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Quinolizidines. XVIII.[1] Syntheses of (−)- and (+)-Ankorines through a Lactim Ether Route

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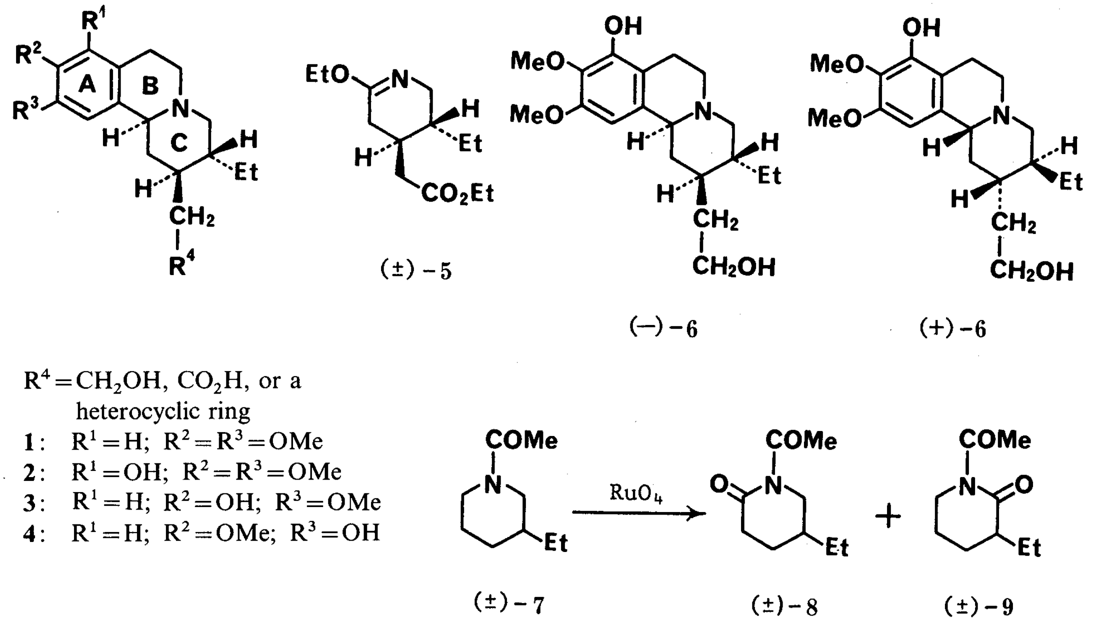
A formal chiral synthesis of the *Alangium* alkaloid (−)-ankorine [(−)-**6**] has been accomplished in the form of the synthesis of the lactam phenol (+)-**14** from the (+)-*trans*-lactim ether (+)-**5** and 2-benzyloxy-3,4-dimethoxyphenacyl bromide through the intermediates (+)-**10** and **11**. A parallel sequence of conversions starting from the (−)-*trans*-lactim ether (−)-**5** and proceeding through the intermediates (−)-**10**, **24**, (−)-**14**, (−)-**25**, **26**, (+)-**27**, and (+)-**28** produced the enantiomer [(+)-**6**] of natural ankorine. For an alternative chiral synthesis of (−)-**6**, ethyl cincholoiponate [(+)-**19**] was acetylated and the resulting *N*-acetyl derivative (+)-**20** was oxidized with RuO_4 to give the 6-piperidone (+)-**21** and 2-piperidone (−)-**23** in 55% and 27% yields, respectively. The (−)-*cis*-lactim ether (−)-**16**, obtained by ethylation of (+)-**21** with triethyloxonium fluoroborate, was then converted into (−)-**13**, a known precursor for the synthesis of (−)-ankorine [(−)-**6**], in good overall yield by a "lactim ether route," which proceeded through (+)-**15** and **12**.

Keywords——*Alangium* alkaloid (−)-ankorine synthesis; ankorine (+)-antipode synthesis; lactim ether alkylation; sodium borohydride phenacyl group reduction; benzylic alcohol catalytic hydrogenolysis; *N*-acetylcincholoiponate ruthenium tetroxide oxidation; regioselective lactam formation; Bischler–Napieralski cyclization; lithium aluminum hydride ester reduction; benzyl ether hydrogenolysis

It is known that the Indian medicinal plant *Alangium lamarckii* THW. (Alangiaceae) contains eighteen benzo[*a*]quinolizidine alkaloids and ten other alkaloids.[1] These benzo[*a*]quinolizidine-type *Alangium* alkaloids may be classified into four groups (**1**—**4**)[2] according to their substitution patterns in the aromatic ring A.[1,3] Our previous studies have shown that the racemic syntheses of all of these types of alkaloids are possible through the "lactim ether route"[4] or "3-acetylpyridine route"[1,5] and the chiral syntheses, through the "cincholoipon-incorporating route."[3,4c,d,h,6] The "lactim ether route" utilizes the racemic lactim ether (±)-**5** as a common key intermediate, and hence its scope has so far been limited to the syntheses in the racemic series. In quite a recent work, however, we were able to prepare both the enantiomers of **5** by optical resolution at a precursor stage.[7] In addition, the chiral equivalent **21** may be available from cincholoipon ethyl ester [(+)-**19**] by the RuO_4 oxidation method,[8,9] which has been shown to convert 1-acetyl-3-ethylpiperidine [(±)-**7**] into the 6-piperidone (±)-**8** and 2-piperidone (±)-**9** in 44% and 34% yields, respectively.[8] In the present study, the extension of the "lactim ether route" to the chiral series has been exemplified by the syntheses of the *Alangium* alkaloid (−)-ankorine [(−)-**6**] and its unnatural (+)-antipode [(+)-**6**] from such optically active lactim ethers.[10]

