Electronic Supplementary Information

Tertiary Amides-based Knoevenagel-type Reactions:

A Direct, General, and Chemoselective Approach to Enaminones

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Contents

General: Melting points were uncorrected. HRFABMS spectra were recorded on a 7.0T FT-MS. ^{1}H NMR and ^{13}C NMR spectra were recorded on a spectrometer at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me_4Si and solvent signals (Me_4Si, 0 ppm for ^{1}H NMR and $CDCl_3$, 77.0 ppm for ^{13}C NMR). Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/ hexane mixture. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over phosphorous pentoxide[1] and was stored for no more than a week before redistilling. All other commercially available compounds were used as received. Dry dichloromethane was distilled over calcium hydride under N_2.

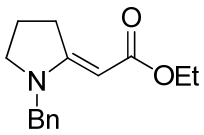
General procedure A: preparation of vinylogous urethanes from amides/ lactams and dimethyl malonate.

Trifluoromethanesulfonic anhydride (185 μL, 1.0 mmol, 1.1 equiv) was added dropwise to a cooled (−78 °C) solution of an amide (1.0 mmol, 1.0 equiv) in dichloromethane (5 mL). The reaction mixture was warmed to 0 °C in an ice bath and stirred for 1 h before re-cooled to −78 °C. A solution of sodium enolate (1.5 mmol, 1.5 equiv), freshly prepared from dimethyl malonate and NHMDS (2.2 mmol, 2.2 equiv), was added dropwise to the resulting mixture then warmed to RT and stirred for 3 h. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the desired vinylogous urethane.

General procedure B: preparation of vinylogous urethanes or enaminones from amides/ lactams and other active methylene compounds.

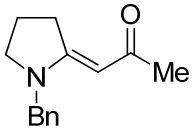
Trifluoromethanesulfonic anhydride (185 μL, 1.0 mmol, 1.1 equiv) was added dropwise to a cooled (−78 °C) solution of an amide (1.0 mmol, 1.0 equiv) in dichloromethane (5 mL). The reaction mixture was warmed to 0 °C in an ice bath and stirred for 1 h before re-cooled to −78 °C. A solution of sodium enolate (1.5 mmol, 1.5 equiv), freshly prepared from ester/ ketone and NHMDS (2.2 mmol, 2.2 equiv), was added dropwise to this resulting mixture keep −78 °C for 3 h then warmed to RT and stirred for 2 h. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the desired vinylogous urethane.

Ethyl (*E*)-2-(1-benzylpyrrolidin-2-ylidene)acetate (3)[2]



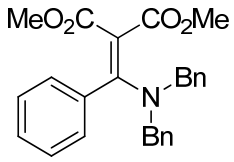
Following the general procedure B, reaction of *N*-benzyl-γ-lactam (**1**) (175 mmg, 1.0 mmol) with ethyl acetate enolate, freshly prepared from ethyl acetate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane) the known vinylogous urethane **3** (179 mg, yield: 73%) as a single geometric isomer. Colorless crystals, m.p. 60-61 °C (EtOAc) (lit.[2] m.p. 61.8–62.9 °C); IR (film): 3061, 3029, 2977, 2941, 2897, 1730, 1682, 1595, 1453, 1300, 1135, 1061, 785, 732, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.97 (tt, *J* = 7.6, 7.2 Hz, 2H), 3.23 (t, *J* = 7.6 Hz, 2H), 3.34 (t, *J* = 7.2 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 4.36 (s, 2H), 4.69 (s, 1H), 7.37-7.16 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 21.0, 32.6, 49.9, 52.4, 58.3, 78.3, 127.1, 127.4, 128.7, 136.0, 165.2, 169.5, ppm; MS (ESI) *m/z* 246 ($M + H^+$). The *Z*/ *E* geometry was determined by correlation with the reported data.[2]

(*E*)-1-(1-Benzylpyrrolidin-2-ylidene)propan-2-one (4)



Following the general procedure B, reaction of *N*-benzyl-γ-lactam (**1**) (175 mmg, 1.0 mmol) with propanone enolate, freshly prepared from propanone and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the only one stereoisomeric enaminone **4** (138 mg, yield: 64%) as a colorless oil; IR (film): 3061, 3029, 2968, 2924, 2869, 1686, 1640, 1548, 1453, 1300, 1209, 1178, 955, 736, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.60 (tt, *J* = 7.6, 7.2 Hz, 2H), 3.31 (t, *J* = 7.6 Hz, 2H), 3.35 (t, *J* = 7.2 Hz, 2H), 4.41 (s, 2H), 5.22 (s, 1H), 7.38-7.16 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 30.6, 33.3, 49.9, 52.1, 89.8, 127.0, 127.5, 128.7, 135.6, 165.5, 194.4 ppm; MS (ESI) *m/z* 216 ($M + H^+$); HRESIMS calcd for $[C_{14}H_{28}NO]^+$ ($M + H^+$): 216.1383; found: 216.1383. The *Z*/ *E* geometry deduced by correlation with compound **4b** ($\delta_{H\ vinylic}$ = 5.21 for **4** versus $\delta_{H\ vinylic}$ = 5.22 for **4b**).

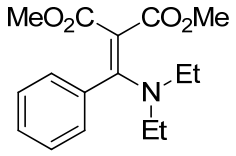
Dimethyl 2-((*N, N*-dibenzylamino)(phenyl)methylene)malonate (7a)



Following the general procedure A, the reaction of amide **6a** (301 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane) the vinylogous urethane **7a** (303 mg, yield: 73%) as a white solid. m.p. 133-135 °C; IR (film) ν_{max}: 3061, 3028, 2942, 1694, 1519, 1432, 1270, 1229, 1150, 1056, 756, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.51 (s, 6H), 4.11 (s, 4H), 7.48-7.18 (m, 15H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.4, 55.8, 100.0, 127.9,

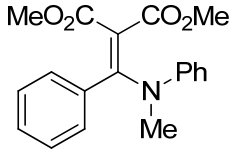
128.5, 128.59, 128.6, 129.9, 130.4, 136.0, 137.2, 168.1, 168.3 ppm; MS (ESI) *m/z* 438 (M + Na^+); HRESIMS calcd for $[C_{26}H_{25}NO_4Na]^+$ (M + Na^+): 438.1676; found: 438.1677.

Dimethyl 2-((*N*, *N*-diethylamino)(phenyl)methylene)malonate (7b)



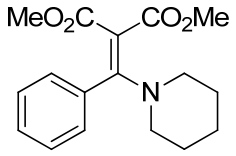
Following the general procedure A, the reaction of amide **6b** (177 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7b** (233 mg, yield: 80%) as a colorless oil; IR (film) ν_{max}: 3061, 3028, 2938, 2910, 1694, 1523, 1436, 1295, 1246, 1188, 1109, 1071, 769, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.1 Hz, 6H), 3.18 (q, J = 7.1 Hz, 4H), 3.40 (s, 6H), 7.36-7.30 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 46.0, 51.1, 98.9, 128.3, 129.6, 130.2, 137.5, 167.9, 169.1 ppm; MS (ESI) *m/z* 314 (M + Na^+); HRESIMS calcd for $[C_{16}H_{21}NO_4Na]^+$ (M + Na^+): 314.1363; found: 314.1369.

Dimethyl 2-[(*N*-methyl-*N*-phenyl amino)(phenyl)methylene]malonate (7c)



Following the general procedure A, the reaction of amide **6c** (211 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7c** (247 mg, yield: 76%) as a white solid. m.p. 163-166 °C; IR (film) ν_{max}: 3061, 3028, 2921, 2847, 1706, 1536, 1490, 1432, 1374, 1300, 1229, 1188, 1084, 1038, 764, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 6H), 3.42 (s, 3H), 7.42-6.97 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.5, 51.4, 106.9, 123.5, 124.3, 128.2, 128.8, 129.9, 130.1, 137.1, 146.9, 167.3, 167.9, ppm; MS (ESI) *m/z* 348 (M + Na^+); HRESIMS calcd for $[C_{19}H_{19}NO_4Na]^+$ (M + Na^+): 348.1206; found: 348.1210.

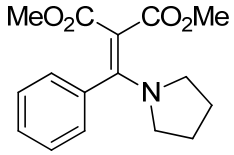
Dimethyl 2-(phenyl(piperidin-1-yl)methylene)malonate (7d)



Following the general procedure A, the reaction of amide **6d** (189 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7d** (236 mg, yield: 78%) as a white solid. m.p. 102-105 °C; IR (film) ν_{max}: 3061, 3028, 2938, 2855, 1689, 1523, 1441, 1362, 1291, 1246, 1154, 1113, 1076, 1009, 764, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67-1.70 (m, 6H), 3.16 (t, J = 5.8 Hz, 4H), 3.50 (s, 6H), 7.37-7.46 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 26.7, 51.1, 52.6, 96.9,128.3, 129.3,130.4, 137.5, 168.0, 169.6

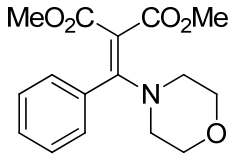
ppm; MS (ESI) *m/z* 326 (M + Na^+); HRESIMS calcd for $[C_{17}H_{21}NO_4Na]^+$ (M + Na^+): 326.1363; found: 326.1363.

Dimethyl 2-(phenyl(pyrrolidin-1-yl)methylene)malonate (7e)



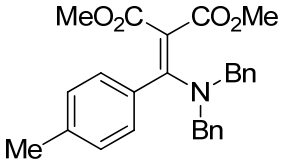
Following the general procedure A, the reaction of amide **6e** (175 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7e** (234 mg, yield: 81%) as a colorless oil; IR (film) ν_{max}: 3061, 3028, 2964, 2349, 1685, 1519, 1498, 1275, 1246, 1192, 1076, 881, 764, 744, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.92-1.89 (m, 4H), 3.29-3.26 (m, 4H), 3.51 (s, 6H), 7.39-7.29 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 51.1, 51.7, 95.3, 128.1, 128.4, 129.1, 137.2, 163.3, 167.9 ppm; MS (ESI) *m/z* 312 (M+Na^+); HRESIMS calcd for $[C_{16}H_{19}NO_4\ Na]^+$ (M + Na^+): 312.1206; found: 312.1208.

Dimethyl 2-(morpholino(phenyl)methylene)malonate (7f)



Following the general procedure A, the reaction of amide **6f** (191 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7f** (228 mg, yield: 75%) as a colorless oil; IR (film) ν_{max}: 3061, 3028, 2921, 2581, 1714, 1636, 1424, 1275, 1113, 1013, 839, 785, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.21 (t, J = 4.8 Hz, 4H), 3.52 (s, 6H), 3.77 (t, J = 4.8 Hz, 4H), 7.46-7.41 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.4, 51.5, 67.1, 98.6, 128.6, 129.6, 130.7, 136.7, 167.75, 167.79 ppm; MS (ESI) *m/z* 328 (M+Na^+); HRESIMS calcd for $[C_{16}H_{19}NO_5Na]^+$ (M + Na^+): 328.1155; found: 328.1157.

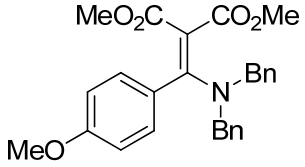
Dimethyl 2-((*N*,*N*-dibenzylamino)(p-tolyl)methylene)malonate (7g)



Following the general procedure A, the reaction of amide **6g** (315 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7g** (326 mg, yield: 76%) as a white solid, m.p. 160-164 °C; IR (film) ν_{max}: 3061, 3028, 2942, 1694, 1523, 1503, 1422, 1412, 1275, 1241, 1076, 823, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.52 (s, 6H), 4.11 (s, 4H), 7.37-7.17 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 51.3, 55.7, 99.5, 127.9, 128.5, 128.53, 129.3, 129.9, 134.1, 136.0, 140.7, 168.2, 168.6 ppm; MS

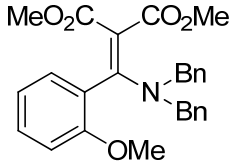
(ESI) *m/z* 452 (M+Na^+); HRESIMS calcd for $[C_{27}H_{27}NO_4Na]^+$ (M + Na^+): 452.1832; found: 452.1841.

Dimethyl 2-((*N*,*N*-dibenzylamino)(4-methoxyphenyl)methylene)malonate (7h)



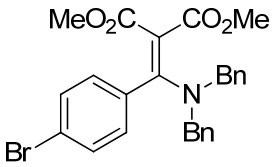
Following the general procedure A, the reaction of amide **6h** (321 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7h** (351 mg, yield: 79%) as a white solid, m.p. 152-154 °C; IR (film) ν_{max}: 3061, 3028, 2938, 1694, 1602, 1499, 1432, 1258, 1170, 1071, 1022, 835, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 6H), 3.81 (s, 3H), 4.13 (s, 4H), 7.42-6.90 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.3, 55.3, 55.7, 99.1, 114.0, 127.8, 128.4, 128.5, 129.2, 131.5, 136.1, 161.4, 168.2, 168.5 ppm; MS (ESI) *m/z* 468 (M+Na^+); HRESIMS calcd for $[C_{27}H_{27}NO_5Na]^+$ (M+ Na^+): 468.1781; found: 468.1797.

Dimethyl 2-((*N*,*N* -dibenzylamino)(2-methoxyphenyl)methylene)malonate (7i)



Following the general procedure A, the reaction of amide **6i** (321 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7i** (338 mg, yield: 76%) as a white solid, m.p. 149-151 °C; IR (film) ν_{max}: 3061, 3028, 2946, 1685, 1594, 1511, 1428, 1287, 1250, 1225, 1142, 1076, 752, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 6H), 3.92 (s, 3H), 3.96 (d, J = 14.8 Hz, 2H), 4.31 (d, J = 14.8 Hz, 2H), 7.38-6.87 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.2, 55.4, 97.6, 110.6, 120.8, 126.2, 127.8, 128.4, 128.6, 131.5, 131.8, 135.8, 157.6, 166.2 ppm; MS (ESI) *m/z* 468 (M+Na^+); HRESIMS calcd for $[C_{27}H_{27}NO_5Na]^+$ (M+Na^+): 468.1781; found: 468.1786.

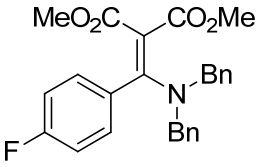
Dimethyl 2-((4-bromophenyl)(*N*,*N* -dibenzylamino)methylene)malonate (7j)



Following the general procedure A, the reaction of amide **6j** (379 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), gave the vinylogous urethane **7j** (345 mg, yield: 70%) as a white solid, m.p. 178-181 °C; IR (film) ν_{max}: 3061, 3028, 2964, 1694, 1586, 1515, 1453, 1432, 1270, 1241, 1142, 1076, 1009, 827, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 6H), 4.09 (s, 4H), 7.53-7.16 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$)

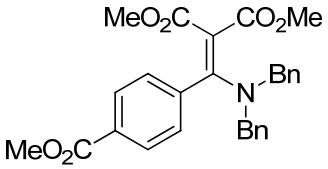
δ 51.5, 55.8, 100.3, 124.8, 128.0, 128.4, 128.6, 131.2, 131.8, 135.7, 136.0, 166.6, 167.7 ppm; MS (ESI) *m/z* 516, 518 (M + Na^+); HRESIMS calcd for $[C_{26}H_{24}BrNO_4Na]^+$ (M + Na^+): 516.0781, 518.0766; found: 516.0790, 518.0770.

Dimethyl 2-((*N*,*N* -dibenzylamino)(4-fluorophenyl)methylene)malonate (7k)



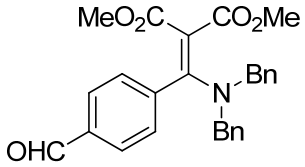
Following the general procedure A, the reaction of amide **6k** (319 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7k** (299 mg, yield: 69%) as a white solid, m.p. 153-157 °C; IR (film) ν_{max}: 3061, 3028, 1291, 1702, 1602, 1499, 1411, 1275, 1246, 1221, 1134, 1076, 839, 744, 698, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 6H), 4.11 (s, 4H), 7.46-7.06 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 167.8, 51.5, 100.3, 124.8, 128.0, 128.4, 128.6, 131.2, 131.8, 135.7, 136.0, 162.6, 165.1, 166.8 ppm; MS (ESI) *m/z* 456, 457 (M + Na^+); HRESIMS calcd for $[C_{26}H_{24}FNO_4Na]^+$ (M + Na^+): 456.1582; found: 456.1584.

Dimethyl 2-((*N*,*N* -dibenzylamino)(4-(methoxycarbonyl)phenyl)methylene)malonate (7l)



Following the general procedure A, the reaction of amide **6l** (359 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7l** (350 mg, yield: 74%) as a white solid, m.p. 150-153 °C; IR (film) ν_{max}: 3061, 3028, 2946, 1723, 1694, 1528, 1432, 1279, 1142, 1109, 1071, 756, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.37-7.20 (m, 10H), 4.12 (s, 4H), 3.93 (s, 3H), 3.55 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 166.5, 166.2 (2C), 141.5, 135.7 (2C), 131.6 (2C), 129.7, 129.6 (4C), 128.6 (4C), 128.3 (2C), 128.0 (2C), 100.6, 55.8 (2C), 52.2 (2C), 51.4 ppm; MS (ESI) *m/z* 496 (M + Na^+); HRESIMS *m/z* calcd for $[C_{28}H_{27}NO_6Na]^+$ (M + Na^+): 496.1731; found: 496.1740.

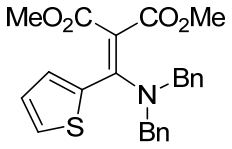
Dimethyl 2-((*N*,*N* -dibenzylamino)(4-formylphenyl)methylene)malonate (7m)



Following the general procedure A, the reaction of amide **6m** (329 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7m**

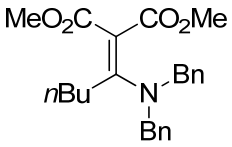
(266 mg, yield: 60%)as a white solid, m.p.145-150 °C; IR (film) ν_{max}: 2921, 2851, 1727, 1694, 1631, 1490, 1424, 1254, 1138, 1080, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 6H), 4.10 (s, 4H), 7.19-7.17 (m, 10H), 7.61 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H), 10.0 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.6, 55.9,167.6, 101.0, 128.1, 128.4, 128.7, 129.7, 130.4, 135.7, 137.2, 143.1, 166.0, 191.3 ppm; MS (ESI) *m/z* 466 (M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{27}H_{25}NO_5\ Na]^+$ (M + Na^+): 466.1625; found: 466.1627.

Dimethyl 2-((*N*,*N* -dibenzylamino)(thiophen-2-yl)methylene)malonate (7n)



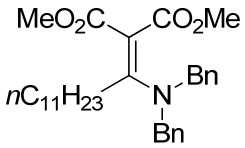
Following the general procedure A, the reaction of amide **6n** (307 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 6-10% EtOAc in hexane), the vinylogous urethane **7n** (303 mg, yield: 72%) as a white solid, m.p. 147-150 °C; IR (film) ν_{max}: 3061, 3028, 2942, 1650, 1511, 1432, 1233, 1208, 1129, 1076, 744, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 6H), 4.18 (s, 4H), 7.04 (dd, J = 4.9, 3.8 Hz, 1H), 7.36-7.18 (m, 11H), 7.54 (dd, J = 4.9, 1.6 Hz, 1H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.4, 56.1, 101.2, 127.4, 127.9, 128.4, 128.5, 130.5, 131.9, 135.9, 139.5, 159.5, 167.5 ppm; MS (ESI) *m/z* 444 (M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{24}H_{23}NO_4SNa]^+$ (M + Na^+): 444.1240; found: 444.1243.

