Supporting information

Scalable Anti-Markovnikov Hydrobromination of Aliphatic and Aromatic Olefins

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Contents

1. General Methods and Procedures

Unless otherwise stated, all reactions were carried out under an atmosphere of air using bench solvents. Prior to addition of bromine to toluene and HBr-AcOH to a solution of the substrate in hexane, the solutions were oxygenated using an air pump for 1 hour. All reactions using bromine were performed with a saturated solution of Na_2SO_3 (or $Na_2S_2O_5$) to hand in case of spillage. All syringes, gloves etc that came into contact with bromine were quenched with this before disposal. For preparation of HBr and bromination reactions, oven dried glassware was cooled in an ice bath prior to use. Pressurised air was supplied by an aquarium air pump (Superfish Air-Flow 2 600 g) and dried by passing through $CaCl_2$. All substrates were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Apollo or Fluorochem and were passed through a short plug of silica before use. For larger scale reactions estragole was distilled prior to use. Tetralin, bromine and HBr in acetic acid 33% wt were purchased from Sigma Aldrich and used directly. AIBN was purchased from Molekula and used without further purification. NMR spectra were recorded on a Bruker AVII400 FT-NMR Spectrometer and a Bruker AVIIIHD500 FT-NMR Spectrometer, at a constant temperature of 300 K. Chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, quint. = quintet, q = quartet, t = triplet, d = doublet, s = singlet, br = broad, ap = apparent. High resolution mass spectrometry was carried out by the Mass Spectrometry services at the University of Edinburgh, using a Thermo Mat 900 XP double focusing high resolution Mass spectrometer.

1.1 Preparation of a Saturated Solution of HBr in Toluene

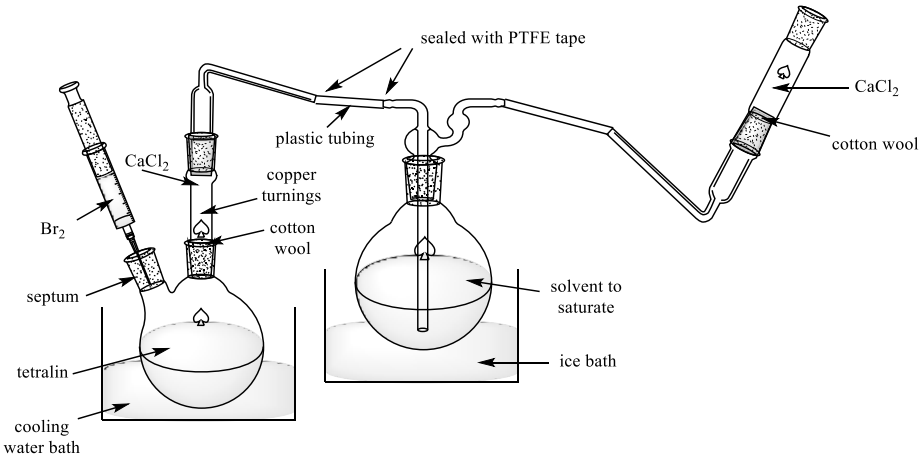


Fig.1 Representation of the apparatus used to saturate toluene with HBr.

1.2 Example Large Scale Procedure

Bromine (50 mL) was added *via* syringe in 5 mL portions to a 2-neck 250 mL RB flask containing tetralin (210 mL) in a rt water bath. Each 5 mL portion was added after the colour of the solution dissipated. The HBr gas formed was passed through a copper turning scrubber (to remove Br_2 gas) and

through $CaCl_2$ (to remove any moisture in the air) and then through plastic tubing (joins sealed gas tight with PTFE tape) into a 1 L flask in an ice bath fitted with a drechsel head containing toluene (500 mL). The excess gas that bubbled through the solvent was passed through plastic tubing to a drying tube containing $CaCl_2$ and into the rear of the fumehood. For storage the solution of HBr in toluene was transferred to a pre-chilled bottle which was tightly sealed and stored in the freezer for later use.

For immediate use in a reaction, the drechsel head was removed, AIBN (5 g) was added, the vessel was sealed with an unpierced septum and the suspension stirred at 0 °C for 5 min. Estragole (**1a**) (35 mL, 0.2234 mol) was then added and the reaction stirred for 2 h at 0 °C. The septum was removed and replaced with a gas adaptor attached to an aspirator pump. After 10 min of aspiration the solvent was removed on a rotary evaporator to give 49.14 g of the pure bromide **3a** (0.214 mol, 96% yield, 97 : 3 linear to branched).

1.3 Example Small Scale Procedure

Bromine (10 mL) was added *via* syringe to a 2-neck 250 mL RB flask containing tetralin (34 mL) in 1 mL portions in a rt water bath. Each 1 mL portion was added after the colour of the solution dissipated. The HBr gas formed was passed through a copper turning scrubber (to remove Br_2 gas) and through $CaCl_2$ (to remove any moisture in the air) and then through plastic tubing (joins sealed gas tight with PTFE tape) into a 1 L flask fitted with a Drechsel head containing toluene (80 mL) in an ice bath. The excess gas that bubbled through the solvent was passed through plastic tubing to a drying tube containing $CaCl_2$ and into the rear of the fumehood. The amount of solution required for brominations was removed by a chilled Pasteur pipette and measured using a chilled measuring cylinder. For storage the solution of HBr in toluene was transferred to a pre-chilled bottle which was tightly sealed and stored in the freezer for later use.

1.4 Hydrobromination reactions

In all cases the ratio **3** : **5** was determined using ^{1}H NMR of the crude product mixture by integration of peaks corresponding to the two products. Where a mixture is produced the signals used for assignment of the product ratios are indicated in the graphical NMR data.

General Procedure 1: HBr in PhMe with AIBN

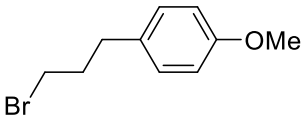
Cold (0 °C) HBr in PhMe (2.2 mL, measured using a chilled measuring cylinder, produced as above) was added *via* pipette to a vessel containing AIBN (22 mg, 0.13 mmol) that was cooled in an ice bath. The vessel was sealed with an unpierced septum and stirred at rt for 5 mins before the substrate (1 mmol) was added *via* syringe (removing the septum), the vessel resealed and stirred at 0 °C for a further 2 h. The reaction mixture was degassed using an aspirator pump, poured onto a pad of silica (1 g) and eluted with petroleum ether (10 mL). The filtrate was concentrated *in vacuo* and the residue analysed by ^{1}H NMR. No further purification was required.

General Procedure 2: HBr-AcOH in hexane

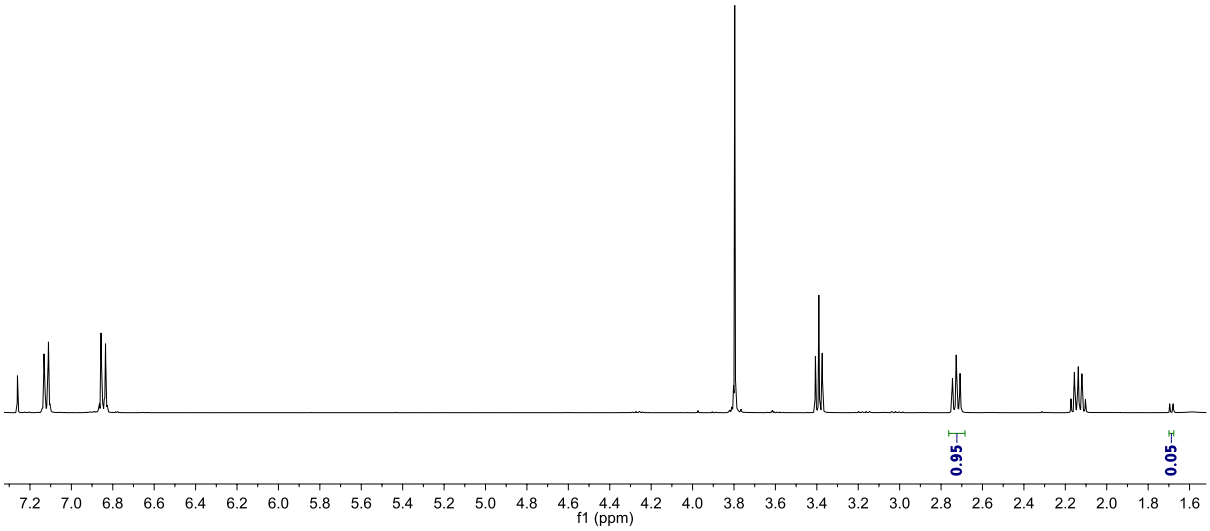
A solution of the substrate (1 mmol, 1 eq.) in hexane (4.5 mL) was stirred at 0 °C and air bubbled through the mixture for 1 h. A 33% w/v solution of HBr in acetic acid (0.37 mL, 2 mmol, 2 eq.) was added *via* syringe, the vessel sealed with an unpierced septum and the reaction mixture stirred at 0 °C for 2 h. The stirring was stopped and after separation of the acetic acid phase, the hexanes were decanted and concentrated *in vacuo* and the residue analysed by ^{1}H NMR. No further purification was required.

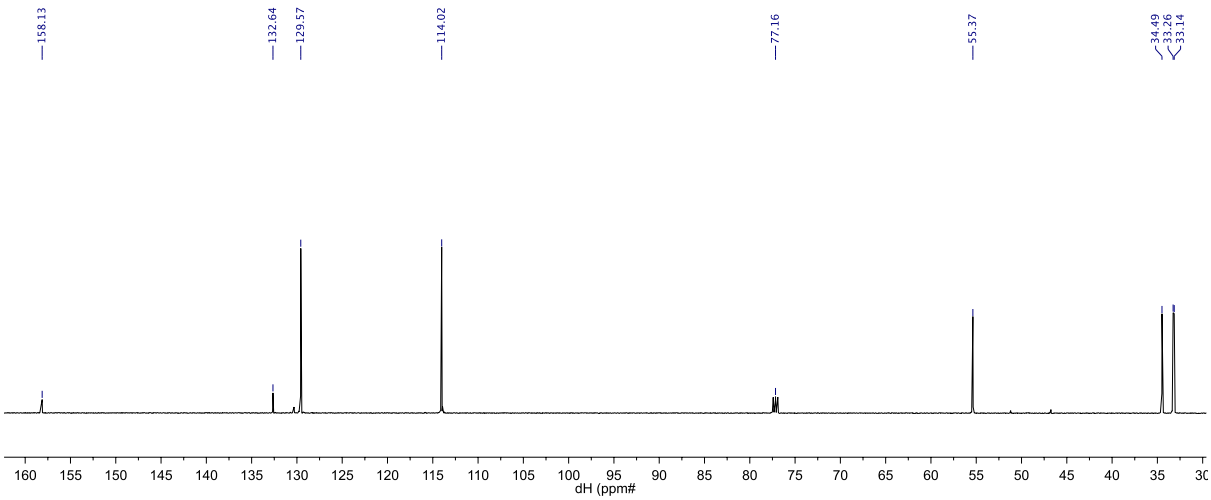
2. Characterisation of products 3

1-(3-Bromopropyl)-4-methoxybenzene 3a



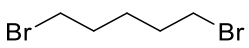
According to **GP2** the title compound was prepared as a pale brown oil in 96% yield and 97:3 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.15 (app. quint, *J*=6.8, 2 H, CH_2), 2.73 (t, *J*=7.2, 2 H, CH_2), 3.40 (t, *J*=6.4, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 6.79 - 6.92 (app. d, *J*=8.8, 2 H, ArCH), 7.13 (app. d, *J*=8.4, 2 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 33.1, 33.3, 34.5, 55.4, 114.1, 129.6, 132.6, 158.1. Data were in accordance with the literature.[1]



