Supplementary Information for:

Site-selective, catalytic and diastereoselective sp^3 C–H hydroxylation and alkoxylation of vicinally functionalized lactams

Timothy K. Beng, Victoria Shearer, Rachel Davey, and Ivianne Redman*

Department of Chemistry, Central Washington University,
Ellensburg, WA 98926, USA
Timothy.beng@cwu.edu

Contents:

2. Experimental Section

All experiments involving air and moisture sensitive reagents such as organolithium reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ stain. Unless otherwise indicated, ^1H, ^{13}C, and DEPT-135 NMR, COSY 45, HMQC, and NOESY spectra were acquired using $CDCl_3$ or C_6D_6 solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^+ data were obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx). The lactam precursors were prepared as previously reported.[1]

General Procedure A: Catalytic hydroxylation

To a solution of lactam ester **1** (1 mmol) and CuF_2 (5 mol%) in anhydrous 2-methyltetrahydrofuran (5 mL) was added cesium carbonate (1.1 mmol, 1.1 equiv). The reaction vessel was sealed, evacuated, refilled with oxygen gas, and stirred at room temperature for the desired time period (TLC and GC-MS monitoring) under oxygen atmosphere (which was maintained with an O_2-filled balloon). The reaction mixture was diluted with an aqueous solution of hydrochloric acid (0.50 M, 10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with hexanes/EtOAc to give the pure alcohol.

General Procedure B: LAH reduction

To a 10 mL round-bottomed flask equipped with a magnetic stir bar under a N_2 atmosphere, in a 0 °C ice/water bath, was added the lactam (0.25 mmol) and THF (10 mL). $LiAlH_4$ (44 mg, 1.12 mmol) was then added portion-wise. The reaction mixture was allowed to warm to room temperature for 3 h (as judged complete by GC-MS analysis). After this time, the reaction mixture was cooled to 0 °C and quenched by slow addition of a solution of 2 N $NaOH_{(aq)}$ (1 mL). The organic layer was decanted and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over

anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the crude tertiary aminodiol, which was purified by flash chromatography on silica.

General Procedure C: **Fe-catalyzed dehydrative coupling of alcohols**

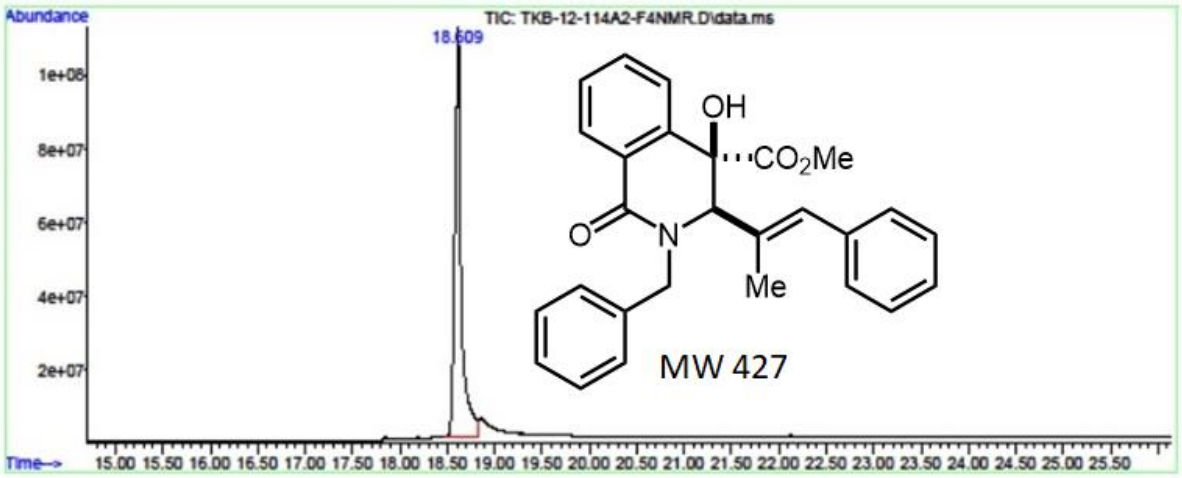
To the hydroxylated dihydroisoquinolone **2** (0.5 mmol), dissolved in 1,2-dichloroethane (2 mL), was added the primary alcohol (1.5 mmol, 3 equiv), ammonium chloride (1.3 mg, 0.025 mmol), and $Fe(OTf)_3$ (12.6 mg, 5 mol %) in a vial equipped with a magnetic stir bar, under open atmosphere. The reaction mixture was stirred at 50 °C. After completion of the reaction (TLC and GC-MS monitoring), the mixture was cooled to room temperature. The solvents were removed *in vacuo* and the crude mixture was dissolved in ethyl acetate and subjected to flash column chromatography on silica gel.

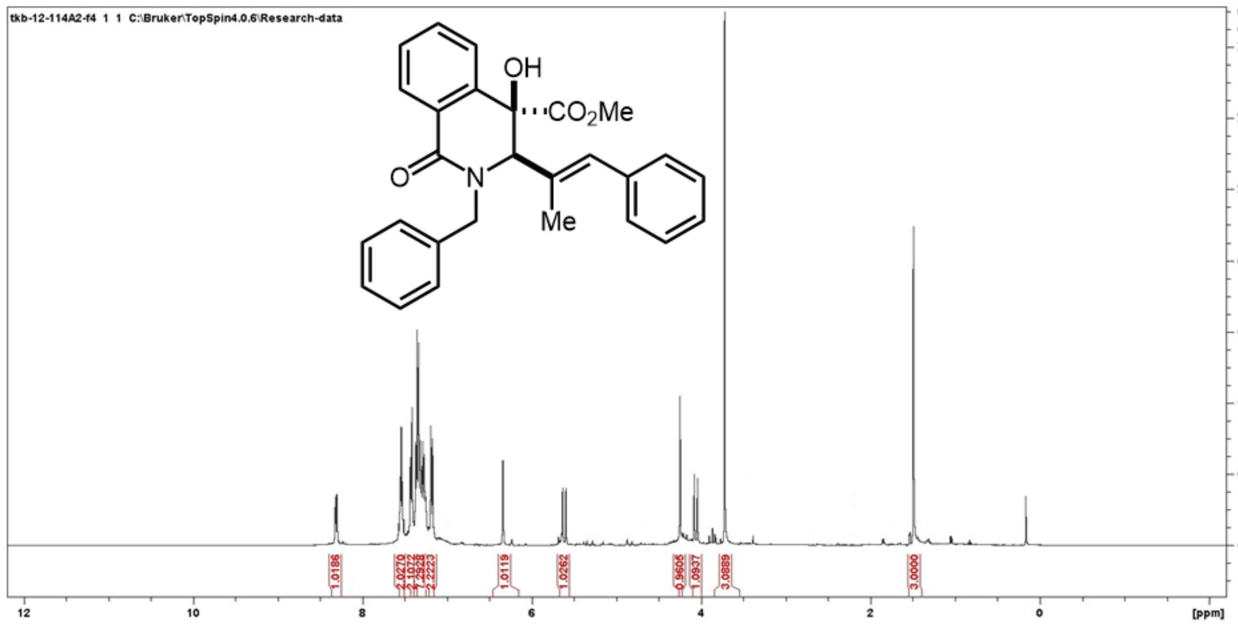
General Procedure D: **Cu-catalyzed dehydrogenative coupling**

To an oven-dried vial equipped with a stir bar was added CuCl (10.0 mg, 0.100 mmol, 20 mol%), 4,4',5,5'-tetrahydro-2,2'-bioxazole (14 mg, 0.100 mmol, 10 mol%), and NFSI (315.2 mg, 1.0 mmol, 2.0 equiv). The capped vial was placed under nitrogen followed by addition of 5 mL of a mixture of 1,2-dichloroethane and HFIP (4:1). The lactam (0.50 mmol, 1.0 equiv) dissolved in 1 mL DCE, methanol (84 μL, 2.0 mmol, 4.0 equiv) and dimethyl phosphonate (24 μL, 0.25 mmol, 0.5 equiv) were added to the septum-capped vial under nitrogen. The contents were then heated to 60 °C under stirring for the desired length of time. After completion of the reaction (TLC and GC-MS monitoring), the mixture was cooled to room temperature and triethylamine (0.5 mL) was added to quench any unreacted NFSI. The solvents were removed *in vacuo* and the crude mixture was dissolved in ethyl acetate and subjected to flash column chromatography on silica gel.

Compound 2a

Prepared from ester **1a** (411.5 mg, 1.0 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Oily substance. Yield = 393 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 6.9, 2.1, 1H), 7.52 – 7.40 (m, 2H), 7.39 – 7.13 (m, 11H), 6.36 (s, 1H), 5.56 (d, *J* = 15.1 Hz, 1H), 4.17 (s, 1H), 4.08 (d, *J* = 15.1 Hz, 1H), 3.85 (br s, 1H), 3.64 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.96, 163.16, 136.58, 136.41, 135.82, 134.07, 132.36, 132.07, 129.57, 129.22, 129.04, 129.01, 128.99, 128.77, 128.70, 128.67, 128.65, 128.59, 128.48, 128.43, 128.40, 128.37, 127.61, 127.38, 127.06, 76.97, 74.27, 53.32, 48.18, 13.60. HRMS calc for $C_{27}H_{25}NO_4$ 427.1784, found 427.1788. FTIR (KBr): 3384.5506, 2924.8333, 1642.2515, 1494.9545, 1448.8548, 1427.0419, 1393.4602 1361.6968, 1328.7144, 1289.7737, 1223.6425, 1198.9141, 1130.0001, 1074.1578, 1030.4745, 988.561, 966.1662, 925.5022, 741.6755, 693.4562.

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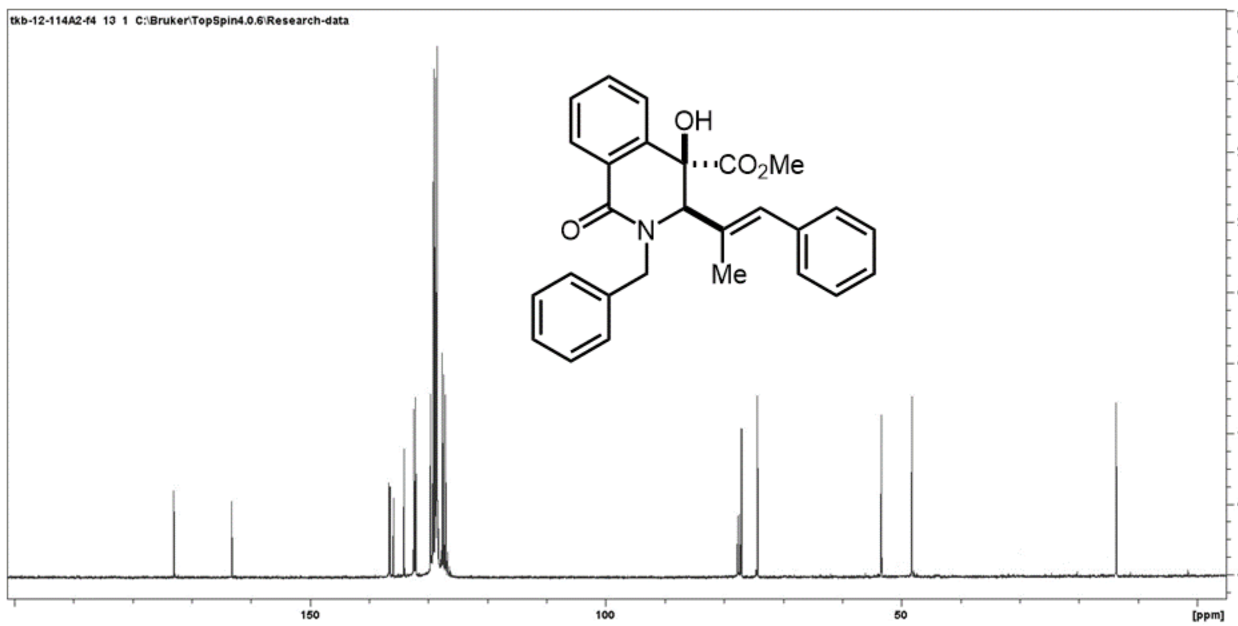
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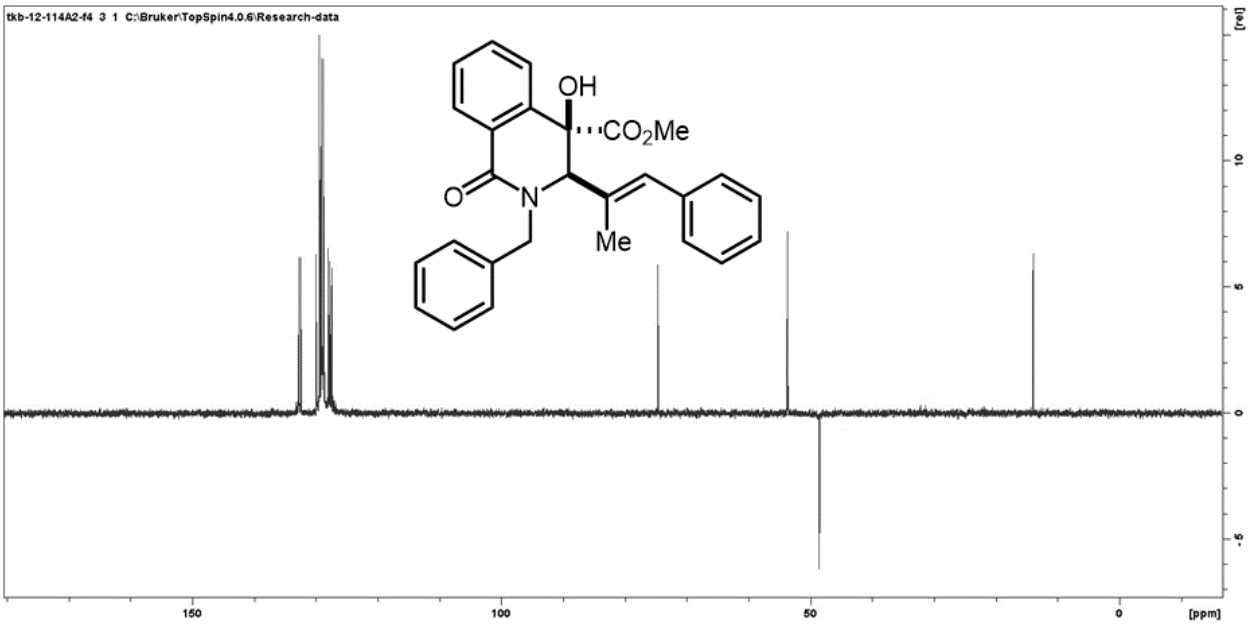
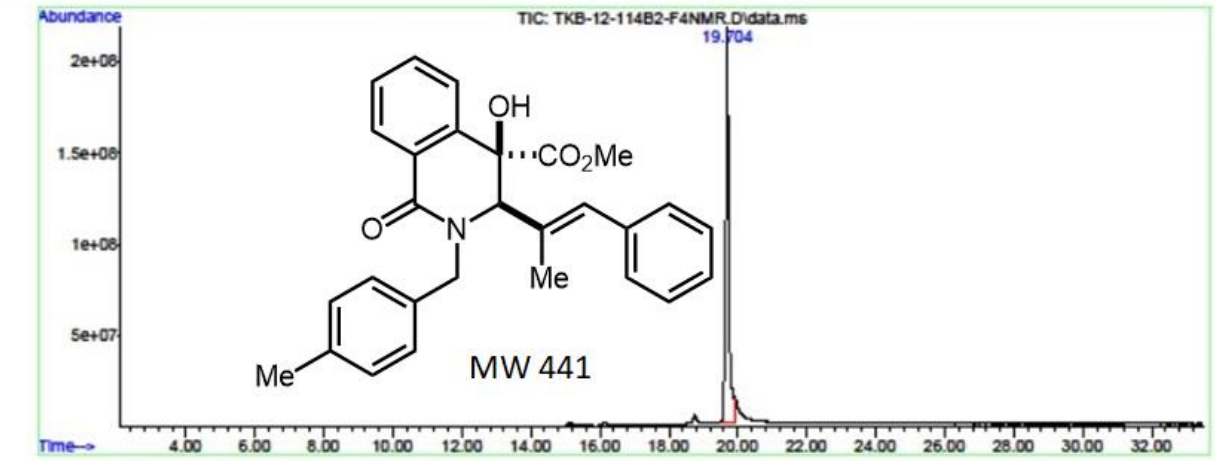


Compound 2b

Prepared from ester **1b** (425.5 mg, 1.0 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Oily substance. Yield = 384 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 6.9, 2.1, 1H), 7.53 – 7.48 (m, 2H), 7.45 – 7.24 (m, 6H), 7.27 – 7.13 (m, 4H), 6.35 (s, 1H), 5.59 (d, *J* = 14.9 Hz, 1H), 4.28 (s, 1H), 4.22 (br. s, 1H), 4.18 (d, *J* = 14.9 Hz, 1H), 3.74 (s, 3H), 2.38 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.89, 163.12, 137.21, 136.48, 135.85, 134.18, 133.46, 132.31, 131.99, 129.52, 129.40, 129.37, 129.27, 129.05, 128.74, 128.65, 128.57, 128.43, 128.39, 127.35, 127.14, 77.02, 74.09, 53.26, 48.01, 21.29, 13.57. HRMS calc for $C_{28}H_{27}NO_4$ 441.1940, found 441.1949. FTIR (KBr): 3489.1994. 3391.272, 3060.2295, 3027.4261, 2924.038, 1724.2643, 1646.3958, 1494.2931, 1474.3358, 1452.8606, 1432.4058, 1361.9422, 1342.0932, 265.3056, 1205.6142, 1140.2378, 1071.7973, 1028.3461, 996.4523, 924.2151, 735.4288, 700.2396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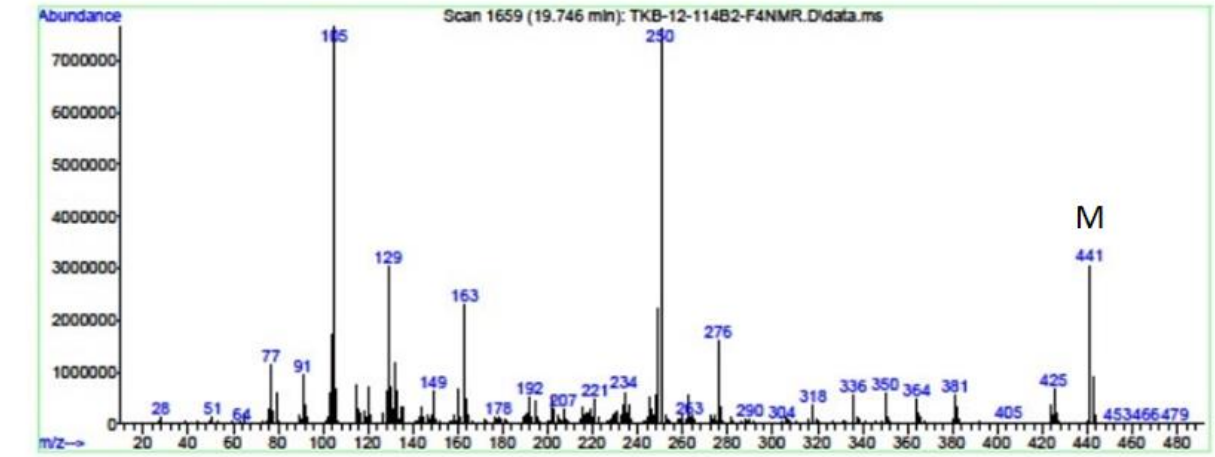
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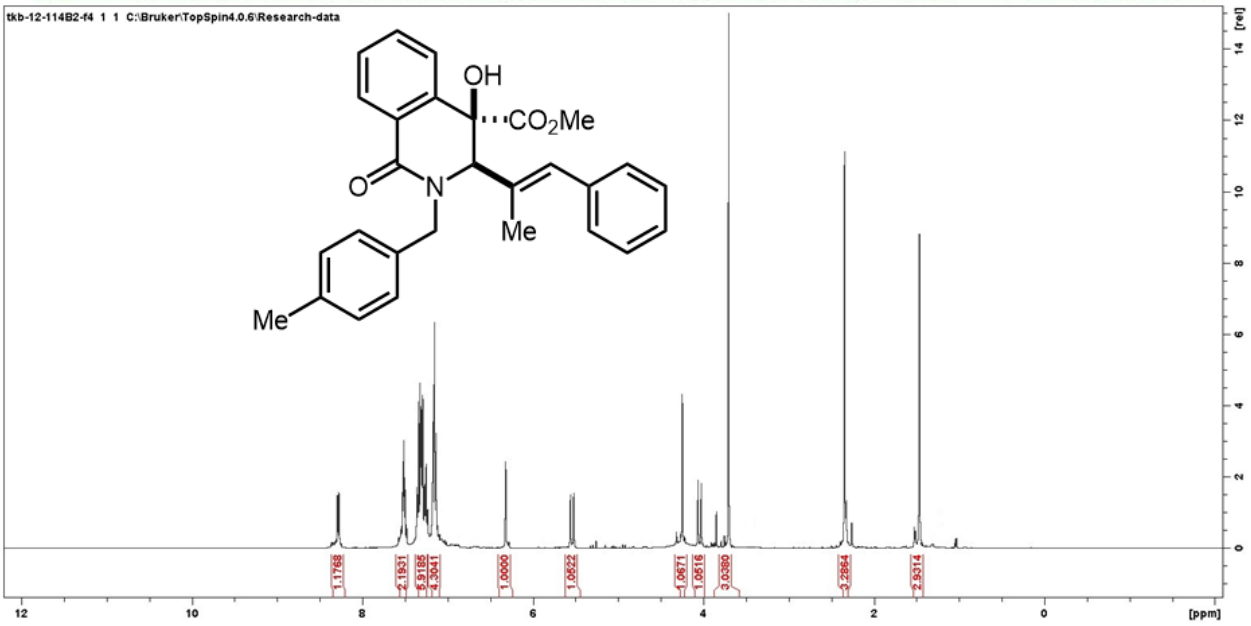
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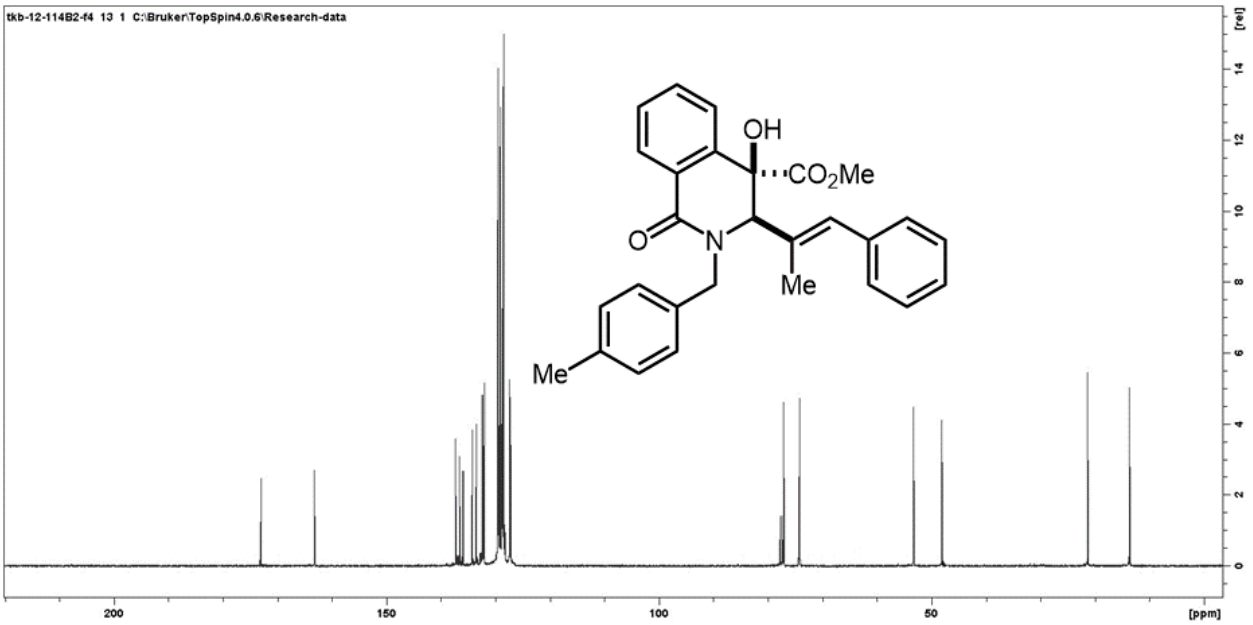
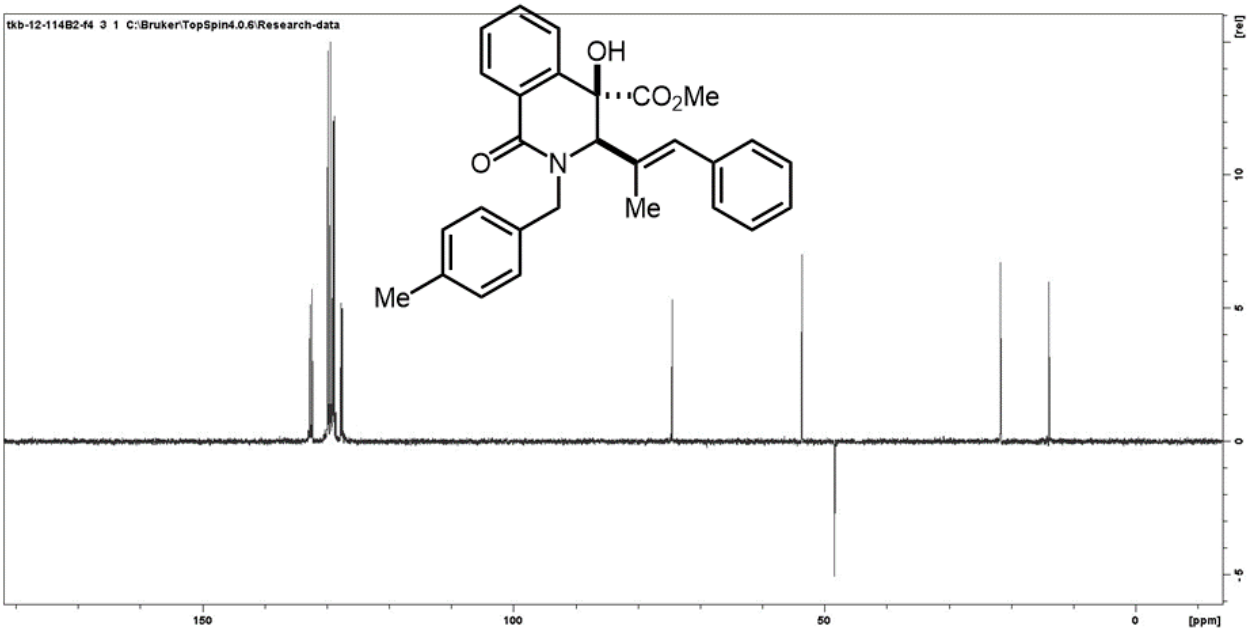
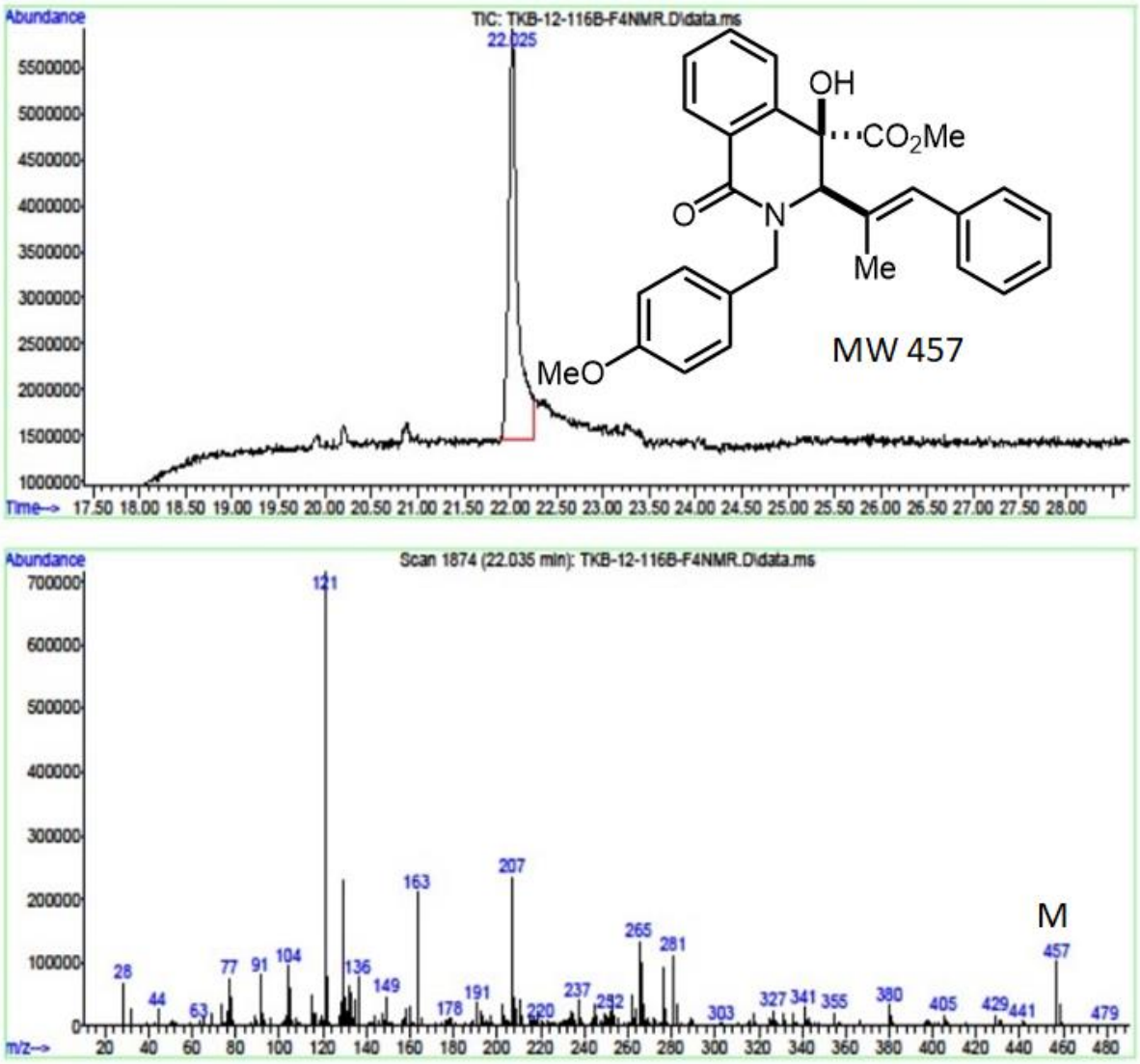


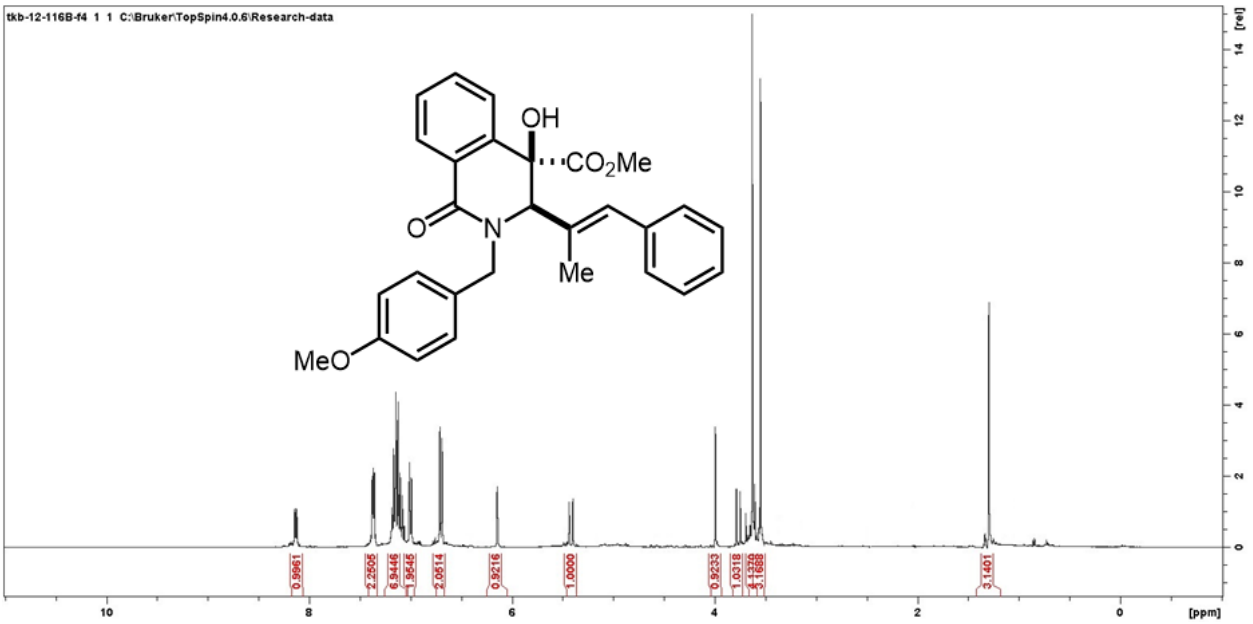


Compound 2c

Prepared from ester **1c** (441.5 mg, 1.0 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Oily substance. Yield = 407 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 6.9, 2.1, 1H), 7.38 (d, *J* = 5.6 Hz, 2H), 7.23 – 7.13 (m, 7H), 7.13 – 7.04 (m, 2H), 6.69 (d, *J* = 5.6 Hz, 2H), 6.15 (s, 1H), 5.42 (d, *J* = 14.8 Hz, 1H), 4.00 (s, 1H), 3.77 (d, *J* = 14.8 Hz, 1H), 3.63 (s, 3H), 3.61 (s, 1H), 3.55 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.08, 162.97, 159.13, 136.41, 135.58, 134.11, 132.29, 131.94, 129.89, 129.58, 129.35, 129.02, 128.78, 128.47, 128.38, 127.35, 126.92, 114.10, 76.84, 73.90, 55.35, 53.34, 47.43, 13.59. HRMS calc for $C_{28}H_{27}NO_5$ 457.1889, found 457.1883. FTIR (KBr): 3384.5368, 2972.9933, 2932.8937, 1638.2038, 1449.1308, 1364.7192, 1290.2159, 1270.3054, 1247.8533, 1206.5967, 1179.918, 1131.1074, 1071.4274, 994.4373, 924.8386, 881.7598, 797.4882, 700.0535

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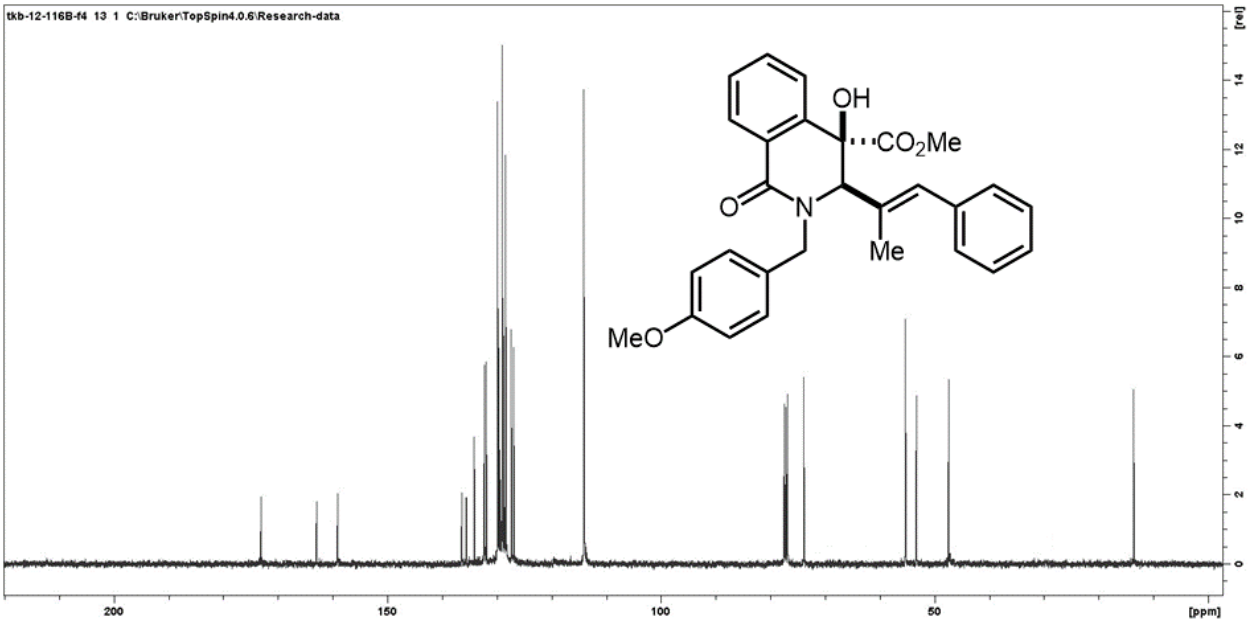
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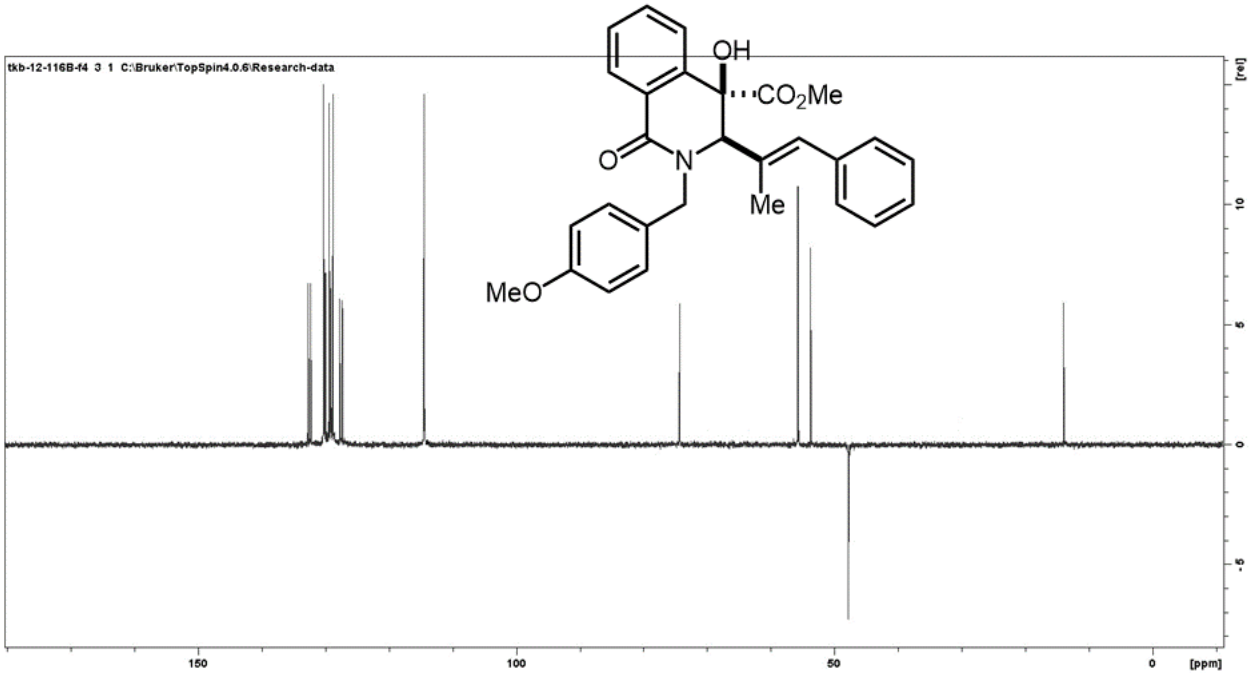
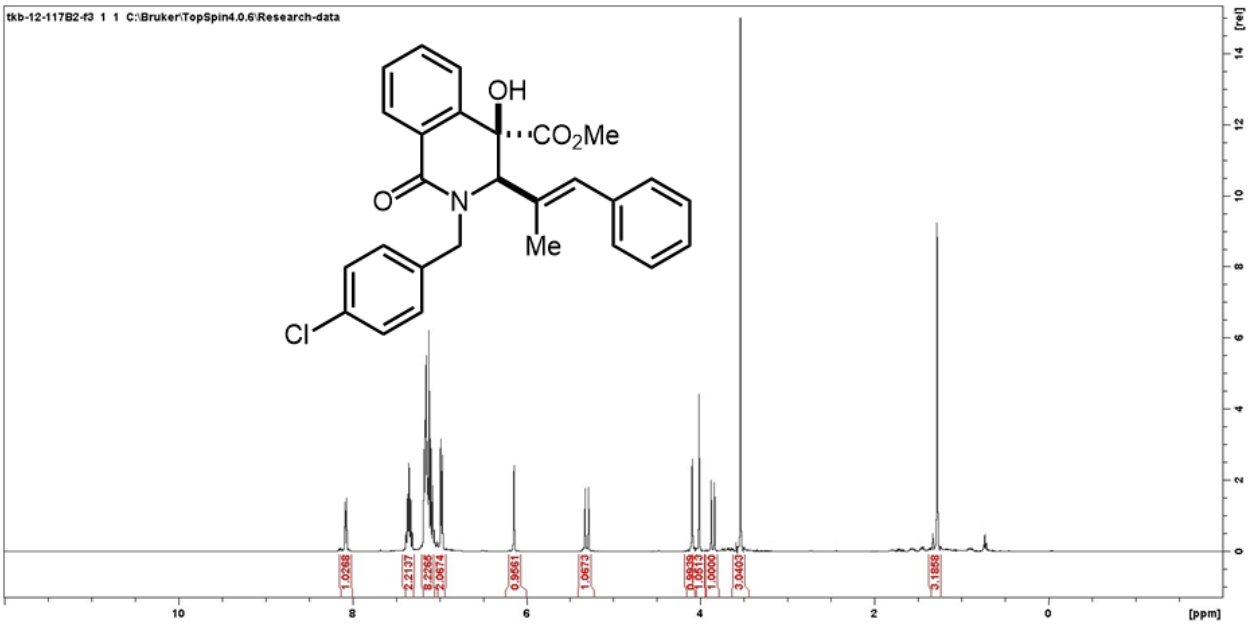


Compound 2d

Prepared from ester **1d** (223 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Oily substance. Yield = 184.8 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 6.8, 2.2, 1H), 7.35 – 7.32 (m, 2H), 7.21 – 7.12 (m, 8H), 6.98 (dd, *J* = 7.0, 1.8 Hz, 2H), 6.25 (s, 1H), 5.31 (d, *J* = 15.2 Hz, 1H), 4.10 (s, 1H), 4.02 (s, 1H), 3.86 (d, *J* = 15.2 Hz, 1H), 3.54 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.86, 163.15, 136.26, 135.82, 135.21, 133.95, 133.36, 132.46, 132.13, 129.81, 129.61, 129.06, 129.00, 128.82, 128.74, 128.44, 127.45, 127.04, 76.93, 74.56, 53.35, 47.65, 13.56. HRMS calc for $C_{27}H_{24}ClNO_4$ 461.1394, found 461.1399. FTIR (KBr): 3384.3862, 3009.7533, 2933.6078, 1647.735, 1607.2444, 1577.183, 1512.0128, 1454.2907, 1427.6278, 1359.8311, 1299.2028, 1250.9581, 1176.0437, 1151.5694, 1119.6948, 1031.3279, 990.3239, 927.8622, 825.4347, 765.0418, 749.7978.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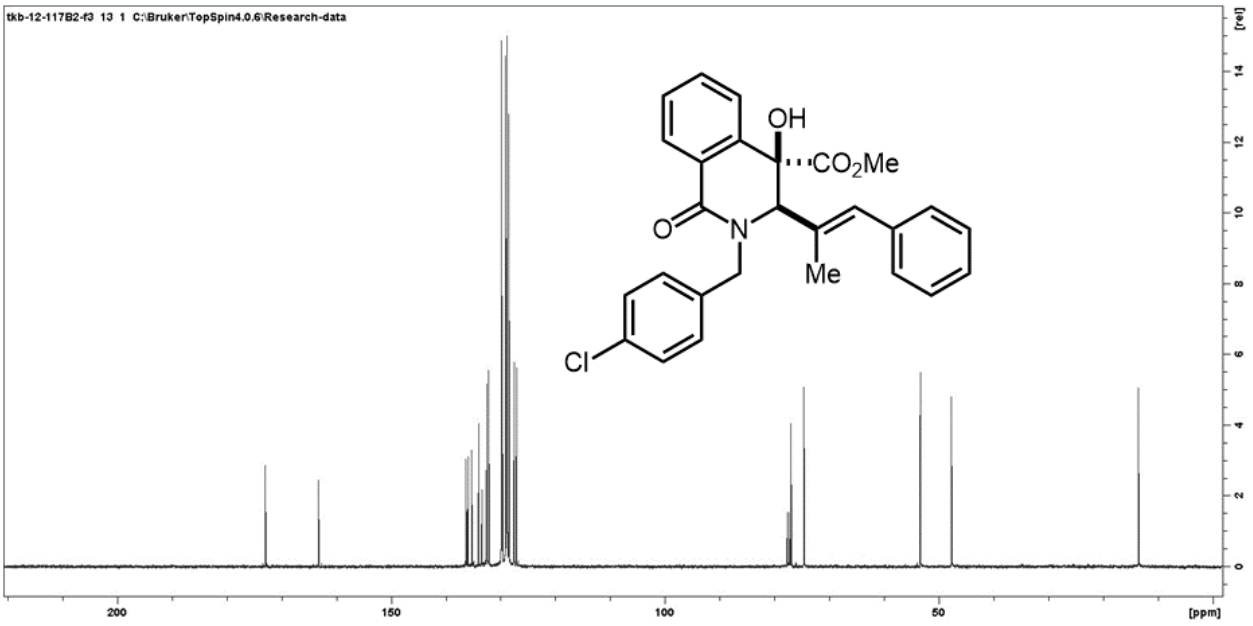
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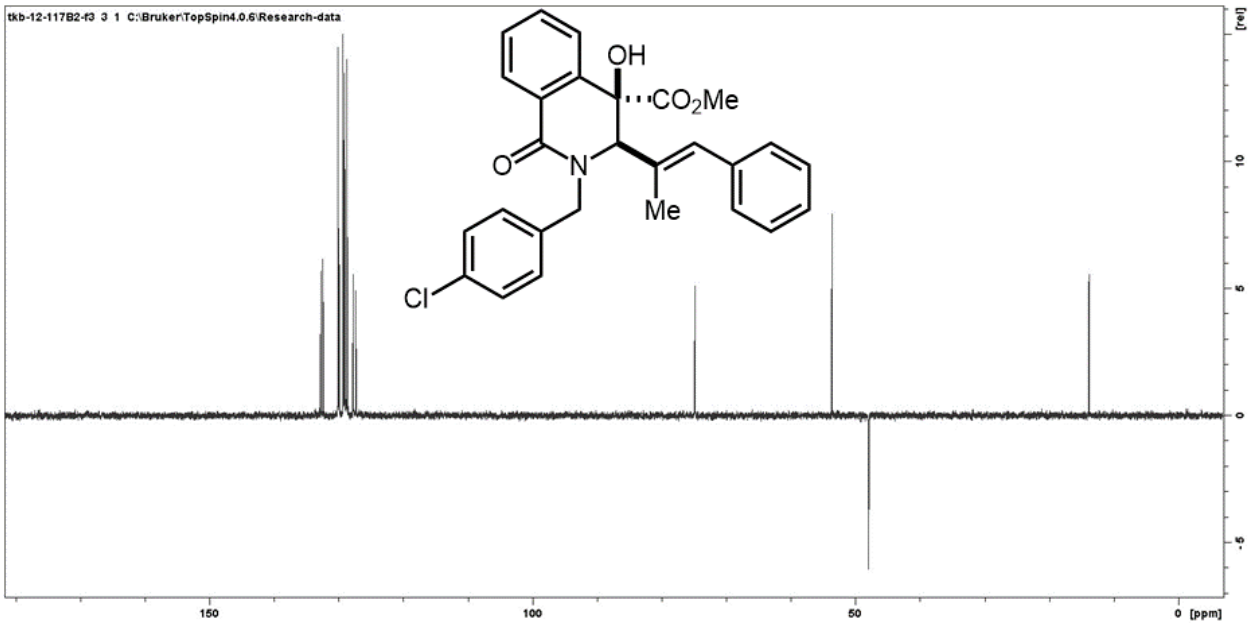
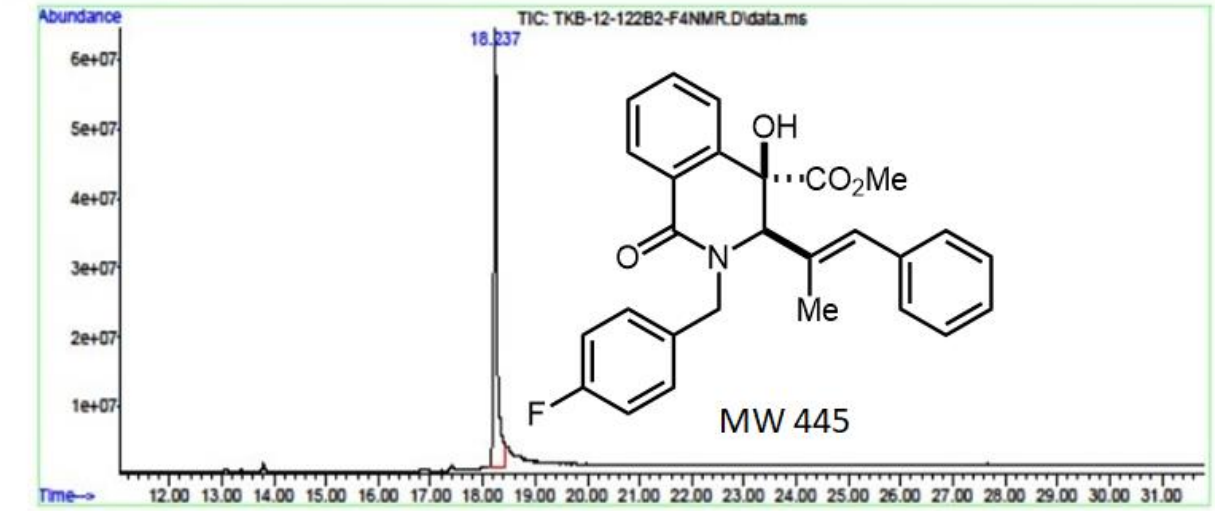


