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Research Article

An efficient laboratory synthesis of α-deuteriated profens

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Summary

An efficient and practical laboratory synthesis of a series of 2-deuterio-2-arylpropionic acids (α-deuterioprofens) is described. The levels of deuterium incorporation are high and the products are synthetically useful. Copyright © 2006 John Wiley & Sons, Ltd.

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Introduction

The synthesis of non-steroidal anti-inflammatory isotopically labelled profens (2-aryl propionic acids) is well documented.[1] These particular derivatives have found widespread use as probes for their biological mode of action.[2]

Results and discussion

The continuing development of novel methodology for direct incorporation of non-radioactive isotopic labels within organic molecules for chemical and biological mechanistic studies is paramount.[3] The majority of this attention has focused on deuterium incorporation involving simple carbon–hydrogen bond exchange reactions.[4] Many of these processes rely on simple

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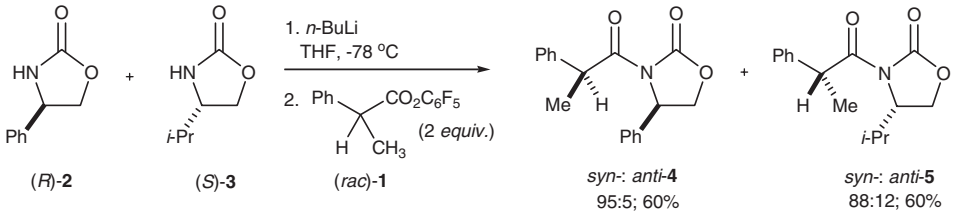

Scheme 1.

deprotonation, followed by deuteriation at mildly acidic centres.[5] For experimental ease, most hydrogen–deuterium exchange reactions are performed under thermodynamic control by using a suitable deuterium donor as the reaction solvent to drive the reaction to completion.[6]

We have recently become interested in the parallel resolution[7] of racemic profen adducts, like (*rac*)-**1**, using a *quasi*-enantiomeric combination of oxazolidinones, such as (*R*)-**2** and (*S*)-**3**, as parallel resolving agents (Scheme 1).[8] Addition of adduct (*rac*)-**1** to a stirred solution of lithiated oxazolidinones [derived from the deprotonation of (*R*)-**2** and (*S*)-**3** with *n*-BuLi] in THF at $-78^{\circ}C$, gave the resolved adducts *syn*-**4** and *syn*-**5** in good yield with high levels of diastereoselectivity (Scheme 1). In order to probe this reaction type further, we were required to synthesize of a series of racemic deuterium labelled profen acids, such as Ibuprofen [D_1]-**9**, based on the parent skeleton of 2-phenyl-propionic acid **6** (Scheme 2). We chose to limit our attention to the synthesis of four structurally related deuterium labelled adducts, namely, 2-deuterio-2-phenyl-propionic acid [D_1]-**6**, 2-deuterio-2-phenyl-butyric acid [D_1]-**7**, 2-deuterio-2-tolyl-propionic acid [D_1]-**8** and 2-deuterio-2-(4-isobutyl-phenyl)-propionic acid [D_1]-**9** as these were structurally similar to the parent 2-phenyl-propionic acid **6** (Scheme 2). We now report our laboratory synthesis for these particular 2-deuterio-2-phenyl-propionic acids.

We first chose to use a synthetic procedure which was scaleable, relatively inexpensive, and required little or no post-purification. With this aim in mind, we first focused our attention on the synthesis of 2-deuterio-2-phenyl-propionic acid [D_1]-**6** (Scheme 3). To ensure efficient proton–deuterium exchange at the less acidic *C*(2) position of this carboxylic acid, we chose to protect the carboxylic acid motif as its ethyl ester derivative. Treatment of the 2-phenyl-propionic acid **6** with toluene-*p*-sulphonic acid in ethanol, gave the corresponding ethyl 2-phenyl-propionate **10** in 98% yield (Scheme 3). With this substrate in hand, we next probed the synthesis of trideuteriomethyl 2-deuterio-2-phenylpropionate [D_4]-**11** using traditional hydrogen–deuterium exchange conditions (Scheme 3). For this hydrogen–deuterium exchange process, we decided to use [D_3]-NaOMe as our Brønsted base (formed by the simple addition of sodium hydride to [D_4]-MeOH) as this process could easily

