Enantioselective synthesis of 2-substituted 4-aminobutanoic acid (GABA) analogues *via* cyanomethylation of chiral enolates

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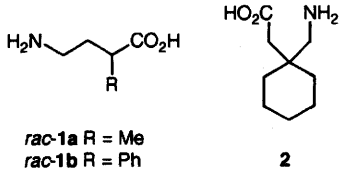
Cyanomethylation by bromoacetonitrile of sodium or lithium enolates derived from (4*S*,5*R*)-3-acyl-4-methyl-5-phenyl-1,3-oxazolidin-2-ones usually shows good stereoselectivity; although the reaction of 3-(3-carboxypropanoyl)oxazolidinone 5d is exceptionally unselective, the 3-(pent-4-enoyl)- and 3-(3,4-dimethoxyhydrocinnamoyl)oxazolidinones 5e and 5f are found to be effective synthetic equivalents of 5d. The cyanomethylation products can be converted into 2-substituted derivatives of 4-aminobutanoic acid (γ-aminobutyric acid, GABA) by the alkaline hydrolysis of the oxazolidinone chiral auxiliary followed by hydrogenation of the cyano group.

Introduction

4-Aminobutanoic acid is an important inhibitory neurotransmitter,[1] many analogues of which have been prepared and subjected to biological evaluation. Recently,[2] the racemic 2-methyl- and 2-phenyl- derivatives *rac*-**1a** and *rac*-**1b** were shown to inhibit binding to synaptic plasma membranes of the rat cerebral cortex by the clinically effective anticonvulsant gabapentin **2**.

We now report a general approach to the enantioselective synthesis of 2-substituted derivatives of 4-aminobutanoic acid *via* the cyanomethylation of enolates from 3-acyloxazolidinones; since the norephedrine-derived chiral auxiliary **3**, originally developed by Evans and co-workers,[3] is available in either enantiomeric form the method is suitable for preparing γ-amino acids of both the (*R*) and the (*S*) series. The alkylation of



rac-**1a** R = Me
rac-**1b** R = Ph

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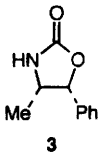

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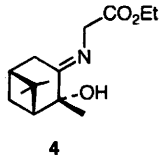

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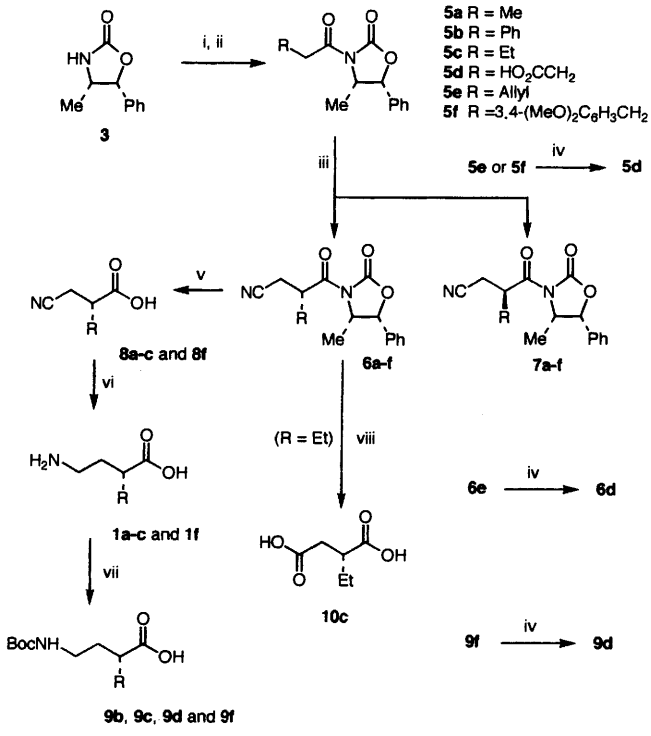
these and related enolates by α-bromo esters has previously been reported to be a means of preparing α-alkylsuccinates stereoselectively;[4] however, we are only aware of one report of asymmetric alkylation by bromoacetonitrile: this is in conjunction with the dianions derived from the glycine imine **4** where, even though the magnesium enolates gave complete stereoselectivity, the diastereoisomeric excesses obtained with lithium enolates did not exceed 33%.[5]

Results and discussion

The 3-acyloxazolidinones **5a–5f** were prepared by acylation of the lithium salt of (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **3** according to the general procedure of Evans (Scheme 1).[6] Compounds **5d–5f** have not previously been described, but all were found to be highly crystalline solids whose preparation presented no difficulty. The succinyl derivative **5d** was prepared by using succinic anhydride as the acylating agent. For **5f** the 3,4-dimethoxyhydrocinnamoyl (hydrocinnamoyl = 3-phenylpropanoyl) group was introduced using the appropriate mixed ethoxycarbonic or pivalic anhydride (70 and 80% yields respectively), by analogy with the work of Hruby.[7]

The 3-acyloxazolidinones **5a–5f** were converted into their enolates using lithium diisopropylamide (LDA) or sodium bis(trimethylsilyl)amide in tetrahydrofuran (THF) at −78 °C.



Scheme 1 *Reagents and conditions:* i, BuLi, THF, −78 °C; ii, RCH_2COCl (for **5a–c** and **5e**) or succinic anhydride (for **5d**) or 3,4-$(MeO)_2C_6H_3CH_2CH_2CO_2H$, Et_3N, Bu^{t}COCl (for **5f**); iii, LDA or $NaN(SiMe_3)_2$, THF, −78 °C then $BrCH_2CN$, −78 °C to −15 °C then NH_4Cl (aq); iv, $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O; v, LiOH, THF, H_2O, −10 °C, then H^+ (reaction not done for R = allyl); vi, H_2, Pd–C, AcOH; vii, Boc_2O, NaOH, THF, H_2O; viii, LiOH, THF, H_2O, 25 °C, then H^+

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Base (2.2 equiv.) was used in conjunction with the succinyl derivative **5d**, so as to effect deprotonation at the carboxylic acid group and to form the enolate. Cyanomethylation by bromoacetonitrile of the enolates of **5a–5f** occurred with moderate stereoselectivity, except in the case of the succinyl compound **5d**: for example, the analysis of 250 MHz ^{1}H NMR spectra of the crude products obtained from the sodium enolates of **5b**, **5c** and **5e** showed that the corresponding products **6** had been formed with diastereoisomeric excesses (de) of 59, 73 and 77% respectively. The choice of LDA or $NaN(SiMe_3)_2$ as base did not appear to have a significant effect on the yield of the major products **6**: for example, the conversion of **5b** to **6b** was performed in 59% yield using LDA and in 60% yield using $NaN(SiMe_3)_2$; the conversion of **5c** to **6c** was achieved in 79% yield using LDA and 78% yield using $NaN(SiMe_3)_2$. The stereochemistry of the major alkylation products was initially assigned on the assumption that the electrophile preferentially attacked the less hindered faces of the chelated enolates of (*Z*)-geometry, according to the model established by Evans and co-workers;[3] in the cases of **5a** and **5c** these assignments were supported by chemical correlation with substances of known absolute configuration as discussed later in this article. The de values are significantly lower than those previously reported for alkylations by other common electrophiles[3] and this lack of selectivity may be a consequence of the small size of bromoacetonitrile, combined with its high reactivity as an electrophile. The major alkylation products **6a–6c**, **6e** and **6f** were purified by chromatography and crystallisation to give analytically pure materials in yields ranging from 59–81%. ^{1}H NMR showed that the recrystallised samples of **6b**, **6c**, **6e** and **6f** did not contain detectable amounts of the corresponding diastereoisomers **7**; recrystallised **6a** still contained approximately 4% of an impurity (presumed to be **7a**) that unfortunately could not be removed.

