# $^{14}$C-LABELLING OF OPTICALLY ACTIVE FENVALERATE, (S)-α-CYANO-3-PHENOXY-BENZYL (S)-2-(4-CHLOROPHENYL)-3-METHYLBUTYRATE (II)

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## SUMMARY

*(S)-α-Cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate (fenvalerate Aα), an optically active insecticide, was labelled with carbon-14 individually at the benzyl ring (1a) and the chlorophenyl ring (1b) for use in metabolic studies. Ullmann reaction of 3-methylphenol-$^{14}C_6$ (2) with bromobenzene followed by oxygen oxidation gave 3-phenoxybenzoic-$^{14}C_6$ acid (4). Reduction of 4 followed by potassium dichromate oxidation of the alcohol (5) gave 3-phenoxybenzaldehyde-$^{14}C_6$ (6). Condensation of 6 with (S)-2-(4-chlorophenyl)-3-methylbutanoyl chloride and sodium cyanide afforded fenvalerate A-(benzyl-$^{14}C_6$), which on optical resolution gave 1a in 29% yield from 2. Isopropylation of 4-chlorophenyl-$^{14}C_6$-acetonitrile (9) followed by hydrolysis gave 2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyric acid which on optical resolution gave the (S)-acid (12). Esterification of the acid with α-cyano-3-phenoxybenzyl bromide yielded fenvalerate A-(phenyl-$^{14}C_6$), which was resolved to give 1b in 9% yield from 9.*

Key Words: Carbon-14, Fenvalerate, Insecticide, Optically Active

## INTRODUCTION

Fenvalerate [α-cyano-3-phenoxybenzyl 2-(4-chlorophenyl)-3-methylbutyrate] is an insecticide which provides high insecticidal activity together with adequate photostability and field persistency[1,2]. This compound has two assymetric carbons, giving four possible optical isomers named Aα, Aβ, Bα, and Bβ. These all differ in biological activity. Among them, fenvalerate Aα [an ester of the (S)-acid and the (S)-alcohol](1) has been found to be the most

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active[3].

Our preceding paper included the synthesis of fenvalerate A-$^{14}C$ (a 1:1 mixture of fenvalerate Aα and Aβ) labelled at the carbonyl, the cyano, and the alcoholic methyne carbons[4]. In the course of the metabolic studies, it was required to synthesize fenvalerate Aα-$^{14}C$. In this report, we describe the synthesis of fenvalerate Aα-$^{14}C$ labelled individually at the benzyl ring (1a) and the chlorophenyl ring (1b).

## DISCUSSION

In the preceding paper[4], we reported that 3-phenoxybenzoic acid was successfully converted by two-step reactions to 3-phenoxybenzaldehyde which in turn was condensed with 2-(4-chlorophenyl)-3-methylbutanoyl chloride and potassium cyanide to give fenvalerate in a good yield. From the fact, the series of reactions shown in Fig. 1 was selected to prepare fenvalerate Aα-(benzyl-$^{14}C_6$)(1a).

3-Phenoxytoluene-$^{14}C_6$ (3) was prepared by Ullmann reaction[5] using 3-methylphenol-$^{14}C_6$ (2) and bromobenzene. A 1:1 mixture of sodium and potassium salts of 2 was heated with an excess of bromobenzene in the presence of cuprous chloride as catalyst at 200° for 4 hr; giving 3 in 76% yield.

It is known that for compounds having a methyl group on an aromatic ring, autoxidation reactions in the presence of heavy metal salts eventually result in a carboxyl group[6,7]. An improved method[8], which included oxidation of 3-phenoxytoluene with oxygen in lower fatty acids and anhydrides using cobalt and bromine compounds, was found to give the best result for the preparation of 3-phenoxybenzoic acid. Thus, 3-phenoxytoluene-$^{14}C_6$ in a mixed solvent of acetic acid and acetic anhydride was oxidized with oxygen in the presence of cobalt (II) acetate, sodium bromide and sodium acetate at 100° for 3 hr to afford 3-phenoxybenzoic-$^{14}C_6$ acid (4) in an excellent yield (94%). Reduction of the acid (4) with lithium aluminum hydride gave 3-phenoxybenzyl-$^{14}C_6$ alcohol (5) in 99% yield.

