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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of 3-heteroaromatic-substituted alanines

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Abstract

An asymmetric synthesis of (*R*)-3-heterocyclic-substituted alanines starting from (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (Schöllkopf reagent) and heteroaromatic halogenomethyl derivatives via hydrolysis of intermediate adducts is reported. The diastereocontrolled addition gives mainly compounds with the (2*S*,5*R*) configuration whose formation is explained on the basis of the accepted model for the alkylation reaction of the Schöllkopf reagent, and structure confirmed by spectroscopic data.

1. Introduction

Derivatives of α-amino acids are important as bioactive compounds[1] and chiral auxiliaries or synthons[2] in organic synthesis. Both (D)- and (L)-α-amino acids have different uses and thus are required in the homochiral form. Moreover, some heterocyclic alanines such as (L)-3-(2-thienyl)-alanine[3] and (L)-3-(2-pyridyl)alanine[4] are useful precursors in the preparation of Bradykinin and Angiotensin II, respectively. The general interest in pyridyl and thienylalanines prompted us to study a method for the stereocontrolled synthesis of β-heteroaromatic-substituted alanines. Although other systems have been described[3,5] for the preparation of the above-mentioned compounds the principal drawbacks to these approaches are that resolution is required to obtain single enantiomers. Methods for preparing enantiomerically enriched α-amino acids such as chemical or kinetic resolution generally suffer some limitations in comparison with asymmetric synthesis.

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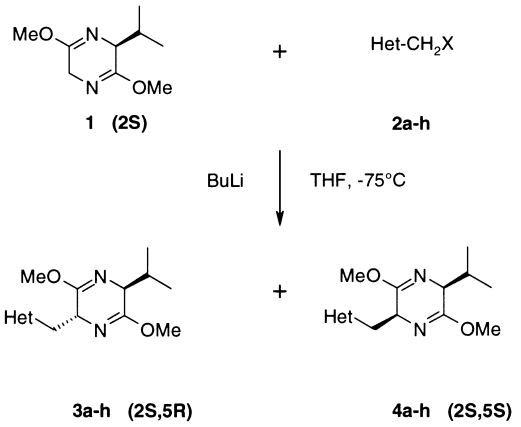
2. Results and discussion

As a part of our current interest in the stereoselective synthesis of heteroaromatic α-amino acid derivatives we now present results on the preparation of β-heteroaromatic-substituted alanines. Our approach to the preparation of homochiral precursors of β-heterocyclic substituted alanines is based on the use of a chiral glycine enolate synthon. Among those available we chose 2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **1**, 'Schöllkopf reagent' owing to its commercial availability in both the enantiopure (*R*)- and (*S*)-forms and the great number of reported examples in asymmetric synthesis.[6] To our knowledge, none of these deals with the use of **1** in nucleophilic substitution with halogenomethyl heteroaromatic compounds.

The reaction of (*S*)-**1** with **2a–h** were carried out in THF solution at –75°C according to the general method described in the Experimental section. TLC and NMR analysis of the crude reaction mixture showed the presence of two diastereoisomers, in different relative ratios. Since these isomers are separable by chromatography it is possible to obtain both as pure compounds. The configurations were assigned on the basis of analytical and spectroscopic data and on the accepted model[6] for the reaction of **1** with **2** (Scheme 1). In this way the (2*S*,5*R*)- and (2*S*,5*S*)-relative configurations can be established for the major **3a–h** and minor **4a–h** adducts respectively. Table 1 lists yields and d.e.s for compounds **3a–h** and **4a–h**.

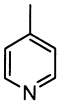
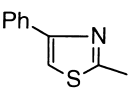
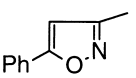


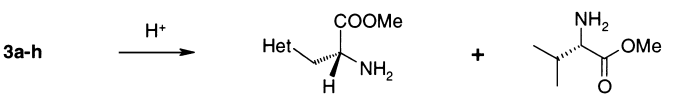
Scheme 1.

