[Chem. Pharm. Bull. 34(2) 496—507 (1986)]

Lactams. XXVI.[1] Regioselectivity in the Mercuric Acetate–Edetic Acid Oxidation of the Ethyl 1-(2-Aryl-2-hydroxyethyl)-3-ethyl-4-piperidineacetate System: Enhancement by a Benzyloxy Group in the Aryl Moiety and by the 3,4-*cis* Configuration

TOZO FUJII,* MASASHI OHBA, MICHIKO TSUCHIDA, KIYOE SAITO, YUKO HIRANO, and JUN SAKAGUCHI

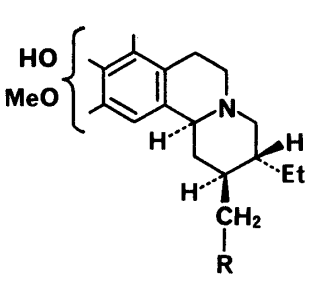
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

(Received June 21, 1985)

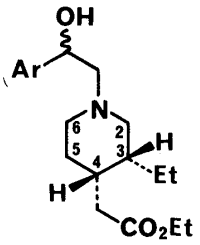
A quantitative analytical study to determine the isomer ratios of the 6-piperidones (type **7**) and 2-piperidones (type **5**) produced by the mercuric acetate–edetic acid (EDTA) oxidation of 1-(2-aryl-2-hydroxyethyl)-3-alkylpiperidines (±)-**4c**, **d**, **f**, **h**, **4e**, **g**, **i**, **j**, and (±)-**38** was carried out. It has been found that all the substrates with a benzyloxy group in the aryl moiety, regardless of its location, undergo oxidation at the 6-position preferentially as compared with the debenzyloxy derivatives such as (±)-**4a**, **b**. Comparison of the quantitative data from **4e** and (±)-**4f** with those from (±)-**4b** indicated that the *cis* acetate chain at the 4-position increases the extent of the 6-oxidation, whereas a *trans* acetate chain at the same position has little effect. These two factors enhance the practical value of the "cincholoipon-incorporating method" for chiral syntheses of the **1**-type *Alangium* alkaloids, in which the mercuric acetate–EDTA oxidation of **4e**, **g**, **i**, **j** to the 6-piperidones (type **3**) is one of the key synthetic operations.

Keywords——1,3-disubstituted piperidine; mercuric acetate–EDTA oxidation; piperidone regioselective formation; pyridine base quaternization; sodium borohydride phenacyl group reduction; benzylic alcohol catalytic hydrogenolysis; piperidone *trans–cis* isomerization; piperidone isomer spectroscopic differentiation

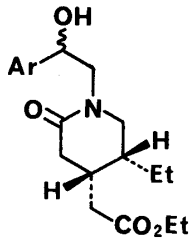
One of the key operations in our "cincholoipon-incorporating method"[2] for chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids (type **1**)[3] is the mercuric acetate–edetic acid (EDTA) oxidation of the *N*-substituted ethyl cincholoiponate derivative **2** to produce the 6-piperidone derivative **3**.[4] Because of the unsymmetrical structure of **2** with respect to the piperidine ring, this operation required some preliminary experiments to determine the effect of the C(3)-ethyl group on the regioselectivity in such functionalization. We have found that treatment of the model compound (±)-**4a** with mercuric acetate–EDTA in boiling 1% aqueous AcOH for 1.5 h afforded both the 6-piperidone (±)-**7a** and the 2-piperidone (±)-**5a** in a ratio of 54:46 in 78% combined yield.[5a] The 3′,4′-dimethoxy analogue (±)-**4b**,[6] another model for **2**, gave similar results (see Table I),[5a,b] indicating that the methoxy groups at the 3′- and 4′-positions may have little or no effect on the regioselectivity in the lactam formation. The observed regioselectivity was not sufficiently high, but it was still encouragingly in favor of the desired 6-oxidation. To our surprise, such regioselectivity was greatly enhanced (**7g**:**5g**=75:25)[7,8] when the same oxidation method was applied to the original compound **4g** (type **2**) during the course of our chiral synthesis of the *Alangium* alkaloid ankorine. In the present study, therefore, we investigated the effects of a benzyloxy group in the aromatic moiety and the stereochemistry of the acetate chain at the 4-position on the position of oxidation.



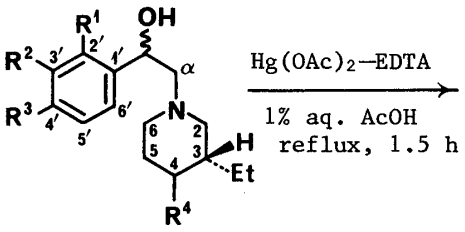
1: R = CH_2OH, CO_2H, or a heterocyclic moiety



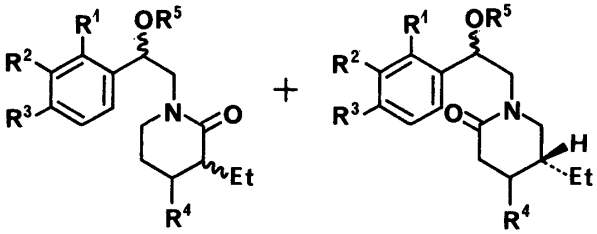
2



3



4



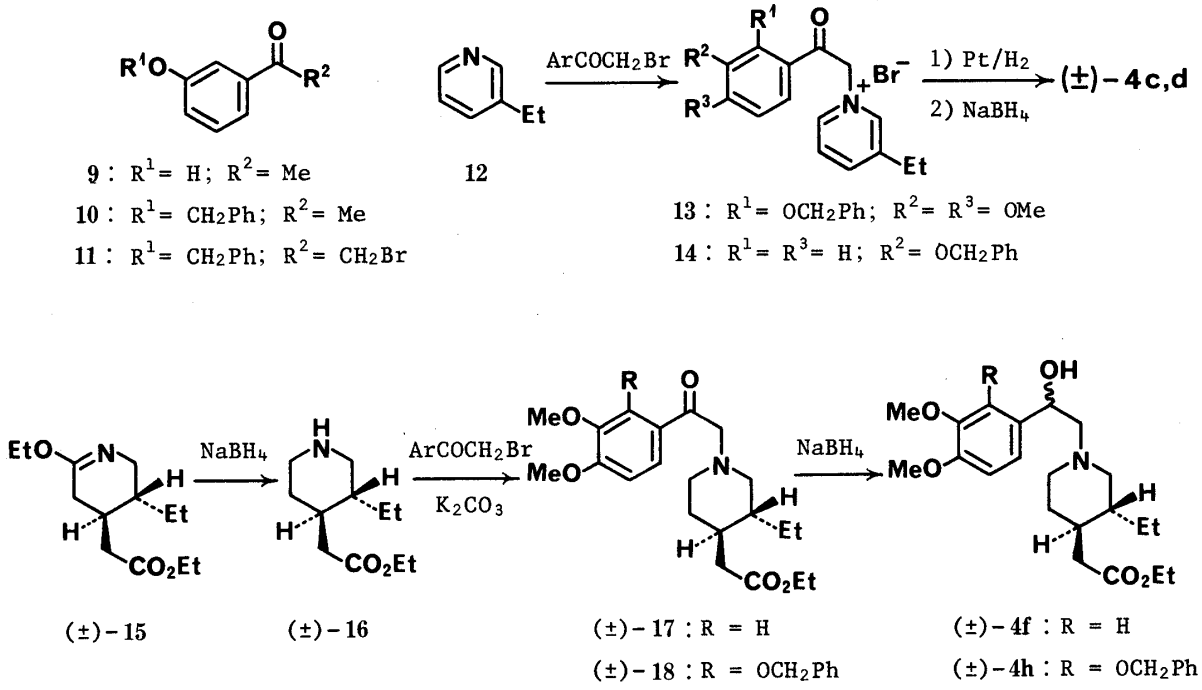
5: R^5 = H
6: R^5 = COMe

7: R^5 = H
8: R^5 = COMe

a: $R^1=R^2=R^3=R^4=H$
b: $R^1=R^4=H$; $R^2=R^3=OMe$
c: $R^1=OCH_2Ph$; $R^2=R^3=OMe$; $R^4=H$
d: $R^1=R^3=H$; $R^2=OCH_2Ph$; $R^4=H$
e: $R^1=H$; $R^2=R^3=OMe$; $R^4=CH_2CO_2Et$ (3,4-*cis*)
f: $R^1=H$; $R^2=R^3=OMe$; $R^4=CH_2CO_2Et$ (3,4-*trans*)
g: $R^1=OCH_2Ph$; $R^2=R^3=OMe$; $R^4=CH_2CO_2Et$ (3,4-*cis*)
h: $R^1=OCH_2Ph$; $R^2=R^3=OMe$; $R^4=CH_2CO_2Et$ (3,4-*trans*)
i: $R^1=H$; $R^2=OCH_2Ph$; $R^3=OMe$; $R^4=CH_2CO_2Et$ (3,4-*cis*)
j: $R^1=H$; $R^2=OMe$; $R^3=OCH_2Ph$; $R^4=CH_2CO_2Et$ (3,4-*cis*)

