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α-Phenylglycinol as Chiral Auxiliary in Diastereoselective Strecker Synthesis of α-Amino Acids

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Abstract: The high diastereoselectivity achieved in Strecker synthesis using inexpensive α-phenylglycinol as chiral auxiliary and its facile removal by oxidative cleavage make it an ideal choice for the large scale preparations of optically active α-amino acids specially α-arylglycines present abundantly in glycopeptide antibiotics. A number of chiral amino acids are synthesized following this method. Also molecular mechanics calculations are carried out to explain the observed diastereoselection.

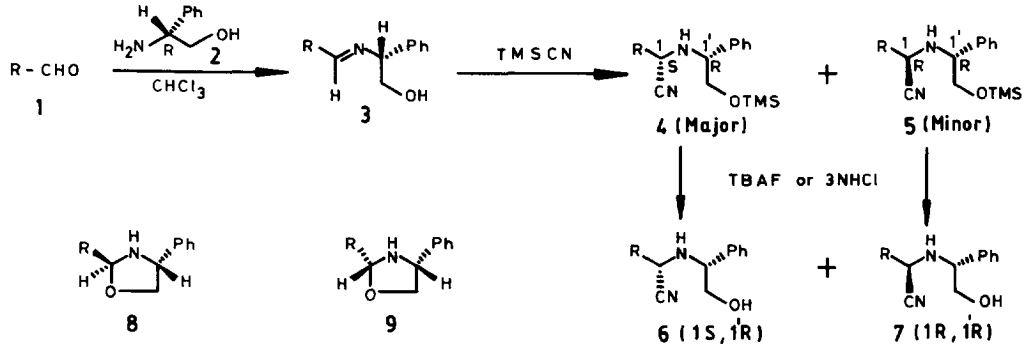
One of the major hurdles encountered in our ongoing project on the total synthesis of vancomycin-ristocetin family of glycopeptide antibiotics[1] is the presence of a large number of unnatural amino acids in these compounds, in particular α-arylglycines which are amongst the most difficult amino acids to obtain in optically pure form. In this paper we detail our studies[2] on the development of a very efficient methodology for the diastereoselective Strecker synthesis of optically pure α-amino acids using α-phenylglycinol as chiral auxiliary and give theoretical explanation for the excellent diastereoselection achieved.

Available in both enantiomeric forms, this excellent chiral auxiliary is suitable for the synthesis of both L- as well as D-amino acids, the (R)-phenylglycinol being used for the former and vice versa. In addition, its facile removal by oxidative cleavage with lead tetraacetate under essentially neutral conditions makes it an ideal choice for the synthesis of α-arylglycines.

Results and Discussion

A series of aldehydes (**1**) were reacted with (R)-phenylglycinol **2**[3](1.0 molar equiv.) in anhydrous $CHCl_3$ (Scheme 1,Table 1). The corresponding imines **3** were formed in 30 min to 1 h which was confirmed by carrying out test reactions in $CDCl_3$ in NMR tube. The resonance at ~ δ 10 corresponding to the starting aldehyde slowly made way for the resonance at ~ δ 8.3 corresponding to the imine formed. Only E-imines were formed as analysed by ^1H NMR. For example, **3b** gave only one singlet at δ 8.32 for C<u>H</u>=N. Under the reaction conditions always 5-10% of 1,3-oxazolidines **8** and **9** were also formed as a mixture of diastereomers (ca 3:2; ^1H NMR signals at δ 5.52 and 5.60 for NC<u>H</u>O of oxazolidine from **3b**) which prevented to achieve even higher diastereoselectivity[4]. In the time range mentioned above the resonance corresponding to the aldehyde totally disappeared

Scheme 1



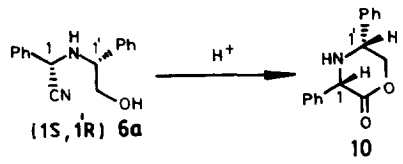
indicating completion of the reaction. After the total formation of the imines, trimethylsilyl cyanide (1.5-2.0 equiv.) was added to the reaction mixture at 0°C. Though the reactions were complete only after a few minutes, in all cases, they were allowed to go for an additional 6-8 h at room temperature. In $CHCl_3$ as the reaction medium, O-silylated products **4** and **5** were obtained. Because of the known instability of primary TMS ethers

Table 1. Diastereoselective Strecker synthesis with R(-)-2-phenylglycinol (2) and various aldehydes

