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A Simple and Efficient Diastereoselective Strecker Synthesis of Optically Pure α-Arylglycines

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Abstract: A simple and economical method for the synthesis of highly functionalised α-amino nitriles, precursors to α-arylglycines with high optical purity is reported. For this purpose, (R) or (S)-2-amino-2-phenylethanol were used as chiral auxiliaries in a 1,3 Strecker reaction. Reactions were studied with a broad range of reagent systems for the generation of cyano nucleophile. Methodology has been extended for the synthesis of (S)-α-(2-iodo-5-nitrophenyl)glycine, (S)-α-(4-methoxyphenyl)glycine and (R)-β-(4-methoxyphenyl)alanine.
Keywords: Asymmetric Strecker reaction; 1,3 induction; (R)-2-amino-2-phenylethanol; α-arylglycines.

In connection with the synthesis of cyclic peptides, we needed a number of functionalised α-amino acids, in particular α-arylglycines with high optical purity. Numerous approaches[1] to synthesise optically pure α-arylglycines were at our disposal. Barring the Strecker reaction, other methodologies require reagents which are not economically viable and lack generality. Diastereoselective Strecker synthesis[2] using a broad variety of chiral inducing agents is already known to furnish α-amino nitriles, precursors to α-amino acids in different optical purity. The advantages of (R) or (S)-2-amino-2-phenylethanol as chiral auxiliaries in the 1,3 diastereoselective Strecker reaction are 1) they can be easily prepared from the corresponding chiral α-phenylglycine, 2) asymmetric induction proceeds with good diastereoselectivity and 3) their removal under mild conditions is facile.

In this paper, we report efficient diastereoselectivity and good yields of α-amino nitriles in the 1,3 asymmetric Strecker reaction using both (R) and (S)-2-amino-2-phenylethanol as chiral inducing agents employing different reagent systems as a source for the cyano nucleophile. The Strecker reaction was initially studied with 1-naphthaldehyde under kinetically controlled conditions. The methodology giving the best results was extended for the synthesis of (S)-α-(2-iodo-5-nitrophenyl)glycine **(16)**, (S)-α-(4-methoxyphenyl)glycine **(18)** and (R)-β-(4-methoxyphenyl)alanine **(20)** from the corresponding aldehydes.

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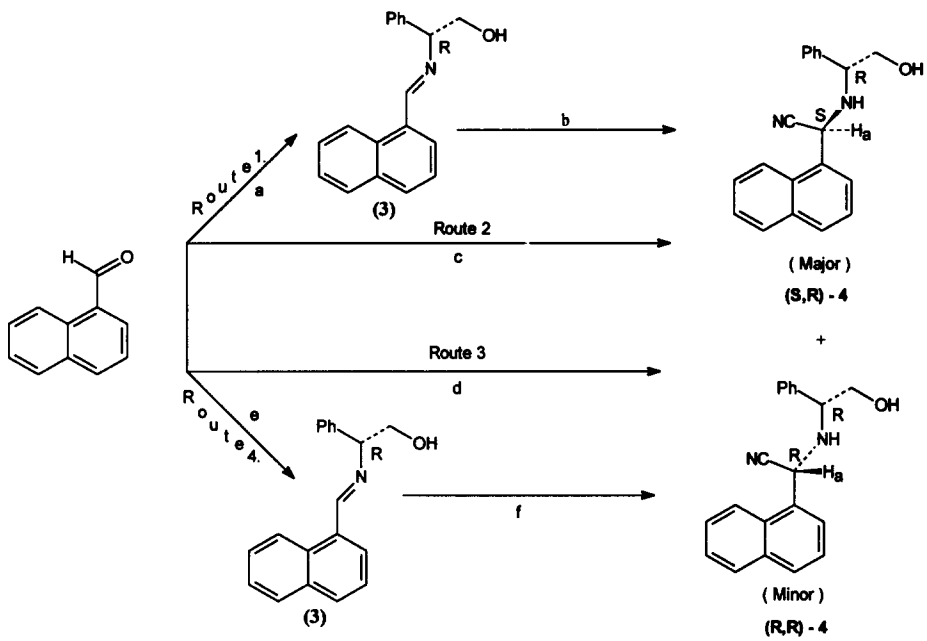
Also available commercially, (R)-2-amino-2-phenylethanol **(1)** and (S)-2-amino-2-phenylethanol **(2)** were prepared from the corresponding chiral α-phenylglycine by esterification[3], followed by reduction[4] of the formed methyl-α-phenylglycinate hydrochloride with sodium borohydride in 50% ethanol.

The 1,3 diastereoselective Strecker reaction using (R)-2-amino-2-phenylethanol **(1)** as chiral auxiliary was studied with 1-naphthaldehyde by generating hydrogen cyanide in four different ways under kinetically controlled conditions **(Scheme 1)**. In the first method,[5, 15] the imino solution was obtained by stirring a mixture of 1-naphthaldehyde and (R)-2-amino-2-phenylethanol **(1)** in chloroform in the presence of anhydrous sodium sulphate. To the imino solution, some methanol was added and the resulting mixture was treated with trimethylsilylcyanide (TMSCN) at 0-5°C. The diastereoisomeric (S,R) and (R,R)-2-[(2-hydroxy-1-phenyl)amino]-2-(1-naphthyl)ethanenitriles **(4)**, which serve as the precursors for α-(1-naphthyl)glycine **(5)** were isolated in 88% yield by silica gel column chromatography (route 1).



Scheme 1. *Reagents: a) $CHCl_3$, (R)-2-amino-2-phenylethanol (1); b) CH_3OH, TMSCN, 0-5°C, 88%; c) CH_3OH : H_2O (1:1), (R)-2-amino-2-phenylethanol (1), $NaHSO_3$, NaCN, 0-5°C, 65%; d) CH_3OH : H_2O (1:1), (R)-2-amino-2-phenylethanol hydrochloride, NaCN, 0-5°C, 70%; e) MeOH, (R)-2-amino-2-phenylethanol (1); f) NH_4Cl, NaCN, 0-5°C, 87%.*

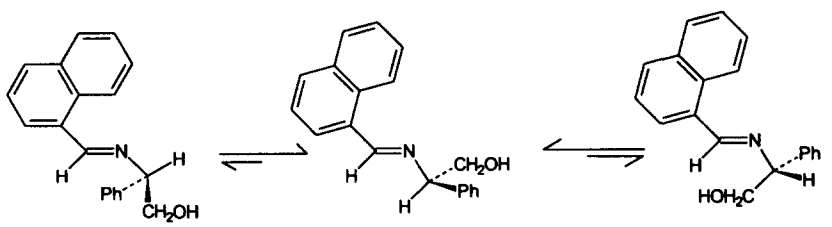
However, if the reaction was carried out in the absence of methanol, then TMSCN first reacts with the hydroxyl group of the chiral auxiliary to form a silyl ether and hydrogen cyanide. It is the liberated hydrogen cyanide that adds across the Schiff's base to provide the α-amino nitrile. It was thus recognised that the role of TMSCN is mere liberation of hydrogen cyanide which serves as the source of the cyano nucleophile. Although use of TMSCN as a source for hydrogen cyanide seems to be promising and safer, its use is not economically advisable particularly when optically active α-arylglycines are prepared on a larger scale. It

was thus decided to employ other easily available reagent systems as a cyano anion source in the Strecker reaction. It is also important that the alternative reagent used, does not lower the diastereoselectivity and the yields of the α-amino nitrile.