Chart 1

The substrates selected for quantitative analytical work to determine the isomer ratios of their mercuric acetate–EDTA oxidation products were **4c—j**, in which the essential partial structures of **4g** are clear. The optically active substrates **4e**,[9] **4g**,[7] **4i**,[10] and **4j**[11] were prepared according to the previously reported procedures, but the racemic substrates (±)-**4c**, **d**, **f**, **h** were newly synthesized through the following routes. Bromination of the ketone **10**, obtained in 90% yield from *m*-hydroxyacetophenone (**9**) by treatment with benzyl bromide and K_2CO_3, with Br_2 gave the phenacyl bromide **11** in 68% yield. Quaternization of 3-ethylpyridine (**12**) with **11** in boiling benzene and catalytic reduction of the resulting salt **14**, followed by $NaBH_4$ reduction, furnished (±)-**4d** in 92% overall yield (from **12**) as a diastereomeric mixture. Compound (±)-**4c** was likewise prepared in good yield from **12** and 2-benzyloxy-3,4-dimethoxyphenacyl bromide through the pyridinium salt **13**. For the synthesis of the 3,4-*trans* ester substrates, the *trans*-lactim ether (±)-**15**[12,13] was reduced with $NaBH_4$ according to the literature procedure,[13] and the resulting piperidineacetate (±)-**16** was condensed with 3,4-dimethoxyphenacyl bromide in benzene containing K_2CO_3 to give the amino ketone (±)-**17** in 81% yield. On reduction with $NaBH_4$, (±)-**17** furnished a diastereomeric mixture of the amino alcohol (±)-**4f** in 94% yield. A parallel sequence of conversions starting with (±)-**16** and 2-benzyloxy-3,4-dimethoxyphenacyl bromide produced (±)-**4h** in 94% overall yield through (±)-**18**. Since each of the substrates **4c—j** was a barely



9 : R^1= H; R^2= Me
10 : R^1= CH_2Ph; R^2= Me
11 : R^1= CH_2Ph; R^2= CH_2Br

12

13 : R^1= OCH_2Ph; R^2= R^3= OMe
14 : R^1= R^3= H; R^2= OCH_2Ph

(±)-15 (±)-16 (±)-17 : R = H (±)-4f : R = H
(±)-18 : R = OCH_2Ph (±)-4h : R = OCH_2Ph

Chart 2

separable mixture of the two possible diastereoisomers due to the difference in configuration at the benzylic position, the mixtures were used in the next oxidation step as they were.

For securing uniformity and for convenience of comparison with the earlier results[5a,b] from (±)-**4a**, **b**, all the mercuric acetate–EDTA oxidations (in boiling 1% aqueous AcOH for 1.5 h) of **4c**—**j** and isolation of the isomeric piperidones (**5c**—**j** and **7c**—**j**) as well as determination of the isomer ratios were carried out according to the previously reported standard procedure.[5a,b] In these oxidations, the concomitant formation of small amounts of the *O*-acetyl derivatives (types **6** and **8**) was detected by thin-layer chromatographic (TLC) analysis of the reaction mixtures. However, treatment of the crude products with NaOH or K_2CO_3 in the work-up process should have converted them, if present, into the corresponding lactam alcohols (types **5** and **7**) as in the previous cases,[5] and this was actually supported by the results of TLC analysis. Although the piperidones (types **5** and **7**) isolated were diastereomeric mixtures, their structures were confirmed by spectral comparison with authentic samples, whenever available, and by the previously reported infrared (IR)[5b] and nuclear magnetic resonance (NMR)[5d] spectral and TLC[5b] criteria for differentiating between the 2-piperidones (type **5**) and the 6-piperidones (type **7**). In the cases of (±)-**5c** and (±)-**7c**, the structures were further confirmed by converting them into the phenolic lactams (±)-**19** (87% yield) and (±)-**20** (77% yield) by catalytic hydrogenolysis (Pd–C/H_2, EtOH–70% aqueous $HClO_4$, 3—3.5 atm, room temp.). On similar hydrogenolysis, (±)-**5f** produced the *trans*-lactam (±)-**21** (63% yield) as well as the *cis*-lactam (±)-**23** (16% yield), whereas (±)-**7f** afforded (±)-**25** in 91% yield. Likewise, (±)-**5h** furnished the *trans*-lactam (±)-**22** (61% yield) as well as the *cis*-lactam (±)-**24** (15% yield); (±)-**7h** gave (±)-**26** in 90% yield. The observed *trans–cis* isomerization of these 2-piperidone derivatives has a precedent in our previous work.[9]

It is interesting to note that the oxidation of **4g** produced ethyl *N*-formylcincholoiponate [(+)-**27**] in 6% yield besides the two expected piperidones **5g** and **7g**. The structure of (+)-**27** was established by its identity with a sample synthesized from ethyl cincholoiponate [(+)-**28**] by formylation. The formation of (+)-**27** suggests that mercuric acetate also oxidizes **4g** at the

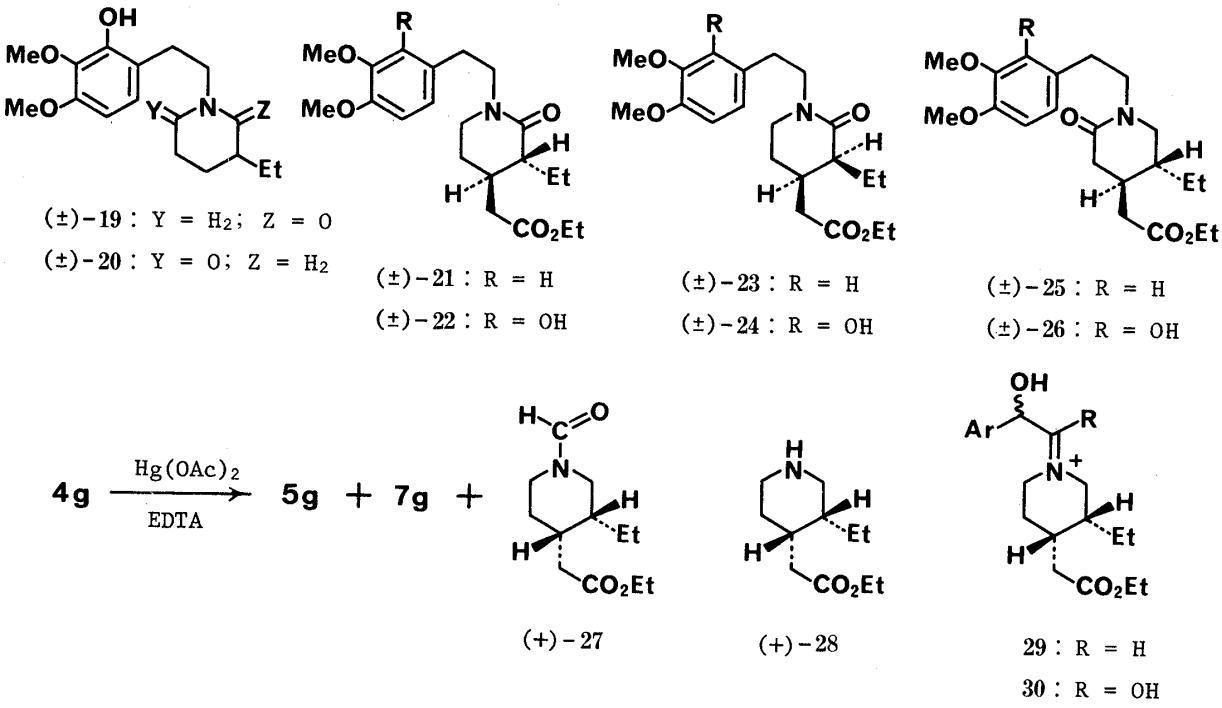


Chart 3

TABLE I. The Mercuric Acetate–EDTA Oxidation of the 3-Ethylpiperidine Derivatives **4**

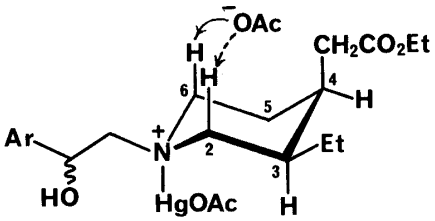
No.	Substrate			Product[a]		
	Alkoxy position[b]		Stereochem.	Combined yield (%)	% 6-oxidation	% 2-oxidation
	OMe	OCH_2Ph	C(3)/C(4)			
(±)-**4a**	—	—	—	78[c]	54 (**7a**)	46 (**5a**)
(±)-**4b**	3′, 4′	—	—	76[c]	54 (**7b**)	46 (**5b**)
(±)-**4c**	3′, 4′	2′	—	84	67 (**7c**)	33 (**5c**)
(±)-**4d**	—	3′	—	87	65 (**7d**)	35 (**5d**)
4e	3′, 4′	—	*cis*	73	62 (**7e**)	38 (**5e**)
(±)-**4f**	3′, 4′	—	*trans*	77	57 (**7f**)	43 (**5f**)
4g	3′, 4′	2′	*cis*	72[d]	66 (**7g**)	34 (**5g**)
(±)-**4h**	3′, 4′	2′	*trans*	73	64 (**7h**)	36 (**5h**)
4i	4′	3′	*cis*	81	68 (**7i**)	32 (**5i**)
4j	3′	4′	*cis*	80[e]	70 (**7j**+**8j**)	30 (**5j**+**6j**)

a) All isomer ratios were determined by chromatographic analysis as reported previously.[5a,b] *b*) For the primed numbers, see note 6. *c*) Taken from ref. 5*a*. *d*) Besides the two piperidones, ethyl *N*-formylcincholoiponate [(+)-**27**] was isolated in 6% yield. *e*) Data from runs in which hydrolysis of the *O*-acetyl derivatives **8j** and **6j** to give **7j** and **5j** was omitted during the work-up process.

