Organocatalytic asymmetric total synthesis of (*R*)-Rolipram and formal synthesis of (3*S*,4*R*)-Paroxetine

Supporting Information

Peter S. Hynes, Paul A. Stupple, Darren J. Dixon*

School of Chemistry, The University of Manchester

Oxford Road, Manchester, M13 9PL, UK

Fax: +44 161 2754939

Tel: +44 161 2751426

E-mail: Darren.Dixon@man.ac.uk

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Section 1: General Experimental

General Techniques

For all reactions conducted under anhydrous conditions glassware was dried in an oven at 100 ^{o}C and carried out under a nitrogen atmosphere, unless otherwise stated.

Solvents and Reagents

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Reagents and solvents used were obtained from commercial suppliers or purified according to standard procedures. Petroleum ether refers to distilled light petroleum of fraction (40–65 °C).

Chromatography

Flash silica gel column chromatography was performed with commercial solvents using Merck Kieselgel 60 silica gel (200–400 mesh). Thin layer chromatography (TLC) was performed on aluminium plates pre-coated with Merck Kieselgel 60 F254 and visualised by ultra-violet radiation or by staining with aqueous basic potassium permanganate. Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on a Hewlett-Packard Series 1050 series system (column and solvent conditions are given with the compound).

Melting Points

Melting points were recorded on a Gallenkamp melting point apparatus with the sample contained in a thin glass tube at ambient pressure and are uncorrected.

Polarimetry

Optical rotations were recorded using an Optical Activity AA-1000 polarimeter; specific rotations ($[\alpha]_D$) are reported in 10^{-1} deg•cm^2•g^{-1}; concentrations (c) are quoted in g•(100 mL)$^{-1}$; *D* refers to the D-line of sodium (589 nm); temperatures (*T*) are given in degrees Celsius (^{o}C).

Infra-Red Spectroscopy

Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 FTIR spectrometer (thin film deposited onto a sodium chloride plate). Only selected absorbencies (ν_{max}) are reported.

NMR Spectroscopy

^{1}H, ^{13}C, DEPT, COSY, HMQC and HMBC NMR spectra were recorded on Brucker 500 MHz and Varian 300 MHz spectrometers Chemical shifts (δ_H) are quoted in parts per million (ppm $\pm$ 0.01 ppm) downfield of tetramethylsilane, relative to the residual protiosolvent (δ_H (C**H**Cl_3) = 7.26 ppm) against an internal deuterium lock. Coupling constants (*J*) are given in Hertz (Hz $\pm$ 0.1). The ^{1}H NMR spectra are reported as follows: δ / ppm (multiplicity, coupling constants *J* / Hz, number of protons, assignment). DEPT and two-dimensional NMR spectroscopy (COSY, HMQC and HMBC) were used where appropriate to assist the assignment of the signals in the ^{1}H NMR and ^{13}C NMR spectra.

Mass Spectrometry

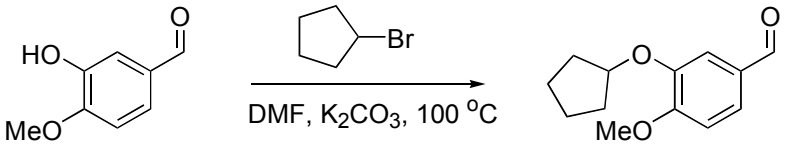
Low resolution mass spectrometry (electron impact / chemical ionisation) was recorded on a Micromass Trio 2000 quadropole mass spectrometer and (electrospray) on a Micromass Platform II spectrometer. High resolution mass spectra (accurate mass) were recorded on a Thermo Finnigan Mat95XP mass spectrometer.

Literature References

Known compounds are indicated by a reference to a previous literature report in their title line. Any data that is referred to from a different source is noted separately in the characterisation text. If a literature procedure was followed, this is indicated explicitly in the method text. Novel compounds are reported in *italics* in the method text.

Section 2: Experimental for the synthesis of *(R)*-Rolipram

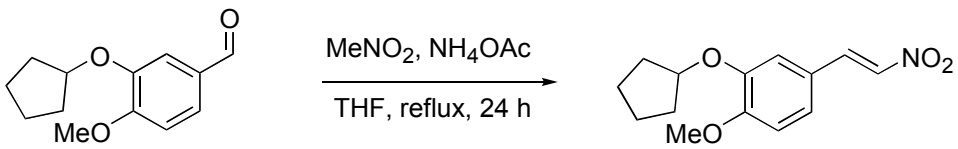
2.1: 3-(Cyclopentyloxy)-4-methoxybenzaldehyde; 7[1]



6 **7**

Following the method of Barnes, [1] cyclopentyl bromide (9.20 mL, 85.4 mmol) and K_2CO_3 (13.6 g, 98.7 mmol) were added to a stirred solution of *iso*vanillin **5** (10.0 g, 65.7 mmol) in DMF (67 mL) and heated at 100 °C for 30 h. The reaction mixture was cooled to rt and quenched with saturated aqueous NH_4Cl (130 mL). The mixture was then stirred for 10 min at rt, the layers were then separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, washed with water (2 × 50 mL), dried (magnesium sulfate) and concentrated *in vacuo*. The crude product **7** (12.6 g, 87% yield) was isolated as a brown oil and carried forward to the next step without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 9.79 (s, 1 H, C<u>H</u>O), 7.38 (dd, *J* = 8.1, 1.7, 1 H, Ar-<u>H</u>), 7.35 (d, *J* = 1.7, 1 H, Ar-<u>H</u>), 6.92 (d, *J* = 8.1, 1 H, Ar-<u>H</u>), 4.85–4.76 (m, 1 H, OC<u>H</u>$(CH_2)_4$), 3.88 (s, 3 H, Ar-OC<u>H</u>$_3$), 2.11–1.70 (m, 6 H, cyclopentyl-<u>H</u>), 1.65–1.50 (m, 2 H, cyclopentyl-<u>H</u>); **MS** *m/z* (CI+) 221 (90%, MH^+). [HRMS (ES+): MNH_4^+, 238.1451. $[C_{13}H_{20}NO_3]^+$ requires 238.1438]. The data was found to be consistent with that reported in the literature.[1]

2.2: 2-(Cyclopentyloxy)-1-methoxy-4-[(*E*)-2-nitroethenyl]benzene; 8[2]

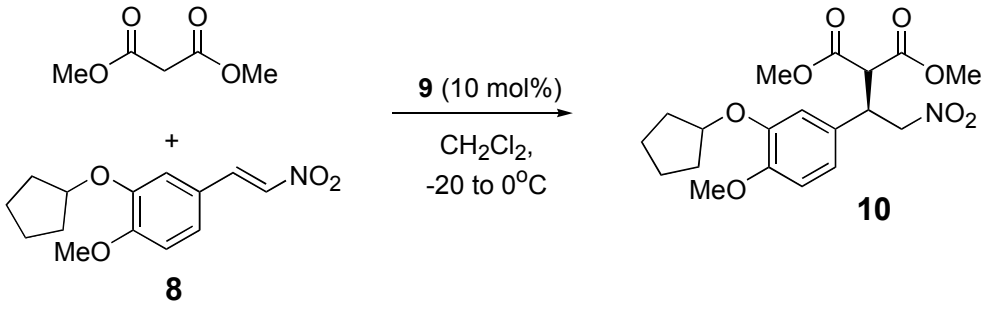


7 **8**

To a stirred solution of the crude aryl aldehyde **7** (13.0 g, 59.1 mmol) and nitromethane (300 mL) was added ammonium acetate (5.01 g, 65.0 mmol). The solution was heated under reflux for 24 hours. The reaction mixture was concentrated *in vacuo* and then dissolved in CH_2Cl_2 / H_2O (1:1), the organics were extracted into CH_2Cl_2 (3 × 200 mL), then washed with brine (100 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. Purification by flash

silica gel chromatography [EtOAc / petroleum ether, (1:5–1:1)] afforded the title compound **8** as an orange solid (14.3 g, 92% yield) after flash silica gel chromatography [EtOAc / petroleum ether (1:20–1:3)]. **MP** 138–140 °C (lit. 134–136 °C [2]); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.95 (d, *J* = 13.6, 1 H, -C<u>H</u>=CHNO$_2$), 7.50 (d, *J* = 13.6, 1 H, -CH=C<u>H</u>NO$_2$), 7.14 (dd, *J* = 8.3, 1.8, 1 H, Ar-<u>H</u>), 7.01 (br d, *J* = 1.8, 1 H, Ar-<u>H</u>), 6.89 (d, *J* = 8.3, 1 H, Ar-<u>H</u>), 4.79 (td, *J* = 9.0, 3.0, 1 H, -OC<u>H</u>(CH$_2$)$_4$), 3.90 (s, 3 H, Ar-OC<u>H</u>$_3$), 2.00–1.80 (m, 6 H, cyclopentyl-<u>H</u>), 1.70–1.60 (m, 2 H, cyclopentyl-<u>H</u>); **MS** *m/z* (ES+) 286 (100%, MNa$^+$). [HRMS (ES+): MH$^+$, 264.1238 [$C_{14}H_{18}NO_4$]$^+$ requires 264.1230]. The data was found to be consistent with that reported in the literature.[2]

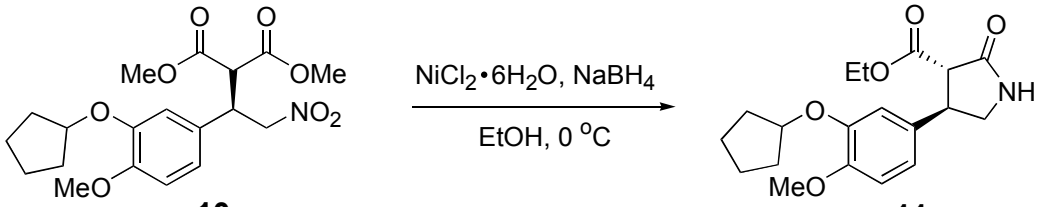
2.3: (–)-Dimethyl-[(1*R*)-1-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-nitroethyl]propanedioate; 10[3]



To a stirred solution of nitro olefin **8** (1.00 g, 3.80 mmol) and dimethyl malonate (1.31 mL, 11.4 mmol) in CH_2Cl_2 (4 mL) was added catalyst **9** (215 mg, 0.38 mmol). The reaction was stirred at –20 °C (48 h) then warmed to 0 °C (48 h) until analysis by TLC indicated that all of nitro olefin **8** had been consumed. Purification by flash silica gel chromatography [EtOAc / petroleum ether (1:15–1:8)] afforded the title compound **10** as a colourless solid (1.44 g, 96% yield) in 94% ee as determined by HPLC analysis [Chiralpak OJ, hexane / IPA, 90:10, 1.0 mL/min, λ 220 nm, t (major) = 37.61 min, t (minor) = 44.71 min]: The product was recrystallised from hexane / TBME, 4:1 to give >99% ee (1.25 g, 87% yield). **MP** 94–96 °C (lit. 97–98 °C [3]); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.78 (d, *J* = 8.0, 1 H, Ar-<u>H</u>), 6.74–6.70 (m, 2 H, Ar-<u>H</u>), 4.87 (dd, *J* = 13.0, 5.2, 1 H, C<u>H</u>$_A$H$_B$-NO$_2$), 4.82 (dd, *J* = 13.0, 9.0, 1 H, CH$_A$<u>H</u>$_B$-NO$_2$), 4.73 (app. qd, *J* = 9.3, 3.0, 1 H, OC<u>H</u>(CH$_2$)$_2$), 4.15 (app. dt, *J* = 9.0, 5.2, 1 H, Ar-*C<u>H</u>), 3.84 (d, *J* = 9.0, 1 H, C<u>H</u>-*C), 3.80 (s, 3 H, OC<u>H</u>$_3$), 3.75 (s, 3 H, OC<u>H</u>$_3$), 3.57 (s, 3 H, OC<u>H</u>$_3$), 1.97–1.88 (m, 2 H, cyclopentyl-<u>H</u>), 1.87–1.76 (m, 4 H, cyclopentyl-<u>H</u>), 1.65–1.56 (m, 2 H,

