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Synthetic Studies on the Starfish Alkaloid Imbricatine. A Chiral Synthesis of Tri-*O*-methylimbricatine

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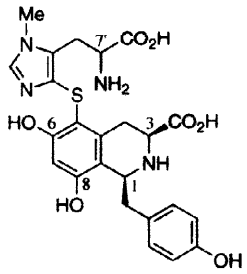
Abstract: A detailed account is given of the chiral synthesis of tri-*O*-methylimbricatine (**3**), the tri-*O*-methyl derivative of the structurally unique benzyltetrahydroisoquinoline alkaloid imbricatine (**2**) isolated from the starfish *Dermasterias imbricata*. The route begins with the asymmetric synthesis of the sulfur-containing D-phenylalanine derivative (*R*)-**11a** and includes its conversion into the *cis*-benzyltetrahydroisoquinoline moiety **26a** possessing the thiol group and construction of the 5-arylthio-3-methyl-L-histidine portion. The correctness of the structure and absolute configuration proposed for imbricatine has been unequivocally confirmed as a result of the present synthesis.

Keywords: amino acids and derivatives; imidazoles/imidazolidinones; isoquinolines; thioethers

INTRODUCTION

Since the initial report by Yentsch and Pierce in 1955 on the unusual "swimming" behavior of the sea anemone *Stomphia coccinea* evoked in response to immediate contact with the starfish *Dermasterias imbricata*,[1] considerable efforts have been directed toward a wide variety of studies on different aspects of the interaction.[2] In search of a chemical substance responsible for eliciting the behavior, Pathirana and Andersen announced the isolation of imbricatine from *D. imbricata* in 1986.[3] The gross structure **1** of imbricatine was elucidated through extensive spectroscopic analysis, in conjunction with chemical degradation. Imbricatine is of particular interest in that it is capable of inducing the detachment and swimming response in *S. coccinea* at very low concentrations;[2,3] it displays significant antineoplastic activity;[3–5] it is the first example of a benzyltetrahydroisoquinoline alkaloid obtained from a nonplant source; and it embodies some structural features (*e.g.*, the carboxy group at the 3-position, the 6,8-dihydroxylation pattern, and the thioether linkage to the 3-methyl-



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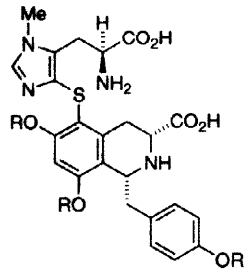
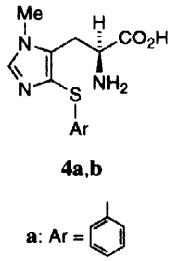


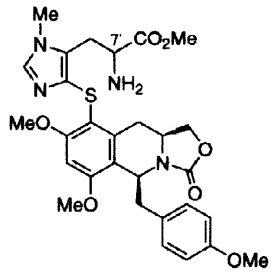
2: R = H
3: R = Me



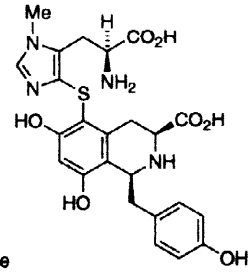
4a,b

a: Ar =

b: Ar =



5: 7'*R*
6: 7'*S*



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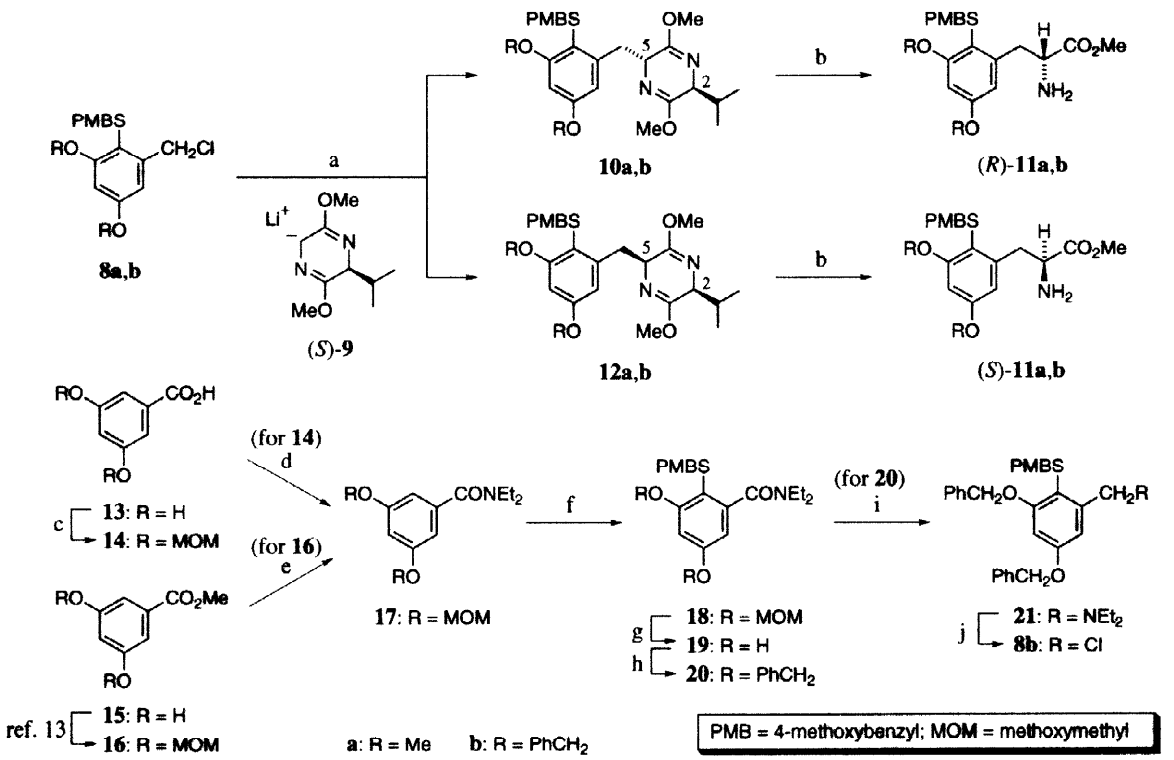
histidine moiety) not previously encountered in this family of alkaloids. Andersen and co-workers, thereafter, proposed the absolute configurations of the three stereogenic centers of imbricatine to be those in **2** (1*R*,3*R*,7'*S*) on the basis of the degradation experiments.[4]

As a prelude to the total synthesis of imbricatine, we have recently achieved the chiral syntheses of 5-arylthio-3-methyl-L-histidines (**4a,b**), a partial form of **2**,[6] and the amino esters **5** and **6** possessing the entire frameworks of *ent*-imbricatine (*ent*-**2**) and its 7'-epimer **7**, respectively,[7] the latter of which was the then prospective (but ultimately wrong) candidate structure for imbricatine according to the first report of Pathirana and Andersen.[3] In the present paper, we wish to record the details of the chiral synthesis of tri-*O*-methylimbricatine (**3**), the tri-*O*-methyl derivative of **2**. A brief account of a part of the results recorded here has been published in a preliminary form.[8]

RESULTS AND DISCUSSION

In connection with our synthetic studies on imbricatine, we have accomplished the asymmetric synthesis of the L-phenylalanine derivative (*S*)-**11a** containing a sulfur substituent at the 2-position[9] and employed it as a starting material for the syntheses of the amino esters **5** and **6**.[7] At the outset of the present synthesis, therefore, we needed the corresponding D-phenylalanine derivative (*R*)-**11a** to reach the temporary target *ent*-**5**, together with *ent*-**6**. On the analogy of our previous synthesis of (*S*)-**11a**,[9] coupling reaction of the benzyl chloride **8a** with the organolithium reagent (*S*)-**9** generated *in situ* from (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-

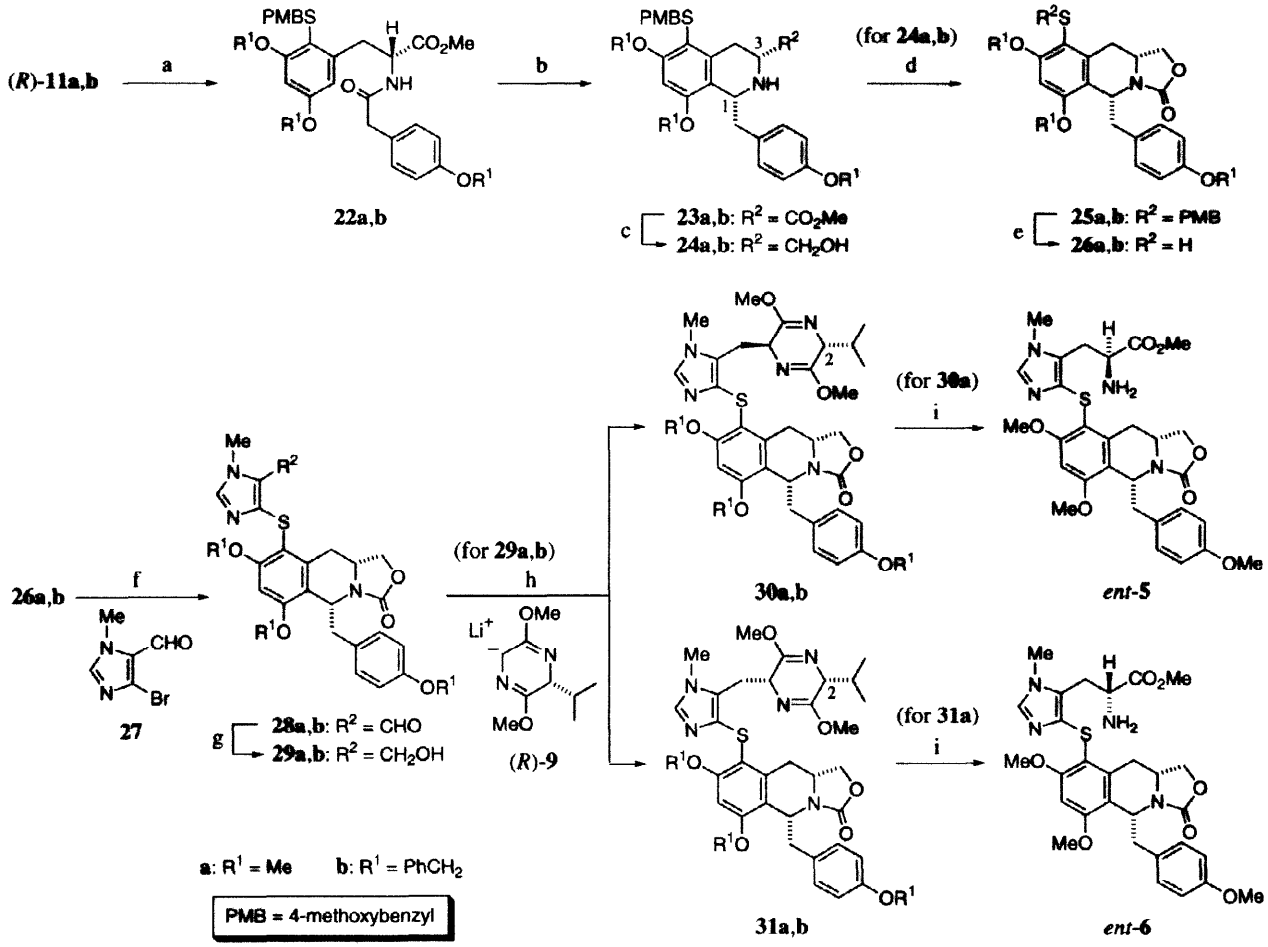


Scheme 1. *Reagents and conditions:* (a) (*S*)-**9**, THF, –78 °C, 2 h, –50 °C, 18 h; (b) 0.25 N aq. HCl, MeOH, rt, 4–9 h; (c) 1) NaH, MOMCl, DMF, rt, 27 h; 2) 2 N aq. NaOH, MeOH, rt, 3 h; (d) Et_2NH, $(EtO)_2P(O)CN$, Et_3N, DMF, rt, 2 h; (e) Me_3Al, Et_2NH, toluene, reflux, 18 h; (f) 1) *sec*-BuLi, TMEDA, THF, –78 °C, 1 h; 2) S, 0 °C, 1.5 h; 3) PMBCl, 0 °C, 2 h; (g) 1 N aq. HCl, MeOH, 60–64 °C, 2.5 h; (h) NaH, $PhCH_2Br$, DMF, rt, 4.5 h; (i) $LiAlH_4$, THF, reflux, 3 h; (j) $ClCO_2Et$, benzene, rt, 23 h.

isopropylpyrazine and LDA in THF at –78 °C, an application of the "bis-lactim ether" method of Schöllkopf,[10] was carried out at –50 °C for 18 h, producing **10a** in 75% yield along with its 5-epimer **12a** (9% yield). The *trans* and *cis* stereochemical assignments to **10a** and **12a**, respectively, were based on our precedent.[9] The major isomer **10a** was then hydrolyzed in MeOH with 0.25 N aqueous HCl to provide the amino ester (*R*)-**11a** in 97% yield. The enantiomeric purity of (*R*)-**11a** was determined to be 96% ee.[11] Similar treatment of the minor isomer **12a** led to (*S*)-**11a**[9] in 96% yield.