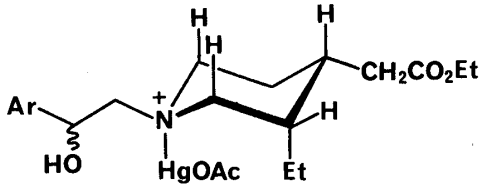
exocyclic α-carbon atom;[14] the iminium salt **29** or the more highly oxidized salt **30** is the most likely precursor.

The above mercuric acetate–EDTA oxidations were run in triplicate or in duplicate at least, and the mean values of the isomer ratios obtained are assembled in Table I. It may be seen that all the substrates with a benzyloxy group in the aromatic moiety, regardless of its location, underwent 6-oxidation preferentially as compared with the debenzyloxy derivatives such as (±)-**4a**, **b**. Comparison of the quantitative data from **4e** and (±)-**4f** with those from (±)-**4b** indicates that the *cis* acetate chain at the 4-position increases the extent of the 6-

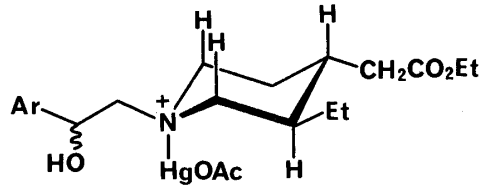
oxidation, whereas a *trans* acetate chain at the same position has little effect. These findings may be interpreted as follows. In previous papers,[5b,c] we have suggested that in the mercuric acetate–EDTA oxidation of 1-aryl-2-(3-substituted piperidino)ethanols [type (±)-**4b**] the possible factors involved in determining its regioselectivity may be steric and electrostatic repulsions, which should be operative between the 3-substituent and the acetate ion approaching the axial C(2)-H atom of the mercurated complex (**31**: H in place of the 4-CH_2CO_2Et group) formed at the first stage. If a similar mechanism is operative in the oxidation of the *cis*-ester **4e**, the two conformers **31** and **32**[15] may be considered for the corresponding mercurated complex (with the axial N(1)–HgOAc bond) in regard to the 3- and 4-substituents. However, the conformer **32** should hardly exist because of severe 1,3-diaxial



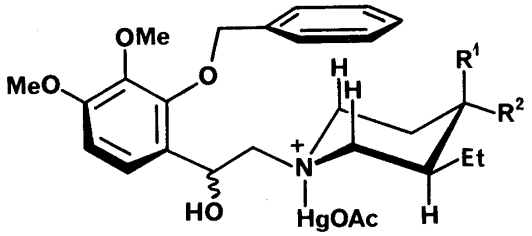
31



32

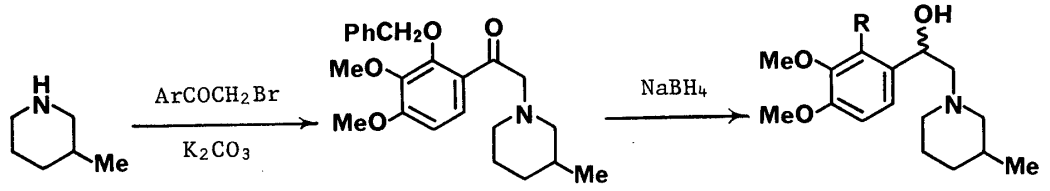


33



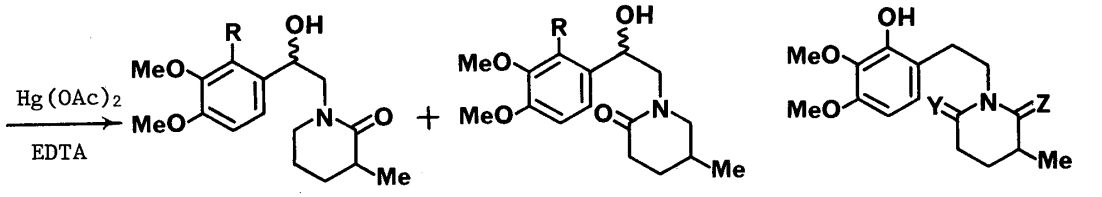
34 : R^1= H or CH_2CO_2Et; R^2= H

35 : R^1= H; R^2= CH_2CO_2Et



(±)-36 (±)-37 (±)-38 : R = OCH_2Ph

(±)-39 : R = H



(±)-40 : R = OCH_2Ph (±)-42 : R = OCH_2Ph (±)-44 : Y = H_2; Z = O

(±)-41 : R = H (±)-43 : R = H (±)-45 : Y = O; Z = H_2

Chart 4

interaction between the N(1)–HgOAc and the C(3)–Et groups. Thus, in the preferred conformer **31**, the approach of the acetate ion to the axial C(2)-H should be hindered by both the equatorial C(3)-Et and the axial C(4)-CH_2CO_2Et groups, and this may account for the rather high regioselectivity with **4e** in favor of the 6-oxidation. The most stable conformer of the mercurated complex derived from the *trans*-ester (±)-**4f** should be **33**, and the equatorial C(4)-substituent apparently exerts no influence on the approach of the acetate ion to the axial C(2)-H or C(6)-H. In the cases of the 2′-benzyloxy derivatives (±)-**4c**, **4g**, and (±)-**4h**, we assume a preferred conformer of **34**- or **35**-type, in which the benzene ring of the benzyloxy group is presumably attracted by the positively charged nitrogen within the same molecule. Such a specific interaction between the benzene ring and the partial positive charge on the nitrogen has been proposed for *N*,*N*-disubstituted amides[16] and 1-(2-arylethyl)pyridones.[17] In the conformer **34** or **35**, the proximity of the benzene ring and axial C(2)-H would, together with the C(3)-Et group, cause the 2-oxidation to become more unfavorable. Inspection of molecular models suggested that similar folded conformations are possible for the mercurated complexes derived from the substrates [(±)-**4d** and **4i**, **j**] with a benzyloxy group at the 3′- or 4′-position.

Such an orienting effect of the 2′-benzyloxy group was also observed when the 3-methyl analogue (±)-**38**, prepared in 95% overall yield from 3-methylpiperidine [(±)-**36**] through the amino ketone (±)-**37**, was subjected to the same oxidation: the isomer ratio (±)-**42** : (±)-**40** = 61 : 39 was higher than that [(±)-**43** : (±)-**41** = 55 : 45] reported[5a,b] for the debenzyloxy analogue (±)-**39**. The combined yield of (±)-**42** and (±)-**40** was 76%, and their structures were supported by the results of hydrogenolysis, giving (±)-**45** and (±)-**44**, respectively.

In conclusion, the present results confirm that the regioselectivity in favor of the 6-oxidation in the mercuric acetate–EDTA oxidation of the original compounds **4e**, **g**, **i**, **j** is higher than that in the case of the models (±)-**4a**, **b**. This is attributable to the presence of the benzyloxy group and/or 3,4-*cis* configuration in the original compounds and enhances the practical value of the "cincholoipon-incorporating method" for chiral syntheses of the **1**-type *Alangium* alkaloids, in which the mercuric acetate–EDTA oxidation of **4e**, **g**, **i**, **j** to the 6-piperidones (type **3**) is one of the most important synthetic operations.

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. See refs. 3*d* and 5*d* 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 = double-of-doublets, m = multiplet, q = quartet, s = singlet, t = triplet.

Materials——Among the substrates used in the $Hg(OAc)_2$–EDTA oxidation study, the following compounds (as diastereomeric mixtures) were prepared according to the reported procedures: (3*R*,4*S*)-1-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic acid ethyl ester (**4e**);[9] (3*R*,4*S*)-1-[2-(2-benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic acid ethyl ester (**4g**);[7] (3*R*,4*S*)-1-[2-(3-benzyloxy-4-methoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic acid ethyl ester (**4i**);[10] (3*R*,4*S*)-1-[2-(4-benzyloxy-3-methoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic acid ethyl ester (**4j**).[11] Other substrates were obtained as described below.

