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SYNTHESIS OF CARBON-13 LABELED IBUPROFEN

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SUMMARY

This report describes the synthesis of ibuprofen* labeled with carbon-13 either at the terminal methyl carbons, or at the methine carbon of the isobutyl side chain. The synthetic route involves the removal of the isopropyl group in the isobutyl side-chain of ibuprofen *via* 2-[4-(2-methyl-1-propenyl)phenyl]propionic acid, followed by restoration of the isopropyl group with a Wittig reaction, using appropriate carbon-13 labeled acetone as the precursor of the isopropyl group. Interesting NMR coupling data attributable to phosphorous and carbon-13 are presented in the experimental section.

Key Words: Synthesis, ibuprofen, carbon-13, acetone, ozonolysis, Wittig reaction, Wadsworth-Emmons modification, crown ether, hydrogenation, NMR.

INTRODUCTION

Recent years have witnessed the development and growth of non-invasive studies of biochemical changes in living cells of intact organisms by means of nuclear magnetic resonance (NMR) spectroscopy (1). However, these techniques have not been extensively used to investigate the *in vivo* biotransformations and pharmacokinetics of drugs and other xenobiotics. As part of a program to explore the potential utility of *in vivo* NMR in studying drug metabolism, we sought to prepare compounds strategically labeled with stable isotopes such as carbon-13 and/or deuterium which might serve as appropriate tools for conducting such studies. Initially we chose ibuprofen *(1)* because its metabolic transformations in test animals and man are already known and its major metabolites are available. Furthermore, this drug has low toxicity and can be

*Ibuprofen is the generic name for 2-[4-(2-methylpropyl)phenyl]propionic acid

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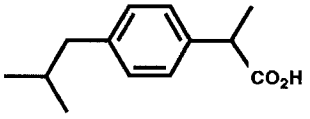
administered at high doses. Thus, it is potentially capable of providing good detection sensitivity. Since metabolic transformations of ibuprofen include oxidation at both the methine and terminal methyl carbons of the isobutyl side-chain to give the hydroxy metabolite *2* and carboxy metabolite *3* respectively (2), we elected to incorporate carbon-13 at the isobutyl methine position, and also at the terminal isobutyl methyl carbons, so that these transformations may be observed by means of ^{13}C-NMR through changes in chemical shifts as well as signal intensities.



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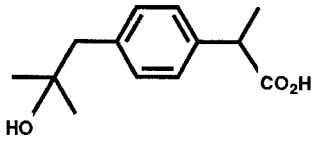

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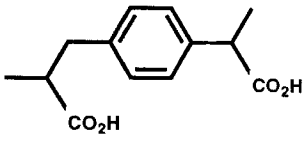

