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Intercalator Amino Acids : Synthesis of Heteroaryl Alanines

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Abstract: Stereoselective alkylation of (*S*)-(-)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolinone with 2-chloromethylquinoline, 2-chloromethylquinoxaline and 5-chloromethyl-1,10-phenanthroline, followed by hydrolysis, afforded the corresponding (*S*)-(+)-α-amino acids with high enantiomeric excess.

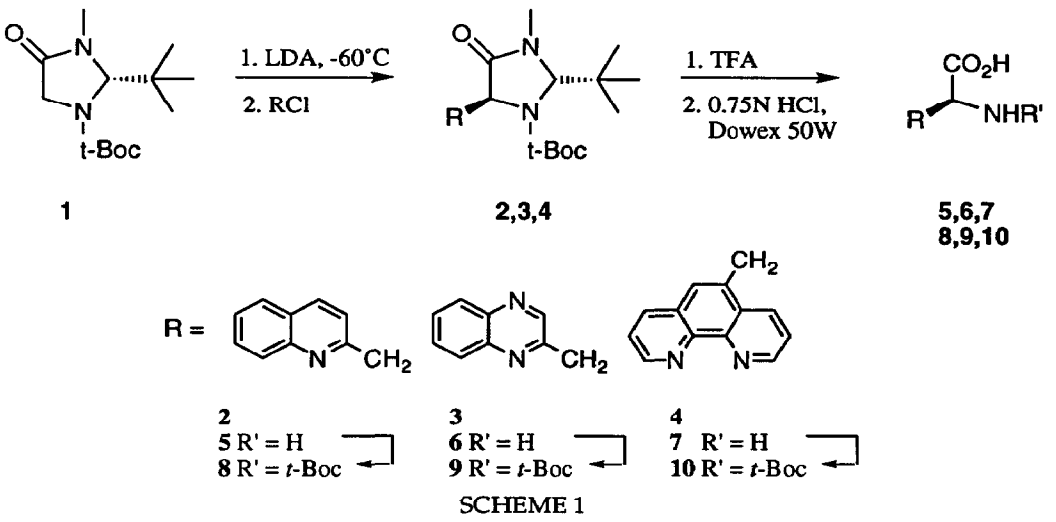
INTRODUCTION:

The importance of intercalation in protein-DNA and drug-DNA interactions is well-established.[1] Due to the high binding constant of intercalative binding, intercalators have been used effectively to target other DNA functionality, particularly groove binders, to DNA.[2] We have been interested in the design and synthesis of short structured peptides to study DNA recognition at the molecular level, and have reported the solution conformations of peptides based on both α-helices[3] and DNA-bisintercalators.[4] In order to increase the binding affinity of short peptides for DNA, and to complement the specificity conferred by natural amino acid sidechains, we required amino acids containing intercalator sidechains. In previous work in this area, intercalators were introduced *via* alkylation of a cysteine residue.[3] However, this method was not general, with experimental conditions being strongly dependent on the amino acid sequence, and some cysteine-containing sequences were unable to be alkylated without significant degradation of the peptides.

We report here the synthesis of three new amino acids, which contain intercalator sidechains, for incorporation into a 8-residue sequence[4] using *t*-Boc solid phase chemistry. The quinolyl and quinoxalyl sidechains were based on the naturally occurring antitumor antibiotics which interact with DNA by bisintercalation,[1a] while phenanthroline has been widely used as a DNA intercalator and cleaving agent in the presence of copper(I).[5] The phenanthrolyl-substituted amino acid also provides a new amino acid with strong metal chelation properties, which like the recently reported (*S*)-(-)-3-amino-(6'-(2',2"-bipyridine))propanoic acid, has potential to be incorporated into *de novo* metalloprotein design.[6]

RESULTS AND DISCUSSION:

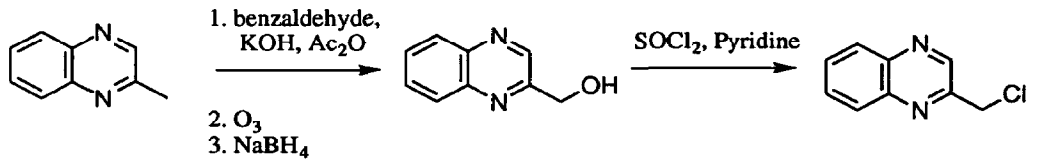
The synthesis of the required amino acids followed the route shown in Scheme 1 starting from commercially available (*S*)-(-)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolininone **1**. The preparation and stereoselective alkylation of **1** has been reported by Seebach *et al.*[7] but alkylation with heterocyclic derived allyl halides has not been reported.



SCHEME 1

Synthesis of Halomethyl Intercalators. The synthetic route (Scheme 1) required the synthesis of appropriately functionalized derivatives of quinoline, quinoxaline and 1,10-phenanthroline.

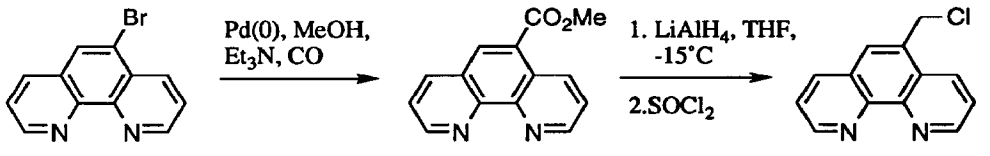
2-Chloromethylquinoline **11** is commercially available as the hydrochloride salt and was converted into the free base in 91% yield by reaction with aqueous sodium bicarbonate. 2-Methylquinoxaline **12** is commercially available and was converted into the 2-chloromethyl derivative as shown in Scheme 2. Thus, condensation of **12** with benzaldehyde gave the 2-styrylquinoxaline **13** in 60% yield.[8] Ozonolysis of the olefin in methanol at -78°C followed by reduction of the crude reaction mixture with sodium borohydride at 0°C gave 2-hydroxymethylquinoxaline **14** in 77% yield. Reaction of the alcohol **14** with thionyl chloride in the presence of two equivalents of pyridine gave 2-chloromethylquinoxaline **15** in 67% yield. In the absence of pyridine the reaction goes to only partial completion.



