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Preparatory Study for the Synthesis of the Starfish Alkaloid Imbricatine. Syntheses of 5-Arylthio-3-methyl-L-histidines

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Chiral syntheses of 3-methyl-5-(phenylthio)-L-histidine (**8a**) and 3-methyl-5-(1-naphthalenylthio)-L-histidine (**8b**), selected as models for the asteroid alkaloid imbricatine (**7**), have been accomplished through a 10-step route starting from 4(5)-bromoimidazole (**9**). The key steps involved were methylation of **9**, hydroxymethylation of 4-bromo-1-methyl-1*H*-imidazole (**11**), replacement of the 4-bromo group by an arylthio group in the aldehyde **14**, and introduction of a chiral α-amino acid moiety into the chlorides **17a** and **17b** by the "bis-lactim ether" method. The synthesis of the 4-(4-methoxybenzyl)thio analogue **17c**, carried out in a similar manner, concluded formal syntheses of ovothiols A and C (**1** and **3**).

Keywords arylthio-L-histidine chiral synthesis; bis-lactim ether; arylmethylation; hydroxymethylation imidazole; bromoimidazole *N*-methylation; imidazolium salt thermal *N*-demethylation

Several marine invertebrate animals contain 5-mer-capto-3-methyl-L-histidine derivatives. Typical examples include ovothiol A (**1**) (and the corresponding disulfide) from unfertilized eggs of the sea urchin *Paracentrotus lividus*,[1] from the ripe gonads of the starfish *Evasterias troschelii*,[2] and from the eggs of the sea urchin *Arbacia lixula*,[1b,c] of the holothurian *Holothuria tubulosa*,[1b,c] and of the asteroids *Marthasterias glacialis*[1b,c] and *Astropecten aurantiacus*[1b,c]; ovothiol B (**2**) from the ovarian tissue of the scallop *Chlamys hastata*[2]; and ovothiol C (**3**) (and the corresponding disulfide) from the eggs of sea urchins *P. lividus*,[1b,c] *Sphaerechinus granularis*,[1b,c] and *Strongylocentrotus purpuratus*.[2,3] Other examples include adenochromines A, B, and C (**4**, **5**, and **6**), structural units of adenochrome [an iron(III)-binding peptide pigment] from the branchial heart of *Octopus vulgaris*[1c,4]; and imbricatine (**7**), a benzyltetrahydroisoquinoline alkaloid, from the starfish *Dermasterias imbricata*.[5]

Among these sulfur-containing histidine derivatives, imbricatine (**7**) is unique in that it is capable of inducing sea anemone (*Stomphia coccinea*) "swimming" behavior at very low concentrations[5]; it exhibits significant activity in antineoplastic assays[5]; and it is an aromatic thioether in which 3-methyl-L-histidine and a benzyltetrahydroisoquinoline with an α-amino acid structure are linked together. A partial form of structure **7** would be 5-arylthio-3-methyl-L-histidine (**8**), and thus we investigated the chiral synthesis of the 5-phenylthio and 5-(1-naphthalenylthio) analogues (**8a** and **8b**) in the present study as a preliminary to a total synthesis of imbricatine (**7**). A brief account of a part of the results reported here has been published.[6]

The starting point selected for the synthesis of the targets **8a** and **8b** was 4(5)-bromoimidazole (**9**)[7] (Chart 1). On methylation with an excess of MeI in EtOH at 65 °C for 10 h in the presence of 1 molar equivalent of NaOH, **9** afforded the 1,3-dimethylimidazolium derivative **10** in 86% yield. This one-step procedure for dimethylation represents an abbreviation of the two-step procedure of Balaban and Pyman,[8] who prepared **10** by methylation (with MeI) of 5-bromo-1-methylimidazole (**12**) or 4-bromo-1-methylimidazole (**11**), obtainable from **9** by methylation with MeI or Me₂SO₄; the former isomer (**12**) was always the major product.[8–10] Pyrolysis of the 1,3-dimethylimidazolium derivative **10** was then effected at 235—245 °C and 28 mmHg according to the literature,[8] and purification of the distillate by flash chromatography[11] gave **11** and **12** in 61% and 13% yields, respectively. It was possible to convert the undesired isomer **12** into the desired isomer **11** through methylation with MeI[8] (to furnish **10**) and
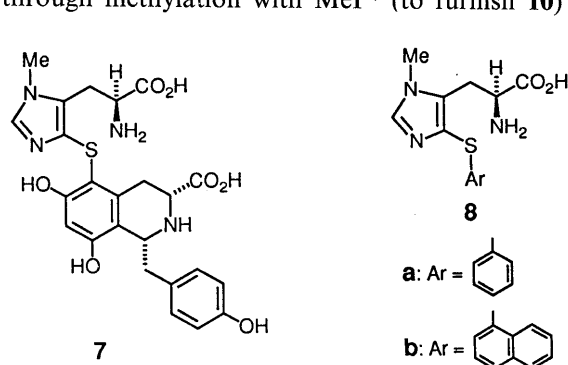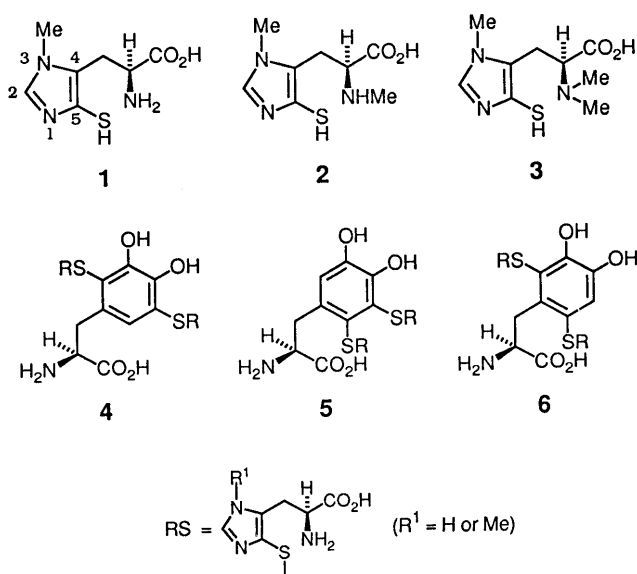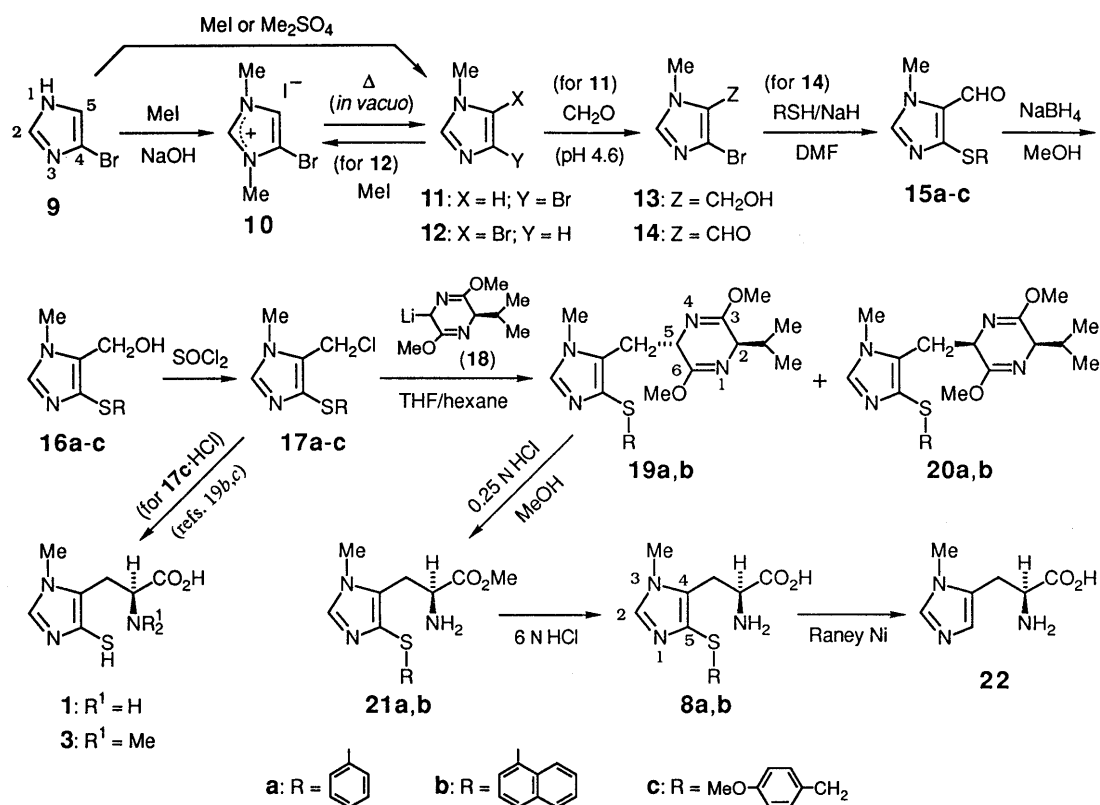
Chart 1

