Tetrahedron: *Asymmetry* 22 (2011) 591–596

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantiopure α-imino glyoxylate: a versatile substrate for the spontaneous asymmetric synthesis of unnatural hydroxyaryl glycinates

Cristina Cimarelli [a], Davide Fratoni [a], Andrea Mazzanti [b], Gianni Palmieri [a,*]

[a] *School of Science & Technology, University of Camerino, v. S.Agostino 1, 62032 Camerino, Italy*
[b] *Dept. of Organic Chemistry"A. Mangini", University of Bologna, viale Risorgimento 4, 40136 Bologna, Italy*

ARTICLE INFO

Article history:
Received 7 February 2011
Accepted 24 March 2011

ABSTRACT

A novel synthesis of useful enantiomerically pure arylglycinates via spontaneous reaction between phenol or naphthol derivatives and enantiopure α-imino glyoxylate in the absence of an acid catalyst is reported. A library of enantiopure substituted phenol or naphthol glycinates was obtained in good yields and high diastereoselectivities. Diastereoisomerically pure aryl glycinates were obtained by direct flash chromatography separation of the crude reaction mixture. The free OH moiety of the phenols or naphthols contributed to the activation of the imino group to form an intermolecular hydrogen bond and promoted the reaction in the absence of an acid catalyst, as shown in the transition state reported. The diastereoselectivity is due to thermodynamic control in the addition step.

1. Introduction

There has been considerable interest within the synthetic community in the development of practical methods to prepare non-natural α-amino acid derivatives,[1] due to their potential pharmacological properties and their use as precursors for novel peptide structures. Arylglycines constitute an important class of non-proteinogenic α-amino acids. Glycopeptidic antibiotics, such as vancomycin, are one of the best studied and most important natural sources of arylglycines. In addition to the naturally occurring arylglycines, there are also a number of synthetic arylglycine derivatives that could serve as a side-chain moiety of semisynthetic penicillins and cephalosporins. Furthermore, it has recently been found that molecules of this type are potent and selective agonists or antagonists of metabotropic glutamate receptors.

The direct asymmetric addition of organic nucleophiles (electron rich aromatic compounds) to preformed or in situ generated α-imino esters has emerged as one of the most promising and intensely investigated routes to enantiomerically enriched α-amino acid derivatives.

In particular, imines derived from ethyl glyoxylate are excellent electrophiles for the stereoselective construction of optically active arylglycine derivatives, which have not received much attention.[2]

A cumbersome non direct synthesis of racemic 2-amino-2-(2′-hydroxinaphthalen-1′-yl)acetic acid hydrochloride, as a Maillard reaction inhibitor, obtained by hydrolysis of the corresponding hydantoin derivative intermediate under alkaline conditions, has already been published.[3]

2. Results and discussion

Herein, we report the spontaneous reaction between either naphthol or phenol derivatives **1** and ethyl glyoxylate imines **2**, in toluene at −15 °C, without the use of an acid catalyst, which affords arylglicinate **3** with moderate to high yields obtained after a few hours (Scheme and Table 1). Chiral α-imino ester **2** was readily prepared by condensing ethyl glyoxylate and the (*R*)-(+)-1-phenylethylamine and can either be synthesized prior to use or one pot in situ, according to described methods.[4] The yields and diastereoselectivities varied in different solvents. The best result was obtained in toluene (0.5 mol solution) at −15 °C for 3–10 h. To evaluate the scope and limitations of the reaction, a variety of substituted phenols and naphthols were employed as substrates giving the results summarized in Table 1.

Moreover, the reaction does not require an anhydrous or inert atmosphere, and takes place in the absence of strong acids, strong bases, heavy metal catalysts or other undesirable chemicals. As shown in Table 1, the reaction of enantiopure ethyl (*E*,*R*)-2-(1-phenylethylimino)glyoxylate with electron rich aromatic compounds **1a**–**g** proceeded smoothly.