The accepted energetically favoured transition state involving attack of the electrophile from the face opposite to the 2-isopropyl group would give the product where the C-2 and C-5 substituents are in the *trans* relationship.[6] This model, verified by a large number of examples, allows the relative configuration of the 5-position of the pyrazine moiety, in a carbon–carbon bond-forming step, to be controlled.

Upon hydrolysis of adducts **3a–h** with 2 equivalents of 0.3N HCl at room temperature for 24–36 h the corresponding alanine methyl ester derivatives **5a–h** were obtained in good yields as well as methyl (L)-valinate **6**, the chiral auxiliary in this protocol. The two products can be separated by flash chromatography or bulb-to-bulb distillation allowing the recovery of substituted alanines reported in Scheme 2.

Table 1

	Het	Yield of 3+4	D.e. (%) of 3	Yield of 5	E.e % of 5
a		68	91	62	>98%
b		73	82	74	>98%
c		73	85	67	>98%
d		55	92	72	>98%
e		95	85	83	>98%
f		68	83	64	>98%
g		51	74	91	>98%
h		44	90[7]	94	>98%



5a-h 6

Scheme 2.

The structures of alanine methyl ester derivatives **5a**–**h** were supported by analytical and spectroscopic data. The (2*R*)-configuration assigned to the products deriving from the major adducts **3a**–**h** was confirmed by comparison of the specific rotation observed for **5a** with the value of methyl (2*R*)-3-(4-pyridyl)propionate prepared by treatment with diazomethane of the corresponding acid, whose configuration has been previously established.[5] Finally, the e.e. was determined by HPLC analysis on chiral OD-R column (eluent MeOH:H_2O = 8:2) by comparison with the racemic material.

3. Experimental

Elemental analyses were performed by the Microanalytical Laboratory of the Department. All the ^{1}H NMR spectra were recorded in $CDCl_3$ solution by means of a Brüker AC 300 spectrometer. Chemical shifts (δ) are reported in ppm and all the coupling constants (J) are in hertz. Optical rotations were measured using a Perkin–Elmer 241 polarimeter.

3.1. General procedure for the preparation of adducts **3a–h** and **4a–h**

To a solution of **1** (0.5 g, 2.72 mmol) in anhydrous THF (25 ml) cooled at –75°C, butyl lithium (3.2 mmol, 2 ml of a 1.6N solution in hexane) was added and the mixture stirred for 30 min. The appropriate halogenomethyl derivate **2a–h** (2.72 mmol) in THF (20 ml) was added and the mixture stirred at –75°C for 4–6 h. The reaction mixture was allowed to warm to 0°C and ammonium chloride (25 ml, 1 M solution) was added. The solvent was evaporated off and the residue taken up with diethyl ether. The organic phase was separated and dried with Na_2SO_4, the solvent evaporated in vacuo and the residue chromatographed on silica gel (toluene:ethyl acetate = 9:1). In this way the following compounds were isolated.

3.1.1. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pyridylmethyl)pyrazine **3a**

Oil; ^{1}H NMR: δ 0.62 (3H, d, J = 6.81, Me_2C), 0.95 (3H, d, J = 6.81, Me_2C), 2.15 (1H, m, Me_2CH), 3.05 (2H, m, CH_2), 3.50 (1H, t, J = 3.52 and 3.49, H-2 pyrazine), 3.63 (3H, s, OMe), 3.73 (3H, s, OMe), 4.30 (1H, m, H-5 pyrazine), 7.05 (2H, d, J = 6.89, H-3 and H-5 pyridyl), 8.43 (2H, d, J = 6.89, H-2 and H-6 pyridyl). Anal. calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.38; H, 7.65; N, 15.19.

3.1.2. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pyridylmethyl)pyrazine **4a**

Oil; ^{1}H NMR: δ 0.30 (3H, d, J = 6.82, Me_2C), 0.91 (3H, d, J = 6.82, Me_2C), 2.01 (1H, m, Me_2CH), 3.00 (2H, m, CH_2), 3.49 (1H, t, J = 3.49 and 3.48, H-2 pyrazine), 3.61 (3H, s, OMe), 3.72 (3H, s, OMe), 4.30 (1H, m, H-5 pyrazine), 7.09 (2H, d, J = 6.85, H-3 and H-5 pyridyl), 8.45 (2H, d, J = 6.85, H-2 and H-6 pyridyl). Anal. calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.33; H, 7.61; N, 15.18.

