461 (M^+) (65), 261 (27), 260 (39), 259 (30), 258 (78), 256 (38), 232 (63), 230 (41), 201 (93), 200 (57), 199 (59), 198 (27), 191 (36), 187 (100), 185 (27), 178 (41), 177 (33), 176 (42); UV λ_{max} (MeOH): 281 nm (ε 12500); λ_{max} (0.1 N aqueous NaOH): 283 (10500), 304 (sh) (8920), 327 (sh) (3740); λ_{max} (0.1 N aqueous HCl): 277.5 (11800); ^1H-NMR (Me_2SO-d_6) δ: 3.72 (3H, s, OMe), 4.10 (1H, d, $J=9.8$ Hz, $H_{(1')}$), 6.50 (1H, dd, $J=8.5$ and 2.2 Hz, $H_{(7')}$), 6.59 (1H, s, $H_{(8)}$), 6.66 (1H, d, $J=2.2$ Hz, $H_{(5')}$), 6.72 (1H, s, $H_{(11)}$), 7.03 (1H, d, $J=8.5$ Hz, $H_{(8')}$), 8.47 (1H, br, indole NH), 10.28 [1H, s, N(2′)H]; ^{13}C-NMR (Table I). *Anal.* Calcd for $C_{28}H_{35}N_3O_3 \cdot 2H_2O$: C, 67.58; H, 7.90; N, 8.44. Found: C, 67.42; H, 7.67; N, 8.36. The TLC mobility and mass, UV, IR (Nujol), and ^1H-NMR spectra of this sample were identical with those of the *Alangium lamarckii* alkaloid (−)-demethyltubulosine dihydrate[5] [mp 198—200 °C (dec.); $[\alpha]_D^{23}$ −51.9° ($c=1$, pyridine)].

[2*R-[2α(*R**),3β,11bβ]]-3-Ethyl-1,3,4,6,7,11b-hexahydro-10-hydroxy-2-[(6-hydroxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methyl]-9-methoxy-2*H*-benzo[*a*]quinolizine [(±)-11]**——Debenzylation of (±)-**12** and work-up of the reaction mixture were effected in a manner similar to that described above for (±)-**2**, giving (±)-**11** (88% yield) as a pale brown solid. Recrystallization of the solid from EtOH and drying over P_2O_5 at 2 mmHg and 50 °C for 15 h produced an analytical sample as colorless minute prisms, mp 215—217 °C (dec.); TLC *Rf* 0.31 [silica gel, $CHCl_3$–MeOH (2 : 1, v/v)]; MS *m/e*: 461 (M^+); UV λ_{max} (MeOH): 278 nm (ε 11900); λ_{max} (0.1 N aqueous NaOH): 284 (10200), 304 (sh) (8520), 327 (sh) (3530); λ_{max} (0.1 N aqueous HCl): 277.5 (10800); ^1H-NMR (Me_2SO-d_6) δ: 3.71 (3H, s, OMe), 3.94 (1H, dull t, $J=5$ Hz, $H_{(1')}$), 6.51 (1H, dd, $J=8.5$ and 2.4 Hz, $H_{(7')}$), 6.56 (1H, s, $H_{(8)}$ or $H_{(11)}$), 6.64 (1H, s, $H_{(11)}$ or $H_{(8)}$), 6.66 (1H, d, $J=2.4$ Hz, $H_{(5')}$), 7.07 (1H, d, $J=8.5$ Hz, $H_{(8')}$), 8.46 (1H, br, indole NH), 10.31 [1H, s, N(2′)H]. *Anal.* Calcd for $C_{28}H_{35}N_3O_3 \cdot 2/3H_2O$: C, 71.01; H, 7.73; N, 8.87. Found: C, 70.84; H, 7.48; N, 8.60.

Acknowledgment This work was supported by a Grant-in-Aid for Special Project Research [to Professor Y. Ban (Sapporo)] from the Ministry of Education, Science and Culture, Japan. We are grateful to Dr. A. Popelak (Mannheim) for the generous gift of demethyltubulosine isolated from *Alangium lamarckii* and to Professor T. Shioiri

(Nagoya) for providing us with diethyl phosphorocyanidate.

References and Notes

1) Paper XIV in this series, M. Ohba, M. Hayashi, and T. Fujii, *Chem. Pharm. Bull.*, **33**, 3724 (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); *c)* W. Wiegrebe, W. J. Kramer, and M. Shamma, *J. Nat. Prod.*, **47**, 397 (1984).

3) K. R. Kirtikar and B. D. Basu, "Indian Medicinal Plants," 2nd ed., Vol. II, L. M. Basu, Allahabad, India, 1933, pp. 1236—1239.

4) R. N. Chopra, I. C. Chopra, K. L. Handa, and L. D. Kapur, "Indigenous Drugs of India," 2nd ed., U. N. Dhar and Sons, Calcutta, 1958, pp. 270—271.

5) A. Popelak, E. Haack, and H. Spingler, *Tetrahedron Lett.*, **1966**, 1081.

6) S. C. Pakrashi and E. Ali, *Tetrahedron Lett.*, **1967**, 2143.

7) M. Ohba, M. Hayashi, and T. Fujii, *Heterocycles*, **14**, 299 (1980).

8) On the other hand, (±)-**1** was quite recently found to correspond to a $C_{28}H_{35}N_3O_3$ alkaloid isolated from another species of the same genus, *Alangium vitiense*. For the details, see ref. 1 and C. Kan-Fan, R. Freire, H.-P. Husson, T. Fujii, and M. Ohba, *Heterocycles*, **23**, 1089 (1985).

9) T. Fujii, M. Ohba, A. Popelak, S. C. Pakrashi, and E. Ali, *Heterocycles*, **14**, 971 (1980).

10) For the "lactim ether route" leading to the benzo[*a*]quinolizidine and indolo[2,3-*a*]quinolizidine systems, see references cited in ref. 11*b*.

11) *a)* T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, *Heterocycles*, **12**, 1463 (1979); *b)* T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **33**, 144 (1985).

12) T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, *Tetrahedron*, **32**, 2211 (1976).

13) T. Fujii, H. Kogen, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, **33**, 1946 (1985).

14) *a)* T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, *Tetrahedron Lett.*, **1979**, 4955; *b)* T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **33**, 583 (1985).

15) E. Ali, R. R. Sinha, B. Achari, and S. C. Pakrashi, *Heterocycles*, **19**, 2301 (1982).

16) T. Fujii, M. Ohba, H. Suzuki, S. C. Pakrashi, and E. Ali, *Heterocycles*, **19**, 2305 (1982).

17) A. Takamizawa, Y. Sato, and S. Tanaka, *Yakugaku Zasshi*, **85**, 298 (1965).

18) L. Bretherick, K. Gaimster, and W. R. Wragg, *J. Chem. Soc.*, **1961**, 2919.

19) *a)* F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); *b)* E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

20) For convenience, each position of the indole ring is indicated by a primed number.