TABLE I. Monomethylation of 4(5)-Bromoimidazole (9) at Room Temperature

Solvent	Reagent[a]	Additive[a]	Time (h)	Yield[b] (%) 11	Yield[b] (%) 12
HCONMe$_2$	MeI (4.0)	Nil	6	0	66
EtOH	MeI (2.1)	NaOH (1.4)	4	48	38
EtOH	MeI (2.0)	NaOH (1.4)	6	51	42
EtOH	MeI (3.0)	NaOH (1.3)	24	44	28[c]
EtOH	Me$_2$SO$_4$ (1.1)	NaOH (1.3)[d]	25	37	27

a) The figure in parentheses refers to the amount of a reagent or an additive in molar equivalent, relative to the amount of **9**. b) Based on the amounts of products separated by flash chromatography.[11] c) 4-Bromo-1,3-dimethyl-1H-imidazolium iodide (**10**) was also isolated in 8% yield by filtration of the reaction mixture. d) Patterned after the literature procedure.[9]

subsequent pyrolysis (of the resulting **10**), thus raising the total yield of **11**.

An alternative synthetic approach to **11** would be regioselective monobromination of 1-methylimidazole or regioselective monomethylation of 4(5)-bromoimidazole (**9**). However, it has been reported that treatment of 1-methylimidazole with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (1 molar eq) did not furnish **11** but the undesired isomer **12** in 66% yield.[12] We therefore examined the monomethylation of **9** at room temperature under several reaction conditions. It may be seen from Table I that treatment of **9** with MeI in N,N-dimethylformamide (DMF) produced only the undesired isomer **12** in 66% yield, in general agreement with the previous results.[8-10] On the other hand, methylation of **9** in EtOH with MeI or Me$_2$SO$_4$ in the presence of NaOH gave an approxi-

mately 1.4:1 mixture of **11** and **12** in 64—93% yield. The observed preference for the formation of **11** over that of **12** under alkaline conditions was in general agreement with what Boulton and Coller[9] briefly mentioned in their paper, but it was still insufficient to make feasible the above direct monomethylation approach.

Yet another approach to **11** would be selective debromination of 2,4,5-tribromo-1-methylimidazole. Katritzky et al.[13] have found that treatment of the tribromide with ethylmagnesium bromide (2 molar eq) in boiling benzene and subsequent hydrolysis did not give the desired monobromide **11** but the 4,5-dibromo derivative. On the other hand, Stensiö et al.[14] obtained 4(5)-bromoimidazole (**9**) in 83% yield when N-unsubstituted 2,4,5-tribromoimidazole was treated with n-BuLi in tetrahydrofuran (THF) at 0 °C, followed by hydrolysis. Application of the latter procedure to 2,4,5-tribromo-1-methylimidazole in the present study, however, gave a complicated mixture of many products, from which we were unable to obtain the desired monobromide **11**.

In reaching the aldehyde **14** from **11**, we first tried to take advantage of a Vilsmeier reaction. However, treatment of **11** in DMF with POCl$_3$/DMF reagent (prepared at 0 °C) at room temperature for 2 h did not afford **14** and resulted in 88% recovery of **11**. This failure led us to examine hydroxymethylation at C(5) instead of the Vilsmeier reaction. Although N(1)-substituted imidazoles usually undergo hydroxymethylation at C(2),[15] 1,4-dimethylimidazole is known to give the 5-hydroxymethyl derivative in 44% yield on treatment with 40% aqueous CH$_2$O in a sealed tube at 125 °C for 6 h.[15a] On the other hand, 4-chloro-1-methylimidazole, an analogue

of **11**, does not undergo hydroxymethylation under similar reaction conditions.[15a)] We found that application of the hydroxymethylation conditions of Godefroi *et al.*[16)] to **11** [35% aqueous CH_2O, AcOH–AcONa buffer (pH 4.6), reflux, 24 h] furnished the 5-hydroxymethyl derivative **13** in 76% yield, together with the 2,5-bis(hydroxymethyl) derivative **23** in 7% yield. The correctness of the structure of **13** was supported by its hydrogenolytic debromination (10% Pd–C/H_2, MeOH, 1 atm, room temp., 30 min), which led to the formation of known 1-methyl-1*H*-imidazole-5-methanol (**24**) in 69% yield. The occurrence of hydroxymethylation mainly at C(5) may be attributable to the electron-donating resonance effect ($+R$ effect)[17)] of the C(4)-Br group on the C(5) atom. Oxidation of the alcohol **13** was then effected with active MnO_2 in boiling $CHCl_3$ for 1 h, producing the corresponding aldehyde **14** in 96% yield. Alternatively, oxidation of **13** with pyridinium dichromate in CH_2Cl_2 at 26 °C for 5 h also gave **14**, but in only 51% yield.

Separate treatments of **14** in DMF with thiophenol (120 °C, 3 h), with 1-naphthalenethiol (100 °C, 3 h), and with 4-methoxy-α-toluenethiol (110 °C, 1 h) in the presence of NaH provided the corresponding thioethers **15a**, **15b**, and **15c** in 73%, 83%, and 73% yields, respectively. The thioethereal aldehydes **15a**—**c** were then converted into the alcohols **16a** (97% yield), **16b** (97%), and **16c** (100%) by $NaBH_4$ reduction (MeOH, room temp., 20—30 min). Chlorinations of **16a**—**c** with $SOCl_2$ (at 0 °C for 30 min, then at room temp. for 30 min) gave the chlorides **17a**—**c**, which were isolated in the form of crude solid hydrochlorides (**17a**—**c**·HCl) in 97—98% yields. These salts were so unstable in H_2O, reverting to the alcohols **16a**—**c**, that an attempt to obtain the free bases themselves was abandoned.