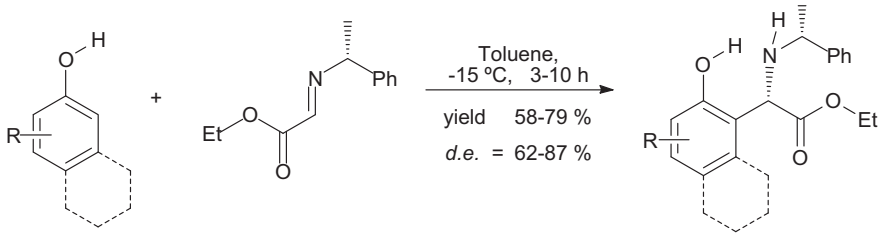
The pure stereoisomers can be isolated without a work-up of the reaction mixture, via the direct flash chromatographic separation of the crude reaction mixture.

We found that the reaction does not occur when the 2-methoxynaphthalene is reacted with glyoxylate imine **2**. The free naphthol OH moiety probably promoted a cyclic transition state,

* Corresponding author. Tel.: +39 0737 402241; fax: +39 0737 637345.
E-mail address: gianni.palmieri@unicam.it (G. Palmieri).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.03.008

Table 1



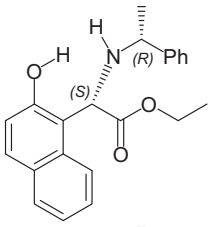
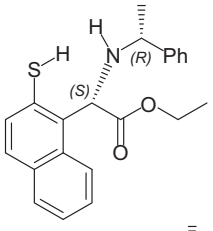
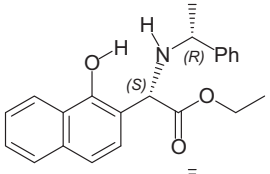
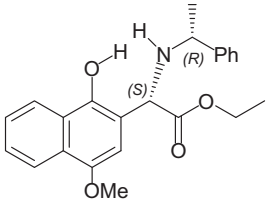
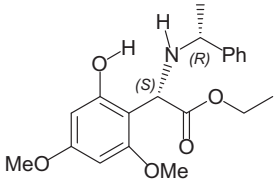
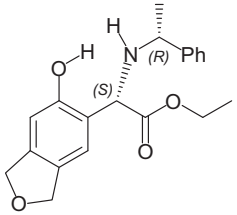
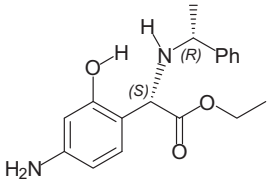
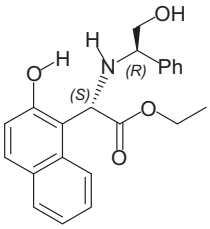
Entry	1	Product 3	3 Yield[a] (%)	dr[b]	$[\alpha]_D^{20}$
1	**1a**		(*R*,*S*)-**3a** 74	82:18	+144.4 (*c* 2.3)
2	**1b**		(*R*,*S*)-**3b** 73	84:16	+213.2 (*c* 2.1)
3	**1c**		(*R*,*S*)-**3c** 58	81:19	+87.9 (*c* 1.3)
4	**1d**		(*R*,*S*)-**3d** 67	86:14	+83.1 (*c* 2.7)
5	**1e**		(*R*,*S*)-**3e** 69	88:12	+70.6 (*c* 2.1)
6	**1f**		(*R*,*S*)-**3f** 79	93:7	+133.3 (*c* 2.7)
7	**1g**		(*R*,*S*)-**3g** 61	86:14	+132.7 (*c* 3.0)

Table 1 (*continued*)

Entry	1	Product **3**	**3** Yield[a] (%)	dr[b]	$[\alpha]_D^{20}$
8	**1a**		(*R*,*S*)-**3h** 70	77:23	−96.7 (*c* 2.1)

[a] Isolated yield.
[b] Determined by ^{1}H NMR.

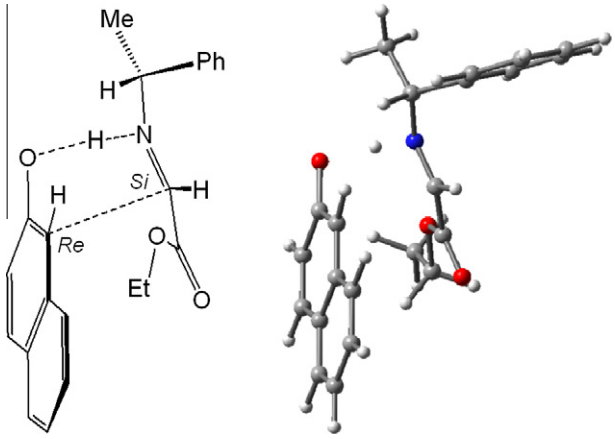


Figure 1. The thermodynamically favoured transition state for the addition step of the direct asymmetric reaction (optimized using DFT at the B3LYP/6-31G(d) level[5]).

activating the imino group in situ via intermolecular hydrogen bonding, and promoting the reaction in the absence of an acid catalyst (Fig. 1).