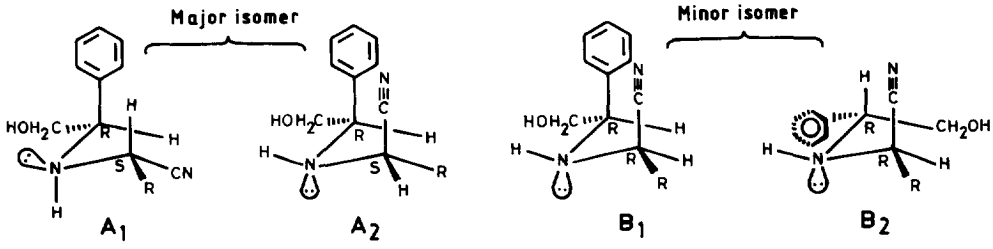
Entry	Aldehyde (**1**)	Diastereoselectivity (1S,1'R)-**6**:(1R,1'R)-**7**	Total yield
1.	Benzaldehyde (**1a**)	82:18	92
2.	p-Tolualdehyde (**1b**)	85:15	90
3.	p-Methoxybenzaldehyde (**1c**)	90:10	95
4.	Phenylacetaldehyde (**1d**)	54:46	87
5.	Isobutyraldehyde (**1e**)	84:16	95
6.	Pivalaldehyde (**1f**)	88:12	92

on silica gel column, the residue obtained after concentration in vacuo was treated with dilute HCl or tetrabutylammonium fluoride to remove the silyl group. In all cases after the usual work-up, the diastereomers **6** and **7** were easily separated by standard silica gel column chromatography. The diastereomeric ratios were determined by measuring peak integrals of appropriate signals (C1-H for **1a-c** and **1f**; C1'-H for **1d** and **1e**) in 400 or 200 MHz ^1H NMR spectra of $CDCl_3$ solution of the concentrated reaction mixtures.

Scheme 2



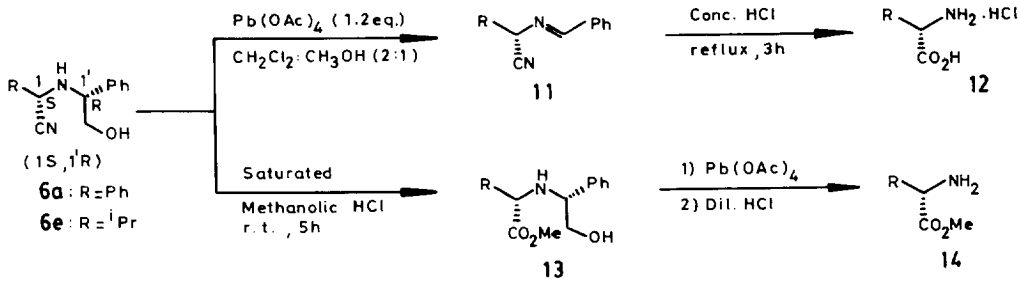
The configurations of the major and minor diastereomeric products were determined by comparing with very similar products described in the literature by Inaba et.al[5]. By analogy to their work, out of six energy minimized conformations of the major diastereomer **6**, $\mathbf{A}_1$ is the most stable one, followed by $\mathbf{A}_2$ whereas $\mathbf{B}_1$ and $\mathbf{B}_2$ are the two lowest energy conformations of the minor isomer **7**. The most stable conformation $\mathbf{A}_1$ of the major isomer **6** clearly places the methine proton, α to cyano group, in the shielding zone of the phenyl moiety. Inspection of the stable conformations $\mathbf{B}_1$ and $\mathbf{B}_2$ for the minor isomer **7** does not indicate any such shielding effect on the same methine proton. Thus, the methine protons of the major diastereomers absorb at higher field than those of the minor diastereomer. A consistent difference of about ~ 0.2 ppm was noticed. Further spectral evidence for the 1S,1'R configuration for the major diastereomer **6** was obtained by NOE effect observed for the compound **10** (Scheme 2) obtained by acid mediated cyclisation of **6a**. Irradiation of C1'-H in **10** resulted in en-



hancement of resonance corresponding to C1-H, thus, confirming the cis-relationship between these two protons. Additional evidence was obtained by converting the major isomers to corresponding L-amino acids by procedure described below. Specific rotations for L-amino acids, thus obtained by our method, [for L- phenylglycine $[\alpha]_D$ + 153.2° (c 1.0, 1N HCl); for L-valine $[\alpha]_D$ + 26.9° (c 8.0, 6N HCl)] compare favourably with the known values[6].