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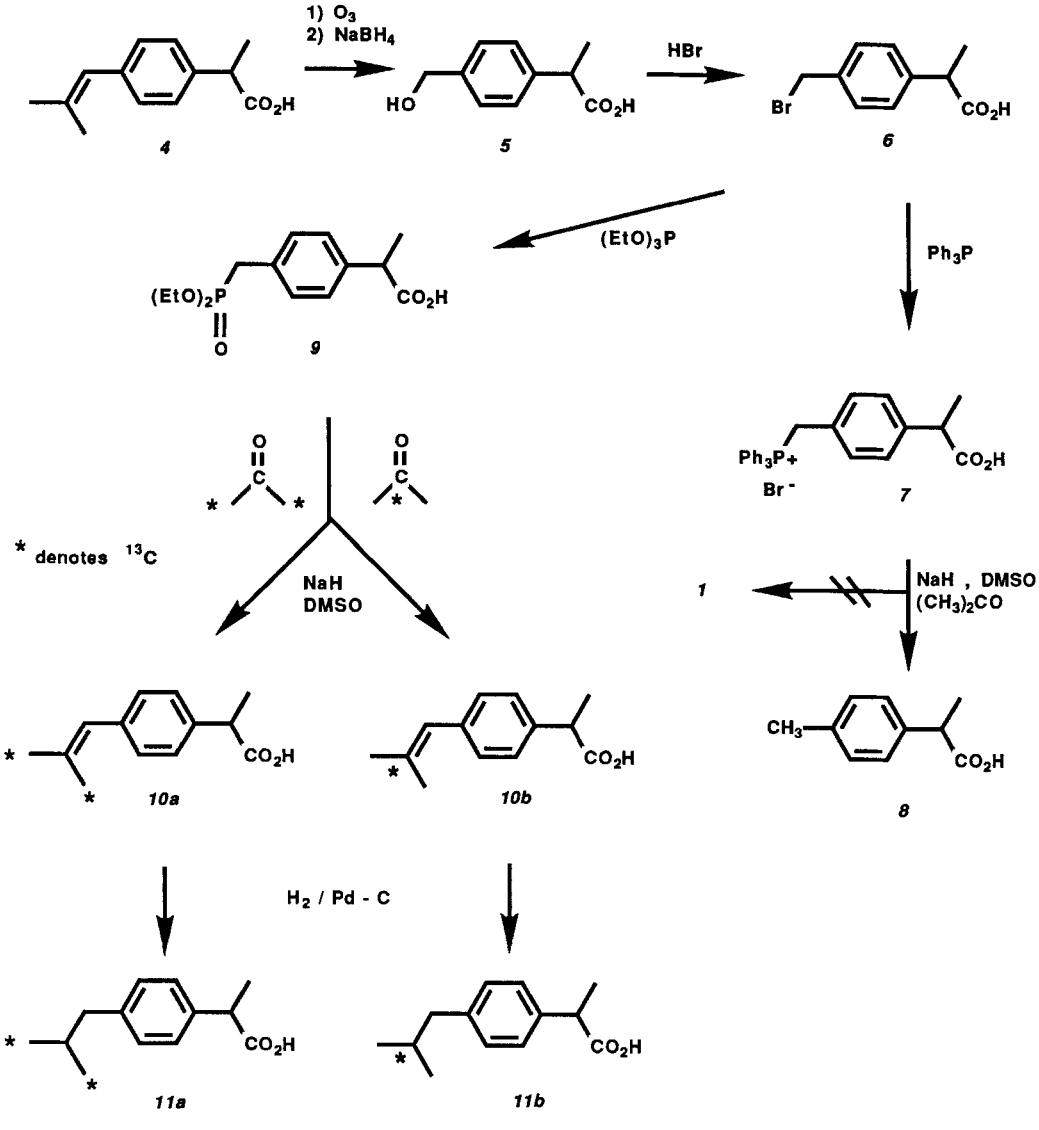
DISCUSSION AND RESULTS

During the development of a practical and efficient synthesis of the hydroxy metabolite *2* from ibuprofen, 2-[4-(2-methyl-1-propenyl)phenyl]propionic acid *(4)* was prepared as an intermediate (3). The same styrene intermediate *4* was also used as an intermediate in the synthesis of the carboxy metabolite *3*. In the latter case the styryl double bond was cleaved by ozonolysis to afford an intermediate aldehyde which was further elaborated to produce *3*. Our plan was to transform the intermediate aldehyde into a suitable Wittig type reagent, and use it as an intermediate to reconstruct C-13 labeled ibuprofen by reaction with commercially available acetone appropriately labeled either at the carbonyl carbon or at the methyl carbons, followed by reduction of the double bond in the Wittig product. The synthesis is outlined in Scheme 1. The styrene *4* was ozonolyzed and the resulting intermediate aldehyde from styrene *4* was reduced *in situ* with sodium borohydride to give 2-(4-hydroxymethyl-phenyl)propionic acid *(5)*, which upon reflux with hydrobromic acid was converted to 2-(4-bromomethyl-phenyl)propionic acid *(6)*. Treatment of the benzyl bromide *6* with triphenyl phosphine afforded the triphenylphosphonium bromide *7*. Several attempts to induce the ylide generated from *7* to react with acetone failed to produce any trace of the desired compound *4*. In all cases, the only product isolated was 2-(4-methylphenyl)propionic

Scheme 1. Synthesis of [^{13}C]Ibuprofen

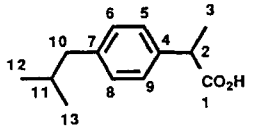


acid *(8)*. Apparently the conjugated ylide derived from *7* was too stable to undergo addition with acetone. We therefore turned to the Wadsworth-Emmons modification (4,5) of the Wittig reaction, which utilizes the phosphonate anion as the more reactive ylide.

