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A short, versatile chemical synthesis of L- and D-amino acids stereoselectively labelled solely in the *beta* position

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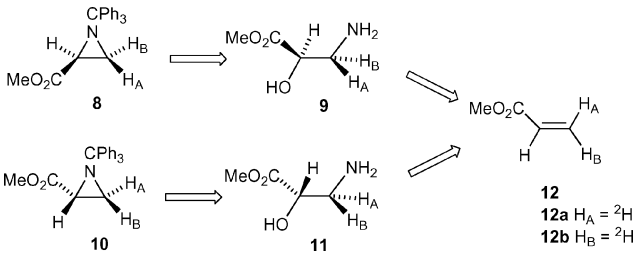
L- and D-Amino acids which are stereoselectively labelled solely either in the 3-*pro*-*R* or in the 3-*pro*-*S*-positions have been prepared by a relatively short chemical synthesis in ee of 81 to 86%. This involves Sharpless' aminohydroxylation and cyclisation with inversion of stereochemistry at C-2 to give the stereoselectively labelled D- and L-aziridines **10a** and **10b**, and **8a** and **8b**. These have previously been modified and cleaved with inversion of stereochemistry at C-3 using a number of nucleophiles to give a large variety of protected amino acids. Synthesis of the labelled D- and L-β-chloroalanines **22a** and **22b** and **25a** and **25b** is described here.

Introduction

Our understanding of the mechanism of action of enzymes which metabolise amino acids has been greatly advanced by elucidation of the stereochemical consequences of these enzymic reactions.[1] In most naturally-occurring amino acids, the β-carbon atom is prochiral and so, to discover the stereochemical consequences of reactions at this centre, stereospecifically labelled substrates and products must be synthesised.[1] We have devised a chemico-enzymatic synthesis which is summarised in part in Scheme 1. This has allowed a large variety of D- and L-amino acids, **5** and **7**, which are stereospecifically labelled at the β-carbon to be prepared.[2,3,4] Compounds prepared in this way were used to study the stereochemistry of some of the many enzyme catalysed reactions of amino acids.[4–8] The synthesis was lengthy, especially for the preparation of the more commonly occurring L-amino acids **7**.[3] Further, it is usual to carry out metabolic studies with epimerically labelled substrates in tandem and so both possible isotopomers at C-3 of the appropriate amino acid are required. Although one isotopomer was always obtained singly labelled at C-3 by our chemico-enzymatic synthesis, the second isotopomer always contained a second label at C-2 because of the symmetrical nature of starting material **1** in the enzymic step (**1** → **2**). While this does not prevent the stereochemical fate of many metabolic reactions being elucidated by a combination of NMR spectroscopy and synthetic studies,[4–8] it has disadvantages when the stereochemical consequences of a reaction need to be derived using kinetic methods. In such cases, isotope effects from the α-label might obscure the effect from the isotope on the β-atom. We now wish to report an entirely chemical route to both D- and L-amino acids which is relatively short and leads to both D- and L-amino acids which are stereoselectively labelled solely on the β-carbon atom.

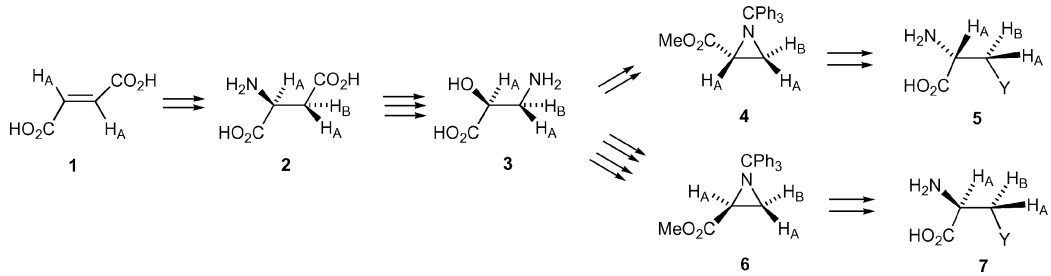
Results and discussion

The utility and versatility of the labelled aziridines **4** and **6** for the preparation of a large variety of stereospecifically labelled D- and L-amino acids **5** and **7** had been amply demonstrated in our earlier chemico-enzymatic synthesis[2,4] and so our aim was to shorten the synthesis of these aziridines and to ensure that they were labelled stereoselectively solely on the β-carbon atom. Our proposed synthesis is shown retrosynthetically in Scheme 2, where the singly labelled isoserine derivatives **9** and **11** (H_A *or* $H_B = {}^2H$) might be prepared by Sharpless aminohydroxylation of methyl (*Z*)- and (*E*)-[3-$^2H_1$]-acrylate, **12a** and **12b** respectively, using an appropriate chiral catalyst.



Scheme 2

Methyl (*Z*)- and (*E*)-[3-$^2H_1$]-acrylate, **12a** and **12b** respectively, were prepared from the corresponding labelled (*Z*)- and (*E*)-[3-$^2H_1$]-acrylic acids **15a** and **15b**,[9] which were prepared in turn from (*Z*) and (*E*)-3-bromoacrylic acids **14a** and **14b**,[10] as shown in Scheme 3. Heating the acids **15a** and **15b** at 75 °C in methanol containing a catalytic quantity of sulfuric acid gave the esters **12a** and **12b** in 46% and 40% yields respectively. The relatively low yields were due in part to polymerisation on distillation and the low boiling point of the esters.



Scheme 1

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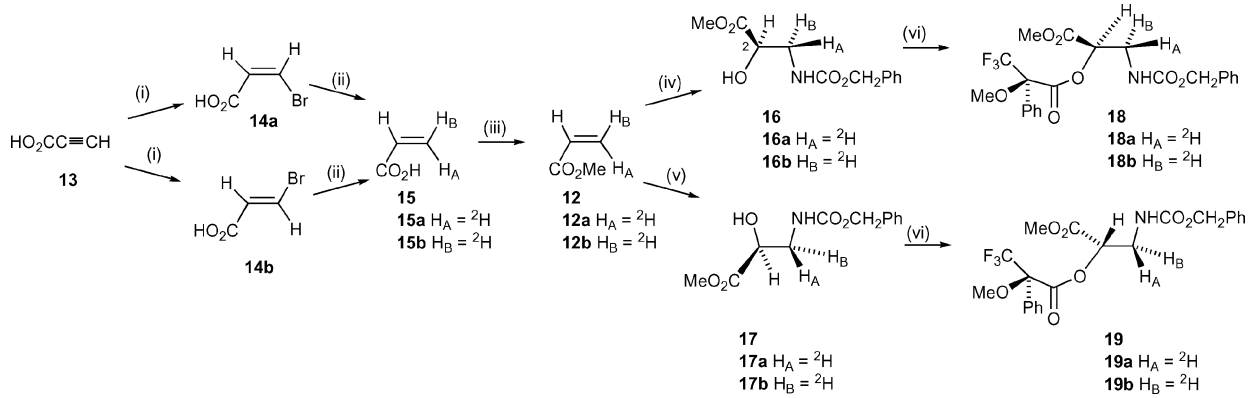
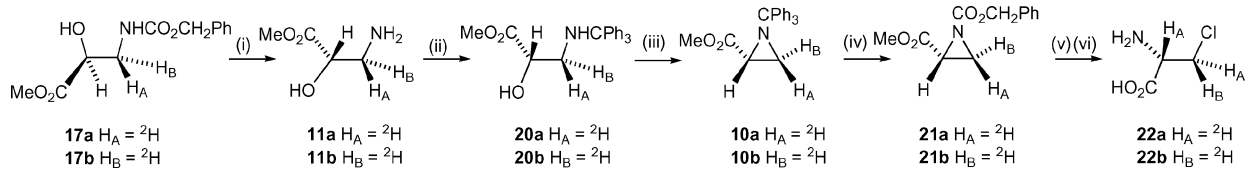


Scheme 3 *Reagents and conditions*: (i) ref. 10 (63% **14a**, 72% **14b**); (ii) ref. 9 (72% **15a**, 75% **15b**); (iii) MeOH/98% H_2SO_4/75 °C, 1.5 h (46% **12a**, 40% **12b**); (iv) (a) $PhCH_2OCONH_2$/NaOH//^{t}BuOCl, (b) **12**/$(DHQ)_2PHAL/K_2OsO_2(OH)_4$/rt, *ca.* 1 h (67% **16**, 82% **16a**, 62% **16b**); (v) (a) $PhCH_2OCONH_2$/NaOH//^{t}BuOCl, (b) **12**/$(DHQD)_2PHAL/K_2OsO_2(OH)_4$/rt, *ca.* 1 h (60% **17**, 81% **17a**, 60% **17b**); (vi) (*R*)-Mosher's acid/CH_2Cl_2/^{i}PrN=C=N^{i}Pr/0 °C, then rt, 60 h (91% **18**, 80% **18a**, 77% **18b**; 94% **19**, 80% **19a**, 85% **19b**).



Scheme 4 *Reagents and conditions*: (i) H_2/10% Pd–C/32% aq HCl/MeOH/rtp, 48 h (quant **11a**, quant **11b**); (ii) $Ph_3CCl/Et_3N/CHCl_3$/0 °C, 4.5 h, then rt, 18 h (61% **20a**, 72% **20b**); (iii) NEt_3/THF/MsCl rt 30 min then reflux 48 h (89% **10a**, 60% **10b**); (iv) (a) TFA/$CHCl_3$ 0 °C, 2.5 h, (b) $ClCO_2CH_2Ph$/EtOAc/aq $NaHCO_3$, 0 °C, then rt, 1.5 h (86% **21a**, 98% **21b**); (v) $TiCl_4/CHCl_3/CH_2Cl_2$ −78 °C, 16 h (80%); (vi) 4 M H_2SO_4 reflux, 3.5 h (57%).

