STEREOSELECTIVE ALDOL ADDITION OF A CHIRAL GLYCINE ENOLATE SYNTHON TO HETEROAROMATIC ALDEHYDES*

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Abstract – The stereocontrolled addition of (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**1**) to heterocyclic aldehydes (**2**) gives mainly a mixture of *syn/anti* isomers (**3**) and (**4**) whose steric configuration was assigned on the basis of spectroscopic data and accepted model for aldol condensation of **1**. The possible conversion of adducts to threo β-substituted heteroaromatic serines is demonstrated.

Introduction

The β-hydroxy-α-amino acids are an important class of compounds being the constituents of biologically active peptides[1] and the precursors of β-lactam antibiotics.[2] Moreover, some heterocyclic serines, namely both the diastereoisomers of β-(2-furyl)- and β-(2-thienyl)serines can be cyclised into alkaloid synthons[3] and *cis/trans* thienopyridines[4] respectively.

Results and discussion

As a part of our current interest in the stereoselective synthesis of heteroaromatic α-amino acid derivatives we now present the results on the preparation of precursors of β-substituted heterocyclic serines.

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* Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday
# Scholarship of Advanced School in Chemical Synthesis, Milan University

A recent method to optically pure (2*R*,3*R*)-3-(2-thienyl)- and furylserines has been described[5] using *Streptomyces amakusaensis*. This has the ability to catalyse the cleavage of (2*S*,3*S*)-isomer to glycine and aldehyde, leaving the pure (2*R*,3*R*)-isomer behind. Our approach to the preparation of homochiral precursors of heteroaromatic substituted serines is based on the use of a chiral glycine enolate synthon. Among these we have choosed (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine (**1**) namely "Schöllkopf reagent" owing to its commercial availability in both the enantiopure forms and great number of reported examples in asymmetric synthesis.[6] Up to date none of these deals with the use of **1** in aldol condensation with heteroaromatic aldehydes.

The reaction of **1** with aldehydes (**2a-f**) was carried out in THF solution at –75°C according to the general method described in experimental. In TLC analysis and in the NMR spectrum of the crude reaction mixture only two of the four possible diastereomers are detectable. Since these isomers are separable by chromatography it is possible to obtain both as pure compounds. The structure and steric configuration were assigned on the basis of analytical and spectroscopic data and the accepted model[6] for aldol type addition of **1** to achiral aldehydes. In this way (1*S*,2'*S*,5'*R*) and (1*R*,2'*S*,5'*R*) relative configurations can be established for **3a-f** and **4a-f** aldol adducts respectively. In Table 1 are reported yield, *syn*/*anti* ratio, d.e. for compounds (**3**) and (**4**).

Scheme 1

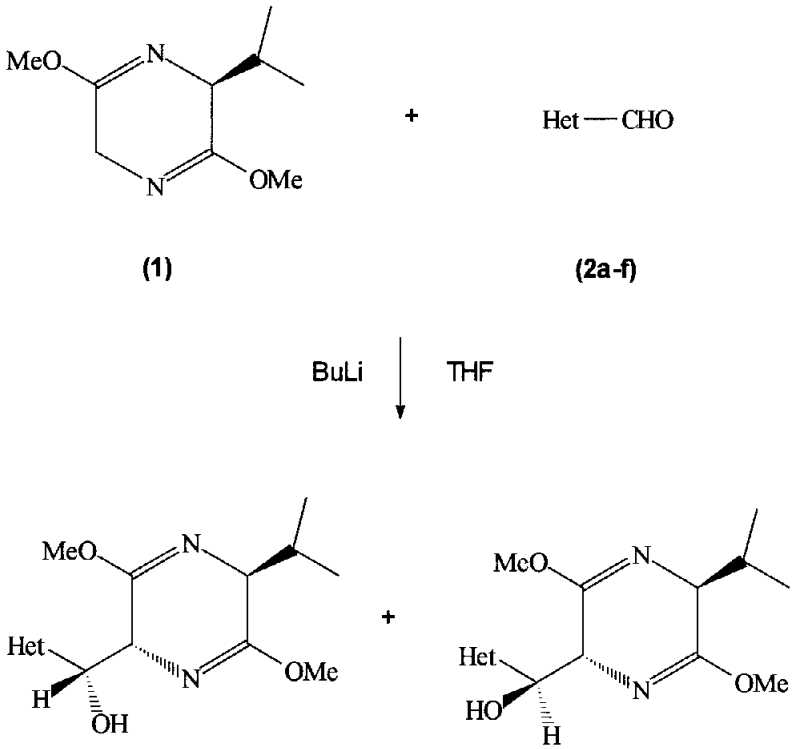
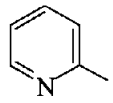
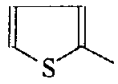
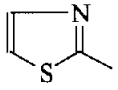
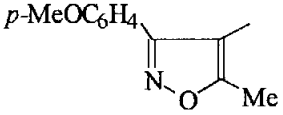
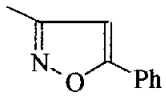
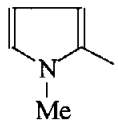


