SYNTHESES OF L-PHENYLALANINE DERIVATIVES CONTAINING A SULFUR SUBSTITUENT AT THE 2-POSITION†

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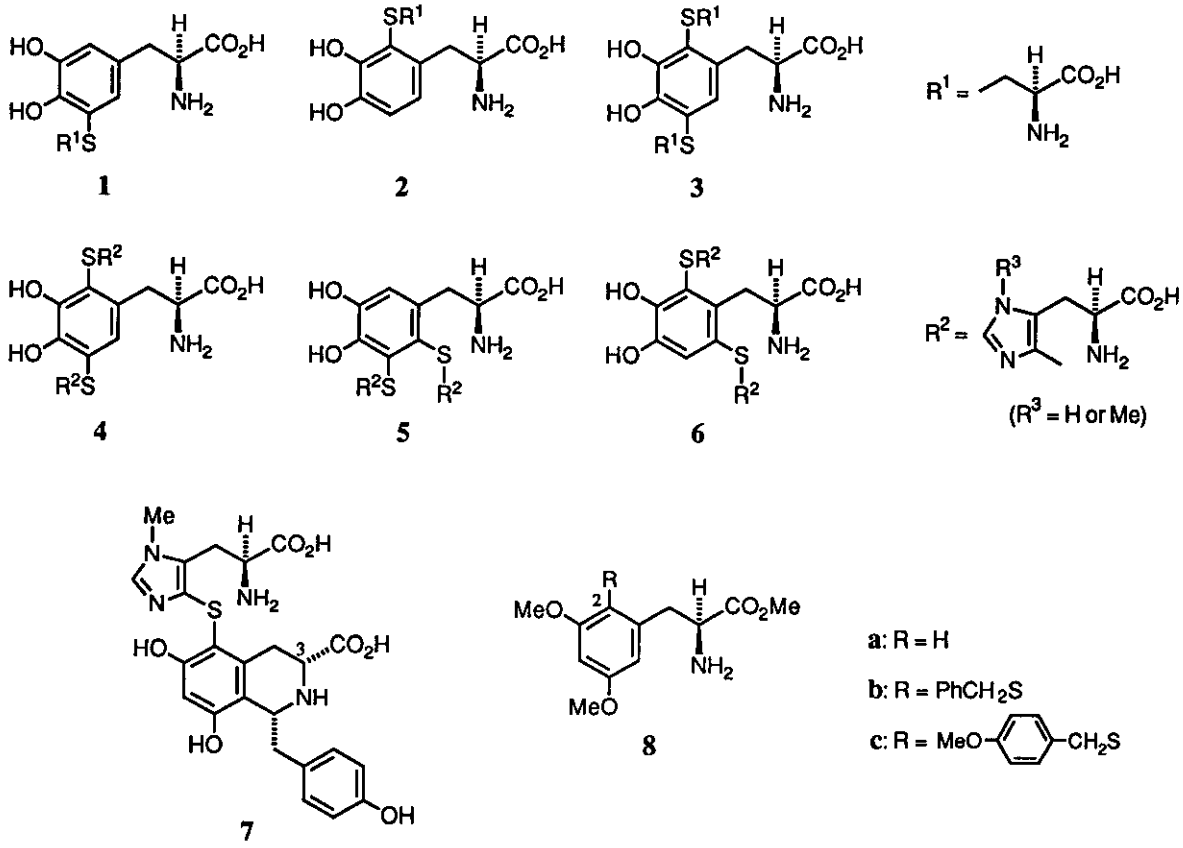
Abstract ——— A full account is given of the chiral syntheses of sulfur-containing L-phenylalanine derivatives (**8b,c**), selected as key intermediates for the synthesis of models for the starfish alkaloid imbricatine (**7**), *via* a 5-step route starting from *N,N*-diethyl-3,5-dimethoxybenzamide (**9**). The key steps involve introduction of a sulfur substituent into **9** at the 2-position and construction of the chiral α-amino acid moiety in the chlorides (**12b,c**) by the "bis-lactim ether" method.