Condensation of the (+)-*trans*-lactim ether (+)-**5**[7] with 2-benzyloxy-3,4-dimethoxyphenacyl bromide was carried out as described previously[4b] for the racemic series, giving the lactam ketone (+)-**10** in 87% yield. Reduction of (+)-**10** with $NaBH_4$ and



(±)-5

(−)-6

(+)-6

$R^4 = CH_2OH$, CO_2H, or a heterocyclic ring

1: $R^1 = H$; $R^2 = R^3 = OMe$

2: $R^1 = OH$; $R^2 = R^3 = OMe$

3: $R^1 = H$; $R^2 = OH$; $R^3 = OMe$

4: $R^1 = H$; $R^2 = OMe$; $R^3 = OH$

(±)-7

(±)-8

(±)-9

Chart 1

hydrogenolysis (10% Pd–C/H_2, EtOH–70% aqueous $HClO_4$, 1 atm, 27 °C, 4 h) of the resulting diastereomeric mixture of the lactam alcohol **11** furnished the *trans*-lactam phenol (+)-**14** [96% overall yield from (+)-**10**], which was identical with an authentic sample synthesized previously[6b] through a different route. Since (+)-**14** has already been converted into (−)-ankorine [(−)-**6**],[6b] alangicine (type **2**),[4d] and alangimarckine (type **2**),[4c] the above sequence of conversions starting with (+)-**5** formally constitutes new chiral syntheses of these *Alangium* alkaloids.

Another new synthesis of (−)-ankorine [(−)-**6**] was started from ethyl cincholoiponate [(+)-**19**], a readily available degradation product[6c] from the *Cinchona* alkaloid cinchonine. Treatment of (+)-**19** with acetyl chloride and aqueous Na_2CO_3 produced the *N*-acetyl derivative (+)-**20** in 97% yield. Oxidation of (+)-**20** with a mixture of RuO_2 and 10% aqueous $NaIO_4$ according to the previously reported standard procedure[9] (for oxidation of proline derivatives) and chromatographic separation of the crude products on alumina gave the 6-piperidone (+)-**21** and 2-piperidone (−)-**23** in 55% and 27% yields, respectively. Deacetylation of the primarily oxidized products (imides) had apparently occurred during the chromatographic separation process. It was advantageous that the observed regioselectivity [(+)-**21**:(−)-**23** = 67:33] in favor of the 6-oxidation was considerably higher than that [(±)-**8**:(±)-**9** = 57:43][8] in the model reaction [(±)-**7**→(±)-**8**+(±)-**9** (Chart 1)] described above. The 6-piperidone structure of (+)-**21** was established by its spectral identity with authentic (±)-**21**;[11] and the *cis*-2-piperidone structure of (−)-**23**, by ethylation of (−)-**23** with triethyloxonium fluoroborate and $NaBH_4$ reduction of the resulting lactim ether (+)-**18** to afford the starting *cis*-ester (+)-**19** in 90% overall yield [from (−)-**23**]. In view of its 2-piperidone structure, it is interesting that (−)-**23** did not epimerize at the 3-position, at any rate during the alumina treatment included in the isolation procedure.[6a]

Hydrolysis of (+)-**21** with KOH in aqueous EtOH at room temperature provided the *cis*-lactam acid (+)-**22** in 83% yield. Based on our knowledge and experience of thermal *cis*–*trans* isomerization in the 5-ethyl-2-oxo-4-piperidineacetic acid system,[12] (+)-**22** was heated neat at 190 °C for 15 min in order to obtain the *trans*-lactam acid (+)-**17**,[7] a synthetic precursor of (+)-**5**. Although carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectral analysis[12] of the product suggested that it was a 66:34 mixture of (+)-**17** and (+)-**22** as expected, every effort