Previously we converted 3-phenoxybenzyl alcohol to 3-phenoxybenzaldehyde in a reasonable yield (85%) by air oxidation in dimethylsulfoxide[4]. Recently,

however, an elaborate procedure using potassium dichromate and phase-transfer catalysts has been developed for oxidation of alcohols to aldehydes[9], and this procedure was applied to obtain 3-phenoxybenzaldehyde-$^{14}C_6$ (6). A mixture of the alcohol (5) and tetra-*n*-butylammonium hydrogensulfate was briefly (30 min) stirred at room temperature with potassium dichromate in 9N sulfuric acid to give an excellent yield (98%) of 3-phenoxybenzaldehyde-$^{14}C_6$ (6).

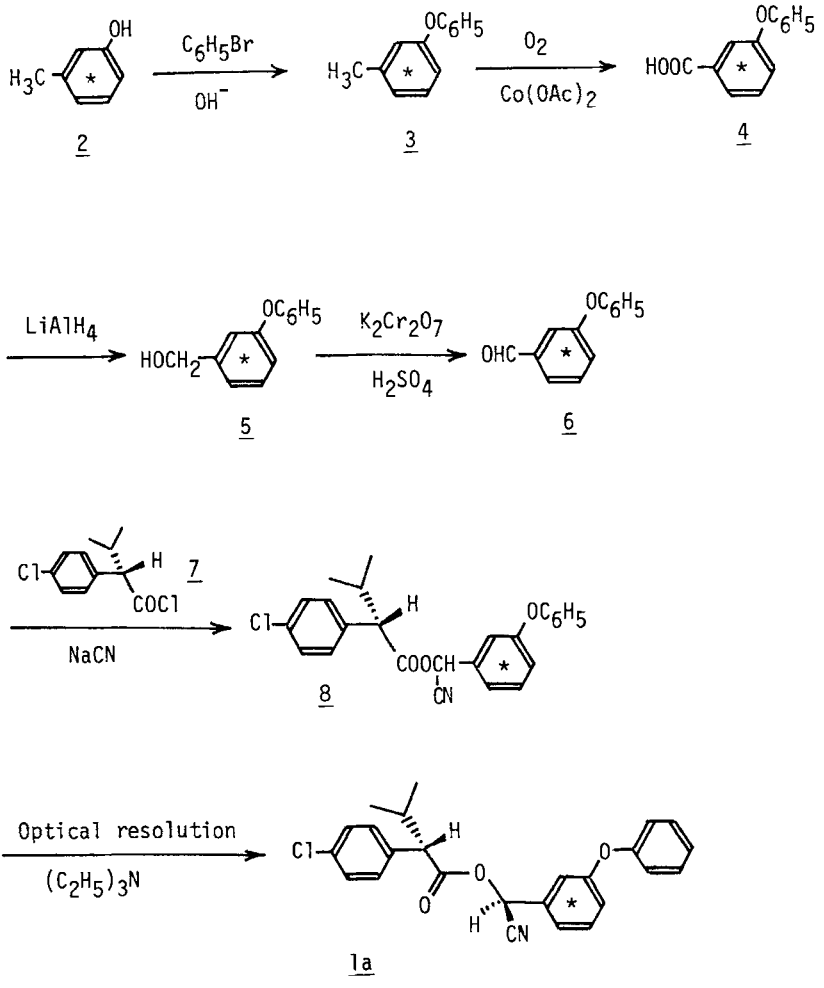


Fig. 1 Scheme for the synthesis of fenvalerate Aα-(benzyl-$^{14}C_6$)

Reaction of the aldehyde (6) with the optically active acid chloride (7) and sodium cyanide in the presence of benzyltriethylammonium chloride as phase-transfer catalyst[4] gave α-cyano-3-phenoxybenzyl-$^{14}C_6$ (S)-2-(4-chlorophenyl)-3-methylbutyrate [fenvalerate A-(benzyl-$^{14}C_6$)](8). After purification by column chromatography, the yield was 94% from 6.

