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Quinolizidines. XVII.[1] A New Access to 9,10-Dimethoxy- and 8-Hydroxy-9,10-dimethoxybenzo[*a*]quinolizidine-Type *Alangium* Alkaloids from 3-Acetylpyridine

TOZO FUJII,* MASASHI OHBA, and SHIGEAKI AKIYAMA

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

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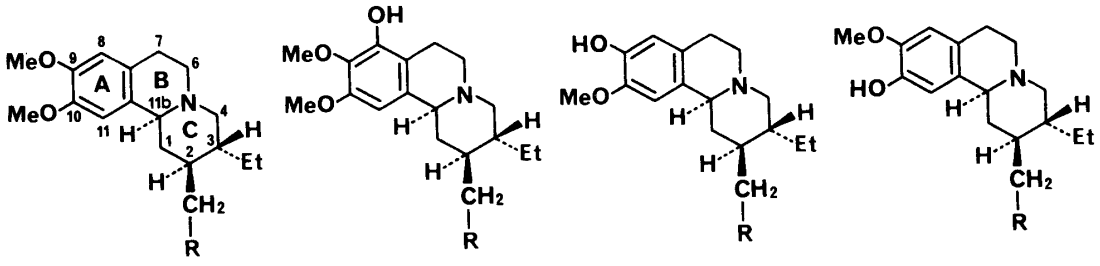
New syntheses of the ipecac and *Alangium* alkaloids possessing the 9,10-dimethoxy- and 8-hydroxy-9,10-dimethoxybenzo[*a*]quinolizidine skeletons (types **1** and **2**) have now become possible through generally applicable routes starting from 3-acetylpyridine (**5**). The routes involve the mercuric acetate–edetic acid oxidation of the 3-acetylpiperidine derivatives **9a**, **b** or the alkaline ferricyanide oxidation of the quaternary salts (**26a**, **b** and **27a**, **b**) of 3-acetylpyridine equivalents, Wolff–Kishner reduction of the acetyl group or reductive desulfurization of the thioketal group, sulfenylation–dehydrosulfenylation of the lactams **12a**, **b**, Michael reaction of the α,β-unsaturated lactams **15a**, **b**, and de-ethoxycarbonylation of the Michael adducts **16a**, **b** as the main operations.

Keywords——ipecac alkaloid synthesis; *Alangium* alkaloid synthesis; piperidine mercuric acetate–edetic acid oxidation; lactam sulfenylation–dehydrosulfenylation; α,β-unsaturated lactam Michael reaction; malonic ester de-ethoxycarbonylation; pyridinium salt ferricyanide oxidation; thioketal reductive desulfurization; *O*-benzyl group hydrogenolysis; phenethyl alcohol bromination

Up to now, the Indian medicinal plant *Alangium lamarckii* THW. (Alangiaceae) has been found to contain eighteen benzo[*a*]quinolizidine alkaloids, which are structurally related to the ipecac bases, as well as ten other alkaloids.[2,3] We have already shown that these benzo[*a*]quinolizidine-type *Alangium* alkaloids may be classified into four groups (**1**—**4**) according to their substitution patterns in the aromatic ring A,[4] and that the racemic



1 2 3 4

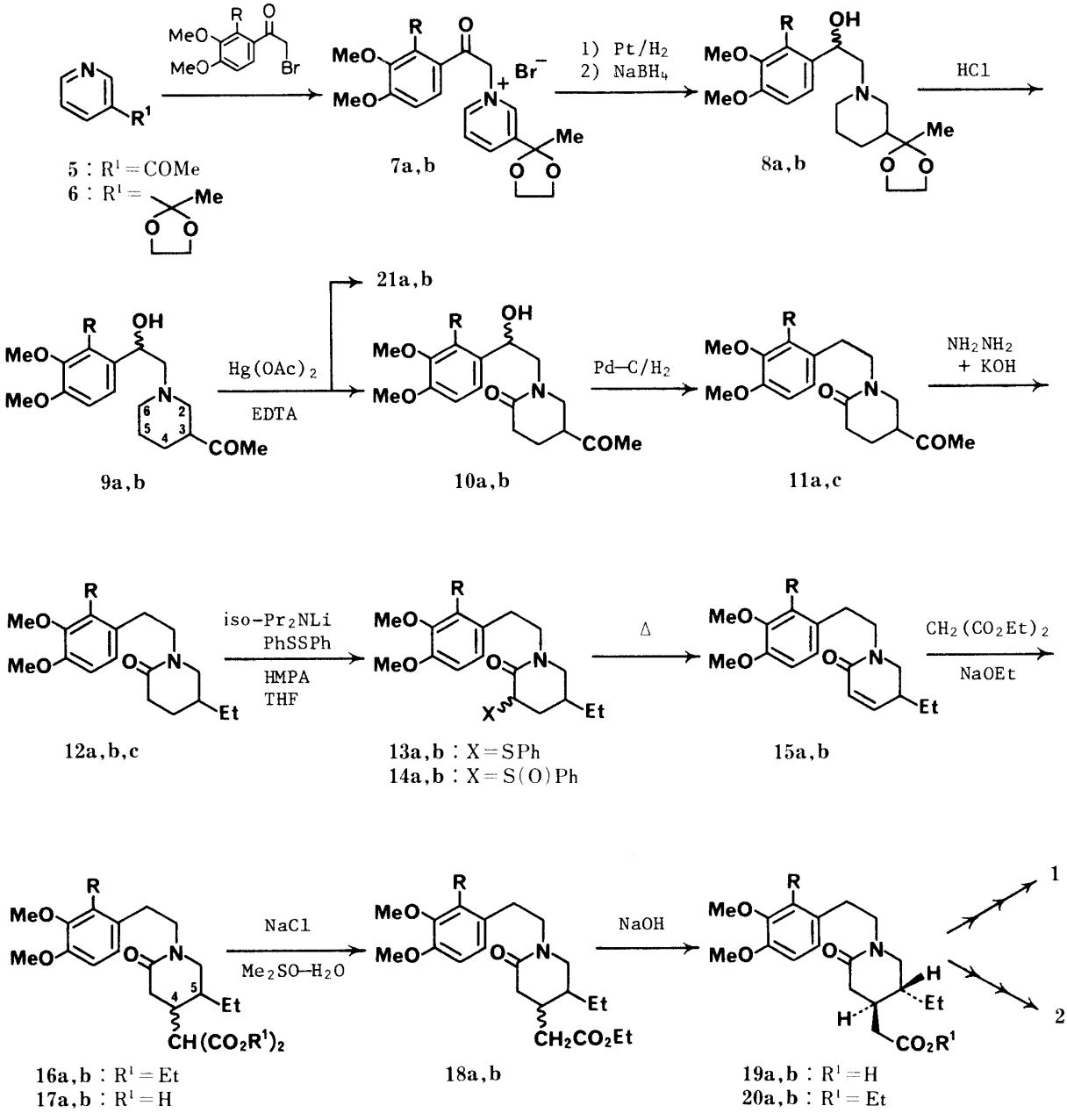
R=CH_2OH, CO_2H, or a heterocyclic ring

synthesis of all of these types of alkaloids is possible through a "lactim ether route" and the chiral synthesis, through a "cincholoipon-incorporating route."[5] In the present study, an alternative route starting from 3-acetylpyridine (**5**) was generated for the racemic synthesis, and its feasibility was demonstrated in the syntheses of some ipecac and *Alangium* alkaloids having the 9,10-dimethoxy- and 8-hydroxy-9,10-dimethoxybenzo[*a*]quinolizidine skeletons (**1** and **2**).[6] These syntheses utilized mercuric acetate–edetic acid (EDTA) oxidation or alkaline ferricyanide oxidation for construction of the lactam carbonyl function at the 6-position of 3-acetylpyridine equivalents, and the resulting lactam carbonyl group played an important role

in the introduction of the acetate chain into the 4-position and in the formation of ring B at later steps.