3.1.3. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-pyridylmethyl)pyrazine **3b**

Oil; ^{1}H NMR: δ 0.60 (3H, d, J = 6.90, Me_2C), 0.97 (3H, d, J = 6.90, Me_2C), 2.15 (1H, m, Me_2CH), 3.02 (1H, AB syst., J = 13.25 and 7.45, CH_2), 3.35 (1H, AB syst., J = 13.25 and 5.28, CH_2), 3.58 (3H, s, OMe), 3.65 (1H, t, J = 3.62 and 3.49, H-2 pyrazine), 3.70 (3H, s, OMe), 4.45 (1H, m, H-5 pyrazine), 7.08 (2H, m, H-3 and H-5 pyridyl), 7.50 (1H, m, H-4 pyridyl), 8.50 (1H, d, J = 5.50, H-6 pyridyl). Anal. calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.39; H, 7.64; N, 15.22.

3.1.4. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-pyridylmethyl)pyrazine **4b**

Oil; ^{1}H NMR: δ 0.58 (3H, d, J = 6.90, Me_2C), 1.05 (3H, d, J = 6.90, Me_2C), 2.05 (1H, m, Me_2CH), 2.90 (1H, AB syst., J = 13.36 and 8.67, CH_2), 3.35 (1H, AB syst., J = 13.36 and 5.31, CH_2), 3.57 (3H, s, OMe), 3.70 (3H, s, OMe), 3.75 (1H, t, J = 3.57, H-2 pyrazine), 4.50 (1H, m, H-5 pyrazine), 7.13 (2H, m, H-3 and H-5 pyridyl), 7.60 (1H, m, H-4 pyridyl), 8.55 (1H, d, J = 5.50, H-6 pyridyl). Anal. calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N,15.26. Found: C, 65.35; H, 7.61; N, 15.21.

3.1.5. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-thienylmethyl)pyrazine ***3c***

Oil; ^{1}H NMR: δ 0.62 (3H, d, $J=6.85$, Me_2C), 0.97 (3H, d, $J=6.85$, Me_2C), 2.17 (1H, m, Me_2CH), 3.22 (1H, AB syst., $J=13.04$ and 5.19, CH_2), 3.32 (1H, AB syst., $J=13.04$ and 5.33, CH_2), 3.55 (1H, t, $J=3.51$ and 3.48, H-2 pyrazine), 3.70 (3H, s, OMe), 3.75 (3H, s, OMe), 4.29 (1H, m, H-5 pyrazine), 6.79 (1H, d, $J=3.45$, H-3 thienyl), 6.88 (1H, dd, $J=5.09$ and 3.45, H-4 thienyl), 7.10 (1H, d, $J=5.09$, H-5 thienyl). Anal. calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99. Found: C, 59.89; H, 7.18; N, 9.87.

3.1.6. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-thienylmethyl)pyrazine ***4c***

Oil; ^{1}H NMR: δ 0.30 (3H, d, $J=6.85$, Me_2C), 0.95 (3H, d, $J=6.85$, Me_2C), 1.99 (1H, m, Me_2CH), 3.48 (2H, m, CH_2), 3.55 (1H, t, $J=3.50$ and 3.45, H-2 pyrazine), 3.70 (3H, s, OMe), 3.72 (3H, s, OMe), 4.20 (1H, m, H-5 pyrazine), 6.75 (1H, d, $J=3.48$, H-3 thienyl), 6.89 (1H, dd, $J=5.05$ and 3.48, H-4 thienyl), 7.05 (1H, d, $J=5.05$, H-5 thienyl). Anal. calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99. Found: C, 59.86; H, 7.15; N, 9.86.

