Electronic Supplementary Material (ESI) for ChemComm.
This journal is © The Royal Society of Chemistry 2014

A Cation-Directed Two-Component Cascade Approach to Enantioenriched Pyrroloindolines

Table of Contents

1. General Information…… 2

2. Substrate Synthesis…… 3

2.1 Synthesis of Isocyanides…… 3

2.2 Synthesis of Michael Acceptors…… 23

3. Diastereoselective Reaction…… 34

4. Enantioselective Reaction…… 48

5. NMR Spectra…… 56

6. HPLC Traces…… 108

7. Assignment of Stereochemistry …… 116

8. Thermodynamic Product…… 117

9. X-ray Crystallography…… 118

1. General information

All NMR spectra were recorded on Bruker AV400, AV500 and DRX500 spectrometers. ^{1}H and ^{13}C NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to $CFCl_3$. The following abbreviations are used to describe multiplicities s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet, br = broad, m = multiplet. NMR spectra were processed in TopSpin 3.1. High resolution mass spectra (HRMS, *m*/*z*) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI), or on a Micromass GCT spectrometer using field ionization (EI/FI) or chemical ionization (CI). IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Absorptions are measured in wavenumbers and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were obtained using the ACD/ILab service. Weighing was performed with a 4-decimal place balance. All solvents were dried on a column of alumina prior to use.

2.1 Synthesis of Isocyanides

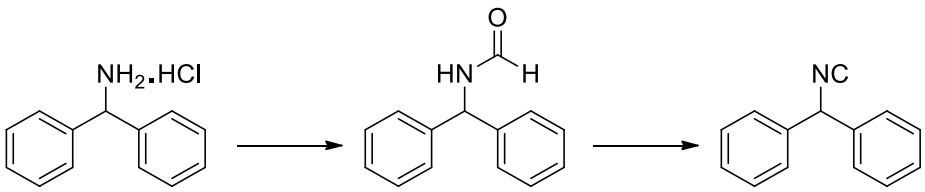
General Procedure A: To a solution of the relevant formamide (1.0 eq) in DCM (1.4 mL/mmol substrate) at 0 °C, triethylamine (2.5 eq) was added. $POCl_3$ (1.0 eq) was then added dropwise, and the reaction mixture was left to stir at 0 °C for 90 min. The reaction was quenched with 10% aqueous sodium carbonate solution and stirred for a further 10 min. The mixture was then diluted with water (5 mL/mmol substrate) and extracted with DCM (3 x 5 mL/mmol substrate). The organic phases were combined, dried over K_2CO_3 and concentrated *in vacuo*.

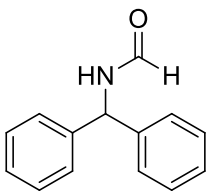
General procedure B: Methyl isocyanoacetate (1.0 eq) was dissolved in DMSO (6.0 mL/mmol substrate) at room temperature. Cesium carbonate (1.5 eq) was added, and the reaction mixture was stirred for 10 min. The relevant fluoronitrobenzene (1.3 eq) was added, and the mixture was stirred for 16 h at room temperature. The mixture was then diluted with water (10 mL/mmol substrate) and extracted with ethyl acetate (3 x 10 mL/mmol substrate). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

General Procedure C: Compounds were prepared by modification of a known procedure (Carney, D. W.; Truong, J. V; Sello, J. K. *J. Org. Chem.* **2011**, *76*, 10279–10285). *N,N'*-Dicyclohexylcarbodiimide (DCC) (1.3 mmol) was dissolved in DCM at 0 °C and formic acid (1.3 mmol) was added dropwise. Upon addition, a precipitate was formed and the reaction mixture was stirred for additional 10 min. The relevant amino acid methyl ester hydrochloride (1.0 mmol), 4-dimethylaminopyridine (DMAP) (0.2 mmol) and Et_3N (1.6 mmol) were added, and the mixture was stirred at room temperature overnight. The reaction was concentrated *in vacuo* and the residue was suspended in EtOAc, filtered through a short silica column and evaporated under reduced pressure. Crude formamide was

dissolved in THF at 0 °C under an argon atmosphere and Et_3N (5 mmol) was added. $POCl_3$ (1.5 mmol) was added dropwise over the course of 10 min and the reaction mixture was stirred for 2 hours. The reaction was quenched with 10 % Na_2CO_3 and was stirred for additional 10 min. The reaction mixture was diluted with EtOAc and washed with brine and water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Pure product was obtained by flash chromatography.

(Isocyanomethylene)dibenzene





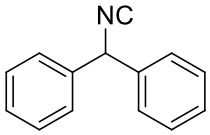
To a suspension of diphenylmethanamine hydrochloride (2.20 g, 10.0 mmol) in ethyl formate (30 mL), triethylamine (2.79 mL, 20.0 mmol) and DMAP (100 mg, 0.819 mmol) were added. The reaction mixture was stirred at 50 °C for 48 h. The mixture was then diluted with ethyl acetate (50 mL) and washed with 1 M hydrochloric acid solution (2 x 50 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford *N*-benzhydrylformamide as a white solid (2.10 g, 99%), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s), 7.39-7.24 (10H, m), 6.52 (1H, br s), 6.34 (1H, d, *J* 8.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 140.9, 128.8, 127.7, 127.4, 55.7.

m.p. 132-133 °C (lit. 135 °C).

Data in accordance with literature (M. Vamos, K. Welsh, D. Finlay, P. S. Lee, P. D. Mace, S. J. Snipas, M. L. Gonzalez, S. R. Ganji, R. J. Ardecky, S. J. Riedl, G. S. Salvesen, K. Vuori, J. C. Reed, N. D. P. Cosford, ACS Chem. Biol. ***2013****, 8, 725).*



This compound was prepared according to general procedure A, using *N*-benzhydrylformamide (1.00 g, 4.74 mmol). Column chromatography (petrol:ethyl acetate [19:1]) afforded the title compound as a white solid (871 mg, 95%).

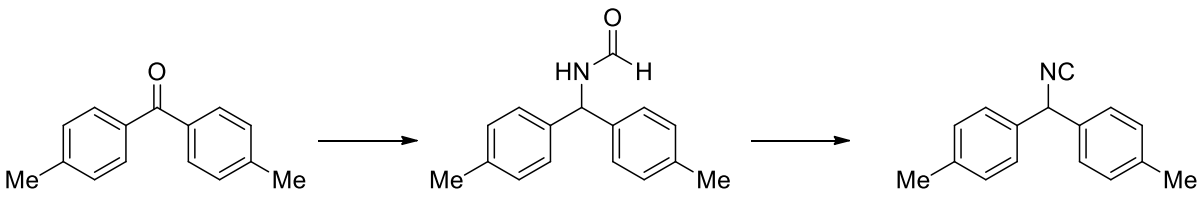
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.34 (10H, m), 5.94 (1H, s).

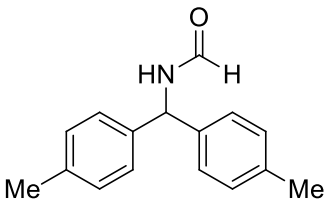
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 137.6, 129.0, 128.5, 126.6, 62.0 (t, *J* 6.6).

m.p. 46-47 °C.

Data in accordance with literature (M. Vamos, K. Welsh, D. Finlay, P. S. Lee, P. D. Mace, S. J. Snipas, M. L. Gonzalez, S. R. Ganji, R. J. Ardecky, S. J. Riedl, G. S. Salvesen, K. Vuori, J. C. Reed, N. D. P. Cosford, ACS Chem. Biol. ***2013****, 8, 725).*

4,4'-(Isocyanomethylene)bis(methylbenzene)





To a solution of di-*p*-tolylmethanone (5.00 g, 23.8 mmol) in formamide (4.73 mL, 119 mmol), formic acid (1.12 mL, 29.7 mmol) was added, and

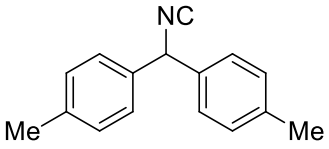
the reaction was stirred at 170 °C for 12 h. The reaction mixture was then allowed to cool to room temperature and dissolved in ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Recrystallisation from chloroform/hexanes afforded *N*-(di-*p*-tolylmethyl)formamide as a colourless solid (5.57 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, s), 7.21-7.11 (8H, m), 6.62 (1H, d, *J* 7.7, N*H*), 6.25 (1H, d, *J* 8.3), 2.36 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 138.3, 137.2, 129.4, 127.3, 55.2, 21.1.

m.p. 117-118 °C (lit. 113-114 °C).

Data in accordance with literature (A. A. Bakibaev, L. G. Tignibidina, V. D. Filimonov, A. V. Pustovoitov, V. K. Gorshkova, A. S. Saratikov, V. A. Krasnov, Pharmaceutical Chemistry Journal, ***1989****, 23 (12), 978-982).*



This compound was prepared according to general procedure A, using *N*-(di-*p*-tolylmethyl)formamide (1.00 g, 4.18 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a white solid (630 mg, 68%).

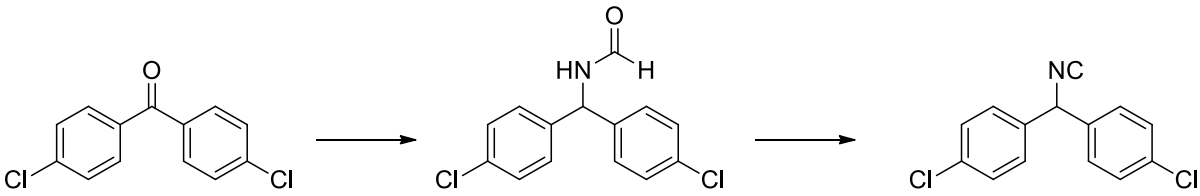
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (4H, d, *J* 8.0), 7.16 (4H, d, *J* 8.0), 5.83 (1H, s), 2.33 (6H, s).

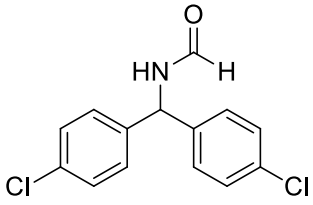
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 138.3, 135.0, 129.6, 126.5, 61.6 (t, *J* 6.3), 21.1.

m.p. 53-54 °C (lit. 57-58 °C).

Data in accordance with literature (L. B. Engemyr, A. Martinsen, J. Songstad, Acta Chemica Scandinavica A ***1974****, 255-266).*

4,4'-(Isocyanomethylene)bis(chlorobenzene)





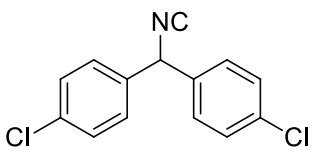
To a solution of bis(4-chlorophenyl)methanone (5.00 g, 19.9 mmol) in formamide (3.95 mL, 99.5 mmol), formic acid (938 µL, 24.9 mmol) was added, and the reaction was stirred at 170 °C for 12 h. The reaction mixture was then allowed to cool to room temperature and dissolved in ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Recrystallisation from chloroform/hexanes afforded *N*-(bis(4-chlorophenyl)methyl)formamide as a colourless solid (3.85 g, 69%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (1H, d, *J* 8.5, N*H*), 8.19 (1H, s), 7.42 (4H, d, *J* 8.4), 7.32 (4H, d, *J* 8.4), 6.23 (1H, d, *J* 8.7).

^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8, 141.2, 132.4, 129.5, 129.0, 53.8.

m.p. 129-131 °C (lit. 125-126 °C).

Data in accordance with literature (A. A. Bakibaev, L. G. Tignibidina, V. D. Filimonov, A. V. Pustovoitov, V. K. Gorshkova, A. S. Saratikov, V. A. Krasnov, Pharmaceutical Chemistry Journal ***1989****, 23 (12), 978-982).*



This compound was prepared according to general procedure A, using *N*-(bis(4-chlorophenyl)methyl)formamide (1.00 g, 3.57 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title

compound as a white solid (851 mg, 91%).

IR (neat) ν_{max} 2974, 2151, 1128, 875 cm^{-1}.

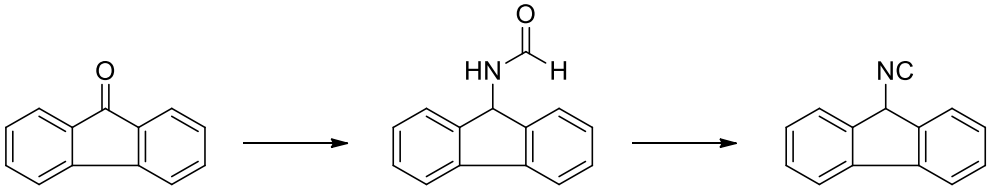
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (4H, d, *J* 8.4), 7.27 (4H, d, *J* 8.4), 5.86 (1H, s).

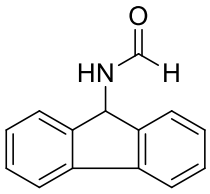
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 135.6, 134.8, 129.3, 128.0, 60.7 (t, *J* 5.1).

m/z HRMS (ESI^+) 284.0012 ($[M+Na]^+$, $C_{14}H_9Cl_2NNa$ requires 284.0004).

m.p. 78-81 °C.

9-Isocyano-9*H*-fluorene





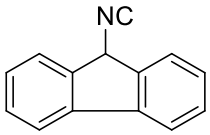
To a solution of 9-fluorenone (5.00 g, 27.7 mmol) in formamide (11.0 mL, 227 mmol), formic acid (1.31 mL, 34.7 mmol) was added, and the reaction was stirred at 170 °C for 12 h. The reaction was then removed from the heat source and solidified after 1 minute. The resulting solid was dissolved in hot ethyl acetate (500 mL), washed with brine (2 x 100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Recrystallisation from ethyl acetate afforded *N*-(9*H*-fluoren-9-yl)formamide as a white solid (2.03 g, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, s), 7.71 (2H, d, *J* 7.5), 7.59 (2H, dd, *J* 7.4, 0.6), 7.43 (2H, t, *J* 7.4), 7.34 (2H, td, *J* 7.4, 1.1), 6.30 (1H, d, *J* 9.0), 5.88 (1H, br s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 143.7, 140.7, 128.9, 127.9, 125.1, 120.1, 53.3.

m.p. 191-194 °C (lit. 209 °C).

Data in accordance with literature (R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Speck, R. V. A. Orru, Org. Lett. ***2003****, 5, 3759).*



To a solution of *N*-(9*H*-fluoren-9-yl)formamide (350 mg, 1.67 mmol) in THF (2 mL) at -78 °C, triethylamine (1.2 mL, 8.37 mmol) was added, followed by $POCl_3$ (172 µL, 1.85 mmol) as a solution in THF (2 mL). The reaction mixture was allowed to warm to RT and stirred for 1 h, before ice water (40 mL) was added. The reaction was then extracted into ether, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a yellow solid (275 mg, 86%).

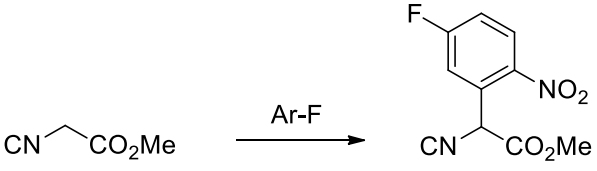
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.70 (4H, m), 7.49 (2H, t, *J* 7.4), 7.41 (2H, td, *J* 7.5, 1.0), 5.64 (1H, s).

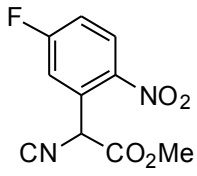
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 140.2, 139.6, 129.8, 128.3, 124.9, 120.4, 56.8 (t, *J* 6.8).

m.p. 92-94 °C (lit. 87-91 °C).

Data in accordance with literature (R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Speck, R. V. A. Orru, Org. Lett. ***2003****, 5, 3759).*

Methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (23)





Prepared according to general procedure B using methyl 2-isocyanoacetate (832 µL, 9.15 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **23** as yellow oil (1.35 g, 62%).

ν_{max} (neat): 2960, 2148, 1758, 1594, 1532, 1348, 1231, 752 cm^{-1}.

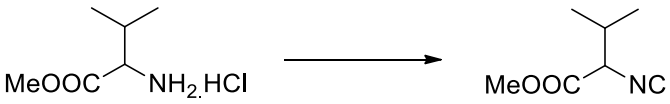
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.28 (1H, m), 7.65-7.57 (1H, m), 7.34 (1H, ddd, *J* 12.3, 7.5, 4.1), 6.44 (1H, s), 3.89 (3H, s).

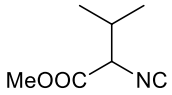
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 164.2, 164.1, 143.0, 130.3 (d, *J* 9.0), 128.9 (d, *J* 10.0), 117.6 (d, *J* 23.0), 116.9 (d, *J* 26.3), 57.3, 54.4.

^{19}F NMR (377 MHz, $CDCl_3$, $\{^{1}H\}$) δ -99.5.

HRMS (ESI): found 261.0270; $C_{10}H_7FN_2NaO_4$ $[M+Na^+]$ requires 261.0282.

Methyl 2-isocyano-3-methylbutanoate





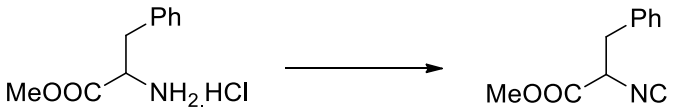
Prepared according to general procedure C using valine methyl ester hydrochloride (1.00 g, 5.95 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound as a colourless oil (570 mg, 68%).

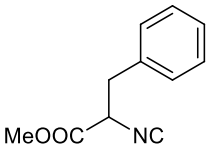
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1H, d, *J* 4.2), 3.76 (3H, s), 2.35-2.19 (1H, m), 1.04 (3H, d, *J* 6.8), 0.94 (3H, d, *J* 6.7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 160.5, 62.9, 53.2, 31.2, 19.3, 16.7.

*Data in accordance with literature (P. C. J. Kamer, M. C. Cleij, R. J. M. Nolte, T. Harada, A. M. F. Hezemans, W. Drenth; J. Am. Chem. Soc., **1988**, 110, 1581–1587).*

Methyl 2-isocyano-3-phenylpropanoate





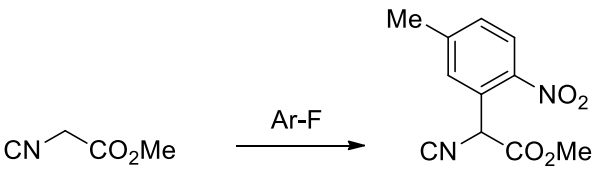
Prepared according to general procedure C using phenylalanine methyl ester hydrochloride (910 mg, 4.21 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound as a colourless oil (581 mg, 73%).

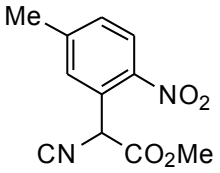
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.15 (5H, m), 4.39 (1H, dd, *J* 8.3, 4.8), 3.72 (3H, s), 3.19 (1H, dd, *J* 13.9, 4.8), 3.07 (1H, dd, *J* 13.8, 8.4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 161.0, 134.4, 129.3, 128.9, 127.9, 58.0, 53.4, 38.9.

*Data in accordance with literature (D. W. Carney, J. V. Truong, J. K. Sello; J. Org. Chem. **2011**, 76 (24), 10279-10285).*

Methyl 2-isocyano-2-(5-methyl-2-nitrophenyl)acetate





Prepared according to general procedure B using methyl 2-isocyanoacetate (909 µL, 10.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as yellow oil (1.51 g, 65 % yield).

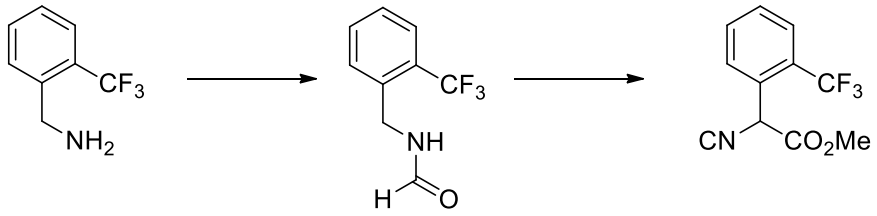
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, d, *J* 8.4), 7.64 (1H, s), 7.44 (1H, dd, *J* 8.4, 1.0), 6.41 (1H, s), 3.86 (3H, s), 2.56 (3H, s).

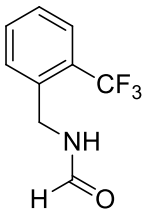
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 162.9, 146.3, 144.7, 131.1, 129.8, 126.7, 126.0, 57.3, 54.1, 21.7.

ν_{max} (neat): 2977, 2154, 1729, 1589, 1538, 1354, 1231, 827 cm^{-1}.

HRMS (ESI): found 257.0538; $C_{11}H_{10}N_2NaO_4$ [M+Na^+] requires 257.0533.

Methyl 2-isocyano-2-(2-(trifluoromethyl)phenyl)acetate





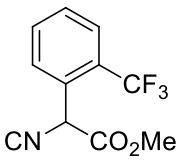
To a solution of (2-(trifluoromethyl)phenyl)methanamine (1.20 g, 6.85 mmol) in ethyl formate (5.0 mL), triethylamine (1.10 mL, 7.54 mmol) was added, and the reaction mixture was stirred and heated to reflux for 48 h. The mixture was then allowed to cool to room temperature and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [1:1]) afforded *N*-(2-(trifluoromethyl)benzyl)formamide as a colourless oil (715 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s), 7.67 (1H, d, *J* 7.9), 7.62-7.52 (2H, m), 7.42 (1H, t, *J* 7.4), 6.19 (1H, br s), 4.67 (2H, d, *J* 6.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 136.0 (q, *J* 2.5), 132.4, 130.9, 128.2 (q, *J* 30.4), 127.8, 126.0 (q, *J* 5.7), 124.5 (q, *J* 273.1), 38.7 (q, *J* 2.1).

^{19}F NMR (377 MHz, $CDCl_3$) δ -59.4 (m).

Data in accordance with literature (Kolycheva, M. T.; Gerus, I. I.; Kukhar, V. P. Journal of Organic Chemistry USSR (English Translation, ***1989****, 25, 2134-2138).*



To a solution of *N*-(2-(trifluoromethyl)benzyl)formamide (700 mg, 3.29 mmol) in DCM (4 mL) at 0 °C, Et_3N (1.14 mL, 8.22 mmol) was added, and then $POCl_3$ (307 µL, 3.29 mmol) dropwise. The reaction was stirred for 90 min. Saturated sodium carbonate solution (5 mL) was then added and stirring was continued for 30 min, before water (8 mL) was added. The aqueous phase was extracted with DCM and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was then dissolved in THF (10 mL) and cooled to -78 °C, before the dropwise addition of LiHMDS (1.21 g, 7.24 mmol) in toluene (7.2 mL). The reaction mixture was left to stir at -78 °C for 1h, after which dimethyl carbonate (332 µL, 3.95 mmol) was added and the reaction was allowed to warm to room temperature. The crude mixture was concentrated *in vacuo*, before the residue was diluted with ethyl acetate (35 mL) and washed with saturated aqueous ammonium chloride solution (35 mL), brine (35 mL) and water (35 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a brown oil (267 mg, 33%).

IR (neat) ν_{max} 3025, 2157, 1612, 1487, 1046 cm^{-1}.

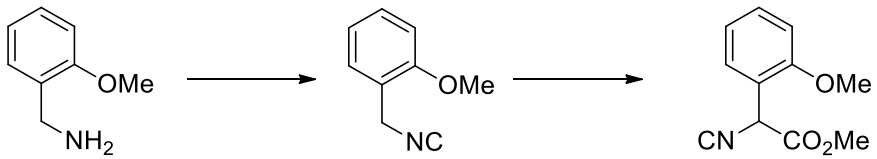
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* 7.6), 7.77 (1H, d, *J* 7.6), 7.71 (1H, t, *J* 7.6), 7.59 (1H, t, *J* 7.6), 5.78 (1H, s), 3.84 (3H, s).

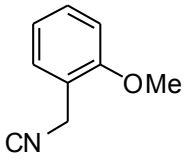
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 161.6, 133.1, 130.8, 130.0, 129.1, 128.2 (q, *J* 31.3), 126.5 (q, *J* 5.4), 123.6 (q, *J* 273.2), 55.8, 54.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -58.4 (m).

m/z HRMS (ESI^+) 266.0398 ($[M+Na]^+$, $C_{11}H_8F_3NO_2Na$ requires 266.0399).

Methyl 2-isocyano-2-(2-methoxyphenyl)acetate





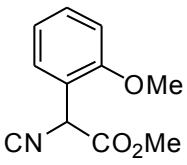
(2-Methoxyphenyl)methanamine (1.31 mL, 10.0 mmol) was dissolved in formic acid (20 mL) at room temperature. Acetic anhydride (1.42 mL, 15.0 mmol) was added dropwise over 2 h, and the mixture was stirred for 16 h. The crude mixture was concentrated *in vacuo*, and the residue was then dissolved in ethyl acetate (20 mL) and filtered through a short silica column. Under an atmosphere of argon, the mixture was dissolved in THF (20 mL) and cooled to 0 °C. Triethylamine (7.00 mL, 50.0 mmol) was added, and then $POCl_3$ (1.40 mL, 15.0 mmol) was added dropwise over 10 min. The reaction mixture left to stir at 0 °C. After 2 h, the reaction was quenched with 10% aqueous sodium carbonate solution, and stirred for a further 10 min. The mixture was concentrated *in vacuo*, before column chromatography (petrol:ethyl acetate [8:1]) afforded 1-(isocyanomethyl)-2-methoxybenzene as a colourless oil (1.07 g, 73%).

IR (neat) ν_{max} 2150, 1604, 1495, 1464, 1249, 1113, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* 7.5), 7.41-7.35 (1H, m), 7.05 (1H, app. t, *J* 7.5), 6.93 (1H, d, *J* 8.2), 4.66 (2H, s), 3.88 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 156.3, 129.7, 127.7, 120.8, 120.7, 110.3, 55.4, 41.2.

HRMS (ESI$^+$) 170.0575 ([M+Na]$^+$, C_9H_9NONa requires 170.0582).



1-(Isocyanomethyl)-2-methoxybenzene (200 mg, 1.36 mmol) was dissolved in THF (5.5 mL) at -78 °C. LiHMDS (502 mg, 3.00 mmol) in THF (3.0 mL) was added dropwise over 10 min, and the reaction mixture was left to stir at -78 °C. After 1 h dimethyl carbonate (137 µL, 1.63 mmol) was added, and the reaction was allowed to warm to room temperature. The crude mixture was concentrated *in vacuo*, before the residue was diluted with ethyl acetate (15 mL) and washed with saturated aqueous ammonium chloride solution (15 mL), brine (15 mL) and water (15 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound as a light yellow oil (170 mg, 61%).

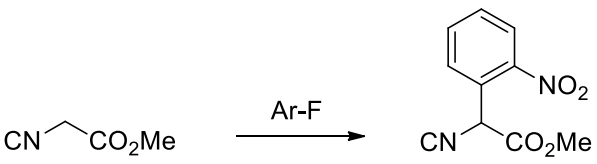
IR (neat) ν_{max} 3027, 2151, 1602, 1495, 1030, 726 cm^{-1}.

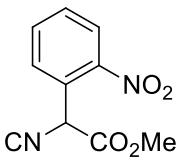
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.37 (2H, m), 7.04 (1H, app. t, *J* 7.5), 6.96 (1H, d, *J* 8.3), 5.76 (1H, s), 3.89 (3H, s), 3.80 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 159.7, 156.2, 131.4, 128.3, 121.2, 121.1, 111.3, 55.9, 54.8, 53.6.

HRMS (ESI$^+$) 228.0630 ([M+Na]$^+$, $C_{11}H_{11}NO_3Na$ requires 228.0637).

Methyl 2-isocyano-2-(2-nitrophenyl)acetate





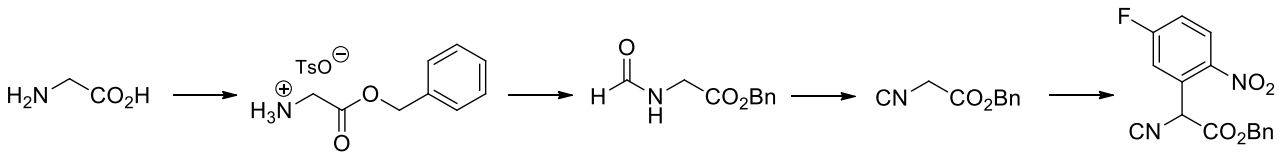
Prepared according to general procedure B, using 1-fluoro-2-nitrobenzene (1.37 mL, 13.0 mmol). Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound as a brown oil (1.29 g, 58%).

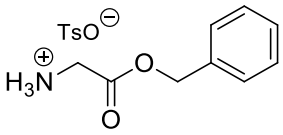
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, dd, *J* 8.2, 1.2), 7.89 (1H, dd, *J* 7.8, 1.4), 7.83 (1H, td, *J* 7.8, 1.3), 7.68 (1H, ddd, *J* 8.1, 7.5, 1.5), 6.42 (1H, s), 3.87 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 163.2, 147.0, 134.6, 130.7, 129.3, 126.8, 125.8, 57.2, 54.2.

Data in accordance with literature (T. Buyck, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. ***2013****, 52, 12714).*

Benzyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate





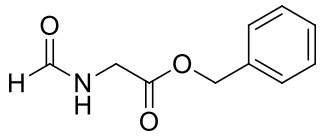
To a suspension of glycine (1.20 g, 16.0 mmol) in benzyl alcohol (32 mL), tosylic acid (2.74 g, 16.0 mmol) was added. The reaction was stirred at 80 °C, before tosyl chloride (3.43 g, 18.0 mmol) was added portionwise. Stirring was continued at 80 °C for 2 h before cooling to room temperature. Ether was then carefully added until precipitation was witnessed, at which point the flask was placed in a freezer for 24 h. The resultant solid was filtered and recrystallised from ethanol/ether to afford 2-(benzyloxy)-2-oxoethanaminium tosylate as a white solid (2.24 g, 41%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (3H, br s), 7.50 (2H, d, *J* 7.8), 7.46-7.35 (5H, m), 7.13 (2H, d, *J* 7.8), 5.25 (2H, s), 3.92 (2H, s), 2.30 (3H, s).

^{13}C NMR (101 MHz, DMSO-d_6) δ 168.1, 146.1, 138.2, 135.7, 129.0, 128.9, 128.7, 128.6, 126.0, 67.3, 40.2, 21.3.

m.p. 132-133 °C (lit. 131-133 °C).

Data in accordance with literature (D.H. Burns, C.S. Jabara, M.W. Burden, Synthetic Communications ***1995****, 25, 379-387).*

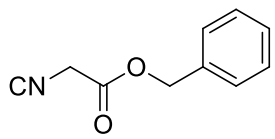


To a suspension of 2-(benzyloxy)-2-oxoethanaminium tosylate (930 mg, 2.76 mmol) in ethyl formate (2.5 mL), triethylamine (423 µL, 3.03 mmol) was added, and the reaction mixture was stirred and heated to reflux for 48 h. The mixture was then allowed to cool to room temperature and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [1:1]) afforded benzyl 2-formamidoacetate as a colourless oil (416 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, s), 7.42-7.34 (5H, m), 6.39 (1H, br s), 5.23 (2H, s), 4.15 (2H, d, *J* 5.4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 161.2, 135.0, 128.7, 128.7, 128.5, 67.4, 40.0.

Data in accordance with literature (C. L. Allen, B. N. Atkinson, J. M. J. Williams, Angew. Chem. Int. Ed. ***2012****, 51, 1383).*



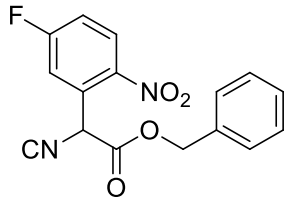
Prepared according to general procedure A using benzyl 2-formamidoacetate (400 mg, 2.07 mmol). The crude compound (368 mg,

99%) was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (5H, m), 5.26 (2H, s), 4.27 (2H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 161.6, 134.4, 129.0, 128.8, 128.7, 68.4, 43.6.

Data in accordance with literature (D. H. Burns, C. S. Jabora, M. W. Burden, Synth. Commun. ***1995****, 25, 379).*



Prepared according to general procedure B using benzyl 2-isocyanoacetate (365 mg, 2.08 mmol). Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound as a brown oil (430 mg, 66%).

IR (neat) ν_{max} 3006, 2152, 1594, 1342, 1277, 1210, 978 cm^{-1}.

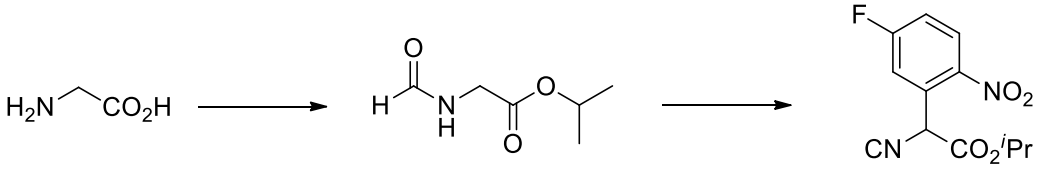
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, dd, *J* 9.2, 5.0), 7.57 (1H, dd, *J* 8.7, 2.7), 7.41-7.28 (6H, m), 6.45 (1H, s), 5.26 (2H, s).

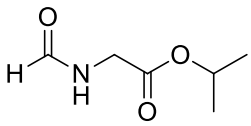
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (d, *J* 261.0), 164.1, 164.1 (d, *J* 2.0), 163.4, 134.0, 130.3 (d, *J* 9.1), 129.0, 128.9 (d, *J* 10.3), 128.8, 128.4, 117.5 (d, *J* 23.0), 116.8 (d, *J* 26.0), 69.4, 57.5.

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ -99.6.

m/z HRMS (ESI^+) 337.0599 ($[M+Na]^+$, $C_{16}H_{11}F_2N_2O_4Na$ requires 337.0595).

Isopropyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate





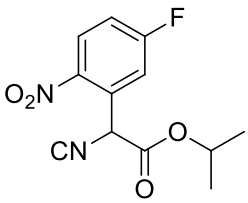
To a solution of glycine (2.40 g, 32.0 mmol) in isopropyl alcohol (50 mL), thionyl chloride (4.60 mL, 64.0 mmol) was added, and the reaction was heated at reflux for 12 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo* to furnish a sticky oil. The crude residue was suspended in ethyl formate (21 mL), and triethylamine (4.9 mL, 35.0 mmol) was then added. The reaction was heated at reflux for 48 h, before cooling to room temperature and concentrating *in vacuo*. Column chromatography (petrol:ethyl acetate [1:1]) afforded isopropyl 2-formamidoacetate as a colourless oil (4.07 g, 88%).

IR (neat) v_{max} 3348, 2989, 1726, 1579, 1202, 1116, 1037 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, s), 6.48 (1H, br s), 5.06 (1H, sept, *J* 6.3), 4.02 (2H, dd, *J* 5.4, 0.8), 1.25 (6H, d, *J* 6.3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 161.2, 69.6, 40.2, 21.7.

m/z HRMS (ESI^+) 168.0639 ($[M+Na]^+$, $C_6H_{11}F_3NO_3Na$ requires 168.0631).



To a solution of isopropyl 2-formamidoacetate (2.00 g, 13.8 mmol) in DCM (15 mL) at 0 °C, triethylamine (4.90 mL, 34.5 mmol) was added, and then $POCl_3$ (1.29 mL, 13.8 mmol) dropwise. The reaction mixture was stirred for 90 min. Saturated sodium carbonate solution (21 mL) was then added and stirring was continued for 30 min, before water (35 mL) was added. The aqueous phase was extracted with DCM and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was then dissolved in DMSO (70 mL) at room temperature. Cesium carbonate (6.7 g, 20.7 mmol) was added, and the mixture was stirred for 10 min. 2,4-Difluoronitrobenzene (1.97 mL, 18.0 mmol) was added dropwise, and the reaction was stirred for 24 hours. The mixture was then diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic phases were combined, dried over anhydrous $MgSO_4$

and concentrated *in vacuo*, before column chromatography (petrol:ethyl acetate [9:1]) afforded isopropyl isocyanoacetate as a brown oil (808 mg, 22%).

IR (neat) ν_{max} 2981, 2152, 1778, 1591, 1541, 1345, 1229, 857 cm^{-1}.

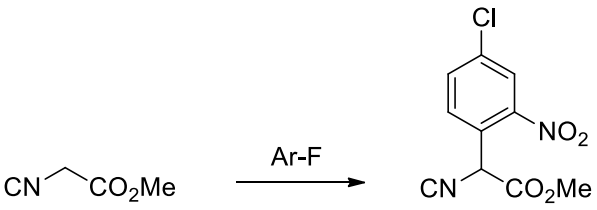
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, dd, *J* 9.2, 5.0), 7.59 (1H, dd, *J* 8.9, 2.8), 7.31 (1H, ddd, *J* 9.1, 6.9, 2.7), 6.36 (1H, s), 5.09 (1H, sept, *J* 6.2), 1.31 (3H, d, *J* 6.2), 1.27 (3H, d, *J* 6.2).

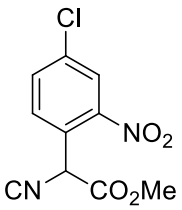
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (d, *J* 260.4), 163.8, 163.0, 130.5 (d, *J* 9.1), 128.8 (d, *J* 9.9), 117.4 (d, *J* 22.7), 116.7 (d, *J* 26.3), 72.4, 57.8, 21.4, 21.3.

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ -99.5.

m/z HRMS (ESI^+) 289.0598 ($[M+Na]^+$, $C_{12}H_{11}FN_2O_4Na$ requires 289.0595).

Methyl 2-(4-chloro-2-nitrophenyl)-2-isocyanoacetate





This compound was prepared according to general procedure B, using 5-chloro-2-fluoronitrotoluene (1.53 mL, 13.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a brown oil (1.78 g, 70%).

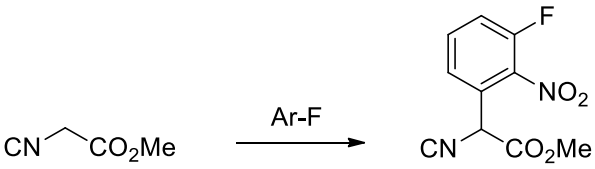
IR (neat) ν_{max} 2992, 2156, 1612, 1337, 1237, 1219, 827cm^{-1}.

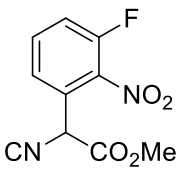
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* 2.0), 7.84 (1H, d, *J* 8.4), 7.79 (1H, dd, *J* 8.4, 2.1), 6.38 (1H, s), 3.87 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 163.8, 147.3, 136.8, 134.5, 130.4, 126.0, 125.2, 56.8, 54.4.

m/z HRMS (ESI^+) 276.9990 ($[M+Na]^+$, $C_{10}H_7ClN_2O_4Na$ requires 276.9987).

Methyl 2-(3-fluoro-2-nitrophenyl)-2-isocyanoacetate





This compound was prepared according to general procedure B, using 2,6-difluoronitrobenzene (2.07 g, 13.0 mmol). Column chromatography (petrol:ethyl acetate [6:1]) afforded the title compound as a brown oil (1.65 g, 69%).

IR (neat) ν_{max} 3001, 2146, 1589, 1335, 1256, 1222 cm^{-1}.

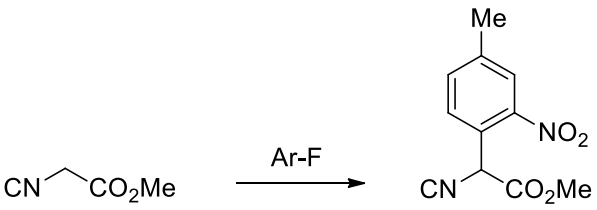
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, td, *J* 8.2, 5.1), 7.62 (1H, d, *J* 8.0), 7.43 (1H, ddd, *J* 9.4, 8.5, 1.2), 6.01 (1H, s), 3.85 (3H, s).

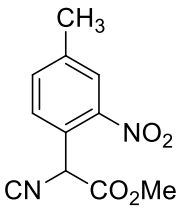
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 164.0, 154.9 (d, *J* 262.2), 141.6, 133.6 (d, *J* 8.8), 127.0, 123.7 (d, *J* 3.8), 119.1 (d, *J* 20.0), 55.6, 54.4.

^{19}F NMR (377 MHz, $CDCl_3$, $\{^1H\}$) δ -119.0.

m/z HRMS (ESI^+) 261.0290 ($[M+Na]^+$, $C_{10}H_7FN_2O_4Na$ requires 261.0282).

Methyl 2-isocyano-2-(4-methyl-2-nitrophenyl)acetate





This compound was prepared according to general procedure B, using 4-fluoro-3-nitrotoluene (2.02 g, 13.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a brown oil (1.46 g, 60%).

IR (neat) ν_{max} 2962, 2150, 1527, 1355, 1257, 1231, 989 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, s), 7.71 (1H, d, *J* = 8.0), 7.60 (1H, dd, *J* = 8.0, 0.8), 6.31 (1H, s), 3.83 (3H, s), 2.51 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 162.8, 146.8, 141.6, 135.2, 129.2, 126.2, 123.9, 57.1, 54.1, 21.0.

m/z HRMS (ESI^+) 257.0535 ($[M+Na]^+$, $C_{11}H_{10}N_2O_4Na$ requires 257.0533).

2.2 Synthesis of Michael Acceptors

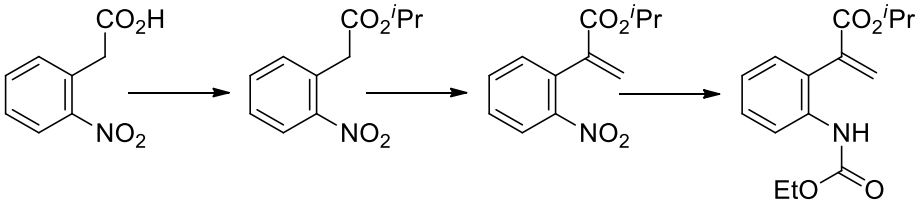
General Procedure D: Zinc dust (10 eq) and ammonium chloride (15 eq) were added to a vigorously stirred room temperature solution of the relevant isopropyl acrylate (1.0 eq) in acetone:water [4:1] (5.0 mL/mmol substrate). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 x 5.0 mL/mmol substrate) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in chloroform (3.0 mL/mmol substrate); pyridine (1.3 eq) was added, and the solution was cooled to 0 °C and stirred. Ethyl chloroformate (1.2 eq) was added dropwise into the reaction mixture. The mixture was stirred for 3 h and allowed to warm to room temperature. The solution was then washed with brine (2.0 mL/mmol substrate) and water (2 x 2.0 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

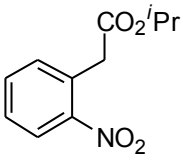
General Procedure E: Potassium carbonate (1.0 eq) and diisopropyl malonate (1.0 eq) were dissolved in DMF (1.7 mL/mmol substrate), and stirred for 10 min at 90 °C. After allowing the reaction mixture to cool to room temperature, the relevant 2-fluoronitrobenzene (1.0 eq) was added, and then stirred for 3 h at 90 °C. After cooling to room temperature, the reaction mixture was diluted with 5% aqueous hydrochloric acid solution (2.5 mL/mmol substrate) and extracted with diethyl ether (3 x 5.0 mL/mmol substrate). The organic phases were combined, washed with brine (5.0 mL/mmol substrate) and water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was then dissolved in DMSO (1.7 mL/mmol substrate), before sodium chloride (1.0 eq) and water (2.0 eq) were added. The reaction mixture was stirred for 24 h at 130 °C. After cooling to room temperature, the mixture was diluted with water (2.5

mL/mmol substrate) and extracted with ethyl acetate (3 x 5.0 mL/mmol substrate). The organic phases were then combined, washed with brine (5.0 mL/mmol substrate) and water (5.0 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

General Procedure F: Paraformaldehyde (2.80 eq), tetrabutylammonium bromide (0.04 eq) and potassium carbonate (3.00 eq) were added to a stirred solution of the relevant isopropyl acetate (1.00 eq) in toluene (1.5 mL/mmol substrate), and the solution was heated to 50 °C. After 20 h the solution was allowed to cool to room temperature, water (3.5 mL/mmol substrate) was added and the aqeuous layer was extracted with toluene (3 x 2.0 mL/mmol). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

Isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (1)



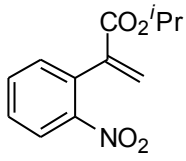


Concentrated sulfuric acid (5.0 mL) was added to a stirred solution of 2-nitrophenylacetic acid (15.0 g, 82.8 mmol) in isopropanol (50 mL) at room temperature. The mixture was then stirred at reflux for 4 h. After allowing to cool to room temperature, EtOAc (200 mL) was added. The mixture was washed with water (100 mL) and then with saturated aqueous sodium bicarbonate solution (2 x 100 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford isopropyl 2-(2-nitrophenyl)acetate as an orange oil (17.2 g, 93%), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* 8.1), 7.57 (1H, app. t, *J* 7.5), 7.49-7.41 (1H, m), 7.33 (1H, d, *J* 7.5), 5.01 (1H, sept, *J* 6.2), 3.97 (2H, s), 1.21 (6H, d, *J* 6.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 148.8, 133.5, 133.3, 130.0, 128.5, 125.2, 68.8, 40.1, 21.7.

Data in accordance with literature (P. Strazzolini, A. G. Giumanini, A. Runcio, M. Scuccato, J. Org. Chem. ***1998****, 63, 952).*



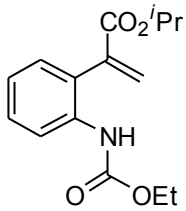
Prepared from isopropyl 2-(2-nitrophenyl)acetate (16.0 g) according to general procedure F to afford isopropyl 2-(2-nitrophenyl)acrylate as an orange oil (15.0 g, 89%), which was used without further purification.

IR (neat) ν_{max} 3071, 2983, 2937, 1716, 1526, 1350, 1207 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* 8.1), 7.65 (1H, app. td, *J* 7.5, 1.5), 7.58-7.46 (1H, m), 7.39 (1H, dd, *J* 7.4, 1.5), 6.53 (1H, d, *J* 1.0), 5.86 (1H, d, *J* 1.0), 5.05 (1H, sept, *J* 6.2), 1.21 (6H, d, *J* 6.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 148.0, 140.5, 133.6, 133.2, 132.1, 129.2, 127.1, 124.5, 69.2, 21.5.

HRMS (ESI^+) 258.0747 ($[M+Na]^+$, $C_{12}H_{13}NO_4Na$ requires 258.0742).



This compound was prepared according to general procedure D, using ethyl chloroformate (2.70 mL, 28.1 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **1** as an orange wax (3.61 g, 56%).

IR (neat) ν_{max} 3343, 2982, 1806, 1714, 1583, 1521, 1451, 1299, 1211, 1105, 1059 cm^{-1}.

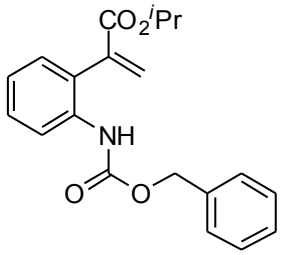
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, app. s), 7.41-7.35 (1H, m), 7.20-7.09 (2H, m), 6.93 (1H, br s, N*H*), 6.57 (1H, d, *J* 1.5), 5.85 (1H, d, *J* 1.5), 5.15 (1H, sept, *J* 6.2), 4.21 (2H, q, *J* 7.1), 1.34-1.28 (9H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 153.9, 139.8, 135.4, 130.5, 130.2, 129.2, 126.9, 124.0, 121.9, 69.3, 61.2, 21.7, 14.6.

HRMS (ESI^+) 300.1208 ($[M+Na]^+$, $C_{15}H_{19}NO_4Na$ requires 300.1212).

m.p. 45-47 °C.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate



This compound was prepared according to general procedure D, using benzyl chloroformate (1.46 mL, 10.2 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound as an orange solid (1.53 g, 53%).

IR (neat) ν_{max} 3340, 2981, 1712, 1584, 1519, 1451, 1298, 1199, 1105, 1042, 937, 817 cm^{-1}.

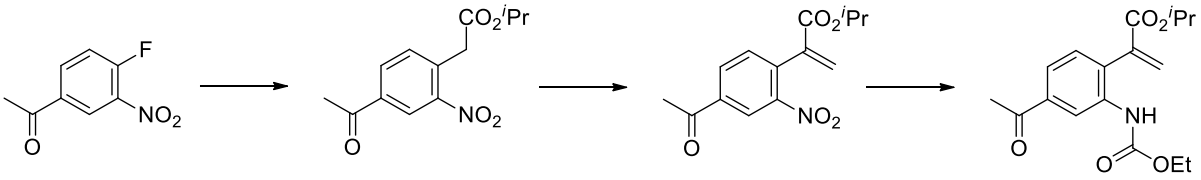
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.84 (1H, m), 7.50-7.30 (6H, m), 7.21-7.11 (2H, m), 7.06 (1H, br s, N*H*), 6.56 (1H, d, *J* 1.4), 5.85 (1H, d, *J* 1.4), 5.21 (2H, s), 5.12 (1H, sept, *J* 6.3), 1.27 (6H, d, *J* 6.3).

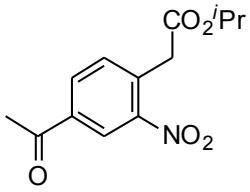
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 153.8, 139.7, 136.2, 135.3, 130.6, 130.3, 129.2, 128.9, 128.6, 128.4, 128.3, 124.1, 122.1, 69.3, 67.0, 21.7.

HRMS (ESI^+) 362.1356 ($[M+Na]^+$, $C_{20}H_{21}NO_4Na$ requires 362.1368).

m.p. 52-58 °C.

Isopropyl 2-(4-acetyl-2-((ethoxycarbonyl)amino)phenyl)acrylate





This compound was prepared according to general procedure E, using 4'-fluoro-3'-nitroacetophenone (4.00 g, 21.8 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded isopropyl 2-(4-acetyl-2-nitrophenyl)acetate as a yellow solid (3.01 g, 52%).

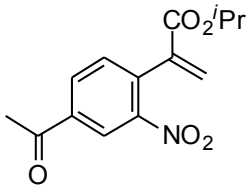
IR (neat) ν_{max} 2983, 1729, 1692, 1619, 1534, 1354, 1254, 1219, 1105 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (1H, d, *J* 1.7), 8.16 (1H, dd, *J* 7.9, 1.7), 7.50 (1H, d, *J* 7.9), 5.04 (1H, sept, *J* 6.3), 4.06 (2H, s), 2.68 (3H, s), 1.24 (6H, d, *J* 6.3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 168.7, 149.0, 137.3, 133.9, 132.4, 132.0, 125.0, 69.3, 40.1, 26.7, 21.7.

HRMS (ESI^+) 288.0853 ($[M+Na]^+$, $C_{13}H_{15}NO_5Na$ requires 288.0842).

m.p. 47-49 °C.



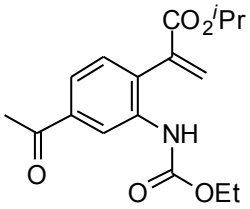
This compound was prepared according to general procedure F, using isopropyl 2-(4-acetyl-2-nitrophenyl)acetate (2.20 g, 8.29 mmol). Column chromatography (petrol:ethyl acetate [3:1]) afforded isopropyl 2-(4-acetyl-2-nitrophenyl)acrylate as a yellow oil (529 mg, 23%).

IR (neat) ν_{max} 3049, 2916, 1736, 1713, 1619, 1499, 1265 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (1H, s), 8.20 (1H, d, *J* 8.0), 7.52 (1H, d, *J* 8.0), 6.59 (1H, app. s), 5.93 (1H, app. s), 5.04 (1H, sept, *J* 6.2), 2.68 (3H, s), 1.20 (6H, d, *J* 6.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 163.6, 148.2, 139.8, 137.8, 137.1, 132.7, 132.6, 128.2, 124.3, 69.6, 26.7, 21.5.

HRMS (ESI^+) 300.0846 ($[M+Na]^+$, $C_{14}H_{15}NO_5Na$ requires 300.0848).



This compound was prepared according to general procedure D, using isopropyl 2-(4-acetyl-2-nitrophenyl)acrylate (500 mg, 1.80 mmol). Column chromatography (petrol:ethyl acetate [3:1]) afforded the title compound as a yellow oil (172 mg, 30%).

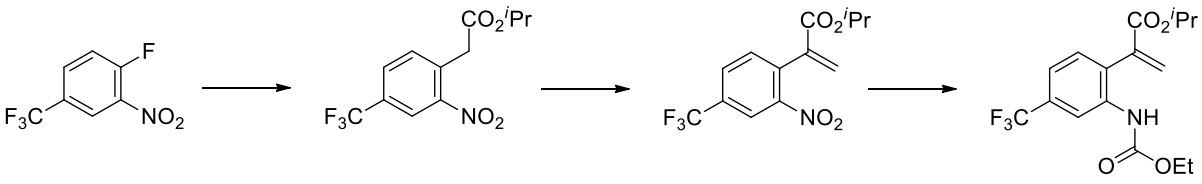
IR (neat) ν_{max} 3322, 2982, 1716, 1686, 1572, 1525, 1422, 1290, 1211, 1096, 1054 cm^{-1}.