The Route through $Hg(OAc)_2$–EDTA Oxidation

For the synthesis of the **1**-type alkaloids, 3-acetylpyridine (**5**) was first converted into the ketonic lactam **11a** *via* the intermediates **6**, **7a**, **8a**, **9a**, and **10a** according to the previously reported procedure.[7a] In the $Hg(OAc)_2$–EDTA oxidation of **9a**, the enamine **21a**, probably derived from the initially formed iminium salt,[7] was obtained in 9% yield besides the main product **10a** (81% yield). The minor product has not been isolated in our previous experiments, and it is now disclosed that oxidation of **9a** also occurs at the 2-position in the form of dehydrogenation and that the ratio of the 6- to the 2-oxidation is 90:10, and not



5 : R^1 = COMe
6 : R^1 =

7a,b

8a,b

21a,b

9a,b

10a,b

11a,c

12a,b,c

13a,b : X = SPh
14a,b : X = S(O)Ph

15a,b

16a,b : R^1 = Et
17a,b : R^1 = H

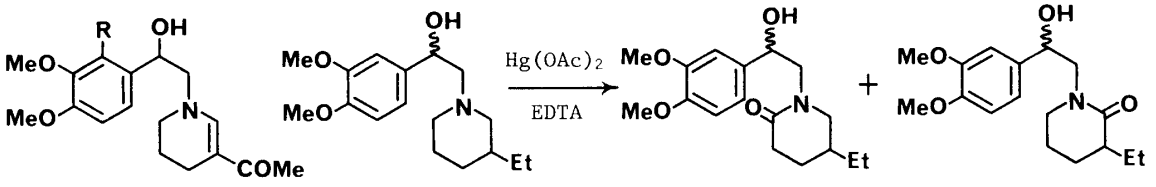
18a,b

19a,b : R^1 = H
20a,b : R^1 = Et

a: R = H, **b**: R = OCH_2Ph, **c**: R = OH

Chart 1

100 : 0 as reported previously;[2b,7a] however, regioselectivity is still high in this reaction. Wolff-Kishner reduction of **11a** was then effected by means of the Huang-Minlon modification to give the lactam **12a** in 82% yield. Although the same lactam **12a** had previously been prepared from 3-ethylpyridine through a parallel sequence of conversions,[8] its overall yield had been much lower than that in the present route. This is apparently owing to the low regioselectivity in the $Hg(OAc)_2$–EDTA oxidation of the ethyl analogue **22**, whereby the 6-piperidone **23** and the 2-piperidone **24** are produced in a ratio of 54 : 46.[2b,7b,8] Sulfenylation[9] of **12a** in



21a: R = H
21b: R = OCH_2Ph

22 **23** **24**

Chart 2

tetrahydrofuran (THF) with diphenyl disulfide in the presence of lithium diisopropylamide and hexamethylphosphoramide (HMPA) at −78 °C furnished **13a** in 91% yield as a diastereomeric mixture. The mixture **13a** was then oxidized with sodium metaperiodate in aqueous MeOH at room temperature, and thermolysis of the resulting sulfoxide **14a** in boiling toluene in the presence of $CaCO_3$ afforded the α,β-unsaturated lactam **15a** in 91% overall yield from **13a**, concluding the dehydrosulfenylation of **13a**. The conversion of **12a** to **15a** *via* **13a** and **14a** by a similar method has been reported by Takano *et al.*,[10] and the analogous introduction of α,β-unsaturation into a six-membered lactam, by Grieco *et al.*[11]

The Michael addition of diethyl malonate to **15a** was carried out according to the previously reported procedure,[12] and the diester **16a** (presumed to be a 13 : 87 mixture of the *cis* and *trans* isomers) was obtained in 69% yield. The adduct **16a** was de-ethoxycarbonylated by heating with NaCl in moist dimethyl sulfoxide[10,13] to produce the monoester **18a** (85% yield), which was shown to be a 9 : 91 mixture of the *cis* and *trans* isomers on carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopic analysis. Hydrolysis of the mixture **18a** with NaOH in aqueous EtOH at room temperature and purification of the products by recrystallization gave the *trans*-lactam acid (±)-**19a** in 84% yield. The structure and stereochemistry of (±)-**19a** were confirmed by its identity with an authentic sample, which was prepared from **15a** through **16a** and **17a** by the method of Battersby and Turner.[12,14]

In view of the previous conversions of (±)-**19a** into (−)-emetine,[14] (+)-*O*-methylpsychotrine,[14] (±)-cephaeline,[15] (±)-tubulosine,[16] (±)-deoxytubulosine,[17] (±)-protoemetinol,[14] (±)-protoemetine,[15] and (±)-emetamine[18] through the ethyl ester (±)-**20a**, the above synthesis of (±)-**19a** from 3-acetylpyridine (**5**) is formally tantamount to new syntheses of these ipecac and/or *Alangium* alkaloids having the 9,10-dimethoxybenzo[*a*]quinolizidine skeleton (type **1**).

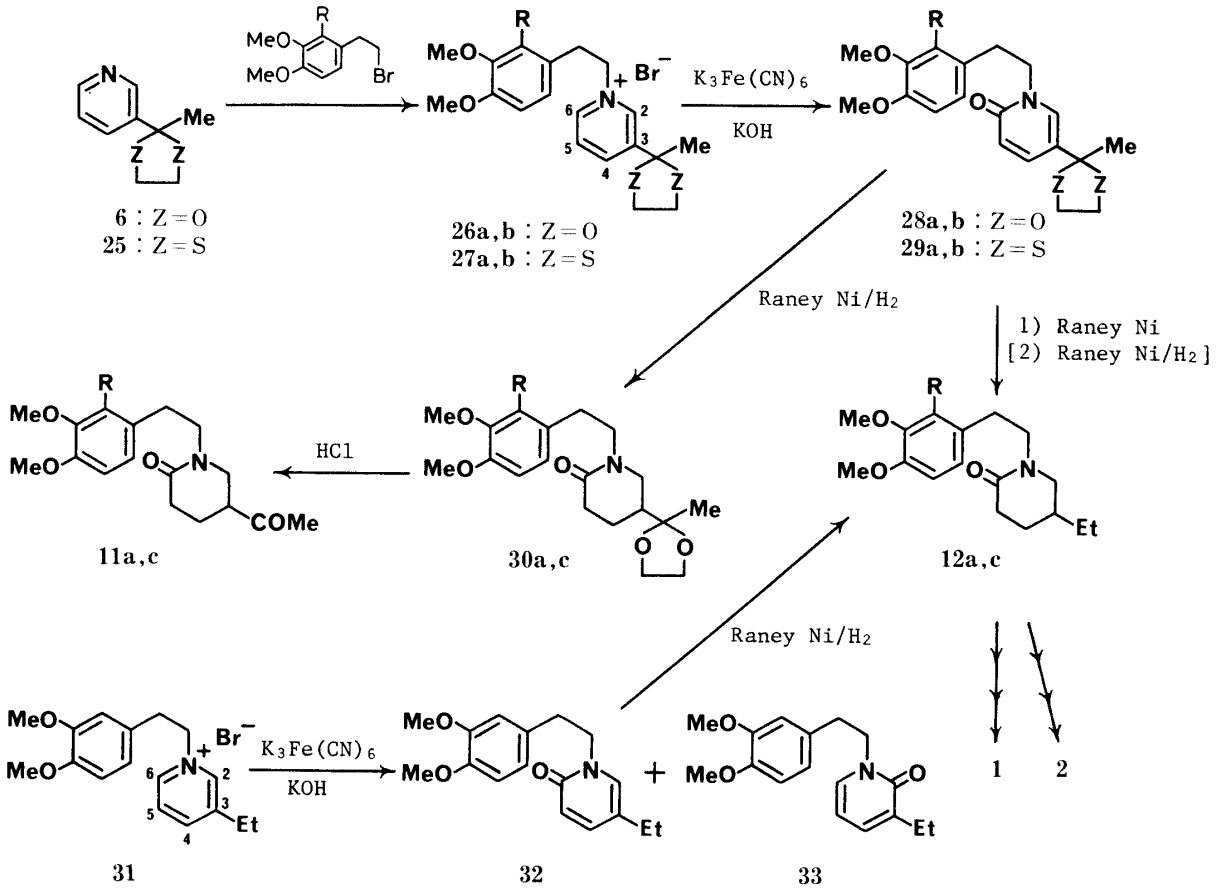
Next, the synthesis of the **2**-type alkaloids was tried by means of a parallel series of conversions, which started with quaternization of **6** with 2-benzyloxy-3,4-dimethoxyphenacyl bromide. The resulting quaternary salt **7b** (99% yield) was reduced first with hydrogen over Adams catalyst and then with $NaBH_4$ to give **8b** in 81% yield as a diastereomeric mixture. Deketalization of **8b** with 1 N hydrochloric acid at 40 °C produced the ketone **9b** (98% yield), which was oxidized with $Hg(OAc)_2$–EDTA according to the previously reported standard procedure,[8,19] affording the 6-piperidone **10b** (as a diastereomeric mixture) and the enamine **21b** in 82% and 10% yields, respectively. Catalytic hydrogenolysis of the mixture **10b** and Wolff-Kishner reduction of the resulting phenolic ketone **11c** (89% yield) provided the