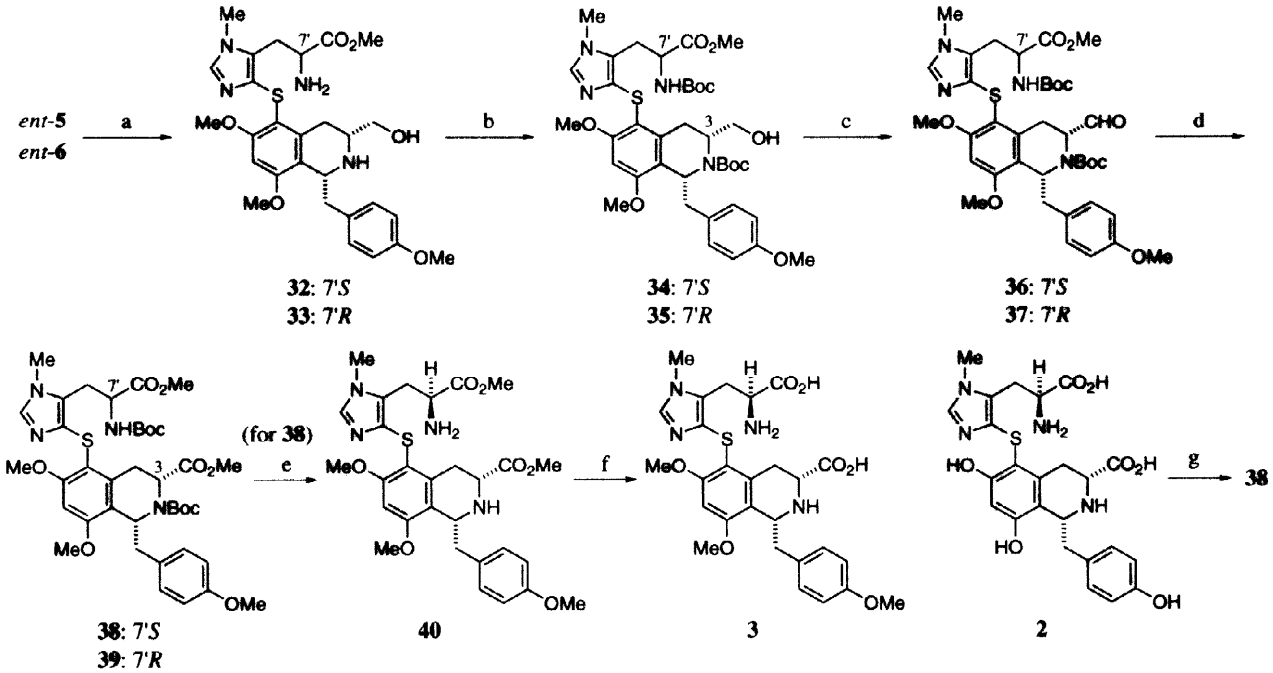
On the other hand, we chose (*R*)-**11b**, carrying the phenolic OH groups protected by the benzyl group, as another starting material and began its preparation *via* a route similar to that employed for (*R*)-**11a**. Thus, treatment of 3,5-dihydrobenzoic acid (**13**) with methoxymethyl (MOM) chloride in the presence of NaH, followed by alkaline hydrolysis of the resulting MOM ester, provided the carboxylic acid **14** (97% yield). Condensation of **14** with Et_2NH was effected using the coupling reagent diethyl phosphorocyanidate,[12] affording the amide **17** in 90% yield. Alternatively, the same amide **17** was also obtained in 74% yield on treatment of **16**, prepared from **15**,[13] with the dimethylaluminum diethylamide reagent *via* Weinreb's procedure.[14] Lithiation of **17** with *sec*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF at –78 °C, followed by successive addition of elemental sulfur and 4-methoxybenzyl (PMB) chloride, proceeded exclusively at the 2-position, giving the thioether **18** in 81% yield as a sole product.[15] Removal of the MOM group in **18** and subsequent benzylation of the resultant phenol **19** gave the benzyl ether **20**. The amide group of **20** was then reduced with $LiAlH_4$ to afford the tertiary amine **21**, which was converted into the benzyl chloride **8b** by treatment with ethyl chloroformate. Alkylation of the organolithium reagent (*S*)-**9** with **8b** was performed as described above for **8a**, furnishing the *trans* isomer **10b** and the *cis* isomer **12b** in 70% and 5% yields, respectively. The stereochemistries of the newly formed stereogenic centers in **10b** and **12b** were determined on the basis of their ratio of formation (**10b**:**12b** = 14:1)[9,10] and ^1H NMR spectral evidence that the C(2)-proton signal (δ 3.63) of **10b** appeared in $CDCl_3$ at higher field than the corresponding proton signal (δ 3.85) of **12b**, because of the shielding effect induced by the tetrasubstituted aromatic ring.[9,10] Both bis-lactim ethers **10b** and **12b** were separately hydrolyzed in MeOH with 0.25 N HCl to provide the enantiomerically pure phenylalanine derivatives (*R*)-**11b** and (*S*)-**11b**, respectively.

Condensation of (*R*)-**11a** with 4-methoxyphenylacetyl chloride was carried out under Schotten–Baumann conditions, providing the amide **22a** (96% yield), which was then submitted to Bischler–Napieralski cyclization using trimethylsilyl polyphosphate (PPSE)[16,17] in $CHCl_3$ followed by $NaBH_4$ reduction in MeOH at –78 °C.[18] Although the sole product **23a** obtained in 81% overall yield was found to be of 91% ee,[11] recrystallization from MeOH readily permitted to secure optically pure **23a**. The 1,3-*cis* relationship of **23a** was confirmed by a 5.8% NOE enhancement observed for the C(1)-proton signal on irradiation of the C(3)-proton signal. The ester group of **23a** was then reduced with $LiAlH_4$ to furnish **24a** in 91% yield, since partial or complete epimerization at the 3-position was assumed to be a potential problem at later stages. The resulting OH group as well as the NH group of **24a** was protected in the form of the oxazolidinone **25a** (98% yield) by treatment with diethyl carbonate in the presence of NaOEt. Removal of the PMB group in **25a** was successfully performed by application of the literature procedure[19] but with minor modification. Thus, on treatment with $(CF_3CO_2)_2Hg$ in EtOH containing anisole followed by $NaBH_4$ reduction of the resultant mercaptide, **25a** provided the thiol **26a** in 95% yield. A parallel sequence of reactions starting from condensation of (*R*)-**11b** with 4-benzyloxyphenylacetyl chloride and proceeding through **22b** (94% yield), **23b** (79%), **24b** (87%), and **25b** (95%) afforded the tris(benzyloxy) thiol **26b** (87%).



Scheme 2. *Reagents and conditions:* (a) 4-methoxyphenylacetyl chloride or 4-benzyloxyphenylacetyl chloride, Na_2CO_3, H_2O–benzene, 8–10 °C, 0.5–1 h; (b) 1) PPSE, $CHCl_3$, reflux, 10 h; 2) $NaBH_4$, MeOH, –78 °C, 1 h; (c) $LiAlH_4$, THF, rt, 1.5 h; (d) $(EtO)_2CO$, NaOEt, EtOH, reflux, 20–23 h; (e) 1) $(CF_3CO_2)_2Hg$, anisole, EtOH, rt, 16–19 h; 2) $NaBH_4$, 0 °C, 15 min; (f) **27**, NaH, DMF, 100 °C, 3–3.5 h; (g) $NaBH_4$, MeOH, rt, 1 h; (h) 1) $SOCl_2$, rt, 1 h; 2) (*R*)-**9**, THF, –78 °C, 2 h, –50 °C, 14 h; (i) 0.25 N aq. HCl, MeOH, rt, 2.5 h.

Having completed the chiral synthesis of the benzyltetrahydroisoquinoline skeleton containing the thiol group, we next initiated the application to **26a,b** of our previously established synthetic route to 5-arylthio-3-methyl-L-histidines (**4a,b**).[6] Separate treatments of the aldehyde **27**[6] in DMF with the thiols **26a** and **26b** in the presence of NaH afforded the corresponding thioethers **28a** and **28b** in 68% and 56% yields, respectively. The thioethereal aldehydes **28a,b** were then converted into the alcohols **29a** (80% yield) and **29b** (90%) by $NaBH_4$ reduction. The structure and stereochemistry of **29a** were secured in the form of a single-crystal X-ray analysis of *ent*-**29a**, whose results appeared in our recent report.[7] Chlorination of **29a** with $SOCl_2$ and subsequent coupling reaction of the resulting chloride with the organolithium reagent (*R*)-**9** provided the *trans* isomer **30a** and the *cis* isomer **31a** in 58% and 34% yields, respectively.[20] The stereochemical assignments to **30a** and **31a** were based on comparison of the chemical shifts of their C(2)-protons (**30a**: δ 3.78; **31a**: δ 3.93) in analogy with our precedents.[6,7,9] Similarly, chlorination of **29b** and subsequent coupling reaction with (*R*)-**9** were carried out, but the yields of the desired products **30b** and **31b** were quite low and we were unable to improve them. This led us to utilize the methoxy series for the next step, abandoning the benzyloxy series at that stage.



Scheme 3. *Reagents and conditions:* (a) 1) 6 N aq. HCl, 100 °C, 1 h; 2) 2 N aq. NaOH, MeOH, 80–85 °C, 60 h; 3) 10% HCl–MeOH, reflux, 7 h; (b) $(Boc)_2O$, $CHCl_3$, rt, 6 h; (c) 1) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h; 2) Et_3N; (d) I_2, KOH, MeOH, 0 °C, 5 h; (e) CF_3CO_2H, CH_2Cl_2, rt, 1.5 h; (f) 1) 3 N aq. HCl, reflux, 1 h; 2) Dowex 50W-X8; (g) 1) 12% HCl–MeOH, reflux, 3 h; 2) $(Boc)_2O$, Et_3N, $CHCl_3$, rt, 6 h; 3) CsF–alumina, MeI, CH_3CN, rt, 1 h.

The *trans* bis-lactim ether **30a** was then subjected to hydrolysis in MeOH with 0.25 N aqueous HCl, producing the amino ester *ent*-**5** in 91% yield. Conversion of *ent*-**5** into the amino alcohol **32** was accomplished in 73% overall yield *via* acid hydrolysis of the ester group, cleavage of the oxazolidinone ring with 2 N aqueous NaOH, and re-esterification of the carboxy group. After protection of both amino functions in **32** with $(Boc)_2O$ to give **34** in 91% yield, Swern oxidation[21] (81% yield) of the hydroxymethyl group at the 3-position of **34** and subsequent alkaline iodine oxidation[22] (71%) of the resulting aldehyde **36** in MeOH gave the dimethyl ester **38** [$[\alpha]_D^{22}$ −15.3° (*c* 0.50, $CHCl_3$)]. The *cis* bis-lactim ether **31a** was similarly converted into the diastereoisomeric dimethyl ester **39** [$[\alpha]_D^{20}$ −25.3° (*c* 0.53, $CHCl_3$)] in a comparable overall yield through the intermediates *ent*-**6**, **33**, **35**, and **37**. In the meantime, natural imbricatine (**2**) was submitted to methyl esterification followed by *N*-protection with $(Boc)_2O$ and *O*-methylation with MeI in the presence of CsF–alumina.[23] The authentic specimen [$[\alpha]_D^{24}$ −13.5° (*c* 0.085, $CHCl_3$)] of **38** thus obtained was found to be virtually identical with the synthetic (7′*S*)-isomer (**38**), but not with the synthetic (7′*R*)-isomer (**39**), by comparison of the IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and mass spectra and TLC behavior (three solvent systems). Finally, removal of the Boc group in **38** with CF_3CO_2H and subsequent acid hydrolysis of the resulting amino ester **40** produced tri-*O*-methylimbricatine (**3**) [$[\alpha]_D^{25}$ +62.2° (*c* 0.67, MeOH)]. Unfortunately, all our efforts to achieve exhaustive *O*-demethylation of **3** leading to imbricatine (**2**) were in vain.