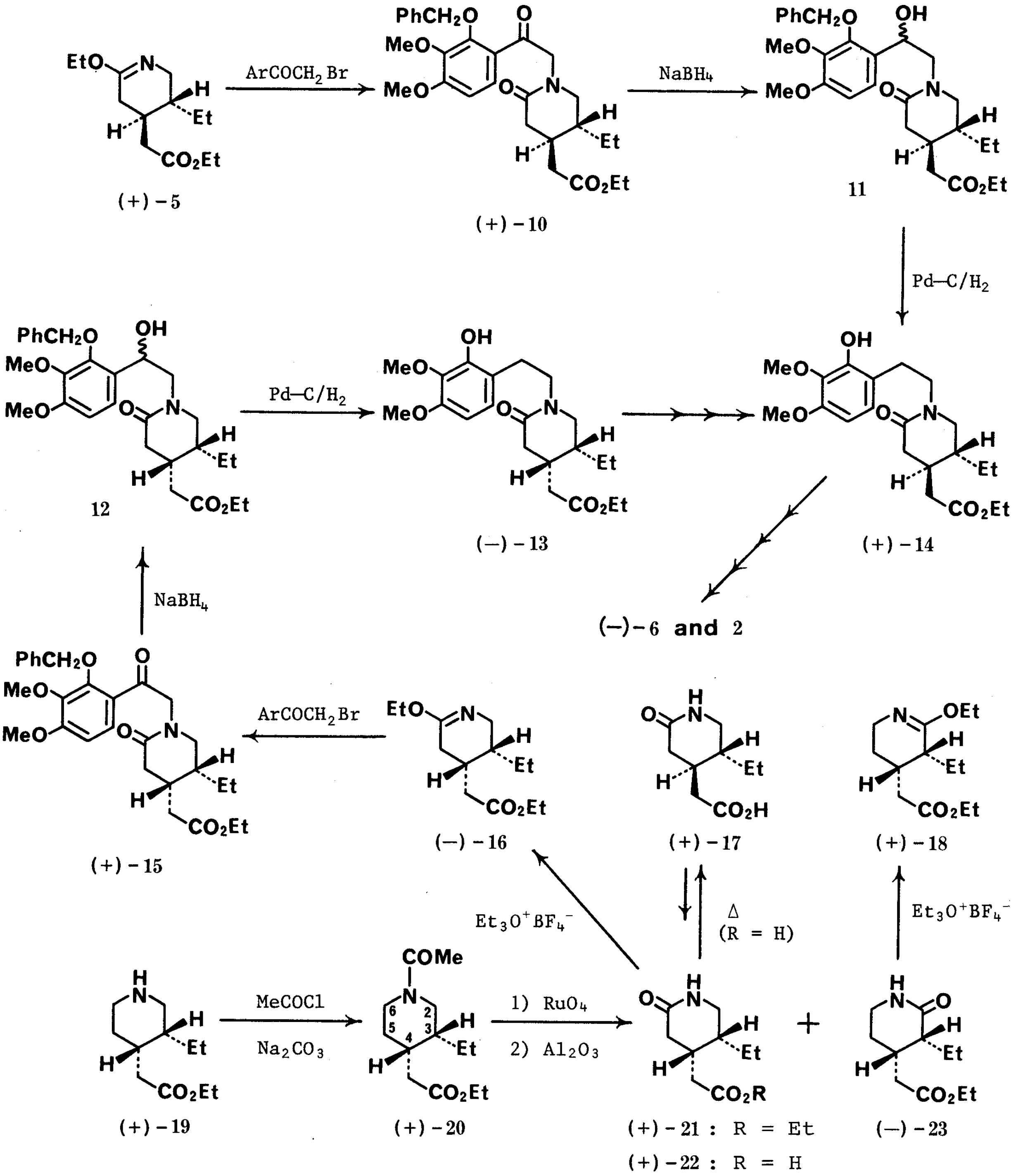


Chart 2

of separating the *trans* isomer from the mixture was in vain. Thus, the alteration of stereochemistry in (+)-**21** was left to be done at a later stage. Ethylation of (+)-**21** with triethyloxonium fluoroborate gave the lactim ether (−)-**16** in 93% yield. Conversion of (−)-**16** into the *cis*-lactam phenol (−)-**13** through (+)-**15** and **12** was effected in 89% overall yield as described above for the parallel conversion of the *trans*-lactim ether (+)-**5** into (+)-**14** through (+)-**10** and **11**. Since (−)-**13** has already been led to the *trans*-lactam phenol (+)-**14** [a synthetic precursor of (−)-ankorine and other **2**-type alkaloids] by a three-step conversion involving thermal *cis–trans* isomerization,[6b)] the reaction sequence (+)-**19**→(+)-**20**→(+)-**21**→(−)-**16**→(+)-**15**→**12**→(−)-**13** is formally tantamount to new syntheses of the **2**-type

Alangium alkaloids. This sequence may be regarded as a hybrid of the original "cincholoipon-incorporating route" and "lactim ether route."

Finally, the "lactim ether route" was extended to cover the antipodal series. The (−)-*trans*-lactim ether (−)-**5**[7)] was converted into the (−)-*trans*-lactam phenol (−)-**14** in 90% overall yield through (−)-**10** and **24**, a series of conversions parallel to that (Chart 2) employed for the synthesis of (+)-**14** from (+)-**5**. Benzylation of (−)-**14** with benzyl bromide and anhydrous K_2CO_3 in boiling acetone furnished the benzyl ether (−)-**25** (92% yield), which was then cyclized with $POCl_3$ in boiling toluene. The resulting iminium salt **26** was reduced with hydrogen activated on Adams catalyst, affording the tricyclic ester (+)-**27** in 48% overall yield [from (−)-**25**]. Reduction of (+)-**27** to the alcohol (+)-**28** was effected in 85% yield with $LiAlH_4$ in boiling ether, and (+)-**28** was debenzylated with hydrogen activated on Pd–C catalyst, giving the target molecule (+)-**6** in 96% yield. Apart from the opposite sign of specific rotation, the synthetic (+)-**6** was identical with natural ankorine [(−)-**6**], confirming the completion of the first synthesis of unnatural ankorine [(+)-**6**]. The syntheses of the antipodes of other **2**-type *Alangium* alkaloids such as alangicine and alangimarckine should also be possible from (+)-**27** since (−)-**27** has already been led to the natural alkaloids.[4c,d)]