Unlabelled methyl acrylate **12** and the labelled esters **12a** and **12b** were now added in separate experiments together with potassium osmate dihydrate to a solution of freshly prepared BnOCONClNa[11] in acetonitrile–water containing 1,3-phthalazinediyl-bis-dihydroquinine [$(DHQ)_2PHAL$]. The products were those of addition from the 2-*re*-face of methyl acrylate, (2*R*)-, (2*R*,3*R*)-[3-$^2H_1$]- and (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinates, **16**, **16a**, and **16b** respectively. When the aminohydroxylation reaction was repeated on the same substrates, but using 1,3-phthalazinediyl-bis-dihydroquinidine [$(DHQD)_2PHAL$] as the ligand, then the products of addition from the 2-*si*-face of the acrylate, (2*S*)-, (2*S*,3*S*)-[3-$^2H_1$]- and (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinates, **17**, **17a** and **17b** respectively, were obtained. The specific rotations of these compounds (Table 1) suggested that the reactions were stereoselective and conversion into the esters **18**, **18a** and **18b**, and **19**, **19a** and **19b** of (*R*)-Mosher's acid allowed the enantiomeric excess (ee) for each product to be determined using ^{19}F NMR spectroscopy. In the ^{19}F NMR spectra of the (2*R*)-esters, **18**, **18a** and **18b**, the major signal was at −71.7 ppm and the minor signal was at −72.2 ppm from $CFCl_3$, whilst in the ^{19}F NMR spectra of the (2*S*)-isomers **19**, **19a** and **19b**, the −71.7 ppm signal was the minor signal and −72.2 ppm was the major signal. The ee for each reaction is also shown in Table 1. Values of ee for the six reactions were reasonably consistent, being between 81 and 86%.

Table 1 Yields, specific rotations and ee[a] of the compounds **16** and **17**

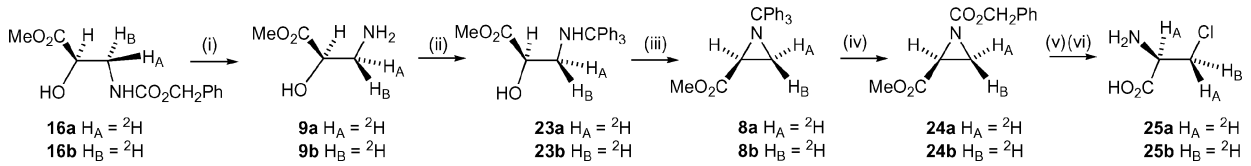
Compound	Yield	$[\alpha]_D$	Ee[a]
(2*R*) **16**	67%	−17.7	81%
(2*R*,3*R*)-[3-$^2H_1$] **16a**	82%	−15.6	85%
(2*R*,3*S*)-[3-$^2H_1$] **16b**	62%	−15.7	83%
(2*S*) **17**	60%	+18.2	86%
(2*S*,3*S*)-[3-$^2H_1$] **17a**	81%	+12.5	84%
(2*S*,3*R*)-[3-$^2H_1$] **17b**	60%	+12.2	85%

[a] Ee derived from ^{19}F NMR spectrum of Mosher's esters **18** and **19**.

Synthesis of the labelled D-aziridines **10** was now completed as shown in Scheme 4 by first hydrogenolysing the (2*S*)-urethane-esters **17a** and **17b** using hydrogen and 10% palladium on charcoal in aqueous, methanolic hydrochloric acid to obtain the methyl isoserinate hydrochlorides **11a** and **11b** in excellent yields. These were then converted into the corresponding *N*-trityl derivatives **20a** and **20b** using trityl chloride and triethylamine at 0 °C. Cyclisation using mesyl chloride and triethylamine at reflux then occurred with inversion of stereochemistry at C-2 to give the (2*R*)-aziridines **10a** and **10b** with ^1H-NMR spectra (Figs. 1d and 1e) in keeping with expectation from the spectra of the products from our chemico-enzymatic synthesis[2] (Figs. 1b and 1c). Since we had already shown that these steps occurred with one inversion and no loss of stereochemical integrity in our chemico-enzymatic synthesis,[2] the aziridines could be assumed to have the same values for ee as the protected isoserines **16**. The specific rotations confirmed the absolute stereochemistry of the labelled aziridines **10**. Although the chemico-enzymatic synthesis is evidently more stereoselective, the products **10a** and **10b** are suitable for metabolic studies where the (2*S*)-enantiomer is not turned over by the enzyme (see following paper).

Synthesis of the labelled L-aziridines **8** is outlined in Scheme 5. This involved the (2*R*)-isoserine derivatives **16a** and **16b** and used the same chemistry as for the synthesis of the D-aziridines. Fig. 2 shows a comparison of the ^1H NMR spectra of the products (Figs. 2d and 2e) with the products of the chemico-enzymatic synthesis[3] (Figs. 2b and 2c). This, with the specific rotations, again confirmed the absolute stereochemistry of the label.

Having improved the synthesis of the singly labelled (2*R*)- and (2*S*)-*N*-tritylaziridine methyl esters, their conversion into a large variety of appropriately labelled D- and L-amino acids by removal of the trityl group and replacement with a more electron-withdrawing group on nitrogen follows from our previous studies.[2,4] When this group is urethane, then reaction with halogen, sulfur and oxygen nucleophiles occurs with inversion of stereochemistry to give the protected labelled amino acids.[2] For reaction with carbon nucleophiles, a sulfonamide is required on nitrogen.[4] The esters **10a/b** and **8a/b** were converted into the corresponding samples of β-chloroalanine **22a/b** and **25a/b**



16a $H_A = {}^2H$ **16b** $H_B = {}^2H$ **9a** $H_A = {}^2H$ **9b** $H_B = {}^2H$ **23a** $H_A = {}^2H$ **23b** $H_B = {}^2H$ **8a** $H_A = {}^2H$ **8b** $H_B = {}^2H$ **24a** $H_A = {}^2H$ **24b** $H_B = {}^2H$ **25a** $H_A = {}^2H$ **25b** $H_B = {}^2H$

Scheme 5 *Reagents and conditions*: (i) H_2/10% Pd–C/32% aq HCl/MeOH/rtp 48 h (quant **9a**, quant **9b**); (ii) $Ph_3CCl/Et_3N/CHCl_3$/0 °C 4.5 h then rt 18 h (65% **23a**, 57% **23b**); (iii) NEt_3/THF/MsCl rt 30 min then reflux 48 h (76% **8a**, 61% **8b**); (iv) (a) TFA/$CHCl_3$ 0 °C, 2.5 h, (b) $ClCO_2CH_2Ph$/EtOAc/aq $NaHCO_3$, 0 °C, then rt, 1.5 h (95% **24a**, 92% **24b**); (v) $TiCl_4/CHCl_3/CH_2Cl_2$ −78 °C, 16 h (76%); (vi) 4 M H_2SO_4 reflux, 3.5 h (55%).

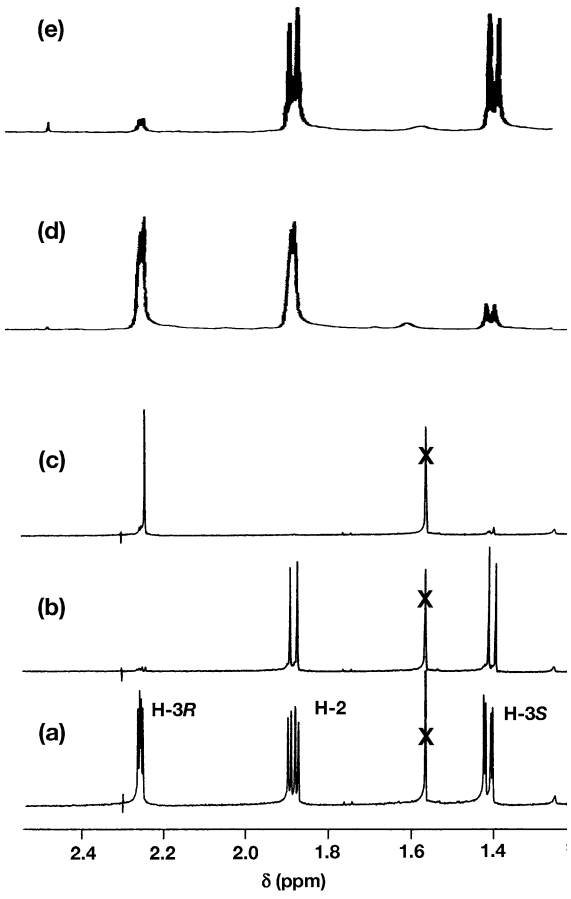


Fig. 1 Part of the ^1H NMR spectra in C^2HCl_3 of (a) methyl (2*R*)-*N*-tritylaziridine-2-carboxylate **4**; (b) methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-tritylaziridine-2-carboxylate **4** ($H_B = {}^2H$) from the chemico-enzymatic synthesis;[2] (c) methyl (2*R*,3*S*)-[2,3-$^2H_2$]-*N*-tritylaziridine-2-carboxylate **4** ($H_A = {}^2H$) from the chemico-enzymatic synthesis;[2] (d) methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-tritylaziridine-2-carboxylate **10a** from the chemical synthesis; (e) methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-tritylaziridine-2-carboxylate **10b** from the chemical synthesis.

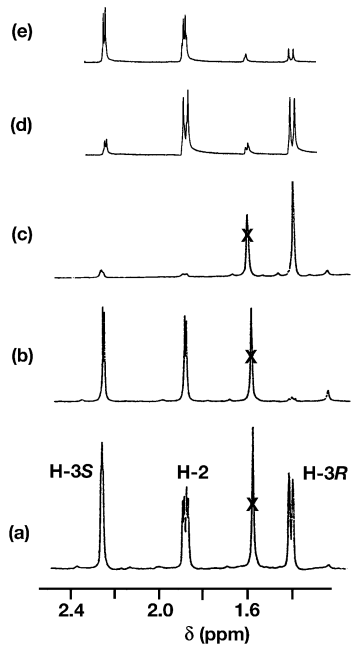


Fig. 2 Part of the ^1H NMR spectra in C^2HCl_3 of (a) methyl (2*S*)-*N*-tritylaziridine-2-carboxylate **6**; (b) methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-tritylaziridine-2-carboxylate **6** ($H_B = {}^2H$) from the chemico-enzymatic synthesis;[3] (c) methyl (2*S*,3*S*)-[2,3-$^2H_2$]-*N*-tritylaziridine-2-carboxylate **6** ($H_A = {}^2H$) from the chemico-enzymatic synthesis;[3] (d) methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-tritylaziridine-2-carboxylate **8a** from the chemical synthesis; (e) methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-tritylaziridine-2-carboxylate **8b** from the chemical synthesis.

by the methods previously used in our chemico-enzymatic synthesis.[2] This is shown in Schemes 4 and 5 and described in the experimental section. The ^1H NMR spectra of the products are shown in Figs. 3 and 4.

