# Synthesis of Optically Pure $^{13}$C-Labelled Propionate from Alanine by Asymmetric Hydrolysis using Porcine Kidney Acylase

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**SUMMARY**

Sodium (R)-[2-$^{2}$H,3-$^{13}$C]propionate, sodium (S)-[2-$^{2}$H,3-$^{13}$C] propionate, sodium (R)-[3-$^{13}$C]-2-fluoropropionate, and sodium (S)-[3-$^{13}$C]-2-fluoropropionate were synthesized from D[(S)]-[3-$^{13}$C]alanine and L[(R)]-[3-$^{13}$C]alanine, which were obtained by asymmetric hydrolysis using acylase from porcine kidney.

Key words; $^{13}$C-labelled propionate, deuterium-labelled propionate, fluorine-labelled propionate, $^{13}$C-labelled alanine, asymmetric hydrolysis.

## INTRODUCTION

Recent developments in FT-NMR spectroscopy have allowed stable isotope-labelled positions in compounds to be identified without the need for chemical degradation. This is particularly valuable in studies of biosynthetic pathways. We have already prepared many $^{13}$C-labelled compounds in our laboratory, and have used them to obtain important information on various biosynthetic processes.[1)]

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We are currently interested in the stereochemistry of the chain elongation steps in the biosynthesis of macrolide and polyether antibiotics. In order to elucidate this, we required chiral $^{13}$C-labelled propionate double-labelled with deuterium or fluorine. We present here details of the synthesis of these compounds.

## RESULTS AND DISCUSSION

### L[(R)]-[3-$^{13}$C]Alanine (4b) and D[(S)]-[3-$^{13}$C]alanine (4c)

Reaction of $^{13}$C-iodomethane (1) with diethyl acetamidomalonate (2) in the presence of sodium in ethyl alcohol gave [1'-$^{13}$C]diethyl acetamidomethylmalonate (3), which was heated under reflux with concentrated hydrochloric acid to afford DL-[3-$^{13}$C]alanine (4a) in 62 % yield from $^{13}$C-iodomethane (1).[2] Resolution of DL-[3-$^{13}$C]alanine (4a) was carried out by an enzymatic method. DL-[3-$^{13}$C]Alanine (4a) was first heated with acetic acid and acetic anhydride to give DL-[3-$^{13}$C]-N-acetylalanine (5a) in 98 % yield. Asymmetric hydrolysis of DL-[3-$^{13}$C]-N-acetylalanine (5a) with porcine kidney acylase in 1.5 N ammonium hydroxide gave L[(R)]-[3-$^{13}$C]alanine (4b) in 38 % yield and D[(S)]-[3-$^{13}$C]-N-acetylalanine (5c). The D[(S)]-[3-$^{13}$C]-N-acetylalanine (5c) was hydrolyzed with 2 N hydrochloric acid to gave D[(S)]-[3-$^{13}$C]alanine (4c) in 32 % yield from DL-[3-$^{13}$C]-N-acetylalanine (5a)[3] (Fig. 1). Both L[(R)]-[3-$^{13}$C]alanine (4b) and D[(S)]-[3-$^{13}$C]alanine (4c) were obtained in high optical purity (100 % ee) as determined by high-performance liquid chromatography (HPLC) using a CROWNPAK CR (-) column.

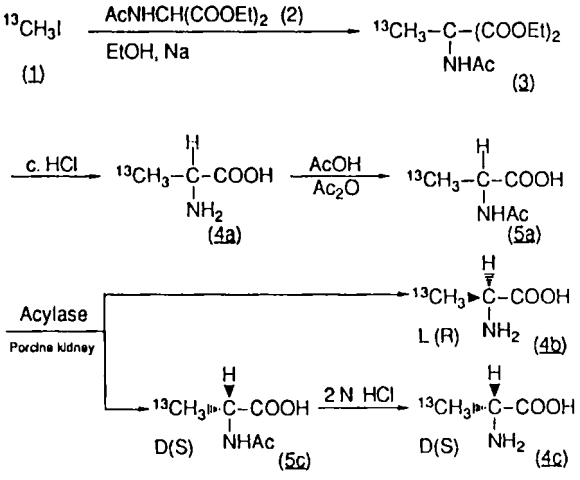



Figure 1

**Sodium (S)-[2-$^{2}$H,3-$^{13}$C]propionate (7c) and sodium (R)-[2-$^{2}$H,3-$^{13}$C]propionate (7b)**

Before $^{13}$C-labelled sodium [2-$^{2}$H]propionate was synthesized from L[(R)]-[3-$^{13}$C]alanine (4b) and D[(S)]-[3-$^{13}$C]alanine (4c), the optical purity and the absolute configuration of $^{13}$C-unlabelled sodium [2-$^{2}$H]propionate, synthesized from D[(R)]-alanine and L[(S)]-alanine, were determined by NMR spectroscopy.