With a view to developing a one pot synthesis of α-amino nitriles, 1,3 diastereoselective Strecker reaction was studied with 1-naphthaldehyde using sodium bisulphite and sodium cyanide as a means for generating the cyano nucleophile. But, the diastereoisomeric mixture of (S,R) and (R,R)-2-[(2-hydroxy-1-phenyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** was obtained in only 65% yield (route 2). In another one pot approach, it was decided to generate hydrogen cyanide *in situ* using the hydrochloride salt of the chiral auxiliary with sodium cyanide (route 3). The Strecker reaction of 1-naphthaldehyde with (R)-2-amino-2-phenylethanol hydrochloride[6] and sodium cyanide in 50% methanol afforded a mixture of diastereoisomeric α-amino nitriles in 70% yield. Finally, it was decided to generate hydrogen cyanide in the asymmetric Strecker reaction by employing ammonium chloride and sodium cyanide in different molar ratios with a view to evaluate the yield of α-amino nitrile (route 4). It was observed that the combined yield of (S,R) and (R,R)-2-[(2-hydroxy-1-phenyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** is optimum (87%) with 3 molar equivalents of sodium cyanide and 2 molar equivalents of ammonium chloride for the imine **(3)** obtained from 1 molar equivalent of 1-naphthaldehyde and (R)-2-amino-2-phenylethanol **(1)**. The diastereomeric ratio [(S,R):(R,R)] of 2-[(2-hydroxy-1-phenyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** in all the above cases was almost the same i.e. 84 : 16. The latter was assigned by integrating the ^{1}H NMR singlet[7] of the methine proton on the carbon bearing the nitrile group.

The mechanism of the Strecker reaction involves exclusive formation of E-imine **(3)** and can be explained on the basis of internuclear distance,[8] bond angles[9] and the coplanarity requirement for resonance stabilisation.[8]

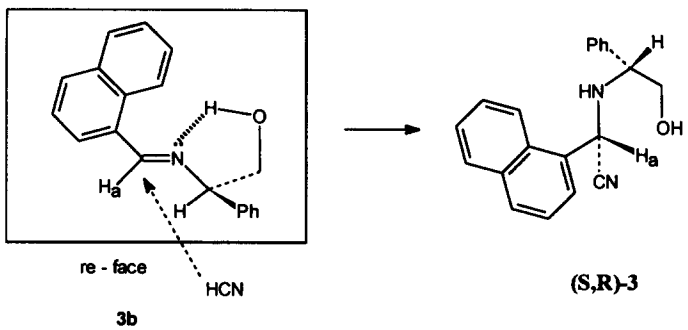
Prochiral E-imine **(3)** represents a heterosubstituted 1,3-allylic system.[10] In such a system the allylic stereocenter shifts[11] the conformational equilibrium towards conformer **3b (Scheme 2)**.



3a **3b** **3c**

Scheme 2.

Further, intramolecular H-bonding studied by Polt *et al.*[12] in β-hydroxy imines reveals that a similar type of intramolecular hydrogen bonding pattern in the prochiral E-imine **(3)** enhances the conformational preference for conformer **3b**. Thus conformer **3b** is the predominant reactive conformer of the prochiral E-imine **(3)**. This "conformational lock"[13] in the ground state of the E-imine should allow the substituents at the allylic stereocenter to shield the diastereotopic faces of the double bond in the transition state of the reaction with the cyano nucleophile.



Scheme 3.

The attack[14] of the cyano nucleophile across the diastereotopic face will be preferentially from the less shielded direction thereby affording (S,R)-2-[(2-hydroxy-1-phenyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** in excess **(Scheme 3)**.

It can be expected that the lowering of reaction temperature in the Strecker reaction would shift the conformational equilibrium towards the predominant reactive conformer **3b** of prochiral E-imine **(3)** leading to higher diastereoselectivity. However, when a series of reactions were studied and monitored by T.L.C., it was observed that the addition of the cyano nucleophile across the prochiral imine takes place at around 20°C. Thus, lowering the reaction temperature with the motive to shift the conformational equilibrium towards the predominant reactive conformer of the prochiral imine did not bring about any enhancement in diastereoselectivity.

The major (S,R)-2-[(2-hydroxy-1-phenyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** was separated from its diastereoisomeric mixture by silica gel column chromatography using pet.ether and ethyl acetate (90:10) as eluants.

Table 1. Chemical yield and diastereomeric ratio of α-amino nitriles

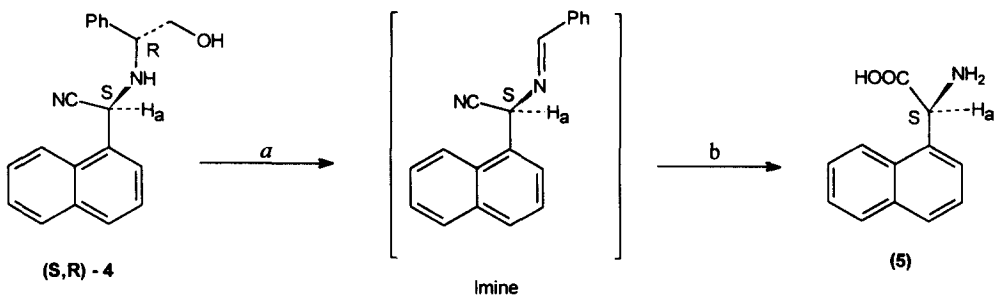
Entry	Aldehyde	Yield[a] (%) of α-amino nitrile (4-9)	Diastereoselectivity (S,R) : (R,R)	Chemical Shift (δ) of α-methine proton (H_a) in (S,R)	(R,R)
1	1-Naphthaldehyde	87	84:16	4.9	5.3
2	2-Naphthaldehyde	88	83:17	4.45	4.75
3	Benzaldehyde	87	82:18	4.4	4.6
4	2-Chlorobenzaldehyde[b]	82	83:17	4.65	4.95
5	2-Methoxybenzaldehyde[b]	84	81:19	4.55	4.8
6	4-Benzyloxybenzaldehyde[b]	83	80:20	4.45	4.65

[a] Yield refers to isolated yields of combined diastereomers; [b] 1,4-Dioxane was used as the solvent instead of methanol.