We prepared diethyl *p*-(α-carboxyethyl)phenylmethanephosphonate *(9)* from triethyl phosphite and the benzyl bromide *6*, using procedures similar to those described for the preparation of analogous aralkylphosphonates (6). The phosphonate anion generated from *9* was allowed to react with [1,3-^{13}C]acetone and [2-^{13}C]acetone to give carbon -13 labeled 2-[4-(2-methyl-1-propenyl)phenyl]propionic acids *10a* and *10b*, respectively. Baker and Sims (7) reported that when reacting the phosphonate anion generated from diethyl phenylmethanephosphonate with various aldehydes and ketones, the use of catalytic amounts of 15-crown-5 significantly, sometimes dramatically, improved the yields of olefins. In our present case, inclusion of 15-crown-5 in the reaction mixture gave only modest yields (34-42%) of the olefins *10a* and *10b*. In the absence of the crown ether, little or no product was obtained. Reduction of the olefins *10a* and *10b* in the presence of palladium-on-charcoal catalyst afforded the carbon-13 labeled ibuprofen *11a* and *11b*, respectively.

EXPERIMENTAL SECTION

Thin-layer chromatographic (TLC) analysis was done on 2.5 x 10 cm glass plates precoated with a 250 μm layer of silica gel GF (Analtech). Developed zones were visualized with UV light (254 nm). Melting points were determined in capillary tubes with a Thomas-Hoover Unimelt and were uncorrected. ^{1}H-NMR spectra of compounds 5 and 6 were recorded on a Varian EM90 instrument. ^{1}H- and ^{13}C-NMR spectra of compounds *7* and *9* and ^{13}C spectra of *5* and *6* were acquired on a Varian XL-200 instrument. ^{1}H- and ^{13}C-NMR spectra of compounds *8*, *10a*, *10b*, *11a* and *11b* were taken on a Bruker AM300 spectrometer. In reporting ^{1}H- and ^{13}C-NMR data, we have arbitrarily assigned numbers to the carbon skeleton, where applicable, as shown in structures *12, 13,* and *14*. Infrared spectra were recorded on a Digilab FTS15E spectrophotometer. Ultra violet spectra were acquired on a Perkin-Elmer Lambda 7 instrument. Mass spectral analyses were performed on a Finnigan MAT 8230 spectrometer. Elemental analyses were carried out with a Perkin-Elmer 240B or a Heraeus CHN-O-RAPID unit, and the results for the indicated elements were all within ±0.4% of theory.



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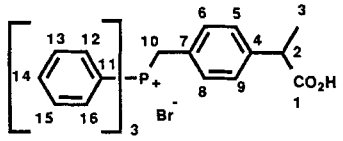

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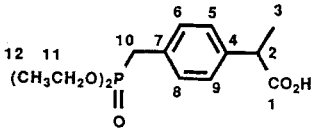

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2-(4-Hydroxymethylphenyl)propionic Acid *(5)*

Ozone (4% in 0_2) was bubbled through a stirred solution of 5.0 g of 2-[4-(2-methyl-1-propenyl)phenyl]propionic acid (*4*, 24.5 mmol) in 50 ml of absolute ethanol at -50°C (dry ice/acetone bath) for 25 minutes. A stream of N_2 was then passed through the solution for 15 minutes, and the reaction mixture warmed to -20°C. Sodium borohydride ($NaBH_4$, 2.78 g, 74.4 mmol) was added in portions with stirring while the reaction mixture was maintained between -20°C and -25°C. After an hour of stirring, more $NaBH_4$ (0.93 g, 24.5 mmol) was added and the mixture was stirred at -20°C for 30 minutes, poured into 50 ml of cold H_20, and acidified to pH2 with 17 ml of 6 N HCl. The resulting mixture containing white precipitates was partitioned with 100 ml of ethyl acetate (EtOAc) and 50 ml of brine. The aqueous phase was extracted with 100 ml of EtOAc, and the combined organic layers were washed with 3 x 50 ml of brine, and dried over $MgSO_4$. After removal of solvents, the residue was chromatographed on 140 g of silica gel packed in and eluted with 25:75:0.5 v/v EtOAc:methylene chloride (CH_2Cl_2):acetic acid (HOAc) at 4 ml per minute. After a forerun of 200 ml, 90 fractions of 16 ml each were collected. Fractions 31-90 were pooled and concentrated at 45°C and 20 torr. The resulting white solids were triturated with 3 x 25 ml of hexane, filtered, and air-dried to give 3.75 g of *5*, 85% yield, mp. 96-7°C; λ_{max} in EtOH nm (ε):212(7820), 219 (8080); mass spectrum: m/z (rel. intensity), 180 (37.7) M+, 135(100) M+-COOH; single component by TLC (5:30:65:1 v/v MeOH:Et_2O:hexane:HOAc, Rf = 0.22); ^{1}H-NMR (200 MHz) δ ($CDCl_3$) (See numbering in structure *12*): 1.52 (d, 3H,