Aketa, *et al.*[10] reported that fenvalerate Aα was prepared effectively from fenvalerate A by carring out simultaneously fractional crystallization and isomerization of the optical isomer (Aβ) to Aα in alcohols containing a basic catalyst. Thus, a solution of 8 and triethylamine in methanol was seeded with a small amount of unlabelled authentic fenvalerate Aα, and the mixture left to stand at -10-0° for approximately 70 hr; giving crude 1a as crystals. Recrystallization of the crude product from toluene-heptane afforded pure 1a in 45% yield from 8. The overall yield of 1a based on 3-methylphenol-$^{14}C_6$ was 29%.

The optical purity of fenvalerate Aα can be determined by the high performance liquid chromatographic (HPLC) method established by Horiba, *et al.*[11] When fenvalerate is reacted with *l*-menthol in hydrochloric acid at 100° for 2 hr, the four isomers of fenvalerate are quantitatively converted to α-*l*-menthyloxycarbonyl-3-phenoxybenzyl 2-(4-chlorophenyl)-3-methylbutyrates. These diastereomers can be separated and determined by HPLC on a μ-Porasil column. The optical purity of 1a determined by this method was 99%, and its optical rotation $[\alpha]_D$ was -12.1°.

Figure 2 illustrates the procedure for the synthesis of fenvalerate Aα-(phenyl-$^{14}C_6$)(1b). This procedure was mostly similar to that previously used for the synthesis of fenvalerate A-(carbonyl-$^{14}C$)[4].

4-Chlorophenyl-$^{14}C_6$-acetonitrile (9) was alkylated with isopropyl bromide in 45% sodium hydroxide aqueous solution containing benzyltriethylammonium chloride as catalyst to yield 2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyronitrile (10) in 68% yield. Hydrolysis of 10 with 64% sulfuric acid followed by optical resolution of the resulting racemic acid (11) with (-)-1-phenylethylamine gave (S)-2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyric acid (12). The yield of 12 was 28% from 10, and the product showed an optical purity of 98% with $[\alpha]_D$= +47.8°. The acid

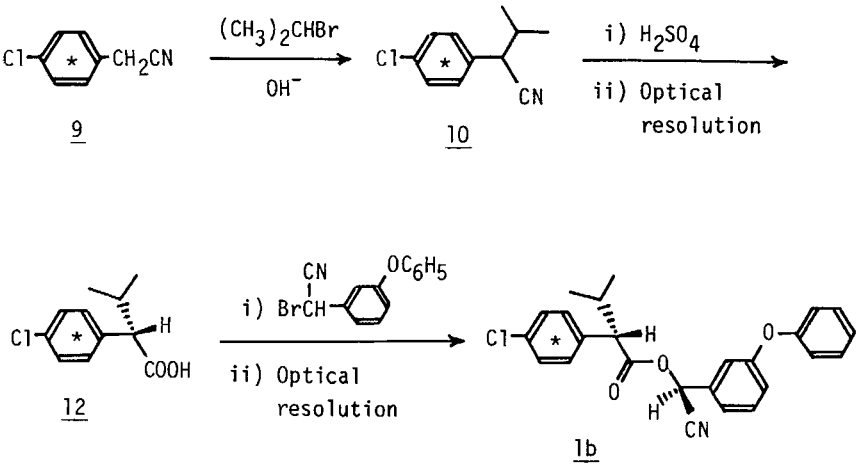


Fig. 2 Scheme for the synthesis of fenvalerate Aα-(phenyl-$^{14}C_6$)

(12) was condensed with α-cyano-3-phenoxybenzyl bromide (13) in methylchloroform-water containing potassium carbonate and tetra-*n*-butylammonium bromide to give fenvalerate A-(phenyl-$^{14}C_6$)(14) in 93% yield. Optical resolution of 14 was achieved by the method described above, and fenvalerate Aα-(phenyl-$^{14}C_6$)(1b) was obtained in 48% yield (an overall yield of 9% based on 9). Analysis of the final product by HPLC indicated an optical purity of 99% ($[\alpha]_D$= -12.0°).

