Journal of Fluorine Chemistry, 59 (1992) 225–232

Microbial asymmetric decarboxylation of fluorine-containing arylmalonic acid derivatives

Kenji Miyamoto, Shigeo Tsuchiya and Hiromichi Ohta

Department of Chemistry, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223 (Japan)

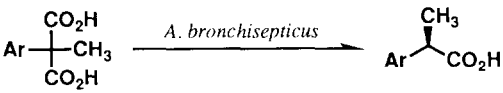
(Received September 23, 1991; accepted March 23, 1992)

Abstract

α-Methyl-α-(trifluoromethylphenyl)malonic acids have been incubated with *Alcaligenes bronchisepticus* to afford optically active α-arylpropionic acids. Generally, the chemical and optical yields of the reaction products were higher when the substituents on the aromatic ring were strongly electron-withdrawing. Decarboxylation of α-fluoro-α-phenylmalonic acid with the aid of the same bacterium afforded optically active α-fluoro-α-phenylacetic acid.

Introduction

Enzymatic and microbial transformation of synthetic substrates are playing an increasingly important role in synthetic organic chemistry, especially in asymmetric synthesis [1]. During the course of our continuing efforts to develop new types of biochemical conversions, we have recently demonstrated that microbial decarboxylation of α-aryl-α-methylmalonic acids (**1**) resulted in the formation of (*R*)-α-aryl-propionic acids (**2**) in high chemical and



1 2 (1)

optical yield [eqn. (1)] [2]. Since this reaction is the first example of the preparation of an optically active compound via enzymatic decarboxylation [3], it would be important to evaluate its scope and limitations. Fluorine-containing compounds often exhibit characteristic physiological activities, as well as unique chemical properties. Thus, we were interested in whether the new reaction could be applied to fluorinated compounds.

Results and discussion

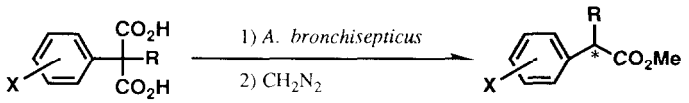
First, α-(fluorophenyl)-α-methylmalonic acids (**3**) were subjected to microbial reaction. Since we have shown previously that steric bulkiness of

0022-1139/92/$5.00

the aryl part of the substrate does not interfere with interaction with the enzyme system [2], the electronic and lipophilic characters of the fluorine atom were expected to control the reactivity. The reaction was carried out using microbial cells grown on phenylmalonic acid, at substrate concentrations of 0.3–0.5% relative to the medium. The results obtained are summarized in Table 1. α-(*o*-Fluorophenyl)-α-methylmalonic acid (**3a**) gave the corresponding propionic acid (**4a**) only in poor yield, with much of the starting material recovered intact. Taking into consideration the fact that the *o*-chloro-substituted compound (**3e**) did not react at all, the steric effect of the *ortho*-substituent appears critical for the reaction. Thus, *ortho* fluorine in **3a**, which is not substantially larger than hydrogen, does give some desired product, although in low yield (12%). The low enantiomeric excess (*e.e.*) of the product **4a** can be attributed, at least in part, to contamination of the racemate formed by co-existing non-enzymatic decarboxylation. The *m*-fluoro derivative (**3b**) afforded the desired chiral α-arylpropionic acid (**4b**) in high chemical and optical yield. On the other hand, the chemical yield of the reaction of the *p*-fluoro derivative (**4c**) was low compared with **4b**. As the reaction of α-(*p*-chlorophenyl)-α-methylmalonic acid proceeded smoothly, the lower reactivity of **3c** cannot be deduced as due to the steric effect of the fluorine atom. The electronic effect of the *p*-fluoro atom is small from the Hammett σ-value. Thus, the lipophilic effect of the atom is considered to be one of

TABLE 1

Microbial decarboxylation of malonic acid derivatives[a]



3 4

Substrate	X	σ-Value	R	Substrate conc. (%)	Yield (%)	*e.e.*[b] (%)	$[\alpha]_D$[d] (°)
a	*o*-F	–	CH_3	0.3	12	54	−33
b	*m*-F	0.34	CH_3	0.5	75	97	−68
c	*p*-F	0.06	CH_3	0.5	54	97	−71
d	H	0.00	CH_3	0.5	80	98	−96
e	*o*-Cl	–	CH_3	0.2	0	–	–
f	*m*-CF_3	0.43	CH_3	0.3	99	>95[c]	−53
				0.5	99	>95[c]	
g	*p*-CF_3	0.54	CH_3	0.3	88	97	−57
				0.5	91	95	
h	*p*-CH_3	−0.17	CH_3	0.3	44	>95[c]	−81
i	H		F	0.1	64	95	−116