Coupling of **17a**·HCl with the organolithium reagent **18** generated *in situ* from (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and *n*-BuLi in THF/hexane at −78 °C, an application of the "bis-lactim ether" method of Schöllkopf,[18)] was carried out at −50 °C for 18 h, affording the *trans* isomer **19a** and the *cis* isomer **20a** in 70% and 5% yields, respectively. The stereochemical assignments to **19a** and **20a** were based on their ratio of formation (**19a**:**20a** = 14:1)[18)] and comparison of the chemical shifts of their C(2)-protons. In $CDCl_3$, the

C(2)-proton of **19a** resonated at δ 3.77 and that of **20a** at δ 3.90. Following Schöllkopf,[18a)] the *trans* and *cis* isomers of this heterocycle should have conformations A and B, respectively. It may be seen from conformation A that the C(2)-H is located within the shielding cone of the imidazole ring, causing its signal to appear at higher field than that of conformation B. This explains the upfield shift (0.13 ppm) observed for the C(2)-H signal of the *trans* isomer **19a**, relative to that of the *cis* isomer **20a**. A similar coupling reaction of **17b**·HCl with the organolithium reagent **18** furnished the *trans* isomer **19b** [^{1}H-NMR ($CDCl_3$) δ: 3.77 [C(2)-H]] in 88% yield, together with the *cis* isomer **20b** [^{1}H-NMR ($CDCl_3$) δ: 3.89 [C(2)-H]] in 5% yield.

The *trans* bis-lactim ethers **19a** and **19b** were then hydrolyzed in MeOH with 0.25 N aqueous HCl at room temperature for 1.5 h, producing the amino esters **21a** and **21b** in 98% and 84% yields, respectively. Both amino esters were shown to be of at least 98% enantiomeric purity, as determined by ^{1}H-NMR spectroscopy using a chiral shift reagent. Finally, separate hydrolyses of **21a** and **21b** with boiling 6 N aqueous HCl for 1 h gave the target compounds **8a** and **8b** in 83% and 86% yields, respectively. The structures, absolute configurations, and high optical purities of **8a** and **8b** were confirmed by desulfurization (Raney Ni, aqueous EtOH, reflux, 8 h), which led in each case to the formation of known 3-methyl-L-histidine (**22**) in 83—87% yield.

In conclusion, the success in the above 10-step synthetic route to 5-arylthio-3-methyl-L-histidines (**8a, b**) from 4(5)-bromoimidazole (**9**) appears to open a way for a total synthesis of the structurally analogous starfish alkaloid, imbricatine (**7**). The first half of this route in series **c** (**9**→→**17c**·HCl) represents new syntheses of ovothiols A and C (**1** and **3**) in a formal sense, since the alcohol **16c** obtained by a different multistep synthesis[19)] has already been led to **1** and **3** through **17c**·HCl *via* a similar "bis-lactim ether" route.[19b,c)]

Experimental

General Notes All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. TLC was run on Merck silica gel 60 F_{254} plates (0.25-mm thickness) or Merck aluminum oxide F_{254} (type E) plates (0.25 mm), and spots were detected by means of UV absorbance measurement (at 254 nm) and/or spraying with the standard $KMnO_4$ or I_2–KI reagent. Flash chromatography[11)] was carried out by using Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on a Hitachi 320 UV spectrophotometer; a JASCO A-202 IR spectrophotometer; a Hitachi M-80 mass spectrometer; or a JEOL JNM-FX-100 NMR spectrometer (^{1}H 100 MHz and ^{13}C 25.0 MHz), equipped with a ^{13}C Fourier-transform NMR system, at 25 °C. The ^{1}H-NMR spectra of the arylthiohistidine derivatives **8a** and **8b** were

23 **24**
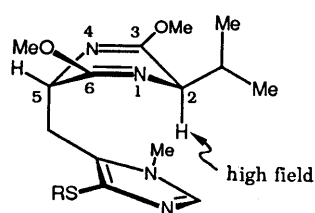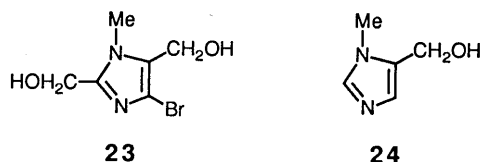
conformation A
(for the *trans* isomer **19**)
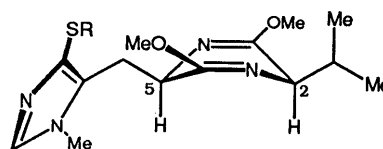
conformation B
(for the *cis* isomer **20**)

recorded on a JEOL JNM-GSX-500 (^{1}H 500 MHz) instrument. Unless otherwise noted, chemical shifts are reported in ppm downfield from internal Me$_4$Si. Optical rotations were measured with a JASCO DIP-181 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: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

4-Bromo-1,3-dimethyl-1H-imidazolium Iodide (10) i) From **9**: A stirred mixture of 4(5)-bromoimidazole (**9**)[7] (76.41 g, 0.520 mol), MeI (443.4 g, 3.124 mol), and NaOH (of 95% purity) (26.28 g, 0.624 mol) in abs. EtOH (1000 ml) was heated in an oil bath kept at 65 °C for 10 h. After cooling, the reaction mixture was kept in a refrigerator overnight, and the precipitate that deposited was filtered off, washed with cold abs. EtOH, and dried to give a first crop (131.7 g, 84%) of **10** as colorless needles, mp 197—199.5 °C (dec.) [lit.[8] mp 202—204 °C (dec.)]. The filtrate and washings were combined, concentrated to a volume of ca. 200 ml, and then kept in a refrigerator. The colorless solid (5.93 g) that deposited was filtered off and recrystallized from abs. EtOH (40 ml) to yield a second crop (3.82 g, 2%) of **10** as colorless needles, mp 195—200 °C (dec.). The total yield of **10** was 135.5 g (86%). Both samples thus obtained were identical (by comparison of the IR spectrum) with the one prepared by method (ii).

ii) From **12**: A solution of 5-bromo-1-methyl-1H-imidazole (**12**) (*vide infra*) (2.68 g, 16.6 mmol) in MeI (20 ml) was heated under reflux for 2.5 h.[8] The reaction mixture was concentrated in vacuo to leave a slightly yellowish solid (4.94 g). Recrystallization of the solid from EtOH (40 ml) afforded **10** (4.83 g, 96%) as colorless needles, mp 199.5—200.5 °C (dec.) [lit.[8] mp 202—204 °C (dec.)].

Pyrolysis of 10 Leading to 4-Bromo-1-methyl-1H-imidazole (11) and 5-Bromo-1-methyl-1H-imidazole (12) The iodide salt **10** (16.76 g, 55.3 mmol) was placed in a Claisen-type distilling flask and heated in an atmosphere of N$_2$ at 28 mmHg in an oil bath kept at 235—245 °C,[8] yielding a brown oily distillate (7.13 g), bp 135—145 °C (28 mmHg). The distillate was then purified by means of flash chromatography[11] (silica gel, AcOEt). Earlier fractions gave **11** (5.41 g, 61%) as an orange oil, ^{1}H-NMR (CDCl$_3$) δ: 3.68 [3H, s, N(1)-Me], 6.86 [1H, d, $J=1.7$ Hz, C(5)-H], 7.31 [1H, br, C(2)-H] (lit.[9] δ: 3.70, 6.87, 7.32); ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.63 [3H, s, N(1)-Me], 7.25 [1H, d, $J=1.6$ Hz, C(5)-H], 7.57 [1H, br, C(2)-H] (lit.[20] δ: 3.65, 7.27, 7.58).