1-(3-Benzyloxyphenyl)ethanone (10)——A solution of benzyl bromide (10.26 g, 60 mmol) in acetone (10 ml) was added dropwise to a stirred mixture of *m*-hydroxyacetophenone (**9**) (6.81 g, 50 mmol) and anhydrous K_2CO_3 (8.29 g, 60 mmol) in acetone (100 ml). The resulting mixture was heated under reflux with stirring for 4 h. After cooling, the reaction mixture was filtered in order to remove the insoluble solid, which was washed with acetone (20 ml). The filtrate and washings were combined and concentrated *in vacuo*, and the residual oil was dissolved in benzene (400 ml). The benzene solution was washed successively with H_2O, 5% aqueous NaOH, and saturated aqueous NaCl, dried, and concentrated to leave a faintly yellow oil. The oil was dissolved in a mixture of benzene (30 ml) and pyridine (5 ml), and the solution was stirred at room temperature overnight and then filtered. The filtrate was washed successively with H_2O, 5% aqueous HCl, and saturated aqueous NaCl, dried, and concentrated to leave a pale yellow

oil (11.01 g). Purification of this oil by vacuum distillation gave **10** (10.16 g, 90%) as a colorless oil, bp 164 °C (2 mmHg) [lit.[18] bp 165—170 °C (0.5 mmHg)]; MS *m/e*: 226 (M^+); IR ν_{max}^{film} cm^{-1}: 1686 (CO); NMR ($CDCl_3$) δ: 2.58 (3H, s, COMe), 5.11 (2H, s, $OC\underline{H}_2Ph$), 7.05—7.6 (9H, m, aromatic protons and $OCH_2\underline{Ph}$).

2-Bromo-1-(3-benzyloxyphenyl)ethanone (11)——A solution of Br_2 (800 mg, 5 mmol) in $CHCl_3$ (5 ml) was added dropwise to an ice-cooled, stirred solution of **10** (1.13 g, 5 mmol) in a mixture of $CHCl_3$ (10 ml) and ether (20 ml) over a period of 1 h. After having been stirred at room temperature for 4 h, the reaction mixture was diluted with ether (15 ml), washed successively with H_2O, ice-cold 5% aqueous NaOH, and H_2O, dried, and concentrated to leave a faintly yellow solid (1.37 g), mp 41—49 °C. Two recrystallizations from hexane–ether gave **11** (751 mg) as colorless needles, mp 56—57 °C. The mother liquors of the two recrystallizations were combined and concentrated *in vacuo*, and the residual oil was purified by column chromatography [silica gel (30 g), hexane–$CHCl_3$ (1 : 1, v/v)] to afford a second crop (292 mg), mp 55.5—56.5 °C. The total yield of **11** was 1.043 g (68%). For analysis, crude **11** was further recrystallized from hexane–ether (10 : 1, v/v) to form colorless needles, mp 58.5—59 °C; IR ν_{max}^{Nujol} cm^{-1}: 1694 (CO); NMR ($CDCl_3$) δ: 4.43 (2H, s, $COCH_2Br$), 5.12 (2H, s, $OC\underline{H}_2Ph$), 7.1—7.65 (9H, m, aromatic protons and $OCH_2\underline{Ph}$). *Anal.* Calcd for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.29. Found: C, 59.22; H, 4.29.

1-(2-Benzyloxy-3,4-dimethoxyphenacyl)-3-ethylpyridinium Bromide (13)——A solution of 3-ethylpyridine (**12**) (9.11 g, 85 mmol) and 2-benzyloxy-3,4-dimethoxyphenacyl bromide[19] (31.0 g, 85 mmol) in dry benzene (250 ml) was stirred at room temperature overnight. The precipitate that resulted was filtered off and recrystallized from isopropyl ether–EtOH (3 : 2, v/v) to give **13** (31.1 g, 78%) as hygroscopic, colorless needles, mp 138.5—140.5 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 1678 (CO). A portion (283 mg, 0.6 mmol) of **13** was dissolved in H_2O (2 ml), and a solution of $NaClO_4$ (220 mg, 1.8 mmol) in H_2O (1 ml) was added. On cooling, the resulting mixture deposited the perchlorate salt (**13**: ClO_4^- for Br^-) (277 mg, 94%), which was recrystallized from EtOH to afford an analytical sample as colorless needles, mp 135—136 °C (dec.). *Anal.* Calcd for $C_{24}H_{26}ClNO_8$: C, 58.60; H, 5.33; N, 2.85. Found: C, 58.69; H, 5.20; N, 2.57.

1-(3-Benzyloxyphenacyl)-3-ethylpyridinium Bromide (14)——A solution of **12** (1.29 g, 12 mmol) and **11** (3.85 g, 12.6 mmol) in dry benzene (20 ml) was heated under reflux for 4 h. After cooling, the insoluble oil that resulted was separated from the supernatant solution by decantation and then dissolved in H_2O (100 ml), while the supernatant was extracted with H_2O. The resulting aqueous solution and extracts were combined, washed with benzene, and concentrated *in vacuo*, and the residue was dried to give crude **14** (5.02 g) as an orange glass. This material was directly used in the next reduction step without further purification.

(±)-*trans*-3-Ethyl-4-piperidineacetic Acid Ethyl Ester [(±)-16]——This was prepared from (±)-**15** by the reported method,[13] but the procedure was slightly modified: An ice-cooled solution of crude (±)-**15**,[12,13] synthesized from ethyl *trans*-5-ethyl-2-oxo-4-piperidineacetate[20] (2.85 g, 13.4 mmol) according to the literature procedure,[13] in abs. EtOH (50 ml) was stirred, and $NaBH_4$ (1.13 g, 30 mmol) was added portionwise over a period of 30 min. After the mixture had been stirred at room temperature for 27 h, acetone (2 ml) was added under ice-cooling. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of benzene and H_2O. The benzene extracts were then washed with 1 N aqueous HCl. The acid washings were alkalified and salted out with K_2CO_3 then extracted with benzene. The resulting benzene extracts were dried (K_2CO_3) and concentrated to leave an orange oil. The oil was purified by vacuum distillation, giving (±)-**16** (2.35 g, 88% overall yield from the lactam) as a colorless oil, bp 87 °C (2 mmHg) [lit.[13] bp 91—92 °C (bath) (0.5 Torr)]; IR ν_{max}^{film} cm^{-1}: 1733 (ester CO); NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 2.66 (1H, s, NH), 4.13 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$).

(±)-*trans*-1-(3,4-Dimethoxyphenacyl)-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(±)-17]——A solution of 3,4-dimethoxyphenacyl bromide[19] (7.00 g, 27 mmol) in dry benzene (40 ml) was added dropwise to a stirred mixture of (±)-**16** (5.38 g, 27 mmol) and anhydrous K_2CO_3 (3.73 g, 27 mmol) in dry benzene (60 ml) over a period of 20 min, and the resulting mixture was heated under reflux with stirring for 8 h. After cooling, the reaction mixture was washed successively with H_2O and 10% aqueous HCl. The acid washings were alkalified with K_2CO_3 and extracted with AcOEt. The AcOEt extracts were washed with saturated aqueous NaCl, dried (K_2CO_3), and concentrated to leave (±)-**17** (8.21 g, 81%) as an unstable, reddish oil; IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1675 (CO); NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.7 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 3.74 (2H, s, $COCH_2N$), 3.93 and 3.95 (6H, s each, two OMe's), 4.13 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 6.88 (1H, d, J=8.3 Hz, $H_{(5')}$), 7.60 (1H, d, J=2.0 Hz, $H_{(2')}$), 7.70 (1H, dd, J=8.3 and 2.0 Hz, $H_{(6')}$).

(±)-*trans*-1-(2-Benzyloxy-3,4-dimethoxyphenacyl)-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(±)-18]——A solution of (±)-**16** (4.78 g, 24 mmol) in dry benzene (120 ml) containing anhydrous K_2CO_3 (3.32 g, 24 mmol) was stirred at room temperature, and 2-benzyloxy-3,4-dimethoxyphenacyl bromide[19] (8.77 g, 24 mmol) was added portionwise. The resulting mixture was stirred at 50 °C for 2 h. After cooling, the reaction mixture was poured into a mixture of H_2O (100 ml) and benzene (100 ml). The benzene layer, after separation from the aqueous layer, was washed successively with 5% aqueous NaOH and H_2O, dried (K_2CO_3), and concentrated to leave a reddish-orange oil (11.72 g). A portion of the oil was purified by column chromatography [silica gel, hexane–AcOEt (1 : 3, v/v)] to give (±)-**18** as an unstable brownish oil, IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1676 (CO); NMR ($CDCl_3$) δ: 0.81 (3H, t, J=6.8 Hz, $CCH_2\underline{Me}$), 1.25 (3H, t, J=7.2 Hz, $OCH_2\underline{Me}$), 3.65 (2H, s, $COCH_2N$), 3.88 and 3.92 (6H, s each, two OMe's),

4.11 (2H, q, J=7.2 Hz, OC$\underline{H}_2$Me), 5.17 (2H, s, OC$\underline{H}_2$Ph), 6.73 (1H, d, J=8.8 Hz, $H_{(5')}$), 7.25—7.5 (5H, m, OCH$_2\underline{Ph}$), 7.51 (1H, d, J=8.8 Hz, $H_{(6')}$).