[a]Incubation was carried out for 5 d.
[b]Determined by HPLC, unless otherwise stated.
[c]Determined by ^1H NMR spectroscopy.
[d]Measured in $CHCl_3$.

the reasons for the low yield. It might exert the effect only when bound directly to the *para* position of the aromatic ring, because the *p*-trifluoromethyl group rather favored the reaction as mentioned below.

The effect of a trifluoromethyl group is dramatic. While the *p*-methylphenyl derivative **3h** gave the malonate **4h** in only 44% yield after 5 day incubation, substitution of methyl by trifluoromethyl resulted in the formation of the corresponding malonate **4g** in excellent high *e.e.* in about 90% yield. The yield and optical purity of α-(*m*-trifluoromethylphenyl)propionate (**4f**) were also high as shown in Table 1. This is estimated to be due to the strong electron-withdrawing character of the trifluoromethyl group. Kinetics studies with the isolated enzyme are expected to give more precise information on the substituent effect on K_m and V_{max}, and investigations on this are now underway.

Variation of the other ligand (R) in **3** is very restrictive, and only when R = Me can the substrate be engaged at the active site of the enzyme. This is presumably due to the steric bulk of alkyl groups. What then will happen when R = F (**3i**)? The substrate was prepared by reaction of ethyl α-bromo-α-phenylacetate with potassium fluoride, followed by ethoxycarbonylation and hydrolysis. As expected, incubation of **3i** with *A. bronchisepticus* followed by methylation with diazomethane afforded optically active (95% *e.e.* by HPLC) methyl α-fluoro-α-phenylacetate in 64% yield. $[\alpha]_D^{25} - 116°$ (*c*, 0.94; $CHCl_3$). Thus, the microbial reaction provides a simple method for the preparation of optically active α-fluorinated carboxylic acid, which may be useful as components of liquid crystals.

The absolute configuration of the fluorine-containing products was tentatively assigned as *R* by comparing the elution order on HPLC and the sign of the optical rotation of the methyl esters with those of other α-aryl propionates [2].

Experimental

Melting points were determined on a Yanaco MP-S3 apparatus and are reported uncorrected. IR spectra were recorded on a JASCO A-202 spectrometer. ^1H NMR spectra were recorded on a JEOL JNM FX-90 or JEOL JNM GX-400 spectrometer using TMS as the internal standard. Optical rotations were measured on a JASCO DIP-360 polarimeter. Mass spectra were obtained on a Hitachi M-80 instrument at 70 eV. Wako Gel B-5F and silica gel 60 K070-WH (70–230 mesh) of Katayama Chemical Co. were used for preparative TLC and column chromatography.

Synthesis of the starting material ***3a–3i*** *[4]*

Dimethyl α-(p-trifluoromethylphenyl)malonate)

To a suspension of NaH (2.03 g, in 60% mineral oil, 50.8 mmol) in anhydrous refluxing THF (50 ml) containing dimethyl carbonate (4.13 g, 45.8 mmol) was added methyl α-(*p*-trifluoromethylphenyl)acetate (5.00 g,

22.9 mmol). The stirring was continued for 2 h. After quenching with water, the mixture was extracted with ether. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to give 3.24 g (52%) of dimethyl α-(*p*-trifluoromethylphenyl)malonate. Melting point, 49 ~ 50 °C. ^{1}H NMR $CDCl_3$ δ: 3.77 (s, 6H, CH_3); 4.71 (s, 1H, α-H); 7.51 (d, J = 8.8 Hz, 2H, Ar–H); 7.65 (d, J = 8.8 Hz, 2H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1740; 1620; 1325; 1220; 1160; 1120; 840.