Based on these results, the diastereoselectivity of this reaction between the electron rich aromatic compounds **1a–g** and chiral imines was next studied.

The stereochemical outcome of the direct asymmetric reactions can be explained by a *Si*-facial attack on the imine that has an *E*-configuration, by the *Re*-face of the naphthol **1a** (Fig. 1).

The single imaginary frequency for the calculated transition state corresponds to the transfer of the hydrogen from the oxygen to the nitrogen atom. An IRC calculation started from this transition structure showed the absence of other transition states. This is in agreement with the experimental data, which shows that the free naphthol OH moiety is necessary for the success of the reaction, in the absence of acid catalysis.

A switch in the facial selectivity is disfavoured by the steric repulsion between the (*R*)-1-phenylethylimino group and the naphthol.[2] The transition state leading to diastereoisomer (*R*,*R*)-**3a**, with an attack on the *Si*-face of naphthol, has an energy of 1.5 kcal/mol greater than that which leads to the obtained product (1*R*,α*S*)-**3a**. The diastereoselectivity is due to thermodynamic control in the addition step.

2.1. Assignment of the absolute configuration

The configurational assignments of aminoesters **3** are based upon X-ray crystallographic analysis of (−)-**3a**·HCl (Fig. 2) and provide a basis for understanding the stereochemistry of the reaction and the induction when 1-(*R*)-phenylethylamine was used as chiral source.

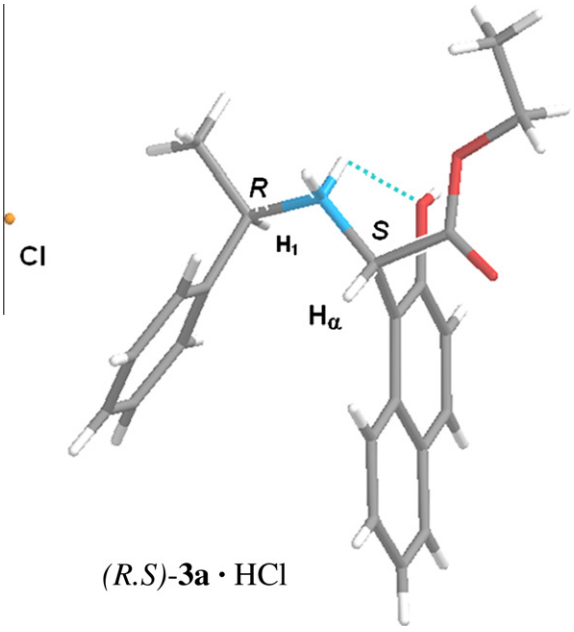


Figure 2. X-ray structure of the glycinate derivate (1*R*,α*S*)-**3a**·HCl.[6] Dotted line indicates an intra-molecular hydrogen bond.

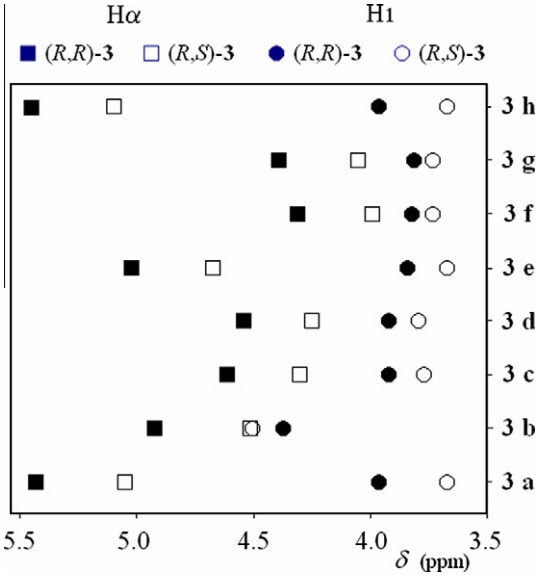


Figure 3. ^{1}H NMR chemical shifts of benzylic proton H1 and Hα of the diastereoisomeric α-aminoesters (*R*,*R*)-**3** and (1*R*,α*S*)-**3**.