Later fractions from the above chromatography furnished **12** (1.16 g, 13%) as an orange oil, ^{1}H-NMR (CDCl$_3$) δ: 3.63 [3H, d, $J=0.4$ Hz, N(1)-Me], 7.02 [1H, d, $J=1.0$ Hz, C(4)-H], 7.56 [1H, br, C(2)-H] (lit.[10] δ: 3.65, 6.99, 7.50); ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.58 [3H, d, $J=0.4$ Hz, N(1)-Me], 6.98 [1H, d, $J=1.1$ Hz, C(4)-H], 7.78 [1H, br, C(2)-H] (lit.[20] δ: 3.60, 7.00, 7.81).

Monomethylation of 4(5)-Bromoimidazole (9) Methylations of **9** with MeI in DMF (5 ml/3.01 mmol **9**), with MeI in EtOH (1.2—2.5 ml/1 mmol **9**) in the presence of NaOH, and with Me$_2$SO$_4$ in EtOH (1.5 ml/1 mmol **9**) in the presence of NaOH were effected at room temperature under the conditions specified in Table I. Each reaction mixture was then concentrated in vacuo. In the case of the methylation with Me$_2$SO$_4$, however, the reaction mixture had been treated with 10% aqueous NH$_3$ before concentration in order to destroy the excess Me$_2$SO$_4$. The resulting residue was partitioned between CHCl$_3$ and H$_2$O or 10% aqueous K$_2$CO$_3$ (in the case of the methylation with MeI/DMF without added base), and the CHCl$_3$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated in vacuo. The residue was then purified by flash chromatography[11] (silica gel, AcOEt), giving **11** from earlier fractions and **12** from later fractions. The results are summarized in Table I.

Hydroxymethylation of 11 Leading to 4-Bromo-1-methyl-1H-imidazole-5-methanol (13) and 4-Bromo-1-methyl-1H-imidazole-2,5-dimethanol (23) A stirred mixture of **11** (804 mg, 4.99 mmol), 35% (w/w) aqueous CH$_2$O (8 ml), AcOH (0.67 ml), and AcONa·3H$_2$O (1.36 g, 10 mmol) was heated under reflux for 24 h. The reaction mixture was concentrated in vacuo, and the residue was co-evaporated with two 3.5-ml portions of H$_2$O in vacuo to leave a slightly yellow syrup, which was mixed with H$_2$O (3.5 ml). The aqueous mixture was brought to pH 10 with 4 N aqueous KOH, saturated with NaCl, and then extracted with CHCl$_3$ by using a continuous extractor for 20 h. The CHCl$_3$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated in vacuo to leave a slightly yellow oil (1.60 g), which was subjected to flash chromatography[11] [silica gel, CHCl$_3$–MeOH (10:1, v/v)]. Earlier fractions provided **13** (728 mg,

76%) as a colorless solid, mp 112—121.5 °C. Recrystallization of the solid from benzene afforded an analytical sample of **13** as colorless needles, mp 124—125 °C; MS m/z: 192, 190 (M$^+$); UV λ_{max}^{MeOH} 222.5 nm (ε 5460); IR v_{max}^{Nujol} 3200 cm^{-1} (OH); ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.65 [3H, d, $J=0.5$ Hz, N(1)-Me], 4.39 (2H, d, $J=5$ Hz, CH$_2$OH), 5.14 (1H, t, $J=5$ Hz, CH$_2$OH), 7.60 [1H, dull s, C(2)-H]. *Anal.* Calcd for C$_5$H$_7$BrN$_2$O: C, 31.44; H, 3.69; N, 14.67. Found: C, 31.33; H, 3.84; N, 14.65.

Later fractions of the above chromatography gave the 2,5-bis(hydroxymethyl) derivative **23** (82 mg, 7%) as a colorless solid, mp 138—142 °C. Recrystallization from AcOEt furnished an analytical sample of **23** as colorless prisms, mp 151—152 °C; MS m/z: 222, 220 (M$^+$); UV λ_{max}^{MeOH} 229.5 nm (ε 6940); IR v_{max}^{Nujol} 3330 cm^{-1} (OH); ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.63 [3H, s, N(1)-Me], 4.39 and 4.42 (2H each, d, $J=5$ Hz each, two CH$_2$OH's), 5.15 and 5.34 (1H each, t, $J=5$ Hz each, two CH$_2$OH's). *Anal.* Calcd for C$_6$H$_9$BrN$_2$O$_2$: C, 32.60; H, 4.10; N, 12.67. Found: C, 32.56; H, 4.10; N, 12.69.

Conversion of 13 into 1-Methyl-1H-imidazole-5-methanol (24) A solution of **13** (96 mg, 0.50 mmol) in MeOH (5 ml) was hydrogenated over 10% Pd–C (100 mg) at atmospheric pressure and room temperature for 30 min. The catalyst was removed by filtration and washed with MeOH (10 ml). The filtrate and washings were combined and concentrated in vacuo to leave a colorless oil, which was dissolved in H$_2$O (5 ml). The aqueous solution was made alkaline with 10% aqueous NaOH and extracted with CHCl$_3$ by using a continuous extractor for 20 h. The CHCl$_3$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated in vacuo to leave the debrominated derivative **24** (39 mg, 69%) as a colorless solid, mp 109—110.5 °C. Recrystallization from benzene gave a pure sample (32 mg, 57%) as colorless prisms, mp 114—115.5 °C (lit.[21] mp 113—114 °C); IR v_{max}^{Nujol} 3200 cm^{-1} (OH); ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.60 [3H, d, $J=0.5$ Hz, N(1)-Me], 4.42 (2H, dull s, CH$_2$OH), 6.77 [1H, dull s, C(4)-H], 7.53 [1H, dull s, C(2)-H].

4-Bromo-1-methyl-1H-imidazole-5-carbaldehyde (14) i) Oxidation of **13** with Active MnO$_2$: A stirred mixture of **13** (5.74 g, 30.0 mmol) and active γ-MnO$_2$[22] (dried at 100 °C for 10 h before use) (26.08 g, 0.30 mol) in CHCl$_3$ (100 ml) was heated under reflux for 1 h. After cooling, the insoluble solid was removed by filtration and washed with CHCl$_3$ (500 ml). The filtrate and washings were combined and concentrated in vacuo to leave **14** (5.47 g, 96%) as a colorless solid, mp 88—89 °C. Recrystallization from hexane yielded an analytical sample as colorless prisms, mp 89.5—90.5 °C; MS m/z: 190, 188 (M$^+$); UV λ_{max}^{MeOH} 232 nm (sh) (ε 2960), 272 (12000); IR v_{max}^{Nujol} 1664 cm^{-1} (ArCHO); ^{1}H-NMR (CDCl$_3$) δ: 3.93 [3H, d, $J=0.7$ Hz, N(1)-Me], 7.51 [1H, dull s, C(2)-H], 9.78 (1H, d, $J=1.0$ Hz, CHO). *Anal.* Calcd for C$_5$H$_5$BrN$_2$O: C, 31.77; H, 2.67; N, 14.82. Found: C, 31.75; H, 2.71; N, 14.90.

ii) Oxidation of **13** with Pyridinium Dichromate (PDC): A mixture of **13** (191 mg, 1.00 mmol) and PDC (of 98% purity) (576 mg, 1.5 mmol) in dry CH$_2$Cl$_2$ (2 ml) was stirred at 26 °C for 5 h.[23] The reaction mixture was combined with ether (5 ml), and the insoluble material was removed by filtration and washed with ether (10 ml). The filtrate and washings were combined and concentrated in vacuo to leave a slightly yellow solid (127 mg). Recrystallization of the solid from hexane (15 ml) afforded **14** (96 mg, 51%) as colorless prisms, mp 89.5—90 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by method (i).