3.1.7. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(3-thienylmethyl)pyrazine ***3d***

Oil; ^{1}H NMR: δ 0.61 (3H, d, $J=6.79$, Me_2C), 0.98 (3H, d, $J=6.79$, Me_2C), 2.18 (1H, m, Me_2CH), 3.12 (2H, m, CH_2), 3.40 (1H, t, $J=3.59$ and 3.50, H-2 pyrazine), 3.68 (3H, s, OMe), 3.71 (3H, s, OMe), 4.27 (1H, m, H-5 pyrazine), 6.83 (1H, d, $J=4.80$, H-4 thienyl), 6.91 (1H, d, $J=2.76$, H-2 thienyl), 7.18 (1H, dd, $J=4.80$ and 2.76, H-5 thienyl). Anal. calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99. Found: C, 59.86; H, 7.15; N, 9.91.

3.1.8. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(3-thienylmethyl)pyrazine ***4d***

Oil; ^{1}H NMR: δ 0.33 (3H, d, $J=6.75$, Me_2C), 0.91 (3H, d, $J=6.75$, Me_2C), 1.95 (1H, m, Me_2CH), 3.12 (2H, m, CH_2), 3.40 (1H, t, $J=3.49$ and 3.41, H-2 pyrazine), 3.67 (3H, s, OMe), 3.71 (3H, s, OMe), 4.27 (1H, m, H-5 pyrazine), 6.82 (1H, d, $J=4.75$, H-4 thienyl), 6.90 (1H, d, $J=2.69$, H-2 thienyl), 7.18 (1H, dd, $J=4.75$ and 2.69, H-5 thienyl). Anal. calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99. Found: C, 59.90; H, 7.15; N, 9.91.

3.1.9. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-furylmethyl)pyrazine ***3e***

Oil; ^{1}H NMR: δ 0.65 (3H, d, $J=6.85$, Me_2C), 1.00 (3H, d, $J=6.85$, Me_2C), 2.20 (1H, m, Me_2CH), 3.00 (2H, d, $J=6.50$, CH_2), 3.60 (1H, t, $J=3.35$ and 3.29, H-2 pyrazine), 3.65 (3H, s, OMe), 3.70 (3H, s, OMe), 4.25 (1H, m, H-5 pyrazine), 5.95 (1H, d, $J=1.85$, H-3 furyl), 6.24 (1H, dd, $J=3.80$ and 1.85, H-4 furyl), 7.28 (1H, d, $J=3.80$, H-5 furyl). Anal. calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.57; H, 7.60; N, 10.52.

3.1.10. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-furylmethyl)pyrazine ***4e***

Oil; ^{1}H NMR: δ 0.50 (3H, d, $J=6.95$, Me_2C), 1.00 (3H, d, $J=6.95$, Me_2C), 2.00 (1H, m, Me_2CH), 3.08 (2H, d, $J=6.47$, CH_2), 3.59 (1H, t, $J=3.23$, H-2 pyrazine), 3.64 (3H, s, OMe), 3.68 (3H, s, OMe), 4.25 (1H, m, H-5 pyrazine), 5.95 (1H, d, $J=1.81$, H-3 furyl), 6.24 (1H, dd, $J=3.75$ and 1.81, H-4 furyl), 7.28 (1H, d, $J=3.75$, H-5 furyl). Anal. calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.58; H, 7.61; N, 10.54.

3.1.11. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-thiazolylmethyl)pyrazine ***3f***

Oil; ^{1}H NMR: δ 0.68 (3H, d, $J=6.92$, Me_2C), 1.01 (3H, d, $J=6.92$, Me_2C), 2.21 (1H, m, Me_2CH), 3.42 (1H, AB syst., $J=13.64$ and 6.17, CH_2), 3.60 (1H, AB syst., $J=13.64$ and 4.91,

CH_2), 3.70 (3H, s, OMe), 3.71 (3H, s, OMe), 3.78 (1H, t, $J=3.51$ and 3.47, H-2 pyrazine), 4.37 (1H, m, H-5 pyrazine), 7.19 (1H, d, $J=3.10$, H-4 thiazolyl), 7.68 (1H, d, $J=3.10$, H-5 thiazolyl). Anal. calcd for $C_{13}H_{19}N_3O_2S$: C, 55.49; H, 6.81; N, 14.93. Found: C, 55.38; H, 6.77; N, 14.90.