J = 7.4 Hz, H-3), 3.76 (q, 1H, J = 7.4 Hz, H-2), 4.68 (s, 2H, H-10), 5.60 (bs, 1H, -OH), 7.33 (s, 4H, H-5,6,8,9); ^{13}C-NMR ppm ($CDCl_3$, TMS) 18.03 (C-3), 44.90 (C-2), 64.87 (C-10), 127.27 and 127.70 (C-5 and C-9; C-6 and C-8), 139.20 and 139.78 (C-4 and C-7), 179.70 (C-1); anal.: C, H.

2-(4-Bromomethylphenyl)propionic Acid *(6)*

Compound *5* (2.71 g, 15.04 mmol) was gently refluxed with stirring under N_2 in 9 ml of 48% HBr for 30 minutes. Copious white precipitates formed within one minute. The mixture was cooled, diluted with 10 ml of cold H_20, and stirred in an ice bath for 10 minutes. The solids were filtered, washed with 5 x 10 ml of cold H_20, air-dried, and finally dried at 0.5 torr for one hour. Recrystallization from 7 ml of hot EtOAc and 25 ml of hexane gave 3.28 g of *6* as a white powder, 89% yield, mp. 129^{0}C; λ_{max} in EtOH nm (ε):237 (10,500); mass spectrum: m/z (rel. intensity), 163 (100) M^+-Br; single component by TLC (2:3:5:0.1 v/v EtOAc:hexane:CH_2Cl_2:HOAC, Rf = 0.45); ^{1}H-NMR (200 MHz) δ ($CDCl_3$) (See numbering in structure *12*): 1.52 (d, 3H, J = 7.4 Hz, H-3), 3.78 (q, 1H, J = 7.4 Hz, H-2), 4.49 (s, 2H, H-10), 7.27-7.41 (m, 4H, H-5,6,8,9) 10.25 (bs, 1H, COOH); ^{13}C-NMR ppm ($CDCl_3$, TMS): 17.89 (C-3), 32.97 (C-10), 44.94 (C-2), 127.98 and 129.24 (C-5 and C-9; C-6 and C-8), 136.82 and 139.84 (C-4 and C-7), 180.46 (C-1); anal.: C, H.

p-(α-Carboxyethyl)benzyltriphenylphosphonium Bromide *(7)*

A solution of 0.58 g of triphenylphosphine (2.20 mmol) and 0.48 g of *6* (1.97 mmol) in 5 ml of absolute EtOH was refluxed with stirring for 30 minutes. Addition of 50 ml of Et_20 to the cooled mixture precipitated the product. The filtered white solids were washed with 5 x 10 ml of Et_20 and air dried to afford 0.96 g of *7*, 96% yield; mp. 186-187^{0}C; λmax in EtOH nm (ε):223 (34,400), 262 (3600), 268 (4160), 276 (3370); mass spectrum m/z (relative intensity) 262 (100) Ph_3P^+, 183 (67.8) Ph_2P^+; ^{1}H-NMR (200 MHz) δ (DMSO-d6) (See numbering in structure *13*): 1.32 (d, 3H, J = 7.4 Hz, H-3), 3.65 (q, 1H, J = 7.4 Hz, H-2), 5.27 (d, 2H, $^2J_{H-P}$ = 15.6 Hz, H-10), 6.97 (dd, 2H, J = 8.0 Hz, $^4J_{H-P}$ = 2.3 Hz, H-6,8), 7.16 (d, 2H, J = 8.0 Hz, H-5,9), 7.65-7.90 (m, 15H, H-12,13,14,15,16); ^{13}C-NMR ppm (DMSO-d6, TMS): 18.18 (C-3), 27.76 (d, $^1J_{C-P}$ = 47 Hz, C-10), 44.11 (C-2), 117.74 (d,