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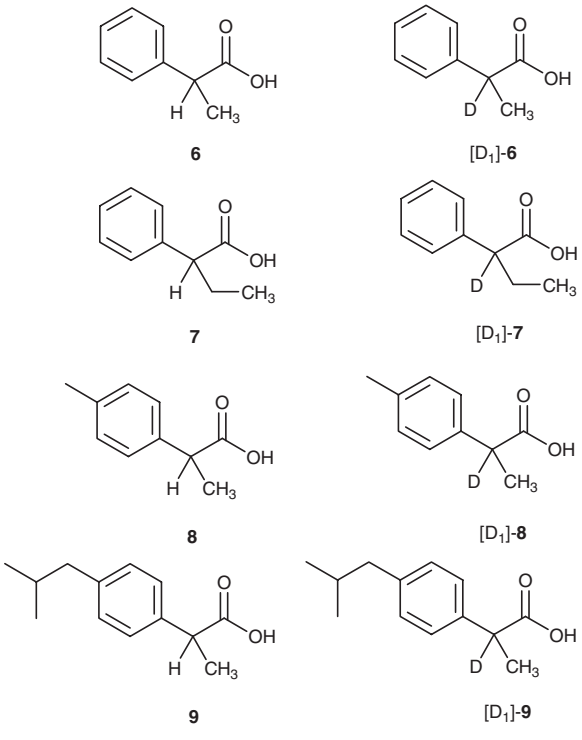
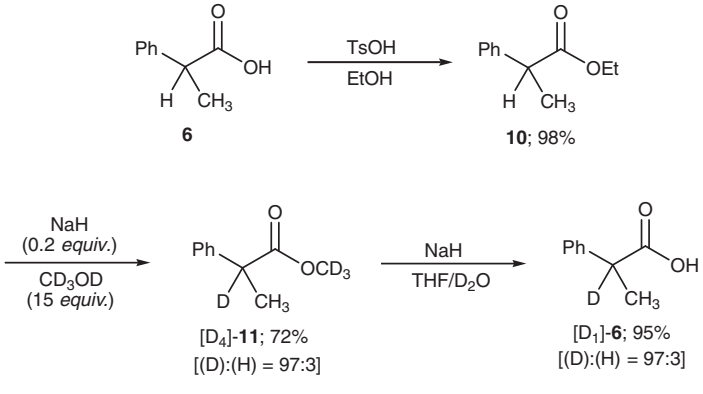


Scheme 2.



Scheme 3.

be monitored by ^{1}H NMR spectroscopy. Addition of sodium hydride (~40 mol%) to a stirred solution of ethyl 2-phenyl-propionate **10** and [D_4]-MeOH (~30 equivalents) in THF at room temperature, gave after 24 h, the required trideuteriomethyl 2-deuterio-2-phenylpropionate [D_4]-**11** in 72% yield with good levels of deuterium incorporation ([D] : [H] = 82 : 18). The

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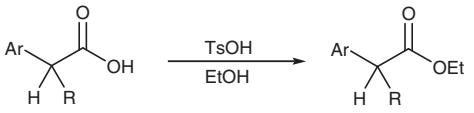

6-9 **10-14**

Entry	Starting material	Ar	R	Ethyl ester
1	**6**	Ph	Me	**10**; 98%
2	**7**	Ph	Et	**12**; 95%
3	**8**	Tol	Me	**13**; 95%
4	**9**	4-*i*-Bu-C_6H_4	Me	**14**; 98%

Scheme 4.

levels of deuterium incorporation could be increased further to > 95 : < 5 ([D] : [H]) by doubly repeating this procedure.[†] It is interesting to note that trans-etherification of the ethyl ester **10** to the trideuteriomethyl ester [D_3]-**11** occurs faster than simple hydrogen–deuterium exchange. Hydrolysis of ester [D_4]-**11** using sodium hydride in THF/D_2O (ratio = 3 : 1 by volume), followed by an acidic work-up [using dilute HCl (3 M)] gave, the required 2-deuterio-2-propionic acid [D_1]-**6** in good yield (95%) and with high levels of deuterium incorporation ([D] : [H] = 97 : 3).

With this information in hand, we next chose to investigate the deuteriation of a variety of 2-aryl-substituted carboxylic acids **6**, **7**, **8** and **9** under our standard conditions (as outlined in Schemes 2 and 3). The ethyl esters **12**, **13** and **14** were efficiently synthesized in good yields (95–98%) by refluxing the corresponding 2-aryl-substituted carboxylic acids **7**, **8** and **9** and toluene-*p*-sulphonic acid in ethanol for 12 h (Scheme 4). Deuteriation of these ethyl esters **10**, **12**, **13** and **14** at their *C*(2)-position was achieved by three sequential hydrogen–deuterium exchange reactions using NaOMe in [D_1]-MeOH to give the corresponding methyl esters [D_1]-**11**, [D_1]-**15**, [D_1]-**16** and [D_1]-**17**, respectively, in good yields (Scheme 5). The levels of deuterium incorporation were determined by ^{1}H NMR spectroscopy and were shown to be excellent ([D] : [H] => 94 : < 6). Formation of the mono-deuteriated 2-aryl-substituted carboxylic acids [D_1]-**6**, [D_1]-**7**, [D_1]-**8** and [D_1]-**9** were achieved in excellent yield (~50%) by addition of sodium hydride to a stirred solution of the methyl esters [D_1]-**11**, [D_1]-**15**, [D_1]-**16** and [D_1]-**17** in THF/D_2O (ratio = 3 : 1 by volume). The levels of deuterium incorporation were found to be

[†] The levels of deuterium incorporation ([D] : [H]) from the first, second and third sequential reactions were 82 : 18, 92 : 8 and 97 : 3, respectively.