Table 1

	Het	Ratio of 3 and 4	Yield (%)	d.e.	Method
a		90 : 10	17	80	A
b		65 : 35	26	30	B
c		100 : 0	43	100	A
d		70 : 30	87	40	A
e		80 : 20	60	61	A
f		87 : 13	95	74	A

Method: A counter ion titanium; B counter ion lithium

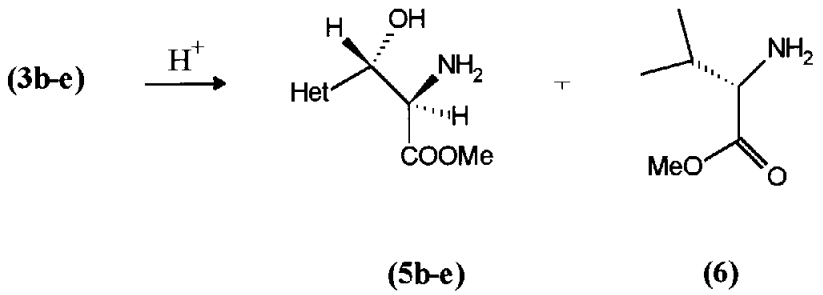
The accepted transition state involving attack of the electrophile from the face opposite to the 2-isopropyl group would be the energetically favoured one giving the product where the C-2 and C-5 substituents have a *trans* relationship. This model, verified on a large number of examples, allows the relative configuration of the 5-position of pyrazine mojety, in the carbon-carbon bond forming step, to be controlled.

When the electrophile is a carbonyl group a second stereocenter is formed on C-1 and as reported in Table 1 the ratio *syn*/*anti* depends on the nature of the counter ion. Generally the titanium derivative of **1** reacts with high diastereoselectivity giving a preference for *syn* attack product owing to a tight transition state[7] promoted by titanium ligand.

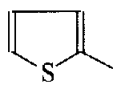
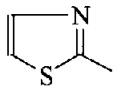
Upon hydrolysis of adducts (**3b-e**) with two equivalents of 0.3 N HCl at room temperature for 24 h., the corresponding serines ester (**5b-e**) were obtained in moderate to good yield as well as methyl L-valinate

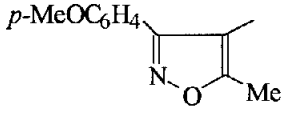
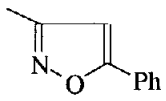
(**6**), the chiral auxiliary in this protocol. The two products can be separated by flash chromatography or bulb to bulb distillation allowing the recovery of substituted serines methyl ester (**5b-e**).