SCHEME 2

While functionalisation of the 2-position of 1,10-phenanthroline is readily achieved, there are few reports of successful chemistry carried out at the 5-position. The synthesis of 5-chloromethyl-1,10-phenathroline **18** from readily available 5-bromo-1,10-phenathroline[9] **16** was achieved via a palladium catalysed carbonyl insertion reaction[10] (Scheme 3). Treatment of **16** with carbon monoxide in the presence of *bis*-(triphenylphosphine)palladium(II) chloride,

triethylamine and methanol afforded the methyl ester **17** in 66% yield. The methyl ester **17** was reduced to 5-hydroxymethyl-1,10-phenanthroline with lithium aluminium hydride in THF at -15°C. The hydroxymethyl compound proved unstable and attempts to purify it by chromatography reduced the yields considerably. Instead the crude 5-hydroxymethyl-1,10-phenanthroline was treated directly with thionyl chloride to give, after chromatography, 5-chloromethyl-1,10-phenanthroline **18** in a yield of 57% for the two-step process.

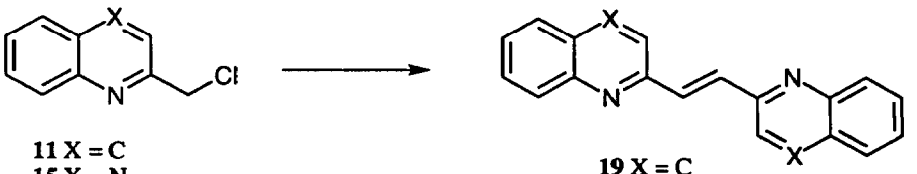


16 **17** **18**

SCHEME 3

Synthesis of Amino Acids. 2-Chloromethylquinoline **11** was treated with the anion of (*S*)-(-)-*t*-Boc-imidazolidinone **1** on a multigram scale to give (2*S*,5*S*)-(+)-5-(2'-quinolylmethyl)-2-*t*-butyl-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone **2** in 82% yield, $[\alpha]_D^{22}$ +84 (*c* 1, CH_2Cl_2), after a single recrystallisation. In a similar manner (2*S*,5*S*)-(+)-5-(2'-quinoxalylmethyl)-2-*t*-butyl-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone **3** and (2*S*,5*S*)-(-)-5-(5'-1',10'-phenanthrolylmethyl)-2-*t*-butyl-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone **4** were prepared in 39%, $[\alpha]_D^{22}$ +72 (*c* 1, CH_2Cl_2) and 70%, $[\alpha]_D^{22}$ -16 (*c* 1, CH_2Cl_2) yields respectively after single recrystallisations. In all cases the ^1H NMR spectra of the crude products were too complex to assign, but after chromatography and a single recrystallisation there was no evidence in the ^1H NMR (400 MHz) of diastereomeric impurity. The stereochemistry of the newly formed stereogenic centre at C5 is assigned as (*S*) on the basis of considerable precedent which has demonstrated that electrophiles add *anti* to the C2 sterically bulky group of lithium enolates of 2-substituted 1-*t*-butyloxycarbonyl-3-methyl-4-imidazolininones and analogous heterocycles.[11]

In the preparation of (2*S*,5*S*)-(+)-**2** and (2*S*,5*S*)-(+)**3** a by-product arose from self coupling of the alkylating agents **11** and **15**. These can be attributed to deprotonation of the heteroaryl halide (Scheme 4), then nucleophilic attack on a second molecule followed by elimination of HCl under the action of a second equivalent of base. In the case of 5-chloromethyl-1,10-phenanthroline **18** the excess aryl halide is recovered unchanged, presumably due to the 5-methyl protons being less acidic.

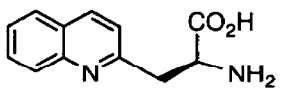
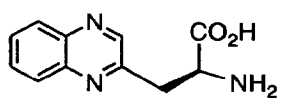
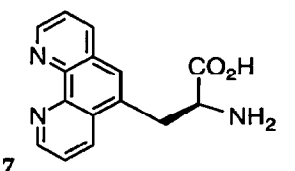


11 X = C
15 X = N

19 X = C
20 X = N

SCHEME 4

The amino acids (*S*)-(+)-**5**, (*S*)-(+)-**6**, and (*S*)-(+)-**7** were released from the imidazolidinone precursors (2*S*,5*S*)-(+)-**2**, (2*S*,5*S*)-(+)**3** and (2*S*,5*S*)-(-)-**4** (table) according to the methodology of Seebach *et al.*[7] Thus, after preliminary removal of the *t*-Boc group with trifluoroacetic acid, the crude products were stirred with Dowex 50Wx8 resin in 0.75 N hydrochloric acid at 100°C for 18-20 hours. With the exception of the (*S*)-(+)-quinolylalanine **5**, the crude amino acids eluted with aqueous ammonia from the Dowex 50W column required further chromatography to give a pure product.

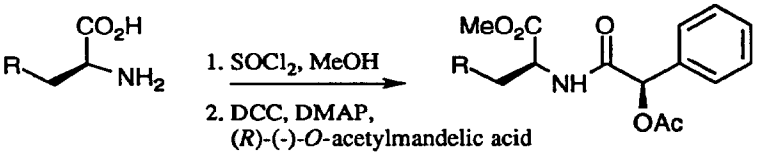
Heteroaryl alanine	Yield, $[\alpha]_D^{22}$	Enantiomeric excess[a]
 **5**	70% +40 (*c* 1, 1.0N HCl)	98%
 **6**	46% +14 (*c* 0.5, 0.1N NH_3)	98%
 **7**	43% +13 (*c* 0.5, 1.0N HCl)	98%

[a] Determined by ^1H NMR (400 MHz) of (*R*)-(-)-*O*-acetylmandelic acid derivatives of the amino acid methyl esters.

The ultimate aim of the syntheses of these unnatural amino acids was their incorporation into short peptides by a suitable solid phase synthetic technique. Toward this end, each of the homochiral amino acids (*S*)-(+)-**5**, (*S*)-(+)-**6**, and (*S*)-(+)-**7** were protected as the *t*-Boc derivatives. This was most conveniently carried out according to the procedure of Ponnusamy *et al.*[12] whereby di-*t*-butyl pyrocarbonate was added to a suspension of the amino acid in methanol and triethylamine. The *t*-Boc protected amino acids (*S*)-(-)-**8**, $[\alpha]_D^{22}$ - 21 (*c* 1, MeOH); (*S*)-(-)-**9**, $[\alpha]_D^{22}$ -27 (*c* 0.5, MeOH) and (*S*)-(-)-**10**, $[\alpha]_D^{22}$ +3.5 (*c* 1, MeOH) were isolated as crystalline materials in moderate to good yields after purification by chromatography.