phenolic lactam **12c** in 84% yield. Compound **12c** was benzylated with benzyl bromide in boiling acetone containing K_2CO_3 to give the benzyl ether **12b** (96% yield), which was then converted into the *trans*-lactam ester (±)-**20b** in 43% overall yield (from **12b**) through the intermediates **13b**, **14b**, **15b**, **16b** (*cis* : *trans* = 12 : 88), **18b** (*cis* : *trans* = 11 : 89), and (±)-**19b** in a manner similar to that described above for the **a**-series. A by-pass from **16b** to (±)-**19b** (54% overall yield from **15b**) consisted of alkaline hydrolysis of the former and decarboxylation of the resulting dicarboxylic acid **17b** in boiling 60% aqueous AcOH.

Since the lactam ester (±)-**20b** thus prepared was identical with an authentic sample synthesized by us[20] through a "lactim ether route" and since (±)-**20b** has already been converted into (±)-ankorine,[20] (±)-alangicine,[21] and (±)-alangimarckine,[22] the above synthesis of (±)-**20b** formally constitutes new racemic syntheses of these three *Alangium* alkaloids possessing the 8-hydroxy-9,10-dimethoxybenzo[*a*]quinolizidine skeleton (type **2**).

The Route through Alkaline Ferricyanide Oxidation

In view of the intermediary function of the ketonic lactam **11a** in the foregoing synthesis of the **1**-type alkaloids, the previously reported preparation of **11a**[7,23a] from the ketal **6** and 3,4-dimethoxyphenethyl bromide through the route involving alkaline ferricyanide oxidation [**6**→**26a**→**28a**→**30a**→**11a** (Chart 3)] represents alternative formal syntheses of these alkaloids. In much the same sense, the lactam **12a** was synthesized in 84% yield by reductive



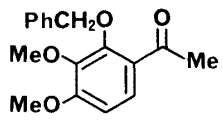
a: R=H, **b**: R=OCH_2Ph, **c**: R=OH

Chart 3

desulfurization (Raney Ni, boiling 70% aqueous EtOH) of **29a**, which was available from initial quaternization of the thioketal **25** with 3,4-dimethoxyphenethyl bromide and subsequent alkaline ferricyanide oxidation of the resulting pyridinium salt **27a** according to the

previously reported procedure,[23a] thus concluding yet another formal synthesis of the **1**-type alkaloids. The same lactam **12a** had previously been prepared from 3-ethylpyridine *via* the quaternary salt **31** and the 6-pyridone **32**, but in a much less efficient manner.[8] This inefficiency is attributed to the high regioselectivity in the alkaline ferricyanide oxidation of **31**, which is in favor of the formation of the undesired 2-pyridone **33** (**32**:**33**=12:88).[8,23b] Interestingly, these formal syntheses of the **1**-type alkaloids from **6** or **25** amount to the realization of the idea of Professor Sugasawa, who attempted to utilize the alkaline ferricyanide oxidation of 1-substituted 3-ethylpyridinium salt or its equivalents for the synthesis of the ipecac alkaloid emetine (type **1**) in the early 1950's.[24]

The scope of this synthetic strategy was then extended to include the syntheses of the **2**-type *Alangium* alkaloids. We first prepared 2-benzyloxy-3,4-dimethoxyphenethyl bromide (**39**), one of the requisite starting materials, from the ketone **34** by the following 5-step synthesis. Treatment of **34** with sulfur and morpholine under Willgerodt–Kindler reaction



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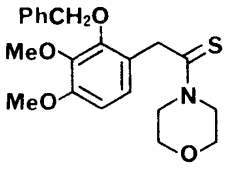

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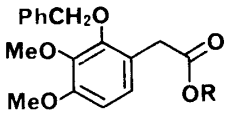
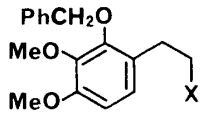


36: R=H
37: R=Et



38: X=OH
39: X=Br

conditions produced the thiomorpholide **35** (62% yield), which was hydrolyzed with KOH in boiling aqueous EtOH to give the carboxylic acid **36** in 93% yield. On esterification with ethanolic HCl, **36** afforded the ester **37** in 97% yield, and the subsequent $LiAlH_4$ reduction of **37** in ether furnished the alcohol **38** in 97% yield. The desired bromide **39** was obtained from **38** in 88% yield by treatment with *N*-bromosuccinimide/Ph_3P reagent[25] in benzene.

The pyridinium salts **26b** and **27b** were then prepared from **6** and **25**, respectively, by quaternization with **39** in benzene. The alkaline ferricyanide oxidations of **26b** and **27b** were effected under the standard conditions described previously,[8,23a] giving the 6-oxidation products **28b** (83% overall yield form **6**) and **29b** (42% overall yield from **25**), respectively. In both oxidations, no 2-oxidation products were obtained, in general agreement with the previous results[2b,23a] from the **a**-series. On catalytic hydrogenation over Raney Ni and subsequent acid hydrolysis, the 6-pyridone **28b** was converted into the phenolic lactam **11c** in 95% yield through **30c**, whereas desulfurization of **29b** with Raney Ni in boiling aqueous EtOH followed by catalytic hydrogenation (Raney Ni/H_2) provided **12c** in 82% yield. The observed hydrogenolysis of the *O*-benzyl group over Raney Ni catalyst in the above two cases is rather unusual, but some precedents have been found in the literature.[26] Since the phenolic lactams **11c** and **12c** have already been led to the **2**-type *Alangium* alkaloids by the route shown in Chart 1, the above syntheses of **11c** and **12c** from **6** and **25** utilizing alkaline ferricyanide oxidation represent additional new formal syntheses of these alkaloids.

Conclusion

The present work has shown that the **1**- and **2**-types of benzo[*a*]quinolizidine alkaloids can be synthesized either from the ketal **6** by employing $Hg(OAc)_2$–EDTA oxidation or from **6** or the thioketal **25** by utilizing alkaline ferricyanide oxidation. Since the starting material **6** or **25** is easily obtainable from 3-acetylpyridine (**5**),[24c] the routes used for the above syntheses may be generalized under the name of the "3-acetylpyridine route." Such a route is probably applicable to the syntheses of the remaining **3**- and **4**-type *Alangium* alkaloids, and work along this line is in progress in our laboratory.