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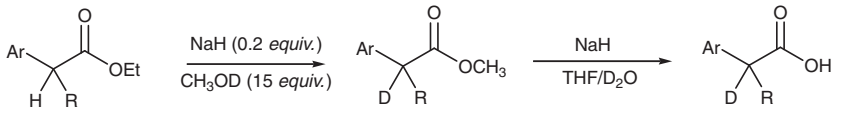
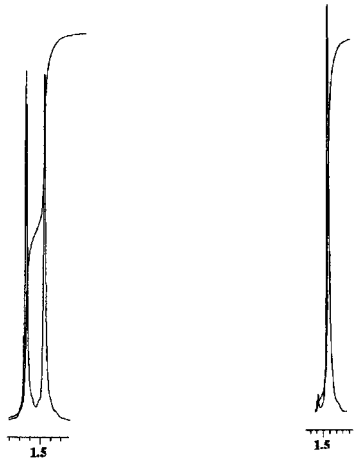


10 and **12-14** [D_1]-**11** and [D_1]-**15-17** [D_1]-**6** and [D_1]-**7-9**

Entry	Ethyl ester	Ar	R	[D_1]-methyl ester	([D]:[H])	[D_1]-carboxylic acid	([D]:[H])
1	**10**	Ph	Me	[D_1]-**11**; 83%	97:3	[D_1]-**6**; 87%	96:4
2	**12**	Ph	Et	[D_1]-**15**; 57%	95:5	[D_1]-**7**; 63%	95:5
3	**13**	Tol	Me	[D_1]-**16**; 48%	97:3	[D_1]-**8**; 83%	97:3
4	**14**	4-*i*-Bu-C_6H_4	Me	[D_1]-**17**; 44%	94:6	[D_1]-**9**; 80%	94:6

Scheme 5.



Methyl doublet for **9** at 1.50 ppm ($^3J_{C,H}$ = 7.2 Hz)

Methyl singlet for [D_1]-**9** at 1.50 ppm

Figure 1. (a) Methyl doublet for 9 at 1.50 ppm ($^3J_{C,H}$ = 7.2 Hz) and (b) methyl singlet for [D_1]-9 at 1.50 ppm

unchanged throughout the synthetic sequence and were determined by ^1H NMR spectroscopy (as illustrated in Figure 1).

In conclusion, we have reported an efficient and cost effective laboratory synthesis of deuteriated 2-aryl-substituted carboxylic acids [D_1]-**6**, [D_1]-**7**, [D_1]-**8** and [D_1]-**9** which requires minimal purification. These products were formed in high yield (for example, [D_1]-**6** formed from **6** in 67% – over three steps) with high levels of isotopic incorporation ([D] : [H] => 97 : <3). The nearest

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analogy for this procedure is that reported by Lloyd and co-workers.[9] They have shown that efficient deuteriation of ethyl 2-phenylpropionate **10** can occur using sodium in deuteriated ethanol (CAUTION – FLAMMABLE), followed by subsequent hydrolysis of ethyl 2-deuterio-2-phenylpropionate [D_1]-**11** using NaOD (formed by addition of sodium deuteride in D_2O) gave, after an acidic work-up (with aqueous HCl) and post-purification (distillation), 2-deuterio-2-phenylpropionic acid [D_1]-**6** in 74% yield of unspecified isotopic incorporation. By comparison, our protocol is less expensive, more practical and requires no post-purification leading to deuteriated profens in good to high yield with defined isotopic incorporation ([D] : [H] => 94 : <6).

Experimental

General. All solvents were distilled before use. All reactions were carried out under nitrogen using oven-dried glassware. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$ silica). Proton and carbon NMR spectra were recorded on a Bruker 250 and 400 MHz Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Infrared spectra were recorded on a Shimadzu 8300 FTIR spectrometer and mass spectra were recorded on a Kratos 50MSTC spectrometer using a DS503 data system for high-resolution analysis. The levels of *D*-incorporation were determined by a combination of mass, proton and carbon NMR spectra.

Ethyl 2-phenylpropionate **10**. Toluene-*p*-sulphonic acid (0.68 g, 3.62 mmol) was added to a stirred solution of 2-phenyl-propionic acid **6** (5.07 g, 33.80 mmol in ethanol (anhydrous, 30 ml) at room temperature. The solution was then heated to 85°C and left to reflux for 12 h. The resulting solution was cooled down to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and washed with aqueous potassium hydroxide (20 ml). The organic phases were dried (over $MgSO_4$) and evaporated under reduced pressure to give the ethyl ester **10** (5.90 g, 98%) as a colourless oil; R_F [light petroleum (40–60°C):diethyl ether (9 : 1)] 0.43; ν_{max} (film)/cm^{-1} 1733 (C=O); δ_H (270 MHz; $CDCl_3$) 7.35–7.20 (5 H, m, 5 × CH; Ph), 4.14–4.10 (1 H, m, CH_2), 3.70 (1 H, q, *J* 7.2, CH), 1.49 (3 H, d, *J* 7.2, $CHCH_3$) and 1.20 (3 H, t, *J* 7.2, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 175.0 (C=O), 141.1 (*i*-C; Ph), 129.0, 128.0 and 127.5 (3 × CH; Ph), 61.1 (CH_2CH_3), 45.9 ($CHCH_3$), 19.0 ($CHCH_3$) and 14.5 (CH_2CH_3) (found MNH_4^+, 196.1331; $C_{11}H_{18}NO_2$ requires 196.1331). The aqueous phase was then acidified to pH = 1 using HCl (3 M) and extracted with dichloromethane

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(3×20 ml). The combined organic phases were dried (over $MgSO_4$) and evaporated under reduced pressure to give recovered 2-phenyl-propionic acid **6** (48 mg, 0.32 mmol) which was spectroscopically identical to that previously obtained.