Measurement of Optical Purity. Samples of the racemic forms of the amino acids (*R*,*S*)-**4**, (*R*,*S*)-**5** and (*R*,*S*)-**6** were prepared from (*R*,*S*)-*t*-Boc-imidazolidinone **1** under similar conditions to those used to prepare the enantiomerically pure amino acids. Diastereomeric derivatives of each amino acid were synthesised by first preparing the amino acid methyl ester which was then coupled with (*R*)-(-)-*O*-acetylmandelic acid using dicyclohexylcarbodiimide and *N*,*N*-dimethylaminopyridine. The ^1H NMR (400 MHz) spectra of each of the (*R*)-(-)-*O*-acetylmandelic amides of the racemic amino acids (2*R*,*S*,2'*R*)-**21**, (2*R*,*S*,2'*R*)-**22** and (2*R*,*S*,2'*R*)-**23** showed distinct

resolution of the *O*-acetyl methyl singlets, for example at δ_H 1.94 and 2.15 ppm for (2*R*,*S*,2'*R*)-**21**. The homochiral amino acids were derivatised in an identical manner and the ^{1}H NMR (400 MHz) spectra clearly showed their high enantiomeric purity where in each case it was the high field signal that was observed.



2 R = quinolyl
3 R = quinoxolyl
4 R = phenanthrolyl

21 R = quinolyl
22 R = quinoxolyl
23 R = phenanthrolyl

In conclusion, the use of Seebach's (*S*)-(-)-imidazolidinone **1** has permitted the synthesis of the required heteroaryl alanines (*S*)-(+)-**2**, (*S*)-(+)-**3** and (*S*)-(+)-**4** with high enantiomeric purity. The *t*-Boc derivatives have been successfully incorporated into peptide sequences by solid phase synthesis. The crystallinity of the imidazolidinone intermediates is perhaps a contributing factor to the high degree of enantiopurity observed in the products. It is also of interest to note that the exposure of the homochiral amino acids to solutions of concentrated aqueous base did not appear to have had a deleterious effect with respect to racemisation.

EXPERIMENTAL:

General Experimental Procedures: Melting points were determined on a Reichert heating stage and are uncorrected. Microanalyses were performed by the Microanalytical unit of the School of Chemistry at the University of New South Wales. Optical rotations were recorded on an Optical Activity polAAr 2001 polarimeter. Infrared spectra (IR) were recorded on a Perkin Elmer 1600 series Fourier transform spectrophotometer. Ultraviolet (UV) spectra were recorded on a Hitachi 150-20 spectrophotometer. ^{1}H NMR spectra are reported as δ ppm relative to TMS and were recorded on an Bruker AC 200F spectrometer at 200 MHz or a Bruker AMX 400 spectrometer at 400 MHz, referenced to residual protio solvent or to sodium 3-(trimethylsilyl)-D_4-propionate when using D_2O. ^{13}C NMR spectra were recorded on a Bruker AC 200F spectrometer at 50.3 MHz and were referenced to residual solvent or to 1,4-dioxane when using D_2O, with relative chemical shifts being reported as δ ppm. Attached protons were determined through DEPT ^{13}C NMR. Electron ionisation mass spectra (MS) and high resolution spectra were determined on a Kratos MS50; chemical ionisation (CI) mass spectra were recorded on a Hewlett Packard 5989A GC/MS with methane as reagent gas. 5-Bromo-1,10-phenanthroline **16**[9] and 2-styrylquinoxaline **13**[8] were prepared according to literature procedures. Chemicals were obtained from Aldrich chemical company. Silica gel refers to Merck Silicagel 60, 40-63 μm. Organic solutions were dried over anhydrous sodium sulfate. All reagents were purified according to Perrin and Armerego[13] and hexane refers to that portion of petroleum ether boiling in the range 67°-70°C.

2-Hydroxymethylquinoxaline (14)- A solution of styrylquinoxaline **13** (5.0 g, 22 mmol) in methanol/dichloromethane (1:1, 250 ml) was cooled to -78°C and sparged with ozone/oxygen gas for 1.5 h. The reaction was purged with gaseous nitrogen and allowed to warm to 0°C, then sodium borohydride (1.9 g, 50 mmol) was added in portions. When the addition was complete the reaction was allowed to warm to room temperature over 2h, then excess sodium borohydride was quenched with 1N citric acid (100 ml) and concentrated *in vacuo*. The aqueous phase was extracted with dichloromethane (2 x 200 ml) then the combined organic fractions were washed with saturated sodium bicarbonate (30 ml) and dried. The organic phase was concentrated *in vacuo* and chromatography of the residue (SiO_2: ethylacetate/ hexanes 1:3 to 1:1) gave 2-hydroxymethylquinoxaline **14** (2.73 g, 17 mmol, 77%) as a white crystalline solid, m.p. 79-81°C from dichloromethane/hexanes (Lit.[14] m.p. 79-81°C): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.83 (s, 1H), 8.09 (m, 2H), 7.77 (m, 2H), 5.02 (d, *J* 5 Hz, CH_2), 3.75 (t, *J* 5 Hz, OH); MS *m/z* 160 ($M^{+\cdot}$, 86%), 131 (100), 103 (78).

2-Chloromethylquinoxaline (15)- Pyridine (3 ml, 37.5 mmol) was added to a solution of thionyl chloride (14 ml, 190 mmol) in benzene (50 ml) at 0°C and the clear solution was stirred for 5 min Quinoxaline **14** (3 g, 18.7 mmol) in benzene (50 ml) was added slowly to the thionyl chloride solution, a white precipitate formed, then the reaction was allowed to warm to room temperature and stirred for 2 h. The mixture was cooled to 0°C and cold saturated sodium bicarbonate (350 ml) and dichloromethane (350 ml) were added with further sodium bicarbonate (77 g, 0.2 mol). The mixture was poured over cracked ice and separated. The aqueous phase was extracted with dichloromethane (200 ml) and the combined organic phases were washed with brine (100 ml) and dried, then concentrated *in vacuo* to give a brown solid. Chromatography of the residiue (SiO_2: dichloromethane) and recrystallisation from hexanes gave 2-chloromethylquinoxaline **15** (2.23 g, 12.5 mmol, 67%) as white needles m.p. 50-52°C (sealed tube) (Lit.[15] 45-46°C): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.00 (s, 1H), 8.08 (m, 2H), 7.77 (m, 2H), 4.85 (s, CH_2Cl); MS *m/z* 178 ($M^{+\cdot}$, 100%), 143 (95).

