3,5-diphenylpent-2-enoic acids as allosteric activators of the protein kinase PDK1: Structure-activity relationships and thermodynamic characterisation of binding as paradigms for PIF-binding pocket-targeting compounds

Adriana Stroba [1], Francis Schaeffer [2], Valerie Hindie [3], Laura Lopez-Garcia [3], Iris Adrian [3], Wolfgang Fröhner [1], Rolf W. Hartmann [1], Ricardo M. Biondi [3] and Matthias Engel [,1]*

Pharmaceutical and Medicinal Chemistry, Saarland University, P.O. Box 151150, D-66041 Saarbrücken, Germany, Unité de Biochimie Structurale (CNRS-URA 2185), Institut Pasteur, F-75724 Paris, France, Department of Internal Medicine I, University of Frankfurt, Theodor-Stern-Kai 7, D-60590 Frankfurt a.M., Germany

Supporting Information

Contents:

1) Synthetic procedures and NMR spectroscopic data of compounds **2c-14c, 21c, 2b-13b, 15b-18b, 21b, 2a-20a, 21*E*a, 3-5*Z*, 9-11*Z*, 14-15*Z*, 18*Z*, 3-11*E*, 13-14*E*, 18*E*, 16-17*E/Z*, 19, 20, 21.**

2) 2D-NOESY spectra for compounds **2E** and **2Z**.

1) Synthetic procedures and NMR spectroscopic data of compounds **2c-14c, 21c, 2b-13b, 15b-18b, 21b, 2a-20a, 21*E*a**, **3-5*Z*, 9-11*Z*, 14-15*Z*, 18*Z*, 3-11*E*, 13-14*E*, 18*E*, 16-17*E/Z*, 19, 20, 21.**

Method A: Claisen-Schmitt condensation

The corresponding benzaldehyde **2-13d** (1 eq) was dissolved in EtOH (2 mL / 1 mmol), a 3 M $NaOH_{aq}$ solution (3 eq) and acetophenone (1 eq) were added and the resulting mixture was stirred at rt for 2 h forming a yellow precipitate. The yellow solid was separated by vacuum filtration and was washed three times with 10 mL ice water. The crude product was purified by recrystallization from MeOH yielding **2-12c**.

3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one, 2c. Synthesised according to Method A using 4-chlorobenzaldehyde **2d** (9.36 g, 67.0 mmol) and acetophenone (8.0 g, 67.0 mmol); pale yellow solid; yield: 15.3 g (94 %); Mp 113-114 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.39 (d, ^3J = 8.5 Hz, 2H), 7.47-7.51 (m, 3H), 7.58-7.60 (m, 3H), 7.75 (d, ^3J = 15.7 Hz, 1H), 8.00-8.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 128.4, 128.7, 129.2, 129.5, 132.1, 132.9, 133.4, 136.4, 138.0, 144.7, 189.9.

3-(3-Chlorophenyl)-1-phenylprop-2-en-1-one, 3c. Synthesised according to Method A using 3-chlorobenzaldehyde **3d** (0.8 mL, 7.11 mmol) and acetophenone (0.83 mL, 7.11 mmol); pale yellow solid; yield: 1.62 g (94 %); Mp 110-111 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.39-7.44 (m, 2H), 7.50-7.55 (m, 4H), 7.60-7.64 (m, 2H), 7.73 (d, ^3J = 15.3 Hz, 1H), 8.02 (d, ^3J = 8.5 Hz, 1H). ^{13}C NMR

($CDCl_3$, 125 MHz): δ = 123.2, 126.8, 127.9, 128.5, 128.7, 130.2, 130.3, 133.0, 134.9, 137.9, 143.0, 190.1.

3-(4-Fluorophenyl)-1-phenylprop-2-en-1-one, 4c. Synthesised according to Method A using 4-fluorobenzaldehyde **4d** (2.0 g, 16.11 mmol) and acetophenone (1.88 mL, 16.11 mmol); yellow solid; yield: 3.35 g (92 %); Mp 88-90 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.09-7.13 (m, 2H), 7.44-7.52 (m, 3H), 7.57-7.65 (m, 3H), 7.77 (d, ^3J = 15.8 Hz, 1H), 8.00-8.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 116.1 (d, ^2J (C, F) = 21.9 Hz, CH), 121.8, 128.4, 128.6, 130.3 (d, ^3J (C, F) = 8.2 Hz, CH), 131.1 (d, ^4J (C, F) = 3.7 Hz, CH), 132.8, 138.1, 143.4, 164,0 (d, ^1J (C, F) = 252.0 Hz, C_{quat}), 190.3.

3-(4-Bromophenyl)-1-phenylprop-2-en-1-one, 5c. Synthesised according to Method A using 4-bromobenzaldehyde **5d** (2.0 g, 10.81 mmol) and acetophenone (1.26 mL, 10.81 mmol); yellow solid; yield: 2.80 g (90 %); Mp 121-123 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.50-7.61 (m, 8H), 7.74 (d, ^3J = 15.7 Hz, 1H), 8.01 (dd, ^4J = 1.4, ^3J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 122.6, 124.8, 128.5, 128.7, 129.8, 132.2, 132.9, 133.8, 138.0, 143.4, 190.2.

3-(4-(Trifluoromethylphenyl)-1-phenylprop-2-en-1-one, 6c. Synthesised according to Method A using 4-trifluoromethylbenzaldehyde **6d** (2.00 g, 11.5 mmol) and acetophenone (1.34 mL, 11.5 mmol); yellow solid; yield: 3.05 g (94 %); Mp 129-131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.50-7.55 (m, 2H), 7.58-7.63 (m, 2H), 7.68 (d, ^3J = 8.5 Hz, 2H), 7.74 (d, ^3J = 8.5 Hz, 2H), 7.81 (d, ^3J = 15.8 Hz, 1H), 8.02-8.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) : δ = 124.3, 125.9 (q, J(C, F) = 3.7, CH), 128.5, 128.6, 128.7, 129.4, 131.9 (d, J(C-F) = 32.6), 132.1, 133.2, 138.1 (d, J (C, F) = 61.4 Hz, CH), 142.7, 190.6.

3-(3,4-Dichlorophenyl)-1-phenylprop-2-en-1-one, 7c. Synthesised according to Method A using 3,4-dichlorobenzaldehyde **7d** (2.00 g, 11.4 mmol) and acetophenone (1.33 mL, 11.4 mmol); pale yellow solid; yield: 3.00 g (94 %); Mp 110-113 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.44-7.53 (m, 5H), 7.59-7.62 (m, 1H), 7.69 (d, ^{3}J = 15.8 Hz, 1H), 7.72 (d, ^{3}J = 1.9 Hz, 1H), 8.00-8.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 123.5, 127.5, 128.5, 128.7, 129.7, 131.0, 133.1, 133.3, 134.4, 134.9, 137.8, 141.9, 189.9.

3-(2,4-Dichlorophenyl)-1-phenylprop-2-en-1-one, 8c. Synthesised according to Method A using 2,4-dichlorobenzaldehyde **8d** (2.0 g, 11.43 mmol) and acetophenone (1.33 mL, 11.43 mmol); yellow solid; yield: 3.1 g (94 %); Mp 175-178 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.39 (dd, ^{4}J = 2.2, ^{3}J = 8.5 Hz, 1H), 7.46-7.53 (m, 4H), 7.59-7.62 (m, 1H), 7.69 (d, ^{3}J = 8.2 Hz, 1H), 8.00-8.10 (m, 2H), 8.10 (d, ^{3}J = 15.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 125.1, 127.6, 127.9, 128.5, 128.6, 128.7, 130.1, 133.1, 136.0, 136.5, 137.8, 139.3, 190.1.

3-(4-Bromo-2-fluorophenyl)-1-phenylprop-2-en-1-one, 9c. Synthesised according to Method A using 4-bromo-2-fluoro-benzaldehyde **9d** (1.50 g, 7.39 mmol) and acetophenone (0.86 mL, 7.39 mmol); yellow solid; yield: 1.81 g (80 %); Mp 166-168 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.33-7.36 (m, 2H), 7.51 (t, ^{3}J = 7.6 Hz, 3H), 7.56-7.63 (m, 1H), 7.63 (d, ^{3}J = 15.8 Hz, 1H), 7.82 (d, ^{3}J = 16.1 Hz, 1H), 8.03-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 119.9 (d, *J* (C, F) = 24.9 Hz, CH), 120.1 (d, *J* (C, F) = 1.6 Hz, CH), 122.2, 124.6 (d, *J* (C, F) = 9.6 Hz, CH), 125.0 (d, *J* (C, F) = 3.8 Hz, CH), 128.0 (d, *J* (C, F) = 7.7 Hz, CH), 128.6, 128.7, 130.6 (d, *J* (C, F) = 3.8 Hz, CH), 133.0, 136.3, 161.0 (d, *J* (C, F) = 252.0 Hz, C_{quat}), 190.2.

3-(4-Ethylphenyl)-1-phenylprop-2-en-1-one, 10c. Synthesised according to Method A using 4-ethylbenzaldehyde **10d** (2.00 g, 14.9 mmol) and acetophenone (1.79 g, 14.9 mmol); yellow oil; yield: 2.60 g (74 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.04 (t, ^{3}J = 7.6 Hz, 3H), 2.47 (q, ^{3}J = 7.6 Hz, 2H), 7.02-7.04 (m, 2H), 7.26-7.32 (m, 3H), 7.34-7.37 (m, 3H), 7.58 (d, ^{3}J = 15.8 Hz, 1H), 7.77-7.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.3, 28.8, 121.2, 128.4, 128.5, 128.6, 131.6, 132.4, 132.6, 138.4, 145.0, 147.4, 190.7.

3-(Biphenyl-4-yl)-1-phenylprop-2-en-1-one, 11c. Synthesised according to Method A using 2-biphenylcarboxaldehyde **11d** (2.00 g, 10.9 mmol) and acetophenone (1.28 g, 10.9 mmol); pale yellow solid; yield: 1.90 g (63 %); Mp 102-104 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37-7.41 (m, 1H), 7.47 (t, ^{3}J = 7.6 Hz, 2H), 7.52 (t, ^{3}J = 7.6 Hz, 2H), 7.56-7.65 (m, 6H), 7.73 (d, ^{3}J = 8.2 Hz, 2H), 7.86 (d, ^{3}J = 15.8 Hz, 1H), 8.03-8.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 121.9, 127.0, 127.6, 127.9, 128.5, 128.6, 128.9, 129.0, 132.8, 133.8, 138.3, 140.1, 143.3, 144.4, 190.2.

3-(Naphthalen-2-yl)-1-phenylprop-2-en-1-one, 12c. Synthesised according to Method A using 2-naphthaldehyde **12d** (2.00 g, 12.8 mmol) and acetophenone (1.49 g, 12.8 mmol); pale yellow solid; yield: 2.85 g (86 %); Mp 158-160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.51-7.55 (m, 4H), 7.59-7.62 (m, 1H), 7.65 (d, ^{3}J = 15.4 Hz, 1H), 7.80 (dd, ^{4}J = 1.7, ^{3}J = 8.5 Hz, 1H), 7.85-7.90 (m, 3H), 7.98 (d, ^{3}J = 15.4 Hz, 1H), 8.04-8.08 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 122.3, 123.7, 126.8, 127.4, 127.8, 128.5, 128.6, 128.7, 130.6, 132.4, 132.8, 133.4, 134.4, 138.3, 144.9, 190.5.

3-(1H-Indol-3-yl)-1-phenylprop-2-en-1-one, 13c. Indole-3-aldehyde **13d** (1 g, 6.89 mmol) was dissolved in EtOH (14 mL). Then the acetophenone (0.8 mL, 6.89 mmol) and afterwards piperidine (0.37 mL, 3.82 mmol) were added. The resulting solution was refluxed for 16 h. The reaction mixture was neutralized with 10 % HCl to pH 7. The formed precipitate was collected by vacuum filtration and

purified by recrystallization from MeOH to give **13c**. Deep yellow solid; yield: 1.18 g (68 %); Mp 161-163 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29-7.33 (m, 2H), 7.44-7.46 (m, 1H), 7.50-7.54 (m, 2H), 7.56-7.62 (m, 3H), 8.01-8.06 (m, 1H), 8.06-8.08 (m, 2H), 8.12 (d, ^{3}J = 15.5 Hz, 1H), 8.84 (s, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 112.0, 114.5, 117.9, 120.7, 121.8, 123.5, 125.4, 128.3, 128.5, 130.3, 132.3, 137.3, 139.0, 139.0, 191.9.