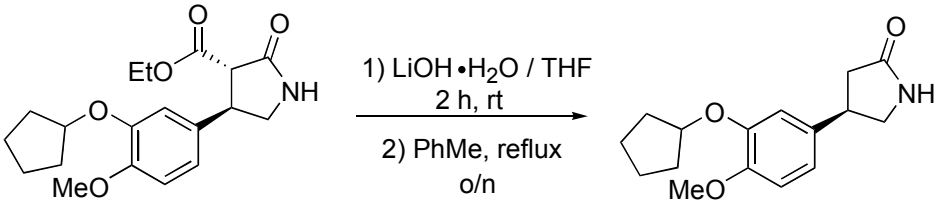
cyclopentyl-H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 167.9 (C=O), 167.3 (C=O), 149.8 (Ar:C-O), 147.6 (Ar:C-O), 128.1 (Ar), 119.9 (Ar), 114.6 (Ar), 111.9 (Ar:C_{quat}), 80.4 ($OCH(CH_2)_2$), 77.7 (C-NO_2), 55.9 (Ar-OCH_3), 54.8 (CH-C=O), 53.0 (OCH_3), 52.8 (OCH_3), 42.6 (Ar-*C), 32.7 (2 × cyclopentyl-CH_2), 24.0 (2 × cyclopentyl-CH_2); **MS** *m/z* (CI+) 413 (100%, MNH_4^+). [HRMS (ES+): MNH_4^+, 413.1910. $[C_{19}H_{29}N_2O_8]^+$ requires 413.1918]; **OR** $[\alpha]_D^{30}$ –9.4 (c 1.15, $CHCl_3$, >99% ee). The NMR and MS data was found to be consistent with that reported in the literature.

2.4: ((+)-Ethyl-(3*S*,4*R*)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-oxo pyrrolidine-3-carboxylate; 11[1]



To a stirred solution of **10** (400 mg, 1.01 mmol) and $NiCl_2$•$6H_2O$ (240 mg, 1.01 mmol) in EtOH (5.0 mL) was added $NaBH_4$ (420 mg, 11.1 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h before being quenched with saturated aqueous NH_4Cl (20 mL). The solution was diluted with $CHCl_3$ (20 mL), extracted with $CHCl_3$ (2 × 20 mL), dried (magnesium sulfate), filtered through Celite and concentrated *in vacuo* to afford the title compound **11** (337 mg, 96% yield) as a yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 7.66 (br s, 1 H, NH), 6.82–6.70 (m, 3 H, Ar-H), 4.77–4.68 (br m, 1 H, Ar-*CH), 4.20 (q, *J* = 7.1, 2 H, OCH_2CH_3), 3.99 (dd, *J* = 18.0, 8.6, 1 H, CH_AH_B-NH), 3.82–3.70 (m, 4 H, Ar-OCH_3 and CH_AH_B-NH), 3.49 (d, *J* = 9.8, 1 H, CH-*C), 3.37 (t, *J* = 9.0, 1 H, $OCH(CH_2)_2$), 1.95–1.70 (m, 6 H, cyclopentyl-H), 1.65–1.50 (m, 2 H, cyclopentyl-H), 1.24 (t, *J* = 7.1, 3 H, OCH_2CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C 173.0 (C=O_{amide}), 169.2 (C=O_{ester}), 149.2 (Ar:C-O), 147.7 (Ar:C-O), 132.0 (Ar), 118.8 (Ar), 113.8 (Ar), 112.1 (Ar:C_{quat}), 80.3 ($OCH(CH_2)_2$), 61.6 (OCH_2CH_3), 55.9 (Ar-OCH_3), 55.6 (CH-C=O), 47.7 (CH_2-NH), 43.9 (Ar-*C), 32.60 (CH_2), 32.59 (CH_2), 23.8 (2 × CH_2), 14.0 (OCH_2CH_3); **MS** *m/z* (CI+) 348 (100%, MH^+). [HRMS (ES+): MH^+, 348.1820. $[C_{19}H_{26}NO_5]^+$ requires 348.1805]. The data was found to be consistent with that reported in the literature.[1]

2.5: (4*R*)-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]pyrrolidin-2-one; 1[1]

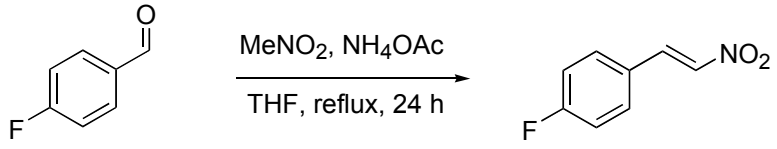


11 **1**

A stirred solution of **11** (118 mg, 0.34 mmol) in THF (5 mL) was treated with a solution of aqueous LiOH until pH 14. The reaction was allowed to stir at rt for 2 h and then acidified to pH 1 with HCl (1 N). The layers were separated and the aqueous layer was extracted with $CHCl_3$ / IPA (3:1) (3 × 5 mL). The organics were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The crude material was dissolved in PhMe (3 mL) and refluxed overnight. Purification by flash silica gel chromatography [EtOAc] afforded the title compound **1** (88.0 mg, 94% yield) as a colourless solid. **MP** 129–132 °C (lit. 132–134 °C[1]); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.22 (br s, 1 H, NH), 6.80 (d, *J* = 8.5, 1 H, Ar-H), 6.77–6.73 (m, 2 H, Ar-H), 4.74 (m, 1 H, OCH$(CH_2)_2$), 3.80 (s, 3 H, Ar-OCH_3), 3.73 (app. t, *J* = 8.9, 1 H, CH_AH_B-NH), 3.63–3.54 (m, 1 H, Ar-*CH), 3.36 (dd, *J* = 9.4, 7.7, 1 H, CH_AH_B-NH), 2.68 (dd, *J* = 16.9, 8.9, 1 H, CH_AH_BCO), 2.45 (dd, *J* = 16.9, 8.9, 1 H, CH_AH_BCO), 1.95–1.74 (m, 6 H, cyclopentyl-H), 1.65–1.52 (m, 2 H, cyclopentyl-H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 178.0 (C=O_{amide}), 149.0 (Ar:C-O), 147.7 (Ar:C-O), 134.5 (Ar), 118.6 (Ar), 113.7 (Ar), 112.0 (Ar:C_{quat}), 80.4 (OCH$(CH_2)_2$), 56.0 (OCH_3), 49.8 (CH_2-C=O), 39.8 (Ar-*C), 38.2 (CH_2), 32.6 (2 × CH_2), 23.9 (2 × CH_2); **MS** *m/z* (CI+) 276 (100%, MH^+). [HRMS (ES+): MNH_4^+, 293.1859. $[C_{16}H_{25}N_2O_3]^+$ requires 293.1860]; **OR** $[\alpha]_D^{25}$ –31.0 (c 1.05, MeOH, >99% ee) (lit. $[\alpha]_D^{25}$ –30.8 (c 1.01, MeOH, 95% ee[1]). The data was found to be consistent with that reported in the literature.[1]

Section 3: Experimental for the formal synthesis of (3*S*,4*R*)-Paroxetine

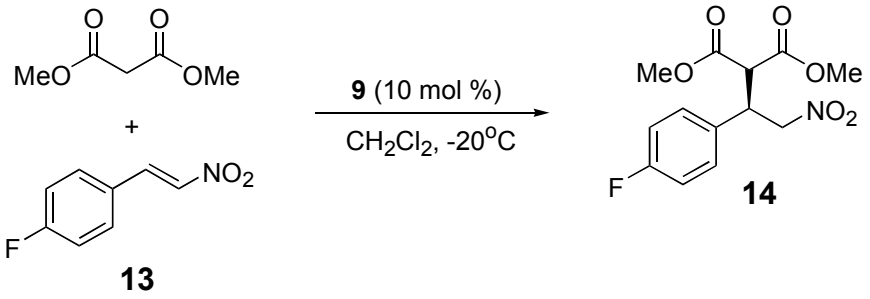
3.1: 1-Fluoro-4-[(*E*)-2-nitroethenyl]benzene; 13[4]



12 **13**

To a stirred solution of the aryl aldehyde **12** (5.00 g, 40.0 mmol) and nitromethane (300 mL) was added ammonium acetate (3.40 g, 44.0 mmol). The solution was heated under reflux for 24 h. The reaction mixture was concentrated *in vacuo* and then dissolved in CH_2Cl_2 / H_2O (1:1), the organics were extracted into CH_2Cl_2 (3 × 100 mL), then washed with brine (100 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo*. Recrystallisation from [EtOAc / petroleum ether (1:10)] afforded the title compound **13** (3.73 g, 92% yield) as a yellow crystalline solid. **MP** 98–100 °C (lit. 100–101 °C [4]); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.98 (d, *J* = 13.6, 1 H, C<u>H</u>=CHNO$_2$), 7.59–7.55 (m, 2 H, Ar-<u>H</u>), 7.54 (d, *J* = 13.6, 1 H, CH=C<u>H</u>NO$_2$), 7.15 (t, *J* = 8.55, 2 H, Ar-<u>H</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 165.0 (d, *J* = 255.0, Ar:<u>C</u>$_{para}$-F), 137.9 (CH=<u>C</u>HNO$_2$), 136.9 (<u>C</u>H=CHNO$_2$), 131.3 (d, *J* = 9.0, 2 × Ar:<u>C</u>$_{ortho}$), 126.3 (d, *J* = 4.0, Ar:<u>C</u>$_{quat}$), 116.9 (d, *J* = 22.0, 2 × Ar:<u>C</u>$_{meta}$); **MS** *m/z* (CI+) 185 (100%, MNH_4^+). [HRMS (ES+): MNH_4^+, 185.0722. $[C_8H_{10}N_2O_2F]^+$ requires 185.0721].