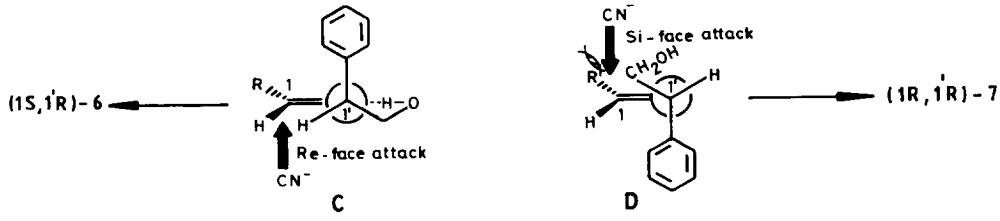
After confirming the absolute configurations of the purified major diastereomers **6**, the next task was to convert the amino nitrile to the desired amino acid. As mentioned in the introduction, our method of choice was oxidative removal of the chiral auxiliary using lead tetraacetate. This was done successfully with two aminonitriles **6a** and **6e** as follows. Aminonitrile **6a** was treated with lead tetraacetate (1.2 eq) in CH_3OH: CH_2Cl_2 (1:2) solvent mixture at 0°C (Scheme 3). The reaction was quantitative and complete in five minutes and resulting Schiff's base **11a** was converted into amino acid **12a** by refluxing with conc. HCl. Alternatively, the same amino nitrile **6a** was first treated with saturated methanolic HCl for 5 h at room temperature to convert the nitrile group into

Scheme 3



methyl ester **13a** and subsequently treated with lead tetraacetate and dil.HCl to obtain the amino acid as its methyl ester **14a**. The same sequence of reactions was carried out with another aminonitrile **6e** to obtain amino acid **12e** or its ethyl ester **14e**. The rotaions obtained for all the amino acids/esters mentioned in scheme 3 matched well with the literature values[6].

The excellent diastereoselectivity achieved in our method can be explained on the basis of aza analogue of Anh-Eisenstein hypothesis[7]. According to this hypothesis nucleophilic attack on the imine should take place antiperiplanar to the α-phenyl group which, having the lowest allylic σ* orbital energy, occupies, in the reactive conformer, a position perpendicular to the imine π – plane enabling maximum overlap between π* and allylic σ* orbitals lowering π* orbital energy and, consequently, minimizing the free energy of activation for the reaction. Further lowering of the energy of the allylic σ* orbital, therefore, should lead to increased overlap with imine π* orbital resulting in decreased free energy of activation. This was indeed found to be true. Using α-(2,6-dichlorophenyl)glycinol[8] as chiral auxiliary 90% diastereoselectivity was achieved with benzaldehyde (**1a**). The chlorine substituents at the ortho position of the phenyl ring decreased allylic σ* orbital energy[7c] leading to an increased percentage of reaction arising via kinetically preferred nucleophilic addition from the less hindered side of the most stable conformer. Though α-(2,6-dichlorophenyl)glycinol could not be used as a better alternative chiral auxiliary due to obvious practical difficulties it helped us to prove our reactive conformer hypothesis.

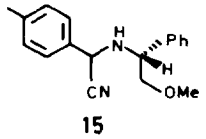


Of the two possible transition state conformations **C** and **D** where the phenyl group is perpendicular to the imine π – plane, conformer **C**, in which the attack takes place from the re-face of the imine giving rise to major (1S,1'R)-**6** diastereomer, is more favourable not only for steric reasons, the hydroxymethyl group being away from the imine moiety and the incoming nucleophile, but also for the extra stabilization through intramolecular 5-membered H-bonding[9]. This explains the enhanced diastereoselectivity observed with α-phenylglycinol in comparison with α-methyl benzylamine as chiral auxiliary where stabilization due to intramolecular H-bonding is not possible. Also it was found that in THF, which acts as a strong H-bond acceptor, loss of intramolecular H-bonding through solvation of hydroxyl group resulted in poor diastereoselectivity (entry 3, Table 2). Addition of anhydrous $MgCl_2$ (entry 4, Table 2) restored the 5-membered transition state through chelation and diastereoselectivity was regained. Comparable H-bond donor characters of glycinol hydroxyl and methanol, when used as solvent, still permitted intramolecular H-bonding favouring formation of isomer (1S, 1'R) - **6** over the other (entry 2, Table 2). In methanol , **6** and **7** were formed directly in the reaction mixture. But the

Table 2. Diastereoselective Strecker synthesis with p-tolualdehyde and various chiral auxiliaries

Entry	Chiral Auxiliary	Solvent	Product	Diastereoselectivity (1S,1'R):(1R,1'R)
1.	R(-)-2-Phenylglycinol	$CHCl_3$	**6b&7b**	85:15
2.	"	CH_3OH	"	78:22
3.	"	THF	"	57:43
4.	"	THF-$MgCl_2$ (anhyd)[a]	"	79:21
5.	R(-)-2-Phenylglycinol O-methyl ether	$CHCl_3$	**15**	75:25
6.	"	CH_3OH	"	66:34
7.	S(-)-Phenylalaninol	$CHCl_3$	**16**	58:42[b]
8.	"	CH_3OH	"	55:45[b]

[a]$MgCl_2$ (anhyd) was added to the imine 15 minutes before the addition of TMSCN; [b]Major diastereomer was assumed to be (1R,1'S) in analogy with phenylglycinol, but not proven. Reaction was very slow and did not go to completion even after 24 h.