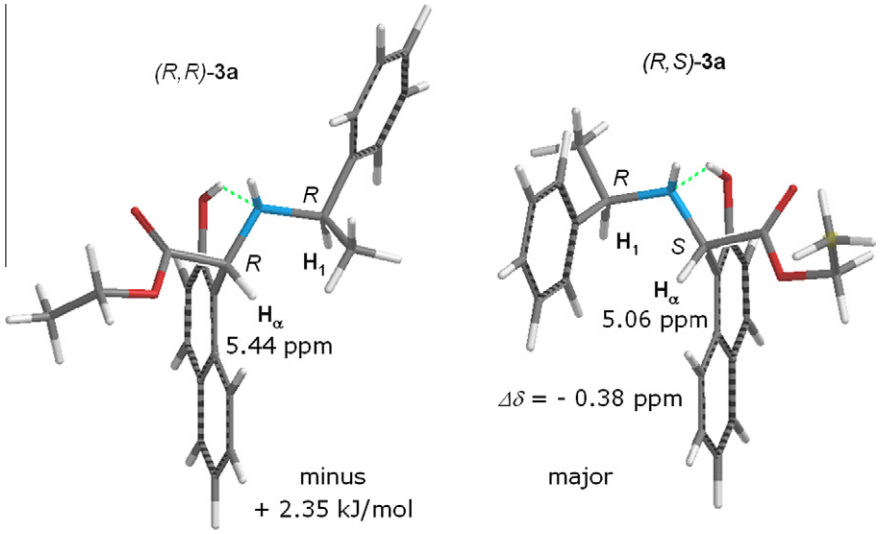


Figure 4. Most stable conformations of glycine derivatives (*R*,*R*)- and (1*R*,α*S*)-**3a** (optimized using DFT at the B3LYP/6-31G level[7]).

The following considerations contribute to the configurational assignments of all the arylglycine **3a**–**h**. In all the pairs of the diastereoisomeric arylglycines (*R*,*S*)-**3** and (*R*,*R*)-**3**, the ^{1}H NMR chemical shifts of benzylic protons H1 and Hα bonded to the two stereogenic carbon atoms show a common trend. In the diastereoisomer (*R*,*S*)-**3** these protons are shifted upfield with respect to the corresponding protons of the diastereoisomer (*R*,*R*)-**3**; the difference in chemical shifts reach up to 0.41 ppm as in the case of **3b** (Fig. 3).

Further confirmation was found when calculating the structure of the more stable conformer for both diastereoisomeric products (*R*,*R*)-**3a** and (1*R*,α*S*)-**3a** (Fig. 4). It was evident that in (1*R*,α*S*)-**3a**, the benzylic proton Hα takes up a position in the shielding cones of the phenyl group attached to the opposite carbon atom. On the basis of the conformational analysis results obtained from molecular modelling (Fig. 4), the major arylglycine (1*R*,α*S*)-**3a**, that derives from the favoured transition state, is the more stable diastereomer (thermodynamic control) and shows a molecular geometry consistent with the X-ray crystallographic structure of (−)-**3a** (Fig. 2).

3. Conclusion

In conclusion, a novel synthesis of useful enantiomerically pure arylglycinates **3** via the spontaneous reaction between either phenol or naphthol derivatives **1** and enantiopure glyoxylate imine **2** in the absence of an acid catalyst was observed. A variety of substituted phenol or naphthol glycinates were obtained in good yields and high diastereoselectivities. Diastereoisomerically pure aryl glycinates were obtained via flash chromatography separation of the crude reaction mixture. O-Substituted naphthols were ineffective in this reaction. The free OH moiety of the phenols or naphthols probably contributed to the activation of the imino group by intermolecular hydrogen bonding and promoted the reaction in the absence of an acid catalyst, as shown in the transition state reported. The diastereoselectivity is due to thermodynamic control in the addition step.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent at ambient temperature and were calibrated using residual undeuterated solvents as the internal reference. Coupling constants (*J*) are given in Hertz. When necessary, assignments of the structures of prepared compounds were aided by a self consistency check using the ^{1}H NOESY correlation spectrum and decoupling experiments. IR spectra were recorded using FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20 °C. All melting points are uncorrected. Where only the major diastereomer was obtained pure, the ^{1}H NMR signals for the minor diastereomer were deduced from the spectra of the crude reaction mixture or of the enriched chromatographic fractions. All reagents were commercially available, purchased at the highest quality, and purified by distillation when necessary.