Methyl 5-(1,10-phenanthrolyl)carboxylate (17)- A solution of 5-bromo-1,10-phenanthroline **16** (3.24 g, 12.5 mmol) and *bis*-(triphenylphosphine)palladium(II) chloride (0.44 g, 0.63 mmol) in triethylamine (3.5 ml, 25 mmol) and methanol (12 ml) was flushed three times and left to stir under 4 atmospheres of carbon monoxide at 100°C for 6 h. The reaction was cooled and the mixture concentrated *in vacuo*. The residue was taken up in dichloromethane (150 ml) and washed with saturated sodium bicarbonate (40 ml). The aqueous phase was extracted with dichloromethane (100 ml), the combined organic phases were washed with brine and dried. The crude product was concentrated *in vacuo* and chromatography of the residue (Al_2O_3 grade I: chloroform/light petrol 1:1) gave methyl 5-(1,10-phenanthrolyl)carboxylate **17** (1.98 g, 8.3 mmol, 66%) as a white solid. An analytically pure sample was obtained by recrystallisation from dichloromethane/hexanes m.p. 146-148°C. (Found: C, 70.9; H, 4.3; N, 11.6. $C_{14}H_{10}N_2O_2$ requires: C, 70.6; H, 4.2; N, 11.8%). IR (KBr) ν_{max} 1712 cm^{-1}; UV (MeOH) λ_{max} 229 (log ε 4.642); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.42 (dd, *J* 8.6, 1.7 Hz, 1H), 9.28 (dd, *J* 4.4, 1.8 Hz, 1H), 9.23 (dd, *J* 4.3, 1.7 Hz, 1H), 8.61 (s, 1H), 8.34 (dd, *J* 8.1, 1.7 Hz, 1H), 7.72 (dd, *J* 8.6, 4.4 Hz, 1H), 7.70 (dd, *J* 7.8, 4.4 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 166.4 (C), 152.3 (CH), 150.2 (CH), 147.5 (C), 146.0 (C),

137.1 (CH), 134.6 (CH), 131.9 (CH), 126.4 (C), 125.3 (C), 123.4 (CH), 52.4 (CH_3); MS *m/z* 238 ($M^{+\cdot}$, 95%), 207 (83), 179 (100).

5-Chloromethyl-1,10-phenanthroline (18)- Methyl 5-(1,10-phenanthrolyl)carboxylate **17** (1.0 g, 4.2 mmol) in THF (25 ml) at -10°C, was added via cannula to a suspension of lithium aluminium hydride (0.2 g, 5.2 mmol) in THF (15 ml) at -15°C over 5 min. The reaction turned a dark claret colour. The reaction was quenched after 5 min by cautious addition of 6N hydrochloric acid (12 ml). The cloudy mixture stirred for 15 min then added dropwise to a mixture of 30% aqueous ammonia (20 ml) and methanol/chloroform (1:10, 200 ml). The organic phase was washed with brine (30 ml) and the combined aqueous phases were extracted with methanol/chloroform (1:10, 200 ml), then the organic phases were dried and concentrated *in vacuo* to give crude 5-hydroxymethyl-1,10-phenanthroline as a yellow-orange oil (Lit.[16] m.p. 205-206°C): IR ν_{max} 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.12 (m, 2H), 8.47 (dd, *J* 8.4, 1.7 Hz, 1H), 8.12 (dd, *J* 8.0, 1.7 Hz, 1H), 7.72 (s, 1H), 7.59 (m, 2H), 5.18 (d, *J* 0.8 Hz, 2H); MS *m/z* 210 ($M^{+\cdot}$, 86%), 193 (14), 181 (100). The crude hydroxymethyl compound was cooled to -10°C then thionyl chloride (7.7 ml, 105 mmol) was added and the solution allowed to warm to room temperature. The mixture was stirred for 30 min then the excess thionyl chloride was removed *in vacuo* (<40°C). The residue was taken up in water (10 ml) and added slowly to a mixture of saturated sodium bicarbonate (30 ml) and methanol/ dichloromethane (1:20, 100 ml) at 5°C. The phases were separated and the aqueous phase extracted with methanol/dichloromethane (1:20, 100 ml). The combined organic phases were washed with brine (30 ml), dried, then concentrated *in vacuo*. The residue was chromatographed (Al_2O_3 grade III: chloroform/ hexanes 1:4 to 2:5) to give 5-chloromethyl-1,10-phenanthroline **18** (0.55 g, 2.4 mmol, 57%) as a pale yellow solid. Recrystallisation from dichloromethane/hexanes gave pale yellow crystals m.p. 181-184°C dec. (Lit.[16] 184.5-185°C): ^1H NMR ($CDCl_3$, 200 MHz) δ 9.23 (dd, *J* 4.4, 1.6 Hz, 1H), 9.20 (dd, *J* 4.4, 1.8 Hz, 1H), 8.56 (dd, *J* 8.4, 1.6 Hz, 1H), 8.23 (dd, *J* 8.1, 1.8 Hz, 1H), 7.86 (s, 1H), 7.72 (dd, *J* 8.3, 4.3 Hz, 1H), 7.65 (dd, *J* 8.1, 4.4 Hz, 1H), 5.08 (s, 2H); MS *m/z* 230 ($M^{+\cdot}$, 26%), 228 (70), 193 (100).

(2*S*,5*S*)-(+)-5-(2'-Quinolylmethyl)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone (2)- A solution of LDA (21 mmol) in THF/hexanes was prepared from n-butyllithium (2.5 M, 8.4 ml, 21 mmol) and diisopropylamine (3.24 ml, 23.1 mmol) in THF (50 ml) at -10°C then cooled to -60°C. The (*S*)-*t*-Boc-imidazolidinone **1** (5.13 g, 20 mmol) in THF (45 ml) was added to the LDA slowly via cannula. The reaction was stirred for 30 min. The 2-chloromethylquinoline **11** (4.44 g, 25 mmol) in THF (45 ml) was added to the mixture over a period of 2 min turning the mixture red. After 1 h at -70°C the mixture warmed slowly to room temperature and stirred overnight. The orange-brown solution was quenched with saturated ammonium chloride (10 ml) and the mixture was concentrated *in vacuo*. The residue was taken up in dichloromethane (250 ml) and washed with 2N citric acid (40 ml), saturated sodium bicarbonate (40 ml) and brine (40 ml) then dried. The solvents were removed *in vacuo* and the residue adsorbed onto silica gel (30 g). Chromatography (SiO_2: hexanes/ethylacetate 4:1) permitted the separation of 1,2-bis(2'-quinolylmethyl)ethylene **19** (0.55 g, 2 mmol, 8%) m.p. 195-197°C: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, *J* 8.5 Hz, 1H), 8.10 (br d, *J* 8.5 Hz, 1H), 7.93 (s, 1H), 7.81 (d, 8.6 Hz, 1H), 7.80 (dd, *J* 8.1, 1.1 Hz, 1H), 7.72 (td, *J* 7.7, 1.4 Hz, 1H), 7.52 (td, *J* 7.5, 1.1 Hz,