In conclusion, a chiral synthesis of tri-*O*-methylimbricatine (**3**), the tri-*O*-methyl derivative of the starfish alkaloid imbricatine, has been accomplished *via* a route featuring the synthesis of the sulfur-containing benzyltetrahydroisoquinoline moiety and the construction of the 5-arylthio-3-methyl-L-histidine portion. As a result, the structure and absolute configuration of imbricatine have now been unambiguously established to be those in formula **2**.

EXPERIMENTAL

General Methods. All melting points were taken on a Büchi model 530 capillary melting point apparatus and are corrected. The ratios of solvents in mixtures are shown in v/v. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. See ref. 7 for details of chromatographies, instrumentation, and measurements. Elemental analyses and MS measurements were performed by Mr. Y. Itatani, Dr. M. Takani, and their associates at Kanazawa University.

3,5-Bis(methoxymethoxy)benzoic Acid (14). A solution of 3,5-dihydroxybenzoic acid (**13**) (925 mg, 6.0 mmol) in DMF (5 ml) was added dropwise over 20 min to an oil dispersion (760 mg) containing 60% NaH (19 mmol) in DMF (15 ml) in an atmosphere of N_2. After the mixture had been stirred for 1 h, MOM chloride (1.5 ml, 20 mmol) was added at such a rate that the inner temperature did not exceed 50 °C. Stirring was continued at room temperature for 27 h, and the insoluble material that resulted was filtered off. Concentration of the filtrate *in vacuo* provided an oily residue, which was partitioned between benzene and H_2O. The benzene extracts were dried and concentrated to leave the methoxymethyl ester as a pale yellow oil. The crude oil was then dissolved in MeOH (10 ml), and the solution, after addition of 2 N aqueous NaOH (5 ml, 10 mmol), was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in H_2O (6 ml). The aqueous solution was washed with benzene and acidified with 10% aqueous HCl. The colorless solid that deposited was filtered off, washed with H_2O, and dried to give **14** (1.41 g, 97%). Recrystallization of the solid from AcOEt–hexane (2:1) afforded an analytical sample as colorless needles, mp 129–129.5 °C; MS *m/z*: 242 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1698 (CO_2H); ^1H NMR ($CDCl_3$) δ: 3.50 (6H, s, two OMe's), 5.21 (4H, s, two CH_2's), 6.98 [1H, t, J = 2.5 Hz, C(4)-H], 7.44 [2H, d, J = 2.5 Hz, C(2)-H and C(6)-H]. *Anal.* Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.39; H, 5.82.

***N,N*-Diethyl-3,5-bis(methoxymethoxy)benzamide (17). (i) From 14.** A solution of **14** (6.28 g, 25.9 mmol) and Et_2NH (2.46 g, 33.6 mmol) in DMF (50 ml) was cooled to 0 °C, and diethyl phosphorocyanidate (5.49 g, 33.7 mmol) and Et_3N (3.41 g, 33.7 mmol) were added in that order. The mixture was stirred at room temperature for 2 h, poured into H_2O (100 ml), and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed successively with 2% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (1:1)] furnished **17** (6.96 g, 90%) as a pale yellow oil, MS *m/z*: 297 (M^+); IR ν_{max}^{film} cm^{-1}: 1634 (amide CO); ^1H NMR ($CDCl_3$) δ: 1.13 and 1.23 (6H, br each, two CMe's), 3.25 and 3.50 (4H, br each, two NCH_2's), 3.47 (6H, s, two OMe's), 5.16 (4H, s, two OCH_2's), 6.70 [2H, d, J = 2 Hz, C(2)-H and C(6)-H], 6.74 [1H, t, J = 2 Hz, C(4)-H]; HRMS *m/z* calcd for $C_{15}H_{23}NO_5$: 297.1577, found: 297.1575.

(ii) From 16. A mixture of toluene (15 ml) and a 1.0 M solution (4.8 ml, 4.8 mmol) of Me_3Al in hexane was cooled to –15 °C in an atmosphere of N_2, and Et_2NH (0.5 ml, 4.8 mmol) was added dropwise over 5 min. After 20 min, the cold bath was removed, and the mixture was stirred at room temperature for a further 45 min. At this time, a solution of **16**[13] (1.03 g, 4.0 mmol) in toluene (3 ml) was added, and the mixture was then heated under reflux for 18 h. After cooling, 15% aqueous Rochelle salt (10 ml) was added. The aqueous layer was separated from the organic layer and extracted with toluene. The toluene extracts and the above organic layer were combined, washed successively with 5% aqueous NaOH, H_2O, 2% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a yellow oil. Purification of the oil by flash chromatography [AcOEt–hexane (1:1)] produced **17** (883 mg, 74%) as a pale yellow oil. The IR and ^1H NMR spectra of this sample were identical with the one obtained by method-(i).

***N,N*-Diethyl-3,5-bis(methoxymethoxy)-2-[[(4-methoxyphenyl)methyl]thio]benzamide (18).** A solution of **17** (6.34 g, 21.3 mmol) and TMEDA (3.9 ml, 25.8 mmol) in THF (100 ml) was cooled to –78 °C in an atmosphere of N_2, and a 1.13 M solution (23 ml, 26.0 mmol) of *sec*-BuLi in cyclohexane was added dropwise over 10 min. After the mixture had been stirred for 1 h, powdered sulfur crystals (956 mg, 29.8 mg-atom) were added in one aliquot. The mixture was then warmed to 0 °C and stirred for 1.5 h. 4-Methoxybenzyl chloride (3.5 ml, 25.8 mmol) was then added, and stirring was continued at 0 °C for a further 2

h. The reaction was quenched by adding saturated aqueous NH_4Cl (40 ml), and the reaction mixture was extracted with ether. The ethereal extracts were washed successively with 2% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a reddish oil, which was purified by flash chromatography [AcOEt–hexane (1:1)] to give **18** (7.77 g, 81%) as a yellow oil, MS *m/z*: 449 (M^+); IR ν_{max}^{film} cm^{-1}: 1634 (amide CO); ^1H NMR ($CDCl_3$) δ: 1.00 and 1.26 (3H each, t, *J* = 7 Hz, two CMe's), 2.92 (2H, m), 3.26 (1H, dq, *J* = 14, 7 Hz), and 3.82 (1H, dq, *J* = 14, 7 Hz) (two NCH_2's), 3.46, 3.49, and 3.76 (3H each, s, three OMe's), 3.87 and 4.12 (1H each, d, *J* = 12 Hz, SCH_2), 5.1–5.2 (4H, m, two OCH_2's), 6.62 and 6.82 [1H each, d, *J* = 2.5 Hz, C(4)-H and C(6)-H], 6.77 [2H, d, *J* = 8.5 Hz, C(3')-H and C(5')-H], 7.17 [2H, d, *J* = 8.5 Hz, C(2')-H and C(6')-H].[24,25]

***N,N*-Diethyl-3,5-dihydroxy-2-[[(4-methoxyphenyl)methyl]thio]benzamide (19).** A mixture of **18** (32.0 g, 71.2 mmol), MeOH (260 ml), and 1 N aqueous HCl (245 ml) was heated at 60–64 °C for 2.5 h. After cooling, the reaction mixture was concentrated *in vacuo* to half the initial volume and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a pale yellow foam, which was crystallized from AcOEt–hexane (3:2) to provide **19** (22.5 g, 87%). Recrystallization from the same solvent system gave an analytical sample as colorless prisms, mp 149–150 °C; MS *m/z*: 361 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3415, 3380 (OH), 1613 (amide CO); ^1H NMR ($CDCl_3$) δ: 1.07 and 1.33 (3H each, t, *J* = 7 Hz, two CMe's), 3.15 (2H, m), 3.37 (1H, dq, *J* = 14, 7 Hz), and 3.90 (1H, dq, *J* = 14, 7 Hz) (two NCH_2's), 3.77 and 3.87 (1H each, d, *J* = 12.5 Hz, SCH_2), 3.78 (3H, s, OMe), 6.30 and 6.35 [1H each, d, *J* = 2.5 Hz, C(4)-H and C(6)-H], 6.45 and 8.91 (1H each, s, two OH's), 6.77 [2H, d, *J* = 9 Hz, C(3')-H and C(5')-H], 7.09 [2H, d, *J* = 9 Hz, C(2')-H and C(6')-H].[24,25] *Anal.* Calcd for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41; N, 3.88. Found: C, 63.10; H, 6.36; N, 3.90.

3,5-Bis(benzyloxy)-*N,N*-diethyl-2-[[(4-methoxyphenyl)methyl]thio]benzamide (20). To an ice-cooled oil dispersion (510 mg) containing 60% NaH (13 mmol) in DMF (60 ml) was added **19** (2.13 g, 5.9 mmol). After stirring at room temperature for 1 h, the mixture was cooled to 0 °C once again. A solution of benzyl bromide (2.21 g, 12.9 mmol) in DMF (3 ml) was added over 10 min, and stirring was continued at room temperature for a further 4.5 h. The reaction mixture was concentrated *in vacuo*; and the residual oil, after addition of H_2O, was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated to leave a brown oil. Purification by flash chromatography [hexane–AcOEt (2:1)] afforded **20** (3.05 g, 96%) as a colorless solid. Recrystallization of the solid from hexane–AcOEt (2:1) yielded an analytical sample as colorless prisms, mp 91–92 °C; MS *m/z*: 541 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1641 (amide CO); ^1H NMR ($CDCl_3$) δ: 0.91 and 1.25 (3H each, t, *J* = 7 Hz, two CMe's), 2.90 (2H, m), 3.25 (1H, dq, *J* = 14, 7 Hz), and 3.83 (1H, dq, *J* = 14, 7 Hz) (two NCH_2's), 3.74 (3H, s, OMe), 3.86 and 4.09 (1H each, d, *J* = 11.5 Hz, SCH_2), 5.00, 5.01, 5.06, and 5.09 (1H each, d, *J* = 12 Hz, two $OC\underline{H}_2Ph$'s), 6.45 and 6.57 [1H each, d, *J* = 2.5 Hz, C(4)-H and C(6)-H], 6.71 [2H, d, *J* = 8.5 Hz, C(3')-H and C(5')-H], 7.10 [2H, d, *J* = 8.5 Hz, C(2')-H and C(6')-H], 7.3–7.5 (10H, m, two Ph's).[24,25] *Anal.* Calcd for $C_{33}H_{35}NO_4S$: C, 73.17; H, 6.51; N, 2.59. Found: C, 73.18; H, 6.55; N, 2.58.

3,5-Bis(benzyloxy)-*N,N*-diethyl-2-[[(4-methoxyphenyl)methyl]thio]benzenemethanamine (21). An ice-cooled suspension of $LiAlH_4$ (3.81 g, 0.10 mol) in THF (300 ml) was stirred in an atmosphere of N_2, and a solution of **20** (27.2 g, 50.2 mmol) in THF (80 ml) was added dropwise over 35 min. After the mixture had been heated under reflux for 3 h, H_2O (4 ml), 10% aqueous NaOH (6 ml), and H_2O (10 ml) were successively added under ice-cooling. The insoluble material that resulted was filtered off and washed with ether. The filtrate and washings were combined, dried over anhydrous K_2CO_3, and concentrated to leave **21** (25.6 g, 97%) as a yellow oil, MS *m/z*: 527 (M^+); ^1H NMR ($CDCl_3$) δ: 0.93 (6H, t, *J* = 7 Hz, two CMe's), 2.37 (4H, q, *J* = 7 Hz, two $NC\underline{H}_2Me$'s), 3.49 [2H, s, C(1)-CH_2], 3.73 (3H, s, OMe), 3.85 (2H, s, SCH_2), 5.04 and 5.12 (2H each, s, two $OC\underline{H}_2Ph$'s), 6.52 and 6.92 [1H each, d, *J* = 2.5 Hz, C(4)-H and C(6)-H], 6.68 [2H, d, *J* = 8.5 Hz, C(3')-H and C(5')-H], 6.94 [2H, d, *J* = 8.5 Hz, C(2')-H and C(6')-H], 7.3–7.55 (10H, m, two Ph's);[24] HRMS *m/z* calcd for $C_{33}H_{37}NO_3S$: 527.2494, found: 527.2494.