Bromination of L[(S)]-alanine (4e) (>98 % ee) with potassium bromide and sodium nitrite in 2.5 N sulfuric acid afforded (S)-2-bromopropionic acid (6e) with retention of configuration in 60 % yield (>98 % ee, the optical purity and absolute configuration were determined by optical rotation; see experimental section). (S)-2-Bromopropionic acid (6e) was heated under reflux with 1 M lithium triethyldeuterioborate in tetrahydrofuran (Superdeuteride; Aldrich) to give sodium [2-$^{2}$H]propionate (7f) in 81 % yield[4] (Fig. 2). Compounds (7e) and (7d) were similarly prepared from D[(R)]-alanine (>98 % ee) and DL-alanine, respectively.

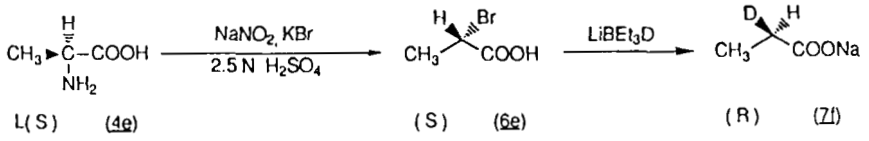
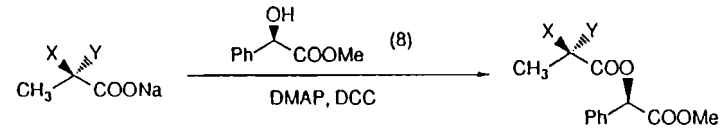



Figure 2

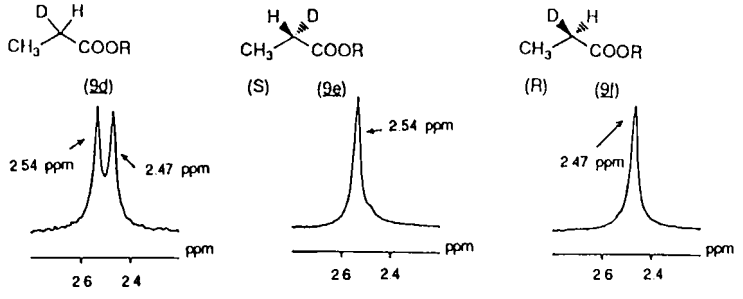
Esterification of each sodium [2-$^{2}$H]propionate (7d, 7e and 7f), derived from DL-, D-, and L-alanine, respectively, with (R)-methyl mandelate (8) using 4-dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC) gave the corresponding methyl mandelate derivatives in 47 % yield (9d, 9e and 9f, respectivery). The optical purity and the absolute configuration were determined by $^{2}$H-NMR spectroscopy with broad-band proton decoupling[4d,5] (Fig. 3). It was established that sodium (R)-[2-$^{2}$H]propionate (7f) (>97 % ee) had been formed from L[(S)]-alanine (4e) (>98 % ee), and sodium (S)-[2-$^{2}$H]propionate (7e) (>97 % ee) from D[(R)]-alanine (>98 %ee). Futhermore, we applied the circular dichroic (CD) spectra to the determination of the sense of chirality of the chiral sodium [2-$^{2}$H]propionate (7e and 7f). The CD spectra are shown in Fig. 4, where (S)-[2-$^{2}$H]propionate (7e) and (R)-[2-$^{2}$H]propionate (7f) show the positive curve and negative curve respectively. These data also indicate that the optical purity of 7e and 7f are numerically almost equal to those described above NMR method.

On the basis of the results, sodium (S)-[3-$^{13}$C,2-$^{2}$H]propionate (7c) (>97 % ee) was prepared via (R)-[3-$^{13}$C]-2-bromopropionic acid (6b) obtained from L[(R)]-[3-$^{13}$C]alanine (4b), and sodium (R)-[3-$^{13}$C,2-$^{2}$H] propionate (7b) (>97 % ee) was similarly prepared via (S)-[3-$^{13}$C]-2-bromopropionic acid (6c) obtained from D[(S)]-[3-$^{13}$C]alanine (4c) (Fig. 5).