Conclusion

We have completed a general synthesis of D- and L-amino acids stereoselectively labelled with one deuterium label on the β-carbon atom. Although the synthesis is less stereoselective than our chemico-enzymatic synthesis, it is much shorter and, since the metabolic reactions which will be studied are stereospecific for C-2, labelled amino acids prepared in this way should serve as substrates with which to assess the stereoselectivity of a large variety of enzymic reactions. This is exemplified in the work reported in the following publication. The fact that all four enantiotopically labelled substrates contain but a single label is a distinct advantage over the previous synthesis, as kinetic methods may be more easily used to probe stereochemical aspects of the mechanism of enzyme catalysed reactions.

Experimental

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Optical rotations (in units of 10^{-1} deg cm^2 g^{-1}) were measured using a Perkin Elmer PE241 polarimeter with a 1 dm path length cell. IR spectra were recorded using a Perkin Elmer 1710 Fourier transform spectrometer. ^1H-NMR spectra and ^1H-decoupled-^{13}C-NMR spectra were recorded using a Bruker DPX 300 (300 MHz for ^1H, 75.5 MHz for ^{13}C) Fourier transform instrument. Residual undeuteriated solvent peaks and tetramethylsilane (TMS) were used as internal references for these spectra. ^{19}F spectra were recorded using a Bruker AMX 500 Fourier transform instrument (376.4 MHz) with $CFCl_3$ as internal standard. DEPT, ^1H COSY and ^1H-^{13}C COSY experiments were used to help assignment of NMR spectra where required. Homonuclear decoupling experiments were used to aid the determination of stereochemistry where necessary. NMR chemical shifts are given in ppm and coupling constants (*J*) in Hz. All NMR spectra were recorded at 25 °C. Mass spectra were obtained by Dr A. Abdul-Sada; low resolution using Kratos MS 80RF (FAB), VG Autospec (EI) or Bruker BioApex III (ESI) double focussing spectrometers; high-resolution using a 4.7 FT-IRC (Bruker BioApex III) spectrometer. Column chromatography was performed using

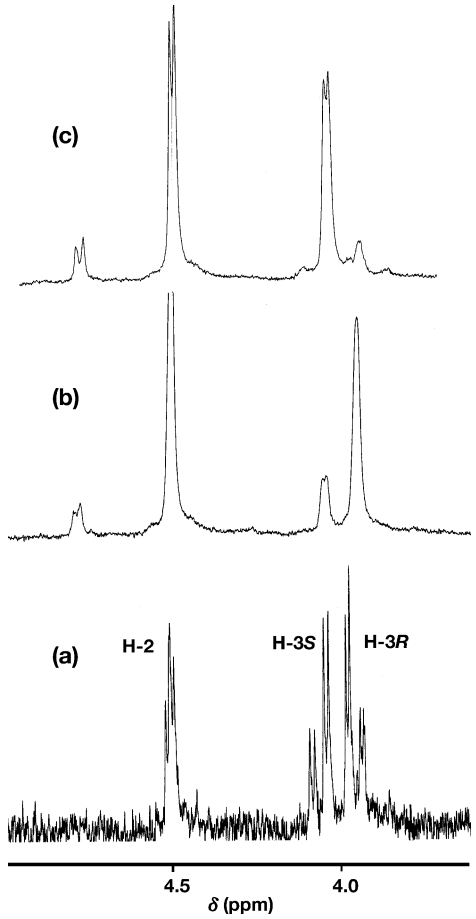


Fig. 3 ^{1}H NMR spectrum in 10% ^{2}HCl/^{2}H$_2$O of (a) (2*S*)-β-chloroalanine; (b) (2*S*,3*S*)-[3-^{2}H$_1$]-β-chloroalanine **22b**; and (c) (2*S*,3*R*)-[3-^{2}H$_1$]-β-chloroalanine **22a**.

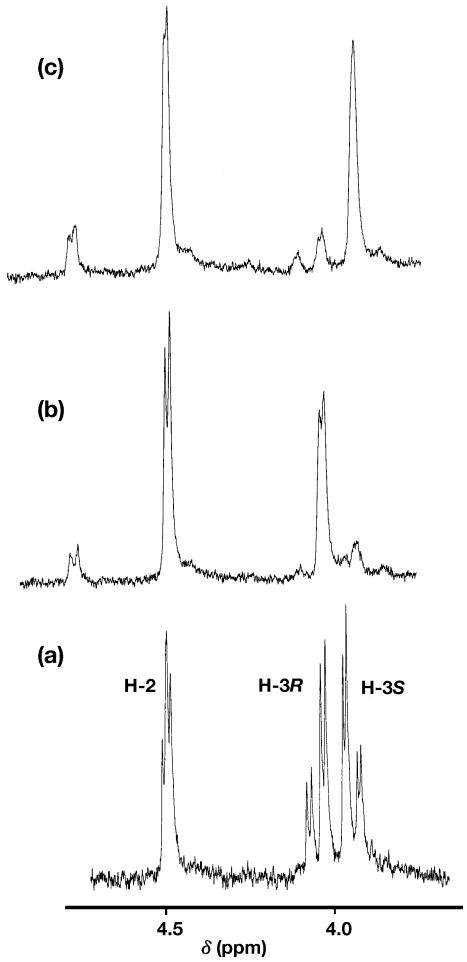


Fig. 4 ^{1}H NMR spectrum in 10% ^{2}HCl/^{2}H$_2$O of (a) (2*R*)-β-chloroalanine; (b) (2*R*,3*S*)-[3-^{2}H$_1$]-β-chloroalanine **25a**; and (c) (2*R*,3*R*)-[3-^{2}H$_1$]-β-chloroalanine **25b**.

Davisil® Silica 60A, 35–70 mesh silica gel. Petroleum ether refers to that fraction of hexanes of boiling point 60–80 °C.

Methyl (*Z*)-[3-^{2}H$_1$]-acrylate (12a)

A solution of a mixture containing (*Z*)-[3-^{2}H$_1$]-acrylic acid **15a**,[9] a little over-reduced material, and some diethyl ether (3.48 g, 47.7 mmol) in methanol (1.98 g, 2.51 ml, 62.0 mmol) and 98% sulfuric acid (90 mg, 0.9 mmol) was heated to an oil bath temperature of 75 °C for 1.5 h and the mixture was left to cool. The resulting light yellow solution was purified by fractional distillation at atmospheric pressure using a 30 cm fractional distillation column. The product methyl (*Z*)-[3-^{2}H$_1$]-acrylate **12a** (1.91 g, 46%) was collected at 70–80 °C as clear liquid containing some diethyl ether, methanol and over-reduced product; *m*/*z* [EI+] 88 [M + H]$^{+}$; δ_H (300 MHz, C^{2}HCl$_3$) 6.12 (1H, m, H-2), 5.81 (1H, d, $J_{3,2}$ 10.5, H-3), 3.78 (3H, s, OCH$_3$), 3.67 (over-reduced product), 2.31 (over-reduced product) and 1.09 (over-reduced product). Due to the volatility of the product, it was used immediately in the next step without further characterisation. The ^{1}H NMR spectrum was in keeping with that of the commercially available unlabelled methyl acrylate; δ_H (300 MHz, C^{2}HCl$_3$) 6.42 (1H, d, $J_{3,2}$ 17.3, H-3*E*), 6.13 (1H, 2 × d, $J_{2,3E}$ 17.3, $J_{2,3Z}$ 10.4, H-2), 5.84 (1H, d, $J_{3,2}$ 10.4, H-3*Z*) and 3.77 (3H, s, OCH$_3$).

Methyl (*E*)-[3-^{2}H$_1$]-acrylate (12b)

This was prepared by the method described previously using (*E*)-[3-^{2}H$_1$]-acrylic acid **15b**[9] (14.50 g, 0.20 mol), methanol (8.26 g, 0.26 mol) and 98% sulfuric acid (390 mg, 4 mmol). The product methyl (*E*)-[3-^{2}H$_1$]-acrylate **12b** (6.89 g, 40%) was obtained as a clear liquid, containing diethyl ether, methanol and the over-reduced product; *m*/*z* [EI+] 88 [M + H]$^{+}$; δ_H (300 MHz, C^{2}HCl$_3$) 6.40 (0.9H, d, $J_{3Z,2}$ 17.4, H-3), 6.13 (1H, d, $J_{2,3Z}$ 17.4, H-2), 5.83 (0.1H, d, *J* 10.2, H-3 of (*Z*)-isomer), 3.77 (3H, s, CH$_3$), 3.66 (over-reduced product) and 2.29 (over-reduced product). Due to the volatility of the product, it was used immediately in the next step without further characterisation.