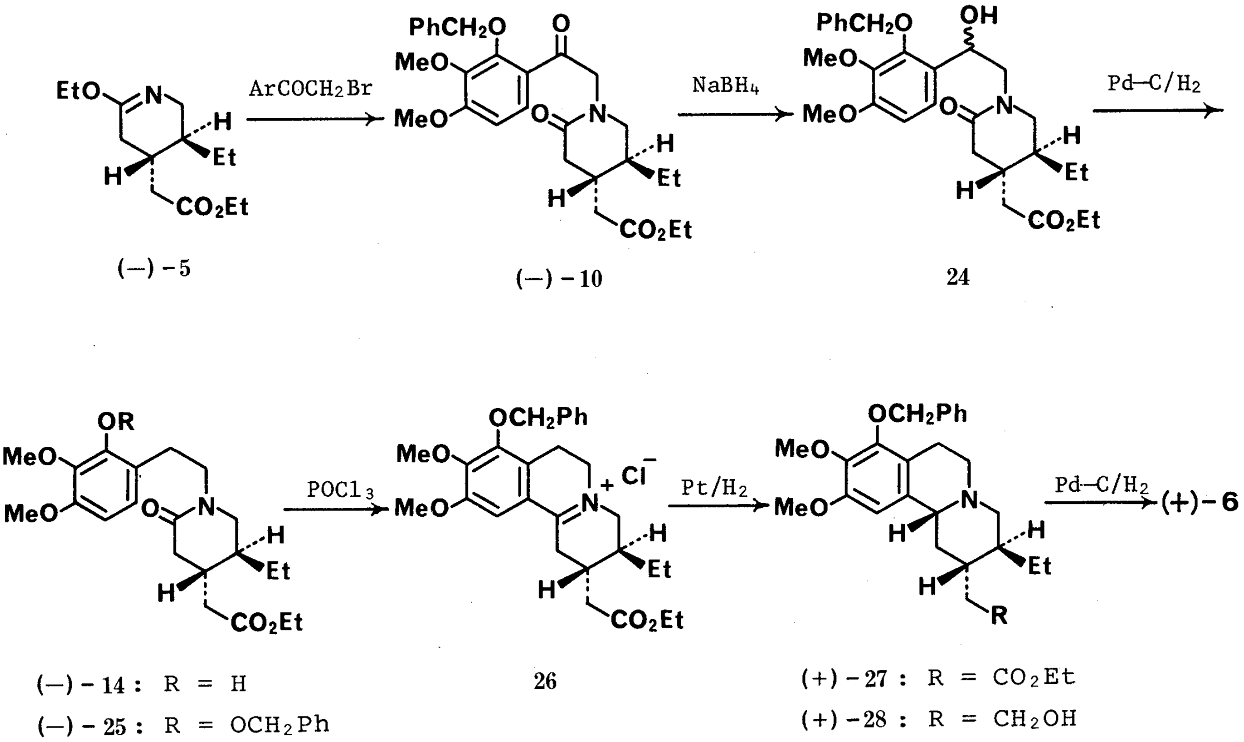


Chart 3

In conclusion, the ready availability of both enantiomers of the *trans*-lactim ether **5** as well as of the (−)-*cis*-lactim ether (−)-**16** from ethyl cincholoiponate [(+)-**19**] has thus enlarged the scope of the original "lactim ether route"[4)] to cover the chiral syntheses of the **2**-type *Alangium* alkaloids. Similar chiral syntheses of the **1**-, **3**-, and **4**-type alkaloids should also be possible if appropriate phenacyl bromides ($ArCOCH_2Br$) are selected for the initial condensation with the lactim ethers (+)-**5**, (−)-**5**, and (−)-**16**, and comparison of biological activities between the natural alkaloids and their antipodes would be of considerable interest.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected; boiling points are uncorrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a Hitachi 320 ultraviolet (UV) spectrophotometer, a JASCO A-202 infrared (IR) spectrophotometer, a Hitachi M-80 mass spectrometer, or a JEOL JNM-FX-100 NMR spectrometer, equipped with a ^{13}C Fourier transform NMR system, at 24 °C with Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-181 polarimeter. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet.

(4*R*,5*R*)-1-(2-Benzyloxy-3,4-dimethoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-10]——A solution of (+)-**5**[7] (640 mg, 2.65 mmol) and 2-benzyloxy-3,4-dimethoxyphenacyl bromide[13] (1.06 g, 2.9 mmol) in $HCONMe_2$ (1 ml) was stirred at 60—65 °C for 10 h. After cooling, the reaction mixture was diluted with pyridine (1 ml), stirred at room temperature overnight, and concentrated *in vacuo* to leave an oily residue. The residue was partitioned by extraction with a mixture of benzene and 5% aqueous HCl. The benzene extracts were washed successively with 5% aqueous HCl and saturated aqueous NaCl, dried, and concentrated to leave (+)-**10** (1.15 g, 87%) as an orange oil, which was shown to be homogeneous on thin-layer chromatographic (TLC) analysis. Purification of the oil by column chromatography [silica gel, AcOEt–hexane (2 : 1, v/v)] gave a pale yellow oil, $[\alpha]_D^{24}$ +26.0 ° ($c = 0.51$, EtOH); MS *m/e*: 497 (M^+). The IR ($CHCl_3$) and ^1H-NMR ($CDCl_3$) spectra and TLC behavior of this sample were identical with those of authentic (±)-**10**.[4b)]

(4*R*,5*R*)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (11)——A solution of (+)-**10**, (1.34 g, 2.7 mmol) in EtOH (20 ml) was stirred under ice-cooling, and $NaBH_4$ (102 mg, 2.7 mmol) was added portionwise. After the mixture had been stirred at room temperature for 4 h, acetone (1 ml) was added. The resulting mixture was further stirred at room temperature for 30 min and then concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of benzene and H_2O. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a diastereomeric mixture of **11** (1.32 g, 98%) as a faintly yellow solid, mp 87—88 °C; $[\alpha]_D^{25}$ +45.3 ° ($c = 0.50$, EtOH); MS *m/e*: 499 (M^+). The IR ($CHCl_3$) and ^1H-NMR ($CDCl_3$) spectra and TLC behavior of this solid were identical with those of authentic (±)-**11**.[4b)]

