Synthetic Studies on the Starfish Alkaloid Imbricatine. Construction of an *ent*-Imbricatine Framework

Masashi OHBA,* Masaaki IMASHO, and Tozo FUJII

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920–0934, Japan.
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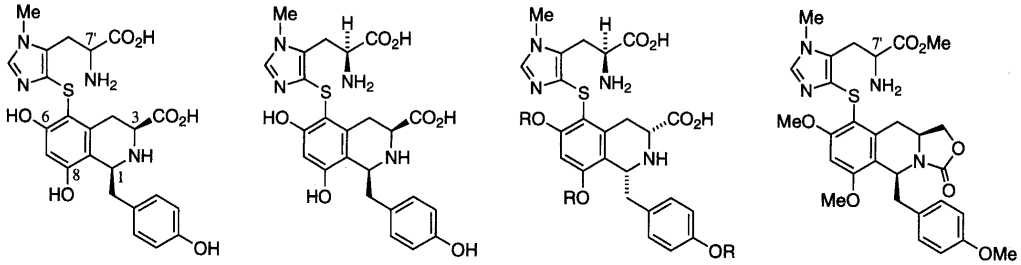
A chiral synthetic route to the amino esters 5 and 6, which contain the fundamental framework of *ent*-imbricatine (*ent*-3), has been developed as a prelude to the total synthesis of the starfish alkaloid imbricatine (3). The route started from the sulfur-containing L-phenylalanine derivative 7 and proceeded through key steps such as cyclization of the amide 8 without racemization, reduction to the 1,3-*cis*-tetrahydroisoquinoline 9, and introduction of a chiral α-amino acid moiety into the chloride 18 by the "bis-lactim ether" method.

Key words imbricatine; benzyltetrahydroisoquinoline alkaloid; arylthiohistidine synthesis; Bischler–Napieralski cyclization; X-ray analysis; bis-lactim ether

In 1986, Pathirana and Andersen reported the isolation of an unusual benzyltetrahydroisoquinoline alkaloid, named imbricatine, from the starfish *Dermasterias imbricata* and proposed the gross structure **1** on the basis of spectroscopic analysis and chemical degradation.[1] Imbricatine is unique in that it is extremely effective at causing the detachment and swimming response in the sea anemone *Stomphia coccinea* at very low concentrations.[1,2] This compound is the first example of a benzyltetrahydroisoquinoline alkaloid obtained from a nonplant source and possesses some structural features, such as the carboxy group at the 3-position, the 6,8-dihydroxylation pattern, and the thioether linkage to the 3-methylhistidine moiety, not previously encountered in this family of alkaloids, and it displays significant activity in antineoplastic assays.[1,3] In view of these striking characteristics, we planned the chiral synthesis of the target structure **2** envisioned as a probable candidate for imbricatine on the assumption that both α-amino acid portions of **1** would be biogenetically derived from the usual L-amino acids. After the present study was undertaken, however, Andersen and coworkers deduced the absolute configurations of the three stereogenic centers of imbricatine to be those in **3** (1*R*,3*R*,7′*S*).[3] In this full account, we describe the synthesis of the amino ester **5** containing the entire framework of *ent*-imbricatine (*ent*-**3**), together with the 7′-epimer **6**, as a prelude to the total synthesis of imbricatine (**3**). On the basis of these syntheses, we have recently accomplished the chiral synthesis of tri-*O*-methylimbricatine (**4**), the tri-*O*-methyl derivative of **3**, and unequivocally confirmed the structure and absolute stereochemistry proposed for imbricatine.[4]

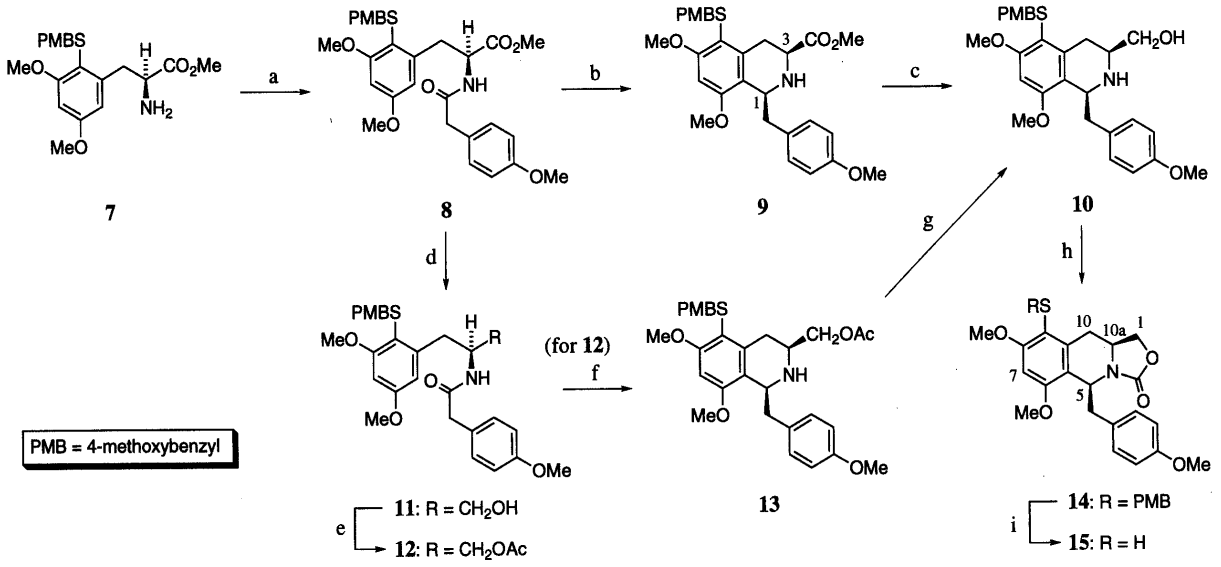
In connection with our ongoing synthetic studies of imbricatine,[5] we have already reported the synthesis of the L-phenylalanine derivative **7** (95% ee) containing at the 2-position a thiol group protected with the 4-methoxybenzyl group.[6] The initial step of the present work was coupling of **7** with 4-methoxyphenylacetyl chloride, which proceeded smoothly under Schotten–Baumann conditions to provide the amide **8** in 98% yield. The optically pure **8**, obtained by recrystallization of the crude amide, was then subjected to Bischler–Napieralski cyclization using $POCl_3$ in toluene at 80 °C for 7 h followed by $NaBH_4$ reduction in MeOH at −78 °C.[7] However, the 1,3-*cis* isomer **9** that resulted as a sole product in 83% overall yield was shown[8] to be of 85% enantiomeric purity. Kametani *et al.* reported that treatment of *N*-acetyl-L-3,4-dimethoxyphenylalanine methyl ester with $POCl_3$ in CH_3CN at room temperature for 2 h produced the corresponding 3,4-dihydroisoquinoline without accompanying racemization.[9] Although cyclization of **8** was very sluggish under the same conditions, it proceeded moderately by heating at 60 °C,[10] giving **9** of 96% ee[8] in 78% overall yield after $NaBH_4$ reduction. Optically pure **9** was readily obtained by recrystallization from MeOH. The ester group of **9** was then reduced with $LiAlH_4$ to afford **10** in 84% yield, since partial or complete epimerization at the 3-position was assumed to be a potential problem at later stages.