Several sulfur-containing phenylalanine derivatives have been found in nature in the form of connecting another amino acid to the aromatic ring through a sulfide bond. Typical examples include L-3,4-dihydroxyphenylalanine (L-dopa) derivatives, *e. g.*, 5- and 2-(cystein-*S*-yl)dopa's (**1** and **2**), the chief building-stones in the biosynthesis of phaeomelanins;[1,2] 2,5-di(cystein-*S*-yl)dopa (**3**) from the eyes of the alligator gar *Lepisosteus spatula*;[3] and 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*.[4] Another example may be seen in the structure of imbricatine (**7**), a benzyltetrahydroisoquinoline alkaloid isolated from the starfish *Dermasterias imbricata*.[5] It possesses an aromatic thioether structure in which 3-methyl-L-histidine and a benzyltetrahydroisoquinoline, anticipated to be accessible from a D-phenylalanine derivative, are linked together. In connection with our ongoing imbricatine synthetic studies,[6] we investigated the synthesis of the L-phenylalanine derivatives (**8b** and **8c**) bearing a benzylthio group at the 2-position together with the debenzylthio analogue (**8a**).[7]

The formation of C–S bonds through the reactions of aromatic organolithium compounds with diaryl or dialkyl sulfides has been a method of choice for introduction of an arylthio or alkylthio group into the aromatic nucleus.[8]

† Dedicated to the memory of Emeritus Professor Dr. Yoshio Ban (Hokkaido University).



In this procedure, elemental sulfur instead of sulfides can be used to afford the corresponding lithium thiophenolates.[9] The requisite organolithium compounds may be prepared with high degree of regioselectivity by the directed ortho metalation reaction of appropriate tertiary benzamides.[10] We therefore decided to incorporate this technology into our present synthesis of **8b** and **8c**. Thus, lithiation of *N,N*-diethyl-3,5-dimethoxybenzamide (**9**)[11] with *sec*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) at –78°C proceeded exclusively at the 2-position.[12] The organolithium intermediate that formed *in situ*, on treatment with elemental sulfur at –78°C followed by separate alkylations of the resulting lithium thiolate with benzyl bromide and 4-methoxybenzyl chloride, furnished the thioethers (**10b**) and (**10c**) in 69% and 73% yields, respectively. Reductions of the thioethereal amides (**10b,c**) with $LiAlH_4$ (boiling ether, 7–10 h) provided the amines (**11b**) (87% yield) and (**11c**) (89%), which were then treated with ethyl chloroformate (benzene, room temperature, 7–16 h)[13] to give the benzyl chlorides (**12b**) (92%) and (**12c**) (94%).

According to the "bis-lactim ether" method of Schöllkopf,[14] coupling reaction of 3,5-dimethoxybenzyl chloride (**12a**) with the organolithium reagent (**13**), generated *in situ* by regioselective metalation of (2*R*)-(–)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with *n*-BuLi in THF/hexane at –78°C, was carried out at –50°C for 15 h, producing the *trans* isomer (**14a**) and the *cis* isomer (**15a**) in 69% and 7% yields, respectively. The