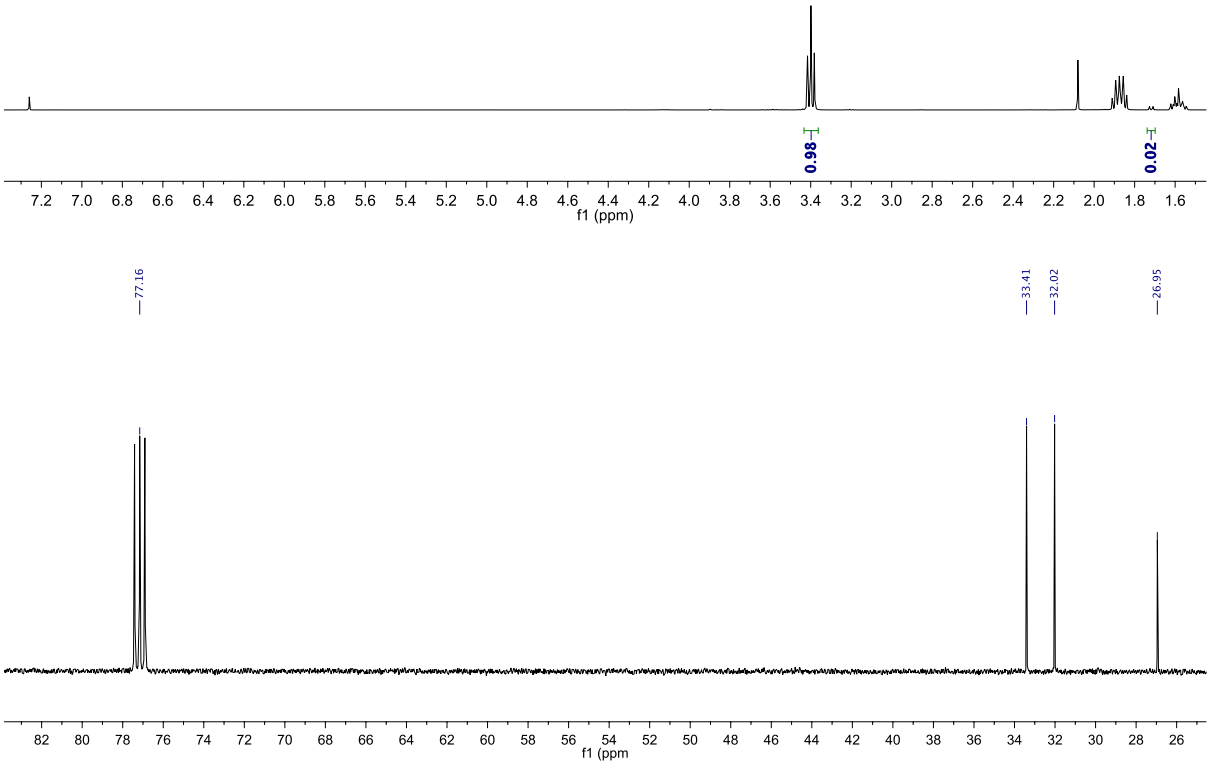


[1] D. F. Taber, C. M. Paquette, P. Gu, W. Tian, *J. Org. Chem*., 2013 , **78**, 9772–9780.

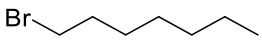
1,5-Dibromopentane 3b



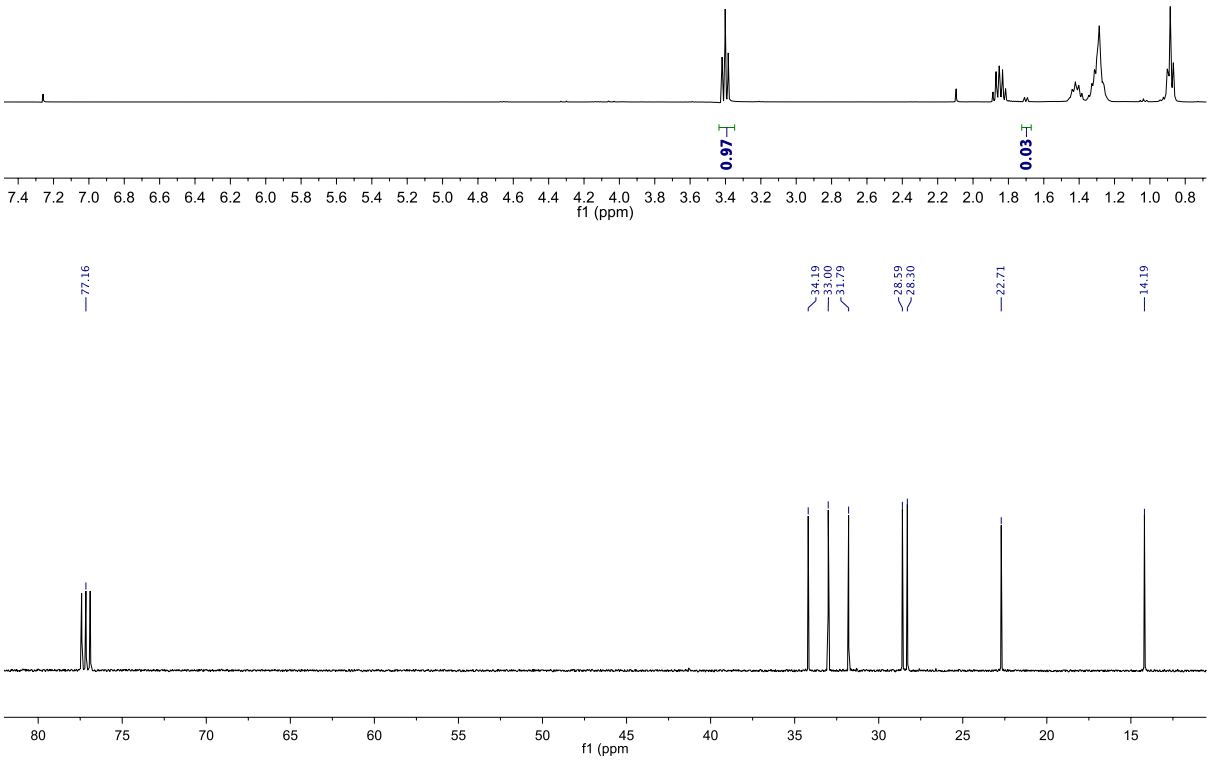
According to **GP2** the title compound was prepared as a pale brown oil in 92% yield and 99:1 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.55 - 1.68 (m, 2 H, CH_2), 1.87 - 1.96 (app. quint, J = 7.6, 4 H, 2×CH_2), 3.44 (t, J = 6.4, 4 H, 2×CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 27.0, 32.0, 33.4. Data was in accordance with a commercial sample.



1-Bromoheptane 3c

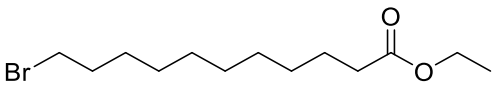


According to **GP2** the title compound was prepared as a pale brown oil in 95% yield and >99:<1 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.80 - 0.95 (m, 3 H, CH_3), 1.22 – 1.365 (m, 6 H, 3 × CH_2), 1.366 - 1.47 (m, 2 H, CH_2), 1.87 (app. quint, J = 7.6, 2 H, CH_2), 3.41 (t, J = 7.2, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 14.2, 22.7, 28.3, 28.6, 31.8, 33.0, 34.2. Data were in accordance with the literature.[2]

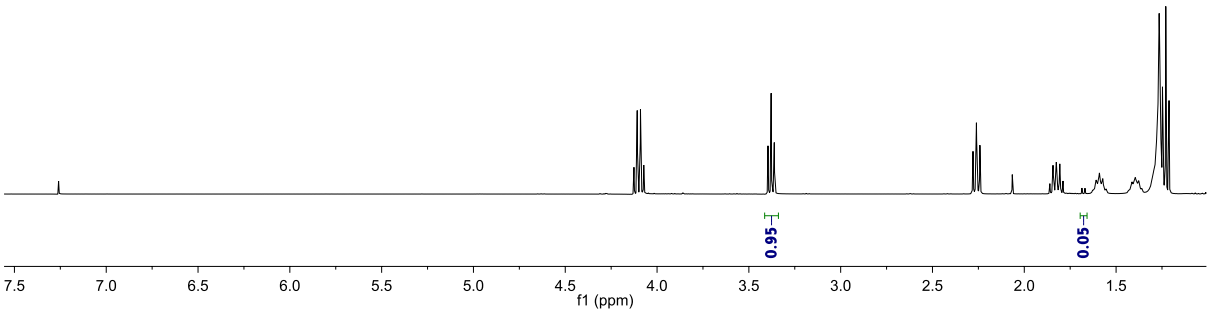


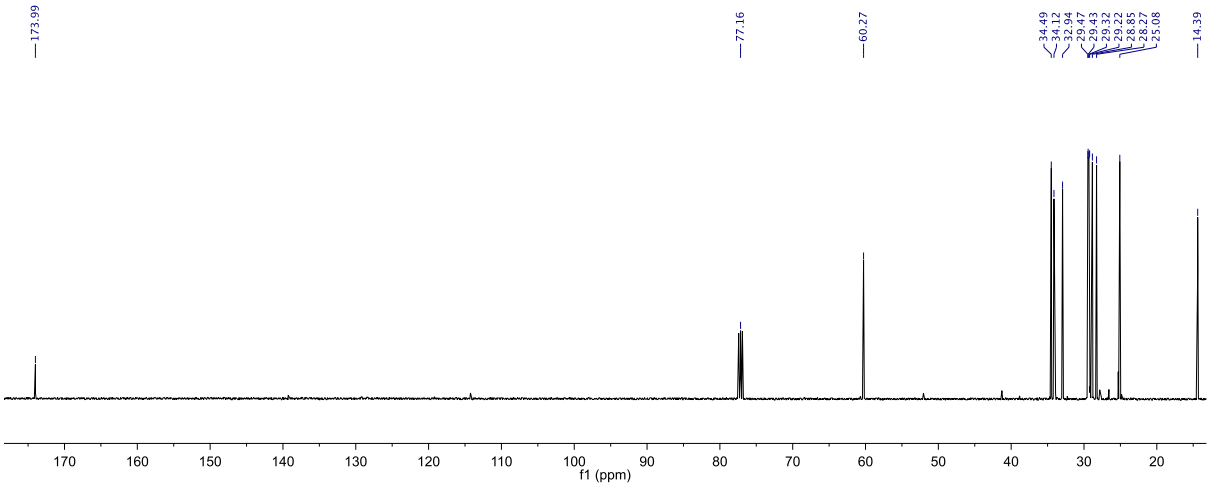
[2] T. V. Nguyen and A. Bekensir, *Org. Lett.* 2014, **16**, 1720−1723.