*Trideuteriomethyl 2-deuterio-2-phenylpropionate [D_4]-***11**. Sodium hydride (71 mg, 60% dispersion in oil, 2.96 mmol) was slowly added to a stirred solution of methanol-d_4 (4.44 g, 5 ml, 126.6 mmol) in THF (20 ml) at 0°C. The resulting solution was stirred for 15 min at 0°C. Ethyl 2-phenylpropionate **10** (1.50 g, 8.41 mmol) was slowly added dropwise and the solution was allowed to warm up to room temperature over 12 h. The reaction was quenched with D_2O (5 ml) and extracted with dichloromethane (3×10 ml). The combined organic layers were dried (over $MgSO_4$) and evaporated under reduced pressure to give trideuteriomethyl 2-deuterio-2-phenylpropionate [D_4]-**11** (1.02 g, 72%) ([D] : [H] = 84 : 16). The procedure was repeated twice more to give the trideuteriomethyl 2-deuterio-2-phenylpropionate [D_4]-11 (1.02 g, 72%) ([D] : [H] = 97 : 3) as an oil; R_F [light petroleum (40–60°C):diethyl ether (9 : 1)] 0.45; ν_{max} (CH_2Cl_2)/cm^{-1} 2200 (C-D) and 1718 (C═O); δ_H (270 MHz; $CDCl_3$) 7.35–7.21 (5 H, m, $5 \times$ CH; Ph) and 1.49 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 175.5 (C═O), 140.9 (*i*-C; Ph), 129.0, 127.9 and 127.5 ($3 \times$ CH; Ph), 51.3 (1 C, septet [1 : 3 : 6 : 7 : 6 : 3 : 1], $^1J_{C,D} = 22.3$, CD_3), 45.1 (1 C, t [1:1:1], $^1J_{C,D}$ 19.9, *C*DCH_3) and 18.9 (CD*C*H_3); (found MNH_4^+, 186.1427; $C_{10}H_{12}D_4NO_2$ requires 186.1427). Isotope shift at C(2) was 0.36 ppm (36.4 Hz at 100.613 MHz). For **6**-d_1; found MNH_4^+, 197.1394; $C_{11}H_{17}DNO_2$ requires 197.1395. Negative isotopic shift for CD_3 group at 51.3 ppm was 74.9 Hz (0.745 ppm at 100.6 MHz) and CD group at 45.4 ppm was 38.0 Hz (0.378 ppm at 100.6 MHz).

*2-Deuterio-2-phenylpropionic acid [D_1]-6: hydrolysis of trideuteriomethyl 2-deuterio-2-phenylpropionate [D_4]-***11**. Sodium hydride (0.20 g, 8.25 mmol) was slowly added to a stirred solution of trideuteriomethyl 2-deuterio-2-phenylpropionate [D_4]-**11** (0.69 g, 4.08 mmol) in THF/D_2O (20 ml, 3 : 1) at room temperature. The resulting solution was stirred for 12 h. The reaction was quenched with water (20 ml), acidified with HCl (4 M, 5 ml), and extracted with dichloromethane (3×20 ml). The combined organic layers were dried (over $MgSO_4$) and evaporated under reduced pressure to give 2-deuterio-2-phenylpropionic acid [D_1]-**6** (0.59 g, 95%) ([D] : [H] = 97 : 3); ν_{max} (film)/cm^{-1} 2305 (CD) and 1705 (C═O); δ_H (270 MHz; $CDCl_3$) 7.36–7.21 (5 H, m, $5 \times$ CH; Ph) and 1.50 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 180.7 (C═O), 140.1 (*i*-C; Ph), 129.1, 128.0 and 127.8 ($3 \times$ CH; Ph), 45.8 (1 C, s, unlabelled *C*DCH_3), 45.4 (1 C, t [1 : 1 : 1], $^1J_{C,D}$ 20.1, *C*DCH_3) and 18.4 (CD*C*H_3) (found

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MNH_4^+, 169.1081; $C_9H_{13}DNO_2$ requires 169.1082). Isotope shift at C(2) was 0.27 ppm (27.1 Hz at 100.613 MHz).