4.2. Synthesis of enantiopure arylglicinates 3a–h

In a typical procedure, sodium sulfate (2.0 g), ethyl glyoxylate (3.0 mmol, 0.6 mL, 50% solution in toluene) and (*R*)-(+)-1-phenylethylamine (3.0 mmol, 0.364 g, 0.382 mL) were mixed in toluene (5 mL) and stirred at rt for 2 h. Into the resulting filtered iminoester solution naphthol or phenol derivatives (3.0 mmol) were added and stirred at −15 °C for 3–10 h. Flash chromatography of the crude reaction mixture on silica gel (hexane/EtOAc, 4:1) afforded the pure diastereomers in the yields reported in the Table 1. The isolated arylglicinates are spectroscopically characterized as follows.

4.2.1. Synthesis of (*S*)-ethyl 2-((*R*)-1-phenylethylamino)-2-(2-hydroxynaphthalen-1-yl)acetate (*R*,*S*)-3a

Crystals; mp 86–88 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20} = +144.4$ (*c* 2.3, $CHCl_3$); IR (Nujol): ν_{max} 3317, 1732, 1263, 1197, 1106, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, 3H, *J* = 7.3 Hz), 1.48 (d, 3H, *J* = 6.8 Hz), 3.22 (br s, 1H), 3.68 (q, 1H, *J* = 6.8 Hz), 3.97 (dq, 1H, *J* = 10.7, 7.3 Hz), 4.07 (dq, 1H, *J* = 10.7, 7.3 Hz), 5.06 (s, 1H), 7.06–7.77 (m, 11H), 12.35 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 23.2, 54.8, 56.6, 61.9, 110.5, 119.8, 121.9, 122.7, 126.5, 126.8, 128.0, 128.8, 128.9, 129.0, 130.5, 133.4, 142.6, 157.0, 171.5. Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.78; H, 6.41; N, 4.22.

4.2.1.1. (*R*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(2-hydroxynaphthalen-1-yl)acetate (*R*,*R*)-3a. Oil, $[\alpha]_D^{20} = -69.2$ (*c* 1.5, $CHCl_3$); IR (Nujol): ν_{max} 3312, 1725, 1463, 1203, 1126, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, 3H, *J* = 7.3 Hz), 1.53 (d, 3H, *J* = 6.4 Hz), 3.20 (br s, 1H), 3.97 (q, 1H, *J* = 6.4 Hz), 4.04 (dq, 1H,

J = 10.7, 7.3 Hz), 4.19 (dq, 1H, J = 10.7, 7.3 Hz), 5.44 (s, 1H), 7.07–7.88 (m, 11H), 12.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.4, 55.2, 57.0, 61.9, 111.4, 119.9, 121.6, 122.7,126.4, 126.7, 127.7, 128.7, 128.8, 128.9, 130.5, 132.9, 142.6, 156.6, 171.2. Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.71; H, 6.49; N, 4.25.

4.2.2. (*S*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(2-mercaptonaphthalen-1-yl)acetate (*R*,*S*)-3b

$[\alpha]_D^{20} = +213.2$ (c 2.1, $CHCl_3$); IR (Nujol): ν_{max} 3345, 1732, 1495, 1181, 812, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, J = 6.8 Hz), 1.41 (d, 3H, J = 6.8 Hz), 2.40 (br s, 1H), 4.14 (dq, 1H, J = 10.7, 6.8 Hz), 4.21 (dq, 1H, J = 10.7, 6.8 Hz), 4.51 (q, 1H, J = 6.8 Hz), 4.52 (s, 1H), 7.25–7.95 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 24.7, 53.8, 61.5, 67.9, 127.5, 127.7, 128.3, 128.4, 128.5, 128.6, 128.7, 129.5, 129.7, 129.8, 133.2, 134.6, 136.2, 143.6, 169.3. Anal. Calcd for $C_{22}H_{23}NO_2S$ (365.49): C, 72.30; H, 6.34; N, 3.83. Found: C, 72.46; H, 6.49; N, 3.98.