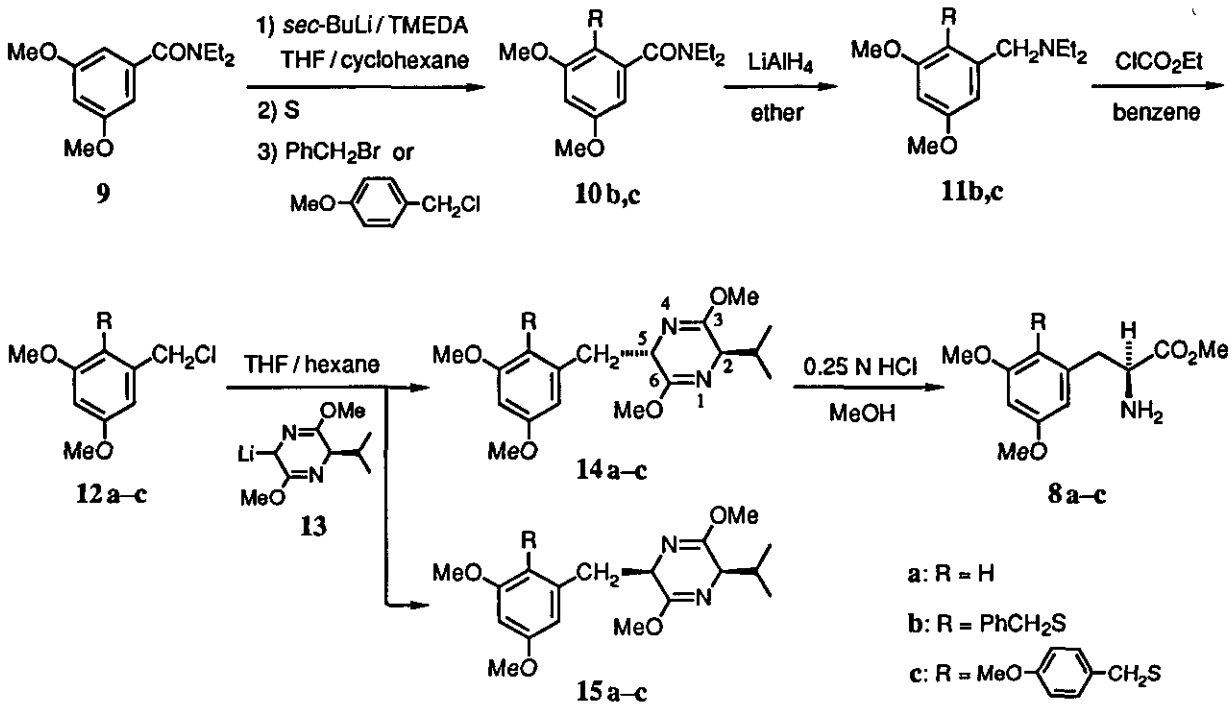


Chart 1

stereochemical assignments to **14a** and **15a** were based on their ratio of formation (**14a** : **15a** = 10 : 1)[6,14] and the ^{1}H nmr spectral outcome that the C(2)-proton (δ 3.46) of **14a** resonated in $CDCl_3$ at higher field than the corresponding proton (δ 3.81) of **15a**, owing to the shielding effect of the aromatic ring.[6b,14a] Parallel coupling reactions of the chlorides (**12b,c**) with the organolithium reagent (**13**) provided the *trans* isomers (**14b**) [61%, ^{1}H nmr ($CDCl_3$) δ: 3.62 [C(2)-H]] and (**14c**) [55%, ^{1}H nmr ($CDCl_3$) δ: 3.63 [C(2)-H]], together with the *cis* isomers (**15b**) [6%, ^{1}H nmr ($CDCl_3$) δ: 3.84 [C(2)-H]] and (**15c**) [7%, ^{1}H nmr ($CDCl_3$) δ: 3.84 [C(2)-H]], respectively. In the latter case, generation of the organolithium species by using lithium diisopropylamide (LDA) instead of *n*-BuLi raised the yield of **14c** to 77%.

Finally, the *trans* bis-lactim ethers (**14a–c**) were separately hydrolyzed in MeOH with 0.25 N aqueous HCl at room temperature for 5–6 h, affording the amino esters (**8a–c**) in 87–89% yields. The enantiomeric purities of **8a–c** thus obtained were determined to be 95–97% by means of ^{1}H nmr spectroscopy using a chiral shift reagent.

In summary, syntheses of the L-phenylalanine derivatives (**8b,c**) bearing a benzylthio group at the 2-position have now become feasible through the above 5-step synthetic route starting from *N,N*-diethyl-3,5-dimethoxybenzamide (**9**). The combination of this route with our general synthetic route[6] to 5-arylthio-3-methyl-L-histidines appears to elevate the potential for the synthesis of the asteroid alkaloid imbricatine (**7**).

EXPERIMENTAL

General Notes. All melting points were taken on a Büchi model 530 capillary melting point apparatus and are corrected. See ref. 6b for details of chromatography, instrumentation, and measurements. Elemental analyses and ms measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: d = doublet, dd = doublet-of-doublets, ddd = doublet-of-dd's, dq = doublet-of-quartets, dt = doublet-of-triplets, m = multiplet, q = quartet, s = singlet, t = triplet.

***N*,*N*-Diethyl-3,5-dimethoxy-2-[(phenylmethyl)thio]benzamide (10b).** A solution of *N*,*N*-diethyl-3,5-dimethoxybenzamide (**9**)[11] (5.93 g, 25.0 mmol) and TMEDA (3.75 ml, 25.0 mmol) in dry THF (150 ml) was stirred at –78°C in an atmosphere of N_2, and a 1.05 M solution (26 ml, 27.3 mmol) of *sec*-BuLi in cyclohexane was added dropwise over 20 min. The mixture was stirred at –78°C for 1 h, and then powdered sulfur crystals (840 mg, 26.2 mg.-atom) were added in one aliquot. After the mixture had been stirred at the same temperature for 45 min, benzyl bromide (3.1 ml, 26 mmol) was added, and stirring was continued for a further 1 h. The reaction was quenched by adding saturated aqueous NH_4Cl (30 ml), and the mixture was allowed to warm to room temperature. The aqueous layer was separated from the organic layer and extracted with ether. The ethereal extracts and the above organic layer were combined, washed successively with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a yellow oil. Purification of the oil by flash chromatography[15] [CH_2Cl_2–AcOEt (10 : 1, v/v)] provided **10b** (6.20 g, 69%) as a colorless oil, ms *m/z*: 359 (M^+); ir $\nu_{max}^{CHCl_3}$ 1620 cm^{-1} (amide CO); ^1H nmr ($CDCl_3$) δ: 0.98 and 1.26 (6H, t each, J = 7 Hz, two CMe's), 2.88 (2H, q, J = 7 Hz), 3.26 (1H, dq, J = 14, 7 Hz), and 3.82 (1H, dq, J = 14, 7 Hz) (two NCH_2's), 3.75 and 3.80 (3H each, s, two OMe's), 3.86 and 4.11 (2H, AB type d's, J = 12 Hz, $SC\underline{H_2}Ph$), 6.37 and 6.39 [2H, AB type d's, J = 2.5 Hz, C(4)-H and C(6)-H], 7.20 (5H, m, $SCH_2\underline{Ph}$).