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 ref. 27 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, dt = doublet-of-triplets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

1-(2-Benzyloxy-3,4-dimethoxyphenacyl)-3-(1,1-ethylenedioxyethyl)pyridinium Bromide (7b)——A solution of **6**[24c] (1.82 g, 11 mmol) and 2-benzyloxy-3,4-dimethoxyphenacyl bromide[28] (3.65 g, 10 mmol) in dry benzene (30 ml) was stirred at room temperature for 5 h. The precipitate that resulted was filtered off, washed with benzene (20 ml), and dried to give **7b** (3.19 g) as a colorless solid, mp 167.5—168.5 °C (dec.). The filtrate and washings were combined, concentrated to a volume of *ca.* 10 ml, and kept at room temperature overnight to yield a second crop (2.08 g) of **7b**. The total yield of **7b** was 5.27 g (99%). Recrystallization of crude **7b** from EtOH furnished an analytical sample as colorless minute needles, mp 169—169.5 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 1685 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, s, CMe), 3.91 and 3.97 (3H each, s, two OMe's), 5.50 (2H, s, $OC\underline{H}_2Ph$), 6.53 (2H, s, $ArCOC\underline{H}_2$), 6.81 (1H, d, J = 9.0 Hz, $H_{(5')}$), 7.25—7.7 (5H, m, Ph), 7.73 (1H, d, J = 9.0 Hz, $H_{(6')}$), 8.02 (1H, dd, J = 7.5 and 6.0 Hz, $H_{(5)}$), 8.41 (1H, s, $H_{(2)}$), 8.46 (1H, d, J = 7.5 Hz, $H_{(4)}$), 9.37 (1H, d, J = 6.0 Hz, $H_{(6)}$). *Anal.* Calcd for $C_{26}H_{28}BrNO_6$: C, 58.88; H, 5.32; N, 2.64. Found: C, 58.75; H, 5.25; N, 2.92.

1-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-[3-(1,1-ethylenedioxyethyl)piperidino]ethanol (8b)——A solution of **7b** (28.6 g, 54 mmol) in 50% aqueous EtOH (250 ml) was hydrogenated over Adams catalyst (500 mg) at room temperature and atmospheric pressure for 18 h, absorbing *ca.* 3.1 mol eq of H_2. The catalyst was removed by filtration and the filtrate was neutralized with 2 N aqueous NaOH (27 ml). The resulting solution was stirred at room temperature overnight, during which time $NaBH_4$ (2.04 g, 54 mmol) was added portionwise. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of H_2O and benzene. The benzene extracts were washed with H_2O, dried over anhydrous K_2CO_3, and concentrated to leave a faintly yellow oil (24.3 g). Purification of the oil by column chromatography [alumina, hexane–AcOEt (2 : 1, v/v)] gave **8b** (20.0 g, 81%) as an almost colorless oil (presumed to be a diastereomeric mixture), MS *m/e*: 457 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (OH); ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, s, CMe), 3.87 (6H, s, two OMe's), 4.8—5.05 [1H, m, $ArC\underline{H}(OH)$], 5.03 and 5.13 (2H, AB type d's, J = 11.0 Hz, $OC\underline{H}_2Ph$), 6.72 (1H, d, J = 8.8 Hz, $H_{(5')}$), 7.21 (1H, d, J = 8.8 Hz, $H_{(6')}$), 7.2—7.5 (5H, m, Ph).

1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-piperidyl Methyl Ketone (9b)——A solution of **8b** (19.2 g, 42 mmol) in 1 N aqueous HCl (120 ml) was stirred at 40 °C for 2 h. The reaction mixture was made basic (pH 10) with K_2CO_3 and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried (K_2CO_3), and concentrated to leave **9b** (17.0 g, 98%) as a faintly yellowish oil. A portion of the oil was purified by column chromatography [alumina, hexane–AcOEt (1 : 1, v/v)] to afford a colorless oil (presumed to be a diastereomeric mixture), MS *m/e*: 413 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (OH), 1706 (CO); ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s, COMe), 3.88 and 3.89 (6H, s each, two OMe's), 4.8—5.0 [1H, m, $ArC\underline{H}(OH)$], 5.04 and 5.15 (2H, AB type d's, J = 11.0 Hz, $OC\underline{H}_2Ph$), 6.72 (1H, d, J = 8.8 Hz, $H_{(5')}$), 7.19 (1H, d, J = 8.8 Hz, $H_{(6')}$), 7.2—7.5 (5H, m, Ph).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-1,2,3,4-tetrahydro-5-pyridyl Methyl Ketone (21a)——The Hg(OAc)$_2$–EDTA oxidation of **9a** and column chromatographic separation of the products were carried out as described previously,[7a] and besides the known 6-piperidone **10a**[7a] (81% yield), the enamine **21a** having a thin-layer chromatographic (TLC) mobility lower than that of **10a** was isolated in 9% yield as a faintly yellowish oil, MS *m/e*: 305 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (OH), 1618 and 1570 (vinylogous amide);[29] ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.95 (2H, m, $H_{(3)}$'s), 2.03 (3H, s, COMe), 2.1—2.4 (2H, m, $H_{(4)}$'s), 3.05—3.65 [5H, m, $H_{(2)}$'s and $ArCH(O\underline{H})C\underline{H}_2$], 3.85 (6H, s, two OMe's), 4.7—4.9 [1H, m, $ArC\underline{H}(OH)$], 6.75—7.0 (3H, m, aromatic protons), 7.24 (1H, s, $H_{(6)}$).

The Hg(OAc)$_2$–EDTA Oxidation of 9b——According to the previously reported[8] standard procedure, **9b** was oxidized with Hg(OAc)$_2$–EDTA in boiling 1% aqueous AcOH and the reaction mixture was worked up to give the 6-piperidone **10b** (as a diastereomeric mixture) and the enamine **21b** in 82% and 10% yields, respectively. Separation of the two products was accomplished by means of column chromatography using silica gel and $CHCl_3$, and **10b** was eluted faster than **21b**. They were characterized as described below.

5-Acetyl-1-[2-(2-benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-2-piperidone (10b)——This diastereomeric mixture was isolated as a faintly yellowish solid, mp 95—99 °C; MS *m/e*: 410 ($M^+ - OH$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1714 (CO), 1619 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 2.07 and 2.10 (3H, s each, diastereomeric COMe's), 3.88 and 3.90 (6H, s each, two OMe's), 4.68 (d, J = 5.1 Hz) and 4.81 (d, J = 4.4 Hz) (1H, diastereomeric OH's), a pair of 4.94 and 5.26 (AB type d's, J = 10.9 Hz) and a pair of 4.98 and 5.29 (AB type d's, J = 11.0 Hz) (2H, diastereomeric $OC\underline{H}_2Ph$'s), 4.95—5.15 [1H, m, $ArC\underline{H}(OH)$], 6.72 (1H, d, J = 8.8 Hz, $H_{(5')}$), 7.1—7.5 (6H, m, $H_{(6')}$ and Ph). Recrystallization of the solid from hexane–AcOEt (1 : 1, v/v) yielded an analytical sample, shown to be stereochemically still impure, as colorless needles, mp 99—101 °C; IR ν_{max}^{Nujol} cm^{-1}: 3360 (OH), 1713 (CO), 1623 (lactam CO); ^{1}H-NMR ($CDCl_3$), identical with that of the above crude sample. *Anal.* Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.14; H, 6.88; N, 3.30.

1-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-2-hydroxyethyl]-1,2,3,4-tetrahydro-5-pyridyl Methyl Ketone (21b)——This was recrystallized from EtOH to give an analytical sample as faintly yellowish scales, mp 164.5—165.5 °C; MS *m/e*: 411 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3290 (OH), 1616 and 1550 (vinylogous amide); [29] ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (2H, m, $H_{(3)}$'s), 2.00 (3H, s, COMe), 2.23 (2H, t, J=6.3 Hz, $H_{(4)}$'s), 2.69 (1H, d, J=4.6 Hz, OH), 2.99 (2H, t, J=5.5 Hz, $H_{(2)}$'s), 3.1—3.3 [2H, m, ArCH(OH)C$\underline{H}_2$], 3.89 (6H, s, two OMe's), 4.8—5.0 [1H, m, ArC$\underline{H}$(OH)], 5.06 and 5.24 (2H, AB type d's, J=11.0 Hz, OC$\underline{H}_2$Ph), 6.71 (1H, d, J=8.8 Hz, $H_{(5')}$), 7.10 (1H, s, $H_{(6)}$), 7.10 (1H, d, J=8.8 Hz, $H_{(6')}$), 7.25—7.5 (5H, m, Ph). *Anal.* Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.97; H, 7.27; N, 3.34.