2-(4-Chlorobenzylidene)-2,3-dihydro-1H-inden-1-one, 21c. Synthesised according to Method A using 4-chlorobenzaldehyde **2d** (1.06 g, 7.57 mmol) and 1-indanone (1.0 g, 7.57 mmol); white solid; yield: 1.6 g (83 %); Mp 156-160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.02 (s, 2H), 7.42-7.45 (m, 3H), 7.55-7.64 (m, 5H), 7.91 (d, ^{3}J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 32.3, 124.5, 126.2, 127.8, 129.2, 131.8, 132.4, 133.9, 134.8, 135.1, 135.6, 137.9, 149.4, 194.0.

Method B: Selective silica gel-catalyzed 1,4-reduction

The corresponding chalcone (1 eq) was stirred under the nitrogen atmosphere with 3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,6-dimethylpyridine (HEH, 1.5 eq) in the presence of silica gel (0.2 g / 0.1 mmol) in toluene (2 mL / 1 mmol) at 70 °C in the dark for 17 h. After removal of toluene under vacuum, the crude mixture was purified by flash column chromatography on silica gel.

3-(4-Chlorophenyl)-1-phenylpropan-1-one, 2b. Synthesised according to Method B using compound **2c** (0.636 g, 2.62 mmol), HEH (1.0 g, 3.93 mmol) and silica gel (5.26 g); white solid; yield: 0.49 g (81 %); Mp 99-100 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.95 (t, ^{3}J = 7.6, 2H), 3.21 (t, ^{3}J = 7.6, 2H), 7.17-7.19 (m, 2H), 7.19 (m, 2H), 7.44-7.47 (m, 2H), 7.55-7.58 (m, 1H), 7.96-7.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.6, 40.4, 128.2, 129.8, 128.9, 130.1, 132.1, 133.4, 137.0, 139.0, 199.1.

3-(3-Chlorophenyl)-1-phenylpropan-1-one, 3b. Synthesised according to Method B using compound **3c** (0.60 g, 2.47 mmol), HEH (0.94 g, 3.70 mmol) and silica gel (4.94 g); white solid; yield: 0.57 g (89 %); Mp 82-84 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.03-3.07 (m, 2H), 3.29-3.32 (m, 2H), 7.27-7.32 (m, 4H), 7.46 (t, ^{3}J = 7.9 Hz, 2H), 7.57 (t, ^{3}J = 7.6 Hz, 1H), 7.96 (d, ^{3}J = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.7, 40.0, 126.3, 126.7, 128.0, 128.6, 128.6, 129.7, 133.2, 134.3, 136.8, 143.3, 198.7.

3-(4-Fluorophenyl)-1-phenylpropan-1-one, 4b. Synthesised according to Method B using compound **4c** (0.50 g, 2.21 mmol), HEH (0.84 g, 3.31 mmol) and silica gel (4.42 g); pale yellow oil; yield: 0.476 g (94 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.05 (t, ^{3}J = 7.6, 2H), 3.29 (t, ^{3}J = 7.6, 2H), 6.99-6.95 (m, 2H), 7.22-7.19 (m, 2H), 7.46 (t, ^{3}J = 7.6 Hz, 2H), 7.58-7.54 (m, 1H), 7.95 (d, ^{3}J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.2, 40.4, 115.2 (d, J (C, F) = 21.1 Hz, CH), 127.9, 128.6, 129.8 (d, J (C, F) = 7.7 Hz, CH), 133.1, 136.7, 136.8, 161,0 (d, J (C, F) = 243.8 Hz, C_{quat}), 198.9.

3-(4-Bromophenyl)-1-phenylpropan-1-one, 5b. Synthesised according to Method B using compound **5c** (0.50 g, 1.74 mmol), HEH (0.661 g, 2.61 mmol) and silica gel (3.48 g); pale yellow solid; yield: 0.479 g (95 %); Mp 73-75 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.03 (t, ^{3}J = 7.6 Hz, 2H), 3.28 (t, ^{3}J = 7.6 Hz, 2H), 7.13 (d, ^{3}J = 8.5 Hz, 2H), 7.30 (d, ^{3}J = 8.5 Hz, 2H), 7.46 (t, ^{3}J = 7.2 Hz, 2H), 7.58-7.55 (m, 1H), 7.94 (dd, ^{4}J = 1.3, ^{3}J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.4, 40.0, 119.9, 128.0, 128.6, 130.2, 131.5, 133.2, 136.7, 140.2, 198.8.

1-Phenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one, 6b. Synthesised according to Method B using compound **6c** (0.50 g, 1.81 mmol), HEH (0.687 g, 2.71 mmol) and silica gel (3.62 g); pale yellow oil;

yield: 0.438 g (87 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.14 (t, ^{3}J = 7.6 Hz, 2H), 3.32 (t, ^{3}J = 7.6 Hz, 2H), 7.37 (d, ^{3}J = 7.9 Hz, 2H), 7.46 (t, J = 7.9 Hz, 2H), 7.54-7.56 (m, 3H), 7.95 (d, ^{3}J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.8, 39.8, 125.2, 125.4, 127.9, 128.7, 128.8, 133.2, 136.7, 145.1, 145.4, 190.8.

3-(3,4-Dichlorophenyl)-1-phenylpropan-1-one, 7b. Synthesised according to Method B using compound **7c** (0.50 g, 1.80 mmol), HEH (0.685 g, 2.70 mmol) and silica gel (3.60 g); pale yellow oil; yield: 0.416 g (83 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.03 (t, ^{3}J = 7.2 Hz, 2H), 3.28 (t, ^{3}J = 7.2 Hz, 2H), 7.09 (dd, ^{4}J = 1.9, ^{4}J = 8.5 Hz, 1H), 7.35-7.34 (m, 2H), 7.46 (t, ^{3}J = 7.2 Hz, 2H), 7.59-7.55 (m, 1H), 7.96-7.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.9, 39.7, 127.9, 128.0, 128.7, 130.0, 130.3, 130.4, 132.3, 133.2, 136.6, 141.5, 198.4.

3-(2,4-Dichlorophenyl)-1-phenylpropan-1-one, 8b. Synthesised according to Method B using compound **8c** (0.50 g, 1.80 mmol), HEH (0.685 g, 2.70 mmol) and silica gel (3.60 g); pale green oil; yield: 0.363 g (72 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.15 (t, ^{3}J = 7.6 Hz, 2H), 3.29 (t, ^{3}J = 7.6 Hz, 2H), 7.17 (dd, ^{4}J = 2.2, ^{3}J = 8.2 Hz, 1H), 7.26 (d, ^{3}J = 8.2 Hz, 2H), 7.37 (d, ^{3}J = 2.2 Hz, 1H), 7.46 (t, ^{3}J = 7.6 Hz, 2H), 7.54-7.59 (m, 1H), 7.95-7.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.7, 38.1, 127.3, 128.0, 128.6, 129.3, 131.7, 132.7, 133.2, 134.6, 136.6, 137.4, 198.6.

3-(4-Bromo-2-fluorophenyl)-1-phenylpropan-1-one, 9b. Synthesised according to Method B using compound **9c** (0.50 g, 1.64 mmol), HEH (0.623 g, 2.46 mmol) and silica gel (3.28 g); pale green oil; yield: 0.395 g (78 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.06 (t, ^{3}J = 7.6 Hz, 2H), 3.28 (t, ^{3}J = 7.6 Hz, 2H), 7.15-7.21 (m, 3H), 7.46 (t, ^{3}J = 7.9 Hz, 2H), 7.54-7.59 (m, 1H), 7.91-7.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.5, 38.4, 118.8, 119.0, 120.0 (d, J (C, F) = 9.6 Hz, CH), 127.3, (t, J (C, F) =

2.9 Hz, CH), 128.0, 128.6, 132.0 (d, *J* (C, F) = 5.8 Hz, CH), 133.2, 136.6, 161.0 (d, *J* (C, F) = 249.5 Hz, C_{quat}), 198.6.

3-(4-Ethylphenyl)-1-phenylpropan-1-one, 10b. Synthesised according to Method B using compound **10c** (0.50 g, 2.11 mmol), HEH (0.84 g, 3.17 mmol) and silica gel (4.22 g); pale yellow oil; yield: 0.284 g (57 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.23 (t, ^{3}J = 7.6 Hz, 3H), 2.63 (q, ^{3}J = 7.6 Hz, 2H), 3.05 (t, ^{3}J = 7.6 Hz, 2H), 3.30 (t, ^{3}J = 7.6 Hz, 2H), 7.14 (d, ^{3}J = 8.2 Hz, 2H), 7.18 (d, ^{3}J = 8.2 Hz, 2H), 7.46 (t, ^{3}J = 7.2 Hz, 2H), 7.54-7.57 (m, 1H), 7.95-7.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.6, 28.4, 29.7, 40.6, 127.9, 128.0, 128.3, 128.6, 133.0, 136.9, 138.4, 142.0, 199.3.

3-(Biphenyl-4-yl)-1-phenylpropan-1-one, 11b. Synthesised according to Method B using compound **11c** (0.50 g, 1.76 mmol), HEH (0.686 g, 2.63 mmol) and silica gel (3.52 g); pale yellow solid; yield: 0.446 g (88 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.13 (t, ^{3}J = 7.6 Hz, 2H), 3.35 (t, ^{3}J = 7.6 Hz, 2H), 7.31-7.35 (m, 3H), 7.42-7.48(m, 4H), 7.55-7.59 (m, 5H), 7.97-8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 29.7, 40.4, 126.9, 127.0, 127.2, 128.0, 128.6, 128.7, 128.9, 133.1, 136.9, 139.1, 140.4, 140.9, 199.1.

3-(Naphthalen-2-yl)-1-phenylpropan-1-one, 12b. Synthesised according to Method B using compound **12c** (0.50 g, 1.936 mmol), HEH (0.735 g, 2.90 mmol) and silica gel (3.86 g); white solid; yield: 0.426 g (85 %); Mp 68-70 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.25 (t, ^{3}J = 8.5 Hz, 2H), 3.40 (t, ^{3}J = 8.5 Hz, 2H), 7.39-7.48 (m, 5H), 7.56 (m, 1H), 7.70 (s, 1H), 7.78-7.82 (m, 3H), 7.98 (dd, ^{4}J = 1.26, ^{3}J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 30.2, 40.3, 125.3, 126.0, 126.5, 127.1, 127.4, 127.6, 128.0, 128.1, 128.6, 132.1, 133.1, 133.6, 136.9, 138.8, 187.9.

3-(1H-Indol-3-yl)-1-phenylpropan-1-one, 13b. Synthesised according to Method B using compound **13c** (1.0 g, 4.04 mmol), HEH (1.53 g, 6.06 mmol) and silica gel (8.08 g); white solid; yield: 0.85 g (84 %); Mp 127-130 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.23 (t, ^{3}J = 7.6 Hz, 2H), 3.39 (t, ^{3}J = 7.6 Hz, 2H), 7.05-7.06 (m, 1H), 7.14 (dt, ^{4}J = 0.9, ^{3}J = 7.2 Hz, 1H), 7.21 (dt, ^{4}J = 1.3, ^{4}J = 8.2 Hz, 1H), 7.36 (d, ^{3}J = 8.2 Hz, 1H), 7.43-7.47 (m, 2H), 7.53-7.57 (m, 1H), 7.64 (d, ^{3}J = 8.5 Hz, 1H), 7.96-7.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 19.7, 39.3, 111.1, 115.5, 118.7, 119.3, 121.5, 122.0, 127.3, 128.0, 128.5, 132.9, 136.3, 137.0, 199.9.