Compound 2e

Prepared from ester **1e** (214.7 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Oily substance. Yield = 171.3 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 6.8, 2.2, 1H), 7.44 – 7.39 (m, 2H), 7.35 – 7.14 (m, 8H), 7.18 – 7.07 (m, 2H), 6.16 (s, 1H), 5.43 (d, *J* = 15.0 Hz, 1H), 3.98 (s, 1H), 3.81 (d, *J* = 15.0 Hz, 1H), 3.57 (s, 3H), 3.28 (s, 1H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.09, 163.57, 163.08, 161.13, 136.26, 135.61, 133.93, 132.44, 132.30, 132.27, 132.09, 130.13, 130.10, 130.05, 130.02, 129.67, 129.45, 129.20, 129.00, 128.82, 128.70, 128.55, 128.52, 128.44, 127.46, 126.84, 126.54, 115.67, 115.45, 76.81, 74.34, 53.44, 47.35, 13.61. HRMS calc for $C_{27}H_{24}FNO_4$ 445.1689, found 445.1685. FTIR (KBr): 3391.475, 2971.495, 2923.9815, 1644.4038, 1491.4705, 1446.8961, 1429.3142, 1391.6056, 1362.4703 1318.9377, 1292.671, 1268.871, 1223.0439, 1199.5844, 1151.3831, 1117.7388, 993.1353, 905.3314, 744.2027, 699.8784.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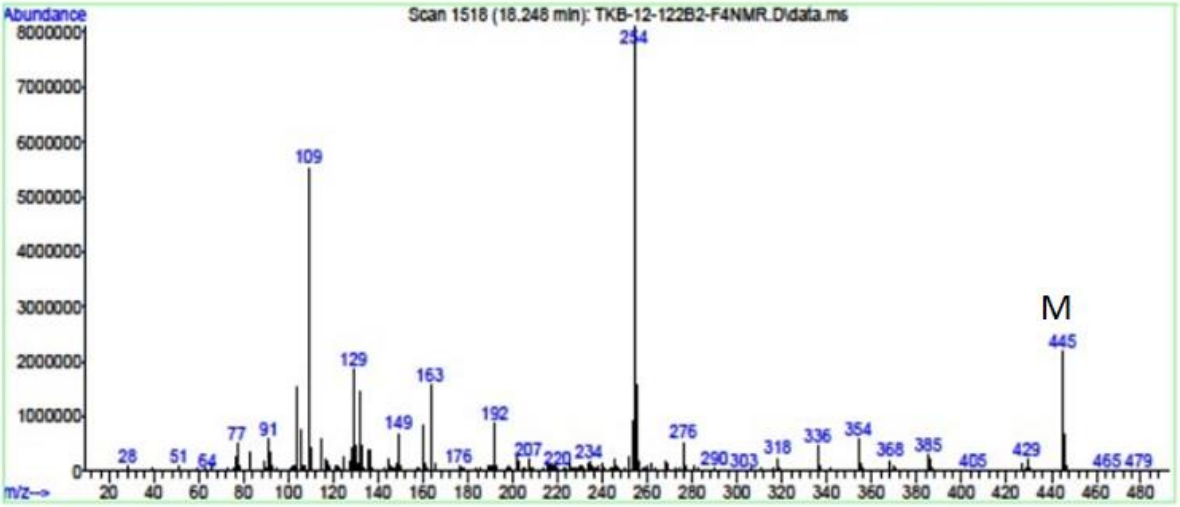
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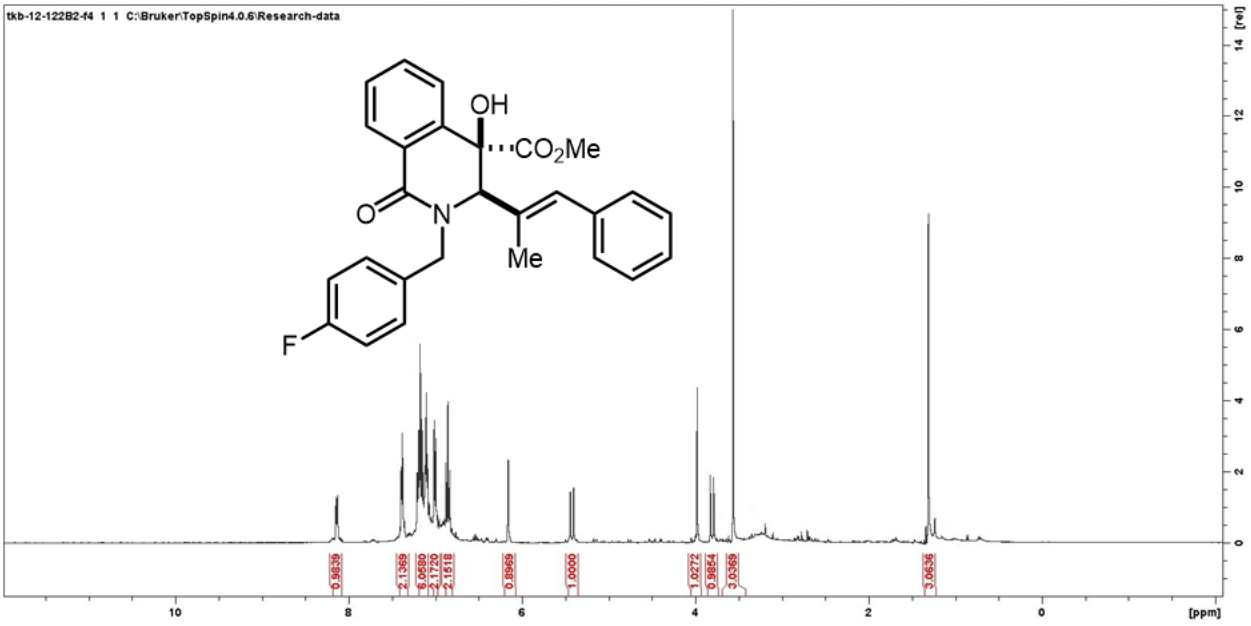
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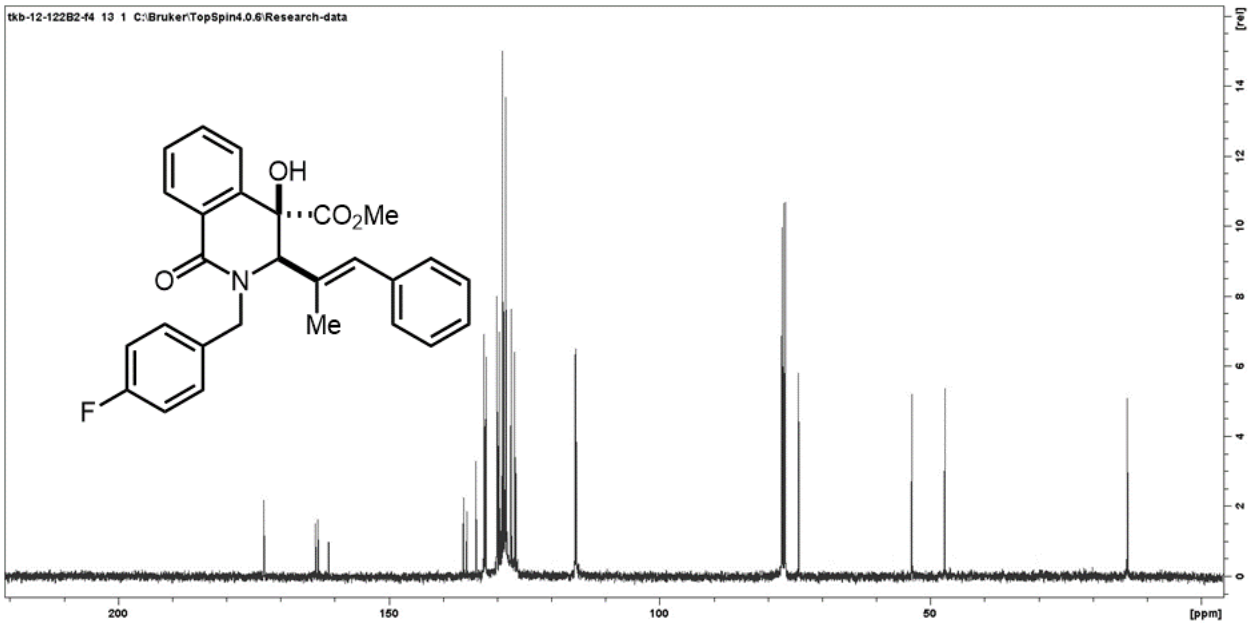
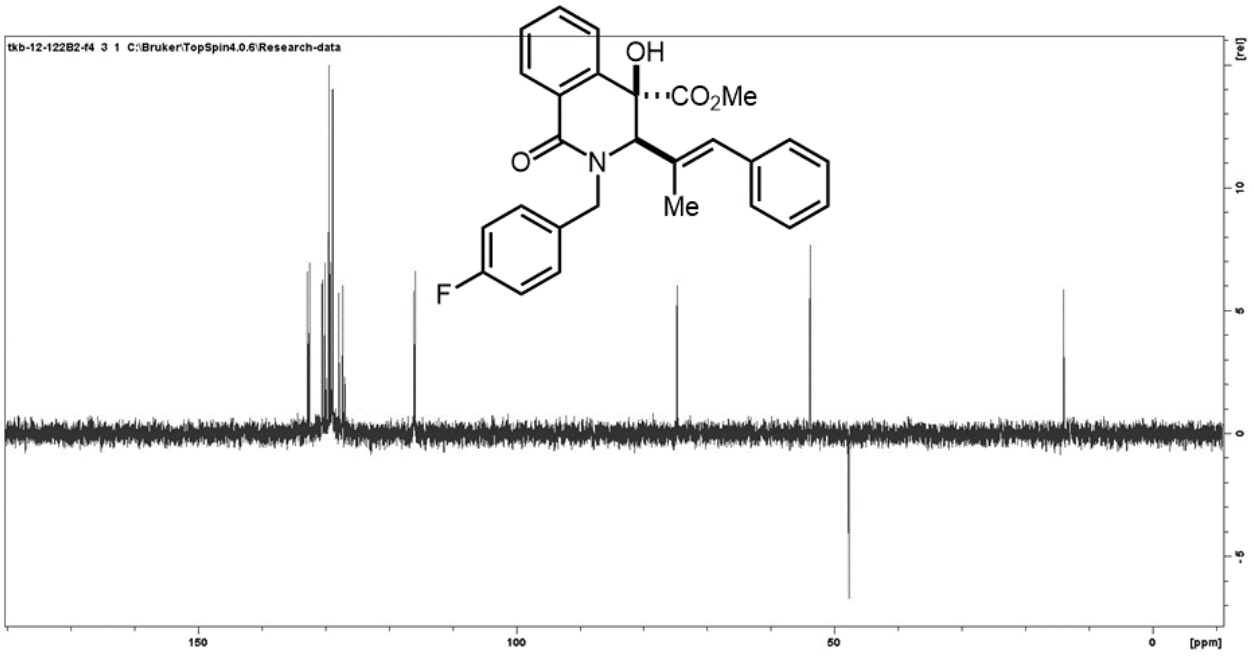
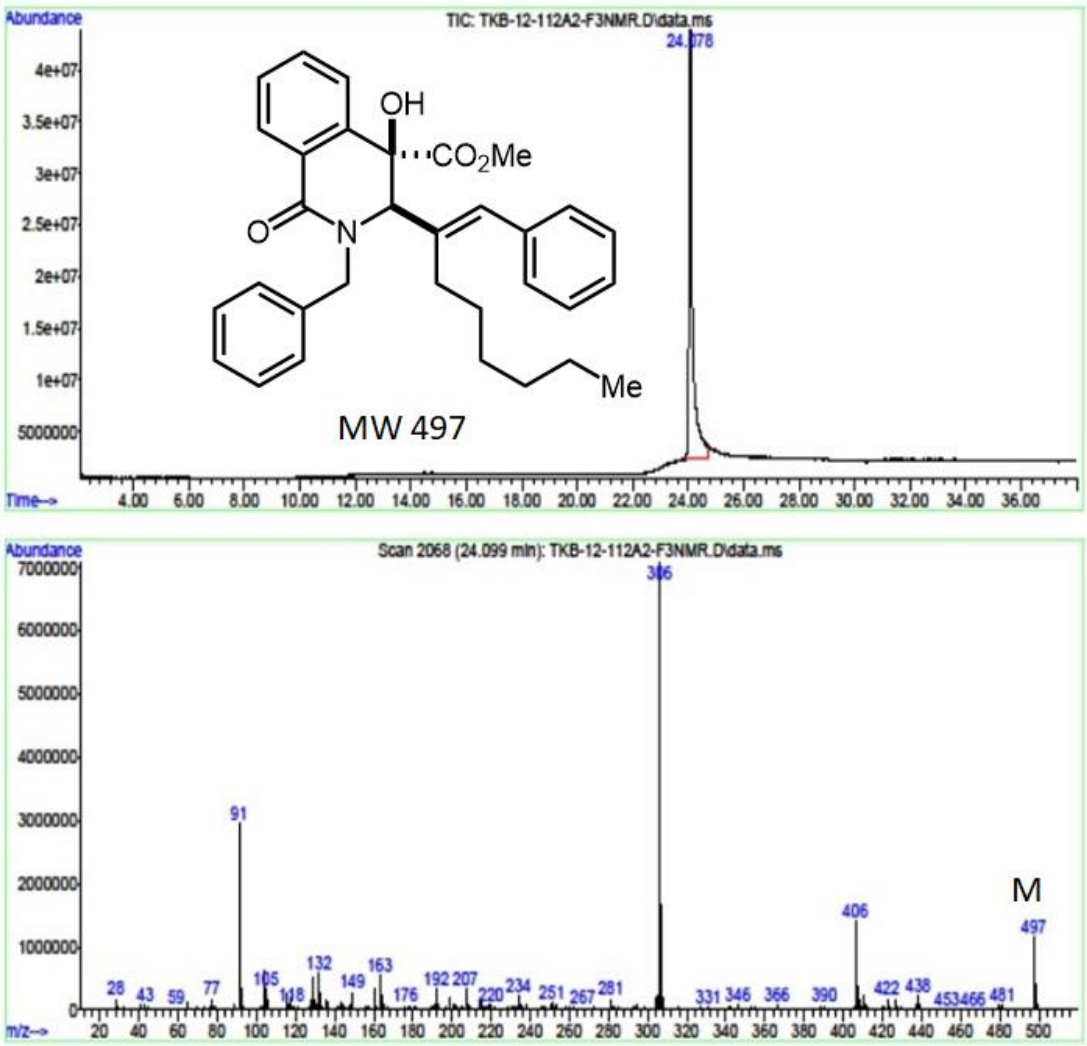


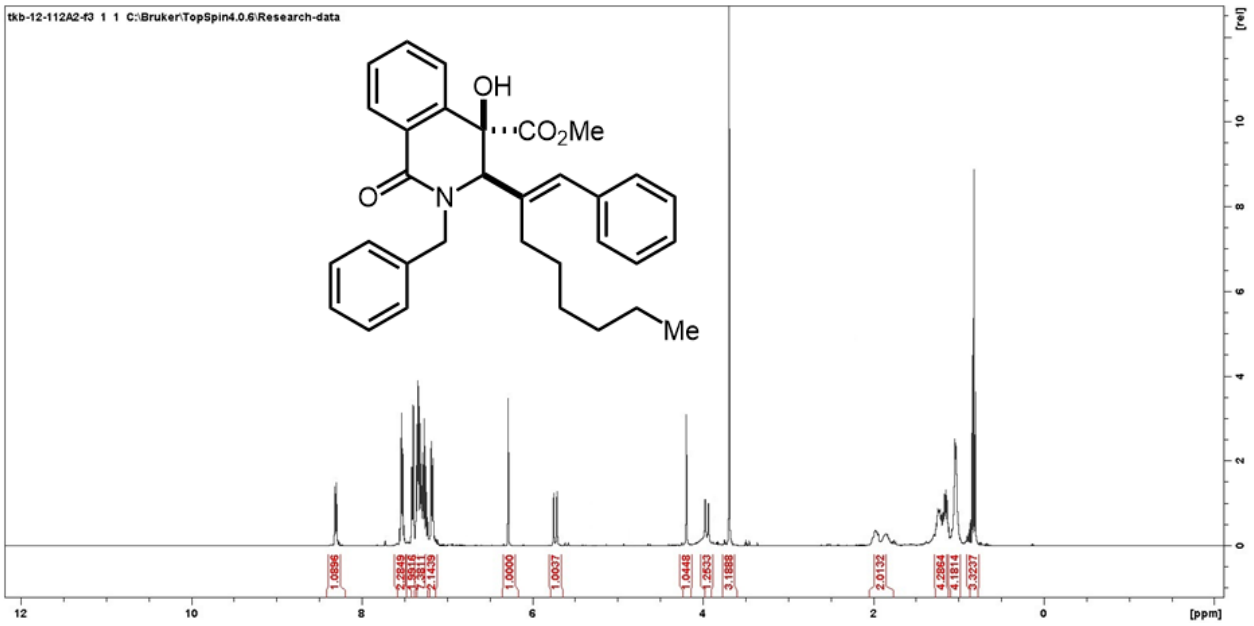


Compound 2f

Prepared from ester **1f** (241 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (85:15). Oily substance. Yield = 211 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 6.7, 2.3, 1H), 7.55 – 7.51 (m, 2H), 7.38 – 7.22 (m, 9H), 7.20 – 7.13 (m, 2H), 6.32 (s, 1H), 5.77 (d, *J* = 15.2 Hz, 1H), 4.23 (s, 1H), 3.99 (d, *J* = 15.3 Hz, 1H), 3.89 (br. s, 1H), 3.63 (s, 3H), 1.99 – 1.81 (m, 2H), 1.38 – 1.15 (m, 4H), 1.08 – 0.91 (m, 4H), 0.67 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.10, 162.91, 138.45, 136.61,

136.50, 135.87, 132.33, 132.06, 129.57, 129.04, 128.78, 128.76, 128.72, 128.62, 128.59, 128.53, 128.23, 127.54, 127.38, 127.00, 77.24, 63.11, 53.29, 47.94, 31.10, 29.68, 28.67, 22.55, 14.12. HRMS calc for $C_{32}H_{35}NO_4$ 497.2566, found 497.2570. FTIR (KBr): 3389.6399, 2934.2038, 1721.2424, 1652.179, 1607.1619, 1511.3616, 1448.8653, 1414.9522, 1341.3255, 1298.4034, 1245.2497, 1180.2533, 1139.4586, 1075.9955, 1032.9326, 999.444, 926.6047, 832.0003, 734.9532, 702.6972.

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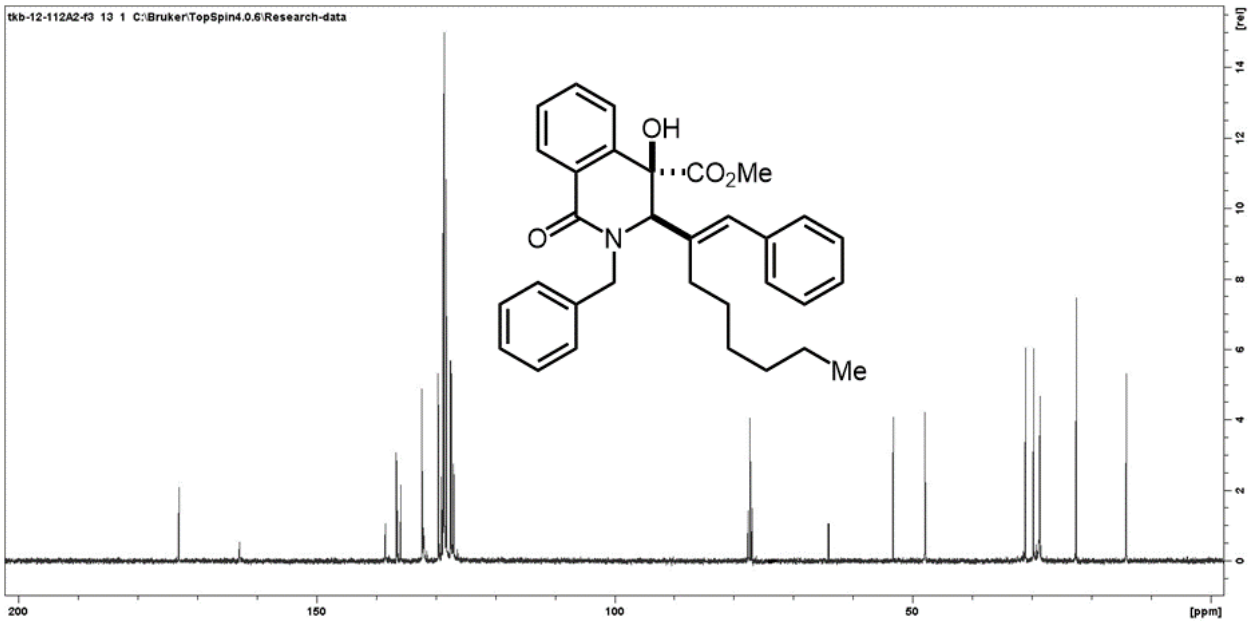
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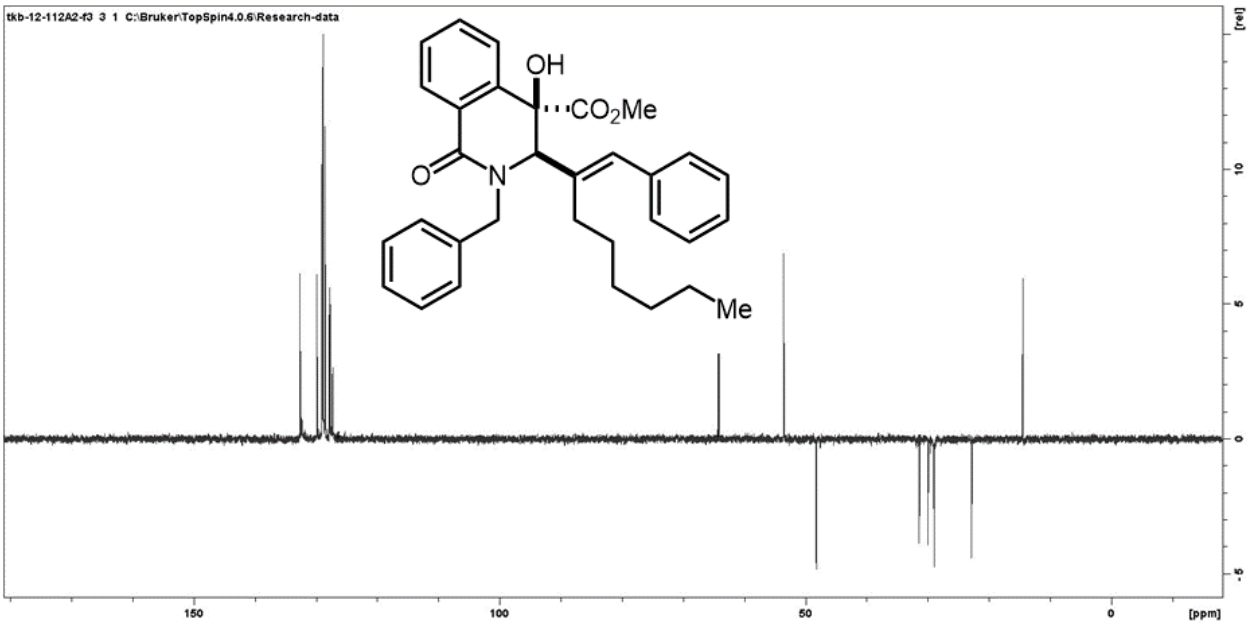
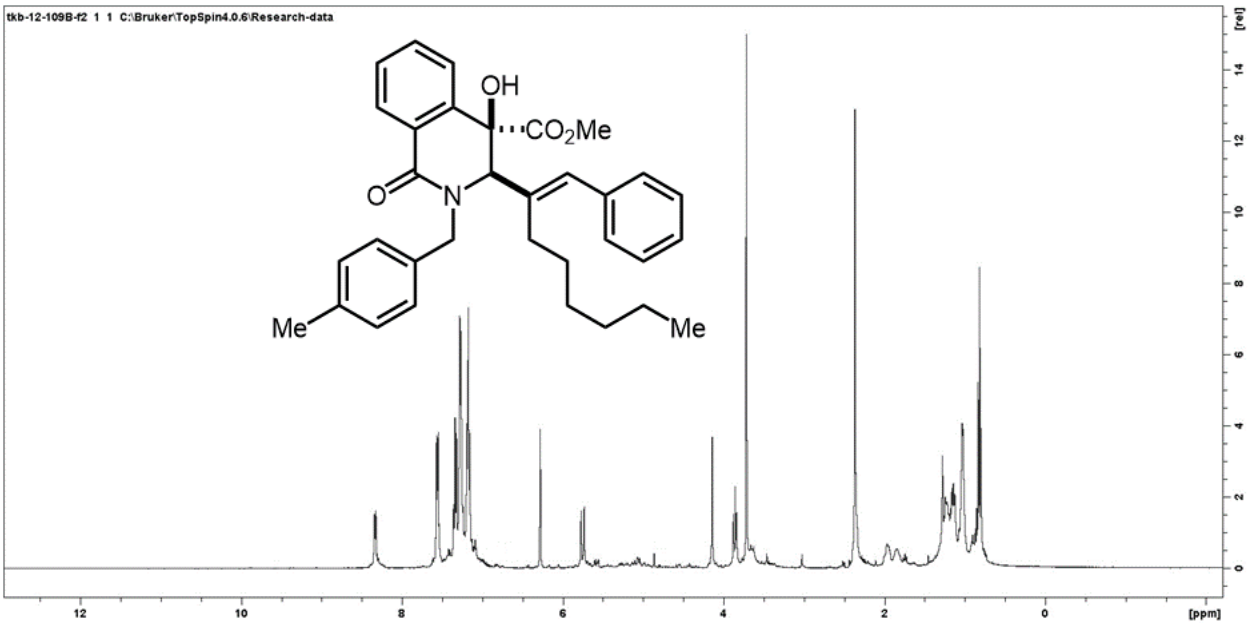


Compound 2g

Prepared from ester **1g** (247.5 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (85:15). Oily substance. Yield = 207 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 6.7, 2.3, 1H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.43 – 7.24 (m, 10H), 6.31 (s, 1H), 5.78 (d, *J* = 15.1 Hz, 1H), 4.17 (s, 1H), 3.83 (d, *J* = 15.1 Hz, 1H), 3.79 (br. s, 1H), 3.74 (s, 3H), 2.39 (s, 3H), 2.04 – 1.88 (m, 2H), 1.38 – 1.15 (m, 4H), 1.08 – 0.91 (m, 4H), 0.67 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.20, 162.74, 138.46, 137.21, 136.50, 135.65, 133.41, 132.28, 129.60, 129.42, 129.27, 129.25, 129.14, 128.93, 128.82, 128.75, 128.68, 128.63, 128.57, 128.51, 128.31, 128.26, 127.35, 126.91, 76.81, 63.92, 53.31, 47.49, 31.09, 29.68, 28.65, 22.53, 21.25, 14.09. HRMS calc for $C_{33}H_{37}NO_4$ 511.2723, found 511.2726.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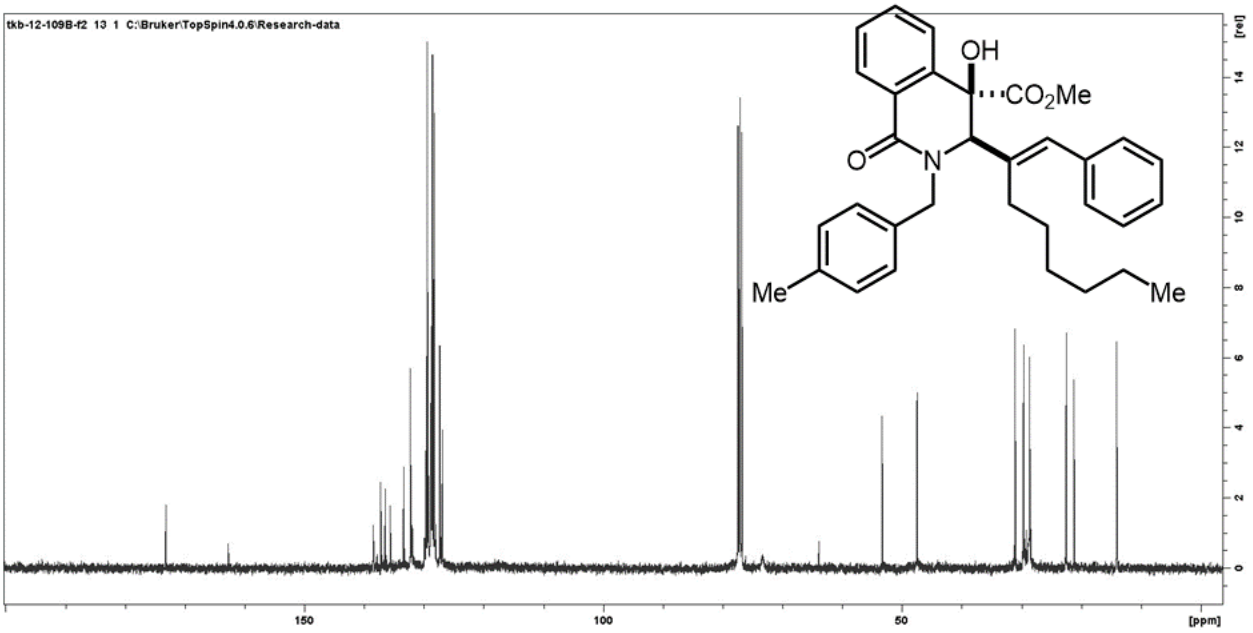
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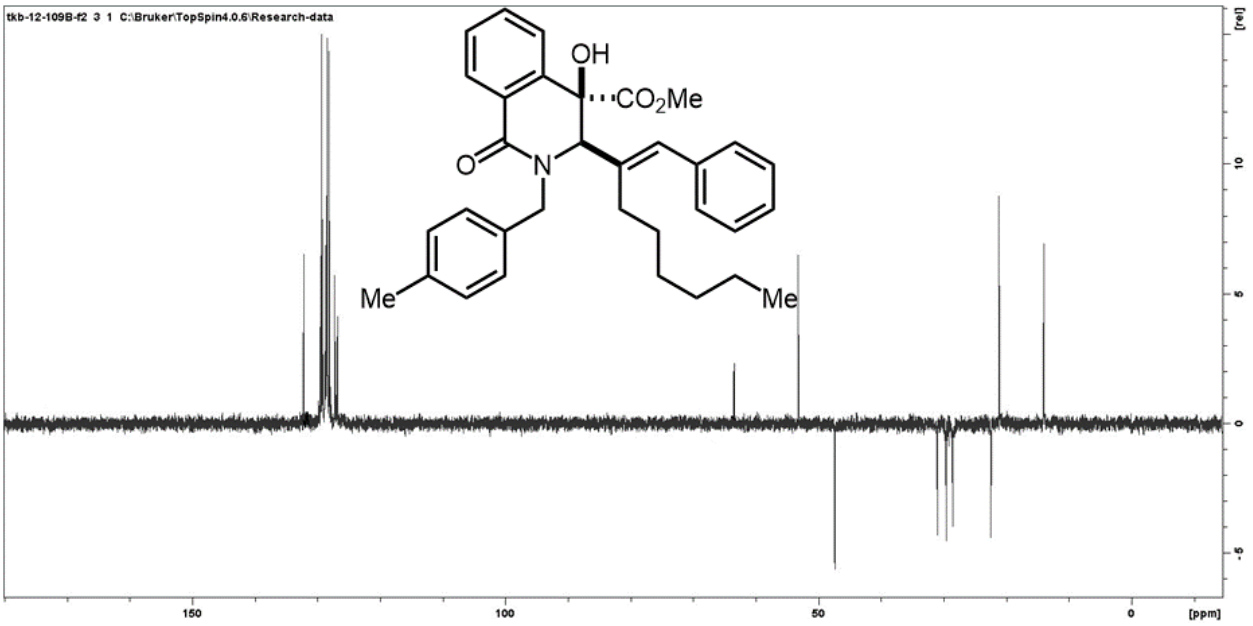
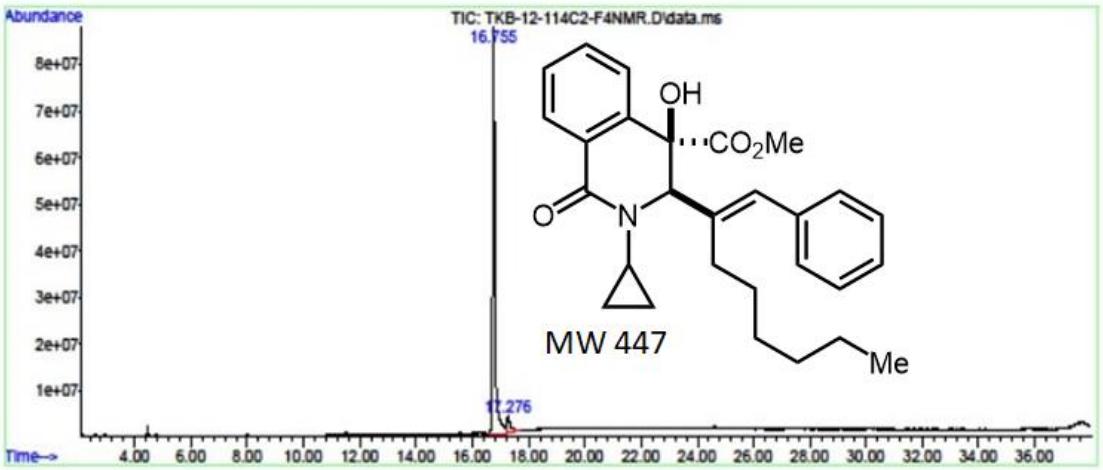


Compound 2h

Prepared from ester **1h** (215.5 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Oily substance. Yield = 167.6 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 6.9, 2.2, 1H), 7.48 – 7.39 (m, 2H), 7.34 – 7.13 (m, 6H), 6.39 (s, 1H), 4.36 (s, 1H), 3.70 (s, 1H), 3.67 (s, 3H), 2.65 (tt, *J* = 7.0, 4.0 Hz, 1H), 1.89 – 1.78 (m, 2H), 1.38 – 0.95 (m, 10H), 0.88 – 0.71 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.25, 164.11, 139.02, 136.76, 135.52, 132.28, 131.16, 129.43, 129.40, 129.36, 128.65, 128.63, 128.60, 128.55, 128.44, 128.31, 128.27, 127.20, 127.18, 75.82, 71.59, 53.29, 31.11, 29.72, 29.64, 28.69, 22.55, 14.09, 9.71, 6.76. HRMS calc for $C_{28}H_{33}NO_4$ 447.2410, found 447.2414.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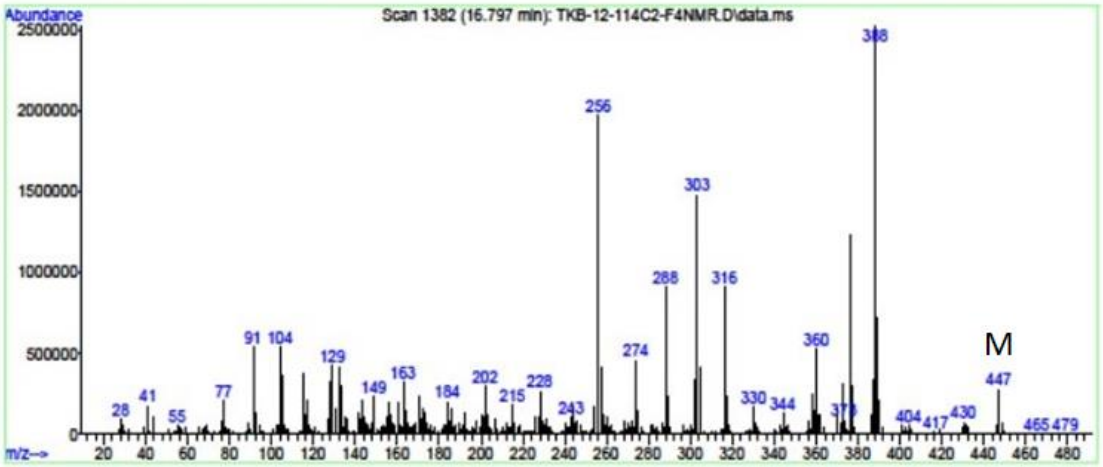
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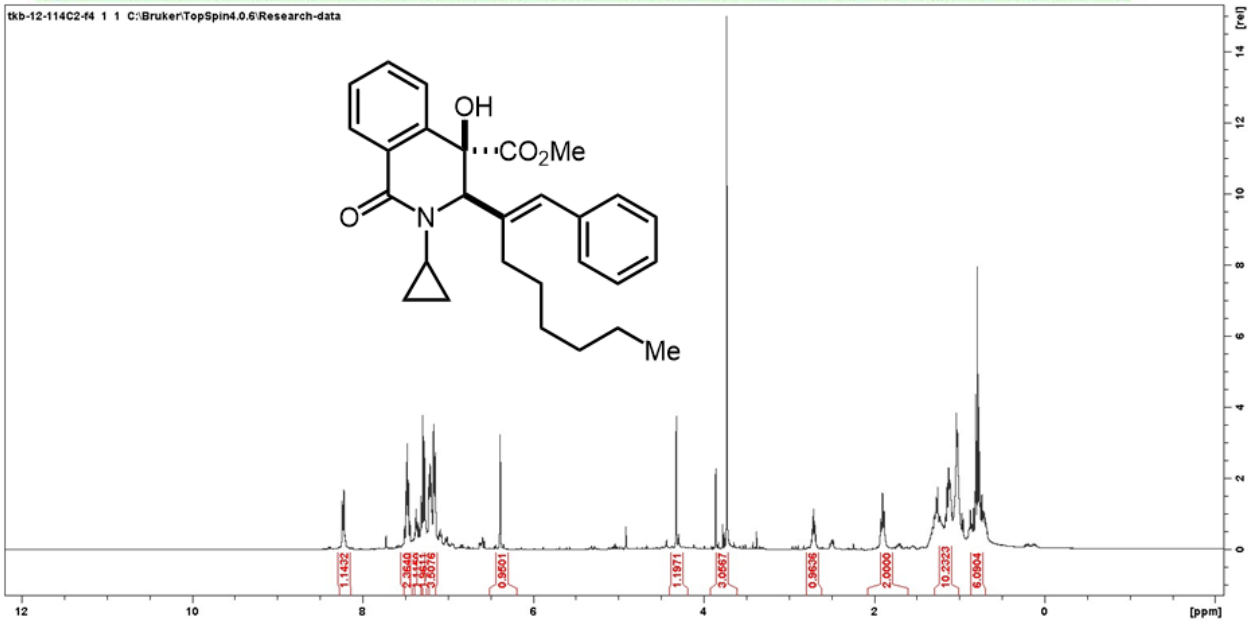
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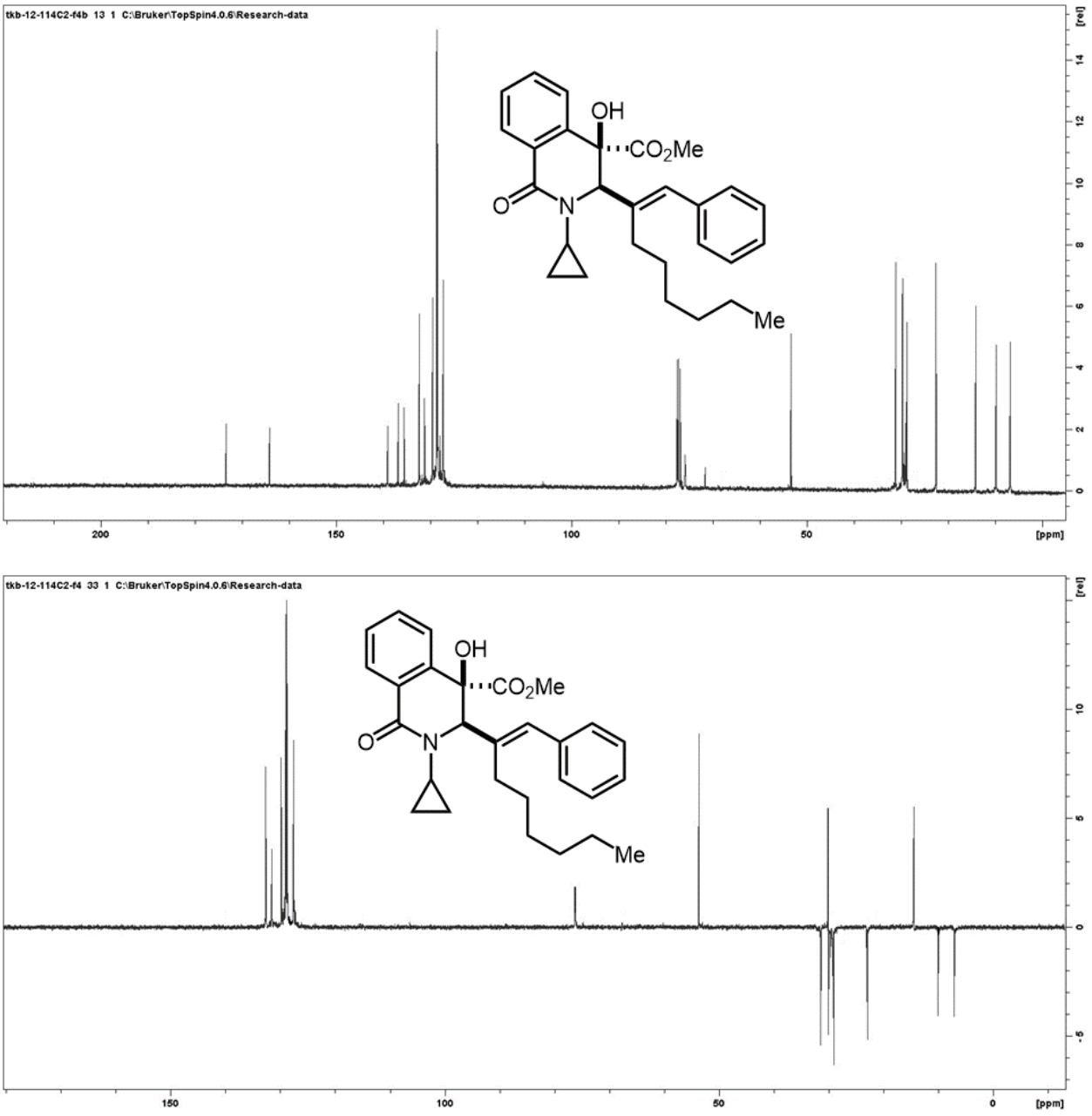
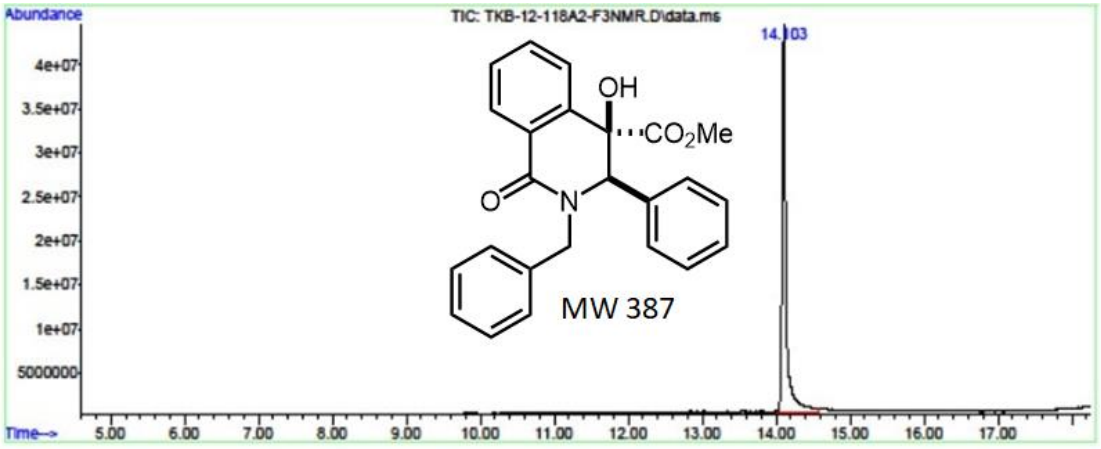
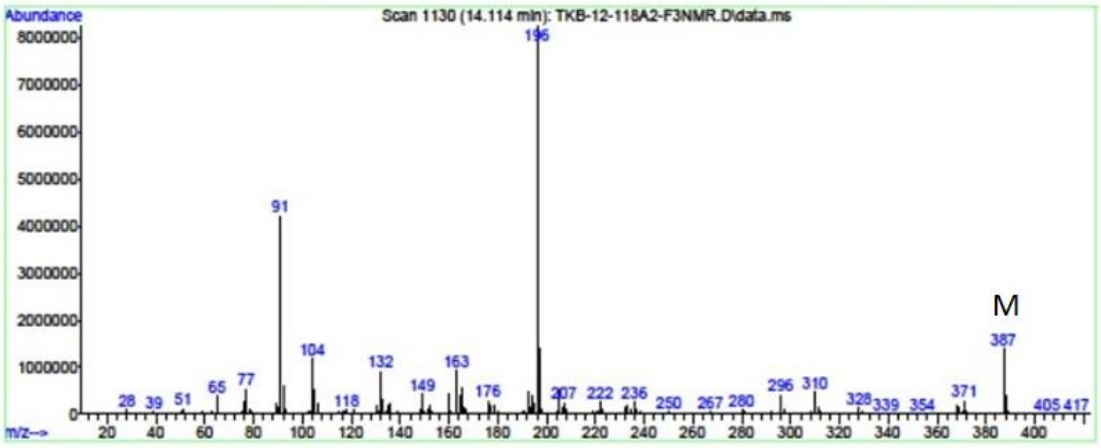


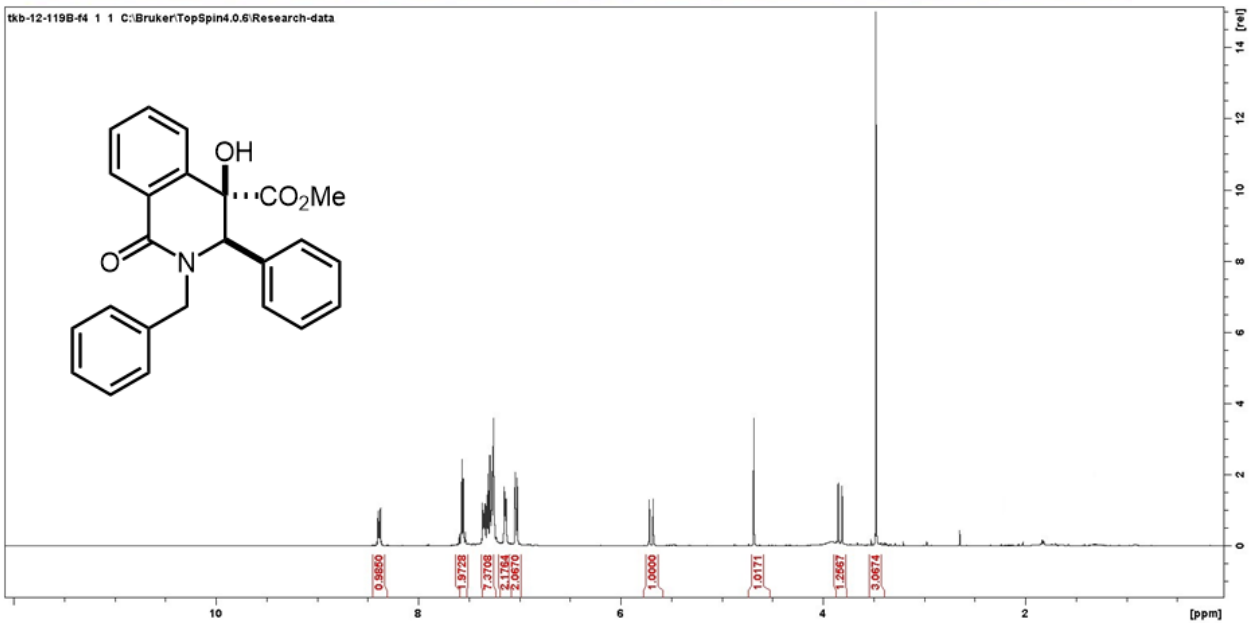
Compound 2i

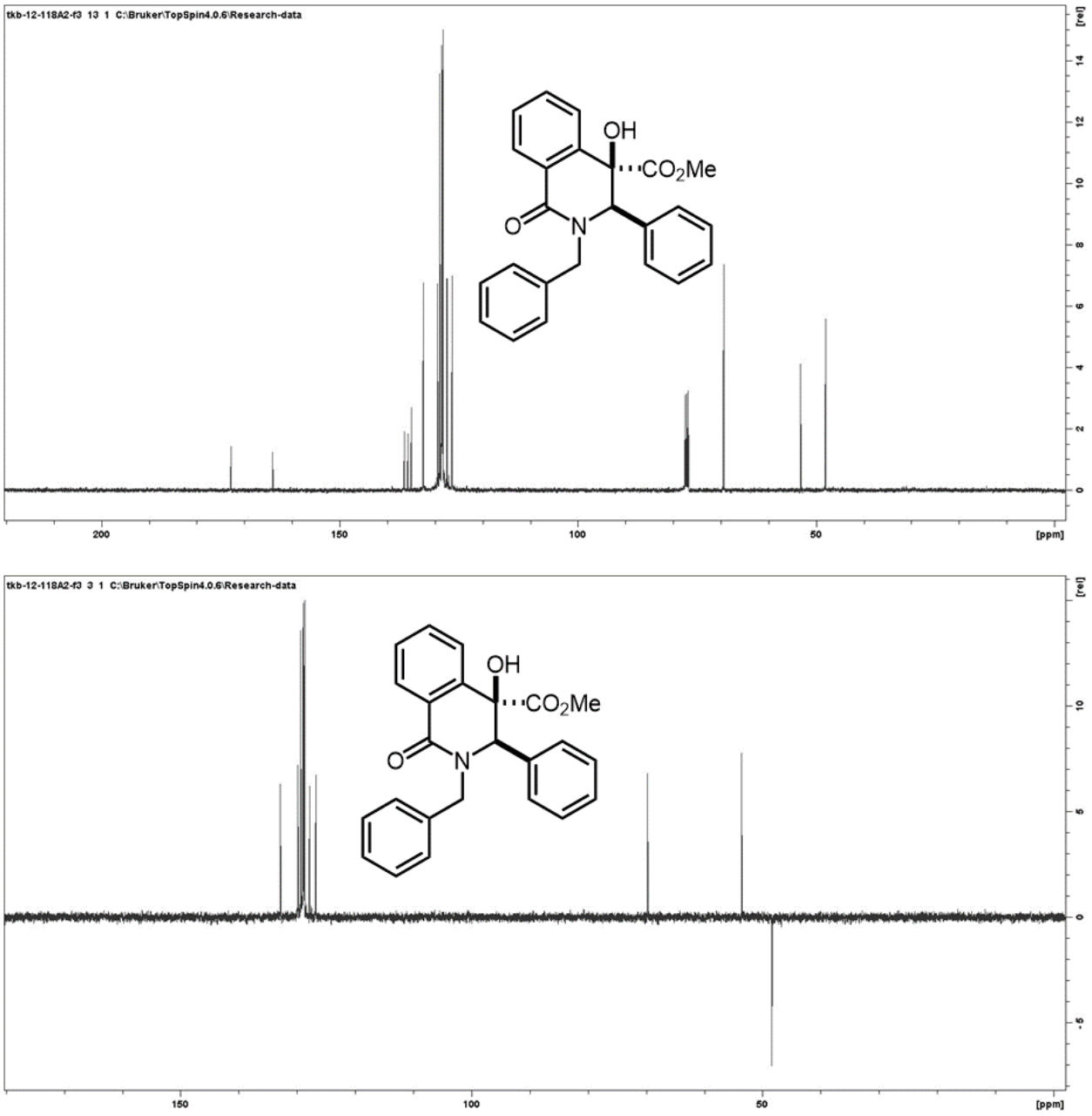
Prepared from ester **1i** (371 mg, 1.0 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Oily substance. Yield = 344.8 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 6.8, 2.4, 1H), 7.55 – 7.51 (m, 2H), 7.38 – 7.23 (m, 7H), 7.16 (dt, *J* = 6.9, 2.5 Hz, 2H), 7.08 (m, 2H), 5.72 (d, *J* = 15.0 Hz, 1H), 4.71 (s, 1H), 3.79 (s, 1H), 3.75 (d, *J* = 15.0 Hz, 1H), 3.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.87, 164.07, 136.43, 135.71, 135.00, 132.50, 129.48, 129.05, 129.01, 128.66, 128.57, 128.53, 128.49, 128.46,

128.36, 127.50, 126.42, 77.03, 69.43, 53.27, 48.06. HRMS calc for $C_{24}H_{21}NO_4$ 387.1471, found 387.1474.