1-Methyl-4-(phenylthio)-1H-imidazole-5-carbaldehyde (15a) A solution of **14** (2.84 g, 15.0 mmol) in dry DMF (50 ml) was added dropwise to a stirred solution of thiophenol (1.83 g, 16.6 mmol) and an oil dispersion (781 mg) containing 60% NaH (19.5 mmol) in dry DMF (50 ml). The resulting mixture was heated at 120 °C in an atmosphere of N$_2$ for 3 h. After cooling, the reaction mixture was concentrated in vacuo to leave a brown oil, which was partitioned between H$_2$O and CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous MgSO$_4$, and concentrated in vacuo to leave a brown oil. Purification of the oil by means of flash chromatography[11] [silica gel, AcOEt–CH$_2$Cl$_2$ (1:4, v/v)] furnished **15a** (2.38 g, 73%) as a yellowish solid, mp 69.5—71 °C. Recrystallization from hexane–AcOEt (6:1, v/v) yielded an analytical sample as colorless prisms, mp 70—71.5 °C; MS m/z: 218 (M$^+$); UV λ_{max}^{MeOH} 246 nm (ε 12500), 298 (4050); IR v_{max}^{Nujol} 1645 cm^{-1} (ArCHO); ^{1}H-NMR (CDCl$_3$) δ: 3.94 [3H, d, $J=0.5$ Hz, N(1)-Me], 7.2—7.5 (5H, m, SPh), 7.60 [1H, dull s, C(2)-H], 10.00 (1H, d, $J=1.0$ Hz, CHO). *Anal.* Calcd for C$_{11}$H$_{10}$N$_2$OS: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.59; H, 4.59; N, 12.91.

1-Methyl-4-(1-naphthalenylthio)-1*H*-imidazole-5-carbaldehyde (15b)
A solution of **14** (284 mg, 1.50 mmol) in dry DMF (5 ml) was added to a stirred mixture of 1-naphthalenethiol[24] [bp 88—92 °C (1 mmHg) [lit.[25] bp 85—88 °C (0.27 mmHg)]; n_D^{20} 1.6803] (269 mg, 1.68 mmol) and an oil dispersion (73 mg) containing 60% NaH (1.83 mmol) in dry DMF (5 ml). The resulting mixture was heated at 100 °C in an atmosphere of N_2 for 3 h. The reaction mixture was worked up in a manner similar to that described above for **15a**, and the crude oily product was purified by flash chromatography[11] (silica gel, AcOEt–CH_2Cl_2 (1 : 4, v/v)] to yield **15b** (334 mg, 83%) as a yellowish syrup, MS *m/z*: 268 (M^+); IR $\nu_{max}^{CHCl_3}$ 1668 cm^{-1} (ArCHO); ^{1}H-NMR (CDCl$_3$) δ: 3.90 [3H, d, $J = 0.5$ Hz, N(1)-Me], 7.3—7.9 [7H, m, C(2′—7′)-H's and C(2)-H], 8.3—8.5 [1H, m, C(8′)-H], 10.07 (1H, d, $J = 1.0$ Hz, CHO).[26]

4-[[(4-Methoxyphenyl)methyl]thio]-1-methyl-1*H*-imidazole-5-carbaldehyde (15c) A solution of **14** (3.78 g, 20.0 mmol) in dry DMF (50 ml) was added dropwise to a stirred solution of 4-methoxy-α-toluenethiol (3.70 g, 24.0 mmol) and an oil dispersion (960 mg) containing 60% NaH (24.0 mmol) in dry DMF (50 ml). The resulting mixture was heated at 110 °C in an atmosphere of N_2 for 1 h. The reaction mixture was worked up as described above for **15a**, and the crude oily product was purified by flash chromatography[11] [silica gel, hexane–AcOEt (2 : 5, v/v)] to give **15c** (3.82 g, 73%) as a yellow solid, mp 79.5—80.5 °C. Recrystallization of the solid from hexane yielded an analytical sample as slightly yellowish needles, mp 80—81.5 °C; MS *m/z*: 262 (M^+); UV λ_{max}^{MeOH} 230.5 nm (ε 15800), 255 (sh) (8830), 277 (sh) (6200), 285 (5840), 300 (5320); IR ν_{max}^{Nujol} 1650 cm^{-1} (ArCHO); ^{1}H-NMR (CDCl$_3$) δ: 3.77 [3H, s, C(4′)-OMe], 3.87 [3H, d, $J = 0.5$ Hz, N(1)-Me], 4.25 [2H, s, C(4)-SCH$_2$Ar], 6.79 [2H, d, $J = 9$ Hz, C(3′)-H and C(5′)-H], 7.18 [2H, d, $J = 9$ Hz, C(2′)-H and C(6′)-H], 7.55 [1H, dull s, C(2)-H], 9.64 [1H, d, $J = 0.7$ Hz, C(5)-CHO].[26] *Anal.* Calcd for C$_{13}$H$_{14}$N$_2$O$_2$S: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.57; H, 5.40; N, 10.52.

1-Methyl-4-(phenylthio)-1*H*-imidazole-5-methanol (16a) A solution of **15a** (2.35 g, 10.8 mmol) in MeOH (50 ml) was stirred at room temperature, and NaBH$_4$ (408 mg, 10.8 mmol) was added in portions. After the mixture had been stirred at room temperature for 30 min, acetone (5 ml) was added. Concentration of the resulting mixture under vacuum left a slightly yellowish solid, which was partitioned by extraction with a mixture of H$_2$O and CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, dried over anhydrous MgSO$_4$, and concentrated *in vacuo* to leave **16a** (2.30 g, 97%) as a colorless solid, mp 128—131 °C. Recrystallization from benzene furnished an analytical sample as colorless needles, mp 130.5—131.5 °C; MS *m/z*: 220 (M^+); UV λ_{max}^{MeOH} 240 nm (ε 12600), 245 (sh) (11800); IR ν_{max}^{Nujol} 3150 cm^{-1} (OH); ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.70 [3H, s, N(1)-Me], 4.52 (2H, d, $J = 5$ Hz, CH$_2$OH), 5.17 (1H, t, $J = 5$ Hz, CH$_2$OH), 6.9—7.3 (5H, m, SPh), 7.75 [1H, s, C(2)-H]. *Anal.* Calcd for C$_{11}$H$_{12}$N$_2$OS: C, 59.98; H, 5.49; N, 12.72. Found: C, 60.16; H, 5.48; N, 12.76.