***N*,*N*-Diethyl-3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]benzamide (10c).** A stirred solution of **9**[11] (23.0 g, 96.9 mmol) and TMEDA (17.6 ml, 117 mmol) in dry THF (320 ml) was cooled to –78°C in an atmosphere of N_2, and a 1.13 M solution (103 ml, 116 mmol) of *sec*-BuLi in cyclohexane was added dropwise over 25 min. After the mixture had been stirred for 30 min, powdered sulfur crystals (4.35 g, 136 mg.-atom) were added in one aliquot. Stirring was then continued for 2.5 h, and 4-methoxybenzyl chloride (19.7 ml, 145 mmol) was added dropwise over 5 min. The reaction mixture was then warmed to 0°C, stirred for 2 h, and worked up in a manner similar to that described above for **10b**. Purification of the crude oily product by flash chromatography[15] [hexane–AcOEt (1 : 1, v/v)] yielded **10c** (27.6 g, 73%) as a pale yellow oil, ms *m/z*: 389 (M^+); ir $\nu_{max}^{CHCl_3}$ 1620 cm^{-1} (amide CO); ^1H nmr ($CDCl_3$) δ: 0.99 and 1.26 (6H, t each, J = 7 Hz, two CMe's), 2.92 (2H, q, J = 7 Hz), 3.28 (1H, dq, J = 14, 7 Hz), and 3.82 (1H, dq, J = 14, 7 Hz) (two NCH_2's), 3.76, 3.78, and 3.80 (3H each, s, three OMe's), 3.83 and 4.07 (2H, AB type d's, J = 11.5 Hz, $SC\underline{H_2}Ar$), 6.37

and 6.40 [2H, AB type d's, J = 2.5 Hz, C(4)-H and C(6)-H], 6.75 [2H, d, J = 9 Hz, C(3')-H and C(5')-H], 7.16 [2H, d, J = 9 Hz, C(2')-H and C(6')-H].[16]

***N,N*-Diethyl-3,5-dimethoxy-2-[(phenylmethyl)thio]benzenemethanamine (11b).** A suspension of $LiAlH_4$ (1.21 g, 31.9 mmol) in dry ether (100 ml) was stirred in an atmosphere of N_2 under ice-cooling, and a solution of **10b** (5.75 g, 16.0 mmol) in dry ether (20 ml) was added dropwise over 20 min. After the mixture had been heated under reflux for 7 h, H_2O (1.2 ml), 15% aqueous NaOH (1.2 ml), and H_2O (3.6 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 and extracted with 10% aqueous HCl (3 × 20 ml). The aqueous solution was made basic with 10% aqueous NaOH and extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave **11b** (4.81 g, 87%) as a faintly yellowish oil. A portion of the oil was purified by flash chromatography[15] (AcOEt) to afford a colorless oil, ms *m/z*: 345 (M^+); ^1H nmr ($CDCl_3$) δ: 0.93 (6H, t, J = 7 Hz, two CMe's), 2.36 (4H, q, J = 7 Hz, two $NC\underline{H_2}Me$'s), 3.43 (2H, s, $NC\underline{H_2}Ar$), 3.81 (3H) and 3.86 (5H) (s each, two OMe's and $SC\underline{H_2}Ph$), 6.36 [1H, d, J = 2.5 Hz, C(4)-H], 6.78 [1H, d, J = 2.5 Hz, C(6)-H], 6.9–7.2 (5H, m, $SCH_2\underline{Ph}$).

***N,N*-Diethyl-3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]benzenemethanamine (11c).** Reduction of **10c** (3.12 g, 8.0 mmol) with $LiAlH_4$ (610 mg, 16.1 mmol) in boiling dry ether (60 ml) for 10 h and work-up of the reaction mixture were conducted as described above for **11b**. Purification of the crude oily product by flash chromatography[15] (AcOEt) afforded **11c** (2.67 g, 89%) as a faintly yellowish oil, ms *m/z*: 375 (M^+); ^1H nmr ($CDCl_3$) δ: 0.94 (6H, t, J = 7 Hz, two CMe's), 2.37 (4H, q, J = 7 Hz, two $NC\underline{H_2}Me$'s), 3.44 (2H, s, $NC\underline{H_2}Ar$), 3.74 (3H), 3.81 (5H), and 3.87 (3H) (s each, three OMe's and $SC\underline{H_2}Ar$), 6.36 [1H, d, J = 2.5 Hz, C(4)-H], 6.70 [2H, d, J = 9 Hz, C(3')-H and C(5')-H], 6.80 [1H, d, J = 2.5 Hz, C(6)-H], 6.97 [2H, d, J = 9 Hz, C(2')-H and C(6')-H].[16]