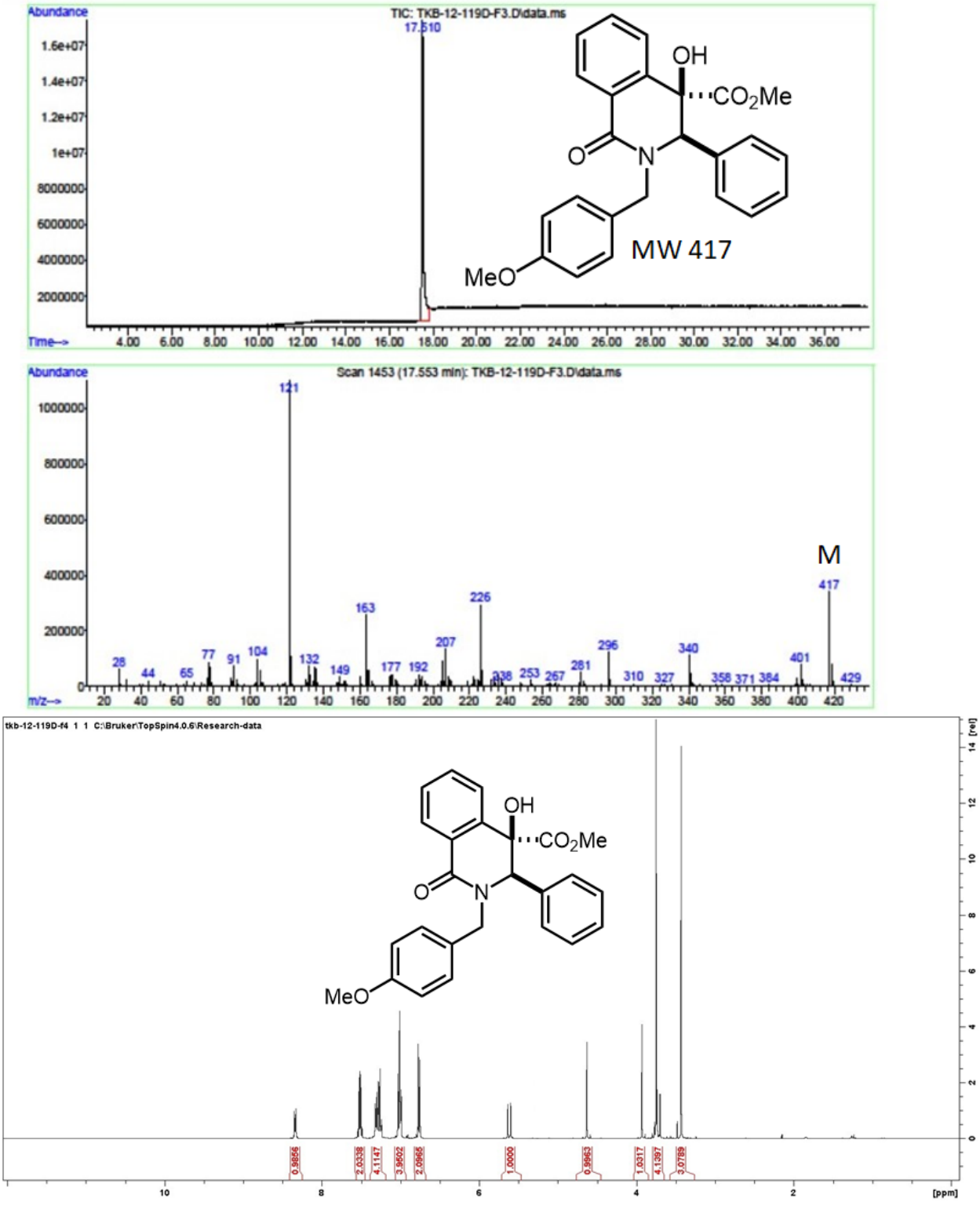


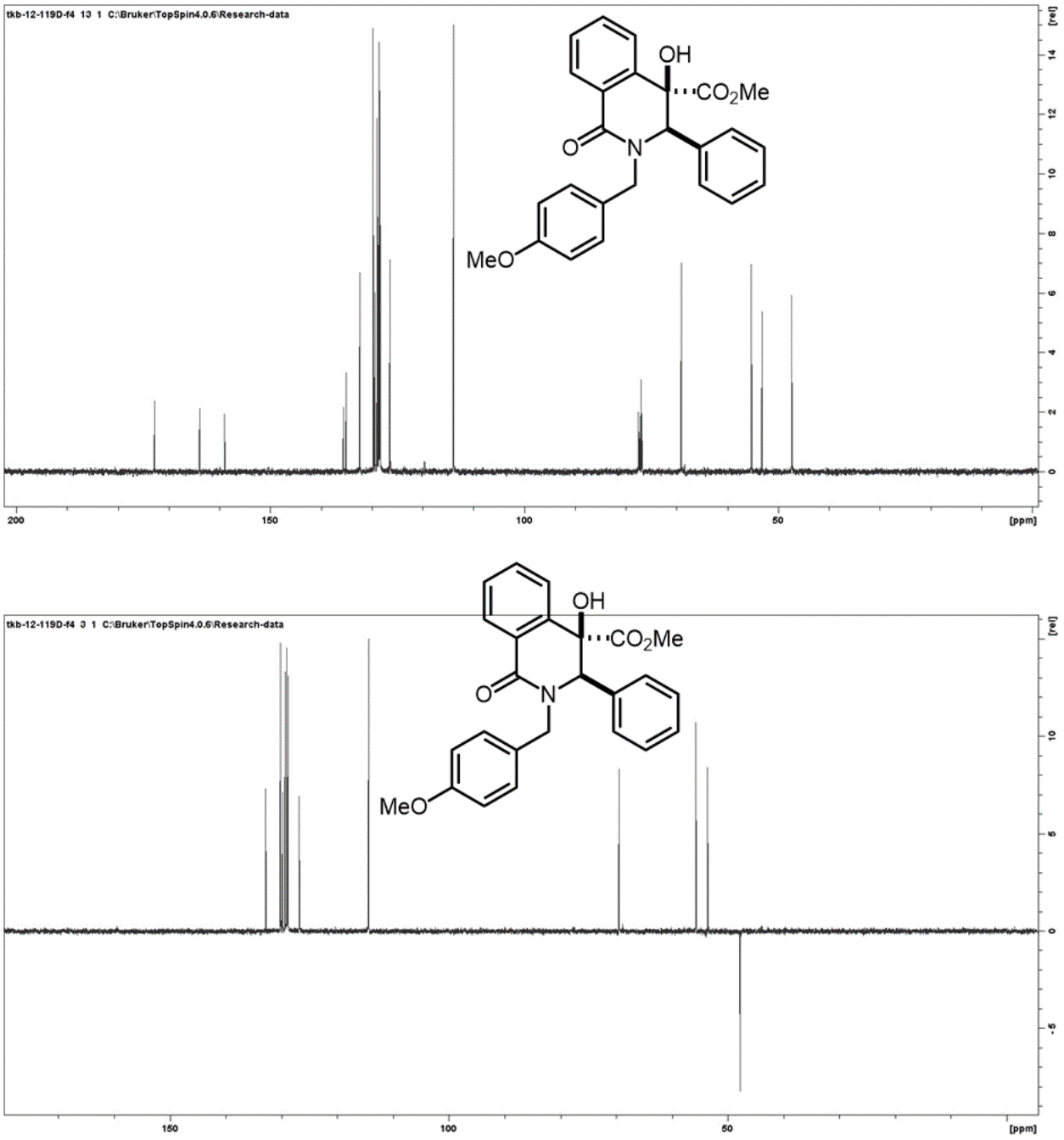


Compound 2j

Prepared from ester **1j** (401 mg, 1.0 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Oily substance. Yield = 363.2 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, J = 6.7, 2.3, 1H), 7.53 – 7.51 (m, 2H), 7.42 – 7.46 (m, 4H), 7.16 – 6.96 (m, 3H), 6.79 (d, J = 7.9 Hz, 2H), 5.66 (d, J = 14.9 Hz, 1H), 4.68 (s, 1H), 3.88 (s, 1H), 3.80 (s, 3H), 3.76 (d, J = 14.9 Hz, 1H), 3.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.83, 163.96, 159.04, 135.65, 135.10, 132.44, 129.79, 129.44, 129.11, 128.96, 128.64, 128.44,

128.39, 126.46, 119.66, 113.96, 77.03, 69.11, 55.31, 53.23, 47.39. HRMS calc for $C_{25}H_{23}NO_5$ 417.1576, found 417.1579.

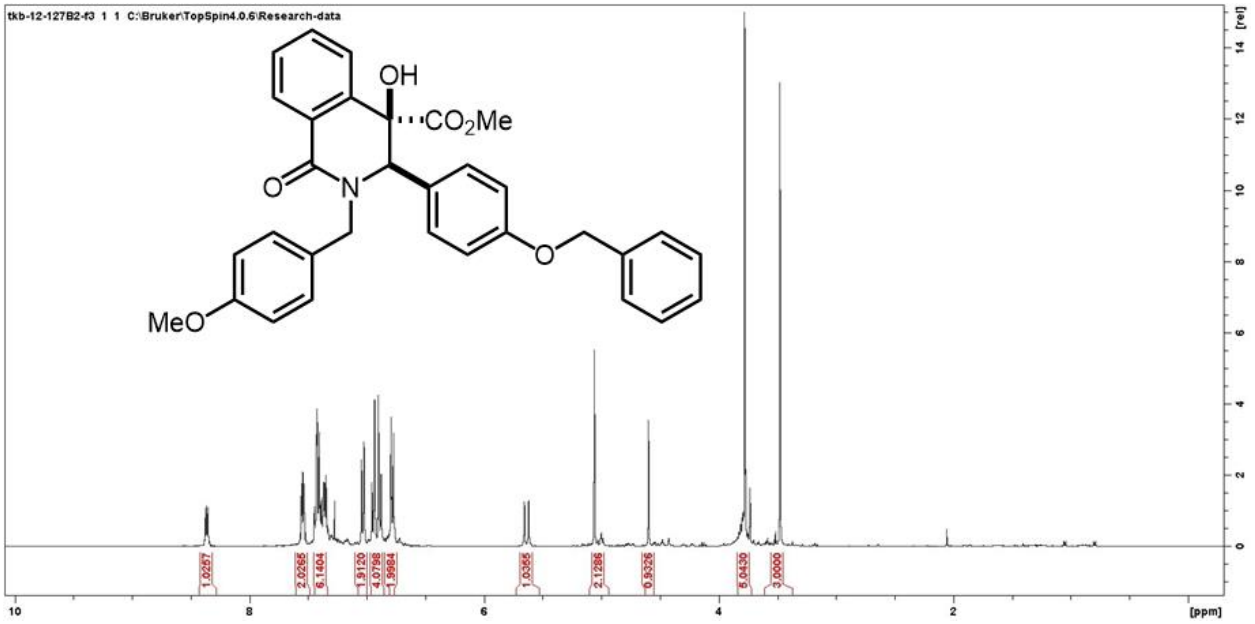


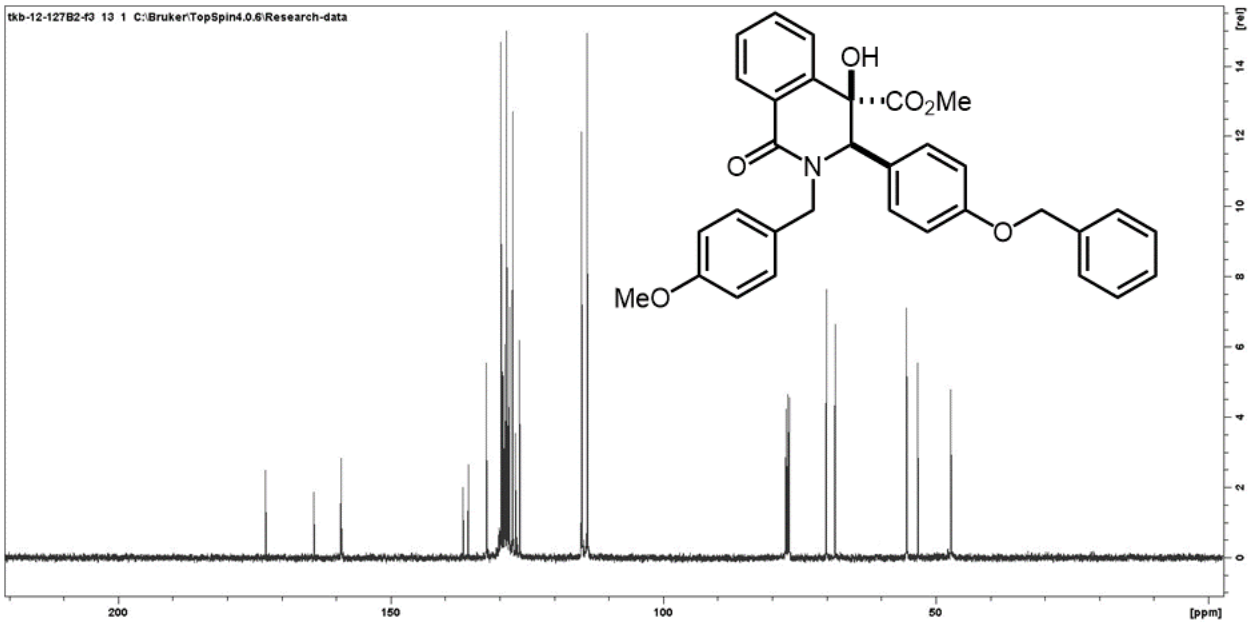


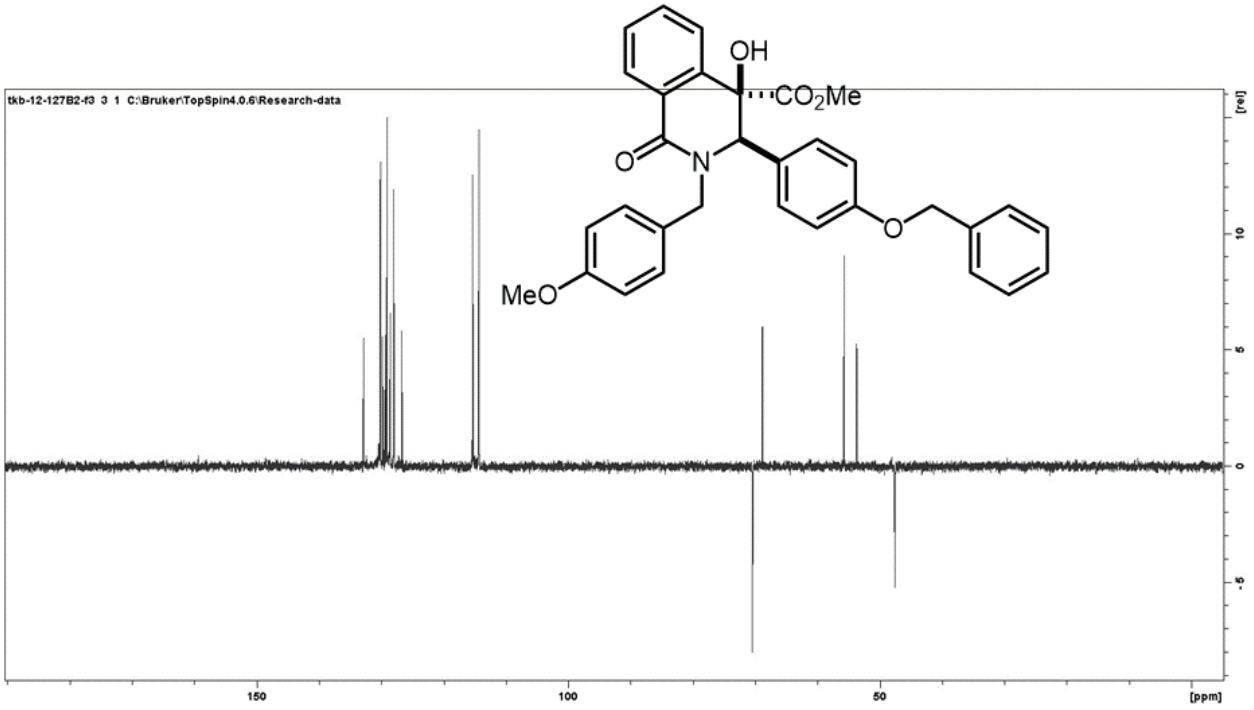
Compound 2k

Prepared from ester **1k** (253.6 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 222.5 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 6.7, 2.3, 1H), 7.58 – 7.52 (m, 2H), 7.47 – 7.39 (m, 6H), 7.23 – 7.11 (m, 2H), 6.96 – 6.83 (m, 4H), 6.67 (d, J = 8.1 Hz, 2H), 5.67 (d, J = 14.8 Hz, 1H), 5.19 (s, 2H), 4.63 (s, 1H), 3.80 – 3.66 (m, 5H), 3.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

172.94, 164.06, 159.12, 159.01, 136.70, 135.72, 132.44, 129.79, 129.74, 129.42, 128.99, 128.73, 128.50, 128.21, 127.62, 127.08, 126.33, 114.95, 113.93, 77.01, 70.08, 68.46, 55.33, 53.33, 47.21. HRMS calc for $C_{32}H_{29}NO_6$ 523.1995, found 523.1991.

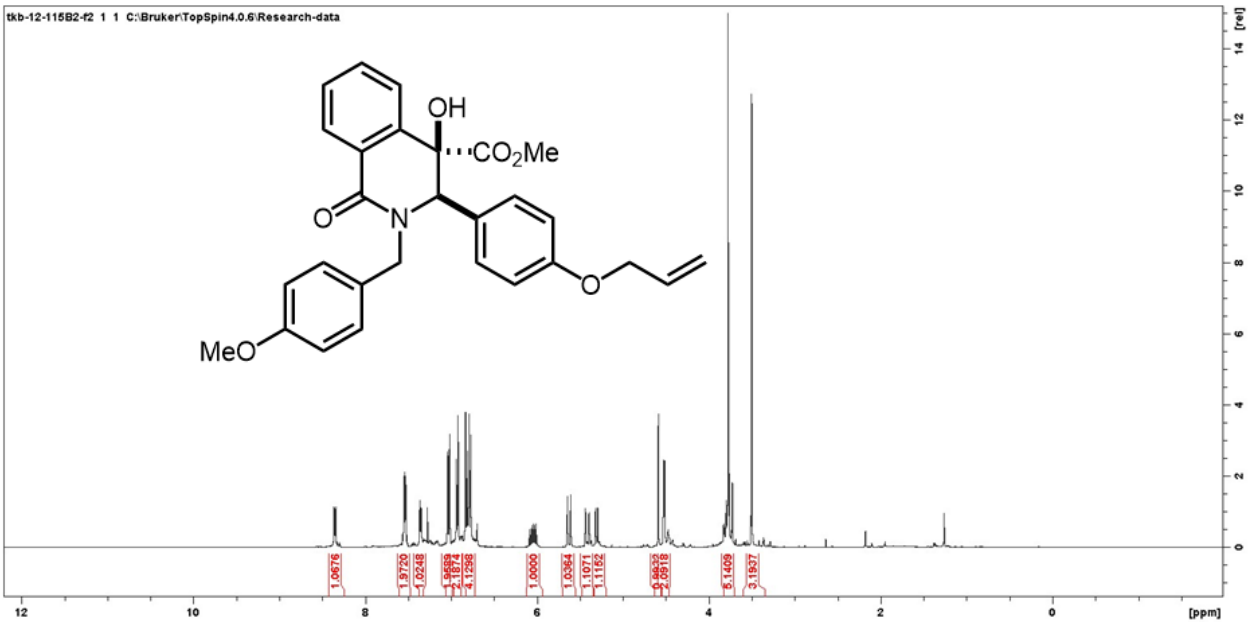






Compound 2l

Prepared from ester **1l** (228.7 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (15:85). Oily substance. Yield = 199 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 6.9, 2.2, 1H), 7.59 – 7.55 (m, 2H), 7.43 – 7.34 (m, 1H), 7.14 – 7.09 (d, 2H), 6.96 – 6.83 (m, 2H), 6.86 – 6.71 (m, 4H), 6.08 (ddt, *J* = 17.4, 10.5, 5.3 Hz, 1H), 5.66 (d, *J* = 14.8 Hz, 1H), 5.42 – 5.26 (m, 2H), 4.62 (s, 1H), 4.55 (dt, *J* = 5.3, 1.6 Hz, 2H), 3.88 – 3.70 (m, 5H), 3.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.92, 164.06, 158.99, 158.97, 135.72, 133.01, 132.42, 129.77, 129.70, 129.40, 129.13, 128.98, 128.50, 126.94, 126.32, 118.00, 114.74, 113.92, 76.99, 68.86, 68.45, 55.32, 53.33, 47.19. HRMS calc for $C_{28}H_{27}NO_6$ 473.1838, found 473.1835.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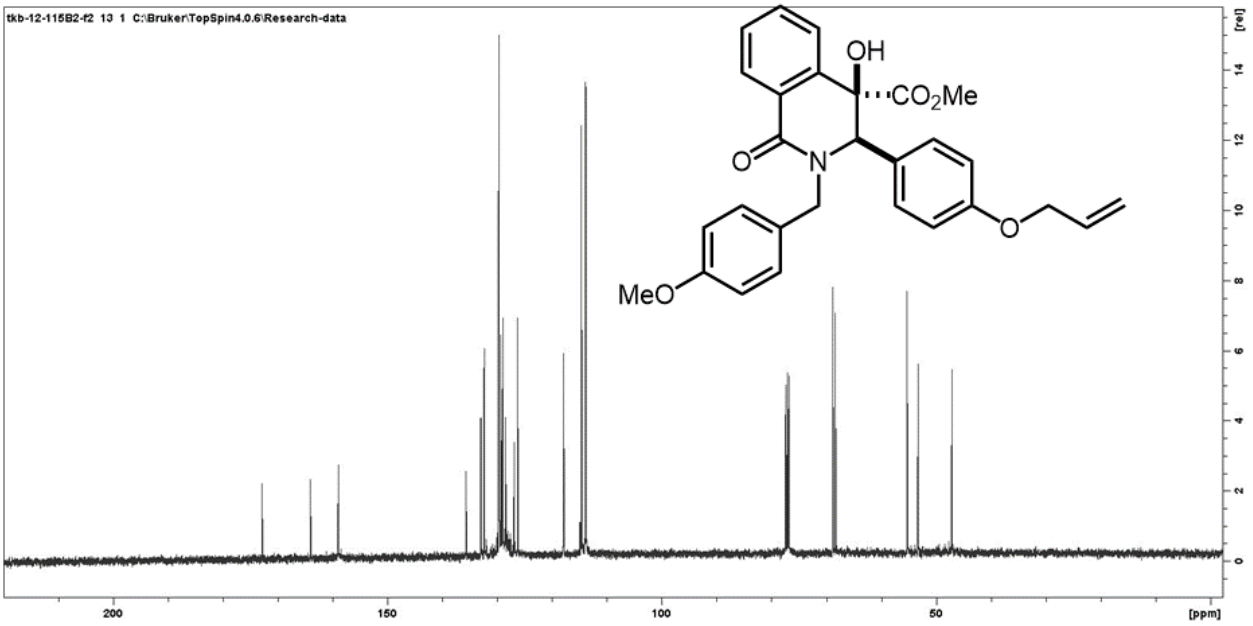
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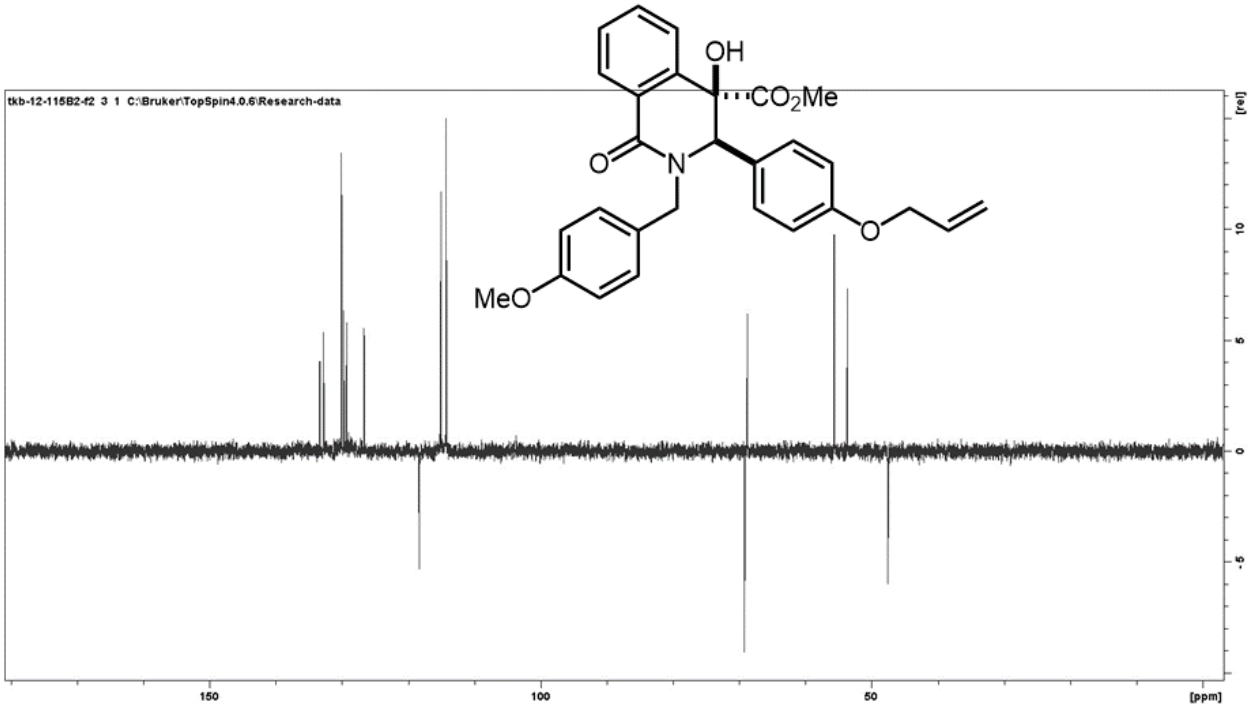
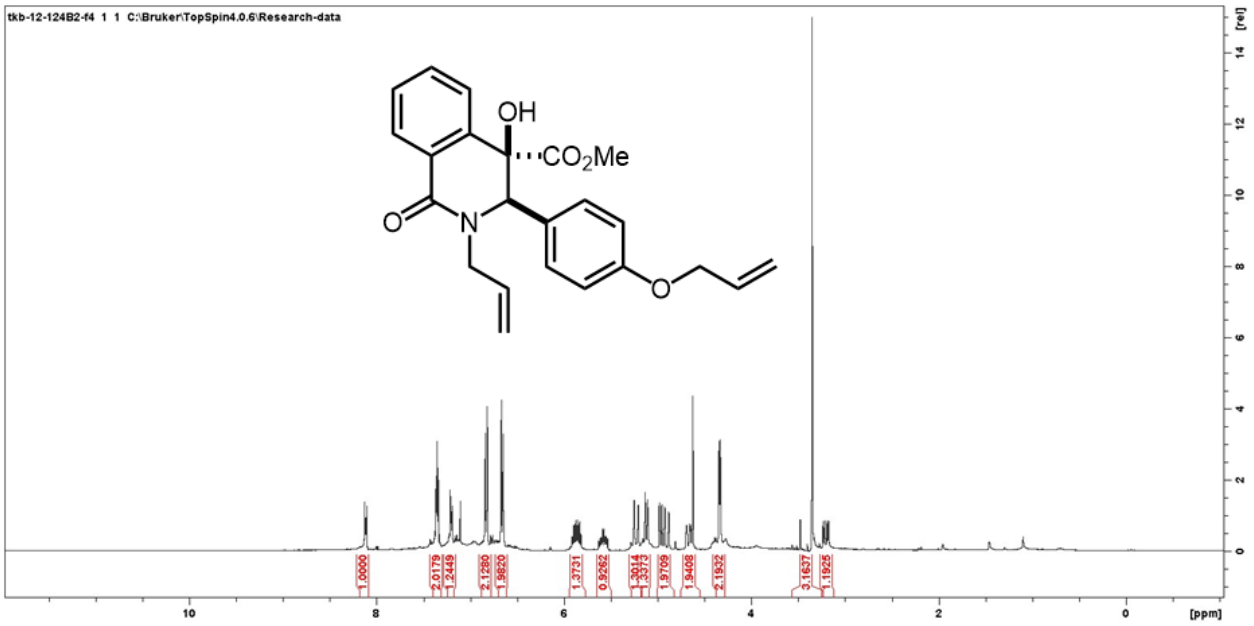


Compound 2m

Prepared from ester **1m** (188.5 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (30:70). Oily substance. Yield = 175.1 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 6.9, 2.2, 1H), 7.47 – 7.30 (m, 2H), 7.25 – 7.18 (m, 1H), 6.83 (d, *J* = 6.6 Hz, 2H), 6.76 (d, *J* = 6.6 Hz, 2H), 5.87 (ddt, *J* = 17.4, 10.6, 5.3 Hz, 1H), 5.58 (dddd, *J* = 17.3, 10.2, 7.3, 4.5 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.18 – 5.08 (m, 1H), 5.10 (s, 1H), 4.97 (dt, *J* = 10.2, 1.5 Hz, 1H), 4.90 (dt, *J* = 17.1, 1.6 Hz, 1H), 4.67 (ddt, *J* = 15.4, 4.7, 1.8 Hz, 1H), 4.63 (s, 1H), 4.45 – 4.31 (m, 2H), 3.35 (s, 3H), 3.34 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.87, 163.76, 159.00, 135.89, 133.02, 132.43, 132.41, 129.57, 129.37, 128.96, 128.83, 127.08, 126.31, 118.15, 117.95, 114.77, 77.08, 68.99, 68.85, 53.31, 47.35. HRMS calc for $C_{23}H_{23}NO_5$ 393.1576, found 393.1579.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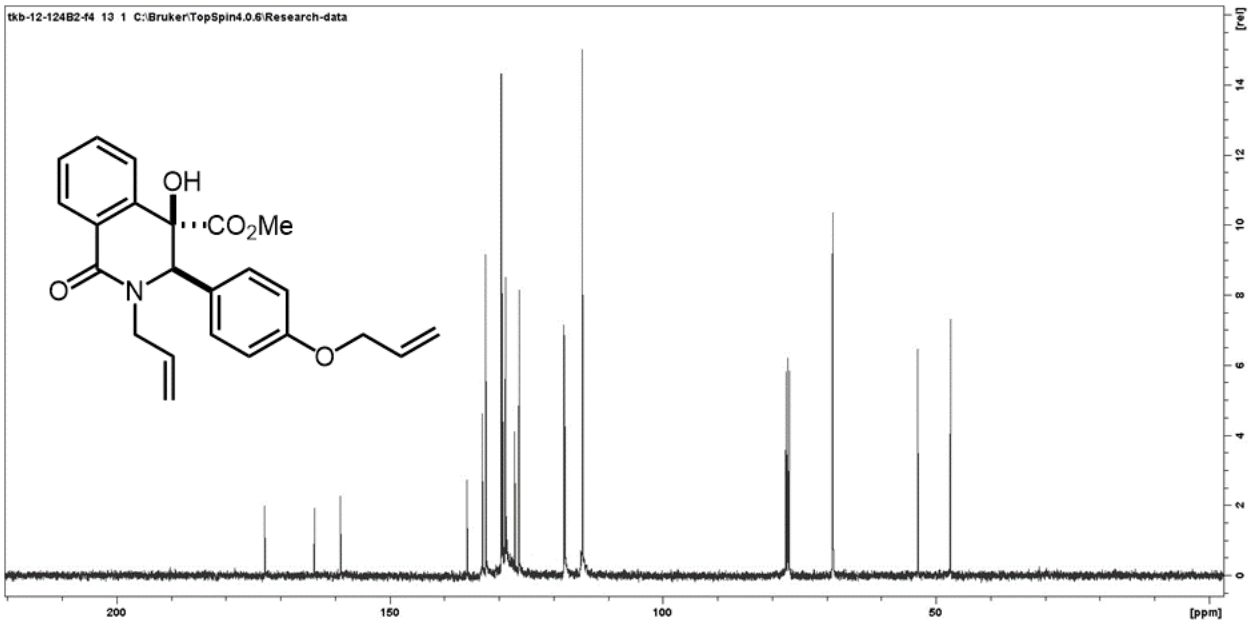
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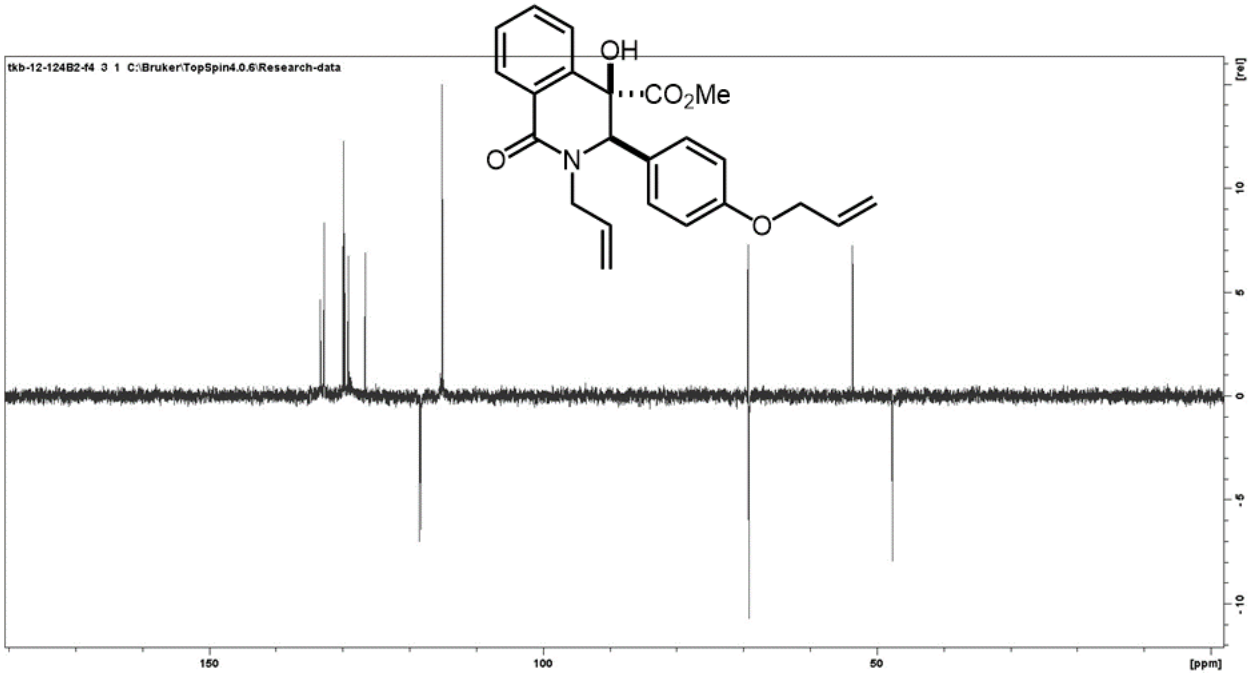

Compound 2n

Prepared from ester **1n** (188.5 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (30:70). Oily substance. Yield = 169 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 6.9, 2.2, 1H), 7.51 – 7.45 (m, 2H), 7.23 (ddd, *J* = 8.9, 7.2, 1.8 Hz, 1H), 7.18 (dd, *J* = 7.2, 1.6 Hz, 1H), 6.85 – 6.72 (m, 3H), 6.26 (ddt, *J* = 17.4, 10.5, 5.1 Hz, 1H), 5.91 – 5.77 (m, 1H), 5.50 (s, 1H), 5.35 (dt, *J* = 17.3, 1.6 Hz, 1H), 5.29 – 5.21 (m, 1H), 5.21 – 5.11 (m, 1H), 5.10 (dt, *J* = 10.1, 1.4 Hz, 1H), 4.78 (ddt, *J* = 15.3, 4.8, 1.7 Hz, 1H), 4.54 – 4.43 (m, 2H), 4.28 (s, 1H), 3.54 (s, 3H), 3.28 (ddt, *J* = 15.3, 7.5, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.84, 163.27, 156.57, 136.00, 132.74, 132.66, 132.35, 129.52, 129.39, 129.19, 128.65, 128.05, 126.62, 124.24, 121.10, 118.29, 117.82, 111.25, 76.98, 69.24, 61.57, 52.98, 48.04. HRMS calc for $C_{23}H_{23}NO_5$ 393.1576, found 393.1579.

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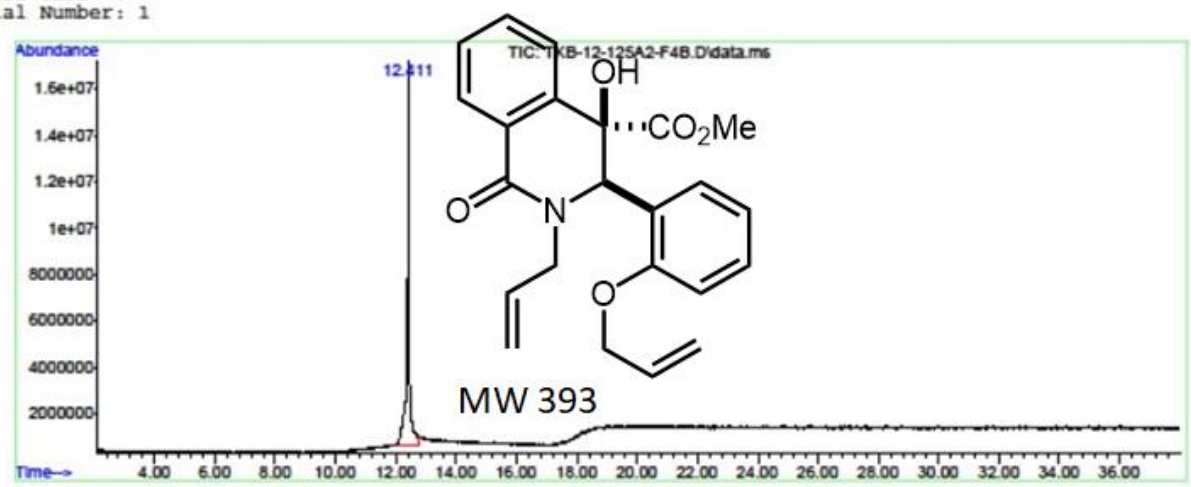

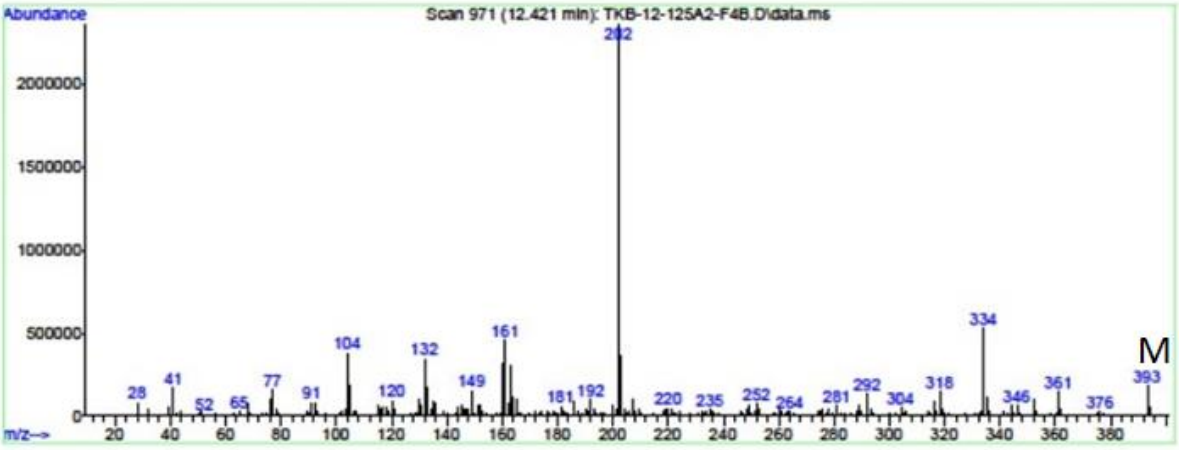

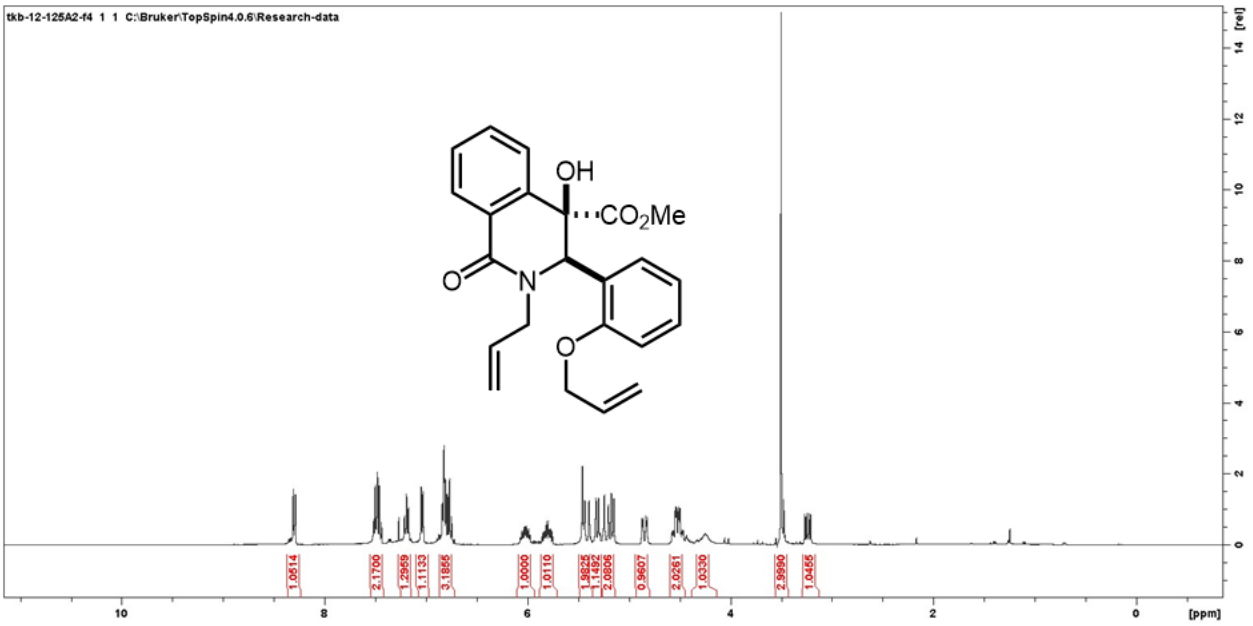
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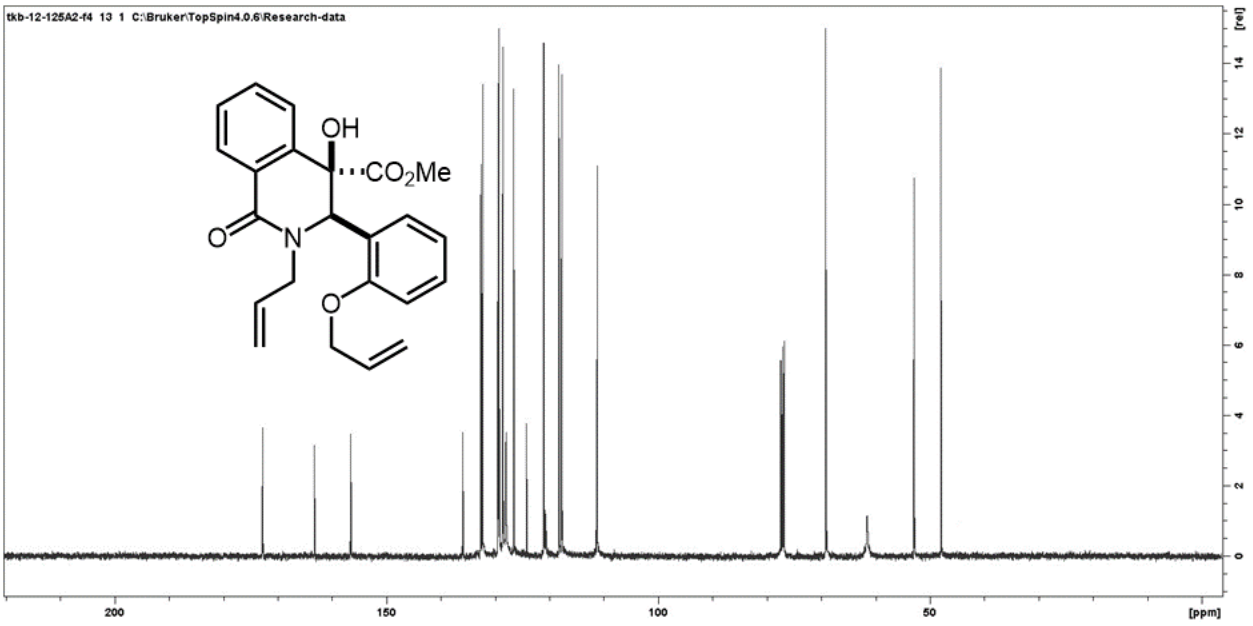
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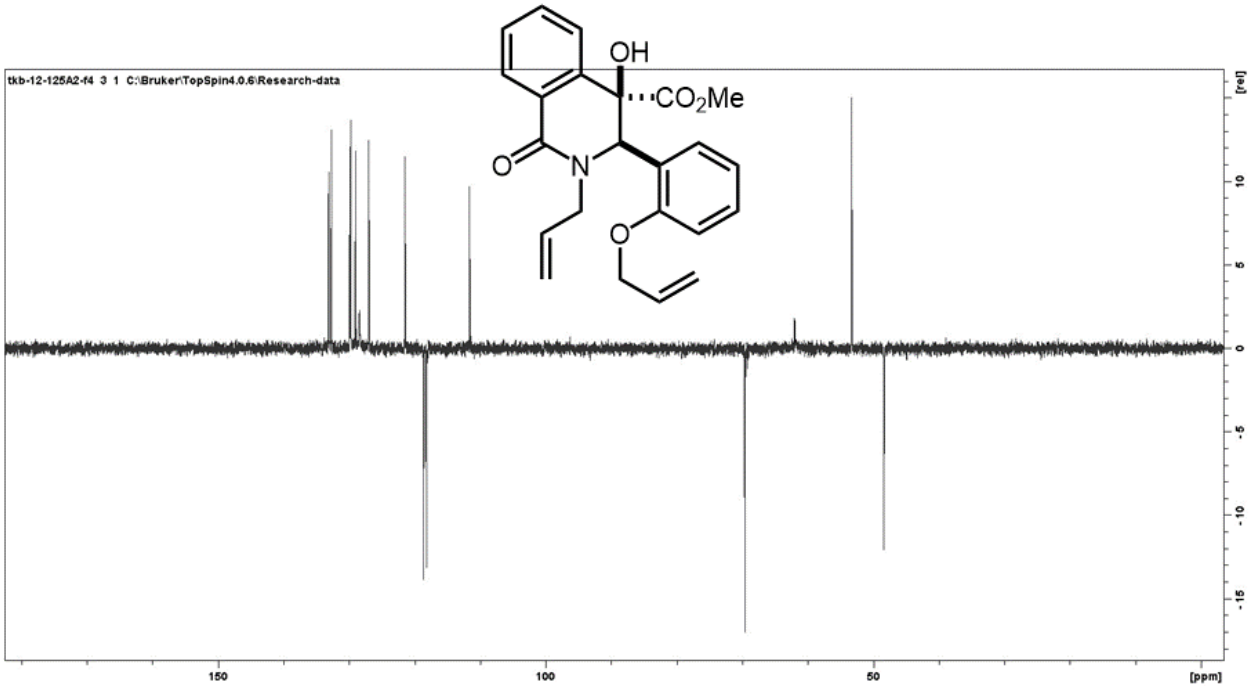

Compound 2o

Prepared from ester **1o** (200 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (40:60). Oily substance. Yield = 177 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 6.9, 2.1, 1H), 7.57 – 7.48 (m, 3H), 7.21 – 7.13 (m, 3H), 6.89 (ddd, *J* = 7.0, 1.5, 0.6 Hz, 1H), 5.78 – 5.63 (m, 1H), 5.54 (s, 1H), 5.31 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 – 5.19 (m, 1H), 4.72 (ddt, *J* = 15.2, 4.9, 1.6 Hz, 1H), 4.49 (s, 1H), 3.61 (s, 3H), 3.29 (ddt, *J* = 15.2, 7.6, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.35, 162.82, 135.77, 135.31, 132.75, 132.60, 132.11, 130.03, 129.67, 128.99, 128.89, 128.81, 127.94, 126.52, 125.29, 119.08, 76.90, 66.86, 53.68, 48.19. HRMS calc for $C_{20}H_{18}BrNO_4$ 415.0419, found 405.0423.