Dimethyl 2-(1-(*N*,*N*-dibenzylamino)pentylidene)malonate (7o)



Following the general procedure A, the reaction of amide **6o** (281 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 5-6% EtOAc in hexane), the vinylogous urethane **7o** (288 mg, yield: 73%) as a colorless oil; IR (film) ν_{max}: 3062, 2925, 2851, 1689, 1532, 1453, 1428, 1286, 1208, 1150, 1071, 748, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.43-1.34 (m, 2H), 1.73-1.65 (m, 2H), 2.65 (t, J = 8.3 Hz, 2H), 4.23 (s, 4H), 7.36-7.16 (m, 10H) 3.73 (s, 6H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 22.7, 30.8, 32.6, 51.5, 54.8, 98.3, 127.8, 127.9, 128.7, 136.2, 168.7, 170.5 ppm; MS (ESI) *m/z* 418 (M + Na^+); HRESIMS calcd for $[C_{24}H_{29}NO_4Na]^+$ (M + Na^+): 418.1989; found: 418.1989.

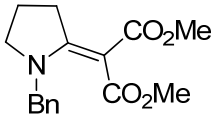
Dimethyl 2-(1-(*N*, *N*-dibenzylamino)dodecylidene)malonate (7p)



Following the general procedure A, the reaction of amide **6p** (379 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column

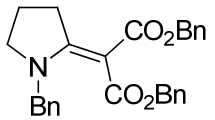
chromatography on silica gel (elution with 5-6% EtOAc in hexane), the vinylogous urethane **7p** (370 mg, yield: 75%) as a colorless oil; IR (film) ν_{max}: 3062, 2921, 2851, 1689, 1552, 1453, 1428, 1286, 1208, 1150, 1071, 748, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.34-1.25 (m, 16H), 1.71-1.66 (m, 2H), 2.64 (t, J = 8.1 Hz, 2H), 3.72 (s, 6H), 4.22 (s, 4H), 7.36-7.16 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 28.8, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 32.9, 51.5, 54.8, 98.3, 127.8, 127.9, 128.7, 136.2, 168.7, 170.5 ppm; MS (ESI) *m/z* 516 (M + Na^+); HRESIMS calcd for $[C_{31}H_{43}NO_4Na]^+$ (M + Na^+): 516.3084; found: 516.3102.

Dimethyl 2-(1-benzylpyrrolidin-2-ylidene)malonate (9a)[3]



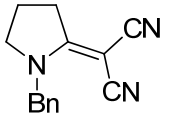
Following the general procedure A, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the known vinylogous urethane **9a**[3] (208 mg, yield: 72%) as a colorless oil; IR (film) ν_{max}: 3061, 3028, 2930, 1739, 1694, 1407, 1200, 1026, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (tt, J = 7.4, 7.5 Hz, 2H), 3.25 (t, J = 7.4 Hz, 2H), 3.34 (t, J = 7.5 Hz, 2H), 3.59 (s, 6H), 4.38 (s, 2H), 7.36–7.18 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 35.4, 51.2, 52.6, 54.1, 89.4, 127.4, 127.6, 128.6, 135.3, 166.1, 168.4 ppm; MS (ESI) *m/z* 312 (M + Na^+).

Dibenzyl 2-(1-benzylpyrrolidin-2-ylidene)malonate (9b)



Following the general procedure A, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with dibenzyl malonate enolate, freshly prepared from dibenzyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the vinylogous urethane **9b** (331 mg, yield: 75%) as a colorless oil; IR (film) ν_{max}: 3062, 2932, 2856, 1750, 1687, 1455, 1262, 1214, 1130, 1113, 740, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (tt, J = 7.4, 7.5 Hz, 2H), 3.28 (t, J = 7.5 Hz, 2H), 3.33 (t, J = 7.4 Hz, 2H), 4.38 (s, 2H), 5.07 (s, 4H), 7.34-7.17 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 35.5, 52.7, 54.1, 66.0, 89.7, 127.6, 127.66, 127.7, 128.0, 128.2, 128.7, 135.3, 136.5, 166.1,167.9 ppm; MS (ESI) *m/z* 464 (M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{28}H_{27}NO_4Na]^+$ (M + Na^+): 464.1838; found: 464.1843.

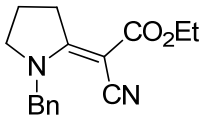
2-(1-Benzylpyrrolidin-2-ylidene)malononitrile (9c)



Following the general procedure A, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with malononitrile enolate, freshly prepared from malononitrile and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the vinylogous urethane **9c** (178 mg, yield: 80%) as a colorless oil; IR (film) ν_{max}: 3062, 2925, 2206, 1681, 1590, 1496, 1452, 1424, 1306, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.04 (tt, J = 6.9, 6.0 Hz, 2H),

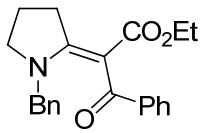
3.07 (t, J = 6.9 Hz, 2H), 3.33 (t, J = 6.0 Hz, 2H), 4.94 (s, 2H), 7.42-7.23 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 36.4, 45.4, 51.1, 56.7, 115.4, 117.3, 127.8, 128.5, 129.2, 137.8, 170.0 ppm; MS (ESI) *m/z* 246 (M+Na^+); HRMS (ESI) *m/z* calcd for $[C_{14}H_{13}N_3Na]^+$ (M + Na^+): 246.1001; found: 246.1002.

Ethyl (*E*)-2-(1-benzylpyrrolidin-2-ylidene)-2-cyanoacetate (9d)[4]



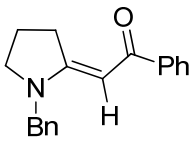
Following the general procedure A, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with ethyl cyanacetate enolate, freshly prepared from ethyl cyanacetate and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the known vinylogous urethane **9d**[3] (211 mg, yield: 78%) as a single geometric isomer. Colorless oil; IR (film) ν_{max}: 3061, 3028, 2975, 2921, 2194, 1694, 1561, 1452, 1292, 1248, 1106, 1059, 754, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 1.95 (tt, J = 7.6, 7.6 Hz, 2H), 3.38 (t, J = 7.6 Hz, 2H), 3.49 (t, J = 7.6 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 5.10 (s, 2H), 7.38-7.26 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 19.6, 36.1, 51.4, 55.2, 60.1, 66.9, 119.0, 127.7, 128.0, 128.8, 134.9, 166.7, 170.9 ppm; MS (ESI) *m/z* 293 (M + Na^+). The *Z*/ *E* geometry not determined.

Ethyl (*E*)-2-(1-benzylpyrrolidin-2-ylidene)-3-oxo-3-phenylpropanoate (9e)



Following the general procedure A, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with ethyl benzoylacetate enolate, freshly prepared from ethyl benzoylacetate and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the vinylogous urethane **9e** (241 mg, yield: 69%) as a single geometric isomer. Colorless oil; IR (film) ν_{max}: 3061, 3028, 2921, 2842, 1740, 1689, 1610, 1597, 1578, 1264, 1196, 1102, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (t, J = 7.1 Hz, 3H), 2.02 (tt, J = 7.5, 7.4 Hz, 2H), 3.31 (t, J = 7.5 Hz, 2H), 3.49 (t, J = 7.4 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.33 (s, 2H), 7.56-7.06 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 20.7, 36.0, 54.3, 55.3, 59.4, 98.1, 127.7, 127.8, 128.0, 128.1, 128.7, 130.7, 134.9, 142.2, 169.0, 169.2, 194.3 ppm; MS (ESI) *m/z* 372 (M + Na^+); HRESIMS calcd for $[C_{22}H_{23}NO_3Na]^+$ (M + Na^+): 372.1570; found: 372.1576. The *Z*/ *E* geometry was determined by NOESY on the basis of the observed correlation between phenyl H ($\delta_{H\ phenylic}$ = 7.21) and benzyl H ($\delta_{H\ Bn}$ = 4.33).

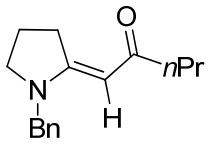
(*E*)-2-(1-Benzylpyrrolidin-2-ylidene)-1-phenylethanone (4a)[2]



Following the general procedure B, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with phenyl methyl ketone enolate, freshly prepared from phenyl methyl ketone and NHMDS,

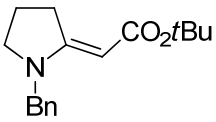
gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the known vinylogous urethane **4a**[4] (158 mg, yield: 57%) as a single geometric isomer. Colorless oil; IR (film) ν_{max}: 3062, 3030, 2920, 2850, 1577, 1536, 1479, 1295, 1216, 725, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (tt, J = 7.6, 7.5 Hz, 2H), 3.43 (t, J = 7.6 Hz, 2H), 3.52 (t, J = 7.5 Hz, 2H), 4.55 (s, 2H), 5.93 (s, 1H), 7.86-7.25 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 33.8, 50.3, 52.6, 86.9, 127.15, 127.17, 127.7, 128.0, 128.9, 130.3, 135.5, 141.9, 167.5, 188.0 ppm; MS (ESI) *m/z* 300 ($M + Na^+$). The *Z*/ *E* geometry was determined by correlation with the reported data.[2]

(*E*)-1-(1-Benzylpyrrolidin-2-ylidene)pentan-2-one (4b)



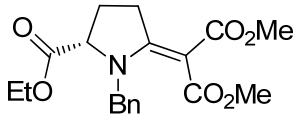
Following the general procedure B, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with methyl ethyl ketone enolate, freshly prepared from methyl ethyl ketone and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the vinylogous urethane **4b** (146 mg, yield: 60%) as a single geometric isomer. Colorless oil; IR (film) ν_{max}: 3062, 3030, 2958, 2929, 2870, 1637, 1548, 1482, 1453, 1299, 1214, 1191, 1134, 700, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.65-1.56 (m, 2H), 1.93-2.01 (m, 2H), 1.97 (tt, J = 7.5, 7.4 Hz, 2H), 3.31 (t, J = 7.5 Hz, 2H), 3.34 (t, J = 7.4 Hz, 2H), 4.40 (s, 2H), 5.21 (s, 1H), 7.37-7.18 (m, 5H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.3, 21.0, 33.3, 45.7, 50.0, 52.1, 89.5, 127.1, 127.5, 128.7, 135.8, 165.4, 197.5 ppm; MS (ESI) *m/z* 266 ($M + Na^+$); HRESIMS calcd for $[C_{16}H_{21}NONa]^+$ ($M + Na^+$): 266.1515; found: 266.1523. The *Z*/ *E* geometry determined by NOESY on the basis of the observed correlation between vinylic H ($\delta_{H\ vinylic}$ = 5.21) and benzyl H ($\delta_{H\ Bn}$ = 4.40).

***tert*-Butyl (*E*)-2-(1-benzylpyrrolidin-2-ylidene)acetate (3a)**[5]



Following the general procedure B, the reaction of *N*-benzyl-γ-lactam (**1**) (175 mg, 1.0 mmol) with *tert*-butyl acetate enolate, freshly prepared from *tert*-butyl acetate and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the known vinylogous urethane **3a**[5] (194 mg, yield: 71%) as a single geometric isomer. White solid, mp 113-115 °C (lit.[5] mp 116 °C); IR (film) ν_{max}: 1683, 1595, 1118, 794, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.94 (tt, J = 7.3, 7.5 Hz, 2H), 3.20 (t, J = 7.5 Hz, 2H), 3.29 (t, J = 7.3 Hz, 2H), 4.34 (s, 2H), 4.63 (s, 1H), 7.35-7.17 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 28.6, 32.4, 49.8, 52.0, 76.6, 80.2, 127.1, 127.3, 128.6, 136.2, 164.4, 169.3 ppm; MS (ESI) *m/z* 296 ($M + Na^+$). The *Z*/ *E* geometry determined by NOESY on the basis of the observed correlation between vinylic H ($\delta_{H\ vinylic}$ = 4.63) and benzyl H ($\delta_{H\ Bn}$ = 4.34).

Dimethyl (*S*)-2-(1-benzyl-5-(ethoxycarbonyl)pyrrolidin-2-ylidene)malonate (10)



Following the general procedure A, the reaction of ethyl *N*-benzylpyroglutamate (**8**) (247 mg, 1.0 mmol) with dimethyl malonate enolate, freshly prepared from dimethyl malonate and NHMDS, gave, after flash column chromatography on silica gel (elution with 10-12% EtOAc in hexane), the vinylogous urethane **10** (253 mg, yield: 70%) as a colorless oil; $[\alpha]_D^{20}$ 87.5 (*c* = 1, $CHCl_3$); IR (film) ν_{max}: 3061, 3028, 2934, 1677, 1494, 1424, 1291, 1262, 1109, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 2.19-2.05 (m, 2H), 3.17-3.08 (m, 1H), 3.52-3.43 (m, 1H), 3.62 (s, 6H), 4.01 (dd, *J* = 3.7, 8.9 Hz, 1H), 4.14 (q, *J* = 7.1 Hz), 4.27 (d, *J* = 15.4 Hz, 1H), 4.56 (d, *J* = 15.4 Hz, 1H), 7.35-7.16 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 25.3, 33.5, 51.4, 51.6, 61.4, 65.0, 91.5, 127.9, 128.0, 128.7, 134.6, 164.8, 168.1, 171.0 ppm; MS (ESI) *m/z* 384 (M + Na^+); HRESIMS calcd for $[C_{16}H_{21}NONa]^+$ (M + Na^+): 384.1418; found: 384.1411.

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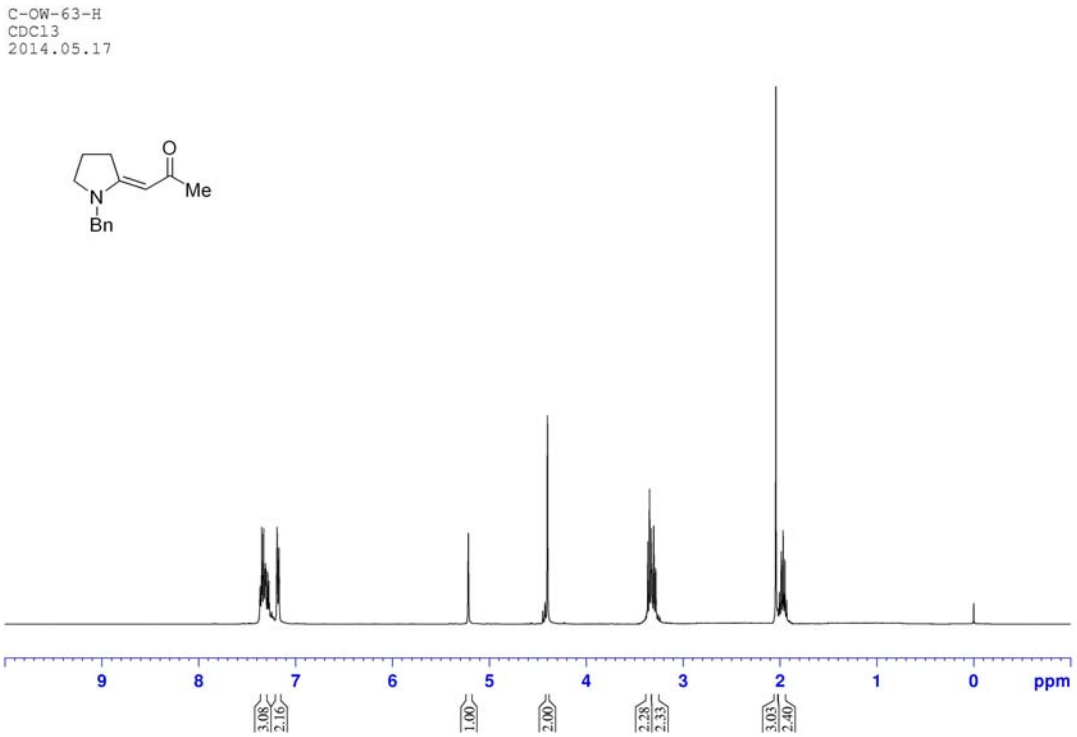
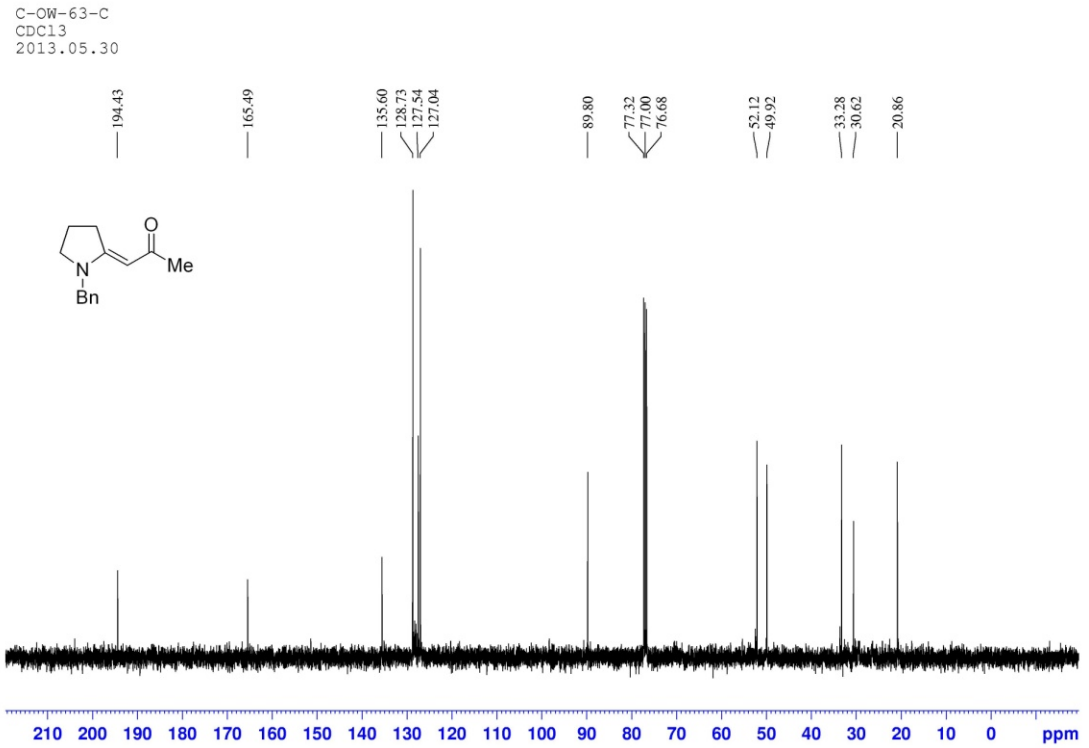
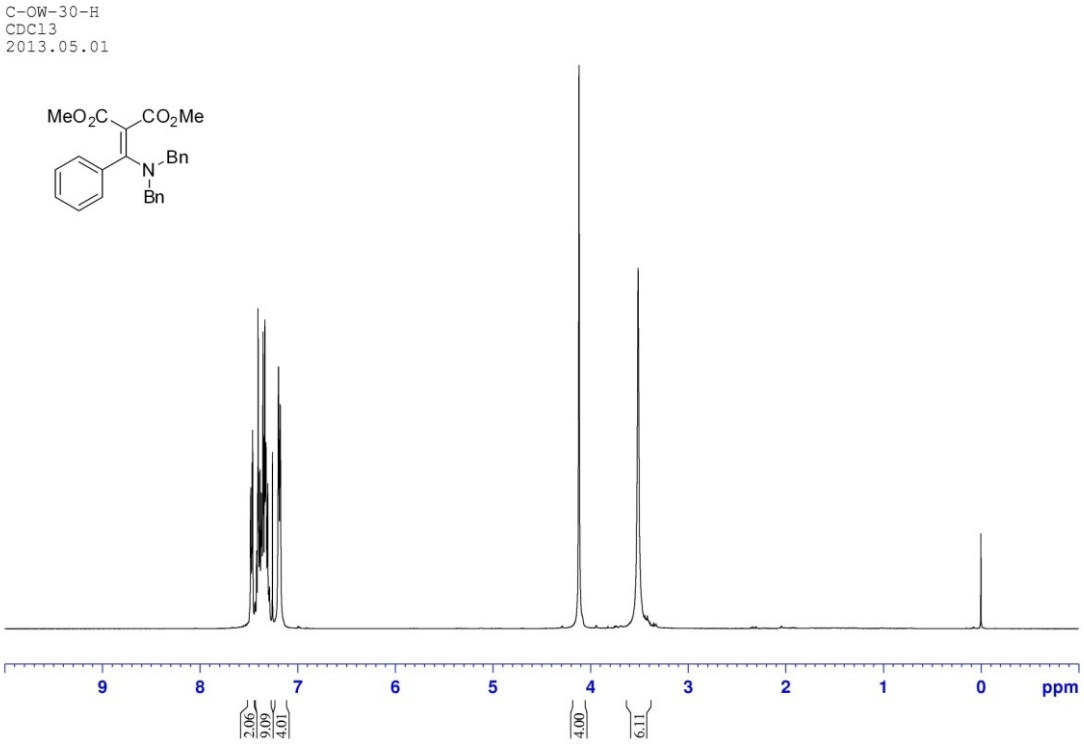
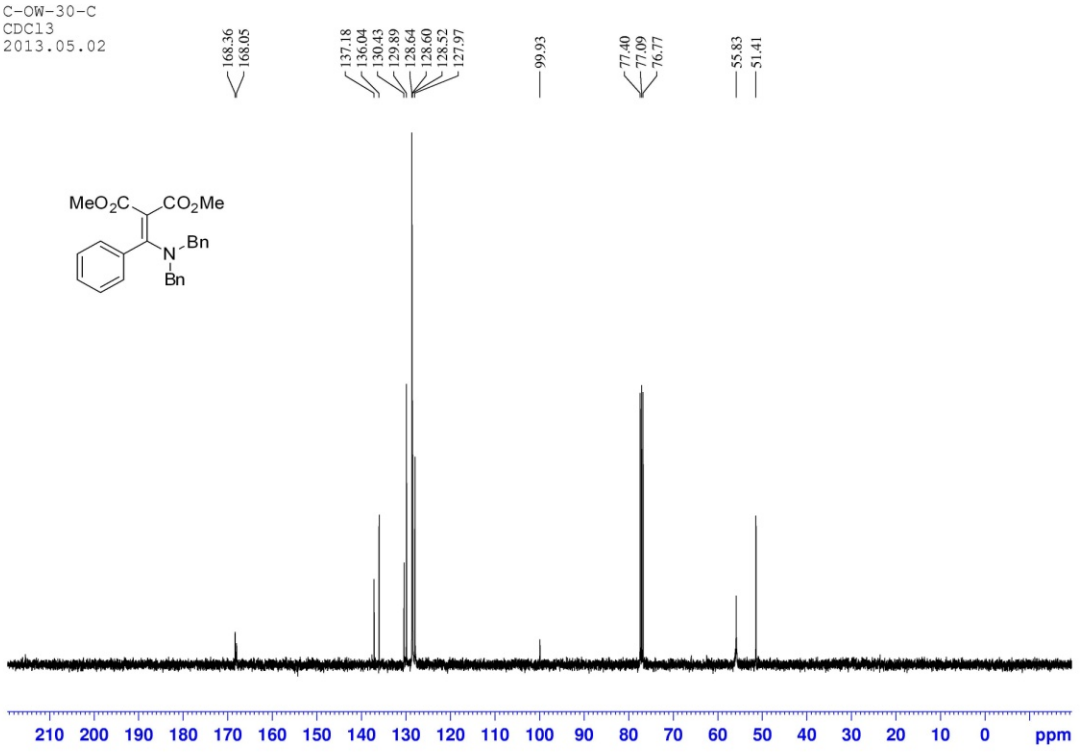
^{1}H and ^{13}C NMR spectra of compound **4**