## EXPERIMENTAL

Radio-thinlayer chromatography (RTLC) was carried out on Silica Gel 60 $F_{254}$ plate (Merck), and the radioactivity on the plate was determined by a Thinlayer Chromatogram Scanner (Aloka, Japan).

Radio-gaschromatography (RGC) was conducted on a Yanako G-80 gaschromatograph (Yanagimoto Co., Ltd., Japan) equipped with a RD-4 Gas-flow GM-counter (Aloka). Glass columns used were as follows: i) 3% Silicone SE-52 on Chromosorb (1.5 m × 3 mm I.D.) for the analyses of 3-phenoxybenzyl-$^{14}C_6$ alcohol and 3-phenoxybenz-aldehyde-$^{14}C_6$, ii) 10% Silicone DC QF-1 on Chromosorb (3 m × 3 mm I.D.) for fenvalerates-$^{14}C_6$, iii) 3% Silicone OV-17 on Chromosorb (2 m × 3 mm I.D.) for

4-Chlorophenyl-$^{14}C_6$-acetonitrile and 2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyronitrile. Operating conditions and retention times of these materials were described in the preceding paper[4].

High performance liquid chromatography was carried out on a Water's model 6000 liquid chromatograph equipped with a Water's model 440 fixed UV-detector (254 nm). A column packed with 10 μm LiChrosorb RP-18 (0.25 m × 4 mm I.D., Water's Associates Inc., Delaware) was used for the analysis of fenvalerate-$^{14}C_6$. The operating condition: mobile phase ethanol/dioxane/water=3/3/4 (v/v/v), pressure 128 Kg/cm$^2$, flow rate 1.2 ml/min, the retention time 29.6 min. A column packed with 10 μm μPorasil (0.3 m × 4 mm I.D.) was used for the analysis of l-menthyl ester of fenvalerate Aα-$^{14}C_6$. The operating condition: mobile phase hexane/ethyl acetate=500/3 (v/v), pressure 28 Kg/cm$^2$, flow rate 2.07 ml/min, the retention time 19.6 min[11]. Optical rotation was measured with a DIP 181 polarimeter (Japan Spectroscopic Co., Ltd.) in chloroform.

3-Phenoxytoluene-$^{14}C_6$ (3) -- A mixture of 3-methylphenol-$^{14}C_6$ (2)(40.5 mCi, 275 mg, 2.55 mmol), potassium hydroxide (67 mg, 1.20 mmol) and sodium hydroxide (48 mg, 1.20 mmol) in anhydrous benzene (10 ml) was heated at the reflux temperature for 1 hr, and the water produced during the period of reflux was azeotropically removed. After removal of benzene, bromobenzene (1.13 g, 7.2 mmol) and cuprous chloride (4 mg) were added to the residue, and the mixture heated with stirring at 190-210° for 4 hr. The reaction mixture was poured into ice-water and extracted with ether. The extract was washed successively with 10% potassium hydroxide solution and water, dried over sodium sulfate, and evaporated. The oily residue was chromatographed on silica gel and eluted with hexane. Evaporation of the main fraction gave 3-phenoxytoluene-$^{14}C_6$ (3)(30.6 mCi, 353 mg); the purity 99% on RTLC (hexane/ether=20/1, $R_f$-value=0.54); NMR (δ, $CDCl_3$): 2.29 (3H, s, $CH_3$), 6.60-7.42 (9H, m, aromatic H); mass spectrum (m/e): 184 ($M^+$, base peak), 169, 141, 91.