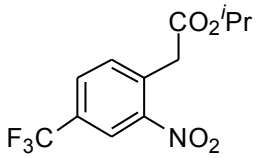
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, s), 7.63 (1H, dd, *J* 7.9, 1.7), 7.17 (1H, d, *J* 7.9), 6.89 (1H, br s, N*H*), 6.54 (1H, app. s), 5.79 (1H, app. s), 5.06 (1H, sept, *J* 6.2), 4.14 (2H, q, *J* 7.1), 2.55 (3H, s), 1.26-1.18 (9H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 165.6, 153.8, 139.1, 137.8, 135.9, 131.3, 130.6, 125.3, 123.3, 122.1, 69.6, 61.5, 26.8, 21.7, 14.5.

HRMS (ESI^+) 342.1310 ($[M+Na]^+$, $C_{17}H_{21}NO_5Na$ requires 342.1317).

Isopropyl 2-(2-((ethoxycarbonyl)amino)-4-(trifluoromethyl)phenyl)acrylate





This compound was prepared according to general procedure E, using 2-fluoro-5-(trifluoromethyl)nitrobenzene (1.34 mL, 9.56 mmol). Column chromatography (petrol:ethyl acetate [8:1]) afforded isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acetate as a yellow oil (2.17 g, 78%).

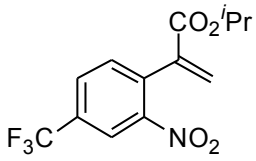
IR (neat) ν_{max} 3096, 2987, 2851, 1715, 1630, 1575, 1538, 1503 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.77 (1H, d, *J* 8.0), 7.45 (1H, d, *J* 8.0), 4.95 (1H, sept, *J* 6.3), 3.98 (2H, s), 1.16 (6H, d, *J* 6.3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 148.9, 134.3, 133.9, 131.2 (q, *J* 34.3), 129.8 (q, *J* 3.5), 122.8 (q, *J* 272.4, *C*F_3), 122.5 (q, *J* 3.8), 69.4, 40.0, 21.6.

^{19}F NMR (377 MHz, {^1H}, $CDCl_3$) δ -63.0.

HRMS (ESI^+) 314.0619 ($[M+Na]^+$, $C_{12}H_{12}F_3NO_4Na$ requires 314.0616).



This compound was prepared according to general procedure F, using isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acetate (2.00 g, 6.87 mmol). Isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acrylate was afforded as a brown oil (1.52 g, 73%), which was used without further purification.

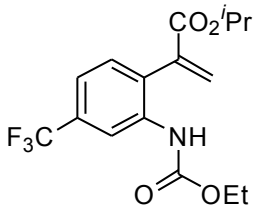
IR (neat) ν_{max} 2940, 1714, 1541, 1352, 1134, 1087, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, s), 7.83 (1H, app. ddd, *J* 8.0, 1.8, 0.6), 7.49 (1H, d, *J* 8.0), 6.54 (1H, d, *J* 0.6), 5.86 (1H, d, *J* 0.6), 5.03 (1H, sept, *J* 6.3), 1.15 (6H, d, *J* 6.3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 148.0, 139.5, 136.6, 133.1, 131.8 (q, *J* 34.3), 130.1 (q, *J* 3.5), 128.4, 122.7 (q, *J* 272.5, *C*F_3), 121.9 (q, *J* 3.8), 69.7, 21.5.

^{19}F NMR (377 MHz, {^{1}H}, $CDCl_3$) δ -62.9.

HRMS (ESI$^+$) 326.0600 ([M+Na]$^+$, $C_{13}H_{12}F_3NO_4Na$ requires 326.0611).



This compound was prepared according to general procedure D, using isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acrylate **(**1.40 g, 4.62 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound as a yellow oil (431 mg, 27%).

IR (neat) ν_{max} 3341, 2985, 1719, 1584, 1534, 1471, 1333, 1214, 1127, 1095 cm^{-1}.

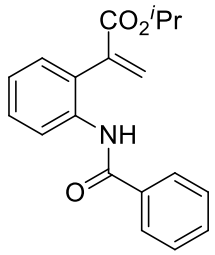
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.15 (1H, m), 7.29-7.22 (1H, m), 7.20-7.14 (1H, m), 6.94 (1H, br s, N*H*), 6.55 (1H, d, *J* 1.2), 5.79 (1H, d, *J* 1.2), 5.06 (1H, sept, *J* 6.3), 4.13 (2H, q, *J* 7.1), 1.24-1.18 (9H, m).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 153.6, 138.7, 136.2, 131.6, 131.3 (q, *J* 32.6), 130.7, 127.9, 123.8 (q, *J* 272.2, *C*F_3), 120.2 (app. br s), 118.3 (app. br s), 69.7, 61.6 (O*C*$H_2$$CH_3$), 21.6, 14.5.

^{19}F NMR (377 MHz, {^{1}H}) δ -62.8.

HRMS (ESI$^+$) 368.1086 ([M+Na]$^+$, $C_{16}H_{18}F_3NO_4Na$ requires 368.1068).

Isopropyl 2-(2-benzamidophenyl)acrylate



Zinc dust (5.58 g, 85.0 mmol) and ammonium chloride (6.83 g, 128 mmol) were added to a vigorously stirred room temperature solution of isopropyl 2-(2-nitrophenyl)acrylate (2.00 g, 8.50 mmol) in acetone:water [4:1] (50 mL). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 x 50 mL) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (50 mL), dried over

anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then dissolved in DCM (30 mL); pyridine (826 µL, 10.2 mmol) was added, and the solution was cooled to 0 °C and stirred. Benzoyl chloride (983 µL, 8.50 mmol) was added dropwise into the reaction mixture. The mixture was stirred for 12 h and allowed to warm to room temperature. The solution was then washed with brine (30 mL) and water (2 x 30 mL/mmol substrate), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound as a light yellow solid (1.76 g, 67%).

IR (neat) ν_{max} 3321, 2982, 1665, 1580, 1518, 1449, 1303, 1199, 1100, 1079 cm^{-1}.

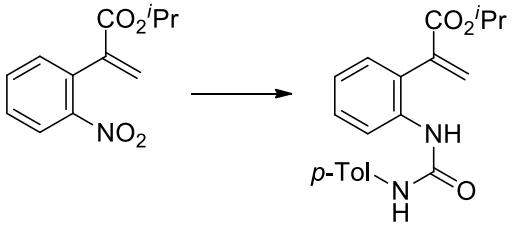
^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (1H, br s, N*H*), 8.06 (1H, d, *J* 8.0), 7.90 (2H, d, *J* 7.6), 7.60-7.42 (4H, m), 7.28-7.18 (2H, m) 6.54 (1H, d, *J* 1.3), 5.91 (1H, d, *J* 1.3), 5.16 (1H, sept, *J* 6.3), 1.30 (6H, d, *J* 6.3).

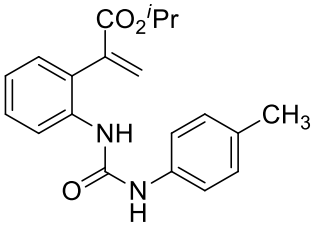
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 165.4, 140.3, 135.3, 134.8, 131.8, 131.0, 130.6, 129.3, 128.7, 127.4, 127.1, 125.2, 124.3, 69.7, 21.7.

m/z LRMS (ESI^+) 332.1 $[M+Na]^+$; HRMS (ESI^+) 332.1259 ($[M+Na]^+$, $C_{19}H_{19}NO_3Na$ requires 332.1263).

m.p. 75-77 °C.

Isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (22)





To a solution of isopropyl 2-(2-nitrophenyl)acrylate (4.26 g, 18.1 mmol) in acetone (80 mL) and water (20 mL) was added zinc powder (5.05 g,

77.2 mmol) followed by NH_4Cl (16.7 g, 311 mmol). The reaction was stirred vigorously for 15 minutes before the solution was decanted from the zinc residue. The residue was washed several times with EtOAc and the washings were combined and filtered through Celite. The filtrate was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue was dissolved in $CHCl_3$ (50 mL) and 1-isocyanato-4-methylbenzene (2.28 mL, 18.1 mmol) was added. The reaction was stirred overnight and the product was filtered to afford the title compound **22** as a white solid (3.44 g, 56 %).

IR (neat) v_{max} 3300, 3024, 1704, 1642, 1549, 1375, 1230, 1209, 1106 cm^{-1}.

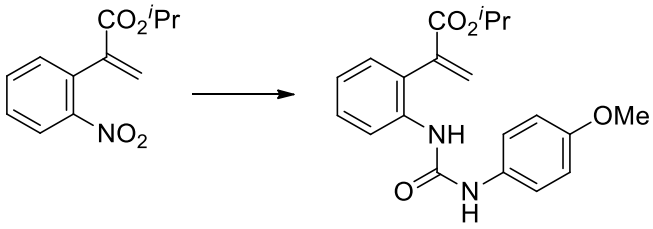
^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* 8.1), 7.43-7.39 (1H, m), 7.25-7.16 (4H, m), 7.15-7.08 (2H, m), 6.94 (1H, br s, N*H*), 6.78 (1H, br s, N*H*), 6.47 (1H, d, *J* 1.4), 5.82 (1H, d, *J* 1.4), 5.01 (1H, sept, *J* 6.2), 2.32 (3H, s), 1.22 (6H, d, *J* 6.2).

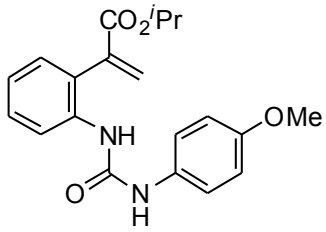
^{13}C NMR (101 MHz) δ 166.5, 153.8, 140.1, 135.7, 135.4, 133.8, 131.9, 130.5, 129.8, 129.7, 129.4, 125.2, 125.0, 121.5, 69.4, 21.6, 20.8.

HRMS (ESI^+) 361.1521 ($[M+Na]^+$, $C_{20}H_{22}N_2O_3Na$ requires 361.1528).

m.p. 160-165 °C.

Isopropyl 2-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate





To a solution of isopropyl 2-(2-nitrophenyl)acrylate (2.35 g, 10.0 mmol) in acetone (50 mL) and water (12 mL) was added zinc powder (2.81 g, 43.0 mmol) followed by NH_4Cl (9.06 g, 171.0 mmol). The reaction was stirred vigorously for 15 minutes before the solution was decanted from the zinc residue. The residue was washed several times with EtOAc and the washings were combined and filtered through Celite. The filtrate was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The crude residue was dissolved in $CHCl_3$ (25 mL) and 1-isocyanato-4-methoxybenzene (1.30 mL, 10.0 mmol) was added. The reaction was stirred overnight before concentrating *in vacuo*. Purification by column chromatography (petrol:ethyl acetate [3:1]) followed by recrystallisation from EtOAc/hexanes afforded the title compound as a colourless oil (1.05 g, 30 %).

IR (neat) ν_{max} 3299, 3028, 1710, 1636, 1551, 1370, 1236, 1216, 1101 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* 8.0), 7.39 (1H, ddd, *J* 7.9, 7.0, 2.2), 7.14-7.25 (4H, m), 6.94 (1H, br s, N*H*), 6.85 (2H, d, *J* 8.9), 6.77 (1H, br s, N*H*), 6.46 (1H, d, *J* 1.4), 5.81 (1H, d, *J* 1.3), 5.00 (1H, sept, *J* 6.3), 3.81 (3H, s), 1.22 (6H, d, *J* 6.3).

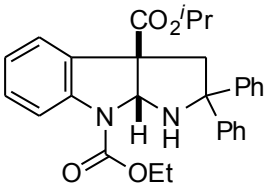
^{13}C NMR (101 MHz) δ 166.5, 154.3, 140.1, 135.8, 133.5, 131.6, 130.7, 130.4, 129.8, 129.3, 125.0, 124.8, 124.0, 114.4, 69.4, 55.5, 21.6.

HRMS (ESI^+) 377.1472 ($[M+Na]^+$, $C_{20}H_{22}N_2O_4Na$ requires 377.1475).

3. Diastereoselective reaction

General Procedure G: The relevant Michael acceptor substrate (1.0 eq), isocyanide (1.0 eq) and tetrabutylammonium bromide (0.1 eq) were dissolved in toluene (10 mL/mmol substrate). The selected base (5.0 eq) was added, and the mixture was stirred at room temperature until both substrates were consumed according to thin layer chromatography (2-24 h). The reaction mixture was then diluted with DCM (20 mL/mmol substrate) and washed with brine (20 mL/mmol substrate) and water (20 mL/mmol substrate). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

8-Ethyl 3a-isopropyl 2,2-diphenyl-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-3a,8(2*H*)-dicarboxylate (4)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, (isocyanomethylene)dibenzene (42 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 72 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **4** as a yellow oil (63%, >20:1 d.r.).

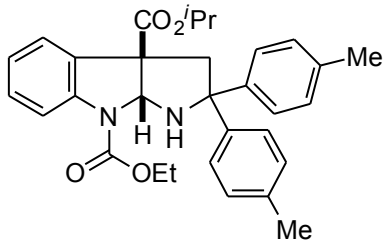
IR (neat) ν_{max} 1717, 1605, 1487, 1375, 1243, 1104, 905 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* 7.5), 7.33-7.25 (2H, m), 7.24-7.16 (3H, m), 7.11 (1H, app. s), 7.06-6.96 (3H, m), 6.96-6.88 (3H, m), 6.81 (1H, t, *J* 7.4), 6.08 (1H, s), 4.85 (1H, sept, *J* 6.2), 4.36-4.19 (2H, m), 3.74 (1H, br s, N*H*), 3.14 (1H, d, *J* 13.0), 3.01 (1H, d, *J* 13.0), 1.39-1.27 (3H, m), 1.09 (6H, app. s).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 152.5, 146.5, 140.7, 129.0, 128.4, 127.6, 126.8, 126.7, 126.3, 126.1, 125.9, 123.8, 123.6, 122.7, 114.7, 80.7, 70.6, 69.3, 62.0, 61.5, 49.7, 21.6, 14.9.

HRMS (ESI$^+$) 493.2098 ([M+Na]$^+$, $C_{29}H_{30}N_2O_4Na$ requires 493.2103).

8-Ethyl 3a-isopropyl 2,2-di-*p*-tolyl-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-3a,8(2*H*)-dicarboxylate (5)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, 4,4'-(isocyanomethylene)bis(methylbenzene) (48 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 72 h. Column chromatography (petrol:ethyl acetate [6:1]) afforded the title compound **5** as a colourless oil (22%, >20:1 d.r.).

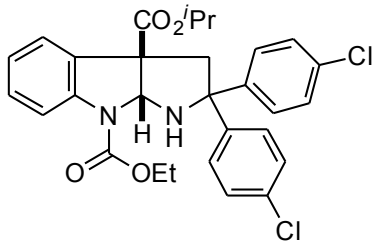
IR (neat) ν_{max} 2981, 1719, 1598, 1511, 1486, 1410, 1377, 1239, 1104, 1059, 908 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (1H, app. s), 7.34-7.22 (2H, m), 7.19-7.06 (4H, m), 7.00 (2H, d, *J* 8.2), 6.92 (1H, t, *J* 7.5), 6.84 (2H, d, *J* 7.4), 6.22-6.07 (1H, s), 4.93 (1H, sept, *J* 6.2), 4.56-4.18 (2H, m), 3.85 (1H, br s, N*H*), 3.26 (1H, d, *J* 13.1), 3.00 (1H, d, *J* 13.1), 2.31 (3H, s), 2.19 (3H, s), 1.34-1.27 (3H, m), 1.23-1.12 (6H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 152.5, 143.4, 141.7, 140.6, 139.8, 136.4, 135.8, 129.5, 129.3, 129.0, 128.8, 128.3, 123.5, 122.7, 114.7, 80.4, 70.0, 69.2, 62.0, 61.5, 49.8, 21.7, 20.9, 20.8, 14.7.

HRMS (ESI$^+$) 521.2421 ([M+Na]$^+$, $C_{31}H_{34}N_2O_4Na$ requires 521.2416).

8-Ethyl 3a-isopropyl 2,2-bis(4-chlorophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-3a,8(2*H*)-dicarboxylate (6)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, 4,4'-(isocyanomethylene)bis(chlorobenzene) (57 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [6:1]) afforded the title compound **6** as a colourless oil (76%, >20:1 d.r.) in an inseparable mixture with a small amount of isopropyl 2,2-bis(4-chlorophenyl)-1-(p-tolylcarbamoyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate.

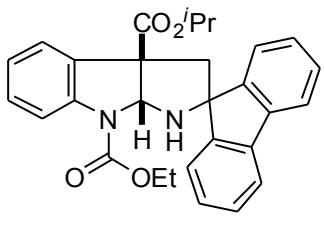
IR (neat) ν_{max} 1719, 1602, 1488, 1232, 1097, 904, 724 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, app. s), 7.26-7.11 (6H, m), 7.05-6.95 (2H, m), 6.93-6.78 (3H, m), 6.12-5.99 (1H, m), 4.88 (1H, sept, *J* 6.2), 4.36-4.10 (2H, m), 3.80 (1H, br s, N*H*), 2.98 (2H, app. br s), 1.37-1.27 (3H, m), 1.13-1.07 (6H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 152.4, 144.8, 143.5, 141.3, 136.2, 132.9, 132.3, 129.7, 128.5, 127.7, 127.5, 127.3, 123.8, 123.0, 114.7, 81.0, 69.9, 69.5, 62.1, 61.6, 49.7, 21.6, 14.7.

HRMS (ESI^+) 561.1323 ($[M+Na]^+$, $C_{29}H_{28}Cl_2N_2O_4Na$ requires 561.1324).

8'-Ethyl 3a'-isopropyl 3',3a'-dihydro-1'*H*-spiro[fluorene-9,2'-pyrrolo[2,3-*b*]indole]-3a',8'(8a'*H*)-dicarboxylate (7)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, 9-isocyano-9*H*-fluorene (41 mg, 0.22

mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **7** as a yellow oil (54%, >20:1 d.r.).

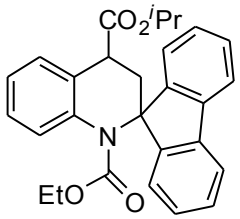
IR (neat) ν_{max} 1716, 1582, 1487, 1330, 1250, 1103, 905 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (1H, app. s), 7.66 (1H, d, *J* 7.5), 7.62-7.55 (2H, m), 7.43-7.35 (3H, m), 7.35-7.25 (2H, m), 7.17-7.07 (2H, m), 7.00 (1H, d, *J* 7.5), 6.62 (1H, s), 5.15 (1H, sept, *J* 6.3), 4.46-4.19 (2H, m), 3.22 (1H, d, *J* 13.9), 3.09 (1H, br s, N*H*), 2.78 (1H, d, *J* 13.9), 1.34-1.23 (9H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 154.4, 152.8, 151.7, 149.5, 141.2, 139.2, 139.1, 129.6, 128.4, 128.3, 128.2, 128.0, 124.6, 124.2, 124.1, 123.2, 119.9, 119.5, 115.5, 82.2, 72.9, 69.7, 62.0, 61.7, 49.2, 21.6, 14.7.

HRMS (ESI^+) 491.1945 ($[M+Na]^+$, $C_{29}H_{28}N_2O_4Na$ requires 491.1947).

The reaction with 9-isocyano-9*H*-fluorene and isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate formed 1'-ethyl 4'-isopropyl 3',4'-dihydro-1'*H*-spiro[fluorene-9,2'-quinoline]-1',4'-dicarboxylate as a separable by-product in 34% yield.



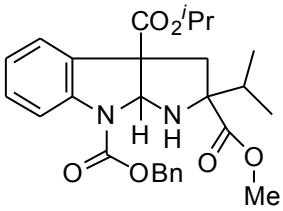
IR (neat) ν_{max} 2982, 2129, 1729, 1590, 1520, 1452, 1220, 1104, 1062, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64-7.57 (3H, m), 7.56 (1H, app. s), 7.42-7.29 (4H, m), 7.20 (1H, t, *J* 7.6), 7.08 (1H, td, *J* 7.7, 1.4), 6.83 (1H, t, *J* 7.4), 6.70 (1H, app. s), 4.52 (1H, sept, *J* 6.2), 4.14 (2H, q, *J* 7.1), 3.49 (1H, dd, *J* 13.9, 8.3), 2.98-2.89 (1H, m), 2.67 (1H, dd, *J* 13.9, 3.4), 1.27 (3H, t, *J* 7.1), 0.87 (3H, d, *J* 6.2), 0.85 (3H, d, *J* 6.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 154.1, 157.1, 142.5, 141.9, 140.1, 139.7, 135.7, 130.2, 130.1, 129.0, 128.8, 128.6, 128.5, 128.2, 124.7, 123.8, 123.6, 120.5, 120.4, 69.6, 67.0 (*C*-9), 61.3, 43.6, 42.1, 21.5, 21.2, 14.7.

HRMS (ESI^+) 442.2013 ($[M+H]^+$, $C_{28}H_{28}NO_4$ requires 442.2018).

8-Benzyl 3a-isopropyl 2-methyl 2-isobutyl-1,2,3,3a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(8a*H*)-tricarboxylate (11)



This compound was prepared according to general procedure G, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate (50 mg, 0.15 mmol) as the Michael acceptor, methyl 2-isocyano-3-methylbutanoate (21 mg, 0.15 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the pyrroloindoline **11** as a colourless oil (75%, 1:1 d.r.).

IR (neat) ν_{max} 2978, 1721, 1485, 1394, 1244, 1104, 752, 698 cm^{-1}.

NMR Data are provided for mixture of diastereomers.

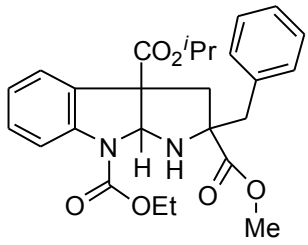
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.08-7.83 (2H, m), 7.35-7.23 (6H, m), 7.19-6.98 (8H, m), 6.93-6.79 (2H, m), 6.32 (1H, s), 6.26 (1H, s), 5.35-5.23 (2H, m), 5.12-5.01 (2H, m), 4.97-4.85 (2H, m), 3.64 (1H, br s, N*H*), 3.45 (3H, s), 3.36 (1H, d, *J* 13.3), 2.99 (3H, s), 2.90 (1H, d, *J* 12.9), 2.59 (1H, d, *J* 12.9), 2.13-2.09 (1H, m), 1.88-1.74 (2H, m), 1.03-0.95 (12H, m), 0.83 (6H, dd, *J* 16.1, 6.9), 0.74 (6H, dd, *J* 14.9, 6.9).

^{13}C NMR (126 MHz, toluene-d_8) δ 175.7, 174.7, 171.3, 171.1, 153.9, 152.1, 142.9, 141.8, 137.2, 137.0, 132.5, 132.0, 131.1, 129.5, 129.2, 128.5, 127.6, 125.4, 124.3, 123.9, 123.2, 123.1, 115.7, 114.8, 82.0,

81.1, 73.0, 72.5, 69.2, 69.1, 67.0, 66.8, 61.2, 61.1, 51.7, 51.3, 44.9, 44.2, 37.2, 35.4, 21.4, 21.3, 18.0, 18.0.

HRMS (ESI$^+$) 503.2131 ([M+Na]$^+$, $C_{27}H_{32}N_2O_6Na$ requires 503.2153).

8-Ethyl 2-methyl 2-benzyl-3a-cyano-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,8(2*H*)-dicarboxylate (12)



This compound was prepared according to general procedure G, using ethyl (2-(1-cyanovinyl)phenyl)carbamate (39 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-3-phenylpropanoate (34 mg, 0.18 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound **12** as a colourless oil (72%, 1:1 d.r.).

IR (neat) ν_{max} 2274, 2120, 1729, 1570, 1488, 1387, 1331, 1050, 840, 821, 754 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d$_8$, 363 K) δ 7.98 (2H, app. s, Ar$_{DS1,DS2}$), 7.27 (2H, app. s, Ar$_{DS1,DS2}$), 7.14 (1H, app. s, Ar$_{DS1}$), 6.90 (2H, d, *J* 7.2, Ar$_{DS1}$), 6.81 (1H, t, *J* 7.5, Ar$_{DS2}$), 6.71 (1H, t, *J* 7.4, Ar$_{DS1}$), ‡, 5.91 (1H, s, $_{DS2}$), 5.67 (1H, s, $_{DS1}$), 4.20-3.94 (2H, m, $_{DS1}$), 3.92-3.74 (2H, m, $_{DS2}$), 3.49 (2H, br s, N*H* $_{DS1,DS2}$), 3.42 (3H, s, $_{DS2}$), 2.98-2.89 (2H, m), 2.85-2.71 (5H, m), 2.67 (1H, d, *J* 12.9), 2.43 (1H, d, *J* 12.9), 2.13 (1H, d, *J* 13.0), 1.90 (1H, d, *J* 13.1), 1.10-0.93 (6H, m, $_{DS1,DS2}$).

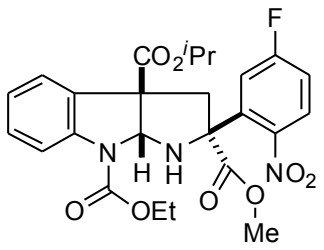
‡Remaining aromatic signals are buried under toluene peaks.

^{13}C NMR (126 MHz, toluene-d$_8$, 363 K) δ 174.3, 174.0, 151.5, 137.3, 137.2, 136.5, 136.1, 129.7, 129.7, 129.2, 128.5, 128.5, 128.2, 127.4, 125.4, 124.1, 123.6, 123.5, 115.8, 114.9 [aromatics**], 120.6, 120.4, 82.8, 82.2, 70.8, 69.8, 62.2, 61.5, 52.1, 51.5, 48.7, 48.6, 48.3, 47.5, 46.0, 44.6, 14.5, 14.4.

**Remaining aromatic signals are buried under toluene peaks.

HRMS (ESI$^+$) 428.1582 ([M+Na]$^+$, $C_{23}H_{23}N_3O_4Na$ requires 428.1586).

8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (13)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (100 mg, 0.36 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (86 mg, 0.36 mmol) as the isocyanide and potassium carbonate (250 mg, 1.8 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **13** as a yellow oil (57%, >20:1 d.r.).

IR (neat) ν_{max} 2972, 2212, 1729, 1533, 1487, 1387, 1257, 1104, 1046, 840, 821 cm^{-1}.

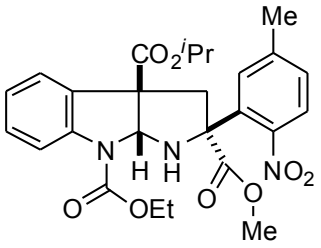
^{1}H NMR (500 MHz, toluene-d$_8$, 363 K) δ 7.85 (1H, app. s), 7.68 (1H, d, *J* 9.0), 7.31 (1H, d, *J* 7.2), 7.29-7.20 (1H, m), 7.16-7.07 (1H, m), 6.87 (1H, t, *J* 7.5), 6.45-6.38 (1H, m), 6.33 (1H, s), 4.87 (1H, sept, *J* 6.3), 4.22-4.04 (2H, m), 3.99 (1H, br s), 3.55 (1H, d, *J* 13.9), 3.13 (3H, s), 3.09 (1H, d, *J* 13.9), 1.12 (3H, t, *J* 7.1), 0.97 (3H, d, *J* 6.3), 0.91 (3H, d, *J* 6.3).

^{13}C NMR (126 MHz, toluene-d$_8$, 363 K) δ 171.6, 170.2, 164.0 (d, *J* 254.3), 152.5, 145.0, 141.8, 140.9, 131.3 (d, *J* 9.3), 129.4, 127.0 (d, *J* 9.5), 123.5, 122.8, 115.5 (d, *J* 26.0), 114.6 (d, *J* 24.0), 114.6, 82.4, 71.1, 69.1, 61.3, 60.9, 51.7, 48.3, 20.5, 14.0.

^{19}F NMR (377 MHz, toluene-d$_8$, {^{1}H}) δ -104.7.

HRMS (ESI$^+$) 538.1591 ([M+Na]$^+$, $C_{25}H_{26}FN_3O_8Na$ requires 538.1602).

8-Ethyl 3a-isopropyl 2-methyl 2-(5-methyl-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (14)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (50 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-2-(5-methyl-2-nitrophenyl)acetate (42 mg, 0.18 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 18 h. Column chromatography (petrol:ethyl acetate [7:2]) afforded the title compound **14** as a yellow oil (70%, >20:1 d.r.).

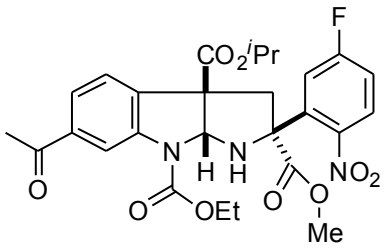
IR (neat) v_{max} 2982, 1722, 1523, 1486, 1346, 1239, 1103, 830, 754 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 7.88 (1H, app. s), 7.66 (1H, app. s), 7.35 (1H, d, *J* 7.5), 7.31-7.24 (1H, m), 7.14-7.11 (1H, m), 6.87 (1H, t, *J* 7.4), 6.64 (1H, d, *J* 8.2), 6.40 (1H, s), 4.87 (1H, sept, *J* 6.2), 4.24-4.03 (3H, m, OC$H_2$$CH_3$, N*H*), 3.61 (1H, d, *J* 13.7), 3.21-3.13 (4H, m), 1.98 (3H, s), 1.15 (3H, t, *J* 7.1), 0.99-0.89 (6H, m).

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 172.8, 170.3, 152.5, 147.3, 142.2, 142.0, 139.1, 136.5, 131.4, 129.4, 126.8, 123.6, 122.8, 122.5, 114.6, 82.2, 71.2, 68.9, 61.3, 60.9, 51.6, 48.4, 20.7, 20.5, 14.0.

HRMS (ESI^+) 534.1855 ($[M+Na]^+$, $C_{26}H_{29}N_3O_8Na$ requires 534.1852).

8-Ethyl 3a-isopropyl 2-methyl 6-acetyl-2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (15)



This compound was prepared according to general procedure G, using isopropyl 2-(4-acetyl-2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.19 mmol) as

the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate **(**44 mg, 0.19 mmol) as the isocyanide and potassium carbonate (130 mg, 0.94 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **15** as a yellow oil (61%, >20:1 d.r.).

IR (neat) ν_{max} 1731, 1668, 1539, 1437, 1255, 1094, 909 cm^{-1}.

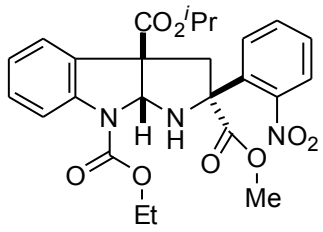
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.40 (1H, app. s), 7.70 (1H, d, *J* 10.0), 7.53 (1H, d, *J* 7.6), 7.34-7.27 (2H, m), 6.49-6.41 (1H, m), 6.34 (1H, s), 4.89 (1H, sept, *J* 6.2), 4.21-4.04 (2H, m), 3.99 (1H, br s, N*H*), 3.55 (1H, d, *J* 14.0), 3.13 (3H, s), 3.09 (1H, d, *J* 14.0), 2.26 (3H, s), 1.14 (3H, t, *J* 7.1), 1.00 (3H, d, *J* 6.2), 0.94 (3H, d, *J* 6.2).

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 195.0, 171.4, 169.7, 164.1 (d, *J* 254.1), 152.6, 144.9, 142.1, 140.8, 135.7, 131.1, 127.1 (d, *J* 9.4), 123.4, 123.2, 115.4 (d, *J* 26.2), 114.8 (d, *J* 23.7), 114.3 , 82.8, 71.0, 69.5, 61.7, 60.8, 51.7, 48.2, 25.5, 20.8, 20.7, 13.9.

^{19}F NMR (377 MHz, toluene-d_8, {^{1}H}) δ -104.3.

HRMS (ESI^+) 558.1876 ($[M+H]^+$, $C_{27}H_{29}FN_3O_9$ requires 558.1888).

8-Ethyl 3a-isopropyl 2-methyl 2-(2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (16)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (50 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-nitrophenyl)acetate (40 mg, 0.18 mmol) as the isocyanide and

potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **16** as a yellow oil (41%, 9:2 d.r. DS1:DS2).

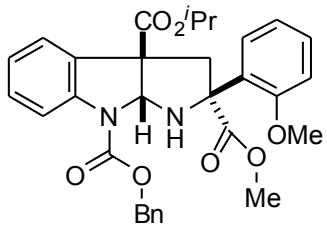
IR (neat) ν_{max} 1730, 1570, 1533, 1487, 1387, 1245, 1044, 840, 821, 753 cm^{-1}.

^1H NMR (500 MHz, toluene-d_8, 363K) δ 7.87 (1H, app. s, Ar_{DS1}), 7.69 (1H, d, *J* 8.0, Ar_{DS1}), 7.56 (1H, d, *J* 7.8, Ar_{DS2}), 7.40 (1H, d, *J* 8.0, Ar_{DS2}), 7.33 (1H, d, *J* 7.6, Ar_{DS1}), 7.27-7.19 (2H, m, $Ar_{DS1,DS2}$), 6.87 (1H, t, *J* 7.5, Ar_{DS1}), 6.84-6.75 (3H, m, $Ar_{DS1,DS2,DS2}$), 6.71 (1H, t, *J* 7.7, Ar_{DS2}), 6.45 (1H, s, $_{DS2}$), 6.35 (1H, s, $_{DS1}$), 4.99 (1H, sept, *J* 6.3, $_{DS2}$), 4.87 (1H, sept, *J* 6.2, $_{DS1}$), 4.25-4.02 (5H, m, $_{DS1,DS2}$, N*H* $_{DS1}$), 3.97 (1H, d, *J* 13.7, $_{DS2}$), 3.78 (1H, br s, N*H* $_{DS2}$), 3.55 (1H, d, *J* 13.7, $_{DS1}$), 3.40 (3H, s, $_{DS2}$), 3.16-3.12 (4H, m, $_{DS1}$, $_{DS1}$), 2.53 (1H, d, *J* 13.7, $_{DS2}$), 1.18-1.12 (6H, m, $_{DS1,DS2}$), 0.98 (6H, *J* 6.3, $_{DS1,DS2}$), 0.92 (6H, *J* 6.3, $_{DS1,DS2}$). Remaining aromatic signals are buried under toluene peaks.

^{13}C NMR (126 MHz, toluene-d_8, 363K) δ 172.3, 172.1, 170.2, 170.2, 152.5, 149.4, 148.9, 142.0, 142.0, 137.3, 136.6, 136.2, 131.2, 131.1, 129.0, 128.9, 128.3, 127.9, 124.2, 123.6, 123.2, 122.8, 122.5, 115.2, 114.6 [aromatics*], 82.1, 81.1, 71.1, 70.5, 69.0, 68.9, 61.1, 61.1, 60.9, 60.8, 51.7, 51.6, 48.4, 47.2 (*C*-8), 21.0, 20.9, 20.9, 20.8, 14.0, 14.0. *Remaining aromatic signals are buried under toluene peaks.

HRMS (ESI^+) 520.1687 ($[M+Na]^+$, $C_{25}H_{27}N_3O_8Na$ requires 520.1696).

8-Benzyl 3a-isopropyl 2-methyl 2-(2-methoxyphenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (17)



This compound was prepared according to general procedure G, using isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)acrylate (70 mg, 0.21 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-

methoxyphenyl)acetate (43 mg, 0.21 mmol) as the isocyanide and potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **17** as a colourless oil (49%, >20:1 d.r.).

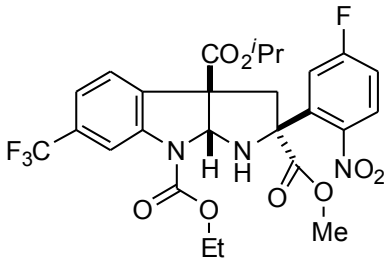
IR (neat) ν_{max} 1728, 1602, 1480, 1352, 1247, 1105, 906 cm^{-1}.

^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 7.96 (1H, app. s), 7.59 (1H, d, *J* 7.6), 7.42 (1H, d, *J* 7.5), 7.32 (2H, d, *J* 7.4), 7.20-6.98 (5H, m), 6.87 (1H, t, *J* 7.5), 6.80 (1H, t, *J* 7.5), 6.59-6.47 (2H, m), 5.36-5.22 (1H, m), 5.20-5.07 (1H, m), 4.86 (1H, sept, *J* 6.2), 4.41 (1H, br s, N*H*), 3.61 (1H, d, *J* 13.1), 3.31 (3H, s), 3.04 (3H, s), 2.99 (1H, d, *J* 13.1), 0.96 (3H, d, *J* 6.2), 0.90 (3H, d, *J* 6.2).

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 173.6, 170.7, 157.2, 152.5, 144.2, 142.3, 136.7, 131.9, 128.7, 128.4, 128.2, 127.9, 127.7, 126.7, 123.7, 122.6, 120.8, 114.7, 111.7, 81.9, 69.8, 68.6, 67.0, 60.9, 54.9, 51.0, 46.8, 20.9.

HRMS (ESI^+) 567.2104 ($[M+Na]^+$, $C_{31}H_{32}N_2O_7Na$ requires 567.2107).

8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-6-(trifluoromethyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (18)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)-4-(trifluoromethyl)phenyl)acrylate (60 mg, 0.17 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (41 mg, 0.17 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **18** as a yellow oil (48%, >20:1 d.r.).

IR (neat) ν_{max} 1730, 1532, 1450, 1324, 1258, 1169, 1130, 1065, 909 cm^{-1}.

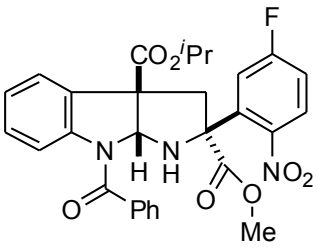
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.16 (1H, app. s), 7.72-7.62 (1H, m), 7.32-7.23 (2H, m), 7.16 (1H, d, *J* 7.9), 6.46-6.39 (1H, m), 6.31 (1H, s), 4.87 (1H, sept, *J* 6.3), 4.15-3.99 (2H, m), 3.95 (1H, br s, N*H*), 3.51 (1H, d, *J* 14.0), 3.11 (3H, s), 3.03 (1H, d, *J* 14.0), 1.09 (3H, t, *J* 7.1), 0.98 (3H, d, *J* 6.3), 0.92 (3H, d, *J* 6.3).

^{13}C NMR (126 MHz, toluene-d_8, 363 K) δ 171.4, 169.6, 164.1, 152.3, 144.8, 142.2, 140.7, 131.7 (q, *J* 32.3), 131.3 (app. br s), 127.1 (d, *J* 9.3), 124.1, 119.8 (q, *J* 4.0), 115.3 (d, *J* 26.7), 114.8 (d, *J* 23.4), 111.4 (q, *J* 3.9), 124.4 (q, J 271.5, *C*F_3), 82.8, 71.0, 69.6, 61.9, 60.6, 51.7, 48.3, 20.8, 20.7, 13.8.

^{19}F NMR (377 MHz, toluene-d_8, {^{1}H}) δ -62.4, -102.5.

HRMS (ESI^{+}) 584.1670 ([M+H]$^{+}$, $C_{26}H_{26}F_4N_3O_8$ requires 584.1656).

3a-Isopropyl 2-methyl 8-benzoyl-2-(5-fluoro-2-nitrophenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (19)



This compound was prepared according to general procedure G, using isopropyl 2-(2-benzamidophenyl)acrylate (70 mg, 0.23 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (54 mg, 0.23 mmol) as the isocyanide and potassium carbonate (160 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **19** as a yellow oil (57%, >20:1 d.r.).

IR (neat) ν_{max} 1728, 1635, 1587, 1528, 1480, 1350, 1244, 1135, 1100, 909 cm^{-1}.

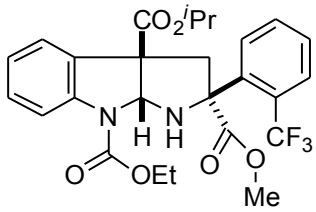
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-7.77 (2H, m), 7.59 (2H, app. d, *J* 7.1), 7.55-7.38 (4H, m), 7.23 (1H, d, *J* 7.1), 7.10-7.01 (1H, m), 7.00-6.82 (2H, m), 6.28 (1H, br s), 4.90 (1H, sept, *J* 6.3), 3.86 (1H, br s, N*H*), 3.52 (1H, d, *J* 14.4), 3.36 (3H, s), 2.90 (1H, d, *J* 14.4), 1.13 (3H, d, *J* 6.3), 1.02 (3H, d, *J* 6.3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 170.4, 169.6, 164.2 (d, *J* 253.5), 143.7, 142.6, 140.9, 136.0, 132.0, 131.1, 128.9, 128.7, 128.1, 127.6, 127.4, 124.1, 123.9, 116.0 (d, *J* 26.2), 115.4 (d, *J* 23.1), 84.1, 71.0, 69.8, 60.1, 53.0, 47.5, 21.5.

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ -101.6.

HRMS (ESI$^+$) 570.1646 ([M+Na]$^+$, $C_{29}H_{26}FN_3O_7Na$ requires 570.1652).

8-Ethyl 3a-isopropyl 2-methyl 2-(2-(trifluoromethyl)phenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2,3a,8(2*H*)-tricarboxylate (20)



This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-(trifluoromethyl)phenyl)acetate (53 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 18 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **20** as a colourless oil (65%, >20:1 d.r.).

IR (neat) ν_{max} 1731, 1564, 1487, 1311, 1244, 1105, 909 cm^{-1}.

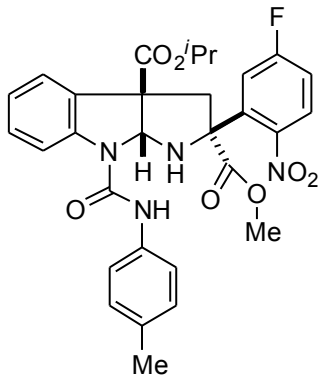
^{1}H NMR (500 MHz, toluene-d_8, 363 K) δ 8.00-7.78 (2H, m), 7.51 (1H, d, *J* 7.7), 7.36 (1H, d, *J* 7.5), 7.16-7.06 (2H, m), 6.95 (1H, t, *J* 7.4), 6.88 (1H, t, *J* 7.4), 6.45 (1H, s), 4.85 (1H, sept, *J* 6.2), 4.25-4.05 (3H, m, OC*H*$_2$CH$_3$, N*H*), 3.59 (1H, d, *J* 13.6), 3.14 (3H, s), 3.07 (1H, d, *J* 13.6), 1.14 (3H, t, *J* 7.1), 0.96 (3H, d, *J* 6.2), 0.88 (3H, d, *J* 6.2).

^{13}C NMR (126 MHz, toluene-d_8, 363K) δ 172.8, 170.3, 152.6, 142.0, 141.5, 131.7, 131.4, 129.1, 128.8, 127.5, 127.3, 123.5, 122.7, 114.6 [aromatics*], 124.6 (q, *J* 273.3, *C*F$_3$), 82.1, 71.7, 68.8, 61.2, 60.9, 51.5, 48.5, 20.8, 20.7, 14.0. *Remaining aromatic signal is buried under toluene peaks.

^{19}F NMR (377 MHz, $CDCl_3$, {^{1}H}) δ -55.6.

HRMS (ESI$^+$) 521.1877 ([M+H]$^+$, $C_{26}H_{28}F_3N_2O_6$ requires 521.1899).

3a-Isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (21)



This compound was prepared according to general procedure G, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (60 mg, 0.18 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (42 mg, 0.18 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [9:2]) afforded the title compound **21** as a colourless oil (54%, >20:1 d.r.).

IR (neat) ν_{max} 2280, 1618, 1539, 1329, 1243, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, dd, *J* 8.2, 5.1), 7.62 (1H, d, *J* 8.1), 7.49 (1H, dd, *J* 9.8, 2.7), 7.32 (2H, d, *J* 8.3), 7.28-7.20 (2H, m), 7.13-7.03 (4H, m), 6.96 (1H, t, *J* 7.5), 5.68 (1H, s), 4.88 (1H, sept, *J* 6.3), 3.50 (3H, s), 3.42 (1H, br s, N*H*), 3.37 (1H, d, *J* 14.2), 2.83 (1H, d, *J* 14.2), 2.25 (3H, s), 1.11 (6H, d, *J* 6.3).

^{13}C NMR (101 MHz) δ 171.2, 170.3, 164.0 (d, *J* 256.3), 152.2, 145.2, 141.6, 137.9, 135.3, 133.4, 130.8 (d, *J* 9.3), 129.8, 129.5, 127.6 (d, *J* 9.5), 124.3, 123.2, 120.3, 116.6 (d, *J* 25.9), 116.0 (d, *J* 23.4), 114.6, 82.1, 70.7, 70.2, 62.3, 53.4, 47.8, 21.5, 20.8.

^{19}F NMR (377 MHz, {^{1}H}) δ -103.4.

HRMS (ESI$^+$) 599.1910 ([M+Na]$^+$, $C_{30}H_{29}FN_4O_7Na$ requires 599.1918).

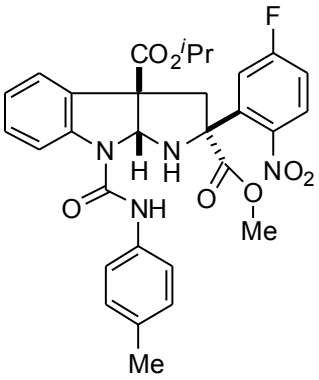
4. Enantioselective reaction

General Procedure H: The relevant Michael acceptor substrate (1.0 eq), isocyanide (1.1 eq) and catalyst **29** (0.1 eq) were dissolved in toluene/$CHCl_3$/H_2O (14:5:1 *v/v*, 10 mL/mmol substrate) at -20 °C. After 10 minutes, K_2CO_3 (5.0 eq) was added, and the mixture was stirred at -20 °C until both substrates were consumed according to thin layer chromatography (24-48 h). The reaction mixture was then loaded directly onto a silica gel column and purified by flash chromatography.

Catalyst synthesis: Catalysts **24**-**31** were synthesized from the appropriate cinchona alkaloid according to the procedure by Chen and co-workers (S. Wu, D. Pan, C. Cao, Q. Wang, F.-X. Chen, *Adv. Synth. Catal.* **2013**, *355*, 1917-1923).

Optimization reactions: To a vial containing isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (20 mg) in solvent (2 mL) was added methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (1.1 eq.), the appropriate catalyst (10 mol %) and finally the base. The reaction was stirred at the appropriate temperature for 24 h before an aliquot was removed and purified by preparative TLC. The sample was analyzed by chiral stationary phase HPLC to determine the e.r. (see Section 6).

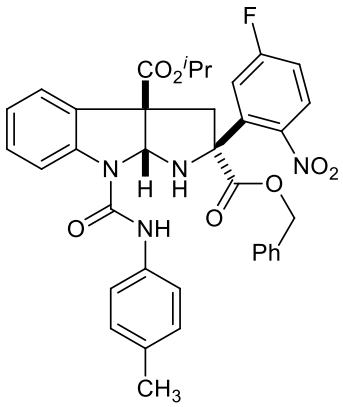
3a-Isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (21)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. Column chromatography (petrol:ethyl acetate [9:2]) afforded the title compound **21** as a colourless oil (60%, >20:1 d.r., 90:10 e.r.).

Data matched with those from the diastereoselective reaction.

2-Benzyl 3a-isopropyl 2-(5-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (32)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and benzyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. The reaction was performed at 0 °C. Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound **32** as a colourless oil (54%, >20:1 d.r., 90:10 e.r.).

IR (neat) ν_{max} 3401, 3270, 2981, 1733, 1593, 1530, 1479, 1345, 1238, 1103 cm^{-1}.

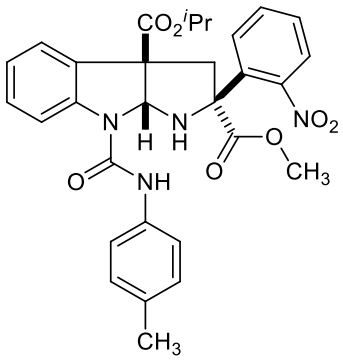
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, dd, *J* 8.9, 5.1), 7.63 (1H, d, *J* 7.7), 7.60 (1H, dd, *J* 9.0, 2.6), 7.41 (2H, d, *J* 8.4), 7.37-7.31 (2H, m), 7.31-7.29 (1H, m), 7.28-7.26 (1H, m), 7.23-7.11 (6H, m), 7.04 (1H, td, *J* 7.6, 0.8), 5.83 (1H, d, *J* 5.7), 5.06-4.98 (2H, m), 4.98 (1H, sept, *J* 6.3), 3.53 (1H, d, *J* 5.8), 3.44 (1H, d, *J* 14.3), 3.00 (1H, d, *J* 14.2), 2.36 (3H, s), 1.21 (3H, d, *J* 6.2), 1.19 (3H, d, *J* 6.1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.3, 164.0 (d, *J* 254.8), 152.1, 145.1, 141.5, 138.2, 135.4, 134.7, 133.3, 130.8, 129.8, 129.5, 128.5, 128.5, 128.2, 127.6 (d, *J* 9.5), 124.3, 123.1, 120.1, 116.6 (d, *J* 26.0), 116.0 (d, *J* 23.3), 114.3, 82.3, 70.9, 70.2, 68.2, 62.2, 47.8, 21.5, 21.5, 20.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ -103.3 (ddd, *J* 9.8, 6.7, 4.9).

m/z HRMS (ESI^+) 675.2222 ($[M+Na]^+$, $C_{36}H_{33}FN_4O_7Na$ requires 675.2225).

3a-Isopropyl 2-methyl 2-(2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (33)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-isocyano-2-(2-nitrophenyl)acetate as the isocyanide. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **33** as a colourless oil (46%, 8.9:1 d.r., 93:7 e.r.).

Data are provided for major DS only.

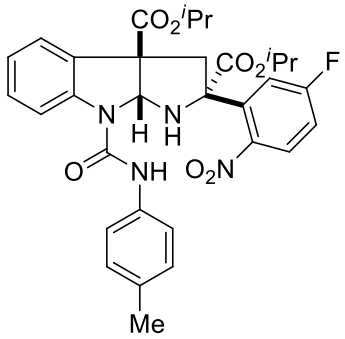
IR (neat) ν_{max} 3404, 3279, 1727, 1532, 1479, 1372, 1238, 1101 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* 8.1), 7.73 (1H, dd, *J* 7.9, 1.1), 7.68 (1H, dd, *J* 7.8, 1.3), 7.57 (1H, td, *J* 7.6, 1.3), 7.51-7.45 (3H, m), 7.43 (1H, br s), 7.36-7.28 (2H, m), 7.17 (2H, d, *J* 8.3), 7.03 (1H, td, *J* 7.5, 0.9), 5.58 (1H, s), 4.90 (1H, sept, *J* 6.2), 3.69 (1H, d, *J* 14.0), 3.63 (3H, s), 2.75 (1H, d, *J* 14.1), 2.34 (3H, s), 1.16 (3H, d, *J* 6.2), 1.12 (3H, d, *J* 6.3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 170.3, 152.1, 149.7, 141.9, 135.5, 133.2, 131.8, 130.5, 129.9, 129.5, 129.5, 129.4, 129.2, 124.8, 124.2, 123.2, 120.3, 115.4, 81.7, 70.6, 70.0, 62.9, 53.4, 47.8, 21.5, 21.5, 20.9.

m/z HRMS (ESI$^+$) 581.2018 ([M+Na]$^+$, $C_{30}H_{30}N_4O_7Na$ requires 581.2007).

Diisopropyl 2-(5-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (34)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and isopropyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound **34** as a colourless oil (49%, >20:1 d.r., 92:8 e.r.).

On a 1.00 g scale (of isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate) this reaction afforded the title compound **34** in a 76 % yield, >20:1 d.r., 92:8 e.r..

IR (neat) ν_{max} 2280, 1618, 1539, 1329, 1243, 812 cm^{-1}.

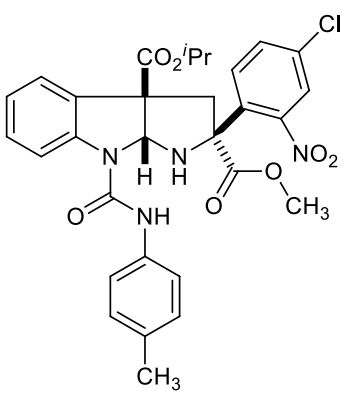
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, dd, *J* 8.8, 5.1), 7.72 (1H, d, *J* 8.1), 7.56 (1H, dd, *J* 9.8, 2.7), 7.42 (2H, d, *J* 8.4), 7.37-7.28 (3H, m), 7.22-7.11 (4H, m), 7.04 (1H, td, *J* 7.5, 0.8), 5.76 (1H, d, *J* 6.0), 4.97 (1H, sept, *J* 6.2), 4.90 (1H, sept, *J* 6.2), 3.43 (1H, d, *J* 6.1), 3.43 (1H, d, *J* 14.2), 2.92 (1H, d, *J* 14.2), 2.34 (3H, s), 1.21 (3H, d, *J* 6.3), 1.18 (3H, d, *J* 6.2), 1.10 (3H, d, *J* 6.3), 1.05 (3H, d, *J* 6.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 170.0, 163.9 (d, *J* 255.4), 152.1, 145.2 (d, *J* 4.4), 141.7, 135.4, 133.2, 130.7, 129.8, 129.5, 128.5 (d, *J* 9.2), 127.4 (d, *J* 9.3), 124.3, 124.3, 123.1, 120.2, 116.6 (d, *J* 25.8), 115.8 (d, *J* 23.1), 114.6, 82.3, 71.0, 70.7, 70.2, 62.4, 47.9, 21.5, 21.5, 21.3, 21.2, 20.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ -103.5 (m).

m/z HRMS (ESI$^+$) 627.2228 ([M+Na]$^+$, $C_{32}H_{33}FN_4NaO_7$ requires 627.2225).