1-Methyl-4-(1-naphthalenylthio)-1*H*-imidazole-5-methanol (16b) A solution of **15b** (304 mg, 1.13 mmol) in MeOH (10 ml) was stirred at room temperature, and NaBH$_4$ (43 mg, 1.14 mmol) was added portionwise. After the mixture had been stirred at room temperature for 20 min, acetone (1 ml) was added. The resulting mixture was concentrated *in vacuo*, and the residual solid was partitioned between H$_2$O and AcOEt. The AcOEt extracts were combined, dried over anhydrous MgSO$_4$, and concentrated *in vacuo* to leave **16b** (296 mg, 97%) as a colorless solid, mp 168—169 °C. Recrystallization of the solid from benzene gave an analytical sample as colorless needles, mp 169—170 °C; MS *m/z*: 270 (M^+); UV λ_{max}^{MeOH} 220 nm (ε 55400), 233 (sh) (24600), 301 (8600), 317 (sh) (5790); IR ν_{max}^{Nujol} 3145 cm^{-1} (OH); ^{1}H-NMR (Me$_2$SO-d_6) δ: 3.72 [3H, s, N(1)-Me], 4.55 (2H, d, $J = 5$ Hz, CH$_2$OH), 5.19 (1H, t, $J = 5$ Hz, CH$_2$OH), 7.0—8.0 [7H, m, C(2′—7′)-H's and C(2)-H], 8.2—8.4 [1H, m, C(8′)-H].[26] *Anal.* Calcd for C$_{15}$H$_{14}$N$_2$OS: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.88; H, 5.16; N, 10.29.

4-[[(4-Methoxyphenyl)methyl]thio]-1-methyl-1*H*-imidazole-5-methanol (16c) Reduction of **15c** (1.32 g, 5.03 mmol) with NaBH$_4$ (191 mg, 5.05 mmol) in MeOH (50 ml) and work-up of the reaction mixture were effected in a manner similar to that described above for **16a**, yielding **16c** (1.33 g, 100%) as a slightly yellowish solid, mp 102—112.5 °C. Recrystallization of the solid from benzene gave an analytical sample of **16c** as colorless scales, mp 113.5—115 °C (lit. mp 113—114 °C[19b]; mp 103—104 °C[19c]); MS *m/z*: 264 (M^+); UV λ_{max}^{MeOH} 229 nm (ε 17000), 275 (sh) (1980), 284 (sh) (1440); IR ν_{max}^{Nujol} 3125 cm^{-1} (OH); $\nu_{max}^{CHCl_3}$ 3570 cm^{-1} (OH); ^{1}H-NMR (CDCl$_3$) δ: 0.8—1.2 (1H, br, CH$_2$OH), 3.61 [3H, s, N(1)-Me], 3.76 [3H, s, C(4′)-OMe], 3.84 [2H, s, C(4)-SCH$_2$Ar], 4.24

(2H, dull s, CH$_2$OH), 6.77 [2H, d, $J = 9$ Hz, C(3′)-H and C(5′)-H], 6.97 [2H, d, $J = 9$ Hz, C(2′)-H and C(6′)-H], 7.45 [1H, s, C(2)-H][26]; ^{13}C-NMR (CDCl$_3$) δ: 32.2 (q, NMe), 39.6 (t, SCH$_2$), 53.1 (t, CH$_2$OH), 55.2 (q, OMe), 113.5 [d, C(3′) and C(5′)], 130.0 [d, C(2′) and C(6′)], 131.0 [s, C(4) and C(5)], 135.5 [s, C(1′)], 138.7 [d, C(2)], 158.5 [s, C(4′)].[26] *Anal.* Calcd for C$_{13}$H$_{16}$N$_2$O$_2$S: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.02; H, 6.16; N, 10.58. The ^{1}H- and ^{13}C-NMR spectral data matched those reported[19c] for authentic **16c**.

5-(Chloromethyl)-1-methyl-4-(phenylthio)-1*H*-imidazole Hydrochloride (17a·HCl) The alcohol **16a** (1.43 g, 6.49 mmol) was added in portions to SOCl$_2$ (20 ml) at 0 °C with stirring. After having been stirred at 0 °C for 30 min and then at room temperature for a further 30 min, the reaction mixture was concentrated *in vacuo* to leave a yellow syrup. The syrup was co-evaporated with three 20-ml portions of dry THF, and the residue was triturated with dry THF (10 ml). The insoluble solid that resulted was collected by filtration, washed with dry THF (5 ml), and dried to give **17a·HCl** (1.74 g, 97%) as a colorless solid. This sample was directly used in the next arylmethylation step without further purification.

5-(Chloromethyl)-1-methyl-4-(1-naphthalenylthio)-1*H*-imidazole Hydrochloride (17b·HCl) Chlorination of **16b** (946 mg, 3.50 mmol) with SOCl$_2$ (10 ml) and work-up of the reaction mixture were carried out in a manner similar to that described above for **17a·HCl**, providing **17b·HCl** (1.11 g, 98%) as a colorless solid. This sample was directly used in the next arylmethylation step without further purification.

5-(Chloromethyl)-4-[[(4-methoxyphenyl)methyl]thio]-1-methyl-1*H*-imidazole Hydrochloride (17c·HCl) Chlorination of **16c** (1.40 g, 5.30 mmol) with SOCl$_2$ (20 ml) and work-up of the reaction mixture were conducted in a manner similar to that described above for **17a·HCl**, giving **17c·HCl** (1.66 g, 98%) as a slightly yellowish solid.

(2*R-trans*)-2,5-Dihydro-3,6-dimethoxy-2-(1-methylethyl)-5-[[1-methyl-4-(phenylthio)-1*H*-imidazol-5-yl]methyl]pyrazine (19a) and (2*R-cis*)-2,5-Dihydro-3,6-dimethoxy-2-(1-methylethyl)-5-[[1-methyl-4-(phenylthio)-1*H*-imidazol-5-yl]methyl]pyrazine (20a) A stirred solution of (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[27] (369 mg, 2.00 mmol) in dry THF (7 ml) was cooled to −78 °C in an atmosphere of N$_2$, and a 1.05 M solution (1.90 ml, 2.00 mmol) of butyllithium in hexane was added dropwise over 10 min. After the mixture had been stirred at −78 °C for 15 min, **17a·HCl** (220 mg, 0.80 mmol) was added in portions, and the resulting mixture was stirred first at −78 °C for 1 h and then at −50 °C for 18 h. The reaction was then quenched by adding saturated aqueous NH$_4$Cl (3 ml) at −50 °C. After having been warmed to room temperature, the aqueous layer was separated from the organic layer and extracted with ether (2 × 3 ml). The ethereal extracts and the above organic layer were combined, washed with saturated aqueous NaCl (3 ml), dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo* to leave a yellow oil (492 mg), which was subjected to flash chromatography[11] [silica gel, CH$_2$Cl$_2$–MeOH (29 : 1, v/v)]. Earlier fractions furnished a colorless solid (243 mg), which was purified by flash chromatography[11] [silica gel, acetone–hexane (1 : 2, v/v)] to give **19a** (215 mg, 70%) as a colorless solid, mp 114—116 °C. Recrystallization from hexane–AcOEt (12 : 1, v/v) yielded an analytical sample of **19a** as colorless prisms, mp 117.5—118.5 °C; $[\alpha]_D^{20}$ −5.80° ($c = 0.50$, CHCl$_3$); MS *m/z*: 386 (M^+); UV λ_{max}^{MeOH} 240 nm (ε 13200), 247 (sh) (12100); IR ν_{max}^{Nujol} 1690 cm^{-1} (C = N); ^{1}H-NMR (CDCl$_3$) δ: 0.61 and 0.96 (3H each, d, $J = 6.5$ Hz, CHMe$_2$), 1.95—2.3 (1H, m, CHMe$_2$), 2.84 (1H, dd, $J = 14.5$ and 8.5 Hz) and 3.41 (1H, dd, $J = 14.5$ and 5 Hz) [C(5′)-CH$_2$], 3.61, 3.67, and 3.71 [3H each, s, N(1′)-Me and two OMe's], 3.77 [1H, dd, $J = 3.5$ Hz each, C(2)-H], 4.0—4.2 [1H, m, C(5)-H], 6.95—7.2 (5H, m, SPh), 7.50 [1H, s, C(2′)-H].[28] *Anal.* Calcd for C$_{20}$H$_{26}$N$_4$O$_2$S: C, 62.15; H, 6.78; N, 14.50. Found: C, 62.04; H, 6.95; N, 14.49.