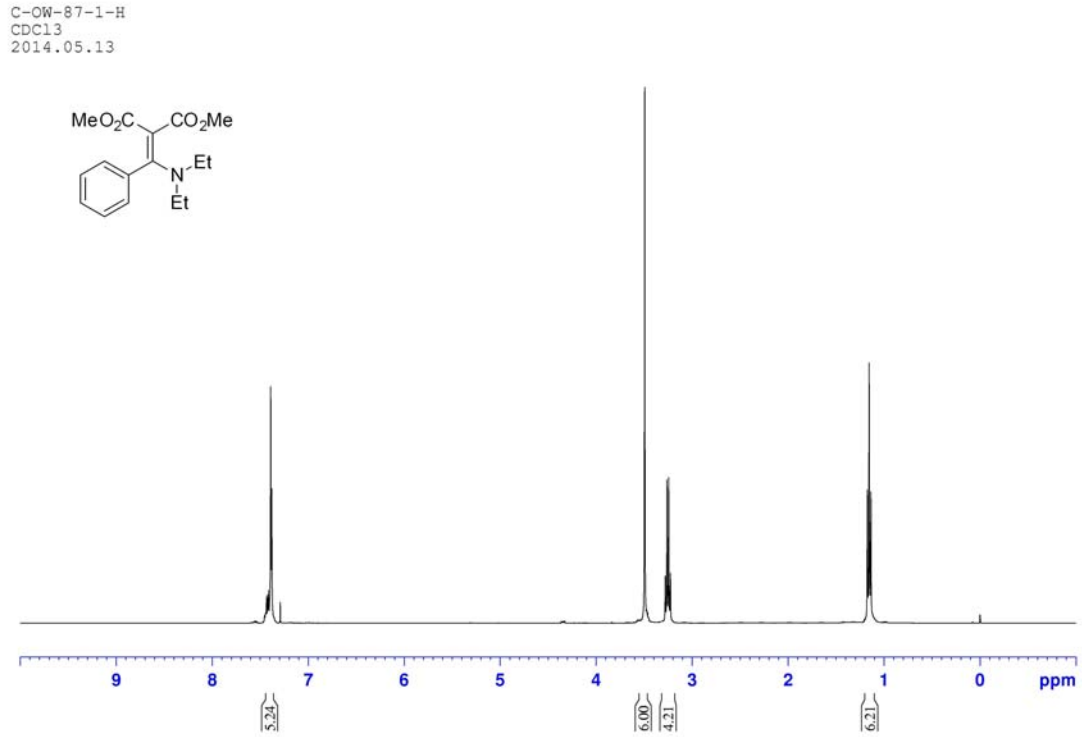


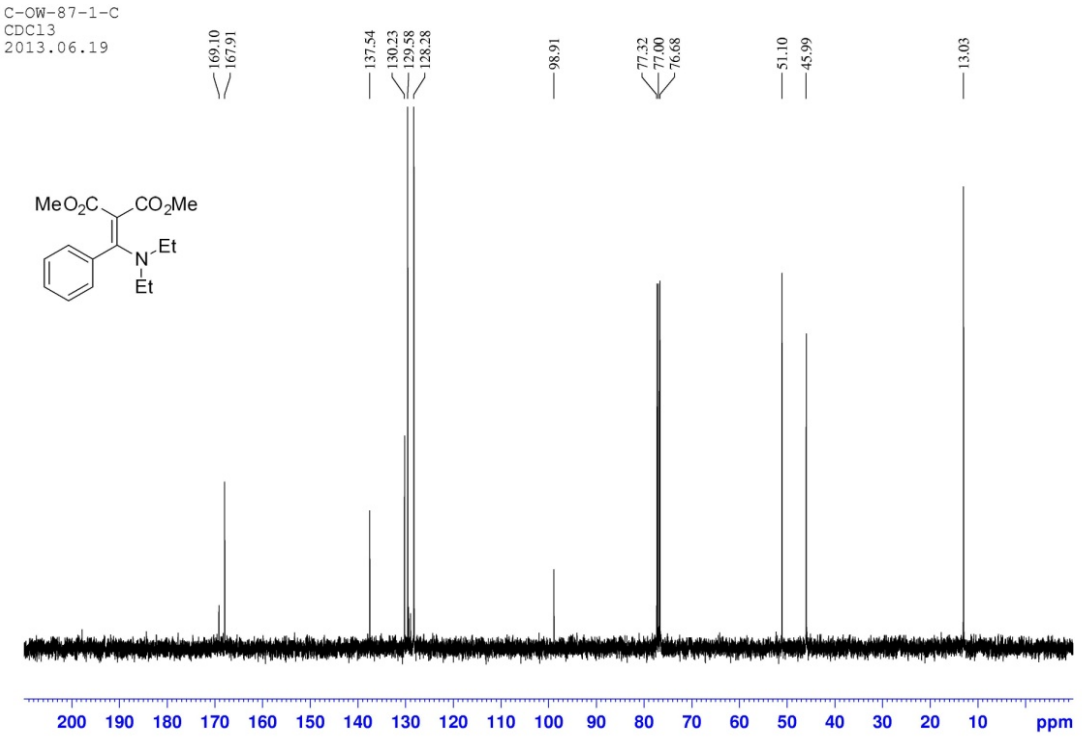
^{1}H and ^{13}C NMR spectra of compound **7a**



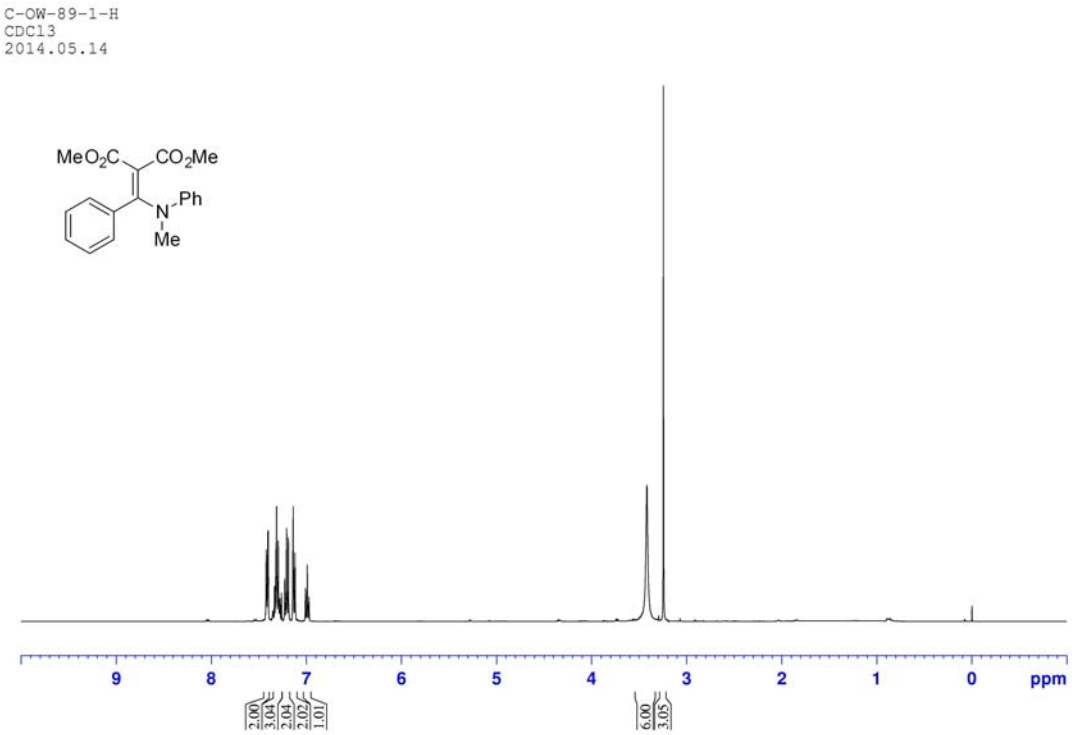


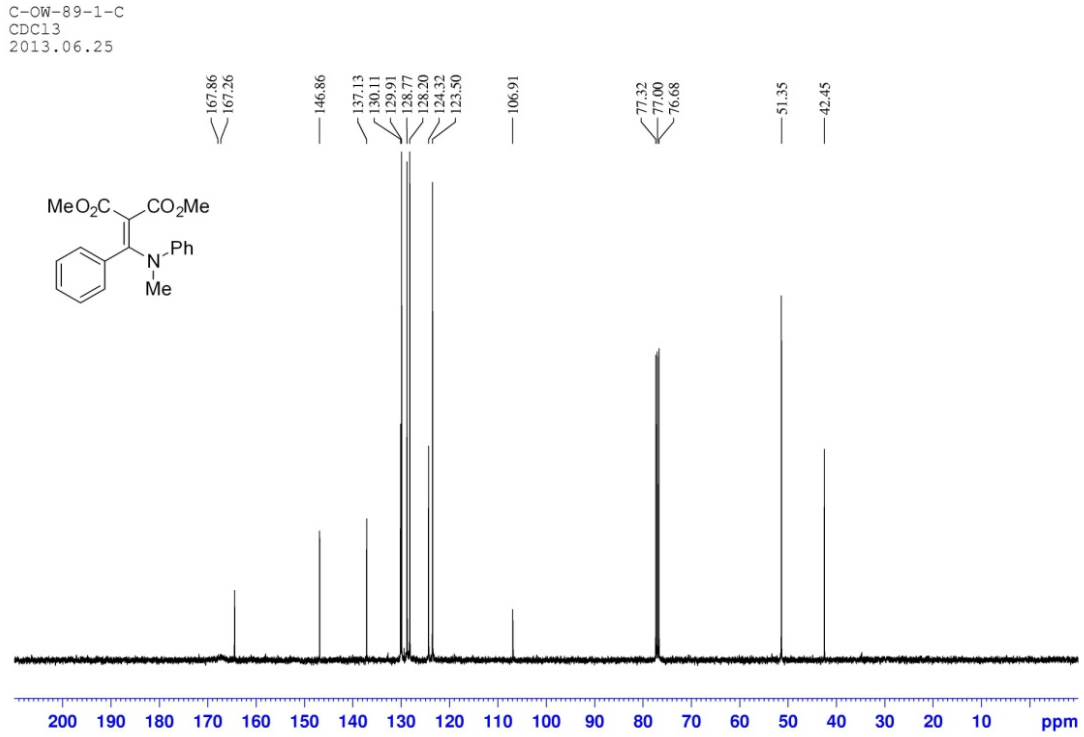
^{1}H and ^{13}C NMR spectra of compound **7b**



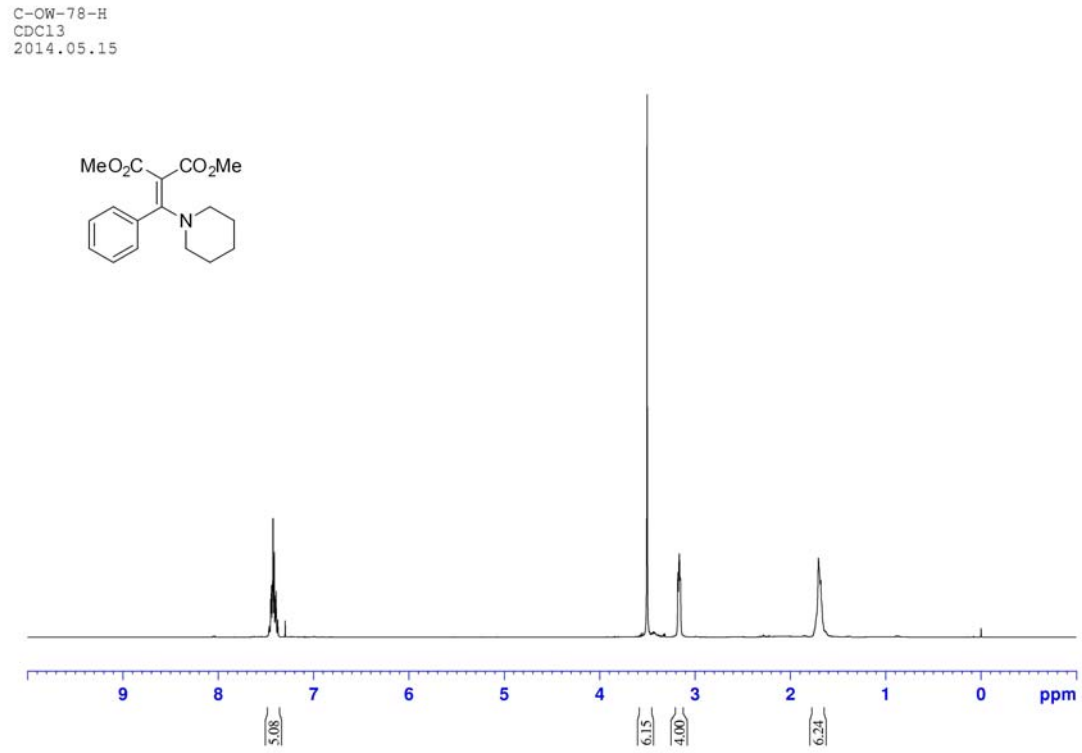


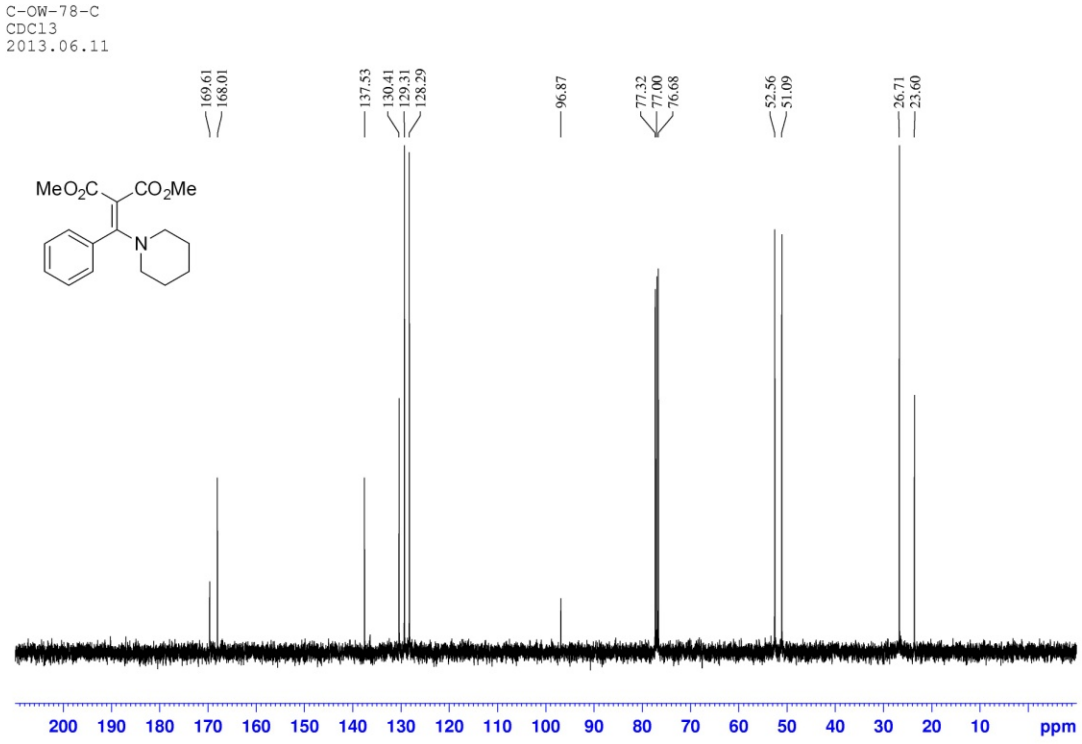
^{1}H and ^{13}C NMR spectra of compound **7c**