(4*R*,5*R*)-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-14]——A solution of **11** (1.10 g, 2.2 mmol) in EtOH (20 ml) containing 70% aqueous $HClO_4$ (0.3 ml) was hydrogenated over 10% Pd–C (300 mg) at atmospheric pressure and 27 °C for 4 h. The catalyst was removed by filtration and washed with EtOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a pale brown oil, which was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated to give (+)-**14** (851 mg, 98%) as a slightly brownish solid, mp 83—85 °C. Recrystallization of the solid from isopropyl ether yielded a pure sample as colorless needles, mp 87.5—88.5 °C; $[\alpha]_D^{27}$ +76.2 ° ($c = 1.00$, EtOH). This sample was identical [by mixture melting point test and comparison of IR (Nujol or $CHCl_3$) and ^1H-NMR ($CDCl_3$) spectra, TLC mobility, and specific rotation] with authentic (+)-**14**.[6b)]

(3*R*,4*S*)-1-Acetyl-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(+)-20]——A mixture of a solution of ethyl cincholoiponate [(+)-**19**][6c)] (23.92 g, 120 mmol) in benzene (100 ml) and a solution of Na_2CO_3 (14.84 g, 140 mmol) in H_2O (140 ml) was stirred under ice-cooling, and a solution of acetyl chloride (10.99 g, 140 mmol) in dry benzene (30 ml) was added dropwise over a period of 1 h. After the mixture had been stirred for 20 min, the benzene layer was separated from the aqueous layer, washed successively with H_2O, 5% aqueous HCl, and H_2O, dried, and concentrated to leave a colorless oil (28.11 g, 97%). Purification of the oil by vacuum distillation afforded (+)-**20** (27.07 g, 93%) as a colorelss oil, bp 143 °C (4 mmHg); $[\alpha]_D^{25}$ +3.5 ° ($c = 2.00$, EtOH); MS *m/e*: 241 (M^+); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1636 (amide CO); ^1H-NMR ($CDCl_3$) δ: 0.96 (3H, unresolved t, $CCH_2\underline{Me}$), 1.26 (3H, t, $J = 7$ Hz, $OCH_2\underline{Me}$), 2.07 (3H, s, COMe), 2.28 (2H, unresolved d, $C\underline{H}_2CO_2Et$), 4.12 (2H, q, $J = 7$ Hz, $OC\underline{H}_2Me$).

(4*S*,5*R*)-5-Ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-21] and (3*R*,4*S*)-3-Ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-23]——A mixture of a solution of (+)-**20** (8.45 g, 35 mmol) in AcOEt (120 ml) and 10% aqueous $NaIO_4$ (340 ml) was stirred at room temperature, and ruthenium dioxide hydrate (Aldrich Chem. Co., Inc.) (150 mg) was added. After the resulting mixture had been stirred at 26—34 °C (inner temp.) for 5 h, the AcOEt layer was separated from the aqueous layer, which was extracted with AcOEt. The combined AcOEt solution, after addition of isopropanol (6 ml), was allowed to stand at room temperature for 3 h. The black precipitate that resulted was removed by filtration, and the filtrate was washed successively with H_2O, 2% aqueous $Na_2S_2O_3$, and H_2O, dried, and concentrated to leave a dark yellow oil (8.93 g). The oil was passed through a column packed with alumina (450 g) using benzene (1 l) followed by benzene–EtOH (20 : 1, v/v) (1.5 l). The eluate was evaporated *in vacuo* to leave a colorless oil, which was shown to be a mixture of two components on TLC analysis. The mixture was then chromatographed on a 550-g alumina column using hexane–AcOEt (1 : 2, v/v) as eluent. Earlier fractions gave (−)-**23** (1.99 g, 27%) as a colorless oil, $[\alpha]_D^{30}$ −18.8 ° ($c = 2.00$, EtOH); MS *m/e*: 213 (M^+); IR ν_{max}^{film} cm^{-1}: 3220 (NH), 1729 (ester CO), 1665 (lactam CO); ^1H-NMR ($CDCl_3$) δ: 1.01 (3H, t, $J = 7$ Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, $J = 7$ Hz, $OCH_2\underline{Me}$), 4.14 (2H, q, $J = 7$ Hz, $OC\underline{H}_2Me$), 6.68—7.0 (1H, br, NH); ^{13}C-NMR ($CDCl_3$) δ: 12.5 ($CCH_2\underline{Me}$), 14.3 ($OCH_2\underline{Me}$), 20.3 ($C\underline{C}H_2Me$), 25.5 (C-5), 31.8 (C-4), 34.6 ($\underline{C}H_2CO_2Et$), 39.5 (C-6), 46.6 (C-3), 60.6 ($O\underline{C}H_2Me$), 172.6 ($\underline{C}O_2Et$), 174.8 (C-2).