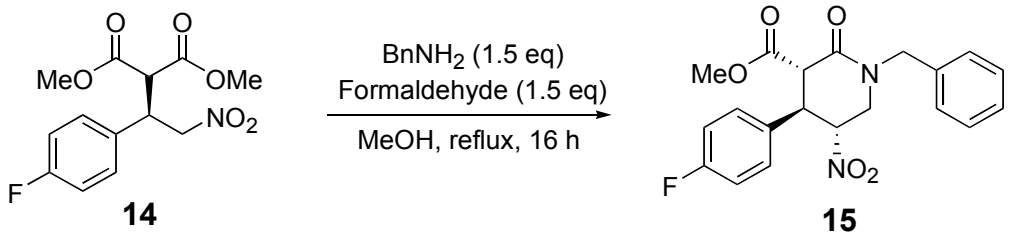
3.2: (–)-Dimethyl[(1*R*)-1-(4-fluorophenyl)-2-nitroethyl]propane dioate; 14[5], [3]



13 **14**

To a stirred solution of nitro olefin **13** (1.00 g, 5.95 mmol) and dimethyl malonate (2.04 mL, 17.9 mmol) in CH_2Cl_2 (6.0 mL) was added catalyst **9** (335 mg, 0.60 mmol). The reaction was stirred at –20 °C until analysis by TLC indicated that all of nitro olefin **13** had been consumed (72 h). Purification by flash silica gel chromatography [EtOAc / petroleum ether (1:15–1:8)] afforded the title compound **14** (1.64 g, 92% yield) as a colourless solid in 92% ee as determined by HPLC analysis [Chiralpak AD, hexane / IPA, 90:10, 1.0 mL/min, λ 210 nm, t (major) = 19.0 min, t (minor) = 33.9 min]; the product was recrystallised from Et_2O / petroleum ether, 1:1 to give >99% ee (1.28 g, 78% yield). **MP** 48–50 °C for >99% ee, (lit. 46–49 °C for 93% ee[3]); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.21 (dd, *J* = 8.7, 5.2, 2 H, Ar-H), 7.01 (t, *J* = 8.7, 2 H, Ar-H), 4.90 (dd, *J* = 13.2, 4.9, 1 H, CH_AH_B-NO_2), 4.83 (dd, *J* = 13.2, 9.3, 1 H, CH_AH_B-NO_2), 3.82 (d, *J* = 9.3, 1 H, CH-*C), 3.76 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 167.7 (C=O), 167.1 (C=O), 162.5, (d, *J* = 248.0, Ar:C_{para}-F), 131.8 (d, *J* = 3.0, Ar:C_{quat}), 129.6 (d, *J* = 8.0, 2 × Ar:C_{ortho}), 116.0 (d, *J* = 22.0, 2 × Ar:C_{meta}), 77.4 (C-NO_2), 54.6 (CH-*C), 53.1 (OCH_3), 52.9 (OCH_3), 42.2 (Ar-*C); **MS** *m/z* (CI+) 317 (100%, MNH_4^+). [HRMS (ES+): MNH_4^+, 317.1136. $[C_{13}H_{18}N_2O_6F]^+$ requires 317.1143]; **OR** $[\alpha]_D^{22}$ –4.2 (c 1.27, $CHCl_3$, >99% ee), (lit. $[\alpha]_D^{25}$ +6.2 (c 1.04, $CHCl_3$ for 97% ee *(S)* enantiomer[5]). The data was found to be consistent with that reported in the literature.[5]

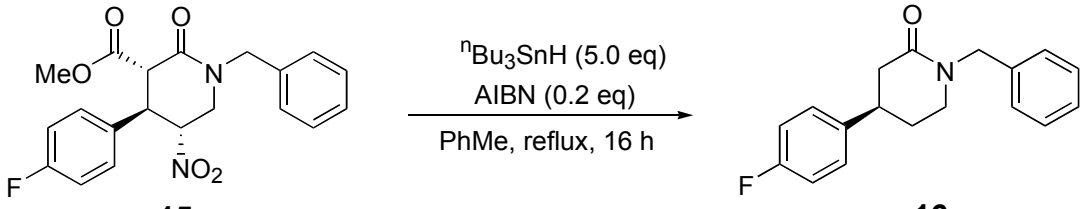
3.3: (+)-Methyl-(3*S*,4*R*,5*R*)-1-benzyl-4-(4-fluorophenyl)-5-nitro-2-oxopiperidine-3-carboxylate; 15



14 **15**

To a stirred solution of the enantiopure Michael adduct **14** (207 mg, 0.70 mmol) in MeOH (8.0 mL), was added formaldehyde (37% solution in water, 79 µL, 1.05 mmol) followed by benzylamine (115 µL, 1.05 mmol). The reaction mixture was refluxed for 16 h. The crude mixture was concentrated *in vacuo* and purification by flash silica gel chromatography [Et_2O / petroleum ether (1:1)] afforded the *title compound* **15** (184 mg, 68% yield) as a colourless solid in >99% ee as determined by HPLC analysis [Chiralpak IB, hexane / IPA, 90:10, 1.0 mL/min, λ 210 nm, t (major) = 19.0 min, t (minor) = 33.9 min] and in >99% de as determined by 500 MHz ^{1}H NMR. **MP** 39–42 ^{o}C; **IR** ν_{max}(film)/cm^{-1} 1745 (C=O_{ester}), 1655 (C=O_{amide}), 1557 and 1350 (N-O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.41–7.33 (m, 3 H, Ar-H), 7.30–7.27 (m, 2 H, Ar-H), 7.21–7.15 (m, 2 H, Ar-H), 7.03 (t, *J* = 8.6, 2 H, Ar-H), 4.97 (ddd, *J* = 10.5, 9.1, 5.5, 1 H, CH-NO_2), 4.86 (d, *J* = 14.5, 1 H, -NCH$_A$H$_B$-Ar), 4.48 (d, *J* = 14.5, 1 H, -NCH$_A$H$_B$-Ar), 4.15 (t, *J* = 11.1, 1 H, Ar-*CH), 3.89 (dd, *J* = 12.6, 9.1, 1 H, -CH$_A$H$_B$-CNO_2), 3.75 (dd, *J* = 12.6, 5.5, 1 H, -CH$_A$H$_B$-CNO_2), 3.71 (d, *J* = 11.7, 1 H, -CH-C(O)OCH_3), 3.66 (s, 3 H, -C(O)O-CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 168.2 (C=O_{amide}), 164.3 (C=O_{ester}), 162.6 (d, *J* = 248, Ar:C$_{para}$-F), 135.1 (Ar), 131.6 (d, *J* = 3, Ar:C$_{ipso}$), 129.1 (d, *J* = 8, 2 × Ar:C$_{ortho}$), 129.0 (Ar), 128.4 (Ar), 128.3 (Ar:C$_{ipso}$), 116.4 (d, *J* = 22, 2 × Ar:C$_{meta}$), 84.4 (C-NO_2), 54.3 (-CH-*C), 52.9 (-C(O)O-CH_3), 50.5 (N-CH_2), 48.1 (N-CH_2), 45.2 (Ar-*C); **MS** *m/z* (CI+) 387 (90%, MH^+). [HRMS (ES+): MH^+, 387.1355. $[C_{20}H_{20}N_2O_5F]^+$ requires 387.1351]; **OR** $[\alpha]_D^{33}$ +23.6 (c 0.97, $CHCl_3$, >99% ee).

3.4: (4*R*)-1-Benzyl-4-(4-fluorophenyl)piperidin-2-one; 16[6]