Scheme 2



(5b-e) **(6)**

Het: b  ; c 

d  ; e 

The structure of serines (**5b-e**) was supported by analytical and spectroscopic data. The (2*R*,3*R*) steric configuration was assigned to the products deriving from adducts (**3b-e**) on the basis of the model reported for the aldol condensation of **1** and HPLC analysis on chiragel OD-R column (eluent MeOH/H_2O=8/2) by comparison with the known racemic threo 3-(2-thienyl)serine[5] (or its methyl ester) taken as reference. In this way it was also possible to determine the enantiomeric excess ($\geq$ 98 %).

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analysis was performed by the Microanalytical Laboratory of the Department. ^{1}H-NMR spectra were taken on a Brüker AC 300 instrument. All chemical shifts are reported in δ (ppm) values relative to residual chloroform.

General procedure for the preparation of adducts (3) and (4). Method A. To a solution of **1** (0.5 g, 2.72 mmol) in anhydrous THF (25 mL), cooled at –75°C, butyllithium (3.20 mmol, 2 mL of a 1.6 N solution in hexane) was added and the mixture stirred for 30 min. Chlorotris(diethylamido)titanium (2.85

mmol, 1.25 mL of a 2.56 N solution in hexane) was added and stirring continued for 1 h. The appropriate aldehyde (**2**) (2.72 mmol) in THF (20 mL) was added and the mixture stirred at –70°C for 12 h. The reaction mixture was allowed to warm to 0°C and phosphate buffer solution (15 mL) was added. The solvent was evaporated off and the residue taken up with ether. The organic phase was separated and dried with Na_2SO_4, the solvent evaporated *in vacuo* and the residue was cromathographed on silica gel (toluene/ethyl acetate 9/1). In this way the following compounds were isolated:

(1*S*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-(2-pyridyl)methanol (3a). mp: 123-125 °C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 0.64 and 1.02 (d, J = 6.90 Hz, 6H, Me_2C), 1.55 (broad, 1H, OH), 2.20 (m, 1H, $Me_2C\underline{H}$), 3.44 and 3.76 (s, 6H, OMe), 3.94 (t, J = 3.21 Hz, 1H, H-2 pyrazine), 4.41 (t, J = 3.21 Hz, 1H, H-5 pyrazine), 5.21 (dd, J = 9.00 and 3.22 Hz, 1H, C<u>H</u>-OH), 7.14-8.55 (m, 4H, pyridine). <u>Anal</u>. Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found C, 61.78; H, 7.25; N, 14.43.

(1*R*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-(2-pyridyl)methanol (4a). mp: 110-112 °C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 0.33 and 0.91 (d, J = 6.88 Hz, 6H, Me_2C), 1.95 (broad, 1H, OH), 3.12 (m, 1H, $Me_2C\underline{H}$), 3.40 and 3.67 (s, 6H, OMe), 3.71 (t, J = 3.16 Hz, 1H, H-2 pyrazine), 4.27 (t, J = 3.16 Hz, 1H, H-5 pyrazine), 6.82 (dd, J = 9.25 and 3.16 Hz, 1H, C<u>H</u>-OH), 6.80-6.90 (m, 4H, pyridine). <u>Anal</u>. Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found C, 61.88; H, 7.20; N, 14.32.

(1*S*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-(2-thienyl)methanol (3b). Oil; ^{1}H-NMR ($CDCl_3$) δ 0.61 and 0.90 (d, J = 6.86 Hz, 6H, Me_2C), 2.13 (m, 1H, $Me_2C\underline{H}$), 2.55 (broad, 1H, OH), 3.59 (t, J = 4.17 Hz, 1H, H-2 pyrazine), 3.58 and 3.71 (s, 6H, MeO), 4.40 (t, J = 4.17 Hz, 1H, H-5 pyrazine), 5.36 (dd, J = 9.07 and 4.17 Hz, 1H, C<u>H</u>-OH), 6.75 (d, J = 3.48 Hz, 1H, H-3 th.), 6.81 (dd, J = 5.05 and 3.48 Hz, 1H, H-4 th.), 7.09 (d, J = 5.05 Hz, 1H, H-5 th.). <u>Anal.</u> Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45. Found C, 56.42; H, 6.68; N, 9.23.