5-Acetyl-1-(3,4-dimethoxy-2-hydroxyphenethyl)-2-piperidone (11c)——A solution of **10b** (12.8 g, 30 mmol) in EtOH (200 ml) containing 70% aqueous $HClO_4$ (3 ml) was hydrogenated over 10% Pd–C (4.0 g) at room temperature and atmospheric pressure for 6 h. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure left a pale yellowish oil, which was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated to leave **11c** (8.54 g, 89%), mp 119—122 °C. Recrystallization from AcOEt yielded an analytical sample as colorless needles, mp 123—124 °C; IR ν_{max}^{Nujol} cm^{-1}: 1700 (CO), 1631 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s, COMe), 3.83 and 3.89 (3H each, s, two OMe's), 6.35 (1H, s, OH), 6.39 (1H, d, J=8.8 Hz, $H_{(5')}$), 6.80 (1H, d, J=8.8 Hz, $H_{(6')}$). *Anal.* Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.25; H, 7.24; N, 4.41.

1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-piperidone (12a)——A mixture of **11a**[7a] (305 mg, 1 mmol), ethylene glycol (2 ml), 80% aqueous hydrazine hydrate (188 mg, 3 mmol), and KOH (200 mg) was placed in a flask equipped with a descending condenser. The mixture was heated in an oil bath at 120 °C for 1 h with stirring. Then, the temperature of the oil bath was slowly raised to 190 °C in 30 min, and the mixture was further heated with stirring at 190—195 °C for 3 h to give a little distillate. After cooling, the reaction mixture was diluted with H_2O (5 ml), neutralized with 10% aqueous HCl, and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a colorless oil (256 mg). Purification of the oil by column chromatography [alumina, hexane–AcOEt (1 : 1, v/v)] furnished **12a** (238 mg, 82%) as a colorless oil. The infrared (IR) spectrum (neat) and TLC behavior of this sample were identical with those of authentic **12a**.[8]

1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-ethyl-2-piperidone (12c)——A mixture of **11c** (3.21 g, 10 mmol), ethylene glycol (20 ml), 80% aqueous hydrazine hydrate (1.25 g, 20 mmol), and KOH (2.0 g) was allowed to react as described above for **12a**. The reaction mixture was poured into H_2O (50 ml), and the resulting solution was acidified with 10% aqueous HCl to pH 2—3 and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a slightly brownish solid, mp 115—118 °C. Recrystallization of the solid from AcOEt gave **12c** (2.25 g) as pale yellow plates, mp 119—120 °C. Evaporation of the solvent from the resulting mother liquor and column chromatography [silica gel, $CHCl_3$–MeOH (20 : 1, v/v)] of the residue yielded a second crop (0.33 g) of **12c**. The total yield was 2.58 g (84%). Further recrystallizations from AcOEt afforded an analytical sample as colorless needles, mp 119.5—120.5 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1620 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6 Hz, CCH$_2$$\underline{Me}$), 3.80 and 3.85 (3H each, s, two OMe's), 6.32 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.73 (1H, d, J=8.5 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.

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-piperidone (12b)——A stirred mixture of **12c** (615 mg, 2 mmol) and benzyl bromide (410 mg, 2.4 mmol) in acetone (10 ml) containing anhydrous K_2CO_3 (332 mg, 2.4 mmol) was heated under reflux for 24 h. The solvent was removed from the reaction mixture 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 H_2O, 5% aqueous KOH, and H_2O, dried, and concentrated to leave a yellow oil, which was dissolved in a mixture of benzene (5 ml) and pyridine (1 ml). After the resulting solution had been kept at room temperature overnight, the solvents were removed by evaporation under reduced pressure. The residue was dissolved in benzene (60 ml), and the benzene solution was washed successively with H_2O, 5% aqueous HCl, and saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. This material was purified on a 10-g silica gel column (AcOEt) to provide **12b** (767 mg, 96%) as a colorless oil, MS *m/e*: 397 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1624 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7.0 Hz, CCH$_2$$\underline{Me}$), 3.86 and 3.88 (3H each, s, two OMe's), 5.09 (2H, s, OC$\underline{H}_2$Ph), 6.62 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.90 (1H, d, J=8.5 Hz, $H_{(6')}$), 7.2—7.5 (5H, m, Ph).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-3-phenylthio-2-piperidone (13a)——A stirred solution of diisopropylamine (1.53 ml, 10.9 mmol) in dry THF (10 ml) was cooled to −78 °C in an atmosphere of N_2, and 1.7 M solution (6.41 ml, 10.9 mmol) of butyllithium in hexane was added dropwise. After the mixture had been stirred at the same temperature for 20 min, a solution of **12a** (1.27 g, 4.36 mmol) in dry THF (2 ml) was added dropwise in 10 min, stirring was continued for 30 min, and a solution of diphenyl disulfide (952 mg, 4.36 mmol) in dry THF (2 ml) containing hexamethylphosphoramide (0.76 ml, 4.4 mmol) was added dropwise in 5 min. The resulting mixture was further stirred at −78 °C for 2 h, brought to room temperature after addition of saturated aqueous NH_4Cl (6 ml), and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellow oil (2.21 g). Purification of the oil by column chromatography [alumina, hexane–AcOEt (3 : 1, v/v)] afforded **13a** (1.59 g, 91%) as a pale yellow oil (presumed to be a diastereomeric mixture), MS *m/e*: 399 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1633 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.82 and 0.85 (3H, t each, J=7 Hz, diastereomeric

CCH_2Me's), 3.85, 3.88, and 3.90 (6H, s each, diastereomeric OMe's), 6.65—6.85 (3H, m, aromatic protons), 7.1—7.65 (5H, m, Ph).

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-3-phenylthio-2-piperidone (13b)——Sulfenylation of **12b** was effected as described above for **13a**, and the crude oily product was purified on an alumina column [hexane–AcOEt (5 : 1, v/v)] to give **13b** in 94% yield as a faintly yellowish oil (presumed to be a diastereomeric mixture), MS *m/e*: 505 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1633 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.77 and 0.81 (3H, t each, J=7 Hz, diastereomeric CCH_2Me's), 3.86 and 3.89 (6H, s each, two OMe's), 5.09 (2H, s, OCH_2Ph), 6.62 and 6.64 (1H, d each, J=8.5 Hz, diastereomeric $H_{(5')}$'s), 6.88 and 6.93 (1H, d each, J=8.5 Hz, diastereomeric $H_{(6')}$'s), 7.1—7.65 (10H, m, SPh and OCH_2Ph).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-5,6-dihydro-2(1*H*)-pyridinone (15a)——A stirred solution of **13a** (1.36 g, 3.4 mmol) in MeOH (25 ml) was cooled in an ice bath, and a solution of $NaIO_4$ (800 mg, 3.7 mmol) in H_2O (5 ml) was added dropwise in 5 min. After the mixture had been stirred at room temperature for 18 h, the insoluble material that resulted was filtered off and washed with MeOH (10 ml). The filtrate and washings were combined and concentrated *in vacuo*, and the residue was dissolved in benzene (50 ml). The benzene solution was washed with saturated aqueous NaCl, dried, and concentrated to leave the sulfoxide **14a** (1.44 g) as an almost colorless oil. A solution of this oil in toluene (40 ml) containing $CaCO_3$ (1.02 g, 10.2 mmol) was then heated under reflux in an atmosphere of N_2 for 1 h. The reaction mixture was filtered, and the filtrate was washed with saturated aqueous NaCl, dried, and concentrated to leave a light yellow oil. Purification of the oil by column chromatography [silica gel, CH_2Cl_2–AcOEt (6 : 1, v/v)] gave **15a** (896 mg, 91% overall yield from **13a**) as a colorless oil, MS *m/e*: 289 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1662 (C=C),[30] 1606 (lactam CO);[30] ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.2 Hz, CH_2Me), 1.2—1.6 (2H, m, CCH_2Me), 2.05—2.4 (1H, m, $H_{(5)}$), 3.86 and 3.87 (3H each, s, two OMe's), 5.89 (1H, dd, J=9.8 and 2.0 Hz, $H_{(3)}$), 6.44 (1H, dd, J=9.8 and 3.5 Hz, $H_{(4)}$), 6.7—6.9 (3H, m, aromatic protons). The IR and ^{1}H-NMR spectra of this sample were identical with those of authentic **15a** prepared by the method of Battersby and Turner.[14]