1-(Chloromethyl)-3,5-dimethoxy-2-[(phenylmethyl)thio]benzene (12b). A solution of **11b** (4.66 g, 13.5 mmol) and ethyl chloroformate (1.76 g, 16.2 mmol) in benzene (100 ml) was stirred at room temperature for 7 h. The reaction mixture was concentrated *in vacuo* to leave a yellow oil. Purification of the oil by flash chromatography[15] [hexane–CH_2Cl_2 (3 : 2, v/v)] gave **12b** (3.83 g, 92%) as a colorless oil, ms *m/z*: 310, 308 (M^+); ^1H nmr ($CDCl_3$) δ: 3.82 and 3.86 (3H each, s, two OMe's), 3.90 (2H, s, $SC\underline{H_2}Ph$), 4.51 (2H, s, CH_2Cl), 6.44 [1H, d, J = 2.5 Hz, C(4)-H], 6.57 [1H, d, J = 2.5 Hz, C(6)-H], 6.95–7.25 (5H, m, $SCH_2\underline{Ph}$).

1-(Chloromethyl)-3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]benzene (12c). A solution of **11c** (3.42 g, 9.1 mmol) and ethyl chloroformate (1.19 g, 11.0 mmol) in benzene (60 ml) was stirred at room temperature for 16 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 oil. Purification of the oil by flash chromatography[15] [hexane–CH_2Cl_2 (3 : 2, v/v)] gave **12c** (2.90 g, 94%) as a colorless solid. Recrystallization from hexane furnished an analytical sample as colorless minute needles, mp 78.5–79.5°C; ms *m/z*: 340, 338 (M^+); ^1H nmr ($CDCl_3$) δ: 3.76 (3H), 3.82 (3H), and 3.87 (5H) (s each, three OMe's and $SC\underline{H}_2Ar$), 4.54 (2H, s, CH_2Cl), 6.44 [1H, d, J = 2.5 Hz, C(4)-H], 6.58 [1H, d, J = 2.5 Hz, C(6)-H], 6.73 [2H, d, J = 9 Hz, C(3')-H and C(5')-H], 7.01 [2H, d, J = 9 Hz, C(2')-H and C(6')-H].[16] *Anal.* Calcd for $C_{17}H_{19}O_3ClS$: C, 60.26; H, 5.65. Found: C, 60.30; H, 5.65.

(2*R-trans*)-2,5-Dihydro-3,6-dimethoxy-5-[(3,5-dimethoxyphenyl)methyl]-2-(1-methylethyl)-pyrazine (14a) and (2*R-cis*)-2,5-Dihydro-3,6-dimethoxy-5-[(3,5-dimethoxyphenyl)methyl]-2-(1-methylethyl)pyrazine (15a). A stirred solution of (2*R*)-(–)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[17] (1.93 g, 10.3 mmol) in dry THF (30 ml) was cooled to –78°C in an atmosphere of N_2, and a 1.47 M solution (7.5 ml, 11.0 mmol) of *n*-BuLi in hexane was added dropwise over 15 min. After the mixture had been stirred at –78°C for 30 min, a solution of 3,5-dimethoxybenzyl chloride (1.87 g, 10.0 mmol) in dry THF (10 ml) was added dropwise over 15 min, and the resulting mixture was stirred first at –78°C for 1 h and then at –50°C for 15 h. The reaction was quenched by adding saturated aqueous NH_4Cl (20 ml) at –50°C. After having been allowed to warm to room temperature, 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 Na_2SO_4, and concentrated *in vacuo* to leave a colorless oil, which was subjected to flash chromatography[15] [CH_2Cl_2–hexane–AcOEt (8 : 6 : 1, v/v)]. Earlier fractions provided **14a** (2.30 g, 69%) as a colorless oil, $[\alpha]_D^{20}$ +65.0° (*c* 0.51, $CHCl_3$); ms *m/z*: 334 (M^+); ir ν_{max}^{film} 1698 cm^{-1} (C=N); ^1H nmr ($CDCl_3$) δ: 0.63 and 0.97 (3H each, d, J = 7 Hz, $CH\underline{Me}_2$), 2.18 (1H, m, $C\underline{H}Me_2$), 3.03 (2H, d, J = 5 Hz, $C\underline{H}_2Ar$), 3.46 [1H, dd, J = 3.5 Hz each, C(2)-H], 3.70 (3H), 3.71 (3H), and 3.74 (6H) (s each, four OMe's), 4.30 [1H, dt, J = 5, 3.5 Hz, C(5)-H], 6.30 (3H, s, aromatic protons).