(±)-1-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-(3-ethylpiperidino)ethanol [(±)-4c]——A solution of **13** (472 mg, 1 mmol) in EtOH (6 ml) was hydrogenated over Adams catalyst (10 mg) at atmospheric pressure and 24 °C for 2 h. The catalyst was removed by filtration, and the filtrate was diluted with EtOH (5 ml) and neutralized with 2 N aqueous NaOH (0.5 ml). After addition of $NaBH_4$ (38 mg, 1 mmol), the mixture was stirred at room temperature overnight and then acetone (0.5 ml) was added. Evaporation of the solvent from the reaction mixture under reduced pressure left a yellowish oil, which was partitioned by extraction with a mixture of benzene (10 ml) and H_2O (5 ml). The benzene extracts were washed with H_2O, dried, and concentrated to leave a diastereomeric mixture of (±)-**4c** (392 mg, 98%) as a faintly yellowish oil, MS *m/e*: 399 (M^+); IR ν_{max}^{film} cm^{-1}: 3440 (br, OH); NMR ($CDCl_3$) δ: 0.85 and 0.87 (3H, t each, J=6.5 Hz, diastereomeric CCH$_2\underline{Me}$'s), 3.65 (1H, br, OH), 3.84 and 3.86 (6H, s each, two OMe's), 4.8—5.1 [1H, m, ArC$\underline{H}$(OH)], 4.99 and 5.09 (2H, AB type d's, J=11 Hz, OC$\underline{H}_2$Ph), 6.67 (1H, d, J=9 Hz, $H_{(5')}$), 7.18 (1H, d, J=9 Hz, $H_{(6')}$), 7.2—7.55 (5H, m, OCH$_2\underline{Ph}$). On standing at room temperature, the oil solidified and the solid was recrystallized from EtOH to yield one of the diastereoisomers of (±)-**4c** as colorless plates, mp 87—87.5 °C; IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH); NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz, CCH$_2\underline{Me}$), 3.87 and 3.89 (6H, s each, two OMe's), 4.0 (1H, br, OH), 4.85—5.1 [1H, m, ArC$\underline{H}$(OH)], 5.03 and 5.14 (2H, AB type d's, J=11 Hz, OC$\underline{H}_2$Ph), 6.72 (1H, d, J=8.8 Hz, $H_{(5')}$), 7.22 (1H, d, J=8.8 Hz, $H_{(6')}$), 7.2—7.55 (5H, m, OCH$_2\underline{Ph}$). *Anal.* Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.37; H, 8.32; N, 3.76.

Replacement of the bromide salt **13** by the perchlorate salt (**13**: ClO_4^- for Br^-) in the above reduction gave a similar result.

(±)-1-(3-Benzyloxyphenyl)-2-(3-ethylpiperidino)ethanol [(±)-4d]——In a manner similar to that described above for (±)-**4c**, crude **14** (5.02 g) was reduced by catalytic hydrogenation [Adams catalyst (100 mg), 50% (v/v) aqueous EtOH, 1 atm, 23 °C, 9 h] followed by treatment with $NaBH_4$ (454 mg, 12 mmol). Purification of the crude oily product (4.01 g) by column chromatography [alumina (30 g), hexane–AcOEt (1 : 1, v/v)] furnished a diastereomeric mixture of (±)-**4d** (3.74 g, 92% yield from **12**) as an almost colorless oil, MS *m/e*: 338 (M^+-1), 321 (M^+-18); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (OH); NMR ($CDCl_3$) δ: 0.89 and 0.91 (3H, t each, J=6.5 Hz, diastereomeric CCH$_2\underline{Me}$'s), 3.8 (1H, br, OH), 4.6—4.8 [1H, m, ArC$\underline{H}$(OH)], 5.07 (2H, s, OC$\underline{H}_2$Ph), 6.75—7.2 (4H, m, aromatic protons), 7.2—7.5 (5H, m, OCH$_2\underline{Ph}$).

(±)-*trans*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(±)-4f]——A solution of (±)-**17** (8.20 g, 21.7 mmol) in EtOH (150 ml) was stirred under ice-cooling, and $NaBH_4$ (821 mg, 21.7 mmol) was added portionwise in 20 min. After the solution had been stirred at room temperature for 5 h, acetone (2 ml) was added and the mixture was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O and AcOEt. The AcOEt extracts were washed with 10% aqueous Na_2CO_3, dried (K_2CO_3), and concentrated to leave an orange oil (7.78 g, 94%). Purification of the oil by column chromatography [alumina (233 g), hexane–AcOEt (3 : 1, v/v)] gave a diastereomeric mixture of (±)-**4f** as a yellow oil, MS *m/e*: 378 (M^+-1); IR ν_{max}^{film} cm^{-1}: 3440 (OH), 1730 (ester CO); NMR ($CDCl_3$) δ: 0.94 (3H, t, unresolved t, CCH$_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, OCH$_2\underline{Me}$), 3.87 and 3.90 (6H, s each, two OMe's), 4.14 (2H, q, J=7.1 Hz, OC$\underline{H}_2$Me), 4.55—4.8 [1H, m, ArC$\underline{H}$(OH)], 6.7—7.0 (3H, m, aromatic protons).

(±)-*trans*-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(±)-4h]——Crude (±)-**18** was reduced with $NaBH_4$ at room temperature for 15 h as described above for (±)-**4f**. Work-up of the reaction mixture also followed that described above for (±)-**4f**, but the product was extracted with benzene instead of AcOEt to furnish crude (±)-**4h** [94% overall yield from (±)-**16**] as an orange oil. For use in the next oxidation step, crude (±)-**4h** was purified by column chromatography [alumina, hexane–AcOEt (3 : 1, v/v)] to give a yellow oil (presumed to be a diastereomeric mixture), MS *m/e*: 467 (M^+-18); IR ν_{max}^{film} cm^{-1}: 3450 (OH), 1732 (ester CO); NMR ($CDCl_3$) δ: 0.84 (3H, unresolved t, CCH$_2\underline{Me}$), 1.26 and 1.27 (3H, t each, J=7.1 Hz, diastereomeric OCH$_2\underline{Me}$'s), 3.88 and 3.89 (6H, s each, two OMe's), 4.13 and 4.14 (2H, q each, J=7.1 Hz, diastereomeric OC$\underline{H}_2$Me's), 4.8—5.1 [1H, m, ArC$\underline{H}$(OH)], 5.03 and 5.14 (2H, AB type d's, J=11 Hz, OC$\underline{H}_2$Ph), 6.72 (1H, d, J=8.8 Hz, $H_{(5')}$), 7.21 (1H, d, J=8.8 Hz, $H_{(6')}$), 7.25—7.5 (5H, m, OCH$_2\underline{Ph}$).

(±)-1-(2-Benzyloxy-3,4-dimethoxyphenacyl)-3-methylpiperidine [(±)-37]——2-Benzyloxy-3,4-dimethoxyphenacyl bromide[19] (913 mg, 2.5 mmol) was added portionwise to a stirred, ice-cooled mixture of (±)-3-methylpiperidine [(±)-**36**] (372 mg, 3.75 mmol) and anhydrous K_2CO_3 (345 mg, 2.5 mmol) in *N*,*N*-dimethylformamide (5 ml). The resulting mixture was stirred under ice-cooling for 2.5 h and then at room temperature for 2 h. After addition of H_2O (20 ml), the reaction mixture was extracted with benzene. The benzene extracts were washed with H_2O, dried (K_2CO_3), and concentrated to leave (±)-**37** (952 mg, 99%) as a yellow but chromatographically pure oil, MS *m/e*: 383 (M^+); UV λ_{max}^{EtOH} 274 nm (ε8390); IR ν_{max}^{film} cm^{-1}: 1678 (CO); NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6 Hz, CH$\underline{Me}$), 3.69 (2H, s, $COCH_2N$), 3.89 and 3.93 (6H, s each, two OMe's), 5.17 (2H, s, OC$\underline{H}_2$Ph), 6.74 (1H, d, J=9 Hz, $H_{(5')}$), 7.25—7.5 (5H, m, OCH$_2\underline{Ph}$), 7.51 (1H, d, J=9 Hz, $H_{(6')}$).