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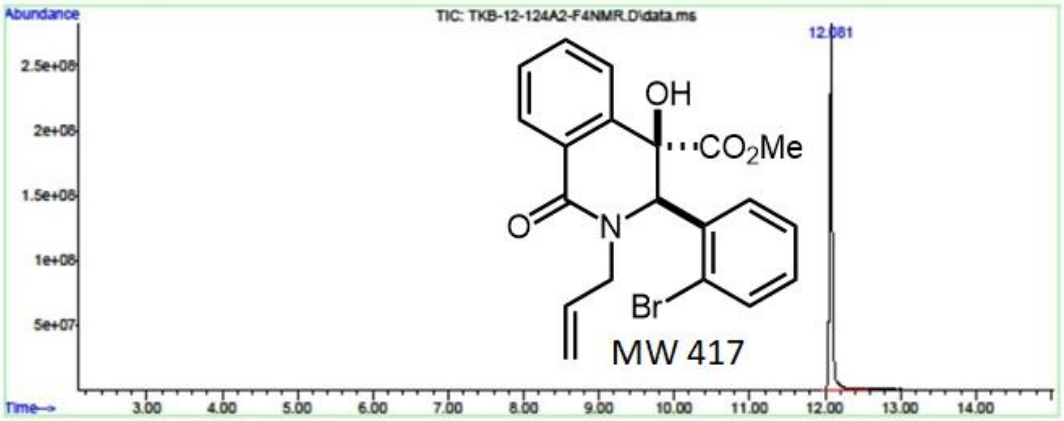

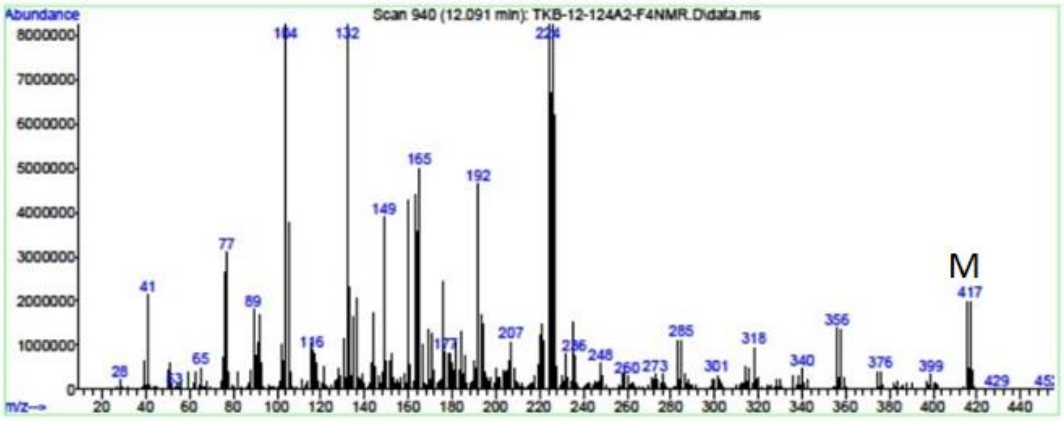

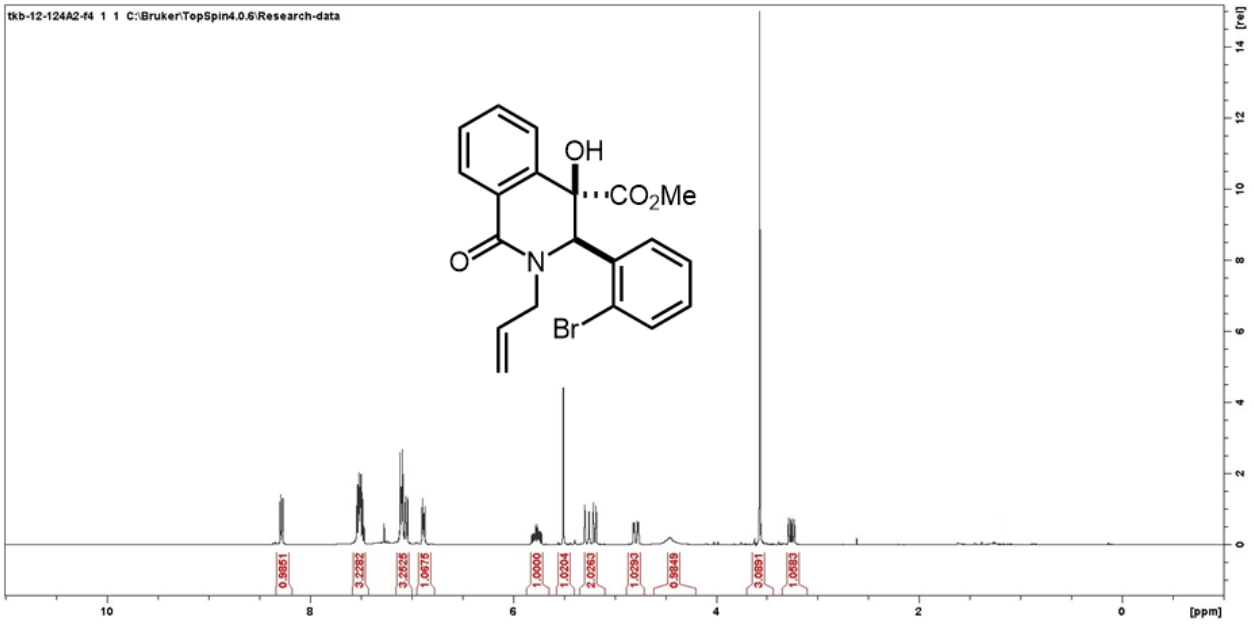

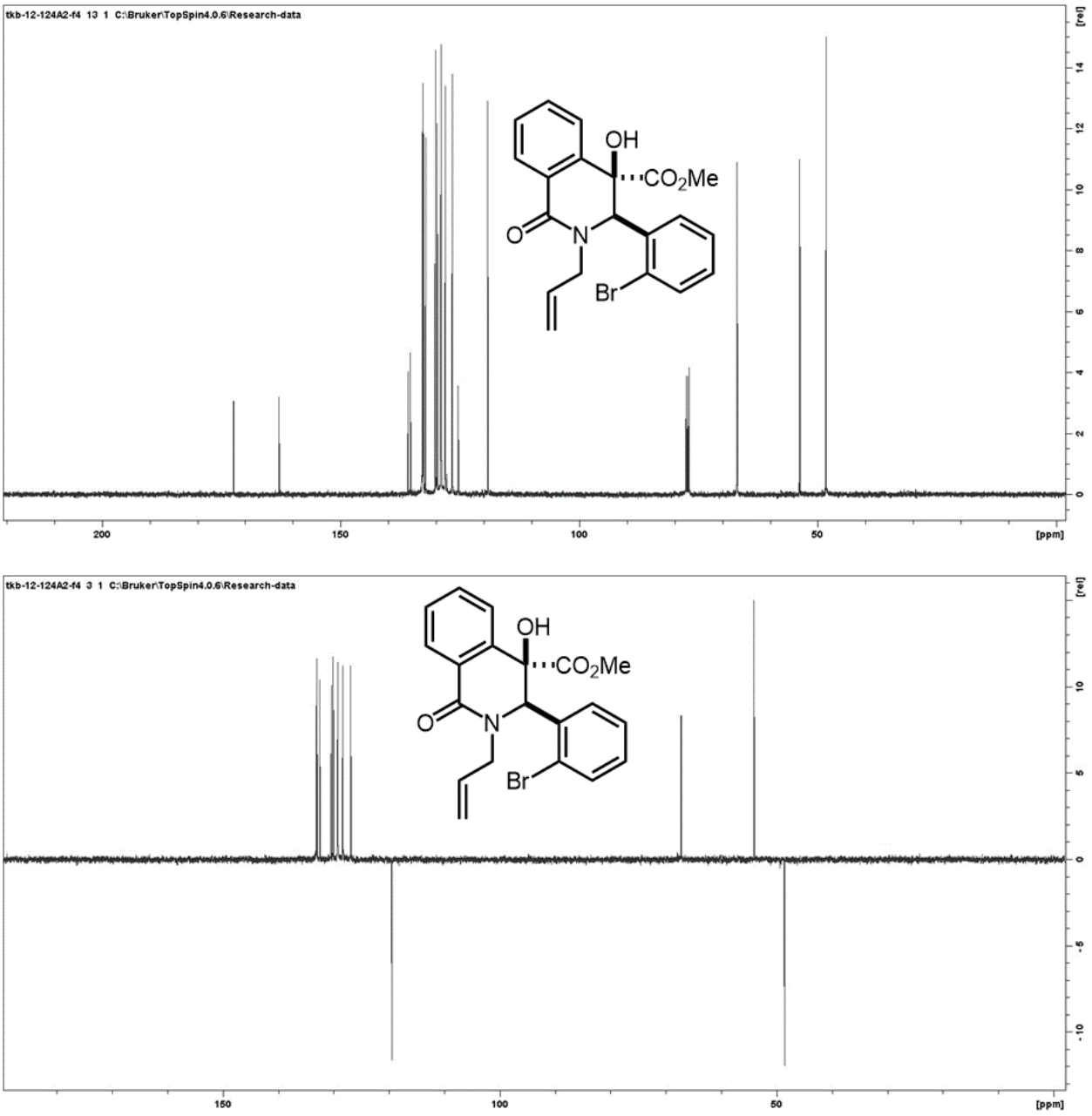

Compound 2p

Prepared from ester **1p** (194.6 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Oily substance. Yield = 178.4 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.66 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.39 – 7.29 (m, 3H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 5.79 (dddd, *J* = 17.2, 10.3, 6.8, 4.5 Hz, 1H), 5.36 – 5.25 (m, 2H), 5.16 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.73 (ddt, *J* = 15.6, 4.6, 1.9 Hz, 1H), 4.57 (s, 1H), 3.47 (s, 3H), 3.35 – 3.24 (m, 1H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 172.01, 162.41, 136.39, 135.75, 135.74, 132.64, 132.29, 131.93, 129.75, 129.04, 128.98, 128.78, 128.75, 128.58, 128.45, 126.34, 125.69, 125.63, 125.61, 122.89, 117.82, 77.22, 64.22, 64.20, 53.14, 48.09. HRMS calc for $C_{21}H_{18}F_3NO_4$ 405.1188, found 405.0423.

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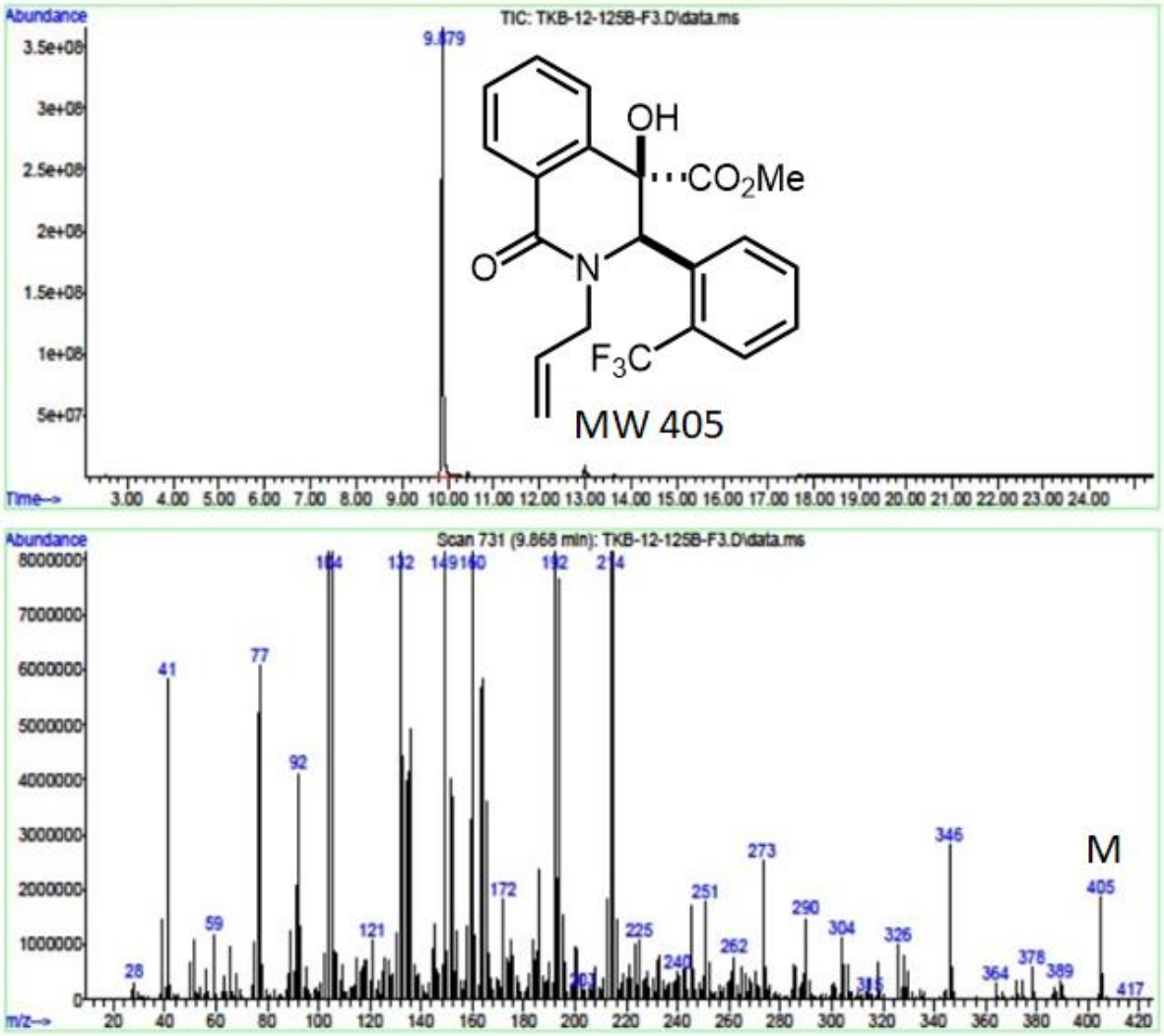

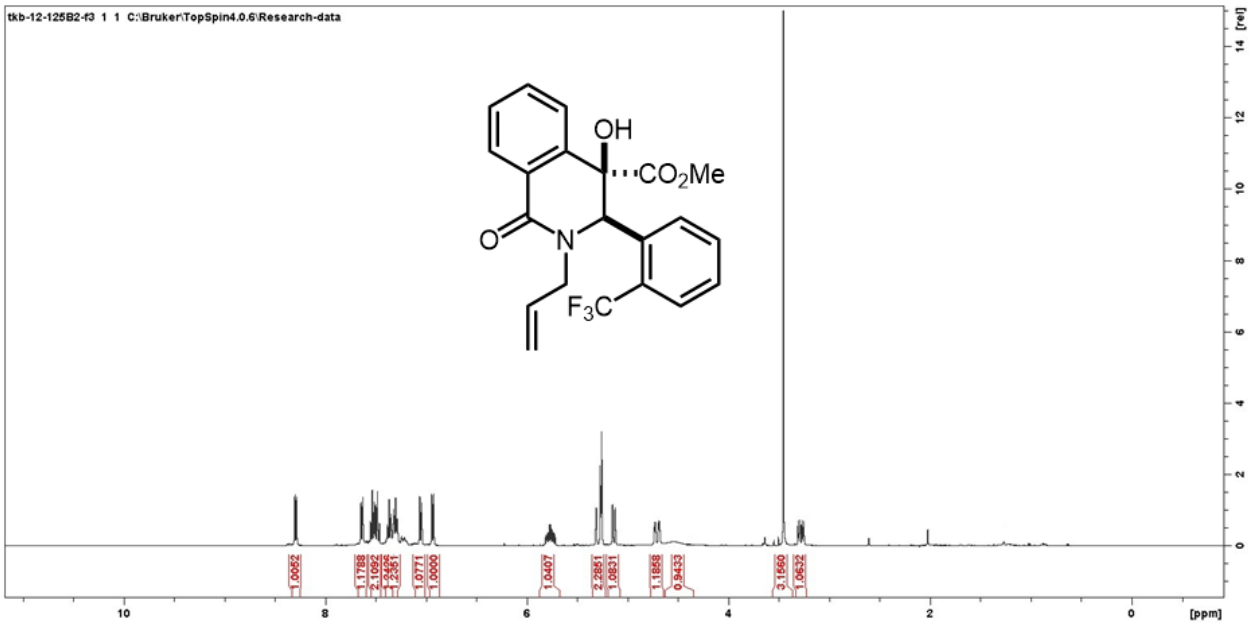
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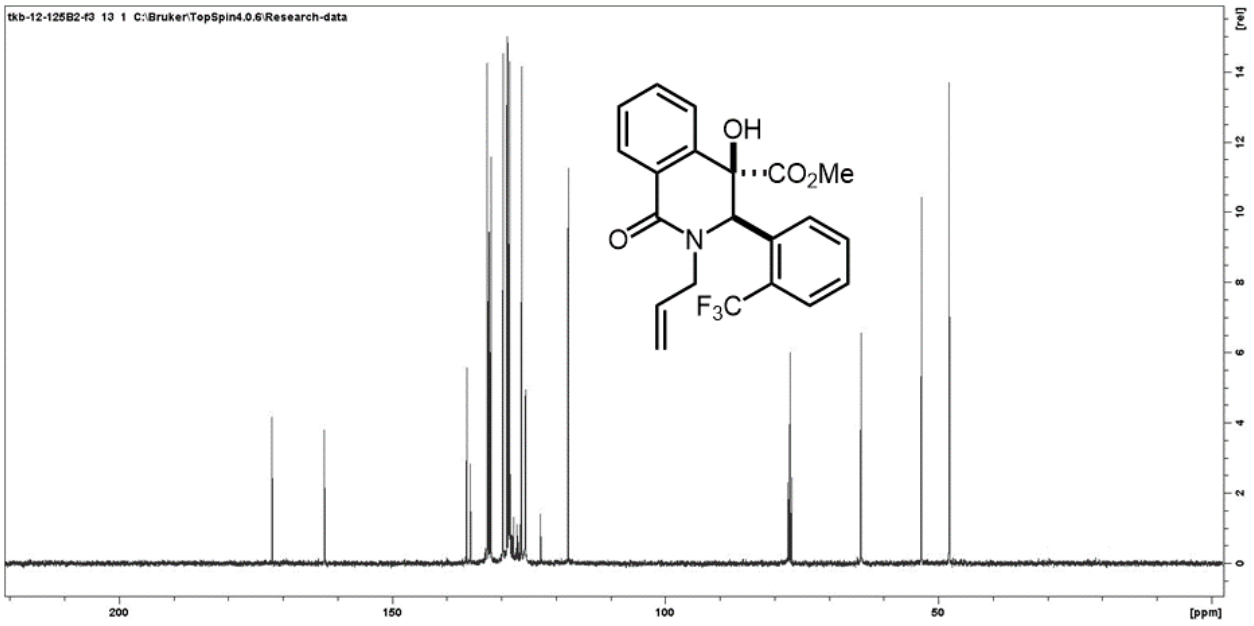
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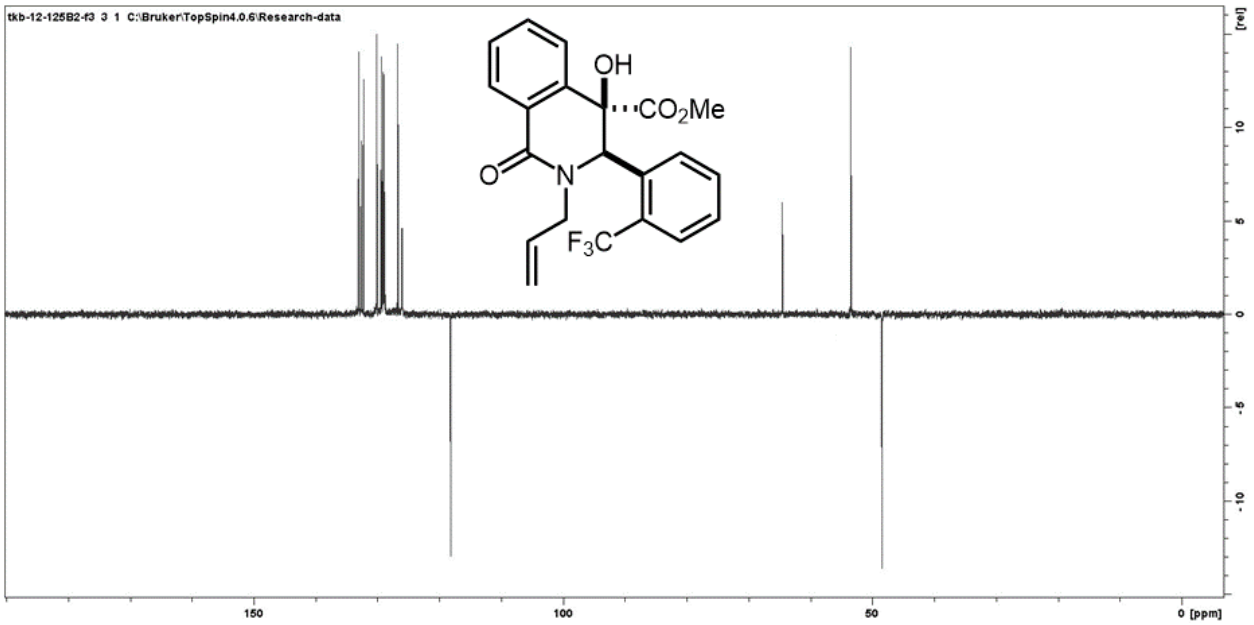
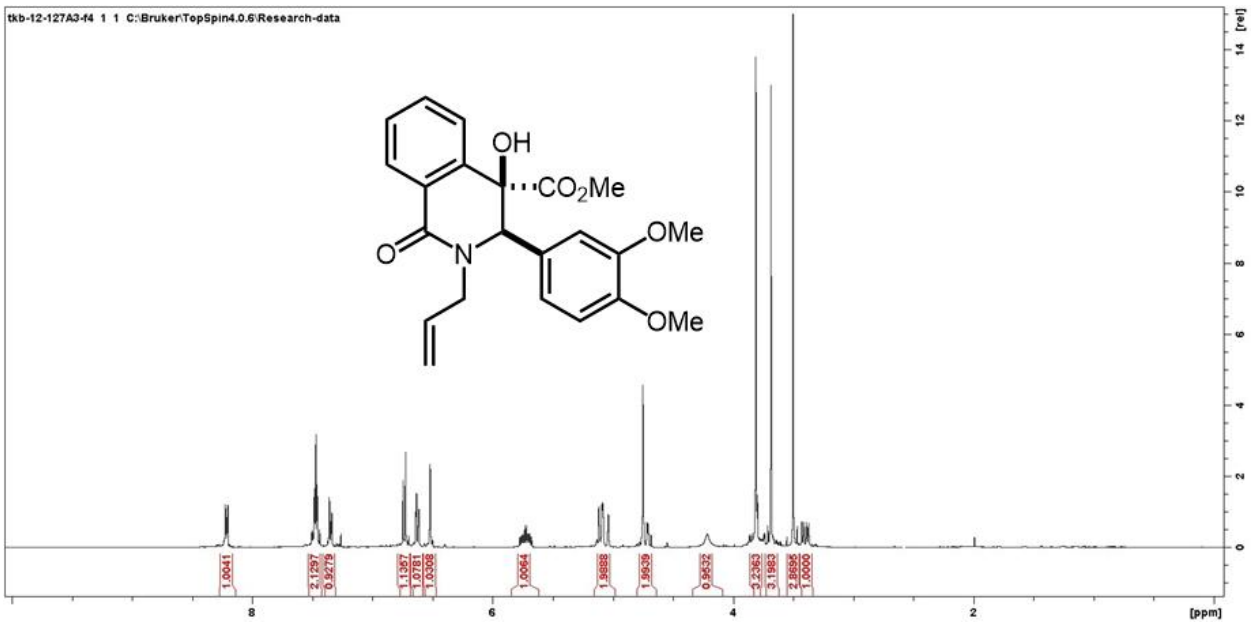


Compound 2q

Prepared from ester **1q** (191 mg, 0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (10:90). Oily substance. Yield = 165 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 7.1, 2.4 Hz, 1H), 7.49 – 7.34 (m, 2H), 7.34 – 7.20 (m, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.61 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.51 (s, 1H), 5.77 (dddd, *J* = 17.3, 10.2, 7.1, 4.6 Hz, 1H), 5.20 – 5.03 (m, 2H), 4.79 (s, 1H), 4.86 – 4.73 (m, 1H), 4.26 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.54 (s, 3H), 3.44 (ddt, *J* = 15.4, 7.2, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.70, 163.83, 149.39, 148.87, 135.98, 132.58, 132.39, 129.33, 128.91, 128.66, 127.27, 126.28, 121.08, 118.05, 111.10, 110.86, 77.03, 69.25, 55.89, 55.84, 53.28, 47.50. HRMS calc for $C_{22}H_{23}NO_6$ 397.1525, found 397.1529.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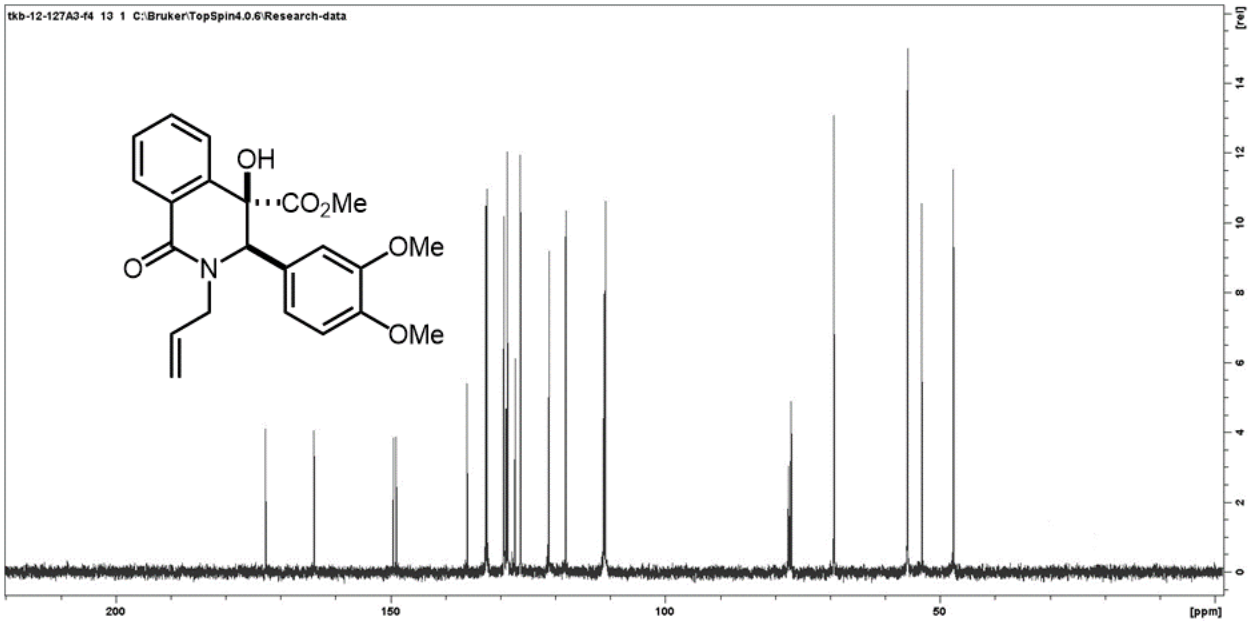
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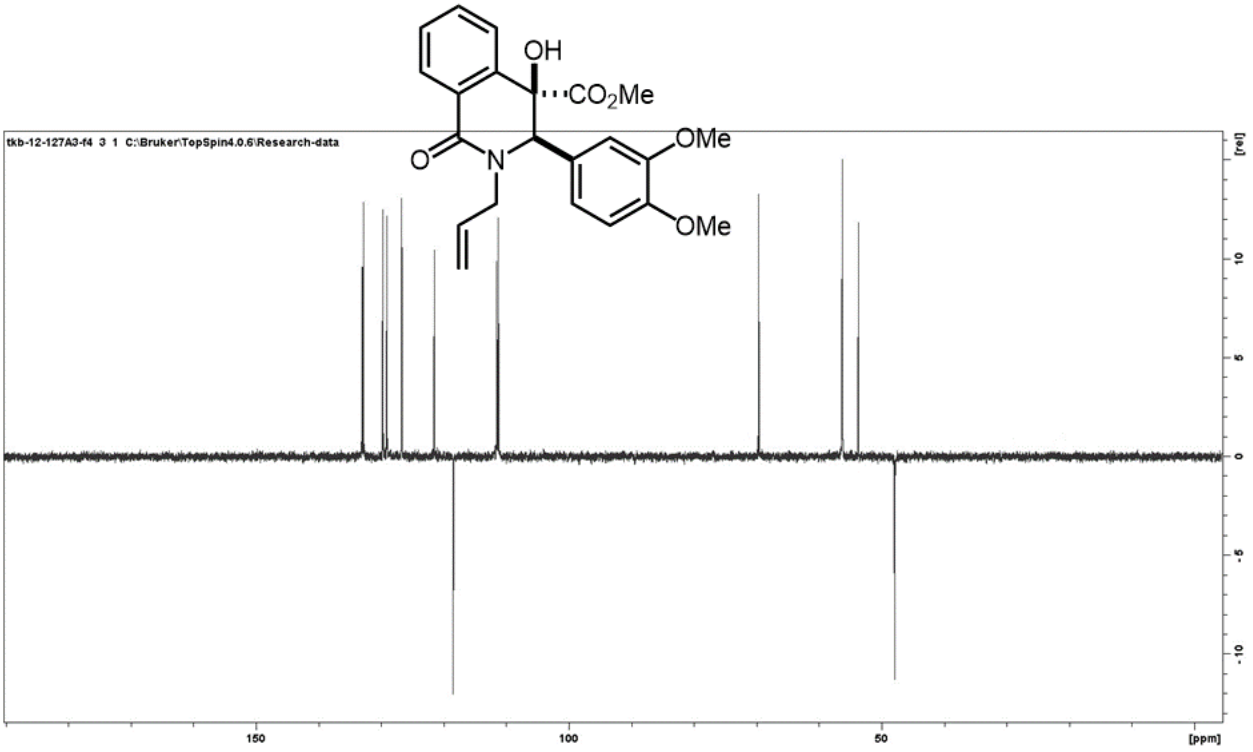
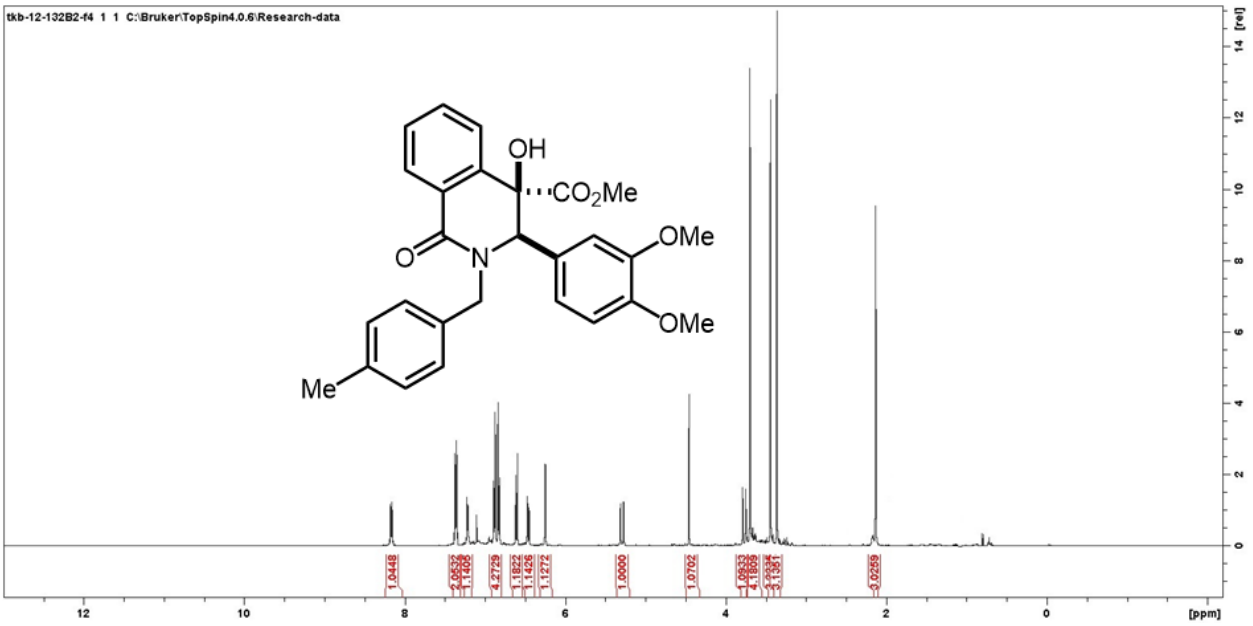


Compound 2r

Prepared from ester **1r** (0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (20:80). Oily substance. Yield = 205.4 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.22 (dt, *J* = 5.6, 3.7 Hz, 1H), 6.98 – 6.80 (m, 4H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.46 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.25 (d, *J* = 2.1 Hz, 1H), 5.29 (d, *J* = 15.0 Hz, 1H), 4.46 (s, 1H), 3.77 (d, *J* = 15.1 Hz, 1H), 3.70 – 3.66 (m, 4H), 3.44 (s, 3H), 3.36 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.87, 164.44, 149.40, 148.78, 137.00, 136.04, 133.73, 132.44, 129.39, 129.18, 129.09, 128.91, 128.27, 126.99, 126.01, 121.32, 111.39, 110.80, 76.87, 69.06, 55.93, 55.68, 53.37, 47.88, 21.18. HRMS calc for $C_{27}H_{27}NO_6$ 461.1838, found 461.1832.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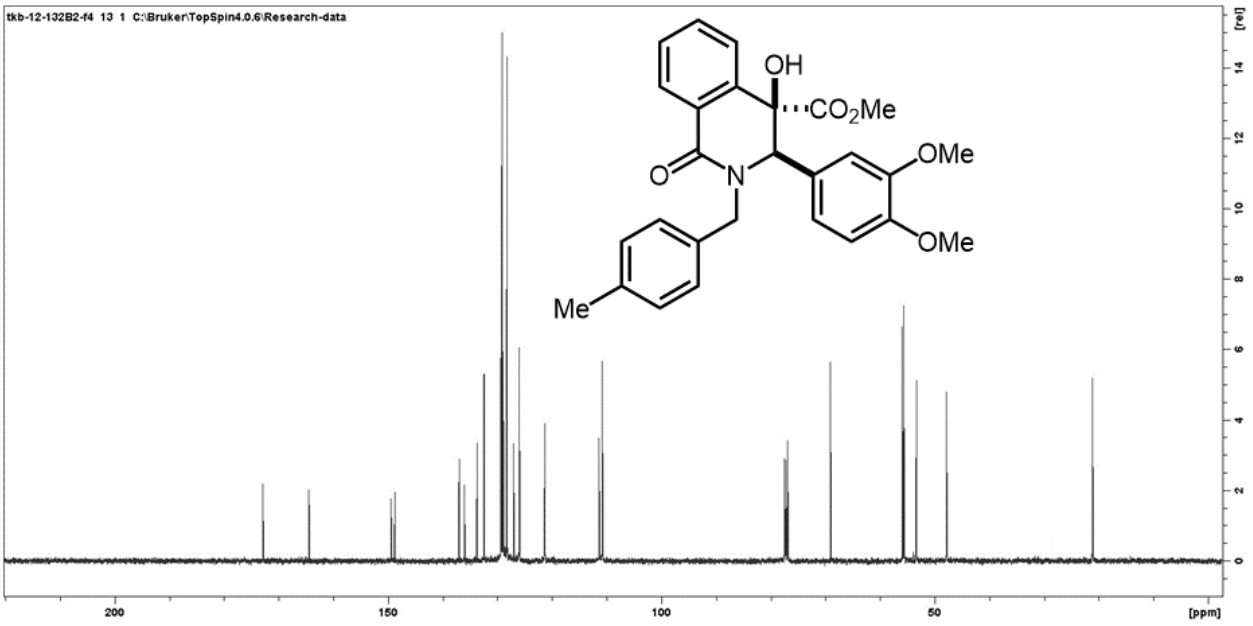
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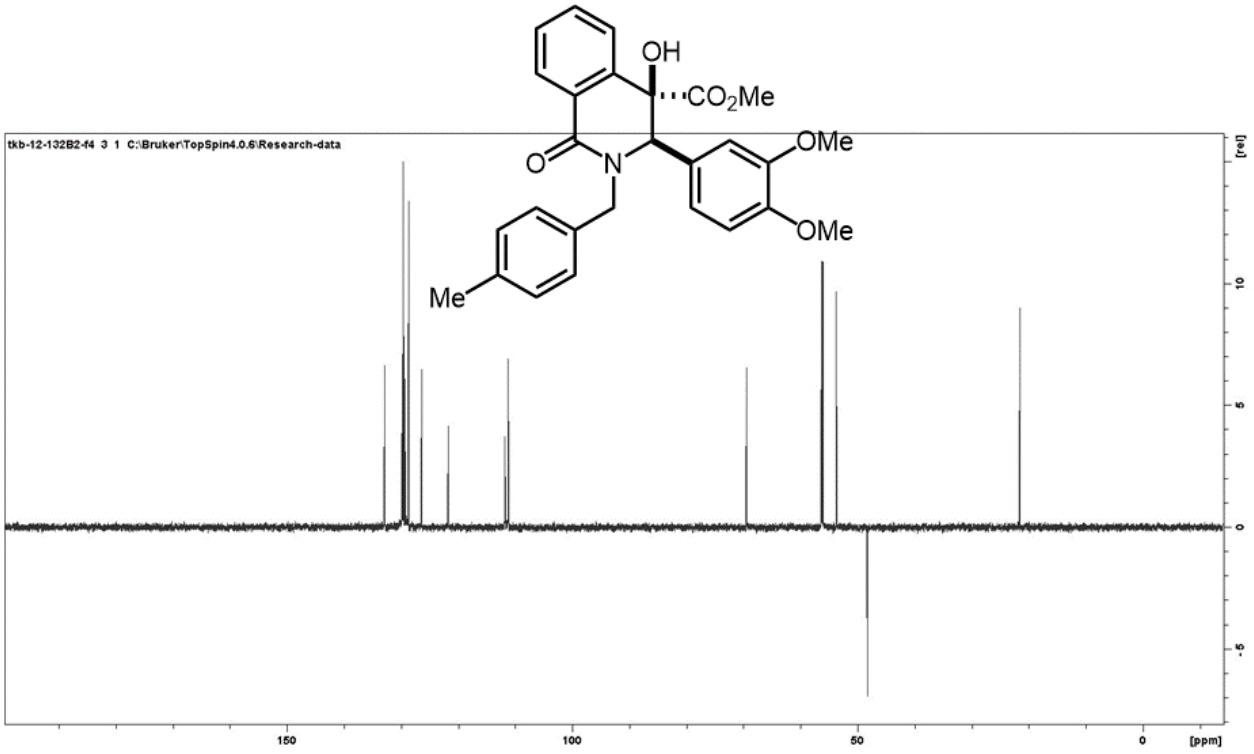
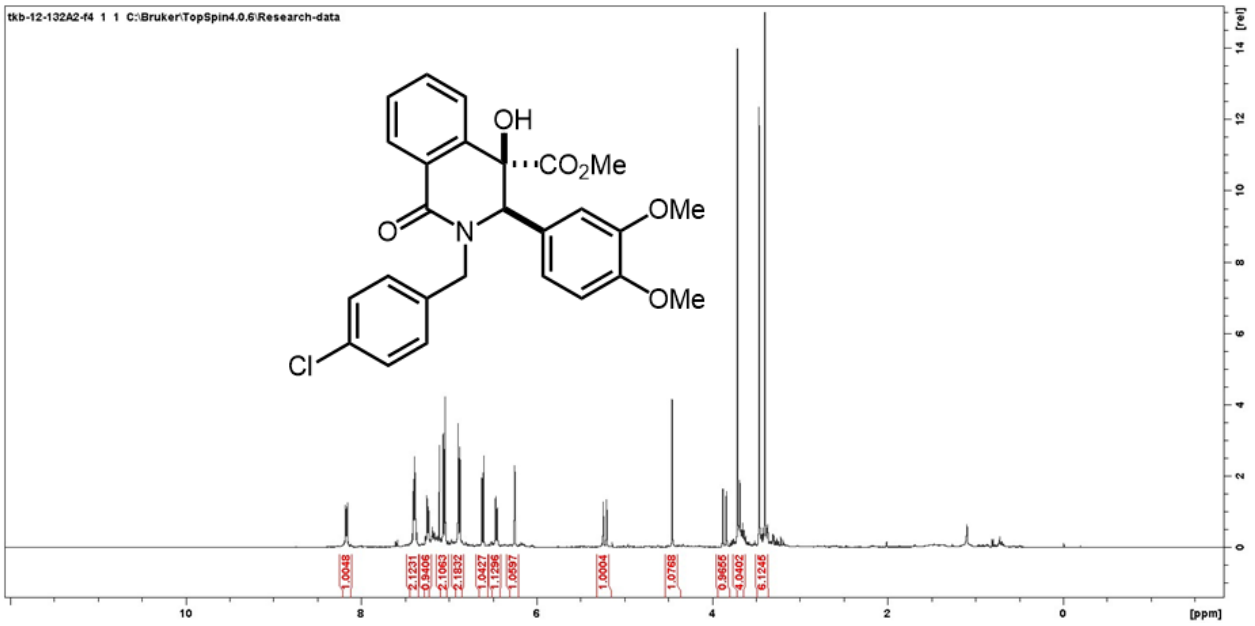


Compound 2s

Prepared from ester **1s** (0.5 mmol) using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Oily substance. Yield = 207.2 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.33 (m, 2H), 7.29 – 7.21 (m, 1H), 7.09 – 7.01 (m, 2H), 6.85 – 6.76 (m, 2H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.46 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.25 (d, *J* = 2.1 Hz, 1H), 5.22 (d, *J* = 15.2 Hz, 1H), 4.46 (s, 1H), 3.86 (d, *J* = 15.2 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 1H), 3.43 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.80, 164.68, 149.56, 148.87, 136.18, 135.51, 133.19, 132.66, 129.61, 129.48, 128.97, 128.83, 128.64, 126.62, 125.87, 121.40, 111.32, 110.85, 76.81, 69.39, 55.96, 55.73, 53.50, 47.65. HRMS calc for $C_{26}H_{24}ClNO_6$ 481.1292, found 481.1295.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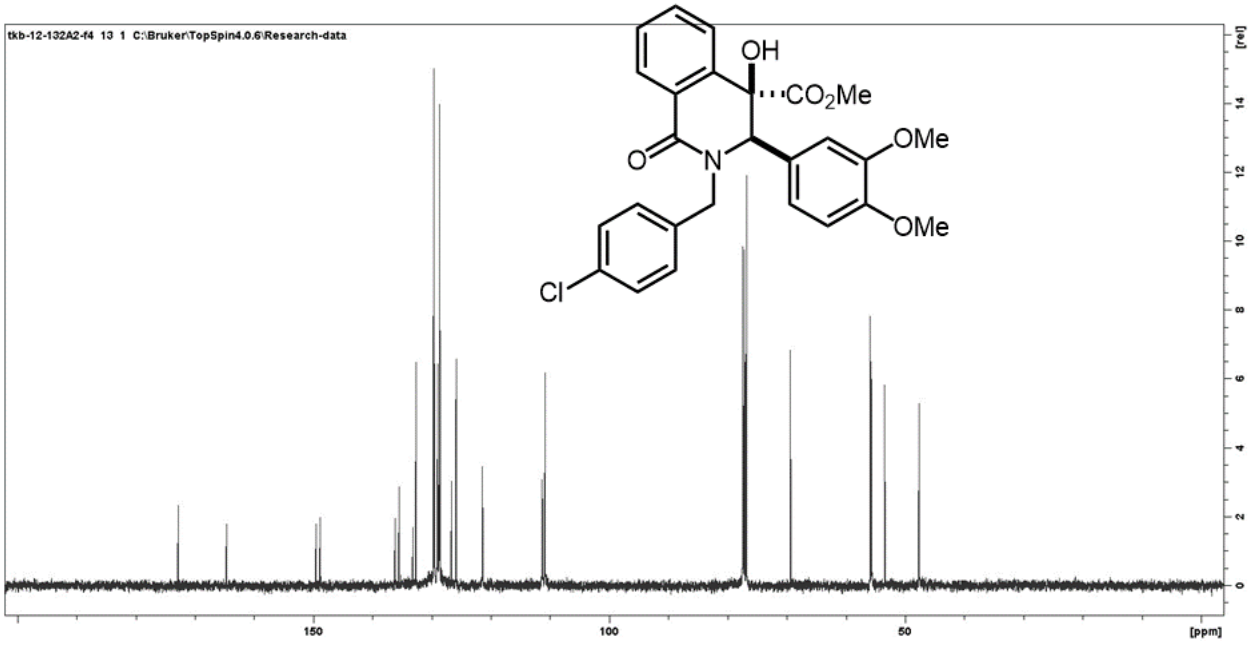
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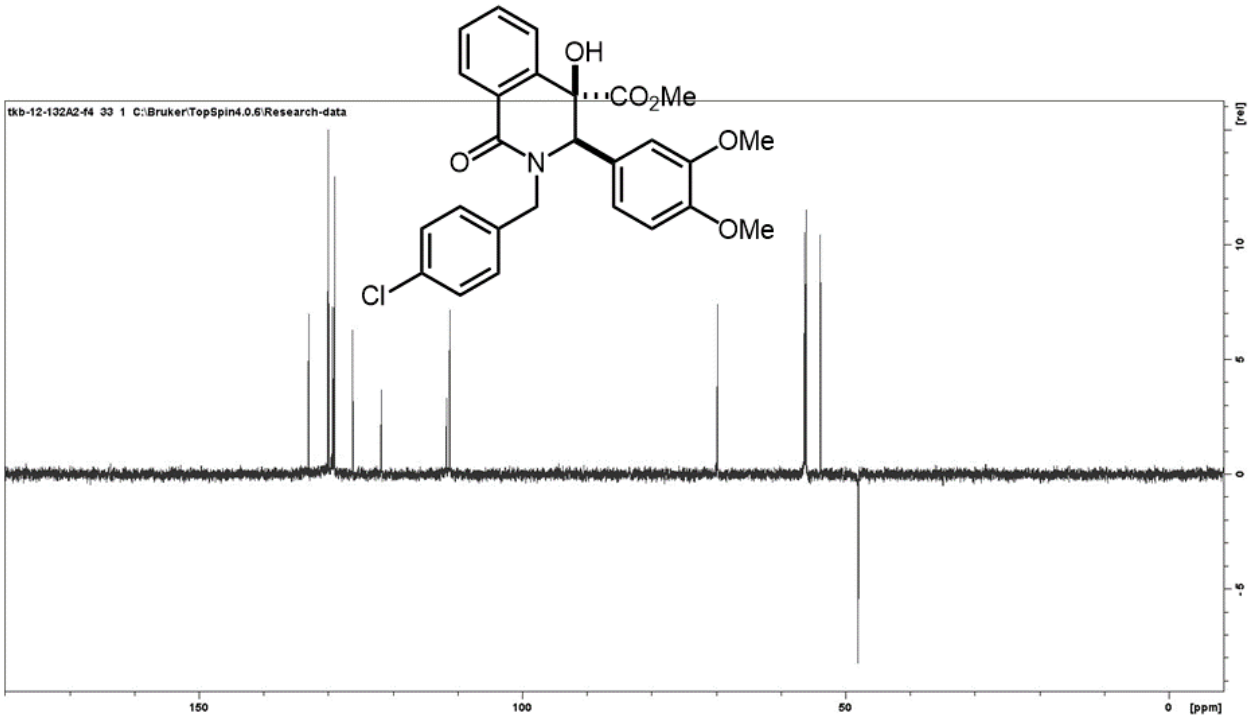
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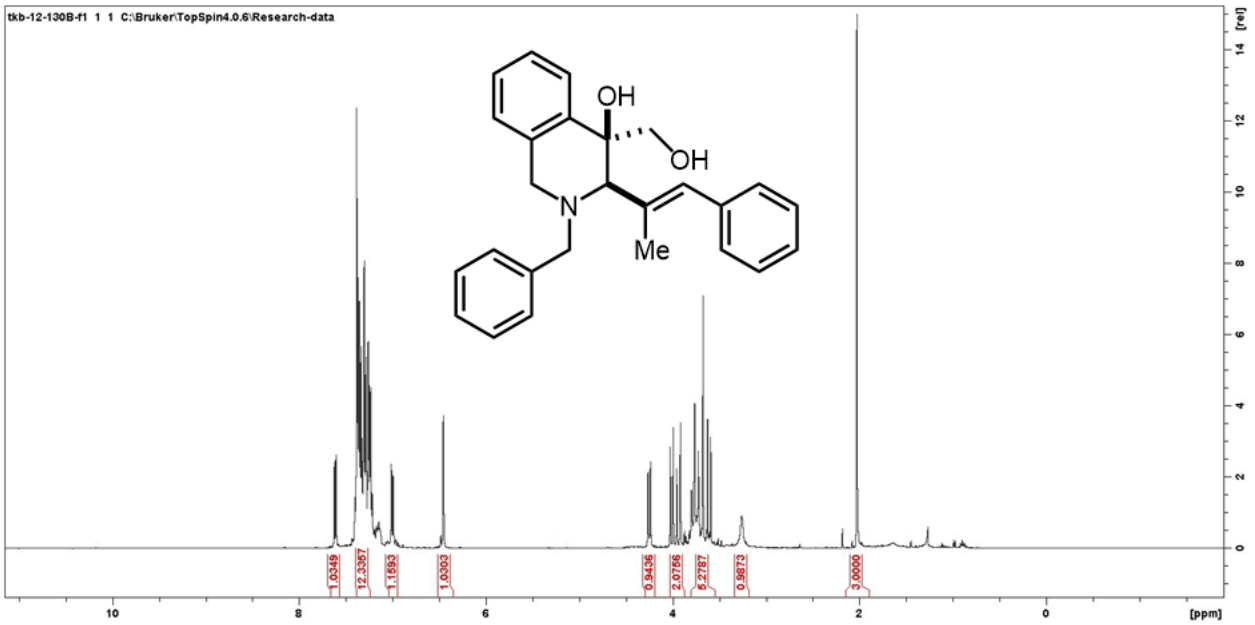
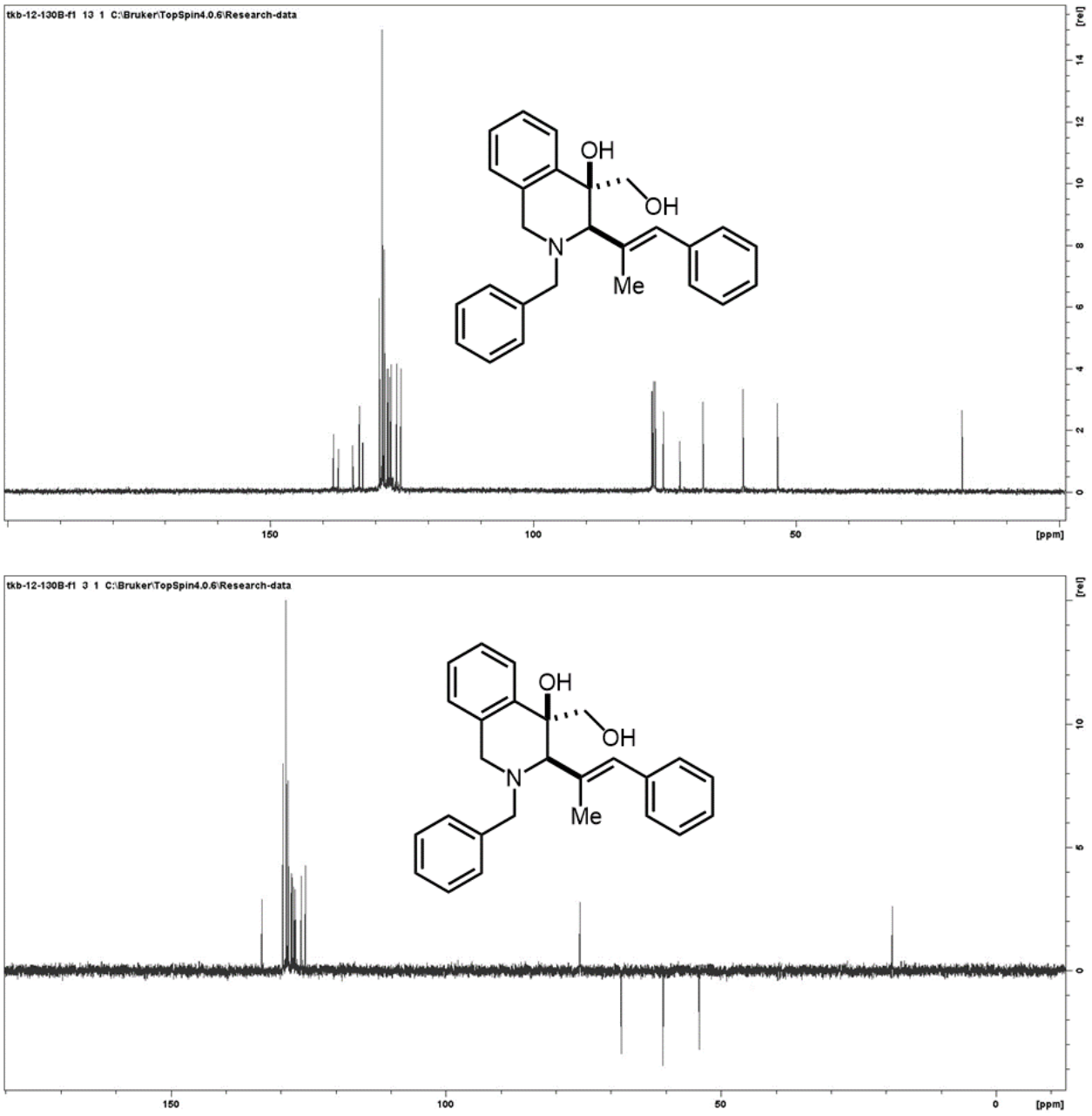
Compound 10a

Prepared from ester **2a** (0.5 mmol) using **General Procedure B.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 175.4 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.49 – 7.29 (m, 12H), 7.05 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.47 (s, 1H), 4.30 (d, *J* = 10.7 Hz, 1H), 4.06 (d, *J* = 13.3 Hz, 1H), 3.98 (d, *J* = 16.0 Hz, 1H), 3.80 – 3.65 (m, 3H), 3.62 (s, 1H), 3.56 (d, *J* = 13.3 Hz, 1H), 3.30 (s, 1H), 1.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.05, 138.04, 137.11, 134.37, 133.12, 132.46, 129.30, 128.77, 128.34, 127.80, 127.63, 127.32, 127.05, 125.99, 125.22, 75.30, 72.14, 67.80, 60.19, 53.60, 18.48. HRMS calc for $C_{26}H_{27}NO_2$ 385.2042, found 385.2047.