Cyanomethylation of the dianion from the succinyl compound **5d** gave, as judged by ^{1}H NMR and TLC comparisons with an authentic sample of **6d**, an inseparable mixture of the diastereoisomers **6d** and **7d** in an approximately 1:1 ratio. We are not aware of any reported attempts to alkylate succinyloxazolidinones such as **5d**, but we have found that benzylation of the dilithium salt of **5d** (THF; −55 °C to +10 °C) also appears to give an inseparable 1:1 mixture of diastereoisomers. Thus it appears that the carboxylate group interferes with the asymmetric alkylation of **5d**. The acyloxazolidinones **5e** and **5f** were therefore evaluated as chiral succinic acid enolate equivalents.

It was found that both the *N*-(pent-4-enoyl)oxazolidinone **5e** and the *N*-(3,4-dimethoxyhydrocinnamoyl)oxazolidinone **5f** could be cleanly oxidised by $RuCl_3$–$NaIO_4$ to give the succinyl compound **5d**. Thus it was established that the vinyl and 3,4-dimethoxyphenyl groups could act as synthetic equivalents of the carboxy group which could be unmasked without damage to the oxazolidinone auxiliary. Similar oxidation of **6e** gave the carboxylic acid **6d** as a single diastereoisomer in 93% yield.

Selective hydrolysis of the oxazolidinone chiral auxiliary of compounds **6a–c** and **6f** in the presence of the cyano group was easily accomplished by the use of lithium hydroxide in aqueous THF at −10 °C. The resultant cyano acids **8** could then be catalytically hydrogenated to give the 2-alkyl-4-aminobutanoic acids **1**. The specific rotation for the (*R*)-(−)-4-amino-2-methylbutanoic acid **1a** was in agreement with the literature value[8] for a sample obtained by a resolution and for which the absolute configuration had been established by chemical correlation. As the amino acids **1b** and **1c** were difficult to crystallise, they were characterised as their *N*-*tert*-butoxycarbonyl (Boc) derivatives **9b** and **9c**. Further confirmation that the stereochemical outcome of the alkylation step followed the usual model due to Evans was obtained by the hydrolysis ($LiOH$–H_2O–THF) of the alkylation product **6c** at room temperature, leading to (*R*)-2-ethylbutanedioic acid **10c**, which had a specific rotation equal and opposite to that previously reported for (*S*)-2-ethylbutanedioic acid.[9]

Cleavage of the chiral auxiliary from the acid **6d** was unsuccessful and we were unable to isolate any product showing a C≡N band in the IR spectrum. We therefore prepared the amino acid **1f** and protected it as its Boc derivative **9f**. Oxidation of **9f** ($RuCl_3$–$NaIO_4$) then gave a 27% yield of the protected amino acid **9d**, as an oil which was slightly impure as judged by an NMR comparison with a sample of *rac*-**9d** prepared from *rac*-**1d**.

Conclusions

We have shown that cyanomethylation of chiral 3-acyloxazolidinones is the key step in a simple and effective route to 2-substituted 4-aminobutanoic acid derivatives of predictable absolute configuration. We have also demonstrated that the pent-4-enoyl- and 3,4-dimethoxyhydrocinnamoyl-oxazolidinones **5e** and **5f** may be used as synthetic equivalents of the succinyloxazolidinone **5d**.

Experimental

'Petrol' refers to the light petroleum fraction bp 40–60 °C and was redistilled. 'Ether' is diethyl ether. '1.5 mol dm^{-3} LDA' refers to a 1.5 mol dm^{-3} solution in cyclohexane of lithium diisopropylamide mono(tetrahydrofuran) complex, purchased from the Aldrich Chemical Company. Sodium bis(trimethylsilyl)-amide was purchased from Aldrich as a 1 mol dm^{-3} solution in THF. We have described the preparation of *rac*-**1d** in a previous account.[10] Experiments involving the use of BuLi, LDA or $NaN(SiMe_3)_2$ were performed under a nitrogen atmosphere. THF was dried by distillation from sodium and benzophenone. Drying of organic extracts was performed using anhydrous $MgSO_4$. All mass spectra were recorded in electron impact mode. Quoted yields refer to chromatographically homogeneous materials which, except where noted in the case of compound **6a**, were diastereoisomerically pure as judged by Fourier transform ^{1}H NMR spectroscopy. Unless stated otherwise, all experiments were performed at 25 °C. TLC was carried out on Merck precoated silica gel 60 F_{254} plates. Reaction components were visualised under UV_{254} illumination and by development with I_2 vapour or ethanolic dodecamolybdophoshoric acid or ninhydrin. Flash chromatography was performed on Sorbsil silica C60 40/60H. $[\alpha]_D$ Values were measured with an Optical Activity Ltd AA-1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured on a Perkin-Elmer 1600 series FTIR spectrometer. ^{1}H NMR spectra were measured with a Bruker WP80 (80 MHz) or AM250 (250 MHz) spectrometer; chemical shifts (δ) are reported in ppm downfield of tetramethylsilane ($\delta = 0$), and J values are given in Hz. Mass spectra were recorded in electron impact mode using a Kratos MS 50RF instrument in conjunction with a Kratos DS 90 data acquisition system.

CAUTION: Great care must be taken to avoid contact with bromoacetonitrile or iodoacetonitrile, low concentrations of which may lead to severe blistering of the skin in susceptible individuals.

(4*S*,5*R*)-3-(3-Carboxypropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 5d by acylation of 3 using succinic anhydride

A solution of (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **3** (1.77 g, 10.0 mmol) in THF (10 cm^3) was cooled to −78 °C and treated with BuLi (2.5 mol dm^{-3} in hexanes; 4.1 cm^3, 10.3 mmol) until the solution just acquired a permanent orange colour. After 2 min a solution of succinic anhydride (1.02 g, 10 mmol) in THF (15 cm^3) was added by cannula over 5 min. The mixture was allowed to attain room temperature over 4 h before being acidified with 2 mol dm^{-3} HCl (aq.) to pH 1 and then

partitioned between ether (25 cm^3) and brine (25 cm^3). The ether layer was washed with a further portion of brine (25 cm^3), then extracted with saturated $NaHCO_3$ (aq.) (3 × 20 cm^3). The combined $NaHCO_3$ extracts were acidified with 2 mol dm^{-3} HCl and extracted with ether (3 × 50 cm^3). Drying and concentration of the ether extracts, followed by addition of petrol, gave (4*S*,5*R*)-3-(3-*carboxypropanoyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **5d** (1.81 g, 65%) as colourless prisms, mp 118–120 °C (Found: C, 60.7; H, 5.4; N, 4.9. $C_{14}H_{15}NO_5$ requires C, 60.6; H, 5.45; N, 5.05%; $[\alpha]_D^{28}$ −17 (*c* 0.99 in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3500–2800 (acid O–H), 1790 (C=O), 1738 (acid C=O) and 1695 (C=O); δ_H(250 MHz, $CDCl_3$) 0.92 (3 H, d, *J* 7, CH_3), 2.65–2.85 (2 H, m, CH_2), 3.17–3.38 (2 H, m, CH_2), 4.77 (1 H, quintet, *J* 7, 4-H), 5.71 (1 H, d, *J* 7, 5-H), 7.27–7.47 (5 H, m, Ph) and 10.3 (1 H, br s, OH); *m*/*z* 277 (M^+, 10%), 177 (14), 134 (26) and 107 (100) (Found: M^+, 277.0967. $C_{14}H_{15}NO_5$ requires *M*, 277.0949).