Since adoption of route 4 gave good yields of α-amino nitriles without affecting the diastereoselectivity, the use of sodium cyanide and ammonium chloride in the 1,3 diastereoselective Strecker reaction was extended to several aromatic aldehydes **(Table 1)**.

It is noteworthy that with 1-naphthaldehyde and 2-naphthaldehyde (entries 1 and 2), the diastereoisomeric mixture of (S,R) and (R,R) α-amino nitriles were directly isolated from the reaction mixture by filtration. The major (S,R) diastereomers were obtained as colourless needles from their diastereisomeric mixture by crystallising twice from ethyl acetate and pet.ether.

Oxidative cleavage[15] of the chiral auxiliary part of (S,R)-2-[(2-hydroxy-1-phenylethyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** was achieved by lead tetraacetate treatment to give an imine and formaldehyde. The imine was converted without purification by acid hydrolysis with 6M hydrochloric acid to (S)-α-(1-naphthyl)glycine **(5)** **(Scheme 4)**.

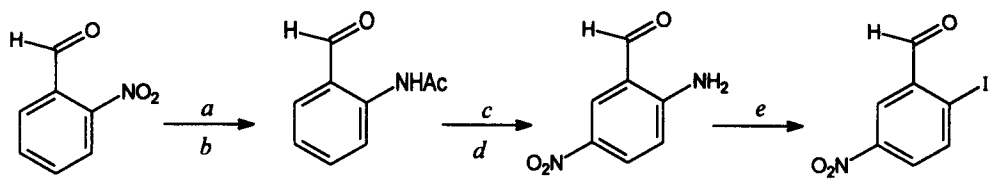


Scheme 4. *Reagents: a) $Pb(OAc)_4$, CH_2Cl_2:MeOH (1:1); b) 6M HCl, $NaHCO_3$.*

Using the same strategy and employing (S)-2-amino-2-phenylethanol **(2)** as the chiral auxiliary, the Strecker reaction with 1-naphthaldehyde gave the expected (R)-α-(1-naphthyl)glycine **(6)**.

The methodology was extended for the synthesis of (S)-α-(2-iodo-5-nitrophenyl)glycine **(16)**, (S)-α-(4-methoxyphenyl)glycine **(18)** and (R)-β-(4-methoxyphenyl)alanine **(20)** from the corresponding aldehydes **(Table 2)**. 2-Iodo-5-nitrobenzaldehyde **(14)** required for the synthesis of (S)-α-(2-iodo-5-nitrophenyl)glycine **(16)** was prepared from 2-aminobenzaldehyde **(7)** **(Scheme 5)**. 2-Aminobenzaldehyde was obtained from 2-nitrobenzaldehyde by reduction with ferrous sulfate heptahydrate and 25% aqueous ammonia with modified workup of the reported procedure.[16] As 2-aminobenzaldehyde **(7)** is prone to undergo polymerisation, it was isolated from the reaction mixture as soon as possible. Smith *et al.* had used steam distillation and then ether extraction for the quantitative isolation of the product. It was observed that extraction of 2-aminobenzaldehyde **(7)** with benzene is better from stability point of view. Acetylation of 2-aminobenzaldehyde **(7)** was problematic, particularly under the acidic conditions. Even acetyl chloride in the presence of pyridine gave a number of side products. Finally, acetylation of 2-aminobenzaldehyde was achieved at room temperature with acetic anhydride and pyridine in dry benzene.

2-Acetamidobenzaldehyde **(12)** was nitrated with fuming nitric acid and concentrated sulfuric acid to give 2-acetamido-5-nitrobenzaldehyde. The nitrated product was hydrolysed with 50% sulfuric acid to give 2-amino-5-nitrobenzaldehyde **(13)** in 91% yield. The amino derivative was diazotised in 70% sulfuric acid with sodium nitrite solution at 0-5°C. The diazonium salt solution on treatment with potassium iodide solution gave 2-iodo-5-nitrobenzaldehyde[17] **(14)** in 51% yield.



(12) (13) (14)

Scheme 5. *Reagents: a) $FeSO_4.7H_2O$, NH_4OH; b) Pyridine, Ac_2O; c) Fum. HNO_3, Conc.H_2SO_4; d) 50% H_2SO_4; e) $NaNO_2$, 50% H_2SO_4, KI*

Table 2. Diastereomeric ratio of α-amino nitriles and chemical yield of α-amino nitriles and the corresponding α-amino acids.

Entry	Aldehyde & Chiral Inductor	Diastereoselectivity **Major : Minor**	Yield[a] (%) of α-amino nitrile **(15, 17 & 19)**	Chemical Shift (δ) of α-methine proton (H_a) in **Major** and **Minor**		Yield[b] (%) of α-amino acids **(16, 18 & 20)**
1	2-Iodo-5-nitro benzaldehyde & **(1)**	(S,R) : (R,R) 80:20	86	4.8	5.15	51
2	4-Methoxy benzaldehyde & **(1)**	(S,R) : (R,R) 83:17	88	4.45	4.65	53
3	4-Methoxyphenyl acetaldehyde & **(2)**	(R,S) : (S,S) 82:18	84	3.55	3.8	49

[a] *Yield refers to isolated yields of combined diastereomers;* [b] *Yield with reference to α-amino nitrile.*

The Strecker reaction of 2-iodo-5-nitrobenzaldehyde **(14)** with (R)-2-amino-2-phenylethanol **(1)** as chiral inductor gave a diastereoisomeric mixture of (S,R) and (R,R)-2-[(2-hydroxy-1-phenyl)amino]-2-(2-iodo-5-nitrophenyl)ethanenitrile **(15)**. The major (S,R) diastereomer was obtained by crystallising twice from ethyl acetate - pet.ether. It was subjected to lead tetraacetate oxidation and acid hydrolysis to afford (S)-α-(2-iodo-5-nitrophenyl)glycine **(16)**.

The synthesis of (S)-α-(4-methoxyphenyl)glycine **(18)** necessitates the use of the (R) enantiomer of the chiral auxiliary. The major (S,R)-2-[(2-hydroxy-1-phenyl)amino]-2-(4-methoxyphenyl)ethanenitrile **(17)**, obtained by silica gel column chromatography, was converted to (S)-α-(4-methoxyphenyl)glycine **(18)** by the standard protocol.

The asymmetric Strecker reaction of 4-methoxyphenylacetaldehyde[18] with (S)-2-amino-2-phenylethanol **(2)** as the chirality transfer reagent provided a mixture of (R,S) and (S,S)-2-[(2-hydroxy-1-phenyl)amino]-2-(4-methoxyphenyl)propanenitrile **(19)**. The diastereoselectivity of the reaction was determined by integrating the double doublet of the α-methine proton displayed by the major (R,S) and minor (S,S) diastereomers at δ3.55 and δ3.8 respectively. The major (R,S)-2-[(2-hydroxy-1-phenyl)amino]-2-(4-

methoxyphenyl)propanenitrile **(19)** isolated by column chromatography was subjected to lead tetraacetate oxidative cleavage and acid hydrolysis to afford (R)-β-(4-methoxyphenyl)alanine **(20)**.