3a-Isopropyl 2-methyl 2-(4-chloro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (35)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-(4-chloro-2-nitrophenyl)2-isocyanoacetate as the isocyanide. The reaction was performed at 0 °C. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **35** as a colourless oil (45%, >20:1 d.r., 86:14 e.r.).

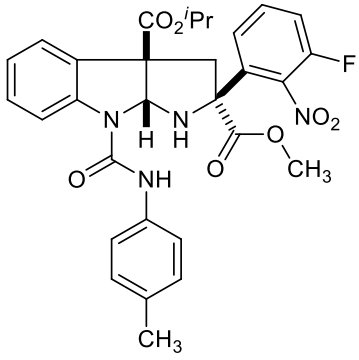
IR (neat) ν_{max} 3401, 3269, 1728, 1531, 1485, 1364, 1240, 1105 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, d, *J* 7.9), 7.72 (1H, d, *J* 8.5), 7.69 (1H, d, *J* 2.2), 7.54 (1H, dd, *J* 8.5, 2.2), 7.44 (2H, d, *J* 8.4), 7.34-7.28 (3H, m), 7.17 (2H, d, *J* 8.2), 7.04 (1H, td, *J* 7.5, 0.8), 5.64 (1H, s), 4.93 (1H, sept, *J* 6.2), 3.60 (3H, s), 3.57 (1H, d, *J* 14.0), 2.81 (1H, d, *J* 14.0), 2.34 (3H, s), 1.17 (3H, d, *J* 6.2), 1.15 (3H, d, *J* 6.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.2, 152.0, 149.8, 141.8, 135.4, 135.2, 133.3, 131.9, 131.7, 130.5, 130.4, 129.9, 129.5, 124.9, 124.2, 123.2, 120.3, 115.1, 81.9, 70.4, 70.1, 62.7, 53.5, 47.7, 21.5, 21.5, 20.9.

m/z HRMS (ESI^+) 615.1610 ($[M+Na]^+$, $C_{30}H_{29}ClN_4O_7Na$ requires 615.1617).

3a-Isopropyl 2-methyl 2-(3-fluoro-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (36)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate **(**50 mg mmol) as the Michael acceptor and methyl 2-(3-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. The reaction was performed at 0 °C. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **36** as a colourless oil (49%, 8.1:1 d.r., 67:37 e.r.).

Data are provided for major DS only.

IR (neat) v_{max} 3403, 3279, 2972, 1728, 1678, 1594, 1543, 1480, 1368, 1237, 1101 cm^{-1}.

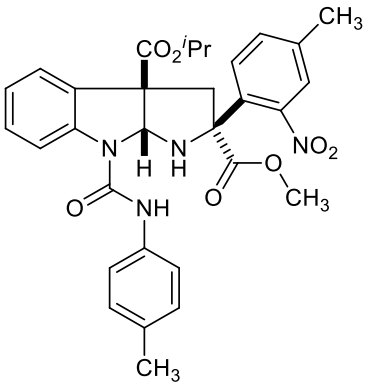
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* 8.0), 7.52 (2H, d, *J* 8.5), 7.47 (1H, dd, *J* 8.2, 5.3), 7.43-7.37 (2H, m), 7.34-7.30 (1H, m), 7.30 (1H, td, *J* 7.8, 1.3), 7.27 (1H, td, *J* 8.3, 1.2), 7.18 (2H, d, *J* 8.3), 7.03 (1H, t, *J* 7.5), 5.62 (1H, s), 4.94 (1H, sept, *J* 6.2), 3.64 (1H, d, *J* 13.7), 3.60 (3H, s), 3.33 (1H, br s), 2.76 (1H, d, *J* 13.8), 2.34 (3H, s), 1.20 (3H, d, *J* 6.2), 1.14 (3H, d, *J* 6.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.2, 154.4 (d, *J* 258.6), 152.0, 142.1, 135.5, 133.2, 132.9, 131.2 (d, *J* 8.1), 130.0, 129.8, 129.5, 129.4, 124.4 (d, *J* 3.2), 124.2, 123.2, 120.5, 117.5 (d, *J* 19.5), 115.6, 81.5, 70.7, 70.1, 63.0, 53.6, 48.1, 21.5, 21.5, 20.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ -122.9 (m).

m/z HRMS (ESI^+) 599.1926 ($[M+Na]^+$, $C_{30}H_{29}FN_4O_7Na$ requires 599.1912).

3a-Isopropyl 2-methyl 2-(4-methyl-2-nitrophenyl)-8-(*p*-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2,3a-dicarboxylate (37)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-isocyano-2-(4-methyl-2-nitrophenyl)acetate as the isocyanide. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound **37** as a colourless oil (83%, 10:1 d.r., 93:7 e.r.).

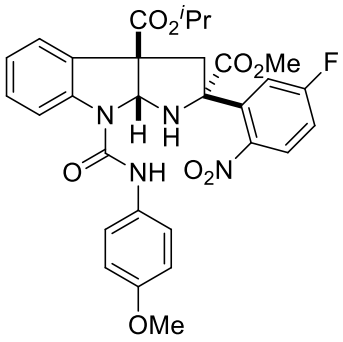
IR (neat) v_{max} 3399, 3267, 1728, 1535, 1479, 1372, 1238, 1102 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* 8.1), 7.56 (1H, d, *J* 8.1), 7.51-7.44 (4H, m), 7.38-7.27 (3H, m), 7.17 (2H, d, *J* 8.3), 7.02 (1H, td, *J* 7.5, 0.9), 5.55 (1H, s), 4.91 (1H, sept, *J* 6.2), 3.68 (1H, d, *J* 13.9), 3.63 (3H, s), 2.70 (1H, d, *J* 14.0), 2.42 (3H, s), 2.34 (3H, s), 1.18 (3H, d, *J* 6.2), 1.13 (3H, d, *J* 6.3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.3, 152.1, 149.6, 141.9, 140.3, 135.6, 133.1, 132.3, 130.4, 129.8, 129.4, 129.4, 129.0, 125.2, 124.2, 123.2, 120.3, 115.5, 81.7, 70.4, 69.9, 63.0, 53.4, 47.8, 21.5, 21.5, 20.9, 20.8.

m/z HRMS (ESI^+) 595.2174 ($[M+Na]^+$, $C_{31}H_{32}N_4O_7Na$ requires 595.2163).

3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-8-((4-methoxyphenyl)carbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (38)



This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. Column chromatography

(petrol:ethyl acetate [4:1]) afforded the title compound **38** as a colourless oil (74%, >20:1 d.r., 90:10 e.r.).

IR (neat) ν_{max} 3402, 3282, 1727, 1677, 1514, 1479, 1372, 1232, 1101 cm^{-1}.

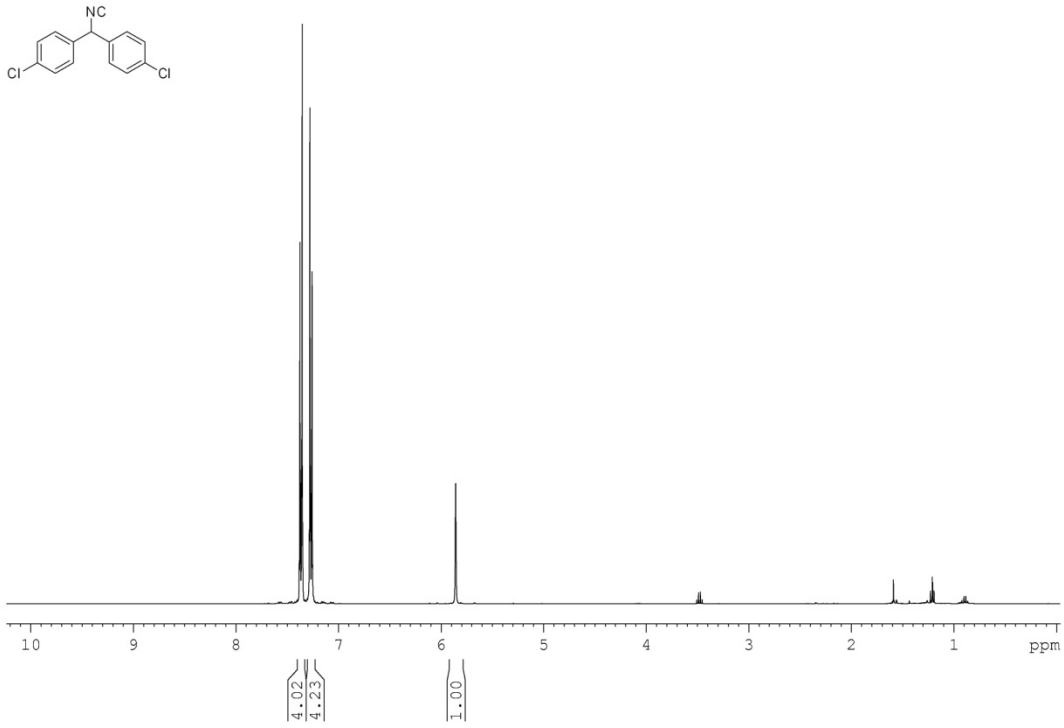
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (1H, dd, *J* 8.8, 5.0), 7.73 (1H, d, *J* 8.1), 7.56 (1H, dd, *J* 9.8, 2.7), 7.45 (2H, d, *J* 9.0), 7.34 (1H, d, *J* 7.4), 7.32 (1H, ddd, *J* 7.9, 7.7, 1.2), 7.20 (1H, s, N*H*), 7.16 (1H, ddd, *J* 8.8, 6.9, 2.7), 7.04 (1H, td, *J* 7.5, 0.8), 6.91 (2H, d, *J* 9.0), 5.73 (1H, s), 4.96 (1H, sept, *J* 6.2), 3.82 (3H, s), 3.60 (3H, s), 3.48 (1H, d, *J* 14.2), 2.88 (1H, d, *J* 14.2), 1.20 (3H, d, *J* 6.3), 1.18 (3H, d, *J* 6.2).

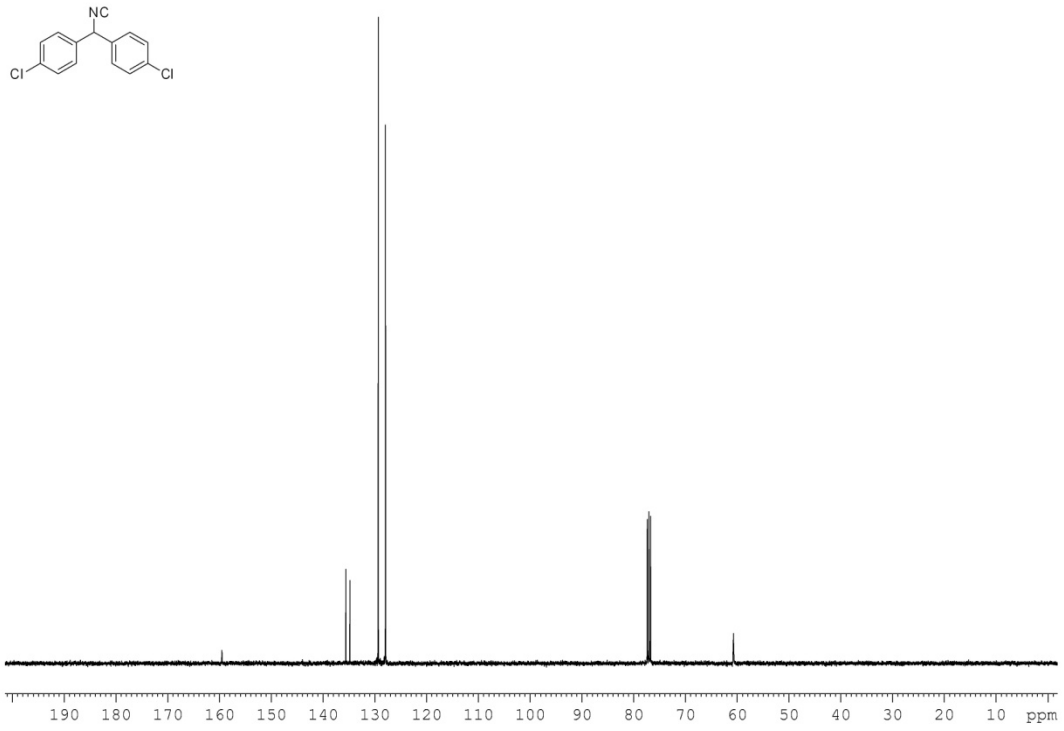
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.3, 163.9 (d, *J* 254.9), 155.2, 152.3, 145.2 (d, *J* 2.9), 141.7, 131.0, 130.7, 129.8, 128.5 (d, *J* 9.8), 127.5 (d, *J* 10.0), 124.3, 123.2, 122.1, 116.6 (d, *J* 25.7), 116.0 (d, *J* 23.4), 114.7, 114.2, 82.0, 70.6, 70.2, 62.4, 55.5, 53.4, 47.8, 21.5, 21.5.

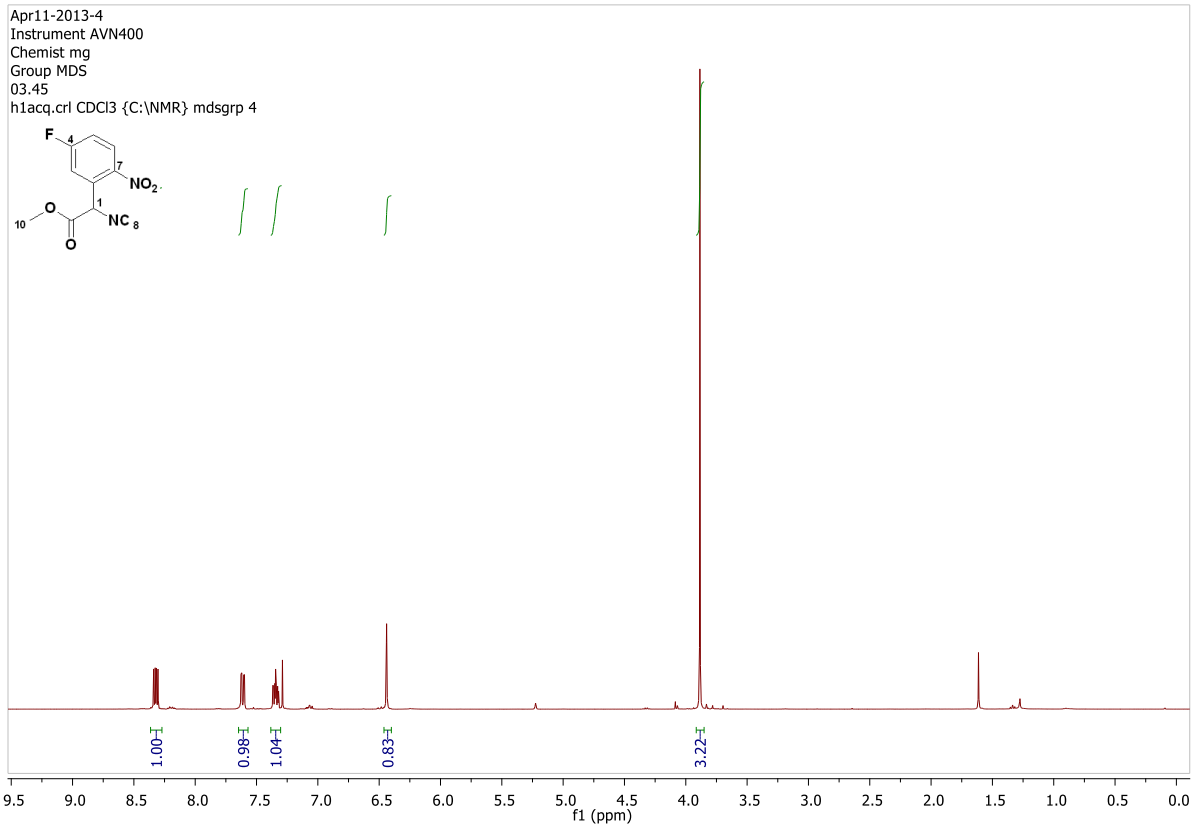
^{19}F NMR (377 MHz, $CDCl_3$) δ -103.5 (m).

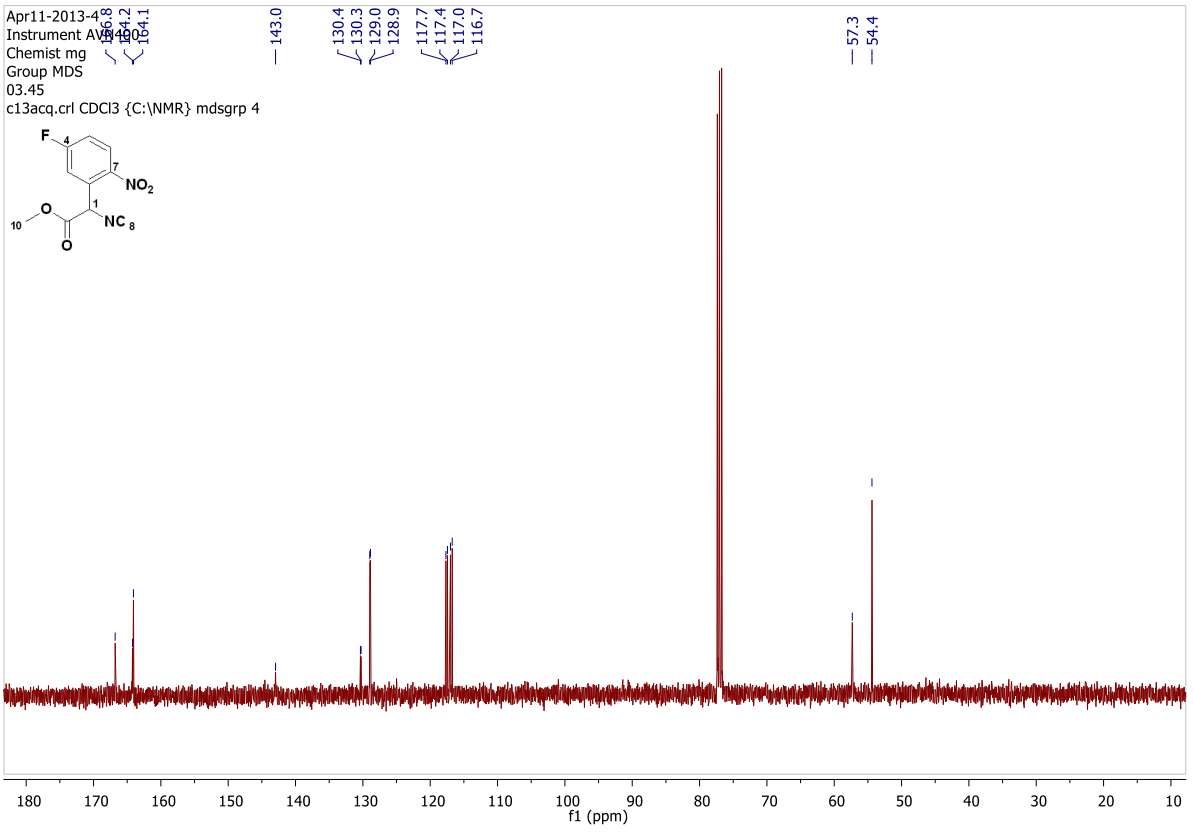
m/z HRMS (ESI^+) 615.1855 ($[M+Na]^+$, $C_{30}H_{29}FN_4NaO_8$ requires 615.1862).

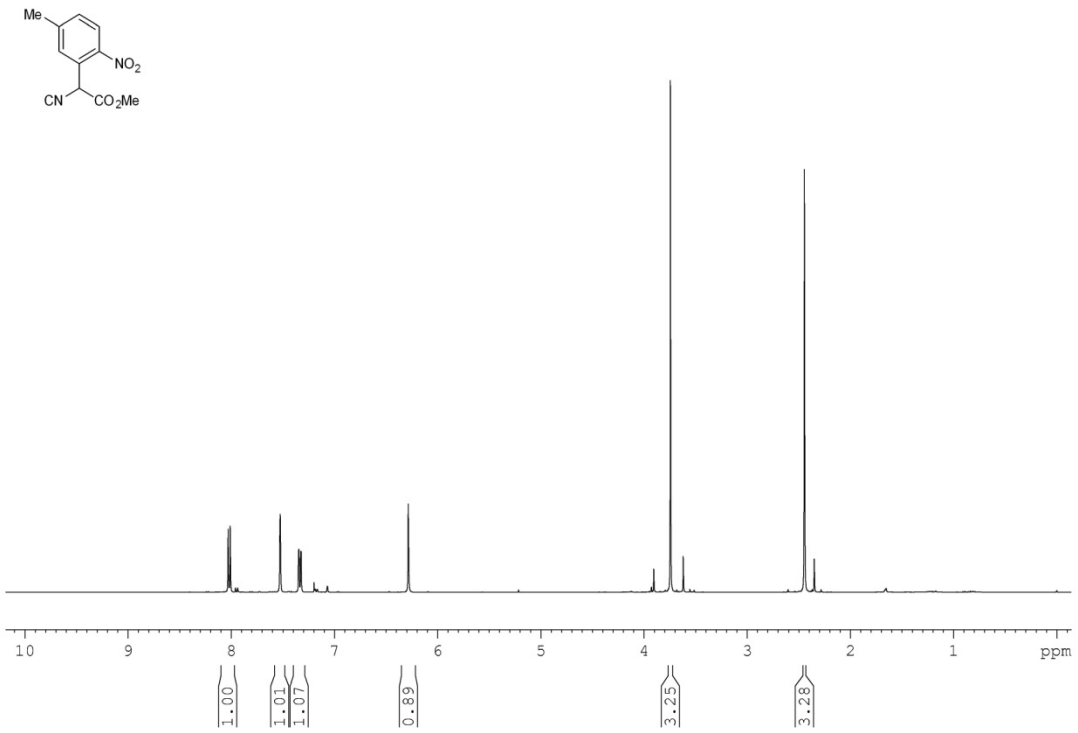
5. NMR Spectra of Novel Compounds

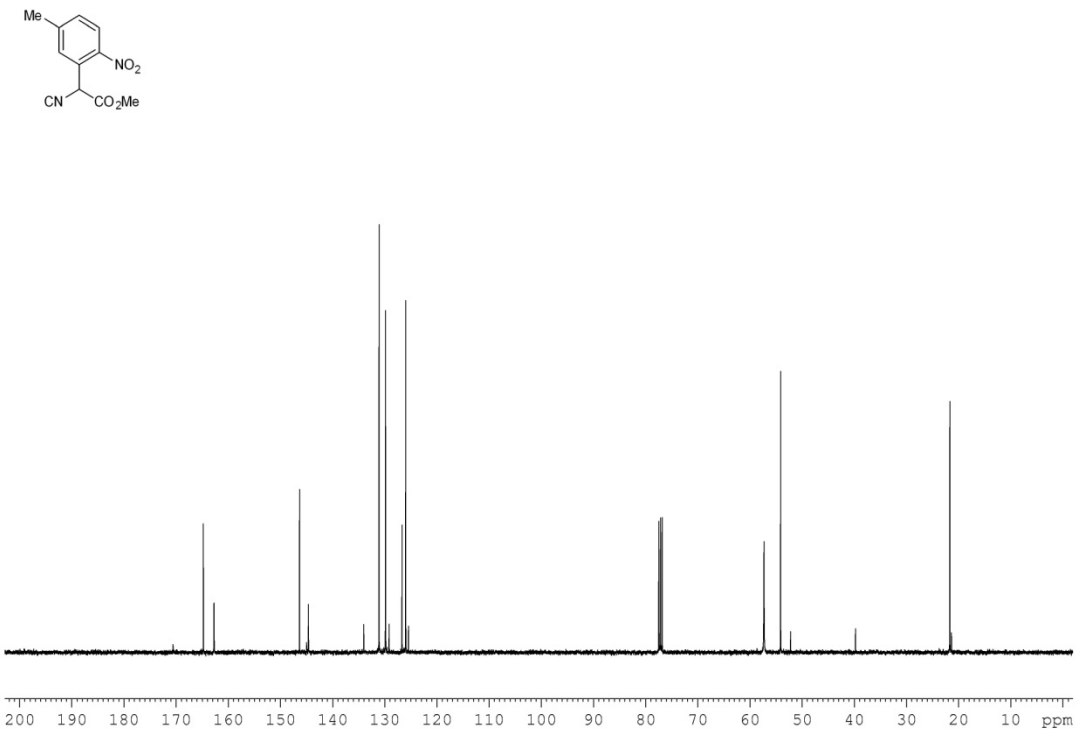


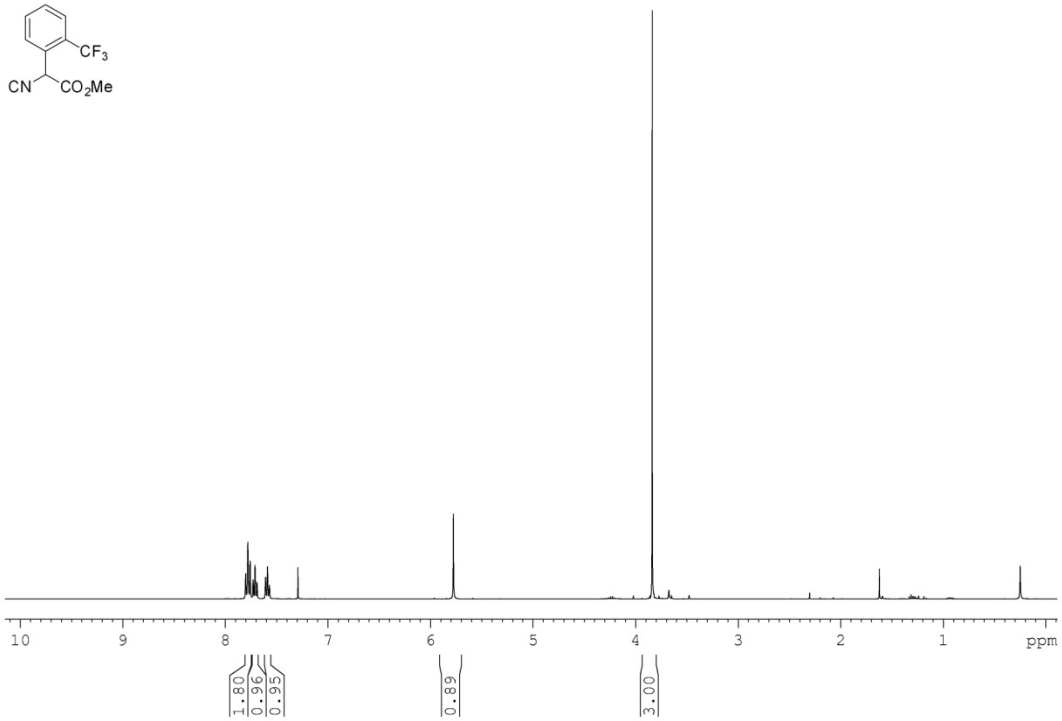


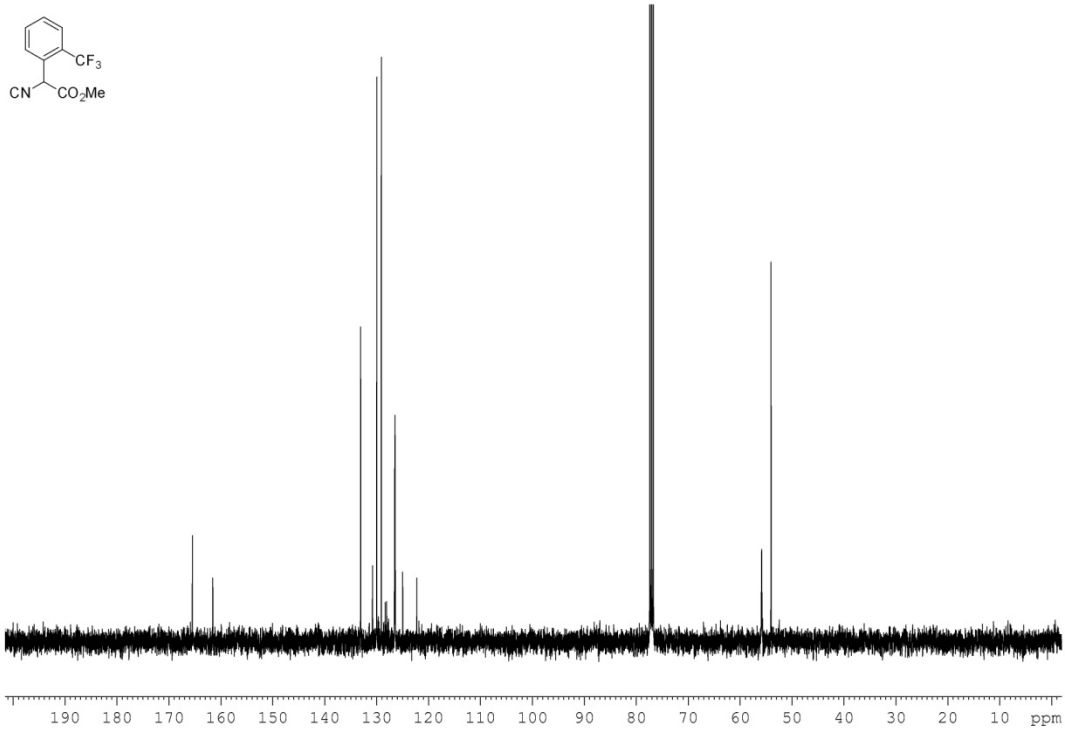

Apr11-2013-4
Instrument AVN400
Chemist mg
Group MDS
03.45
h1acq.crl CDCl3 {C:\NMR} mdsgrp 4
1.00
0.98
1.04
0.83
3.22
f1 (ppm)

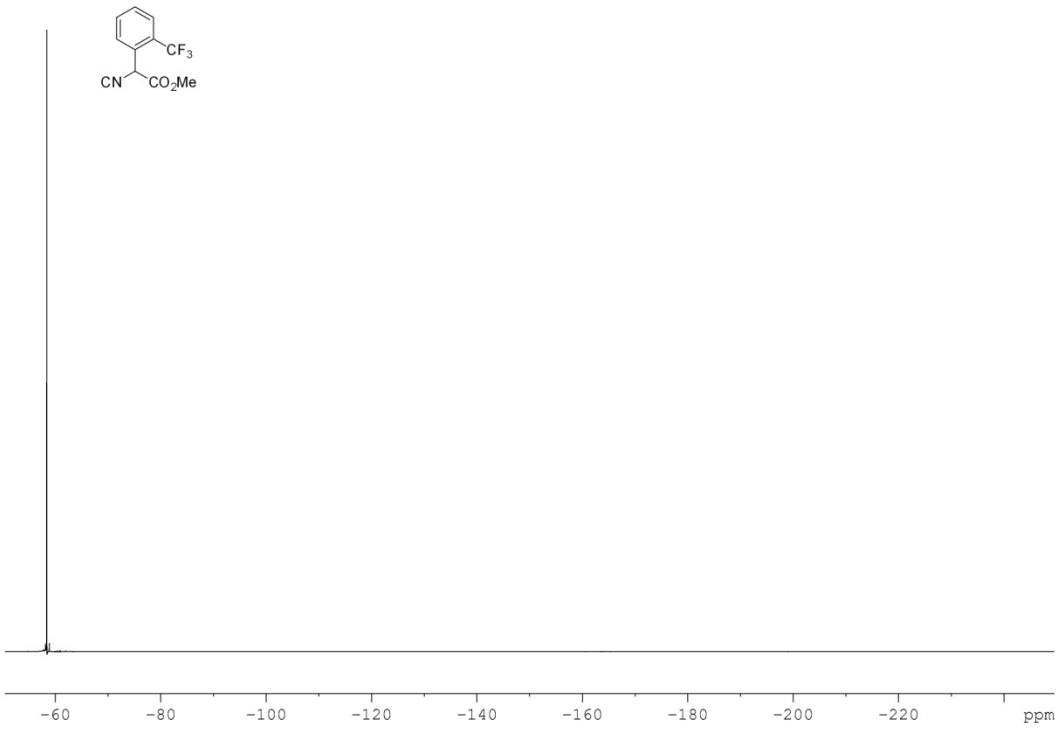

Apr11-2013-4
Instrument AVN400
Chemist mg
Group MDS
03.45
c13acq.crl CDCl3 {C:\NMR} mdsgrp 4
166.8
164.2
164.1
143.0
130.4
130.3
129.0
128.9
117.7
117.4
117.0
116.7
57.3
54.4
f1 (ppm)

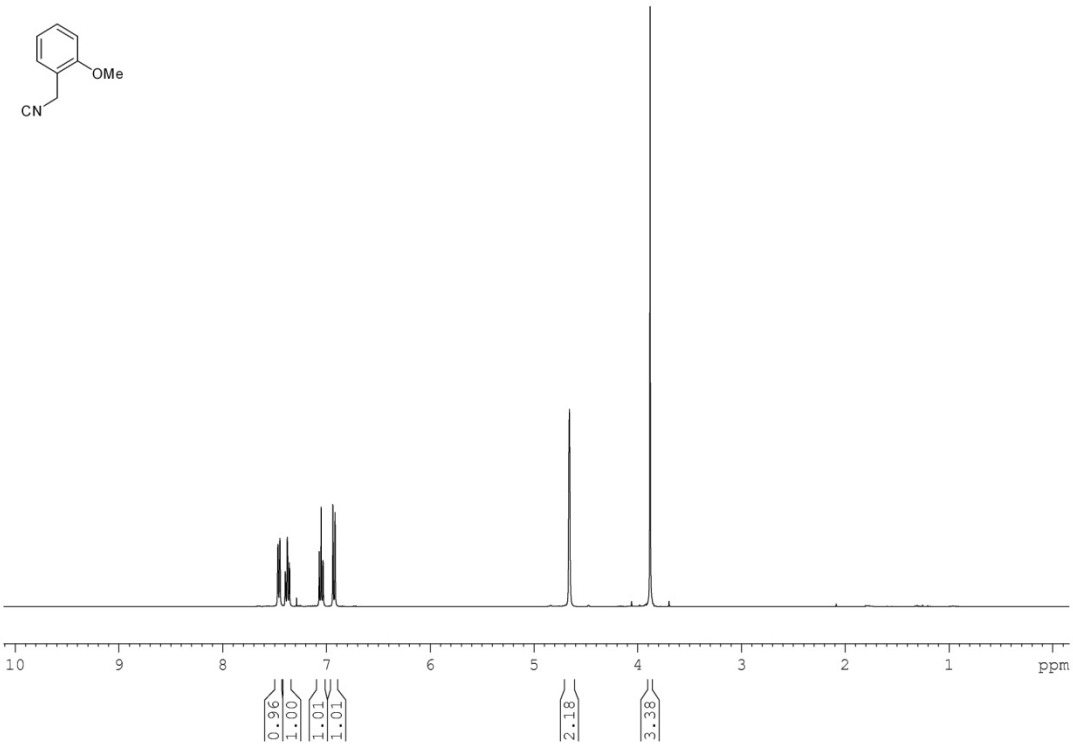

Me
NO2
CN
CO2Me
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
1.07
0.89
3.25
3.28

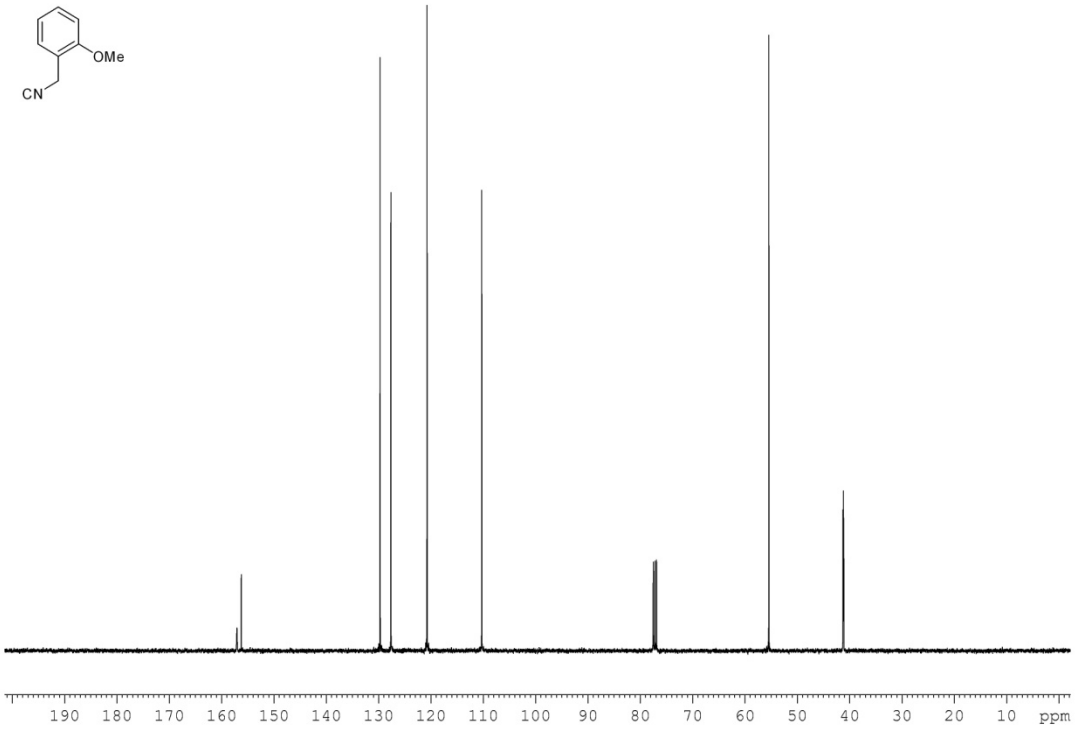

Me
NO2
CN
CO2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

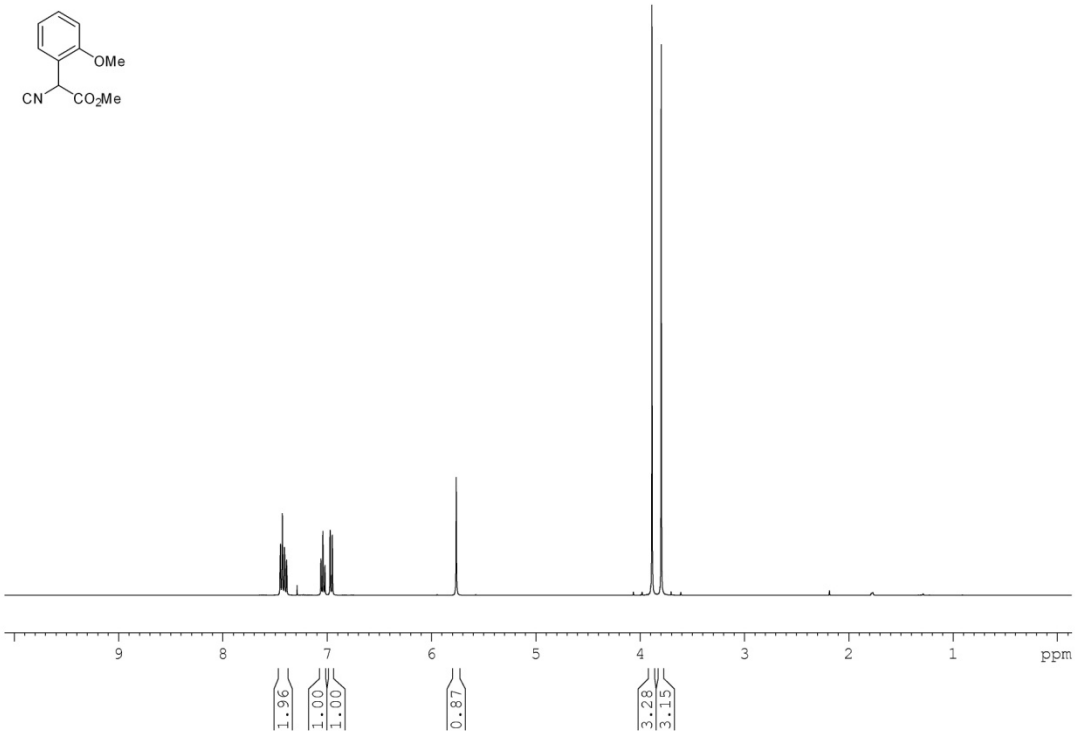

CF3
CN
CO2Me
10
9
8
7
6
5
4
3
2
1
ppm
1.80
0.96
0.95
0.89
3.00

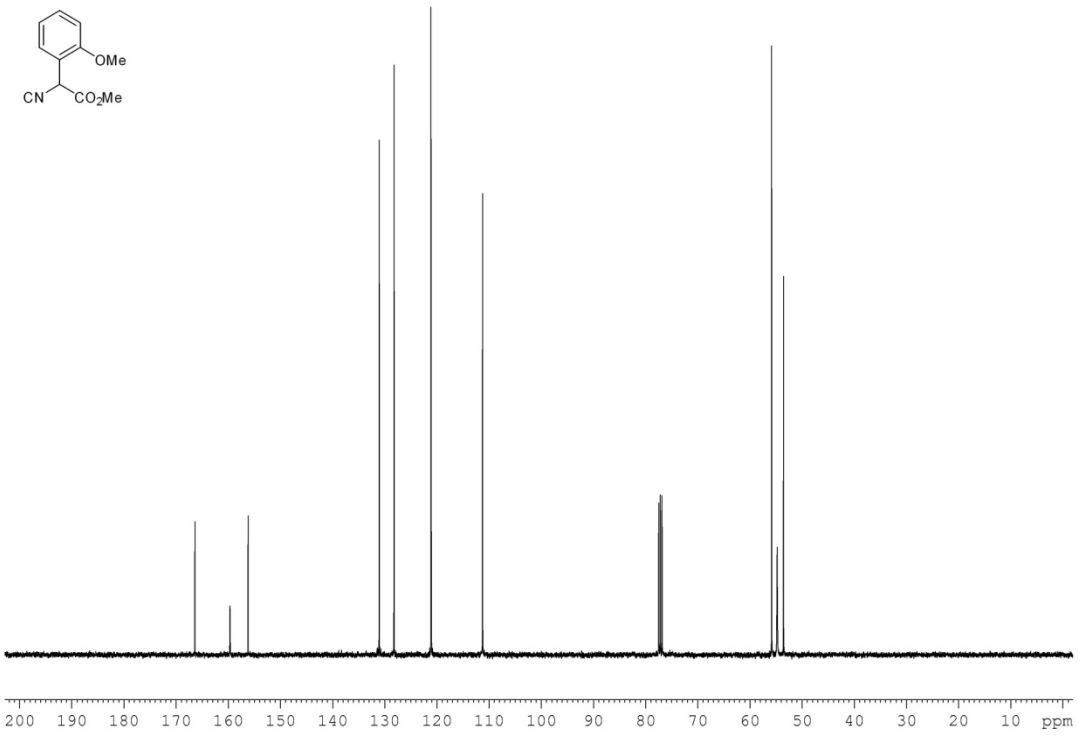

CF3
CN
CO2Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

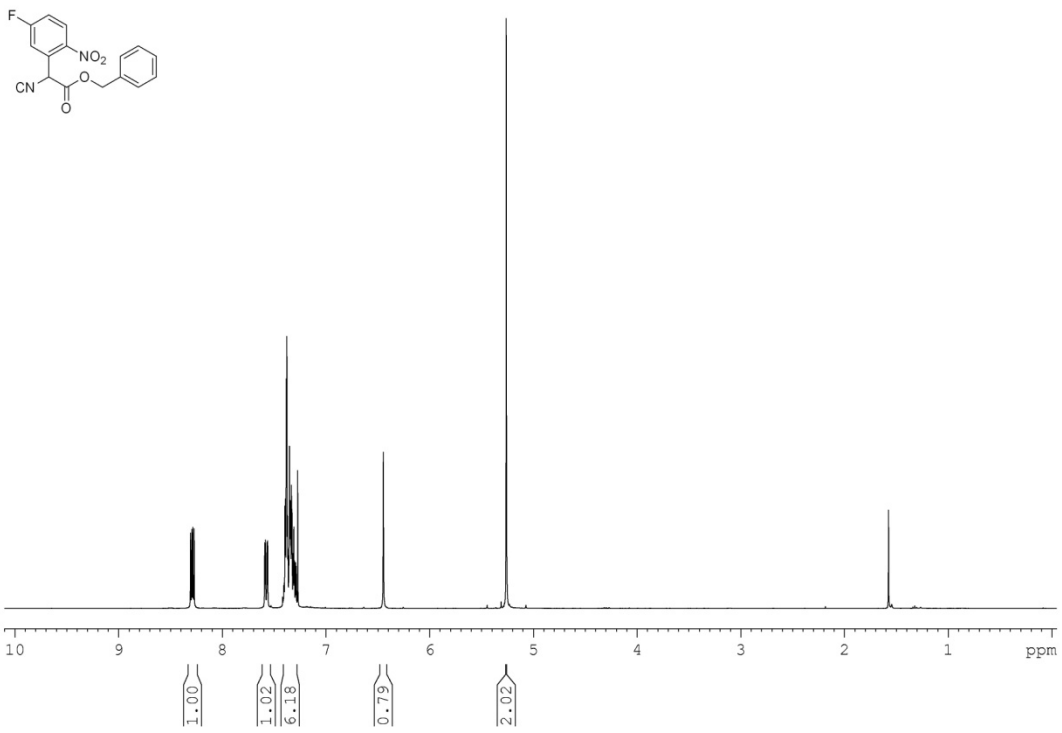

CF3
CN
CO2Me
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

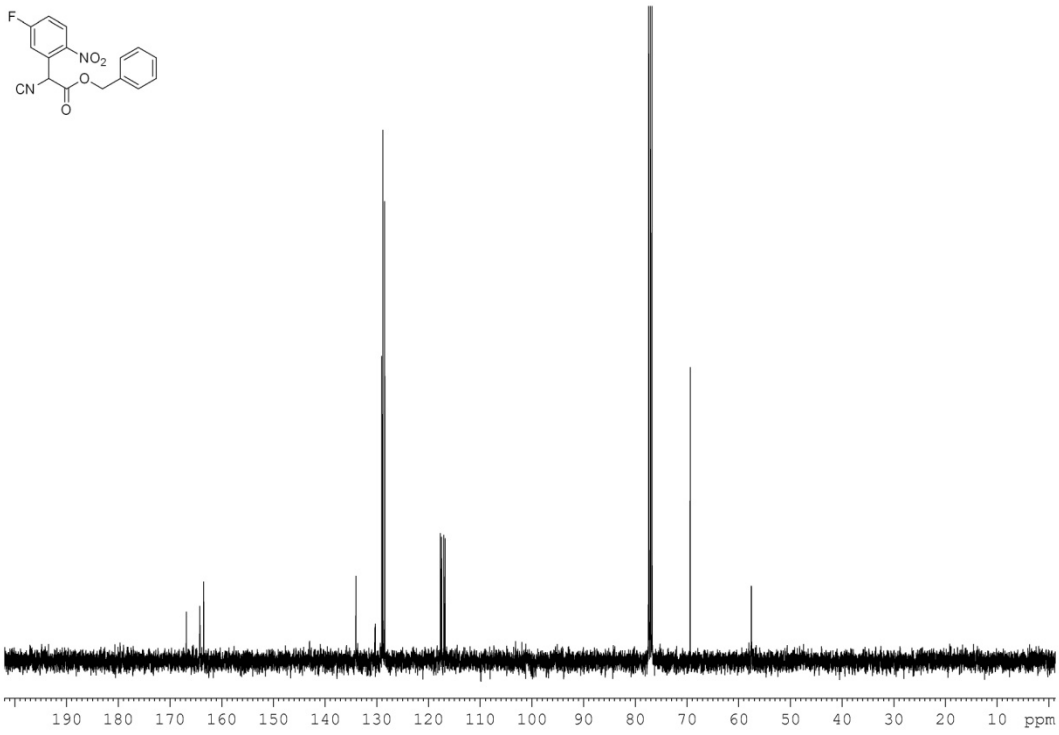

OMe
CN
10
9
8
7
6
5
4
3
2
1
ppm
0.96
1.00
1.01
1.01
2.18
3.38

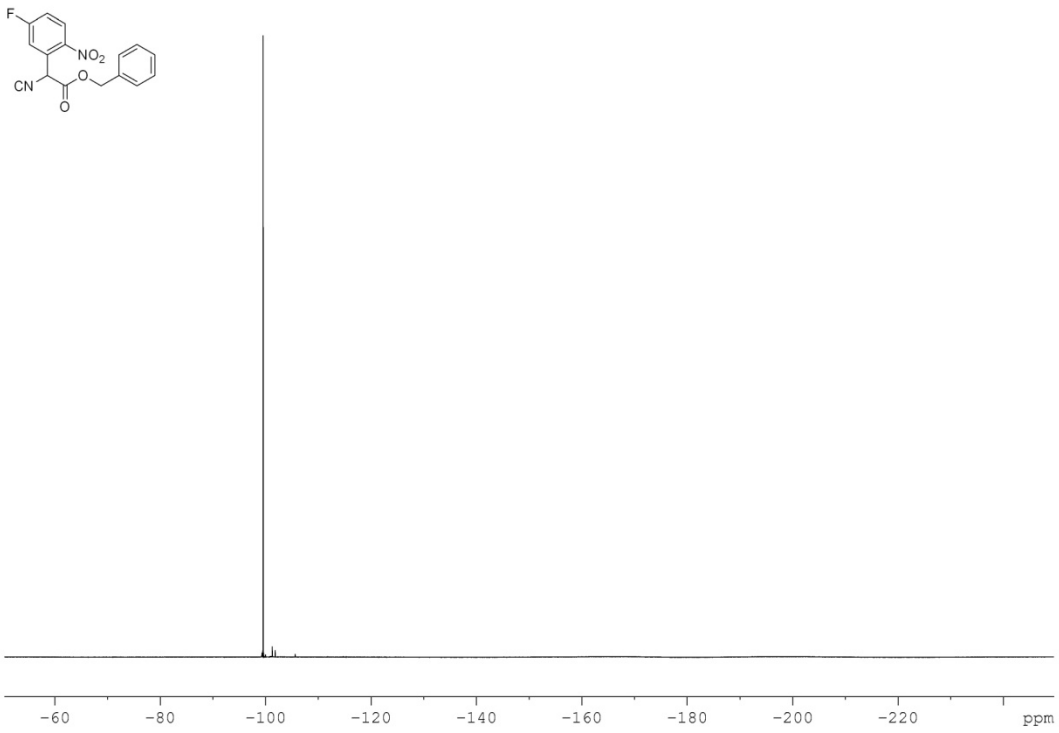

OMe
CN
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

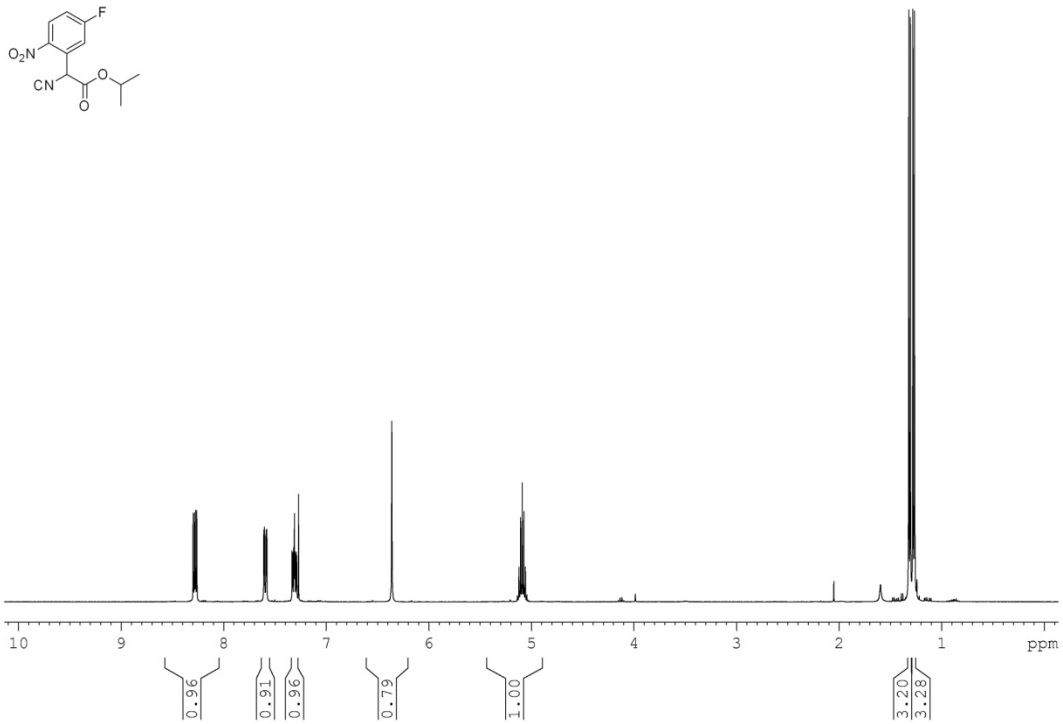

OMe
CN
CO2Me
9 8 7 6 5 4 3 2 1 ppm
1.96
1.00
1.00
0.87
3.28
3.15

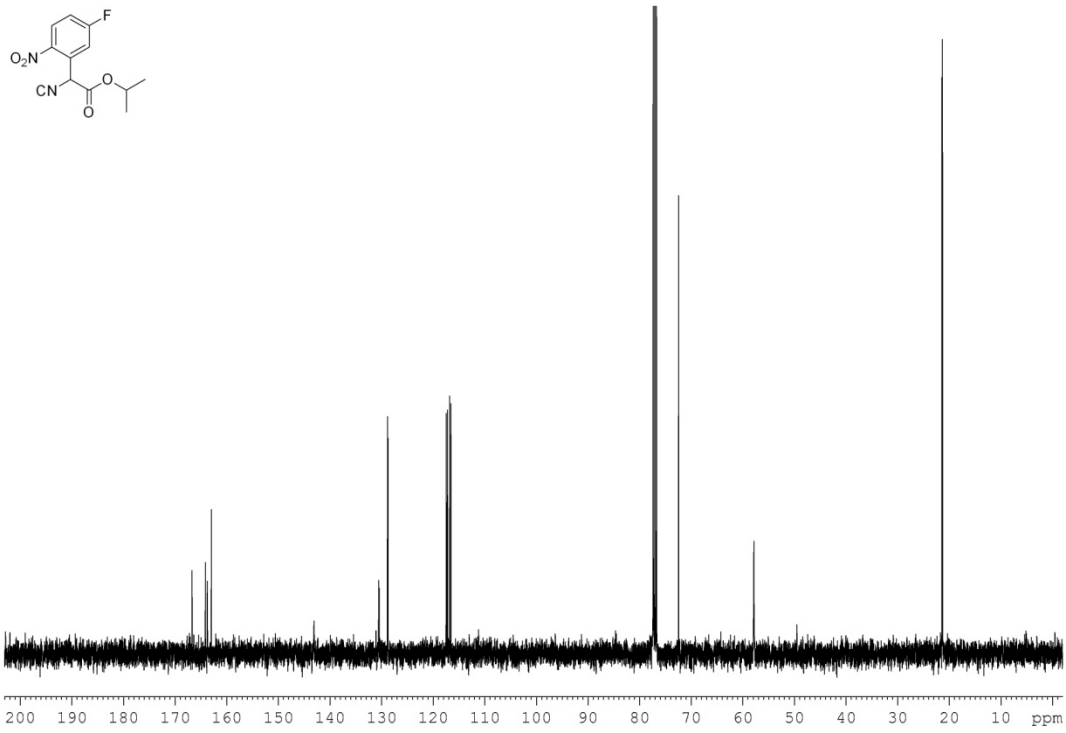

OMe
CN
CO2Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

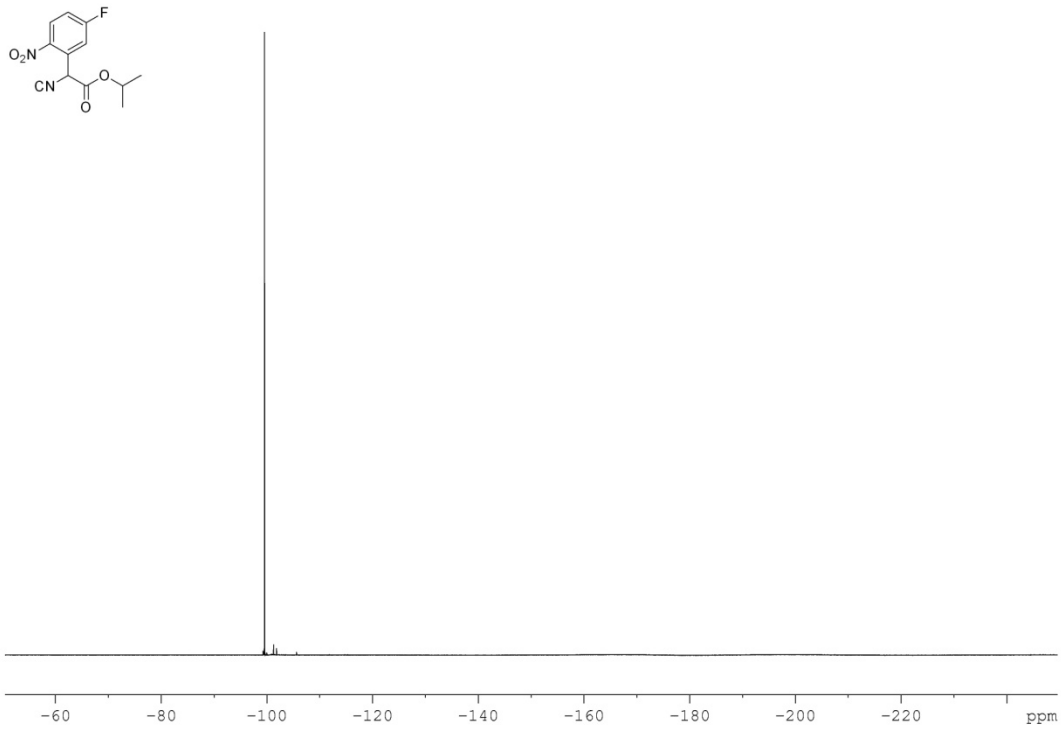

F
NO2
CN
O
O
10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.02
6.18
0.79
2.02