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-5,6-dihydro-2(1*H*)-pyridinone (15b)——The sulfide **13b** was dehydrosulfenylated *via* the sulfoxide **14b** in a manner similar to that described above for **15a**, and **15b** was obtained in 88% overall yield (from **13b**) as a pale yellow oil, MS *m/e*: 395 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1661 (C=C),[30] 1605 (lactam CO);[30] ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.2 Hz, CH_2Me), 1.1—1.5 (2H, m, CCH_2Me), 1.95—2.35 (1H, m, $H_{(5)}$), 3.86 and 3.89 (3H each, s, two OMe's), 5.10 (2H, s, OCH_2Ph), 5.84 (1H, dd, J=9.8 and 2.0 Hz, $H_{(3)}$), 6.39 (1H, dd, J=9.8 and 3.3 Hz, $H_{(4)}$), 6.62 (1H, d, J=8.4 Hz, $H_{(5')}$), 6.91 (1H, d, J=8.4 Hz, $H_{(6')}$), 7.2—7.55 (5H, m, Ph).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidinemalonic Acid Diethyl Ester (16a)——The following procedure[12] is a modification of that reported in the literature.[14] A solution of **15a** (810 mg, 2.8 mmol) in abs. EtOH (3 ml) was added dropwise in 30 min in an atmosphere of N_2 to a stirred solution of diethyl malonate (897 mg, 5.6 mmol) in a mixture of Na (97 mg, 4.2 mg.-atom) and abs. EtOH (5 ml). The resulting solution was heated at 70 °C for 2 h and then under reflux for 6 h. After addition of AcOH (0.3 ml), the reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of H_2O and benzene. The benzene extracts were washed successively with 5% aqueous Na_2CO_3 and saturated aqueous NaCl, dried, and concentrated to leave a pale yellow oil (1.46 g). The excess of diethyl malonate was removed from this oil by vacuum distillation [100—110 °C (bath temp.) at 2 mmHg, 1 h], and the pale yellow oil (1.10 g) that remained was purified by column chromatography (silica gel, AcOEt) to yield **16a** (865 mg, 69%) as a colorless oil, MS *m/e*: 449 (M^+); IR ν_{max}^{film} cm^{-1}: 1750 (sh) and 1728 (ester CO), 1641 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7.0 Hz, CH_2Me), 1.27 (6H, t, J=7.1 Hz, two OCH_2Me's), 3.85 and 3.88 (3H each, s, two OMe's), 4.20 (4H, q, J=7.1 Hz, two OCH_2Me's), 6.65—6.9 (3H, m, aromatic protons). On the basis of the results of ^{13}C-NMR spectroscopic analysis,[31] this sample was estimated to be a 13 : 87 mixture of the 4,5-*cis* isomer [^{13}C-NMR ($CDCl_3$) δ: 12.3 (CCH_2Me), 17.7 (CCH_2Me)] and the 4,5-*trans* isomer [δ: 11.1 (CCH_2Me), 24.0 (CCH_2Me)].

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidinemalonic Acid Diethyl Ester (16b)——The Michael addition of diethyl malonate to **15b** was carried out as described above for **16a**, giving **16b** in 71% yield as a colorless oil, MS *m/e*: 555 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (sh) and 1730 (ester CO), 1632 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, t, J=7.2 Hz, CH_2Me), 1.26 and 1.27 (6H, t each, J=7.1 Hz, two OCH_2Me's), 3.86 and 3.89 (3H each, s, two OMe's), 4.19 (4H, q, J=7.1 Hz, two OCH_2Me's), 5.10 (2H, s, OCH_2Ph), 6.63 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.89 (1H, d, J=8.5 Hz, $H_{(6')}$), 7.2—7.5 (5H, m, Ph). The ^{13}C-NMR spectroscopic analysis[31] of this sample suggested that it was a 12 : 88 mixture of the 4,5-*cis* isomer [^{13}C-NMR ($CDCl_3$) δ: 12.3 (CCH_2Me), 17.6 (CCH_2Me)] and the 4,5-*trans* isomer [δ: 11.1 (CCH_2Me), 23.9 (CCH_2Me)].

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidinemalonic Acid (17b)——A crude sample (1.54 g) of **16b** obtained from **15b** (1.19 g, 3 mmol) as described above was dissolved in EtOH (6 ml) containing 2 N aqueous NaOH (3 ml). The resulting solution was stirred at 50 °C for 20 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (30 ml) and benzene, and the aqueous extracts were acidified with 10% aqueous HCl to pH 2 and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave **17b** (1.10 g, 73% from **15b**) as a colorless glass, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726 (CO_2H), 1598 (lactam CO);[30a] ^{1}H-NMR ($CDCl_3$) δ: 3.84 and 3.87 (3H each, s, two OMe's), 5.08 (2H, s, OCH_2Ph), 6.62 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.84 (1H, d, J=8.5 Hz, $H_{(6')}$), 11.0 (2H, br, two CO_2H's). The ^{13}C-NMR spectroscopic analysis[31] of this

sample suggested that it was a 13:87 mixture of the 4,5-*cis* isomer [^{13}C-NMR ($CDCl_3$) δ: 12.2 (CCH_2Me)] and the 4,5-*trans* isomer [δ: 10.4 (CCH_2Me)].

1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (18a)——A solution of **16a** (450 mg, 1 mmol) in Me_2SO (2 ml) containing powdered NaCl (12 mg, 0.2 mmol) and H_2O (36 mg, 2 mmol) was heated in an atmosphere of N_2 at 160—165 °C (bath temp.) for 8 h. After cooling, the reaction mixture was diluted with H_2O (20 ml) and extracted with ether. The ether extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave an orange oil (373 mg). Purification of the oil by column chromatography [silica gel, hexane–AcOEt (1:2, v/v)] produced **18a** (322 mg, 85%) as a pale yellow oil. Although the IR (neat) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were virtually identical with those of authentic **18a**,[12] the ^{13}C-NMR spectrum suggested this oil to be a 9:91 mixture of the 4,5-*cis* isomer [^{13}C-NMR ($CDCl_3$) δ: 11.9 (CCH_2Me), 20.8 ($C\underline{C}H_2$Me)] and the 4,5-*trans* isomer [δ: 11.0 (CCH_2Me), 23.6 ($C\underline{C}H_2$Me)].[31] In a separate experiment, it was confirmed that a pure sample of the 4,5-*trans* isomer[12] of **18a** did not isomerize to the *cis* isomer at all under the above de-ethoxycarbonylation conditions.

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (18b)——The diester **16b** was de-ethoxycarbonylated for 7 h as described above for **18a**. The crude product was purified on a silica gel column [hexane–AcOEt (1:1, v/v)] to furnish **18b** in 88% yield as a pale yellow oil. Although the IR (neat) and ^{1}H-NMR ($CDCl_3$) spectra of this oil were virtually identical with those of authentic **18b**,[20] the ^{13}C-NMR spectrum suggested the oil to be an 11:89 mixture of the 4,5-*cis* isomer [^{13}C-NMR ($CDCl_3$) δ: 11.9 (CCH_2Me), 20.9 ($C\underline{C}H_2$Me)] and the 4,5-*trans* isomer [δ: 10.9 (CCH_2Me), 23.5 ($C\underline{C}H_2$Me)].[31]

(±)-*trans*-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid (19a)——A solution of **18a** (189 mg, 0.5 mmol) in EtOH (3 ml) containing 1 N aqueous NaOH (1.5 ml) was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and the oily residue was partitioned between H_2O (10 ml) and ether. The aqueous extracts were made acid to Congo red with 10% aqueous HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a colorless solid. Recrystallization of the solid from 50% aqueous acetone gave **19a** (147 mg, 84%) as colorless pillars, mp 154—155.5 °C. This sample was identical [by mixture melting point test and by comparison of IR (Nujol), ^{1}H-NMR ($CDCl_3$), and ^{13}C-NMR ($CDCl_3$) spectra] with authentic **19a**.[12]