Thus a simple and economical protocol using an easily available reagent system as a substitute for the expensive TMSCN in the 1,3 diastereoselective Strecker reaction employing (R) or (S)-2-amino-2-phenylethanol as chiral auxiliary has been developed. Using this methodology a wide variety of optically pure α-amino nitriles, precursors to α-amino acids, can be synthesised.

Experimental:

IR spectra were recorded on a Shimadzu FTIR-4200 instrument. ^{1}H NMR were scanned on Varian EM-360 L(60MHz) or FT-NMR Varian Gemini-200 (200MHz) machines. Elemental analyses were determined using a Carlo Elora, C, H, N, EA-1108-elemental analyser. Optical rotations were measured on a Jasco DIP model 370 polarimeter using a one decimeter cell path length with concentrations expressed in grams per 100mL.

Pet.ether refers to the petroleum ether fraction bp 40-60°C. (D)-α-Phenylglycine, $[\alpha]^{22}_D$ -156 (c 1.0, 1N HCl), was obtained from IOC, Khopoli, India, while (L)-α-Phenylglycine, $[\alpha]^{22}_D$ +156.1 (c 1.0, 1N HCl), was supplied by Lancaster. 4-Methoxyphenylacetaldehyde was prepared by Darzen's condensation of 4-methoxy benzaldehyde with methyl chloroacetate according to the literature procedure.[18]

General Procedures

Strecker Reaction of 1-Naphthaldehyde with (R)-2-Amino-2-Phenylethanol (1): (S,R) and (R,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(1-Naphthyl)ethanenitrile (4):

Method 1:

A mixture of 1-naphthaldehyde (1.56g, 10mmoles) and (R)-2-amino-2-phenylethanol **(1)** (2.2g, 16mmoles) in 30mL of chloroform was stirred at room temperature and when the mixture became turbid, it was passed through anhydrous sodium sulfate and stirred again for 4 h. Evaporation of solvent gave the crude imine as a yellow oil which was dissolved in 20mL chloroform and 3mL methanol. The imino solution was cooled to 0°C and TMSCN (2.8mL, 20mmoles) was added under stirring. The reaction mixture was slowly warmed to room temperature and stirred for 24 h. Concentration of the mixture in vacuum left a pale yellow residual oil (2.96, 98%) which on silica gel (60-120 mesh) column chromatography (pet.ether-ethyl acetate, 80:20) yielded a mixture of (S,R) and (R,R)-2-[(2-hydroxy-1-phenylethyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** as a colourless solid, (2.66g, 88%); m.p. 103°C. (S,R):(R,R) diastereomeric ratio of 84:16 was determined by integrating the ^{1}H NMR singlet of the α-methine proton (NCHCN) of the isomeric mixture.

^{1}H NMR (60MHz, $CDCl_3$) δ=7.9-6.9 [m, 12H, ArH of (S,R) & (R,R)], 5.3 [s, 1H, NCHCN of (R,R)], 4.9 [s, 1H, NCHCN of (S,R)], 4.35-3.95 [m, 1H, NCHPh of (S,R) & (R,R)], 3.7-3.3 [m, 2H, CH_2-O of (S,R) & (R,R)], 2.15 [br s, 1H, NH of (S,R) & (R,R)], 1.25 [br s, 1H, OH of (S,R) & (R,R)]; IR (KBr) 3650-3150, 3050, 2950-2850, 2250, 1600, 1510, 1460, 1050, 800-770, 700 cm^{-1}. Found: C, 79.13%; H, 6.11%; N, 9.2%. Calcd for $C_{20}H_{18}N_2O$: C, 79.47%; H, 5.96%; N, 9.27%.

Method 2:

To a suspension of 1-naphthaldehyde (1.56g, 10mmoles) in 20mL of water at 0-5°C, were added sodium bisulfite (2.08g, 20mmoles), sodium cyanide (0.98g, 20mmoles) and a solution of (R)-2-amino-2-phenylethanol **(1)** (2.2g, 16mmoles) in 20mL of methanol under stirring. The reaction mixture was allowed to

come to room temperature and stirred (18 h). To the reaction mixture, 100mL of water was added and the oily product obtained was extracted with chloroform (3 x 25mL). The combined organic extracts were dried (Na_2SO_4) and distilled under vacuum to give a residual oil (2.9g, 96%). Silica gel column chromatography (pet.ether-ethyl acetate, 80:20) of the residue gave a mixture of (S,R) and (R,R)-2-[(2-hydroxy-1-phenylethyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** as a pale yellow solid, (1.97g, 65%); m.p. 99°C. (S,R):(R,R) diastereomeric ratio of 82:18 was determined by integrating the ^{1}H NMR singlet of the α-methine proton (NCHCN) of the diastereomeric mixture.

Method 3:

To a suspension of 1-naphthaldehyde (1.56g, 10mmoles) in 30mL of water at 0-5°C, were added sodium cyanide (0.98g, 20mmoles) and a solution of (R)-2-amino-2-phenyl ethanol hydrochloride (3.48g, 20mmoles) in 30mL of methanol under stirring. The reaction mixture was allowed to come to room temperature and stirred (18 h). To the reaction mixture, 100mL of water was added and the oily product obtained was extracted with chloroform (3 x 25mL) and the combined organic extracts were dried (Na_2SO_4) and distilled under vacuum to give a residual oil (2.93, 97%). Silica gel column chromatography (pet.ether-ethyl acetate, 80:20) of the residue gave a mixture of (S,R) and (R,R)-2-[(2-hydroxy-1-phenylethyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** as a pale yellow solid (2.12g, 70%); m.p. 101°C. (S,R):(R,R) diastereomeric ratio of 83:17 was determined by integrating the ^{1}H NMR singlet of the α-methine proton (NC<u>H</u>CN) of the isomeric mixture.

Method 4:

A mixture of 1-naphthaldehyde (1.56g, 10mmoles) and (R)-2-amino-2-phenylethanol **(1)** (2.2g, 16mmoles) in 20mL of methanol was stirred at room temperature (4 h). The resulting imino solution was added to a solution of sodium cyanide (1.48g, 30mmoles) and ammonium chloride (1.06g, 20mmoles) in 20mL of water at 0-5°C under stirring. The reaction mixture was allowed to come to room temperature and stirred for 12 h. To the reaction mixture, 100mL of water was added and the pale yellow solid obtained was filtered and dried (2.96g, 98%); mp 71°C. Silica gel column chromatography (pet.ether-ethyl acetate, 80:20) of the solid gave a mixture of (S,R) and (R,R)-2-[(2-hydroxy-1-phenylethyl)amino]-2-(1-naphthyl)ethanenitrile **(4)** as a colourless solid, (2.63g, 87%); m.p. 102°C. (S,R):(R,R) diastereomeric ratio of 84:16 was determined by integrating the ^{1}H NMR singlet of the α-methine proton (NC<u>H</u>CN) of the isomeric mixture.