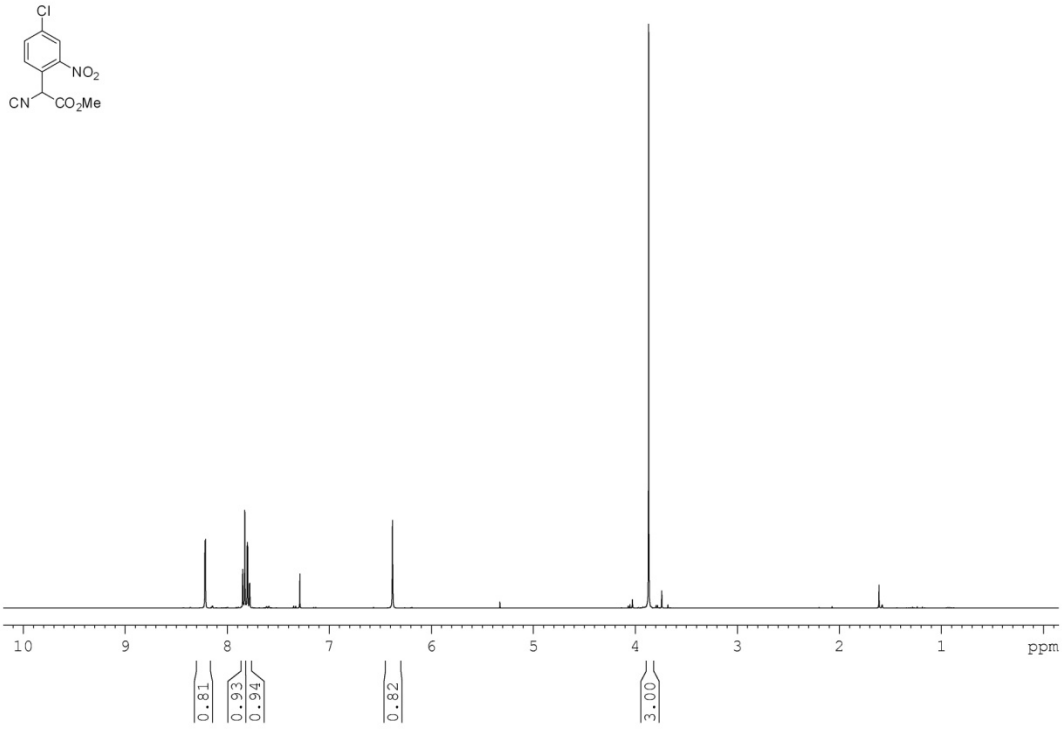

F
NO2
CN
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

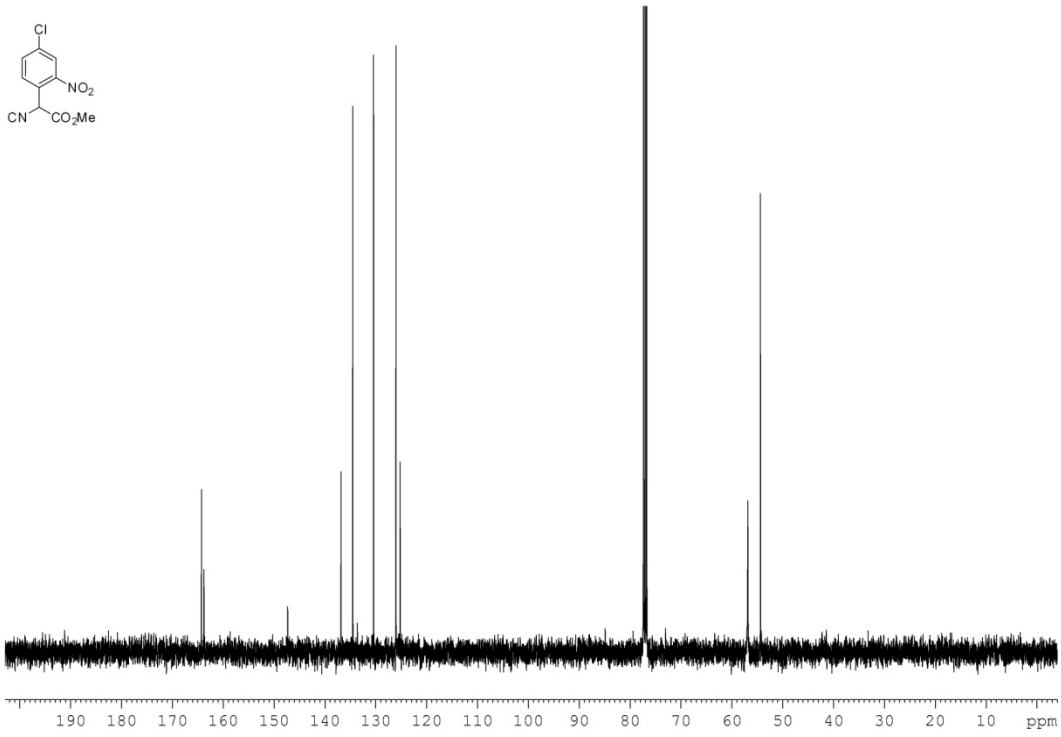

F
NO2
CN
O
O
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

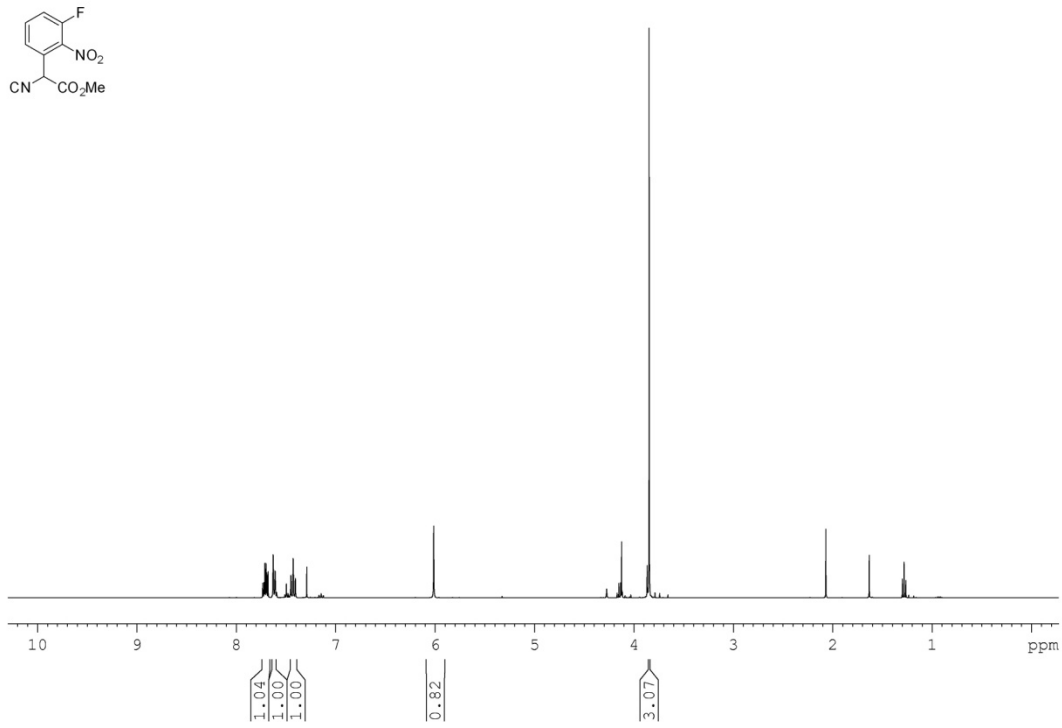

F
O2N
CN
O
O
10
9
8
7
6
5
4
3
2
1
ppm
0.96
0.91
0.96
0.79
1.00
3.20
3.28

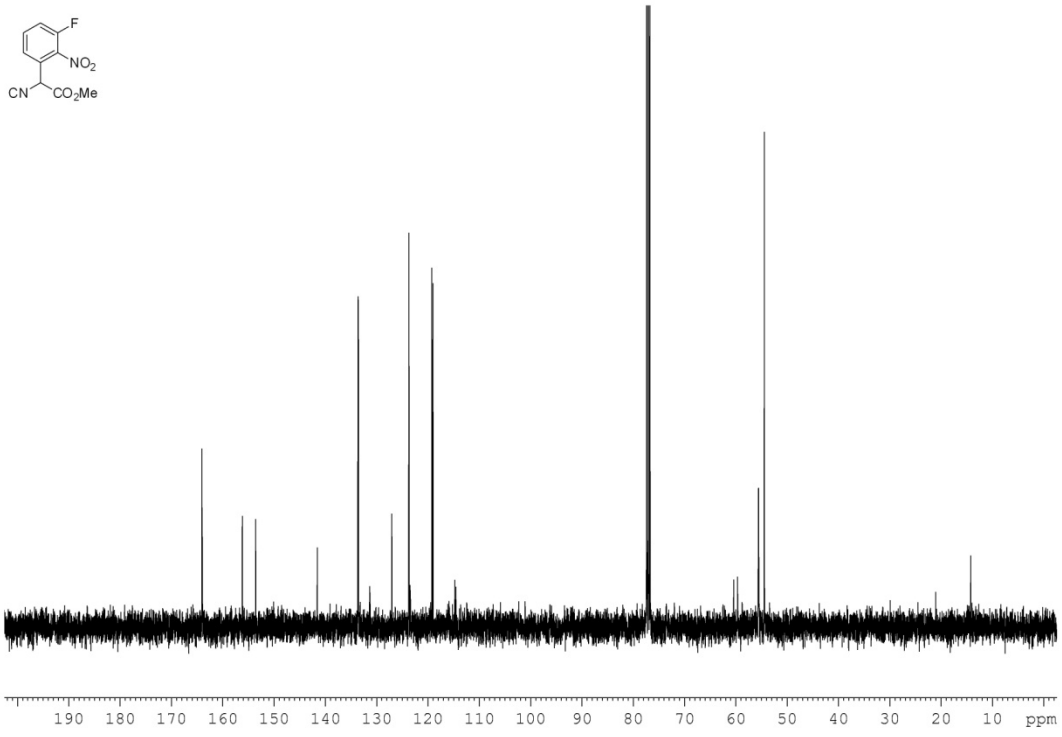

F
O2N
CN
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

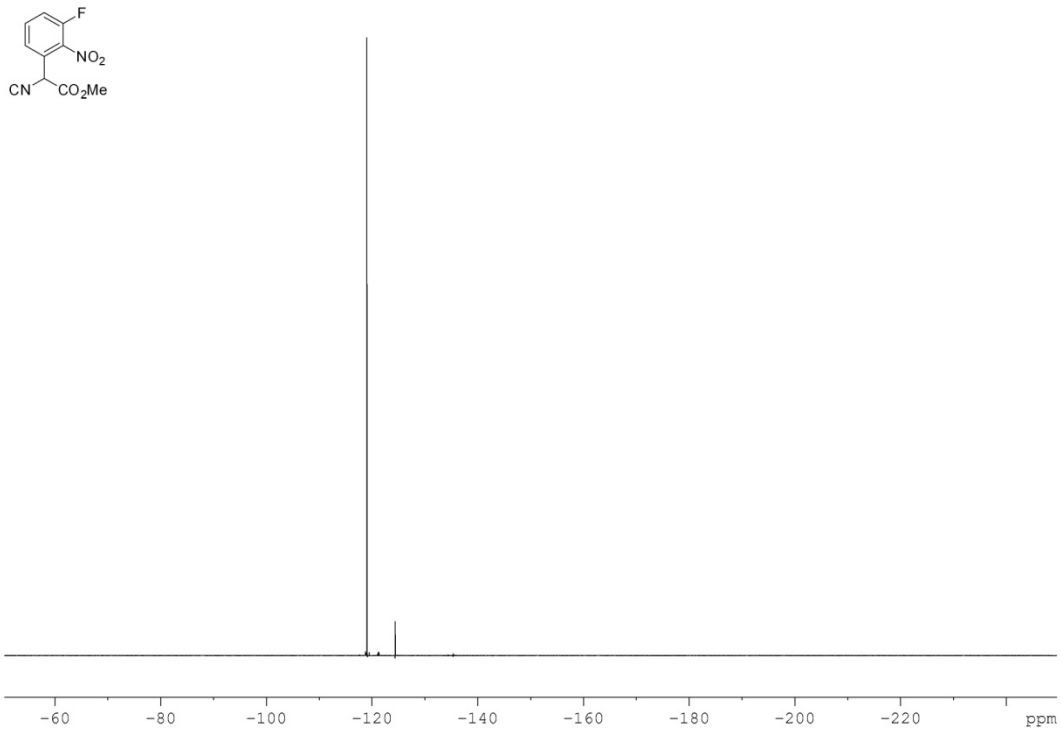

F
O2N
CN
O
O
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

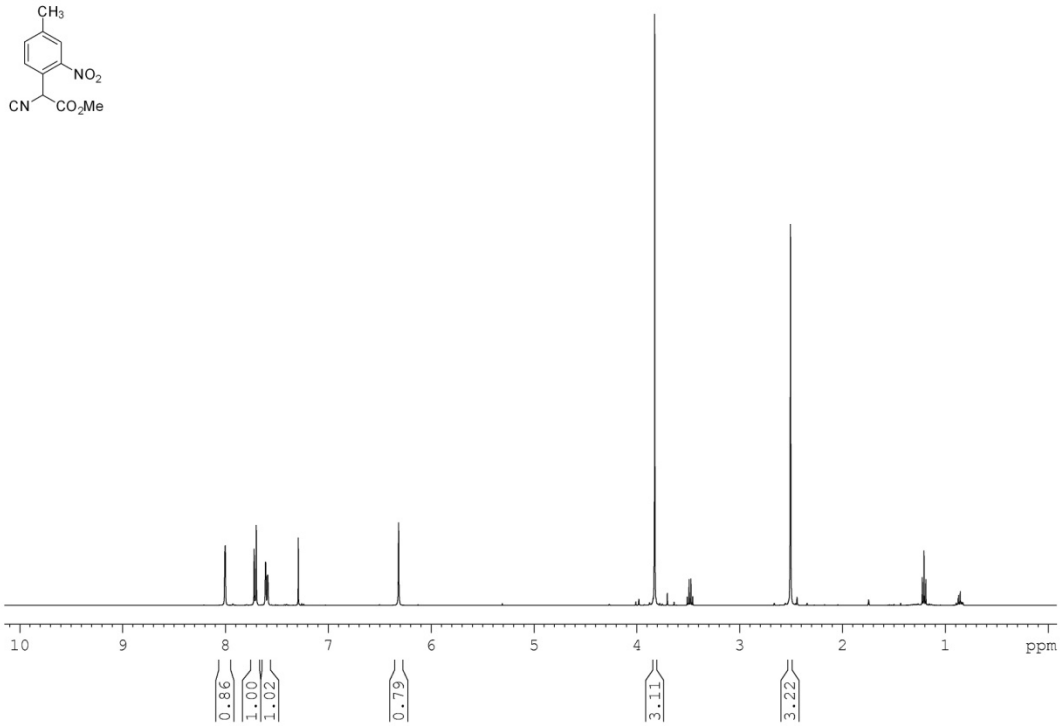

Cl
NO2
CN
CO2Me
10
9
8
7
6
5
4
3
2
1
ppm
0.81
0.93
0.94
0.82
3.00

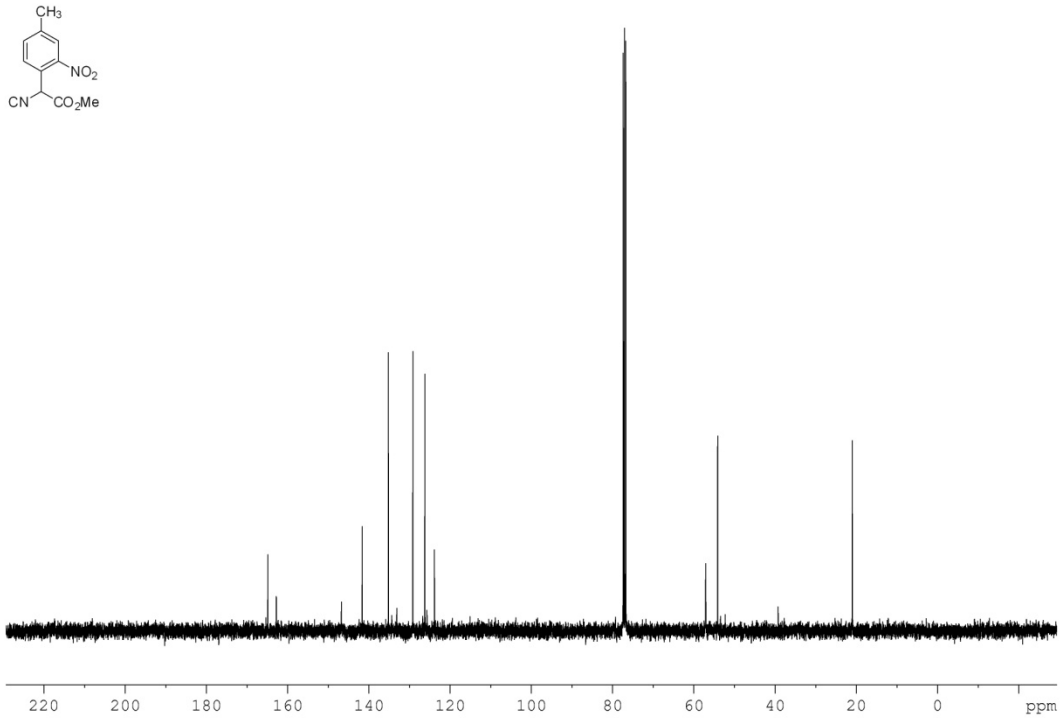

Cl
NO2
CN
CO2Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

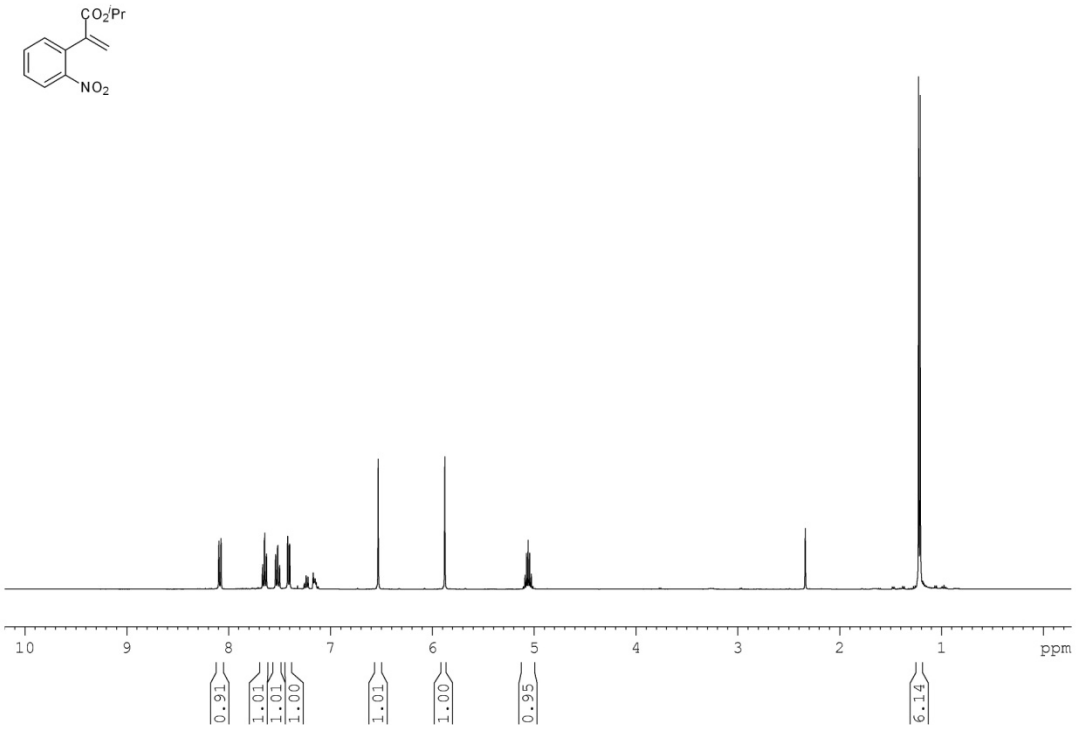

F
NO2
CN
CO2Me
10 9 8 7 6 5 4 3 2 1 ppm
1.04
1.00
1.00
0.82
3.07

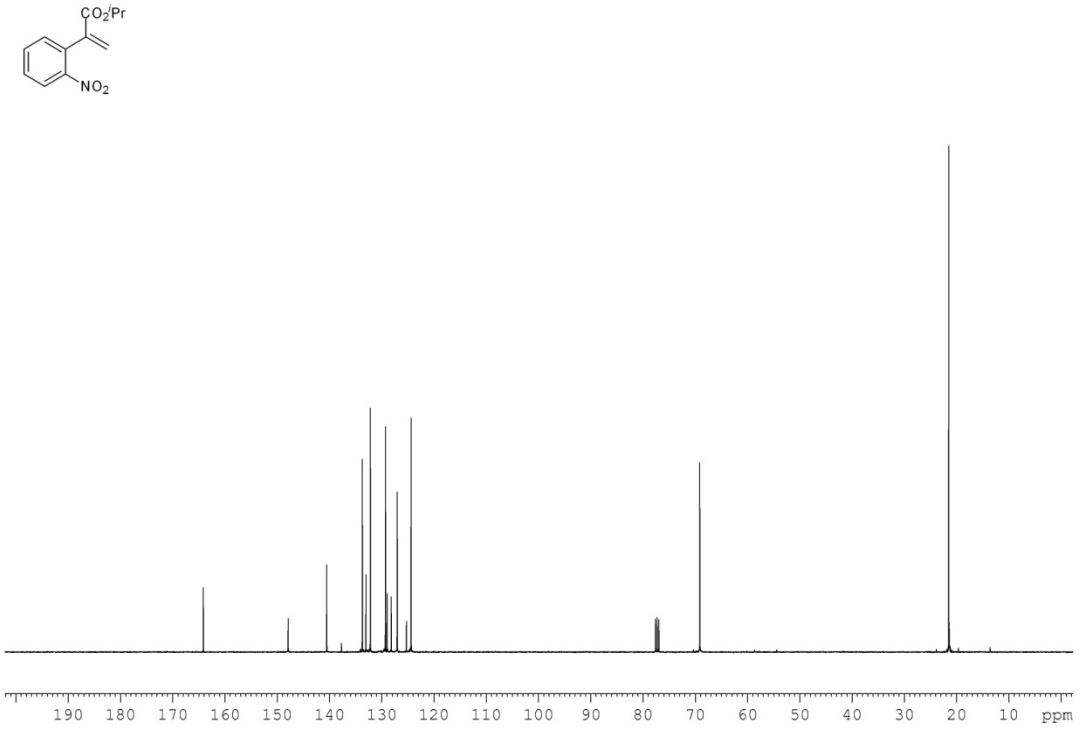

F
NO2
CN
CO2Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

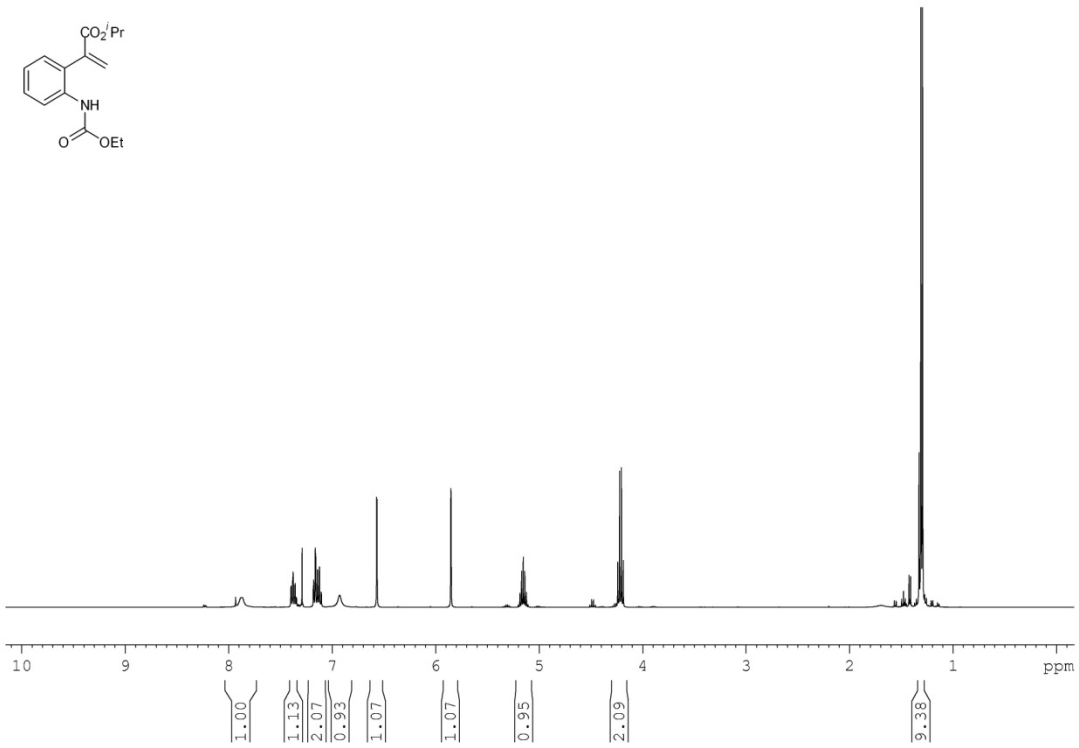

F
NO2
CN
CO2Me
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm

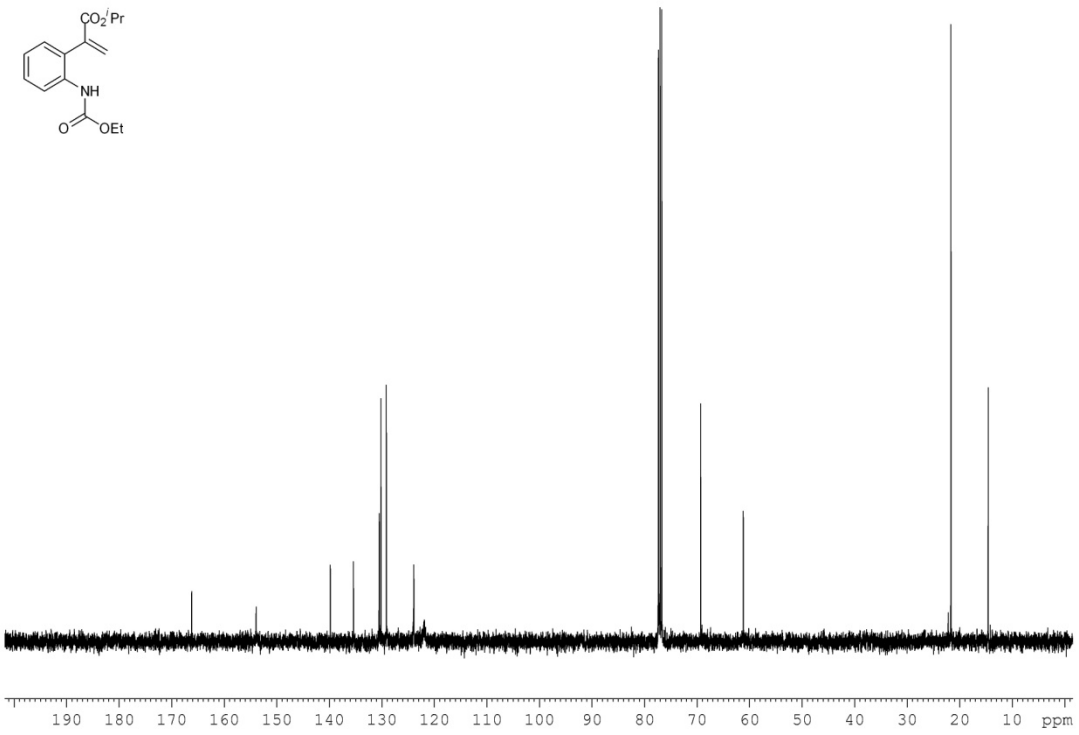

CH3
NO2
CN
CO2Me
10
9
8
7
6
5
4
3
2
1
ppm
0.86
1.00
1.02
0.79
3.11
3.22

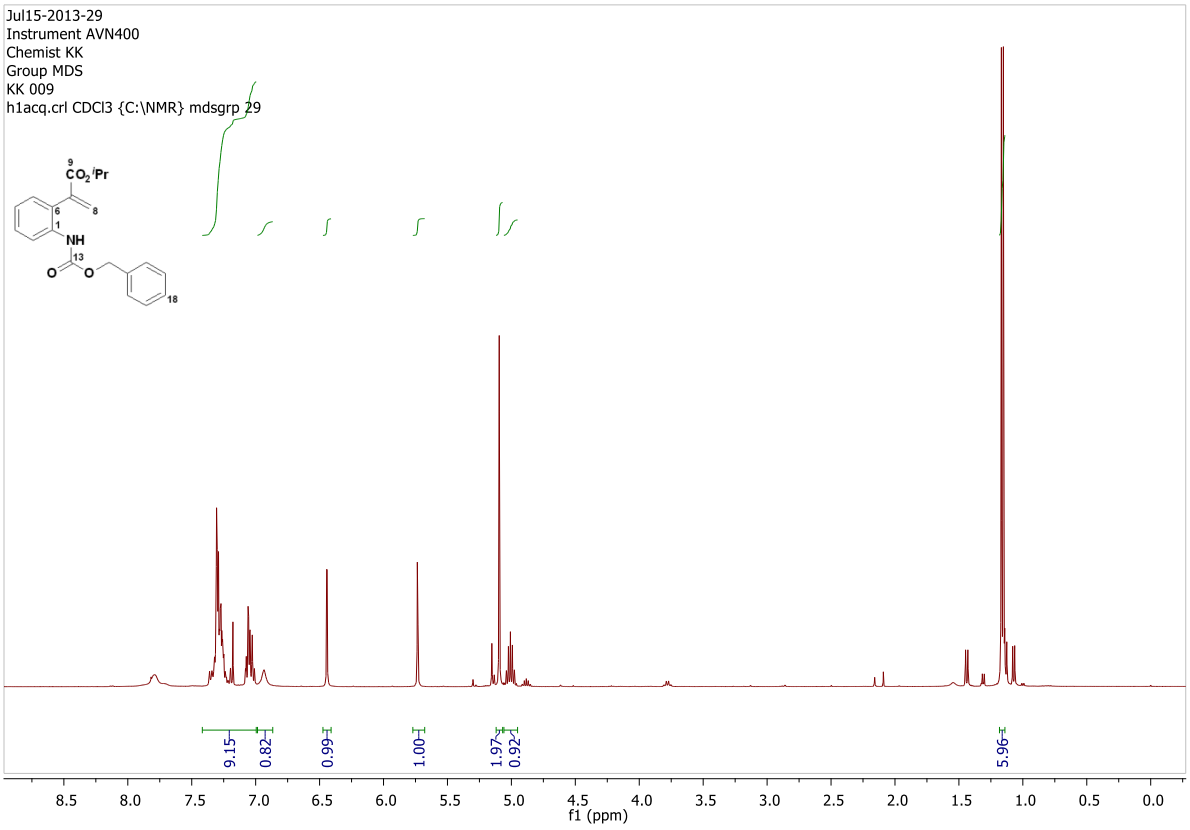

CH3
NO2
CN
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

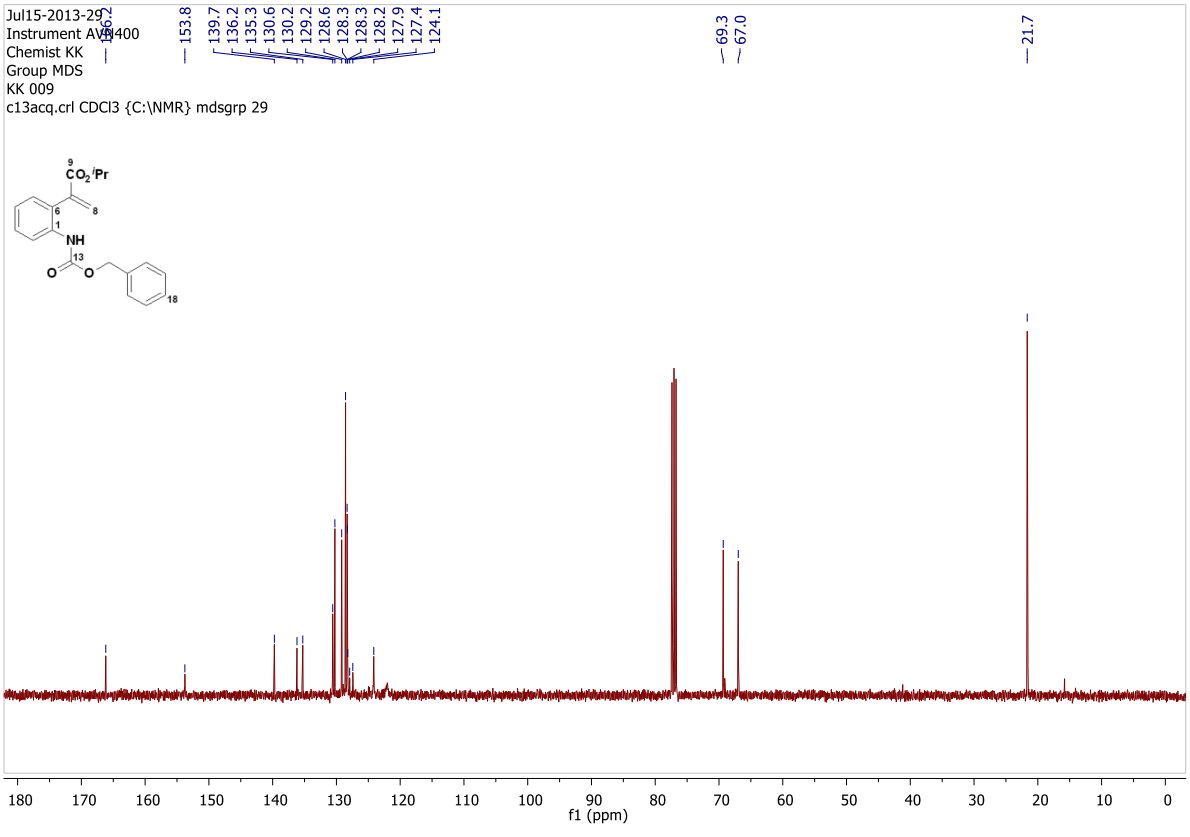

CO2iPr
NO2
10
9
8
7
6
5
4
3
2
1
ppm
0.91
1.01
1.01
1.00
1.01
1.00
0.95
6.14

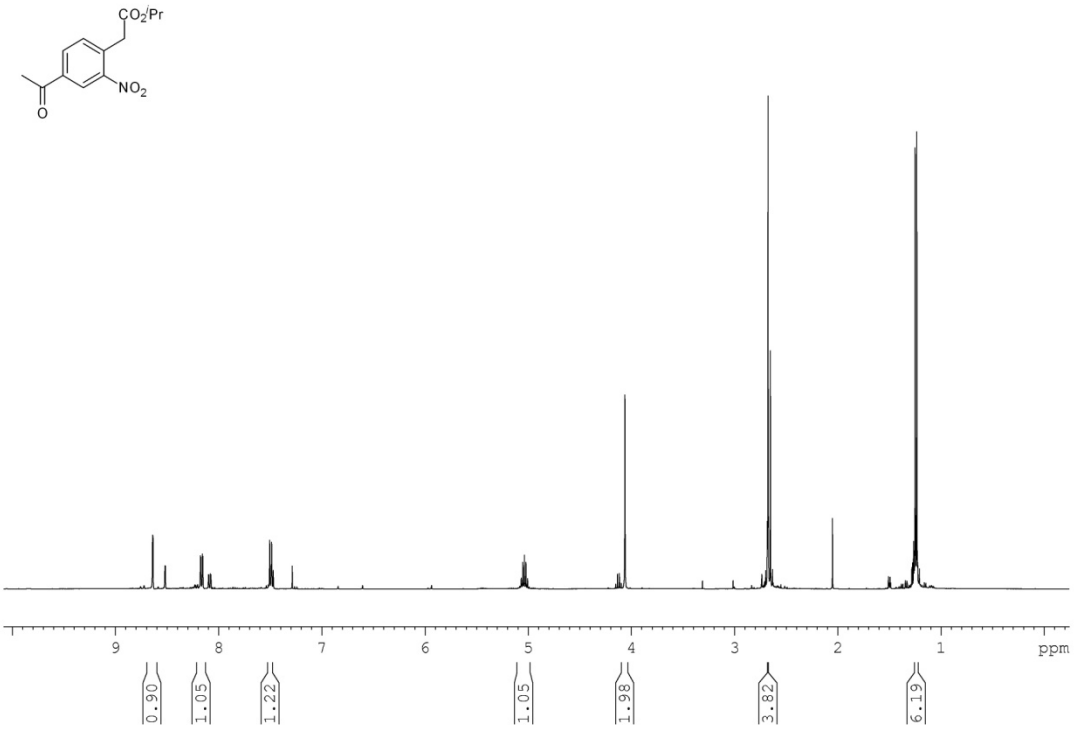

CO2iPr
NO2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

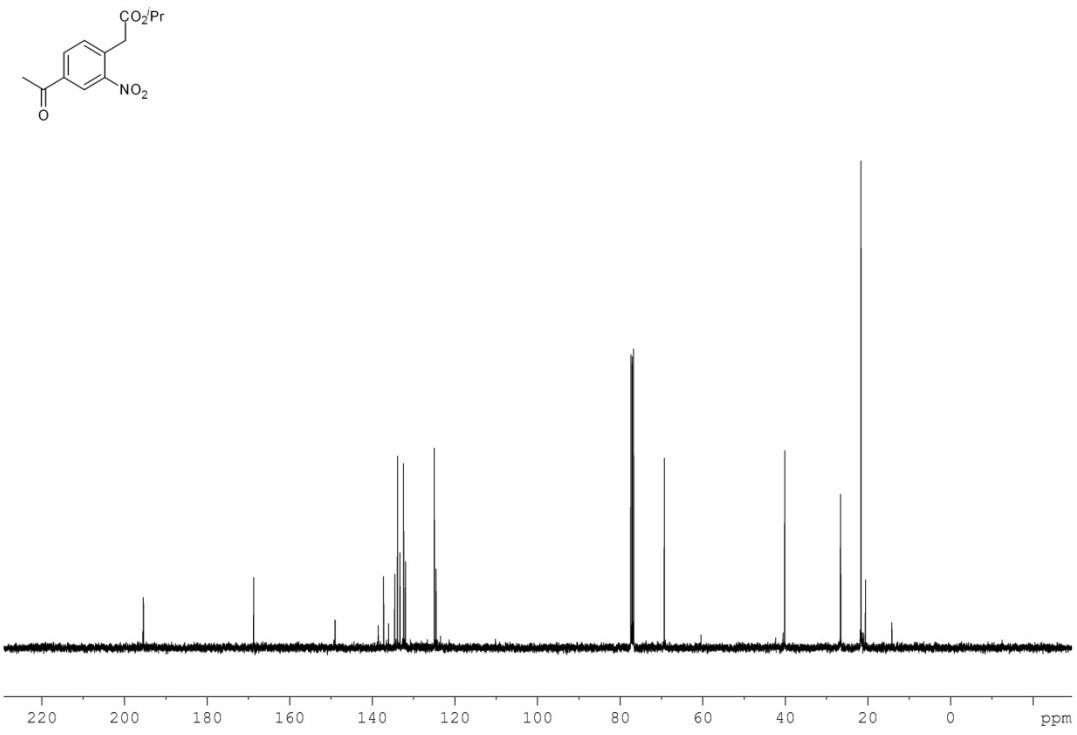

CO2iPr
NH
O
OEt
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.13
2.07
0.93
1.07
1.07
0.95
2.09
9.38

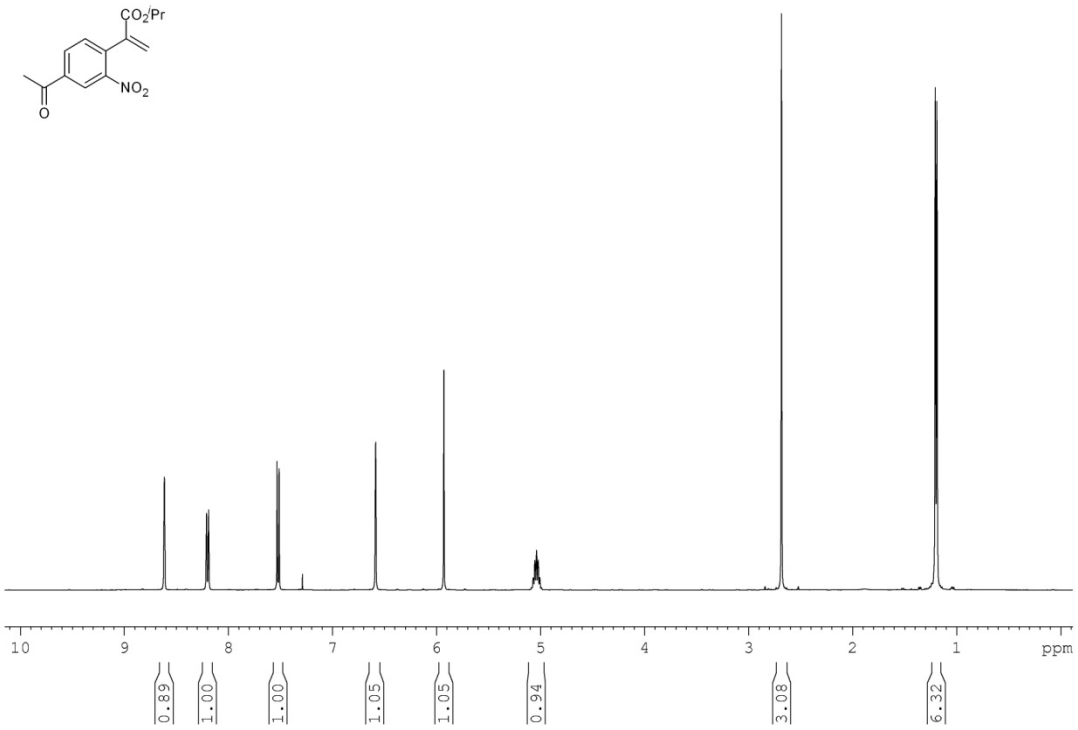

CO2iPr
NH
O
OEt
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

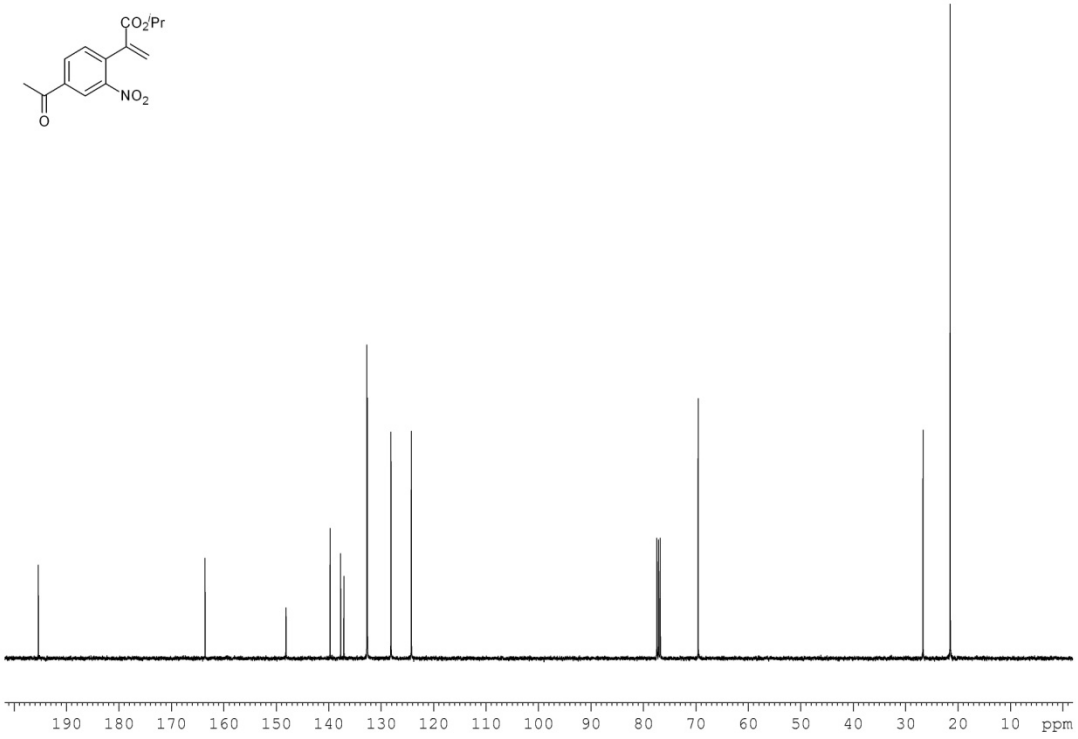

Jul15-2013-29
Instrument AVN400
Chemist KK
Group MDS
KK 009
h1acq.crl CDCl3 {C:\NMR} mdsgrp 29
9.15
0.82
0.99
1.00
1.97
0.92
5.96
f1 (ppm)

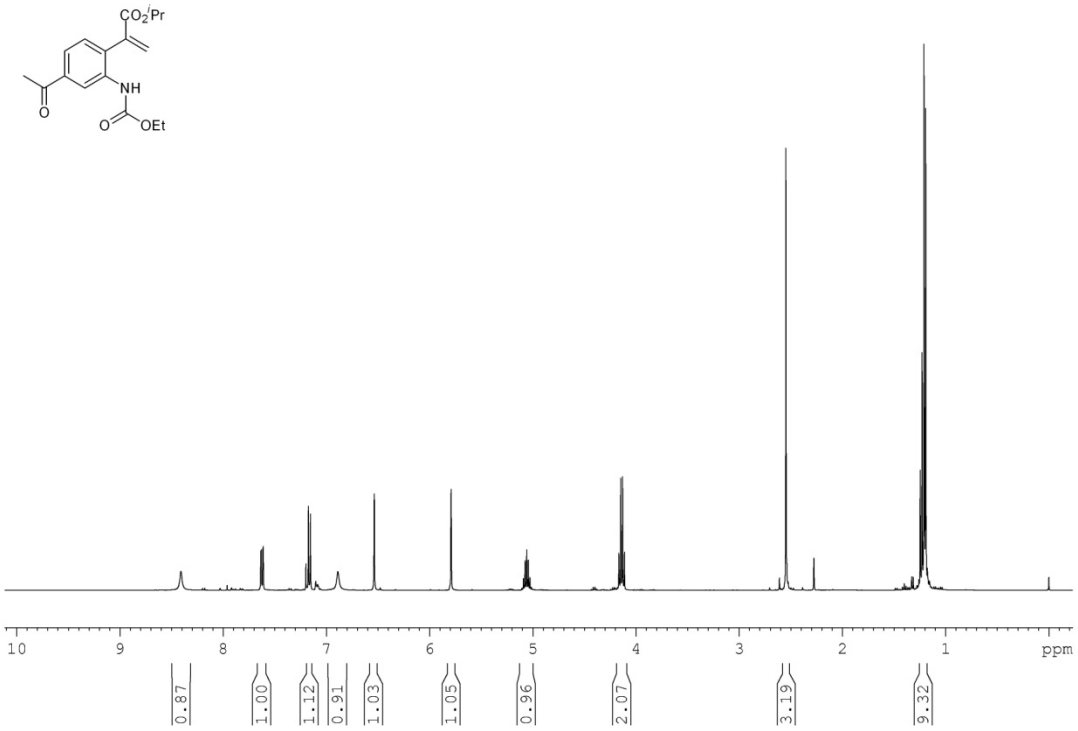

Jul15-2013-29
Instrument AVN400
Chemist KK
Group MDS
KK 009
c13acq.crl CDCl3 {C:\NMR} mdsgrp 29
153.8
139.7
136.2
135.3
130.6
130.2
129.2
128.6
128.3
128.3
128.2
127.9
127.4
124.1
69.3
67.0
21.7
f1 (ppm)