4.2.2.1. (*R*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(2-mercaptonaphthalen-1-yl)acetate (*R*,*R*)-3b. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 7.3 Hz), 1.39 (d, 3H, J = 6.6 Hz), 2.40 (br s, 1H), 4.16–4.22 (m, 2H), 4.38 (q, 1H, J = 6.6 Hz), 4.93 (s, 1H), 7.25–7.95 (m, 12H);

4.2.3. (*S*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(1-hydroxynaphthalen-2-yl)acetate (*R*,*S*)-3c

Crystals; mp 110–112 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20} = +87.9$ (c 1.3, $CHCl_3$); IR (Nujol): ν_{max} 3315, 1729, 1623, 1198, 1106, 735, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, 3H, J = 7.3 Hz), 1.52 (d, 3H, J = 6.8 Hz), 3.12 (br s, 1H), 3.78 (q, 1H, J = 6.8 Hz), 4.04 (dq, 1H, J = 10.7, 7.3 Hz), 4.13 (dq, 1H, J = 10.7, 7.3 Hz), 4.31 (s, 1H), 7.01–8.35 (m, 11H), 12.20 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.6, 55.0, 62.1, 62.4, 112.2, 118.6, 122.6, 125.1, 125.6, 126.6, 126.7, 127.4, 128.0, 128.2, 129.2, 134.4, 142.6, 154.1, 171.6. Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.40; H, 6.45; N, 4.26.

4.2.3.1. (*R*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(1-hydroxynaphthalen-2-yl)acetate (*R*,*R*)-3c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, J = 7.3 Hz), 1.54 (d, 3H, J = 6.8 Hz), 3.15 (br s, 1H), 3.93 (q, 1H, J = 6.8 Hz), 4.22 (dq, 1H, J = 10.7, 7.3 Hz), 4. 31 (dq, 1H, J = 10.7, 7.3 Hz), 4.62 (s, 1H), 6.95–8.29 (m, 11H), 12.10 (br s, 1H).

4.2.4. (*S*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(1-hydroxy-4-methoxynaphthalen-2-yl)acetate (*R*,*S*)-3d

Oil, $[\alpha]_D^{20} = +83.1$ (c 2.7, $CHCl_3$); IR (Nujol): ν_{max} 3302, 1732, 1459, 1213, 731, 658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, 3H, J = 7.0 Hz), 1.52 (d, 3H, J = 6.8 Hz), 2.60 (br s, 1H), 3.80 (q, 1H, J = 6.8 Hz), 3.92 (s, 3H), 4.07 (dq, 1H, J = 10.7, 7.0 Hz), 4.14 (dq, 1H, J = 10.7, 7.0 Hz), 4.26 (s, 1H), 6.37 (s, 1H), 7.18–8.33 (m, 9H), 11.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.7, 55.1, 56.1, 62.0, 62.8, 106.4, 111.1, 121.6, 122.4, 125.8, 126.1, 126.2, 126.3, 126.7, 127.9, 129.1, 142.8, 147.7, 148.3, 171.5. Anal. Calcd for $C_{23}H_{25}NO_4$ (379.45): C, 72.80; H, 6.64; N, 3.69. Found: C, 72.68; H, 6.41; N, 3.87.

4.2.5. (*S*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(2-hydroxy-4,6-dimethoxyphenyl)acetate (*R*,*S*)-3e

Oil; $[\alpha]_D^{20} = +70.6$ (c 2.1, $CHCl_3$); IR (Nujol): ν_{max} 3318, 1721, 1413, 1193, 1106, 731, 650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, 3H, J = 6.8 Hz), 1.42 (d, 3H, J = 6.8 Hz), 3.02 (br s, 1H), 3.66 (s, 3H), 3.68 (q, 1H, J = 6.8 Hz), 3.78 (s, 3H), 4.05 (dq, 1H, J = 10.7, 6.8 Hz), 4.09 (dq, 1H, J = 10.7, 6.8 Hz), 4.68 (s, 1H), 6.02 (d, 1H, J = 2.6 Hz), 6.09 (d, 1H, J = 2.6 Hz), 7.14–7.38 (m, 5H), 11.17 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.3, 54.6, 54.8, 55.3, 55.8, 61.8, 90.9, 94.3, 126.7, 127.7, 127.8, 128.8, 142.9, 159.6, 160.0, 161.3, 172.2. Anal. Calcd for $C_{20}H_{25}NO_5$ (359.42): C, 66.83; H, 7.01; N, 3.90. Found: C, 66.69; H, 6.81; N, 4.12.