1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 155.3 (C), 148.2 (C), 136.4 (CH), 134.5 (CH), 129.8 (CH), 129.3 (CH), 127.5 (CH), 126.5 (CH), 119.4 (CH); MS *m/z* 282 ($M^{+\cdot}$ 74%), 281 (100): from (2*R*,5*R*)-(+)-5-(2'-quinolylmethyl)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone **2** which was further purified by recrystallisation from ethylacetate/hexanes to give **2** (6.56 g, 16.5 mmol, 82%): m.p. 170-171°C. (Found C 70.0, H 8.0, N 10.7; $C_{23}H_{31}N_3O_3$ requires: C 69.5, H 7.9, N 10.6%). $[\alpha]_D^{22}$ +84 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 1702 cm^{-1}; UV (MeOH) λ_{max} 208 (log ε 4.631), 225 (4.527); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (br d, *J* 8.4 Hz, 1H), 7.81 (br d, *J* 8.4 Hz, 1H), 7.69 (br d, *J* 8.1 Hz, 1H), 7.59 (td, *J* 7.6, 1.5 Hz, 1H), 7.42 (td, *J* 7.5, 1.2 Hz, 1H), 7.21 (br d, *J* 8.3 Hz, 1H), 4.9 (m, 1H), 4.37 (m, 1H), 4.17 (m, 1H), 3.67 (dd, *J* 16.3, 2.3 Hz, 1H), 3.08 (s, 3H), 1.06 (br s, 9H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 172.9 (C), 157.3 (C), 153.1 (C), 147.3 (C), 135.3 (CH), 128.9 (CH), 128.7 (CH), 127.1 (CH), 126.3 (C), 125.4 (CH), 121.8 (CH), 81.9 (CH), 80.0 (C), 58.2 (CH), 40.2 (C), 36.3 (CH_2), 32.8 (CH_3), 27.6 (CH_3), 26.2 (CH_3); MS (CI^+, CH_4) *m/z* 398 ($M^{+\cdot}$ +1, 1%), 340 (24), 240 (100), 182 (65).

(2*S*,5*S*)-(+)-5-(2'-Quinoxalylmethyl)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone (3)- The (*S*)-*t*-Boc-imidazolidinone **1** (1.0 g, 3.9 mmol) in THF (9 ml) was added to LDA (4.1 mmol) in THF/hexanes (11:1, 12 ml) at -60°C according to the procedure described above. A solution of 2-chloromethylquinoxaline **15** (0.87 g, 4.9 mmol) in THF (8 ml) at -70°C was added quickly via cannula to the reaction mixture to give a pink-purple then brown solution. After 1 h at -60°C the mixture warmed to room temperature overnight. The reaction was quenched and worked up in the usual way. Chromatography of the residue adsorbed onto silica gel (9 g) (SiO_2: ethyl acetate/hexanes 1:3) separated 1,2-bis(2'-quinoxalylmethyl)ethylene **20** (58 mg, 0.2 mmol, 8%): m.p. 233-234°C; ($CDCl_3$, 400 MHz) δ 9.14 (s, 1H), 8.17 (s, 1H), 8.12 (m, 2H), 7.79 (m, 2H) ; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 149.3 (C), 144.1 (CH), 142.5 (C), 142.1 (C), 132.2 (CH), 130.6 (CH), 129.5 (CH), 129.2 (CH); MS *m/z* 282 ($M^{+\cdot}$ 58%), 283 (100); from (2*S*,5*S*)-(+)-5-(2'-quinoxalylmethyl)-2-*t*-buty1-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone **3** which was recrystalised from hexanes to give **3** (0.6 g, 1.5mmol, 39%) m.p. 148-150°C. (Found C 66.6, H 7.9, N 14.0; $C_{22}H_{30}N_4O_3$ requires: C 66.3, H 7.6, N 14.1%). $[\alpha]_D^{22}$ +72 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 1703 cm^{-1}; UV (MeOH) λ_{max} 202 (log ε 4.358), 236 (4.324); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (s, 1H), 8.00 (m, 1H), 7.83 (m, 1H), 7.66 (m, 2H), 4.80 (m, 1H), 4.44 (d, *J* 7.6 Hz, 1H), 4.25 (m, 1H), 3.69 (d, *J* 15.9 Hz, 1H), 3.09 (s, 3H), 1.05 (br, 9H), 0.97 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 172.4 (C), 152.7 (C), 146.2 (CH), 141.4 (C), 140.7 (C), 129.5 (CH), 128.9 (CH), 128.8 (CH), 81.9 (CH), 80.5 (C), 57.8 (CH), 40.2 (C), 34.1 (CH_2), 32.7 (CH_3), 27.6 (CH_3), 26.2 (CH_3); MS (CI^+ CH_4) *m/z* 399 ($M^{+\cdot}$ +1, 0.5%), 341 (17), 241 (100), 183 (28).

(2*S*,5*S*)-(-)-5-(5'-1',10'-Phenanthrolylmethyl)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone (4)- The (*S*)-*t*-Boc-imidazolidinone **1** (1.69 g, 6.6 mmol) in THF (17 ml) at was added to LDA (6.9 mmol) in THF/hexanes (17:3, 20 ml) at -60°C according to the procedure described above. The 5-chloromethyl-1,10-phenanthroline **18** (1.8 g, 7.9 mmol) in dichloromethane (30 ml) was cooled to -70°C and added via cannula to the reaction mixture over 25 min to turn the mixture orange-brown. After 1 h at -60°C the mixture warmed to room temperature overnight. The reaction contained a yellow precipitate which disappeared upon quenching and was worked up in the usual way. Chromatography of the residue adsorbed onto