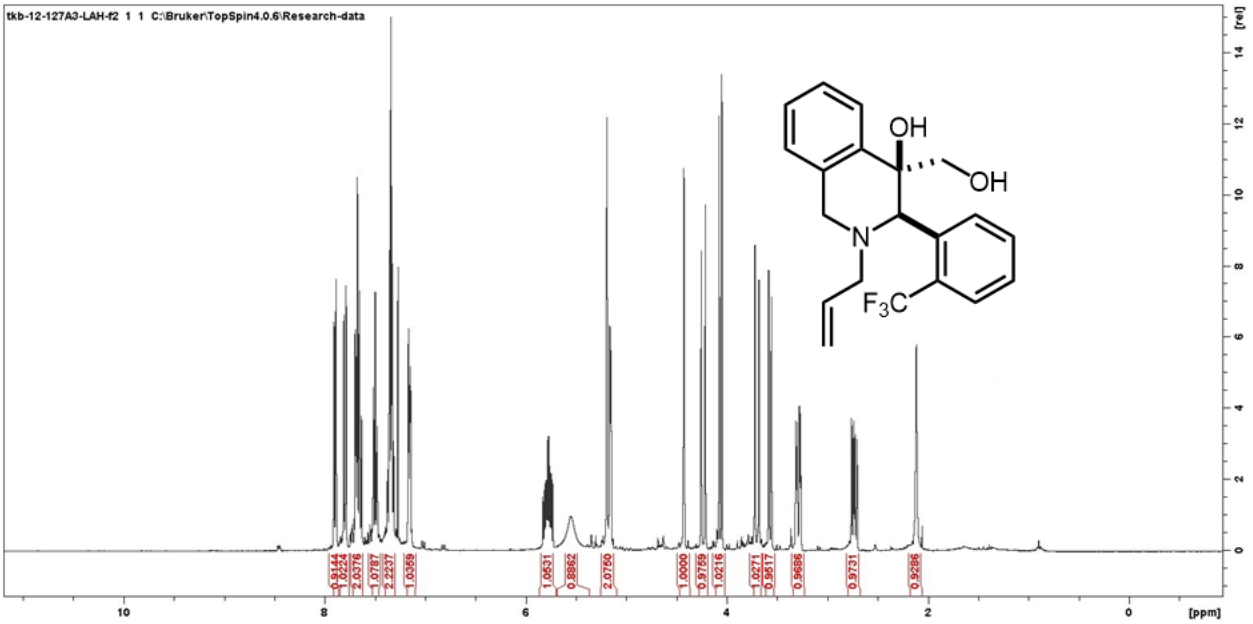


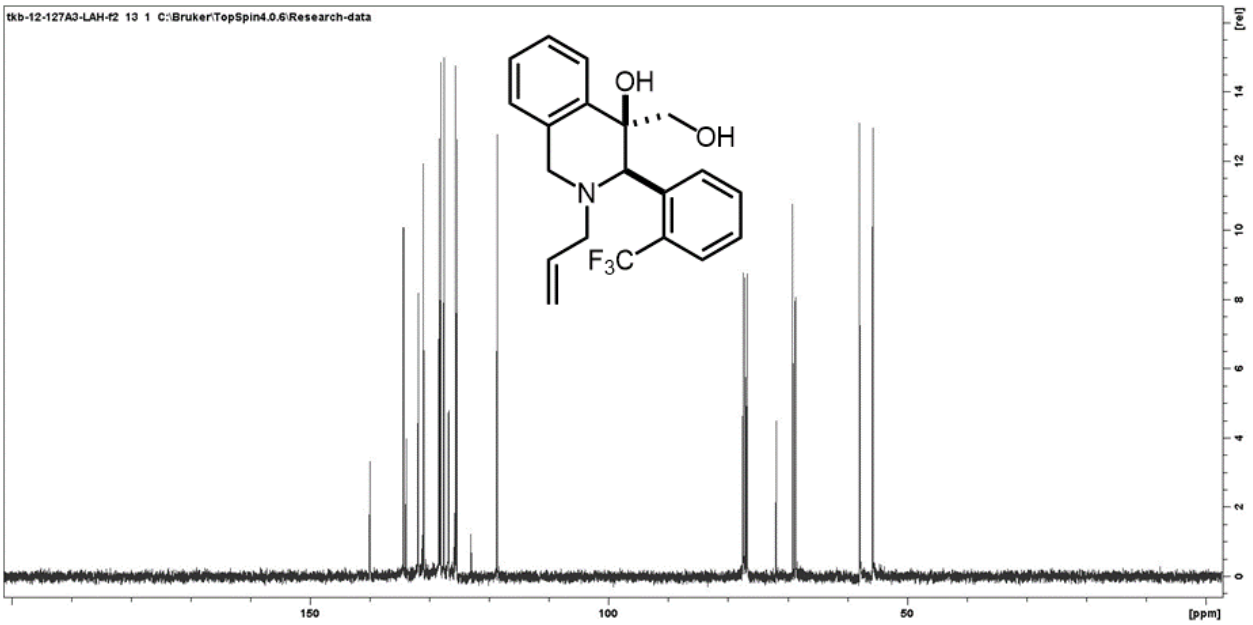


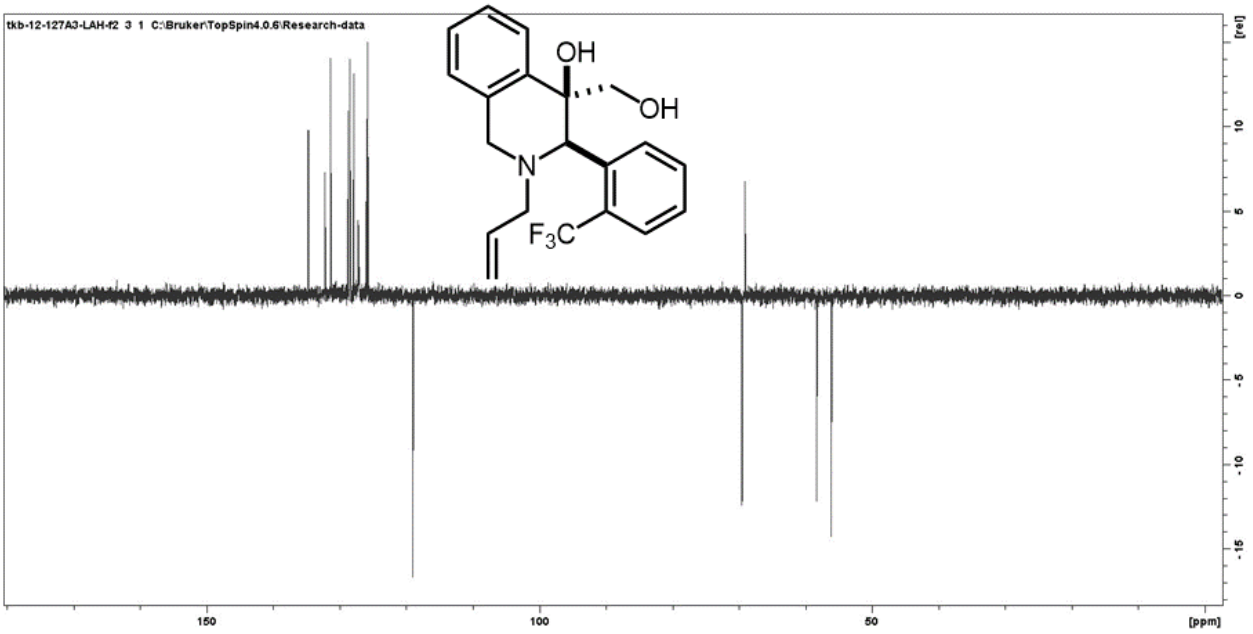
Compound 10b

Prepared from ester **2p** (0.25 mmol) using **General Procedure B.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (40:60). Oily substance. Yield = 85.4 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.9 Hz, 1H), 7.73 (dd, J = 8.1, 1.4 Hz, 1H), 7.68 – 7.50 (m, 2H), 7.48 – 7.39 (m, 1H), 7.34 – 7.26 (m, 2H), 7.12 – 7.06 (m, 1H), 5.81 (dddd, J = 17.6, 9.7, 8.0, 5.0 Hz, 1H), 5.59 (s, 1H), 5.30 – 5.24 (m, 2H), 4.46 (s, 1H), 4.27 (d, J = 16.0 Hz, 1H), 4.10 (d, J = 10.8 Hz, 1H), 3.74 (d, J = 16.0 Hz, 1H), 3.51 (d, J = 10.8 Hz, 1H), 3.33 (dd, J =

13.7, 5.0 Hz, 1H), 2.77 (dd, J = 13.7, 8.0 Hz, 1H), 2.15 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.92, 134.36, 133.87, 131.86, 131.01, 128.36, 128.10, 127.53, 126.85, 126.79, 125.61, 125.43, 123.04, 118.63, 71.94, 69.18, 68.74, 57.98, 55.77. HRMS calc for $C_{20}H_{20}F_3NO_2$ 363.1446, found 363.1149.



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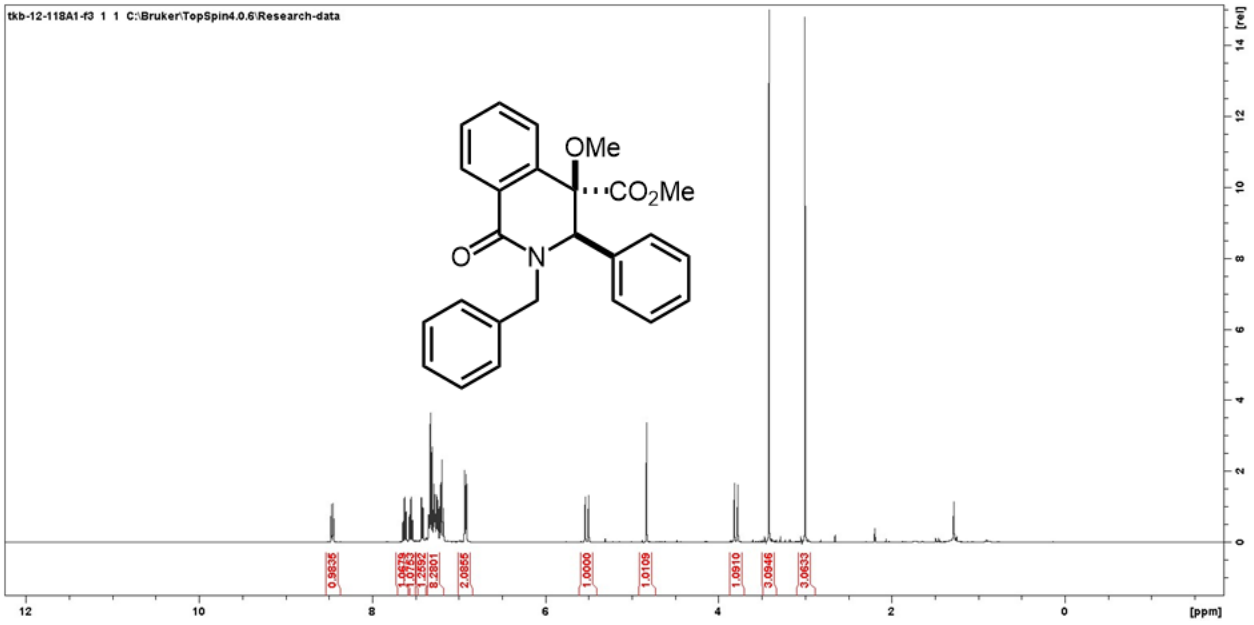
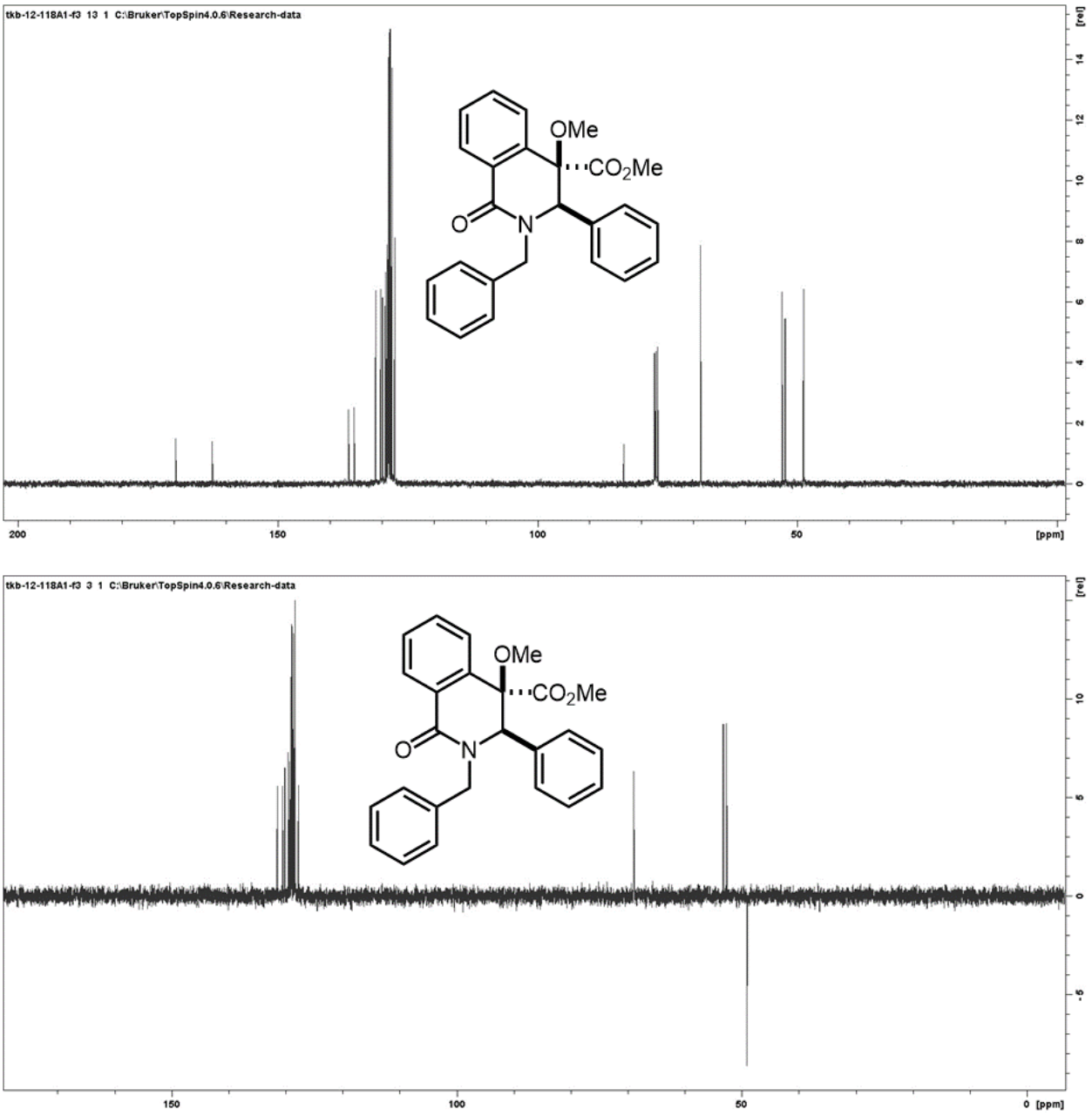
[ppm]
[rel]

Compound 3a

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Oily substance. Yield = 158.6 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 7.7 Hz, 1H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H), 7.57 (td, *J* = 7.6, 1.3 Hz, 1H), 7.45 (d, *J* = 7.3 Hz 1H), 7.32 – 7.27 (m, 8H), 6.85 (d, *J* = 7.2 Hz, 2H), 5.54 (d, *J* = 15.2 Hz, 1H), 4.85 (s, 1H), 3.82 (d, *J* = 15.2 Hz, 1H), 3.44 (s, 3H), 3.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.57, 162.56, 136.33, 135.27, 131.18, 131.12, 130.18, 129.81, 129.79, 129.24, 128.93, 128.67, 128.54, 128.30, 127.98, 127.44, 83.35, 68.62, 52.89, 52.30, 48.76. HRMS calc for $C_{25}H_{23}NO_4$ 401.1627, found 401.1633. FTIR (KBr): 2976.0754, 2927.2335, 1721.7979, 1650.1792, 1492.0415, 1438.4625, 1362.2698, 1320.5399, 1290.1484, 1206.364, 1180.3512, 1146.7618, 1132.397, 995.8166, 918.8793, 700.1334

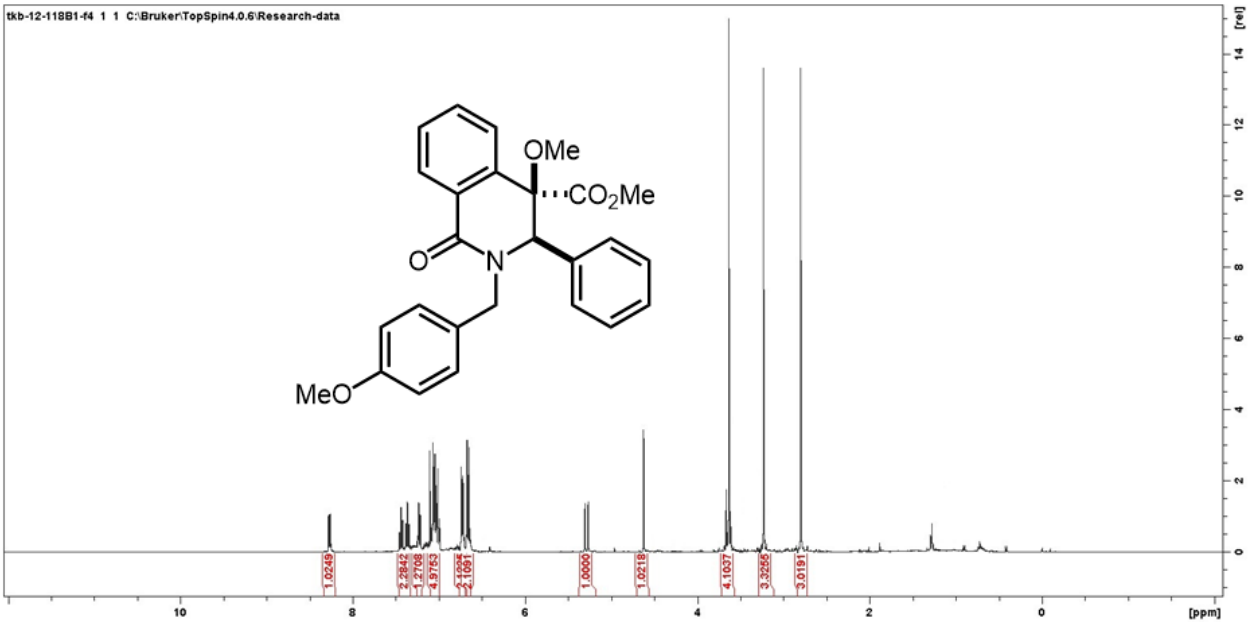


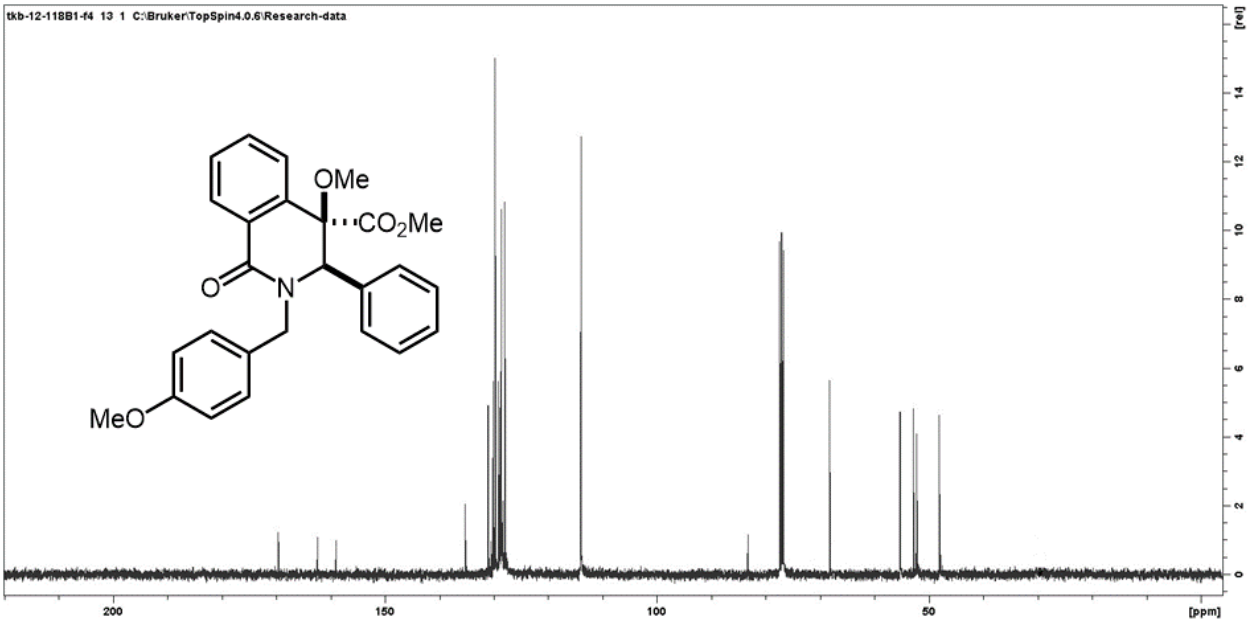


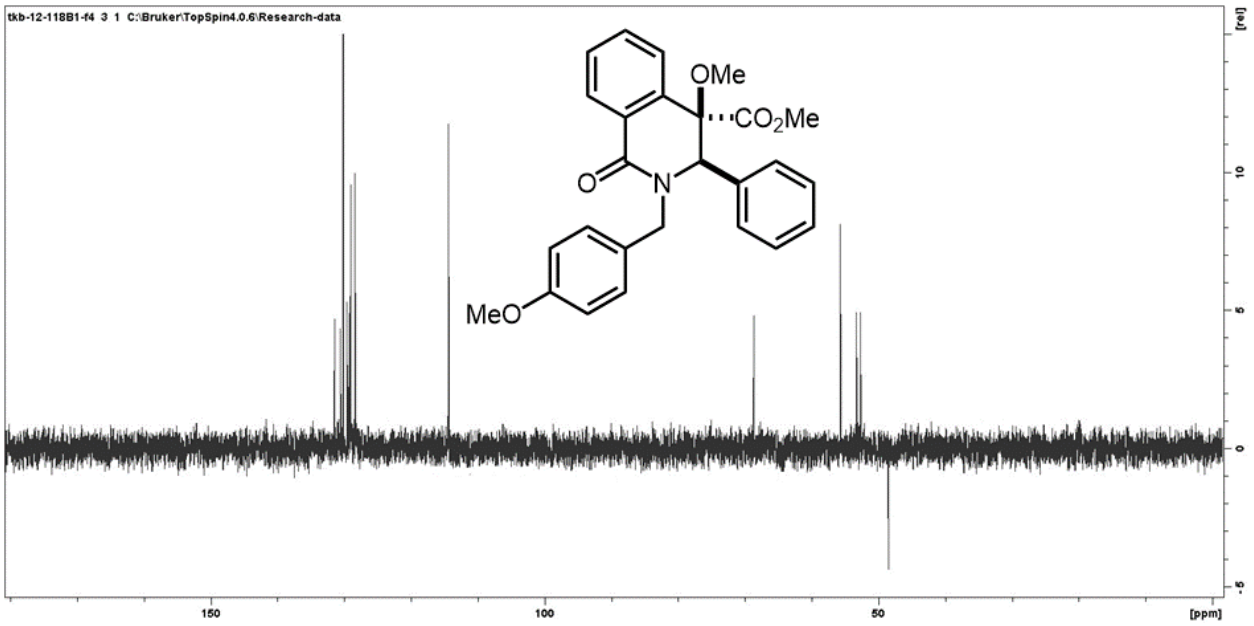
Compound 3b

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (10:90). Oily substance. Yield = 176.9 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.2 Hz 1H), 7.44 (tt, *J* = 7.6, 1.8 Hz, 1H), 7.37 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.27 – 7.21 (m, 5H), 6.75 – 6.60 (m, 4H), 5.29 (d, *J* = 15.0 Hz, 1H), 4.63 (s, 1H), 3.68 – 3.62 (m, 4H), 3.23 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.62, 162.44, 159.04, 135.33, 131.07, 130.15, 129.76, 129.72, 129.21, 129.19, 128.87, 128.64, 127.98,

114.02, 113.99, 83.31, 68.27, 55.33, 52.87, 52.29, 48.12. HRMS calc for $C_{26}H_{25}NO_5$ 431.1733, found 431.1736. FTIR (KBr): 2930.9333, 1721.7229, 1664.1745, 1606.8615, 1576.9493, 1511.8758, 1422.3889, 1359.3077, 1300.0014, 1250.9591, 1175.8146, 1113.165, 1031.2694, 996.2804, 970.248, 923.7263, 826.1509, 764.8959.



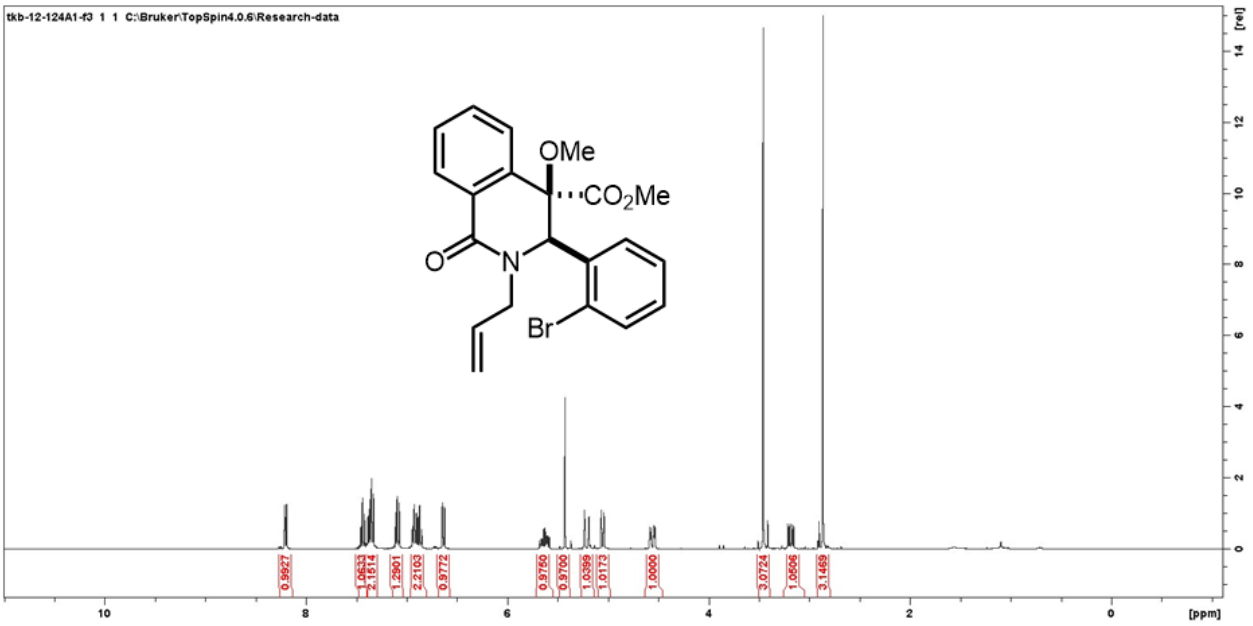




Compound 3c

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 178.5 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1H), 7.35 (ddd, *J* = 13.8, 7.7, 1.5 Hz, 2H), 7.13 – 7.05 (m, 1H), 6.89 (dtd, *J* = 21.4, 7.5, 1.7 Hz, 2H), 6.63 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.63 (dddd, *J* = 17.3, 10.2, 7.2, 4.9 Hz, 1H), 5.42 (s, 1H), 5.21 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.05 (dq, *J* = 10.1, 1.3 Hz, 1H), 4.56 (ddt, *J* = 15.2, 4.9, 1.7 Hz, 1H), 3.46 (s, 3H), 3.18 (ddt, *J* = 15.2, 7.3, 1.3 Hz, 1H), 2.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.20, 162.01, 135.13, 132.76, 132.12, 131.77, 131.36, 130.17, 129.98, 129.80, 129.67, 129.22, 129.14, 127.93, 124.90, 118.89, 82.76, 65.53, 53.21, 52.77, 48.27. HRMS calc for $C_{21}H_{20}BrNO_4$ 429.0576, found 429.0583.

FTIR (KBr): 2932.4213, 1721.5204, 1666.3806, 1606.9472, 1511.0233, 1448.5693, 1414.7191, 1384.979, 1357.4641, 1298.7878, 1247.5543, 1179.3944, 1135.9684, 1031.8974, 995.8644, 968.9312, 919.9415, 831.0313, 750.2581, 694.7613.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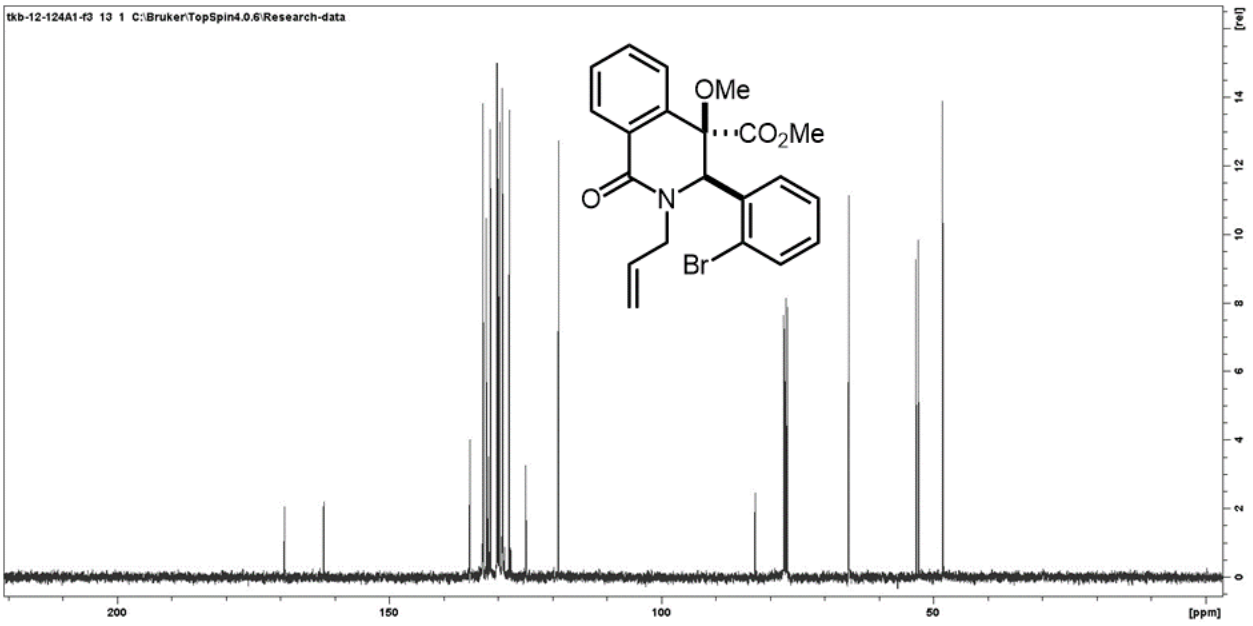
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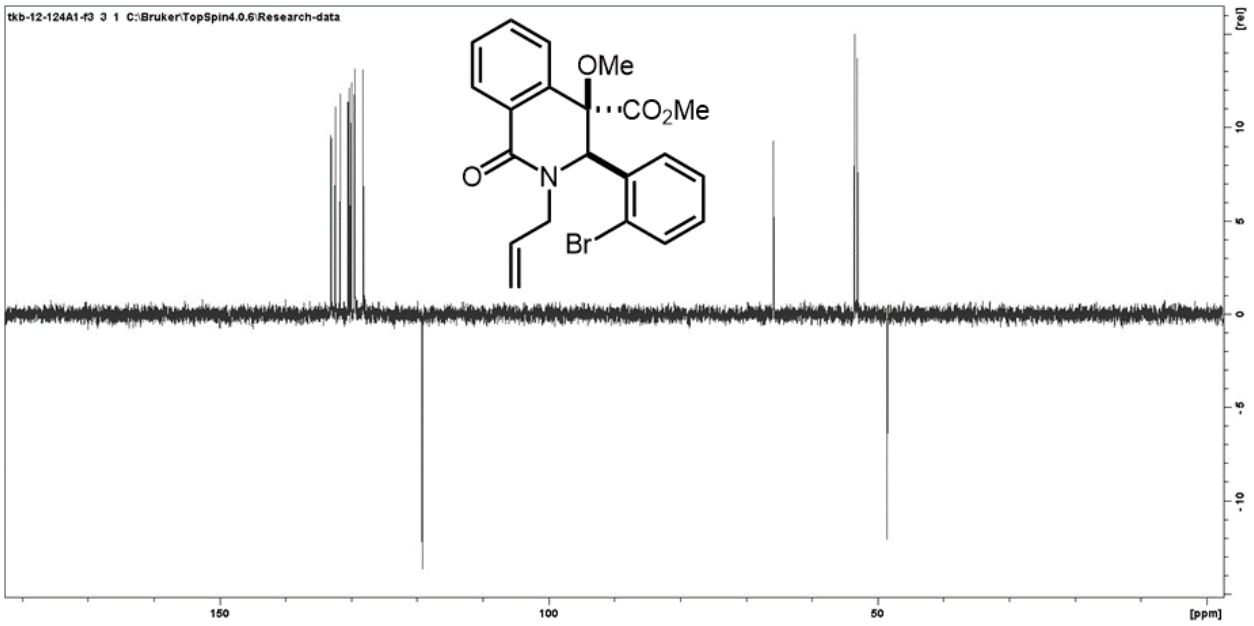
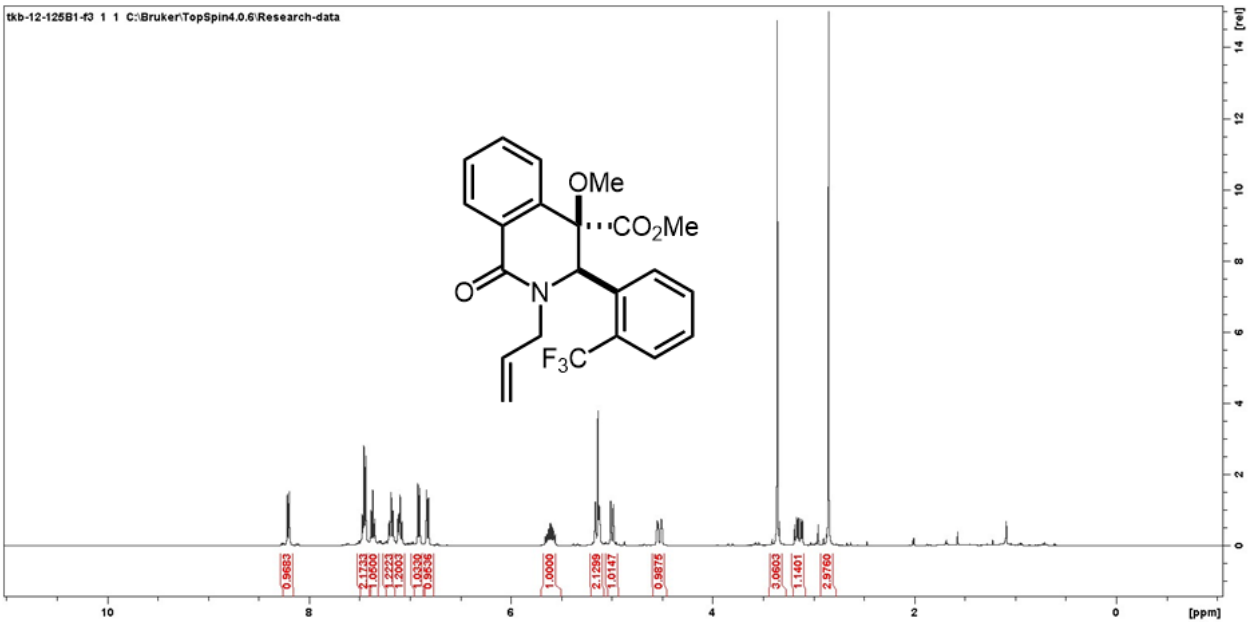


Compound 3d

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 167.8 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.55 – 7.41 (m, 2H), 7.37 (td, *J* = 7.6, 1.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.10 (td, *J* = 7.8, 1.5 Hz, 1H), 6.91 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.61 (dddd, *J* = 17.1, 10.7, 6.6, 4.5 Hz, 1H), 5.19 – 5.10 (m, 2H), 5.00 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.53 (ddt, *J* = 15.6, 4.2, 1.8 Hz, 1H), 3.36 (s, 3H), 3.21 – 3.08 (m, 1H), 2.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.15, 162.03, 135.30, 132.53, 132.16, 131.85, 131.61, 130.18, 129.79, 129.39, 129.38, 129.09, 128.68, 125.69, 125.63, 122.83, 117.79, 83.26, 62.79, 62.77, 53.26, 52.40, 47.95. HRMS calc for $C_{20}H_{20}F_3NO_4$ 419.1344, found 419.1349. FTIR (KBr): 2932.5571, 1721.483, 1665.4081, 1607.2449, 1511.11, 1431.8598, 1414.7076, 1344.99, 1298.4941, 1245.6515, 1179.4413, 1135.306, 1031.8607, 996.7789, 921.8434, 832.167, 701.6744.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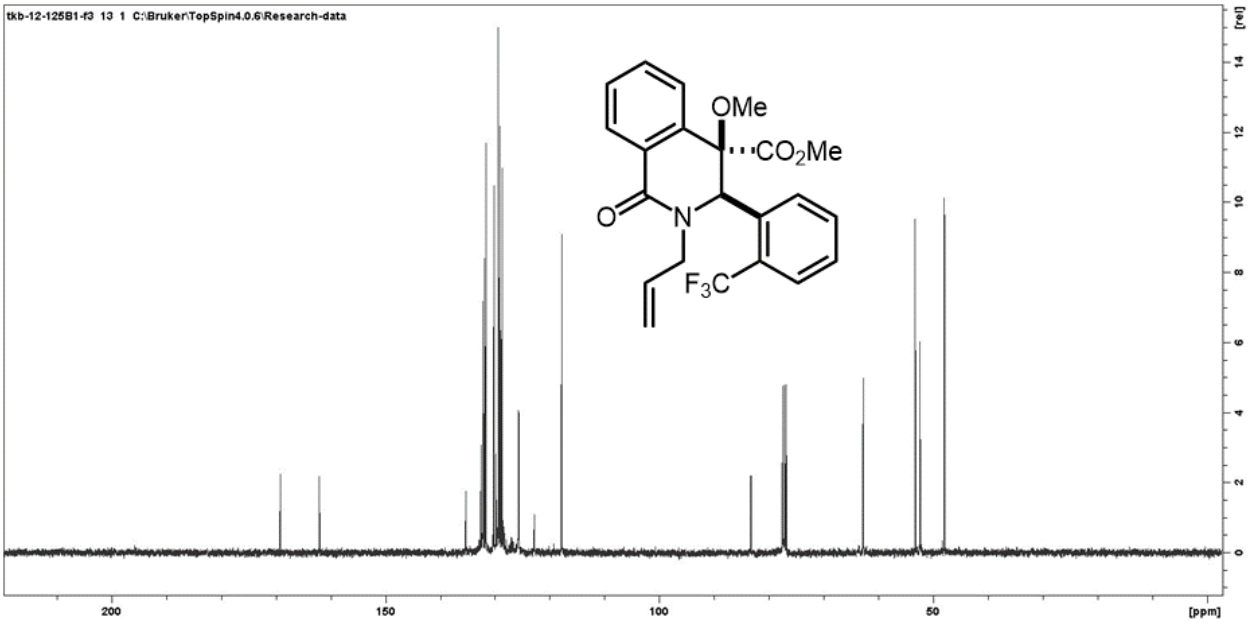
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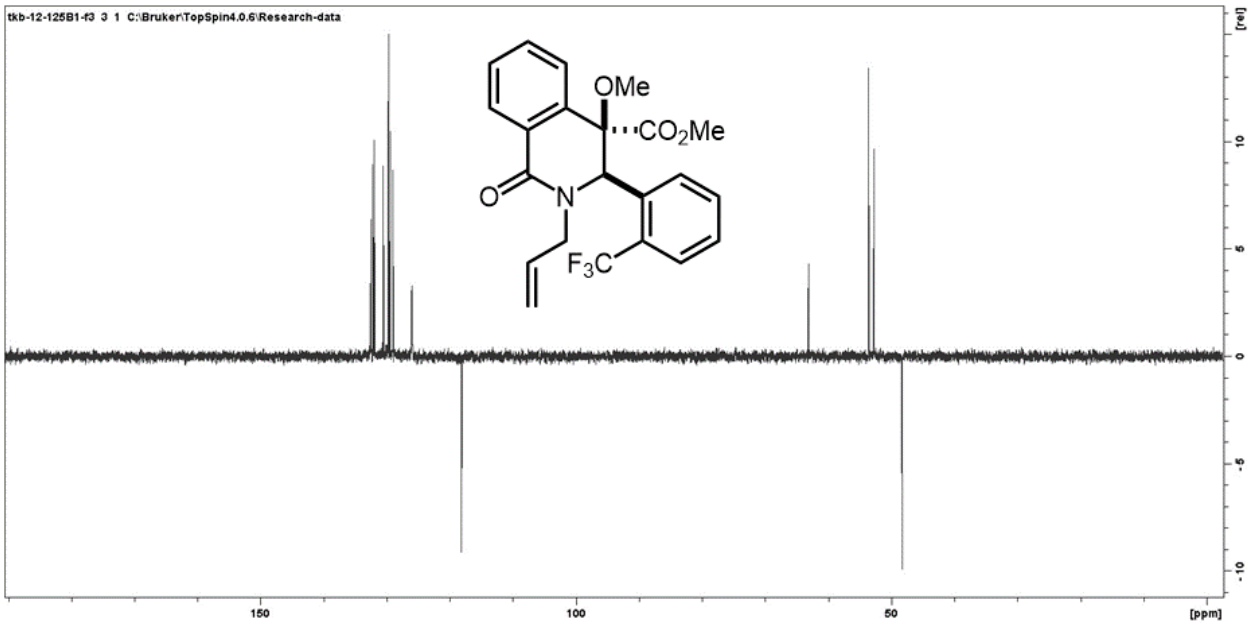
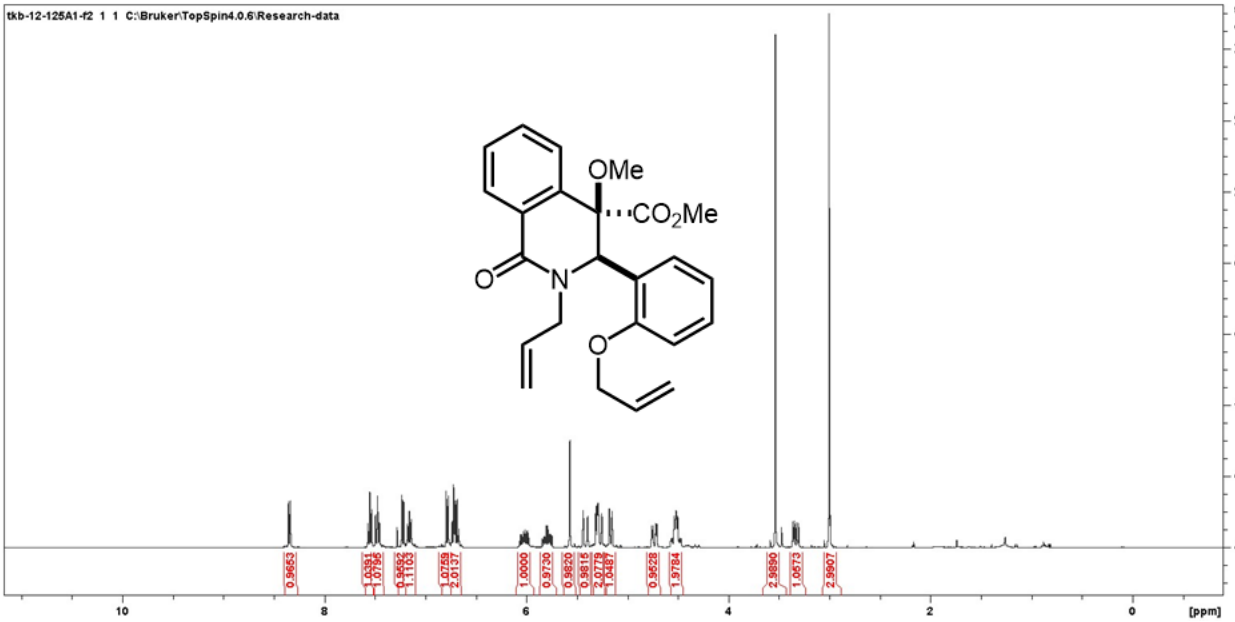


Compound 3e

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (40:60). Oily substance. Yield = 156.9 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1H), 7.50 (td, *J* = 7.6, 1.5 Hz, 1H), 7.33 – 7.22 (m, 2H), 6.81 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.79 – 6.65 (m, 2H), 6.05 (ddt, *J* = 17.4, 10.5, 5.2 Hz, 1H), 5.82 (dddd, *J* = 17.3, 10.2, 7.2, 4.9 Hz, 1H), 5.60 (s, 1H), 5.44 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.38 – 5.30 (m, 1H), 5.34 – 5.25 (m, 2H), 5.20 (dt, *J* = 10.2, 1.4 Hz, 1H), 4.76 (ddt, *J* = 15.3, 4.9, 1.7 Hz, 1H), 4.52 – 4.47 (m, 2H), 3.56 (s, 3H), 3.36 (ddt, *J* = 15.3, 7.3, 1.3 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.45, 162.65, 156.37, 132.95, 132.66, 132.23, 131.05, 130.07, 129.62, 129.60, 129.52, 128.91, 128.43, 123.87, 120.93, 118.30, 117.76, 111.28, 83.05, 69.19, 60.00, 53.15, 52.23, 48.23. HRMS calc for $C_{24}H_{25}NO_5$ 407.1733, found 407.1736.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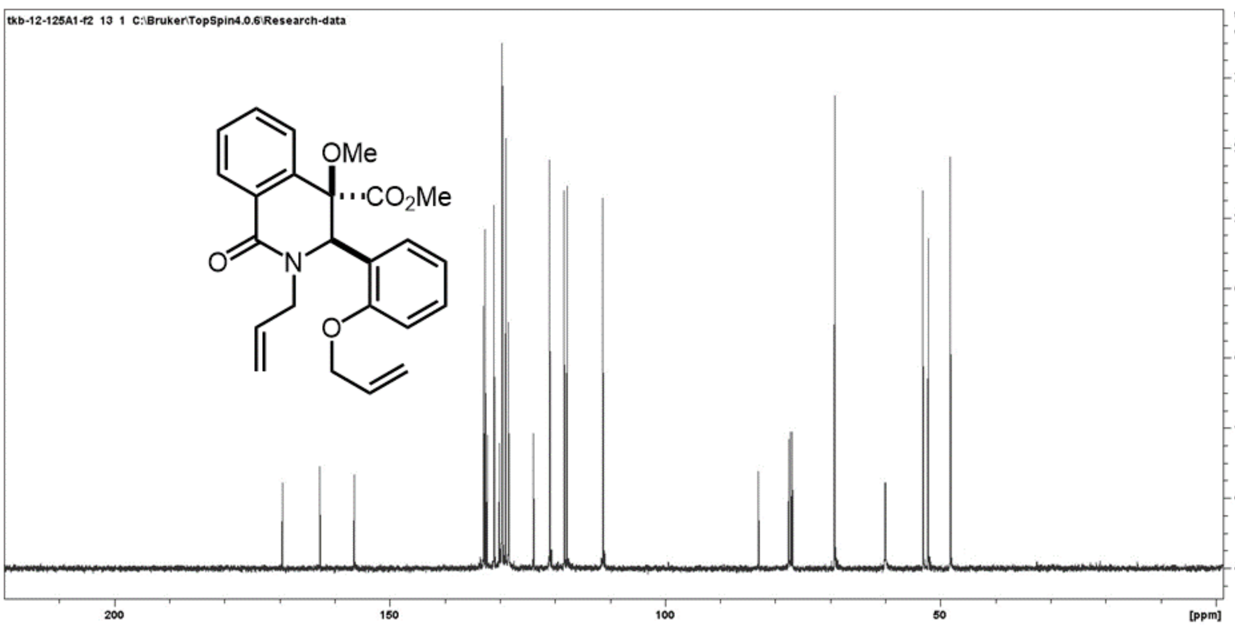
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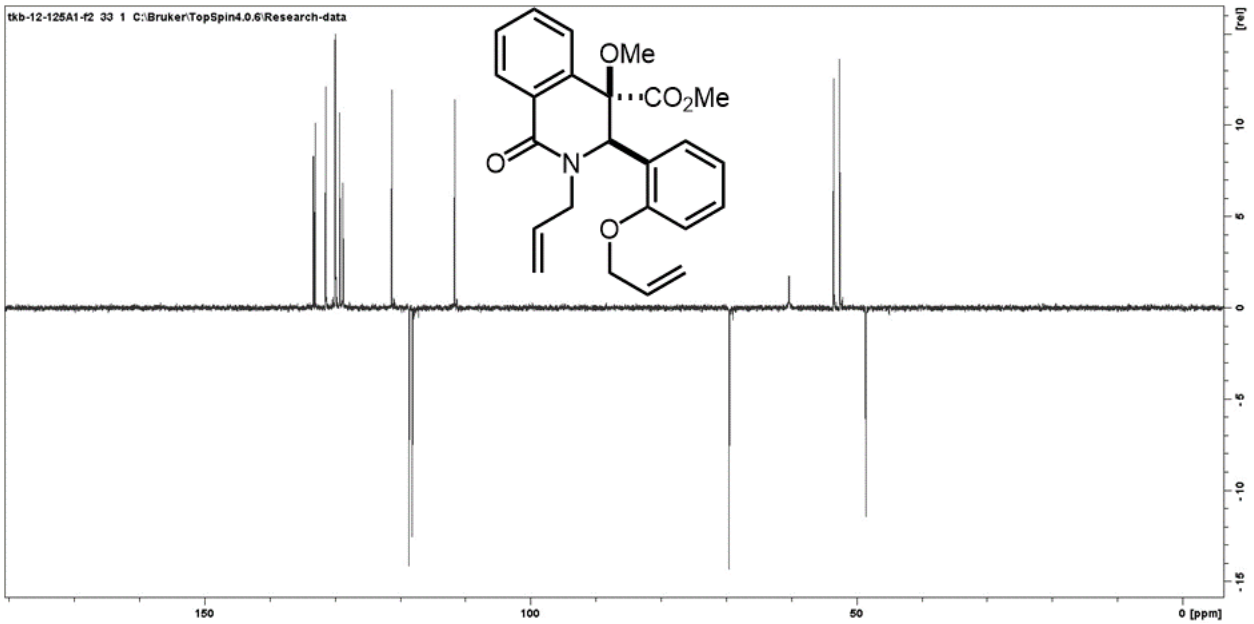
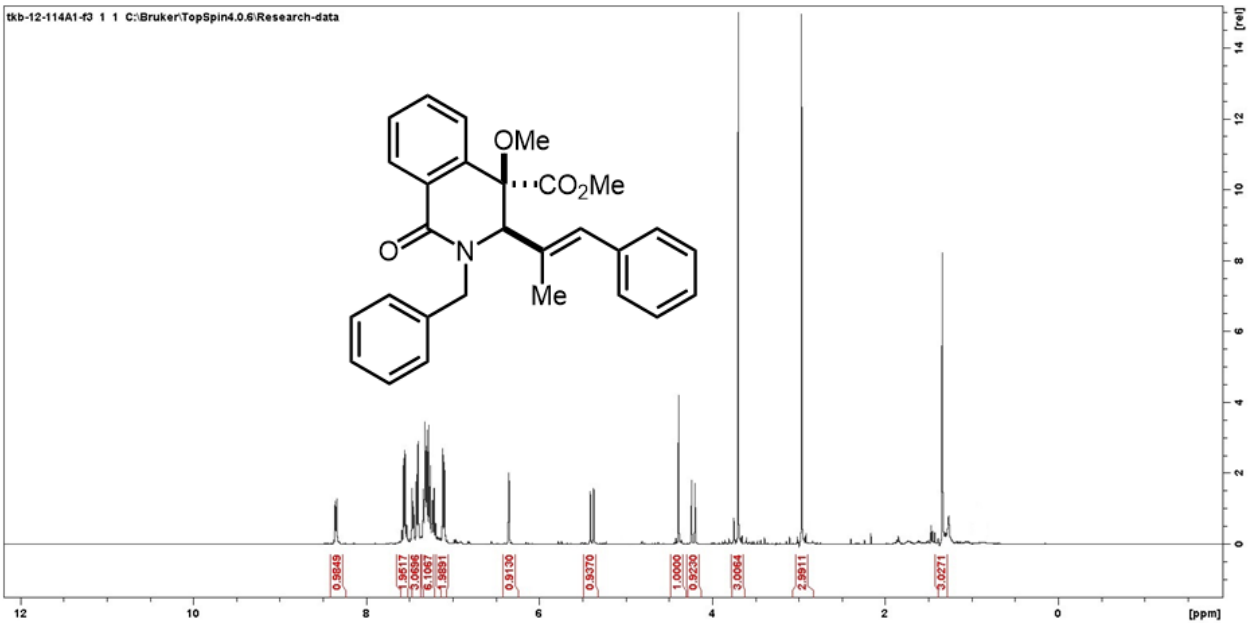