Ethyl 11-bromoundecanoate 3d



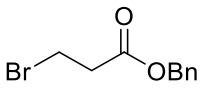
According to **GP2** the title compound was prepared as a pale brown oil in 75% yield and 98:2 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 - 1.33 (m, 13 H, CH_3, 5 × CH_2), 1.33 - 1.49 (m, 2 H, CH_2), 1.54 - 1.66 (m, 2 H, CH_2), 1.83 (app. quint., J = 7.6, 2 H, CH_2), 2.26 (t, J = 7.6, 2 H, CH_2), 3.38 (t, J = 6.8, 2 H, CH_2), 4.10 (q, J = 6.8, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 14.4, 25.1, 28.3, 28.9, 29.2, 29.3, 29.4, 29.5, 33.0, 34.1, 34.5, 60.3, 174.0. Data were in accordance with the literature.[3]



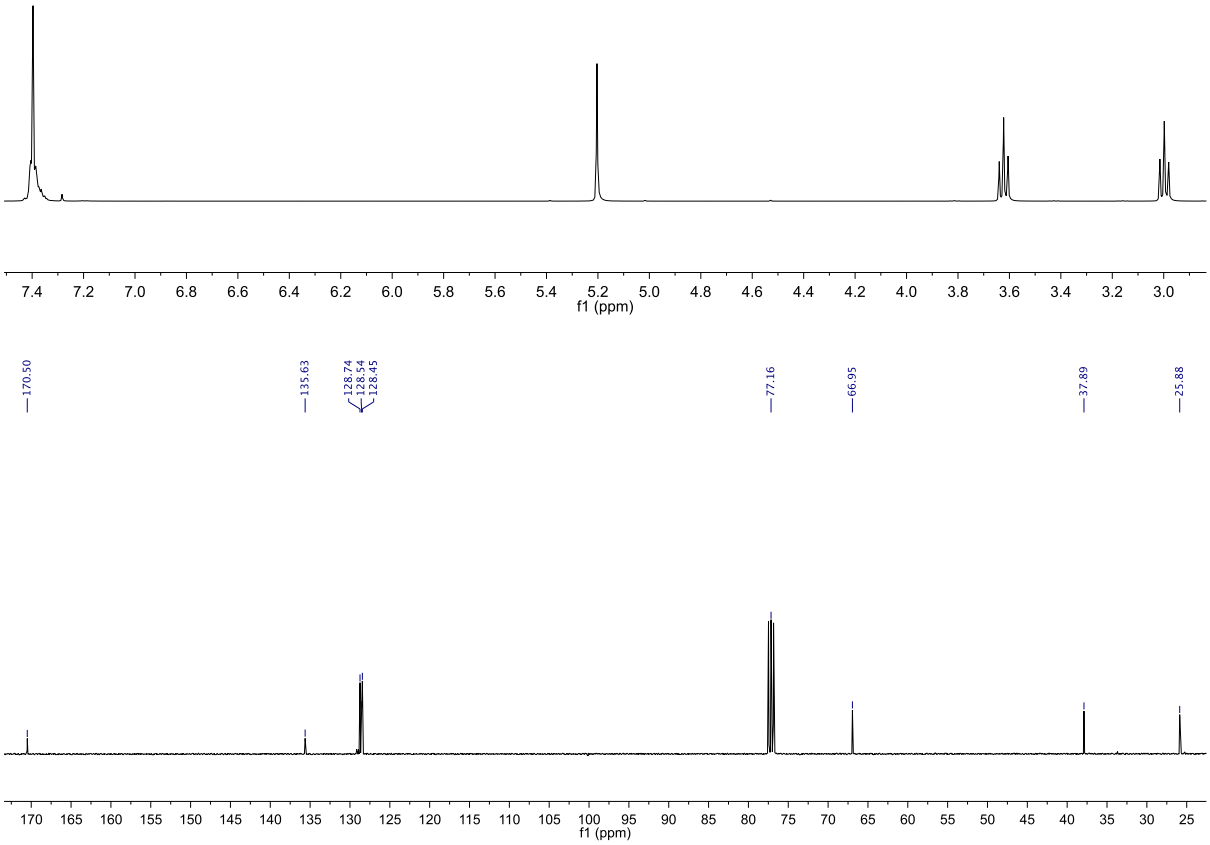


[3] N. M. T. Lourenço, C. M. Monteiro and C. A. M. Afonso, *Eur. J. Org. Chem*. 2010, **36**, 6938–6943.

Benzyl 3-bromopropanoate 3e

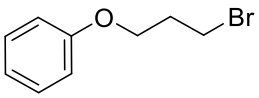


According to **GP2** the title compound was prepared as a pale brown oil in 86% yield and >99:<1 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.97 (t, J = 6.8, 2 H, CH_2), 3.60 (t, J = 6.8, 2 H, CH_2), 5.18 (s, 2 H), 7.34 - 7.42 (m, 5 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 25.9, 37.9, 67.0, 128.4, 128.5, 128.7, 135.6, 170.5. Data were in accordance with the literature.[4]

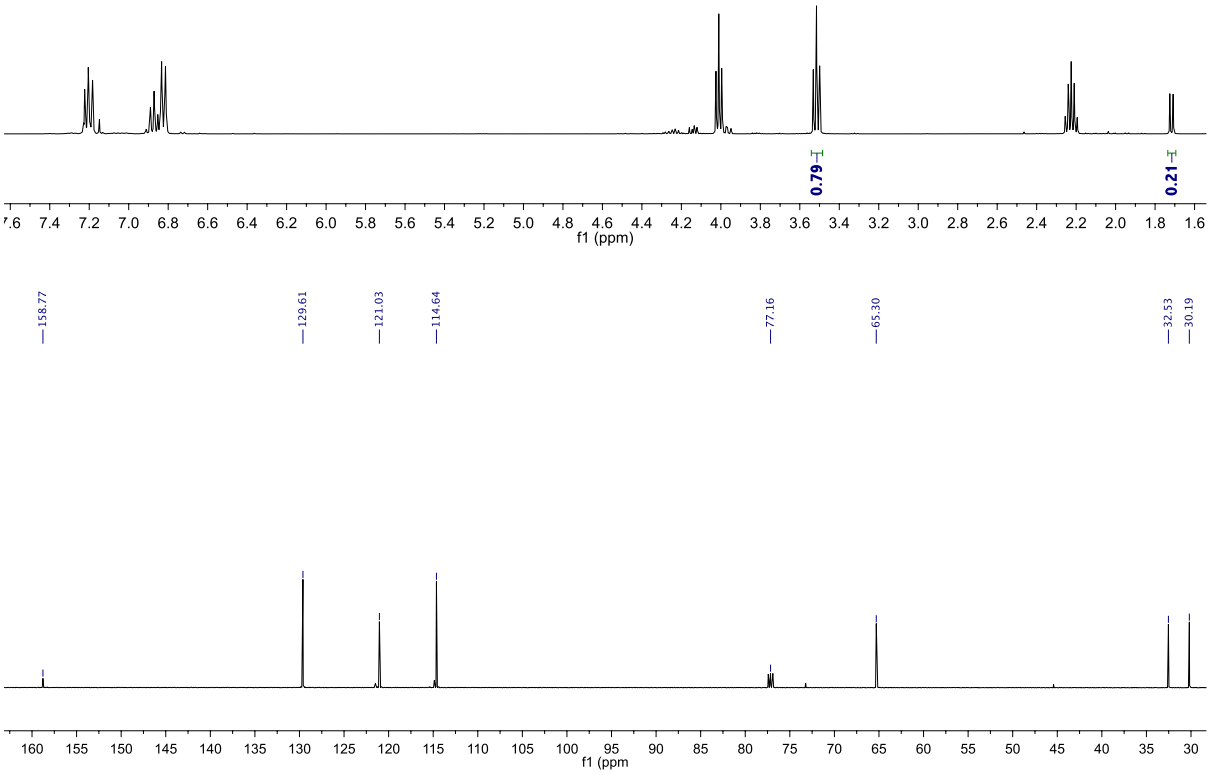


[4] R. C. Strauch, D. J. Mastarone, P. A. Sukerkar, Y. Song, J. J. Ipsaro, and T. J. Meade, *J. Am. Chem. Soc.*, 2011, **133**, 16346–16349.

(3-Bromopropoxy)benzene 3f

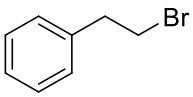


According to **GP2** the title compound was prepared as a pale brown oil in 74% yield and 85:15 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.34 (app. quint., J = 6.0, 2 H, CH_2), 3.62 (t, J = 6.4, 2 H, CH_2), 4.12 (t, J = 5.7, 2 H, CH_2), 6.88 - 7.03 (m, 3 H, ArCH), 7.33 (app. t, J = 8.0, 2 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 30.2, 32.5, 65.3, 114.6, 121.0, 129.6, 158.8. Data were in accordance with the literature.[5]

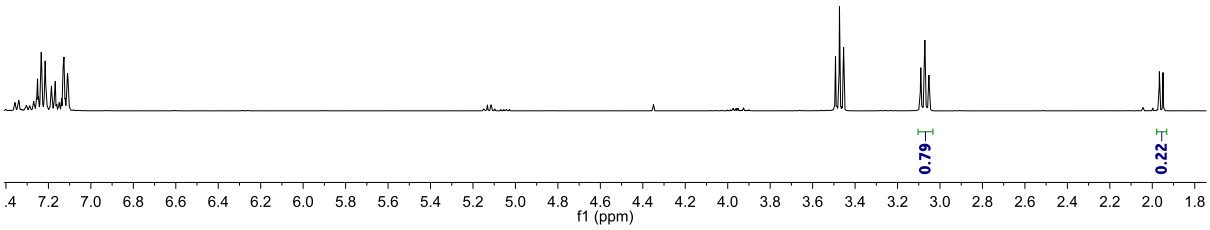


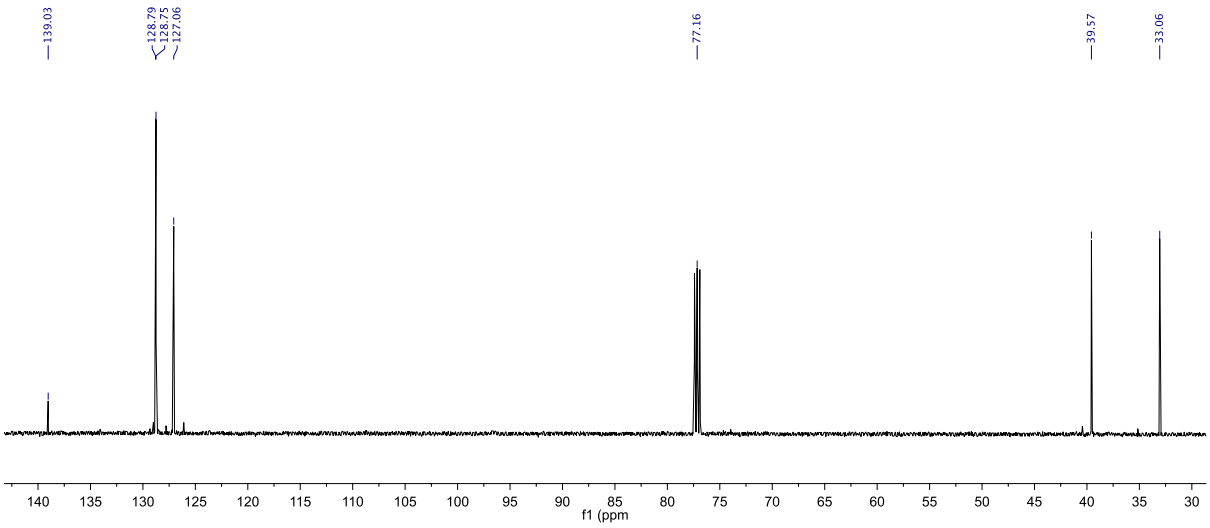
[5] K. J. Frankowski, J. E. Golden, Y. Zeng, Y. Lei and J. Aubé, *J. Am. Chem. Soc*., 2008, **130**, 6018–6024.