2-(4-Chlorobenzyl)-2,3-dihydro-1H-inden-1-one, 21b. Synthesised according to Method B using compound **21c** (0.435 g, 1.71 mmol), HEH (0.650 g, 2.56 mmol) and silica gel (3.42 g); white solid; yield: 0.359 g (82 %); Mp 80-82 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.68-2.73 (m, 1H), 2.81-2.86 (m, 1H), 2.95-3.00 (m, 1H), 3.16-3.21 (m, 1H), 3.32-3.36 (m, 1H), 7.15-7.19 (m, 2H), 7.25-7.29 (m, 2H), 7.36-7.42 (m, 2H), 7.58 (dt, ^{4}J = 1.2, ^{3}J = 7.2 Hz, 1H), 7.78 (d, ^{3}J = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 32.0, 36.2, 48.7, 124.0, 126.6, 127.5, 128.6, 130.3, 132.2, 134.9, 136.5, 138.0, 153.4, 207.3.

Method C: Horner-Wadsworth-Emmons reaction

Triethyl phosphonoacetate (1-3 eq) was added dropwise at 20 °C to a slurry of sodium hydride (abs. 60 % in oil) (1-3 eq) in anhydrous 1,2-dimethoxyethane under nitrogen. The reaction mixture was stirred at rt for 1 h until the gas evolution had ceased and the appropriate reduced chalcone, **(2-13c),** (1 eq) was added. After stirring at 80 °C for 4 hours the resultant solution was poured into ice water (50 mL) and then extracted with dichloromethane (3 x 20 mL). The extract was washed with brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to afford a crude which was purified by flash column chromatography to obtain **2-13*E*a** and **2-13*Z*a**, respectively.

Ethyl 5-(4-chlorophenyl)-3-phenylpent-2-enoate, 2a. Synthesised according to Method C using compound **2b** (0.346 g, 1.41 mmol), NaH (0.17 g, 4.23 mmol) and triethyl phosphonoacetate (0.96 mL, 4.23 mmol);

2*E*a: colourless oil; yield: 0.19 g (42 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (t, ^{3}J = 7.2 Hz, 3H), 2.68-2.72 (m, 2H), 3.36-3.39 (m, ^{3}J = 8.3 Hz, 2H), 4.20 (q, ^{3}J = 7.2 Hz, 2H), 6,06 (s, 1H), 7.12-7.15 (m, 2H), 7.21-7.23 (m, 2H), 7.38-7.40 (m, 3H), 7.42-7.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 32.9, 34.4, 59.9, 118.1, 126.7, 128.3, 128.7, 129.0, 129.9, 131.6, 139.9, 140.9, 158.9, 165.9.

2*Z*a: colourless oil; yield: 0.17 g (38 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, ^{3}J = 7.2 Hz, 3H), 2.65-2.68 (m, 2H), 2.69-2.72 (m, 2H), 4.98 (q, ^{3}J = 7.2 Hz, 1H), 5.87 (s, 1H), 7.05 (d, 3J = 8.2 Hz, 2H), 7.17 (d, ^{3}J = 7.8 Hz, 2H), 7.23 (d, ^{3}J = 8.2 Hz, 2H), 7.37-7.34 (m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 33.1, 41.8, 59.9, 118.1, 127.2, 127.8, 127.9, 128.5, 129.6, 131.9, 139.2, 139.6, 157.8, 164.9.

Ethyl 5-(3-chlorophenyl)-3-phenylpent-2-enoate, 3a. Synthesised according to Method C using compound **3b** (0.40 g, 1.63 mmol), NaH (0.20 g, 4.89 mmol) and triethyl phosphonoacetate (0.97 mL, 4.89 mmol);

3*E*a: colourless oil; yield: 0.22 g (43 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.32 (t, ^{3}J = 6.9 Hz, 3H), 2.69-2.74 (m, 2H), 3.37-3.41 (m, 2H), 4.21 (q, ^{3}J = 7.2 Hz, 2H), 6.07 (s, 1H), 7.16-7.20 (m, 4H), 7.42-7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 32.7, 34.7, 59.9, 118.1, 126.1, 126.7, 128.6, 128.7, 129.0, 129.5, 133.9, 140.9, 141.3, 143.5, 158.8, 166.3.

3*Z*a: colourless oil; yield: 0.19 g (38 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (t, ^{3}J = 7.2 Hz, 3H), 2.66-2.70 (m, 2H), 2.74-2.79 (m, 2H), 3.98 (q, ^{3}J = 7.2 Hz, 2H), 5.88 (s, 1H), 7.05 (d, ^{3}J = 7.2 Hz, 1H),

7.11 (s, 1H), 7.16-7.21 (m, 4H), 7.30-7.37 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 33.5, 41.7, 59.9, 118.0, 126.3, 126.5, 127.8, 128.0, 128.4, 129.7, 134.2, 139.6, 142.8, 157.7, 165.8.

Ethyl 5-(4-fluorophenyl)-3-phenylpent-2-enoate, 4a. Synthesised according to Method C using compound **4b** (0.40 g, 1.75 mmol), NaH (0.21 g, 5.26 mmol) and triethyl phosphonoacetate (1.2 mL, 5.42 mmol);

4*E*a: colourless oil; yield: 0.193 g (37%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, ^3J = 7.2 Hz, 3H), 2.65-2.75 (m, 4H), 3.98 (q, ^3J = 7.2 Hz, 2H), 5.87 (s, 1H), 6.93-6.97 (m, 2H), 7.06-7.09 (m, 2H), 7.16-7.18 (m, 2H), 7.31-7.38 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 32.9, 42.1, 59.8, 115.0, 115.1 (d, *J* (C, F) = 22.1 Hz, CH), 117.9, 127.2, 127.7, 127.8, 127.9, 129.6 (d, *J* (C, F) = 7.7 Hz, CH), 136.4, 139.7, 158.0, 161.0 (d, *J* (C, F) = 243.8 Hz, C_{quat}), 165.8.

4*Z*a: colourless oil; yield: 0.189 g (36 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.29 (t, ^3J = 7.2 Hz, 3H), 2.69-2.72 (m, 2H), 3.36-3.39 (m, 2H), 4.20 (q, ^3J = 7.2 Hz, 2H), 6.06 (s, 1H), 6.92-6.96 (m, 2H), 7.15-7.18 (m, 2H), 7.46-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 31.1, 34.3, 59.9, 115.0 (d, *J* (C, F) = 21.1 Hz, CH), 117.9, 126.7, 128.6, 129.0, 129.8 (d, *J* (C, F) = 7.7 Hz, CH), 137.1, 140.9, 159.1, 161.0 (d, *J* (C, F) = 243.8 Hz, C_{quat}), 166.3.

Ethyl 5-(4-bromophenyl)-3-phenylpent-2-enoate, 5a. Synthesised according to Method C using compound **5b** (0.40 g, 1.38 mmol), NaH (0.166 g, 4.15 mmol) and triethyl phosphonoacetate (0.94 mL, 4.15 mmol);

5*E*a: colourless oil; yield: 0.226 g (46 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (t, ^3J = 7.2 Hz, 3H), 2.67-2.70 (m, 2H), 3.36-3.92 (m, 2H), 4.20 (q, ^3J = 7.2 Hz, 2H), 6.06 (s, 1H), 7.08 (d, ^3J = 8.5 Hz, 2H),

7.38-7.45 (m, 7H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 32.8, 34.5, 59.9, 118.1, 119.7, 126.7, 128.7, 129.1, 130.3, 131.3, 140.9, 158.9, 166.2.

5*Z*a: colourless oil; yield: 0.205 g (41 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, ^3J = 7.2 Hz, 3H), 2.63-2.75 (m, 4H), 3.98 (q, ^3J = 7.2 Hz, 2H), 5.87 (s, 1H), 7.00 (d, ^3J = 8.5 Hz, 1H), 7.16-7.18 (m, 2H), 7.31-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.2, 33.4, 42.0, 60.1, 118.3, 120.2, 127.4, 128.0, 128.2, 130.3, 131.7, 139.8, 140.0, 158.0, 166.1.

Ethyl 3-phenyl-5-(4-(trifluoromethyl)phenyl)pent-2-enoate, 6a. Synthesised according to Method C using compound **6b** (0.35 g, 1.26 mmol), NaH (0.151 g, 3.77 mmol) and triethyl phosphonoacetate (0.86 mL, 3.77 mmol);

6*E*a: colourless oil; yield: 0.19 g (43 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (t, ^3J = 7.2 Hz, 3H), 2.79-2.81 (m, 2H), 3.40-3.44 (m, 2H), 4.20 (q, ^3J = 7.2 Hz, 2H), 6.07 (s, 1H), 7.31 (d, ^3J = 8.2 Hz, 2H), 7.39-7.45 (m, 5H), 7.50 (d, ^3J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 32.6, 34.9, 59.9, 118.2, 125.0, 125.2 (d, *J* (C, F) = 3.9 Hz, CH), 126.7, 128.4, 128.5, 128.6, 128.8, 129.1, 140.8, 145.5, 158.8, 166.3;

6*Z*a: colourless oil; yield: 0.162 g (36 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, ^3J = 7.2 Hz, 3H), 2.73-2.79 (m, 4H), 3.98 (q, ^3J = 7.2 Hz, 2H), 5.89 (s, 1H), 7.18 (d, ^3J = 8.2 Hz, 2H), 7.23 (d, ^3J = 8.2 Hz, 2H), 7.32-7.39 (m, 3H), 7.52 (d, ^3J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 33.6, 41.5, 59.9, 118.1, 125.2, 125.3 (d, *J* (C, F) = 3.9 Hz, CH), 125.4, 127.2, 127.9, 128.0, 128.4, 128.6, 139.4, 144.9, 157.5, 165.8;

Ethyl 5-(3,4-dichlorophenyl)-3-phenylpent-2-enoate, 7a. Synthesised according to Method C using compound **7b** (0.35 g, 1.25 mmol), NaH (0.15 g, 3.76 mmol) and triethyl phosphono-acetate (0.85 mL, 3.76 mmol);

7*E*a: colourless oil; yield: 0.204 g (47 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (t, ^{3}J = 7.2 Hz, 3H), 2.67-2.71 (m, 2H), 3.36-3.39 (m, 2H), 4.20 (q, ^{3}J = 7.2 Hz, 2H), 6.06 (s, 1H), 7.04 (dd, ^{4}J = 1.9, ^{3}J = 8.2 Hz, 1H), 7.28 (d, ^{4}J = 2.2, ^{3}J = 8.2 Hz, 1H), 7.30 (d, ^{3}J = 8.2 Hz, 1H), 7.38-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 32.5, 34.1, 60.0, 118.3, 126.7, 128.1, 128.7, 129.1, 129.8, 130.1, 130.5, 132.0, 140.7, 141.6, 158.6, 166.3.

7*Z*a: colourless oil; yield: 0.178 g (41 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.01 (t, ^{3}J = 6.9 Hz, 3H), 2.75-2.63 (m, 4H), 3.98 (q, ^{3}J = 6.9 Hz, 2H), 5.87 (s, 1H), 6.96 (dd, ^{4}J = 2.2, ^{3}J = 8.2 Hz, 2H), 7.17 (d, ^{3}J = 8.2 Hz, 2H), 7.20 (s, 1H), 7.32-7.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 32.9, 41.5, 59.9, 118.2, 127.2, 127.8, 127.9, 128.0, 130.1, 130.2, 130.3, 132.3, 139.3, 141.0, 157.3, 165.8.