*Dimethyl α-methyl-α-(*p*-trifluoromethylphenyl)malonate*

To a suspension of NaH (0.49 g, in 60% mineral oil, 12.4 mmol) in anhydrous THF (30 ml) was added dimethyl α-(*p*-trifluoromethylphenyl)-malonate (2.21 g, 8.00 mmol) and the mixture was stirred for 15 min at 0 °C. Then iodomethane (5.70 g, 40.2 mmol) was added and the resulting mixture was stirred for 2 h at 60 °C. After quenching with water, the mixture was extracted with ether. The organic layer was washed with 10% $NaHSO_3$ (aq.) solution, water and brine. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to give 1.76 g (76%) of dimethyl α-methyl-α-(*p*-trifluoromethylphenyl)-malonate. ^{1}H NMR $CDCl_3$ δ: 1.89 (s, 3H, CH_3); 3.78 (s, 6H, CH_3); 7.46 (d, J = 9.0 Hz, 2H, Ar–H); 7.62 (d, J = 9.0 Hz, 2H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1740; 1620; 1330; 1255; 1165; 1120; 840.

*α-Methyl-α-(*p*-trifluoromethylphenyl)malonic acid (**3g**)*

Dimethyl α-methyl-α-(*p*-trifluoromethylphenyl)malonate (1.15 g, 3.96 mmol) was added to a mixture of 2 N aqueous KOH (12 ml) and EtOH (12 ml), and the resulting mixture was stirred overnight at room temperature. After evaporation of ethanol, the mixture was acidified with 2 N HCl, saturated with NaCl and extracted with ether. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization from ether/hexane to afford 0.85 g of α-methyl-α-(*p*-trifluoromethylphenyl)malonic acid (**3g**) as colorless crystals (84%). Melting point, 145 ~ 146 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 1.95 (s, 3H, CH_3); 6.64–6.90 (broad s, 2H, COOH); 7.51–7.70 (m, 4H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1705; 1615; 1330; 1260; 1210; 1160; 1125; 830.

Other substrates were prepared in essentially the same manner as above.

*α-(o-Fluorophenyl)-α-methylmalonic acid (**3a**)*

Melting point, 138 ~ 139 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 1.94 (s, 3H, CH_3); 5.90–6.36 (broad s, 2H, COOH); 6.94–7.53 (m, 4H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1710; 1615; 1585; 1495; 1280; 1240; 1210; 1125; 1100; 760.

*α-(m-Fluorophenyl)-α-methylmalonic acid (**3b**)*

Melting point, 144.5 ~ 146 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 1.92 (s, 3H, CH_3); 5.30–6.60 (broad s, 2H, COOH); 6.75–7.55 (m, 4H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1720; 1610; 1590; 1495; 1290; 1250; 1180; 1165; 1130; 785; 710.

*α-(p-Fluorophenyl)-α-methylmalonic acid (**3c**)*

Melting point, 149 ~ 151 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 1.92 (s, 3H, CH_3); 6.80–7.70 (broad s, 2H, COOH); 6.80–7.70 (m, 4H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1710; 1600; 1510; 1295; 1270; 1240; 1210; 1170; 1140; 835; 695.

*α-Methyl-α-phenylmalonic acid (**3d**)*

Melting point, 157 ~ 158 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 1.93 (s, 3H, CH_3); 6.50–6.90 (broad s, 2H, COOH); 7.17–7.60 (m, 5H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1700; 1500; 1295; 1270; 1130; 748; 695.

*α-(o-Chlorophenyl)-α-methylmalonic acid (**3e**)*

Melting point, 137 ~ 138 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 2.05 (s, 3H, CH_3); 7.32–7.57 (m, 4H, Ar–H); 940–10.20 (broad s, 2H, COOH) ppm. IR KBr ν_{max} cm^{-1}: 1700; 1280; 1235; 1200; 1130; 743.

*α-Methyl-α-(m-trifluoromethylphenyl)malonic acid (**3f**)*

Melting point, 126 ~ 128 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 1.95 (s, 3H, CH_3); 6.60–7.10 (broad s, 2H, COOH); 7.46–7.75 (m, 4H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1730; 1600; 1500; 1330; 1280; 1215; 1165; 1120; 810; 705.

*α-Methyl-α-(p-methylphenyl)malonic acid (**3h**)*

Melting point, 153 ~ 155 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6 = 9:1 δ: 1.89 (s, 3H, CH_3); 2.33 (s, 3H, Ar–CH_3); 5.90–6.65 (broad s, 2H, COOH), 7.14 (d, J = 7.7 Hz, 2H, Ar–H); 7.35 (d, J = 7.7 Hz, 2H, Ar–H) ppm. IR KBr ν_{max} cm^{-1}: 1700; 1615; 1520; 1295; 1270; 1210; 1190; 820; 510.