(S,R) and (R,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(2-Naphthyl)ethanenitrile (5):

Similarly, diastereomeric mixture [(S,R)/(R,R)=83:17] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(2-naphthyl)ethanenitrile **(5)** was obtained as a colourless solid in 88% yield; mp 134°C.

^{1}H NMR (60MHz, $CDCl_3$) δ=7.9-6.8 [m, 12H, Ar<u>H</u> of (S,R) & (R,R)], 4.75 [s, 1H, NC<u>H</u>CN of (R,R)], 4.45 [s, 1H, NC<u>H</u>CN of (S,R)], 4.35-3.9 [m, 1H, NC<u>H</u>Ph of (S,R) & (R,R)], 3.65-3.3 [m, 2H, C<u>H</u>$_2$-O of (S,R) & (R,R)], 2.5 [br s, 1H, N<u>H</u> of (S,R) & (R,R)], 1.95 [br s, 1H, O<u>H</u> of (S,R) & (R,R)]; IR (KBr) 3650-3150, 3050, 2925-2850, 2225, 1640, 1600, 1510, 1460, 1050, 900, 870, 830, 760, 700 cm^{-1}. Found: C, 78.98%; H, 5.68%; N, 9.31%. Calcd for $C_{20}H_{18}N_2O$: C, 79.47%; H, 5.96%; N, 9.27%.

(S,R) and (R,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(Phenyl)ethanenitrile (6):

Similarly, diastereomeric mixture [(S,R)/(R,R)=82:18] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(phenyl)ethanenitrile **(6)** was obtained as a colourless viscous oil in 87% yield.

^{1}H NMR (60MHz, $CDCl_3$) δ=7.4-7.1 [m, 10H, ArH of (S,R) & (R,R)], 4.6 [s, 1H, NCHCN of (R,R)], 4.4 [s, 1H, NCHCN of (S,R)], 4.3-4.1 [dd, J 4, 9.2 Hz, 1H, NCHPh of (S,R) & (R,R)], 3.65 [m, 2H, CH_2-O of (S,R)], 3.5 [m, 2H, CH_2-O of (R,R)], 2.5 [br s, 2H, NH, OH of (S,R) & (R,R)]; IR ($CHCl_3$) 3600-3100, 3010, 2850, 2290, 1650, 1600, 1500, 1450, 1040, 760, 700 cm^{-1}. Found: C, 75.97%; H, 5.98%; N, 10.85%. Calcd for $C_{16}H_{16}N_2O$: C, 76.19%; H, 6.35%; N, 11.11%.

(S,R) and (R,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(2-Chlorophenyl)ethanenitrile (7):

Similarly, diastereomeric mixture [(S,R)/(R,R)=83:17] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(2-chlorophenyl)ethanenitrile **(7)** was obtained as a colourless liquid in 82% yield.

^{1}H NMR (60MHz, $CDCl_3$) δ=7.5-7.0 [m, 9H, ArH of (S,R) & (R,R)], 4.95 [s, 1H, NCHCN of (R,R)], 4.65 [s, 1H, NCHCN of (S,R)], 4.3-3.9 [m, 1H, NCHPh of (S,R) & (R,R)], 3.7-3.3 [m, 2H, CH_2-O of (S,R) & (R,R)], 2.6 [br s, 2H, NH, OH of (S,R) & (R,R)]; IR ($CHCl_3$) 3600-3200, 3030, 2850, 2250, 1640, 1600, 1500, 1490-1440, 1040, 760, 700 cm^{-1}. Found: C, 66.94%; H, 5.61%; Cl, 12.22; N, 9.51%. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.02%; H, 5.24%; Cl, 12.39; N, 9.77%.

(S,R) and (R,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(2-Methoxyphenyl)ethanenitrile (8):

Similarly, diastereomeric mixture [(S,R)/(R,R)=81:19] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(2-methoxyphenyl)ethanenitrile **(8)** was obtained as a colourless viscous oil in 84% yield.

^{1}H NMR (60MHz, $CDCl_3$) δ=7.5-6.65 [m, 9H, ArH of (S,R) & (R,R)], 4.8 [s, 1H, NCHCN of (R,R)], 4.55 [s, 1H, NCHCN of (S,R)], 4.35-3.95 [m, 1H, NCHPh of (S,R) & (R,R)], 3.9-3.4 [m and s overlapped, 5H, CH_2-O and O-CH_3 of (S,R) & (R,R)], 2.45 [br s, 2H, NH, OH of (S,R) & (R,R)]; IR ($CHCl_3$) 3650-3150, 3050, 2950-2850, 2250, 1600, 1500-1440, 1250, 1040, 760, 700 cm^{-1}. Found: C, 71.98%; H, 6.14%; N, 10.18%. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.34%; H, 6.38%; N, 9.93%.

(S,R) and (R,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(4-Benzyloxyphenyl)ethanenitrile (9):

Similarly, diastereomeric mixture [(S,R)/(R,R)=80:20] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(4-benzyloxyphenyl)ethanenitrile **(9)** was obtained as a yellow oil in 83% yield.

^{1}H NMR (60MHz, $CDCl_3$) δ=7.6-6.8 [m, 14H, ArH of (S,R) & (R,R)], 5.1 [s, 2H, PhCH_2-O of (S,R) & (R,R)], 4.65 [s, 1H, NCHCN of (R,R)], 4.45 [s, 1H, NCHCN of (S,R)], 4.35-4.05 [m, 1H, NCHPh of (S,R) & (R,R)], 3.75-3.45 [s, 2H, CH_2-O of (S,R) & (R,R)], 2.45 [br s, 2H, NH, OH of (S,R) & (R,R)]; IR ($CHCl_3$) 3650-3150, 3050, 2925-2850, 2280, 1600, 1510, 1460, 1250, 1025, 750, 700 cm^{-1}. Found: C, 76.99%; H, 6.41%; N, 7.69%. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.10%; H, 6.15%; N, 7.82%.