Ethyl 5-(2,4-dichlorophenyl)-3-phenylpent-2-enoate, 8a. Synthesised according to Method C using compound **8b** (0.30 g, 1.07 mmol), NaH (0.13 g, 3.22 mmol) and triethyl phosphonoacetate (0.73 mL, 3.22 mmol);

8*E*a: colourless oil; yield: 0.147 g (39 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.29 (t, ^{3}J = 7.2 Hz, 3H), 2.83-2.86 (m, 2H), 3.35-3.38 (m, 2H), 4.20 (q, ^{3}J = 7.2 Hz, 2H), 6.10 (s, 1H), 7.14 (dd, ^{3}J = 2.2, ^{3}J = 8.2 Hz, 1H), 7.23 (d, ^{3}J = 8.2 Hz, 2H), 7.31 (d, ^{3}J = 2.2 Hz, 1H), 7.37-7.41 (m, 3H), 7.48-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 30.9, 32.3, 60.0, 118.1, 126.7, 127.0, 128.6, 129.0, 129.1, 131.5, 132.3, 134.4, 137.7, 140.6, 158.6, 166.3.

8*Z*a: colourless oil; yield: 0.179 g (48 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (t, ^{3}J = 7.2 Hz, 3H), 2.70-2.79 (m, 4H), 3.99 (q, ^{3}J = 7.2 Hz, 2H), 5.91 (s, 1H), 7.05 (d, ^{3}J = 8.2 Hz, 1H), 7.15 (dd, ^{4}J = 2.2,

^{3}J =8.2 Hz, 1H), 7.19-7.21 (m, 2H), 7.31-7.38 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 31.4, 39.8, 59.9, 118.0, 127.1, 127.3, 127.9, 128.0, 129.3, 131.1, 132.6, 134.5, 137.0, 139.4, 157.6, 165.9.

Ethyl 5-(4-bromo-2-fluorophenyl)-3-phenylpent-2-enoate, 9a. Synthesised according to Method C using compound **9b** (0.30 g, 0.98 mmol), NaH (0.117 g, 2.93 mmol) and triethyl phosphonoacetate (0.67 mL, 3.05 mmol);

9*E*a: colourless oil; yield: 0.145 g (39 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (t, ^{3}J = 6.9 Hz, 3H), 2.73-2.76 (m, 2H), 3.35-3.38 (m, 2H), 4.19 (q, ^{3}J = 6.9 Hz, 2H), 6.09 (s, 1H), 7.10-7.18 (m, 3H), 7.37-7.39 (m, 3H), 7.45-7.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 28.0, 31.1, 60.0, 118.2, 118.6 (d, *J* (C, F) = 24.9 Hz, CH), 119.7 (d, *J* (C, F) = 9.6 Hz, CH), 126.7, 127.1 (d, *J* (C, F) = 3.9 Hz, CH), 127.4, 128.6, 129.1, 131.9, 132.0, 140.6, 158.4, 160.5 (d, *J* (C, F) = 249.5 Hz, C_{quat}).

9*Z*a: colourless oil; yield: 0.154 g (42 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, ^{3}J = 7.2 Hz, 3H), 2.66-2.75 (m, 4H), 3.98 (q, ^{3}J = 7.2 Hz, 2H), 5.87 (s, 1H), 6.96 (t, ^{3}J = 8.2 Hz, 1H), 7.18 (d, ^{3}J = 8.8 Hz, 4H), 7.31-7.38 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 27.1, 40.1, 60.0, 118.1, 118.9, 119.0, 119.5 (d, *J* (C, F) = 9.6 Hz, CH), 126.8, 127.1, 127.2, 127.3, 127.9 (d, *J* (C, F) = 9.6 Hz, CH), 131.5 (d, *J* (C, F) = 5.8 Hz, CH), 139.4, 158.5 (d, *J* (C, F) = 299.4 Hz, C_{quat}), 165.8.

Ethyl 5-(4-ethylphenyl)-3-phenylpent-2-enoate, 10a. Synthesised according to Method C using compound **10b** (0.25 g, 1.05 mmol), NaH (0.126 g, 3.15mmol) and triethyl phosphonoacetate (0.72 mL, 3.15 mmol);

10*E*a: colourless oil; yield: 0.143 g (44 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.25 (d, ^{3}J = 7.6 Hz, 3H), 1.30 (t, ^{3}J = 7.2 Hz, 3H), 2.61 (q, ^{3}J = 7.6 Hz, 2H), 2.69-2.72 (m, 2H), 3.37-3.40 (m, 2H), 4.21 (q, ^{3}J = 7.2 Hz, 2H), 6.07 (s, 1H), 7.10 (d, ^{3}J = 8.2 Hz, 2H), 7.15 (d, ^{3}J = 8.2 Hz, 2H), 7.38-7.41 (m, 3H), 7.46-

7.48 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 15.7, 28.5, 33.3, 34.8, 59.9, 117.8, 126.7, 127.8, 128.4, 128.6, 128.9, 138.8, 141.1, 141.8, 159.5, 166.3.

10*Z*a: colourless oil; yield: 0.133 g (41 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, ^3J = 7.2 Hz, 3H), 1.22 (t, ^3J = 7.6 Hz, 3H), 2.60 (q, ^3J = 7.6 Hz, 2H), 2.72-2.76 (m, 4H), 3.98 (q, ^3J = 7.2 Hz, 2H), 5.90 (s, 1H), 7.05 (d, ^3J = 7.9 Hz, 2H), 7.10 (d, ^3J = 7.9 Hz, 2H), 7.20-7.18 (m, 2H), 7.38-7.30 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 15.6, 28.4, 33.4, 42.1, 59.8, 117.6, 127.2, 127.7, 127.9, 128.2, 138.1, 139.9, 142.0, 158.6, 166.0.

Ethyl 5-(biphenyl-4-yl)-3-phenylpent-2-enoate, 11a. Synthesised according to Method C using compound **11b** (0.35 g, 1.22 mmol), NaH (0.147 g, 3.67mmol) and triethyl phosphonoacetate (0.83 mL, 3.67 mmol);

11*E*a: colourless oil; yield: 0.171 g (39 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.31 (t, ^3J = 7.2 Hz, 3H), 2.77-2.81 (m, 2H), 3.42-3.46 (m, 2H), 4.22 (q, ^3J = 7.2 Hz, 2H), 6.09 (s, 1H), 7.30-7.37 (m, 3H), 7.38-7.48 (m, 5H), 7.49-7.51 (m, 4H), 7.56-7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 33.1, 34.8, 59.9, 117.9, 126.7, 126.9, 127.0, 127.1, 128.6, 128.7, 128.9, 129.0, 138.9, 140.7, 141.0, 141.1, 159.3, 166.3.

11*Z*a: colourless oil; yield: 0.194 g (45 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (t, ^3J = 7.2 Hz, 3H), 2.73-2.82 (m, 4H), 3.99 (q, ^3J = 7.2 Hz, 2H), 5.93 (s, 1H), 7.20-7.22 (m, 4H), 7.31-7.39 (m, 4H), 7.42 (t, ^3J = 7.5 Hz, 2H), 7.49-7.51 (m, 2H), 7.56-7.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 33.4, 42.0, 59.8, 117.8, 127.0, 127.1, 127.2, 127.3, 127.7, 127.9, 128.7, 138.6, 139.0, 139.8, 139.9, 140.9, 158.3, 166.0.

Ethyl 5-(naphthalen-2-yl)-3-phenylpent-2-enoate, 12a. Synthesised according to Method C using compound **12b** (0.35 g, 1.34 mmol), NaH (0.161 g, 4.03mmol) and triethyl phosphonoacetate (0.91 mL, 4.03 mmol);

12*E*a: colourless oil; yield: 0.178 g (40 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.29 (t, ^{3}J = 7.2 Hz, 3H), 2.89-2.92 (m, 2H), 3.48-3.52 (m, 2H), 4.20 (q, ^{3}J = 7.2 Hz, 2H), 6.08 (s, 1H), 7.39-7.50 (m, 8H), 7.63 (s, 1H), 7.75-7.80 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 33.0, 35.3, 59.9, 118.0, 125.1, 125.8, 126.4, 126.8, 127.4, 127.5, 127.6, 127.8, 128.6, 129.0, 132.1, 133.6, 139.1, 141.1, 159.3, 166.4.

12*Z*a: colourless oil; yield: 0.188 g (42 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, ^{3}J = 7.2 Hz, 3H), 2.83-2.90 (m, 4H), 3.98 (q, ^{3}J = 7.2 Hz, 2H), 5.94 (s, 1H), 7.21 (dd, ^{4}J = 1.7, ^{4}J = 8.2 Hz, 2H), 7.23-7.28 (m, 2H), 7.32-7.47 (m, 5H), 7.56 (s, 1H), 7.76 (d, ^{3}J = 7.9 Hz, 2H), 7.80 (d, ^{3}J = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 34.0, 41.9, 59.8, 117.8, 125.3, 126.0, 126.4, 127.0, 127.3, 127.4, 127.6, 127.8, 127.9, 128.0, 132.1, 133.6, 138.3, 139.8, 158.4, 165.9.

Ethyl 5-(1H-indol-3-yl)-3-phenylpent-2-enoate, 13a. Synthesised according to Method C using compound **13b** (0.50 g, 2.0 mmol), NaH (0.250 g, 6.01mmol) and triethyl phosphonoacetate (1.2 mL, 6.01 mmol);

13*E*a: pale brown oil; yield: 0.175 g (27 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.29 (t, ^{3}J = 7.2 Hz, 3H), 2.87-2.91 (m, 2H), 3.49-3.52 (m, 2H), 4.19 (q, ^{3}J = 7.2 Hz, 2H), 6.09 (s, 1H), 7.00-7.01 (m, 1H), 7.10 (dt, ^{4}J = 1.3, ^{3}J = 8.2 Hz, 1H), 7.17 (dt, ^{4}J = 1.3, ^{3}J = 8.2 Hz, 1H), 7.33 (d, ^{3}J = 8.2 Hz, 2H), 7.37-7.41 (m, 3H), 7.48-7.50 (m, 2H), 7.63 (d, ^{3}J = 7.9 Hz, 1H), 7.91 (s, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 24.7, 31.9, 59.9, 110.9, 116.1, 117.7, 119.0, 119.1, 121.3, 121.8, 126.7, 127.4, 128.5, 128.9, 136.2, 141.2, 159.8, 166.4.

13*Z*a: pale brown oil; yield: 0.189 g (30 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (t, ^{3}J = 6.9 Hz, 3H), 2.82-2.90 (m, 4H), 3.99 (q, ^{3}J = 6.9 Hz, 2H), 5.94 (s, 1H), 6.96 (s, 1H), 7.10 (dt, ^{4}J = 0.9, ^{3}J = 7.9 Hz,

1H), 7.19-7.23 (m, 3H), 7.31-7.38 (m, 4H), 7.51 (d, ^3J = 7.9 Hz, 1H), 7.93 (s, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 23.3, 40.8, 59.8, 111.1, 115.1, 117.5, 118.6, 119.2, 121.2, 121.9, 127.2, 127.9, 128.0, 128.5, 136.2, 140.0, 159.1, 166.1.

Ethyl 4-(4-chlorophenoxy)-3-phenylbut-2-enoate, 14a. Synthesised according to Method C using compound **14b** (0.60 g, 2.43 mmol), NaH (0.29 g, 7.30 mmol) and triethyl phosphonoacetate (1.61 mL, 7.30 mmol);

14*Z*a: colourless oil; yield: 0.135 g (18 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.01 (t, ^3J = 6.9 Hz, 3H), 3.94 (q, ^3J = 6.9 Hz, 2H), 4.63 (d, ^3J = 1.9 Hz, 2H), 6.19 (t, ^{3}J = 1.9 Hz, 1H), 6.77-6.82 (m, 2H), 7.16-7.20 (m, 4H), 7.28-7.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 60.1, 71.1, 116.1, 117.4, 126.4, 127.5, 128.2, 128.4, 129.5, 136.6, 152.4, 156.5, 165.6.

14*E*a: colourless oil; yield: 0.40 g (52 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.32 (t, ^3J = 7.2 Hz, 3H), 4.25 (q, ^3J = 7.2 Hz, 2H), 5.56 (s, 1H), 6.25 (s, 1H), 6.81-6.83 (m, 2H), 7.17-7.21 (m, 2H), 7.35-7.38 (m, 3H), 7.46-7.48 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.2, 60.5, 64.4, 116.3, 120.5, 125.9, 127.2, 128.4, 129.2, 129.3, 138.2, 153.5, 157.0, 165.6.