The picrate of (±)-**37** was obtained from a small portion of the above oil by dissolving it in EtOH and adding a solution of picric acid in EtOH. Recrystallization from EtOH gave yellow prisms, mp 138—139 °C; NMR (pyridine-d_5) δ: 0.79 (3H, d, J=6.5 Hz, CH$\underline{Me}$), 3.73 and 3.81 (6H, s each, two OMe's), 4.56 (2H, s, $COCH_2N$), 5.30 (2H, s,

OCH_2Ph), 6.70 (1H, d, $J=9$ Hz, $H_{(5')}$), 7.2—7.6 (5H, m, OCH_2Ph), 7.67 (1H, d, $J=9$ Hz, $H_{(6')}$), 8.13 (1H, br, NH^+), 8.77 [2H, s, aromatic protons (picrate)]. *Anal.* Calcd for $C_{29}H_{32}N_4O_{11}$: C, 56.86; H, 5.26; N, 9.15. Found: C, 56.81; H, 5.16; N, 9.04.

(±)-1-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-(3-methylpiperidino)ethanol [(±)-38]——The foregoing amino ketone (±)-**37** was reduced as described above for (±)-**4h**, producing a diastereomeric mixture of (±)-**38** in 96% yield as a brownish oil, MS *m/e*: 385 (M^+); IR ν_{max}^{film} cm^{-1}: 3450 (br, OH); NMR ($CDCl_3$) δ: 0.84 (3H, d, $J=6$ Hz, CHMe), 3.88 and 3.89 (6H, s each, two OMe's), 4.85—5.05 [1H, m, ArCH(OH)], 5.04 and 5.15 (2H, AB type d's, $J=11$ Hz, OCH_2Ph), 6.74 (1H, d, $J=9$ Hz, $H_{(5')}$), 7.24 (1H, d, $J=9$ Hz, $H_{(6')}$), 7.25—7.6 (5H, m, OCH_2Ph).

The Mercuric Acetate–EDTA Oxidation of the Piperidinoethanols (±)-4c, d, f, h, 4e, g, i, j, and (±)-38——The oxidations of these piperidinoethanols, which were presumably diastereomeric mixtures, with $Hg(OAc)_2$–EDTA were carried out in boiling 1% aqueous AcOH for 1.5 h according to the previously reported standard procedure.[5] Work-up of the reaction mixtures and determination of the isomer ratios (**7**:**5**) by chromatographic analysis also followed that procedure. In the cases of the ester substrates [except for **4j** (see footnote *e* in Table I)], hydrolysis of the *O*-acetyl derivatives (types **8** and **6**) to give **7** and **5**, a procedure included in the standard work-up, was effected in EtOH (room temp., 4—24 h) with anhydrous K_2CO_3 instead of 50% aqueous NaOH[5a] or anhydrous Na_2CO_3.[5c] The column chromatographic conditions employed for separation of the two piperidone isomers were alumina and hexane–AcOEt [1:1, v/v [for (±)-**40** and (±)-**42**]; 1:2, v/v [for (±)-**5c** and (±)-**7c**]], silica gel and hexane–AcOEt [1:1, v/v [for (±)-**5d** and (±)-**7d**]; 1:2, v/v [for **5e**, **i**, (±)-**5f** and **7e**, **i**, (±)-**7f**]; 1:3, v/v [for **5g**, (±)-**5h** and **7g**, (±)-**7h**]], and silica gel and hexane–AcOEt (1:3, v/v) followed by alumina and hexane–$CHCl_3$ (1:3, v/v) (for **5j**, **6j** and **7j**, **8j**). In the cases of (±)-**4c** and (±)-**38**, high-performance liquid chromatographic (HPLC) analyses of the crude products were alternatively achieved, giving isomer ratios comparable to those obtained by the above column chromatographic analyses. The HPLC analyses were carried out on a Waters ALC/GPC 204 liquid chromatograph [Corasil II, CH_2Cl_2–EtOH (98:2, v/v), 100—150 p.s.i., 1.0 ml/min], and the peak height of each isomer was determined. The isomer ratio was then estimated from calibration curves which had been obtained with pure samples of the piperidone isomers (diastereomeric mixtures). All the oxidations were run in triplicate or in duplicate at least, and the mean values of the isomer ratios were obtained. The results are summarized in Table I as well as in the text. In all cases, the 2-piperidone (type **5** or **40**) was eluted faster than the 6-piperidone (type **7** or **42**) in the chromatographic analyses. The isolated lactam alcohols, presumed to be diastereomeric mixtures, were identified by IR spectral comparison with authentic samples, whenever they were known (*i.e.*, **5e**,[9] **7e**,[9] **5g**,[7] **7g**,[7] **5i**,[10] **7i**,[10] **5j**,[11] **6j**,[11] **7j**,[11] **8j**[11]), or characterized as follows.

(±)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-2-piperidone [(±)-5c]——This was recrystallized from hexane–AcOEt (1:1, v/v) to yield colorless prisms, mp 131—132 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (br, OH), 1605 (lactam CO); NMR ($CDCl_3$) δ: 0.93 (3H, t, $J=7$ Hz, CCH_2Me), 3.87 (6H, s, two OMe's), 4.39 [1H, s, ArCH(OH)], 4.9—5.2 [1H, m, ArCH(OH)], 4.96 and 5.27 (2H, AB type d's, $J=11$ Hz, OCH_2Ph), 6.67 (1H, d, $J=8.8$ Hz, $H_{(5')}$), 7.2—7.55 (5H, m, OCH_2Ph), 7.22 (1H, d, $J=8.8$ Hz, $H_{(6')}$). *Anal.* Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.74; H, 7.51; N, 3.25.

(±)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-piperidone [(±)-7c]——This was recrystallized from hexane–AcOEt (1:1, v/v) to give colorless prisms, mp 98.5—100 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (br, OH), 1611 (lactam CO); NMR ($CDCl_3$) δ: 0.77 and 0.82 (3H, unresolved t each, CCH_2Me), 3.85 (6H, s, two OMe's), 4.32 [1H, s, ArCH(OH)], 4.9—5.2 [1H, m, ArCH(OH)], 4.91 and 5.23 (2H, AB type d's, $J=11$ Hz, OCH_2Ph), 6.68 (1H, d, $J=8.8$ Hz, $H_{(5')}$), 7.19 (1H, d, $J=8.8$ Hz, $H_{(6')}$), 7.2—7.55 (5H, m, OCH_2Ph). *Anal.* Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.64; H, 7.49; N, 3.34.

(±)-1-[2-(3-Benzyloxyphenyl)-2-hydroxyethyl]-3-ethyl-2-piperidone [(±)-5d]——This was obtained as a faintly yellow oil, MS *m/e*: 353 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1605 (lactam CO); NMR ($CDCl_3$) δ: 0.95 (3H, t, $J=7.2$ Hz, CCH_2Me), 4.07 (1H, br, OH), 4.9—5.05 [1H, m, ArCH(OH)], 5.07 (2H, s, OCH_2Ph), 6.75—7.55 (9H, m, OCH_2Ph and aromatic protons).

(±)-1-[2-(3-Benzyloxyphenyl)-2-hydroxyethyl]-5-ethyl-2-piperidone [(±)-7d]——This was isolated as a faintly yellow oil, MS *m/e*: 353 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1611 (lactam CO); NMR ($CDCl_3$) δ: 0.79 and 0.87 (3H, t each, $J=6.6$ Hz, diastereomeric CCH_2Me's), 4.8—5.1 [1H, m, ArCH(OH)], 5.07 (2H, s, OCH_2Ph), 6.7—7.5 (9H, m, OCH_2Ph and aromatic protons).

(±)-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-5f]——This was a mixture of the 3,4-*trans* and the 3,4-*cis* isomers and was obtained as an orange oil, MS *m/e*: 393 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1728 (ester CO), 1612 (lactam CO); NMR ($CDCl_3$) δ: 0.93 (3H, t, $J=7.3$ Hz, CCH_2Me), 1.26 (3H, t, $J=7.1$ Hz, OCH_2Me), 3.87 and 3.89 (6H, s each, two OMe's), 4.14 (2H, q, $J=7.1$ Hz, OCH_2Me), 4.67 (d, $J=4.5$ Hz) and 4.79 (d, $J=3.9$ Hz) (1H, isomeric OH's), 4.85—5.05 [1H, m, ArCH(OH)], 6.7—7.05 (3H, aromatic protons).