(±)-*trans*-1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid (19b)——i) From **18b**: Alkaline hydrolysis of **18b** was effected as described above for **19a**, and the crude product was recrystallized from AcOEt to afford **19b** in 85% yield as colorless scales, mp 124—126 °C. This sample was identical [by mixture melting point test and by comparison of IR (Nujol) spectrum] with the one prepared by method (ii) (see below).

ii) From **17b**: A solution of **17b** (800 mg, 1.6 mmol) in 60% aqueous AcOH (20 ml) was heated under reflux for 6 h. The reaction mixture was concentrated *in vacuo* to leave a yellow oil, which was dissolved in $CHCl_3$ (50 ml). The $CHCl_3$ solution was washed with H_2O, dried, and concentrated, leaving a pale yellow solid (724 mg; mp 114—121 °C), which was presumed to be a 19:81 mixture of the *cis* and *trans* isomers on the basis of ^{13}C-NMR spectroscopic analysis.[31c,32] Two recrystallizations of the solid from AcOEt yielded stereochemically pure **19b** (543 mg, 74%), mp 125—127 °C. For analysis, this sample was further recrystallized from AcOEt to give colorless scales, mp 126—128 °C; IR ν_{max}^{Nujol} cm^{-1}: 1710 (CO_2H), 1593 (lactam CO);[30a] ^{1}H-NMR ($CDCl_3$), identical with that of authentic (+)-**19b**.[31c] *Anal.* Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.35; H, 7.40; N, 3.23.

(±)-*trans*-1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (20b)——A solution of **19b** (137 mg, 0.3 mmol) in 10% (w/w) ethanolic HCl (3 ml) was stirred at room temperature for 24 h. The mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of benzene (10 ml) and H_2O (5 ml). The benzene extracts were washed sequentially with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to afford **20b** (141 mg, 97%) as a colorless oil. This sample was identical [by comparison of the IR (neat or in $CHCl_3$) spectrum and TLC mobility] with authentic **20b**.[20]

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-3-(1,1-ethylenedioxyethyl)pyridinium Bromide (26b)——A mixture of **6**[24c] (10.3 g, 62.4 mmol) and **39** (24.0 g, 68.3 mmol) in dry benzene (57 ml) was heated under reflux for 72 h. After cooling, the reaction mixture was extracted with H_2O (85 ml), and the aqueous extracts of **26b** were used in the next oxidation step without further purification.

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-3-(1,1-ethylenedithioethyl)pyridinium Bromide (27b)——A mixture of **25**[24c] (2.67 g, 13.5 mmol) and **39** (5.22 g, 14.9 mmol) in dry benzene (10 ml) was heated under reflux for 72 h. After cooling, the reaction mixture was diluted with benzene (10 ml) and extracted with H_2O (30 ml). Evaporation of the aqueous extracts under reduced pressure and drying of the residue gave crude **27b** (7.01 g, 94%) as an orange oil, which was used in the next oxidation step without further purification.

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-(1,1-ethylenedioxyethyl)-2(1*H*)-pyridinone (28b)——The foregoing aqueous solution of **26b** was subjected to alkaline ferricyanide oxidation according to the previously reported[8,23a] standard procedure, and crude **28b** (23.5 g, 83% yield from **6**) was obtained as a reddish-brown oil, which was shown to be isomer-free by a single spot on TLC analysis. A portion of this oil was purified on a silica gel column [hexane–AcOEt (3:7, v/v)] to afford a pale orange oil, MS *m/e*: 451 (M^+); UV λ_{max}^{EtOH} 283.5 nm (sh) (ε 3350), 309 (5300); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1666 (pyridone); ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, s, CMe), 2.92 (2H, t, J=6.7 Hz, ArCH_2), 3.45—4.0

(4H, m, OCH_2CH_2O), 3.82 and 3.90 (3H each, s, two OMe's), 4.02 (2H, t, J=6.7 Hz, $ArCH_2CH_2$), 5.10 (2H, s, OCH_2Ph), 6.51 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.52 (1H, d, J=9.4 Hz, $H_{(3)}$), 6.64 (1H, d, J=8.5 Hz, $H_{(6')}$), 6.86 (1H, d, J=2.4 Hz, $H_{(6)}$), 7.31 (1H, dd, J=9.4 and 2.4 Hz, $H_{(4)}$), 7.2—7.55 (5H, m, Ph).

1-(2-Benzyloxy-3,4-dimethoxyphenethyl)-5-(1,1-ethylenedithioethyl)-2(1*H*)-pyridinone (29b)——The foregoing crude **27b** was oxidized in the same manner as described above for **28b**, giving the crude product (5.75 g) as a dark red oil. Purification of the oil on a silica gel column [hexane–AcOEt (2:3, v/v) or CH_2Cl_2–AcOEt (5:1, v/v)] furnished **29b** (2.74 g, 42% overall yield from **25**) as an orange oil. The oil was crystallized from hexane–AcOEt (3:2, v/v) to afford yellow prisms (mp 72—74 °C), which turned to an oil on drying over P_2O_5 at 2 mmHg and room temperature for 20 h. When allowed to stand in a vessel saturated with H_2O, the oil again crystallized to form **29b**·1/2H_2O, mp 72—74 °C; MS *m/e*: 483 (M^+); UV λ_{max}^{EtOH} 227.5 nm (sh) (ε 19200), 281.5 (2900), 313.5 (4800); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1662 (pyridone); ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, s, CMe), 2.19 (1H, s, 1/2H_2O), 2.91 (2H, t, J=6.7 Hz, $ArCH_2$), 3.0—3.5 (4H, m, SCH_2CH_2S), 3.84 and 3.90 (3H each, s, two OMe's), 4.01 (2H, t, J=6.7 Hz, $ArCH_2CH_2$), 5.10 (2H, s, OCH_2Ph), 6.52 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.55 (1H, d, J=9.5 Hz, $H_{(3)}$), 6.63 (1H, d, J=8.5 Hz, $H_{(6')}$), 6.98 (1H, d, J=2.4 Hz, $H_{(6)}$), 7.2—7.5 (5H, m, Ph), 7.61 (1H, dd, J=9.5 and 2.4 Hz, $H_{(4)}$). *Anal.* Calcd for $C_{26}H_{29}NO_4S_2$·1/2H_2O: C, 63.39; H, 6.14; N, 2.84. Found: C, 63.42; H, 6.24; N, 2.97.

1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-(1,1-ethylenedioxyethyl)-2-piperidone (30c)——A solution of **28b** (6.49 g, 14.4 mmol) in EtOH (150 ml) was hydrogenated over Raney Ni W-2 catalyst (7 ml) at atmospheric pressure at room temperature for 1 h and then at 35 °C for 12 h. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure afforded a colorless oil, which was dissolved in $CHCl_3$ (200 ml). The $CHCl_3$ solution was dried and concentrated to leave **30c** (5.24 g, 100%) as a colorless solid. Recrystallization from AcOEt yielded an analytical sample as colorless prisms, mp 99—101 °C; MS *m/e*: 365 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1621 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, s, CMe), 3.83 and 3.89 (3H each, s, two OMe's), 6.39 (1H, d, J=8.5 Hz, $H_{(5')}$), 6.79 (1H, d, J=8.5 Hz, $H_{(6')}$). *Anal.* Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.44; H, 7.37; N, 3.96.

Deketalization of 30c——A solution of **30c** (194 mg, 0.53 mmol) in EtOH (1.5 ml) containing 10% aqueous HCl (0.4 ml) was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$ after addition of H_2O (5 ml) and subsequent neutralization with $NaHCO_3$. The $CHCl_3$ extracts were dried and concentrated to leave **11c** (163 mg, 95%) as a yellow powder, mp 120—122 °C. Recrystallization from AcOEt gave a pure sample as colorless needles, mp 124—125 °C. This sample was identical [by mixture melting point test and comparison of the IR (Nujol) spectrum] with authentic **11c** obtained *via* the foregoing alternative route.