(1*R*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-(2-thienyl)methanol (4b). Oil; ^{1}H-NMR ($CDCl_3$) δ 0.72 and 1.01 (d, J = 6.85 Hz, 6H, Me_2C), 2.18 (m, 1H, $Me_2C\underline{H}$), 2.47 (broad, 1H, OH), 3.91 (t, J = 3.48 Hz, 1H, H-2 pyrazine), 3.70 and 3.78 (s, 6H, MeO), 4.28 (t, J = 3.48 Hz, 1H, H-5 pyrazine), 5.37 (dd, J = 8.10 and 3.48 Hz, 1H, C<u>H</u>-OH), 6.95 (dd, J = 5.08 and 3.51 Hz, 1H,

H4-th.), 7.04 (d, J = 3.51 Hz, 1H, H3-th.), 7.23 (d, J = 5.08 Hz, 1H, H5-th.). Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45. Found C, 56.84; H, 6.77; N, 9.52.

(1*S*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-(2-thiazolyl)methanol (3c). Oil; ^{1}H-NMR ($CDCl_3$) δ 0.75 and 1.05 (d, J = 6.92 Hz, 6H, Me_2C), 2.21 (m, 1H, Me_2CH), 3.09 (broad, 1H, OH); 3.68 and 3.78 (s, 6H, OMe), 4.00 (t, J = 3.18 Hz, 1H, H-2 pyrazine), 4.60 (t, J = 3.18 Hz, 1H, H-5 pyrazine), 5.51 (m, 1H, CH-OH), 7.29 and 7.75 (d, J = 3.10 Hz, 2H, H-5 and H-4 thiazol). Anal. Calcd for $C_{13}H_{19}N_3O_3S$: C, 52.51; H, 6.44; N, 14.13. Found C, 52.20; H, 6.32; N, 13.95.

(1*S*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-[5-methyl-3-(4-methoxy)phenyl-isoxazol-4-yl]methanol (3d). mp: 85-87°C (cyclohexane); ^{1}H-NMR ($CDCl_3$) δ 0.64 and 0.98 (d, J = 7.10 Hz, 6H, Me_2C), 2.28 (m, 1H, Me_2CH), 2.53 (s, 3H, CH_3); 3.38 (d, J = 4.30 Hz, 1H, OH); 3.53, 3.68 and 3.85 (s, 9H, OMe), 3.92 (t, J = 3.57 Hz, 1H, H-2 pyrazine), 4.10 (dd, J = 6.00 and 3.57 Hz, 1H, H-5 pyrazine), 4.91 (dd, J = 6.00 and 4.30 Hz, 1H, CH-OH), 6.98 (d, J = 3.22 Hz, 2H, H-3 phenyl), 7.55 (d, J = 3.22 Hz, 2H, H-2 phenyl). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found C, 62.87; H, 6.38; N, 10.23.

(1*R*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-[5-methyl-3-(4-methoxy)phenyl-isoxazol-4-yl]methanol (4d). mp: 70-72° C (cyclohexane); ^{1}H-NMR ($CDCl_3$) δ 0.58 and 0.95 (d, J = 6.85 Hz, 6H, Me_2C), 2.28 (m, 1H, Me_2CH), 2.45 (s, 3H, CH_3); 3.69 (d, J = 4.03 Hz, 1H, OH); 3.36, 3.48 and 3.84 (s, 9H, OMe), 3.70 (t, J = 3.75 Hz, 1H, H-2 pyrazine), 4.29 (dd, J = 6.41 and 3.75 Hz, 1H, H-5 pyrazine), 5.06 (dd, J = 6.41 and 4.03 Hz, 1H, CH-OH), 6.95 (d, J = 3.18 Hz, 2H, H-3 phenyl), 7.51 (d, J = 3.18 Hz, 2H, H-2 phenyl) . Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found C, 63.05; H, 6.58; N, 10.62.