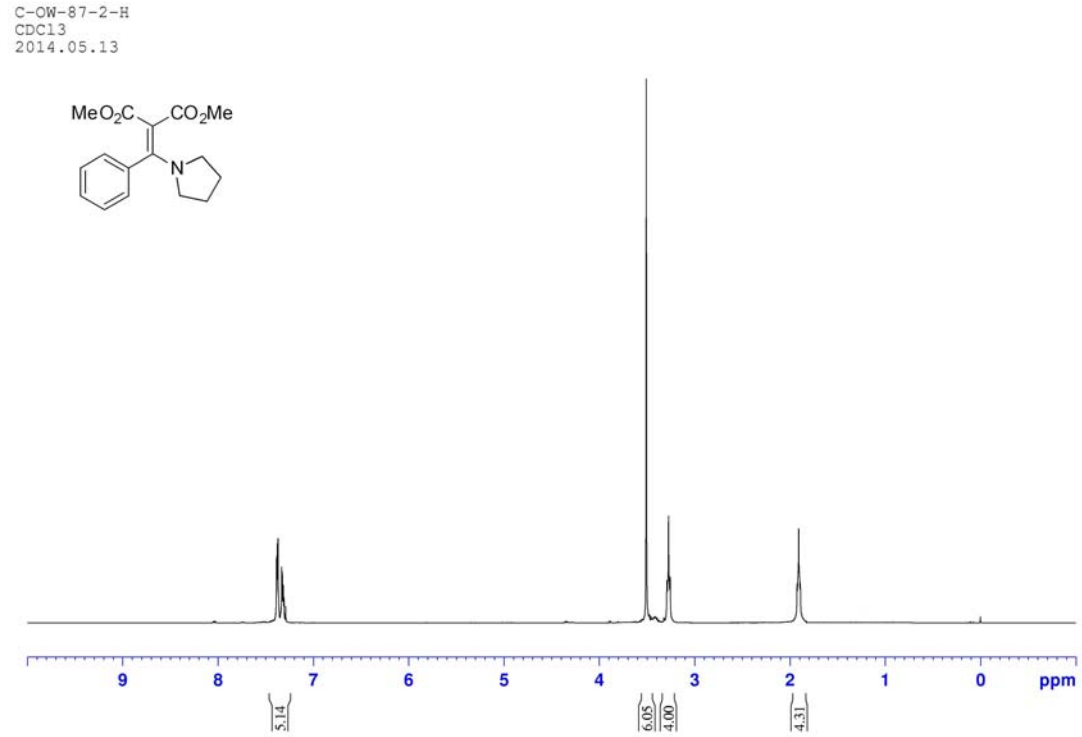


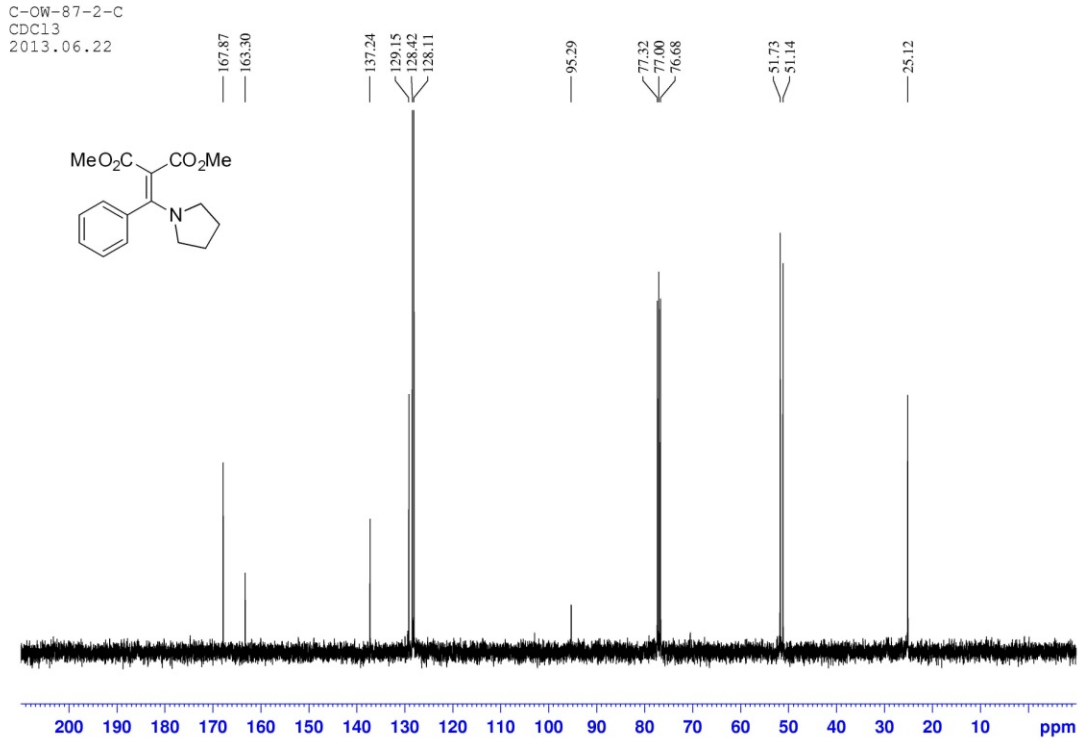
^{1}H and ^{13}C NMR spectra of compound **7d**



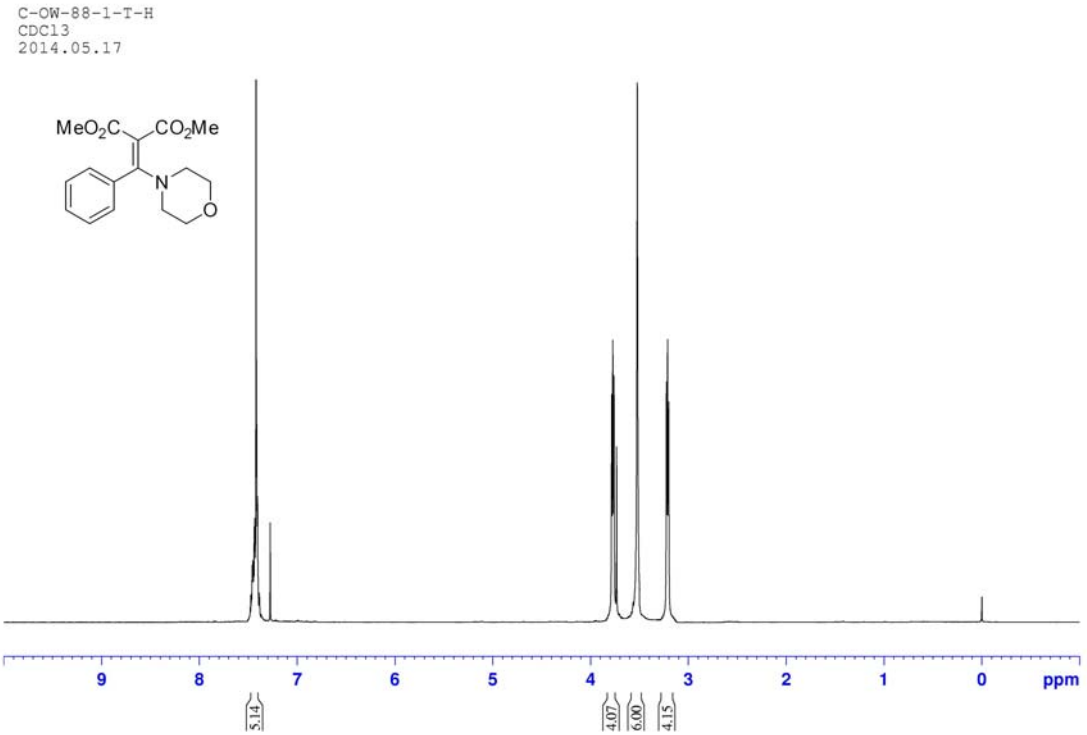


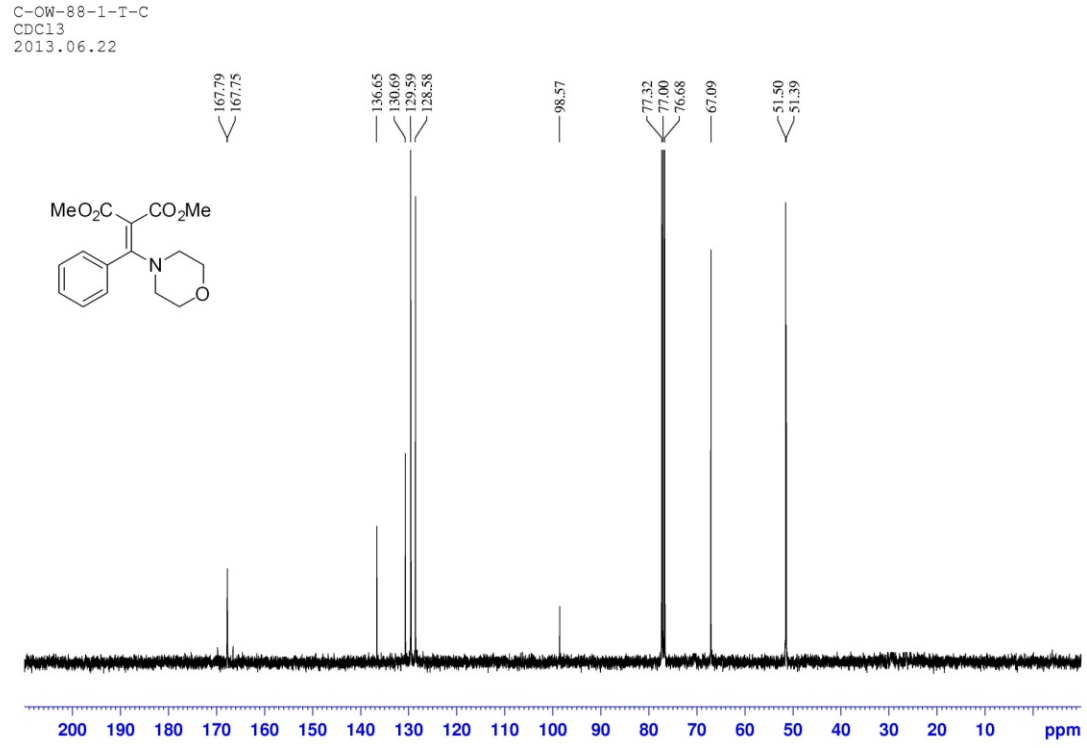
^{1}H and ^{13}C NMR spectra of compound **7e**



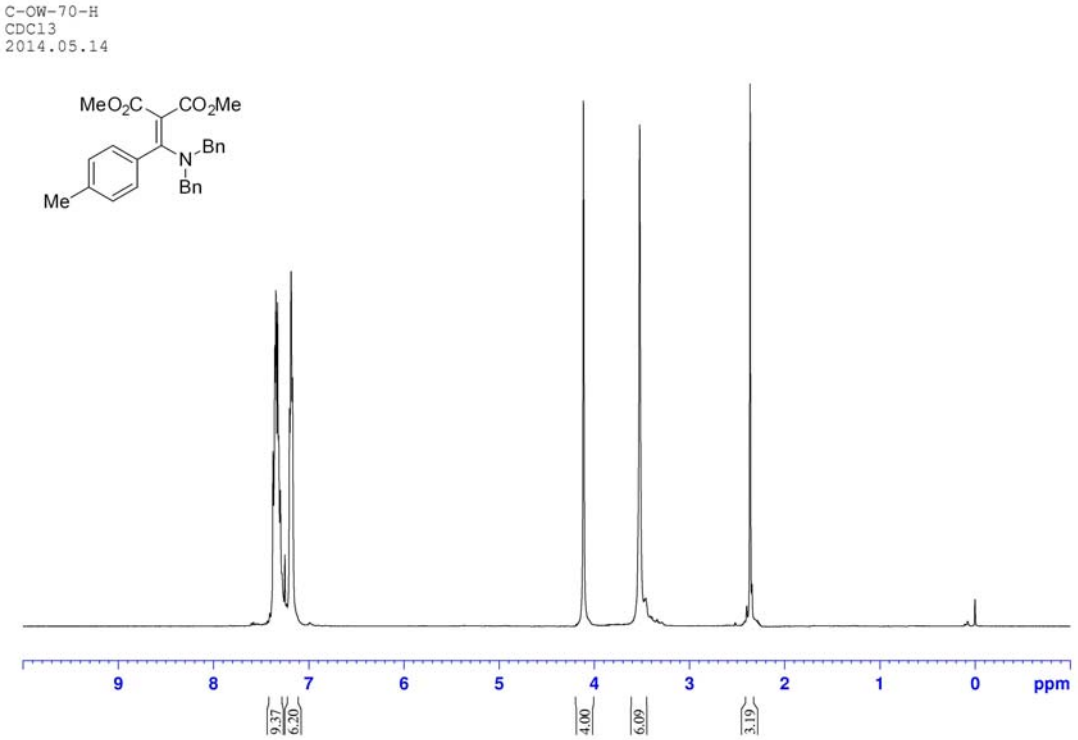


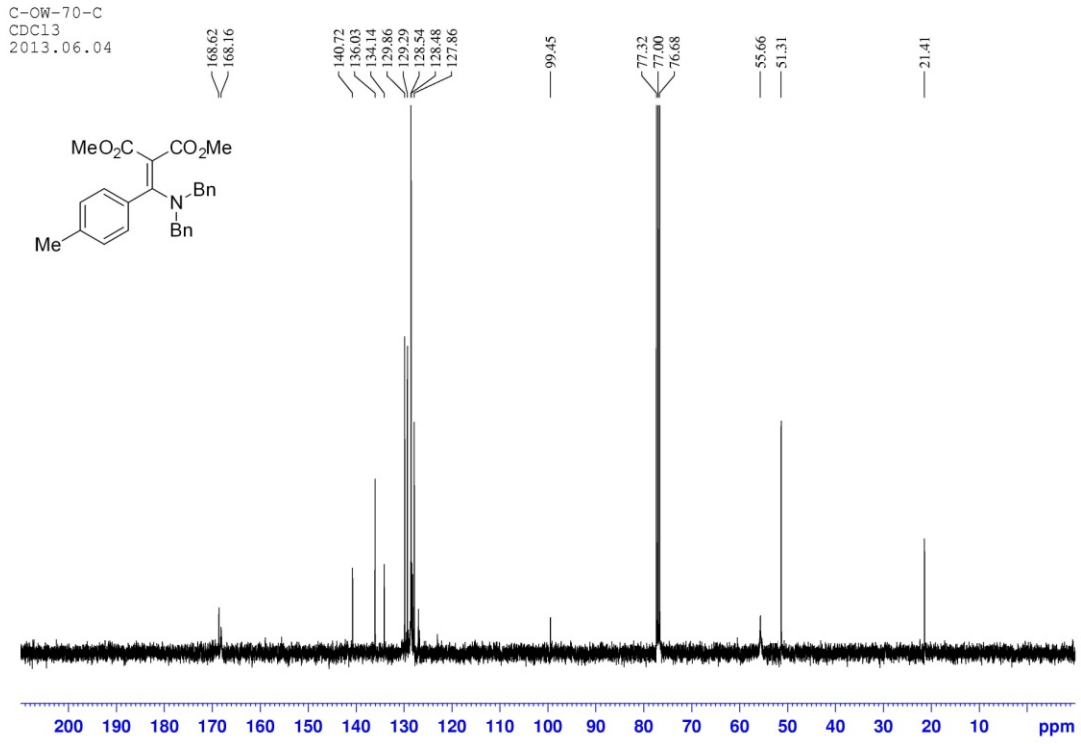
^{1}H and ^{13}C NMR spectra of compound **7f**



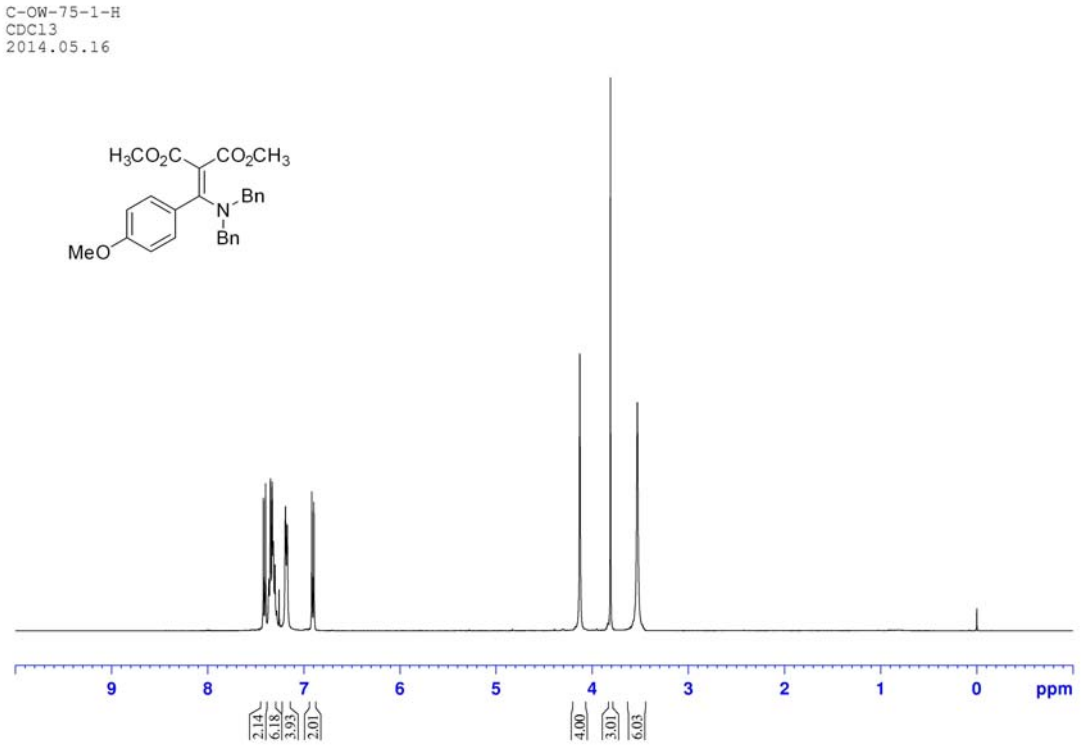


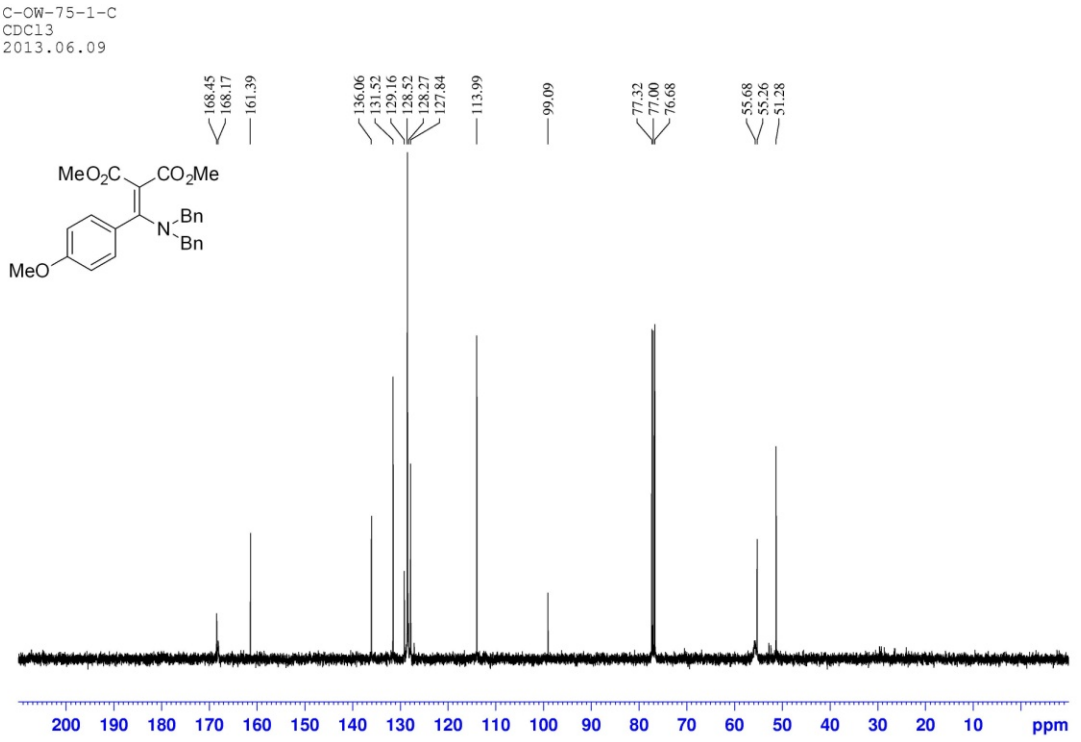
^{1}H and ^{13}C NMR spectra of compound **7g**