alumina (grade III, 40 g), (Al_2O_3 grade III: chloroform/hexanes 1:1) separated 5-chloromethyl-1,10-phenanthroline **18** (0.34 g, 1.5 mmol, 12%) from (2*S*,5*S*)-(-)-5-(5'-1',10'-phenanthrolylmethyl)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone **4** which was further recrystallised from dichloromethane/hexanes to give **4** (2.06 g, 4.6 mmol, 70%) as white needles, m.p. 214-215°C. (Found: C, 60.3; H, 6.5; N, 10.6. $C_{26}H_{32}N_4O_3.CH_2Cl_2$ requires: C, 60.8; H, 6.4; N, 10.5%). $[\alpha]_D^{22}$ -16 (*c* 1, CH_2Cl_2); IR (KBr) ν_{max} 3399 w, 3033 w, 2968 s, 1694 cm^{-1}; UV (MeOH) λ_{max} 231 (logε 4.583), 268 (4.441); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* 4.3, 1.6 Hz, 1H), 9.12 (dd, *J* 4.4, 1.7 Hz, 1H), 8.77 (br d, *J* 8.1 Hz, 1H), 8.12 (dd, *J* 8.0, 1.7 Hz, 1H), 7.67 (dd, *J* 8.4, 4.3 Hz, 1H), 7.58 (dd, *J* 8.0, 4.4 Hz, 1H), 7.54 (br s, 1H), 4.92 (br s, 1H), 4.48 (br d, *J* 6.2 Hz, 1H), 4.05 (dd, *J* 15.3, 2.1 Hz, 1H), 3.82 (dd, *J* 15.3, 6.7 Hz, 1H), 2.91 (s, 3H), 1.57 (s, 9H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 171.7 (C), 152.8 (C), 149.9 (CH), 149.7 (CH), 146.3 (C), 145.6 (C), 135.6 (CH), 132.9 (CH), 131.9 (C), 128.3 (C), 127.9 (C), 126.6 (CH), 123.1 (CH), 122.7 (CH), 81.4 (C), 81.0 (CH), 58.7 (CH), 40.9 (C), 32.0 (CH), 31.1 (CH_3), 28.1 (CH_3), 26.5 (CH_3); MS (CI, CH_4) *m/z* 449 ($M^{+\cdot}$ +H).

(*S*)-(+)-2-Amino-3-(2'-quinolyl)propionic acid (5)- Trifluoroacetic acid (13 ml, 170 mmol) was added slowly to (*S*,*S*)-(+)-quinolylmethyl imidazolidinone **2** (6.62 g, 16.6 mmol) in dichloromethane (42 ml) at 0°C. The reaction was warmed to room temperature overnight. The solvents were removed *in vacuo* and the residue taken up in a mixture of 0.75N HCl (165 ml) and acetic acid (14 ml) then toluene (25 ml) was added. This solution was added to Dowex 50W X8 50/100 mesh (75 ml wet; H^+ form), the flask sealed with a glass stopper and the suspension stirred at 100°C for 20 h. The appearance of the free amino acid was monitored by TLC (SiO_2: dichloromethane/methanol/acetic acid; 70:27:3); ninhydrin gave a red spot. The reaction was cooled and the resin collected in a column. The filtrate was concentrated *in vacuo* and reapplied to the resin. A further portion of resin (15 ml) was necessary to retain all the amino acid on the column. The resin was washed with ethanol (200 ml), water (200 ml) and then the product was eluted with 25% aqueous ammonia. The eluent was concentrated *in vacuo* until a precipitate began to form. The concentrate was refridgerated (4°C) overnight and, after drying *in vacuo* over phosphorous pentoxide, (*S*)-(+)-2-amino-3-(2'-quinolyl)propionic acid **5** (2.67 g, 12.3 mmol, 74%) was recovered as fine, off-white needles m.p. 188-189°C (dec.), 98% ee by ^1H NMR ($CDCl_3$, 400 MHz) of the *O*-acetyl mandelic acid amide **21**. (Found C 66.9, H 5.9, N 12.9; $C_{12}H_{13}N_2O_2$ requires: C 66.6, H 5.6, N 12.9%). $[\alpha]_D^{22}$ + 40 (*c* 1, 1.0N HCl); IR (KBr) ν_{max} 3146 m, 3026 m, 2342 m, 1615 s, 1594 cm^{-1}; UV (H_2O) λ_{max} 204 (logε 4.630), 230 (4.582), 315 (3.636); ^1H NMR (D_2O, 400 MHz) δ 8.32 (d, *J* 8.4 Hz, 1H), 8.17 (br d, *J* 8.3 Hz, 1H), 7.95 (br d, *J* 9.0 Hz, 1H), 7.81 (m, 1H), 7.63 (m, 1H), 7.46 (d, *J* 8.4 Hz, 1H), 4.26 (dd, *J* 8.0, 5.0 Hz, 1H), 3.59 (dd, *J* 15.6, 5.0 Hz, 1H), 3.47 (dd, *J* 15.6, 8.0 Hz, 1H); ^{13}C NMR (D_2O, 50.3 MHz) δ 173.5 (C), 157.1 (C), 146.4 (C), 138.2 (CH), 130.2 (CH), 127.9 (CH), 127.2 (CH), 126.7 (CH), 121.9 (CH), 54.3 (CH), 37.5 (CH_2); MS *m/z* 216 ($M^{+\cdot}$, 32%), 171 (32), 143 (100).

(*S*)-(+)-2-Amino-3-(2'-quinoxalyl)propionic acid (6)- The deprotection of (*S*,*S*)-(+)-quinoxalylmethyl imidazolidinone **3** (2.1 g, 5.3 mmol) was carried out in the usual manner; first overnight with triflouroacetic acid (4.1 ml, 53 mmol), then for 21 h s at 100°C with a mixture of 0.75N HCl (65 ml), acetic acid (4 ml), toluene (10 ml) and Dowex 50W X8 50/100 mesh (24 ml wet; H^+ form). The appearance of the free amino acid was monitored by TLC

(dichloromethane/methanol/acetic acid; 70:27:3); ninhydrin gave a purple spot. The crude product was eluted from the resin with 25% aqueous ammonia; further chromatography (Merck LiChroprep RP-18 25-40 μm: water to water/methanol 19:1) gave after drying *in vacuo* over phosphorous pentoxide, (*S*)-(+)-2-amino-3-(2'-quinoxalyl)propionic acid **6** (0.53 g, 2.4 mmol, 46%) m.p. 202°C (dec.), >98% ee by ^{1}H NMR ($CDCl_3$, 400 MHz) of the *O*-acetyl mandelic acid amide **22**. (Found: C, 58.6; H, 5.5; N, 18.5. $C_{11}H_{11}N_3O_2.(MeOH)_{0.5}$ requires: C, 59.2; H, 5.6; N, 18.0%). $[\alpha]_D^{22}$ +14 (*c* 0.5, 0.1N NH_3); IR (KBr) ν_{max} 3385 s, 3179 s, 2556 s, 2120 w, 1620 s, 1590 cm^{-1}; UV (H_2O) λ_{max} 237 (logε 4.432), 317 (3.833); ^{1}H NMR (D_2O, 400 MHz) δ 8.82 (s, 1H), 8.11 (m, 2H), 7.90 (m, 2H), 4.33 (dd, *J* 7.1, 5.3 Hz, 1H), 3.70 (dd, *J* 16.3, 5.3 Hz, 1H), 3.62 (dd, *J* 16.3, 7.4 Hz, 1H); ^{13}C NMR (D_2O, 50.3 MHz) δ 173.2 (C), 152.5 (C), 145.4 (CH), 140.8 (C), 139.9 (C), 130.9 (CH), 130.4 (CH), 128.0 (CH), 127.7 (CH), 53.4 (CH), 35.0 (CH_2); MS *m/z* 217 ($M^{+\cdot}$ 37%), 200 (23), 172 (72), 144 (100); HRMS *m/z* 217.0838 ($M^{+\cdot}$, $C_{11}H_{11}N_3O_2$ requires 217.0851).