(1*S*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-[5-phenylisoxazol-3-yl]methanol (3e). Oil; ^{1}H-NMR ($CDCl_3$) δ 0.72 and 1.02 (d, J = 7.05 Hz, 6H, Me_2C), 2.25 (m, 1H, Me_2CH), 2.90 (broad, 1H, OH); 3.68 and 3.78 (s, 6H, OMe), 4.02 (t, J = 3.62 Hz, 1H, H-2 pyrazine), 4.39 (t, J = 3.62 Hz, 1H, H-5 pyrazine), 5.37 (dd, J = 9.75 and 3.62 Hz, 1H, CH-OH), 6.60 (s, 1H, H-4 isoxazol), 7.45-7.80 (m, 5H, aromatics). Anal. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.49; N, 11.76. Found C, 63.95; H, 6.09; N, 11.68.

(1*R*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-[5-phenylisoxazol-3-yl]methanol (4e). Oil; ^{1}H-NMR ($CDCl_3$) δ 0.22 and 0.92 (d, J = 7.05 Hz, 6H, Me_2C), 2.20 (m, 1H, $Me_2C\underline{H}$), 2.95 (broad, 1H, OH); 3.70 and 3.75 (s, 6H, OMe), 3.90 (t, J = 3.61 Hz, 1H, H-2 pyrazine), 4.52 (t, J = 3.61 Hz, 1H, H-5 pyrazine) 5.42 (dd, J = 9.80 and 3.61 Hz, 1H, C<u>H</u>-OH), 6.35 (s, 1H, H-4 isoxazol), 7.48-7.76 (m, 5H, aromatics). <u>Anal</u>. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.49; N, 11.76. Found C, 64.11; H, 6.13; N, 11.72.

(1*S*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-[1-methylpyrrol-2-yl] methanol (3f). Oil; ^{1}H-NMR ($CDCl_3$) δ 0.73 and 1.03 (d, J = 6.98 Hz, 6H, Me_2C), 2.23 (m, 1H, $Me_2C\underline{H}$), 2.34 (broad, 1H, OH); 3.62 (s, 3H, N-CH_3); 3.70 and 3.75 (s, 6H, OMe), 4.00 (t, J = 3.62 Hz, 1H, H-2 pyrazine), 4.40 (t, J = 3.62 Hz, 1H, H-5 pyrazine) 5.04 (dd, J = 10.35 and 3.62 Hz, 1H, C<u>H</u>-OH), 6.03-6.58 (m, 3H, pyrrole). <u>Anal</u>. Calcd for $C_{15}H_{23}N_3O_3$: C, 61.41; H, 7.90; N, 14.32. Found C, 61.31; H, 7.77; N, 14.25.

(1*R*)-1-[(2'*S*,5'*R*)-2',5'-Dihydro-2'-isopropyl-3',6'-dimethoxy-5'-pyrazinyl]-1-[1-methylpyrrol-2-yl] methanol (4f). Oil; ^{1}H-NMR ($CDCl_3$) δ 0.70 and 1.00 (d, J = 6.85 Hz, 6H, Me_2C), 2.22 (m, 1H, $Me_2C\underline{H}$), 2.35 (broad, 1H, OH); 3.59 (s, 3H, N-CH_3); 3.70 and 3.75 (s, 6H, OMe), 3.89 (t, J = 4.11 Hz, 1H, H-2 pyrazine), 4.48 (t, J = 4.11 Hz, 1H, H-5 pyrazine), 5.04 (dd, J = 8.65 and 4.11 Hz, 1H, C<u>H</u>-OH), 5.70-6.50 (m, 3H, pyrrole). <u>Anal</u>. Calcd for $C_{15}H_{23}N_3O_3$: C, 61.41; H, 7.90; N, 14.32. Found C, 61.48; H, 7.80; N, 14.38.