(4*S*,5*R*)-4-Methyl-3-(pent-4-enoyl)-5-phenyl-1,3-oxazolidin-2-one 5e

A solution of (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **3** (2.49 g, 14.1 mmol) in THF (20 cm^3) was cooled to −78 °C and treated with BuLi (1.6 mol dm^{-3} in hexanes; 9.0 cm^3, 14.4 mmol) until the solution just acquired a permanent orange colour. After 5 min pent-4-enoyl chloride[11] (2.00 g, 16.9 mmol) was added by syringe over 2 min. The mixture was maintained at −70 °C for 90 min before being quenched with saturated NH_4Cl (aq.) and allowed to warm to room temperature. The mixture was partitioned between ether (40 cm^3) and brine (20 cm^3). The ether layer was washed with $NaHCO_3$ (aq.) (2 × 20 cm^3) and again with brine (20 cm^3). Drying and evaporation of the ether extract gave pale yellow crystals, which were subjected to flash chromatography [gradient from CH_2Cl_2–petrol (1:2) to (2:1)] followed by recrystallisation from ether–petrol, to yield (4*S*,5*R*)-4-*methyl*-3-(*pent*-4-*enoyl*)-5-*phenyl*-1,3-*oxazolidin*-2-*one* **5e** (3.11 g, 85%) as colourless plates, mp 71–72 °C (Found: C, 69.5; H, 6.85; N, 5.4. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); $[\alpha]_D^{35}$ −34 (*c* 1.0 in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1779 (C=O), 1699 (C=O) and 1641 (C=C); δ_H(250 MHz, $CDCl_3$) 0.90 (3 H, d, *J* 7, CH_3), 2.39–2.50 (2 H, m, 3′-H_2), 2.94–3.18 (2 H, m, 2′-H_2), 4.77 (1 H, quintet, *J* 7, 4-H), 5.00–5.15 (2 H, m, 5′-H_2), 5.67 (1 H, d, *J* 8, 5-H), 5.80–5.97 (1 H, m, 4′-H) and 7.24–7.46 (5 H, m, Ph); *m*/*z* 259 (M^+, 100%), 177 (10) and 107 (37) (Found: M^+, 259.1208. $C_{15}H_{17}NO_3$ requires *M*, 259.1208).

(4*S*,5*R*)-3-[3-(3,4-Dimethoxyphenyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 5f

A solution of 3-(3,4-dimethoxyphenyl)propanoic acid (1.22 g, 5.9 mmol) in THF (6 cm^3) was cooled to −78 °C. Triethylamine (0.89 cm^3, 6.4 mmol) was then added dropwise, followed by pivaloyl chloride (0.79 cm^3, 6.4 mmol). The mixture was stirred at −78 °C for 30 min, then at 0 °C for 90 min, before being recooled to −78 °C and treated with a solution prepared from (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **3** (0.85 g, 4.8 mmol) and BuLi (2.5 mol dm^{-3} in hexanes; 2.23 cm^3, 5.3 mmol) in THF (5 cm^3) at −78 °C. The mixture was maintained at −78 °C for 30 min, then allowed to warm to room temperature and stirred for a further 30 min before being quenched with saturated NH_4Cl (20 cm^3). The mixture was partitioned between ether (20 cm^3) and water (20 cm^3). The ether layer was washed with saturated $NaHCO_3$ (aq.) (20 cm^3) and again with water (20 cm^3). Drying and evaporation of the ether extract gave white crystals, which were subjected to flash chromatography [gradient from EtOAc–petrol (1:9) to (3:7)] followed by recrystallisation from EtOAc–petrol, to yield (4*S*,5*R*)-3-[3-(3,4-*dimethoxyphenyl*)-*propanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **5f** (1.41 g, 80%) as a white solid, mp 105–106 °C (Found: C, 68.1; H, 6.1; N, 3.7. $C_{21}H_{23}NO_5$ requires C, 68.3; H, 6.3; N, 3.8%); $[\alpha]_D^{25}$ −22 (*c* 1.1 in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1780 (C=O), 1702 (C=O) and 1606 (aromatic); δ_H(250 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 7, CH_3), 2.90–3.01 (2 H, m, CH_2), 3.16–3.39 (2 H, m, CH_2), 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.75 (1 H, quintet, *J* 7, 4-H), 5.63 (1 H, d, *J* 7, 5-H), 6.81 (3 H, s, Ar-H_3) and 7.25–7.47 (5 H, m, Ph); *m*/*z* 369 (M^+, 100%), 192 (26), 151 (92) and 107 (10) (Found: M^+, 369.1576. $C_{21}H_{23}NO_5$ requires *M*, 369.1576).

(4*S*,5*R*)-3-(3-Carboxypropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 5d by oxidation of 5e

A mixture of (4*S*,5*R*)-4-methyl-3-(pent-4-enoyl)-5-phenyl-1,3-oxazolidin-2-one **5e** (99.6 mg, 0.38 mmol), acetonitrile (2 cm^3), CCl_4 (2 cm^3) and water (3 cm^3) was treated with $NaIO_4$ (0.44 g, 2.1 mmol) and $RuCl_3$ (2.3 mg, 0.01 mmol) then stirred vigorously at room temperature for 4 h. The mixture was then partitioned between water (5 cm^3) and CH_2Cl_2 (10 cm^3). The lower layer was extracted with saturated aqueous $NaHCO_3$, which was separated, acidified to pH 1 with 2 mol dm^{-3} HCl, and extracted with EtOAc (3 × 15 cm^3). The combined EtOAc extracts were dried ($MgSO_4$), filtered, evaporated and recrystallised from CH_2Cl_2–Et_2O–petrol to yield (4*S*,5*R*)-3-(3-carboxypropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **5d** as white crystals (76 mg, 75%), mp 138–140 °C; $[\alpha]_D^{26}$ −16 (*c* 1.05 in CH_2Cl_2); the ^1H NMR and IR spectra of the product were identical to those of a sample of **5d** prepared by acylation of **4** using succinic anhydride.