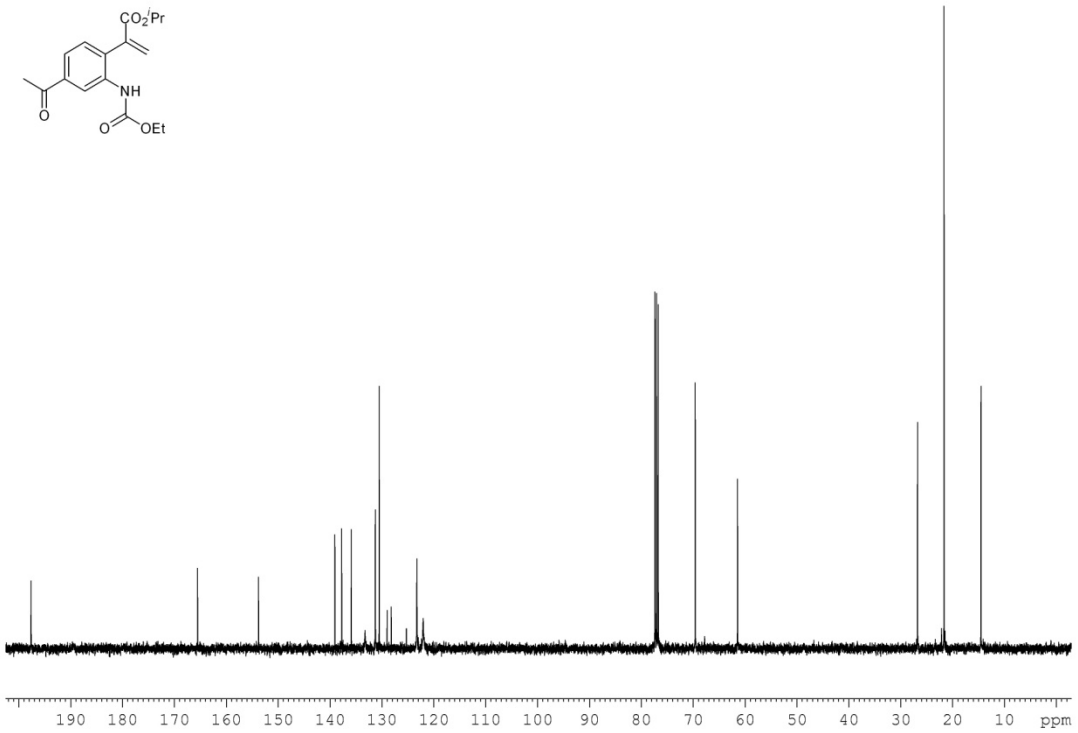

CO2iPr
NO2
O
9
8
7
6
5
4
3
2
1
ppm
0.90
1.05
1.22
1.05
1.98
3.82
6.19

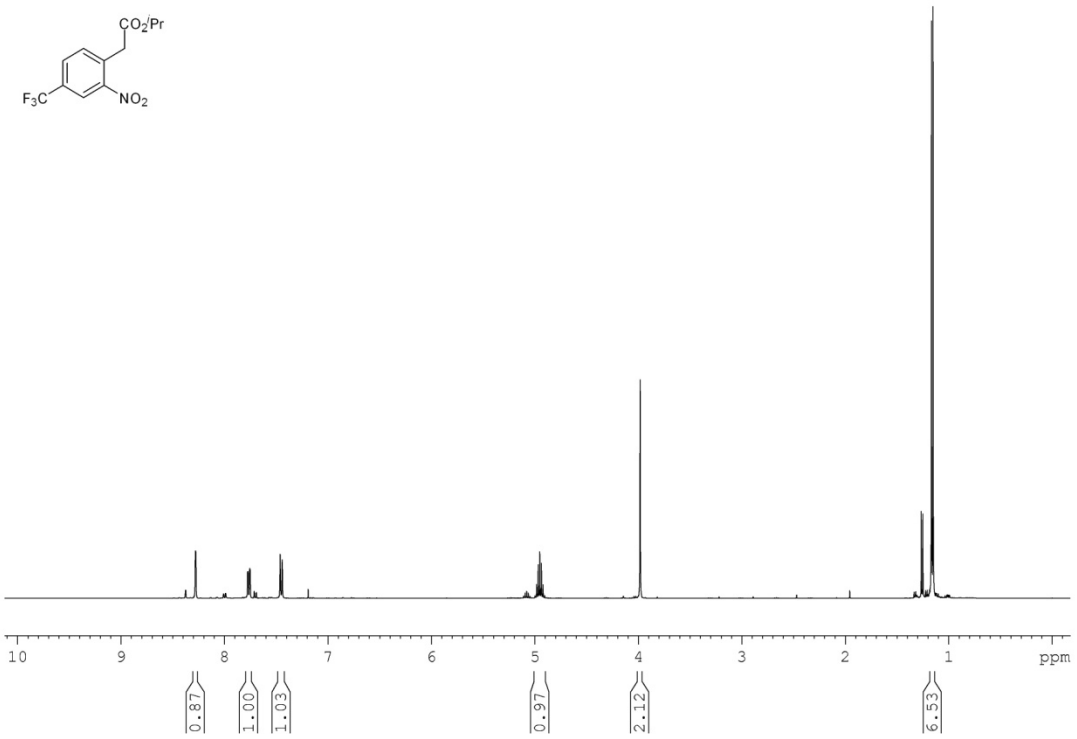

CO2iPr
NO2
O
220
200
180
160
140
120
100
80
60
40
20
0
ppm

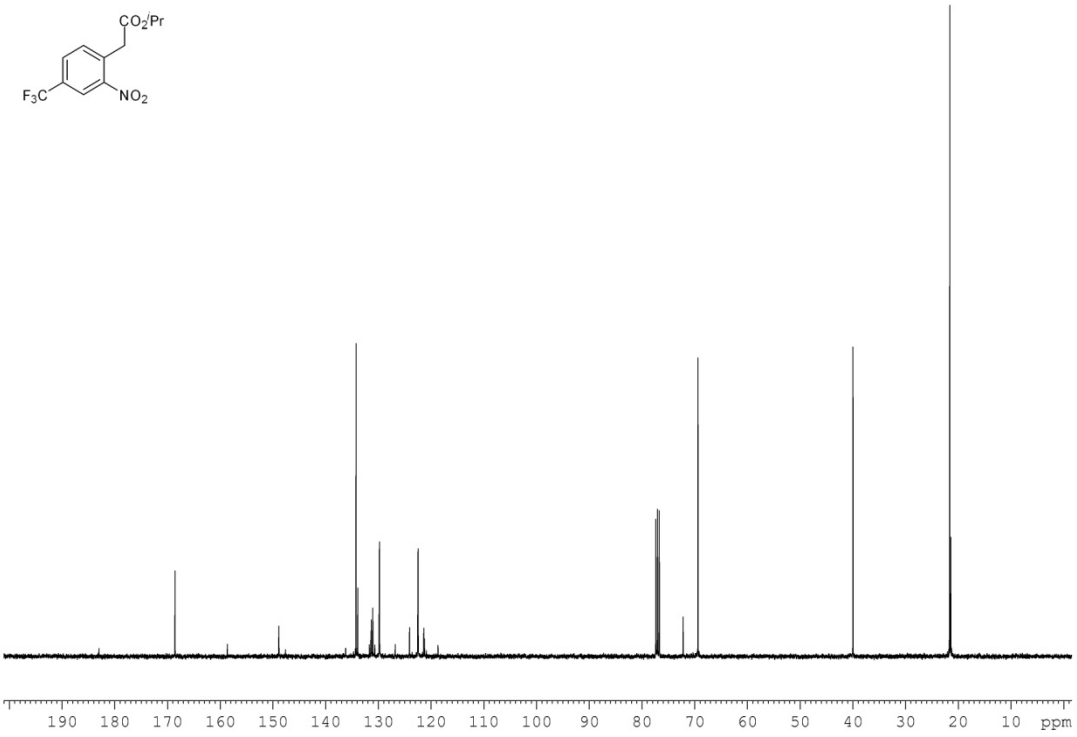

CO2iPr
NO2
O
10
9
8
7
6
5
4
3
2
1
ppm
0.89
1.00
1.00
1.05
1.05
0.94
3.08
6.32

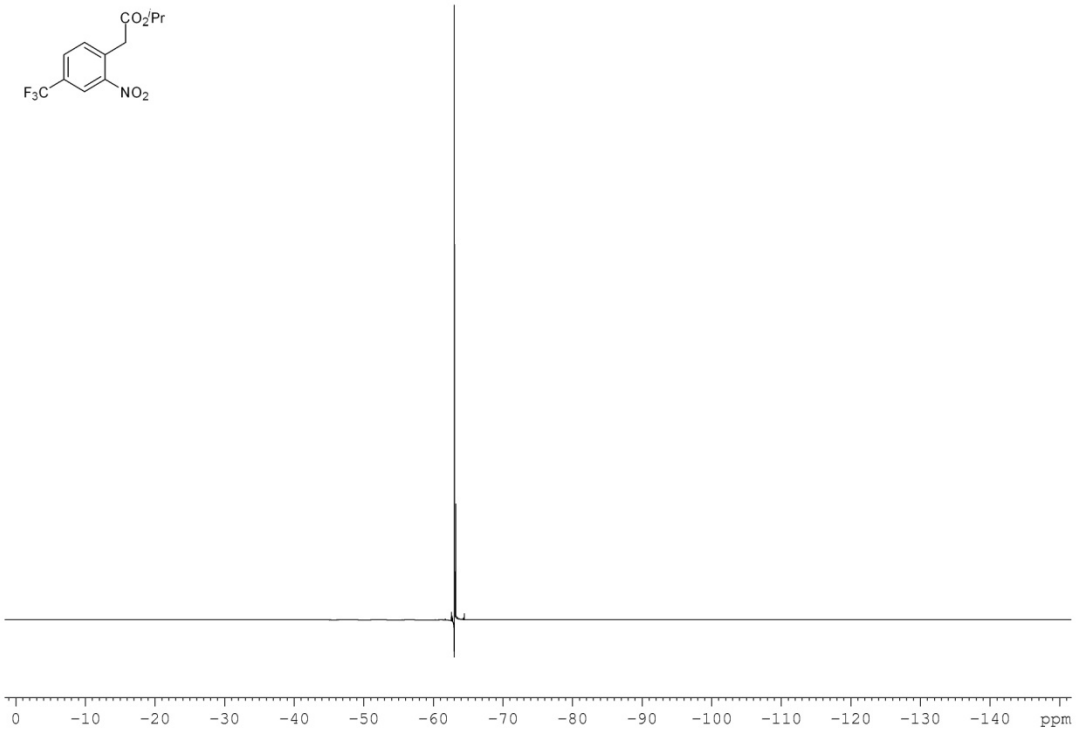

CO2iPr
NO2
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

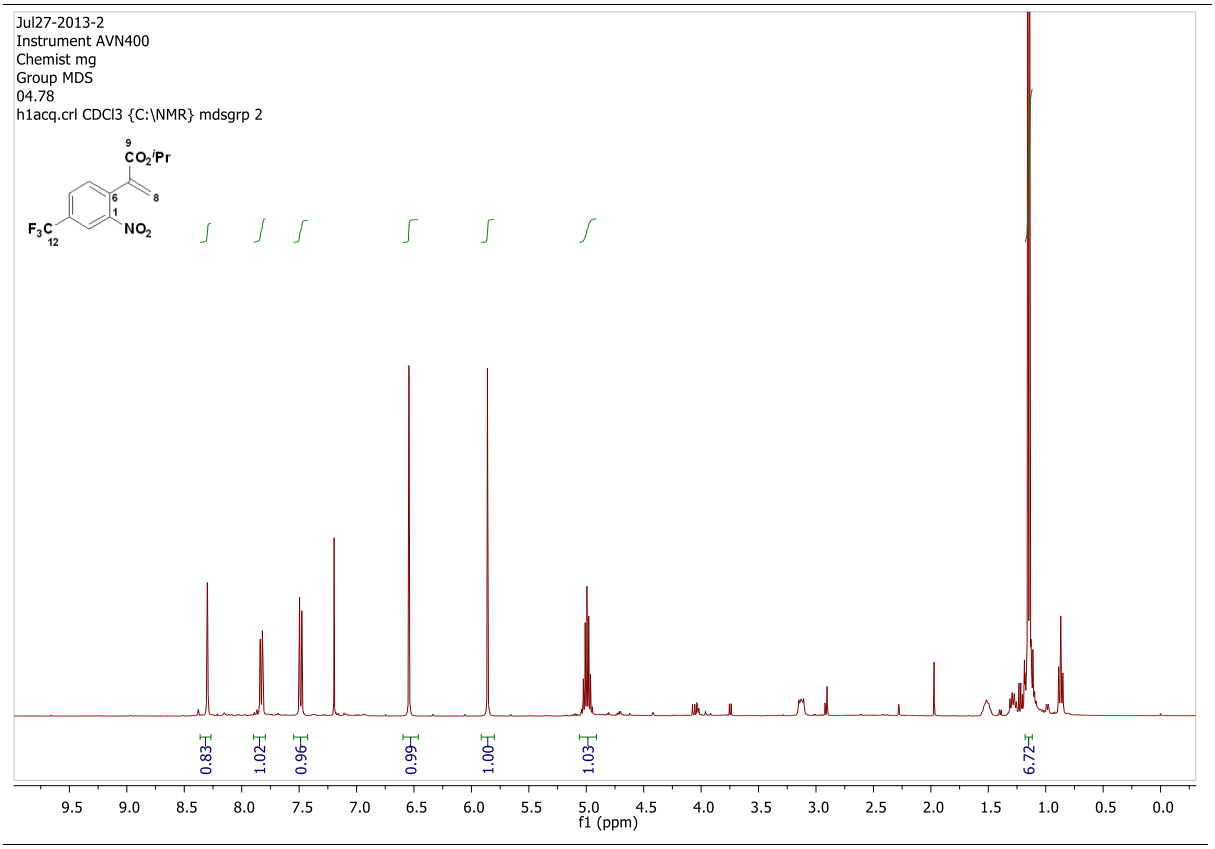

CO2iPr
NH
O
O
OEt
10
9
8
7
6
5
4
3
2
1
ppm
0.87
1.00
1.12
0.91
1.03
1.05
0.96
2.07
3.19
9.32

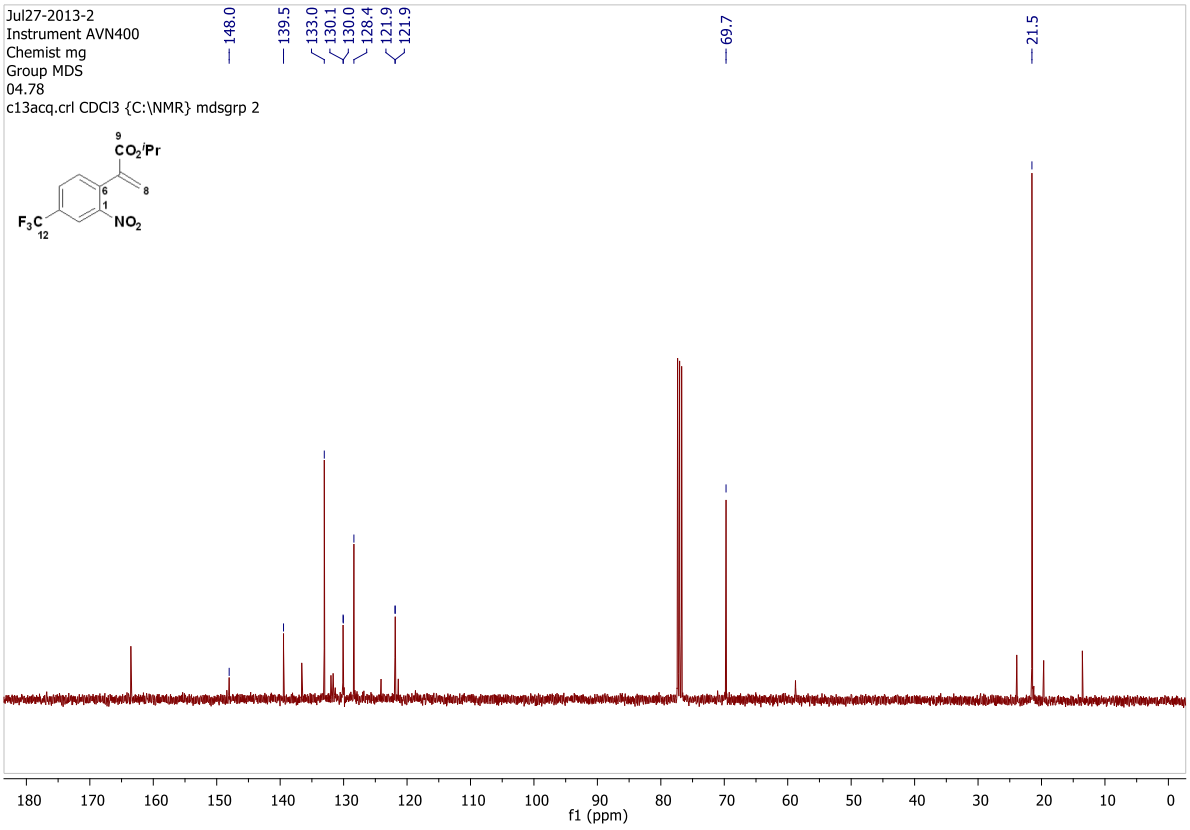

CO2iPr
NH
O
O
OEt
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

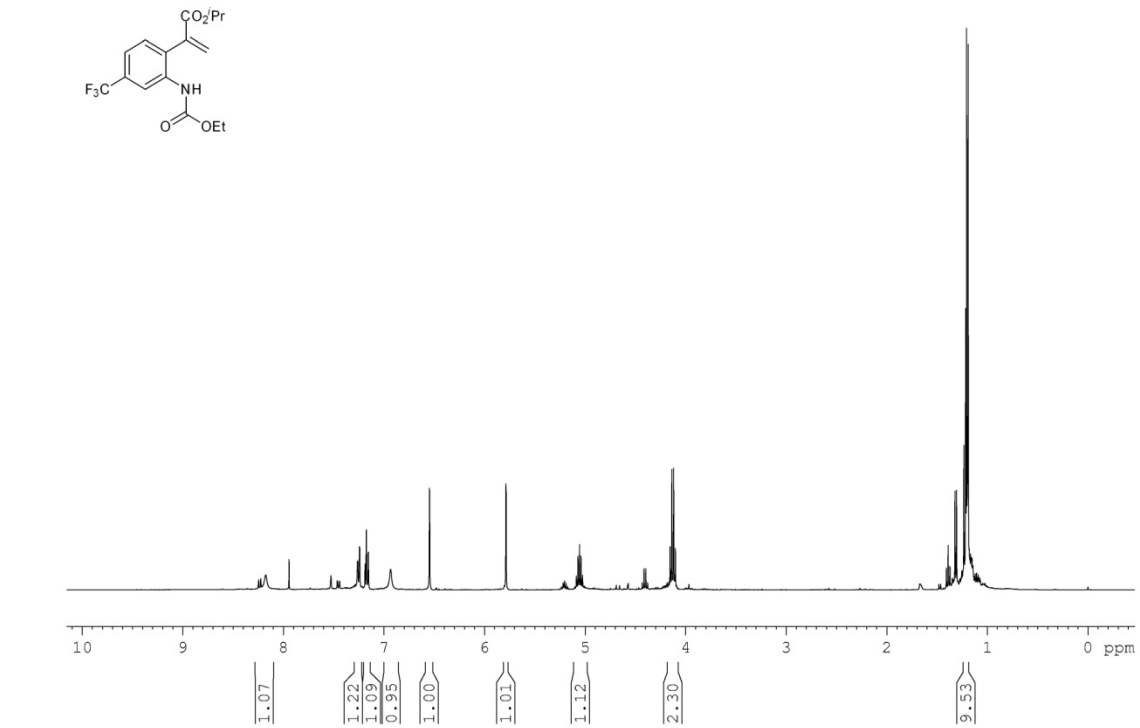

CO2iPr
F3C
NO2
10
9
8
7
6
5
4
3
2
1
ppm
0.87
1.00
1.03
0.97
2.12
6.53

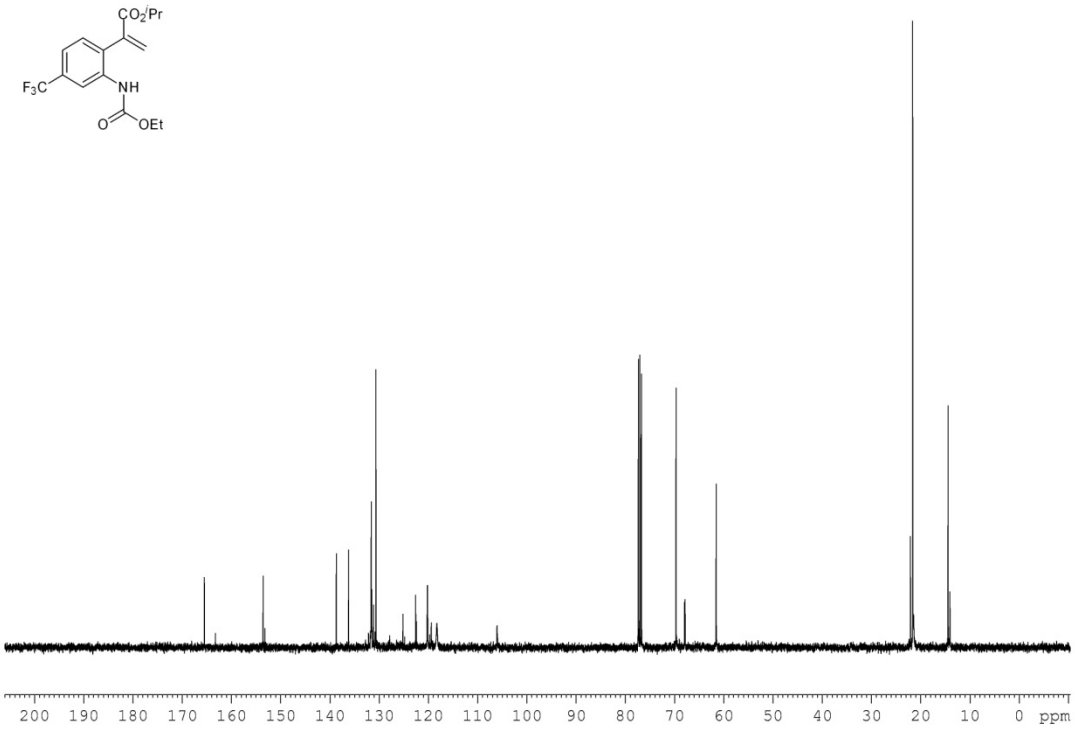

CO2iPr
F3C
NO2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

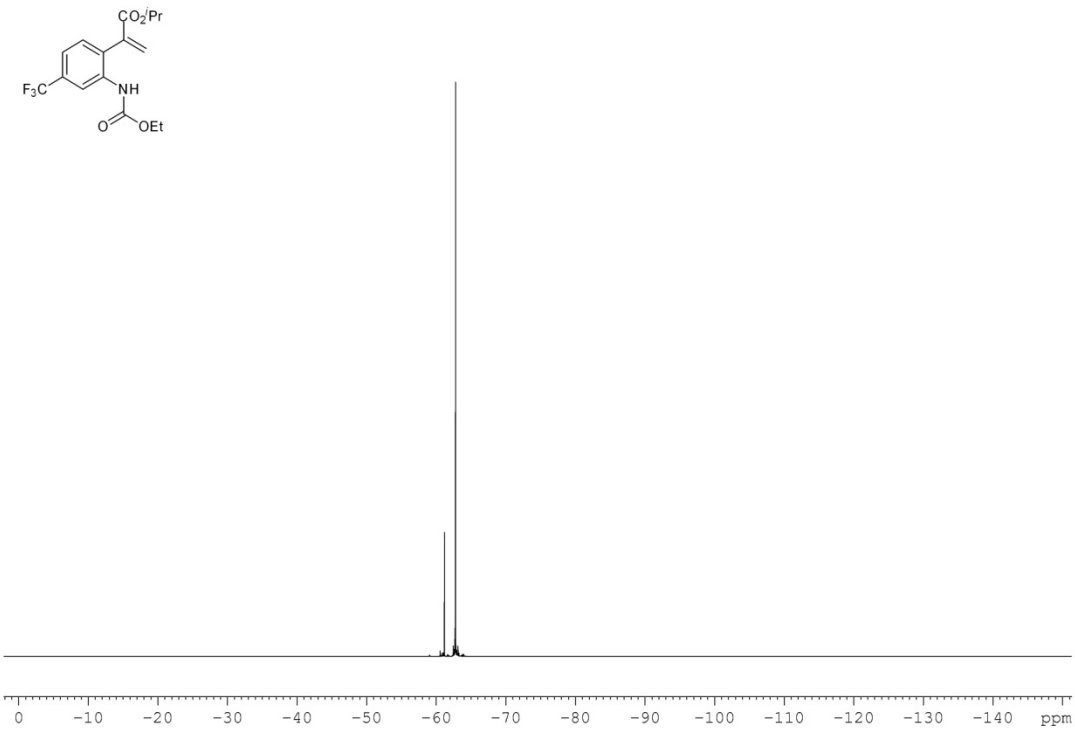

CO2iPr
F3C
NO2
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
ppm

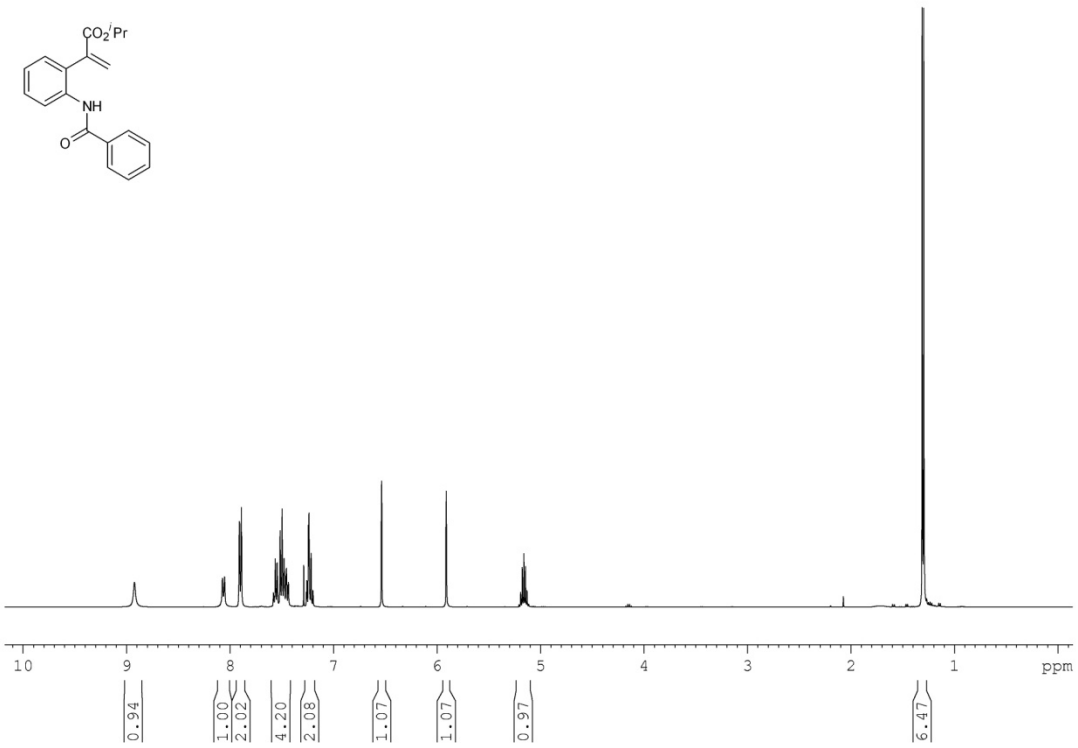

Jul27-2013-2
Instrument AVN400
Chemist mg
Group MDS
04.78
h1acq.crl CDCl3 {C:\NMR} mdsgrp 2
9
CO2iPr
6
8
1
F3C
12
NO2
0.83
1.02
0.96
0.99
1.00
1.03
6.72
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

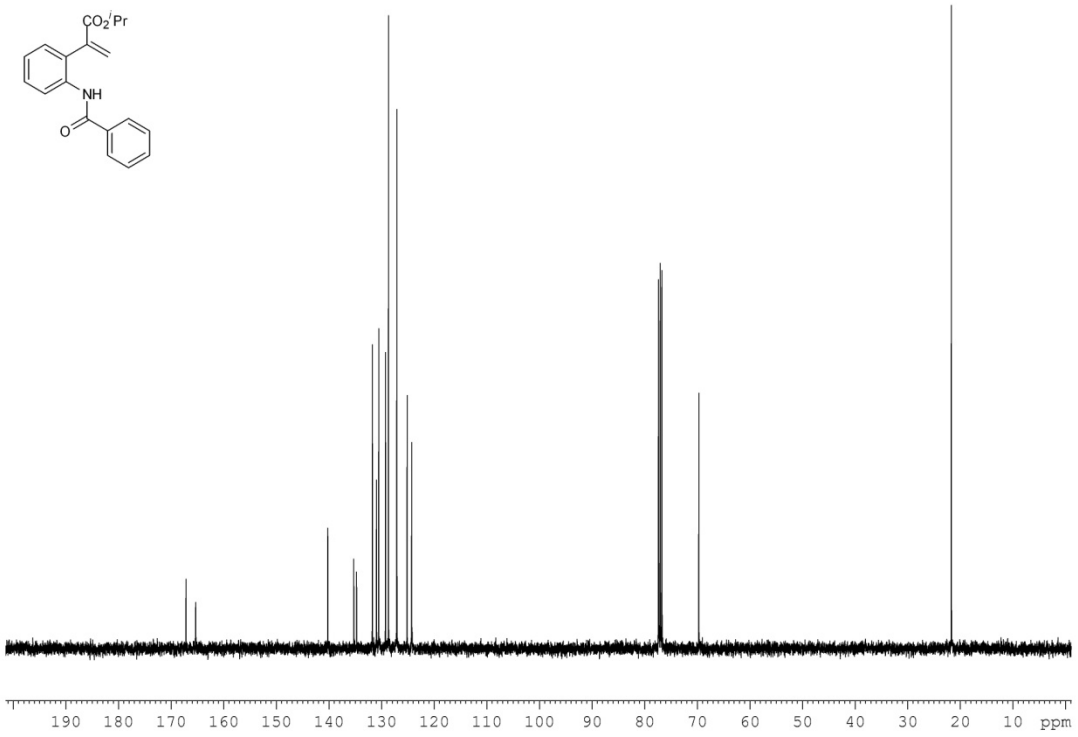

Jul27-2013-2
Instrument AVN400
Chemist mg
Group MDS
04.78
c13acq.crl CDCl3 {C:\NMR} mdsgrp 2
148.0
139.5
133.0
130.1
130.0
128.4
121.9
121.9
69.7
21.5
f1 (ppm)

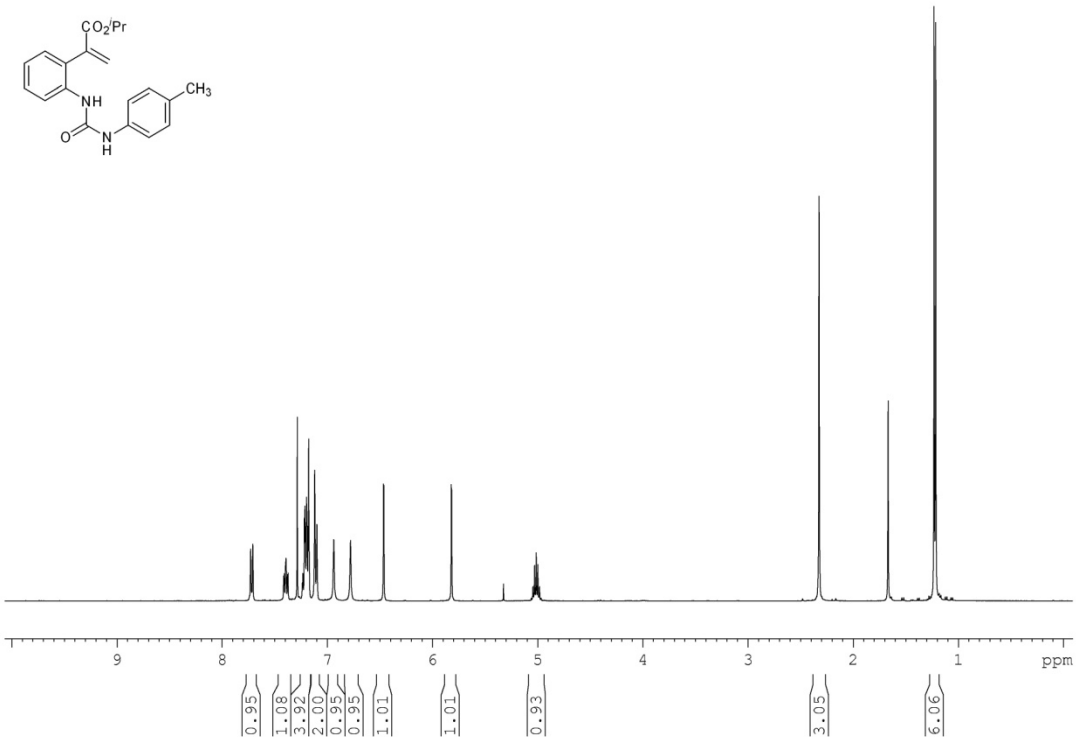

ppm
1.07
1.22
1.09
0.95
1.00
1.01
1.12
2.30
9.53

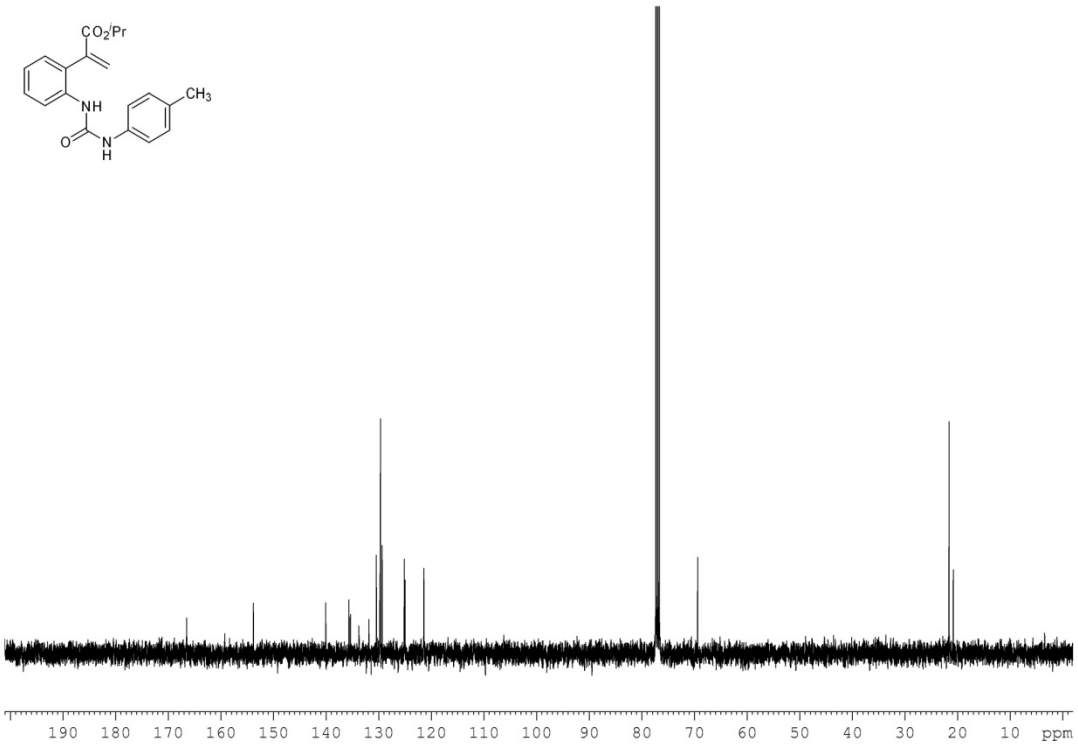

CO2iPr
F3C
NH
O
OEt
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

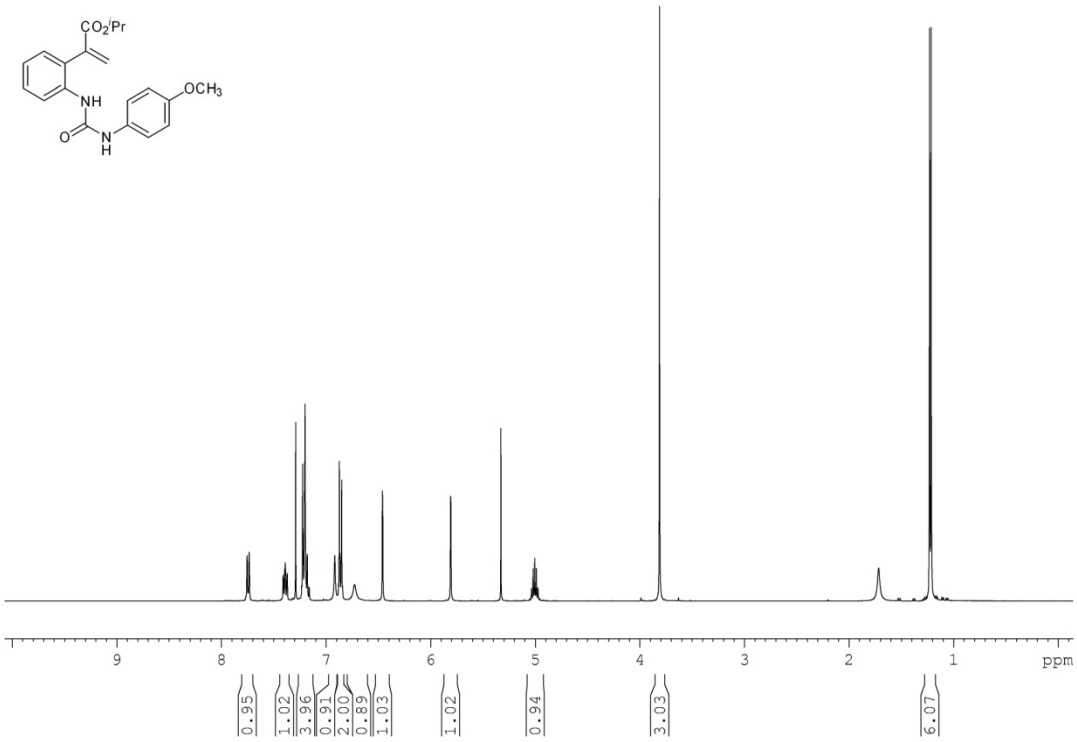

CO2iPr
F3C
NH
O
OEt
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 ppm

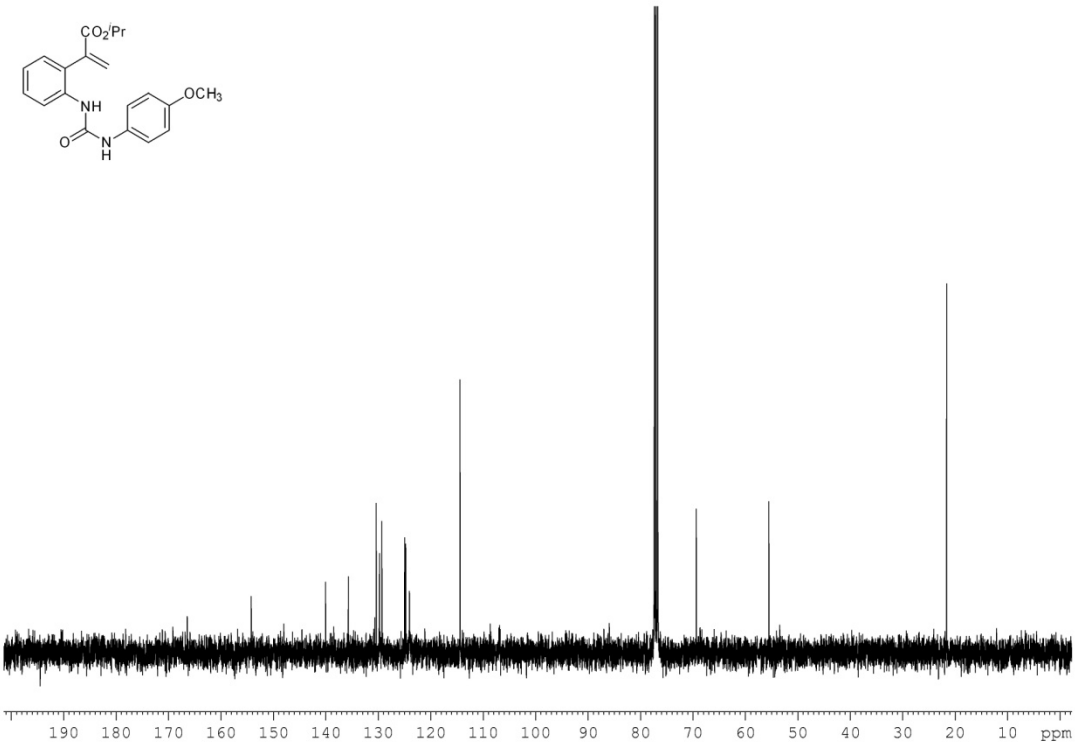

CO2iPr
NH
O
10
9
8
7
6
5
4
3
2
1
ppm
0.94
1.00
2.02
4.20
2.08
1.07
1.07
0.97
6.47

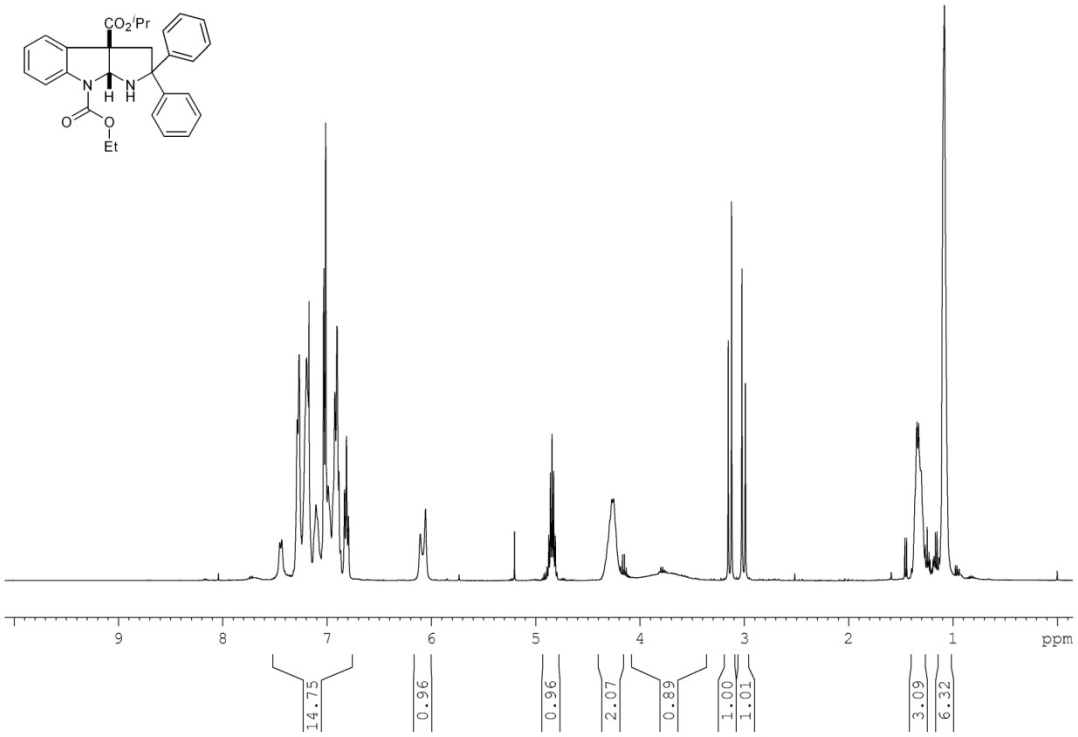

CO2iPr
NH
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

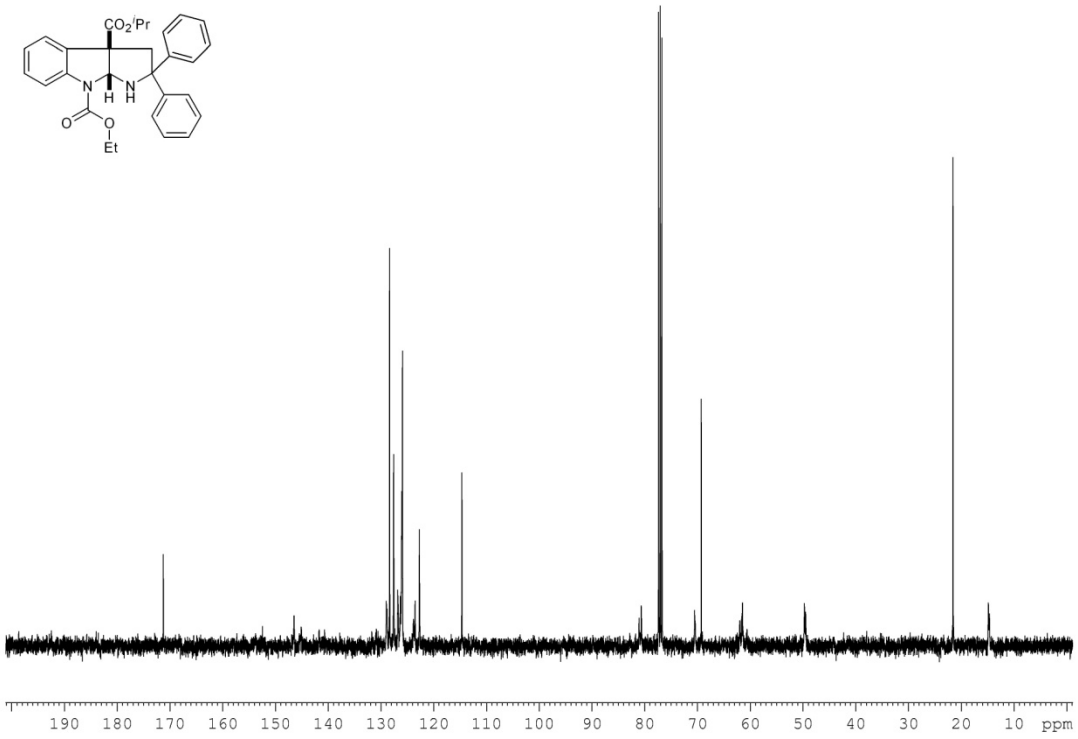

CO2iPr
NH
O
N
H
CH3
9
8
7
6
5
4
3
2
1
ppm
0.95
1.08
3.92
2.00
0.95
0.95
1.01
1.01
0.93
3.05
6.06

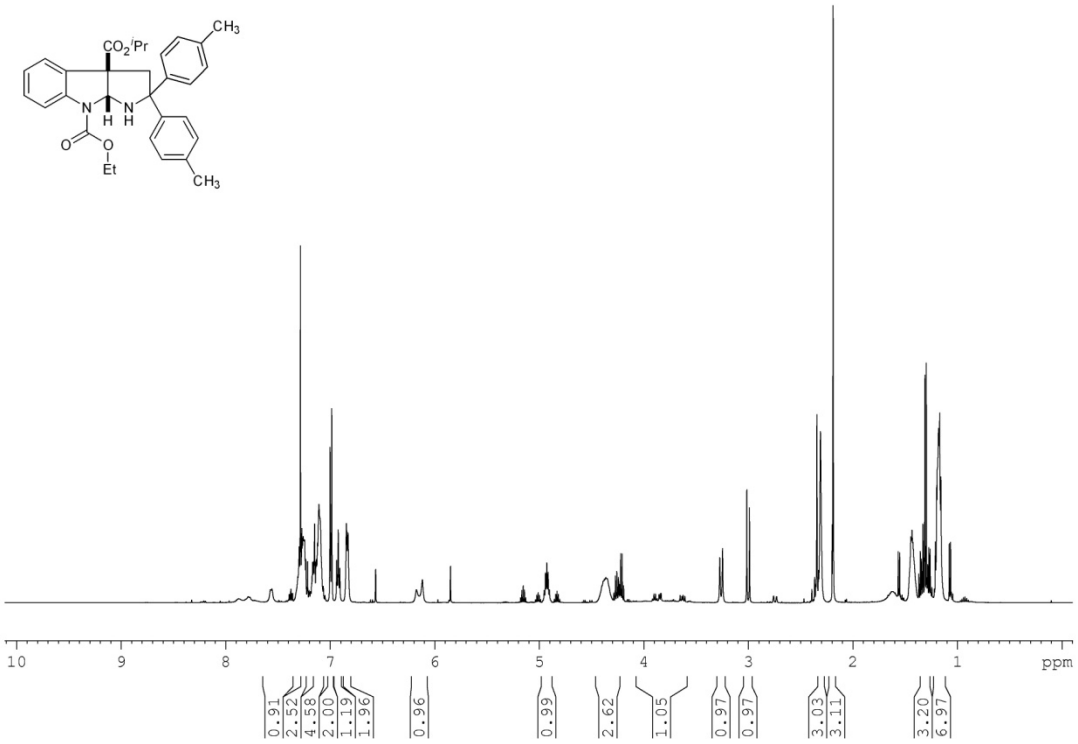

CO2iPr
NH
O
N
H
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

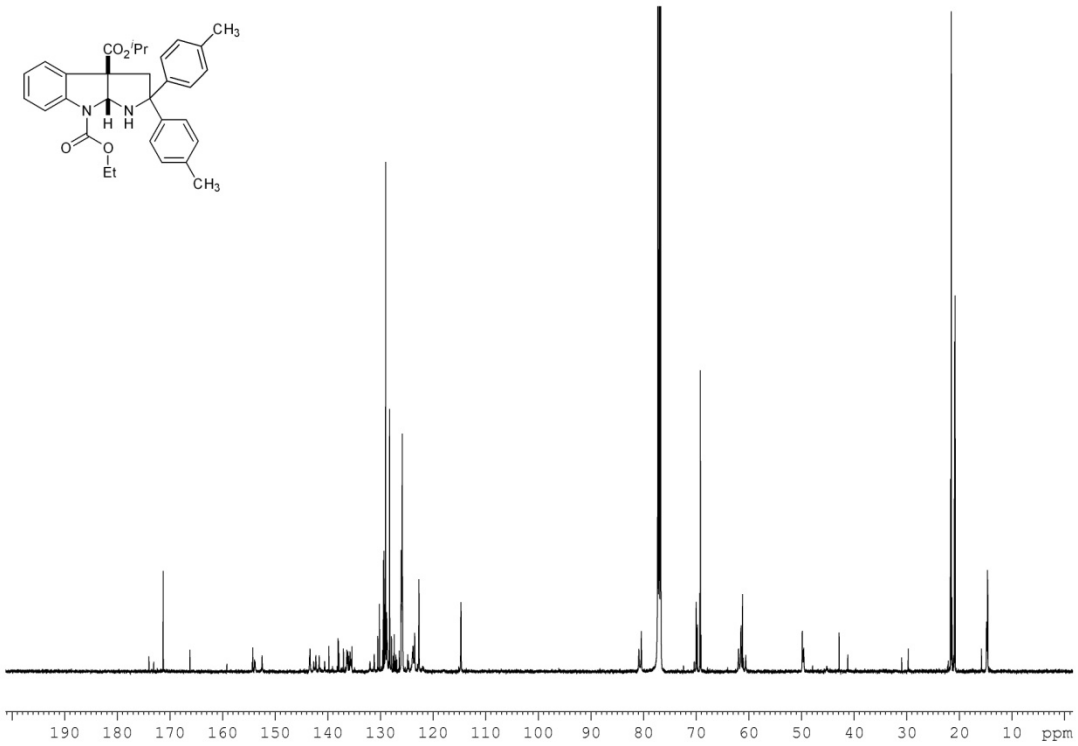

CO2iPr
NH
O
N
H
OCH3
9
8
7
6
5
4
3
2
1
ppm
0.95
1.02
3.96
0.91
2.00
0.89
1.03
1.02
0.94
3.03
6.07

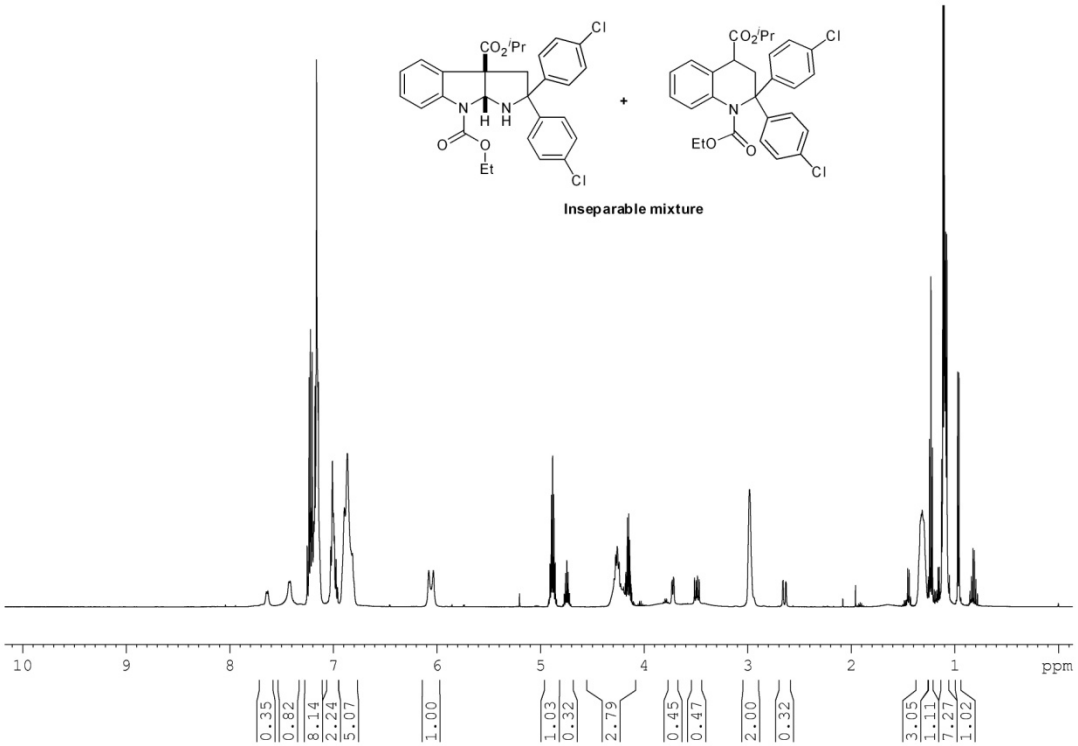

CO2iPr
NH
O
N
H
OCH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

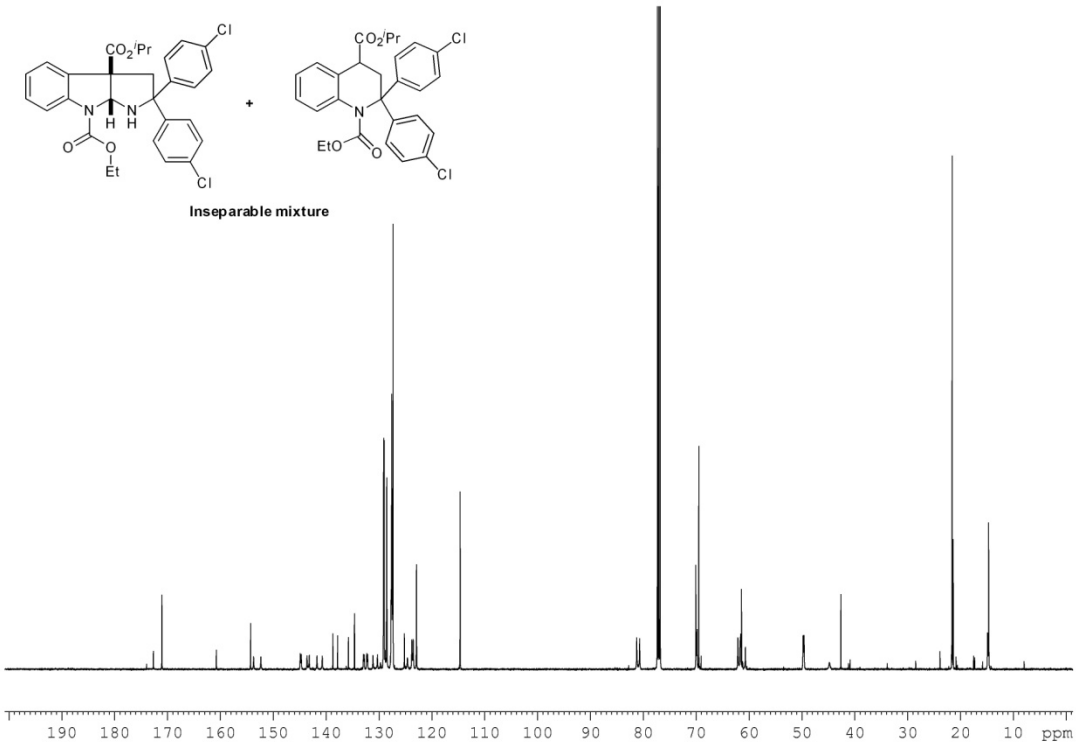

CO2iPr
N
H
N
H
O
O
Et
9
8
7
6
5
4
3
2
1
ppm
14.75
0.96
0.96
2.07
0.89
1.00
1.01
3.09
6.32