3.1.12. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2-thiazolylmethyl)pyrazine ***4f***

Oil; ^{1}H NMR: δ 0.51 (3H, d, $J=6.89$, Me_2C), 1.00 (3H, d, $J=6.89$, Me_2C), 2.12 (1H, m, Me_2CH), 3.22 (1H, AB syst., $J=13.00$ and 5.05, CH_2), 3.60 (1H, AB syst., $J=13.04$ and 4.23, CH_2), 3.69 (3H, s, OMe), 3.70 (3H, s, OMe), 3.81 (1H, t, $J=3.41$ and 3.29, H-2 pyrazine), 4.30 (1H, m, H-5 pyrazine), 7.19 (1H, d, $J=3.10$, H-4 thiazolyl), 7.68 (1H, d, $J=3.10$, H-5 thiazolyl). Anal. calcd for $C_{13}H_{19}N_3O_2S$: C, 55.49; H, 6.81; N, 14.93. Found: C, 55.39; H, 6.77; N, 14.91.

3.1.13. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[(4-phenylthiazol-2-yl)methyl]pyrazine ***3g***

Oil; ^{1}H NMR: δ 0.73 (3H, d, $J=6.85$, Me_2C), 1.03 (3H, d, $J=6.85$, Me_2C), 2.24 (1H, m, Me_2CH), 3.46 (2H, AB syst., $J=14.46$ and 6.94, CH_2), 3.72 (2H, AB syst., $J=14.46$ and 4.32, CH_2), 3.72 (3H, s, OMe), 3.74 (3H, s, OMe), 3.85 (1H, t, $J=3.56$ and 3.47, H-2 pyrazine), 4.42 (1H, m, H-5 pyrazine), 7.35 (1H, s, H-5 thiazolyl), 7.28–7.91 (5H, m, phenyl). Anal. calcd for $C_{19}H_{23}N_3O_2S$: C, 63.84; H, 6.49; N, 11.75. Found: C, 63.77; H, 6.43; N, 11.68.

3.1.14. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[(4-phenylthiazol-2-yl)methyl]pyrazine ***4g***

Oil; ^{1}H NMR: δ 0.53 (3H, d, $J=6.83$, Me_2C), 1.04 (3H, d, $J=6.83$, Me_2C), 2.24 (1H, m, Me_2CH), 3.29 (2H, m, CH_2), 3.72 (3H, s, OMe), 3.76 (3H, s, OMe), 3.78 (1H, t, $J=3.53$ and 3.42, H-2 pyrazine), 3.95 (1H, m, H-5 pyrazine), 7.35 (1H, s, H-5 thiazolyl), 7.28–7.91 (5H, m, phenyl). Anal. calcd for $C_{19}H_{23}N_3O_2S$: C, 63.84; H, 6.49; N, 11.75. Found: C, 63.76; H, 6.43; N, 11.69.

3.1.15. (2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[(5-phenylisoxazol-3-yl)methyl]pyrazine ***3h***

Oil; ^{1}H NMR: δ 0.69 (3H, d, $J=6.79$, Me_2C), 1.10 (3H, d, $J=6.79$, Me_2C), 2.21 (1H, m, Me_2CH), 3.09 (1H, AB syst., $J=14.30$ and 6.66, CH_2), 3.28 (1H, AB syst., $J=14.30$ and 4.30, CH_2), 3.67 (3H, s, OMe), 3.73 (3H, s, OMe), 3.82 (1H, t, $J=3.53$ and 3.50, H-2 pyrazine), 4.32 (1H, m, H-5 pyrazine), 6.35 (1H, s, H-4 isoxazolyl), 7.40–7.70 (5H, m, phenyl). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.80; H, 6.76; N, 12.25.