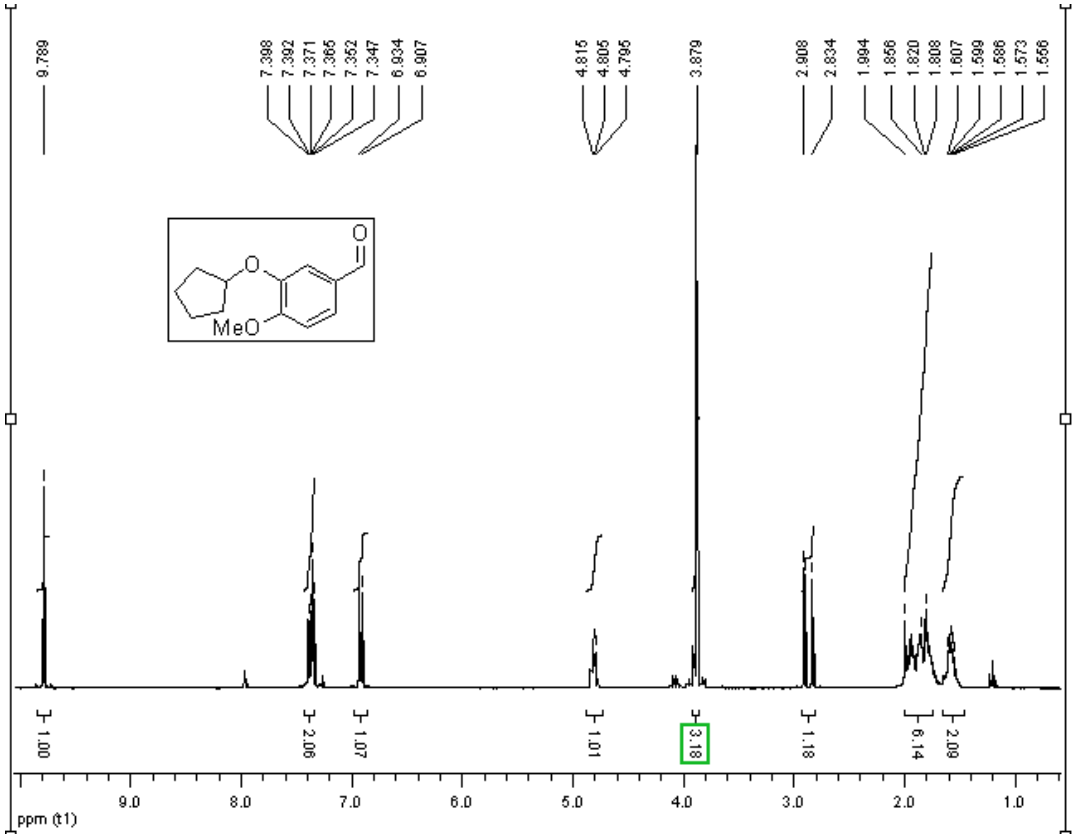


15 **16**

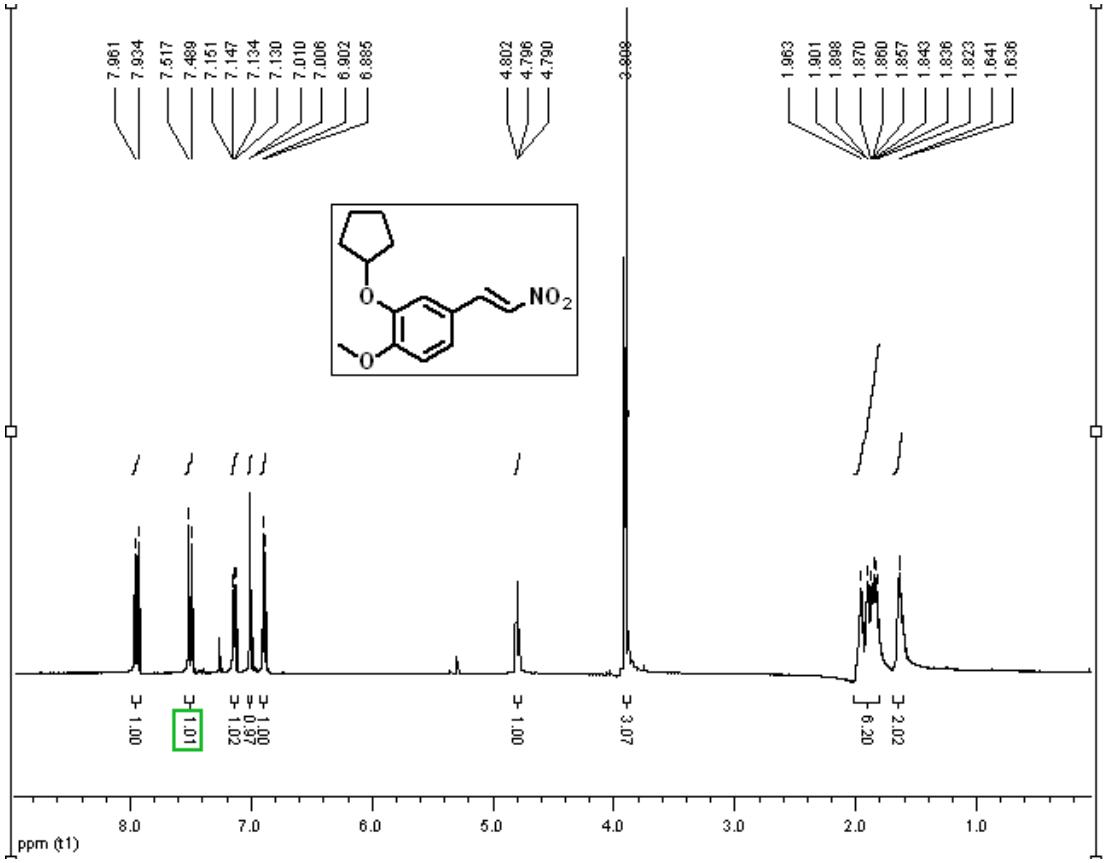
To a stirred solution of **15** (100 mg, 0.26 mmol) in PhMe (3 mL) was added $^{n}Bu_3SnH$ (349 µL, 1.30 mmol), AIBN (9 mg, 0.05 mmol) and then degassed *in vacuo*. The reaction was then refluxed for 16 h. The crude mixture was concentrated *in vacuo* and purification by flash silica gel chromatography [Et_2O] afforded the title compound **16** (57.3 mg, 78% yield) as a colourless solid in >99% ee as determined by HPLC analysis [Chiralpak AD, hexane / IPA, 95:05, 1.0 mL / min, λ 210 nm, t (minor) = 32.7 min, t (major) = 35.5 min] **MP** 66–68 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.37–7.31 (m, 2 H, Ar-H), 7.31–7.26 (m, 3 H, Ar-H), 7.17–7.12 (m, 2 H, Ar-H), 7.01 (t, *J* = 8.7, 2 H, Ar-H), 4.74 (d, *J* = 14.5, 1 H, NC$H_A$$H_B$-Ph), 4.55 (d, *J* = 14.5, 1 H, NC$H_A$$H_B$-Ph), 3.34–3.22 (m, 2 H, NC$H_2$$CH_2$), 3.09 (m, 1 H, Ar-*CH), 2.80 (ddd, *J* = 17.5, 5.4, 2.0, 1 H, C$H_A$$H_B$CO), 2.55 (dd, *J* = 17.5, 1.1, 1 H, C$H_A$$H_B$CO), 2.10–2.02 (m, 1 H, CH_2C$H_A$$H_B$-*C), 1.90 (dddd, *J* = 13.3, 11.2, 10.9, 5.4, 1 H, CH_2C$H_A$$H_B$-*C); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 169.0 (C=O_{amide}), 161.6 (d, *J* = 245.0, Ar:C_{para}-F), 139.0 (d, *J* = 3.0, Ar:C_{quat}), 137.0 (Ar), 128.6 (Ar), 128.1 (Ar), 127.9 (d, *J* = 8.0, 2 × Ar:C_{ortho}), 127.5 (Ar), 115.5 (d, *J* = 21.0, 2 × Ar:C_{meta}), 50.0 (N-CH_2Ar), 46.2 (N-$CH_2$$CH_2$), 39.6 ($CH_2$CO), 37.9 (Ar-*CH), 30.3 ($CH_2$$CH_2$-*C); **MS** *m/z* (CI+) 306 (100%, MNa^+). [HRMS (ES+): MNa^+, 306.1261. $[C_{18}H_{18}NOFNa]^+$ requires 306.1265]; **OR** $[\alpha]_D^{21}$ = +34.6 (c 1.09, $CHCl_3$, >99% ee), (lit. $[\alpha]_D^{20}$ +33 (c 1.07, $CHCl_3$, 96% ee[6]). The data was found to be consistent with that reported in the literature; no MP was reported.[6]

Section 4: Spectra for total synthesis of (*R*)-Rolipram

4.1: 3-(Cyclopentyloxy)-4-methoxybenzaldehyde; 7

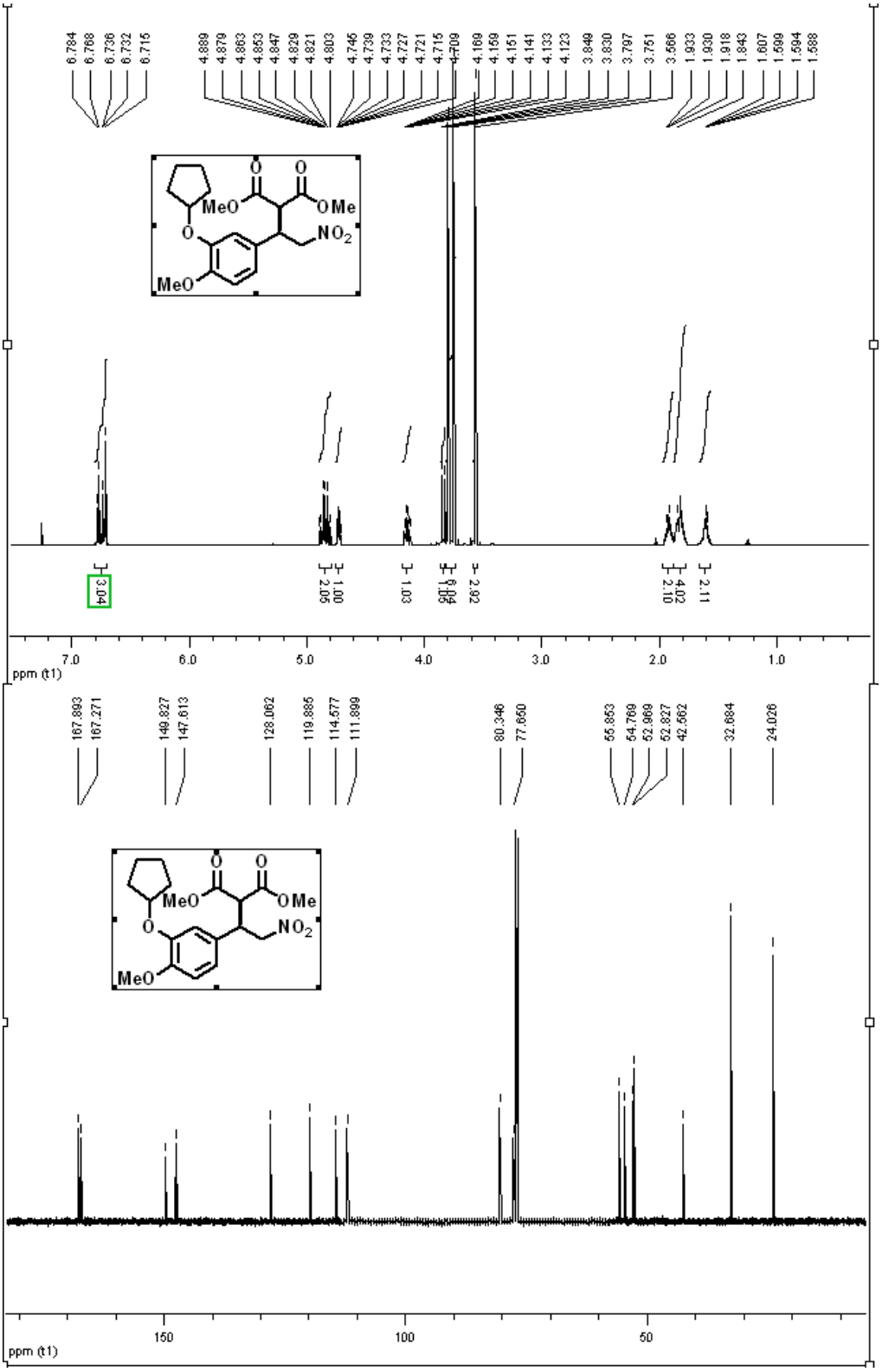


4.2: 2-(Cyclopentyloxy)-1-methoxy-4-[(*E*)-2-nitroethenyl]benzene; 8

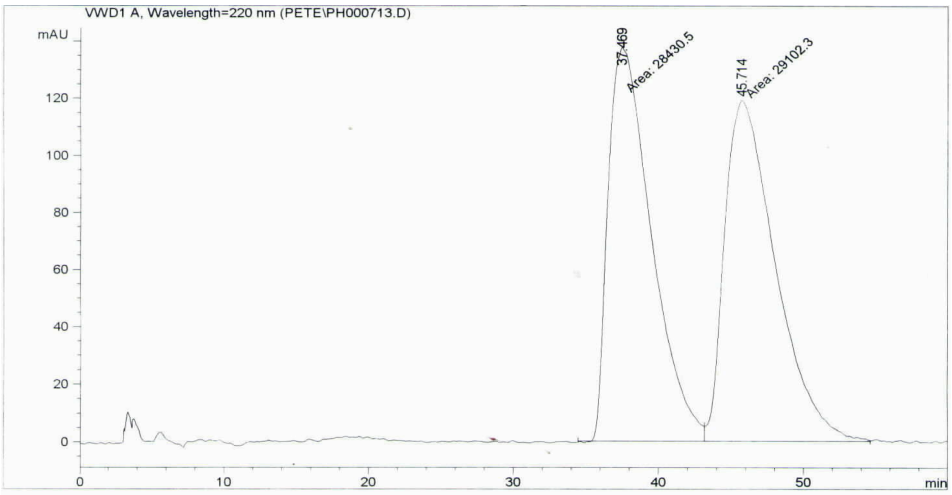


4.3: (–)-Dimethyl-[(1*R*)-1-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-nitroethyl] propanedioate; **10**

NMR; **10**



HPLC; **10**

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Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
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   2  45.714 FM    4.0707 2.91023e4   119.15239  50.5838