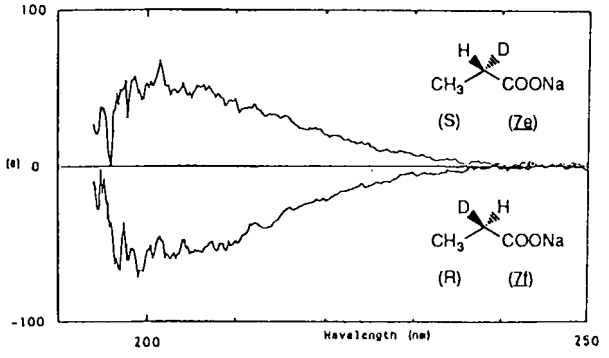

X, Y = H, D (7d) X, Y = H, D (9d)
X = D, Y = H (R) (7f) X = D, Y = H (R) (9f)
X = H, Y = D (S) (7e) X = H, Y = D (S) (9e)

$^{2}H$-NMR ($CDCl_3$, 41 MHz) of the corresponding methyl mandelate derivatives




R = (R)-methyl mandelate

Figure 3




0.1% $H_2O$ solution 1mm cell

Figure 4

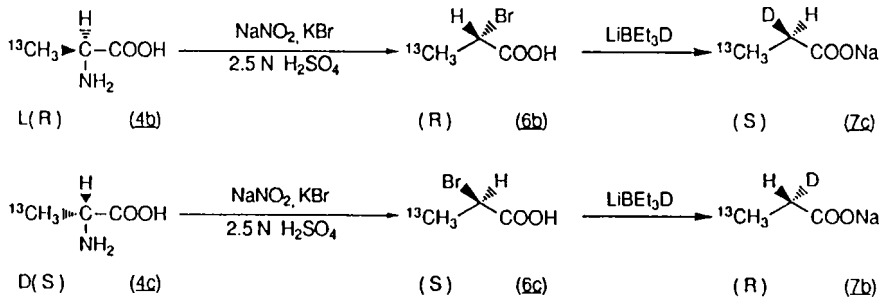



Figure 5

**Sodium (R)-[3-$^{13}$C]-2-fluoropropionate (10b) and sodium (S)-[3-$^{13}$C]-2-fluoropropionate (10c)**

In the same way, the optical purity of $^{13}$C-unlabelled sodium 2-fluoropropionate, synthesized from D- and L-alanine, was determined by NMR. With retention of configuration as aforesaid

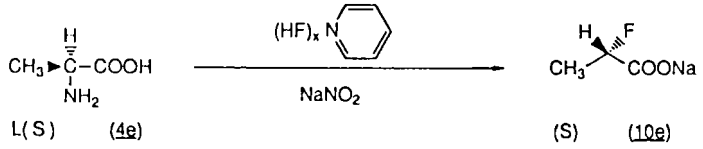
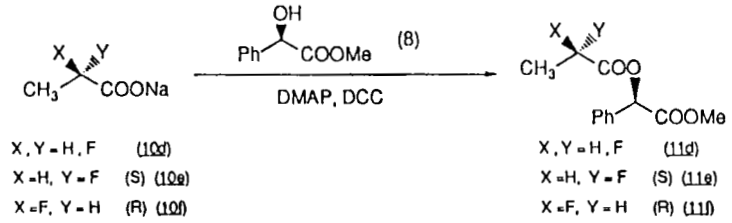


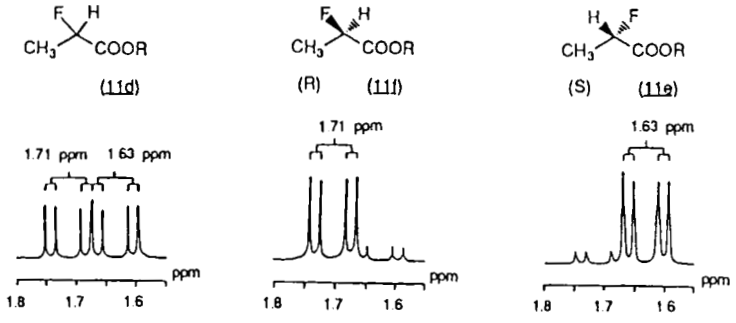

Figure 6

bromination, L[(S)]-alanine (4e) was treated with sodium nitrite in hydrogen fluoride-pyridine to give sodium (S)-2-fluoropropionate (10e) in 95 % yield[6] (Fig. 6). Compounds (10f) and (10d) were similarly prepared from D- and DL-alanine.