(±)-*trans*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-7f]——This was isolated as a pale yellow solid, MS *m/e*: 393 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1728 (ester CO), 1620 (lactam CO); NMR ($CDCl_3$) δ: 0.78 and 0.82 (3H, t each, $J=7$ Hz, diastereomeric CCH_2Me's), 1.26 (3H, t, $J=7.2$ Hz, OCH_2Me), 3.87 and 3.90 (6H, s each, two OMe's), 4.14 (2H, q, $J=7.2$ Hz, OCH_2Me), 4.55 and 4.65 [1H, dull

d each, $J=4$ Hz, diastereomeric ArCH(OH)'s], 4.8—5.05 [1H, m, ArCH(OH)], 6.7—7.05 (3H, m, aromatic protons). Repeated recrystallizations of the solid from hexane–AcOEt (3 : 1, v/v) and drying over P_2O_5 at 2 mmHg and room temperature for 24 h gave one of the diastereoisomers as colorless plates, mp 70.5—72 °C; MS *m/e*: 393 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1728 (ester CO), 1620 (lactam CO); NMR ($CDCl_3$) δ: 0.78 (3H, t, $J=7.1$ Hz, CCH_2Me), 1.26 (3H, t, $J=7.2$ Hz, OCH_2Me), 1.74 (1H, s, $1/2H_2O$), 3.87 and 3.90 (6H, s each, two OMe's), 4.14 (2H, q, $J=7.2$ Hz, OCH_2Me), 4.66 [1H, d, $J=4.4$ Hz, ArCH(OH)], 4.85—5.05 [1H, m, ArCH(OH)], 6.75—7.05 (3H, m, aromatic protons). *Anal.* Calcd for $C_{21}H_{31}NO_6 \cdot 1/2H_2O$: C, 62.67; H, 8.01; N, 3.48. Found: C, 62.91; H, 8.13; N, 3.51.

(±)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-5h]——This was a mixture of the 3,4-*trans* and the 3,4-*cis* isomers and was obtained as an orange oil, MS *m/e*: 481 (M^+-18); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1730 (ester CO), 1608 (lactam CO); NMR ($CDCl_3$) δ: 0.88 and 0.91 (3H, t each, $J=7$ Hz, isomeric CCH_2Me's), 1.26 (3H, t, $J=7$ Hz, OCH_2Me), 3.88 (6H, s, two OMe's), 4.13 and 4.14 (2H, q each, $J=7$ Hz, isomeric OCH_2Me's), 4.94 and 5.28 (2H, AB type d's, $J=11$ Hz, OCH_2Ph), 4.9—5.3 [2H, m, ArCH(OH)], 6.71 (1H, d, $J=8.8$ Hz, $H_{(5')}$), 7.15—7.5 (6H, m, OCH_2Ph and $H_{(6')}$).

(±)-*trans*-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-7h]——This was obtained as a colorless solid, mp 88.5—91 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (OH), 1730 (ester CO), 1614 (lactam CO); NMR ($CDCl_3$) δ: 0.71 (3H, t, $J=7$ Hz, CCH_2Me), 1.26 (3H, t, $J=7.1$ Hz, OCH_2Me), 3.88 and 3.89 (6H, s each, two OMe's), 4.13 (2H, q, $J=7.1$ Hz, OCH_2Me), 4.95 and 5.28 (2H, AB type d's, $J=11$ Hz, OCH_2Ph), 4.9—5.2 [2H, m, ArCH(OH)], 6.73 (1H, d, $J=8.8$ Hz, $H_{(5')}$), 7.15—7.5 (6H, m, OCH_2Ph and $H_{(6')}$). The IR spectrum (0.2 M $CHCl_3$ solution) of this sample was identical with that of authentic (±)-**7h** prepared from (±)-**15** by the "lactim ether method."[21]

(±)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-methyl-2-piperidone [(±)-40]——This was recrystallized from hexane–AcOEt (1 : 1, v/v) to form colorless needles, mp 133.5—135 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (br, OH), 1603 (lactam CO); NMR ($CDCl_3$) δ: 1.20 and 1.22 (3H, d each, $J=7$ Hz, diastereomeric $CHMe$'s), 3.92 (6H, s, two OMe's), 4.95 and 5.28 (2H, AB type d's, $J=11$ Hz, OCH_2Ph), 4.85—5.3 [2H, m, ArCH(OH)], 6.74 (1H, d, $J=8.5$ Hz, $H_{(5')}$), 7.2—7.6 (6H, m, OCH_2Ph and $H_{(6')}$). *Anal.* Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 68.85; H, 7.27; N, 3.57.

(±)-1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-5-methyl-2-piperidone [(±)-42]——This was recrystallized from hexane–AcOEt (1 : 1, v/v) to provide colorless needles, mp 127—127.5 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (br, OH), 1609 (lactam CO); NMR ($CDCl_3$) δ: 0.78 and 0.80 (3H, d each, $J=6.5$ Hz, diastereomeric $CHMe$'s), 3.90 and 3.92 (6H, s each, two OMe's), 4.95 and 5.30 (2H, AB type d's, $J=11$ Hz, OCH_2Ph), 4.95—5.3 [2H, m, ArCH(OH)], 6.74 (1H, d, $J=8.5$ Hz, $H_{(5')}$), 7.2—7.6 (6H, m, OCH_2Ph and $H_{(6')}$). *Anal.* Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.01; H, 7.40; N, 3.43.

(3*R*,4*S*)-3-Ethyl-1-formyl-4-piperidineacetic Acid Ethyl Ester [(+)-27]——i) From **4g**: The column chromatography of the crude products from the above $Hg(OAc)_2$–EDTA oxidation of **4g** (2.91 g, 6 mmol) yielded an oily substance which was eluted slightly more slowly than the 6-piperidone **7g**. Further purification of this oil by column chromatography [silica gel, hexane–AcOEt (1 : 5, v/v) afforded (+)-**27** (87 mg, 6%) as a brownish oil, MS *m/e*: 227 (M^+); IR ν_{max}^{film} cm^{-1}: 1730, 1673; NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7.1$ Hz), 4.15 (2H, q, $J=7.1$ Hz), 7.95 and 8.05 (1H, s each). The IR and NMR spectra of this sample were superimposable on those of a sample prepared by method (ii) (see below).

ii) From (+)-**28** by Formylation:[22] A 2 M solution of HCO_2H in $CHCl_3$ (5 ml) was added dropwise to a stirred, ice-cooled solution of *N,N'*-dicyclohexylcarbodiimide (825 mg, 4 mmol) in $CHCl_3$ (5 ml). After having been stirred for 5 min, the mixture was added dropwise to a stirred, ice-cooled solution of ethyl cincholoiponate [(+)-**28**][23] (399 mg, 2 mmol) in pyridine (5 ml) over a period of 30 min. The resulting mixture was further stirred under ice-cooling for 3 h. The reaction mixture was filtered in order to remove the solid that deposited. The filtrate was concentrated *in vacuo*, and ether (50 ml) was added to the residue. The resulting mixture was filtered to remove the insoluble solid, and the filtrate was washed successively with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a pale yellow oil. The oil was purified by column chromatography [silica gel, hexane–AcOEt (1 : 3, v/v)] to give (+)-**27** (245 mg, 54%) as a colorless oil, $[\alpha]_D^{23}$ +4.69° ($c=4.306$, EtOH); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1673 (NCHO); NMR ($CDCl_3$) δ: 0.75—1.05 (3H, m, CCH_2Me),[24] 1.26 (3H, t, $J=7.1$ Hz, OCH_2Me), 4.15 (2H, q, $J=7.1$ Hz, OCH_2Me), 7.96 and 8.05 (1H, s each, NCHO).[24]

Hydrogenolysis of the Lactam Alcohols [(±)-5c, f, h, (±)-40, (±)-7c, f, h, and (±)-42] to the Lactams [(±-19—(±)-26, (±)-44, and (±)-45]——All the hydrogenolytic reactions were effected [10% Pd–C/H_2, EtOH–70% aqueous $HClO_4$, 2.7—4 atm (1 atm for **5h** and **7h**), room temp., 6—10 h (3 h for **5h** and **7h**)] in a manner similar to that reported previously[5a] for the analogous hydrogenolysis of (±)-**41**. Typical examples of the work-up procedure employed are described below under the names of the lactams (±)-**21**, (±)-**23**, and (±)-**44**. The products isolated were characterized as follows.

(±)-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-3-ethyl-2-piperidone [(±)-19]——This was obtained from (±)-**5c** in 87% yield and recrystallized from hexane–AcOEt (1 : 3, v/v) to form colorless prisms, mp 102—103 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1616 (lactam CO); NMR ($CDCl_3$) δ: 0.92 (3H, t, $J=7$ Hz, CCH_2Me), 3.80 and 3.86 (3H each, s, two OMe's), 6.32 (1H, d, $J=8.6$ Hz, $H_{(5')}$), 6.60 (1H, s, OH), 6.73 (1H, d, $J=8.6$ Hz, $H_{(6')}$). *Anal.* Calcd for

$C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.64; H, 8.27; N, 4.85.

(±)-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-ethyl-2-piperidone [(±)-20]——This was obtained from (±)-**7c** in 77% yield and recrystallized from AcOEt to give colorless needles, mp 119.5—120.5 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1620 (lactam CO); NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz, $CCH_2\underline{Me}$), 3.80 and 3.86 (3H each, s, two OMe's), 6.32 (1H, d, J=8.6 Hz, $H_{(5')}$), 6.73 (1H, d, J=8.6 Hz, $H_{(6')}$). *Anal.* Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.48; H, 8.32; N, 4.39.