Methyl (2*R*)-*N*-benzyloxycarbonylisoserinate (16)

A solution of sodium hydroxide (122 mg, 3.05 mmol) in water (5 ml), followed by freshly prepared[12] *tert*-butyl hypochlorite (331 mg, 3.05 mmol) were added to a solution of benzyl carbamate (486 mg, 3.1 mmol) in acetonitrile (4 ml). A solution of (DHQ)$_2$PHAL (40 mg, 0.05 mmol) in acetonitrile (3.5 ml) and water (2.5 ml) was added and the mixture was stirred for 5 min at room temperature. Methyl acrylate **12** (86 mg, 1 mmol) was added, followed by potassium osmate dihydrate (15 mg, 0.04 mmol). The mixture turned dark purple and gradually became lighter. Stirring was continued at room temperature until TLC indicated that the reaction was complete (*ca.* 50 min on this scale). Ethyl acetate (7 ml) was added and the layers were separated. The aqueous layer was washed with ethyl acetate (3 × 10 ml). The combined organic layers were washed with brine (10 ml) and water (10 ml), and dried (MgSO$_4$). The solvent was removed under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel using petroleum ether–ethyl acetate (4 : 1) as eluent. The solvent was removed from the fractions determined to be homogeneous by TLC to yield methyl (2*R*)-*N*-benzyloxycarbonylisoserinate **16** as an orange oil (170 mg, 67%); $[\alpha]_D^{29}$ −17.7 (*c* 1.42, MeOH) (lit[13] $[\alpha]_D^{23}$ +18.8 (*c* 1.42, MeOH) for (2*S*)-enantiomer); *m*/*z* (ES+) Found 276.0831, [C$_{12}$H$_{15}$NO$_5$ + Na]$^{+}$ requires 276.0842; ν_{max} (film)/cm^{-1} 3369 (OH) and 1724 (br, ester + urethane); δ_H (300 MHz,

C^2HCl_3) 7.32 (5H, br s, ArH), 5.10 (2H, s, OCH_2Ph), 4.28 (1H, br s, H-2), 3.78 (3H, s, OCH_3) and 3.57 (2H, unresolved *ABX*, H-3); δ_C (75.5 MHz, C^2HCl_3) 173.4 (ester), 157.0 (urethane), 136.6–128.5 (Ar), 70.429 (C-2), 67.4 (OCH_2Ph), 53.3 (OCH_3) and 44.6 (C-3).

Methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate (16a)

This was prepared by the method described above using freshly prepared impure methyl (*Z*)-[3-$^2H_1$]-acrylate **12a** (2.98 g, 34 mmol), and $(DHQ)_2PHAL$ (1.33 g, 1.7 mmol) as the ligand. The product, methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **16a** (7.10 g, 82%) was obtained as an orange oil; $[\alpha]_D^{27}$ −15.62 (*c* 1.42, MeOH); *m/z* (ES+) Found 277.0906, $[C_{12}H_{14}NO_5{}^2H + Na]^+$ requires 277.0905; ν_{max} (film)/cm^{-1} 3370 (OH) and 1720 (br, ester + urethane); δ_H (300 MHz, C^2HCl_3) 7.33 (5H, br s, ArH), 5.08 (2H, s, OCH_2Ph), 4.28 (1H, br s, H-2), 3.75 (3H, s, OCH_3) and 3.56 (1H, br s, H-3*S*); δ_C (75.5 MHz, C^2HCl_3) 173.8 (ester), 157.1 (urethane), 136.7–128.49 (Ar), 70.4 (C-2), 67.4 (OCH_2Ph), 53.2 (OCH_3) and 44.3 (t, $J_{C,D}$ 21, C-3).

Methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate (16b)

This was prepared by the method described above using freshly prepared impure methyl (*E*)-[3-$^2H_1$]-acrylate **12b** (6.89 g, 79 mmol) and $(DHQ)_2PHAL$ (3.08 g, 4 mmol) as the ligand. The product methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **16b** (12.45 g, 62%) was obtained as an orange oil; $[\alpha]_D^{35}$ −15.76 (*c* 1.42, MeOH); *m/z* (ES+) Found 277.0907, $[C_{12}H_{14}NO_5{}^2H + Na]^+$ requires 277.0905; ν_{max} (film)/cm^{-1} 3367 (OH) and 1724 (br, ester + urethane); δ_H (300 MHz, C^2HCl_3) 7.33 (5H, s, ArH), 5.09 (2H, s, OCH_2Ph), 4.28 (1H, br s, H-2), 3.76 (3H, s, OCH_3) and 3.51 (1H, d, $J_{3R,2}$ 5.0, H-3*R*); δ_C (75.5 MHz, C^2HCl_3) 173.82 (ester), 157.1 (urethane), 136.7–128.5 (Ar), 70.4 (C-2), 67.4 (OCH_2Ph), 53.2 (OCH_3) and 44.3 (t, $J_{C,D}$ 20, C-3).

Methyl (2*S*)-*N*-benzyloxycarbonylisoserinate (17)

This was prepared by the method described above using methyl acrylate **12** (86 mg, 1 mmol) and $(DHQD)_2PHAL$ (40 mg, 0.05 mmol). The product, methyl (2*S*)-*N*-benzyloxycarbonylisoserinate **17** (153 mg, 60%) was obtained as an orange oil; $[\alpha]_D^{30}$ +18.2 (*c* 1.42, MeOH) (lit[13] $[\alpha]_D^{23}$ +18.8 (*c* 1.42, MeOH); *m/z* (ES+) Found 276.0839, $[C_{12}H_{15}NO_5 + Na]^+$ requires 276.0842; ν_{max} (film)/cm^{-1} 3369 (OH) and 1724 (br, ester + urethane); δ_H (300 MHz, C^2HCl_3) 7.33 (5H, br s, ArH), 5.08 (2H, s, OCH_2Ph), 4.28 (1H, t, $J_{2,3}$ 4.5, H-2), 3.75 (3H, s, OCH_3) and 3.55 (2H, unresolved *ABX*, H-3); δ_C (75.5 MHz, C^2HCl_3) 173.8 (ester), 157.1 (urethane), 136.7–128.5 (Ar), 70.5 (C-2), 67.4 (OCH_2Ph), 53.2 (OCH_3) and 44.6 (C-3).

Methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate (17a)

This was prepared by the method described previously using freshly prepared impure methyl (*Z*)-[3-$^2H_1$]-acrylate **12a** (2.48 g, 290 mmol) and $(DHQD)_2PHAL$ (1.11 g, 1.4 mmol) as the ligand. The product, methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **17a** (5.90 g, 81%) was obtained as an orange oil; $[\alpha]_D^{30}$ +12.5 (*c* 1.42, MeOH); *m/z* (ES+) Found 277.08945, $[C_{12}H_{14}NO_5{}^2H + Na]^+$ requires 277.09052; ν_{max} (film)/cm^{-1} 3372 (OH) and 1723 (br, ester + urethane); δ_H (300 MHz, C^2HCl_3) 7.31 (5H, s, ArH), 5.05 (2H, s, OCH_2Ph), 4.27 (1H, br s, H-2), 3.70 (3H, s, OCH_3) and 3.52 (1H, br s, H-3*R*); δ_C (75.5 MHz, C^2HCl_3) 173.8 (ester), 157.2 (urethane), 136.7–128.5 (Ar), 70.4 (C-2), 67.3 (OCH_2Ph), 53.1 (OCH_3) and 44.3 (t, $J_{C,D}$ 21, C-3).

Methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate (17b)

This was prepared by the method described above using freshly prepared impure methyl (*E*)-[3-$^2H_1$]-acrylate **12b** (4.62 g, 53 mmol) and $(DHQD)_2PHAL$ (2.07 g, 2.7 mmol) as the ligand. The product, methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **17b** (8.05 g, 60%) was obtained as an orange oil; $[\alpha]_D^{27}$ +12.20 (*c* 1.42, MeOH); *m/z* (ES+) Found 277.08999, $[C_{12}H_{14}NO_5{}^2H + Na]^+$ requires 277.09052; ν_{max} (film)/cm^{-1} 3373 (OH) and 1720 (br, ester + urethane); δ_H (300 MHz, C^2HCl_3) 7.31 (5H, s, ArH), 5.06 (2H, s, OCH_2Ph), 4.27 (1H, d, $J_{2,3S}$ 5.3, H-2), 3.71 (3H, s, OCH_3) and 3.48 (1H, t, $J_{3S,2}$ 5.3, H-3*S*); δ_C (75.5 MHz, C^2HCl_3) 173.8 (ester), 157.2 (urethane), 136.7–128.5 (Ar), 70.4 (C-2), 67.3 (OCH_2Ph), 53.1 (OCH_3) and 44.4 (t, $J_{C,D}$ 21, C-3).

Mosher's ester (18) of methyl (2*R*)-*N*-benzyloxycarbonylisoserinate

(*R*)-α-Methoxy-α-(trifluoromethyl)-phenylacetic acid (930 mg, 0.4 mmol), DMAP (24 mg, 0.2 mmol) and 1,3-diisopropylcarbodiimide (50 mg, 0.06 ml, 0.4 mmol) were added to a solution of methyl (2*R*)-*N*-benzyloxycarbonylisoserinate **16** (50 mg, 0.2 mmol) in dichloromethane (0.5 ml) at 0 °C. The mixture was left to warm to room temperature, and stirred for 60 h. Addition of diethyl ether (5 ml) gave a white precipitate which was removed by filtration and washed with diethyl ether (10 ml). The ether layer was washed with saturated aqueous ammonium chloride (5 ml). The two phases were separated and the aqueous phase was extracted with diethyl ether (3 × 5 ml). The combined ether layers were washed with saturated aqueous ammonium chloride (5 ml), water (5 ml) and brine (5 ml). The solution was filtered and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography on silica gel using petroleum ether–ethyl acetate (4 : 1) as eluent. The solvent was removed from the fractions determined to be homogeneous by TLC to give the product **18** (84 mg, 91%) as a clear oil; $[\alpha]_D^{28}$ +23.82 (*c* 1, $CHCl_3$); *m/z* (ES+) Found 492.1218, $[C_{22}H_{22}NO_7F_3 + Na]^+$ requires 492.1240; ν_{max} (film)/cm^{-1} 3350 (OH), 1755 (ester) and 1732 (ester); δ_H (300 MHz, C^2HCl_3) 7.79 (2H, d, *J* 8, ArH), 7.17–7.02 (8H, m, ArH), 5.12 (1H, dd, $J_{2,3R}$ 6.3, $J_{2,3S}$ 4.5, H-2), 4.96 and 4.92 (2H, AB, J_{AB} 12.3, OCH_2Ph), 4.25 (1H, br, NH), 3.61 (3H, d, $J_{H,F}$ 1.2, OCH_3), 3.21 (3H, s, OCH_3) and 3.17 (2H, m, H-3), [signals at 3.47 (OCH_3) and 3.38 (m, H-3) were present for *ca.* 14% of the (2*S*)-diastereoisomer]; δ_C (75.5, C^2HCl_3) 167.7 (ester), 166.3 (ester), 156.0 (urethane), 129.9–128.2 (Ar), 85.11 (q, $J_{C,F}$ 28.2, CF_3) 73.0 (C-2), 66.9 (OCH_2Ph), 55.8 (OCH_3), 52.2 (OCH_3) and 41.4 (C-3); δ_F (376.4 MHz, C^2HCl_3) −72.2 [0.28F, s, (2*S*)-isomer] and −71.7 [2.72F, s, (2*R*)-isomer].