Esterification of each sodium 2-fluoropropionate (10d, 10e and 10f) with (R)-methyl mandelate (8) gave the corresponding methyl mandelate derivative in 49 % yield (11d, 11e and 11f, respectively). The optical purity were determined by $^{1}$H-NMR spectroscopy (Fig. 7) and CD spectra (Fig. 8). It was established that sodium (S)-2-fluoropropionate (10e) (>93 % ee) had been formed from L[(S)]-alanine (4e) (>98 % ee) and sodium (R)-2-fluoropropionate (10f) (>93 % ee) from D[(R)]-alanine (>98 % ee).




$^{1}H$-NMR ($CDCl_3$, 400 MHz) of the corresponding methyl mandelate derivatives




R = (R)-methyl mandelate

Figure 7

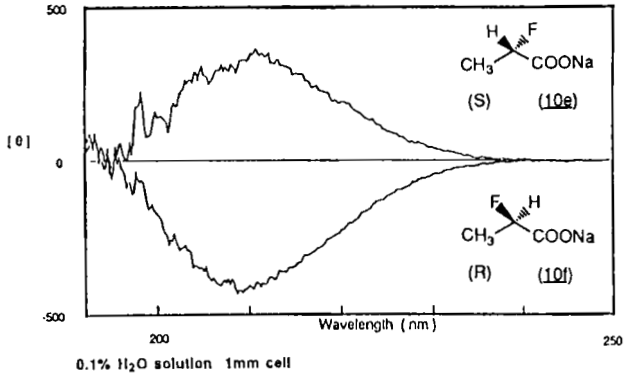



Figure 8

On the basis of the above results, sodium (R)-[3-$^{13}$C]-2-fluoropropionate (10b) (>93 % ee) was prepared from L[(R)]-[3-$^{13}$C]alanine (4b), and sodium (S)-[3-$^{13}$C]-2-fluoropropionate (10c) (>93 % ee) was similarly prepared from D[(S)]-[3-$^{13}$C]alanine (4c) (Fig. 9).

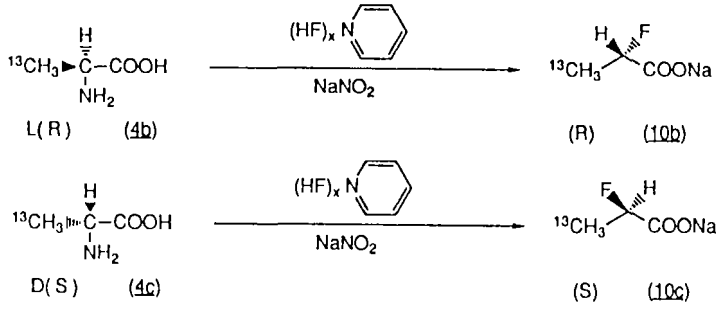



Figure 9

## EXPERIMENTAL

### Materials

$^{13}$C-Iodomethane (99 atom % $^{13}$C) was supplied by Cambridge Isotope Laboratories. Lithium triethyldeuterioborate (1 M in tetrahydrofuran) (Superdeuteride) and hydrogen fluoride-pyridine were obtained from Aldrich. D-Alanine (>98 % ee) and L-alanine (>98 % ee) were obtained from Tokyo Kasei Kogyo. (R)-Methyl mandelate (99 % ee) was prepared from (R)-mandelic acid (99 %ee), which was obtained from Merck. Other reagents were obtained from Tokyo Kasei Kogyo and Wako. Acylase from porcine kidney was purchased from Sigma and had a specific activity of 1580 units per mg of protein. Water was ion-exchanged and distilled before use.

### Instruments

Melting point (m.p.) determinations were carried on a Yazawa micro melting point apparatus, Type BY-1; values are uncorrected. Infrared spectra (IR) were recorded on a JASCO DS-801 spectrometer, and positions of absorption maxima are reported in reciprocal centimeters. $^{1}$H-NMR spectra were recorded on a JEOL GSX-400 spectrometer in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard, or in $D_2O$ solution referenced to the solvent peak. $^{13}$C-NMR spectra were recorded on a JEOL

GSX-400 (100 MHz) spectrometer in $CDCl_3$ solution referenced to the solvent peak, or in $D_2O$ solution with sodium 3-trimethylsilylpropionate (TSP) as an internal standard. $^{2}H$-NMR spectra were recorded on a JEOL GSX-270 (41.3 MHz) spectrometer in $CDCl_3$ solution referenced to the solvent peak, with broad-band proton decoupling. Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL JMS-DX302. CD spectra were recored on a JASCO J-500C spectrometer. The HPLC system consisted of a JASCO 880-PU pump and a JASCO 870-UV detector; column, CROWNPAK CR (-), 15 cm X 0.4 cm I.D. (Daicel); column temperature, 0 °C; mobile phase, aqueous $HClO_4$ pH 1.0; flow rate, 0.4 ml/min; UV detection wavelength, 200 nm. The retention times observed were 5.6 min for L[(R)]-[3-$^{13}C$]alanine (4b), and 12.6 min for D[(S)]-[3-$^{13}C$]alanine (4c). Optical rotation were recorded on a JASCO DIP-360 polarimeter.