(4*S*,5*R*)-3-(3-Carboxypropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one 5d by oxidation of 5f

(4*S*,5*R*)-3-[3-(3,4-Dimethoxyphenyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **5f** (100 mg, 0.27 mmol) was oxidised in a mixture of acetonitrile (3 cm^3), CCl_4 (3 cm^3) and water (4.5 cm^3) using $NaIO_4$ (0.77 g, 3.7 mmol) and $RuCl_3$ (7 mg, 0.03 mmol) at room temperature for 3 h. The mixture was then treated as in the preceding experiment, except that the product was recrystallised from Et_2O–petrol to yield (4*S*,5*R*)-3-(3-carboxypropanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one **5d** as white crystals (57.4 mg, 76%), mp 138–139 °C; the ^1H NMR spectrum of the product was identical to that of a sample of **5d** prepared by acylation of **3** using succinic anhydride.

(4*S*,5*R*,2′*R*)-3-[2-(Cyanomethyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6a

A 1.5 mol dm^{-3} solution of LDA (3.0 cm^3, 4.5 mmol) was cooled to −78 °C and treated with a solution of (4*S*,5*R*)-4-methyl-5-phenyl-3-propanoyl-1,3-oxazolidin-2-one **5a** (0.94 g, 4.0 mmol) in THF (9 cm^3) dropwise over 5 min. The mixture was maintained at −78 °C for 30 min, then bromoacetonitrile (1.62 cm^3, 20.0 mmol) in THF (4 cm^3) was added over 1 min. The mixture was allowed to warm to −15 °C over 7 h, then acidified with acetic acid and partitioned between water and ether. The ether extract was washed with saturated $NaHCO_3$ (aq.), before being dried, evaporated and subjected to flash chromatography [gradient from CH_2Cl_2–petrol (1:1) to CH_2Cl_2] to yield (4*S*,5*R*,2′*R*)-3-[2-(*cyanomethyl*)*propanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **6a** (0.89 g, 81%) as a pale yellow solid. After recrystallisation from ether–petrol the product was obtained as colourless crystals, mp 82–88 °C (Found: C, 66.1; H, 6.0; N, 10.1. $C_{15}H_{16}N_2O_3$ requires C, 66.15; H, 5.9; N, 10.3%); $[\alpha]_D^{28}$ −35 (*c* 1.01 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2250 (C≡N), 1785 (C=O) and 1696 (C=O); δ_H(250 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 7.5, CH_3), 1.40 (3 H, d, *J* 7.5, CH_3), 2.59 (1 H, dd, *J* 17 and 7, CHCN), 2.72 (1 H, dd, *J* 17 and 7, CHCN), 4.11 (1 H, sextet, *J* 7.5, CHCO), 4.77 (1 H, quintet, *J* 7.5, 4-H), 5.71 (1 H, d, *J* 7.5, 5-H) and 7.28–7.47 (5 H, m, Ph); *m*/*z* 272 (M^+, 7%), 176 (6), 134 (100) and 106 (93) (Found: M^+, 272.1162. $C_{15}H_{16}N_2O_3$ requires *M*, 272.1161). The NMR spectrum of the recrystallised sample indicated the presence of *ca.* 4 mol% of another oxazolidinone, δ_H *inter alia*

0.89 (d, *J* 7.5), which was considered to be (4*S*,5*R*,2′*S*)-3-(2-cyanomethylpropanoyl)-4-methyl-5-phenyloxazolidin-2-one **7a**.

(4*R*,5*S*,2′*S*)-3-[2-(Cyanomethyl)phenylacetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6b

(4*S*,5*R*)-4-Methyl-3-phenylacetyl-5-phenyl-1,3-oxazolidin-2-one **5b** (0.99 g, 3.39 mmol) was cyanomethylated according to the procedure used for the preparation of **6a** above, except that $NaN(SiMe_3)_2$ was used as the base in place of LDA. The crude product obtained after solvent extraction was analysed by 250 MHz ^1H NMR spectroscopy: integration of the signals from the oxazolidinone 5-H and 4-Me protons, and from the PhC*H*CO proton, indicated that the ratio of the diastereoisomeric products **6b** and **7b** was 3.86:1, *i.e.* 59% de. Flash chromatography [gradient from CH_2Cl_2–petrol (1:1) to CH_2Cl_2] gave (4*S*,5*R*,2′*S*)-3-[2-(*cyanomethyl*)*phenylacetyl*]-4-*methyl*-5-*phenyloxazolidin*-2-*one* **6b** (0.67 g, 60%) as a white solid. After recrystallisation from CH_2Cl_2–ether–petrol the product was obtained as colourless crystals, mp 157–160 °C (Found: C, 71.6; H, 5.5; N, 8.1. $C_{20}H_{18}N_2O_3$ requires C, 71.8; H, 5.4; N, 8.4%); $[\alpha]_D^{28}$ −99 (*c* 1.05 in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 2244 (C≡N), 1796 (C=O) and 1691 (C=O); δ_H(250 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 7.5, CH_3), 2.80 (1 H, dd, *J* 17 and 7, CHCN), 3.07 (1 H, dd, *J* 17 and 7, CHCN), 4.71 (1 H, quintet, *J* 7.5, 4-H), 5.39 (1 H, dd, *J* 8 and 7, CHCO), 5.50 (1 H, d, *J* 7, 5-H) and 7.23–7.45 (10 H, m, 2 × Ph); *m*/*z* 334 (M^+, 100%), 178 (20), 118 (62) and 77 (19) (Found: M^+, 334.1317. $C_{20}H_{18}N_2O_3$ requires *M*, 334.1317).

A minor product, which eluted just after **6b** during flash chromatography, was obtained as a colourless oil and was considered to be (4*S*,5*R*,2′*R*)-3-[2-(*cyanomethyl*)*phenylacetyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **7b** (0.16 g, 14%) on the basis of the following properties: $[\alpha]_D^{37}$ −75 (*c* 0.15 in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 2251 (C≡N), 1782 (C=O) and 1696 (C=O); δ_H(250 MHz, $CDCl_3$) 0.76 (3 H, d, *J* 7, CH_3), 2.77 (1 H, dd, *J* 17 and 7, CHCN), 3.08 (1 H, dd, *J* 17 and 8, CHCN), 4.88 (1 H, quintet, *J* 7, 4-H), 5.30 (1 H, dd, *J* 8.5 and 6.5, CHC=O), 5.69 (1 H, d, *J* 7, 5-H) and 7.1–7.4 (10 H, m, 2 × Ph); *m*/*z* 334 (M^+, 67%), 178 (19), 118 (100) and 77 (32) (Found: M^+, 334.1317. $C_{20}H_{18}N_2O_3$ requires *M*, 334.1317).

(4*S*,5*R*,2′*R*)-3-[2-(Cyanomethyl)butanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6c

Using LDA as base. (4*S*,5*R*)-3-Butanoyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one **5c** (0.99 g, 4.0 mmol) was cyanomethylated with LDA as base, according to the procedure used for the preparation of **6a** above. Flash chromatography [gradient from CH_2Cl_2–petrol (3:2) to CH_2Cl_2] gave (4*S*,5*R*,2′*R*)-3-[2-(*cyanomethyl*)*butanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **6c** (0.91 g, 79%) as a pale yellow solid. After recrystallisation from ether–petrol the product was obtained as colourless crystals, mp 102–104 °C (Found: C, 67.1; H, 6.3; N, 9.7. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%); $[\alpha]_D^{28}$ −16 (*c* 1.05 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2241 (C≡N), 1778 (C=O) and 1698 (C=O); δ_H(250 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 7, CH_3), 1.01 (3 H, t, *J* 7, CH_3), 1.64–1.99 (2 H, m, CH_2), 2.61 (1 H, dd, *J* 17 and 7, CHCN), 2.73 (1 H, dd, *J* 17 and 7, CHCN), 4.10 (1 H, quintet, *J* 7, CHCO), 4.78 (1 H, quintet, *J* 7.5, 4-H), 5.71 (1 H, d, *J* 7.5, 5-H) and 7.26–7.48 (5 H, m, Ph); *m*/*z* 286 (M^+, 11%), 176 (10) and 107 (93) (Found: M^+, 286.1315. $C_{16}H_{18}N_2O_3$ requires *M*, 286.1317).