3-Phenoxybenzoic-$^{14}C_6$ Acid (4) -- To a reaction flask equipped with an oxygen

inlet tube, a thermometer and a condenser were added 3-phenoxytoluene-$^{14}C_6$ (3) (30.6 mCi, 353 mg, 1.92 mmol), cobalt (II) acetate (100 mg), sodium bromide (45 mg), sodium acetate (17 mg), acetic acid (7 ml) and acetic anhydride (5 ml). Oxygen was bubbled through the vigorously stirred reaction mixture, which was heated at 100-110° for 3 hr. The mixture was cooled, made up to 50 ml with ice-water, and extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to give 3-phenoxybenzoic-$^{14}C_6$ acid (4)(28.8 mCi, 387 mg); the purity 99% on RTLC (hexane/ethyl acetate=4/1, $R_f$-value=0.25); IR νmax ($CHCl_3$): 1695 $cm^{-1}$ (C=O).

3-Phenoxybenzyl-$^{14}C_6$ Alcohol (5) -- A mixture of 3-phenoxybenzoic-$^{14}C_6$ acid (4) (28.8 mCi, 387 mg, 1.81 mmol) and lithium aluminum hydride (750 mg, 20 mmol) in anhydrous ether (50 ml) was refluxed for 1 hr. The reaction mixture was cooled in an ice bath and ether saturated with water was added portionwise to destroy excess lithium aluminum hydride. The mixture was acidified with concentrated hydrochloric acid and extracted with ether. The extract was washed with 5% sodium carbonate solution and then with water, dried over sodium sulfate, and evaporated to give 3-phenoxybenzyl-$^{14}C_6$ alcohol (5)(28.5 mCi, 358 mg); the purity 99% on both GC and RTLC (chloroform methanol=9/1, $R_f$-value=0.44; ether/hexane=2/1, $R_f$-value=0.28); IR νmax ($CHCl_3$): 3600-3300 (OH), 1595 $cm^{-1}$ (phenyl).

3-Phenoxybenzaldehyde-$^{14}C_6$ (6) -- To a solution of 3-phenoxybenzyl-$^{14}C_6$ alcohol (5)(28.5 mCi, 387 mg, 1.79 mmol) in methylene chloride (8.8 ml) was added at room temperature a mixture of potassium dichromate (174 mg, 0.70 mmol) and tetra-*n*-butylammonium hydrogensulfate (54 mg) in 9N sulfuric acid (8.8 ml), and the mixture vigorously stirred at the same temperature for 0.5 hr. The methylene chloride solution was allowed to separate from the aqueous phase, and the aqueous phase was extracted with methylene chloride. The methylene chloride solution and the extract were combined, washed with water, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave an oily residue, which was chromatographed on silica gel and eluted with benzene. The main fraction was

was evaporated to give 3-phenoxybenzaldehyde-$^{14}C_6$ (6)(28.0 mCi, 348 mg); the purity 99% on both RGC and RTLC (benzene, ether/hexane=2/1, hexane/ethyl acetate =4/1, $R_f$-values=0.36, 0.46, 0.33, respectively); IR νmax (liquid film): 1690 $cm^{-1}$ (CHO); NMR (δ, $CDCl_3$): 6.84-7.70 (9H, m, aromatic H), 9.85 (1H, s, CHO); mass specturm (m/e): 198 ($M^+$, base peak), 169, 141, 93, 77, 51.