3,5-Bis(benzyloxy)-1-(chloromethyl)-2-[[(4-methoxyphenyl)methyl]thio]benzene (8b).

A solution of **21** (14.2 g, 26.9 mmol) and ethyl chloroformate (3.51 g, 32.3 mmol) in benzene (150 ml) was stirred at room temperature for 23 h. The reaction mixture was then washed successively with H_2O, 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a pale yellow solid. Recrystallization from hexane–AcOEt (1:1) gave a first crop (8.83 g) of **8b**. A second crop (1.77 g) of **8b** was obtained by concentration of the mother liquor and subsequent purification of the residue by flash chromatography [hexane–AcOEt (2:1)]. Total yield of **8b** was 10.6 g (80%). Further recrystallization from hexane–AcOEt (1:1) afforded an analytical sample as colorless needles, mp 95.5–97.5 °C; MS *m/z*: 492, 490 (M^+); ^1H NMR ($CDCl_3$) δ: 3.75 (3H, s, OMe), 3.90 (2H, s, SCH_2), 4.59 (2H, s, CH_2Cl), 5.03 and 5.12 (2H each, s, two $OC\underline{H}_2Ph$'s), 6.60 and 6.70 [1H each, d, J = 2.5 Hz, C(4)-H and C(6)-H], 6.70 [2H, d, J = 8.5 Hz, C(3')-H and C(5')-H], 6.97 [2H, d, J = 8.5 Hz, C(2')-H and C(6')-H], 7.3–7.55 (10H, m, two Ph's).[24] *Anal.* Calcd for $C_{29}H_{27}ClO_3S$: C, 70.93; H, 5.54. Found: C, 70.97; H, 5.54.

(2*S*-*trans*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-dimethoxy-2-[[(4-methoxyphenyl)-methyl]thio]phenyl]methyl]-2-(1-methylethyl)pyrazine (10a) and (2*S*-*cis*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]phenyl]methyl]-2-(1-methylethyl)pyrazine (12a). Alkylation of (*S*)-**9**, generated from (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[26] (5.20 g, 28.2 mmol) and LDA, with **8a** (9.08 g, 26.8 mmol) and work-up of the reaction mixture were effected as reported previously[9] for the syntheses of *ent*-**10a** and *ent*-**12a**, giving **10a** (9.73 g, 75%) as a colorless oil [$[\alpha]_D^{28}$ –57.5° (c = 0.45, $CHCl_3$)] and **12a** (1.15 g, 9%) as a colorless oil [$[\alpha]_D^{28}$ +58.5° (c = 0.50, $CHCl_3$)]. The IR, ^1H NMR, and mass spectra of these two samples were identical with those of *ent*-**10a** and *ent*-**12a**, respectively.[9]

(2*S*-*trans*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-bis(benzyloxy)-2-[[(4-methoxyphenyl)-methyl]thio]phenyl]methyl]-2-(1-methylethyl)pyrazine (10b) and (2*S*-*cis*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-bis(benzyloxy)-2-[[(4-methoxyphenyl)methyl]thio]phenyl]methyl]-2-(1-methylethyl)pyrazine (12b). A stirred solution of diisopropylamine (1.8 ml, 12.8 mmol) in THF (20 ml) was cooled to –78 °C in an atmosphere of N_2, and a 1.6 M solution (8.0 ml, 12.8 mmol) of BuLi in hexane was added dropwise. After the mixture had been stirred for 30 min, a solution of (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[26] (2.03 g, 11.0 mmol) in THF (8 ml) was added dropwise. Stirring was then continued for 20 min, and a solution of **8b** (4.91 g, 10.0 mmol) in THF (20 ml) was added over 20 min. After the resulting mixture had been stirred first at –78 °C for 2 h and then at –50 °C for 18 h, the reaction was quenched by adding saturated aqueous NH_4Cl (20 ml). The aqueous layer was separated from the organic layer and extracted with ether. The ethereal extracts and the above organic layer were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to leave a yellow oil, which was purified by two successive flash chromatographies [CH_2Cl_2; CH_2Cl_2–AcOEt (30:1)]. Earlier fractions afforded **10b** (4.49 g, 70%) as a colorless oil, $[\alpha]_D^{26}$ –35.9° (c = 0.50, $CHCl_3$); MS *m/z*: 638 (M^+); IR ν_{max}^{film} cm^{-1}: 1694 (C=N); ^1H NMR ($CDCl_3$) δ: 0.63 and 0.99 (3H each, d, J = 7 Hz, $CH\underline{Me}_2$), 2.19 (1H, dqq, J = 3.5, 7, 7 Hz, $C\underline{H}Me_2$), 2.88 (1H, dd, J = 13, 8 Hz) and 3.43 (1H, dd, J = 13, 4.5 Hz) [C(5)-CH_2], 3.61, 3.70, and 3.74 (3H each, s, three OMe's), 3.63 [1H, dd, J = 3.5 Hz each, C(2)-H], 3.84 (2H, s, SCH_2), 4.21 [1H, ddd, J = 8, 4.5, 3.5 Hz, C(5)-H], 4.97 and 5.12 (2H each, s, two $OC\underline{H}_2Ph$'s), 6.48 and 6.51 [1H each, d, J = 2.5 Hz, C(4')-H and C(6')-H], 6.68 [2H, d, J = 9 Hz, C(3")-H and C(5")-H], 6.96 [2H, d, J = 9 Hz, C(2")-H and C(6")-H], 7.3–7.55 (10H, m, two Ph's);[27] HRMS *m/z* calcd for $C_{38}H_{42}N_2O_5S$: 638.2814, found: 638.2814.

Later fractions of the above chromatography gave **12b** (310 mg, 5%) as a colorless oil, $[\alpha]_D^{25}$ +40.2° (c = 0.50, $CHCl_3$); MS *m/z*: 638 (M^+); IR ν_{max}^{film} cm^{-1}: 1694 (C=N); ^1H NMR ($CDCl_3$) δ: 0.70 and 1.03 (3H each, d, J = 7 Hz, $CH\underline{Me}_2$), 2.05 (1H, m, $C\underline{H}Me_2$), 2.84 (1H, dd, J = 13, 9 Hz) and 3.36 (1H, dd, J = 13, 5 Hz) [C(5)-CH_2], 3.60, 3.67, and 3.74 (3H each, s, three OMe's), 3.82 and 3.84 (1H each, d, J = 12 Hz, SCH_2), 3.85 [1H, dd, J = 4.5 Hz each, C(2)-H], 4.19 [1H, ddd, J = 9, 5, 4.5 Hz, C(5)-H], 5.00 and 5.12 (2H each, s, two $OC\underline{H}_2Ph$'s), 6.51 and 6.55 [1H each, d, J = 2.5 Hz, C(4')-H and C(6')-H], 6.68 [2H, d, J = 8.5 Hz, C(3")-H and C(5")-H], 6.95 [2H, d, J = 8.5 Hz, C(2")-H and C(6")-H], 7.3–7.55 (10H, m, two Ph's);[27]

HRMS *m/z* calcd for $C_{38}H_{42}N_2O_5S$: 638.2814, found: 638.2814.

3,5-Dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]-D-phenylalanine Methyl Ester [(*R*)-11a]. Hydrolysis of **10a** (4.78 g, 9.8 mmol) with 0.25 N aqueous HCl (80 ml) in MeOH (80 ml) and work-up of the reaction mixture were carried out as reported previously[9] for the synthesis of (*S*)-**11a**, affording (*R*)-**11a** (3.74 g, 97%) as a slightly yellow solid, mp 50–51 °C. The enantiomeric purity of this sample was determined to be 96% ee.[11] Recrystallization of the solid from hexane–AcOEt (3:1) yielded an analytical sample as colorless fluffy needles, mp 51–52 °C; $[\alpha]_D^{21}$ −8.9° (*c* = 0.92, MeOH). *Anal.* Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.21; H, 6.54; N, 3.75. The IR, ^{1}H NMR, and mass spectra of this sample were identical with those of (*S*)-**11a**.[9]

3,5-Dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]-L-phenylalanine Methyl Ester [(*S*)-11a]. Hydrolysis of **12a** (460 mg, 0.95 mmol) with 0.25 N aqueous HCl (8 ml) and work-up of the reaction mixture were effected in a manner similar to that reported previously[9] for the synthesis of (*S*)-**11a** from *ent*-**10a**, giving (*S*)-**11a** (355 mg, 96%) as a colorless solid, mp 49.5–51 °C. This sample was identical (by comparison of the IR and ^{1}H NMR spectra and optical rotation) with authentic (*S*)-**11a**.[9]

3,5-Bis(benzyloxy)-2-[[(4-methoxyphenyl)methyl]thio]-D-phenylalanine Methyl Ester [(*R*)-11b]. A mixture of **10b** (1.66 g, 2.6 mmol) and 0.25 N aqueous HCl (21 ml) in MeOH (45 ml) was stirred at room temperature for 9 h. The reaction mixture was concentrated *in vacuo* and the residue, after addition of H_2O (20 ml), was made basic with 10% aqueous Na_2CO_3 and extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (2:1)] provided (*R*)-**11b** (1.12 g, 79%) as a colorless solid. Recrystallization from AcOEt–hexane (1:1) furnished an analytical sample as colorless needles, mp 90–91 °C; $[\alpha]_D^{22}$ −3.2° (*c* = 0.99, MeOH); MS *m/z*: 543 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3360, 3270 (NH_2), 1732 (ester CO); ^{1}H NMR ($CDCl_3$) δ: 1.48 (2H, s, NH_2), 2.83 (1H, dd, *J* = 13, 9 Hz) and 3.13 (1H, dd, *J* = 13, 5.5 Hz) (Ar$C\underline{H}_2$CH), 3.60 (1H, dd, *J* = 9, 5.5 Hz, ArCH$_2$C$\underline{H}$), 3.67 and 3.75 (3H each, s, two OMe's), 3.87 and 3.90 (1H each, d, *J* = 12 Hz, SCH_2), 5.01 and 5.13 (2H each, s, two O$C\underline{H}_2$Ph's), 6.44 and 6.56 [1H each, d, *J* = 2.5 Hz, C(4)-H and C(6)-H], 6.69 [2H, d, *J* = 8.5 Hz, C(3')-H and C(5')-H], 6.96 [2H, d, *J* = 8.5 Hz, C(2')-H and C(6')-H], 7.3–7.55 (10H, m, two Ph's).[24] *Anal.* Calcd for $C_{32}H_{33}NO_5S$: C, 70.69; H, 6.12; N, 2.58. Found: C, 70.61; H, 6.11; N, 2.64.

3,5-Bis(benzyloxy)-2-[[(4-methoxyphenyl)methyl]thio]-L-phenylalanine Methyl Ester [(*S*)-11b]. Hydrolysis of **12b** (214 mg, 0.33 mmol) with 0.25 N aqueous HCl (3.2 ml) and work-up of the reaction mixture were carried out as described above for (*R*)-**11b**, yielding (*S*)-**11b** (115 mg, 63%) as a colorless solid. Recrystallization from AcOEt–hexane (1:1) gave an analytical sample as colorless needles, mp 90–90.5 °C; $[\alpha]_D^{16}$ +3.1° (*c* = 1.00, MeOH). *Anal.* Calcd for $C_{32}H_{33}NO_5S$: C, 70.69; H, 6.12; N, 2.58. Found: C, 70.62; H, 6.12; N, 2.56. The IR, ^{1}H NMR, and mass spectra of this sample were identical with those of (*R*)-**11b**.

***N*-[(4-Methoxyphenyl)acetyl]-3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]-D-phenylalanine Methyl Ester (22a).** Condensation of (*R*)-**11a** (391 mg, 1.0 mmol) with 4-methoxyphenylacetyl chloride (185 mg, 1.0 mmol) and work-up of the reaction mixture were performed as described previously[7] for the synthesis of *ent*-**22a**, giving **22a** (518 mg, 96%) as a slightly pinkish solid. Recrystallization of the solid from AcOEt–hexane (1:1) provided an analytical sample as colorless minute needles, mp 120–121 °C; $[\alpha]_D^{25}$ −19.0° (*c* = 0.50, $CHCl_3$). *Anal.* Calcd for $C_{29}H_{33}NO_7S$: C, 64.55; H, 6.16; N, 2.60. Found: C, 64.57; H, 6.15; N, 2.58. The IR, ^{1}H NMR, and mass spectra of this specimen were identical with those of *ent*-**22a**.[7]

***N*-[[4-(Benzyloxy)phenyl]acetyl]-3,5-bis(benzyloxy)-2-[[(4-methoxyphenyl)methyl]thio]-D-phenylalanine Methyl Ester (22b).** A mixture of 4-benzyloxyphenylacetic acid[28] (2.81 g, 11.6 mmol) and PCl_5 (2.42 g, 11.6 mmol) in hexane (20 ml) was heated under reflux for 30 min. After cooling, the mixture was decanted, and the residual colorless precipitate was washed with four 5-ml portions of hexane and dissolved in benzene (85 ml).