Using $NaN(SiMe_3)_2$ as base. (4*S*,5*R*)-3-Butanoyl-4-methyl-5-phenyloxazolidin-2-one **5c** (0.903 g, 3.65 mmol) was cyanomethylated with $NaN(SiMe_3)_2$ as base, by analogy with the above procedures. The 250 MHz ^1H NMR spectrum of the crude product showed the presence of **6c** and of a related species, which was presumed to be the diastereoisomer **7c**; integration of the doublets at δ 0.94 and 0.90 indicated that **6c** and **7c** were present in the ratio 6.3:1, a diastereoisomeric excess of 73%. Chromatography gave the major product **6c** (0.813 g, 78%), identical by ^1H NMR with the fully characterised sample which had previously been prepared using LDA as the base.

(4*S*,5*R*,2′*R*)-3-[2-(Cyanomethyl)pent-4-enoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6e

A 1.0 mol dm^{-3} solution of $NaN(SiMe_3)_2$ in THF (1.1 cm^3, 1.1 mmol) at −78 °C was treated with (4*R*,5*S*)-4-methyl-3-(pent-4-enoyl)-5-phenyl-1,3-oxazolidin-2-one **5e** (0.257 g, 1.0 mmol) in THF (4 cm^3). After 30 min bromoacetonitrile (0.21 cm^3, 3.0 mmol) was added to the reaction mixture over 1 min, then the mixture was allowed to warm to −25 °C over 5 h. A mixture of acetic acid (0.8 cm^3) and ether (0.2 cm^3) was added, then the mixture was allowed to attain room temperature before being partitioned between ether (20 cm^3) and brine (20 cm^3). The ethereal layer was washed in turn with 2 mol dm^{-3} hydrochloric acid (20 cm^3), brine (20 cm^3), saturated aqueous $NaHCO_3$ (2 × 20 cm^3) and brine (20 cm^3). The ether extract was dried and evaporated to leave the crude product as an oil, the ^1H NMR spectrum of which showed the presence of the major product **6e** and of a related species [δ_H *inter alia* 0.88 (d)], which was presumed to be the diastereoisomer **7e**, in the ratio 7.8:1, *i.e.* 77% de. Flash chromatography [CH_2Cl_2–petrol gradient from (1:1) to (2:1)], followed by crystallisation from Et_2O–CH_2Cl_2–petrol, gave (4*S*,5*R*,2′*R*)-3-[2-(*cyanomethyl*)*pent*-4-*enoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **6e** (0.173 g, 59%) as white plates, mp 70–72 °C (Found: C, 68.6; H, 6.1; N, 9.3. $C_{17}H_{18}N_2O_3$ requires C, 68.4; H, 6.1; N, 9.4%); $[\alpha]_D^{28}$ −7.4 (*c* 0.95 in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 2248 (C≡N), 1774 (C=O) and 1691 (C=O); δ_H(250 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 7, CH_3), 2.35–2.76 (4 H, m, 3′-H_2 and CH_2CN), 4.21 (1 H, quintet, *J* 7, CHCO), 4.77 (1 H, quintet, *J* 7, 4-H), 5.18–5.25 (2 H, m, 5′-H_2), 5.69 (1 H, d, *J* 7, 5-H), 5.78 (1 H, ddt, *J* 17, 10 and 7, 4′-H) and 7.28–7.48 (5 H, m, Ph); *m*/*z* 298 (M^+, 91%), 258 (95), 214 (19) and 160 (28) (Found: M^+, 298.1321. $C_{17}H_{18}N_2O_3$ requires *M*, 298.1317).

(4*S*,5*R*,2′*S*)-3-[2-(Cyanomethyl)-3-carboxypropanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6d by oxidation of 6e

A mixture of (4*S*,5*R*,2′*R*)-3-[2-(cyanomethyl)pent-4-enoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6e** (0.61 g, 2.0 mmol), acetonitrile (9 cm^3), CCl_4 (9 cm^3) and water (13.5 cm^3) was treated with $NaIO_4$ (2.49 g, 11.2 mmol) and $RuCl_3$ (15.9 mg, 0.08 mmol), then stirred vigorously at room temperature for 5.5 h. The mixture was then partitioned between water (20 cm^3) and CH_2Cl_2 (20 cm^3). The aqueous layer was further washed with CH_2Cl_2 (3 × 20 cm^3). The combined CH_2Cl_2 layers were extracted with saturated aqueous $NaHCO_3$ (3 × 20 cm^3). The combined $NaHCO_3$ layers were acidified to pH 1 with 2 mol dm^{-3} HCl and extracted with EtOAc. The combined EtOAc layers were dried ($MgSO_4$), filtered and evaporated to give (4*S*,5*R*,2′*S*)-3-[2-(*cyanomethyl*)-3-*carboxypropanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidin*-2-*one* **6d** (0.57 g, 89%) as a pale purple oil; $[\alpha]_D^{27}$ +12 (*c* 1.05 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2600–3600 (acid O–H), 2254 (C≡N), 1780 (C=O) and 1701 (C=O); δ_H(250 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 7, CH_3), 2.74 (1 H, dd, *J* 17, 5, 3′-H or 3″-H), 2.80 (2 H, 'd', *J* 7, 3″-H_2 or 3′-H_2), 3.12 (1 H, dd, *J* 17 and 9, 3′-H or 3″-H), 4.34–4.45 (1 H, m, 2′-H), 4.82 (1 H, quintet, *J* 7, 4-H), 5.76 (1 H, d, *J* 7, 5-H) and 7.30–7.47 (5 H, m, Ph); *m*/*z* 316 (M^+, 0.3%), 227 (0.3), 177 (17) and 107 (100) (Found: M^+, 316.1049. $C_{16}H_{16}N_2O_5$ requires *M*, 316.1059).