(2-Bromoethyl)benzene 3g

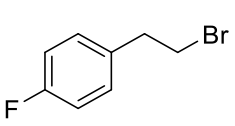


According to **GP2** the title compound was prepared as a colourless oil in 95% yield and 87:13 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.10 (t, J = 7.6, 2 H, CH_2), 3.51 (t, J = 7.6, 2 H, CH_2), 7.23 - 7.43 (m, 5 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 33.1, 39.6, 127.1, 128.8, 128.8, 139.0. Data were in accordance with the literature.[2]

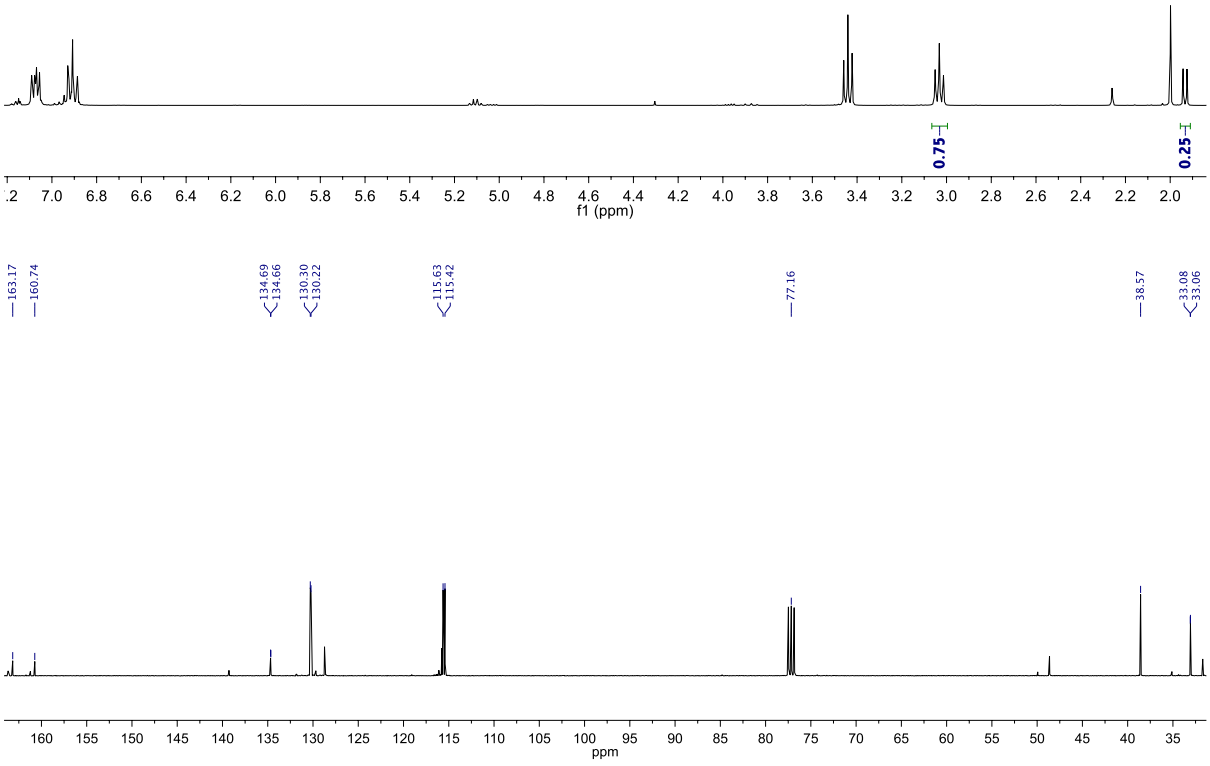




1-(2-Bromoethyl)-4-fluorobenzene 3h

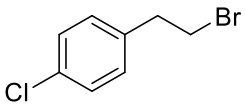


According to **GP2** the title compound was prepared as a colourless oil in 98% yield and 82:18 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.14 (t, *J* = 7.2, 2 H), 3.55 (t, *J* = 7.6, 2 H), 6.95 - 7.07 (m, 2 H), 7.11-7.21 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 33.1 (d, *J* = 1.5), 38.6, 115.5 (d, *J* = 21.3), 130.3 (d, *J* = 7.7), 134.7 (d, *J* = 3.2), 162.0 (d, *J* = 245.1). ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm – 116.0. Data were in accordance with the literature.[6]

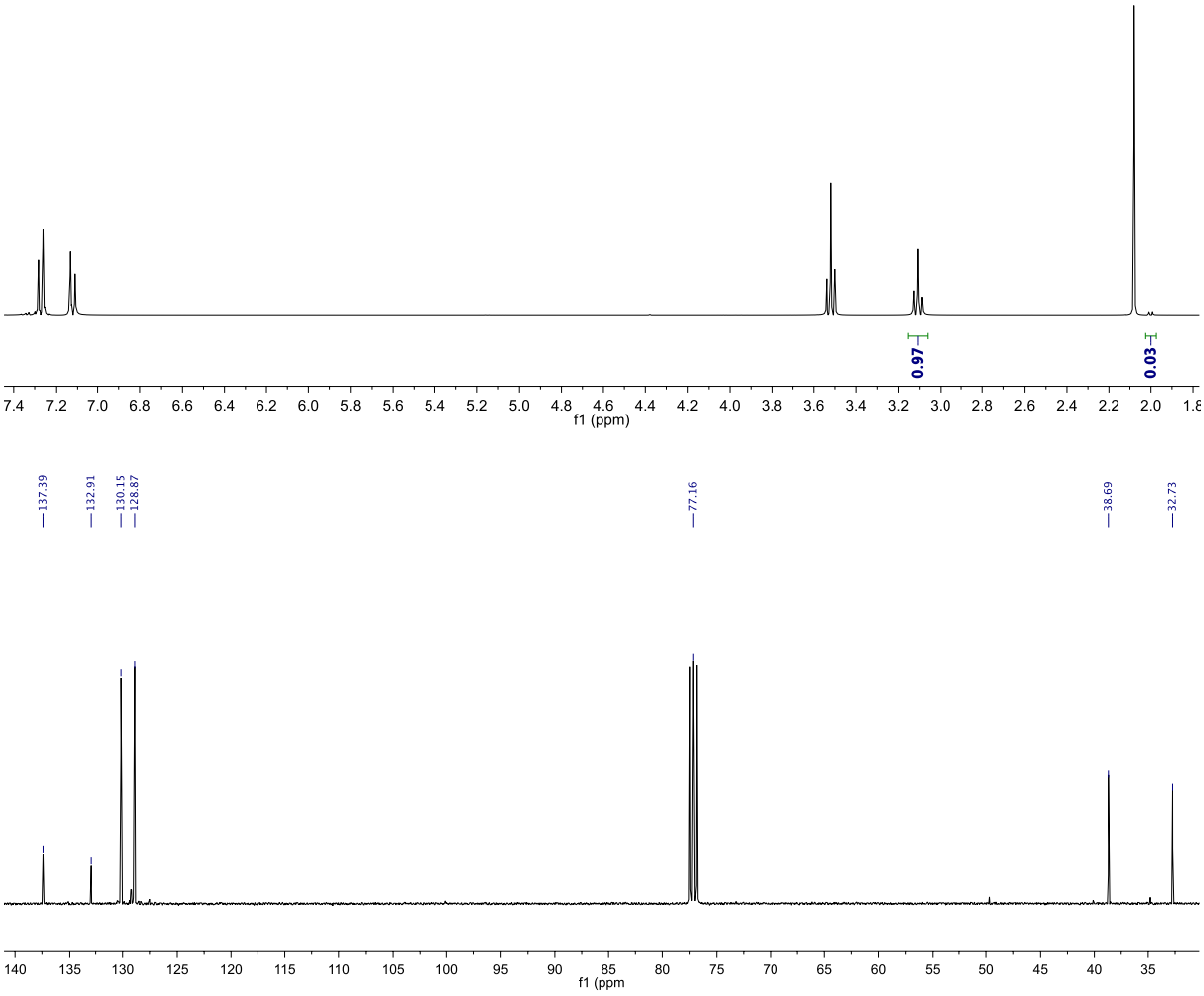


[6] D. J. Morris , A. M. Hayes and M. Wills, *J. Org. Chem*., 2006, **71**, 7035–7044.

1-(2-Bromoethyl)-4-chlorobenzene 3i

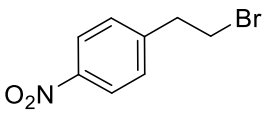


According to **GP2** the title compound was prepared as a colourless oil in 74% yield and 98:2 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.14 (t, J = 7.6, 2H, CH_2), 3.55 (t, J = 7.6, 2H, CH_2), 7.16 (d, J = 8.4, 2H, ArCH), 7.29 (d, J = 8.4, 2H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 32.7, 38.7, 128.9, 130.1, 132.9, 137.4. Data were in accordance with the literature.[7]

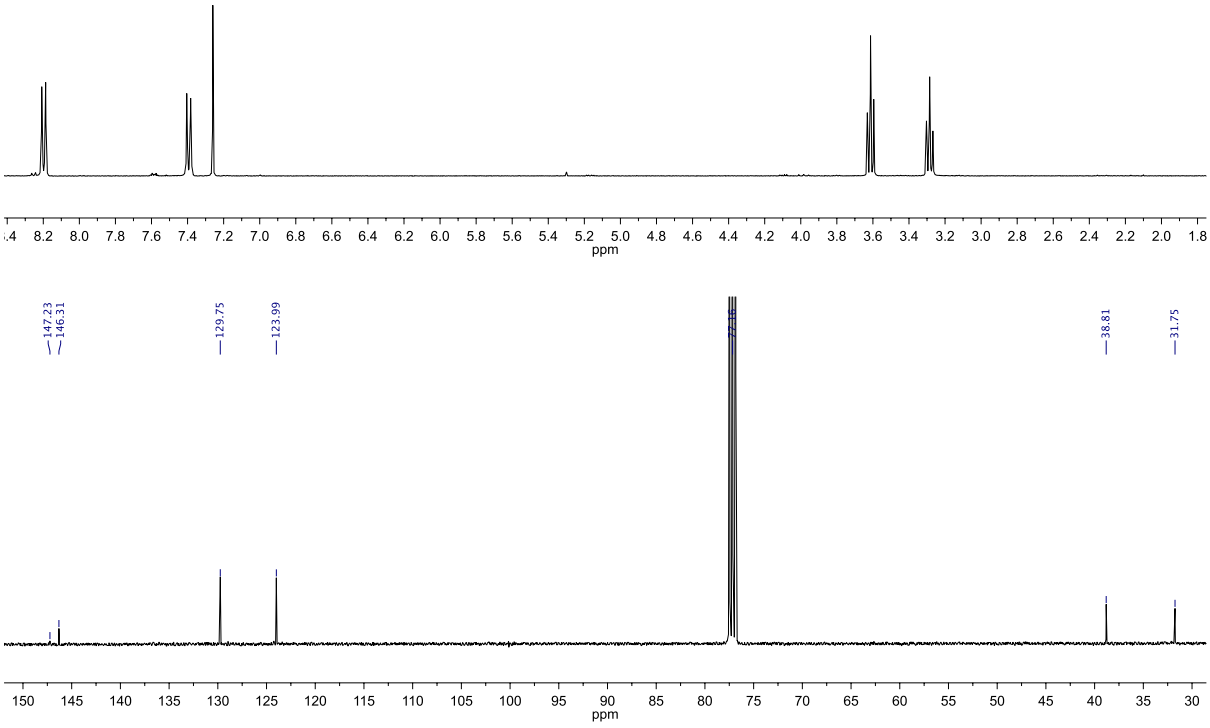


[7] T. Moriya, S. Yoneda, K. Kawana, R. Ikeda,T. Konakahara and N. Sakai, *Org. Lett*., 2012, **14**, 4842–4845.