In a separate flask, a mixture of a solution of (*R*)-**11b** (5.26 g, 9.7 mmol) in benzene (100 ml) and a

solution of Na_2CO_3 (1.54 g, 14.5 mmol) in H_2O (100 ml) was stirred under ice-cooling, and the above benzene solution of the acid chloride was added dropwise over 10 min. After the mixture had been stirred at 8–10 °C for 1 h, the aqueous layer was separated from the benzene layer and 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 a colorless solid. Recrystallization from AcOEt–hexane (1:1) gave a first crop (6.04 g) of **22b**. Concentration of the mother liquor and recrystallization of the residue afforded a second crop (0.98 g) of **22b**. Total yield of **22b** was 7.02 g (94%). Further recrystallization from the same solvent system provided an analytical sample as colorless minute needles, mp 132.5–134 °C; $[\alpha]_D^{20}$ –8.4° (c = 0.50, $CHCl_3$); MS m/z: 767 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1736 (ester CO), 1653 (amide CO); ^1H NMR ($CDCl_3$) δ: 2.99 (1H, dd, J = 14, 9 Hz) and 3.10 (1H, dd, J = 14, 5.5 Hz) ($ArCH_2CH$), 3.40 (2H, s, $ArCH_2CO$), 3.67 and 3.73 (3H each, s, two OMe's), 3.80 and 3.81 (1H each, d, J = 12.5 Hz, SCH_2), 4.72 (1H, ddd, J = 9, 8, 5.5 Hz, $ArCH_2CH$), 4.92, 4.94, and 5.11 (2H each, s, three OCH_2Ph's), 5.77 (1H, d, J = 8 Hz, NH), 6.33 and 6.53 [1H each, d, J = 2.5 Hz, C(4)-H and C(6)-H], 6.67, 6.84, 6.93, and 7.03 (2H each, d, J = 8.5 Hz, 4-$MeOC_6H_4$ and 4-$PhCH_2OC_6H_4$), 7.3–7.55 (15H, m, three Ph's). *Anal.* Calcd for $C_{47}H_{45}NO_7S$: C, 73.51; H, 5.91; N, 1.82. Found: C, 73.54; H, 5.83; N, 1.73.

(1*R*,3*R*)-6,8-Dimethoxy-1-[(4-methoxyphenyl)methyl]-5-[[(4-methoxyphenyl)methyl]-thio]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (23a). A mixture of hexamethyldisiloxane (37.6 g, 0.232 mol), P_2O_5 (19.2 g, 0.135 mol), and dry $CHCl_3$ (100 ml) was heated under reflux in an atmosphere of Ar for 30 min.[16] After addition of **22a** (10.4 g, 19.3 mmol), the mixture was heated gently under reflux for a further 10 h. The reaction mixture was poured into cold 10% aqueous Na_2CO_3 (250 ml), and the aqueous layer was separated from the $CHCl_3$ layer and extracted with $CHCl_3$. The $CHCl_3$ extracts and the original $CHCl_3$ layer were combined, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to leave a pale yellow jelly. The jelly was dissolved in MeOH (300 ml), and the solution was cooled to –78 °C. $NaBH_4$ (1.46 g, 38.6 mmol) was added in small portions, and the mixture was stirred at –78 °C for 1 h. After addition of acetone (10 ml), the reaction mixture was warmed to room temperature and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (1:1)] furnished **23a** (8.16 g, 81%) as a colorless solid. The enantiomeric purity of this solid was found to be 91% ee.[11] Recrystallization of the solid from MeOH gave an analytical sample as colorless needles, mp 134–135.5 °C; $[\alpha]_D^{28}$ +230° (c = 0.29, $CHCl_3$). *Anal.* Calcd for $C_{29}H_{33}NO_6S$: C, 66.52; H, 6.35; N, 2.67. Found: C, 66.35; H, 6.39; N, 2.67. The IR, ^1H NMR, and mass spectra of this sample were identical with those of *ent*-**23a**.[7]

(1*R*,3*R*)-6,8-Bis(benzyloxy)-1-[[4-(benzyloxy)phenyl]methyl]-5-[[(4-methoxyphenyl)-methyl]thio]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (23b). Cyclization of **22b** (2.15 g, 2.8 mmol) with PPSE, work-up of the reaction mixture, and subsequent reduction with $NaBH_4$ (159 mg, 4.2 mmol) were carried out as described above for **23a**, giving a crude orange oil. Purification of the oil by flash chromatography [hexane–AcOEt (3:2)] produced **23b** (1.67 g, 79%) as a pale yellow solid. Recrystallization of the solid from MeOH furnished an analytical sample as colorless needles, mp 76.5–77.5 °C; $[\alpha]_D^{19}$ +176° (c = 0.25, $CHCl_3$); MS m/z: 751 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 1734 (ester CO); ^1H NMR ($CDCl_3$) δ: 2.18 [1H, dd, J = 16, 11 Hz, C(4)-H_α], 2.65 (1H, dd, J = 13.5, 8 Hz) and 3.27 (1H, dd, J = 13.5, 3 Hz) [C(1)-CH_2], 3.13 [1H, dd, J = 11, 2.5 Hz, C(3)-H], 3.27 [1H, dd, J = 16, 2.5 Hz, C(4)-H_β], 3.71 and 3.72 (3H each, s, two OMe's), 3.78 and 3.83 (1H each, d, J = 12.5 Hz, SCH_2), 4.46 [1H, dd, J = 8, 3 Hz, C(1)-H], 4.99 (2H, s), 5.06 (2H, s), 5.14 (1H, d, J = 12.5 Hz), and 5.15 (1H, d, J = 12.5 Hz) (three OCH_2Ph's), 6.55 [1H, s, C(7)-H], 6.67, 6.78, 6.89, and 6.91 (2H each, d, J = 8.5 Hz, 4-$MeOC_6H_4$ and 4-$PhCH_2OC_6H_4$), 7.3–7.5 (15H, m, three Ph's). *Anal.* Calcd for $C_{47}H_{45}NO_6S$: C, 75.07; H, 6.03; N, 1.86. Found: C, 75.06; H, 5.98; N, 1.82. The enantiomeric purity of this analytical sample was >98% ee.[11]

(1*R*,3*R*)-3-Hydroxymethyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-5-[[(4-methoxyphenyl)methyl]thio]-1,2,3,4-tetrahydroisoquinoline (24a). Reduction of **23a** (2.10 g, 4.0

mmol) with $LiAlH_4$ (228 mg, 6.0 mmol) and work-up of the reaction mixture were performed as described previously[7] for the synthesis of *ent*-**24a**, giving **24a** (1.80 g, 91%) as a colorless solid. Recrystallization from EtOH produced an analytical sample as colorless minute needles, mp 169.5–173.5 °C; $[\alpha]_D^{20}$ +234° (*c* = 0.25, $CHCl_3$). *Anal.* Calcd for $C_{28}H_{33}NO_5S$: C, 67.85; H, 6.71; N, 2.83. Found: C, 67.93; H, 6.74; N, 2.80. The IR, ^1H NMR, and mass spectra of this sample were identical with those of *ent*-**24a**.[7]

(1*R*,3*R*)-6,8-Bis(benzyloxy)-1-[[4-(benzyloxy)phenyl]methyl]-3-hydroxymethyl-5-[[(4-methoxyphenyl)methyl]thio]-1,2,3,4-tetrahydroisoquinoline (24b). A suspension of $LiAlH_4$ (90 mg, 2.4 mmol) in THF (18 ml) was stirred under ice-cooling, and a solution of **23b** (1.18 g, 1.6 mmol) in THF (20 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) (1.8 ml) was added under ice-cooling. Stirring was continued at room temperature for 30 min, and the insoluble material was filtered off. The filtrate was concentrated *in vacuo* to leave a pale yellow solid, which was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated. Recrystallization of the residual solid from AcOEt–hexane (2:1) gave a first crop (821 mg) of **24b**. A second crop (173 mg) of **24b** was obtained by concentration of the mother liquor and subsequent purification of the residue by flash chromatography [AcOEt–hexane (3:1)]. Total yield of **24b** was 994 mg (87%). Further recrystallization from AcOEt-hexane (2:1) provided an analytical sample as colorless needles, mp 153.5–156.5 °C; $[\alpha]_D^{26}$ +182° (*c* = 0.25, $CHCl_3$); MS *m/z*: 723 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH and OH); ^1H NMR ($CDCl_3$) δ: 1.91 [1H, dd, *J* = 16, 11 Hz, C(4)-H_α], 2.49 [1H, m, C(3)-H], 2.63 (1H, dd, *J* = 13.5, 8 Hz) and 3.15 (1H, dd, *J* = 13.5, 3.5 Hz) [C(1)-CH_2], 2.89 [1H, dd, *J* = 16, 2.5 Hz, C(4)-H_β], 3.30 (1H, dd, *J* = 10.5, 6 Hz) and 3.51 (1H, dd, *J* = 10.5, 3.5 Hz) ($C\underline{H}_2OH$), 3.72 (3H, s, OMe), 3.78 and 3.81 (1H each, d, *J* = 12.5 Hz, SCH_2), 4.46 [1H, dd, *J* = 8, 3.5 Hz, C(1)-H], 4.99 (2H, s), 5.04 (2H, s), 5.15 (1H, d, *J* = 12 Hz), and 5.16 (1H, d, *J* = 12 Hz) (three $OC\underline{H}_2Ph$'s), 6.53 [1H, s, C(7)-H], 6.67, 6.77, 6.85, and 6.90 (2H each, d, *J* = 8.5 Hz, 4-$MeOC_6\underline{H}_4$ and 4-$PhCH_2OC_6\underline{H}_4$), 7.3–7.5 (15H, m, three Ph's). *Anal.* Calcd for $C_{46}H_{45}NO_5S$: C, 76.32; H, 6.27; N, 1.93. Found: C, 76.29; H, 6.27; N, 1.90.

(5*R*,10a*R*)-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 (25a). A 1.0 M solution (7.2 ml, 7.2 mmol) of NaOEt in absolute EtOH and diethyl carbonate (4.4 ml, 36 mmol) were added to a stirred suspension of **24a** (1.78 g, 3.6 mmol) in absolute EtOH (50 ml) in an atmosphere of N_2, and the resulting mixture was heated under reflux for 20 h. The reaction mixture was worked up as reported previously[7] for the synthesis of *ent*-**25a**, furnishing **25a** (1.84 g, 98%) as a colorless foam, $[\alpha]_D^{22}$ +323° (*c* = 0.25, $CHCl_3$). The IR, ^1H NMR, and mass spectra of this sample were identical with those of *ent*-**25a**.[7]

(5*R*,10a*R*)-6,8-Bis(benzyloxy)-5-[[4-(benzyloxy)phenyl]methyl]-9-[[(4-methoxyphenyl)methyl]thio]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (25b). A solution of **24b** (1.06 g, 1.5 mmol) in absolute EtOH (45 ml) was stirred in an atmosphere of N_2, and a 1.0 M solution (2.9 ml, 2.9 mmol) of NaOEt in absolute EtOH and diethyl carbonate (3.5 ml, 29 mmol) were added. The resulting mixture was then heated under reflux for 23 h. After addition of AcOH (1 ml), the reaction mixture was concentrated *in vacuo*, and the residue was partitioned between CH_2Cl_2 and 10% aqueous HCl. The CH_2Cl_2 extracts were washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated. Purification of the residual oil by flash chromatography [hexane–AcOEt (2:1)] afforded **25b** (1.04 g, 95%) as a colorless solid. Recrystallization from EtOH produced an analytical sample as colorless minute needles, mp 155 °C (sintered at 113 °C); $[\alpha]_D^{27}$ +262° (*c* = 0.25, $CHCl_3$); FABMS *m/z*: 750 (MH^+); IR ν_{max}^{Nujol} cm^{-1}: 1767 (oxazolidinone CO); ^1H NMR ($CDCl_3$) δ: 0.62 [1H, dd, *J* = 15, 11.5 Hz, C(10)-H_α], 2.84 (1H, dd, *J* = 13.5, 2 Hz) and 3.58 (1H, dd, *J* = 13.5, 5 Hz) [C(5)-CH_2], 2.91 [1H, dd, *J* = 15, 3 Hz, C(10)-H_β], 3.16 [1H, dddd, *J* = 11.5, 11, 8, 3 Hz, C(10a)-H], 3.44 (1H, dd, *J* = 11, 8 Hz) and 4.10 (1H, dd, *J* = 8 Hz each) [C(1)-H's], 3.63 and 3.74 (1H each, d, *J* = 12.5 Hz, SCH_2), 3.72 (3H, s, OMe), 4.92, 4.94, 5.16, and 5.20 (1H each, d, *J* = 12 Hz) and 5.08 (2H, s) (three $OC\underline{H}_2Ph$'s), 5.33 [1H, dd, *J* = 5, 2 Hz, C(5)-H], 6.44, 6.657, 6.659, and 6.86 (2H each, d, *J* = 8.5 Hz, 4-$MeOC_6\underline{H}_4$ and 4-$PhCH_2OC_6\underline{H}_4$), 6.59 [1H, s, C(7)-H], 7.25–7.5 (15H, m, three Ph's). *Anal.* Calcd for $C_{47}H_{43}NO_6S$: C,

75.28; H, 5.78; N, 1.87. Found: C, 75.24; H, 5.70; N, 1.86.