Later fractions in the above first chromatography provided a yellow syrup (56 mg), which was purified by two successive flash chromatographies[11] [silical gel, acetone–hexane (1 : 2, v/v); silica gel, CH$_2$Cl$_2$–EtOH (29 : 1, v/v)] to give **20a** (16 mg, 5%) as a slightly yellowish oil, $[\alpha]_D^{20}$ −68.9° ($c = 0.50$, CHCl$_3$); MS *m/z*: 386 (M^+); ^{1}H-NMR (CDCl$_3$) δ: 0.71 and 1.05 (3H each, d, $J = 6.5$ Hz, CHMe$_2$), 1.95—2.3 (1H, m, CHMe$_2$), 2.84 (1H, dd, $J = 14.5$ and 9 Hz) and 3.35 (1H, dd, $J = 14.5$ and 5 Hz) [C(5′)-CH$_2$], 3.60, 3.66, and 3.68 [3H each, s, N(1′)-Me and two OMe's], 3.90 [1H, dd, $J = 4.5$ Hz each, C(2)-H], 4.05—4.25 [1H, m, C(5)-H], 6.95—7.2 (5H, m, SPh), 7.50 [1H, s, C(2′)-H].[28]

(2*R-trans*)-2,5-Dihydro-3,6-dimethoxy-2-(1-methylethyl)-5-[[1-methyl-4-(1-naphthalenylthio)-1*H*-imidazol-5-yl]methyl]pyrazine (19b) and (2*R-cis*)-2,5-Dihydro-3,6-dimethoxy-2-(1-methylethyl)-5-[[1-methyl-

4-(1-naphthalenylthio)-1*H*-imidazol-5-yl]methyl]pyrazine (20b) A stirred solution of (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[27] (1.57 g, 8.52 mmol) in dry THF (30 ml) was cooled to −78 °C in an atmosphere of N_2, and a 1.47 M solution (5.80 ml, 8.53 mmol) of butyllithium in hexane was added dropwise over 10 min. After the mixture had been stirred at −78 °C for 10 min, **17b**·HCl (1.10 g, 3.38 mmol) was added portionwise, and the resulting mixture was stirred first at −78 °C for 1 h and then at −50 °C for 20 h. The reaction mixture was worked up in a manner similar to that described above for **19a** and **20a**, and the crude products were separated by flash chromatography[11] [silica gel, CH_2Cl_2–MeOH (24:1, v/v)]. Earlier fractions gave **19b** (1.30 g, 88%) as a slightly yellowish syrup, $[\alpha]_D^{21}$ −28.6° (*c*=0.50, $CHCl_3$); MS *m/z*: 436 (M+); IR $\nu_{max}^{CHCl_3}$ 1693 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ: 0.58 and 0.93 (3H each, d, *J*=6.5 Hz, CH$\underline{Me}_2$), 1.95—2.3 (1H, m, C$\underline{H}Me_2$), 2.84 (1H, dd, *J*=14.5 and 8.5 Hz) and 3.44 (1H, dd, *J*=14.5 and 4.5 Hz) [C(5')-CH_2], 3.62, 3.66, and 3.68 [3H each, s, N(1')-Me and two OMe's], 3.77 [1H, dd, *J*=3.5 Hz each, C(2)-H], 4.0—4.2 [1H, m, C(5)-H], 7.1—7.9 [7H, m, C(2″—7″)-H's and C(2')-H], 8.35—8.5 [1H, m, C(8″)-H].[28,29]

Later fractions from the above chromatography afforded a yellowish syrup, which was purified by flash chromatography[11] [silica gel, AcOEt–EtOH (14:1, v/v)] to give **20b** (77 mg, 5%) as a colorless syrup, $[\alpha]_D^{21}$ −48.6° (*c*=0.50, $CHCl_3$); MS *m/z*: 436 (M+); IR $\nu_{max}^{CHCl_3}$ 1695 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ: 0.70 and 1.04 (3H each, d, *J*=6.5 Hz, CH$\underline{Me}_2$), 1.95—2.3 (1H, m, C$\underline{H}Me_2$), 2.7—3.0 (1H, m) and 3.38 (1H, dd, *J*=14.5 and 5 Hz) [C(5')-CH_2], 3.62, 3.65, and 3.68 [3H each, s, N(1')-Me and two OMe's], 3.89 [1H, dd, *J*=4.5 Hz each, C(2)-H], 4.05—4.25 [1H, m, C(5)-H], 7.2—7.9 [7H, m, C(2″—7″)-H's and C(2')-H], 8.35—8.5 [1H, m, C(8″)-H].[28,29]

3-Methyl-5-(phenylthio)-L-histidine Methyl Ester (21a) A mixture of **19a** (2.05 g, 5.30 mmol) and 0.25 N aqueous HCl (64 ml) in MeOH (32 ml) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated *in vacuo* to a volume of *ca.* 40 ml, brought to pH *ca.* 8 by addition of 10% aqueous NH_3, and extracted with CH_2Cl_2 (4×40 ml). The CH_2Cl_2 extracts were combined, washed with saturated aqueous NaCl (100 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow oil. Purification of the oil by flash chromatography[11] [silica gel, CH_2Cl_2–MeOH (14:1, v/v)] gave **21a** (1.51 g, 98%) as a slightly yellowish syrup, $[\alpha]_D^{21}$ +24.8° (*c*=0.50, MeOH); MS *m/z*: 291 (M+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 and 3320 (NH_2), 1738 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 1.60 (2H, s, NH_2), 2.88 (1H, dd, *J*=14.5 and 8.5 Hz) and 3.17 (1H, dd, *J*=14.5 and 5.5 Hz) [C(4)-CH_2], 3.67 [1H, dd, *J*=8.5 and 5.5 Hz, C(4)-$CH_2C\underline{H}$], 3.68 and 3.69 [3H each, s, N(3)-Me and CO_2Me], 7.0—7.2 (5H, m, SPh), 7.52 [1H, s, C(2)-H]. The enantiomeric purity[30] of this sample was shown to be at least 98% by means of ^{1}H-NMR spectroscopy using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] in $CDCl_3$.

3-Methyl-5-(1-naphthalenylthio)-L-histidine Methyl Ester (21b) Hydrolysis of **19b** (1.27 g, 2.91 mmol) in MeOH (20 ml) with 0.25 N aqueous HCl (35 ml) and work-up of the reaction mixture were effected in a manner similar to that described above for **21a**. Purification of the crude oily product by flash chromatography[11] [silica gel, CH_2Cl_2–EtOH (9:1, v/v)] yielded **21b** (838 mg, 84%) as a yellowish syrup, $[\alpha]_D^{21}$ +25.5° (*c*=0.51, MeOH); MS *m/z*: 341 (M+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 and 3320 (NH_2), 1737 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 1.55 (2H, s, NH_2), 2.87 (1H, dd, *J*=14.5 and 9 Hz) and 3.18 (1H, dd, *J*=14.5 and 5.5 Hz) [C(4)-CH_2], 3.65 and 3.69 [3H each, s, N(3)-Me and CO_2Me], 3.67 [1H, dd, *J*=9 and 5.5 Hz, C(4)-$CH_2C\underline{H}$], 7.1—7.9 [7H, m, C(2'—7')-H's and C(2)-H], 8.3—8.5 [1H, m, C(8')-H].[26] The enantiomeric purity of this sample was determined, as in the case of **21a**, to be at least 98%.