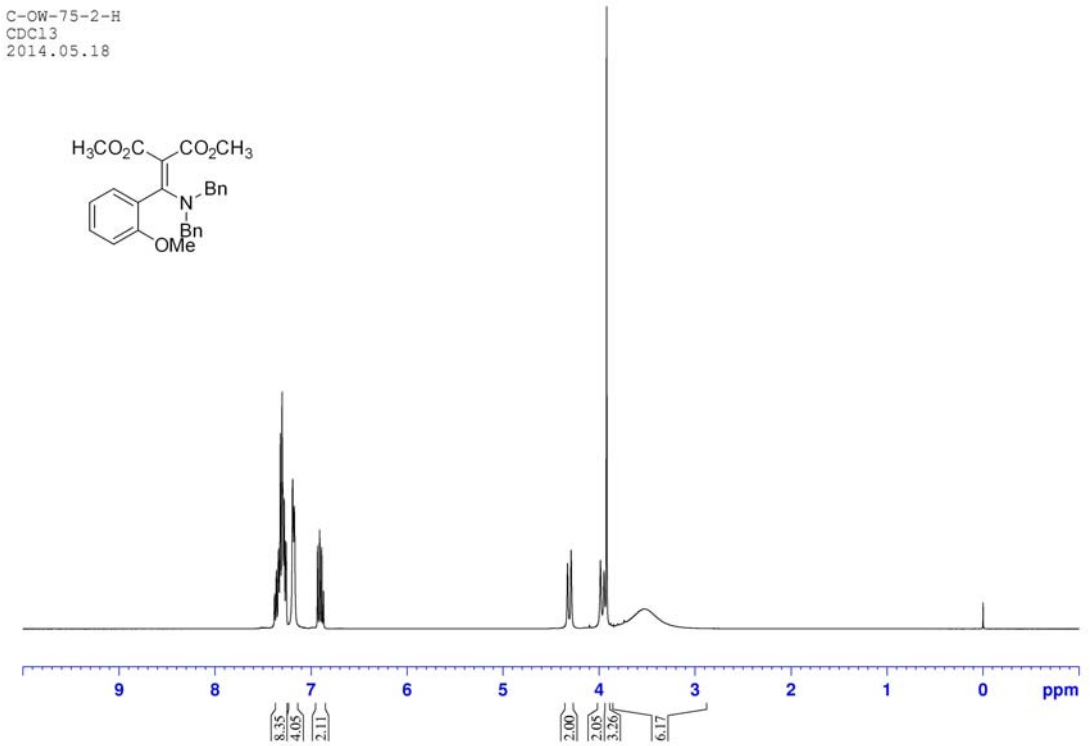


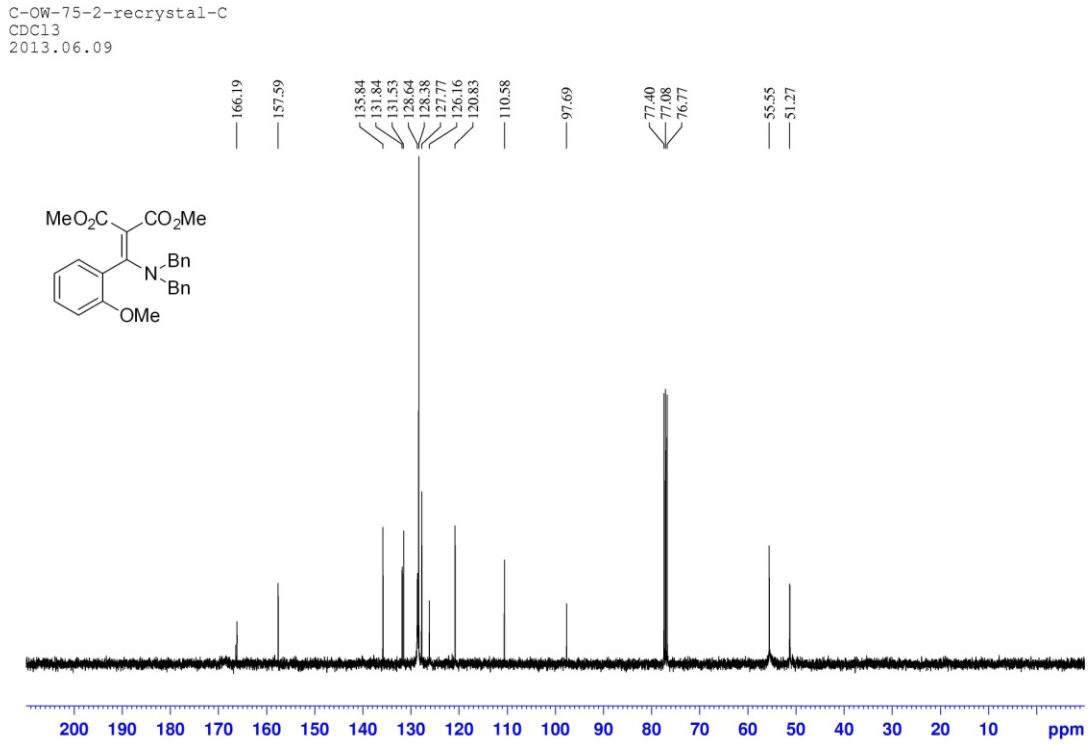
^{1}H and ^{13}C NMR spectra of compound **7h**



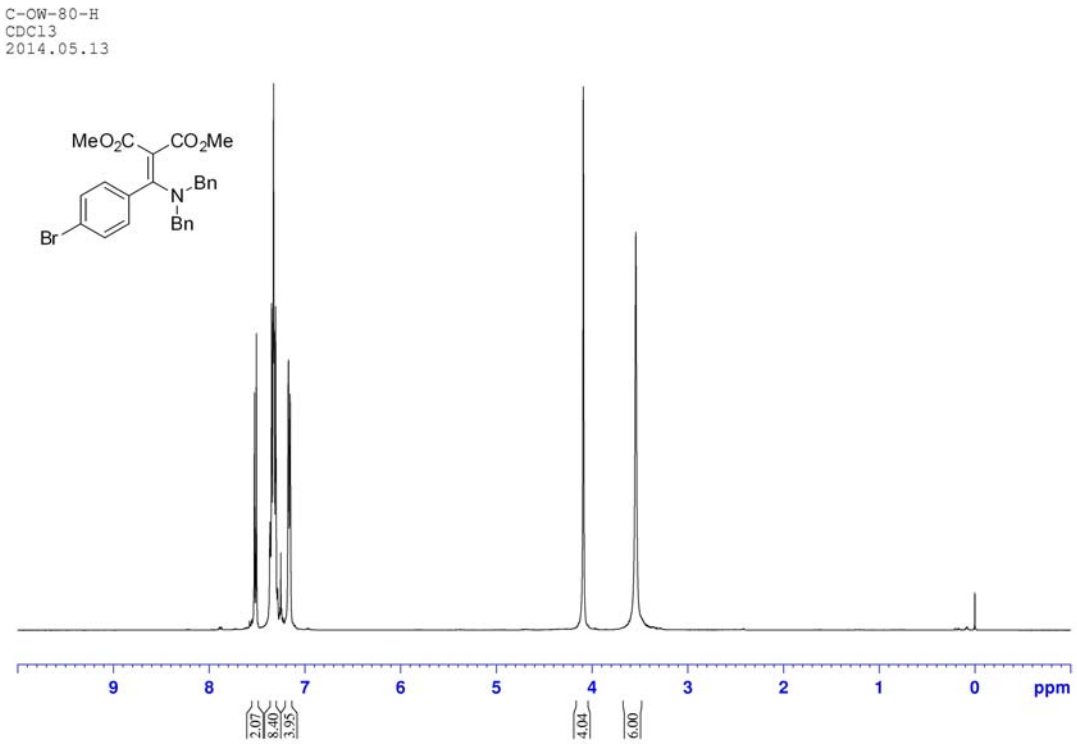


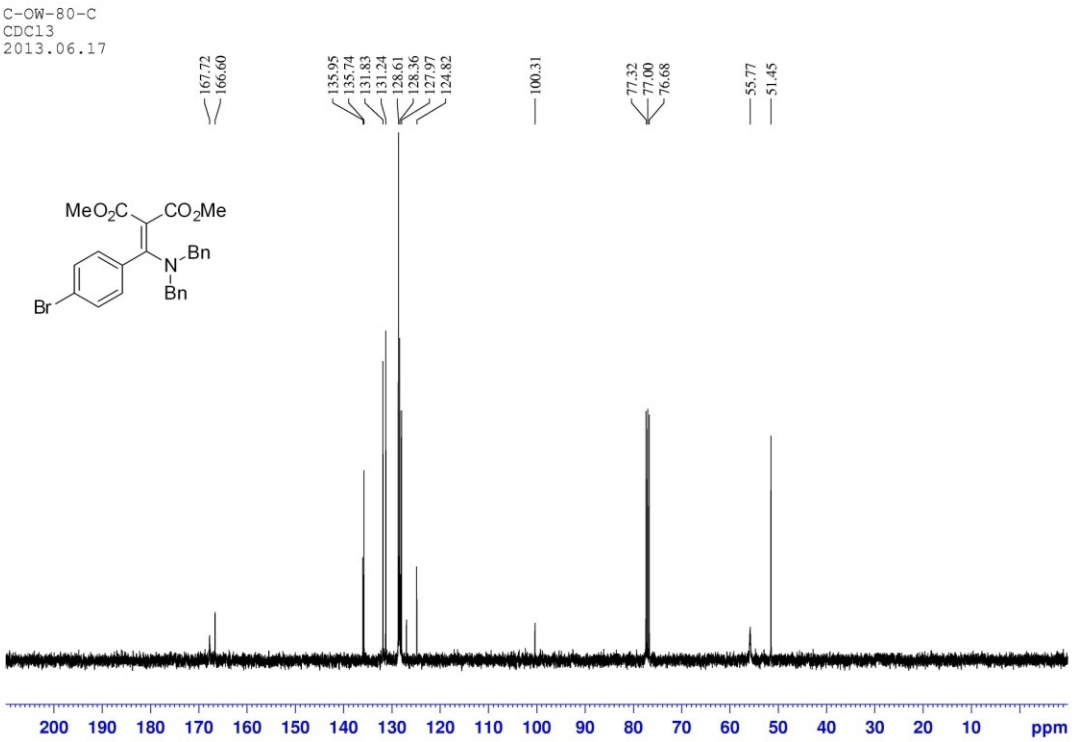
^{1}H and ^{13}C NMR spectra of compound **7i**



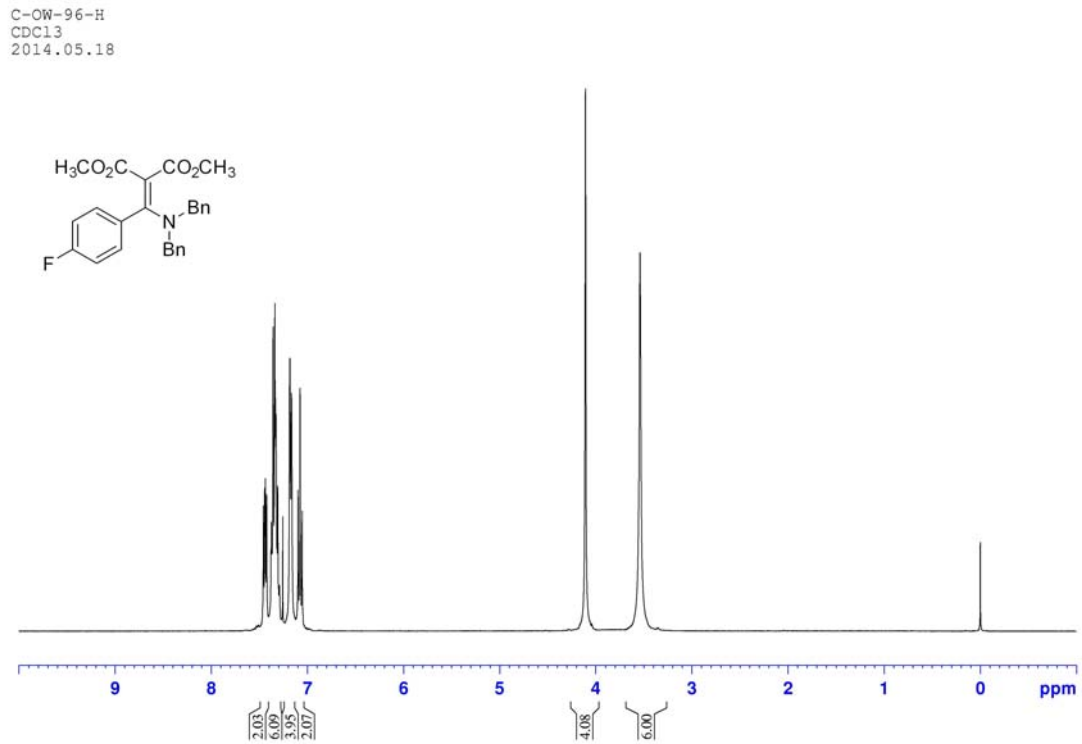


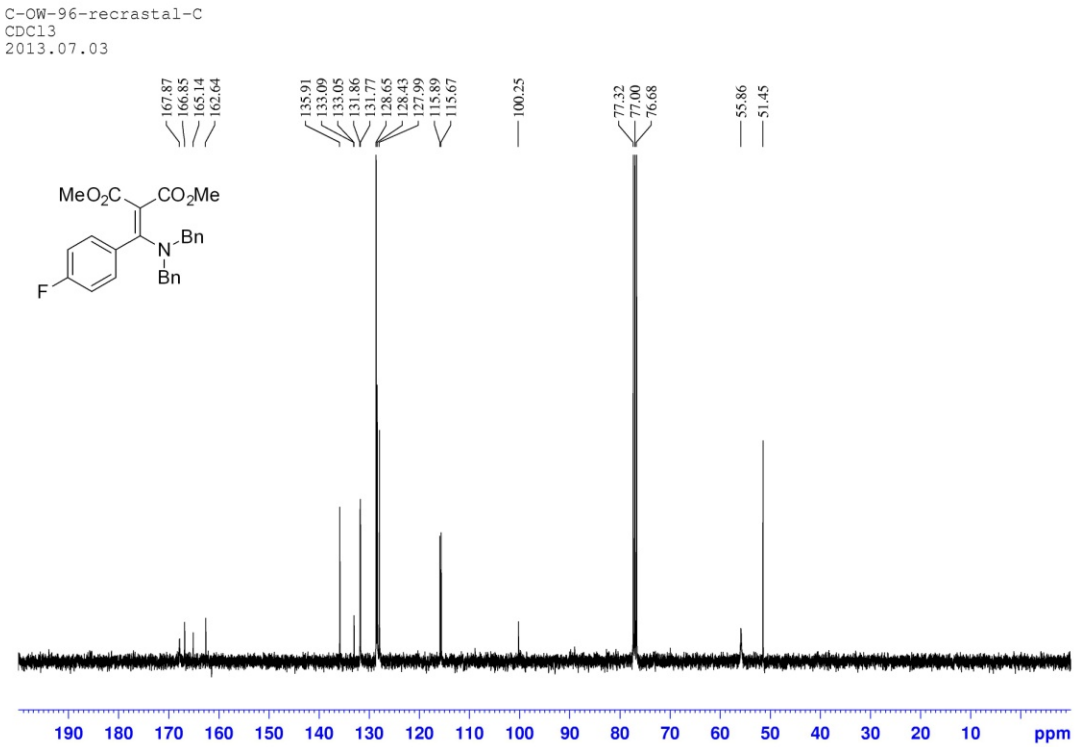
^{1}H and ^{13}C NMR spectra of compound **7j**



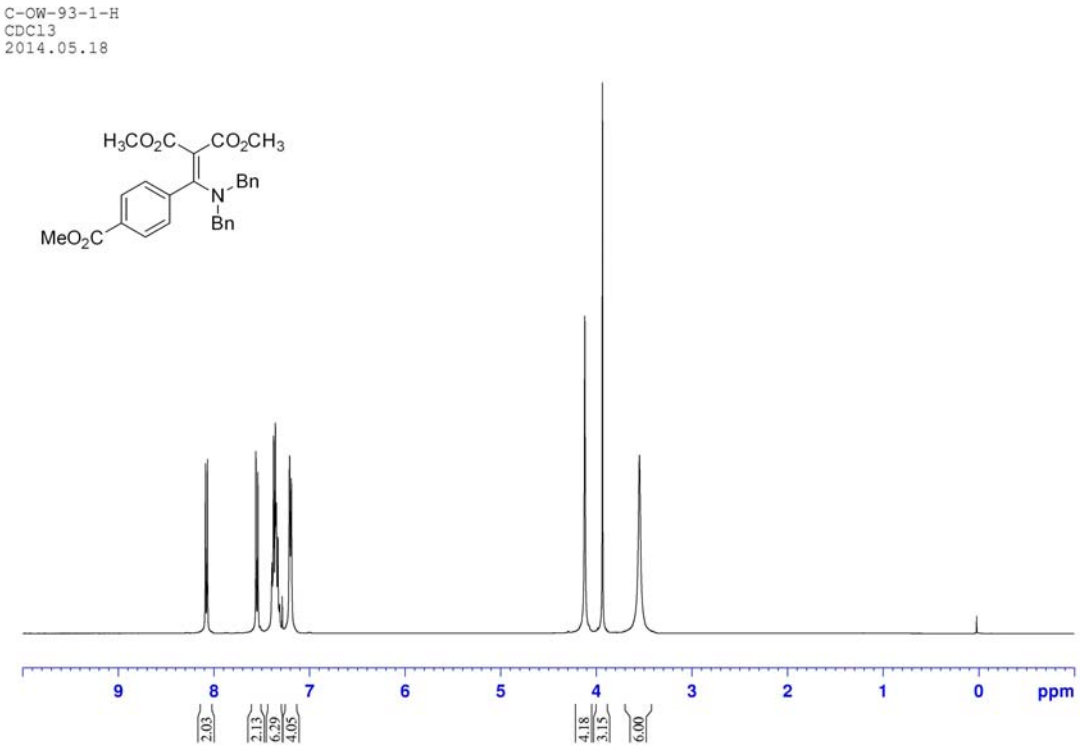


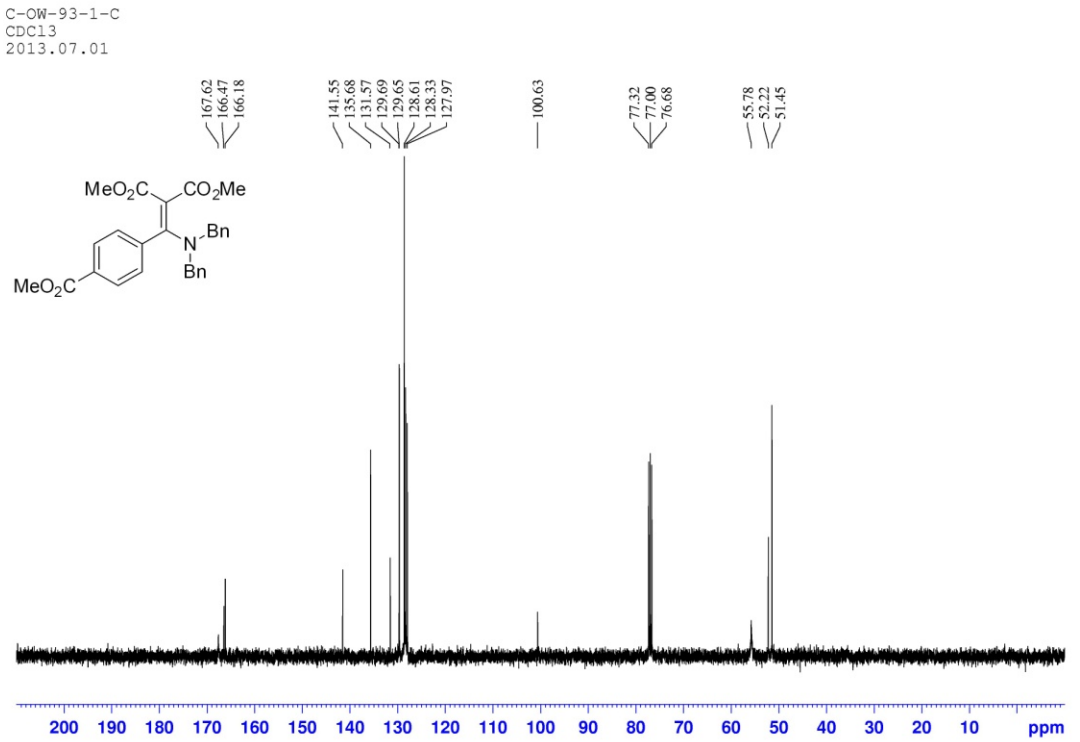
^{1}H and ^{13}C NMR spectra of compound **7k**