3.1.16. (2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[(5-phenylisoxazol-3-yl)methyl]pyrazine ***4h***

Oil; ^{1}H NMR: δ 0.57 (3H, d, $J=6.75$, Me_2C), 1.05 (3H, d, $J=6.75$, Me_2C), 2.19 (1H, m, Me_2CH), 2.94 (1H, AB syst., $J=14.24$ and 6.42, CH_2), 3.32 (1H, AB syst., $J=14.24$ and 4.21, CH_2), 3.69 (3H, s, OMe), 3.71 (3H, s, OMe), 3.92 (1H, t, $J=3.51$ and 3.50, H-2 pyrazine), 4.34 (1H, m, H-5 pyrazine), 6.47 (1H, s, H-4 isoxazolyl), 7.40–7.60 (5H, m, phenyl). Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.78; H, 6.75; N, 12.24.

3.2. General procedure for the hydrolysis of adducts ***3a–h***

Adducts **3a–h** (2.0 mmol) were dissolved in acetonitrile (20 ml) and 20 ml of a 0.2N solution of HCl (4 mmol) were added. The mixture was stirred for 36 h at room temperature. The solvent

was evaporated and the residue treated with conc. ammonia until pH 9 and the product extracted with dichloromethane (2×20 ml). The organic phase was dried with Na_2SO_4 and the solvent was removed in vacuo. The residue was distilled bulb-to-bulb to eliminate **6** as forerun. The residue was purified by chromatography (SiO_2, methanol:ethyl acetate:conc. ammonia = 1.9:8.0:0.1).

*3.2.1. Methyl (2*R*)-2-amino-3-(4-pyridyl) propionate* ***5a***

Oil; $[\alpha]_D^{20} = -9.9$ (*c* 1, EtOH); ^{1}H NMR: δ 1.50 (2H, broad, NH_2), 2.81 (1H, AB syst., $J = 13.58$ and 7.91, H-3), 3.00 (1H, AB syst., $J = 13.58$ and 5.36, H-3), 3.61 (3H, s, COOMe), 3.65 (1H, dd, $J = 7.91$ and 5.36, $CHNH_2$), 7.12 (2H, d, $J = 7.01$, H-3 and H-5 pyridyl), 8.50 (2H, d, $J = 7.01$, H-2 and H-6 pyridyl). Anal. calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.82; H, 6.70; N, 15.41.

*3.2.2. Methyl (2*R*)-2-amino-3-(2-pyridyl) propionate* ***5b***

Oil; $[\alpha]_D^{20} = -3.3$ (*c* 1, EtOH); ^{1}H NMR: δ 1.90 (2H, broad, NH_2), 2.23 (1H, AB syst., $J = 13.11$ and 6.67, H-3), 3.02 (1H, AB syst., $J = 13.11$ and 4.95, H-3), 3.67 (3H, s, COOMe), 3.95 (1H, dd, $J = 6.67$ and 4.95, $CHNH_2$), 7.10 (2H, m, H-3 and H-5 pyridyl), 7.52 (1H, m, H-4 pyridyl), 8.49 (1H, d, $J = 5.5$, H-6 pyridyl). Anal. calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.91; H, 6.69; N, 15.50.

*3.2.3. Methyl (2*R*)-2-amino-3-(2-thienyl) propionate* ***5c***

Oil; $[\alpha]_D^{20} = -16.4$ (*c* 1, EtOH); ^{1}H NMR: δ 1.60 (2H, broad, NH_2), 3.15 (1H, AB syst., $J = 12.95$ and 6.25, H-3), 3.22 (1H, AB syst., $J = 12.95$ and 4.74, H-3), 3.70 (3H, s, COOMe), 3.70 (1H, dd, $J = 6.25$ and 4.74, $CHNH_2$), 6.85 (1H, d, $J = 3.48$, H-3 thienyl), 6.92 (1H, dd, $J = 5.05$ and 3.48, H-4 thienyl), 7.12 (1H, d, $J = 5.05$, H-5 thienyl). Anal. calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56. Found: C, 51.79; H, 5.92; N, 7.48.