(4*S*,5*R*,2′*R*)-3-[2-Cyanomethyl-3-(3,4-dimethoxyphenyl)-propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one 6f

(4*S*,5*R*)-3-[3-(3,4-Dimethoxyphenyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **5f** (0.308 g, 0.83 mmol) was cyanomethylated by analogy with the reaction of **6e** above, but CH_2Cl_2–Et_2O (98:2) was used as the eluent for the flash chromatography. Recrystallisation of the major product from EtOAc–petrol gave (4*S*,5*R*,2′*R*)-3-[2-*cyanomethyl*-3-(3,4-

dimethoxyphenyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6f** (0.220 g, 70%) as white needles, mp 132 °C (Found: C, 67.5; H, 5.8; N, 6.9. $C_{23}H_{24}N_2O_5$ requires C, 67.6; H, 5.9; N, 6.9%); $[\alpha]_D^{28}$ +41 (*c* 0.92 in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 2246 (C≡N), 1782 (C=O) and 1704 (C=O); δ_H(250 MHz, $CDCl_3$) 0.93 (3 H, d, *J* 7, CH_3), 2.53 (1 H, dd, *J* 17 and 5, $\frac{1}{2}$ × CH_2), 2.65 (1 H, dd, *J* 17 and 7.5, $\frac{1}{2}$ × CH_2), 2.80 (1 H, dd, *J* 13.5, 9, $\frac{1}{2}$ × CH_2), 3.11 (1 H, dd, *J* 13.5 and 6, $\frac{1}{2}$ × CH_2), 3.86 (3 H, s, OMe), 3.91 (3 H, s, OMe), 4.34–4.47 (1 H, m, CHCO), 4.67 (1 H, quintet, *J* 7, 4-H), 5.49 (1 H, d, *J* 7, 5-H), 6.78–6.88 (3 H, m, C_6H_3) and 7.21–7.47 (5 H, m, Ph); *m/z* 408 (M^+, 90%), 203 (11), 152 (11) and 151 (100) (Found: M^+, 408.1684. $C_{23}H_{24}N_2O_5$ requires *M*, 408.1685).

(*R*)-4-Amino-2-methylbutanoic acid 1a

A solution of (4*S*,5*R*,2′*R*)-3-[2-(cyanomethyl)propanoyl]-4-methyl-5-phenyloxazolidin-2-one **6a** (0.43 g, 1.58 mmol) in THF (5 cm^3) was cooled to −10 °C and treated with a solution of LiOH·H_2O (95.3 mg, 2.27 mmol) in H_2O (4 cm^3). After 2.5 h TLC [CH_2Cl_2–Et_2O (98:2)] indicated that **6a** had been completely consumed. The THF was evaporated under reduced pressure and the aqueous residue was repeatedly extracted with CH_2Cl_2 (3 × 40 cm^3) before being acidified with 2 mol dm^{-3} hydrochloric acid to pH 1 and extracted with EtOAc (3 × 30 cm^3). The combined EtOAc extracts were dried and evaporated to leave (*R*)-2-(cyanomethyl)propanoic acid **8a** (0.16 g, 90%) as a pale yellow oil; δ_H(80 MHz, $CDCl_3$) 1.40 (3 H, d, CH_3), 2.5–3.1 (3 H, m, CH_2 and CH) and 10.7 (1 H, br s, CO_2H).

The aforementioned (*R*)-2-(cyanomethyl)propanoic acid **8a** was dissolved in AcOH (15 cm^3) and shaken with 5% Pd on C (0.46 g) under H_2 gas (3 atm) for 3 d. The mixture was filtered (Celite); the filtrate was evaporated under reduced pressure and the residue was repeatedly evaporated from water before being recrystallised from ethanol to yield (*R*)-4-amino-2-methylbutanoic acid **1a** (0.163 g, 88% from **6a**) as fine white crystals, mp 187–190 °C (lit.,[8] 196–197 °C); $[\alpha]_D^{28}$ −6.5 (*c* 3.1, H_2O) [lit.,[8] −6.7 (*c* 2.8, H_2O)]; ν_{max}(KBr)/cm^{-1} 2400–3300 (NH_3^+) and 1579 (CO_2^-); δ_H(250 MHz, D_2O) 1.16 (3 H, d, *J* 7, CH_3), 1.68–1.99 (2 H, m, 3-H_2), 2.42 (1 H, sextet, *J* 7, 2-H) and 2.95–3.12 (2 H, m, 4-H_2).

(*S*)-3-Cyano-2-phenylpropanoic acid 8b

(4*S*,5*R*,2′*S*)-3-[2-(Cyanomethyl)phenylacetyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6b** (0.152 g, 0.53 mmol) was treated with LiOH·OH–THF–H_2O for 1 h as described for **6a** above. Solvent extraction gave (*S*)-3-*cyano*-2-*phenylpropanoic acid* **8b** (0.082 g, 91%) as a white solid, which after recrystallisation from ether–petrol had mp 95–97 °C; $[\alpha]_D^{28}$ +154 (*c* 1.04, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 2900–3300 (O–H), 2273 (C≡N) and 1735 (C=O); δ_H(250 MHz, $CDCl_3$) 2.82 (1 H, dd, *J* 17 and 7.5, CHCN), 3.05 (1 H, dd, *J* 17 and 7.5, CHCN), 3.99 (1 H, t, CH) and 7.25–7.46 (5 H, m, Ph); *m/z* 175 (M^+, 62%), 130 (100) and 104 (89) (Found: M^+, 175.0631. $C_{10}H_9NO_2$ requires *M*, 175.0633).

(*R*)-2-(Cyanomethyl)butanoic acid 8c

A solution of (4*S*,5*R*,2′*R*)-3-[2-(cyanomethyl)butanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6c** (0.59 g, 2.05 mmol) in THF (6 cm^3) was cooled to −10 °C and treated with a solution of LiOH·H_2O (104 mg, 2.76 mmol) in H_2O (3 cm^3). After 2 h TLC [CH_2Cl_2–Et_2O (98:2)] indicated that **8c** had been completely consumed. The THF was then evaporated under reduced pressure and the aqueous residue was washed with CH_2Cl_2 (3 × 15 cm^3) before being acidified with 2 mol cm^{-3} HCl to pH 1 and extracted with EtOAc (3 × 15 cm^3). The combined EtOAc extracts were dried, filtered and evaporated to leave (*R*)-2-(cyanomethyl)butanoic acid **8c** (0.22 g, 83%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 3300–2800 (O–H), 2273 (C≡N) and 1755 (C=O); δ_H(80 MHz, $CDCl_3$) 1.05 (3 H, t, *J* 7, CH_3), 1.63–2.10 (2 H, m, CH_2) and 2.50–2.98 (3 H, m).

(*R*)-2-(Cyanomethyl)-3-(3,4-dimethoxyphenyl)propanoic acid 8f

A solution of (4*S*,5*R*,2′*R*)-3-[2-cyanomethyl-3-(3,4-dimethoxyphenyl)propanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6f** (107 mg, 0.26 mmol) in THF (6 cm^3) was cooled to −10 °C and treated with a solution of LiOH·H_2O (13.0 mg, 0.31 mmol) in H_2O (2 cm^3). After 30 min TLC [CH_2Cl_2–Et_2O (98:2)] indicated that **6f** had been completely consumed. The mixture was then diluted with water (10 cm^3) and washed with CH_2Cl_2 (5 × 6 cm^3). The aqueous phase was acidified with 2 mol dm^{-3} HCl to pH 3 and extracted with EtOAc (4 × 8 cm^3). The combined EtOAc extracts were dried, filtered and evaporated to leave (*R*)-2-(cyanomethyl)-3-(3,4-dimethoxyphenyl)propanoic acid **8f** (63.4 mg, 97%) as a colourless oil; ν_{max}(film)/cm^{-1} 3740–3630 (O–H) and 2252 (C≡N); δ_H(80 MHz, $CDCl_3$) 2.4–2.7 (2 H, m, CH_2), 2.8–3.35 (3 H, m, CH_2 and CH), 3.9 (6 H, s, 2 × MeO), 6.6–7.0 (3 H, m, C_6H_3) and 9.2 (1 H, br s, OH).