Alternatively, conversion of **8** into **10** was achieved without partial racemization by exploiting a route *via* cyclization of an equivalent amide bearing a protected hydroxymethyl group instead of the methoxycarbonyl group, such as **12**. Thus, the amide ester **8** was first reduced with $LiBH_4$ in 99% yield, and the resulting amide alcohol **11** was then protected with an acetyl group by treatment with acetic anhydride and



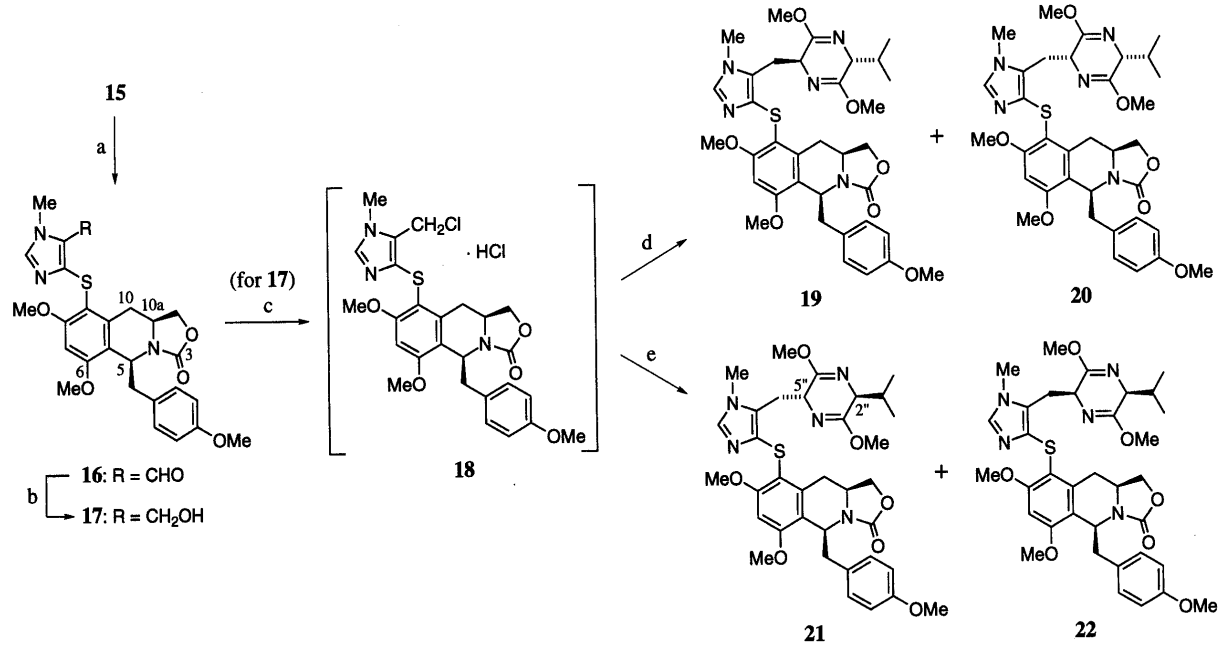
1 **2** **3**: R = H, **4**: R = Me **5**: 7′*R*, **6**: 7′*S*

* To whom correspondence should be addressed.



Reagents and Conditions: (a) 4-methoxyphenylacetyl chloride, Na_2CO_3, H_2O–benzene, 8–10 °C, 30 min; (b) 1) $POCl_3$, toluene, 80 °C, 7 h or $POCl_3$, CH_3CN, 60 °C, 10 h; 2) $NaBH_4$, MeOH, –78 °C, 1 h; (c) $LiAlH_4$, THF, rt, 1.5 h; (d) $LiBH_4$, THF, rt, 1.5 h; (e) Ac_2O, pyridine, rt, 1.5 h; (f) 1) $POCl_3$, toluene, reflux, 1.5 h; 2) $NaBH_4$, MeOH, –78 °C, 1 h; (g) K_2CO_3, aqueous MeOH, rt, 1 h; (h) $(EtO)_2CO$, NaOEt, EtOH, reflux, 6 h; (i) $(CF_3CO_2)_2Hg$, anisole, EtOH, rt, 14.5 h, then $NaBH_4$, 0 °C, 15 min

Chart 1



Reagents and Conditions: (a) **23**, NaH, DMF, 100 °C, 3 h; (b) $NaBH_4$, MeOH, rt, 1 h; (c) $SOCl_2$, rt, 1 h; (d) (*R*)-**24**, THF, –78 °C, 2 h, –50 °C, 20 h; (e) (*S*)-**24**, THF, –78 °C, 2 h, –50 °C, 20 h

Chart 2

pyridine to furnish **12** in 93% yield. Bischler–Napieralski cyclization of **12** with $POCl_3$ in boiling toluene for 1.5 h, followed by $NaBH_4$ reduction, provided **13** in 88% overall yield. Finally, deacetylation of **13** with K_2CO_3 in aqueous MeOH gave the optically pure **10** in 86% yield. After the OH and NH groups of **10** were protected in the form of the oxazolidinone **14** (91% yield) by treatment with diethyl carbonate and NaOEt in EtOH, conversion into the thiol **15** was examined. Among several methods reported in the literature[11] for deprotection of the *S*-(4-methoxybenzyl) group, Fujino's procedure[12] with minor modification was found to be most effective. Thus, treatment of **14** with $(CF_3CO_2)_2Hg$ in EtOH containing anisole and subsequent $NaBH_4$ reduction of the resulting mercaptide provided **15** in 90% yield.

Having developed a chiral synthesis of the benzyltetrahydroisoquinoline moiety possessing the thiol group required for construction of *ent*-imbricatine, we set out to explore the application to **15** of our previously established synthetic

Table 1. ^{1}H-NMR Spectral Data for the Oxazolidinones **14**—**17**[a] in $CDCl_3$