Methyl 2-deuterio-2-phenylpropionate [D_1]-**11**. Sodium hydride (0.18 g, 60% dispersion in oil, 4.50 mmol) was slowly added to a stirred solution of methanol–d_1 (4.06 g, 123 mmol) in THF (20 ml) at 0°C. The resulting solution was stirred for 15 min at 0°C. Ethyl 2-phenylpropionate **10** (4.01 g, 22.50 mmol) was slowly added dropwise and the solution was allowed to warm up to room temperature over 12 h. The reaction was quenched with H_2O (20 ml) and extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried (over $MgSO_4$) and evaporated under reduced pressure to give methyl 2-deuterio-2-phenylpropionate [D_1]-**11** (3.05 g, 83%) ([D] : [H] => 97 : <3); ν_{max} (film); cm^{-1} 2185 (C-D) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 7.27–7.15 (5 H, m, 5 × CH; Ph) and 1.41 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 174.9 (C=O), 140.4 (*i*-C; Ph), 128.6, 127.4 and 127.1 (3 × CH; Ph), 51.9 (CH_3), 44.7 (1 C, t [1:1:1], $^1J_{C,D}$ 20.0, *C*DCH_3) and 18.4 (CD*C*H_3); (found MNH_4^+, 197.1394; $C_{11}H_{17}DNO_2$ requires 197.1395). The negative isotope shift at *C*(2) was 0.37 ppm (37.6 Hz at 100.6 MHz).

2-Deuterio-2-phenylpropionic acid [D_1]-6: hydrolysis of methyl 2-deuterio-2-phenylpropionate [D_1]-**11**. Sodium hydride (0.554 g, 13.85 mmol) was slowly added to a stirred solution of methyl 2-deuterio-2-phenylpropionate [D_1]-**11** (1.90 g, 11.50 mmol) in THF/D_2O (20 ml, 3 : 1) at room temperature. The resulting solution was stirred for 12 h. The reaction was quenched with water (20 ml), acidified with HCl (2 M, 10 ml), and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried (over $MgSO_4$) and evaporated under reduced pressure to give 2-deuterio-2-phenylpropionic acid [D_1]-**6** (1.52 g, 87%) ([D] : [H] = 96 : 4) as an oil, which was spectroscopically identical to that previously obtained.

Ethyl 2-phenyl butyrate **12**. In the same way as ethyl ester **10**, 2-phenyl-butyric acid **7** (5.11 g, 31.5 mmol) and toluene-*p*-sulphonic acid (0.62 g, 3.27 mmol) in EtOH (30 ml) gave, the ethyl ester **12** (5.69 g, 95%) as an oil; ν_{max} (film); cm^{-1} 1733 (C=O); δ_H (400 MHz; $CDCl_3$) 7.33–7.23 (5 H, m, Ph), 4.19–4.05 (2 H, m, OCH_2), 3.49 (1 H, t, *J* 7.5, PhCH), 2.12–2.08 (1 H, m, $CH_AH_BCH_3$), 1.82–1.78 (1 H, m, $CH_AH_BCH_3$), 1.20 (3 H, t, *J* 7.1, CH_3CH_2O) and 0.89 (3 H, t, *J* 7.3, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 174.0 (C=O), 139.2 (*i*-C; Ph), 128.4, 127.9 and 127.0 (3 × CH; Ph), 60.5 (CH_2O), 53.5 (PhCH), 26.7 (CH_2CH), 14.1 (CH_3CH_2O) and 12.1 (CH_3CH_2) (found MH^+, 193.1221; $C_{12}H_{17}O_2$ requires 193.1223).

Ethyl 2-tolyl-propionate **13**. In the same way as ethyl ester **10**, 2-tolyl-propionic acid **8** (5.20 g, 31.7 mmol) and toluene-*p*-sulphonic acid (0.61 g,

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3.22 mmol) in EtOH (30 ml) gave, the ethyl ester **13** (5.76 g, 95%) as an oil; ν_{max} (film); cm^{-1} 1733 (C═O); δ_H (400 MHz; $CDCl_3$) 7.19 (2 H, d, *J* 8.2, 2 × CH; Ar), 7.11 (2 H, d, *J* 8.2, 2 × CH; Ar), 4.18–4.04 (2 H, m, OCH_2), 3.65 (1 H, q, *J* 7.1, PhCH), 2.32 (3 H, s, CH_3; Ar), 1.46 (3 H, d, *J* 7.1, CH_3CH) and 1.19 (3 H, t, *J* 6.9, CH_3CH_2O); δ_C (100 MHz; $CDCl_3$) 174.7 (C═O), 137.7 and 136.6 (2 × *i*-C; Ar), 129.2 and 127.2 (2 × CH; Ar), 60.6 (CH_2O), 45.1 (PhCH), 21.0 (CH_3; Ar), 18.6 (CH_3CH_2) and 14.1 (CH_3CH_2O); *m*/z 91.1 (50%, $CH_3C_6H_4$), 118.9 (100, M – CO_2Et) and 192 (40, M^+).