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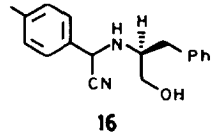

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best result was obtained in $CHCl_3$ (dielectric constant 4.8) known to be highly favourable for intramolecular H-bonding[10] (entry 1, Table 2). With R(-)-2-phenylglycinol O-methyl ether (entries 5 and 6, Table 2), loss of intramolecular H-bonding reduced the selectivity though the increased steric bulk, still, favoured conformer **C**. As expected with S(-)-phenylalaninol (entries 7 and 8, Table 2), having no significant steric or electronic factor to decide in favour of any particular transition state conformation, diastereoselectivity was completely lost. The nature of aldehyde also decides diastereoselectivity as evident with low selectivity observed with phenylacetaldehyde (entry 4, Table 1). Though the exact role of R in diastereoselection is not yet clearly understood, from our observed results (Table 1) it can be concluded that a bulkier R gives better selectivity.

Finally, a detailed theoretical study was carried out to support the above hypothesis put forward by us to explain our results. Simple molecular mechanics energy minimization in vacuo with concomitant charge iteration of the two conformers **C** and **D** showed that conformer **C** is more stable than conformer **D** by ~ 2.46 kcal/mol. Most of the difference comes from the angle strain and there was no significant extra stabilization in **C** due to intramolecular H-bonding. Though disappointing it did not come as a surprise, because molecular mechanics is not adequately equipped to take into account small ring H-bonds. Also, gas phase energy minimization does not represent the true picture about what happens in solution. Although a difference of ~ 2.5 kcal/mol should have led to exclusive diastereoselectivity, the inadequacy of molecular mechanics parameters has to be taken into consideration before drawing any conclusion. Also one has to remember the formation of ~10% oxazolidines **8** and **9**, as described above, which are also opened up with TMSCN giving mixture of isomers and, thus, effecting

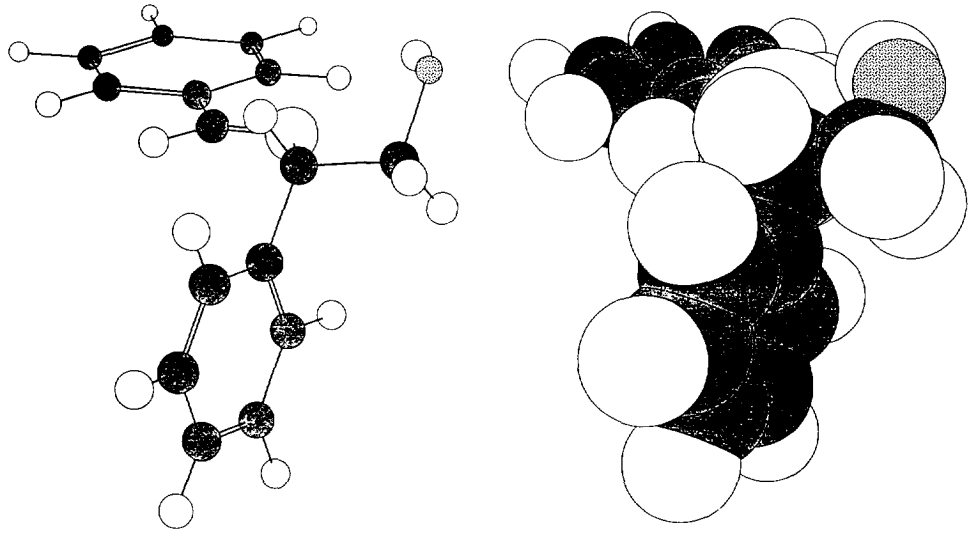

Figure 1. Lowest energy conformation of (S)-**3a** (left: ball and stick; right: CPK representation), obtained by using MacroModel and BatchMin molecular modeling programs (version 3.1 X).