Protons[b]	Chemical shift (ppm)			
	14	**15**	**16**	**17**
C(1)-H's	3.50 (1H, dd) [J=11, 8 Hz]	3.62 (1H, dd) [J=11, 7.5 Hz]	3.63 (1H, dd) [J=11, 7.5 Hz]	3.68 (1H, dd) [J=10.5, 7 Hz]
	4.10 (1H, dd) [J=8 Hz each]	4.33 (1H, dd) [J=7.5 Hz each]	4.33 (1H, dd) [J=7.5 Hz each]	4.38 (1H, dd) [J=7 Hz each]
C(5)-H	5.28 (1H, dd) [J=5, 2 Hz]	5.34 (1H, dd) [J=5, 2 Hz]	5.33 (1H, dd) [J=5, 2 Hz]	5.30 (1H, dd) [J=5, 2.5 Hz]
C(10)-H_α	2.87 (1H, dd) [J=14.5, 3 Hz]	2.72 (1H, dd) [J=14.5, 3 Hz]	3.42 (1H, dd) [J=15, 3 Hz]	3.87 (1H, dd) [J=15, 2.5 Hz]
C(10)-H_β	0.63 (1H, dd) [J=14.5, 11.5 Hz]	0.78 (1H, dd) [J=14.5, 11 Hz]	0.87 (1H, dd) [J=15, 11.5 Hz]	0.95 (1H, dd) [J=15, 11 Hz]
C(10a)-H	3.12 (1H, dddd) [J=11.5, 11, 8, 3 Hz]	3.71 (1H, dddd) [J=11, 11, 7.5, 3 Hz]	3.74 (1H, dddd) [J=11.5, 11, 7.5, 3 Hz]	3.74 (1H, dddd) [J=11, 10.5, 7, 2.5 Hz]
C(5)-CH_2	2.78 (1H, dd) [J=13.5, 2 Hz]	2.78 (1H, dd) [J=13.5, 2 Hz]	2.80 (1H, dd) [J=13.5, 2 Hz]	2.77 (1H, dd) [J=13.5, 2.5 Hz]
	3.54 (1H, dd) [J=13.5, 5 Hz]	3.64 (1H, dd) [J=13.5, 5 Hz]	3.65 (1H, dd) [J=13.5, 5 Hz]	3.63 (1H, dd) [J=13.5, 5 Hz]
OMe[c]	3.68 (3H, s)	3.74 (3H, s)	3.74 (3H, s)	3.66 (3H, s)
	3.74 (3H, s)	3.90 (3H, s)	3.88 (3H, s)	3.75 (3H, s)
	3.90 (3H, s)	3.96 (3H, s)	3.90 (3H, s)	3.88 (3H, s)
	3.97 (3H, s)		3.92 (3H, s)	3.97 (3H, s)
C(7)-H	6.46 (1H, s)	6.49 (1H, s)	6.49 (1H, s)	6.46 (1H, s)
C(3′)-H and C(5′)-H	6.46 (2H, d) [J=8.5 Hz]	6.46 (2H, d) [J=8.5 Hz]	6.47 (2H, d) [J=9 Hz]	6.42 (2H, d) [J=8.5 Hz]
C(2′)-H and C(6′)-H	6.60 (2H, d) [J=8.5 Hz]	6.65 (2H, d) [J=8.5 Hz]	6.54 (2H, d) [J=9 Hz]	6.49 (2H, d) [J= 8.5 Hz]
Others	3.60 (1H, d) [J=12.5 Hz]	3.74 (1H, s)	7.39 (1H, s)	2.13 (1H, t) [J=6 Hz]
	3.71 (1H, d) [J=12.5 Hz]		9.98 (1H, s)	4.74 (1H, dd) [J=13, 6 Hz]
	6.69 (2H, d) [J=8.5 Hz]			4.78 (1H, dd) [J=13, 6 Hz]
	6.87 (2H, d) [J=8.5 Hz]			7.25 (1H, s)

a) See formula **14** in Chart 1 for the numbering system. *b*) For convenience, each aromatic carbon in the 4-methoxybenzyl group substituted at the 5-position is indicated by a primed number. *c*) Data for **16** and **17** include *N*-Me signals.

route to 5-arylthio-3-methyl-L-histidines.[5] Coupling of **15** with the bromo aldehyde **23**[5] was carried out in DMF in the presence of NaH at 100 °C for 3 h, affording the thioether **16** (82% yield), which was then converted into the alcohol **17** (mp 250.5—251.5 °C) in 82% yield by $NaBH_4$ reduction.

During these studies, it was noted that one of the C(10)-protons of the oxazolidinone **14** was found to resonate at extraordinarily high field (δ 0.63), as shown in Table 1, compared to the corresponding proton (δ 1.82) of the amino alcohol **10**. Similarly, large upfield shifts were observed for the C(10)-H_β signals of the other oxazolidinones **15**—**17**. In order to ascertain the reason for such upfield shifts of the proton signals in question, as well as to confirm the stereochemistry of the oxazolidinones, the alcohol **17** was subjected to a single crystal X-ray analysis. The derived molecular structure (Fig. 1) established the 5,10a-*cis* stereochemistry for the tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one moiety of **17**. Furthermore, it can be seen from Fig. 1 that the plane of the 4-methoxyphenyl ring system lies over the C(10)-H_β, probably owing to steric repulsion by the carbonyl group at the 3-position and the methoxy group at the 6-position, causing its proton signal to appear at higher field.

With the stereochemistry of **17** confirmed, we next turned our attention to the completion of the histidine moiety by means of the "bis-lactim ether" method of Schöllkopf.[13]

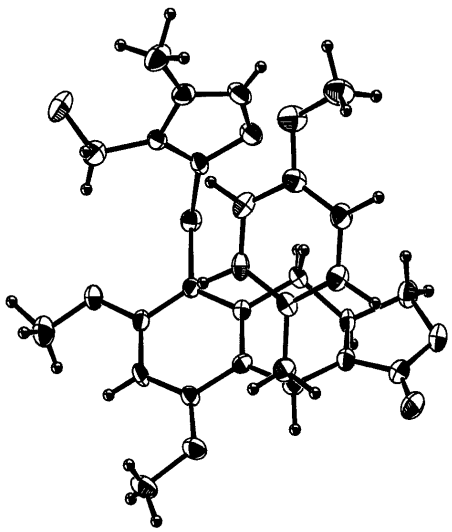


Fig. 1. ORTEP Representation of the Crystal Structure of **17**

Chlorination of **17** with $SOCl_2$ at room temperature for 1 h and subsequent coupling of the resulting chloride **18** with the organolithium reagent (*R*)-**24**, generated *in situ* by regioselective metalation of (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with LDA in THF–hexane at −78 °C,