Later fractions in the above column chromatography yielded (+)-**21** (4.12 g, 55%) as a colorless oil, $[\alpha]_D^{30}$ +4.4° (c=2.00, EtOH); MS *m/e*: 213 (M^+); ^{13}C-NMR ($CDCl_3$) δ: 11.9 ($CCH_2\underline{Me}$), 14.2 ($OCH_2\underline{Me}$), 20.5 ($C\underline{C}H_2Me$), 32.2 (C-4), 34.7 ($\underline{C}H_2CO_2Et$), 36.0 (C-3), 37.6 (C-5), 44.1 (C-6), 60.6 ($O\underline{C}H_2Me$), 171.7 (C-2), 172.4 ($\underline{C}O_2Et$). The IR (neat) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were superimposable on those of authentic (±)-**21**.[11)]

(4*S*,5*R*)-5-Ethyl-2-oxo-4-piperidineacetic Acid [(+)-22]——A mixture of a solution of (+)-**21** (3.42 g, 16 mmol) in EtOH (30 ml) and a solution of KOH (1.12 g, 20 mmol) in H_2O (2 ml) was kept at 24—27 °C for 24 h. The mixture was concentrated *in vacuo*, and the residue was acidified (pH 1) with conc. aqueous HCl under ice-cooling. The precipitate that resulted was filtered off, washed with cold H_2O (3 ml), and dried to give (+)-**22** (2.46 g, 83%), mp 185—186 °C. Recrystallization from EtOH yielded an analytical sample as colorless prisms, mp 186—187 °C; $[\alpha]_D^{24}$ +10.6° (c=0.500, EtOH); MS *m/e*: 185 (M^+). *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.51; H, 8.27; N, 7.68. The IR (Nujol), ^{1}H-NMR (Me_2SO-d_6), and ^{13}C-NMR (Me_2SO-d_6) spectra of this sample were identical with those of authentic (±)-**22**.[14)]

Isomerization Study of the *cis*-Lactam Acid (+)-22——A small amount of (+)-**22** was heated neat at 190 °C for 15 min. On cooling, the oily reaction mixture solidified. The ^{13}C-NMR spectroscopic analysis[12,14a)] of the resulting colorless solid indicated that it was a 66:34 mixture of the *trans* isomer [(+)-**17**] [^{13}C-NMR (Me_2SO-d_6) δ: 11.0 ($CCH_2\underline{Me}$), 23.2 ($C\underline{C}H_2Me$)] and the *cis* isomer [(+)-**22**] [^{13}C-NMR (Me_2SO-d_6) δ: 11.8 ($CCH_2\underline{Me}$), 20.2 ($C\underline{C}H_2Me$)]. Attempts to isolate the *trans* isomer from the reaction mixture by recrystallization (EtOH or MeCN) and by other methods were all in vain.

(3*R*,4*S*)-2-Ethoxy-3-ethyl-3,4,5,6-tetrahydro-4-pyridineacetic Acid Ethyl Ester [(+)-18]——A solution of triethyloxonium fluoroborate[15)] (1.5 g, 7.9 mmol) in dry CH_2Cl_2 (8 ml) was added dropwise to a stirred, ice-cooled solution of (−)-**23** (1.28 g, 6 mmol) in dry CH_2Cl_2 (8 ml) over a period of 20 min. After having been stirred at room temperature for 24 h, the mixture was concentrated *in vacuo* to leave a colorless oil, which was poured into 10% aqueous K_2CO_3 (15 ml) under ice-cooling. The precipitate that resulted was removed by filtration and washed with CH_2Cl_2, and the aqueous filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 washings and extracts were combined, dried, and concentrated to leave a pale yellow oil. Vacuum distillation of the oil gave (+)-**18** (1.20 g, 83%) as a colorless oil, bp 112—113 °C (1 mmHg); $[\alpha]_D^{26}$ +65.8° (c=1.00, EtOH); MS *m/e*: 241 (M^+); IR ν_{max}^{film} cm^{-1}: 1737 (ester CO), 1675 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.3 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $CO_2CH_2\underline{Me}$), 4.01 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 4.15 (2H, q, J=7.1 Hz, $CO_2C\underline{H}_2Me$); ^{13}C-NMR ($CDCl_3$) δ: 13.0 ($CCH_2\underline{Me}$), 14.2 ($OCH_2\underline{Me}$ or $CO_2CH_2\underline{Me}$), 14.4 ($CO_2CH_2\underline{Me}$ or $OCH_2\underline{Me}$), 20.7 ($C\underline{C}H_2Me$), 25.4 (C-5), 32.1 (C-4), 36.0 ($\underline{C}H_2CO_2Et$), 41.0 (C-3), 45.4 (C-6), 60.0 ($O\underline{C}H_2Me$ or $CO_2\underline{C}H_2Me$), 60.4 ($CO_2\underline{C}H_2Me$ or $O\underline{C}H_2Me$), 164.5 (C-2), 172.5 ($\underline{C}O_2Et$).