the overall diastereoselectivity. More rigorous minimization was carried out using MacroModel and BatchMin molecular modeling programs[11] (version 3.1x) on Silicon Graphics Iris 4D workstation. Imine from benzaldehyde (**1a**) and (S)- α -phenylglycinol was subjected to batch minimization with the AMBER forcefield and PRCG minimization method using $CHCl_3$ as the solvent. The energy minimized structure was then subjected to Monte Carlo-style conformational search. The lowest energy, conformation emerged from that search is shown in Figure-1. It shows clearly that nucleophilic attak can take place only from the top. The N . . . H distance in this minimized structure is 2.34 A°; O....H is 0.95 A° and N....O, 2.82 A°. The N...H—O angle is 110.88 degree. But, still, it did not show any intramolecular H-bonding though the N...H—O angle and N...H distance were favourable for such H-bond. We are sure from our experimental results that conformer **C** is further stabilized through intramolecular H-bonding. The forcefield in that particular version of MacroModel used was not parameterized well to account for such H-bonds. Recently AMBER force field was modified and the new version, called AMBER* is now better equipped for modeling small ring intramolecular H-bonds like Gellman amides[12]. We are yet to try this modified force field to support our experimental findings. Anyway, all our calculations indicated beyond doubt that the lowest energy conformer has hydroxymethylene group away from the imine moiety as in **C** and antiperiplanar nucleophilic attack from the less hindered side then leads to the major isomer.

In conclusion, a highly efficient method for the synthesis of chiral α - amino acids in optically pure form is described and theoretical calculations are put forward in support of the excellent diastereoselectivity achieved.

Experimental Section

General Procedures. NMR spectra were recorded on Varian Gemini 200 and Varian Unity 400 instruments. IR spectra were recorded on Shimadzu IR-470. MS were recorded on a Finnigan Mat 1210 spectrometer under electron impact (EI) or chemical ionization (CI) conditions. Elemental analyses were performed at University of Hyderabad and IDPL, Hyderabad. Optical rotations were measured on a JASCO DIP-360 instrument.

All reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E.Merck silica gel plates (60F-254) with UV light, I_2, and 7% ethanolic phosphomohybdic acid-heat as developing agents. Acme, India, silica gel (finer than 200 mesh) was used for flash column chromatography.

All reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

General Procedure for the Preparation of 6 and 7:

To a solution of aldehyde **1** (10 mmol) in dry chloroform (100 mL) was added R-phenylglycinol (**2**) (1.37 g, 10 mmol) under nitrogen atmosphere and stirred for 1 h at room temperature. After 1 h the reaction mixture was cooled to 0°C, TMSCN (1.98 g, 20 mmol) was added and stirred for 6 h at room temperature. To the reaction mixture was added 3N HCl (50 mL), extracted with $CHCl_3$, dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 5-50% EtOAc in pet ether) of the residue afforded **6** (72-81%) and **7** (9-18%) (see Table 1) as colourless liquids.

N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-α-aminobenzeneacetonitrile (6a):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.58-7.35 (m, 10H, 2 Ph), 4.51 (bs, 1H, C<u>H</u>CN), 4.29 (dd, J=9.2, 4.0 Hz, 1H, C<u>H</u>-CH_2OH), 3.92-3.55 (m, 2H, C<u>H_2</u>OH), 2.55 (bs, 1H, N<u>H</u>), 1.95 (bs, 1H, O<u>H</u>). IR (Neat): ν_{max} 3550, 3455, 3000, 2240, 1580, 1285, 1140, 740, 690 cm^{-1}. MS(EI): m/e 252 (M^+), 221 (M^+-CH_2OH). Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.11. Found: C, 76.13; H, 6.37; N, 11.14.

N-[(R)-2-Hydroxy-1-phenylethyl]-(R)-α-aminobenzeneacetonitrile (7a):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.55-7.32 (m, 10H, 2 Ph), 4.72 (bs, 1H, C<u>H</u>CN), 3.91 (dd, J=8.2, 4.4 Hz, 1H, C<u>H</u>-CH_2OH), 3.80-3.60 (m, 2H, C<u>H_2</u>OH), 2.40 (bs, 1H, N<u>H</u>), 2.05 (bs, 1H, O<u>H</u>). IR (Neat): ν_{max} 3550, 3455, 3000, 2240, 1580, 1285, 1140, 745, 695 cm^{-1}. MS(EI): m/e 252 (M^+), 221 (M^+-CH_2OH). Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.11. Found: C, 76.12; H, 6.36; N, 11.13.

N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-α-amino-4-methylbenzeneacetonitrile (6b):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.50-7.25 (m, 7H, Ph, C2-H and C6-H), 7.19 (d, J=8.1 Hz, 2H, C3-H and C5-H), 4.46 (s, 1H, C<u>H</u>CN), 4.22 (dd, J=9.8, 3.8 Hz, 1H, C<u>H</u>-CH_2OH), 3.76-3.50 (m, 2H, C<u>H_2</u>OH), 2.61 (s, 1H, N<u>H</u>), 2.34 (s, 3H, C<u>H_3</u>). IR (Neat): ν_{max} 3550, 3455, 3020, 2930, 1580, 1285, 1140, 830 cm^{-1}. MS(EI): m/e 266 (M^+), 235 (M^+-CH_2OH). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.60; H, 6.79; N, 10.50.