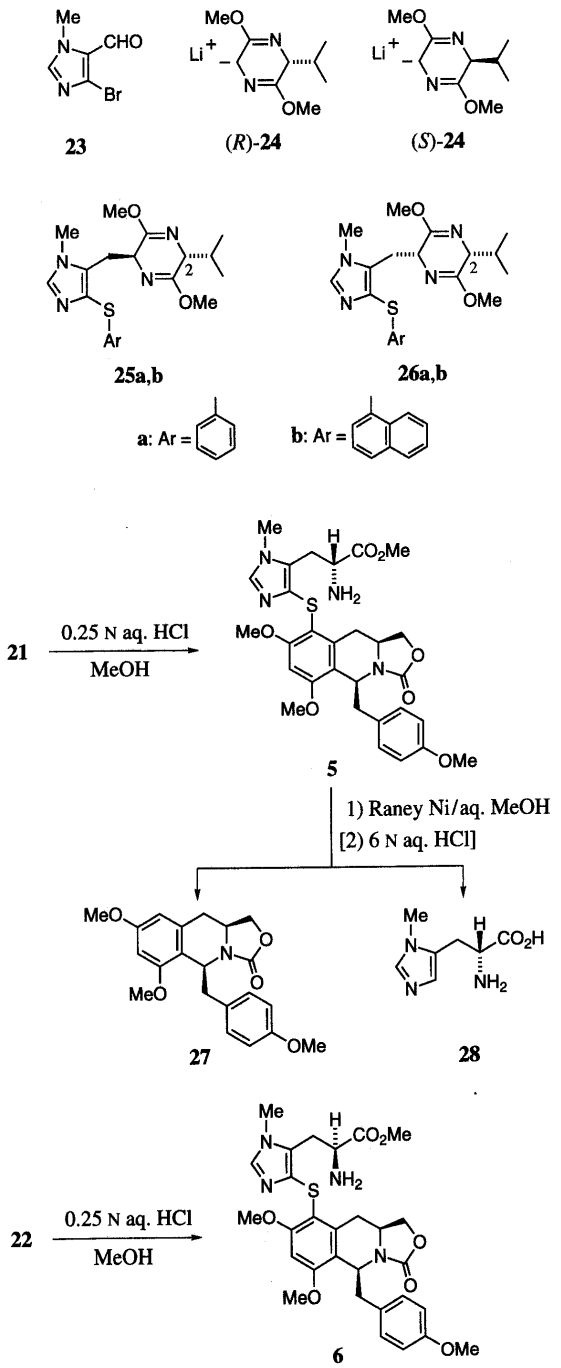


Chart 3

afforded an inseparable 1.4 : 1 diastereoisomeric mixture[14] of **19** and **20**[15] in 56% yield from **17**. Similarly, treatment of **18** with the enantiomeric organolithium reagent (*S*)-**24** also gave a mixture of two diastereoisomers, but the mixture could be separated by flash chromatography[16] to provide **21** and **22** in 55% and 31% yields, respectively, from **17**. The stereochemistries of the newly formed stereogenic centers in **21** and **22** were determined on the basis of comparison of the chemical shifts of their C(2″)-protons. In $CDCl_3$, the C(2″)-proton (δ 3.78) of **21** resonated at higher field than the corresponding proton (δ 3.93) of **22**. This permitted us to assign **21** and **22** to the *trans* and *cis* structures, respectively, since the C(2)-proton signals of the *trans* isomers **25a, b** are known to appear at 0.12—0.13 ppm upfield of those of the *cis* isomers **26a, b**, because of the shielding effect induced by the imidazole ring.[5b] The observed low diastereoselectivity in the formation of **19** and **20** (1.4 : 1) as well as **21** and **22** (1.8 : 1), compared with the cases of **25a, b** and **26a, b** (**25a** : **26a** = 14 : 1; **25b** : **26b** = 17 : 1) in a similar alkylation of (*R*)-**24** generated from the (2*R*)-dihydropyrazine and BuLi,[5] was an entirely unexpected result, although different bases were used for preparation of the organolithium reagents (*R*)-**24** and (*S*)-**24**.

Finally, the *trans* and *cis* bis-lactim ethers **21** and **22** were separately hydrolyzed with 0.25 N aqueous HCl in MeOH to furnish the desired amino esters **5** and **6** in 71% and 75% yields, respectively. In order to confirm the structure and absolute configuration of **5**, desulfurization was effected with Raney Ni in boiling H_2O–MeOH (1 : 4, v/v), giving the oxazolidinone **27** in 83% yield, together with the amino acid **28** obtained in 46% yield after hydrolysis with 6 N aqueous HCl. The latter amino acid was identified as 3-methyl-D-histidine by comparison of its ^{1}H-NMR spectrum and optical rotation with those of commercially available 3-methyl-L-histidine.

In conclusion, the present work has developed a synthetic route to the amino esters **5** and **6** containing the fundamental framework of *ent*-imbricatine (*ent*-**3**). Furthermore, this effort led to our successful chiral synthesis of tri-*O*-methylimbricatine (**4**), which confirmed the structure and absolute configuration assigned to the starfish alkaloid imbricatine (**3**).[4]

Experimental

General Notes All melting points were determined on a Büchi model 530 capillary melting point apparatus and are corrected. TLC and preparative TLC were run on Merck 0.25-mm and 0.50-mm precoated silica gel 60 F_{254} plates, respectively. Flash chromatography[16] was carried out by using Merck silica gel 60 (No. 9385). Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on either a Hitachi M-80 or a JEOL JMS-SX102A mass spectrometer, either a JASCO A-202 or a Shimadzu FTIR-8100 IR spectrophotometer, and either a JEOL JNM-GSX-500 (^{1}H 500 MHz) or a JEOL JNM-EX-270 (^{1}H 270 MHz) NMR spectrometer. Chemical shifts are reported in ppm downfield from internal Me_4Si. Optical rotations were measured with either a JASCO DIP-181 or a Horiba SEPA-300 polarimeter using a 1-dm sample tube. Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: d=doublet, dd=doublet-of-doublets, ddd=doublet-of-dd's, dddd=doublet-of-ddd's, m=multiplet, s=singlet, t=triplet.

***N*-[(4-Methoxyphenyl)acetyl]-3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]-L-phenylalanine Methyl Ester (8)** A mixture of a solution of 3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]-L-phenylalanine methyl ester (**7**)[6] (666 mg, 1.7 mmol) in benzene (12 ml) and a solution of Na_2CO_3 (180 mg, 1.7 mmol) in H_2O (12 ml) was stirred under ice-cooling, and a solution of 4-methoxyphenylacetyl chloride (314 mg, 1.7 mmol) in benzene (3 ml) was added dropwise over 5 min. After the mixture had been stirred at 8—10 °C for 30 min, the benzene layer was separated from the aqueous layer, which was extracted with benzene. The combined benzene solutions were washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave **8** (902 mg, 98%) as a colorless solid. Recrystallization of the solid from AcOEt–hexane (1 : 1, v/v) gave an analytical sample as colorless minute needles, mp 120—121 °C; $[\alpha]_D^{20}$ +19.8° (*c*=0.50, $CHCl_3$); MS *m/z*: 539 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 1740 (ester CO), 1667 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 2.92 (1H, dd, *J*=13.5, 9 Hz) and 3.05 (1H, dd, *J*=13.5, 5.5 Hz) (ArC$\underline{H}_2$CH), 3.40 (2H, s, ArC$\underline{H}_2$CO), 3.67, 3.72, 3.75, 3.79, and 3.88 (3H each, s, five MeO's), 3.77 and 3.78 (1H each, d, *J*=12.5 Hz, ArC$\underline{H}_2$S), 4.68 (1H, ddd, *J*=9, 8, 5.5 Hz, ArCH$_2$C$\underline{H}$), 5.74 (1H, d, *J*=8 Hz, NH), 6.19 and 6.36 [1H each, d, *J*=2.5 Hz, C(4)-H and C(6)-H], 6.71 (2H, d, *J*=8.5 Hz), 6.81 (2H, d, *J*=9 Hz), 6.96 (2H, d, *J*=9 Hz), and 7.04 (2H, d, *J*=8.5 Hz) (two 4-MeOC$_6\underline{H}_4$'s). *Anal.* Calcd for $C_{29}H_{33}NO_7S$: C, 64.55; H, 6.16; N, 2.60. Found: C, 64.44; H, 6.11; N, 2.55.

(1*S*,3*S*)-6,8-Dimethoxy-1-[(4-methoxyphenyl)methyl]-5-[[(4-methoxyphenyl)methyl]thio]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (9) i) *Via* Bischler–Napieralski Cyclization Using Toluene as a Solvent: A stirred mixture of **8** (216 mg, 0.40 mmol), $POCl_3$ (307 mg, 2.0 mmol), and toluene (4 ml) was heated at 80 °C for 7 h. After cooling, the solvent and excess $POCl_3$ were distilled off *in vacuo*, and the residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a pale brown glass. The glass was dissolved in MeOH (12 ml), and the solution was cooled to −78 °C. $NaBH_4$ (30 mg, 0.8 mmol) was then added in small portions, and the mixture was stirred at −78 °C for 1 h. After addition of acetone (0.3 ml), the reaction mixture was brought to room temperature and concentrated *in vacuo*. The residual colorless solid was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a reddish oil. Purification of the oil by flash chromatography [hexane–AcOEt (3 : 2, v/v)] furnished **9** (173 mg, 83%) as a colorless solid. The enantiomeric purity of this solid was determined to be 85% ee.[8] Recrystallization from MeOH afforded an analytical sample as colorless needles, mp 135—136 °C; $[\alpha]_D^{20}$ −225° (*c*=0.25, $CHCl_3$); MS *m/z*: 522 (M^+-1); IR ν_{max}^{Nujol} cm^{-1}: 3375 (NH), 1725 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 2.07 [1H, dd, *J*=16, 11 Hz, C(4)-H_β], 2.71 (1H, dd, *J*=13.5, 7.5 Hz) and 3.21 (1H, dd, *J*=13.5, 3.5 Hz) [C(1)-CH_2], 3.10 [1H, dd, *J*=11, 3 Hz, C(3)-H], 3.20 [1H, dd, *J*=16, 3 Hz, C(4)-H_α], 3.70, 3.74, 3.76, 3.91, and 3.92 (3H each, s, five MeO's), 3.73 and 3.79 (1H each, d, *J*=12.5 Hz, ArCH_2S), 4.45 [1H, dd, *J*=7.5, 3.5 Hz, C(1)-H], 6.42 [1H, s, C(7)-H], 6.70, 6.78, 6.92, and 7.01 (2H each, d, *J*=9 Hz, two 4-MeOC_6H_4's). *Anal.* Calcd for $C_{29}H_{33}NO_6S$: C, 66.52; H, 6.35; N, 2.67. Found: C, 66.37; H, 6.35; N, 2.80. The enantiomeric purity of this analytical sample was >98% ee.[8]