(S,R) -2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(1-Naphthyl)ethanenitrile (4):

Major (S,R)-**4** eluted out first using silica gel (100-200 mesh) column chromatography (pet.ether-ethyl acetate, 90:10) of its diastereoisomeric mixture [(S,R)/(R,R)]=84/16] (2.06g). (S,R)-**(4)** was obtained as colourless crystals (1.9g, 74%); mp 126-7°C; $[\alpha]_D^{22}$ -159.4 (c 0.5, CH_2Cl_2)

^{1}H NMR (60MHz, $CDCl_3$) δ=7.89-7.82 (m, 3H, ArH),7.71 (d, J 2.3, 1H, ArH), 7.57-7.20 (m, 8H, ArH), 4.90 (s, 1H, NCHCN), 4.25 (dd, J 3.9, 9.1 Hz, 1H, NCHPh), 3.55 (m, 2H, CH_2O), 2.15 (br s, 1H, NH), 1.25 (br s, 1H, OH); IR (KBr) 3650-3150, 3050, 2950-2850, 2250, 1600, 1510, 1460, 1050, 800-770, 700 cm^{-1}. Found: C, 79.24%; H, 6.07%; N, 9.21%. Calcd for $C_{20}H_{18}N_2O$: C, 79.47%; H, 5.96%; N, 9.27%.

(S)-α-1-Naphthylglycine (10):

To a solution of (S,R)-**(4)** (1.52g, 5mmoles) in 10mL of methylene chloride and 5mL of methanol was added lead tetraacetate (2.2g, 5mmoles) under ice-cooling. After stirring at this temperature (5 min), the reaction mixture was neutralised by addition of aq. sat. $NaHCO_3$ solution (50mL). The resulting insoluble

impurities were removed by filtration (Celite) and washed with methylene chloride (2 x 15mL). The organic layer was separated and the aq. layer was extracted twice with methylene chloride (2 x 15mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuum to afford the crude imine as a yellowish brown oil which was subjected to acid hydrolysis as such. The crude imine was treated with 50mL of 6M hydrochloric acid and the mixture was stirred at room temperature (1 h) and then on steam bath at 90°C (45 minutes). The reaction mixture was extracted twice with diethyl ether (2 x 10mL). The ether extract was discarded and the aqueous layer was poured and concentrated in an evaporating dish to dryness. The solid residue obtained was dissolved in the minimum quantity of water (20mL) and then neutralised with solid $NaHCO_3$ under ice cooling (5-10°C). The colourless solid obtained was filtered, washed with diethyl ether and dried. Yield of (S)-α-(1-naphthyl)glycine **(10)** was 0.55g (55%); colourless crystals; mp 171°C (decomp,); $[\alpha]_D^{22}$ +164.7 (c 0.7, 1M HCl).

^{1}H NMR (CF_3COOD, 200MHz) δ=8.5-8.40 (m, 3H, ArH), 8.1-7.9 (m, 4H, ArH), 6.7 (s, 1H, NCHCOO); IR (KBr) 3000, 1610, 1500, 1360, 1330, 795, 770 cm^{-1}. Found: C, 71.57%; H, 5.44%; N, 6.91%. Calcd for $C_{12}H_{11}NO_2$: C, 71.68%; H, 5.47%; N, 6.96%.

(R,S) -2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(1-Naphthyl)ethanenitrile (4):

Similarly, diastereomeric mixture [(R,S)/(S,S)=83:17] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(2-naphthyl)ethanenitrile **(4)** was obtained following general procedure from 1-naphthaldehyde and (S)-2-amino-2-phenylethanol **(2)**, as a colourless solid in 86% yield; mp 98°C.

^{1}H NMR (60MHz, $CDCl_3$) δ=7.9-6.9 [m, 12H, ArH of (R,S) & (S,S)], 5.3 [s, 1H, NCHCN of (S,S)], 4.9 [s, 1H, NCHCN of (R,S)], 4.35-3.95 [m, 1H, NCHPh of (R,S) & (S,S)], 3.7-3.3 [m, 2H, CH_2-O of (R,S) & (S,S)], 2.15 [br s, 1H, NH of (R,S) & (S,S)], 1.25 [br s, 1H, OH of (R,S) & (S,S)]; IR (KBr) 3650-3150, 3050, 2950-2850, 2250, 1600, 1510, 1460, 1050, 800-770, 700 cm^{-1}. Found: C, 79.13%; H, 6.11%; N, 9.2%. Calcd for $C_{20}H_{18}N_2O$: C, 79.47%; H, 5.96%; N, 9.27%.

Major (R,S)-**4** was eluted out first using silica gel (100-200 mesh) column chromatography (pet.ether-ethyl acetate, 90:10) of its diastereoisomeric mixture [(S,R)/(R,R)]=84/16] as colourless crystals; mp 122-3°C; $[\alpha]_D^{22}$ +143.1 (c 0.5, CH_2Cl_2).

^{1}H NMR (60MHz, $CDCl_3$) δ=7.89-7.82 (m, 3H, ArH), 7.71 (d, J 2.2 Hz, 1H, ArH), 7.57-7.20 (m, 8H, ArH), 4.9 (s, 1H, NCHCN), 4.25 (dd, J 3.9, 9.1 Hz, 1H, NCHPh), 3.55 (m, 2H, CH_2O), 2.15 (br s, 1H, NH), 1.25 (br s, 1H, OH); IR (KBr) 3650-3150, 3050, 2950-2850, 2250, 1600, 1510, 1460, 1050, 800-770, 700 cm^{-1}. Found: C, 79.24%; H, 6.07%; N, 9.21%. Calcd for $C_8H_{11}NO$: C, 79.47%; H, 5.96%; N, 9.27%.

(R)-α-1-Naphthylglycine (11):

(R,S)-**4** was oxidised as described before to give (R)-α-(1-naphthyl)glycine **(11)** as a colourless solid in 53% yield; mp 171°C (decomp,); $[\alpha]_D^{22}$ +7.9 (c 0.4, H_2O) [lit.[19] $[\alpha]_D^{25}$ +8.0 (c 0.05, H_2O)].

^{1}H NMR (200MHz, CF_3COOD) δ=8.5-8.40 (m, 3H, ArH), 8.1-7.9 (m, 4H, ArH), 6.7 (s, 1H, NCHCOO); IR (KBr) 3000, 1600, 1510, 1360, 1330, 795, 770 cm^{-1}. Found: C, 71.61%; H, 5.45%; N, 6.89%. Calcd for $C_{12}H_{11}NO_2$: C, 71.68%; H, 5.47%; N, 6.96%.

2-Acetamidobenzaldehyde (12):

2-Aminobenzaldehyde was prepared by reduction of 2-nitrobenzaldehyde (12g, 80mmoles) with ferrous sulfate heptahydrate (210g, 760mmoles) with a slight variation in the workup of the reported[16] procedure. The reaction mixture was steam distilled to collect three 200mL fractions. The combined fraction

was extracted with benzene (3 x 30mL). The combined benzene extract was dried (Na_2SO_4) and concentrated under reduced pressure to 25mL volume.