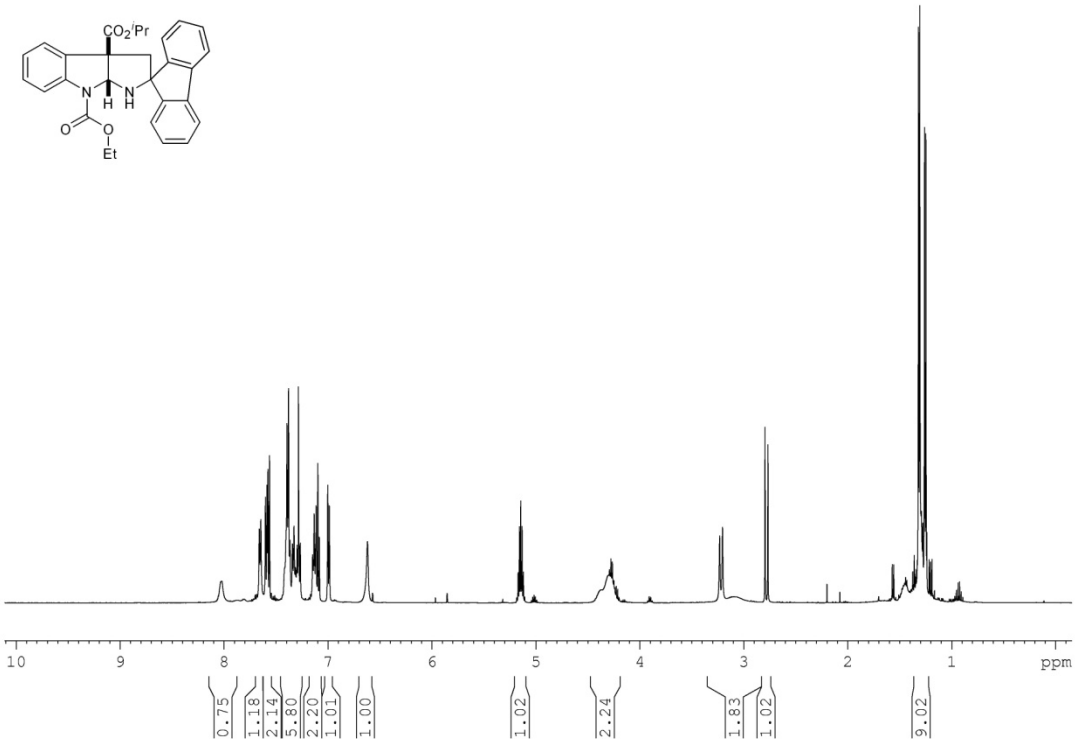

CO2iPr
N
H
N
H
O
O
Et
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

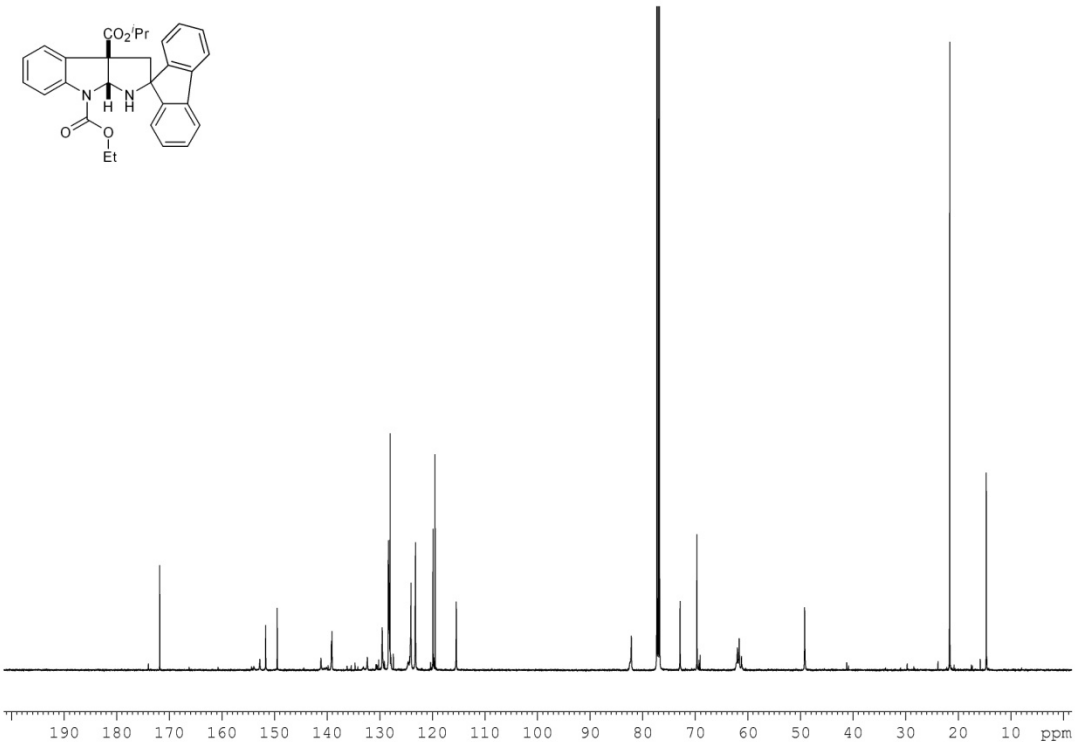

CO2iPr
CH3
N
H
N
H
O
O
Et
CH3
10
9
8
7
6
5
4
3
2
1
ppm
0.91
2.52
4.58
2.00
1.19
1.96
0.96
0.99
2.62
1.05
0.97
0.97
3.03
3.11
3.20
6.97

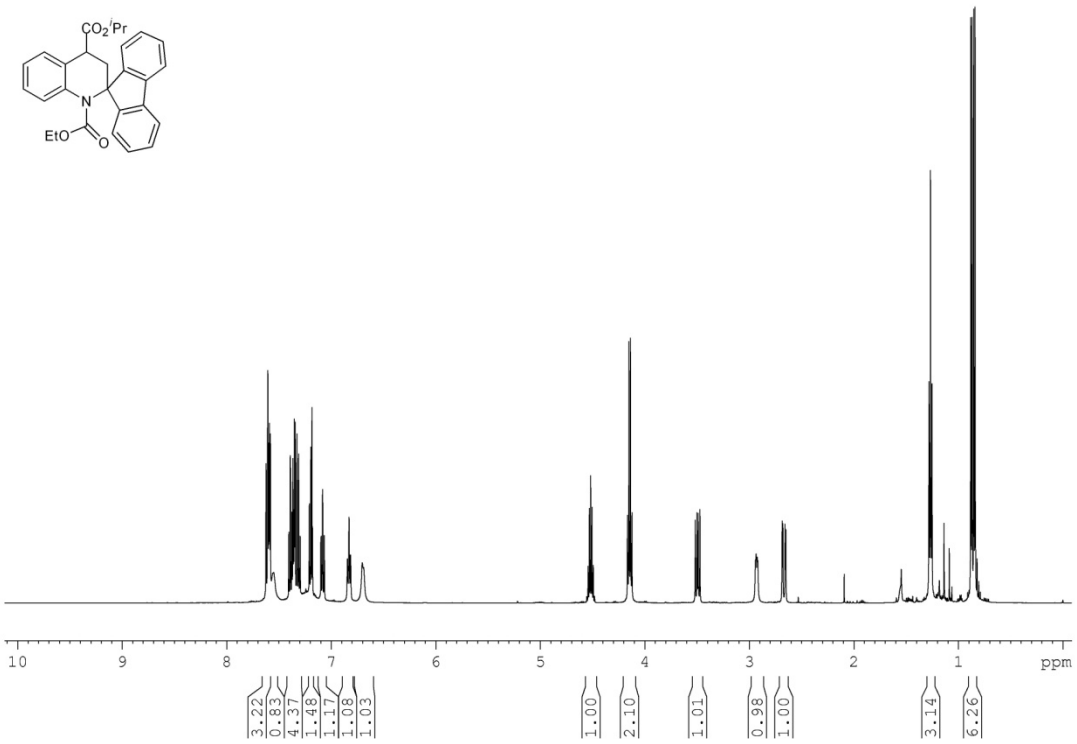

CO2iPr
CH3
N
H
N
H
O
O
Et
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

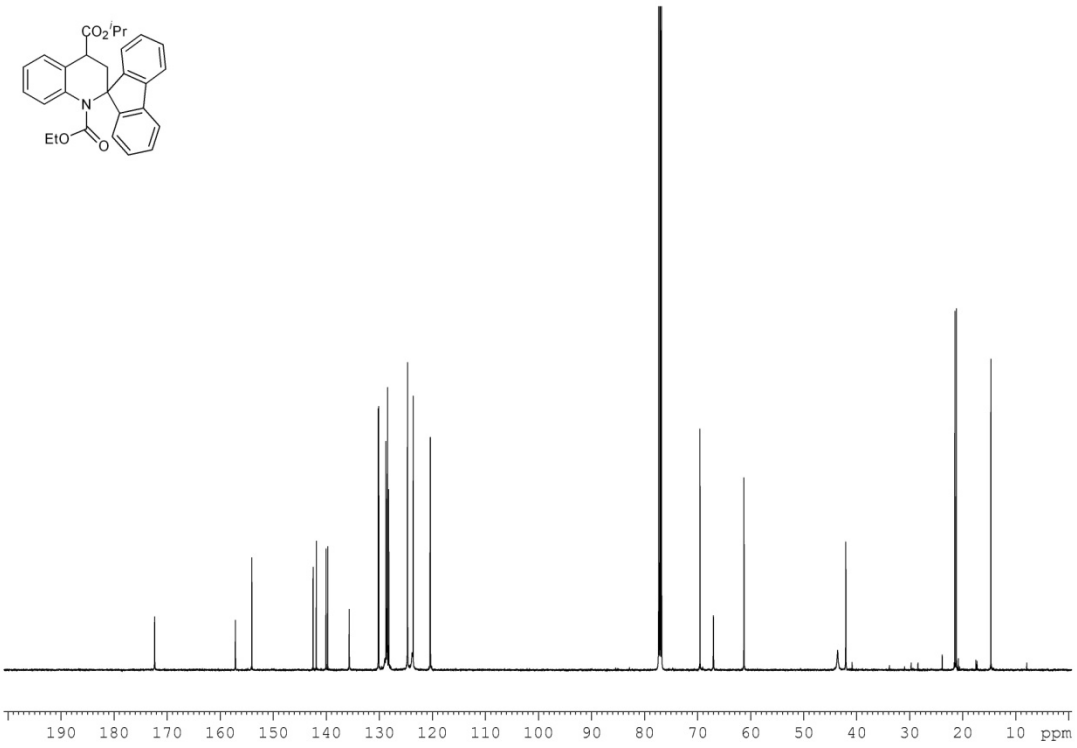

Inseparable mixture
10 9 8 7 6 5 4 3 2 1 ppm
0.35 0.82 8.14 2.24 5.07 1.00 1.03 0.32 2.79 0.45 0.47 2.00 0.32 3.05 1.11 7.27 1.02

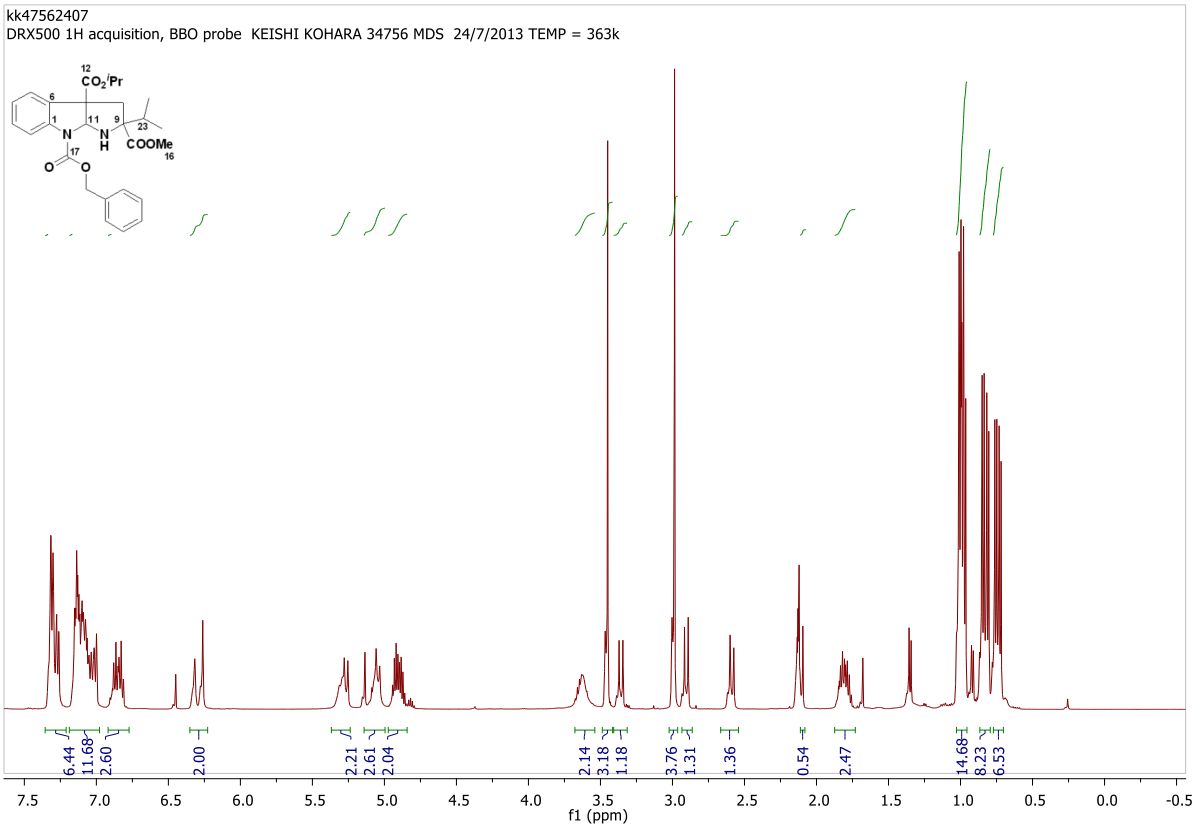

Inseparable mixture
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

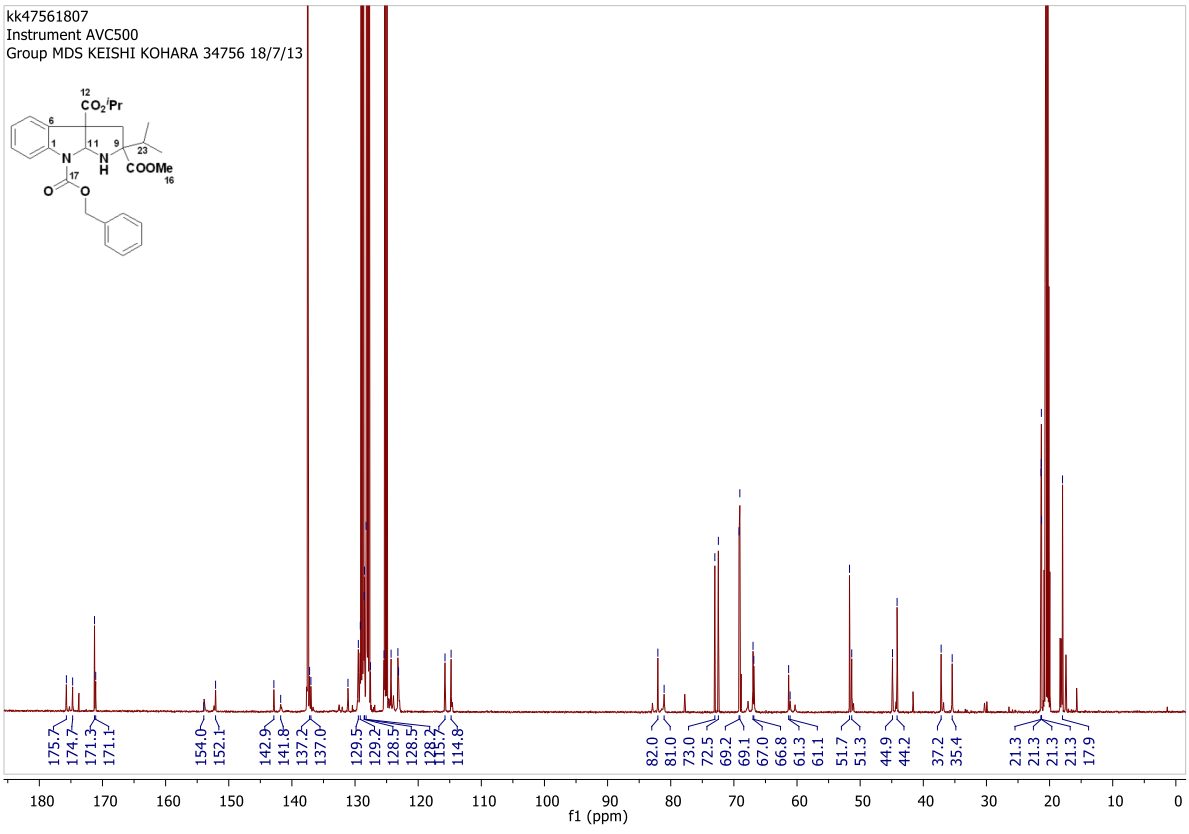

CO2iPr
N
H
N
H
O
O
Et
10
9
8
7
6
5
4
3
2
1
ppm
0.75
1.18
2.14
5.80
2.20
1.01
1.00
1.02
2.24
1.83
1.02
9.02

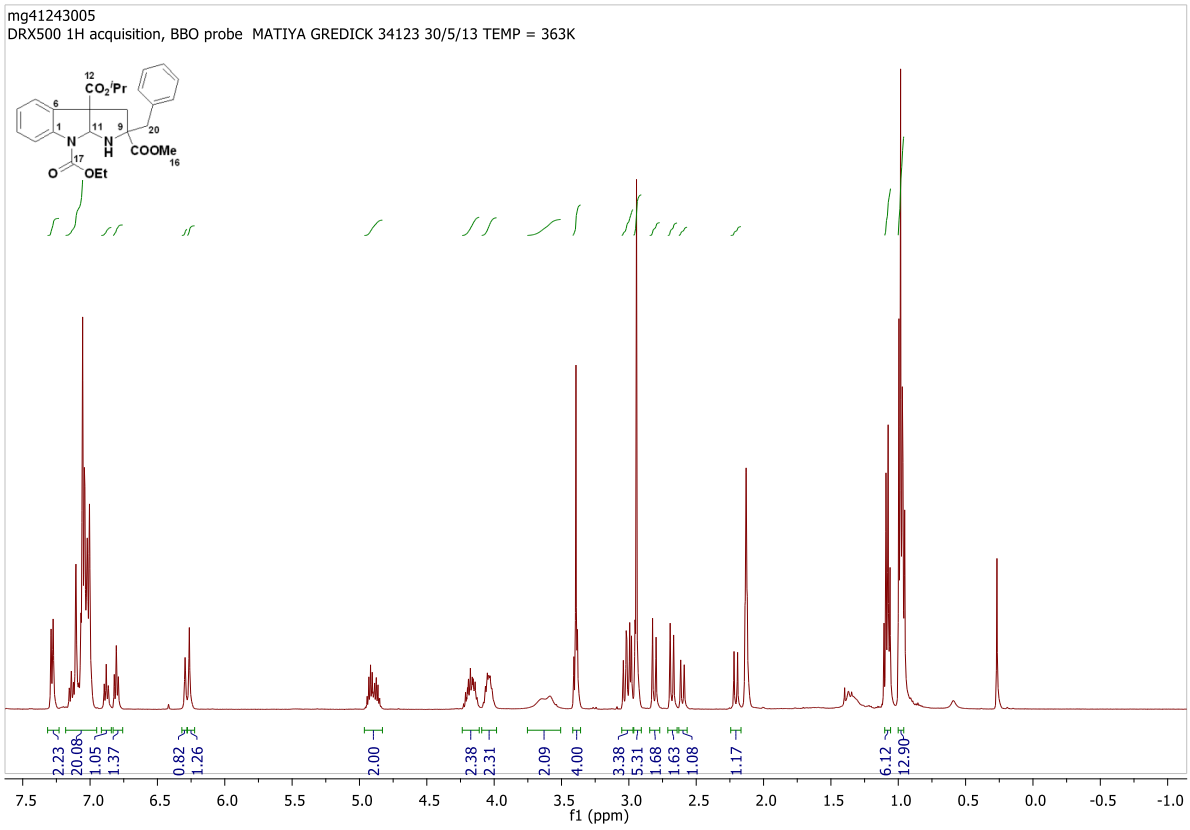

CO2iPr
N
H
N
H
O
O
Et
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

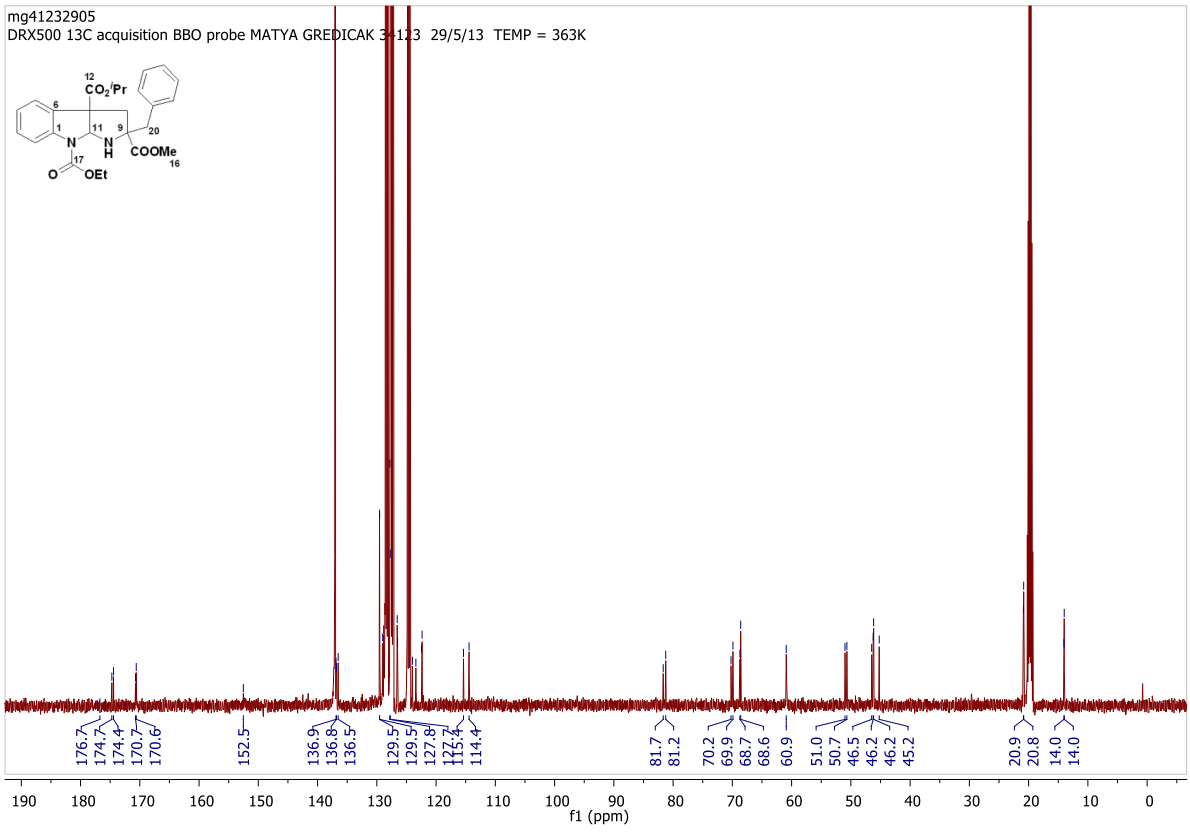

CO2iPr
N
EtO
O
10
9
8
7
6
5
4
3
2
1
ppm
3.22
0.83
4.37
1.48
1.17
1.08
1.03
1.00
2.10
1.01
0.98
1.00
3.14
6.26

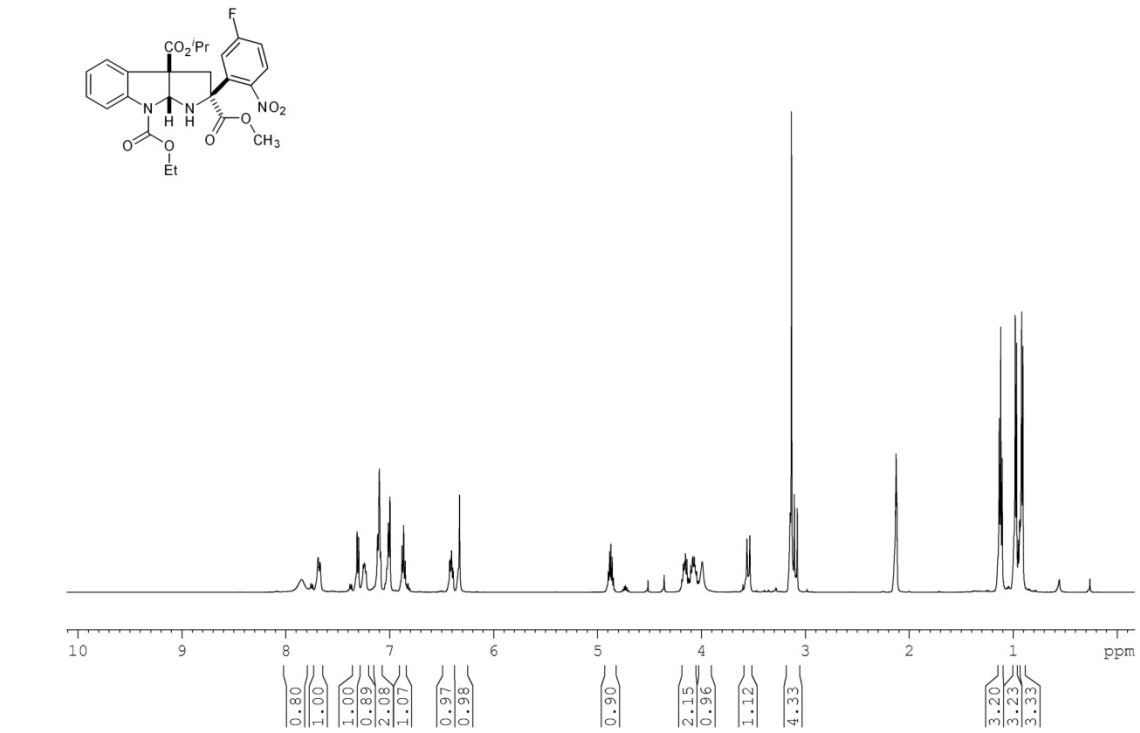

CO2iPr
N
EtO
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

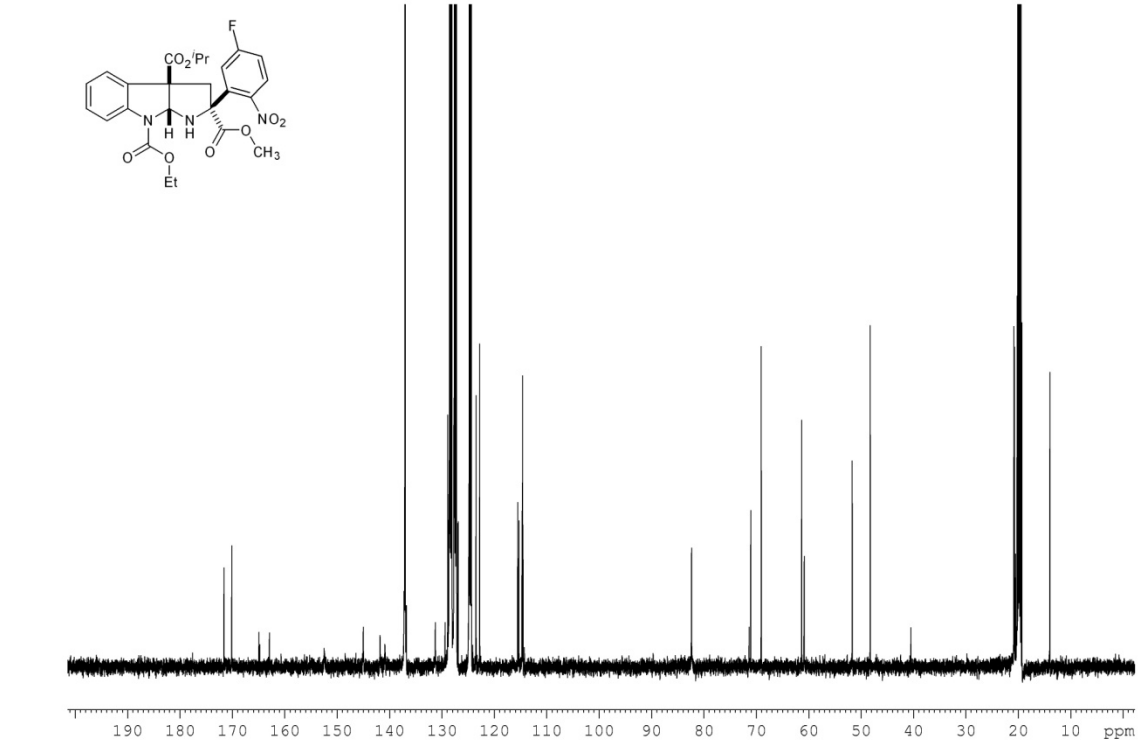

kk47562407
DRX500 1H acquisition, BBO probe KEISHI KOHARA 34756 MDS 24/7/2013 TEMP = 363k
6.44
11.68
2.60
2.00
2.21
2.61
2.04
2.14
3.18
1.18
3.76
1.31
1.36
0.54
2.47
14.68
8.23
6.53
f1 (ppm)

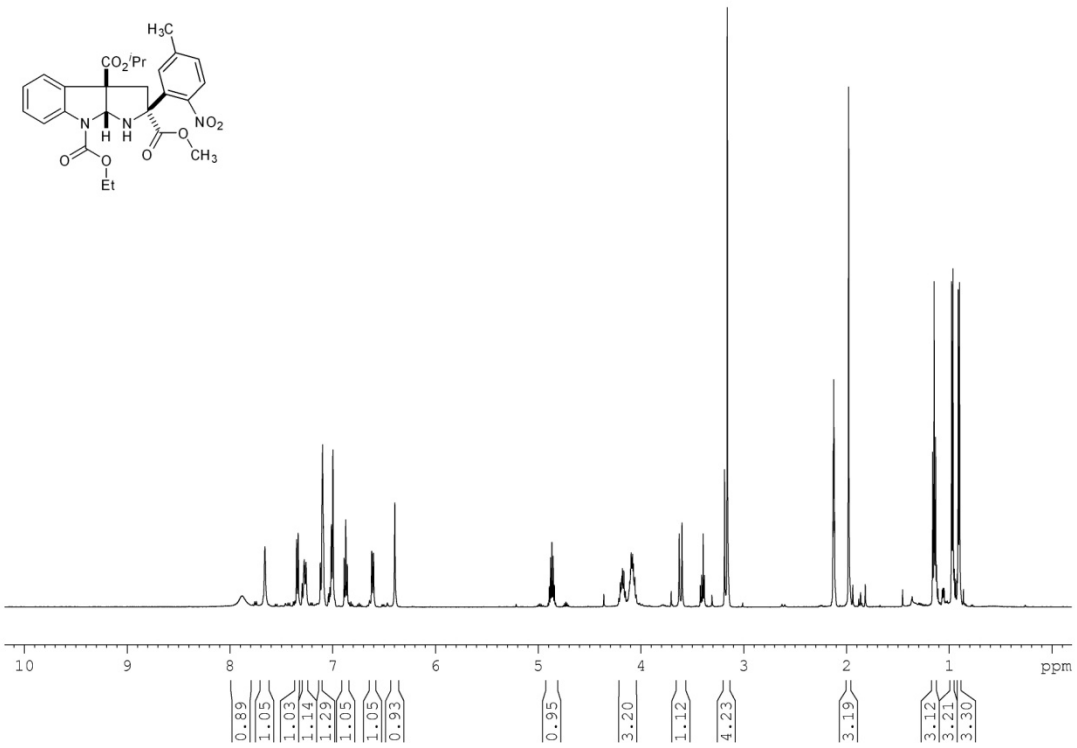

kk47561807
Instrument AVC500
Group MDS KEISHI KOHARA 34756 18/7/13
175.7
174.7
171.3
171.1
154.0
152.1
142.9
141.8
137.2
137.0
129.5
129.2
128.5
128.5
128.2
128.1
114.8
82.0
81.0
73.0
72.5
69.2
69.1
67.0
66.8
61.3
61.1
51.7
51.3
44.9
44.2
37.2
35.4
21.3
21.3
21.3
21.3
17.9
f1 (ppm)

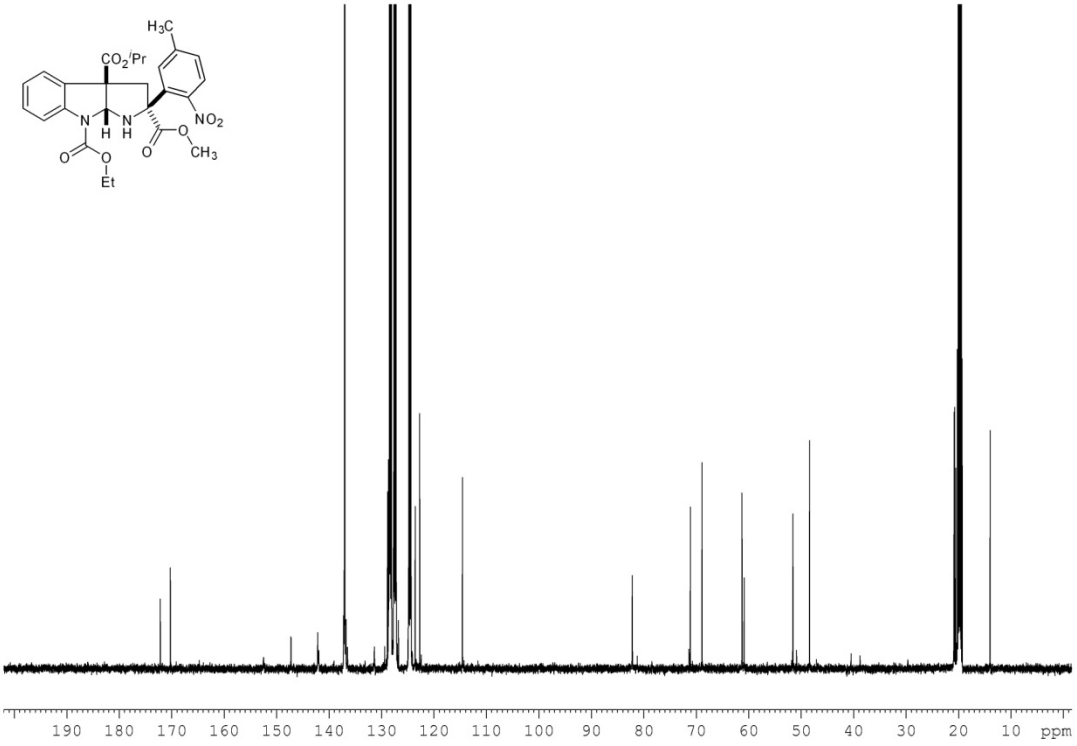

mg41243005
DRX500 1H acquisition, BBO probe MATIYA GREDICK 34123 30/5/13 TEMP = 363K
f1 (ppm)

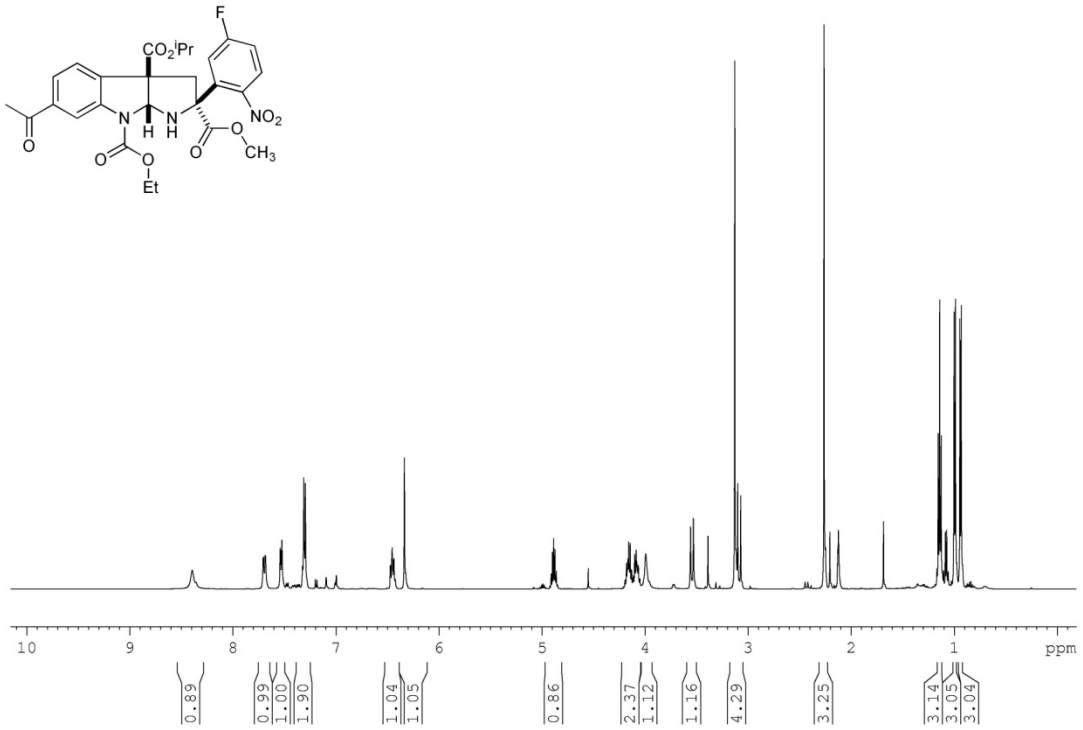

mg41232905
DRX500 13C acquisition BBO probe MATYA GREDICAK 34123 29/5/13 TEMP = 363K
f1 (ppm)

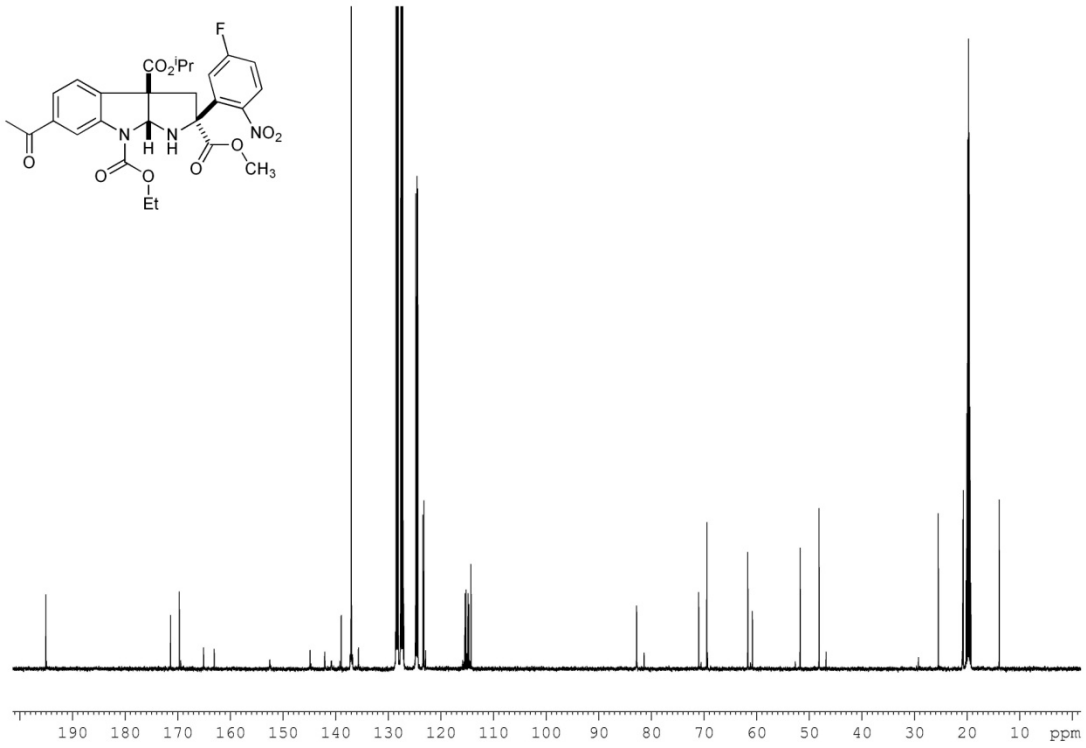

F
CO2iPr
NO2
N
H
H
N
O
O
O
CH3
O
Et
10
9
8
7
6
5
4
3
2
1
ppm
0.80
1.00
1.00
0.89
2.08
1.07
0.97
0.98
0.90
2.15
0.96
1.12
4.33
3.20
3.23
3.33

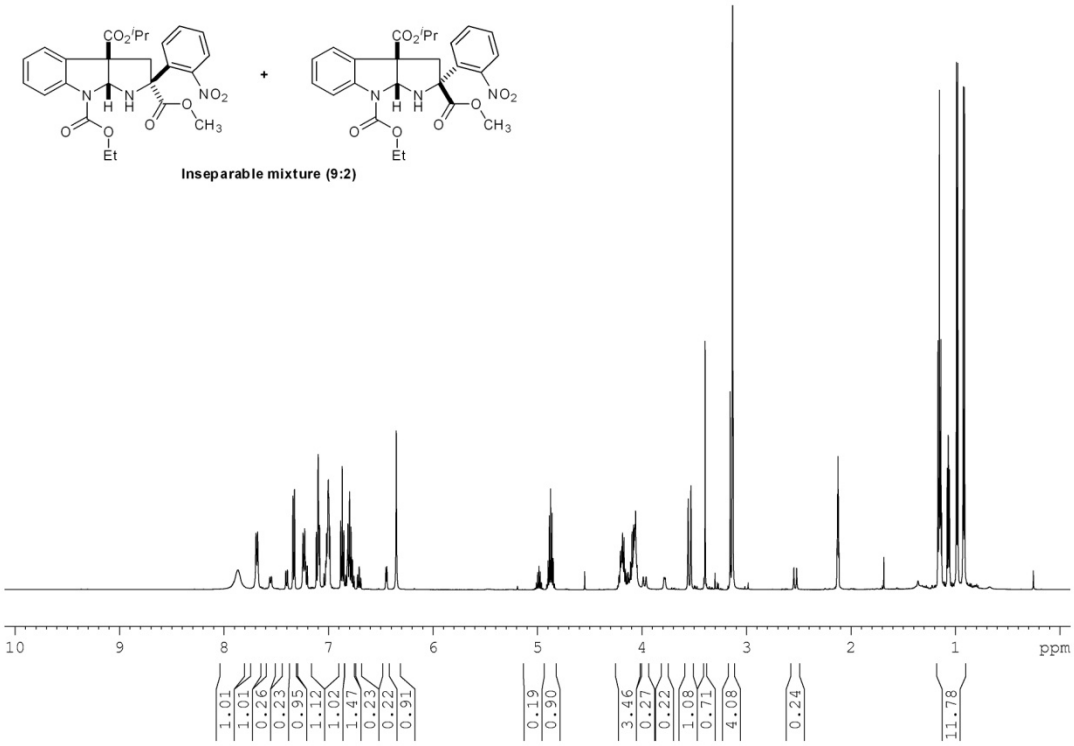

F
CO2iPr
NO2
N
H
H
N
O
O
O
CH3
O
Et
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

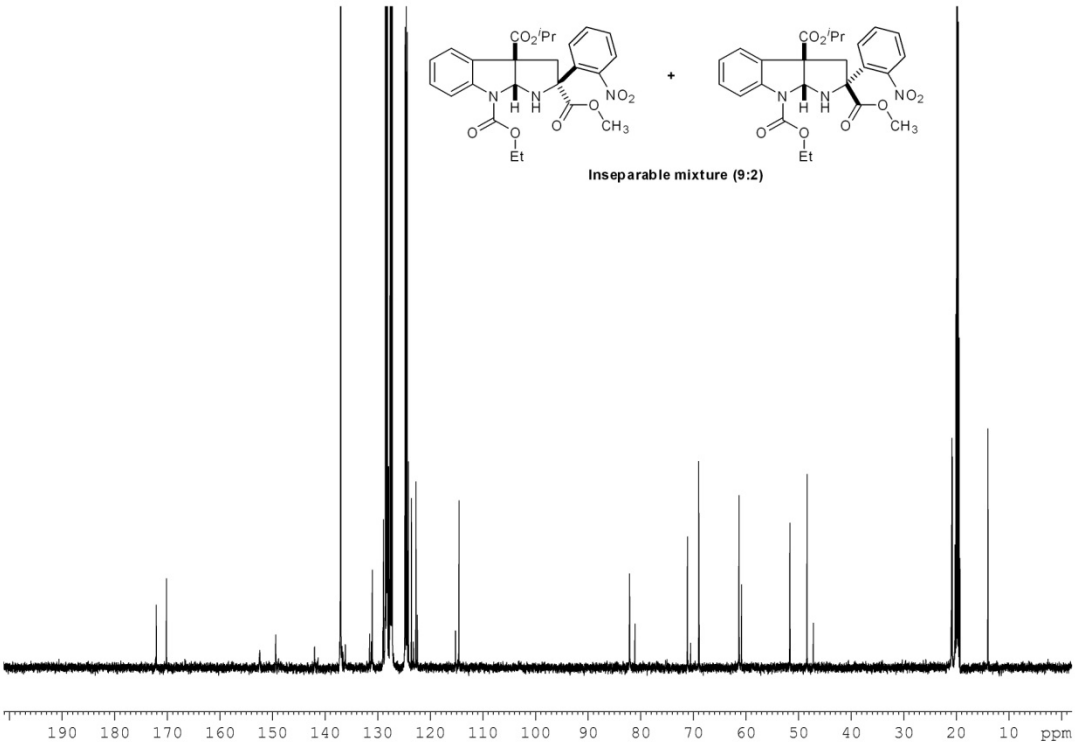

H3C
CO2iPr
NO2
N
H
H
N
O
O
O
CH3
O
Et
10
9
8
7
6
5
4
3
2
1
ppm
0.89
1.05
1.03
1.14
1.29
1.05
1.05
0.93
0.95
3.20
1.12
4.23
3.19
3.12
3.21
3.30

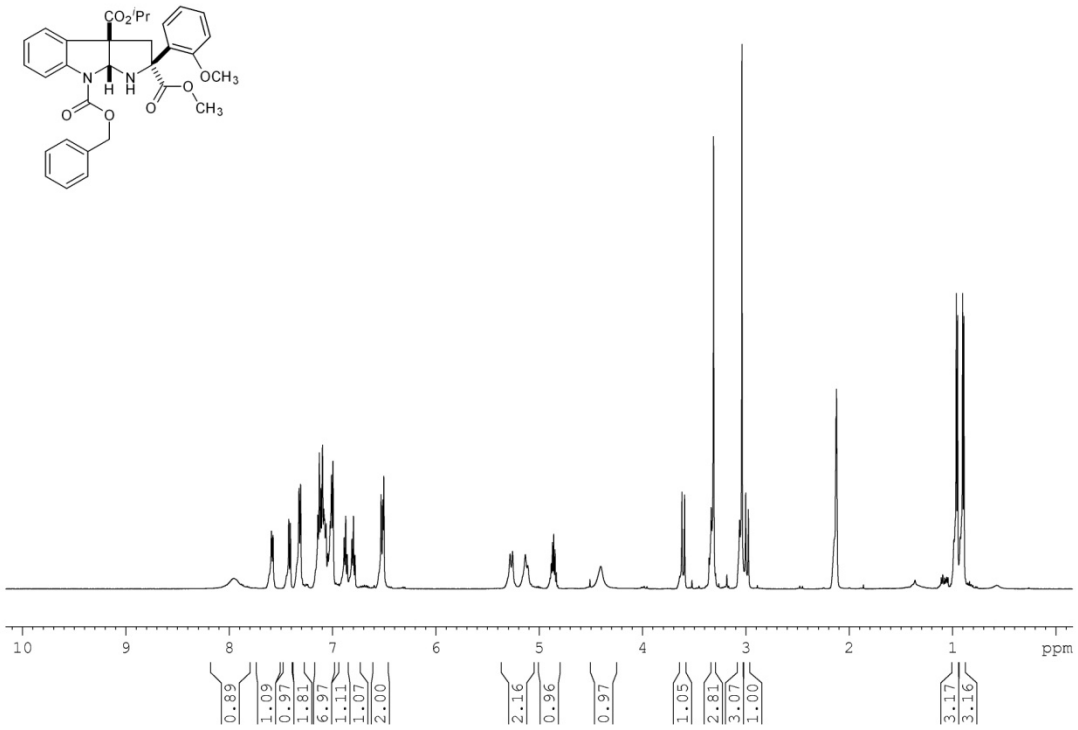

H3C
CO2iPr
NO2
N
H
H
N
O
O
O
CH3
O
Et
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

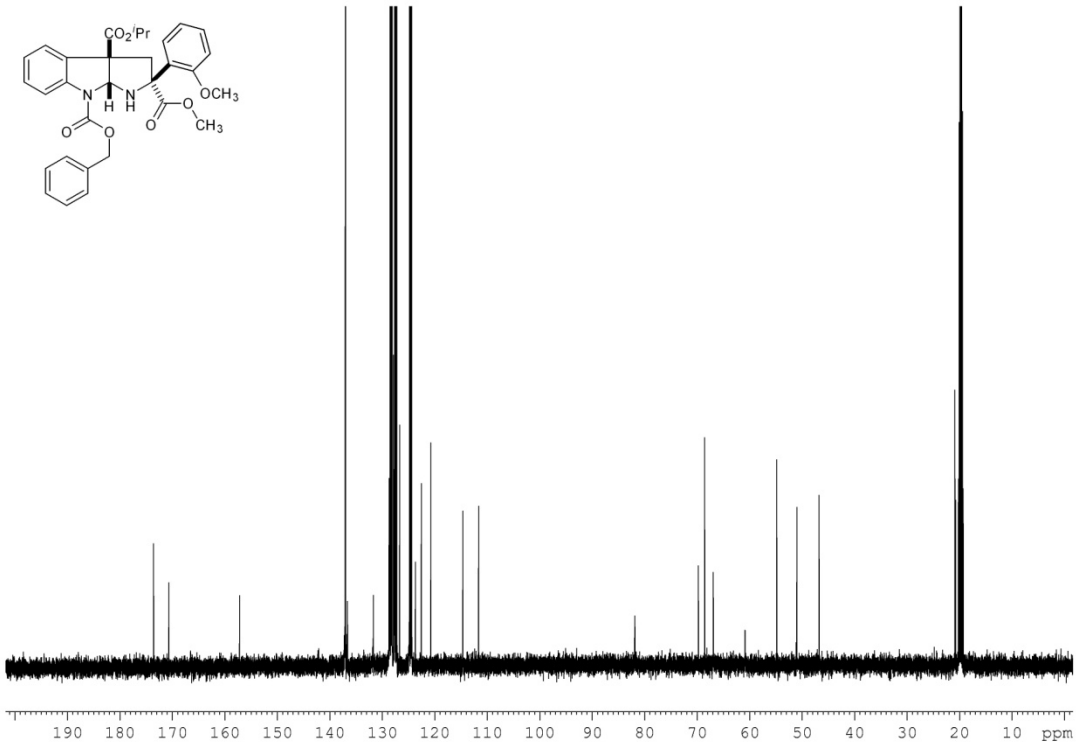

F
CO2iPr
NO2
N
H
N
H
O
O
O
O
O
CH3
Et
10
9
8
7
6
5
4
3
2
1
ppm
0.89
0.99
1.00
1.90
1.04
1.05
0.86
2.37
1.12
1.16
4.29
3.25
3.14
3.05
3.04