ii) *Via* Bischler–Napieralski Cyclization Using CH_3CN as a Solvent: A stirred mixture of **8** (54 mg, 0.10 mmol), $POCl_3$ (30 mg, 0.20 mmol), and CH_3CN (0.5 ml) was heated at 60 °C for 10 h. Work-up of the reaction mixture and subsequent reduction with $NaBH_4$ (7.6 mg, 0.2 mmol) were carried out in a manner similar to method-(i), giving **9** (41 mg, 78%) as a colorless solid after purification by preparative TLC [AcOEt–hexane (1 : 1, v/v)]. The enantiomeric purity of this solid was found to be 96% ee.[8]

(*S*)-*N*-[2-[3,5-Dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]phenyl]-1-(hydroxymethyl)ethyl]-4-methoxybenzeneacetamide (11) A stirred solution of **8** (108 mg, 0.20 mmol) in THF (4 ml) was cooled to 0 °C, and $LiBH_4$ (26 mg, 1.2 mmol) was added in portions. After stirring at room temperature for 1.5 h, the reaction mixture was cooled in an ice bath, acidified with 10% aqueous HCl, and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual solid by flash chromatography (AcOEt) yielded **11** (101 mg, 99%) as a colorless solid. Recrystallization from MeOH furnished an analytical sample as colorless needles, mp 134.5—135 °C; $[\alpha]_D^{16}$ −4.2° (*c*=0.54, $CHCl_3$); MS *m/z*: 511 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3390, 3320 (NH and OH), 1636 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 2.68 and 2.81 (1H each, dd, *J*=13.5, 7.5 Hz, ArCH_2CH), 3.17 (1H, t, *J*=6.5 Hz, OH), 3.39—3.50 (2H, m, CH_2OH), 3.42 (2H, s, ArCH_2CO), 3.749, 3.751, 3.80, and 3.87 (3H each, s, four MeO's), 3.77 and 3.83 (1H each, d, *J*=12.5 Hz, ArCH_2S), 3.87 (1H, m, ArCH$_2$CH), 5.71 (1H, d, *J*=7.5 Hz, NH), 6.31 and 6.36 [1H each, d, *J*=2.5 Hz, C(4)-H and C(6)-H], 6.71, 6.83, 6.96, and 7.05 (2H each, d, *J*=8.5 Hz, two 4-MeOC_6H_4's). *Anal.* Calcd for $C_{28}H_{33}NO_6S$: C, 65.73; H, 6.50; N, 2.74. Found: C, 65.74; H, 6.62; N, 2.77.

(*S*)-*N*-[2-(Acetyloxy)-1-[[3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]phenyl]methyl]ethyl]-4-methoxybenzeneacetamide (12) A mixture of **11** (537 mg, 1.05 mmol) and Ac_2O (0.4 ml, 4.2 mmol) in pyridine (3 ml) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to leave a slightly yellowish solid. Recrystallization from AcOEt–hexane (1 : 1, v/v) gave a first crop (450 mg) of **12**. Concentration of the mother liquor and recrystallization of the residue afforded a second crop (90 mg) of **12**. Total yield of **12** was 540 mg (93%). Further recrystallization from the same solvent system produced an analytical sample as colorless fluffy needles, mp 116—117.5 °C; $[\alpha]_D^{27}$ −10.2° (*c*=0.52, $CHCl_3$); MS *m/z*: 553 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3275 (NH), 1732 (ester CO), 1653 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s, CH_3CO), 2.71 (1H, dd, *J*=14, 6.5 Hz) and 2.76 (1H, dd, *J*=14, 9 Hz) (ArCH_2CH), 3.36 (2H, s, ArCH_2CO), 3.73, 3.75, 3.80, and 3.89 (3H each, s, four MeO's), 3.78 and 3.83 (1H each, d, *J*=12.5 Hz, ArCH_2S), 3.92 (1H, dd, *J*=11, 4.5 Hz) and 3.94 (1H, dd, *J*=11, 5.5 Hz) (CH_2OAc), 4.31 (1H, m, ArCH$_2$CH), 5.37 (1H, d, *J*=8.5 Hz, NH), 6.25 and 6.36 [1H each, d, *J*=2.5 Hz, C(4)-H and C(6)-H], 6.71, 6.82, 6.97, and 7.02 (2H each, d, *J*=8.5 Hz, two 4-MeOC_6H_4's). *Anal.* Calcd for $C_{30}H_{35}NO_7S$: C, 65.08; H, 6.37; N, 2.53. Found: C, 64.91; H, 6.46; N, 2.34.

(1*S*,3*S*)-3-Acetyloxymethyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-5-[[(4-methoxyphenyl)methyl]thio]-1,2,3,4-tetrahydroisoquinoline (13) A stirred mixture of **12** (332 mg, 0.60 mmol) and $POCl_3$ (460 mg, 3.0 mmol) in toluene (8 ml) was heated under reflux for 1.5 h. Work-up of the reaction mixture followed by reduction with $NaBH_4$ (45 mg, 1.2 mmol) in MeOH (18 ml) at −78 °C for 1 h was effected as described above for **9**, furnishing a crude yellow oil. Purification of the oil by flash chromatography [AcOEt–hexane (1 : 1, v/v)] gave **13** (283 mg, 88%) as a slightly yellowish oil, $[\alpha]_D^{27}$ −205° (*c*=0.43, $CHCl_3$); MS *m/z*: 536 (M^+-1); IR $\nu_{max}^{CHCl_3}$ 1732 cm^{-1} (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 1.75 [1H, dd, *J*=16, 11 Hz, C(4)-H_β], 2.02 (3H, s, CH_3CO), 2.52 [1H, m, C(3)-H], 2.74 (1H, dd, *J*=13.5, 7 Hz) and 3.13 (1H, dd, *J*=13.5, 3.5 Hz) [C(1)-CH_2], 2.79 [1H, dd, *J*=16, 2.5 Hz, C(4)-H_α], 3.71 and 3.77 (1H each, d, *J*=12.5 Hz, ArCH_2S), 3.73, 3.75, 3.91, and 3.93 (3H each, s, four MeO's), 3.84 (1H, dd, *J*=11, 6 Hz) and 3.98 (1H, dd, *J*=11, 4 Hz) (CH_2OAc), 4.44 [1H, dd, *J*=7, 3.5 Hz, C(1)-H], 6.42 [1H, s, C(7)-H], 6.69, 6.75, 6.90, and 6.95 (2H each, d, *J*=8.5 Hz, two 4-MeOC_6H_4's); high-resolution MS calcd for $C_{30}H_{35}NO_6S$: 537.2185, found: 537.2182.