(5*R*,10a*R*)-9-Mercapto-6,8-dimethoxy-5-[(4-methoxyphenyl)methyl]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (26a). Deprotection of **25a** (1.82 g, 3.5 mmol) with mercuric trifluoroacetate (2.24 g, 5.3 mmol) in the presence of anisole (1.9 ml, 17.5 mmol) and work-up of the reaction mixture were effected as reported previously[7] for the synthesis of *ent*-**26a**, affording **26a** (1.33 g, 95%) as a colorless glass, $[\alpha]_D^{23}$ +236° (*c* = 0.25, $CHCl_3$). The IR, ^1H NMR, and mass spectra of this glass were identical with those of *ent*-**26a**.[7]

(5*R*,10a*R*)-6,8-Bis(benzyloxy)-5-[[4-(benzyloxy)phenyl]methyl]-9-mercapto-1,5,10,-10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (26b). A mixture of **25b** (885 mg, 1.2 mmol), anisole (643 mg, 5.9 mmol), mercuric trifluoroacetate (779 mg, 1.8 mmol), and absolute EtOH (70 ml) was stirred at room temperature for 19 h. After addition of $NaBH_4$ (180 mg, 4.8 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 filtered off, 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 over anhydrous $MgSO_4$, and concentrated. Purification of the residual yellow oil by flash chromatography [hexane–AcOEt (2:1)] provided **26b** (644 mg, 87%) as a colorless foam, $[\alpha]_D^{26}$ +232° (*c* = 0.25, $CHCl_3$); FABMS *m/z*: 630 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2590 (SH), 1742 (oxazolidinone CO); ^1H NMR ($CDCl_3$) δ: 0.70 [1H, dd, *J* = 14.5, 11.5 Hz, C(10)-H_α], 2.66 [1H, dd, *J* = 14.5, 3.5 Hz, C(10)-H_β], 2.84 (1H, dd, *J* = 13.5, 2.5 Hz) and 3.66 (1H, dd, *J* = 13.5, 5 Hz) [C(5)-CH_2], 3.52 (1H, dd, *J* = 11, 8 Hz) and 4.30 (1H, dd, *J* = 8 Hz each) [C(1)-H's], 3.70 [1H, dddd, *J* = 11.5, 11, 8, 3.5 Hz, C(10a)-H], 3.83 (1H, s, SH), 5.02 (2H, s) and 5.06, 5.09, 5.11, and 5.16 (1H each, d, *J* = 11.5 Hz) (three $OC\underline{H}_2Ph$'s), 5.39 [1H, dd, *J* = 5, 2.5 Hz, C(5)-H], 6.43 [2H, d, *J* = 8.5 Hz, C(3')-H and C(5')-H], 6.59 [1H, s, C(7)-H], 6.71 [2H, d, *J* = 8.5 Hz, C(2')-H and C(6')-H], 7.25–7.45 (15H, m, three Ph's);[24] HRFABMS *m/z* calcd for $C_{39}H_{36}NO_5S$: 630.2314, found: 630.2332.

(5*R*,10a*R*)-9-[(5-Formyl-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 (28a). Coupling of **26a** (1.32 g, 3.3 mmol) with 4-bromo-1-methyl-1*H*-imidazole-5-carbaldehyde (**27**)[6] (686 mg, 3.6 mmol) and work-up of the reaction mixture were performed as described previously[7] for the synthesis of *ent*-**28a**, yielding **28a** (1.14 g, 68%) as a pale yellow foam, $[\alpha]_D^{20}$ +104° (*c* = 0.25, $CHCl_3$). The IR, ^1H NMR, and mass spectra of this specimen were identical with those of *ent*-**28**.[7]

(5*R*,10a*R*)-6,8-Bis(benzyloxy)-5-[[4-(benzyloxy)phenyl]methyl]-9-[(5-formyl-1-methyl-1*H*-imidazol-4-yl)thio]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (28b). To a stirred mixture of **26b** (503 mg, 0.80 mmol) and an oil dispersion (38 mg) containing 60% NaH (0.95 mmol) in DMF (6 ml) in an atmosphere of Ar was added a solution of **27**[6] (166 mg, 0.88 mmol) in DMF (6 ml). The resulting mixture was then heated at 100 °C for 3.5 h. After cooling, the reaction mixture was concentrated *in vacuo*, and the residue was partitioned between AcOEt and H_2O. The AcOEt extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a brown oil, which was purified by flash chromatography [AcOEt–hexane (2:1)] to provide **28b** (328 mg, 56%) as a slightly yellow foam, $[\alpha]_D^{28}$ +134° (*c* = 0.25, $CHCl_3$); FABMS *m/z*: 738 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1744 (oxazolidinone CO), 1664 (aldehyde CO); ^1H NMR ($CDCl_3$) δ: 0.84 [1H, dd, *J* = 15, 11.5 Hz, C(10)-H_α], 2.87 (1H, dd, *J* = 13.5, 2.5 Hz) and 3.68 (1H, dd, *J* = 13.5, 5 Hz) [C(5)-CH_2], 3.41 [1H, dd, *J* = 15, 3 Hz, C(10)-H_β], 3.56 (1H, dd, *J* = 11, 8 Hz) and 4.32 (1H, dd, *J* = 8 Hz each) [C(1)-H's], 3.73 (3H, s, NMe), 3.77 [1H, dddd, *J* = 11.5, 11, 8, 3 Hz, C(10a)-H], 5.00 (2H, s) and 5.01, 5.07, 5.10, and 5.12 (1H each, d, *J* = 11.5 Hz) (three $OC\underline{H}_2Ph$'s), 5.39 [1H, dd, *J* = 5, 2.5 Hz, C(5)-H], 6.46 [2H, d, *J* = 9 Hz, C(3')-H and C(5')-H], 6.59 [1H, s, C(7)-H], 6.63 [2H, d, *J* = 9 Hz, C(2')-H and C(6')-H], 7.25–7.45 (16H, m, imidazole ring proton and three Ph's), 9.87 (1H, s, CHO);[24] HRFABMS *m/z* calcd for $C_{44}H_{40}N_3O_6S$: 738.2637, found: 738.2651.

(5*R*,10a*R*)-9-[(5-Hydroxymethyl-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 (29a). Reduction of **28a** (1.12 g, 2.2 mmol) with $NaBH_4$ (84 mg, 2.2 mmol) and work-up of the reaction

mixture were effected as reported previously[7] for the synthesis of *ent*-**29a**, giving **29a** (899 mg, 80%). Recrystallization from MeOH afforded an analytical sample as colorless prisms, mp 249–250 °C; $[\alpha]_D^{21}$ +90.4° (c = 0.26, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{29}N_3O_6S$: C, 61.04; H, 5.71; N, 8.21. Found: C, 60.95; H, 5.70; N, 8.19. The IR, ^1H NMR, and mass spectra of this sample were identical with those of ***ent*-29a**.[7]

(5*R*,10a*R*)-6,8-Bis(benzyloxy)-5-[[4-(benzyloxy)phenyl]methyl]-9-[(5-hydroxymethyl-1-methyl-1*H*-imidazol-4-yl)thio]-1,5,10,10a-tetrahydroxazolo[3,4-*b*]isoquinolin-3(3*H*)-one (29b). To a stirred solution of **28b** (328 mg, 0.44 mmol) in MeOH (13 ml) was added $NaBH_4$ (18.5 mg, 0.49 mmol), and the mixture was stirred at room temperature for 1 h. After addition of acetone (2 ml), the reaction mixture was concentrated *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, and concentrated. Purification of the residue by flash chromatography [AcOEt–EtOH (10:1)] furnished **29b** (295 mg, 90%) as a colorless foam, $[\alpha]_D^{21}$ +107° (c = 0.25, $CHCl_3$); FABMS *m/z*: 740 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (OH), 1743 (oxazolidinone CO); ^1H NMR ($CDCl_3$) δ: 0.93 [1H, dd, J = 15, 11.5 Hz, C(10)-Hα], 1.68 (1H, br, OH), 2.85 (1H, dd, J = 13.5, 2.5 Hz) and 3.66 (1H, dd, J = 13.5, 5 Hz) [C(5)-CH_2], 3.49 (3H, s, NMe), 3.63 (1H, dd, J = 11, 8 Hz) and 4.37 (1H, dd, J = 8 Hz each) [C(1)-H's], 3.77 [1H, dddd, J = 11.5, 11, 8, 3 Hz, C(10a)-H], 3.86 [1H, dd, J = 15, 3 Hz, C(10)-Hβ], 4.54 (2H, br, CH_2OH), 5.00 (2H, s) and 5.03, 5.06, 5.08, and 5.14 (1H each, d, J = 11.5 Hz) (three OCH_2Ph's), 5.36 [1H, dd, J = 5, 2.5 Hz, C(5)-H], 6.40 [2H, d, J = 9 Hz, C(3')-H and C(5')-H], 6.54 [1H, s, C(7)-H], 6.57 [2H, d, J = 9 Hz, C(2')-H and C(6')-H], 7.19 (1H, s, imidazole ring proton), 7.3–7.45 (15H, m, three Ph's);[24] HRFABMS *m/z* calcd for $C_{44}H_{42}N_3O_6S$: 740.2794, found: 740.2784.

(5*R*,10a*R*)-9-[[5-[[(2*R*-*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 (30a) and (5*R*,10a*R*)-9-[[5-[[(2*R*-*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 (31a). Chlorination of **29a** (835 mg, 1.6 mmol) with $SOCl_2$, followed by alkylation of (*R*)-**9**, prepared from (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[26] (903 mg, 4.9 mmol), with the resulting chloride and work-up of the reaction mixture were carried out as reported previously[7] for the syntheses of *ent*-**30a** and *ent*-**31a**, affording **30a** (642 mg, 58%) [$[\alpha]_D^{21}$ +31.0° (c = 0.36, $CHCl_3$)] and **31a** (375 mg, 34%) [$[\alpha]_D^{21}$ +8.0° (c = 0.37, $CHCl_3$)]. The IR, ^1H NMR, and mass spectra of these samples were identical with those of *ent*-**30a** and *ent*-**31a**, respectively.[7]

(5*R*,10a*R*)-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 (*ent*-5). Hydrolysis of **30a** (605 mg, 0.89 mmol) with 0.25 N aqueous HCl (16 ml) in MeOH (8 ml) and work-up of the reaction mixture were performed as reported previously[7] for the synthesis of **5**, yielding *ent*-**5** (473 mg, 91%) as a colorless glass, $[\alpha]_D^{18}$ +91.0° (c = 0.29, $CHCl_3$). The IR, ^1H NMR, and mass spectra of this glass were identical with those of **5**.[7]

(5*R*,10a*R*)-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 (*ent*-6). Hydrolysis of **31a** (326 mg, 0.48 mmol) with 0.25 N aqueous HCl (8 ml) in MeOH (4 ml) was carried out at room temperature for 2.5 h. Work-up of the reaction mixture in a manner similar to that described previously[7] for the synthesis of **6** gave *ent*-**6** (253 mg, 90%) as a colorless glass, $[\alpha]_D^{18}$ +71.4° (c = 0.26, $CHCl_3$). The IR, ^1H NMR, and mass spectra of this sample were identical with those of **6**.[7]