**[1'-$^{13}C$]Diethyl acetamidomethylmalonate (3)**

A solution of sodium (0.85 g, 37.0 mmol) in dry ethyl alcohol (16 ml) was added to a solution of diethyl acetamidomalonate (2) (7.65 g, 35.2 mmol) in dry ethyl alcohol (19 ml) at 0 °C under argon, and the mixture was stirred for 10 min at room temperature. To this solution, $^{13}C$-iodomethane (1) (5.0 g, 35.0 mmol) was added dropwise at 0 °C, and the whole was stirred for 5 min at this temperature, then heated under reflux for 15 hr. The reaction was quenched with water (10 ml) and the mixture was extracted with ether (50 X 8 ml). The combined extracts were washed with brine (200 ml), dried over magnesium sulfate and evaporated. Chromatography of the crude product on silica gel with hexane:ether (1:1) gave [1'-$^{13}C$]diethyl acetamidomethylmalonate (3) (5.50 g, 68 %), m.p. 88.0 ∿ 89.8 °C; $^{1}H$-NMR ($CDCl_3$) 1.26 (t, 6H, $J_{HH}$=7.2 Hz, $C\underline{H}_3CH_2$), 1.75 (d, 3H, $J_{^{13}CH}$=131.9 Hz, $^{13}C\underline{H}_3C$), 2.02 (s, 3H, $C\underline{H}_3CO$), 4.25 (q, 4H,

$J_{HH}$=7.2 Hz, $CH_3\underline{CH}_2$); $^{13}$C-NMR ($CDCl_3$) 20.8; FAB-MS m/z 233 ($M^+$+1, 100 %); IR ($CHCl_3$) 3425 (NH), 1735 (COOC), 1685 (NC).

**DL-[3-$^{13}$C]Alanine (4a)**

A solution of [1'-$^{13}$C]diethyl acetamidomethylmalonate (3) (5.50 g, 23.7 mmol) in concentrated hydrochloric acid (25 ml) was heated under reflux for 2 hr. The reaction mixture was cooled to room temperature and evaporated. The residue was dissolved in a minimum volume of 50 % ethyl alcohol. Pyridine was added to this solution until crystallization occurred, and the crystals were collected by centrifugation at 1400 G for 15 min and washed with ethyl alcohol. Recrystallization from water-ethyl alcohol gave DL-[3-$^{13}$C]alanine (4a) (1.94 g, 91 %), m.p. 292 ∿ 294 °C; $^1$H-NMR ($D_2O$) 1.38 (dd, 3H, $J_{HH}$=7.2 Hz, $J_{13CH}$=129.6 Hz, $^{13}C\underline{H}_3CH$), 3.68 (dq, 1H, $J_{HH}$=7.2 Hz, $J_{13CCH}$=4.6 Hz, $^{13}CH_3\underline{CH}$); $^{13}$C-NMR ($D_2O$) 18.9; FAB-MS m/z 91 ($M^+$+1, 34 %); IR (KBr) 3082 (NH), 1685, 1590 (COOH).

**DL-[3-$^{13}$C]-N-Acetylalanine (5a)**

A suspension of DL-[3-$^{13}$C]alanine (4a) (2.34 g, 26.0 mmol) in acetic acid (11 ml) was heated to 100 °C for 5 hr. Acetic anhydride (3.5 ml) was then added and the mixture was heated to 110 °C until a solution was formed. This temperature was held for 5 min, then the reaction mixture was quenched with water (50 ml) and evaporated. Recrystallization from water-acetone gave DL-[3-$^{13}$C]-N-acetylalanine (5a) (3.36 g, 98 %), m.p. 123 ∿ 125 °C; $^1$H-NMR ($D_2O$) 1.31 (dd, 3H, $J_{HH}$=7.3 Hz, $J_{13CH}$=130.3 Hz, $^{13}C\underline{H}_3CH$), 1.92 (s, 3H, $C\underline{H}_3CO$), 4.23 (m, 1H, $^{13}CH_3\underline{CH}$); $^{13}$C-NMR ($D_2O$) 20.2; FAB-MS m/z 133 ($M^+$+1, 100 %); IR (KBr) 3330 (NH), 1720 (CO), 1590 (NC).