Compound 3f

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Oily substance. Yield = 183.2 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.1 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.53 – 7.24 (m, 9H), 7.28 – 7.23 (m, 2H), 6.40 (s, 1H), 5.44 (d, *J* = 15.1 Hz, 1H), 4.44 (s, 1H), 4.27 (d, *J* = 15.1 Hz, 1H), 3.75 (s, 3H), 2.99 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.01, 162.67, 136.67, 136.47, 134.00, 132.25, 132.07, 130.98, 129.91, 129.72, 129.25, 129.17, 129.04, 128.58, 128.40, 128.29, 127.47, 127.28, 82.75, 73.14, 52.74, 52.68, 48.59, 13.27. HRMS calc for $C_{28}H_{27}NO_4$ 441.1940, found 441.1936.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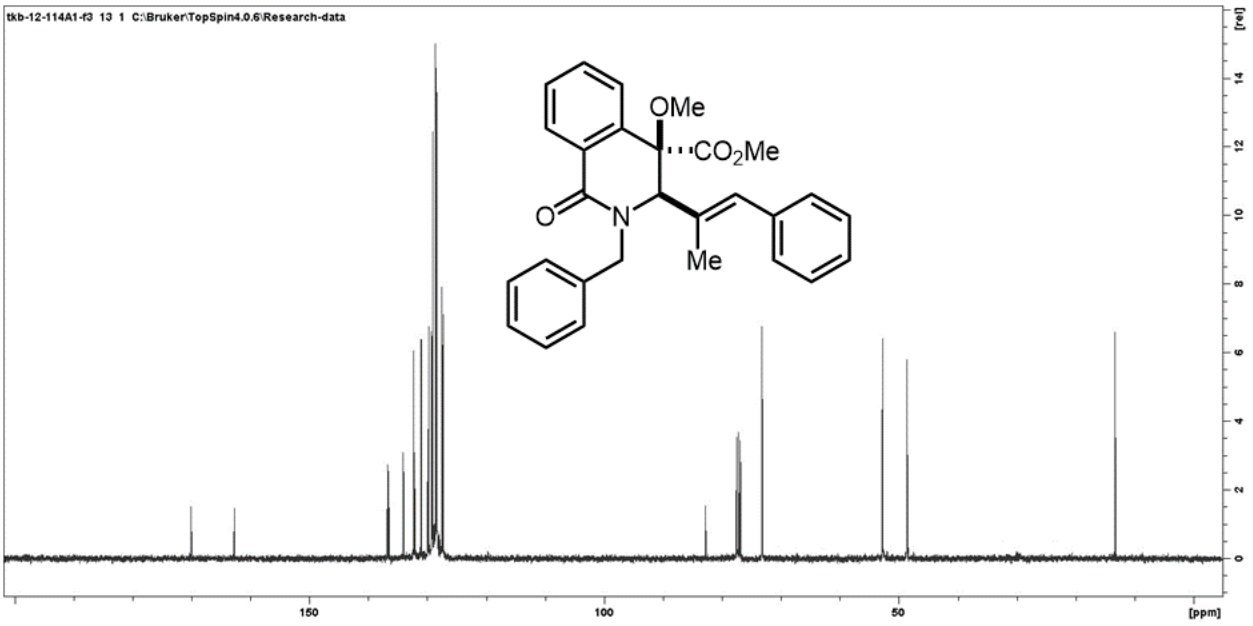
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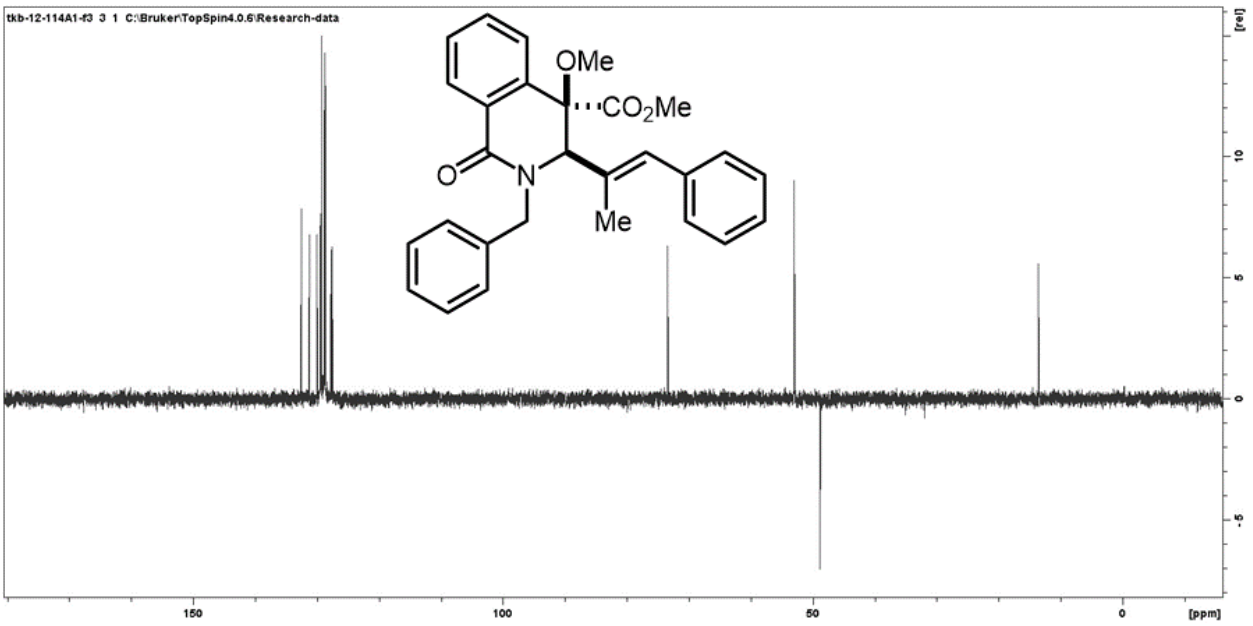
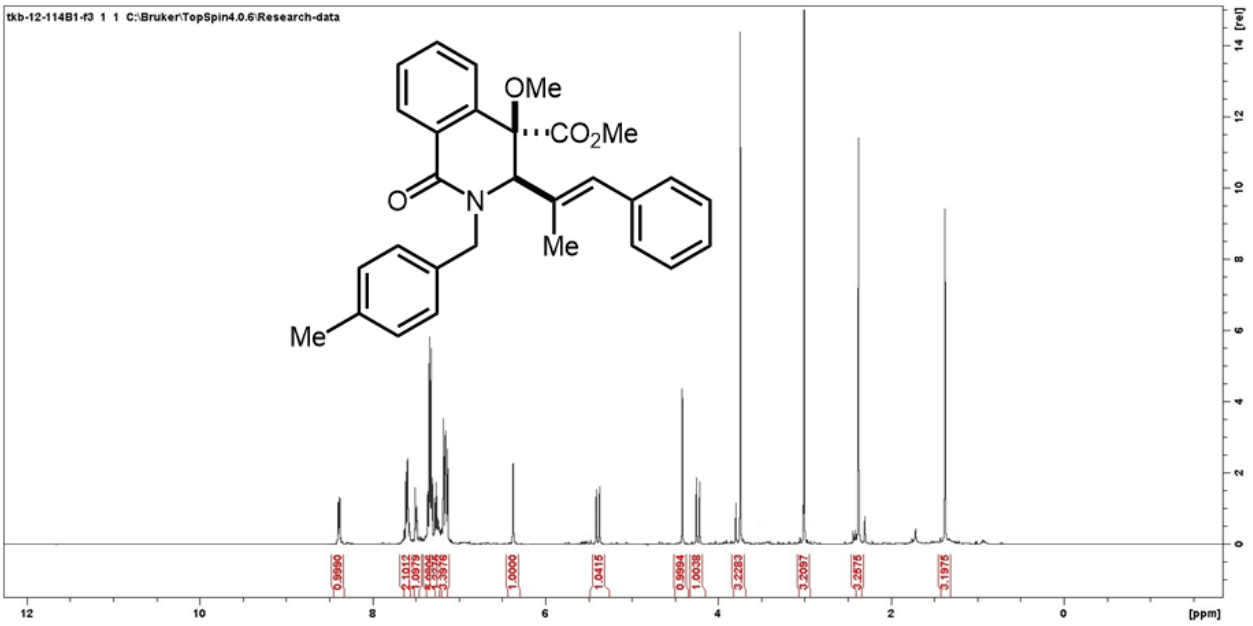


Compound 3g

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Oily substance. Yield = 180 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.3 Hz, 1H), 7.68 – 7.53 (m, 2H), 7.50 (d, *J* = 3.3 Hz, 1H), 7.33 – 7.17 (m, 9H), 6.37 (s, 1H), 5.39 (d, *J* = 14.9 Hz, 1H), 4.41 (s, 1H), 4.23 (d, *J* = 14.9 Hz, 1H), 3.74 (s, 3H), 3.00 (s, 3H), 2.46 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.05, 162.59, 137.05, 136.52, 134.04, 133.53, 132.18, 132.03, 130.92, 129.99, 129.69, 129.28, 129.23, 129.15, 129.03, 128.49, 128.27, 127.23, 82.73, 72.90, 52.72, 52.67, 48.33, 21.24, 13.26. HRMS calc for $C_{29}H_{29}NO_4$ 455.2097, found 455.2093.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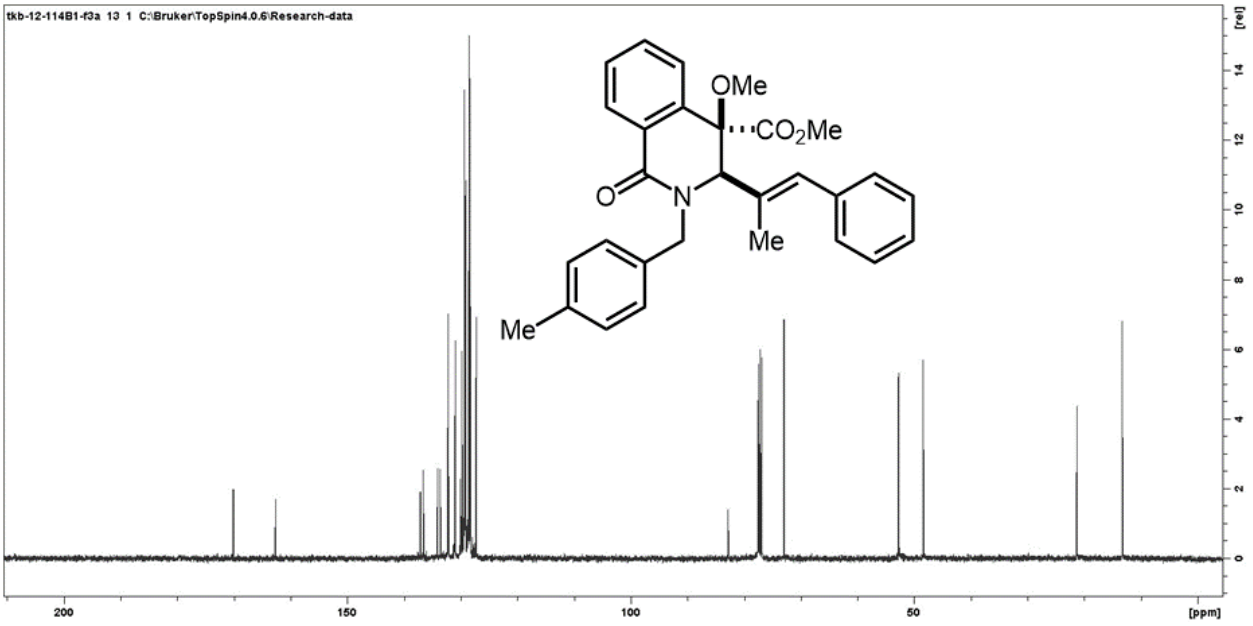
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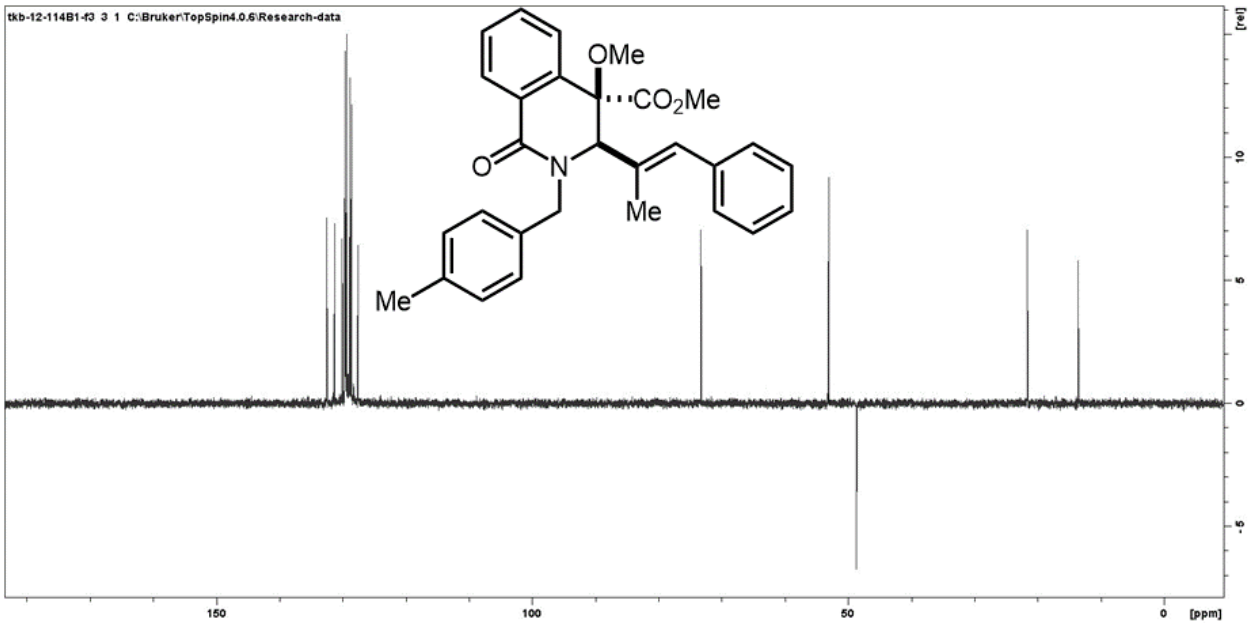
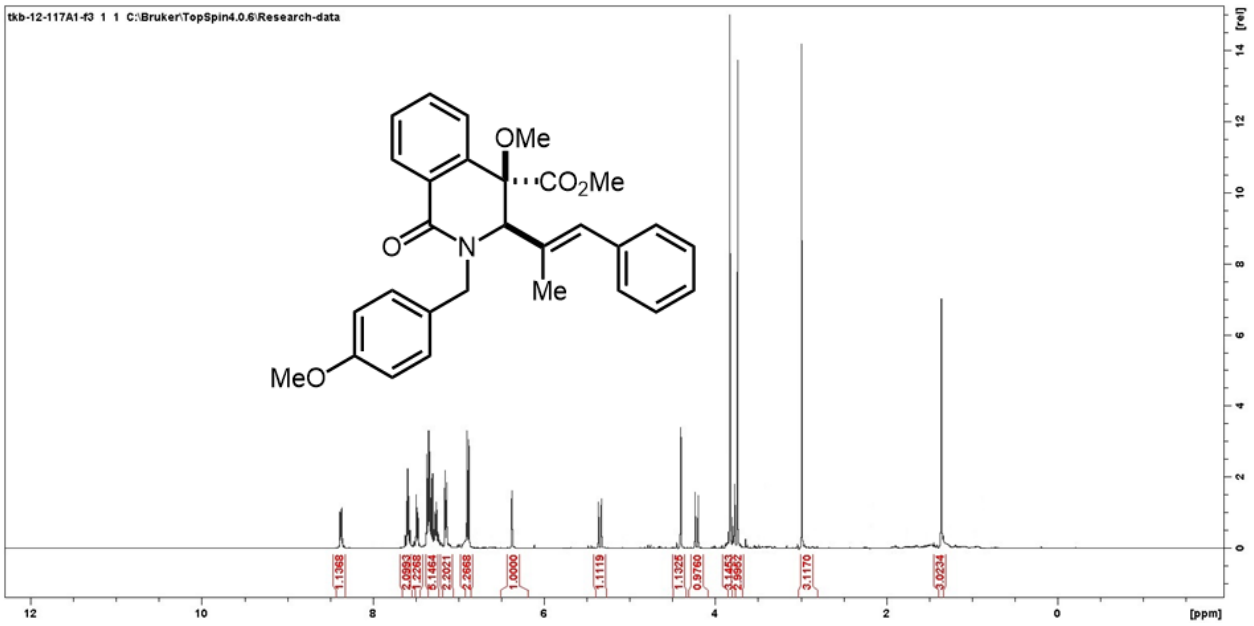


Compound 3h

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Oily substance. Yield = 202.8 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.7 Hz 1H), 7.65 – 7.54 (m, 3H), 7.43 – 7.31 (m, 5H), 7.25 (d, *J* = 7.1 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.38 (s, 1H), 5.39 (d, *J* = 14.8 Hz, 1H), 4.41 (s, 1H), 4.22 (d, *J* = 14.8 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 2.99 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.05, 162.56, 159.03, 136.50, 134.09, 132.10, 131.98, 130.93, 130.50, 129.98, 129.87, 129.70, 129.23, 129.14, 129.04, 128.65, 128.28, 127.25, 114.13, 113.99, 113.91, 82.73, 72.85, 55.32, 52.75, 52.68, 48.07, 13.26. HRMS calc for $C_{29}H_{29}NO_5$ 471.2046, found 471.2051.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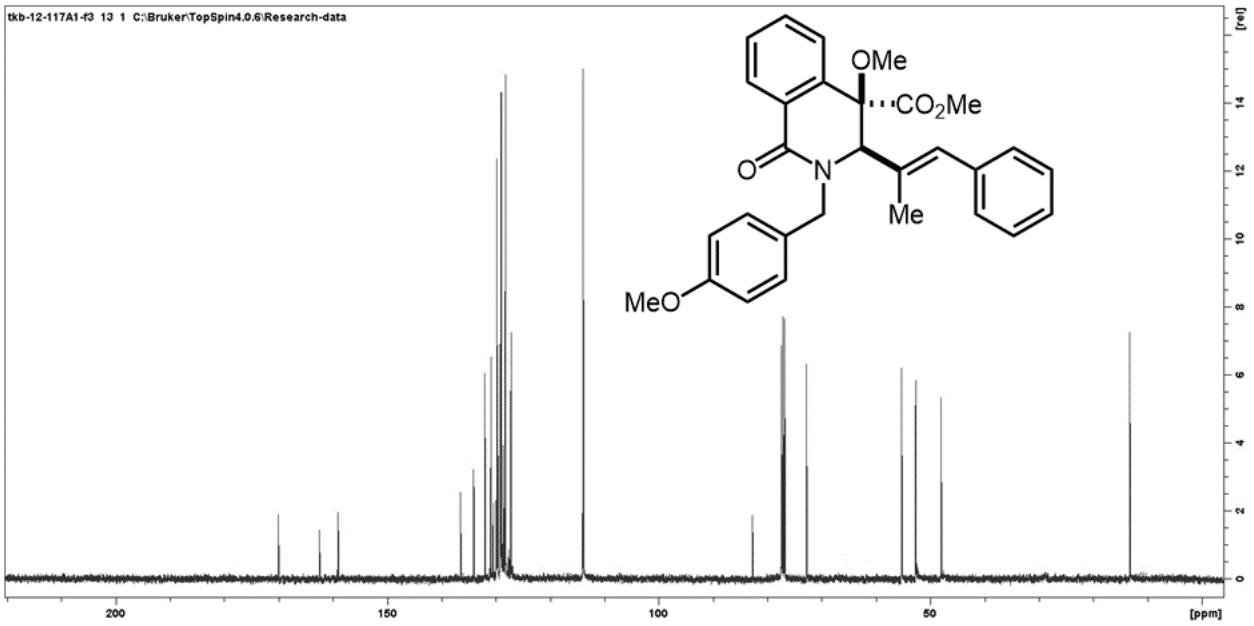
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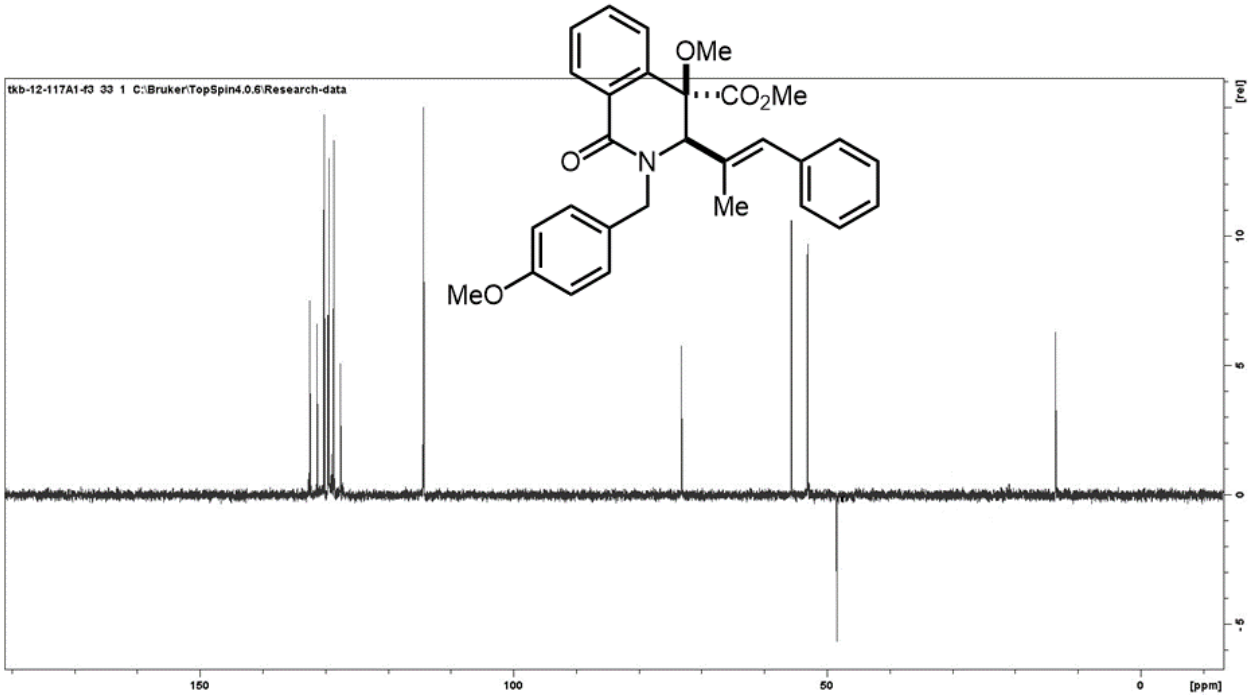
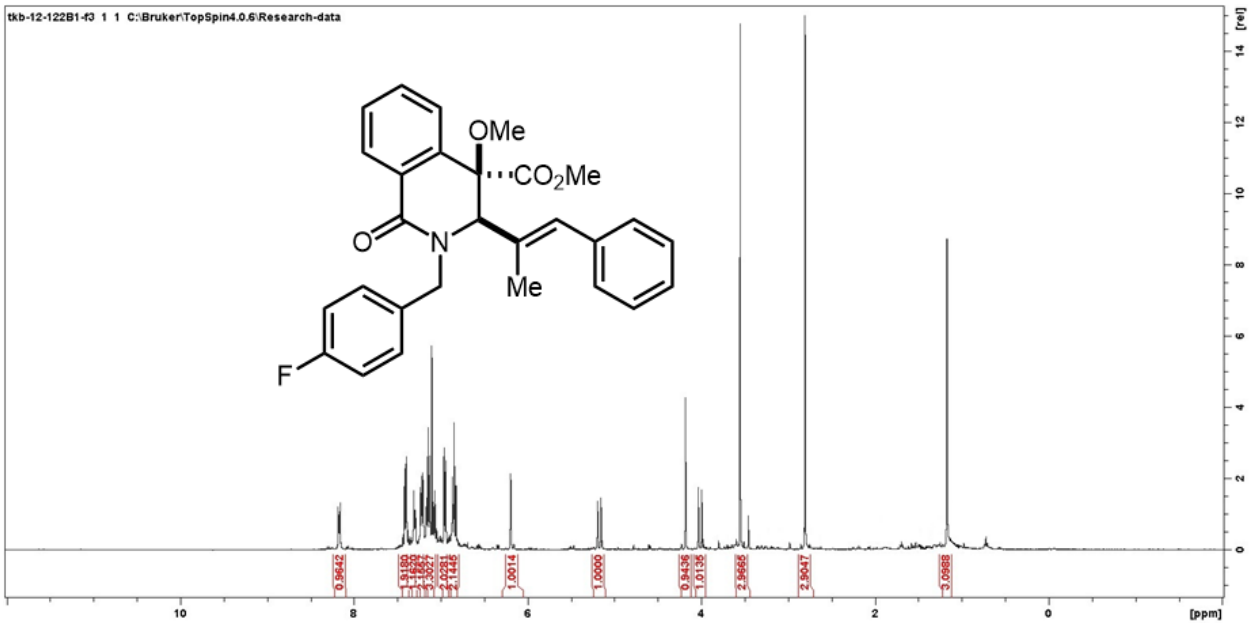


Compound 3i

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (25:75). Oily substance. Yield = 172.3 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.42 – 7.17 (m, 7H), 7.22 – 7.06 (m, 2H), 6.92 – 6.75 (m, 2H), 6.20 (s, 1H), 5.18 (d, *J* = 15.1 Hz, 1H), 4.19 (s, 1H), 4.02 (d, *J* = 15.1 Hz, 1H), 3.56 (s, 3H), 2.81 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.93, 163.53, 162.66, 161.09, 136.35, 133.91, 132.26, 131.98, 131.05, 130.07, 129.99, 129.79, 129.77, 129.26, 129.17, 129.01, 128.34, 127.36, 115.54, 115.33, 82.72, 73.22, 52.79, 52.70, 47.92, 13.26. HRMS calc for $C_{28}H_{26}FNO_4$ 459.1846, found 459.1852.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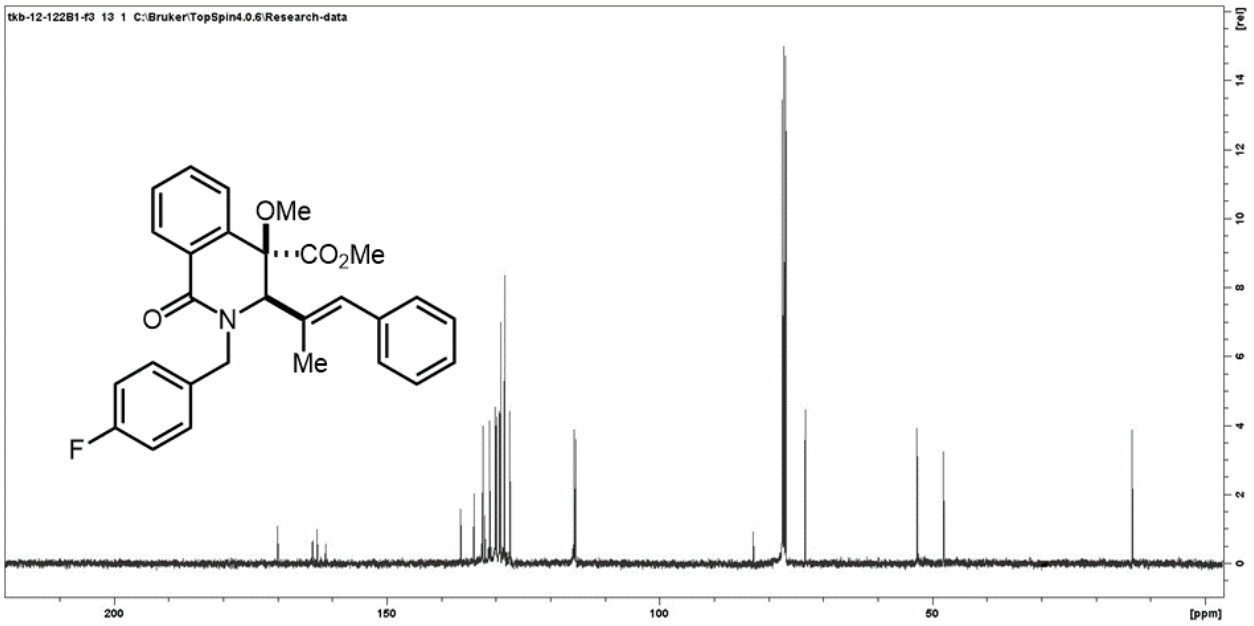
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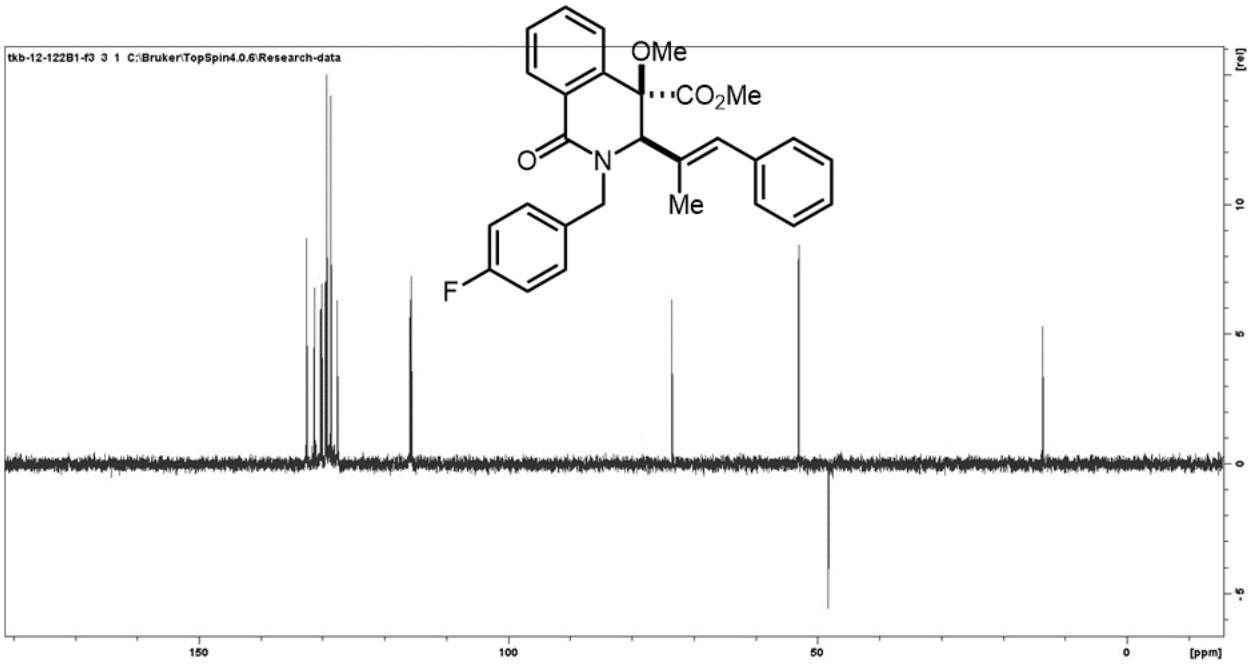
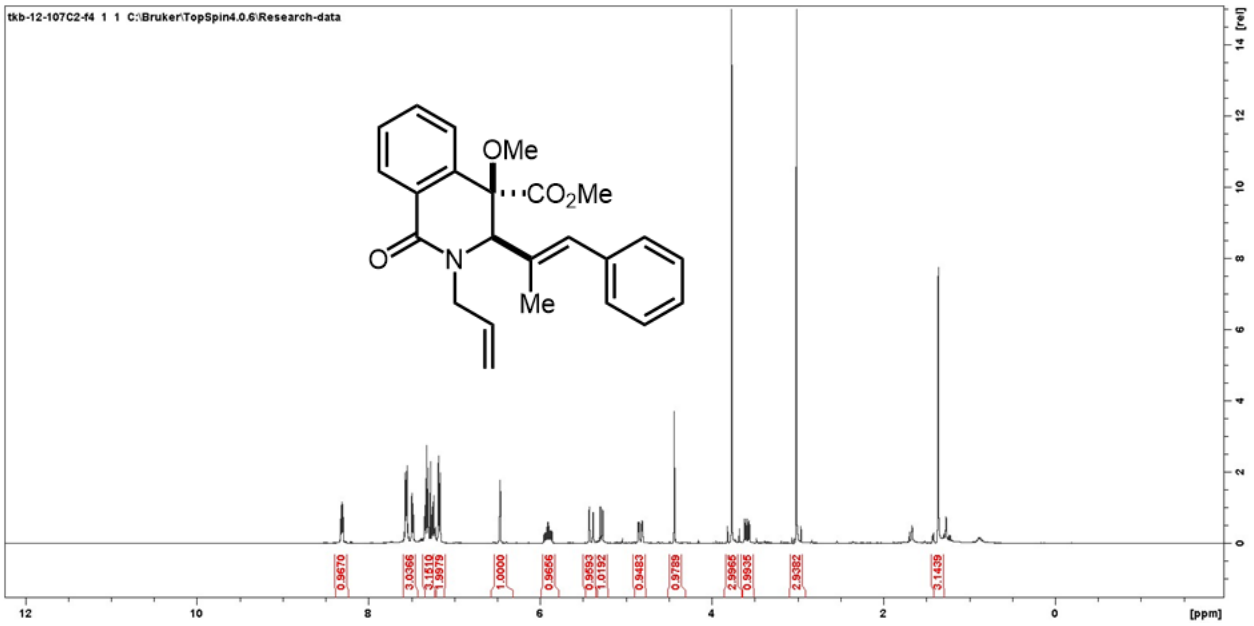


Compound 3j

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 150.7 mg, 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 1H), 7.55 – 7.50 (m, 3H), 7.42 – 7.38 (m, 3H), 7.30 – 7.17 (m, 2H), 6.49 (s, 1H), 5.84 (dddd, *J* = 17.3, 10.2, 7.1, 4.7 Hz, 1H), 5.43 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.31 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.86 (ddt, *J* = 15.3, 4.7, 1.8 Hz, 1H), 4.47 (s, 1H), 3.80 (s, 3H), 3.67 – 3.57 (m, 1H), 3.04 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.03, 162.13, 136.48, 133.96, 132.47, 132.08, 131.86, 130.88, 129.92, 129.70, 129.21, 129.04, 128.33, 127.30, 118.37, 82.74, 72.75, 52.81, 52.76, 47.46, 13.26. HRMS calc for $C_{24}H_{25}NO_4$ 391.1784, found 391.1789.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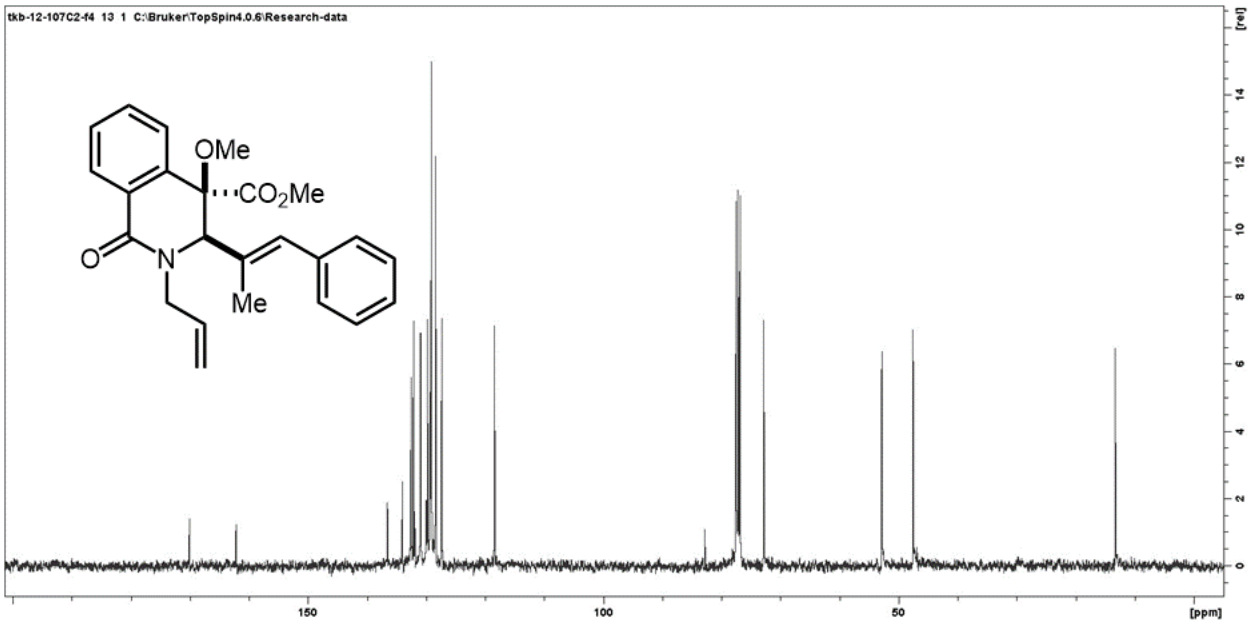
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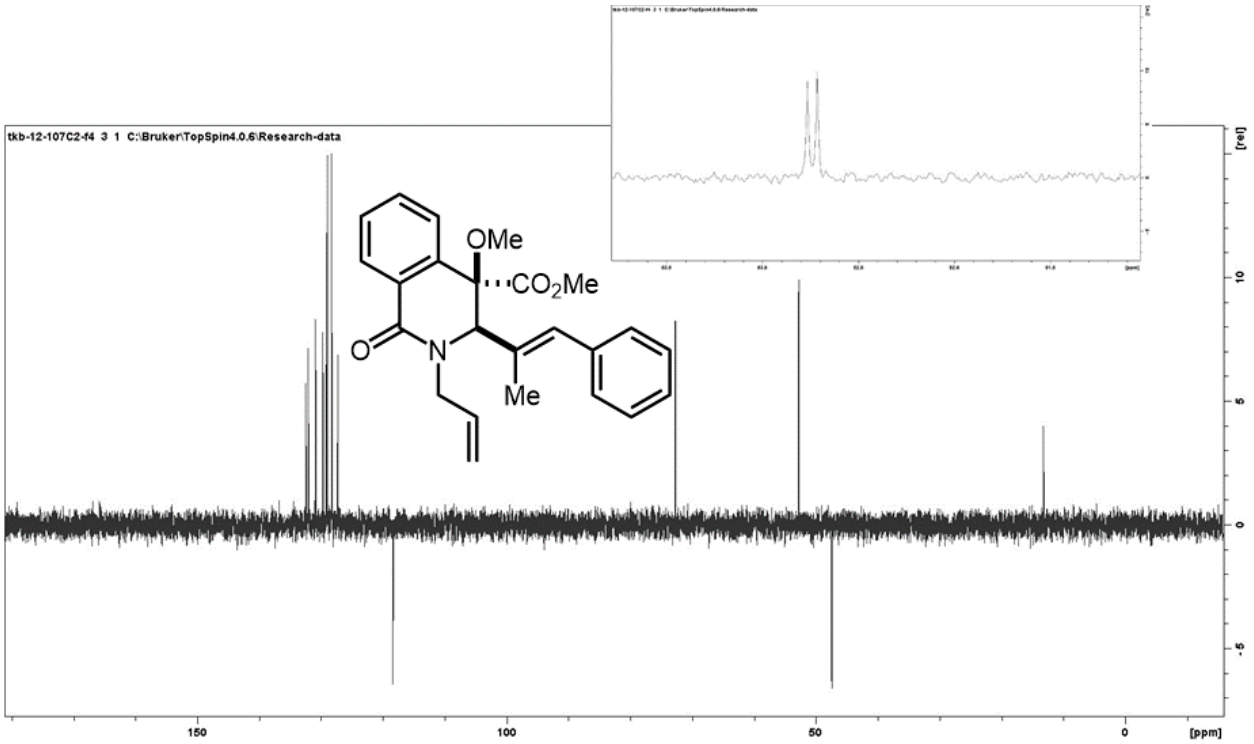
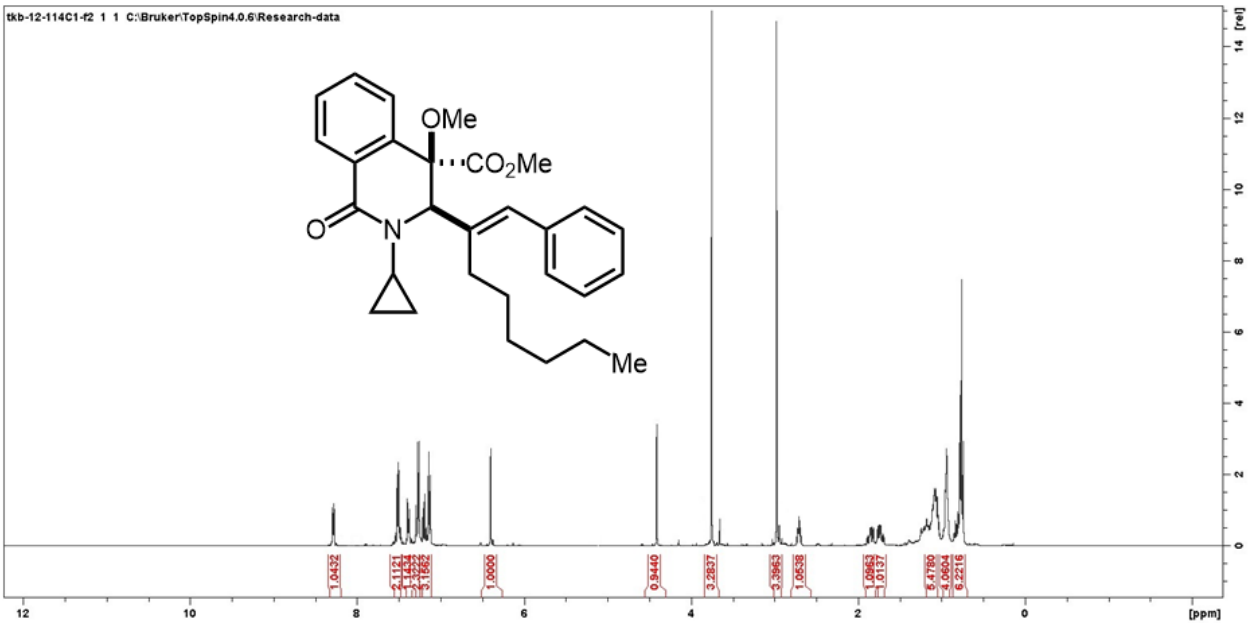


Compound 3k

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Oily substance. Yield = 166.2 mg, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.38 – 7.24 (m, 6H), 6.45 (s, 1H), 4.46 (s, 1H), 3.80 (s, 3H), 2.99 (s, 3H), 2.71 – 2.61 (m, 1H), 1.80 (ddd, *J* = 14.0, 11.7, 5.1 Hz, 1H), 1.68 (ddd, *J* = 14.0, 11.7, 5.1 Hz, 1H), 1.24 – 0.76 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.23, 163.69, 138.60, 136.79, 131.99, 131.60, 130.89, 130.13, 129.62, 129.41, 128.87, 128.62, 128.39, 128.37, 127.16, 82.97, 74.73, 52.81, 52.67, 31.04, 29.74, 29.59, 28.69, 28.38, 22.50, 14.05, 8.95, 6.47. HRMS calc for $C_{29}H_{35}NO_4$ 461.2566, found 461.2569.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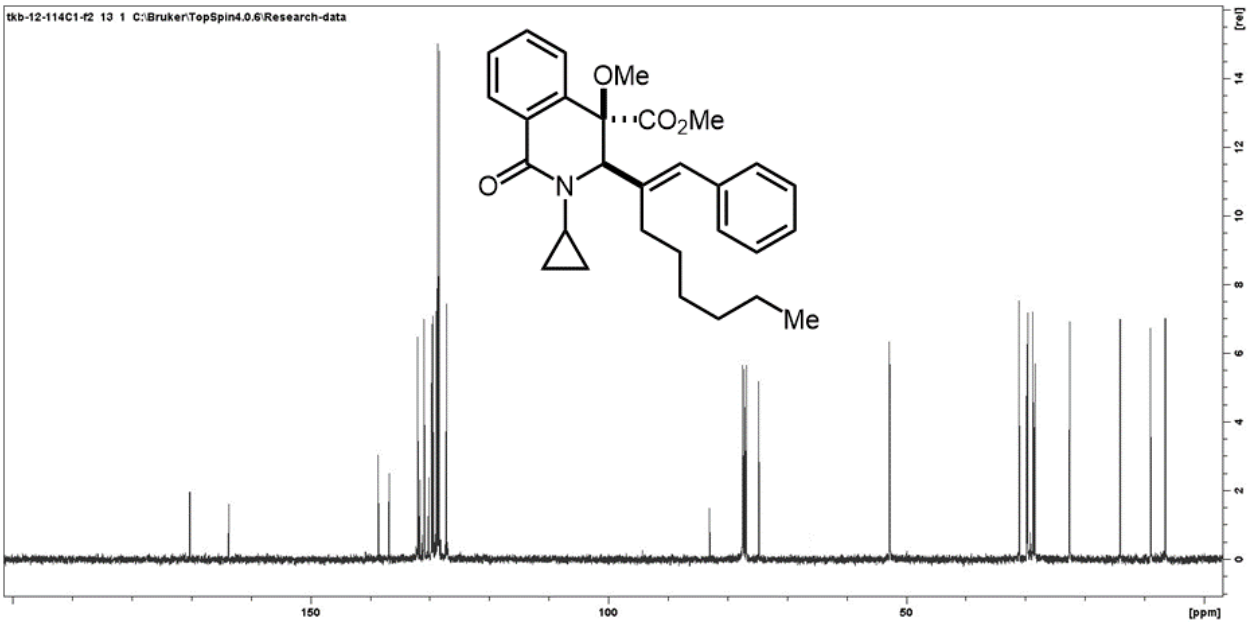
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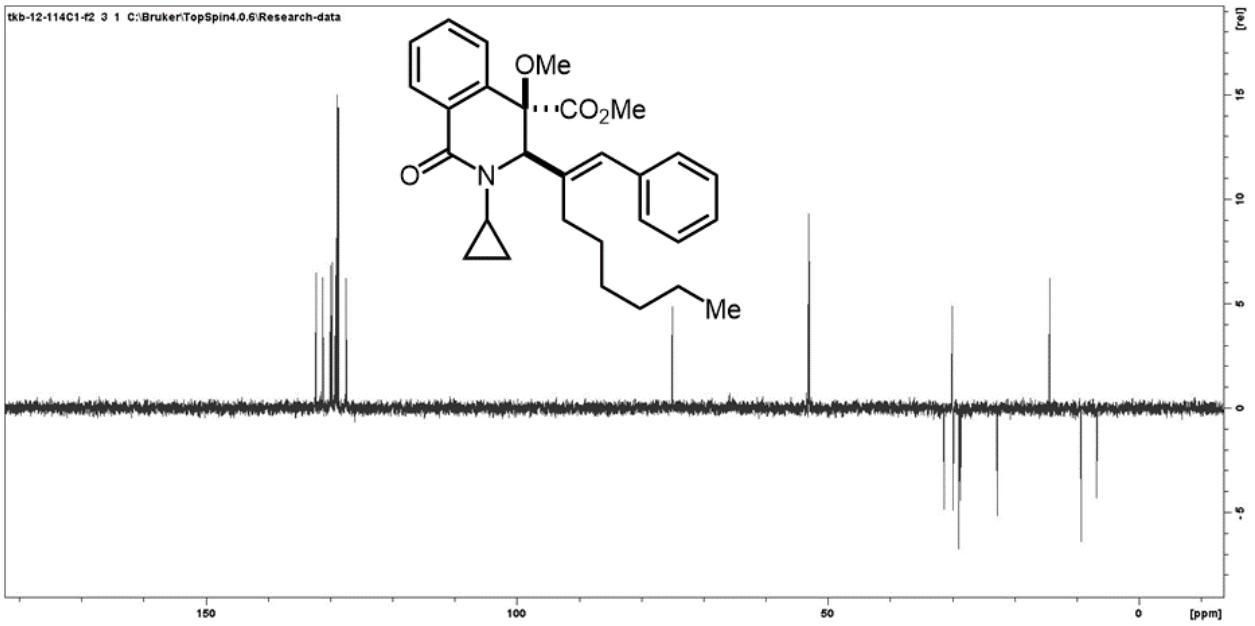
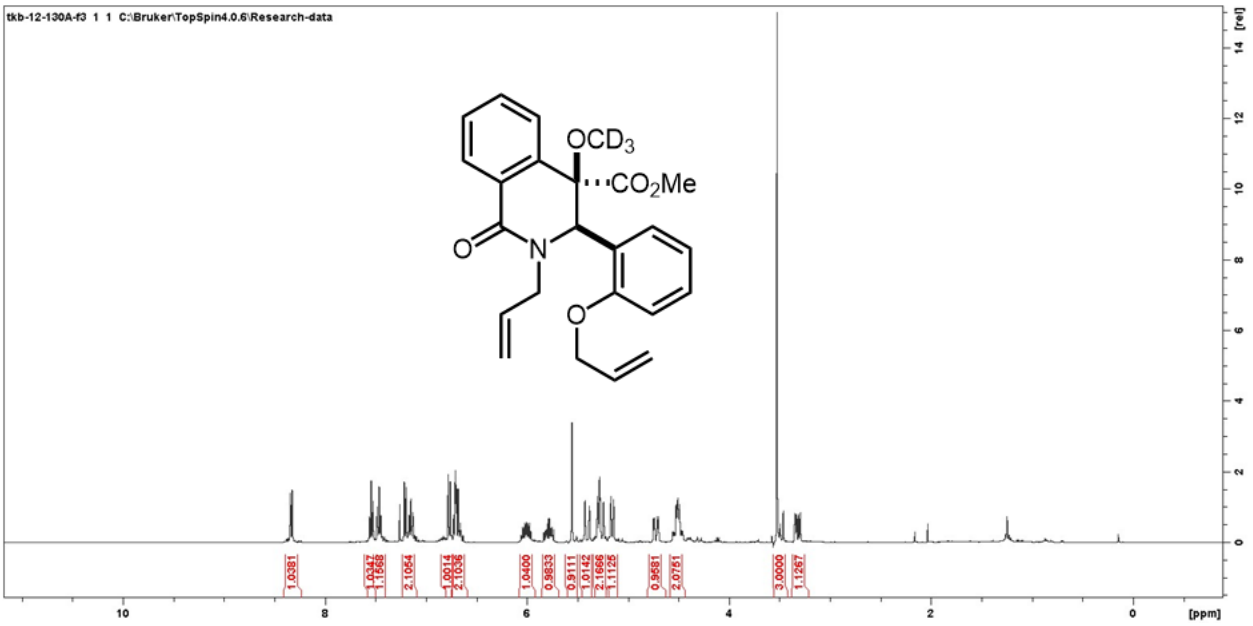