*α-Fluoro-α-phenylmalonic acid (**3i**)*

Ethyl α-bromo-α-phenylacetate: A mixture of α-bromo-α-phenylacetic acid (10.01 g, 46.53 mmol) and *p*-toluenesulfonic acid monohydrate (500 mg) in EtOH (200 ml) was stirred under reflux for 5 h. After evaporation of the solvent, ether and saturated $NaHCO_3$ solution were added. The ether layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent *in vacuo* gave a residue which was purified by distillation to afford 9.48 g (84%) of ethyl α-bromo-α-phenylacetate as a colorless oil. Boiling point, 152 ~ 153 °C/34 mmHg. ^{1}H NMR $CDCl_3$ δ: 1.28 (t, J = 7.5 Hz, 3H, CH_3); 4.24 (q, J = 7.5 Hz, 2H, CH_2); 5.34 (s, 1H, α-H); 7.20–7.70 (m, 5H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1740; 1390; 1366; 1342; 1302; 1272; 1211; 1167; 1139; 1020; 692.

Ethyl α-fluoro-α-phenylacetate: A mixture of ethyl α-bromo-α-phenylacetate (6.01 g, 24.27 mmol), potassium fluoride (4.31 g, 74.22 mmol) and acetamide (20 g) was stirred overnight at 120 °C. After cooling to room temperature and addition of 2 N HCl, the mixture was extracted with ether. The ether layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the mixture was concentrated *in vacuo* and the residue was purified by Kugelrohr distillation to give 3.20 g (71%) of ethyl α-fluoro-α-phenylacetate as a colorless oil. Boiling point [5] 120~140 °C/1 mmHg. ^{1}H NMR $CDCl_3$ δ: 1.26 (t, J=7.0 *Hz*, 3H, CH_3); 4.25 (dq, J_1=7.0 Hz, J_2=1.3 Hz, 2H, CH_2); 5.77 (d, J=47.9 Hz, 1H, α-H); 7.30–7.63 (m, 5H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1757; 1370; 1270; 1215; 1185; 1083; 1052; 1022; 730; 695.

Diethyl α-fluoro-α-phenylmalonate: To a solution of diisopropylamine (1.08 g, 10.71 mmol) in dry THF (10 ml) was added a 1.49 M solution of Bu^nLi in hexane (6.64 ml, 9.89 mmol) with stirring at 0 °C for 15 min. Ethyl α-fluoro-α-phenylacetate (1.50 g, 8.23 mmol) was added at −78 °C and the mixture was stirred for 5 min at that temperature. Then ethyl chloroformate (1.07 g, 9.89 mmol) was added and the stirring was continued for 15 min at the same temperature. The mixture was quenched with phosphate buffer (pH 6.8) and extracted with ether. The ether layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate=9:1) to give 2.09 g (100%) of diethyl α-fluoro-α-phenylmalonate as a colorless oil. ^{1}H NMR $CDCl_3$ δ: 1.27 (t, J=7.5 Hz, 6H, CH_3); 4.29 (q, J=7.5 Hz, 4H, CH_2); 7.18–7.73 (m, 5H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1755; 1368; 1265; 1218; 1097; 1068; 1040; 1015; 732; 695.

α-Fluoro-α-phenylmalonic acid monohydrate (**3i**): to a mixture of 85% aqueous KOH (2.24 g, 33.93 mmol) and dry ethanol (40 ml) was added diethyl α-fluoro-α-phenylmalonate (2.09 g, 8.22 mmol) at room temperature and the mixture was stirred for 10 min. The resulting salt was filtered and dissolved in water. The solution was cooled to 0 °C and made acidic (pH 2) with 2 N HCl, saturated with NaCl and extracted with ether. The ether layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent gave a residue which was purified by recrystallization four times from a mixture of ether/benzene/hexane to give 0.99 g (61%) of α-fluoro-α-phenylmalonic acid monohydrate (**3i**) as colorless crystals. Melting point 111~112 °C (dec.). ^{1}H NMR $CDCl_3$/acetone-d_6=9:1 δ: 7.21–7.85 (m, 7H) ppm. IR KBr ν_{max} cm^{-1}: 1720; 1500; 1270; 1230; 1200; 1125; 1102; 1072; 1040; 725; 690. Anal.: Found: C, 50.16; H, 4.00%. Calcd. for $C_9H_7FO_4 \cdot H_2O$: C, 50.01; H, 4.20%.