Later fractions of the above chromatography afforded a colorless oil (295 mg), which was purified by flash chromatography[15] [hexane–AcOEt (5 : 1, v/v)] to give **15a** (229 mg, 7%) as a colorless oil, $[\alpha]_D^{20}$ –90.5° (*c* 0.50, $CHCl_3$); ms *m/z*: 334 (M^+); ir ν_{max}^{film} 1696 cm^{-1} (C=N); ^1H nmr ($CDCl_3$) δ: 0.36 and 0.93 (3H each, d, J = 7 Hz, $CH\underline{Me}_2$), 1.88 (1H, m, $C\underline{H}Me_2$), 2.96 (1H, dd, J = 13, 6 Hz) and 3.09 (1H, dd, J = 13, 4.5 Hz) ($C\underline{H}_2Ar$), 3.67 (3H), 3.72 (3H), and 3.75 (6H) (s each, four OMe's), 3.81 [1H, dd, J = 5, 4 Hz, C(2)-H], 4.30 [1H, ddd, J = 6, 5, 4.5 Hz, C(5)-H], 6.25–6.4 (3H, m, aromatic protons).

(2*R-trans*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-dimethoxy-2-[(phenylmethyl)thio]phenyl]-methyl]-2-(1-methylethyl)pyrazine (14b) and (2*R-cis*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-dimethoxy-2-[(phenylmethyl)thio]phenyl]methyl]-2-(1-methylethyl)pyrazine (15b). A stirred solution of (2*R*)-(–)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[17] (1.22 g, 6.6 mmol) in dry THF (20 ml)

was cooled to –78°C in an atmosphere of N_2, and a 1.18 M solution (6.1 ml, 7.2 mmol) of *n*-BuLi in hexane was added dropwise over 10 min. After the mixture had been stirred for 20 min, a solution of **12b** (1.85 g, 6.0 mmol) in dry THF (5 ml) was added dropwise over 10 min, and the resulting mixture was stirred first at –78°C for 1 h and then at –50°C for 14 h. The reaction mixture was worked up in a manner similar to that described above for **14a** and **15a**, and the crude oily products were separated by flash chromatography[15] (CH_2Cl_2). Earlier fractions furnished **14b** (1.67 g, 61%) as a colorless oil, $[\alpha]_D^{26}$ +50.9° (*c* 0.55, $CHCl_3$); ms *m/z*: 456 (M^+); ir $\nu_{max}^{CHCl_3}$ 1694 cm^{-1} (C=N); ^1H nmr ($CDCl_3$) δ: 0.62 and 0.98 (3H each, d, *J* = 7 Hz, CH<u>Me</u>$_2$), 2.17 (1H, m, C<u>H</u>Me$_2$), 2.81 (1H, dd, *J* = 13, 7.5 Hz) and 3.36 (1H, dd, *J* = 13, 4.5 Hz) [C(5)-CH_2], 3.61, 3.70, 3.76, and 3.85 (3H each, s, four OMe's), 3.62 [1H, dd, *J* = 3.5 Hz each, C(2)-H], 3.83 (2H, s, SC<u>H</u>$_2$Ph), 4.17 [1H, ddd, *J* = 7.5, 4.5, 3.5 Hz, C(5)-H], 6.35 [2H, s, C(4')-H and C(6')-H], 6.95–7.2 (5H, m, SCH$_2$<u>Ph</u>).[18]

Later fractions of the above chromatography afforded a yellowish oil, which was purified by flash chromatography[15] [hexane–AcOEt (4 : 1, v/v)] to give **15b** (175 mg, 6%) as a slightly yellowish oil, $[\alpha]_D^{26}$ –66.0° (*c* 0.53, $CHCl_3$); ms *m/z*: 456 (M^+); ir $\nu_{max}^{CHCl_3}$ 1694 cm^{-1} (C=N); ^1H nmr ($CDCl_3$) δ: 0.68 and 1.01 (3H each, d, *J* = 7 Hz, CH<u>Me</u>$_2$), 1.99 (1H, m, C<u>H</u>Me$_2$), 2.76 (1H, dd, *J* = 13, 8.5 Hz) and 3.29 (1H, dd, *J* = 13, 5 Hz) [C(5)-CH_2], 3.60, 3.67, 3.78, and 3.86 (3H each, s, four OMe's), 3.82 (2H, s, SC<u>H</u>$_2$Ph), 3.84 [1H, dd, *J* = 4.5 Hz each, C(2)-H], 4.15 [1H, ddd, *J* = 8.5, 5, 4.5 Hz, C(5)-H], 6.36 and 6.42 [2H, AB type d's, *J* = 2.5 Hz, C(4')-H and C(6')-H], 6.95–7.2 (5H, m, SCH$_2$<u>Ph</u>).[18]