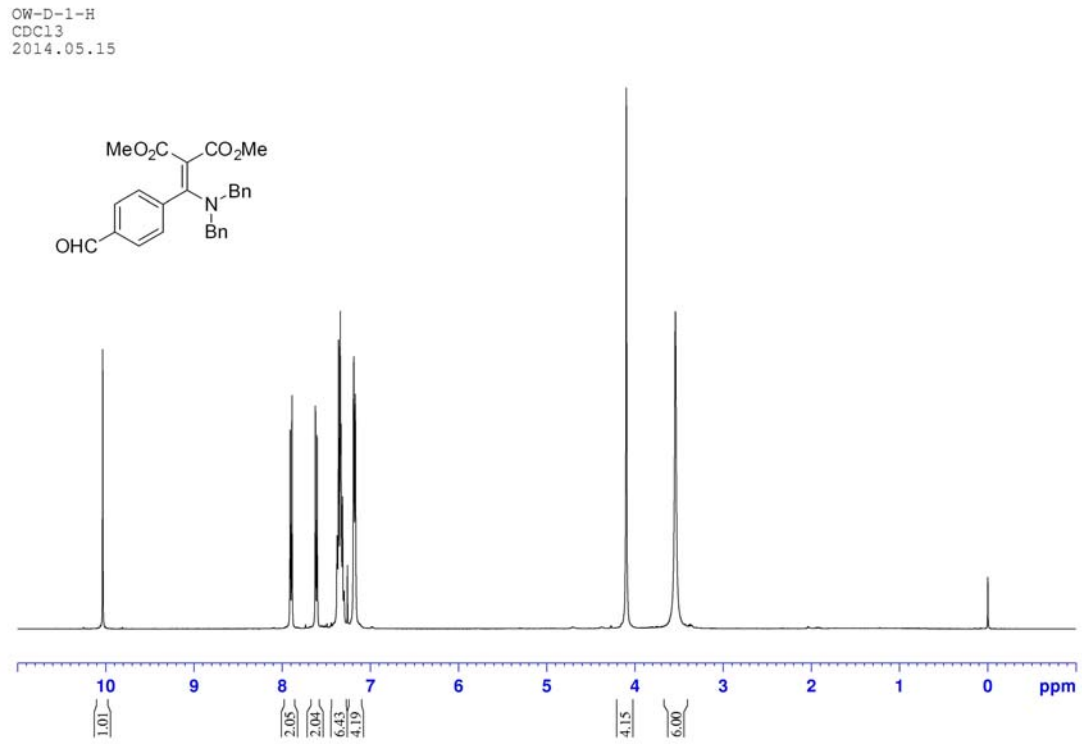


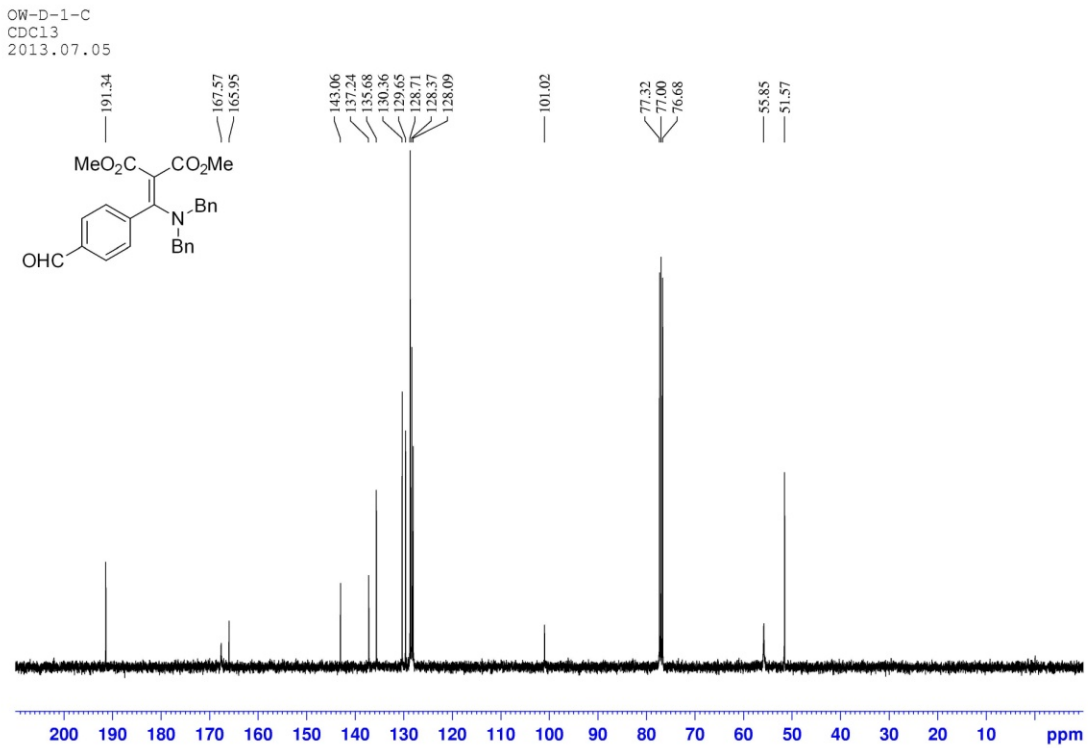
^{1}H and ^{13}C NMR spectra of compound **7l**



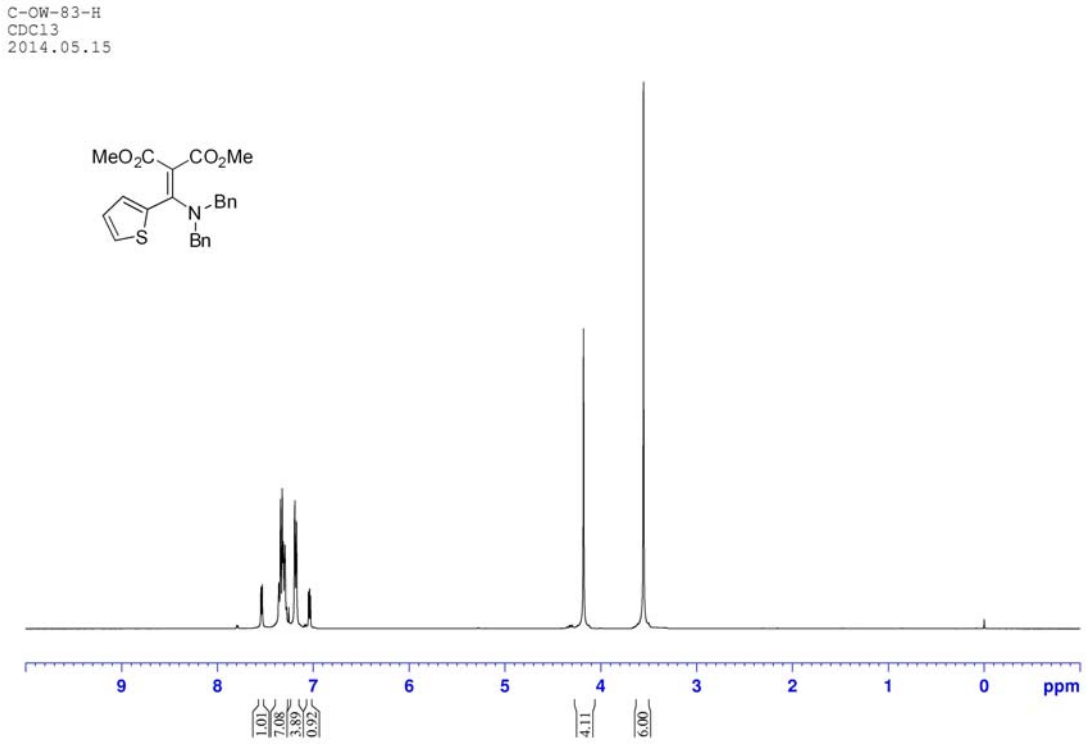


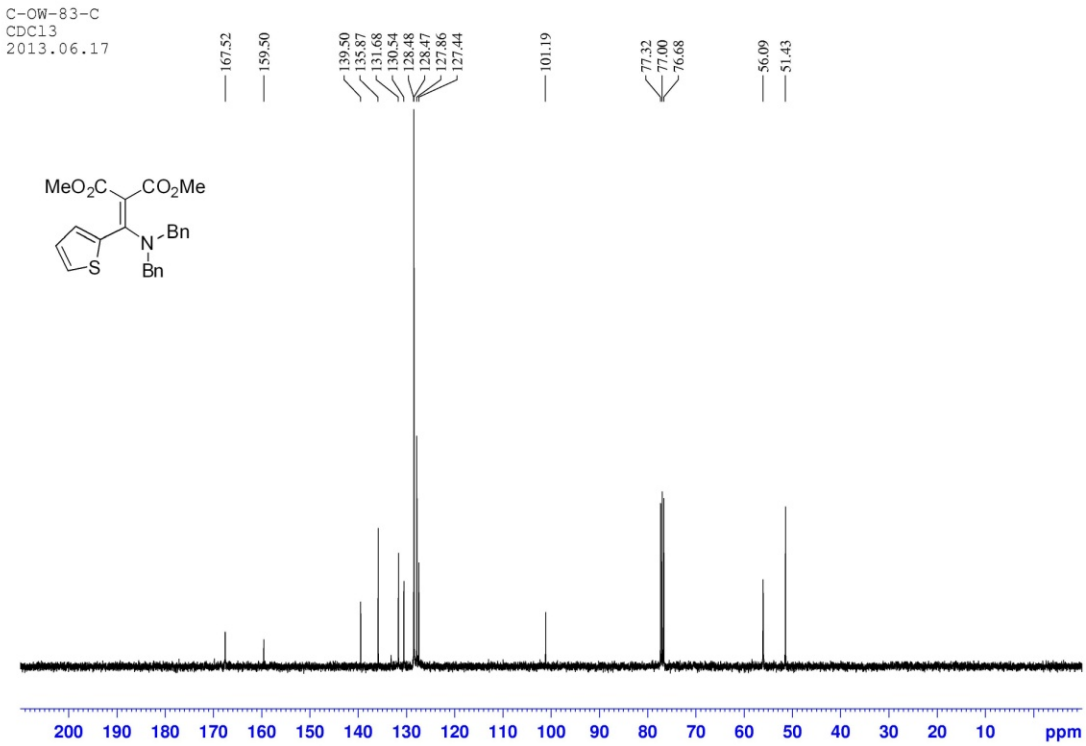
^{1}H and ^{13}C NMR spectra of compound **7m**



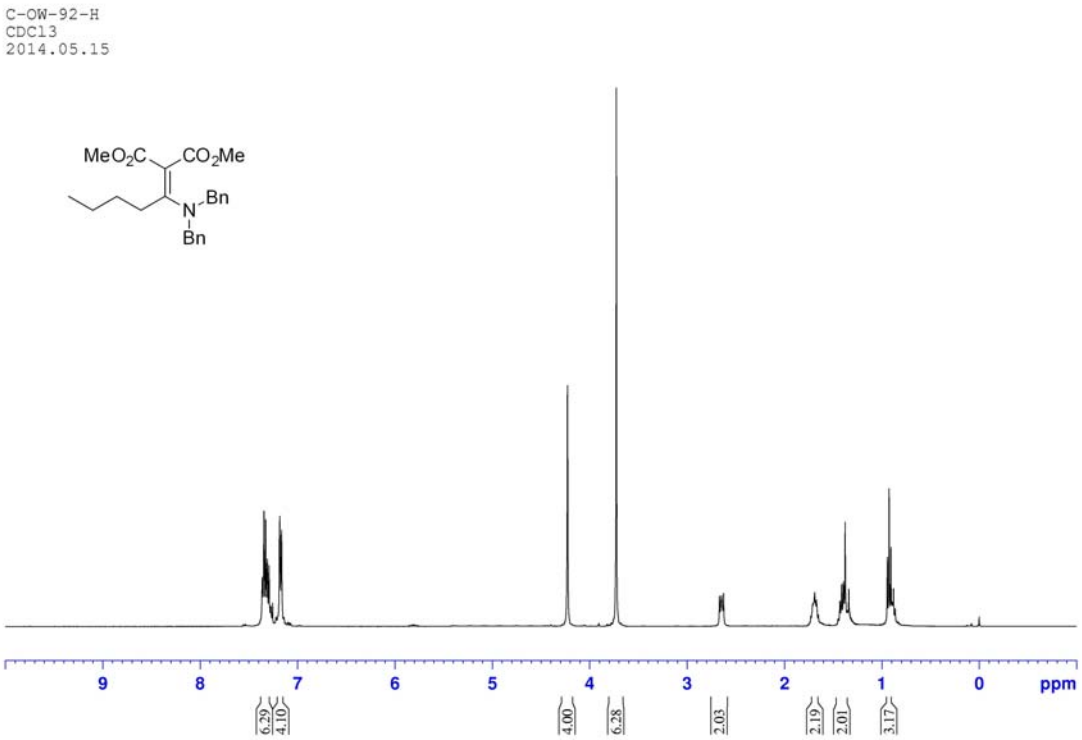


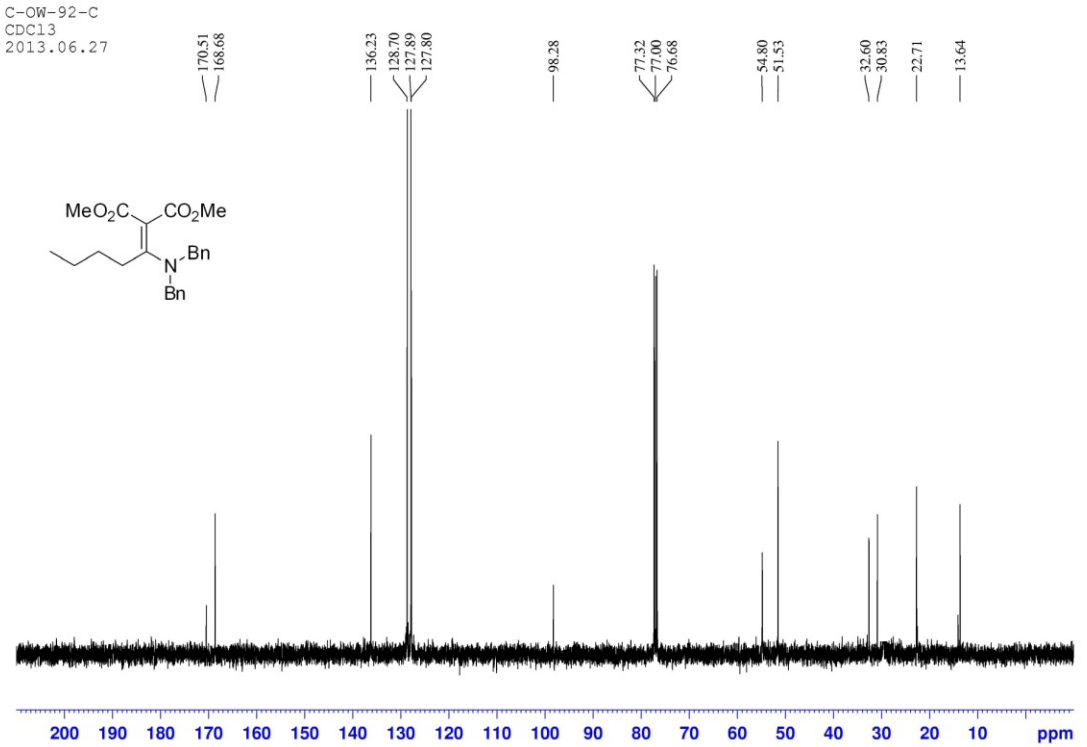
^{1}H and ^{13}C NMR spectra of compound **7n**