Microbial reaction

The composition of the basal medium was as follows; 1% $(NH_4)_2HPO_4$, 0.2% K_2HPO_4, 0.03% $MgSO_4 \cdot 7H_2O$, 10 ppm $FeSO_4 \cdot 7H_2O$, 8 ppm $ZnSO_4 \cdot 7H_2O$, 8 ppm $MnSO_4 \cdot 4H_2O$, 0.02% yeast extract and 0.01 ppm D-biotin, pH 7.2.

To a 500 ml Sakaguchi flask was added the sterilized basal medium (50 ml) containing phenylmalonic acid (250 mg) and peptone (50 mg). The mixture was inoculated with *A. bronchisepticus* and shaken for 4 d at 30 °C. The substrate **3** was then added to the resulting suspension and the incubation was continued for an additional 5 d. The broth was made acidic with 2 N HCl, saturated with NaCl and extracted four times with ether. The ether layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was esterified with diazomethane, followed by purification by preparative TLC (hexane/ethyl acetate = 4:1).

*Microbial reaction products (**4a–4i**)*

*Methyl α-(o-fluorophenyl)propionate (**4a**)*

^{1}H NMR $CDCl_3$ δ: 1.50 (d, J = 7.0 Hz, 3H, CH_3 at α-C); 3.68 (s, 3H, CH_3); 4.03 (q, J = 7.0 Hz, 1H); 6.93–7.38 (m, 4H, Ar–H) ppm. Ir ν_{max} cm^{-1}: 1740; 1620; 1590; 1495; 1340; 1230; 1210; 1170; 1110; 760. Ms m/z (rel. intensity): 77 (6); 103 (26); 123 (100); 182 (27, M^+); 183 (3, M + 1).

*Methyl α-(m-fluorophenyl)propionate (**4b**)*

^{1}H NMR $CDCl_3$ δ: 1.49 (d, J = 7.0 Hz, 3H, CH_3); 3.68 (s, 3H, CH_3); 3.72 (q, J = 7.0 Hz, 1H); 6.84–7.40 (m, 4H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1740; 1610; 1590; 1490; 1335; 1260; 1230; 1200; 1170; 1145; 1100; 780; 690. MS m/z (rel. intensity): 40 (29); 44 (8); 77 (6); 103 (28); 123 (100); 182 (32, M^+); 183 (3, M + 1).

*Methyl α-(p-fluorophenyl)propionate (**4c**)*

^{1}H NMR $CDCl_3$ δ: 1.48 (d, J = 7.0 Hz, 3H, CH_3); 3.66 (s, 3H, CH_3); 3.71 (q, J = 7.0 Hz, 1H); 6.89–7.34 (m, 4H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1740; 1605; 1510; 1340; 1225; 1210; 1160; 840. MS m/z (rel. intensity): 40 (23); 69 (26); 103 (47); 123 (100); 182 (26, M^+).

*Methyl α-phenylpropionate (**4d**)*

^{1}H NMR $CDCl_3$ δ: 1.50 (d, J = 7.0 Hz, 3H, CH_3); 3.65 (s, 3H, CH_3); 3.72 (q, J = 7.0 Hz, 1H); 7.22–7.50 (m, Ar–H) ppm. IR ν_{max} cm^{-1}: 1740; 1602; 1497; 1330; 1245; 1207; 1162; 770; 734. MS m/z (rel. intensity): 40 (41); 43 (16); 44 (13); 51 (13); 69 (14); 77 (24); 79 (15); 91 (15); 103 (14); 105 (100); 119 (17); 164 (14, M^+).

*Methyl α-(m-trifluoromethylphenyl)propionate (**4f**)*

^{1}H NMR $CDCl_3$ δ: 1.54 (d, J = 8.0 Hz, 3H, CH_3 at α-C); 3.69 (s, 3H, CH_3); 3.79 (q, J = 8.0 Hz, 1H at α-C); 7.43–7.56 (m, 4H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1740; 1600; 1495; 1330; 1255; 1210; 1165; 1115; 870; 810; 705. MS m/z (rel. intensity): 59 (12); 77 (4); 103 (6); 127 (11); 133 (40); 153 (31); 173 (100); 213 (16); 232 (82, M^+); 233 (13, M + 1).