Totals :                  5.75327e4   256.71767
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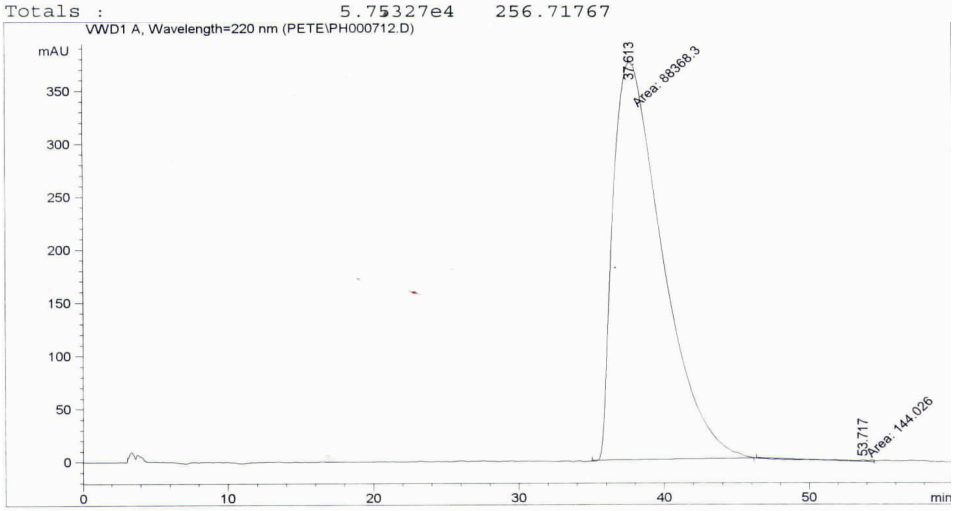


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                    Area Percent Report
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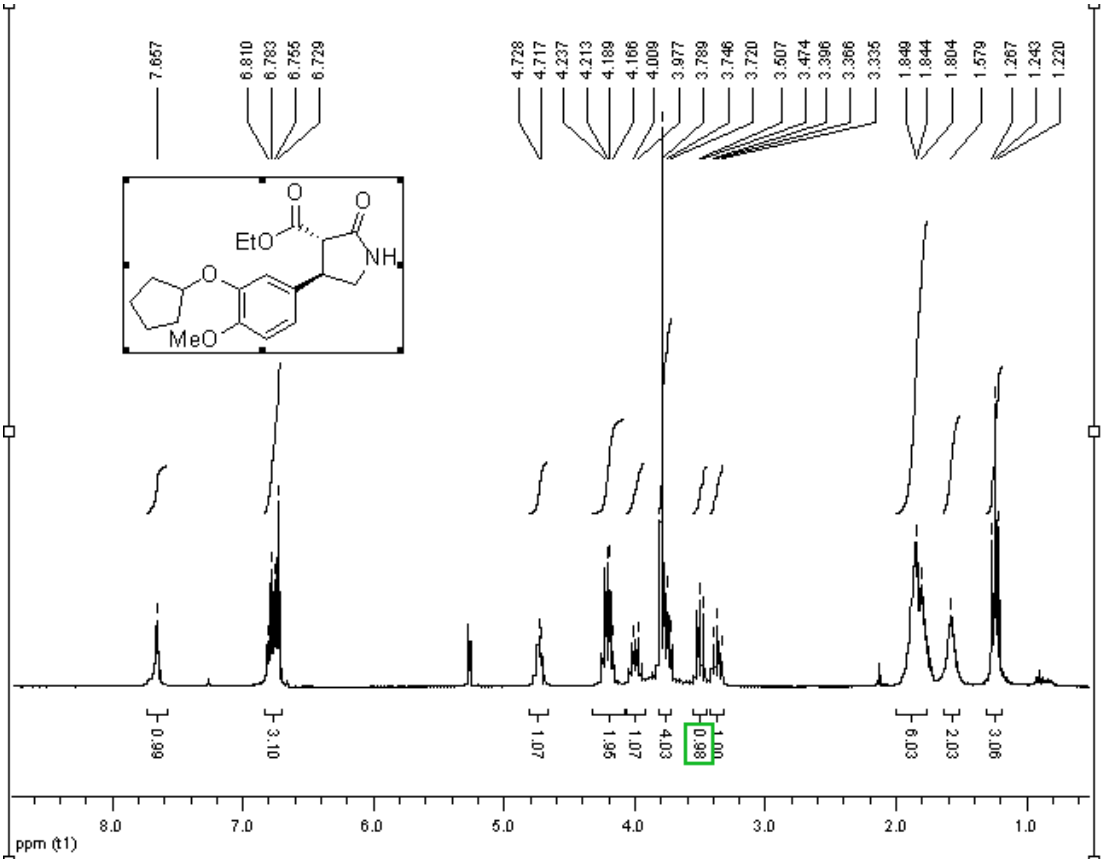
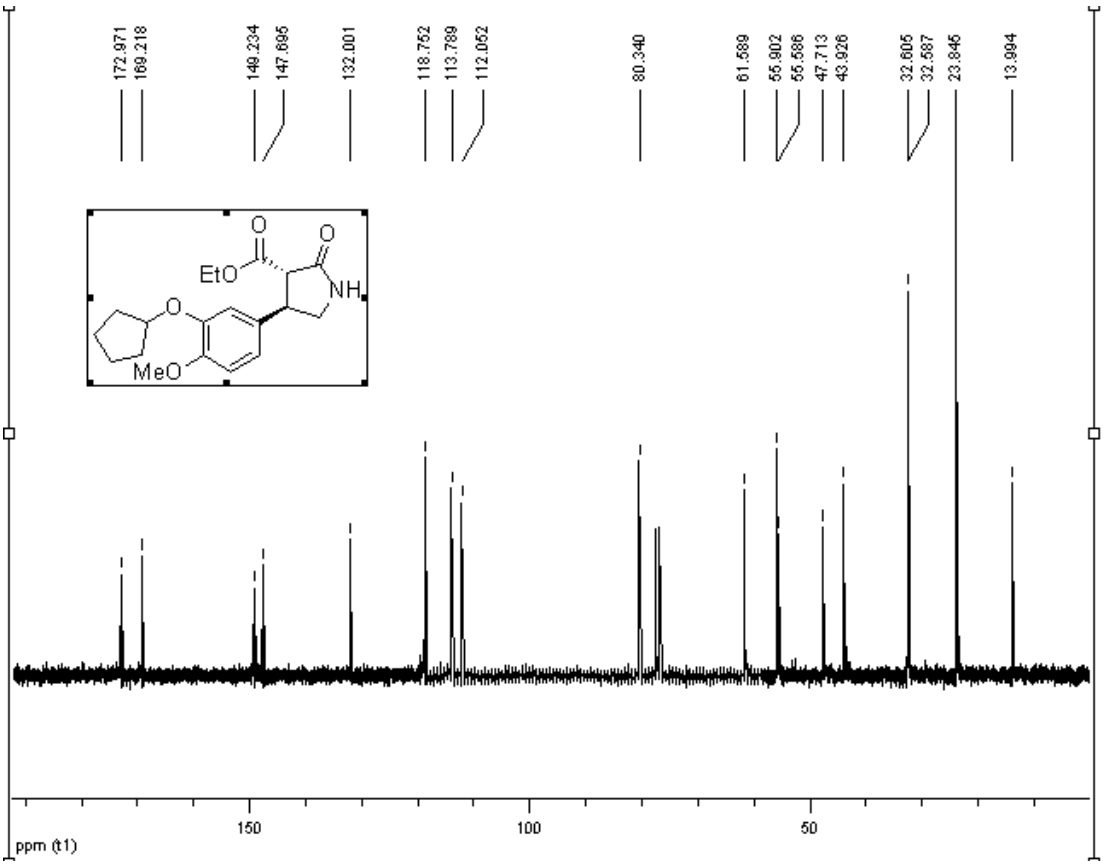
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=220 nm