(*Z*)-Ethyl 4-(4-chlorophenylthio)-3-phenylbut-2-enoate, 15*Z*a. Synthesised according to Method C using compound **15b** (0.50 g, 1.90 mmol), NaH (0.228 g, 5.71 mmol) and triethyl phosphonoacetate (1.26 mL, 5.71 mmol); pale yellow oil; yield: 0.401 g (63 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.23 (t, ^3J = 7.2 Hz, 3H), 3.77 (s, 2H), 4.14 (q, ^3J = 7.2 Hz, 2H), 6.69 (s, 1H), 7.27-7.31 (m, 3H), 7.32-7.36 (m, 4H), 7.38-7.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.1, 37.8, 61.0, 124.8, 125.8, 127.7, 128.6, 129.2, 130.5, 132.6, 134.3, 136.1, 140.1, 170.3.

(*E/Z*)-Ethyl 3-(5-chlorobenzofuran-2-yl)-3-phenylacrylate, 16*E/Z*a. Synthesised according to Method C using compound **16b** (0.60 g, 2.34 mmol), NaH (0.187 g, 4.68 mmol) and triethyl phosphonoacetate (1.08 mL, 4.91 mmol); pale yellow oil; yield: 0.702 g (92 %; 3:1, *E/Z*); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.12 (t, ^{3}J = 7.2 Hz, 1H, *Z*), 1.24 (t, ^{3}J = 7.2 Hz, 3H, *E*)), 4.06 (q, ^{3}J = 7.2 Hz, 0.6H, *Z*), 4.24 (q, ^{3}J = 7.2 Hz, 2H, *E*), 6.27 (s, 1H, *E*), 6.36 (s, 0.3H, *Z*), 6.78 (s, 0.3H, *Z*), 6.83 (s, 1H, *E*), 7.45-7.26 (m, 10H), 7.55 (d, ^{3}J = 2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 14.2, 60.2, 60.7, 109.5, 110.6, 112.3, 116.8, 121.0, 121.1, 125.5, 126.4, 128.0, 128.4, 128.5, 128.6, 129.6, 128.4, 141.5, 143.9, 153.4, 154.2, 165.6, 165.9.

(*E/Z*)-Ethyl 3-(5-methylbenzofuran-2-yl)-3-phenylacrylate, 17*E/Z*a. Synthesised according to Method C using compound **17b** (0.60 g, 2.54 mmol), NaH (0.204 g, 5.10 mmol) and triethyl phosphonoacetate (1.18 mL, 5.33 mmol); pale yellow oil; yield: 0.721 g (93 %; 2.5:1, *E/Z*); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.12 (t, ^{3}J = 7.0 Hz, 1.2H, *Z*), 1.25 (t, ^{3}J = 7.0 Hz, 3H, *E*)), 2.41 (s, 1.2H, *Z*), 2.44 (s, 3H, *E*), 4.06 (q, ^{3}J = 7.0 Hz, 0.8H, *Z*), 4.26 (q, ^{3}J = 7.0 Hz, 2H, *E*), 6.20 (s, 1H, *E*), 6.35 (s, 0.4H, *Z*), 6.77 (s, 0.4H, *Z*), 6.81 (s, 1H, *E*), 7.17-7.14 (m, 1.4H), 7.24 (s, 0.4H), 7.32-7.45 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 14.2, 21.2, 21.3, 60.0, 60.7, 110.0, 110.8, 111.3, 115.6, 120.0, 121.2, 126.7, 127.6, 127.9, 128.3, 128.4, 128.7, 128.8, 129.4, 132.4, 132.7, 136.2, 138.9, 141.8, 144.6, 152.9, 153.5, 153.9, 155.6, 165.8, 166.3.

Ethyl 3-(5-chlorobenzo[b]thiophen-2-yl)-3-phenylacrylate, 18a. Synthesised according to Method C using compound **18b** (0.17 g, 0.62 mmol), NaH (0.05 g, 1.24 mmol) and triethyl phosphonoacetate (0.29 mL, 1.24 mmol);

18*Z*a: pale yellow oil; yield: 0.086 g (41 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.17 (t, ^{3}J = 6.9 Hz, 3H), 4.14 (q, ^{3}J = 6.9 Hz, 2H), 6.39 (s, 1H), 7.27 (s, 1H), 7.27-7.32 (m, 2H), 7.34-7.41 (m, 5H), 7.71-7.74 (m,

2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.0, 60.5, 120.4, 123.2, 123.4, 125.2, 125.4, 128.2, 128.5, 128.7, 130.6, 138.8, 139.0, 140.4, 141.9, 147.9, 165.5.

18*E*a: pale yellow oil; yield: 0.077 g (36 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.11 (t, ^3J = 6.9 Hz, 3H), 4.04 (q, ^3J = 6.9 Hz, 2H), 6.46 (s, 1H), 6.90 (s, 1H), 7.29-7.31 (m, 3H), 7.35-7.46 (m, 3H), 7.59 (d, ^4J = 1.9 Hz, 1H) 7.69 (d, ^3J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 60.2, 118.0, 123.3, 123.8, 126.3, 126.9, 128.0, 128.4, 128.6, 135.0, 137.4, 138.0, 140.7, 146.5, 156.8, 165.3.

(*E*)-Ethyl 2-(2-(4-chlorobenzyl)-2,3-dihydro-1H-inden-1-ylidene)acetate, 21*E*a. Synthesised according to Method C using compound **21b** (0.30 g, 1.17 mmol), NaH (0.234 g, 3.51 mmol) and triethyl phosphonoacetate (0.70 mL, 3.51 mmol); pale yellow oil; yield: 0.126 g (33 %);^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.33 (t, ^3J = 7.2 Hz, 3H), 2.22 (t, ^3J = 11.0 Hz, 1H), 2.72 (d, ^3J = 17.0 Hz, 1H), 2.95 (m, 1H), 3.17 (dd, ^4J = 3.5, ^3J = 13.2 Hz, 1H), 4.09-4.17 (m, 1H), 4.25 (q, ^3J = 7.2 Hz, 2H), 6.32 (d, ^3J = 1.6 Hz, 1H), 7.24-7.30 (m, 6H), 7.35 (t, ^3J = 7.6 Hz, 1H) 7.59 (d, ^3J = 7.6 Hz, 1H).^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.4, 35.6, 40.7, 44.2, 59.9, 108.1, 122.0, 125.2, 126.0, 127.0, 128.2, 128.3, 130.6, 131.0, 131.9, 139.2, 139.2, 165.8.

2-(4-Chlorophenoxy)-1-phenylethanone, 14b. 4-Chlorophenol **14c** (0.774 g, 6.02 mmol) was refluxed with 2-bromoacetophenone (1.0 g, 5.02 mmol) in DMF (10 mL) with potassium carbonate (3.5 g, 25.1 mmol) for 2 hours. The reaction mixture was taken up in water (50 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel [PE / EtOAc (10:1)]; pale yellow solid; yield: 1.22 g (99 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.26 (s, 2H), 6.85-6.89 (m, 2H), 7.22-7.25 (m,

2H), 7.51 (t, ^{3}J = 7.4 Hz, 2H), 6.09-6.42 (m, 1H), 7.97-8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 71.0, 116.2, 126.6, 128.0, 128.9, 129.4, 133.9, 134.5, 156.7, 194.1.

2-(4-Chlorophenylthio)-1-phenylethanone, 15b. 2-Bromoacetophenone (1.0 g, 6.91 mmol), 4-chlorothiophenol **15c** (1.37 g, 6.91 mmol) and 5 % benzyltriethylammonium chloride (0.078 g, 0.35 mmol) were dissolved in 20 mL dichloromethane. Under vigorous stirring sodium hydroxide (0.61 g, 15.21 mmol) in 2 mL water was added and the stirring maintained for 16 hours. The mixture was diluted with water (50 mL), the dichloromethane organic layer (60 mL) separated and washed successively with brine (20 mL), dried over $MgSO_4$ and evaporated. The resultant oil was further purified by column chromatography on silica gel [PE / EtOAc (12:1)]; pale yellow solid; yield 0.74 g (41 %); Mp 82-84 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.26 (s, 2H), 7.24-7.28 (m, 2H), 7.31-7.34 (m, 2H), 7.46-7.50 (m, 2H), 7.58-7.62 (m, 1H), 7.92-7.97 (m, 2H).

Method E: Rap-Stoermer reaction

The corresponding salicylaldehyde (1 eq) and 2-bromoacetophenone (1 eq) were dissolved in ethanol and then treated with potassium carbonate (2.2 eq). The resultant mixture was heated at 80 °C for 1 hour, and the reaction mixture was taken up in water (50 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resultant oil was subjected to silica gel chromatography to give the appropriate product (**16-17b**).

Benzofuran-2-yl-(4-chlorophenyl)methanone, 16b. Synthesised according to Method E using compound **16c** (2.0 g, 12.77 mmol), 2-bromoacetophenone (1.85 g, 12.77 mmol) and K_2CO_3 (3.53 g,

25.54 mmol); white solid, yield: 1.85 g (57 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.44-7.48 (m, 2H), 7.53-7.58 (m, 13), 7.64-7.68 (m, 1H), 7.70 (d, ^{3}J = 2.2 Hz, 1H), 8.03-8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 113.7, 115.4, 122.6, 126.5, 128.2, 128.6, 128.7, 129.5, 129.6, 133.2, 136.9, 154.2, 184.1.

Benzofuran-2-yl-(p-tolyl)methanone, 17b. Synthesised according to Method E using compound **17c** (1.0 g, 7.35 mmol), 2-bromoacetophenone (1.06 g, 7.35 mmol) and K_2CO_3 (2.03 g, 14.69 mmol); pale yellow solid, yield: 1.1 g (64 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.47 (s, 3H), 7.31 (dd, ^{4}J = 1.9, ^{3}J =8.2 Hz, 1H), 7.46 (s, 1H), 7.49-7.55 (m, 4H), 7.61-7.66 (m, 1H), 8.03-8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.3, 112.1, 116.4, 122.7, 128.5, 129.4, 130.0, 132.8, 133.6, 137.3, 152.4, 154.6, 184.4.

1-Benzothiophen-2-yl-(4-chlorophenyl)methanone, 18b. To a cold solution (ice bath) containing 5-chloro-2-nitrobenzaldehyde (0.2 g, 1.31 mmol) and anhydrous potassium carbonate (0.221 g, 1.60 mmol) in DMF was added dropwise a solution of thioacetophenone (0.243 g, 1.31 mmol). The mixture was stirred from 0 °C to rt within 3 hours. The mixture was then poured into ice water, extracted with dichloromethane and dried over $MgSO_4$. The oily crude product was purified by column chromatography on silica gel [PE / EtOAc (10:1)]; pale yellow solid; yield 0.31 g (87 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.45 (dd, ^{4}J = 1.9, ^{3}J = 8.8 Hz, 1H), 7.53-7.56 (m, 2H), 7.63-7.67 (m, 1H), 7.79 (s, 1H), 7.83-7.86 (m, 2H), 7.91-7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 124.0, 124.9, 125.3, 126.7, 127.9, 128.6, 129.3, 130.9, 131.3, 132.7, 137.5, 144.9, 189.3.

Method F: Catalytic transfer hydrogenation

To a solution of the corresponding (*E*)-ethyl 3-(benzofuran-2-yl)-3-phenylacrylate (1eq) in ethanol (10 mL) was added Pd/C (10 %) and a solution of sodium hypophosphite (1.5 eq) in 7 mL of water. The mixture was stirred at 50 °C for 1.5 hours. After the completion of the reaction the catalyst was filtered off and the crude hydrolyzed (50 mL), extracted with dichloromethane (3 x 20 mL), dried over $MgSO_4$ and evaporated. The resultant oil was subjected to silica gel chromatography to give the appropriate product (**19-20a**).