N-[(R)-2-Hydroxy-1-phenylethyl]-(R)-α-amino-4-methylbenzeneacetonitrile (7b):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.50-7.30 (m, 7H, Ph, C2-H and C6-H), 7.19 (d, J=8.1 Hz, 2H, C3-H and C5-H), 4.64 (s, 1H, C<u>H</u>CN), 4.09 (dd, J=8.6, 4.0 Hz, 1H, C<u>H</u>-CH_2OH), 3.76-3.50 (m, 2H, C<u>H_2</u>OH), 2.61 (s, 1H, N<u>H</u>), 2.40 (s, 3H, C<u>H_3</u>). IR (Neat): ν_{max} 3550, 3455, 3020, 2930, 1580, 1285, 1140, 830 cm^{-1}. MS(EI): m/e 266 (M^+), 235 (M^+-CH_2OH). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.62; H, 6.78; N, 10.52.

N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-α-amino-4-methoxybenzeneacetonitrile (6c):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.56-7.30 (m, 7H, Ph, C2-H and C6-H), 6.95 (d, J=7.8 Hz, 2H, C3-H and C5-H), 4.46 (s, 1H, C<u>H</u>CN), 4.35 (dd, J=8.2, 3.8 Hz, 1H, C<u>H</u>-CH_2OH), 3.83 (s, 3H, O<u>CH_3</u>), 3.78-3.60 (m, 2H, C<u>H_2</u>OH), 1.95 (bs, 2H, N<u>H</u> and O<u>H</u>). IR (Neat): ν_{max} 3500, 3450, 3010, 2940, 2245, 1580, 1280, 1205, 1140, 830 cm^{-1}. MS(EI): m/e 282 (M^+). Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.30; H, 6.41; N, 9.90.

N-[(R)-2-Hydroxy-1-phenylethyl]-(R)-α-amino-4-methoxybenzeneacetonitrile (7c):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.56-7.30 (m, 7H, Ph, C2-H and C6-H), 6.95 (d, J=7.8 Hz, 2H, C3-H and C5-H), 4.64 (s, 1H, C<u>H</u>CN), 4.05 (dd, J=8.6, 4.0 Hz, 1H, C<u>H</u>-CH_2OH), 3.85 (s, 3H, O<u>CH_3</u>), 3.78-3.60 (m, 2H, C<u>H_2</u>OH), 1.95 (bs, 2H, N<u>H</u> and O<u>H</u>). IR (Neat): ν_{max} 3500, 3450, 3010, 2940, 1580, 1280, 1205, 1140, 830 cm^{-1}. MS(EI): m/e 282 (M^+). Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.33; H, 6.40; N, 9.95.

N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-α-aminobenzenepropanenitrile (6d):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45-7.20 (m, 10H, 2Ph), 4.09 (dd, J=8.3, 4.0 Hz, 1H, C<u>H</u>-CH_2OH), 3.80-3.45

(m, 3H, C<u>H</u>$_2$-OH and C<u>H</u>CN), 3.05 (d, J=6.0 Hz, 2H, Ph-C<u>H</u>$_2$), 2.08 (bs, 2H, N<u>H</u> and O<u>H</u>). IR (Neat): ν_{max} 3550, 3455, 3000, 2960, 2240 1580, 1285, 1140, 740, 690 cm^{-1}. MS(EI): m/e 266 (M$^+$). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.60; H, 6.83; N, 10.50.

N-[(R)-2-Hydroxy-1-phenylethyl]-(R)-α-aminobenzenepropanenitrile (7d):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45-7.20 (m, 10H, 2Ph), 4.00 (dd, J=8.0, 3.8 Hz, 1H, C<u>H</u>-CH$_2$OH), 3.70-3.45 (m, 3H, C<u>H</u>$_2$-OH and C<u>H</u>CN), 2.90 (d, J=4.8 Hz, 2H, Ph-C<u>H</u>$_2$), 2.00 (bs, 2H, N<u>H</u> and O<u>H</u>). IR (Neat): ν_{max} 3550, 3455, 3010, 2960, 2440 1580, 1285, 1140, 740, 690 cm^{-1}. MS(EI): m/e 266 (M$^+$). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.62; H, 6.78; N, 10.54.

N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-2-amino-3-methylbutanenitrile (6e):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40 (m, 5H, Ph), 4.10 (dd, J=9.3, 4.0 Hz, 1H, C<u>H</u>-CH$_2$OH), 3.80 (dd, J=10.9, 4.0 Hz, 1H, C<u>H</u>$_2$-OH) 3.58 (dd, J=10.5, 9.3 Hz, 1H, C<u>H</u>$_2$-OH) 3.10 (d, J=6.2 Hz, 1H, C<u>H</u>CN), 2.18 (bs, 2H, N<u>H</u> and O<u>H</u>), 1.98 (m, 1H, CH$_3$-C<u>H</u>-CH$_3$), 1.08 & 1.06 (two d, J=6.5 Hz, 6H, C<u>H</u>$_3$). IR (Neat): ν_{max} 3550, 3350, 3020, 2940, 2860, 2240, 1580, 1280, 745, 690 cm^{-1}. MS(EI): m/e 218 (M$^+$). Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.45; H, 8.28; N, 12.80.