$^{1}J_{C-P}$ = 87 Hz, C-11), 126.27 (d, $^{2}J_{C-P}$ = 9 Hz, C-7), 127.71 (d, $^{4}J_{C-P}$ = 4 Hz, C-5 and C-9), 129.96 (d, $^{2}J_{C-P}$ = 12 Hz, C-12 and C-16), 130.78 (d, $^{3}J_{C-P}$ = 5 Hz, C-6 and C-8), 133.94 (d, $^{3}J_{C-P}$ = 10 Hz, C-13 and C-15), 134.96 (d, $^{4}J_{C-P}$ = 3 Hz, C-14), 141.46 (d, $^{5}J_{C-P}$ = 4 Hz, C-4), 174.9 and 174.88 (C-1); anal.: C, H.

2-(4-Methylphenyl)propionic Acid (*8*) from *7*

A solution of 64 mg of acetone (1.1 mmol) and 511 mg of *7* (1.0 mmol) in 2.5 ml of DMSO was added dropwise with stirring to a suspension of 93 mg of sodium hydride (57% suspension in mineral oil, 2.2 mmol) in the same solvent. The reation mixture developed a red color in 10 minutes, and was orange after stirring under N_2 at room temperature for 15 hours. To the crude reaction mixture was added 10 ml of cold H_20. The precipitated triphenylphosphine oxide was removed by filtration and the pH 12 solution was extracted with 3 x 25 ml of CH_2Cl_2, and acidified to pH 2 with 2.2 ml of 1 N HCl. The liberated acid was extracted with 3 x 25 ml of EtOAc, and the combined organic layers were washed with 4 x 50 ml of H_20, followed by 50 ml of brine, and dried over $MgSO_4$. The extracts were concentrated to give 0.13 g of *8*, 64% yield, oil with single component by TLC (20:30:50:1.0 v/v EtOAc:hexane: CH_2Cl_2:HOAc, Rf = 0.47); ^{1}H-NMR (300 MHz) δ ($CDCl_3$) (see numbering in structure *12*): 1.46 (d, 3H, J = 7.2 Hz, H-3), 2.32 (s, 3H, H-10), 3.68 (q, 1H, J = 7.2 Hz, H-2), 7.12 (d, 2H, J = 8.0 Hz H-6,8), 7.20 (d, 2H, J = 8.0 Hz, H-5,9), 10.38 (s, 1H, COOH); ^{13}C-NMR ppm ($CDCl_3$, TMS) 18.08 (C-3), 21.04 (C-10), 44.99 (C-2), 127.46 and 129.36 (C-5 and C-9; C-6 and C-8), 136.81 and 137.05 (C-4 and C-7), 180.46 (C-1).

Diethyl p-(α-Carboxyethyl)phenylmethanephosphonate (*9*)

Compound *6* (8.25 g, 33.9 mmol) and triethylphosphite (33.90 g, 204.0 mmol) were stirred under N_2 in a 120°C oil bath for 4 hours. After 5 minutes of heating, reflux of ethyl bromide was observed. After cooling to room temperature, the solution was added to 60 ml of cold H_2O, and made basic by the addition of 75 ml of 2 N NaOH. The pH 11 mixture was washed with 5 x 100 ml of EtOAc, and adjusted to pH 2 by the addition of 27 ml of 1N HCl. The acidic layer was partitioned with 250 ml of EtOAc, and extracted with 2 x 90 ml of EtOAc. The combined organic layers were washed with 2 x