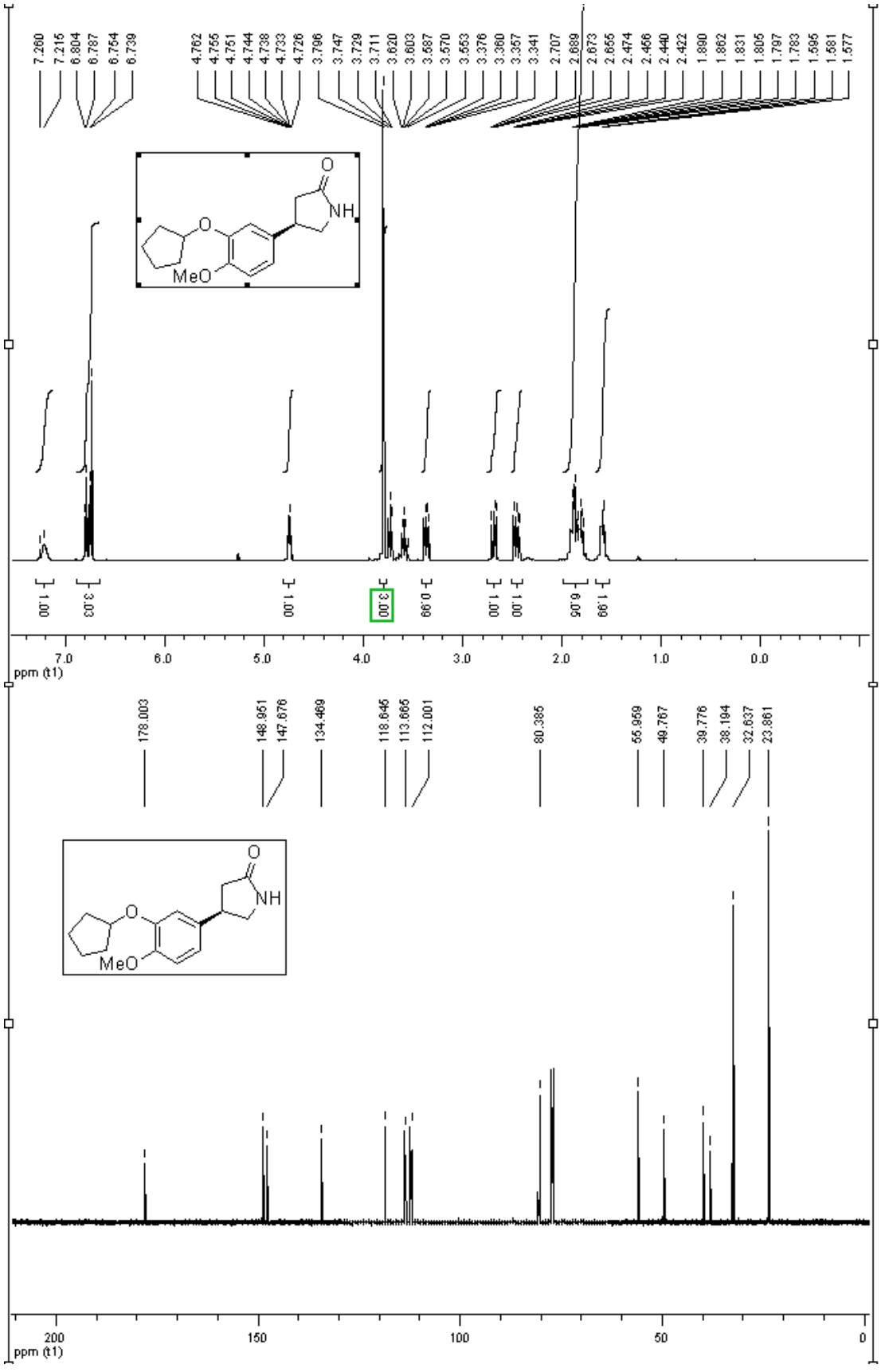
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  37.613 MM    3.9274 8.83683e4   375.00674  99.8373
   2  53.717 MM    1.7257  144.02629    1.39101   0.1627
```

4.4: (+)-Ethyl-(3*S*,4*R*)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-oxo pyrrolidine-3-carboxylate; 11



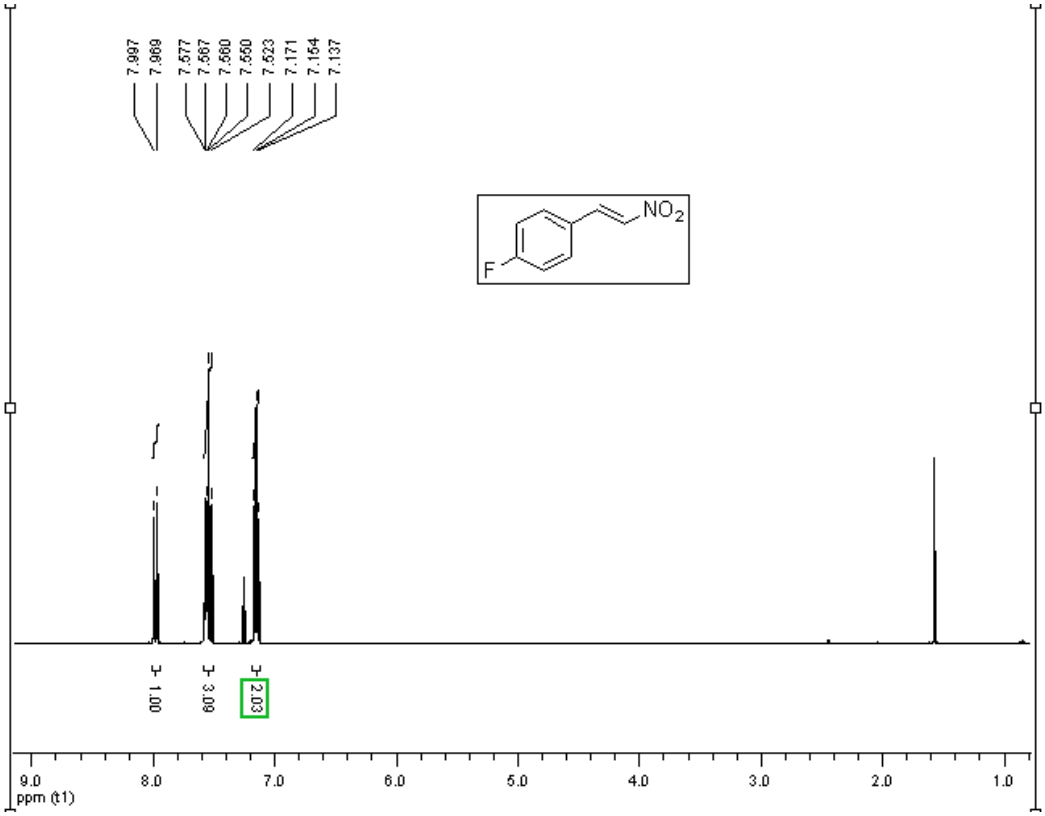


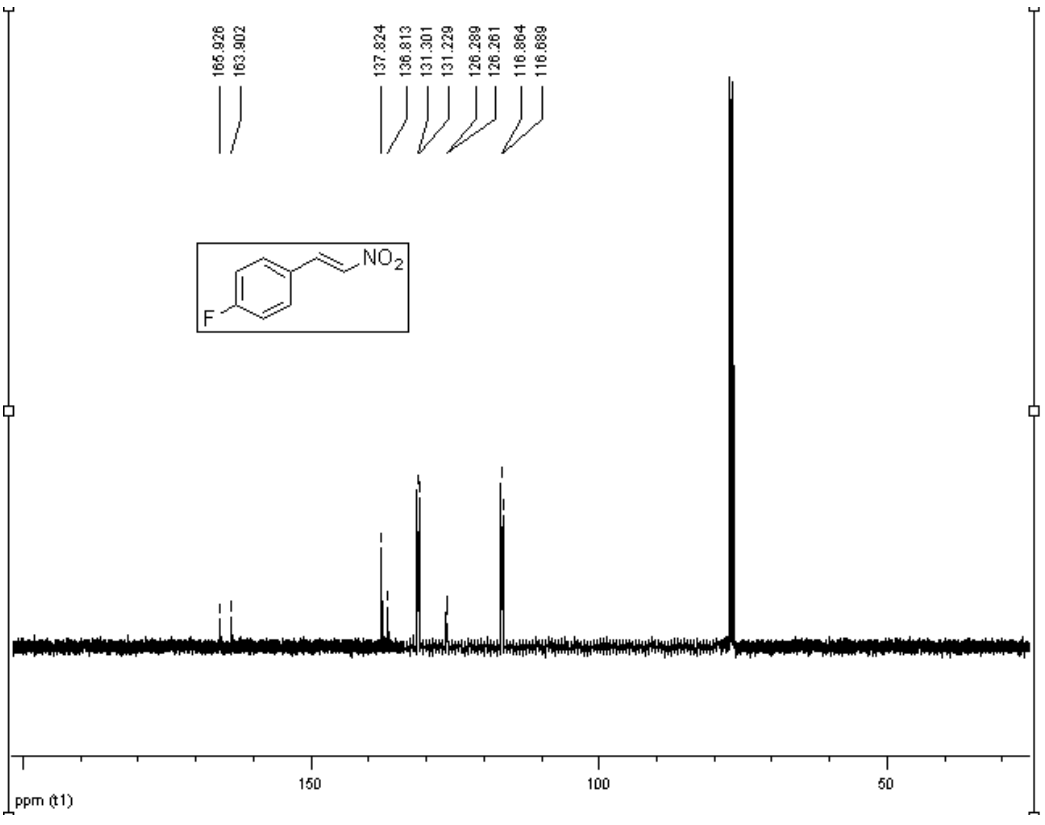
4.5: (4*R*)-4-[3-(Cyclopentyloxy)-4-methoxyphenyl]pyrrolidin-2-one; 1



Section 5: Spectra for formal synthesis of (3*S*,4*R*)-Paroxetine

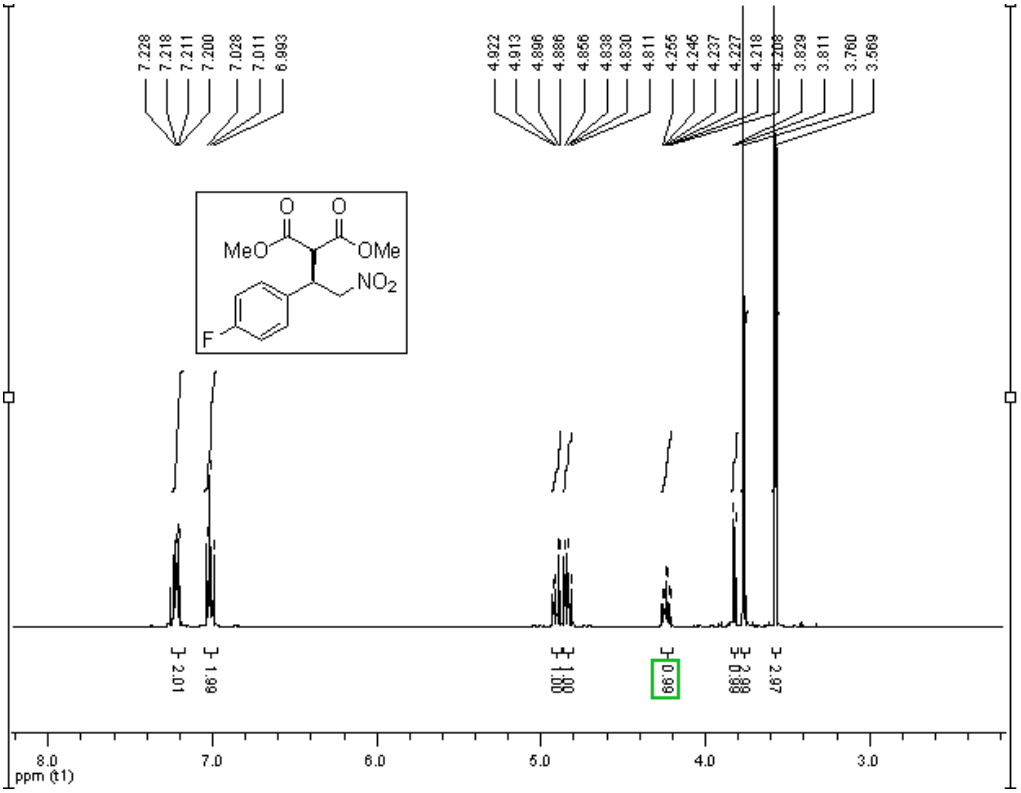
5.1: 1-Fluoro-4-[(*E*)-2-nitroethenyl]benzene; 13

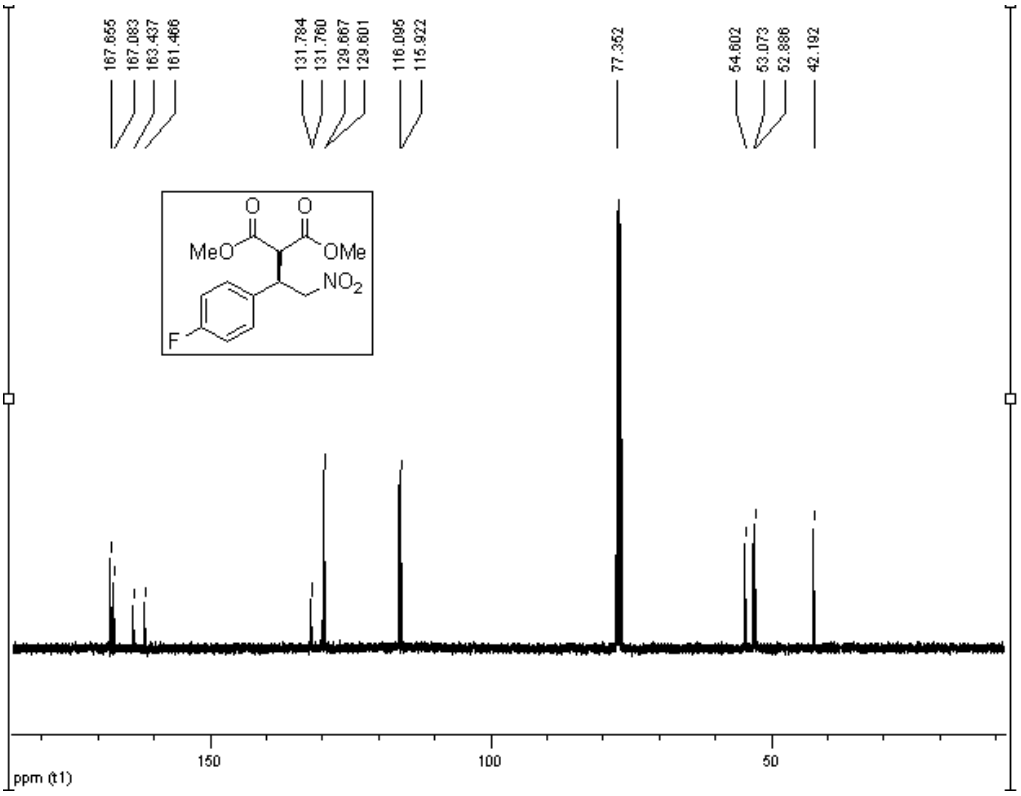




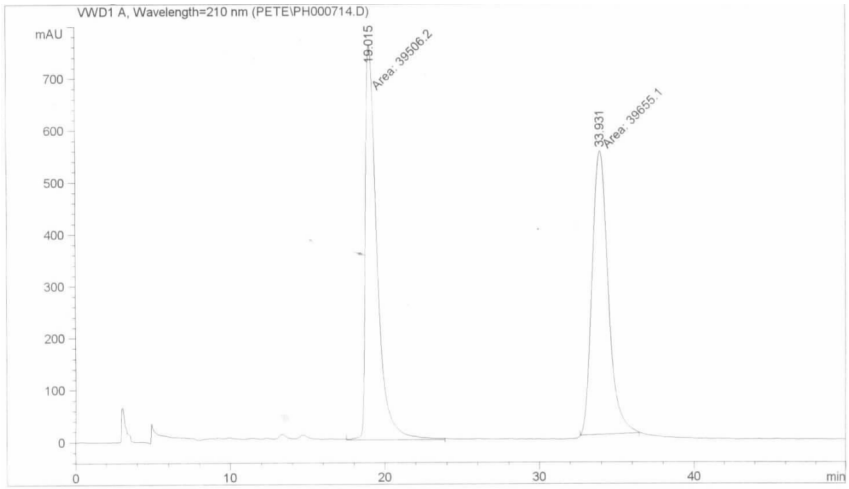
5.2: (–)-Dimethyl[(1*R*)-1-(4-fluorophenyl)-2-nitroethyl]propane dioate; 14

NMR; **14**





HPLC; **14**

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Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=210 nm

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  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.015 MM    0.8672 3.95062e4   759.24890  49.9059
   2  33.931 MM    1.2104 3.96551e4   546.03821  50.0941

Totals :                  7.91613e4  1305.28711
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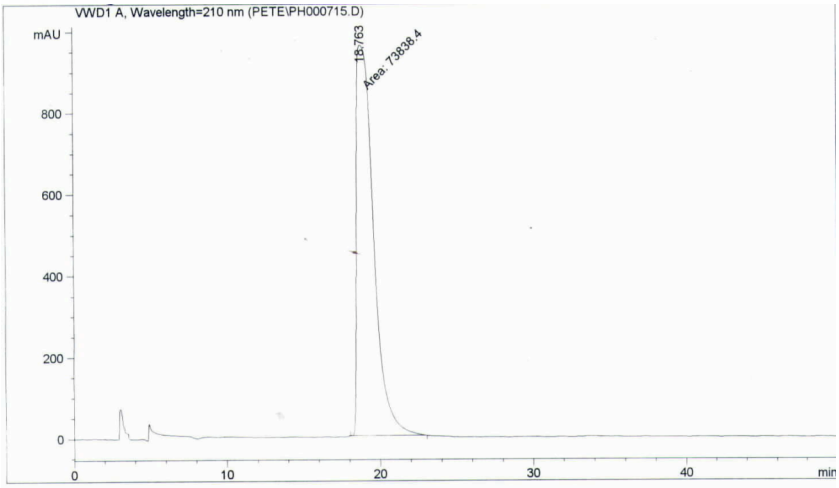


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

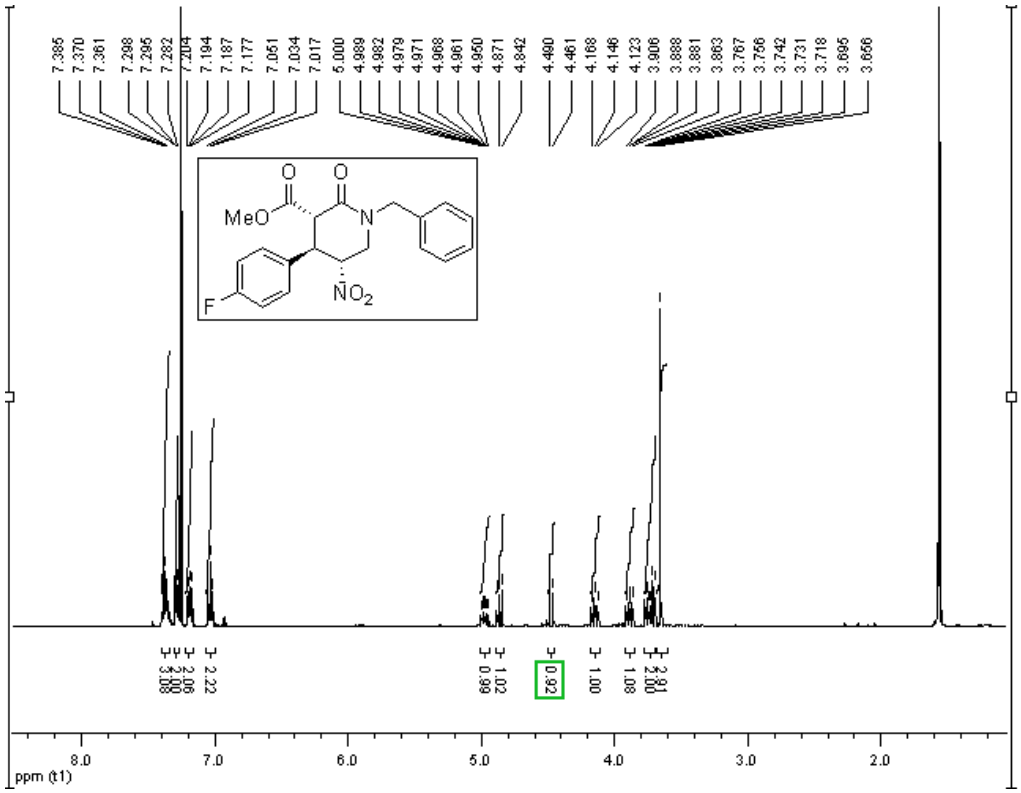
Signal 1: VWD1 A, Wavelength=210 nm

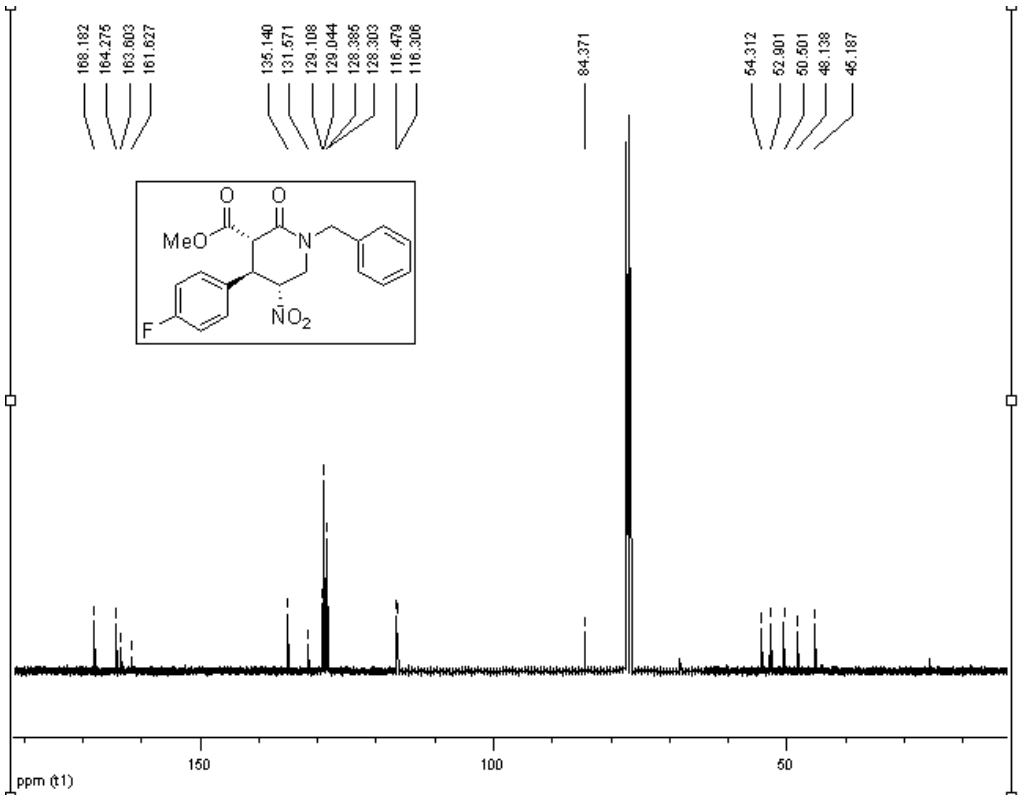
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.763 MM    1.2826 7.38384e4   959.45923 100.0000

Totals :                  7.38384e4   959.45923
```