(2*R-trans*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]-thio]phenyl]methyl]-2-(1-methylethyl)pyrazine (14c) and (2*R-cis*)-2,5-Dihydro-3,6-dimethoxy-5-[[3,5-dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]phenyl]methyl]-2-(1-methylethyl)-pyrazine (15c). (i) By the *n*-BuLi Method: Alkylation of (2*R*)-(–)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine[17] (1.01 g, 5.5 mmol) with **12c** (1.69 g, 5.0 mmol) and work-up of the reaction mixture were effected in a manner similar to that described above for **14a** and **15a**, and the crude oily products were separated by flash chromatography[15] [hexane–AcOEt (4 : 1, v/v)]. Earlier fractions provided **14c** (1.34 g, 55%) as a colorless oil, $[\alpha]_D^{20}$ +58.9° (*c* 0.54, $CHCl_3$); ms *m/z*: 486 (M^+); ir ν_{max}^{film} 1695 cm^{-1} (C=N); ^1H nmr ($CDCl_3$) δ: 0.62 and 0.98 (3H each, d, *J* = 7 Hz, CH<u>Me</u>$_2$), 2.18 (1H, m, C<u>H</u>Me$_2$), 2.84 (1H, dd, *J* = 13, 7.5 Hz) and 3.38 (1H, dd, *J* = 13, 4.5 Hz) [C(5)-CH_2], 3.61, 3.70, 3.75, 3.76, and 3.86 (3H each, s, five OMe's), 3.63 [1H, dd, *J* = 3.5 Hz each, C(2)-H], 3.80 (2H, s, SC<u>H</u>$_2$Ar), 4.19 [1H, ddd, *J* = 7.5, 4.5, 3.5 Hz, C(5)-H], 6.35 [2H, s, C(4')-H and C(6')-H], 6.70 [2H, d, *J* = 9 Hz, C(3")-H and C(5")-H], 6.99 [2H, d, *J* = 9 Hz, C(2")-H and C(6")-H].[18] Later fractions of the above chromatography gave **15c** (166 mg, 7%) as a colorless oil, $[\alpha]_D^{20}$ –57.3° (*c* 0.43, $CHCl_3$); ms *m/z*: 486 (M^+); ir ν_{max}^{film} 1695 cm^{-1} (C=N); ^1H nmr ($CDCl_3$) δ: 0.68 and 1.02 (3H each, d, *J* = 7 Hz, CH<u>Me</u>$_2$), 2.00 (1H, m, C<u>H</u>Me$_2$), 2.79 (1H, dd, *J* = 13, 8.5 Hz) and 3.33 (1H, dd, *J* = 13, 5 Hz) [C(5)-CH_2], 3.60 (3H), 3.68 (3H), 3.75 (3H), 3.78 (5H), and 3.87 (3H) (s each, five OMe's and SC<u>H</u>$_2$Ar), 3.84 [1H, dd, *J*

= 4.5 Hz each, C(2)-H], 4.17 [1H, ddd, J = 8.5, 5, 4.5 Hz, C(5)-H], 6.36 and 6.42 [2H, AB type d's, J = 2.5 Hz, C(4')-H and C(6')-H], 6.69 [2H, d, J = 9 Hz, C(3")-H and C(5")-H], 6.98 [2H, d, J = 9 Hz, C(2")-H and C(6")-H].[18]

(ii) By the LDA Method: A stirred solution of diisopropylamine (3.7 ml, 26.4 mmol) in dry THF (45 ml) was cooled to –78°C in an atmosphere of N_2, and a 1.11 M solution (24 ml, 26.6 mmol) of *n*-BuLi in hexane was added dropwise. After the mixture had been stirred for 40 min, a solution of (2*R*)-(–)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[17] (4.08 g, 22.1 mmol) in dry THF (12 ml) was added dropwise over 5 min. Stirring was then continued for 20 min, and a solution of **12c** (6.78 g, 20.0 mmol) in dry THF (23 ml) was added dropwise over 10 min. After having been stirred at –78°C for a further 2 h and then at –50°C for 24 h, the reaction mixture was worked up as described above for **14a** and **15a**. Purification of the crude oily products by two successive flash chromatographies[15] [CH_2Cl_2; hexane–AcOEt (4 : 1, v/v)] afforded **14c** (7.50 g, 77%), $[\alpha]_D^{16}$ +63.7° (*c* 0.50, $CHCl_3$) and **15c** (879 mg, 9%), which were identical [by comparison of the ir and ^1H nmr spectra] with authentic samples obtained by method (i).