50 ml of H_2O and 2 x 50 ml of brine, dried over $MgSO_4$, and concentrated to a white solid. Recrystallization from 30 ml of hot EtOAc and 220 ml of hexane gave 6.18 g of *9*, 61% yield; mp. 124-125°C; λ_{max} in EtOH nm (ε):212 (8,460), 222 (9,680); mass spectrum: m/z (rel. intensity), 256 (100) M^+-COOH, 227 (44.5) M^+-CH_3CH_2COOH, 199 (22.3) M^+-CH_3CH_2COOH and CH_3CH_2, 163 (23.44) M^+-PO $(CH_2CH_3)_2$, 118 (99.3) M^+-COOH and PO $(CH_2CH_3)_2$; single component by TLC (3:7:0.1 EtOAc:CH_2Cl_2:HOAc v/v, Rf = 0.28); ^{1}H-NMR (200 MHz) ($CDCl_3$) (see numbering in structure *14*): 1.24 (dt, 6H, J = 6.9 Hz, $^4J_{H-P}$ = 1.7 Hz, H-12), 1.51 (d, 3H, J = 6.8 Hz, H-3), 3.16 (d, 2H, $^2J_{H-P}$ = 22 Hz, H-10), 3.73 (q, 1H, J = 7.3 Hz, H-2), 3.9-4.1 (m, 4H, H-11), 7.20-7.32 (m, 4H, H-5,6,8,9), 10.77 (s, 1H, COOH); ^{13}C-NMR ppm ($CDCl_3$, TMS): 16.26 and 16.38 (C-12), 18.30 (C-3), 33.15 (d, $^1J_{C-P}$ = 138 Hz, C-10), 44.99 (C-2), 62.49 and 62.35 (2d, $^2J_{C-P}$ = 6.8 Hz, C-11), 127.78 (d, $^4J_{C-P}$ = 2 Hz, C-5 and C-9), 130.00 (d, $^3J_{C-P}$ = 7 Hz, C-6 and C-8), 139.11 (d, $^5J_{C-P}$ = 4 Hz, C-4), 130.08 (d, $^2J_{C-P}$ = 15 Hz, C-7), 178.08 and 178.11 (C-1); anal.: C, H.

2-[4-(2-[^{13}C]Methyl-1-[3-^{13}C]propenyl)phenyl]propionic Acid (*10a*)

To a stirrred solution of 1.68 g of 57% NaH (40 mmol) in mineral oil and 2.72 g of 15-crown-5 (12.38 mmol) in 75 ml of THF at 0°C was added 0.82 g of [1,3-^{13}C]acetone (13.61 mmol) and 3.72 g of compound *9* (12.38 mmol). The reaction mixture was allowed to warm to 20°C, stirred under N_2 for 41 hours, and poured into 200 ml of cold H_20. The resulting mixture was extracted with 3 x 60 ml of CH_2Cl_2 followed by 60 ml of EtOAc and acidified to pH2 with 30 ml of 1N HCl. The acidic aqueous phase was extracted with 3 x 80 ml of CH_2Cl_2. The combined organic layers were washed with 80 ml of brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on 120 g of silica gel packed in and eluted with 5:30:65:0.5 v/v MeOH:Et_20:hexane:HOAc at 3.5 ml per minute. Forty-five fractions of 14 ml each were collected. The pooling and concentration of fractions 23-39 at 45° and 20 torr gave an oil which crystallized under a stream of N_2. The crystals were dried for 15 hours at 0.5 torr and room temperature. There was obtained 0.89 g of *10a*, 34% yield (31% based on [1,3-^{13}C]acetone, 34% based on *9*; mp.57-58°C; mass spectrum: m/z (rel. intensity), 206 (44.0) M^+; 161 (100) M^+-COOH; single component by TLC (15:85:1 v/v EtOAc:CH_2Cl_2:HOAc, Rf = 0.43; 5:95:1 v/v EtOAc:CH_2Cl_2:HOAc, Rf = 0.29) identical to a