To this solution of 2-aminobenzaldehyde, acetic anhydride (7.2mL, 75mmoles) and pyridine (4mL, 50mmoles) were added at room temperature. After stirring the reaction mixture for 18 h, benzene was distilled out and 100mL of water was added. The reaction mixture was allowed to stand for 30 min and then neutralised with sat. $NaHCO_3$ solution. The colourless product was collected by filtration and washed with water. Crystallisation from chloroform-pet.ether gave colourless needles of 2-acetamidobenzaldehyde **(12)** (7.6g, 58%); m.p. 70°C (lit.[20] mp 71°C).

^{1}H NMR (60MHz, $CDCl_3$) δ=11.4 (br s, 1H, NHCO), 9.85 (s, 1H, CHO), 8.7 (d, J 9.3 Hz, 1H, ArH), 7.7-7.0 (m, 3H, ArH), 2.2 (s, 3H, $COCH_3$); Found: C, 66.19%; H, 5.45%; N, 8.61%. Calcd for $C_9H_9NO_2$: C, 66.24%; H, 5.52%; N, 8.58%.

2-Iodo-5-Nitrobenzaldehyde (14):

2-Acetamidobenzaldehyde **(12)** (6.5g, 40mmoles) in 20mL acetic anhydride was added to 20mL of the nitrating mixture, prepared from 10mL conc. sulfuric acid and 10mL fuming nitric acid (Sp.gr 1.5), with stirring under ice cooling. After addition was complete, temperature of the reaction was gradually raised to room temperature. The reaction mixture was stirred (30 min) and then poured into 200mL of ice-cold water. The pale yellow product obtained was filtered and washed with water. Crystallisation from water gave needle shaped crystals of 2-acetamido-5-nitrobenzaldehyde (6.7g, 81%); m.p. 160°C (lit.[20] mp 160-161°C).

2-Acetamido-5-nitrobenzaldehyde (6g, 29mmoles) was added to 20mL of 50% sulfuric acid and reaction mixture was heated on the steam bath (1 h). The reaction mixture was cooled to room temperature and poured into 100mL of ice-cold water. The yellow solid obtained was filtered and washed with water. Crystallisation from alcohol gave yellow prisms of 2-amino-5-nitrobenzaldehyde **(13)** (4.3g, 91%), m.p. 201°C (lit.[20] mp 202°C).

2-Amino-5-nitrobenzaldehyde **(13)** (3.32g, 20mmoles) was added to 40mL 75% sulfuric acid and the reaction mixture was cooled to 0°C. A cold solution of sodium nitrite (2.76g, 40mmoles) in 30mL water was added slowly with stirring. 30 min after the addition was complete, the mixture was filtered rapidly into a flask containing crushed ice and was immediately added to a solution of potassium iodide (3g) in 30mL water. The resulting mixture was heated on a steam bath for 30 min, cooled in ice and filtered. The residue was dissolved in chloroform and solution was successively washed with water, aq. sodium carbonate solution, aq. sodium thiosulphate solution and water and then dried (Na_2SO_4). Evaporation of solvent left a solid residue which yielded 2-iodo-5-nitrobenzaldehyde **(14)** (2.8g, 51.3%) as yellow flakes after crystallisation from alcohol; m.p. 112°C (lit.[17] m.p. 111-112°C).

^{1}H NMR (60MHz, $CDCl_3$) δ=10.4 (s, 1H, CHO), 8.6 (weakly splitted d, J 2.3 Hz, 1H, ArH) 8.1 (m, 2H, ArH); IR (KBr) 2950, 2850, 1680, 1610, 1530, 1350, Found: C, 29.84%; H, 1.78%; N, 4.89%. Calcd for $C_7H_4INO_3$: C, 30.33%; H, 1.44%; N, 5.05%.

(S,R) and (R,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(2-Iodo-5-Nitrophenyl)ethanenitrile (15):

Similarly, diastereomeric mixture [(S,R)/(R,R)=80:20] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(2-iodo-5-nitrophenyl)ethanenitrile **(15)** was obtained following general procedure from 2-iodo-5-nitrobenzaldehyde **(14)** and (R)-2-amino-2-phenylethanol **(2)**, as a colourless solid in 86% yield; mp 113°C.

^{1}H NMR (200MHz, $CDCl_3$) δ=8.3 [d, J 2.4 Hz, 1H, ArH of (S,R) & (R,R)], 8.1 [m, 1H, ArH of (S,R) & (R,R)], 7.9 [m, 1H, ArH of (S,R) & (R,R)], 7.5-7.3 [m, 5H, ArH of (S,R) & (R,R)], 5.15 [s, 1H, NCHCN of

(R,R)], 4.8 [s, 1H, NCHCN of (S,R)], 4.4-4.25 [m, 1H, NCHPh of (S,R) & (R,R)], 3.95-3.7 [m, 2H, CH_2-O of (S,R) & (R,R)], 2.3 [br s, 2H, NH, OH of (S,R) & (R,R)]; IR (KBr) 3650-3150, 3050, 2925-2850, 2225, 1600, 1570, 1525, 1470, 1345, 1020, 750, 700 cm^{-1}. Found: C, 45.21%; H, 3.28%; N, 10.01%. Calcd for $C_{26}H_{14}IN_3O_3$: C, 45.39%; H, 3.31%; N, 9.93%.

Major (S,R)-**15** was isolated as needle shaped crystals from its diastereomeric mixture by crystallising twice from ethyl acetate and pet. ether; mp 135°C; $[\alpha]_D^{22}$ +165.5 (c 1, CH_2Cl_2) (200MHz, $CDCl_3$) δ=8.3 (d, J 2.4 Hz, 1H, ArH), 8.1 (m, 1H, ArH), 7.9 (m, 1H, ArH), 7.5-7.3 (m, 5H, ArH), 4.8 (s, 1H, NCHCN), 4.4-4.25 (m, 1H, NCHPh), 3.95-3.7 (m, 2H, CH_2-O), 2.3 (br s, 2H, NH, OH); IR (KBr) 3650-3150, 3050, 2925-2850, 2225, 1610, 1570, 1525, 1470, 1345, 1020, 760, 700 cm^{-1}. Found: C, 45.13%; H, 3.24%; N, 9.91%. Calcd for $C_{26}H_{14}IN_3O_3$: C, 45.39%; H, 3.31%; N, 9.93%.

(S)-α-(2-Iodo-5-Nitrophenyl)glycine (16):

(S,R)-**15** was oxidised and hydrolysed as described before to give (R)-α-(2-iodo-5-nitrophenyl)glycine **(16)** as a colourless solid in 51% yield; mp >200°C (decomp,); $[\alpha]_D^{25}$ -78.8 (c 0.612, 1N HCl).

^1H NMR (CF_3COOD, 200MHz) δ=8.5-8.40 (m, 3H, ArH), 8.2 (m, 2H, ArH), 7.9 (m, 1H, ArH), 5.6 (s, 1H, NCHCOO); IR (KBr) 3400- 2700, 1610, 1560, 1525, 1469, 1345, 780, 720 cm^{-1}. Found: C, 29.79%; H, 2.09%; N, 8.64%. Calcd for $C_8H_7IN_2O_4$: C, 29.81%; H, 2.17%; N, 8.70%.