Hydrolysis of the Bis-lactim Ethers (14a–c) to the Amino Esters (8a–c). The hydrolyses of **14a–c** (1 mmol) were separately carried out in a mixture of 0.25 N aqueous HCl (8 ml) and MeOH (8 ml). After having been stirred at room temperature for 5–6 h, the reaction mixtures were concentrated *in vacuo* to half the initial volume, made basic (pH 9–10) with anhydrous Na_2CO_3 or 28% aqueous NH_3, and extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Separate purifications of the oily residues by flash chromatography[15] [CH_2Cl_2–MeOH (20 : 1, v/v) for **8a**; AcOEt for **8b,c**] furnished the amino esters (**8a–c**), which were characterized as follows.

3,5-Dimethoxy-L-phenylalanine Methyl Ester (8a). Obtained in 89% yield as a colorless oil, $[\alpha]_D^{20}$ +19.0° (*c* 1.03, MeOH); ms *m/z*: 239 (M^+); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 and 3330 (NH_2), 1738 (ester CO); ^1H nmr ($CDCl_3$) δ: 1.54 (2H, s, NH_2), 2.79 (1H, dd, J = 13.5, 8 Hz) and 3.05 (1H, dd, J = 13.5, 5 Hz) ($CHC\underline{H}_2Ar$), 3.74 (1H, dd, J = 8, 5 Hz, $C\underline{H}CH_2Ar$), 3.74 (3H) and 3.77 (6H) (s each, three OMe's), 6.35 (3H, s, aromatic protons). The enantiomeric purity[19] of this sample was shown to be 97% by means of ^1H nmr spectroscopy using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] in $CDCl_3$.

3,5-Dimethoxy-2-[(phenylmethyl)thio]-L-phenylalanine Methyl Ester (8b). Isolated in 87% yield as a colorless oil, $[\alpha]_D^{24}$ +1.6° (*c* 1.05, MeOH); ms *m/z*: 361 (M^+); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 and 3330 (NH_2), 1736 (ester CO); ^1H nmr ($CDCl_3$) δ: 1.38 (2H, s, NH_2), 2.75 (1H, dd, J = 13, 9 Hz) and 3.05 (1H, dd, J = 13, 5.5 Hz) ($CHC\underline{H}_2Ar$), 3.55 (1H, dd, J = 9, 5.5 Hz, $C\underline{H}CH_2Ar$), 3.68 (3H), 3.78 (3H), and 3.88 (5H) (s each, three OMe's and $SC\underline{H}_2Ph$), 6.31 and 6.39 [2H, AB type d's, J = 2.5 Hz, C(4)-H and C(6)-H], 6.95–7.25 (5H, m, $SCH_2\underline{Ph}$). The enantiomeric purity of this sample was determined, as in the case of **8a**, to be 95%.

3,5-Dimethoxy-2-[[(4-methoxyphenyl)methyl]thio]-L-phenylalanine Methyl Ester (8c). Obtained in 89% yield as a colorless solid, mp 50–51°C. The enantiomeric purity of this specimen was determined, as in the case of **8a**, to be 95%. Recrystallization of the solid from hexane–AcOEt (3 : 1, v/v) afforded an analytical sample as colorless fluffy needles, mp 51–52°C; $[\alpha]_D^{21}$ +8.9° (*c* 1.03, MeOH); ms *m/z*: 391 (M^+); ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 and 3320 (NH_2), 1736 (ester CO); ^1H nmr ($CDCl_3$) δ: 1.40 (2H, s, NH_2), 2.79 (1H, dd, J = 13, 8.5 Hz) and 3.08 (1H, dd, J = 13, 5.5 Hz) ($CHC\underline{H}_2Ar$), 3.60 (1H, dd, J = 8.5, 5.5 Hz, $C\underline{H}CH_2Ar$), 3.68, 3.76, 3.79, and 3.89 (3H each, s, four OMe's), 3.86 (2H, s, $SC\underline{H}_2Ar$), 6.33 and 6.39 [2H, AB type d's, J = 2.5 Hz, C(4)-H and C(6)-H], 6.72 [2H, d, J = 9 Hz, C(3')-H and C(5')-H], 7.00 [2H, d, J = 9 Hz, C(2')-H and C(6')-H].[16] *Anal.* Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.32; H, 6.54; N, 3.57.

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