standard sample of compound *4*; ^{1}H-NMR (300 MHz) δ ($CDCl_3$) (see numbering in structure *12*): 1.51 (d, 3H, J = 7.2 Hz, H-3), 1.85 (ddd, 3H, $^1J_{C-H}$ = 126 Hz, $^3J_{C-H}$ = 3.4 Hz, $^4J_{H-H}$ = 0.9 Hz, H-13), 1.89 (ddd, 3H, $^1J_{C-H}$ = 126 Hz, $^3J_{C-H}$ = 3.4 Hz, $^4J_{H-H}$ = 1.0 Hz, H-12), 3.72 (q, 1H, J = 7.2 Hz, H-2), 6.23 (dd, 1H, $^3J_{C-H\ Trans}$ = 7.8 Hz, $^1J_{C-Hcis}$ = 7.8 Hz, H-10), 7.17 (d, 2H, J = 8.2 Hz, H-5,9), 7.26 (d, 2H, J = 8.2 Hz, H-6,8); ^{13}C-NMR ppm ($CDCl_3$, TMS) for unlabled compound *10*: 18.06 (C-3), 19.42 and 26.88 (C-12 and C-13), 45.07 (C-2), 124.69 (C-10), 127.28 and 129.01 (C-5 and C-9; C-6 and C-8), 135.65 (C-11), 137.11 and 137.92 (C-4 and C-7), 180.76 (C-1): ^{13}C-NMR for undiluted *10a* in $CDCl_3$ with TMS: two intense signals at 19.44 and 26.90 ppm (C-12 and C-13).

2-[4-(2-Methyl-1-[2-^{13}C]propenyl)phenyl]propionic Acid (*10b*)

To a stirred solution of 0.84 g of 57% NaH (20 mmol) and 1.1 g of 15-crown-5 (5 mmol) in 30 ml THF at 0°C was added 0.33 g of [2-^{13}C]acetone (5.5 mmol) and 1.50 g of compound *9* (5 mmol). The reaction mixture was allowed to warm to 20°C, stirred under N_2 for 23 hours, and poured into 100 ml of cold H_20. The resulting solution was extracted with 4 x 30 ml of CH_2Cl_2 with 35 ml of 0.5 N HCl. The aqueous phase was extracted with 3 x 30 ml of CH_2Cl_2. The combined organic layers were washed with 50 ml of brine, dried over $MgS0_4$, and concentrated. The residue was chromatographed on 60 g of silica gel packed in and eluted with 50:50:0.5 v/v hexane:CH_2Cl_2:HOAc at 2.5 ml per minute. After a forerun of 325 ml, 70 fractions of 10 ml each were collected. Fractions 40-58 were pooled and concentrated at 45° and 20 torr, and the residue allowed to crystallize under a stream of N_2. The crystals were dried for 2 hours at 0.5 torr and room temperature to give 0.42 g of *10b* (42% yield based on *10b*, 37% based on [2-^{13}C]acetone); mp. 57-58°C; mass spectrum: m/z (rel. intensity), 205 (37.6) M^+, 160 (100) M^+-COOH; single component by TLC 5:30:65:1 v/v MeOH:Et_20:hexane:HOAc, Rf = 0.36; 50:50:1 v/v hexane:CH_2Cl_2:HOAc, Rf = 0.18) identical to a standard sample of compound *4*; ^{1}H-NMR (300 MHZ) δ ($CDCl_3$) (see numbering in structure *12*): 1.51 (d, 3H, J = 7.2 Hz, H-3), 1.85 (dd, 3H, $^2J_{C-H}$ = 6.3 Hz, $^4J_{H-H}$ = 1.1 Hz, H-12), 1.89 (dd, 3H, $^2J_{C-H}$ = 6.3 Hz, $^4J_{H-H}$ = 1.1 Hz, H-13), 3.72 (q, 1H, J = 7.2 Hz, H-2), 6.23 (s, 1H, H-10), 7.18 (d, 2H, J = 8.2 Hz, H-5,9), 7.26 (d, 2H, J = 8.2 Hz, H-6,8); ^{13}C-NMR for undiluted *10b* in $CDCl_3$

with TMS: single intense signal at 135.68 ppm (C-11); see ^{13}C-NMR of unlabeled *10* above.