Compound 3l

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 162.2 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (td, *J* = 7.6, 1.5 Hz, 1H), 7.33 – 7.10 (m, 2H), 6.83 – 6.66 (m, 3H), 6.00 (ddt, *J* = 17.2, 10.4, 5.1 Hz, 1H), 5.83 (dddd, *J* = 17.2, 10.1, 7.2, 4.9 Hz, 1H), 5.60 (s, 1H), 5.45 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.37 – 5.31 (m, 1H), 5.30 (dt, *J* = 13.6, 1.6 Hz, 1H), 4.77 (ddt, *J* = 15.2, 5.0, 1.7 Hz, 1H), 4.63 – 4.53 (m, 2H), 3.57 (s, 3H), 3.42 – 3.31 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.49, 162.66, 156.37, 132.96, 132.66, 132.25, 131.06, 130.07, 129.62, 129.60, 129.49, 128.94, 128.44, 123.88, 120.94, 118.31, 117.78, 111.27, 83.00, 69.20, 60.01, 52.24, 48.24. HRMS calc for $C_{24}H_{22}D_3NO_5$ 410.1921, found 410.1926.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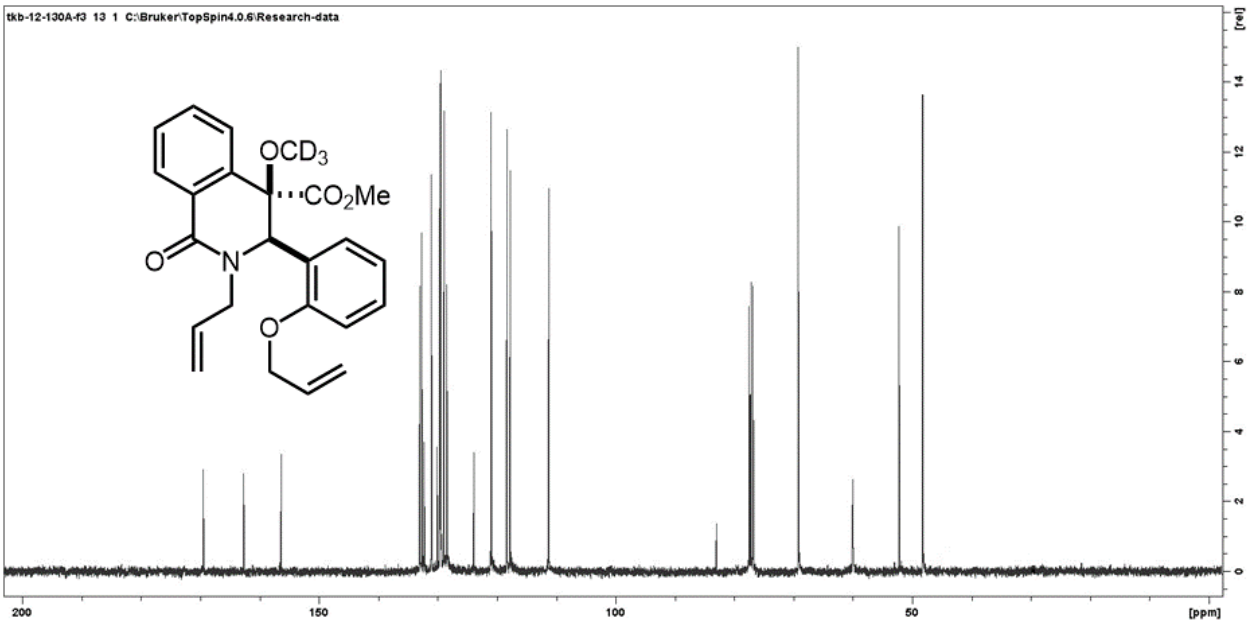
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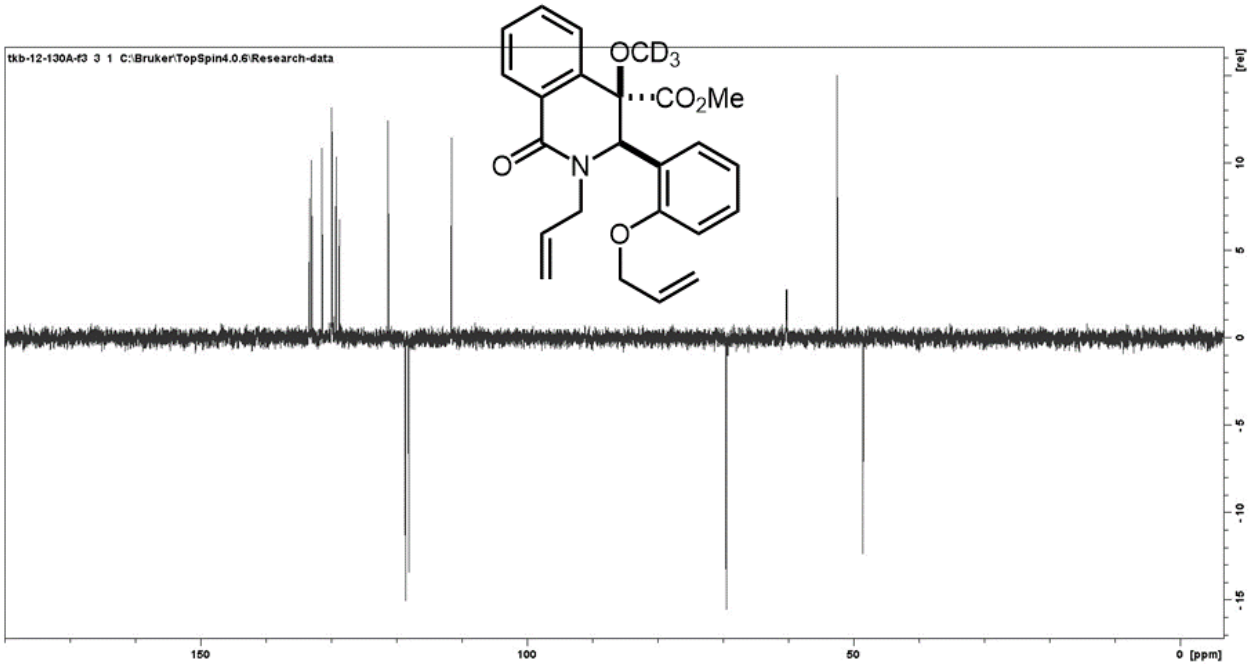
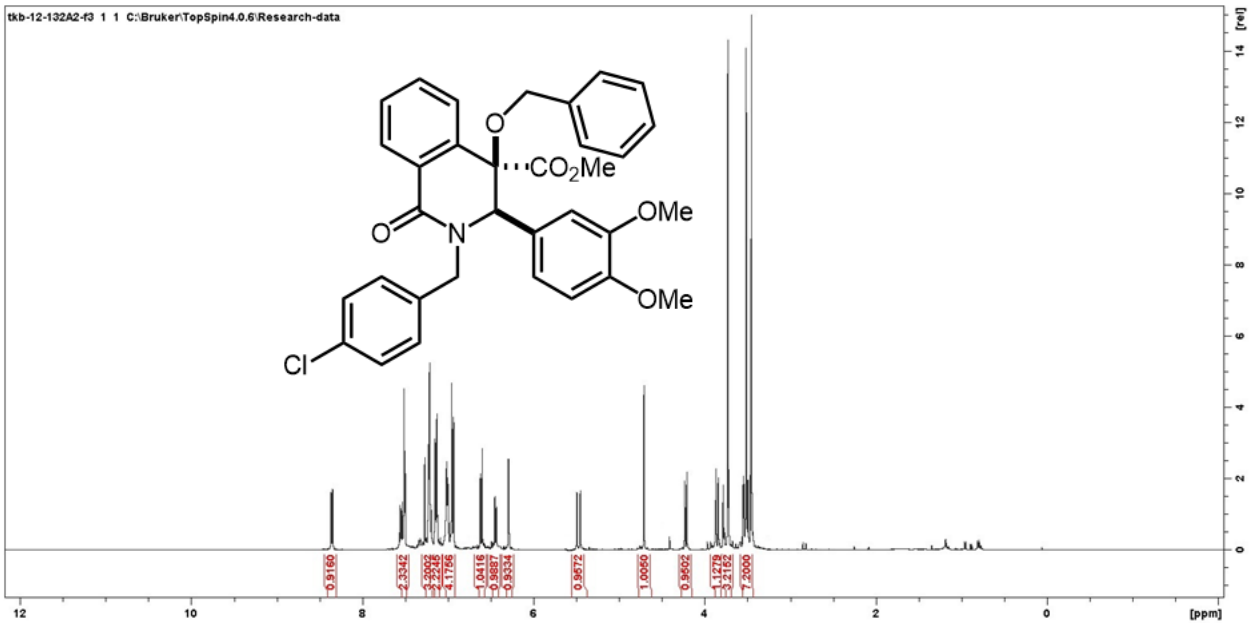


Compound 3m

Prepared in 0.5 mmol scale using **General Procedure C.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 248.8 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.39 (m, 2H), 7.29 – 7.11 (m, 5H), 7.05 – 6.92 (m, 4H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.46 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.25 (d, *J* = 2.1 Hz, 1H), 5.39 (d, *J* = 15.5 Hz, 1H), 4.62 (s, 1H), 4.24 (d, *J* = 10.0 Hz, 1H), 3.77 (d, *J* = 10.1 Hz, 1H), 3.64 (s, 3H), 3.53 – 3.32 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.45, 162.55, 149.53, 148.97, 137.00, 134.89, 133.01, 131.81, 131.44, 129.98, 129.92, 129.49, 129.21, 128.62, 128.33, 127.90, 127.89, 126.96, 120.60, 110.95, 110.59, 82.96, 68.19, 67.47, 55.88, 55.68, 52.53, 47.65. HRMS calc for $C_{33}H_{30}ClNO_6$ 571.1762, found 571.1769. FTIR (KBr): 2965.2971, 2872.3128, 1716.4748, 1650.8904, 1612.9884, 1585.9456, 1513.1051, 1455.3449, 1359.3702, 1304.1365, 1251.3997, 1177.4761, 1135.5369, 1033.8548, 996.7497, 896.0777, 833.6912, 804.9269.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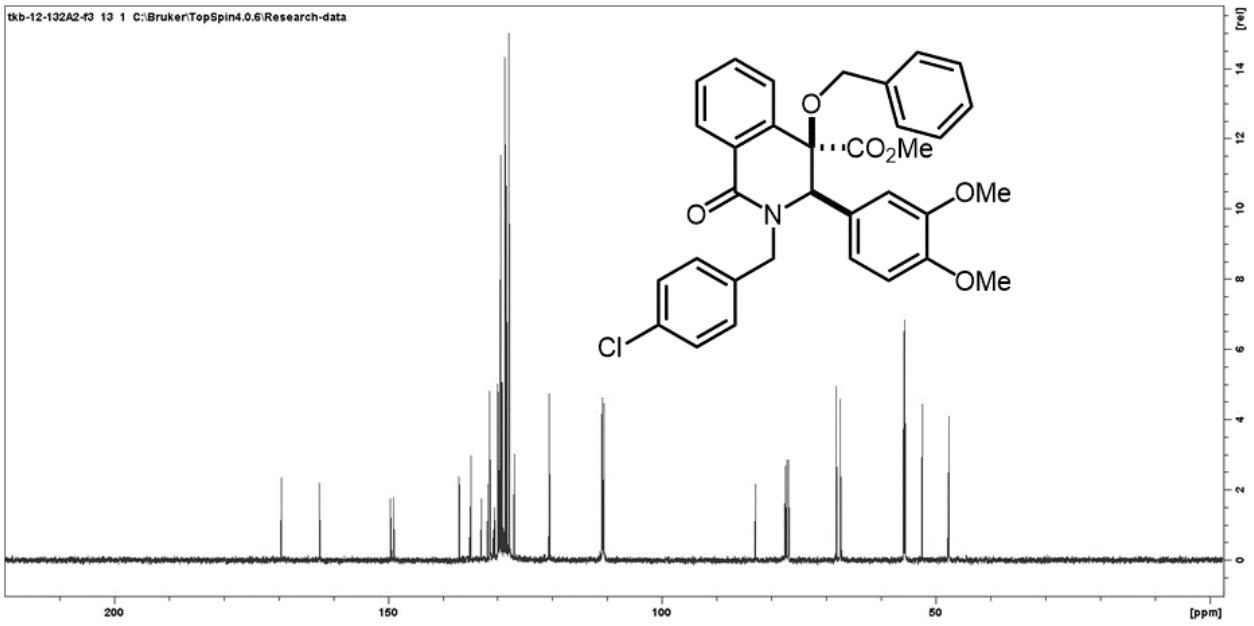
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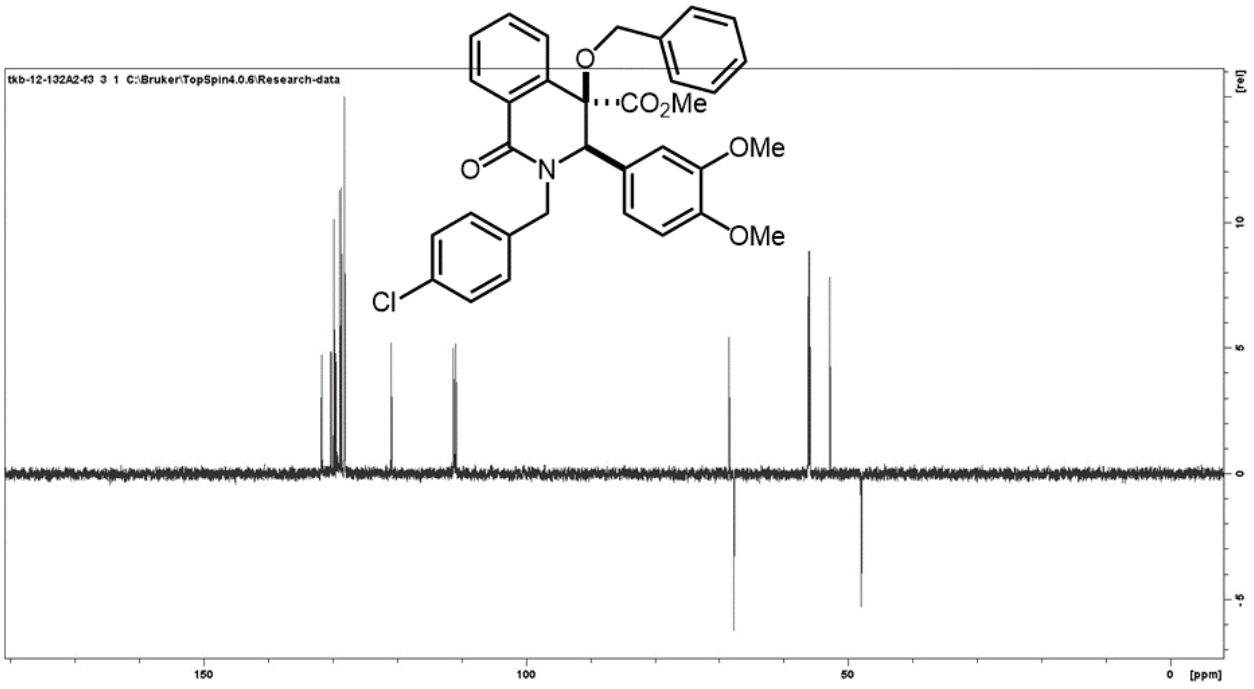
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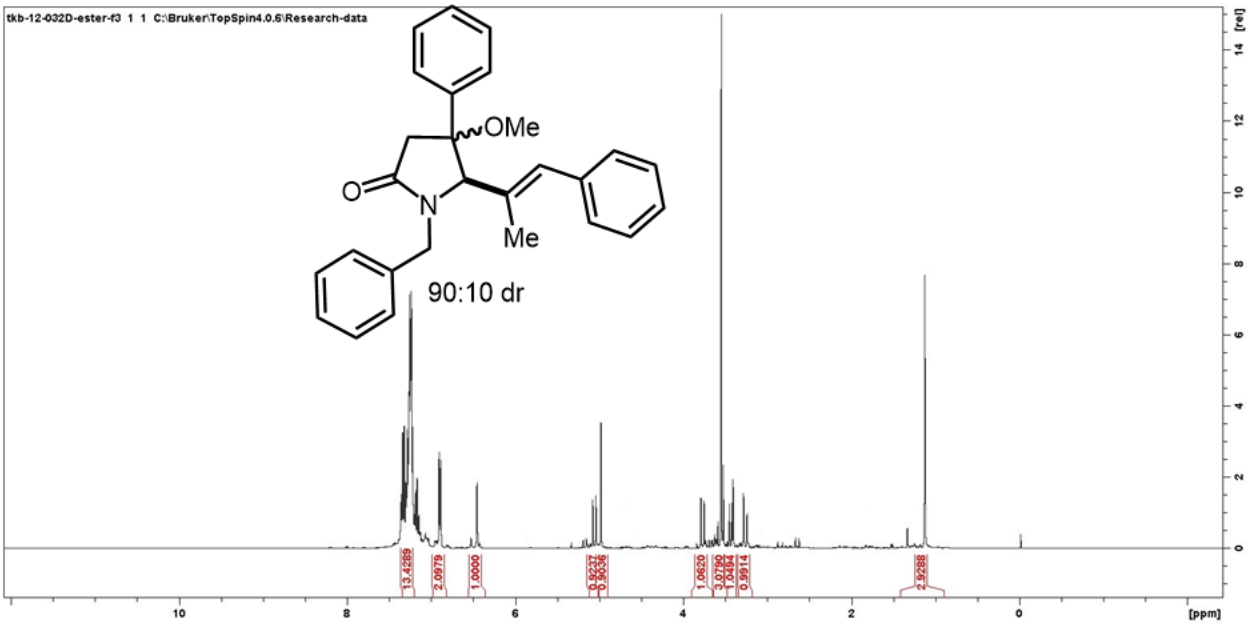
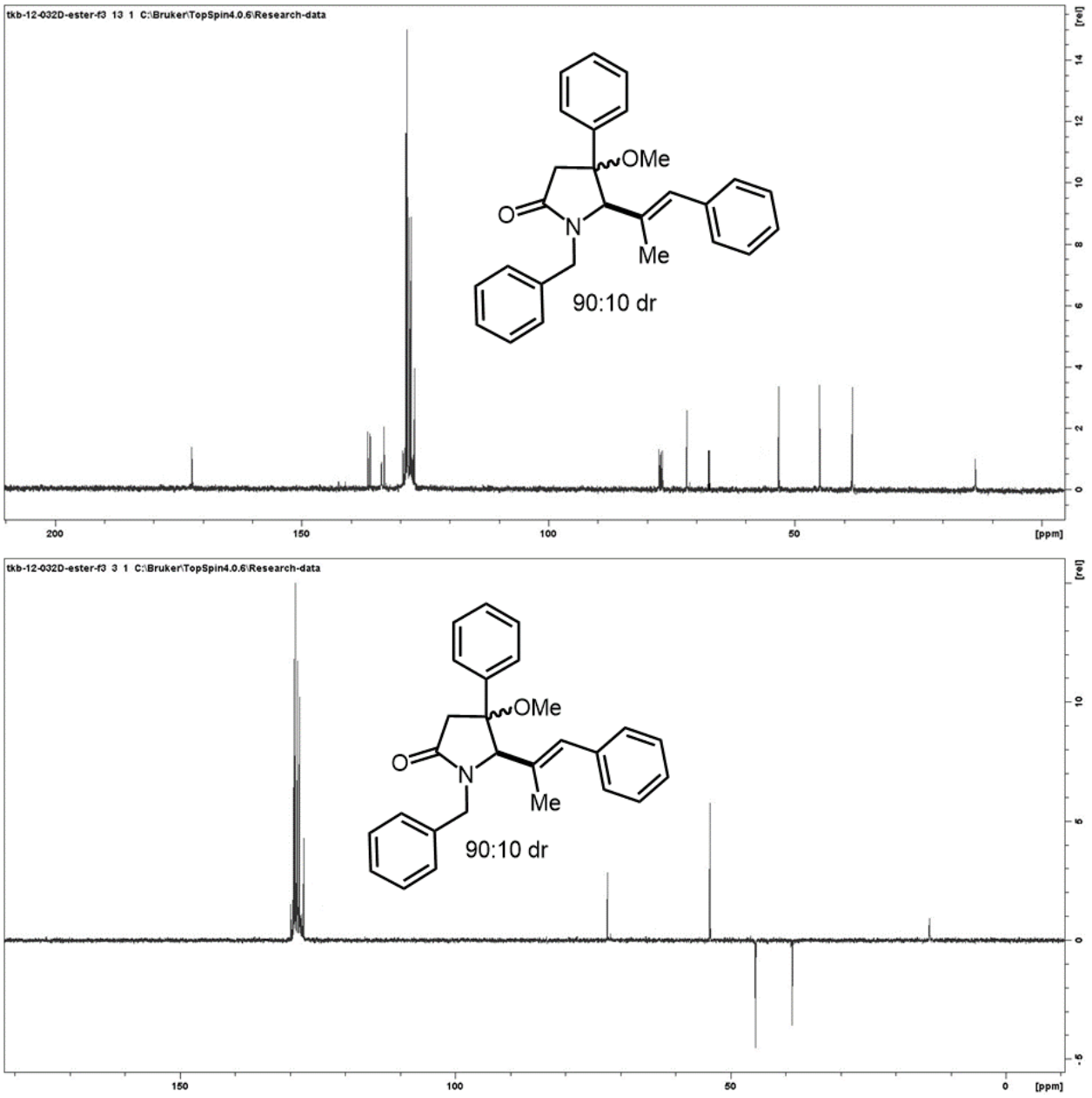
Compound 5a

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Oily substance. Yield = 143.1 mg, 72%, 90:10 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 13H), 6.84 – 6.79 (m, 2H), 6.54 (s, 1H), 5.20 (d, J = 14.6 Hz, 1H), 5.06 (s, 1H), 3.70 (d, J = 14.6 Hz, 1H), 3.53 (s, 3H), 3.49 (d, J = 16.8 Hz, 1H), 3.37 (d, J = 16.8 Hz, 1H), 1.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.30, 136.64, 136.19, 136.09, 133.39, 128.92, 128.66, 128.28, 128.24, 127.97, 127.89, 127.83, 127.14, 71.98, 67.10, 53.36, 45.05, 38.43, 13.49. HRMS calc for $C_{27}H_{27}NO_2$ 397.2042, found 397.2048.

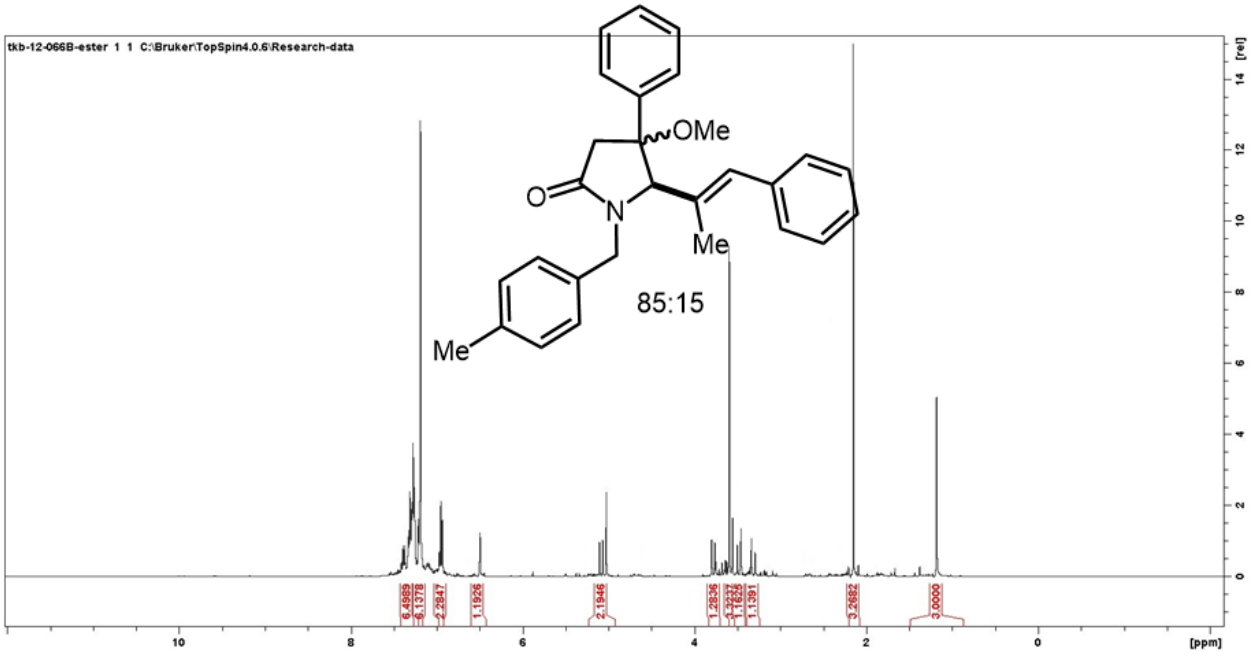


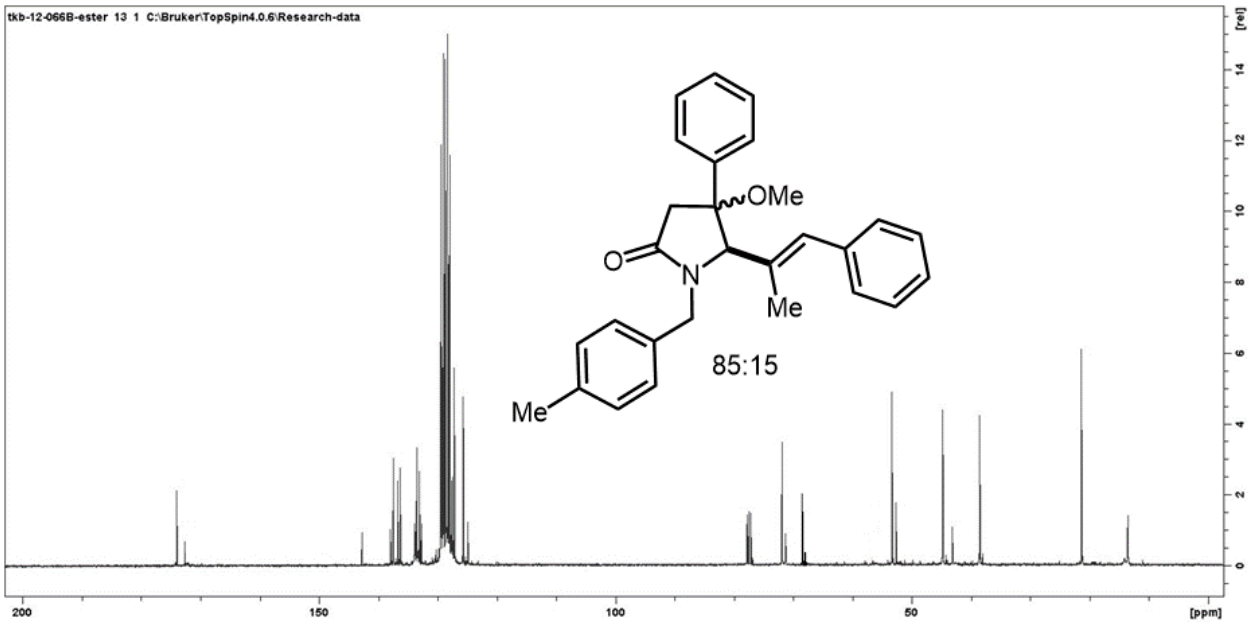


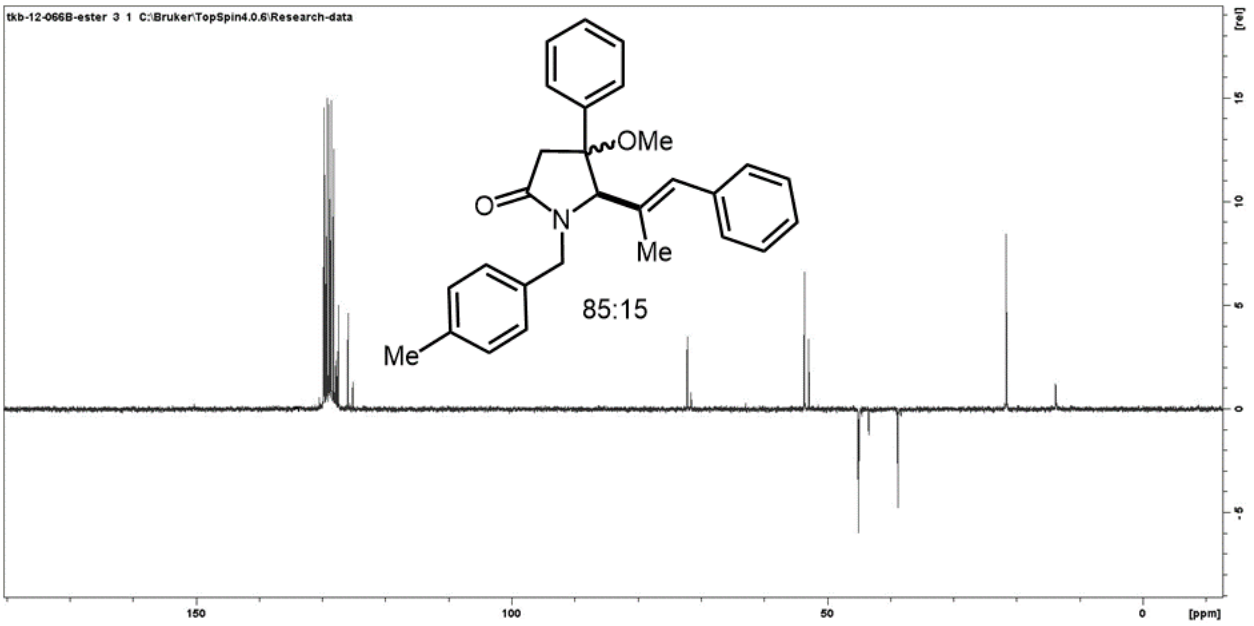
Compound 5b

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Oily substance. Yield = 142.0 mg, 69%, 85:15 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 12H), 6.97 – 6.95 (m, 2H), 6.52 (s, 1H), 5.07 (d, *J* = 17.1 Hz, 1H), 5.02 (s, 1H), 3.76 (d, *J* = 17.1 Hz, 1H), 3.62 (s, 3H), 3.51 (d, *J* = 16.2 Hz, 1H), 3.35 (d, *J* = 16.2 Hz, 1H), 2.20 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.91, 142.70, 137.38, 136.68, 136.25, 133.41, 132.98, 129.46, 129.44, 129.32, 129.11, 128.91, 128.89, 128.83,

128.60, 128.57, 128.50, 128.29, 128.26, 128.22, 127.95, 127.89, 127.54, 127.42, 127.11, 125.61, 71.84, 67.51, 56.08, 53.30, 52.61, 44.75, 44.65, 43.10, 38.48, 21.31, 13.50. HRMS calc for $C_{28}H_{29}NO_2$ 411.2198, found 411.2195.

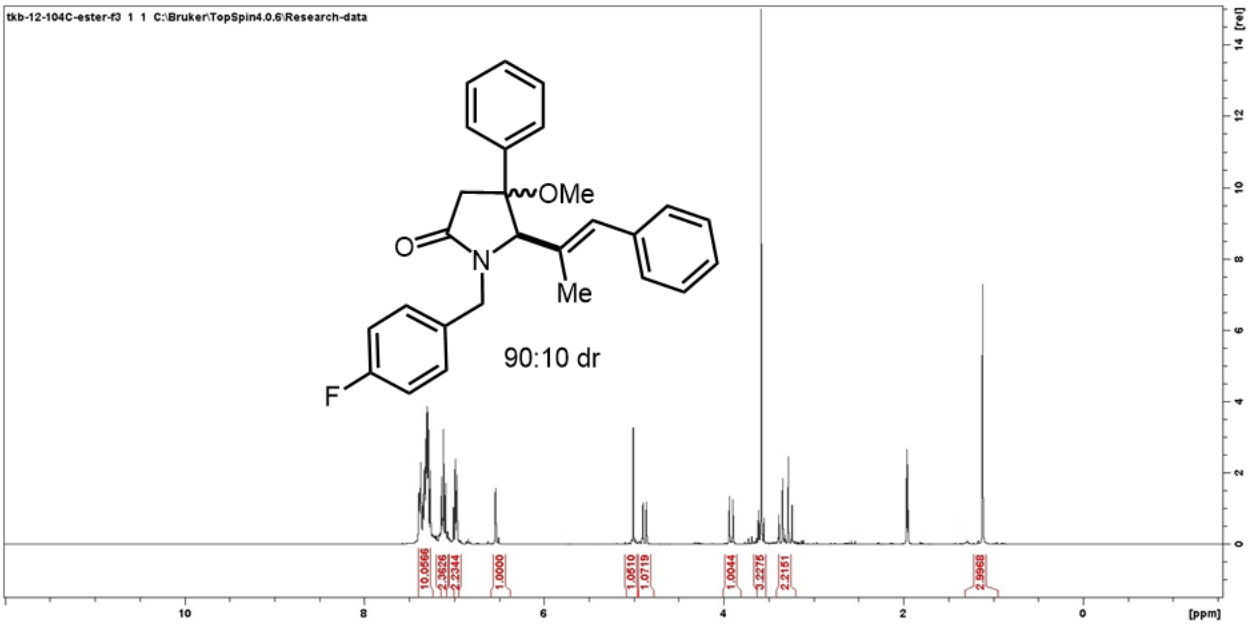






Compound 5c

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (70:30). Oily substance. Yield = 128.8 mg, 62%, 90:10 dr. ^{1}H NMR (400 MHz, CD_3CN) δ 7.37 – 7.25 (m, 10H), 7.19 – 7.09 (m, 2H), 7.04 – 6.95 (m, 2H), 6.56 (s, 1H), 5.03 (s, 1H), 4.90 (d, *J* = 15.0 Hz, 1H), 3.84 (d, *J* = 14.9 Hz, 1H), 3.61 (s, 3H), 3.34 – 3.25 (m, 2H), 1.04 (s, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ 171.65, 163.40, 160.98, 136.86, 136.46, 130.54, 130.45, 128.82, 128.21, 128.10, 128.08, 127.81, 127.04, 117.42, 115.28, 115.06, 75.11, 71.99, 52.96, 43.89, 37.84, 12.94. HRMS calc for $C_{27}H_{26}FNO_2$ 415.1948, found 415.1953.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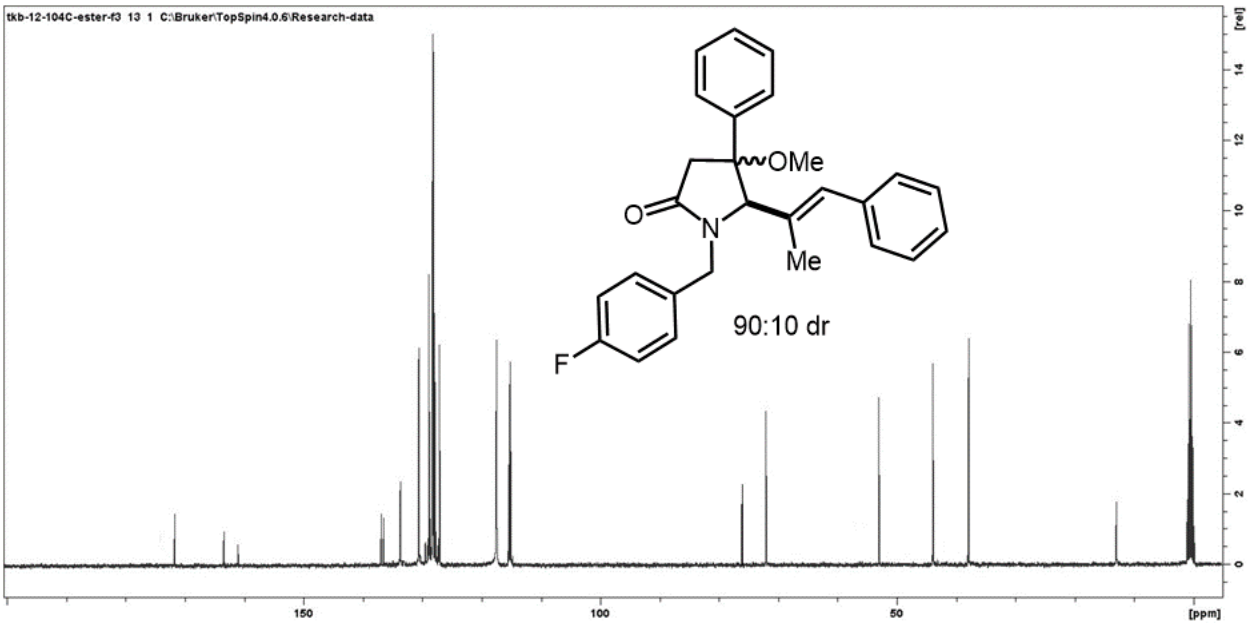
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O
N
Me
F
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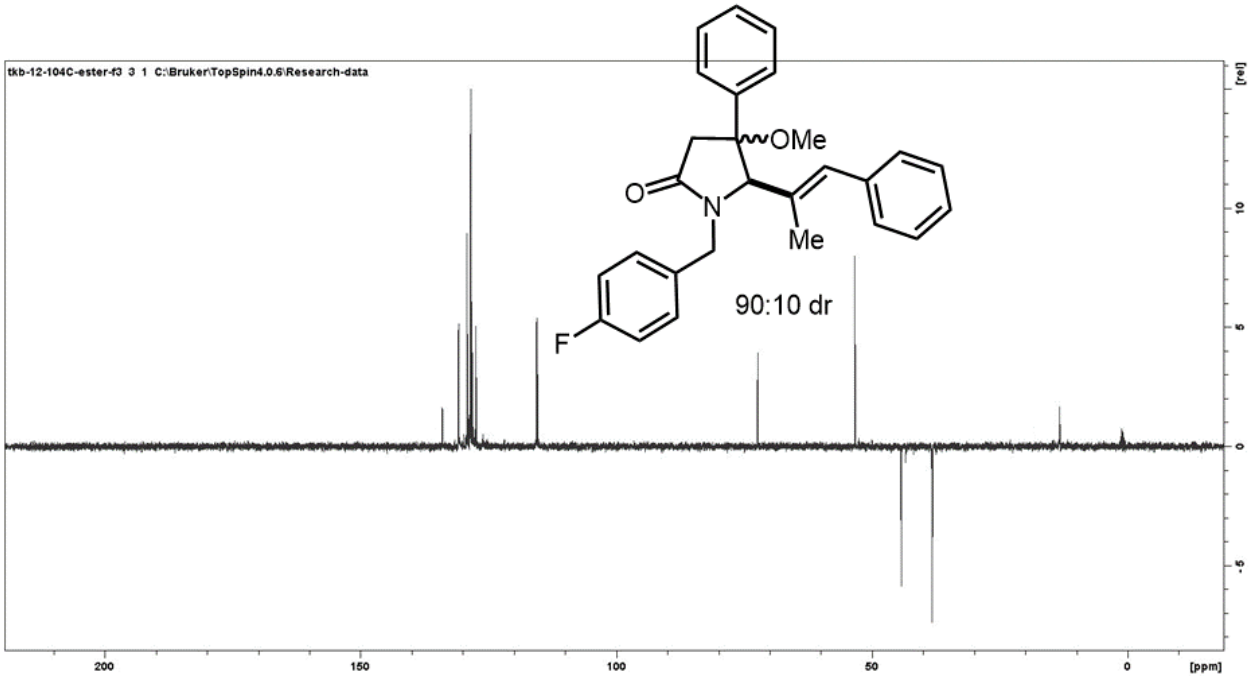
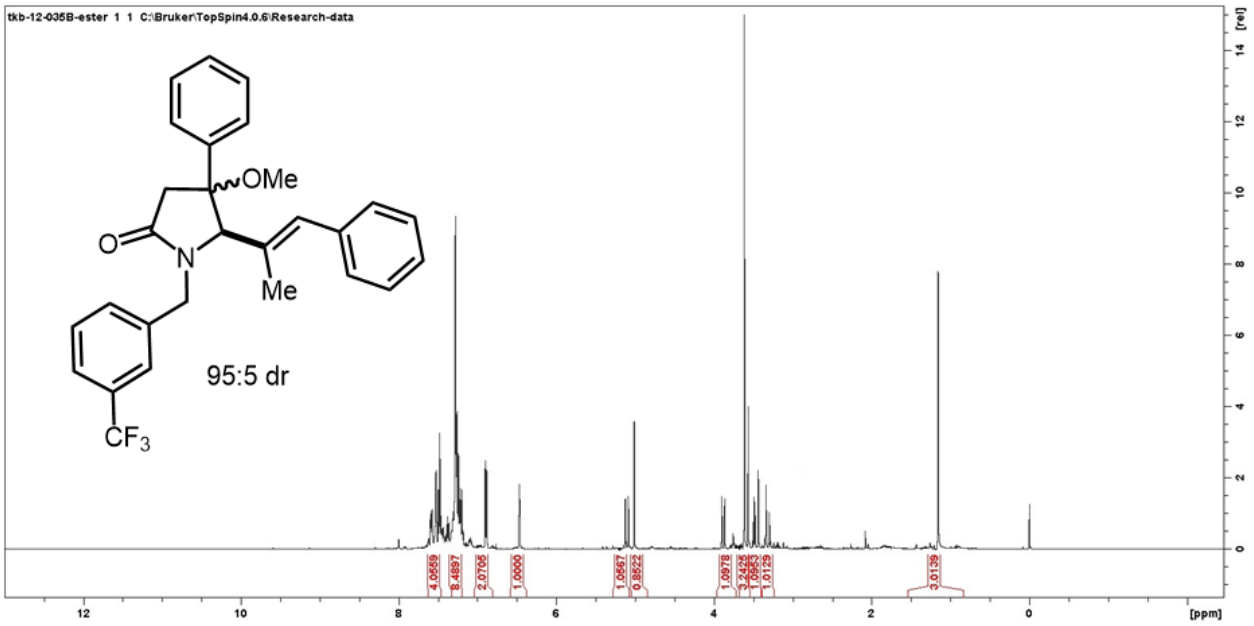
100
50
[ppm]



Compound 5d

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (70:30). Oily substance. Yield = 137.3 mg, 59%, 90:10 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.44 (m, 4H), 7.37 – 7.26 (m, 8H), 6.84 (dd, *J* = 7.0, 1.8 Hz, 2H), 6.52 (s, 1H), 5.23 (d, *J* = 15.0 Hz, 1H), 5.06 (s, 1H), 3.83 (d, *J* = 15.0 Hz, 1H), 3.67 (s, 3H), 3.54 (d, *J* = 5.8 Hz, 1H), 3.47 (d, *J* = 5.8 Hz, 1H), 1.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.42, 137.23, 136.35, 135.96, 133.11, 131.88, 129.17, 129.08, 129.03, 129.02, 128.88, 128.52, 128.35, 128.30, 128.28, 128.05, 127.75, 127.56, 127.23, 125.38, 125.18, 125.14, 124.73, 124.69, 119.66, 72.14, 68.11, 53.44, 44.62, 38.18, 13.45. HRMS calc for $C_{28}H_{26}F_3NO_2$ 465.1916, found 465.1920.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Me
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CF3
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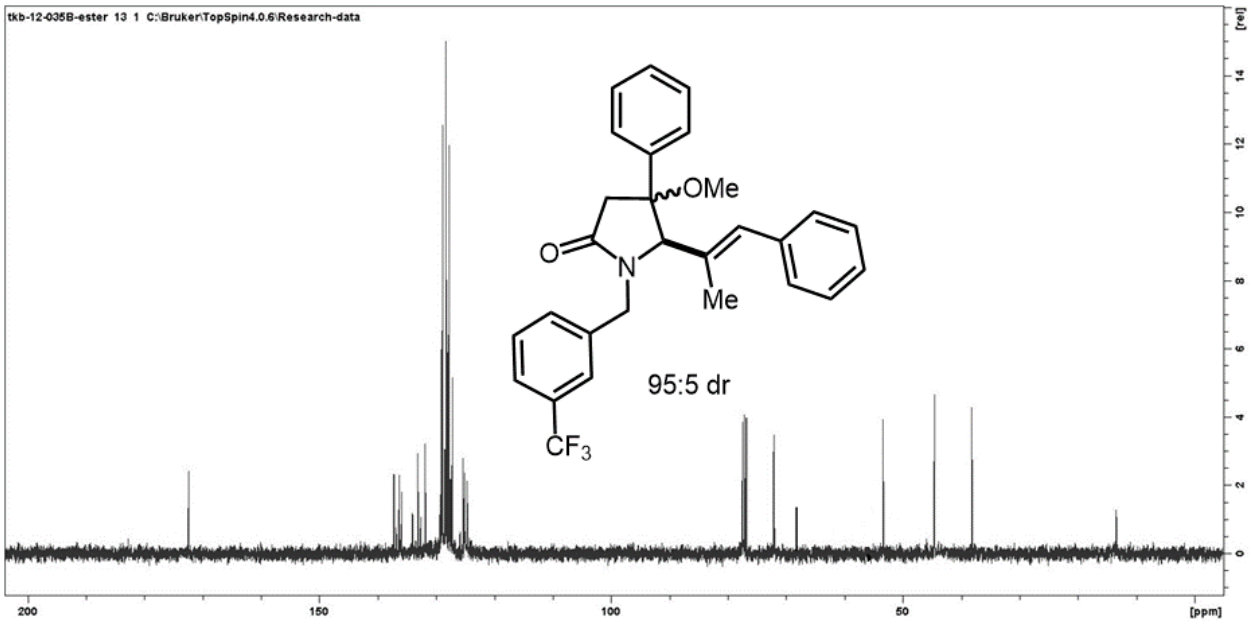
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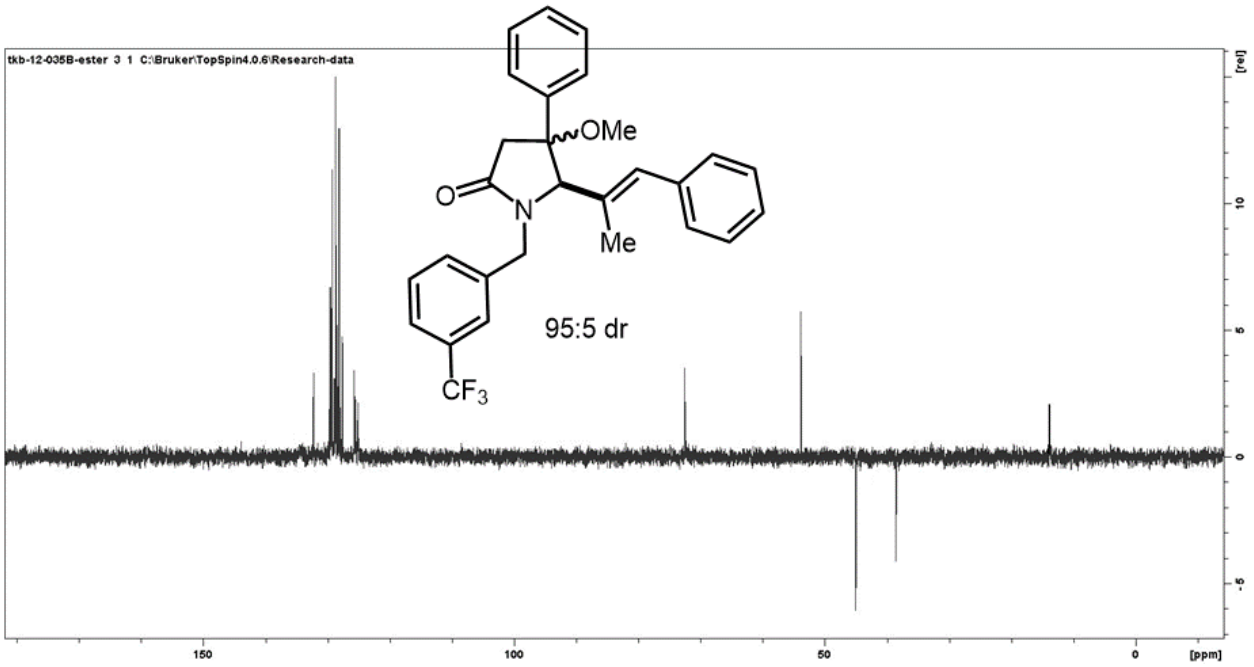
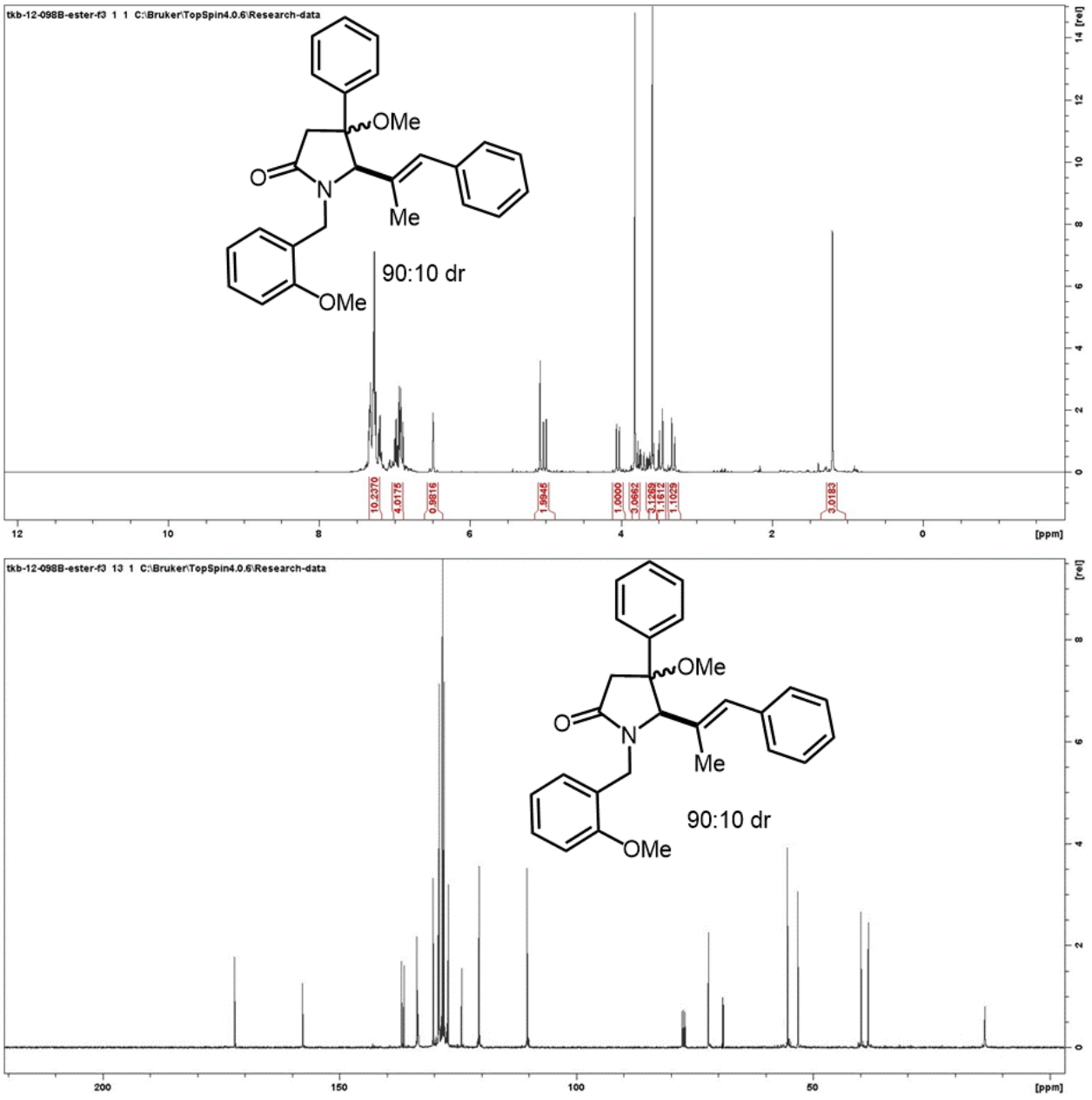
N
Me
95:5 dr
CF3
[ppm]