**L[(R)]-[3-$^{13}$C]Alanine (4b) and D[(S)]-[3-$^{13}$C]Alanine (4c)**

Porcine kidney acylase (158 mg, 250 K units) was added to a solution (pH 8.0) of DL-[3-$^{13}$C]-N-acetylalanine (5a) (2.77 g, 21.0 mmol) in 1.5 N ammonium hydroxide (18 ml), and the mixture was stirred at 38 °C. After 23 hr, the reaction mixture was boiled for a few minutes, and the denatured enzyme was removed by centrifugation at 1400 G for 15 min. The supernatant solution was concentrated, ethyl alcohol (5 ml) was added, and the resulting crystals were separated from the solution, collected by centrifugation at 1400 G for 15 min, and washed with ethyl alcohol (5 ml). The process was repeated twice, and finally recrystallization from water-ethyl alcohol gave L[(R)]-[3-$^{13}$C]alanine (4b) (721 mg, 38 %). After isolation of crude L[(R)]-[3-$^{13}$C]alanine (4b), the supernatant solution was evaporated. The residue was subjected to column chromatography on Dowex 50W X-4 and elution with water afforded D[(S)]-[3-$^{13}$C]-N-acetylalanine (5c) (1.28 g, 46 %). A solution of D[(S)]-[3-$^{13}$C]-N-acetylalanine (5c) (1.28 g, 9.70 mmol) in 2 N hydrochloric acid (20 ml) was heated under reflux for 4 hr, then cooled to room teperature and evaporated. The residue was dissolved in a minimum volume of 50 % ethyl alcohol. Pyridine was added to this solution until crystallization occurred, and the crystals were collected by centrifugation at 1400 G for 15 min and washed with ethyl alcohol. Recrystallization from water-ethyl alcohol gave D[(S)]-[3-$^{13}$C]alanine (4c) (605 mg, 32 %, 2 steps). Analytical data of 4b and 4c were exactly harmonized with DL-[3-$^{13}$C]alanine (4a) and no distinguished between 4b and 4c.

**(R)-[3-$^{13}$C]-2-Bromopropionic acid (6b) and (S)-[3-$^{13}$C]-2-Bromopropionic acid (6c)**

Sodium nitrite (1.0 g, 14.5 mmol) was added to a solution of

L[(R)]-[3-$^{13}$C]alanine (4b) (404 mg, 4.48 mmol) and potassium bromide (3.5 g, 29.4 mmol) in 2.5 N sulfuric acid (37 ml) at -10 °C, and the reaction mixture was stirred for 3 hr, then extracted with ether (150 X 3 ml). The combined extracts were washed with brine (200 ml), dried over magnesium sulfate and evaporated. Distillation gave (R)-[3-$^{13}$C]-2-bromopropionic acid (6b) (411 mg, 60 %); b.p. 95 °C (18 mmHg), $^{1}$H-NMR ($CDCl_3$) 1.85 (dd, 3H, $J_{HH}$=6.9 Hz, $J_{13CH}$=131.0 Hz, $^{13}C\underline{H}_3CHBr$), 4.41 (dq, 1H, $J_{HH}$=6.9 Hz, $J_{13CCH}$=2.6 Hz, $^{13}CH_3C\underline{H}Br$); $^{13}$C-NMR ($CDCl_3$) 21.4; FAB-MS m/z 154 ($M^+$+1, 4 %), 156 ($M^+$+3, 4 %); IR ($CHCl_3$) 1725 (CO).

2-Bromopropionic acid, $^{1}$H-NMR ($CDCl_3$) 1.85 (d, 3H, $J_{HH}$=6.9 Hz, $C\underline{H}_3CHBr$), 4.41 (q, 1H, $J_{HH}$=6.9 Hz, $CH_3C\underline{H}Br$).

(S)-2-Bromopropionic acid (6e) prepared from L[(S)]-alanine (4e), $[\alpha]^{23}_D$=-26.2 (c=15.1, $CHCl_3$), Lit; $[\alpha]^{25}_D$=-25.3 (c=15.0, $CHCl_3$)[7].

(R)-2-Bromopropionic acid prepared from D[(R)]-alanine, $[\alpha]^{23}_D$=26.6 (c=15.1, $CHCl_3$).