Ethyl 3-(5-chlorobenzofuran-2-yl)-3-phenylpropanoate, 19a. Synthesised according to Method F using compound **16*E/Z*** (0.4 g, 1.22 mmol), sodium hypophosphite (0.194 g, 1.83 mmol) and Pd/C (0.13 g, 0.12 mmol); pale yellow oil; yield: 0.249 g (88 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.16 (t, ^3J = 7.2 Hz, 3H), 2.95-3.01 (m, 1H), 3.17-3.24 (m, 1H), 4.03-4.13 (m, 2H), 4.69 (t, ^3J = 7.9 Hz, 1H), 6.45 (s, 1H), 7.16-7.32 (m, 4H), 7.38-7.49 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.1, 41.8, 60.6, 102.8, 111.0, 120.6, 122.6, 123.9, 127.4, 127.8, 128.2, 128.7, 129.8, 140.4, 153.2, 159.3, 171.0.

Ethyl 3-(5-methylbenzofuran-2-yl)-3-phenylpropanoate, 20a. Synthesised according to Method F using compound **17*E/Z*** (0.2 g, 0.65 mmol), sodium hypophosphite (0.103 g, 0.98 mmol) and Pd/C (0.07 g, 0.065 mmol); white oil; yield: 0.182 g (91 %); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.15 (t, ^3J = 7.2 Hz, 3H), 2.40 (s, 3H), 2.95-3.00 (m, 1H), 3.17-3.22 (m, 1H), 4.02-4.12 (m, 2H), 4.67 (t, ^3J = 7.9 Hz, 1H), 6.37 (s, 1H), 7.02 (dd, ^4J = 1.6, ^3J = 9.1 Hz, 1H), 7.23-7.33 (m, 7H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.1, 21.2, 39.5, 41.8, 60.6, 102.6, 110.5, 120.5, 124.8, 127.2, 127.9, 128.5, 128.6, 132.0, 140.4, 153.2, 159.4, 171.1.

Method D: Hydrolysis

(*E*)-5-(3-Chlorophenyl)-3-phenylpent-2-enoic acid, 3*E*. Synthesised according to Method D using compound **3*E*a** (0.2 g, 0.63 mmol) and $NaOH_{aq}$ (2.1 mL, 6.3 mmol); white solid; yield: 0.158 g (88 %); Mp 98-100 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.72-2.77 (m, 2H), 3.40-3.43 (m, 2H), 6.13 (s, 1H), 7.09 (d, ^3J = 7.2 Hz, 1H), 7.19-7.15 (m, 3H), 7.41-7.45 (m, 3H), 7.46-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.0, 34.8, 117.0, 126.6, 126.7, 126.8, 128.6, 129.5, 129.6, 134.0, 140.7, 143.3, 162.0, 170.8; LC/MS (+ESI): *m/z* = 288.6 [MH^+]; R_t = 14.06 (≥ 97 %).

(*Z*)-5-(3-Chlorophenyl)-3-phenylpent-2-enoic acid, 3*Z*. Synthesised according to Method D using compound **3*Z*a** (0.17 g, 0.54 mmol) and $NaOH_{aq}$ (1.8 mL, 5.4 mmol); white solid; yield: 0.135 g (87 %); Mp 102-104 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.63-2.67 (m, 2H), 2.74-2.77 (m, 2H), 5.85 (s, 1H), 6.98 (td, ^4J = 1.6, ^3J = 7.2 Hz, 1H), 7.09-7.10 (m, 1H), 7.15-7.18 (m, 3H), 7.18-7.21 (m, 1H), 7.31-7.33 (m, 1H), 7.33-7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.3, 42.0, 117.0, 126.0, 126.4, 127.2, 128.1, 128.2, 128.4, 128.6, 129.7, 138.8, 142.6, 160.6, 170.1; LC/MS (+ESI): *m/z* = 288.6 [MH^+]; R_t = 13.43 (≥ 99 %).

(*E*)-5-(4-Fluorophenyl)-3-phenylpent-2-enoic acid, 4*E*. Synthesised according to Method D using compound **4*E*a** (0.185 g, 0.62 mmol) and $NaOH_{aq}$ (2.1 mL, 6.2 mmol); white solid; yield: 0.150 g (90 %); Mp 95-98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.72-2.75 (m, 2H), 3.38-3.42 (m, 2H), 6.12 (s, 1H), 6.92-6.96 (m, 2H), 7.13-7.16 (m 2H), 7.41-7.42 (m, 3H), 7.46-7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.4, 34.4, 115.0 (d, *J* (C, F) = 21.1 Hz, CH), 116.9, 126.8, 128.7, 129.4, 129.8 (d, *J* (C, F) = 8.6 Hz, CH), 136.9, 140.8, 149.5, 161.0 (d, *J* (C, F) = 240.9 Hz, C_{quat}), 170.9; LC/MS (+ESI): *m/z* = 271.5 [MH^+]; R_t = 13.24 (≥ 99 %).

(*Z*)-5-(4-Fluorophenyl)-3-phenylpent-2-enoic acid, 4*Z*. Synthesised according to Method D using compound **4*Z*a** (0.18 g, 0.60 mmol) and $NaOH_{aq}$ (2.0 mL, 5.4 mmol); white solid; yield: 0.135 g (83 %); Mp 90-92 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.63-2.67 (m, 2H), 2.73-2.77 (m, 2H), 5.87 (s, 1H), 6.93-7.07 (m, 2H), 7.16-7.23 (m, 2H), 7.34-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 34.3, 42.4, 116.0 (d, *J* (C, F) = 21.1 Hz, CH), 117.9, 127.2, 128.2, 128.6, 129.6, 132.0 (, *J* (C, F) = 7.7 Hz, CH), 141.5, 160.4, 161.5 (d, *J* (C, F) = 264.9 Hz, C_{quat}), 168.2; LC/MS (+ESI): *m/z* = 271.5 [MH^+]; R_t = 12.73 (≥ 98 %).

(*E*)-5-(4-Bromophenyl)-3-phenylpent-2-enoic acid, 5*E*. Synthesised according to Method D using compound **5*E*a** (0.20 g, 0.56 mmol) and $NaOH_{aq}$ (0.56 mL, 1.68 mmol); white solid; yield: 0.162 g (88 %); Mp 137-140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.70-2.73 (m, 2H), 3.38-3.40 (m, 2H), 6.12 (s, 1H), 7.07 (d, ^{3}J = 8.2 Hz, 2H), 7.37 (d, ^{3}J = 8.5 Hz, 2H), 7.41-7.45 (m, 3H), 7.45-7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.2, 34.5, 116.8, 126.8, 128.8, 129.5, 130.2, 131.4, 131.7, 140.2, 140.7, 162.1, 169.9; LC/MS (+ESI): *m/z* = 332.3 [MH^+]; R_t = 14.53 (≥ 99 %).

(*Z*)-5-(4-Bromophenyl)-3-phenylpent-2-enoic acid, 5*Z*. Synthesised according to Method D using compound **5*Z*a** (0.18 g, 0.50 mmol) and $NaOH_{aq}$ (0.5 mL, 1.5 mmol); white solid; yield: 0.148 g (90 %); Mp 120-122 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.62-2.65 (m, 2H), 2.73-2.76 (m, 2H, ^{3}J = 8.3 Hz, 2H), 5.85 (s, 1H), 6.98 (d, ^{3}J = 8.5 Hz, 2H), 7.11 (d, ^{3}J = 8.5 Hz, 2H), 7.29-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.1, 35.7, 116.9, 127.4, 128.5, 130.0, 130.5, 131.6, 133.1, 139.5, 141.4, 160.8, 169.9; LC/MS (+ESI): *m/z* = 332.3 [MH^+]; R_t = 13.93 (≥ 99 %).

(*E*)-3-Phenyl-5-(4-(trifluoromethyl)phenyl)pent-2-enoic acid, 6*E*. Synthesised according to Method D using compound **6*E*a** (0.19 g, 0.54 mmol) and $NaOH_{aq}$ (1.80 mL, 5.45 mmol); white solid; yield:

0.163 g (95 %); Mp 127-129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.80-2.83 (m, 2H), 3.41-3.45 (m, 2H), 6.13 (s, 1H), 7.30 (d, ^{3}J = 8.2 Hz, 2H), 7.41-7.48 (m, 5H), 7.51 (d, ^{3}J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 32.9, 34.9, 117.0, 125.2 (d, *J* (C, F) = 3.7 Hz, CH), 126.7, 128.3, 128.6, 128.8, 128.8, 129.1, 129.5, 140.6, 145.3 (d, *J* (C, F) = 1.9 Hz, CH), 162.0, 170.9; LC/MS (+ESI): *m/z* = 321.5 [MH^+]; R_t = 14.27 (≥ 99 %).

(*E*)-5-(3,4-Dichlorophenyl)-3-phenylpent-2-enoic acid, 7*E*. Synthesised according to Method D using compound **7*E*a** (0.10 g, 0.29 mmol) and $NaOH_{aq}$ (0.96 mL, 2.86 mmol); white solid; yield: 0.09 g (95 %); Mp 120-123 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.70-2.73 (m, 2H), 3.38-3.41 (m, 2H), 6.13 (s, 1H), 7.02 (dd, ^{4}J = 1.9, ^{3}J = 8.2 Hz, 1H), 7.27 (d, ^{4}J = 2.2 Hz, 1H), 7.31 (d, ^{3}J = 8.2 Hz, 1H), 7.41-7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 32.8, 34.2, 117.0, 126.7, 128.0, 128.8, 129.6, 130.0, 130.2, 130.4, 132.1, 140.5, 141.4, 170.4, 196.6; LC/MS (+ESI): *m/z* = 322.6 [MH^+]; R_t = 14.88 (≥ 99 %).

(*E*)-5-(2,4-Dichlorophenyl)-3-phenylpent-2-enoic acid, 8*E*. Synthesised according to Method D using compound **8*E*a** (0.10 g, 0.31 mmol) and $NaOH_{aq}$ (0.32 mL, 0.93 mmol); white solid; yield: 0.09 g (87 %); Mp 118-120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.85-2.89 (m, 2H), 3.40-3.72 (m, 2H), 6.16 (s, 1H), 7.14 (dd, ^{4}J = 2.2, ^{3}J = 8.2 Hz, 2H), 7.19 (d, ^{3}J = 8.2 Hz, 2H), 7.32 (d, ^{3}J = 1.9 Hz, 1H), 7.40-7.41 (m, 3H), 7.51-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 31.1, 32.4, 116.8, 125.9, 126.8, 127.1, 128.7, 129.1, 129.6, 131.5, 132.5, 137.1, 137.5, 140.0, 169.9; LC/MS (+ESI): *m/z* = 322.2 [MH^+]; R_t = 13.12 (≥ 93 %).

(*E*)-5-(4-Bromo-2-fluorophenyl)-3-phenylpent-2-enoic acid, 9*E*. Synthesised according to Method D using compound **9*E*a** (0.10 g, 0.26 mmol) and $NaOH_{aq}$ (0.27 mL, 0.79 mmol); white solid; yield: 0.075 g (82 %); Mp 110-113 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.76-2.79 (m, 2H), 3.37-3.41 (m, 2H), 6.14

(s, 1H), 7.08 (d, ^{3}J = 8.2 Hz, 1H), 7.14-7.19 (m, 2H), 7.40-7.41 (m, 3H), 7.48-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 28.1, 31.4, 117.0, 118.7, 118.9, 119.9, 126.7, 127.2 (d, *J* (C, F) = 2.8 Hz, CH), 127.3, 128.7, 129.5, 131.9 (d, *J* (C, F) = 6.4 Hz, CH), 160.9 (d, *J* (C, F) = 250.2 Hz, C_{quat}), 161.6, 170.9; LC/MS (+ESI): *m/z* = 350.3 [MH^+]; R_t = 12.90 (≥ 98 %).