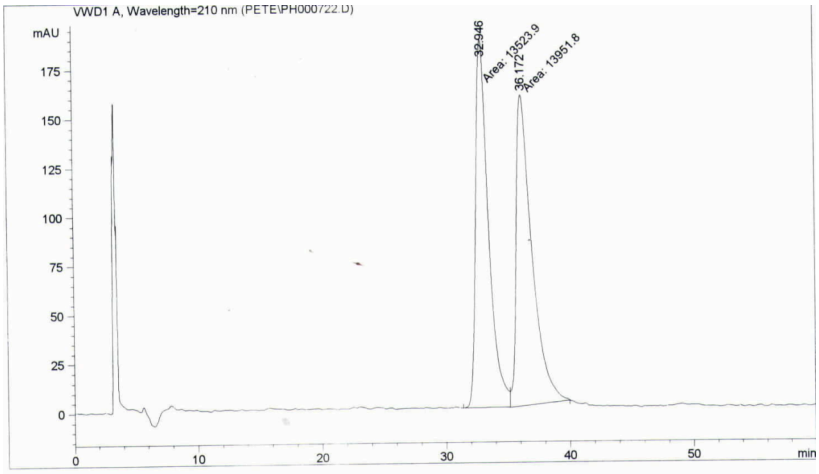
5.3: (+)-Methyl-(3*S*,4*R*,5*R*)-1-benzyl-4-(4-fluorophenyl)-5-nitro-2-oxopiperidine-3-carboxylate; 15