(S,R)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(4-Methoxyphenyl)ethanenitrile (17):

Similarly, diastereomeric mixture [(S,R)/(R,R)=83:17] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(4-methoxyphenyl)ethanenitrile **(17)** was obtained as a pale yellow viscous oil in 88% yield.

^1H NMR (60MHz, $CDCl_3$) δ=7.5-6.85 [m, 9H, ArH of (S,R) & (R,R)], 4.65 [s, 1H, NCHCN of (R,R)], 4.45 [s, 1H, NCHCN of (S,R)], 4.3-3.95[m, 1H, NCHPh of (S,R) & (R,R)], 3.85-3.45 [m and s overlapped, 5H, CH_2-O and O-CH_3 of (S,R) & (R,R)], 2.35 [br s, 2H, NH, OH of (S,R) & (R,R)]; IR ($CHCl_3$) 3650-3150, 3050, 2950-2850, 2250, 1600, 1510, 1440, 1250, 1040, 760, 710 cm^{-1}. Found: C, 72.12%; H, 6.24%; N, 9.91%. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.34%; H, 6.38%; N, 9.93%.

Major (S,R)-**17** was eluted out first using silica gel (100-200 mesh) column chromatography (pet.ether-ethyl acetate, 90:10) of its diastereoisomeric mixture [(S,R)/(R,R)]=83/17] as colourless oil. A analytical sample for specific rotation was obtained as its hydrochloride salt, mp 83°C, $[\alpha]_D^{22}$ -58.1 (c 0.6, CH_2Cl_2).

^1H NMR (60MHz, $CDCl_3$) δ=7.5-6.85 (m, 9H, ArH), 4.45 [s, 1H, NCHCN), 4.3-3.9 [dd, J 4.1, 9.1Hz, 1H, NCHPh), 3.85-3.6 [m and s overlapped, 5H, CH_2-O and O-CH_3), 2.35 [br s, 2H, NH, OH); IR ($CHCl_3$) 3650-3150, 3050, 2950-2850, 2250, 1600, 1510, 1440, 1250, 1040, 760, 710 cm^{-1}. Found: C, 72.23%; H, 6.34%; N, 9.89%. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.34%; H, 6.38%; N, 9.93%.

(S)-α-(4-Methoxyphenyl)glycine (18):

(S,R)-**17** was oxidised and hydrolysed as described previously to afford (R)-α-(4-methoxyphenyl)glycine **(18)** as a colourless solid in 53% yield; mp >200°C; $[\alpha]_D^{25}$ +151.9 (c 0.8, 1N HCl) [lit.[21] $[\alpha]_D^{22}$ +156 (c 1, 3N HCl)].

^1H NMR (CF_3COOD, 200MHz) δ=7.86 (d, J 7.8 Hz, 2H, ArH), 7.52 (d, J 7.9 Hz, 2H, ArH), 5.78 (s, 1H, NCHCOO), 4.37 (s, 3H, OCH_3) ; IR (KBr) 2950, 1610, 1500, 1525, 1390, 1250, 1180, 1030, 900, 800, 580 cm^{-1}. Found: C, 59.61%; H, 5.98%; N, 7.88%. Calcd for $C_9H_{11}NO_3$: C, 59.66%; H, 6.12%; N, 7.73%.

(R,S)-2-[(2-Hydroxy-1-Phenylethyl)amino]-2-(4-Methoxyphenyl)propanenitrile (19):

Similarly, diastereomeric mixture [(R,S)/(S,S)=82:18] of 2-[(2-hydroxy-1-phenylethyl)amino]-2-(4-methoxyphenyl)propanenitrile **(19)** was obtained following general procedure from 4-

methoxyphenylacetaldehyde and (S)-2-amino-2-phenylethanol **(2)** as a yellow viscous oil in 84% yield. Diastereomeric ratio was assigned by integrating the ^{1}H NMR signal (double doublet) of the α-methine proton due to (R,S) diastereomer at δ3.55 and (S,S) diastereomer at δ3.8.

Major (R,S)-**19** was eluted out first as thick yellow viscous oil using silica gel (100-200 mesh) column chromatography (pet.ether-ethyl acetate, 90:10) of its diastereoisomeric mixture [(R,S)/(S,S)]=82/18]. Hydrochloride salt of (R,S)-**19** for recording specific rotation could not be obtained as crystals.

^{1}H NMR (200MHz, $CDCl_3$) δ=7.4-7.15 (m, 7H, ArH), 6.85 (d, J 8.1 Hz, 2H, ArH), 4.1 (dd, J 4.0, 8.8Hz, 1H, PhCHN), 3.8 (m, 4H, -CH_2O & OCH_3), 3.65 (m, 1H, CH_2O), 3.55 (dd, J 4.2, 10.7 Hz, 1H, NCHCN), 3.05 (d, J 6.5 Hz, 2H, p-MeO-C_6H_4-CH_2), 2.4 (br s, 2H, NH, OH); IR ($CHCl_3$) 3650-3150, 3100, 2950-2850, 2280, 1600, 1510, 1460, 1250, 1030, 760, 710 cm^{-1}. Found: C, 72.59%; H, 6.68%; N, 9.39%. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.97%; H, 6.76%; N, 9.46%.

(R)-β-(4-Methoxyphenyl)alanine (20):

(R,S)-2-[(2-Hydroxy-1-phenylethyl)amino]-2-(4-methoxyphenyl)propanenitrile **(19)** was oxidised and hydrolysed as described earlier to give (R)-α-(4-methoxyphenyl)glycine **(20)** as a colourless solid in 49% yield; mp >200°C; Hydrochloride salt $[\alpha]_D^{25}$ +27.3 (c 0.9, H_2O) [lit.[22] $[\alpha]_D^{26}$ +27.5 (c 0.51, H_2O)].

^{1}H NMR (200MHz, CF_3COOD) δ=6.95 (d, J 7.7Hz, 2H, ArH), 6.7 (d, J 7.9 Hz, 2H, ArH), 4.15 (s, 1H, NCHCOO), 3.95 (s, 3H, OCH_3) 3.25 (dd, J 5.8, 11.7Hz, 1H, PhC$H_a$$H_b$), 3.0 (dd, J 6.2, 11.8 Hz, 1H, PhC$H_a$$H_b$); IR (KBr) 3130-2700, 1600, 1500, 1430, 1260, 770, 700 cm^{-1}. Found: C, 61.39%; H, 6.71%; N, 7.04%. Calcd for $C_{10}H_{13}NO_3$: C, 61.54%; H, 6.67%; N, 7.18%.

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