1-(2-bromoethyl)-4-nitrobenzene 3j

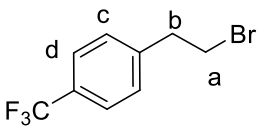


According to **GP1** the title compound was prepared as a pale brown oil in 73% yield and >99:<1 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.29 (t, J = 6.8, 2 H, CH_2), 3.61 (t, J = 6.8, 2 H, CH_2), 7.39 (d, J = 8.4, 2 H, ArCH), 8.20 (d, J = 8.8, 2 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 31.8, 38.8, 124.0, 129.8, 146.3, 147.2. Data were in accordance with the literature.[8]

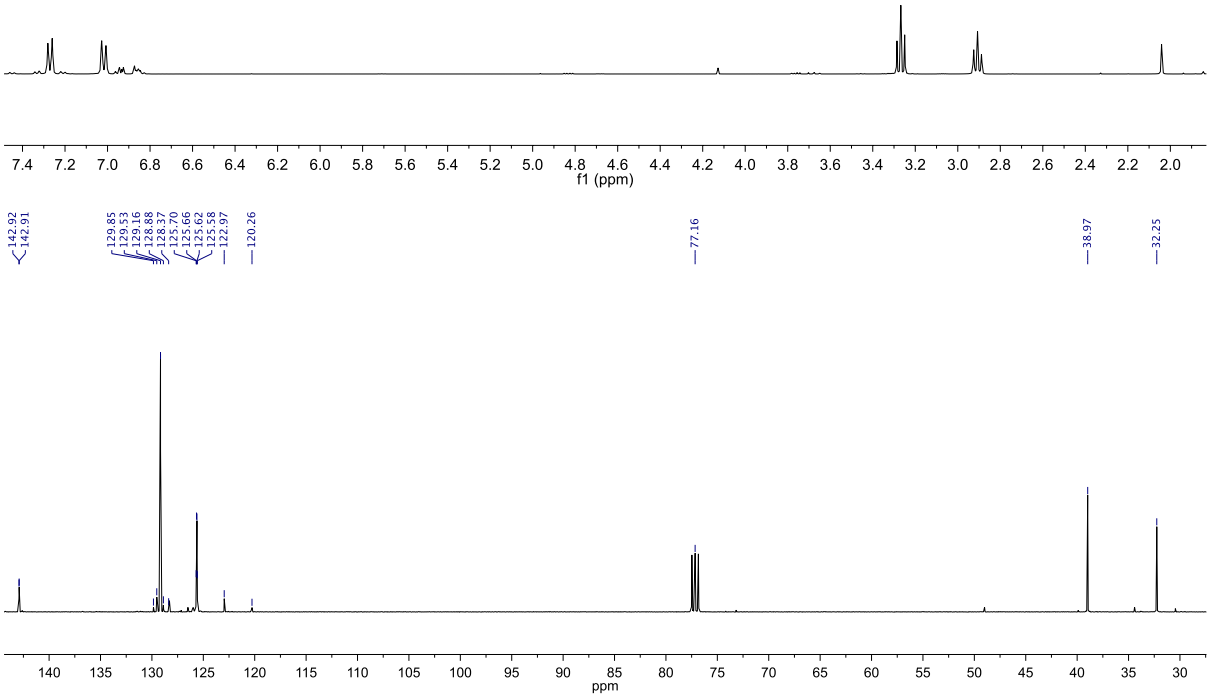


[8] Kyungwon Enterprise Co. Ltd. Patent: WO2007/126262 A1, 2007

1-(2-bromoethyl)-4-(trifluoromethyl)benzene 3k



According to **GP2** the title compound was prepared as a pale brown oil in 87% yield and >99:<1 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.23 (t, J = 7.2, 2 H, CH_2, H_b), 3.59 (t, J = 7.2, 2 H, CH_2, H_a), 7.34 (d, J = 8.0, 2 H, ArCH, H_c), 7.59 (d, J = 8.0, 2 H, ArCH, H_d). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 32.3, 39.0, 124.3 (q, J = 27.9), 125.6 (q, J = 3.8), 129.2, 129.4 (q, J = 32.4), 143.0 (br m). ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm -62.6. HRMS (EI +ve) m/z found 251.97611 $[M]^+$ (calc. for $C_9H_8BrF_3$ 251.97560). Data were in accordance with the literature.[9]



[9] Aurigene DiscoveryTechnologies Ltd. patent: WO2015/101928 A1, **2015**

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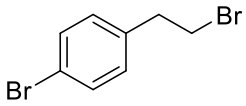
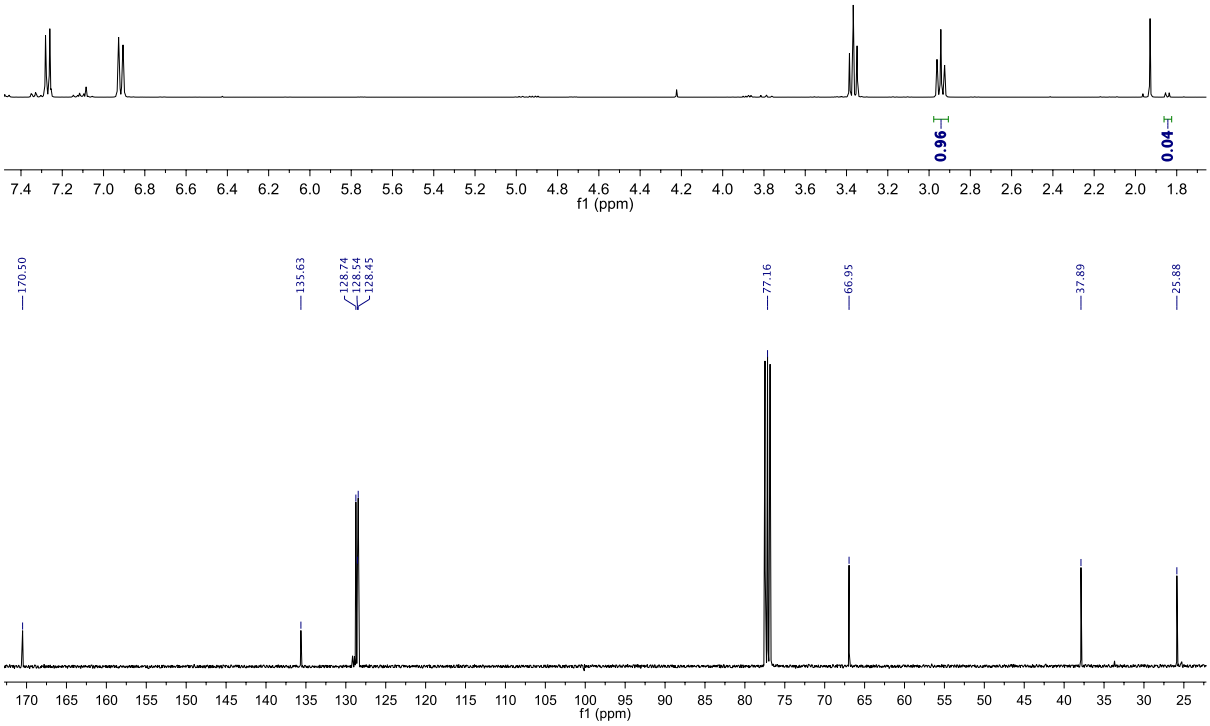
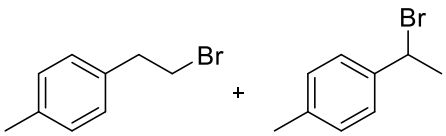
1-(2-Bromoethyl)-4-bromobenzene 3l



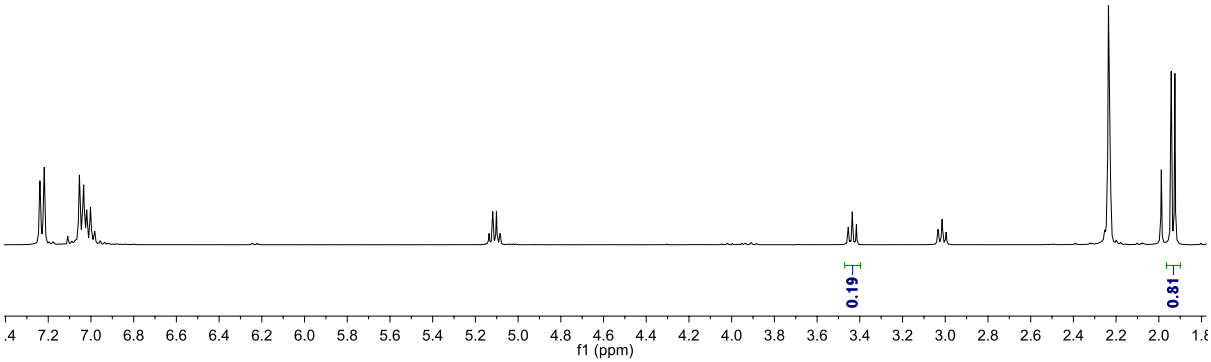
According to **GP2** the title compound was prepared as a colourless oil in 96% yield and 97:3 selectivity (linear:branched). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.12 (t, *J* = 6.0, 2 H, CH_2), 3.54 (t, *J* = 6.0, 2 H, CH_2), 7.10 (d, *J* = 7.9, 2 H, ArCH), 7.45 (d, *J* = 7.9, 2 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 32.6, 38.7, 120.9, 130.5, 131.8, 137.9. Data were in accordance with the literature.[7]

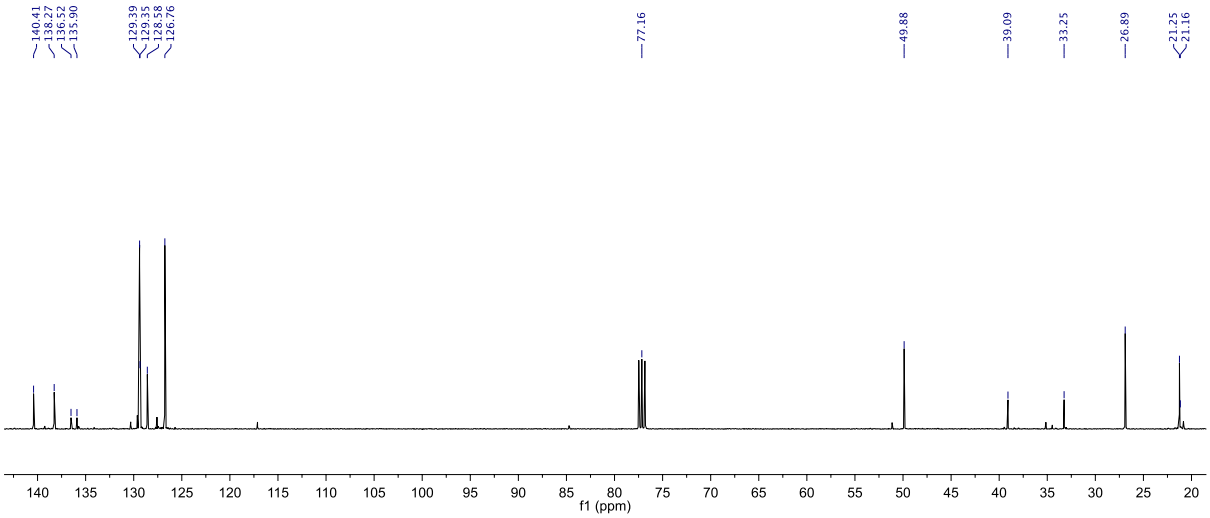


1-(2-Bromoethyl)-4-methylbenzene 3m and 1-(1-bromoethyl)-4-methylbenzene 5m



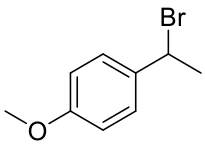
According to **GP2** the title compound was prepared as a colourless oil in 91% and 25:75 selectivity (linear:branched). *NB:A refers to **3m** and B refers to **5m***: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.05 (d, *J* = 6.8, 1 H, B-CH_3), 2.22 - 2.33 (m, 6 H, A-CH_3, B-CH_3), 3.06 (t, *J* = 7.6, 2 H, A-CH_2), 3.48 (t, *J* = 7.6, 2 H, A-CH_2), 5.15 (q, *J* = 6.9, 1 H, B-CH), 7.05 - 7.23 (m, 6 H, Ar-CH), 7.26 - 7.37 (m, 2 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 21.2 (B), 21.3 (A), 26.9 (A), 33.3 (A), 39.1 (A), 49.9 (A), 126.8 (A), 128.6 (B), 129.4 (B), 129.4 (A), 135.9 (B), 136.5 (B), 138.3 (A), 140.4 (A). Data were in accordance with the literature.[10]