Mosher's ester (18a) of methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate

This was prepared by the method described above using methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **16a** (50 mg, 0.2 mmol). The product **18a** (75 mg, 80%) was obtained as a clear oil; $[\alpha]_D^{32}$ +30.72 (*c* 1, $CHCl_3$); *m/z* [ES+] Found 493.1293, $[C_{22}H_{21}NO_7F_3{}^2H + Na]^+$ requires 493.1303; ν_{max} 3349 (film)/cm^{-1} (OH), 1755 (ester) and 1732 (ester); δ_H (300 MHz, C^2HCl_3) 7.79 (2H, d, *J* 8, ArH), 7.17–7.01 (8H, m, ArH), 5.14 (1H, d, $J_{2,3}$ 4.1, H-2), 4.96 and 4.92 (2H, AB, J_{AB} 12.4, OCH_2Ph), 4.42 (1H, d, *J* 6.2, NH), 3.61 (3H, d, $J_{H,F}$ 1.0, OCH_3), 3.23 (3H, s, OCH_3) and 3.19 (1H, d, $J_{3S,2}$ 4.1, H-3*S*), a signal was present at 3.39 for OCH_3 of the (2*S*)-isomer; δ_C (75.5 MHz, C^2HCl_3) 167.8 (ester), 166.3 (ester), 156.0 (urethane), 129.9–127.5 (Ar), 85.1 (q, $J_{C,F}$ 27.8, CF_3), 72.9 (C-2), 66.9 (OCH_2Ph), 55.8 (OCH_3), 52.3 (OCH_3) and 41.2 (t, $J_{C,D}$ 22, C-3); δ_F (376.4 MHz, C^2HCl_3) −72.2 [0.225F, s, (2*S*)-isomers] and −71.7 [2.775F, s, (2*R*)-isomers].

Mosher's ester (18b) of methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate

This was prepared by the method described above using methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **16b** (50 mg, 0.2 mmol). The product **18b** (72 mg, 77%) was obtained as a

clear oil; $[\alpha]_D^{32}$ +34.41 (*c* 1, $CHCl_3$); *m/z* [ES+] Found 493.1351, $[C_{22}H_{21}NO_7F_3{}^2H + Na]^+$ requires 493.1303; ν_{max} (film)/cm^{-1} 3352 (OH), 1754 (ester) and 1725 (ester); δ_H (300 MHz, C^2HCl_3) 7.79 (2H, d, *J* 8, ArH), 7.17–7.01 (8H, m, ArH), 5.13 (1H, d, $J_{2,3}$ 6.4, H-2), 4.93 (2H, 2 × d, $J_{A,B}$ 12.4, OCH_2Ph), 3.61 (3H, d, $J_{H,F}$ 0.9, OCH_3), 4.36 (1H, d, *J* 6.7, NH), 3.22 (3H, s, CO_2CH_3) and 3.15 (2H, d, $J_{3R,2}$ 6.4, H-3*R*), a signal was present at 3.39 for OCH_3 of the (2*S*)-isomer; δ_C (75.5 MHz, C^2HCl_3) 167.8 (ester), 166.3 (ester), 156.0 (urethane), 129.9–127.8 (Ar), 85.1 (q, $J_{C,F}$ 27.7, CF_3), 72.9 (C-2), 66.9 (OCH_2Ph), 55.8 (OCH_3), 52.3 (OCH_3) and 41.2 (t, $J_{C,D}$ 22, C-3); δ_F (376.4 MHz, C^2HCl_3) −72.2 [0.26F, s, (2*S*)-isomers] and −71.7 [2.74F, s, (2*R*)-isomers].

Mosher's ester (19) of methyl (2*S*)-*N*-benzyloxycarbonylisoserinate

This was prepared by the method described above using methyl (2*S*)-*N*-benzyloxycarbonylisoserinate **17** (50 mg, 0.2 mmol). The product **19** (88 mg, 94%) was obtained as a clear oil; $[\alpha]_D^{25}$ +8.13 (*c* 1, $CHCl_3$); *m/z* [ES+] Found 492.1217, $[C_{22}H_{22}NO_7F_3 + Na]^+$ requires 492.1240; ν_{max} (film)/cm^{-1} 3345 (OH), 1755 (ester) and 1732 (ester); δ_H (300 MHz, C^2HCl_3) 7.79 (2H, d, *J* 8, ArH), 7.17–7.02 (8H, m, ArH), 5.12 (1H, m, H-2), 4.97 and 4.93 (2H, AB, J_{AB} 12.2, OCH_2Ph), 4.50 (1H, br t, NH), 3.60 (0.3H, s, other isomer OCH_3), 3.39 (3H, d, $J_{H,F}$ 1.1, OCH_3), 3.29 (2H, m, H-3) and 3.19 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 167.6 (ester), 166.1 (ester), 156.1 (urethane), 129.8–127.9 (Ar), 85.3 (q, $J_{C,F}$ 28.2, CF_3), 72.9 (C-2), 66.9 (OCH_2Ph), 55.5 (OCH_3), 52.1 (OCH_3) and 41.4 (C-3); δ_F (376.4 MHz, C^2HCl_3) −72.2 [2.79F, s, (2*S*)-isomer] and −71.7 [0.21F, s, (2*R*)-isomer].

Mosher's ester (19a) of methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate

This was prepared by the method described above using methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **17a** (50 mg, 0.2 mmol). The product **19a** (76 mg, 80%) was obtained as a clear oil; $[\alpha]_D^{32}$ +13.32 (*c* 1, $CHCl_3$); *m/z* [ES+] Found 493.1289, $[C_{22}H_{21}NO_7F_3{}^2H + Na]^+$ requires 493.1303; ν_{max} (film)/cm^{-1} 3346 (OH), 1754 (ester) and 1727 (ester); δ_H (300 MHz, C^2HCl_3) 7.79 (2H, d, *J* 8, Ar), 7.16–7.02 (8H, m, ArH), 5.12 (1H, d, $J_{2,3S}$ 4.2, H-2), 4.96 and 4.92 (2H, AB, J_{AB} 12.3, OCH_2Ph), 4.5 (1H, d, *J* 5.6, NH), 3.39 (3H, d, $J_{H,F}$ 1.0, OCH_3), 3.29 (1H, br s, H-3*R*) and 3.20 (3H, s, OCH_3), a signal was present at 3.60 for OCH_3 of the (2*R*)-isomer; δ_C (75.5 MHz, C^2HCl_3) 167.6 (ester), 166.3 (ester), 156.1 (urethane), 129.9–127.4 (Ar), 85.3 (q, $J_{C,F}$ 27.3, CF_3), 72.9 (C-2), 66.9 (OCH_2Ph), 55.5 (OCH_3), 52.2 (OCH_3) and 41.2 (t, $J_{C,D}$ 21, C-3); δ_F (376.4 MHz, C^2HCl_3) −72.2 [2.75F, s, (2*S*)-isomers] and −71.7 [0.25F, s, (2*R*)-isomers].

Mosher's ester (19b) of methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate

This was prepared by the method described above using (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **17b** (50 mg, 0.2 mmol). The product **19b** (80 mg, 85%) was obtained as a clear oil; $[\alpha]_D^{32}$ +14.55 (*c* 1, $CHCl_3$); *m/z* [ES+] Found 493.1298, $[C_{22}H_{21}NO_7F_3{}^2H + Na]^+$ requires 493.1303; ν_{max} (film)/cm^{-1} 3351 (OH), 1753 (ester) and 1725 (ester); δ_H (300 MHz, C^2HCl_3) 7.79 (2H, d, *J* 8, Ar), 7.16–7.03 (8H, m, ArH), 5.13 (1H, d, $J_{2,3S}$ 6.5, H-2), 4.97 and 4.93 (2H, AB, J_{AB} 13.8, OCH_2Ph), 4.57 (1H, d, *J* 6.5, NH), 3.39 (3H, d, $J_{H,F}$ 1.0, OCH_3), 3.28 (1H, d, $J_{3S,2}$ 6.5, H-3*S*) and 3.20 (3H, s, OCH_3), a signal was present at 3.60 for OCH_3 of the (2*R*)-isomer; δ_C (75.5 MHz, C^2HCl_3) 167.6 (ester), 166.1 (ester), 156.1 (urethane), 128.6–127.4 (Ar), 85.3 (q, $J_{C,F}$ 27.8, CF_3), 72.9 (C-2), 66.9 (OCH_2Ph), 55.5 (OCH_3), 52.1 (OCH_3) and 41.2 (t, $J_{C,D}$ 21, C-3); δ_F (376.4 MHz, C^2HCl_3) −72.2 [2.275F, s, (2*S*)-isomers] and −71.7 [0.025F, s, (2*R*)-isomers].