Ethyl 2-(2-isobutylphenyl)-propionate **14**. In the same way as ethyl ester **10**, 2-(2-isobutylphenyl)-propionic acid **9** (5.08 g, 24.6 mmol) and toluene-*p*-sulphonic acid (0.49 g, 2.6 mmol) in EtOH (30 ml) gave, the ethyl ester **14** (5.63 g, 98%) as an oil; ν_{max} (film); cm^{-1} 1734 (C═O); δ_H (400 MHz; $CDCl_3$) 7.20 (2 H, d, *J* 8.1, 2 × CH; Ar), 7.09 (2 H, d, *J* 8.1, 2 × CH; Ar), 4.19–4.06 (2 H, m, OCH_2), 3.67 (1 H, q, *J* 7.1, PhCH), 2.44 (2 H, d, *J* 7.1, $CHCH_2$), 1.84 (1 H, septet, *J* 6.6, $CH(CH_3)_2$), 1.47 (3 H, d, *J* 7.1, CH_3CH), 1.20 (1 H, t, *J* 6.9, CH_3CH_2O) and 0.88 (6 H, d, *J* 6.6, $CH(CH_3)_2$); δ_C (100 MHz; $CDCl_3$) 174.4 (C═O), 140.4 and 137.8 (2 × *i*-C; Ar), 129.2 and 127.1 (2 × CH; Ar), 60.6 (CH_2O), 45.1 (PhCH), 45.1 ($CH(CH_3)_2$), 30.1 ($ArCH_2$) 22.3 ($CH(CH_3)_2$), 18.5 (CH_3CH_2) and 14.1 (CH_3CH_2O) (found MNa^+, 257.1513; $C_{15}H_{22}O_2Na$ requires 257.1512).

Methyl 2-deuterio-2-phenyl butyrate [D_1]-**15**. In the same way as methyl ester [D_1]-**11**, ethyl 2-phenyl-butyrate **12** (4.05 g, 21.09 mmol) and sodium hydride (0.34 g, 60% dispersion in oil, 8.45 mmol) and [D_1]-MeOH (5 ml) in THF (20 ml) gave, after three repetitions the methyl ester [D_1]-**15** (2.14 g, 57%) as an oil; ν_{max} (CH_2Cl_2); cm^{-1} 2158 (CD) and 1732 (C═O); δ_H (400 MHz; $CDCl_3$) 7.33–7.23 (5 H, m, Ph), 3.65 (3 H, s, OCH_3), 2.12–2.08 (1 H, m, $CH_AH_BCH_3$), 1.84–1.80 (1 H, m, $CH_AH_BCH_3$) and 0.89 (3 H, t, *J* 7.3, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 174.4 (C═O), 139.0 (*i*-C; Ph), 128.5, 127.8 and 127.1 (3 × CH; Ph), 52.8 (1 C, t [1 : 1 : 1], *J* 19.9, PhCD), 51.7 (CH_3O), 26.5 (CH_2CD) and 12.1 (CH_3CH_2) (found MNH_4^+, 197.1396; $C_{11}H_{17}DNO_2$ requires 197.1395). The negative Isotopic shift at 0.89 ppm (for CH_3) is 0.006 ppm (2.52 Hz at 400 MHz) and at 52.8 (Ph*C*D) is 0.413 ppm (41.5 Hz at 100.6 MHz).

Methyl 2-deuterio-2-tolyl-propionate [D_1]-**16**. In the same way as methyl ester [D_1]-**11**, ethyl 2-tolyl-propionate **13** (4.00 g, 20.85 mmol) and sodium hydride (0.36 g, 60% dispersion in oil, 8.40 mmol) and [D_1]-MeOH (5 ml) in THF (20 ml) gave, the methyl ester [D_1]-**16** (1.80 g, 48%) as an oil; ν_{max} (CH_2Cl_2); cm^{-1} 2146 (CD) and 1737 (C═O); δ_H (400 MHz; $CDCl_3$) 7.21 (2 H, d, *J* 8.2, 2 × CH; Ar), 7.15 (2 H, d, *J* 8.2, 2 × CH; Ar), 3.66 (3 H, s, OCH_3), 2.33 (3 H, s,

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CH_3; Ar) and 1.49 (3 H, s, CH_3CD); δ_C (100 MHz; $CDCl_3$) 175.0 (C═O), 137.4 and 136.6 (2 × *i*-C; Ar), 129.2 and 127.2 (2 × CH; Ar), 51.8 (CH_3O), 44.5 (1 C, t [1 : 1 : 1], *J* 19.9, PhCD), 20.9 (CH_3; Ar) and 18.4 (CH_3CH) (found MNH_4^+, 197.1398; $C_{11}H_{17}DNO_2$ requires 197.1395). The negative isotopic shift at 44.5 ppm was 0.367 ppm (39.9 Hz at 100.6 MHz).