NMR; **15**





HPLC; **15**

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                          Area Percent Report
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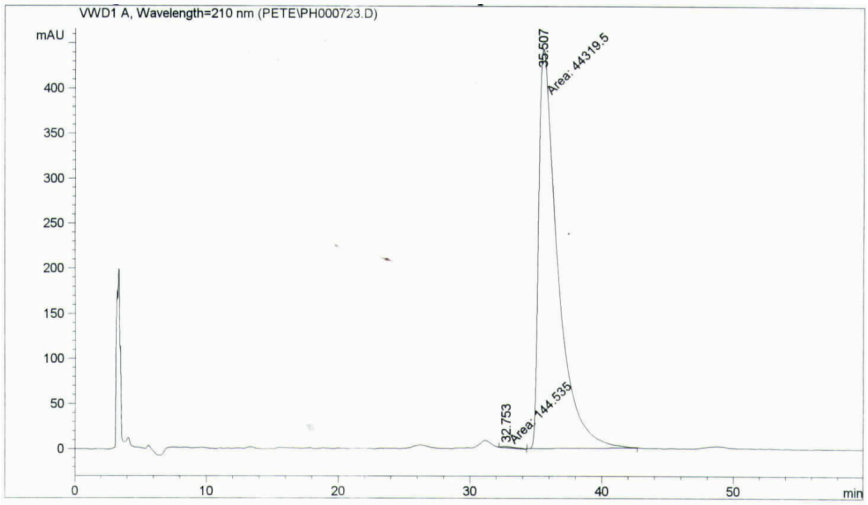
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  32.946 MM    1.2017 1.35239e4   187.56104  49.2213
   2  36.172 MM    1.4664 1.39518e4   158.57718  50.7787

Totals :                  2.74757e4   346.13821
```

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                          Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

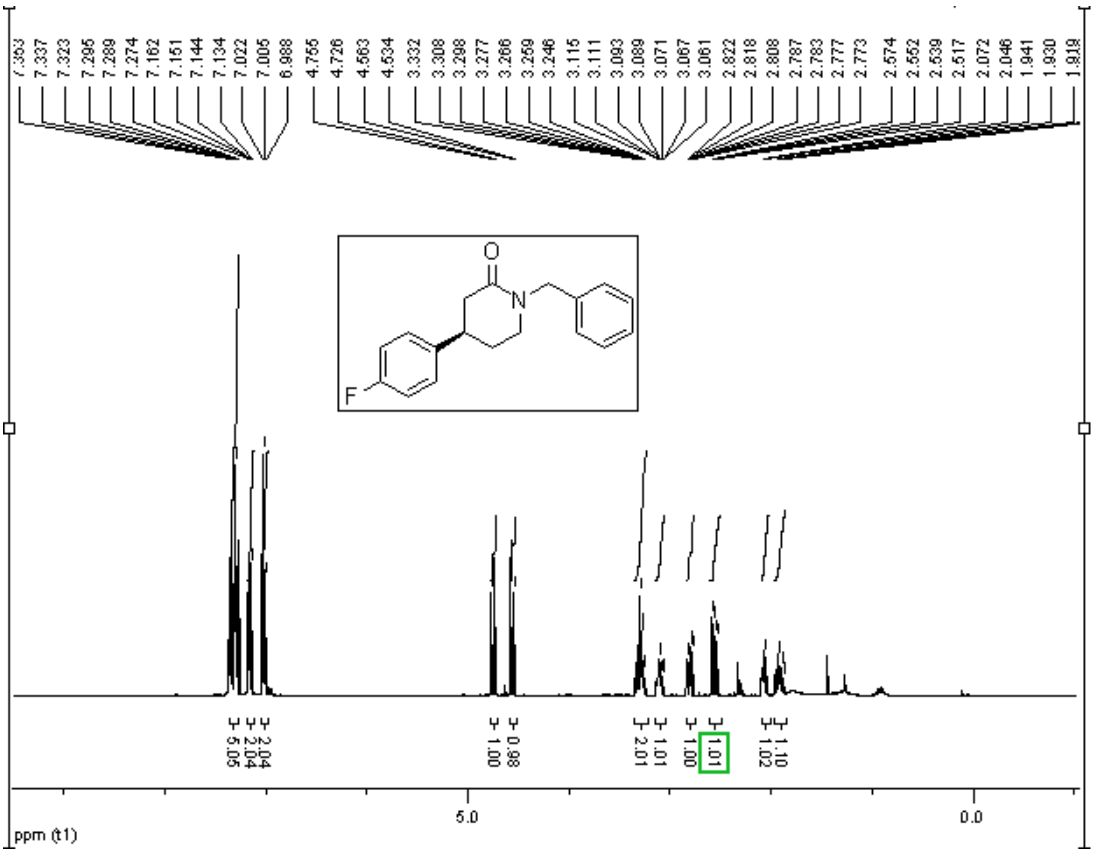
Signal 1: VWD1 A, Wavelength=210 nm

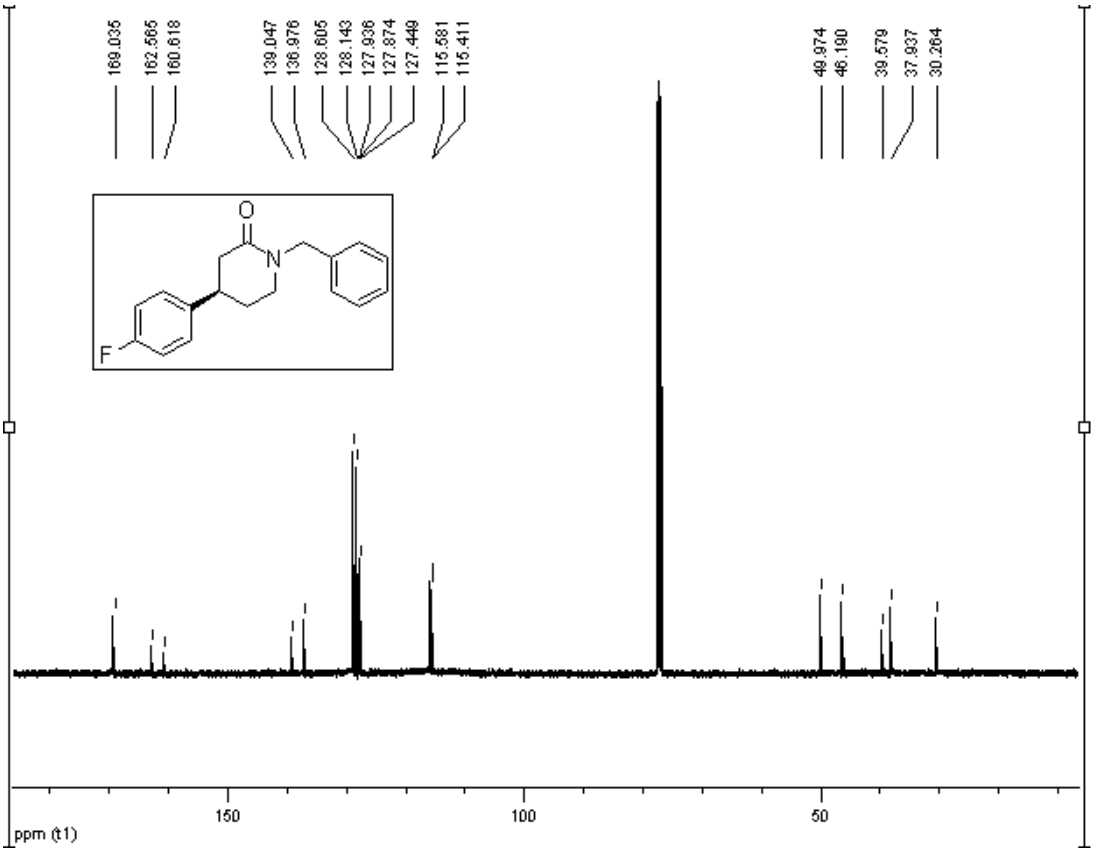
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  32.753 MM    1.3389  144.53526    1.79921   0.3251
   2  35.507 MM    1.6659 4.43195e4   443.40460  99.6749

Totals :                  4.44640e4   445.20381
```

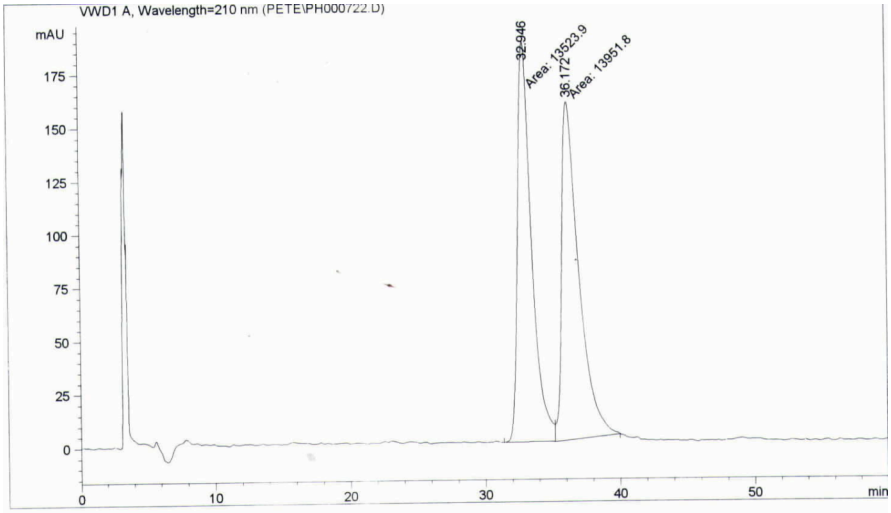
5.4: (4*R*)-1-Benzyl-4-(4-fluorophenyl)piperidin-2-one; 16

NMR; **16**





HPLC; **16**

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                          Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  32.946 MM    1.2017 1.35239e4   187.56104  49.2213
   2  36.172 MM    1.4664 1.39518e4   158.57718  50.7787

Totals :                  2.74757e4   346.13821
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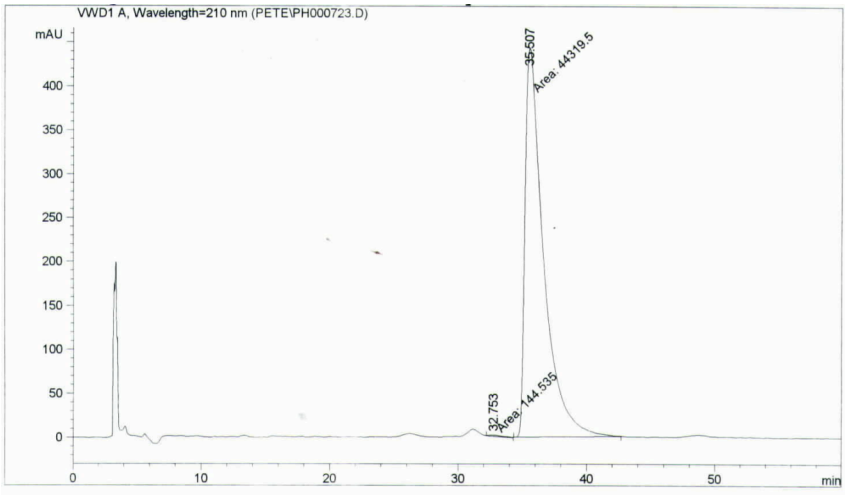


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                          Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  32.753 MM    1.3389  144.53526    1.79921   0.3251
   2  35.507 MM    1.6659 4.43195e4   443.40460  99.6749

Totals :                  4.44640e4   445.20381
```

Section 6: References

[1] Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, M. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097.

[2] Hawkins, L. D. *US Patent 4971959*, **1988**.

[3] Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148.

[4] Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Andersen, K. K.; Davis, G. T. *J. Am. Chem. Soc.* **1963**, *85*, 3146.

[5] Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.

[6] Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852.