4.2.5.1. (*R*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(2-hydroxy-4,6-dimethoxyphenyl)acetate (*R*,*R*)-3e. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, 3H, J = 7.0 Hz), 1.48 (d, 3H, J = 6.6 Hz), 3.12 (br s, 1H), 3.74 (s, 6H), 3.85 (q, 1H, J = 6.6 Hz), 4.10 (dq, 1H, J = 10.7, 6.8 Hz), 4.18 (dq, 1H, J = 10.7, 7.3 Hz), 5.03 (s, 1H), 5.95 (d, 1H, J = 2.6 Hz), 6.01 (d, 1H, J = 2.6 Hz), 7.18–7.36 (m, 5H), 11.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.1, 55.0, 55.1, 55.4, 56.0, 61.8, 90.9, 94.6, 102.2, 126.8, 127.6, 128.6, 143.2, 159.0, 159.7, 161.3, 172.4.

4.2.6. (*S*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(1,3-dihydro-5-hydroxyisobenzofuran-6-yl)acetate (*R*,*S*)-3f

Oil; $[\alpha]_D^{20} = +133.3$ (c 2.7, $CHCl_3$); IR (Nujol): ν_{max} 3319, 1728, 1213, 1119, 743, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 3H, J = 7.3 Hz), 1.47 (d, 3H, J = 6.8 Hz), 2.90 (br s, 1H), 3.74 (q, 1H, J = 6.8 Hz), 4.00 (s, 1H), 4.07 (dq, 1H, J = 10.7, 7.3 Hz), 4.13 (dq, 1H, J = 10.7, 7.3 Hz), 5.87–5.92 (m, 4H), 6.36 (s 1H), 6.44 (s, 1H), 7.15–7.21 (m, 5H), 12.35 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.6, 27.1, 54.8, 62.1, 99.4, 101.1, 109.7, 110.9, 126.6, 127.9 128.0, 129.2, 140.5, 142.3 148.5, 155.3, 171.4. Anal. Calcd for $C_{20}H_{23}NO_4$ (341.40): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.18; H, 6.95; N, 3.92.

4.2.6.1. (*R*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(1,3-dihydro-5-hydroxyisobenzofuran-6-yl)acetate (*R*,*R*)-3f. $[\alpha]_D^{20} = +14.4$ (c 1.9, $CHCl_3$); IR (Nujol): ν_{max} 3322, 1726, 1210, 1123, 741, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, J = 7.2 Hz), 1.48 (d, 3H, J = 6.6 Hz), 2.90 (br s, 1H), 3.83 (q, 1H, J = 6.6 Hz), 4.22 (dq, 1H, J = 10.7, 7.2 Hz), 4.29 (dq, 1H, J = 10.7, 7.2 Hz), 4.32 (s, 1H), 5.82–5.86 (m, 4H), 6.37 (s 2H), 7.10–7.40 (m, 5H), 10.35 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 22.6, 56.2, 62.0, 62.1, 99.6, 101.2, 107.8, 112.1, 127.1, 128.1, 128.9, 129.0, 140.6, 142.5, 148.4, 153.1, 171.7. Anal. Calcd for $C_{20}H_{23}NO_4$ (341.40): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.49; H, 7.02; N, 4.01.

4.2.7. (*S*)-Ethyl 2-((*R*)-1-phenylethylamino)-2-(4-amino-2-hydroxyphenyl)acetate (*R*,*S*)-3g

Oil: $[\alpha]_D^{20} = +132.7$ (c 3.0, $CHCl_3$); IR (Nujol): ν_{max} 3273, 1733, 1243, 1121, 743, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, 3H, J = 6.4 Hz), 1.45 (d, 3H, J = 6.8 Hz), 3.02 (br s, 2H), 3.74 (q, 1H, J = 6.8 Hz), 3.97–4.15 (m, 3H), 4.06 (s, 1H), 6.14 (dd, 1H, J = 8.1, 2.1 Hz), 6.20 (d, 1H, J = 2.1 Hz), 6.67 (d, 1H, J = 8.1 Hz), 7.14–7.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 23.6, 54.7, 61.9, 62.0, 103.6, 106.8, 110.1, 126.7, 127.9, 129.1, 131.5, 142.9, 148.1, 159.0, 172.1. Anal. Calcd for $C_{18}H_{22}N_2O_3$ (314.38): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.92; H, 7.22; N, 9.18.