N-[(R)-2-Hydroxy-1-phenylethyl]-(R)-2-amino-3-methylbutanenitrile (7e):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.50-7.35 (m, 5H, Ph), 3.98 (dd, J=7.2, 3.9 Hz, 1H, C<u>H</u>-CH$_2$OH), 3.82-3.64 (m, 2H, C<u>H</u>$_2$-OH) 3.50 (d, J=4.4 Hz, C<u>H</u>CN), 2.00 (m, 1H, CH$_3$-C<u>H</u>-CH$_3$), 1.82 (bs, 2H, N<u>H</u> and O<u>H</u>), 1.10 & 1.08 (two d, J=6.5 Hz, 6H, C<u>H</u>$_3$). IR (Neat): ν_{max} 3550, 3350, 3020, 2940, 2860, 2240, 1580, 1280, 745, 690 cm^{-1}. MS(EI): m/e 218 (M$^+$). Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83 Found: C, 71.48; H, 8.33; N, 12.82.

N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-2-amino-3,3-dimethylbutanenitrile (6f):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35 (s, 5H, Ph), 4.05 (dd, J=8.3, 4.0 Hz, C<u>H</u>-CH$_2$OH), 3.70-3.41 (m, 2H, C<u>H</u>$_2$-OH) 2.95 (s, 1H, C<u>H</u>CN), 2.31 (bs, 1H, N<u>H</u>), 2.00 (bs, 1H, -O<u>H</u>), 1.10 (s, 9H, -(C<u>H</u>$_3$)$_3$). IR (Neat): ν_{max} 3550, 3350, 3020, 2940, 2860, 2245, 1580, 1280, 745, 690 cm^{-1}. MS(EI): m/e 232 (M$^+$). Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.37; H, 8.68; N, 12.06 Found: C,72.30; H, 8.65; N, 12.04.

N-[(R)-2-Hydroxy-1-phenylethyl]-(R)-2-amino-3,3-dimethylbutanenitrile (7f):

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30 (s, 5H, Ph), 3.95 (dd, J=7.6, 4.0 Hz, C<u>H</u>-CH$_2$OH), 3.70-3.48 (m, 2H, C<u>H</u>$_2$-OH) 3.42 (s, 1H, C<u>H</u>CN), 2.31 (bs, 1H, N<u>H</u>), 2.02 (bs, 1H, -O<u>H</u>), 1.09 (s, 9H, -(C<u>H</u>$_3$)$_3$). IR (Neat): ν_{max} 3550, 3350, 3020, 2940, 2860, 2245, 1580, 1280, 745, 690 cm^{-1}. MS(EI): m/e 232 (M$^+$). Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.37; H, 8.68; N, 12.06 Found: C,72.34; H, 8.66; N, 12.02.

α-Aminobenzeneacetic acid (12a) and 2-aminobutanoic acid (12e):

Lead tetraacetate (5.30 g, 12 mmol) was added to a solution of **6** (10 mmol) in methylenechloride:methanol

(2:1, 100 mL) at 0°C and the reaction mixture was stirred for 5 min at the same temperature. To this reaction mixture was added phosphate buffer (0.2 M, 100 mL, pH 7) and stirred for 0.5 h at room temperature. The reaction mixture was then filtered through celite and the organic layer was separated. The aqueous layer was extracted with methylene chloride (2x100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford the crude imine **11**. To the imine was added conc. HCl and refluxed for 3-5 h. The reaction mixture was cooled and washed with ether to remove benzaldehyde. The aqueous layer was concentrated in vacuo to afford crude amino hydrochloride salt of **12**. The crude amino hydrochloride was purified by passing through a small pad of Dowex H^+ with aqueous NH_3 (10%) which yielded amino acid (**12**). ^1H NMR of **12a** (D_2O, 200 MHz): δ 7.40-7.25 (m, 5H, Ph), 5.12 (s, 1H, C<u>H</u>). IR (Nujol):ν_{max} 3550-3320, 1710 cm^{-1}.^1H NMR of **12e** (D_2O, 200 MHz): δ 3.00 (d, J=8.0 Hz, 1H, C<u>H</u>N), 1.95 (m, 1H, CH_3-C<u>H</u>), 0.92 and 0.90 (two d, J=6.0 Hz, 6H, C<u>H</u>$_3$). IR (Nujol):ν_{max} 3600-3460, 3350, 1710 cm^{-1}.