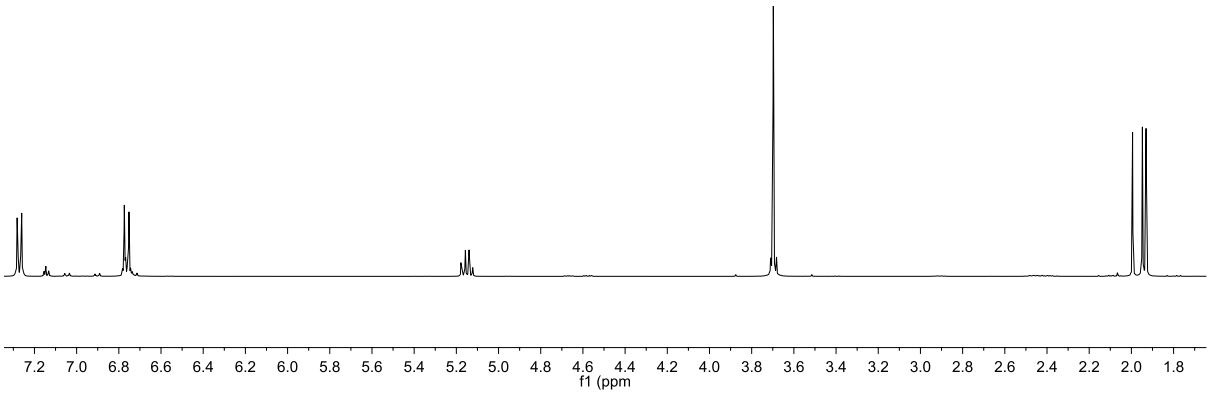


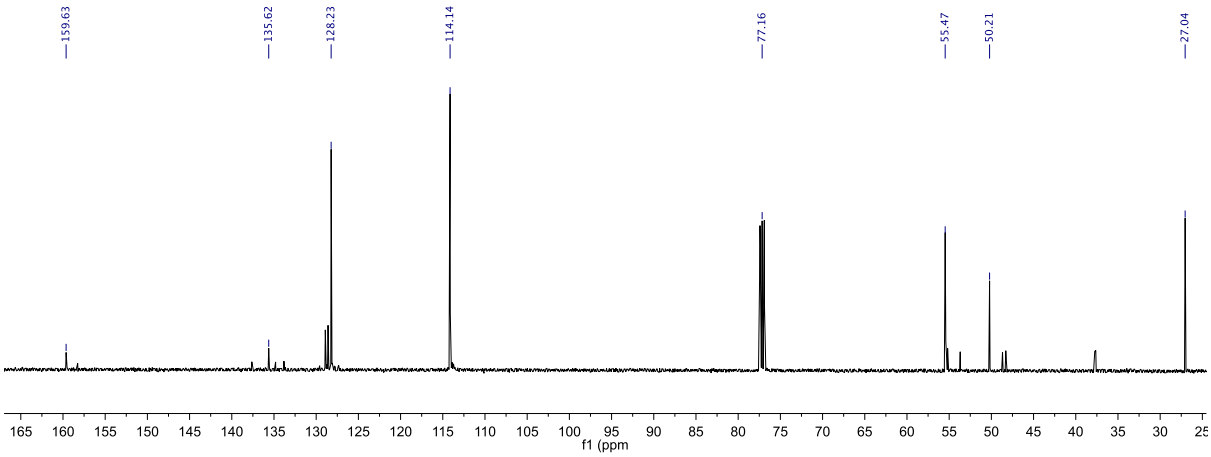
[10] **3m**: C.P. Burke and Y. Shi, *Org. Lett*., 2009, **11**, 5150–5153; **5m**: F. O. Arp, G. C. Fu, *J. Am. Chem. Soc*., 2005, **127**, 10482–10483.

1-(1-Bromoethyl)-4-methoxybenzene 5n



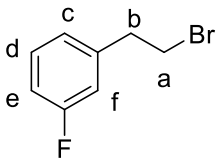
According to **GP2** the title compound was prepared as a colourless oil in 88% yield and 0:100 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 2.04 (d, J = 7.2, 3 H, CH_3), 3.81 (s, 3 H, O-CH_3), 5.25 (q, J = 6.9, 1 H, CH), 6.86 (d, J = 8.8, 2 H, ArCH), 7.37 (d, J = 8.7, 2 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 27.0, 50.2, 55.5, 114.1, 128.2, 135.6, 159.6. Data were in accordance with the literature. [11]



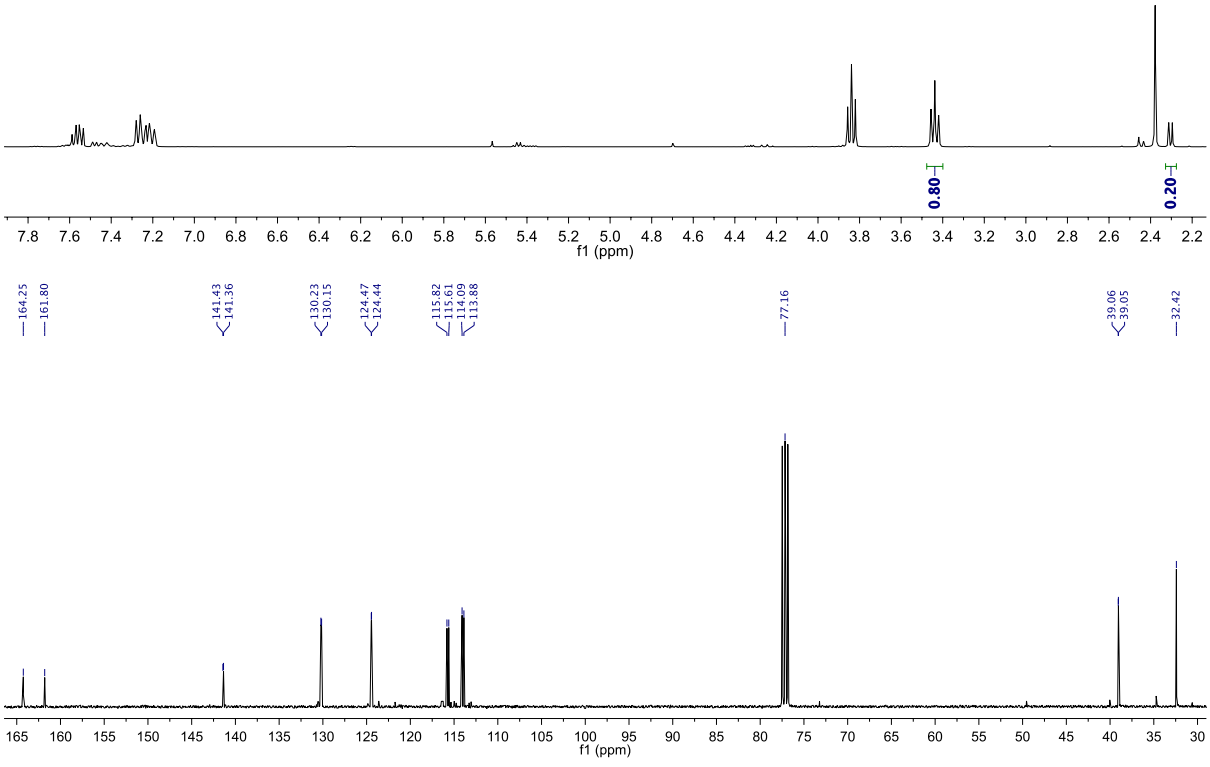


[11] S. D. Bull, S. G. Davies, S. W. Epstein, A. C. Garner, N. Mujtaba, P. M. Roberts, E. D. Savory, A. D. Smith, J. A. Tamayo and D. J. Watkin, *Tetrahedron*, 2006, **62**, 7911–7925.

1-(2-Bromoethyl)-3-fluorobenzene 3o

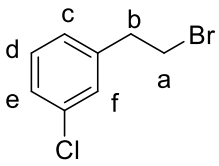


According to **GP2** the title compound was prepared as a colourless oil in 82% yield and 86:14 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.15 (t, J = 7.6, 2H, CH_2, H_b), 3.55 (t, J = 7.6, 2H, CH_2, H_a), 6.88 - 7.03 (m, 1 H, ArCH, H_f), 7.21 - 7.36 (m, 3 H, ArCH, H_{c+d+e}). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 32.4, 39.1 (d, J = 1.8), 114.0 (d, J = 21.0), 115.7 (d, J = 21.2), 124.5 (d, J = 2.9), 130.2 (d, J = 8.2), 141.4 (d, J = 7.3), 163.0 (d, J = 246.1). ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm -117.3. HRMS (EI +ve) m/z found 201.97846 $[M]^+$ (calc. for C_8H_8BrF 201.97879). Data were in accordance with the literature.[12]

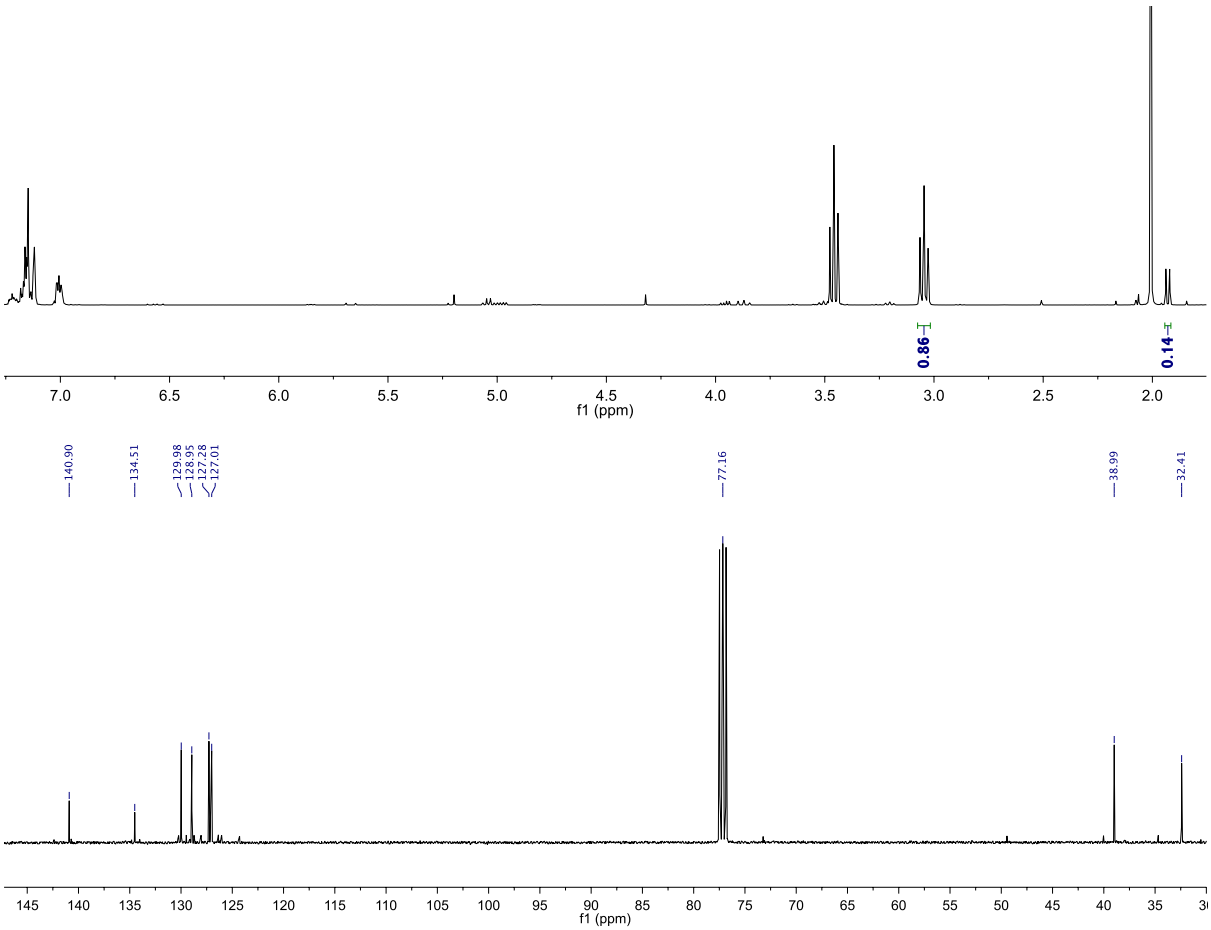


[12] Eli Lilly and Company Patent: WO2004/26305 A1, 2004.