(*S*)-(+)-2-amino-3-(5'-(1',10'-phenanthrolyl))propionic acid (7)- The deprotection of (*S,S*)-(-)-phenanthrolylmethyl imidazolidinone **4** (0.9 g, 2 mmol) was carried out in the usual manner; first overnight with triflouroacetic acid (1.7 ml, 22 mmol), then for 18 h at 100°C with a mixture of 0.75N HCl (20 ml), acetic acid (1 ml), toluene (4 ml) and Dowex 50W X8 50/100 mesh (10 ml wet; H^+ form). The appearance of the free amino acid was monitored by TLC (SiO_2: ethanol/15% aqueous ammonia; 9:1); ninhydrin gave a purple spot. The crude product was eluted from the resin with 30% aqueous ammonia; further chromatography (i. SiO_2: ethanol/15% aqueous ammonia 19:1; ii. Dowex 50W X8 50/100 mesh: 30% aqueous ammmonia) gave after drying *in vacuo* over phosphorous pentoxide, (*S*)-(+)-2-amino-3-(5'-(1',10'-phenanthrolyl))propionic acid **7** (0.23 g, 0.9 mmol, 43%), >98% ee by ^{1}H NMR ($CDCl_3$, 400 MHz) of the *O*-acetylmandelic acid derivative **23**. An analytically pure sample was obtained by recrystallisation from dilute aqueous ammonia, m.p. 235°C (dec.). (Found: C, 59.0; H, 5.9; N, 13.7. $C_{15}H_{13}N_3O_2.(H_2O)_2$ requires: C, 59.4; H, 5.6; N, 13.8%). $[\alpha]_D^{22}$ +13 (*c* 0.5, 1.0N HCl); IR (KBr) ν_{max} 3416 s, 2616 w, 2362 w, 1622 s, 1513 cm^{-1}; UV (H_2O) λ_{max} 230 (logε 4.523), 267 (4.397); ^{1}H NMR (D_2O/DCl pH 3, 200 MHz) δ 9.18 (dd, *J* 4.9, 1.4 Hz, 1H), 9.14 (dd, *J* 5.0, 1.5 Hz, 1H), 8.97 (dd, *J* 8.5, 1.4 Hz, 1H), 8.87 (dd, *J* 8.3, 1.4 Hz, 1H), 8.11 (m, 2H), 8.07 (s, 1H), 4.15 (dd, *J* 8.1, 6.7 Hz, 1H), 3.88 (dd, *J* 14.6, 6.8 Hz, 1H), 3.68 (dd, *J* 14.7, 6.8 Hz, 1H); ^{13}C NMR (D_2O/DCl pH 3, 50.3 MHz) δ 172.8 (C), 147.8 (CH), 146.2 (CH), 141.2 (CH), 138.2 (C), 137.1 (C), 136.5 (CH), 132.6 (C), 128.6 (C), 128.3 (C), 127.7 (C), 125.4 (CH), 54.6 (CH), 33.1 (CH_2); MS m./z 250 ($M^{+\cdot}$ - OH, 0.6%), 194 (100).

(*S*)-(-)-2-*t*-Butyloxycarbonylamino-3-(2'-quinolyl)propionic acid (8)- Addition of di-*t*-butylpyrocarbonate (3.95 ml, 17.2 mmol) to a suspension of (*S*)-(+)-quinolylalanine **5** (1.68 g, 7.8 mmol) in methanol (12 ml) and triethylamine (1.5 ml) induced some effervescence and after heating at 40°C the suspension formed a clear solution which was stirred for 30 min. The reaction was cooled to room temperature and water/acetic acid (95:5, 20 ml) was added, then the mixture was stirred for 20 min before removal of the solvents *in vacuo*. The residue was taken up in methanol and applied to a column of Dowex 1 50/100 mesh (HO^- form, 75 ml wet). The column was washed with methanol then eluted with a gradient of 1% to 10% acetic acid in methanol. The product, (*S*)-(-)-2-*t*-butyloxycarbonylamino-3-(2'-quinolyl)propionic acid **8** (2.14 g, 6.77 mmol, 87%), a white-yellow powder, was dried *in vacuo* over phosphorous pentoxide. An

analytically pure sample of **8** was obtained by recrystallisation from dichloromethane/hexanes m.p. 162°C (dec.). (Found: C, 64.3; H, 6.6; N, 8.6. $C_{17}H_{20}N_2O_4$ requires: C, 64.5; H, 6.4; N, 8.8%). $[\alpha]_D^{22}$ - 21 (*c* 1, MeOH); IR (KBr) ν_{max} 3368 s, 2496 m, 1947 w, 1723 sh, 1696 s, 1530 cm^{-1}; UV (MeOH) λ_{max} 209 (logε 4.319), 229 (4.482), 269 br (3.551), 303 (3.581), 316 (3.672); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.29 (d, *J* 8.5 Hz, 1H), 8.04 (br d, *J* 8.0 Hz, 1H), 7.88 (br d, *J* 8.0 Hz, 1H), 7.80 (m, 1H), 7.62 (m, 1H), 7.50 (d, *J* 8.4 Hz, 1H), 6.04 (d, *J* 4.4 Hz, 1H), 4.61 (m, 1H), 3.61 (dd, *J* 16.5, 2.4 Hz, 1H), 3.45 (dd, *J* 16.5, 9.5 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 173.1 (C), 158.1 (C), 155.3 (C), 144.1 (C), 139.3 (CH), 131.2 (CH), 127.8 (CH), 127.3 (CH), 126.9 (C), 126.0 (CH), 122.4 (CH), 79.8 (C), 52.4 (CH), 39.5 (CH_2), 28.3 (CH_3); MS *m/z* 316 ($M^{+\cdot}$ 1%), 272 (10), 243 (17), 216 (25), 171 (63), 143 (100).