N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-2-aminobenzeneacetic acid methyl ester (13a) and N-[(R)-2-Hydroxy-1-phenylethyl]-(S)-2-amino-3-methylbutanoicacid methyl ester (13e):

To a solution of **6** (5 mmol) in methanol (50 mL) was added dry ethereal HCl (25 mL) and stirred for 5 h at room temperature under nitrogen atmosphere. Methanol was removed in vacuo and the residue was neutralized with phosphate buffer (pH 7), extracted with chloroform (2x60 mL). The organic layer was washed with water (50 mL) and saturated aqueous NaCl (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2) afforded **13** (70%) as colourless liquid.

^1H NMR of **13a** ($CDCl_3$, 200 MHz): δ 7.40 (s, 5H, Ph), 7.38 (s, 5H, Ph), 4.31 (s, 1H, C<u>H</u>-CO_2Me), 3.82 (dd, J=8.3, 4.0 Hz, 1H, C<u>H</u>-CH_2OH), 3.75-3.67 (m, 2H, C<u>H</u>$_2$-OH) 3.62 (s, 3H, OC<u>H</u>$_3$), 2.70 (bs, 2H, N<u>H</u> and O<u>H</u>). IR (Neat): ν_{max} 3550, 3400, 3020, 2940, 1725, 1580, 1280, 1190, 740, 695 cm^{-1}. MS(EI): m/e 285 (M^+). Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91 Found: C,71.51; H, 6.70; N, 4.89.

^1H NMR of **13e** ($CDCl_3$, 200 MHz): δ 7.35 (bs, 5H, Ph), 3.75 (s, 3H, OC<u>H</u>$_3$), 3.74-3.50 (m, 3H, C<u>H</u>-CH_2-OH), 2.90 (d, J=6.2 Hz, 1H, C<u>H</u>-CO_2Me), 2.25 (bs, 2H, N<u>H</u> and O<u>H</u>), 1.92 (m, 1H, CH_3-C<u>H</u>-CH_3), 0.92 and 0.94 (two d, J=7.0 Hz, 6H, C<u>H</u>$_3$). IR (Neat): ν_{max} 3545, 3400, 3010, 2980, 2860 1730, 1585, 1280, 1195, 745, 690 cm^{-1}. MS(EI): m/e 251 (M^+).

α-Aminobenzeneacetic acid methyl ester (14a) and 2-amino-3-methylbutanoicacid methyl ester (14e):

Lead tetraacetate (2.66 g, 6 mmol) was added to a solution of **13** (5 mmol) in methylene chloride: methanol (2:1, 50 mL) at 0°C and the reaction mixture was stirred at the same temperature for 5 min. To the reaction mixture was added phosphate buffer (0.2M, 50 mL, pH 7) and stirred for 0.5 h at room temperature. The reaction mixture was then filtered through celite and the organic layer was separated. The aqueous layer was extracted with methylene chloride (2x50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford the crude imine which was dissolved in ether (25 mL) and treated with 3N HCl (25 mL). The reaction mixture was stirred for 15 min at room temperature. The aqueous layer was separated and washed with ether (2x25 mL) to remove organic impurities. Water was removed in vacuo to give a solid which

was neutralized with phosphate buffer (0.2M, pH 7) and extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated in vacuo to afford **14** (70%) as a syrupy liquid.

^{1}H NMR of **14a** ($CDCl_3$, 200 MHz): δ 7.42-7.38 (m, 5H, Ph), 4.62 (s, 1H, C<u>H</u>), 3.73 (s, 3H, C<u>H</u>$_3$), 1.95 (bs, 2H, N<u>H</u>$_2$). IR ($CHCl_3$): ν_{max} 3490, 3020, 1725, 1580, 1190, 740, 690 cm^{-1}. MS(EI): m/e 165 (M^+). Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48 Found: C, 65.38; H, 6.69; N, 8.50.

^{1}H NMR of **14e** ($CDCl_3$, 200 MHz): δ 3.75 (s, 3H, C<u>H</u>$_3$), 3.31 (d, J=6.2 Hz, 1H, C<u>H</u>CO$_2$Me), 2.10 (bs, 2H, N<u>H</u>$_2$), 1.95 (heptet J=6.2 Hz, 1H, CH_3-C<u>H</u>-CH_3), 0.98 and 1.00 (two d, J=6.2 Hz, 6H, C<u>H</u>$_3$).IR (Neat): ν_{max} 3470, 2920, 2860, 1730, 1190 cm^{-1}. MS(EI): m/e131 (M^+). Anal. Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68 Found: C, 55.00; H, 10.02; N, 10.71.

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