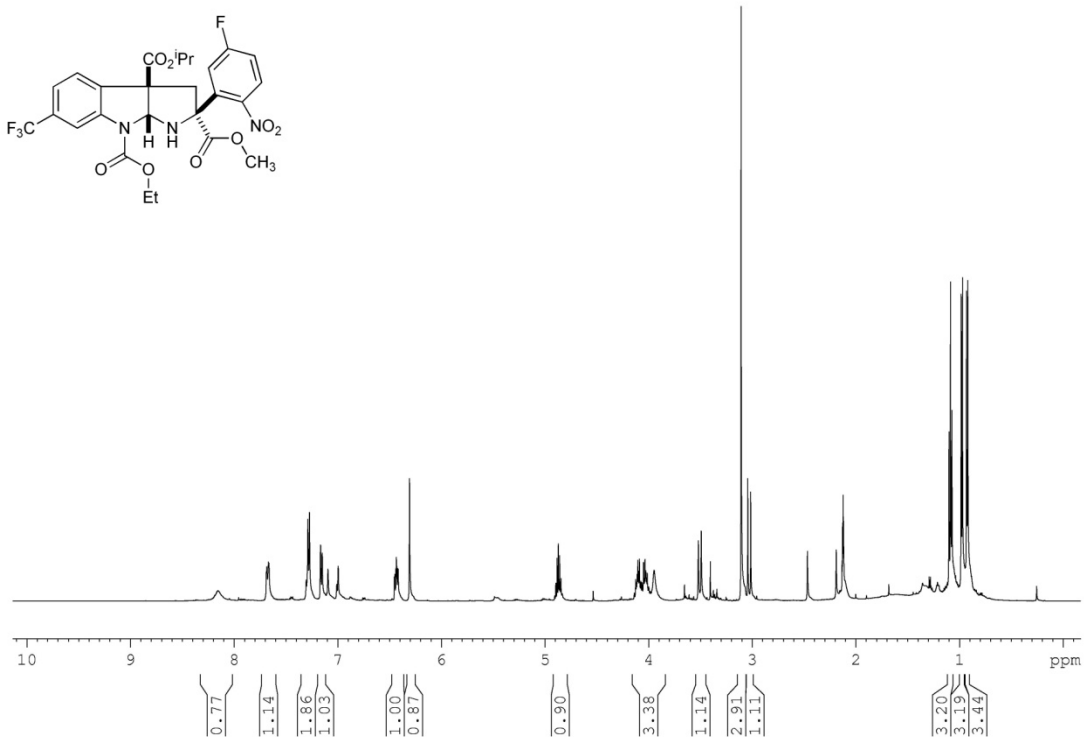

F
CO2iPr
NO2
N
H
N
H
O
O
O
O
O
CH3
Et
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

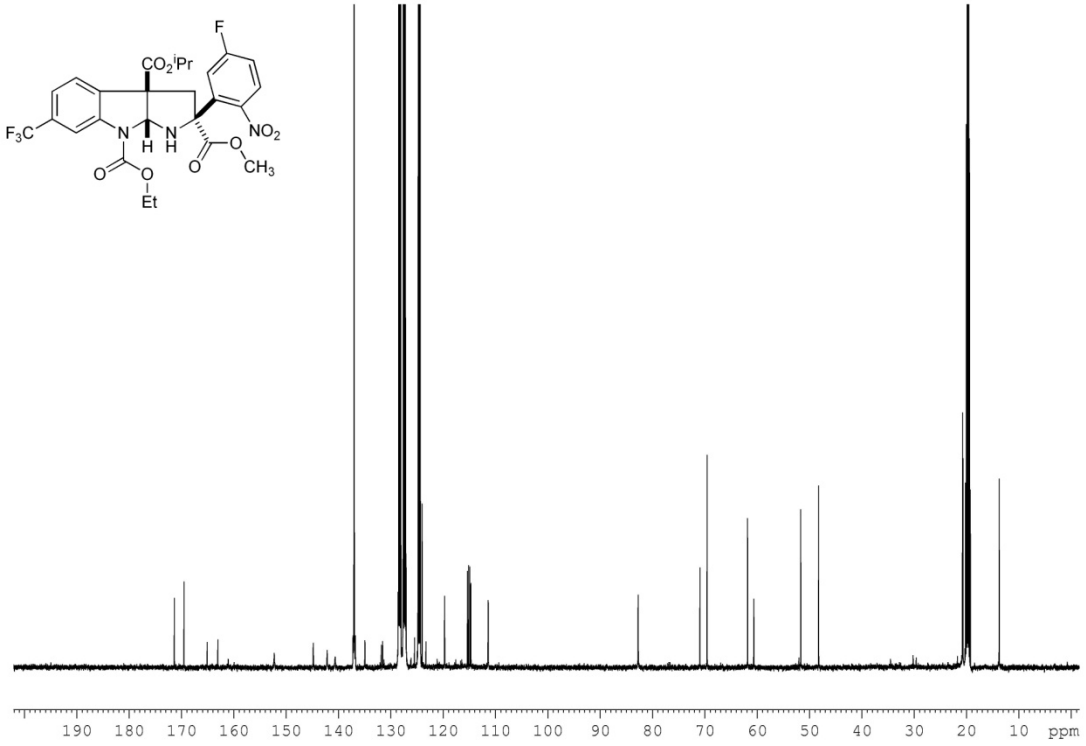

CO2iPr
NO2
O
CH3
Et
Inseparable mixture (9:2)
10 9 8 7 6 5 4 3 2 1 ppm
1.01 1.01 0.26 0.23 0.95 1.12 1.02 1.47 0.23 0.22 0.91
0.19 0.90
3.46 0.27 0.22 1.08 0.71 4.08
0.24
11.78

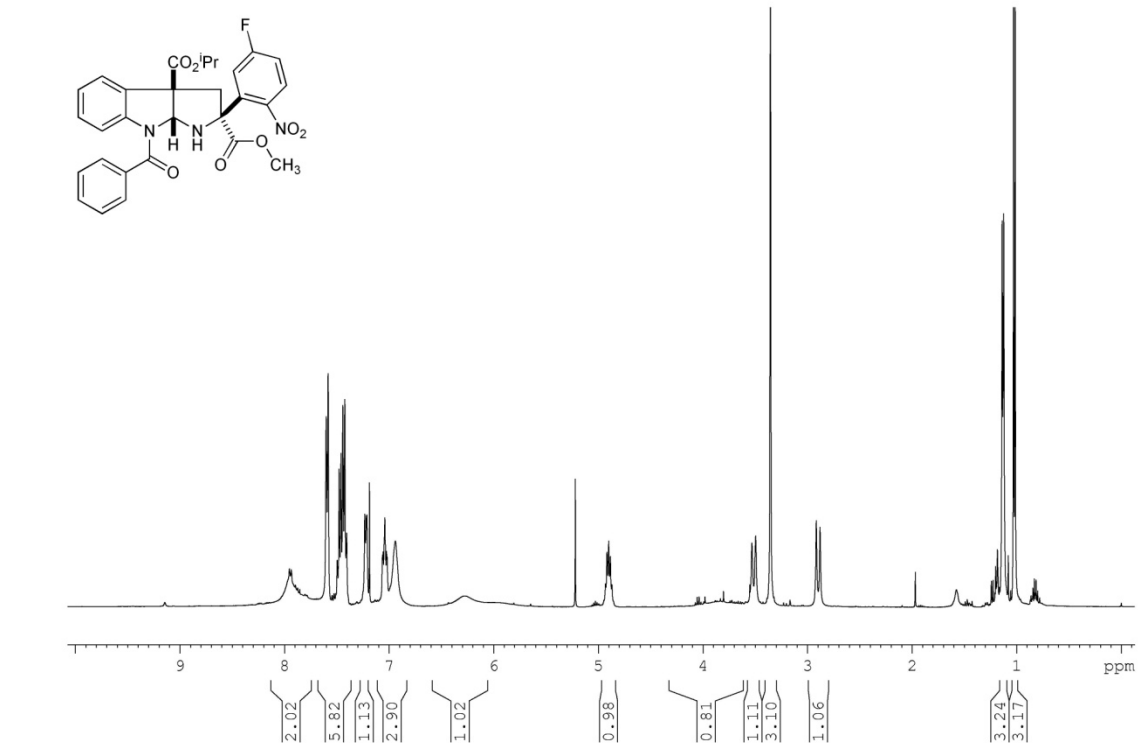

CO2iPr
NO2
O
CH3
Et
Inseparable mixture (9:2)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

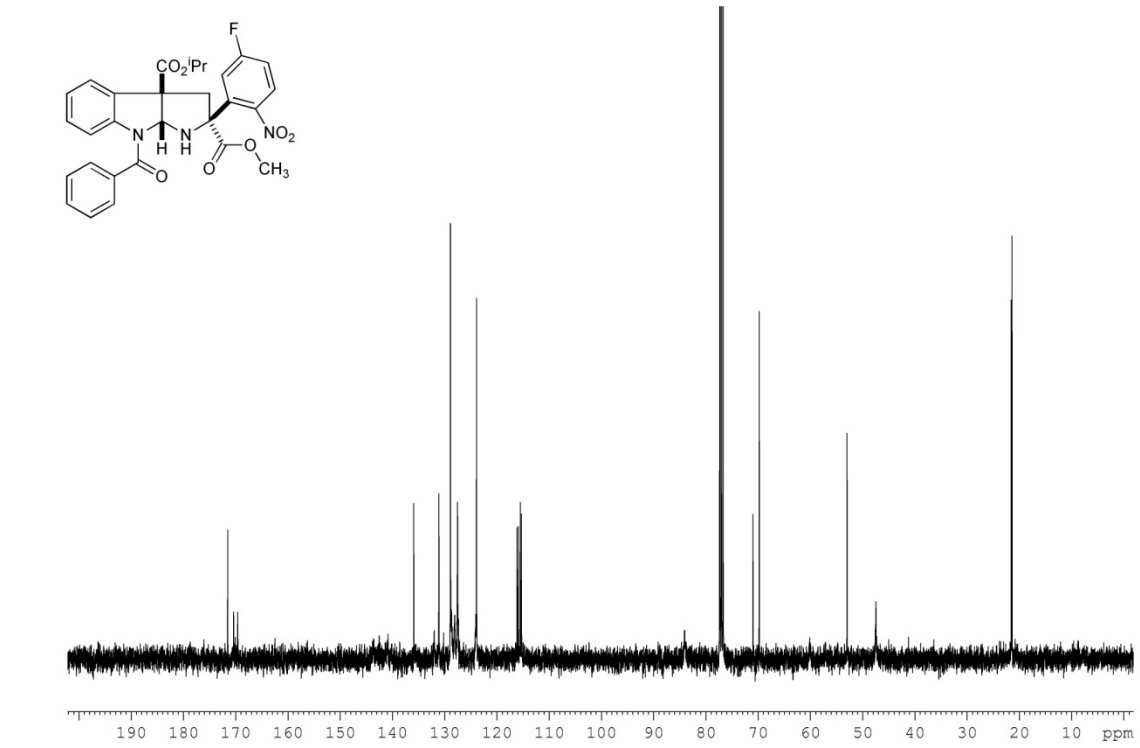

CO2iPr
OCH3
CH3
10
9
8
7
6
5
4
3
2
1
ppm
0.89
1.09
0.97
1.81
6.97
1.11
1.07
2.00
2.16
0.96
0.97
1.05
2.81
3.07
1.00
3.17
3.16

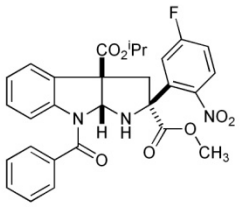

CO2iPr
OCH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

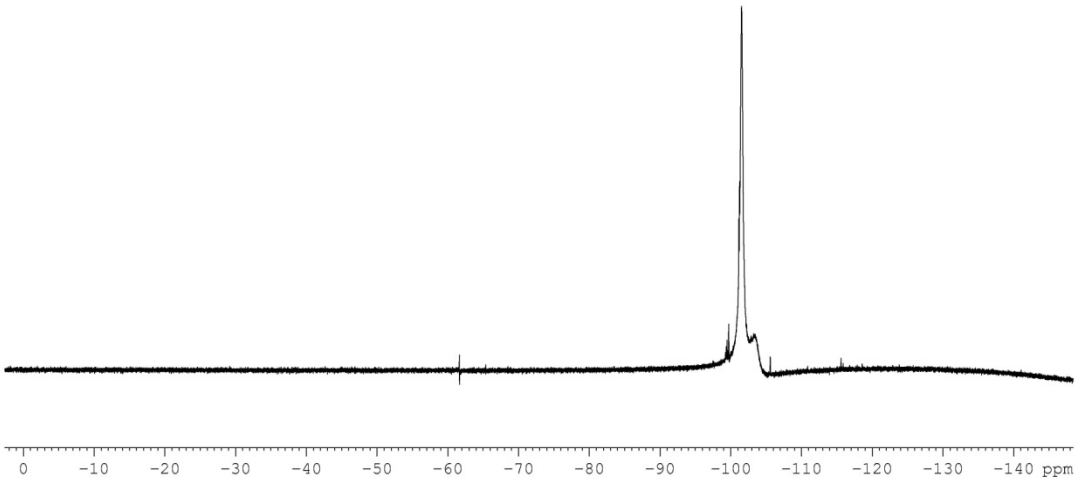

F
CO2iPr
F3C
N
H
N
H
NO2
O
O
CH3
O
O
Et
10
9
8
7
6
5
4
3
2
1
ppm
0.77
1.14
1.86
1.03
1.00
0.87
0.90
3.38
1.14
2.91
1.11
3.20
3.19
3.44

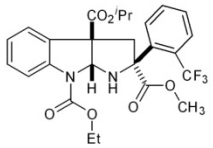

F
CO2iPr
F3C
N
H
N
H
NO2
O
O
CH3
O
O
Et
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

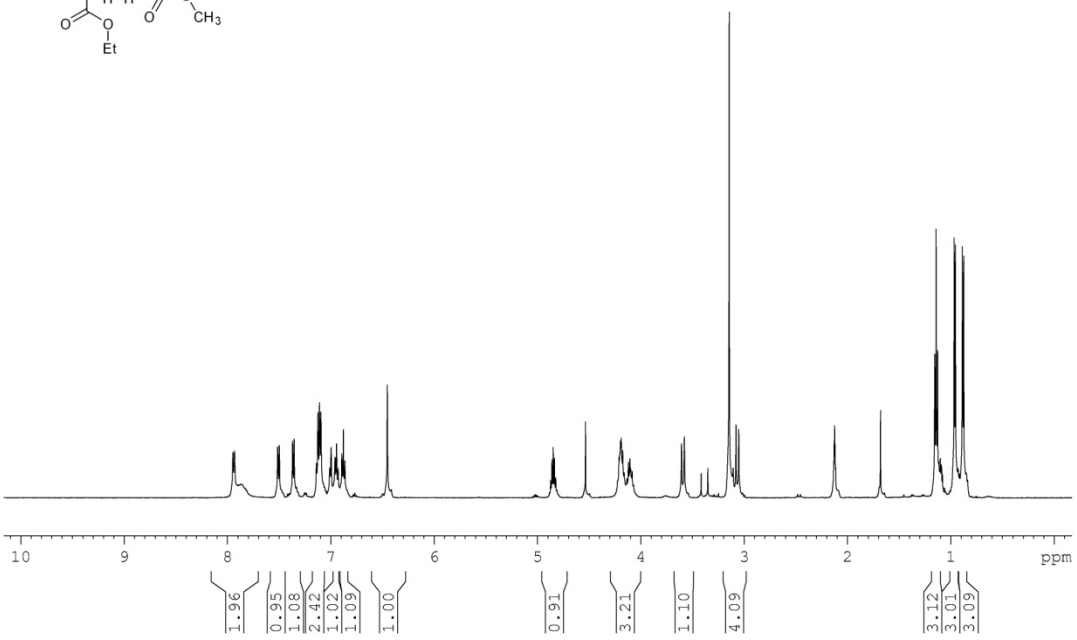

F
CO2iPr
NO2
N
H
N
H
O
O
O
CH3
9
8
7
6
5
4
3
2
1
ppm
2.02
5.82
1.13
2.90
1.02
0.98
0.81
1.11
3.10
1.06
3.24
3.17

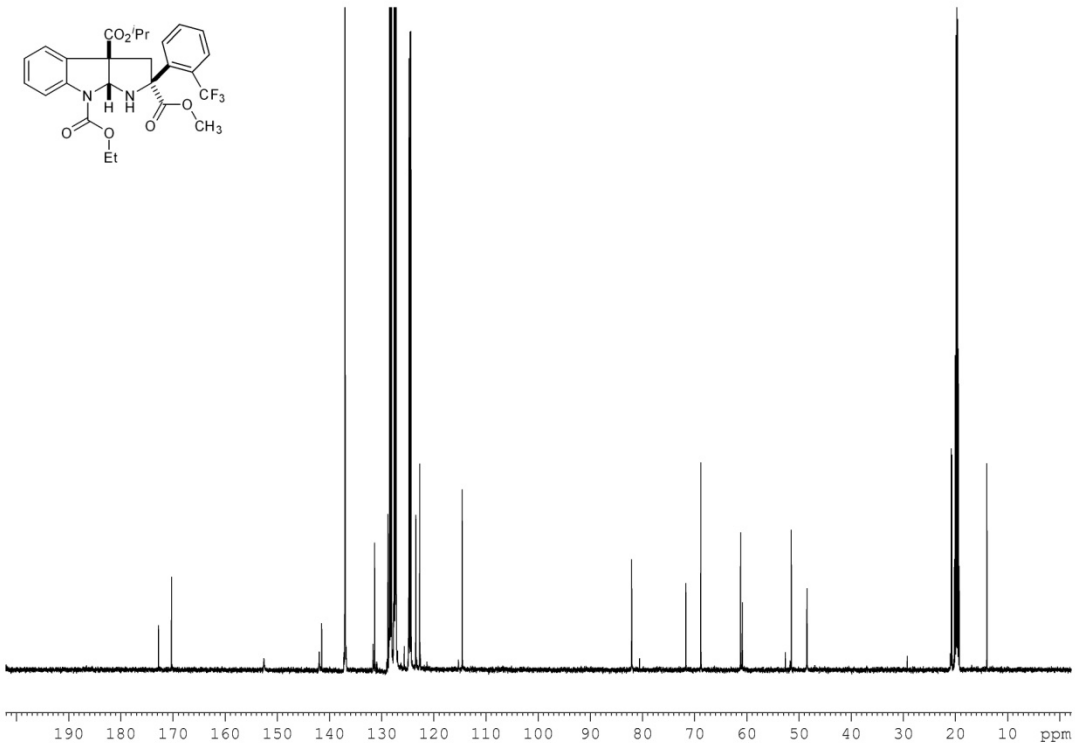

F
CO2iPr
NO2
N
H
N
H
O
O
O
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

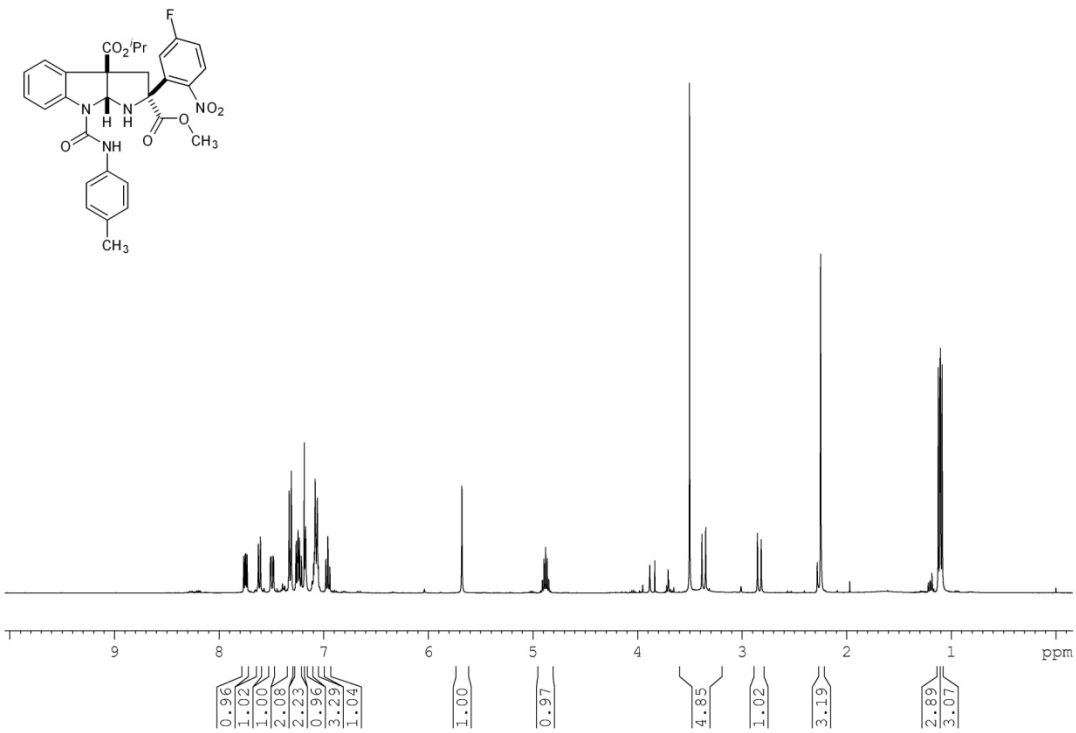

F
CO2iPr
NO2
N
H
N
H
O
O
O
CH3

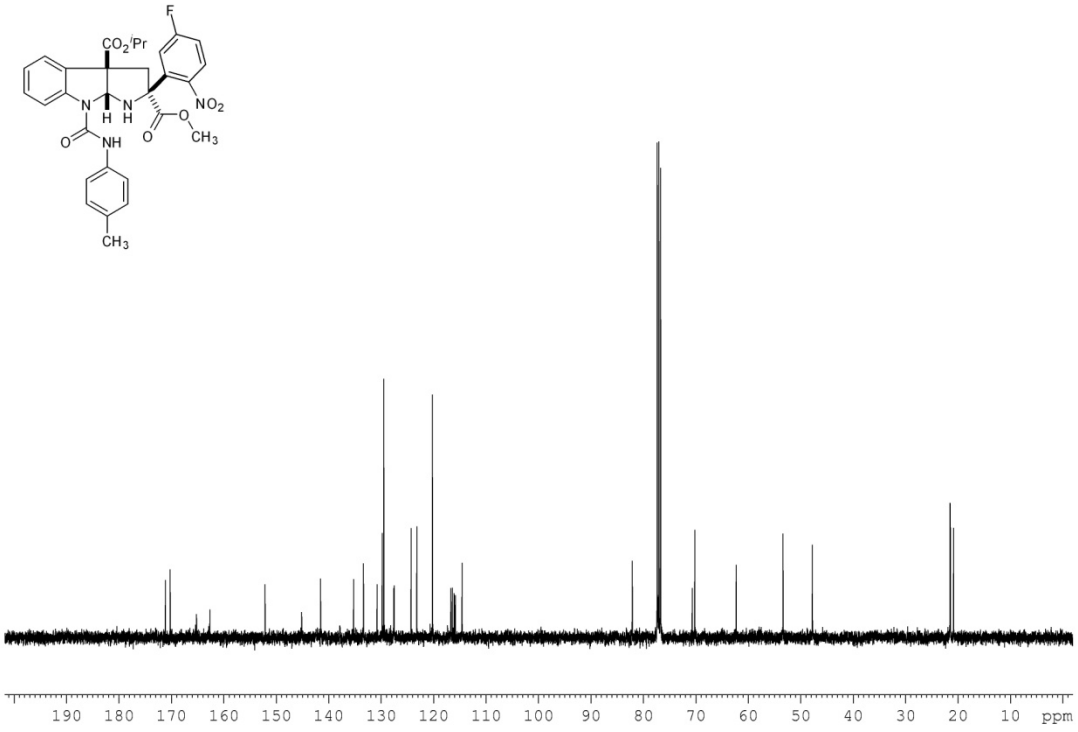

0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140 ppm

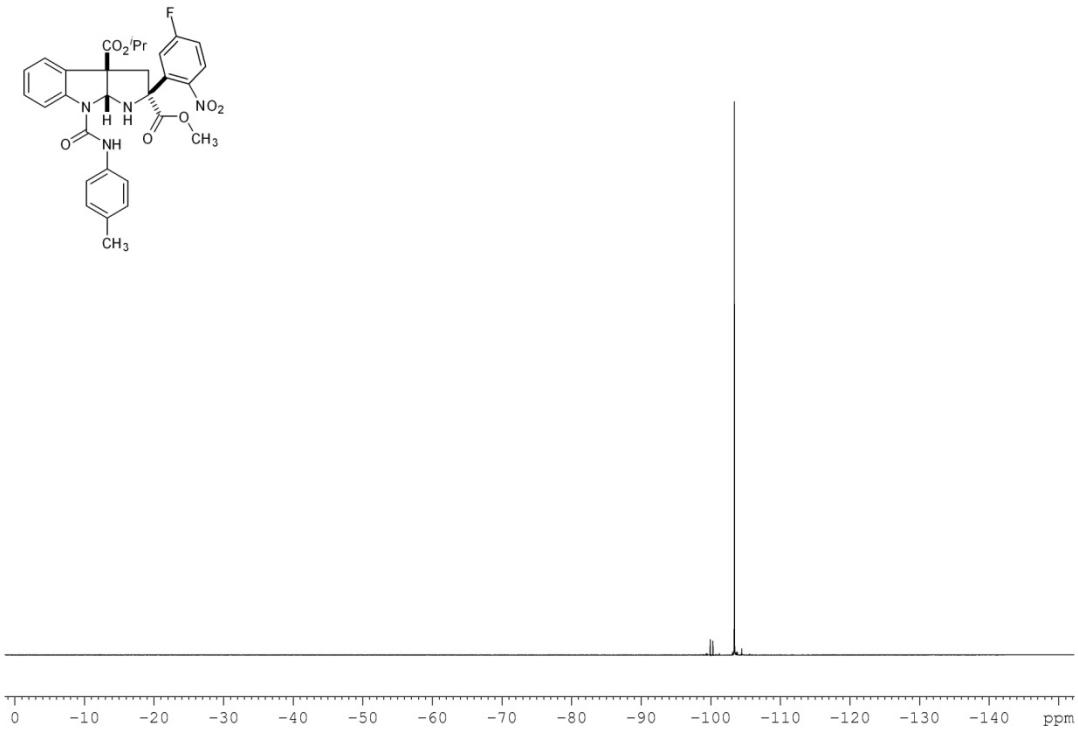

CO2iPr
CF3
N
H
N
H
O
O
O
CH3
O
Et

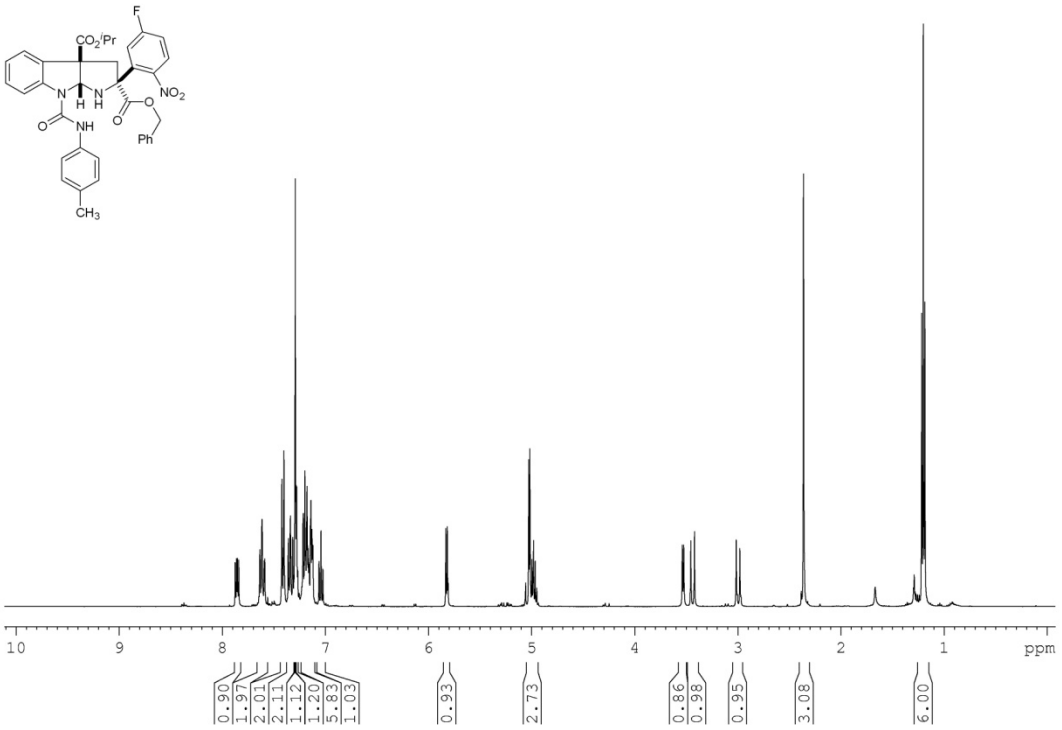

10
9
8
7
6
5
4
3
2
1
ppm
1.96
0.95
1.08
2.42
1.02
1.09
1.00
0.91
3.21
1.10
4.09
3.12
3.01
3.09

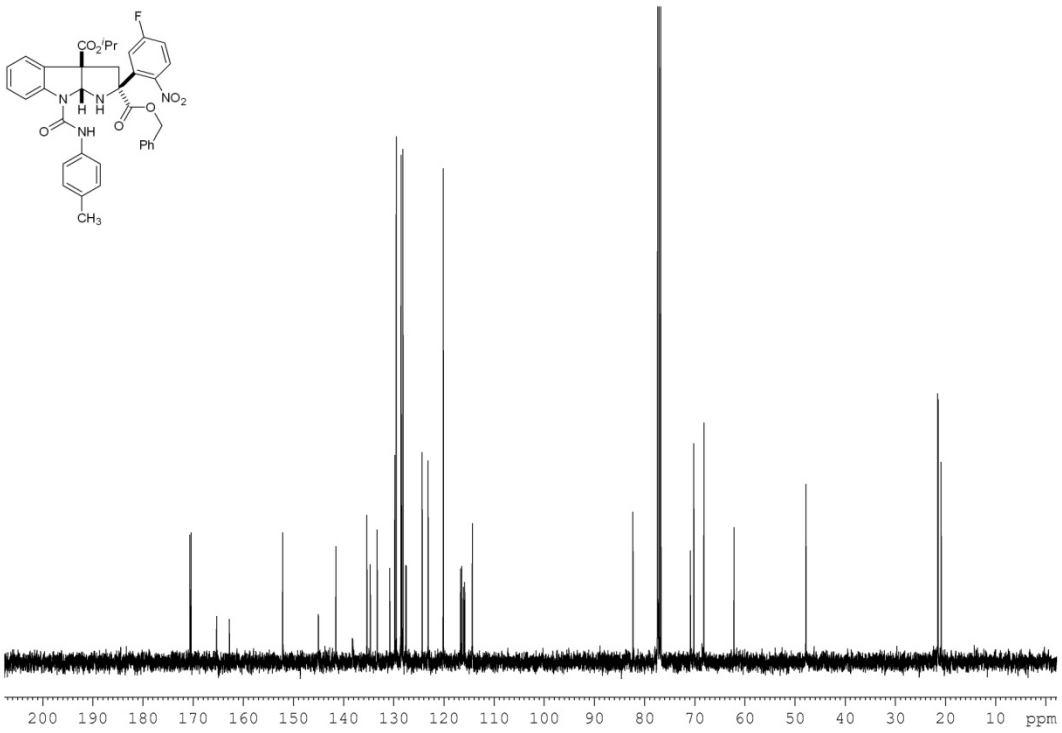

CO2iPr
CF3
N
H
N
H
O
O
CH3
O
Et
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

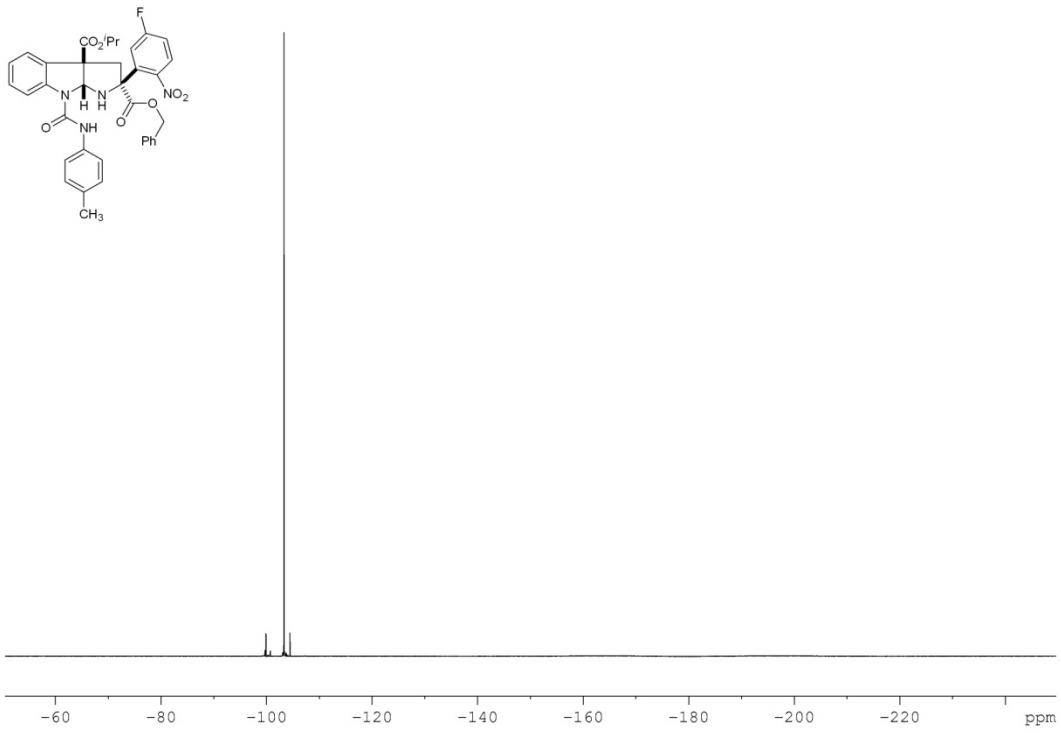

F
CO2iPr
NO2
N
H
N
H
O
NH
O
CH3
CH3
9 8 7 6 5 4 3 2 1 ppm
0.96
1.02
1.00
2.08
2.23
0.96
3.29
1.04
1.00
0.97
4.85
1.02
3.19
2.89
3.07

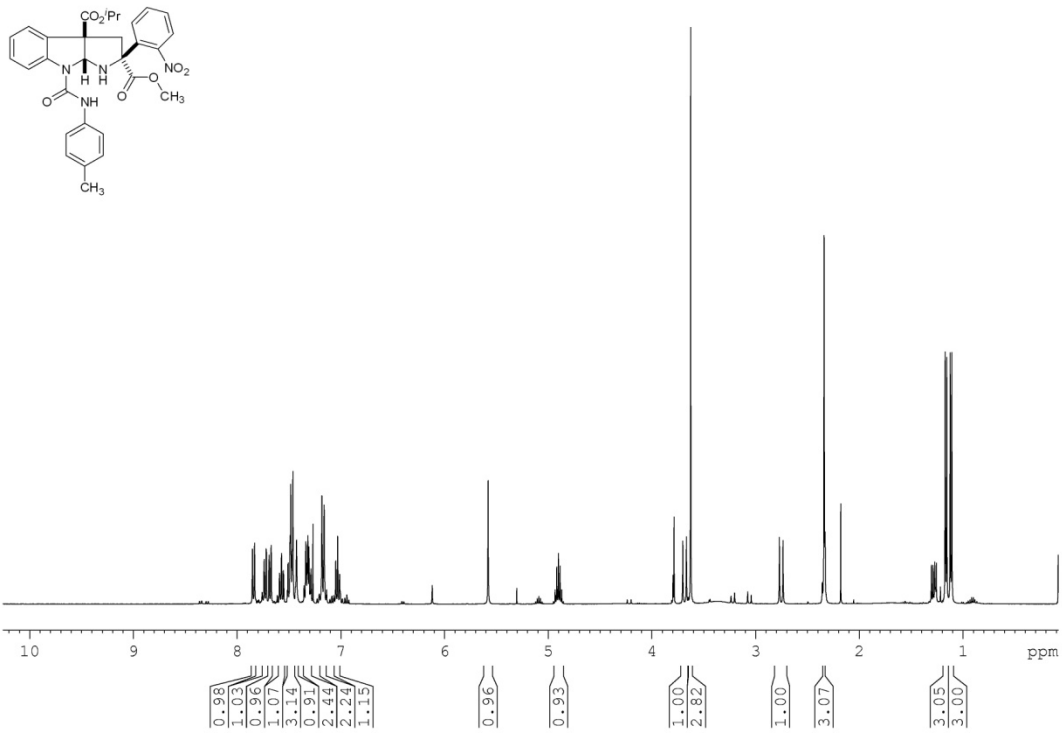

F
CO2iPr
NO2
N
H
H
N
O
NH
O
O
CH3
CH3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

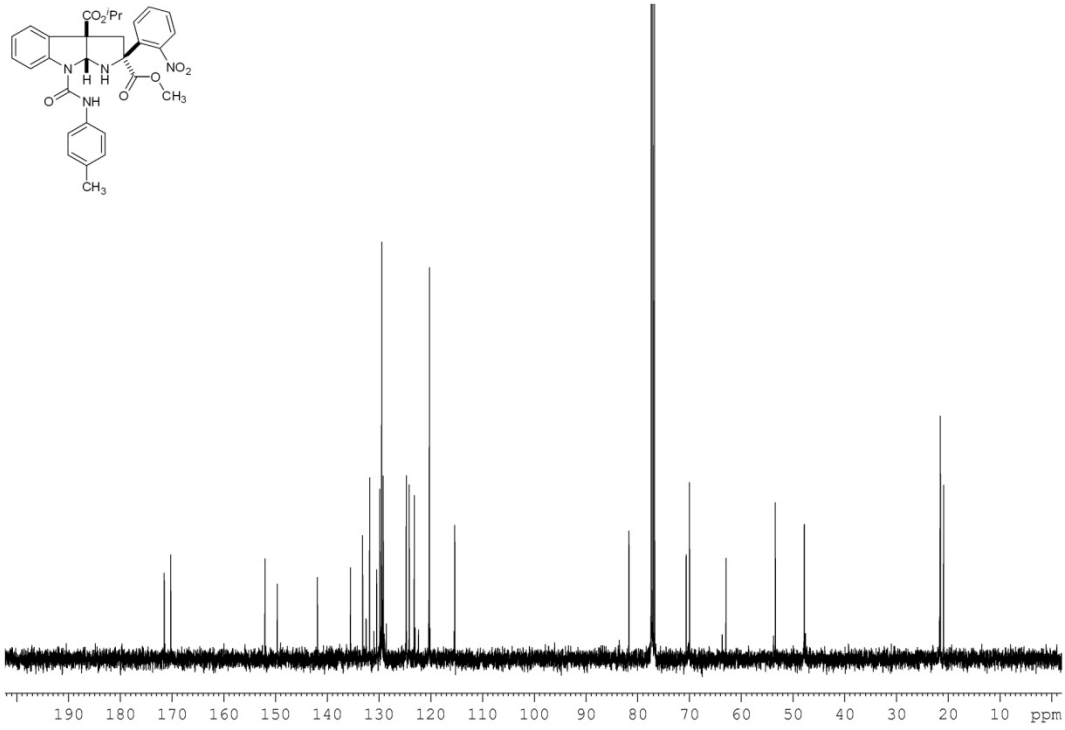

F
CO2iPr
NO2
N
H
H
N
O
NH
O
O
CH3
CH3
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 ppm

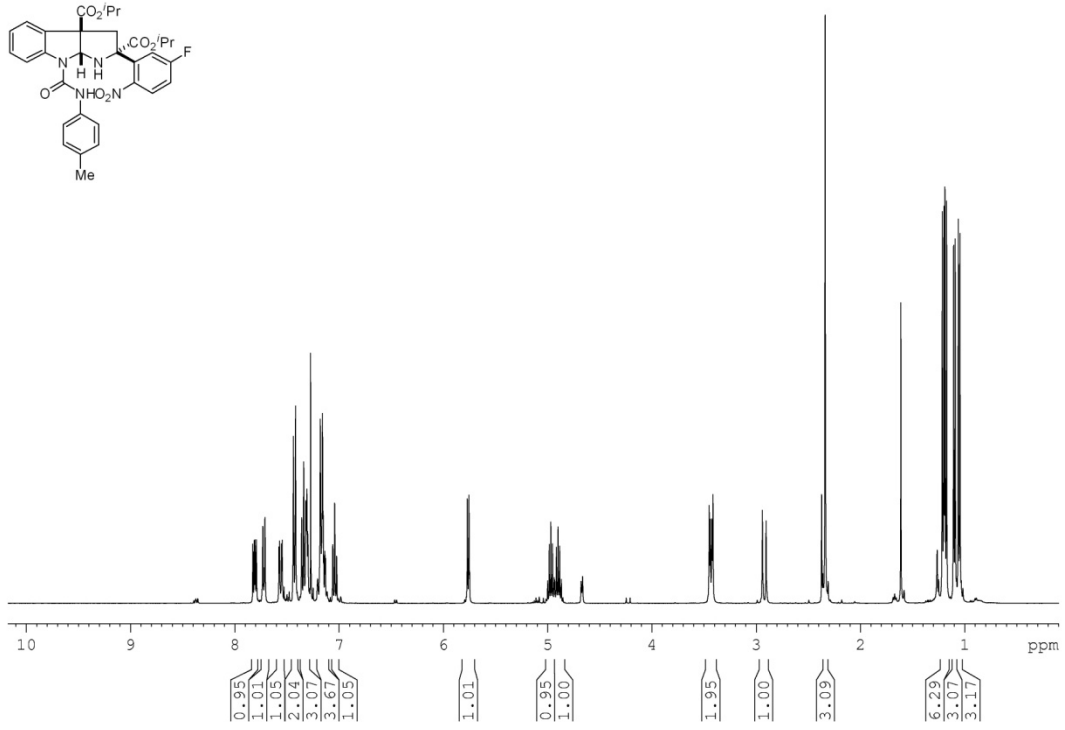

F
CO2iPr
NO2
N
H
N
H
O
NH
O
O
Ph
CH3
10
9
8
7
6
5
4
3
2
1
ppm
0.90
1.97
2.01
2.11
1.12
1.20
5.83
1.03
0.93
2.73
0.86
0.98
0.95
3.08
6.00

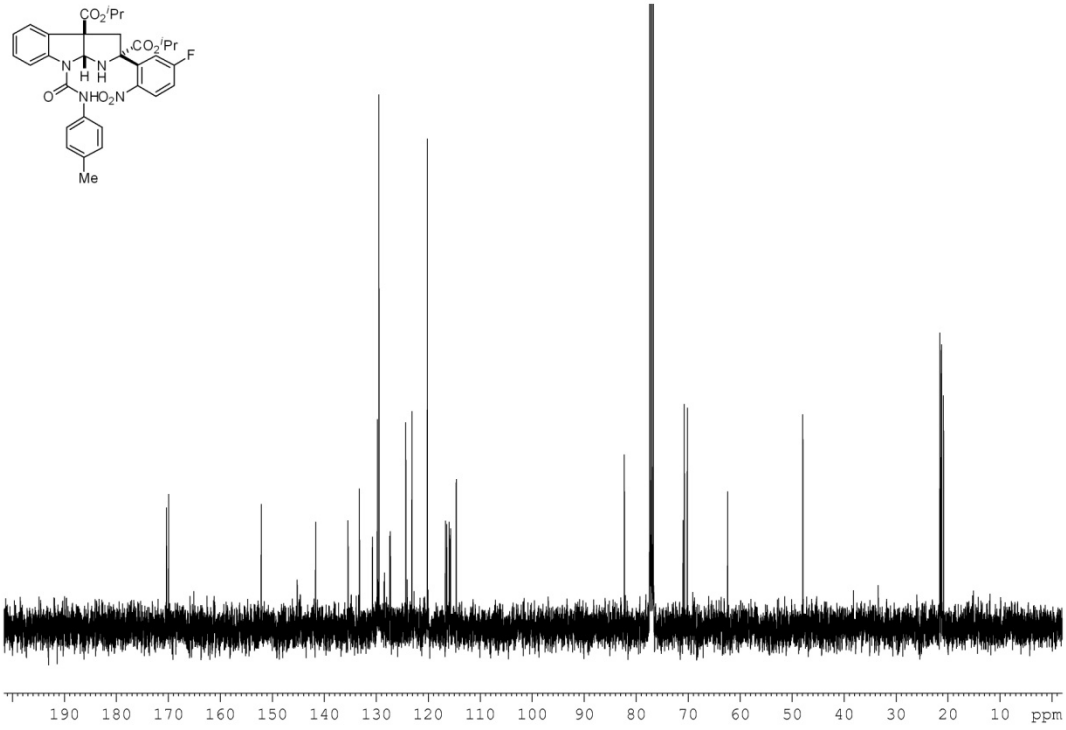

F
CO2iPr
NO2
N
H
N
H
O
NH
O
O
Ph
CH3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

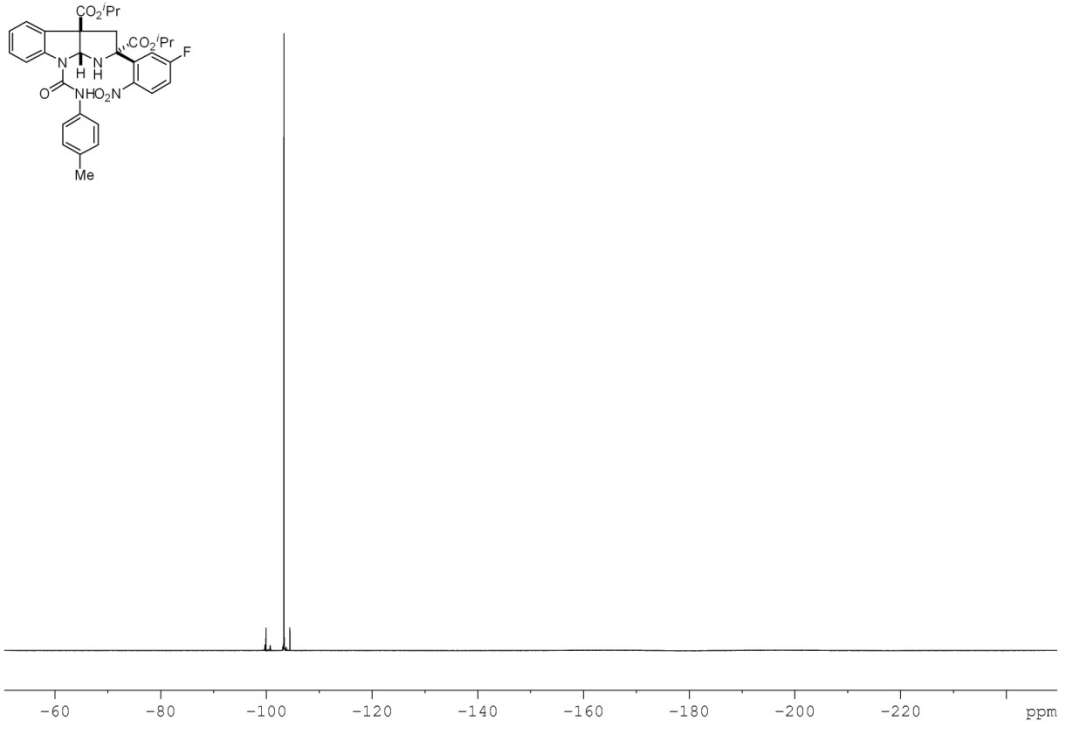

F
CO2iPr
NO2
N
H
N
H
O
NH
O
O
Ph
CH3
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

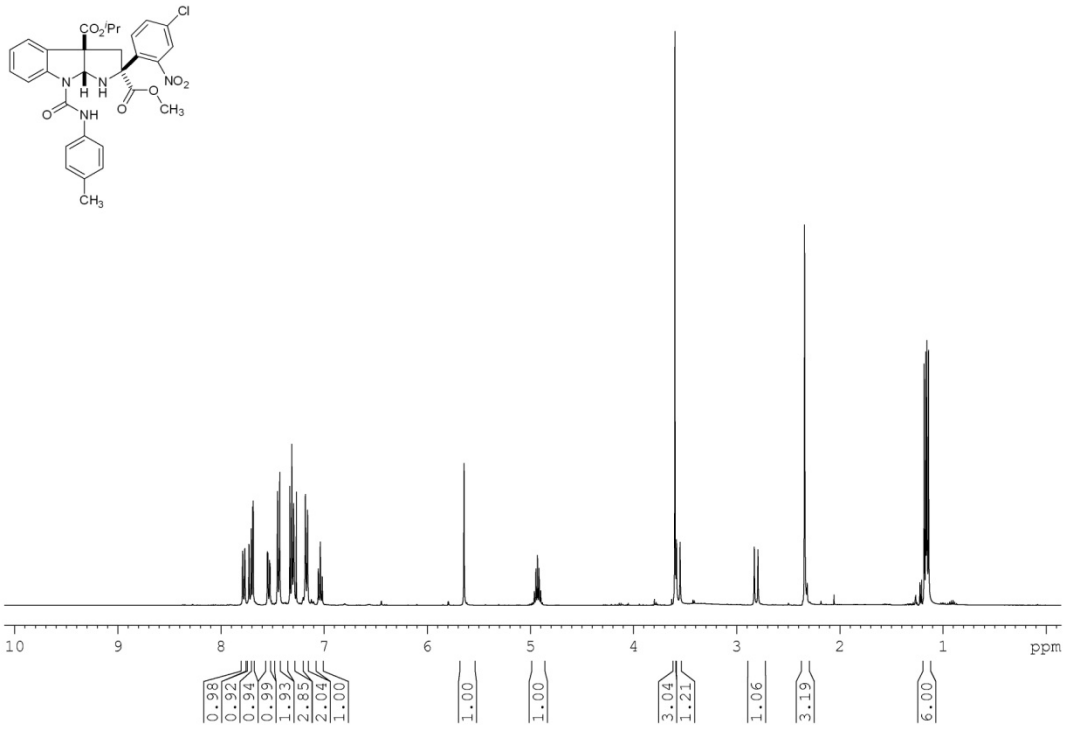

CO2iPr
NO2
N
H
N
H
O
NH
O
O
CH3
CH3
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.03
0.96
1.07
3.14
0.91
2.44
2.24
1.15
0.96
0.93
1.00
2.82
1.00
3.07
3.05
3.00