Reduction of the *cis*-Lactim Ether (+)-18 to Ethyl Cincholoiponate [(+)-19]——Crude (+)-**18**, obtained from (−)-**23** (1.07 g, 5 mmol) as described above, was dissolved in abs. EtOH (20 ml). The solution was stirred under ice-cooling, and $NaBH_4$ (454 mg, 12 mmol) was added portionwise over a period of 20 min. The mixture was then stirred at room temperature for 24 h. After addition of acetone (0.5 ml) under ice-cooling, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in H_2O (10 ml), and the aqueous solution was salted out with anhydrous K_2CO_3 and extracted with benzene. The benzene extracts were washed with 1 N aqueous HCl. The acid washings were alkalified and salted out with K_2CO_3 and extracted with benzene. The resulting benzene extracts were dried (K_2CO_3) and concentrated to leave (+)-**19** (902 mg, 90%) as a colorless oil. Distillation of the oil gave a pure sample as a colorless oil, bp 83—84 °C (1 mmHg); $[\alpha]_D^{23}$ +16.4° (neat). The IR (neat), ^{1}H-NMR ($CDCl_3$), and ^{13}C-NMR ($CDCl_3$) spectra and specific rotation of this sample were identical with those of authentic ethyl cincholoiponate [(+)-**19**].[14a)]

For further identification, a small sample of the distilled oil was converted into the hydrochloride by dissolving it in 10% (w/w) ethanolic HCl and evaporating the resulting solution. Recrystallization of the residue from acetone afforded (+)-**19**·HCl as colorless needles, mp 160—161 °C; $[\alpha]_D^{24}$ −11.5° (c=3.00, EtOH). This salt was identical [by mixture melting point test and comparison of the IR (Nujol) spectrum and specific rotation] with an authentic sample.[14a)]

(3*R*,4*S*)-6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetic Acid Ethyl Ester [(−)-16]——A solution of triethyloxonium fluoroborate[15)] (2.1 g, 11 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise to a stirred, ice-cooled solution of (+)-**21** (1.71 g, 8 mmol) in dry CH_2Cl_2 (10 ml) over a period of 20 min. After having been stirred at room temperature for 24 h, the reaction mixture was worked up as described above for (+)-**18**, yielding (−)-**16** (1.79 g, 93%) as a colorless oil, bp 105—106 °C (2 mmHg); $[\alpha]_D^{25}$ −14.2° (c=0.51, EtOH); MS *m/e*: 241 (M^+); IR ν_{max}^{film} cm^{-1}: 1736 (ester CO), 1679 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=6.7 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J=7.0 Hz, $OCH_2\underline{Me}$), 1.26 (3H, t, J=7.2 Hz, $CO_2CH_2\underline{Me}$), 4.03 (2H, q, J=7.0 Hz, $OC\underline{H}_2Me$), 4.14 (2H, q, J=7.2 Hz, $CO_2C\underline{H}_2Me$). The assignment of the methyl and methylene proton signals was based on a comparison with those of the corresponding methyl ester.[16)]

(4*S*,5*R*)-1-(2-Benzyloxy-3,4-dimethoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-15]—— This was obtained from (−)-**16** and 2-benzyloxy-3,4-dimethoxyphenacyl bromide[13)] in 92% yield in a manner similar to that described above for (+)-**10**. Column chromatographic purification [alumina, AcOEt–hexane (1:2, v/v)] furnished (+)-**15** as a pale orange oil, $[\alpha]_D^{25}$ +1.0° (c=0.50, EtOH); MS *m/e*: 497 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727 (ester

CO), 1679 (CO), 1632 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.0 Hz, $CCH_2\underline{Me}$), 1.27 (3H, t, J=7.2 Hz, $OCH_2\underline{Me}$), 3.89 and 3.93 (3H each, s, two OMe's), 4.15 (2H, q, J=7.2 Hz, $OC\underline{H_2}Me$), 4.34 and 4.80 (2H, AB type d's, J=18.1 Hz, $ArCOC\underline{H_2}$), 5.21 (2H, s, $OC\underline{H_2}Ph$), 6.75 (1H, d, J=9.0 Hz, $H_{(5')}$), 7.25—7.7 (5H, m, $OCH_2\underline{Ph}$), 7.60 (1H, d, J=9.0 Hz, $H_{(6')}$).

(4*S*,5*R*)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (12)——Reduction of (+)-**15** with $NaBH_4$ was effected as described above for **11**, giving **12** in 99% yield as a pale yellow oil, $[\alpha]_D^{25}$ −6.4° (c=1.00, EtOH). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were identical with those of authentic **12**.[6b]

(4*S*,5*R*)-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-13]——This was prepared in 98% yield from **12** by catalytic hydrogenolysis similar to that described above for (+)-**14**. Purification by means of column chromatography [silica gel, AcOEt–hexane (2 : 1, v/v)] provided (−)-**13** as a faintly yellow oil, $[\alpha]_D^{25}$ −10.1° (c=1.50, EtOH); MS *m/e*: 393 (M^+). This sample was identical [by comparison of IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra and specific rotation] with authentic (−)-**13**.[6b]

(4*S*,5*S*)-1-(2-Benzyloxy-3,4-dimethoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-10]——Condensation of (−)-**5**[7] with 2-benzyloxy-3,4-dimethoxyphenacyl bromide[13] was carried out as described above for (+)-**10** except that the reaction time was prolonged to 15 h. The crude oily product (93% yield) was purified on an alumina column [AcOEt–hexane (2 : 3, v/v)] to provide (−)-**10** as a yellow oil, $[\alpha]_D^{20}$ −25.6° (c=0.46, EtOH); MS *m/e*: 497 (M^+). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra and TLC mobility of this sample were identical with those of authentic (±)-**10**[4b] as well as those of (+)-**10**.

(4*S*,5*S*)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (24)——According to the procedure described above for **11**, except that the reaction time was extended to 5 h, (−)-**10** was reduced with $NaBH_4$ to give the diastereomeric mixture **24** in 99% yield as a faintly yellow solid, mp 86—87 °C; $[\alpha]_D^{19}$ −42.9° (c=0.48, EtOH); MS *m/e*: 499 (M^+). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra and TLC mobility of this sample were identical with those of (±)-**24**[4b] as well as those of **11**.