α-Cyano-3-phenoxybenzyl-$^{14}C_6$ (S)-2-(4-Chlorophenyl)-3-methylbutyrate (8) -- To a stirred solution of 3-phenoxybenzaldehyde-$^{14}C_6$ (6)(28.0 mCi, 348 mg, 1.76 mmol) and (S)-2-(4-chlorophenyl)-3-methylbutanoyl chloride (7)(486 mg, 2.10 mmol) in toluene-heptane (3/7 v/v, 2 ml) was added, at room temperature, a solution of sodium cyanide (230 mg, 4.80 mmol) and benzyltriethylammonium chloride (17 mg) in water (1 ml); and the mixture vigorously stirred at the same temperature for 5 hr. The reaction mixture was diluted with water (10 ml), extracted with ether, and the extract washed with water. Concentration of the dried extract gave an oily residue. Chromatography of the residue on silica gel with hexane-benzene (4/1-1/1 v/v) gave α-cyano-3-phenoxybenzyl-$^{14}C_6$ (S)-2-(4-chlorophenyl)-3-methylbutyrate (8)(26.4 mCi, 697 mg); the purity 99% on both RGC and RTLC (benzene, hexane/ether=2/1, chloroform/methanol=9/1, $R_f$-values=0.38, 0.45, 0.74, respectively); IR νmax ($CHCl_3$): 2300 (CN), 1745 $cm^{-1}$(C=O).

(S)-α-Cyano-3-phenoxybenzyl-$^{14}C_6$ (S)-2-(4-Chlorophenyl)-3-methylbutyrate (1a) -- To a solution of α-cyano-3-phenoxybenzyl-$^{14}C_6$ (S)-2-(4-chlorophenyl)-3-methylbutyrate (8)(26.4 mCi, 697 mg, 1.66 mmol) and triethylamine (20 mg) in methanol (1.5 ml) was seeded at -10° the crystals (8 mg) of unlabelled (S)-α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate. The mixture was stirred at -10-0° for 6 hr and then left to stand at the same temperature for 65 hr. The crystals precipitated was collected by filtration and washed with cold methanol. Recrystallization of the crystals from toluene-heptane (1/9 v/v, 1 ml) gave (S)-α-cyano-3-phenoxybenzyl-$^{14}C_6$ (S)-2-(4-chlorophenyl)-3-methylbutyrate (1a)(11.8 mCi, 318 mg, 15.5 mCi/mmol) as prisms; mp and mixed mp 61-62°; $[\alpha]_D^{20}$= -12.1° (c=1.5); IR νmax ($CH_2Cl_2$): 2320 (CN), 1745 $cm^{-1}$ (C=O); NMR (δ,

$CDCl_3$): 0.70 and 0.94 (each 3H, each d, J=7 Hz, isopropyl methyl H), 2.00-2.60 (1H, m, isopropyl methyne H), 3.21 (1H, d, J=10 Hz, -CH-CH$(CH_3)_2$), 6.33 (1H, s, -CH(CN)Ph), 6.85-7.58 (13H, m, aromatic H); mass spectrum (m/e): 419 ($M^+$), 225, 181, 169, 167, 152, 125 (base peak), 77; the purity 99% on GC, HPLC and RTLC; the optical purity determined as the *l*-menthyl ester 99% on HPLC.

2-(4-Chlorophenyl-$^{14}C_6$)-3-methylbutyronitrile (10) -- A mixture of 4-chlorophenyl-$^{14}C_6$-acetonitrile (9)(117 mCi, 592 mg, 3.19 mmol; purchased from Commissariat a L'Energie Atomique, France), isopropyl bromide (870 mg, 7.08 mmol), benzyltriethylammonium chloride (20 mg) and 44.7% sodium hydroxide solution (2 ml) was stirred at 50-55° for 3 hr. After adding benzyltriethylammonium chloride (16 mg), the mixture was stirred at the same temperature for further 3 hr. The mixture was extracted with ether; and the extract washed with water, dried over sodium sulfate, and evaporated. Column chromatography of the oily residue (116 mCi) on silica gel with hexane-ether (97/3 v/v) gave 2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyronitrile (10)(79.8 mCi, 517 mg); the purity 99% on both RGC and RTLC (hexane/ether=5/1, $R_f$-value=0.27); IR νmax ($CHCl_3$): 2250 $cm^{-1}$ (CN); mass spectrum (m/e): 195 and 193 ($M^+$), 103 (base peak), 101.