*3.2.4. Methyl (2*R*)-2-amino-3-(3-thienyl) propionate* ***5d***

Oil; $[\alpha]_D^{20} = -11.2$ (*c* 1, EtOH); ^{1}H NMR: δ 1.60 (2H, broad, NH_2), 2.97 (1H, AB syst., $J = 12.93$ and 6.02, H-3), 3.10 (1H, AB syst., $J = 12.93$ and 4.64, H-3), 3.70 (3H, s, COOMe), 3.70 (1H, dd, $J = 6.02$ and 4.64, $CHNH_2$), 6.90 (1H, d, $J = 4.80$, H-4 thienyl), 7.01 (1H, d, $J = 2.80$, H-2 thienyl), 7.28 (1H, dd, $J = 4.80$ and 2.80, H-5 thienyl). Anal. calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99; N, 7.56. Found: C, 51.76; H, 5.92; N, 7.50.

*3.2.5. Methyl (2*R*)-2-amino-3-(2-furyl) propionate* ***5e***

Oil; $[\alpha]_D^{20} = -15.9$ (*c* 1, EtOH); ^{1}H NMR: δ 1.70 (2H, broad, NH_2), 2.97 (1H, AB syst., $J = 13.18$ and 6.88, H-3), 3.08 (1H, AB syst., $J = 13.18$ and 4.77, H-3), 3.71 (3H, s, COOMe), 3.77 (1H, dd, $J = 6.88$ and 4.77, $CHNH_2$), 6.10 (1H, d, $J = 1.85$, H-3 furyl), 6.29 (1H, dd, $J = 3.80$ and 1.85, H-4 furyl), 7.35 (1H, d, $J = 3.80$, H-5 furyl). Anal. calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.75; H, 6.52; N, 8.20.

*3.2.6. Methyl (2*R*)-2-amino-3-(2-thiazolyl) propionate* ***5f***

Oil; $[\alpha]_D^{20} = -5.9$ (*c* 1, EtOH); ^{1}H NMR: δ 1.60 (2H, broad, NH_2), 3.35 (1H, AB syst., $J = 13.57$ and 6.62, H-3), 3.48 (1H, AB syst., $J = 13.57$ and 4.88, H-3), 3.77 (3H, s, COOMe), 3.98 (1H, dd, $J = 6.62$ and 4.88, $CHNH_2$), 7.20 (1H, d, $J = 3.05$, H-4 thiazolyl), 7.70 (1H, d, $J = 3.05$, H-5 thiazolyl). Anal. calcd for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.41; N, 15.04. Found: C, 45.03; H, 5.39; N, 14.96.

3.2.7. Methyl (2R)-2-amino-3-(4-phenylthiazol-2-yl) propionate ***5g***

Oil; $[\alpha]_D^{20} = -1.6$ (*c* 1, EtOH); ^{1}H NMR: δ 1.90 (2H, broad, NH_2), 3.30 (1H, AB syst., $J = 14.78$ and 7.82, H-3), 3.50 (1H, AB syst., $J = 14.78$ and 4.70, H-3), 3.74 (3H, s, COOMe), 4.00 (1H, dd, $J = 7.82$ and 4.70, $CHNH_2$), 7.31 (1H, s, H-5 thiazolyl), 7.25–7.98 (5H, m, phenyl). Anal. calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 12.22. Found: C, 59.41; H, 5.35; N, 12.01.

3.2.8. Methyl (2R)-2-amino-3-(5-phenylisoxazol-3-yl) propionate ***5h***

Oil; $[\alpha]_D^{20} = -7.6$ (*c* 1, EtOH); ^{1}H NMR: δ 1.65 (2H, broad, NH_2), 3.05 (1H, AB syst., $J = 14.78$ and $J = 7.82$, H-3), 3.20 (1H, AB syst., $J = 14.78$ and 4.71, H-3), 3.75 (3H, s, COOMe), 3.90 (1H, dd, $J = 7.82$ and 4.71, $CHNH_2$), 6.45 (1H, s, H-4 isoxazolyl), 7.45–7.70 (5H, m, phenyl). Anal. calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.34; H, 5.71; N, 11.18.

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7. In this case, starting from (*R*)-**1** and **2h** according to the method described, a mixture of **3h**:**4h** (6:94) was obtained. After separation and hydrolysis of **4h** methyl (2*S*)-2-amino-3-(5-phenylisoxazol-3-yl) propionate was isolated: $[\alpha]_D^{20} = +7.55$ (*c* 1 in EtOH).