(1*S*,3*S*)-6,8-Dimethoxy-3-hydroxymethyl-1-[(4-methoxyphenyl)methyl]-5-[[(4-methoxyphenyl)methyl]thio]-1,2,3,4-tetrahydroisoquinoline (10) i) From **9**: A stirred suspension of $LiAlH_4$ (42 mg, 1.1 mmol) in THF (8 ml) was cooled to 0 °C, and a solution of **9** (388 mg, 0.74 mmol) in THF (6 ml) was added dropwise over 10 min. After the mixture had been stirred at room temperature for 1.5 h, THF–H_2O (4 : 1, v/v) (2 ml) was added under ice-cooling. Stirring was continued at room temperature for 20 min, and the insoluble material was filtered off. The filtrate was concentrated *in vacuo* to leave a pale yellow solid, which was taken up in $CHCl_3$. The $CHCl_3$ solution was washed with saturated aqueous NaCl, dried, and concentrated. Recrystallization of the residual solid from EtOH afforded **10** (309 mg, 84%) as colorless minute needles. Further recrystallization from EtOH provided an analytical sample, mp 171.5—174.5 °C; $[\alpha]_D^{17}$ −227° (*c*=0.25, $CHCl_3$); MS *m/z*: 495 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3305, 3165 (NH and OH); ^{1}H-NMR ($CDCl_3$) δ: 1.82 [1H, dd, *J*=16, 11.5 Hz, C(4)-H_β], 2.45 [1H, m, C(3)-H], 2.67 (1H, dd, *J*=13.5, 7.5 Hz) and 3.10 (1H, dd, *J*=13.5, 4 Hz) [C(1)-CH_2], 2.82 [1H, dd, *J*=16, 2.5 Hz, C(4)-H_α], 3.27 (1H, dd, *J*=10.5, 6 Hz) and 3.49 (1H, dd, *J*=10.5, 4 Hz) (CH_2OH), 3.72 and 3.77 (1H each, d, *J*=12.5 Hz, ArCH_2S), 3.74, 3.76, 3.89, and 3.93 (3H each, s, four MeO's), 4.44 [1H, dd, *J*=7.5, 4 Hz, C(1)-H], 6.41 [1H, s, C(7)-H], 6.69, 6.77, 6.91, and 6.97 (2H each, d, *J*=8.5 Hz, two 4-MeOC_6H_4's). *Anal.* Calcd for $C_{28}H_{33}NO_5S$: C, 67.85; H, 6.71; N, 2.83. Found: C, 68.05; H, 6.93; N, 2.83.

ii) From **13**: A solution of **13** (108 mg, 0.20 mmol) in MeOH (3 ml) was cooled to 0 °C, and a solution of K_2CO_3 (69 mg, 0.50 mmol) in H_2O (0.3 ml) was added. After stirring at room temperature for 1 h, the reaction mixture was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to leave a colorless solid. Recrystallization of the solid from EtOH yielded **10** (86 mg, 86%) as colorless fluffy needles, mp 171—173 °C. This sample was identical (by comparison of the IR spectrum and TLC behavior) with the one obtained by method-(i).

(5*S*,10a*S*)-6,8-Dimethoxy-5-[(4-methoxyphenyl)methyl]-9-[[(4-methoxyphenyl)methyl]thio]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (14) A suspension of **10** (464 mg, 0.94 mmol) in absolute EtOH (17 ml) was stirred at room temperature, and a 1.0 M solution (1.9 ml, 1.9 mmol) of NaOEt in absolute EtOH and diethyl carbonate (1.2 ml, 9.9 mmol) were added. The resulting mixture was then heated under reflux for 6 h. After addition of AcOH (1.5 ml), the reaction mixture was concentrated *in vacuo*, and the residue was partitioned between $CHCl_3$ and 10% aqueous HCl. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography [hexane–AcOEt (1 : 1, v/v)] furnished **14** (446 mg, 91%) as a colorless foam, $[\alpha]_D^{18}$ −331° (*c*=0.25, $CHCl_3$); MS *m/z*: 520 (M^+-1); IR $\nu_{max}^{CHCl_3}$ 1742 cm^{-1} (oxazolidinone CO); ^{1}H-NMR (Table 1).

(5*S*,10a*S*)-6,8-Dimethoxy-9-mercapto-5-[(4-methoxyphenyl)methyl]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (15) A mixture of **14** (436 mg, 0.84 mmol), anisole (452 mg, 4.2 mmol), mercuric trifluoroacetate (544 mg, 1.3 mmol), and absolute EtOH (17 ml) was stirred at room temperature for 14.5 h. After addition of $NaBH_4$ (127 mg, 3.4 mmol) under ice-cooling, the reaction mixture was stirred at 0 °C for 15 min and then acidified with 10% aqueous HCl. The insoluble material was removed

by filtration, and the filtrate was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. Purification of the oil by flash chromatography [hexane–AcOEt (1 : 1, v/v)] gave **15** (301 mg, 90%) as a colorless glass, $[\alpha]_D^{17}$ −235° (c=0.25, $CHCl_3$); MS *m/z*: 400 (M^+-1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2590 (SH), 1742 (oxazolidinone CO); ^{1}H-NMR (Table 1).

(5*S*,10a*S*)-6,8-Dimethoxy-9-[(5-formyl-1-methyl-1*H*-imidazol-4-yl)thio]-5-[(4-methoxyphenyl)methyl]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (16) A mixture of **15** (128 mg, 0.32 mmol) and an oil dispersion (14 mg) containing 60% NaH (0.35 mmol) in dry DMF (3 ml) was stirred at room temperature, and 4-bromo-1-methyl-1*H*-imidazole-5-carbaldehyde (**23**)[5] (66 mg, 0.35 mmol) was added. The resulting mixture was heated at 100 °C in an atmosphere of N_2 for 3 h. After cooling, the reaction mixture was concentrated *in vacuo* to leave an orange oil, which was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual yellow oil by flash chromatography [AcOEt–EtOH (20 : 1, v/v)] furnished **16** (134 mg, 82%) as a yellowish foam, $[\alpha]_D^{16}$ −107° (c=0.25, $CHCl_3$); MS *m/z*: 508 (M^+-1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1741 (oxazolidinone CO), 1662 (CHO); ^{1}H-NMR (Table 1).

(5*S*,10a*S*)-6,8-Dimethoxy-9-[(5-hydroxymethyl-1-methyl-1*H*-imidazol-4-yl)thio]-5-[(4-methoxyphenyl)methyl]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (17) A solution of **16** (248 mg, 0.49 mmol) in MeOH (5 ml) was stirred at room temperature, and $NaBH_4$ (20 mg, 0.53 mmol) was added in small portions. After the mixture had been stirred at room temperature for 1 h, acetone (2 ml) was added. The resulting mixture was concentrated *in vacuo*, and the residual solid was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a colorless solid. Recrystallization from MeOH gave a first crop (180 mg) of **17**. A second crop (24 mg) of **17** was obtained by concentration of the mother liquor and subsequent purification of the residue by flash chromatography [AcOEt–EtOH (5 : 1, v/v)]. Total yield of **17** was 204 mg (82%). Further recrystallization from MeOH provided an analytical sample as colorless prisms, mp 250.5—251.5 °C; $[\alpha]_D^{20}$ −87.5° (c=0.25, $CHCl_3$); MS *m/z*: 511 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3180 (OH), 1753 (oxazolidinone CO); ^{1}H-NMR (Table 1). *Anal.* Calcd for $C_{26}H_{29}N_3O_6S$: C, 61.04; H, 5.71; N, 8.21. Found: C, 60.87; H, 5.74; N, 8.19.