(*S*)-(-)-2-*t*-Butyloxycarbonylamino-3-(2'-quinoxalyl)propionic acid (9)- Preparation of the t-Boc derivative of (*S*)-(+)-quinoxalyl alanine **6** (0.2 g, 0.9 mmol) was carried out in the usual way. The crude product was purified by chromatography (SiO_2: dichloromethane/methanol/acetic acid 95:4.5:0.5) to give (*S*)-(-)-2-*t*-butyloxycarbonylamino-3-(2'-quinoxalyl)propionic acid **9** (136 mg, 0.43 mmol, 48%), a yellow-brown powder. Recrystallisation from methanol gave flakes of **9**, an off-white solid, m.p. 172-173°C. (Found: C, 60.0; H, 6.2; N, 13.0. $C_{16}H_{19}N_3O_4$ requires: C, 60.6; H, 6.0; N, 13.2%). $[\alpha]_D^{22}$ -27 (*c* 0.5, MeOH); IR (KBr) ν_{max} 3359 m, 2578 w, 2508 w, 1733 m, 1681 cm^{-1}; UV (MeOH) λ_{max} 202 (logε 4.387), 236 (4.390), 318 (3.852); ^1H NMR (CD_3OD, 200 MHz) δ 8.85 (s, 1H), 8.10 (m, 2H), 7.85 (m, 2H), 4.77 (dd, *J* 8.8, 5.1 Hz, 1H), 3.64 (dd, *J* 14.3, 5.1 Hz, 1H), 3.42 (dd, *J* 14.3, 9.0 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (CD_3OD, 50.3 MHz), δ 174.8 (C), 157.6 (C), 155.3 (C), 147.3 (CH), 143.2 (C), 142.2 (C), 131.4 (CH), 130.9 (CH), 129.8 (CH), 129.6 (CH), 80.6 (C), 54.3 br (CH), 38.9 (CH_2), 28.5 (CH_3); MS *m/z* 318 ($M^{+\cdot}$ +H 1%), 317 ($M^{+\cdot}$ 1), 261 (11), 172 (35), 144 (78), 57 (100); HRMS *m/z* 261.0751 ($M^{+\cdot}$ +H - *t*-butyl, $C_{12}H_{11}N_3O_4$ requires: 261.0749).

(*S*)-(+)-2-*t*-Butyloxycarbonylamino-3-(5'-(1',10'-phenanthrolyl))propionic acid (10)- Preparation of the t-Boc derivative of (*S*)-(+)-phenanthrolylalanine **7** (0.13 g, 0.5 mmol) was carried out in the usual way. The crude product was purified by ion-exchange chromatograpy (Dowex 1 X 10 50/100 mesh: methanol to methanol/acetic acid 19:1) and then recrystallised from chloroform/hexanes to give (*S*)-(+)-2-*t*-butyloxycarbonylamino-3-(5'-(1',10'-phenanthrolyl))-propionic acid **10** (0.14 g, 0.38 mmol, 77%) as a white powder, m.p. 207-209°C (dec.). (Found: C, 65.1; H, 5.9; N, 11.4. $C_{20}H_{21}N_3O_4$ requires: C, 65.4; H, 5.8; N, 11.4%). $[\alpha]_D^{22}$ +3.5 (*c* 1, MeOH); IR (KBr)ν_{max} 3425 s, 2493 w, 1925 w, 1698 cm^{-1}; UV(MeOH) λ_{max} 230.5 (logε 4.580), 268.5 (4.486); ^1H NMR (CD_3OD, 200 MHz) δ 9.10 (dd, *J* 4.3, 1.3 Hz, 1H), 9.03 (dd, *J* 4.4, 1.6 Hz, 1H), 8.78 (dd, *J* 8.4, 1.3 Hz, 1H), 8.40 (dd, *J* 8.1, 1.6 Hz, 1H), 7.85 (dd, *J* 8.4, 4.3 Hz, 1H), 7.83 (s, 1H), 7.75 (dd, *J* 8.1, 4.4 Hz, 1H), 4.54 (dd, *J* 9.6, 4.9 Hz, 1H), 3.82 (dd, *J* 14.2, 4.7 Hz, 1H), 3.38 (dd, *J* 14.2, 9.6 Hz, 1H), 1.20 (s) and 0.81 (s) (4:1, 9H); ^{13}C NMR (CD_3OD, 50.3 MHz, T = 350K) δ 175.3 (C), 158.7 (C), 150.6 (CH), 146.8 (C), 146.1 (C), 138.2 (C), 137.9 (CH), 134.9 (CH), 130.2 (C), 129.1 (CH), 128.8 (C), 125.3 (CH), 125.0 (CH), 124.8 (C), 81.0 (C), 56.1 (CH), 36.8 (CH_2), 28.8 (CH_3); MS *m/z* 367 ($M^{+\cdot}$ 0.1%), 311 (0.5), 222 (0.7), 194 (11), 56 (24), 41 (100).

Preparation of (*R,S*)-2-amino-3-heteroarylpropionates (5), (6) and (7)- Samples of the racemic arylalanines **5**, **6**, and **7** were prepared in a similar manner to the homochiral analogues but from (2*R,S*)-(±)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone **1**.

Preparation of (2*R*,*S* or 2*S*)-methyl 2-((*R*)-O-acetylmandelicamido)-3-heteroarylpropionates (21), (22) and (23)- Thionyl chloride (50 µl, 0.7 mmol) was added dropwise to the amino acid (60 µmol) in methanol (0.5 ml) at 0°C. The reaction was warmed to room temperature overnight. The solvents were removed *in vacuo* and the residue taken up in *i.* ethyl acetate (3 ml) from **5** or **6**; *ii.* chloroform/methanol (9:1, 3 ml) from **7**. The organic phase was washed with sodium bicarbonate solution (1 ml). The aqueous phase was extracted with further solvent (3.0 ml) and the combined organic phases were washed with brine and dried. Removal of the solvent *in vacuo* gave the amino acid methyl esters which were used without further purification. Dicyclohexylcarbodiimide (14 mg, 66 µmol) in dichloromethane (0.5 ml) was added slowly to a solution of the amino acid methyl ester (50 µmol), (*R*)-(-)-*O*-acetylmandelic acid (12 mg, 60 µmol) and dimethylaminopyridine (2 mg, 16 µmol) in dichloromethane (0.5 ml) at 0°C. The reaction was warmed to room temperature overnight. The urea precipitate was removed by filtration and the residue washed with a small portion of dichloromethane. The filtrate was concentrated *in vacuo* and the residue passed through a short plug of silica (ethyl acetate/hexanes 7:3) for **21** or **22** or alumina (grade III; chloroform/hexanes 1:1) for **23** to remove baseline material. There was no separation of isomers observed in the TLC analysis of the diastereomers prepared from racemic amino acid methyl esters. In a typical ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) the (*R*)-*O*-acetylmandelic amide derivative (2*R*,*S*,2'*R*)-**21** has signals for the *O*-acetyl group that were observed at δ_H 1.94 ppm for (2*S*, 2'*R*)-**21** and δ_H 2.15 ppm (2*R*, 2'*R*)-**21**.

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