(*Z*)-5-(4-Bromo-2-fluorophenyl)-3-phenylpent-2-enoic acid, 9*Z*. Synthesised according to Method D using compound **9*Z*a** (0.10 g, 0.26 mmol) and $NaOH_{aq}$ (0.27 mL, 0.79 mmol); white solid; yield: 0.078 g (85 %); Mp 82-84 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.65-2.68 (m, 2H), 2.74-2.78 (m, 2H), 5.86 (s, 1H), 7.18-7.22 (m, 3H), 7.27-7.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 27.0, 28.0, 35.6, 40.5, 116.9, 118.8 (d, *J* (C, F) = 5.5 Hz, CH), 119.2 (d, *J* (C, F) = 9.2 Hz, CH), 120.1, 126.0, 127.5 (d, *J* (C, F) = 3.7 Hz, CH), 128.5, 131.4 (d, *J* (C, F) = 5.5 Hz, CH), 141.4, 161.0 (d, *J* (C, F) = 258.4 Hz, C_{quat}), 169.8; LC/MS (+ESI): *m/z* = 350.3 [MH^+]; R_t = 14.00 (≥ 99 %).

(*E*)-5-(4-Ethylphenyl)-3-phenylpent-2-enoic acid, 10*E*. Synthesised according to Method D using compound **10*E*a** (0.10 g, 0.32 mmol) and $NaOH_{aq}$ (1.07 mL, 3.24 mmol); white solid; yield: 0.085 g (94 %); Mp 98-100 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.22 (t, ^{3}J = 7.6 Hz, 3H), 2.62 (q, ^{3}J = 7.6 Hz, 2H), 2.72-2.76 (m, 2H), 3.39-3.42 (m, 2H), 6.13 (s, 1H), 7.11 (d, ^{3}J = 8.2 Hz, 2H), 7.15 (d, ^{3}J = 8.2 Hz, 2H), 7.40-7.41 (m, 3H), 7.48-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.7, 28.5, 33.6, 34.9, 116.7, 126.8, 127.8, 128.3, 128.7, 129.3, 140.9, 141.9, 145.5, 162.6, 170.8; LC/MS (+ESI): *m/z* = 289.4 [MH^+]; R_t = 14.68 (≥ 97 %).

(*Z*)-5-(4-Ethylphenyl)-3-phenylpent-2-enoic acid, 10*Z*. Synthesised according to Method D using compound **10*Z*a** (0.10 g, 0.32 mmol) and $NaOH_{aq}$ (1.07 mL, 3.24 mmol); white solid; yield: 0.083 g (92 %); Mp 96-98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.15 (t, ^{3}J = 7.6 Hz, 3H), 2.54 (q, ^{3}J = 7.6 Hz, 2H),

2.64-2.68 (m, 2H), 3.34 (m, 2H), 6.05 (s, 1H), 7.03 (d, ^3J = 8.2 Hz, 2H), 7.07 (d, ^3J = 8.2 Hz, 2H), 7.33-7.35 (m, 3H), 7.41-7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.7, 28.5, 33.6, 34.8, 116.5, 126.8, 127.8, 128.2, 128.3, 128.7, 129.3, 140.9, 141.9, 162.2, 170.8; LC/MS (+ESI): *m/z* = 289.4 [MH^+]; R_t = 14.15 (≥ 97 %).

(*E*)-5-(Biphenyl-4-yl)-3-phenylpent-2-enoic acid, 11*E*. Synthesised according to Method D using compound **11*E*a** (0.16 g, 0.45 mmol) and $NaOH_{aq}$ (1.50 mL, 4.49 mmol); white solid; yield: 0.125 g (85 %); Mp 139-141 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.79-2.83 (m, 2H), 3.44-3.48 (m, 2H), 6.15 (s, 1H), 7.29-7.32 (m, 3H), 7.39-7.44 (m, 5H), 7.50-7.52 (m, 4H), 7.55-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.5, 34.9, 116.8, 126.6, 126.8, 127.0, 127.1, 128.7, 128.7, 128.9, 129.4, 139.0, 140.5, 140.8, 141.1, 162.3, 170.7; LC/MS (+ESI): *m/z* = 329.8 [MH^+]; R_t = 12.60 (≥ 97 %).

(*Z*)-5-(Biphenyl-4-yl)-3-phenylpent-2-enoic acid, 11*Z*. Synthesised according to Method D using compound **11*Z*a** (0.185 g, 0.52 mmol) and $NaOH_{aq}$ (1.75 mL, 5.19 mmol); white solid; yield: 0.145 g (85 %); Mp 185-188 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.72-2.75 (m, 2H), 2.78-2.83 (m, 2H), 5.91 (s, 1H), 7.20 (t, ^3J = 7.9 Hz, 4H), 7.30-7.39 (m, 4H), 7.42 (t, ^3J = 7.9 Hz, 2H), 7.50 (d, ^3J = 8.2 Hz, 2H), 7.56-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 33.4, 42.3, 116.6, 127.0, 127.1, 127.2, 127.2, 128.1, 128.1, 128.7, 128.8, 139.1, 139.7, 140.9, 141.5, 160.9, 173.7; LC/MS (+ESI): *m/z* = 329.8 [MH^+]; R_t = 14.70 (≥ 96 %).

(*E*)-5-(1H-Indol-3-yl)-3-phenylpent-2-enoic acid, 13*E*. Synthesised according to Method D using compound **13*E*a** (0.20 g, 0.63 mmol) and $NaOH_{aq}$ (0.65 mL, 1.89 mmol); white solid; yield: 0.135 g (73 %); Mp 157-160 °C; ^{1}H NMR (CD_3OD, 500 MHz): δ = 2.72-2.75 (m, 2H), 3.39-3.43 (m, 2H), 6.05 (s, 1H), 6.95 (dt, ^3J = 0.9, 8.2 Hz, 1H), 7.05 (dt, ^4J = 0.9, ^4J =7.9 Hz, 1H), 7.11-7.12 (d, ^3J = 2.2 Hz, 1H),

7.31 (d, ^3J = 8.2 Hz, 1H), 7.39-7.46 (m, 3H), 7.57-7.60 (m, 3H), 10.76 (s, NH), 12.29 (s, OH); ^{13}C NMR (CD_3OD, 125 MHz): δ = 34.3, 40.9, 120.8, 123.6, 127.5, 127.6, 128.0, 130.3, 131.6, 136.1, 136.6, 138.2, 138.5, 145.8, 150.1, 168.0, 176.8; LC/MS (+ESI): *m/z* = 292.5 [MH^+]; R_t = 12.37 (≥ 96 %).

(*Z*)-4-(4-Chlorophenoxy)-3-phenylbut-2-enoic acid, 14*Z*. Synthesised according to Method D using compound **14*Z*a** (0.15 g, 0.47 mmol) and $NaOH_{aq}$ (1.6 mL, 4.7 mmol); white solid; yield: 0.10 g (74 %); Mp 115-117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.48 (s, 2H), 6.21 (s, 1H), 6.71-6.74 (m, 2H), 7.10-7.13 (m, 2H), 7.28-7.33 (m, 3H), 7.38-7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 64.5, 116.3, 119.2, 126.1, 127.3, 128.5, 129.3, 129.7, 137.8, 156.7, 156.9, 170.4; LC/MS (+ESI): *m/z* = 289.4 [MH^+]; R_t = 13.26 (≥ 95 %).

(*E*)-4-(4-Chlorophenoxy)-3-phenylbut-2-enoic acid, 14*E*. Synthesised according to Method D using compound **14*E*a** (0.06 g, 0.18 mmol) and $NaOH_{aq}$ (0.61 mL, 1.8 mmol); white solid; yield: 0.05 g (86 %); Mp 110-112 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.43 (s, 2H), 6.61 (s, 1H), 7.00 (d, ^3J = 9.1 Hz, 2H), 7.25-7.27 (m, 1H), 7.28 (d, ^3J = 8.8 Hz, 2H), 7.33-7.36 (m, 2H), 7.53-7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 38.0, 115.8, 118.1, 127.4, 127.9, 128.3, 128.4, 129.6, 135.4, 141.2, 155.7, 177.4; LC/MS (+ESI): *m/z* = 289.4 [MH^+]; R_t = 13.01 (≥ 99 %).

(*Z*)-4-(4-Chlorophenylthio)-3-phenylbut-2-enoic acid, 15*Z*. Synthesised according to Method D using compound **15*Z*a** (0.20 g, 0.60 mmol) and $NaOH_{aq}$ (1.0 mL, 3 mmol); white solid; yield: 0.11 g (60 %); Mp 137-139 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.76 (s, 2H), 6.66 (s, 1H), 6.71-6.74 (m, 2H), 7.20-7.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 37.3, 125.6, 125.7, 127.9, 128.7, 129.3, 130.7, 133.1, 134.0, 134.8, 139.7, 176.2; LC/MS (+ESI): *m/z* = 305.6 [MH^+]; R_t = 13.84 (≥ 99 %).

(*E/Z*)-3-(5-Chlorobenzofuran-2-yl)-3-phenylacrylic acid, 16*E/Z*. Synthesised according to Method D using compound **16*E/Z*a** (0.20 g, 0.63 mmol) and $NaOH_{aq}$ (2.1 mL, 6.3 mmol); pale yellow solid; yield: 0.147 g (78 %; 3:1, *E/Z*); Mp 164-166 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.27 (s, 1H, *E*), 6.39 (s, 0.3H, *Z*), 6.78 (s, 0.3H, *Z*), 6.88 (s, 1H, *E*), 7.26-7.47 (m, 10H), 7.55 (d, ^4J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 110.4, 110.4, 111.6, 112.5, 115.5, 119.4, 121.1, 121.3, 125.8, 126.8, 128.0, 128.6, 128, 7, 128.8, 129.4, 129.6, 130.0, 138.3, 144.2, 153.5, 156.6, 170.3, 207.6, 210.0; LC/MS (+ESI): *m/z* = 299.4 [MH^+]; R_t (*E*) = 13.39, R_t (*Z*) = 14.33; (≥ 99 %).

(*E/Z*)-3-(5-Methylbenzofuran-2-yl)-3-phenylacrylic acid, 17*E/Z*. Synthesised according to Method D using compound **17*E,Z*a** (0.25 g, 0.63 mmol) and $NaOH_{aq}$ (2.73 mL, 8.2 mmol); pale yellow solid; yield: 0.189 g (83 %; 2.5:1, *E/Z*); Mp 200-204 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.41 (s, 1.3H, *Z*), 2.44 (s, 3H, *E*), 6.21 (s, 1H, *E*), 6.37 (s, 0.4H, *Z*), 6.76 (s, 0.4H, *Z*), 6.88 (s, 1H, *E*), 7.13-7.19 (m, 1.5H), 7.24 (s, 0.4H), 7.33-7.46 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.1, 21.3, 110.0, 110.9, 111.0, 111.2, 114.2, 118.4, 121.2, 121.3, 126.9, 127.1, 127.9, 128.5, 128.6, 128.9, 129.2, 129.8, 132.6, 133.6, 137.9, 138.8, 143.1, 143.8, 144.6, 145.4, 146.6, 152.2, 152.4, 154.3, 154.8, 169.7, 169.9; LC/MS (+ESI): *m/z* = 279.5 [MH^+]; R_t = 14.09 (≥ 98 %).

(*Z*)-3-(5-Chlorobenzo[b]thiophen-2-yl)-3-phenylacrylic acid, 18*Z*. Synthesised according to Method D using compound **18*Z*a** (0.075 g, 0.22 mmol) and $NaOH_{aq}$ (0.75 mL, 2.28 mmol); pale yellow solid; yield: 0.05 g (74 %); Mp 210-212 °C; ^{1}H NMR ($(CD_3)_2SO$, 500 MHz): δ = 6.48 (s, 1H), 7.38-7.41 (m, 2H), 7.41-7.43 (m, 4H), 7.43-7.46 (m, 1H), 7.97 (d, ^4J = 2.2 Hz, 1H), 8.00 (d, ^3J = 8.5 Hz, 1H); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz): δ = 122.3, 123.1, 123.8, 124.6, 124.8, 125.8, 127.7, 128.5, 129.4, 129.5, 138.4, 139.4, 140.4, 141.9, 166.3; LC/MS (+ESI): *m/z* = 315.4 [MH^+]; R_t = 14.14 (≥ 99 %).