3-Methyl-5-(phenylthio)-L-histidine (8a) A solution of **21a** (1.49 g, 5.11 mmol) in 6 N aqueous HCl (50 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 30-ml portions of H_2O and then with EtOH (30 ml) to leave a colorless syrup, which was dissolved in H_2O (10 ml). The aqueous solution was brought to pH *ca.* 8 by addition of 10% aqueous NH_3, and the colorless solid that resulted was filtered off, washed with cold H_2O (10 ml), and recrystallized from MeOH–H_2O (4:1, v/v) to give **8a**·H_2O (1.25 g, 83%) as colorless needles, mp 193.5—194.5 °C (dec.). Further recrystallization from the same solvent system and drying over P_2O_5 at 2 mmHg and 60 °C for 10 h provided an analytical sample of **8a**·H_2O as colorless fine needles, mp 193.5—194.5 °C (dec.); $[\alpha]_D^{19}$ +29.8° (*c*=0.50, 0.1 N aqueous HCl); MS *m/z*: 277 (M+); UV $\lambda_{max}^{H_2O}$ 238 nm (ε 12500); IR ν_{max}^{Nujol} 1595 cm^{-1} (CO$_2^-$); ^{1}H-

NMR (500 MHz) (Me_2SO-d_6) δ: 2.86 (1H, dd, *J*=15 and 8 Hz) and 3.12 (1H, dd, *J*=15 and 7 Hz) [C(4)-CH_2], 3.1—3.5 (5H, br, NH_3^+ and H_2O), 3.27 [1H, dd, *J*=8 and 7 Hz, C(4)-$CH_2C\underline{H}$], 3.62 [3H, s, N(3)-Me], 7.0—7.25 (5H, m, SPh), 7.69 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{13}H_{15}N_3O_2S$·H_2O: C, 52.87; H, 5.80; N, 14.23. Found: C, 52.75; H, 5.84; N, 13.96.

3-Methyl-5-(1-naphthalenylthio)-L-histidine (8b) A solution of **21b** (787 mg, 2.30 mmol) in 6 N aqueous HCl (20 ml) was heated under reflux for 1 h. The reaction mixture was worked up in a manner similar to that described above for **8a**, and the crude product was recrystallized from MeOH to give **8b**·1/2H_2O (663 mg, 86%) as colorless fine needles, mp 213—214 °C (dec.). Further recrystallization from MeOH and drying over P_2O_5 at 2 mmHg and 70 °C for 10 h furnished an analytical sample of **8b**·1/2H_2O as colorless fine needles, mp 212.5—213.5 °C (dec.); $[\alpha]_D^{23}$ +29.4° (*c*=0.50, 0.1 N aqueous HCl); MS *m/z*: 327 (M+); UV $\lambda_{max}^{H_2O}$ 221 nm (ε 54200), 300 (8130); IR ν_{max}^{Nujol} 1613 cm^{-1} (CO$_2^-$); ^{1}H-NMR (500 MHz) (Me_2SO-d_6) δ: 2.90 (1H, dd, *J*=15 and 8 Hz) and 3.16 (1H, dd, *J*=15 and 7 Hz) [C(4)-CH_2], 3.1—3.5 (4H, br, NH_3^+ and 1/2H_2O), 3.31 [1H, dd, *J*=8 and 7 Hz, C(4)-$CH_2C\underline{H}$], 3.64 [3H, s, N(3)-Me], 7.05—7.95 [6H, m, C(2'—7')-H's], 7.75 [1H, s, C(2)-H], 8.29 [1H, d, *J*=8 Hz, C(8')-H].[26] *Anal.* Calcd for $C_{17}H_{17}N_3O_2S$·1/2H_2O: C, 60.70; H, 5.39; N, 12.49. Found: C, 60.96; H, 5.14; N, 12.65.

3-Methyl-L-histidine (22) i) From **8a**: A mixture of **8a**·H_2O (118 mg, 0.40 mmol), EtOH (2 ml), H_2O (8 ml), and Raney Ni catalyst[31] (1.5 ml) was heated under reflux for 8 h, and 6 N aqueous HCl (4 ml) was then added to the reaction mixture while it was hot. The insoluble material was removed by filtration and washed with H_2O (20 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a yellowish green solid, which was dissolved in H_2O (3 ml). The aqueous solution was applied to a column of Dowex 50W-X2 (H+ form in 1 N aqueous HCl) (1.5×18 cm), and the column was eluted with 1 N aqueous HCl. The first 40 ml contained Ni^{2+}, and later fractions showing a positive reaction to the ninhydrin test were combined and concentrated *in vacuo*, leaving a bluish green solid. The solid was dissolved in H_2O (1 ml) and applied to a column of Dowex 50W-X8 (H+ form in H_2O) (4 ml). The column was first eluted with H_2O (*ca.* 40 ml) until the eluate became neutral, and then with 2% aqueous NH_3 (70 ml). The ammoniacal eluates were combined and concentrated *in vacuo* to leave a colorless solid. The solid was triturated with H_2O (5 ml), and the insoluble material was removed by filtration and washed with H_2O (5 ml). The filtrate and washings were combined and concentrated *in vacuo* to dryness to leave **22**·H_2O (65 mg, 87%) as a colorless solid, mp 224—227 °C (dec.). The solid was recrystallized by dissolving it in a small amount of hot H_2O and adding EtOH to afford an analytical sample of **22**·H_2O (dried over P_2O_5 at 2 mmHg and 80 °C for 8 h and then kept in a closed vessel saturated with H_2O at room temp. for 6 h) as colorless fine needles, mp 231—233 °C (dec.); $[\alpha]_D^{26}$ +13.2° (*c*=0.30, 0.1 N aqueous HCl); MS *m/z*: 169 (M+). *Anal.* Calcd for $C_7H_{11}N_3O_2$·H_2O: C, 44.91; H, 7.00; N, 22.45. Found: C, 44.92; H, 7.21; N, 22.43. The IR spectrum of this sample was superimposable on that of a commercial sample of **22**·H_2O [mp 225—228 °C (dec.); $[\alpha]_D^{23}$ +10.8° (*c*=0.30, 0.1 N aqueous HCl)].

ii) From **8b**: Reductive desulfurization of **8b**·1/2H_2O (135 mg, 0.40 mmol) with Raney Ni catalyst[31] (1.5 ml) in a mixture of EtOH (2 ml) and H_2O (8 ml) and work-up of the reaction mixture were conducted in a manner similar to that described above under item (i), giving **22**·H_2O (62 mg, 83%) as a colorless solid, mp 220—221.5 °C (dec.). For analysis, the solid was recrystallized and dried as described above under item (i) to yield colorless fine needles, mp 232.5—234 °C (dec.); $[\alpha]_D^{26}$ +12.7° (*c*=0.30, 0.1 N aqueous HCl); MS *m/z*: 169 (M+). *Anal.* Calcd for $C_7H_{11}N_3O_2$·H_2O: C, 44.91; H, 7.00; N, 22.45. Found: C, 44.71; H, 7.19; N, 22.30. This sample was identical (by comparison of the IR spectrum) with the one obtained by method (i).

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