X-Ray Structure Determination of 17 For X-ray diffraction analysis, colorless transparent prisms of **17** were grown from MeOH. A crystal measuring 0.20×0.10×0.10 mm was selected from among them and used for all data collection. Unit cell constants and intensity data were obtained with a Rigaku AFC-5R four-circle diffractometer controlled by the MSC/AFC program package, using graphite-monochromated Mo K_α radiation (λ=0.71069 Å), in the 2θ–ω scan mode. Crystal data of **17**: $C_{26}H_{29}N_3O_6S$; M=511.59; orthorhombic; space group $P2_12_12_1$; Z=4; a=11.703(6) Å; b=18.496(5) Å; c=11.653(2) Å; V=2522(1) Å^3; D_{calcd}=1.347 g/cm^3. Reflections (1307) with intensity above the $3\sigma(I)$ level were used for the structure determination. The structure was solved by a direct method using Mithril[17] and refined by the full-matrix least-squares method with anisotropic temperature factors for non-hydrogen atoms. All hydrogen atoms were clearly located on the difference Fourier maps and refined with isotropic temperature factors. The final R value was 0.036 (R_w=0.036).

(5*S*,10a*S*)-9-[[5-[(2*S-trans*)-2,5-Dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazin-5-yl]methyl-1-methyl-1*H*-imidazol-4-yl]thio]-6,8-dimethoxy-5-[(4-methoxyphenyl)methyl]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (21) and (5*S*,10a*S*)-9-[[5-[(2*S-cis*)-2,5-Dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazin-5-yl]methyl-1-methyl-1*H*-imidazol-4-yl]thio]-6,8-dimethoxy-5-[(4-methoxyphenyl)methyl]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (22) A mixture of **17** (560 mg, 1.1 mmol) and $SOCl_2$ (3.3 ml) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*, and the residual oil was co-evaporated with three 10-ml portions of THF to leave **18** as a pale yellow glass. This sample was directly used in the next step without further purification.

In a separate flask, a stirred solution of diisopropylamine (0.46 ml, 3.3 mmol) in THF (4 ml) was cooled to −78 °C in an atmosphere of Ar, and a 1.48 M solution (2.25 ml, 3.3 mmol) of BuLi in hexane was added dropwise. After the mixture had been stirred for 40 min, a solution of (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[18] (607 mg, 3.3 mmol) in THF (2 ml) was added dropwise. Stirring was then continued for 20 min, and a solution of the above chloride **18** in THF (5 ml) was added dropwise over 3 min. The resulting mixture was stirred first at −78 °C for 2 h and then at −50 °C for 20 h. The reaction was quenched by adding saturated aqueous NH_4Cl (5 ml) at −50 °C, and the mixture was allowed to warm to room temperature. The THF was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to leave a pale brown oil, which was then subjected to flash chromatography [AcOEt–acetone (1 : 1, v/v)]. Earlier fractions furnished **21** (410 mg, 55%) as a colorless glass, $[\alpha]_D^{19}$ −32.2° (c=0.53, $CHCl_3$); MS *m/z*: 676 (M^+-1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742 (oxazolidinone CO), 1693 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 0.69 and 0.97 (3H each, d, J=7 Hz, CH<u>Me</u>$_2$), 0.85 [1H, dd, J=15, 11 Hz, C(10)-H$_\beta$], 2.13 (1H, m, C<u>H</u>Me$_2$), 2.72 (1H, dd, J=13.5, 2 Hz) and 3.61 (1H, dd, J=13.5, 5 Hz) [C(5)-CH$_2$], 2.76 (1H, dd, J=14.5, 9.5 Hz) and 3.66 (1H, dd, J=14.5, 4.5 Hz) [C(5″)-CH$_2$], 3.61, 3.63, 3.74, 3.78, 3.86, and 3.88 (3H each, s, NMe and five MeO's), 3.64 (1H, dd, J=11, 7.5 Hz) and 4.35 (1H, dd, J=7.5 Hz each) [C(1)-H's], 3.73 [1H, m, C(10a)-H], 3.78 [1H, dd, J=4 Hz each, C(2″)-H], 3.80 [1H, dd, J=15, 3.5 Hz, C(10)-H$_\alpha$], 4.06 [1H, ddd, J=9.5, 4.5, 4 Hz, C(5″)-H], 5.30 [1H, dd, J=5, 2 Hz, C(5)-H], 6.37 [2H, d, J=8.5 Hz, C(3′)-H and C(5′)-H], 6.40 [1H, s, C(7)-H], 6.48 [2H, d, J=8.5 Hz, C(2′)-H and C(6′)-H], 7.24 (1H, s, imidazole ring proton).[19]

Later fractions in the above chromatography gave **22** (230 mg, 31%) as a colorless glass, $[\alpha]_D^{19}$ −8.7° (c=0.46, $CHCl_3$); MS *m/z*: 676 (M^+-1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742 (oxazolidinone CO), 1693 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 0.73 and 1.07 (3H each, d, J=7 Hz, CH<u>Me</u>$_2$), 0.87 [1H, dd, J=15.5, 12 Hz, C(10)-H$_\beta$], 2.17 (1H, m, C<u>H</u>Me$_2$), 2.79 (1H, dd, J=13.5, 2.5 Hz) and 3.61 (1H, dd, J=13.5, 5 Hz) [C(5)-CH$_2$], 2.96 (1H, dd, J=14.5, 9.5 Hz) and 3.30 (1H, dd, J=14.5, 4.5 Hz) [C(5″)-CH$_2$], 3.58 (3H), 3.63 (3H), 3.75 (6H), and 3.86 (6H) (s each, NMe and five MeO's), 3.63 (1H, dd, J=11, 8 Hz) and 4.35 (1H, dd, J=8 Hz each) [C(1)-H's], 3.72—3.80 [2H, m, C(10)-H$_\alpha$ and C(10a)-H], 3.93 [1H, dd, J=4.5 Hz each, C(2″)-H], 4.24 [1H, ddd, J=9.5, 4.5, 4.5 Hz, C(5″)-H], 5.31 [1H, dd, J=5, 2.5 Hz, C(5)-H], 6.42 [1H, s, C(7)-H], 6.45 [2H, d, J=9 Hz, C(3′)-H and C(5′)-H], 6.51 [2H, d, J=9 Hz, C(2′)-H and C(6′)-H], 7.24 (1H, s, imidazole ring proton).[19]