Reductive Desulfurization of 29a——A mixture of **29a**[23a] (1.89 g, 5 mmol), 70% (v/v) aqueous EtOH (100 ml), and Raney Ni[33] (20 ml) was heated under reflux for 3 h. The catalyst was removed by filtration and washed with EtOH. The filtrate and washings were combined and concentrated *in vacuo*, and the residue was partitioned between H_2O (20 ml) and benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave **12a** (1.22 g, 84%) as a colorless oil. The IR (neat) spectrum and TLC behavior of this oil were identical with those of authentic **12a**.[8]

Reductive Desulfurization of 29b——A mixture of **29b**·1/2H_2O (300 mg, 0.61 mmol), 70% (v/v) aqueous EtOH (20 ml), and Raney Ni[33] (3 ml) was heated under reflux for 6 h. Removal of the catalyst by filtration and concentration of the filtrate left an oil, which was dissolved in benzene (50 ml). The benzene solution was washed with H_2O, dried, and concentrated to leave a colorless oil, which was hydrogenated in EtOH (15 ml) over Raney Ni W-2 catalyst (0.5 ml) at atmospheric pressure and room temperature for 3.5 h. The usual work-up of the reaction mixture gave **12c** (154 mg, 82%) as a colorless solid, mp 114—118 °C. Recrystallization of the solid from AcOEt yielded colorless needles (mp 119—120 °C), which were identical [by mixture melting point test and comparison of IR (Nujol) and ^{1}H-NMR ($CDCl_3$) spectra and TLC mobility] with authentic **12c** prepared by the foregoing alternative method.

4-[2-(2-Benzyloxy-3,4-dimethoxyphenyl)-1-thioxoethyl]morpholine (35)——A mixture of **34**[28] (60.0 g, 0.21 mol), sulfur (10.1 g, 0.315 mol), and morpholine (27.5 g, 0.316 mol) was heated at 80 °C for 1 h and then under reflux for 4 h. Removal of the excess morpholine from the reaction mixture by vacuum distillation left a reddish-brown oil, which was crystallized from EtOH to afford **35** (50.1 g, 62%) as a yellow powder, mp 103—108 °C. Recrystallization from EtOH gave an analytical sample as yellow plates, mp 110—111 °C; MS *m/e*: 387 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1500 [C(S)N]; ^{1}H-NMR ($CDCl_3$) δ: 3.87 and 3.89 (3H each, s, two OMe's), 4.08 (2H, s, $ArCH_2$), 5.09 (2H, s, OCH_2Ph), 6.66 (1H, d, J=8.7 Hz, $H_{(5')}$), 7.08 (1H, d, J=8.7 Hz, $H_{(6')}$), 7.37 (5H, s, Ph). *Anal.* Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 64.83; H, 6.53; N, 3.65

2-Benzyloxy-3,4-dimethoxyphenylacetic Acid (36)——A mixture of **35** (42.0 g, 0.108 mol) and 50% aqueous KOH (140 ml) in EtOH (420 ml) was heated under reflux for 9 h. The reaction mixture was concentrated *in vacuo* to leave an orange oil, which was partitioned by extraction with a mixture of H_2O (500 ml) and benzene. The aqueous extracts were made acid to Congo red with conc. aqueous HCl and extracted with benzene. The benzene extracts were washed with H_2O, dried, and concentrated to leave **36** (30.5 g, 93%) as a yellow powder. Recrystallization from hexane–AcOEt (3:2, v/v) produced an analytical sample as colorless prisms, mp 113—114 °C; MS *m/e*: 302 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1700 (CO_2H); ^{1}H-NMR ($CDCl_3$) δ: 3.52 (2H, s, $ArCH_2$), 3.87 (6H, s, two OMe's), 5.09 (2H, s, OCH_2Ph), 6.65 (1H, d, J=8.5 Hz, $H_{(5)}$), 6.89 (1H, d, J=8.5 Hz, $H_{(6)}$), 7.25—7.55 (5H, m, Ph), 8.9 (1H, br, CO_2H). *Anal.* Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.26; H, 5.98.

2-Benzyloxy-3,4-dimethoxyphenylacetic Acid Ethyl Ester (37)——A mixture of **36** (45.0 g, 0.149 mol) and 10% (w/w) ethanolic HCl (90 ml) in abs. EtOH (90 ml) was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* to leave a yellow oil, which was dissolved in benzene (500 ml). The benzene solution was washed successively with H_2O, 4% aqueous NaOH, and H_2O, dried, and concentrated to afford **37** (47.8 g, 97%) as a pale yellow oil, bp 185—187 °C (3 mmHg); MS *m/e*: 330 (M^+); IR ν_{max}^{film} cm^{-1}: 1735 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 3.53 (2H, s, $ArC\underline{H}_2$), 3.86 and 3.87 (3H each, s, two OMe's), 4.08 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 5.08 (2H, s, $OC\underline{H}_2Ph$), 6.65 (1H, d, J=8.5 Hz, $H_{(5)}$), 6.91 (1H, d, J=8.5 Hz, $H_{(6)}$), 7.2—7.55 (5H, m, Ph).

2-Benzyloxy-3,4-dimethoxyphenethyl Alcohol (38)——A solution of **37** (45.0 g, 0.136 mol) in dry ether (200 ml) was added dropwise in 1 h to a stirred, chilled (0—5 °C) suspension of $LiAlH_4$ (5.17 g, 0.136 mol) in dry ether (200 ml). After the mixture had been stirred at room temperature for 4 h, H_2O (5.2 ml), 15% aqueous NaOH (5.2 ml), and H_2O (15 ml) were successively added dropwise under ice-cooling and stirring. The insoluble material that resulted was filtered off, and the filtrate was dried and concentrated to leave **38** (38.2 g, 97%) as a faintly yellow oil, bp 180—190 °C (0.08 mmHg); MS *m/e*: 288 (M^+); IR ν_{max}^{film} cm^{-1}: 3420 (OH); ^{1}H-NMR ($CDCl_3$) δ: 1.82 (1H, s, OH), 2.77 (2H, t, J=6.4 Hz, $ArC\underline{H}_2$), 3.73 (2H, t, J=6.4 Hz, $C\underline{H}_2OH$), 3.86 and 3.88 (3H each, s, two OMe's), 5.08 (2H, s, $OC\underline{H}_2Ph$), 6.64 (1H, d, J=8.5 Hz, $H_{(5)}$), 6.87 (1H, d, J=8.5 Hz, $H_{(6)}$), 7.2—7.55 (5H, m, Ph).

2-Benzyloxy-3,4-dimethoxyphenethyl Bromide (39)——Triphenylphosphine (27.3 g, 0.104 mol) was added portionwise to a stirred, ice-cooled solution of **38** (30.0 g, 0.104 mol) in benzene (160 ml). *N*-Bromosuccinimide (18.5 g, 0.104 mol) was then added portionwise at such a rate that the inner temperature did not exceed 10 °C. After having been stirred at room temperature for 2 h, the reaction mixture was filtered. The filtrate was washed successively with 5% aqueous $Na_2S_2O_3$, 0.5 N aqueous NaOH, and saturated aqueous NaCl, dried, and concentrated. The residue was triturated with hexane–AcOEt (5 : 1, v/v) (20 ml) and the mixture was filtered in order to remove the insoluble material. The filtrate was then passed through a column packed with silica gel (60 g). Concentration of the eluate under reduced pressure left **39** (32.3 g, 88%) as an orange solid. For analysis, the solid was recrystallized from hexane to give colorless prisms, mp 45.5—47 °C; MS *m/e*: 352, 350 (M^+); ^{1}H-NMR ($CDCl_3$) δ: 3.02 (2H, t, J=7.2 Hz, $ArC\underline{H}_2$), 3.43 (2H, t, J=7.2 Hz, CH_2Br), 3.86 and 3.88 (3H each, s, two OMe's), 5.10 (2H, s, $OC\underline{H}_2Ph$), 6.62 (1H, d, J=8.5 Hz, $H_{(5)}$), 6.85 (1H, d, J=8.5 Hz, $H_{(6)}$), 7.2—7.55 (5H, m, Ph). *Anal.* Calcd for $C_{17}H_{19}BrO_3$: C, 58.13; H, 5.45. Found: C, 58.36; H, 5.48.

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