**Sodium (S)-[2-$^{2}$H,3-$^{13}$C]propionate (7c) and Sodium (R)-[2-$^{2}$H,3-$^{13}$C]propionate (7b)**

(R)-[3-$^{13}$C]-2-Bromopropionic acid (6b) (411 mg, 2.67 mmol) was added to 1 M lithium triethyldeuterioborate in tetrahydrofuran (5 ml) at 0 °C under argon. This mixture was heated under reflux for 4 hr, then the reaction was quenched with water (10 ml), and the solution was adjusted to pH 4.0 with concentrated sulfuric acid. Leaving a minimum volume of the solvent, the propionate was distilled off with water. Water was added to the residue, and distillation was continued. The distillate was combined, and adjusted to pH 8.0 with a 0.1 N aqueous sodium carbonate solution. Freeze-drying gave sodium (S)-[2-$^{2}$H,3-$^{13}$C]propionate (7c) (211 mg, 81 %), $^{1}$H-NMR ($D_2O$) 0.93 (dd, 3H, $J_{HH}$=7.6 Hz, $J_{13CH}$=127.2 Hz, $^{13}C\underline{H}_3CHD$), 2.05 (m, 1H, $^{13}CH_3C\underline{H}D$); $^{13}$C-NMR ($D_2O$) 12.9.

Sodium [2-$^{2}$H]propionate (7d, 7e and 7f), $^{1}$H-NMR ($D_2O$) 0.96 (d, 3H, $J_{HH}$=7.7 Hz, $C\underline{H}_3CHD$), 2.07 (tq, 1H, $J_{HH}$=7.7 Hz, $J_{HD}$=2.3 Hz, $CH_3C\underline{H}D$).

**Sodium (R)-[3-$^{13}$C]-2-fluoropropionate (10b) and Sodium (S)-[3-$^{13}$C]-2-fluoropropionate (10c)**

Sodium nitrite (260 mg, 3.77 mmol) was added to a solution of L[(R)]-[3-$^{13}$C]alanine (4b) (99 mg, 1.10 mmol) in hydrogen fluoride-pyridine (2 ml) at -10 °C. The reaction mixture was stirred for 3 hr at room temperature, then the reaction was quenched with water (10 ml). The resulting solution was adjusted to pH 4.0 with a sodium hydrogen carbonate solid. Leaving a minimum volume of the solvent, the propionate was distilled off with water. Water was added to the residue and distillation was continued. The distillate was combined, and adjusted to pH 8.0 with a 0.1 N aqueous sodium carbonate solution. Freeze-drying gave sodium (R)-[3-$^{13}$C]-2-fluoropropionate (10b) (119 mg, 95 %), $^{1}$H-NMR ($D_2O$) 1.40 (ddd, 3H, $J_{HH}$=6.9 Hz, $J_{HF}$=24.4 Hz, $J_{13CH}$=128.6 Hz, $^{13}C\underline{H}_3CHF$), 4.83 (ddq, 1H, $J_{HH}$=6.9 Hz, $J_{HF}$=51.1 Hz, $J_{13CCH}$=2.8 Hz, $^{13}CH_3C\underline{H}F$); $^{13}$C-NMR ($D_2O$) 21.2 (d, $J_{HF}$=22.0 Hz).
Sodium 2-fluoropropionate (10d, 10e and 10f), $^{1}$H-NMR ($D_2O$) 1.41 (dd, 3H, $J_{HH}$=6.9 Hz, $J_{HF}$=24.4 Hz, $C\underline{H}_3CHF$), 4.84 (dq, 1H, $J_{HH}$=6.9 Hz, $J_{HF}$=50.8 Hz, $CH_3C\underline{H}F$).

**(R)-Methyl mandelate derivatives (9d, 9e, 9f, 11d, 11e and 11f) of $^{13}$C-unlabelled propionates**

A solution of deuterium-labelled sodium propionate (7d) (202 mg, 2.08 mmol) in water was adjusted to pH 4.0 with 1 N hydrochloric acid and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated. Dicyclohexylcarbodiimide (DCC) (454 mg, 2.20 mmol) and (R)-methyl mandelate (8) [(R)-methyl 2-hydroxy-2-phenylethanoate] (292 mg,

1.76 mmol) were added to a solution of the residue and 4-dimethylaminopyridine (DMAP) (4.7 mg) in dry dichloromethane (10 ml) at -10 °C under argon, and the reaction mixture was stirred for 3 hr at room temperature, then filtered and evaporated. Chromatography of the crude product on silica gel with ether:hexane (1:2) gave the corresponding (R)-methyl mandelate derivative (9d) (185 mg, 47 %) of sodium [2-$^{2}$H]propionate (7d).

(R)-Methyl mandelate derivative (9d) of sodium [2-$^{2}$H]propionate (7d), $^{1}$H-NMR ($CDCl_3$) 1.20 (d, 3H, $J_{HH}$=7.4 Hz, $C\underline{H}_3CHD$), 2.45, 2.51 (tq, 1H, $J_{HH}$=7.4 Hz, $J_{HD}$=2.4 Hz, $CH_3C\underline{H}D$), 3.72 (s, 3H, $C\underline{H}_3O$), 5.94 (s, 1H, $C\underline{H}O$), 7.39, 7.46 (m, 5H, phenyl); $^{2}$H-NMR ($CDCl_3$) 2.47, 2.54 (br, 1D, $CH\underline{D}$).