2-[4-(2-[^{13}C]Methyl-[3-^{13}C]propyl)phenyl]propionic Acid (*11a*)

A solution of 0.85 g of *10a* (4.14 mmol) in 20 ml of EtOAc containing 100 mg of 10% Pd/C catalyst was stirred under H_2 gas at ambient temperature and pressure. The uptake of H_2 stopped after 135 ml had been absorbed in one hour. The mixture was filtered through Celite, and filtrate was concentrated to an oil which crystallized spontaneously. Recrystallization from 3 ml of MeOH and 2 ml of H_20 gave 0.81 g of *11a*, 94% yield; mp. 71-72^{0}C; λmax in EtOH nm (ε): 212 (8280), 220 (8640); mass spectrum: m/z (rel. intensity), 208 (25.3) M$^+$, 163 (100) M$^+$-COOH; single component by TLC (30:68:2 v/v Et_2O:hexane:HOAc, Rf = 0.41) identical to a standard sample of ibuprofen; ^{1}H-NMR (300 mHz) δ ($CDCl_3$) (see numbering in structure *12*): 0.84 (ddd, 6H, $^1J_{C-H}$ = 98.6 Hz, $^3J_{H-H}$ = 6 Hz, $^3J_{C-H}$ = 6 Hz, H-12,13), 1.49 (d, 3H, J = 7.2 Hz, H-3), 1.77-1.93 (m, 1H, H-11), 2.44 (dt, 2H, $^3J_{H-H}$ = 7.1 Hz, $^3J_{C-H}$ = 4.2 Hz, H-10), 3.70 (q, 1H, J = 7.2 Hz, H-2), 7.10 (d, 2H, J = 8.1 Hz, H-5,9), 7.23 (d, 2H, J = 8.1 Hz, H-6,8); ^{13}C-NMR for unlabeled ibuprofen, ppm ($CDCl_3$, TMS) identical to a standard sample of ibuprofen: 18.10 (C-3), 22.40 (C-12 and C-13), 30.17 (C-11), 44.97 (C-2), 45.06 (C-10), 127.29 and 129.40 (C-5 and C-9; C-6 and C-8), 136.98 and 140.87 (C-4 and C-7), 180.97 (C-1); ^{13}C-NMR for undiluted [$^{13}C_2$]ibuprofen *11a* in $CDCl_3$ with TMS: single intense signal at 22.4 ppm (C-12 and C-13).

2-[4-(2-Methyl-[2-^{13}C]propyl)phenyl]propionic Acid (*11b*)

A solution of 0.54 g of *10b* (2.64 mmol) in 15 ml EtOAc containing 100 mg of 10% Pd/C catalyst was stirred under H_2 gas at ambient temperature and pressure. The uptake of H_2 stopped after 91 ml had been absorbed. The mixture was filtered through Celite and filtrate was concentrated to an oil which crystallized spontaneously. Recrystallization from 2 ml of MeOH and 1.2 ml of H_20 afforded 0.50 g of *11b*, 91% yield; mp. 71-72^{0}C; λ_{max} in EtOH nm (ε):212 (8290), 220 (8590), mass spectrum: m/z (rel. intensity), 207 (49.9) M$^+$, 163 (100) M$^+$-COOH $^+$H, 162 (94.9) M$^+$-COOH; single

component by TLC (5:30:65:1 v/v MeOH:Et_2O:hexane:HOAc, Rf = 0.35); ^{1}H-NMR (300 mHz) δ ($CDCl_3$) (see numbering in structure *12*):0.89 (dd, 6H, $^3J_{H-H}$ = 6.6 Hz, $^2J_{C-H}$ = 4.1 Hz, H-12,13), 1.50 (d, 3H, J = 7.2 Hz, H-3), 1.55-1.69 (m, 1H, H-11), 1.84 (doublet of triplets of septets, 1H, $^1J_{C-H}$ = 135 Hz, $^3J_{H-H}$ = 6.7 Hz, $^3J_{H-H}$ = 6.7 Hz, H-11), 2.45 (dd, 2H, $^2J_{C-H}$ = 7.6 Hz, $^3J_{H-H}$ = 6.7 Hz, H-10), 3.71 (q, 1H, J = 7.2 Hz, H-2), 7.09 (d, 2H, J = 8.1 Hz, H-5,9), 7.21 (d, 2H, J = 8.1 Hz, H-6,8); see ^{13}C-NMR data for standard ibuprofen listed in compound *11a*; ^{13}C-NMR for undiluted [^{13}C]ibuprofen *11b* in $CDCl_3$ with TMS: single intense signal at 30.16 ppm (C-11).

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