4.2.8. (*S*)-Eethyl 2-((*R*)-2-hydroxy-1-phenylethylamino)-2-(2-hydroxynaphthalen-1-yl)acetate (*R*,*S*)-3h

Oil: $[\alpha]_D^{20} = -96.7$ (c 2.1, $CHCl_3$); IR (Nujol): ν_{max} 3303, 1722, 1623, 1211, 743, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (td, 3H, J = 7.3, 1.7 Hz), 3.70 (t, 1H, J = 5.1 Hz), 3.80–3.89 (m, 2H), 4.00 (dqd, 1H, J = 10.7, 7.3, 1.7 Hz), 4.09 (dqd, 1H, J = 10.7, 7.3, 1.7 Hz), 4.55 (br s, 2H) 5.15 (s, 1H), 7.07–7.79 (m, 11H), 12.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 56.2, 61.4, 62.3, 65.8, 109.7, 118.4, 119.6, 121.7, 128.1, 128.4, 128.6, 128.8, 129.0, 129.1, 129.3, 131.2, 133.8, 156.4, 171.0. Anal. Calcd for $C_{22}H_{23}NO_4$ (365.42): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.51; H, 6.46; N, 4.02.

4.2.8.1. (*R*)-Ethyl 2-((*R*)-2-hydroxy-1-phenylethylamino)-2-(2-hydroxynaphthalen-1-yl)acetate (*R*,*R*)-3h. ^{1}H NMR

(400 MHz, $CDCl_3$): δ 1.06 (td, 3H, J = 7.3, 1.7 Hz), 3.87–4.22 (m, 5H), 4.55 (br s, 2H) 5.45 (s, 1H), 6.95–7.82 (m, 11H), 12.05 (br s, 1H).

Acknowledgements

The financial support of this research by a grant from University of Camerino and from MIUR-PRIN is gratefully acknowledged.

References

1. (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989; (b) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11; (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (d)*Amino Acids*; Ager, D. G., Ed.; Wiley-VCH, 2009; p 495; (e) Petasis, N. A.; Zavialov, I. *J. Am. Chem. Soc.* **1997**, *119*, 445–446; (f) Mauksch, M.; Tsogoeva, S. B.; Martynova, I. M.; Wei, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 393–396; (g) Wang, X.; Zhang, Y.; Tan, H.; Wang, Y.; Han, P.; Wang, D. Z. *J. Org. Chem.* **2010**, *75*, 2403–2406.
2. (a) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10–19; (b) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112; (c) Jiang, B.; Yang, C.-G.; Gu, X.-H. *Tetrahedron Lett.* **2001**, *42*, 2545–2547; (d) Chen, Y.-J.; Lei, F.; Liu, L.; Wang, D. *Tetrahedron* **2003**, *59*, 7609–7614; (e) Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, *13*, 2198–2204.
3. (a) Sato, F.; Ikobe, A.; Koizumi, T.; Katsuno, K.; Kobayashi, Y. Jpn. Kokai Tokkyo Koho JP 09059233, 1997.; (b) Garcia, M. J.; Azerad, R. *Tetrahedron: Asymmetry* **1997**, *8*, 85–92.
4. (a) Palmieri, G. *Eur. J. Org. Chem.* **1999**, 805–811; (b) Borrione, E.; Prato, M.; Scorrano, G.; Stivanello, M.; Lucchini, V. J. *Heterocycl. Chem.* **1998**, *25*, 1831–1835; (c) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575–580; (d) Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759–4765; (e) Cimarelli, C.; Palmieri, G. *Chirality* **2009**, *21*, 218–232.
5. GAUSSIAN 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.
6. CCDC 811046 [(1*R*,α*S*)-**3a**·HCl] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
7. Spartan' 06, Wavefunction, Inc., Irvine, CA.