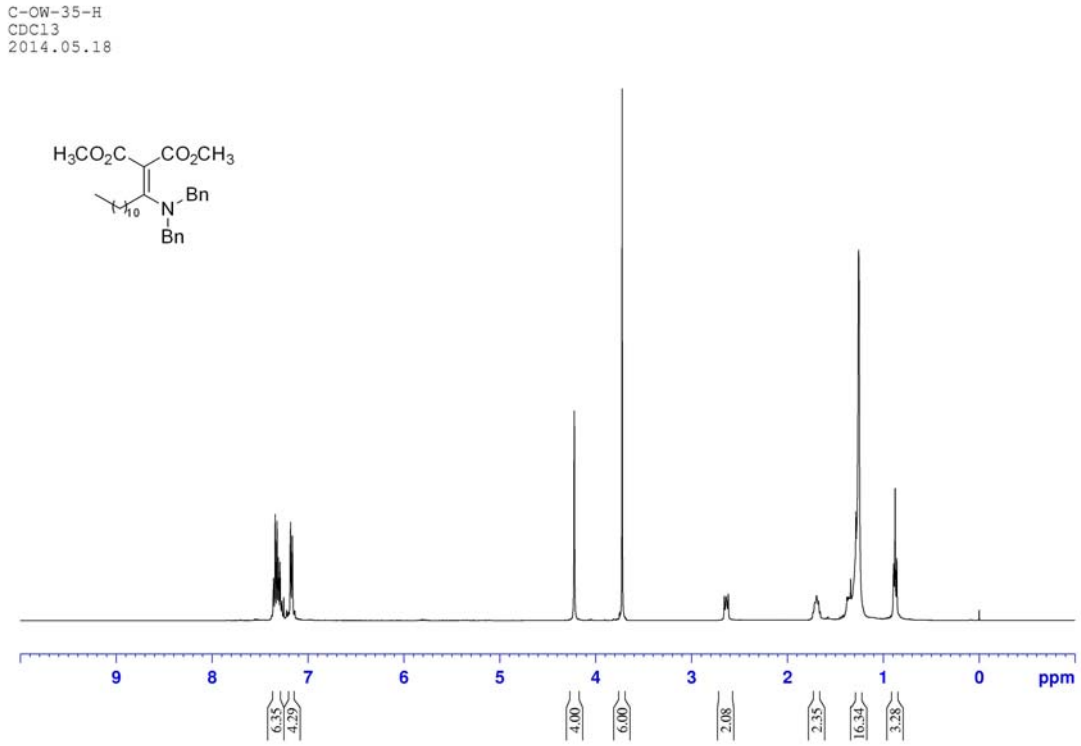


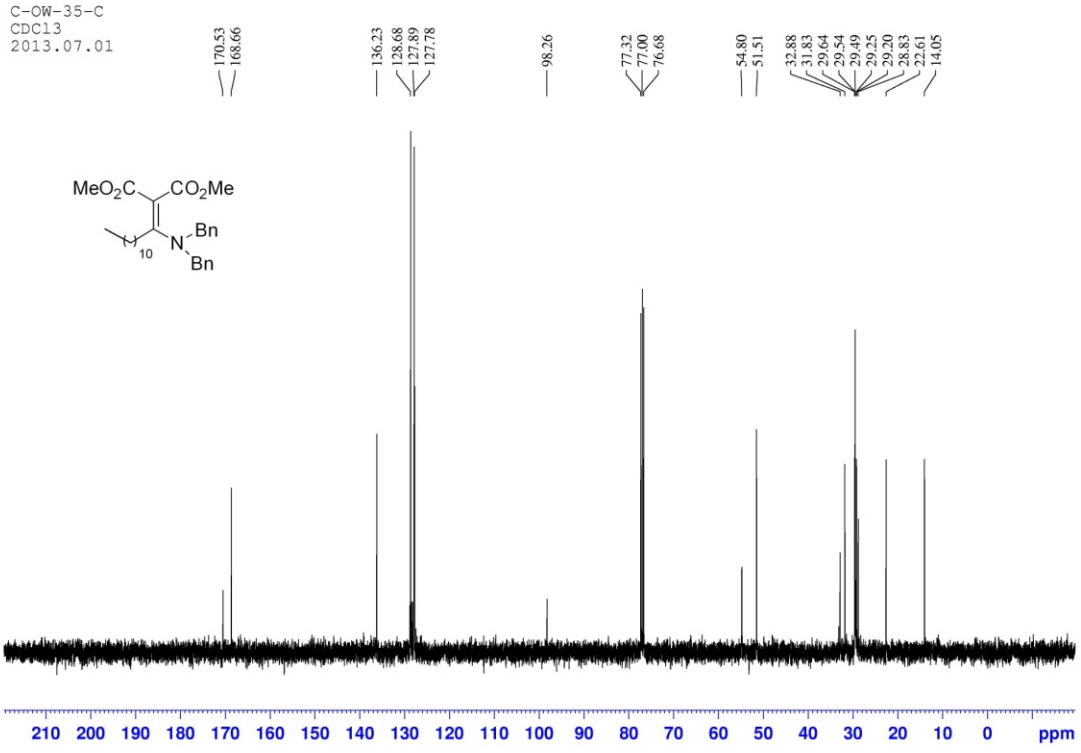
^{1}H and ^{13}C NMR spectra of compound **7o**



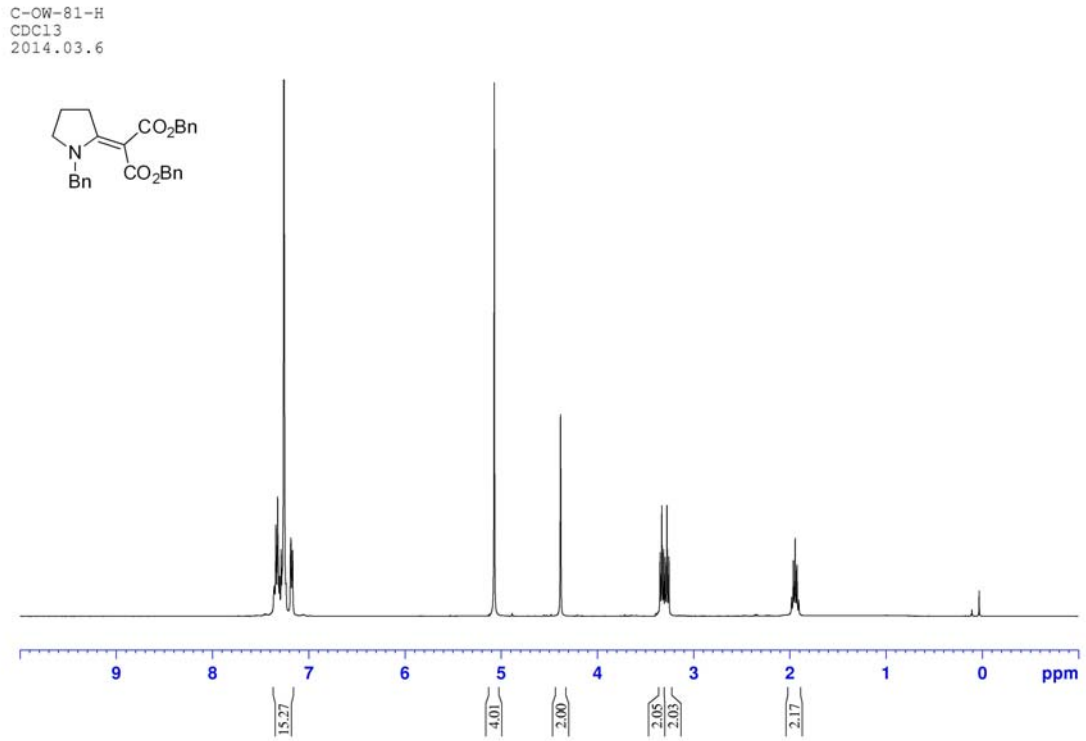


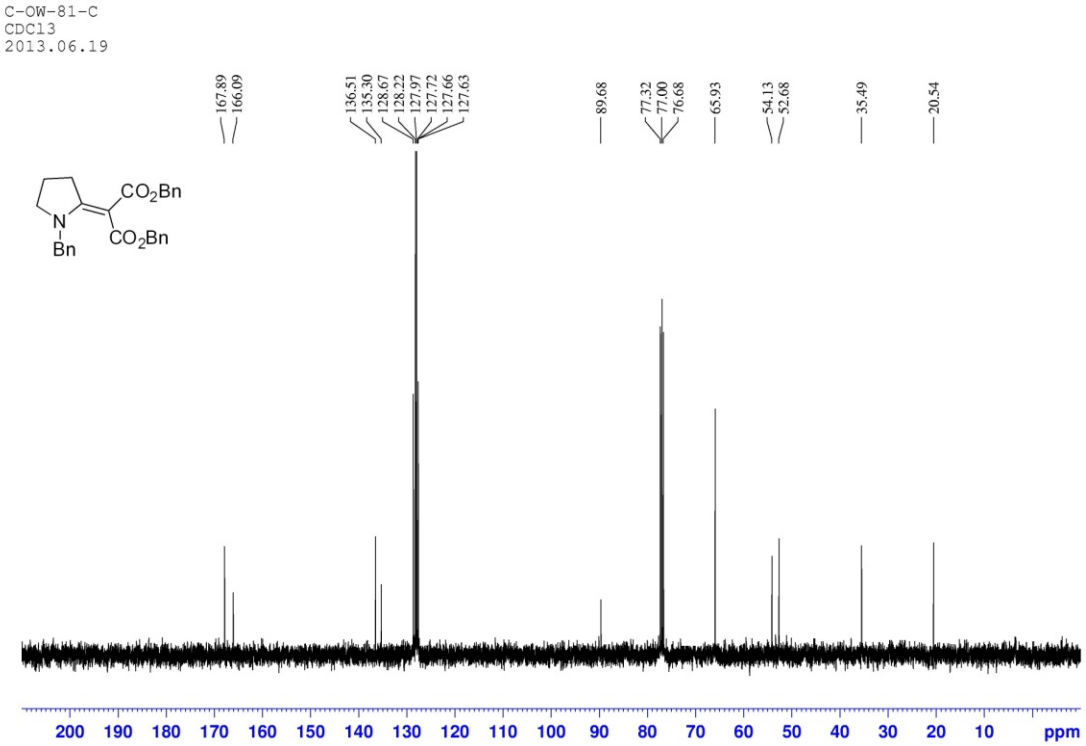
^{1}H and ^{13}C NMR spectra of compound **7p**



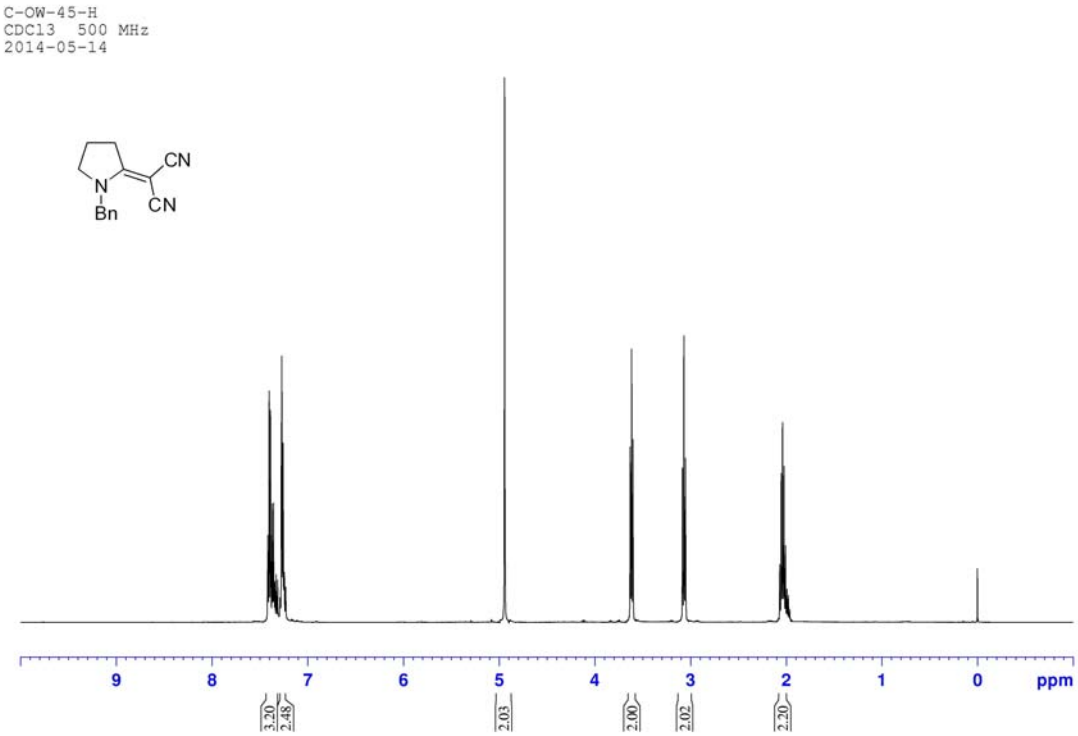


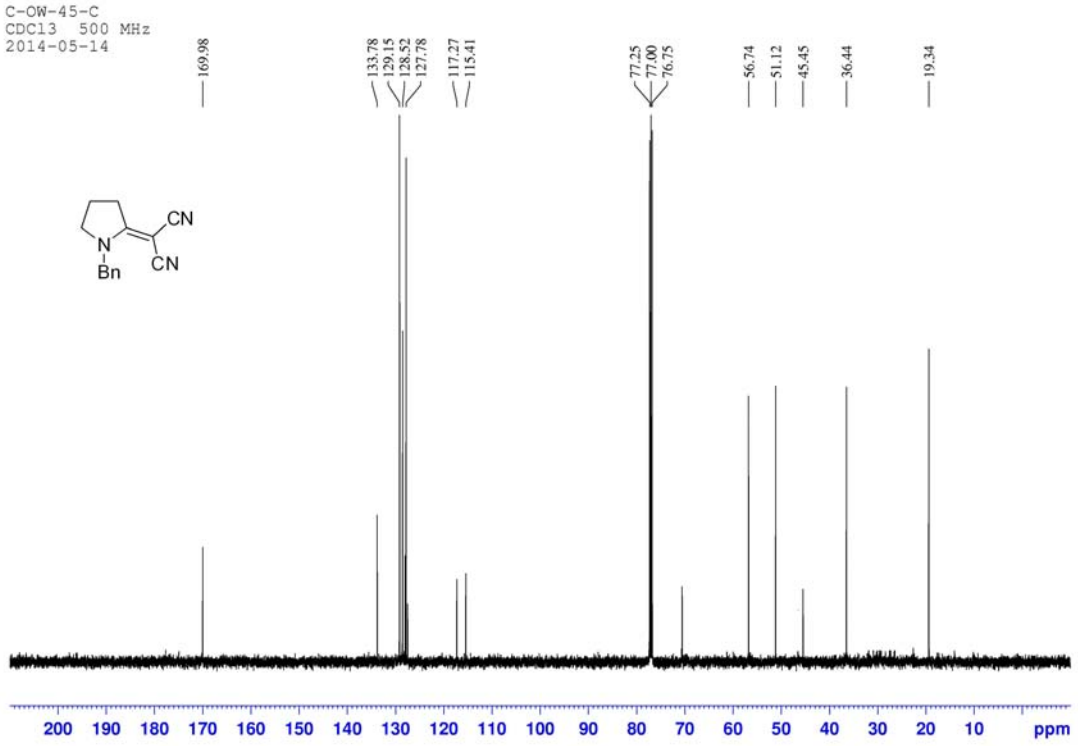
^{1}H and ^{13}C NMR spectra of compound **9b**



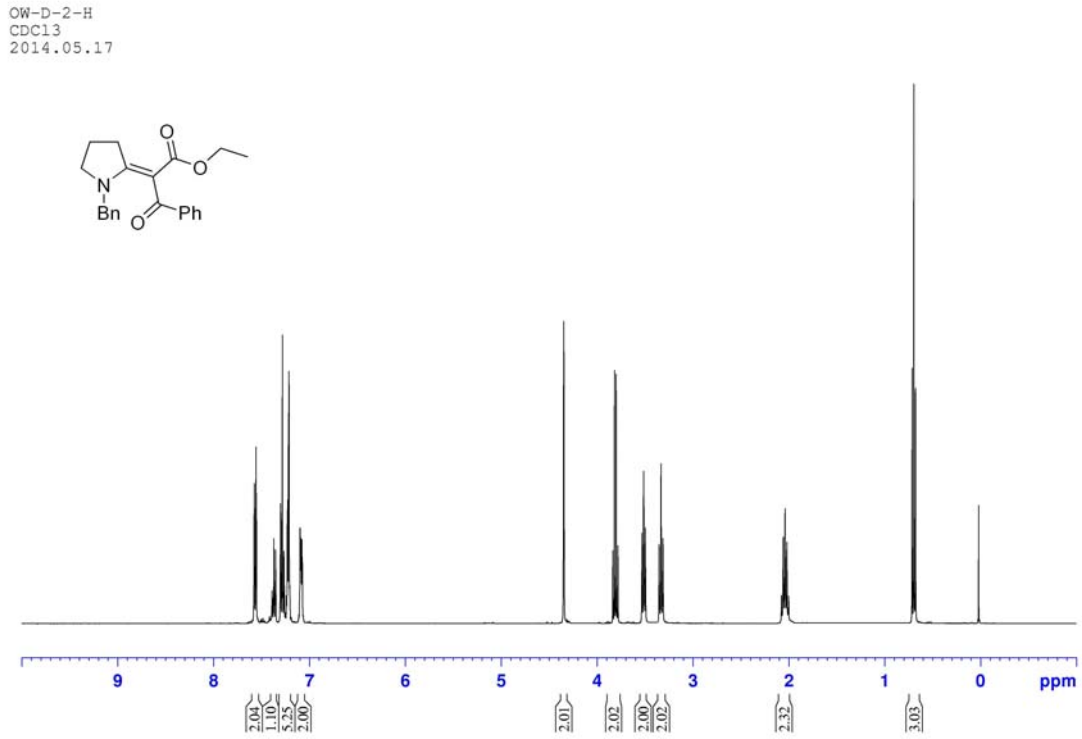


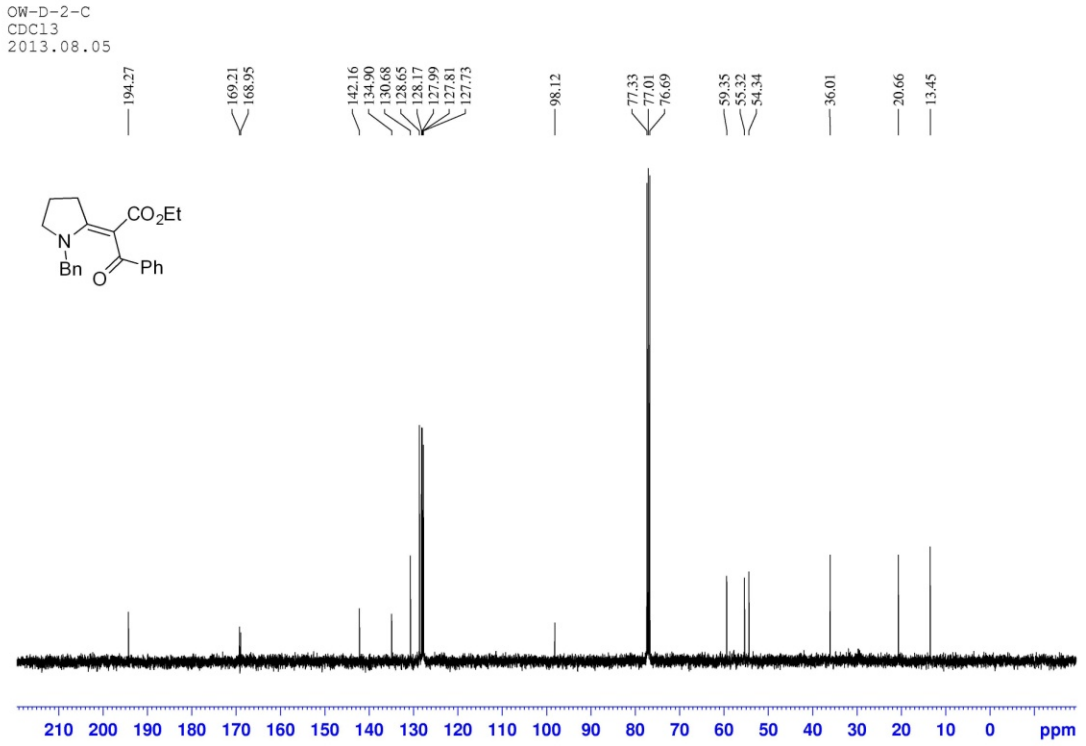
^{1}H and ^{13}C NMR spectra of compound **9c**