(±)-*trans*- and (±)-*cis*-1-(3,4-Dimethoxyphenethyl)-3-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Esters [(±)-21 and (±)-23]——The reaction mixture from the hydrogenolysis of (±)-**5f** (590 mg, 1.5 mmol) was filtered to remove the catalyst, and the filtrate was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed successively with 10% aqueous Na_2CO_3 and H_2O, dried, and concentrated to leave a pale yellow oil (500 mg). The oil was chromatographed on a 57-g silica gel column using hexane–AcOEt (1 : 5, v/v) as the eluent. Earlier fractions gave the *cis* isomer (±)-**23** (90 mg, 16%) as a pale yellow oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1623 (lactam CO); NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.2 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 3.85 and 3.87 (6H, s each, two OMe's), 4.13 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 6.77 (3H, s, aromatic protons). The IR and NMR spectra of this sample were identical with those of an authentic sample of the (−)-isomer.[9]

On the other hand, later fractions in the above chromatography yielded the *trans* isomer (±)-**21** (357 mg, 63%) as a pale yellow oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1620 (lactam CO); NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.2 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.2 Hz, $OCH_2\underline{Me}$), 3.86 and 3.87 (6H, s each, two OMe's), 4.14 (2H, q, J=7.2 Hz, $OC\underline{H}_2Me$), 6.77 (3H, s, aromatic protons). The IR and NMR spectra of this oil were superimposable on those of an authentic sample of the (+)-isomer.[9]

(±)-*trans*-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-25]——This was obtained from (±)-**7f** in 91% yield as a faintly yellow oil and identified by IR and NMR spectral comparison with authentic (±)-**25**.[12]

(±)-*trans*- and (±)-*cis*-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-3-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Esters [(±)-22 and (±)-24]——The oily crude product (514 mg) derived from the hydrogenolysis of (±)-**5h** (739 mg, 1.48 mmol) was chromatographed on a column packed with silica gel (57.5 g) using hexane–AcOEt (1 : 2, v/v) as the eluent. Earlier fractions afforded the *cis* isomer (±)-**24** (89 mg, 15%) as a pale yellow solid. Recrystallization of the solid from hexane–AcOEt (4 : 1, v/v) produced an analytical sample as colorless needles, mp 75—76 °C; MS *m/e*: 393 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545 (OH), 1728 (ester CO), 1620 (lactam CO); NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.3 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 3.83 and 3.89 (3H each, s, two OMe's), 4.14 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 6.38 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.79 (1H, d, J=8.5 Hz, $H_{(6')}$). *Anal.* Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.88; H, 8.12; N, 3.56.

Later fractions in the above chromatography gave the *trans* isomer (±)-**22** (357 mg, 61%) as a pale yellow solid, mp 82—84.5 °C. Recrystallization from hexane–AcOEt (3 : 1, v/v) produced an analytical sample as colorless needles, mp 84—87.5 °C; MS *m/e*: 393 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545 (OH), 1728 (ester CO), 1620 (lactam CO); NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz, $CCH_2\underline{Me}$),[25] 1.26 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 3.83 and 3.89 (3H each, s, two OMe's), 4.14 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 6.38 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.79 (1H, d, J=8.5 Hz, $H_{(6')}$). *Anal.* Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 64.15; H, 8.11; N, 3.33.

(±)-*trans*-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-26]——This was prepared from (±)-**7h** in 90% yield and recrystallized from hexane–AcOEt (2 : 1, v/v) to form colorless prisms, mp 88.5—89.5 °C (lit.[21] mp 90—91 °C), which were identical with authentic (±)-**26**.[21]

(±)-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-3-methyl-2-piperidone [(±)-44]——The reaction mixture from the hydrogenolysis of (±)-**40** (240 mg, 0.6 mmol) was filtered in order to remove the catalyst, and the filtrate was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of benzene and H_2O. The benzene extracts were washed successively with saturated aqueous $NaHCO_3$ and H_2O, dried, and concentrated to leave a pale yellow solid (145 mg, 82%). Recrystallization of the solid from hexane–AcOEt (1 : 3, v/v) furnished an analytical sample of (±)-**44** as colorless prisms, mp 100.5—101.5 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1617 (lactam CO); NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7.2 Hz, $CH\underline{Me}$), 3.79 and 3.85 (3H each, s, two OMe's), 6.31 (1H, d, J=8.6 Hz, $H_{(5')}$), 6.73 (1H, d, J=8.6 Hz, $H_{(6')}$). *Anal.* Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.27; H, 7.85; N, 5.07.

(±)-1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-methyl-2-piperidone [(±)-45]——This was obtained from (±)-**42** in 77% yield and recrystallized from AcOEt to give colorless prisms, mp 140—141 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1620 (lactam CO); NMR ($CDCl_3$) δ: 0.95 (3H, d, J=6.0 Hz, $CH\underline{Me}$), 3.80 and 3.86 (3H each, s, two OMe's), 6.31 (1H, d, J=8.8 Hz, $H_{(5')}$), 6.72 (1H, d, J=8.8 Hz, $H_{(6')}$). *Anal.* Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.53; H, 8.03; N, 4.68.

Acknowledgment We are grateful to Professor S. Yamada (Tokyo) for financial assistance in the form of a grant from Japan Research Foundation for Optically Active Compounds and to Messrs. H. Suzuki and H. Hatakeyama (Kanazawa) for technical assistance.

References and Notes

1) Paper XXV in this series, T. Fujii, Y. Takai, M. Ohba, H. Kogen, and M. Ōki, *Chem. Pharm. Bull.*, **33**, 2697 (1985).
2) For this synthetic method, see references cited in ref. 11.
3) 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); *d*) T. Fujii, M. Ohba, and S. Akiyama, *Chem. Pharm. Bull.*, **33**, 5316 (1985).
4) Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations. The optical rotation descriptors (+) and (−) are omitted in the cases where optically active compounds are mixtures of diastereoisomers or they are represented by general formulas.
5) *a*) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.*, **21**, 2695 (1973); *b*) T. Fujii, K. Yoshida, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 2336 (1977); *c*) T. Fujii, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 3042 (1977); *d*) T. Fujii, T. Hiraga, and M. Ohba, *ibid.*, **29**, 2691 (1981).
6) For convenience, each position of the aromatic ring is indicated by a primed number.
7) T. Fujii and S. Yoshifuji, *J. Org. Chem.*, **45**, 1889 (1980).
8) This ratio was based on data from a preparative run and did not cover that of other 6- and 2-oxidation products in the form of the *O*-acetyl derivatives (**8g** and **6g**).
9) T. Fujii and S. Yoshifuji, *Tetrahedron*, **36**, 1539 (1980).
10) T. Fujii and M. Ohba, *Chem. Pharm. Bull.*, **33**, 583 (1985).
11) T. Fujii, M. Ohba, and H. Suzuki, *Chem. Pharm. Bull.*, **33**, 1023 (1985).
12) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **27**, 1486 (1979).
13) J. Gutzwiller, G. Pizzolato, and M. R. Uskoković, *Helv. Chim. Acta*, **64**, 1663 (1981).
14) The mercuric acetate oxidation of such an exocyclic α-carbon has been considered to be conformationally highly unfavored: H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **299**, 23 (1966).
15) For ease of comparison with the other conformer (**31**), a conformation of the antipode of **4e** is represented in formula **32**.
16) *a*) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960); *b*) *Idem, ibid.*, **5**, 139 (1962).
17) T. Fujii, S. Yoshifuji, K. Yoshida, M. Ohba, S. Ikegami, and M. Kirisawa, *Chem. Pharm. Bull.*, **23**, 993 (1975).
18) W. A. Bolhofer, *J. Am. Chem. Soc.*, **75**, 4469 (1953).
19) T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, **26**, 3218 (1978).
20) T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, **26**, 645 (1978).
21) T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron*, **36**, 965 (1980).
22) The reported formylation procedure for amino acid *tert*-butyl esters [M. Waki and J. Meienhofer, *J. Org. Chem.*, **42**, 2019 (1977)] was applied here.
23) *a*) V. Prelog and E. Zalán, *Helv. Chim. Acta*, **27**, 535 (1944); *b*) A. Kaufmann, E. Rothlin, and P. Brunschweiler, *Ber. Dtsch. Chem. Ges.*, **49**, 2299 (1916); *c*) T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.*, **23**, 2094 (1975).
24) The observed complexity of the proton signals is probably a result of *cis–trans* isomerism of the *N*-formyl group.
25) This methyl proton signal appears upfield from that of the *cis* isomer (±)-**24** by 0.1 ppm, and such a relation also holds for the corresponding signals of the *trans* isomer (±)-**21** and the *cis* isomer (±)-**23**.