1-(2-Bromoethyl)-3-chlorobenzene 3p

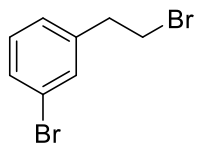


According to **GP2** the title compound was prepared as a colourless oil in 95% yield and 90:10 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.16 (t, J = 7.6, 2 H, CH_2, H_b), 3.57 (t, J = 7.6, 2 H, CH_2, H_a), 7.08 – 7.16 (m, 1H, H_c) 7.22 - 7.33 (m, 3 H, ArCH, H_{d+e+f}). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 32.4, 39.0, 127.0, 127.3, 129.0, 130.0, 134.5, 140.9. HRMS (EI +ve) m/z found 217.94949 $[M]^+$ (calc. for C_8H_8BrCl 217.94924). Data were in accordance with the literature.[13]

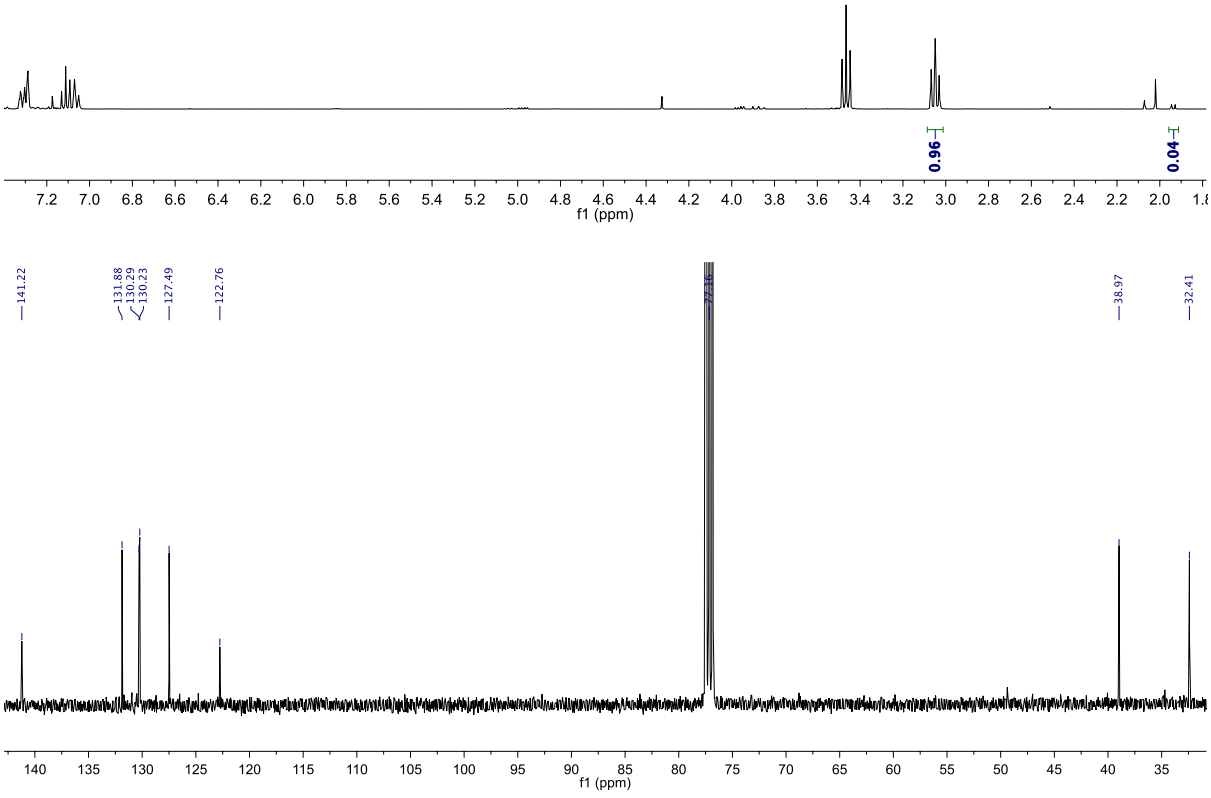


[13] a) Eli Lilly and Company Patent: WO2004/26305 A1, 2004; b) AstraZeneca AB Patent: WO2005/33115 A1, 2005.

1-Bromo-3-(2-bromoethyl)benzene 3q

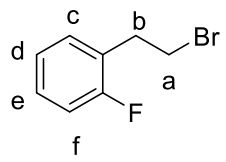


According to **GP2** the title compound was prepared as a colourless oil in 84% yield and 97:3 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.14 (t, J = 7.6, 2 H, CH_2), 3.55 (t, J = 7.2, 2 H, CH_2), 7.13 - 7.24 (m, 2 H, ArCH), 7.37 - 7.44 (m, 2 H, ArCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 32.4, 39.0, 122.8, 127.5, 130.2, 130.3, 131.9, 141.2. Data were in accordance with the literature.[14]

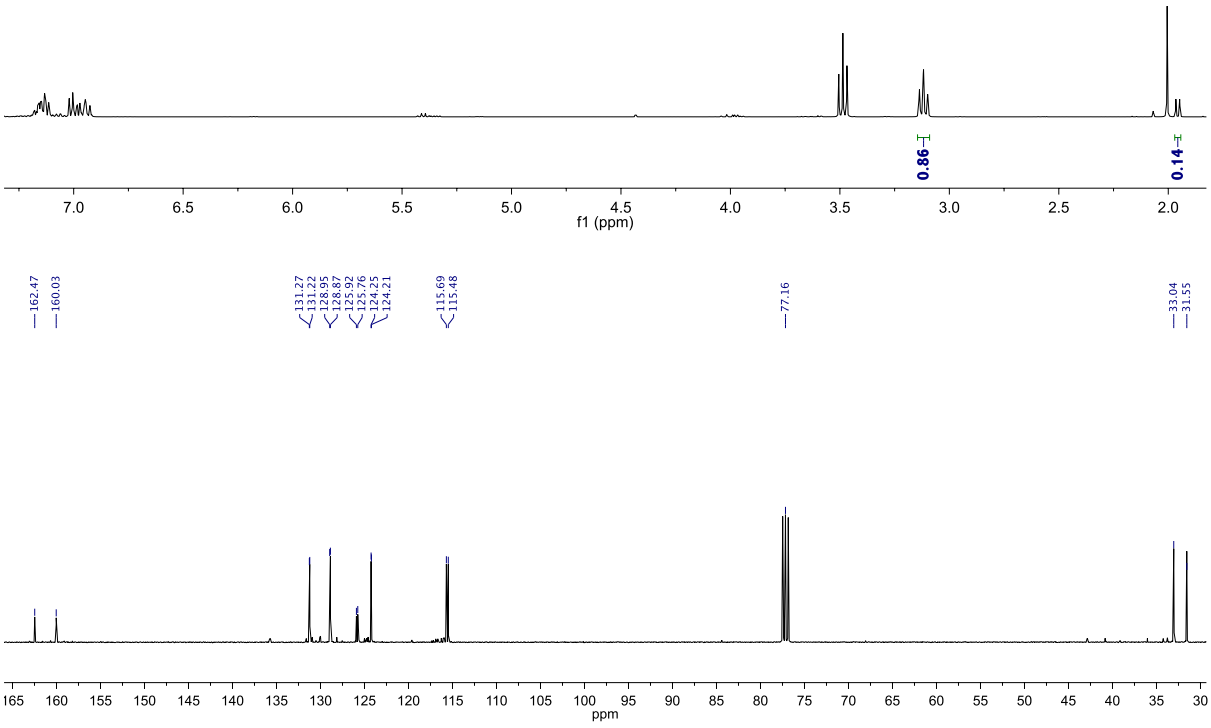


[14] M. Berube, F. Kamal, J. Roy, D. Poirier, *Synthesis*, 2006, **18**, 3085–3091.

1-(2-Bromoethyl)-2-fluorobenzene 3r

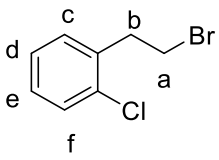


According to **GP2** the title compound was prepared as a colourless oil in 80% yield and 90:10 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.14 (t, J = 7.5, 2 H, CH_2, H_b), 3.51 (t, J = 7.5, 2 H, CH_2, H_a), 6.90-6.98 (m, 1 H, ArCH, H_f), 7.00-7.05 (m, 1 H, ArCH, H_e), 7.08 - 7.25 (m, 2 H, ArCH, H_{c+d}). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 31.5 (d, J = 2.0), 33.0 (d, J = 2.0), 115.6 (d, J = 21.9), 124.2 (d, J = 4.0), 125.8 (d, J = 15.6), 128.9 (d, J = 8.3), 131.2 (d, J = 4.6), 161.3 (d, J = 246.4). ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm -118.8. HRMS (EI +ve) m/z found 201.97895 $[M]^+$ (calc. for C_8H_8BrF 201.97879). Data were in accordance with the literature.[15]

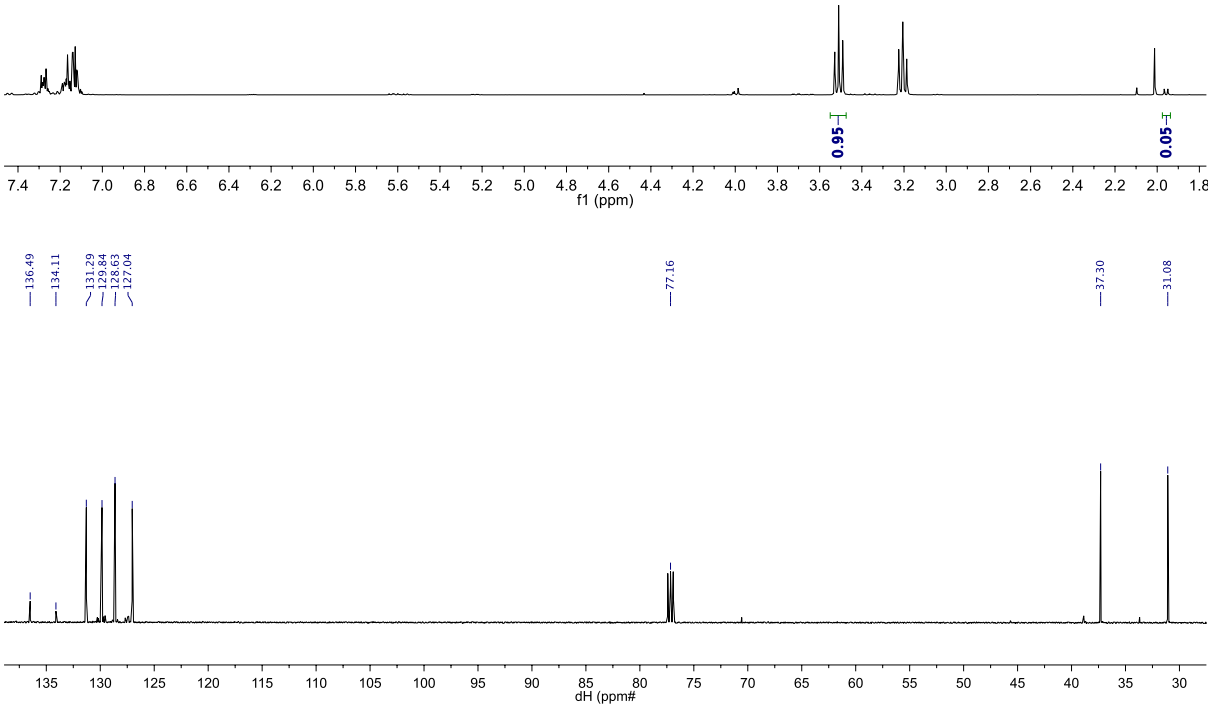


[15] Eli Lilly and Company Patent: WO2004/26305 A1, 2004.