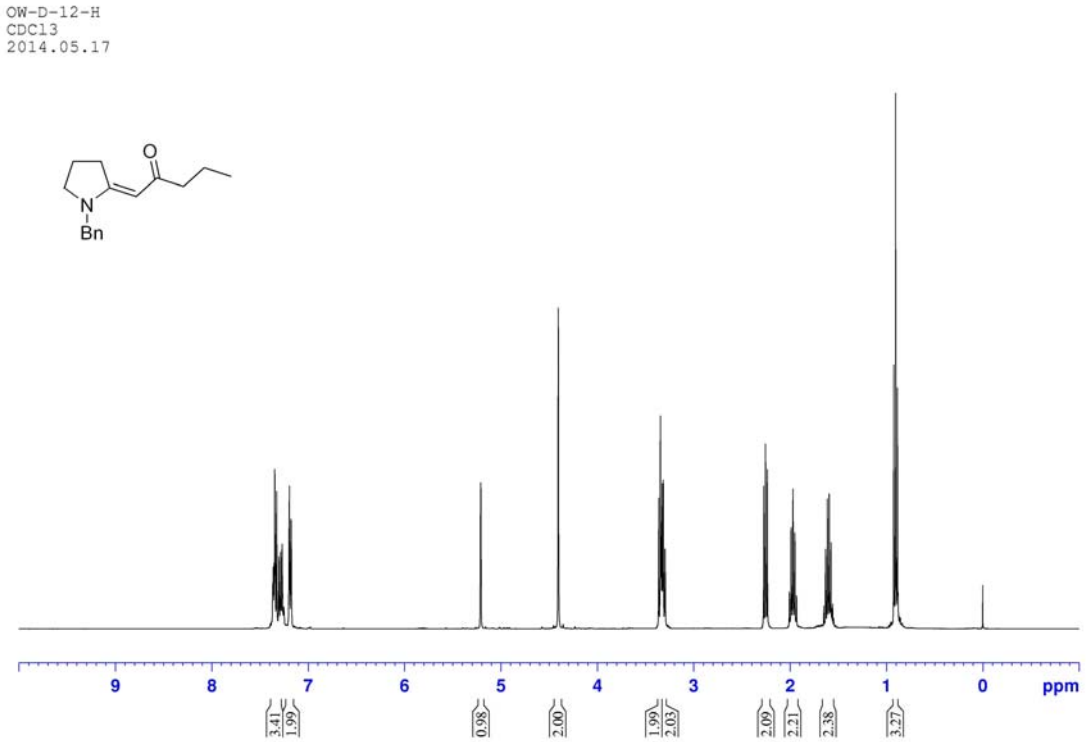


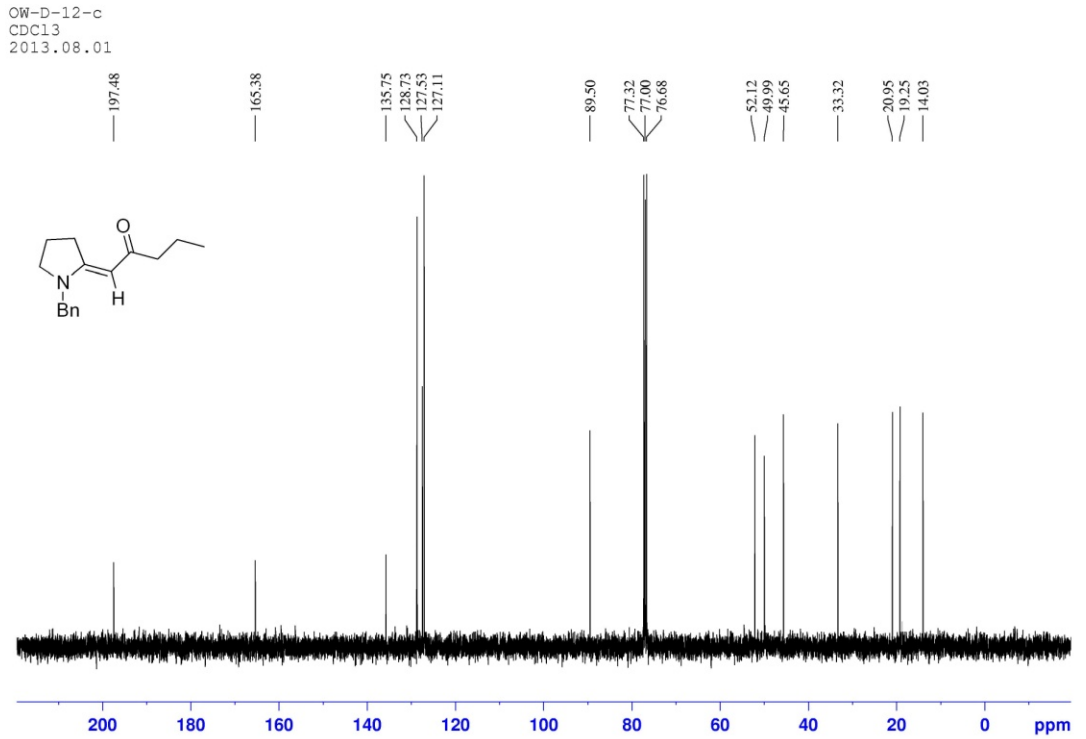
^{1}H and ^{13}C NMR spectra of compound **9e**



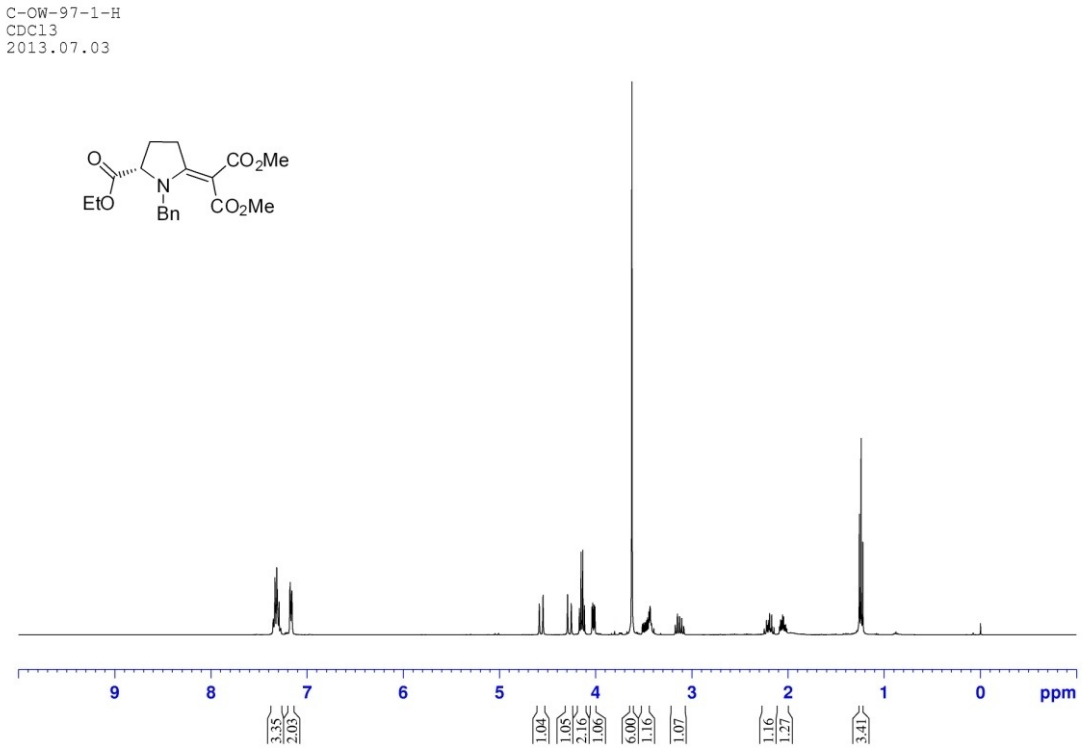


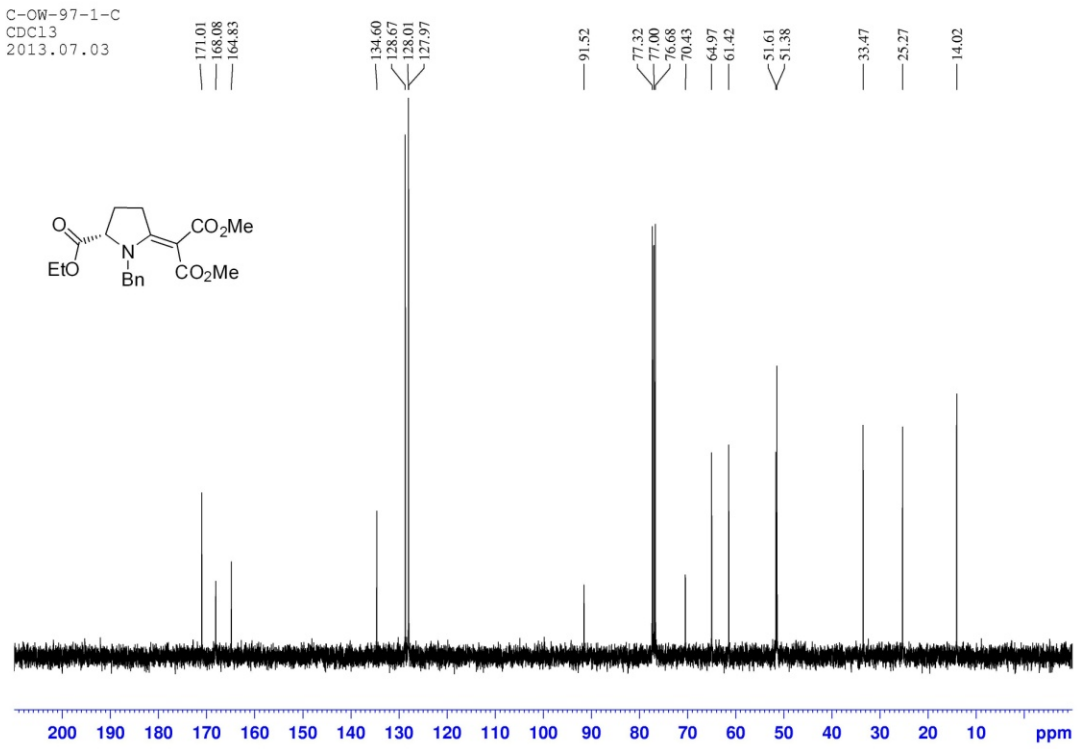
^{1}H and ^{13}C NMR spectra of compound **4b**



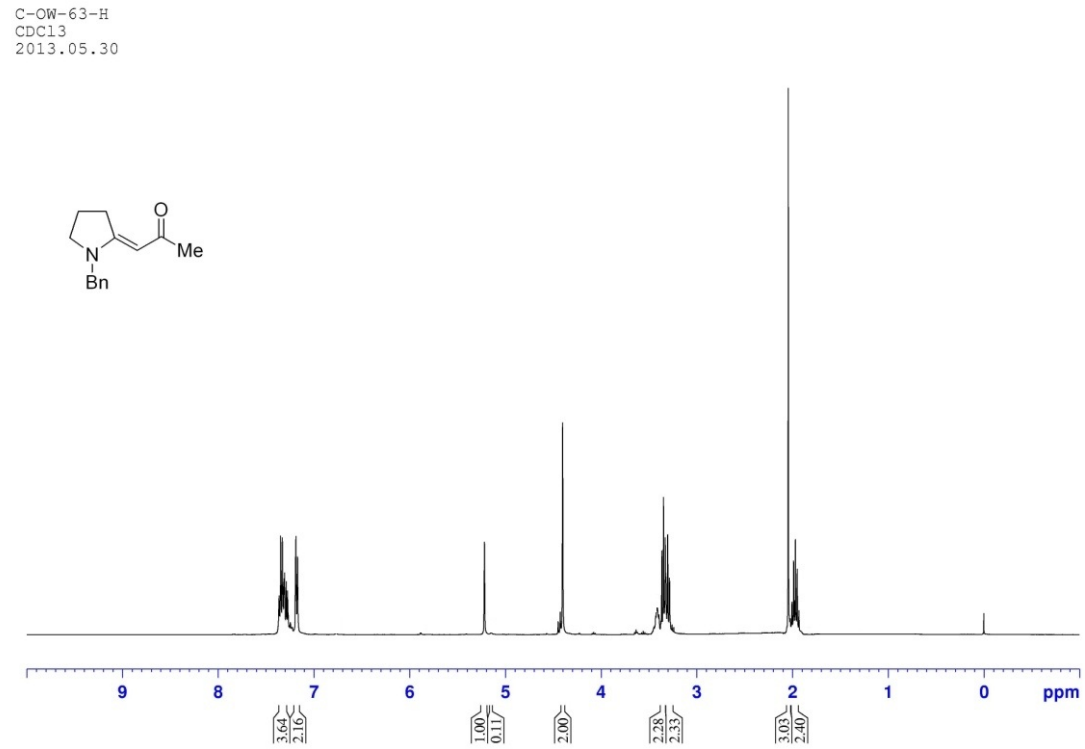


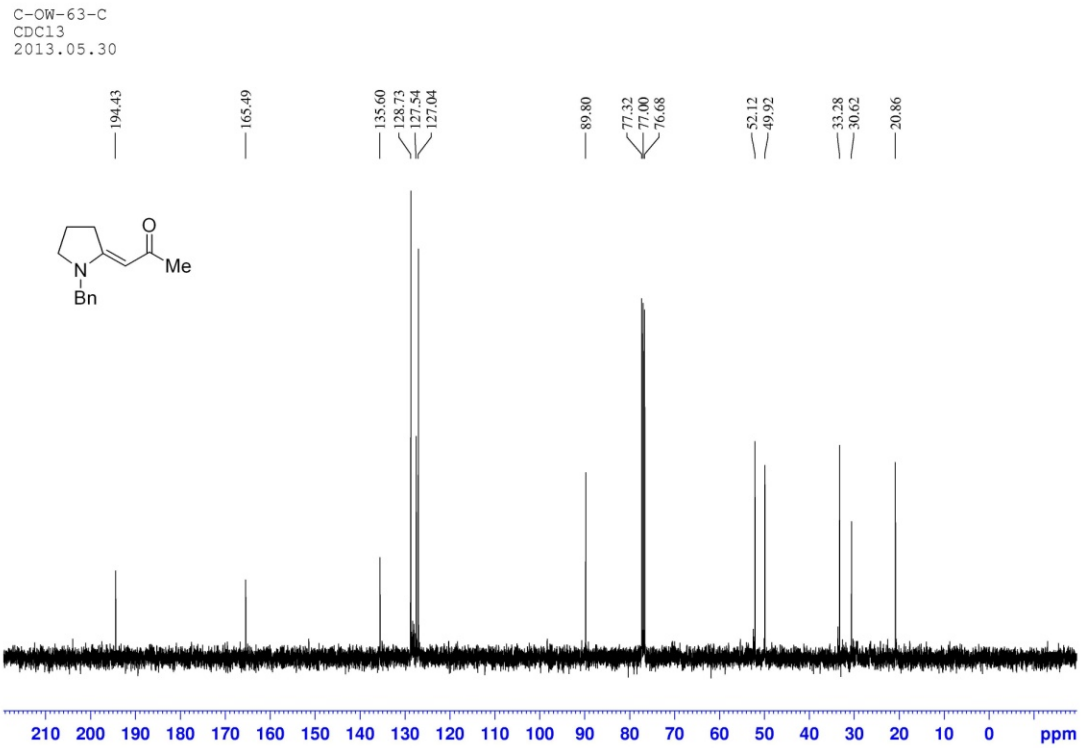
^{1}H and ^{13}C NMR spectra of compound **10**



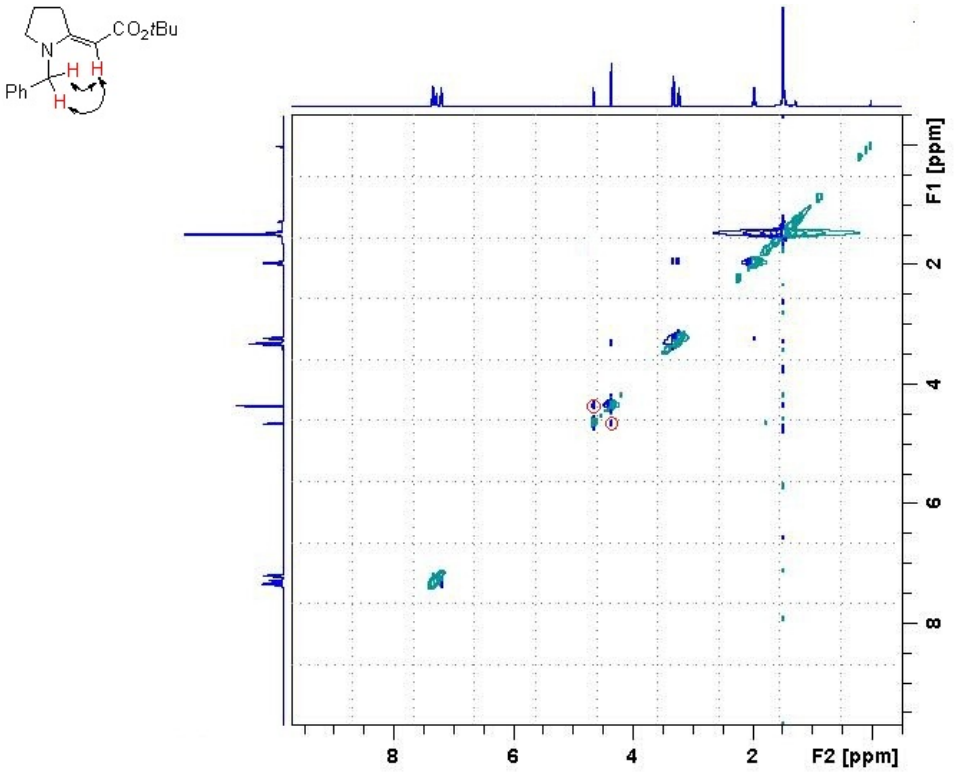


^{1}H and ^{13}C NMR spectra of compound **4**

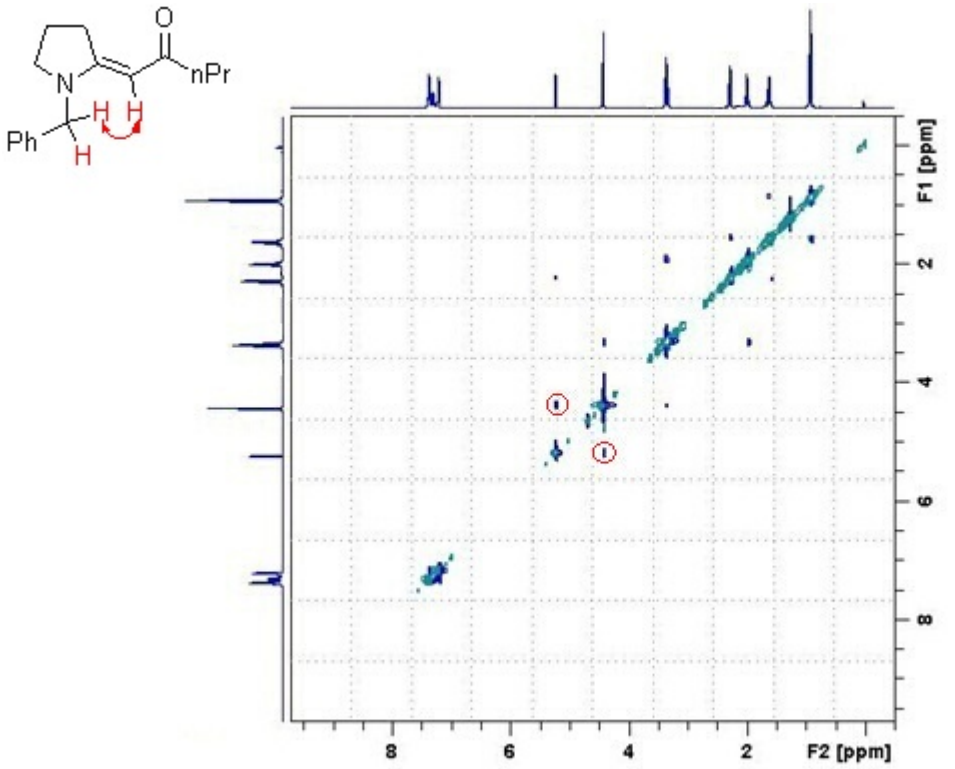




NOESY spectrum of compound **3a**



NOESY spectrum of compound **4b**



NOESY spectrum of compound **9e**