(5*S*,10a*S*)-5-[[6,8-Dimethoxy-5-[(4-methoxyphenyl)methyl]-3(3*H*)-oxo-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-9-yl]thio]-3-methyl-D-histidine Methyl Ester (5) A mixture of **21** (59 mg, 0.087 mmol) and 0.25 N aqueous HCl (3.5 ml) in MeOH (1.8 ml) was stirred at room temperature for 8.5 h. The reaction mixture was concentrated *in vacuo* to half the initial volume, made basic with 28% aqueous NH_3, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated. Purification of the residual yellow oil by flash chromatography [CH_2Cl_2–EtOH (9 : 1, v/v)] gave **5** (36 mg, 71%) as a colorless glass; $[\alpha]_D^{22}$ −87.8° (c=0.25, $CHCl_3$); MS *m/z*: 581 (M^+-1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 and 3320 (NH_2), 1740 (ester and oxazolidinone CO's); ^{1}H-NMR ($CDCl_3$) δ: 0.84 [1H, dd, J=15.5, 11.5 Hz, C(10′)-H$_\beta$], 2.77 (1H, dd, J=13.5, 2 Hz) and 3.62 (1H, dd, J=13.5, 5 Hz) [C(5′)-CH$_2$], 2.88 (1H, dd, J=14.5, 9.5 Hz) and 3.19 (1H, dd, J=14.5, 5.5 Hz) [C(4)-CH$_2$], 3.60, 3.74, 3.76, 3.89, and 3.91 (3H each, s, NMe and four MeO's), 3.65 (1H, dd, J=10.5, 7.5 Hz) and 4.36 (1H, dd, J=7.5 Hz each) [C(1′)-H's], 3.70—3.78 [2H, m, C(10′)-H$_\alpha$ and C(10′a)-H], 3.77 [1H, dd, J=9.5, 5.5 Hz, C(4)-CH$_2$C<u>H</u>], 5.30 [1H, dd, J=5, 2 Hz, C(5′)-H], 6.42 [2H, d, J=9 Hz, C(3″)-H and C(5″)-H], 6.45 [1H, s, C(7′)-H], 6.47 [2H, d, J=9 Hz, C(2″)-H and C(6″)-H], 7.25 [1H, s, C(2)-H].[20]

(5*S*,10a*S*)-5-[[6,8-Dimethoxy-5-[(4-methoxyphenyl)methyl]-3(3*H*)-oxo-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-9-yl]thio]-3-methyl-L-histidine Methyl Ester (6) A mixture of **22** (230 mg, 0.34 mmol) and 0.25 N aqueous HCl (13.5 ml) in MeOH (3 ml) was stirred at room temperature for 26 h. The reaction mixture was worked up as described above for **5**, giving **6** (149 mg, 75%) as a colorless glass; $[\alpha]_D^{20}$ −67.7° (c=0.25, $CHCl_3$); MS *m/z*: 581 (M^+-1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 and 3320 (NH_2), 1740 (ester and oxazolidinone CO's); ^{1}H-NMR ($CDCl_3$) δ: 0.87 [1H, dd, J=15.5, 11.5 Hz, C(10′)-H$_\beta$], 2.77 (1H, dd, J=13.5, 2.5 Hz) and 3.62 (1H, dd, J=13.5, 4.5 Hz) [C(5′)-CH$_2$], 3.01 (1H, dd, J=14.5, 9 Hz) and 3.09 (1H, dd, J=14.5, 5.5 Hz) [C(4)-CH$_2$], 3.60, 3.74, 3.77, 3.89, and 3.91 (3H each, s, NMe and four MeO's), 3.66 (1H, dd, J=11, 7.5 Hz) and 4.36 (1H, dd, J=7.5 Hz each) [C(1′)-H's], 3.73 [1H, dd, J=15.5, 3 Hz, C(10′)-H$_\alpha$], 3.74 [1H, m, C(10′a)-H], 3.85 [1H, dd, J=9, 5.5 Hz, C(4)-CH$_2$C<u>H</u>], 5.31 [1H, dd, J=4.5, 2.5 Hz, C(5′)-H], 6.42 [2H, d, J=9 Hz, C(3″)-H and C(5″)-H], 6.44 [1H, s, C(7′)-H], 6.46 [2H, d, J=9 Hz, C(2″)-H and C(6″)-H], 7.26 [1H, s, C(2)-H].[20]

(5*S*,10a*S*)-6,8-Dimethoxy-5-[(4-methoxyphenyl)methyl]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (27) and 3-Methyl-D-histidine (28) A stirred mixture of **5** (36 mg, 0.062 mmol), MeOH (4 ml), H_2O (1 ml), and Raney Ni[21] (0.5 ml) was heated under reflux for 1 h. The catalyst was removed by filtration and washed with MeOH. The filtrate and the washings were combined and concentrated *in vacuo*. Purification of the residue by flash chromatography [CH_2Cl_2–MeOH (20 : 1, v/v)] furnished **27**

(19 mg, 83%) as a colorless glass; $[\alpha]_D^{17}$ −267° (c=0.28, $CHCl_3$); MS m/z: 368 (M^+-1); IR $\nu_{max}^{CHCl_3}$ 1742 cm^{-1} (oxazolidinone CO); ^{1}H-NMR ($CDCl_3$) δ: 1.07 [1H, dd, J=14, 11.5 Hz, C(10)-H_β], 2.27 [1H, dd, J=14, 3 Hz, C(10)-H_α], 2.85 (1H, dd, J=13.5, 2 Hz) and 3.66 (1H, dd, J=13.5, 5 Hz) [C(5)-CH_2], 3.58 (1H, dd, J=11, 7.5 Hz) and 4.30 (1H, dd, J=7.5 Hz each) [C(1)-H's], 3.77 [1H, m, C(10a)-H], 3.74, 3.79, and 3.87 (3H each, s, three MeO's), 5.30 [1H, dd, J=5, 2 Hz, C(5)-H], 6.04 [1H, d, J=2 Hz, C(9)-H], 6.43 [1H, d, J=2 Hz, C(7)-H], 6.52 [2H, d, J=8.5 Hz, C(3′)-H and C(5′)-H], 6.64 [2H, d, J=8.5 Hz, C(2′)-H and C(6′)-H].[19] The catalyst, obtained by filtration of the original reaction mixture described above, was added to cold 6 N aqueous HCl (50 ml), and the mixture was stirred at room temperature for 4 h. The insoluble material was filtered off, and the filtrate was concentrated *in vacuo* to leave a greenish glass, which was dissolved in H_2O. The aqueous solution was applied to a column of Dowex 50W-X2 (H^+ form), and the column was eluted with 1 N aqueous HCl. After elution of Ni^{2+}, fractions showing a positive reaction to the ninhydrin test were combined and concentrated *in vacuo*. The residue was then dissolved in H_2O and applied to a column of Dowex 50W-X8 (H^+ form). The column was first eluted with H_2O until the eluate became neutral, and then with 2% aqueous NH_3. The ammoniacal eluates were combined and concentrated *in vacuo* to leave a colorless solid. The solid was triturated with H_2O, and the insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* to dryness to leave **28**·H_2O (5.3 mg, 46%) as a colorless solid, $[\alpha]_D^{21}$ −11.3° (c= 0.31, 0.1 N aqueous HCl). The ^{1}H-NMR spectrum (D_2O) and TLC mobility of this sample were identical with those of a commercial sample of 3-methyl-L-histidine monohydrate (*ent*-**28**·H_2O) [$[\alpha]_D^{23}$ +10.8° (c=0.30, 0.1 N aqueous HCl)].

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20) For convenience, each skeletal atom in the oxazolo[3,4-*b*]isoquinoline moiety is indicated by a primed number and each aromatic carbon in the 4-methoxyphenyl moiety by a doubly primed number.
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