(*E*)-3-(5-Chlorobenzo[b]thiophen-2-yl)-3-phenylacrylic acid, 18*E*. Synthesised according to Method D using compound **18*E*a** (0.085 g, 0.26 mmol) and $NaOH_{aq}$ (0.9 mL, 2.61 mmol); pale yellow solid; yield: 0.06 g (74 %); Mp 208-210 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.26 (s, 1H), 7.16-7.29 (m, 7H), 7.58-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 120.9, 123.3, 123.5, 125.3, 125.5, 128.4, 128.6, 129.9, 130.7, 139.3, 140.9, 140.5, 142.1, 148.0, 167.8; LC/MS (+ESI): *m/z* = 315.4 [MH^+]; R_t = 14.70 (≥ 99 %).

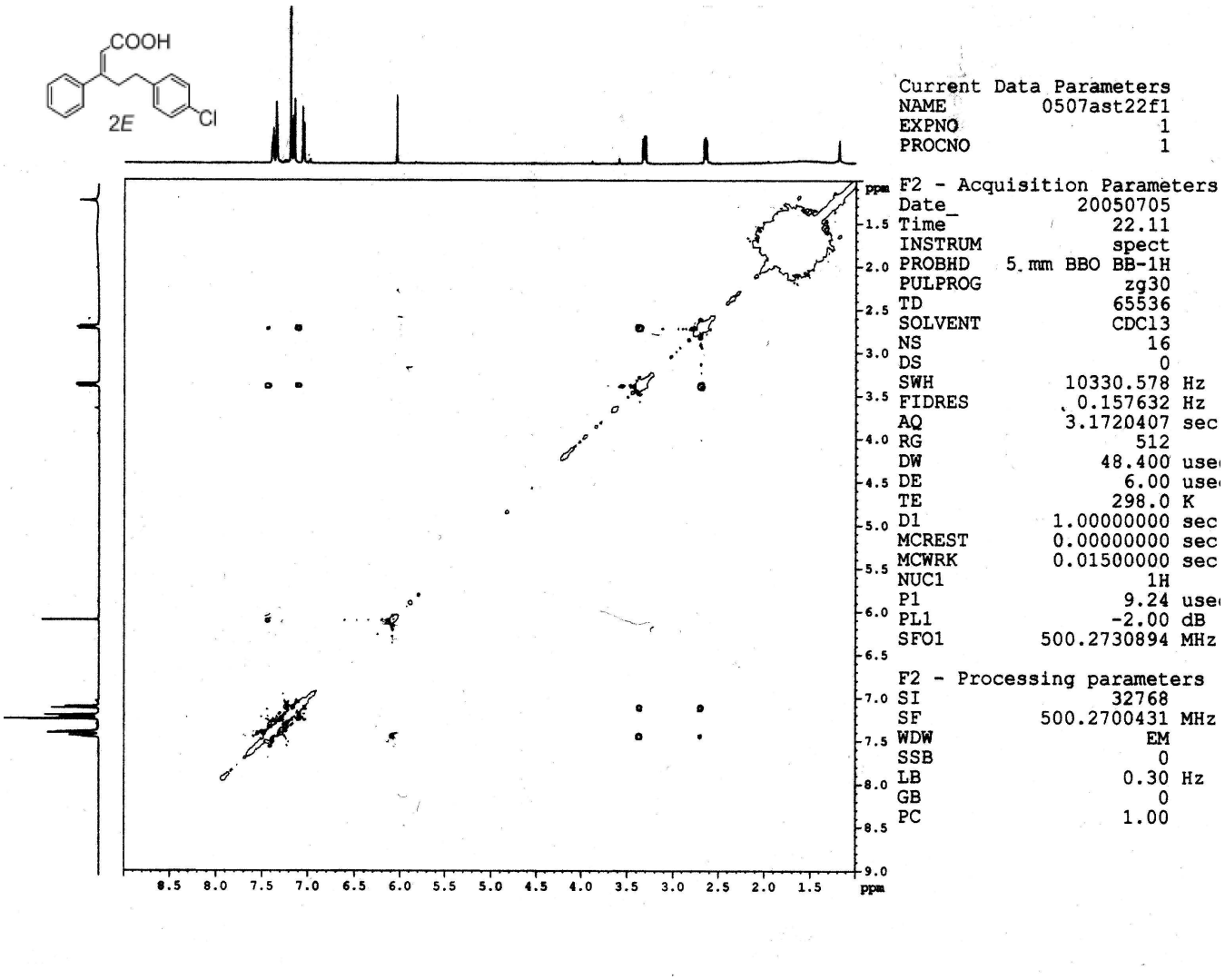
3-(5-Chlorobenzofuran-2-yl)-3-phenylpropanoic acid, 19. Synthesised according to Method D using compound **19a** (0.2 g, 0.61 mmol) and $NaOH_{aq}$ (2.0 mL, 6.01 mmol); white solid; yield: 0.14 g (76 %); Mp 135-138 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.03-3.06 (m, 1H), 3.25-3.29 (m, 1H), 4.67 (t, ^{3}J = 7.6 Hz, 1H), 6.45 (s, 1H), 7.15-7.30 (m, 4H), 7.39-7.47 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 38.9, 41.4, 102.9, 112.0, 117.8, 120.6, 122.7, 123.8, 127.4, 127.7, 127.8, 128.4, 128.9, 154.8, 160.5; LC/MS (+ESI): *m/z* = 301.6 [MH^+]; R_t = 13.45 (≥ 99 %).

3-(5-Methylbenzofuran-2-yl)-3-phenylpropanoic acid, 20. Synthesised according to Method D using compound **20a** (0.15 g, 0.48 mmol) and $NaOH_{aq}$ (1.6 mL, 4.86 mmol); white solid; yield: 0.101 g (75 %); Mp 124-127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.40 (s, 3H), 2.99-3.04 (m, 1H), 3.23-3.28 (m, 1H), 4.64 (t, ^{3}J = 8.2 Hz, 1H), 6.37 (s, 1H), 7.01 (dd, ^{4}J = 1.6, ^{3}J =8.8 Hz, 1H), 7.23-7.33 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.3, 38.8, 41.5, 102.7, 110.6, 120.1, 120.5, 124.9, 125.7, 127.3, 127.8, 128.5, 128.8, 132.1, 153.3, 158.9, 175.6; LC/MS (+ESI): *m/z* = 281.5 [MH^+]; R_t = 13.03 (≥ 99 %).

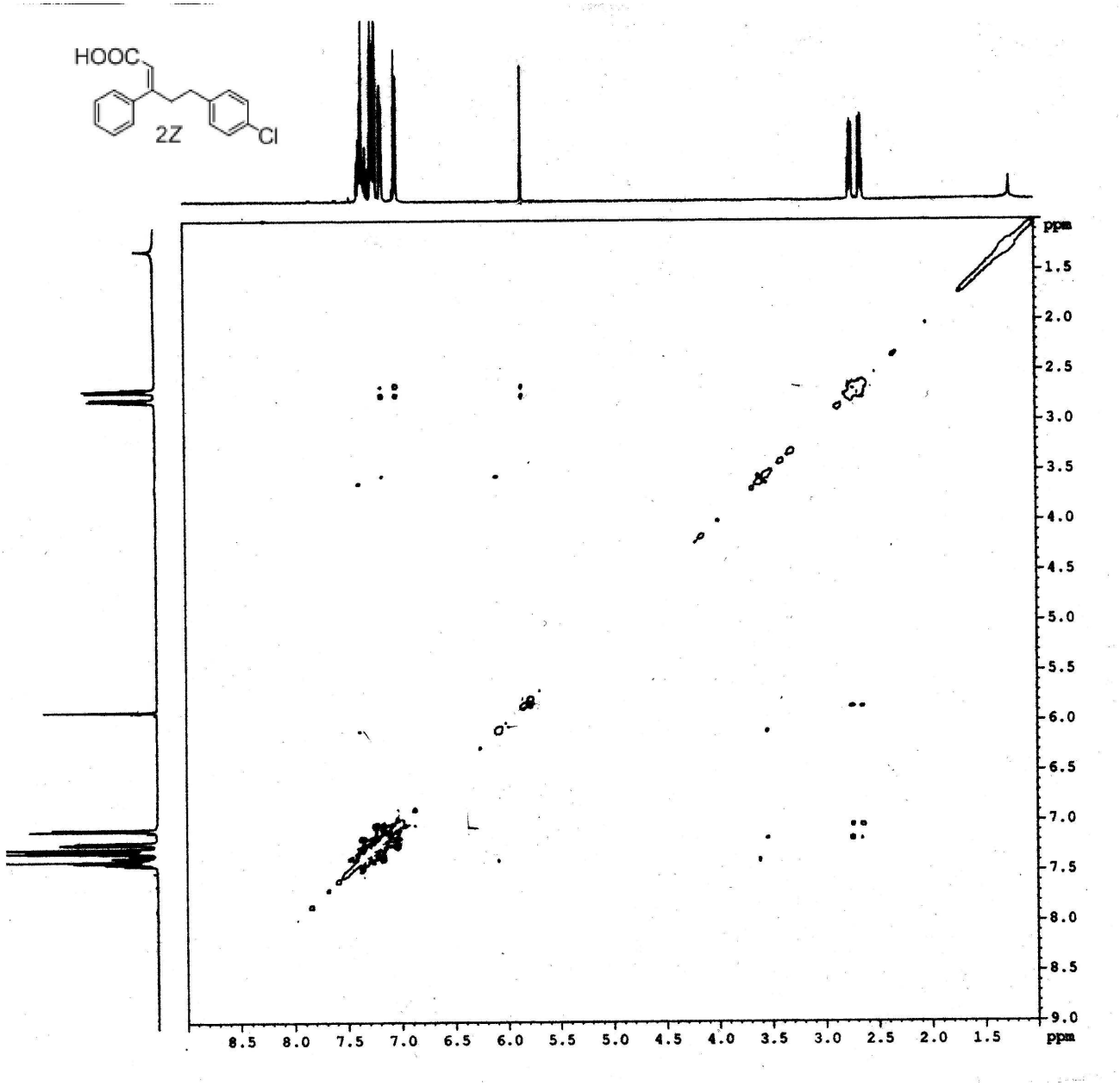
(*E*)-2-(2-(4-Chlorobenzyl)-2,3-dihydro-1H-inden-1-ylidene)acetic acid, 21. Synthesised according to Method D using compound **21*E*a** (0.10 g, 0.30 mmol) and $NaOH_{aq}$ (1.0 mL, 3.06 mmol); white solid; yield: 0.07 g (79 %); Mp 216-219 °C; ^{1}H NMR ($(CD_3)_2SO$, 500 MHz): δ = 2.23 (dd, ^{3}J = 11.0 Hz, 1H),

2.68 (d, ^{3}J = 17.0 Hz, 1H), 2.94 (dd, ^{3}J = 7.2 Hz, 1H), 3.08 (dd, ^{4}J = 2.8, ^{3}J = 12.9 Hz, 1H), 3.98-4.04 (m, 1H), 6.39 (s, 1H), 7.26-7.32 (m, 1H), 7.34-7.41 (m, 6H), 7.77 (d, ^{3}J = 7.9 Hz, 1H); ^{13}C NMR ($(CD_3)_2SO$, 125 MHz): δ = 34.9, 40.1, 43.4, 109.2, 122.0, 125.9, 126.9, 128.1, 130.6, 130.9, 138.7, 139.4, 146.7, 164.8, 167.4; Mp 115-118 °C; LC/MS (+ESI): *m/z* = 299.5 [MH^+]; R_t = 14.6 (≥ 96 %).

2) 2D-NOESY spectra for compounds **2E** and **2Z**.



Supplementary Figure 1A. 2D-NOESY spectrum of compound **2*E***.



Supplementary Figure 1B. 2D-NOESY spectrum of compound **2*Z***.