(*S*)-4-(*tert*-Butoxycarbonylamino)-2-phenylbutanoic acid 9b

(*S*)-3-Cyano-2-phenylpropanoic acid **8b** (0.19 g, 1.1 mmol) was dissolved in AcOH (10 cm^3) and shaken with 5% Pd on C (0.30 g) under H_2 gas (3 atm) for 24 h. The mixture was filtered (Celite) and the filtrate was evaporated under reduced pressure to leave crude (*S*)-4-amino-2-phenylbutanoic acid **1b** (0.18 g) as a pale pink glass which was difficult to crystallise, but which was found to be essentially pure by ^{1}H NMR spectroscopy: δ_H(250 MHz, D_2O) 2.10–2.22 (1 H, m, 3-H), 2.30–2.45 (1 H, m, 3-H), 2.89–3.12 (2 H, m, 4-H_2), 3.58–3.67 (1 H, m, 2-H) and 7.36–7.51 (5 H, m, Ph).

A portion of the above sample of crude (*S*)-4-amino-2-phenylbutanoic acid **1b** (0.154 g, *ca.* 0.86 mmol) was dissolved in 1 mol dm^{-3} aqueous NaOH (0.95 cm^3, 0.95 mmol) and treated with a solution of di-*tert*-butyl dicarbonate (0.247 g, 1.12 mmol) in THF (1 cm^3). The mixture was stirred at room temperature for 3.5 h, after which TLC [HCO_2H–H_2O–Pr^{i}OH (10:5:85)] showed that **1b** had been completely consumed. The aqueous phase was washed with diethyl ether (3 × 10 cm^3), cautiously acidified to pH 4 with 1 mol dm^{-3} aqueous $KHSO_4$ and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined CH_2Cl_2 extracts were dried, filtered and evaporated to yield (*S*)-4-(tert-*butoxycarbonylamino*)-2-*phenylbutanoic acid* **9b** (0.166 g, 69%) as a pale yellow oil which crystallised on standing, mp 106–108 °C (Found: C, 64.7; H, 7.55; N, 4.9. $C_{15}H_{21}NO_4$ requires C, 64.5; H, 7.6; N, 5.0%); $[\alpha]_D^{28}$ +62 (*c* 0.7, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3304 (N–H), 1708 (C=O) and 1645 (C=O); δ_H(250 MHz, $CDCl_3$; the broadness of the peaks and the presence of two NH peaks suggested that two interconverting rotamers were present) 1.42 (9 H, s, Bu^t), 1.84–2.04 (1 H, m, 3-H), 2.19–2.39 (1 H, m, 3-H), 3.01–3.19 (2 H, m, CH_2), 3.61 (1 H, t, *J* 7, CH), 4.62 (0.6 H, br s, NH), 6.13 (0.4 H, br s, NH), 7.22–7.36 (5 H, m, Ph) and 10.33 (1 H, br s, OH); *m/z* 279 (M^+, 0.3%), 261 (24), 223 (11) and 57 (100) (Found: M^+, 279.1483. $C_{15}H_{21}NO_4$ requires *M*, 279.1471).

(*R*)-4-(*tert*-Butoxycarbonylamino)-2-ethylbutanoic acid 9c

(*R*)-2-(Cyanomethyl)butanoic acid **8c** (0.22 g, 1.71 mmol) was dissolved in AcOH (15 cm^3) and shaken with 5% Pd on C (0.32 g) under H_2 gas (3 atm) for 2 d. The mixture was filtered (Celite) and the filtrate was evaporated under reduced pressure to leave (*R*)-4-amino-2-ethylbutanoic acid **1c** (0.19 g) as a pale yellow glass which was difficult to crystallise, but which was found to be essentially pure by ^{1}H NMR spectroscopy: δ_H(250 MHz, D_2O) 0.88 (3 H, t, *J* 7, CH_3), 1.51 (2 H, quintet, *J* 7, CH_3CH_2), 1.69–1.94 (2 H, m, 3-H_2), 2.21 (1 H, m, 2-H) and 2.89–3.06 (2 H, m, 4-H_2).

A portion of the above sample of crude (*R*)-4-amino-2-ethylbutanoic acid **1c** (60 mg, *ca.* 0.46 mmol) was dissolved in 1 mol dm^{-3} aqueous NaOH (0.51 cm^3, 0.51 mmol) and treated

with a solution of di-*tert*-butyl dicarbonate (0.124 g, 0.56 mmol) in THF (1.5 cm^3). The mixture was stirred at room temperature for 6.5 h, after which TLC [HCO_2H–H_2O–Pr^iOH (10:15:75)] showed that **1c** had been completely consumed. The mixture was diluted with H_2O (2 cm^3) and the aqueous phase was washed with diethyl ether (3 × 3 cm^3), carefully acidified to pH 4 with 1 mol dm^{-3} aqueous $KHSO_4$ and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined CH_2Cl_2 extracts were dried, filtered and evaporated to yield (*R*)-4-(tert-*butoxycarbonylamino*)-2-*ethylbutanoic acid* **9c** (70 mg, 55% from **8c**) as an oil; $[\alpha]_D^{29}$ −16 (*c* 0.42, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3344 (N–H) and 1706 (C=O); δ_H(250 MHz, $CDCl_3$; the broadness of the peaks and the presence of two NH peaks suggested that two interconverting rotamers were present) 0.93 (3 H, t, *J* 7, Me), 1.43 (9 H, s, Bu^t), 1.50–1.93 (4 H, m, 2 × CH_2), 2.18–2.41 (1 H, m, CH), 3.00–3.31 (2 H, m, CH_2), 4.73 (0.75 H, br s, NH), 6.10 (0.25 H, br s, NH) and 9.61 (1 H, br s, OH); *m/z* 232 (MH^+, 0.1%), 130 (12), 114 (10), 88 (11) and 57 (100) (Found: MH^+, 232.1549. $C_{11}H_{21}NO_4$ requires *M* + H, 232.1549).