1-(2-Bromoethyl)-2-chlorobenzene 3s

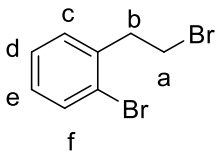


According to **GP2** the title compound was prepared as a colourless oil in 99% yield and 97:3 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.32 (t, J = 7.6, 2 H, CH_2, H_b), 3.63 (t, J = 7.6, 2 H, CH_2, H_a), 7.08 – 7.21 (m, 3 H, ArCH, H_{c+d+e}), 7.24 – 7.31 (m, 1 H, ArCH, H_f). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 31.1, 37.3, 127.0, 128.6, 129.8, 131.3, 134.1, 136.5. HRMS (EI +ve) m/z found 217.95032 $[M]^+$ (calc. for C_8H_8BrCl 217.94924). Data were in accordance with the literature.[16]

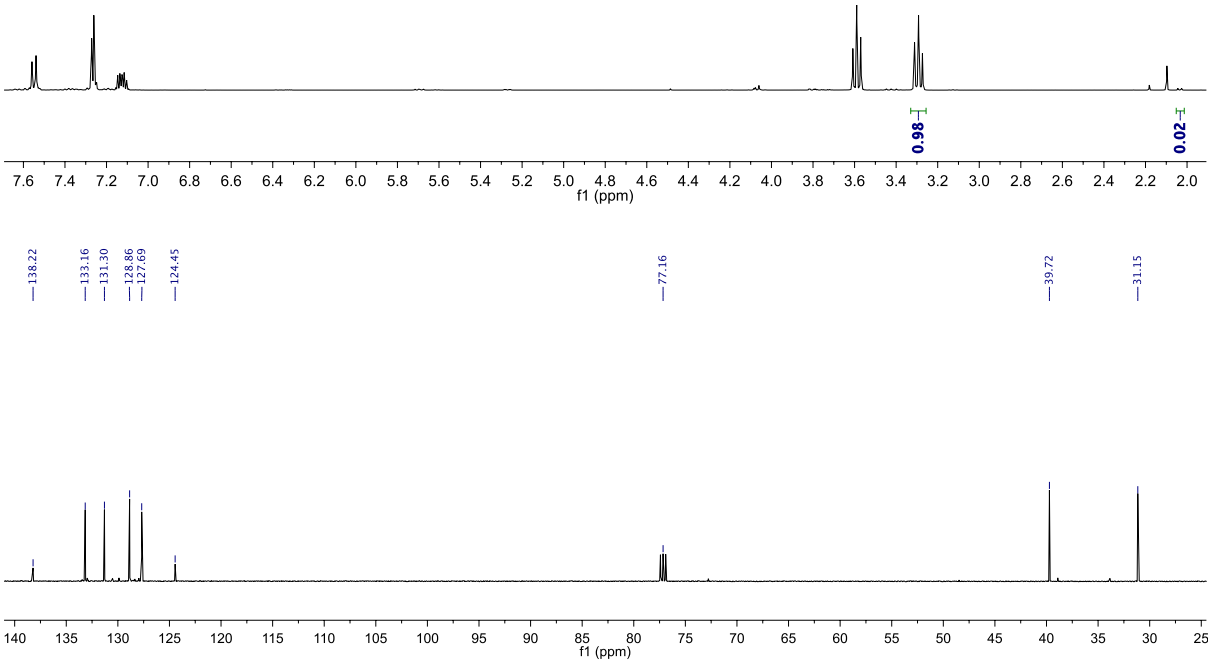


[16] Y. Han, B. Zheng and Y. Peng, *Adv. Synth. Catal.* 2015, **357**, 1136–1142.

1-Bromo-2-(2-bromoethyl)benzene 3t

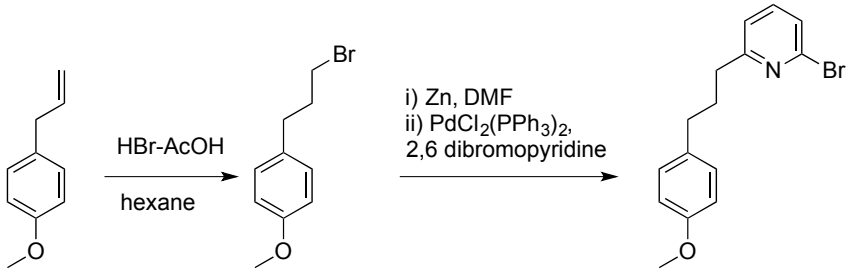


According to **GP2** the title compound was prepared as a colourless oil in 89% yield and 99:1 selectivity (linear:branched). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.29 (t, *J* = 7.6, 2 H, CH_2 H_b), 3.59 (t, *J* = 7.6, 2 H, CH_2, H_a), 7.07 - 7.21 (m, 1 H, ArCH, H_c), 7.21 - 7.34 (m, 2 H, ArCH, H_{d+e}), 7.55 (d, *J* = 8.0, 1 H, ArCH, H_f). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 31.1, 39.7, 124.4, 127.7, 128.9, 131.3, 133.2, 138.2.[17] HRMS (EI +ve) m/z found 261.89987 $[M]^+$ (calc. for $C_8H_8Br_2$ 261.89872). Data were in accordance with the literature.

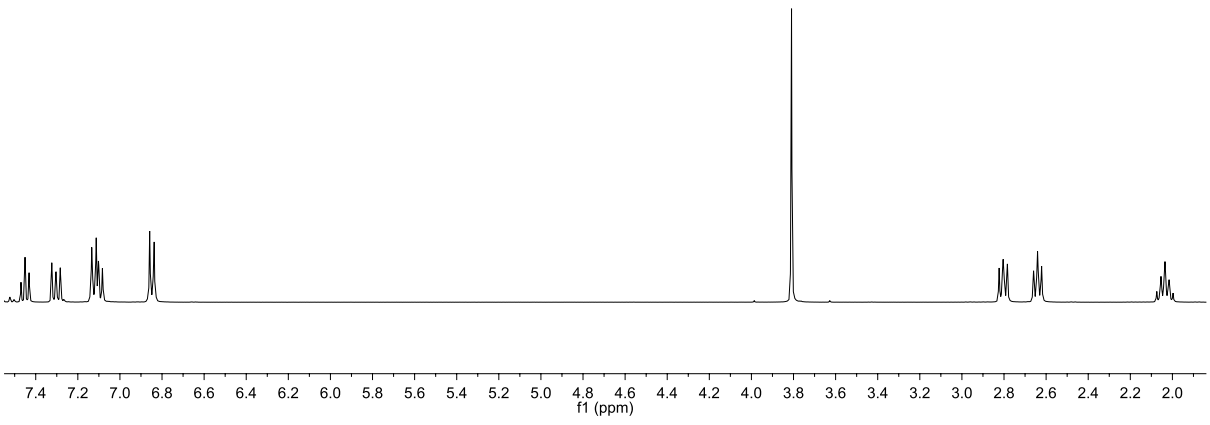


[17] D. J. Carr, J. S. Kudavalli, K. S. Dunne, H. Müller-Bunz, and D. G. Gilheany, *J. Org. Chem.*, 2013, **78**, 10500−10505.

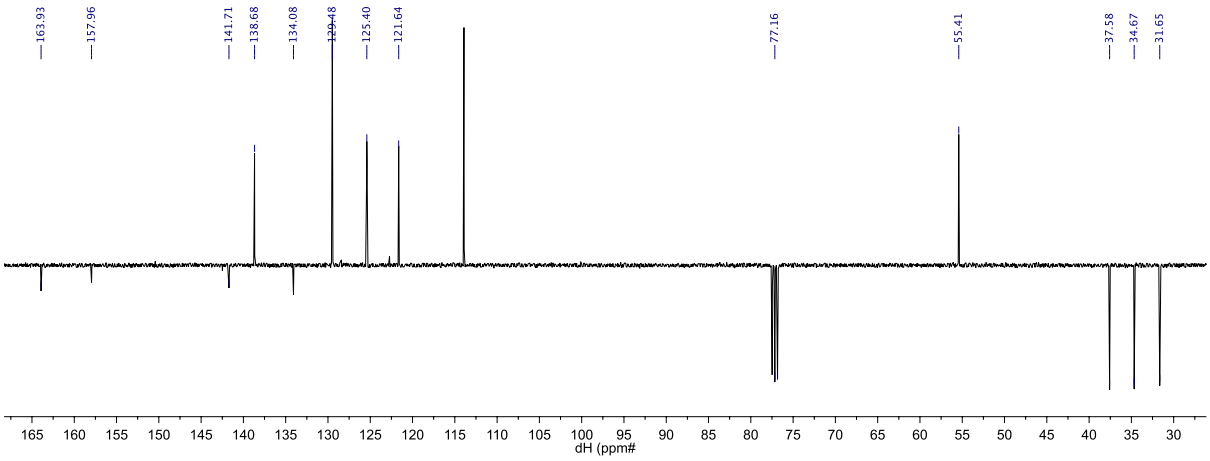
Large scale synthesis of 2-bromo-6-(3-(4-methoxyphenyl)propyl)pyridine (2)[18]



A solution of estragole (**1a**, 17.0 mL, 109.0 mmol) in hexane (570 mL) was stirred at 0 °C and air was bubbled for 2 h through the mixture. A 33% w/v solution of HBr in AcOH (48 mL, 259.5 mmol, 2 eq) was added *via* syringe, and the reaction mixture stirred at 0 °C for 2 h. The stirring was stopped, the phases allowed to separate and the hexane layer was decanted, washed with 1 M $NaHCO_3$ (300 mL), brine (330 mL), dried (Na_2SO_4) and concentrated to give 22.5 g of bromide **3a** (98.0 mmol, 90% yield). This residue was added to a suspension of Zn dust (9.53 g, 147 mmol) and I_2 (1.19 g, 4.7 mmol) in anhydrous DMF (80 ml) and the resulting mixture was stirred vigorously at 90 °C for 2 h. The reaction mixture was cooled to rt and the suspension allowed to settle before the solution of organozinc was cannulated under an inert atmosphere into a flask containing $Pd(PPh_3)_2Cl_2$ (550 mg, 0.79 mmol, 1 mol%) and 2,6-dibromopyridine (18.6 g, 79 mmol). This reaction mixture was then stirred for 2 h at rt before being quenched with a saturated aqueous solution of NH_4Cl (320 ml) and extracted with Et_2O (320 ml × 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (SiO_2; petrol-Et_2O 95 : 5) gave bromopyridine **2** as a viscous oil (14.4 g, 60% based on 2,6-dibromopyridine; 43% over two steps based on **1a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.02 (app. quint., J = 8.0, 2H, CH_2), 2.64 (t, J = 8.0, 2H, CH_2), 2.79 (t, J = 8.0, 2H, CH_2), 3.80 (s, 3H, CH_3), 6.84 (app. d, J = 7.6, 2H, ArH), 7.06 - 7.14 (m, 3 H, ArH, pyH), 7.25 - 7.32 (m, 1 H, pyH), 7.48 (app. t, J = 8.0, 1 H, pyH). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 31.7, 34.7, 37.6, 55.4, 113.9, 121.6, 125.4, 129.5, 134.1, 138.7, 141.7, 158.0, 163.9. Data were in accordance with the literature.[18]



[18] R.J. Bordoli and S. M. Goldup, *J. Am. Chem.Soc.*, 2014, **136**, 4817–4820.


163.93
157.96
141.71
138.68
134.08
129.48
125.40
121.64
77.16
55.41
37.58
34.67
31.65
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
dH (ppm#