Methyl (2*R*,3*R*)-[3-$^2H_1$]-isoserinate hydrochloride (9a)

A mixture of methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl isoserinate **16a** (9 g, 35 mmol), 10% palladium on activated charcoal (3.75 g) and 32% aqueous hydrochloric acid (1.41 g) in methanol (100 ml) was stirred vigorously under hydrogen at room temperature and pressure for 48 h. The solution was filtered through a pad of Celite® and washed with methanol (100 ml). The solvent was removed under reduced pressure to give a yellow oil. Trituration with diethyl ether yielded methyl (2*R*,3*R*)-[3-$^2H_1$]-isoserinate hydrochloride **9a** (5.54 g, quant.) as a white solid; mp 99–101 °C [lit[3] 104–105 °C]; $[\alpha]_D^{29}$ +12.88 (*c* 1, H_2O) [lit[3] $[\alpha]_D^{23}$ +18.9 (*c* 1, H_2O)]; *m/z* [ES+] Found 241.1372, $[2 \times C_4H_8NO_3{}^2H + H]^+$ requires 241.1368; *m/z* [EI+] 121 [M + H, free amine]$^+$; ν_{max} (film)/cm^{-1} 3200 (br, NH_3^+ + OH) and 1732 (ester); δ_H (300 MHz, ^2H_2O) 4.53 (1H, br s, H-2), 3.75 (3H, s, OCH_3) and 3.38 (1H, br s, H-3*S*); δ_C (75.5 MHz, ^2H_2O) 173.0 (ester), 67.1 (C-2), 53.4 (OCH_3) and 41.5 (t, $J_{C,D}$ 23, C-3).

Methyl (2*R*,3*S*)-[3-$^2H_1$]-isoserinate hydrochloride (9b)

This was prepared by the method described above using methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylisoserinate **16b** (7.3 g, 28.7 mmol). The product, methyl (2*R*,3*S*)-[3-$^2H_1$]-isoserinate hydrochloride **9b** (4.49 g, quant.) was obtained as a white solid; mp 99–102 °C (lit[3] 104–105 °C); $[\alpha]_D^{29}$ +12.08 (*c* 1, H_2O) [lit[3] +18.6 (*c* 1, H_2O)]; *m/z* [ES+] Found 241.1366, $[2 \times C_4H_8NO_3{}^2H + H]^+$ requires 241.1368; *m/z* [EI+] 121 [M + H, free amine]$^+$; ν_{max} (film)/cm^{-1} 3200 (br, NH_3^+ + OH) and 1733 (ester); δ_H (300 MHz, ^2H_2O) 4.54 (1H, d, $J_{2,3R}$ 8.3, H-2), 3.76 (3H, s, OCH_3) and 3.17 (1H, d, $J_{3R,2}$ 8.3, H-3*R*); δ_C (75.5 MHz, ^2H_2O) 173.0 (ester), 67.2 (H-2), 53.5 (OCH_3) and 41.5 (t, $J_{C,D}$ 22, C-3).

Methyl (2*S*,3*S*)-[3-$^2H_1$]-isoserinate hydrochloride (11a)

This was prepared by the method described above using methyl (2*S*,3*S*)-*N*-benzyloxycarbonylisoserinate **17a** (14.0 g, 55 mmol). The product, methyl (2*S*,3*S*)-[3-$^2H_1$]-isoserinate hydrochloride **11a** (8.63 g, quant) was obtained as a white solid; mp 98–100 °C (lit[2] 102–104 °C); $[\alpha]_D^{29}$ −15.54 (*c* 1, H_2O) [lit[2] $[\alpha]_D^{22}$ −16.6 (*c* 1, H_2O)]; *m/z* [ES+] Found 241.1370, $[2 \times C_4H_8NO_3{}^2H + H]^+$ requires 241.1368; *m/z* [EI+] 121 [M + H, free amine]$^+$; ν_{max} (film)/cm^{-1} 3015 (OH + NH_3^+) and 1716 (br, ester); δ_H (300 MHz, ^2H_2O) 4.55 (1H, d, $J_{2,3R}$ 3.8, H-2), 3.76 (3H, s, OCH_3) and 3.39 (1H, br s, H-3*R*); δ_C (75.5 MHz, H_2O) 173.0 (ester), 67.2 (C-2), 53.4 (OCH_3) and 41.5 (t, $J_{C,D}$ 22, C-3).

Methyl (2*S*,3*R*)-[3-$^2H_1$]-isoserinate hydrochloride (11b)

This was prepared by the method described above using methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-bezyloxycarbonylisoserinate **17b** (15.81 g, 60 mmol). The product, methyl (2*S*,3*R*)-[3-$^2H_1$]-isoserinate hydrochloride **11b** (9.74 g, quant.) was obtained as a white solid; mp 100–104 °C (lit[2] 101–103 °C); $[\alpha]_D^{26}$ −15.68 (*c* 1, H_2O) [lit[2] $[\alpha]_D^{21}$ −18.2 (*c* 1, H_2O)]; *m/z* [ES+] Found 241.1366, $[2 \times C_4H_8NO_3{}^2H + H]^+$ requires 241.1368; *m/z* [EI+] 121 [M + H, free amine]$^+$; ν_{max} (film)/cm^{-1} 2960 (br, OH + NH_3^+) and 1733 (ester); δ_H (300 MHz, ^2H_2O) 4.55 (1H, d, $J_{2,3S}$ 8.4, H-2), 3.76 (3H, s, OCH_3) and 3.18 (1H, d, $J_{3S,2}$ 8.4, H-3*S*); δ_C (75.5 MHz, ^2H_2O) 173.0 (ester), 67.2 (C-2), 53.4 (OCH_3) and 41.5 (t, $J_{C,D}$ 22, C-3).

Methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate (23a)

Methyl (2*R*,3*R*)-[3-$^2H_1$]-isoserinate hydrochloride **11a** (3.6 g, 23 mmol) was suspended in chloroform (50 ml) at room temperature. Freshly distilled triethylamine (5.12 g, 51 mmol) was added, and the mixture was stirred for 15 min. The reaction was cooled to 0 °C, triphenylmethyl chloride (6.48 g, 24 mmol) was added in three portions over a period of 30 min, and the mixture was stirred at 0 °C for 4 h. The reaction was allowed to

warm to room temperature and stirred for a further 18 h. The mixture was washed with 10% aqueous citric acid (3 × 25 ml) and water (3 × 25 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The resulting clear oil was purified by flash chromatography on silica gel using petroleum ether–ethyl acetate (6 : 1) as eluent. The solvent was removed from the fractions determined to be homogeneous by TLC to give methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate **23a** (5.43 g, 65%) as a white solid; mp 77–81 °C [lit[3] 94–96 °C, (2*S*)-isomer]; $[\alpha]_D^{36}$ −16.09 (*c* 1, $CHCl_3$) [lit[3] $[\alpha]_D^{25}$ −16.9 (*c* 1, $CHCl_3$) of (2*S*)-isomer]; *m*/*z* [ES+] Found 385.16456, $[C_{23}H_{22}NO_3{}^2H + Na]^+$ requires 385.1633; *m*/*z* [EI] 361 $[M\text{-}H]^+$; ν_{max} (film)/cm^{-1} 3467 (OH) and 1736 (ester); δ_H (300 MHz, C^2HCl_3) 7.45–7.15 (15H, m, ArH), 4.28 (1H, d, $J_{2,3S}$ 3.2, H-2), 3.85 (3H, s, OCH_3) and 2.46 (1H, d, $J_{3S,2}$ 3.2, H-3*S*); δ_C (75.5 MHz, C^2HCl_3) 175.1 (ester), 146.0 (*ipso* Ar), 129.0–126.8 (Ar), 70.8 (C-2), 70.6 (N*C*Ph_3), 53.0 (OCH_3), and 46.3 (t, $J_{C,D}$ 21, C-3).

Methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate (23b)

This was prepared by the method described above using methyl (2*R*,3*S*)-[3-$^2H_1$]-isoserinate hydrochloride **9b** (5.51 g, 35.2 mmol). The product methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate **23b** (6.9 g, 57%) was obtained as a white solid; mp 80–82 °C; $[\alpha]_D^{34}$ −15.42 (*c* 1, $CHCl_3$); *m*/*z* [ES+] Found 385.1626, $[C_{23}H_{22}NO_3{}^2H + Na]^+$ requires 385.1633; *m*/*z* [EI+] 361 $[M\text{–}H]^+$; ν_{max} (film)/cm^{-1} 3466 (OH) and 1734 (ester); δ_H (300 MHz, C^2HCl_3) 7.46–7.03 (15H, m, ArH), 4.29 (1H, d, $J_{2,3R}$ 4.5, H-2), 3.86 (3H, s, OCH_3) and 2.51 (1H, d, $J_{3R,2}$ 4.5, H-3*R*); δ_C (75.5 MHz, C^2HCl_3) 175.1 (ester), 146.0 (*ipso* Ar), 129.0–126.8 (Ar), 70.8 (C-2), 70.6 (N*C*Ph_3), 53.0 (OCH_3) and 46.4 (t, $J_{C,D}$ 21, C-3).

Methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate (20a)

This was prepared by the method described above using methyl (2*S*,3*S*)-[3-$^2H_1$]-isoserinate hydrochloride **11a** (3.10 g, 20 mmol). The product methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate **20a** (4.40 g, 61%) was obtained as a white solid; mp 78–83 °C [lit[2] 82–84 °C); $[\alpha]_D^{33}$ +16.42 (*c* 1, $CHCl_3$) [lit[2] $[\alpha]_D^{24}$ +15.2 (*c* 1, $CHCl_3$)]; *m*/*z* [ES+] Found 385.1628, $[C_{23}H_{22}NO_3{}^2H + Na]^+$ requires 385.1633; *m*/*z* [EI] 361 $[M\text{–}H]^+$; ν_{max} (film)/cm^{-1} 3481 (OH) and 1737 (ester); δ_H (300 MHz, C^2HCl_3) 7.45–6.90 (15H, m, ArH), 4.28 (1H, d, $J_{2,3R}$ 3.5, H-2), 3.84 (3H, s, OCH_3) and 2.46 (1H, d, $J_{3R,2}$ 3.5, H-3*R*); δ_C (75.5 MHz, C^2HCl_3) 175.1 (ester), 146.1 (*ipso* Ar), 129.0–126.8 (Ar), 70.8 (H-2), 70.7 (N*C*Ph_3), 53.0 (OCH_3), 46.4 (t, $J_{C,D}$ 21, C-3).

Methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate (20b)

This was prepared by the method described above using methyl (2*S*,3*R*)-[3-$^2H_1$]-isoserinate hydrochloride **11b** (4.97 g, 32 mmol). The product methyl (2*S*,3*R*)-[3-^{2}H]-*N*-triphenylmethylisoserinate **20b** (8.30 g, 72%) was obtained as a white solid; mp 80–84 °C; $[\alpha]_D^{33}$ +15.24 (*c* 1, $CHCl_3$) [lit[2] $[\alpha]_D^{24}$ +15.6 (*c* 1, $CHCl_3$)]; *m*/*z* [ES+] Found 385.1651, $[C_{23}H_{22}NO_3{}^2H + Na]^+$ requires 385.1633; *m*/*z* [EI] 361 $[M\text{–}H]^+$; ν_{max} (film)/cm^{-1} 3468 (OH) and 1736 (ester); δ_H (300 MHz, C^2HCl_3) 7.45–6.92 (15H, m, ArH), 4.29 (1H, d, $J_{2,3S}$ 4.7, H-2), 3.87 (3H, s, OCH_3) and 2.51 (1H, d, $J_{3S,2}$ 4.7, H-3*S*); δ_C (75.5 MHz, C^2HCl_3) 175.1 (ester), 146.0 (*ipso* Ar), 129.0–126.8 (Ar), 70.8 (C-2), 70.7 (N*C*Ph_3), 53.0 (OCH_3) and 46.4 (t, $J_{C,D}$ 22, C-3).

Methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate (10a)

Methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate **20a** (3.10 g, 8.56 mmol) was dissolved in THF (45 ml), triethylamine (3.08 g, 30 mmol) was added and the mixture was stirred at room temperature for 5 min. Methanesulfonyl chloride (1.48 g, 12.9 mmol) was added dropwise over 15 min and the reaction was stirred at room temperature for 30 min. The reaction was heated at reflux for 48 h, allowed to cooled to room temperature, and the solvent was removed under reduced pressure to give an orange gum. Ethyl acetate (50 ml) was added, and the solution was washed with 10% aqueous citric acid (3 × 25 ml) and saturated aqueous sodium hydrogen carbonate (3 × 25 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product as orange gum. The orange gum was dissolved in a small amount of methanol and left standing overnight to give methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **10a** (2.6 g, 89%) as white crystals; mp 126–129 °C; $[\alpha]_D^{24}$ +81.69 (*c* 0.7, MeOH) [lit[2] $[\alpha]_D^{23}$ +103.0 (*c* 0.7, MeOH)]; *m*/*z* [ES+] Found 367.1538, $[C_{23}H_{20}NO_2{}^2H + Na]^+$ requires 367.1527; ν_{max} (film)/cm^{-1} 1748 (ester); δ_H (300 MHz, C^2HCl_3) 7.51–7.19 (15H, m, ArH), 3.76 (3H, s, OCH_3), 2.25 (1H, d, $J_{3R,2}$ 2.7, H-3*R*) and 1.88 (1H, d, $J_{2,3R}$ 2.7, H-2); δ_C (75.5 MHz, C^2HCl_3) 172.4 (ester), 144.0 (*ipso* Ar), 129.7–127.4 (*m*, *p*, *o* Ar), 74.8 (N*C*Ph_3), 52.6 (OCH_3), 32.0 (C-2) and 28.9 (t, $J_{C,D}$ 25. C-3).

Methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate (10b)

This was prepared by the method above using methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate **20b** (9.80 g, 27.1 mmol). The product methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **10b** (5.68 g, 60%) was obtained as white crystals; mp 124–126 °C; $[\alpha]_D^{27}$ +66.64 (*c* 0.7, MeOH) [lit[2] $[\alpha]_D^{23}$ +101.6 (*c* 0.7, MeOH)]; *m*/*z* [ES+] Found 367.1522, $[C_{23}H_{20}NO_2{}^2H + Na]^+$ requires 367.1527; ν_{max} (film)/cm^{-1} 1749 (ester); δ_H (300 MHz, C^2HCl_3) 7.51–7.20 (15H, m, ArH), 3.77 (3H, s, OCH_3), 1.88 (1H, d, $J_{2,3S}$ 6.2, H-2) and 1.41 (1H, d, $J_{3S,2}$ 6.2, H-3*S*); δ_C (75.5 MHz, C^2HCl_3) 172.4 (ester), 144.0 (*ipso* Ar), 129.7–127.3 (Ar), 74.8 (N*C*Ph_3), 52.5 (OCH_3), 32.0 (C-2) and 28.8 (t, $J_{C,D}$ 26. C-3).

Methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate (8a)

This was prepared by the method described above using methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate **23a** (4.7 g, 13 mmol). The product methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **8a** (3.38 g, 76%) was obtained as white crystals; mp 123–125 °C (lit[3] 126–128 °C); $[\alpha]_D^{27}$ −99.40 (*c* 0.7, MeOH) [lit[3] $[\alpha]_D^{25}$ −86.8 (*c* 0.7, $CHCl_3$)]; *m*/*z* [ES+] Found 367.1526, $[C_{23}H_{20}NO_2{}^2H + Na]^+$ requires 367.1527; ν_{max} (film)/cm^{-1} 1748 (ester); δ_H (300 MHz, C^2HCl_3) 7.52–7.20 (15H, m, ArH), 3.77 (3H, s, OCH_3), 2.25 (1H, d, $J_{3S,2}$ 2.6, H-3*S*) and 1.88 (1H, d, $J_{2,3S}$ 2.6, H-2); δ_C (75.5 MHz, C^2HCl_3) 172.4 (ester), 144.0 (*ipso* Ar), 129.7–127.3 (Ar), 74.8 (N*C*Ph_3), 52.5 (OCH_3), 32.0 (C-2) and 28.8 (t, $J_{C,D}$ 26. C-3).

Methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate (8b)

This was prepared by the method described above using methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylisoserinate **23b** (5.8 g, 16 mmol). The product methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **8b** (3.36 g, 61%) was obtained as white crystals; mp 125–128 °C (lit[3] mp 127–129 °C)); $[\alpha]_D^{27}$ −73.97 (*c* 0.7, MeOH) (lit[3] $[\alpha]_D^{25}$ −86.3 (*c* 1, $CHCl_3$); *m*/*z* [ES+] Found 367.1532, $[C_{23}H_{20}NO_2{}^2H + Na]^+$ requires 367.1527; ν_{max} (film)/cm^{-1} 1747 (ester); δ_H (300 MHz, C^2HCl_3) 7.51–7.20 (15H, m, ArH), 3.76 (3H, s, OCH_3), 1.88 (1H, d, $J_{2,3R}$ 6.2, H-2) and 1.41 (1H, d, $J_{3R,2}$ 6.2, H-3*R*); δ_C (75.5 MHz, C^2HCl_3) 172.4 (ester), 144.0 (*ipso* Ar), 129.7–127.3 (*m*, *p*, *o* Ar), 74.8 (N*C*Ph_3), 52.5 (OCH_3), 32.0 (C-2) and 28.8 (t, $J_{C,D}$ 27, C-3).

Methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate (21a)

This was prepared by the method reported in ref. 2 using methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **10a** (500 mg, 1.45 mmol) to yield methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **21a** (295 mg, 86%) as a clear oil; $[\alpha]_D^{25}$ +53.3 (*c* 0.7, $CHCl_3$) [lit[2] $[\alpha]_D^{23}$ +42.5 (*c* 0.7, $CHCl_3$)]; *m/z* (ES+) Found 259.0819, $[C_{12}H_{12}NO_4{}^2H + Na]^+$ requires 259.07996; ν_{max} (film)/cm^{-1} 1732 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.45–7.29 (5H, br s, ArH), 5.15 (2H, s, OCH_2Ph), 3.71 (3H, s, OCH_3), 3.11 (1H, d, $J_{2,3R}$ 3.2, H-2) and 2.59 (1H, d, $J_{3R,2}$ 3.2, H-3*R*); δ_C (75.5 MHz, C^2HCl_3) 168.6 (ester), 160.7 (urethane), 135.3 (*ipso* Ar), 128.6–128.1 (Ar), 68.6 (OCH_2Ph), 52.7 (OCH_3), 34.8 (C-2) and 31.1 (t, $J_{C,D}$ 27, C-3).

Methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate (21b)

This was prepared as above using methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **10b** (1 g, 2.9 mmol) to yield methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **21b** (669 mg, 98%) as a clear oil; $[\alpha]_D^{35}$ +59.8 (*c* 0.7, $CHCl_3$) [lit[2] $[\alpha]_D^{24}$ +40.6 (*c* 0.7, $CHCl_3$)]; *m/z* (ES+) Found 259.0824, $[C_{12}H_{12}NO_4{}^2H + Na]^+$ requires 259.07996; ν_{max} (film)/cm^{-1} 1745 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.36 (5H, br s, ArH), 5.15 (2H, s, OCH_2Ph), 3.72 (3H, s, OCH_3), 3.11 (1H, d, $J_{2,3S}$ 5.4, H-2) and 2.48 (1H, d, $J_{3S,2}$ 5.4, H-3*S*); δ_C (75.5 MHz, C^2HCl_3) 169.0 (ester), 161.1 (urethane), 135.7 (*ipso* Ar), 129.0–128.9 (Ar), 69.0 (OCH_2Ph), 53.0 (OCH_3), 35.2 (C-2) and 31.5 (t, $J_{C,D}$ 27, C-3).

Methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate (24a)

This was prepared by the method described above using methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **8a** (500 mg, 1.45 mmol). The product methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **24a** (325 mg, 95%) was obtained as a clear oil; $[\alpha]_D^{36}$ −21.0 (*c* 0.7, $CHCl_3$); *m/z* (ES+) Found 259.0814, $[C_{12}H_{12}NO_4{}^2H + Na]^+$ requires 259.07996; ν_{max} (thin film)/cm^{-1} 1736 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.36 (5H, br s, ArH), 5.15 (2H, s, OCH_2Ph), 3.72 (3H, s, OCH_3), 3.11 (1H, d, $J_{2,3S}$ 3.2, H-2) and 2.60 (1H, d, $J_{3S,2}$ 3.2, H-3*S*); δ_C (75.5 MHz, C^2HCl_3) 168.6 (ester), 160.7 (urethane), 135.3 (*ipso* Ar), 128.6–127.0 (Ar), 68.6 (OCH_2Ph), 52.7 (OCH_3), 34.7 (C-2) and 31.1 (t, $J_{C,D}$ 27, C-3).

Methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate (24b)

This was prepared by the method described above using methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-triphenylmethylaziridine-2-carboxylate **8b** (500 mg, 1.45 mmol). The product methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **24b** (313 mg, 92%) was obtained as a clear oil; $[\alpha]_D^{36}$ −45.6 (*c* 0.7, $CHCl_3$); *m/z* (ES+) Found 259.0810, $[C_{12}H_{12}NO_4{}^2H + Na]^+$ requires 259.07996; ν_{max} (thin film)/cm^{-1} 1744 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.36 (5H, br s, ArH), 5.15 (2H, s, OCH_2Ph), 3.72 (3H, s, OCH_3), 3.11 (1H, d, $J_{2,3R}$ 5.4, H-2) and 2.48 (1H, d, $J_{3R,2}$ 5.4, H-3*R*); δ_C (75.5 MHz, C^2HCl_3) 168.6 (ester), 160.7 (urethane), 135.3 (*ipso* Ar), 128.6–127.0 (Ar), 68.6 (OCH_2Ph), 52.7 (OCH_3), 34.8 (C-2) and 31.5 (t, $J_{C,D}$ 27, C-3).

Methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate

This was prepared as above using methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **24a** (200 mg, 0.85 mmol) to yield methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate (174 mg, 76%) as a white solid; mp 52.0–53.1 °C; $[\alpha]_D^{30}$ −27.9 (*c* 1.5, $CHCl_3$) [lit[2] $[\alpha]_D^{30}$ −35.5 (*c* 1.5, $CHCl_3$)]; *m/z* [ES+] Found 295.0579, $[C_{12}H_{13}NO_4{}^2HCl + Na]^+$ requires 295.0566; ν_{max} (film)/cm^{-1} 3337 (NH) and 1720 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.34 (5H, br s, ArH), 5.76 (1H, br, NH), 5.13 (2H, s, OCH_2Ph), 4.77 (1H, m, H-2), 3.96 (0.1H, br s, unlabelled), 3.86 (0.9H, d, $J_{3S,2}$ 3.3, H-3*S*) and 3.81 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 169.6 (ester), 156.0 (urethane), 136.3 (*ipso* Ar), 129.0–128.5 (Ar), 67.7 (OCH_2Ph), 55.1 (C-2), 53.4 (OCH_3) and 45.4 (t, $J_{C,D}$ 23, C-3).

Methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate

This was prepared as above using methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **24b** (500 mg, 2.13 mmol) to yield methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate (267 mg, 46%) as a white solid; mp 51.9–54.2 °C; $[\alpha]_D^{30}$ −29.21 (*c* 1.5, $CHCl_3$) [lit[2] $[\alpha]_D^{22}$ −35.9 (*c* 1.03, $CHCl_3$)]; *m/z* [ES+] Found 295.0562, $[C_{12}H_{13}NO_4{}^2HCl + Na]^+$ requires 295.0566; ν_{max} (film)/cm^{-1} 3337 (NH) and 1723 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.37 (5H, br s, ArH), 5.70 (1H, br, NH), 5.14 (2H, s, OCH_2Ph), 4.77 (1H, m, H-2), 3.99 (0.92H, d, $J_{3R,2}$ 2.9, H-3*R*), 3.86 (0.08H, br s, unlabelled) and 3.81 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 169.6 (ester), 156.0 (urethane), 136.3 (*ipso* Ar), 129.0–128.5 (Ar), 67.7 (OCH_2Ph), 55.1 (C-2), 53.5 (OCH_3) and 45.4 (t, $J_{C,D}$ 24, C-3).

Methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate

This was prepared by the method described above using methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **24a** (200 mg, 0.85 mmol). Methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate (186 mg, 80%) was obtained as a white solid; mp 52.5–55.7 °C; $[\alpha]_D^{32}$ +13.9 (*c* 1.5, $CHCl_3$); *m/z* [ES+] Found 295.0577, $[C_{12}H_{13}NO_4{}^2HCl + Na]^+$ requires 295.0566; ν_{max} (thin film)/cm^{-1} 3337 (NH) and 1721 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.34 (5H, br s, ArH), 5.75 (1H, br, NH), 5.13 (2H, s, OCH_2Ph), 4.77 (1H, m, H-2), 3.96 (0.06H, br s, unlabelled), 3.86 (0.94H, d, $J_{3R,2}$ 3.2, H-3*R*) and 3.81 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 169.6 (ester), 156.0 (urethane), 136.3 (*ipso* Ar), 129.0–128.5 (Ar), 67.7 (OCH_2Ph), 55.1 (C-2), 53.4 (OCH_3) and 45.4 (t, $J_{C,D}$ 23, C-3).

Methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate

This was prepared by the method described above using methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonylaziridine-2-carboxylate **24b** (200 mg, 0.85 mmol). Methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate (199 mg, 86%) was obtained as a white solid; mp 50.9–53.4 °C; $[\alpha]_D^{32}$ +37.07 (*c* 1.5, $CHCl_3$); *m/z* [ES+] Found 295.0573, $[C_{12}H_{13}NO_4{}^2HCl + Na]^+$ requires 295.0566; ν_{max} (thin film)/cm^{-1} 3338 (NH) and 1720 (br, ester and urethane); δ_H (300 MHz, C^2HCl_3) 7.34 (5H, br s, ArH), 5.70 (1H, br, NH), 5.13 (2H, s, OCH_2Ph), 4.77 (1H, m, H-2), 3.96 (0.93H, br s, H-3*S*), 3.88 (0.07H, br s, unlabelled) and 3.80 (3H, s, OCH_3); δ_C (75.5 MHz, C^2HCl_3) 169.6 (ester), 156.0 (urethane), 136.3 (*ipso* Ar), 129.0–128.5 (Ar), 67.7 (OCH_2Ph), 55.1 (C-2), 53.4 (OCH_3) and 45.4 (t, $J_{C,D}$ 24, C-3).

(2*S*,3*R*)-[3-$^2H_1$]-β-Chloroalanine (22a)

This was prepared by the method reported in ref. 2 from methyl (2*S*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate **21a** (70 mg, 0.26 mmol) to yield (2*S*,3*R*)-[3-$^2H_1$]-β-chloroalanine **22a** (18 mg, 55%) as a cream solid; decomp on mp; $[\alpha]_D^{37}$ +4.92 (*c* 0.5, H_2O) [lit[2] $[\alpha]_D^{26}$ +7.1 (c 0.57, H_2O)]; δ_H (300 MHz, 10% ^2HCl in ^2H_2O, Fig. 3c) 4.50 (1H, br s, H-2) and 3.93 (1H, br s, H-3*S*); δ_C (75.5 MHz, 10% ^2HCl in ^2H_2O) 167.6 (acid), 53.0 (C-2) and 40.8 (t, $J_{C,D}$ 22, C-3).

(2*S*,3*S*)-[3-$^2H_1$]-β-Chloroalanine (22a)

This was prepared as for the (2*R*)-isomer above from methyl (2*S*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate (70 mg, 0.26 mmol) to yield (2*S*,3*S*)-[3-$^2H_1$]-β-chloroalanine **22a** as a cream solid; decomp on mp; $[a]_D^{37.5}$ +3.76 (*c* 0.5, H_2O); δ_H (300 MHz, 10% ^{2}HCl in ^2H_2O, Fig. 3b) 4.50 (1H, d, $J_{2,3R}$ 4.0, H-2) and 3.90 (1H, d, $J_{3R,2}$ 4.0, H-3*R*); δ_C (75.5 MHz, 10% ^{2}HCl in ^2H_2O) 167.6 (acid), 53.0 (C-3) and 41.0 (t, $J_{C,D}$ 23, C-3).

(2*R*,3*S*)-[3-$^2H_1$]-β-Chloroalanine (25a)

This was prepared by the method described above using methyl (2*R*,3*S*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate (89 mg, 0.33 mmol). The product, (2*R*,3*S*)-[3-$^2H_1$]-β-chloroalanine **25a** was obtained as a cream solid (25 mg, 64%); mp decomp; $[a]_D^{34}$ −6.83 (*c* 0.5, H_2O); δ_H (300 MHz, 10% ^{2}HCl in ^2H_2O, Fig. 4b) 4.50 (1H, d, $J_{2,3R}$ 3.0, H-2) and 3.95 (1H, br s, H-3*R*); δ_C (75.5 MHz, 10% ^{2}HCl in ^2H_2O) 167.6 (acid), 53.0 (C-2) and 41.0 (br m, C-3).

(2*R*,3*R*)-[3-$^2H_1$]-β-Chloroalanine (25b)

This was prepared by the method described above using methyl (2*R*,3*R*)-[3-$^2H_1$]-*N*-benzyloxycarbonyl-β-chloroalaninate (100 mg, 0.37 mmol). (2*R*,3*R*)-[3-$^2H_1$]-β-Chloroalanine (**142**) (26 mg, 57%), was obtained as a cream solid; mp decomp; $[a]_D^{30}$ −7.11 (*c* 0.5, H_2O); δ_H (300 MHz, 10% ^{2}HCl in ^2H_2O, Fig. 4c) 4.50 (1H, d, $J_{2,3S}$ 4.2, H-2) and 4.04 (1H, d, $J_{3S,2}$ 4.2, H-3*S*); δ_C (75.5 MHz, 10% ^{2}HCl in ^2H_2O) 167.6 (acid), 53.0 (C-2) and 41.0 (t, $J_{C,D}$ 23, C-3).

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