Methyl 2-deuterio-2-(2-isobutylphenyl)-propionate [D_1]-**17**. In the same way as methyl ester [D_1]-**11**, ethyl 2-(2-isobutylphenyl)-propionate **14** (4.01 g, 17.13 mmol) and sodium hydride (0.27 g, 60% dispersion in oil, 6.98 mmol) and [D_1]-MeOH (5 ml) in THF (20 ml) gave, the methyl ester [D_1]-**17** (1.65 g, 44%) as an oil; ν_{max} (CH_2Cl_2); cm^{-1} 2196 (CD) and 1739 (C═O); δ_H (400 MHz; $CDCl_3$) 7.21 (2 H, d, *J* 8.1, 2 × CH; Ar), 7.10 (2 H, d, *J* 8.1, 2 × CH; Ar), 3.65 (3 H, s, OCH_3), 2.45 (2 H, d, *J* 7.2, C*H*CH_2), 1.84 (1 H, septet, *J* 6.7, C*H*$(CH_3)_2$), 1.48 (3 H, s, CH_3CH) and 0.90 (6 H, d, *J* 6.7, $CH(CH_3)_2$); δ_C (100 MHz; $CDCl_3$) 175.1 (C═O), 140.4 and 137.7 (2 × *i*-C; Ar), 129.2 and 127.0 (2 × CH; Ar), 51.8 (CH_3O), 45.0 ($CH(CH_3)_2$), 44.7 (1 C, t [1 : 1 : 1], *J* 19.5, PhCD), 30.1 ($ArCH_2$) 22.3 ($CH(CH_3)_2$) and 18.4 (CH_3CH) (found MNH_4^+, 239.1863; $C_{14}H_{19}DNO_2$ requires 239.1864). The negative isotopic shift at 44.7 ppm was 0.393 ppm (39.5 Hz at 100.6 MHz).

2-Deuterio-2-phenyl butyric acid [D_1]-**7**. In the same way as carboxylic acid [D_1]-**6**, methyl 2-deuterio-2-phenyl-butyrate [D_1]-**15** (1.0 g, 5.63 mmol) and sodium hydride (0.28 g, 60% dispersion in oil, 7.05 mmol) in THF/D_2O (20 ml, 3 : 1) gave, 2-deuterio-2-phenyl butyric acid [D_1]-**7** (0.59 g, 63%) as an oil; ν_{max} (CH_2Cl_2); cm^{-1} 3500–3000 (br OH), 2313 (CD) and 1704 (C═O); δ_H (400 MHz; $CDCl_3$) 7.34–7.25 (5 H, m, Ph), 2.10 (1 H, dq, *J* 14.6 and 7.3, CH_AH_B), 1.80 (1 H, dq, *J* 14.6 and 7.3, CH_AH_B) and 0.9 (3 H, t, *J* 7.3, CH_3); δ_C (100 MHz; $CDCl_3$) 180.2 (C═O), 138.3 (*i*-C; Ph), 128.6, 128.0 and 127.4 (3 × CH; Ph), 52.8 (1 C, t [1 : 1 : 1], *J* 20.0, PhCD), 26.1 (CH_2CD) and 12.0 (CH_3CH_2) (found MNH_4^+, 183.1237; $C_{10}H_{11}DNO_2$ requires 183.1238). The negative isotopic shift at 52.8 ppm was 0.413 ppm (41.5 Hz at 100.6 MHz).

2-Deuterio-2-tolyl-propionic acid [D_1]-**8**. In the same way as carboxylic acid [D_1]-**6**, methyl 2-deuterio-2-tolyl-propionate [D_1]-**16** (1.06 g, 5.90 mmol) and sodium hydride (0.29 g, 60% dispersion in oil, 7.20 mmol) in THF/D_2O (20 ml, 3 : 1) gave, 2-deuterio-2-tolyl-propionic acid [D_1]-**8** (0.81 g, 83%) as an oil; m.p. 38–39°C; ν_{max} (CH_2Cl_2); cm^{-1} 2305 (CD) and 1707 (C═O); δ_H (400 MHz; $CDCl_3$) 7.15 (2 H, dt, *J* 8.2 and 2.0, 2 × CH; Ar), 7.14 (2 H br d, 8.2, 2 × CH; Ar), 2.39 (3 H, s, CH_3; Ar) and 1.48 (3 H, s, CH_3CD); δ_C (100 MHz; $CDCl_3$) 180.7 (C═O), 137.0 and 136.6 (2 × *i*-C; Ar), 129.3 and 127.4 (2 × CH; Ar), 44.5 (1 C, t [1 : 1 : 1], *J* 20.3, ArCD), 21.0 (CH_3) and 17.0

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(CH_3) (found MNH_4^+, 183.1234; $C_{10}H_{11}DNO_2$ requires 183.1238). The negative isotopic shift at 44.5 ppm was 0.336 ppm (36.9 Hz at 100.6 MHz).