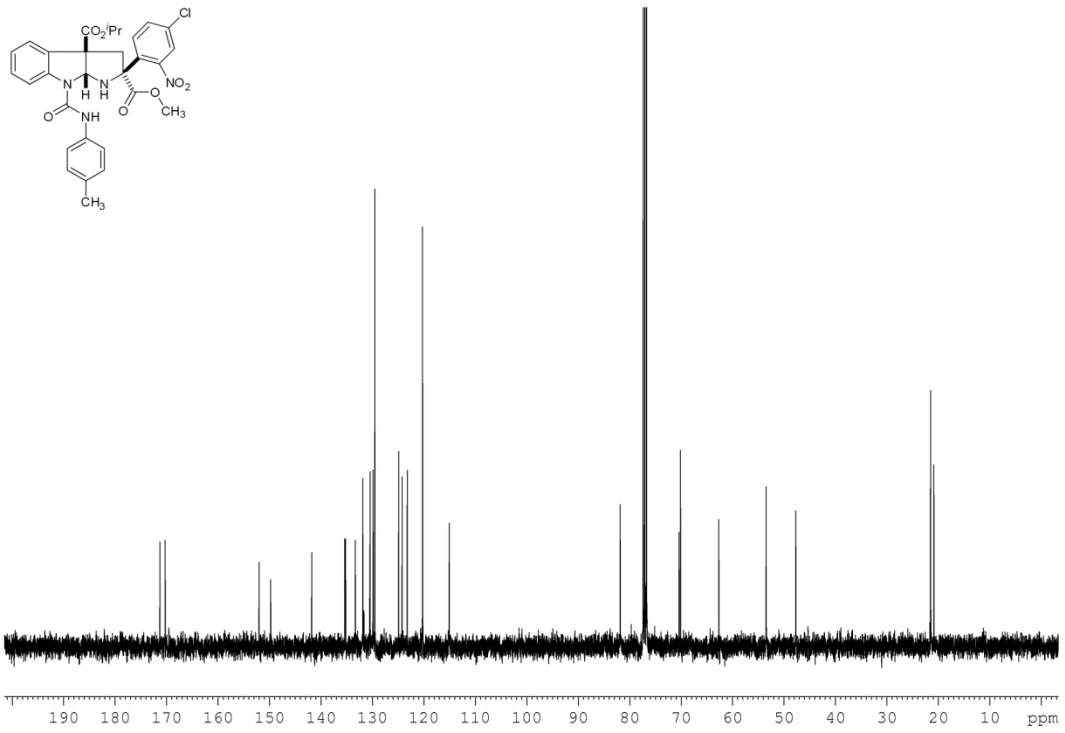

CO2iPr
NO2
O
CH3
NH
CH3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

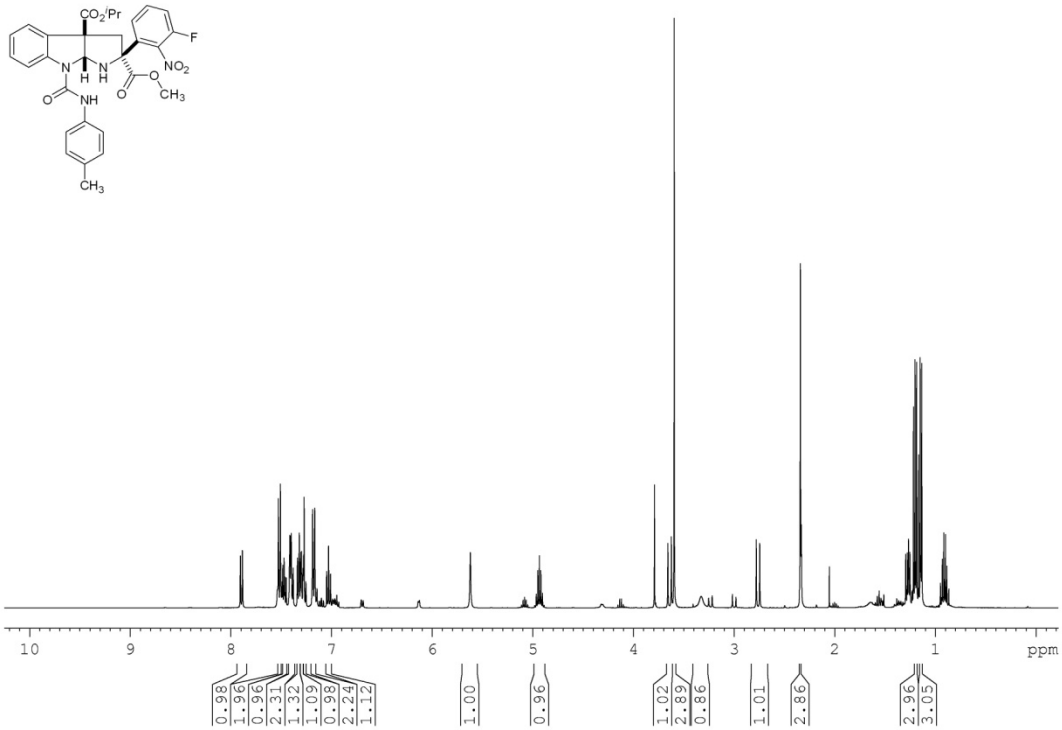

CO2iPr
CO2iPr
F
NHO2N
Me
10 9 8 7 6 5 4 3 2 1 ppm
0.95
1.01
1.05
2.04
3.07
3.67
1.05
1.01
0.95
1.00
1.95
1.00
3.09
6.29
3.07
3.17

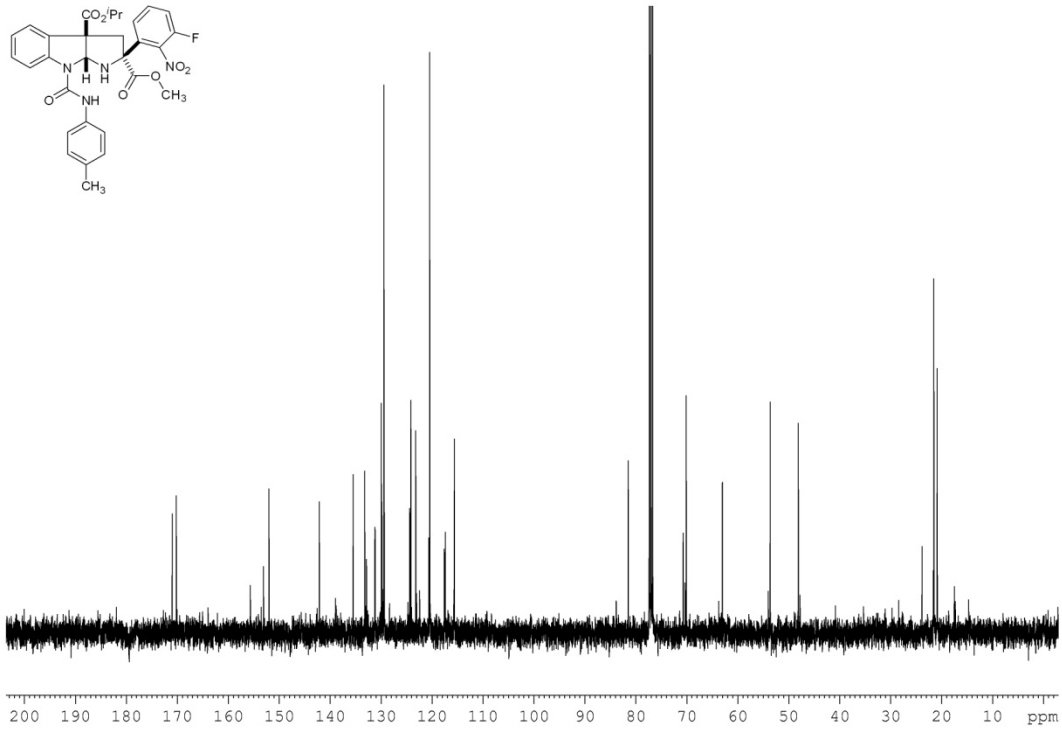

CO2iPr
CO2iPr
F
N
H
N
H
O
NHO2N
Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

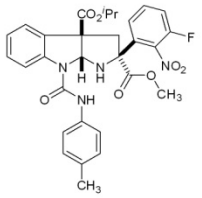

CO2iPr
CO2iPr
F
N
H
N
H
O
NHO2N
Me
-60 -80 -100 -120 -140 -160 -180 -200 -220 ppm


CO2iPr
Cl
NO2
N
H
N
H
O
NH
O
O
CH3
CH3
10
9
8
7
6
5
4
3
2
1
ppm
0.98
0.92
0.94
0.99
1.93
2.85
2.04
1.00
1.00
1.00
3.04
1.21
1.06
3.19
6.00

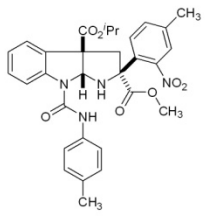

CO2iPr
Cl
NO2
N
H
N
H
O
NH
O
O
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


CO2iPr
F
NO2
N
H
N
H
O
NH
O
O
CH3
CH3
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.96
0.96
2.31
1.32
1.09
0.98
2.24
1.12
1.00
0.96
1.02
2.89
0.86
1.01
2.86
2.96
3.05

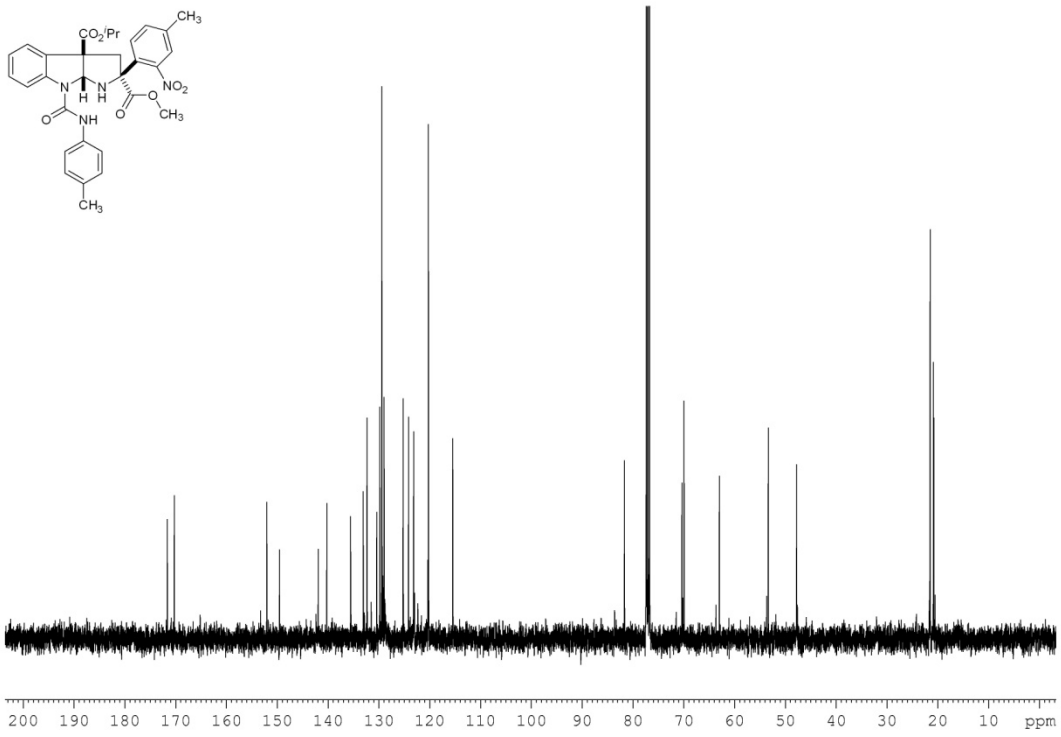

CO2iPr
F
NO2
N
H
N
H
O
NH
O
O
CH3
CH3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

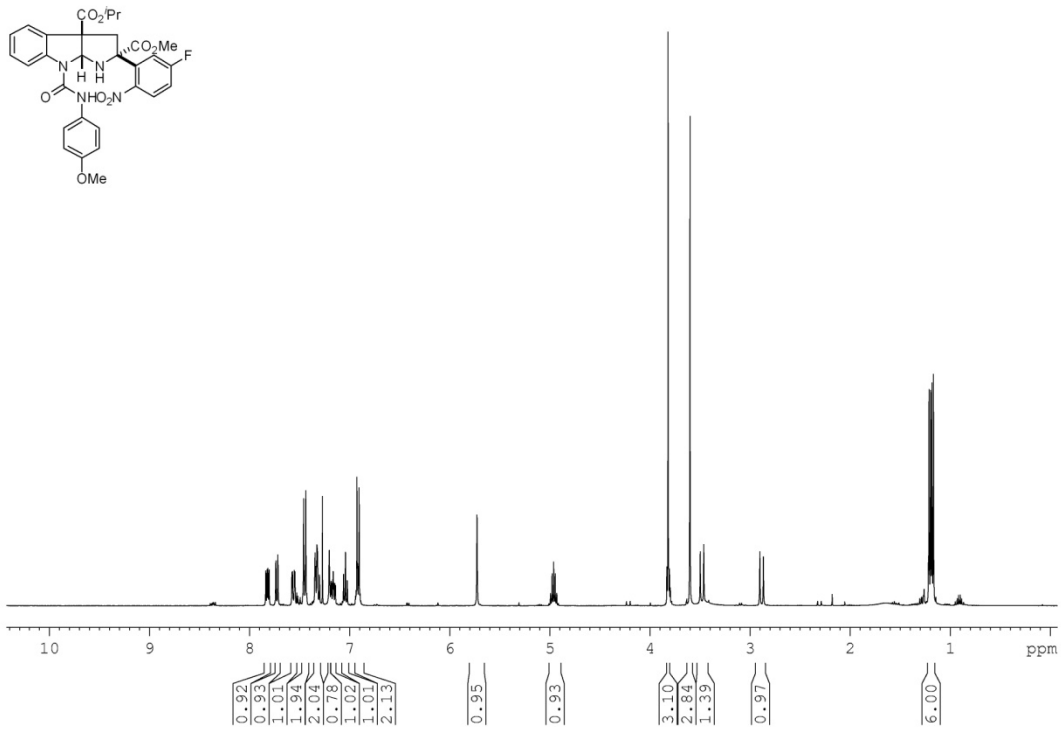

CO2iPr
F
NO2
N
H
N
H
O
NH
O
O
CH3
CH3

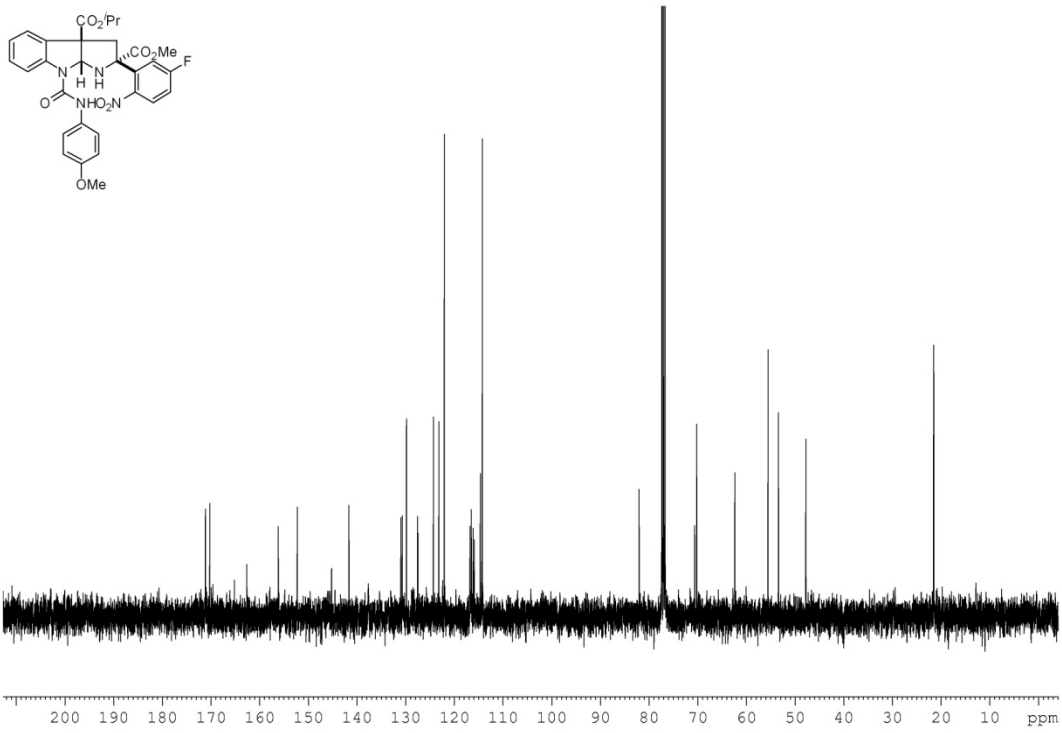
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm

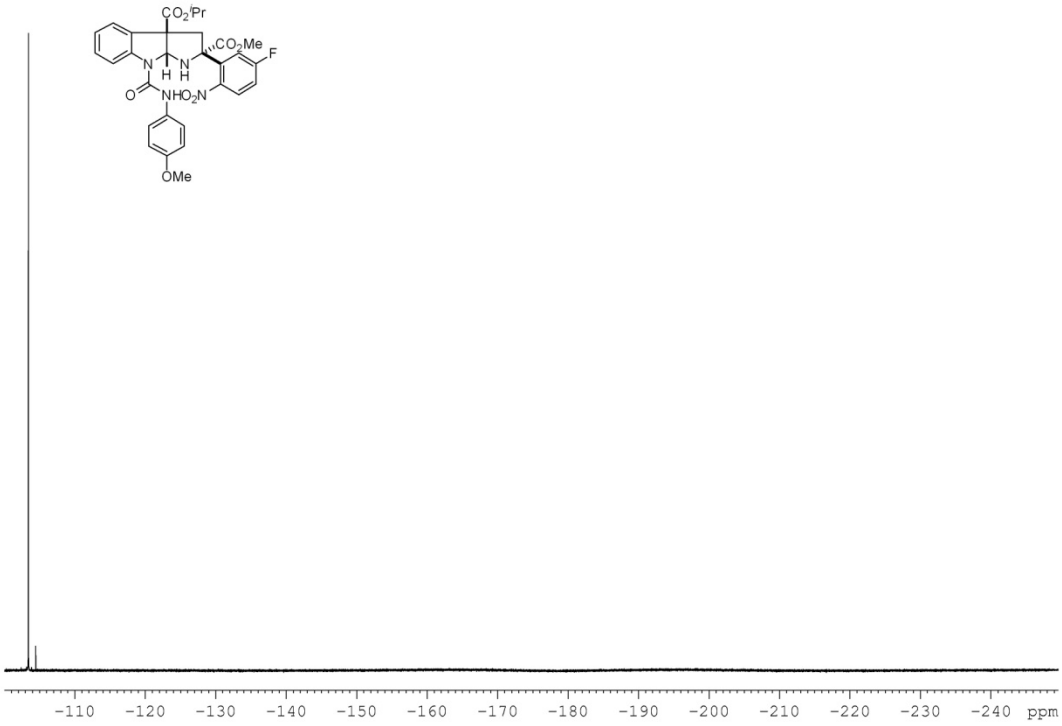

CH3
CO2iPr
NO2
N
H
N
H
O
NH
O
O
CH3
CH3

10
9
8
7
6
5
4
3
2
1
ppm
0.97
1.04
4.23
3.34
2.23
1.05
1.00
0.99
0.98
2.93
1.00
2.96
3.32
2.97
3.11


CO2iPr
CH3
NO2
O
CH3
N
H
N
H
O
NH
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

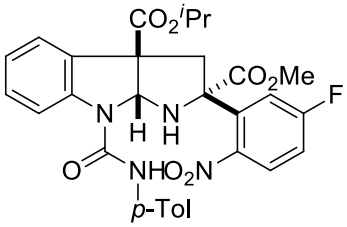

CO2iPr
CO2Me
F
N
H
N
H
O
NH
O2N
OMe
10 9 8 7 6 5 4 3 2 1 ppm
0.92
0.93
1.01
1.94
2.04
0.78
1.02
1.01
2.13
0.95
0.93
3.10
2.84
1.39
0.97
6.00


CO2iPr
CO2Me
F
N
H
N
H
O
NH
O2N
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


CO2iPr
CO2Me
F
N
H
N
H
O
NH
O2N
OMe
-110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 ppm

6. HPLC Traces

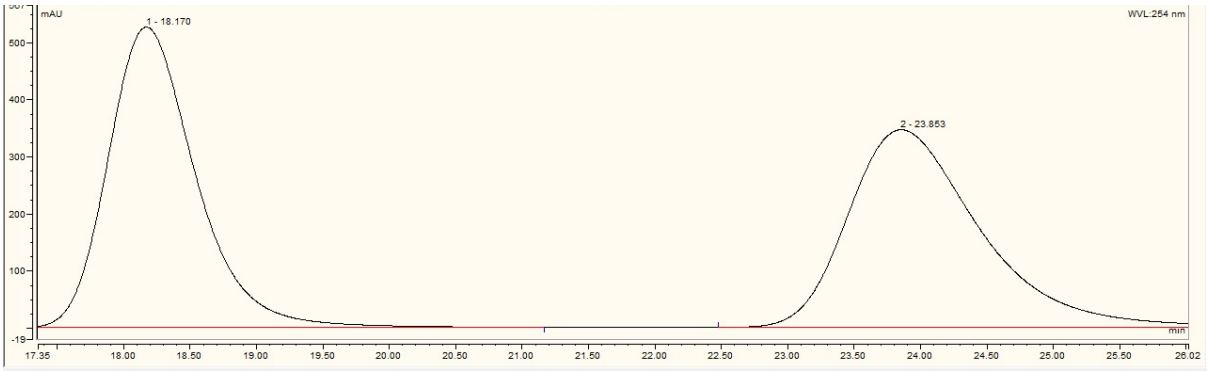
Compound 21



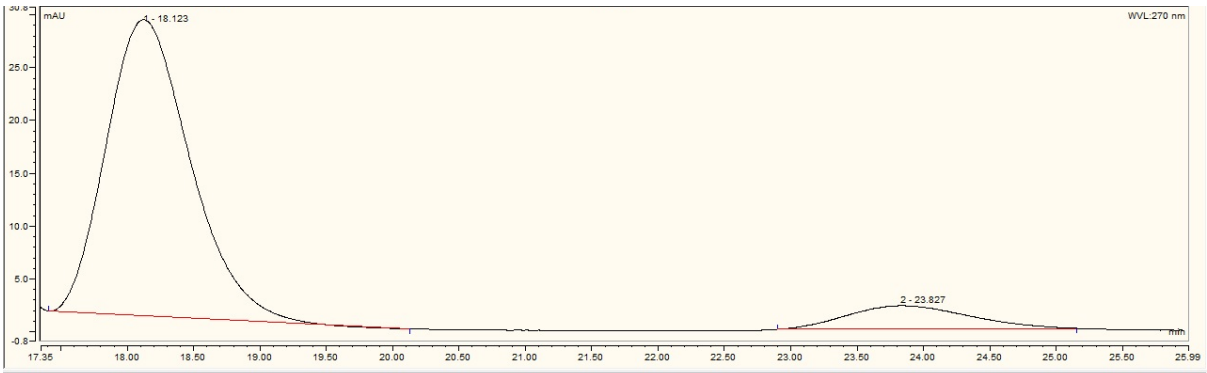
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 25 % IPA in hexane, 1 mL/min

Retention times: 18.2 min, 23.9 min

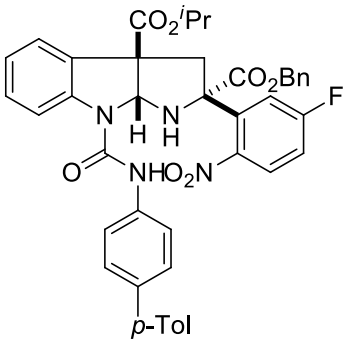


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	18.170	403.5536	n.a.	BMB	526.429	50.20	3.90
2	n.a.	23.853	400.2847	n.a.	BMB*	346.097	49.80	n.a.
Total:			803.8384	0.0000		872.527	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	18.123	20.5860	n.a.	BMB*	28.041	89.85	3.95
2	n.a.	23.827	2.3250	n.a.	BMB*	2.192	10.15	n.a.
Total:			22.9110	0.0000		30.233	100.00	

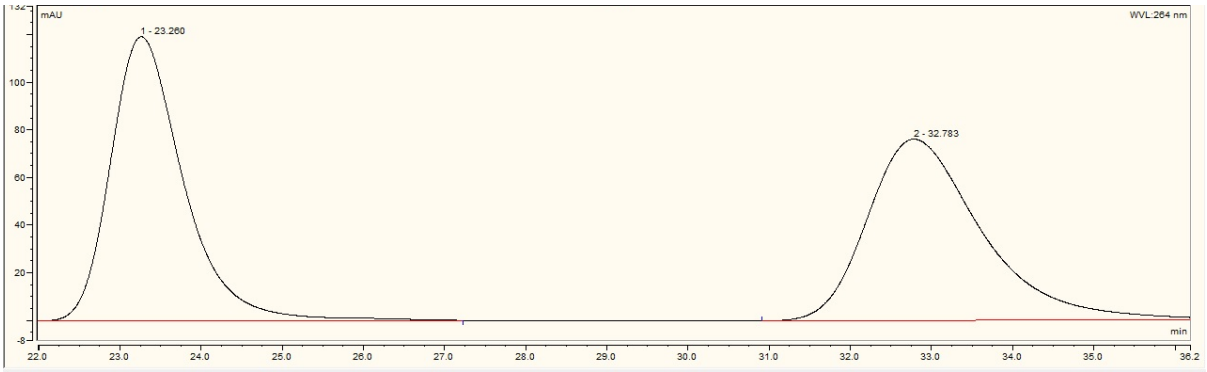
Compound 32



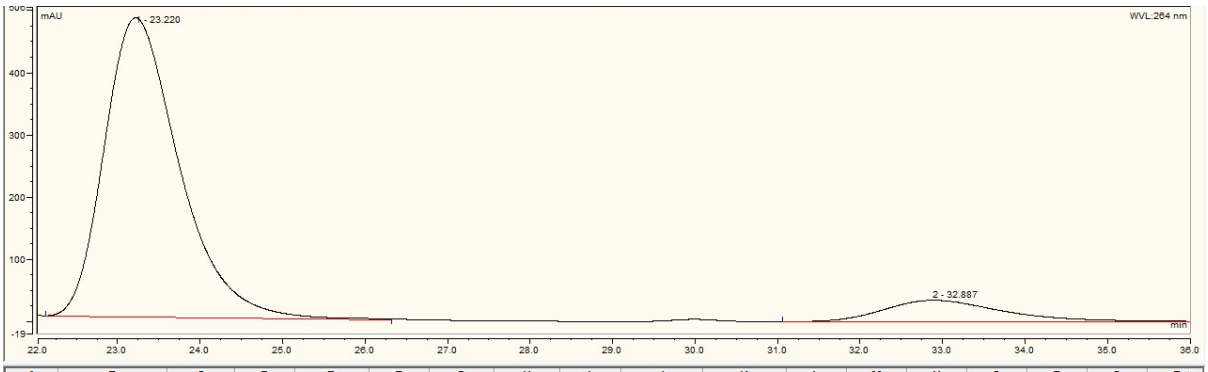
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 15 % IPA in hexane, 1 mL/min

Retention times: 23.3 min, 32.8 min

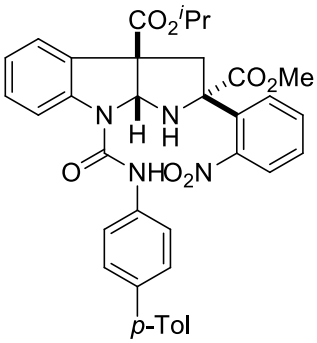


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	23.260	123.9863	n.a.	BMB	119.200	49.71	4.73
2	n.a.	32.783	125.4253	n.a.	BMB	76.187	50.29	n.a.
Total:			249.4116	0.0000		195.388	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	23.220	504.4019	n.a.	BM *	480.555	89.78	4.66
2	n.a.	32.887	57.4118	n.a.	BMB	34.322	10.22	n.a.
Total:			561.8137	0.0000		514.877	100.00	

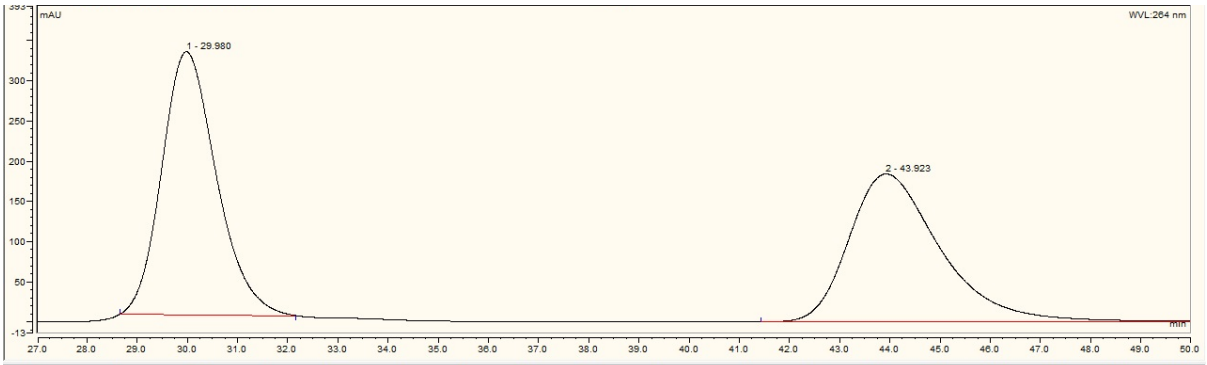
Compound 33



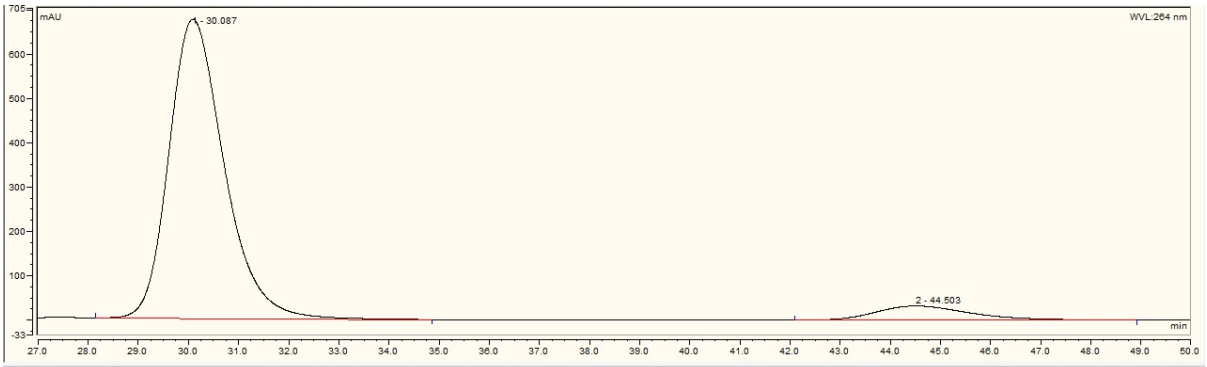
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 25 % IPA in hexane, 1 mL/min

Retention times: 30.1 min, 44.5 min

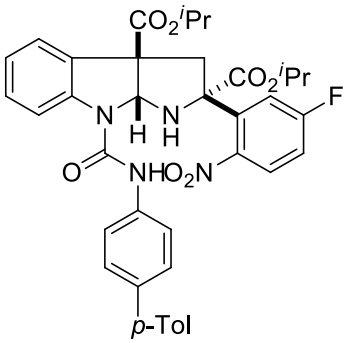


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	29.980	412.2367	n.a.	BMB*	326.992	51.64	5.42
2	n.a.	43.923	386.0364	n.a.	BMB	183.825	48.36	n.a.
Total:			798.2731	0.0000		510.816	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	30.087	861.0129	n.a.	BMB*	675.131	92.51	5.44
2	n.a.	44.503	69.7476	n.a.	BMB	31.990	7.49	n.a.
Total:			930.7606	0.0000		707.121	100.00	

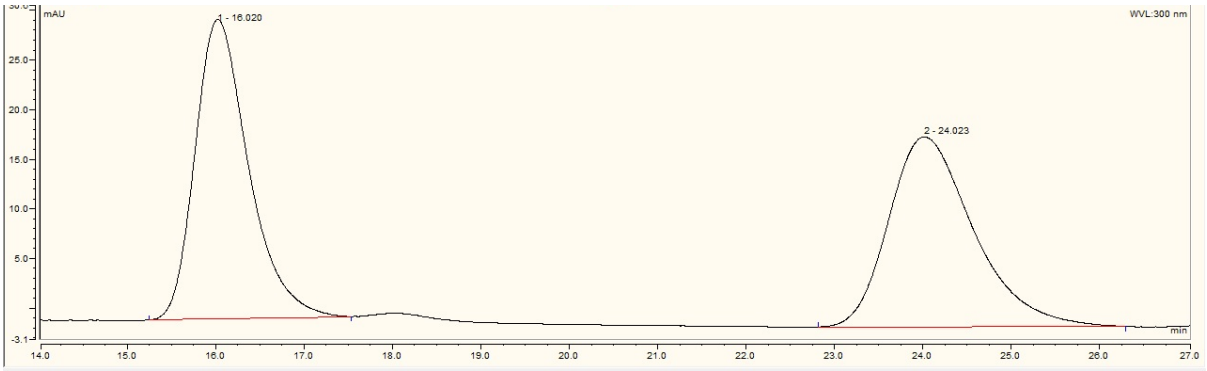
Compound 34



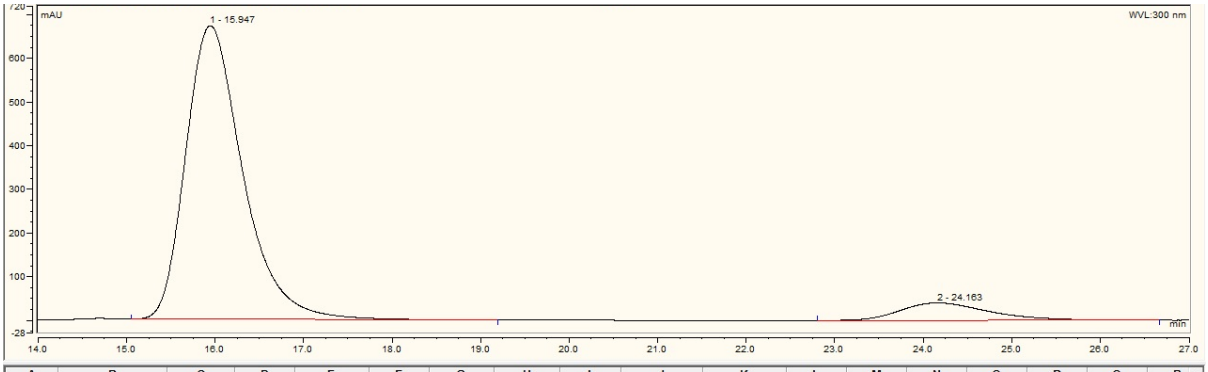
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 15 % IPA in hexane, 1 mL/min

Retention times: 16.0 min, 24.0 min

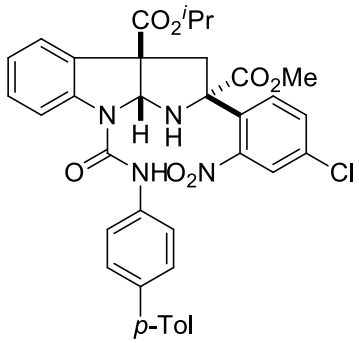


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	16.020	21.1360	n.a.	BMB	30.174	49.84	5.75
2	n.a.	24.023	21.2760	n.a.	BMB	19.144	50.16	n.a.
Total:			42.4120	0.0000		49.318	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	15.947	502.2939	n.a.	BMB*	672.059	91.51	5.62
2	n.a.	24.163	46.5775	n.a.	BMB	39.980	8.49	n.a.
Total:			548.8714	0.0000		712.039	100.00	

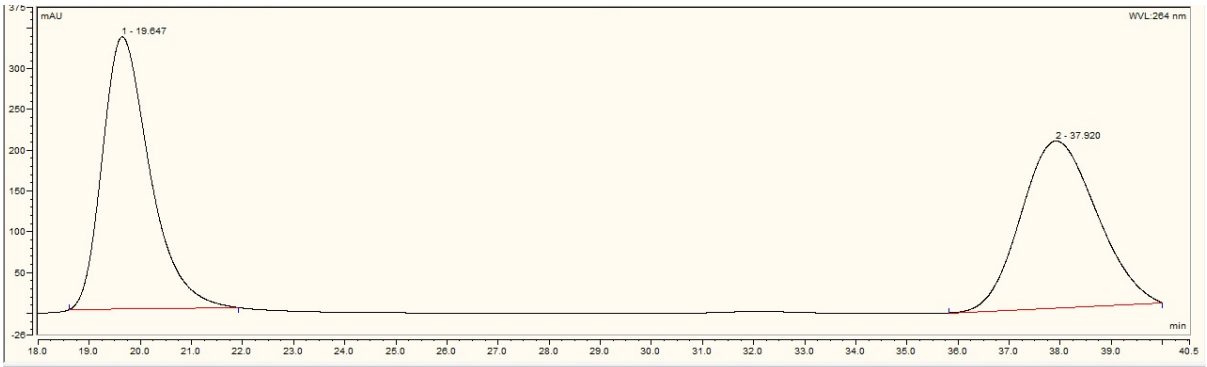
Compound 35



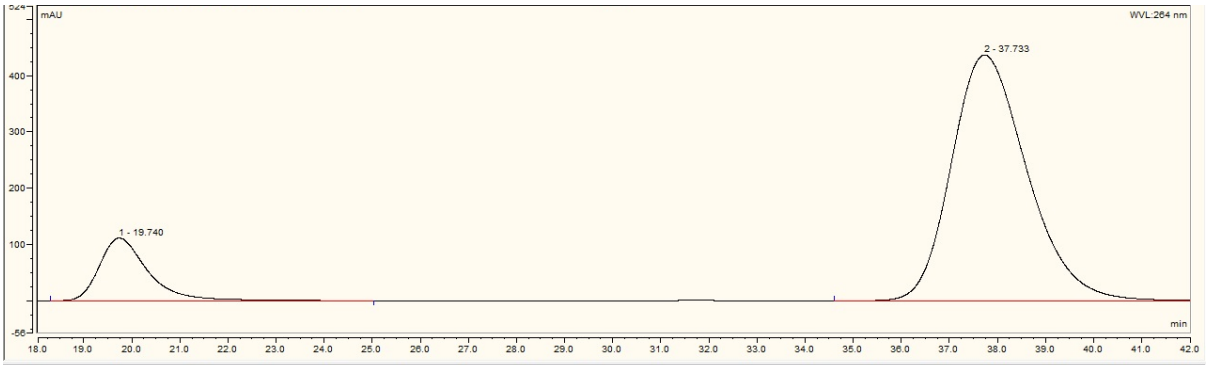
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 40 % IPA in hexane, 1 mL/min

Retention times: 19.7 min, 37.7 min

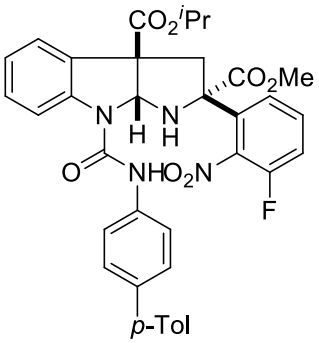


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	19.647	359.0804	n.a.	BMB*	333.968	50.61	8.29
2	n.a.	37.920	350.3730	n.a.	BMB	204.634	49.39	n.a.
Total:			709.4534	0.0000		538.602	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	19.740	131.6039	n.a.	BMB	111.414	14.13	7.88
2	n.a.	37.733	799.5851	n.a.	BMB	437.249	85.87	n.a.
Total:			931.1890	0.0000		548.663	100.00	

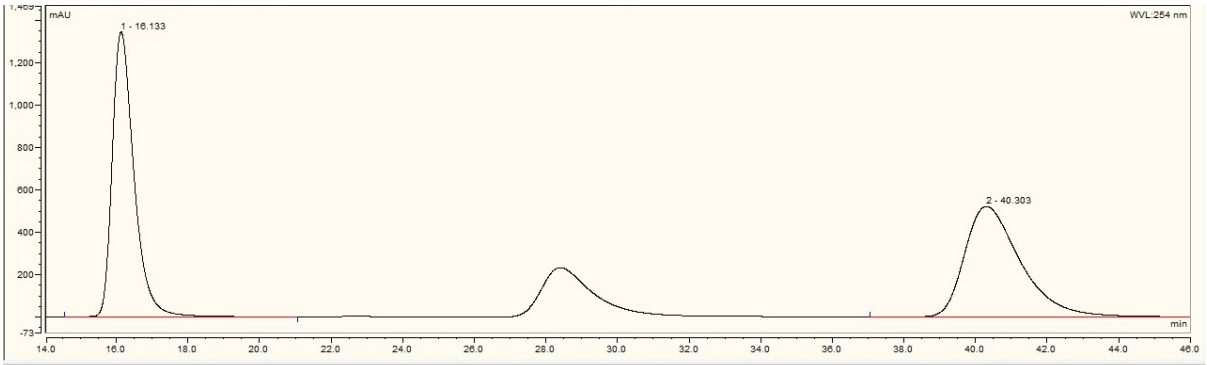
Compound 36



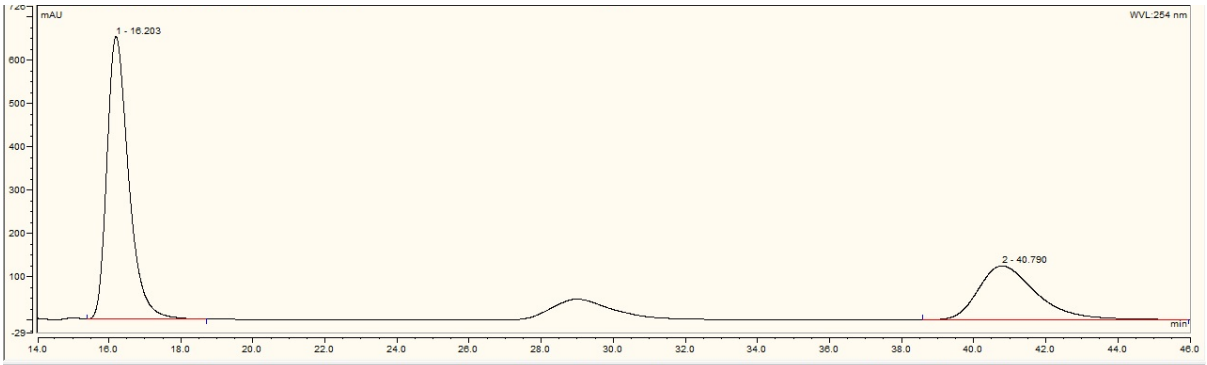
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 20 % IPA in hexane, 1 mL/min

Retention times: 16.1 min, 40.3 min

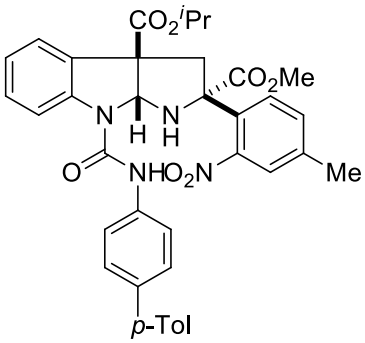


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	16.133	949.6583	n.a.	BMB	1345.288	50.19	12.67
2	n.a.	40.303	942.4892	n.a.	BMB*	520.735	49.81	n.a.
Total:			#########	0.0000		1866.023	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	16.203	455.8716	n.a.	BMB*	653.219	66.36	12.65
2	n.a.	40.790	231.1194	n.a.	BMB	124.167	33.64	n.a.
Total:			686.9910	0.0000		777.385	100.00	

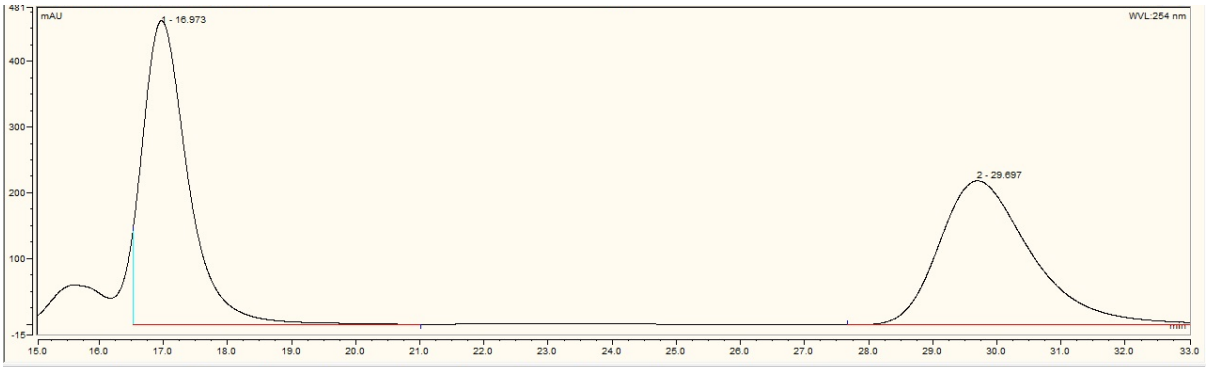
Compound 37



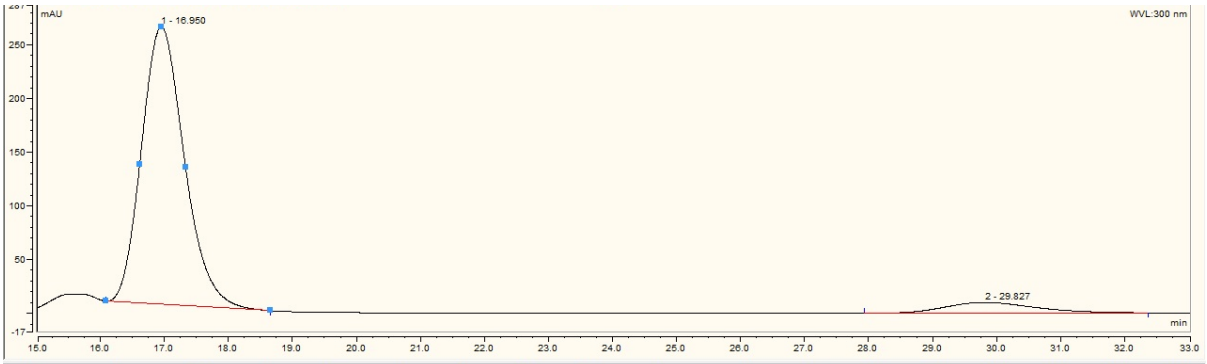
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 40 % IPA in hexane, 1 mL/min

Retention times: 17.0 min, 29.8 min

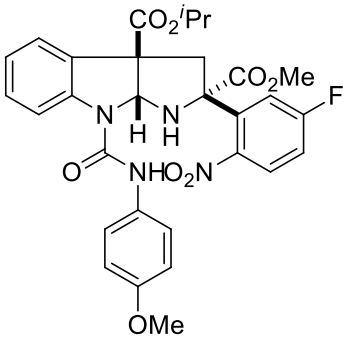


No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	16.973	371.9305	n.a.	MB*	461.261	50.39	6.73
2	n.a.	29.697	366.1318	n.a.	BMB	218.637	49.61	n.a.
Total:			738.0624	0.0000		679.898	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	16.950	200.1929	n.a.	BMB*	258.610	92.56	6.85
2	n.a.	29.827	16.1027	n.a.	BMB*	9.883	7.44	n.a.
Total:			216.2956	0.0000		268.493	100.00	

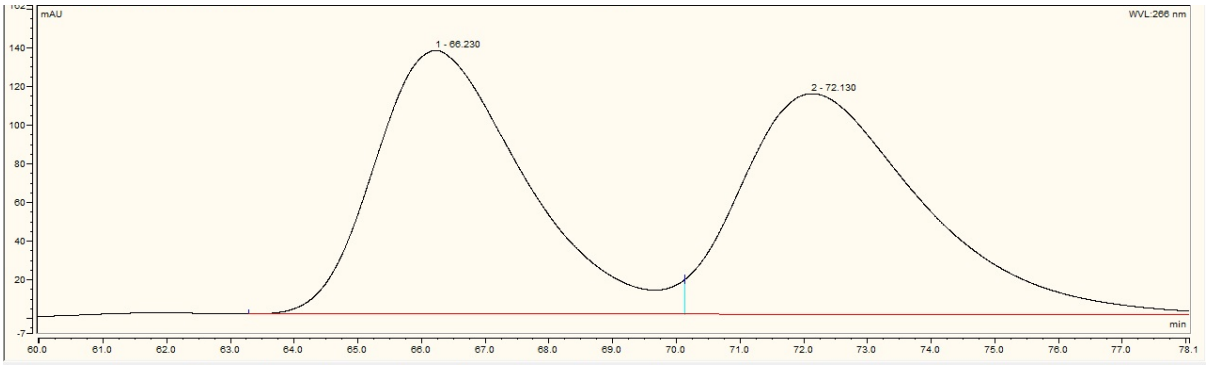
Compound 38



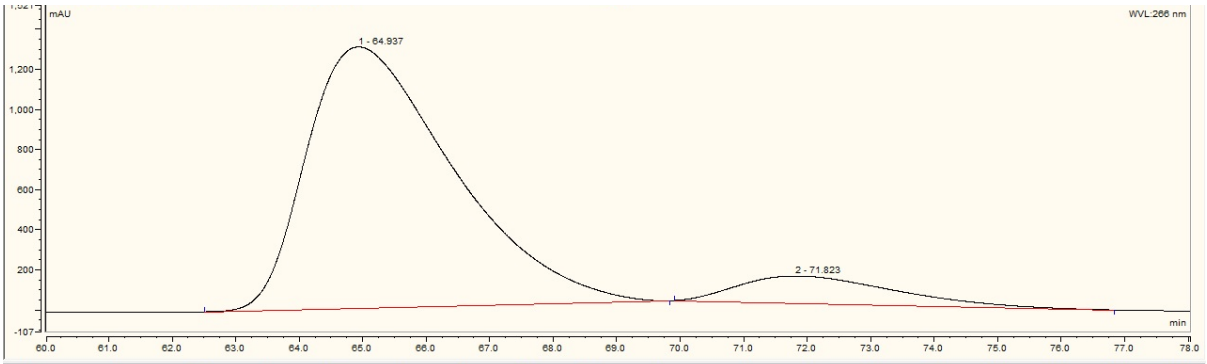
Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 15 % IPA in hexane, 1 mL/min

Retention times: 64.9 min, 71.8 min



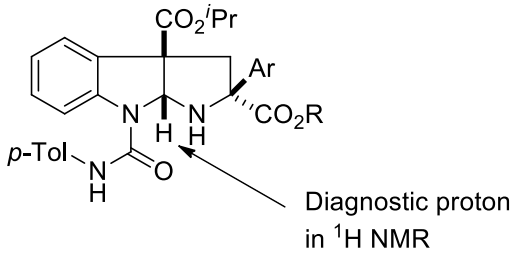
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	66.230	374.1590	n.a.	BM *	136.487	49.81	1.27
2	n.a.	72.130	376.9789	n.a.	MB*	114.228	50.19	n.a.
Total:			751.1379	0.0000		250.715	100.00	



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	64.937	########	n.a.	BMB*	1301.301	90.06	1.56
2	n.a.	71.823	383.7827	n.a.	BMB*	134.923	9.94	n.a.
Total:			########	0.0000		1436.224	100.00	

7. Assignment of Stereochemistry

Assignment of relative stereochemistry of compounds was done by analogy to compounds **13** and **14**, whose relative stereochemistry was unambiguously assigned by X-ray crystallography. The ring junction proton was used as a diagnostic shift in ^{1}H NMR as follows:



As an illustration, comparison of several compounds is shown below. The major diastereomer exhibits a shift with a lower δ in ^{1}H NMR.

Compound	**^{1}H shift Major**	**^{1}H shift Minor**
13 (X-ray)	6.33	6.41
14 (X-ray)	6.40	6.50
16	6.35	6.45
33	5.58	6.12
36	5.62	6.13
37	5.55	6.11
	Lower δ	**Higher δ**

8. Thermodynamic Product

Information is provided for Scheme 1 in the main text. Pyrroloindoline **21** was synthesised according to Table 4 in 90:10 e.r.. The isolated product was then redissolved in toluene and TBAB (20 mol %), and K_2CO_3 (5.0 eq.) was added. The reaction was stirred for 48 h, after which all pyrroloindoline **21** had been consumed and a significant amount of an unidentified compound had been formed as a single diastereomer (>20:1 d.r.). This product was isolated and a single crystal was grown. Its identity was revealed by X-ray crystallographic analysis of this crystal as being that of pyrroline **39** (CCDC number 1020474). The e.r. of **39** was found to be 90:10 using chiral stationary phase HPLC.

During the development of the methodology, we noted that exchanging the Michael acceptor from a urea bearing a 4-MeC_6H_4- substituent to one featuring a 3,5-$(CF_3)_2C_6H_3$- group led to faster formation (24 h vs 48 h) of the thermodynamic spirocyclic pyrroline compound, but as a mixture of diastereomers (9:1 d.r.). Both diastereomers were crystallised and X-ray structures were obtained (CCDC numbers 1020475 and 1020476) to confirm that the formation of this thermodynamic product is a general phenomenon.

X-ray Crystallography

Crystals were mounted using the oil technique, in perfluoropolyether oil at 150(2) K (Cu and Mo) or 100(2) K (Synchrotron) with a Cryostream N_2 open-flow cooling device.

Molybdenum Radiation

Single crystal X-ray diffraction data were collected using graphite monochromated Mo-Ka radiation (0.71073 Å) using a Nonius KappaCCD diffractometer. Series of μ-scans were generally performed to provide sufficient data in each case to a maximum resolution of 0.77 Å. Data collection and cell refinement were carried out using DENZO-SMN. Intensity data were processed and corrected for absorption effects by the multi-scan method, based on multiple scans of identical and Laue equivalent reflections using SCALEPACK (within DENZO-SMN). Structure solution was carried out with direct methods using the programs SIR9219 within the CRYSTALS software suite. Refinement was carried out using full-matrix least-squares within the CRYSTALS suite on F2. In general, all non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generally visible in the difference map and their positions and displacement parameters were refined using restraints prior to inclusion into the model using riding constraints.

Copper Radiation

Single crystal X-ray diffraction data were collected using graphite monochromated Cu K radiation (λ= 1.54184 Å) on an Oxford Diffraction SuperNova diffractometer. Series of ω-scans were performed in such a way as to collect all unique reflections to a maximum of 0.80 Å. Cell parameters and intensity data (including inter-frame scaling) were processed using CrysAlis Pro. The structures were solved by charge-flipping methods using SUPERFLIP and refined using full-matrix least-squares on F2 within the CRYSTALS suite. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generally visible in the difference map and their positions and displacement parameters were refined using restraints prior to inclusion into the model using riding constraints.

Synchrotron Radiation

Single crystal X-ray diffraction data were collected using silicon double crystal monochromated synchrotron radiation (λ = 0.68890 Å) at Diamond Light Source beamline I19 using a custom-built Rigaku diffractometer equipped with a Cryostream N_2 open-flow cooling device. The data were collected via a series of ω-scans that were performed in such a way as to cover a full-sphere of data to a maximum resolution of 0.77 Å. Cell parameters and intensity data (including inter-frame scaling) were processed using CrysAlis Pro.8. The structures were solved by charge-flipping methods using SUPERFLIP and refined using full-matrix least- squares on F2 within the CRYSTALS suite. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generally visible in the difference map and their positions and displacement parameters were refined using restraints prior to inclusion into the model using riding constraints.