*Methyl α-(p-trifluoromethylphenyl)propionate (**4g**)*

^{1}H NMR $CDCl_3$ δ: 1.52 (d, J = 7.0 Hz, 3H, CH_3); 3.68 (s, 3H, CH_3); 3.79 (q, J = 7.0 Hz, 1H); 7.40 (d, J = 8.6 Hz, 2H, 2-H, 6-H); 7.59 (d, J = 8.6 Hz, 3-H, 5-H) ppm. IR ν_{max} cm^{-1}: 1740; 1615; 1320; 1250; 1210; 1160;

1120; 840. MS *m/z* (rel. intensity): 40 (30); 59 (31); 69 (11); 77 (11); 103 (17); 119 (13); 127 (22); 133 (52); 151 (14); 153 (31); 173 (100); 213 (12); 232 (20, M^+).

*Methyl α-(p-methylphenyl)propionate (**4h**)*

^{1}H NMR $CDCl_3$ δ: 1.47 (d, J=7.5 Hz, 3H, CH_3); 2.32 (s, 3H, Ar–CH_3); 3.65 (s, 3H, CH_3); 3.70 (q, J=7.5 Hz, 1H); 7.14–7.22 (m, 4H, Ar–H) ppm. Ir ν_{max} cm^{-1}: 1740; 1610; 1580; 1515; 1340; 1250; 1165; 860; 820. MS m/z (rel. intensity): 39 (16); 40 (19); 51 (11); 65 (14); 77 (19); 91 (31); 103 (14); 117 (23); 119 (100); 178 (19, M^+)

*Methyl α-fluoro-α-phenylacetate (**4i**)*

^{1}H NMR $CDCl_3$ δ: 3.37 (s, 3H, CH_3); 5.74 (d, J=49.5 Hz, 1H); 7.26–7.57 (m, 5H, Ar–H) ppm. IR ν_{max} cm^{-1}: 1752; 1484; 1271; 1210; 1192; 1077; 1045; 1015; 1000; 963; 775; 723; 686. MS *m/z* (rel. intensity): 40 (20); 59 (15); 74 (9); 83 (9); 105 (28); 109 (100); 110 (6); 168 (15, M^+); 169 (1, M+1).

Determination of the enantiomeric excess

The enantiomeric excess (*e.e.*) was determined from the 400 MHz ^{1}H NMR spectrum in the presence of a chiral shift reagent tris[3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] for **4f** and **4h**. The *e.e.* of all the other products was determined by HPLC analysis (chiral cell OJ of Daicell Chem. Ind. Ltd., 4.6 mm×250 mm, eluent: hexane/isopropanol=50:1, 0.2 ml min^{-1}).

References

1 Recent reviews: (a) H. Yamada and S. Shimizu, *Angew. Chem., Int. Ed. Engl., 27* (1988) 622; (b) C.-S. Chen and C. J. Sih, *Ibid., 28* (1989) 695; (c) C.-H. Wong, *Science, 244* (1989) 1145; (d) C.-H. Wong, *Chemtracts (Org. Chem), 3* (1990) 91. (e) D. H. G. Crout and M. Christen, in R. Scheffold, (ed.), *Modern Synthetic Methods*, Springer-Verlag, Berlin, Heidelberg, Vol. 1, 1989, p. 1.

2 (a) K. Miyamoto and H. Ohta, *J. Am. Chem. Soc., 112* (1990) 4077; (b) K. Miyamoto and H. Ohta, *Biocatalysis, 5* (1991) 49.

3 (a) O. Toussaint, P. Capdevielle and M. Maumy, *Tetrahedron Lett., 28* (1980) 539; (b) L. Verbit, T. R. Halbert and R. B. Patterdon, *J. Org. Chem., 40* (1975) 1649.

4 J. M. Domagala and R. D. Bach, *J. Org. Chem., 44* (1979) 2429.

5 D. Bethall and K. McDonald, *J. Chem. Soc. Perkin Trans. 2,* (1977) 671.