(1*R*,3*R*)-5-[[3-Hydroxymethyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-L-histidine Methyl Ester (32). A mixture of *ent*-**5** (442 mg, 0.76 mmol) and 6 N aqueous HCl (8 ml) was heated at 100 °C for 1 h. The reaction mixture was concentrated *in vacuo* to leave a slightly yellow solid, which was dissolved in a mixture of 2 N aqueous NaOH (6 ml) and MeOH (6 ml). The resulting solution was then heated at 80–85 °C for 60 h. After cooling, 6 N aqueous HCl (2 ml) was added, and the mixture was concentrated *in vacuo*. An insoluble material, after

addition of MeOH, was removed by filtration and washed with MeOH. The filtrate and washings were combined and concentrated *in vacuo*. The pale yellow solid that resulted was taken up in 10% HCl–MeOH (16 ml). After heating under reflux for 7 h, the reaction mixture was concentrated *in vacuo* to leave a yellowish oil, which was dissolved in H_2O, made basic with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated. Purification of the residual oil by flash chromatography [$CHCl_3$–MeOH (3:1)] gave **32** (307 mg, 73%) as a colorless glass, $[\alpha]_D^{18}$ +102° (*c* = 0.50, $CHCl_3$); MS *m/z*: 555 (M^+–1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3630 (OH), 3380, 3320 (NH_2 and NH), 1736 (ester CO); ^1H NMR ($CDCl_3$) δ: 2.33 [1H, dd, *J* = 16.5, 11 Hz, C(4)-H_α], 2.73 (1H, dd, *J* = 13.5, 7.5 Hz) and 3.23 (1H, dd, *J* = 13.5, 3.5 Hz) [C(1)-CH_2], 2.90 [1H, m, C(3)-H], 2.92 (1H, dd, *J* = 15, 9 Hz) and 3.16 (1H, dd, *J* = 15, 5.5 Hz) [C(6')-H's], 3.50 [1H, dd, *J* = 16.5, 3 Hz, C(4)-H_β], 3.52 (1H, dd, *J* = 10.5, 6.5 Hz) and 3.72 (1H, dd, *J* = 10.5, 4.5 Hz) ($C\underline{H}_2OH$), 3.57, 3.76, 3.77, 3.87, and 3.88 (3H each, s, NMe and four OMe's), 3.74 [1H, dd, *J* = 9, 5.5 Hz, C(7')-H], 4.51 [1H, dd, *J* = 7.5, 3.5 Hz, C(1)-H], 6.39 [1H, s, C(7)-H], 6.74 [2H, d, *J* = 8.5 Hz, C(3")-H and C(5")-H], 6.99 [2H, d, *J* = 8.5 Hz, C(2")-H and C(6")-H], 7.30 [1H, s, C(2')-H];[29] HRFABMS *m/z* calcd for $C_{28}H_{37}N_4O_6S$: 557.2434, found: 557.2407.

(1*R*,3*R*)-5-[[3-Hydroxymethyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-D-histidine Methyl Ester (33). In a manner similar to that described above for **32**, this compound was prepared from *ent*-**6** (245 mg, 0.42 mmol) in 55% yield as a colorless glass, $[\alpha]_D^{18}$ +85.8° (*c* = 0.49, $CHCl_3$); MS *m/z*: 555 (M^+–1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3630 (OH), 3380, 3320 (NH_2 and NH), 1736 (ester CO); ^1H NMR ($CDCl_3$) δ: 2.35 [1H, dd, *J* = 16, 10.5 Hz, C(4)-H_α], 2.72 (1H, dd, *J* = 13.5, 7.5 Hz) and 3.23 (1H, dd, *J* = 13.5, 3 Hz) [C(1)-CH_2], 2.91 [1H, m, C(3)-H], 2.98 (1H, dd, *J* = 14.5, 9 Hz) and 3.13 (1H, dd, *J* = 14.5, 5.5 Hz) [C(6')-H's], 3.50 [1H, dd, *J* = 16, 2.5 Hz, C(4)-H_β], 3.52 (1H, dd, *J* = 11, 5.5 Hz) and 3.73 (1H, dd, *J* = 11, 4.5 Hz) ($C\underline{H}_2OH$), 3.57, 3.766, 3.770, 3.87, and 3.88 (3H each, s, NMe and four OMe's), 3.83 [1H, dd, *J* = 9, 5.5 Hz, C(7')-H], 4.52 [1H, dd, *J* = 7.5, 3 Hz, C(1)-H], 6.39 [1H, s, C(7)-H], 6.74 [2H, d, *J* = 8.5 Hz, C(3")-H and C(5")-H], 6.99 [2H, d, *J* = 8.5 Hz, C(2")-H and C(6")-H], 7.30 [1H, s, C(2')-H];[29] HRFABMS *m/z* calcd for $C_{28}H_{37}N_4O_6S$: 557.2434, found: 557.2435.

(1*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-5-[[2-(*tert*-butoxycarbonyl)-3-hydroxymethyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-L-histidine Methyl Ester (34). A mixture of **32** (295 mg, 0.53 mmol) and di-*tert*-butyl dicarbonate (347 mg, 1.6 mmol) in $CHCl_3$ (10 ml) was stirred at room temperature for 6 h. After concentration of the reaction mixture under reduced pressure, the residual oil was purified by flash chromatography [$CHCl_3$–MeOH (20:1)] to provide **34** (365 mg, 91%) as a colorless glass, $[\alpha]_D^{20}$ +88.0° (*c* = 0.57, $CHCl_3$); FABMS *m/z*: 757 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3355 (OH and NH), 1744 (ester CO), 1705, 1680 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.18 (9H, br s) and 1.34 (9H, s) (two *tert*-Bu's), 2.69 (1H, br), 2.90 (1H, br), 3.14 (1H, dd, *J* = 14.5, 5 Hz), and 3.4–4.0 (m) [C(1)-CH_2, $C\underline{H}_2OH$, C(4)-H's, and C(6')-H's], 3.58, 3.78, 3.81, and 3.88 (s each, NMe and four OMe's), 4.42 (br) and 4.54 (m) [1H each, C(3)-H and C(7')-H], 5.43 (1H, d, *J* = 8.5 Hz, NH), 5.58 [1H, br, C(1)-H], 6.33 [1H, br, C(7)-H], 6.81 [2H, br, C(3")-H and C(5")-H], 7.15 [2H, d, *J* = 8.5 Hz, C(2")-H and C(6")-H], 7.30 [1H, s, C(2')-H];[29] HRFABMS *m/z* calcd for $C_{38}H_{53}N_4O_{10}S$: 757.3482, found: 757.3485.

(1*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-5-[[2-(*tert*-butoxycarbonyl)-3-hydroxymethyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-D-histidine Methyl Ester (35). Protection of **33** (62 mg, 0.11 mmol) with di-*tert*-butyl dicarbonate (73 mg, 0.33 mmol) and work-up of the reaction mixture were performed as described above for **34**, giving **35** (82 mg, 97%) as a colorless glass, $[\alpha]_D^{20}$ +58.2° (*c* = 0.50, $CHCl_3$); FABMS *m/z*: 757 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3355 (OH and NH), 1746 (ester CO), 1703, 1680 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.15 (br s), 1.20 (s), and 1.31 (br) (18H, two *tert*-Bu's), 2.62 (1H, br), 2.97 (1H, br), 3.16 (1H, dd, *J* = 15, 6 Hz), and 3.4–4.0 (m) [C(1)-CH_2, $C\underline{H}_2OH$, C(4)-H's, and C(6')-H], 3.62, 3.79, 3.81, and 3.96 (s each, NMe and four OMe's), 4.56 [2H, br, C(3)-H and C(7')-H], 5.52 and 5.80 [1H each, br, C(1)-H and NH], 6.39 [1H, br s,

C(7)-H], 6.82 [2H, br, C(3")-H and C(5")-H], 7.18 [2H, d, J = 8.5 Hz, C(2")-H and C(6")-H], 7.31 [1H, s, C(2')-H];[29] HRFABMS m/z calcd for $C_{38}H_{53}N_4O_{10}S$: 757.3482, found: 757.3485.

(1*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-5-[[2-(*tert*-butoxycarbonyl)-3-formyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-L-histidine Methyl Ester (36). A solution of oxalyl chloride (175 mg, 1.4 mmol) in CH_2Cl_2 (3 ml) was cooled to –78 °C in an atmosphere of Ar, and a solution of DMSO (216 mg, 2.8 mmol) in CH_2Cl_2 (1 ml) was added. After the mixture had been stirred for 3 min, a solution of **34** (350 mg, 0.46 mmol) in CH_2Cl_2 (3 ml) was added dropwise. Stirring was then continued at –78 °C for a further 1 h. The reaction mixture, after addition of Et_3N (0.9 ml), was brought to room temperature and 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. Purification of the residue by flash chromatography [hexane–acetone (6:5)] furnished **36** (283 mg, 81%) as a colorless foam, $[\alpha]_D^{23}$ +35.6° (c = 0.50, $CHCl_3$); FABMS m/z: 755 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3360 (NH), 1736 (CHO), 1701, 1675 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.337, 1.342, and 1.38 (18H, s each, two *tert*-Bu's), 2.22 (3/5H, dd, J = 15, 13.5 Hz) and 2.44 (2/5H, dd, J = 16, 14.5 Hz) [C(4)-H_α], 2.8–3.0 [2H, m, C(1)-CH_2], 3.15 (dd, J = 14.5, 5 Hz), 3.16 (dd, J = 14.5, 5 Hz), 3.28 (dd, J = 14.5, 9 Hz), and 3.30 (dd, J = 14.5, 9 Hz) [2H, C(6')-H's], 3.58, 3.60, 3.70, 3.75, 3.77, 3.79, 3.88, and 3.91 (15H, s each, NMe and four OMe's), 3.94 (ddd, J = 13.5, 5.5, 3 Hz), 4.0–4.1 (m) and 4.12 (dd, J = 15, 5.5 Hz) [2H, C(3)-H and C(4)-H_β], 4.48 [1H, m, C(7')-H], 5.42 (2/5H, d, J = 8.5 Hz) and 5.46 (3/5H, d, J = 8.5 Hz) (NH), 5.50 (2/5H) and 5.71 (3/5H) [t each, J = 6.5 Hz, C(1)-H], 6.28 (3/5H) and 6.34 (2/5H) [s each, C(7)-H], 6.66 (6/5H) and 6.74 (4/5H) [d each, J = 8.5 Hz, C(3")-H and C(5")-H], 6.87 (6/5H) and 6.96 (4/5H) [d each, J = 8.5 Hz, C(2")-H and C(6")-H], 7.28 (2/5H) and 7.30 (3/5H) [s each, C(2')-H], 9.48 (3/5H, d, J = 3 Hz) and 9.61 (2/5H, d, J = 2.5 Hz) (CHO);[29] HRFABMS m/z calcd for $C_{38}H_{51}N_4O_{10}S$: 755.3326, found: 755.3323.

(1*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-5-[[2-(*tert*-butoxycarbonyl)-3-formyl-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-D-histidine Methyl Ester (37). Oxidation of **35** (100 mg, 0.13 mmol) with oxalyl chloride (50 mg, 0.39 mmol) and DMSO (61 mg, 0.78 mmol) and work-up of the reaction mixture were carried out as described above for **36**. Purification of a crude yellow glass by flash chromatography [$CHCl_3$–MeOH (20:1)] provided **37** (83 mg, 83%) as a colorless glass, $[\alpha]_D^{18}$ –5.9° (c = 0.50, $CHCl_3$); FABMS m/z: 755 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435, 3360 (NH), 1736 (CHO), 1701, 1675 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.35, 1.36, and 1.37 (18H, s each, two *tert*-Bu's), 2.26 (3/5H, dd, J = 15, 13 Hz) and 2.45 (2/5H, dd, J = 16.5, 14 Hz) [C(4)-H_α], 2.82 (2/5H, dd, J = 13.5, 7 Hz), 2.85 (2/5H, dd, J = 13.5, 6 Hz), 2.92 (3/5H, dd, J = 13.5, 6 Hz), and 2.95 (3/5H, dd, J = 13.5, 7 Hz) [C(1)-CH_2], 3.1–3.35 [2H, m, C(6')-H's], 3.58, 3.59, 3.70, 3.75, 3.775, 3.779, 3.784, 3.79, 3.87, and 3.90 (15H, s each, NMe and four OMe's), 3.85–4.1 [2H, m, C(3)-H and C(4)-H_β], 4.51 [1H, m, C(7')-H], 5.51 (2/5H) and 5.72 (3/5H) [dd each, J = 7, 6 Hz, C(1)-H], 5.52 (1H, d, J = 8.5 Hz, NH), 6.29 (3/5H) and 6.34 (2/5H) [s each, C(7)-H], 6.67 (6/5H) and 6.73 (4/5H) [d each, J = 8.5 Hz, C(3")-H and C(5")-H], 6.88 (6/5H) and 6.95 (4/5H) [d each, J = 8.5 Hz, C(2")-H and C(6")-H], 7.29 (2/5H) and 7.30 (3/5H) [s each, C(2')-H], 9.47 (3/5H, d, J = 3.5 Hz) and 9.59 (2/5H, d, J = 2.5 Hz) (CHO);[29] HRFABMS m/z calcd for $C_{38}H_{51}N_4O_{10}S$: 755.3326, found: 755.3327.