2-(4-Chlorophenyl-$^{14}C_6$)-3-methylbutyric Acid (11) -- A mixture of 2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyronitrile (10)(56.9 mCi, 368 mg, 1.90 mmol) and 64% sulfuric acid (3.5 ml) was stirred at 145-150° for 7 hr. The reaction mixture was cooled, diluted with water (40 ml), and extracted with ether. The ethereal solution was extracted with 5% sodium hydroxide solution. The aqueous solution was acidified with concentrated hydrochloric acid and re-extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to give 2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyric acid (11)(55.0 mCi, 391 mg); the purity 99% on RTLC (chloroform/methanol=3/2, $R_f$-value=0.56); IR νmax (nujol): 1705 $cm^{-1}$ (C=O).

(S)-2-(4-Chlorophenyl-$^{14}C_6$)-3-methylbutyric Acid (12) -- To a stirred solution of

2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyric acid (11)(55.0 mCi, 391 mg, 1.84 mmol) in 80% ethanol (3 ml) was added at room temperature a solution of (-)-1-phenylethylamine (156 mg, 1.29 mmol) in 80% ethanol (3 ml); and white precipitates appeared shortly thereafter. The mixture was diluted with 80% ethanol (2.2 ml) and refluxed until a clear solution was obtained. The solution was cooled slowly and allowed to stand at room temperature for 2 hr. Crystals precipitated were collected by filtration, and recrystallized from the same solvent (6 ml). The purified crystals were collected and washed with cold 80% ethanol. A mixture of the crystals and 5% hydrochloric acid (50 ml) was stirred at room temperature for 10 min, and extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to give (S)-2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyric acid (12)(16.0 mCi, 114 mg); the purity 99% on RTLC; $[\alpha]_D^{20}$ = +47.8° (c=1.0); mass spectrum (m/e): 214 and 212 ($M^+$), 169, 167 (base peak).

α-Cyano-3-phenoxybenzyl (S)-2-(4-Chlorophenyl-$^{14}C_6$)-3-methylbutyrate (14) -- To a solution of (S)-2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyric acid (12)(16.0 mCi, 114 mg, 0.54 mmol), unlabelled (S)-2-(4-chlorophenyl)-3-methylbutyric acid (50 mg, 0.23 mmol) and α-cyano-3-phenoxybenzyl bromide (13)(214 mg, 0.74 mmol) in methylchloroform (4 ml) was added, at room temperature, a mixture of potassium carbonate (55 mg), tetra-*n*-butylammonium bromide (25 mg) in water (2.5 ml). The mixture was stirred at 60-62° for 5 hr, diluted with water (30 ml), and extracted with methylchloroform. The extract was washed successively with 5% potassium carbonate solution, 5% hydrochloric acid, and water, and dried over sodium sulfate. The extract was evaporated under reduced pressure to give an oily residue which was chromatographed on silica gel with hexane-benzene (13/7 v/v). Evaporation of the main fraction gave α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl-$^{14}C_6$)-3-methylbutyrate (14)(14.9 mCi, 300 mg, 20.8 mCi/mmol); the purity 99% on RGC and RTLC; IR νmax ($CHCl_3$): 2300 (CN), 1745 $cm^{-1}$ (C=O).

(S)-α-Cyano-3-phenoxybenzyl (S)-2-(4-Chlorophenyl-$^{14}C_6$)-3-methylbutyrate (1b) -- To a solution of α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl-$^{14}C_6$)-3-methyl-

butyrate (14)((14.9 mCi, 300 mg, 0.72 mmol) and triethylamine (9 mg) in methanol (1 ml) was seeded a small amount of unlabelled (S)-α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate, and the mixture treated in the same manner described above for 1a. Recrystallization of the crude product from toluene-heptane (1/9 v/v) gave (S)-α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl-$^{14}C_6$)-2-methylbutyrate (1b)(7.12 mCi, 143 mg, 20.8 mCi/mmol); the purity 99% radiochemically, chemically, and optically; $[\alpha]_D^{20}$= -12.0° (c=1.0). The product was identical in every respect with the unlabelled authentic sample.

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