(*R*)-4-(*tert*-Butoxycarbonylamino)-2-(3,4-dimethoxybenzyl)-butanoic acid 9f

(*R*)-2-(Cyanomethyl)-3-(3,4-dimethoxyphenyl)propanoic acid **8f** (63.4 mg, 0.25 mmol) in AcOH (5 cm^3) was stirred with 5% Pd on C (100 mg) under a balloon of H_2 gas for 4.5 h. The mixture was filtered (Celite) and the filtrate was evaporated under reduced pressure to leave a colourless glass (73 mg) which was dissolved in 0.55 mol dm^{-3} aqueous NaOH (0.49 cm^3, 0.27 mmol) and stirred with a solution of Boc_2O (68 mg, 0.31 mmol) in THF (0.8 cm^3) at 0 °C for 90 min and then at room temperature overnight. The mixture was diluted with saturated aqueous $NaHCO_3$ (10 cm^3) and washed with CH_2Cl_2 (3 × 10 cm^3). The aqueous phase was acidified to pH 4 with 1 mol dm^{-3} aqueous $KHSO_4$ and extracted with EtOAc (4 × 10 cm^3). The combined EtOAc extracts were dried, filtered and evaporated, then subjected to flash chromatography [gradient elution; Et_2O–CH_2Cl_2 (1:4) to Et_2O–CH_2Cl_2 (1:1)] to yield (*R*)-4-(*tert*-butoxycarbonylamino)-2-(3,4-dimethoxybenzyl)butanoic acid **9f** (38.2 mg, 43%) as a colourless oil; $[\alpha]_D^{31}$ +14.5 (*c* 1.2, CH_2Cl_2); ν_{max}(film)/cm^{-1} 3500–2500 (br, O–H), 3375 (N–H) and 1706 (C=O); δ_H(250 MHz, $CDCl_3$) 1.42 (9 H, s, Bu^t), 1.62–1.83 (2 H, m, $CHCH_2CH_2$), 2.60–2.74 (2 H, m, CH_2Ar), 2.92–3.02 (1 H, m, $CHCO_2H$), 3.08–3.22 (1 H, m, CH_2N), 3.84 (6 H, s, 2 × MeO), 4.7 (0.5 H, br s, N–H, one rotamer), 6.1 (0.2 H, br s, N–H, second rotamer), 6.69–6.79 (3 H, m, Ar-H_3) and 7.6 (vbr s, not integrable); *m/z* 353 (M^+, 11%), 297 (23), 235 (11), 151 (69) and 41 (100) (Found: M^+, 353.1839. $C_{18}H_{27}NO_6$ requires *M*, 353.1838).

(*RS*)-2-[2-(*tert*-Butoxycarbonylamino)ethyl]butanedioic acid *rac*-9d

(*RS*)-2-(2-aminoethyl)butanedioic acid[10] *rac*-**1d** (49.2 mg, 0.31 mmol), 1 mol dm^{-3} aqueous NaOH (0.68 cm^3, 0.65 mmol), $(Boc)_2O$ (88.9 mg, 0.40 mmol) and THF (1 cm^3) were stirred together at room temperature for 48 h. The mixture was then diluted with water (1 cm^3) and washed with ether (3 × 1 cm^3). The aqueous extract was acidified to pH 4 using 1 mol dm^{-3} aqueous $KHSO_4$, then extracted with EtOAc (3 × 2 cm^3). Drying and evaporation of the combined EtOAc extracts yielded a colourless oil (71.8 mg) which was recrystallised from EtOAc–petrol to yield *rac*-**9d** (68.5 mg, 86%) as fine white crystals, mp 124 °C; ν_{max}(KBr)/cm^{-1} 3200–2700 (O–H), 1708 (C=O) and 1648 (C=O); δ_H(250 MHz, [$^2H_6$]acetone) 1.41 (9 H, s, Bu^t), 1.64–1.95 (2 H, m, $BocNHCH_2CH_2$), 2.53 (1 H, dd, *J* 17 and 5, ½ × CH_2CO_2H), 2.70 (1 H, dd, *J* 17 and 9, ½ × CH_2CO_2H), 2.80–2.91 (1 H, m, CH_2CHCO_2H) and 3.18 (2 H, t, *J* 7, CH_2NH); *m/z* 261 (M^+, 2%), 188 (25) and 57 (100) (Found: M^+, 261.1214. $C_{11}H_{19}NO_6$ requires *M*, 261.1212).

(*S*)-2-[2-(*tert*-Butoxycarbonylamino)ethyl]butanedioic acid 9d

(*R*)-4-(*tert*-Butoxycarbonylamino)-2-(3,4-dimethoxybenzyl)-butanoic acid **9f** (34.6 mg, 98 μmol), CCl_4 (1 cm^3) and MeCN (1 cm^3) were stirred at room temperature and treated with $NaIO_4$ (0.26 g, 1.49 mmol) in H_2O (1.5 cm^3) followed by $RuCl_3$ (3 mg, 14 μmol). After 100 min the mixture was treated with 10% aqueous Na_2SO_3 (5 cm^3) and 1 mol dm^{-3} aqueous $KHSO_4$ was added to pH 3. The mixture was extracted with EtOAc (4 × 10 cm^3) and the combined organic extracts were washed with aqueous $Na_2S_2O_3$, then dried and evaporated. The residue was redissolved in aqueous $NaHCO_3$ (15 cm^3) before being washed with CH_2Cl_2 (3 × 10 cm^3). The aqueous layer was acidified to pH 3 and extracted with EtOAc (4 × 15 cm^3). Drying and evaporation of the organic extracts gave a yellow oil (10.6 mg) which was subjected to flash chromatography [gradient elution; EtOAc–CH_2Cl_2 (1:1) to EtOAc] to yield (*S*)-2-[2-(tert-*butoxycarbonylamino)ethyl]butanedioic acid* **9d** (6.9 mg, 27%) as a colourless oil; $[\alpha]_D^{32}$ −22 (*c* 0.24, acetone), identified by TLC and ^1H NMR comparisons with the sample of *rac*-**9d** described in the preceding experiment. An impurity (*ca.* 10%) was detectable in the NMR spectrum of the optically active **9d**, δ_H(250 MHz, [$^2H_6$]acetone, integrals relative to Bu^t of **9d** = 9 H) *inter alia* 1.1–1.2 (0.4 H, m) and 1.48 (0.8 H, s, Bu^t?).

(*R*)-2-Ethylbutanedioic acid 10c

A solution of (4*S*,5*R*,2′*R*)-3-[2-(cyanomethyl)butanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one **6c** (0.43 g, 1.5 mmol) was dissolved in THF (6.5 cm^3) and treated with $LiOH{\cdot}H_2O$ (97.8 mg, 2.33 mmol) in water (4 cm^3) at −10 °C for 2.5 h and then at 25 °C for 1 h. Most of the THF was removed by rotary evaporation and the aqueous residue was washed with CH_2Cl_2 (3 × 30 cm^3). The aqueous layer was then acidified to pH 1 with 2 mol dm^{-3} hydrochloric acid and extracted with EtOAc (3 × 30 cm^3). The combined EtOAc extracts were dried and evaporated to give (*R*)-2-ethylbutanedioic acid **10c** as a pale yellow oil (0.16 g, 73% from **6c**), which after crystallisation from ether–petrol was obtained as white crystals; $[\alpha]_D^{28}$ +24 (*c* 1.01 in acetone), [lit.,[9] −24 (*c* 3 in acetone) for (*S*)-2-ethylbutanedioic acid]; ν_{max}(KBr)/cm^{-1} 2500–3600 (O–H), 1703 (C=O) and 1689 (C=O); δ_H(250 MHz, [$^2H_6$]DMSO) 0.96 (3 H, t, *J* 7.5, CH_3), 1.56–1.77 (2 H, m, CH_2), 2.34 (1 H, dd, *J* 15 and 5, 3-H), 2.59 (1 H, dd, *J* 15 and 8, 3-H), 2.72–2.83 (1 H, m, 2-H), 5.9 (1 H, br s, OH) and 6.6 (1 H, br s, OH); *m/z* 128 ($M^+ - H_2O$, 2%), 127 (3), 112 (3), 99 (10) and 59 (100) (Found: $M^+ - H_2O$: 128.0476. Calculated for $C_6H_8O_3$, $M - H_2O$, 128.0473).

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