2-Deuterio-2-(2-isobutylphenyl)-propionic acid [D_1]-**9**. In the same way as carboxylic acid [D_1]-**6**, methyl 2-deuterio-2-(2-isobutylphenyl)-propionate [D_1]-**17** (1.02 g, 4.61 mmol) and sodium hydride (0.24 g, 60% dispersion in oil, 5.90 mmol) in THF/D_2O (20 ml, 3 : 1) gave, 2-deuterio-2-(2-isobutylphenyl)-propionic acid [D_1]-**9** (0.76 g, 80%) as an oil; m.p. 71–73°C; ν_{max} (CH_2Cl_2); cm^{-1} 2345 (CD) and 1704 (C═O); δ_H (400 MHz; $CDCl_3$) 7.22 (2 H, dt, *J* 8.2 and 2.2, 2 × CH; Ar), 7.10 (2 H, dt, *J* 8.2 and 2.2, 2 × CH; Ar), 2.42 (2 H, d, *J* 6.9, CH_2Ar), 1.88 (1 H, m, C*H*(CH_3)$_2$), 1.49 (3 H, s, CH_3CD) and 0.88 (6 H, d, *J* 6.6, C*H*(CH_3)$_2$); δ_C (100 MHz; $CDCl_3$) 180.6 (C═O), 140.8 and 136.8 (2 × *i*-C; Ar), 129.3 and 127.2 (2 × CH; Ar), 45.0 (CH(CH_3)$_2$), 44.6 (1 C, t [1 : 1 : 1], *J* 19.9, ArCD), 30.1 (CH_2) 22.3 (CH(*C*H_3)$_2$) and 17.0 (CH_3) (found MNH_4^+, 225.1709; $C_{13}H_{17}DNO_2$ requires 225.1708). The negative isotopic shift at 44.6 ppm was 0.369 ppm (36.5 Hz at 100.6 MHz).

Characterization data for unlabelled acids

2-Phenylpropionic acid **6**. ν_{max}($CHCl_3$)/cm^{-1} 1706 (C═O); δ_H (250 MHz; $CDCl_3$) 7.45–6.98 (5 H, m, 5 × CH; Ph), 3.75 (1 H, q, *J* 7.2, C*H*CO) and 1.5 (3 H, d, *J* 7.2, C*H*$_3$CH); δ_C (67.9 MHz; $CDCl_3$) 181.4 (C═O), 139.9 (*i*-C; Ph), 128.9, 127.8 and 127.6 (3 × CH; Ph), 45.6 (PhCH) and 18.3 (CH_3) (found MH^+ 151.0750. $C_9H_{11}NO_2$ requires 151.0759).

2-Phenyl butyric acid **7**. ν_{max} (CH_2Cl_2); cm^{-1} 3500–3000 (br OH) and 1704 (C═O); δ_H (400 MHz; $CDCl_3$) 7.34–7.24 (5 H, m, Ph), 3.46 (1 H, t, *J* 7.7, PhCH), 2.12–2.08 (1 H, m, C*H*$_A$H$_B$), 1.82–1.78 (1 H, m, CH$_A$*H*$_B$) and 0.9 (3 H, t, *J* 7.3, CH_3); δ_C (100 MHz; $CDCl_3$) 180.7 (C═O), 138.3 (*i*-C; Ph), 128.6, 128.0 and 127.4 (3 × CH; Ph), 53.3 (PhCH), 26.2 (*C*H_2CH) and 12.0 (*C*$H_3$$CH_2$) (found MNH_4^+, 182.1177; $C_{10}H_{16}NO_2$ requires 182.1176).

2-Tolyl-propionic acid **8**. ν_{max} (CH_2Cl_2); cm^{-1} 1707 (C═O); δ_H (400 MHz; $CDCl_3$) 7.23 (2 H, dt, *J* 8.2 and 2.0, 2 × CH; Ar), 7.14 (2 H br d, 8.2, 2 × CH; Ar), 2.39 (3 H, s, CH_3; Ar), 3.72 (1 H, q, *J* 7.2, PhCH), 2.34 (3 H, s, CH_3; Ar) and 1.50 (3 H, d, *J* 7.3, C*H*$_3$CH); δ_C (100 MHz; $CDCl_3$) 181.1 (C═O), 137.0 and 136.7 (2 × *i*-C; Ar), 129.3 and 127.4 (2 × CH; Ar), 44.9 (ArCH), 21.0 (CH_3) and 18.0 (CH_3) (found MNH_4^+, 182.1177; $C_{10}H_{16}NO_2$ requires 182.1176).

2-(2-Isobutylphenyl)-propionic acid **9**. ν_{max} (CH_2Cl_2); cm^{-1} 1704 (C═O); δ_H (400 MHz; $CDCl_3$) 7.22 (2 H, dt, *J* 8.2 and 2.2, 2 × CH; Ar), 7.11 (2 H, dt, *J* 8.2 and 2.2, 2 × CH; Ar), 3.71 (1 H, q, *J* 7.2, PhCH), 2.42 (2 H, d, *J* 7.1, CH_2Ar), 1.88 (1 H, br nonet, *J* 6.6, C*H*(CH_3)$_2$), 1.50 (3 H, d, *J* 7.2, C*H*$_3$CH) and 0.90

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(6 H, d, *J* 6.6, C*H*(CH_3)$_2$); δ_C (100 MHz; $CDCl_3$) 181.0 (C═O), 140.8 and 136.9 (2 × *i*-C; Ar), 129.3 and 127.2 (2 × CH; Ar), 45.0 (CH(CH_3)$_2$), 44.9 (ArCH), 30.1 (CH_2) 22.3 (CH(*C*H_3)$_2$) and 18.0 (CH_3) (found MNH_4^+, 224.1648; $C_{13}H_{22}NO_2$ requires 224.1651).

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