(1*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-5-[[2-(*tert*-butoxycarbonyl)-6,8-dimethoxy-3-(methoxycarbonyl)-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-L-histidine Methyl Ester (38). (i) From 36. A mixture of **36** (280 mg, 0.37 mmol), KOH (63 mg, 1.1 mmol), and iodine (122 mg, 0.48 mmol) in MeOH (8 ml) was stirred at 0 °C for 2 h. After further additions of a solution of KOH (63 mg, 1.1 mmol) in MeOH (1.5 ml) and a solution of iodine (122 mg, 0.48 mmol) in MeOH (1.5 ml), stirring was continued at 0 °C for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 extracts were washed successively with 2% aqueous $NaHSO_3$, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated to leave a slightly yellow glass. Purification by flash chromatography [acetone–hexane (1:1)] gave **38** (206 mg, 71%) as a colorless glass, $[\alpha]_D^{22}$ –15.3° (c = 0.50, $CHCl_3$); FABMS m/z: 785 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3360 (NH), 1746 (ester CO), 1701 (carbamate CO); ^1H NMR

($CDCl_3$) δ: 1.25, 1.26, 1.34, and 1.37 (18H, s each, two *tert*-Bu's), 2.70 (2/5H, dd, *J* = 13.5, 5.5 Hz), 2.77 (3/5H, dd, *J* = 13.5, 8.5 Hz), 3.09 (2/5H, dd, *J* = 13.5, 8 Hz), and 3.18 (3/5H, dd, *J* = 13.5, 6 Hz) [C(1)-CH_2], 2.90 (3/5H) and 2.99 (2/5H) [dd each, *J* = 15.5, 13 Hz, C(4)-H_α], 3.15 (1H, dd, *J* = 15, 5 Hz) and 3.33 (1H, dd, *J* = 15, 9.5 Hz) [C(6')-H's], 3.38, 3.58, 3.60, 3.62, 3.74, 3.78, 3.80, 3.82, 3.84, 3.85, and 3.89 (18H, s each, NMe and five OMe's), 4.20 (3/5H, dd, *J* = 13, 5.5 Hz) and 4.24 (2/5H, dd, *J* = 13, 6 Hz) [C(3)-H], 4.45–4.55 [2H, m, C(4)-H_β and C(7')-H], 5.42 (2/5H) and 5.46 (3/5H) (d each, *J* = 8.5 Hz, NH), 5.50 (2/5H, dd, *J* = 8, 5.5 Hz) and 5.67 (3/5H, dd, *J* = 8.5, 6 Hz) [C(1)-H], 6.17 (3/5H) and 6.29 (2/5H) [s each, C(7)-H], 6.68 (6/5H) and 6.79 (4/5H) [d each, *J* = 8.5 Hz, C(3")-H and C(5")-H], 7.01 (6/5H) and 7.19 (4/5H) [d each, *J* = 8.5 Hz, C(2")-H and C(6")-H], 7.29 (2/5H) and 7.32 (3/5H) [s each, C(2')-H];[29] HRFABMS *m/z* calcd for $C_{39}H_{53}N_4O_{11}S$: 785.3432, found: 785.3436.

(ii) From Imbricatine (2). A solution of **2** (6.3 mg, 12 μmol) in 12% methanolic HCl (2 ml) was heated under reflux for 3 h. The reaction mixture was concentrated *in vacuo* to leave a pale brown glass, which was dissolved in $CHCl_3$ (0.5 ml). The solution, after additions of Et_3N (55 μl, 0.39 mmol) and a solution of di-*tert*-butyl dicarbonate (25 mg, 0.11 mmol) in $CHCl_3$ (0.2 ml), was stirred at room temperature for 6 h. Concentration of the reaction mixture and purification of the residual pale brown solid by flash chromatography [acetone–hexane (1:1)] afforded a colorless solid (5.8 mg). A mixture of the solid, CsF–alumina[23] (40 mg), MeI (24 mg, 0.17 mmol), and CH_3CN (0.5 ml) was then stirred at room temperature for 1 h. An insoluble material was filtered off and washed with CH_3CN. The filtrate and washings were combined and concentrated *in vacuo* to leave a pale brown glass, which was purified by preparative TLC [silica gel, AcOEt–EtOH (10:1)] to provide **38** (2.9 mg, 30%) as a colorless glass, $[\alpha]_D^{24}$ −13.5° (*c* = 0.085, $CHCl_3$). This sample was identical [by comparison of the IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and mass spectra and TLC mobility in three solvent systems] with the one obtained by method-(i).

(1*R*,3*R*)-*N*-(*tert*-Butoxycarbonyl)-5-[[2-(*tert*-butoxycarbonyl)-6,8-dimethoxy-3-(methoxycarbonyl)-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-D-histidine Methyl Ester (39). Oxidation of **37** (78 mg, 0.10 mmol) with KOH and iodine in MeOH and work-up of the reaction mixture were performed as described above for **38**, giving **39** (68 mg, 84%) as a colorless glass, $[\alpha]_D^{20}$ −25.3° (*c* = 0.53, $CHCl_3$); FABMS *m/z*: 785 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435, 3360 (NH), 1746 (ester CO), 1703 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.25 and 1.36 (18H, s each, two *tert*-Bu's), 2.70 (2/5H, dd, *J* = 13, 6 Hz), 2.78 (3/5H, dd, *J* = 13, 8.5 Hz), 3.09 (2/5H, dd, *J* = 13, 8.5 Hz), and 3.18 (3/5H, dd, *J* = 13, 6.5 Hz) [C(1)-CH_2], 2.94 (3/5H) and 3.02 (2/5H) [dd each, *J* = 15.5, 13 Hz, C(4)-H_α], 3.15 and 3.31 [2H, m each, C(6')-H's], 3.39, 3.58, 3.59, 3.62, 3.74, 3.778, 3.784, 3.79, 3.82, 3.836, 3.842, and 3.88 (18H, s each, NMe and five OMe's), 4.17 [1H, dd, *J* = 13, 5.5 Hz, C(3)-H], 4.40 (2/5H) and 4.44 (3/5H) [dd each, *J* = 15.5, 5.5 Hz, C(4)-Hβ] 4.51 [1H, m, C(7')-H], 5.50 (2/5H) and 5.67 (3/5H) [dd each, *J* = 8.5, 6 Hz, C(1)-H], 5.58 and 5.59 (1H, d each, *J* = 8.5 Hz, NH), 6.18 (3/5H) and 6.29 (2/5H) [s each, C(7)-H], 6.69 (6/5H) and 6.79 (4/5H) [d each, *J* = 8.5 Hz, C(3")-H and C(5")-H], 7.03 (6/5H) and 7.20 (4/5H) [d each, *J* = 8.5 Hz, C(2")-H and C(6")-H], 7.31 (2/5H) and 7.33 (3/5H) [s each, C(2')-H];[29] HRFABMS *m/z* calcd for $C_{39}H_{53}N_4O_{11}S$: 785.3432, found: 785.3436.

(1*R*,3*R*)-5-[[6,8-Dimethoxy-3-(methoxycarbonyl)-1-[(4-methoxyphenyl)methyl]-1,2,-3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-L-histidine Methyl Ester (40). A solution of **38** (20.0 mg, 25 μmol) in CH_2Cl_2 (2 ml) was cooled to 0 °C, and CF_3CO_2H (1 ml) was added. After stirring at room temperature for 1.5 h, the reaction mixture was concentrated *in vacuo*. The residual pale yellow oil was dissolved in H_2O, made basic with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated. Purification of the residual oil by preparative TLC [silica gel, $CHCl_3$–MeOH (10:1)] furnished **40** (12.3 mg, 83%) as a colorless glass, $[\alpha]_D^{25}$ +55.0° (*c* = 0.44, $CHCl_3$); FABMS *m/z*: 585 (MH^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390, 3330 (NH and NH_2), 1736 (ester CO); ^1H NMR ($CDCl_3$) δ: 2.44 [1H, dd, *J* = 16.5, 11 Hz, C(4)-H_α], 2.65 (1H, dd, *J* = 13.5, 8 Hz) and 3.34 (1H, dd, *J* = 13.5, 3 Hz) [C(1)-CH_2], 2.87 (1H, dd, *J* = 14.5, 9 Hz) and 3.17 (1H, dd, *J* = 14.5, 5.5 Hz) [C(6')-H's], 3.46 [1H, dd, *J* = 11, 3 Hz, C(3)-H], 3.56, 3.72, 3.75, 3.78, 3.887, and 3.889 (3H each, s, NMe and five OMe's), 3.7–3.8 [2H, m, C(4)-Hβ and C(7')-H], 4.43 [1H, dd, *J* = 8, 3 Hz, C(1)-H], 6.42

[1H, s, C(7)-H], 6.77 [2H, d, J = 8.5 Hz, C(3")-H and C(5")-H], 7.05 [2H, d, J = 8.5 Hz, C(2")-H and C(6")-H], 7.30 [1H, s, C(2')-H];[29] HRFABMS *m/z* calcd for $C_{29}H_{37}N_4O_7S$: 585.2383, found: 585.2394.

(1*R*,3*R*)-5-[[3-Carboxy-6,8-dimethoxy-1-[(4-methoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-5-yl]thio]-3-methyl-L-histidine (Tri-*O*-methylimbricatine) (3). A solution of **40** (16.5 mg, 28 μmol) in 3 N aqueous HCl (1.5 ml) was heated under reflux for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was co-evaporated *in vacuo* with two 3-ml portions of H_2O to leave a pale yellow solid, which was dissolved in H_2O (0.4 ml). The aqueous solution was applied to a column of Dowex 50W-X8 (H^+ form in H_2O). The column was first eluted with H_2O until the eluate became neutral, and then with H_2O–pyridine (3:2). The aqueous pyridine eluates were combined and concentrated *in vacuo* to leave a colorless solid. Purification of the solid by preparative TLC [silica gel, $CHCl_3$–MeOH–H_2O (6:6:1)] provided **3** (12.2 mg, 78%) as a colorless solid, $[\alpha]_D^{25}$ +62.2° (c = 0.67, MeOH); FABMS *m/z*: 557 (MH^+); IR ν_{max}^{KBr} cm^{-1}: 1635, 1588 (CO_2^-); ^1H NMR [(Me_2SO-d_6–D_2O (7:1)] δ: 2.77 [1H, dd, J = 16.5, 12.5 Hz, C(4)-Hα], 2.88 (1H, dd, J = 14, 8.5 Hz) and 3.10 (1H, dd, J = 14, 5 Hz) [C(1)-CH_2], 2.96 (1H, dd, J = 15, 9 Hz) and 3.33 (1H, dd, J = 15, 6.5 Hz) [C(6')-H's], 3.19 [1H, dd, J = 12.5, 4.5 Hz, C(3)-H], 3.53, 3.725, 3.733, and 3.82 (3H each, s, NMe and three OMe's), 3.62 [1H, dd, J = 9, 6.5 Hz, C(7')-H], 4.15 [1H, dd, J = 16.5, 4.5 Hz, C(4)-Hβ], 4.63 [1H, dd, J = 8.5, 5 Hz, C(1)-H], 6.54 [1H, s, C(7)-H], 6.87 [2H, d, J = 8.5 Hz, C(3")-H and C(5")-H], 7.13 [2H, d, J = 8.5 Hz, C(2")-H and C(6")-H], 7.46 [1H, s, C(2')-H];[29] HRFABMS *m/z* calcd for $C_{27}H_{33}N_4O_7S$: 557.2070, found: 557.2065.

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