General procedure for the hydrolysis of adducts (3b-e). Adducts (2 mmol) were dissolved in acetonitrile (20 mL) and 20 mL of a 0.2 N solution of HCl (4 mmol) were added. The mixture was stirred for 24 h at rt. The solvent was evaporated off and the residue treated with conc. ammonia until pH=8-10. The product was extracted with methylene dichloride (2X20 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/chloroform/conc. ammonia=1/1/0.1).

Methyl (2*R*,3*R*)-2-amino-3-hydroxy-3-(2-thienyl)propionate (5b). Oil; ^{1}H-NMR ($CDCl_3$) δ 3.65 (s, 3H, COOMe), 3.69 (d, J = 4.16 Hz, 1H, C<u>H</u>NH_2), 5.10 (d, J = 4.16 Hz, 1H, C<u>H</u>-OH), 6.70 (s, 1H, OH), 6.90 (s, 2H, NH_2), 6.97-7.32 (m, 3H, aromatics). Yield 55%; $[\alpha]^{20}_D$ + 42° (c 1, MeOH). The ester was hydrolized by treatment with 10% sodium hydroxide at rt for 4 h and the pH of the mixture adjusted at

4.5 with 10% acetic acid. The precipitate was filtered and crystallized from water/ethanol=8/2. mp: 170° C, $[\alpha]^{20}_D$ +54° (c 1, H_2O). Lit.[5], mp: 172° C; $[\alpha]^{20}_D$ + 55.1° (c 0.7, H_2O). Anal. Calcd for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51; N, 6.96. Found C, 47.62; H, 5.41; N, 6.88.

Methyl (2*R*,3*R*)-2-amino-3-hydroxy-3-(2-thiazolyl)propionate (5c). Oil; ^{1}H-NMR ($CDCl_3$) δ 3.75 (s, 3H, COOMe), 4.05 (d, J = 3.92 Hz, 1H, C<u>H</u>NH_2), 5.35 (dd, J = 5.20 and 3.95 Hz, 1H, C<u>H</u>-OH), 6.75 (d, J = 5.20 Hz, 1H, OH), 6.90 (s, 2H, NH_2), 7.57-7.85 (m, 2H, thiazole). Yield 45%; $[\alpha]^{20}_D$ + 45° (c 1, MeOH). Anal. Calcd for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; N, 13.85. Found C, 41.50; H, 4.88; N, 13.78.

Methyl (2*R*,3*R*)-2-amino-3-hydroxy-3-[4-(4-methoxyphenyl-5-methyl)isoxazolyl]propionate (5d). Oil; ^{1}H-NMR ($CDCl_3$) δ 2.00 (s, 2H, NH_2), 2.50 (s, 3H, 5-Me), 3.50 (s, 3H, OMe), 3.80 (s, 3H, COOMe), 3.96 (d, J = 3.97 Hz, 1H, C<u>H</u>NH_2), 4.48 (dd, J = 5.96 and 3.97 Hz, 1H, C<u>H</u>-OH), 6.96 (d, J = 3.10 Hz, 2H, aromatics), 7.10 (d, J = 5 96 Hz, 1H, OH), 7.52 (d, J = 3.10 Hz, 2H, aromatics). Yield 87%; $[\alpha]^{20}_D$ + 33° (c 1, MeOH). Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found C, 58.58; H, 5.78; N, 9.59.

Methyl (2*R*,3*R*)-2-amino-3-hydroxy-3-[3-(5-phenyl)isoxazolyl]propionate (5e). Oil; ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 3H, COOMe), 4.72 (d, J = 3.98 Hz, 1H, C<u>H</u>NH_2), 5.30 (dd, J = 5.41 and 3.98 Hz, 1H, C<u>H</u>-OH), 6.45 (d, J = 5.41 Hz, 1H, OH), 6.95 (s, 1H, isoxazole), 7.55-7.85 (m, 5H, aromatics), 8.40 (s, 2H, NH_2). Yield 77%; $[\alpha]^{20}_D$ + 35° (c 1, MeOH). Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found C, 59.78; H, 5.28; N, 10.29.

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