Compound 5e

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 134.7 mg, 63%, 90:10 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 10H), 7.07 – 6.89 (m, 4H), 6.53 (s, 1H), 5.09 (s, 1H), 5.05 (d, *J* = 14.8 Hz, 1H), 4.08 (d, *J* = 14.8 Hz, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 3.47 (d, *J* = 16.8 Hz, 1H), 3.25 (d, *J* = 16.8 Hz, 1H), 1.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.13, 157.76, 136.87, 136.34, 133.61, 130.19, 129.11, 128.94, 128.21, 127.92, 127.89, 127.00, 124.20, 120.52, 110.40, 72.07, 68.26, 55.39, 53.25, 39.86, 38.33, 13.70. HRMS calc for $C_{28}H_{29}NO_3$ 427.2147, found 427.2144.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Me
OMe
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0.9616
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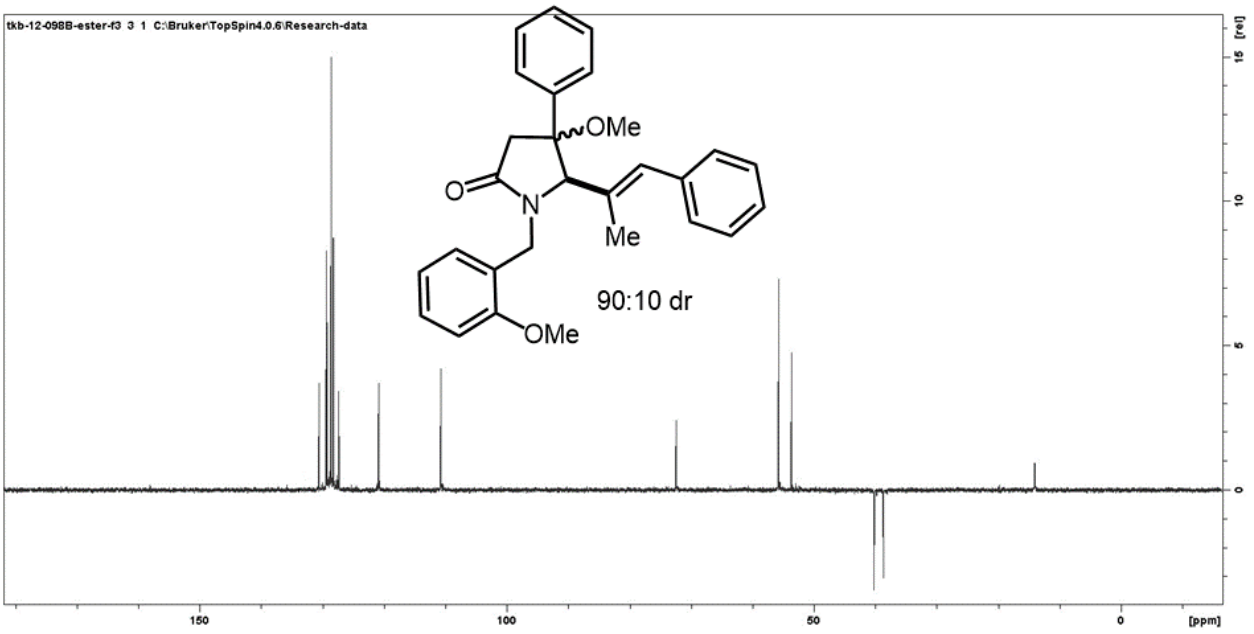
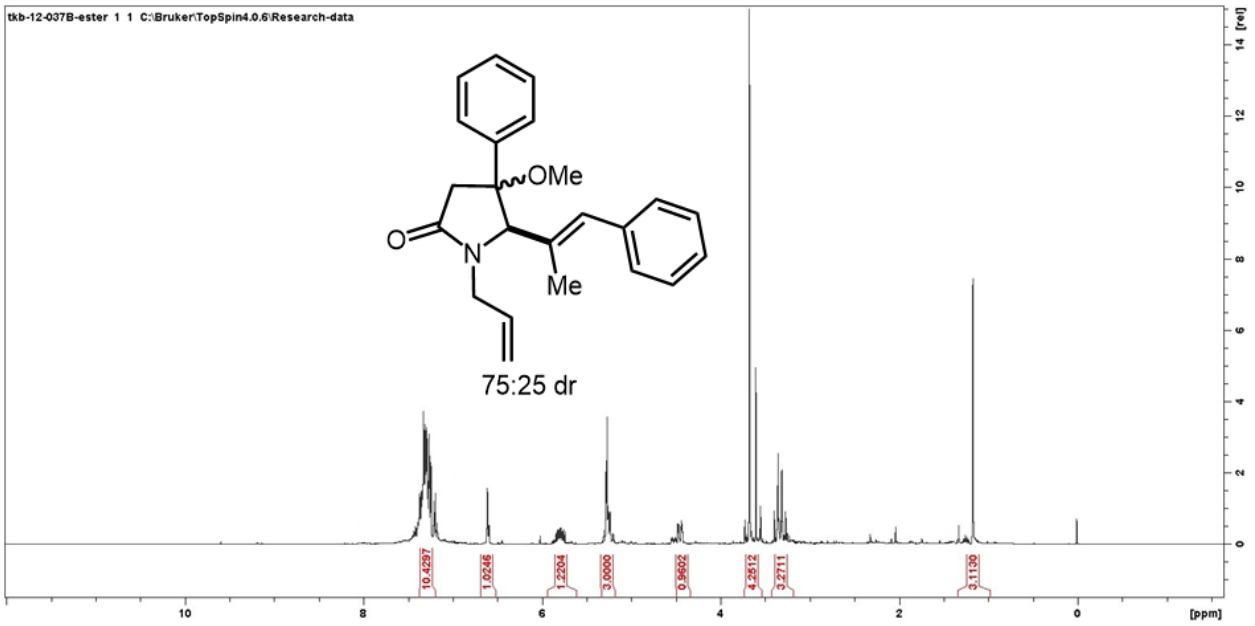
1.1268
1.1612
1.1029
3.0183
12
10
8
6
4
2
0
[ppm]
tkb-12-098B-ester-f3 13 1 C:\Bruker\TopSpin4.0.6\Research-data
OMe
O
N
Me
90:10 dr
OMe
200
150
100
50
[ppm]



Compound 5f

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 112.9 mg, 65%, 75:25 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 10H), 6.62 (s, 1H), 5.82 – 5.74 (m, 1H), 5.37 – 5.19 (m, 3H), 4.49 – 4.46 (m, 1H), 3.70 (s, 3H), 3.36 – 3.17 (m, 3H), 1.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.82, 133.45, 128.88, 128.30, 128.24, 127.98, 127.72, 127.08, 125.56, 119.92, 118.49, 71.85, 64.32, 53.45, 52.68, 43.80, 43.67, 38.28, 13.61. HRMS calc for $C_{23}H_{25}NO_2$ 347.1885, found 347.1889.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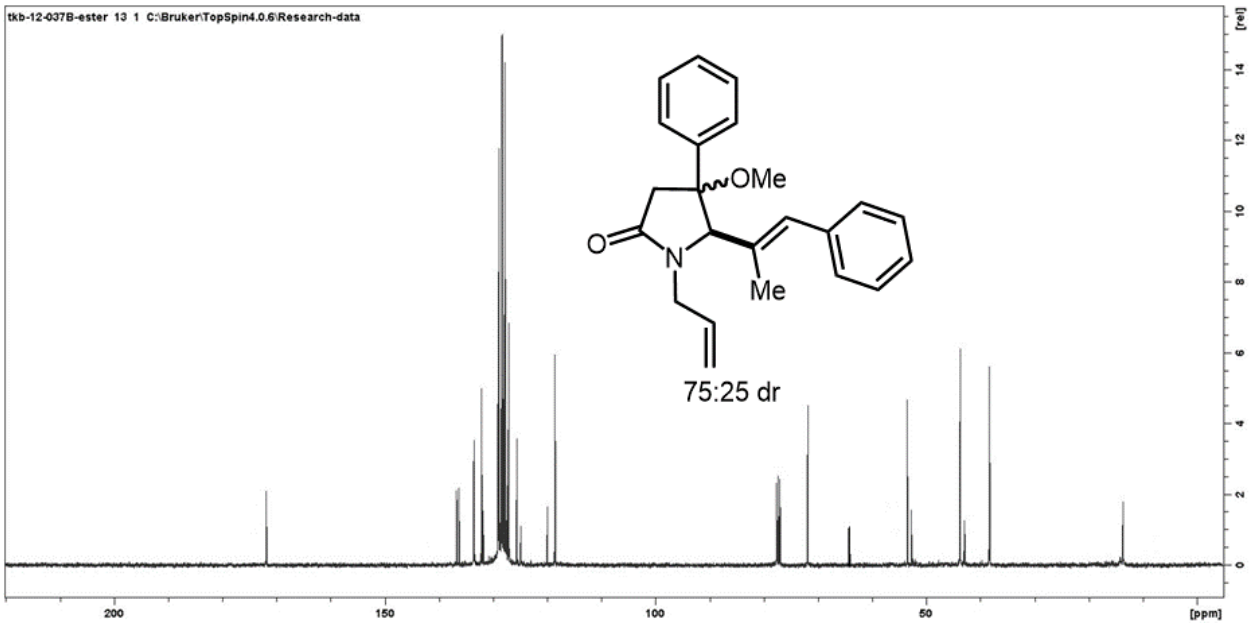
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O
N
Me
75:25 dr
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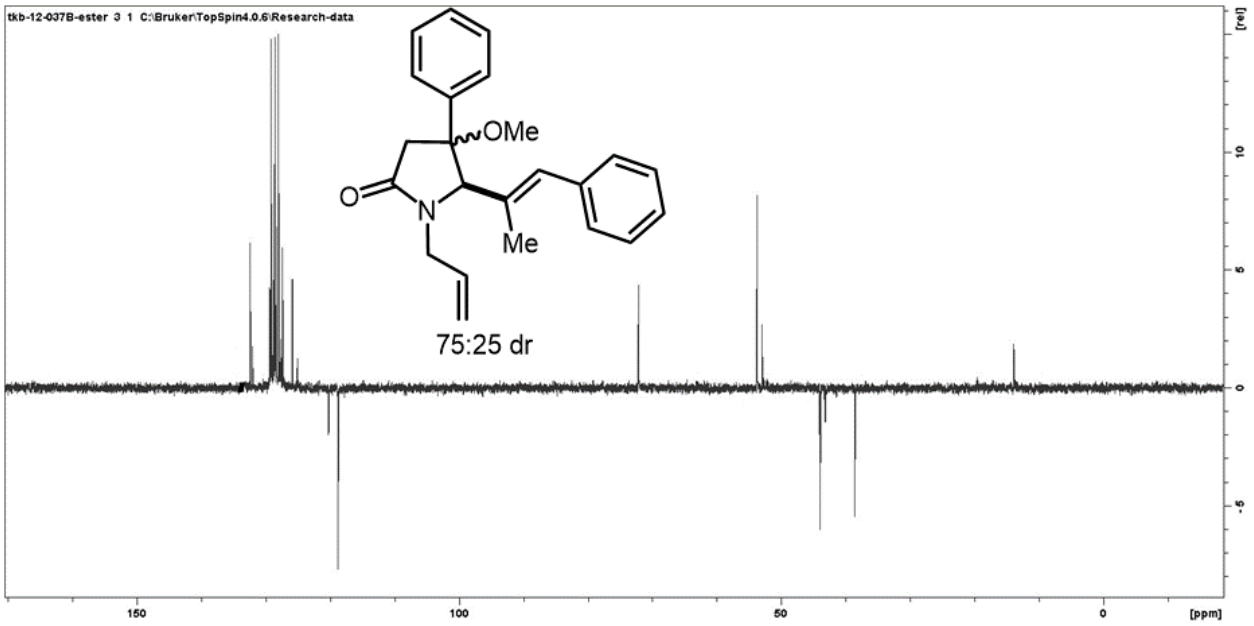
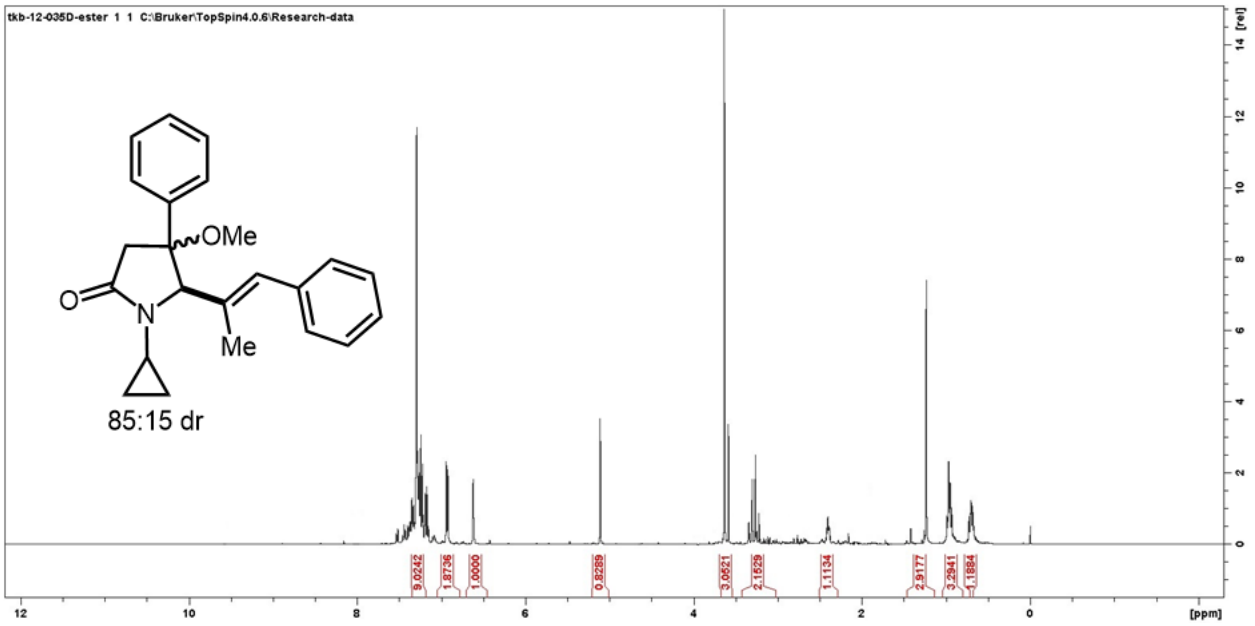
150
100
50
[ppm]



Compound 5g

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Oily substance. Yield = 118.1 mg, 68%, 85:15 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 8H), 6.99 – 6.90 (m, 2H), 6.64 (s, 1H), 5.13 (s, 1H), 3.56 (s, 3H), 3.30 – 3.12 (m, 2H), 2.45 – 2.33 (m, 1H), 1.26 (s, 3H), 0.97 – 0.80 (m, 3H), 0.69 – 0.58 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.24, 136.76, 136.08, 134.12, 132.39, 128.94, 128.36, 128.20, 127.98, 127.54, 126.98, 125.31, 73.94, 73.65, 66.41, 53.38, 52.65, 38.83, 24.66, 24.46, 14.16, 7.24, 6.72, 4.56, 4.37. HRMS calc for $C_{23}H_{25}NO_2$ 347.1885, found 347.1889.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Me
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6
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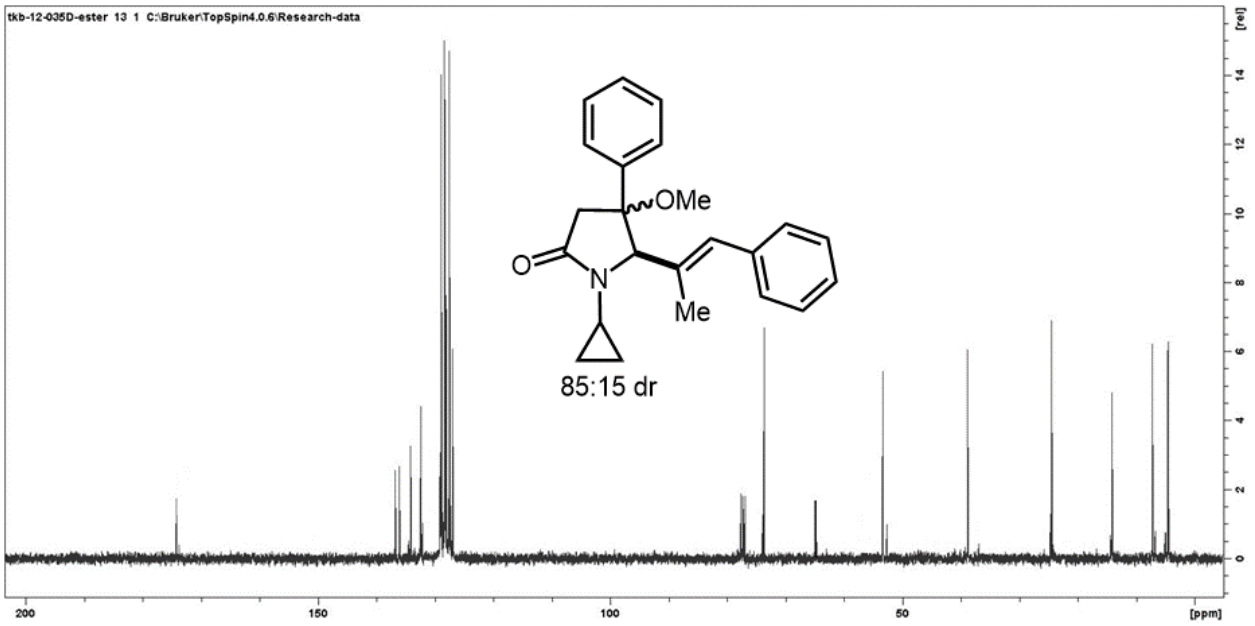
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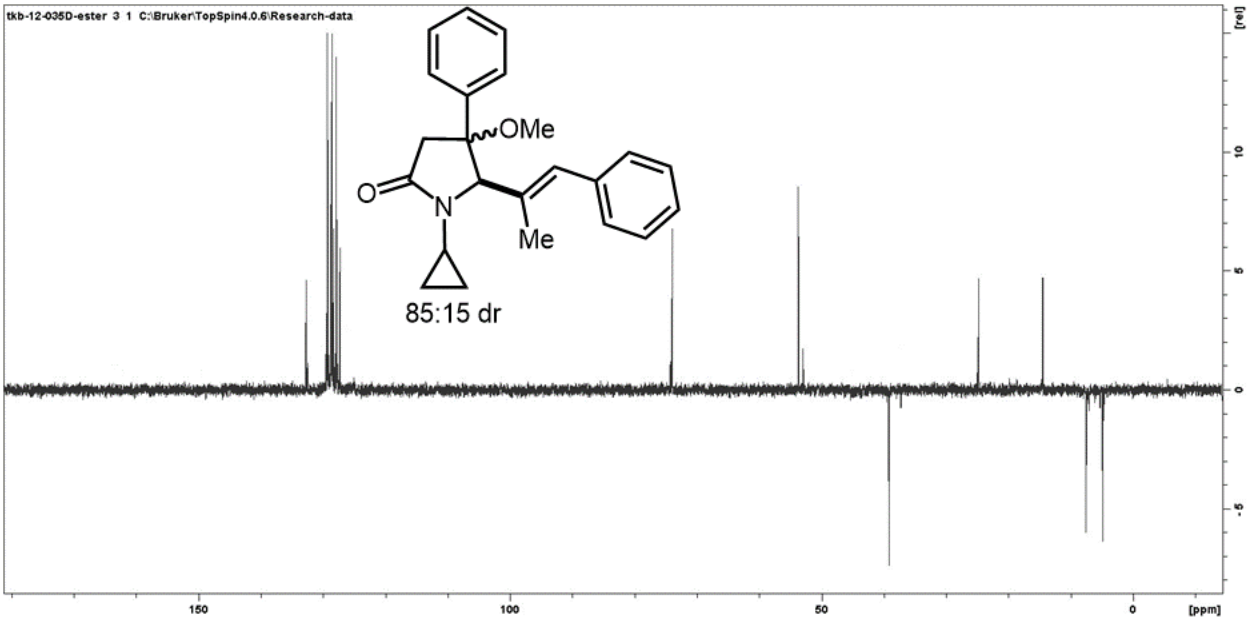
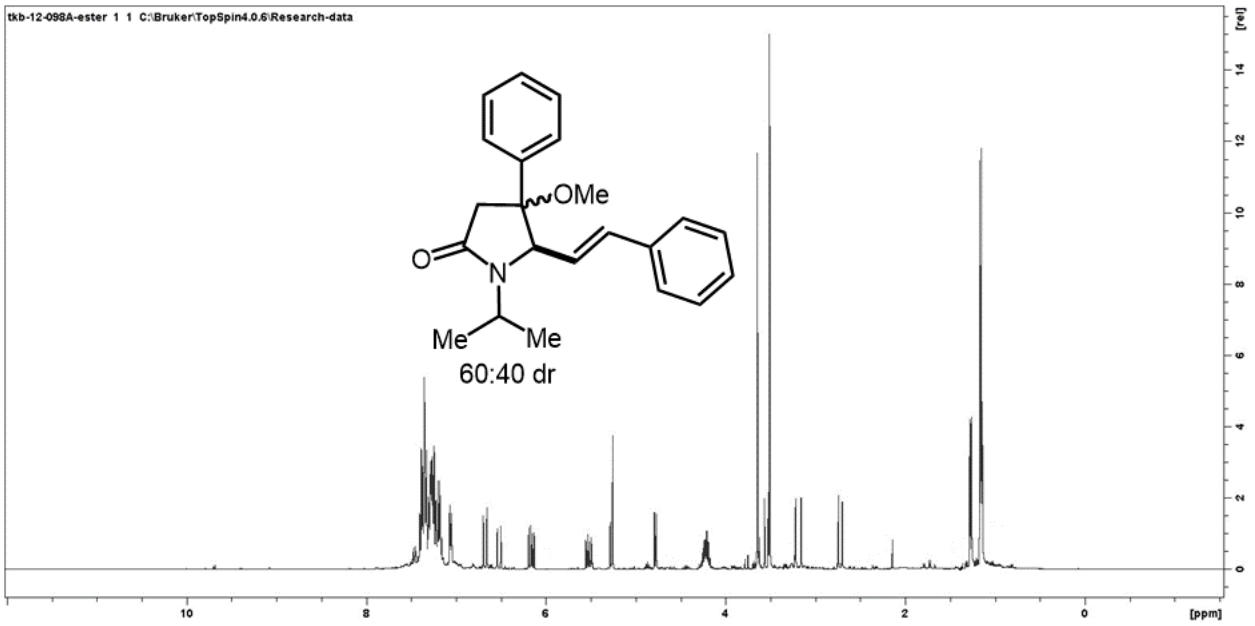


Compound 5h

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Oily substance. Yield = 93.9 mg, 56%, 60:40 dr. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 7.38 – 7.17 (m, 10H), 6.73 + 6.52 (d, *J* = 15.8 Hz, 1H), 6.21 + 5.50 (dd, *J* = 15.8, 8.6 Hz, 1H), 5.33 + 4.75 (d, *J* = 8.6 Hz, 1H), 4.27 – 4.17 (m, 1H), 3.70 + 3.56 (s, 3H), 3.15 + 2.25 (d, *J* = 16.1 Hz, 1H), 1.21 - 1.16 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.00, 171.53, 140.60, 136.17, 135.94, 134.44, 134.31, 129.01, 128.91, 128.87, 128.85, 128.65, 128.63, 128.60, 128.51, 128.07, 128.03, 127.92, 127.87, 127.63, 127.61, 127.42, 126.72, 126.49, 126.22, 126.03, 74.11, 73.68, 65.23, 64.62, 53.27, 52.66, 44.81, 44.69, 41.10, 37.79, 21.56, 21.42, 20.01, 19.73. HRMS calc for $C_{22}H_{25}NO_2$ 335.1885, found 335.1882.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Me
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60:40 dr
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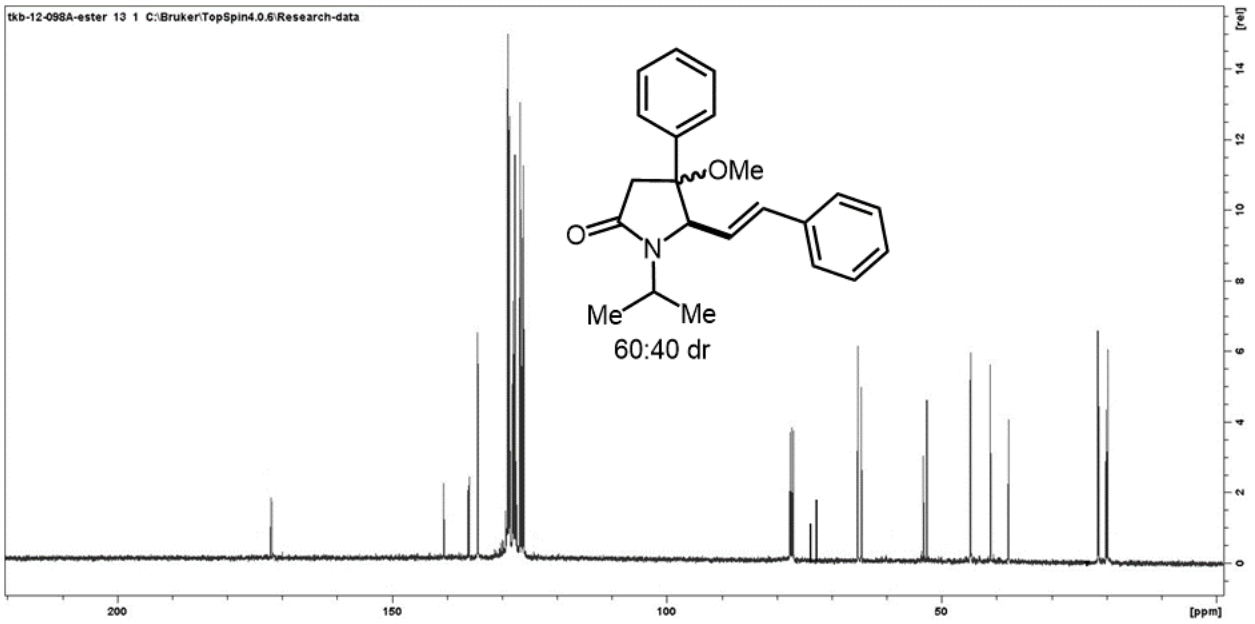
[ppm]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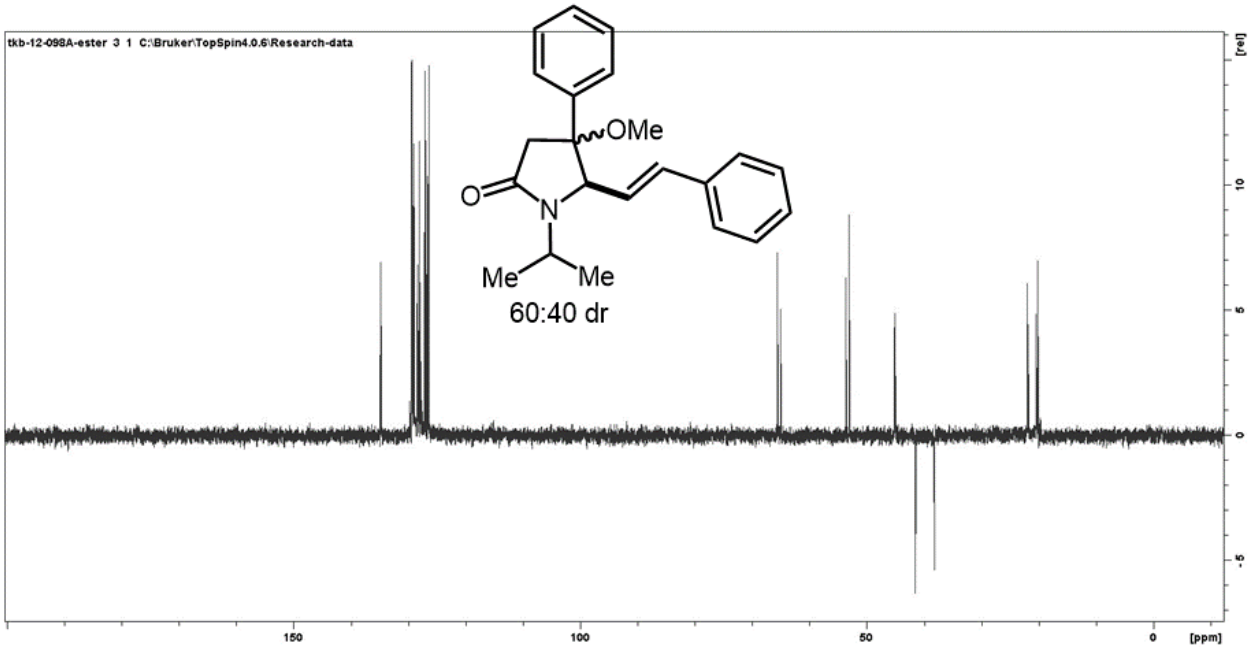
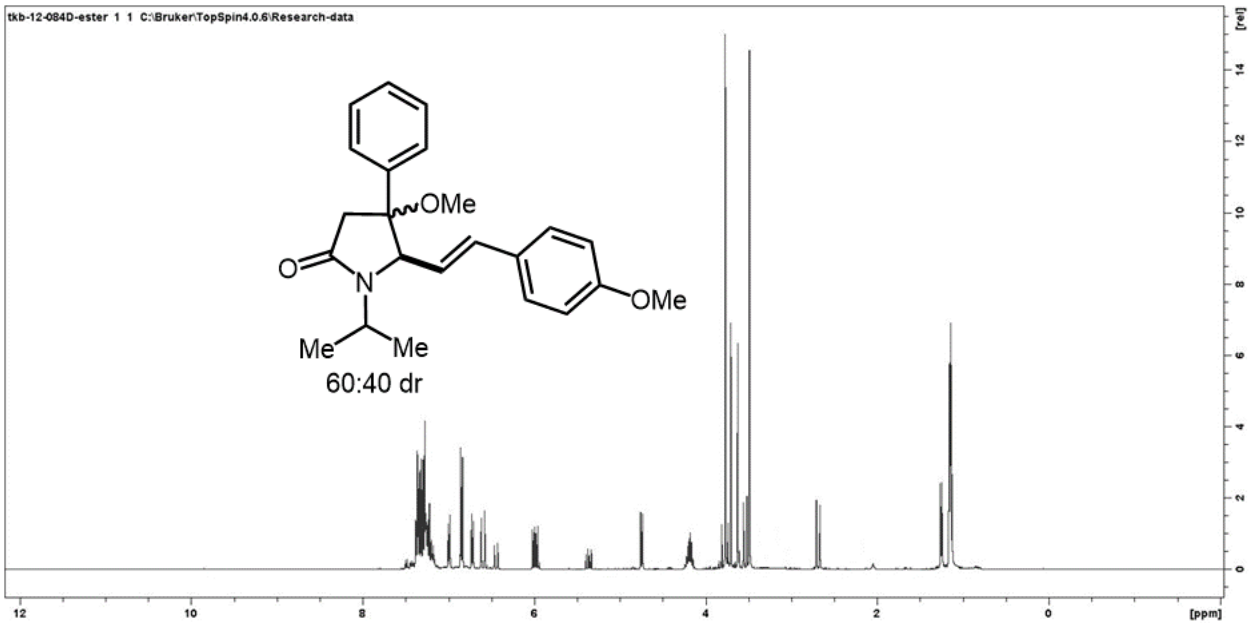
[ppm]



Compound 5i

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (60:40). Oily substance. Yield = 107.8 mg, 59%, 60:40 dr. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 7.49 – 7.22 (m, 7H), 6.90 – 6.81 (m, 2H), 6.81 – 6.42 (m, 1H), 6.05 – 5.36 (m, 1H), 4.81 (d, *J* = 8.7 Hz, 1H), 4.26 (dp, *J* = 9.8, 6.9 Hz, 1H), 3.84 (s, 3H), 3.60 (d, *J* = 16.8 Hz, 1H), 3.55 (s, 3H), 2.75 (d, *J* = 16.8 Hz, 1H), 1.24 – 1.17 (m, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 172.06, 171.62, 159.94, 159.59, 140.74, 136.14, 133.89, 133.75, 128.98, 128.58, 127.98, 127.86, 127.70, 127.67, 126.05, 123.79, 114.30, 114.04, 70.21, 69.12, 65.38, 64.82, 55.41, 55.33, 53.22, 52.60, 44.79, 44.69, 41.22, 37.83, 21.54, 21.39, 19.99, 19.72. HRMS calc for $C_{23}H_{27}NO_3$ 365.1991, found 365.1996.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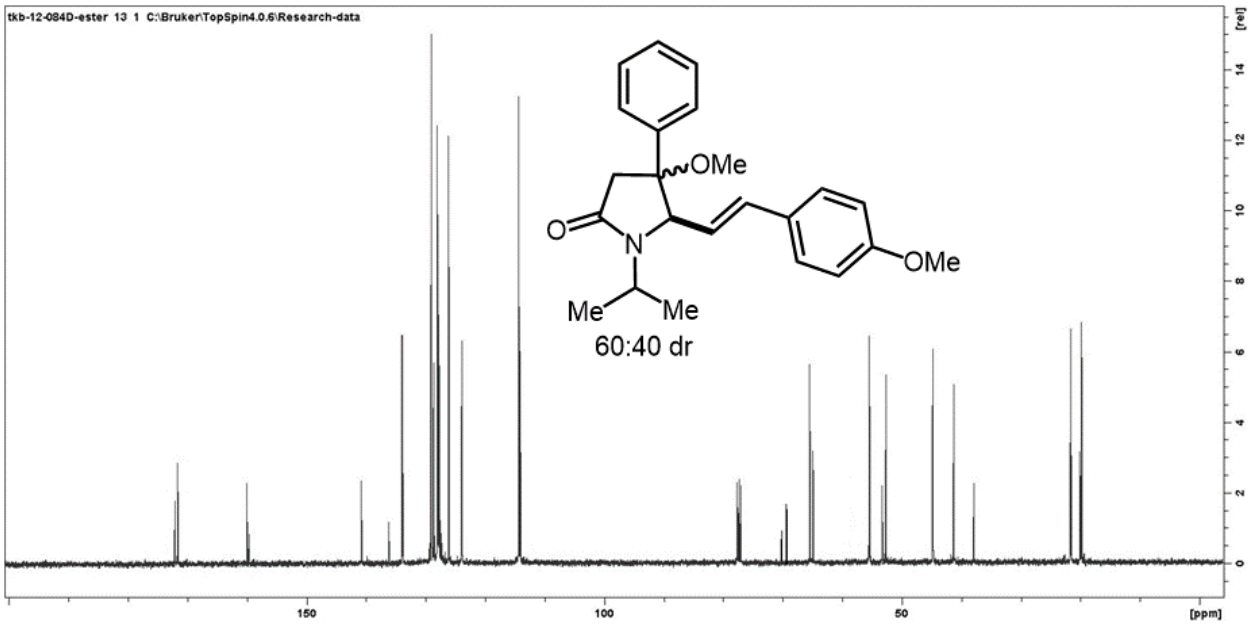
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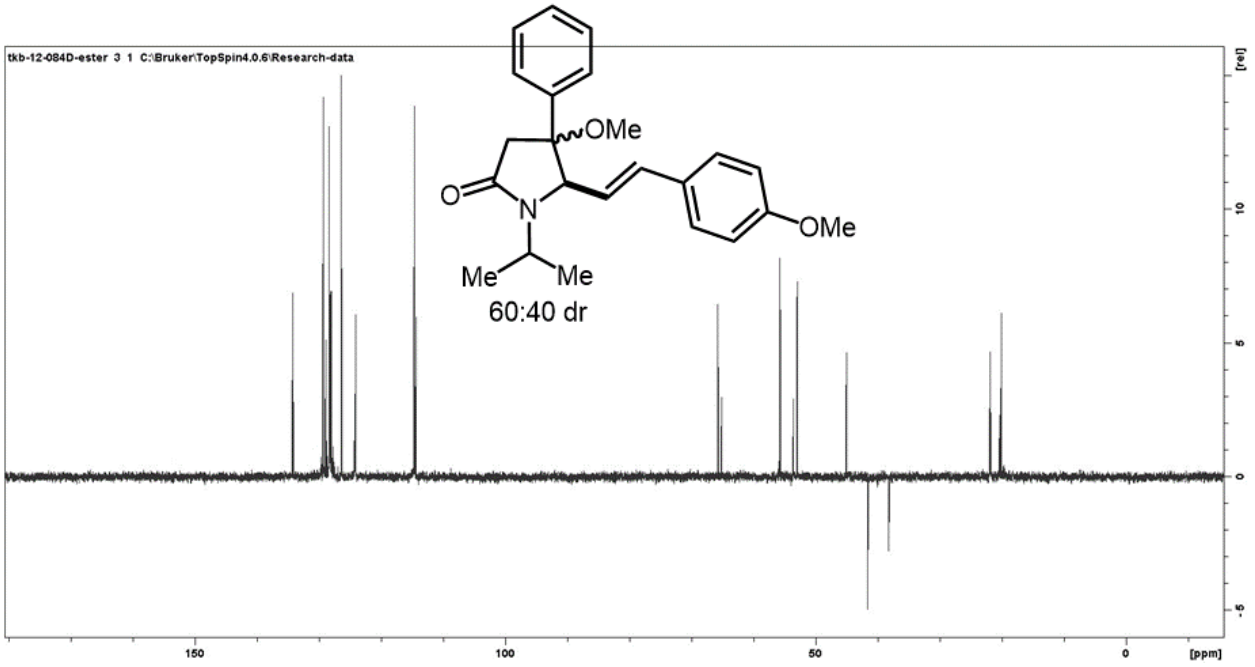
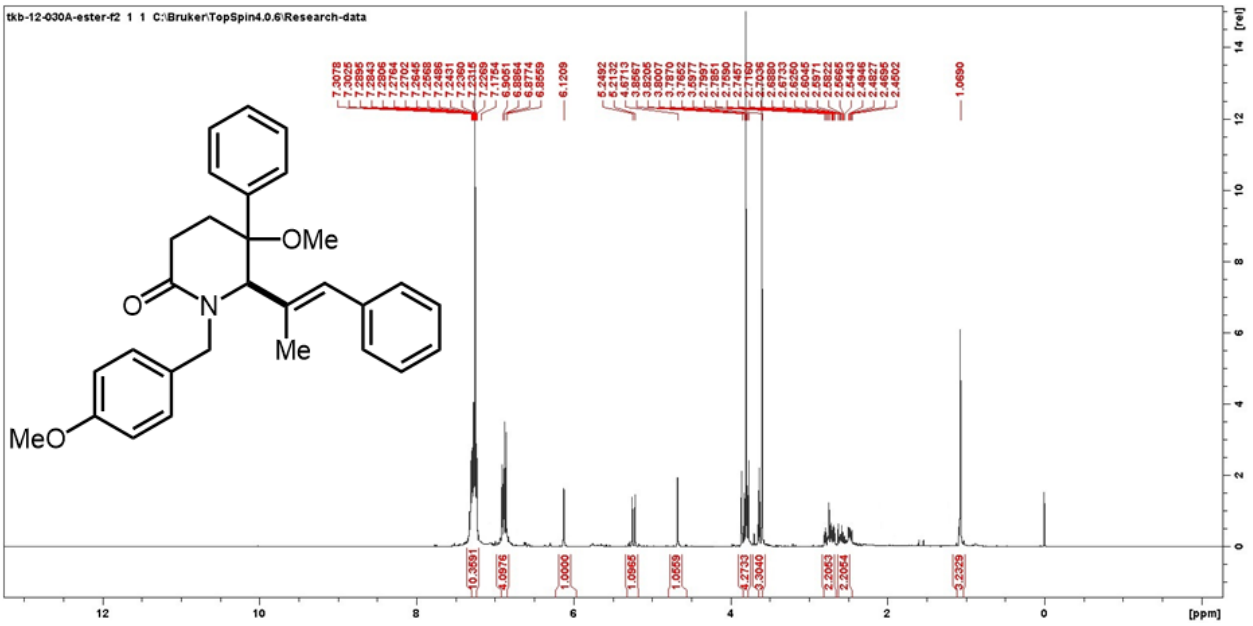


Compound 5j

Prepared in 0.5 mmol scale using **General Procedure D.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Oily substance. Yield = 152.3 mg, 69%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 10H), 6.90 – 6.85 (m, 4H), 6.12 (s, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 4.67 (s, 1H), 3.85 – 3.76 (m, 4H), 3.59 (s, 3H), 2.79 – 2.70 (m, 2H), 2.62 – 2.42 (m, 2H), 1.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.08, 158.13, 136.41, 135.58, 134.11, 132.29, 131.94, 129.89, 129.58, 129.35, 129.02, 128.78, 128.47, 128.38, 127.35, 126.92, 114.10, 72.84, 67.90, 55.35, 53.34, 48.43, 29.59, 23.59, 17.32. HRMS calc for $C_{29}H_{31}NO_3$ 441.2304, found 441.2309.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Me
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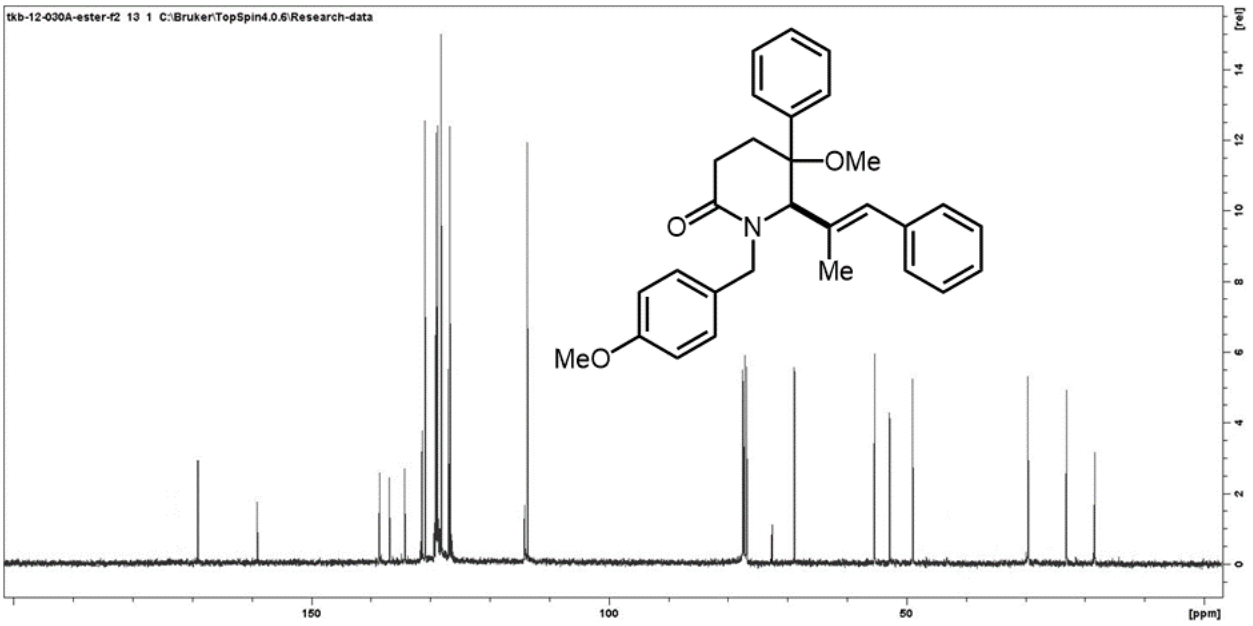
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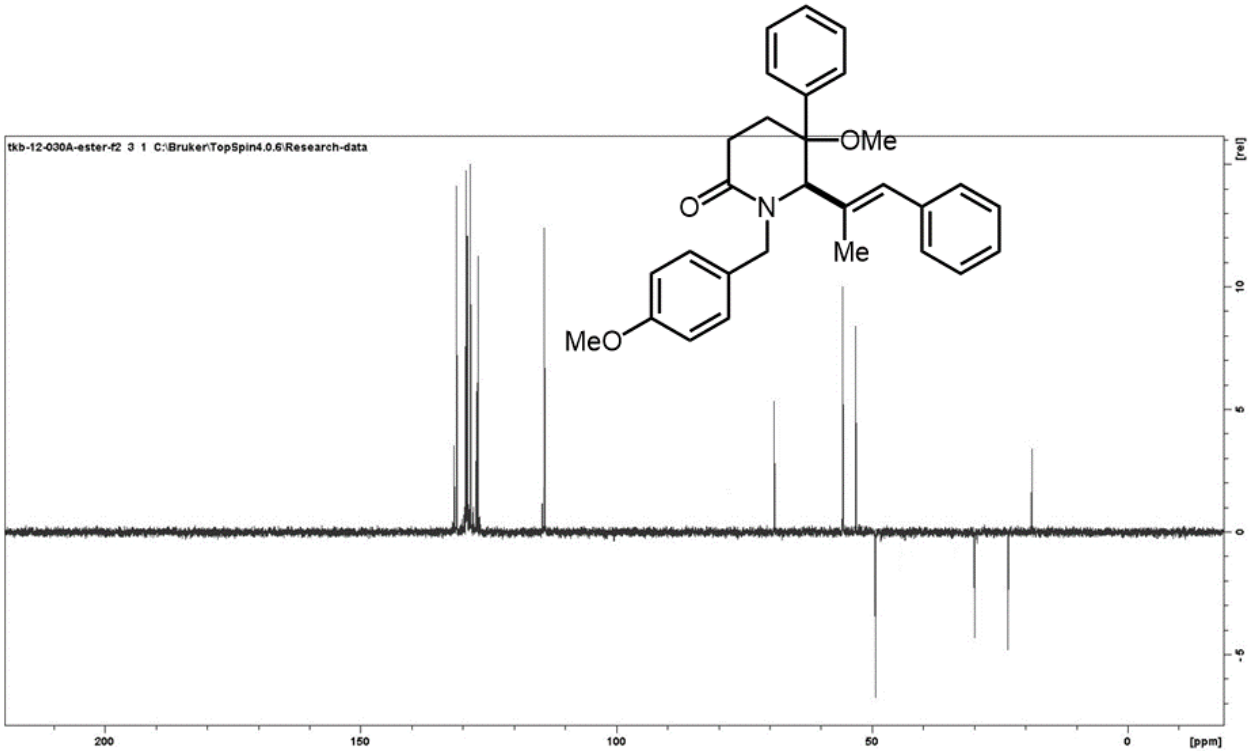

References

1. **Timothy K. Beng** and Antonio Moreno; "*Catalytic, selective, and stereocontrolled construction of C4 quaternary and homobenzylic dihydroisoquinolones by sp³ C–H benzylation*", *RSC Advances,* **2020**, *10, 8805 - 8809.*