(R)-Methyl mandelate derivative (9f) of sodium (R)-[2-$^{2}$H]propionate (7f), $^{1}$H-NMR ($CDCl_3$) 1.20 (d, 3H, $J_{HH}$=7.4 Hz, $C\underline{H}_3CHD$), 2.51 (tq, 1H, $J_{HH}$=7.4 Hz, $J_{HD}$=2.4 Hz, $CH_3C\underline{H}D$), 3.72 (s, 3H, $C\underline{H}_3O$), 5.94 (s, 1H, $C\underline{H}O$), 7.39, 7.46 (m, 5H, phenyl); $^{2}$H-NMR ($CDCl_3$) 2.47 (br, 1D, $CH\underline{D}$).

(R)-Methyl mandelate derivative (9e) of sodium (S)-[2-$^{2}$H]propionate (7e), $^{1}$H-NMR ($CDCl_3$) 1.20 (d, 3H, $J_{HH}$=7.4 Hz, $C\underline{H}_3CHD$), 2.45 (tq, 1H, $J_{HH}$=7.4 Hz, $J_{HD}$=2.4 Hz, $CH_3C\underline{H}D$), 3.72 (s, 3H, $C\underline{H}_3O$), 5.94 (s, 1H, $C\underline{H}O$), 7.39, 7.46 (m, 5H, phenyl); $^{2}$H-NMR ($CDCl_3$) 2.54 (br, 1D, $CH\underline{D}$).

A solution of sodium 2-fluoropropionate (10d) (241 mg, 2.11 mmol) in water was adjusted to pH 4.0 with 1 N hydrochloric acid and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated. Dicyclohexylcarbodiimide (DCC) (561 mg, 2.72 mmol) and (R)-methyl mandelate (8) [(R)methyl 2-hydroxy-2-phenylethanoate] (291 mg, 1.75 mmol) were added to a solution of the residue and 4-dimethylaminopyridine (DMAP) (4.7 mg) in dry dichloromethane (10 ml) at -10 °C under argon, and the reaction mixture was stirred for 3 hr at room temperature, then

filtered and evaporated. Chromatography of the crude product on silica gel with ether:hexane (1:5) gave the corresponding (R)-methyl mandelate derivative (11d) (206 mg, 49 %) of sodium 2-fluoropropionate (10d).

(R)-Methyl mandelate derivative (11d) of sodium 2-fluoropropionate (10d), $^{1}$H-NMR ($CDCl_3$) 1.63, 1.71 (dd, 3H, $J_{HH}$=6.9 Hz, $J_{HF}$=23.6 Hz, $C\underline{H}_3CHF$), 3.74 (s, 3H, $C\underline{H}_3O$), 5.14, 5.18 (dq, 1H, $J_{HH}$=6.9 Hz, $J_{HF}$=48.4 Hz, $CH_3C\underline{H}F$), 6.03 (s, 1H, $C\underline{H}O$), 7.41, 7.46 (m, 5H, phenyl).

(R)-Methyl mandelate derivative (11e) of sodium (S)-2-fluoropropionate (10e), $^{1}$H-NMR ($CDCl_3$) 1.63 (dd, 3H, $J_{HH}$=6.9 Hz, $J_{HF}$=23.6 Hz, $C\underline{H}_3CHF$), 3.74 (s, 3H, $C\underline{H}_3O$), 5.18 (dq, 1H, $J_{HH}$=6.9 Hz, $J_{HF}$=48.4 Hz, $CH_3C\underline{H}F$), 6.03 (s, 1H, $C\underline{H}O$), 7.41, 7.46 (m, 5H, phenyl).

(R)-Methyl mandelate derivative (11f) of sodium (R)-2-fluoropropionate (10f), $^{1}$H-NMR ($CDCl_3$) 1.71 (dd, 3H, $J_{HH}$=6.9 Hz, $J_{HF}$=23.6 Hz, $C\underline{H}_3CHF$), 3.74 (s, 3H, $C\underline{H}_3O$), 5.14 (dq, 1H, $J_{HH}$=6.9 Hz, $J_{HF}$=48.4 Hz, $CH_3C\underline{H}F$), 6.03 (s, 1H, $C\underline{H}O$), 7.41, 7.46 (m, 5H, phenyl).

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