(4*S*,5*S*)-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-14]——This was obtained in 98% yield from **24** by catalytic hydrogenolysis similar to that described above for (+)-**14**, except that the reaction time was prolonged to 5 h. Recrystallization from isopropyl ether gave (−)-**14** as colorless needles, mp 87—88 °C; $[\alpha]_D^{20}$ −76.6° (c=1.00, EtOH); MS *m/e*: 393 (M^+). *Anal.* Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 64.08; H, 8.01; N, 3.75. The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were superimposable on those of authentic (+)-**14**.[6b]

(4*S*,5*S*)-1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-25]——A stirred mixture of (−)-**14** (1.18 g, 3 mmol), benzyl bromide (616 mg, 3.6 mmol), anhydrous K_2CO_3 (498 mg, 3.6 mmol), and acetone (12 ml) was heated under reflux for 20 h. The solvent was removed by vacuum distillation, and the residue was partitioned by extraction with a mixture of benzene and H_2O. The benzene extracts were washed successively with cold 5% aqueous NaOH and saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. The oil was dissolved in benzene (10 ml) containing pyridine (300 mg), and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was diluted with benzene (30 ml), washed successively with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a yellow oil (1.43 g). Purification of the oil by column chromatography [alumina, AcOEt–hexane (1 : 2, v/v)] furnished (−)-**25** (1.33 g, 92%) as a faintly yellow oil, $[\alpha]_D^{23}$ −50.7° (c=1.02, EtOH); MS *m/e*: 483 (M^+). The IR (neat) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were identical with those of authentic (±)-**25**.[4b]

(2*S*,3*S*,11b*R*)-8-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid Ethyl Ester [(+)-27]——A solution of (−)-**25** (1.26 g, 2.6 mmol) and $POCl_3$ (2.0 g, 13 mmol) in dry toluene (15 ml) was heated under reflux for 2 h. After cooling, the solvent and excess $POCl_3$ were distilled off, and the residue was partitioned by extraction with a mixture of $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with H_2O, dried, and concentrated to leave crude **26** (1.37 g) as a reddish-brown oil. The oil was dissolved in EtOH (15 ml), and the solution was hydrogenated over Adams catalyst (50 mg) at atmospheric pressure and 22 °C for 40 min. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to leave an oil, to which cold 5% aqueous NaOH (10 ml) was added. The aqueous mixture was then extracted with benzene, and the benzene extracts were washed with H_2O, dried (K_2CO_3), and concentrated to afford a reddish-orange oil (1.13 g). Without delay, the oil was purified on an alumina column [AcOEt–hexane (1 : 3, v/v)] to give (+)-**27** [585 mg, 48% overall yield from (−)-**25**] as an unstable, slightly yellow oil, $[\alpha]_D^{24}$ +19.7° (c=0.55, EtOH). The IR (neat) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were identical with those of authentic (±)-**27**.[4b]

(2*S*,3*S*,11b*R*)-8-Benzyloxy-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-ethanol [(+)-28]——A solution of (+)-**27** (374 mg, 0.8 mmol) in dry ether (5 ml) was added dropwise to a stirred, ice-cold suspension of $LiAlH_4$ (61 mg, 1.6 mmol) in dry ether (5 ml) over a period of 10 min. After the mixture had been heated under reflux for 4 h, small amounts of H_2O, 10% aqueous NaOH, and H_2O were successively added (in that order) under ice-cooling. The supernatant ethereal solution was separated by decantation from the insoluble solid, which was washed with ether. The ethereal solution and washings were combined, dried (K_2CO_3), and concentrated to leave an orange oil (314 mg). Purification of the oil by column chromatography [alumina, AcOEt–hexane (1 : 1, v/v)] yielded (+)-**28** (291 mg, 85%) as a pale yellow oil, $[\alpha]_D^{22}$ +32.7° (c=0.67, EtOH); MS *m/e*: 425 (M^+). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were superimposable on those of authentic (±)-**28**.[4b)]

(2*S*,3*S*,11b*R*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-ethanol [(+)-Ankorine] [(+)-6]——A solution of (+)-**28** (280 mg, 0.66 mmol) in EtOH (10 ml) was hydrogenated over 10% Pd–C (120 mg) at atmospheric pressure and 22 °C for 1.5 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave (+)-**6** (211 mg, 96%) as a faintly brown solid, mp 173—175 °C. Recrystallization of the solid from acetone containing a little EtOH produced an analytical sample as colorless prisms, mp 176—177 °C; $[\alpha]_D^{27}$ +58.2° (c=0.24, $CHCl_3$); UV λ_{max}^{EtOH} 273 nm (log ε 2.95); $\lambda_{max}^{H_2O\,(pH\,13)}$ 287 (3.42); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3630, 3530 (OH), 2800, 2750 (*trans*-quinolizidine ring);[17)] ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 3.84 and 3.86 (3H each, s, two OMe's), 5.95 (br, OH), 6.32 (1H, s, $H_{(11)}$); MS *m/e*: 335 (M^+). *Anal.* Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.09; H, 8.83; N, 4.10. The UV, IR, ^{1}H-NMR, and mass spectra and TLC behavior of this sample were identical with those of (−)-ankorine [(−)-**6**][6b)] [lit.[6b)] mp 176—177 °C; $[\alpha]_D^{16}$ −58±1° (c=0.23, $CHCl_3$)].

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